Microsecond Sensitivity of the Human Visual System to Irregular Flicker

Abstract. *A flickering light presented to the eye produces a small alternating voltage at the scalp of a subject. This alternating voltage indicates the following response of the brain to the flicker. If every other flash in the flicker is displaced temporally by as little as 30 microseconds, an asymmetry appears in the brain's alternating voltage. The results suggest an underlying mechanism that may enhance visual detection of high-frequency flicker.*

The alternating voltage produced at a subject's scalp by a viewed light flickering at more than 7 Hz is termed the steady-state evoked potential (EP). According to Regan (*1*), a property of the steady-state EP is that no individual cycle in the EP alternating response can be associated with a particular stimulus cycle, that is, a particular flash. However, results from Diamond (*2*) suggest that such an association can be made. These experiments were designed to explore this possibility.

The experimental design was based on an asynchrony in the flickering light: every other flash was displaced temporally by a small amount. If stimulus-response (S-R) association existed, the asynchronous flash would be expected to produce an associated asynchrony, or irregularity, in the EP response. An associated irregularity did appear in the EP, an irregularity that could be produced by a flash displacement as small as 30 μsec.

The subject binocularly viewed a flickering circular test screen 6.2° (visual angle) in diameter and backlighted by flashes each 9 μsec in duration (half-wave width). The EP recordings were made with an electrode (Beckman) from the midline occipital scalp 2 cm above the inion, with a reference electrode clipped to the right earlobe and a ground electrode to the left earlobe. Scalp potentials, amplified by an electroencephalograph (EEG) (Schonander), were averaged from 128 successive sweeps of an averaging computer (Fabritek 1070). Each sweep of the averager sampled 128 msec of the EP response following a flash. Signals below 3 Hz and above 700 Hz were attenuated at least 3 dB by amplifier filters.

Light flashes were produced by a photostimulator (Grass) triggered externally by an interval timer with a range of 1 μsec to 999 seconds. Random fluctuation in the average of the 512 flashes (required to produce one averaged EP record) was less than 2 μsec in timing and 3 percent in luminance. These fluctuations were shown to have no systematic effect on the averaged EP record in a control experiment (Fig. 1f). Although flash luminance changed systematically with inter-flash interval (IFI), such luminance change was shown in control experiments to have a negligible effect on the phenomena studied.

Since the subject's visual sensitivity affected the EP, a stimulation-adaptation cycle was established during data collection. This cycle consisted of stimulation by a flicker train of a maximum of 512 flashes followed by a steady adapting illumination from a tungsten bulb operated at 43 V, 1.53 A (d-c), which backlighted the test screen for 35 seconds. The luminance of the flicker, measured at 20 Hz (close to flicker fusion frequency), was 53.2 cd/m^2; that of the adapting light, 15.3 cd/m^2; and that of a dim, steady surround, 0.17 cd/m^2 (approximately 20° square and used to minimize the effects of light scatter in the eye).

Since Jeffreys (*3*) has reported differences in the EP to stimulation of the upper and lower retina, the subject was instructed to fixate a small black point 1.6° below the upper border of the test circle along a vertical radius. Of the six subjects tested, four were male and two were female; all had normal or corrected vision and viewed the flicker through natural pupils. The results described in Fig. 1 for subjects A.D. and C.W. (one male and the other female) are representative of all six subjects unless otherwise stated.

In experiment 1, which investigated S-R association, the light was flickered in such a way that the time intervals between the successive flashes alternated between 40 and 47 msec. Thus, starting with the first flash, if successive flashes were designated A, B, $\underline{A}$, . . . and so forth, the time interval, $\overline{AB}$ (between A and B) was 40 msec, the next time interval $\overline{BA}$ was 47 msec, the next, $\overline{AB}$, 40 msec and so forth. Of the two flashes, only flash A was used to trigger the sweeps of the signal averager. In this manner, a flash A is always located at 0 on the sweep duration axis (Fig. 1). The A was thus a constant temporal reference for any change in the EP.

The alternation of the time intervals in the flicker, between 40 msec ($\overline{AB}$) and 47 msec ($\overline{BA}$), produced alternating small and large areas under the EP curve (small-large alternations) (Fig. 1, a and b). In Fig. 1a, if we consider the area bounded by the EP curve and the dashed lines, the area between negative peaks N_1 and N_2 is smaller than that between N_2 and $\underline{N_3}$. Furthermore, if the time intervals $\overline{AB}$ and $\overline{BA}$ are reversed in duration, the small and large areas included between the two sets of negative peaks are also reversed (Fig. 1b). Although from these data alone it cannot be determined which stimulus interval is associated with which EP area, an association exists between stimulus interval and EP area. An S-R association thus apparently exists in the steady-state EP, at least for the experimental conditions studied.

In experiment 2, intended as a control test of this S-R association, six subjects were asked to view a regularly spaced, flickering light in which intervals did not alternate. With no alternation in the flicker, none was expected in the EP. Nevertheless, for three subjects, the alternation still appeared in the EP (*4*). This result now appeared to refute an S-R association hypothesis.

Experiment 3 showed, however, that of critical importance was the fact that flash A was always the first flash of the entire 512 flash-flicker train. That is, if B was made the first flash of the train, the EP alternation was reversed (in the same manner as from curve a to curve b in Fig. 1).

These control results suggested that an asynchronous interval still existed in our "regularly spaced" flicker and furthermore, that this interval was somehow related to the first flash of the flicker train. In our experiments, an intertrain interval of 35 seconds preceded each flicker train and, of course, its first flash. Possibly the intertrain interval could have had the effect of a greatly increased IFI or an asynchrony occurring once in 512 flashes. To test this hypothesis, in experiment 4 I presented a regularly spaced 32-flash train with a 47-msec IFI to six subjects. (I used 32 flashes rather than 512 because most subjects had difficulty suppressing blinks for the longer train.) The intertrain interval was 122 msec. In two separate conditions, the first flash of the train following the 122-msec interval was either A or B, respectively.

The alternation occurred again in the EP and reversed when the first flash following the intertrain interval was changed from A to B (Fig. 1, c and d). It seems, then, that whether an asynchrony occurred in flicker every 2, 32, or 512 flashes (*5*) (or whether we term the asynchronous interval an IFI or an intertrain interval), the asynchrony could establish an alternation in the EP. In addi-

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tion, the order in which the alternation occurred was related to the first flash of the flicker train following the asynchronous interval. For flicker trains in which the asynchronous interval occurs only once in every 32 or 512 flashes, the alternation is possibly sustained by a type of resonance similar to that already noted in the steady-state EP (*6*).

A useful control procedure resulted from experiment 4. During flicker, an eye blink may occlude more than 100 msec of flashes and thereby reverse the alternation by randomly introducing an asynchronous interval into the flicker. But, with frequent interjection of an increased interval into the flicker, and always before the same flash (A for example), one can repeatedly reset the EP alternation to the flash that began the train.

The results to this point thus seemed to support the possibility of an S-R association in the steady-state EP. In the testing of this hypothesis, however, it was found that a 32-second or 122- or 7-msec asynchrony in flicker established the small-large alternation. It then became of interest to determine the smallest asynchrony capable of establishing EP alternation. Experiment 5 was conducted with a procedure similar to that of experiment 1. A basic flicker of 40-msec IFI was used. The time interval $\overline{AB}$ was then minimally increased until an area alternation appeared in the EP (as in Fig. 1a). Next, $\overline{AB}$ was minimally decreased until the reverse area alternation occurred (as in Fig. 1b). This reverse in alternation was produced twice for all six subjects. As a measure of the extent of area reversal in the EP, the difference between the two EP curves, resulting from the minimal reversal in $\overline{AB}$, was computed (Fig. 1e). For a control comparison, a similar difference curve was computed from the arithmetic difference of the two EP curves produced when the same value of $\overline{AB}$ was simply repeated (Fig. 1f). Blinks were also compensated for, as before, by the interjection every 32 flashes of an interval 2 msec longer than the IFI.

The minimum change necessary in $\overline{AB}$ to produce a measurable and consistent change in EP alternation was surprisingly small: between 30 and 90 μsec for the six subjects (*7*). Not surprisingly, none of the subjects reported any changes in their perception of the flicker.

Apparently a temporal irregularity in flicker as small as 30 μsec can establish an alternation between large and small EP's. The temporal acuity of the visual system might thus be enhanced when the system reacts mainly to every other flash, thus effectively doubling the detectable frequency. Indeed, perceptual research (*8*) indicates that for very rapid flicker, subjects report seeing fewer flashes than are actually in the flicker.

If this temporal acuity hypothesis is correct, the small-large EP alternation should occur more to the faster than to the slower frequencies, and therefore, more to the shorter IFI's. To test this hypothesis, in experiment 6 the EP was measured to a regular flash train alternating with a 35-sec intertrain interval. The first flash of each train was varied from A to B, as was the IFI from 40 to 85 msec. Blinks were also compensated for with the interjection into the flicker of an increased interval (75 msec longer than the IFI) every 32 flashes, always preceding the same flash that began the flash train (A or B).

Each curve plotted in Fig. 1g is similar to that which would result from the arithmetic subtraction of curve d from curve c in Fig. 1. Such a difference curve indicates the amount of change (reversal) in the EP alternation resulting from a change in the first flash (A to B) of the flicker train. If there is little EP alternation, as hypothesized for the long IFI's, the first flash would have no effect, and the difference curve would be relatively flat. Since for all subjects the EP amplitude increased with an increase in IFI (a factor of 1.6 for A.D. and 1.7 for C.W.), the difference curves are plotted as a percentage of the EP amplitude at each IFI.

The flattest difference curves are at the two longest IFI's (Fig. 1g). Thus, an asynchrony in the flicker has the least effect at the slower flicker frequencies and the greatest effect at the faster frequencies.

An asynchrony in flickering light can thus establish an associated asymmetry

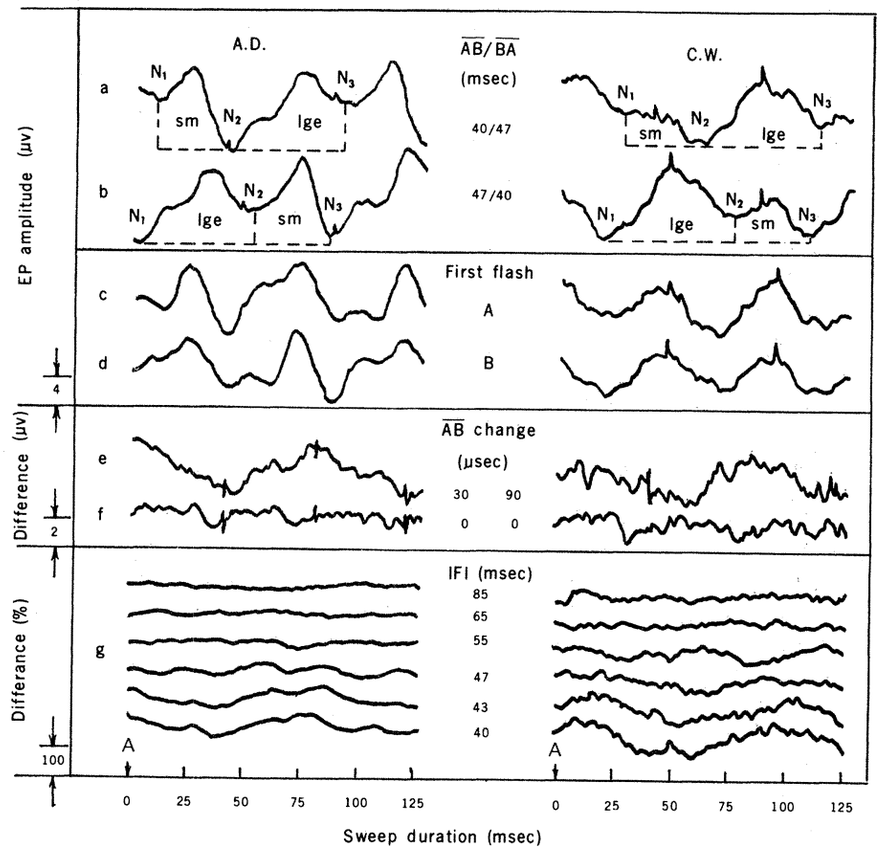

Fig. 1. Steady-state response curves to flickering light, averaged over a 128-msec sweep duration of an averaging computer, for two subjects (*A.D.* and *C.W.*). Curves are positive up. Small pips are flash artifacts. (a) The alternation in area between large and small under the EP curve resulting from a 40- to 47-msec alternation in IFI, $\overline{AB}$ to $\overline{BA}$. The small EP area is included between negative peaks N_1 and N_2, the large area between N_2 and N_3. (b) These areas reverse when the $\overline{AB}$–$\overline{BA}$ alternation is reversed. (c and d) A reversal in the EP area alternation is also associated with a change, from A to B, in the first flash of the entire flicker train. (e) Difference produced in the EP curve by a minimal change in the flicker interval $\overline{AB}$. (f) Difference control. (g) For different IFI's, the percentage change produced in the EP curve by a change in the first flash from A to B. (The curve at 47-msec IFI was calculated from the difference between curves c and d.) Each difference curve is expressed as a percentage of the largest peak-to-peak amplitude at each IFI. A flat difference curve suggests minimal EP alternation relative to the EP amplitude.

in the EP response to the flicker. This EP asymmetry is measured as an alternating large and small area under the EP curve. It is greater for the faster than for the slower flicker frequencies and may thereby enhance visual detection of high-frequency flicker. This apparent enhancement mechanism is sensitive to as little as 30-μsec change in the flicker asynchrony.

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References and Notes

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5. For subject A.D., an increased interval was introduced every 2, 4, 8, 16, 32, 128, or 256 flashes, with the alternation consistently associated with the asynchrony regardless of the number of flashes in the flicker train.
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7. As measured in two subjects, A.D. and C.W., this microsecond sensitivity holds for a twofold change in the light-adapting luminance, as well as for a change in visual fixation to the center of the test field. Fixation near the lower border significantly reduces both this sensitivity and EP amplitude. An alternation in luminance between successive flashes has less than one-tenth the effect on the EP as the alternation in duration of the IFI does.
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Phase Advance of the Circadian Sleep-Wake Cycle as an Antidepressant

Abstract. *Sleep in depressed patients resembles sleep in normal subjects whose circadian rhythms of temperature and rapid-eye-movement sleep are phase-advanced (shifted earlier) relative to their sleep schedules. If this analogy is relevant to the pathophysiology of depressive illness, advancing the time of sleep and awakening should temporarily compensate for the abnormal timing of depressed patients' circadian rhythms. Four of seven manic-depressive patients studied longitudinally spontaneously advanced their times of awakening (activity onset) as they emerged from the depressive phase of their illness. In a phase-shift experiment, a depressed manic-depressive woman was twice brought out of depression for 2 weeks by advancing her sleep period so that she went to sleep and arose 6 hours earlier than usual. The antidepressant effect of the procedure was temporary and similar in duration to circadian desynchronization induced by jet lag in healthy subjects. This result supports the hypothesis that abnormalities of sleep patterns in some types of depression are due to abnormal internal phase relationships of circadian rhythms.*

The human circadian system has been described (*1–3*) as consisting of multiple, self-sustained oscillators that are mutually coupled and that can be entrained by the zeitgebers in the environment to ensure temporal order within the organism. Aschoff has recently concluded (*3*): "It is still unknown whether there are illnesses specific to changes in circadian organization, and whether these disturbances can be sufficiently characterized to enable their use as diagnostic criteria. Although the hypothesis of desynchronized circadian rhythms in affective illness [*4, 5*] underlies much psychiatric theorizing, there is not yet a sound experimental base to these theories" (*3*, p. 1855). We describe a clinical study that directly tests this hypothesis.

In patients with major depressive illness, disturbed sleep is a primary symptom. The architecture of sleep and the duration of sleep are regulated by processes that undergo circadian fluctuations. When sleep is sampled during short naps around the clock in normal subjects, rapid-eye-movement (REM) sleep exhibits a circadian rhythm, with a maximum in midmorning and a minimum in the late afternoon (*6*). Thus, REM sleep normally predominates in the latter half of the sleep period. Extensive electroencephalographic studies of the sleep-wake cycle in depression indicate that in depressed patients REM sleep occurs earlier in the sleep period than it does in controls (*7*). The sleep disturbance of depression can be mimicked in some respects—short REM latency (elapsed time from sleep onset to REM sleep onset), short total sleep time, and increased awakening at the end of the sleep period—by shifting the onset of normals' sleep period from 10 p.m. to 10 a.m. (*8*). Furthermore, experimental manipulations of the circadian sleep-wake cycle in healthy subjects have shown that it is possible to change internal phase relationships between different circadian rhythms (*1, 2, 9*) and that these changes may be associated with psychopathological symptoms ranging from emotional and psychosomatic disturbances (*1, 10*) to depressive reactions, hostility, and even suicide (*11*).

Thus, it has been inferred that, in depression, the circadian rhythm of REM sleep may occur abnormally early, that is, phase-advanced relative to the sleep period (*8, 12*). Additional evidence from biochemical and physiological measurements supports the hypothesis that certain circadian rhythms of depressive patients are phase-advanced (*13, 14*).

If this inference is relevant to the etiology of affective illness, advancing a depressive patient's sleep period by several hours should alter the internal phase relationship between the circadian sleep-wake cycle and other circadian rhythms (such as temperature or the probability of REM sleep) so as to normalize both sleep architecture and mood.

We now report some clinical observations and an experiment based on this model. In seven manic-depressive patients (*15*) we continuously monitored the 24-hour rest-activity cycle with a computer-based nontelemetered ambulatory monitor worn on the nondominant wrist (*16, 17*). Plots of motor activity data (Fig. 1) revealed that four patients rapidly advanced their time of awakening as they emerged from the depressive phase of their illness (usually patients switched from depression into mania or hypomania). Although each patient's total sleep time was also markedly reduced, the shortening of the sleep period was almost entirely due to the earlier onset of awakening. In some cases patients reported that they were drowsy early in the evening, but did not go to bed until later because of hospital routine. If this earlier awakening represents a sudden spontaneous phase advance of the sleep-wake cycle relative to other rhythms, it suggests that such a procedure could be associated with improvement in depression.

These observations encouraged us to test the circadian rhythm phase-advance hypothesis directly by advancing the sleep period of one of the patients by several hours during a depressive episode. The patient, a 57-year-old woman, had a history of responses to tricyclic antidepressants, monoamine oxidase inhibitors, electroconvulsive treatment, and sleep deprivation therapy. We found that a 6-hour phase advance of her sleep-wake cycle was sufficient to normalize sleep architecture and cause a rapid remission of symptoms (characteristic of a

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