

# Original Article

## Comparison of three tests using the frequency doubling illusion to diagnose glaucoma

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### ABSTRACT

**Purpose:** The introduction of the FDT perimeter prompted the comparison of three tests employing frequency doubling (FD) stimuli. These measures compared different visual field locations and contrast ranges. Frequency of seeing curves were examined for the method most similar to FDT.

**Methods:** For 146 eyes the following were obtained: (i) contrast matches to two suprathreshold FD stimuli (normal subjects, ocular hypertensive suspects, primary open angle glaucoma subjects); (ii) two alternative forced choice (2AFC) thresholds for horizontally versus vertically orientated FD gratings; and (iii) contrast thresholds determined by method of adjustment (MOA) for five different stimulus types.

**Results:** A model based on the worst of the MOA hemi-field thresholds performed best. The suprathreshold contrast matching tests performed worst. Frequency of seeing curves were fitted for the 146 eyes of the 2AFC tests. Although the MOA thresholds were higher than the 2AFC thresholds (for normals mean  $\pm$  SE,  $8.47 \pm 0.43$  dL,  $P < 0.0000$ ), the best diagnostic concordance was at lower limens (75% or 80% correct) of the fitted frequency of seeing curves.

**Conclusions:** There was good diagnostic concordance between the MOA and 2AFC methods although the thresholds were 1.8-fold different on a log-scale. This suggests that the same neural mechanism mediates both thresholds for rapidly flickering, spatially coarse, patterns.

**Key words:** contrast sensitivity, frequency-doubling, frequency-of-seeing curves, glaucoma, perimetry.

### INTRODUCTION

Low spatial frequency gratings whose contrast is modulated at rates above 15 Hz are seen as an illusory grating having twice the spatial frequency of the stimulus. This is the frequency doubling (FD) illusion.<sup>1</sup> Subjects with glaucoma were found to perceive FD stimuli poorly.<sup>2–6</sup> These early findings have been supported by results<sup>7–12</sup> obtained with the subsequently introduced Frequency Doubling Technology (FDT) perimeter (Zeiss Humphrey Systems, Dublin, CA, USA).<sup>3,6</sup>

The FD illusion is highly suggestive of the action of the retinal contrast gain control system of the non-linear Y-like retinal ganglion cells of the magnocellular pathway, the so-called  $M_y$ -cells.<sup>13,14</sup> This system enhances responses to large transient stimuli.<sup>13–15</sup> Psychophysical<sup>16</sup> and pattern electroretinogram (PERG) experiments<sup>17–19</sup> implicate these cells in FD.  $M_y$ -cells are the largest retinal ganglion cells in the M-pathway and glaucomatous damage is correlated with cell size.<sup>20,21</sup> More importantly, perhaps, the array of  $M_y$ -cells is very sparse,<sup>4,16</sup> making detection of cell loss relatively easy.<sup>4</sup> Thus, FD stimuli may provide a sensitive test of the viability of the retinal contrast gain control system.<sup>5,16,17,19</sup> The same gain control system also modifies the responsiveness (but less so) of the more linear primate  $M_x$ -cells,<sup>13,14</sup> therefore, defects in the gain control system could produce the subtle visual field variability that has been suggested as the earliest sign of glaucomatous damage obtainable with achromatic automated perimetry (AAP).<sup>22,23</sup> Frequency doubling tests may therefore directly test mechanisms associated with early

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Declaration of commercial interest: The Australian National University owns patents on the use of frequency doubling stimuli for the diagnosis of glaucoma. These patents are under license to Welch Allyn Ltd, USA, and are the basis for the FDT Perimeter marketed by Humphrey-Zeiss. Ted Maddess derives royalty income from the licensed patents. The present work does not use the FDT perimeter but does compare frequency doubling methods covered by the patents.

loss. Certainly, sensitivity and specificity obtained for large FD stimuli are more related to glaucoma than the mean defect of AAP,<sup>24–26</sup> suggesting that diffuse early loss is better quantified by FD tests.

The value of using large stimuli has been demonstrated for FD based tests for glaucoma.<sup>24–26</sup> Our earlier study of 330 subjects that examined the contrast threshold for hemi-field FD stimuli yielded sensitivities of 91% obtained at specificities of 95%.<sup>24</sup> Those thresholds were obtained using a method of adjustment (MOA). Interestingly, the MOA thresholds were higher than those for FDT, which uses a two alternative forced choice (2AFC) threshold method.<sup>27</sup> The MOA test-retest standard deviation (2.22 dB) was nevertheless similar to that obtained with the FDT perimeter.<sup>28</sup> Test-retest variability for both methods is thus much lower than for AAP<sup>29</sup> or short wavelength automated perimetry (SWAP),<sup>30</sup> which may suggest that the same mechanism is being accessed by all FD methods.

Frequency doubling is seen under extremes of transient presentation and low spatial frequency, stimulus conditions producing flicker equivalent to high image speeds. Early work by Kulikowski showed that when coarse gratings are presented transiently or at high flicker rates FD is seen.<sup>31</sup> Perhaps more importantly, FD is better seen as the contrast is reduced to threshold levels.<sup>31,32</sup> Taken together these facts are consistent with the idea that as stimulus conditions approach the perceivable limits of high speed and low contrast that our percept becomes dominated by mechanisms that have high gain under these conditions. The fact that the last percept seen is an FD one indicates the last system functioning not only has the high contrast gain for low spatial frequencies but also has a rectifying character (rectification being equally strong down to zero signal strength), all features of primate M<sub>v</sub>-cells.<sup>13,14</sup> Thus, the 2AFC method of FDT and the MOA method of our previous study may produce similar results for glaucoma because they may both test the visual system last standing in the face of extremes of high speed and low contrast. The differing tasks set the subjects may then provide different outcomes in terms of absolute contrast values.

Although the introduction of the FDT perimeter makes investigation of contrast thresholds interesting, we have shown that high-contrast FD stimuli can provide highly accurate diagnosis of glaucoma when employed in a multi-region PERG.<sup>25,26</sup> Given the above we decided to investigate three types of psychophysical tests that employed FD stimuli: (i) a suprathreshold contrast matching task; (ii) a 2AFC contrast threshold method similar to that used in FDT; and (iii) our earlier MOA threshold method.<sup>24</sup> To make the data from the three tests comparable both across tests, and with our earlier work,<sup>24–26</sup> we have employed similar shaped stimuli. For the 2AFC method, eight or more reversals were examined to obtain enough data to fit frequency of seeing (FOS) curves. This provides a comparison with other work on FOS curves in glaucoma and a way to directly compare the 2AFC and MOA thresholds. Sensitivities and specificities were estimated using the same

discriminant analyses and receiver operator curve (ROC) methods used in our larger study,<sup>24</sup> providing direct comparison with that work.

## METHODS

### Stimuli

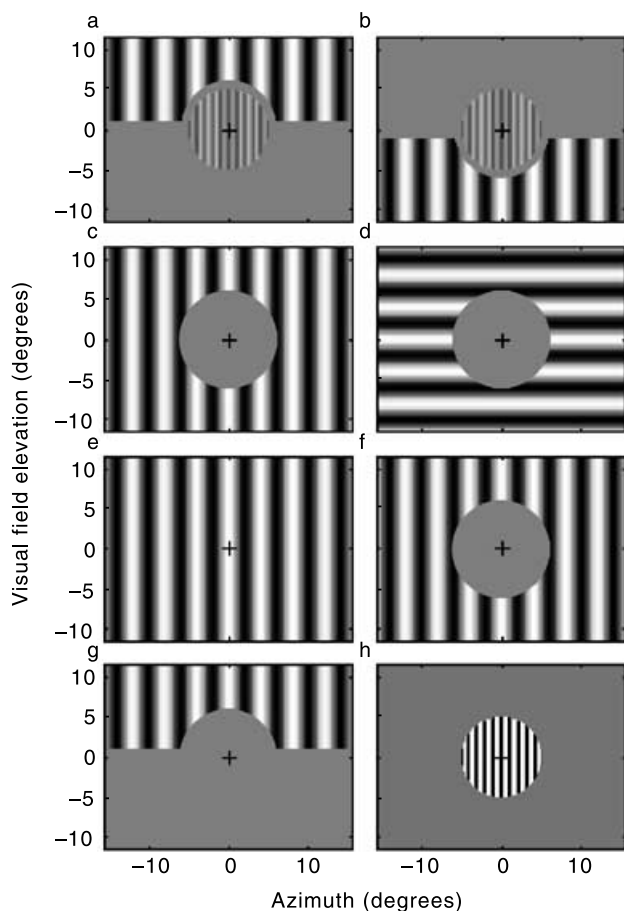
Achromatic grating stimuli (6500 °K) were presented on a monitor (Barco, Kortrijk, Belgium; refresh rate 102 Hz, mean luminance 45 cd/m<sup>2</sup>). All stimuli were gamma corrected. Figure 1 illustrates the spatial layout and angular extent of all the stimuli employed. A video summing amplifier combined weighted sums of the RGB outputs of the graphics card (Truevision Vista, Shadeland Station, IN, USA) to provide achromatic stimuli with a contrast resolution of 1 part in 1024. Except where noted, the gratings had a spatial frequency of 0.25 c/deg grating and had their contrast square wave modulated at 25.5 Hz. The user interface was a track-ball style mouse and its keys. Subjects viewed the monitor monocularly from a distance of 60 cm. Both eyes were tested.

### *Suprathreshold contrast matching*

Subjects matched the apparent contrast of 0.25 c/deg gratings presented in the superior and inferior visual fields with a static 4 c/deg grating presenting in the central 10° (Fig. 1a,b). In the actual tests, the peripheral grating was a 0.25 c/deg grating modulated at 25.5 Hz, the central pattern was unmodulated and held at contrast 0.2. Matching was achieved by method of adjustment where rolling the mouse track-ball left or right changed the contrast of the outer grating. In training runs, all subjects first practised matching temporally unmodulated patterns of the same spatial frequency (0.5 c/deg: matching the appearance of the frequency doubled grating used in the actual tests), one pattern presented in the centre and one in the surrounding portion of the superior visual field. A second training sequence involved matching an unmodulated 0.5 c/deg grating in the periphery with an unmodulated 4 c/deg central target.

### *Two alternative forced choice thresholds*

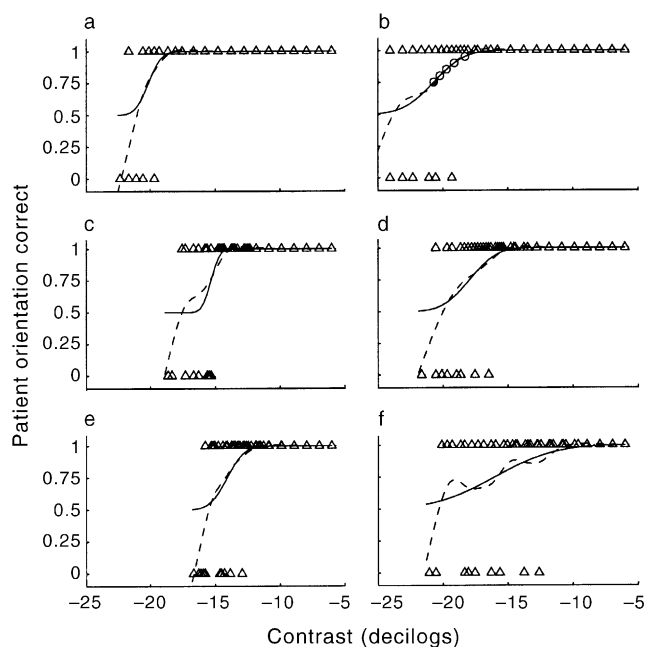
The stimuli (Fig. 1c,d) were annular (Fig. 1f) where the orientation of the 0.25 c/deg gratings could be either vertical or horizontal. The contrast threshold for detecting the orientation was established by an automated staircase procedure.<sup>5</sup> Subject responses were recorded as mouse button-presses, left button for horizontal, right for vertical. These choices were then stored as either (1) correct or (0) incorrect (see Fig. 2). The initial contrast was 0.25, and 50 trials were gathered from each eye guaranteeing that at least eight reversals were obtained. We examined thresholds based on average of the last eight reversals (Rev Ave), the first four of the eight reversals (Rev First 4), and the final four reversals (Rev Last 4).



**Figure 1.** Examples of the stimuli used in the experiments. Unless otherwise stated all gratings were at 0.25 c/deg reversed contrast at 25.5 Hz. (a,b) Suprathereshold contrast matching: (a) superior; (b) inferior. Subjects matched the apparent contrast of modulated 0.25 c/deg gratings presented in the superior and inferior visual fields with a static 4 c/deg (contrast 0.2) grating presented within the central 10 deg. (c,d) Two alternative forced choice stimuli: (c) vertical; (d) horizontal. Contrast thresholds were computed from the last eight reversals of a staircase procedure to discriminate vertically versus horizontally orientated gratings presented at > 11 deg eccentricity. Fitted frequency of seeing curves provided the 75% correct points (limens). (e–h) Method of adjustment threshold stimuli: (e) whole; (f) annulus; (g) superior; (h) central. The central pattern displayed a 4 c/deg grating, the others displayed 0.25 c/deg gratings.

### Method of adjustment thresholds

Some of the stimuli are similar to those of a larger study.<sup>24</sup> In the so-called Whole Field case (Fig. 1e) grating stimuli were presented over the whole of the computer monitor. In the other cases, the gratings were displayed within an annulus ( $\geq 11^\circ$ ; Fig. 1f compared to Fig. 1c,d), or in the superior (Fig. 1g) or inferior (not shown but was the vertical inversion of Fig. 1g, as Fig. 1b is to Fig. 1a) visual fields less the central  $11^\circ$ . In the final MOA test, a 4 c/deg grating was presented to the central  $10^\circ$ . All these gratings reversed



**Figure 2.** Example frequency of seeing data for each diagnostic group: (a,b) normal subjects; (c,d) ocular hypertensive suspects; (e,f) primary open angle glaucoma subjects. ( $\Delta$ ) subject responses (0 or 1); (—) curve fit to  $\frac{1}{2}(1 + \text{ERF}(c))$ ; (- - -) cubic splines with bending energy for comparison with the fitted functions. The splines represent a smoothed average of the data as an attempt to show the true shape of the FOS curves without the assumptions of any model. ( $\circ$ ) from left to right, the 75, 80, 85, 90 and 95% limens for the frequency of seeing curve. There is good agreement between the methods at limens near 0.75 (Table 4).

contrast at 25.5 Hz. On each trial, subjects initially were presented with the patterns at 100% contrast and were asked to adjust the contrast using the track ball. They were asked to ‘make the striped pattern fainter until it could not be seen’ and then to raise the contrast somewhat and make further fine adjustments ‘until they could only just see the same striped pattern they had seen at the outset’. Thresholds are reported as decilog ( $dL = 10 \log_{10}$ ) contrast and are the mean of six repetitions for each stimulus.

### Stimulus presentation

The tests were presented in a set sequence. In fact, two sequences were generated because the first eye tested for a given subject, Eye 1, was alternatively the left or right for successive subjects. The first 10 tests were the MOA tests, then the suprathereshold tests, and finally the 2AFC tests. All tests were completed in an average  $\pm$  SD time of  $54.1 \pm 15.0$  min (median 51 min). Among the MOA tests the order of tested visual fields was: Eye 1, whole, annular, central; Eye 2, whole, annular, central; Eye 2 superior, inferior; Eye 1 superior, inferior. In all cases the untested eye was covered by a white translucent eye patch that transmitted no form vision but kept the untested eye light-adapted to permit rapid

exchange between eyes. Overall, the concept behind the test order was to group tests that were spatially similar. Therefore, whole field and annular tests were done temporally near each other. Similarly, the suprathreshold tests were done after the inferior and superior visual MOA test, allowing subjects to familiarize themselves with the hemifield stimuli and track-ball use.

## Analysis

Both linear and quadratic discriminant analysis were carried out on the subject data,<sup>33</sup> permitting models where data from either one or both eyes were considered. The same method was used previously in similar experiments on a much larger group,<sup>24</sup> and sensitivities and specificities were determined from ROC. The two-eye method takes advantage of differences in the MOA hemifield thresholds between fellow eyes of glaucoma subjects of the order of  $\pm 5$  dB.<sup>24</sup> Principal components of the MOA thresholds were also examined. This meant that some comparisons used data from both eyes. A much larger study has shown that threshold data obtained for the same stimuli as used for the superior and inferior hemifields here (Fig. 1c,d) showed significantly independent data from the two eyes.<sup>24</sup> We therefore used the previously used<sup>24</sup> two-eye ROC models here to provide direct comparison with that work. Another study provides a mathematical appendix and figures describing the discriminant methods.<sup>25</sup>

We also examined the psychometric functions, or FOS curves, for the 2AFC data sets. To do this the raw 2AFC true/false data was represented as 0 or 1 (e.g. Figure 2) and fitted with  $\frac{1}{2}(1 + \text{ERF}(c))$ , where ERF is the cumulative normal distribution or 'error function', and  $c$  refers to contrast. The fitting procedure was an iterative Gauss-Newton procedure, extensive details of which are presented elsewhere.<sup>16</sup> The method permitted errors in the fitted FOS thresholds and slopes to be estimated. The fitted FOS curves allowed us to estimate higher limens than 75%, that is, higher than 75% correct points on the FOS curves (e.g. Fig. 2b), for comparison with the higher MOA thresholds.

To examine if the fitted (i.e. parametric) model was adequate we also fitted the data with a non-parametric cubic spline with bending energy.<sup>34</sup> This spline provided a continuous average curve from the discontinuous raw data. If this average curve, which assumes no particular model shape, differed significantly in shape from the parametric fit to  $\frac{1}{2}(1 + \text{ERF}(c))$  this would indicate that the ERF model poorly represented the measured psychometric functions.

## Subjects

The study contained three groups: normal subjects (Normal), ocular hypertensive subjects (Suspect), and primary open angle glaucoma (POAG) subjects (Glaucoma; data summary in Table 1). There was no significant difference between the ages (Table 1) of the Normals and Glaucomas ( $t_{df=34} = 1.51$ ,  $P = 0.148$ ; combined Normal and Glaucoma *vs* Suspect:  $t_{df=70} = 0.602$ ,  $P = 0.566$ ). The

proportion of men was higher in all groups, averaging 67%, but was not significantly different between the Normals and Glaucomas ( $t_{df=35} = 0.658$ ,  $P = 0.531$ ; combined Normal & Glaucoma *vs* Suspect:  $t_{df=71} = 0.411$ ,  $P = 0.700$ ). Subjects were not dilated for the tests.

Disc condition was categorized, as previously described,<sup>5</sup> into one of four classes ranging from normal to pathological. That system allowed referring physicians to employ cues such as pallor to categorize subjects into the four classes while others used only vertical cup to disc ratios to rank the discs into the four categories according to a provided schedule.<sup>5</sup> Intraocular pressure (IOP) was assessed by applanation tonometry. The IOP data in Table 1 for the Normal subjects is based on a sample of seven of the 17 Normal subjects. The IOP figures given for the Suspect and Glaucoma subjects are based on the highest ever recorded, all of these subjects being on topical beta-blockers at the time of the experiments. No subjects had undergone ocular surgery and their ocular media were clear.

Glaucoma subjects showed reproducible glaucomatous scotomas, typically on HFA 24–2 automated perimetry but in some cases with other automated perimetry devices. Criteria for classification of glaucomatous fields conformed to the strict definition of Caprioli.<sup>35</sup> No subjects showed a split field or similar gross field defect. Suspects were defined as having elevated IOP ( $> 21$  mmHg) and abnormal optic disc appearance (category  $> 1$ ) but no scotoma in either eye. The primary objective of the study was to compare how various tests segregated the study groups when all the tests were given during one visit.

The research presented followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from the subjects after explanation of the nature and possible consequences of the study were explained to them. The research was approved by the Australian National University Human Experimentation Ethics Committee under protocol M881.

## RESULTS

### Suprathreshold contrast matching

Despite substantial subject training (see Methods) the suprathreshold contrast matching algorithm performed worst at diagnosing subjects as Normals or Glaucomas. Several measures derived from these data were examined, the best performance being provided by examining the worst hemifield match, that is to say the hemifield providing the highest matching contrast (Sensitivity [Sens] 55.0%, Specificity [Spec] 52.9%; Table 2).

### Two alternative forced choice thresholds

The next most interesting method was the 2AFC method for discriminating horizontal versus vertical gratings. As a minimum of eight reversals were obtained for each eye we examined means of all eight reversal contrasts and the means

of the first and last four. The 'Rev Last 4' threshold was the most accurate: for linear discriminant models on the individual eye data, sensitivity was 76.9% at a specificity of 81.8%. This improved when data from the two eyes were used in a quadratic discriminant analysis (Sens 80.8%, Spec 81.8%). We also examined the 75% correct limen of psychometric functions fitted to the raw 2AFC data, which performed somewhat worse in the linear discriminant case but better in the two-eye model (Table 2).

As the fitted FOS functions were cumulative normal probability distributions, the fitted parameters are the central point of the FOS curve  $\mu$  (as the fit is to  $\frac{1}{2}(1 + \text{ERF}(c))$ , this corresponds to the 75% correct limen) and the standard deviation  $\sigma$ , the central slope being  $1/(\sigma \sqrt{2\pi})$ . Both measures have units of decilogs,  $\sigma$  being the characteristic width of the sloping region. Table 3 provides an indication of the errors in the fits to  $\mu$  and  $\sigma$ . Notice that although average  $\mu_{\text{Mean}}$  is large compared to  $\mu_{\text{SE}}$  ( $-18.54$  dL vs  $0.28$  dL for Normal subjects),  $\sigma_{\text{Mean}}$  is only about threefold larger than its error  $\sigma_{\text{SE}}$  ( $-1.33$  dL vs  $0.45$  dL for Normal subjects). The  $\sigma_{\text{Mean}}$  for Normal subjects was not significantly smaller

than that of the Glaucoma group. Discriminant models including  $\mu$  and  $\sigma$  were better than with  $\sigma$  only; however, none of these models was better than that for the 75% limen alone (Table 3).

### Method of adjustment thresholds

The MOA thresholds proved to be diagnostically the most accurate. As an initial approach we calculated the principal components of the five different types of decilog MOA thresholds. Only the first component was significant and it was essentially the mean of thresholds of the four non-central stimuli (Fig. 1a–d), so we took the simple mean of these four thresholds as a variable for discriminant analysis. We also computed discriminant functions for all the individual thresholds and the worst hemifield threshold (WHT) and best hemifield threshold, the latter being the hemifields giving the highest and lowest contrast thresholds, whether inferior or superior. The data for WHT are compared with the above two 2AFC cases in Table 2. The WHT alone gave a sensitivity of 90.0% at a specificity of 91.2%. Discriminant

Table 1. Subject data for each study group

Group	No. subjects	No. men	Mean age $\pm$ SD (years)	Age range (years)	Mean optic disc condition $\pm$ SD*	Mean highest IOP $\pm$ SD (mmHg)
Normal	17	12	56.4 $\pm$ 13.1	24–76	1.00 $\pm$ 0.00	16.7 $\pm$ 1.89
Suspect	36	25	57.8 $\pm$ 11.6	33–78	1.92 $\pm$ 0.84	25.2 $\pm$ 5.27
Glaucoma	20	12	62.3 $\pm$ 10.1	41–80	2.52 $\pm$ 0.98	23.0 $\pm$ 6.39

\*Disc condition was categorized, as previously described,<sup>5</sup> into one of four classes ranging from normal (1) to pathological (4). IOP, intraocular pressure.

Table 2. The simultaneously highest sensitivity and specificity obtained from receiver operator curves

Threshold	One-eye (linear)		Two-eye (quadratic)	
	Sensitivity	Specificity	Sensitivity	Specificity
Contrast matching	50.0	52.9	55.0	52.9
2AFC Rev Last 4	76.9	81.8	80.8	81.8
2AFC 75% limen	71.2	72.7	84.6	86.4
MOA average	73.1	74.3	77.5	82.4
MOA WHT	76.9	78.6	90.0	91.2

2AFC, two alternative forced choice; Rev Last 4, final four of eight reversals; MOA, method of adjustment; WHT, worst hemifield threshold.

Table 3. Two alternative forced choice frequency of seeing (FOS) curves fitted parameters for all subjects

Group	75% limen of FOS curves		Characteristic width of FOS curves	
	$\mu_{\text{Mean}} \pm$ SD (dL)	$\mu_{\text{SE}} \pm$ SD (dL)	$\sigma_{\text{Mean}} \pm$ SD (dL)	$\sigma_{\text{SE}} \pm$ SD (dL)
Normal	$-18.54 \pm 1.76$	$0.28 \pm 0.11$	$1.33 \pm 0.72$	$0.45 \pm 0.20$
Suspect	$-18.34 \pm 1.43$	$0.38 \pm 0.39$	$1.83 \pm 2.00$	$0.65 \pm 0.86$
Glaucoma	$-16.68 \pm 1.63$	$0.35 \pm 0.20$	$1.72 \pm 1.24$	$0.56 \pm 0.37$

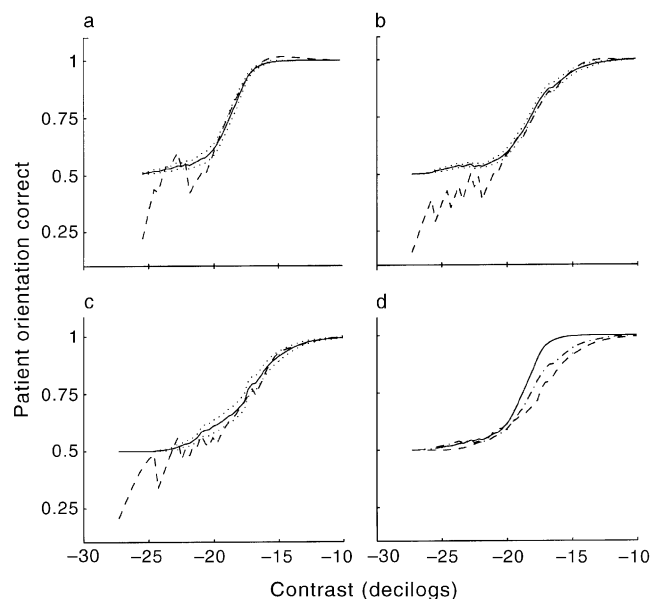
Note that the average standard errors for  $\mu$  ( $\mu_{\text{SE}}$ ) is part in  $54.05 \pm 6.09$  SE of the average fitted  $\mu$  ( $\mu_{\text{Mean}}$ ) whereas the comparable ratio for  $\sigma_{\text{Mean}}/\sigma_{\text{SE}}$  is  $3.47 \pm 0.59$  SE.

models based on last four reversals for the 2AFC method, the average MOA threshold and the WHT were unremarkable in diagnosing about half the Suspects group as POAG (not shown).

### Comparing 2AFC and MOA thresholds

The thresholds obtained for the 2AFC and MOA experiments were markedly different, MOA thresholds being higher than the 2AFC thresholds. For example, for Normal subjects the average  $\pm$  SE MOA thresholds for non-central stimuli was  $8.47 \pm 0.43$  dL higher ( $P < 0.0000$ ) than that obtained for the average of the last four 2AFC reversals. One possibility is that the MOA thresholds, given the nature of the task, were simply reporting a threshold corresponding to a higher limen (Methods; Fig. 2b) of FOS curves provided by the 2AFC tests. We therefore computed the higher limens from the fitted 2AFC FOS functions and examined correlations between these and the MOA thresholds. Before comparing these data, it is reasonable to ask if the fitted FOS functions are an accurate representation of the actual psychometric functions.

Figure 2 shows examples of the 2AFC raw data, the splined average FOS and the fitted FOS functions ( $\frac{1}{2}(1 + \text{ERF}(c))$ ). There is good agreement between the splines and the fitted curves, both for individual cases (Fig. 2), and the subject averages functions (Fig. 3). This indicated that higher limens computed from the fitted functions are accurate; that is, the fitted curves match the FOS shape derived from a



**Figure 3.** Average psychometric functions by group. Overall glaucoma was indicated by changes in both the 75% limen and the slope of the psychometric functions. (a) Normal subjects; (b) ocular hypertensive suspects; (c) primary open angle glaucoma subjects; (d) average of all groups. (—) Average of all the fitted functions; (...)  $\pm$  SE; (- - -) the average of all the splined FOS curves (see Figure 2).

simple non-parametric average. Correlations between all the thresholds considered and the WHT and the annular MOA threshold are given in Table 4. Notice that the highest two correlations for WHT are between the 2AFC 75% limen and the average of the last four reversals of the 2AFC thresholds. Progressively higher 2AFC limens are progressively less correlated with the WHT. The annulus is most highly correlated with the Best hemifield threshold, indicating that subjects use their best performing hemifield to set their annulus threshold.

### DISCUSSION

The average durations of the tests ( $\pm$  SD) were: inferior or superior MOA  $2.57 \pm 1.92$  min; other MOA  $2.75 \pm 1.47$  min; suprathreshold tests  $2.63 \pm 1.87$  min; 2AFC  $7.03 \pm 2.45$  min. These times include the time for any rests, explanations and demonstrations. It is possible that fatigue affected the outcome of the 2AFC results; however, given that the median time for all tests was 51 min, and no eye was used for more than about 10 min without a rest, we believe these effects would be minimal. Also, subjects had completed the annular MOA test before the AFC test thus giving them practise with annular targets. The inferior and superior MOA tests were not among the first tests and so test order did not favour these stimuli.

The good performance of the WHT, 90.0% sensitivity at a specificity of 91.2%, is in agreement with a study on 330 subjects that included the same hemifield tests.<sup>24</sup> Nevertheless, those sensitivities and specificities are for a two-eye model and the number of subjects used here is insufficient to validate it. We included the two-eye models because the

**Table 4.** Correlation summary

Measure	WHT	Annulus
Method of adjustment		
WHT	1.000	0.959
BHT	0.955	0.966
Average	0.974	0.963
Annulus	0.959	1.000
Two alternative forced choice (reversal)		
Reversal average	0.385	0.340
Rev First 4	0.297	0.284
Rev Last 4	0.421	0.348
Two alternative forced choice (limen)		
75% limen	0.418	0.363
80% limen	0.393	0.338
85% limen	0.362	0.310
90% limen	0.327	0.277
95% limen	0.282	0.236

WHT, worst hemifield threshold; BHT, best hemifield threshold; Rev First 4, first four of eight reversals; Rev Last 4, final four of eight reversals. WHT is most correlated with the two alternative forced choice orientation discrimination threshold based on the last four reversals, and the predicted 75% limen of the same threshold. Correlation grows worse for higher limens.

larger study validated the two-eye models for WHT.<sup>24</sup> For the 2AFC tests the best diagnostic concordance and correlation was between the 75% limen and the Worst Hemifield Threshold (Tables 3,4). One might expect higher limens drawn from the FOS curves of the 2AFC data (Fig. 2) to correspond to the higher MOA thresholds but they were less correlated and provided poorer diagnoses. This may indicate that the contrast gain-control process<sup>13–15</sup> is changing the FOS curves at higher contrasts, making the MOA and 2AFC/FOS-derived thresholds less comparable. The MOA and 2AFC threshold procedure patterns were nevertheless both quite effective in diagnosing glaucoma despite the thresholds being sevenfold different. In contrast, on a log-scale (e.g. Figs 2,3) the thresholds differ by only 1.8-fold. Given this smaller difference, the diagnostic similarities and correlations between the thresholds, it is possible that the same mechanism determines both threshold types. For MOA subjects were instructed that at threshold they should just be able to see the FD pattern. In the 2AFC case enough form was available for subjects to distinguish orientation 75% (or more for higher limens) of the time.

This raises the question of what is seen at the 2AFC orientation thresholds? More specifically, was FD seen or was some other pattern seen? A complicating factor is the Apparent Fineness Illusion<sup>31,32</sup> where interactions between cortical channels cause gratings composed of two similar spatial frequencies, say  $F$  and  $2F$ , to be seen as a pattern with a textural fineness between that of the two components. This illusion occurs for both real and illusory (FD) spatial second harmonics.<sup>32</sup>

Even under near optimal conditions for seeing FD ( $2F$ ) some residual fundamental ( $F$ ) grating is present,<sup>31,36</sup> so, as when real  $F$  and  $2F$  components are present, a percept of an intermediate spatial frequency is observed.<sup>31,32</sup> Pure frequency doubling has been reported for contrasts as low as 2% ( $-17$  dL),<sup>31</sup> becoming increasingly obvious as contrast declines.<sup>31,32</sup> This in turn is consistent with the underlying non-linearity for FD being rectification,<sup>36</sup> which, unlike other non-linearities, operates down to zero signal strength. The increasingly vivid FD percept with declining contrast is also consistent with the proposed origin for FD being the Y-like retinal ganglion cells of the magnocellular pathway,<sup>4,5,16,36</sup> because Y-cells show the same non-linearity<sup>15</sup> and their contrast gain control mechanism<sup>13,14</sup> would boost the apparent FD contrast. A study where subjects matched the spatial frequency of what is seen just above threshold indicates that the Apparent Fineness Illusion is operating<sup>37</sup> and that therefore at least some FD grating is present. Of course, it will always be difficult to determine if FD is seen at threshold given that, by definition, one is seeing the stimulus with low reliability, and cortical mechanisms determining the final percept may be compromised near threshold.

The average splined psychometric functions (Fig. 3) indicate that subjects may have performed below chance (50%) at low contrasts. This is possible because the 0.25 c/deg gratings used may have been at or below the critical sampling density<sup>16</sup> of the  $M_y$ -cells producing an orientation

alias<sup>38</sup> leading subjects to misjudge the actual pattern orientation. A misoriented alias near threshold would be further evidence for the presence of a FD pattern as the FD pattern, but not the fundamental, would produce an alias.<sup>16</sup>

Suprathreshold contrast discrimination of static gratings has been examined in glaucoma.<sup>39</sup> As in the present study, the outcome for static gratings was not very promising. In our study, subjects reported that they found the task too difficult even after extensive training.

Fixation errors have been suggested as a source of variability in FOS curves;<sup>40–42</sup> however, studies that are more recent cast doubt on the magnitude of the effect.<sup>43</sup> The present study demonstrates changes in the slope of FOS curves in glaucoma similar to those shown for other stimuli.<sup>43–48</sup> Given our large stimuli, fixation loss is unlikely to contribute to any such FOS changes.

Although somewhat better diagnostic power can be obtained by considering both the FOS slope and the threshold,<sup>47</sup> this may not be very useful in the clinic. This stems from the fact that a function and its derivative are orthogonal, that is, uncorrelated. So, for example, sampling theory tells us that we can obtain twice the resolution of a sampled function by sampling both the function and its derivative at each point,<sup>49</sup> twice as many uncorrelated samples being obtained by this 'point-slope' sampling. The corollary of this is that to obtain information about a function and its derivative one needs to sample twice as frequently, even when there is no noise. In the present study, this effect translated into proportionately greater errors for  $\sigma$  than for  $\mu$  (Table 3). To our knowledge, this is the first report of the relative reliability of the fits to  $\sigma$  than for  $\mu$  in glaucoma. From a clinical standpoint this means that little is obtained by trying to additionally estimate the FOS slope, as more repeats would be necessary to get the extra information. One might be better off doing the extra repeats, to improve estimates of  $\mu$ , but by using a threshold estimation method that does not assume anything about the shape of the psychometric function.<sup>50</sup>

## CONCLUSIONS

In agreement with other studies,<sup>5,6,24–26,51</sup> even large stimuli can provide good diagnostic discrimination when FD stimuli are employed, particularly when comparisons of the superior and inferior hemifield thresholds are made.<sup>24</sup> The MOA and 2AFC threshold methods can lead to different thresholds being obtained; however, in the case of FD stimuli the most diagnostically accurate 2AFC limen (75%) was best correlated with the MOA thresholds. This may indicate that the same mechanism determines both thresholds. This study indicates that considerable orientated form is seen at threshold and several lines of evidence indicate that a significant FD component is present. These results are relevant to the FDT perimeter since the thresholds obtained by the method used in that device are comparable to the 2AFC thresholds reported here.<sup>2</sup>

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