Photopic Temporal Processing in Retinitis Pigmentosa

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PURPOSE. The relation between early changes in the photopic flicker electroretinogram (ERG) and photopic psychophysical changes in retinitis pigmentosa (RP) is poorly understood. Here, abnormalities in foveal and extrafoveal temporal contrast sensitivity functions (TCSFs) were studied in a group of carefully selected patients with RP who had relatively preserved macular function. The psychophysical results were compared with changes in the timing of the multifocal ERG.

METHODS. Subjects were patients with RP who had acuity ≥20/32 and no visual field defects within 6° from the fovea. Maxwellian-view and direct-view optical systems were used to obtain foveal and extrafoveal TCSFs under a range of test conditions, including high retinal illuminances that yielded temporal contrast sensitivity independent of mean retinal illuminance. TCSFs were described using log sensitivity and corner frequency parameters.

RESULTS. Foveal TCSFs in these patients showed overall reductions in sensitivity but no frequency-dependent defects. Also, no macular defects were found in the timing of the multifocal ERG. TCSFs from extrafoveal locations in moderate field defects, obtained at retinal illuminances that were sufficient to render flicker sensitivity independent of effective mean luminance, showed reductions in overall sensitivity as well as changes in temporal tuning. The multifocal ERGs from these extrafoveal locations showed signs of temporal slowing.

CONCLUSIONS. Changes in temporal tuning (both psychophysical and electroretinographic) were found only within visual field scotomas, whereas changes of the log sensitivity parameter were found also in the relatively preserved foveas of this group of patients with early stage RP. (Invest Ophthalmol Vis Sci. 1999;40:2932–2944)

Retinitis pigmentosa (RP) is a family of degenerative retinal diseases that result in characteristic fundus abnormalities, a reduced or absent electroretinogram, and symptoms of night blindness and progressive peripheral vision loss.¹ It appears that in all forms of RP both rod and cone photoreceptors are affected. Although damage seems to occur predominantly in rods, the cone system is compromised in various degrees in different types of RP.³ Remaining cone function is often used as a measure of the progression of the disease, because rod function may be undetectable. It is not well understood how decreased cone function relates to rod photoreceptor damage, and it is unclear what causes early changes in the cone pathway. Nevertheless, a typical electrophysiological measure for cone function, the photopic full-field flicker electroretinogram (flicker ERG hereafter) with a stimulus flash rate of around 30 Hz has proven useful in monitoring progression of RP. In patients with RP the flicker ERG has a reduced amplitude and, more particularly, a delayed implicit time¹⁴ even in early stages of the disease. The flicker ERG is routinely used in clinical assessment¹⁵ of RP and is part of the standard International Society for Clinical Electrophysiology of Vision protocol for ERG testing.⁹

Abnormalities in photopic flicker sensitivity in RP have also been found using psychophysical techniques. Several behavioral studies have addressed changes in temporal processing in patients with RP, reporting reduced temporal contrast sensitivity,¹⁰ delayed impulse response functions,¹¹ but normal temporal integration¹² in patients with RP.

It would be useful to establish a link between retinal function and visual function, which would help the understanding of the ERG and the development of sensitive psychophysical tests. However, the relationship between abnormalities in the flicker ERG and altered psychophysical temporal processing is complicated. First, several different factors can cause the alterations in ERG and psychophysical thresholds that are typical in RP. Elevated psychophysical thresholds may be due to a reduced number of photoreceptors or to a reduction in quantum catch of the photoreceptors (e.g., due to misalignment of the cones,¹³ or to shortened cone outer segments¹⁴). A delay in the implicit time of the flicker ERG may be the result of slowing of the transduction process, or of a loss of sensitivity of the transduction process.¹⁵ Furthermore, recent reports indicate that at least part of the flicker ERG signal originates from postsynaptic processes,¹⁶ rather than from the cone photoreceptors. Psychophysical thresholds presumably represent a combination of retinal and cortical filtering. Additionally, both psychophysical thresholds and the time course of the ERG are known to vary across the retina (or, correspondingly, the visual field) in normals, and even more so in patients with RP.

Second, large interindividual variability in the relationship between psychophysical sensitivity and ERG measures has...
been reported among patients with RP, even in data from patients with the same mode of inheritance of RP (autosomal dominant, autosomal recessive, or X-linked recessive), or from patients with the same known mutation.

The first aim of this study was to investigate early changes in foveal temporal contrast sensitivity due to RP, using stimulus conditions and patient selection criteria that were designed to help distinguish between the possible causes of the psychophysical abnormalities mentioned above. From a large patient population we selected patients with early stages of RP who had good acuity and many of whom showed no signs of reduced quantum catch of the foveal cones. Our second aim was to reduce the effects of retinal inhomogeneities on the comparison between psychophysical measures and the ERG. Using optimized stimulus conditions, extrafoveal temporal contrast sensitivity functions (TCSFs) were obtained from specific regions of the retina that were selected on the basis of the patients’ multifocal ERGs and visual fields.

**METHODS**

**Subjects**

Eighteen patients with RP were recruited from the files of the Retina Foundation of the Southwest. All had previously been diagnosed by ophthalmologists specializing in retinal diseases. Patients were required to have good visual acuity (20/32 or better), clear ocular media, and a measurable photopic 30-Hz full-field flicker electroretinogram (flicker ERG). Furthermore, patients were excluded who had field defects within 6° from the fovea (as assessed with kinetic perimetry; Goldmann spot size V). Main characteristics, including rod ERG amplitude, of the patients who served as subjects are given in Table 1. Note that not all subjects participated in all experiments in this study. Although all patients had both a delayed implicit time of the flicker ERG and visual field defects, there is considerable interindividual variability in both visual field and flicker ERG measures, as can be seen in Table 1.

Normal subjects were free of known eye disease; they had visual acuity 20/20 or better, normal contrast sensitivity on the Regan Contrast Sensitivity Charts, and normal color vision (normal on anomaloscopy, and on Ishihara, SPP-II, Farnsworth D-15, and Adams desaturated D-15 tests).

This study followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from all subjects after the nature and possible consequences of the study were explained. This research was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

**Apparatus**

A two-channel Maxwellian-view optical system with a 2-mm artificial pupil was used to obtain foveal TCSFs in experiment 1. The test was provided by a diffused light-emitting diode.
(LED) in the first channel, controlled by a Macintosh II computer with an AO-6 12-bit, 6-channel analog output (National Instruments, Austin, TX) and a high-speed DMA-8 timing board (National Instruments). The LED was linearized using a pulse-density method described elsewhere. A diffused tungsten light source in the second channel provided the surround. The lights from the two channels were combined by a photometric cube and passed through a 570-nm interference filter, resulting in a 2°-diameter uniform circular test field yielding a mean retinal illuminance of 50 Td (1.7 log Td), surrounded by a 10° square, steady field of 35 Td. The fairly dim green test was chosen to avoid effects of long-wavelength adaptation.\textsuperscript{22,25}

For experiments 2 and 3, which involve parafoveal and extrafoveal stimuli, a direct-view optical system was used. A diffused green LED, controlled as described above, subtended 4° of visual angle and had a maximum mean luminance of 160 cd/m\textsuperscript{2}, thus yielding a uniform maximum mean retinal illuminance of 3.9 log Td for an 8-mm-diameter pupil (taking into account the Stiles–Crawford effect\textsuperscript{23}). The surround was formed by a large white screen with a luminance of 170 cd/m\textsuperscript{2}. Subjects fixated the LED for the foveal measurements. For extrafoveal measurements a fixation mark was placed on the white screen, such that the stimulus would fall in the visual field location of interest.

**Psychophysical Procedures**

In all psychophysical experiments a temporal 2-alternative forced-choice (2AFC) paradigm was used. A computer-generated voice indicated the beginning of each stimulus interval and provided feedback after each trial. In each measurement 2 staircases for different frequencies were run in a randomly interleaved manner with 10 reversals each, after a 2-down/1-up rule. Contrast changed in octave steps, changing to half-octave steps after the second reversal. For measurements of the critical flicker frequency (CFF), the test frequency was varied initially in steps of 2 Hz, and in steps of 1 Hz after the second reversal. Threshold was defined as the 75%-correct point of a staircase for different frequencies were run in a randomly interleaved manner with 10 reversals each, after a 2-down/1-up rule. Contrast changed in octave steps, changing to half-octave steps after the second reversal. For measurements of the critical flicker frequency (CFF), the test frequency was varied initially in steps of 2 Hz, and in steps of 1 Hz after the second reversal. Threshold was defined as the 75%-correct point of a 3-parameter Weibull function that was fit to the data using maximum likelihood estimation. All testing was done monocularly. For the direct-view stimuli (experiments 2 and 3), subjects were dilated and subjectively refracted in the apparatus.

**Stimulus Conditions**

Obtaining reliable psychophysical threshold data from a patient population requires careful stimulus design. The forced-choice paradigm was adopted to minimize the variability resulting from inter- and intraindividual differences in decision criteria.

The 2AFC paradigm entails choosing a finite temporal waveform of the stimuli instead of continuous stimulation. At high test frequencies a small bandwidth is desired to prevent biased results at the steep fall-off of the De Lange curve. However, small bandwidth stimuli involve larger numbers of cycles, which may become problematic at low frequencies, for which this results in long durations. Patients may not be able to fixate properly for the duration of each stimulus presentation. Also, the total duration of the experiment may become a limiting factor, because relatively large numbers of presentations are needed for reliable data in a clinical population. Furthermore, long-duration stimuli may cause adaptation effects.\textsuperscript{26,27} Here, a trade-off was made between the temporal frequency bandwidth and the duration of the stimuli. Two types of temporal waveform were used. In experiment 1, which included relatively low test frequencies, the waveform was the 6\textsuperscript{th} derivative of a gaussian (D6 pattern), which is a relatively ‘short’ waveform and has a fixed bandwidth of 1 octave.\textsuperscript{28} For the subsequent measurements, in which only CFF (experiment 2) or only the high-frequency portion of the TCSF (experiment 3) was obtained, the waveform was a temporal Gabor pattern, defined as

\[
G(t) = \exp\left(-\frac{2\pi ft}{\alpha}\right)^2 \sin(2\pi ft).
\]

Note that the stimulus frequency \(f\) appears in the exponential, causing the bandwidth of the Gabor to be frequency independent. The value of \(\alpha\) was set at 20, resulting in a fixed bandwidth of 0.24 octaves.

To avoid effects of mean retinal illuminance (e.g., due to changes in optical density of the cones) in the extrafoveal measurements of experiment 3, relatively bright stimulus conditions were chosen. For increasing mean retinal illuminance, temporal contrast sensitivity for a given test frequency first increases and then levels off to a constant level,\textsuperscript{29-32} and thus becomes independent of mean retinal illuminance. Furthermore, this asymptote is reached at higher values of mean retinal illuminance for increasing temporal (and spatial) frequency of the stimulus.\textsuperscript{34} Therefore, when mean luminance becomes high enough that CFF levels off to an asymptote, contrast sensitivity for all lower frequencies should also be independent of mean luminance. Accordingly, for most subjects this asymptotic behavior was verified for CFF only. For a small number of normal subjects asymptotic behavior was verified for the entire TCSF once CFF had reached an asymptotic value (results not shown).

**Data Analysis**

All TCSFs were fit with a linear-filter model. The individual data from experiment 1, which included relatively low test frequencies, were fit by a three-parameter model defined as the difference of two \(n\)-stage linear filters, for which the amplitude response equals:

\[
A_{sens} = \frac{f_{c}^n_{exc}}{(f^2 + f_{c}^2)^{n/2}} - A_{inhb} \frac{f_{c}^{n_{inh}}}{(f^2 + f_{c}^{2})^{n_{inh}/2}}.
\]

Similar models have been useful in previous studies, with the number of stages not being very crucial and typically between 5 and 10.\textsuperscript{21,33,34} The number of stages was set to 5 for the positive component and to 10 for the inhibitory component; both components have the same time constant. The three free parameters in this model were as follows: log sensitivity (\(A_{sens}\), defined as the sensitivity of the positive component), log inhibition (\(A_{inhb}\), defined as the sensitivity of the inhibitory component), and corner frequency (\(f_{c}\), defined as the frequency at which sensitivity has dropped 3 dB). In experiment 3, in which only the high-frequency portion of the TCSFs was measured, individual data were fit by a single \(n\)-stage linear filter having log sensitivity and corner frequency as its 2 free parameters.

The CFF-vs-retinal illuminance functions (experiment 2) were fit with a Michaelis–Menten function...
\[ \text{CFF}(J) = \text{CFF}_{\text{max}} + \log \frac{I^k}{I^c + I^s}, \]

in which \( I \) is the retinal illuminance. This model describes behavior predicted by the Ferry-Porter law\(^{31} \) for lower retinal illuminances, combined with an asymptote at higher illuminances.\(^{10,35,36} \) The 3 free parameters were the slope of the ascending portion \(( k)\), the critical retinal illuminance \(( I_c)\) at which CFF asymptotes, and the asymptotic CFF \( \text{CFF}_{\text{max}} \).

**Experiment 1: Foveal TCSFs**

To study abnormalities in foveal temporal contrast sensitivity in patients with relatively preserved macular function, foveal TCSFs were obtained in 9 patients with RP (age, mean ± SD, 40.9 ± 10.7 years) and 10 age-similar normals (age, 38.3 ± 6.8 years) and 10 age-similar normals (age, 39.4 ± 8.6 years). 2AFC contrast thresholds for 2° diameter D6 stimuli were measured for test frequencies ranging from 1.4 to 22 Hz and CFF. The Maxwellian-view optical system was used for this experiment. Mean luminance of the test field was 50 Td.

All 9 patients in experiment 1 had participated in an earlier study,\(^{34} \) which found Rayleigh matches within the normal range, indicating that the most sensitive foveal cones of these patients did not have reduced optical densities.

**Experiment 2: CFF as a Function of Retinal Illuminance**

To study the asymptotic behavior of temporal contrast sensitivity for increasing retinal illuminances for our stimulus conditions, CFFs were measured in 15 patients (age, 40.9 ± 10.7 years) and 16 age-similar normals (age, 41.9 ± 10.5 years) for a range of mean luminances, starting at 1.5 log units (or occasionally 2.0 or 2.5 log units) below maximum, and increasing in 0.5 log steps to the maximum mean luminance of 160 cd/m\(^2\). Using the direct-view optical system, CFFs were obtained for Gabor stimuli at each luminance level, for foveal and 5° extrafoveal test locations on the horizontal meridian of the temporal retina.

**Experiment 3: TCSFs in Relative Scotomas**

A subgroup of the patients in experiment 2, consisting of 6 subjects (age, 41.0 ± 7.2 years; selected on availability and willingness to undergo further testing), participated in experiment 3. Results were compared with the results from 6 age-similar normals (age, 41.5 ± 7.1 years).

The multifocal ERG technique\(^{37} \) was used to obtain responses from 103 locations across the central retina. In short, the stimulus was presented at 200 cd/m\(^2\) mean luminance on an M2400 black and white monitor (Dotronix, New Brighton, MN), and consisted of a 47° by 39° two-dimensional hexagonal array of 103 elements. The luminance of each element was alternated between 400 and 0.4 cd/m\(^2\) in a pseudorandom sequence (m-sequence) at the frame refresh rate of the monitor (75 frames per second). Stimulus control and data collection were performed by VERIS Scientific software (Electro-Diagnostic Imaging, San Mateo, CA). A Burian-Allen contact lens electrode was used to record the corneal ERG from one eye with dilated pupil, refracted for the test distance.

On the basis of the multifocal ERG results and the results of automated static perimetry (24-2 threshold program on an HFA 640 perimeter; Humphrey Systems, Dublin, CA) one location in the visual field of each patient was selected for further psychophysical testing. This location showed a delay ≥5 msec in the peak of the multifocal ERG but no absolute defect in the visual field (<1.0 log unit threshold elevation for 3 patients, and 1.0–1.5 log unit elevation for 2 patients), and was typically around 10° eccentricity. Control data were obtained in locations of corresponding eccentricity in the normal subjects. To improve signal-to-noise, multifocal ERG responses were averaged over 7 hexagons centered on the extrafoveal test location. For comparison, the macular (i.e., central) 7 hexagons of each multifocal ERG were also averaged.

Using the direct-view optical system, the high-frequency portion of the TCSF was measured using 4° diameter temporal Gabor stimuli at the maximum mean luminance of 160 cd/m\(^2\) for frequencies ranging from 14 to 40 Hz in half-octave steps. Note that only the high-frequency portion of the TCSF was measured. To verify that the mean luminance was sufficient to bring CFF in or near the asymptotic region, CFFs were obtained at the maximum mean luminance (160 cd/m\(^2\)), and at 1.0 and 0.5 log units below the maximum.

**RESULTS**

The psychophysical paradigm used in this study allowed us to gather temporal contrast sensitivity data for a range of stimulus conditions in patients with RP and age-similar normal volunteers. The psychometric functions corresponding to the reported data all had upper asymptotes ≥97%.

The foveal TCSFs obtained in experiment 1 are shown in Figure 1 for normals (Fig. 1A) and patients (Fig. 1B). Interindividual variability in the patient group appears to be larger than in the normals; TCSFs tend to be lower in the patients than in the normals; but at CFF no obvious differences between the groups are readily seen in Figure 1. Fits of the linear filter model to the data are also given in Figure 1. The three-parameter model produced reasonable fits for each data set, capturing individual differences in shape and sensitivity of the TCSFs (Fig. 1).

To compare the two groups, Figure 2 (left panel) shows the fits for all subjects replotted from Figure 1. No significant differences between the patient and normal groups were found in any of the three parameters (\( t = 1.01, \ P = 0.16 \) for log sensitivity; \( t = 0.041, \ P = 0.68 \) for log inhibition; and \( t = 0.70, \ P = 0.25 \) for corner frequency). The larger interindividual variability in the patient group (as compared with the normals) that was noted above is reflected in a larger variability in the log sensitivity parameter for the patients (SD = 0.19 log units) than for the normals (SD = 0.10 log units), whereas the variabilities of the other free parameters differ by less than 10% across the two groups. Comparing individual patients with the mean normal data, two patients had sensitivity below the 95% confidence limit for normal, whereas one patient had an abnormally high sensitivity. None of the patients showed abnormal values for corner frequency or inhibition. In the right panel of Figure 2 the individual fits were normalized to their log sensitivity parameter, to better show variations in temporal tuning across subjects. (Note here that this normalization does not necessarily make the curves converge to a single point at, for example, 0 Hz, because the inhibitory components of the fits may still differ.)

The CFF-versus-retinal illuminance functions obtained in experiment 2 are presented in Figure 3. For virtually all
subjects CFF increases linearly with log retinal illuminance (known as the Ferry–Porter law; e.g., Tyler and Hamer\textsuperscript{31}), until a plateau is reached. For some subjects CFF does not quite asymptote for the brightest stimuli. However, CFF has started to level off for most of these subjects, making it possible to fit the model function to the data, thus yielding an estimate for CFF\textsubscript{max}. For the few remaining data sets, CFF\textsubscript{max} and \( I_c \) were set at the highest values obtained in these subjects. Table 2 shows the mean values and standard deviations of the fit parameters for both groups. For the normal subjects, values for CFF\textsubscript{max} tend to be higher in the extrafoveal test location than in the fovea.\textsuperscript{31} Slopes of the Ferry–Porter portion tend to be steeper in the extrafoveal test location than in the fovea, in agreement with previous findings.\textsuperscript{31} No significant group differences between normals and patients were found for the three parameters. In particular, the fact that on average CFF\textsubscript{max} is not smaller for the patient group is consistent with the results for the TCSF

**Figure 1.** Results from experiment 1. Foveal TCSFs for 10 normal subjects (A) and 9 patients with RP (B), obtained in Maxwellian view at 1.7 log Td. Each panel contains the data for one subject. *Solid lines* correspond to best fits of the linear filter model described in the text. Goodness-of-fit: Individual residual standard deviations all \( \leq 0.21 \).
measurements at 50 Td, where no mean differences in sensitivity or corner frequency were found between the normal and patient groups. Also, values for \( I_{c} \) were similar in both groups, meaning that CFF reaches its asymptote in the same range of retinal illuminances (around 3.2 log Td). This may indicate that on average these patients do not have a reduced quantum catch of the cones in the locations tested.

For the six patients that participated in further testing (experiment 3), mean multifocal ERG responses were calculated, averaging over the seven elements in the macular (central 8°) area, and over the seven elements centered on each extrafoveal test location, and subsequently normalized in amplitude. For each patient these normalized mean responses are shown in Figure 4, together with the results from a normal subject. All patients showed normal timing in the central 8° area but increased implicit times at the extrafoveal test location.38,39

Figure 5 gives the CFF-versus-retinal illuminance data obtained from each of the six patients at the same extrafoveal test locations, as well as data from the six age-similar normal subjects. Normal values for asymptotic CFF were considerably higher at these extrafoveal locations than at the fovea, with flicker frequencies up to 100 Hz being detected.31 Note also, that although temporal contrast sensitivity was in or near the asymptotic region for most subjects, for two patients it was not. TCSFs, obtained from each subject at the maximum value for log retinal illuminance (corresponding to the right-most data points in Fig. 5), were measured at these same test locations and are shown in Figure 6. The best fits of the two-parameter linear filter model described above are also shown in Figure 6. For interindividual comparisons the fitted curves were replotted in Figure 7 (left panel). Significant reductions were found for the patient group compared with the normal group for the mean values of the log sensitivity parameter (\( t = 2.17, P = 0.028 \)) and of the corner frequency parameter (\( t = 2.14, P = 0.029 \)). In the patient group a larger variability was found than in the normal group for both parameters; this variability increase was most pronounced in the log sensitivity parameter. To illustrate the difference between changes in sensitivity and abnormalities in timing, the fits were normalized for log sensitivity (DC component) (Fig. 7, right panel). Of the six patients, three patients had corner frequencies below the normal range, and two patients had corner frequencies at the lower end of the normal range.

**DISCUSSION**

Understanding the relationship between typical alterations in the flicker ERG and the temporal aspects of psychophysical thresholds in patients with RP has been impeded by the multiplicity of factors that affect these measures. Furthermore, large interindividual variation in the relation between ERG and visual field exists, even when subpopulations of patients with the same mode of inheritance are examined.17-19

In an attempt to minimize this interindividual variability in our study population, strict selection criteria were applied. In particular, patients with field defects entering the macula were excluded, to avoid large variability in patients’ macular visual function. Note here that this exclusion criterion was based on a different visual field measure than parameters typically used, which describe the “amount” of field loss in patients with RP. Massof et al.40 calculated the total area of the remaining visual field, including any peripheral islands. Sandberg et al.12 used a similar parameter and converted this into an “equivalent field diameter.” Both of these methods ignore the shape of the visual field or the distribution of scotomas. Conversely, the “nearest field defect” criterion adopted here contains no information about the total area or the extent of the remaining visual field. (For comparison, an estimate of the more widely used equivalent field diameter for each patient is given in Table 1. The correlation between the equivalent field diameter and the flicker ERG amplitude was borderline significant; \( P = 0.054 \)).

The patients that participated in experiment 1 were examined previously20 to estimate cone optical density. None showed signs of reduced optical density. Of the 9 patients tested in experiment 1, 3 showed reduced sensitivity, but 0 showed altered temporal tuning of the foveal TCSF. Dagnelie and Massof41 measured foveal TCSFs in a group of patients with RP of various pathophysiological and inheritance sub-
types. They found reductions of flicker sensitivity that after transformation to the time domain showed delays in the impulse response function, corresponding to a reduction in corner frequency. Earlier, Tyler et al.\textsuperscript{10} found reductions of foveal temporal contrast sensitivity in RP that were more pronounced for frequencies above 10 Hz than for lower frequencies. This,

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<th>Table 2. CFF-Versus-Log Retinal Illuminance: Best Fit Parameters</th>
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<td><strong>Fovea</strong></td>
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Values are mean ± SD.
also, indicates a shift of the TCSF along the frequency-axis rather than the sensitivity-axis. Both these studies may have included patients with field defects close to the macula. Tyler et al.\textsuperscript{10} included patients with Goldmann visual field radii of 2° and larger. In the study by Dagnelie and Massof\textsuperscript{11} disease severity was reported in terms of years past critical age, which is based on total area of the remaining visual field\textsuperscript{40} and hence contains no information on the distribution of defects across the visual field.

A crucial parameter that varied across these studies, as well as the experiments reported here, is the mean retinal illuminance at which the results were obtained. Tyler et al.'s\textsuperscript{10} experiments were performed at a maximum mean luminance of 40 cd/m\textsuperscript{2}, which for the reported pupil diameters of 8 to 9 mm corresponds to a retinal illuminance of approximately 3 log Td (taking into account the Stiles–Crawford effect\textsuperscript{24}). Dagnelie and Massof\textsuperscript{11} measured at 500 Td (2.7 log Td). TCSFs shift to lower temporal frequencies when retinal illuminance is reduced.\textsuperscript{41} More importantly, the “effective” mean retinal illuminance may vary within each of these studies if the patients tested have reduced quantum catch of the cones. Thus, alterations in temporal tuning of the TCSF could have been caused by reductions in cone optical density. Patients with RP who have retained good acuity may have a 0.3 log unit reduction in foveal cone optical density.\textsuperscript{42,43} (To simulate the effects of the resulting change in effective mean retinal illuminance, we obtained foveal TCSFs in 9 young normal observers at mean retinal illuminances of 50 Td and 25 Td. The results confirmed a significant effect of mean retinal illuminance on corner frequency in our test conditions; $t = 3.50, P = 0.008$.)

We also studied functional characteristics of selected extrafoveal retinal locations corresponding to moderate field defects (threshold $<1.5$ log units above mean normal). Because cone optical density is likely to be reduced in these locations,
relatively bright stimulus conditions and dilated pupils were used, which rendered the TCSFs independent of effective retinal illuminance. Graham and Hood give an extensive review of normal data that show a transition from "constant amplitude threshold" behavior to "constant contrast threshold" behavior with increasing luminance. This transition implies that temporal contrast sensitivity reaches an asymptotic value at high retinal illuminances. Such asymptote has also been found in X-linked dichromats and in patients with RP. We found this asymptotic behavior for normals and for patients with RP (experiment 2), assuring that the maximum mean luminance of our direct-view stimuli was sufficiently high to bring subjects in or near this asymptotic region.

The transition to "constant contrast threshold" behavior is known to occur for higher illuminances at higher temporal frequencies. Therefore, if the mean retinal illuminance is not quite sufficient to reach asymptotic CFF for a given patient for a given retinal location, constant contrast threshold behavior may hold at lower temporal frequencies, whereas constant amplitude threshold behavior holds at higher temporal frequencies. A reduction of cone optical density would then affect contrast sensitivity at higher frequencies more than at lower frequencies, resulting in a reduced corner frequency of the TCSF.

Of the six patients for which TCSFs were obtained from extrafoveal locations corresponding to field defects (experiment 3), three patients showed altered temporal tuning (corner frequency below 95% confidence limit for normal) of the TCSF measured from a defective area of the visual field, and two patients scored at the lower end of the normal range. Note here that patient 3206 showed a reduced corner frequency (Fig. 7, right) but normal sensitivity (Fig. 6B). However, CFF was not quite in the asymptotic range for this patient at the retinal location tested (Fig. 5), and the abnormal corner frequency could therefore be due, in part, to a reduction in cone optical density.

Summarizing our psychophysical results, we found significant changes in temporal contrast sensitivity in this group of patients with RP. Abnormalities in TCSFs obtained from areas that were normal on perimetry (i.e., these patients’ foveas) appeared to be reductions in log sensitivity rather than corner frequency, whereas the abnormalities in TCSFs corresponding to extrafoveal field defects showed a combination of changes in log sensitivity and corner frequency. We must restate here, however, that a clear understanding of the results is hampered by interindividual variability, even though the spread of the log sensitivity and corner frequency values in the patient group is not much larger than in the normal group. Figure 8 shows the TCSF parameters obtained here as a function of the clinical visual function data presented in Table 1. A hint of a relationship is seen between the foveal corner frequency parameter and the distance to the nearest visual field defect, between the extrafoveal corner frequency and the visual field diameter, and between the extrafoveal log sensitivity and the two flicker ERG parameters. However, no significant correlation was found between any of the TCSF and clinical visual function parameters. Although this may be attributed in part to the relatively small number of patients in this study, the much larger study by Dagnelie and Massof also found rather poor correlation between similar TCSF attributes and visual field area. (Their test conditions and inclusion criteria were somewhat different from ours, however, and only foveal data were reported; See comments above.) The poor correlation is therefore more likely to be due to interindividual variability, reflecting the notion that the physiological processes that underlie each of the parameters tested do not necessarily have similar spatial
distributions across the retina and/or follow the same time course in patients with RP.

Although all patients had a delayed full-field flicker ERG, they all showed normal timing of the main positive peak of the multifocal ERG in the central elements corresponding to the macula, as has been seen earlier. In the extrafoveal test locations the main positive peak of the multifocal ERG was delayed, also in accordance with previous reports. Hood et al. found that the main positive peak of the multifocal ERG shows similarities with the photopic full-field ERG b-wave. Furthermore, it has been shown that the topography of changes in the timing of the multifocal ERG correlates with the topography of visual field defects in patients with RP.

When the present ERG findings are compared with our psychophysical results, we see reduced sensitivity but normal timing of the foveal TCSFs in combination with normal timing of the multifocal ERG. We conclude therefore that abnormalities in the flicker ERG implicit time are related to changes in temporal tuning of the psychophysical TCSF, provided that retinal illuminance is sufficiently high to yield constant contrast threshold behavior. Alterations in the timing of the multifocal ERG in patients with RP have been shown to be multiplicative rather than additive, indicating a slowing of the response rather than a simple delay. This may be due, in part, to a broadening of the impulse response of the cones, which, in turn, would cause the psychophysical corner frequency to be reduced. However, a quantitative relation was not found between the timing of the peak of the multifocal ERG and either psychophysical corner frequency or log sensitivity parameters.

A model for changes in the TCSF that includes both sensitivity and corner frequency parameters follows from the assumption that achromatic temporal contrast is processed via the magnocellular pathway, which is mediated by the parasol retinal ganglion cells. The receptive field centers of these ganglion cells receive input from several cone photoreceptors. If only a small fraction of the cones in a given region of the retina are damaged (i.e., not functioning or functioning abnormally), the flickering stimulus may be mediated by parasol ganglion cells whose receptive field centers have lost input from a few, but not all, cones. Because the input to such ganglion cell is proportional to the number of cones feeding into its receptive field, a greater stimulus increment is needed from a few, but not all, cones. Because the input to such ganglion cell is proportional to the number of cones feeding into its receptive field, a greater stimulus increment is needed for the subject to perceive flicker. This would correspond to a decreased sensitivity in this region of the retina. However, assuming that detection of the stimulus in this case is mediated by remaining "healthy" cones, the temporal response properties will still be determined by these remaining cones and

**FIGURE 6.** Results from experiment 3. Extrafoveal TCSFs for 6 normal subjects (A) and 6 patients with RP (B), obtained in direct view at the maximum mean luminance of the stimulus (160 cd/m²), yielding a mean retinal illuminance of ~3.2 log Td. Each panel contains the data for one subject. Solid lines correspond to best fits of the linear filter model described in the text. Goodness-of-fit: Individual residual standard deviations all ≤0.22.
FIGURE 8.  Relationships between the obtained TCSF parameters and the clinical visual function data presented in Table 1.  **Left:** The foveal log sensitivity and corner frequency parameters from experiment 1 plotted against the distance to the nearest visual field defect.  **Right:** The extrafoveal log sensitivity and corner frequency parameters from Experiment 3 plotted against the equivalent visual field diameter, and against the flicker ERG amplitude and the flicker ERG implicit time.  Each data point represents one patient (\(n = 9\) for the foveal data; \(n = 6\) for the extrafoveal data).

**FIGURE 7.**  **Left:** All curves from Figure 6 replotted in one panel.  **(Solid lines)** Patients with RP;  **(dotted lines)** Age-similar normals.  **Right:** Fits from left panel, normalized to their log sensitivity parameter.  **(Shaded region)** Range covered by the normals.  **(Solid lines)** Patients with RP.
therefore not necessarily abnormal. Thus, it is feasible that sensitivity changes occur while temporal tuning is unaltered in early stages of photoreceptor damage. When a larger fraction of cones in a given region of the retina function abnormally, which is possibly the case for mild visual field defects, the flicker stimulus may be mediated by parasol ganglion cells whose receptive field receives input from mostly abnormal photoreceptors. Beside a further decrease in sensitivity, temporal response properties may in this case be determined by predominantly “sick” photoreceptors. Note here that this latter case would still be considered a relatively early stage of photoreceptor damage.

In summary, the cause of reductions in psychophysical flicker sensitivity in RP may depend on the mean retinal illuminance. Abnormalities may be related to reduced cone optical density for values of retinal illuminance in the constant–amplitude range, and related to temporal dysfunction of the cones in the constant–contrast range. Furthermore, the TCSF, visual field, and ERG parameters discussed here correlate poorly, supporting the idea that the underlying physiological processes do not change hand-in-hand during the progression of RP.

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References