Supplementary

Appendix 1

DTI technicalities

The methodological parameters used in a study are directly tied to the obtained findings and understanding the nature of how DTI parameters may relate to and/or impact the obtained results is of value.

Diffusion weighting factor (b value)

The diffusion-weighting factor (i.e., b value) has repeatedly been shown to impact the diffusivity values obtained with distinct b values have certain strengths and weaknesses for imaging different types of bodily tissue (152). The reason for this complexity is because DTI has an underlying assumption that diffusion occurs in a free and unrestricted environment (i.e., a Gaussian distribution), meaning that it has a mono-exponential dependance on the b value. Yet the brain's inherent architecture tends to restrict and guide the flow of water, yielding a discrepancy between the model of analysis and that which is being analyzed (152). Consequently, the results obtained from DTI of the brain are dependent on the selected b value, and this b value may be optimized depending on what type of analysis is being conducted.

Generally, high b values are associated with detecting slow water molecule diffusion in a perpendicular orientation to the axonal direction (152,153). Hence, the use of a high b value can be effective for reducing the distorting effect which blood flow can have in the diffusion weighted signal yet can lead to a low signal-to-noise ratio and more eddy current distortion (152). On the other hand, a low b value is suggested to emphasize fast water diffusion and micro-perfusion (154). Accordingly, low b values have been shown to be sensitive to detecting axial diffusivity (AD), whilst high b values were most sensitive to radial diffusivity (RD) (152). However, fractional anisotropy (FA) has been found to have no obvious correlation with b value magnitude (154). A simple rule of thumb which has been introduced for optimal b value selection is that the product of the average mean diffusivity (MD) of the tissue under investigation and the b-value should be close to one (45).

Number of diffusion-encoding directions (NDED) and resolution

To obtain a correct estimate of a diffusion tensor, at least 6 noncollinear diffusion directions along with an extra non-diffusion-weighted image (obtained with a b value of 0) are required (155). The minimum number of directions is 6 because there are six unknown elements obtained for each diffusion tensor (D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}). To increase the signal-to-noise ratio and have a more accurate diffusion tensor estimate, NDED may be increased, although this increases the time required for scanning. Nevertheless, sampling more directions reduces the orientational dependence of the obtained information, thus increasing the accuracy of the diffusion parameters (45). Finally, the spatial voxel size utilized during scanning can be decreased to obtain clearer and more defined diffusion estimates, which is increasingly important for delineating relatively small white matter tracts (45).

Future directions

DTI parameters

As seen in *Figure S1* there has yet to be a significant agreement amongst researchers regarding the ideal DTI parameters when it comes to delineating the effects of optic neuropathies. This observable level of heterogeneity found between the reviewed studies serves as potential evidence for the lack of agreement found between studies and is most likely counter-productive to developing a robust and verifiable model of how each neuropathy characteristically impacts the entire visual system with respect to time of onset and severity.

DTI research specific to optic neuropathies could likely benefit from increasing the focus given to understanding that nature of how different DTI measures impact the obtained results and in order to work towards an agreed upon strategy. This shared DTI parameter strategy could serve as a common ground between studies and aid in elevating the comparability

https://dx.doi.org/10.21037/qims-23-779

Table S1 Summary of DTI parameters used throughout the reviewed studies

DTI metric	Summary metric	POAG	ON	TON
Resolution (mm)	Range	1.33–16.19	0.73–14.89	3.72–7.08
	Median	8	6.02	6.43
	Mean	8.37	7.3	5.74
Directions	Range	4–64	6–64	6–13
	Median	30	12	9
	Mean	34.6	22.75	9.25
B values (s/mm^2)	Range	250–2,500	600–1,200	600–1,000
	Median	1,000	600	1,000
	Mean	1,014	791	866.67

Resolution is measured by multiplying x*y*z axis dimensions of an individual voxel. *, a few studies did not report either their b values, directions, or full resolution information. DTI, diffusion tensor imaging; POAG, primary open-angle glaucoma; ON, optic neuritis; TON, traumatic optic neuropathy.

Table S2 Summary table of all reviewed primary open-angle glaucoma DTI studies

Study	Visual regions assessed	Diffusion measures	# of directions	Max b value (s/mm^2)	Resolution (mm)
(73)	ONerve, OR	FA, MD	15	800	1.3
(156)	ONerve, OT, OR	FA	15	1,000	12.9
(71)	ONe	FA, MD, RD, AD	32	800	1.3
(81)	ONerve, OT, OR	FA, MD	16	700	9.7
(74)	ONerve, OT, OR	FA, MD	30	800	7.0
(72)	ONerve, OT, OR	FA, MD, RD, AD	30	800	8.0
(75)	ONerve, OT, OR	FA	64	1,000	Not available
(157)	OR	FA	25	1,000	3.7
(82)	OR	FA, MD, RD, AD	64	1,000	8.0
(158)	OR	FA	15	1,000	4.93
(91)	OR	FA	Not available	Not available	Not available
(93)	OR	FA, MD	64	1,000	3.4
(85)	ONerve, OT, OR	FA, RD, AD	32	1,000	15.6
(76)	OR	FA, MD, RD, AD	32	1,000	7.9
(92)	OR	FA, MD, RD, AD	15	1,000	7.0
(99)	OT, OR	FA, MD, RD, AD	64	1,000	Not available
(78)	OT, OR	FA, MD	20	1,000	9.7
(159)	OR	FA	64	1,000	12.0
(77)	ONerve, OT, OR	FA, MD	30	800	7.0
(87)	ONe	FA	48	2,000	8.0
(98)	ONerve, OT, OR	FA, MD	25	1,000, 2,000	16.0
(140)	ONerve, OT, OR	FA, MD	64	1,000	6.7
(143)	OT	FA, MD, RD, AD	4 (when b=250), 20 (when b=1,000), then 60 (when b=2,000)	250, 1,000, 2,000	12.2
(70)	OR	FA, MD	Cohort 1: 60; cohort 2: 64	Cohort 1: 800; cohort 2: 1,000	Cohort 1: 7.03; cohort 2: 3.54
(133)	OT & OR	FA, MD	64	1,000 and 2,500	8
(67)	OR	FA, MD, RD, AD	64	1,000	8
(160)	OT & OR	FA	20	1,000	2.2
(79)	OR	FA, MD, RD, AD	30	1,000	10
(101)	ONerve, OT, OR	FA, AD, RD	32	1,000	15.63
(88)	ONerve	FA, MD, RD, AD	25	312–600 (mean 450)	2.2
(90)	ONerve	FA, MD	15	800	5.36
(96)	ONerve	FA, MD, RD, AD	6	600	11.56
(94)	ONerve, OR	FA	15	1,000	3.24
(161)	OR	FA, MD, RD, AD	20	1,000	16.2
(162)	OT, OR	FA, MD	64	1,000	8
(100)	ONerve, OT, OR	FA, AD, RD	32	1,000	15.63
Correlation-based studies					
(89)	ONerve	FA, MD	32	800	8.0
(83)	OR	FA, MD, RD, AD	15	1,000	16.1
(84)	OR	FA	15	1,000	3.2
(86)	ONerve, OR	FA, MD	32	700	10.5

ONerve, optic nerve; OR, optic radiations; FA, fractional anisotropy; MD, mean diffusivity; OT, optic tract; RD, radial diffusivity; AD, axial diffusivity.

between studies.

Reviewed studies

Tables S2-S7 document the significant findings obtained throughout the review process. Tables are segregated based on DTI feature and visual system region of interest, and all combinations of which show the number of significant results compared to the number of studies analyses that were performed in the "Sig. Ratio" row. The reference numbers here are associated with the reference list specific to this supplementary material.

https://dx.doi.org/10.21037/qims-23-779

Table S3 Summary table of all reviewed optic neuritis DTI studies

Study	Visual regions assessed	Diffusion measures	Comparisons	Acute *vs.* remote	Time-from-onset	# of directions	Max b value (s/mm^2)	Resolution (mm)
(108)	ONe	MD	Between & within	Remote	Greater than 1 year	6	600	Not available
(109)	ONe	FA, MD, RD, AD	Between & within	Remote	3.1±1.7 (range, 1.0–6.7) years	6	600	Not available
(25)	ONe	FA, MD, RD, AD	Within	Acute and remote	Within 30 days (acute) & greater than 1 year (remote)	12	600	2.3
(110)	ONe	FA, MD, RD, AD	Between & within	Remote	Mean 4 (range, 3.4–4.8) years	6	600	5.9
(26)	ONe	FA, MD, RD, AD	Between & within	Remote	At least 6 months prior (years elapsed since first ON onset: 4.0 (range, 1–41)	12	600	2.2
(103)	ONe, OR	FA, MD, RD, AD	Between	Acute & subacute & remote	Range from 8 days to 13 years (subdivided into distinct groups)	Optic nerve: 6 Optic radiations: 15	Optic nerve: 600; optic radiations: 1,000	Optic nerve: 14.8; optic radiations: 14.1
(102)	OR	FA, MD, RD, AD	Between & within	Remote	4±0.4 (range: 3.4–4.8) years	60	1,000	10.55
(27)	ONe	RD, AD	Within	Acute	Within 2 weeks of symptom onset	6	600	6.0
(28)	ONe	FA, MD, RD, AD	Between & within	Acute and sub-acute	All were "recently referred" for evaluation—scanned at baseline and 6 months after onset	11	850	10.5
(107)	OT, OR	FA, MD, RD, AD	Between	Remote	1.54±0.69 (range, 1–3) years	64	1,000	Not available
(105)	OR	FA, MD, RD, AD	Between	Acute	2-weeks after symptoms	60	1,200	8.0
(106)	OR	FA, RD, AD	Between	Acute→remote	Scanned at baseline (within 1 month of onset of optic neuritis), 3, 6 and 12 months later	61	1,200	12.1
(104)	ON	FA, MD, RD, AD	Between	Acute	8 (range, 3–34) days	13	1,000	0.729
Correlation-based studies								
(113)	ON	FA, MD, RD, AD	Longitdunala correlation	Acute → remote	Baseline (<31 days), 3-, 6-, and 12-months post-onset	12	600	2.20
(111)	ONerve	FA, MD, AD, RD		Acute → subacute	Measured 1 and 3-months post-onset	6	600	5.92

AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity.

https://dx.doi.org/10.21037/qims-23-779

Table S4 Summary table of all reviewed primary traumatic optic neuropathy DTI studies

Study	Visual regions assessed	Diffusion measures	# of directions	Max b value (s/mm^2)	Resolution (mm)
(114)	ONerve	FA, MD	13	1,000	7.03
(117)	ONerve	FA, RD, MD, AD	6	600	3.70
(115)	ONerve	FA, RD, MD, AD	6 or 12	1,000	6.41

FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; AD, axial diffusivity.

Table S5 POAG's impact on DTI measures throughout the visual system along with these findings correlations with ophthalmological measures

Location	↓ FA				↑RD			↑MD			↓/↑ AD		
	ONe	OT	OR		ONe	OT	OR	ONe	OT	OR	ONe	OT	OR
Between- and withing-group contrast based POAG DTI findings													
Sig. ratio	7/18	10/17	25/30		2/7	2/6	7/11	5/11	2/11	9/20	3/7	1/6	5/11
↑/↓ DTI metric	(71)	(74)	(93)	(99)	(88)	(72)*	(72)	(71)	(74)	(74)	↑	↑	↑
	(26)	(72)*	(74)	(75)	(96)	(143)	(82)	(73)	(133)	(73)	(88)	(85)	(67)
	(141)	(77)	(91)	(98)			(92)	(98)	(162)	(82)	(96)		(101)
	(99)	(143)	(73)	(70)			(76)	(88)		(76)†	(100)		(85)
	(89)	(133)	(82)	(133)			(67)	(96)		(70)			↓
	(97)	(160)	(92)	(67)			(79)			(133)			(92)
	(95)	(101)	(157)	(160)			(161)			(67)			(79)
		(85)	(140)	(79)						(79)			
		(162)	(78)	(94)						(161)			
		(100)	(76)	(161)									
			(85)	(162)									
			(100)	(164)									
			(163)										
Correlation between POAG DTI findings and ophthalmological measures													
Severity	(73)	(72)*	(77)		(88)	(72)*	(76)	(88)	(83)	(83)	↓		
	(87)		(92)					(90)			(88)		
	(88)		(83)										
Cup/Disk	(87)	(74)	(74)				(76)	(89)	(74)				
	(89)	(78)							(78)				
RNFLT	(87)	(74)	(93)				(76)	(89)	(74)				
	(86)	(162)	(74)										
	(90)		(85)										
			(76)										
MDVF		(78)					(76)		(78)	(99)			
		(162)											
FDT			(83)				(83)						
NFI								(89)					
VFS							(67)			(67)			↓
													(67)
mfVEP			(67)				(67)			(67)			
CCT							(67)						
V1T			(67)										
Rim area	(88)				(88)			(88)			↓		
											(88)		
HFA MD	(90)							(90)					
TD c16	(90)												
MPL	(96)				(96)			(96)					
ONerve atrophy	(94)		(94)										
Spatial-temporal CS	(94)		(94)										
WML Volume			(84)										

*, this finding was specific to the optic chiasm; †, this finding did not cross the threshold of significance, but displayed a clear trend. CCT, calcarine cortex thickness; Cup/Disk, cup-disk ratio; FDT, frequency doubling test; HFA MD, Humphrey Field Analyzer mean deviation; MDVF, mean deviation of visual field; mfVEP, multifocal visually evoked potential; MPL, mean perimetric loss; NFI, nerve fiber index; ONe, optic nerve; OR, optic radiations; OT, optic tract; RNFLT, retinal nerve fiber layer thickness; Sig. Ratio, $\frac{\text{signifcant results}}{\text{performed contrasts}}$, Spatial-temporal CS , spatial temporal contrast sensitivity; TD c16, average total deviation of the central 16 test points (4×4 points square) of the HFA; V1T, primary visual cortex thickness; VFS, visual field sensitivity.

https://dx.doi.org/10.21037/qims-23-779

Table S6 ON's impact on DTI magnitudes throughout the visual system along with these findings correlations with ophthalmological measures

Measure	↓ FA			↑RD			↑MD			↓/↑ AD		
Location	ONe	OT	OR	ONe	OT	OR	ONe	OT	OR	ONe	OT	OR
Contrast based and classification based ON DTI findings												
Sig. ratio	5/15	0/1	5/8	11/16	0/1	5/8	8/17	0/1	1/6	7/16	1/1	1/8
↑/↓ DTI Metric	(103)$^{a/b}$ (103)$^{r/b}$ (110)$^{r/w}$ (109)$^{r/w}$ (104)$^{a/b}$		(103)$^{r/b}$ (102)$^{r/w}$ (105)$^{a/b}$ (106)$^{r/b}$ (107)$^{r/b}$	(26)$^{r/b}$ (26)$^{r/w}$ (103)$^{a/b}$ (103)$^{r/b}$ (109)$^{r/b}$ (109)$^{r/w}$ (104)$^{a/b}$ (27)$^{a/w}$ (25)$^{r/b}$ (28)$^{a/b}$ (28)$^{a/w}$		(103)$^{r/b}$ (102)$^{r/w}$ (105)$^{a/b}$ (106)$^{r/b}$ (107)$^{r/b}$	(103)$^{r/b}$ (109)$^{r/b}$ (109)$^{r/w}$ (104)$^{a/b}$ (102)$^{r/w}$ (25)$^{r/b}$ (28)$^{a/w}$ (108)$^{r/w}$		(105)$^{a/b}$	↓ (103)$^{a/b}$ (27)$^{a/w}$ (102)$^{r/w}$ (28)$^{a/b}$ (28)$^{a/w}$ ↑ (104)$^{a/b}$ (25)$^{r/b}$ Non-linear longitudinal trend (27) (25) (28)	↓ (107)$^{r/b}$	↓ (102)$^{r/w}$
Correlation between ON DTI findings and ophthalmological measures												
RNFLT	(25)^{r}			(26)^{r} (25)^{r} (111)^{p}			(25)^{r}			(27)^{a} (113)^{p} (111)^{p}		(105)^{a}
V1 Thinning	(105)^{a}					(105)^{a}	(105)^{a}					
CS	(25)^{r}			(25)^{r} (26)^{r}			(25)^{r} (113)^{p}			(25)^{a} (113)^{p}		
VEP	(110)^{r} (25)^{r}			(25)^{r} (26)^{r} (109)^{r}			(108)^{r} (25)^{r} (109)^{r} (113)^{p}			(27)^{a} (113)^{p} (111)^{p}		(102)^{r}
VA	(25)^{r}			(25)^{r} (26)^{r}			(108)^{r} (25)^{r}					
Severity				(26)^{r}								
Transduction												(102)^{r}
Abnor θ												(102)^{r}
T2 lesion length	(110)^{r}			(110)^{r}			(110)^{r}			(110)^{r}		
Acuity							(113)^{p}			(113)^{p}		
5% contrast sensitivity							(113)^{p}			(113)^{p}		

^{a}, acute optic neuritis; ^{r}, remote optic neuritis; $^{/b}$, between-group contrast between ON and healthy controls; $^{/w}$, within-group contrast between the affected and intact eye; ^{p}, significant prediction/longitudinal correlation. Abnormal θ: abnormal angle of deviation in primary eigenvector; CS, contrast sensitivity; LGN, lateral geniculate nucleus; OCT, optical coherence tomography; OL, occipital lobe; ONe, optic nerve; OR, optic radiations; OT, optic tract; retinal nerve fiber layer thickness; Sig. ratio, $\frac{\text{signifcant results}}{\text{performed contrasts}}$; VA, visual acuity; VEP, visually evoked potential.

https://dx.doi.org/10.21037/qims-23-779

Table S7 DTI findings for TON

DTI metric	Study	Location	Magnitude change	Correlation
FA	(114)	Optic Nerve	↓	Not performed
	(117)		↓	RNFLT
	(115)		No change	Not performed
RD	(114)	Optic Nerve	Not performed	Not performed
	(117)		↑	RNFLT and GCCT
	(115)		↓ (trend)	Not performed
MD	(114)	Optic Nerve	↑	Not performed
	(117)		↑	RNFLT and GCCT
	(115)		↓	
AD	(114)	Optic Nerve	Not performed	Not performed
	(117)		↓ then ↑ then ↓	
	(115)		↓	Not performed

AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; RNFLT, retinal nerve fiber layer thickness; GCCT, ganglion cell complex thickness.

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