Published in final edited form as:

Optom Vis Sci. 2013 December ; 90(12): 1353–1360. doi:10.1097/OPX.000000000000078.

Correlating Perimetric Indices with Three Nerve Fiber Layer Thickness Measures

Deborah Goren, PhD, Shaban Demirel, BScOptom, PhD, FAAO, Brad Fortune, OD, PhD, FAAO, and Stuart K. Gardiner, PhD

Devers Eye Institute, Legacy Research Institute, Portland, Oregon

Abstract

Purpose—To determine which of three estimates of retinal nerve fiber layer thickness (RNFLT) correlate best with visual field sensitivity measured using standard automated perimetry (SAP).

Methods—Data were collected from 400 eyes of 209 participants enrolled in the Portland Progression Project. These individuals ranged from high-risk suspects to having non-end-stage glaucoma. In each eye, three measures of average RNFLT (spectral domain optical coherence tomography [SDOCT], scanning laser polarimetry [SLP], confocal scanning laser tomography [CSLT]) and SAP (Humphrey HFAII) were performed on the same day. Mean Deviation (MD), Mean sensitivity (MS), and Pattern standard deviation (PSD) were linearized using the equations $MD_{Lin}=10^{(MD*0.1)}$, $MS_{Lin}=10^{(MS*0.1)}$ and $PSD_{Lin}=10^{(PSD*-0.1)}$. Correlations between each of the estimates of RNFLT and each of the functional metrics were calculated (nine total). Pearson correlations and Generalized estimating equations (GEE) were used to calculate the strength and significance of the correlations.

Results—Linearized MS had the strongest correlation with SDOCT ($r=0.57$), intermediate with SLP ($r=0.40$) and weakest with CSLT ($r=0.13$). When multiple RNFLT measures were included in a GEE model to predict MS_{Lin} , SDOCT was consistently predictive ($p<0.001$) whereas CSLT was never predictive in these multivariate models. Similar findings were observed for MD_{Lin} and PSD_{Lin} .

Conclusions—Average RNFLT estimated from SDOCT predicts SAP status significantly better than average RNFLT estimated from SLP or CSLT.

Keywords

structure-function relation; glaucoma; retinal nerve fiber layer thickness; standard automated perimetry; spectral-domain optical coherence tomography; scanning laser polarimetry; confocal scanning laser tomography

There are currently several functional and structural assessments used clinically to assist with the diagnosis and management of patients with glaucoma. However, none of these tests have sufficiently good diagnostic performance (sensitivity and specificity) to be relied upon in isolation. Identifying structural features that change concurrently with functional measures could indicate a causal relationship, shedding light on the pathophysiological processes leading to vision loss. Moreover, relating structural and functional findings in eyes

Corresponding author: Deborah Goren, Devers Eye Institute, Legacy Research Institute, 1225 NE 2nd Ave, Portland, OR 97232, dgoren@deverseye.org.

Potential conflict of Interest: A GDxPRO device was loaned to the Portland Progression Project (Author BF).

Parts of this work were presented at the May 2012 meeting of The Association for Research in Vision and Ophthalmology (ARVO).

that are developing, or that have developed glaucoma, provides an opportunity to improve our understanding of this disease. This in turn may lead to the development of better diagnostic tools and better methods for monitoring change over time. It may also allow structural measures that have fewer drawbacks than perimetry (e.g. better repeatability^{1, 2}, shorter test times, better patient acceptance³) to be used as surrogates for function.

One additional benefit to understanding structure-function relationships is that differences in the strength of correlation between function and structural tests that all purport to measure the same anatomical feature can be used to make conclusions about the relative ‘noisiness’ of the different structural tests. An improvement in correlation strength brought about by using a different structural test or a better model of the structure-function relation (i.e. exponential vs linear) would imply that variability has been reduced. Even with these enhancements, the correlation between structure and function will almost certainly never reach 1.0 due to factors such as inter-subject variability and temporal disconnects between structural and functional change.

Functional deficits are related to decreases in the density of retinal ganglion cells and a corresponding thinning of the retinal nerve fiber layer (RNFL) in experimental models of glaucoma.⁴ Even though both structural and functional measures describe important aspects of the glaucomatous disease process, and they should certainly be related, some patients display seemingly conflicting results: loss in one, and no loss in the other. One reason for discrepancies between structure and function is variability both between and within patients.⁵ A second reason is the reliance of different structural measures on distinct theoretical underpinnings. This results in different definitions of the term RNFL, each referring to the presence, or estimated integrity, of different underlying structures. A third reason is that functional testing (such as SAP) typically only assesses a small portion of the retina, in particular the central 25 to 30°. In contrast, most structural measures assess the entire optic nerve head (ONH) or the vast majority of the axons within the RNFL. As a result, there are portions of the ONH and peripapillary RNFL that are not represented within the most commonly used visual field patterns.

Three techniques are commonly used in clinical practice to obtain objective measurements of the ‘thickness’ of the peripapillary RNFL. Of these, only one directly measures RNFLT: optical coherence tomography (OCT) measures the distance between the vitreoretinal boundary at the inner limiting membrane (ILM) and the anterior border of the retinal ganglion cell layer (RGCL).⁶ Scanning laser polarimetry (SLP) measures the relative phase retardance of a scanning laser beam as its polarization state is varied over 360 deg at each double pass traverse through the tissue.⁷ Normal retardance of the RNFL is known to be dependent on the integrity of the axonal cytoskeleton.^{8, 9} The retardance measurement is then typically converted to RNFLT by assuming a linear relation between them.^{7, 10} Confocal scanning laser tomography (CSLT) calculates the average height of the peripapillary retinal surface around the disc margin relative to a reference plane and uses this as its measure of RNFLT. The indirect measures of RNFLT produced by SLP and CSLT do not preclude their ability to provide an important structural measure that correlates with function. For the sake of simplicity, all three estimates (from spectral domain [SD] OCT, SLP and CSLT) will be referred to as ‘RNFLT’ for the remainder of this manuscript.

The literature contains studies that employ a range of techniques to analyze structure-function relations. This has resulted in many structure-function relations that are difficult to compare due to differences in study design. In order to determine the strongest structure-function relation among several techniques, it is necessary to study the same cohort, preferably acquiring multiple structural and/or functional measures on the same day. One such study by Bowd et al (2006)¹¹ assessed the relation between SAP and three measures of

RNFLT (SLP, time domain [TD] OCT and CSLT as measured by GDxVCC, Stratus OCT, and HRT II respectively). SAP hemifield sensitivity was better correlated with the corresponding sectors of the peripapillary RNFLT measured with TDOCT than with SLP or CSLT. This was true both when assuming linear or logarithmic relations between RNFLT and visual function. A secondary analysis of global RNFLT versus mean visual field sensitivity found that TDOCT produced the strongest association and CSLT the weakest.

Since the Bowd et al study was performed, newer forms of OCT and SLP have become available. SDOCT has greater axial resolution and faster scanning times (with potentially less eye movement artifact) than TDOCT. For SLP, the introduction of enhanced corneal compensation (GDx ECC) has reduced the number of patients who manifest an atypical retardation pattern, which were difficult to interpret when using variable corneal compensation (GDx VCC).¹² Since these advancements have been made, no studies have compared correlations of these three structural measures to visual function. The current study was designed to determine which of three estimates of RNFLT (SDOCT, SLP and CSLT) correlated best with SAP in a cohort of participants who were either high-risk ocular hypertensives or who had non-endstage glaucoma.

METHODS

Participants

Data from 400 eyes of 209 qualifying participants from the Portland Progression Project (P3)^{13, 14} were analyzed as part of the current study. All protocols utilized in the P3 study were approved by the Legacy Health Institutional Review Board and adhere to the tenets of the declaration of Helsinki. Prior to commencing the study, protocols were explained to participants, including the risks and benefits of participating, and informed consent was obtained. Participants had high-risk ocular hypertension or a diagnosis of glaucoma (early to moderate) as determined by their ophthalmic physician and were required to have no other ocular pathologies likely to affect the visual field. Their age ranged between 38 and 91 years (mean: 65.7±11 years) and average MD for the included visits was −0.31dB (sd: 2.87dB, range: −16.20 to 3.27dB).

All data for each eye was collected on the same day. The data were analyzed cross-sectionally and the most recent visit for each eye on which all data was available was used to maximize the range of disease severities and more widely span the glaucomatous continuum. SDOCT and SLP scans were excluded if they had inadequate quality scores (SDOCT ≤ 15 , SLP < 8). In the case of participants with excluded scans, the next most recent date on which quality data was available for all four measures was chosen. In some cases this resulted in different dates being used for the two eyes of an individual but for each eye all of the data was collected on the same day.

Retinal Nerve Fiber Layer Thickness

Three techniques (CSLT, SDOCT and SLP) were used to measure the global average RNFLT for each eye.

At each session, several 10° scans were performed using CSLT as implemented by HRT (HRT Classic; Software version: 1.2.10.0; Heidelberg Engineering, Inc., Heidelberg, Germany). A mean topography was computed from three scans of sufficient quality based on fixation stability, even illumination and image alignment.¹⁵ HRT stereometric parameters in the current study were based on a 320µm reference plane, measured from the machine defined reference ring.¹⁶

The SDOCT measure of peripapillary RNFLT was based on a circular B-scan with a 6° radius containing 1536 A-scans (Spectralis, Software version: 5.1; Heidelberg Engineering, Inc.). Experienced operators refined all of the automated RNFL boundary segmentations produced by the device. RNFL segmentations were corrected wherever an obvious error had occurred (e.g. refractile element in the vitreous instead of the intended ILM). Segmentation editing was performed without knowledge or regard for the particulars of this (or any) study goal, thereby minimizing potential bias arising from this data quality assurance procedure.

Enhanced corneal compensation (ECC) SLP scanning was performed in the peripapillary region using a GDxPRO device (Software version: 1.1.0.10; Carl Zeiss Meditec, Inc., Dublin, CA). Average RNFLT was automatically calculated by the SLP instrument for an annular region from 8.5–11.0° diameter in an emmetropic eye. Auto focus was used and the average of three scans was calculated. The GDxPRO calculates RNFLT at any given location by multiplying retardance at the location by 1.67.^{7, 10} Although the metric captured by the device is retardance, multiplying all retardance values by 1.67 will not affect the correlation between SLP derived measures of RNFLT and visual function.

For both SDOCT and SLP scans, no attempt was made to remove the contribution of blood vessels to the peripapillary RNFLT, consistent with the manner in which these data are used in the clinical setting.¹⁷

Function

SAP was performed using the 24-2 test pattern and the SITA-standard threshold algorithm¹⁸ (Humphrey Field Analyzer II, Carl Zeiss Meditec, Dublin, CA). Unweighted global indices MD and PSD were calculated using published formulae in reference to a previously published normative dataset.¹⁹ Mean Sensitivity (MS) was calculated as the unweighted mean sensitivity from the 52 non-blindspot locations (i.e. excluding locations 15° temporal, 3° superior/inferior).

Upon initial inspection, plots of both OCT and SLP RNFLT against SAP suggested non-linear associations, as has also been reported by others.^{20, 21} This is perhaps not surprising since SAP is measured in log units (dB) and RNFLT is measured in linear units (μm). Therefore, SAP units were linearized²⁰ as follows: $MS_{Lin} = 10^{MS*0.1}$, $MD_{Lin} = 10^{MD*0.1}$, and $PSD_{Lin} = 10^{PSD*(-0.1)}$.

Analysis

For each of the linearized functional metrics, the univariate relation with each RNFLT measure was examined. Deming regression (DR), which acknowledges the existence of measurement error in both variables, was performed to determine the predictive association between each functional and each structural measure. DR requires an estimate of the ratio of error variance for the two variables being compared. Each variable's error variance was estimated by calculating the standard deviation of the difference between the visit used in the correlation analysis and the preceding visit, only if such a visit had occurred within the previous nine months. Although progression may have affected these error estimates, this should affect all metrics roughly equally, with minimal influence on the ratio of error variances. To assess the robustness of the method, Deming regression was repeated with variance ratios (VR) that were double and half the ratio estimated from the data. Doubling or halving the VRs estimated from the data did not affect the outcomes in any meaningful way (data not shown).

Pearson correlation coefficients (r) were calculated and used as a measure of the strength of association in the univariate analyses described above. Generalized estimating equations (GEE) were used to determine the significance of the associations, accounting for inter-eye

correlations within subjects.²² Note that results from Deming regression do not affect the Pearson correlation coefficients reported. Multivariate GEE models were also built to determine the significance of the relations between each functional measure and combinations of structural measures (e.g. OCT & SLP; OCT & SLP & CSLT etc).

Two methods were used to compare correlation strengths of the three structure-function relations. The first, Steiger's Z test, is a significance test which allows for comparisons between non-independent data²³. The second, bootstrapping, was performed 500 times (with replacement) to calculate 95% confidence intervals, assuming a normal distribution, about the correlation coefficients.

RESULTS

As seen in Figure 1, MS_{Lin} was most strongly correlated with RNFLT as determined by SDOCT (Pearson correlation $r=0.57$). The correlation with SLP was of intermediate strength ($r=0.40$) and the weakest correlation was found with CSLT ($r=0.13$). These correlations were significantly different from each other according to Steiger's Z test ($p<0.001$) and showed almost no overlap in bootstrapped estimates of confidence intervals (Table 1, column 1). However, all of these correlations were statistically significant in univariate analyses (GEE $p<0.01$). Using multivariate GEE models that included all three measures of RNFLT to predict MS_{Lin} , only SDOCT was a significant predictor ($p<0.001$). CSLT was not significant in models that included all three RNFLT measurements ($p=0.50$), or bivariate models when included with SDOCT ($p=0.51$) or SLP ($p=0.22$). When SDOCT and SLP RNFLT measures were used as predictors, only SDOCT was a significant predictor (SDOCT $p<0.001$, SLP $p=0.89$).

Figure 1A shows the relation between SDOCT RNFLT and linearized SAP MS that predicts a residual RNFL thickness of $35.2\mu m$ when $MS_{Lin}=1$, which is equivalent to $MS=0dB$ (perimetrically blind).

It has been suggested that taking the simple arithmetic mean of decibel values does not give the best estimate of the 'average' functional status across the visual field due to the effects of log transformations.²⁴ In particular, the difference between these two methods of generating a mean sensitivity estimate is most apparent when damage within the visual field is very localized. The two methods become identical when damage within the visual field is totally diffuse. To accommodate these concerns, a second MS measure was calculated by taking the average of anti-logged values ($10^{0.1*dB}$), before converting them back onto a decibel scale.^{24, 25} This new index, MS^* , differed on average from the arithmetic mean of dB values (MS) by $-1.02\pm 1.42dB$. Correlations between MS^* (expressed on a linear scale) and the three RNFLT estimates followed the same pattern as for MS_{Lin} ($r_{SDOCT}=0.52$, $r_{SLP}=0.37$, $r_{CSLT}=0.11$). Given the similarity of the structure-function correlations obtained, regardless of which method was used to calculate mean sensitivity (MS or MS^*), the simpler arithmetic mean (MS_{Lin}) was used.

As seen in Figure 2, MD_{Lin} showed similar patterns of correlation with RNFLT as MS_{Lin} . MD_{Lin} was most strongly correlated with SDOCT, moderately correlated with SLP and most weakly correlated with CSLT ($r=0.57$, 0.41 & 0.18 respectively). All three associations were still statistically significant in univariate analyses ($p<0.01$) but were significantly different from each other (Steiger's Z, $p<0.001$). A comparison of bootstrapped confidence intervals for the correlation coefficients showed very minimal overlap (Table 1, column 2). As with MS_{Lin} , when all three RNFLT measures were used in a trivariate model to predict MD_{Lin} only SDOCT was a significant predictor ($p<0.001$). In models that included only two of the RNFLT measures, CSLT was never significant (with SDOCT $p=0.86$, with SLP $p=0.35$).

When SDOCT and SLP were used to model MD_{Lin} , only SDOCT was a significant predictor (SDOCT $p<0.001$; SLP $p=0.61$).

The association between PSD_{Lin} and structure demonstrated the same pattern as MS_{Lin} and MD_{Lin} . PSD_{Lin} was most strongly correlated with SDOCT ($r=0.62$), had intermediate correlation with SLP ($r=0.44$) and correlated most weakly with CSLT ($r=0.19$). Similar to the case with MS_{Lin} and MD_{Lin} , in multivariate models SDOCT was always a significant predictor of PSD_{Lin} , whereas CSLT never was. Correlation coefficients between RNFLT estimates and PSD_{Lin} were all significantly different from each other ($p<0.001$) and showed almost no overlap in bootstrapped confidence intervals (Table 1, column 3).

As seen in Figure 3, SDOCT and SLP RNFLT measurements were highly correlated with each other ($r=0.67$). CSLT was weakly correlated with both SDOCT ($r=0.22$) and SLP ($r=0.27$). Due to the different assumptions, methods and algorithms used by the three devices to estimate RNFLT, their means and distributions are also quite different. Based on the current analyses, there is no clear association between MS_{Lin} (dark vs. light symbols, Fig 3) and the strength of the correlation between estimates of RNFLT. However, more recent, unpublished analyses from our lab show disease-stage dependent correlation strengths.²⁶

It has been suggested that HRT was not designed primarily to measure RNFLT and it is therefore unfair to compare HRT derived estimates of RNFLT to those produced by SDOCT.¹¹ In order to address these concerns, we analyzed correlations between the three functional measures used in this study and two other HRT parameters that have been shown to be informative: rim area (RA) and cup volume (CV). RA correlated poorly with MS_{Lin} ($r=0.20$), MD_{Lin} ($r=0.24$) and PSD_{Lin} ($r=0.30$) and was not a significant predictor for any when included in trivariate models with RNFLT as measured by SDOCT and SLP ($p_{MS_{Lin}}=0.19$; $p_{MD_{Lin}}=0.09$; $p_{PSD_{Lin}}=0.74$). CV also correlated poorly with MS_{Lin} ($r=-0.11$), MD_{Lin} ($r=-0.21$) and PSD_{Lin} ($r=-0.28$). It was not a significant predictor for MS_{Lin} or MD_{Lin} ($p_{MS_{Lin}}=0.68$; $p_{MD_{Lin}}=0.48$) when included in trivariate models with RNFLT as measured by SDOCT and SLP, but was a significant predictor of PSD_{Lin} ($p=0.01$).

DISCUSSION

RNFLT as estimated by SDOCT was most strongly associated with function as estimated by SAP. This was true for all three of the SAP metrics examined. Similar to the current study, Bowd et al found global mean sensitivity correlated best with RNFLT as estimated by TDOCT ($R^2_{Linear}:0.23$; $R^2_{Log}:0.25$), worst with RNFLT as estimated by CSLT ($R^2_{Linear}:0.11$; $R^2_{Log}:0.11$) and intermediate with RNFLT as estimated by SLP ($R^2_{Linear}:0.14$; $R^2_{Log}:0.14$). The current study used r as a metric of correlation, whereas Bowd used R^2 . If the statistical metrics used in the two studies are equated, R^2 values of 0.32 for SDOCT, 0.16 for SLP and 0.02 for CSLT are found for the current study. SLP provided similar correlation values in the two studies, whereas CSLT correlated more weakly and SDOCT correlated more strongly with SAP in the current study. Similar to the findings of Bowd et al,¹¹ both RA and CV were found to be poor predictors of function.

SDOCT, SLP and CSLT all produce an estimate of RNFLT but with distinctly different methodologies that result in substantially different thickness estimates. Based on the results of the current study, the mean distance between the vitreoretinal boundary at the ILM and the anterior boundary of the RGCL at the location of the peripapillary ONH circle scan (6° radius) is most closely associated with visual function as measured by visual field global indices at a given point in time. The average distance between the vitreoretinal boundary and the reference plane used by CSLT has the weakest association with visual function. Additionally, a SAP sensitivity of 0dB is predicted when RNFLT reaches approximately

35 μ m as measured with SDOCT. This falls within the expected range of residual RNFLT observed in eyes with extensive perimetric damage when evaluated with SDOCT (35 μ m–45.4 μ m).^{27–29}

According to Huang et al.,⁸ variation in the association between retardance and RNFLT is seen in normal individuals. These authors also suggest that glaucomatous changes may be apparent with SLP before RNFL thickness changes are manifest in OCT scans.⁸ The implication of this finding is that microtubule or other cytoskeletal disorganization (which affects measures made by SLP) does not occur at the same time as axonal degradation and RNFL thinning (which affects measures made by SDOCT) and therefore, the two techniques are measuring different characteristics of the RNFL. Studies by Fortune et al have shown that optic nerve injury by surgical transection³⁰ or experimental glaucoma^{31, 32} resulted in decreases in SLP-measured retardance prior to changes in OCT-measured RNFLT, implying that axonal cytoskeletal changes can exist without concurrent changes to RNFL thickness. The stronger correlations seen in the current study between SDOCT and SAP may reflect the temporal disconnect between changes identified by SLP and SAP. Namely, changes in microtubules may not immediately result in altered vision as assessed by standard perimetry. Microtubule breakdown is also likely to negatively impact axonal active transport, which may or may not manifest as loss of visual function measured by SAP. In contrast, a decrease in OCT-measured RNFLT reflects retinal ganglion cell axonal loss and/or bulk axonal bundle thinning. Any loss of axonal connectivity from the eye to its central projections (e.g. geniculate nucleus) would be expected to result in a loss of visual function.

Due to the cross-sectional nature of the current study, it is impossible to conclude that the differences in correlation strength between SDOCT or SLP and function are due to one process (e.g. microtubule disorganization/axonal degradation) occurring before another. Future analyses of the longitudinal data generated by this ongoing study may reveal more about temporal sequences of changes in these various structural measures and their association with changes in visual function as have already been demonstrated in experimental models.^{30, 31}

RNFLT measurements are not typically age corrected. Similarly, MS is not referenced to age expected normal function and is simply a ‘raw’ assessment of average functional performance. MD and PSD, in contrast, are age referenced. Therefore, perhaps the fairest comparison between structure and function is via MS_{Lin}. The current study showed similar correlations between structure and each functional metric. Although non-age corrected visual field metrics remove the need for any assumptions about how visual function changes with age, both in terms of rate and mode of change (linear or accelerating), age-corrected indices produce similar results.

A potential concern with the use of any global index is that localized field loss can be missed. Regional analyses are underway to assess the correlations between specific regions within the RNFL and locations within the visual field.

It is likely that factors such as connective tissue changes (known to occur in glaucomatous optic neuropathy) and the ambient level of intraocular pressure will influence optic disc topography to a greater extent than they affect RNFLT. Therefore, the CSLT estimate of RNFLT is more likely to be affected by these factors since it is defined at the optic disc margin. Ambient intraocular pressure has been shown to affect ONH architecture^{33–35} but to only influence RNFLT close to the ONH margin³⁶ (such as the measurement produced by CSLT³⁵). Unlike CSLT, RNFLT measures taken further from the ONH, such as peripapillary RNFLT measures made between 4.3° and 6° from the ONH center (the most common loci for clinical assessment, as used by SDOCT and SLP), are not noticeably

influenced by ambient IOP. Therefore, ambient IOP likely confounds the structure-function association for CSLT to a greater extent than for SDOCT or SLP.^{34, 36, 37} Similarly, evidence from non-human primate experimental glaucoma suggests that deeper ONH (e.g. laminar cribrosa) and peripapillary connective tissue deformation can occur – with substantial influence on optic disc topography (surface height) as measured by CSLT – prior to any change in SDOCT measured change in RNFLT. Such ONH deformation without axon loss would be likely to influence CSLT estimates of RNFLT more than SDOCT or SLP estimates of RNFLT.^{31, 37}

An important methodological difference that exists between SDOCT and SLP is the diameter of the SDOCT scanning circle versus the default location of the annulus assessed in SLP, and therefore the exact region of the peripapillary RNFL that is assessed. The default annulus for SLP assessment is slightly closer to the ONH than the peripapillary circle scan acquired by SDOCT. Though it is possible that this difference could impact the results of this study, it should only be a small effect and it is difficult to predict which technique, if any, would be ‘favoured’. In addition, in order to maintain consistency with the outputs available to clinicians, all three average RNFLT measures were calculated without trying to account for the fact that the 24-2 test pattern of the Humphrey Visual Field Analyzer only assesses a small portion of all axons that enter the ONH. Similar to the difference in scan position discussed above, it is unlikely that use of unweighted average RNFLT values would favour any of the three imaging techniques in our analysis.

Hood et al⁵ attempted to explain the sources of variability in the structure-function relation by examining within and between subject variability. Measuring within-subject variability by taking repeated measurements over a short period of time demonstrated that test-retest RNFLT variability when using OCT was unaffected by the severity of glaucomatous damage. In contrast, SAP test-retest variability depended on the severity of damage, similar to previous studies.^{1, 38} Even though within-subject variability complicates the association between structure and function, most of the variability is due to between-subject differences (in normals OCT: 87%, SAP: 71%).⁵ Longitudinal analyses may provide a partial solution to this problem by providing individually normalized measures of change for each metric while eliminating the influence of between subject variability. Data collection to enable this analysis is currently underway in the Portland Progression Project.

Acquisition and analysis software is constantly evolving and it will likely continue to do so for the foreseeable future, despite the relative maturity of each of the imaging modalities evaluated in this study. For example, it is likely that in the very near future, commercial OCT instruments will combine Doppler methods like those used to create non-invasive angiograms with other retinal layer segmentations to account for the blood vessel components within a given layer of interest. This should improve both accuracy and precision of layer thicknesses and volumes for clinical decisions based on OCT. It might also further improve the correlation between RNFLT measured by OCT and visual sensitivity measured by SAP. In contrast, the SLP instrument “bridges” the otherwise minimal phase retardance produced by blood vessels⁸ in order to produce an uninterrupted peripapillary (“TSNIT”) profile. It is unclear whether this data processing step would significantly alter the relationship between SAP sensitivity and SLP-derived RNFLT or whether the default analysis (bridging vessels) will change. Thus it is possible, but unlikely, that future iterations of similar structure-function comparisons will produce findings that are fundamentally different than the conclusions drawn here.

In summary, in a group of eyes with high-risk ocular hypertension or non-endstage glaucoma, SDOCT estimates of RNFLT correlate more strongly with SAP functional measures than two other commonly available measures of RNFLT. The ability of the three

imaging devices to reliably predict functional progression was not addressed by this study and is still unknown. However, when SDOCT RNFLT is available on a cross-sectional basis, the addition of SLP and CSLT estimates of RNFLT does not significantly improve the ability to predict functional status.

Acknowledgments

This project was funded by NEI EY19674 (SD) and The Legacy Good Samaritan Foundation. The funding organizations had no role in the design or conduct of this research. SD was involved in a clinical trial using the Spectralis OCT.

REFERENCES

1. Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophthalmol.* 1989; 108:130–135. [PubMed: 2757094]
2. Heijl A, Lindgren G, Olsson J. Normal variability of static perimetric threshold values across the central visual field. *Arch Ophthalmol.* 1987; 105:1544–1549. [PubMed: 3675288]
3. Gardiner SK, Demirel S. Assessment of patient opinions of different clinical tests used in the management of glaucoma. *Ophthalmology.* 2008; 115:2127–2131. [PubMed: 19041473]
4. Harwerth RS, Charles F. Prentice Award Lecture 2006: a neuron doctrine for glaucoma. *Optom Vis Sci.* 2008; 85:436–444. [PubMed: 18521013]
5. 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; 50:4254–4266. [PubMed: 19443710]
6. Townsend KA, Wollstein G, Schuman JS. Imaging of the retinal nerve fibre layer for glaucoma. *Br J Ophthalmol.* 2009; 93:139–143. [PubMed: 19028735]
7. Weinreb RN, Dreher AW, Coleman A, Quigley H, Shaw B, Reiter K. Histopathologic validation of Fourier-ellipsometry measurements of retinal nerve fiber layer thickness. *Arch Ophthalmol.* 1990; 108:557–560. [PubMed: 2322159]
8. Huang XR, Bagga H, Greenfield DS, Knighton RW. Variation of peripapillary retinal nerve fiber layer birefringence in normal human subjects. *Invest Ophthalmol Vis Sci.* 2004; 45:3073–3080. [PubMed: 15326123]
9. Huang XR, Knighton RW. Microtubules contribute to the birefringence of the retinal nerve fiber layer. *Invest Ophthalmol Vis Sci.* 2005; 46:4588–4593. [PubMed: 16303953]
10. Carl Zeiss Meditech I. Chapter 2: Principles of Scanning Laser Polarimetry. 2013 Available at: [http://www.smt.zeiss.com/C125679E00525939/EmbedTitelIntern/GDxPrimerChapter2/\\$File/GDx_Primer_Chapter2.pdf](http://www.smt.zeiss.com/C125679E00525939/EmbedTitelIntern/GDxPrimerChapter2/$File/GDx_Primer_Chapter2.pdf).
11. Bowd C, Zangwill LM, Medeiros FA, Tavares IM, Hoffmann EM, Bourne RR, Sample PA, Weinreb RN. Structure-function relationships using confocal scanning laser ophthalmoscopy, optical coherence tomography, and scanning laser polarimetry. *Invest Ophthalmol Vis Sci.* 2006; 47:2889–2895. [PubMed: 16799030]
12. Reus NJ, Zhou Q, Lemij HG. Enhanced imaging algorithm for scanning laser polarimetry with variable corneal compensation. *Invest Ophthalmol Vis Sci.* 2006; 47:3870–3877. [PubMed: 16936099]
13. Gardiner SK, Johnson CA, Demirel S. Cup size predicts subsequent functional change in early glaucoma. *Optom Vis Sci.* 2011; 88:1470–1476. [PubMed: 21912304]
14. Spry PG, Johnson CA, Mansberger SL, Cioffi GA. Psychophysical investigation of ganglion cell loss in early glaucoma. *J Glaucoma.* 2005; 14:11–19. [PubMed: 15650598]
15. Chauhan BC, Hutchison DM, Artes PH, Caprioli J, Jonas JB, LeBlanc RP, Nicolela MT. Optic disc progression in glaucoma: comparison of confocal scanning laser tomography to optic disc photographs in a prospective study. *Invest Ophthalmol Vis Sci.* 2009; 50:1682–1691. [PubMed: 19060290]

16. Asaoka R, Strouthidis NG, Kappou V, Gardiner SK, Garway-Heath DF. HRT-3 Moorfields reference plane: effect on rim area repeatability and identification of progression. *Br J Ophthalmol*. 2009; 93:1510–1513. [PubMed: 19535359]
17. Hood DC, Fortune B, Arthur SN, Xing D, Salant JA, Ritch R, Liebmann JM. Blood vessel contributions to retinal nerve fiber layer thickness profiles measured with optical coherence tomography. *J Glaucoma*. 2008; 17:519–528. [PubMed: 18854727]
18. Bengtsson B, Heijl A, Olsson J. Evaluation of a new threshold visual field strategy, SITA, in normal subjects. Swedish Interactive Thresholding Algorithm. *Acta Ophthalmol Scand*. 1998; 76:165–169. [PubMed: 9591946]
19. Johnson CA, Sample PA, Cioffi GA, Liebmann JR, Weinreb RN. Structure and function evaluation (SAFE): I. criteria for glaucomatous visual field loss using standard automated perimetry (SAP) and short wavelength automated perimetry (SWAP). *Am J Ophthalmol*. 2002; 134:177–185. [PubMed: 12140023]
20. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007; 26:688–710. [PubMed: 17889587]
21. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. *Prog Retin Eye Res*. 2010; 29:249–271. [PubMed: 20226873]
22. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986; 42:121–130. [PubMed: 3719049]
23. Davies RB. Hypothesis testing when a nuisance parameter is present only under the alter-native. *Biometrika*. 1987; 74:33–43.
24. Hood DC, Greenstein VC, Odel JG, Zhang X, Ritch R, Liebmann JM, Hong JE, Chen CS, Thienprasiddhi P. Visual field defects and multifocal visual evoked potentials: evidence of a linear relationship. *Arch Ophthalmol*. 2002; 120:1672–1681. [PubMed: 12470141]
25. Gardiner SK, Demirel S, Johnson CA, Swanson WH. Assessment of linear-scale indices for perimetry in terms of progression in early glaucoma. *Vision Res*. 2011; 51:1801–1810. [PubMed: 21704057]
26. Marin-Franch I, Malik R, Crabb DP, Swanson WH. Choice of statistical method influences apparent association between structure and function in glaucoma. *Invest Ophthalmol Vis Sci*. 2013; 54:4189–4196. [PubMed: 23640041]
27. 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; 47:2006–2010. [PubMed: 16639009]
28. Hood DC. Relating retinal nerve fiber thickness to behavioral sensitivity in patients with glaucoma: application of a linear model. *J Opt Soc Am (A)*. 2007; 24:1426–1430.
29. 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; 27:176–179. [PubMed: 17895816]
30. Fortune B, Cull GA, Burgoyne CF. Relative course of retinal nerve fiber layer birefringence and thickness and retinal function changes after optic nerve transection. *Invest Ophthalmol Vis Sci*. 2008; 49:4444–4452. [PubMed: 18566463]
31. Fortune B, Burgoyne CF, Cull GA, Reynaud J, Wang L. Structural and functional abnormalities of retinal ganglion cells measured in vivo at the onset of optic nerve head surface change in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2012; 53:3939–3950. [PubMed: 22589428]
32. Fortune B, Burgoyne CF, Cull G, Reynaud J, Wang L. Onset and progression of peripapillary retinal nerve fiber layer (RNFL) retardance changes occur earlier than RNFL thickness changes in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2013; 54 epub ahead of print:
33. Agoumi Y, Sharpe GP, Hutchison DM, Nicolela MT, Artes PH, Chauhan BC. Laminar and prelaminar tissue displacement during intraocular pressure elevation in glaucoma patients and healthy controls. *Ophthalmology*. 2011; 118:52–59. [PubMed: 20656352]
34. Strouthidis NG, Fortune B, Yang H, Sigal IA, Burgoyne CF. Effect of acute intraocular pressure elevation on the monkey optic nerve head as detected by spectral domain optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2011; 52:9431–9437. [PubMed: 22058335]

35. Heickell AG, Bellezza AJ, Thompson HW, Burgoyne CF. Optic disc surface compliance testing using confocal scanning laser tomography in the normal monkey eye. *J Glaucoma*. 2001; 10:369–382. [PubMed: 11711833]
36. Fortune B, Yang H, Strouthidis NG, Cull GA, Grimm JL, Downs JC, Burgoyne CF. The effect of acute intraocular pressure elevation on peripapillary retinal thickness, retinal nerve fiber layer thickness, and retardance. *Invest Ophthalmol Vis Sci*. 2009; 50:4719–4726. [PubMed: 19420342]
37. Strouthidis NG, Fortune B, Yang H, Sigal IA, Burgoyne CF. Longitudinal change detected by spectral domain optical coherence tomography in the optic nerve head and peripapillary retina in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2011; 52:1206–1219. [PubMed: 21217108]
38. Chauhan BC, Johnson CA. Test-retest variability of frequency-doubling perimetry and conventional perimetry in glaucoma patients and normal subjects. *Invest Ophthalmol Vis Sci*. 1999; 40:648–656. [PubMed: 10067968]

Figure 1.

Associations between MS_{Lin} and RNFLT as measured by three techniques (A, SDOCT; B, SLP; C, CSLT). Solid lines denote the relation as determined by Deming regression. Pearson correlation coefficients (r) are shown in the upper right corner of each plot.

Figure 2.

Associations between MD_{Lin} and RNFLT as measured by three techniques (A, SDOCT; B, SLP; C, CSLT). Solid lines denote the relation as determined by Deming regression. Pearson correlation coefficients (r) are shown in the upper right corner of each plot.

Figure 3.

Associations between different RNFLT measurements. Solid lines denote the relation as determined by Deming regression. Pearson correlation coefficients (r) are shown in the upper right corner of each plot. Perimetric performance is denoted by symbol shading. Light shading denotes higher MS_{Lin} values, whereas dark shading denotes lower MS_{Lin} values.

Table 1

Bootstrapped correlation coefficient ranges (95% confidence limits). Five hundred bootstrap iterations with replacement were performed.

RNFLT\SAP	MS_{Lin}	MD_{Lin}	PSD_{Lin}
SDOCT	0.49–0.64	0.49–0.64	0.54–0.69
SLP	0.31–0.50	0.32–0.51	0.34–0.54
CSLT	0.02–0.23	0.08–0.28	0.09–0.29