Deficits in Temporal Integration for Contrast Processing in Retinitis Pigmentosa

Kenneth R. Alexander, Claire S. Barnes, and Gerald A. Fishman

PURPOSE. The purpose of this study was to evaluate the properties of foveal temporal integration in patients with retinitis pigmentosa (RP) within the framework of contrast processing by the magnocellular (MC) and parvocellular (PC) pathways.

METHODS. Temporal integration functions were measured in eight patients with RP whose visual acuities ranged from 20/25 to 20/63. Contrast thresholds were obtained at durations ranging from 15 to 480 ms, using steady-pedestal and pulsed-pedestal paradigms to bias performance toward the MC and PC pathways, respectively. The patients’ results were compared with those of 10 age-similar control observers with normal vision. For both paradigms, contrast thresholds as a function of duration were fit with a two-limbed function to derive the critical duration for temporal integration ($t_c$) and the asymptotic threshold at long durations ($\Delta t_o$).

RESULTS. The log $t_c$ of the patients with RP were significantly longer than those of the control subjects for the steady-pedestal paradigm (presumed MC-pathway mediation; $t = 3.67, P < 0.001$), but not for the pulsed-pedestal paradigm (presumed PC-pathway mediation; $t = 0.76, P = 0.45$). Further, the patients with RP showed a significant correlation between log $t_c$ and log $\Delta t_o$ for the steady-pedestal paradigm ($r = 0.72, P < 0.05$) but not for the pulsed-pedestal paradigm ($r = -0.37, P = 0.36$).

CONCLUSIONS. The patients with RP in this study showed greater deficits in contrast sensitivity and a more prolonged critical duration under test conditions that favor the MC rather than the PC pathway. A likely explanation is a high-frequency response attenuation at the level of the cone photoreceptors that has a differential effect on contrast-processing tasks that emphasize different postreceptorial mechanisms. (Invest Ophthalmol Vis Sci. 2003;44:3163–3169) DOI:10.1167/iovs.02-0812

Retinitis pigmentosa (RP) refers to a heterogeneous group of hereditary retinal degenerations that are characterized by night blindness, peripheral visual field depressions or scotomata, abnormalities in the electroretinogram (ERG) of the rod and cone systems, intraretinal bone-spicule–like pigmentation, and narrowing of the retinal vessels.1 Molecular genetic studies of patients with RP (reviewed by Ref. 2) and studies of transgenic animal models of RP (reviewed by Ref. 3) have shown that many forms of this retinal degeneration result from mutations in genes that encode structural proteins or enzymes that are necessary for the normal development and structure of rod photoreceptors or that are involved in the rod phototransduction cascade or the visual cycle that regenerates rod photopigment.

Because rod function is often severely impaired in patients with RP, an evaluation of the integrity of the cone system is frequently the primary means of monitoring disease progression and of assessing the effectiveness of potential therapeutic regimens. Furthermore, recent studies have highlighted the significant relationship between dysfunction of the foveal cone system and patients’ ability to perform tasks in everyday life.4–6 Therefore, it is of considerable interest to define the nature and extent of cone system impairment within the foveas of patients with RP.

Foveal impairment in RP typically is manifested clinically as a reduction in visual acuity.1 However, patients with RP can also show reduced contrast sensitivity across a broad range of spatial frequencies.8–9 In addition, the ability of patients with RP to discriminate among different contrast levels can be impaired. With the use of “steady-pedestal” and “pulsed-pedestal” paradigms to emphasize the magnocellular (MC) and parvocellular (PC) pathways, respectively, it was determined recently that patients with RP have greater deficits in contrast processing under conditions that favor the MC pathway.10

One of the fundamental determinants of visual sensitivity is the extent to which there is temporal integration of light stimuli. Typically, for stimuli shorter than a critical duration, increasing the stimulus duration results in increased sensitivity. For stimuli longer than the critical duration, however, sensitivity is independent of stimulus duration. The limits of temporal integration have been shown to differ depending on the nature of the contrast-processing task. For visually normal observers, temporal integration extends to longer durations for the pulsed-pedestal paradigm, favoring the PC pathway, than for the steady-pedestal paradigm, favoring the MC pathway.11

The previous study of contrast-processing deficits in patients with RP10 used a relatively short stimulus duration of 30 ms, which is within the normal limits of temporal integration for both contrast-processing paradigms. Other durations were not investigated. However, there is reason to expect that patients with RP may show greater deficits in temporal integration under test conditions that favor the MC pathway. First, some patients with RP have been reported to show abnormalities in flicker sensitivity at high temporal frequencies,12,13 a task that is thought to be mediated by the MC pathway in visually normal subjects.14 Given the close relationship between the corner frequency of the temporal contrast response function (i.e., frequency at which the sensitivity has decreased by 3 dB) and the critical duration for temporal integration,15 a reduction in high-frequency sensitivity would be expected to be accompanied by a longer critical duration. Second, temporal integration for letter identification has been observed to be normal in patients with RP.16 The relatively long temporal integration time for letter identification in visually normal sub-

From the 1Department of Ophthalmology and Visual Sciences  and the 2Department of Psychology, University of Illinois at Chicago, Chicago, Illinois.

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The purpose of the present study, therefore, was to evaluate the hypothesis that deficits in temporal integration in patients with RP are greater for test conditions that favor the MC pathway. This possibility was assessed by measuring temporal integration in a group of patients with RP using steady-pedestal and pulsed-pedestal psychophysical paradigms of contrast processing that are designed to bias performance toward the MC and PC pathways, respectively.11

METHODS

Subjects

Eight patients (three women and five men) with typical RP (n = 6) or type 2 Usher syndrome (n = 2), a recessively inherited variant of RP accounted for by a congenital neurosensory hearing impairment, participated in the study. Their ages and visual characteristics are listed in Table 1. Patients were selected who had a visual acuity of 20/25 or worse with only a minimal or no posterior subcapsular cataract in the tested eye. Seven of the eight (patients 1–7) had participated in a previous study of contrast discrimination.10 The contrast thresholds of the patients with RP were compared with those from 10 (7 women and 3 men) age-similar control observers with normal vision (age range, 23–53 years). The control observers had best corrected visual acuities of 20/20 or better in the tested eye, clear ocular media, and normal-appearing fundi on ophthalmologic examination. The study adhered to the tenets of the Declaration of Helsinki, and it was approved by the institutional review board of the University of Illinois at Chicago. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained to them. All participants were remunerated for their participation.

Test Stimuli

The test stimuli and procedure were based on those used previously.10 Stimuli were generated by a computer (Macintosh PowerPC 750/100; Apple Computer, Cupertino, CA) and were presented on a high-resolution gray-scale display (Apple). A 10-bit video board (Thunderpower 30/1600; Radius, Sunnyvale, CA) and a linearized lookup table controlled the stimulus luminances, which were calibrated with a photometer (LS-110; Minolta, Osaka, Japan). The test stimulus durations were 15, 30, 60, 120, 240, and 480 ms (i.e., multiples of the 66.67-Hz video frame rate). Stimulus durations were confirmed with a photocell and oscilloscope.

As illustrated in Figure 1, the stimulus was an array of four squares (the pedestal), one of which (the test stimulus) was incremented in luminance during a trial. Each square subtended 1° of visual angle, and the squares were separated by 9.2 arcmin. The four squares were presented within a steady surround that subtended 12° horizontally by 9° vertically and filled the region between the squares. A black fixation dot 9.2 arcmin in width was presented in the center of the display at all times. Stimuli were viewed monocularly with the natural pupil through the best optical correction in a phoropter at a test distance of 1 m.

Pedestal and surround luminances were chosen such that they were within the Weber region for both patients and control observers, based on previous data.10 The use of luminance levels within the Weber region minimizes the effect of any possible differences in retinal illumination among subjects. For the steady-pedestal paradigm, the pedestal luminance was equal to the surround luminance (60 cd/m²), to minimize any potential contribution from the PC pathway, which responds to border contrast between the pedestal and surround (the gray outlines in Fig. 1B indicate the location of the pedestal squares but were not present in the stimulus display).10 For the pulsed-pedestal

![Figure 1. Illustration of the stimulus configuration and testing sequence.](image-url)
paradigm, the pedestal luminance was the same as for the steady-pedestal paradigm, but the surround luminance was reduced to 30 cd/m² to introduce a contrast signal between the pedestal and surround that would favor the PC pathway. Reducing the surround luminance should have no effect on the MC pathway, the sensitivity of which is governed by local adaptation to the pedestal luminance, independent of the surround luminance. This was verified in a pilot study, described in the following section, in which a different pedestal was performed on the 14 patients with RP from a previous study, which were required to reduce the contrast, whereas a single incorrect criterion size of 1.56% of the initial step size was reached, and then it observers, based on pilot work. The step size was then halved until a step was set at a adaptive staircase procedure with no feedback. The initial staircase response button to con appeared to differ from the other three. The observer pressed a button to move the cross to the outer corner of the square that had the observer pressed the appropriate diagonal portion of a joystick compared with the 95% confidence intervals for the data of the control subjects (shaded regions). The solid lines in Figures 2 and 3 correspond to the best fits of the equation to the data of the individual patients with RP. The best-fitting values of log tₜ and log ΔLₜ for each patient and control subject, and the corresponding correlation coefficients and standard errors of the estimates are given in Table 2. Of note, the standard errors of the estimates were approximately twice as great for the pulsed-pedestal as for the steady-pedestal paradigm for both the patients with RP and the control subjects, which indicates the greater difficulty of the pulsed-pedestal discrimination task.

For the control subjects, the mean critical duration (log tₜ) for temporal integration was significantly longer (t = 8.59, P < 0.001) for the pulsed-pedestal paradigm (98.3 ms) than for the steady-pedestal paradigm (37.2 ms), in agreement with a previous report. In addition, the mean asymptotic threshold (log ΔLₜ) of the control subjects was significantly higher (t = 7.26, P < 0.001) for the pulsed-pedestal paradigm (0.38 log cd/m²) than for the steady-pedestal paradigm (0.02 log cd/m²), as expected. The control subjects showed a significant correlation between their asymptotic thresholds (log ΔLₜ) for the steady-pedestal paradigm and their log contrast sensitivities (r = −0.83, P < 0.01), but no other correlations between the parameters of temporal integration and foveal visual function were significant. Further, the control subjects showed no significant correlations between the parameters of temporal integration for the two contrast-processing paradigms.

For the patients with RP, the overall pattern of performance was quite different for the steady-pedestal and pulsed-pedestal paradigms. For the steady-pedestal paradigm (Fig. 2), the critical duration (log tₜ) of the patients with RP was significantly longer than that of the control subjects (t = 3.88, P < 0.001).

**Results**

The visual characteristics of the patients with RP are provided in Table 1. There was a statistically significant correlation between their log contrast sensitivities and log minimum angle of resolution (MAR) values (r = −0.75, P < 0.05), as has been reported previously for other patients with RP. Further, there was a significant correlation between the patients’ log contrast sensitivities and their log visual field areas (r = 0.89, P < 0.01), as has been noted previously in patients with RP, although the correlation between log contrast sensitivity and nearest visual field defect was not significant (r = 0.67, P = 0.07). There were no significant correlations between logMAR and either of the two visual field measures (r = −0.68, P = 0.06; and r = −0.41, P = 0.31; for log visual field area and nearest defect, respectively).

Figures 2 and 3 show the temporal integration data obtained with the steady-pedestal and pulsed-pedestal paradigms, respectively, for the individual patients with RP (symbols) compared with the 95% confidence intervals for the data of the control subjects (shaded regions). The solid lines in Figures 2 and 3 correspond to the best fits of the equation to the data of the individual patients with RP. The best-fitting values of log tₜ and log ΔLₜ for each patient and control subject, and the corresponding correlation coefficients and standard errors of the estimates are given in Table 2. Of note, the standard errors of the estimates were approximately twice as great for the pulsed-pedestal as for the steady-pedestal paradigm for both the patients with RP and the control subjects, which indicates the greater difficulty of the pulsed-pedestal discrimination task.

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For the patients with RP, the overall pattern of performance was quite different for the steady-pedestal and pulsed-pedestal paradigms. For the steady-pedestal paradigm (Fig. 2), the critical duration (log tₜ) of the patients with RP was significantly longer than that of the control subjects (t = 3.88, P < 0.001).
In addition, the asymptotic thresholds (log $\Delta L_c$) of the patients with RP were elevated significantly above those of the control subjects ($t = 4.88, P < 0.001$). Further, the patients with RP showed a significant correlation between their values of log $\Delta L_c$ and log $t_c$ ($r = 0.72$, $P < 0.05$), such that the higher the asymptotic threshold, the longer the critical duration. This correlation is indicated by the dashed line in Figure 2, which represents a least-squares bivariate regression line fit to the inflection points of the patients’ temporal integration functions.

For the pulsed-pedestal paradigm (Fig. 3), by comparison, there was no significant difference between the critical durations (log $t_c$) of the patients with RP and control subjects ($t = 0.77$, $P = 0.44$), although the asymptotic thresholds (log $\Delta L_c$) of the patients with RP were significantly higher than those of the control subjects ($t = 4.51$, $P < 0.001$). Further, there was no correlation between the patients’ critical durations and their asymptotic thresholds for the pulsed-pedestal paradigm ($r = -0.37$, $P = 0.36$). Finally, there were no correlations between the parameters for the pulsed-pedestal and steady-pedestal paradigms for either the critical duration ($r = 0.29$, $P = 0.48$) or the asymptotic threshold ($r = 0.40$, $P = 0.32$). Therefore, the properties of temporal integration were quite different for the two paradigms, as would be expected if they are mediated by different contrast-processing streams.

Further differences between the two paradigms of contrast processing were apparent in comparing the parameters of temporal integration with other aspects of the visual function of the patients with RP. For the steady-pedestal paradigm, there were significant correlations between the patients’ asymptotic thresholds at long durations (log $\Delta L_c$) and their log contrast sensitivities ($r = -0.88$, $P < 0.01$), logMAR ($r = 0.90$, $P < 0.01$), and log visual field areas ($r = -0.76$, $P < 0.05$), although the correlation between log $\Delta L_c$ and the nearest visual field defect was not statistically significant ($r = -0.68$, $P = 0.06$). In addition, there were significant correlations between the patients’ log $t_c$ values for the steady-pedestal paradigm and their log contrast sensitivities ($r = -0.73$, $P < 0.05$) and closest visual field defects ($r = -0.83$, $P < 0.05$), although there was no correlation between log $t_c$ and either logMAR ($r = 0.44$, $P = 0.27$) or log visual field area ($r = 0.69$, $P = 0.06$). Thus, these patients with RP showed systematic relationships between the characteristics of temporal integration within the steady-pedestal paradigm and other measures of their visual function.

In comparison to the results for the steady-pedestal paradigm, there were no significant correlations between the patients’ asymptotic thresholds (log $\Delta L_c$) for the pulsed-pedestal paradigm and their log contrast sensitivities ($r = -0.69$, $P = 0.06$), logMAR values ($r = 0.29$, $P = 0.48$), log visual field areas ($r = -0.50$, $P = 0.21$), or nearest visual field defects ($r = -0.38$, $P = 0.36$). Further, there were no significant correlations between the patients’ critical durations (log $t_c$) for the pulsed-pedestal paradigm and their log contrast sensitivities ($r = -0.23$, $P = 0.58$), logMAR ($r = 0.66$, $P = 0.07$), log visual field areas ($r = -0.18$, $P = 0.68$), or nearest visual field defects ($r = -0.18$, $P = 0.67$).
Table 2. Temporal Integration Parameters for the Control Subjects and Patients with RP

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<th>Ctrl</th>
<th>Steady-Pedestal</th>
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<td>0.93</td>
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Mean: τc, critical duration (ms); ΔL∞, asymptotic threshold (cd/m²); r, correlation coefficient; SE, standard error of the estimate; SD, standard deviation.

DISCUSSION

The purpose of this study was to evaluate temporal integration for contrast processing in patients with RP by using two paradigms, steady-pedestal and pulsed-pedestal, that were intended to emphasize the MC and PC pathways, respectively. That is, the relatively long temporal integration time for letter identification in visually normal subjects indicates that thresholds for letter identification are normal in patients with RP. 16

The primary finding was that the properties of temporal integration for the patients were quite different for these two paradigms of contrast processing. First, the patients' critical durations for temporal integration were significantly longer than those of the control subjects for the steady-pedestal paradigm but were not significantly different from normal for the pulsed-pedestal paradigm. Second, there was a significant correlation between the patients’ critical durations and their asymptotic thresholds at long durations for the steady-pedestal paradigm, but not for the pulsed-pedestal paradigm. Third, the patients showed significant correlations between the parameters of temporal integration and other aspects of foveal function for the steady-pedestal paradigm, but not for the pulsed-pedestal paradigm.

The finding that the critical duration of patients with RP was not different from that of the control subjects under conditions that favor the PC pathway is consistent with a previous report that the critical duration for temporal integration for letter identification is normal in patients with RP. 16

That is, the relatively long temporal integration time for letter identification in visually normal subjects indicates that thresholds for letter identification are probably mediated by the PC pathway. It should be noted, however, that the greater errors of the estimates for the best-fit parameters of the pulsed-pedestal functions (Table 2) limit the ability of this paradigm to identify abnormalities in the critical duration for temporal integration.

The patients with RP in this study showed a greater threshold elevation at short durations for the steady-pedestal paradigm than for the pulsed-pedestal paradigm. That is, five of the eight patients with RP had thresholds above the normal limit for the steady-pedestal paradigm at short durations, but only one (patient 5) had elevated thresholds for the pulsed-pedestal paradigm under these conditions. The greater threshold elevations at short durations for the steady-pedestal paradigm confirm those of a previous study in predominantly the same patients, in which different adapting conditions and a single stimulus duration of 30 ms were used. 18 Of note, RP patient 5 had also shown elevated thresholds within the pulsed-pedestal paradigm in the original study of contrast discrimination in RP, using a 30-ms test duration (patient 13 in Ref. 10). Further, this patient showed a pattern of temporal integration in our pilot study that was similar to that shown in Figures 2 and 3, as did another RP patient with a similar level of visual acuity (patient 14 in Ref. 10), suggesting that elevated pulsed-pedestal thresholds at short durations may be characteristic of patients with RP with a more pronounced visual acuity loss.

The relatively greater deficit in contrast processing under conditions that target the MC pathway was attributed in a previous study 10 to a random loss of cone photoreceptors that reduced the summed input to the receptive field centers of MC ganglion cells. Based on the electrophysiological properties of MC ganglion cells, it was suggested that, in turn, would effectively decrease the contrast sensitivity of the affected MC ganglion cells, accounting for the patients’ elevated contrast thresholds. A similar mechanism was proposed recently to account for the overall reductions in temporal contrast sensitivity observed in patients with RP. However, it is difficult to reconcile the increase in the critical duration for the steady-pedestal paradigm observed in the present study with a random loss of cone photoreceptors per se.

A more likely explanation for the present findings is that the differentially elevated contrast thresholds and the prolonged temporal integration of the patients with RP under conditions that favor the MC pathway are due to a selective sensitivity loss at high temporal frequencies, owing to ailing cone photoreceptors. For example, for visually normal subjects, altering the temporal waveform of the stimulus from abrupt onset and offset to a raised cosine temporal profile, thereby effectively low-pass filtering the stimulus, desensitizes the MC pathway but has little effect on PC-pathway sensitivity. Consequently, effective low-pass temporal filtering due to a selective loss of high-frequency sensitivity of abnormal foveal cone photoreceptors could produce the threshold elevation and prolonged critical duration in patients with RP under testing conditions that favor the MC pathway.

In support of this explanation, losses in temporal contrast sensitivity at high temporal frequencies have been noted in some patients with RP. Further, impulse response functions that were derived from foveal temporal contrast sensitivity functions have shown prolonged rise times in patients with RP consistent with a reduction in high-frequency sensitivity and a more sluggish temporal response. Nevertheless, it was reported recently that patients with RP who had visual acuities...
of 20/32 or better showed an overall reduction in temporal contrast sensitivity but no change in the corner frequency, indicating no preferential loss of sensitivity at high temporal frequencies, which casts doubt on the validity of this explanation. However, our results suggest that the apparent discrepancy between these various findings may be due to the degree of focal impairment present in patients with RP. Those patients in our study who had visual acuities of 20/32 or better had critical durations for the steady-pedestal paradigm that were within or just beyond the normal range, in agreement with the normal corner frequencies of the patients with RP examined by Felius and Swanson. Those patients in our study who had a greater visual acuity loss showed a critical duration that was beyond the normal range, consistent with a loss of sensitivity at high temporal frequencies.

Further evidence that the foveal cone photoreceptors in RP may have an abnormal temporal response at high frequencies has been provided by a report of a selective reduction in the amplitude of the focal ERG at high temporal frequencies in patients with RP. Nevertheless, this interpretation has been called into question recently by a report that the flicker ERG of the cone system at high temporal frequencies is primarily the sum of the responses of the depolarizing and hyperpolarizing bipolar cells, with little direct contribution from the cone photoreceptors. However, the shape of the ERG temporal response function at high frequencies is thought to be governed by the response properties of the cone photoreceptors, even though the actual ERG response may be generated primarily by postreceptoral neurons. Therefore, a high-frequency attenuation of the focal ERG may well represent temporal dysfunction at the level of the cone photoreceptors, as originally proposed.

An alternative explanation for a predominant loss of temporal sensitivity at high temporal frequencies in RP is a decreased quanta catch by the foveal cone photoreceptors, resulting from a reduced cone photopigment optical density. Such a reduction in quanta catch is equivalent to a decrease in effective stimulus luminance, which is known to produce a lower corner frequency of the temporal contrast sensitivity function and therefore would produce a longer critical duration for temporal integration. A reduced quanta catch or “dark glasses” model might seem a likely explanation for the present findings, given the histologic reports of shortened cone outer segments, an abnormal Stiles-Crawford effect, reduced foveal cone double densities, and color match abnormalities in patients with RP, all of which are consistent with a reduced quanta catch by the foveal cones, although it should be noted that Swanson and Fish reported no evidence for a reduced quanta catch in patients with RP who have visual acuities of 20/32 or better.

The available evidence indicates, however, that a reduced quanta catch is not likely to be the primary explanation for the differentially elevated contrast thresholds and the prolonged temporal integration shown by the patients with RP in the present study under conditions that emphasize the MC pathway. First, as discussed in a previous study of contrast processing in RP, the steady-pedestal luminance thresholds of patients with RP, measured as a function of pedestal luminance, are inconsistent with a reduced quanta catch model. This model predicts that the patients’ functions for threshold luminance versus pedestal luminance would be translated along a 45° axis, because the effective luminance of both the pedestal and the test stimulus would be reduced in equal proportion. As a consequence, the threshold luminance versus pedestal luminance functions of the patients with RP would join those of the control subjects at the higher pedestal luminances if a reduced quanta catch were the sole explanation for the deficits in contrast processing within the steady-pedestal paradigm.

stead, the threshold luminance versus pedestal luminance functions of the patients with RP were displaced vertically from those of the control subjects at all pedestal luminances. This finding is in agreement with previous studies of increment threshold functions in RP, which have reported that patients’ increment thresholds are displaced vertically from those of control subjects at high luminance levels, contrary to the dark glasses model. Further, the reduction in the amplitude of the focal ERG at high temporal frequencies shown by patients with RP could not be simulated in control subjects by having them view the stimuli through a neutral density filter to mimic a reduced quanta catch. Therefore, although a reduced quanta catch may exist in the foveas of patients with RP, it appears to play at most a minor role in accounting for their deficits in temporal contrast processing.

In conclusion, our results indicate that patients with RP show increases in temporal integration that are greater for conditions that favor the MC pathway rather than the PC pathway. A likely explanation is a high-frequency response attenuation at the level of the cone photoreceptors that effectively low-pass filters transient stimuli, thereby decreasing contrast sensitivity and prolonging the critical duration for temporal integration under conditions that emphasize the MC pathway. An increase in the critical duration for temporal integration may be a way in which the visual systems of patients with RP can partially compensate for a decreased contrast sensitivity, although at the expense of temporal resolution.

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References


