Psychopharmacologia (Berl.) 29, 365—384 (1973)

The Effects of a Single Administration of Etifoxine on Several Psychological Tests

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Received December 29, 1972

Abstract. The effects of etifoxine on healthy *Ss* was measured employing perceptual, psychophysiological and motor tests, in addition to which a personality inventory was given. All *Ss* took both drug and placebo with an interval of one week according to a balanced design. The same experimental procedure was used on both occasions under double blind conditions. The difference between the two sessions was tested for significance. Analyses of covariance were carried out with respect to the personality factors psychoticism, extraversion and neuroticism. The drug had depressant effects on performance in perceptual tests, particularly flicker fusion, and it also affected habituation to tones of both the evoked cortical potential and the GSR in the same direction. The drug seemed completely inactive with respect to motor performance. There was a distinct interaction between drug-effect and personality factors. *Ss* whose scores indicated a low level of cortical arousal were less affected by the drug than others.

Key words: Psychotropic Drugs — Level of Arousal — Perceptual Tests — Psychophysiological Tests — Motor Tests — Questionnaires.

Introduction

Etifoxine (HOE 36.801) is a new psychotropic compound developed in the Hoechst Laboratories. Its systematic name is 6-chloro-2-ethylamino-4-methyl-4-phenyl-4H-3, 1-benzoxazine. The compound has been found to have tranquilizing effects with an anti-convulsive spasmolytic and anticholinergic action. As very little is known about the drug an exhaustive study of its behavioural effects was planned to confirm its general action and reveal any specific effects. A generally depressive or stimulant action would affect all tests used in the predicted direction according to the Yerkes-Dodson-Law. More often however, psychotropic drugs act selectively on different brain structures in a dose-dependent manner. A comprehensive review on the use of psychological tests measuring drug action is given by Trouton and Eysenck (1960).

A battery of tests comprising perceptual, motor, psycho-physiological and questionnaire measures was employed in the present study to obtain a full description of the effects of the drug on normal *Ss*. Twelve tests and

a peronality inventory were administered in two separate studies since the total time of testing would have exceeded what is considered reasonable for the *S*. But as the experimental design and methodology are the same in both studies, a combination of the two seemed justified. The timing of drug-administration and testing differs slightly between one study and the other since in the latter more information about the absorption gradient was supplied by the Hoechst Pharmacological Laboratories.

Method

Subjects

The *S*s had a medical check before being accepted for the experiment. Their general state of health, proneness to allergies and gastric disorders and any past diseases were taken into account. *S*s were accepted for the experiment on condition that they refrained from taking any alcohol or drugs 24 h before testing day (*S*s who were under medication with drugs were excluded). They had to have at least 7 hrs of sleep before the testing day and were not allowed to smoke for at least 2 hrs before the testing session. For safety reasons they were asked not to drink alcohol or drive for 2 days following the testing day. The *S*s were all working in the Institute of Psychiatry and medical supervision was provided. A total of 16 male *S*s was employed for both studies. Their average age was 24 years (*SD* 1.15), their average height was 177 cm (*SD* 6.8 cm), and their average weight was 77.39 kg (*SD* 8.47 kg). Each of the *S*s had 2 testing sessions with an interval of one week. The drug and its corresponding placebo were administered according to a balanced design. Half of the Ss took the drug first and placebo on the second occasion and vice versa with the other half of the *S*s. Comparisons between drug and placebo could thus be made within *S*s. The *S*s were paid at the end of their last testing session. The experiment was carried out under double blind conditions.

All *S*s filled in the PI (Personality Inventory) at one occasion. The test gives scores for three personality factors: Psychoticism, Extraversion and Neuroticism (Eysenck and Eysenck, 1969) which were expected to interact with drugs affecting the level of arousal.

Study 1

1. Critical Flicker Fusion (CFF)

The critical flicker fusion threshold is the lowest frequency at which a flickering light appears to be "steady". This test seems to be most appropriate to generally establish whether an agent had an effect on the level of cortical arousal. It has been shown in a vast number of experiments that the threshold varies according to the level of arousal (Simon and Brozek, 1952). Under high arousal the fusion frequency is higher; the individual can still discriminate flickers at a frequency which would have led to the impression of a steady light under lower arousal. The CFF test has therefore become a widely used instrument for testing drugs which affect the level of arousal (Ikeda, 1960; Holland, 1960; Warwick and Eysenck, 1968). The CFF was used in the present study to find out if the drug had any effect on the central nervous system and specifically to confirm its depressant action.

Apparatus. To avoid problems of adaptation found with ascending and descending flicker frequencies, and also to increase certainty of the subjective judgement

as to when the light appeared to be "steady", a different method was devised. Four lights of equal brightness were used only one of which flickered.

The flicker fusion apparatus[1] consisted of 4 Monsanto MV4H light-emitting diodes (LED) which are described in a Monsanto data sheet (Electronics, ESP, June 1970). The LEDs received power, 55 mA each, for a voltage regulated power supply (model DS 50/5). The LEDs were driven by switching transistors whose switching rate was determined by either a fixed frequency oscillator (480 Hz) or flip-flops. The flip-flops provide an exact 1:1 light-dark ratio. The UJG and flip-flop circuits were based on a standard design (Cleary, 1964, p. 338). On each presentation one randomly selected LED was driven by the variable frequently oscillator and the remaining three LEDs were driven by the higher frequency oscillator to keep the differences in intensity between the flickering light and the "steady" lights unnoticeable. The three "steady" lights were driven at 480 Hz rather than DC so that their transistor drivers could still be used in the switching mode, thus avoiding power dissipation problems and maintaining the simplicity of the circuit. The 4 LEDs were mounted in a 2.5 cm square such that they subtended a visual angle of 1° when viewed from 60-in. The LEDs were mounted immediately behind 0.56 cm circular holes through which their columnated light projected.

The experiment was set up on line with a LINC-8 computer. The measurement of the flicker frequency was done in terms of period (time lapse between flickers in msec). The program[2] estimated which period of flicker resulted in a given level of performance in terms of the percentage of correct responses. The three levels of performance were 50, 67 and 80% correct responses. They were achieved by alternating the period on the basis of the subjects immediately preceding response. Essentially if the S is right the difficulty of the task is increased (period shortened), while if he is wrong the difficulty is decreased (period lengthened). Varying the ratios of the two step sizes allows different average difficulty levels to be maintained. The difficulty levels were presented alternately to ensure that the *S* would find some trials relatively easy and not become discouraged. The reaction time of the *S*s from the onset of the lights was stored in addition to the periods of the presented frequencies.

Procedure. The *S* was seated in a chair looking at the light panel and operating with one hand a set of keys corresponding to the four lights; the room was lit during the testing session. To avoid withdrawal of attention from the task during presentation of the lights the *S* started the trial himself by pressing a fifth key. All four lights then came on with one of them flickering. As soon as the *S* had decided which one was flickering he pressed the corresponding key after which the light went off again. The *S* was instructed to guess if he could not make out which one of the 4 lights was flickering. The exposure time of the light was 2 sec and the trial was scored incorrect if the *S* had not responded until then. The first 30 trials, lasting for about four minutes, were allowed for flicker adaptation and their results discarded.

2. Body Temperature

The body temperature was measured orally with a standard commercial thermometer.

3. Subjective Tension

Bartenwerfer's AZA-scale (Allgemeine Zentrale Aktiviertheits-Skala, Bartenwerfer, 1969) was administered repeatedly throughout the experiment. This provides

1 The flicker fusion apparatus was developed and built by Mr. Robert A. Stewart.

2 The programs for the Linc-8 computer were kindly provided by Dr. C. D. Frith.

a measure of tension on a scale of 0 (relaxed) to 50 (highly tense). The object of administering this scale was to find out whether a decrease of arousal due to the drug could be assessed subjectively by the *S*.

4. Evoked Potential

Several studies (Buchsbaum and Silverman, 1968; Silverman, Buchsbaum, and Henkin, 1969; Lader and Norris, 1968) have shown that intrinsic and extrinsic arousal affect the latency and amplitude of the Averaged Cortical Evoked Potential (AEP). The effect is such that higher arousal, whether from the Subjects resting level or induced by drugs or stimulus effects, leads to larger response amplitudes and shorter response latencies. A combined description of the apparatus for psychophysiological measurement is given later.

5. Galvanic Skin Response

With the Skin Conductance Response (GSR) increased arousal has been found to be characterised by higher basal conductance, increased spontaneous fluctuation rate, slower response habituation and larger response amplitude. Experiments with drugs (Kristofferson and Cormack, 1960; Mitchell and Zax, 1958; Carren, 1958; Martin, 1960; Lader, 1964) shows that manipulation of the arousal level of the subject affects the scores on some of these measures in the predicted direction.

6. Heart Rate

Literature on the effects of drugs on the Heart Rate (HR) Response to stimuli is rather scanty, although an effect by a depressant drug to increase the number of spontaneous fluctuations has been shown (Lader, 1965). There is a larger amount of work done on the relationship between the HR Response and arousal. This has been reviewed by Graham and Clifton (1966). In general it is found that the more arousing stimuli produce larger subsequent HR acceleration.

If Etifoxine has a depressant action we would predict longer latencies and smaller amplitudes in the AEP, and a decrease in GSR and HR measures of arousal. As there was no control for direct peripherial action of the drugs in the present experiment, the possibility of this must be considered in interpreting GSR and HR results.

Apparatus. The skin resistance was obtained by the use of an apparatus built in the department and described elsewhere (Venables and Martin, 1967, p. 73). The consistancy of the current flow was achieved by the use of a transistor circuit in place of R1 in model b1). The electrodes were Ag/AgCl and of a diameter of 64.19 mm^2. The state of the Ag/AgCl coat of the electrodes was repeatedly tested and rechloriding was carried out whenever necessary. Their placement was bipolar, from the first to the second finger of the left hand. The sites were wiped clean with cotton wool, afterwards an adhesive plaster (Devices Ltd.) was placed over the site. This has a central hole which allows an area of contact of 1 cm^2 with the skin. The electrolyte used was a commercial saline gell (Johnson and Johnson). The electrode was fastened with white tape.

EEG and EKG were measured with a Mingograf EEG machine. Electrodes were Ag/AgCl, the chloride coat was repeatedly tested and replaced when necessary. The area of the skin to which the electrodes were attached was first cleaned with Acetone. Electrodes were then attached to the scalp (Areas Cz and T3) with Collodium and with double sided adhesive discs to the relatively hairless areas. Electrolytic gelly (Neptic Electrode Gell) was introduced between the electrode

and the skin through a central hole in the electrode using a bluntened hypodermic. This was also used to abrade the skin under the electrode in order to reduce the skin resistance to an acceptable level. Skin resistance was tested through the Mingograf and reduced by further abrasion of the skin if necessary. The same electrode attachment procedure was used for both EEG and EKG electrodes. EEG readings were taken with a time constant of 0.3 sec and subjected to a filter of 70 c.p.s.

Both EEG and EKG, together with the GSR and a stimulus marker were recorded on a four channel analog tape recorder and at the same time on a polygraph paper output from the Minograf.

Tonal stimuli were generated by a LF Oscillator and presented binaurally to the subject through stereophonic headphones. The tone was switched on and off automatically through a relay controlled by a counter and timer.

The GSR, EEG and EKG were all recorded on magnetic tape in analog form and analysed using a Linc-8 Computer.

Experimental Procedure. Etifoxine was administered orally in one dose (3×100 mg capsules per *S*). The full dose was taken by the *S* at 13.00 after a light lunch and no more than one cup of coffee or tea, it had to be the same beverage at both occasions. The *S*s went back to work after taking the drug and came to the experimenting room at 15.30. The *S* was allowed a resting period between 15.30 and 16.00 hours. He was seated in a comfortable chair in a sound-proofed room. GSR electrodes were fixed to the first and second fingers of the left hand. EEG bipolar electrodes were attached to the head with collodium in positions Cz and T3 (International Standard). Compensation ground electrodes were attached to the mastoid bones. EKG electrodes were also attached, one on the left forearm and the other behind the right ear. The PI form was then completed on one occasion. The actual testing started at 16.00. Etifoxine was thus allowed 3 hrs to be absorbed. The testing took 1 hr and it was hoped that the drug would be at its peak level of effectiveness during this time.

After the *S* had filled in the tension scale his body temperature was measured. For the CFF test the *S* had to put on an artificial pupil which consists of adjustable spectacles allowing him to see with the left eye only, through a hole of 2 mm in diameter. This precaution was taken to avoid possible confounding of pupil dilation and generally arousing effects of the drugs on the performance. The *S* had 90 trials on the CFF experiment during which he stayed in the room on his own, being watched through a one-way mirror from the room next door. The 90 trials took about 12 min on the average to complete.

Following this CFF experiment the EEG and EKG electrodes had the area underneath them abraded with a blunt needle and the electrolyte injected between the electrode and the skin. The subject was then given the following instructions: "In this experiment we will be measuring your physiological responses to noise. You will hear tones through the headphones. Each tone is of 1 sec duration while there is an interval of about 30 sec between tones. There will be between 20 and 25 tones altogether so that the experiment lasts about 15 min. You do not have to do anything while listening to the tones. Just sit back and relax. The lights will be turned off during the experiment and I would like you to keep your eyes closed during this time. The tones will begin in about 3 min."

The subject then put on the headphones, the light was turned off and the experimenter left the room. Following 1 or 2 min in which the calibration of the apparatus was checked the tonal sequence was initiated.

During each session the subject was presented with 21 tones. The tones were all at 1000 Hz and at 95 Db (ref. 0.0002 dynes/cm^2). The sound level was frequently

checked with a sound level meter. The stimulus sequence was automatically scheduled to give a 1 sec stimulus every 33 sec. The three output channels (EEG, EKG and GSR) were constantly monitored on polygraph paper output to enable range and baseline adjustments to be made when necessary. They were also, together with the marker channel, recorded on magnetic tape for later computer analysis.

Finally another CFF test was made identical to the previous one and the subjective tension and body temperature assessed again at the end of the experiment.

Study II

7. Spiral After-Effect

The spiral after-effect is an apparent countermovement of a spiral after it has stopped rotating; this illusion can be experienced with any moving surface provided it has discriminable contours. Following Eysenck's drug postulate (1957) the spiral was introduced as a measure of drug effects. Depressant drugs are expected to shorten the duration of the after-effect while stimulant drugs are expected to lengthen it. This hypothesis has been supported by studies with d-amphetamine and sodium amylobarbitone (Eysenck and Easterbrook, 1960; Eysenck, Holland, and Trouton, 1957), and also with meprobamate (Costello, in: Eysenck, 1963).

Apparatus. A four-throw spiral 18 cm in diameter was mounted on an electric motor and set up at an appropriate distance from the *S* subtending a visual angle of 5°. The speed of rotation was 100 r.p.m. and a black circle in the middle of the spiral provided a fixation point.

All *S*s were allowed a practice trial on the day before the actual testing took place.

The time from switching off the spiral until the *S* said "now" was measured with a stop-watch. 5 trials were given each of which had a different time of stimulation (that is the time the spiral was actually rotated before being stopped). The stimulation times were 15, 30, 80, and 100 sec. Other tests were administered between the trials to avoid massed administration.

8. Mood Adjective Check List (MACL)

Obtaining a subjective judgement of the *S*'s mood seemed appropriate mainly to assess whether the drug induced a certain disposition in the *S* but also to have a control on whether the *S*'s performance was due to some transitional emotional state rather than to the drug. Nowlis (in Tomkins and Izard, 1965), factoranalyzed 120 mood adjectives and established 12 moodfactors of which 8 were considered relevant to the present study:

A. Aggression (angry, irritable, annoyed, frustrated, touchy, fed-up).

B. Anxiety (fearful, jittery, startled, anxious, tense, nervous).

C. Surgency (lively, witty, carefree, playful, vivacious, cheerful).

D. Elation (refreshed, pleased, relaxed, happy, lighthearted).

E. Concentration (concentrating, serious, thoughtful, attentive, introspective, absorbed).

F. Fatigue (tired, bored, drowsy, uninterested, weary, distracted).

H. Sadness (low, insecure, listless, sad, downhearted, gloomy).

K. Vigour or general Activation (alert, active, energetic, vigourous, stimulated, quick).

The scoring was done by means of a key counting 0 for "no", 1 for "?", 2 for "+", and 3 for "++". A summative score was obtained for each factor.

It was expected that a depressant drug would lower the scores of the factors A, B, C, D, E, and K and raise F and H.

9. Mirror Drawing

This is a co-ordination task requiring the *S* to trace along with a stylus while observing his performance in a mirror. No drug studies on mirror drawing are known to us; however, since the task proved to be sensitive to different levels of arousal in an earlier study (Eysenck and Sartory, 1971) it was chosen to test for drug effect. Arousal seemed to have a differential effect on the two parameters, error and speed, observed at this task. High arousal induces a slow and accurate performance while low arousal leads to a fast and inaccurate performance.

Apparatus. The design of the mirror drawing track is curved in such a way that the curvature is equal throughout. The S has to follow the track with a stylus made of metal. He was instructed to go as fast as possible but to avoid touching the metal border on either side of the path. To make certain that *S*s cannot disobey instructions and slide the stylus along the side of the path, small niches are used to form part of the border. *S*s could see the track and their performance in a mirror mounted on a rack behind the track. The actual design was covered by a blind at an appropriate height to allow for free movement of the arm. The track is connected to an electric clock which counts the time of performance and registers every contact with the brass border. The *S* had the task explained and demonstrated and was given a practice trial on the day before the first testing session.

10. Tapping

Tapping is a test of psychomotor functions; the *S* has to tap with one finger at a high speed and constant rate for about 1 min. It is therefore a measure not only of co-ordination but also fatigue and reactive inhibition. According to Eysenck's drug-postulate (1957) one would expect the tapping speed to be higher and more constant under stimulant drugs than under placebo while depressant drugs are expected to impair the performance in terms of speed and constancy of movement.

Apparatus. The tapping apparatus consists of a panel on which the *S* rests his dominant hand. A plastic bar prevents the fingers from moving except for the middle finger which lies upon the bar and moves a little metal lever while tapping. The lever operates an oscillometer providing electrical impulses which are recorded on a tape. A scale shows the tapping rate and *S*s were instructed to keep the rate constant at 5 taps/sec. A visual control for the tapping was considered beneficial in that it decreases interindividual and day-to-day differences in motivation. The tapping performance lasted for 1 min.

11. Reaction Time Task (RT)

Reaction time is an important measure for testing drugs that act on the CNS not only in providing information about the drug but also for its implications in everday life.

Apparatus. Six lights and six corresponding buttons were mounted on a metal panel; they were arranged in a semi-circle around a centrepoint on which *S*s had to rest their index finger. *S*s were instructed to press the corresponding buttons with this finger as soon as a light came on. The task was set up on-line with a computer (LINC-8); an appropriate program provided the experimental conditions. Three series of RT were given; one with two lights operating, the second with four lights, and the third with six lights. Each of these series contained 2 sets of 24 trials

each; in one set the light appeared until it was switched off by the *S* in the other the light only appeared for 0.5 sec and disappeared if not switched off by then. Half a second was found in a previous experiment to be the average RT for this apparatus. The trials of these two types were intermixed at random. The trials with the short exposure of the light were thought to exert pressure upon the *Ss* not to slow down during the experiment.

12. Tracking Tasks

Tracking tasks are eye-hand co-ordination tests; in the present design a moving target has to be chased by a pointer operated by the *S*. These tasks require complex skills that are very much a part of every day activities. The most common tracking task apparatus is the pursuit rotor which has been used several times to test the effects of drugs (e.g. Eysenck. *et al.*, 1957; Treadwell, 1960).

In both reports the impairment of the performance was more clearly shown in the later stages due to an increased build-up of reactive inhibition occuring with these automatic and repetitive movements. It is assumed that in the later stages of learning the visual feed-back is not an essential part of the performance since in the case of the pursuit-rotor the track of the target is highly predictible and soon "perceptually learned". It seemed of interest to investigate the effects of drugs on unpredictible target movements whose mastering requires constant visual feed-back and therefore becomes more like a vigilance task.

Three different tracks were employed in the present study:

a) A fast predictible track with properties very much comparable to the pursuit-rotor. As with the latter task one would expect performance to deteriorate progressively with depressant drugs.

b) A slow unpredictible track: This was kept at a rather slow speed to encourage *Ss* to follow it as accurately as possible. The respective impairment and improvement induced by the drugs was expected to show up right from the start since learning the track should be more difficult in this case.

c) A predictible track with varying speed according to the speed of the *S*'s performance. It was expected to rule out individual differences in skill and give each *S* the opportunity to perform around his upper limit of tracking ability.

Apparatus. The experimental set-up consisted of an extension scope to the LINC-8 computer and a tracking device whose movements were fed back into the computer. Appropriate programs provided the chosen experimental conditions. A square target moved up and down the screen such that the movement described a sine-wave when plotted over time. The pointer consisted of a cross that could be moved up and down the screen by moving a stick attached to the tracking device. The device was placed on the side of the *S*'s dominant hand; it was positioned at such a height that the stick could be moved backwards and forwards while the arm was subtending a right angle at the elbow. The predictible track consisted of a since-wave of 88 r.p.m.; the task lasted for 5 min (Fig. 1).

The unpredictible track was a combination of sine waves of 5, 17.5, 32.5, and 42.5 r.p.m.; *Ss* had to track it for 3 min 45 sec (Fig. 2).

The variable speed track started slowly and the S's performance was sampled every 8 cycles. Provided that the frequencies of the performance coincided with those of the target the latter was increased to a set level for the next 7 cycles of the performance, etc. until the performance was slower than the target. The target was then slowed down, and so on. The task lasted for 5 min.

13. The PI (Personality Inventory) was administered in both studies to obtain a measure of the three personality factors; Psychoticism, Extraversion and Neuroticism (Eysenck and Eysenck, 1969). Particularly the first of the three has been

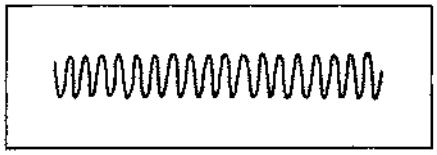

Fig. 1

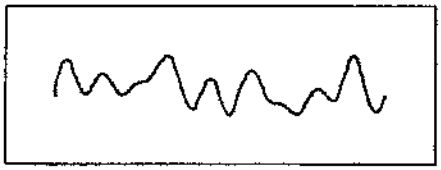

Fig. 2

Fig. 1. The predictible track; movement of the target plotted against time

Fig. 2. The unpredictible track

shown to indicate the level of cortical arousal and was therefore expected to interact with the drug effects.

Experimental Procedure. In the second study 300 mg of etifoxine was administered at 11.00 hours and the testing started at 15.00 thus allowing the drug 4 hrs to be absorbed. Two experimenting rooms were used; the apparatus for the spiral after-effect and the tapping were set up in one of them and the extension scope for the tracking task, the reaction time panel, and the mirror drawing apparatus in the other one. The order in which the tasks were administered required the *S* to leave one testing room and go to the other one four times. It was hoped in this way to make the testing procedure less tiresome and provide some "airing" for the *S*s.

The order in which the tests were administered was:

1. Spiral after-effect, 15 sec stimulation
2. Tapping
3. Spiral after-effect, 30 sec stimulation
4. MACL
5. Spiral after-effect, 100 sec stimulation
6. Unpredictible track
7. Reaction time task, 4 lights operating
8. Spiral after-effect, 80 sec stimulation
9. Track with varying speed
10. Mirror drawing
11. Reaction time task, 2 lights operating
12. Fast track
13. Reaction time task, 6 lights operating
14. Spiral after-effect, 50 sec stimulation.

E stayed in the room with the *S* during all tasks except for the tracking task and the reaction time task. In both cases the *S*'s performance was observed on the computer.

Results and Discussion

1a. CFF Period

The data obtained in the CFF study were 3 mean periods (each of them averaging 30 trials) for each of the 3 levels of performance (50% of the responses correct, 67% correct, and 80% correct). The means of the first 30 trials were discarded since they were used to find the approximate threshold of the given level of performance and also served as practice trials leaving 2 values ("Trials") for every session.

The data can be described in terms of a 4-factor paradigm: Conditions (2) × Sessions (2) × Trials (2) × Replications (8), conditions being the 2 drug and the 2 placebo treatments. Sessions signify the two testing sessions one before and one after the habituation experiment; the factor "Trial" applies to the two measures obtained in every session; replications stand for the Ss. The raw scores were replaced by transformed scores contrasting the various levels of the factors and interactions. They were tested against the replications (i.e. error term) in a one way analysis of variance.

At the performance level of 50% correct choices the trial effect is significant ($F = 6.103$, $df = 1/7$, $p < 0.04$). The performance improves from 27.545 c/s to 28/135 c/s towards the end of the task.

Etifoxine proved to have a markedly consistent detrimental effect on the performance at all levels of difficulty. Since the results at the 3 performance levels were in the same direction, an attempt to combine them for this drug to gain a more reliable result seemed advisable. A principal component analysis was carried out which proved that the variables in question had one factor underlying them that covered 77.36% of the variance. A combination of the 3 scores into one seemed therefore justified. In the analysis of variance with the new variables the same result with higher significance was achieved ($F = 8.424$, $df = 1/7$, $p < 0.02$). When combining the mean scores separately for the drug and the placebo condition the mean threshold after intake of etifoxine is 24.214 c/s and after placebo 26.993 c/s. The difference is therefore 1.770 c/s.

No results were expected from the personality scores since there were only 8 *Ss* employed in the experiment. After finding a significant correlation between Psychoticism and the difference score of the etifoxine—placebo performance however an analysis of covariance was run for the personality factor. The correlation is $r = -0.758$ which is significant at the 5% level ($df = 7$). It indicates that the difference between the two conditions is smaller for the high P-scorers. Plotting the CFF scores of the placebo condition against the corresponding P-scores showed in fact that high P-scorers tend to have an inferior performance as compared to low P-scorers (Fig. 3). After eliminating the covariate Psychoticism the difference in the CFF threshold for etifoxine *vs* placebo reached a 1% level of significance in the analysis of variance ($F = 13.320$, $df = 1/7$, $p < 0.01$). Due to the small number of *Ss* this result is far from being a proof for the basic notion that the personality-derived arousal interacts with changes in arousal induced by psychotropic drugs. It merely suggests that low P-scorers react more strongly to the drug than do high P-scorers as far as can be measured in the CFF task. To decide whether high P-scorers absorb less of the drug and are therefore less affected or

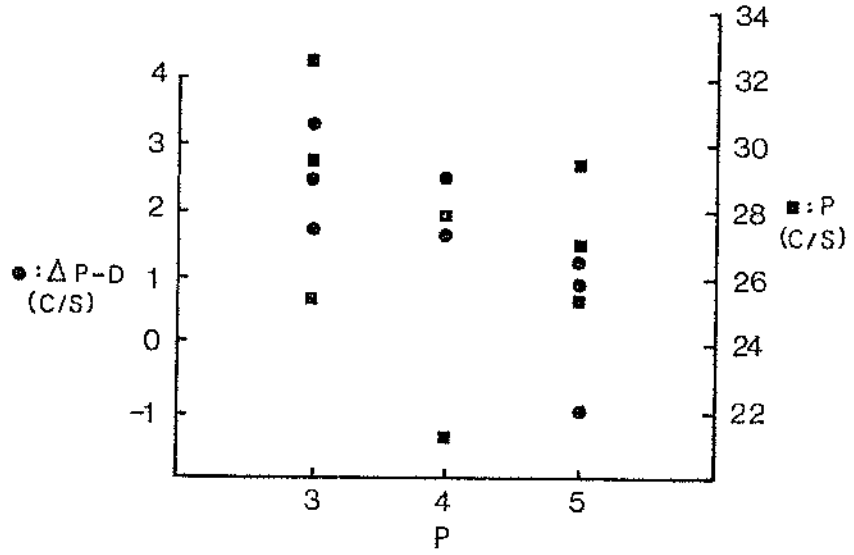

Fig. 3. Difference between Etifoxine and placebo in the CFF threshold plotted against the corresponding Psychoticism-scores (circles): CFF threhold of placebo condition plotted against Psychoticism (squares)

whether their performance is less impaired by the drug because it is inferior in the first place is not possible in the present study.

1b. CFF Reaction Time

No significant result was obtained with the CFF reaction time. The drug had no influence upon the time when the decision was made as to which light was flickering.

2. Temperature

The only result obtained in the analysis of variance of the body temperature was its significant decrease from the beginning of the session to the end, irrespective of drug or placebo condition ($F = 11.548$, $df = 1/7$, $p < 0.01$). The drop in temperature was from 36.93°C to 36.69°C combining all scores of the drug *vs* the placebo condition. The result can be explained by the character of the experiment which made it necessary for the *S*s to sit still during the whole hour of testing.

3. Subjective Tension

The drug could not be shown to have any systematic effects on the rating of the Bartenwerfer tension scale. The only significant result obtained in the analysis of variance is an increase in tension from the beginning of the testing session to the end. ($F = 8.207$, $df = 1/7$, $p < 0.02$). Combining the ratings at the beginning of the testing session across the condition and also at the end the score rises from 21.14 to 23.78 scale units. This result

can probably be explained by assuming that the *Ss* got slightly annoyed with the testing since the procedure, being the same on both occasions soon lost its novelty.

4. EEG Evoked Potential Analysis

The EEG output was sampled every millisecond for 500 milliseconds after stimulus onset to give the evoked potential for each stimulus. These were then averaged across twenty stimulus presentations (the response to the first stimulus was ignored). Responses showing excessive muscle potential responses were left out of the average, these however were few. No other selective criteria were used. The measure obtained from the averaged evoked potentials were:

1. P2 Latency (milliseconds)
2. N2 Latency (milliseconds)
3. P3 Latency (milliseconds)
4. N3 Latency (milliseconds)
5. P2-N2 amplitude (peak to trough amplitude in microvolts)
6. N2-P3 amplitude (peak to trough amplitude in microvolts)
7. P3-N3 amplitude (peak to trough amplitude in microvolts)

Multivariate Analysis of Variance was carried out for each response system together with Univariate Analysis of Variance for the Individual Variables. For the AEP the Multivariate test was not significant. The Univariate test for P3 Latency gave an F of 4.437 ($p < 0.047$) while the

Table 1. Mean values for some of the psychophysiological tests used. Change score are in terms of orthogonial polynomial coefficients for linear trends

Variable	Etifoxine	Control
AEP P3 Latency (milliseconds)	252.2	225.9
GSR rasal conductance (root conductance)	11.24	10.16
GSR Basal conductance change	− 0.70	− 2.05
GSR Number of zero responses	7.13	7.38
GSR Onset latency (seconds)	2.20	2.14
GSR Onset latency change	0.82	0.43
GSR Peak latency (seconds)	4.23	3.97
GSR Peak latency change	1.09	− 0.03
GSR Half recovery latency (seconds)	7.69	6.57
GSR Half recovery latency change	− 1.24	− 0.92
GSR Number of spontaneous responses per minute	1.05	1.14
GSR Change in number of spontaneous responses	0.32	− 0.06
GSR Response amplitude (log conductance)	7.69	7.15
GSR Response amplitude change	− 7.10	− 11.61
GSR Response magnitude (log conductance)	5.19	5.17
GSR Response magnitude change	− 9.91	− 12.08

remaining variables showed no significant difference. The lack of significance for the other latency measures is not surprising as other experiments have shown that P3 letency is not correlated with other latency measures for the stimulus paradigm used here. The means are given in Table 1 and show that the effect is in the predicted direction. However if the effect is due to arousal ot would be reasonable to except the amplitude measures to be a more sensitive test of this whereas in fact they show no difference.

5. GSR Analysis

The Skin Resistance was sampled by the Linc every 50 milliseconds for 5 seconds before and 20 seconds after each stimulus. It was then scored automatically for response onset (a significant increase in slope), for response peak (the first maximum following an onset), and for half recovery. A response was then identified as a response to a stimulus if its onset was the first to occur in the five seconds following stimulus onset. The output from the Linc was then fed into the London University CDC 6600 computer with a program to give mean value and linear trends for the following variables:

1. Base level (in square root conductance units)
2. Number of stimuli to which there was no response
3. Response Onset Latency (seconds)
4. Response Peak Latency (seconds)
5. Response half recovery latency (seconds)
6. Number of spontaneous responses (responses other than those to stimuli) which occur per minute.
7. Response Magnitude (square root conductance ignoring responses of zero amplitude)
8. Response Amplitude (square root conductance including responses of zero amplitude)

For the GSR the Multivariate Test gives a highly significant result ($F = 16.4$, $p < 0.0006$). Looking at the Univariate tests for the sixteen GSR measures we find significant results for Response Magnitude change ($F = 7.97$, $p < 0.011$), and Peak Latency Change ($F = 6.57$, $p < 0.019$) while Basal Conductance change ($F = 3.89$, $p < 0.062$) and half recovery latency ($F = 4.31$, $p < 0.051$) are approaching significance. It is noticeable that three of these results are from change scores in situations where the means for the same score do not differ (see Table 1). This indicates a cross-over effect as such a pattern amounts to a Drug by Trials Interaction. The plot of Response Amplitude over trials for blocks of four trials is given in Table 2. It can be seen that the drug has considerably suppressed the initial level of responding while for the later stimuli the difference disappears or even reverses.

Table 2. Mean values obtained over trials for the response magnitude scores (Square root conductance units)

Trials	Etifoxine	Control
1—4	26.0	28.6
5—8	13.6	18.4
9—12	10.2	12.6
13—16	14.3	14.0
17—20	13.8	10.5

These results suggest that etifoxine has reduced the susceptability of the subject to extrinsic arousal. The non-significant results for most of the GSR variables, on the other hand, suggest that the intrinsic arousal level of the subject is not affected by the drug. It should be noticed that, for the subjects used, the absolute levels of arousal in both drug and control groups are quite low. No conclusions can be drawn about the effect of the drug on higher levels of intrinsic arousal.

6. Heart Rate Analysis

The Linc computer sampled the EKG output every 5 milliseconds for five seconds before and twenty seconds after each stimulus. A slope criterion was used to detect the R-wave, the inter-beat interval from R-wave to R-wave was measured and recorded as a histogram of Inter-beat Interval against time. This histogram was inverted to give a rate measure of beats per minute (BPM) against time. All maximum and minimum values of this measure were scored and used to calculate the following variables:

1. Basal Heart Rate (Beats per minute)
2. Number of Oscillations per minute (rate of sinus arhythmia)
3. Mean peak to trough amplitude of oscillations
4. Latency of the largest maximum to occur within nine seconds after the stimulus (in seconds)
5. Amplitude of the above in BPM
6. Latency of the smallest minimum to occur within nine seconds after the stimulus (in seconds)
7. Amplitude of the above (in BPM)

The above measures were obtained for the first five stimuli only. Analysis on the CDC 6600 gave mean values and linear trends for these variables. For HR measures neither the Multivariate Test nor any of the Univariate tests gave significant results.

7. Spiral After-Effect

The five scores were transformed into three indices which proved to be more reliable than the raw scores (Holland, 1965). The three derived

scores are a kind of orthogonal polynomial transformation representing the level code, the linear trend, and the quadratic trend.

A. Height: the absolute magnitude of the after-effect (AE) duration which is in fact the mean of the five scores:

$$A = \frac{AE(15) + AE(30) + AE(50) + AE(80) + AE(100)}{5}.$$

B. Slope: the rate of acquisition with increasing lengths of stimulation up to the maximum. This is the net increase or decrease from the reading after the 15 sec stimulation to the one after the 100 sec stimulation.

$$B = AE(15) - AE(100).$$

C. Distance: the accceleration of the curve to the maximum, it measures the curvature of the growth function of the slope.

$$C = \frac{4\,AE(30) + AE(50) + AE(80) + 6\,B - 12\,AE(15)}{(16 + B^2)^{1/2}}.$$

No positive results were obtained with etifoxine as far as the derived scores A and B are concerned. However, the drug had a consistent effect of marginal significance on C in that it produced a higher positive acceleration of the slope than the placebo, i.e. the drug suppresses the acquisition of the spiral after-effect after such short stimulation periods, ($F = 3.437$, $df = 1/7$, $p < 10$). Extraversion correlated significantly with the change (that is the difference in performance between the drug and the placebo): $r = -0.828$ ($df = 7$). This indicates that extraverts are less affected in their "distance" measure by the drug than introverts. Covarying out extraversion from the score C elevated the above mentioned trend to the 1% level of significance ($F = 13.137$, $df = 1/7$, $p < 0.017$).

Assuming therefore that all *Ss* had the same E-score, i.e. that they were at the same level of arousal before the intake of the drug, a clear-cut difference in the shape of the acquisition curve between drug and placebo results. This supports the assumption that the depressant drug shortens the SAE duration or rather that the acquisition curve does not rise as fact with increasing stimulation time under the drug at it does under placebo.

8. MACL

The only positive effect etifoxine had, was on factor B-anxiety. The anxiety felt by the *Ss* was less after the intake of the drug as compared to the placebo ($F = 4.667$, $df = 1/7$, $p < 0.06$). The difference was 1.0125 units ($SD = 1.310$). Psychotism correlates significantly with the change ($r = 0.845$, $df = 7$) in the expected direction; the higher the P-score the smaller the difference between the drug and placebo-condition in this

variable. Covarying out Psychoticism renders the above result significantly on a higher level ($F = 6.395$, $df = 1/7$, $p < 0.04$). The size of the sample is again too small to establish whether this result is due to the lower degree of anxiety felt by high P-scorers in the experimental condition in general, or whether the drug has a less powerful effect on them.

9. Mirror Drawing

The total time it took the *S* to go round the track (speed) was recorded and also the total time the *S* had touched the brass border of the track (error). Etifoxine had no positive effect on the first parameter and an effect of only marginal significance on the error: in that the mean error score was 2.19 sec higher under placebo than it was under the influence of the drug ($F = 5.045$, $df = 1/7$, $p < 0.06$). The result is inconsistent with expectations in respect of the speed-parameter.

10. Tapping

Three different measures were obtained for every 15 sec of the 1-min performance.

a) Number of taps.

b) Standard Deviation: a measure of the variability of the tapping rate.

c) Number of involuntary rest pauses (IRPs): the time intervals between the taps were averaged and every interval lasting 1.5 times the average was recorded as an IRP. (This is assumed to be a measure of reactive inhibition. Whenever the reactive inhibition gets higher than the motivation to carry on with the task an IRP occurs during which the reactive inhibition is dissipated until the drive to carry on the task is again higher than the reactive inhibition).

The four scores of each measure were transformed into polynomial coefficients and the derived scores (level, linear trend, quadratic trend and cubic trend) subjected to the analysis of variance. No positive results were obtained for the number of taps and the IRPs with the drug. There was however, an effect of marginal significance on the linear trend of the standard deviation of the performance ($F = 3.404$, $df = 1/7$, $p < 0.10$). The drug seems to reduce the irregularity of the tapping rate towards the end of the one-minute performance. It is expected that this trend would have increased had the performance gone on for longer.

11. Reaction Time

The scores obtained were: mean reaction time, mean number of correct responses.

Mean number of incorrect responses, and the mean number of failed responses, each of them averaging 8 trials. Etifoxine did not have an effect on any of the variables.

12. Tracking Tasks

In the cases of the fast and the unpredictable tracks three measures of performance in relation to the target were taken for every ten seconds: total time on target (TOT), mean absolute distance from the target (MAD), and the average length of unbroken contact with the target (AHL). For the frequency analysis the position of the *S*s pointer was recorded every 50 msec. This was done for the first 24 sec of every 75 sec of the performance. These segments were subjected to a Fourier transformation which gave the amplitude and phase lag of the frequency components of interest namely the ones in the respective track. In the case of the third track the position of the pointer was not recorded in relation to the target but merely the frequency and the amplitude of the movement as the speed of the target was changed according to the frequency of the movement anyway.

All repeated measures were transformed into polynomial coefficients and submitted to a one-way analysis of variance.

a) Fast Track

Etifoxine had no significant effect on the mean absolute distance (MAD), total time on target (TOT), and average hit length (AHL). Nor was the learning and performance affected in terms of the amplitude of the essential frequency component and phase lag by the drug. This is somewhat suprising as this task seems to be comparable with the pursuit-rotor which proved to be sensitive to drug action (Treadwell, 1960). It is assumed that the task was not given for a long enough time considering that the impairment of the performance on the pursit-rotor was most pronounced in later stages of the training period, i.e. it occured in the 9th or 10th min and could therefore not be shown in the present 5 min period.

b) Irregular Track

None of the differences between etifoxine and placebo were significant as far as MAD, TOT and AHL are concerned. Nor did etifoxine have any noticeable effects on the frequency and phase lag parameters.

c) Variable Track

The drug failed to change the performance in either direction. The performance characteristics varied considerably between *S*s but were

fairly consistent between sessions i.e. within one *S* irrespective of drug-placebo conditions. As there is little known about the essential factors determining the performance on this task no further interpretation can be given.

General Discussion

Etifoxine was shown in the first part of the study to have tranquillizing effects by lowering the critical flicker fusion threshold. The results for the psychophysiological tests also suggest that the drug reduces the susceptibility of the *S* to extrinsic arousal. This was shown both by the pattern of the GSR results and by the significant changes in the P3 Latency in the AEP. The latter variable involves the P3 component which has been suggested to be an orienting response (Ritter and Vaughan, 1969). The type of result found for the GSR is unlikely to be caused by peripheral effects of the drug as the variables most sensitive to this (basal level and spontaneous activity) do not differ between conditions. The drug also had effects on the subjectively assessed anxiety in that the Ss felt less anxious under its influence.

The drug seemed completely inert with respect to motor performance. However, it is not impossible that, as with other psychiatric drugs, it might have an effect upon fatigue in the later stages of the performance. This hypothesis has not been tested in the present study. Another explanation might be that the dose used in the present study (approximately 4 mg/kg body-weight) was too low. In animal studies carried out by the Hoechst Pharmacological Laboratories motor disturbance was obtained from a dose of 25 mg/kg upwards, but for safety reasons it was decided against either a higher dose than the one employed or repeated administration of the drug.

Though the possibly confounding effect of stimulant beverages like coffee or tea with the drug was considered, it was decided not to demand abstinence from normal beverage intake. The latter might have induced a mild withdrawal effect that could have had a stronger effect on the performance than the stimulating beverage.

One fairly consistent, though due to the low number of *S*s only marginally significant, result was the interaction of the drug with Psychoticism and, in one case, with Extraversion, both measured with the Personality Inventory. Both dimensions are related to arousal and it can therefore be expected that a psychotropic drug interacts with them. A high score on either the Extraversion or Psychoticism scale represents low cortical arousal. The fact that extraverts are less susceptible to depressant drugs has been observed before (Costello, 1963). This author explained the effect by homeostatic mechanisms which prevent the *S* from going below a certain limit in his performance no matter what state of

arousal he is in. Another explanation would be to assume a different gradient of absorption due to metabolic differences between high and low E scorers.

A number of other studies have also shown that sensitivity to psychotropic drugs is related to personality factors. (eg. Claridge and Herrington, 1963; Suwa and Yamashita, 1972) thus supporting the proposal by Eysenck (1957) that differences in the response to drugs are due to different levels of arousal.

It was shown in the present study that high P-scorers responded less strongly to the drug (eg. in their subjective assessments and in CFF) since their basal scores were already very low. As yet the reasons for this mechanism are not known and further investigations must be carried out to elucidate them.

We are indebted to Hoechst Pharmaceuticals Ltd. for the support of this investigation.

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