Test-retest variability of visual sensitivity measurements: contribution of small eye movements studied near blind spots and scotomas

By

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[1.0] Introduction

Automated static perimetry is an important tool for the detection and management of many conditions of the visual system. In a progressively worsening disease such as glaucoma, perimetry can be used to monitor the visual field over time. One difficulty with perimetry is that results are subject to test-retest variability, in which the measured sensitivity of an area can change with each measurement. Increased variability has been found especially in areas of decreased sensitivity, e.g. for glaucoma and optic neuritis. (Heijl, Lindgren, 1989; Chauhan & Johnson, 1999)

In visual fields of glaucoma patients, clinicians view an area of decreasing sensitivity as a possible result of glaucomatous progression. A scotoma is an area of the visual field with a loss of sensitivity (relative to norms). When a scotoma is detected, more than one visual field is often taken to increase the confidence of the diagnosis. However, test-retest variability of visual fields makes it difficult to differentiate fluctuation from progression in assessing glaucomatous damage. A better understanding of the sources of test-retest variability would ultimately improve the analysis of a visual field. Aside from a true decrease in sensitivity, other possible causes of variability include variations in retinal cell behavior, reduction in numbers of cells generating the signal, and fixational eye movements (Wyatt et al., 2007).

Generally speaking, there is a non-monotonic relationship between variability and sensitivity. A scatterplot of test-retest variability versus sensitivity appears as an inverted U-shaped curve (Flammer et al., 1984; Piltz & Starita, 1990; Artes et al., 2005; Wyatt et al., 2007). At very low sensitivities, the variability is low since even the brightest stimulus provided by the machine will likely not be seen by the patient. Variability could in principle be present, but due to limitations of the device, is not detected due to a "floor" effect (Wyatt et al., 2007). At high sensitivities, where healthy retina is being tested, the variability is also low. At the mid-range sensitivities down to 10dB, variability tends to be greatest. (Flammer et al., 1984; Artes et al., 2005) As a result, it is particulary difficulty to distinguish progressing glaucomatous disease from variability in this range of sensitivities.

The edges of scotomas due to glaucoma and cerebral blindness have been associated with high variability. (Haefliger & Flammer, 1989; Haefliger & Flammer, 1991; Demirel et al. 1997; Kasten et al.

1998) Moreover, variability was found to be correlated with the number of steep scotoma boundaries of a visual field (Henson & Bryson, 1990). Wyatt et al. (2007) found that the correlation of variability with the local slope of sensitivity was especially strong at scotoma edges in patients with glaucoma. The slope refers to the change in sensitivity as a function of change in retinal location. In healthy retina, sensitivity has a central peak at the fovea and falls off gradually towards the periphery; i.e., the slope is small. Retinal areas with a steep slope will have large changes in sensitivity over a short distance. Within thirty degrees of fixation in a normal visual field, a steep slope is observed only at the edge of the blindspot. In glaucoma patients, scotomas can also have steep edges (Haefliger & Flammer, 1991; Wyatt et al., 2007).

The optic disc of a normal eye is a region where the ganglion cell axons leave the eye to form the optic nerve. It subtends approximately 5 degrees of visual angle horizontal by 7 degrees vertical (Polyak, 1941). The optic disc lacks photoreceptors, and is therefore an absolute scotoma such that the maximum stimulus presented by the perimeter can not be perceived, unless light scatters into surrounding functional retina. The blindspot, corresponding to the optic disc, refers to the physiological scotoma found in the visual field of all normal subjects. The blindspot has been shown to vary somewhat in size as a function of the test stimulus size and luminance (Meyer et al, 1997).

In the past, a few studies have focused on measuring the sensitivity near the blindspot. The work by Wyatt et al. (2007) was the first to measure slope of sensitivity at the edge of the blindspot. A study by Meyer et al. used microperimetry with 0.5 degree spacing across the horizontal meridian of the blindspot (Meyer et al., 1997). Their aim, however, was to study the blindspot size as a function of luminance and size of the stimulus. Data were not presented to show the steepness of the edges. An older study by Israel also measured blindspot edges. This study used a Goldmann perimeter and only placed test locations along the horizontal meridian. (Israel, 1968).

Haefliger and Flammer (1989) compared sensitivity and variability at the edges of blindspots and scotomas and found that test-retest variability was high at both. They believed that the variability was related to measurements being made in the transition zone, but the basis for this was not explicitly formulated. Later work by Haefliger and Flammer found greater variability at edges of glaucomatous

scotomas than at edges of the blindspot, yet the slope appeared to be steeper at blindspot edges than scotoma edges (Haefliger, 1991). This led them to conclude that local slope per se had only a minor influence on the variability, and other factors were likely involved.

Haefliger and Flammer suggested that glaucoma patients might have greater fixational errors than normal subjects, but this idea was not followed up. Some supporting evidence was found by Katz et al (1991): glaucoma patients had worse reliability indices, including more fixation losses, than normal patients.

In general, "steady fixation," as during perimetry, typically includes small, involuntary eye movements called microsaccades of less than 1 degree in amplitude (Yarbus, 1967). Moreover, fixation losses of up to five degrees are not reliably caught by blindspot monitoring, a standard in detecting poor fixation (Demirel et al., 1992). Earlier evidence suggested that subjects fixated within ± 3 degrees while performing a visual field (Murphy P, 1990). A more recent study by Toepfer et al. (2008) found that subjects spent 97% of the time positioned within ± 1 degrees from fixation.

Haefliger and Flammer (Fig. 1, 1991) found the width of the border of glaucomatous scotomas to be larger than blindspot borders despite the similar appearance of both edges in the visual field printout. They speculated that the border of glaucomatous scotomas may differ from blindspot borders, and could reflect a succession of relative or absolute microscotomas at the junction between normal and pathologic areas.

In this paper, a fine two-dimensional grid was used to assess the characteristics of normal blindspot edges. Even finer arrays of 1-degree spacing were then used to further characterize blindspot and scotoma edges. The eyetracker data provided by the perimeter were used to approximately evaluate fixation errors of the normal subjects and glaucoma patients during visual field testing.

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[2.0] Methods

[2.1] Customized Test of Visual Function of the Blindspot in Normal Subjects

Apparatus

Software that controlled stimulus presentation was developed using the Psychophysics Toolbox (Brainard, DH. The Psychophysics Toolbox. Department of Psychology, UC Santa Barbara, CA. http://color.psych.ucsb.edu/psychtoolbox. 1997) with Yi-Zhong Wang's interface in Matlab 5.2 (The MathWorks. http://www.mathworks.com/products/matlab. 1998). The program ran on a Power Macintosh G3 computer, which was connected to a 21" CRT monitor with a 38.0 x 27.8 cm active area, 832 x 624 pixels resolution, and 75 Hz. frame rate (Radius PressView 21SR, Miro Displays, Inc., Germany). Parameters included fixation point location, stimulus and background intensity, and temporal frequency of the stimulus. The monitor was placed 75cm from the eye being recorded, and the visual angle subtended at the eye was 29.1 degrees horizontally and 21.8 degrees vertically.

The computer was connected to a PC-based eye-tracker (ISCAN EC-101, ISCAN, Inc., Burlington, MA). The eye-tracker consisted of a serial card installed in a PC, a video camera, an infrared spotlight, and a video monitor. The infrared light source and video camera were placed at approximately the same distance from the subject. The video monitor displayed the subject's eye and was used for aligning the system to the subject's pupil. The eye-tracker recorded the horizontal and vertical pupil diameter as well as the positions of the pupil center and corneal reflex 60 times/sec; data were saved in both software-specific raw data files and ASCII files.

Subjects

In the initial study, seven subjects (4 males, 3 females) were recruited from the community at SUNY State College of Optometry whose average age was 30 years (aged 22 to 64).

In all studies, data were collected from the right eye of all normal subjects and patients with glaucoma. The non-tested eye was patched and any subjects with refractive error were fully corrected. All subjects in the normal group had received a complete ocular examination within one year of the testing,

and had been determined to be free of ocular disease. An assessment of their visual field using a full threshold staircase method showed no visual field defects up to 30 degrees of eccentricity.

Patients in the glaucoma study had characteristic visual field loss consistent with glaucoma and were free of any eye diseases other than glaucoma. To be eligible for the study, an eye was required to have a scotoma within 10 degrees of fixation; the scotoma had to contain steep edges going from relatively normal sensitivity to abnormal sensitivity. Visual acuity was required to be no worse than 20/40 in the tested eye.

This study and all subsequent studies were approved by the SUNY College of Optometry Institutional Review Board (IRB), and written informed consent was obtained from each subject after having the nature of the experiment explained in detail.

Protocol

Subjects were seated in an examination chair directly in front of the monitor with their head leaning against a stable headrest. All subjects wore appropriate refractive correction. In all cases, the left eye was patched while the pupil and corneal reflex signals were recorded for the right eye. A yellow spot, 0.4 degrees in diameter, with a luminance of 54.4 cd/m^2, served as a fixation point on a uniform gray background of 5 cd/m^2 luminance. Because the right eye was the recorded eye, the fixation point was located 6 degrees left of center of the 29^o wide monitor, allowing stimuli to be presented out to 20^o eccentricity in the temporal field. The image of the subject's eye was centered and focused on the eye-tracker's video monitor. Testing procedures were implemented once a stable pupil and corneal reflex signal were acquired.

Each subject participated in 1 preliminary session and 2 testing sessions, all performed on different days within a six week period. In the preliminary session, potential subjects were asked to perform calibration eye-movements and a fixation task (explained below).

During the two sessions that followed the preliminary session, subjects performed an eye-position calibration task, a test of visual function, which was followed by a ten minute break, and an attention task

(explained below). The second testing session repeated the same tests except the test of visual function and attention task were reversed in sequence. This eliminated a fatigue bias of the tests, if any.

Fixation task

The fixation task was performed once on each subject. It assessed the subject's ability to fixate for a prolonged period. The task consisted of staring at a stationary target for 5 minutes while eye movement recordings of 1.5 seconds were taken every 15 seconds. Subjects were instructed to blink naturally.

Calibration

Calibrations were performed at the start of each session to determine the relationship between gaze direction, corneal reflex, and pupil center. The target consisted of a central yellow dot and four other fixation points, 3 degrees from the center, in the up, down, left, and right directions. The subject alternated fixation between the fixation target and each of the four targets while recordings were made.

Attention Task

The attention task was used to study eye movements during fixation with no peripheral distractors, and also to determine the subject's rate of false positive errors in a stimulus test. Subjects were asked to fixate one target for five minutes. The fixation target would blink off every 1.5 seconds. Long blinks (0.2 second) occurred with an 80% probability and short blinks (0.1 second) with a 20% probability. The subjects were told to click on a mouse button after noticing a long blink, but not after a short blink. The duration of long and short blinks were lengthened for two subjects who had difficulty differentiating long from short blinks. Gaze direction and pupil diameter were recorded during the experiment.

Test of Visual Function

Tests of visual function was performed using a customized test consisting of a 4x7 array of test locations, spaced 2 degrees apart, centered at 14 degrees temporal, 2 degrees inferior to fixation. The 28 locations were tested with size III targets (0.43 degrees diameter). This is the standard size for which most normative data is obtained and can compensate for any subjects with slight uncorrected refractive error. (Heijl & Patella, Essential Perimetry, Ch. 3) There were 12 other test targets distributed nasally, superiorly and inferiorly to maintain a global distribution of the subject's attention. These points also served as control points. Test locations are shown in figure 1. The array of stimuli was designed to test nasal, superior and inferior portions of the average blindspot.

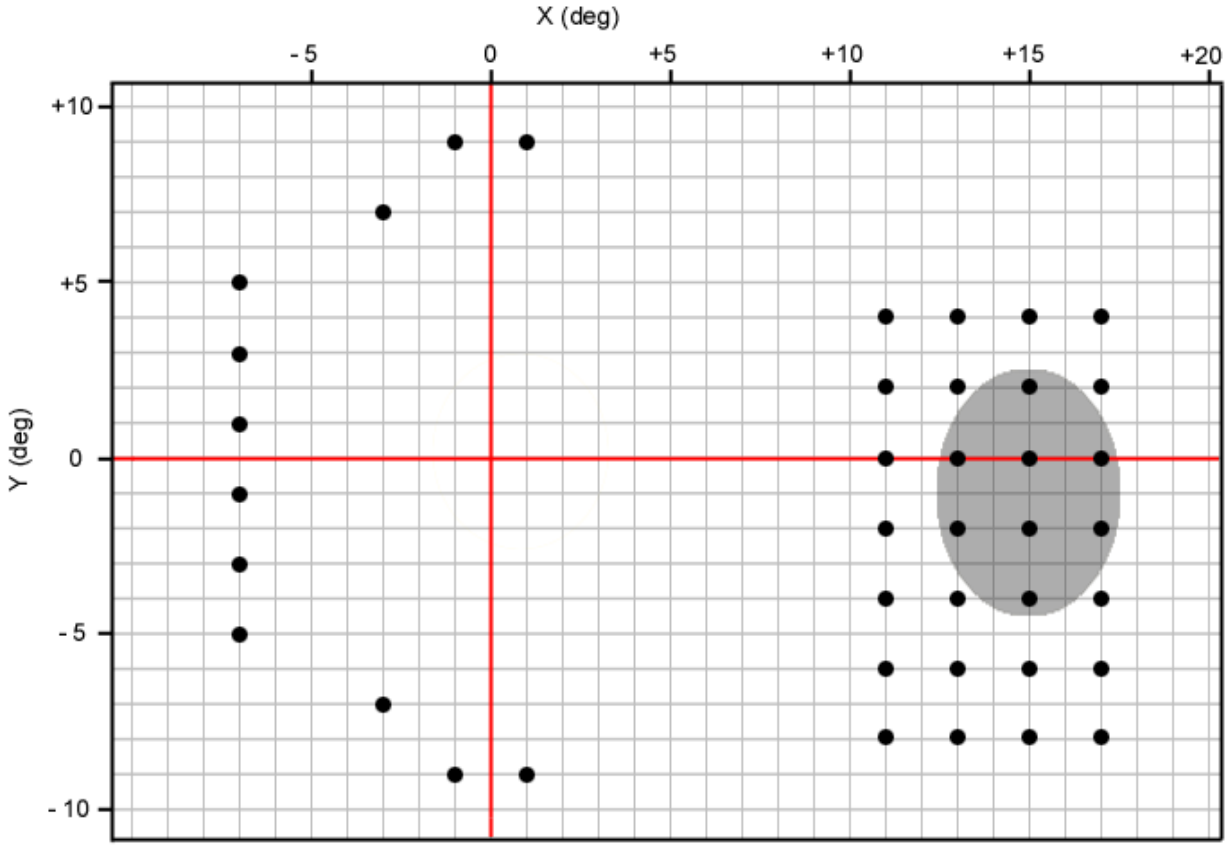


Figure 1. The array to test for visual function. The small black circles represent test locations of 0.43 deg diameter and are drawn to scale. The light-gray region represents the size and position of the average blindspot. The locations in the 4x7 grid are spaced 2 degrees apart, vertically and horizontally, centered at 14 deg temporal and 2 deg inferior to fixation. The red lines represent the horizontal and vertical meridians of the visual field.

Each stimulus was presented for 0.1 second with a 1.0 second interval between each stimulus presentation. Background luminance during the visual field was 5 cd/m^2. Initial stimulus luminance was randomized at either 8.09 or 6.23 cd/m^2. For test locations presented at locations likely to be in the blindspot, initial stimulus luminance was 20.50 cd/m^2. A continuous recording of the positions of pupil center and pupil diameter were taken at a rate of 60 Hz.

Threshold was determined using a 2/1 dB staircase, 2-reversal protocol, as follows: If the first stimulus was seen, subsequent stimuli were dimmed in 2 dB steps. Once the stimulus was not seen, marking the first reversal, subsequent stimuli were brightened in 1 dB steps until the stimulus was seen again, marking the second reversal. On the other hand, if the first stimulus was not seen, it was subsequently brightened in 2 dB steps until it was seen. The stimulus was then dimmed in 1 dB steps until it was not seen, marking the second reversal. In both cases, the last seen value at the time of the second reversal was taken as the threshold at that test location.

In all studies, sensitivity at a given location was taken to be the average of the values from repeated testing at that location. Variability was taken to be the SD of sensitivity from repeated testing at that location.

Estimating the Slope of Sensitivity

The magnitude of the slope for a test location, $|\nabla S|$, was determined from the 8 nearest-neighbor test locations. To estimate the slope at a test location, the partial derivatives in the horizontal (x) and vertical (y) directions were first estimated. For example, given three adjacent points in the x-direction with three sensitivities, S_{-1}, S_0, S_{+1}, the partial derivative is calculated by taking the difference between points S_{-1} and S_0 and the difference between S_0 and S_{+1}, which are then averaged together. This equation is equivalent to finding the difference in sensitivity between two points, S_{+1} and S_{-1}, and dividing by 2. The result is the slope in dB per grid interval.

$$\frac{\partial S}{\partial x} \approx \frac{(S_{+1} - S_0) + (S_0 - S_{-1})}{2} = \frac{(S_{+1} - S_{-1})}{2}$$

The estimate of the x-derivative, which we refer to as the "axial" estimate, was combined with similar estimates made using differences of diagonally-adjacent points. For example, in the plus-45-degree direction, we would use points S(x= +1, y= +1) instead of S_{+1}, and S(x= -1, y= -1) instead of S_{-1}. The point separation in the diagonal is greater by a factor of $\sqrt{2}$, so the sensitivity is divided by $\sqrt{2}$ to get an estimated component in the x-direction in dB per grid interval. Similarly, we obtained an estimate of the x-component of the slope in the minus-45-degree direction. The sum of the two x-components of these diagonal estimates gives a second, independent estimate for $\frac{\partial S}{\partial x}$, which we refer to as the "diagonal" estimate. The average of the axial and diagonal estimates was used to obtain the final estimate of $\frac{\partial S}{\partial x}$.

The estimate of $\frac{\partial S}{\partial y}$ was obtained in analogous fashion. The magnitude of the slope was then estimated using $|\nabla S| = \sqrt{\left(\frac{\partial S}{\partial x}\right)^2 + \left(\frac{\partial S}{\partial y}\right)^2}$

(The slope values presented here have been converted from dB per grid interval to dB/deg.)

Only the central 5x2 array of points, within the 7x4 array, have all 8 nearest-neighbor points. For convenience, we will refer to the central 5x2 points as the "core" locations. The estimates of slopes are more reliable at these locations, and only these locations were used for correlation. Estimating slopes at the other locations is possible if fewer surrounding points are employed. The calculations are similar, except further modifications of the formulas are required. These slope calculations were made to provide additional graphical information for illustrations.

[2.2] Fine Resolution Test of Visual Function of the Physiological Blindspot in Normal Subjects

In the initial study, the test points in the array for the blindspot were spaced 2 degrees apart, horizontally and vertically. Changes in retinal sensitivity are suspected to occur very fast, especially at the edge of the blindspot. By using an array with 1 degree spacing, we can determine changes in sensitivity over a change in retinal location of 1 degree.

Apparatus

All tests of visual function were performed on a Humphrey Visual Field Analyzer HFA-II (Carl Zeiss, Meditec, Inc., Dublin, CA).

Normal Subjects

Six normal subjects (average age 31 years; range 22 - 64) were recruited from the community at SUNY State College of Optometry; 4 of the 6 subjects had also participated in the previous study.

Sensitivity

Stimulus intensity in the Humphrey perimeter ranges from 0.08 to 10,000 apostilbs (asb). Sensitivity values are reported in decibels (dB) where 1 dB = 0.1 log units. The decibel value of 0 dB corresponds to a maximum brightness (10,000 asb) that the perimeter can produce and 51 dB represents the lowest brightness (0.08 asb) the perimeter can produce, and still be detected. The typical range of normal sensitivity in humans is between 20 to 30 dB. (Heijl & Patella, Essential Perimetry, Ch. 2)

Estimating the Slope of Sensitivity

Points located midway between actual test locations were used for analysis. The gradient that can be derived in these locations provides information at a finer-scale. This is illustrated by an example. Suppose you have sensitivity values S_{-1}, S_0, S_{+1} with values of 10, 20, and 10, respectively, and tested at X_{-1}, X_0, X_{+1}, respectively. Calculating the gradient at X_0 would require the neighboring sensitivity values of X_{-1} and X_{+1}. The gradient obtained is 0, or no change. Although sensitivity does in fact stay the same going from X_{-1} to X_{+1}, it does not reveal the changes in sensitivity that can potentially occur within these 3

retinal locations. In contrast, if the gradient was calculated between actual test locations, then the gradient between X_{-1} and X_0 equals +10 and the gradient between X_0 to X_{+1} equals -10. These two gradients reveal that from retinal location X_{-1} to X_0, the sensitivity was increasing, whereas from retinal location X_0 to X_{+1}, the sensitivity was decreasing. The latter method clearly gives information at a finer-scale. The calculated gradient is not the full vector gradient, but is $\partial S/\partial x$., the gradient of sensitivity along the x-direction vector. The gradients for the y-direction vector created by vertical eye movements were examined similarly.

We estimated the gradient in the x- and y-directions: $\frac{\Delta S}{\Delta x}$ and $\frac{\Delta S}{\Delta y}$, where S represents the average sensitivity values (across repeats). The gradient was determined by the two-point difference in sensitivities, $(S_{n+1} - S_n)$, where n is position in degrees. This gives an estimate for the gradient midway between the two test locations.

Protocol

The distance from the fixation point to the blindspot was determined for each subject by either analyzing the subject's previous test data or performing a quick, automated visual test that located the blindspot of the subject.

Thresholds were determined using a full threshold, 4-2 dB staircase method (See Methods under *Tests of Visual Function*). Intensity starts initially at 25 dB and a size III stimulus was used. A custom test array, based on each subject's blindspot location, was created under the instrument operating system. As shown in figure 2, there were 4 arrays crossing the temporal, nasal, superior and inferior edges of the blindspot. Each array consisted of 5 locations in a row, 1 degree apart, for a total of 20 points. A vertical array of 6 test locations, spaced 2 degrees apart and 7 degrees nasal to the fixation point, was tested to maintain a global distribution of attention and also served as control points. Thus, 26 test locations were used in the test.

The operating system of the Humphrey analyzer instrument prevented custom test locations at this eccentricity from being closer together than 2 degrees. In order to space stimulus locations one degree apart, each complete test was divided into two sessions, with the test locations in each session having 2 degree spacing. The illustration in figure 2 shows test arrays with bi-colored points that differentiate part 1 and part 2 of the complete visual test. Subsequently, all test results were combined. The 6 control points were included in every session.

Each subject performed 3 complete tests of visual function, and was therefore tested 6 times. Testing was performed over 2 visits, with 3 "half" tests performed in each visit. The 2 visits were spaced at least 2 days apart, and no more than 2 weeks apart. The subjects were allowed to rest between tests.

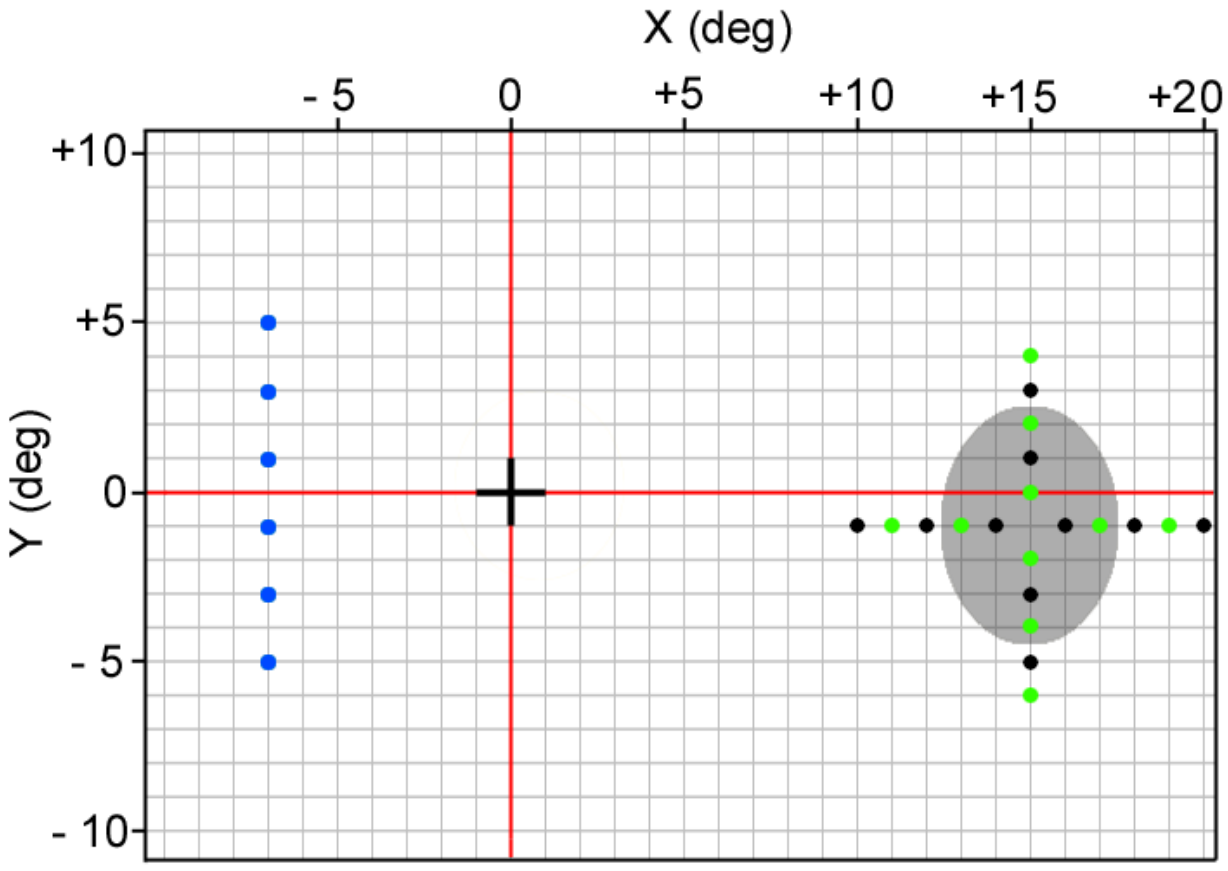


Figure 2. Test pattern for normal blindspots. The red lines represent the horizontal and vertical meridians of fixation. The light-gray region represents the location and size of the blindspot in typical normals. The small, filled circles of black and green are test array points, and the blue circles are control points.

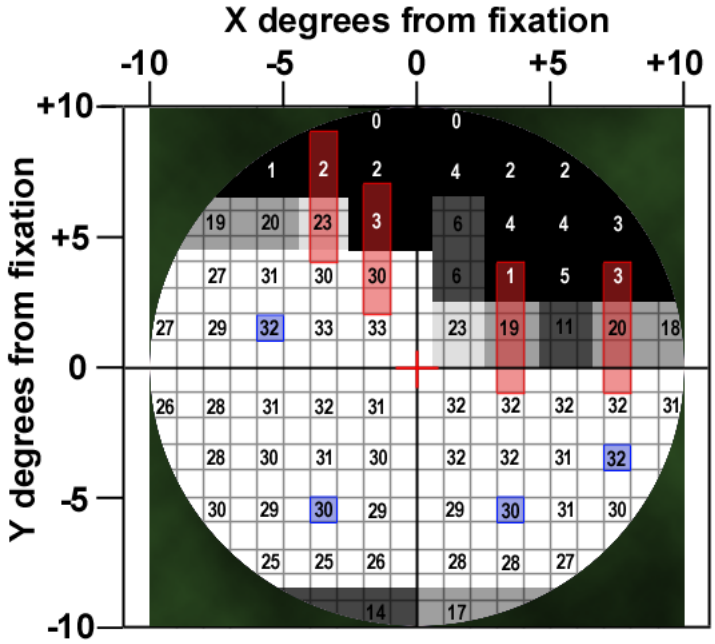
[2.3] Visual Testing of Patients with Glaucoma for Edge Analysis of Scotomas

Patients

Six patients with glaucoma (GP) were recruited from the Glaucoma Institute in the University Optometric Center at SUNY College of Optometry (average age 66.0; range 51.7 – 79.5) to participate in these tests.

Testing was similar to the protocols for normals. Locations of scotomas were determined from visual fields of earlier studies. (Wyatt et al., 2007) Figure 3(a) shows an example of a visual field with scotomas. The test patterns, as shown in Figure 3(b), were vertical arrays of 5 locations each (1 deg apart) crossing scotoma edges. In each GP eye, three or four vertical arrays were used. Three or four control points of high sensitivities were also selected.

GP eyes were tested in two sessions, each location tested twice per session. Repeats performed automatically by the HFA software were noted. The two visits were at least 2 days apart and no more than 21 days apart.



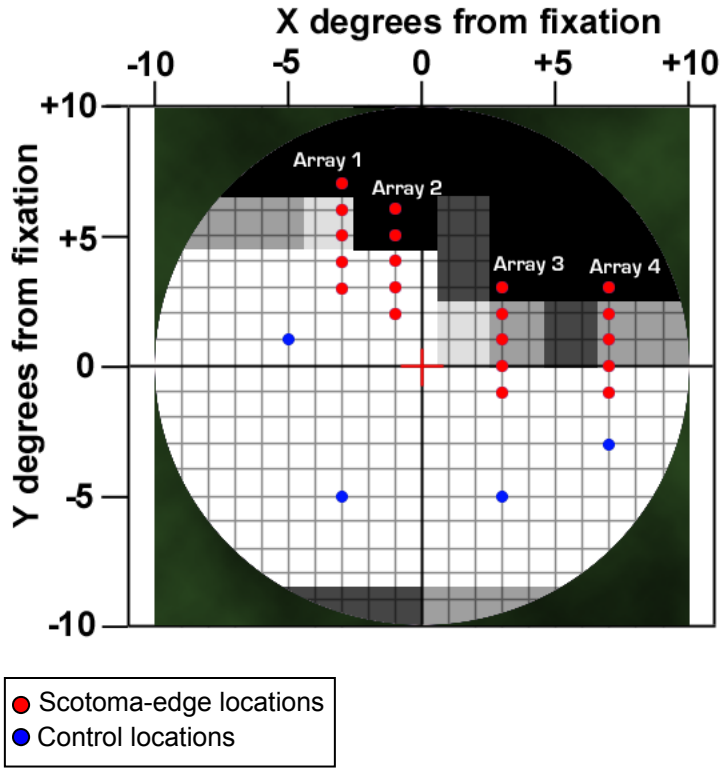


Figure 3. (a) One glaucoma patient's HFA 10-2 visual field data (dB) averaged over multiple sessions. The grayscale represents varying sensitivities of the visual field, with darker shades as lower areas of sensitivity. Four vertical arrays crossing scotoma edges were selected and are designated in red border outlines. Four control points, designated in blue border outlines, were also selected. The arrays and control points make up the customized test of visual function in **(b).** The red crosshair marks the fixation point.

Measuring Fixation Inaccuracies

Data on fixation inaccuracies of GP and NS were based on recordings directly from the HFA Eyetracker, which provides an approximate value for the magnitude of the deviation between the target and the point of regard (ie. the radial distance from the fixation point). We assumed that the eye position histogram was approximately isotropic (equal in all directions).

[2.4] Test of Visual Function of the Physiological Blindspot in a Patient with Glaucoma

One glaucoma patient (age 65.7) who had participated in the scotoma portion of the study also performed a customized test of the blindspot, similar to the protocol for normal subjects. For this patient, the array testing the superior blindspot edge was excluded because of glaucomatous damage in that area.

[3.0] Results

[3.1] *Responses of Normal Subjects to the Test of Visual Function*

In the 2x2 grid array used to measure sensitivity at the edge of the blindspot in detail, the average time to complete the test was 4′ 24″ (range: 3′ 53″ – 4′ 54″). Figure 4 shows a 2-dim histogram of typical eye fixations for two subjects and the fraction of time spent per fixating position. In normal subjects, the average variability of horizontal eye positions was 0.43 ± 0.19 deg during testing. Two of the seven subjects had reliable vertical eye position data, which showed fixation varied on average 0.36 ± 0.06 deg.

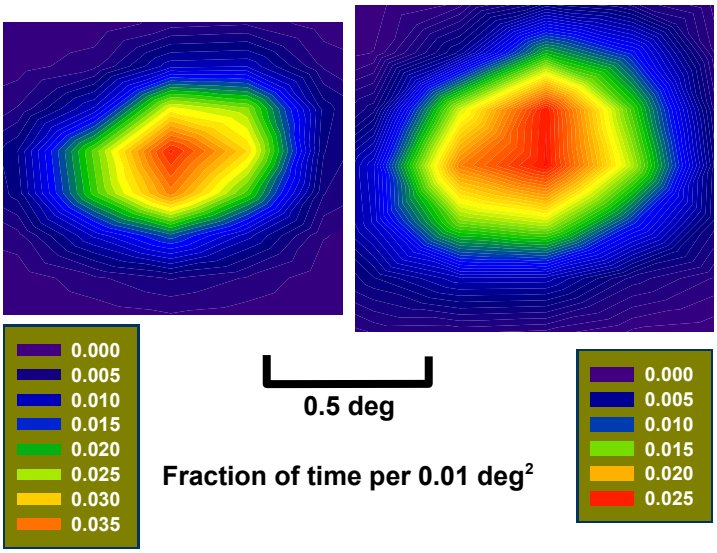


Figure 4. Two subjects' 2-dimensional histograms of typical eye fixations during a visual field. The plot labels the fraction of time spent per 0.01 deg^2.

Figure 5 shows one subject's 2-dim contour plots of sensitivity, variability (derived from repeated sensitivity measurements as standard deviation), and local |slope| (taken as an absolute value) near the edge of a blindspot. Only a core of points, as described in the methods section, was used for subsequent analysis of the data. As shown in figure 5, these points were designated within the white outline rectangle. It may be seen that the variability plot resembles the slope plot. The correlation of variability with the slope of sensitivity was 0.58 ± 0.09. Variability of sensitivity averaged 1.6 dB (range: 0 to 7 dB).

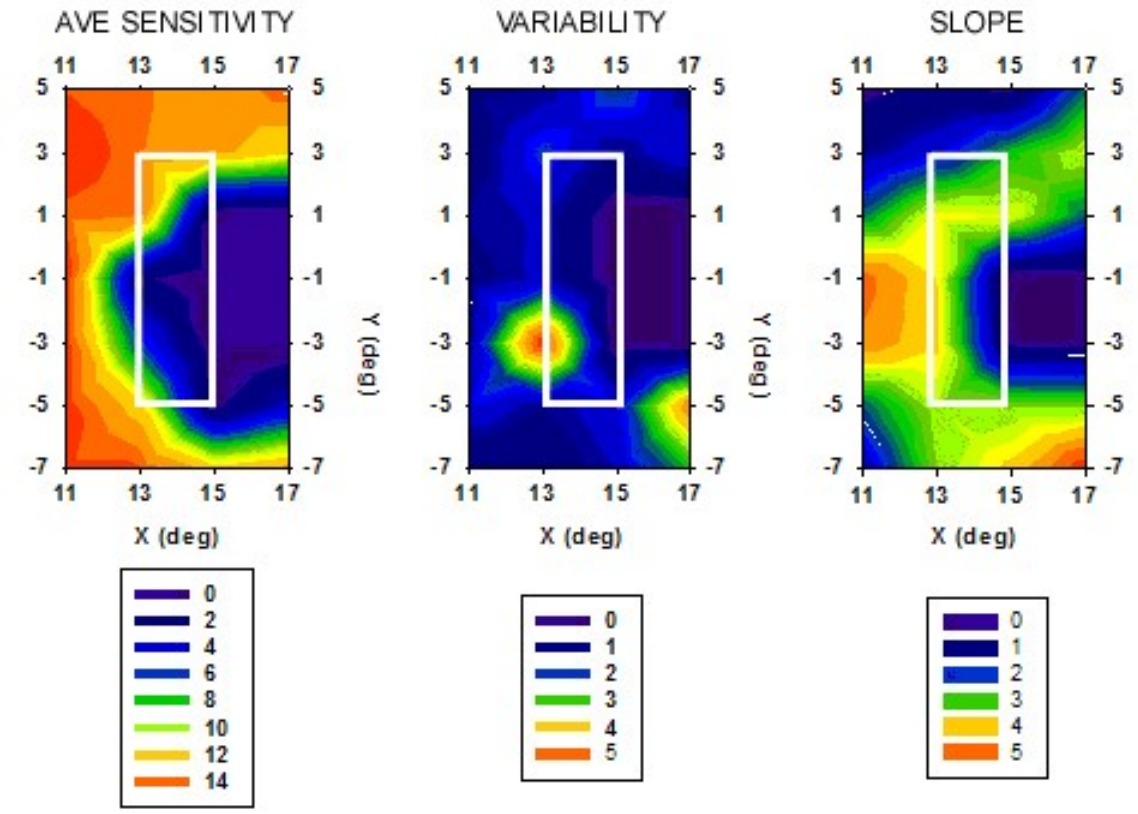


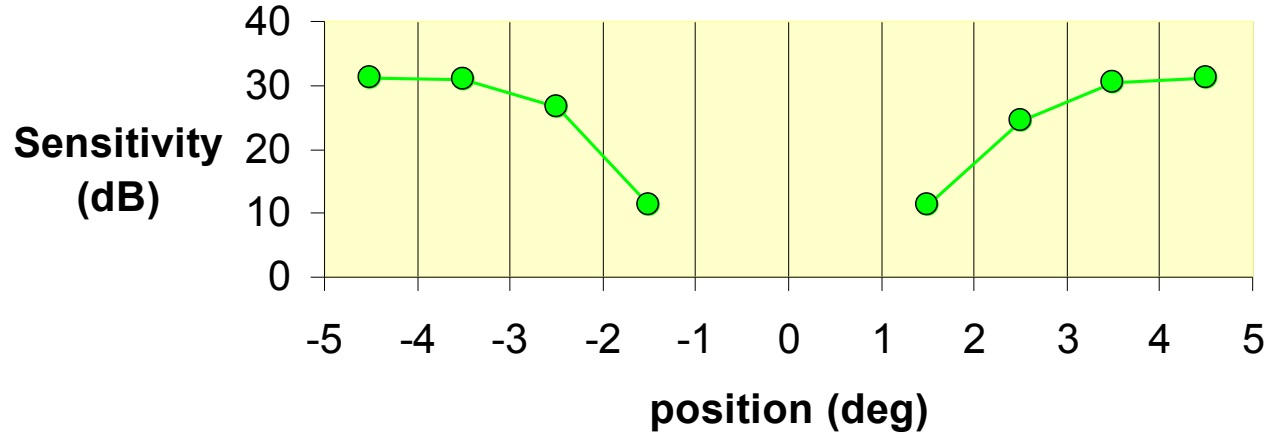
Figure 5. From left to right: **(a)** Contour plot of the average sensitivity (dB) of a subject's visual field near the edge of the blindspot. **(b)** Contour plot of the variability (dB) and **(c)** the slope of sensitivity (dB/deg) for the same region are also shown.

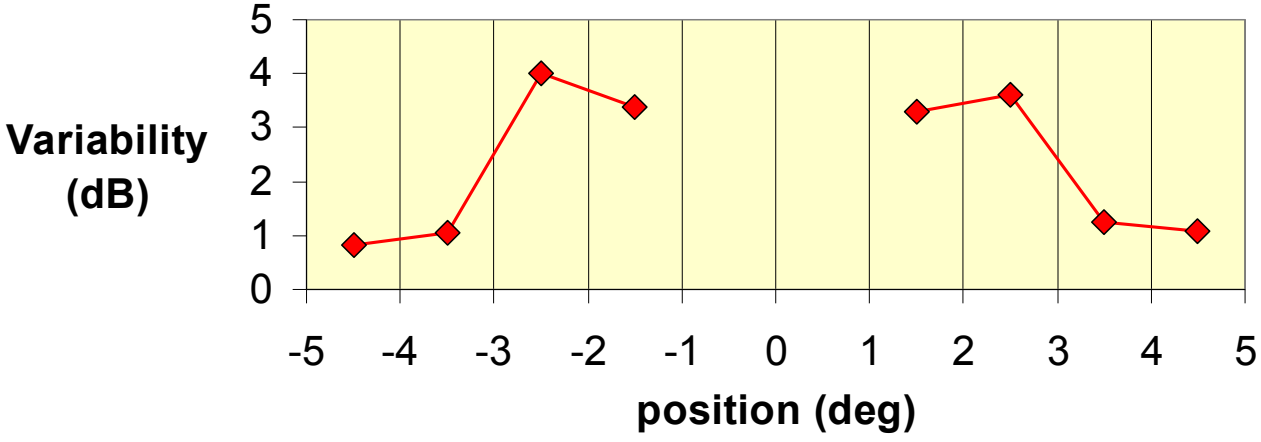
[3.2] Finer resolution test of visual function

Given the very rapid changes in sensitivity that were observed, further testing was carried out with 1-deg spacing. Using the finer arrays, the average time to complete a field of visual function in normal subjects (NS) was 8′37″ (range: 7′06″ – 9′31″). This field was split into two testing sessions with rest time given in between. The average number of test points (including locations tested more than once) per field was 51.5 ± 1.6. The average time to complete a test of visual function in patients with glaucomatous scotomas (GP) was 5′59″ (range: 4′20″ – 7′27″). The average number of test points here was 31.0 ± 4.0. The shorter test time correlates with the fewer locations tested for GP.

The average sensitivity of control points for NS was 32.63 ± 1.02 dB and the variability was 1.08 ± 0.33 dB. The average sensitivity of control points for GP was 27.81 ± 3.22 dB and the variability was 1.95 +/- 1.26 dB.

Figure 6 shows profile plots of sensitivity, variability, and local slope across the horizontal blindspot edge for one normal subject. As mentioned in methods, sensitivity was calculated as the average between two test locations separated by 1 degree apart to yield finer-scale information. Subsequently, variability and slope calculations were between test locations as well. The x-axis represents the retinal position relative to the approximate center of the blindspot, which is set at 0. The sensitivity at position 0 was not measured. Sensitivity decreased rapidly as position approaches 0 from both sides. The variability profile showed greatest variability near the edge of the blindspot, where the slope was also steep.


Sensitivity
(dB)
40
30
20
10
0
-5
-4
-3
-2
-1
0
1
2
3
4
5
position (deg)


Variability
(dB)
5
4
3
2
1
0
-5
-4
-3
-2
-1
0
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5
position (deg)

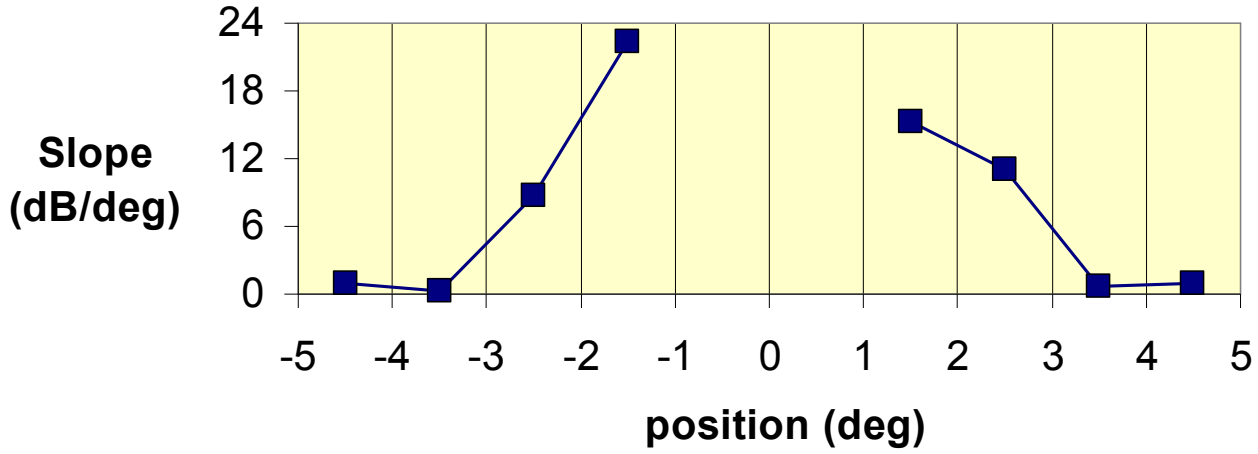
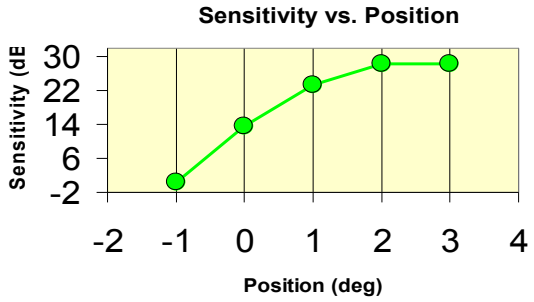


Figure 6. For one subject, horizontal profile plots of **(a)** sensitivity vs. position; **(b)** variability vs. position; **(c)** slope vs. position. The figure shows that variability is greatest near the edge of the blindspot, where the slope was also steep.

Profile plots of vertical blindspot edges are not presented here. Vertical slopes were found to be less steep than horizontal slopes, but the data at vertical edges were particularly noisy, probably due to the presence of retinal vessels, which branch superiorly and inferiorly. These vessels obscure parts of the retina and can cause scattering of the stimulus, making it difficult to obtain true sensitivity measurements.

Figure 7 shows profile plots of sensitivity, variability and slope across a scotoma edge for one glaucoma patient. The general trends present in these plots are similar to those for the blindspot data of Fig. 6.



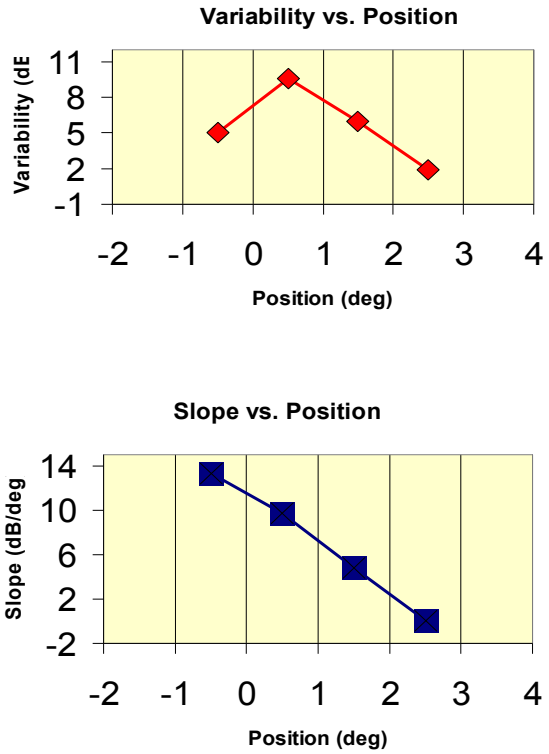
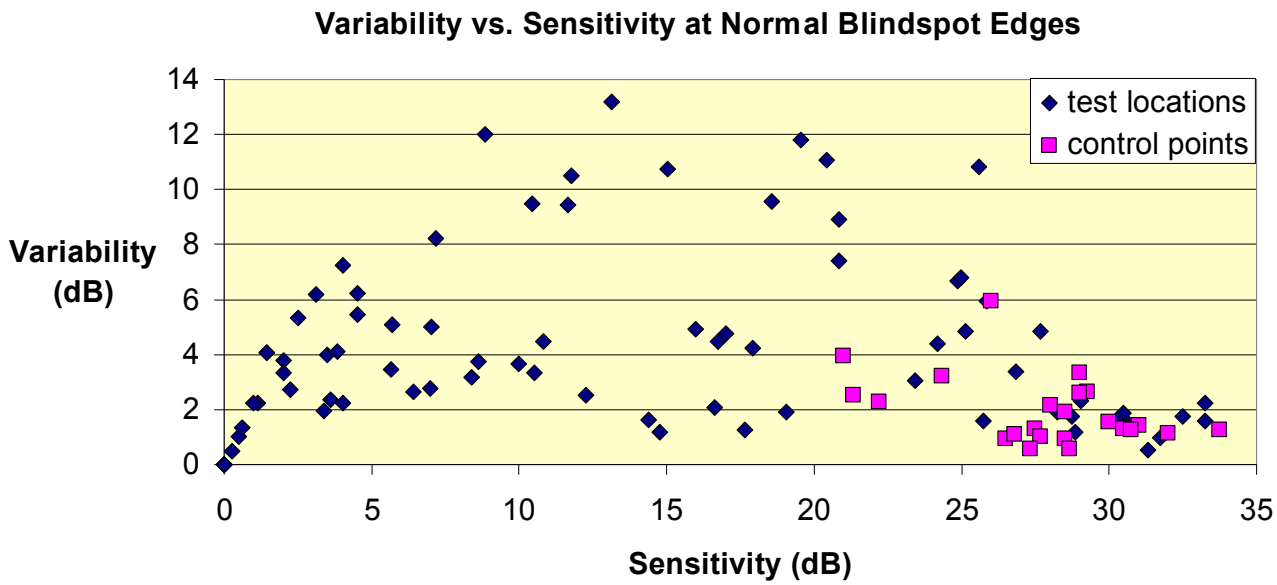


Figure 7. For one glaucoma patient, profile plot across a scotoma edge of **(a)** sensitivity vs. position; **(b)** variability vs. position; **(c)** slope vs. position.

[3.3] The Relationship of Variability and Sensitivity in NS and GP

Figures 8(a) and 8(b) show scatterplots of variability versus sensitivity in NS and GP for individual test locations. Note that variability could be as high as 14 dB for normal subjects. The greatest variability was found in the mid-sensitivity range (ie. between 10 and 20 dB). The relationship between variability and sensitivity followed an inverted, U-shaped curve in both groups. Points that had high sensitivity or low sensitivity were associated with low variability. The majority of points tended to fall in either end of the sensitivity range. The purple, square points are control locations and typically had high sensitivity.



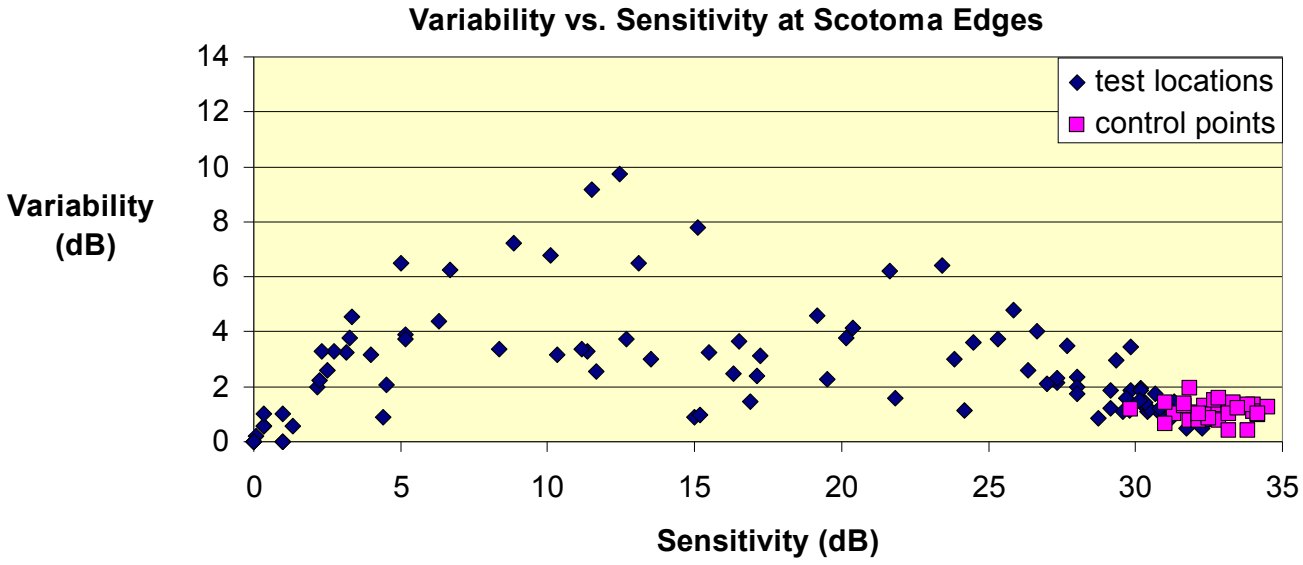


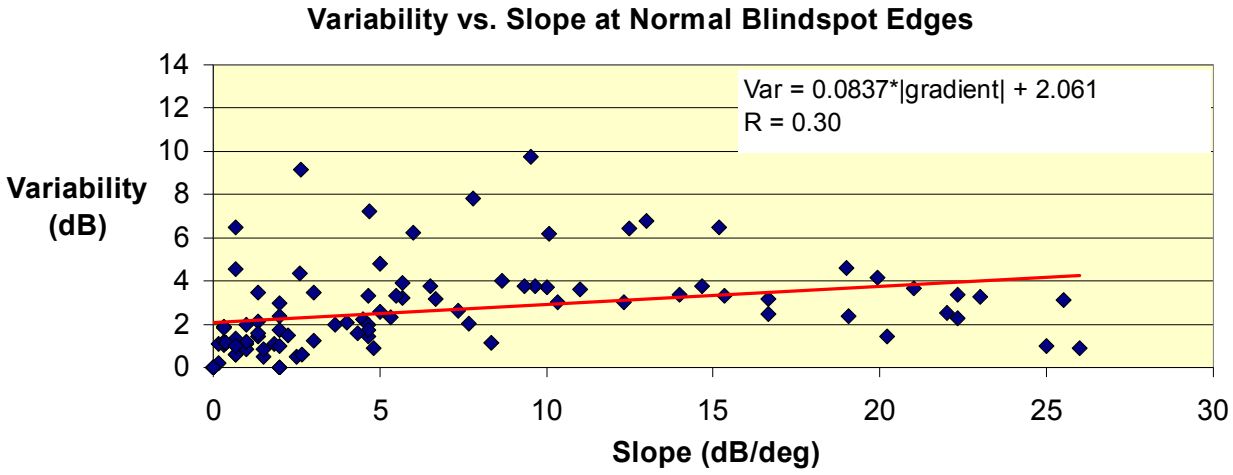
Figure 8. (a) Plot of variability versus sensitivity in six normal subjects. **(b)** Plot of variability vs. sensitivity at the scotoma edges in six glaucoma patients. Test locations are shown as diamond symbols. Control points were represented in square symbols.

For each individual array crossing blindspot edges and scotoma edges, the variability with the largest value (ie. peak variability) was identified. All the values of peak variability were averaged separately for NS and for GP, with GP (6.3 ± 3.3 dB) greater than NS (3.1 ± 1.4 dB). This difference was statistically significant with a P-value < 0.001.

[3.4] Relationship of variability and slope in NS and GP

Figure 9 shows the relationship of variability and local |slope| for NS and GP. When analyzed as a group, there was a modest correlation of variability and slope. As the slope increased, variability tended to increase. The majority of points can be found in the low variability and shallow areas of the graphs. The plot of linear regression had a correlation of 0.30 for controls, and 0.11 for patients with glaucoma.

Regression lines were also shown in figures 9(a) and 9(b). The slope of the linear regression was measured in terms of $\Delta y/\Delta x$, where y is variability (dB) and x is slope (dB/deg). Therefore, the slope is in units of degrees, which was the unit of measure for the grid spacings of the test locations. NS had a slope of 0.08 deg and GP had a slope of 0.05 deg.



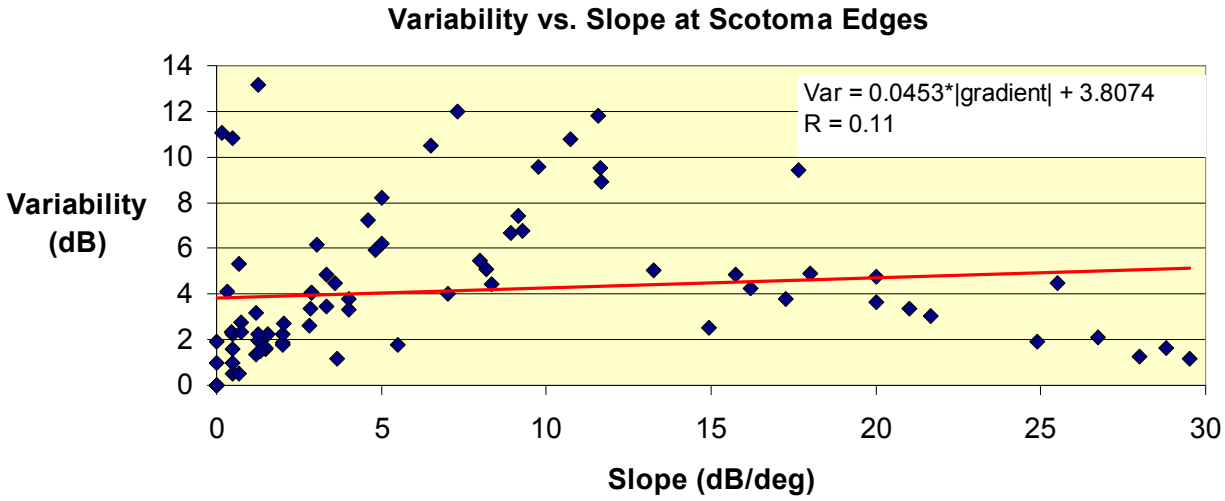


Figure 9. (a) Plot of variability (dB) vs. slope (dB/deg) in seven normal subjects. **(b)** Plot of variability vs. slope at the scotoma edges in six glaucoma patients.

Individual relationships of slope and variability in NS and GP

Comparisons have been made between normals and glaucoma patients as a group. However, information might be lost in this grouping. Individuals may have subtle differences (eg. eye movements) that could affect the correlation between slope and variability. Individual correlations were presented in Table 1. The average correlation in NS was 0.55 (range: 0.39-0.81) and for GP was 0.30 (range: 0.11-0.83). Individual slopes of linear regression were also calculated for NS and GP. There was no difference in slopes of linear regression (average: 0.095 controls, 0.090 patients, $p < 0.47$).

Normals	R	Slope of linear regression	Patients	R	Slope of linear regression
NS1	0.81	0.13	GP1	0.83	0.20
NS2	0.39	0.03	GP2	0.25	0.19
NS3	0.52	0.14	GP3	0.17	0.02
NS4	0.70	0.06	GP4	0.11	0.00

NS5	0.44	0.04	GP5	0.25	0.13
NS6	0.45	0.03	GP6	0.21	0.04
Mean	0.55	0.095	Mean	0.30	0.090

Table 1. Normal subject and glaucoma patient correlations and slopes of linear regression with excluded vertical data.

Eyes with larger slopes of linear regression had stronger correlations between variability and slope. In GP, three subjects (GP1, GP2, GP5), and in NS, two subjects (NS1, NS3), had relatively stronger correlations and steeper slopes of linear regression. In contrast, individuals with weaker correlations had slopes of linear regression that were nearly zero.

[3.5] Comparisons of fixation inaccuracy, variability, and slope between NS and GP

Fixation inaccuracies in the test of visual function

As defined earlier, fixation inaccuracy is the average amount of error from the fixation point. Figure 10(a) and (b) showed fixation inaccuracies for each individual and also the average on the far left. Results were ordered from increasing fixation inaccuracy. The values were not significantly different: 1.2 ± 0.6 deg for normals and 1.3 ± 0.6 deg for patients, (p-value of < 0.9).

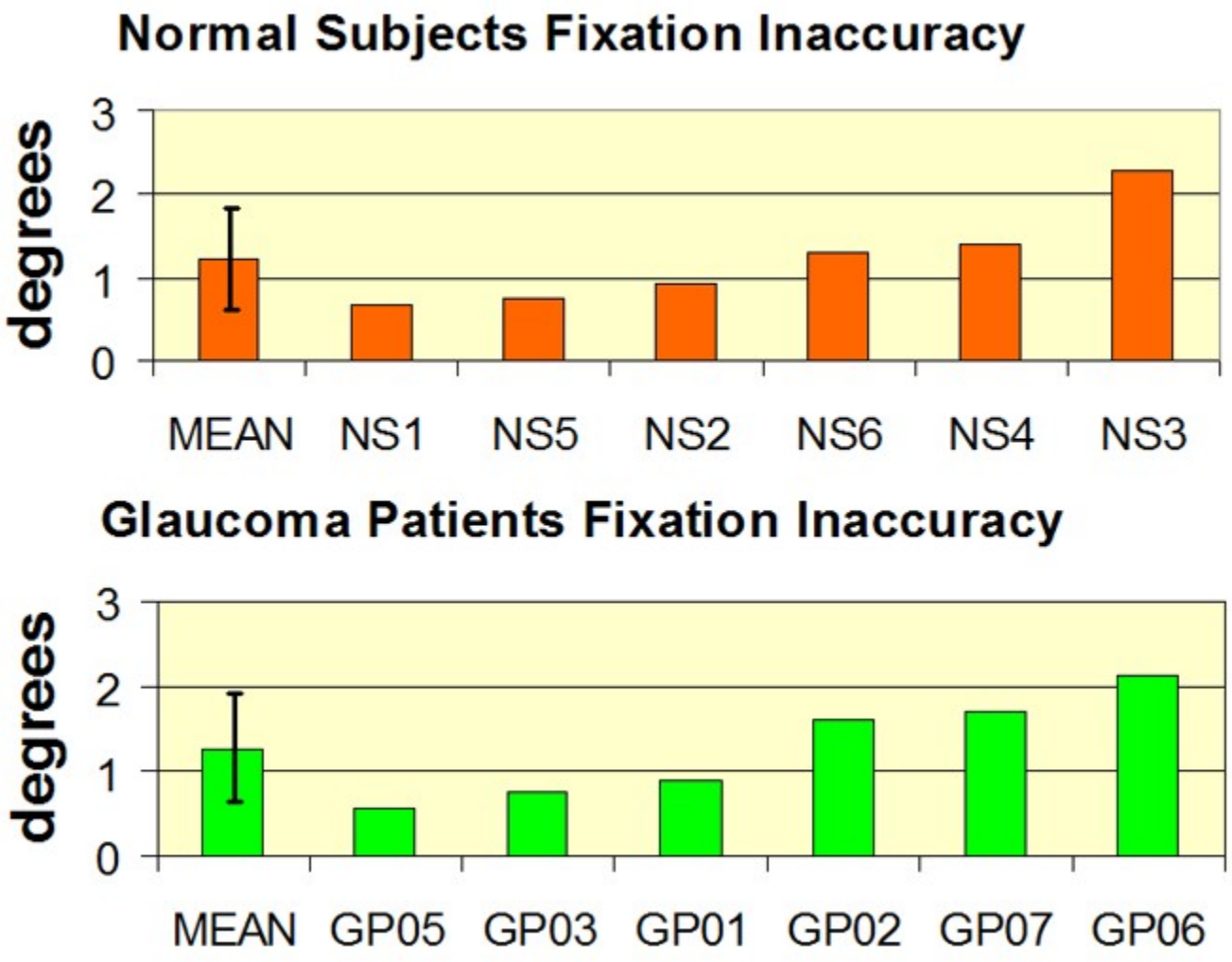


Figure 10. (a) Glaucoma patients fixation inaccuracies. **(b)** Normal subjects fixations inaccuracies. Means for each group are presented in the first bin.

Fixation inaccuracies in the test of visual function versus the attention task

A test requiring peripheral attention might negatively influence the ability to maintain fixation. If so, then an attention task with no peripheral stimuli should create a narrower eye position distribution. Fixation inaccuracies were continually recorded. The total time for each attention test was fixed at 5 minutes. The false positive rates, which showed how often a subject responded positively in the absence of a true stimulus, were low: 1.9 ±1.6% (range: 0% - 4.1%).

For each subject performing the attention task, the observed variability of eye position was calculated and was measured as standard deviation (SD) from fixation. Although the pupil tracker recorded the fixation inaccuracy along the horizontal and vertical meridians, only horizontal data are presented here. Some subjects' vertical data were contaminated by lid intrusion.

For comparison, the same subjects performed a test of visual function with peripheral targets. The average horizontal variability of all subjects in the visual function test was 0.43 +/- 0.19 deg versus 0.32 +/- 0.06 deg in the attention task. In figure 11, intra-subject comparison showed less horizontal fixation inaccuracies in the attention task than in the visual function test for most subjects. However, this difference was not significant by paired t-test (p-value < 0.12). Note that eye position variability in the attention task was substantial despite the absence of peripheral distractors.

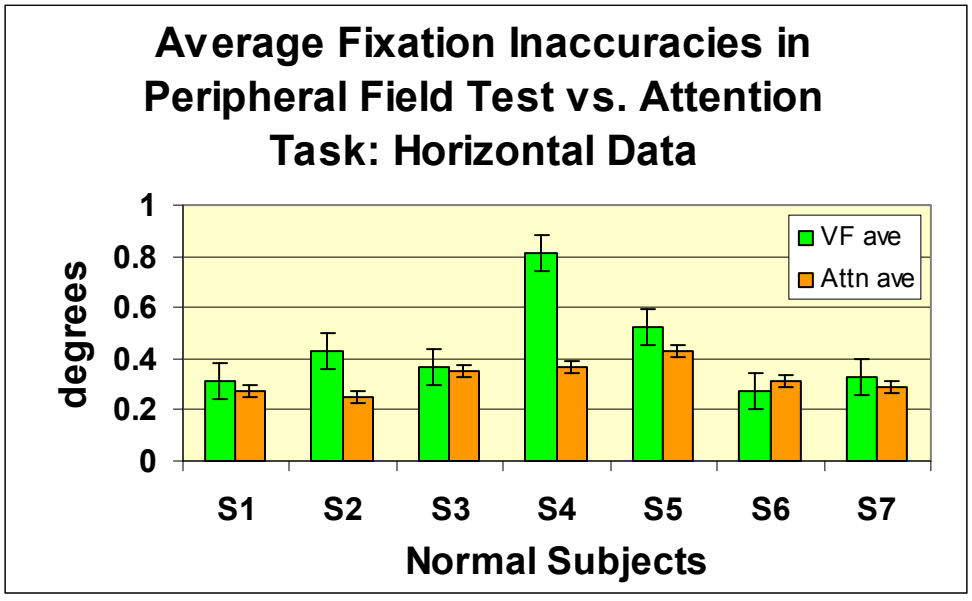


Figure 11. Comparison of average horizontal fixation inaccuracies in peripheral field test versus attention task for seven normal subjects.

Variability and Slope in the mid-sensitivity range

To compare variability in NS versus GP, only points within the mid-sensitivity range of 10 to 20 dB were used. The points in this range exhibited sensitivity with the greatest variability over repeated measurements, and this variability was thought to be randomly distributed.* GP had greater variability than NS, but not significantly ($p<0.09$).

*To show that the points within the mid-sensitivity range were randomly distributed, a Normal Plot was created as shown in figure 9. The Normal Plot is a cumulative frequency distribution for the data against the cumulative frequency distribution for the standard normal distribution. (Bland, M. An Introduction to Medical Statistics) A normal distribution of data is indicated by the degree to which the plot is linear. For GP and NS, the normal plot of variability data has a linear regression with a correlation of R=0.95 and R=0.93, respectively.

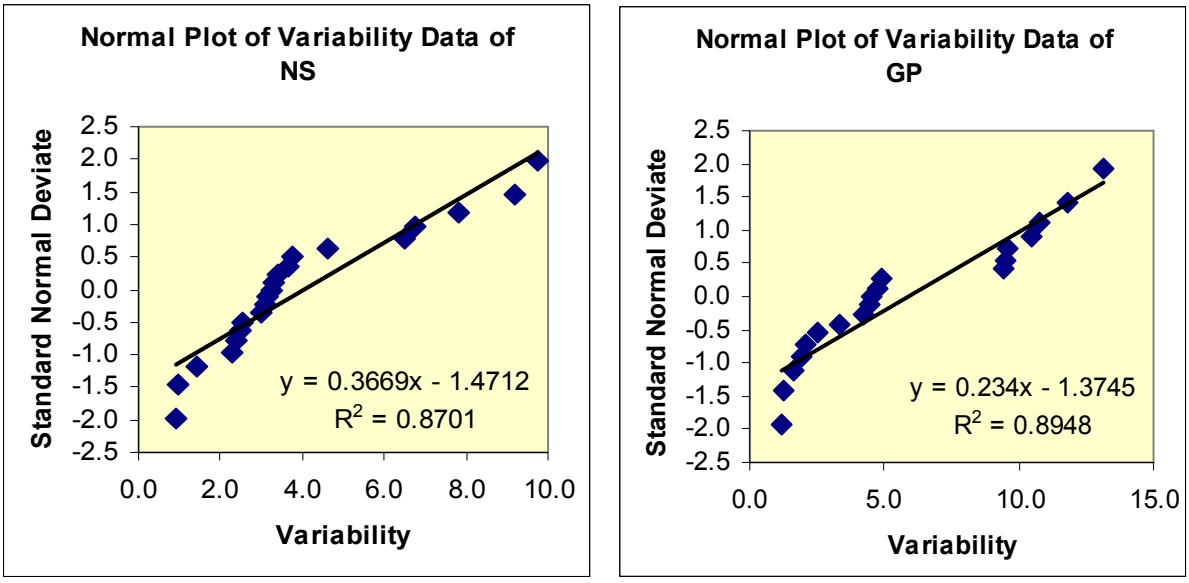


Figure 12. Plot of the standard normal deviate against observed variability for **(a)** GP and **(b)** NS data. In both groups, the correlation of variability with the standard normal curve is strong, signifying a random distribution for the variability data.

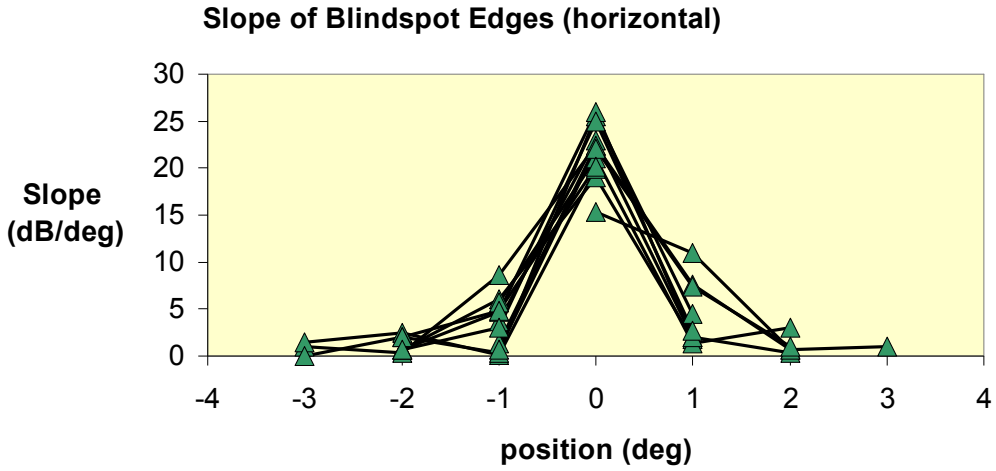
Slope of sensitivity in blindspot edges versus scotoma edges

Figure 13(a) shows slope of sensitivity values from all horizontal linear arrays that crossed the blindspot edges in NS. Similarly, figure 13(b) shows slope values from all linear arrays that crossed scotoma edges in GP.

In these plots, the maximum slope for each test array was arbitrarily positioned at 0 degrees on the x-axis. The x-axis represents a relative value that describes, for a point in an array, the degrees of retinal position from the maximum local slope of that array.

Note that most slopes that were ± 2 degrees away from the maximum slope were very low. As you approach the edge of a physiological or scotomatous edge, the slopes increased very fast.

The maximum slope of sensitivity can vary widely. In GP, slopes were as high as 29.5 dB/deg. For the blindspots, the horizontal edge slopes ranged from 15.3 to 26.0 dB/deg.



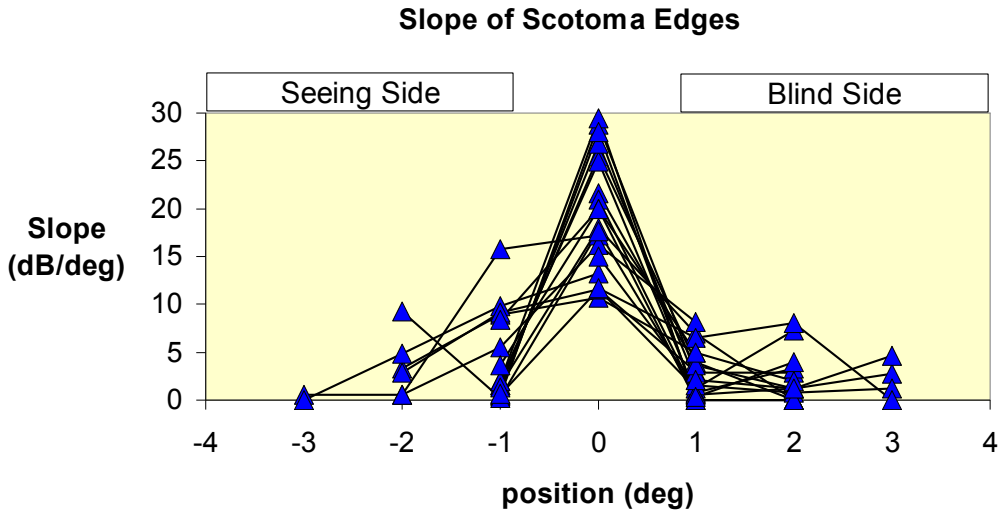


Figure 13. (a) Horizontal slopes of sensitivity of NS across blindspot edges. **(b)** Slopes of sensitivity of GP across scotoma edges. Arrays were positioned from healthy retina (Seeing Side) to sick retina (Blind Side).

[3.6] Comparisons of variability at the scotoma edge versus the blindspot edge in one glaucoma patient

In a glaucoma patient (GP03), two separate tests of visual function were performed: one across edges of glaucomatous scotomas and the other across edges of the physiological blindspot. Blindspot edges used in testing were free from glaucomatous damage. For this patient, damage was found only at the superior edge of the blindspot. Fixation inaccuracy was measured based on the gaze-tracking records of the HFA with 0.75 deg (range: 0.54 – 0.97) for scotoma data and 0.79 deg (range: 0.57 – 0.96) for blindspot data. There was no clear difference between the two sets of data.

The average variability of sensitivity for the scotoma visual field was 2.09 +/- 1.68 dB, while the average variability of sensitivity for the blindspot was 4.27 +/- 2.58 dB. The difference was slightly significant by t-test (p-value < 0.06).

For GP03 alone, the correlation of variability and slope for horizontal blindspot edges was 0.55. The same correlation for scotoma edges for GP03 was 0.17; however, if two data points with very steep slopes were removed, the correlation became 0.58. Issues concerning data with extremely steep slopes are examined in Discussion.

[4.0] Discussion

Test-retest variability was found to be correlated with the local slope of sensitivity. Wyatt et al. previously found this correlation in particular in 10-2 perimetry data (Wyatt et al., 2007). The correlation was especially strong at scotoma edges of glaucoma patients and blindspot edges in normals. Using 1-degree test spacing, average correlations of 0.55 for normals were very similar to previous studies using 2-deg spacing. (Wyatt et al., 2007; Wyatt, ARVO abstract, 2007)

Haefliger and Flammer (1989) observed greater variability at scotoma edges (2-15 dB) compared to blindspot edges (1.5-5 dB). In general agreement with Haefliger and Flammer, the present study also observed greater variability at scotoma edges, but the difference was less significant ($p < 0.09$).

[4.1] Contributing factors to variability

This study was to determine whether eye movements, especially near steep slopes, could be the basis for the correlation between test-retest variability and local slope of sensitivity. Other possible contributing factors to variability such as inhomogeneity of the edge and choice of testing protocol were also considered.

Slope

The examination of Haefliger and Flammer's Figures showed slopes at blindspot and scotoma edges as high as 15 dB/deg (blindspot: Haefliger & Flammer, 1989, Fig. 3; blindspot and scotoma:

Haefliger & Flammer, 1991, Fig. 1). In contrast, calculated slopes in the present study were as high as 26 and 30 dB/deg for blindspot and scotoma edges, respectively, with no significant difference in both groups of data. Since the present study and their studies all used 1-degree spacing, the reason for the disparity in slope is not immediately apparent. One possibility is the configuration of the test array; many glaucomatous scotomas are arcuate with edges approximately parallel to the fiber bundles in the retinal nerve fiber layer. Theoretically, the greatest slope should be found when the array is placed perpendicular to the scotoma edge. The present work approximated this method by vertically orienting the arrays. It is uncertain from Haefliger and Flammer's paper (1991), which were based on coarse-grid visual fields, whether the best orientations were used along the contours. It is possible that steeper slopes may have been present along contours with other orientations.

From analysis of tabulated data in an earlier study by Israel (1968), blindspot edges were never steeper than 15 dB/deg. That study used test locations along the horizontal meridian which is often vertically displaced from the blindspot center. The array was therefore probably not perpendicular to the blindspot edge.

Larger slopes were found when changing test arrays from 2-deg spacing to 1-deg spacing. It is possible that even larger slopes could be found with testing of finer than 1-deg test spacing. However, the size III targets (0.4 deg diameter) would overlap if spacing were much less than 0.5 deg. In addition, it is not clear that effective test spacing can be made meaningfully smaller than fixation inaccuracy, and the latter was approximately within ± 1 deg.

Fixation inaccuracies

The magnitudes of fixation inaccuracies were statistically similar in both normals and patients. Given the hypothesis that fixation inaccuracy, interacting with the local slope of sensitivity, forms the basis for variability, the similarities in fixation inaccuracies does not provide an explanation for the difference in variability between scotoma and blindspot edges.

Henson and Bryson (1990) hypothesized that the magnitude of fixation inaccuracies might cause a portion of test-retest variability. Henson et al. (1996) later rejected this hypothesis because substantial variability remained even when fixational eye movements were smaller than 1 deg. However, Wyatt et al. (2007) had found that at very steep slopes, even small eye movements (< 1 deg) can generate large changes in sensitivity.

The nature of the scotoma edge versus the blindspot edge

It is possible that the characteristics of the scotoma edge could explain the greater variability here. For example, glaucomatous scotoma edges might contain an inhomogeneous mixture of healthy and damaged ganglion cells. In repeated testing, small fixational eye movements can shift testing at one nominal location, which might include some healthy ganglion cells, to a location of only damaged ganglion cells in the next test. This sort of inhomogeneous "patchiness" could occur over distances considerably smaller than the test spacing, and would not be noticed in the calculation of slopes.

It should be noted that any situation in which variability is related to small eye movements, whether the larger-scale slopes or finer-scale inhomogeneity, will be affected by the standard staircase algorithms used in perimetry: a single threshold determination, involving repeated test presentations, will actually test a number of slightly different locations at different steps in the determination.

A different hypothesis regarding scotoma edges is that on one side of an edge, ganglion cells are relatively healthy, on the other side they are badly damaged, and near the edge they are "sick" and therefore highly unpredictable in their responses to a given stimulus. This sort of increase in intrinsic variability of a given population of cells would not depend on fixational eye movements; however, it would still be found in close association with edges. Kasten et al. (1998), after testing patients with cerebral blindness, concluded that unreliable responses was a functional expression of residual visual structures in the damaged brain. It is worth noting, however, that this hypothesis would not explain the high variability also observed at blindspot edges.

Variability from testing protocols

Another source of test-retest variability might be related to the nature of testing protocols. The HFA perimeter employs the SITA standard algorithm, which is based on a "growth pattern". Four primary locations are tested first, and initial stimulus values for neighboring locations are based on the results at the primary locations (Anderson & Patella, 1999). If a primary location was tested at a scotoma edge, which is variable, then the estimates of neighboring location stimulus values could contain greater error. Previous studies have shown that the starting stimulus value affects the final value when employing this algorithm (Malik et al., 2006), and it is possible that this algorithm might make greater estimate errors near scotoma edges. However, an investigation by Pan, Swanson, and Dul (2006) measured all test locations starting with the same (maximum) initial stimulus value and still found greater variability at damaged areas. Therefore, this sort of protocol-based variability source is not likely to have played a substantial role in the present findings.

[4.2] The relationship between test-retest variability and slope

The linear regressions of variability vs. slope, as seen in Results Figures 9(a) and (b), had slopes which averaged 0.083 for patients and 0.045 for normals. It was suggested by Wyatt et al. (2007) that the slopes of such regressions could directly relate to the amount of fixation inaccuracy. (If there is no fixation inaccuracy, local slope does not create variability.) In the present results, normals had a smaller regression slope, which might be taken as less fixation inaccuracy; however, fixation inaccuracies for normal subjects and glaucomatous patients did not appear to differ. Moreover, individual regression slopes were not found to be directly associated with their average fixation inaccuracies.

In Table 1 of Results, the average correlation of variability vs. slope was 0.30 in patients and 0.55 in normals, a clear difference. It should be noted, however, that the higher *correlation* was found for the normal subjects, although the greater *variability* was found at scotoma edges.

Based on results of modeling, Wyatt has suggested that if scotoma edges are very sharp, while blindspot edges are more gradual, greater variability would be observed at the former, even though the difference in steepness could be undetectable by conventional perimetry (American Academy of Optometry, 2008). Close to sharp edges, more or less *any* amount of eye movement can generate large differences in test results; near more gradual edges, amount of variability is more related to amount of eye movement and slope of the edge. Thus, the behavior near sharp edges could result in lower correlation between variability and (measured) slope, as found for the glaucoma patients.

Patients and normals with better control of their fixation are less likely to show a correlation of variability with slope. For example, the two glaucoma patients with the lowest correlation also showed the smallest fixation inaccuracies. This would fit with the suggestion that fixation inaccuracies play a role in variability.

[4.3] Attention task

Fixation inaccuracies were reduced, but not significantly, in an attention task vs. a peripheral visual field test in normals. In the attention task, subjects tended to deviate less from central fixation, but substantial eye movements were still present. The subjects who performed this test were mainly younger subjects, and it is possible that greater differences might be found in a group of older subjects.

[4.4] Blindspot of a glaucoma patient

The variability at the blindspot of one glaucoma patient (GP03) was found to be rather high, but within the range of values found for normals. For GP03, the average variability for the scotoma edges was 2.1 ± 1.7 dB, while the average variability for the blindspot edges was 4.3 ± 2.6 dB. The two types of edges in this patient showed a marginally significant difference by t-test ($p < 0.06$). It is interesting that the variability at scotoma edges with respect to blindspot edges for GP03 was the reverse of what was found for the subject and patient groups, mainly due to the low scotoma-edge variability found for GP03.

It would be interesting to explore this further in other glaucoma patients with preserved disk edges. Fixation inaccuracies were similar during testing of blindspot edges versus scotoma edges in GP03.

[4.5] A non-linear correlation of slope and variability

As discussed, it has generally been found that test-retest variability is correlated with the local slope of sensitivity. This turned out to be less true at the very steepest measured slopes. Consider the following case where a slope of 30 dB/deg was measured. For 1 degree test spacing, points A and B must have sensitivities of approximately 30 and 0 dB, or vice versa. (The maximum sensitivity detected by a normal subject on a Humphrey perimeter is typically about 34 dB). In order for average sensitivity to be 30 dB at a point, the variability at that point *must* be very small. Consider the contrary: if there is high variability (say thresholds of 30, 20, 30, and 15 dB and SD = 7.5 dB), then the average sensitivity is reduced to 23.8 dB. In order to get an average sensitivity of 30, without any values much above 30, requires that no values fall far below 30 either; i.e., variability must be low. In other words, extreme values of sensitivity can only occur with a group of test repeats that shows very little variability.

The property of data, that extreme sensitivity values can only be measured when a subject gives a set of values with very low variability, means that very high slope values are derived from points with low variability. This runs counter to the general trend that larger slopes of sensitivity are associated with increased variability, and a few such extreme points can reduce the overall correlation. To assess the importance of this effect, the correlation between variability and slope was determined using different values of a "cutoff slope" or maximum slope permitted. (If a location had slope greater than a nominal cutoff slope, that location was not included in the correlation determination.) As shown in Figure 14 below, as the cutoff slope value was reduced, the correlation strengthened. For normals, the correlation peaked at a cut-off slope of 20 dB/deg. For glaucoma patients, the correlation peaked at 15 dB/deg. The aim here was not to precisely locate these peaks, but rather to illustrate the point that extreme slope values can reduce the correlations. Further study is needed on this interesting topic.

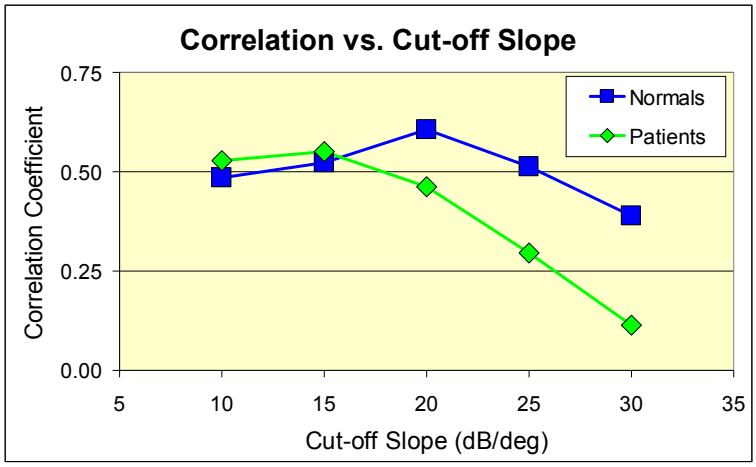


Figure 14. Plot of correlation versus cut-off slope in normals and patients. For both groups, the strength of correlation coefficients tapered at very steep slopes.

Steep local slopes, together with small fixational eye movements, were likely to contribute to variability in both controls and glaucoma patients. It was observed that scotoma edges had greater variability than blindspot edges, confirming the findings of Haefliger and Flammer. This *could* be caused by factors such as subtle differences in eye movements, or differences in the nature of scotoma edges vs. blindspot edges. Further testing with accurately stabilized test locations will be needed to distinguish the possible causes of greater variability at scotoma edges.

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