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Shelton, Keith L.
Beardsley, Patrick M.

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Interaction of Extinguished Cocaine-Conditioned Stimuli and Footshock on Reinstatement in Rats

Keith L. Shelton and Patrick M. Beardsley
Virginia Commonwealth University, U.S.A.

The reinstatement paradigm has been proposed as an animal model of human drug relapse. In most reinstatement studies, conditioned stimuli accompany drug infusions during self-administration, responding in extinction, as well as responding during reinstatement tests. The importance of these extinguished drug-paired stimuli during stress-induced reinstatement has not been examined. In this study, rats were trained to self-administer 0.5 mg/kg/infusion cocaine during daily, 2-h sessions until behavior stabilized. Each cocaine infusion was accompanied by a 6-s flashing light + tone conditioned stimulus (CS). In two groups of rats, responding during subsequent extinction and reinstatement had no scheduled consequences (CS Omitted). In two other groups of rats, responding produced the light + tone but no cocaine injections (CS Present). Footshock did not significantly reinstate cocaine seeking behavior in CS Omitted rats. Footshock significantly reinstated cocaine-seeking behavior over multiple test sessions in both CS Present groups, regardless of whether footshock reinstatement was examined on consecutive days or with trials spaced two days apart. These data show that environmental stimuli and stressors which are ineffective by themselves to occasion reinstatement of cocaine-seeking behavior can do so if concurrently present.

Relapse is a major impediment to successful substance abuse treatment (O'Brien 1997). The vast majority of drug abusers relapse on multiple occasions (Haynes, 1998; Hunt, Barnett, & Branch, 1971) and relapse may be particularly problematic in cocaine abusers (Washton & Stone-Washton, 1990). At least three major classes of relapse-promoting events have been hypothesized, although other factors may clearly be involved. These classes include brief exposure to the previously abused drug or a related drug, exposure to environmental or other stimuli that had been paired with drug self-administration, and exposure to stressors (Jaffe, Cascella, Kumor, & Sherer, 1989; Kreek & Koob, 1998; Robbins, Ehrman, Childress, & O'Brien, 1997). Understanding how these events trigger relapse may be extremely important for designing successful behavioral and pharmacological relapse prevention strategies.

The drug reinstatement paradigm in experimental animals has been used extensively over the past decade and is thought to model some aspects of human drug relapse (Koob, 2000; Meil & See, 1996; Shaham, Shalev, Lu, De Wit, & Stewart, 2002). In the reinstatement procedure, animals are trained to self-administer a drug until some stability criteria are reached. Subsequently, over a period of hours to sometimes many days responding is extinguished by discontinuing drug reinforcement. Noncontingent drug administration, exposure to previously drug-paired environmental stimuli and experimental stressors all can produce re-

newed drug-seeking behavior following this extinction period (Shaham, Erb, & Stewart, 2000; Shaham et al., 2002; Shalev, Grimm, & Shaham, 2002).

During self-administration training that precedes reinstatement testing, discrete visual or auditory stimuli such as darkening of the operant chamber, retraction of operant response levers, flashing of stimulus lights, presentation of tones or compound stimuli (lights + tones) usually accompany drug self-injections (Erb, Shaham, & Stewart, 1996; Self, Karanian, & Spencer, 2000; Tran-Nguyen, Bellew, Grote, & Neisewander, 2001). Although these stimuli are not a prerequisite for acquisition of drug self-administration, they are generally employed and have been shown to facilitate acquisition (Caggiula et al., 2002; Deroche-Gamonet, Piat, Le Moal, & Piazza, 2002) as well as enhance cocaine and heroin intake under maintenance conditions (Panlilio, Weiss, & Shindler, 1996; 2000). In addition to facilitating acquisition and increasing drug intake, several studies have shown that both response-contingent and noncontingent presentation of these previously drug-paired conditioned stimuli (CS) can themselves reinstate drug-seeking behavior when self-administration has been extinguished in their absence (Alleweireldt, Weber, Kirschner, Bullock, & Neisewander, 2002; Bespalov, Zvartau, Balster, & Beardsley, 2000; Crombag, Grimm, & Shaham, 2002; Kantak, Black, Valencia, Green-Jordan, & Eichenbaum, 2002; Meil & See, 1996). In studies employing experimental stressors to induce reinstatement, drug-paired external stimuli are usually extinguished by presenting them response contingently in the absence of reinforcement (Shaham et al. 2000; Shaham et al. 2002). These same stimuli are generally also presented response contingently during reinstatement testing following exposure to the reinstating event. Exposure to previously drug-paired stimuli during extinction has been shown to lengthen the duration of the extinction process (Arroyo, Markou, Robbins, & Everitt, 1998; Weiss et al., 2001), but after sufficient extinction, responding is reduced to near-zero levels and their presence appears without effect. In the present study we examined the role of extinguished response contingent cocaine-paired stimuli, hereafter referred to as the CS, on footshock-induced reinstatement in four groups of rats. Two groups were used to determine whether CS presentations, versus their omission would differentially affect the ability of footshock to reinstate responding over three consecutive, daily, test sessions. Studies have shown that periods of abstinence can enhance footshock-, drug-and cue-induced reinstatement (Lu, Grimm, Dempsey, & Shaham, 2004; Shaham, Rajabi, & Stewart, 1996; Shaham, Rodaros, & Stewart, 1994; Shalev, Morales, Hope, Yap, & Shaham, 2001). For this reason, two additional groups of rats were tested under similar CS presence and omission conditions, but two days in the homecage without any manipulations were interposed between each footshock reinstatement test day.

Method

Subjects

Subjects were 40 adult, male, experimentally naïve Long-Evans rats (Charles River Laboratories, U.S.A.) rats. The rats had continuous access to water except during the experimental sessions and were maintained at a body weight of 320 g for the duration of the study. The animals were individually housed in standard plastic rodent cages in a temperature-controlled (22 $^{\circ}$C) 12-h reversed light/dark cycle (lights off 07:00 h) colony room. All training and testing was conducted during the dark portion of the cycle.

Surgical Procedure

Rats were anesthetized with a combination of 2 mg/kg morphine, 60 mg/kg ketamine, 1 mg/kg acepromazine and 20 mg/kg pentobarbital. A tapered catheter constructed from 3.5 French polyurethane tubing (Access Technologies, U.S.A.) was then implanted into each rat's right jugular vein. The distal end of the catheter was passed subcutaneously to a cannula connector pedestal (Plastics One, U.S.A.) implanted subcutaneously in the midscapular region. The catheters were flushed with 0.2 ml heparinized normal saline before each experimental session. Following each self-administration session catheters were filled with 0.1 ml of a 50% glycerol/50% sterile saline solution to which was added 500 units/ml heparin, 250 mg/ml ticarcillin and 9 mg/ml clavulanic acid (Timentin, SmthKline Beacham, U.S.A.) to help maintain patency. Rats were permitted a minimum of five days of postoperative recovery before beginning self-administration training. If a catheter failed during cocaine self-administration training, it was removed, the left jugular vein was catheterized and the animal was returned to the study.

Drugs

Cocaine HCl (National Institute on Drug Abuse, U.S.A.) was diluted in heparinized (5 units/ml) sterile saline for the intravenous self-administration solution.

Apparatus

Experiments were conducted in 24 operant conditioning chambers housed inside individually-isolated and ventilated enclosures (Med Associates, U.S.A.). The front wall of each chamber was equipped with two retractable response levers with a white stimulus light above each lever. A 5-w house light and Sonalert tone generator were located in the rear wall of the chamber. During each session, infusion tubing, protected by a stainless steel spring tether (Plastics One, U.S.A.), connected the back-mounted pedestal implanted in each rat to a balanced liquid swivel suspended above each chamber (Lomir Biomedical, Canada). Infusions were delivered by a syringe pump located outside each chamber (Med Associates, U.S.A.). Scrambled intermittent footshock (15 min of 0.5 s per shock, 1.02 mA intensity with a 40 s intershock interval) was delivered via the chamber floor bars using constant current, feedback regulated shockers (VCU Custom Design and Fabrication, U.S.A.). Schedule parameters were controlled by MED-PC IV software (Med Associates, U.S.A.) running on IBM PC compatible computers.

Procedure

Due to the number of animals tested, the study took place over several consecutive months. All of the subjects from each experimental group were run at the same time, but each group was trained and tested in succession. In all 4 groups, cocaine self-administration training sessions were conducted five days per week (Monday to Friday) for two hours daily. Initially, each response (fixed ratio 1) on the active lever resulted in delivery of a 0.5 mg/kg cocaine infusion (0.18 ml/6 s). For the duration of the infusion, a 2900 Hz, 60 dB tone sounded and the stimulus lights above both levers flashed at 3 Hz (tone + light CS). Active-lever responses during the infusion as well as all inactive lever responses were recorded, but had no scheduled consequences. On each day in which a rat received 15 or greater cocaine infusion in the 2 h training session, the fixed-ratio (FR) requirement for each infusion was increased by 1 up to a final value of FR5. Rats were eligible for extinction and reinstatement testing only after they received 15 or more cocaine infusions per session for 4 consecutive sessions at FR5.

Extinction sessions were conduced daily for 2 h. The animals were placed into the self-administration chambers as during cocaine self-administration training, but no infusions were given following each FR5 completion. Two groups of rats (CS Present/Consecutive trials and CS Present/Spaced trials) were response-contingently presented with the 6 s tone + light CS that had been previously paired with cocaine self-administration after each completed FR5 during extinction. The other two groups of rats (CS Omitted/Consecutive trials and CS Omitted/Spaced trials) were not presented with the previously cocaine-paired tone + light CS during extinction. In groups CS Present/Consecutive trials and CS Omitted/Spaced trials extinction was fixed at 11 daily sessions. In groups CS Omitted/Consecutive trials and CS Present/Spaced trials rats responding was extinguished

until total active lever responses were less than 15 for the final session with the provision that extinction was continued for a minimum of 4 and a maximum of 11 total sessions.

Following extinction, each group of rats was exposed to a different reinstatement procedure as detailed in Table 1. Briefly, group CS Present/Consecutive trials ($n = 9$) received one additional 2-h no shock control session followed by daily 2-h footshock reinstatement test sessions for 3 consecutive days. Each of these reinstatement sessions was preceded by 15 m of 1.02 mA intermittent footshock (0.5 s shock on with a 40 s mean intershock interval). In the 15 m shock interval, both levers were retracted and the stimulus and house lights were not illuminated. During the test session each completed FR5 resulted in tone + light CS presentation, but no cocaine delivery. Group CS Omitted/Consecutive trials ($n = 8$), which had not been presented with the tone + light CS during extinction, received the same 4 test sessions, but operant responding during the control and shock reinstatement test sessions had no scheduled consequences.

Group CS Present/Spaced trials ($n = 8$) was given one, 2-h no shock control test session, followed by 2 days of abstinence during which the animals were left in the colony room and not exposed to the operant chambers. The group then received three, 2-h shock reinstatement test sessions, each of which was separated by a 2 day period in the homecage without testing. During the control and shock reinstatement tests, each completed FR5 resulted in tone + light CS presentation. Group CS Omitted/Spaced trials (n = 15), which had not received contingent tone + light CS presentations during extinction, was also given one no shock control and three shock test sessions, each of which was separated by a 2 day period in the homecage without testing. Each completed FR5 during these sessions had no scheduled consequences.

Table 1
Extinction, Reinstatement, and Abstinence Conditions in Each Test Group.

Group	Light+ tone during extinction and reinstatement	2 days between test sessions
CS Present/Consecutive trials	yes	no
CS Omitted/Consecutive trials	no	no
CS Present/Spaced trials	yes	yes
CS Omitted/Spaced trials	no	yes

Active-lever (right lever) and inactive-lever (left lever) presses and infusions were recorded for each subject daily. Statistical analysis was performed using SuperAnova (Abacus Concepts, U.S.A.). Separate one way analysis of variance (ANOVA) tests were used to determine if the groups were comparable in terminal self-administration rates and final levels of extinction responding. The effect of CS presentation was analyzed separately for the rats that were tested for footshock on consecutive days and those that were tested for footshock with two day periods in the homecage between trials. The effects of footshock and stimulus condition were compared using a 2-way mixed ANOVA. Further analysis comparing individual shock test days to the no shock control were conducted using Tukey's HSD Post-Hoc tests only if main effects or the interaction was significant.

Results

Cocaine Self-Administration and Extinction

Figure 1 shows active-lever responding on the last day of self-administration and the first 3 days of extinction in each of the four test groups. Total mean active-lever responses in the CS Omitted/Consecutive trials (filled squares) and CS Present/Consecutive trials (filled circles) groups on the last day of self-administration were 140 (±11) and 112 (±15) responses, respectively. This corresponded to 28 (±2) cocaine deliveries in the CS Omitted/Consecutive trials group and 22 (±3) deliveries in the CS Present/Consecutive trials group. Total

mean active-lever responses in the CS Omitted /Spaced trials (open squares) and CS Present/Spaced trials (open circles) groups on the last day of self-administration were 157 (±12) and 154 (±15) responses, respectively. This corresponded to 31(±2) cocaine deliveries in the CS Omitted/Spaced trials group and 31 (±3) deliveries in the CS Present/Spaced trials group. Statistical analysis indicated no difference between groups, F (3, 36) = 2.41, p = 0.08, in terminal self-administration responding. Inactive lever responding was low throughout training and testing and is not depicted. Figure 1 also depicts responding on the first 3 days of extinction in all four groups. In the two groups that did not receive CS presentations during extinction (CS Omitted/Consecutive trials and CS Omitted/Spaced trials), responding decreased to less than 50% of that produced on the last day of self-administration on the first day of extinction and very little on the subsequent extinction days. In the two groups in which the CS was present during extinction (CS Present/Consecutive trials and CS Present/Spaced trials), responding on the first extinction day decreased to a lesser degree than that in the groups in which the CS was omitted. In fact, in group CS Present/Consecutive trials, responding on the first day of extinction was no lower than that on the last day of self-administration. However, by day 2 of extinction, responding in all three groups had decreased to similar levels and were not significantly different, F (3, 36) = 0.22, p = 0.88, from one another.
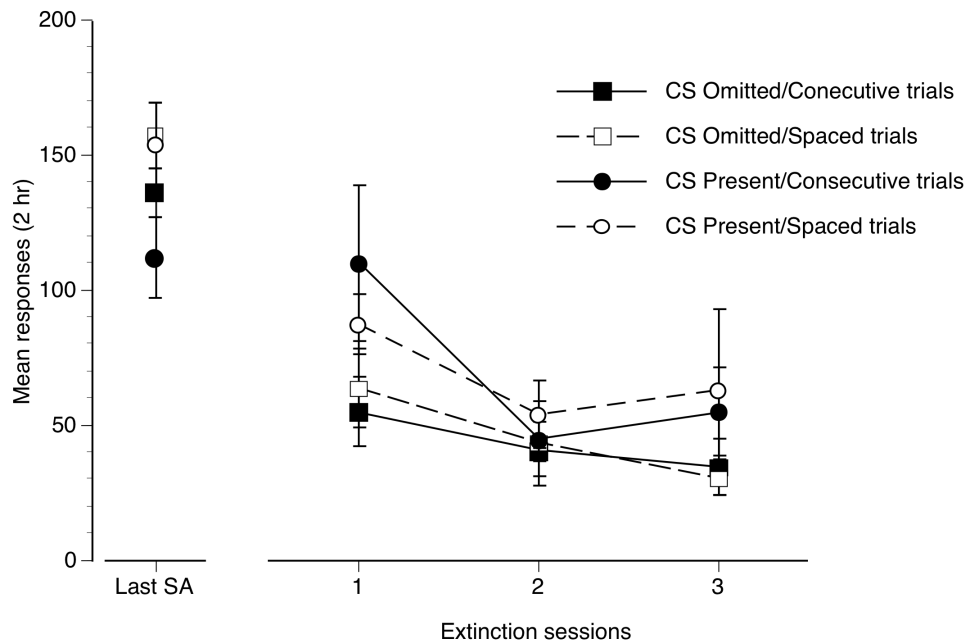

Figure 1. Self-administration and extinction responding: Symbols above "Last SA" show group mean (±*SEM*) responses per 2-h session on the final day of cocaine self-administration for all four test groups. Connected points show mean (±*SEM*) responses per 2-h session on the first 3 days of extinction for all four test groups.

Effect of Extinguished Tone + Light CS on Consecutive Footshock Reinstatement Tests

Each of the four panels of figure 2 show the no shock control day and the three footshock test sessions for individual groups. Statistical analysis indicated that operant responding on the no shock control session (NS) was not statistically different, F (3, 36) = 1.87, p = 0.15, across test groups. Figure 2A shows active-lever responding on the no shock control day and the three footshock test sessions in rats that did not receive tone + light CS presentations during extinction and reinstatement testing (CS Omitted/Consecutive trials). Figure 2B shows data obtained from similar conditions in rats that received tone + light CS presentations during both extinction and reinstatement testing (CS Present/Consecutive trials). Statistical analysis showed that there was a significant main effect of stimulus condition, F (1, 15) = 8.03, p = 0.01, as well as a significant main effect of shock, F (3, 15) = 4.12, p = 0.01, but no significant stimulus condition X shock interaction, F (3, 15) = 2.01, p = 0.12. Post hoc analysis indicated that shock was not effective in producing significant reinstatement on any of the three consecutive test days in the rats that did not receive tone + light CS presentations (Figure 2A). In contrast, in the animals that received tone + light CS presentations during extinction and shock reinstatement test sessions, significant reinstatement, $p < .05$, was produced on shock test days 2 and 3 (Figure 2B).

Effect of Extinguished Tone + Light CS on Repeated, Spaced Trials Footshock Reinstatement Tests

Figure 2C shows active-lever responding on the no shock control day and the three footshock test sessions in rats that did not receive tone + light CS presentations (CS Omitted/Spaced trials) during extinction and reinstatement testing. Figure 2D shows data from similar conditions in rats that received tone + light CS presentations during extinction and reinstatement testing (CS Present/Spaced trials). In both groups, the no shock control session and each of the three shock test sessions was separated by two days without exposure to the test environment. Statistical analysis indicated a main effect of stimulus condition, F (1,21) = 4.78, p = 0.01, as well as an interaction of stimulus condition and shock, F (3,21) = 4.90, $p < 0.01$, but no main effect of shock, F (3,21) = 0.48, p = 0.70. Post hoc analysis indicated that shock did not produce significant reinstatement on any of the three test sessions in the rats that did not receive tone + light CS presentations (CS Omitted/Spaced trials). Indeed, reinstatement responding on all three shock reinstatement test days was less than that on the no shock control session. In contrast, shock produced significant reinstatement, $p < 0.05$, on all three test sessions in the rats that received tone + light CS presentations during both extinction and reinstatement testing (CS Present/Spaced trials).

Discussion

The present data replicate the findings from several different laboratories showing that footshock is effective in reinstating cocaine-seeking behavior in rats (Ahmed & Koob, 1997; Erb et al., 1996; Mantsch & Goeders, 1999; Shaham, Erb,

Leung, Buczek, & Stewart, 1998). It also extends those findings by showing that significant levels of footshock-induced reinstatement can be generated on at least three consecutive test sessions and that the reinstating efficacy of footshock does not diminish and may even increase over three repeated tests.
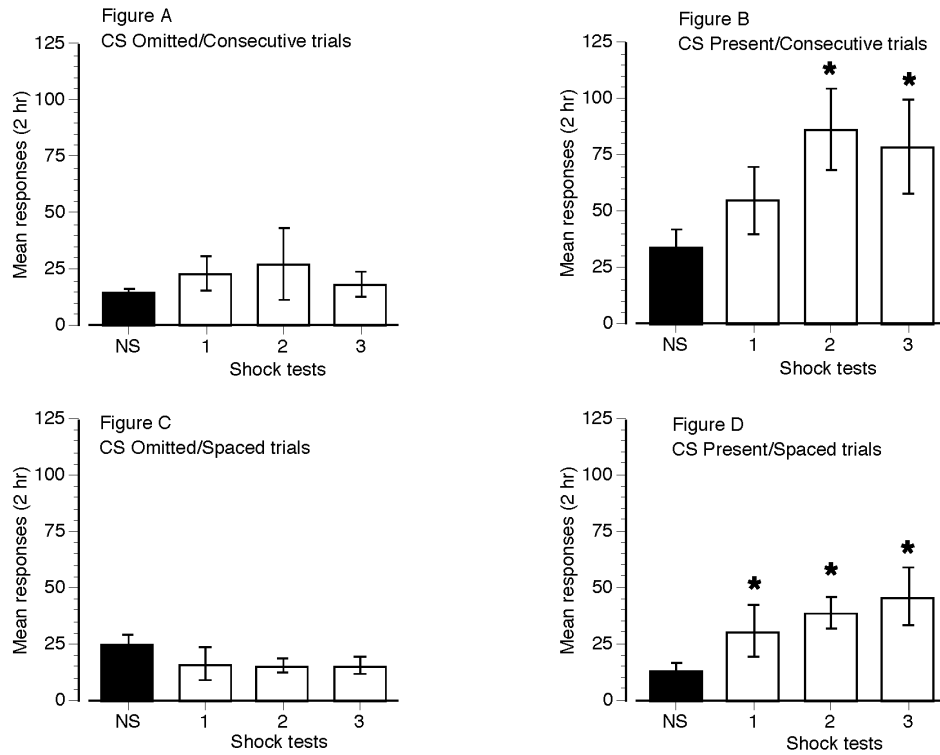

Figure 2. Effect of response-contingent conditioned stimulus presentation on footshock reinstatement. Figure A shows the effect of footshock in rats in which cocaine-paired stimuli were not presented during extinction and reinstatement (CS Omitted/Consecutive trials). Figure B shows the effect of footshock in rats in which response-contingent cocaine-paired stimuli were presented during extinction and reinstatement (CS Present/Consecutive trials). Figure C shows the effect of footshock in rats in which cocaine-paired stimuli were not presented during extinction and reinstatement and each reinstatement test was separated by 2 days in the homecage without testing (CS Omitted/Spaced trials). Figure D shows the effect of footshock in rats in which cocaine-paired stimuli were presented during extinction and reinstatement and each reinstatement test was separated by 2 days in the homecage without testing (CS Present/Spaced trials). For all graphs, the first bar (NS) shows mean (±*SEM*) responding on the no shock control test sessions. The final three bars (shock 1, 2, 3) depict mean (± *SEM*) responses on each of the three shock reinstatement test sessions. * denote statistically significant effects ($p < 0.05$).

In the present study, each of the four groups were trained and tested sequentially and two different extinction criteria were employed, therefore history prior to reinstatement testing could be confounding factor. In all four groups, the self-administration training procedures and performance criteria were identical and statistical analysis indicated that there were no significant differences between groups in terminal self-administration rate. However, in groups CS Omitted/Consecutive trials and CS Present/Spaced trials, the extinction criteria was based upon each rat reaching a low level of responding during extinction. In contrast, in groups CS Present/Consecutive trials and CS Omitted/Spaced trials, the

number of extinction days were fixed at 11. Statistically analysis revealed that mean responses on the no shock control day were not different across groups, indicating that these two criteria resulted in comparable levels of extinction. The similar levels of terminal self-administration and extinction performances suggest that any difference in reinstatement responding were not likely the result of prior self-administration or extinction history.

Abstinence prior to reinstatement testing has been shown to enhance the expression of drug, cue and footshock-induced reinstatement (De Vries, Schoffelmeer, Binnekade, Raaso, & Vanderschuren, 2002; Erb et al., 1996; Grimm, Hope, Wise, & Shaham, 2001; Lu et al., 2004). In the present study, placing two days without testing between each footshock test session did not markedly alter reinstatement. This is probably not surprising given the data showing that this "incubation" effect, as it has been termed, is most pronounced following weeks or even months of abstinence (Lu et al. 2004). What was most striking in the present data was the degree to which extinguished drug-paired stimuli affected the expression of footshock reinstatement. In the current study, the omission of response-contingent CS presentation during extinction and reinstatement testing completely abolished footshock-induced reinstatement regardless of whether the shock test sessions were given over consecutive days or footshock test sessions were separated by two days without testing.

Human cocaine abusers often report craving as well as attribute the cause of their cocaine relapse to contextual variables such seeing drug paraphernalia or being in a setting in which they previously took drug (Avants, Margolin, Kosten, & Cooney, 1995; Dudish-Poulsen & Hatsukami, 1997; Wallace, 1989). In parallel animal studies, response-contingent and experimenter-presented drug-paired conditioned stimuli have been shown by a number of laboratories to produce significant levels of reinstatement (Crombag et al., 2002; de Wit & Stewart, 1981; Deroche-Gamonet et al., 2002; Tran-Nguyen et al., 2001). The human data and animal studies convincingly show that environmental stimuli that predict or accompany self-administered cocaine infusions are powerful motivators of cocaine-seeking behavior and can result in dramatic enhancement in responding during maintenance as well as extinction (Panlilio et al. 1996, 2000). In almost all animal studies of cue-induced reinstatement, the conditioned stimuli that were previously paired with cocaine injections are explicitly not extinguished. Under these conditions, cue presentations would clearly be expected to and, in fact, do result in reinstatement. In contrast, most stress-induced cocaine reinstatement studies have presented contingent drug-paired stimuli during acquisition of self-administration, extinction and reinstatement testing (Mantsch & Goeders, 1999; Sutton, Karanian, & Self, 2000). Since the cocaine-paired conditioned stimuli are actively extinguished, and at the time of reinstatement testing do not themselves continue to evoke responding, they might be assumed to be neutral, neither promoting nor attenuating reinstatement. The present data would suggest that, even after being actively extinguished, these previously cocaine-paired CS presentations are, at least under the testing conditions in the present studies, critical for the expression of reinstatement.

The mechanism by which extinguished cocaine-paired stimuli controlled the expression of footshock-induced reinstatement in the present study is unclear. The simplest explanation would be that these stimuli still had some reinstating efficacy at the time of reinstatement testing despite being extinguished. It has been

shown in cue-induced reinstatement procedures that lights in combination with tone, such as were used in the present study, are more effective reinstating stimuli than are either lights or tones alone (See, Grimm, Kruzich, & Rustay, 1999). Other investigators have shown additive summation of operant responding for drug and food, as well as responding under shock avoidance schedules, resulting from compounding discriminative stimuli (Emurian and Weiss, 1972; Panlilio et al. 1996; Weiss 1969). Therefore, it is certainly possible that the light + tone CS still had some sub-threshold reinstating efficacy, which when combined with shock would produce more robust reinstatement than shock alone. This interpretation would seem more plausible were footshock in the CS Omitted conditions to have shown some trend toward producing reinstatement. Quite the contrary, in the CS Omitted/Consecutive trials group there was only a very modest, non-significant increase in responding and in the CS Omitted/Spaced trials rats the trend was actually toward a suppression of responding by footshock in the absence of CS presentations.

A second possible hypothesis centers on the fact that the light + tone CS was contingently presented to all of the rats during self-administration training, but omitted during extinction and testing in the CS Omitted groups. At least two studies (one presented only in abstract form) have shown that in order for footshock or restraint stress to be effective reinstating events it was necessary that they be administered in the reinstatement test chamber (Buczek et al., 1998; Shalev, Highfield, Yap, & Shaham, 2000). Importantly, in both of these studies, the reinstatement test environment was also that in which cocaine self-administration had been acquired and extinguished. In the present study, the stimulus conditions during extinction and reinstatement testing in the CS Omitted groups were not the same as those present during self-administration training. As such, the extinction and reinstatement test environment might be conceptualized as unique from that in which drug was self-administered. If this were the case, footshock would not be expected to produce reinstatement, but perhaps for a slightly different reason than that promoted in the two previous studies. Specifically, it may be the case that footshock must be applied in the same environment in which drug is self-administered in order to be effective, rather than that footshock must be applied in the same environment in which reinstatement testing occurs, although in practice these two environments could be difficult to separate. It could also be the case that the stressor must be applied in the same environment in which cocaine is self-administered, extinguished and reinstated in order to be effective. Additional studies will be necessary in order to answer this question definitively.

Pavlov (1927) noted that an extinguished CR would reappear if the CS was presented with a novel stimulus. He discussed this as an instance of "disinhibition", namely as "inhibition of inhibition" because he felt that the CR was temporarily restored by the removal of the extinction-produced inhibitory process by another inhibitory process. Brimer (1970) successfully extended the investigation of disinhibition from classically conditioned to operant behavior. He reported that noncontingent activation of a white noise or light (both of which suppressed responding maintained by food on a variable interval 2.5 min schedule) increased response rates suppressed by experimental extinction or food satiation. In the present experiment, it might be argued that the re-emergence of responding to the conditioned stimuli during reinstatement tests with shock functionally resembles the phenomenon of disinhibition. Here, after responding, produced at least in part by

the conditioned stimuli, was suppressed by extinction, shock appeared to disinhibit the suppression resulting in increased response rates during reinstatement testing. It should be observed that the intensity of shock used during the present studies has been reported to be an effective punishing stimulus (suppressor) of positively-reinforced behavior (Appel, 1963), and, as such, can serve as an inhibiting stimulus. According to this analysis, that the CS-Omitted Groups did not demonstrate reinstatement while the CS-Present Groups did, might be attributed to an absence of extinction-suppressed, CS-related behavior to be disinhibited in the CS-Omitted Groups.

Based upon the interpretation described above, disinhibition could be at least contributing to instances of foot-shock induced reinstatement of extinguished cocaine-reinforced responding. The observation that foot-shock does not reinstate extinguished, food-reinforced responding (Ahmed & Koob, 1997) could be interpreted as weakening this hypothesis. However, just as there are reinforcer-dependent determinants for other behavioral phenomena such as selective associations (e.g., Garcia et al., 1968; Weiss et al., 2005) there could be reinforcer-dependent determinants of disinhibitory phenomena as well.

Finally, the present data may have important implications for the use of extinction and cue exposure treatments to prevent cocaine relapse (O'Brien, Childress, McLellan, & Ehrman, 1992; O'Brien, Childress, McLellan, & Ehrman, 1990; Weinstein, Wilson, Bailey, Myles, & Nutt, 1997). These behavioral strategies, which entail repeated presentation of drug-associated stimuli during treatment sessions have shown little, or at best, very modest effectiveness in preventing relapse (Drummond & Glautier 1994; Niaura et al. 1999; O'Brien et al. 1990). Our data would suggest that even were new cue exposure treatments to be developed (Kuntze et al. 2001; Lee et al. 2003) that completely eliminated relapse resulting from drug-associated stimuli alone, they might have little or no protective value in preventing cocaine relapse resulting from compounding of drug-associated stimuli and stress. Comprehensive treatment strategies that also directly target stress would be necessary to minimize the possibility of relapse under these circumstances.

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