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# Establishment of Secondary Reinforcement in Sign Tracking and Place Preference Tests Following Pimozide Treatment

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TOMBAUGH, T. N., L. J. GRANDMAISON AND K. A. ZITO. *Establishment of secondary reinforcement in sign tracking and place preference tests following pimozide treatment.* PHARMAC. BIOCHEM. BEHAV. 17(4) 665–670, 1982.—The effects of pimozide (1.0 mg/kg), a DA receptor blocker, on the capacity of environmental stimuli to acquire secondary reinforcing properties was investigated using two different paradigms. In the first experiment rats pretreated with either pimozide or its vehicle, were exposed to light-food pairings. When tested under drug-free extinction conditions, these animals approached the light cue significantly more frequently than did control animals who never had the cue associated with food during training. No differences in approach behavior were observed between the pimozide and vehicle groups that received the light-food pairings. The second experiment employed a place preference paradigm where animals were confined in distinctive compartments under reinforced (S+) or nonreinforced (S−) conditions. Pimozide and vehicle treated animals, when tested drug-free and given unrestricted access to both chambers under extinction conditions, spent comparable amounts of time in the S+ chamber relative to vehicle subjects that had never received food in either chamber. The results from these two studies indicate that an animal's ability to code relevant environmental information and to use this encoded information to guide and direct food seeking behavior is relatively independent of dopaminergic activity. The results also have significance for any theory which assumes that dopamine mediates reward processes.

Secondary reinforcement  Sign tracking  Place preference  Pimozide

THE anhedonia hypothesis proposed by Wise [14] posits that dopamine (DA) containing neurons play an important mediational role in reward mechanisms. Blockade of DA receptors by neuroleptic drugs (e.g., haloperidol and pimozide) are postulated to blunt the hedonic attributes of normally rewarding stimuli such as food, electrical self-stimulation and cocaine. Additionally, it is predicted that pimozide will reduce or eliminate the ability of stimuli paired with primary rewarding stimuli to acquire conditioned rewarding or incentive motivational properties. That is, since the hedonic attributes of primary reward have been reduced or rendered functionally neutral by pimozide, stimuli associated with it would not be expected to gain any rewarding characteristics which could serve to initiate or maintain goal directed behavior. This prediction has received experimental support from two recently completed studies. Davis and Smith [8] paired a buzzer with injections of apomorphine, a DA agonist possessing reinforcing properties. Immediately prior to the pairings rats were injected systemically with either saline or haloperidol. The conditioned reinforcing effectiveness of the buzzer was determined in a subsequent drug-free session where it was presented briefly following each bar press. Elevated response rates were observed only for control subjects, suggesting that haloperidol interfered with the establishment of conditioned reinforcement effects. Beninger and Phillips [5], using a choice paradigm where depression of one of two levers produced the CS (tone), reported similar findings. That is, pimozide administered prior to CS (tone)-UCS (food) pairings prevented the tone from acquiring secondary reinforcing attributes.

While these results support the anhedonia hypothesis, they are inconsistent with an ever increasing body of literature that indicates that DA does not mediate S-S (CS-UCS) associative learning processes [1, 2, 3, 4, 11]. The results reported by Davis and Smith [8] and Beninger and Phillips [5] may, however, demonstrate that while DA is typically not essential for S-S learning, there may be some instances where DA does play a critical role. For example, it is possible that DA is involved in situations where the environmental stimuli acquire hedonic or positively motivating attributes (e.g., those involved in approach, goal-seeking behaviors). Alternatively, the testing procedures used may have been insensitive or inappropriate for assessing the effects of neuroleptics on the ability of previously neutral stimuli to gain incentive motivational properties. In this respect, it should be noted that the procedures employed in the two experiments required the animals to learn a new response during the secondary reinforcement test. As such, it is

possible that the neuroleptics administered during conditioning may have induced sensory-motor deficits which subsequently prevented animals from either associating the conditioned cue with the preceding instrumental response, or acquiring the response per se. The latter alternative could have been eliminated if the putative conditioned reinforcer had been made contingent upon the emission of a previously learned or naturally occurring response. Additionally, the use of a natural response is recommended by the fact that many conditioned reinforcement effects are temporary and dissipate rapidly when prolonged testing procedures are used. Consequently, the following two experiments further evaluated the effects that pimozide has on the establishment of incentive motivation by using an animal's natural response tendency to approach a location where food is frequently delivered.

## EXPERIMENT 1

Experiment 1 employed a naturally occurring ambulatory approach response to determine if pimozide impaired the ability of rats to "sign-track"—behaviorally locating and approaching a specific environmental feature previously associated with a primary reinforcer such as food [9]. If pimozide disrupts S-S learning when hedonic stimuli are employed, as previously suggested [5,8], then rats pre-exposed to "light-food" pairings under pimozide should be behaviorally impaired in tracking the light cue (food absent) when its spatial location is randomly varied from trial to trial in a subsequent drug-free test.

### METHOD

*Subjects*

Twelve naive male Sprague-Dawley rats purchased from the Holtzman Co., Madison, WI served as subjects. The animals were individually housed and were approximately 90 days old (300–325 g) at the beginning of the experiment.

*Apparatus*

Four experimental chambers (61×71×74 cm) constructed of 1.91 cm plywood and sound insulated with acoustical ceiling tile were used. Each chamber was equipped with a 100 CFM Dayton blower and contained a wire test cage (25×20×19 cm) suspended from the center of the chamber. Indexing reinforcement magazines were positioned under the right and left sides of the test cage. Each device contained a magazine plate (30 cm diameter) with 72 holes (food cups) drilled around the periphery. This was covered by a second plate. Both plates rested on a base that advanced one position per trial, thereby exposing a new cup while concurrently covering the previous food cup. Two openings (3.5×3.5 cm) in the cage floor permitted access to the food cup. The distance between the two magazine apertures was 15 cm. A 24 V DC cue lamp was positioned behind a Plexiglas covered circle (2.5 cm diameter) located immediately above each of the magazine apertures. General illumination was provided by a 24 V DC lamp situated above an opaque faceplate mounted flush with the top of the cage. Experimental contingencies and data collection were controlled by a PDP-8I digital computer located in a separate room.

*Procedure*

*Training.* Nineteen days prior to the beginning of the experiment animals were placed on a daily restricted diet of 16 g of Purina Laboratory Chow. Water was freely available in the home cage. Three days before training, a food cup containing ten 45 mg Noyes pellets was placed in the home cage to familiarize rats with the type of food to be used for reinforcement. Animals were randomly divided into three groups. During training two groups (Vehicle-Paired and Pimozide-Paired) received light-food pairings. For these groups the commencement of a trial was marked by the onset of one of the cue lamps. One-half second later the appropriate magazine cycled, presenting a single food pellet. Offset of the cue lamp occurred 1 sec following a consummatory response or after 15 sec had elapsed. For the third group (Control) the light and magazine cycles were negatively correlated such that the magazine cycled either 15, 30 or 45 sec after the offset of the cue light. The cue lamps, presented in a random sequence, appeared an equal number of times on the left and right sides of the cage with an interstimulus interval (ISI) of 80 sec.

Four hours prior to being placed in the test apparatus, animals in Group Pimozide-Paired were injected with 1.0 mg/kg of pimozide while subjects in the other two groups received its vehicle. This dose was selected on the basis of data from previous experiments which showed that it was highly effective in producing behavioral effects in a wide variety of experimental paradigms [2, 3, 6, 13]. Pimozide was dissolved in 2–3 drops of acetic acid and a heated dextrose solution (5.5%) added to make up a concentration of 1 mg/ml. Four training sessions were given, each consisting of 36 pellet presentations, 18 on each side of the test cage. Animals were conditioned twice a week (Tuesdays and Fridays). An observer recorded the number and latency of approach and consummatory responses that occurred during light presentations in training as well as in the subsequent test session. An approach response was defined as movement from any part of the chamber to a location where the rat's head was positioned above the magazine aperture associated with the illuminated cue lamp. A consummatory response was recorded if the animal placed its nose through the aperture during the light presentation. Number of pellets consumed during the ISI was also recorded.

*Nonreinforced test.* Three days after completion of training all animals received a single drug-free test session. Experimental parameters were identical to those in training except that reward was not presented when the magazine cycled.

### RESULTS

The mean number of approach and consummatory responses were computed for each group. However, since both measures showed essentially the same relationship and produced comparable levels of statistical significance, only the approach data will be presented. Figure 1A shows the mean number of approach responses during each of the four training sessions and the single test phase. Mean approach response latency scores are presented in Fig. 1B.

*Training.* An analysis of variance with repeated measures was performed over all four training sessions. Degrees of freedom appropriate to a Geisser-Greenhouse conservative F-test were used [10]. A significant Groups effect, $F(2,9)=30.81$, $p<0.01$, was due to the relatively greater number of responses made by the two vehicle groups. Pair-wise comparisons ($\alpha=0.05$) revealed that the pimozide group made significantly fewer responses than either of the

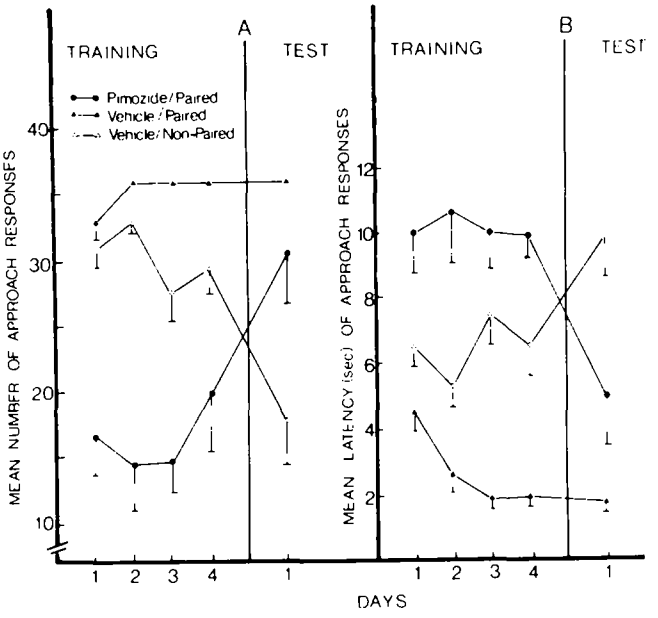


FIG. 1. Mean (±SEM) number of approach responses (A) and latency of approach responses (B) emitted to a light cue which during training had been paired with food for the experimental groups. Data are shown for the four training sessions and the single drug-free extinction test session. During training light-food pairings were administered to two groups injected with either 1.0 mg/kg pimozide (Group Pimozide-Paired) or vehicle (Group Vehicle-Paired). For a third group (Group Vehicle-Nonpaired) the light was never paired with food (negatively correlated) under vehicle conditions.

vehicle groups which did not differ significantly from each other. Although Fig. 1A illustrates that the number of approach responses gradually decreased over sessions for Group Control while they tended to increase for Group Pimozide-Paired, neither the Session, $F(1,9) < 1$, nor Groups × Session, $F(2,9)=1.28$, $p>0.05$, effects approached statistical significance.

Inspection of Fig. 1B shows that Group Vehicle-Paired had the shortest approach latencies followed by Groups Control and Pimozide-Paired. An analysis of variance performed over these data showed a significant Groups effect, $F(2,9)=52.23$, $p<0.01$. Subsequent pair-wise comparisons ($\alpha=0.05$) revealed that the differences between all groups were statistically reliable. No statistically significant Session, $F(1,9)=1.24$, $p>0.05$, or Groups × Session, $F(2,9)=2.54$, $p>0.05$, effects were obtained.

Analysis of the total number of pellets consumed during training, $F(2,9)=14.81$, $p<0.01$, revealed that pimozide-paired subjects ate significantly fewer pellets than rats in either of the two vehicle groups which, in turn, consumed a comparable number of pellets. An additional analysis performed between the pimozide-paired and vehicle-paired conditions showed that pimozide treated subjects consumed a significantly greater proportion (40%) of their pellets during the ISI when the cue light was not illuminated, $F(1,9)=18.61$, $p<0.01$.

Behavioral observations revealed differences among the groups in patterns of responding. Animals in the vehicle-paired condition immediately oriented toward and approached the food hopper when the cue lamp was illuminated. Control animals in the non-paired condition, however, continuously alternated between the two hopper locations, independent of the cue lamp status. While this strategy enabled them to locate and consume the vast majority of food pellets, there was no evidence that their behavior was under the control of the magazine light. In addition, early in training pimozide treated animals displayed considerably less locomotor behavior and tended to stay toward the back of the cage where changes in illumination were more difficult to detect. However, as training progressed a second behavioral pattern emerged for this group. Animals remained for extended periods of time on the side where food most recently had been consumed placing their heads directly over the reinforcement aperture. One major consequence of this behavior was a frequent failure to respond when the cue lamp on the opposite side of the cage was illuminated.

*Nonreinforced test.* Figure 1A illustrates that both vehicle-paired and pimozide-paired subjects emitted substantially more responses than did the control subjects, $F(2,9)=10.48$, $p<0.01$. Pair-wise comparisons ($\alpha=0.05$) showed that a significant difference existed between the control group and each of the other two groups. The difference between the two light-food paired groups was not significant indicating that the pimozide animals, although deficient in training, now performed as well as the vehicle-paired animals. An analysis of latency data (Fig. 1B) revealed a significant difference among the groups, $F(2,9)=38.38$, $p<0.01$. Pair-wise comparisons ($\alpha=0.05$) showed that the control group took significantly longer to respond than either of the other two experimental groups. The difference between the two light-food groups was also statistically reliable with vehicle animals responding more quickly.

## DISCUSSION

The major finding of Experiment 1 was that rats trained under pimozide were able to acquire the association between two environmental cues and to subsequently utilize this information to guide and direct their behavior. That is, pimozide-treated animals conditioned to light-food pairings made significantly more approach and consummatory responses when tested under drug-free extinction conditions than did vehicle animals who never received the light-food pairings. Latency data also supported the contention that pimozide animals learned and utilized the environmental cues relative to the non-paired control group. The comparable level of test performance observed between the pimozide-paired and vehicle-paired rats shows that under the present set of conditions pimozide did not retard acquisition or utilization processes. Moreover, this sign-tracking behavior occurred in spite of the fact that during training pimozide-treated animals actually received 40% fewer light-food pairings than did the vehicle-paired group. This latter fact is probably related to the extrapyramidal motor effects commonly reported with similar doses of pimozide.

## EXPERIMENT 2

In order to test the generality of the conclusions advanced in Experiment 1 a second study was undertaken employing a place preference procedure. During training animals injected with either pimozide or vehicle were confined in distinctive compartments under reinforced (S+) or nonreinforced (S−) conditions. Subsequently in a drug-free test they were given unrestricted access to both chambers (food removed). Sec-

ondary reinforcing effectiveness was measured by the degree to which animals changed their preference toward the chamber associated with food. If pimozide disrupts the capacity of stimuli to function as conditioned motivators, then pre- and post-training preference scores should be comparable for animals injected with pimozide prior to conditioning placements. However, if DA receptor activation is not essential for the establishment of secondary reinforcers, increased preference toward the S+ compartment should occur for pimozide as well as vehicle animals.

## METHOD

### *Subjects*

Forty naive male Sprague-Dawley rats (300–325 g) purchased from the Holtzman Co., were used as subjects. Upon receipt from the supplier they were individually housed and placed on ad lib food and water.

### *Apparatus*

The test apparatus (111×13×16 cm), constructed of sheet metal, was divided into three compartments. The center compartment (15 cm) contained a wooden floor and was painted gray. One end compartment (48 cm) was painted white and had a smooth white wooden floor while the other end chamber (48 cm) was painted black and contained a black wire mesh floor. During conditioning trials a wooden block was placed between the two end compartments. A pellet hopper positioned outside of the white chamber dispensed 45 mg pellets into a food tray flush with the end of the chamber. Ten test chambers were used, divided equally between two rooms. A piece of clear Plexiglas was placed over the chambers to prevent animals from escaping. All conditioning and test sessions were video-taped.

### *Procedure*

*Habituation.* Five days prior to the beginning of the experiment all rats were placed on a daily restricted feeding schedule of 15 g of Purina Laboratory Chow. Four consecutive habituation sessions were then administered, one per day, where animals were allowed to freely explore the alley for 15 minutes. In order to habituate animals to the sound of the hopper solenoid the empty pellet dispensers cycled every 20 sec.

*Conditioning.* Six conditioning days were employed where animals were confined for two 20 minute periods in one of the two compartments. Conditioning sessions were conducted twice a week (Mondays and Thursdays). Each placement was separated by an interplacement interval of $2^1/_2$ hours. The chamber in which the animals were placed (black vs white) alternated between conditioning days. Half of the animals were placed into the white side for both daily sessions on odd numbered days and into the black compartment on even numbered days. The opposite sequence was used for the remaining half of the animals. Since the majority of animals showed comparable preference between the two compartments on the last habituation day, food was always delivered in the white compartment. This eliminated periodical changing of the equipment between sessions thereby reducing the possibility of equipment malfunction. During the first two training days a single 45 mg Noyes pellet was dispensed every 20 sec. This was changed to a variable interval 35 sec schedule for the remaining four sessions. On each conditioning day animals were injected (IP) with either 1.0 mg/kg of pimozide or its vehicle (1 ml/kg). Four hours later they were placed into the apparatus where they received either food or no food.

Based on black/white preference scores on the last day of habituation (baseline) animals were divided into five equivalent groups. The animals in four of the groups received food in the white (S+) chamber while no food was presented in the black (S−) compartment. These four groups differed according to whether they were given pimozide (P) or vehicle (V) for the food (F) and no food (N) pairings. That is, Group PF-PN received both food (white chamber) and no food (black chamber) placements under pimozide, while Group VF-VN received the same placements after vehicle injections. Group PF-VN was placed in the food chamber following pimozide pretreatment, and in the no food chamber following vehicle injections. Group VF-PN received the opposite sequence of drug injections. Finally, a fifth group (Group VN-VN) was included to determine if confinement per se altered chamber preference. In this case animals were injected with vehicle but food was not presented in either chamber. However, when the rats were confined in the white compartment the food magazine cycled periodically, as it did for the four experimental groups, but no food was delivered.

If pimozide impairs S-S learning then Group PF-PN should not acquire the association between the environmental cues and food to the same degree as Group VF-VN. Moreover, comparison of the scores of Groups PF-VN and Group VF-PN will determine if pimozide itself produces any aversive effects. That is, if the pimozide state is aversive, Group PF-VN should show less preference for the food side relative to Group PF-PN. Additionally, Group VF-PN should show greater preference for the food side than Group VF-VN.

*Test.* Four days following the last conditioning day, a single drug-free test session was administered under conditions identical to those present during the last habituation session.

## RESULTS

The mean percent of time which each group spent in the white chamber during baseline (last day of habituation) and test day is shown in Fig. 2. One subject in Group VN-VN was discarded due to a procedural error. Inspection of this figure shows that all groups exhibited similar baseline preferences. This observation was confirmed by an analysis of variance, $F(4,32) < 1$. An analysis of variance performed over the test data was statistically significant, $F(4,32)=5.49$, $p<0.01$. Figure 2 shows that presentation of food in the white compartment during conditioning increased preference toward the S+ chamber for all experimental groups regardless of whether they had been trained under pimozide or vehicle conditions. The mean test preference score for the non-paired control group, on the other hand, did not change significantly from baseline. Pair-wise comparisons ($\alpha=0.05$) revealed that the performance of the control group was significantly different from each of the experimental groups. However, none of the comparisons between the experimental groups approached statistical significance.

To determine if place preference systematically changed during the course of testing, preference scores were computed over three successive five minute blocks and subjected to an analysis of variance with repeated measures. Degrees of freedom appropriate to a Geisser-Greenhouse conservative F test were used [10]. The analysis of baseline data

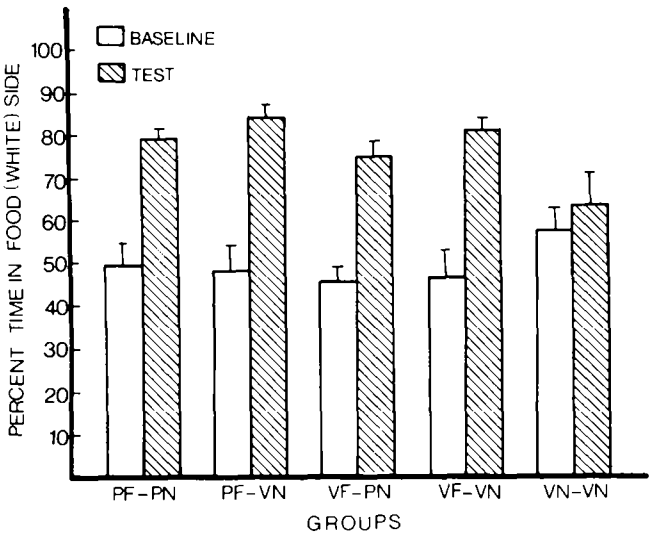


FIG. 2. Mean (±SEM) percent of time animals spent on the food (white) side of the place preference apparatus during baseline (last day of apparatus habituation) and test. During conditioning rats received either food (F) or no food (N) under conditions of pimozide (P) or Vehicle (V). The dose of pimozide used was 1.0 mg/kg. See Method section, Experiment 2, for description of the procedure employed for individual groups.

showed that preference remained stable over the three periods, $F(2,32)=2.33$, $p>0.05$. During the test phase a significant Trials effect occurred, $F(2,32)=10.68$, $p<0.01$. This was due to a general tendency for all groups to progressively increase their preference toward the white side, with the most substantial increases occurring during the second five minute block. The failure to obtain a Groups × Trials interaction, $F(4,32)<1$, indicates that the relationship among the groups exhibited in Figure 2, was maintained across all five minute blocks.

### DISCUSSION

The results of Experiment 2 support the conclusion previously advanced in Experiment 1 that pimozide does not interfere with the ability of animals to learn the association between environmental cues and food. This is clearly illustrated by the fact that all experimental groups showed a comparable increase in their preference toward the S+ chamber, relative to the control group. Moreover, there was no evidence supporting the speculation that pimozide injections produced an aversive state. If this were the case, groups that received pimozide during nonreinforced exposures should have developed a greater proportional aversion toward the S− cues (or conversely, preference toward S+ cues) in comparison to animals that received nonreinforced exposure under vehicle. Consequently, Groups PF-PN and VF-PN should have displayed relatively greater preference toward the cues (S+) paired with food compared to Groups PF-VN and VF-VN, respectively. Inspection of Fig. 2 shows a slight but nonsignificant trend in the opposite direction.

It is also noteworthy that the failure of pimozide to decrease S+ preference scores cannot be explained by state dependent learning. While an appeal to state dependency might be appropriate if the pimozide groups had displayed a lower level of performance, particularly Group PF-PN relative to Group VF-VN, it is difficult to understand how it is applicable when equivalent levels of preference were observed. Moreover, data from at least one other study failed to demonstrate that state dependency effects occur with pimozide-treated subjects [5].

## GENERAL DISCUSSION

The present research assessed the degree to which pimozide, a DA receptor blocker, influenced the capacity of environmental stimuli to acquire incentive motivational properties. By virtue of conditioning processes, situational stimuli acquire the ability to direct and reinforce behavior when they are positively correlated with appetitive stimuli (e.g., food). If the acquisition of incentive motivators is mediated primarily by DA, animals pretreated with pimozide should be unable to acquire the significance of environmental stimuli paired with food. Such a demonstration would support the DA reward hypothesis, exemplified by the anhedonia theory [14], which posits that central dopamine provides the neural substrate for reward processes. Within this framework there are two major theoretical avenues by which pimozide may inhibit the formation of incentive motivators. One approach is to assume that pimozide directly effects associative processes by its ability to blunt or block the "hedonic" or rewarding attributes of food. Based on this assumption, it has been explicitly predicted that pimozide should significantly retard or eliminate acquisition processes in both operant and classical conditioning paradigms [14]. Alternatively, it may be hypothesized that pimozide does not directly influence S-S learning, but renders food "motivationally neutral." Consequently, even though the S-S association is learned, environmental stimuli paired with food do not gain any motivational attributes or provide animals with information which they may use to anticipate either the presentation or spatial location of rewards. Contrary to the above theoretical speculations, data from the current set of experiments show that the establishment of incentive motivators was not influenced by pimozide.

In Experiment 1, animals conditioned under either pimozide or vehicle received several sessions where the onset of a stimulus lamp preceded presentation of food pellets. A drug-free extinction test demonstrated that pimozide did not disrupt the ability of animals to spatially track the light cue. A similar conclusion was advanced in Experiment 2. In contrast to the first experiment, where choice behavior was measured only after each discrete presentation of the relevant stimulus, Experiment 2 permitted animals to continuously sample stimuli previously correlated with either the presence or absence of food. Here, too, conditioning under pimozide did not block or impair the establishment of conditioned reinforcers as revealed in the drug-free extinction test. Thus, the data from both experiments suggest that pharmacological blockade of DA receptors does not prevent animals from coding relevant environmental stimuli or using this encoded information to guide and direct food-seeking behavior. In short, environmental cues functioned as incentive motivators.

Finally, the present demonstration that cue acquisition and utilization were relatively independent of DA, a finding incongruent with other studies [5,8], is probably related to three factors—lack of a strong baseline position preference, use of a natural response, and presence of discrete food-associated cues. Strong position preferences have been re-

ported in experiments where neuroleptic effects on associative processes were assessed by providing animals with a choice between two response alternatives [5,12]. When these biases exist the test stimuli typically are paired with the least preferred alternative. This strategy, when applied to conditioned reinforcement determinations, may mask incentive motivational effects by requiring animals to overcome their strong natural response biases in order to select those stimuli possessing putative reinforcing properties. Consequently, the current study used experimental parameters which avoided strong position preferences. A second feature involved the selection of a response which would readily reflect whether or not the environmental cues had gained incentive motivational properties. Following the lead of Bolles [7], a natural approach response was chosen which is more or less automatically elicited by food. This presumably eliminated (or at least substantially reduced) S-R learning thereby making the testing situation more sensitive to the effects of S-S learning (see also [2,11]). A third aspect was the discrete presentation of the food pellets coupled with a salient cue signalling the delivery and locus of food. This was considered important in order to offset any sensory diminuation that might be produced by pimozide and to increase the probability that animals would attend to the presentation of the food. Whether the same effects reported here will occur in situations with less powerful environmental stimuli or when the animal is less motivated to seek food remains to be determined.

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