Chromatic and luminance sensitivity in diabetes and glaucoma

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The effects of glaucoma and diabetes on the sensitivities of the opponent and achromatic systems were investigated by measuring thresholds along theoretically defined axes in a three-dimensional color space. Thresholds were measured along two equiluminant chromatic axes and one achromatic axis in patients with diabetes or glaucoma and in glaucoma suspects. The results were compared with measures of sensitivities of short- and middle-wavelength-sensitive-cone pathways [S (Stiles $\pi 1$) and M (Stiles $\pi 4$), respectively] and with measures of hue discrimination by use of the Farnsworth–Munsell 100-hue test. The glaucoma suspects and diabetic patients showed preferential S-cone-pathway sensitivity losses. For glaucoma patients, however, these losses were associated with significant decreases in the sensitivity of the L–M opponent system and with decreased sensitivity to achromatic contrast.

Diabetes and glaucoma lead to defects in color vision. These defects are found during the early stages of the disease process and appear to be selective for the S-cone system. For example, researchers who have used spectral-sensitivity techniques have reported decreased sensitivity in S-cone pathways in patients with early diabetic retinopathy.[1–4] Similar findings have been reported for patients with early primary open-angle glaucoma and for patients with ocular hypertension.[2,5,6] In a recent study, we used a two-color increment threshold technique to compare the sensitivities of an M (Stiles $\pi 4$)- and an S (Stiles $\pi 1$)-cone pathway in patients with these diseases. Although the diabetic patients with early background retinopathy showed selective losses in S-cone-pathway sensitivity, the glaucoma patients showed losses in M- and S-cone-pathway sensitivity.[7]

The objective of the present study was to assess the effects of diabetes and glaucoma on the sensitivities of the opponent and achromatic systems. There is evidence that the visual system consists of a series of stages. The first stage comprises three independent cone mechanisms (the L-, M- and S-cone mechanisms), and the second stage comprises two independent chromatic mechanisms and one achromatic mechanism. In this study we assume that the spectral sensitivities of the cones correspond to the Smith–Pokorny fundamentals[8] and that the mechanisms at the second stage correspond to the cardinal directions of Krauskopf *et al.*[9] Our aim was to determine whether the sensitivities of the second-stage mechanisms were selectively affected by diabetes and glaucoma. To make this determination we measured thresholds to lights that were varied along theoretically defined axes in a three-dimensional color space. Thresholds were measured along three axes corresponding to the cardinal directions of Krauskopf *et al.*[9]: two equiluminant chromatic axes and one achromatic axis (see Fig. 1). The axes are defined in terms of changes in cone excitation. The limits of the axes are given as (L, M, S) excitations in MacLeod–Boynton coordinates,[10] where L, M, and S refer to excitations of the long-, middle-, and short-wavelength-sensitive cones, respectively. The *YV* axis is defined by changes only in S-cone input; L- and M-cone excitations remain constant. The *RG* axis is defined by changes in L- and M-cone excitations in equal but opposite steps. The sum of the L- and M-cone excitations is kept constant, as is S-cone excitation. Along the *LD* axis all three cone inputs are varied in equal proportions. The sensitivities of the S–(L + M) and L–M opponent systems were evaluated by measuring thresholds to lights along the *YV* and *RG* axes, respectively. Sensitivity to achromatic contrast was assessed by measuring thresholds to lights along the *LD* axis. The results were compared with measures of S ($\pi 1$)- and M ($\pi 4$)-cone-pathway sensitivities that were obtained by use of a selective-adaptation technique and with measures of hue discrimination by use of the Farnsworth–Munsell (FM) 100-hue test.

METHODS

Subjects

Four groups of subjects participated in the study: seven patients with Type I diabetes, eight patients with open-angle glaucoma (OAG), six glaucoma suspects, and thirteen age-similar control subjects. All patients had corrected visual acuity equal to or better than 20/30 in the tested eye. The age range was 36–57 years (mean, 46 ± 8.6 years) for the diabetic group, 16–55 years (mean, 42.7 ± 14.6 years) for the glaucoma suspects, and 27–56 years (mean, 39.4 ± 8.3 years) for the glaucoma group.

Tables 1 and 2 summarize the patients' clinical characteristics. All seven diabetic patients had early background retinopathy (see Table 1 for details). The level of

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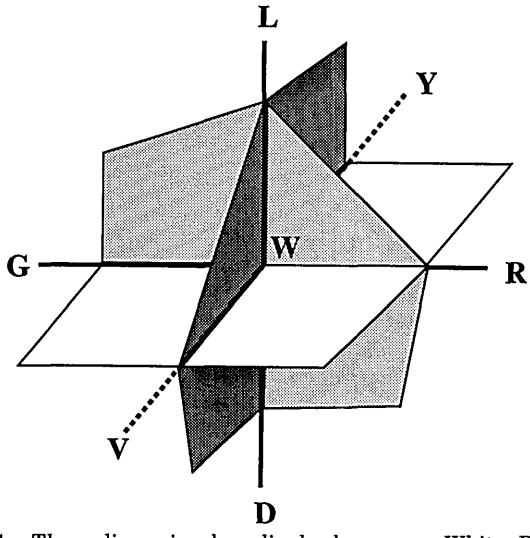

Fig. 1. Three-dimensional cardinal color space. White, *RG/YV* equiluminant plane; light gray, *RG/LD* plane; dark gray, *YV/LD* plane. *RG* axis: L- and M-cone excitations change linearly in equal but opposite steps; (L + M)- and S-cone excitations remain constant. *YV* axis: S-cone excitations change linearly; L- and M-cone excitations remain constant. *LD* axis: S-, M-, and L-cone excitations change proportionately from dark to light. The maximum values attainable on the axes are (L, M, S) excitations in MacLeod–Boynton coordinates[10]: $W = (0.66, 0.34, 0.023)$; $L = (1.32, 0.68, 0.046)$; $D = (0, 0, 0)$; $R = (0.71, 0.29, 0.023)$; $G = (0.61, 0.39, 0.023)$; $Y = (0.66, 0.34, 0.004)$; $V = (0.66, 0.34, 0.041)$. Midwhite (W) is at 50 cd/m^2.

Table 1. Clinical Characteristics of Diabetic Patients[a]

Subject	Age	Acuity	Type	Retinopathy Level	Edema
1	36	20/20–2	1	2	0
2	57	20/20	1	2	0
3	48	20/20	1	2	0
4	50	20/20–3	2	3	0.5
5	55	20/20	1	2	0.5
6	41	20/20	1	2	0
7	36	20/15	1	2	0

[a]The level of retinopathy and the degree of macular edema were assessed by two independent graders. Retinopathy levels: 1, normal fundus; 2, one or more microaneurysms; 3, microaneurysms with one or more nonproliferative lesions. Grade edema: 0, no macular edema; 1, questionable macular edema.

retinopathy and degree of macular edema were determined by two independent examiners and were based on the results of slit-lamp biomicroscopy with a contact lens, color fundus photographs, and fluorescein angiography.

The glaucoma patients had varying degrees of visual-field loss (see Table 2 for details) and intraocular pressures that were controlled clinically at the time of examination. Patients with pupil diameters <2 mm were excluded from the study. Pupil diameters ranged from 2 to 4 mm. The term glaucoma suspect was applied to patients who had elevated intraocular pressure (readings ≥22 mm Hg on two or more occasions) but who showed no other evidence of glaucoma, such as pathological cupping of the optic disk or glaucomatous field defects. Two of the patients included in the glaucoma-suspect group had questionable early disk changes. None of the patients in the three groups had a history of hypertension or other systemic disease, and none of the eyes studied showed evidence of significant lens opacities. Another requirement for inclusion in the study was that the patients show no evidence of congenital red–green color-vision defects. Diagnosis of congenital red–green color defects was based on history and on the midmatching point and matching range obtained on a Nagel-type anomaloscope.

The thirteen subjects who constituted the control group ranged in age from 24 to 53 years (mean, 41 ± 10 years). They had no known abnormality of the visual system and corrected visual acuity of 20/20 or better. Informed consent was obtained from all subjects before testing.

Chromatic and Achromatic Discrimination Thresholds

Apparatus

Stimuli were displayed on a Tektronix 690SR color-television monitor. The screen was refreshed at 120 interlaced frames/s. The 512 × 480 pixel display subtended 10.67 deg × 10 deg of visual angle. The mean luminance of the screen was 50 cd/m^2. The CIE chromaticities (x, y coordinates) of the television phosphors were as follows: red (0.63, 0.34), green (0.31, 0.595), and blue (0.155, 0.070). Images were generated by using an Adage 3000 raster-based frame-buffer generator. The Adage permitted 10-bit specification of the output of each TV gun leading to a palette of 2^{30} possible colors, 256 of which could be displayed on any one frame. For a detailed description of the calibration procedure see Zaidi *et al.*[11] and Zaidi and Halevy.[12] All stimulus generation and data collection was done automatically under computer control.

Stimuli

The range of lights used in this study is shown in Fig. 1 (adapted from Ref. 13). The lights are specified in a

Table 2. Clinical Characteristics of Glaucoma Patients and Glaucoma Suspects

Subject	Age	Acuity	Visual-Field Loss[a]	Diagnosis[b]
1	40	20/25	4	OAG (PG)
2	37	20/20–2	4	Juv. POAG
3	27	20/30	4	Juv. POAG
4	34	20/20	3	OAG (PG)
5	56	20/25	2	OAG (XFS)
6	38	20/20	4	OAG (PG)
7	40	20/20	2	POAG (NT)
8	43	20/20	2	OAG (PG)
1	16	20/20	1	GS
2	51	20/20	1	GS
3	48	20/20	1	GS
4	36	20/20	1	GS
5	50	20/20	1	GS
6	55	20/20	1	GS

[a]Visual-field loss: 1, normal field; 2, isolated small defect or arcuate scotoma; 3, moderate visual-field loss (defects ≥10 deg from central fixation); 4, severe visual-field loss (large loss of peripheral field).

[b]Diagnosis: PG, pigmentary glaucoma; Juv. POAG, juvenile primary open-angle glaucoma; XFS, exfoliation syndrome; NT, normal-tension glaucoma; GS, glaucoma suspect.

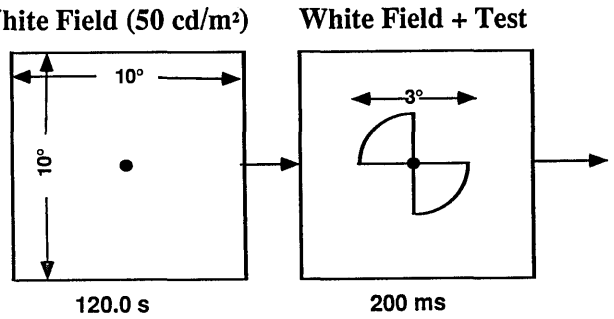

Fig. 2. Spatial and temporal paradigm for the measurement of chromatic- and achromatic-discrimination thresholds.

three-dimensional color space with axes corresponding to the cardinal directions of Krauskopf *et al.*[9] These axes are labeled *YV*, *RG*, and *LD*. The labels represent the approximate color appearance of the end points and are to be used solely as mnemonics. The axes can be related to relative quantal absorption of the three cone types. *W*, the center of the space is an achromatic light with a luminance of 50 cd/m^2.

Procedure

The subject's nontested eye was occluded. The subject first adapted for 120 s to a 10-deg steady white adapting field of 50 cd/m^2. A small dark spot in the center of the 10-deg adapting field served as a fixation point. Discrimination thresholds were then obtained for a foveally fixated test light consisting of two quadrants of a 3-deg disk, 200 ms in duration (see Fig. 2 for the spatial and temporal paradigm). The subject's task was to indicate whether he or she could discriminate the test light from the adapting background. Two random interleaved staircases tracked the 71% position on a psychometric function by increasing or decreasing the distance of the test light from *W* along a cardinal axis. This distance is referred to as a discrimination threshold. A transition was said to occur when the distance was increased after a sequence of decreases and vice versa. The value of each threshold is the mean of eight transitions.[14] It took ~20 min to complete the test.

Equiluminance along the *RG* and *YV* cardinal axes was checked for each observer with the use of flicker photometry at 22.5 Hz. We obtained means and standard deviations (SD's) of the equiluminant settings for each observer. Observers with mean settings >2 SD from the equiluminant plane were excluded from the study.

Farnsworth–Munsell 100-Hue Test

Hue discrimination was evaluated with the FM 100-hue test administered under standard Illuminant-C lighting conditions (MacBeth easel lamp with an illumination of 290 lx). The subject's correction for the viewing distance (40 cm) was worn, and the nontested eye was occluded. The order of presentation of the boxes was varied randomly, and no time limit was imposed. The error scores were calculated by use of the Farnsworth method and were compared with age-similar data obtained by Verriest *et al.*[15] for normal observers for monocular testing. Quadrant analysis was performed on the raw scores to evaluate the tendency toward a tritan, protan, or deutan defect. Total error scores were partitioned into blue–yellow and red–green partial scores as described by Smith *et al.*[16]

Two-Color Increment-Threshold-Test Measurement of the Sensitivities of an M- and an S-Cone Pathway

Light stimulation was provided by a two-channel Maxwellian-view system described previously.[4] Monochromatic light for the test channel was provided by 480- and 540-nm narrow-band interference filters with half bandwidths of ~6 nm; for the background channel it was provided by a 600-nm narrow-band interference filter. The retinal illumination was calibrated with an EG&G (Salem, Mass.) Model 550 photometer and was calculated by use of the method described by Westheimer.[17]

A two-color increment threshold procedure was used to measure the foveal sensitivities of an M (Stiles $\pi 4$)- and an S (Stiles $\pi 1$)-cone pathway. Foveal increment thresholds were obtained for a 480-nm test light (1.2 deg, 200 ms) superimposed on 14-deg steady adapting fields (see Greenstein *et al.*[4] for details of the procedure). Use of the same test light (480 nm) permitted us to measure the relative thresholds of the M- and the S- cone pathways that were unaffected by differences in preretinal absorption. The contribution of macular pigment density to the threshold measures was estimated by comparing the value of M-cone thresholds obtained by use of a 480-nm test light at an adapting background of 0.96 log Td with the thresholds obtained by use of a 540-nm test light. Macular pigment absorption at 540 nm is minimal.[18,19] If M-cone sensitivity were decreased as a result of increased macular pigment density and/or yellowing of the lens rather than as a result of disease, then the decrease would be negligible for data obtained with a 540-nm test light.

The sensitivity losses of the M ($\pi 4$)- and S ($\pi 1$)-cone pathways were calculated at 0.96 log Td and at 3.87 log Td, respectively. In a previous study these levels of adaptation were found to provide adequate measures of M- and S-cone pathways.[7] All thresholds were adjusted for the contribution of increased macular pigment and/or yellowing of the lens.

RESULTS

Chromatic and Achromatic Discrimination Thresholds

The threshold data for each group were averaged. The difference in thresholds for each cardinal direction relative to the mean thresholds for control subjects was calculated for each patient group. The mean data are shown in Fig. 3. The difference in log discrimination threshold is plotted against cardinal direction for the three groups. Vertical bars represent ±1 SD. For the glaucoma group [Fig. 3(a), filled circles], mean discrimination thresholds are significantly higher for all cardinal directions compared with those of the control group. The differences between the glaucoma group and the control group, however, are greater for the *YV* and *LD* axes; the greatest increase occurs for the *YV* axis. For the glaucoma-suspect group [Fig. 3(b), large circles], thresholds are significantly higher only for the *YV* axis in both *Y* and *V* directions. For the diabetic group [Fig. 3(c), squares], thresholds are increased, and the greatest increase is again for the *YV* axis (see Table 3 for details and *P* values).

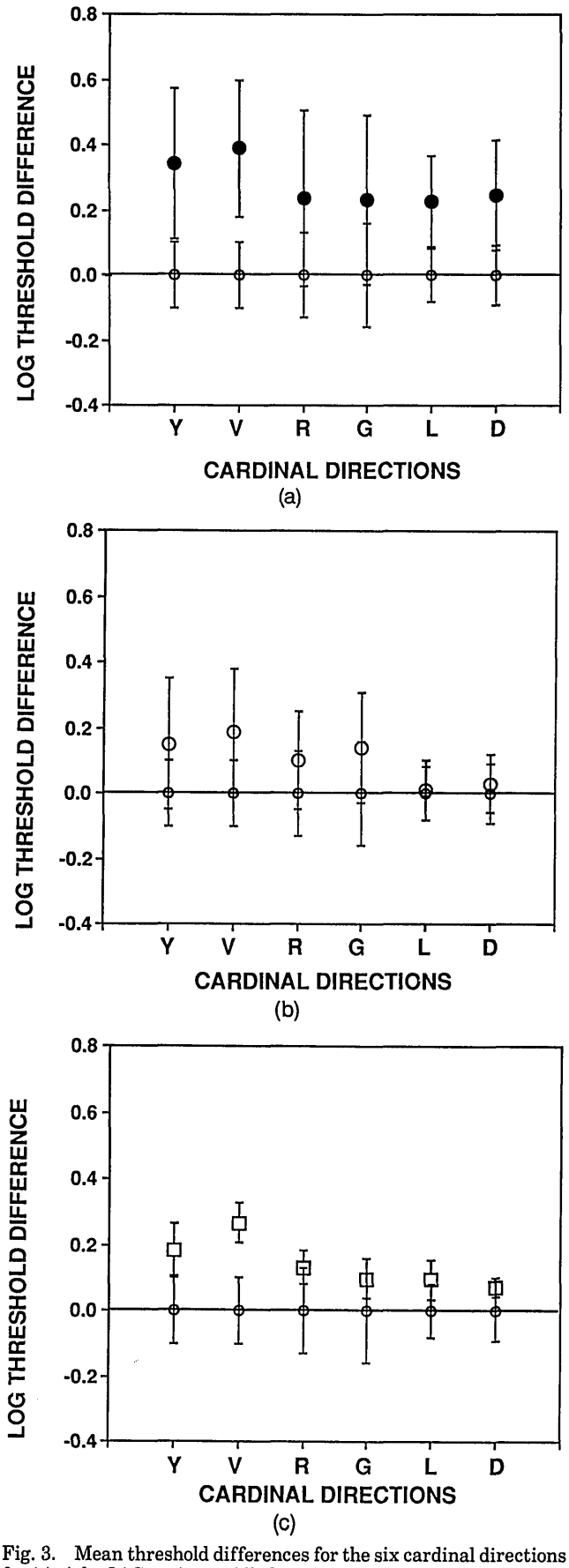

Fig. 3. Mean threshold differences for the six cardinal directions for (a) eight OAG patients (filled circles), (b) six glaucoma suspects (large circles), and (c) seven diabetic patients (squares). Small open circles represent controls; vertical bars represent ±1 SD.

Hue Discrimination with the Farnsworth–Munsell 100-Hue Test

Only one diabetic and one OAG patient had error scores that exceeded the 95th-percentile score for age-matched normals.[15] Because we were interested in evidence for selective S-cone-pathway deficits, we calculated the differences between the square roots of the blue–yellow and the red–green partial scores (the difference scores). Figure 4(a) shows the age-corrected difference score for glaucoma suspects (open circles) and for OAG patients (filled circles) versus the degree of visual-field loss. The age-corrected difference score for diabetics versus the level of retinopathy is shown in Fig. 4(b). Difference scores above +2.8 on the ordinate (top dashed line) indicate a significant blue–yellow axis, whereas data below −2.8 (bottom dashed line) indicate a significant red–green axis.[16] Although all but one patient have difference

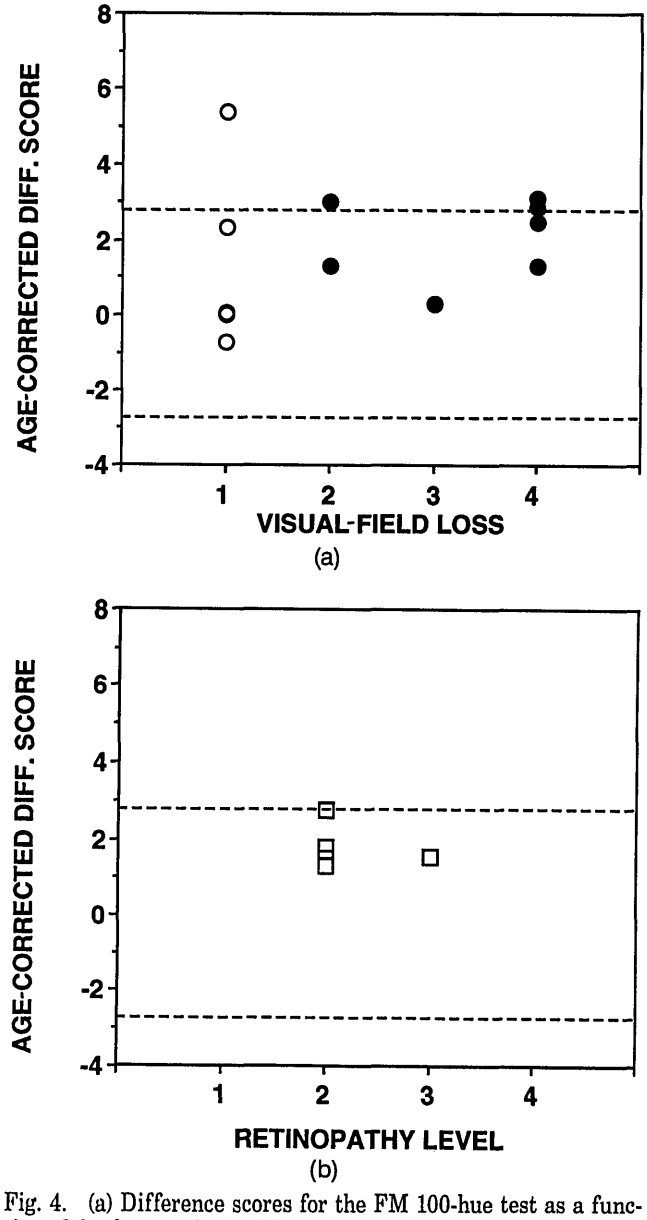

Fig. 4. (a) Difference scores for the FM 100-hue test as a function of the degree of visual-field loss for eight OAG patients (filled circles) and six glaucoma suspects (open circles). (b) Difference scores as a function of the level of retinopathy for seven diabetic patients. The dashed lines at +2.8 and −2.8 represent ±2 SD.[15]

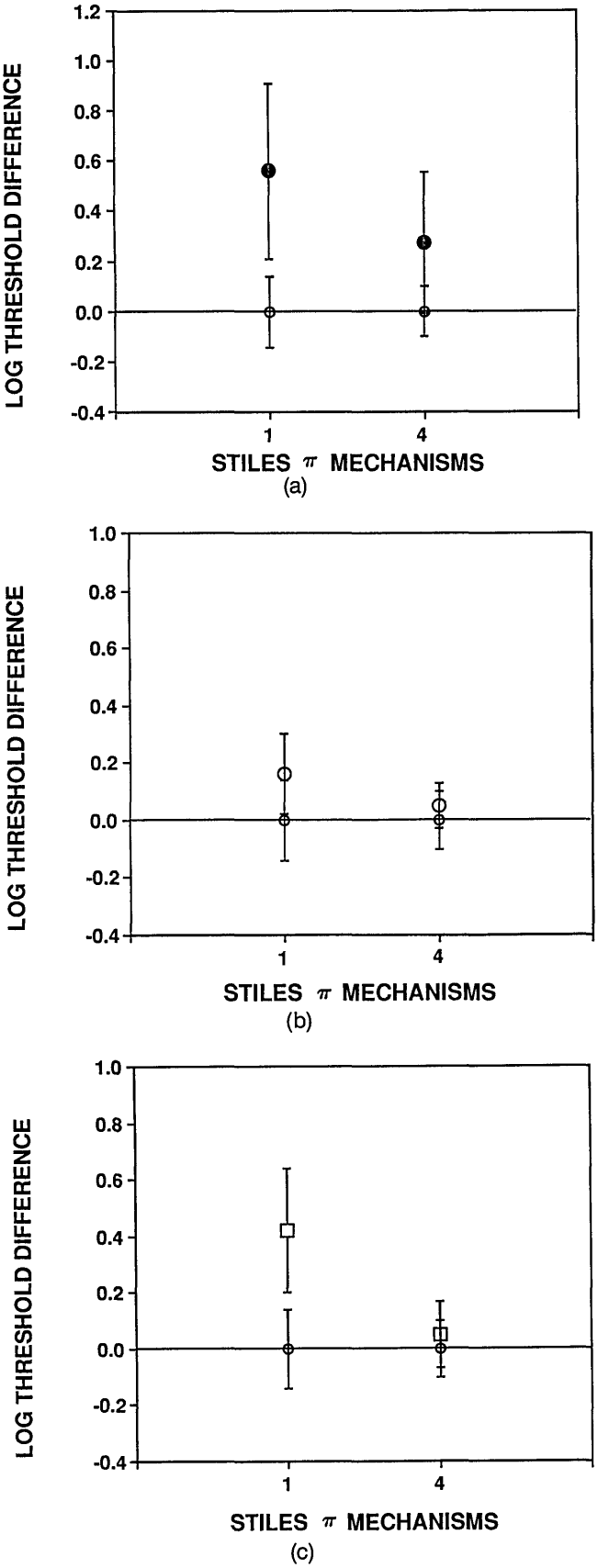

Fig. 5. Mean threshold differences for an S (π1)- and an M (π4)-cone pathway for (a) eight OAG patients (filled circles), (b) six glaucoma suspects (large open circles), and (c) seven diabetic patients (squares). Small open circles represent controls; vertical bars represent ±1 SD.

scores greater than zero, consistent with a trend in the data toward tritan defects, only three patients (two glaucoma patients and one glaucoma suspect) have significant defects.

Two-Color Increment-Threshold Test

The threshold data were averaged for the three groups of subjects. Figure 5 shows the differences in log thresholds ±1 SD for an S (π1)- and an M (π4)-cone pathway relative to the mean thresholds for the control group. S-cone-pathway thresholds are significantly increased for all three groups, with glaucoma and diabetic patients showing the greatest increases [see Figs. 5(a) and 5(c)]. M-cone-pathway thresholds are also significantly increased for the glaucoma group (see Table 3 for details).

DISCUSSION

The chromatic and achromatic threshold data obtained from the diabetic and glaucoma-suspect groups provide evidence for more pronounced S-cone-pathway deficits. For both glaucoma suspects and diabetics, discrimination thresholds were significantly increased for the *YV* axis; lights along this axis produced changes only in S-cone input. The glaucoma group showed the largest S-cone-pathway deficits, but for this group thresholds were also significantly higher for the *RG* and *LD* axes. The results of the two-color increment threshold technique provide additional evidence for more pronounced S-cone-pathway deficits. For both diabetics and glaucoma suspects, S (π1)-cone-pathway thresholds were significantly increased. The glaucoma group also showed increases in S-cone-pathway thresholds, but the increases were accompanied by significant increases in M (π4)-cone-pathway thresholds. The foveal S-cone-pathway sensitivity losses that we found cannot be attributed to preretinal factors such as yellowing of the lens because we used a 480-nm test light in the increment threshold technique to measure both M- and S-cone-pathway thresholds, and thresholds were adjusted for the contribution of increased macular pigment and/or yellowing of the lens.

The results of the two threshold techniques, a reduction in S-cone-pathway sensitivity for all three groups and a reduction in achromatic and L–M sensitivity for the glau-

Table 3. Threshold Differences

	Axis			π Mechanism	
	YV	*RG*	*LD*	π1	π4
Glaucoma Group					
Log threshold	0.37	0.23	0.24	0.57	0.27
t Value	5.43	2.63	4.78	4.797	3.077
P	<0.001	0.02	<0.001	<0.001	0.006
Glaucoma-Suspect Group					
Log threshold	0.17	0.11	0.03	0.17	0.05
t Value	2.75	1.56	0.60	2.503	1.11
P	0.01	0.14	0.56	0.02	0.28
Diabetic Group					
Log threshold	0.23	0.11	0.09	0.42	0.03
t Value	6.35	1.99	2.56	5.179	0.709
P	<0.001	0.06	0.02	<0.001	0.487

coma group, are in agreement with those of previous studies that used increment threshold techniques.[1–7,20] They are also in general agreement with the few studies that have used stimuli specified in terms of cardinal directions to investigate the effects of these diseases on opponent systems. For example, patients with ocular hypertension or glaucoma showed the largest sensitivity losses along a tritan axis,[21] and sensitivity losses along the equivalent of the *YV* axis were found for diabetic patients.[22,23] We can interpret our discrimination threshold results in terms of current theories of underlying physiological pathways. We assume that lights along the *LD* axis provide for relatively greater excitation of magnocellular-pathway cells, whereas lights along the *YV* and *RG* axes provide for relatively greater excitation of parvocellular-pathway cells. According to this assumption, for glaucoma patients the finding of increased thresholds along all three axes presumably would reflect deficits in both magnocellular and parvocellular pathways, whereas the data from the glaucoma suspects would be consistent with a defect in a subclass of parvocellular-pathway cells receiving S-cone input.

When we compare the results of the two threshold techniques with measures of hue discrimination that were made by use of the FM 100-hue test, we find discrepancies, particularly for the glaucoma suspects and the diabetics. Although the FM 100-hue-test data show a trend toward a tritan defect for all patients except one, significant tritan defects were found for only three patients: one glaucoma suspect and two glaucoma patients. This result is perhaps not surprising for the glaucoma patients, who show accompanying M-cone-pathway sensitivity losses and losses along the *RG* axis. It is more difficult to account for the failure to find significant tritan defects for the glaucoma suspects and diabetics. We and other investigators have observed a similar discrepancy between FM 100-hue-test results and detection thresholds in previous studies of diabetic patients with early retinopathy.[1,4,20] A possible approach toward reconciling these findings was suggested by Pokorny *et al.*[24] They proposed a unified model for analyzing detection and discrimination data. The model is based on the calculation of S-cone troland levels for increment threshold conditions and for FM 100-hue test caps at different illumination levels and on the construction of an increment threshold curve (see Ref. 24). If some of the S-cone-pathway sensitivity loss in glaucoma suspects and diabetic patients can be attributed to a decrease in quantal catch at the level of the S-cone receptors, then the effective intensity of both the test and the background lights would be decreased. The increment threshold function would be shifted up and over compared with the normal function. Thresholds would be increased at low background levels but would approach the normal at higher background levels.[25,26]

The FM 100-hue test was performed at a background level in the Weber region of the increment threshold function. The two-color increment threshold test was performed at a low background level at which incremental thresholds are independent of background illumination. If disease resulted in a decrease in quantal catch, then performance on the FM 100-hue test would not be affected. This could be an explanation for our failure to find significant tritan defects on the FM 100-hue test. It could also account for the discrepancy between measures of S-cone-pathway sensitivity produced by use of the two-color increment threshold test and the chromatic-discrimination-threshold test. For the three groups of patients there was a greater increase in $\pi 1$ thresholds than in *YV* thresholds. The chromatic-discrimination task was performed at a background level close to or in the Weber region. Again, if a decrease in quantal catch could account for some of the S-cone sensitivity loss, thresholds would be higher for the two-color increment threshold task than for the chromatic-discrimination task.

The above explanation assumes that diabetes and glaucoma lead to decreases in quantal catch. This assumption is problematic because glaucoma is primarily an inner retinal disease, and, with regard to diabetes, we recently found evidence in patients with early diabetic retinopathy that the site of S-cone-pathway loss was postreceptoral. In addition, in the same study the ratio of diabetic to normal S-cone thresholds was constant for background luminances ranging from 0 to 100 cd/m^2.[27] Possible alternative explanations include the difference in the size of the test light for the two paradigms and that the two-color increment threshold test leads to a polarized state of the S-cone pathway induced by the chromatic background.

In conclusion, the results that we obtained in this study confirm earlier findings of preferential S-cone-pathway sensitivity losses in patients with early diabetic retinopathy.[1–4] Glaucoma suspects also showed a preferential S-cone-pathway sensitivity loss. In glaucoma patients, this loss was associated with significant decreases in the sensitivity of the L–M opponent system and with decreased sensitivity to achromatic contrast.

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