Differences in the Relation Between Perimetric Sensitivity and Variability Between Locations Across the Visual Field

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Purpose. Perimetric sensitivities become more variable with glaucomatous functional loss. This study examines the extent to which this relation varies between locations, and whether this can be predicted by eccentricity-related differences in spatial summation.

Methods. Longitudinal series of visual fields from standard automated perimetry were obtained from participants with suspected or extant glaucoma. For each location in the 24-2 visual field, heterogeneous fixed-effects models were fit to the data, assuming that variability increased exponentially as sensitivity decreased. The predicted variability at each location was calculated when sensitivity was either 30 dB or 25 dB.

Results. Variability significantly increased with damage at all 52 locations. When sensitivity was 30 dB, variability increased with eccentricity, with \( P = 0.0005 \). The average SD was 1.54 dB at the four most central locations, versus 1.74 dB at the most peripheral locations. When sensitivity was 25 dB, variability did not vary predictably with eccentricity, with \( P = 0.340 \). The average SD was 2.56 dB at the four central locations, versus 2.24 dB at the most peripheral locations.

Conclusions. The relation between sensitivity and variability differed by eccentricity. Among healthy locations, variability was lower centrally, where the stimulus size is larger than Ricco’s area, than peripherally. Among damaged locations, variability did not systematically vary with eccentricity. This could be because Ricco’s area expands in glaucoma, such that stimuli were now smaller than this area at all locations.

Keywords: perimetry, variability, Ricco’s area, statistics

Automated perimetry remains an essential part of clinical management of glaucoma, not least because it measures outcomes that correlate directly with a patient’s quality of life, but also because its results are notoriously variable between tests for the same eye, delaying detection of damage and disease progression. Most perimetric research can be framed as a series of gradual improvements to the signal-to-noise ratio, to reduce this variability in future functional testing paradigms, it is important to first understand the sources of the variability in current testing.

There are several factors that contribute to test-retest variability in perimetry, including the amount of experience the patient has had with the test, the experience level of the technician conducting the test, the time of day, and even the time of year. However, the biggest source of variability is short-term fluctuation related to the psychometric function. The psychophysical response to a stimulus presentation involves an increase in the rate at which retinal ganglion cells produce neural spikes, but this spiking rate is inherently probabilistic. Therefore, the observer will not always respond to stimuli of greater contrast than the physiologic detection threshold, and will sometimes respond to stimuli of lesser contrast. Indeed, perimetric testing algorithms aim to converge to a contrast to which the observer will respond on a certain percentage of presentations, and not respond to the remaining presentations.

In regions of glaucomatous visual field loss, not only does the sensitivity decrease, but the psychometric function becomes shallower. This causes an increase in intratest variability, a major component of test-retest variability, because there is a broader range of contrasts at which the response probability will be neither 0% nor 100%. Heijl et al. suggested that this increase in variability may vary by distance from fixation, whereby variability was lower in the central visual field than peripherally in eyes with near-normal sensitivity, but there was no apparent correlation between variability and eccentricity in eyes with moderate glaucomatous loss. That study was performed by testing 51 patients four times within a month. The effect may be confounded by the fact that normal sensitivities are higher centrally than peripherally, which would also be expected to result in lower variability.

Several facets of retinal physiology change with distance from the fovea. Most relevantly for perimetry, the density of retinal ganglion cells decreases with eccentricity, while the size of their receptive fields increases. A related psychophysical feature of the normal visual system is that Ricco’s area increases with visual field eccentricity. For stimuli smaller than Ricco’s area, complete spatial summation occurs, such that stimulus area multiplied by stimulus intensity is constant at the detection threshold (hence, a smaller stimulus must have proportionately higher intensity for it to be equally detectable). For stimuli larger than Ricco’s area, only partial spatial summation occurs. Ricco’s area is also larger in glaucomatous eyes than in normal eyes. The difference in detection contrast between normal and glaucomatous locations appears to be greater for stimuli smaller than Ricco’s area. It has therefore been suggested that

### References

modifying stimulus size so that it remains within Ricco’s area may be a way to increase the signal-to-noise ratio of perimetry.27–29

The size III stimulus (0.43° diameter) that is most commonly used in clinical perimetry is larger than Ricco’s area at central locations in the visual field, and so partial spatial summation occurs. At the most peripheral locations in the visual field,30 and more centrally in glaucomatous eyes,27 the size III stimulus is approximately equal to or smaller than Ricco’s area, causing complete spatial summation to occur in many eyes. The slope of partial summation (the change in threshold for a given change in stimulus size) becomes steeper with increasing eccentricity,31 while the relation for complete spatial summation remains unchanged.32 Therefore, existing perimetric data can be used to reveal important information about the consequences of using stimuli larger or smaller than Ricco’s area. In particular, if the relative size of the stimulus and Ricco’s area is indeed a key determinant of perimetric variability, then the sensitivity-variability relation should differ with eccentricity.

This study aims to confirm and extend the conclusions of Heijl et al.22 using a longitudinal dataset, analyzed in a manner so as to remove the effects of possible disease progression. The advantages of this approach are 2-fold: first, it represents a more clinically realistic scenario in particular with regard to learning effects,33 because the intertest interval is 6 months rather than just a week; and second, it allows a much larger dataset to be used so that more precise pointwise results can be generated. If variability is indeed lower when stimulus size is larger than Ricco’s area, then this will provide an essential piece of information concerning the expected variability when deciding on the optimal balance between stimulus size and contrast in testing algorithms.

METHODS

Data were obtained from participants in the Portland Progression Project (P3), a longitudinal study of glaucomatous progression.33 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. Exclusion criteria were an inability to perform reliable visual field testing, best-corrected visual acuity worse than 20/40, substantial cataract or media opacities likely to increase light scatter, or other conditions or medications that may significantly affect the visual field. A visual field defect was not a requirement for study entry. 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.

The longitudinal series used in this study date back as far as 1999 for some eyes, at which time participants attended annually; this was changed to twice annual testing in 2009. Visual field testing is performed on both eyes (when eligible), annually; this was changed to twice annual testing in 2009. The model assumes that location (the pointwise sensitivity values at the chosen locations), Eye (a unique identifier for each eye in the dataset), and TestDate (the date on which the visual field was taken, expressed as the number of days since the start of the series). The model assumes that Sensitivity changes linearly with TestDate, with a different starting point and rate for each eye.

The weights argument in the model fitting function means that the error variance is assumed to be related exponentially to Sensitivity, as in previous empirical studies.21 For a given value of Sensitivity, the SD of the error terms is assumed to be given by $SD(Sensitivity) = A_0 e^{B(Sensitivity)}$ which simplifies to $SD(Sensitivity) = A e^{B(Sensitivity)}$. The starting value for the algorithm was set to a value of $B = -0.08$, as this was found to result in successful convergence of the algorithm for all test locations. For heteroscedastic linear models, weighting observations according to the reciprocal of the error variance function has been shown to be more robust to model misspecification than transforming the data to achieve homoscedasticity.39

The fitted value of parameter $A$ was extracted from the fitted model using the code sigma(Fit). The fitted value of parameter $B$ was extracted together with its approximate 95% confidence interval (based on a normal approximation to the distribution of the maximum likelihood estimator), using the code intervals(Fit)$\text{StarStruct}$. These were then used to calculate the predicted SD of errors when the sensitivity is 30 dB or 25 dB, to provide examples of the predictions and illustrate the differences in behavior across the visual field (note that these examples are based on the results from the entire dataset, not just on locations with these particular sensitivities).

Two further models were also fit to the pointwise data. The first of these assumes homoscedasticity (i.e., that the error variance is constant across sensitivities):
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Fit.Homoscedastic < − gls(Sensitivity ~ Eye + Eye:TestDate, data = LongitudinalData)

The models Fit and Fit.Homoscedastic were compared by Akaike’s Information Criterion (AIC) to assess whether incorporating heteroscedasticity improves the fit of the model to the observed data, which can be taken as an indication of whether the error variance is significantly related to sensitivity. The null hypothesis is that the error variance is independent of sensitivity, in which case the homoscedastic and heteroscedastic models will fit the data equally well.

The final model allows the error terms to be temporally correlated:

Fit.CAR < − gls(Sensitivity ~ Eye + Eye:TestDate, data = LongitudinalData, weights = varExp(fixed = B_10c, form = ~ Sensitivity), correlation = corCAR1(0.1, form = ~ Test.Date[Eye]))

Here, the correlation between the residuals decreases as the time between the measurements increases, according to a continuous autoregressive (CAR) correlation structure. A recent study used an autoregressive moving average correlation structure for similar analyses; however, that approach discretized time using “visit number” as its covariate, and a CAR model would be expected to be more realistic in a situation in which the intervisit time interval can vary substantially (for example, if data from one test visit was excluded due to unreliability of the sensitivity value, resulting in an intervisit interval of 1 year instead of 6 months). When fitting the Fit.CAR model, the value of the variance function coefficient was fixed at the value of B found in the primary model for this location. Principally, this is to ensure that direct comparisons between Fit and Fit.CAR are affected only by the presence of an autocorrelation term, and not by differing values of the variance function coefficient; a secondary advantage is that fixing this coefficient greatly aids with achieving algorithmic convergence. The comparison provided by anova(Fit, Fit.CAR) can then be used to assess whether significant autocorrelation is present.

Note that Fit is nested within Fit.CAR, hence they can be formally compared using an ANOVA, whereas Fit and Fit.Homoscedastic are not nested (due to the different weightings of observations) and so have to be compared using AIC.

RESULTS

Data were available from 504 eyes of 255 participants who had series of at least five visits. Their clinical characteristics are outlined in the Table. The mean deviation on their most recent visit was −1.6 dB (range, −26.6 to +2.7 dB). A total of 210 of those eyes (42%) had Pattern Standard Deviation outside normal limits on their most recent visit, and 214 had Glaucoma Hemifield Test results of “outside normal limits” or “borderline,” indicating significant localized functional loss. It should be noted, however, that the exact sample size varied slightly according to which location was being tested, because visual fields at which the sensitivity at that particular location was <15 dB were excluded.

Figure 1 shows, for each location, the fitted values of the variance function coefficient B (top left); the fitted value of A, equivalent to the SD of the error terms that would be predicted when Sensitivity = 0 dB (top right); and the fitted SDs of the error terms when Sensitivity = 30 dB (bottom left) and when Sensitivity = 25 dB (bottom right) as examples illustrating the difference in behavior at different sensitivities. Note that the predicted SD of the test-retest variability would be a factor of \(\sqrt{2}\) greater than this, due to there being variability in both the test and the retest observations. Notably, the variance function coefficient was negative at all locations (B was significantly less than zero with \(P < 0.05\), consistent with previous findings that variability decreases as sensitivity increases.\(^{21}\) Averaging across all locations gave mean values of \(A = 14.8\) and \(B = -0.070\).

At Sensitivity = 30 dB, the predicted variability generally increases with eccentricity, from a mean SD of 1.54 dB at the four central locations to a mean of 1.74 dB at the most peripheral ring of locations. The Pearson correlation between eccentricity and the fitted SD at Sensitivity = 30 dB was 0.485, with \(P = 0.003\). The width of the 95% confidence interval for the variance function coefficient B varied by location, from \(±0.0037\) dB to \(±0.0067\) dB. Treating the values of A as fixed, this results in 95% intervals for the fitted SD at Sensitivity = 30 dB with widths ranging from \(±0.14\) to \(±0.31\) dB away from the values shown. This indicates that the coefficients at locations around the edge of the 24-2 field were significantly higher than those at central locations with \(P < 0.05\).

By contrast, at Sensitivity = 25 dB, there is no obvious trend of variability against eccentricity. The Pearson correlation between eccentricity and the fitted SD at Sensitivity = 25 dB was 0.135, with \(P = 0.340\). Now, the mean predicted SD was 2.36 dB at the four central locations, versus a mean of 2.24 dB at the most peripheral locations. At this sensitivity, the 95% confidence intervals for the fitted SDs had widths ranging from \(±0.15\) dB to \(±0.39\) dB. It is therefore possible that central locations may be even more variable than many of the peripheral locations once this level of functional loss has been sustained. However, such conclusions must be viewed with caution, because the proportion of eyes that had sensitivity between 15 dB and 25 dB was below 1.6% at all of the most central locations, compared with more than 20% at the four most superior locations.

The model incorporating heteroscedasticity (designated as Fit in the Methods section above) fit the data significantly better than the homoscedastic model (Fit.Homoscedastic) at all 52 locations, as evidenced by a lower AIC value. The model incorporating autocorrelation between observations that were close together in time significantly improved the fit of the model at 5 of the 52 locations. However, even at these locations, the fitted value of the correlation between the residuals at two observations 1 year apart was below 0.01, indicating that any autocorrelation was not meaningfully affecting the results.

To provide an example of the eccentricity effect, two locations were chosen at which the variance functions appeared to differ substantially. At location (−15°, +3°) (in right eye orientation), the fitted SD was 1.06 dB when sensitivity was 35 dB, increasing to 1.43 dB when sensitivity

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Only eyes with at least five visual fields are included.

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was 30 dB and 1.92 dB when sensitivity was 25 dB, as seen in Figure 1. At location (+15°, −15°), the fitted SD was higher in near-normal eyes, being 1.47 dB when sensitivity was 35 dB and 1.78 dB when sensitivity was 30 dB; but more similar in damaged eyes, being 2.16 dB when sensitivity was 25 dB.

To ensure that the results are not merely an artifact of the heteroscedastic model fitting process, the fitted values from the homoscedastic model Fit.Homoscedastic at each of the 52 locations were split into 1-dB-wide bins, and the SDs of the residuals from all data points within each bin were calculated. These results are plotted in Figure 2 for the two locations chosen above. It can be clearly seen that when the sensitivity is near-normal, the variance is higher for location (+15°, −15°) than for location (−9°, +3°), but this difference disappears once more substantial damage has occurred. Note that the apparently high variability at location (−9°, +3°) for sensitivities 34 to 35 dB may not be a reliable result, because only 30 visual fields (0.4%) fell within that bin.

The range of these individual-location SDs, among all 52 locations, can be taken as a measure of spatial heterogeneity, and is shown for each 1-dB-wide bin in the boxplot in Figure 3. It is seen that although variability increases with damage, spatial heterogeneity is lowest when sensitivity is approximately 28–29 dB, indicating that the variability is most homogeneous between locations at this sensitivity level.

**DISCUSSION**

As expected, variability significantly increased as sensitivity decreased at all locations, as evidenced by the significantly
negative fitted values of the variance function coefficient $B$. The SD for an averaged location was given by $SD(Sensitivity) = 14.8 * e^{-0.070*Sensitivity}$. Equivalently, $\log(SD) = -0.070*Sensitivity + 2.70$. This is close to, but slightly smaller than, the estimate from Henson et al.\textsuperscript{21} of $\log(SD) = -0.081*Sensitivity + 3.27$. It is not surprising that these differ, because that article was estimating the slopes of frequency-of-seeing curves, and does not incorporate the effect of the perimetric testing algorithm. However, the similarity in the form of the function and in the magnitude of its parameters is reassuring. Other studies using perimetric data but with otherwise different methodologies have shown very similar effect sizes. In our results, averaging all locations, the predicted SD was 1.10 dB at a sensitivity of 35 dB, and 2.15 dB at a sensitivity of 25 dB. By way of comparison, Artes et al.\textsuperscript{42} reported SDs of approximately 0.9 dB and 2.1 dB at those sensitivities, whereas Russell et al.\textsuperscript{43} reported SDs of 1.2 dB and 2.2 dB.

This study goes farther than those, also assessing the effect of location on this sensitivity-variability relation. The variability was lower at central locations than peripheral locations when sensitivity was high. This implies that a healthy peripheral location whose sensitivity is (for example) 30 dB would be more variable than a central location in the same eye whose sensitivity has declined to 30 dB due to glaucoma. However, this eccentricity effect did not persist as the amount of damage increased. By the time sensitivity was reduced to 25 dB, the variability was similar at locations across the visual field; the correlation between eccentricity and variability was no longer significant, with $P = 0.340$. This confirms and extends previous findings by Heijl et al.\textsuperscript{22}

The magnitude of the intratest variability (and its effect on the test-retest variability) is clinically relevant, because it indicates the magnitude of apparent change in sensitivity that is required before a clinician can conclude that functional status has truly changed. The finding that variability is lower at central than peripheral locations for the same sensitivity, when above approximately 28 dB, implies that even small changes at those central locations are more likely to represent true change, and so can be considered clinically meaningful. The study also has implications for researchers interested in psychophysics and/or the development of perimetric techniques for future clinical use. The best stimulus size to use for clinical perimetry remains an open question; the reduction in variability when using larger stimuli may be accompanied by a reduction in the ability to detect early defects.\textsuperscript{29} and indeed it may be suboptimal to use the same stimulus size at all locations and all levels of damage.\textsuperscript{13} This study demonstrates that the optimal stimulus size will not only be affected univariately by damage level and location, but also by the interaction between them.

A possible explanation for this finding follows from spatial summation. Rico's area increases both with eccentricity\textsuperscript{30,31} and with glaucoma,\textsuperscript{7} but contrast sensitivity for a stimulus of area equal to Rico's area has been reported to remain constant.\textsuperscript{27-32,44} It seems reasonable to propose then that variability might also remain constant between locations at which the sensitivity has deteriorated (due to aging and/or glaucoma) to the point at which Rico's area exactly equals the stimulus size. In a healthy eye, Rico's area equals that of a size III target at locations that are around the edge of, or just outside, the 24-2 visual field grid. At such locations, normal sensitivity for a subject of the average age in our cohort is between 27 and 30 dB. Notably, as seen in Figure 3, variability was most spatially homogeneous when sensitivity was 28 to 29 dB.

Once sensitivity has deteriorated below this point, Rico's area is now larger than the stimulus size, and so complete spatial summation occurs: the stimulus luminance at the detection threshold is inversely proportional to stimulus area. This relation does not depend on eccentricity or disease status. Similarly, in the results shown here, variability (for a given sensitivity) does not appear to vary with eccentricity once sensitivity is below approximately 28 to 29 dB, however, when sensitivity is above this point, the stimulus is still larger than...
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Ricco's area, and so partial spatial summation occurs. The slope of partial summation (the change in threshold for a given change in stimulus size) becomes steeper with increasing eccentricity.\(^{28}\) Similarly here, variability (for a given sensitivity) does appear to vary with eccentricity while sensitivity is above approximately 20 to 29 dB. There may be a discontinuity in the sensitivity-variability relation at the point at which Ricco's area starts to exceed the 0.43\(^{a}\) diameter of the size III stimulus, with the magnitude of this change in the relation varying with eccentricity.

Apart from spatial summation, another factor that varies with eccentricity is the presence and magnitude of optical aberrations.\(^{45}\) It is possible that these aberrations are the limiting factor for contrast sensitivity in normal eyes, causing variability to increase with eccentricity; whereas in a glaucomatous eye, undersampling resulting from loss of retinal ganglion cells may become the limiting factor and so the eccentricity effect is diminished. Further evidence would be needed before concluding that the magnitude of such an effect could entirely explain our results.

The correlation between variability and eccentricity was approximately equally common in our dataset. When locations of the same eccentricity had higher variability when sensitivity was 35 dB than other locations of the same eccentricity. It is possible that this is caused by fixation instability and anatomic differences between eyes causing a proportion of stimuli at these locations to fall within the blind spot. It has previously been reported that fluctuation is increased near the blind spot,\(^{46}\) even though this effect is not as pronounced as at the edge of a glaucomatous scotoma.\(^{47}\)

We have previously reported that sensitivities below 15 to 19 dB are unreliable in clinical perimetry, having very low correlation (R\(^2\) < 0.1) with sensitivities at the same location measured more accurately using frequency-of-seeing curves.\(^{25}\) This is consistent with the fitted SD of the error terms increasing exponentially as sensitivity decreases. In this study, locations with sensitivity ≤ 15 dB were excluded from the analysis, so that this unreliability would not affect the main results; however, it should be noted that the heteroscedastic linear model used in this study fits the model by weighting observations according to the reciprocal of the error variance.\(^{39}\) Therefore sensitivities ≤ 15 dB would have low weighting in the regression model, and so their omission is unlikely to have greatly affected our results or conclusions.

As with any research, the best statistical analysis to use depends on the details of the question being asked. We have previously shown that an accelerating exponential model (whereby the rate of change worsens over time) may fit longitudinal perimetric data better than a linear model (whereby the rate of change is constant over time) when conducting mixed effects model analyses.\(^{40,48}\) as would be performed when analyzing possible risk factors for rapid progression. Intuitively, such an exponential model is more consistent with longitudinal series in which the eye is perfectly healthy for an extended period of time before consistent with longitudinal series in which the eye is progressing. Intuitively, such an exponential model is more consistent with longitudinal series in which the eye is progressing.

In conclusion, variability increases as sensitivity decreases in automated perimetry, but the magnitude of this increase differs between locations. In damaged visual fields, the variability observed at locations with the same sensitivity does not vary consistently with eccentricity; however, when sensitivity is near-normal, variability is lower in the central visual field than peripherally (for the same sensitivity). This
suggests that using stimuli larger than Rico’s area of complete spatial summation may lower test-retest variability, although the effect on the signal-to-noise ratio remains to be determined.

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