Altered White Matter Structure in the Visual System Following Early Monocular Enucleation

Nikita A. Wong ^{1,2} Sara A. Rafique ^{1,2} Krista R. Kelly,³
Stefania S. Moro,^{1,2,4} Brenda L. Gallie,⁴ and Jennifer K. E. Steeves ^{1,2,4*}

¹Department of Psychology, York University, Toronto, Ontario, Canada

²Centre for Vision Research, York University, Toronto, Ontario, Canada

³Retina Foundation of the Southwest, Dallas, Texas

⁴Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract: Partial visual deprivation from early monocular enucleation (the surgical removal of one eye within the first few years of life) results in a number of long-term morphological adaptations in adult cortical and subcortical visual, auditory, and multisensory brain regions. In this study, we investigated whether early monocular enucleation also results in the altered development of white matter structure. Diffusion tensor imaging and probabilistic tractography were performed to assess potential differences in visual system white matter in adult participants who had undergone early monocular enucleation compared to binocularly intact controls. To examine the microstructural properties of these tracts, mean diffusion parameters including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were extracted bilaterally. Asymmetries opposite to those observed in controls were found for FA, MD, and RD in the optic radiations, the projections from primary visual cortex (V1) to the lateral geniculate nucleus (LGN), and the interhemispheric V1 projections of early monocular enucleation participants. Early monocular enucleation was also associated with significantly lower FA bidirectionally in the interhemispheric V1 projections. These differences were consistently greater for the tracts contralateral to the enucleated eye, and are consistent with the asymmetric LGN volumes and optic tract diameters previously demonstrated in this group of participants. Overall, these results indicate that early monocular enucleation has long-term effects on white matter structure in the visual pathway that results in reduced fiber organization in tracts contralateral to the enucleated eye. *Hum Brain Mapp* 39:133–144, 2018. © 2017 Wiley Periodicals, Inc.

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*Correspondence to: Jennifer K. E. Steeves; 1032 Sherman Health Science Research Centre, York University, 4700 Keele St., Toronto, ON M3J 1P3, Canada. E-mail: steeves@yorku.ca

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INTRODUCTION

At birth, the visual system is far from mature, and normal development continues well into adolescence. During this period, typical postnatal maturation of the visual system is vulnerable to changes in sensory input, particularly in the first few years of life [Garey and de Courten, 1983; Huttenlocher and de Courten, 1987]. In instances where there is a complete loss of input from a sensory modality (e.g., blindness), neural reorganization often follows so that other sensory systems recruit brain regions previously engaged by the lost sense [Merabet and Pascual-Leone, 2010].

Monocular enucleation is the surgical removal of one eye, resulting in the complete deafferentation of 50% of the visual input to the brain. Often the result of retinoblastoma, a childhood cancer of the retina, the removal of one eye is distinct from other forms of developmental monocular visual deprivation, such as cataract, strabismus, ptosis, or anisometropia. Unlike these other types of partial vision loss, in which degraded visual input continues to reach the brain, monocular enucleation completely removes all forms of visual input from one eye, making it a unique model for examining the consequences of the loss of binocularity during a critical period of neural development [Steeves et al., 2008].

The long-term behavioral consequences of losing one eye early in life, during postnatal development of the visual system, are well documented. Adults who have undergone early monocular enucleation exhibit maintained, and in some cases enhanced, performance on certain visual tasks. For example, following early monocular enucleation, individuals demonstrate heightened low contrast letter acuity compared to monocular viewing controls and comparable acuity to binocular viewing controls [Reed et al., 1997]. The ability to detect and recognize texture-defined letters is also maintained following early monocular enucleation [Steeves et al., 2002]. On the other hand, mild impairments for visual motion perception and oculomotor abilities are observed [for review, see Kelly et al., 2012b; Steeves et al., 2008]. On tasks requiring participants to process the shape and spacing of internal facial features, individuals who have undergone early monocular enucleation also demonstrate mild impairments compared to both monocular and binocular viewing controls [Kelly et al., 2012a].

Few studies have investigated the morphological development of the human visual system following partial visual deprivation from early monocular enucleation. Recently, differences in the adult anterior visual system have been demonstrated in the optic nerve, optic chiasm, and optic tract of individuals who have undergone early monocular enucleation. Analysis of the lateral geniculate nucleus (LGN) also revealed bilateral reductions in volume; however, overall these changes were considerably less than might have been expected given the 50% loss of visual input. Surprisingly, reductions in the volume of the LGN and the diameter of the optic tract were significantly

less ipsilateral to the enucleated eye compared to the respective contralateral structures [Kelly et al., 2014]. Increased surface area and gyrification in visual, auditory (supramarginal), and multisensory (superior temporal, inferior parietal, superior parietal) cortices have also been reported following early monocular enucleation. Gray matter changes to visual cortex were restricted to primary visual cortex (V1) and inferior temporal cortex of the hemisphere ipsilateral to the enucleated eye only, consistent with the previous LGN findings [Kelly et al., 2015]. Structural changes have similarly been examined in the auditory pathway of this group, specifically at the level of the medial geniculate body (MGB), the auditory nucleus of the thalamus. Independent of eye of enucleation, the left MGB volume of adult participants who have undergone early monocular enucleation was significantly larger than the right MGB, a hemispheric asymmetry that was not present in controls [Moro et al., 2015].

It is clear that enucleation of one eye during postnatal development results in considerable changes to the morphology of both the visual and auditory systems. There are numerous mechanisms that could support such structural changes, including: Wallerian degeneration, Wilbrand's knee [Horton, 1997], neural recruitment of deafferented cells [Grigoris et al., 1986; Rakic, 1981], corticothalamic feedback [Bartlett, 2013; Horton and Hocking, 1998; Sloper, 1993; Toosy et al., 2001; Zhang et al., 1997], and impaired synaptic pruning [Godement et al., 1987; Grigoris et al., 1986]. Changes in white matter can influence gyrification, which in turn is intimately connected to surface area [Hilgetag and Barbas, 2006; Van Essen, 1997]. Importantly, white matter maturation continues into adolescence, and thus it is highly possible that its development is affected by early monocular enucleation [Barnea-Goraly et al., 2005; Gao et al., 2009]. Yet, white matter structure within the brain has not previously been assessed in adulthood following the early surgical removal of one eye.

Diffusion tensor imaging (DTI) is a common magnetic resonance imaging (MRI) based technique for noninvasively mapping structural connections in the living brain. DTI measures the natural movement of water molecules (i.e., diffusion), relying on the fact that water will diffuse differently throughout the brain depending on the type of tissue or barriers present. The various aspects of a diffusion process can be described by four diffusion parameters: fractional anisotropy (FA; a scalar value from 0 to 1 that describes the degree of directionality, or anisotropy, of a diffusion process), mean diffusivity (MD; the average rate of diffusion within a voxel), axial diffusivity (AD; the principal eigenvalue of the diffusion tensor [λ_1], representing the degree of diffusion parallel to the axon), and radial diffusivity (RD; the average of the second and third eigenvalues of the diffusion tensor [$\lambda_2 + \lambda_3/2$], representing the diffusion perpendicular to the axon). Diffusion-weighted data can also be used to perform tractography, a method for creating 3D reconstructions of fiber tracts and for

TABLE I. Patient histories for ME participants

Participant	Age (years)	Sex	Snellen acuity	Enucleated eye	AAE (months)
ME01	28	Male	20/12.5	Right	4
ME02	30	Male	20/20 + 3	Left	13
ME03	43	Female	20/12.5 + 2	Right	18
ME04	17	Female	20/12.5 + 1	Right	26
ME05	36	Female	20/16 + 4	Left	18
ME06	21	Male	20/16	Left	60
ME07	16	Male	20/20 + 4	Left	32

AAE, age at enucleation.

quantifying the intervoxel connectivity of these projections between brain regions [Mori, 2007]. Specifically, probabilistic tractography models the desired white matter structure using a connectivity index to describe the likelihood of a voxel being part of the tract connecting the specified regions of interest [Jones, 2008; Mori and van Zijl, 2002].

The aim of this study was to investigate how the enucleation of one eye early in life, and thereby a 50% deafferentation of input to the visual system, affects the development of white matter within the brain. Using DTI indices (FA, MD, AD, and RD) and probabilistic tractography, the structure of several white matter tracts was examined relative to binocularly intact controls. Given the known morphological changes to cortical and subcortical structures throughout the adult visual system following early monocular enucleation [Kelly et al., 2014, 2015], we identified three tracts of interest: (1) the optic radiations, (2) feedback projections connecting V1 to the LGN, and (3) interhemispheric projections between left and right V1.

METHODS

Participants

Monocular enucleation (ME) participants

Seven participants (3 female) who had undergone early monocular enucleation participated in this study. All ME participants had been unilaterally eye-enucleated (3 right eye removed) due to retinoblastoma, a childhood cancer of the retina, at a mean age of 24 months (SD = 18.1 months, range = 4–60 months). Mean age at participation was 27.3 years (SD = 10.0 years, range = 16–43 years). All ME participants had taken part in at least one previous structural neuroimaging study conducted in this group [Kelly et al., 2014, 2015; Moro et al., 2015]. Individual patient histories are presented in Table I.

Binocular control participants

Eleven binocularly intact age-matched controls (7 females; 9 right-eye dominant as assessed by acuity and the Porta test [Durand and Gould, 1910]) were recruited to participate in this study. The mean age at participation was 27.8 years

(SD = 5.7 years, range 18–40 years). All control participants had normal stereoacuity (40″; Titmus stereo test, Stereo Optical Co., Inc., Chicago, IL). Six of these participants had also been tested in one or more of the studies conducted by Kelly et al. [2014, 2015] and Moro et al. [2015].

All participants (both ME and controls) had normal or corrected-to-normal visual acuity ($\geq 20/20$; ETDRS chart, Precision Vision™, La Salle, IL) and had no known contraindications to MRI. All participants gave written informed consent prior to their inclusion in this study, which was approved by the York University Office of Research Ethics and conducted in accordance with the 1964 Declaration of Helsinki.

Data Acquisition

All scans were acquired on a Siemens MAGNETOM® Tim Trio 3T MRI scanner with a 32-channel head coil (Erlangen, Germany). High-resolution whole brain anatomical images were obtained sagittally using T1-weighted 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequencing, for each participant (1 mm³ isotropic voxels, TR = 1,900 ms, TE = 2.52 ms, imaging matrix = 256 × 256, FOV = 256 mm, and flip angle = 9°, number of slices = 192). The DTI protocol consisted of a whole brain diffusion-weighted echoplanar imaging sequence (1.5 × 1.5 × 2.0 mm voxels, TR = 6,900 ms, TE = 86 ms, imaging matrix = 128 × 128, FOV = 192 mm, number of contiguous axial slices = 56, parallel imaging [GRAPPA with acceleration factor of 3]), with 64 diffusion directions, b value = 1,000 s/mm², including a single reference volume, $b_0 = 0$ s/mm².

Data Processing

Processing of both anatomical and diffusion-weighted images—and probabilistic tract reconstruction—was conducted using tools from the open source FMRIB3s Software Library (FSL, version 5.0.8; <http://www.fmrib.ox.ac.uk/fsl>) [Smith et al., 2004].

Preprocessing

T1-weighted anatomical images were brain extracted to remove the skull and other nonbrain tissue using the Brain

Extraction Tool (BET) [Smith, 2002], and registration of all images to the standard Montreal Neurological Institute (MNI) space template was performed using FSL's Linear Registration Tool (FLIRT) [Jenkinson et al., 2002; Jenkinson and Smith, 2001].

Corrections for potential eddy current distortions and simple head motion were applied to the raw diffusion data using affine registration to the b_0 (reference) volume, prior to brain extraction. Registration of these brain-extracted diffusion-weighted images to the MNI space template as well as to the T1-weighted structural image was performed using FSL's Non-Linear Registration Tool (FNIRT) [Andersson et al., 2007a, 2007b]. A diffusion tensor model was fitted at each voxel through FSL's DTIFIT function using a least-squares linear regression approach. Prior to probabilistic tract reconstruction, Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques for modeling Crossing Fibers (BEDPOSTX) was run through FSL's Diffusion Toolbox (FDT) in order to estimate the necessary diffusion parameters. BEDPOSTX runs Markov Chain Monte Carlo sampling to build up distributions on diffusion parameters at each voxel and importantly allows modeling of crossing fibers within each voxel of the brain [Behrens et al., 2003, 2007].

Probabilistic tractography

Reconstructions of the optic radiations (LGN-V1), V1-LGN tracts, and interhemispheric V1 projections were performed in each hemisphere separately through FDT using the Probabilistic Tracking with Crossing Fibers (PROBTRACKX) tool. Bilateral masks necessary for reconstruction were extracted for the LGN, V1, and cerebral white matter from the Jülich Histological [Eickhoff et al., 2006; Eickhoff et al., 2007; Eickhoff et al., 2005] and Harvard-Oxford Subcortical Structural [Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006] atlases available through FSL. All masks were thresholded and subsequently overlaid onto each participant's MNI space T1-weighted anatomical image to confirm their proper size and location. Using default settings, a total of 5,000 individual pathways were drawn from each voxel in the seed mask at a curvature threshold of 0.2 and a maximum of 2,000 steps. Step length was set at 0.5 mm and distance correction was used. Modified Euler integration for computing probabilistic streamlines (tracts) was selected for increased accuracy. To reduce the number of spurious tracts, the termination region was also set as a waypoint mask (requiring the all tracts pass through the specified region), and an exclusion mask of the opposite cerebral white matter was used for reconstruction of the optic radiations and V1-LGN projections [Behrens et al., 2003, 2007].

Extraction of diffusion parameters

Values for the four main diffusion indices were obtained for each tract of interest, in the left and right hemispheres separately, and on an individual basis, using FSL's Tract-Based

Spatial Statistics (TBSS). Each participant's MNI space diffusion-weighted data were skeletonized at a threshold of $FA > 0.2$ to create a mean FA skeleton representing the average FA values in all tracts. The FA, MD, AD, and RD data were then aligned using affine nonlinear registration (FNIRT) and individually projected on to this skeleton [Smith et al., 2006]. Masks of the PROBTRACKX generated tracts were used to exact values for the diffusion indices in the bilateral optic radiations, V1-LGN projections, and interhemispheric V1 projections.

Statistical Analysis

All statistical analyses were conducted using the open source program R (version 3.2.2) (<http://www.R-project.org>). Independent and repeated-measures pairwise comparisons were performed for each of the tracts of interest between ME participants and binocular controls, as well as within groups, relative to the enucleated eye (ME participants) or nondominant eye (controls) for the four diffusion parameters. Owing to the non-normality of the data, these comparisons were conducted using Yuen's test (T_y) with 10% trimmed means. Multiple comparisons were controlled for using the false-discovery rate (FDR).

RESULTS

There were no significant group differences in sex for the four diffusion parameters across each of the optic radiations, V1-LGN projections, and interhemispheric V1 projections, $P > 0.05$. Therefore, sex was not taken into consideration in the following analyses.

All subsequent results will be reported relative to the non-dominant eye, for both the control and ME participants, to draw comparisons across groups. Results for the control group will be referred to as either ipsilateral or contralateral to the non-dominant eye, whereas findings reported for the ME group will be ipsilateral or contralateral to the enucleated (i.e., nondominant) eye.

Optic Radiations (LGN-V1)

Pairwise comparisons within the control group revealed significant asymmetries in AD, $T_y(17) = -11.179$, $P < 0.001$, MD, $T_y(17) = -11.183$, $P < 0.001$, and RD, $T_y(17) = -11.185$, $P < 0.001$, such that larger values were observed in the optic radiation ipsilateral, compared to contralateral, to the nondominant eye (Fig. 1). Correspondingly, mean FA values for the control group were higher in the tracts contralateral to the nondominant eye, $T_y(17) = 6.985$, $P < 0.001$. Analyses conducted in the ME group likewise revealed significantly larger values of AD, $T_y(11) = -9.204$, $P < 0.001$, MD, $T_y(11) = -9.207$, $P < 0.001$, and RD, $T_y(11) = -9.209$, $P < 0.001$, in the optic radiation ipsilateral to the enucleated eye; however, unlike controls, ME participants exhibited FA values that were significantly higher in the hemisphere ipsilateral, rather than

Figure 1.

Transverse sections showing examples of the probabilistic tractography (PROBTRACKX) reconstructions of the optic radiations, V1-LGN projections, and interhemispheric V1 projections overlaid on individual T1-weighted MNI space images in a single binocular control participant and monocular enucleation participant.

contralateral, to the enucleated eye, $T_y(11) = -5.847$, $P < 0.001$. Values extracted for the ME group did not differ significantly from those of binocularly intact controls across all diffusion parameters, $P > 0.05$. Mean AD, FA, MD, and RD values for the optic radiations of both control and ME participants are shown in Figure 2.

V1-LGN Projections

The V1-LGN projections ipsilateral to the non-dominant eye of control participants had significantly higher FA, $T_y(17) = -7.236$, $P < 0.001$, AD, $T_y(17) = -11.179$, $P < 0.001$, and MD, $T_y(17) = -11.183$, $P < 0.001$, compared to the projections contralateral to the non-dominant eye. The same asymmetries were also observed in ME participants, with significantly larger values of FA, $T_y(11) = -6.008$, $P < 0.001$, AD, $T_y(11) = -9.204$, $P < 0.001$, and MD, $T_y(11) = -9.207$, $P < 0.001$, in the projections ipsilateral to the enucleated eye. However, the asymmetries observed in RD were not consistent across groups. The control group had significantly larger RD values ipsilateral to the non-dominant eye, $T_y(17) = -11.185$, $P < 0.001$, whereas the ME group exhibited higher values of RD in the tracts contralateral to the enucleated eye, $T_y(11) = 9.209$, $P < 0.001$ (Fig. 2). Yet similar to the optic radiations, values for the measured diffusion indices in the V1-LGN projections did not differ significantly between the ME group and the binocularly intact controls, $P > 0.05$ (Fig. 1).

Interhemispheric V1 Projections

Between groups pairwise comparisons revealed significantly lower FA in ME participants compared to control participants in both the ipsilateral-to-contralateral, $T_y(12) = 2.687$, $P = 0.021$, and contralateral-to-ipsilateral, $T_y(13) = 3.219$, $P = 0.009$, interhemispheric V1 projections (Fig. 2). Within groups comparisons revealed significantly higher FA in the ipsilateral-to-contralateral than the contralateral-to-ipsilateral interhemispheric V1 projections in both controls, $T_y(17) = -7.056$, $P < 0.001$, and ME participants, $T_y(11) = -6.091$, $P < 0.001$. Significantly larger ipsilateral-to-contralateral values in the control group, $T_y(17) = -11.185$, $P < 0.001$, and ME group, $T_y(11) = -9.209$, $P < 0.001$, were also observed for AD. Further, there were higher MD, $T_y(17) = 11.183$, $P < 0.001$, and RD, $T_y(17) = 11.185$, $P < 0.001$, values in the contralateral-to-ipsilateral V1 tracts of controls; however, the ME group exhibited opposite asymmetries with larger ipsilateral-to-contralateral compared to contralateral-to-ipsilateral values for MD, $T_y(11) = -9.207$, $P < 0.001$, and RD, $T_y(11) = -9.208$, $P < 0.001$. The PROBTRACKX generated reconstructions of these tracts are shown in Figure 1.

DISCUSSION

Using DTI and probabilistic tractography, this study investigated the long-term consequences of early monocular

Figure 2.

Mean values of the measured diffusion parameters (AD [$\times 10^{-3} \text{ mm}^2/\text{s}$], FA, MD [$\times 10^{-3} \text{ mm}^2/\text{s}$], and RD [$\times 10^{-3} \text{ mm}^2/\text{s}$]) in the ipsilateral (to the enucleated or non-dominant eye) and contralateral tracts of interest for binocularly intact controls (BC) and monocular enucleation participants (ME). Error bars report

standard error of the mean. BC = binocular control group; ME = monocular enucleation group; AD = axial diffusivity; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

enucleation on the development of white matter in several visual system structures. Compared to binocularly intact controls, we report microstructural differences in the optic radiations, V1-LGN projections, and interhemispheric V1 projections of participants who have undergone early monocular enucleation. Specifically, we observed changes in the diffusion indices in ME participants relative to the control group, which were dependent on the eye of enucleation. These results are consistent with the previously demonstrated morphological asymmetries in the visual system of this sample of ME participants [Kelly et al., 2014, 2015], and together suggest that early monocular enucleation has long-term effects on the development of distal white matter structures throughout the visual system.

Our analysis of the optic radiations revealed significantly higher FA but lower AD, MD, and RD in the tracts

contralateral to the nondominant eye of binocular control participants (for summary, see Fig. 3). Given that larger values of FA suggest improved coherence of fiber orientation, and reductions in the degree of RD reflect less diffusion perpendicular to the axon, this combination of asymmetrical diffusion parameters may be interpreted as improved fiber organization in the optic radiation of controls contralateral to the nondominant eye [Jones, 2008; Jones et al., 2013]. This may be the result of a number of differences in the microstructural characteristics, including smaller axon diameter, denser axonal packing, or higher myelination [Le Bihan, 2003; Pierpaoli and Basser, 1996]. There is evidence for left- and/or rightward asymmetries in varying combinations of FA, AD, MD, and RD in the optic radiations of healthy participants, yet to our knowledge, previous research has not accounted for any

Figure 3.

Schematic depicting a summary of all significant results ($P < 0.05$, FDR corrected) observed in the binocular control group for the optic radiations, V1-LGN projections, and interhemispheric V1 projections in relation to the nondominant eye. Findings reported in red indicate a significant difference compared to the monocular enucleation group. All other results are significant relative to the opposite hemisphere. Broken lines represent a postulated trend based on previous data. References: ¹Menon et al. [1997]; Miki et al. [2001]; Rombouts et al. [1996]; Toosy et al. [2001].

differences dependent on eye dominance [Dayan et al., 2015; de Schotten et al., 2011; Sherbondy et al., 2008]. Ocular dominance is shown to influence functional activity in V1 such that the proportion of activation is considerably greater when the dominant eye is stimulated compared to the nondominant eye [Menon et al., 1997; Rombouts et al., 1996]. Additionally, it has been shown that during monocular viewing, activation is greater in V1 contralateral to the stimulated eye [Miki et al., 2001; Toosy et al., 2001]. Together, these previous findings suggest that V1 ipsilateral to the nondominant eye receives stronger physiological input. If this is the case, then the improved fiber organization observed in the present study in the optic radiations contralateral to the nondominant eye of controls

may reflect more efficient communication of information to accommodate for the relatively less visual input to V1 contralateral to the nondominant eye. Of course, differences in functional activity do not necessarily influence white matter structure [Bridge et al., 2009; Rakic, 1988]. Nevertheless, future studies should investigate the effects of ocular dominance on the previously observed left and right asymmetries in the optic radiations of healthy participants.

Similar to the control group, ME participants exhibited lower AD, MD, and RD in the optic radiations contralateral, compared to ipsilateral, to the enucleated eye. However, the FA asymmetry in the ME group was opposite to that of control participants (i.e., FA was lower in the tracts contralateral to the enucleated eye; for summary, see Fig. 4), suggesting that there is some orientation-dependent difference in the microstructure of the optic radiations contralateral to the enucleated eye in ME participants. The smaller FA value contralateral to the enucleated eye may be explained by the relatively smaller LGN and optic tract volumes previously demonstrated contralateral to the enucleated eye in this specific ME sample [Kelly et al., 2014]. Previous studies of long-term visual deprivation have commonly interpreted a reduction in FA as the consequence of transneuronal degeneration or axonal immaturity [Boucard et al., 2016; Shu et al., 2009a]. Transneuronal degeneration could certainly account for the observed change in FA if, for example, the smaller LGN contralateral to the enucleated eye supports fewer efferent fibers extending to V1, or if the reduction in visual input results in disuse atrophy. In other nonprimate mammals, monocular deprivation has also been associated with the retraction and shortening of the thalamocortical projections from the deprived eye [Dahlhaus and Levelt, 2010]. In addition, due to the bias toward crossed versus uncrossed retinal fibers [Chacko, 1948; Horton, 1997], the effects of the degeneration of projections serving the enucleated eye would be greater in the contralateral hemisphere.

Furthermore, the tendency toward stronger activity in contralateral V1 has also been demonstrated in children who have undergone monocular enucleation [Barb et al., 2011]. Although the optic radiations mature early in life, often before three years of age [Kinney et al., 1988], refinement of the fiber bundles is experience-dependent [Alix and Domingues, 2011; Sengpiel and Kind, 2002]. Therefore, a decrease in the activity throughout the visual pathway contralateral to the enucleated eye may impede the later stages of development of the optic radiations. However, findings from animal research suggest that monocular deprivation in higher mammals more commonly results in axonal retraction, rather than immaturity (which is seen in rodents), thus favoring transneuronal degeneration as the mechanism for the changes observed in the contralateral optic radiations of ME participants [Dahlhaus and Levelt, 2010].

Our results support those of Barb et al. (2011) who found no significant differences in FA or MD in the optic radiations of children who had undergone early monocular enucleation and control children. In contrast, relative to early blind

Figure 4.

Schematic depicting a summary of all significant results ($P < 0.05$, FDR corrected) observed in the monocular enucleation group for the optic radiations, V1-LGN projections, and interhemispheric V1 projections in relation to the enucleated eye. Findings reported in red indicate a significant difference compared to the binocular control group. All other results are significant relative to the opposite hemisphere. Broken lines represent a postulated trend based on previous data. References: ¹Kelly et al. [2014]; ²Kelly et al. [2015]; ³Barb et al. [2011]; ⁴Menon et al. [1997]; Miki et al. [2001]; Rombouts et al. [1996]; Toosy et al. [2001].

and visually impaired individuals (e.g., amblyopia, glaucoma), who demonstrate significant bilateral reductions in FA and associated increases in MD and RD in the optic radiations [Shimony et al., 2006; Shu et al., 2009a, 2009b; Xie et al., 2007; Zhang et al., 2015], our results in the ME group are considerably less severe. Instances of monocular vision loss, such as amblyopia, which continue to send degraded visual input to the brain, have widespread detrimental effects on the visual system both behaviorally and structurally [Joly and Frankó, 2014; Levi, 2006]. While the neural mechanisms of amblyopia are not fully understood, it seems

that some aspect of the continued interactions between the affected and normal eyes, or the known functional abnormalities of visual cortex [Kiorpes et al., 1998], result in more disruptive changes compared to the complete deafferentation of visual input that occurs following enucleation. A more detailed review of the observed changes in visual function following early monocular enucleation compared to amblyopia is presented in Steeves et al. [2008]. Although we did not assess our participants in childhood, together these findings suggest that the effects of early monocular enucleation on the development of the optic radiations occur over the long term, and are less pervasive than changes following other forms of vision loss.

Aside from the opposite FA asymmetry in ME participants compared to controls, the optic radiations of ME participants remain largely unchanged. Considering the role the optic radiations play in relaying information from the subcortical LGN to V1, the preservation of this key visual system tract could contribute to the intact visual processing previously demonstrated in ME participants [Kelly et al., 2012b; Steeves et al., 2008]. For example, lower FA in the optic radiations of children with amblyopia has been associated with reduced visual acuity [Li et al., 2015]. Thus, it is possible that the less extensive changes to the optic radiations following early monocular enucleation may be associated with the fact that ME participants demonstrate equivalent acuity compared to binocular viewing controls [Reed et al., 1997].

Similar to the optic radiations, control participants demonstrated significantly lower AD, MD, and RD in the V1-LGN projections contralateral to the nondominant eye. Such asymmetries suggest a reduction in the average rate of diffusion per voxel (MD) relative to the hemisphere ipsilateral to the nondominant eye that is likely the result of decreased diffusion both parallel (AD) and perpendicular to the axon (RD) [Jones, 2008]. However, in contrast to the optic radiations, the feedback tracts extending back from V1 to the LGN exhibited higher FA ipsilateral, compared to contralateral, to the nondominant eye. Relative to the optic radiations, the investigation of the V1-LGN projections is much less common and there appears to be no previous reports of diffusion parameters in these tracts to which we can compare our results. As activation is lower in V1 contralateral to the nondominant eye [Rombouts et al., 1996; Toosy et al., 2001], we have previously postulated this could result in greater FA in the optic radiations on that side (for summary, see Fig. 3). One could then speculate that in order to maintain an equal rate of information flow along these pathways across both hemispheres, the contralateral V1-LGN tracts should exhibit lower FA. The lower FA in V1-LGN tracts contralateral to the nondominant eye may alternatively, or additionally, be a result of the reduced V1 activity in this hemisphere causing weaker feedback signals to the LGN, and consequently less refined V1-LGN projections [Alix and Domingues, 2011; Sengpiel and Kind, 2002].

As in controls, ME participants demonstrated lower AD, FA, and MD values in V1-LGN projections contralateral to the enucleated eye. The ME group exhibited the opposite asymmetry in RD compared to controls, with larger RD values contralateral to the enucleated eye. A larger degree of diffusion perpendicular to the axon (i.e., RD) can indicate a number of structural changes that increase axonal diameter or the extracellular space around axons (e.g., demyelination, degeneration), and which also commonly cause a decrease in FA [Le Bihan, 2003; Jones, 2008; Jones et al., 2013; Pierpaoli and Basser, 1996]. These observed changes may be an extension of the alterations to the optic radiations and more anterior visual system structures (i.e., the LGN and optic tract) previously demonstrated in these participants in the hemisphere contralateral to the enucleated eye [Kelly et al., 2014]. For example, if the optic radiations have indeed degenerated in the hemisphere contralateral to the enucleated eye, it is possible that their terminations in V1 have resulted in Wallerian degeneration of the V1-LGN tracts causing the elevated RD and reduced FA values [Shimony et al., 2006; Shu et al., 2009b]. However, these differences may also be more directly related to the reduction in visual input. The relatively weaker physiological input to the hemisphere contralateral to the nondominant eye [Toosy et al., 2001], or in this case, the enucleated eye, is likely compounded by changes to the visual pathway structures (e.g., optic tract and LGN) [Kelly et al., 2014] in the same hemisphere resulting in further reduced V1 activity [Barb et al., 2011]. Reduced functional activity can disrupt normal corticothalamic feedback [Cudeiro and Sillito, 2006], causing axonal degeneration or immaturity [Boucard et al., 2016; Shu et al., 2009a], and likely results in the disorganization of the V1-LGN tracts. Similarly, the structural changes in V1 of these ME participants may also play a role. The relatively smaller cortical surface area and degree of gyrification in V1 contralateral to the enucleated eye [Kelly et al., 2015] may support fewer or less refined projections back to the LGN. These mechanisms are characteristic of elevated RD (and lowered FA) observed in our results and in other white matter structures following long-term complete or partial visual deprivation [Shimony et al., 2006; Shu et al., 2009a; Zhang et al., 2015].

The precise functional effects of feedback from V1 on the LGN have yet to be elucidated. However, there is accumulating evidence that corticothalamic feedback can result in changes in contrast gain, as well as in the spatial and temporal properties of the LGN [Ghodrati et al., in press]. For example, animal studies have shown that with cortical feedback, the length and size tuning to moving stimuli only is significantly tighter than without cortical feedback [Jones and Sillito, 1991]. This suggests that the functional influence of V1 on the LGN includes some motion processes. Therefore it may be that the changes in motion perception observed following early monocular enucleation [for review, see Kelly et al., 2012b; Steeves

et al., 2008] could be related to the increased disorganization in the V1-LGN projections in this group. Yet, like the optic radiations, the V1-LGN projections are relatively unchanged in ME participants, showing differences only in the directionality of the RD asymmetry. Given our growing understanding of the importance of the LGN and corticothalamic feedback for visual processing, the maintenance of this tract may contribute to the intact visual processes reported following early monocular enucleation (e.g., contrast sensitivity) [Nicholas et al., 1996].

Investigating the interhemispheric projections connecting V1 in controls revealed significantly lower AD and FA, with higher MD and RD, in the contralateral-to-ipsilateral tracts. This reflects lower coherence of fiber orientation, along with a higher rate of average diffusion that is likely due to larger amounts of diffusion perpendicular to the axon. Together, these diffusion indices might indicate thinner myelination, wider axonal diameter, or larger spaces between the axons [Le Bihan, 2003; Jones, 2008]. To date, the interhemispheric connection between V1 has not been widely investigated using tractography that directly seeds left and right V1 [Dougherty et al., 2005]. Much of the DTI literature reconstructing posterior interhemispheric connections has examined the splenium, which has projections to parietal and temporal cortex as well as V1 [Lebel et al., 2011; Schulte et al., 2005; Takao et al., 2011], and is subject to considerable interindividual variation [Putnam et al., 2010], making accurate comparisons between these tracts difficult. Since V1 ipsilateral to the nondominant eye receives stronger physiological input [Toosy et al., 2001], reduced FA between contralateral-to-ipsilateral tracts may be to limit input to the hemisphere with already greater visual activity (for summary, see Fig. 3), resulting in less refined activity-dependent projections [Alix and Domingues, 2011]. Yet these asymmetries may also reflect inherent developmental asymmetries resulting from other differences in function or gray matter [Hellige, 1993] that have yet to be considered.

In contrast to the control group, higher ipsilateral-to-contralateral MD and RD were observed in the interhemispheric V1 projections of ME participants, suggesting increased extra-axonal space. Additionally, although the same asymmetries in AD and FA were observed across groups, compared to controls, ME participants demonstrated significantly lower FA bidirectionally in these tracts. Together these findings suggest a general reduction in the coherence of fiber orientation (or organization) in the interhemispheric V1 projections of participants who have undergone early monocular enucleation, and this difference is more marked in the ipsilateral-to-contralateral projections. This within-group asymmetry may, in part, be attributed to the smaller surface area and gyrification of V1 contralateral, compared with ipsilateral, to the enucleated eye in these ME participants [Kelly et al., 2015]. Previous research has shown that larger cortical areas can support denser and more numerous fiber bundles,

compared to smaller cortical regions, as they provide developing axons with relatively larger amounts of target space on which to synapse [Putnam et al., 2010; Saron et al., 2003]. The interhemispheric V1 projections were the only visual system tract demonstrating significant changes between groups. These changes may contribute to the mild deficit in motion perception observed in individuals following early monocular enucleation [for review, see Kelly et al., 2012b; Steeves et al., 2008], as effective motion processing has been shown to rely on interhemispheric communication between V1 [Brandt et al., 2003]. As well, given the relative lateralization of many face processes, interhemispheric communication can be necessary for efficient functioning [Mohr et al., 2002]. The significant bidirectional reduction in FA in the interhemispheric V1 projections of ME participants may therefore contribute to the slower response latencies and impaired holistic face processing reported in this group [Kelly et al., 2012a].

While DTI is a valuable method as one of the few noninvasive neuroimaging techniques for visualizing white matter structure *in vivo*, all studies employing DTI share the limitation that it is difficult to precisely interpret what structural changes can be inferred from alterations in diffusion indices [Jones et al., 2013]. A number of both macro- and microstructural properties of white matter can influence the diffusion process and be reflected as similar changes to the diffusion parameters, making it difficult to draw conclusions about the specific nature of any changes. For example, a decrease in FA is often interpreted as a reduction in white matter integrity; however, it could also be the result of crossing or kissing fibers, among other factors [Jones, 2008]. In an attempt to account for this uncertainty, we have presented several potential mechanisms for each of the significant changes observed in the diffusion measures. Our rationale for the mechanisms put forward is supported by behavioral neuroimaging findings (e.g., fMRI, proton density scans) in other forms of visual deprivation [Shimony et al., 2006; Shu et al., 2009b] and controls, and postmortem results from monocularly enucleated animals [Nys et al., 2015; Toldi et al., 1996]. Moreover, given that we are using standardized methods and comparing between groups, we are confident that our findings reflect true differences between participants who have undergone early monocular enucleation and binocularly intact controls.

To conclude, we are the first to report long-term developmental changes to white matter structure in adults who had undergone early monocular enucleation. Relative to binocularly intact controls, significant differences, which were consistently greater for tracts contralateral to the removed eye, were observed in the optic radiations, V1-LGN projections, and interhemispheric V1 projections of ME participants. Such asymmetrical changes were likely driven by the alterations to the LGN and optic tract contralateral to the enucleated eye previously demonstrated in this sample following early monocular enucleation [Kelly

et al., 2014], in addition to the relatively less visual activity in that hemisphere (i.e., ipsilateral to the enucleated eye) [Barb et al., 2011]. These results contribute to our understanding of the morphological adaptations underlying the behavioral changes seen in individuals who have undergone early monocular enucleation [Kelly et al., 2014], and expand our knowledge of neuroplasticity following altered sensory input early in life.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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