

dysphoric effects was reported by four subjects 20 to 30 minutes after the 25-mg intravenous dose, and by two subjects 45 to 60 minutes after the 100-mg intranasal dose. This dysphoria, referred to as "post-coke blues" or "crashing," was characterized by feelings of anxiety, depression, fatigue, and wanting more cocaine.

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References and Notes

- Accurate estimates of nonmedical use of cocaine are very difficult to obtain. In a 1971 survey of 56,745 students in the 7th through 12th grades in Dallas, Texas, 2108 or 4 percent reported having used cocaine, with 1250 acknowledging that they had used it at least one time during the week the questionnaire was given [J. T. Gossett, J. M. Lewis, V. A. Phillips, *J. Am. Med. Assoc.* **216**, 1464 (1971)]. In 1973 the National Commission on Marihuana and Drug Abuse estimated that nationwide use of cocaine was 3.2 percent for adults and 1.5 percent for youth. A recent national survey estimates that cocaine use among youths 12 to 17 years old doubled between 1972 and 1974 [H. I. Abelson and R. B. Atkinson, *Public Experience with Psychoactive Substances: A Nationwide Study Among Adults and Youth* (Response Analysis Corporation, Princeton, N.J., August 1975)]. A nationwide study in 1974 of a representative sample of men aged 20 to 30 years found that 12 percent of those who live in cities with populations of a million or more reported using cocaine within the preceding year [J. A. O'Donnell, H. L. Voss, R. B. Clayton, G. T. Slatin, R. G. W. Room, *Young Men and Drugs—A Nationwide Survey* (NIDA Research Monograph 5, National Institute on Drug Abuse, Rockville, Md., 1976)].
- There is a report of clinical and cardiovascular responses of cocaine infusions given to patients hospitalized for depression [R. M. Post, J. Kotin, F. K. Goodwin, *Am. J. Psychiatry* **131**, 511 (1974)].
- A report comparing cardiovascular and subjective effects of intravenous cocaine and dextroamphetamine appeared after submission of the present report [M. W. Fischman, C. R. Schuster, L. Resnekov, J. F. Shick, N. A. Krasnegor, W. Fennell, D. X. Freedman, *Arch. Gen. Psychiatry* **33**, 983 (1976)].
- J. M. Ritchie and P. J. Cohen, in *The Pharmacological Basis of Therapeutics*, L. S. Goodman and A. Gilman, Eds. (Macmillan, New York, 1975), p. 379.
- E. H. Hill, C. A. Haertzen, A. B. Wolbach, E. J. Miner, *Psychopharmacologia* **4**, 184 (1963).
- The initial four subjects were run under single-blind and the remainder under double-blind conditions.
- The largest effects for an individual subject were as follows. At a dose of 10 mg, one subject's heart rate increased from 70 to 135 beats per minute and another subject's blood pressure rose from 114/68 to 142/116 mm-Hg. At 25 mg, one subject's heart rate rose from 66 to 156 beats per minute and another's blood pressure increased from 114/78 to 176/140 mm-Hg.
- Plasma levels of cocaine appear to reach peak concentration at 60 minutes following application to nasal mucosa according to C. Van Dyke, P. G. Barash, P. Jatlow, and R. Byck [*Science* **191**, 859 (1976)].
- These nine items were more frequently rated "true" for higher doses and for the intravenous route of administration.
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Rod Photoreceptors Detect Rapid Flicker

Abstract. *It is widely believed that human rods cannot detect rapid flicker. With rod-isolation techniques, however, light-adapted rods detect flicker frequencies as high as 28 hertz, and the function relating rod critical flicker frequency to stimulus intensity contains two distinct branches. Human rod vision may, therefore, depend on two independent mechanisms.*

Human vision is mediated by cone receptors in bright light and by rod receptors in dim light (1). Because of this, psychophysical measures of temporal resolution contain two distinct regions (2). At low, rod intensities, the maximum frequency of visible flicker (or critical flicker frequency, CFF) increases with stimulus intensity, so that observers can see higher frequencies as the flickering stimulus is made brighter. This improvement in resolution terminates in a plateau at about 15 hertz, however, and unless the light stimulates cones, further increases in intensity do not affect CFF. At high, cone intensities, temporal resolution improves again, and cones can detect flicker frequencies above 50 hertz when the stimulus is very bright (3).

This suggests that rods achieve their special sensitivity at the price of a sluggish response; that although rods can see dim light, they cannot see rapid flicker (above 15 hertz). The rod response does not stop when cones become active, however; rather it continues, concealed from measurement by the larger cone response. Using techniques that desensitize cones and reveal rod responses (4), we have measured rod CFF at high intensities. Contrary to popular belief, rods can detect rapid flicker.

Our experiments required bright, spectrally pure stimuli; these were provided

by a 900-watt xenon arc lamp. The test stimulus, which flickered sinusoidally, was a short-wavelength disk seen in Maxwellian view (5). It subtended 9° of visual angle and was centered on a deep red (670 nm), 13° background, which was located on the temporal retina, 16° from the fovea (6). The test light (but not the background) was obliquely incident on the retina.

These experimental conditions enhanced the rod response in several ways. First, rods are very sensitive to short-wavelength light, but cones are not; the spectral composition of the flickering field, therefore, helped rods and hindered cones. Second, cones are relatively sensitive to red light, but rods are not; the red background, therefore, reduced the modulation depth of the stimulus, as seen by cones, without much affecting its appearance for rods (7). Third, rods outnumber cones in the retinal periphery, and they integrate their signals over large areas; the location and size of the stimuli, therefore, facilitated rod detection of the flickering field. Fourth, rods are highly sensitive to obliquely incident light, but cones are not (see below).

Observers adjusted the frequency of the flickering stimulus to determine the highest frequency (CFF) that was visible at each of many intensities (Fig. 1A, open symbols). As expected at low in-

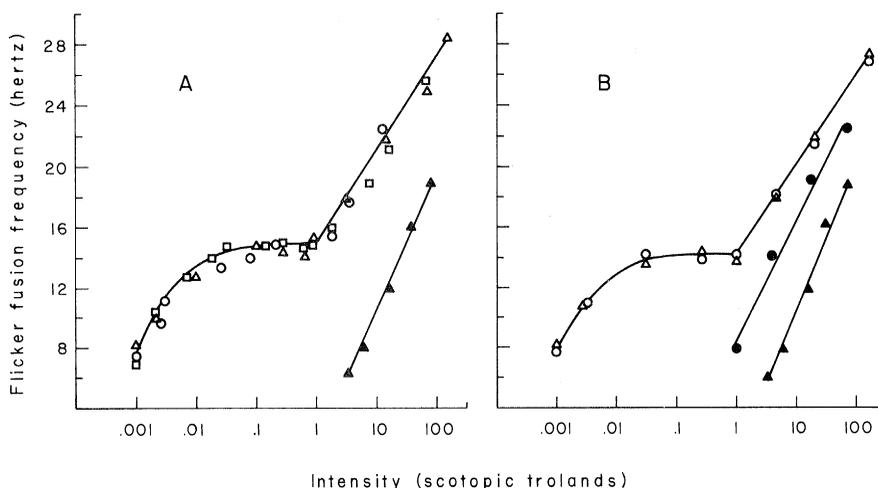


Fig. 1. Critical flicker frequency versus stimulus intensity. (A) Settings obtained either after complete dark adaptation and with a test stimulus of 430 nm (open squares), 469 nm (open triangles), or 520 nm (open circles), or during the cone plateau phase of dark adaptation and with a test stimulus of 469 nm (closed triangles). (B) Settings made after complete dark adaptation (open symbols) and during the cone plateau phase (closed symbols) for a 469 nm stimulus, which struck the photoreceptors either axially (circles) or obliquely (triangles).

tensities, when CFF had increased to 15 hertz, further intensity increases (by as much as 30-fold) did not change CFF. However, at higher intensities, previously uninvestigated for rods, the 15-hertz limit was easily surpassed, and CFF rose sharply with increasing intensity (8). Although our experimental conditions were chosen to isolate rod responses, this high-intensity improvement in temporal resolution is more consistent with the behavior of cones than with current beliefs about the behavior of rods. Our efforts to isolate rod responses at high intensities, then, might have failed. In order to examine this possibility, we conducted three additional experiments, which determined the roles of rods and cones in the first experiment.

1) Since the spectral sensitivity functions of rods and cones are different, a pair of lights that affect rods equally will not affect cones equally. Therefore, CFF settings obtained with rod-equated stimuli (stimuli that have an equal effect on rods) will be independent of wavelength only if the flicker is detected by rods. As the CFF functions from experiment 1 (Fig. 1A, open symbols) have the same shape and overlap completely, the visual mechanism operating must have the spectral sensitivity of rods.

2) An extremely bright light bleaches a large fraction of visual pigment and reduces visual sensitivity during the period following the bleach. Although cones regain their sensitivity in about 5 minutes, rods require about 30 minutes to recover. Thus, there is an interval (the cone plateau) bounded by the full recovery of cones from bleaching and the later recovery of the rods. If cones detected the flickering light in the first experiment, observers would make identical CFF settings during the cone plateau before the rods had recovered from being bleached. After a 30-second exposure to a bleaching light (9), observers made CFF settings for many stimulus intensities. Settings made on the cone plateau (Fig. 1A, closed triangles) are lower at every intensity than those obtained in the first experiment. Therefore, the visual mechanism responsible for the two-branched curve does not have the dark-adaptation properties of cones.

3) Cone thresholds are higher for obliquely incident light than for light which strikes them axially, but rod

thresholds are independent of the angle of incident light (10). If flicker is detected by rods, therefore, CFF settings obtained with axially and obliquely incident light will be the same. If cones detect the flicker, however, the CFF settings obtained with oblique light will be lower than those obtained with axial light. Figure 1B compares CFF settings made with axial and oblique light (11). During the cone plateau, as expected, CFF settings with oblique light (filled triangles) were lower than those with axial light (filled circles). Settings made when the observer was fully recovered from the bleaching exposure, however, were the same for oblique and axial stimuli (open symbols). Therefore, the visual mechanism responsible for the two-branched CFF curve lacks directional sensitivity.

Thus, under the special conditions described here, we find that the function relating CFF to luminance contains three sections: (i) a rising, low-intensity branch; (ii) a moderate-intensity plateau; and (iii) a rising, high-intensity branch, which extends to high frequencies. The photoreceptors responsible for these data have the spectral sensitivity of rods, the dark-adaptation properties of rods, and the directional-sensitivity properties of rods. We conclude, therefore, that these photoreceptors are indeed rods, whose temporal properties change abruptly at high luminances, permitting the detection of rapid flicker.

Green and Siegel (12) reached a similar conclusion in a study of CFF in the allrod skate retina. After prolonged exposure to a flickering stimulus, the skate CFF function contains a low-intensity branch, a short plateau, and a high-intensity branch rising to 30 hertz. Green and Siegel's results and ours have serious implications for comparative studies of vision: a two-branched CFF function does not establish the presence of both rods and cones.

Our results, showing that the temporal properties of human rods change at high intensities, contradict the common generalization that rods are sluggish, for, at high intensities, the response of human rods is comparatively brisk. The nature of the changes that allow rods to see rapid flicker are unknown, but they may reflect either of two retinal properties. (i) Rod vision may be mediated, as is widely believed, by a single mechanism, and the temporal properties of this mechanism

may change abruptly at high luminances. (ii) Rod vision may be mediated by two independent systems: one which responds sluggishly and in dim light, and another which responds briskly and in bright light.

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2. S. Hecht and S. Shlaer, *J. Gen. Physiol.* **19**, 965 (1936).
3. These frequencies (15 and 50 hertz) are approximate; they vary with stimulus intensity, modulation depth, size, and location.
4. For a discussion of rod-isolation techniques, see M. Aguilar and W. S. Stiles, *Optica Acta* **1**, 59 (1954).
5. Maxwellian view stimulators are discussed by R. M. Boynton in *Experimental Methods and Instrumentation in Psychology*, J. B. Sidowski, Ed. (McGraw-Hill, New York, 1966), p. 273.
6. Spectral stimuli were produced using high-quality interference filters (half power bandwidth \approx 7 nm). Retinal illuminances were calculated from radiometric measures made with radiometer/photometer (EG&G model 450-1). Sinusoidal flicker was obtained by passing the test beam through a fixed polarizer and a rotating analyzer, whose motion was controlled by an electric motor (Minarik TR9020U) equipped with feedback speed regulation. Flicker frequencies were calibrated with a frequency meter and an oscilloscope. The modulation depth of the stimulus (flickering stimulus plus steady background), as seen by rods, was 85 percent. The intensity of the steady background was a fixed fraction of the flickering stimulus intensity.
7. We refer to relative sensitivities; the spectral sensitivities of rods and cones are such that when the modulation depth of the stimulus is 85 percent for rods, it is only about 1 percent in photopic luminance.
8. The shape of the CFF function depends on many parameters (3). If stimulus modulation depth is low, the plateau occurs at frequencies less than 15 hertz. At illuminances approaching 1000 scotopic trolands, the second, high-frequency branch is followed by a dip. That is, CFF decreases with further increases in intensity. We attribute this to rod saturation. Also, the CFF function develops a third branch, from cones, at very high intensities, but these cone branches have been omitted from Fig. 1 for clarity.
9. The bleaching light produced about 7.6 log troland-seconds of light and produced a cone plateau that lasted about 5 minutes.
10. M. H. Pirenne, in *The Eye*, H. Davson, Ed. (Academic Press, New York, 1962), vol. 2, p. 31. Rods exhibit a very small loss in sensitivity for very oblique stimuli, but with our stimuli this was not noticeable. [See J. A. Van Loo, Jr., and J. M. Enoch, *Vision Res.* **15**, 1065 (1975).]
11. The flickering test beam was focused to form a compact image of the source in the plane of the observer's pupil. When this image was centered in the pupil, the light would strike the receptors axially; when the image was focused near the pupil's margin, the light would strike the receptors obliquely.
12. D. Green and I. Siegel, *Science* **188**, 1120 (1975). Electrophysiological evidence that rods follow rapid flicker has also been obtained in other animals, for instance in the cat [C. Enroth-Cugell and R. M. Shapley, *J. Physiol.* **233**, 271 (1973)].
13. This work was supported by NIH grant EY 01711 and by the Center for Human Information Processing.

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