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The Effect of Test Variability on the Structure-Function Relation in Early Glaucoma

Stuart K Gardiner, PhD^{1,*}, Chris A Johnson, PhD², and Shaban Demirel, BScOptom, PhD¹

¹Discoveries In Sight Laboratories, Devers Eye Institute, Legacy Health, Portland, OR

²Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA

Abstract

Purpose—To determine whether the weakness of the structure-function relation could be produced by test variability alone, without implying underlying dissociation between the true rates of structural and functional change.

Methods—Perimetric Mean Deviation (MD), and Rim Area (RA) and Cup Volume (CV) from confocal scanning laser ophthalmoscopy, over six visits, were taken from 166 eyes of 92 participants with high risk ocular hypertension or suspected / early glaucoma in the Portland Progression Project. Models were created of each measure's variability. A further model predicted the rate of functional change from the rate of structural change. These were used to generate realistic simulated sequences of both functional and structural data with different standard deviations σ between the underlying rates of change. 'Observed' structure-function relations were calculated. An empirical p-value was derived, equaling the proportion of simulated series for which the 'observed' structure-function dissociation was greater than that seen in patient data.

Results—The correlation between the rates of structural (RA) and functional (MD) change was 0.171, consistent with $\sigma < 0.02$ dB/yr. Using CV, the correlation was -0.091 , consistent with $\sigma < 0.01$ dB/yr. By comparison, the models predicted that the standard deviation of the rate of functional change for a healthy eye due to test variability would be 0.18 dB/yr.

Conclusion—Test variability is sufficiently large that realistic patient data can be simulated without requiring a large variability between the underlying rates of structural and functional change. This absence of implied dissociation is a necessary condition for it to be valid to combine structural and functional measures to improve estimates of functional change and/or to reduce perimetric variability.

Keywords

Glaucoma; Perimetry; Confocal Scanning Laser Ophthalmoscopy; Structure-Function Relation; Simulation; Variability

Introduction

Variability of functional and structural testing is a critical barrier in the assessment and management of patients with Primary Open-Angle Glaucoma (POAG). Visual field testing is a cornerstone of glaucoma management and the clinical standard for detecting functional damage and progression. Standard Automated Perimetry (SAP) is currently the most commonly used functional test.[1, 2] However, results can sometimes vary substantially

*Corresponding author: Address: Stuart Gardiner, Devers Eye Institute, Legacy Health System, 1225 NE 2nd Ave, Portland, OR 97232, USA, sgardiner@deverseye.org, Tel: +1 503 413 5315, Fax: +1 503 413 5179.

from test to test. When perimetric contrast sensitivity is measured at a moderately damaged visual field location, the 95% confidence interval for retest covers the majority of the assumed effective dynamic range of the instrument.[3] Both the evaluation of a single visual field (to detect glaucomatous damage) and the evaluation of a series of visual fields (to detect progression) are hampered by this variability.

Recently, the Ocular Hypertension Treatment Study (OHTS) concluded: “Early medical treatment decreases the cumulative incidence of POAG. The absolute effect is greatest in high-risk individuals. Conversely, there is little absolute benefit of early treatment in individuals with ocular hypertension at low risk of developing POAG.”[4] Therefore, it is crucial that patients at the highest risk of developing visual disability should be identified as early in their disease course as possible, both for the benefit of the patient and to improve cost-effectiveness for the payer. Patients with more damaged visual fields are at higher risk of subsequent rapid progression.[5, 6] In eyes with early glaucoma, variability hinders the ability to distinguish true damage from response inconsistency / noise, making it difficult to identify patients at high risk of visual disability. As an example, when the true sensitivity is near normal at 30dB, the expected standard deviation of the frequency of seeing curve is 2.3dB.[7] Assuming a linear relation between structural and functional losses,[8, 9] a 41% reduction in the retinal ganglion cell count within the area under the stimulus would be required to produce a loss of sensitivity one standard deviation below the baseline value. The impact of variability on detection of glaucomatous progression is equally significant. It is important to identify rapidly progressing patients as early as possible, so that their clinical management can be tailored accordingly. Yet in more advanced glaucoma, variability is even greater, further hampering detection of change.[3, 7]

Ocular imaging techniques for measuring damage to the optic nerve head and retinal nerve fiber layer are improving. Their speed and relative objectivity make them attractive for clinical use, and patients find them more tolerable than functional testing.[10] However, they do not measure a patient’s visual function. In addition, while structural and functional measures are correlated, the correlation is relatively weak.[11–15] It has also been reported that the dynamic range (when defined as the number of ‘steps’ over which progression exceeding the test-retest variability can occur) may be smaller for structural testing than for perimetry.[16] These factors have led some to question whether it is feasible to use structural measures as a surrogate for function, and/or to combine structural and functional tests to reduce variability.[17, 18] If the underlying changes occurring in structure and function are proportional (on some scaling) and temporally coincident, then results from the two can be productively combined to improve detection and measurement of damage and of change. However, if there is a substantial discrepancy between structural and functional change, for example with damage to one modality occurring prior to damage evident using the other modality, then the benefits of combining the two would be reduced, and may even harm detection of damage and progression by introducing an additional source of variability.

The hypothesis tested in this study is that the observed weakness of the structure-function relation in ocular hypertension (OHT) and suspected / early glaucoma could be entirely accounted for by the variability inherent in clinical testing. This would imply that combining information from the two modalities might be able to help reduce the variability. We assess whether the variability would be sufficient to produce an observed correlation between rates of structural change and functional change equal to that obtained from patient data, even if the underlying structural and functional changes in early glaucoma were perfectly correlated and temporally coincident. In this instance, we compare structural data obtained from Confocal Scanning Laser Ophthalmoscopy (CSLO) to functional data obtained from SAP, although the methodology could also be used for other combinations of structural and functional tests. It has been shown that test variability may be able to explain the frequency

with which patients appear to be progressing by only one of these modalities but not the other.[19] This study extends that concept to determine whether differences between the observed rates of change are consistent with structure and function progressing in tandem, using simulations based on real patient data. While this would not definitively prove that structural and functional changes do in fact occur together, it is a necessary condition for results from structural and functional tests to be combined.

Material and Methods

In order to test the hypothesis, simulations assuming a certain level of variability between the true rates of structural and functional change were compared with patient data. Patient data was used both to estimate the observed structure-function relation, and also to derive models from which realistic simulations could be produced.[20]

Subjects

Data for this study were obtained from the Portland Progression Project, an ongoing longitudinal study of progression in participants with OHT or suspected / early glaucoma, at Devers Eye Institute in Portland, Oregon, USA. The protocol was approved by the Legacy Health Institutional Review Board. The study adheres to the tenets of the Declaration of Helsinki and complies with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Each subject provided written informed consent, after having the risks and benefits of participation explained to them.

Initially, subjects were tested annually with a variety of structural and functional tests. Over the last two years, subjects have been tested at six-monthly intervals. The majority of sequences of tests used in this study straddle that change in protocol, with the subject transitioning from annual to six-monthly testing. The change in protocol applied to all subjects, and so no resultant biases were introduced. At study entry, subjects either had early glaucoma with visual field loss less severe than -6 dB for SAP Mean Deviation (MD), or had ocular hypertension (untreated intraocular pressure repeatedly >22 mmHg) together with one or more risk factors for glaucoma as determined by their eye care specialist (e.g. age >70 [21, 22], systemic hypertension [23], migraine [24], diet controlled diabetes [25], peripheral vasospasm [26], African ancestry [21] or self-reported family history of glaucoma [27]) and/or previously diagnosed glaucomatous optic neuropathy or suspicious optic nerve head appearance (cup-disc ratio asymmetry >0.2 , neuroretinal rim notching or narrowing, disc hemorrhage). [11, 28] Subjects with other diseases or using medications likely to affect the visual field, or who had undergone ocular surgery (except for uncomplicated cataract surgery), were excluded. In addition, subjects with visual acuity worse than 20/40 in either eye, or with worse than mild glaucoma, media change or cataract at study entry (as judged by their eye care specialist), were excluded.

SAP visual field testing was performed using a Humphrey Field Analyzer II [1] (Carl Zeiss Meditec Inc, Dublin, CA, USA), employing the 24-2 testing pattern and conventional test procedures. The SITA standard algorithm [29] was used for all testing. An optimal lens correction was placed before the tested eye, and the fellow eye was occluded with a translucent eye patch. All subjects had previous experience with visual field testing prior to entering the study, and most had performed multiple previous tests. Tests with $>33\%$ fixation losses or false negatives, or $>15\%$ false positives, were excluded as being unreliable. CSLO optic nerve head scanning was performed using a Heidelberg Retina Tomograph Classic (a.k.a. HRT1, software version 3.15; Heidelberg Engineering, GmbH, Heidelberg, Germany) following standard operating procedures.[30] Acceptable image quality ($SD < 25$) was checked for each scan, and contour lines were drawn by an experienced operator viewing the participant's entire sequence of scans up to that date.

Subjects were included in the analysis if they had undergone at least six SAP visual field tests, together with a CSLO scan within 30 days of each visual field test. If more than six such visual fields were available, the most recent six were used for analysis. For the primary analysis, both eyes were used for each participant. As a secondary analysis to remove any effect of inter-eye correlations, only the worst eye was used, chosen based on their rate of functional change measured by MD. 166 eyes of 92 participants satisfied the entry criteria for the primary analysis.

Analysis of patient data

Step 1: Calculate rates of functional and structural change for the patient data

—First, fixed effects linear regression was used to obtain the rate of functional change over time for each eye. For each eye's sequence of visual fields with mean deviations of MD₁, MD₂... MD₆, measured at times T₁, T₂... T₆, a regression was performed:

$$MD_i = \text{Int}_F + T_i * \text{Slope}_F + R_{Fi}$$

where Slope_F is the rate of functional change over time, Int_F is the intercept term, and R_{Fi} is the residual (error term). T₁ was set to equal zero in all cases in effect making T the time since baseline. The least squares regression minimizes $\sum R_{Fi}^2$ for each eye. It should be noted that this primary analysis uses the Mean Deviation, as reported by the perimeter. Some recent studies have suggested that using a linear scale for sensitivity rather than the logarithmic-based dB scale used to calculate MD could result in better structure-function correlations.[31, 32] Therefore, a secondary analysis was performed using a linear-based Mean Deviation, calculated by converting the total deviation value for each point to a linear scale using $TD_{Lin} = 10^{TD/10}$ before averaging these TD_{Lin} values across locations.

Similarly, Rim Area (RA) as measured using CSLO was used to estimate the rate of structural change over time:

$$RA_i = \text{Int}_S + T_i * \text{Slope}_S + R_{Si}$$

These steps give an estimate of Slope_F and an estimate of Slope_S for each eye, together with residuals R_{Fi} and R_{Si} for each time point for each eye. Note that although change is being measured over almost exactly the same period of time, the times T_i could differ by up to 30 days between the structural and functional tests. The observed correlation between structural and functional rates of change was calculated, and forms the first outcome variable for comparison against the simulated data:

$$\text{Cor}_{SF} = \text{cor}(\text{Slope}_F, \text{Slope}_S)$$

This measure is unaffected by differences in the scales used for the two slopes, but assumes a linear relation between the two.

Step 2: Predict rate of functional change from rate of structural change based on the patient data

—If the underlying structure-function relation were perfect, then it would be theoretically possible to predict the rate of functional change based on the rate of structural change. Therefore, a Deming regression model accounting for errors in variables[33] was formed:

$$\text{Model}_{\text{SF}}: \text{Slope}_F = \text{Int}_{\text{SF}} + \text{Coef}_{\text{SF}} * \text{Slope}_S + \varepsilon_{\text{SF}}$$

where Slope_F and Slope_S are the rates of functional and structural change derived in Step 1; Int_{SF} is an intercept term (this will account for the fact that the rate of functional change would be zero in a theoretical healthy individual, since MD is age-adjusted, whereas this is not the case for the rate of structural change); Coef_{SF} is the appropriate regression coefficient; and ε_{SF} is the error term.

Step 3: Calculate the prediction errors for the patient data—Using Model_{SF} from Step 2, the predicted rate of functional change $\text{Slope}_F(\text{Pred})$ is given for each eye by:

$$\text{Slope}_F(\text{Pred}) = \text{Int}_{\text{SF}} + \text{Coef}_{\text{SF}} * \text{Slope}_S$$

Functional data $\text{MD}(\text{Pred})_i$ for that eye can be predicted from the structural data using the initial observed value MD_1 together with this predicted rate $\text{Slope}_F(\text{Pred})$ and the times T_i , using the equation:

$$\text{MD}(\text{Pred})_i = \text{MD}_1 + \text{Slope}_F(\text{Pred}) * T_i$$

The absolute difference between this predicted value and the observed value gives the error at that time point:

$$\text{Diff}_i = \text{abs}(\text{MD}(\text{Pred})_i - \text{MD}_i)$$

Therefore, there is one value of Diff_i for each time point for each eye. If the prediction of Slope_F is not perfect, these differences will increase over time (since $\text{MD}(\text{Pred})_i = \text{MD}_1$, and so $\text{Diff}_1 = 0$ in all cases). This principal is illustrated in schematic form in Figure 1. The slope of a regression over time of these differences (considering all eyes and all time points together) was found by the regression:

$$\text{Diff}_i = \text{Int}_{\text{Diff}} + \text{Slope}_{\text{Diff}} * T_i + \varepsilon_i$$

where ε_i is the error term (i.e. the regression minimizes $\sum \varepsilon_i^2$). This slope $\text{Slope}_{\text{Diff}}$ forms the second outcome variable for comparison against the simulated data.

Step 4: Model the measurement variability in the patient data—The sizes of the residuals R_{Si} and R_{Fi} in Step 1 are measures of variability. These are dependent on the level of damage, and will vary between subjects. Therefore, two further regression models can be formed:

$$\text{Model}_S: R_{Si}^2 = \text{Var}_{\text{SubS}} + \text{Coef}_{\text{SevS}} * \text{RA}_i + \varepsilon_S$$

$$\text{Model}_F: R_{Fi}^2 = \text{Var}_{\text{SubF}} + \text{Coef}_{\text{SevF}} * \text{MD}_i + \varepsilon_F$$

Note that the squares of the residuals are used, since variances of different terms add linearly to give the overall variance. There is one value of R_{Si} and one value of R_{Fi} for each time point for each eye. Var_{SubS} and Var_{SubF} give the variance due to the subject for each individual eye (assumed to be constant across visits for a given eye); $Coef_{SevS}$ gives the change in variance caused by a $1mm^2$ greater RA; $Coef_{SevF}$ gives the change in variance caused by a 1dB greater MD; and ϵ_S and ϵ_F are the error terms.

Data Simulation

Simulated data were then generated using the assumption that the underlying rates of functional change are equivalent (other than using different scales) to the underlying rates of structural change, plus variability given by standard deviation σ . Therefore, setting $\sigma=0dB/yr$ assumes that the underlying rates of change are the same, with only measurement variability reducing the observed correlation.

Step 5: Create a simulated patient—A simulated patient is created, with:

- Underlying rate of structural change $Slope_S$ given by randomly sampling from the observed rates of structural change in the patient data (introducing between-subjects variability)
- Equivalent predicted rate of functional change given by $Slope_F(Pred) = Int_{SF} + Coef_{SF} * Slope_S$ (from $Model_{SF}$, as in Step 3)
- Underlying rate of functional change $Slope_F$ given by randomly sampling from a normal distribution with mean $Slope_F(Pred)$ and standard deviation σ (introducing within-subjects variability)
- Baseline structural and functional data, RA_1 and MD_1 , equal to those observed in a randomly chosen eye (not necessarily the same eye whose rate of structural change was used; again, introducing between-subjects variability)
- Variances due to the subject, Var_{SubF} and Var_{SubS} , equal to the average of those values over all eyes

Step 6: Generate ‘observed’ data for the simulated patient—Simulated data is assumed to have been measured annually; therefore, $T_1 = 0$, $T_2 = 1$ etc. Using the values from the simulated patient created in Step 5, the ‘observed’ structural data sequence is given by randomly sampling from a normal distribution with mean $RA_i = RA_1 + T_i * Slope_S$, and variance $R_{Si}^2 = Var_{SubS} + Coef_{SevS} * RA_i$ (from $Model_S$). The ‘observed’ functional data is given by randomly sampling from a normal distribution with mean $MD_i = MD_1 + T_i * Slope_F$, and variance $R_{Fi}^2 = Var_{SubF} + Coef_{SevF} * MD_i$ (from $Model_F$).

Step 7: Calculate ‘observed’ rates of change for the simulated patient—As in Step 1, the rates of structural and functional change, $Slope_S(obs)$ and $Slope_F(obs)$, are calculated by linear regression over time (note that these may not be exactly the same as the underlying rates $Slope_S$ and $Slope_F$, due to the variability added to the ‘observations’ in Step 6).

Step 8: Calculate ‘observed’ prediction errors for the simulated patient—As in Step 3, the prediction error at each time point is calculated as the absolute difference between the ‘observed’ MD and that predicted using the ‘observed’ rate of structural change together with $Model_{SF}$.

Steps 5–8 were repeated 166 times (or 92 times for the secondary “worst eye only” analysis), to generate a simulated dataset with sample size equal to that in the patient dataset.

The correlation between ‘observed’ rates of structural and function change, $\text{cor}(\text{Slope}(\text{obs})_S, \text{Slope}(\text{obs})_F)$, and the slope of ‘observed’ prediction errors over time, $\text{Slope}_{\text{Diff}}$, were calculated and recorded.

Comparison between patient data and simulated data

The simulation was repeated 1000 times. Each run generated a correlation between rates of structural and functional change, and a slope of prediction errors over time, based on 166 simulated patients (or 92 patients when carrying out the secondary “worst eye only” analysis). These were then compared against the equivalent values calculated from the patient data, in Steps 1 and 3, to give an empirical p-value. If the simulated structure-function correlation was less than the correlation observed in the patient data on x% of runs, indicating that the simulated data had greater structure-function dissociation than the patient data, then the empirical p-value for this first outcome variable was recorded as x%. Similarly, if the simulated slope of prediction errors over time was greater than that observed in the patient data on y% of runs, indicating that the simulated data had greater structure-function dissociation than the patient data, then the empirical p-value for the second outcome variable was recorded as y%.

This was repeated using different values for σ (0.00dB/yr to 0.15dB/yr at steps of 0.01dB/yr), the standard deviation of the variability between the underlying rate of structural and functional change. Finally, the entire analysis was repeated using Cup Volume instead of Rim Area as the CSLO parameter measuring structural change.

Results

Table 1 summarizes the patient characteristics in the dataset. The rate of change of MD was significantly worse than zero ($p < 0.0001$). When only the worst eye per patient (according to their rate of change of MD) was considered, the mean rate of change was -0.241dB/yr (standard deviation 0.247dB/yr), also significantly worse than zero ($p < 0.0001$).

In the patient data when both eyes were used, the test-retest variance of the functional data for an average participant with zero damage (i.e. the average squared residual from the trend over time that would be expected when $\text{MD}=0$; given by the mean value of Var_{SubF} in Model_F from Step 4) was 0.543dB^2 . Equivalently, the standard deviation was 0.737dB , approximately 2% of an assumed dynamic range of 30dB . This variance increased by $\text{Coef}_{\text{SevF}}=0.126\text{dB}$ for each 1dB lower (more damaged) MD ($p < 0.001$). In Model_S , the test-retest variability for rim area (for an average participant with $\text{RA}=1.5\text{mm}^2$) had standard deviation 0.034mm^2 (also approximately 2% of the dynamic range based on this mean value). For cup volume (for an average participant with $\text{CV}=0.19\text{mm}^3$) this standard deviation was 0.012mm^3 (approximately 6% of the dynamic range). The variance did not change significantly with damage level for either structural measure ($p=0.650$ for RA, and $p=0.936$ for CV).

The observed correlation between the rates of change in structure (rim area from CSLO) and function (SAP MD) calculated in Step 1 was $\text{Cor}_{\text{SF}}=0.171$ when both eyes were used, significant with $p=0.028$; and $\text{Cor}_{\text{SF}}=0.280$ ($p=0.007$) when using only the worst eye for each subject. The observed slopes of residuals over time calculated in Step 3 were $\text{Slope}_{\text{Diff}}=0.121\text{dB/yr}$ (both eyes) and $\text{Slope}_{\text{Diff}}=0.127\text{dB/yr}$ (worst eye only).

As seen in Table 2, the variability between the underlying rates of true structural and functional change must be non-zero but very small for the slope of residuals over time to take the value observed in the patient data (since when $p < 0.025$ or $p > 0.975$, the hypothesis that the true value of σ is as shown would be rejected at the $p < 5\%$ level in a two-tailed

significance test). For the correlation between rates of structural and functional change, the range of plausible values of σ is larger.

Table 3 gives the equivalent results when using cup volume (from CSLO) as the structural measure, instead of rim area. In this case, in the patient data, the observed correlations between the rates of change in structure and function were $\text{Cor}_{\text{SF}} = -0.091$ (both eyes, $p = 0.243$) and $\text{Cor}_{\text{SF}} = -0.092$ (worst eye only, $p = 0.385$). The observed slopes of residuals over time were $\text{Slope}_{\text{Diff}} = 0.123 \text{ dB/yr}$ (both eyes) and $\text{Slope}_{\text{Diff}} = 0.129 \text{ dB/yr}$ (worst eye only). Even though the structure-function correlation was not found to be statistically significant in this case, a high variability between the true rates of structural and functional change was not required for consistency between simulations and the patient data.

When linear averaging was used to generate a linearly-scaled equivalent of MD, the correlations between rates of structural and functional change in our patient data were 0.126 (both eyes) and 0.210 (worst eye only) when using rim area, consistent with σ being below 0.07 dB/yr; and -0.067 (both eyes) and -0.123 (worst eye only) when using cup volume, consistent with σ being below 0.05 dB/yr.

Discussion

This study shows that the observed weakness of the structure-function relation in OHT or suspected / early glaucoma could be explained substantially by test variability. In our data, the correlation between the observed rates of change in function (SAP MD) and structure (Rim Area) was 0.171. While this correlation is statistically significant, it may not be clinically meaningful, since it explains less than 5% of the variance between the two observed rates. This would agree with the results of the OHTS, which concluded that both structure and function should be evaluated in patients with ocular hypertension, rather than relying on one modality in isolation.[34] However, it is not necessary to assume a large discrepancy between the two underlying (noise-free) rates of change, such as would be produced if structural and functional progression were not temporally coincident. Indeed, a large temporal asynchrony is incompatible with the observed structure-function relation being as strong as it is. To be compatible with the patient data for the correlation between residuals and time, $\sigma < 0.02 \text{ dB/yr}$ both when rim area and cup volume are used as the structural measures.

To put this value into context, the average rate of functional change in this dataset was -0.19 dB/yr . In the absence of test variability, the rates of change that would be predicted from the structural data would follow a normal distribution with mean -0.19 dB/yr and standard deviation below 0.02 dB/yr. For comparison, the expected test variability of functional testing for a healthy eye was found to have standard deviation 0.74 dB. For a sequence of six annual tests, this would result in the observed rate of functional change over time having a standard deviation of 0.18 dB/yr. This test variability increases still further with greater damage. Indeed, in our data there was a significant relation between perimetric sensitivity and variability, consistent with previous reports in the literature.[7] Although we did not find a significant increase in variability of rim area or cup volume with level of damage, such an increase has been found in some previous studies.[35] Test variability (in both functional and structural testing) may be the only reason that functional change cannot be predicted with this level of accuracy from structural measures.

The linear regressions used in this study may not be optimal,[36] and indeed the relation between sensitivity and variability has previously been described using a non-linear model[7] (although the model of Henson et al could not be used for this study, since it is based on an exponential relation between sensitivity loss and variability, and so produces

unrealistically high variability when extrapolated to sensitivities below those that their model was based on). Series were limited to six tests, as a compromise between reducing variability in slope estimates and reducing the influence of these non-linearities in progression. The choice to assume linear relations was made in part because there is as yet no consensus regarding an alternative formulation, and in part because the Pearson correlation coefficient (which assumes a linear relation) has previously been used to assess the structure-function relation.[11] The effect of non-linear progression, especially if the degree of non-linearity differs between structure and function (e.g. function decreasing non-linearly while structure changes linearly over time) would be to reduce the observed correlation between the rates of structural and functional change. This would make the patient data appear to be consistent with a higher value of σ than is really the case. This could explain the apparent disconnect in Tables 2 and 3, whereby the empirical p-values for the structure-function correlation in Tables 2 and 3 seem to require a higher value of σ than the empirical p-values for the slope of residuals over time. The results based on the slope of residuals over time should be less affected by this issue, since it would not cause a systematic bias; if the prediction of the rate of functional change in Step 3 were inaccurate, nonlinearity in functional progression would cause the divergence between predicted and observed function in Figure 1 to accelerate for some simulated patients, but to converge later in the series for others, resulting in little net affect on the correlation between residuals and time. Therefore, we believe the results based on this latter correlation (giving σ below 0.02dB/yr) to be more reliable than the results based on the correlation between rate of structural and functional change.

The sources of this substantial test variability are not yet completely understood. Automated perimetry relies on the subject pushing a button when they detect a stimulus presentation. However, even for an ideal observer the internal response to the stimulus is inherently probabilistic due to the nature of neural firing,[37] with the detection threshold being defined as the stimulus intensity to which the observer responds on 50% of trials. Additionally, the detection threshold may vary throughout the test due to fluctuations in attention, especially in prolonged testing. As well as this within-subject variability, there is also substantial between-subject variability, caused by differences in the disease courses of individuals and by anatomical differences in the numbers of retinal ganglion cells between pre-diseased eyes.[38, 39]

Histological studies have suggested that 25% of retinal ganglion cells may be lost at a given retinal location before a significant reduction in perimetric sensitivity occurs.[40] This has been taken as evidence that structural change can occur prior to functional change, and that as such, structural testing could provide earlier detection of glaucomatous damage. However, this view has recently been challenged, based on evidence that some patients exhibit functional damage before structural change is observed,[34] and that a linear relation seems to exist between structural and functional loss when results are expressed on an appropriate scale.[8, 9, 31, 38, 41–45] This study reconciles these two viewpoints, by demonstrating that even if structure and function do change together according to a linear relation, test variability is sufficient to explain the high level of damage that must occur before functional change exceeds normal variability and becomes detectable. Our study also implies the reverse; a large amount of functional damage can occur before structural change exceeds normal variability, and so some patients will show evidence of abnormality first by function rather than structure, as has been observed in clinical trials.[34, 46–48] We did not find evidence that underlying structural change (in the absence of test variability) precedes underlying functional change. Indeed, a large time lag between the two modes of change would cause the variability between them to be greater than observed, and would seem to be incompatible with our patient data.

Previous attempts to reduce the variability in functional testing have relied on processing of the measured thresholds.[49–51] If SAP and CSLO are both measuring the same underlying disease progression rate, results from the two could be combined to provide a unified measure with reduced variability. It has been shown that the locations of visual field defects are related to the locations of damage at the optic nerve head.[11, 52–54] Significant advances are being made in models to predict function from structural measures.[36, 38, 44] The findings from this study are a necessary prerequisite for such models to be accurate and reliable, and indicate that such work could fruitfully be used to reduce difficulties caused by variability, resulting in earlier and more accurate detection of both damage and progression.

There are several limitations to this study. The measurements of function and structure that were chosen are commonly used, but may not be optimal. For example, it has been suggested that perimetric sensitivities should be averaged on a linear scale when constructing indices such as MD, rather than on a logarithmic dB scale, to better relate structure with function.[31, 32] Using linear averaging, the correlations between rates of structural and functional change in our patient data were consistent with σ being between 0.03 and 0.07 for rim area; and between 0.02 and 0.05 for cup volume. A further limitation of this study is that the simulations were based on the same dataset against which the results were compared. This removes problems caused by use of a validation dataset that has different characteristics than the dataset used to construct the simulations (e.g. different inclusion / exclusion criteria, a different distribution of disease stages, etc); such a dataset could potentially have a different underlying structure-function correlation, and hence give misleading results. However, it would be desirable to validate the conclusions either by repeating the methodology using a separate dataset both to generate and test the simulations, or by using another dataset with nearly identical characteristics.

Other structural measures may show evidence of damage prior to functional change, such as posterior deformation of the lamina cribrosa.[55] Similarly, other functional tests may be able to detect damage at an earlier stage, especially in the presence of dysfunctional retinal ganglion cells that would not necessarily lead to change evident in CSLO images.[56] For reasons of longitudinal consistency, this study used the HRT Classic; newer versions of the HRT are available that may have improved test-retest repeatability. The methodology described in this manuscript could be applied to other combinations of tests to look for evidence of temporal dissociation, or to show that results from the different tests can justifiably be combined into a unified measure of progression.

Our study cohort consists of participants with OHT or suspected / early glaucoma; indeed, the average MD was greater than zero. A previous analysis of data from the same study found that approximately half exhibited glaucomatous optic neuropathy at baseline evident on examination of stereophotographs, with one quarter of CSLO scans being classified as abnormal by Moorfields Regression Analysis.[57] Given the relatively mild disease stage in this cohort, our conclusions may not hold in later disease. In particular, disease cannot be monitored once it has progressed beyond the effective dynamic range of each instrument, which may not be at the same damage level for CSLO as it is for SAP.

This study compared the rates of change of SAP and CSLO, not the actual values measured. There is considerable variability between normal eyes,[38] a proportion of which can be explained by aging effects.[58] The correlation between baseline MD and Rim Area was 0.265, significant with $p=0.0005$; the correlation between MD and Cup Volume at baseline was -0.083 , not significant with $p=0.286$. Therefore, even if a perfect model could be constructed to predict the rate of functional change from structural change, it would not allow the baseline functional sensitivity to be predicted accurately from the baseline structural testing. Perimetry would still be necessary to determine a patient's functional

status. Replacing functional testing with structural testing alone may be preferred by patients,[10] but this may not yet be advisable.

The conclusion of this study is that the inter-test variability, as modeled by Model_S and Model_F above, is sufficiently large that the observed dissociation between the rates of structural change (as measured by CSLO Rim Area or Cup Volume) and functional change (as measured by SAP Mean Deviation) could plausibly be caused by this variability alone. It is not necessary to introduce a large discrepancy between the underlying rates of change to simulate realistic patient data. Therefore, it is feasible to combine data from structural and functional tests to reduce the variability in results, without having to worry that this combination process may be invalid due to a temporal dissociation between the two modes of change or due to differences in their dynamic ranges.

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Figure 1.

Schematic illustrating the principle used at Step 3. Upper plot: the true rates of functional and structural change are the same (i.e. in the absence of test variability, structure and function would be perfectly correlated under appropriate scaling). The magnitude of the residuals (the difference between the observed function and that predicted using the baseline and the rate of structural change) does not depend on time since baseline. Lower plot: the true rates of change differ, due to imperfect concordance between structural and functional change. This causes the magnitude of the residuals to increase over time.

Table 1

Patient characteristics at baseline; together with the rate of change in Mean Deviation, Rim Area and Cup Volume over the six visits.

	Mean	Standard Deviation
Age in years	61 yrs	10 yrs
Mean Deviation (MD)	1.0dB	2.4dB
Pattern Standard Deviation (PSD)	2.3dB	2.0dB
Visual Field Index (VFI)	98%	5%
Rim Area (RA)	1.5mm ²	0.4mm ²
Cup Volume (CV)	0.19mm ³	0.17mm ³
Rate of change of MD	-0.186dB/yr	0.234dB/yr
Rate of change of RA	-0.002mm ² /yr	0.013dB/yr
Rate of change of CV	0.0005dB/yr	0.0046dB/yr

Table 2

Empirical p-values testing the equality of simulated and observed outcome variables, for different input σ . The value of σ gives the standard deviation of variability between the true rate of functional change (perimetric Mean Deviation), and the rate that would be predicted from the rate of structural change (rim area). An empirical p-value <0.025 or >0.975 indicates that the value of σ is incompatible with the observed patient data given the assumptions present in the simulation (i.e. $p < 5\%$ level for a two-tailed significance test).

	All Eyes (n=166)		Worst Eye Only (n=92)	
σ (dB/yr)	Empirical p-value for structure-function correlation	Empirical p-value for slope of residuals over time	Empirical p-value for structure- function correlation	Empirical p-value for slope of residuals over time
0.00	0.000	0.000	0.001	0.047
0.01	0.000	0.843	0.001	0.910
0.02	0.001	1.000	0.042	1.000
0.03	0.023	1.000	0.241	1.000
0.04	0.143	1.000	0.497	1.000
0.05	0.316	1.000	0.670	1.000
0.06	0.442	1.000	0.772	1.000
0.07	0.588	1.000	0.873	1.000
0.08	0.660	1.000	0.882	1.000
0.09	0.730	1.000	0.920	1.000
0.10	0.788	1.000	0.938	1.000
0.11	0.842	1.000	0.946	1.000
0.12	0.844	1.000	0.956	1.000
0.13	0.858	1.000	0.959	1.000
0.14	0.887	1.000	0.962	1.000
0.15	0.896	1.000	0.971	1.000

Table 3

Empirical p-values testing the equality of simulated and observed outcome variables, for different input σ . σ gives the standard deviation of variability between the underlying rate of change in function (perimetric Mean Deviation) and the rate that would be predicted from structural change (optic disc cup volume).

	All Eyes (n=166)		Worst Eye Only (n=92)	
σ (dB/yr)	Empirical p-value for structure- function correlation	Empirical p-value for slope of residuals over time	Empirical p-value for structure- function correlation	Empirical p-value for slope of residuals over time
0.00	0.000	0.000	0.000	0.003
0.01	0.001	1.000	0.007	1.000
0.02	0.120	1.000	0.126	1.000
0.03	0.310	1.000	0.273	1.000
0.04	0.471	1.000	0.394	1.000
0.05	0.569	1.000	0.458	1.000
0.06	0.590	1.000	0.481	1.000
0.07	0.621	1.000	0.523	1.000
0.08	0.684	1.000	0.539	1.000
0.09	0.680	1.000	0.576	1.000
0.10	0.721	1.000	0.595	1.000
0.11	0.696	1.000	0.580	1.000
0.12	0.715	1.000	0.591	1.000
0.13	0.702	1.000	0.580	1.000
0.14	0.704	1.000	0.609	1.000
0.15	0.756	1.000	0.588	1.000