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AUDITORY FLUTTER FUSION AS A MEASURE OF THE ACTIONS OF CENTRALLY ACTING DRUGS: MODIFICATION OF THE THRESHOLD FOR FUSION AND THE INFLUENCE OF ADAPTING STIMULI

BY

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Interrupted random (or " white ") noise is perceived to be fused when the frequency of interruption is greater than a critical value. This critical frequency is called the auditory flutter fusion threshold (A.F.F.T.) and is analogous to the visual critical flicker fusion threshold (C.F.F.T.) (Miller & Taylor, 1948 ; Symmes, Chapman & Halstead, 1955). If, before measuring the A.F.F.T., the subject is exposed to another interrupted auditory stimulus, then his subsequently determined A.F.F.T. is shifted toward the frequency of this preceding stimulus. The relation between the frequency of the preceding " adapting " stimulus and that of the subsequently determined A.F.F.T. is linear (Besser, 1966, 1967). This is an example of perceptual adaptation which was described by Helson (1948, 1964).

The present paper reports the differential changes in A.F.F.T. and its adaptation induced by some centrally acting drugs in common clinical use. The threshold was found to be sensitive to small single doses of chlorpromazine, amylobarbitone, diazepam and dl-amphetamine but resistant to perphenazine and meprobamate ; the adaptation was not altered by any drug tested. A preliminary account of these studies has been given (Besser, Duncan & Quilliam, 1966).

METHOD

A modification of the technique of Miller & Taylor (1948) was used.

The apparatus consisted of a transistorized random noise generator from which the signal passed through an interrupter having an on-off (or mark-space) ratio of 9:1. The rate of interruption was determined by an oscillator and could be adjusted in steps of 1.0 interruption per sec (i/sec) from 1.5 to 100 i/sec, and in steps of 2.5 i/sec from 100 to 275 i/sec. The interrupter was automatically switched on and off by a low frequency oscillator at intervals of 1.0 sec, so that the signal, presented binaurally to the subject, was composed of alternating 1 sec sequences of continuous and interrupted noise, with no intervening gap.

The signal was transduced by a pair of Telephonics earphones (TDH 39), fitted with rubber ear muffs. The intensity of the noise as delivered by the earphones in these experiments was 55 d.B. (re. 0.0002 dyn./sq cm as generated in a 6 c.c. rigid acoustic coupler) and there was less than 0.5

d.B. difference between the interrupted and continuous phases of the signal. The interrupted signal cut-off was rectangular and there was over 35 d.B. intensity difference between the on and the off portions.

The response of the earphones was linear over the frequency range 500–6,000 c/s. The noise as transduced contained all the frequencies in this range equally represented and interruption of the signal caused the appearance of no predominant frequency. "Chopping" and "switching" spikes were balanced out of the wave form. A switch allowed the alternation between the continuous and interrupted portions of the cycle to be stopped so that the signal was then either continuous or interrupted.

All experiments were conducted in a sound insulated room. The subject was presented binaurally with the stimulus and instructed to say "yes" if he could clearly distinguish the repeated bursts of interrupted noise. If he could not, or if there was doubt, he was to say "no." The starting interruption rate was 100 i/sec, well above fusion for all subjects. The frequency of interruption was reduced in steps of 10 i/sec until a point was reached approximately 10 i/sec above that of the subject's threshold (this had been determined approximately at the start of the session). Then the frequency was further reduced in steps of 1 i/sec until the A.F.F.T. was passed. The A.F.F.T. was taken to be the fastest interruption rate at which the auditory flutter (that is the interruptions) could be clearly distinguished, and below which "yes" responses were given consistently. The descending sequence of interruption rates was used in all experiments. Interrupted pure tones were not used as then a change in interruption rate would introduce a change in apparent pitch (Miller, 1948).

The subjects were 18 unpaid volunteers, members of the staff and clinical students at this medical college (mean age 26.7 yr., S.D. 3.6) and cross-over latin square designs were used to ensure a randomized balanced allocation of subjects to drug and placebo treatments. Each subject acted as his own control. Drugs and placebos were always taken at the same time, between 9 a.m. and 10 a.m., at intervals of 7 days, at least 30 min after a light breakfast without coffee or tea.

Each set of observations usually consisted of three threshold determinations at intervals of 5 min. When preceding adapting stimuli were used, they were presented for 60 sec at rates of 10 i/sec and 200 i/sec immediately before the threshold was determined. Each set then consisted of four threshold measurements at 5 min intervals, in the order 10–200–10–200 or 200–10–200–10 and allocation of subjects to the two orders was randomized and balanced. A set of measurements was made before tablet administration, as a baseline, and at 90 min and 180 min afterwards. The changes in the mean values of the thresholds at 90 min and 180 min compared with the baseline values on active and placebo treatments were analysed by analysis of variance for factorial designs (Snedecor, 1956). This gave a comparison between the overall means on the active and placebo treatments and the significance of the overall differences between these means was tested using the variance ratio. The significance of the differences at 90 and 180 min after drug administration was found using the *t*-test and the standard error derived from the residual error in the analysis of variance.

There were six subjects in each treatment group. When adaptation was studied, different subjects were used from those in the corresponding experiments without adapting stimuli. The drugs and doses were as follows: chlorpromazine 25 and 50 mg, perphenazine 4 mg, amylobarbitone 50 and 100 mg, diazepam 10 mg, meprobamate 800 mg, dl-amphetamine 10 and 15 mg and a mixture of amylobarbitone 100 mg and dl-amphetamine 15 mg. These are in the range of doses used clinically. Each drug was given in its normal tablet or capsule form, and each was matched with a placebo of identical appearance. Subjects were told the name of the drug being studied but neither they nor the experimenter knew the allocation of active or placebo treatments until the completion of the investigation of each drug.

RESULTS

Chlorpromazine

In the experiment in which thresholds were studied without adapting stimuli, the initial baseline starting mean A.F.F.T.s were: chlorpromazine 25 mg, 39.12 i/sec,

chlorpromazine 50 mg 36.78 i/sec, and the placebo 33.48 i/sec. Figure 1, which illustrates the changes in threshold after the initial baseline determinations, shows that the A.F.F.T. rose with the placebo treatment over 180 min, as is usually found, but failed to rise with either dose of chlorpromazine. The overall reduction in A.F.F.T. with chlorpromazine compared with the placebo was significant ($P<0.001$) and there was no difference between the effects of the two doses ($P>0.20$). The mean A.F.F.T. after 50 mg chlorpromazine

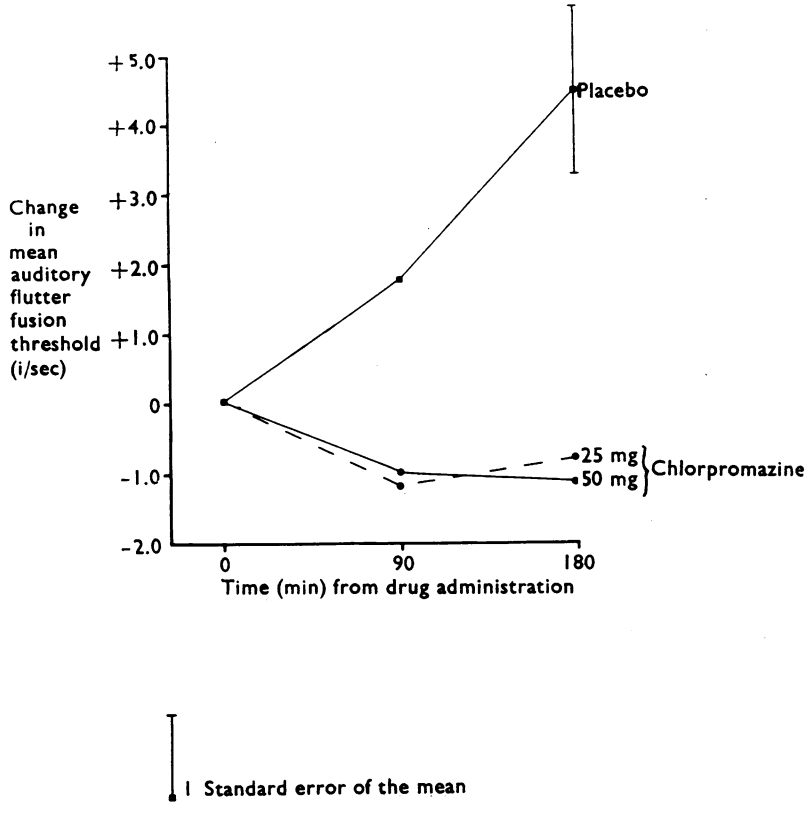

Fig. 1. The change in A.F.F.T. following placebo and chlorpromazine 25 mg (interrupted line) and 50 mg (continuous lines) in six subjects. S.E. of mean = 1.20. For the overall difference between active and placebo means $P<0.001$, S.E. of difference between means = 1.70. The initial baseline thresholds on the three treatments are represented by the zero point on the A.F.F.T. axis, and subsequent A.F.F.T.s have been expressed as changes from this point.

was 2.75 i/sec less than after the placebo at 90 min (for the difference $P<0.10$), and at 180 min 5.63 i/sec less (for the difference $P<0.01$, S.E. of the difference = 1.47 at both times). Full details of the statistical analysis of this and subsequent sections are available elsewhere (Besser, 1966).

When adapting stimuli were used the mean thresholds were consistently higher after the preceding adapting stimulus at 200 i/sec than after the 10 i/sec stimulus ($P<0.001$)

(Fig. 2). The difference between the values for the thresholds after the two adapting stimuli on each treatment represents the " shift " in threshold due to the adapting stimuli. There was no difference between the shifts after either dose of chlorpromazine compared with the placebo ($P>0.20$) so that the drug seemed not to influence the adaptation effect. However, the rise in mean threshold over the 3 hr period after the two active treatments

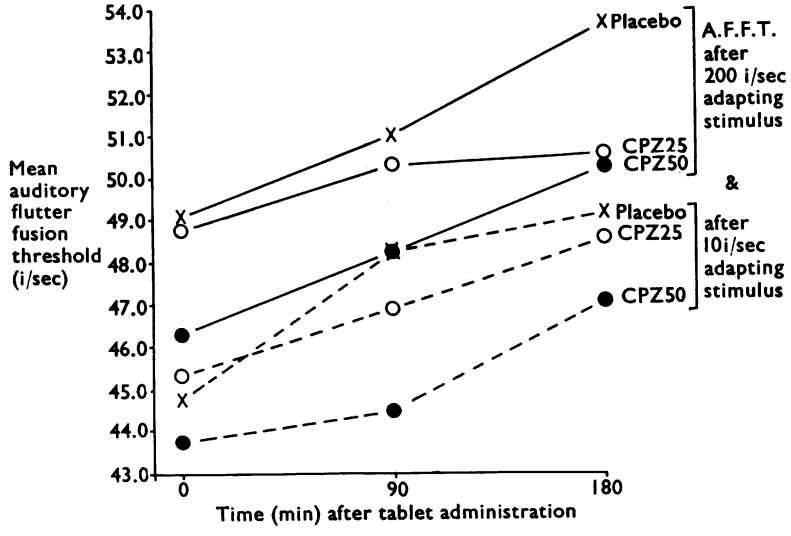

Fig. 2. Mean A.F.F.T. following placebo and chlorpromazine (CPZ) 25 and 50 mg in six subjects. The thresholds were determined after exposure of subjects to preceding adapting stimuli at 10 i/sec (interrupted line) and 200 i/sec (continuous line). The difference between the pairs of lines on each treatment represents the shift in A.F.F.T. due to the adapting stimuli. Chlorpromazine did not alter this shift in threshold ($P>0.20$). S.E. of means=2.10, S.E. of difference between changes in means after the three treatments=2.45, S.E. of shift=1.44, S.E. of difference between changes in shifts after the three treatments=2.74. For the overall shift due to adapting stimuli $P<0.001$.

was less than after the placebo—by 1.17 i/sec after the 10 i/sec adapting stimulus and 2.75 i/sec after 200 i/sec stimulus for chlorpromazine 25 mg, and by 1.09 i/sec and 0.66 i/sec after 50 mg of the drug, at 180 min. These depressions of threshold did not reach statistical significance ($P>0.20$) and were considerably smaller than had occurred in the previous study of chlorpromazine on thresholds determined without adapting stimuli (see Table 1). The changes induced by the drug were in the same direction as before, but the presence of the adapting stimuli seemed to make the A.F.F.T. less sensitive to chlorpromazine.

Perphenazine

Perphenazine 4 mg was not found to modify significantly the rise in A.F.F.T. seen after the placebo treatment (+3.10 i/sec after the placebo, +4.00 i/sec after perphenazine, at 180 min. S.E. for difference between means=1.20, $P>0.20$).

Amylobarbitone

Amylobarbitone in a dose of 100 mg induced a depression in A.F.F.T. Starting at a mean A.F.F.T. of 42.93 i/sec before placebo treatment and 43.10 i/sec before the amylobarbitone, the threshold was 5.17 i/sec less with the active drug at 90 min and 5.27 i/sec less at 180 min. The overall depression was significant ($P<0.001$) and as great at 90 min as at 180 min, being significant at both times ($P<0.01$). Figure 3 shows this depression of thresholds compared with those after the placebo which are represented by the zero line.

The dose of 50 mg amylbarbitone did not alter the threshold consistently in any direction.

When the adapting stimuli were used with 100 mg amylobarbitone, the thresholds were once again significantly depressed overall compared with the placebo ($P<0.05$) but the amount of the depression was much less than occurred when no adapting stimuli were used (-2.67 i/sec after 10 i/sec stimulus and -2.33 i/sec after the 200 i/sec stimulus at 180 min, S.E. for difference between the means $=1.34$, $P<0.02$). The shift in threshold due to the adapting stimuli was not different on the active as compared with the placebo treatment ($P>0.20$). As with chlorpromazine, the adaptation effect, but not the thresholds themselves, was resistant to the action of amylobarbitone, and once again the drug-induced threshold depressions after adapting stimuli were smaller than without these stimuli (Table 1).

TABLE 1

CHANGES IN MEAN A.F.F.T. AFTER CHLORPROMAZINE, AMYLOBARBITONE AND DL-AMPHETAMINE, EACH STUDIED OVER 180 min IN 12 SUBJECTS

Differences are shown between the changes after the drug and after the placebo, with and without preceding adapting stimuli. The changes without these adapting stimuli were consistently greater

Drug (mg)		Mean A.F.F.T. change at 180 min (i/sec)		
		Without adapting stimuli	With adapting stimuli at 10 i/sec	With adapting stimuli at 200 i/sec
Chlorpromazine	25	−5·23*	−1·17	−2·75
	50	−5·63*	−1·09	−0·66
Amylobarbitone	100	−5·27*	−2·67†	−2·33†
Dl-amphetamine	10	+4·63*	−0·16	+1·17
	15	+3·93*	+1·17	+2·17

* Significantly different from zero ($P<0·01$). † Significantly different from zero ($P<0·02$).

Diazepam

Figure 3 shows the significant depression of A.F.F.T. following a dose of 10 mg of diazepam (for overall depression $P<0.001$). The diazepam threshold was 3.07 i/sec less than the placebo threshold at 90 min ($P<0.01$) and 2.75 i/sec less at 180 min ($P<0.02$). There was no difference between the drug effect at 90 and 180 min ($P>0.20$).

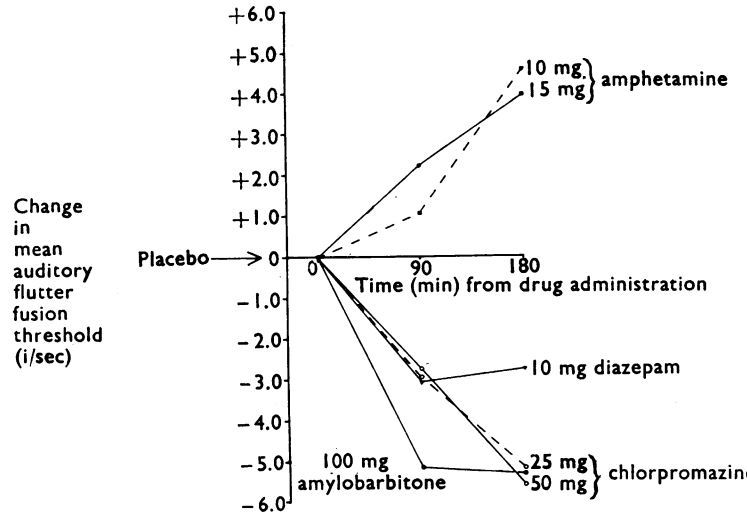

Fig. 3. Summary of the changes in A.F.F.T. from baseline values after dl-amphetamine (10 and 15 mg), chlorpromazine (25 and 50 mg), amylobarbitone (100 mg) and diazepam (10 mg) each compared with its own placebo over 180 min. The placebo threshold values are represented by the zero line. Each mean is derived from six subjects. The overall means are significantly different from their corresponding placebo means.

Meprobamate

A dose of 800 mg meprobamate was compared with its placebo, as with the other drugs. In order to test the effect of giving placebo tablets on the threshold, a third set of threshold measurements was made under the same conditions, except that no tablets were given. Since the treatments were this time obviously different to the subjects, heterogeneity of the variance was sought by Bartlett's test (Snedecor, 1956) but was not found. This allowed normal variance analysis to be carried out. There was no significant difference between the threshold changes over 180 min with the three procedures (overall $P>0.20$) nor were there any obvious trends. It was concluded that neither meprobamate 800 mg nor placebo tablet administration could be shown to have an effect on the A.F.F.T.

Dl-amphetamine

The rise in A.F.F.T. which occurred with both doses of dl-amphetamine (10 and 15 mg) was greater than that with the placebo over 180 min ($P<0.01$). The changes are illustrated in Fig. 3. The difference between the placebo and amphetamine means at 90 min (+1.06 i/sec for 10 mg and +2.23 i/sec for 15 mg) was not significant ($P>0.20$) but was greater at 180 min (+4.63 i/sec for 10 mg, +3.93 i/sec for 15 mg) when it was significant ($P<0.01$). There was no difference between the effects of the two doses ($P>0.20$).

When preceding adapting stimuli were used a significantly greater overall rise in threshold did not occur with either dose of dl-amphetamine compared with the placebo

($P>0.20$). However, six out of eight changes in threshold recorded after dl-amphetamine were greater than after the placebo, though in no case was this increase significant. There was no suggestion that amphetamine had any effect on the shift in thresholds due to the adapting stimuli. Over the 180 min the drug-induced changes in threshold were greater when no adapting stimuli were used, as was also the case with chlorpromazine and amylobarbitone (Table 1).

Amylobarbitone 100 mg plus dl-amphetamine 15 mg

The mixture of the doses of amylobarbitone and dl-amphetamine which, given individually had opposite effects on A.F.F.T. (Fig. 3), when given together resulted in an apparent mutual cancellation. The rise in A.F.F.T. with the mixture over the 180 min was not significantly different from that with the placebo ($P>0.20$).

DISCUSSION

The auditory flutter fusion threshold is a measure of the ability of the subject to discriminate between rapidly repeated white noise stimuli. This ability (the "flutter acuity") may be altered by exposure to immediately preceding interrupted "adapting" stimuli, the threshold and the acuity increasing when the adapting stimulus rate is relatively high and decreasing when it is relatively low (Besser, 1967) as has been confirmed in the work reported here. Thus when investigating the actions of drugs on the flutter fusion process it was important to record the effects both on the thresholds themselves and on the shifts produced by adapting stimuli.

Determination of the A.F.F.T. as defined in the present paper, inevitably depends on sensory reception of the stimuli, judgement as to their quality and an overt response. Drugs or other factors might differentially affect any part of this system, by direct or indirect actions, but only the net overall effect as measured by changes in the response—that is, the threshold—can be recorded.

Measurement of the auditory flutter fusion threshold appeared to provide a sensitive technique for the investigation of the central actions of drugs. Thus chlorpromazine produced a marked depression of A.F.F.T. in doses of 25 and 50 mg, whereas significant impairment of other perceptual functions have been generally reported to occur only after doses of 100 mg or more. For example Shurtleff, Mostofsky & DiMascio (1962) tested doses of chlorpromazine from 25 to 200 mg in subjects who were required to compare the frequencies of different bursts of rapidly repeated auditory clicks. Significant impairment in discrimination was found only with doses of 100 mg and over. Similarly, reaction times to auditory stimuli (Lehmann & Csank, 1957; Delay, Pichot, Nicolas-Charles & Perse, 1959), continuous auditory and visual vigilance tests (Mirsky, Primac & Bates, 1959; Mirsky & Cardon, 1962), visual critical flicker fusion threshold (Lehmann & Csank, 1957), and tests of intellectual and motor performance (Kornetsky, Humphries & Evarts, 1957; Kornetsky, Vates & Kessler, 1959; DiMascio, Havens & Klerman, 1963 a, b) have been shown to be significantly impaired only by doses of chlorpromazine of 100 mg and more.

The piperazine phenothiazine derivative, perphenazine, had no effect on A.F.F.T. in a dose of 4 mg, usually regarded as approximately equipotent with 50 mg chlorpromazine for clinical purposes. DiMascio *et al.* (1963a, and b) found that while the aliphatic phenothiazines, chlorpromazine and promethazine, impaired various tests of intellectual and motor function, the piperazine derivatives, perphenazine and trifluoperazine, in equivalent doses did not.

Amylobarbitone 100 mg depressed A.F.F.T. while 50 mg did not. Eysenck & Easterbrook (1960) in the only other published account of the affects of drugs on A.F.F.T. were unable to show any change with 90 mg sodium amylobarbitone. However, the interruption rate of their stimulus was varied in the relatively large steps of 10 i/sec over the whole range of frequencies. Since the maximum change in A.F.F.T. with any drug used in the present investigation was about 5 i/sec (Fig. 3) such changes might well have been missed. Auditory functions have not previously been shown to be impaired by amylobarbitone but it is well established that 100–200 mg doses of various barbiturates depress C.F.F.T. (Roback, Krasno & Ivy, 1952 ; Ideström, 1954 ; Lehmann & Csank, 1957 ; Aiba, 1959 ; Granger & Ikeda, 1961). Turner (1965) reported significant depression of C.F.F.T. after only 60 mg amylobarbitone sodium.

Diazepam, which depressed A.F.F.T. in a dose of 10 mg, is a 1:4 benzodiazepine compound related to chlordiazepoxide. Both are anti-anxiety drugs, and diazepam is effective in about half the dose of chlordiazepoxide. Chlordiazepoxide significantly depresses C.F.F.T. in a dose of 40 mg or more (Ideström & Cadenius, 1963 ; Holmberg & Williams-Olsson, 1963). Diazepam 10 mg has been shown to depress C.F.F.T. significantly, the effect lasting 6–8 hr (Besser & Duncan, 1967). This drug also impairs the pegboard-placement test but not other tests of intellectual or motor behaviour, with or without alcohol (Lawton & Cahn, 1963 ; Hughes, Forney & Richards, 1965).

Dl-amphetamine increased A.F.F.T. equally in doses of 10 and 15 mg. Eysenck & Easterbrook (1960) reported no change in A.F.F.T. after 5 mg d-amphetamine in the study referred to previously. Goldstone, Boardman & Lhamon (1958) showed that 15 mg d-amphetamine resulted in overestimation of the duration of a sound signal. Lehmann & Csank (1957) showed that 12.5 or 15 mg d-amphetamine shortened auditory reaction time and elevated C.F.F.T. This has been shown by many other workers (for example, Roback *et al.*, 1962 ; Aiba, 1959 ; Smart & Turner, 1966).

Combined treatment with amylobarbitone 100 mg, which given alone depressed A.F.F.T., and dl-amphetamine, which alone elevated A.F.F.T., had no effect on the threshold, so that the actions of one drug appeared to be cancelled by those of the other. This apparent mutual cancellation of the opposite actions seems to occur with most motor and behavioural tests in man but not with measures of mood. With combinations such as these, Steinberg and co-workers (Dickins, Lader & Steinberg, 1965) found in tests of motor performance that the amphetamine effect compensated for the decrement due to a barbiturate drug (cyclobarbitone), but that the total incidence of symptoms of mood change was greater with the combination than after the individual drugs alone. Amphetamine-barbiturate mixtures may stimulate the exploratory activity of naive rats more than the sum of the maximum effects of the drugs given separately (Steinberg, Rushton & Tinson, 1961 ; Rushton & Steinberg, 1963). Weiss & Laties (1964) showed

that there was a greater increase in the rate of food-rewarded button-pressing in dogs given amphetamine together with pentobarbitone or alcohol than when the drugs were given individually.

It is evident from the work on animals and man that the final effects obtained with drug combinations depend not only on the total dose of the drugs administered, but also on the relative concentrations of the constituents. In the work reported in this paper, a ratio of amylobarbitone to dl-amphetamine of 6.7 : 1 was used. The commonly used combination of these drugs contains a ratio of 6.5 : 1 of amylobarbitone to d-amphetamine. As the d-isomer of amphetamine is 1.5–2 times as potent in its central effects as the racemic form (Prinzmetal & Alles, 1940), the central stimulant in the mixture used here is somewhat less in proportion to the amylobarbitone than in the proprietary preparation.

Meprobamate in a dose of 800 mg did not alter the A.F.F.T., and, indeed, significant effects on intellectual perceptual and motor tests have not been consistently reported in doses less than 1,600 mg (for example, Marquis, Kelly, Miller, Gerard & Rapoport, 1957 ; Kelly, Miller, Marquis, Gerard & Uhr, 1958 ; Kornetsky, 1958 ; Uhr & Miller, 1960a, b ; Idestrom, 1962). Placebo treatment of itself had no effect on the A.F.F.T.

Adaptation

The term " perceptual adaptation " refers to the change in the perception of a given stimulus produced by an immediately preceding stimulus of greater or less magnitude. It reflects an aspect of the influence of context upon judgements. The flutter fusion threshold is a measure of the nul point between fusion and flutter and its shift along a linear path towards the adapting stimulus allows one to measure some determinants of adaptation (Besser, 1967). It is of great interest that, although the A.F.F.T. itself is highly sensitive to chlorpromazine, amylobarbitone and amphetamine, the adaptation effect as reflected in the shift in threshold appeared to be entirely resistant. This has also been found to be true of adaptation in weight perception (Besser, 1966). The presence of the adapting stimuli appeared to stabilize the flutter fusion threshold and to make it more resistant to the actions of chlorpromazine, amylobarbitone and amphetamine: when such stimuli were used the changes in A.F.F.T. induced by the drugs were consistently smaller than without the adapting stimuli (Table 1).

Time course of drug action

Amylobarbitone and diazepam induced changes in A.F.F.T. which were as great at 90 min after oral administration as at 180 min. However, after amphetamine and chlorpromazine the changes in A.F.F.T. were greater at 180 min than at 90 min, indicating a difference in their time courses of action. DiMascio *et al.* (1963), Kornetsky *et al.* (1959b) and Latz & Kornetsky (1965) found that the maximum action of chlorpromazine on several motor and mood tests occurred 3½–4 hr after oral administration, while Kornetsky and co-workers showed that a barbiturate, quinalbarbitone, is maximally effective within ½–1 hr after oral administration. Legge & Steinberg (1962) showed that the maximum action of an oral dose of 300 mg cyclobarbitone on several tests of motor function occurred at 40–60 min. Schwartz, Koechlin, Postma, Palmer & Krol (1965) using tritiated diazepam in two subjects showed that peak blood levels were obtained at

2 and 4 hr after oral administration. The findings with A.F.F.T. are consistent with these reports. A.F.F.T. provides a sensitive technique for following the time course of action of centrally acting drugs, and this has been explored in other work (Besser & Duncan, 1967).

SUMMARY

1. The critical frequency at which interrupted random noise stimuli appear to fuse (the auditory flutter fusion threshold, A.F.F.T.) has been shown in man to be sensitive to centrally acting drugs.

2. Chlorpromazine (50 mg and 25 mg), amylobarbitone (100 mg, but not 50 mg) and diazepam 10 mg significantly depressed the A.F.F.T., while dl-amphetamine (10 and 15 mg) significantly raised it when measured 90 and 180 min after an oral dose. The changes produced by amylobarbitone and diazepam were as great at 90 min as at 180 min, but those after chlorpromazine and amphetamine continued to increase after 90 min ; this indicated that the changes differed in their time course.

3. Exposure of subjects for 60 sec to interrupted random noise signals at 10 i/sec and 200 i/sec immediately before the A.F.F.T. was determined resulted in a marked shift in the A.F.F.T. toward the frequency of the preceding stimulus. This shift is an example of perceptual adaptation and allows its precise quantification.

4. While the thresholds themselves could be readily modified by the centrally acting drugs, the shift due to adaptation was in no case influenced by them. Further, when the preceding adapting stimuli were used, the changes in threshold due to the drugs were smaller than when no preceding adapting stimuli were used. These stimuli, therefore, appeared to stabilize the A.F.F.T.

5. Perphenazine, in a dose of 4 mg, did not influence the A.F.F.T. ; neither did meprobamate 800 mg nor did the administration of placebo tablets.

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REFERENCES

AIBA, S. (1959). The effects of dexamphetamine, sodium amobarbital and meprobamate on critical frequency of flicker under two different surround illuminations. *Psychopharmacologia*, **1**, 89–101.

BESSER, G. M. (1966). Some physiological and psychopharmacological studies on auditory flutter fusion and qualitative weight perception in normal subjects. Two new psychopharmacological tools. M.D. Thesis, University of London.

BESSER, G. M. (1967). Some physiological characteristics of auditory flutter fusion in man. *Nature, Lond.* **214**, 17–19.

BESSER, G. M. & DUNCAN, C. (1967). The time course of action of single doses of diazepam, chlorpromazine and some barbiturates as measured by auditory flutter fusion and visual flicker fusion thresholds in man. *Br. J. Pharmac. Chemother.*, **30**, 341–348.

BESSER, G. M., DUNCAN, C. & QUILLIAM, J. P. (1966). Modification of the auditory flutter fusion threshold by centrally acting drugs in man. *Nature, Lond.*, **211**, 751.

DELAY, J., PICHOT, P., NICOLAS-CHARLES, P. & PERSE, J. (1959). Etude psychométrique des effets de l'amobarbital (amytal) et de la chlorpromazine sur des sujets normaux. *Psychopharmacologia*, **1**, 48–58.

DICKINS, D. W., LADER, M. H. & STEINBERG, H. (1965). Differential effects of two amphetamine-barbiturate mixtures in man. *Br. J. Pharmac. Chemother.*, **24**, 14–23.

DiMASCIO, A., HAVENS, L. L. & KLERMAN, G. L. (1963a). Psychopharmacology of phenothiazine compounds: comparative study of the effects of chlorpromazine, promazine, trifluoperazine and perphenazine in normal males. I. Introductions, aims and methods. *J. Nerv. ment. dis.*, **136**, 15–28.

DiMASCIO, A., HAVENS, L. L. & KLERMAN, G. L. (1963b). Psychopharmacology of phenothiazine compounds: comparative study of the effects of chlorpromazine, promazine, trifluoperazine and perphenazine in normal males. II. Results and discussion. *J. Nerv. ment. dis.*, **136**, 168–186.

EYSENCK, H. J. & EASTERBROOK, J. A. (1960). Drugs and personality XI. The effects of stimulant and depressant drugs upon auditory flutter fusion. *J. Mental Sci.*, **106**, 855–857.

GOLDSTONE, S., BOARDMAN, W. K. & LHAMON, W. T. (1958). Effect of quinalbarbitone, dextro-amphetamine, and placebo on apparent time. *Br. J. Psychol.*, **49**, 324–328.

GRANGER, G. W. & IKEDA, H. (1961). Effect of amobarbital sodium on the flicker-intensity function for human fovea. *Psychopharmacologia*, **2**, 258–267.

HELSON, H. (1948). Adaptation-level as a basis for a quantitative theory of frames of reference. *Psychol. Rev.*, **55**, 297–313.

HELSON, H. (1964). Current trends and views in adaptation level theory. *Am. Psychol.*, **19**, 26–37.

HOLMBERG, G. & WILLIAM-OLSSON, U. (1963). Effect of benzquinamide in comparison with chlordiazepoxide and placebo, on performance in some psychological tests. *Psychopharmacologia*, **4**, 402–417.

HUGHES, F. W., FORNEY, R. B. & RICHARDS, A. B. (1965). Comparative effect in human subjects of chlordiazepoxide, diazepam, and placebo on mental and physical performance. *Clin. Pharmac. Therap.*, **6**, 139–145.

IDESTRÖM, C-M. (1954). Flicker-fusion in chronic barbiturate usage. *Acta psychiat. neurol. scand.*, Suppl. 91, 1–93.

IDESTRÖM, C-M. (1962). Effect of γ-phenyl-propylcarbamate (gamaqine) compared with meprobamate and placebo. An experimental psychological study. *Psychopharmacologia*, **3**, 15–22.

IDESTRÖM, C-M. & CADENIUS, B. (1963). Chlordiazepoxide, dipiperon and amobarbital. Dose effect studies on human beings. *Psychopharmacologia*, **4**, 235–246.

KELLY, E. L., MILLER, J. G., MARQUIS, D. G., GERARD, R. W. & UHR, L. (1958). Continued meprobamate and prochlorperazine administration and behaviour. *A.M.A. Archs. Neurol. Psychiat.*, **80**, 247–252.

KORNETSKY, C. (1958). Effects of meprobamate, phenobarbital and dextro-amphetamine on reaction time and learning in man. *J. Pharmac. exp. Therap.*, **123**, 216–219.

KORNETSKY, C., HUMPHRIES, O. & EVARTS, E. V. (1957). Comparison of psychological effects of certain centrally acting drugs in man. *A.M.A. Archs. Neurol. Psychiat.*, **77**, 318–324.

KORNETSKY, C., VATES, T. S. & KESSLER, E. K. (1959). A comparison of hypnotic and residual psychological effects of single doses of chlorpromazine and secobarbital in man. *J. Pharmac. exp. Therap.*, **127**, 51–54.

LATZ, A. & KORNETSKY, C. (1965). The effect of chlorpromazine and secobarbital under two conditions of reinforcement on the performance of chronic schizophrenic subjects. *Psychopharmacologia*, **7**, 77–88.

LAWTON, M. P. & CAHN, B. (1963). The effects of diazepam (Valium) and alcohol on psychomotor performance. *J. nerv. ment. Dis.*, **136**, 550–554.

LEGGE, D. & STEINBERG, H. (1962). Actions of a mixture of amphetamine and a barbiturate in man. *Br. J. Pharmac. Chemother.*, **18**, 490–500.

LEHMANN, H. E. & CSANK, J. (1957). Differential screening of phrenotopic agents in man. Psychophysiologic test data. *J. clin. exp. Psychopath.*, **18**, 222–235.

MARQUIS, D. G., KELLY, E. L., MILLER, J. G., GERARD, R. W. & RAPOPORT, A. (1957). Experimental studies of behavioral effects of meprobamate on normal subjects. *Ann. N.Y. Acad. Sci.*, **67**, 701–711.

MILLER, G. A. (1948). The perception of short bursts of noise. *J. acoust. soc. Amer.*, **20**, 160–170.

MILLER, G. A. & TAYLOR, W. G. (1948). The perception of short bursts of noise. *J. acoust. soc. Amer.*, **20**, 171–182.

MIRSKY, A. F., PRIMAC, D. W. & BATES, R. (1959). The effects of chlorpromazine and secobarbital on the C.P.T. *J. nerv. ment. Dis.*, **128**, 12–17.

MIRSKY, A. F. & CARDON, P. V. (1962). A comparison of the behavioral and physiological changes accompanying sleep deprivation and chlorpromazine administration in man. *Electroenceph. clin. Neurophysiol.*, **14**, 1–10.

PRINZMETAL, M. & ALLES, G. A. (1940). The central nervous stimulant effects of dextro-amphetamine sulphate. *Am. J. med. Sci.*, **200**, 665–673.

ROBACK, G. S., KRASNO, L. R. & IVY, A. C. (1952). Effect of analeptic drugs on the somnifacient effect of seconal and antihistamines as measured by flicker fusion threshold. *J. appl. Physiol.*, **4**, 566–574.

RUSHTON, R. & STEINBERG, H. (1963). Mutual potentiation of amphetamine and amylobarbitone measured by activity in rats. *Br. J. Pharmac. Chemother.*, **21**, 295–305.

SCHWARTZ, M. A., KOECHLIN, B. A., POSTMA, E., PALMER, S. & KROL, G. (1965). Metabolism of diazepam in rat, dog and man. *J. pharmac. exp. Therap.*, **149**, 423–435.

SHURTLEFF, D., MOSTOFSKY, D. & DIMASCIO, A. (1962). The effects of some phenothiazine derivatives on the discrimination of auditory clicks. *Psychopharmacologia*, **3**, 153–165.

SMART, J. V. & TURNER, P. (1966). Influence of urinary pH on the degree and duration of action of amphetamine on the critical flicker fusion frequency in man. *Brit. J. Pharmac. Chemother.*, **26**, 468–472.

SNEDECOR, G. W. (1956). *Statistical Methods.* 5th ed. Collegiate Press, Ames, Iowa.

STEINBERG, H., RUSHTON, R. & TINSON, M. (1961). Modification of the effects of an amphetamine-barbiturate mixture by the past experience of rats. *Nature, Lond.*, **192**, 533–535.

SYMMES, D., CHAPMAN, L. F. & HALSTEAD, W. C. (1955). The fusion of intermittent white noise. *J. acoust. soc. Amer.*, **27**, 470–473.

TURNER, P. (1965). The changes in critical flicker fusion frequency induced by some physiological procedures and by drugs, together with observations on the reliability of olfactory testing. M.D. Thesis, Univ. London.

UHR, L. & MILLER, J. G. (1960a). Behavioural toxicity of emylcamate (Striatran). *Am. J. med. Sci.*, **240**, 197–203.

UHR, L. & MILLER, J. G. (1960b). Experimentally determined effects of emylcamate (Striatran) on performance, autonomic response, and subjective reactions under stress. *Am. J. med. Sci.*, **240**, 204–212.

WEISS, B. & LATIES, V. G. (1964). Effects of amphetamine, chlorpromazine, pentobarbital, and ethanol on operant response duration. *J. pharmac. exp. Therap.*, **144**, 17–23.