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RENEWAL IN THE CONTEXT OF STRESS: A POTENTIAL MECHANISM OF STRESS-INDUCED REINSTATEMENT

A Dissertation Presented

by

Scott T. Schepers

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
For the Degree of Doctor of Philosophy
Specializing in Psychology

October, 2017

Defense Date: June 28, 2017
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ABSTRACT

In the animal laboratory, stressors can produce the relapse of drug-seeking behaviors after the behavior has been inhibited by extinction. This type of relapse has been called *stress-induced reinstatement*, and it models the relapse that is commonly reported in human populations. Interestingly, in the laboratory, stress does not typically reinstate extinguished behaviors that have been reinforced by food. One account of the discrepancy is that drugs of abuse may induce stress; therefore, when organisms learn to respond for drugs, they might learn to make the response in the "context" of stress. If so, then stress-induced reinstatement may be better described as *renewal* in a stress context. Renewal is the type of relapse that occurs when a behavior is returned to the original training context (or is shifted to a new context) after it has been inhibited or suppressed by extinction. Although renewal has usually been studied with contexts that differ in their exteroceptive cues, *interoceptive* cues (e.g., mood, food deprivation, and drug states) may also provide contexts. Accordingly, if an interoceptive stress state is present when food-seeking behavior is learned, then extinguished food seeking, like drug seeking, should also renew when the organism is stressed after extinction. In this dissertation, I discuss six experiments that investigated this hypothesis. Experiment 1 found that stressors renew extinguished food-seeking if they are also present during instrumental training. Experiments 2 and 3 then provided preliminary evidence that this effect is not exclusively due to incentive learning. Experiment 4 then suggested that interoceptive stress, and not the particular stressor that produces it, may indeed serve as a general interoceptive context that controls the effect. Experiment 5 found that stressors present for acquisition but not extinction training render behavior susceptible to stress induced relapse. The final experiment found that food-reinforced behavior learned in a context created by a cocaine injection renews after cocaine administration but not after footshock stress. Overall, the results indicate that the presence of interoceptive stress stimuli may play the role of context in a renewal paradigm and promote behavioral relapse when re-encountered after extinction. The implications for relapse that often occur following successful suppression of drug use and overeating behaviors are both discussed.

ACKNOWLEDGEMENTS

I'd first like to express my gratitude to my advisor, Mark Bouton, for his guidance, support, and patience. It has been an honor to have had an opportunity learn from him each day for the previous 5 years. I'd also like to thank the members of the Bouton Laboratory and Biobehavioral Cluster, past and present, for their friendship and collaboration. The community of graduate students, faculty, and staff in the Psychological Science Department at the University of Vermont are exceptional and make this a truly special place. The unwavering support from my family and friends have been my source of stability and made this journey possible. Finally, I'd like to acknowledge and thank the members of my dissertation committee for volunteering valuable time and expertise throughout this process.

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RENEWAL IN THE CONTEXT OF STRESS: A POTENTIAL MECHANISM OF STRESS-INDUCED REINSTATEMENT

The study of instrumental learning has been deemed important as a means of understanding the mechanisms of voluntary behavior. The performance of instrumental behavior usually occurs in accordance with its outcome; behaviors that produce "satisfying" outcomes are likely to be learned and repeated. However, if an acquired behavior no longer produces a reinforcing outcome, its performance declines in a process known as *extinction*. One view has described the decline of behavior during extinction as involving a gradual erasure of the original learning (see Delamater & Westbrook, 2014). However, a great deal of research has indicated that behavior suppressed through extinction returns to performance (i.e., relapses) when the conditions of extinction change. The fact that extinguished behavior relapses provides a strong argument against an erasure explanation; the original learning or memory seemingly remains intact. Instead, relapse after extinction suggests that extinction involves learning to inhibit the original behavior. Furthermore, this inhibition is especially dependent on the context in which it is learned for its expression (e.g., Bouton, 2002, 2004, 2010, 2014).

Understanding the behavioral mechanisms that underlie extinction and relapse may be especially important when considering new treatments for problematic human behaviors (e.g., drug use, overeating; see Bouton, 2014). Currently, even therapies that have been most successful in reducing problem behaviors have high rates of relapse at their conclusion (Silverman, DeFulio, & Sigurdsson, 2012). One potential explanation for these high rates of relapse is that the conclusion of treatment can be seen as causing a change in the context.

In the animal laboratory, renewal experiments have been used to examine the context dependency of extinction (Bouton, Todd, Vurbic, & Winterbauer, 2011; Nakijima, Tanaka, Urushihara, & Imada, 2000). In instrumental learning, renewal experiments often involve the reinforcement of a lever press response in one context (Context A) followed by its extinction in a second one (Context B). The behavior suppressed during extinction *renews* when animals are returned to the original context (ABA Renewal) or moved to a new context (ABC Renewal) for a test. A shift to a new context can also produce renewal when the acquisition and extinction phases occurred in the same context (AAB Renewal). Most often, the contexts in renewal experiments are different apparatuses or operant chambers that contain different visual, tactile, and olfactory cues. In other words, the contexts differ in terms of their exteroceptive features. However, research has also indicated that internal "feelings," or interoceptive cues (e.g., drug states, mood states), can also gain contextual control over behavior (Bower, 1981; Davidson 1993; for a review, see Bouton 1991).

Razran (1961) described several early studies of interoceptive conditioning conducted in the former Soviet Union in the late 1920s. In these experiments, subjects were typically implanted with balloons or other devices designed to allow experimenters to produce different types of internal sensations. In one example, dogs were trained to discriminate between inflations of balloons that were implanted into two different parts of their intestinal tract. Food reinforcers were given after one balloon was inflated (the CS+); the dogs did not receive food when the 2nd was inflated (the CS-). Over several trials, the dogs began to discriminate between the different internal sensations and came to salivate immediately after the 1st balloon was inflated.

More recently, Schepers and Bouton (2017) found that internal stimuli associated with different degrees of food deprivation (i.e., hunger vs. satiety) could function as contexts in a renewal paradigm. In these experiments, rats learned to press a lever for either sucrose or sweet-fatty pellets while they were satiated (Context A). They then received several extinction sessions in which they were food-deprived (after 23 hrs without access to homecage chow; i.e., Context B). In a somewhat paradoxical result, extinguished responding recovered in a test when the animals were satiated again, suggesting ABA Renewal controlled by satiety and hunger cues. Intuition and other views (e.g., Hull, 1943) would suggest that a shift to a satiated state from a hunger state should weaken, rather than enhance, responding for food. In contrast, the results offered a more nuanced view and a potential explanation of why some dieting attempts may ultimately fail: Overeating behaviors inhibited during a diet may renew when a simple lapse in the diet produces satiety stimuli that had been present when they were learned.

The finding that interoceptive stimuli can function as contexts in renewal also provides potentially interesting explanations for other, seemingly different, types of relapse phenomena (e.g., reinstatement). The present experiments were designed to examine whether the interoceptive context produced by *stress* might also produce renewal effects. They did so by examining the well-known *stress-induced reinstatement* paradigm. "Reinstatement" generally refers to another class of relapse effects that can occur after extinction. Unlike renewal, reinstatement does not involve changes in the physical context. Instead, acquisition, extinction, and testing are usually conducted within the same instrumental (operant) chamber. However, in reinstatement, extinguished

responding can recover (i.e., reinstate) when different types of "reinstating stimuli" are presented prior to the test.

Food- and drug-induced reinstatement describes response recovery that occurs when the training reinforcer (e.g., a food pellet after training with a food reinforcer or drug infusion after training in a drug self-administration paradigm) is re-experienced after extinction. Cue-induced reinstatement generally describes responding that recovers after a cue (e.g., a light or a tone) that had been associated with the original training is presented before a test. It may be important that in each of these, stimuli that reinstate extinguished behavior can usually be seen as having been directly associated with behavioral acquisition. For this reason, we have suggested that reinstatement may be better described as a special type of renewal effect (see Bouton 2002; 2014). In other words, the presentation of stimuli associated with the original learning could constitute a "return" to the original training context.

In contrast, the mechanisms underlying stress-induced reinstatement (for a review, see Mantsch, Funk, Lê, & Shaham, 2015) are currently less clear. Stress-induced reinstatement experiments (e.g., Ahmed & Koob, 1997; Buczek, Le, Wang, Stewart, & Shaham, 1999; Erb, Shaham, & Stewart, 1996; Shaham & Stewart, 1995) involve an animal learning to perform an instrumental response that is reinforced with drug infusions (e.g., pressing a lever for an infusion of cocaine). The response is then extinguished in a second phase (i.e., lever pressing no longer produces cocaine). Drug-seeking behavior suppressed through extinction is then reinstated when animals receive a stressor (e.g., a footshock) before testing. Exposure to stressors may produce reinstatement of drug-seeking by activating the mesocorticolimbic dopamine (DA) system; activation of the DA

system may serve to enhance the incentive value of drug-related stimuli (see Robinson & Berridge, 1993). In other words, stressors may reinvigorate the motivating value of stimuli that had been associated with reinforcement during training. Another view suggests that stressors reinstate behavior by merely disinhibiting extinguished drug responding (Shaham et al., 1997; Shaham, Erb, & Stewart, 2000). However, for reasons noted below, neither of these views accounts for all the data.

It may be especially important that stress-induced reinstatement is exclusive to behaviors that were originally reinforced by drugs of abuse (e.g., cocaine, heroin). In contrast, extinguished behaviors that had been initially reinforced by food do not generally reinstate after stress (e.g., Ahmed & Koob, 1997). One notable exception is that food-seeking behavior is reliably reinstated by yohimbine, an α-2 adrenoceptor antagonist, that has been suggested to produce stress-like states in humans and in animals (Calu, Chen, Kawa, Nair, & Shaham, 2014; Nair, Adams-Deutsch, Epstein, & Shaham, 2009). However, Chen et al. (2015) found that yohimbine reinstates behavior independent of any history of food-seeking. In fact, they found similar reinstatement for an extinguished lever response that had been reinforced with food and a light cue as a response that had only produced a light cue during acquisition. These results suggested that yohimbine may simply enhance responding to auditory and visual stimuli and therefore its relevance to the reinstatement of food- or drug-seeking behavior is questionable.

The failure to observe stress-induced reinstatement after food seeking is extinguished is not predicted by either the DA activation or disinhibition views mentioned above. However, the absence of stress-induced reinstatement in the case of

food seeking may provide an important insight into its mechanism. Drugs of abuse (but not food reinforcers) can cause cascades of stressful physiological and/or subjective effects. As described below, earning drug but not food reinforcers during acquisition may therefore produce an interoceptive stress state that becomes associated with the instrumental response. Stress after extinction may return the organism to a similar stressful interoceptive state. On this view, a stress-like state that has been associated with drug seeking (and was absent during extinction) will cause ABA renewal when the organism is returned to the context of stress. Stress-induced reinstatement may thus be another example of the renewal effect.

Research has, in fact, indicated that drug use and the stress system are intricately related. While the relationship between stress and drug use is complex, acute exposures to stress or drugs can produce secretions of stress hormones such as cortisol and ACTH as well as increases in blood pressure, heart rate, and skin conductance (for a review, see Sinha, 2008). Interestingly, dependence on drugs is often elevated in individuals with stress-related pathologies such as PTSD (Jacobsen, Southwick, & Kosten, 2001). Moreover, individuals report greater drug use when their stress symptoms are highest (Hoffman & Su, 1997). Likewise, in the rat laboratory, Goeders (2002) reported that injections of cocaine and exposure to footshock stress or a stress hormone (corticosterone) all increased the rate that cocaine was self-administered. Like the effects of stress, extended access and chronic exposure to cocaine also increase its self-administration rate (Ahmed & Koob, 1998). Koob and LeMoal (2001) have suggested that escalations in drug-seeking and the quantities consumed become motivated by a stress-like "anti-reward" system generated by the drug itself. According to this view, drug

seeking is initially motivated by the drug's pleasurable effects. However, over extended periods and chronic exposures, the pleasurable effects are replaced by withdrawal-induced aversive ones. As a result, the rate of drug-seeking may escalate in an effort to counteract the stress-like effects of the drug (see also Solomon & Corbit, 1974). Furthermore, it has been shown that extended exposures to cocaine can also facilitate greater stress-induced reinstatement after extinction (Mantsch et al., 2008).

Unlike drug seeking, food-seeking behavior has not generally been reported to produce interoceptive stimuli similar to stress. In fact, Egan and Ulrich-Lai (2015) reported that rats given access to sucrose or saccharin drinks exhibited only small increases in several measures of stress over 16 days of exposure. Furthermore, these small increases did not differ from a water drink and gradually declined over exposures, suggesting that the early increases in stress were related to novelty.

As previously mentioned, drugs can produce an extensive array of salient interoceptive stimuli that may have the capacity to exert control over behavior (Verdejo-Garcia, Clark, & Dunn, 2012). Interestingly, drugs purported to produce similar interoceptive effects can reinstate extinguished behaviors that had been reinforced by each other (for reviews, see DeWit, 1996; Overton 1985). For example, injections of amphetamine can reinstate extinguished cocaine seeking and vice versa. Furthermore, the reinstatement of drug-seeking behavior can be attenuated when pharmacologically similar drugs precede extinction training. For example, injections of caffeine prior to extinction training effectively eliminate cocaine-induced reinstatement (Schenk, Worley, McNamara, & Valdez, 1996). Presumably, the presence of similar interoceptive stimuli during extinction produces ambiguity between the experimental phases (Bouton, 2002).

On this view, reinstatement typically occurs when the absence of drug stimuli disambiguates the extinction context from acquisition and facilitates renewal when the drug is given before a test. The fact that these reinstatement effects generalize within a drug class (e.g., stimulants) may help explain the previously mentioned question of how a stressor that has not been directly connected with training can reinstate extinguished responding. Perhaps exposure to a stressor produces "reinstatement" when the effects of stress *sufficiently generalize* to the interoceptive state that was produced by drug stimuli during acquisition (for a discussion, see Ahmed & Koob, 1997). Overall, the literature suggests a potentially unique role for stress in the acquisition of drug seeking. It is also consistent with the proposed hypothesis that stress may play the role of context in producing stress-induced reinstatement.

The current experiments were designed to test and extend this hypothesis. More specifically, they aimed to examine whether interoceptive stress may serve as a context in a renewal of extinguished food-seeking paradigm. The major new result is that extinguished food-seeking behaviors can become susceptible to stress-induced reinstatement if stressors are introduced during training and have presumably become part of the original context of acquisition. These results may have important implications for understanding why exposure to stress may result in the relapse of a variety of problem behaviors (e.g., overeating and drug taking) even after they have been successfully inhibited through treatment. The experiments were not designed to make direct inferences regarding specific neural substrates responsible for these behavioral observations. Rather, they were designed to provide important behavioral observations relating to the

theoretical construct of stress (i.e., as an intervening variable) that may also be described eventually from a neural perspective (Bolles, 1975).

Experiment 1

Experiment 1 was designed to test whether extinguished food seeking can be made susceptible to stress-induced reinstatement if stress is first associated with the acquisition of food seeking. One group of rats was given daily exposure to different stressors immediately before sessions in which they were trained to make a lever press response to earn sucrose pellets. Stressors were given using a Chronic Variate Stress (CVS) procedure that has been used and described elsewhere (e.g., Hammack, Cheung, Rhodes, Schutz, Falls, Braas, & May, 2009). A control group received identical lever press training, but did not receive the daily stressors. In a second extinction phase, the response was no longer reinforced in a series of sessions in which neither group received stressors. Finally, each rat was tested for responding in two separate sessions conducted in a counterbalanced order. In one session, responding was tested immediately after exposure to a stressor, and in the other, it was tested after the rat received approximately equal handling (but no stressor). Previous research in other laboratories indicated that stress exposure would not normally produce recovery of extinguished food seeking (e.g., Buczek et al., 1999; Koob & LeMoal, 1997). However, the hypothesis was that the addition of stressors prior to training sessions would render extinguished behavior susceptible to reinstatement after stressor exposure.

Method

Subjects

The subjects were 32 naïve female Wistar rats (*ns* = 16) purchased from Charles River Laboratories (St. Constance, Quebec). They were between 75 and 90 days old at the start of the experiment and were individually housed in suspended wire mesh cages in a room maintained on a 16:8-h light: dark cycle. Experimentation took place during the light period of the cycle. Rats were deprived to 90% of their free feed weight prior to the beginning of the experiment.

Apparatus

Two sets of four conditioning chambers housed in separate rooms of the laboratory were used. Each box was housed in its own sound attenuation chamber. All boxes were of the same design (Med Associates model ENV-008-VP, St. Albans, VT). The side walls and ceilings were made of clear acrylic plastic, while the front and rear walls were made of brushed aluminum. They measured 30.5 cm × 24.1 × 21.0 cm (*l* × *w* × *h*). The first set of boxes had a 1.5 cm vertical gray stripe down the center of one acrylic side wall and the grids of the floor were spaced 1.6 cm apart (center-to-center). The other set of boxes had no adornment on the side walls and the floor consisted of alternating stainless steel grids with different diameters (0.5 and 1.3 cm, spaced 1.6 cm apart).

Recessed 5.1 cm × 5.1 cm food cups were centered in the front walls approximately 2.5 above the level of the floor. Retractable levers (Med Associates model ENV-112CM) were positioned to the left and right of the food cup. These levers were 4.8 cm long and positioned 6.2 cm above the grid floor. The right lever protruded 1.9 cm

when extended (the left lever remained retracted throughout the experiment). A 28-V panel light (2.5 cm in diameter) was attached to the wall 10.8 cm above the floor and 6.4 cm both to the left and right of the food cup. Two identical panel lights were also mounted in the same positions on the back wall. The chambers were illuminated by one 7.5-W incandescent bulb mounted to the ceiling of the sound attenuation chamber, approximately 34.9 cm from the grid floor at the front wall of the chamber. Ventilation fans provided background noise of 65 dBA.

The apparatuses were controlled by computer equipment located in an adjacent room. Food rewards consisted of 45 mg sucrose pellets (TestDiet, Richmond, IN, USA).

Chronic Variate Stress

Stressed rats in Experiments 1-3 were exposed to a 7-day chronic variate stress paradigm adopting procedures used in the stress literature (e.g., Hammack et al., 2009). When the stress protocol was in effect, rats received 1 of 4 different types of stressor procedures each day:

Oscillation stress (O). Rats were placed inside a plastic chamber (28 × 17 × 13 cm) that was secured to a clinical rotator (Fisher Scientific, Morris Plains, NJ) and were oscillated for 30 min at 30 rpm in a lighted room in the laboratory.

Footshock (F). Rats were placed inside a conditioning chamber (Med Associates, St. Albans, VT) measuring 30 × 25 ×35 cm that differed from the chamber in which instrumental training occurred in terms of visual (i.e., designs on the walls), tactile (i.e., floor grates), and olfactory stimuli (i.e., scents). After a 5-min acclimation period, two 1.0-mA 5-s footshocks were delivered through the grid floor with a 1-min interval between them.

Restraint (R). Rats were placed in a 9 × 15 cm (D × H) Broome Style Rodent Restrainer (Plas Labs, Lansing MI, 554-BSRR) and restrained for 60 min in a lighted room in the laboratory.

Pedestal stress (P). Rats were placed on an elevated 20 × 20 cm platform that was 60 cm from the floor for 30 min in a lighted room in the laboratory.

In practice, each stressor was repeated once over the 7 days with the exception of the Pedestal Stressor, which was given only once. The order of stressors in Experiments 1-3 was ORFPORF for half the rats and ORFPOFR for the other half.

Procedure

Magazine training. On the first two days, each rat received a daily session in which pellets were delivered freely on average every 30 s. The lever was retracted and unavailable during these sessions.

Acquisition. On each of the next 10 days, all rats received a single daily session in which lever presses resulted in a pellet delivery every 30 s on average (a VI 30-s reinforcement schedule). Sessions began with the insertion of the left-hand lever following a 2-min delay. Sessions ended with the retraction of the lever after 30 min. No special response shaping was necessary. Beginning on Day 4, rats in Group Acquisition Stress began receiving a stressor from the CVS protocol immediately prior to each daily session. Rats in Group No Acquisition Stress received approximately equal handling, but did not receive a stressor; they were similarly shuttled to the laboratory from the home cage and then returned immediately while the rats in Group Acquisition Stress received stressors.

Extinction. On each of the next 5 days, all rats received a single daily session in

which lever presses were available but had no programmed consequence. The extinction sessions also began when the lever was inserted following the 2-min delay. The sessions ended after 30 min when the left lever was retracted from the chamber. Rats did not receive stressors prior to the extinction sessions.

Renewal Test. On each of the final 2 days, each rat received a single test session, identical to extinction, except that it was only 10 min in duration. Rats received one test session after stressor exposure and another after approximately equivalent handling. For half the rats in each group, the stressor was restraint (R) and for the other half it was footshock (F). For Group Stress Renewal, the test stressor was the same type of stressor that was received prior to the final acquisition training session. The Stressor was novel for rats in the No Acquisition Stress Group.

Results

The results of acquisition, extinction, and testing are shown in Figure 1. The chronic variate stress procedure given prior to sessions 4 through 10 did not affect the rate of lever press acquisition (left panel) or extinction (middle panel). In contrast, stressors did have an effect during the final tests. Rats that had received the stressors

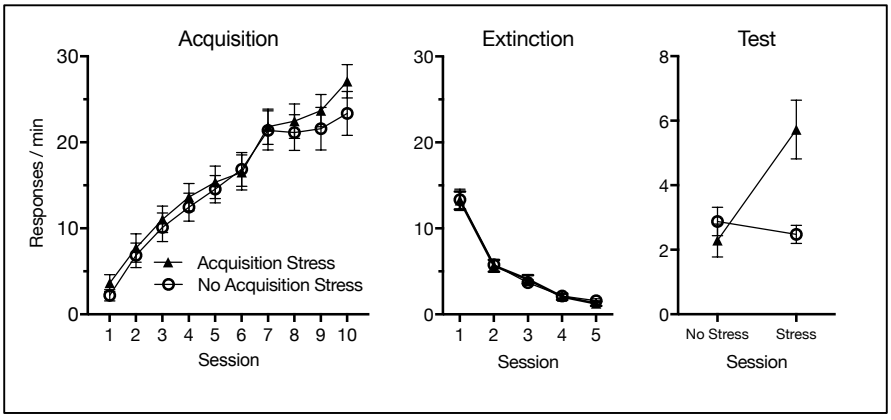

Figure 1. Results of Experiment 1. Mean lever responses per minute during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions.

during acquisition made more responses in the test preceded by a stressor than the test that was not. In contrast, rats that had not received stressors during acquisition responded at similarly low rates in both tests.

Acquisition and Extinction

A 10 (Session) x 2 (Group) ANOVA confirmed that response rate increased over the acquisition sessions, $F(9, 270) = 122.40$, $MSE = 13.94$, $p < .001$. Neither the group effect nor the session by group interaction was significant, Fs < 1, suggesting that stress did not have an effect on response rates during lever press training. Similarly, a 5 (Session) x 2 (Group) ANOVA found that responses decreased during extinction, $F(4, 120) = 52.26$, $MSE = 173.25$, $p < .001$. Non-significant group and interaction effects suggested no differences in the rate of extinction, Fs < 1.

Test

A 2 (Session: No Stress vs. Stress) x 2 (Group) ANOVA indicated a main effect of session, $F(1, 30) = 7.33$, $MSE = 5.03$, $p = .01$, $\eta_p^2 = .20$. There was also a significant session by group interaction, $F(1, 30) = 11.71$, $MSE = 5.03$, $p = .002$, $\eta_p^2 = .28$, and a main effect of group $F(1, 30) = 28.36$, $MSE = 4.81$, $p = .036$, $\eta_p^2 = .49$. The interaction indicated that the groups exhibited a different pattern of responding over the tests. Fisher's LSD tests confirmed that Group Acquisition Stress made more responses in the test session preceded by stressor exposure than the non-stressed test, $p < .001$. Responding in Group No Acquisition Stress did not differ between the test sessions, $p = .62$.

Discussion

Rats that had received stressors prior to lever press training sessions responded more in a test that was preceded by a stressor than in one that was not. In contrast, rats that had not received stressors during training responded at similar rates in both test sessions. This lack of recovery in Group No Stress is consistent with an extensive literature indicating that stress does not generally reinstate extinguished food seeking (e.g., Buczek et al., 1999; Koob & LeMoal, 1997). In a preliminary way, the contrasting recovery of responding in Group Acquisition Stress suggests that stress exposure during training may have allowed stress to play the role of Context A in an ABA renewal design. In other words, animals may have learned that lever responses were reinforced in the context of stress (Context A) and were extinguished in its absence (Context B). On this view, stressor exposure produced stress-induced reinstatement by returning the rat to the conditioning context.

An alternative or additional explanation is that the pre-session stressors had their effect by influencing the value the rats learned to attribute to the sucrose reinforcers. That is, response recovery may have occurred due to *incentive learning* (Dickinson & Balleine, 1994). During acquisition the animals might have learned that sucrose pellets were valuable (e.g., made them feel better) after exposure to a stressor; as a consequence, stressor exposure prior to the test could have increased responding because it increased the motivation to respond for sucrose. This view is essentially a "comfort food" hypothesis. In a well-known example of incentive learning, Balleine (1992) found that shifts in deprivation states (e.g., from satiety to hunger) had no effect on responding during extinction unless rats had previously had an opportunity to learn about the

reinforcer in the tested hunger state. Similarly, only rats that had tasted food pellets while sated reduced their response rate accordingly when shifted from hunger to satiation. Other experiments have shown that rats also must learn about the value of heat when they are cold (Hendersen & Graham, 1979). In some cases, organisms thus learn about the value of reinforcers in specific states. One unique feature of the current experiment is that the sucrose pellets were already demonstrably reinforcing in our moderately food deprived rats. Any increase in their value attributed to consuming them under stress would have to be recognized as being above and beyond this baseline value. Nonetheless, consistent with this possibility, it has been suggested that organisms may attribute even greater value to highly palatable foods when they are consumed while under stress (for a review, see Adam & Epel, 2007).

If incentive learning did have a role in the key result of Experiment 1, mere exposure to sucrose after a stressor may be sufficient to make extinguished responding recover after stress. Experiments 2 and 3 were designed to examine this possibility.

Experiment 2

Experiment 2 contained two groups. The groups were similar to those from Experiment 1. Group Acquisition Stress again received daily exposure to stressors prior to lever press acquisition sessions (but not extinction sessions). Group Incentive Learning received identical lever press acquisition and extinction, but did not receive stressors during either phase. Instead, the rats received the same sequence of stressors that animals in Group Acquisition Stress did, but over a separate 7-day pre-exposure period before lever press training began. At this time, they received an opportunity to eat sucrose pellets in the homecage immediately following each daily stressor. If incentive learning

were responsible for renewal in Experiment 1, allowing animals to consume the pellets following stress should produce a similar result.

Method

Subjects and Apparatus

The subjects were 32 naïve female Wistar rats (*ns* = 16) of the same age and from the same vendor as those in Experiment 1. They were also maintained under the same conditions. The apparatus was also the same as that used in Experiment 1.

Procedure

Preexposure. In Experiment 2, all rats received pre-exposure to the sucrose reinforcers for 7 days prior to the beginning of instrumental lever-press training. Rats received the pellets in cups placed homecages once each day; the number of pellets was the same as the average received by Group Acquisition Stress in Experiment 1 during the training sessions preceded by stress (i.e., 51, 51, 52, 53, 53, 54, 55). In addition, Group Incentive Learning received a stressor from the 7-day chronic variate stress procedure (in the same sequence described in Experiment 1) immediately before their daily sucrose pellets. Group Stress Renewal was instead given similar handling immediately (as previously described) before receiving their daily access to sucrose in the home cage. All rats ate all the sucrose pellets given each day.

Magazine training. Magazine training proceeded as described in Experiment 1.

Acquisition. On each of the next 10 days, all rats then received a single daily session in which lever presses were reinforced on the VI 30-s reinforcement schedule. Sessions began with the insertion of the left-hand lever following a 2-min delay. No special response shaping was necessary. Sessions ended with the retraction of the lever

after 30 min. Beginning on day 4, rats in Group Stress Renewal received a stressor from the CVS protocol, in the same sequence as Group Incentive Learning had received during pre-exposure (as described in Experiment 1), immediately prior to their daily lever press training sessions. Rats in Group Incentive Learning were shuttled to and from the laboratory when Group Acquisition Stress was to receive stressors but were not exposed to them before their training sessions.

Extinction. Extinction sessions proceeded as described in Experiment 1.

Renewal Test. Test sessions proceeded as described in Experiment 1. As before, half the rats were tested after the footshock stressor, and half after restraint, during their stress session.

Results

The results of acquisition, extinction, and testing are shown in Figure 2. The groups acquired (left panel) and extinguished (middle panel) lever responding similarly. Critically, in a replication of Experiment 1, rats in the Acquisition Stress Group demonstrated stress-induced reinstatement. The results were less clear in the Incentive Learning Group.

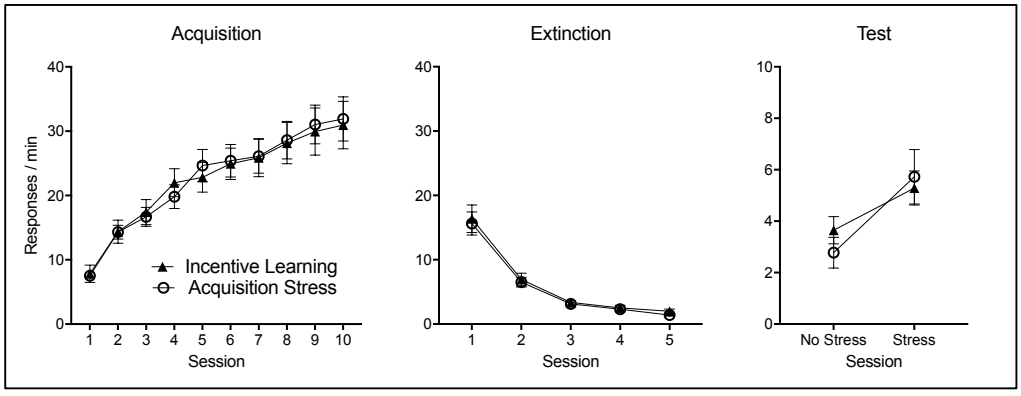

Figure 2. Results of Experiment 2. Mean lever responses per minute during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions.

Acquisition and Extinction

A 10 (Session) x 2 (Group) ANOVA indicated that the response rates increased over the acquisition sessions, $F(9, 270) = 57.72$, $MSE = 31.91$, $p < .001$. The main effect of group and the session by group interaction were not significant, Fs < 1, indicating that the groups did not differ. Similarly, a 5 (Session) x 2 (Group) ANOVA found that responding that decreased over extinction training, $F(4, 120) = 107.92$, $MSE = 10.34$, $p < .001$, did not differ between or interact with the groups, Fs < 1.

Test

A 2 (Test Session: No Stress vs. Stress) x 2 (Group: Acquisition Stress vs. Incentive Learning) ANOVA indicated a main effect of test session, F (1, 30) = 12.84, $MSE = 6.56$, $p = .001$, $\eta_p^2 = .30$, suggesting that stress generally increased responding. Neither the main effect of group nor the interaction were significant, largest $F = 1.05$. Planned follow-up comparisons indicated that rats in Group Acquisition Stress made significantly more responses in the test preceded by a stressor ($p = .003$). The increase in the test after stress fell short of the conventional criterion for statistical significance in Group Incentive Learning ($p = .08$).

Discussion

Group Acquisition Stress made significantly more responses in a test session that was preceded by a stressor than in a session that was not. This result replicated the stress-induced reinstatement of food-seeking observed in Experiment 1. However, the effects of the test stressor were less clear in the Incentive Learning Group. The lack of a significant

interaction between the groups over the two tests is consistent with the possibility that there were no differences between them. However, the renewal effect did not reach statistical significance in Group Incentive Learning, a result that might cast some doubt on the incentive learning hypothesis. Nonetheless, it was clearly necessary to investigate the incentive learning hypothesis further, and that is one of the goals of subsequent experiments.

Experiment 3

One objective of Experiment 3 was to collect more data regarding the effects of the incentive learning received by Group Incentive Learning in Experiment 2. Another was to test another alternative account of the stress-induced reinstatement observed in both Experiments 1 and 2. Specifically, it was also possible that stress-induced recovery was a mere result of prior exposure to stress, rather than stress's actual association with either lever pressing or the sucrose pellets. That is, neither Experiment 1 nor Experiment 2 contained control groups that examined whether pre-exposure to stress itself was somehow sufficient for a stressor at test to produce recovery of the extinguished response. Experiment 3 therefore included three groups that received identical lever press acquisition and extinction phases during which stressors were not delivered at any time. The groups differed, however, in the treatments they received *before* lever training. Two groups received the usual 7-day chronic variate stress procedure during this pre-exposure phase. Group Incentive Learning had an opportunity to eat the sucrose reinforcers after each daily stressor, whereas a new group, Group Stress Only, was immediately returned to the home cage after stress exposure without having an opportunity to eat sucrose after stress (they had received similar exposure to sucrose over the previous 7 days). The third

group, Group Sucrose Only, simply received 7 days of sucrose exposure prior to the beginning of training. Together, the groups in this design allowed a further examination of a potential incentive learning effect and provided an opportunity to distinguish any role of incentive learning from what may result from mere exposure to stress or sucrose pellets alone.

Method

Subjects and Apparatus

The subjects were 60 naïve female Wistar rats (*ns* = 20) of the same age and from the same vendor as those in Experiment 1 and 2. They were also maintained under the same conditions. The apparatus was also the same.

Procedure

Pre-exposure. The rats first received different experiences over a 14-day pre-exposure period. Rats in each group received access to sucrose pellets via cups placed in the home cages on 7 of those days (as described in Experiment 2). Group Incentive Learning received a stressor from the CVS paradigm immediately before their daily ration of sucrose pellets. Group Stress Only received the same daily stressors in the same sequence but did not eat sucrose pellets afterward (they had equivalent exposure to sucrose during the prior 7 days). Rats in Group Sucrose Only were merely pre-exposed to sucrose pellets during pre-exposure (1/2 during the 1st 7 days and ½ during the 2nd 7 days). They received no stress.

Magazine training. Magazine training proceeded exactly as described in Experiments 1 and 2.

Acquisition and Extinction. Lever press training and extinction were conducted exactly as described in Experiments 1 and 2. However, no animals received stressor exposure at any time during these phases.

Test. Test sessions proceeded exactly as described in Experiment 1.

Results

The results of acquisition, extinction, and testing are shown in Figure 3. The different groups acquired (left panel) and extinguished (middle panel) lever responding similarly. The results of the test (right panel) suggested that stress prior to testing did not produce a recovery of responding in any group.

Acquisition and Extinction

A 10 (Session) x 3 (Group) ANOVA indicated that response rate increased over acquisition sessions, $F(9, 513) = 108.42$, $MSE = 17.43$, $p < .001$. The main effect of group and the session by group interaction were not significant, Fs < 1. Similarly, a 5 (Session) x 3 (Group) ANOVA found that responding decreased over extinction training, $F(4, 228) = 300.34$, $MSE = 4.34$, $p < .001$, that did not depend on group or an interaction between group and session, Fs < 1.

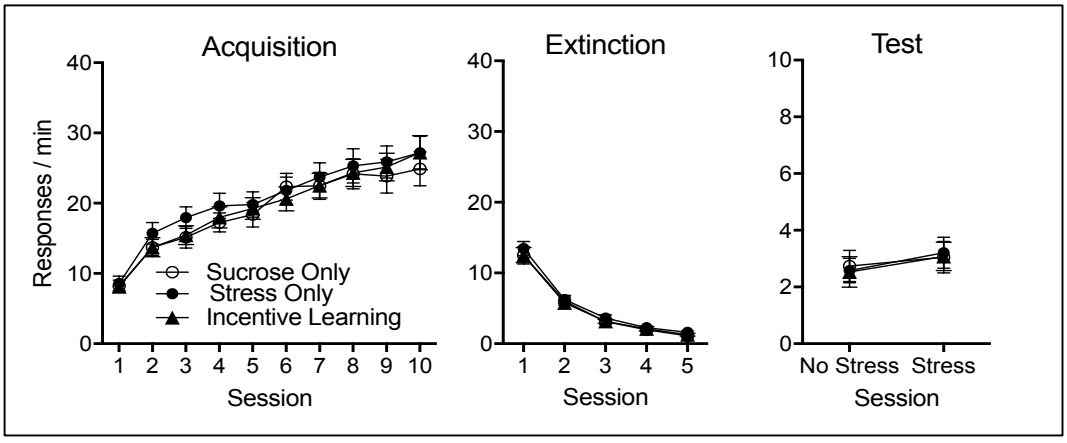

Figure 3. Results of Experiment 3. Mean lever responses per minute during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions.

Test

A 2 (Session: No Stress vs. Stress) x 3 (Group) ANOVA did not find an effect of Session, F (1, 57) = 2.51, MSE = 2.94, p = .12; the main effect of group and the group by session interaction were also not significant, $F < 1$.

To further understand the possible role of incentive learning, I used all the data that had been collected in Experiments 1-3 with rats that had been given the Acquisition Stress treatment (Experiments 1 and 2, total n = 32) and the Incentive Learning treatment (Experiments 2 and 3, total n = 36). The mean test data, collapsing over experiment, are presented in Figure 4. A 2 (Session: No Stress vs. Stress) x 2 (Group: Acquisition Stress vs. Incentive Learning) ANOVA was conducted on the data in figure; because of the large ns, this analysis had relatively high statistical power. The ANOVA revealed a main effect of Session, F (1, 66) = 25.21, MSE = 6.01, $p < .001$, $\eta_p^2 = .25$, and a significant session by group interaction, F (1, 66) = 6.58, MSE = 6.01, p = .01, $\eta_p^2 = .09$. The main effect of group was not significant, F = 1.17. Planned comparisons found that Group Acquisition Stress made significantly more responses in the test session that followed stressor exposure ($p < .001$), whereas the corresponding effect in Group Incentive Learning again fell short of statistical significance (p =.08).

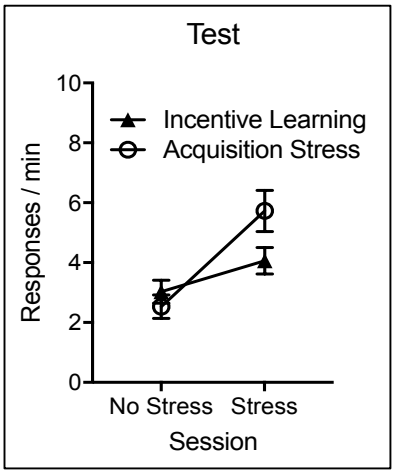

Figure 4. Mean responses per minute during the first 5 min of test sessions collapsed over Experiments 1-3.

Discussion

In Experiment 3, neither pre-exposure to sucrose alone, stress alone, or sucrose after receiving a stressor rendered behavior susceptible to stress-induced reinstatement.

Among other things, these results suggest that Incentive Learning may not be sufficient to account for the stress-induced reinstatement effects observed in Experiments 1 and 2. A further analysis that used all the data collected in these conditions over experiments confirmed that the effect in the Acquisition Stress condition was stronger than any effect in the Incentive Learning condition. Indeed, if there was any overall effect of the incentive learning treatment, it was weak. Thus, the overall evidence suggests that the stress-induced reinstatement observed in Experiments 1 and 2 was more than an incentive learning effect. Nonetheless, I will make another attempt at separating the incentive learning and context renewal hypotheses in Experiment 5.

The results of Experiment 3 also suggest that neither pre-exposure to sucrose alone or to stress alone were sufficient to render extinguished food seeking susceptible to recovery after stressor exposure. Instead, it appears that the stress-induced reinstatement observed in Experiments 1 and 2 may rely in large part on the presence of stressors prior to the actual instrumental training sessions.

Experiment 4

It should be noted that the renewal effects in Experiments 1 and 2 were produced by stressors of a type that had also preceded two of the training sessions. That is, rats that were tested with footshock or restraint stressors had received the same stressor prior to lever training on acquisition sessions 6 and 10. This made it possible that animals had learned about (and responded to) the presence of the *exteroceptive* components of specific stressors rather than general interoceptive stress stimuli that might be produced in common by all of them. Furthermore, while care was taken to provide equal handling between the stressed and unstressed test sessions, it was also possible that rats had

learned to use exteroceptive cues that were not uniquely related to stressor exposure. That is, on days when stressors were delivered (and thus reinforcers could be earned), the rats received relatively lengthy exposures to various exteroceptive stimuli (e.g., restraint tubes, plastic boxes, etc.). In contrast, extinction was in effect when the rats were placed more directly into the conditioning context without any prior apparatus stimulation. Animals may have simply learned that responses were reinforced in sessions when they had received a relatively lengthy exposure to a context (the stressor situation) before being placed in the conditioning chamber.

Experiment 4 was therefore designed to examine whether the stress-induced reinstatement effect in Experiments 1 and 2 depended on these other factors. It contained three groups that all received stressors prior to lever press acquisition but not extinction sessions. However, during testing, the rats were tested after (1.) a stressor that had been associated with acquisition (Group Paired), (2.) a stressor that had not been associated with acquisition (Group Unpaired), or (3.) exposure to a neutral plastic box in a darkened room (Group Control). If the reinstatement effects in Experiments 1 and 2 had been produced by learning about stress (see Figure 5a) rather than a specific stressor associated with conditioning, then it should occur equivalently in Groups Paired and Unpaired. If it is contrastingly caused by learning only about the specific stressors (see Figure 5b), it should occur only in Group Paired. Finally, if the effect was merely a result of exposure to another apparatus in a different room immediately before testing, the effect should also be evident in Group Control.

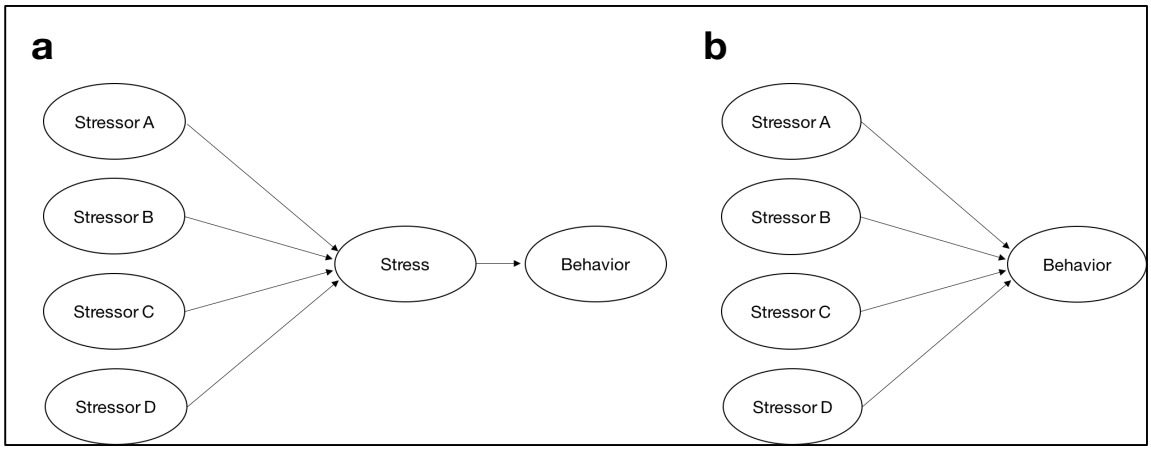

Figure 5. Panel a describes the proposed account of interoceptive stress control over behavior. Stress stimuli that that are common across different stressors produce an interoceptive context of stress which comes to exert contextual control over the behavior. Panel b describes an alternative account in which individual stressors are directly and separately associated with the performance of the behavior.

Method

Subjects and Apparatus

The subjects were 36 naïve female Wistar rats (*ns* = 12) of the same age and from the same vendor as those in the previous experiments. The apparatus and maintenance conditions were also the same with the exception of two new "stressor" apparatuses described below.

Procedure

Pre-exposure. During each of the first two days of the pre-exposure period, all rats were individually placed into transparent plastic shoebox containers (39.4 cm x 30 cm) enclosed with woodchip bedding on their floors in a darkened room of the laboratory for 35 min before being returned to their home cage. During days 3 and 4, half the rats received the usual footshock stressor and the other half received restraint (both as previously described). Following stressor exposure, rats were returned to the homecage. This procedure was used so that the stressors used during testing were not novel in any of the groups.

Magazine training. Magazine training then proceeded as in the previous experiments.

Acquisition. Lever press training was then conducted as described in Experiments 1-3. All rats received stressor exposures prior to training sessions 4-9. In this experiment, a new stressor, 5 min of exposure to an open field stressor ("X"), was given to all animals prior to Session 4. This involved placing the rats in a 232-cm square opaque container with 60.96-cm sidewalls in a lighted room in the laboratory for 5 min. The open field stressor replaced the restraint or footshock stressor that was removed to allow the paired and unpaired testing conditions. Half the rats in each group received stressors in the sequence XOFPOF and half received XORPOR.

Renewal Test. Test sessions proceeded as described in Experiment 1-3. However, here the groups differed in whether the tested stressor had been received prior to actual acquisition sessions (Group Paired) or during the days of pre-exposure (Group Unpaired). As usual, half the rats in Groups Paired and Unpaired received restraint and half received footshock. For Group Paired, that stressor had also been received prior to two training sessions; that is, rats tested with F had received XOFPOF and rats tested with R had received XORPOR. For Group Unpaired, however, the tested stressor had only been received during pre-exposure, and was thus not connected with lever press training. Here, rats tested with F had received XORPOR during instrumental training and rats tested with R had received XOFPOF. Prior to their "stressed" test, rats in Group Control were simply placed into the familiar control shoebox with woodchip bedding in a darkened room for 35 min.

Results

The results of acquisition, extinction, and testing are shown in Figure 6. The groups learned (left panel) and extinguished (middle panel) lever responding similarly. The results of the test (right panel) indicated a stress-induced recovery in both the Paired and Unpaired Groups.

Acquisition and Extinction

A 9 (Session) x 3 (Group) ANOVA indicated that response rate increased over acquisition sessions, $F(8, 224) = 74.21$, $MSE = 20.68$, $p < .001$; the main effect of group and the session by group interaction did not approach significance, Fs < 1. A 5 (Session) x 2 (Group) ANOVA similarly found that responding decreased over extinction training, $F(4, 112) = 73.82$, $MSE = 8.78$, $p < .001$; there was no group effect or interaction, largest $F = 1.49$.

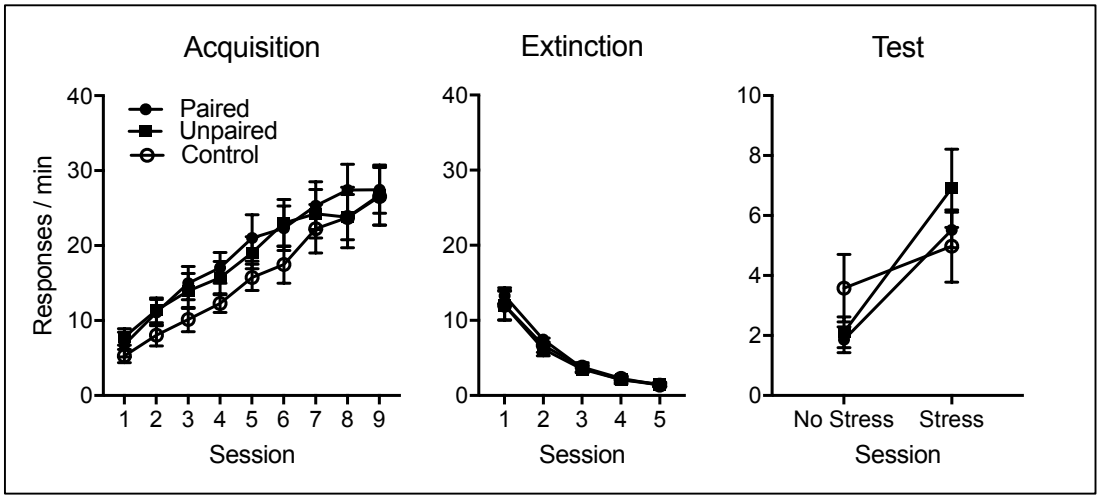

Figure 6. Results of Experiment 4. Mean lever responses per minute during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions.

Test

A 2 (Session: No Stress vs. Stress) x 3 (Group) ANOVA indicated a main effect of Session, $F(1, 28) = 33.83$, $MSE = 167.09$, $p < .001$, $\eta_p^2 = .55$. The group by session interaction approached significance, $F(2, 28) = 3.14$, $MSE = 15.53$, $p = .059$, $\eta_p^2 = .18$, although there was no main effect of group, $F < 1$. Planned comparisons indicated that Groups Paired and Unpaired both made more responses in the session following stressor exposure ps $\leq .001$. In contrast, there was no change in responding in the Control Group over sessions ($p = .17$). A subsequent analysis including only Groups Paired and Unpaired found a session effect, $F(1, 19) = 38.85$, $MSE = 4.83$, $p < .001$, $\eta_p^2 = .60$, but no group effect or a group by session interaction, Fs < 1.

Discussion

The results of Experiment 4 suggest that the present stress-induced reinstatement effect does not depend on testing with a stressor that had been directly associated with the instrumental lever-press training during the acquisition phase. Rather, equally familiar stressors that had never been connected with training (Group Unpaired) also produced a robust recovery that was similar to the one observed in rats that had received the tested stressor prior to acquisition sessions (Group Paired). Furthermore, a lack of renewal in the control group suggests that response recovery cannot be simply attributed to mere placement in a different apparatus before testing. The results are thus consistent with the notion that the stress-induced reinstatement effect produced here is created by a common interoceptive stress state that is produced by the different stressors present during acquisition training and then absent during extinction (see Figure 5a). Thus, renewal

occurs upon returning the animal to that general interoceptive stress state or context that had been associated with training.

Experiment 5

Together, Experiments 1-4 suggest that exposure to stress may play the role of context in an ABA renewal design. That is, instrumental behavior acquired after a recent stress (Context A), and extinguished in its absence (Context B), can return (renew) when a stress is encountered again before a test (Context A). Experiments 2 and 3 further suggest that stress needs to be associated with performance of the instrumental response rather than merely the food-pellet outcome (i.e., incentive learning). Exposure to the outcome alone following stress was not sufficient for stress to produce recovery of the extinguished response. Moreover, Experiment 4 provides evidence that the stress-induced reinstatement here occurred due to common interoceptive state across the different types of stressors. That is, the animals had learned that the response was reinforced in a general interoceptive context rather than being connected with exteroceptive stimuli associated with individual stressors themselves.

Experiment 5 further pits the idea that stress is acting as a context against the incentive learning mechanism also tested in Experiments 2 and 3. If an interoceptive stress context functions similarly to exteroceptive ones, then it should be equally serviceable as an *extinction* context rather than an acquisition context. If stress were to also control extinction performance, it would be difficult to attribute this to incentive learning, because stressors received during extinction would not be expected to affect the value the rat attributes to sucrose pellets—which are entirely absent during extinction.

Therefore, this experiment allows a comparison of the effectiveness of stressors given during acquisition with those given during extinction to exert control over behavior.

The design of Experiment 5 is sketched in Table 1. In this experiment, in addition to a group that received stressors prior to acquisition sessions, another group received the same stressors (in the same sequences) prior to their extinction sessions. When tested after extinction, stress should theoretically cue acquisition performance (increase responding) in Group Acquisition Stress but extinction performance (a suppression of responding) in Group Extinction Stress. As usual, each rat was tested in two separate sessions. For one test, rats were simply handled as described in previous experiments. Prior to the other test, rats in each group received the appropriate footshock or restraint stressor to which they had received during pre-exposure but had never occurred prior to an acquisition or extinction session.

Table 1

Design of Experiment 5

Group	Acquisition	Extinction	Test
Acquisition Stress	Stress → R+	R-	
			Stress → R-; R-
Extinction Stress	R+	Stress → R-	

Note: Stressors occurred immediately before acquisition sessions 4-10 (Group Acquisition Stress) or extinction sessions 1-6 (Group Extinction Stress). The test stressors (footshock or restraint; counterbalanced) had been pre-exposed prior to the beginning of acquisition but were not included in series of stressors that preceded the sessions. R+ = reinforced session; R- = non-reinforced session

Method

Subjects and Apparatus

The subjects were 32 naïve female Wistar rats (*ns* = 8) of the same age and from the same vendor as those in previous experiments. The apparatus and maintenance conditions were the same as described in Experiment 4.

Procedure

Pre-exposure. As in previous experiments, during each of the first 2 days rats were pre-exposed to their eventual test stressor. For half the rats this was the footshock stressor and for the other half it was restraint (as previously described). Following each stressor exposure, rats were returned to the homecage.

Magazine training. On each of the next two days, a daily magazine training session proceeded as in the previous experiments.

Acquisition. Over the next 10 days, lever-press training and stressor exposures proceeded exactly as described in Experiment 4 for rats in the Acquisition Stress group. Beginning with Session 4, half of those rats received stressors in the sequence XOFPOF and half received XORPOR. Rats in the Extinction Stress Group received similar handling, without stress, prior to each acquisition session.

Extinction. Then, over the next 6 days, all rats received daily extinction training sessions as described in Experiments 1-5. However, for this experiment, rats in the Extinction Stress group were also exposed to a stressor before each session. These rats received the same stressors in the same orders (i.e., XOFPOF or XORPOR) as rats in the Acquisition Stress Group had received before acquisition sessions.

Renewal Test. Test sessions proceeded exactly as described in Experiment 4. All animals were tested with the stressor they had received during pre-exposure, which had not occurred before an acquisition (Group Acquisition Stress) or extinction (Group Extinction Stress) session. As usual, half the rats received one test after restraint and the other half after a footshock. Before the other test rats were not exposed to a stressor but received similar handling.

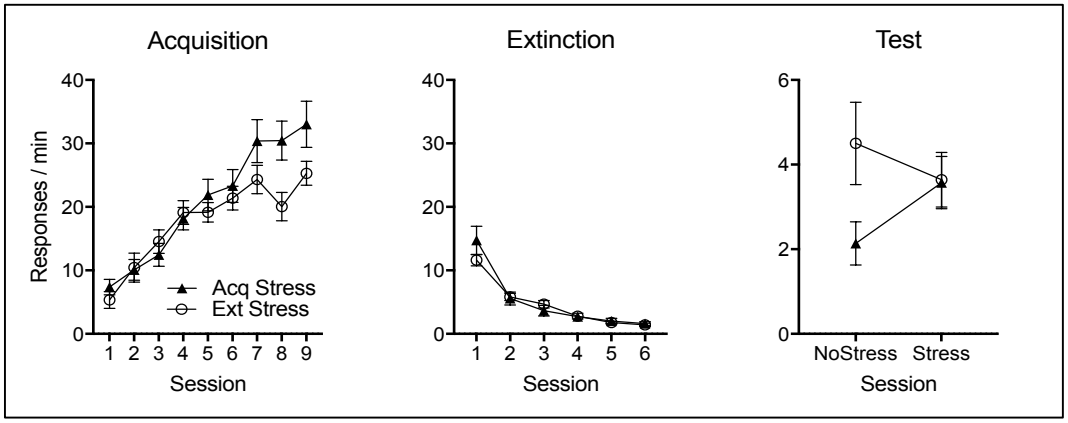

Figure 7. Results of Experiment 5. Mean lever responses per minute during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions.

Results

The results of acquisition, extinction, and testing are shown in Figure 7. Both groups learned the response, which increased in rate over the acquisition sessions (left panel). Then, both groups extinguished the response over extinction (middle panel). Visual inspection of the test data (right panel) suggested that each group showed evidence of the predicted renewal effects. That is, rats responded more during a session when their pre-session treatment (Stress or No Stress) was consistent with their acquisition treatment, and less when the pre-session treatment (No Stress or Stress) was consistent with their extinction treatment. However, statistical analyses indicated that a reliable renewal effect only occurred in the Acquisition Stress Group.

Acquisition and Extinction

A 9 (Session) x 2 (Group) ANOVA indicated that lever presses increased over acquisition sessions, $F(8, 224) = 60.99$, $MSE = 30.06$, $p < .001$. The main effect of group was not significant, $F(1, 28) = 1.34$, $MSE = 468.11$, $p = .257$. However, a significant session by group interaction, $F(8, 224) = 4.40$, $MSE = 30.06$, $p < .001$, indicated that response rate differed over sessions between the groups. Follow-up analyses revealed that

rats in the acquisition stress group responded at a greater rate in the 8th session, $p = .01$. Significant differences in responding did not occur in any other session.

A 6 (Session) x 2 (Group) ANOVA on the extinction data indicated that responding declined over extinction, $F(5, 140) = 89.05$, $MSE = 6.35$, $p < .001$. The main effect of group was not significant, $F < 1$. A significant session by group interaction, $F(5, 140) = 2.40$, $MSE = 6.35$, $p = .040$, suggested group differences over the extinction sessions. Follow up analyses indicated that the groups did not differ significantly during any session, smallest $p = .224$. However, one-way ANOVAs examining the first 5 min of each session revealed that the Extinction Stress Group made more responses during this period in Session 2, $F(1, 28) = 5.32$, $MSE = 20.96$, $p = .029$, and Session 3, $F(5, 140) = 6.77$, $MSE = 23.36$, $p = .015$.

Test

A 2 (Session) x 2 (Group) ANOVA on the test data revealed a significant interaction, $F(1, 28) = 6.52$, $MSE = 3.02$, $p = .016$, $\eta_p^2 = .19$. Thus, the effect of stress during testing depended on when it had been received during training. Neither the main effect of session or of group was significant, Fs < 1. While the groups made a similar number of responses in the session after stress, $F < 1$, rats in the Extinction Stress Group responded more than the Acquisition Stress Group in the test when a stressor had not occurred, $F(1, 30) = 4.33$, $MSE = 8.15$, $p = .046$, $\eta_p^2 = .13$. Planned comparisons revealed that rats in the Acquisition Stress Group differed between the tests, making more responses in the test after a stressor had been given ($p = .027$). Response rates in the Extinction Stress Group did not differ statistically between the tests ($p = .202$).

Discussion

These results suggest that the capacity of stressors to promote relapse differs depending on whether they are present during response acquisition versus extinction. As in Experiments 1, 2, and 4, stressor exposures prior to acquisition rendered behavior subject to renewal when stress was re-encountered at test. In contrast, no such effect was observed when the stressors had instead preceded extinction training. The results thus continue to suggest that stressors must be associated with acquisition to allow them to cause stress-induced reinstatement. However, the renewal effect in Group Extinction Stress, which should have taken the opposite form of more responding in the absence of stress than in its presence, was not statistically significant. This could be seen as being inconsistent with the idea that an interoceptive stress context functions similarly to a conventional exteroceptive context.

It should be noted, however, that the groups differed in rates during the test in the absence of stress, though not during the test after stress. Interestingly, the pre-session stress appeared to have an unconditional effect on performance in this experiment. For example, it elevated responding during the early portions of the extinction sessions (see Figure 8). It is possible that this tendency was also present during testing, and thus artifactually increased the level of responding in the presence of stress. The tendency may be consistent with a literature suggesting that while exposure to acute stress often inhibits feeding behavior, chronic exposure may, in some

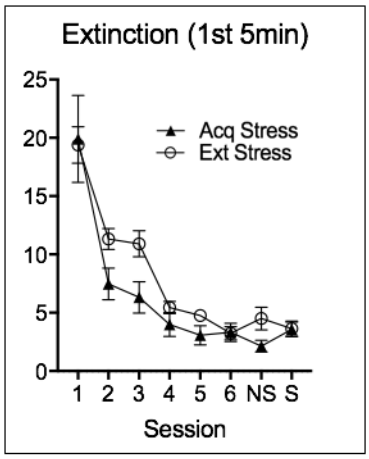

Figure 8. Results of Experiment 5. Mean lever responses per minute during the first 5 min of each extinction and test session.

cases, promote it (Ely et al., 1997; Pecoraro et al., 2004). Any inhibition of performance conditioned to a stress context in Group Extinction Stress would have to compete with any such effect.

An incentive learning mechanism would have difficulty explaining the notable, though nonsignificant, elevation of responding in the absence of stress in the Extinction Stress Group. If stress had previously produced renewal simply through enhancing motivation for sucrose, any differences between the groups in its absence would be unexpected. Rather, it seems most likely that stress, and its absence, may serve as a context, and come to control the performance or inhibition of food-seeking behavior.

Overall, these results, together with those of the previous experiments, remain most consistent with the idea of stress serving the role of context in a renewal paradigm. The fact that stress did not renew behavior after extinction stress further confirms that renewal after stress is not caused simply by prior exposure to chronic stress (see also Experiment 3). In addition, the current experiment suggests that even very recent exposure to chronic stress is not sufficient for stress to renew extinguished behavior.

Experiment 6

The final experiment was designed to connect the current results more directly with experiments on stress-induced reinstatement in the drug self-administration paradigm (e.g., Ahmed & Koob, 1997; Buczek et al., 1999; Erb et al., 1996; Shaham & Stewart, 1995). I have argued that stress-induced reinstatement of cocaine seeking (for example) occurs when an interoceptive stress state created by cocaine itself produces a "context" that becomes connected with instrumental conditioning (see also Ahmed & Koob, 1997). Earlier work has shown that acute and chronic administration of cocaine

can produce changes in stress hormones that are consistent with responses observed to stress (Heesch et al., 1995; Moldow & Fischman, 1987). Furthermore, chronic cocaine exposure, like exposure to chronic stress, produces anxiety-like responses in rats (Goeders, Bienvenu, & De Souza, 1990). Therefore, as in the present experiments, when stress is introduced after extinction of a cocaine-seeking response, it may return the organism to a facsimile of the original acquisition context and therefore cause renewal. To further test this hypothesis, Experiment 6 was designed to potentially produce stress prior to acquisition sessions with cocaine injections instead of the CVS procedure used in Experiments 1-5. After extinction without the drug, I tested the effects of exposure to a stressor on the extinguished response. The hypothesis was that, provided the stress at test generalized to potential stress created by cocaine injections during acquisition, the stressor would renew the extinguished behavior. I also tested whether re-exposure to the cocaine injection itself created a context that caused a renewal of responding.

Experiment 6 utilized four groups (see Table 2). Each group received two daily i.p injections during the acquisition phase; one of cocaine (10 mg/kg) and another of saline. A 10 mg/kg cocaine dose was selected based on previous research suggesting that its stimulus effects may generalize to interoceptive stimuli produced by some types of restraint and footshock stressors (i.e., Mantsch & Goeders, 1998, 1999). Also new to Experiment 6 was the insertion of a second, inactive lever, which had no programmed consequences but has become conventional in the drug self-administration literature. Half the rats (i.e., the Paired Cocaine Groups) received injections of cocaine 15 mins prior to daily lever press training sessions and then saline injections 4 hrs later. The other half (i.e., the U/P Cocaine Groups) received the reverse: They received saline injections 15

min before their acquisition sessions and cocaine injections 4 hrs later. This design ensured that the groups had the same number of injections and equal exposure to cocaine and saline but differed in terms of whether the effects of cocaine were present during instrumental training. Then over six extinction sessions, rats in both groups merely received injections of saline before each session. Finally, as in previous experiments, the rats were tested in two separate sessions in a counterbalanced order. Both tests began 15

Table 2
Design of Experiment 6

Group	Acquisition	Extinction	Test
Paired Cocaine - Coc	Coc → R+ / Sal	Sal → R-	Coc → R-; Sal → R-
Paired Cocaine - Stress			Sal + Shock → R-; Sal → R-
U/P Cocaine - Coc	Sal → R+ / Coc		Coc → R-; Sal → R-
U/P Cocaine - Stress			Sal + Shock → R-; Sal → R-

Note: Pre-Session injections (i.e., paired) always occured 15 min before placement into the experimental chambers and "Unpaired" (U/P) injections were given 4 hours after the session ended. The footshock at test had been pre-exposed prior to the beginning of acquisition but never preceeded a session. The second, inactive lever, which had no consequences was always available. Arrows (→) signal the 15 mins between the beginning of a treatment (e.g., an injection) and a session. Slashers (/) signal the 4 hrs between a session and an unpaired injection. The two test sessions were given in counterbalanced order.

min after rats had received an injection. For all rats, one of the tests occurred after a saline injection. Before the other test, half the rats in each group received an injection of cocaine. The other half again received a saline injection that was followed by exposure to the footshock stressor. (Rats in both groups had been pre-exposed to the footshock stressor before the beginning of training. Because of its 60-min duration, the restraint stressor used in previous experiments would have not fit within the 15-min interval from injection to the beginning of the session.) The hypothesis was that an injection of cocaine prior to the test would produce renewal in the paired but not in the unpaired cocaine groups. Furthermore, the renewal might generalize and also occur after footshock stress.

Method

Subjects and Apparatus.

The subjects were 32 naïve female Wistar rats (*ns* = 8) of the same age and from the same vendor as those in previous experiments. The apparatus and maintenance conditions were also the same as described previously.

Procedure.

Pre-exposure. During two days of pre-exposure, as in the previous experiments, all rats were pre-exposed to the eventual test stressor (i.e., 1-mA 5-s footshock, delivered following the usual procedure). Following stressor exposure, rats were returned to the homecage.

Magazine training. During days 3 and 4, magazine training proceeded as described in the previous experiments.

Acquisition. On each of the next 10 days, each rat received daily acquisition sessions that began with the insertion of two levers following a 2-min delay. Lever presses on the "active" lever (left or right lever counterbalanced) were reinforced with the usual sucrose pellets on the usual VI 30-s reinforcement schedule. Responses on the opposite "inactive" lever were recorded but not reinforced. No special response shaping was necessary. Sessions ended with the retraction of the levers after 30 min. Beginning on Day 4, half the rats received i.p. injections of Cocaine HCL (10 mg/kg; Penro Specialty Compounding; Colchester VT) and half received saline (0.9%) injections 15 min before the session. To equate daily exposure to cocaine, each rat also received an injection of the opposite in the home cage 4 hours after the session ended.

Extinction. On each of the next 6 days, rats received single daily sessions in which

both lever responses remained available but had no programmed consequences. The extinction sessions also began when the levers were inserted following the 2-min delay and ended after 30 min when they were retracted from the chamber. All rats received saline injections (0.9% i.p.) 15 min prior to being placed in the chamber each day.

Renewal Test. On each of the final two days, rats received test sessions that were identical to the extinction sessions except that they were only 10 min in duration. For each rat, the two tests (order counterbalanced) differed in the treatments that preceded them. As in extinction, each rat received an injection of saline 15 min before being placed in the chamber for one test. The groups differed in terms of the treatment they received before the other test. Fifteen minutes before this test, half the rats received an injection of cocaine. The other half received an injection of saline that was followed by exposure to the footshock stressor.

Results

The results of each phase of the experiment are shown in Figure 9. Both groups acquired the active lever response, which increased in rate over the acquisition sessions (left panel). However, rats that received cocaine injections before the acquisition sessions (vs. 4 hours later) responded at lower rates. Similarly, responding decreased over extinction (middle panel) but was at a reduced rate in rats that had received cocaine prior to the acquisition sessions. Results of the test (right panel) indicated a clear renewal of

active lever responding in the cocaine-paired rats when they received cocaine. No other groups appeared to differ between the test sessions.

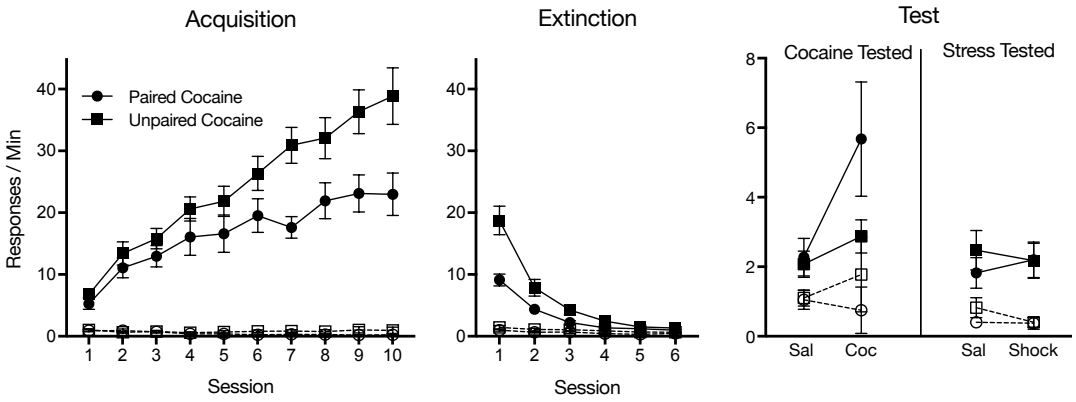

Figure 9. Results of Experiment 6. Mean lever responses per minute on the active (filled shapes-solid line) and inactive levers (open shapes-dashed lines) during each 30-min session of Acquisition (left), and Extinction (middle). The right panel shows the mean responses per minute during the first 5 min of the test sessions separated by stress and cocaine tested animals.

Acquisition

A 10 (Session) x 2 (Lever: Active vs. Inactive) x 2 (Acquisition Treatment: Cocaine Paired vs. Unpaired x 2 (Test Treatment: Cocaine vs. Saline + Footshock) ANOVA indicated main effects of session, $F(9, 252) = 40.11$, $MSE = 24.92$, $p < .001$, acquisition treatment, $F(1, 28) = 7.10$, $MSE = 354.91$, $p = .013$, and of lever, $F(1, 28) = 169.83$, $MSE = 371.91$, $p < .001$. The ANOVA indicated significant session by lever, $F(9, 252) = 41.42$, $MSE = 25.60$, $p < .001$, and session by acquisition treatment, $F(9, 252) = 4.85$, $MSE = 24.92$, $p < .001$, interactions. In addition, a significant session by lever by acquisition treatment interaction, $F(9, 28) = 95.89$, $MSE = 25.60$, $p < .001$, indicated that changes in responding over sessions depended on the lever and that the overall pattern depended on the timing of cocaine injections (15 min before vs. 4 hr after their sessions). Follow-up analyses indicated that groups that received cocaine before their sessions made fewer responses over acquisition on the active lever (ps <.001), but not the inactive lever (smallest $p = .24$), compared with rats that had that received cocaine 4 hrs after the

sessions. No main effects or interactions with the eventual test treatment were significant.

Extinction

A 6 (Session) x 2 (Lever Type) x 2 (Acquisition Treatment) ANOVA revealed main effects of session, $F(5, 140) = 98.63$, $MSE = 4.33$, $p < .001$, lever, $F(1, 28) = 74.69$, $MSE = 18.97$, $p < .001$, and of acquisition treatment, $F(1, 28) = 11.56$, $MSE = 21.05$, $p = .002$. The interactions between session and lever, $F(5, 140) = 79.81$, $MSE = 4.36$, $p < .001$, session and acquisition treatment, $F(5, 140) = 11.87$, $MSE = 4.33$, $p = .001$, and a session by lever by acquisition treatment , $F(5, 140) = 11.23$, $MSE = 4.36$, $p < .001$, were also significant, indicating that differences in responding over extinction depended on the lever and that the overall pattern was dependent on the pre-acquisition session treatments. Follow-up analyses found that rats that received pre-acquisition cocaine responded less on the active lever, $p = .004$, and inactive lever, $p = .046$, over extinction. However, an ANOVA conduced on the final extinction session found no differences between groups on either lever, largest $F = 1.05$. Finally, no main effects or interactions with the type of test animals would eventually receive were significant over acquisition or extinction Fs < 1.

Test

A 2 (Session) x 2 (Lever) x 2 (Acquisition Treatment) x 2 (Test Treatment) ANOVA revealed main effects of session, $F(1, 28) = 5.09$, $MSE = 1.73$, $p = .032$, $\eta_p^2 = .15$, lever, $F(1, 28) = 111.01$, $MSE = 4.31$, $p < .001$, $\eta_p^2 = .80$, and of test treatment, $F(1, 28) = 5.02$, $MSE = 4.75$, $p = .033$, $\eta_p^2 = .15$. The main effect of acquisition treatment was not significant, $F < 1$. Significant interactions were identified between session and lever, $F(1, 28) = 9.46$, $MSE = 1.63$, $p < .001$, $\eta_p^2 = .25$, session and test treatment, $F(1, 28) =$

12.25, *MSE* = 1.73, p = .013, η_p^2 = .30, and session by lever by acquisition treatment, $F(1, 28)$ = 11.23, *MSE* = 1.63, p = .042, η_p^2 =.29. In addition, session by lever by test treatment, $F(1, 28)$ = 3.34, *MSE* = 1.63, p = .078, η_p^2 = .11, and session by lever by acquisition treatment by test treatment interactions, $F(1, 28)$ = 3.34, *MSE* = 1.63, p = .078, η_p^2 = .11, were marginally significant. Follow-up comparisons revealed that the rats in Group Paired Cocaine-Cocaine made more responses on the active lever after receiving cocaine than after saline injection, $p < .001$; their responding did not differ between the sessions on the inactive lever (p = .611). Response rates did not differ between tests on either lever for any other group, smallest p = .234. A separate 2 (Test Session) x 2 (Lever) x 2 (Acquisition Treatment) ANOVA conducted only on the stress-tested rats confirmed a main effect of lever, $F(1, 28)$ = 25.17, *MSE* = 1.77, $p < .001$, η_p^2 = .47. The ANOVA also revealed a significant session by acquisition treatment interaction, $F(1, 28)$ = 5.88, *MSE* = .197, p = .029, η_p^2 = .17, indicating that differences over the tests depended on the rats treatment prior to acquisition sessions. A follow up analysis indicated that rats in the Unpaired Cocaine Group made fewer total responses (collapsed over lever) in the test after shock than in the test after saline, p = .037. Responding in the Paired Cocaine did not differ between the tests, p = .283.

Discussion

Instrumental food-seeking acquired in an interoceptive context produced by a prior injection of cocaine and then extinguished in its absence renewed when cocaine was again administered before a test. Cocaine injections given four hours after (rather than 15 min before) response training did not support this effect. This result, consistent with other

research (i.e., Keiflin et al., 2008), indicates that the stimulus properties of cocaine may play the role of context and produce renewal of food seeking in an ABA renewal paradigm. In contrast, the stimulus properties of cocaine did not generalize to those produced by the footshock stressor tested here. Rats that had received the cocaine treatment during acquisition did not show a similar increase in response rate during testing after footshock stress. This lack of renewal created by stress was not consistent with the hypothesis. However, the fact that responding associated with one specific dose of cocaine would not generalize to the specific footshock treatment used here may not be that surprising. It may the case that other combinations of drug dose and stressor intensity might yield better generalization and thus produce renewal (see below for further discussion).

General Discussion

The results of these experiments suggest that internal sensations produced by stress, like external stimuli that comprise a physical environment, can play the role of context and exert control over the performance of instrumental behavior. In Experiments 1, 2, 4, and 5, food-seeking behavior that was learned in sessions that followed exposure to stress, and was inhibited through extinction while stress was absent, renewed when a stressor was re-encountered before a test. In contrast, food-seeking remained inhibited after the test stressor if stress had not preceded acquisition sessions. The results of Experiments 4 and 5 provide further evidence that the context that controlled behavior was interoceptive and generalized across specific stressors (see Figure 5a). First, renewal did not depend on testing with a stressor that had been directly associated with instrumental training. Second, spending time in a neutral (nonstressful) apparatus before

testing did not renew responding, suggesting that animals had not merely learned that being placed in another apparatus before an instrumental session signaled reinforcement. Together, the results have direct implications for understanding the effects of stress on inhibited food seeking, and more tentatively, the effects of stress on inhibited drug seeking.

Experiments 2, 3, and 5 suggest that renewal after stress depended on animals receiving stressors immediately before the instrumental training sessions. Stress failed to renew behavior if the same stressors had been given during an earlier pre-exposure phase (Experiments 2 and 3) or during a subsequent extinction phase (Experiment 5). However, an incentive learning treatment in which the rats had the opportunity to merely eat the sucrose pellets after stress produced a marginal increase in responding during the test (collapsed over Experiments 2 and 3). This suggests that exposure to sucrose pellets after stress enabled animals to learn that they are especially reinforcing in that state. This seems plausible in that research indicates that consuming sucrose can alleviate some effects of stress (Ulrich-Lai, 2016). On this view, "renewal" may have occurred in part because the stress state increased the value of sucrose during testing, thus motivating responding during the test. Furthermore, the relatively small effect in the Incentive Learning Group could be attributed to the longer length of time that had passed between sucrose/stress exposures and the test (18 or 19 days) compared with that in the Acquisition Stress Group (7 or 8 days). Balleine (1992) showed that incentive learning treatments have similar effects on behavior when they occur 7 days before a test (compared with 1 hr before), but it is unknown whether such effects would persist over as many as 19 days here.

However, an incentive learning account may have difficulty explaining the effects of extinction stress in Experiment 5. That experiment compared the effects of stress that had been associated with extinction vs acquisition of instrumental food seeking. Despite the lack of a significant renewal effect in the form of higher responding in the absence than the presence of stress in Group Extinction Stress, responding in the absence of stress was significantly higher if stress had been associated with extinction than when it had been associated with acquisition (Group Acquisition Stress). That effect is best explained by a renewal account; after extinction stress, the absence of stress before the test changed the context and released the inhibition that it controlled. While a role for incentive learning cannot be ruled out, these results along with reasons described below suggest that it may be relatively minor.

Another potential problem for an incentive learning account arises from the training parameters used in the current experiments. Although the methods were not designed to distinguish between goal-directed actions and goal-independent habits (e.g., Dickinson, 1985), other research suggests that the amount of instrumental training given here might have favored the development of habit. Importantly, lever pressing that has transitioned to a habit (and is performed independently of the value of its outcome) may not be influenced by earlier incentive learning. Dickinson, Balleine, Watt, Gonzales, and Boakes (1995) reported that the effects of an incentive learning treatment that were present after rats earned 120 pellets on an RI 30-s reinforcement schedule were no longer present after extended training in which they had earned 360 pellets, an amount previously shown to produce habitual behavior. In our laboratory, Thrailkill and Bouton (2015) have also shown the development of habit after rats earned 360 pellets on a VI 30-

s schedule. In the current experiments, rats earned more than 500 pellets on that schedule over the acquisition sessions (e.g., $M = 534.09$ in Experiment 2). Furthermore, exposure to stress or drugs has been shown to accelerate habit formation (Nelson & Killcross, 2006; Schwabe & Wolf, 2009). Thus, after the extensive training and stress exposure involved here, it seems likely that behavior had transitioned to habit; thus, any effect of incentive learning at test would be diminished. These considerations suggest that the contribution of an incentive learning mechanism might be relatively minor in the present experiments.

The results of Experiment 6 may lead some to question the relevance of the present experiments to stress-induced reinstatement for cocaine seeking. But they may depend critically on generalization between the doses of cocaine and stress. Previous experiments, most often using discrimination paradigms in which animals received repeated training with drug and non-drug states, suggest that the stimulus properties of cocaine can in fact generalize to stress. For example, Mantsch and Goeders (1998, 1999) found that rats generalize between systemic cocaine injections and stress produced by 15 min of restraint or 15 min of exposure to intermittent footshock. In their studies, rats received injections of either cocaine (10 mg/kg) or saline before daily training in which one of two levers (R1 or R2) was reinforced with food pellets. The lever that was reinforced in each session was signaled by the type of injection that preceded the session: One lever was reinforced in sessions after cocaine and the opposite lever was reinforced in sessions after saline. Over an average of 29 sessions, rats learned the discrimination and directed their responses to the appropriate lever. Then, in a final generalization test, rats made more than 80% of their responses on the cocaine-appropriate lever when

restraint stress or intermittent footshock was substituted for a drug injection. However, as previously mentioned, the parameters of the administration of cocaine and stress would likely affect any generalization between them. As in Experiment 6 here, Mantsch and Goeders (1999) used a 10 mg/kg dose of cocaine during training. However, the footshock stressor in the current experiments involved two 5-s, 1-mA footshocks, whereas Mantsch and Goeders (1999) tested generalization to cocaine with sixty 0.1-s, 0.6-mA footshocks.

In another interesting series of experiments using the reinstatement paradigm, Mihindou, Vouillac, Koob, and Ahmed (2011), reported results that suggested generalization between a 15 mg/kg dose of cocaine and approximately twenty-two 0.86-mA, 0.5-s footshocks. First, they found that cocaine-induced reinstatement of cocaine seeking was eliminated by injections of cocaine before extinction sessions. Presumably, the presence of cocaine during extinction weakened its association with acquisition, thus preventing renewal in an interoceptive cocaine context. Second, and of most interest to the current experiments, the extinction cocaine treatments also abolished footshock-induced reinstatement. Apparently, certain doses of cocaine may generalize quite well with certain parameters of footshock stress, but apparently did not do so with the parameters used in Experiment 6.

At least two factors may explain the lack of stressor-cocaine generalization in Experiment 6. First, models of associative learning would predict less generalization to a new stressor with the procedures used in Experiment 6 than those used in Experiments 1, 2, 4, and 5 (e.g., McLaren & Mackintosh, 2002). In the earlier experiments, different stressors preceded different acquisition sessions, whereas only a single, repeated cocaine "stimulus" preceded acquisition sessions in Experiment 6. Theoretically, each different

stressor in the earlier experiments would be conceptualized as being comprised of a stimulus element unique to itself as well as an element common to all the stressors (e.g., Ax, Bx, Cx). The result of using multiple stressors would be that the common element (x) would be the best predictor of reinforcement, and would therefore acquire the most associative strength of any stimulus element. Strong conditioning of x would allow strong responding (generalization) to a new stressor that also contained a common element (conceptualized, e.g., as Dx). In contrast, there would be less conditioning of x when acquisition sessions were preceded by a single and identical daily dose of cocaine (e.g., Ax, Ax, Ax). Here, x is not the most predictive stimulus, leading to less conditioning of x, and therefore less responding (generalization) to the new stressor (Dx) that was presented during testing.

A second factor that might have created less generalization in Experiment 6 is that the footshock stressor used in the current experiments, which was the only test stressor used in Experiment 6, always occurred outside of the instrumental learning context. In contrast, footshock-induced reinstatement of drug seeking is typically studied after footshocks are given within the drug-seeking context. In fact, reinstatement has not been observed in experiments when footshocks are delivered outside the instrumental conditioning context (Shalev, Highfield, Yap, and Shaham, 2000). The context-dependency of footshock-induced reinstatement could be analogous to findings that have been described in the reinstatement of extinguished fear conditioning. For example, Bouton and Bolles (1979; see also Bouton, 1984; Bouton & King, 1983) found that presentation of a footshock US in the conditioning context, but not in an alternative one, reinstated extinguished fear. This suggests some similarities between the mechanisms

involved in the reinstatement of fear responding and drug-seeking. However, Carroll (1985) reported that acute food deprivation stress (a manipulation completed outside of the context) did, in fact, reinstate cocaine-seeking behavior. Furthermore, stress-induced reinstatement occurs following injections of a variety of stress-producing drugs administered outside the drug-seeking context (Mantsch et al., 2015). One perhaps notable similarity between interoceptive stimuli produced by hunger and by drugs is that their effects persist for a relatively long period of time. For example, cocaine may have effects that persist throughout the entirety of a conditioning session. Similarly, footshocks given within the context may produce extended conditioned contextual fear. In contrast, removal from a feared context in which footshocks were delivered (as in the current experiments) could have generated different and perhaps more temporary interoceptive stimuli. On this view, responding that had become associated with "stress-like" stimuli produced by cocaine injections may have failed to generalize (in order to renew responding) with temporary stimuli present after a recent stressor.

Together, the current experiments suggest that the stimuli produced by stress, like other interoceptive stimuli, are sufficient to exert control over behavior (e.g., Besheer, Palmatier, Metschke, & Bevins, 2004; Brener & Jones, 1974; Sample, Jones, Hargrave, Jarrad, & Davidson, 2016; Schepers & Bouton, 2017; Schuster & Brady, 1971), thus leaving it susceptible to renew in their presence after extinction. On the other hand, perfecting the ABA paradigm used here to understand its importance to stress-induced drug relapse will require more research (e.g., factorial designs with different "doses" at input and at testing).

The present results may have especially direct relevance for understanding the effects of stress on behavior reinforced by food. Obesity-related illness and death are a substantial financial burden on health care systems in the United States and around the world. As of 2014, an estimated 35% of men and 40% of women in the United States were considered obese. Ubiquitous access to and excessive intake of highly palatable and energy-dense foods has been described as major contributor to the obesity epidemic (Flegal et al., 2016). Moreover, frequent exposure to stress may compound the problem. In 2013, 38% of adults reported that stress caused them to overeat or consume unhealthy foods over the previous month (American Psychological Association, 2013). The current experiments suggest that even though palatable food-seeking behaviors can be suppressed through extinction, if they had been learned in the presence of stress they may be subject to relapse when stress is reencountered. Consistent with an incentive learning hypothesis, "stress-eating" has been suggested to develop in a manner consistent with a self-medication hypothesis. That is, "comfort foods" may be especially valued after stress in that they may alleviate some of its effects (Ulrich-Lai, 2016). However, the present results suggest that learning to perform the behavior itself in the context of stress may also be a critical factor. In other words, relapse may occur when stress becomes linked with the performance of the original instrumental behavior itself (e.g., eating), rather than any specific outcome that it had produced (e.g., comfort food). Recent clinical research suggests that treatments that target stress, such as mindfulness meditation, may be effective in helping to control weight and reduce emotional eating (Katterman, Kleinman, Hood, Nackers, & Corsica, 2014; Mason et al., 2016). The present results suggest that

one reason why stress management strategies are effective is that they might reduce a stress-induced renewal effect.

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