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Critical Flicker Frequency (CFF) and Psychotropic Drugs in Normal Human Subjects – A Review*

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Abstract. This literature review presents summary methodological and statistical data on 33 studies in which critical flicker frequency (CFF) thresholds were used to evaluate the effects of acute oral doses of single psychotropic drugs in normal human subjects. In all, 96 drug-dose-study combinations are represented. CFF was found to be altered to a statistically significant degree ($P < 0.05$) in 51 (65%) of the 79 instances in which inferential statistical methods were used to evaluate the results. As expected, stimulants increased CFF while hypnotics decreased it. There is also a discussion of important methodological considerations in the design of psychopharmacological studies employing CFF. While many studies have shown CFF to be sensitive to the effects of psychotropic drugs, there have not always been adequate controls for extraneous factors (especially, set and suggestion, changes in pupillary diameter, and the presence of other commonly used drugs). Finally, consideration is given to the attempts to increase the sensitivity of the CFF test to drug effects.

Key words: Critical flicker frequency (CFF) – Flicker – Fusion frequency – Psychotropic drugs – Perception.

The critical flicker frequency (CFF) may be defined as the point at which a flickering light gives rise to the subjective sensation of a steady light. Though the CFF threshold has been studied for a long time (cf. Landis, 1953), and there were many early indications of its usefulness in drug research (cf. Simonson and Brožek, 1952), it is only recently that the CFF test has received more wide spread attention in this field. While this may be attributed in part to the increase in drug research in general and to improvements in CFF equipment, it is also undoubtedly due to the accumulation of evidence from diverse fields that CFF is affected by a variety of conditions which influence the functional efficiency of the cerebral cortex (McGuire, 1958; Misiak and Loranger, 1961; Honigfeld, 1962; Goldman et al., 1968; Parsons et al., 1968; Riklan et al., 1972). Although many have concluded on the basis of these results that CFF is a sensitive and relatively uncontaminated behavioral measure of central nervous system functioning, others, using a signal detection model, have focused on changes in subjective criteria and their effect on CFF (Clark, 1966; Clark et al., 1967).

The last published survey of the use of CFF in drug research appeared as a section of a general review of CFF by Simonson and Brožek in 1952 (op. cit.). An indication of the need for a more recent review of this literature is the fact that in several recent articles involving CFF and drug conditions it is obvious that the investigators were completely unaware of some highly relevant CFF literature. Two practical reasons might account for this failure to coordinate research efforts in this area. First, articles involving CFF and drug conditions have appeared in the journals of many different disciplines – psychology, ophthalmology, neurology, and psychopharmacology, to name but a few. Furthermore, these references are not easily located since CFF often does not appear in the title of the article but is included in the experimental design along with a host of other dependent variables. These considerations have made it very difficult for the researcher to become aware of the CFF-drug literature relevant to his own interests, especially if CFF played only a limited role in his research plan.

The aim of this report is to review the literature published in English on CFF and psychotropic drugs

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in normal human subjects, so that this information will be readily available to investigators wishing to use CFF in this area. References were obtained primarily from three sources: (a) standard reference works such as *Index Medicus* and *Psychological Abstracts*; (b) CFF review: Landis (1953, 1954), Simonson and Brožek (1952), and especially the excellent recent bibliography by Ginsburg (1970); and (c) cross checks of the references cited in the material located in (a) and (b) above.

Before beginning the literature review proper, perhaps a word should be noted about the instrumentation and methodology of CFF. While many of the early investigators employed mechanical devices to produce flicker (e.g. a rotating sectored disk in the path of constant light source), most of the recent CFF researchers employ an electronic device (e.g. a square wave pulse generator and a glow modulator tube). The most frequently used psychophysical method for obtaining CFF thresholds is the method of limits. Twenty of the 33 studies summarized in this review utilized this technique. The usual procedure is to hold the intensity of the flickering light source constant and progressively to increase or decrease the frequency until the subject reports a change in his perception of flicker (i.e. from flicker to fusion or from fusion to flicker). Using this technique, thresholds are reported in hertz (cycles per second) and increased CFF sensitivity is reflected in increased (i.e. higher) hertz values. One group who has done extensive investigations of CFF and drug effects (namely, Ideström and his associates) used a variation in which they maintained the frequency constant at 40 hertz and varied the intensity of the flickering source through the use of neutral density filters. With this latter technique, thresholds are reported in log filter units and increased CFF sensitivity is reflected in increased log filter values, i.e. the ability to perceive flicker at a lower intensity.

Table 1 contains information from all those CFF studies which employed *acute oral doses of single psychotropic drugs in non-psychiatric subjects*. These results are presented by drug groups as defined by the International Reference Center Psychotropic Drug Classification (Psychopharmacology Bulletin, 1973). Excluded from this table are those studies which involved chronic drug doses, and those acute studies which employed other than the oral route of administration, or combinations of drugs. Also eliminated were those studies in which CFF response to a drug was used not as an index of the drug activity itself but rather as an indication of the presence of some other medical condition (e.g. toxemia of pregnancy).

Several points should be made in regard to Table 1. First, several of the studies cited also included other drug conditions which do not appear in Table 1 since they were excluded on the basis of the criteria listed above. Many of these studies also employed other tests (physiological, psychomotor, perceptual, etc.) in addition to CFF. Second, a directional CFF effect (increase or decrease) is indicated if, on the basis of the statistical analysis presented, the investigator concluded that there had been a drug effect on CFF significant at at least the 0.05 level. Naturally, there are many different ways to analyze these data (differences from baseline, differences from a placebo control group at the same post-test time, etc.). No attempt was made in Table 1 to differentiate among these approaches. Third, in two of the studies (Landis and Zubin, 1951; Aiba, 1959) the total dose indicated was achieved by the ingestion of smaller doses during the course of a single day. Finally, a dash (−) in the columns headed "Double Blind" and "Artificial Pupil" indicates that the report contains no specific mention of the use of these controls. While this does not necessarily mean that the controls were not employed, in many of these cases it appeared obvious that they were not.

In all, Table 1 contains data from 33 studies, yielding 96 drug-dose-study combinations. In 79 of these 96 combinations, inferential statistical methods were used to evaluate the results. The outcomes of these 79 combinations, grouped by psychotropic drug class, are presented in Table 2.

As expected, stimulants were found to significantly increase CFF. The hypnotics were singularly effective in significantly decreasing CFF while the neuroleptics and anxiolytics show a roughly equal number of instances in which CFF was significantly decreased or showed no significant change. In none of the four instances were antidepressants found to exert a significant CFF effect. The two inferential studies of the effect of psychotomimetics on CFF presented an equivocal picture: LSD was found to significantly decrease CFF while marijuana was found to significantly increase CFF. In overview, of the 79 cases in which inferential statistics were applied, CFF was found to be altered to a statistically significant degree in 51 instances (65%).

Some Important Considerations in the Design of CFF-Drug Studies

Since CFF in these studies is generally regarded as a behavioral measure of the effect of psychotropic drugs on the functioning of the central nervous system and since the magnitude of CFF changes is typically small, careful attention should be given to the control of unrelated sources of variability. Some of these factors are discussed below.

Table 1. Critical flicker frequency (CFF) results of studies involving acute oral doses of single psychotropic in non-psychiatric subjects

Drug name	Dosage (mg)	CFF effect[a]	No. of subjects	Double blind[b]	Artificial pupil[b]	Study
Neuroleptics, phenothiazine derivatives						
Chlorpromazine	10	unknown	?	yes	–	Turner (1965b)
	25	unknown	?	yes	–	Turner (1965b)
	25	decrease	6	yes	–	Turner (1966)
	50	decrease	12	yes	–	Besser and Duncan (1967)
	100–150	decrease	18	–	–	Lehman and Csank (1957)
Fluphenazine	1	none	6	yes	–	Turner (1966)
	2	none	8	yes	–	Lind and Turner (1968)
Prochlorperazine	10	none	15	yes	–	Ideström (1960)
	20	decrease	15	yes	–	Ideström (1960)
	30	decrease	15	yes	–	Ideström (1960)
	30–60	none	16	–	–	Lehmann and Csank (1957)
Neuroleptics, butyrophenones						
Dipiperon	20	decrease	21	yes	–	Ideström and Cadenius (1963)
	40	decrease	21	yes	–	Ideström and Cadenius (1963)
Neuroleptics, rauwolfias						
Reserpine	1–2	none	11	–	–	Lehmann and Csank (1957)
Anxiolytics						
Benzquinamide	200	decrease	20	yes	–	Holmberg and William-Olsson (1963)
Chlordiazepoxide	10	none	8	yes	–	Lind and Turner (1968)
	20	none	21	yes	–	Ideström and Cadenius (1963)
	20	none	8	yes	–	Lind and Turner (1968)
	40	decrease	21	yes	–	Ideström and Cadenius (1963)
	60	decrease	20	yes	–	Holmberg and William-Olsson (1963)
Diazepam	10	decrease	12	yes	–	Besser and Duncan (1967)
Emylcamate	1200	none	8	yes	–	Jonsson and Andersén (1960)
	1800	none	8	yes	–	Jonsson and Andersén (1960)
Gamaquil	1600	none	20	yes	–	Ideström (1962)
Meprobamate	200–300	none	8	–	yes	Aiba (1959)
	400	decrease	24	–	–	Holland (1960b)
	400	none	5	yes	yes	Misiak et al. (1966)
	800	none	5	yes	yes	Misiak et al. (1966)
	1200	none	8	yes	–	Jonsson and Andersén (1960)
	1200	decrease	12	yes	yes	Jonsson et al. (1967)
	1600	decrease	20	yes	–	Ideström (1962)
	1600	decrease	12	yes	yes	Jonsson et al. (1967)
	1800	none	8	yes	–	Jonsson and Andersén (1960)
Trioxazine	1200	decrease	12	yes	yes	Jonsson et al. (1967)
	1600	decrease	12	yes	yes	Jonsson et al. (1967)
Antidepressants, dibenzazepine compounds						
Desmethylimipramine	25	none	20	yes	–	Ideström and Cadenius (1964)
	50	none	20	yes	–	Ideström and Cadenius (1964)
Imipramine	25	none	20	yes	–	Ideström and Cadenius (1964)
	50	none	20	yes	–	Ideström and Cadenius (1964)

[a] *Increase* denotes a statistically significant increase in the ability to discriminate flicker (i.e. perception of flicker at a lower intensity or at a higher hertz) at the 0.05 level or better; *decrease* denotes a statistically significant decrease in the ability to discriminate flicker (i.e. perception of flicker at a higher intensity or at a lower hertz) at the 0.05 level or better; *none* denotes that there was no statistically significant change in the ability to discriminate flicker; *unknown* denotes that no inferential statistics were employed to analyze the CFF effect.

[b] – Denotes that there was no specific mention of the use of this control.

Table 1 (Continued)

Drug name	Dosage (mg)	CFF effect[a]	No. of subjects	Double blind[b]	Artificial pupil[b]	Study
Stimulants						
Amphetamine	5	increase	10	–	–	Roback et al. (1952)
	10	increase	12	–	–	Roback et al. (1952)
	10	unknown	16	–	–	Adler et al. (1950)
	10–15	unknown	6	–	–	Simonson et al. (1941)
	15	increase	4	yes	–	Smart and Turner (1966)
	15	increase	6	yes	–	Smart and Turner (1966)
Dextroamphetamine	5	increase	11	–	–	Roback et al. (1952)
	5	increase	44	yes	–	Ideström and Schalling (1970)
	10	unknown	10	–	–	Adler et al. (1950)
	10	none	24	yes	yes	Misiak and Rizy (1968)
	10	increase	10	–	–	Roback et al. (1952)
	10	none	6	–	–	Holland (1960a)
	10	unknown	30	yes	–	Sjöberg and Jonsson (1967)
	10	unknown	6	yes	–	Turner (1965b)
	10–15	increase	8	–	yes	Aiba (1959)
	12.5–15	increase	14	–	–	Lehmann and Csank (1957)
	15	increase	44	yes	–	Ideström and Schalling (1970)
Methamphetamine	5	unknown	16	–	–	Adler et al. (1950)
	5–7.5	unknown	11	–	–	Simonson and Enzer (1942)
Psychotomimetics						
LSD-25	1 µg per kg	decrease	10	–	yes	Holliday et al. (1965)
Marijuana	1 g of 1.5% THC	increase	31	–	–	Schwin et al. (1974)
Marijuana extract	12.5 mg/lb	unknown	12	–	–	Clark and Nakashima (1968)
	20.0 mg/lb	unknown	12	–	–	Clark and Nakashima (1968)
	30.0 mg/lb	unknown	12	–	–	Clark and Nakashima (1968)
Psilocybin	0.05 mg/kg	unknown	2	–	yes	Keeler (1963)
	0.20 mg/kg	unknown	5	–	yes	Keeler (1963)
Hypnotics, barbiturate						
Amobarbital	60	unknown	?	yes	–	Turner (1965b)
	100	none	15	yes	–	Ideström (1960)
	100	decrease	6	yes	–	Turner (1965a)
	100	decrease	12	yes	–	Besser and Duncan (1967)
	120	unknown	?	yes	–	Turner (1965b)
	150	decrease	21	yes	–	Ideström and Cadenius (1963)
	150	decrease	44	yes	–	Ideström and Schalling (1970)
	195	decrease	6	–	–	Holland (1960a)
	200	decrease	15	yes	–	Ideström (1960)
	200	unknown	6	–	yes	Granger and Ikeda (1961)
	180–270	decrease	8	–	yes	Aiba (1959)
	300	decrease	6	–	–	Ideström (1954)
	300	decrease	15	yes	–	Ideström (1960)
	300	none	21	yes	–	Ideström and Cadenius (1963)
	300	decrease	44	yes	–	Ideström and Schalling (1970)
	450	decrease	21	yes	–	Ideström and Cadenius (1963)
Aprobarbital	300	none	6	–	–	Ideström (1954)
Barbital	600	none	6	–	–	Ideström (1954)
Cyclobarbital	300	decrease	6	–	–	Ideström (1954)
Hexobarbital	300	decrease	6	–	–	Ideström (1954)
Phenobarbital	65	none	24	yes	yes	Smith (1970)
	65	decrease	24	yes	yes	Misiak and Rizy (1968)
	100	decrease	12	yes	–	Besser and Duncan (1967)
	200	decrease	72	yes	–	Landis and Zubin (1951)
	300	decrease	6	–	–	Ideström (1954)

Table 1 (Continued)

Drug name	Dosage (mg)	CFF effect[a]	No. of subjects	Double blind[b]	Artificial pupil[b]	Study
Secobarbital	50	none	24	yes	yes	Smith (1970)
	96	decrease	15	–	–	Roback et al. (1952)
	100	decrease	12	yes	–	Besser and Duncan (1967)
	100–200	decrease	13	–	–	Lehmann and Csank (1957)
Hypnotics, non-barbiturate						
Chloral hydrate	2000	decrease	6	–	–	Ideström (1954)
Glutethimide	250	decrease	24	–	–	Holland (1960b)

Table 2. Summary of Table 1 CFF results which were analyzed by means of inferential statistics

Drug group	CFF effect[a]		
	Increase	Decrease	None
Neuroleptics	0	7	5
Anxiolytics	0	10	11
Antidepressants	0	0	4
Stimulants	10	0	2
Psychotomimetics	1	1	0
Hypnotics	0	22	6
Totals	11	40	28

[a] *Increase* denotes a statistically significant increase in the ability to discriminate flicker (i.e. perception of flicker at a lower intensity or at a higher hertz) at the 0.05 level or better; *decrease* denotes a statistically significant decrease in the ability to discriminate flicker (i.e. perception of flicker at a higher intensity or at a lower hertz) at the 0.05 level or better; *none* denotes that there was no statistically significant change in the ability to discriminate flicker.

Set and Suggestion. Since CFF has been shown to be sensitive to the effects of instructional set (Knox, 1945; Landis and Hamwi, 1954; Holland, 1961; Clark, 1966), research strategies employed should either minimize these factors as much as possible, or, using a signal detection model, enable an evaluation of attitudinal bias independently of sensory sensitivity. Using the latter approach, Clark and his associates (Clark, 1966; Clark et al., 1967) have demonstrated that shifts in response criterion (L_x, an attitudinal or "psychological" variable) can produce as great a change in the CFF threshold as a shift in sensory sensitivity (d', a physiological measure). Unfortunately, none of the 33 studies cited in this review was designed to provide simultaneous measures of sensory sensitivity and attitudinal bias.

With regard to minimizing the effects of suggestion (on the part of both the subjects and the investigators), the use of the double blind technique is strongly recommended whenever possible, even though there is no guarantee of complete success in this effort (Cole, 1968). Of the 33 studies represented in Table 1, 19 contained explicit mention of the use of this technique.

Pupillary Diameter. Many psychotropic drugs alter pupillary diameter and pupillary responsiveness (Eysenck and Easterbrook, 1960; Ban, 1969) and CFF has been shown to be sensitive to changes in pupillary diameter since these result in changes in the level of retinal illumination (Miles, 1950; Landis, 1954; Alpern and Jampel, 1959). It is therefore imperative for any investigator interested in CFF as a measure of CNS functioning to control for variations in pupillary diameter. One of the simplest means of assuring control over this factor is through the use of an artificial pupil[1]. The apparatus is constructed so that the subject must view the CFF stimulus through an aperture (usually 2 mm) which is close to the smallest pupillary diameter possible. Although several investigators (Holliday et al., 1965; Smart and Turner, 1966; Smith, 1970) have alluded to the need for this control in CFF-drug research, of the 33 studies cited in Table 1, only 8 (24%) contained specific mention of its use.

Concomitant Presence of Other Drug Conditions. CFF has been shown to be sensitive to the effects of a number of nonprescription drugs in general use. The most prominent of these with a demonstrated CFF effect are caffeine (Roback et al., 1952), nicotine (Clarkson et al., 1950; Fabricant and Rose, 1951; Warwick and Eysenck, 1963; Barlow and Baer, 1967) and alcohol (Goldberg, 1943; Enzer et al., 1944; Bjerver and Goldberg, 1950; Ideström and Cadenius, 1968; Lewis et al., 1969). Although several of the studies cited in Table 1 (Roback et al., 1952; Ideström, 1954; Smart and Turner, 1966; Besser and Duncan, 1967; Jonsson et al., 1967; Misiak and Rizy, 1968;

[1] Other techniques (e.g. Maxwellian view, correcting the data) are available to take account of variations in pupillary diameter but these are quite demanding technically. Only one of the CFF-drug studies reviewed mentioned the use of any of these other techniques. In that study (Granger and Ikeda, 1961) the Maxwellian view was employed along with an artificial pupil.

Idestrom and Schalling, 1970; Smith, 1970) restricted the intake of one or more of these substances during the course of their experiments, in general control of these factors appears to have been lax. Restrictions on the intake of any of these substances (as found, for example, in cigarettes, coffee, tea, cola and alcoholic beverages) as well as any other drugs should be strictly adhered to in any CFF-drug study not specifically concerned with the interactions of these substances with psychotropic drugs.

Attempts to Increase the Sensitivity of CFF to Drug Effects

Several attempts have been made to increase the sensitivity of the CFF test by varying one or more of the conditions under which CFF thresholds are obtained. Drawing upon all the literature related to CFF and drug effects (i.e. not only those acute studies in normal subjects included in this review), the parameters whose manipulation was *not* found to increase CFF-drug sensitivity significantly are: intensity of the test patch (Landis and Clausen, 1954; Alpern and Jampel, 1959; Granger and Ikeda, 1961; Karp and Pollack, 1963), intensity of the surround (Aiba, 1959), retinal location of the stimulus (Holland, 1960a, b) and the frequency of the adapting light (Turner 1965a, b; Smart and Turner, 1966). While descending thresholds obtained with the method of limits were found to be more sensitive to drug effects in one study (Aiba, 1959), two other studies (Kelly et al., 1958; Smith, 1970) found no evidence of a differential sensitivity in this regard.

With respect to light-dark ratio (LDR, the ratio of the light portion of one cycle to the dark portion of the same cycle), the results of two studies (Sloan and Gilger, 1947; McFarland et al., 1958) suggest an increase in CFF sensitivity with lower light-dark ratios (i.e. with decreases in the length of the light phase relative to the dark phase of a cycle). Landis and Clausen (1955) also note that their previous experience indicated that lower LDRs are probably more sensitive to drug induced changes than a 1:1 LDR.

Much of the speculation concerning the relative sensitivity of different LDRs to drug effects is based on results obtained with different types of equipment (namely, strobotac and episcotister devices) and is complicated therefore by the fact that these devices usually differ in several respects other than LDR. The results of one drug study (Smith, 1970) which contrasted the CFF thresholds obtained with LDRs of 1:1 and 1:9 in the same equipment shed little light on the question of differential sensitivity since relatively low doses of barbiturates were administered and no statistically significant CFF effects were obtained under either LDR condition.

In conclusion, the CFF test has been widely used in studies of psychotropic drugs in normal subjects and is sensitive to the effects of these drugs. However, many investigators appear to have failed to employ the required controls to insure that the CFF results they observed reflected only the CNS changes induced by the drugs. A good indication of this failure is the fact that in only four (Misiak et al., 1966; Jonsson et al., 1967; Misiak and Rizy, 1968; Smith, 1970) of the 33 studies summarized in this review is there any indication of the use of *both* the double-blind technique and an artificial pupil. Hopefully, this review will serve not only to facilitate the use of CFF in psychopharmacological investigations but also to encourage the use of appropriate controls.

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