

SPONTANEOUS RECOVERY DURING, BUT NOT FOLLOWING, EXTINCTION OF THE DISCRIMINATIVE STIMULUS EFFECTS OF NICOTINE IN RATS: REINSTATEMENT OF STIMULUS CONTROL

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Extinction of the discriminative stimulus effects of drugs has received little research attention. Using a one-lever food-reinforcement (VI-1 min) operant procedure with rats ($N = 16$), the studies reported here assessed extinction, spontaneous recovery, and reinstatement of responding to the discriminative stimulus effects of nicotine. Experiment 1 found evidence for retention of differential responding to IP administrations of nicotine after a 3-month (87 days) delay following acquisition. Experiment 2 compared *spontaneous recovery* of discriminative control 2 and 4 weeks following extinction. Additionally, the impact of noncontingent reinforcement on discriminative control was evaluated (*reinstatement*). During extinction training, nicotine (.4 mg/kg) or saline was administered 15 min prior to each 15-min session, as they were during training, but responding was not reinforced under either stimulus condition. Spontaneous recovery (SR) of responding under the S^D condition occurred during a session (11th) preceded by two consecutive S^A sessions. Matched by response rate, 8 rats were randomly assigned to either a 2-week delay group or a 4-week delay group. There was no evidence for SR of discriminated responding to the drugs 2 or 4 weeks following the final extinction session. Between-group comparisons further revealed that SR did not vary as a function of delay following extinction. Reinstatement of stimulus control was observed following 2 brief sessions of noncontingent food delivery (levers retracted and conducted in the absence of the drug cues). These results suggest that the maintenance and extinction of the discriminative stimulus effects of nicotine are temporally stable. Theoretical ideas regarding drug self-administration, craving, and therapy are entertained.

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The discriminative stimulus (S^D) functions of a variety of drugs in the pharmacopoeia have been well documented (e.g., Overton, 1982) along with respective receptor mechanisms of action. Although there is remarkable parallel between the stimulus control functions of interoceptive drug stimuli and exteroceptive stimuli (visual or auditory stimuli), only three studies have evaluated the impact of extinction procedures on stimulus control of drugs (Harris & Balster, 1971; Rijnders, Jarbe, & Slangen, 1990; Zarcone & Ator, 2000).

A related phenomenon, spontaneous recovery, was first observed by Pavlov (1927) and is operationally defined as a return of the conditioned response following a delay period after extinction (e.g., Brooks & Bouton, 1993; Mackintosh, 1974; Rescorla, 1997a, 2001; Robbins, 1990). Spontaneous recovery of operant behavior to a S^D has also been reported (Rescorla, 1997b, 2001).

Recently, this laboratory Troisi (in press) observed that 20 sessions of nonreinforced lever pressing in rats under nicotine or ethanol states (previously predictive of food availability or nonavailability) suppressed overall responding as well as stimulus control. Several instances of spontaneous recovery of responding under the S^D , but not the S^A , drug conditions occurred throughout the 20 sessions of nonreinforcement, although there were differences as a function of drug. SR occurred specifically during the S^D session that was preceded by two consecutive S^A sessions. Most interestingly, no evidence of spontaneous recovery of differential responding under the drug conditions was observed 2 weeks later following extinction, but weak evidence was found 4 weeks following extinction, within the same subjects. These data may be interpreted in view of reports of spontaneous recovery of responding to exteroceptive S^D s. Sufficiently smaller time intervals (within 1 week) have been reported to produce spontaneous recovery following extinction of responding to exteroceptive stimuli in Pavlovian preparations (e.g., Brooks & Bouton, 1993; Robbins, 1990). Rescorla (1997b) reported spontaneous recovery of food-reinforced lever pressing to operant S^D s in rats after a 5-day delay. As suggested by Rescorla, recovery of responding appears to increase over time. This issue has clinical relevance as it may provide additional information about the behavioral mechanisms of relapse to *interoceptive* cues, (e.g., drug cues or emotional states) predictive of drug reinforcement in humans.

The discriminative stimulus properties of some drugs appear to be temporally stable (e.g., Schechter, Signs, & Boja, 1989). In terms of retention of stimulus control following a delay after discrimination training, Spear, Smith, Sherr, and Bryan (1979) reported that the state-dependent properties of pentobarbital remained present 2 months (60 days) following the last day of training. If stimulus control by drugs endures time (retention), it is possible that extinction of the discriminative stimulus effects of drugs may also be retained over extended time periods, thereby inhibiting spontaneous recovery of responding to the drug S^D s.

Using nicotine as a training drug, the discriminative stimulus effects of

which have been well established (e.g., Schechter & Meehan, 1992; Schechter & Rosecrans, 1972; Stolerman, Garcha, Pratt, & Kumar, 1984), the present studies sought to address the issues outlined above using a one-lever appetitive operant procedure with quasi-random alternations between reinforced (S^D) and nonreinforced (S^A) extinction sessions (go/no-go).

Experiment 1

Experiment 1 investigated the potential for retention of the discriminative stimulus effects of nicotine following a 3-month (87 days) delay following acquisition. In view of the findings of Spear et al. (1979) who found evidence for stimulus control by pentobarbital 60 days following training, it was predicted here that differential responding to nicotine would be evident following the delay after acquisition.

Method

Subjects

Sixteen male Sprague Dawley rats approximately 8 months old at the start of the study (Harlan, Indianapolis, IN) served as subjects (Ss) and were maintained at 80% of their free feeding weights (80% range was approximately 270-335 g). The rats were housed in individual stainless-steel cages in the vivarium with ad-lib access to water and were maintained on 12-hr light-dark cycle (0700 to 1900). Animals were used in accord with the ethical guidelines of the American Psychological Association and this institution's Institutional Animal Care and Use Committee and were in accord with Public Health Service Guide for the Care and Use of Laboratory Animals.

Apparatus

Sessions took place in eight stainless-steel/Plexiglas operant chambers (Med-Associates, Georgia VT, Model ENV-001) measuring L 28 x W 21 x H 21 cm. Each chamber was equipped with one lever located 2 cm to the left of the centrally located food magazine (which delivered 45 mg food pellets, PJ Noyes, Lancaster, NH) and 7 cm above the grid floor. The chambers were spaced 2 to 3 feet apart about the perimeter of the sound- and light-attenuated experimental conditioning room measuring L 16.5 x W 9 feet. Low level (approximately 15 W) overhead incandescent lights signaled session time. Experimental events were programmed via Med-PC Software (Version 2.08) and by a DIG interface (Med-Associates, Georgia, VT) to a 386 PC.

Procedures

Two daily sessions were run Monday through Friday at approximately 1000 and 1400. Magazine training and shaping of lever pressing took place over the 1st week. Responding was shaped on a FR-1 schedule of reinforcement on the 1st day of training. The schedule was gradually

increased in the following order: FR-3, FR-5, FR-10, VI-30 sec to a VI-1 min over the next 3 days. All discrimination training sessions were 15 min. Test sessions were 3 min and two tests followed each phase (one under each stimulus condition).

Initial drug discrimination (DD) acquisition training. All rats were trained to respond differentially between 15-min S^D (reinforcement) and S^A (extinction) sessions. Sessions alternated quasi-randomly in that, generally, no more than two sessions of any one condition occurred consecutively. The only violations to this sequence occurred at mid-training in Experiments 1 and 2. Two sessions under one drug condition could occur within a given day under the condition that the next session on the following day would be run under the opposite drug condition. Responding was maintained on a variable interval (VI-1 min) schedule of food reinforcement during S^D sessions and extinction during S^A sessions. Twenty-four sessions were run initially (12 S^D and 12 S^A) for the first squad (S1 through S8), and (13 S^D and 11 S^A) for the second squad (S9 through S18). Rats received intraperitoneal injections of either of (-)-nicotine (RBI, Natick, MA) (0.2 mg/kg, dissolved in .9% saline, and delivered in a volume of 1 ml/kg) or vehicle. The 15-min training session commenced 15 min later.

Testing. To determine if the drugs had acquired stimulus control, on the day immediately following the final two drug discrimination training sessions, two nonreinforced extinction tests were conducted (a.m. and p.m.). Eight rats were tested under the nicotine condition in the morning. For 4 of these rats nicotine served as the S^D; for the remaining 4 it served as the S^A. The remaining 8 rats were tested under saline in the morning. For 4 of these rats saline served as S^D; for the remaining 4 it served as the S^A. In the afternoon, subjects received the opposite drug condition. Testing was therefore completely counterbalanced by time of day and discriminative roles of nicotine and saline. All extinction tests described below were carried out in a similar manner. Over the next 87 days, all rats were maintained at their 80% free feeding weights and housed in the vivarium. Exactly 87 days following the initial tests, all rats were tested identically to the previous test. To increase stimulus saliency, so as to evoke retention, the dose of nicotine was increased from .2 mg to .4 mg/kg. A failure to show discriminative control 3 months later would prompt testing at this dose. Additionally, all 16 rats were administered the same dose to maintain statistical power as well as to evaluate direct drug effects on behavior. Little to no difference in discriminability between these doses has been reported elsewhere (e.g., Stolerman et al., 1984).

Results

Figure 1 displays the results of the initial discrimination acquisition phase. Group data are presented for Rats 1-8 (top panels) and 9-16 (bottom panels). The left panels illustrate acquisition for Rats 1-4 and 9-12, trained under the condition where nicotine functioned as S^D and saline functioned

as S^{Δ} ($N+/S-$). The right panels show the mean data for Rats 5-8 and 13-16 trained under $S+/N-$. Inspection of Figure 1 reveals that all 8 rats exhibited markedly higher rates of responding during S^D compared to S^{Δ} sessions throughout the initial acquisition. Descriptively, there were no differences in response levels between the $N+/S-$ rats compared to the $S+/N-$ rats. Therefore, nicotine appeared to have no direct effect on response rate.

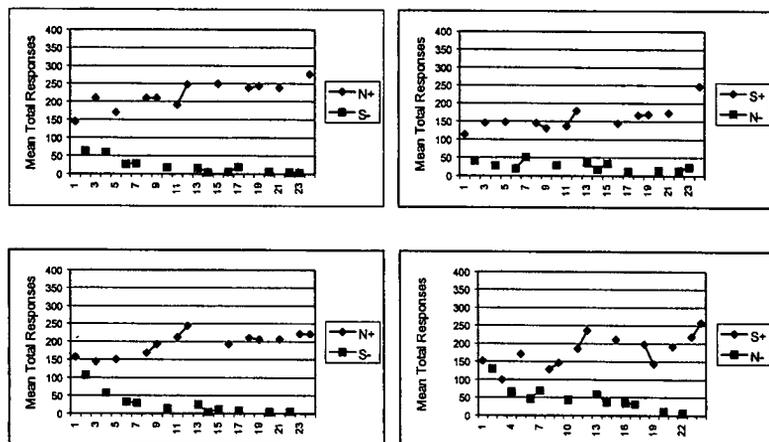


Figure 1. Drug discrimination acquisition data for 16 rats trained to respond differentially between .4 mg/kg of nicotine (N) and saline (S). Mean total responses/session are displayed. Each panel represents data from 4 rats. For 8 rats (left panels) $N+$ predicted 15-min food-reinforced sessions (VI-1 min) and $S-$ predicted nonreinforcement sessions. The stimulus role of nicotine was reversed (counterbalanced) for the remaining 8 rats (right panels). Top panels represent data for the first squad (Rats 1-8). Bottom panels represent the second squad (Rats 9-16).

Data from the 3-min extinction tests conducted immediately and 3 months following the final acquisition training sessions were averaged. Total responses across all 16 rats were calculated as mean S^D and S^{Δ} responses averaged across $N+$ plus $S+$ (for S^D) and $N-$ plus $S-$ (for S^{Δ}) conditions, respectively. There were significantly greater total responses under the S^D conditions ($M = 45.34$) compared to S^{Δ} conditions ($M = 10.00$) immediately following initial acquisition, $t(15) = 10.02$, $p = .000$. Similar results were obtained after the 3-month delay with significantly greater total responses under the S^D condition ($M = 26.44$) compared to S^{Δ} condition ($M = 13.34$), $t(15) = 2.84$, $p = .012$. Mean discrimination indices (S^D responses/ S^D + S^{Δ} responses) were calculated over the two tests as % S^D responses. Rats that failed to respond under either of the stimulus conditions were included in the N to calculate the denominator (16) upon which the percentage was derived. The mean discrimination index after the initial acquisition was 86% and decreased over the 3-month delay (67%). Despite this decrease, stimulus control remained evident with more than 50% of the total responses emitted under the S^D stimulus condition.

Discussion

The results of Experiment 1 suggest that the discriminative stimulus effects of nicotine endures time. These results are consistent with the results obtained by Spear et al. (1979) who demonstrated stimulus control 2 months following acquisition. It is possible, but unlikely, that the decline in discriminative control observed here was partially attributable to the dosage increase of nicotine following the delay. It is unknown, whether stimulus control would have been evident following the 3-month delay under the .2-mg dose, but is highly likely. A failure to obtain control at this dose would have prompted testing under .4 mg. Hence, the rationale for the dosage increase. On balance, little difference in discriminative control between these two doses has been shown elsewhere (Stolerman et al., 1984). However, there are no reported studies involving differences in these doses over delays following acquisition of discriminative control. Nevertheless, there was significantly greater responding under the S^D condition than under the S^A condition as well as evidence for stimulus control by nicotine 3 months following training.

Experiment 2

Experiment 1 provided evidence that the discriminative stimulus effects of nicotine were evident 3 months following conditioning. The objective for Experiment 2 was to first establish discriminative control with nicotine and then to parametrically vary the delay (weeks) following extinction of differential responding to the S^D functions of nicotine. A failure to observe discriminative control after either a 2-week or 4-week delay following extinction would be unlikely attributable to a "memory failure" of the discrimination in that these same rats showed evidence that the discrimination was retained, at least partially, over a remarkably longer time frame. Unlike Experiment 1, Experiment 2 employed a randomized two-group design matched by response rate following extinction training. In view of the results, and the interpretations by Rescorla (1997b) that spontaneous recovery increases with time, it was predicted here that there would be greater recovery of responding, if any, 4 weeks compared to 2 weeks following extinction. It was also predicted that there would be a greater discrimination index 4 weeks compared to 2 weeks following extinction.

An additional purpose of Experiment 2 following the delays after extinction was to assess the impact of noncontingent food delivery on discriminative control by the drugs. Procedures of this sort are commonly referred to as *reinstatement* in the Pavlovian literature in that they arrange for presentations of the US (without the CS preceding) following extinction. When the CS is subsequently presented again, conditioned responding is evoked. Reinstatement has been demonstrated following extinction of fear conditioning in rats (e.g., Rescorla & Heth, 1975; Westbrook, Iordanova, McNally, Richardson, & Harris, 2002) as well as in operant conditioning

procedures involving drug-reinforced operant responding (e.g., de Wit & Stewart, 1981, 1983; Katner, Magalong, & Weiss, 1999; McFarland & Ettenberg, 1997). However, there are no known studies that have reported reinstatement of discriminated operant responding under discriminative control by drugs by noncontingent reinforcement following extinction. Based on this assumption, it was predicted that noncontingent delivery of food following extinction of discriminative control would reinstate differential responding to the drug cues.

Method

Subjects and Apparatus

The descriptions of subjects and apparatus in Experiment 1 are the same for Experiment 2.

Procedures

Four of the rats from the first squad (1-8, Exp. 1) were assigned to the 2-week delay group (2 assigned from N+/S- condition and 2 from S+/N- condition); the remaining 4 rats were assigned to the 4-week delay group. Similarly, 4 of the rats from the second squad (9-16, Exp. 1) were assigned to the 2-week delay group (2 from N+/S- and 2 from S+/N-) with the remaining 4 rats assigned to the 4-week delay group. Group assignment was determined following extinction training in that rats were matched by rate of responding at the end of extinction. Training and testing sessions were identical to those employed in Experiment 1.

Initial training and testing. On the day immediately following the delay test of Experiment 1, drug discrimination training for all 16 rats was reacquired. The dose of nicotine was increased to .4 mg/kg. Thirty sessions were conducted for all rats (15 S^D and 15 S^A). Stimulus control was then tested on the following day as described in Experiment 1. Discriminative roles of nicotine and time-of-day were counterbalanced. One 3-min test session took place in the morning and one in the afternoon. One half of the rats were tested under the S^D condition in the morning; the remaining were tested under the S^A condition. Drug conditions were reversed in the afternoon. Testing was counterbalanced by time-of-day and discriminative role of nicotine for both groups.

Extinction training. Four sessions subsequently followed to reestablish stimulus control prior to carrying out extinction. Extinction sessions then followed (two/day as described for acquisition). The drug conditions were administered identically to the acquisition phase, but responding was not reinforced throughout each of the twenty-four 15-min extinction sessions (13 under S^D and 11 under S^A). The 2-week and 4-week delay groups were then maintained in their home cages during their respective delay periods.

Spontaneous recovery tests. On the day immediately following the final day of their respective delay periods each group underwent two 3-min extinction test sessions conducted and controlled as described in the previous phase.

Reinstatement and testing. The levers were removed from the operant chambers 7 days later. Each rat was then placed in a chamber but was not injected with either nicotine or saline prior to the 10-min session. Ten food pellets then were dispensed noncontingently at fixed 1-min intervals for each group. Two of these noncontingent food delivery sessions took place for each group, one in the morning and one in the afternoon. On the day immediately following, the levers were reinserted and testing took place as usual.

Results

As in Experiment 1 rats exhibited markedly higher levels of responding during S^D sessions compared to S^A sessions from the onset of, and throughout, reacquisition (data not illustrated). Response levels between rats trained under the N+/S- condition compared to the rats under the S+/N- conditions did not differ markedly, thus demonstrating control over the discriminative roles of nicotine. As in Experiment 1, there was no evidence of a direct effect of nicotine on response levels.

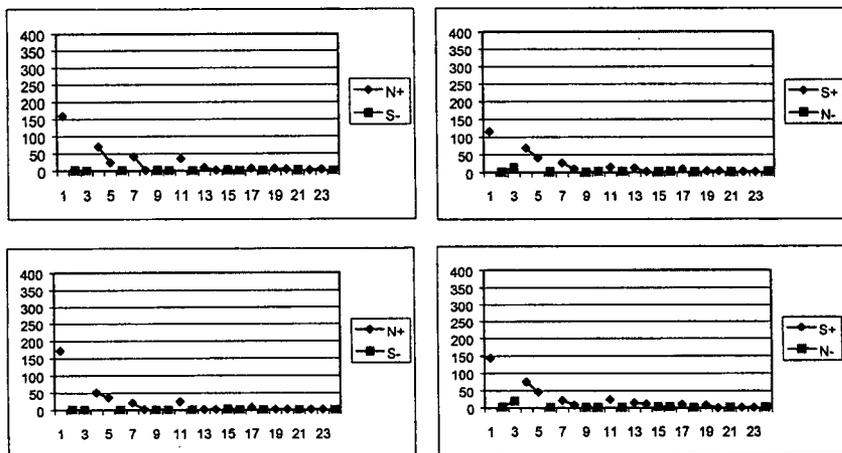


Figure 2. Extinction of responding under nicotine (N) and saline (S). Mean total responses/15-min session are displayed. Each panel represents data for 4 rats. For 8 rats (left panels) N+ previously predicted food and S- previously predicted nonreinforcement during the initial acquisition phase. The roles of the drug conditions were reversed for the remaining 8 rats (right panels). Top panels represent data for the 8 rats which were to be tested for spontaneous recovery 2 weeks following extinction training. Bottom panels represent the data for the 8 rats which were to be tested 4 weeks following extinction training.

The results of the extinction training sessions are displayed in Figure 2. The 2-week delay group data are presented in the top panels and the 4-week delay group data are presented in the bottom panels. Mean responding under the S^D conditions gradually diminished to zero levels over the final three sessions for both groups. Responding under the S^A condition was at zero, or near-zero, levels throughout each of the nonreinforcement

sessions. Descriptively, there were striking similarities in responding across groups and counterbalanced stimulus conditions. Interestingly, although S^D responding decreased to near-zero levels for both groups by the 8th session, it increased significantly above that level on the 11th session, a session preceded by two S^A sessions. Averaged across all rats, there was a significant increase in S^D responding from the 8th session ($M = 4.06$ total responses) to the 11th session ($M = 24.44$ total responses), $t(15) = 4.26$, $p = .001$. These data are consistent with data obtained by this laboratory (Troisi, in press) which observed instances of spontaneous recovery of discriminated responding between nicotine and EtOH under the S^D , but not S^A , drug conditions throughout sessions of nonreinforcement.

Figure 3 illustrates the results of the 3-min extinction tests for stimulus control immediately following initial reacquisition, after 2- or 4-week delays following extinction, and following reinstatement. Averaged within group (across counterbalanced conditions), there was significantly greater S^D compared to S^A responding for the to-be-assigned 2-week delay group, $t(7) = 6.93$, $p = .000$, and the to-be-assigned 4-week group, $t(7) = 7.95$, $p = .000$, following reacquisition of the discrimination. There were no differences between S^D and S^A responding after the 2-week delay (2-week delay group) or the 4-week delay (4-week delay group). Most importantly, there were

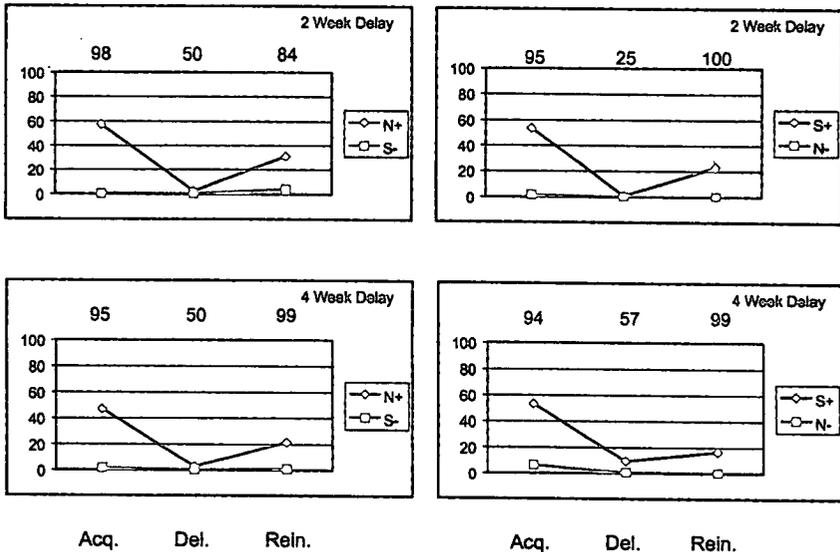


Figure 3. Three-min extinction test results for Exp. 2. Mean total responses/3-min session are displayed. Testing took place following initial acquisition of a nicotine (N) vs. saline (S) discrimination (Acq.), after delays following extinction of stimulus control (Del.) and following reinstatement by noncontingent food delivery (Rein.) Top panels illustrate the results for the rats assigned to the 2-week delay group. Bottom panels illustrate the results for the 4-week delay group. For 8 rats (left panels) N+ previously predicted food delivery during training and S- predicted nonreinforcement. The role of nicotine was reversed for the remaining rats (right panels). Percentages of S^D responses are displayed above each set of test results for each test condition.

significant differences in responding between drug conditions following reinstatement for the 2-week delay group, $t(7) = 4.53$; $p = .003$, and for the 4-week delay group, $t(7) = 3.17$; $p = .02$. No significant between-group differences in S^D responding following acquisition, following the delays after extinction, and following reinstatement were revealed. Finally, greater than 80% S^D responding after acquisition and following reinstatement was evident. By contrast, there was less than 60% S^D responding following both delays after extinction.

Discussion

Experiment 2 demonstrated that nonreinforcement of responding under the original S^D and S^A conditions was sufficient to extinguish responding and disrupt stimulus control by nicotine. Evidence for spontaneous recovery of responding was specific to occasions in which a S^D session was preceded by two consecutive S^A sessions. These sessions occurred during the first half of the extinction phase. Responding declined to a zero level and was stable by the end of extinction training, but neither a 2- or 4-week delay was sufficient to evoke spontaneous recovery of differential responding between nicotine and saline. That stimulus control was reinstated by the two brief sessions of noncontingent food suggests that the original discrimination was not merely forgotten. Additionally, there was no difference in reinstatement of stimulus control as a function of the delay following extinction. These results suggest that although stimulus control by nicotine was disrupted equally following delays after extinction, the potential for stimulus control of differential responding was retained.

General Discussion

The present experiments sought to evaluate retention of the discriminative stimulus effects of nicotine following delays after acquisition of stimulus control and following extinction. The mere passage of time did not greatly undermine stimulus control by nicotine. As revealed in Experiment 1, differential responding to the discriminative stimulus function of nicotine was evident following a 3-month delay. Similarly, the results of Experiment 2 showed that although responding remained suppressed following 2- or 4-week delays after extinction, noncontingent food delivery reinstated stimulus control to comparable between-groups magnitudes.

The results of Experiment 1 suggest that the discriminative stimulus functions of nicotine are retained, at least partially, over an *extended* time. Although it is true that there was a decline in discriminated responding over the 3-month interval, stimulus control continued to be evident at the .4-mg dose. The delay time following extinction in Experiment 2 was no more than 4 weeks. Because at least 67% S^D responding was evident following a 3-month delay at the .4-mg dose (a dose twice that of training) in Experiment 1, it is not likely that there would be a decline in stimulus

control over a 4-week interval following acquisition and testing at the .4-mg dose in Experiment 2. Thus, the failure to show spontaneous recovery following delays after extinction was not caused by "forgetting" the original discrimination. The reinstatement data revealed clear evidence of retention of stimulus control attesting to this argument.

The reason for the failure to show spontaneous recovery of discriminated responding to nicotine after either a 2- or 4-week delay following extinction is not clear, however is not likely to be attributed to a degradation of the drug-reinforcer relationship due to the mere passage of time. A more likely possibility is that extinction of stimulus control was retained over time in the same manner that discriminated control was partially retained following a 3-month delay in Experiment 1 (and as demonstrated by Spear et al., 1979). By contrast, Rescorla (1997b, 2001) suggested that recovery of discriminated operant responding increases over time. The reason for this discrepancy is not clear, but may be caused by procedural differences. For instance, the present experiments carried out two sessions/day whereas Rescorla ran one session/day.

The spontaneous recovery observed on the 11th extinction session of Experiment 2 occurred during the first S^D session following zero- or near-zero level responding—a session preceded by two consecutive S^A sessions. Additional extinction sessions under both stimulus conditions were then carried out. It is plausible that these additional extinction sessions promoted the failure to evoke spontaneous recovery following the delays. Pavlov (1927) found that additional extinction trials following zero responding promoted less spontaneous recovery; extinction and spontaneous recovery are inversely related. This phenomenon has been known as *silent extinction* (cf., Brogden, Lipman, & Culler, 1938). The concept of silent extinction has not clearly been applied to operant procedures, yet alone to discriminated operant responding under drug S^Ds. Nevertheless, there was no difference in recovery of differential responding between the 2- and 4-week delay groups following extinction. This may suggest that extinction of discriminated operant responding previously under discriminative control by drug states is temporally stable in not recovering. This lab (Troisi, in press) found weak evidence for SR 4 weeks following extinction; however, those rats had extensive histories of extinction and reacquisition of a nicotine vs. ethanol discrimination. Further studies that parametrically vary extinction and dosage are warranted to determine the extent of spontaneous recovery of differential responding to drug cues.

The present study found clear evidence for reinstatement of differential responding to nicotine by the two sessions of noncontingent food delivery. Reinstatement of stimulus control here was evoked by an inherently respondent (Pavlovian) manipulation—response-independent presentation of the food. Surreptitious reinforcement of lever-pressing was prevented during these brief noncontingent food delivery sessions in that the levers had been removed from the operant chambers. It is plausible that reinstatement restored the context- (operant chamber-)

reinforcer relationship (e.g., Westbrook et al., 2002) thereby "unmasking" the more recent inhibitory effects promoted by (and retained following) extinction. Consequently, stimulus control to the drug conditions was restored. To our knowledge, the present study is the first to show evidence for reinstatement by noncontingent reinforcement of discriminated operant responding following extinction.

The current findings may also be clinically relevant. To be sure, the reinstatement effect has served as the working model of drug abuse relapse and has been demonstrated following extinction of drug-reinforced operant responding in animal models of drug self-administration (e.g., de Wit & Stewart, 1981, 1983; Katner et al., 1999; McFarland & Ettenberg, 1997). Reinstatement of drug self-administration can also be evoked by noncontingent presentations of the drug-related stimuli following extinction. For instance, Katner et al. (1999) found evidence that exteroceptive olfactory, but not auditory, cues previously associated with ethanol reinstated ethanol-reinforced responding following extinction. This laboratory (Troisi, in press) evaluated extinction and spontaneous recovery of the S^D properties of drugs in the manner in which exteroceptive stimuli have been evaluated. This issue is clinically relevant because exteroceptive cues previously paired with drugs USs (i.e., drug paraphernalia, social settings) have been demonstrated to evoke drug craving in recreational drug abusers, and repeated exposure to such cues without drug-reinforcement decreases drug craving, presumably through Pavlovian extinction (e.g., Childress, Mozley, McElgin, Fitzgerald, Reivich, & O'Brien, 1999; Ehrman, Robbins, Childress, & O'Brien, 1992; Robbins & Ehrman, 1998; cf., Conklin & Tiffany, 2002). For these reasons the drug discrimination paradigm is appealing in that it simulates how interoceptive events predict outcomes (operant reinforcement or nonreinforcement)—*perhaps drug reinforcement* as well, (e.g., Beardsley, Anthony, & Lopez, 1992). Thus, regarding polydrug abuse, one drug may precede self-administration of a second drug. For example, cigarette smokers frequently report increases in craving and smoking behavior following the consumption of alcohol (Burton & Tiffany, 1997; Glautier, Clements, White, Taylor, & Stolerman, 1996; Mintz, Boyd, Rose, Charuvastra, & Jarvik, 1985; Mitchell, de Wit, & Zacny, 1995). Similarly, nicotine has been demonstrated to have CS effects for the US effects of alcohol (Clements, Glautier, Stolerman, White, & Taylor, 1996). Conceptualized in this manner, alcohol possesses CS effects in evoking craving for nicotine as well as a S^D in "setting the occasion" (Skinner, 1938) for perhaps requesting a cigarette from another individual engaged in cigarette smoking.

Further evaluation of extinction, spontaneous recovery, reinstatement, and perhaps context renewal of the discriminative properties of drugs (cf., Troisi, in press) may model how interoceptive changes in the nervous system previously correlated with reinforcement, *even drug reinforcement*, can be extinguished, thereby decreasing the likelihood of relapse of drug-seeking behavior and drug self-administration. Ultimately, interoceptive antecedent drug events share CS

as well as S^D functions embedded within the three-term operant contingency: $S^D: R \rightarrow S^+$.

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