

Characteristics of Frequency-of-Seeing Curves in Normal Subjects, Patients With Suspected Glaucoma, and Patients With Glaucoma

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Purpose. The authors performed this study to determine factors that affect the characteristics of frequency-of-seeing curves in normal subjects, patients with suspected glaucoma, and patients with glaucoma.

Methods. The sample consisted of 70 subjects (22 normal subjects, 12 patients with suspected glaucoma, and 36 patients with glaucoma). A program was written to interface with the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA) to measure frequency-of-seeing curves. The authors presented stimuli 8 dB either side of the estimated threshold in 1-dB intervals with five repetitions at each stimulus intensity. The authors tested four to six locations in each subject, with randomization of the stimulus intensity and location. Fixation was monitored with the Heijl-Krakau method. Using a probit program, the authors calculated the threshold and slope (estimated by the interquartile range) of each curve.

Results. The authors obtained 124 curves from the normal subjects, 71 from the patients with suspected glaucoma, and 183 from the patients with glaucoma. In all three groups, the slope of the frequency-of-seeing curve was correlated highly with the threshold or threshold deviation, although the correlation was significantly higher in the normal subjects compared with the patients with suspected glaucoma and patients with glaucoma, even after controlling for the range of the threshold and threshold deviation. For this reason, the authors found considerably different frequency-of-seeing curves, between subject groups and also within the group of patients with glaucoma, in locations with the same threshold.

Conclusions. There may be fundamental differences in areas of normal subjects and patients with glaucoma with similar thresholds or threshold deviations. These differences also may exist within patients with glaucoma. *Invest Ophthalmol Vis Sci.* 1993;34:3534–3540.

Frequency-of-seeing curves describe the relationship between the probability of seeing a stimulus and a stimulus property such as contrast or size. They can be thought of as cumulative Gaussian functions that depict local threshold variability.¹ Frequency-of-seeing curves measured with stimuli used in conventional perimetry have been described previously in normal sub-

jects^{2,3} and patients with glaucoma,^{3,4} but the number of subjects generally has been small.

The characteristics of frequency-of-seeing curves have implications not only for perimetric thresholds and their variability, but also for modeling perimetric responses in simulation experiments. Previous studies describing such experiments have assumed that the threshold and threshold variability are related linearly,^{5,6} with lower thresholds (or higher sensitivities) yielding lower variability. In frequency-of-seeing curves, a steep slope reflects low threshold variability, whereas a more shallow slope reflects higher variability. Perimetric responses in simulation experiments generally are determined with the slope of the frequency-of-seeing curve because the probability of seeing a stimulus of a given intensity is known. Perimetric

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Supported in part by research grant MT-11357 from the Medical Research Council of Canada (BCC).

Submitted for publication November 25, 1992; accepted May 19, 1993.

Proprietary interest category: N.

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responses in normal subjects can be modeled theoretically with considerable accuracy because the slope of the frequency-of-seeing curve can be described by the local threshold, visual field location, and age.² It is not clear whether the same applies to responses in patients with glaucoma.

We wanted to perform a comprehensive study of the characteristics of frequency-of-seeing curves in normal subjects, patients with suspected glaucoma, and patients with glaucoma. We also planned to determine whether the same type of theoretic modeling as that used to simulate normal visual fields could be applied to glaucomatous fields. We particularly wanted to compare frequency-of-seeing curves obtained at locations in patients with glaucoma and normal subjects with similar thresholds and similar threshold deviations from age-corrected normal values.

SUBJECTS AND METHODS

Subjects

The study sample consisted of 22 normal subjects (mean age, 54.27 years; range, 34 to 76 years), 12 patients with suspected glaucoma (mean age, 54.83 years; range, 36 to 77 years), and 36 patients with open-angle glaucoma (mean age, 66.78 years; range, 36 to 86 years). The normal subjects were recruited from a group of subjects undergoing other psychophysical studies. All normal subjects had normal visual fields defined by the Statpac program of the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA)⁷ and a negative family history of glaucoma. The patients with suspected glaucoma and those with glaucoma were recruited consecutively from the clinical practice of one of us (RPL). Patients with suspected glaucoma had normal visual fields as defined above; however, 10 of 12 of these patients had consistently increased intraocular pressures (> 22 mm Hg), whereas the remaining 2 had suspect optic disks on the grounds of asymmetry with the fellow eye. Patients with glaucoma had glaucomatous visual fields (with early to advanced damage) and optic disks. All subjects had an ophthalmic examination, visual acuity of 6/9 or better, previous experience with perimetric examinations, pupil diameter of at least 3 mm when tested, and a spectacle correction not exceeding 4.00 diopters (equivalent sphere). The study was approved by the Camp Hill Medical Centre Research Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject.

Testing Methods

The Humphrey Field Analyzer can be controlled externally by a personal computer through a series of

commands. We have written a computer program that uses these commands and allows us to conduct many customized tests, including the measurement of frequency-of-seeing curves.

In normal subjects and patients with suspected glaucoma, we tested locations along the 45, 135, 225, or 315 meridian, chosen randomly. In patients with glaucoma, we tested locations in scotomas and areas with normal thresholds. Only one eye of each subject was tested. In most subjects we tested six locations, although in a small number of patients with glaucoma we tested four or five locations. All locations were tested with a white Goldmann size III stimulus (visual angle = 0.43) on a white background of 31.5 asb.

We first used the computer program to carefully determine the center of the blind spot. The thresholds at the chosen test locations then were estimated with a standard 4-2 staircase procedure.⁸ We then presented stimuli within a range of 8 dB either side of the estimated threshold in 1-dB steps, with five trials at each stimulus intensity. Therefore, there were 85 trials per location. The location and stimulus intensity were randomized during testing. Fixation was monitored with the Heijl-Krakau technique,⁹ with a maximum luminosity stimulus (10,000 asb) presented in the measured center of the blind spot every fifth presentation during the first 50 presentations, and every twenty-fifth presentation thereafter. Numerically, the rate of fixation losses was the percentage of blind spot presentations reported by the subject over the total number of blind spot presentations.

Data Analysis

The frequency-of-seeing at each stimulus intensity was computed. These data were subjected to a probit analysis, which fitted a frequency-of-seeing curve to the data. The threshold was taken as the stimulus intensity corresponding to the 50% frequency-of-seeing of the fitted curve. The threshold deviation was computed by subtracting the threshold from the age-corrected normal value for that specific location. The slope of the curve was estimated by calculating the interquartile range (stimulus intensity interval corresponding to 25% to 75% frequency-of-seeing) of the fitted curve. Figure 1 shows an example of a frequency-of-seeing curve with the calculated parameters.

Correlations between variables were examined with the Spearman correlation. Differences between correlation coefficients were determined with standard tests.¹⁰ An analysis of covariance was used to analyze the pooled data. Residuals of the regressions between the dependent variables and covariates were tested for normality and homoscedasticity. Where necessary, log transforms were performed. All statistical tests were two tailed, and statistical significance was set at $P < 0.05$.

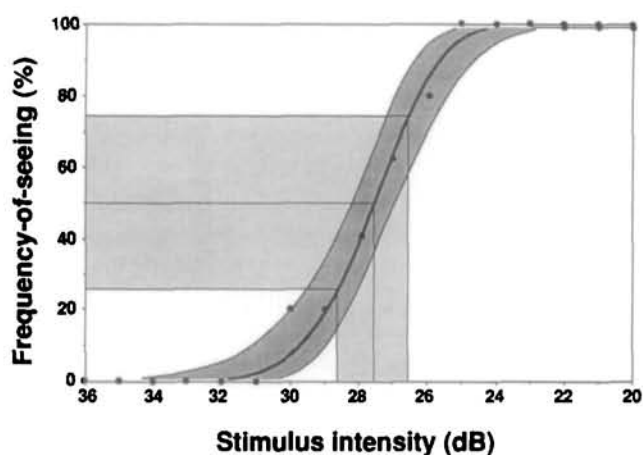


FIGURE 1. Example of a frequency-of-seeing curve. The data points represent the raw data; the solid line, the fitted curve; and the shaded area around the curve, the 95% confidence interval. The threshold is the stimulus intensity corresponding to 50% frequency-of-seeing. The interquartile range is an estimate of the slope of the curve and represents the stimulus intensity interval corresponding to the 25% to 75% frequency-of-seeing.

RESULTS

The median rates of fixation losses during testing in normal subjects, patients with suspected glaucoma, and patients with glaucoma were 4.3% (minimum 0%, maximum 19.1%), 4.3% (minimum 0%, maximum 21.3%), and 6.38% (minimum 0%, maximum 25.5%), respectively. None of the normal subjects, one patient with suspected glaucoma (8.3%), and two patients with glaucoma (5.5%) exceeded the current suggested fixation loss criteria ($\geq 20\%$ fixation losses) for unreliable fields.⁷

We were able to fit frequency-of-seeing curves to 124 of the 132 (94%) tested locations in normal subjects, 71 of the 72 (98%) tested locations in patients with suspected glaucoma, and 183 of the 203 (90%) tested locations in patients with glaucoma. Table 1 shows the distribution characteristics of the curves in the three groups. There were statistically significant differences between the patients with glaucoma and the groups with normal subjects and patients with suspected glaucoma in the eccentricity, threshold, threshold deviation, and interquartile range of the tested

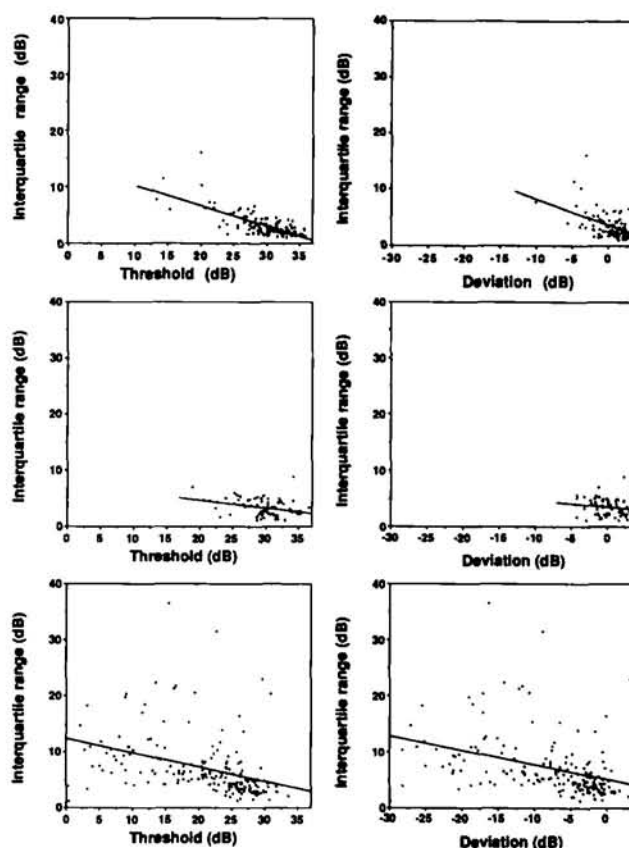


FIGURE 2. Relationship between interquartile range and the threshold (left) and threshold deviation (right) of the frequency-of-seeing curves obtained in normal subjects (top), patients with suspected glaucoma (center), and patients with glaucoma (bottom). The solid line represents the least-squares linear fit through the data.

locations ($P < 0.05$); however, the differences between the patients with suspected glaucoma and normal subjects in any of the four corresponding variables were not significant ($P > 0.05$).

There was a significant correlation ($P < 0.005$) between interquartile range and threshold in all three subject groups (Fig. 2, left). The degree of correlation in the normal group ($r = -0.71$), however, was considerably higher ($P < 0.005$) than that in the patients with suspected glaucoma ($r = -0.32$) or patients with glaucoma ($r = -0.37$). Although the relationship between the interquartile range and threshold was statistically

TABLE 1. Summary Statistics of the Parameters of the Frequency-of-Seeing Curves

	<i>Normals</i>	<i>Glaucoma suspects</i>	<i>Glaucoma patients</i>
Eccentricity of tested location ($^{\circ}$)	21.2 (2.8, 42.4)	17.2 (2.8, 35.4)	15.8 (2.8, 31.1)
Threshold (dB)	30.2 (13.3, 35.9)	29.9 (18.9, 36.5)	23.1 (0.3, 37.0)
Deviation (dB)	1.3 (-10.0, 5.0)	0.1 (-4.4, 4.5)	-5.3 (-29.9, 3.6)
Interquartile range (dB)	2.9 (1.0, 16.1)	3.4 (1.2, 8.9)	5.4 (1.1, 36.6)

Values shown are median (minimum, maximum).

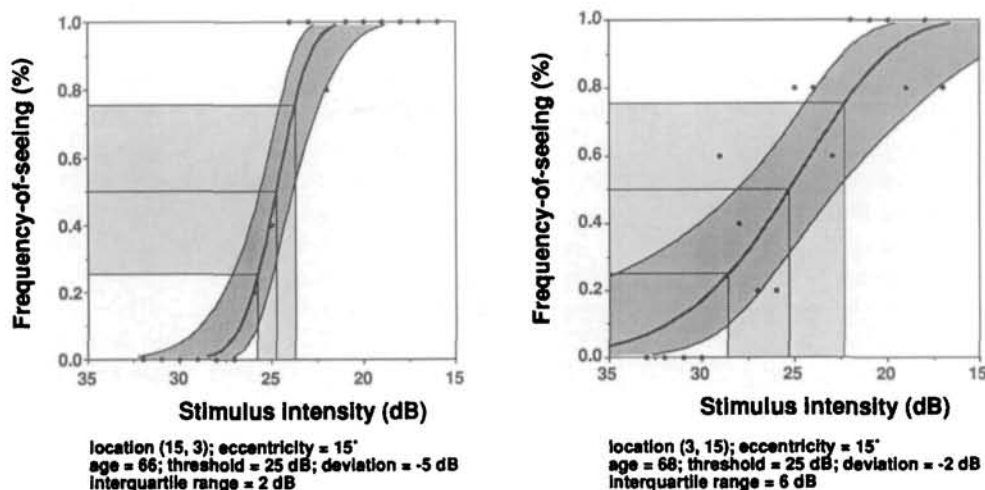


FIGURE 3. Frequency-of-seeing curves obtained from two patients with glaucoma with similar ages, at locations with identical eccentricities and thresholds. One curve (*left*) has a relatively steep slope, whereas the other (*right*) has a considerably more shallow slope (by a factor of 3).

strong, some data points in the group of patients with glaucoma deviated considerably from the least-squares linear fit (Fig. 2, bottom left). Consequently, some patients with glaucoma with identical thresholds produced quite different frequency-of-seeing curves (Fig. 3).

The same patterns were evident in the three groups when we examined the relationship between the interquartile range and threshold deviation (Fig. 2, right). The deviations from the least-squares linear fit were most evident in the patients with glaucoma, with some patients with identical deviations showing frequency-of-seeing curves with markedly different slopes (Fig. 4).

To compare the groups across matched thresholds, we next included only those locations with thresholds lower than 24 dB (sensitivities ≥ 25 dB). There were 116 curves in the normal group, 64 in the group with suspected glaucoma, and 74 in the group with glaucoma. A computer program was written to identify each of the 549,376 possible triplet combinations for normal subjects, patients with suspected glaucoma, and patients with glaucoma and select those with a maximum threshold range (across each combination) of 0.5 dB with a limitation that each curve could be used only once. We identified 43 triplet combinations where the median threshold range across each combination was 0.12 dB and the maximum was

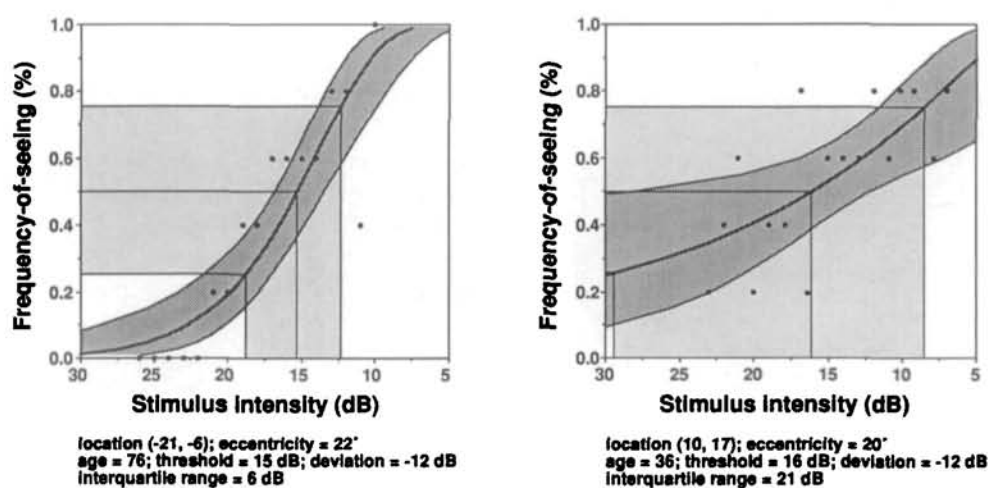


FIGURE 4. Frequency-of-seeing curves obtained from two patients with glaucoma at locations with identical threshold deviations and similar eccentricities. One curve (*left*) has a relatively steep slope, whereas the other (*right*) has a considerably more shallow slope (by a factor of 3.5).

0.47 dB. A persistence was found of the same trends detected in the whole data. An analysis of covariance (after applying a log transform to the interquartile range) confirmed that the group factor was highly significant (Table 2).

We performed a similar analysis to compare the groups across matched threshold deviations and included only those locations depressed from age-corrected normal values by 5 dB or less (deviations ≥ -5 dB). There were 117 curves in the normal group, 68 in the group with suspected glaucoma, and 93 in the group with glaucoma, allowing 739,908 possible triplet combinations. After the same limitations were applied as before, 35 triplet combinations were identified in which the median and maximum deviation ranges across each combination were 0.14 dB and 0.48 dB, respectively. The analysis of covariance again confirmed a significant group difference (Table 2).

These results indicate that even in locations with normal or mildly elevated thresholds, the relationship between interquartile range and threshold (or deviation) was different in the normal subjects, patients with suspected glaucoma, and patients with glaucoma. As an example, Figure 5 shows frequency-of-seeing curves obtained from subjects in the three groups. The locations tested had identical thresholds and threshold deviations, yet the curves obtained were very different. The normal subject showed a steep and "clean" curve, the patient with glaucoma had a shallow and "noisy" curve, and the patient with suspected glaucoma had a curve between the two extremes.

TABLE 2. Results (*P* Values) From the Analysis of Covariance in Matched Normal, Glaucoma Suspect, and Glaucoma Patient Combinations With Interquartile Range* as the Dependent Variable

	Data included if:	
	Threshold† <24 dB	Deviation‡ ≥ -5 dB
Factor		
Group	0.004	0.035
Covariate		
Threshold	0.002	—
Deviation	—	0.032
Age	0.941	0.056
Eccentricity of tested location	0.737	<0.001

* Log transformed.

† In clinical perimetry the measurement scales are inverted; therefore, thresholds <24 dB correspond to measured sensitivities ≥ 25 dB.

‡ On the Humphrey Field Analyzer, deviations ≥ -5 dB correspond to measured sensitivities that are depressed by ≤ 5 dB from age-corrected normal values.

DISCUSSION

Our study showed a relationship between the slope of the frequency-of-seeing curve (as estimated by the interquartile range) and threshold in normal subjects, patients with suspected glaucoma, and patients with glaucoma. This relationship is analogous to that reported previously between short-term fluctuation and threshold, which was determined with staircase procedures.^{11,12} We found that, although the relationship was statistically strong, the degree of correlation found in the group with suspected glaucoma and the group with glaucoma was much lower than that found in normal subjects. These differences persisted even after controlling for the range of threshold or threshold deviation. For this reason, we believe that in some cases there may be fundamental differences between normal subjects, patients with suspected glaucoma, and patients with glaucoma in visual field locations with similar thresholds (or deviations). We also found that the threshold or deviation cannot predict the shape of the frequency-of-seeing curve reliably in patients with suspected glaucoma and patients with glaucoma. This suggests that differences also may exist between areas of patients with glaucoma with similar thresholds or deviations.

Studies such as ours that report threshold characteristics at discrete visual field locations assume that the study subjects have fixated accurately because incorrect fixation during presentation of the stimulus may stimulate a location with a different threshold. Therefore, the effect of inaccurate fixation is related to the threshold gradient around the location tested. When the tested location is at the border of a scotoma, the effect of poor fixation is more significant compared with that when the tested location is situated in a normal area with a relatively flat threshold gradient (eg, between 5° and 10° from fixation).^{13,14} Similarly, if the tested location is within a scotoma with a flat threshold gradient, the effects of poor fixation will be less critical. Threshold variability is highest at the borders of scotomas¹⁵ and has led to suggestions that threshold variability can be attributed to small eye movements.^{16,17}

In our study, fixation was monitored with the Heijl-Krakau technique,⁹ which theoretically may not detect fixation errors subtending almost the size of the blind spot. The rate of fixation errors in all three subject groups in our study was considerably lower compared with those in previous articles.^{18–20} Although we cannot conclusively rule out the possibility of fixation errors producing frequency-of-seeing curves such as those shown in Figures 3 (right) and 4 (right), there are three reasons why it is unlikely that fixation errors are confounding our results. First, the differences in the relationship between slope and threshold (or deviation)

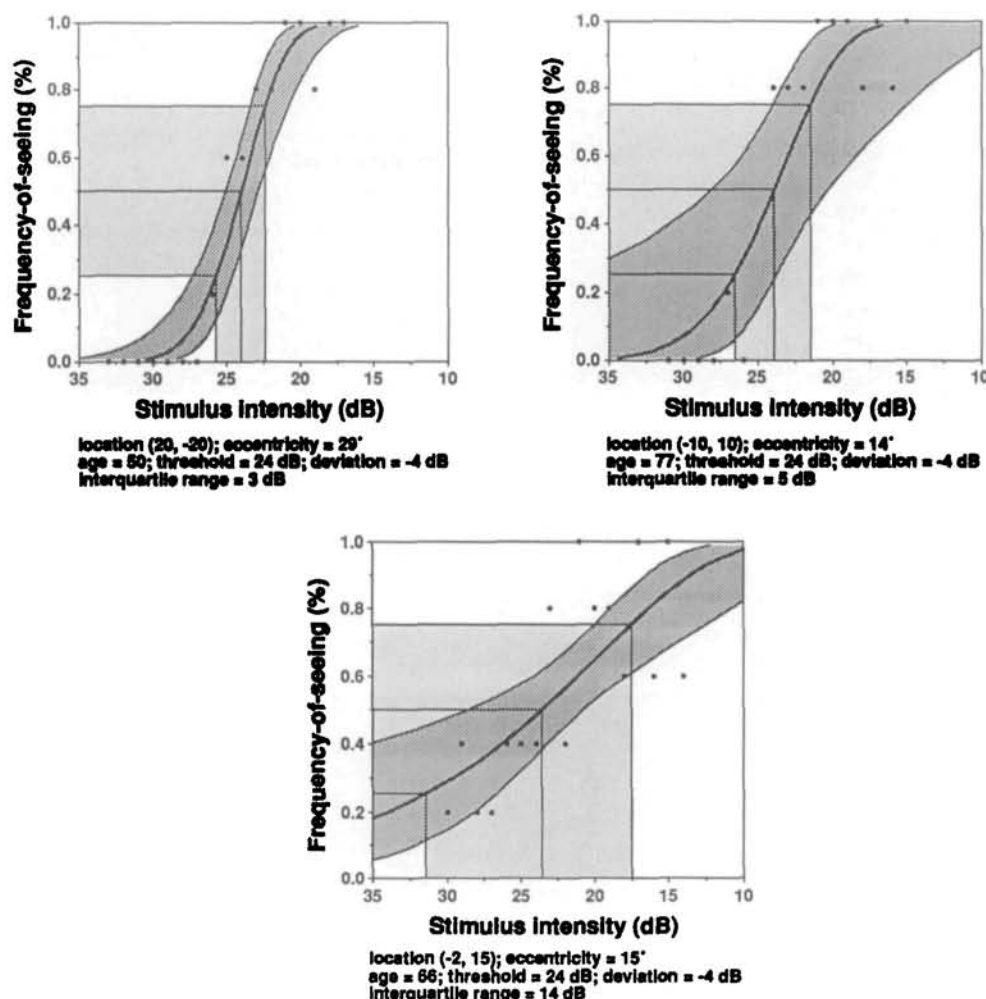


FIGURE 5. Frequency-of-seeing curves obtained from a normal subject (*top left*), patient with suspected glaucoma (*top right*), and patient with glaucoma (*bottom*). The thresholds and deviations for all three patients are identical, yet the curves are remarkably different.

tion) in the patients with suspected glaucoma and patients with glaucoma were significantly less than the differences between the patients with suspected glaucoma and normal subjects. Because the visual fields of the normal subjects and patients with suspected glaucoma were very similar (both groups were required to have normal fields for inclusion), we would expect the relationship between the slope and threshold to be similar in the normal subjects and patients with suspected glaucoma if fixation errors were the sole cause of noisy curves with shallow slopes. We did not find that this was the case. There were greater similarities between the patients with suspected glaucoma and patients with glaucoma, who had very dissimilar fields. Second, we re-examined three patients with glaucoma who each produced curves with both steep and shallow slopes approximately 3 weeks after the initial examination and obtained virtually identical results. Such results on re-examination would not have been likely if fixation errors were a significant factor. Finally, we

purposely tested locations that were in normal and scotomatous areas and avoided borders of scotomas in which the effects of small fixation errors would be most pronounced.

The results of this study have implications for modeling perimetric responses in simulation experiments. It generally is assumed that threshold variability increases with increasing threshold (or decreasing sensitivity). We have shown that the correlation between the slope of the frequency-of-seeing curve and threshold is high in normal subjects; therefore, the error incurred in assuming a monotonic relationship between fluctuation level and threshold may be small. Because the relationship is not as strong in patients with glaucoma, the corresponding errors associated with theoretic modeling may be significant. Simulation experiments based on real data may be more accurate.

The explanation for finding considerably different frequency-of-seeing curves in locations with the same threshold both within and between subject

groups is not obvious. Our finding that the slope of the curve in patients with glaucoma with identical thresholds and deviations can differ by a factor of 3 or more (Figs. 2, 3, 4) indicates that, after controlling for the level of the threshold or deviation, threshold variability in some cases is considerably higher than others. Variables other than those examined in this study are likely responsible for the increased variability. Recent studies have shown that patients with suspected glaucoma can show significant hypersensitivity followed by hyposensitivity at discrete retinal locations with stimuli used in short-wavelength sensitive cone perimetry²¹ and flicker perimetry.²² Eisner (personal communication) also has examined patients with glaucoma with unexplained hypersensitivity to flickering stimuli when tested at different retinal adaptation levels. These effects may result from changes in the slope of the linear portion (the operating portion for most psychophysical tests) of the Weber-Fechner function. Spontaneous changes in threshold, not explained by the actual threshold, age, or visual field location, can cause alterations in the shape of the frequency-of-seeing curve.

Additional studies clearly are needed to explain why some locations are associated with a lower threshold variability in patients with glaucoma, whereas others with the same threshold or threshold deviation exhibit variability that is magnitudes higher. Characterizing frequency-of-seeing curves at different retinal adaptation levels may provide insight regarding these questions. Such studies are underway.

Key Words

frequency-of-seeing curves, threshold, threshold variability, glaucoma, normal vision

Acknowledgment

The authors thank Humphrey Instruments for providing the Humphrey Field Analyzer.

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