

# Clinical and Epidemiology

## Testing for glaucoma with the frequency-doubling illusion in the whole, macular and eccentric visual fields

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### ABSTRACT

**Purpose:** The frequency doubling (FD) illusion is the basis for new diagnostic methods for glaucoma. The FD illusion is seen when low spatial frequency grating patterns are contrast modulated at high rates. The present experiments examined which spatial frequencies might be optimal and whether high flicker rates are required.

**Methods:** We determined contrast thresholds for the following: W1, a wide-field 0.25 c/deg grating at 27 Hz contrast reversal; W2, as W1 but no flicker; MAC, 27 Hz, 4 c/deg grating presented to the central 4°; and E1 to E7, seven spatial frequencies in the range 0.063-0.813 c/deg 27 Hz, presented in a 5° aperture at 15° (nasal) eccentricity.

**Results:** W1 was the best predictor of glaucoma. Of the eccentrically presented stimuli, E6 (0.688 c/deg) was the best predictor of glaucoma while the lower spatial frequencies performed less well. Only MAC was significantly age dependent.

**Key words:** frequency doubling, glaucoma, illusion, perimetry, threshold.

### INTRODUCTION

When persons observe low spatial frequency gratings whose contrast is modulated at rates above 15 Hz the percept is of a stable grating with twice the spatial frequency of the stimulus. This frequency doubling (FD) illusion suggests the retinal gain control action of the 'Y-like retinal ganglion cells' of the magnocellular pathway, the so-called  $M_y$  cells. Psychophysical experiments indicate that retinal density of the units responsible for the FD illusion is equal to the

anatomical expectation for  $M_y$  cells<sup>3</sup>. A pattern electroretinogram signal embodying characteristics of the retinal gain control is recorded when persons see the FD illusion<sup>4,5</sup>. At the same time, there is evidence suggesting that  $M_y$  cells are the largest retinal ganglion cells and glaucomatous damage is correlated with cell size<sup>6</sup>. Finally the array of  $M_y$  cells is very sparse, making detection of cell loss relatively easy<sup>3</sup>. As might be predicted from these findings subjects with glaucoma perceive FD stimuli poorly.<sup>7-9</sup>

The present experiments are designed to compare the relative effectiveness of FD stimuli with related visual stimuli in classifying glaucoma suspects. In particular the range of spatial frequencies and the need for high temporal frequency contrast modulation are examined. Centrally presented visual stimuli are also compared to more peripherally biased stimuli.

### METHODS

Visual stimuli were presented on a Barco monitor (refresh rate 108 Hz, mean luminance 45 cd/m<sup>2</sup>). Subjects viewed the monitor monocularly from a distance of 60 cm. The four test conditions examined were W1 (Fig 1a), a wide-field 0.25 c/deg grating at 27 Hz contrast reversal, W2, as W1 but no flicker; MAC (Fig 1b), a 4 c/deg grating contrast reversed at 27 Hz presented to the central 4°, and E1 to E7 (Fig 1c), seven spatial frequencies in the range 0.063-0.813 c/deg (1/16 - 13/16 c/deg in increments of 1/8 c/deg) contrast reversed at 27 Hz, presented in a 5° aperture at 15° (nasal) eccentricity. Except for W2, contrast thresholds (10-bit accuracy) were assessed by method of adjustment (MOA) in repeated trials (n = 6). At the beginning of each trial of the MOA procedure subjects were first

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Commercial interest: T Maddess holds the patents for the Humphrey FDT Visual Field Instrument manufactured by Welch Allyn Ltd (Skaneateles Falls, NY, USA). The results of this paper could be construed as supporting the basic for that Instrument.

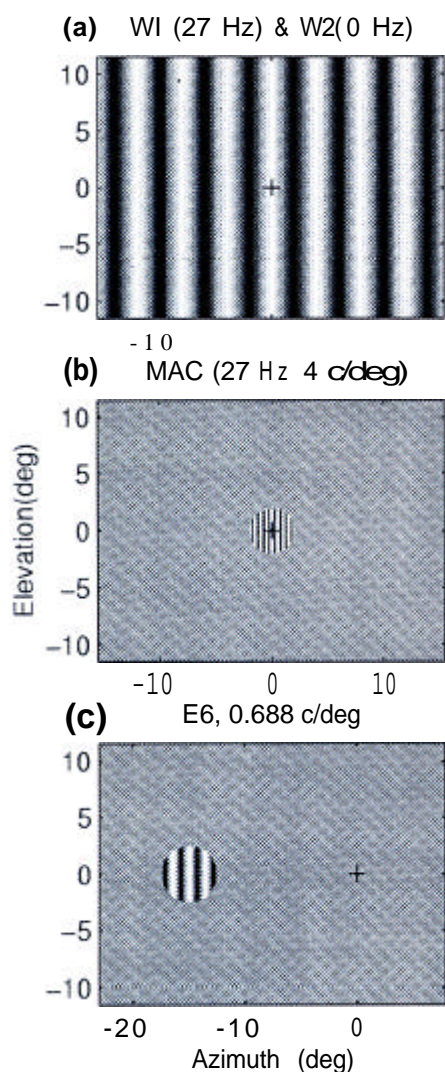


Figure 1. Spatial layout of the visual stimuli (a) for tests W1 and W2; (b) for the perimacular test MAC (except the spatial frequency of the grating was twice that shown), (c) for tests E1 to E7 In the case of W2 the gratings were displayed in cosine phase with respect to the aperture centre In the other contrast-reversed tests the gratings were displayed in  $\pm$ cosine phase with respect to the centre of their aperture The grey backgrounds of (b) and (c) Indicate the mean luminance of  $45 \text{ cd/m}^2$ . The + indicates the position of a fixation cross, which was red In the test and  $0.25^\circ$  square

shown the test pattern at 100% contrast. They were then asked to reduce the contrast to a point where they were just unable to see the test pattern: Then they were asked to make fine adjustments until they found a point at which they felt they could only just see the test pattern. W2 thresholds were determined in a 2AFC staircase method<sup>7</sup> where the alternative stimulus was a blank field at the mean luminance and six reversals were determined for each threshold. Multivariate regression and discriminant analysis were conducted with SPSS, all thresholds being expressed in decibel contrast. We

Table 1. Univariate one-way ANOVA

Test	F (1,21)	Significance
W1	23.14	0.0001
w2	9.36	0.0059
MAC	16.61	0.0005
AGE	9.63	0.0054
E1	4.51	0.0457
E2	10.09	0.0045
E3	10.49	0.0039
E4	15.07	0.0009
E5	12.47	0.0020
E6	17.41	0.0004
E7	15.98	0.0007

Table 2. Correlation with discriminant function

Test	Coefficient
W1	0.85
E3	0.77
E4	0.75
E6	0.74
E7	0.71
E2	<b>0.69</b>
E5	0.68
MAC	0.58
E1	0.55
W2	0.54
AGE	0.30

examined 10 normal subjects (mean age  $46.7 \pm 9.1$  years SD) and 15 primary open angle glaucoma suspects ( $60.0 \pm 11.9$  years SD). The age ranges permitted significant age dependencies to be estimated The suspects had glaucomatous optic disc cupping (vertical cup-to-disc ratio of 0.6 or greater by colour or contour) and a highest recorded intra-ocular pressure (IOP) of 20 mmHg or greater. All subjects gave Informed written consent under the ANU human ethics protocol no. M881.

## RESULTS

Univariate measures indicated that W1, MAC and E4 to E7 were all reasonable predictors of glaucoma (Table 1). A multiple regression analysis comparing the W1, W2 and MAC thresholds showed that only MAC was significantly correlated with AGE ( $P = 0.358, 0.163$  and  $0.000$ , respectively) There was no measurable effect of gender.

In a more rigorous approach to comparing the various methods, we conducted a discriminant analysis including all the thresholds and the AGE data. The discriminant analysis selected only W1 and E6 (F statistics for exclusion: 23.14 and 15.15, respectively). The canonical discriminant function, sensitivity and specificity for this model are 86.7 and 90% (88% or 22/25 correctly classified) Correlation coefficients for all the variables (Table 2) revealed that W1, E3,

Table 3. Thresholds in decibels

	Normal		Suspect	
	Mean	SD	Mean	SD
W1	-21.76	3.93	-15.54	4.83
W 2	-29.17	7.73	-19.21	8.53
MAC	-16.38	4.62	-9.28	3.56
E6	-15.58	6.63	-4.74	3.36

E4, E6 and E7 were most strongly correlated with the discriminant function, while W2 and AGE were the least correlated. As W1 was the variable that was the best predictor of glaucoma it is reasonable to question how it alone could classify the groups. A discriminant analysis using only W1 produced sensitivities and specificities of 80 and 84.6%, respectively. Table 3 gives the mean decibel thresholds and the population standard deviations, for normals and suspects, for the thresholds W 1, W2, MAC and E6.

## DISCUSSION

As suggested by the univariate comparisons (Table 1), discriminant analysis showed W1 and E6 to be the best predictors of glaucoma. The resulting classification rate, 88% correct, was reasonable, especially as the persons in the test group were suspected of having glaucoma and none had a definite scotoma. Of the eccentrically presented stimuli, E3, E4 and E6 (0.313, 0.438, 0.688 c/deg) were best correlated with the discriminant function. In other words, thresholds for these intermediate spatial frequencies were well correlated with being a glaucoma suspect. The lowest spatial frequencies performed less well, indicating that stimulation by eccentric targets of very low spatial frequency is suboptimal. It would appear, therefore, that targets containing a moderate amount of structure are required. Only

MAC was significantly age-dependent ( $P = 0.000$ ) and was poorly correlated with the discriminant function. This is surprising given that the percentage loss of ganglion cells appears to be highest in the central retina.<sup>10</sup> Perhaps, therefore, other age-related processes affecting retinal function mask the diagnostic potential of the macula for glaucoma. Studies with lower spatial frequencies presented centrally (0.5 c/deg), indicating less age dependence,<sup>11</sup> so it might be that the 4 c/deg grating used for the MAC test produced dependence in the observed age group. W2, the test examining the absolute contrast threshold for a temporally unmodulated, low spatial frequency-grating pattern, was interesting because it was least correlated with being a glaucoma suspect. The relatively poor performance of W2 may be the result of the relatively large changes to 'population variance' (Table 3). Low test-retest variation, especially of serious defects, is a feature of FD perimetry of glaucoma.<sup>12,13</sup> The relative age-independence of W1 and the tolerance to defocus of low spatial frequencies is encouraging as it makes easier the diagnosing of older subjects.

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