Psychopharmacology 62, 1 – 7 (1979)

**Psychopharmacology**


*Original Investigations*

# Diazepam and Flurazepam: Effects on Conditioned Fear as Measured With the Potentiated Startle Paradigm

Michael Davis

Yale University, School of Medicine and Connecticut Mental Health Center, New Haven, Connecticut 06508, U.S.A.

**Abstract.** Diazepam (0.3, 0.6, 1.2, or 2.5 mg/kg) produced a dose-dependent reduction of the potentiated startle effect where acoustic startle amplitude is normally increased in the presence of a light previously paired with a shock. Even the lowest dose tested (0.3 mg/kg) significantly attenuated potentiated startle. The effect was selective since the same doses did not depress baseline startle amplitude measured in the same animals in the same test session. A 2 × 2 design in which rats were trained and tested under the same or different drug condition (diazepam or saline) showed the results could not be explained by state-dependent learning. The primary effect of diazepam was to block expression of rather than acquisition of fear as measured by potentiated startle. Flurazepam (2.5, 10, or 20 mg/kg) also reduced potentiated startle selectively but was 6 – 8 times less potent than diazepam. These and other results suggest that the potentiated startle paradigm, as a measure of classical conditioning that involves no operant, might provide a useful adjunct to behavioral methods currently being used to analyze antianxiety compounds.

**Key words:** Startle – Fear – Diazepam – Flurazepam – State-dependent – Conditioning

The magnitude of the startle reflex can be augmented by presenting the eliciting stimulus in the presence of a cue that has previously been paired with shock (Brown et al., 1951). This phenomenon has been termed the potentiated startle effect and has been replicated a number of times (Anderson et al., 1969; Bridger and Mandel, 1967; Chi, 1965; Galvani, 1970; Kurtz and Siegel, 1966; Wagner et al., 1967). The effect has been used as evidence that startle is increased by fear and could provide a useful model system to study how drugs alter fear.

Recently we found that the potentiated startle effect bears a non-monotonic relationship to the shock intensity used in training (Davis and Astrachan, 1978). Low or high shock levels in training produced little potentiation, whereas intermediate levels produced marked potentiation. This nonmonotonic curve also was found when shocks were delivered to the back instead of the feet. These results resolved several apparent inconsistencies in the literature (e.g., Chalmers et al., 1974; Kurtz and Siegel, 1966) and provided further evidence that startle is sensitive to prior fear conditioning.

If potentiated startle does reflect fear, then it should be attenuated or blocked by drugs that are thought to reduce fear or anxiety in other situations. Consistent with this expectation, Chi (1965) found that sodium amytal produced a dose-related reduction in potentiated startle. D. R. Williams (reported by Miller and Barry, 1960) found a similar reduction using alcohol. In both cases the effect was somewhat selective since the same doses did not alter baseline levels of acoustic startle. In contrast, amphetamine, mescaline or dimethoxyphenylethylamine have been reported to increase the potentiated startle effect, when administered before a combined training and testing session (Bridger and Mandel, 1967).

The potentiated startle effect involves no operant. Thus changes in bar press rates (e.g., in the conditioned emotional response paradigm or the operant-conflict paradigm) or avoidance rates (e.g., in avoidance paradigms) are not required to measure the effectiveness of a given drug. Because of this, potentiated startle might provide a useful alternative to compare with other

Offprint requests should be sent to: Michael Davis, Yale University, School of Medicine, 34 Park Street, New Haven, CT 06508, U.S.A.

0033-3158/79/0062/001/$01.40

methods currently being used to evaluate drugs that affect fear or anxiety. The purpose of the present series of experiments was to test how diazepam (Valium), a drug used widely to reduce anxiety, would affect potentiated startle. A new design was used in which potentiated and baseline startle were measured in the same animal following conditioning. In addition, the degree to which the effects of diazepam could be explained by state-dependent learning was tested. Finally, the effect of another benzodiazepine, flurazepam (Dalmane), was tested to see if the method could discriminate between drugs that have similar structures but differ in potency in other behavioral tests.

## Experiment 1 — Effects of Various Doses of Diazepam

### *Method*

*Subjects.* In this and subsequent experiments the subjects were experimentally naive male albino Sprague-Dawley rats that weighed between 250 and 300 g. Upon receipt from the supplier (Charles River Co.) the rats were housed in group cages of four or five rats each and maintained on a daily schedule of 12 h light, 12 h dark. Food and water were continuously available.

*Training Apparatus.* Four identical boxes ($30 \times 25 \times 25$ cm) were used during training. The sides and tops of the boxes were made of aluminium and the fronts and backs of clear Plexiglas. The floors were composed of 4.76 mm stainless steel bars spaced 19 mm apart. The boxes were located on a shelf within a $2.5 \times 2.5 \times 2$-m ventilated, sound-attenuated chamber (Industrial Acoustic Co. – IAC).

The conditioned stimulus (CS) consisted of two 60 W incandescent bulbs located on the opposite wall of the IAC chamber, 2.1 m from the cages. The shocks (US) were delivered from four Lehigh Valley Shock Generators (SGS-004) located outside the chamber. Shock intensities were measured with an oscilloscope across a 1 K resistor in series with a 100 K resistor connected between adjacent grid bars in the shock boxes. Shock intensity was defined as the root mean square voltage across the 1 K resistor computed as mA $= 0.707 \times 0.5 \times$ Peak-Peak voltage.

*Startle Testing Apparatus.* Four separate stabilimeter devices were used to record the amplitude of the startle response. Each stabilimeter consisted of a $8 \times 15 \times 15$-cm Plexiglas and wire mesh cage suspended within a $25 \times 20 \times 20$-cm steel frame. Within this frame the cage was sandwiched between four compression springs above, and a $5 \times 5$-cm rubber stopper below, with an accelerometer (M. B. Electronics Type 302) located between the bottom of the cage and the top of the rubber cylinder. Cage movement resulted in displacement of the accelerometer and the resultant voltage was fed to a matched accelerometer amplifier (M. B. Electronics Model N504), the output of which was proportionate to the amplitude of the rat's startle.

The amplified signal was then fed to a specially designed sample and hold circuit. Basically this circuit consisted of four channels, one for each stabilimeter, and was used to sample the peak accelerometer voltage that occurred during a 200-ms time band immediately after the onset of the startle-eliciting stimulus. Immediately prior to this sample period, each channel was discharged so that any spontaneous activity occurring between stimulus exposures was erased. In this way the amplitude of the startle response of four rats was recorded simultaneously and stored in one of the four channels. Immediately after the sample period the output of each channel was digitized through a specially designed analog-to-digital converter and fed into a 14-channel Newport Printer. With two print-channels per cage, startle amplitude could vary from 0 to 99, allowing appreciable resolution among various startle amplitudes.

The four stabilimeters were located on another wall of the IAC chamber described above. They were placed 1.1 m from an Altec high-frequency loud speaker, which was used to provide a 4000-Hz, 90-ms tone shaped through a Grason-Stadler electronic switch to have a rise-decay time of 5 ms. Background white noise was provided by a Grason-Stadler noise generator. The intensities of the tone (105 – 110 db) and of the white noise (46 db) were measured with a General Radio Model 1551-C sound level meter (A scale – re 20 $\mu N/m^2$) by placing the microphone in each cage and positioning the cages to have comparable readings. During testing the two 60-W bulbs were located 2.1 m from the startle test cages.

*Matching Procedure.* A total of 60 rats was used for the dose-response study. Prior to the main experiment 20 rats were placed in the startle test cages and 5 min later presented with 10 tones at a 20-s inter-stimulus interval. Based on the mean startle amplitude across these 10 tones the rats were divided in five groups of four rats each, with each group having similar mean startle amplitudes.

*Training Procedure.* The rats were placed in the shock cages and 5 min later presented with 45 light-shock pairings (trials) in which a 0.4 mA-shock was presented during the last 0.5 s of the 3-s CS. The trials were presented at an average inter-trial interval of 60 s (range 45 – 75 s). The 45 conditioning trials were presented on two successive training days beginning 2 days after matching.

*Testing Procedure.* At 24 h after the second training day the rats were placed in the startle cages and 5 min later presented with 80 tones delivered at an average 30-s interstimulus interval (range 25 – 35 s). Half of the tones were 110 db, half were 105 db. Half of the 110-db tones and half of the 105-db tones were preceded by the light, which was turned on 2.5 s before the tone (light-tone trials). The rest of the tones were presented in darkness (tone-alone trials). The four types of test trials were presented irregularly across the session with the restriction that each trial type occurred once within each successive block of four trials and that each was distributed uniformly across the entire session. The two tone intensities were used to increase the probability that baseline as well as potentiated startle would be measured over a wider range of the scale. In exploratory studies this proved to be a more sensitive method than using only a single test intensity.

Ten minutes before being placed in the test chamber (i.e. 15 min before the first test tone) the rats were injected intraperitoneally with either 50% ethylene glycol, 0.31, 0.62, 1.25, or 2.50 mg/kg diazepam, using one of the matched groups for each condition. Diazepam was diluted with 25% ethylene glycol and all substances were given in a volume of 0.25 cc/per 300 g rat. A 50% ethylene glycol solution was used since this was roughly the final concentration of ethylene glycol that resulted when the injectable diazepam solution was diluted with 25% ethylene glycol. Injections were done in the colony room and the animals were returned to their home cages during the injection-test interval.

Three replications of these procedures were carried out, creating a total of 12 rats in each of the five conditions. The replications were identical except that the time of day in which training and testing was conducted for the various groups was varied so that across all replications the time when training and testing occurred was as similar as possible for all conditions.

Another 16 rats were matched as described above and were used as the random control groups. To devise a random schedule the 45-min training sessions were divided into 540 5-s epochs. The 45 shocks were distributed across the session at an average interval of 60 s, as they were for the paired groups described above. The 45 occurrences of the lights were distributed to maximize the similarity of the probability that the light would occur either during the shock, or during any of the 12 epochs of 5-s each before or after the shock. The lights and shocks were delivered through a papertape reader using conventional electromechanical programming equipment. During testing half these animals were injected with the vehicle and half with 2.5 mg/kg diazepam. These groups were included to test if diazepam would affect startle in the presence of a light that had not been explicitly paired with a shock.

In this and the next experiments the mean startle amplitude across the 40 tone-alone trials and the 40 light-tone trials was computed for each rat. Analyses of variance or $t$-tests were performed using as scores the percent differences between the two trial types: [(light-tone-tone alone)/tone alone] $\times 100$.

## *Results and Discussion*

Figure 1 shows the mean amplitude startle response on the tone-alone trials and the light-tone trials during testing after injection of the vehicle or the various doses of diazepam. The data have been combined over the two test intensities and across the entire 40-min test session. Figure 1 indicates that diazepam decreased startle amplitude on the light-tone trials in a dose-dependent fashion. In contrast, at these doses diazepam did not alter startle in any systematic way on the tone-alone trials. Exploratory work did show, however, that higher doses (e.g., 5 – 10 mg/kg) will depress baseline levels of startle. An overall analysis of variance using the percent difference between the light-tone and tone-alone trials as scores showed a significant difference across the five conditions, $F(4,55) = 10.17$, $P < 0.001$, which was linearly related to the log-dose, $F(1,55) = 33.46$, $P < 0.001$. Subsequent individual comparisons using the pooled within-group variance as the error estimate revealed that the magnitude of potentiated

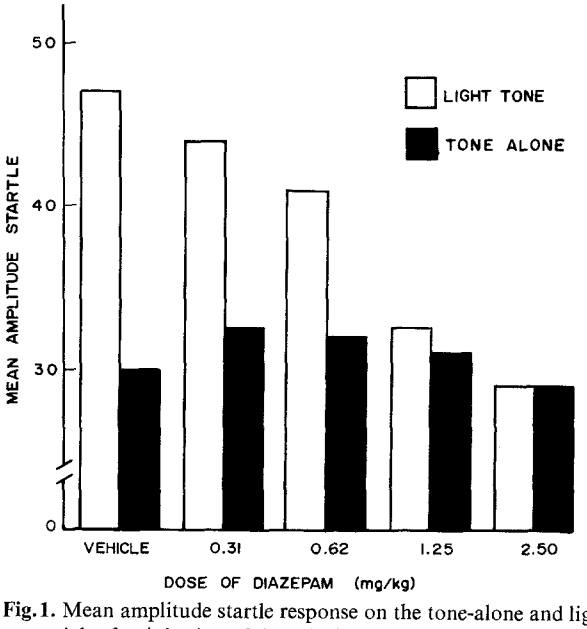


**Fig. 1.** Mean amplitude startle response on the tone-alone and light-tone trials after injection of the vehicle or various doses of diazepam

startle was significantly less at each dose ($P$ at most less than 0.05) than it was after the vehicle alone.

The typical effect of increased tone intensities augmenting startle amplitudes (Davis and Wagner, 1968), still occurred under diazepam. For example, in the vehicle-treated rats the average startle amplitude on the tone-alone trials at the 100-db test intensity was 37.9. At 105 db it was 20.7. Comparable values after the highest dose of diazepam were 35.9 and 21.3. This indicates that diazepam does not depress all methods of producing increased startle. It also provides further evidence that the drug acts somewhat selectively, which will be discussed later.

In addition, diazepam had no detectable effect on startle elicited in the presence of a light not paired with shock. Thus in the random control groups, the mean startle amplitude on the light-tone vs. tone-alone trials was 28.6 vs. 30.8 for the group injected with the vehicle and 24.2 vs. 25.3 for the group injected with 2.5 mg/kg diazepam. None of these differences approached statistical significance.

## Experiment II — Testing for State-Dependent Learning

Experiment I indicated that the potentiated startle paradigm is sensitive to diazepam, since a dose as low as 0.3 mg/kg had a statistically significant effect. The data are consistent with the hypothesis that potentiated startle reflects fear and diazepam reduces potentiated startle by decreasing fear. An equally plausible alternative possibility, however, is that the reduction in potentiated startle represents generalization decrement caused by a change in state between training and testing (cf. Overton, 1968). To evaluate this, a $2 \times 2$ design was employed in Experiment II in which groups were trained after injection of either diazepam or saline and then tested either in the same or different drug state.

### *Methods*

A total of 32 rats were matched into four groups of 8 rats each as described in Experiment I. All features of the apparatus were the same except that a 0.3-mA instead of a 0.4-mA shock and a 0.5-s instead of a 2.5-s CS-US interval were used in training, and a 0.5 instead of a 2.5-s CS-tone interval was used in testing. These parameters were found in concurrent experiments to produce somewhat more consistent conditioning from animal to animal, although the absolute magnitude of the effect is about the same.

Ten minutes prior to each of the two training sessions, half of the rats were injected with saline and half with diazepam at a dose of 1.25 mg/kg. Ten minutes prior to testing, half of the rats previously trained under diazepam were injected with diazepam (1.25 mg/kg) and half with saline. Similarly, half of the rats trained under saline were injected with diazepam and half with saline. All other aspects of testing were identical to those in Experiment I.

### *Results and Discussion*

Table 1 shows the mean percent potentiated startle for each of the four groups. Consistent with Experiment 1, the group trained under saline but tested under diazepam showed essentially no potentiated startle relative to the group trained and tested under saline. Most interesting, however, is that this effect cannot be explained by state-dependent learning. Thus the group trained under diazepam but then tested under saline (i.e., a change in state) still displayed potentiated startle. In contrast, the group trained and tested under diazepam (i.e., no state change) had essentially no potentiation. An overall analysis of variance revealed a significant difference among the four groups $F(3,28) = 14.09$, $P < 0.001$. Subsequent individual comparisons found the groups connected by solid lines in Table 1 to be statistically different ($P < 0.01$) whereas those connected by dotted lines were not. The data indicate, therefore, that diazepam blocks the expression of fear as measured by potentiated startle (Groups Saline-Diazepam and Diazepam-Diazepam) but apparently not the learning of fear (Group Diazepam-Saline).

## Experiment III — Effect of Flurazepam

Experiment III was designed to test how another benzodiazepine, flurazepam (Dalmane), would affect potentiated startle. The purpose was not to do an exhaustive study on the relative potencies of various benzodiazepines, since that is beyond the scope of this laboratory. Rather it was to test whether the paradigm could distinguish between two compounds that have similar structures but differ in potency in other animal tests, and have different clinical uses. Flurazepam was chosen since it is about eight times less potent than diazepam in the operant-conflict test (Cook and Sepin-

**Table 1.** Mean percent potentiated startle during testing after the different training-testing drug combinations

| Training condition | Testing condition | |
|---|---|---|
| | Saline | Diazepam |
| Saline | 65.5 | 0.4 |
| Diazepam | 51.4 | 3.7 |

wall, 1975) and is more widely used as a hypnotic-sedative than as an antianxiety drug (Goodman and Gilman, 1973).

*Method*

A total of 32 rats were matched for startle into four groups of eight rats each. The rats were trained for 2 days using procedures identical to those used in Experiment I. Ten minutes before testing the groups were injected i.p. with saline, 2.5, 10, or 20 mg/kg flurazepam and then tested for potentiated startle in the same way as in Experiment I.

*Results*

Flurazepam also attenuated the potentiated startle effect. This is illustrated in Fig. 2, which shows the mean percent block of the potentiated startle effect for flurazepam in Experiment III and, for comparison, of diazepam in Experiment I. Percent block was computed as [(Mean % potentiation under saline minus mean % potentiation under the drug at each dose)/Mean % potentiation under saline] × 100. Like diazepam, flurazepam produced a dose-dependent reduction in potentiated startle. Again the effect was selective since at these doses flurazepam did not produce any systematic changes on the tone-alone trials. However, higher doses of flurazepam (40 mg/kg) were found to depress baseline startle levels in exploratory studies. An analysis of variance using the percent change between the light-tone and tone-alone trials as individual scores found a significant difference among the various doses, $F(3,28) = 6.63$, $P < 0.005$, which was linearly related to the log-dose, $F(1,28) = 17.70$, $P < 0.001$. Consistent with other behavioral tests, however, flurazepam was less potent than diazepam in blocking potentiated startle. Although the log-dose response curves were not exactly parallel, the 6–8-fold difference in potency is similar to that obtained in the operant-conflict test (Cook and Sepinwall, 1975) and indicates that potentiated startle is capable of distinguishing between different benzodiazepines.

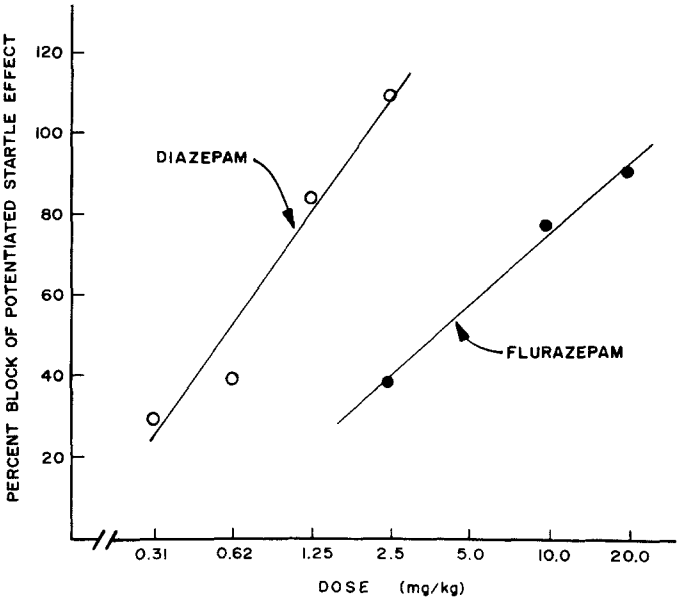


**Fig. 2.** Mean percent block of the potentiated startle effect relative to the respective vehicle groups in each experiment after diazepam or flurazepam

## General Discussion

The present results lend further support to the conclusion that the potentiated startle effect reflects fear (Brown et al., 1951). Three drugs (diazepam, flurazepam, sodium amytal) which are thought to reduce fear in other behavioral tests (cf. Gray, 1977) and anxiety clinically, all attenuate the potentiated startle effect in a dose-related way. To the extent to which it is possible to make comparisons across different studies (i.e., Chi, 1965, the present study), the rank order of potency of these three compounds in blocking potentiated startle is the same as it is in the operant conflict test and that seen clinically (Cook and Sepinwall, 1975). Of course many more compounds would have to be tested before any firm statement on this issue could be made. In terms of absolute dosage, potentiated startle was respectably sensitive, since a dose of 0.3 mg/kg of diazepam was effective. This is about half the minimum effective dose reported for the operant-conflict test (Cook and Sepinwall, 1975).

The effect of the benzodiazepines in the present study was selective in the sense that they only depressed startle on the light-tone trials and not on the tone-alone trials at the doses used. Chi (1965) found similar results using sodium amytal in a between-subject design. Chi reported, however, that this drug also reduced startle or flinch responses elicited by electrical footshocks in a dose-related fashion. These groups were included to test whether sodium amytal would depress "a startle response of the same size as that of the potentiated startle to a sound". This finding has been used to question the validity of the potentiated startle paradigm in the measurement of fear (Gray, 1977), although, as Chi argued, the effect might just as well be used to support a fear interpretation since shocks were used to elicit startle. In the present study different tone intensities were used on both the tone-alone and light-tone trials. Under these test conditions, diazepam still was selective, since it only depressed startle on the light-

tone trials, regardless of whether a 110 or 105-db tone was used. In fact, startle amplitude on the tone-alone trials at 110 db was higher under all doses of diazepam than it was on the light-tone trials at 105 db, similar to that normally found after the vehicle. Thus diazepam blocked augmentation of startle when it was produced by presenting the tone in the presence of a fear-eliciting light, but did not block augmentation of startle when it was produced by using a higher tone intensity.

Under the present conditions diazepam did not completely block the acquisition of fear as measured by potentiated startle at a dose which did completely block the expression of fear. Rats trained under diazepam but tested under saline still had a highly significant level of potentiated startle as did rats trained and tested under saline. In contrast, diazepam given shortly before testing blocked potentiated startle regardless of whether training occurred under the drug or saline. In this situation the pattern of test results cannot be entirely explained therefore by state dependent learning. Instead they conform to performance or retrieval deficits (Overton, 1974) indicating the drug acts by altering changes in behavior which normally occur following fear conditioning.

In his thorough and integrative review of the literature, Gray (1977) concluded that "None of the minor tranquilizers has yet been shown unequivocally to affect the conditioning of fear or the expression of fear that has been purely classically conditioned (i.e., with no possibility of adventitious punishment effects)." p. 490. Since the potentiated startle effect involves no operant, adventitious punishment could not explain the present results. It would seem fair to conclude, therefore, that at least the two benzodiazepines tested herein do act by blocking the expression of fear.

At the present time it is premature to speculate on the pharmacological mechanism by which the benzodiazepines block the potentiated startle effect. However, it is worth noting that the potentiated startle paradigm could provide a sensitive behavioral test system with which to study the mechanism of action of these compounds. Using the present design, potentiated startle can be defined as a within-subject difference in response magnitude (light-tone vs. tone-alone trials). This makes it sensitive, since it reduces problems caused by between-subject variability in startle. Second, it allows an evaluation of specific (light-tone) vs. nonspecific (tone-alone) drug effects, so that qualitative as well as quantitative drug profiles can be compared. Third, different tone intensities can be used within the same test session to elicit startle on the tone-alone and light-tone trials. This allows potentiated and baseline startle to be measured at comparable points of the scale, thereby circumventing problems which can arise when markedly different parts of the scale are involved (e.g., rate-dependent drug effects in operant paradigms; percent figures employed with very different baselines). Fourth, no shocks are used during testing. Thus drug effects observed in testing cannot be explained in terms of changes in sensitivity to shock. Fifth, the fact that training and testing sessions are separated allows one to evaluate if a drug alters original learning or performance. Sixth, and perhaps most important, potentiated startle does not involve any obvious operant. Thus the animal is not required to make or not make a voluntary response to demonstrate fear or lack of fear. Because of this, drug-induced effects that might be expected to alter operant performance (e.g., rate-dependent, motivational, or disinhibitory motor effects) are circumvented. Many of these features make the potentiated startle paradigm an attractive one that might serve as a useful adjunct to the widely used operant-conflict test or conditioned emotional response in the behavioral analysis of antianxiety compounds.

*Acknowledgements.* This research was supported by National Science Foundation Grant BMS-75-01470, by National Institute of Mental Health Grants MH-25642, and MH-18949, by Research Scientist Development Award MH-00004 to Michael Davis, and by the State of Connecticut. My sincere thanks are given to Lee S. Schlesinger for running the experiments and to Dr. Barry I. Gold for suggesting the use of and supplying the flurazepam.

## References

Anderson, D. C., Johnson, D., Kemptom, H.: Second order fear conditioning as revealed through augmentation of a startle response: Part I. Psychon. Sci. **16**, 5–7 (1969)

Bridger, W. H., Mandel, I. J.: The effects of dimethoxyphenylethylamine and mescaline on classical conditioning in rats as measured by the potentiated startle response. Life Sci. **6**, 775–781 (1967)

Brown, J. S., Kalish, H. I., Farber, I. E.: Conditional fear as revealed by magnitude of startle response to an auditory stimulus. J. Exp. Psychol. **41**, 317–327 (1951)

Chalmers, D. V., Hofh, J. C., Levine, S.: The effects of prior shock stimulation on the behavioral and physiological responses to intense acoustic stimuli. Physiol. Behav. **12**, 711–718 (1974)

Chi, C. C.: The effect of amobarbital sodium on conditional fear as measured by the potentiated startle response in rats. Psychopharmacologia **7**, 115–122 (1965)

Cook, L., Sepinwall, J.: Behavioral analysis of the effects and mechanisms of action of benzodiazepines. In: Mechanism of action of benzodiazepines, E. Costa and P. Greengard, eds., pp. 1–28. New York: Raven Press 1975

Davis, M., Astrachan, D. I.: Conditioned fear and startle magnitude: Effects of different footshock and backshock intensities in training. J. Exp. Psychol.: Anim. Behav. Proc. **4**, 95–108 (1978)

Davis, M., Wagner, A. R.: Startle responsiveness following habituation to different intensities of tone. Psychon. Sci. **12**, 337–338 (1968)

Galvani, P. F.: Air-puff-elicited startle: Habituation over trials and measurement of a hypothetical emotional response. Behav. Res. Meth. Instrum. **2**, 232–233 (1970)

Goodman, L. S., Gilman, A.: The pharmacological basis of therapeutics. New York: The MacMillan Co. 1973

Gray, J. A.: Drug effects on fear and frustration: Possible limbic site of action of minor tranquilizers. In: Handbook of psychopharmacology, L. L. Iverson, S. D. Iverson, and S. H. Synder, eds., vol. 8, pp. 433–529. New York: Plenum Press 1977

Kurtz, K. H., Siegel, A.: Conditional fear and magnitude of startle response: A replication and extension. J. Comp. Physiol. Psychol. **62**, 8–14 (1966)

Miller, N. E., Barry, H. III.: Motivational effects of drugs: methods which illustrate some general problems in psychopharmacology. Psychopharmacologia **1**, 169–199 (1960)

Overton, D. A.: Dissociated learning in drug states (state-dependent learning). In: D. H. Efron et al., eds., Psychopharmacology: A review of progress 1957–1967. U.S. Public Health Service Publication No. 1836, U.S. Govt. Printing Office, Washington, D.C. pp. 918–930, 1968

Overton, D. H.: Experimental methods for the study of state-dependent learning. Fed. Proc. **33**, 1800–1813 (1974)

Wagner, A. R., Siegel, L. S., Fein, G. S.: Extinction of conditioned fear as a function of percentage of reinforcement. J. Comp. Physiol. Psychol. **63**, 160–164 (1967)

Received May 11, 1978