眼部疾患中视网膜时间反应的精神物理学评价*

PSYCHOPHYSICAL EVALUATION OF THE TEMPORAL RESPONSE OF THE RETINA IN OCULAR DISEASE

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〔摘要〕 用精神物理学方法测量了闪烁光视觉敏感度以表示为时间频率的函数。使用这种方法测试了不同的视网膜病患者，包括青光眼组、几种类型的视网膜色素变性、糖尿病性视网膜病变和尼古丁中毒。结果表明在同一种疾病或同一亚组病人中，中央视网膜敏感度实际受损形式是相似的。不同类型的疾病敏感度受损的形式是不同的。本文结果提示，在视网膜对视觉信息的处理中，受试验的视网膜疾病对视网膜的不同部位会有影响。

[ABSTRACT] Visual sensitivity to flickering lights was measured as a function of temporal frequency by a psychophysical technique. Patients with a variety of retinal diseases were tested by this method, including groups with glaucoma, several types of retinitis pigmentosa, diabetic retinopathy and nicotine toxicity. The results show substantial losses in central retina which tend to have a similar form in each disease or subgroup of patients. The form of sensitivity loss is also different between many of these disease types. These results suggest that the retinal diseases tested may affect different loci in the retinal processing of visual information.

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Introduction

The overall goal of this study was to evaluate the temporal response of the visual system as an indicator of neural damage in diseases of the retina. The temporal visual response to sinusoidally flickering stimuli has been shown to be a sensitive measure of glaucomatous visual loss, in both central and peripheral retina (Tyler, 1981; Stamper and Tyler, 1984; Breton et al., 1984). Temporal losses can be measured rapidly and accurately, so they seem to be a good candidate for evaluation of early damage in retinal diseases.

There is increasing evidence that losses of visual function can occur at a stage in the disease before the earlier detectable visual field defects, which are currently the defining criterion for visual loss. This is most clearly evident in glaucoma patients with an asymmetrical condition such that there is an abnormal elevation of intraocular pressure (IOP) in both eyes, but detectable field losses (i.e. glaucoma) in only one eye. In these cases, the fellow eye with only IOP elevation is regarded as having a very high risk (approaching 100%) of developing glaucoma, and therefore the population of eyes with the highest probability of showing early defects prior to visual field losses.

In such eyes, Quigley (1983) has found observable defects in the nerve fibre layer of the retina in 28% of cases. Zwas et al. (1984) have reported color vision abnormalities of the central retina in 33% of such cases. In comparison, significant temporal sensitivity losses were found in 90% of such cases (Tyler, 1981). These rates compare with about 5% expected for an unselected population of ocular hypertensive eyes with no field loss in the fellow eye. These numbers suggest that temporal sensitivity losses may be the most sensitive indicator of early visual losses in glaucoma.

Another disease where the temporal response may prove to be a useful indicator of loss is retinitis pigmentosa (RP). Current evidence suggests that RP is not solely a disease of rods, but affects cones as well (Berson, 1977). In many cases cone function is at least as much disturbed as rod function (Massof and Finkelstein, 1981). Furthermore, in advanced stages of the disease, the rods may be so drastically affected that only cone function is measurable. Finally, temporal sensitivity for photopic flicker shows interesting complexity in normals, and might be expected to provide more differential information between the genetic types of RP.

We therefore used the temporal visuogram method

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(Tyler, 1981) to measure photopic sensitivity losses in glaucoma, in several genetic groups of RP patients, and also in patients with diabetic retinopathy and a group of heavy smokers who might be subject to nicotine toxicity of the retina.

Methods

Apparatus

The flicker apparatus (Tyler, 1981) consisted of a square array of 25 high-luminance 575 nm light-emitting diodes (LEDs). These light sources have current/luminance function which is approximately linear. A steady DC signal maintained the mean luminance at 40 cd/m^2 (measured with an SEI photometer)

The field of 25 light-emitting diodes was set behind a circular diffusing sheet in a tube with a white inner surface, so as to give the appearance of a uniform field 2.5 cm in diameter. This field was placed in a large (40 cm) equiluminant steady field made by projection of 4 incandescent bulbs onto a diffusing surface. There was a 1 mm dark border around the flickering field. The apparatus was viewed from a forehead and chin rest at a distance of 28.5 cm, so that the flickering field subtended 5°.

Temporal Visuograms

It is difficult to measure the temporal response of the human retina directly by psychophysical methods. Instead, the usual approach is to measure modulation sensitivity as a function of temporal frequency, which is related to the temporal response mathematically by the Fourier Transform. Thus if the temporal response of the abnormal retina is slowed, the temporal frequency response will show reduced sensitivity to high frequencies. Other changes in the form of the temporal response will be reflected in predictable changes in the frequency response.

Modulation sensitivity is defined as the reciprocal of the threshold amplitude for detection of a sinusoidal modulation about a fixed mean luminance level. The ratio of sensitivity in a given patient to the normal sensitivity can be plotted graphically to provide a temporal visuogram of the losses at each frequency relative to normal. This differential plotting method has the advantage of providing a profile of the losses uncontaminated by the large changes in slope seen in the normal sensitivity function. In a disease which is known to affect only the retina, the differential losses observed in the visuogram may be attributed solely to the abnormal retinal function, even if the normal function reflects later cortical processing.

Procedure

Our approach to flicker sensitivity was to measure sensitivity loss for sinusoidal modulation at a fixed mean luminance level by the method of adjustment. Modulation depth of a sinusoidally flickering light was adjusted to perceptual threshold for various frequencies. The frequency range chosen was usually from 5 Hz upwards, both because pilot data below 5 Hz showed greater variability than above this frequency and because it is above the range of which pupil responses are elicited. In some cases a lower frequencies were also used to extend the range towards static stimulus conditions.

For the studies reported here a method of adjustment was used, although comparable results have been obtained with a more rigorous forced-choice staircase procedure (Stamper and Tyler, 1984). At each frequency tested the experimenter adjusted the log potentiometer until flicker had just disappeared, then increased until the patient first reported that flicker reappeared. Usually each point was measured twice, but at some intermediate frequencies only one reading was taken. CFF for the maximum modulation of 86% was measured by varying the test frequency while modulation remained at the maximum. Normal pupils were used for comparison with previous results.

Results

Normal flicker sensitivity

The normal flicker sensitivity profile for 12 normal observers as a function of temporal frequency is shown in Fig. 1 (upper panels), for central observation (filled circles) and peripheral observation for a position at 20° eccentricity above the blind spot (open circles). Error bars represent 1 S.D. of the variability across normal observers. The corresponding sensitivity functions for a glaucoma patient are shown in the centre panels. The temporal visuograms of the ratio between the patient and normal data are shown in the lower panels, with the shaded areas representing the degree of loss at each location.

The level at which sensitivity loss regarded as significant will be taken as 2.3 S.D. of the response distribution across normal observers below the normal mean, as shown by the dashed lines in Fig. 1 (lower panels). By this criterion, only 1% of normals would spuriously show a significant loss at any particular frequency, which is an appropriately low false-positive rate.

It is important to determine the reliability of the test, both in older normals to match the age of the typical glaucoma patients, and in patients showing large losses, in whom increased variability might be expected. Almost all patients showed good reliability under the method of experimenter adjustment, with a mean standard deviation of only 1.2 db (15%) of the mean threshold across all patients and temporal frequencies. As reported previously for temporal sensitivity up to age 70 (Tyler, 1981; Stamper and Tyler, 1984; Tyler, Ernst and Lyness, 1985), the sensitivities showed insignificant correlation with age in these normals (R = −0.05, 0.01, 0.24, 0.10, 0.32 and 0.52 at 5, 10, 15, 20, 30 and 40 Hz respectively).

Visuogram Losses in Glaucoma and Ocular Hypertension

A previous report has detailed the form of the temporal visuogram in glaucoma and ocular hypertension (Tyler, 1981) in 46 eyes with varying degrees of Goldmann field loss. Temporal sensitivity losses were measured for both central and peripheral viewing of the 5° flickering field. The results have

now been analysed to provide a template of the average loss function. This was achieved by scaling the logarithm of the loss ratio relative to normal in proportion to the mean loss at all frequencies tested, weighted by the number of frequencies tested. Under the assumption that the form of the visuogram loss is constant, with patients only differing by a logarithmic scaling factor, the effect of this procedure is to produce a template of the form of the loss. Only eyes showing a significant loss at some frequency were included in the sample, as lower values would introduce unnecessary noise in the normalisation procedure.

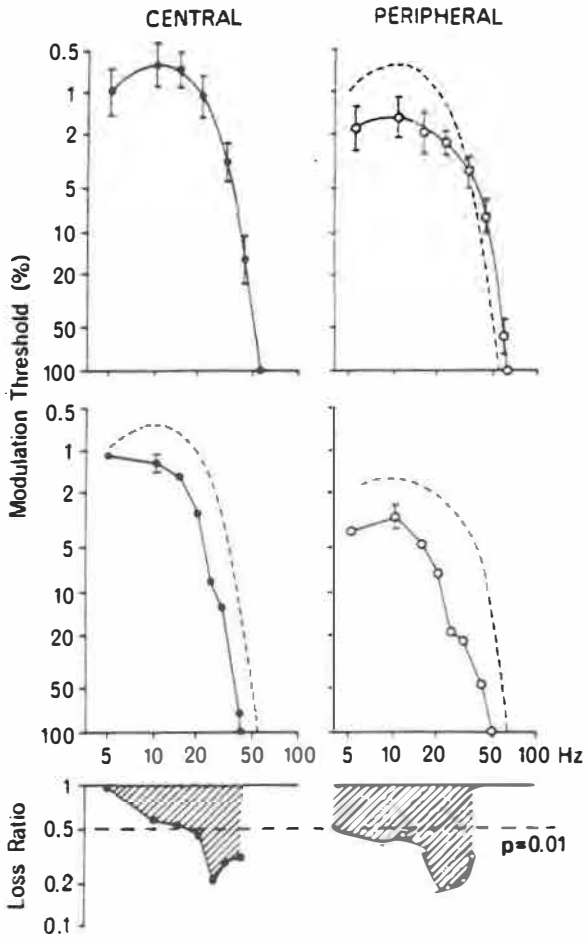

Fig. 1 (Upper panels) Flicker modulation sensitivity plotted in terms of percent modulation at threshold as a function of temporal frequency. Mean of 12 normal observers for central (left) and peripheral (right) observation of a 5° field. Error bars represent ± standard deviation of the normal mean.
(Centre panels) Results from a typical glaucoma patient.
(Lower panels) Temporal visuogram of sensitivity loss relative to normal for glaucoma patient (full line, filled circles). Dashed lines show 2.3 x standard deviation at each frequency. Points below this level are significantly different from normal at p ½ 0.01 in this and subsequent graphs.

The results of the template procedure are shown in Fig. 2 for the two retinal locations tested. The loss increases from a low value at 5 Hz to a maximum value at 30 Hz for central stimulation and at 40 Hz for the peripheral location. Beyond this maximum the loss decreases to some extent for both locations. The normalised template thus supports the conclusions reached on the basis of the individual data (Tyler, 1981), that the typical loss in glaucoma is maximal at a frequency below the CFF value, and that is of similar form in central and peripheral retina, although minor differences are evident.

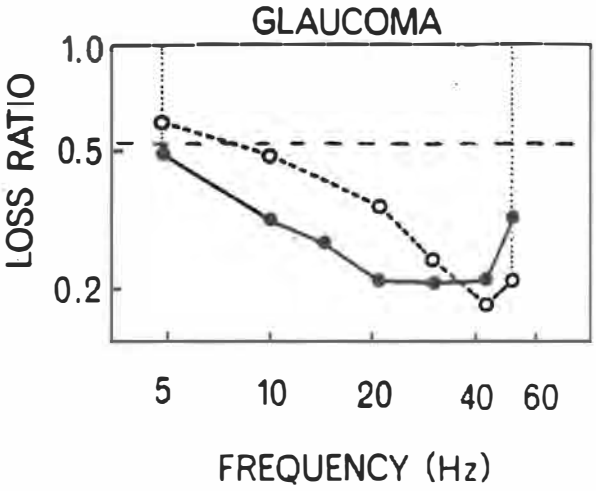

Fig. 2 Normalized templates of visuogram loss for a group of patients with glaucoma and ocular hypertension.

VISUOGRAM LOSSES IN THE GENETIC GROUPS OF RETINITIS PIGMENTOSA

Patients

The patients were drawn from a population diagnosed into RP groups by the Genetics Clinic of Moorfields Eye Hospital, London. The groups selected were simplex, multiplex, autosomal dominant (with a subgroup of sector RP), and x-linked heterozygotes or hemizygotes. In each case information was available on three or more generations of the family. Only those patients with childhood onset of the disease and with Goldmann fields greater than 2° with the IV_4 target were selected. Individuals with a high consumption of alcohol or tobacco were eliminated from the sample as this may affect the results of the test, and none of the patients had high consumption levels.

Simplex and Multiplex RP

Temporal visuograms were obtained as described in Methods for 11 eyes of 9 simplex RP patients (and for 7 eyes of four patients with multiplex RP). The sensitivity losses as a function of flicker frequency are shown for the simplex patients in Fig. 3 (left eyes shown as dashed lines). In every case the most pronounced loss occurred at the highest frequency. All showed a progressive loss as frequency was

increased above 10 Hz. All except the two patients who were most affected had flicker sensitivity within normal limits up to 10 Hz. Finally, the less affected patients appear to show a tendency toward supernormal sensitivity at the lowest temporal frequency. In six of the eyes the sensitivity at 5 Hz is significantly higher than normal at the 1% level of probability.

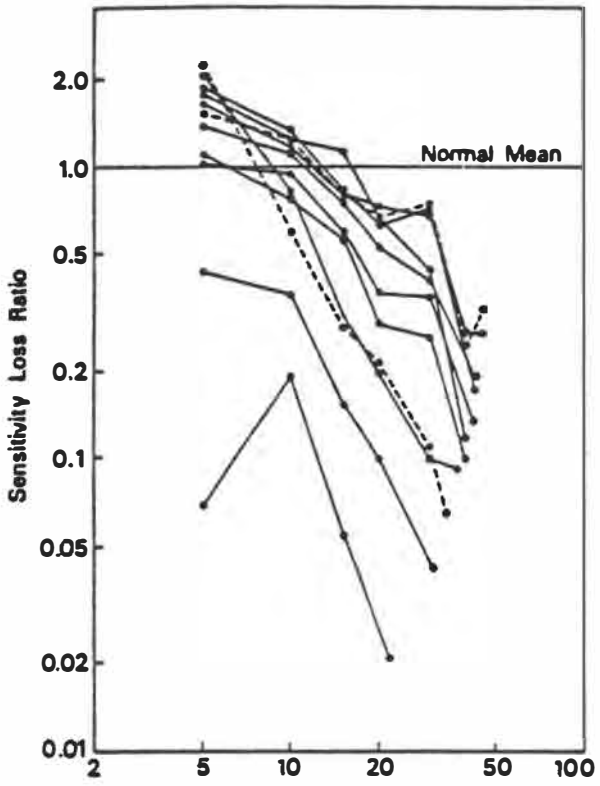

Fig. 3 Temporal visuograms showing sensitivity loss as a function of frequency for eleven eyes with simplex RP. Note dissimilarity of loss function from that of Fig. 2.

The most noteworthy feature of these results is the similarity between the loss functions in this group of patients, although each patient is at a different stage of the disease, and they would therefore be expected to show varying degrees of loss. This is further borne out by comparison with the functions of a group of multiplex patients (Fig. 4). Three eyes of two patients (upper three curves) show a pattern of loss almost identical to that of the less affected simplex cases. The lower four curves (both eyes of two further patients) show more severe effects, but they are superimposable in form to the other curves if shifted upwards by about one log unit.

Autosomal dominant RP

Temporal visuograms were obtained for 12 patients with a well defined dominant pattern of familial occurrence. As it happened, all patients in this group were classified as Type II by the Massof, Finkelstein and Boughman (1982) criterion, showing elevation of cone as well as rod function in affected areas of the retina. The photopic temporal visuograms for this group (Fig. 5) had a variegated pattern, with some showing greater loss at medium frequencies and others at high frequencies. However, the overall trend was towards a fairly uniform loss across all temporal frequencies, as distinct from the simplex and multiplex pattern of increasing loss with increasing frequency. In fact, only one patient from the dominant group has a pattern of loss that might be confused with that of the simplex/multiplex group, in showing a progressive decline in sensitivity above 20 Hz. None show the enhanced sensitivity at low frequencies exhibited by the more mildly affected simplex/multiplex cases.

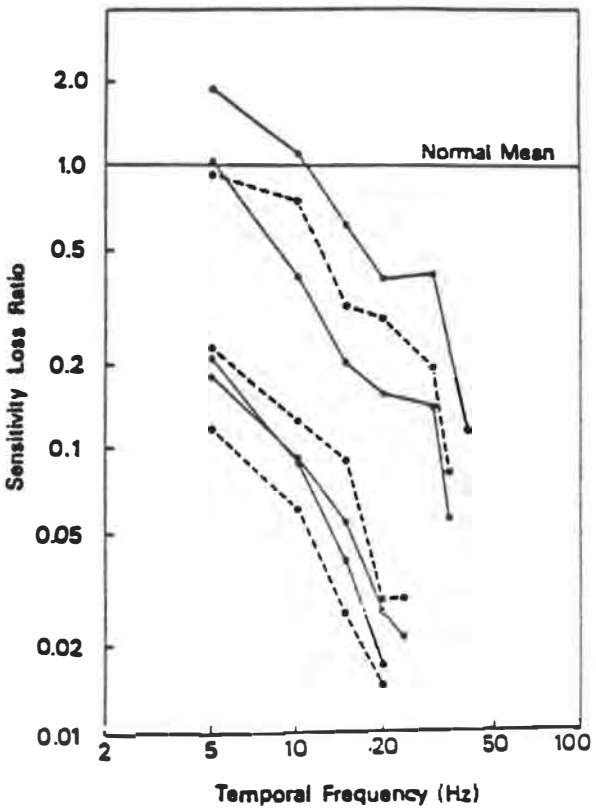

Fig. 4 Temporal visuograms for 7 eyes with multiplex RP. Note similarity of loss function to that of Fig. 3.

Sector RP

A subgroup of dominant inheritance, patients showing a sectorial visual field loss are sometimes considered to have a separate form of the disease. To see whether the temporal visuograms shed any light on this distinction, we include 5 patients from 3 families with sector RP (Fig. 6). In each case the loss, which was fairly uniform across temporal frequency, was somewhat greater in the mid-frequency dominant group, 5 of whom showed a similar pattern. This suggests that further testing would be worthwhile to determine whether a larger sample would sustain the pattern of loss seen in this group.

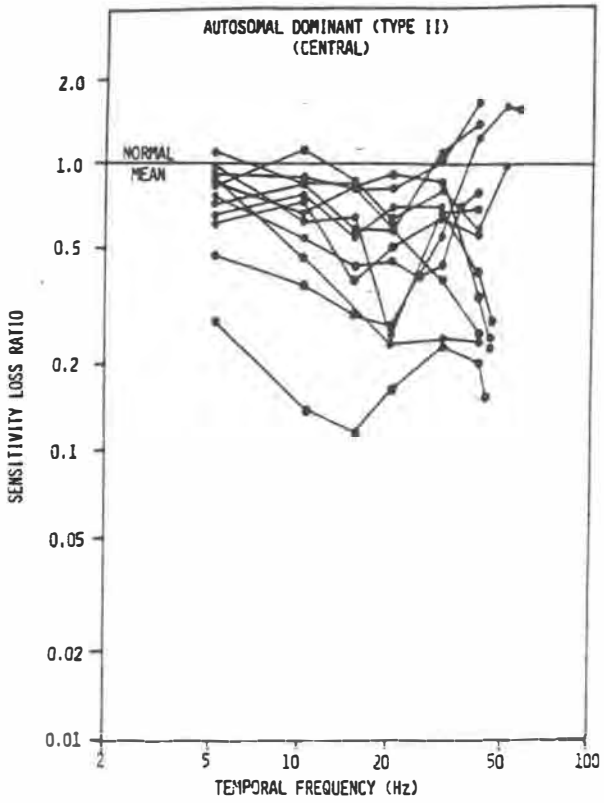

Fig. 5. Temporal visuograms for patients with autosomal dominant RP. Note dissimilarity of loss functions from those of Figs. 2, 3 and 4.

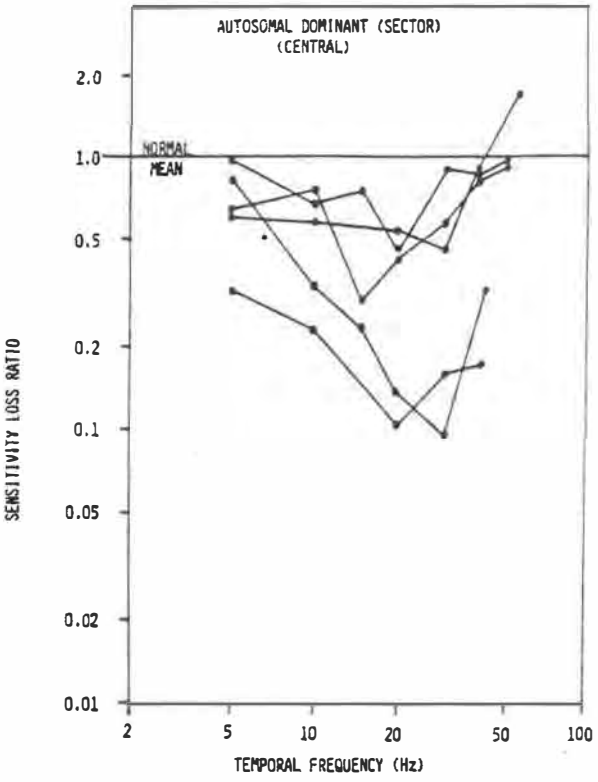

Fig. 6. Temporal visuograms for patients with sector RP. Note uniform tendency to mid-frequency losses.

X-linked heterozygotes

The females from families with a sex-linked familial pattern of RP often show mild symptoms of fundus pigmentation, with minor or undetectable field losses in the periphery. However, losses in the temporal visuograms of 8 of such patients (Fig. 7) show that in several cases sensitivity losses in central vision are as severe as for the dominant group. The pattern of loss is also similar, being predominantly uniform across temporal frequency, with slightly greater losses in either the mid or high frequency ranges. Once again there is no resemblance to the simplex/multiplex pattern.

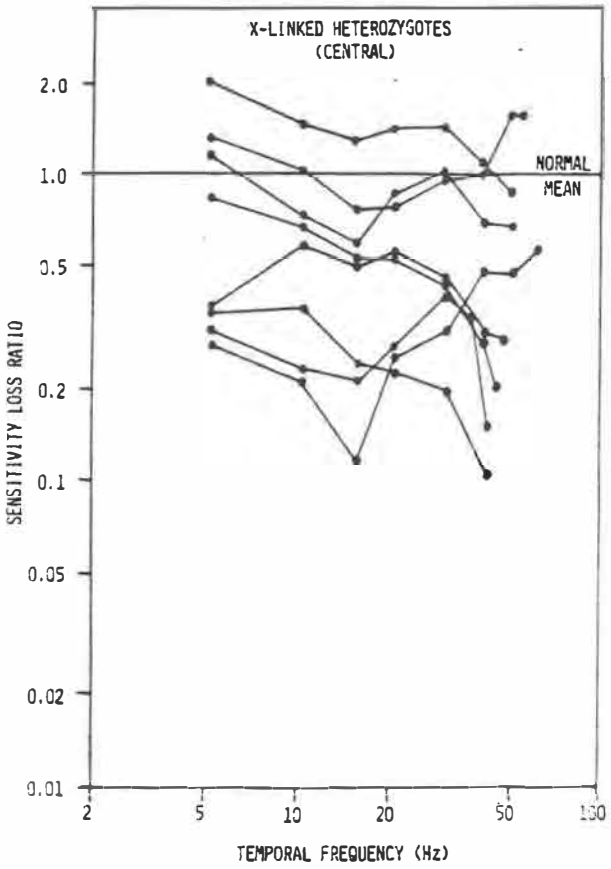

Fig. 7. Temporal visuograms for x-linked heterozygotic RP. Note similarity of loss function to that of Fig. 5 and dissimilarity from those of Figs. 2, 3 and 4.

X-linked hemizygotes

The males from the families with a sex-linked inheritance pattern are usually severely affected, but we were able to test 5 eyes of three patients with at least 10° of visual field remaining, and thus comparable in severity with the majority of the simplex and multiplex cases. In this small sample the losses exhibited a further distinct pattern (Fig. 8). Sensitivity declined by about 1.5 log units between 5 and 20 Hz, a steeper decline in this frequency region than was seen in any of the simplex or multiplex cases. In one of the eyes sensitivity recovered by 0.7 log units at higher temporal frequencies. The sharp

notch at 17 Hz thus produced was validated by repeated testing in the 10-20 Hz region (without alerting the patient to the reason for further testing) so that those points represent four readings at each frequency. Further testing of the remaining eyes at higher frequencies did not reveal other examples of high frequency sensitivity.

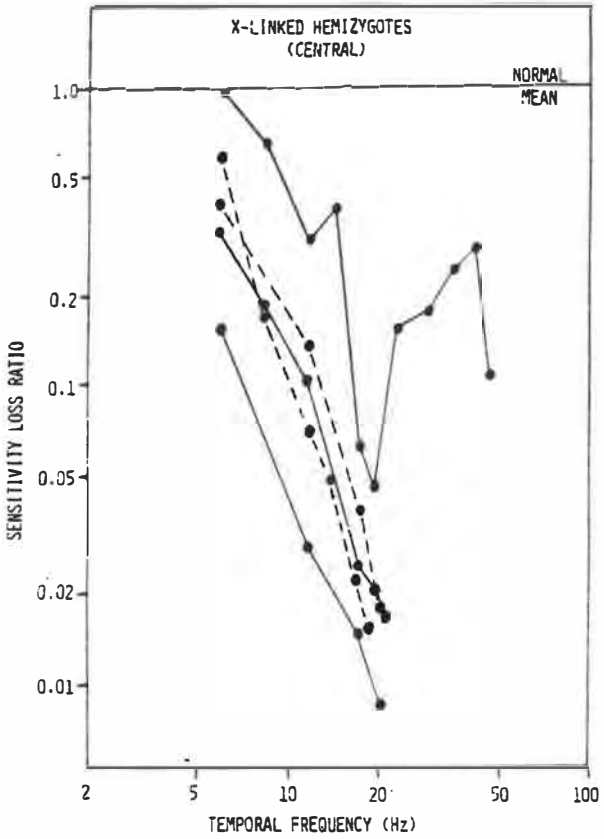

Fig. 8. Temporal visuograms for patients with x-linked hemizygotic RP. Note dissimilarity of loss functions from those of all previous figures.

Temporal Visuograms in Other Retinal Dystrophies

Diabetic retinopathy

Fig. 9 shows the temporal visuogram losses obtained in four patients with diabetic retinopathy as defined by clinical fundus signs and mild field losses. Interestingly, the temporal losses are of very similar form in all four, and are different again from either the typical glaucomatous loss or from those seen in any of the RP groups tested. Shallow losses within the normal range were seen up to about 15 Hz, followed by a steep decline thereafter. This can be differentiated from either the steep decline from low frequencies found in x-linked hemizygotic RP, or the progressive decline from an increased low frequency sensitivity obtained in the simplex patients. Thus a further variety of visuogram can be added to the vocabulary of those obtained previously; one that implies selective disruption of the high frequency aspects of retinal processing.

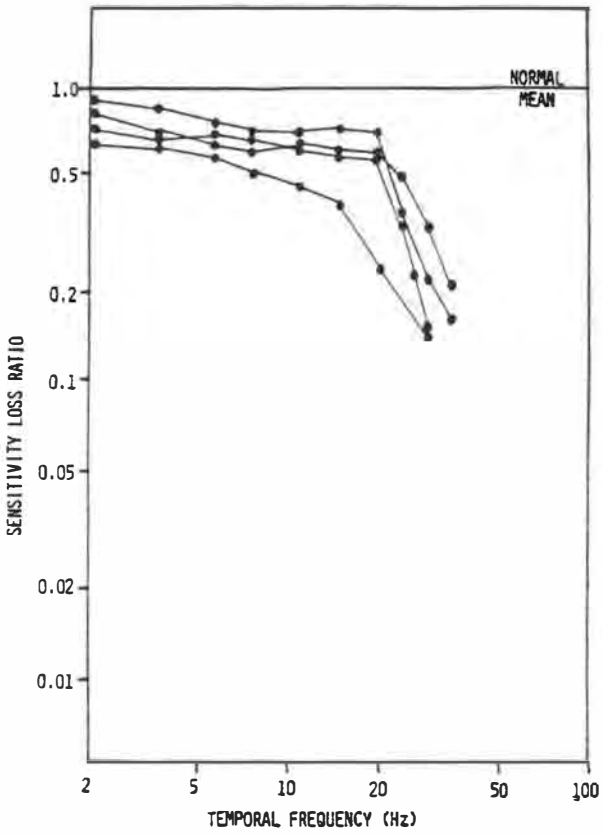

Fig. 9. Temporal visuograms for patients with diabetic retinoapthy. Note dissimilarity of loss functions from those of all previous figures.

Nicotine toxicity

A final group that was evaluated for temporal sensitivity loss consisted of four heavy smokers without fundus signs of retinal dysfunction. Nevertheless, it appeared that they were suffering from mild nicotine toxicity since the temporal visuograms of all four fell outside the normal range in the peripheral testing location, with one showing central losses as well (Fig. 10). Sensitivities as poor as 20% of the normal level are evident, while the form of the loss is fairly flat across temporal frequency. It is most similar to that seen in the autosomal dominant groups of RP and some glaucoma patients.

Discussion

The question posed in this project is whether there are different characteristic forms of temporal frequency loss associated with different types of retinal disease that might be confused in standard clinical tests. The data reported here begin to give affirmative answers to this question. In RP photopic sensitivity shows losses in the central fields which appear normal by Goldmann field and absolute threshold techniques. The form of the loss is substantially different for different genetic types of RP. In those with dominant heredity, the loss is generally uniform across temporal frequency, indicating an overall sensitivity loss. In the simplex and

multiplex groups of patients the loss increases strongly towards high frequencies.

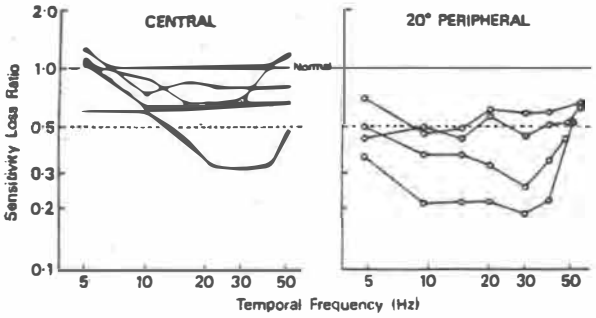

Fig. 10. Temporal visuograms for several heavy smokers in both central and peripheral observation. Note significant losses in peripheral sensitivity at most intermediate frequencies.

The five x-linked heterozygotes with significant losses showed a fairly uniform reduction across temporal frequency, with some variability above 30 Hz. Thus, apart from the high frequency region, data for the dominant and x-linked heterozygote groups are compatible with the hypothesis of Ripps, Brin and Weale (1978) that the main defect is a shortening of the receptor outer segments. This has been demonstrated for both rods and cones in the eye of an x-linked heterozygote (Berson, 1981).

Finally, the striking pattern of a steep decline up to 17 Hz, with a recovery in sensitivity at higher frequencies in the least affected patient was seen in the few x-linked hemizygotes tested (Fig. 7B). Again, in these few patients the results are consistently different from those of all groups. The replicable notch loss in the least affected eye indicates a remarkable degree of specificity in the temporal visuogram.

Relationships to changes in normal temporal sensitivity

Note that the pattern of mid-frequency loss described above for glaucoma is different from any of the RP types. This pattern of visuogram losses in glaucoma and OH is somewhat similar to the change in shape of the temporal frequency functions of normal retina when luminance is reduced. Figure 11 shows the effect of luminance reduction on the temporal visuogram. The original 2° field data of de Lange (1958) have been reanalyzed in the form of a visuogram. The values from two observers for a luminance of 31.8 cd/m^2 (100 photopic td) have been used as the reference for values obtained at three lower luminances. The pattern of sensitivity loss with luminance reduction is similar for the three luminances and increases progressively with temporal frequency up to 20-30 Hz, then diminishes substantially at higher frequencies. A similar pattern is evident in the template of characteristic loss for glaucoma patients (Fig. 2), and may therefore reflect a change in the light adaptation mechanism of the abnormal retina. Thus the approach through temporal response characteristics appears likely to yield useful information for differential diagnosis of diseases affecting the retina.

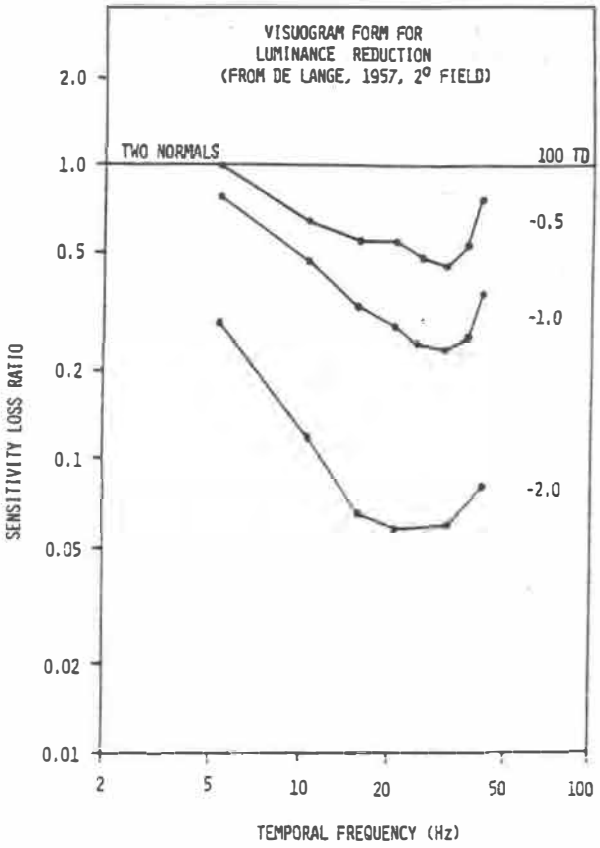

Fig. 11. Temporal visuograms showing sensitivity for three levels of luminance reduction. Mean of 2 observers from de Lange (1958).

The analysis of losses through changes found in normal observers may further be applied to the interpretation of the RP patients' data. The temporal visuograms of the simplex group do not show the loss in the mid-frequencies expected for a luminance reduction. Hence a luminance reduction hypothesis cannot explain the visuogram results. One possible explanation for the shape of the simplex/multiplex visuogram is an overall slowing of visual processing, together with a decrease of signal-to-noise ratio in the advanced cases (Ripps, Brin and Weale, 1978). Figure 12 shows the sort of effect slowing could have. The flicker sensitivity curve has been shifted leftwards on the frequency axis by a factor of 1.6. The resulting visuogram (lower panel) has a form similar to those seen in most of the present group of patients, including an increase in sensitivity at low temporal frequencies and a progressive loss with increasing frequency to about 1 log unit at 40 Hz.

Finally, a decrease in signal-to-noise ratio would reduce sensitivity equally at all temporal frequencies, and would appear as a uniform downward vertical shift of both flicker sensitivity curves (Ernst, Clover

and Faulkner, 1981) and visuograms. The patient data for autosomal dominant and x-linked heterozygotic RP, and also for nicotine toxicity, can therefore be explained by a reduction in signal-to-noise ratio of the retinal response. Obviously, such a reduction can be produced either by a reduction in signal strength, or by an increase in the noise level. In either case it is distinct from an effective luminance reduction. For example, a reduction in signal strength might be produced by a reduction in the voltage produced by the outer segments of the receptors, with normal quantities of photopigment. Conversely, an effective luminance reduction might correspond to a depletion of the amount of photopigment with otherwise normal voltage production.

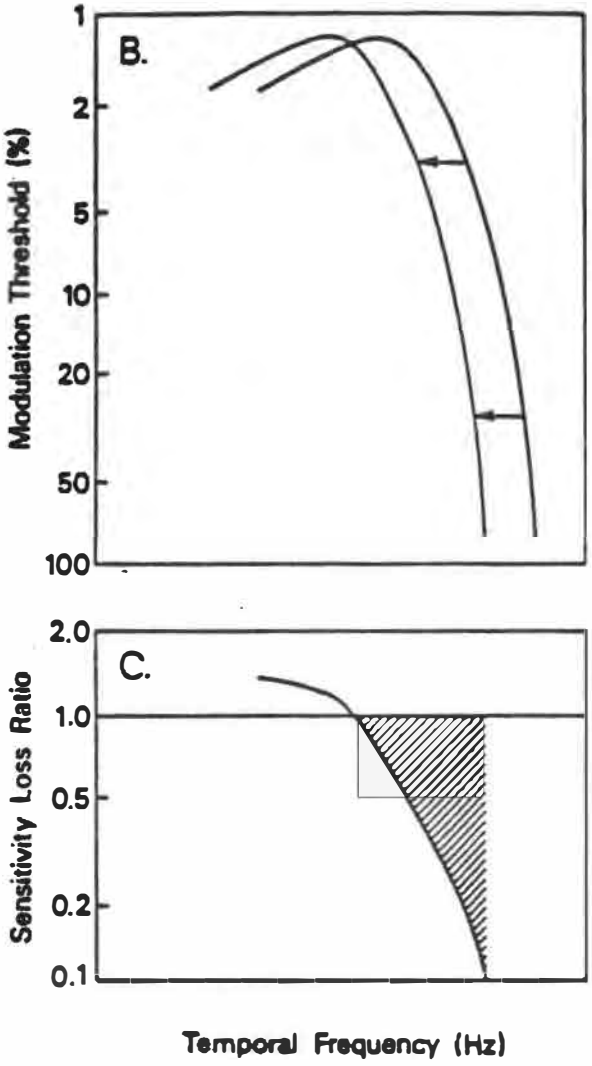

Fig. 12. Upper panel – Theoretical effect of overall slowing of temporal response as in a shift of the sensitivity curve to the left by a factor of 1.6. Lower panel – Corresponding temporal visuogram. Note similarity to RP losses of Figs 3 and 4.

Conclusion

This paper represents an exploratory study into the question of differential temporal losses in different types of retinal disease. Although none of the types were represented by a sufficient number of patients to allow definitive conclusions to be drawn as to the nature of the loss in each type of disease, the results were sufficiently uniform in each group to be regarded as providing a hypothesis as to the type of loss in each type. Most of the conditions described show losses that fall into distinct types, which need to be further validated by more extensive studies. Several of the loss characteristics are amenable to simple interpretation in terms of retinal mechanisms that may be affected by the disease. This leads to suggestions of the specific effects of each disease category on the retina, which can be explored in future studies.

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