

Damage to the Immature Optic Radiation Causes Severe Reduction of the Retinal Nerve Fiber Layer, Resulting in Predictable Visual Field Defects

Finn Lennartsson,^{1,2} Maria Nilsson,³ Olof Flodmark,^{1,2} and Lena Jacobson⁴

¹Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden

²Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden

³Department of Clinical Neurosciences, Unit of Optometry, Karolinska Institutet, Stockholm, Sweden

⁴Department of Clinical Neurosciences, Ophthalmology and Vision, Karolinska Institutet, Stockholm, Sweden

Correspondence: Finn Lennartsson, Department of Neuroradiology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden; finn.lennartsson@karolinska.se.

Submitted: May 30, 2014

Accepted: October 13, 2014

Citation: Lennartsson F, Nilsson M, Flodmark O, Jacobson L. Damage to the immature optic radiation causes severe reduction of the retinal nerve fiber layer, resulting in predictable visual field defects. *Invest Ophthalmol Vis Sci.* 2014;55:8278–8288. DOI:10.1167/iovs.14-14913

PURPOSE. The aim of the present study was to seek evidence of a relationship between damage to the optic radiation (OR) in the immature brain and subsequent development of the retinal nerve fiber layer (RNFL) and associated visual manifestations.

METHODS. Seven cases (2 males and 5 females ranging in age from 18 to 35 years old) were selected from a large cohort of individuals with known white matter damage of immaturity (WMDI), who had presented with visual dysfunction. They underwent magnetic resonance imaging (MRI), including diffusion-weighted MRI. Visual function was evaluated by best-corrected visual acuity and visual field (VF) testing using Goldmann perimetry and Humphrey field analyzer (HFA). RNFL thickness was measured by optical coherence tomography.

RESULTS. A homogeneous lesion pattern with bilateral WMDI predominantly in the superior posterior periventricular white matter was seen in all subjects. However, as shown by white matter fiber tractography, only cases with injuries to the superior portion of the OR had corresponding inferior VF defects. In the individuals showing structural abnormalities in the OR, a commensurate reduction in the peripapillary RNFL was seen. The RNFL loss was most pronounced in the subjects suffering from the more extensive lesions, and it followed the pattern of OR damage in the sense that damage in the superior portion of the OR gave a reduced RNFL thickness in the superior part of the peripapillary RNFL.

CONCLUSIONS. Primary injuries in the immature OR are associated with reduced RNFL thickness, and examination of the RNFL may be a helpful predictor of VF defects.

Keywords: early brain injuries, optic radiation, retinal nerve fiber layer, visual field, visual pathways

Periventricular white matter damage, occurring in the immature brain before 34 gestational weeks, may cause visual impairment in children. This occurs due to adverse events in the neonatal period of prematurely born infants or during the last trimester in utero. Survivors with pre- and perinatal brain damage will present to ophthalmologists who may not be familiar with these clinical features. Patients may exhibit a wide spectrum of visual symptoms, ranging from subnormal visual acuity (VA) or early onset esotropia to severe cerebral visual impairment.¹ Abnormal appearance of the optic discs, which may be small or normal in size with extensive cupping, have been described; the proposed mechanism being retrograde trans-synaptic degeneration.²

The primary white matter lesions, often referred to as white matter damage of immaturity (WMDI),³ occur between 24 and 34 gestational weeks (early third trimester) and are commonly detected with magnetic resonance imaging (MRI). In WMDI, the posterior periventricular white matter is often affected and damage may involve the optic radiation (OR).⁴ Injuries to the OR in the immature brain can be detected by conventional structural MRI; however, the exact location and structure of the fiber tract affected cannot be judged. Diffusion-weighted MRI

(DWI) is a novel MRI technique which can infer on the structural composition of cerebral white matter,⁵ whereas fiber tractography can be used to trace white matter fiber tracts in vivo.⁶ The optic radiation's well-known retinotopic organization⁷ can be studied by means of fiber tractography.⁸ Studies in premature neonates using DWI and fiber tractography show changes in diffusion parameters in the OR indicating altered white matter microstructure.^{9–11} These changes show correlation with assessment of visual ability^{9,10} and visual evoked potentials¹¹ but are independent of whether focal brain lesions are detected. This implies the generalized vulnerability of the developing visual system during the third trimester.¹² However, the actual effects of focal lesions to the immature OR on the visual function have yet to be investigated in any detail.

The pathogenesis of WMDI is multifactorial with primary destructive injuries and secondary effects from impaired maturational mechanisms or from trophic disturbances.¹³ An interruption in the thalamic neurons that travel from the lateral geniculate nucleus (LGN) to the striate cortex and/or their supporting glial cells can impair both thalamic and cortical development and cause hypomyelination. However, in the early third trimester, thalamostriate afferent nerves are still entering

TABLE 1. Visual Assessment of Conventional Structural MRI and Fiber Tractography of the Optic Radiation in the Subject Group

Patient/ Sex/Year Born	GA/BW	Periventricular White Matter*		Affects to the Visual Pathways†				Fiber Tracking of the OR
		Degree of WM Reduction	Gliosis	Optic Chiasm	Optic Tract	LGN	OR	
A/M/1977	34+0/1890	Mild/moderate (A), severe (M, P)	Extensive (A, M, P)	Affected	Bilateral	Bilateral	Bilateral	Bilaterally reduced number of fibers in the superior portion and fewer fibers in the central portion on the left side
B/F/1993‡	33+6/2255	Mild/moderate (left A, M), severe (P)	Extensive (A, M, P)	Affected	Bilateral	Left	Bilateral	Bilaterally slightly reduced number of fibers in superior portion (right>left)
C/F/1989	33+0/2670	Mild/moderate (M), severe (P)	Extensive (A, M, P)	Affected	Bilateral	Bilateral	Bilateral	Bilaterally a reduced number of fibers in the superior portion and fewer fibers in the central portion on the left side
D/F/1988§	27+4/1040	Mild/moderate (right M), severe (left M, P)	Discrete (M, P)	Affected	Bilateral	Left	Bilateral	Bilaterally slightly reduced numbers of fibers in superior portion
E/F/1985	40/3370	Mild/moderate (M), severe (P)	-	-	-	-	Bilateral	Slightly reduced number of fibers in the central portion on the right side
F/M/1991	27+4/1100	Mild/moderate (left M, left P)	Discrete (M, left P)	-	-	-	Left (discrete gliosis)	Normal appearance
G/F/1995¶	26/727	Mild/moderate (left P), severe (right M, right P)	Discrete (right M)	-	-	-	Right	Normal appearance

A, anterior; BW, birth weight (g); GA, gestational age (weeks + days); LGN, lateral geniculate nuclei; M, middle; OR, optic radiation; P, posterior.

* The damage was bilateral unless the side is indicated (left or right). The extent of periventricular WM damage was classified as mild/moderate or severe if <50% or >50%, respectively, if the bulk of periventricular WM was reduced. An abnormally high signal on FLAIR images in the periventricular WM was considered gliosis.

† Visual pathways were considered affected if size or appearance was abnormal on visual inspection of conventional structural MRI.

‡ Small hemorrhage in the left caudate nucleus.

§ Left-sided periventricular hemorrhage.

|| MRI pattern indicates prenatal injury at approximately 28 gestational weeks.

¶ Right-sided periventricular hemorrhage.

the cortex. The particular cellular environment they experience, with extensive expression of molecules for growth promotion and axonal guidance cues,¹⁴ could potentially allow neural plasticity mechanisms to be invoked when establishing cortical neuronal circuits. It has also been shown that thalamic neurons can reside among the transient subplate neurons before entering the cortex.¹⁵ In this way, axons bypassing the white matter lesion could connect with cortical areas that were originally destined for the interrupted axons. Fiber tractography of the developing somatosensory system in WMDI has illustrated fibers bypassing focal lesions,¹⁶ and there are indications that this is also possible in the visual system.¹⁷

Retinal ganglion cell (RGC) projections to the LGN are retinotopically organized in adjacent, nonoverlapping, eye-specific layers. However, in early development, the RGC projection patterns are intermixed within a large portion of the LGN.¹⁸ The early retinogeniculate synapses are capable of synaptic transmission, and the initial segregation into specific monocular layers results from a competitive interaction of retinal input from each eye. The bulk of the synaptic pruning in the LGN occurs before mid-gestation.¹⁵ In higher mammals, this occurs in utero, prior to input from photoreceptors. It has been linked to retinotopically coordinated, spontaneous waves of firing in the RGCs all over the retina,¹⁸ which becomes important for establishing the retinocortical system.

Studies of visually evoked potentials in premature infants indicate that once the eyes have opened, neural connections to the brain are refined, strengthened, and stabilized into an adult-like pattern that is essentially established by the time of normal birth.¹⁹ Thereafter, visual stimuli enhance maturation of the structural organization of the retina and cortical development.²⁰

Cowey et al.²¹ described transneuronal retrograde degeneration of RGC after damage to the striate cortex in monkeys. Prematurely born children with visual impairment due to WMDI demonstrate abnormal appearance of the optic discs, with reduced neural tissue manifesting as either small discs or discs with large cups, a finding supporting the hypothesis that in humans also lesions to the immature posterior visual system lead to retrograde trans-synaptic degeneration of the RGC.^{2,22}

The functional consequences of WMDI depend on the location and the extent of the lesion and may include cerebral palsy, learning disabilities, and attention deficit disorders. When the visual pathways are affected, visual function is characterized by subnormal linear VA, often slightly, visual field (VF) defects, ocular motor disorders, and cognitive visual impairment.²³ The aim of the present study was to seek evidence of any specific relationship between damage to the optic radiation in the immature brain and subsequent development of the retinal nerve fiber layer and associated visual manifestations. Clinicians should be aware of VF loss in children known to have WMDI who cannot perform perimetry, and they should be aware of WMDI in children with visual

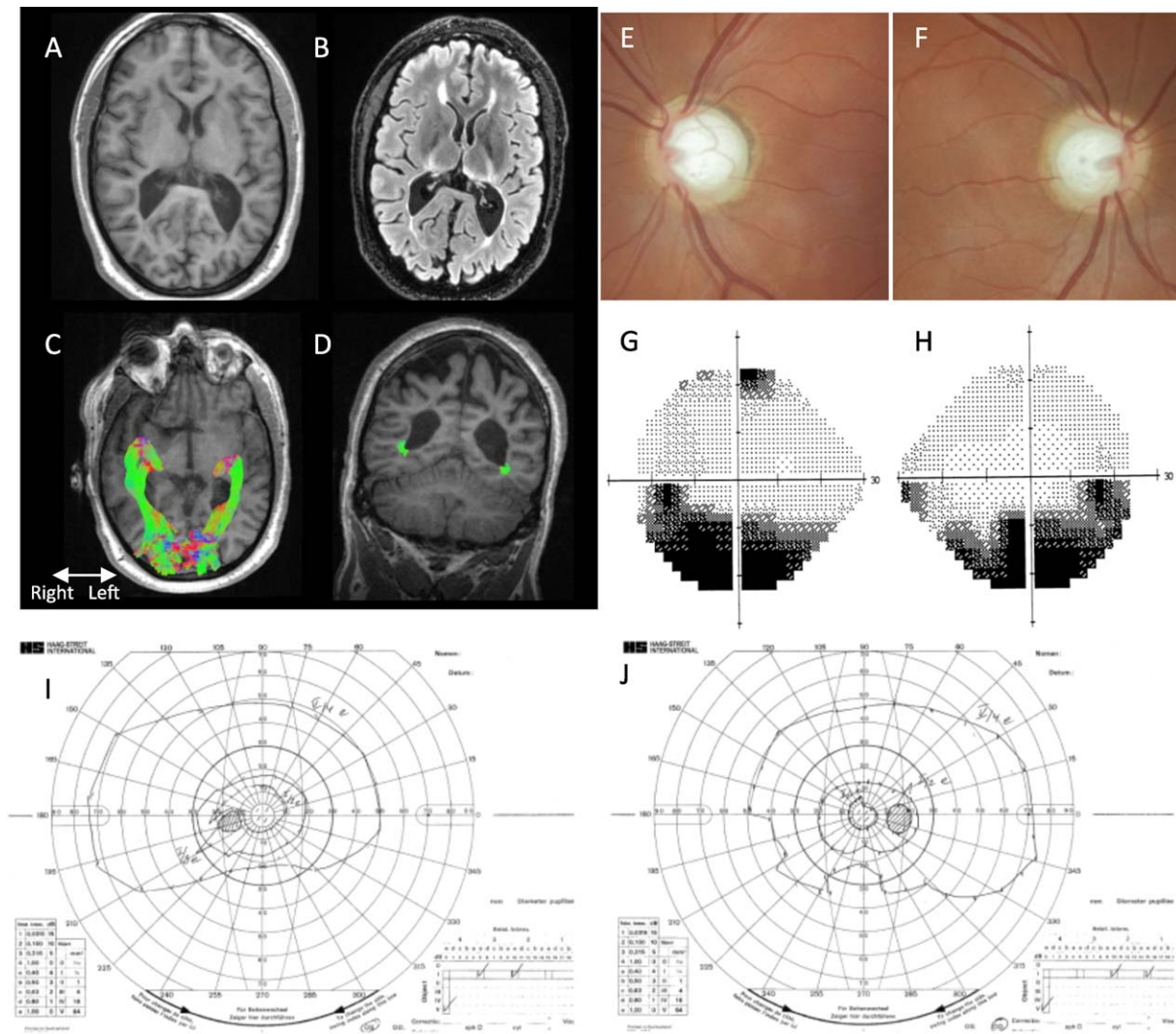


FIGURE 1. Subject A. (A, B) MRI reveals a *bilateral* WMDI with extensive reduction of and gliosis in the periventricular white matter, most pronounced in the posterior white matter. (C, D) Fiber tractography shows a marked reduction of fibers in the *superior* portion of the OR. (E, F) Fundus photograph shows large cupping of the discs. (I, J) Goldmann perimetry shows inferior constriction in the peripheral VFs, also shown with the HFA (G, H).

dysfunction. In addition, more knowledge about the ocular and visual manifestations of WMDI is necessary to avoid misinterpretation and confusion with glaucoma.

SUBJECTS AND METHODS

The study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki. All participants provided signed informed consent.

Subjects

From a large cohort of individuals with WMDI who presented with visual dysfunction as children, collected over 25 years by LJ in clinical pediatric ophthalmology care, 30 have reached adulthood. Those with the best intellectual, attention, and motor prerequisites, who could cooperate in the demanding MRI sessions (without spastic movements to sound) and with ability to maintain fixation during optical coherence tomography (OCT) and who could follow instructions and carry out a standardized perimetry test, were selected. Most individuals

with visual dysfunction due to WMDI cannot be included in such a study. We selected eight individuals, two males and six females, ranging from 18 to 35 years of age. One female declined participation in the study. Subjects are presented in Table 1.

Six subjects were born prematurely, and one at full term. None had any history of retinopathy of prematurity. The brain damage had occurred in the perinatal or neonatal period in 4 individuals (A, D, E, and G) and may have occurred prenatally in 3 (B, C, and F). Five subjects had early onset strabismus (A, B, C, D, and F), 2 had nystagmus (A and C); 5 had cognitive visual problems (A, B, C, D, and G)²⁴; and 5 had cerebral palsy (A, B, D, E, and G).

Methods

Visual function was evaluated through best-corrected VA testing using the standardized Early Treatment of Diabetic Retinopathy Study letter chart and binocular evaluation with a cover test. Color fundus photographs were obtained for documentation and illustration.

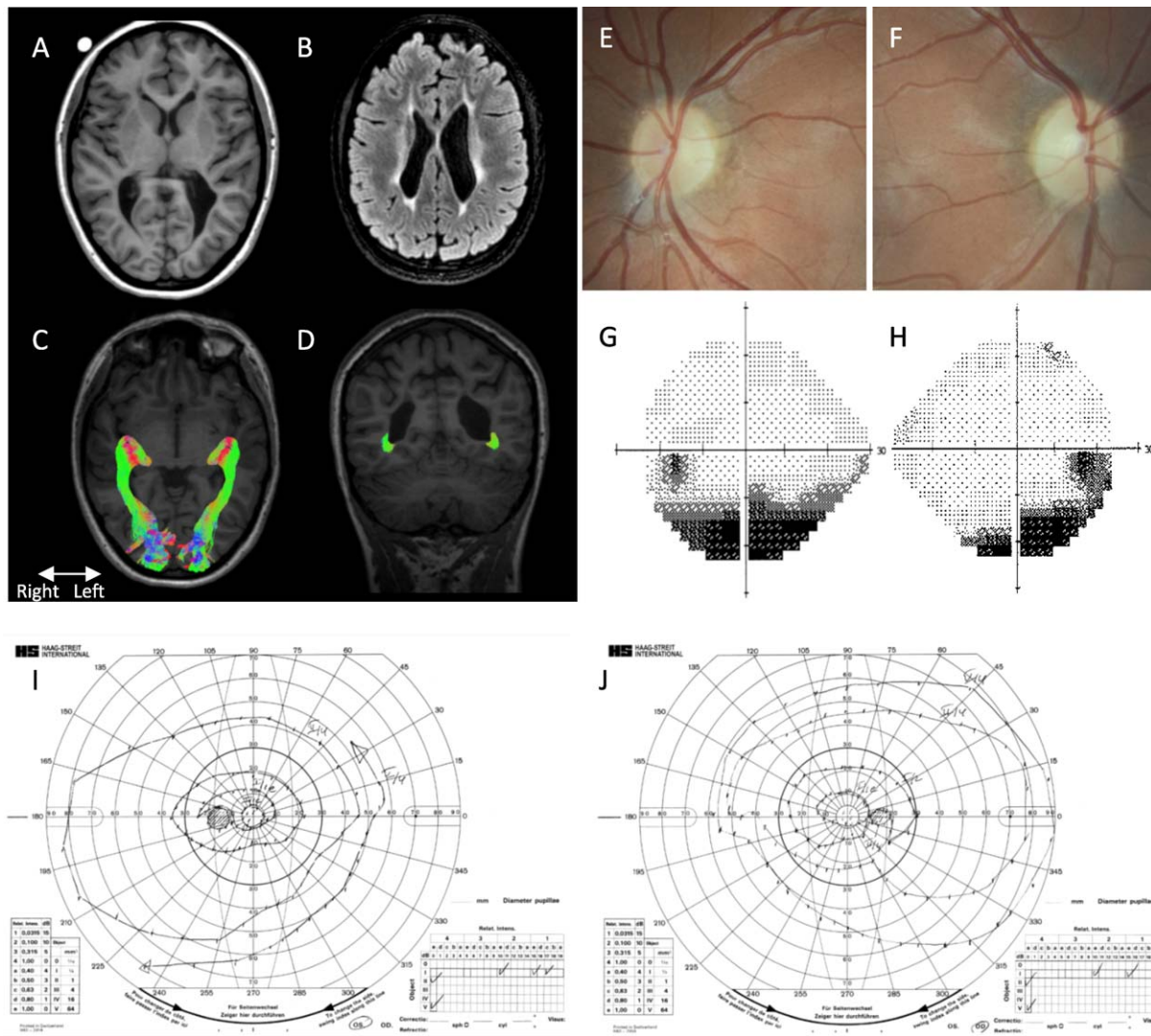


FIGURE 2. Subject B. (A, B) MRI confirms *bilateral* WMDI with extensive reduction of and gliosis in the periventricular white matter, especially in the posterior white matter. (C, D) Fiber tractography shows *bilaterally* reduced number of fibers in the *superior* OR. (E, F) Fundus photograph reveals discs with minimal cupping. *Inferior* constriction in the peripheral Goldmann VFs (I, J), also shown with the HFA (G, H).

Neuroimaging. MRI was performed with a 3-Tesla MR system (Discovery MR750; GE Medical Systems, Milwaukee, WI, USA). Conventional structural images included 3-dimensional T1-weighted and fluid-attenuated inversion recovery (FLAIR) images. DWI images (twice-refocused SS-EPI, TR/TE = 6000–7800/91.6 ms; voxel size, 2.3 mm³, ASSET factor 2) were acquired with two baseline images at $b = 0$ s/mm² and 60-gradient directions at $b = 2200$ s/mm². Two additional images at $b = 0$ s/mm² were collected with reversed phase-encoding polarity to correct for susceptibility-induced image artifacts during postprocessing. Conventional structural images were visually assessed for lesion type, location, and extent, with a special focus on the periventricular white matter and visual pathways. Radiological assessments were carried out by the primary study rater (FL.) and discussed with an experienced pediatric neuroradiologist (O.F.).

Fiber Tracking of Optic Radiation. DWI data were corrected for motion, susceptibility, and eddy current-induced artifacts and were coregistered to T1-weighted images using tools in FSL.²⁵ MRtrix²⁶ was used to estimate diffusion tensors and fiber orientation distributions with constrained spherical

deconvolution (CSD).²⁷ Probabilistic streamline fiber tractography of the OR was performed. A streamline is generated in a step-wise process by following the directions of the estimated fiber orientations in every voxels. The algorithm is initiated in a starting (seed) point and run iteratively until stopping criteria are met (e.g., leaving the white matter). The result is a curved path, a streamline, following the underlying nerve fiber structure. In our study, geniculostriate connections were generated by seeding streamlines in a 4-mm sphere encapsulating the LGN⁸ and using a 30-mm-radius sphere centered in an occipital pole (covering the calcarine sulcus) as an ipsilateral target. Streamlines that did not enter the occipital target sphere were rejected. The fiber-tracking algorithm was run until 10⁴ accepted streamlines had been generated. To exclude connections of (very) low probability (typically false positives), streamlines that entered voxels with a visitation count of less than 10 (i.e., voxels through which less than 0.1 % of the streamlines passed) were rejected, and the set of remaining streamlines were considered the desired OR tract. The OR tracts were visually assessed in relation to their expected topography^{7,8} and to lesions identified on structural

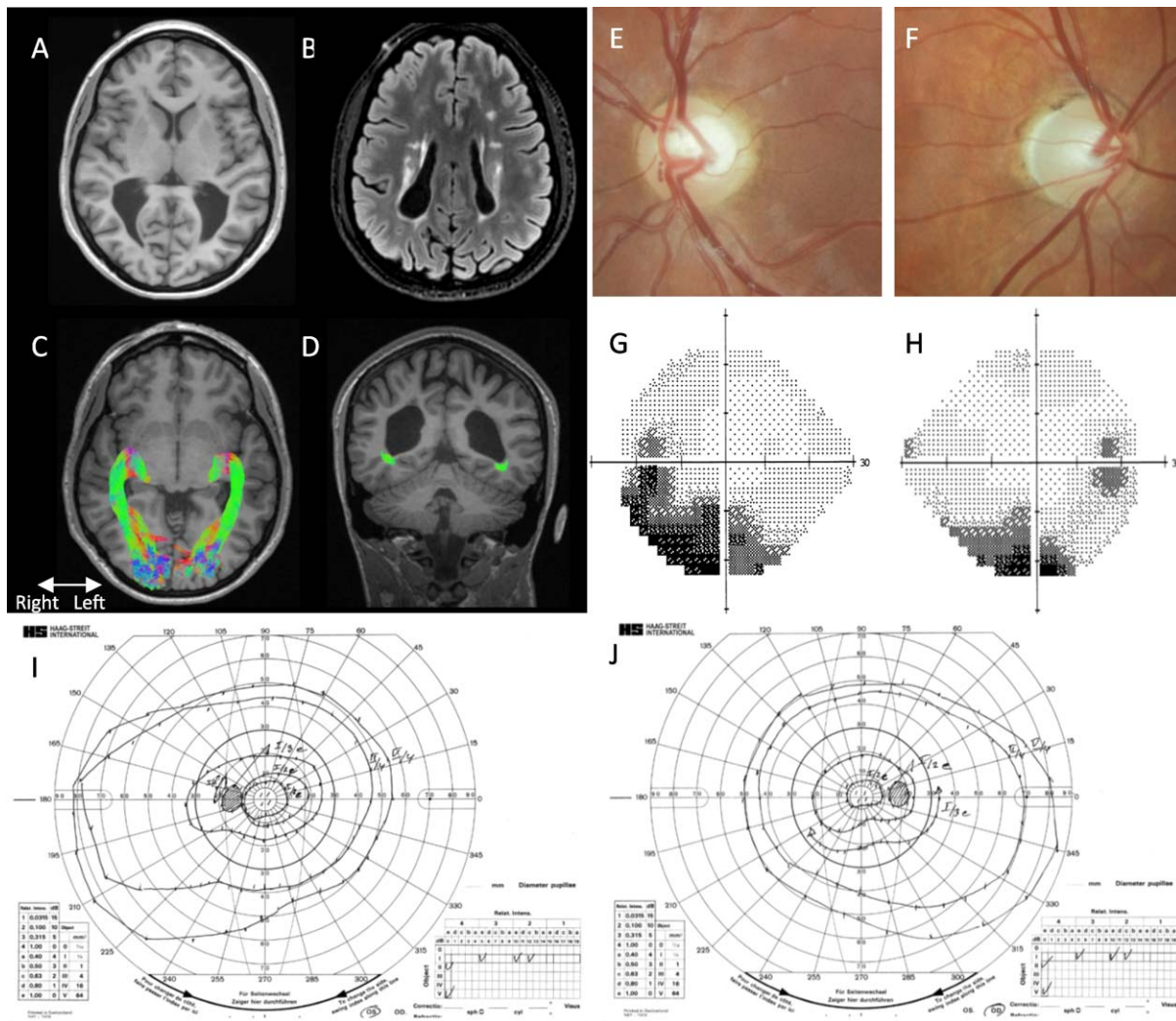


FIGURE 3. Subject C. (A, B) MRI shows *bilateral* WMDI with reduction of, especially *posteriorly*, and extensive gliosis in the periventricular white matter. (C, D) Fiber tractography shows a marked reduction of fibers in the *superior* portion of the OR. (E, F) Fundus photograph shows large cupping of the discs. Decreased sensitivity in the inferior Goldmann VFs (I, J) with close to normal extent for large stimuli. Corresponding defects are also shown with the HFA (G, H).

MRI. Cases where the number of streamlines (streamline density) in the OR tracts were clearly fewer (lower) than expected were considered abnormal (Figs. 1-7, graph D).

Visual Field Examination. All VF examinations were performed by experienced examiners, and all test subjects underwent two different VF tests. Standard kinetic Goldmann perimetry was performed.²⁸ The extent of the VF was determined by using V/4e or II/4 stimulus. For the central VF, one or more of the stimuli, I/3e, I/2e, or I/1e, were used. In cases where these stimuli were not detected, I/2d was used for the central 10°. Standard automated perimetry was used for quantitative measurements of VF defects, using the SITA Fast 24-2 test (Humphrey field analyzer [HFA]; Carl Zeiss Meditec, Dublin, CA, USA). Results are expressed as mean deviations (MD), an overall value of the total amount of VF impairment.

Optical Coherence Tomography. Retinal nerve fiber layer (RNFL) thickness was mapped and measured with the Optic Disc Cube protocol, using spectral domain OCT (HD-CIRRUS version 4.0; Carl Zeiss). The average RNFL thickness was reported as well as the RNFL in the four quadrants (i.e., superior, inferior, nasal, and temporal). The automatic comparison of RNFL thickness with that in the normative database

was used for classification into normal, subnormal, or abnormal values. Only scans without artifacts caused by blinking or eye movements together with a signal strength ≥ 7 were accepted for analysis.

RESULTS

Visual inspection of structural MRI scans revealed WMDI of different degrees and patterns involving the periventricular white matter and visual pathways in all subjects (Table 1). In general, the largest injuries were found in the posterior periventricular white matter in which the superior parieto-occipital white matter was clearly more affected than the inferior occipitotemporal part (Figs. 1-7). In four subjects (A, B, C, and D) similar patterns of bilateral injury to the visual pathways were found. One subject (E) had relatively mild bilateral damage to the expected OR on visual inspection, whereas two subjects (F and G) had only discrete unilateral injuries within their expected ORs.

Best-corrected VA in the better eyes ranged between logMAR VA 0.10 and -0.10 and 0.50 and 0.00 in the fellow

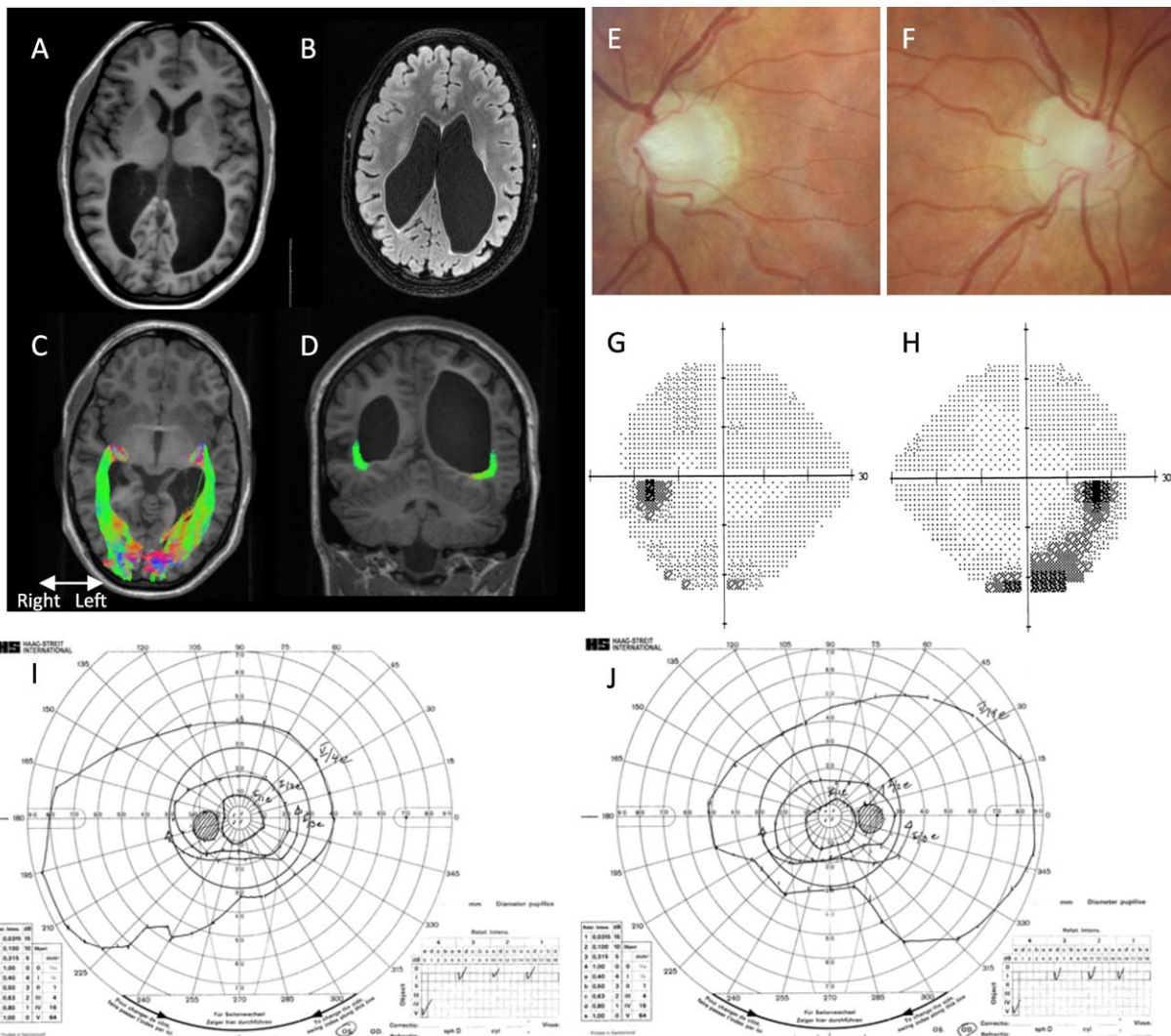


FIGURE 4. Subject D. (A, B) MRI shows large *bilateral* WMDI with severe reduction of the posterior white matter but only discrete gliosis in the periventricular white matter. (C, D) Fiber tractography shows a slight reductions of fibers in the *superior* portion of the ORs. (E, F) Fundus photograph shows tilted discs with cupping. Inferior constriction in the peripheral Goldmann VFs (I, J), shown as general sensitivity decrease in the HFA VFs (G, H).

eye, indicating near normal resolution in at least one eye in all patients. Goldmann VFs showed various degrees of inferior constriction in subjects A, B, C, and D. Corresponding defects were also identified using the HFA. In one subject (E), Goldmann testing showed a defect of the nasal VF of the left eye that was confirmed with the HFA, inferiorly for the right eye (normal HFA result). Near normal Goldmann VF and normal HFA fields were obtained in subjects F and G.

Fiber tractography of the OR revealed marked loss of fibers predominantly in the superior OR in four subjects (A, B, C, and D), corresponding with the injuries to the visual pathways on structural MRI, resulting in inferior VF defects (Table 1; Figs. 1–4). Fiber tractography of the OR in subject E showed an ostensibly normal appearance but with slight reduction of fibers in the central OR on the right side (Fig. 5). These results are consistent with the close-to-normal central VF outcome for the right eye and the slightly affected VF in the left eye. In two subjects (F and G), fiber tractography of the OR showed normal appearances consistent with their discrete unilateral injuries in the posterior visual pathways on structural MRI, their near normal Goldmann VF, and their normal HFA results

(Figs. 6, 7). In these three subjects, the white matter areas were assumed to have sustained injuries to the expected OR on visual inspection of the structural MRI but appeared to harbor fibers in the fiber tractography of the OR. This implies that fiber tractography conveys salient additional information.

Average RNFL thickness was markedly reduced in four subjects (A, B, C, and D), and subject E also showed reduced RNFL in one eye and with minimal reduction in the other eye, whereas subjects F and G showed normal values according to the normative OCT database (Table 2). The subgroup of patients with reduced RNFL thicknesses showed abnormal VF, contrary to that in patients with normal RNFL thicknesses. There was a significant correlation between the average RNFL thickness and HFA MD (Fig. 8). From clinical observation, the most pronounced RNFL loss was in the superior portion of the peripapillary RNFL, whereas the peripapillary macular bundles were least reduced. The clinical structural appearance of retinal axon loss thus correlated with the outcome of the VF examinations, showing somewhat spared central VF in all patients but restricted inferior VFs in the patients with reduced superior mean RNFL thickness.

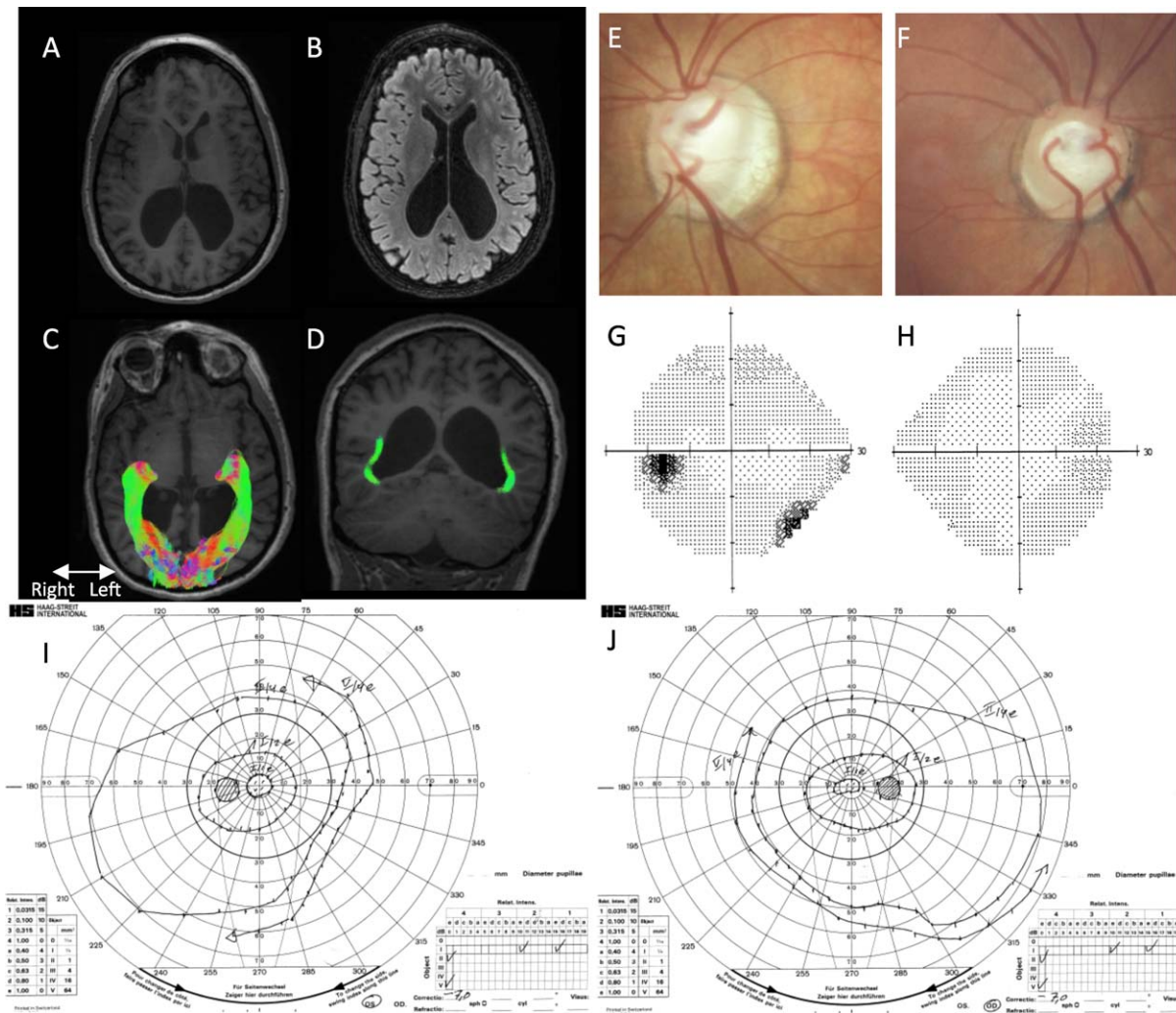


FIGURE 5. Subject E. (A, B) MRI shows *bilateral* WMDI with reduction of middle and posterior white matter without any gliosis. (C, D) Fiber tractography shows slightly reduced number of fibers in the central OR on the right side but otherwise normal. (E, F) Fundus photograph shows large cupping of the discs. Note the nasal defect in the *left* peripheral Goldmann VF (I), also shown in the HFA (G), and the minor inferior constriction in the *right* peripheral Goldmann VF (J), with no effect on the central HFA field (H).

DISCUSSION

In the present study, we evaluated young adults with previously known WMDI causing visual dysfunction, in an attempt to map and correlate structural abnormalities of the

visual system to visual function. The strict inclusion criteria (i.e., patients with WMDI causing visual dysfunction who were capable of consistently performing all the tests accurately) allowed us to assess the independent effects of damage to the immature OR and its correlates with mature retinal structure

TABLE 2. Humphrey Visual Field Assessment, Optic Cup-to-Disc Ratios, and Measurements of Retinal Nerve Fiber Layer in all Subjects

Subject/ Sex/Year Born	HFA MD OD/OS	Cup-to-Disc Ratio OD/OS	Average RNFL OD/OS	RNFL Quadrant Superior OD/OS	RNFL Quadrant Inferior OD/OS	RNFL Quadrant Nasal OD/OS	RNFL Quadrant Temporal OD/OS
A/M/1977	-10.64/-12.65	0.66/0.75	55†/49†	57†/47†	91†/80†	42†/35†	30†/36†
B/F/1993	-6.23/-8.82	0.20/0.15	58†/60†	61†/65†	87†/86†	48†/43†	37†/44†
C/F/1989	-6.4/-8.54	0.42/0.65	62†/72†	62†/78†	89†/122	53*/49*	46*/42†
D/F/1988	-4.8/-4.83	0.52/0.54	66†/60†	66†/57†	92†/91†	54*/44†	54/50
E/F/1985	-2.47/-4.42	0.62/0.69	80*/72†	97*/76†	104/96*	60/57	61/59
F/M/1991	-1.11/-2.03	0.23/0.30	88/85	116/106	112/113	58/61	64/61
G/F/1995	-1.27/-0.99	0.10/0.21	89/92	121/123	105/113	59/63	70/70

Humphrey visual field assessment (HFA) values are mean deviations (MD) in decibels. Retinal nerve fiber layer (RNFL) thickness values are in micrometers. OD, right eye; OS, left eye.

* Subnormal values (unmarked values were within the range of normal values).

† Abnormal values (unmarked values were within the range of normal values).

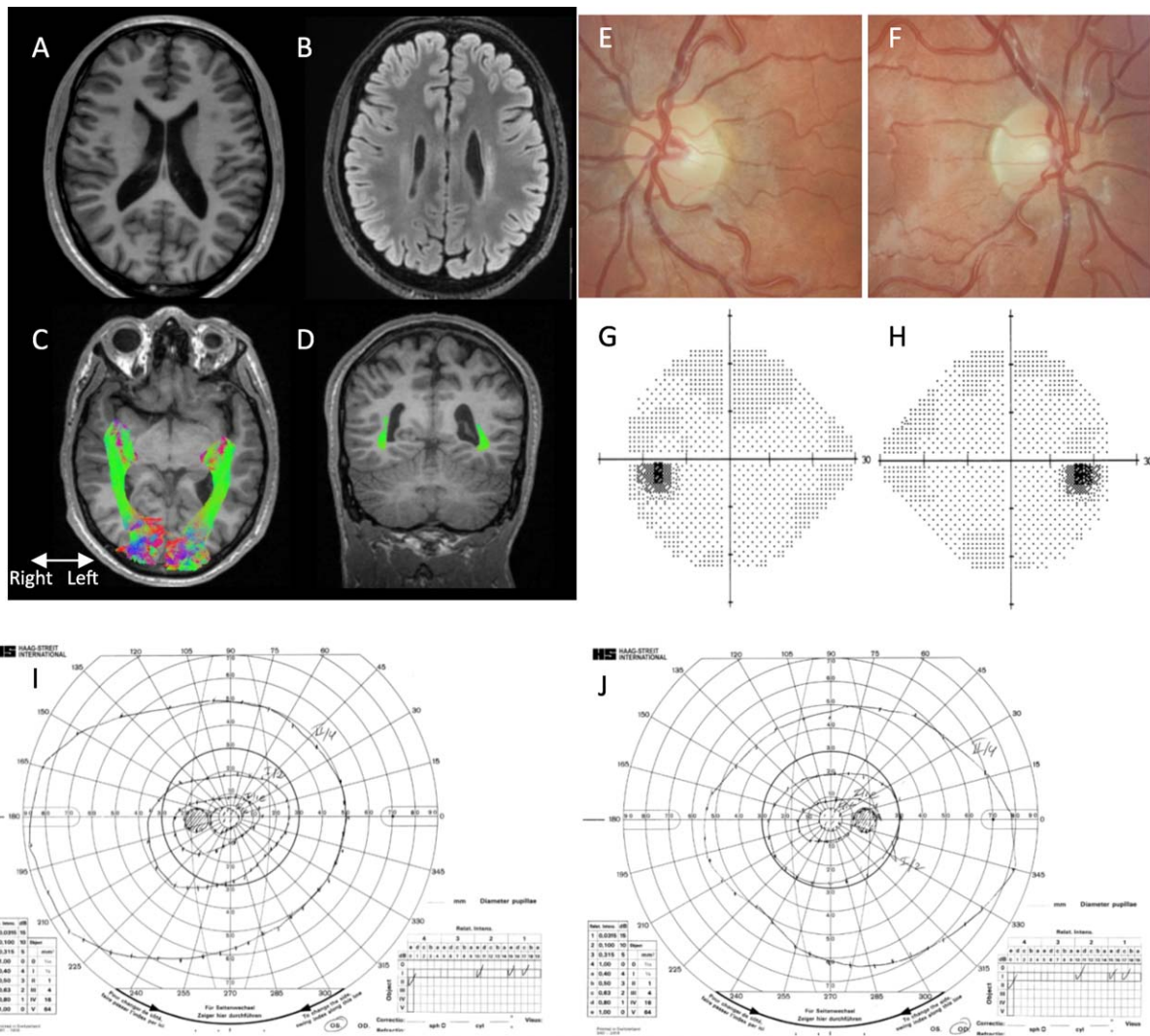


FIGURE 6. Subject F. (A, B) MRI shows *bilateral* WMDI with minor reduction of the *left* middle and *left* posterior periventricular white matter and discrete *bilateral* gliosis. (C, D) Fiber tractography shows normal appearance of the ORs. (E, F) Fundus photograph shows normal disc appearance. Visual field function within normal range in both eyes, with both Goldmann (I, J) and HFA (G, H) methods.

and function. In all subjects, we saw a homogeneous lesion pattern with bilateral WMDI predominantly in the superior posterior periventricular white matter. However, only in the patients with injuries of the superior portion of the OR, shown from white matter fiber tractography, were corresponding inferior VF defects noticed. Our study findings are in line with those of previous studies of structural MRI showing that concurrent damage to the OR and thalamus/LGN commonly cause VF defects, whereas damage to the OR only may not result in any VF defects.²⁹ Importantly, the extent of involvement of the OR is difficult to infer from conventional structural MRI. The individuals with the most extensive lesions and damage as revealed by fiber tractography of the OR also presented with marked changes in the LGN, the optic tracts, and optic chiasm. We concluded that fiber tractography of the OR clearly improved detection of abnormalities in the OR and could, in our cases, differentiate symptomatic lesions causing VF defects, as well as more subtle or asymptomatic lesions. Moreover, in the individuals showing abnormalities in the fiber tractography of the OR, a commensurate reduction of the peripapillary RNFL was seen. The RNFL loss was most pronounced in the subjects suffering from the most extensive lesions and followed the pattern of the OR damage in the sense

that damage in the superior portion of the OR, as shown by the fiber tractography, gave a reduced RNFL thickness in the superior part of the peripapillary RNFL. Our fiber tractography findings may support evidence for retrograde trans-synaptic degeneration through the LGN, which has been proposed as the pathogenic mechanism in the case of WMDI.²

In a recent study that evaluated six prematurely born children with isolated optic disc cupping, a similar pattern of RNFL loss was seen (i.e., a significantly reduced overall RNFL as well as thinning in the superior quadrant³⁰). The inferior, nasal, and temporal quadrants also showed reduced RNFL thicknesses, although this was not statistically significant compared to those in age-matched normal controls. Compared with normal children, the children studied did not present with any other ocular disorders or abnormalities or manifest any developmental delay. However, neither VF examinations nor MRI were performed in those children. Our study confirms, as previously suggested,² that extensive optic disc cupping should be considered a possible sign of retrograde trans-synaptic degeneration. However, just as important is the fact that RNFL thinning and brain damage can also be present in children without evidence of cupping of the optic discs (e.g., subject B). Thus, RNFL measurements should be recognized as a

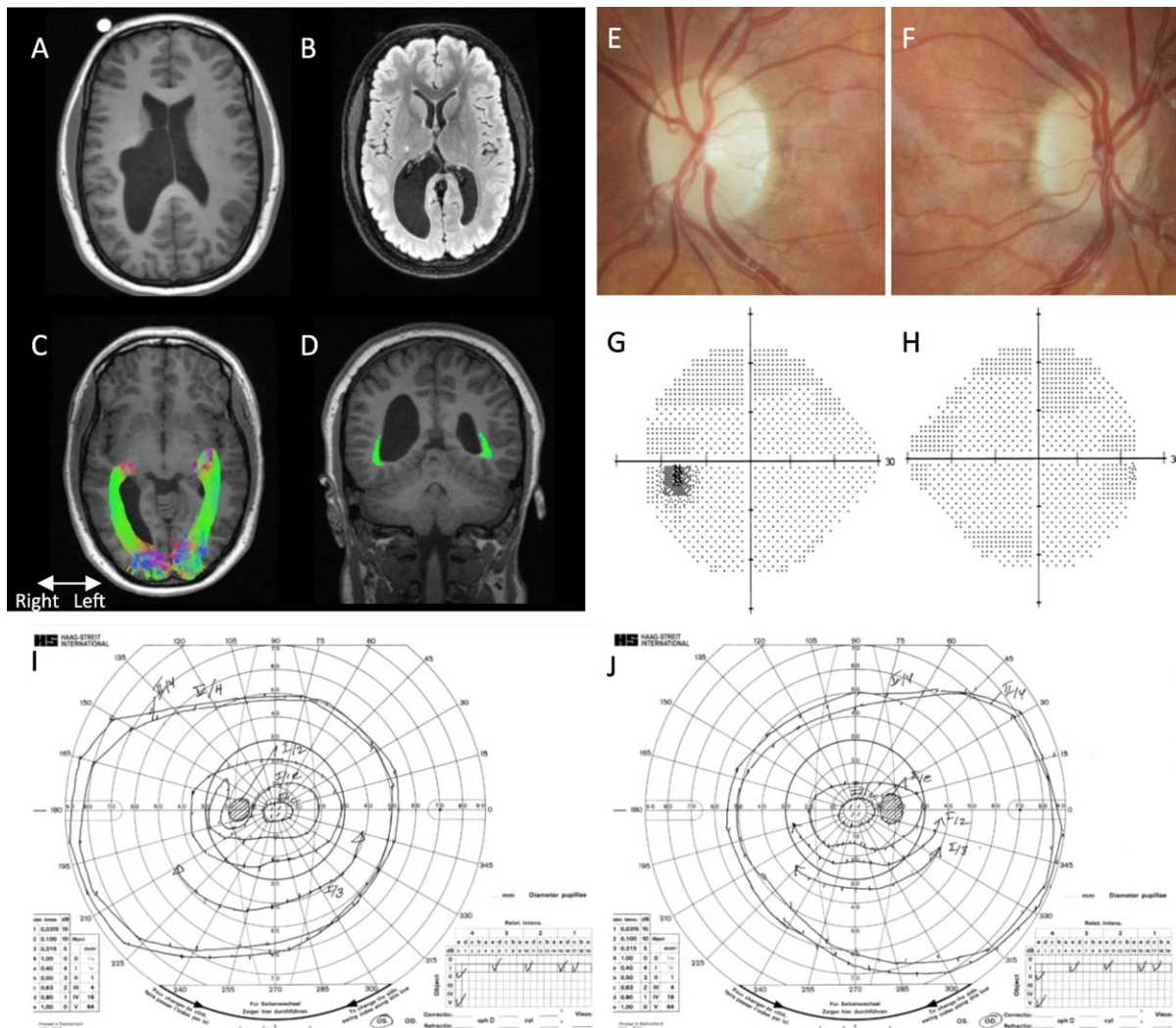


FIGURE 7. Subject G. (A, B) MRI shows *bilateral* WMDI with extensive reduction of the middle and posterior white matter, especially on the right side, but only subtle gliosis in the right middle periventricular white matter. (C, D) Fiber tractography shows normal appearance of the ORs. Normal disc appearance with minor cupping (E, F). (I, J) Goldmann VF show slightly decreased defects for small stimuli, probably within the normal range, with normal HFA visual fields (G, H).

promising and valuable tool in the examination of all children who present with early onset otherwise unexplainable strabismus, nystagmus, or subnormal VA, as an indication of a potential underlying brain lesion. In children with WMDI who cannot perform reliable conventional perimetry, abnormal RNFL findings may give objective and important information about the VF function.

WMDI occurs between 24 and 34 gestational weeks (GW), which is a crucial time frame in the development of the visual system. In the posterior visual system, most of the geniculostriate afferents have reached the cortical subplate before the 24 GW or even earlier, at approximately 20 GW.³¹ During the 24 to 32 GW period, they enter the cortex to branch and form synapses with targets in layer IV.³² The bulk of the synaptogenesis coincides with the formation of the gyri along the calcarine sulcus at approximately 27 GW,³³ and at this time, evoked potentials can be recorded from the visual cortex, confirming the establishment of geniculostriate circuits.³⁴ However, there is evidence from postmortem studies in human fetuses that the axons can wait for weeks in the cortical subplate,¹⁵ implying that this process could extend slightly further into the early third trimester. Therefore, the potential

for thalamic afferents to redirect and synapse with targets destined for damaged axons would be approximately 28 GW, rather than toward 34 GW in WMDI.

Among those with earliest dated lesions (approximately 28 GW), two subjects (F and G) had lesions that did not affect the OR on fiber tracking and relatively normal VF perimetry values (Figs. 6, 7). Subject E had large lesions in the posterior periventricular white matter, but on fiber tracking, the only affected part of the OR was the central part on one side (right), and her VF perimetry values were relatively unaffected (Fig. 5). Subject D had large bilateral periventricular lesions, which slightly affected the superior portions of the OR on fiber tracking (left more than right side). She had inferior constrictions in the peripheral VF, which contributed to a general sensitivity loss on HFA (Fig. 4). Subjects A, B, and C had lesions dated toward the later end of the WMDI time frame. They commonly manifested evident injuries to the superior portion of the OR on fiber tracking, complying with their inferior restrictions on the peripheral VF (Goldmann) but also corresponding with central VF restrictions (HFA) (Figs. 1-3). This distinction between the subjects with earlier and later timed WMDI may be coincidental, but other studies have

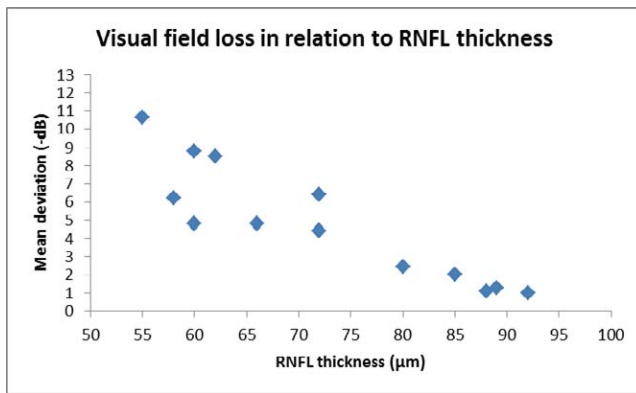


FIGURE 8. Visual field loss, given as mean deviation plotted relative to the average RNFL thickness, showed a significant negative correlation ($r = -0.92$, $P < 0.0001$).

suggested that the timing of the pathology is important for the VF outcome.^{17,35} Our results may indicate that even within the WMDI time frame, timing is important. As discussed above, the potential for plasticity should be greater at earlier stages when the geniculostriate circuits are being established. Another speculation concerns potential plasticity during retinal growth and development. Early functional adjustment to reduced numbers of ganglion cells could result in their developing enlarged receptive fields and/or a strategic displacement of receptive fields to cover up and to favor the central VF on behalf of more peripheral parts of the VF. Retinal plasticity has been shown in mice subjected to perinatal retinal injury.³⁶ Maiorano and Hindges³⁶ genetically induced localized retinal lesions in mice to show that the remaining RGC both expanded over the retina and changed their collicular projection patterns, in order, as believed, to ensure a uniform retinotopic map. In contrast, in WMDI, the lesion occurs when the retinogeniculate projection pattern is already established. However, with the evidence for retinal injury in our subjects, potentially caused by retrograde trans-synaptic degeneration, the possibility for retinal plasticity to favor outcome should also be considered. Future studies of retinal functional reorganization using retinotopic mapping (e.g., with functional MRI³⁷ and visual electrophysiology) may facilitate inference of the cortical representation of the VF maps in cases of early brain injury. Also the topography of the OR could be studied by labeling fibers in the OR in relation to their endpoints on the corresponding cortical VF maps.

In the present study we examined a small but well-defined group of subjects with WMDI affecting the OR, recruited from a larger cohort. Only highly performing subjects were selected to be able to perform all the tests giving reliable results and might therefore not be representative for the entire group suffering from WMDI. On the other hand this selection might be the only way to enable extensive and systematic mapping of structural changes and its correlates to function, in individuals with WMDI. Therefore, the study provides important information regarding children who are at risk of suffering from WMDI and its relationship to visual function. One single measurement that seems relevant to continue characterizing is the RNFL morphology, as it correlates well with both the visual function and the pattern of brain pathology. The pronounced reduction in RNFL seen in this group indicates a significant loss of retinal ganglion cells. When comparing our data to a model based on RNFL reduction caused by glaucoma, the estimated loss of ganglion axons could, in theory, range between 20% and 80% among our subjects.³⁸ Whether a thin RNFL or cupping alone could be a risk factor for developing glaucoma in the future is

difficult to predict from existing data, but with an increased number of prematurely born children surviving and growing old, it will be a clinical challenge to monitor and distinguish cupping caused by early brain damage from glaucoma. To enable establishment of clinical management guidelines, it is necessary to continue characterizing the RNFL appearance in this group of subjects. For that purpose, OCT has the potential to serve as a sophisticated method that offers noninvasive, easily performed measurement with high sensitivity and reproducibility. Retinal nerve fiber layer measurement is also important as a follow-up tool because of the difficulties in performing reliable perimetry in children or in patients with brain damage. Based on the findings in our study, we suggest that children presenting to pediatric ophthalmologists with strabismus, nystagmus, subnormal VA and/or VF defects generously should be examined with OCT of the RNFL; a tool to identify those having an indication for further investigation with MRI of the brain.

CONCLUSIONS

Primary injuries in the immature optic radiation are associated with injuries in the retina, revealed as reduced thickness of the RNFL and a loss of the corresponding peripheral VF function. Thus, we suggest that examining the RNFL may be a helpful predictor for VF defects in individuals with damage to the immature optic radiation.

Acknowledgments

Supported by grants from the Maj Lalanders Foundation for Neuroradiology Research (FL, MN) and the Sigvard and Marianne Bernadotte Research Foundation for Children's Eye Care (LJ).

Disclosure: **F. Lennartsson**, None; **M. Nilsson**, None; **O. Flodmark**, None; **L. Jacobson**, None

References

- Cioni G, Fazzi B, Coluccini M, Bartalena L, Boldrini A, van Hof-van Duin J. Cerebral visual impairment in preterm infants with periventricular leukomalacia. *Pediatr Neurol.* 1997;17:331-338.
- Jacobson L, Hellström A, Flodmark O. Large cups in normal-sized optic disc is a variant of optic nerve hypoplasia in children with periventricular leukomalacia. *Arch Ophthalmol.* 1997;115:1263-1269.
- Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy. *JAMA* 2006;296:1602-1608.
- Krägeloh-Mann I. Imaging of early brain injury and cortical plasticity. *Exp Neurol.* 2004;190:84-90.
- Beaulieu C. The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomed.* 2002;15:435-455.
- Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann Neurol.* 1999;45:265-269.
- Ebeling U, Reulen HJ. Neurosurgical topography of the optic radiation in the temporal lobe. *Acta Neurochir (Wien).* 1988; 92:29-36.
- Sherbondy AJ, Dougherty RF, Napel S, Wandell BA. Identifying the human optic radiation using diffusion imaging and fiber tractography. *J Vis.* 2008;8(10):12.
- Bassi L, Ricci D, Volzone A, et al. Probabilistic diffusion tractography of the optic radiations and visual function in preterm infants at term equivalent age. *Brain.* 2008;131:573-582.

10. Berman JI, Glass HC, Miller SP, et al. Quantitative fiber tracking analysis of the optic radiation correlated with visual performance in premature newborns. *Am J Neuroradiol.* 2008;30:120-124.
11. Glass HC, Berman JI, Norcia AM, et al. Quantitative fiber tracking of the optic radiation is correlated with visual-evoked potential amplitude in preterm infants. *Am J Neuroradiol.* 2010;31:1424-1429.
12. Groppo M, Ricci D, Bassi L, et al. Development of the optic radiations and visual function after premature birth. *Cortex.* 2014;56:30-37.
13. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol.* 2009;8:110-124.
14. Kostović I, Judaš M. The development of the subplate and thalamocortical connections in the human foetal brain: human foetal cortical circuitry. *Acta Paediatr.* 2010;99:1119-1127.
15. Hevner RF. Development of connections in the human visual system during fetal mid-gestation: a DiI-tracing study. *J Neuropathol Exp Neurol.* 2000;59:385-392.
16. Staudt M, Braun C, Gerloff C, Erb M, Grodd W, Krägeloh-Mann I. Developing somatosensory projections bypass periventricular brain lesions. *Neurology.* 2006;67:522-525.
17. Guzzetta A. Plasticity of the visual system after congenital brain damage: a few weeks can matter. *Dev Med Child Neurol.* 2010;52:699-699.
18. Shatz CJ. Emergence of order in visual system development. *J Physiol Paris.* 1996;90:141-150.
19. Kelly KR, McKetton L, Schneider KA, Gallie BL, Steeves JKE. Altered anterior visual system development following early monocular enucleation. *Neuroimage Clin.* 2014;4:72-81.
20. Braddick O, Atkinson J. Development of human visual function. *Vision Res.* 2011;51:1588-1609.
21. Cowey A, Stoerig P, Perry VH. Transneuronal retrograde degeneration of retinal ganglion cells after damage to striate cortex in macaque monkeys: selective loss of P beta cells. *Neuroscience.* 1989;29:65-80.
22. Jacobson L, Hård AL, Svensson E, Flodmark O, Hellström A. Optic disc morphology may reveal timing of insult in children with periventricular leucomalacia and/or periventricular hemorrhage. *Br J Ophthalmol.* 2003;87:1345-1349.
23. Jacobson LK, Dutton GN. Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. *Surv Ophthalmol.* 2000;45:1-13.
24. Houliston MJ, Taguri AH, Dutton GN, Hajivassiliou C, Young DG. Evidence of cognitive visual problems in children with hydrocephalus: a structured clinical history-taking strategy. *Dev Med Child Neurol.* 1999;41:298-306.
25. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. *Neuroimage.* 2012;62:782-790.
26. Tournier J-D, Calamante F, Connelly A. MRtrix: diffusion tractography in crossing fiber regions. *Int J Imaging Syst Technol.* 2012;22:53-66.
27. Tournier J-D, Calamante F, Connelly A. Robust determination of the fiber orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. *Neuroimage.* 2007;35:1459-1472.
28. Sample PA, Dannheim F, Artes PH, et al. Imaging and Perimetry Society standards and guidelines. *Optom Vis Sci.* 2011;88:4-7.
29. Guzzetta A, Fiori S, Scelfo D, Conti E, Bancale A. Reorganization of visual fields after periventricular haemorrhagic infarction: potentials and limitations. *Dev Med Child Neurol.* 2013;55:23-26.
30. Glass LRD, Cioffi GA, Blumberg DM. Retinal nerve fiber layer analysis of cupping in children born prematurely. *J Glaucoma.* 2014;23:e1-5.
31. Haynes RL, Borenstein NS, Desilva TM, et al. Axonal development in the cerebral white matter of the human fetus and infant. *J Comp Neurol.* 2005;484:156-167.
32. Raybaud C, Ahmad T, Rastegar N, Shroff M, Nassar M. The premature brain: developmental and lesional anatomy. *Neuroradiology.* 2013;55:23-40.
33. Chi JG, Dooling EC, Gilles FH. Gyral development of the human brain. *Ann Neurol.* 1977;1:86-93.
34. Vanhatalo S, Kaila K. Development of neonatal EEG activity: from phenomenology to physiology. *Semin Fetal Neonatal Med.* 2006;11:471-478.
35. Jacobson L, Rydberg A, Eliasson A-C, Kits A, Flodmark O. Visual field function in school-aged children with spastic unilateral cerebral palsy related to different patterns of brain damage: visual field function in children with spastic unilateral CP. *Dev Med Child Neurol.* 2010;52:e184-e187.
36. Maiorano NA, Hindges R. Restricted perinatal retinal degeneration induces retina reshaping and correlated structural rearrangement of the retinotopic map. *Nat Commun.* 2013;4:1938.
37. Wandell BA, Dumoulin SO, Brewer AA. Visual field maps in human cortex. *Neuron.* 2007;56:366-383.
38. Medeiros FA, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. *Invest Ophthalmol Vis Sci.* 2012;53:6939-6946.