

Comparing a Parallel PERG, Automated Perimetry, and Frequency-Doubling Thresholds

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PURPOSE. A pattern electroretinogram (PERG) simultaneously displaying the frequency-doubling (FD) illusion in nine parts of the visual field was compared with two other methods for ability to detect glaucoma. This multiregion FD PERG (MFP) was compared with results from achromatic automated perimetry and psychophysical tests using FD stimuli.

METHODS. MFP data were compared with that from the Humphrey Field Analyser (HFA; Humphrey, San Leandro, CA) 24-2 program. Contrast thresholds were also determined in different visual field locations for FD stimuli. Thin-plate spline methods were used to derive comparisons from the tests, each of which sampled the visual field differently.

RESULTS. Significant correlation with HFA could be obtained, providing seven to nine (of nine) MFP amplitudes were themselves significant. Evidence showed that both the psychophysical tests using FD stimuli and the MFP detect glaucomatous damage not detected by the HFA.

CONCLUSIONS. The comparisons between HFA perimetry, the MFP, and FD thresholds indicate that both FD-based tests quantify a form of diffuse loss in early glaucoma as well as the scotomas of later glaucoma. (*Invest Ophthalmol Vis Sci.* 2000;41:3827-3832)

The present study expands on a companion study in which the multiregion frequency-doubling (FD) pattern electroretinogram (PERG), termed the MFP, was evaluated for its ability to diagnose glaucoma.¹ Each of the MFP stimuli of that study displayed the FD illusion. The FD illusion has been shown to have value in diagnosing glaucoma.²⁻¹⁰ In this study we compared the MFP data from the previous study with the results from each subject's Humphrey Field Analyser (HFA; Humphrey, San Leandro, CA) thresholds and made other comparisons to assess the potential of the new MFP method.

Others have compared perimetry and PERG-based data, generally comparing averaged or summed thresholds from several visual field locations with conventional PERG output. Wanger and Persson¹¹ noted correlation between Goldmann perimetry and PERG, with somewhat better correlation being obtained from the central 30° than from the central 10°. Good correlations between averages of superior or inferior hemifield HFA thresholds and PERGs obtained from those hemifields have been reported,¹² with a 1.9 Hz pattern reversal providing better correlation than quicker (7.5 Hz) stimulation. Korth et al.¹³ showed good correlation between mean defect and PERG amplitudes obtained for 3.4 cyc/deg (square wave) gratings but not those for 0.2 cyc/deg.¹³ In a second study¹⁴ significant correlation between mean defect and PERG amplitude was obtained for chromatic (red-green) gratings but not luminance gratings (black-green), both tested at 0.3 cyc/deg. In both cases

pattern onset–offset stimulation was used with a repeat time of approximately 1.5 Hz. Apparently, for visual stimulation rates of 1 to 2 Hz, good correlation between achromatic automated perimetry (AAP; and other psychophysical tests) and PERG amplitudes can be obtained for patterns that stimulate the smaller field, chromatic cells of the parvocellular pathway (for review see Reference 15.) Several lines of evidence suggest that we access a different pathway by using FD stimuli.^{2,3,16-21}

Both this study and the companion study¹ were part of a larger study. In that study an initial cohort of 330 subjects was tested up to seven times over 2 years using an FD contrast threshold method.³ The MFP data presented here were obtained on the same day as one of the threshold tests, and we also compared the MFP data with the thresholds obtained for FD stimuli.

METHODS

MFP Stimuli

The MFP stimuli used are described in detail in the companion study.¹ Subjects viewed the MFP stimuli on a monitor (mean luminance 45 candelas [cd]/m²) from a distance of 30 cm (Fig. 1). A bright green fixation spot was presented in the screen's center. The screen of the monitor was divided into nine zones or regions (Fig. 1). Each region contained an achromatic (6500° K) sinusoidal grating at 95% contrast. The scale of the gratings increased with eccentricity according to the putative M_y-cell density.¹⁹

To permit extraction of responses to the different regions while recording with one electrode pair,¹ the contrast of each stimulus region was sinusoidally modulated in time, each region at a slightly different, incommensurate, temporal frequency.¹ We averaged a minimum of 4 and a maximum of 12 repeats of the 40.4-second stimulus sequence. A fast Fourier

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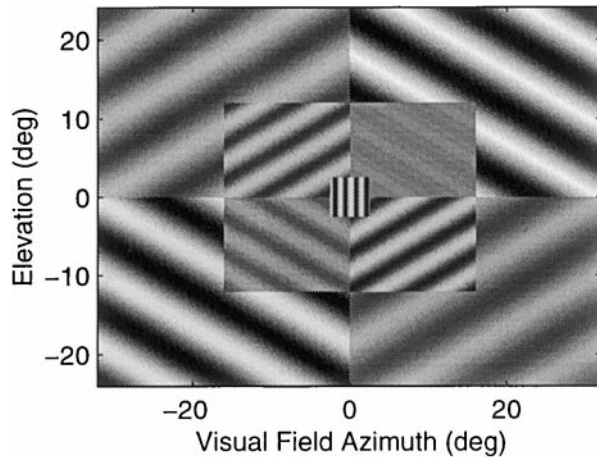


FIGURE 1. Illustration of MFP test stimuli. The spatial scale of the stimulus present on the monitor screen is demonstrated along with the scale of the gratings. The displayed spatial frequencies represent the input spatial frequencies, not the illusory second harmonic observed: central region 1, $\frac{3}{4}$ cyc/deg; middle regions 2 through 5, $\frac{1}{4}$ cyc/deg; and outer regions 6 through 9, $\frac{1}{8}$ cyc/deg. The gratings are presented here at different contrasts to permit the nine regions to be distinguished.

transform (FFT) was computed for each sequence, and the complex Fourier transfer coefficients were averaged and the significance of the Fourier components monitored online.¹

Poor tolerance of the electrodes (ERG-Jet; Universo SA, La Chaux-de-Fonds, Switzerland), or a transient loss of synchronization between stimulus presentation and analogue-to-digital converter (ADC) sampling, lead to a few partial or corrupted MFP data sets. These problems led to the loss of one subject from each of the normal, strongly suspect, and glaucoma categories, and six of the weakly suspect group, leaving 77 eyes in the study. The nine corrupted data sets have been incorporated into the analysis of Figure 3 to extend that analysis to encompass less significant data sets.

Subjects

As described in the companion article¹ we used the 24-2 program of the HFA to obtain visual field threshold data from all subjects. Subjects were classified into four groups: normal subjects, persons with glaucoma weakly suspected (weakly suspect group), persons with glaucoma strongly suspected (strongly suspect group), and persons with diagnosed glaucoma (known glaucoma group; see Table 1 of the companion article).¹ Of the glaucoma group 12 of 14 met the strict HFA criteria of Capriolli (companion study,¹ Reference 83) for glau-

TABLE 1. Correlations between MFP and HFA Data by Diagnostic Group

Study Group	<i>t</i>	<i>P</i>
Normal subjects	4.03 ± 0.88	0.005 ± 0.042
Weakly suspect	2.14 ± 0.32	0.071 ± 0.039
Strongly suspect	1.36 ± 0.53	0.220 ± 0.066
Known glaucoma	2.46 ± 0.46	0.044 ± 0.064

Data are means ± SD. The poorest correlation was obtained for the strongly suspect group.

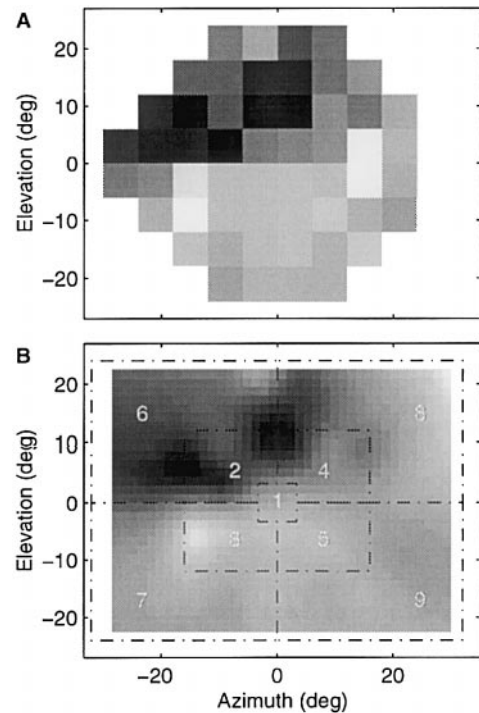


FIGURE 2. Illustration of the method of comparison between perimetry data and the MFP responses. (A) An HFA 24-2 threshold data set from a subject with a severe superior nasal defect in the right eye. Darker regions indicate more visual impairment. (B) The same data set after being splined onto a finer grid. The spline was fitted with no residual; thus, the resultant splined membrane passed through the original HFA threshold points. The two vertically oriented white pixels of (A) corresponded to the normal blind spot. The splined data of (B) were interpolated through this region of no data.

coma diagnosis; all met his moderate criteria. The strongly suspect group did not meet either of these visual field criteria but had a highest ever recorded elevated intraocular pressure (IOP), determined by applanation tonometry, of more than 20 mm Hg and a glaucomatous change in the optic disc verified by repeated fundus camera photography over several years. The weakly suspect group had either elevated IOP or suspect discs but had no observed change in the discs over several years. Further details of the diagnostic criteria are given elsewhere.^{1,3}

The research presented followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from the subjects after the nature and possible consequences of the study were explained to them. The research was approved by the Australian National University's Human Experimentation Ethics Committee under protocol M 881.

Comparison of MFP and Perimetry Data

We compared the MFP data with the total deviations provided by the HFA 24-2 program. The regions of the visual field used by the perimetric investigation and the MFP study were largely overlapping (Fig. 2A, 2B). The relatively fine spatial resolution of the perimetry data made it practical to extract a set of predicted values for each of the nine image regions covered by our MFP stimulus and then to compare these values with those obtained from the MFP itself. To assist in making the comparisons as accurate as possible, we first used a two-dimensional

thin-plate spline²² to interpolate the perimetric data onto a finer grid of values with 1.5° spacing (Fig. 5B). The spline used no smoothing, so that the splined data were forced to go through the measured threshold points. If we had used any smoothing, as is possible with the thin-plate technique,²² the values obtained would have been less conservative from a statistical standpoint. We then calculated the mean integrals of the interpolated data points falling within each of the nine regions of visual space defined by the zones of the MFP stimulus to produce nine perimetry-derived measures for comparison with the nine MFP results.

The MFP amplitude varied systematically with stimulus zone (region). It was therefore necessary to compute a model describing the systematic variation of the MFP data to permit comparison with the perimetry data. In simple terms the modeling provided weights for the perimetry data, according to spatial variations in the MFP data, that were common to all normal subjects. These weights were used to transform the perimetry-based data into a form that could be compared with the MFP data from each zone. We first transformed the MFP amplitude data into decibels and then fitted an additive model to the data of the normal subjects in our study group to obtain an experiment-wise and a zone-wise term. The zone-wise term is effectively the mean of the MFP decibel data across the normal subjects, which is the same as the geometric mean of the raw MFP amplitudes. These zone-wise terms were then converted back to weights in the MFP amplitude domain, and these weights were used, together with the mean spatial integrals over the zones of the interpolated perimetric data, to give a set of zone amplitude equivalents for the perimetric data derived from each subject. The main purpose of these measures was to compare how MFP and perimetry data performed relatively across our diagnostic groups.

RESULTS

Correlation of MFP Signals with Perimetry

Figure 2 illustrates the process of analysis for a subject with glaucoma. Figure 2A displays the raw HFA 24-2 threshold data for a subject with glaucoma. The same data are shown mapped onto the MFP stimulus zones after the thin-plate spline interpolation (see Reference 22 and the Methods section). Some extrapolation in regions corresponding to the monitor screen's corners was permitted. The thin-plate spline used was restricted so that the splined output was forced through the HFA data points; this stiffness criterion prevented wild extrapolation at the corners. Nevertheless, we accept that the necessary extrapolation could reduce the correlation between our HFA and MFP data. The mean threshold data from each of the nine splined regions was computed for each subject. These nine regional thresholds derived from the original perimetry data were regressed against the nine MFP signals for each subject. Note that the present MFP method insures that nine Fourier coefficients are orthogonal—that is, uncorrelated. The linear regression analyses provided a *t* value and a probability (*P*) describing the significance of the correlations between the MFP and HFA data for each subject. The means and SDs of these *t* and *P* values are summarized by diagnostic group in Table 1.

In general, the significance of the correlation is very good with the exception of the strongly suspect group. As expected,

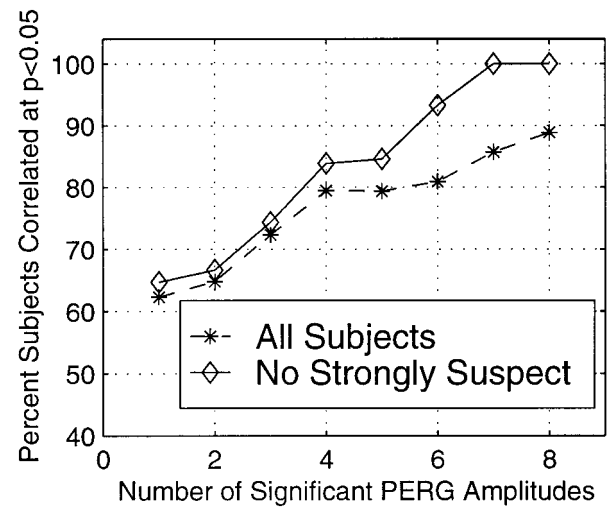


FIGURE 3. The proportion of subjects with significant correlation between their MFP and perimetry results increased as the number of significant regional MFP signals increased. The ordinate shows the proportion of subjects with significant ($P < 0.05$) correlations between MFP and perimetry data. The abscissa indicates the number of regional MFP signals that were significantly different from noise. The result for all subjects is shown by the *dashed line with asterisks*. *Solid line with diamonds*: Outcome when subjects with strongly suspect eyes are removed. Nine incomplete data sets have been included to illustrate what happens for fewer than the normal minimum of four repeats.

if data are further categorized on the basis of the number of MFP zone amplitudes that are significant, the significance of the correlation increases for subjects with a larger number of significant MFP amplitudes. For example, if MFP are chosen data with three or more significant zone amplitudes, 74.6% of these data have $P \leq 0.05$ (Fig. 3). The data shown in Figure 3 include nine partial or damaged data sets (explained in the Methods section) to extend the analysis to show what happens when relatively few regional amplitudes are significant. If the sample is further restricted to MFP data sets with seven or more significant zone amplitudes, the proportion with $P < 0.05$ increases to 85.7%. Apparently, if averaging the data were continued until all regions were significant, there would be significant correlation between HFA and MFP data for nearly all subjects.

The MFP as a Function of Subject Diagnosis

In the absence of a confirmed visual field defect, it is possible that some of our the strongly suspect group did not have glaucoma; however, that a photographically recorded deleterious change in the optic disc was observed in all these eyes makes this possibility unlikely. Alternately, the observed non-correlation (Table 1) could be explained by the MFP's picking up early defects that perimetry does not. As a first attempt at examining this possibility, we plotted the relationship between significant MFP-perimetry correlation and the number of significant MFP amplitudes for all subjects (Fig. 3, dashed curve, asterisks) and for all subjects less the data of the 13 with strongly suspected glaucoma (Fig. 3, solid line, diamonds). Clearly, the proportion of subjects with significant correlation between the MFP and perimetry data are markedly improved, with all remaining subjects showing significant ($P < 0.05$)

correlation between the two methods when seven or more individual MFP zone amplitudes are significantly higher than the noise level. Finally, although the criterion used here for MFP amplitudes was $P < 0.05$, the numbers obtained are little different if we use $P < 0.02$ and even $P < 0.01$, because in most cases the individual amplitudes are much more significant than 0.05 (see Reference 1; Figs. 2B, 4).

Comparing MFP, FD Thresholds, and Perimetry

It seemed that there was something odd about the strongly suspect group. In an attempt to resolve what was different about them we examined data obtained from a psychophysical test conducted immediately before the MFP measurements. The psychophysical test is also based on the FD illusion and in large-scale clinical trials has been shown to discriminate subjects with glaucoma from normal subjects very effectively.³ If the psychophysical test indicates that most of the strongly suspect group had glaucoma, then this would be good evidence that the MFP test was picking up glaucomatous damage that automated perimetry did not.

We briefly explain the method for the psychophysical test (for a more detailed explanation see Reference 3), with the present subjects being a subset of a group of 330 subjects who took the same psychophysical threshold test up to seven times over 2 years. The psychophysical test involved finding the contrast threshold for seeing FD stimuli in four regions of the visual field (Fig. 4). Note that the FD effect is observed down to threshold,^{20,23-26} probably as a result of being generated by a rectifying nonlinearity.^{25,27} In each of the present threshold experiments, a coarse grating whose contrast was modulated at 25.2 Hz was presented in each zone. We used the thin-plate spline method to derive four aggregate measures for HFA perimetry data for comparison with the four regions of the FD threshold experiments. To derive measures from the MFP to compare with the threshold data, we simply took weighted sums of the MFP amplitudes, for which the weights represented the proportion of MFP zone areas overlapping with each FD threshold region.

When we constructed measures to compare the MFP and HFA data, we generated an additive model based on data from normal subjects to compensate for systematic variations in the MFP zone amplitudes. When comparing the MFP, perimetry, and threshold data we scaled the MFP amplitudes according to the additive model. This meant that smaller, less reliable MFP amplitudes were scaled up and reliable amplitudes scaled down. The final data types for comparison were MFP amplitudes scaled to correct for systematic zone-to-zone variation in normal subjects, HFA perimetry data, and FD threshold data; all data are expressed in decibels. In fact, all other possible ways of preparing the data including using amplitudes instead of decibels and inversely weighting the perimetry and FD threshold data were also examined. The method reported gave results as good or better than any other treatment.

We first submitted the four measures from each experimental method to a principal components (PC) analysis and then used the significant components from each method to form a linear discriminant function^{1,3,28} from the normal and glaucoma data. The FD threshold method yielded two significant principal components (with eigenvalues > 1 , i.e., the proportion of variance for one of four independent variates). The question arises of whether the data rotation implicit in principal component analysis should be based on the glaucoma

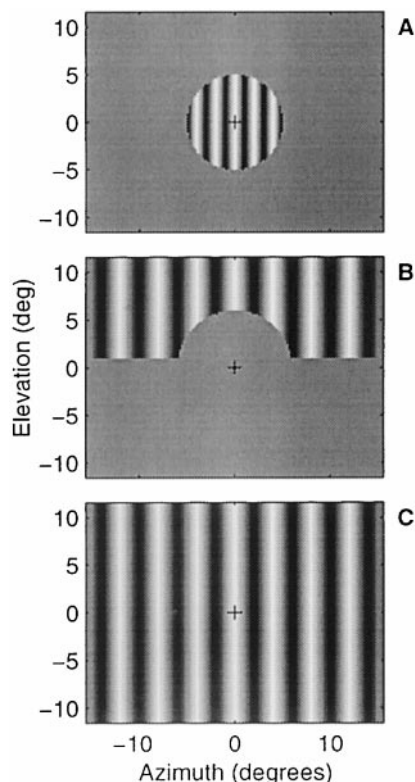


FIGURE 4. FD threshold stimuli. Three of the four test stimuli are shown. Contrast thresholds were determined for just being able to see FD stimuli with the right eye. Each threshold was measured by the method of adjustment 3 times and the average was used for the present analysis. (A) The center stimulus displayed a 0.5-cyc/deg grating in the central 10° of the visual field, (B) the superior stimulus displayed a 0.25-cyc/deg grating to the superior portion of the visual field excluding the central 10°, and (C) the whole-field stimulus spanned the monitor screen with a 0.5-cyc/deg grating. A fourth stimulus, the inferior test condition, was the vertical inversion of (B). All stimuli had contrast reversed at 25.2 Hz. Subjects initially were presented with the gratings at 100% contrast to acquaint them with the appearance of the FD pattern.

and normal data only, or on the data from all subjects. We tried both and found little difference in the outcomes. The average of the two methods is presented in graphic form in Figure 5. Overall, the threshold method performed best, followed by the MFP and finally the perimetry-based measures. Note that the proportions of the strongly suspect group with diagnosis of glaucoma are reversed for the perimetry method compared with the two methods, when stimuli are used that elicit the FD illusion.

DISCUSSION

MFP amplitudes and measures derived from HFA perimetry were well correlated, in that significant correlation increasing with the number of significant MFP amplitudes obtained per eye (Table 1, Fig. 3). The strongly suspect group showed the worst correlation with HFA AAP. Taken together, the results presented in Figures 3 and 5 suggest that the noncorrelation between HFA and the MFP for the strongly suspect group was due to HFA's not detecting loss detected by both the MFP and

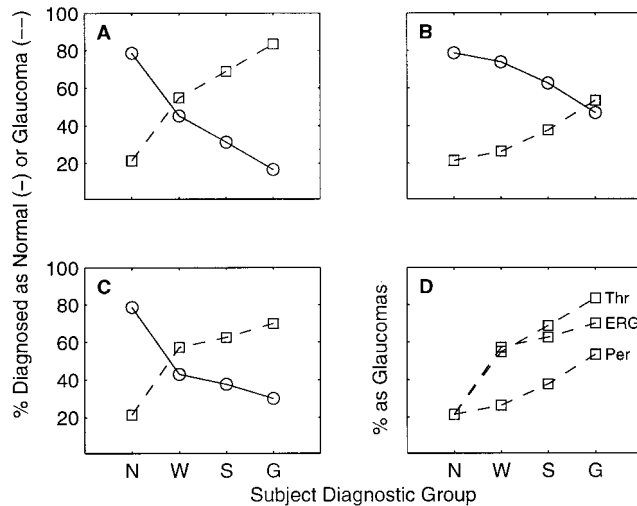


FIGURE 5. Probability of subjects receiving diagnoses of glaucoma (□) or normal (○) by subject diagnostic group. (A) Summary for the four FD thresholds (Fig. 4), (B) outcome for the four measures derived from HFA 24-2 thresholds, (C) outcome for the four weighted sums of the MFP data, and (D) sensitivity by different diagnostic groups and test method. Thr, FD Threshold; ERG, Multi-region FD MFP; Per, summed thresholds from HFA 24-2; N, W, S, G: normal, weakly suspect, strongly suspect, and known glaucoma group, respectively.

the FD thresholds. Abnormal PERGs for visual field regions that are normal on automated perimetry have been reported before²⁹ as has good correlation between PERGs from the four quadrants of the visual field³⁰ and AAP. The large stimulus regions used here mean the detected loss is probably diffusely distributed in agreement with contrast threshold studies using similar stimuli.³ The results obtained for the strongly suspect group in the current study (Figs. 3 and 5) indicate that diffuse early loss can be quantified by the MFP.

Comparison with Perimetry

At a fundamental level it is not surprising that some system should outperform AAP in detecting early loss, given that a focal loss of 20% of ganglion cells produces approximately a 5- to 8-dB sensitivity change.³¹⁻³³ The test-retest variability of automated perimetry is also quite high.³⁴⁻³⁶ We cannot say anything yet about the test-retest variability of MFP; however, variability for FD testing is less than white-on-white perimetry, particularly in regions of more serious defects.^{37,38} Test-retest variability for conventional PERG studies of glaucoma are impressive.^{39,40} Sensitivity for AAP is in the range of 86% to 93% and specificity is between 81% and 87%.³⁶ Better performance has been reported for FD threshold testing.^{3,4,8,9} Test-retest variability for short-wavelength automated perimetry (SWAP) seems to be somewhat worse than for AAP.⁷

Previous comparisons between PERGs and AAP have yielded the best results for slower modulation of finer patterns^{12,13} and red-green chromatic stimuli.¹⁴ These data all suggest that AAP thresholds are related to parvocellular pathway defects. Correlations of approximately 0.7 have been reported between AAP mean defects and the PERG.^{11,13,14,30,41} SWAP thresholds may be related to koniocellular pathway function.^{42,43} Several lines of evidence suggest MFP is stimulating part of the magnocellular pathway.^{2,3,16-21} PERGs recorded

with a 8.3-Hz, 0.5-cyc/deg, stimuli have been recorded in the four quadrants of the visual field.³⁰ Those conditions are similar to the present study, and nasotemporal differences similar to those shown here (Fig. 3) were reported.

SUMMARY

The finding of good correlation between MFP and HFA perimetry was encouraging. The present study indicates that PERG signal components associated with the FD illusion¹⁶⁻¹⁸ appear to be highly selective for glaucomatous damage. The good sensitivity obtained for our strongly suspect group (and not for the weakly suspect group) by both the MFP and the FD thresholds indicates that information about early glaucoma is obtained from such stimuli.^{3,21,44,45} The low spatial frequencies required to produce the FD illusion are a positive advantage from the clinical standpoint, because little demodulation of contrast can be expected, even by ± 5 D of defocus.

Acknowledgments

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