Primate Flicker Sensitivity: Psychophysics and Electrophysiology

Abstract. *A quantitative comparison is made between the psychophysical flicker response of man and similar data obtained electrophysiologically from the cones of macaque monkeys. When the psychophysical data are obtained from an eye that is strongly light-adapted, there is excellent agreement between the two sets of data at high frequencies. Under this condition, both kinds of data fit a distributed-parameter model, whose time constant also agrees with that derived from studies of the phosphenes elicited by electrical stimulation of the human eye. On the other hand, psychophysical data obtained with fully modulated stimuli (which minimally adapt the eye) yield a longer time constant for the same model. These results imply that the psychophysical flicker thresholds are normally controlled by a distributed filtering process that is proximal to the receptor stage. This slower, psychophysical process is evidently desensitized by intense adapting lights, so that the faster one that governs the electrophysiological responses can be detected.*

Such diverse processes as heat conduction, fluid diffusion, and transmission through an electric cable are governed by Fourier's equation (*1*). Appropriate solutions of this differential equation have also been found to describe certain temporal properties of the visual process (*2–4*). The first such model of flicker sensitivity was proposed by Ives (*2*), who speculated that the underlying mechanism might resemble a miniature electric cable. More recently, Veringa imposed boundary conditions that were based on ". . . the diffusion of a transmitter molecule inside the retinal receptor cells," to obtain an exact solution of Fourier's equation (*3*). Finally, Kelly simplified Veringa's solution and tested it against his photopic sine-wave flicker thresholds (*4*). (Although he dropped one of Veringa's boundary conditions, Kelly retained Veringa's "diffusion" terminology.)

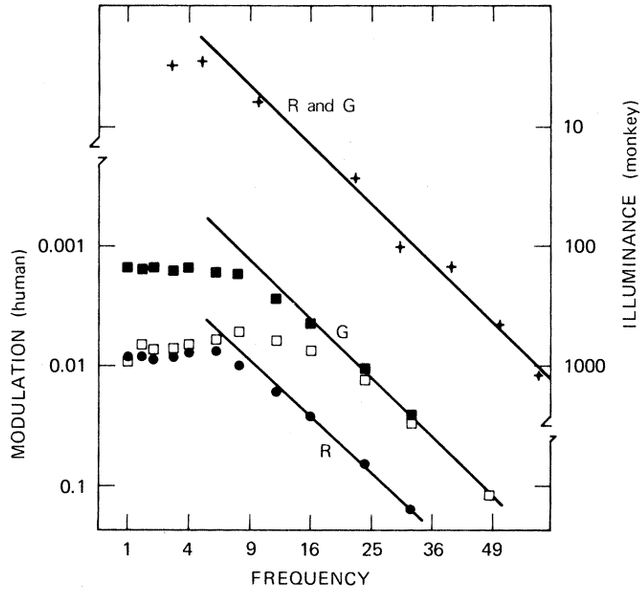
In this report, we need not assume that flicker sensitivity is governed by current flow, transmitter diffusion, or any other specific mechanism. However, our results do obey Kelly's solution of Fourier's equation. The physical constants (for example, loss rate or conductivity) of any such process must be distributed throughout an appreciable region of space [as opposed to, for example, the local, lumped-constant model of Fuortes and Hodgkin (*5*)]. We shall therefore refer to Kelly's theoretical transfer function as the "distributed" model, in order to avoid more speculative connotations.

Measured in terms of the luminous amplitude of the fundamental Fourier component of the stimulus, photopic flicker thresholds lie on a smooth curve of amplitude versus frequency, and this curve is independent of the stimulus waveform (*6*). The same curve also forms the common envelope for all sine-wave flicker thresholds at high frequencies (*7, 8*). If this high-frequency behavior is governed by the distributed model, then the shape of the curve should be given by the exponential square-root function (*4*)

$$G(\omega) \sim \exp(-\sqrt{\omega\tau}) \qquad (1)$$

where G is the amplitude sensitivity, ω is the flicker frequency multiplied by 2π, and τ is the time constant of the distributed filtering process. This envelope function describes the results of three different types of experiments: psychophysical, electrophysiological, and electrical-phosphene [the last is sometimes considered to be an intermediate category between the first two (*9*)].

The time constant of the distributed model has been calculated from each of these types of experiments. The values of τ previously obtained from human psychophysical thresholds were considerably greater than those provided by the other two methods. However, we have produced much better agreement by modifying the psychophysical conditions, which leads us to propose an explanation for the discrepancy.



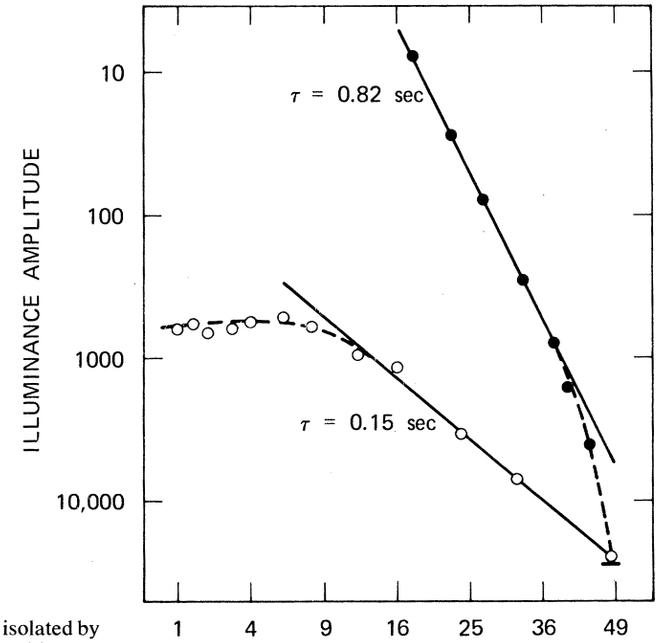


Fig. 1 (left). Flicker-sensitivity curves of red and green cone mechanisms isolated by chromatic adaptation, for the monkey late-receptor potential (crosses) and human thresholds (squares and circles). Data are replotted from figures 5 and 8 of (*14*) and figure 6 of (*15*), in units of the logarithm of the amplitude (trolands) versus the square root of the frequency (hertz). The straight lines fitted to the data are all described by Eq. 1, with $\tau = 0.19 \pm 0.01$. Fig. 2 (right). Achromatic, human, flicker-sensitivity curves, obtained with a constant modulation of 100 percent (closed circles) (the usual method of determining the psychophysical envelope), and with a constant background of 25,000 trolands (open circles). The coordinates are the same as in Fig. 1, but here a counterphase-flickering checkerboard target was used throughout. The short, horizontal bar represents 100 percent modulation at 25,000 trolands.

Kelly fitted the high-frequency envelope of his psychophysical, homochromatic thresholds for 65° and 8° flickering fields by setting $\tau = 0.5$ and 0.74 second, respectively (*4, 10*). Veringa (*3*) obtained a value of 0.37, but his calculation was based on DeLange's 2°, scotopic data.

A much smaller value of τ was obtained in the electrophysiological experiments of Baron and Boynton (*11*), who measured the foveal late receptor potential (LRP) of the cynomolgus macaque monkey. For a criterion response of 10 μv, their amplitude sensitivity envelope also had the exponential square root form but was best fitted by setting $\tau = 0.19$ in Eq. 1. This result implies that the LRP is not attenuated as rapidly at high frequencies as the psychophysical sensitivity.

One interpretation of this discrepancy is that the high-frequency flicker signal encounters another distributed filtering process proximal to the site at which the receptor potential is measured. The electrical-phosphene experiments also tend to confirm this speculation.

Sensations of light (phosphenes) are produced when weak electric currents are passed through the human retina (by placing electrodes on the head) (*12*). By varying the direction of these currents, Brindley (*13*) inferred that the electrical stimulus enters the visual pathways just inside the outer limiting membrane, near the site where receptor cells form synapses with horizontal and bipolar cells.

With an electrical waveform as the comparison stimulus for an optical one, it is possible to measure the amplitude and phase characteristics of the visual pathways as far as the site of the electrical stimulation. (Presumably the system treats the electrical and optical signals alike beyond this point; hence the subsequent pathways do not affect the comparison). In an early experiment of this type, Brindley (*14*) combined luminous, square-wave flicker and short electrical pulses at frequencies between 40 and 120 hertz.

From Brindley's data, Veringa (*15*) derived phase shifts that fitted his diffusion model, with $\tau = 0.19$ second. He also confirmed this result by measuring the amplitudes and phases at which sinusoidal luminous and electrical stimuli cancel each other (*9, 16*). (Phase can be measured more accurately than amplitude in this way, but the phosphene amplitude data are not inconsistent with this value of τ.)

This excellent agreement between the LRP and electrical-phosphene results suggests that electric fields may produce phosphenes by affecting the visual pathways near the site where the receptor potentials are measured [in the neighborhood hypothesized by Brindley (*13*) on the basis of his phosphene-pattern experiments].

These results raise an important question: Why is the time constant that governs the psychophysical envelope so much slower than the one revealed by electrical phosphenes and receptor potentials? We have found that this difference is not always present but can be eliminated under certain conditions.

In order to isolate the characteristics of the red-sensitive and green-sensitive cone mechanisms, Kelly (*17*) measured flicker thresholds for red and green stimuli superimposed on intense blue-green and purple backgrounds. Boynton and Baron (*18*) conducted a similar experiment using a criterion response of the macaque LRP and compared their results to Kelly's. Values of τ were not calculated in either study, but similarly shaped curves were obtained in both (*18*). We therefore examined the relevant data from both studies in order to determine whether they obey the distributed model and, if so, to determine the value of τ on which the heterochromatic human thresholds and monkey receptor potentials agree.

This time constant is readily deduced by plotting the logarithm of the threshold amplitude against the square root of the stimulus frequency. If the data obey Eq. 1, they will fall on a straight line whose slope is proportional to $\sqrt{\tau}$. The heterochromatic data from both psychophysical (*17*) and electrophysiological (*18*) experiments are plotted on the appropriate scales in Fig. 1, which shows that the psychophysical slope was the one that changed (the electrophysiological data still gave $\tau = 0.19$). Kelly's red curve is fitted by $\tau = 0.18$ and his green curve by $\tau = 0.20$. Thus, under these conditions, the psychophysical data also yield a flatter slope (a shorter time constant) similar to that obtained from the electrical-phosphene and LRP results.

The slower process that limits the homochromatic envelope is probably not a result of interaction between the red and green mechanisms, because the same low value of τ can be obtained psychophysically without heterochromatic stimulation, simply by adapting the retina to a bright, constant background. Thus our results support the suggestion of Baron and Boynton (*11*) that the unadapted psychophysical thresholds are governed by a later stage in the visual system rather than by the receptors.

As Kelly (*19*) has shown, the linear behavior of the high-frequency, homochromatic amplitude threshold (ΔB) gives way to a constant modulation ($\Delta B/B$) as the adaptation level increases (*20*). The same behavior occurs under heterochromatic conditions, which implies that the color mechanism being stimulated has a modulation sensitivity curve of fixed shape (*17*) (otherwise, the desired characteristic could not be isolated). Thus, in order to determine the shape of each flicker-sensitivity curve in the heterochromatic, psychophysical experiments, the retina was always adapted to an intense background; this adaptation evidently caused the decrease in the high-frequency slope.

Figure 2 shows two flicker-sensitivity functions measured in white light, with the same subject, the same pattern (a diagonal checkerboard of 30′ diamonds), a 10° field, and a 2.3-mm artificial pupil. Both are plotted in terms of ΔB, but in one case the adaptation level was constant at 25,000 trolands, and in the other it was proportional to ΔB.

At frequencies greater than 40 hertz, even these fully modulated thresholds depart from the exponential square-root asymptote. This occurs only at very high adaptation levels (*21*), where Weber's law is obeyed even at high flicker frequencies (*17, 19*). The two sets of data in Fig. 2 must intersect at the point where $B = 25{,}000$ trolands at 100 percent modulation, because the two stimuli are identical there.

At frequencies between 10 and 40 hertz, both curves are well fitted by the exponential square-root function, with time constants of 0.82 second for the fully modulated envelope and 0.15 second for the constant-background curve. Since the former is in reasonably good agreement with Kelly's homochromatic data (*10*) and the latter with the various heterochromatic data of Fig. 1, the change of slope in Fig. 2 fully accounts for the difference between the two. Thus any background (homochromatic or heterochromatic) that is intense enough to desensitize the slower process governing the psychophysical envelope will reveal the faster process that is shown by the electrical-phosphene and LRP data at much lower adaptation levels.

In this context, the terms "faster" and "slower" refer only to the time constants that control the slopes of the flicker curves and not to the critical flicker frequency (CFF) under these conditions. If the two curves are equated at zero frequency (as is customary in comparing the bandwidths of different low-pass filters), then the faster time constant corre-

sponds to the higher cut-off frequency at any flicker amplitude. But in the actual measurements, it is only because the slower process is psychophysically more sensitive than the faster one that both can be detected by appropriate manipulations. Thus, at a fixed amplitude in Fig. 2 (for example, 1000 trolands), the cut-off frequency for the adapted condition is much lower than in the fully modulated condition.

However, the slower, unadapted process that governs all the classical flicker thresholds (*6*) never appears in the LRP or electrical-phosphene data. Our results support the explanation that this psychophysical flicker envelope represents a further stage of temporal filtering proximal to the photoreceptors. Both of these stages seem to be controlled by some type of distributed filter mechanism.

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20. Linearity requires the amplitude response (ΔB) to be independent of the background (B). Therefore, Weber's law ($\Delta B \sim B$) is a form of nonlinearity.
21. Part of this loss of sensitivity can be attributed to the bleaching of cone pigments. W. A. H. Rushton and G. H. Henry [*Vision Res.* **8**, 617 (1968)] found a half-bleach constant of 20,000 trolands, which would displace the 48-hertz point below the upper solid line in Fig. 2 by a factor of about 2.2. The remainder of the loss must involve other adaptive effects that also obey Weber's law (*17*).
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Time-Dependent Disruption of Morphine Tolerance by Electroconvulsive Shock and Frontal Cortical Stimulation

Abstract. *Electroconvulsive shock or frontal cortex stimulation administered to rats at 5 but not at 180 minutes after an initial administration of morphine sulfate disrupted the development of one-trial tolerance to the analgesic effects of morphine sulfate. It is suggested that development of tolerance may be mediated by cellular mechanisms and memory processes similar to those thought to underlie conventional learning.*

A number of investigators (*1*) have suggested that tolerance to morphine may represent a form of learning which may be mediated by memory processes and cellular mechanisms similar to those underlying conventional learning. Support for this position comes from a series of studies showing that protein synthesis inhibitors attenuate or abolish not only retention of a number of learning experiences, but also tolerance to morphine as revealed in tests for analgesia (*2*).

One presumed characteristic of memory is that a consolidation process is required for efficient storage of newly acquired experiences. This consolidation process is inferred from studies demonstrating that specific treatments such as electroconvulsive shock (ECS) or discrete brain stimulation are capable of producing a time-dependent disruption in long-term retention of recent experiences (*3*). In other words, an ECS treatment is capable of disrupting long-term retention when applied immediately after a learning experience, but becomes increasingly ineffective when delayed a few minutes or a few hours. Thus, the present study examined the possibility that the development of tolerance to analgesic effects of morphine is also mediated by time-dependent processes (perhaps similar to consolidation), by administering ECS immediately, or after various delays, subsequent to an initial morphine experience. We found that ECS or frontal cortex stimulation treatments can, on a time-dependent basis, disrupt the development of morphine tolerance.

Since previous research (*4*) has demonstrated that morphine tolerance can develop following a single dose (one-trial), it was possible in the present study to examine the effects of ECS on the temporal course of tolerance development. Fifty-eight male Long-Evans rats were divided into seven groups. All experimental groups received initial injections of saline or morphine sulfate (30 mg/kg, intraperitoneally). The initial dose of 30 mg/kg was selected because in our laboratory it represented the threshold dose above which there was a high incidence of mortality. Forty-eight hours later animals received injections of saline or morphine sulfate (15 mg/kg, intraperitoneally), followed 30 minutes later by a standard test of analgesia (*5*). The morphine test dose of 15 mg/kg was selected because at that level the greatest difference in responsiveness to shock (analgesic test) was found between saline- and morphine-injected animals. This difference was not as pronounced at other morphine dose levels.

The first group (N = 8, M-M) received the initial morphine (30 mg/kg) injections followed 48 hours later by the second morphine injection (15 mg/kg). The second group (N = 8, S-M) was injected with saline followed 48 hours later by morphine. The third (N = 8), fourth (N = 8), and fifth (N = 8) groups (M-ECS-M) received initially morphine followed either 5, 60, or 180 minutes later by an ECS (35 ma, 0.5 second duration) treatment administered through earclips attached to the pinnae. The sixth group (N = 10, ECS-M-M) received an ECS treatment 5 minutes prior to the initial morphine injection. Forty-eight hours later, the third, fourth, fifth and sixth groups of animals received the second injection of morphine (15 mg/kg). The last group (N = 8, S-S) received two injections of saline spaced 48 hours apart.

Thirty minutes after the second injection all animals were given a shock threshold test to determine their sensitivity to pain. Each animal was introduced and adapted for 1 minute to a small box with a grid floor. After the adaptation period, foot shocks (starting with 0.1 ma intensity) were delivered in ascending order of shock intensity until jump and squeal responses were observed for three consecutive foot shocks or until a 10 ma intensity was reached. Shocks were delivered via a constant current scrambler for 0.5 second; pulse repetition rate was 200 hertz and 4 msec pulse duration. From 0.1 to 1.0 ma successive test shocks were increased by 0.1 ma, and from 1.0 to 10 ma by 0.2 ma. The intershock interval was approximately 6 seconds, but shocks were delivered only when the animal was making contact with the grid floor with all four paws. The behavioral responses to each shock