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Spatial visual filtering in diabetes mellitus

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Abstract *Purpose:* To investigate spatial visual filtering in a group of diabetic patients and compare the results with those of a group of controls. *Methods:* The luminance threshold of a moving 2° achromatic target, viewed against a 17° achromatic background grating, was measured as a function of grating periodicity from 0.21 to 31.4 cpd in 22 diabetic patients and 12 controls, giving a response characteristic of the spatial function of a sustained-response type of visual channel. A previously published model of spatiotemporal filtering, integrating photoreceptor kinetics with difference-of-Gaussian circularly symmetric receptive fields, was used to analyse the data. *Methods:* The model gave a good fit to the data in the control group, with a mean central space constant of 0.046° and centre:surround ratio of 1:5.2 and mean R^2=0.78 (SD 0.12). The mean central space constant in the diabetic group was 0.051° and the centre:surround ratio 1:4.2, although best fit was significantly worse, at R^2=0.54 (SD 0.19), P=0.001. The best fit for diabetic subjects with grade 2 maculopathy was significantly worse than for those with no maculopathy (P=0.03). *Conclusion:* The study demonstrates a disruption of circularly symmetric centre–surround receptive field structure of the sustained-response channel in the diabetic retina to a degree that is consistent with the retinal level of anatomical change in diabetic maculopathy.

Introduction

Diabetic eye disease and in particular diabetic retinopathy is a leading cause of blindness in the working-age population in the developed world [34]. The middle and inner retinal layers are affected by diabetic retinopathy, and study of functional changes related to these layers of the visual system is of interest. Presently, the only treatment available for sight-threatening retinopathy is laser surgery, and this can reduce the incidence of severe visual loss by 50% [19, 46]. There is increasing evidence that medical treatment will become paramount in reducing the onset and progression of diabetic retinopathy and consequently visual loss [1, 45, 48, 49]. Visual function parameters may be useful in the future for monitoring retinopathy progression or the efficacy of current or new treatments.

Diabetes results in a pan-ocular disease, with effects on the cornea [29], lens [8, 13, 32, 35, 36, 39, 42, 50], macular pigment [13], photoreceptors [20] and the middle and inner retinal layers [22]. Many studies of spatial visual function in diabetes to date have used letter or grating contrast sensitivity tests that do not select function from specific levels of visual processing [2, 4, 5, 9, 10, 11, 15, 16, 18, 23, 24, 26, 27, 31, 37, 41, 47]. The changes found in contrast sensitivity have been conflicting, with some researchers finding abnormality only in diabetics with retinopathy [2], whilst others found abnormality in aretinopathic patients as well [16, 18, 23, 41]. The loss of sensitivity did not, however, correlate well

with the degree of retinopathy [4, 5, 9]. Differences between the ocular media of diabetics and normals [8, 13, 32, 35, 36, 39, 42, 50] may explain some of the difficulties associated with measuring contrast sensitivity as a test to investigate retinal dysfunction.

In this study we used the first of two achromatic spatiotemporal responses (designated ST1 and ST2) developed by Barbur and Ruddock [6, 7] and Holliday and Ruddock [25] that are less dependent on changes in the ocular media and select a response from particular neuronal populations. Such tests may have advantages over non-selective tests, as abnormality in the results can be correlated more tightly with abnormality in the anatomical area of interest.

In the ST1 and ST2 responses, the luminance threshold of a small achromatic moving target is measured as a function of a variable parameter of a larger, supra-threshold background. The threshold level is modulated by the pathway most sensitive to the type of background used. The ST1 response is elicited by a background containing a high-contrast linear square wave grating [6] and the ST2 response by a background of temporal sine wave flicker [25]. The original study showed that the ST1 response was invariant with target speed in the range 0–50°/s and target size 0.1°–3.5°, independent of grating orientation, and showed a Weber-type response for increasing background luminance [6]. Further study in the temporal domain showed a sustained-type response, strongly suggesting that the ST1 response is characteristic of the spatial properties of the parvocellular pathway [25].

We used a model of retinal ganglion cell response to a spatiotemporal stimulus [17] to analyse the data obtained in a group of diabetic patients and compared the results to those from a group of controls.

Methods

Although the original work on the spatiotemporal responses was performed using a Maxwellian view optical system, it was later shown that the functions could be obtained reliably using a system of free viewing [38]. A two-beam projector system was used to elicit the ST1 spatial response. The projectors were arranged just to the side of the patient, who sat 1.5 m from a viewing screen. The stimulus background consisted of an achromatic square wave 50:50 duty cycle, high-contrast grating and was projected through an aperture giving a circle of 17° visual angle in diameter (Fig. 1). The achromatic circular target subtended 2° of visual angle and its excursion was fixed over the central 10° of the background field. With central fixation on the background, the target excursion on the retina was approximately 3 mm, passing over the macular region defined by the ETDRS study [19]. The threshold of perception of the 2° target, moving at a velocity of 20°/s, was measured using a single staircase controlled by the operator (the first author for all subjects). To elicit the ST1 spatial response, a series of 13 square wave gratings of different periodicity were used (0.21 cpd to 31.4 cpd).

The observer wore a pair of trial frames. The left eye was occluded with a blank, whilst the right eye viewed the screen through a 1-mm-diameter pinhole, to remove inter-individual variation of pupil size and to reduce the effect of ocular aberrations on image quality. The pinhole, however, could worsen image quality by the effect of diffraction. Calculation shows that the diffraction limit of resolution through a 1-mm circular aperture corresponds to a grating of approximately 32 cpd. This periodicity is at the upper limit of the gratings in our experiment, implying that the effect of diffraction would not significantly effect the image for the range of grating periodicities used.

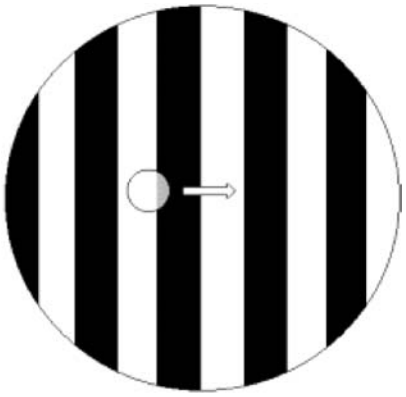

Fig. 1 Schematic of the stimulus used for the ST1 spatial response. The background subtended 17° and the target 2° of visual angle and traversed over the central 10° of the background

The observer was instructed to fixate the central region of the background and to respond 'yes' whenever the target was seen traversing the centre of the image and 'no' if the background appeared unchanged during the stimulus presentation. Any sensation of movement across the screen during presentation was reported as a 'yes'. An estimate of the error was made from the smallest luminance increment that resulted in a change in response around the threshold point. Following each experiment the luminance of the background was measured for each grating. The threshold values were corrected for the luminance of the appropriate background to eliminate the effect of any variation of background luminance arising from differences in the slides containing the gratings. The mean background luminance was 53 cd/m^2, giving retinal illuminance of 1.62 log Trol when viewed through a 1 mm diameter pinhole. The luminance contrast of each grating was greater than 98%.

The tenets of the Declaration of Helsinki were observed, the study had approval from the Research and Ethics Committee of St Mary's Hospital, Imperial College of Science, Technology and Medicine, London, UK and all patients gave written consent. Twenty-two diabetics and 12 controls performed the experiment. The mean age of the diabetic group was 45 years (SD 10.7 years) and of the control group 50.4 years (SD 11.5 years) (P=0.18). Each patient underwent a full ophthalmic examination with dilated fundoscopy and the level of retinopathy and grade of maculopathy was assessed using the modified Airlie House classification [33]. The diabetic group contained 12 patients with no maculopathy, 3 with grade 1 maculopathy and 7 with grade 2 maculopathy. Twelve patients had had no laser treatment, 4 patients had had macular photocoagulation, 5 had had pan-retinal photocoagulation and 1 had had both forms of treatment. Blood glucose and glycosylated haemoglobin levels were measured for each patient at the end of the test. The mean blood glucose level was 12.1 mmol/l (SD 5.3) and the mean HbA1c level was 8.3% (SD 1.8).

Modelling the ST1 spatial response

Donner and Hemila [17] have developed a general model of ganglion cell response to a spatiotemporal stimulus, integrating the output of a two-dimensional difference-of-Gaussian receptive field with known photoreceptor temporal kinetics. Their model predicts the response of a single ganglion cell to spatiotemporal stimulation from a drifting, sinusoidal grating. This model has been adapted for the square wave background used in the ST1 spatial response.

The model assumes a linear response from the photoreceptor and the ganglion cell. Although the assumption of linearity is restrictive it is applicable to a response obtained at threshold, as in the ST1 spatial experiment.

In brief, the model is split into consideration of the photoreceptor response, the ganglion cell response, the stimulus function, and the spatial and temporal responses. For greater detail the reader is referred to the original work [17].

The integration of drifting sinusoidal grating over a Gaussian receptive field shows that the spatial and temporal components are separable (Donner and Hemila's equation 10 [17]). The response of a parvocellular ganglion cell to a static grating can therefore be modelled using the spatial component.

The spatial response G for a sinusoidal grating and a Gaussian receptive field is given in Eq. 1 (Donner and Hemila's equation 13)

$$G = e^{-\pi^2 F^2} \tag{1}$$

where F is the spatial frequency of the grating, normalised for the space constant of the Gaussian $F = f_\sigma$, where σ is the Gaussian space constant and f the spatial frequency of the grating sinusoid. For a difference of Gaussian receptive field the response U is given by

$$U = G_c - KG_s \tag{2}$$

where G_c is the centre response with space constant σ_c and G_s the surround response with space constant σ_s. K is the balance factor between centre and surround.

ST1 background

The square wave background of the ST1 spatial experiment can be incorporated into this model by expanding the square wave as a Fourier series, the spatial response for centre and surround becoming

$$G_{squarewave} = \frac{2}{\pi}e^{-\pi^2F^2} - \frac{2}{3\pi}e^{-9\pi^2F^2} + \frac{2}{5\pi}e^{-25\pi^2F^2} - \frac{2}{7\pi}e^{-49\pi^2F^2} + \ldots \tag{3}$$

Incorporating the Fourier expansion for G_c and G_s into Eq. 2 gives the ganglion cell response to a square wave grating. In the model the first 15 terms of the Fourier expansion were included, to give a reasonable approximation to a square wave grating.

The above model takes no account of the ocular media. The increment threshold nature of the measurement and the Weber-type response found by Barbur in the original study indicates that light loss due to media absorption has little or no effect on the response function [6]. The model assumes, however, that the square wave grating is imaged sharply at the retinal surface, which in reality is determined by the line spread function of the ocular media.

The mean visual acuity of the subjects in this study was 0.04 log units (SD 0.08), assessed using a single-letter scoring method on an EDTRS logMAR chart. Karbassi et al. [30] measured the line spread function in a group of patients with early cataract using a modified slit lamp. They found a significant difference only between the line spread functions of patients with Snellen acuities of 6/9 and those with Snellen acuities of 6/6 or better. A Snellen acuity of 6/9 corresponds to a logMAR acuity of 0.18 log units, which is worse than that recorded in the patients in this study. Given the good acuity in the patients and the use of a pinhole, it is unlikely that there is a difference in line spread function between the two groups of subjects.

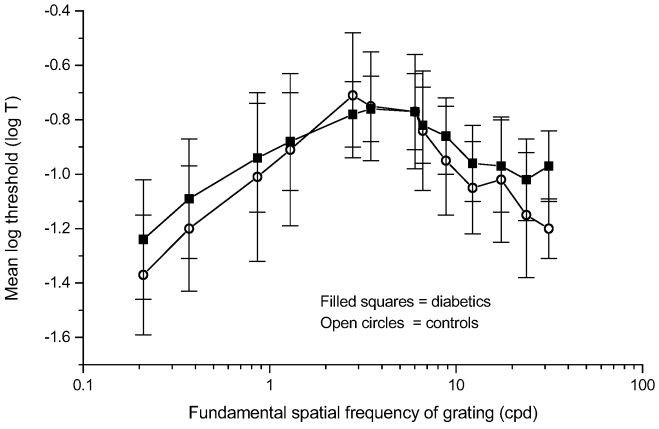

Fig. 2 ST1 spatial functions for the diabetic (*filled squares*) and control (*open circles*) groups. The *error bars* are ±1 standard deviation. The peak of the function occurs at around 3–4 cpd

Results

The mean threshold and standard deviation were calculated in each subject group for each grating periodicity and are shown in Fig. 2. An unpaired *t*- test was used at each spatial frequency and the Bonferroni correction was applied, requiring a P value of 0.004 for significance. The diabetic patients were separated into groups with respect to grade of maculopathy and the mean values recalculated for each group and compared with each other and with the control group. The results of this analysis showed no significant differences between the means of the threshold levels obtained in the two groups at the Bonferroni-corrected level.

The model was used to investigate the shape of the spatial response function for both the pooled data and for the measurements obtained for each individual. Best fits of the spatial model to the experimental data were found using the method of least squares, the centre and surround space constants being the only freely variable parameters. The difference of Gaussian receptive field was balanced with K=1 in all cases. The parameters obtained from the model fitting were the best-fit values of the centre and surround space constants in the difference of Gaussian receptive field and a correlation coefficient for the goodness of fit.

The results for individual fitting to the controls gave a mean central space constant of 0.046° (SD 0.021°) and surround 0.24° (SD 0.11°), with mean R^2=0.74 (SD 0.12). For the diabetic patients the mean centre size was

Table 1 Centre and surround space constant values that give the best fit of the model to the experimental data

Group	Centre (deg)	Surround (deg)	Ratio	R^2
Control group				
	0.096	0.536	5.579	0.784
	0.035	0.339	9.671	0.748
	0.025	0.128	5.100	0.794
	0.030	0.208	6.933	0.836
	0.050	0.230	4.600	0.709
	0.030	0.133	4.433	0.761
	0.045	0.200	4.433	0.833
	0.030	0.183	6.100	0.871
	0.065	0.172	2.639	0.531
	0.030	0.133	4.433	0.744
	0.050	0.230	4.600	0.784
	0.060	0.241	4.017	0.454
Diabetic group				
Grade 0	0.050	0.080	1.600	0.339
	0.020	0.197	9.850	0.716
	0.031	0.122	3.942	0.853
	0.020	0.197	9.850	0.671
	0.045	0.200	4.433	0.633
	0.050	0.105	2.100	0.595
	0.040	0.219	5.475	0.781
	0.045	0.100	2.211	0.577
	0.055	0.136	2.464	0.419
	0.032	0.290	9.069	0.724
	0.020	0.197	9.850	0.744
	0.100	0.260	2.600	0.353
Grade 1	0.100	0.185	1.850	0.095
	0.080	0.188	2.350	0.625
	0.050	0.080	1.600	0.558
Grade 2	0.055	0.086	1.555	0.417
	0.050	0.080	1.600	0.399
	0.100	0.135	1.350	0.457
	0.075	0.133	1.767	0.260
	0.020	0.197	9.850	0.602
	0.035	0.214	6.100	0.646
	0.055	0.086	1.555	0.397

Table 2 Means and standard deviations of the best-fit parameters obtained for the ST1 spatial data

Group	Centre (deg)	Surround (deg)	Ratio	R^2
Control group				
Mean	0.046	0.228	5.212	0.737
SD	0.021	0.113	1.769	0.124
Diabetic group				
All subjects				
Mean	0.051	0.158	4.228	0.539
SD	0.026	0.063	3.295	0.188
Grade 0				
Mean	0.042	0.175	5.287	0.617
SD	0.022	0.066	3.408	0.168
Grade 1				
Mean	0.077	0.151	1.933	0.426
SD	0.025	0.062	0.382	0.289
Grade 2				
Mean	0.056	0.133	3.397	0.454
SD	0.026	0.055	3.312	0.132

Table 3 *P* values of Student's *t*-test comparing the means of the best-fit parameters obtained for the different subject groups after fitting to the ST1 spatial model

	Centres	Surrounds	Ratios	R^2
Diabetics vs controls	0.480	0.070	0.266	0.001
Grade 0 vs grade 1	0.125	0.588	0.006	0.371
Grade 0 vs grade 2	0.278	0.153	0.256	0.030
Grade 1 vs grade 2	0.299	0.683	0.291	0.886

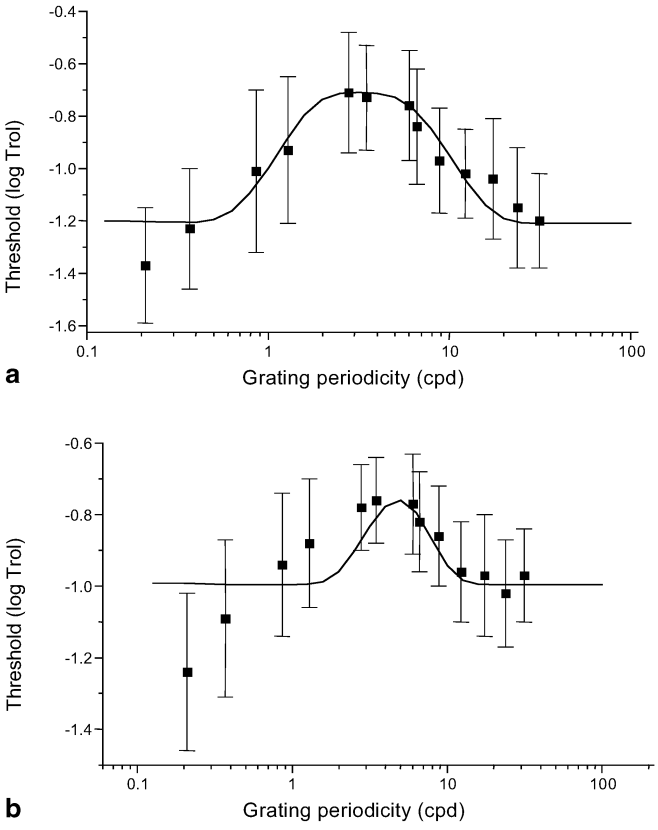

Fig. 3 Best fits of the model to the pooled data for (**a**) controls (r^2=0.88) and (**b**) diabetics (r^2=0.58)

0.051° (SD 0.026°) and 0.158° (SD 0.063°) for the surround, mean R^2=0.54 (SD 0.19). Statistical comparison showed no difference between the estimated centre and surround sizes, but the diabetic group showed a significantly worse model fitting (*P*=0.001). The mean R^2 value was 61.8% for the diabetics with no maculopathy, but fell to 45% in the diabetics with grade 2 maculopathy (*P*=0.03).

The results of the model fitting for both groups are summarised in Table 1 and Table 2 with a statistical comparison in Table 3. The best fits for the pooled data are shown in Fig. 3 and examples of the best and worst fits for individuals from the control group are shown in Fig. 4 and for the diabetic group in Fig. 5.

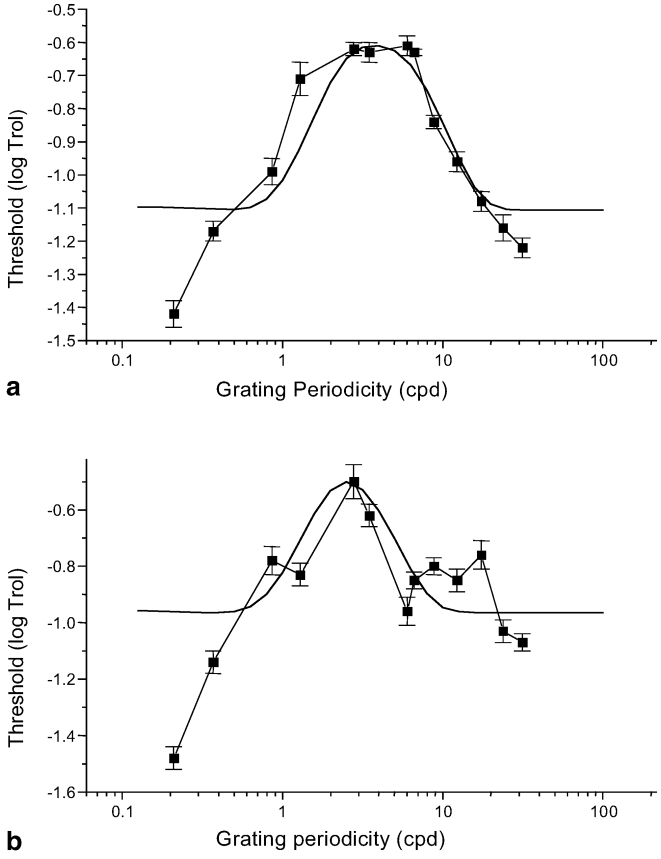

Fig. 4a, b Best and worst model fits to subjects from the control group. The upper graph (**a**) shows the best fit, with centre=0.03°, surround=0.183°, ratio 1:6.1, R^2=0.87. The lower graph (**b**) shows the worst fit, with centre=0.06°, surround=0.241°, ratio 1:4, R^2= 0.45

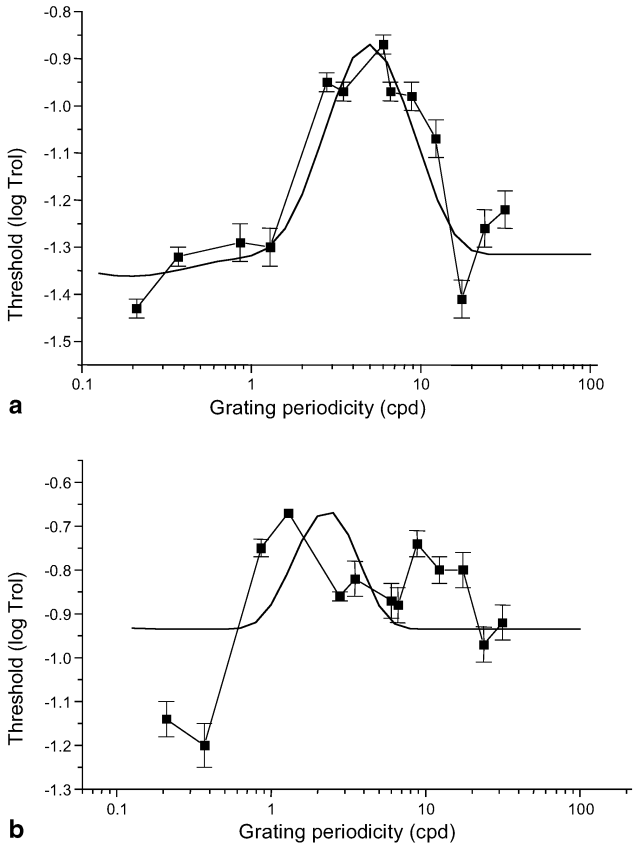

Fig. 5a, b Best and worst fits for individuals in the diabetic group. The upper graph (**a**) shows the best fit, with centre=0.031°, surround=0.122°, ratio=1:3.94, R^2=0.85. The lower graph (**b**) shows the worst fit, with centre=0.10°, surround=0.185°, ratio=1.85, R^2=0.09

Discussion

The data for the control group fit the model reasonably well, with a mean correlation coefficient of R^2=0.74 (SD 0.12). The space constant for the central Gaussian agrees with values obtained previously [6, 43]. The surround values give a mean centre to surround ratio that is slightly greater than the ratios obtained previously using neurophysiological techniques [12, 21, 28], although psychophysically measured field sizes are larger than those measured neurophysiologically by a factor of 1.3–2 [44]. The similarity of the values obtained from the model fitting to those obtained from direct measurement suggests that the use of a DOG model to fit the ST1 spatial data is valid. The good fit of the purely spatial model to the response obtained supports the notion that the ST1 spatial function originates in a pathway that produces a sustained response rather than in a transient pathway [6, 25].

Donner and Hemila suggest that the success of single cell models in explaining psychophysical data arises from an averaging process, the response being averaged over many similar ganglion cells, the signal to noise ratio being significantly reduced.

However, we found that the model did not fit the thresholds measured at low and high spatial frequencies in most subjects. Psychophysical threshold detection contains two forms of averaging that will affect the response function obtained, those of spatial summation and integration of spatial detail [17]. Firstly, spatial summation favours detection of targets against low spatial frequency backgrounds (wider bars in the grating allow greater spatial summation). Secondly, the integration of spatial detail may favour detection of the target against the higher spatial frequencies, as the target size encompasses a larger number of grating cycles. Rovamo [40] showed that with a fixed stimulus area, only the higher spatial frequencies give the full limit of response.

It is probable that the departure of the psychophysical data from the single-cell model at low and high frequencies is explained by these two forms of signal averaging, which are not accounted for in the model.

Considering the data obtained from the diabetic patients, the situation is different. Although there is no significant difference between the centre and surround parameters obtained from the fitting routine and those from the control group, there is a statistically significant difference in the goodness of fit (P=0.001, Table 3). The thresholds for low and high spatial frequencies depart from the model as in the control group, but also the thresholds obtained in the mid-range do not follow the prediction of the model.

The implication of this is that there is a disturbance in the processing of spatial information in diabetes and the calculated values of centre and surround space constants cannot be taken as reliable parameters in the diabetic group. This finding is consistent with the abnormality seen in the contrast sensitivity response to the Hermann–Hering grid illusion in diabetes [14].

The anatomical disturbance occurring in diabetic maculopathy is at the level of the middle and inner retina. The integrity of the deep capillary plexus, at the level of the outer nuclear layer with the inner plexiform layer, is affected by diabetes, either by leakage (with subsequent intraretinal oedema and exudate) or by closure (with subsequent ischaemia). The involvement of the middle retinal layers is seen ophthalmoscopically by retinal thickening, exudate and blot haemorrhages and that of the inner retinal layers by cotton wool spots and nerve fibre layer haemorrhages.

The anatomical disruption of the middle and inner retinal layers that occurs in diabetes is accompanied by dysfunction of lateral inhibition processing, illustrated by the lack of correlation with the difference-of-Gaussian receptive field model. The breakdown of the data from the diabetic subjects into groups with different levels of maculopathy adds support to this, as there is a statistically significant difference in the correlation coefficients with respect to maculopathy, indicating an increasing departure of the ST1 spatial response from that predicted by the model with increasing grade of maculopathy.

Many studies have measured the contrast sensitivity of the diabetic eye and have shown a loss of sensitivity at some spatial frequencies [2, 4, 5, 9, 10, 11, 15, 16, 18, 23, 24, 26, 27, 31, 37, 41, 47]. The results of these studies have been rather variable, with some researchers finding abnormality only in diabetics with retinopathy [2], whilst others found abnormality in aretinopathic patients as well [16, 18, 23, 41]. The loss of sensitivity did not correlate well with the degree of retinopathy in some studies [4, 5, 9]. Sokol et al. [41] found that patients classified as having NIDDM without retinopathy had abnormal contrast sensitivity at high spatial frequencies, but that there was abnormal contrast sensitivity at all spatial frequencies in the presence of retinopathy. Trick [47] noted loss of contrast sensitivity in mid- to high-range spatial frequencies. The grating periodicities that revealed differences between normals and diabetics were different for different authors, 6 cpd in one study [9], 22.8 cpd in another [41] and a wide range of low frequencies in another [16].

The variation in the findings of contrast sensitivity illustrates how dependent the function is on the method used and the test criteria. Sokol [41] suggested that this difficulty with contrast sensitivity measurement diminishes its significance as a clinical test.

Contrast sensitivity has been used to estimate the effect of lens opacities in diabetes [10]. Correcting the contrast sensitivity for Snellen acuity and for interferometric acuity, the authors found that the degree of nuclear lens opacity could account for a portion of the loss of sensitivity at 6 and 12 cpd.

Contrast sensitivity improved significantly after breathing 100% O_2 in patients with early background retinopathy [24] and remained abnormal even when lens density was accounted for [26] in both retinopathic and aretinopathic patients. Loss of contrast sensitivity has been correlated with decreased capillary blood velocity in diabetes, with increased perifoveal capillary area and also with increased extent of the foveal avascular zone at 12 cycles per degree [3]. The correlation of the sensitivity loss with the perifoveal inter-capillary area and FAZ extent was, however, rather weak (with R^2=0.29 and 0.36 respectively). The abnormalities in contrast sensitivity in the diabetics are attributable to neural dysfunction in these studies.

The variability found in the studies presented above may arise from the fact that a grating or letter contrast sensitivity function is not specific to one neuronal population and may be influenced by changes in the ocular media. The analyses in the studies above were limited to comparison of thresholds at individual spatial frequencies between the normals and the diabetics and were not been extended to an analysis of the overall shape of the response function.

The ST1 spatial response is more robust than contrast sensitivity with respect to stimulus parameters and is likely, therefore, to reflect the function of a single mechanism [6]. The use of the model to investigate the data has the advantage of taking into account all of the data measured in the response (i.e. the overall shape of the response curve).

The ST1 spatial response represents the function of a sustained-type channel in the visual system [25] and is explained in the mid-range grating periodicities by the circularly symmetric difference-of-Gaussian receptive field model in normals. The results obtained in the diabetic patients show an abnormal ST1 response that is not well explained by the model. Further study of sustained channel dysfunction in diabetic subjects would be of great interest to assess its usefulness in monitoring the functional progress of the disease.

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