

# Concurrent Positive and Negative Goalbox Events Produce Runway Behaviors Comparable to Those of Cocaine-Reinforced Rats

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GEIST, T. D., AND A. ETTENBERG. *Concurrent positive and negative goalbox events produce runway behaviors comparable to those of cocaine-reinforced rats.* PHARMACOL BIOCHEM BEHAV 57(1/2) 145–150, 1997—Rats traversing a straight-alley for reinforcing stimuli typically exhibit faster running times as training proceeds. In previous work from this laboratory, animals running for a reinforcement consisting of intravenous infusions of cocaine, unexpectedly demonstrated a progressive increased time to enter the goalbox over trials. Closer observation revealed that the animals were exhibiting a unique retreat behavior (i.e., stopping their forward advance toward the goalbox and returning toward the startbox). It was hypothesized that the retreat behavior reflected an inherent conflict that originated from concurrent positive and negative associations with the goalbox. Such associations were attributed to cocaine's dual and well documented reinforcing and anxiogenic effects. To test this idea, the present study compared the runway behavior of animals that concurrently received food and mild foot shock in the goalbox to the behavior of other animals running for cocaine. Results demonstrated that food + shock reinforced animals took longer to enter the goalbox and made more retreats than a control group that received only food in the goalbox. Both these effects were reversed by pretreatment with the anticonflict, anxiolytic drug, diazepam. The behavior pattern of animals that received the combination of food and footshock was found to strongly resemble that of IV cocaine-reinforced rats, a result consistent with the notion that chronic cocaine administration has both positive and negative consequences. © 1997 Elsevier Science Inc.

Cocaine    Operant behavior    Runway    Anxiety    Conflict    Diazepam

CHRONIC human cocaine users typically report initial sensations of euphoria followed by feelings of agitation, depression and anxiety (4,24,25,31). Chronic cocaine abuse is now believed to cause increasingly aversive reactions to the drug (1,28). These clinical studies have been complemented with animal models of cocaine abuse that generally describe cocaine's reinforcing actions using drug self-administration (10, 22) and place preference conditioning paradigms (18,21,26). Other paradigms have examined cocaine's anxiogenic qualities as seen in: potentiation of conflict behavior (11), increases in defensive withdrawal (30), and decreases in time spent in the open arm of an elevated plus maze (23).

In two recent reports (8,9), we described a runway paradigm sensitive to both the reinforcing and anxiogenic effects of cocaine in the same animals at the same time. Rats well

trained to run a straight alley for a goalbox reinforcement consisting of intravenous injections of cocaine, developed an approach-avoidance response to that goalbox (i.e. they left the startbox with normal latencies, approached the goalbox, but then turned and retreated back to the startbox). Several observations suggested that this cocaine-induced retreat behavior was a manifestation of conflict resulting from concurrent positive and negative associations with the goalbox (8,9). For example, the locations where rats stopped, turned and retreated in the alley, were not randomly distributed throughout the runway but concentrated just outside the goalbox door. This result is consistent with Neil Miller's (19) classic description of approach-avoidance situations in which greater behavioral conflict was demonstrated to occur with closer proximity to a goal having mixed positive and negative attri-

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butes. In addition, as with other forms of approach-avoidance conflict (2,3,6,15,20) the retreat behavior in the alley was reversible with pretreatments of the anxiolytic agent, diazepam. In the present study, a further test of the cocaine conflict hypothesis was conducted by examining the runway behavior of animals presented with a more conventional approach-avoidance situation, i.e. the presentation of food + shock in the runway goalbox (7,13,17,19,27). Our intent was to see whether the behavior of these food + shock animals resembled that observed in cocaine reinforced animals.

#### METHOD

##### *Subjects*

The Subjects were 21 male Sprague-Dawley rats obtained from Charles River Laboratories (weighing between 300 and 345 g at the onset of food deprivation). Each animal was individually housed in hanging metal wire cages located in a temperature controlled (23°C) vivarium environment (12 h light-dark cycle with lights on at 0700 h). Subjects were handled daily for one week prior to the first training trial. Each rat was then placed on a food-restricted diet intended to reduce and maintain its body weight at 85% of free-feeding values. Daily food rations were provided 1–3 hours after each operant session.

##### *Runway Apparatus*

Single daily trials were conducted in one of two identical wooden straight-arm runways (155 cm long × 17 cm wide × 45 cm high). Identically-sized startboxes and goalboxes (24 cm × 25 cm × 45 cm) were attached to opposite ends of the alleys. The floors of the apparatus consisted of steel rods (3 mm in diameter 1.2 cm apart) laid parallel across the width of the entire apparatus. A vertically sliding door separated each startbox from the alley and another marked the threshold between the alley and each goalbox. These doors, plus all timers and feeders, were controlled by a 386 IBM-compatible personal computer wired to custom interfaces designed and constructed in the UCSB Psychology Electronics Shop. An animal's position in the runway was automatically recorded in real time by the computer from a series of input sensors which consisted of 13 infrared photocell emitter-detector pairs arranged along the long axis of the alley 2.5 cm above the floor at 15 cm intervals. A fourteenth photocell emitter-detector pair was placed within a small metal rectangular feeding cup centered on the far wall facing the alley inside the goalbox.

##### *Procedure*

The animals were randomly assigned to one of three ( $n = 7$  each) groups: a "Food Only" group, a "Shock Only" group, and a "Food+Shock" group. The experiment consisted of three phases:

*Phase 1—food training.* Each rat was trained in the same manner, irrespective of its group assignment. Training consisted of single daily trials for 10 days (every five consecutive days of training were followed by two rest days). At the beginning of each trial a rat would be gently placed into the startbox. After a 5 s delay, the startbox door was opened. Subjects then traversed the alley and entered the goalbox at which time the goalbox door was closed, and 2 s later, a food pellet dispenser delivered six 45 mg food pellets at a rate of 1 pellet/s (Noyes Company Improved Formula A Small Rodent Diet). After a 24 s delay, another set of 6 food pellets was delivered and this

sequence was continued for a total of five sets of food deliveries over a 2 min period. Three min after the delivery of the final set of six food pellets, each rat was removed from the goalbox and returned to its home cage. Note that on every trial, the time required for an animal to traverse the alley (after leaving the startbox) and enter the goalbox (i.e., Run Time) was recorded along with the presence and location of any retreat behaviors that occurred within the alley. A retreat was behaviorally defined as a stop in forward progress followed by a return toward the startbox.

*Phase 2—food+shock training.* The second phase of the experiment was conducted over 15 days. The Food Only group continued to receive food in the goalbox on every trial (as in Phase 1). The Shock Only group no longer received food in the goalbox. After 2.5 min in the goalbox these animals experienced a series of five mild foot shocks (0.15 mA 0.5 s each, over a period of 5 s delivered by a Lafayette Instruments A-615A Shocker). The Food+Shock group received both the food and the series of five foot shocks.

After five days of food, shock, or food + shock presentations, an additional ten days of testing were conducted during which the intensity of the foot shock for the Shock Only and Food+Shock groups was increased (from 0.15 mA to 0.3 mA). The Food Only group continued to receive food in the goalbox. Once again, Run Times and the number and spatial location of retreats in the alley were recorded on every trial.

*Phase 3—diazepam treatment.* Beginning three days after the completion of Phase 2, the seven animals of the Food + Shock group continued to be tested in the runway five days each week (5 days testing, 2 days off). Diazepam pretreatments (0.0, 0.5, 1.0, or 2.0 mg/kg delivered in an injection volume of 1.0 ml/kg) were administered IP 30 min prior to behavioral testing. Each animal experienced each dose of drug in a counterbalanced manner with a minimum of four intervening non-treatment trials/days between diazepam injections.

*Cocaine comparison group.* The present experiment was devised to determine whether or not animals that experience food+shock (concurrent positive and negative stimuli) in the goalbox come to develop intramaze behaviors similar to those previously reported by the authors in cocaine-reinforced animals (8,9). We have, therefore, added appropriate comparison groups from Ettenberg and Geist (8) to two of our figures. This is not intended as a republication of already reported results, but merely as an aid for readers to compare the results from the two treatments (food+shock versus IV cocaine). The cocaine-reinforced subjects ( $n = 7$ ) were tested in the same runway apparatus and in the same manner as that already described above. Instead of a goalbox delivery of food and/or shock, the drug-reinforced animals traversed the alley for five intravenous 0.1 ml injections of 0.75 mg/kg/inj cocaine hydrochloride (Sigma Chemical Company) delivered at 30 s intervals. Each animal remained in the goalbox for a total of five minutes and was then removed from the apparatus and returned to its home cage. Animals were tested once daily for 17 days. Additional methodological details can be found in Ettenberg and Geist (8).

#### RESULTS

Although the animals continued to traverse the runway throughout this experiment, there were reliable differences in the nature and pattern of their operant behavior. Figure 1 shows the mean Run Times for each of the three groups. A two-factor analysis of variance (ANOVA) with repeated measures on one factor was computed on the data illustrated

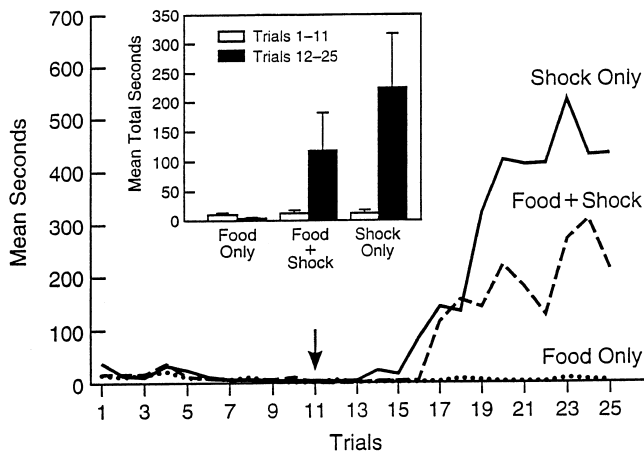


FIG. 1. The line graph represents the daily mean Run Times of each of the three groups (Food Only, Food+Shock, Shock Only) over trials. On trial 11 (arrow) Phase 2 of the experiment began with the application of mild foot-shock in the goalbox for the Food+Shock and Shock only groups. The bar graph in the left corner of this figure depicts the mean Run Times (+ SEM) across the first 10 trials when all groups received food and no foot-shock (light bars) and the last 15 trials (dark bars) when two of the three groups received foot-shock.

in the figure. The ANOVA revealed a reliable difference in overall Group performance  $F(2,18) 4.52, p = 0.026$ , Trials  $F(24,432) = 8.08, p < 0.0001$  and a Group  $\times$  Trial interaction  $F(48,432) 2.85, p < 0.0001$ . The bar graph insert in Fig. 1 helps summarize these results. The group means (+ SEM) for Run Times during the first 10 trials (light bars) when all groups received food and no shock were highly comparable to one another. However, the same data averaged across the last 15 trials (dark bars), when two of the three groups received foot shock, were dramatically different. The Food Only group decreased its Run Times (they ran faster) over the second half of the Experiment in contrast to the Food+Shock and the Shock Only groups both of which increased their Run Times (they ran more slowly) in the last part of the experiment.

Figure 2 illustrates the typical retreat behavior of individual representative animals in this experiment and a comparison IV cocaine subject from Ettenberg and Geist (8). The number 1 on the ordinate corresponds to the infrared photocell located on the threshold between the startbox and alley. As one moves up the ordinate the corresponding location in the alley moves closer to the goalbox with the number 10 representing the threshold to the goalbox. These spatiotemporal records reveal that the two animals that received foot shock on the 14 previous trials/days behaved in a manner comparable to an animal having received IV cocaine in the goalbox on 14 previous trials. Note that while three of these subjects had long Run Times, the steep slopes of the response records indicate fast running speeds, albeit with many retreats. Rats in the Food Only group ran just as quickly but rarely made any retreats.

Figure 3 graphs the locations where retreats occurred (i.e., the positions within the alley where animals stopped, turned, and ran back toward the startbox). The data are expressed as mean (+ SEM) total frequency of retreats per animal averaged across each group at each location within the alley. As described for rats reinforced with IV cocaine (Fig. 3, Panel C redrawn from Ettenberg and Geist (8)) the Food+Shock

(Panel A) and Shock Only (Panel B) groups tended to exhibit retreats at locations in close proximity to the goalbox entry (as opposed to randomly distributed retreats throughout the alley). A mixed two-factor (Group  $\times$  Location) ANOVA was computed on the data depicted in Fig. 3 (note that the Food Only Group was not included in either the figure or the data analyses since these animals exhibited virtually no retreats throughout the course of the experiment). The ANOVA confirmed that all three groups in Fig. 3 behaved in a similar manner: there was a highly reliable main effect for retreat location ( $F(9,162) = 11.34, p < 0.0001$ ), but no main effect for Group, ( $F(2,18) = 0.97, n.s.$ ), nor a Group  $\times$  Location interaction, ( $F(18,162) = 0.99, n.s.$ ). Thus, groups having had goalbox experiences of Food only followed by Food + Shock, or Food only followed by Shock only, exhibit patterns of retreat frequency and location that are highly comparable to animals running the same alley for IV cocaine.

Figure 4 illustrates the mean number of retreats emitted by Food+Shock animals pretreated with four doses of diazepam (black bars). In the figure, baseline trials (white bars) represent the mean performance of subjects on the trial that occurred 24 h before the drug trial. A two-factor (within subject) ANOVA calculated on the data depicted in Fig. 4 confirmed that diazepam significantly reduced the number of retreats in drug treated animals:  $F(1,6) = 15.54, p = 0.0076$  (no other statistically reliable outcome resulted from the analysis). These reductions in retreat behavior were not a consequence of some form of generalized drug-induced behavioral impairment since animals exhibited shorter Run Times as a function of diazepam dose (mean Run Times ( $\pm$  SEM) for animals treated with vehicle, low dose, medium dose or high dose of diazepam were 422.74 ( $\pm$  154.9), 279.36 ( $\pm$  160.4), 179.01 ( $\pm$  122.1) and 29.5 ( $\pm$  9.7) respectively).

#### DISCUSSION

The intent of this report was to test the hypothesis that retreat behaviors previously observed in cocaine-reinforced rats (8,9) were the result of conflicting positive and negative associations with the cocaine-paired goalbox. The current study tested this hypothesis by determining whether qualitatively comparable behaviors would be produced by animals explicitly administered known positive (food) and negative (shock) stimuli concurrently in the goalbox, stimuli reported by others to produce approach-avoidance conflict situations (2,7,13,17,19).

While the authors recognize that argument by analogy does not resolve the issue with any degree of certainty, the resulting data were nevertheless strongly consistent with our hypothesis. The punished groups emitted longer Run Times and more numerous retreats than the unpunished control group. Indeed, it seems likely that the elevated Run Times of the Food+Shock and Shock Only groups (Fig. 1) were directly related to the increased occurrence of retreats (Fig. 3) in these two groups. Clearly, animals that spend more time stopping and retreating will take longer to enter the goalbox. Of particular significance were the qualitative patterns of the retreat behaviors (Fig. 2 and 3) which strongly resembled those observed in rats receiving IV cocaine in the goalbox (8,9). Thus, the shock groups produced spatiotemporal records that were highly comparable to those seen in cocaine-reinforced subjects (Fig. 2) and both the frequency and location of retreats (near the goalbox door) are consistent with a common underlying approach-avoidance conflict regarding entry into the goal box.

The combination of food and foot shock in a runway experi-

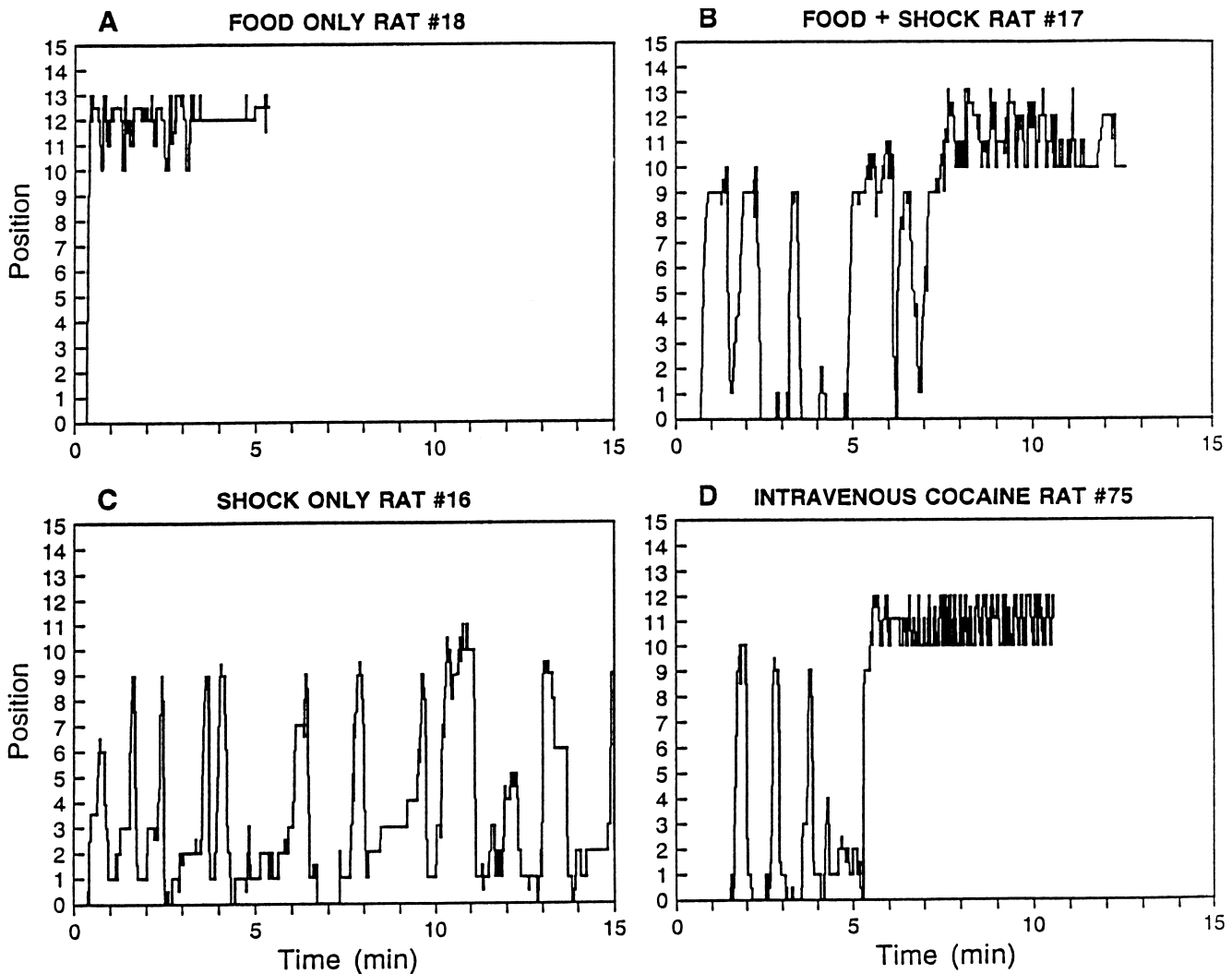


FIG. 2. Spatiotemporal records from three representative animals (one from each group) and a comparison cocaine animal from Ettenberg and Geist (8). Each record depicts the location of the subject in the alley (ordinate) over the course of a single trial (i.e. the last day of foot shock). Position 1 on the ordinate corresponds to the threshold of the startbox while position 10 corresponds to the location just outside the goalbox entryway. The speed with which these animals ran the alley is reflected by the steepness of the slopes. Retreat behaviors are clearly identified by lines that approach the goalbox position and then turn back toward the startbox position. Note that the location where animals stopped their forward progress tended to be in close proximity to the goalbox entrance.

ment is not in itself unique. Pioneering work by such people as Miller (19) using rats, or Masserman (17) using cats, have reported similar types of approach-avoidance behavior as described here, and more recent studies have continued to employ food+shock test protocols (12,14,32). The present study, however, provides an enhanced level of analysis for the direct comparison of detailed quantitative and qualitative features of runway behavior emitted by animals in the same apparatus, in the same lab, under very similar test conditions, but with variations in their goalbox experiences. This work has identified a striking similarity between the putative "conflict" behavior of animals having been presented food and shock (either together or sequentially) and others running the exact same alley for intravenous cocaine.

Along somewhat similar lines, in a non-shock experiment Yamamoto and Ueki (29) also reported that rats would emit

an advance-retreat behavior pattern when placed into a novel U-shaped alley which had food pellets laid at intervals along the alley's length. These researchers described how animals would backup from the position where the last food pellet was obtained before moving on to the next pellet in the alley, an effect that was attenuated by anxiolytics (29). Similarly, in the present study diazepam reduced the number of retreats emitted by animals who had previously experienced a combination of food plus foot-shock in the runway goalbox. Diazepam also reduced the occurrence of retreats in animals trained to approach a goalbox for IV cocaine reinforcement (8). Such results cannot easily be accounted for by a diazepam-induced interference with the retrieval of goalbox associations since both human "memories" and animal conditioned responses acquired prior to the administration of diazepam, have been shown to remain intact under diazepam challenge (5,16,27).

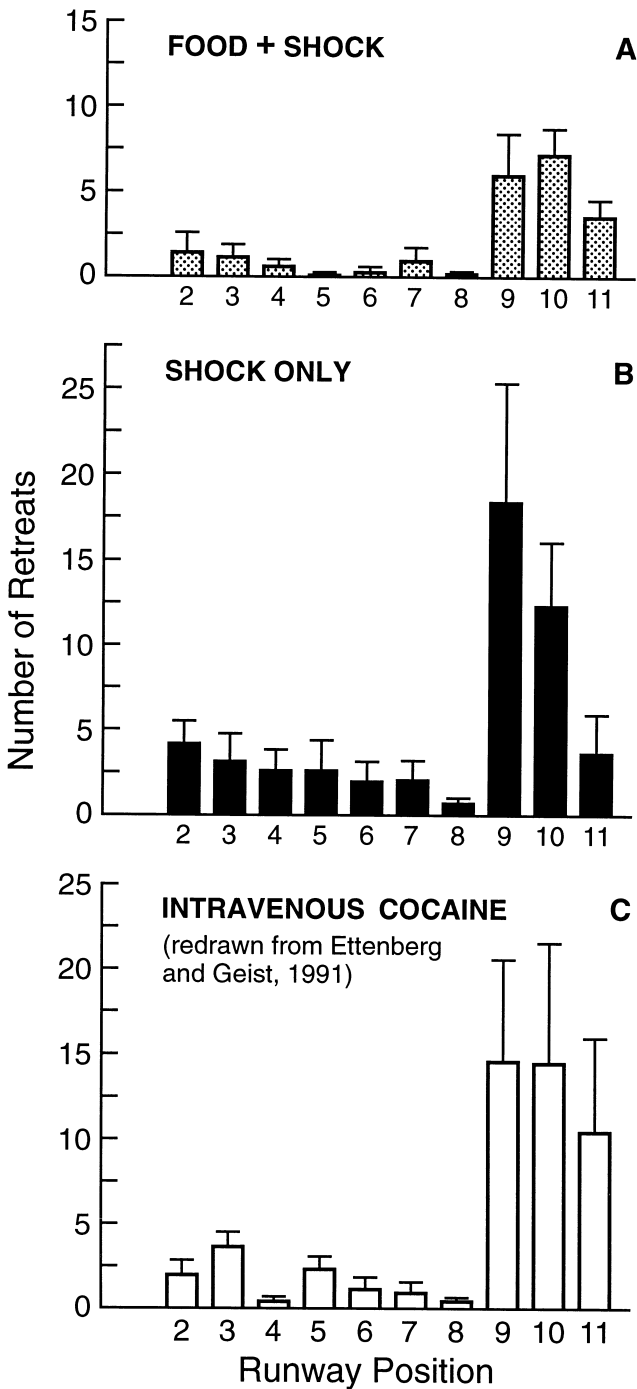


FIG. 3. The positions within the alley where retreats occurred (i.e. the pivot points). The data are expressed as mean (+ SEM) total frequency (across all trials) for each group at each position within the alley. The positions within the alley are depicted on the abscissa with position 1 representing a location near the startbox and position 10 representing a location just outside the goalbox entryway. Fig. 3-A and 3-B display data for the Food+Shock and Shock Only groups, respectively. Fig. 3-C represents data from a previous experiment where rats traversed a runway for IV cocaine (8).

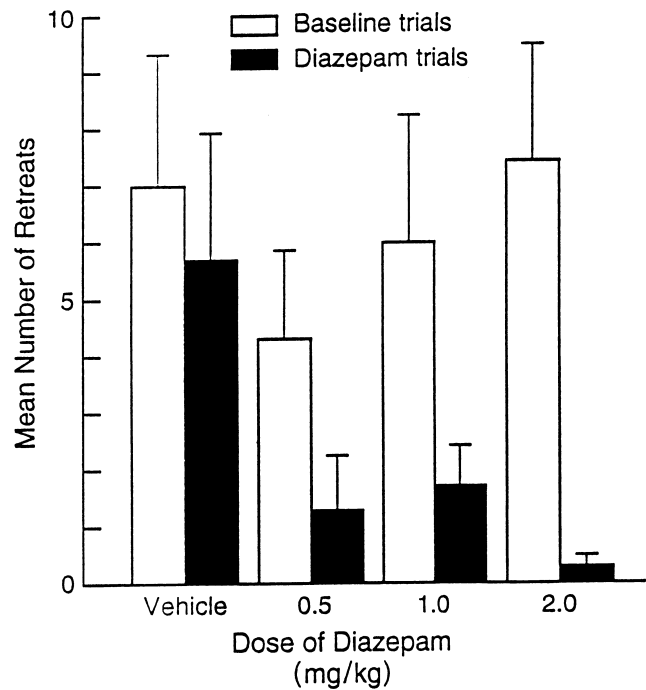


FIG. 4. Mean (+ SEM) number of retreats in diazepam treated rats that previously experienced Food+Shock in the goalbox. The white bars represent baseline trials the day before each of the drug-test trials (dark bars).

It would seem then that in each of these studies, diazepam's actions were a consequence of its anxiolytic conflict-reducing properties.

Note that because trials were conducted but once per day, an animal's propensity to run the alley on any given day was in large part determined by what transpired in that goalbox on the previous day(s). Thus, the occurrence of "retreat" behavior is thought to result from a subject's mixed positive and negative associations with the goalbox based upon the outcomes of previous trials. This would account for why animals that only found food in the goalbox exhibited fast Run Times and no retreats—the goalbox for these animals was associated with solely or predominantly positive events. On the other hand, food-deprived animals that originally found only food and later food+shock in the goalbox, would be expected to have both positive and negative associations with that goalbox and hence be more likely to exhibit approach-avoidance behaviors that result in longer Run Times and increased retreats—which is precisely what occurred. The results from the remaining Shock Only Group are a little more difficult to interpret in large part because this group does not represent an aversive only condition. Consider the fact that these animals were trained to approach and enter the goalbox for food reinforcement and that they remained food-deprived throughout the experiment. Hence when the shock only condition was initiated midway through the experiment, these animals would still be expected to initially approach and enter the goalbox, albeit with Run Times that progressively slowed and retreats that progressively increased over trials. So even for this group an approach-avoidance conflict should continue to exist. Of course it remains a possibility (even a likelihood) that with repeated trials the Shock Only group would eventu-

ally cease their approach to (and retreat from) the goalbox. Similarly, it is possible that IV cocaine could with repeated trials eventually lose its reinforcing properties and become in essence a relatively pure aversive event. Unfortunately, neither the current study nor the Ettenberg and Geist experiment (8) ran sufficient trials to test this hypothesis. What these studies do show is that within the time frame examined, all three groups (Food+Shock, Shock Only and Cocaine) exhibit highly comparable patterns and frequencies of retreat behavior. Miller's (19) classic explanation for such behavior is that there exists concurrent underlying positive and negative attributes of the goalbox that pull and push the animal's behavior. Thus the comparability in the performance of those rats that

experienced both food and shock (or even food then shock) to those of Ettenberg and Geist's (8,9) IV cocaine reinforced rats, is certainly consistent with the view that a common diazepam-reversible approach-avoidance conflict is responsible for the retreat behaviors in both experiments.

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