Published in final edited form as:

Am J Ophthalmol. 2016 October ; 170: 75–82. doi:10.1016/j.ajo.2016.07.020.

Localized Changes in Retinal Nerve Fiber Layer Thickness as a Predictor of Localized Functional Change in Glaucoma

Stuart K Gardiner*, Brad Fortune, and Shaban Demirel

Devers Eye Institute

Abstract

Purpose—To determine how well rates of localized retinal nerve fiber layer thickness (RNFLT) change correlate with rates of sensitivity change at corresponding locations in the visual field in glaucoma.

Design—Retrospective Cohort Study

Methods—364 eyes of 191 participants, with suspected or confirmed glaucoma as judged by experienced clinicians, were tested every six months with perimetry and optical coherence tomography (OCT). For each 24-2 visual field location, the corresponding sectoral peripapillary RNFLT was defined using a 30° sector, centered on the angle of nerve fiber entry into the optic nerve head. Rates of change of pointwise sensitivity and sectoral RNFLT were calculated over the last 8 visits at which reliable data were obtained. Passing-Bablok regression was used to predict the rate of pointwise sensitivity change from the rate of sectoral RNFLT change, for each location.

Results—Rates of sectoral RNFLT change were significantly predictive of rates of pointwise sensitivity change at all locations in the field. Correlations were modest, averaging 0.15, ranging from 0.03 to 0.25 depending on the location. A 1µm/y more rapid thinning in corresponding sectors was associated with 0.3dB/y more rapid loss in the superior visual field, but less than 0.1dB more rapid loss at many locations in the inferior visual field.

Conclusions—Localized RNFL thinning is associated with sensitivity loss at corresponding locations in the visual field, and their rates of change are significantly correlated. Peripapillary RNFLT may be used to monitor localized changes caused by glaucoma that have measurable consequences for a patient's vision.

* Corresponding author. Phone: +1 503-413-1199. Address: Devers Eye Institute, Legacy Research Institute, Legacy Health, 1225 NE 2nd Ave, Portland, OR 97232, sgardiner@deverseye.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

b. Financial Disclosures:

SKG is a consultant for and has received fees/reimbursements from Haag-Streit Inc, and has been a consultant for Carl Zeiss Meditec Inc.

SD is a consultant for Pfizer Inc.

BF has no financial disclosures.

c. No other acknowledgments.

All authors attest that they meet the current ICMJE criteria for authorship.

Introduction

Optical coherence tomography (OCT) allows visualization and measurement of ocular structures with high resolution in three dimensions.¹ Glaucomatous eyes have been shown to have reduced retinal nerve fiber layer thickness (RNFLT),^{2,3} optic nerve head minimum rim width (MRW),⁴ and macular inner retinal layer thickness,^{5,6} among other structural abnormalities that can be quantified using OCT. Furthermore, reductions in these measures correlate with reduced function,^{2,7,8} and imaging tests are preferred over perimetry by patients.⁹ Therefore it has been suggested that structural measures derived from OCT could be used both diagnostically and in clinical trials.⁸ Since preserving function is the ultimate goal of almost all interventions in glaucoma, it is essential to know how closely OCT relates to commonly-used functional measures.

Unfortunately, correlations between structural and functional measures are not as strong as may be anticipated.^{10,11} We have previously reported that the correlation between global average peripapillary RNFLT and Mean Deviation (MD) from standard automated perimetry was modest, with $r=0.646$; and that the correlation between MRW and MD was weaker still ($r=0.546$).¹² The strength of these correlation coefficients depends on the range of severities of glaucomatous damage in the cohort, but are similar to studies in other cohorts (e.g. $r=0.549$).¹³ When localized to smaller regions of the retina and associated visual field, reported correlations range from as high as 0.81,² down to around 0.3,¹⁴ depending on both the cohort and the size of the regions studied. Due to this weakness of the structure-function relation, concerns have been raised by the Food and Drug Administration in the USA about the sole use of structural measures of progression as endpoints in clinical trials.¹⁵

There are at least three plausible explanations for this dissociation. It is possible that structural and functional changes, as measured clinically, do not coincide; it has been suggested that structural changes may precede functional changes along a continuum,¹⁶ with important clinical consequences and mechanistic implications. Alternatively, it may be that the substantial test-retest variability observed in clinical test results obscures the true strength of the underlying structure-function relation. Using confocal scanning laser tomography, we showed that the test-retest variability was sufficiently high that it could be the sole cause of the structure-function dissociation.¹⁷ In addition, we have previously shown that the inter-test variability (defined as the standard deviation of residuals from the longitudinal trend) was as high as 170% of the typical (median) annual rate of change in RNFLT, and 230% of the median rate of change for MRW, among managed glaucoma patients;¹⁸ and that perimetry was as much as 80% more variable than RNFLT when compared to their respective rates of change.¹⁹ A third possibility is that each individual's visual system is tailored to the number of retinal ganglion cells present in that eye, for example by adjusting gains associated with retino-cortical connections. There is considerable inter-individual variability in RNFLT for the same level of sensitivity in healthy eyes,²⁰ and this could contribute to the structure-function dissociation observed in cross-sectional studies of glaucomatous eyes.²¹

While studies that examine the cross-sectional correlation between OCT and perimetry have been performed, the strength of the correlation between the longitudinal rates of change in

these measures remains uncertain. As noted above, there is a considerable range of RNFLT for normal eyes with the same level of function.^{22,23} It is therefore possible that structural and functional measures could progress in perfect correspondence for each eye separately, while still resulting in a weak cross-sectional structure-function relation due to this population variability. This would allow structure and function to be used interchangeably for monitoring progression, provided that a reliable baseline has been determined for each.

Evidence is now emerging that there is indeed a significant correlation between rates of structural change (from OCT) and functional change (from automated perimetry). We have previously reported a significant correlation of $r=0.361$ between the rates of change of MD and global average RNFLT.²⁴ However, glaucomatous disease manifests in a predominantly localized or asymmetric manner, both between the two eyes of an individual and within an eye. To our knowledge no studies have yet looked at the strength of the correlation between the rates of localized functional and structural change using these testing modalities. The use of global measures of progression such as MD reduces variability (in the same way that the mean of two measures will be less variable than either one alone), and so it remains possible that for pointwise or localized analyses, the structure-function correlation between rates of change may not be statistically significant; and/or it may be that the correlations observed when global rates of change are examined are an artifact of non-corresponding regions of the visual field and RNFLT changing at the same time with a temporal disconnect. In this study, we ask whether the rates of localized RNFLT thinning correlate with the rates of sensitivity reduction at corresponding areas of the visual field. Such a relation would support the principle of using OCT to supplement functional assessment via automated perimetry in clinical applications.¹¹

Methods

Population

Data for this study were obtained from participants in the Portland Progression Project (P3), a prospective longitudinal cohort study of the course and risk factors for glaucomatous progression.²⁵ Participants were recruited to and tested at a tertiary glaucoma clinic at the Devers Eye Institute in Portland, Oregon, USA. Inclusion criteria were a diagnosis of primary open-angle glaucoma, and/or likelihood of developing glaucomatous damage (e.g. ocular hypertension with other risk factors such as a suspicious-looking optic disc or a family history of glaucoma), as determined by each participant's physician. A visual field defect was not a requirement for study entry, nor was having an abnormal RNFLT. Exclusion criteria were an inability to perform reliable visual field testing, best-corrected visual acuity worse than 20/40, cataract or media opacities likely to significantly increase light scatter, or other conditions or medications that may affect the visual field. Participants provided written informed consent once all of the risks and benefits of participation were explained to them. All protocols were approved and monitored by the Legacy Health Institutional Review Board, and adhered to the Health Insurance Portability and Accountability Act of 1996 and the tenets of the Declaration of Helsinki.

Participants were tested using a variety of methods, including automated perimetry and OCT, approximately every six months. Since damage may not occur at a constant rate over

long periods of time due to variation in pathophysiological course and/or treatment decisions,^{26,27} data were used from the most recent eight visits at which reliable measurements (as outlined below) were acquired.

Testing Protocol

Functional testing was performed using automated white-on-white perimetry with a Humphrey Field Analyzer (HFA II, Carl-Zeiss Meditec, Dublin, CA, USA), with a size III stimulus, SITA standard algorithm, and 24-2 test pattern. Visual field tests were excluded from analysis if they had greater than 20% false positives or 33% fixation losses. For the primary analysis, pointwise sensitivities in decibels (dB) were used, as output by the perimeter; these will be denoted $Sens_{db}$. Since it has been reported that the structure-function relation may be non-linear,^{28,29} and that functional progression may also be non-linear when expressed in dB,^{26,30} a secondary analysis was performed expressing pointwise sensitivities on a linear scale of $10^{(dB-30)/10}$, such that 0dB→0.001, 10dB→0.01, 20dB→0.1, and 30dB→1.0 etc. Sensitivities on this scale, which will be denoted $Sens_{Lin}$, may then be more linearly related to RNFLT,^{28,29} and hence to axon counts; and may also progress more linearly over time.^{26,30} A third analysis was performed after setting all pointwise sensitivities below 15dB to equal exactly 15dB, on the basis that sensitivities below 15-19dB are unreliable;³¹ this has been shown to aid the detection of pointwise change in glaucoma.³² Pointwise sensitivities that have undergone this process will be denoted $Sens_{15}$.

Spectral domain OCT was performed using a Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). The peripapillary RNFLT was derived on each test date from a single circular B-scan with a radius of 6° centered on the optic disc. The operator centered the position of the circular B-scan on the optic disc at baseline, and each follow-up scan was registered in real-time to the location of the baseline reference scan for each eye using the instrument's automated eye tracking capability. Nine to 16 sweeps were averaged to comprise the final recorded B-scan for each eye on each test date. Scans with quality score less than 15 were excluded as recommended by the manufacturer.³³ The instrument's automated segmentations of the Inner Limiting Membrane and the posterior border of the RNFL were manually adjusted if necessary by experienced technicians, in order to address obvious segmentation errors (without reference to the functional results or knowledge of this study's specific hypothesis).³⁴

Localization

The “average angles” where nerve fiber bundles enter the optic disc from each of the 52 nonblindspot visual field locations were taken from the map of Garway-Heath et al.³⁵ Since the exact angle of entry will vary between eyes, and may vary between scans for the same eye based on factors such as head position during scanning, sectoral RNFL thicknesses were calculated within peripapillary sectors centered on each of these average angles, rather than just using the value from a single A-scan exactly corresponding with the average angle. In order to smooth out artifacts caused by blood vessels or other irregularities being just inside or just outside the sector edge, a trapezoidally-weighted average thickness was used. A-scans within $\pm 10^\circ$ of the average angle were assigned a weighting of 1.0. A-scans within

10°-20° either side of the average angle were assigned weightings that decreased linearly with distance, from a weighting of 1.0 at $\pm 10^\circ$ down to a weighting of 0.0 at $\pm 20^\circ$ from the average angle. Thus these sectors are conceptually equivalent to a 30° wide sector centered on the average angle of entry, and they will henceforth be referred to as “30° sectors”, and the sectoral thickness will be denoted $RNFLT_{\text{sector}}$.

Analysis

Analyses were performed using the R language and environment for statistical computing (Version 2.15.3; R Core Team, Vienna, 2013, <http://www.R-project.org/>). For each non-blindspot visual field location in each eye, the rates of change of $Sens_{dB}$, $Sens_{Lin}$, $Sens_{15}$, and $RNFLT_{\text{sector}}$ for the corresponding sector, were calculated over the most recent 8 visits by least-squares linear regression.

In order to determine whether the rate of localized structural change is a statistically significant predictor of the rate of pointwise functional change, global analyses were performed. Mixed effects models were formed to predict the rate of pointwise functional change (either $\frac{d}{dt} Sens_{dB}$, $\frac{d}{dt} Sens_{Lin}$, or $\frac{d}{dt} Sens_{15}$), using the concurrent rate of localized structural change $\frac{d}{dt} RNFLT_{\text{sector}}$, at all 52 non-blindspot visual field locations concurrently. The models were of the form:

$$\frac{d}{dt} Sens = Int + \varepsilon_{ID} + \varepsilon_{Eye} + (\lambda + \lambda_{Loc}) \frac{d}{dt} RNFLT_{\text{sector}}$$

Here, ε_{ID} , ε_{Eye} and λ_{Loc} are normally distributed, taking a different value for each person, for each eye of the same person, and for each location within the visual field, respectively. Thus, the rate of functional change that would be expected in the absence of any RNFL thinning can vary between people, and can also vary between fellow eyes; in addition, the effect of a given rate of RNFL thinning can vary between visual field locations (but be the same at corresponding locations of different eyes within the cohort). These models were compared against the equivalent models with no effect of $\frac{d}{dt} RNFLT_{\text{sector}}$, i.e. with $\lambda=0$ and $\lambda_{Loc}=0$. Since these models are nested, ANOVA may be used to assess the statistical significance of including $\frac{d}{dt} RNFLT_{\text{sector}}$ in the model, in order to determine whether $\frac{d}{dt} RNFLT_{\text{sector}}$ is a useful predictor of $\frac{d}{dt} Sens$.

To assess whether disease severity affected the results, supplementary analyses were performed using the same mixed effects technique after splitting the data into two halves, according to whether the final MD in the visual field series for an eye was greater than or less than the median value in the cohort. Splitting the data in this way could not be performed for single-location analyses, because the reduced sample size caused the results to appear unreliable (with neighboring locations having unrealistically differing results). However when all 52 locations are used, the sample size is sufficient to allow this subset analysis.

Having determined that a statistically significant relation exists, the next step is to use the rates of localized structural change to make predictions of the rates of pointwise functional change at individual locations. For this purpose, it is desirable to reduce the effect of outliers

that could influence the predictive model; and also to allow the predictive models to vary between locations. Therefore, Passing-Bablok regression was used to determine the relation between the rates of pointwise functional change and sectoral structural change.³⁶ This non-parametric technique calculates the slope of a line connecting each pair of observations in turn; the median of these pairwise slopes represents an unbiased, robust estimate of the true relation, and its confidence interval can be derived. For each location, this gives the rate of functional change that would be expected for a 1µm/y thinning in the corresponding RNFL sector. Additionally, the Pearson correlation between these rates is reported.

Results

Data from 364 eyes of 191 participants were available for this analysis (including only eyes with at least 8 visits at which data of sufficient quality were obtained for both OCT and perimetry on the same day). Characteristics of the cohort are summarized in Table 1. At their most recent test date, 214 eyes were “Within Normal Limits” according to the Glaucoma Hemifield Test, with 37 “Borderline”, 103 “Outside Normal Limits”, and 10 in other categories; although it should be noted that many of the eyes classified as “Within Normal Limits” displayed structural damage, with the exact proportion depending on the specific criterion used. The cohort contained 110 females and 81 males, and 178 (93%) were self-identified as Caucasian. The mean rate of change of MD (from linear regression) was -0.15dB/y, with a median rate of -0.11dB/y, which is slightly more rapid than has been reported for a different clinical population of patients with glaucoma.³⁷

In the mixed effects models combining all locations, including $\frac{d}{dt}$ RNFLT in the model significantly improved the ability to predict $\frac{d}{dt}$ Sens_{dB}, with $p < 0.0001$. This was also true for both halves of the cohort (when split according to the final MD in the series); and when either $\frac{d}{dt}$ Sens₁₅ or $\frac{d}{dt}$ Sens_{Lin} were used as the outcomes (all $p < 0.0001$).

The Pearson correlations at individual locations between the rates of change of pointwise sensitivity Sens_{dB} and the corresponding sectoral RNFLT_{sector} averaged $r = 0.146$, ranging from 0.029 to 0.248. The average correlation increased slightly to $r = 0.163$ when using Sens₁₅ (range 0.035 to 0.261), likely due to the reduced variability of the sensitivity measures when constrained in this manner. This improvement was significant with $p = 0.0003$ (Wilcoxon signed rank test). Expressing sensitivities on a linear scale (Sens_{Lin}) reduced the average correlation between rates of functional and structural change to $r = 0.088$ (range -0.015 to 0.181) which was significantly worse than Sens_{dB} with $p < 0.0001$.

Figure 1 shows the effect of the rate of sectoral RNFLT change on the rate of functional change at the corresponding visual field location, defined using either $\frac{d}{dt}$ Sens_{dB} (left column) or $\frac{d}{dt}$ Sens₁₅ (right column). For example, if the value at a location is 0.2, then a 1µm/y more rapid loss of RNFLT in the corresponding sector predicts a 0.2dB/y more rapid loss of sensitivity at that location. Note that there is also an intercept term, which varies between locations, averaging -0.05µm/y; but this is small compared with the mean rate of RNFLT_{sector} change which was -0.98µm/y. The top panel of each column in Figure 1 shows the median slope from the Passing-Bablok regression for each location, which is the best estimate of the true effect (arranged as a right eye 24-2 visual field). The middle and lower

panels show the lower and upper limits of the 95% confidence interval for this median respectively.

The first thing to note in Figure 1 is the finding that the 95% confidence interval for the relation does not include zero at any of the visual field locations. This is equivalent to saying that the correlation between the rates of structural and functional change is positive and statistically significant at the $p < 5\%$ level for all locations, whether using Sens_{dB} or Sens₁₅.

A second notable result is the variation between different visual field locations. A $1 \mu\text{m/y}$ more rapid deterioration in RNFLT_{sector} is associated with a 0.05 dB/y more rapid deterioration in Sens_{dB} at location ($9^\circ, -9^\circ$) (95% confidence interval 0.03 to 0.07 dB/y); while the same rate of structural deterioration is associated with a 0.37 dB/y more rapid deterioration of Sens_{dB} at location ($9^\circ, 21^\circ$) (95% confidence interval 0.30 to 0.46 dB/y). Taking into account the intercept term, if the RNFLT in the inferior nasal quadrant of the disc was thinning at $-2 \mu\text{m/y}$, the expected rate of functional loss at ($9^\circ, 21^\circ$) in the superior temporal region would be -0.74 dB/y ; whereas if the same rate of structural deterioration occurred in the superior portion of the disc, then the expected rate of functional deterioration at ($9^\circ, -9^\circ$) would be -0.19 dB/y . The rates of change at these two locations are shown in Figure 2, together with the Passing-Bablok regression lines.

Discussion

RNFLT may now be the most common structural measure for clinical diagnosis and monitoring of glaucoma.³⁸⁻⁴⁰ Evidence to date suggests that it provides better diagnostic performance than OCT assessment of the macula in glaucoma,^{5,6} though it will sometimes miss highly localized damage that can be detected by macular OCT analysis.⁴¹ Average peripapillary RNFLT is highly repeatable; in a study using the Cirrus OCT (Carl-Zeiss Meditec Inc.) it was reported to have a 1.9% intra-visit coefficient of variation.⁴² It also correlates reasonably well with function.²⁴ Indeed, in our cohort, the cross-sectional correlation between RNFLT and MD was 0.674. Longitudinally, the correlation between the rates of change of RNFLT and MD was only 0.349, in part because the variability is greater compared with the range of values.

In localized analyses, we found that these correlations are reduced in both cross-sectional and longitudinal analyses. This is perhaps not surprising since MD is a weighted average of 52 visual field locations, and so its variability (when measured as test-retest standard deviation) is reduced by a factor of around 7 compared to any single visual field location. However, crucially, both cross-sectional and longitudinal localized correlations are still strongly significant. This implies that RNFLT sectoral thinning does indeed correspond with a gradual loss of sensitivity at the corresponding location in the visual field over the same time period.

While these correlations were statistically significant, they were modest, averaging $r=0.146$. This is not surprising given the variability of both RNFLT and perimetry measurements.^{18,19} Clinically, it is advisable to utilize both techniques, since the one that detects change sooner will vary between patients.¹¹ However, both appear to be measuring the same underlying

pathophysiology, and changes observed by one modality are likely to appear within the corresponding region in the other modality eventually.

The data used in this study consists primarily of early, well-managed glaucoma. Only 34 out of 364 eyes in the cohort had MD worse than -6dB , a value often taken to indicate the transition between mild and moderate functional damage. Around half of the eyes did not yet have significant functional damage when assessed by MD alone (although many of these had structural evidence of damage or small areas of localized visual field damage). These data therefore represent an important clinical scenario, where early signs of functional progression are sought. Our findings may not be applicable in severe glaucoma, where a floor effect is present in both RNFLT⁴³⁻⁴⁵ and visual field sensitivity.³¹ It seems likely that neither measure is particularly useful for monitoring regions of severe damage late in the disease process, with their use being restricted to monitoring of remaining healthier regions of the RNFL and visual field. Strategies such as increasing the stimulus size for perimetry may extend diagnostic capabilities further into the range of more severe glaucoma in the functional realm.^{46,47}

This study does not rule out the possibility that RNFLT may change before or after sensitivity loss. The analysis did not incorporate any potential time lag between the observed changes, since each measure was assumed to change linearly over time. Furthermore, we looked solely at concurrent rates of functional change, as the aim was to determine whether the rate of RNFLT change would predict the rate of functional change occurring during that same time period, rather than to predict the rate of subsequent functional change. Further studies using longer series of data are needed to assess the temporal order of these changes. However, clinically this study provides an important finding: that OCT may be used to monitor localized changes caused by glaucoma that have measurable consequences for a patient's vision.

In summary, the results of this study demonstrate that localized longitudinal thinning of the peripapillary RNFL is associated with a reduction in sensitivity at corresponding locations in the visual field. Moreover, the rates of such localized changes are significantly correlated. Thinning in inferior sectors of the peripapillary RNFL was associated with more rapid functional loss (at the corresponding visual field locations) than the same rate of thinning in other regions. These results encourage increased use of OCT for monitoring patients with suspected or confirmed glaucoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

a. Funding/Support:

NIH NEI grant R01-EY020922 (SKG)

NIH NEI grant R01-EY019674 (SD)

NIH NEI grant R01-EY019327 (BF)

Unrestricted research support from The Legacy Good Samaritan Foundation, Portland, OR, USA.

References

1. Chen TC, Cense B, Pierce MC, et al. Spectral domain optical coherence tomography: Ultra-high speed, ultra-high resolution ophthalmic imaging. *Arch Ophthalmol*. 2005; 123(12):1715–1720. [PubMed: 16344444]
2. Horn FK, Mardin CY, Laemmer R, et al. Correlation between Local Glaucomatous Visual Field Defects and Loss of Nerve Fiber Layer Thickness Measured with Polarimetry and Spectral Domain OCT. *Invest Ophthalmol Vis Sci*. 2009; 50(5):1971–1977. [PubMed: 19151389]
3. Chen TC. Spectral domain optical coherence tomography in glaucoma: qualitative and quantitative analysis of the optic nerve head and retinal nerve fiber layer (an AOS thesis). *Trans Am Ophthalmol Soc*. 2009; 107:254–281. [PubMed: 20126502]
4. Chauhan BC, O'Leary N, AlMobarak FA, et al. Enhanced Detection of Open-angle Glaucoma with an Anatomically Accurate Optical Coherence Tomography-Derived Neuroretinal Rim Parameter. *Ophthalmology*. 2013; 120(3):535–543. [PubMed: 23265804]
5. Oddone F, Lucenteforte E, Michelessi M, et al. Macular versus Retinal Nerve Fiber Layer Parameters for Diagnosing Manifest Glaucoma. *Ophthalmology*. 2016; 123(5):939–949. [PubMed: 26891880]
6. Wong JJ, Chen TC, Shen LQ, Pasquale LR. Macular imaging for glaucoma using spectral-domain optical coherence tomography: a review. *Semin Ophthalmol*. 2012; 27(5-6):160–166. [PubMed: 23163271]
7. Chang RT, Knight ORJ, Feuer WJ, Budenz DL. Sensitivity and Specificity of Time-Domain versus Spectral-Domain Optical Coherence Tomography in Diagnosing Early to Moderate Glaucoma. *Ophthalmology*. 2009; 116(12):2294–2299. [PubMed: 19800694]
8. Yu M, Lin C, Weinreb RN, Lai G, Chiu V, Leung CK-S. Risk of Visual Field Progression in Glaucoma Patients with Progressive Retinal Nerve Fiber Layer Thinning: A 5-Year Prospective Study. *Ophthalmology*. 2016; 123(6):1201–1210. [PubMed: 27001534]
9. Gardiner SK, Demirel S. Assessment of Patient Opinions of Different Clinical Tests Used in the Management of Glaucoma. *Ophthalmology*. 2008; 115(12):2127–2131. [PubMed: 19041473]
10. Artes PH, Chauhan BC. Longitudinal changes in the visual field and optic disc in glaucoma. *Prog Retin Eye Res*. 2005; 24(3):333–354. [PubMed: 15708832]
11. Medeiros FA, Tatham AJ. Structure versus Function in Glaucoma: The Debate That Doesn't Need to Be. *Ophthalmology*. 2016; 123(6):1170–1172. [PubMed: 27210598]
12. Gardiner SK, Ren R, Yang H, Fortune B, Burgoyne CF, Demirel S. A Method to Estimate the Amount of Neuroretinal Rim Tissue in Glaucoma: Comparison With Current Methods for Measuring Rim Area. *Am J Ophthalmol*. 2014; 157(3):540–549. [PubMed: 24239775]
13. Cvenkel B, Šket Kontestabile A. Correlation between nerve fibre layer thickness measured with spectral domain OCT and visual field in patients with different stages of glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2010; 249(4):575–584. [PubMed: 20949277]
14. Ferreras A, Pablo LsE, Garway-Heath DF, Fogagnolo P, García-Feijoo Jn. Mapping Standard Automated Perimetry to the Peripapillary Retinal Nerve Fiber Layer in Glaucoma. *Invest Ophthalmol Vis Sci*. 2008; 49(7):3018–3025. [PubMed: 18378581]
15. Weinreb RN, Kaufman PL. Glaucoma Research Community and FDA Look to the Future, II: NEI/FDA Glaucoma Clinical Trial Design and Endpoints Symposium: Measures of Structural Change and Visual Function. *Invest Ophthalmol Vis Sci*. 2011; 52(11):7842–7851. [PubMed: 21972262]
16. Weinreb RN, Friedman DS, Fechtner RD, et al. Risk assessment in the management of patients with ocular hypertension. *Am J Ophthalmol*. 2004; 138(3):458–467. [PubMed: 15364230]
17. Gardiner SK, Johnson CA, Demirel S. The effect of test variability on the structure-function relationship in early glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2012; 250(12):1851–1861. [PubMed: 22527311]
18. Gardiner SK, Boey PY, Yang H, Fortune B, Burgoyne CF, Demirel S. Structural Measurements for Monitoring Change in Glaucoma: Comparing Retinal Nerve Fiber Layer Thickness With

- Minimum Rim Width and Area. *Invest Ophthalmol Vis Sci*. 2015; 56(11):6886–6891. [PubMed: 26501416]
19. Gardiner SK, Fortune B, Demirel S. Signal-to-Noise Ratios for Structural and Functional Tests in Glaucoma. *Transl Vis Sci Technol*. 2013; 2(6):3.
 20. Hood DC, Anderson SC, Wall M, Raza AS, Kardon RH. A Test of a Linear Model of Glaucomatous Structure-Function Loss Reveals Sources of Variability in Retinal Nerve Fiber and Visual Field Measurements. *Invest Ophthalmol Vis Sci*. 2009; 50(9):4254–4266. [PubMed: 19443710]
 21. Ashimatey BS, Swanson WH. Between-Subject Variability in Healthy Eyes as a Primary Source of Structural-Functional Discordance in Patients With Glaucoma. *Invest Ophthalmol Vis Sci*. 2016; 57(2):502–507. [PubMed: 26873511]
 22. Rao HL, Zangwill LM, Weinreb RN, Leite MT, Sample PA, Medeiros FA. Structure-function relationship in glaucoma using spectral-domain optical coherence tomography. *Arch Ophthalmol*. 2011; 129(7):864–871. [PubMed: 21746976]
 23. Hood D. Relating retinal nerve fiber thickness to behavioral sensitivity in patients with glaucoma: application of a linear model. *J Opt Soc Am A*. 2007; 24(5):1426–1430.
 24. Gardiner SK, Demirel S, Reynaud J, Fortune B. Changes in Retinal Nerve Fiber Layer Reflectance Intensity as a Predictor of Functional Progression in Glaucoma. *Invest Ophthalmol Vis Sci*. 2016; 57(3):1221–1227. [PubMed: 26978028]
 25. Gardiner SK, Johnson CA, Demirel S. Factors predicting the rate of functional progression in early and suspected glaucoma. *Invest Ophthalmol Vis Sci*. 2012; 53(7):3598–3604. [PubMed: 22570353]
 26. Pathak M, Demirel S, Gardiner SK. Nonlinear, Multilevel Mixed-Effects Approach for Modeling Longitudinal Standard Automated Perimetry Data in Glaucoma. *Invest Ophthalmol Vis Sci*. 2013; 54(8):5505–5513. [PubMed: 23833069]
 27. Gardiner SK, Demirel S, de Moraes CG, et al. Series length used during trend analysis affects sensitivity to changes in progression rate in the Ocular Hypertension Treatment Study. *Invest Ophthalmol Vis Sci*. 2013; 54(2):1252–1259. [PubMed: 23349433]
 28. Hood D, Kardon R. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007; 26(6):688–710. [PubMed: 17889587]
 29. Garway-Heath D, Caprioli J, Fitzke F, Hitchings R. Scaling the hill of vision: the physiological relationship between light sensitivity and ganglion cell numbers. *Invest Ophthalmol Vis Sci*. 2000; 41(7):1774–1782. [PubMed: 10845598]
 30. Pathak M, Demirel S, Gardiner SK. Nonlinear Trend Analysis of Longitudinal Pointwise Visual Field Sensitivity in Suspected and Early Glaucoma. *Transl Vis Sci Technol*. 2015; 4(1):8.
 31. Gardiner SK, Swanson WH, Goren D, Mansberger SL, Demirel S. Assessment of the reliability of standard automated perimetry in regions of glaucomatous damage. *Ophthalmology*. 2014; 121(7):1359–1369. [PubMed: 24629617]
 32. Gardiner SK, Swanson WH, Demirel S. The Effect of Limiting the Range of Perimetric Sensitivities on Pointwise Assessment of Visual Field Progression in Glaucoma. *Invest Ophthalmol Vis Sci*. 2016; 57(1):288–294. [PubMed: 26824408]
 33. Spectralis HRA+OCT User Guide Software Version 5.1. 2010; 26:55–56.
 34. Menda S, Fortune B, Mansberger SL, Gardiner SK, Demirel S. The effect of manually refining automated image segmentations on retinal nerve fiber layer thickness measurements from optical coherence tomography (OCT) scans. *Invest Ophthalmol Vis Sci*. 2015; 56(7):4551–4551.
 35. Garway-Heath D, Poinoosawmy D, Fitzke F, Hitchings R. Mapping the visual field to the optic disc in normal tension glaucoma eyes. *Ophthalmology*. 2000; 107(10):1809–1815. [PubMed: 11013178]
 36. Passing H, Bablok W. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. *J Clin Chem Clin Biochem*. 1983; 21(11):709–720. [PubMed: 6655447]

37. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT, Artes PH. Rates of Glaucomatous Visual Field Change in a Large Clinical Population. *Invest Ophthalmol Vis Sci*. 2014; 55(7):4135–4143. [PubMed: 24917147]
38. Townsend KA, Wollstein G, Schuman JS. Imaging of the retinal nerve fibre layer for glaucoma. *Br J Ophthalmol*. 2009; 93(2):139–143. [PubMed: 19028735]
39. Leung CK-S. Diagnosing glaucoma progression with optical coherence tomography. *Curr Opin Ophthalmol*. 2014; 25(2):104–111. [PubMed: 24370973]
40. Miki A, Medeiros FA, Weinreb RN, et al. Rates of retinal nerve fiber layer thinning in glaucoma suspect eyes. *Ophthalmology*. 2014; 121(7):1350–1358. [PubMed: 24629619]
41. Wang DL, Raza AS, de Moraes CG, et al. Central Glaucomatous Damage of the Macula Can Be Overlooked by Conventional OCT Retinal Nerve Fiber Layer Thickness Analyses. *Transl Vis Sci Technol*. 2015; 4(6):4.
42. Mwanza J-C, Chang RT, Budenz DL, et al. Reproducibility of Peripapillary Retinal Nerve Fiber Layer Thickness and Optic Nerve Head Parameters Measured with Cirrus HDOCT in Glaucomatous Eyes. *Invest Ophthalmol Vis Sci*. 2010; 51(11):5724–5730. [PubMed: 20574014]
43. Mwanza J-C, Kim HY, Budenz DL, et al. Residual and Dynamic Range of Retinal Nerve Fiber Layer Thickness in Glaucoma: Comparison of Three OCT PlatformsRNFL Residual and Dynamic Range in Glaucoma. *Invest Ophthalmol Vis Sci*. 2015; 56(11):6344–6351. [PubMed: 26436887]
44. Chan CK, Miller NR. Peripapillary nerve fiber layer thickness measured by optical coherence tomography in patients with no light perception from long-standing nonglaucomatous optic neuropathies. *J Neuroophthalmol*. 2007; 27(3):176–179. [PubMed: 17895816]
45. Sihota R, Sony P, Gupta V, Dada T, Singh R. Diagnostic capability of optical coherence tomography in evaluating the degree of glaucomatous retinal nerve fiber damage. *Invest Ophthalmol Vis Sci*. 2006; 47(5):2006–2010. [PubMed: 16639009]
46. Gardiner SK, Demirel S, Goren D, Mansberger SL, Swanson WH. The Effect of Stimulus Size on the Reliable Stimulus Range of Perimetry. *Transl Vis Sci Technol*. 2015; 4(2):10.
47. Wall M, Woodward KR, Doyle CK, Zamba GJ. The Effective Dynamic Ranges of Standard Automated Perimetry Sizes III and V and Motion and Matrix Perimetry. *Arch Ophthalmol*. 2010; 128(5):570–576. [PubMed: 20457977]

Figure 1.

For each location in the 24-2 visual field, the difference in the rate of functional change (in decibels per year) that is associated with a 1 micron per year difference in the rate of structural change in the corresponding sector, in eyes with early or suspected glaucoma. Presented in right eye orientation. Left column: functional change based on reported sensitivities. Right column: functional change after censoring sensitivities 15dB to equal 15dB. Top row: the predicted relation. Middle and Bottom rows: the upper and lower limits

of the 95% confidence interval for this prediction. Values below 0.1 appear in blue; values above 0.2 appear in red.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 2.

The relations between the rate of functional change (in decibels per year) and the rate of structural change in the corresponding sector (in microns per year) in glaucoma patients, at two different visual field locations.

The Passing-Bablok regression line is shown in each case.

Table 1

Summary of the cohort used, in a study showing how the localized rate of retinal nerve fiber layer thinning is related to the rate of localized functional loss.

	Mean	Standard Deviation	Range
Series length (y)	4.0	0.6	3.0 to 5.1
Age at end of series (y)	70.1	12.0	42 to 90
Most recent MD (dB)	-1.22	3.40	-22.5 to +2.9
Rate of change of MD (dB/y)	-0.15	0.33	-2.0 to +0.9
Most recent RNFLT (μm)	84.3	3.40	34 to 125
Rate of change of RNFLT ($\mu\text{m}/\text{y}$)	-0.77	0.33	-12.6 to +2.6

MD = Mean Deviation (from automated perimetry). RNFLT = global average Retinal Nerve Fiber Layer Thickness (from optical coherence tomography). Rates of change were calculated by linear regression over the 8 most recent reliable tests for an eye. Data for series length and age are summarized per participant having at least one eye that met the inclusion criteria; data for MD and RNFLT are summarized per eligible eye.