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THE EFFECTS OF ENVIRONMENTAL ENRICHMENT ON ABSTINENCE AND RELAPSE
USING AN ANIMAL CONFLICT MODEL

by

JOSHUA A. PECK

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the
requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

THE EFFECTS OF ENVIRONMENTAL ENRICHMENT ON ABSTINENCE AND RELAPSE
USING AN ANIMAL CONFLICT MODEL

by

Joshua A. Peck

Advisor: Professor Robert Ranaldi

Heroin addiction is a significant health and societal problem for which there is no effective and well-accepted long-term behavioral or pharmacological treatment. Therefore, strategies that prolong heroin abstinence should be the primary focus of heroin treatment research. There is promising evidence that environmental enrichment may indeed support drug abstinence in animals using the reinstatement model of abstinence and relapse. The current studies used an animal conflict model that captures the aversive consequences of drug seeking (as are typical in humans, e.g., arrest, incarceration, job loss, and strained social relationships) to test the effects of environmental enrichment on heroin abstinence, prolonged abstinence, and relapse. In Experiment 1, the procedure consisted of three phases: drug self-administration (Phase 1), electric barrier application (Phase 2) that resulted in abstinence, and the continued assessment of prolonged abstinence (Phase 3). For phase 1, male rats were trained to self-administer intravenous heroin under a fixed-ratio schedule of reinforcement. After self-administration was acquired, environmentally enriched animals (EE) were housed in environmental enrichment boxes, while control rats with no enrichment (NEE) were transferred to standard cages, drug-free in both cases. Each rat continued to reside in their respective EE or NEE housing conditions until the

end of the abstinence and prolonged abstinence phases. During abstinence in phase 2, all rats were introduced to an electric barrier by electrifying the floor area near the levers in order to model the aversive consequences of continued drug seeking in humans. Shock intensities increased over sessions until no active lever responses occurred for three consecutive sessions (abstinence achieved). After the abstinence criterion was met, in phase 3 all rats continued daily abstinence sessions until they resumed responding on the active lever as a measure of prolonged abstinence or until the maximum number of sessions (30) allotted without resumption of responding had been reached. It was found that EE rats achieved abstinence in significantly fewer sessions than NEE rats. Further, EE rats remained abstinent for significantly more sessions than NEE rats. In Experiment 2, the same self-administration (phase 1) and abstinence procedure (phase 2) as in Experiment 1 was employed except that EE rats were housed in their respective enrichment boxes after abstinence was achieved. Further, in phase 3 the ability of non-contingent drug cue presentations to induce relapse was assessed. Each rat was placed in its respective housing conditions for three days of either EE or NEE before being returned to the operant chambers for the relapse test. During the relapse test, the electric barrier was turned on at the shock intensity that previously led to 3 consecutive sessions with no active lever presses for each rat. Further, each rat was exposed to non-contingent presentations of the drug cue previously paired with drug infusions during self-administration training. The cue was presented for 20 s every 5 min during the entire 30-min relapse test session. It was found that EE rats displayed significantly less individual relapse than NEE rats. The current studies' use of the abstinence-conflict model to investigate environmental enrichment as a behavioral strategy to induce drug abstinence will help in the development of effective treatment outcomes for human addicts by bringing together both the positive consequences of abstinent behavior in an enriched

environment with the aversive consequences of drug seeking (e.g., electric barrier). Collectively, these results support the use of environmental enrichment to induce and prolong abstinence, and to protect against relapse in heroin seeking rats.

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This dissertation is dedicated to my grandfather John E. Manning.

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Introduction

Drug addiction is a serious and growing epidemic in the United States and costs Americans upwards of half a trillion dollars each year, when considering the combined medical, economic, criminal, and social impact (www.nida.nih.gov). Every year, abuse of illicit drugs and alcohol contributes to the death of more than 100,000 Americans, while tobacco is linked to an estimated 440,000 deaths per year. This has led to an increasing need for effective drug treatments that will help addicted individuals stop compulsive drug seeking and use.

Consequently, a tremendous amount of resources have been devoted to the development of pharmacotherapies for drug addiction. Pharmacotherapy treatments have been observed to safely manage the acute physical symptoms of withdrawal and can, for some, pave the way for effective long-term addiction treatment. However, medication alone is rarely sufficient to help addicted individuals achieve long-term abstinence (Koob, Lloyd, & Mason, 2009; Kreek, LaForge, & Butelman, 2002). Thus, it is argued that a successful drug-treatment program will be one that focuses on both the neurological mechanisms within the addicted individual and the environmental contingencies that mediate drug use.

For example, research shows that when combining treatment medications, where available, with behavioral therapy it is a more effective way to help sustain long-term abstinence (Carroll et al., 2005; Silverman et al., 1996; Higgins et al., 2005; Haug, Svikis, & Diclemente, 2004). Further, behavioral treatment approaches for drug addiction provide incentives to remain abstinent, and teach important life skills that will help support abstinence in the presence of stressors or other environmental cues that may trigger intense craving for drugs. Increasing our understanding about which behavioral factors determine successful long-term abstinence will lead to more efficient treatment strategies in drug addiction.

One potential treatment strategy that could help sustain long-term abstinence is environmental enrichment. Environmental Enrichment (EE) can be defined as the non-contingent delivery of alternative non-drug rewards such as food, social interaction, novelty objects and voluntary physical activity either in the presence of drug, that is concurrent or in the absence of drug, that is non-concurrent (Carroll 1993; Zlebnik et al. 2010; Chauvet et al. 2009; Thiel et al. 2009). Access to nondrug alternatives can impede or prevent acquisition of and decrease drug-maintained responding (Carroll et al. 1989; Lynch et al. 2010). For example, animal studies have shown that exercise reduces cocaine's reinforcing effects when concurrently available with the drug (Smith et al. 2008; Zlebnik et al. 2012) as well as facilitating extinction and attenuating relapse (Cosgrove et al. 2002; Grimm et al. 2008; Zlebnik et al. 2010). Further, the removal of such non-drug alternatives may also result in increased drug taking (Podlesnik et al. 2006).

Typically, in animals, the effect of environmental enrichment is demonstrated by presenting a choice concurrently between drug and other types of rewards (e.g. food, social interaction, and exercise) where the organism prefers the alternative reward(s) over drug (Carroll, 1993; Carroll et al., 1989; Panksepp et al. 1997; Lett et al. 2000). Further, environmental enrichment is typically used during periods of abstinence so that the organism can learn that another choice is concurrently available besides relapse (Cosgrove et al., 2002; Mattson et al., 2001; Rodefer & Carroll, 1996; Bevins & Besheer 2005).

The use of non-contingent procedures that deliver alternative rewards while the drug remains available (concurrent), have also shown to be effective in supporting abstinence in humans (Solinas et al., 2010). For example, it has been shown that human drug addicts that participate in non-drug pleasurable activities have remained abstinent longer than those who do

not engage in such activities (Schottenfeld et al., 2000; Schnabel, 2009; Setlow, 2008), suggesting that environmental enrichment could support human drug abstinence. Further, in humans, researchers have suggested a link between the removal of alternative, reinforcing events and increases in drug intake or instances of relapse after periods of abstinence. For example, Falba et al. (2005) examined data from a Health and Retirement study in order to explore the relationship between involuntary job loss and smoking intensity as well as relapse in abstinent smokers. Falba et al. (2005) found that involuntary job loss contributed significantly to elevated levels of smoking in individuals who already smoked. Furthermore, risk of relapse doubled after job loss in ex-smokers.

Research has also demonstrated that environmental enrichment provided non-concurrently with the drug attenuates the probability of drug seeking. For example, Stairs, Klein and Bardo (2006) found that housing rats with other rats and novel objects enhanced extinction of amphetamine-maintained behavior and also increased the reinstatement threshold for priming doses of amphetamine (i.e., larger doses were required to reinstate drug seeking in rats housed in the enriched conditions). Chauvet et al. (2009) and Thiel et al. (2009) found that enriched housing conditions reduced responding in extinction and attenuated cue-induced relapse to cocaine. Further, environmental enrichment provides stimulation that has been shown to disrupt neural circuits in areas involved in drug seeking (Chauvet et al., 2009). The common feature the previous studies all demonstrate is that when stimulation or reward is derived from a source other than the drug itself (enrichment), there is a reduction in the reinforcing effects of the drug(s), thereby sustaining abstinence.

The most commonly used animal model to study the effects of environmental enrichment on abstinence and relapse is the reinstatement model. In this model, laboratory animals are

trained to self-administer drug accompanied by a discrete stimulus (e.g., tone, light), usually by pressing a lever. Then, after extinction of the drug-taking response by withholding the drug reinforcer in the absence of the discrete stimulus, nonreinforced reinstatement of responding is induced by either acute exposure to the discrete cue, drug priming, contextual cues, or stress (De Wit & Stewart, 1983; Meil & See, 1996; Crombag et al., 2008; Shaham & Stewart, 1995; Feltenstein & See, 2008). For example, studies in rats have shown that after extinction of cocaine or heroin-reinforced lever pressing, lever pressing is reliably reinstated by acute injections of the drug (drug priming) or by presenting cues (discrete, discriminative or contextual) that were associated with the drug (Crombag et al., 2008; Feltenstein & See, 2008). Given that there is promising evidence that environmental enrichment may indeed support drug abstinence in animals using the reinstatement model of abstinence and relapse (Cosgrove et al., 2002; Chauvet et al., 2009; Thiel et al., 2009), it is important that this possibility be explored using other animal models of abstinence and relapse. For example, one should test an animal model that captures the aversive consequences of drug seeking to test the effects of environmental enrichment on abstinence and relapse.

In humans, drug abstinence often results from the aversive consequences that coincide with drug seeking (Epstein & Preston 2003; Cooper et al., 2007). For example, some of the aversive consequences that may occur while drug-seeking are hiding from law enforcement, family and friends, loss of employment, and securing the funds for obtaining the drug. Therefore, human drug-seeking episodes during abstinence often involve a ‘conflict’ situation, which usually involves a choice between experiencing the positive effects of the drug and the potential for aversive consequences of drug seeking (Cooper et al., 2007). Therefore, the abstinence ‘conflict’ model, in which aversive consequences occur during drug seeking, is useful

in further characterizing the different behavioral contingencies involved in human drug abstinence.

Cooper et al. (2007) developed a conflict-based abstinence/relapse model wherein aversive consequences occur during cocaine seeking. This model was based on an earlier model that used the 'Columbia Obstruction Box' method, which assessed rats' motivation for rewards under different deprivation conditions, while in the presence of an electric barrier (Jenkins et al., 1926). In the Cooper et al. (2007) study, rats were trained to lever press for cocaine infusions paired with a discrete light stimulus. An electric barrier was then introduced by electrifying the floor area near the levers, while the drug continued to be available; thus, the animals could continue to self-administer the drug but doing so necessitated enduring electric shock. Then the researchers increased the electric shock intensities daily until the rats stopped emitting the drug-taking response (i.e., lever pressing), an outcome operationally defining abstinence. In a relapse test with the electric barrier remaining activated, the effect of non-contingent cocaine cue presentations led to the resumption of drug seeking (relapse).

Recently, we (Peck et al., 2013) used a similar abstinence/relapse conflict model with heroin self-administration. We found that abstinence was achieved for all heroin-seeking rats by increasing the electric shock intensity. Further, during the relapse test while shock was present, non-contingent heroin cue presentations led to the resumption of drug responding for all heroin seeking rats despite the presence of the electric barrier. Our results, as well as previous research (Cooper et al., 2007, Barnea-Ygael et al., 2012), suggest that the abstinence/relapse conflict model may represent important features of the human abstinence condition wherein aversive consequences are present during drug seeking. Further, the model demonstrates how the aversive consequences of drug use play an integral part in the initiation and maintenance of drug

abstinence and the elicitation of relapse. Therefore, using the abstinence conflict model to investigate behavioral treatments such as environmental enrichment could lead to more effective treatment outcomes for human addicts by bringing together both the positive consequences of abstinent behavior (e.g., enrichment) with the aversive consequences of drug seeking (e.g., electric barrier).

The purpose of the current studies was to investigate the effects of environmental enrichment on heroin-seeking in both abstinence and relapse using an animal conflict model. In Experiment 1, we investigated the effects of environmental enrichment on achieving abstinence and maintaining abstinence. Male rats were trained to self-administer intravenous heroin under a fixed ratio schedule of reinforcement in Phase 1. Then after self-administration was acquired (operationally defined as 15 sessions of stable drug intake), enriched animals (EE) were housed in environmental enrichment boxes (large bins with running wheels, tubes, and various toys) while non-enriched rats (NEE) remained in standard cages (Phase 2). Each rat continued to reside in its respective EE or NEE housing condition until the end of subsequent abstinence (Phase 2) and prolonged abstinence (Phase 3). During abstinence in Phase 2, all rats were introduced to an electric barrier by electrifying the floor area near the levers in order to model the aversive consequences of continued drug seeking. Shock intensities were increased over sessions until no active lever responses occurred for three consecutive sessions (abstinence achieved). After the abstinence criterion was met, in Phase 3 all rats continued daily abstinence sessions, with the shock still present, until they resumed responding on the active lever as a measure of prolonged abstinence. It was hypothesized that EE rats would achieve abstinence in significantly fewer sessions than NEE rats. Further, it was hypothesized that EE rats would remain abstinent for significantly more sessions than would NEE rats.

In Experiment 2, the same self-administration training (Phase 1) and abstinence procedure (Phase 2) as described above was employed except that EE rats were housed in their respective enrichment boxes only after abstinence was achieved. Further, in Phase 3, the ability of non-contingent drug cue presentations to induce relapse was assessed. Each rat was placed in its respective housing condition for 72 hrs of either EE or NEE before being returned to the operant chambers for the relapse test (Phase 3). During the relapse test, the electric barrier was turned on at the shock intensity that previously led to 3 consecutive sessions with no active lever presses for that rat. Further, each rat was exposed to non-contingent presentations of the drug cue previously paired with drug infusions during self-administration training in Phase 1. It was hypothesized that EE rats would display significantly less relapse than would NEE rats. Collectively, our expected results will show that the use of environmental enrichment is effective in inducing and prolonging abstinence and protecting against relapse in heroin seeking rats.

Experiment 1

Although pharmacological treatments can safely manage the acute physical symptoms of withdrawal and can, for some, pave the way for effective long-term addiction treatment, medication alone is rarely sufficient to help addicted individuals achieve long-term abstinence. Moreover, tremendous resources have been devoted to the development of pharmacotherapies for drug addiction, with relatively little or no long-term success reported (Kreek et al., 2002; Koob et al., 2009). Thus, we argue that a successful drug addiction treatment program likely will be one that focuses on both the neural mechanisms within the addicted individual, and the environmental contingencies that mediate drug use (Siegel, 1975; Robinson & Berridge, 1993).

One potential environmental strategy that could help sustain long-term drug abstinence is environmental enrichment. In animal models, environmental enrichment provided non-concurrently with drug is typically used during periods of abstinence so that EE rats respond significantly less for drug because the drug is no longer as reinforcing as the enriched or novel context from where they were just removed (Reynolds, 1961; Grimm et al., 2013). For example, research has demonstrated that environmental enrichment provided non-concurrently with the drug attenuates the probability of drug taking (Lenoir & Ahmed 2007; Ahmed 2005).

Therefore, one aim of Experiment 1 was to test whether or not non-concurrent (EE administered in a separate context than the drug context) delivery of environmental enrichment would lead to heroin seeking rats achieving abstinence in significantly fewer sessions when compared to controls using an animal conflict abstinence model. Another aim was to examine whether or not EE rats would remain abstinent for significantly more sessions (prolonged abstinence) than NEE rats. If these results were to be observed, then this would lend more support for the use of environmental enrichment to facilitate and prolong drug abstinence.

Method

Subjects

Subjects consisted of sixteen male Long Evans rats weighing between 350 and 400 g at the time of surgery. Each rat was individually housed under a reversed 12 hour light:12 hour dark cycle (lights on at 1900h). All rats had access to food (Lab Diet rat chow) and water at all times except when in operant conditioning chambers.

Catheterization Surgery

Each rat was anesthetized using sodium pentobarbital (65 mg/ml, administered intraperitoneally). An incision was made in the neck area and the jugular vein was isolated and opened. A silastic catheter (Dow Corning, Midland, MI) was inserted into the vein so that the tip penetrates to the position just before the right atrium. The other end of the catheter was fed subcutaneously to the back of the neck and exited through an opening on the scalp. A 22-gauge stainless steel tube was inserted into the catheter and secured to the skull by dental acrylic and four stainless steel screws. This tube served as a connector between the catheter and the drug infusion line. The catheter was flushed with heparin solution (200 U/ml) immediately after surgery and every day thereafter.

Apparatus

The experiments were performed in operant conditioning chambers controlled by a Med Associates (Georgia, VT) interface and computer program. Each chamber measures 26 x 26 x 30 cm. Three walls are made of aluminum and the front and top walls are made of transparent plastic. The top wall serves as the door. The floor consists of stainless steel rods. The back wall of each chamber is equipped with two levers positioned 10 cm above the floor. One lever is designated as active and the other as inactive. Each chamber has a white cue light 3 cm above

each lever. Polyethylene tubing was connected to each animal's catheter assembly, through a fluid swivel, to a drug-filled syringe in a pump (Razel, 3.33 rpm). The electric barrier was provided by constant-current aversive stimulators (Model ENV-414; Med Associates) that are connected to two thirds of the floor adjacent to the levers. The stimulators produced a constant current, and when the rat touches any two of the rods it closes the electrical circuit, resulting in the delivery of a shock. The remaining one third of the chamber floor with no current served as a no-shock zone.

Materials

Drug

Heroin (a gift from the National Institute on Drug Abuse, Bethesda, MD) was dissolved in 0.9 % saline to achieve a dose of 0.05 mg/kg.

Procedure

The procedure consists of three phases: drug self-administration, electric barrier application that resulted in abstinence, and the continued assessment of prolonged abstinence. After self-administration was acquired (operationally defined as 15 sessions of stable drug intake), enriched animals (EE) were housed in environmental enrichment boxes (large bins with running wheels, tubes, and various toys) while control rats (NEE) remained in standard cages. Each rat continued to reside in its respective EE or NEE housing condition until the end of subsequent abstinence and prolonged abstinence phases (see Table 1).

Heroin Self-Administration (Phase 1)

Three days after surgery, each animal began self-administration training in operant conditioning chambers in daily 3-h sessions. All self-administration sessions were conducted during the dark phase of the light:dark cycle. Each press on the active lever illuminated the cue

light above it for 20 s and activated the pump delivering an injection of 0.05 mg/kg of heroin in a 0.125 ml volume of saline over 4.5 s. A time-out of 20 s began at the start of each infusion. Presses on the inactive lever produced no consequences for all three phases. Each rat was trained to self-administer drug on a fixed-ratio one (FR1) schedule of reinforcement until attainment of 15 consecutive stable sessions. Stable responding was defined as follows: 15 consecutive sessions where the total number of rewards obtained per session is greater than 12 and where the total number of rewards per session for the last three consecutive sessions is within $\pm 10\%$ of the mean for these three sessions.

Environmental Enrichment

After stable FR1 responding was established for each rat, they were then individually assigned to either the environmental enrichment (EE) or no-environmental enrichment (NEE) group. There was 48 hrs in which rats remain in their respective housing conditions before the electric barrier phase began. Enriched animals (EE) were housed in environmental enrichment cages measuring 36 x 66 x 41 cm, while control rats (NEE) remained in standard cages. Each enrichment cage was equipped with beta chip bedding, a running wheel, and a 10-cm diameter tunnel, and two additional objects that were rotated daily, including a jingly ball, mirrored bowl, toy car and dog chew. Further, all toys were rotated daily across each environmental enrichment cage. The components of the enrichment cage are similar to those used in other enrichment studies that have shown effects of the treatment (Green, Gehrke, & Bardo, 2002; Chauvet et al. 2009; Ranaldi et al. 2011). Each rat continued to reside in their respective EE or NEE housing conditions until the end of both the abstinence and prolonged abstinence sessions.

Electric Barrier (Phase 2)

Each daily session began with the illumination of the house light. Then rats were placed in the no-shock zones with the electric barrier already activated and 5 min later the levers were inserted and the self-administration began. On the first session, the current was set to 0.25 mA, and was increased after sessions when rats emitted one or more active lever presses by an increment of 0.04 mA but did not increase after sessions where rats emitted no active lever presses. This procedure continued until there were no active lever presses during the 30-min session for three consecutive daily sessions. During the electric barrier phase drug was available under a FR2 20-s timeout reinforcement schedule for 30 min/day. This schedule of reinforcement has been used to establish abstinence (no presses on the active lever) (Cooper et al. 2007; Barnea-Ygael et al. 2012; Peck et al., 2013). Further, the electric barrier current did not exceed 1.00 mA for any individual rat. If a rat reached this maximum current level, they remained at that level until the criteria for abstinence was met.

Prolonged Abstinence (Phase 3)

After the abstinence criterion was met (3 sessions of no active lever press), all rats remained in their respective EE or NEE housing conditions and continued daily abstinence sessions until they resumed responding on the active lever or 30 consecutive sessions had occurred without active lever responding as a measure of prolonged abstinence.

Tail Flick Assay

Immediately before the start of the electric barrier phase and again, immediately after the completion of the prolonged abstinence phase each animal was tested for pain sensitivity by using a tail-flick latency measure. A tail-flick analgesiometer (IITC) provided a radiant heat source that was mounted 8 cm above a photocell upon which the rat's tail was placed. Radiant heat was applied 3–9 cm proximal to the tip of the rat's tail; removal of the tail activated the

photocell and determined the latency (0.01 s accuracy). The thermal intensity of the radiant heat source was set so that the average baseline tail-flick latencies would be between 2 and 4.0 s. Each session consisted of three latency determinations at different points on the tail at 10-s intervals. To avoid tissue damage, trials were automatically terminated if a response did not occur within 10 s.

Statistical Analyses

The dependent variables consisted of the total number of sessions to reach the abstinence criteria, the total number of active lever responses during abstinence and prolonged abstinence, and the number of sessions that rats remain abstinent for both EE and NEE groups. Two separate independent sample two-tailed t-tests analyses were conducted. One test compared the number of sessions to reach the abstinence criteria during the electric barrier condition for both EE and NEE groups. The second test, compared the number of sessions that each group remained abstinent. A separate two-way ANOVA with abstinence and prolonged abstinence conditions as one factor and EE and NEE (between groups) as the other factor was conducted on the number of active lever presses. A significant two-way interaction was further analyzed by tests of simple main effects.

A separate two-way ANOVA with abstinence and prolonged abstinence conditions as one factor and EE and NEE (between groups) as the other factor was conducted on the tail-flick latency data. A significant two-way interaction was further analyzed by tests of simple main effects.

Results

Electric barrier and abstinence threshold

During the electric barrier Phase 2, the final shock intensities for individual EE rats that led to three sessions of no active lever presses ranged from 0.25 to 0.49 mA with a mean of 0.40 ± 0.03 mA (Figure 1). Further, the number of sessions that led to abstinence for individual EE rats ranged from 3 to 10 sessions (Figure 1). The final shock intensities for individual NEE rats that led to abstinence ranged from 0.29 to 0.89 mA with a mean of 0.61 ± 0.06 mA (Figure 1). In contrast, the number of sessions that led to abstinence for individual NEE heroin rats ranged from 4 to 23 sessions (Figure 1). In summary, the rats in the EE condition appeared to achieve the abstinence criteria in fewer sessions than the rats in the NEE condition (Figure 1). A two-tailed t-test on these data revealed a significant difference between the two groups ($t(14) = 5.37$; $p < .05$).

Prolonged Abstinence

During the prolonged abstinence Phase 3, the number of sessions that individual EE rats remained abstinent (no active lever presses) ranged from 3 to 30 (Figure 2). In contrast, the number of sessions that individual NEE rats remained abstinent ranged from 1 to 6 (Figure 2). Rats in the EE condition remained abstinent for longer than rats in the NEE condition (Figure 2). This observation was supported by a two-tailed t-test revealing a significant difference between the groups ($t(14) = 2.29$; $p < .05$). Further, signaling the completion of prolonged abstinence, rats in the EE and NEE conditions produced similar active and inactive lever presses when resumption of responding occurred (Figure 3). A two-way ANOVA with group (between-subjects) and lever (repeated measures) comparing prolonged abstinence active and inactive lever presses of resumed responding between the two groups revealed no significant group [F (1,

28) = 1.69, $p > .05$], lever [$F(1, 28) = 2.46, p > .05$] or group by lever interactions [$F(1, 28) = 2.19, p > .05$]. Of consideration was active lever response rate based on the time from the first response to the end of the last 30-min prolonged abstinence session for both groups. The differences between EE and NEE individual response latencies from the first active lever response to the end of the prolonged abstinence session per 5-min increments was not found to be significantly different with a mean of 11.25 ± 1.83 min and 10.00 ± 1.89 min respectively ($t(14) = 0.64; p > .05$).

Tail Flick

EE and NEE rats showed similar tail flick latencies at both pre and post-prolonged abstinence phases. Further, for both groups, the tail flick latencies did not change between pre and post-prolonged abstinence phases (Figure 4). A two-way ANOVA with group (between-subjects) and pre-abstinence and post-prolonged abstinence conditions comparing tail-flick latency between the two groups revealed no significant group [$F(1, 31) = 0.28, p > .05$], pre and post-prolonged abstinence conditions [$F(1, 31) = 0.09, p > .05$] and group by pre and post-prolonged abstinence condition interaction [$F(1, 31) = 0.75, p > .05$].

Discussion

In the present study, we used an animal conflict model of abstinence and relapse that has some important implications for human drug addiction; abstinence occur while the drug is readily available, and drug seeking may occur despite the aversive consequences for its pursuit and consumption. In Experiment 1, abstinence was achieved for all rats by increasing the electric shock intensities daily until the rats stop responding for heroin for three consecutive sessions. Further, we found that EE rats achieved abstinence in significantly fewer sessions than NEE rats. Also, under the same conditions, EE rats remained abstinent for significantly more sessions than NEE rats. The results suggest that the non-contingent and non-concurrent availability of alternative non-drug rewards in an enriched context other than the drug-taking context can reduce drug seeking within the drug context.

From a behavior analytical perspective, the introduction of rewarding stimulation that is experienced in the enriched environment might reduce the significance (or effectiveness) of the drug or drug-related stimuli through a contrast mechanism. Behavioral contrast refers to a change in the rate of reinforcement on one component of a multiple schedule produces an opposite change in the rate of response on another component creating an inverse relationship (Reynolds, 1961; Williams, 2002). For example, a change to a high reinforcement rate in one component typically results in a lower response rate in the other component even if reinforcement rate in that component remains unchanged. That is, changes in response rate in the other component occur despite no direct changes to the contingencies controlling that response. A relevant example for the current experiment is when environmental enrichment studies provide concurrent access to alternative reinforcement (e.g., wheel running) during either

acquisition or extinction of the drug taking response leading to a decrease in drug operant responding (Cosgrove et al., 2002; Grimm et al., 2008; Zlebnik et al., 2010).

In the present study, alternative reinforcement occurred in a context other than the operant conditioning chamber (non-concurrent) and led to a decrease in operant responding for drug, suggesting that EE effects may be transferable. Previous research that used non-concurrent environmental enrichment to attenuate operant responding in a different context has yielded similar results. For example, Grimm et al. (2013) found that brief exposure to enriched environments non-concurrently with sucrose, reduced sucrose cue-reactivity and consumption in self-administering rats after 1 or 30 days of forced abstinence compared to control rats. The authors noted that exposure to enrichment may have created a contrast effect such that environmentally enriched rats responded significantly less for the sucrose-paired cue because it was no longer as reinforcing as the enriched context from where they were just removed (Reynolds 1961; Grimm et al. 2013).

Another explanation for why EE rats abstained earlier and remained abstinent longer than NEE rats is environmental enrichment's possible reduction of stress. Solinas and colleagues (2010) have suggested that EE's reducing effects on drug seeking or taking may be due to the anti-stress effects of EE. Anti-stress effects have been examined in recent studies of drug self-administration in rats. For example, decreased plasma levels of corticosterone (stress hormone) were found after environmental enrichment exposure in rats with a history of cocaine self-administration when compared to controls (Thiel et al. 2009). In general, stress has been shown to increase responding for drugs of abuse, including cocaine, amphetamine, and heroin (Goeders, 2002; Lu et al., 2003; Marinelli & Piazza, 2002). Further, exposure to stress is a potent inducer of reinstatement and relapse in animals and humans, respectively (Shaham et al., 2000; Stewart,

2000). In contrast, environmental enrichment has been shown to reduce stress and protect against the development of drug-seeking and drug-taking behaviors (Green et al., 2002; Solinas et al., 2008; Solinas et al., 2010). Therefore, in the present study, EE rats may have experienced lower stress levels throughout the abstinence and prolonged abstinence phases that led to a decrease in drug seeking when compared to the NEE rats.

During the abstinence and prolonged abstinence phases, a conflict situation was presented which involved a choice between pursuing the path that leads to experiencing the positive effects of drug(s) accompanied with aversive consequences and the path that avoids the aversive consequences of drug seeking (Epstein & Preston 2003; Cooper et al., 2007). Further, it is plausible that the conflict situation during abstinence can also be viewed as a stressful situation. That is, it is entirely likely that drug-seeking rats experienced some level of stress during abstinence when being presented with a choice to pursue drug that is accompanied with shock or remain abstinent and not experience the drug's rewarding effects. If so, it follows that while in abstinence, NEE rats would have experienced higher levels of stress than EE rats due to the anti-stress effects of EE. Therefore, the higher stress levels experienced by NEE rats may have led to an increase in drug seeking for heroin when compared to EE rats during abstinence and an earlier onset of resumed responding during prolonged abstinence. It is important to note, that there was no significant difference in tail-flick latencies between EE and NEE rats as a measure of pain sensitivity. Thus, this suggests that differences in abstinence and prolonged abstinence performances cannot be explained by the possibility that EE rats were more hyperalgesic than NEE rats when shock was experienced.

In summary, the Experiment 1 results suggest that environmental enrichment as a

behavioral strategy played an integral part in achieving and maintaining abstinence. Moreover, the present study's results support previous research findings using non-concurrent enrichment by demonstrating that when stimulation or reward is derived from a source other than the drug itself (enrichment), there is a reduction in the reinforcing effects of the drug, thereby supporting abstinence. However, we are still speculative regarding the precise mechanism(s) of the EE effects observed in this study. Yet, the non-contingent delivery of alternative reinforcement that occurred in one context (non-concurrent) led to a decrease in operant responding for drug upon returning back to the drug context, suggesting that EE effects may be transferable.

Experiment 2

Research has demonstrated that environmental enrichment provided non-concurrently with drug is not only a behavioral treatment strategy to facilitate and maintain drug abstinence in animals but also can protect against relapse in the presence of discrete drug associative stimuli (Zlebnik et al., 2010; Chauvet et al., 2009; Thiel et al., 2009; Cosgrove et al., 2002). For example, Chauvet et al. (2009) and Thiel et al. (2009) found that non-concurrent environmental enrichment reduced responding not only in extinction but also in reinstatement tests where reinstatement was induced by discrete cocaine cue presentations. Similarly, Ranaldi et al. (2011) found that non-concurrent environmental enrichment attenuated responding not only in extinction but also in a drug-context renewal test compared to non-enriched subjects. Further, animal studies have shown that exercise reduces cocaine's reinforcing effects when concurrently available with drug that leads to the attenuation of relapse in the presence of discrete drug cue presentations (Cosgrove et al., 2002; Grimm et al., 2008; Zlebnik et al., 2010).

Therefore, the aim of Experiment 2 was to test whether or not the non-concurrent delivery of environmental enrichment would lead to heroin seeking rats displaying significantly less relapse than NEE rats using an animal conflict model. To examine this, each rat was exposed to non-contingent presentations of the drug cue previously paired with drug infusions during self-administration training. Collectively, if EE rats exhibit less individual relapse than NEE rats this would support the use of environmental enrichment as a behavioral treatment strategy not only for supporting abstinence (Experiment 1) but also for protecting against relapse in heroin seeking rats when exposed to drug-related cues. Obviously, this would have significant implications for the treatment of drug addiction in humans.

Method

Procedure

The drug self-administration (Phase 1) and electric barrier (Phase 2) for Experiment 2 were identical to Experiment 1 with the exception that there were no prolonged abstinence sessions. After rats met the abstinence criterion of three sessions with no active lever presses, they moved on to a relapse challenge test (Phase 3) during which rats were exposed to presentations of drug-associated stimuli.

Relapse Test

After rats reached the abstinence criterion of three sessions with no active lever presses, all rats were assigned to either an environmental enrichment (EE) or no-environmental enrichment (NEE) group. The rats remained in their respective housing conditions for 72 h before the relapse test was administered. Then, individual rats for both groups encountered one 30-min relapse test. Five min before the start of each relapse test, each rat was connected to the infusion line and placed in the no-shock zone of the chamber with the electric barrier turned on at the shock intensity that previously led to 3 sessions with no active lever presses for that rat.

The daily session began with the illumination of the house light. During the relapse test each rat was exposed to non-contingent presentations of the drug cue previously paired with drug infusions during training. The cue was presented for 20 s every 5 min during the entire 30-min relapse test session. Presses on the active lever led to saline infusions instead of drug and no cue. Presses on the active and inactive levers were recorded and analyzed for the EE and NEE groups.

Tail Flick Assay

The same procedure used in Experiment 1 to test for pain sensitivity by using a tail-flick latency measure was carried out in Experiment 2. However, it was administered immediately

after the completion of abstinence and before entering the EE or NEE conditions and then again, immediately after the individual relapse tests.

Statistical analyses

The dependent variables consisted of total active and inactive lever presses during the test session. Two separate single sample one-tailed t-test analyses were conducted, one for each EE and NEE group that compared the responses during the relapse test (when animals received non-contingent presentations of the cue) to the response criterion reached during the electric barrier condition (zero). This particular analysis was chosen because the population mean of active lever presses in the electric barrier condition was already known. In addition, a two-way ANOVA with EE and NEE (between-subjects) and lever (repeated measures) was conducted comparing relapse test presses between EE and NEE groups. Interactions were further analyzed by tests of simple main effects. Further, a one-way ANOVA was conducted comparing each group's final electric shock intensities. This analysis was used to ensure group equivalence before the administration of the relapse tests. A separate two-way ANOVA with post-abstinence and post-relapse as levels of one factor and EE and NEE (between groups) as levels of the other factor was conducted on the tail-flick latency data.

Results

Electric barrier and abstinence threshold

During the electric barrier phase, the final shock intensities for individual rats that led to 3 sessions of no active lever presses for the EE group ranged from 0.29 to 0.93 mA (Figure 5). The final shock intensities for individual rats that led to abstinence in the NEE group ranged from 0.25 to 0.69 mA (Figure 5). Further, a one-way ANOVA failed to reveal a significant difference between groups [$F(1, 15) = 1.41, p > .05$].

Relapse Tests

Five out of eight heroin animals in the NEE group resumed lever pressing during the relapse test, when they were exposed to non-contingent presentations of the heroin cue (Figure 6). A single sample two-tailed t-test revealed a significant difference between active lever presses during the relapse test and presses during the last session of the abstinence phase for the NEE group ($t(7) = 2.57; p < .05$) (Figure 6). However, in the EE group only one out of eight animals resumed lever pressing during the relapse test (Figure 6). Also, a single sample two-tailed t-test revealed no significant difference between active lever presses during the relapse test and presses during the last session of the abstinence phase for the EE group ($t(7) = 1.00; p > .05$) (Figure 6).

Further, a two-way ANOVA with EE and NEE groups (between-subjects) and lever (repeated measures) comparing number of presses between the groups during the relapse test revealed significant group [$F(1, 28) = 7.28, p < .05$], lever [$F(1, 28) = 5.65, p < .05$] and group by lever interaction [$F(1, 28) = 6.77, p < .05$] effects (Figure 6). Tests of simple effects of lever (active and inactive) at each level of group revealed significantly more active than inactive lever presses during the relapse phase for the NEE group [$F(1, 28) = 8.12, p < .05$] but no significant

difference between active and inactive lever presses during the relapse phase for the EE group [$F(1, 28) = 0.27, p > .05$].

Tail Flick

Tail-flick latencies for individual EE heroin rats for post-abstinence ranged from 2.89 to 5.10 s and 3.53 to 7.14 for post-relapse (Figure 7). Further, tail-flick latencies for individual NEE heroin rats for post-abstinence ranged from 3.21 s to 5.46 and 3.67 to 6.08 for post-relapse (Figure 7). A two-way ANOVA with group (between-subjects) and post-abstinence and post-relapse conditions comparing tail-flick latency between the two groups revealed no significant group [$F(1, 31) = 1.99, p > 0.05$], post-abstinence and post-relapse conditions [$F(1, 31) = 0.04, p > .05$] and group by condition interaction [$F(1, 32) = 0.08, p > .05$].

Discussion

In Experiment 2, abstinence was achieved for all rats by increasing the electric shock intensities daily until the rats stopped responding for heroin for three consecutive sessions. During the relapse test, non-contingent heroin cue presentations led to the resumption of active lever responding for 5 out of 8 NEE rats, while non-contingent heroin cue presentations led to only one of the 8 EE rats resuming active lever responding. Further, for the NEE group, non-contingent heroin cue presentations led to large individual differences in rate of active lever responding in the cue-induced relapse test, which ranged from 0 to 11 total active lever responses. The results suggest that environmental enrichment delivered non-concurrently can attenuate cue-induced heroin seeking in rats.

The present results are in accord with other studies showing that the delivery of non-concurrent environmental enrichment can lead to a decrease in cue-induced reinstatement for both drug and sucrose seeking in rats (Chauvet et al., 2009; Thiel et al., 2009; Grimm et al., 2013). However, almost all studies with enrichment manipulations have animals enriched for several weeks prior to drug cue-induced testing. Interestingly, in the present study, our finding of reduced heroin seeking in rats was observed after only 72 hrs of environmental enrichment. The observed large decrease in cue-induced responding for EE rats when compared to NEE controls suggest that acute exposure of EE (72 hrs) may be as effective in protecting against relapse as chronic exposure to EE (several weeks).

The possible explanations (anti-stress effects of EE or behavioral contrast) given previously for why environmental enrichment can induce abstinence earlier and maintain abstinence longer when compared to controls may also be relevant here in explaining why there were significant differences in relapse propensities between EE and NEE rats. However, we

offer a few other possible behavioral explanations for the differences in individual cue-induced relapse observed between EE and NEE heroin seeking rats. One is based on positive reinforcement, perhaps indicating a difference in the role in relapse of heroin-associated discrete cues between EE and NEE rats, and another explanation is that environmental enrichment may blunt the effects of static cues (e.g., drug context) that are associated with the drug.

The greater individual relapse in NEE versus EE heroin trained rats may rest on the possibility of differential incentive motivational effects between EE and NEE rats and heroin-associated discrete stimuli. It has been suggested (Robinson & Berridge, 1993) that drug-associated stimuli acquire incentive salience; that is, drug-predictive stimuli acquire increased motivational value. Moreover, Robinson and Berridge (1993) argue that increased responsiveness to drug-associated cues following repeated drug exposure underlies compulsive drug use and relapse. Further, it is possible that environmental enrichment blunted the approach-eliciting state induced by heroin-associated stimuli (Solinas et al., 2010; Stairs & Bardo, 2009). Perhaps, in this study, the heroin cue had higher incentive motivational effects for the NEE group than the EE group, leading to greater incentive-motivation for NEE rats and, therefore, the observed greater likelihood of resumption of lever pressing during the relapse tests.

As in Experiment 1, the present study provided alternative reinforcement in a context other than the operant conditioning chamber (non-concurrent) that led to a decrease in operant responding during cue-induced relapse tests for EE rats, suggesting that EE effects may indeed be transferable. Further, EE reduced responding during relapse tests supports the notion that environmental enrichment can decrease drug seeking, at least as elicited by phasic, discrete drug-associated cues (Chauvet et al., 2009; Thiel et al., 2009). However, in the present study, another possible explanation for lower individual relapse in EE heroin seeking rats is the blunted effects

enrichment may have had on the non-phasic, long duration cues, such as the heroin-taking context.

For example, Ranaldi et al. (2011) examined the effects of non-concurrent environmental enrichment on cocaine context renewal of responding in rats. They found that during a drug-context renewal test, enriched animals pressed significantly less on the drug-associated lever than did non-enriched animals. Ranaldi et al. (2011) put forth an explanation why environmental enrichment could potentially protect against renewal of drug seeking when rats are placed back in the drug-associated context. Environmental stimuli and contexts that are paired with drug use often produce reinforcing and motivational effects to continue using the drug (Ehrman et al., 1992; Robinson & Berridge 1993; Ranaldi & Roberts 1996; Conklin & Tiffany 2002). Further, non-concurrent or concurrent environmental enrichment may decrease the reinforcing effects of drug associated contexts thereby leading to a decrease in drug use (Conklin & Tiffany, 2002; Crombag & Shaham, 2002; Chauvet et al., 2009). Similarly, in the present study, the delivery of non-concurrent environmental enrichment after abstinence was effective in protecting against relapse upon returning back to the drug context and in the presence of environmental stimuli that were previously paired with heroin use. Therefore, as in previous studies, environmental enrichment may have decreased the reinforcing effects of the heroin associated context and discrete stimuli that led to a decrease in heroin seeking for EE rats.

In summary, the results of Experiment 2 suggest that environmental enrichment played a protective role against individual relapse in the presence of heroin-associated cues. Further, as in Experiment 1, the non-contingent delivery of alternative reinforcement that occurred in one context (non-concurrent) led to a decrease in operant responding upon returning back to the drug context providing more evidence that EE effects may indeed be transferable.

General Discussion

The results of Experiment 1 and 2 suggest that the use of environmental enrichment as a behavioral treatment strategy supports abstinence and also protects against relapse in heroin seeking rats when exposed to cues that are associated with the drug. Further, the use of the conflict model of abstinence and relapse in the present studies extends the promising evidence that environmental enrichment may indeed support drug abstinence in animals as it does in other animal models of abstinence and relapse (e.g. reinstatement model). Moreover, the use of the abstinence conflict model to investigate environmental enrichment as a behavioral strategy for drug abstinence brought together both the positive consequences of abstinent behavior in an enriched environment with the aversive consequences of drug seeking (e.g., electric barrier). Thus, the abstinence conflict model might serve an important complementary role in drug abuse research by emphasizing features of human drug abstinence (e.g., aversive consequences for drug seeking) that are not emphasized by other models.

The mechanisms whereby the use of non-concurrent environmental enrichment can lead to supporting heroin abstinence and reduce the effects of heroin-associated stimuli on relapse are not well understood. However, as indicated earlier, these mechanisms may involve both neurobiological (e.g., stress reduction) and behavioral (e.g., behavioral contrast) pathways.

From a behavioral perspective, it is possible that non-concurrent rewarding stimulation reduces the effectiveness of drug or drug-related stimuli on continued drug seeking through a contrast mechanism. Typically, the behavioral contrast phenomenon is observed within the same context where in the rate of reinforcement on one component of a concurrent schedule produces an opposite change in the rate of response on another component (Reynolds, 1961; McSweeney,

1979; Williams, 2002). We argue that the present experiments could possibly be classified as an instance of behavioral contrast in that environmental enrichment was provided non-concurrently during abstinence that led to a significant decrease in drug operant responding when compared to controls in both abstinence and relapse conditions (Ranaldi et al., 2011; Grimm et al., 2013; Zlebnik et al., 2010). Further, for EE rats, heroin consumption during abstinence decreased despite there being no changes to contingencies related to heroin consumption.

One account of behavioral contrast posits that changes in response rate result from the matching law (Herrnstein, 1970). The matching law is a quantitative relationship that holds between the relative rates of response and the relative rates of reinforcement in multiple schedules of reinforcement (Herrnstein, 1970; Baum, 1974; McDowell, 1982). Further, matching in concurrent schedules is based on allocating behavior to the components according to relative rates of reinforcement, and is described by the following equation:

$$P_1 = \frac{kR_1}{R_1 + mR_2 + R_0}$$

P_1 refers to the behavior occurring in one component, R_1 and R_2 are the rates of reinforcement in each component, R_1 refers to the rate of unscheduled reinforcements (e.g., grooming or exploring the operant chamber), which according to Herrnstein (1970) should take a value close to zero, k is the asymptotic response rate, and m characterizes the interaction between the two components (varies from 0 to 1). Thus, the equation predicts positive contrast if R_2 decreases because the denominator becomes smaller resulting in an increase in P_1 and negative contrast when R_2 increases resulting in a decrease in P_1 .

The matching law applies reliably when subjects are exposed to concurrent variable schedules; its applicability in other situations is less clear, depending on the assumptions made and the details of the experimental situation. Consequently, subsequent research has shown that

data normally depart from strict matching (according to the equation above), but are fitted to a very good approximation by a power function generalization of the strict matching law (Baum, 1974; McDowell, 1982, 2005). Further, the matching equation accurately predicts differences in performance under concurrent and non-concurrent schedules of reinforcement carried out within the same context (Herrnstein, 1970; Shimp & Wheatley, 1971). However, to our knowledge there is no evidence to support the extent to which the matching equation will accurately describe or predict differences in performance under non-concurrent schedules of reinforcement provided in separate contexts (e.g., drug context and EE context). Therefore, the matching law may reliably predict differences in abstinence performance and individual relapse rates in manipulations using concurrent environmental enrichment (same context). However, in the present studies, the ability of the matching law to predict abstinence and relapse performances given the delivery of environmental enrichment in a separate context is not known. Future research should investigate under what conditions the matching law is applicable to separate context treatment manipulations.

Another possible behavioral mechanism discussed previously is the blunting effect non-concurrent environmental enrichment may have on both discrete heroin paired cues and drug contextual cues that can lead to supporting heroin abstinence and protect against relapse. To date, there are several theories that propose that environmental stimuli associated with early drug use contribute to the chronic, habitual nature of drug consumption (Solomon & Corbit, 1974; Siegel, 1975; Robinson & Berridge, 1993; Koob & LeMoal, 1997). One theory previously discussed is Robinson and Berridge's (1993) theory of incentive sensitization where the presentation of drug-predictive stimuli can lead to an increased responsiveness to drug-associated cues following repeated drug exposure. It is argued that these drug-associated stimuli

acquire incentive salience so that in their presence there is an increase in the motivational value for the drug. In Experiment 2, this may help explain the greater individual relapse in NEE versus EE heroin trained rats because of the differential incentive motivational effects between EE and NEE rats when heroin associated discrete stimuli were presented. That is, the protective effects of environmental enrichment on relapse could be due to an EE-produced reduction in the control of incentive stimuli over drug-seeking.

Perhaps, for the present studies, another theory that will help explain some of the differences in abstinence and relapse performance between EE and NEE heroin seeking rats is Siegel's conditioning theory of tolerance. Siegel's (1975) conditioning theory of tolerance was one of the first theories that applied behavioral principles to drug addiction phenomena. Siegel's (1975) theory suggests that the development of tolerance can be attributed to learning an association between the systemic effects of the drug with environmental cues that reliably precede it. The development of an association between environmental stimuli (CS) and drug (US) can be demonstrated by presenting the conditioned pre-drug cues without the US (drug) and measure the conditioned response that occurs. A major tenet that stems from the conditioning theory of tolerance is that the demonstration of the conditioned response is usually opposite to that of the drug's physiological effects, what Siegel called the "anticipatory compensatory response" (Siegel, 1978). What Siegel (1975, 1978) demonstrated was that after repeated CS-US pairings the conditioned response that occurs during the test (CS alone) is opposite to the effects of the drug's unconditioned responses. Further, Siegel argued that repeated exposure to drug cue-drug pairings can lead to a reduction of the drug's effect (tolerance).

For example, Siegel (1975) examined the relationship between the environmental context in which a drug was administered and its effects on the development of tolerance. Siegel (1975)

administered morphine to two groups of rats, one that received morphine in the test environment, and one that received morphine in the home cage (away from test environment). It was hypothesized that rats that received morphine in the test environment would demonstrate significantly more tolerance to morphine compared to animals that received morphine in the home cage. Tolerance was assessed and measured by the latency to lick their paws after being placed on a hot plate. A short latency demonstrated an increase in pain sensitivity, whereas a long latency demonstrated a decrease in pain sensitivity.

Siegel (1975) found when rats received morphine in the same environmental context as the hot plate, significantly greater tolerance was demonstrated. Tolerance was experimentally validated because only animals that received morphine in the environmental context developed tolerance to morphine, in that they exhibited shorter paw-lick latency. Siegel argued that the increase in pain sensitivity resulted from the conditioned anticipatory effects of the presentation of drug-paired CSs. More recently, Siegel (2005) found tolerance to caffeine (decrease in heart rate) was more pronounced when caffeine is consumed in a context that has been paired with prior caffeine ingestion than in a novel context. Siegel attributed this finding to the possibility that the contextual cues were functioning as CSs in the presence of caffeine, which provides further evidence of the situational specificity of tolerance in drug-paired environments.

Siegel and Ramos (2002) coined this drug-related phenomenon as “drug preparation symptoms”. That is, after an individual learns the drug cue/drug relationship from repeated pairings and no longer receives the drug in the context or in the presence of stimuli paired with drug, the conditioned compensatory responses will still persist since they are elicited by drug cues. Moreover, withdrawal symptoms can be experienced in the absence of the drug (even after long periods of abstinence when it is unlikely that residuals of the drug are still present) as soon

as when drug-paired cues are present because the organism remains in a drug preparatory state. Therefore, during abstinence, the individual becomes more motivated to seek the drug in order to alleviate the symptoms associated with the conditioned compensatory responses. Further, Siegel and Ramos (2002) argue that drug preparation symptoms can make an individual more vulnerable to relapse in order to alleviate the negative withdrawal symptoms (psychological and/or physiological). In summary, according to Siegel and others, the environmental stimuli paired with drugs elicit conditioned compensatory responses that counteract the unconditioned effects of the drug, and therefore results in greater tolerance in the presence of these cues.

In the present studies, the presentation of both discrete heroin paired cues and drug contextual cues associated with drug use most likely contributed to the habitual nature of heroin consumption during self-administration, abstinence, and eventually relapse for heroin seeking rats. Further, as suggested by Siegel (1975,1978), in the present studies, environmental stimuli paired with drugs may have elicited conditioned compensatory responses that over self-administration sessions decreased the unconditioned effects of heroin, and therefore resulted in greater tolerance in the presence of these heroin paired cues. If so, greater tolerance for heroin could have led to increases in heroin consumption across experimental phases. As noted earlier, non-concurrent environmental enrichment may have blunted the effects of both discrete heroin paired cues and drug contextual cues that led to early and prolonged abstinence and afforded protection against relapse. Perhaps, the EE effects on environmental stimuli paired with drugs (discrete or contextual) diminished the elicited conditioned compensatory responses and therefore resulted in an overall decrease of drug tolerance in the presence of these cues when compared to NEE rats. If so, NEE rats during abstinence sessions and relapse tests would have been more motivated to seek the drug in order to alleviate the negative symptoms associated with

the elicited conditioned compensatory responses. In contrast, EE rats with lower drug tolerance would have exhibited less heroin consumption when compared to NEE rats and presumably, would have experienced less “drug preparation symptoms”. Therefore, according to Siegel and Ramos (2002), individual EE rats when compared to NEE rats would have been less vulnerable to relapse in order to alleviate the negative withdrawal symptoms associated with the drug preparation symptoms. This phenomenon, however speculative, may account for some of the differences in performances observed during abstinence and relapse between EE and NEE heroin seeking rats.

For the present studies, a behavioral account has been the primary focus for explaining the observed differences between EE and NEE heroin seeking rats in their abstinence and relapse performances. However, we want to point out that there are some possible neural mechanisms that may help explain how the use of non-concurrent environmental enrichment can lead to supporting heroin abstinence and reduce the effects of heroin-associated stimuli on relapse. Further, these neural mechanisms may provide more evidence that support the possible behavioral mechanisms involved in environmental enrichment manipulations discussed here.

For example, one neural mechanism whereby environmental enrichment may exert control over heroin seeking in rats is by disrupting neural circuits in areas involved in drug seeking (Chauvet et al., 2009; Grimm, 2013). The disruption of neural circuitry by environmental enrichment is supported by reports that found non-concurrent enriched rats previously trained to self-administer cocaine and after cue-induced relapse tests for cocaine had activated cFos in the mesocorticolimbic system to a lesser extent than in non-enriched animals (Chauvet et al., 2009; Thiel et al., 2009). The diminished activation of cFos, particularly in areas highly implicated in drug seeking (mesocorticolimbic pathway), suggests environmental

enrichment may play a disruptive role in the neural mechanisms associated with drug seeking. Further, this may help explain how the non-concurrent introduction of rewarding stimulation (EE), may have the effect of reducing the significance of drug-related stimuli through a behavioral contrast mechanism (Ranaldi et al., 2011). Lastly, as previously mentioned, EE may reduce responding in abstinence and relapse because it produces an anti-stress effect by lowering release of stress-responsive hormones (e.g., adrenocorticotrophic and corticosterone) compared with those housed in a non-enriched environment (Bardo et al., 2001; Belz et al., 2003; Solinas et al., 2008; Solinas et al., 2010). Further, stress has been shown to increase responding for several drugs of abuse and perhaps more importantly, stress has been shown to induce relapse (Goeders, 2002; Lu et al., 2003; Marinelli & Piazza, 2002; Shaham et al., 2000; Stewart, 2000). Therefore, in the present study, EE rats may have experienced lower stress levels throughout abstinence, prolonged abstinence, and relapse phases that led to a decrease in drug seeking across phases when compared to the NEE rats.

Finally, the behavioral treatment strategies to support abstinence that employ not only positive consequences for remaining abstinent, but also aversive consequences for drug-seeking have been the most successful in supporting abstinence in humans (Peck & Ranaldi, 2014). Further, abstinence in humans often occurs because the drug's rewarding effects are outweighed by the aversive consequences of drug seeking or drug taking (Panlilio et al., 2003, 2005; Cooper et al., 2007; Barnea-Ygael et al., 2012). Consequently, we argue that the conflict model of abstinence and relapse most closely represents the human abstinence condition of the aversive consequences that are present during drug seeking (Peck et al., 2013; Peck & Ranaldi, 2014; Cooper et al., 2007).

That is, the present studies' use of an animal conflict model for abstinence and relapse contained some important characteristics of human drug addiction, where abstinence occurs while drug is readily available and the animal must endure aversive consequences for its pursuit and consumption. Therefore, using the abstinence conflict model to investigate behavioral treatments could lead to more effective treatment outcomes for human addicts by bringing together both the positive consequences of abstinent behavior (e.g., enrichment) and the negative consequences of drug seeking (e.g., electric barrier). Thus, the abstinence conflict model seems suitable for further developing behavioral, environmental, and neurobiological (i.e., pharmacotherapeutic) strategies to support long-term drug abstinence in humans.

In summary, the non-concurrent delivery of environmental enrichment played an integral part in achieving and maintaining abstinence, and in the prevention of relapse for heroin seeking rats. Moreover, the present results support previous research findings using non-concurrent enrichment by demonstrating that when stimulation or reward is derived from a source other than the drug itself (enrichment), there is a reduction in the reinforcing effects of the drug, thereby supporting abstinence. Further, to our knowledge, this is the first study to have investigated the effects of environmental enrichment on cue-induced relapse in heroin seeking rats. Thus, the results of Experiment 2 provide support that environmental enrichment may also provide protection against cue-induced reinstatement not only for cocaine, amphetamines, alcohol and sucrose seeking rats, but also for heroin seeking rats (Zlebnik et al., 2010; Chauvet et al., 2009; Thiel et al., 2009; Cosgrove et al., 2002; Grimm et al., 2008; Grimm et al., 2013; Podlesnik et al., 2006). However, these results have largely only been found in animal studies using environmental enrichment. In humans, whether or not environmental enrichment can sustain long-term abstinence is relatively unknown (Solinas et al., 2010). Further, given that there is

promising evidence that environmental enrichment may indeed support drug abstinence in animals, it is imperative that future research explore this possibility in humans.

Table 1

Experimental Design for Experiment 1

Group	Phase 1	Phase 2	Phase 3
EE	IVSA (15 sessions) Same for both groups	Abstinence EE begins	Prolonged Abstinence EE ends after responding
NEE	IVSA (15 sessions) Same for both groups	Abstinence NEE begins	Prolonged Abstinence NEE ends after responding

Note. Environmental Enrichment (EE) and Intravenous Self-Administration (IVSA); n = 8 for each group.

Table 2

Experimental Design for Experiment 2

Group	Phase 1	Phase 2	Phase 3
EE	IVSA (15 sessions) Same for both groups	Abstinence 72 hrs of EE begins after abstinence criteria is met	Relapse Test After 72 hrs of EE ends
NEE	IVSA (15 sessions) Same for both groups	Abstinence 72 hrs of Non-EE begins after abstinence criteria is met	Relapse Test After 72 hrs of Non-EE ends

Note. Environmental Enrichment (EE) and Intravenous Self-Administration (IVSA); n = 8 for each group.

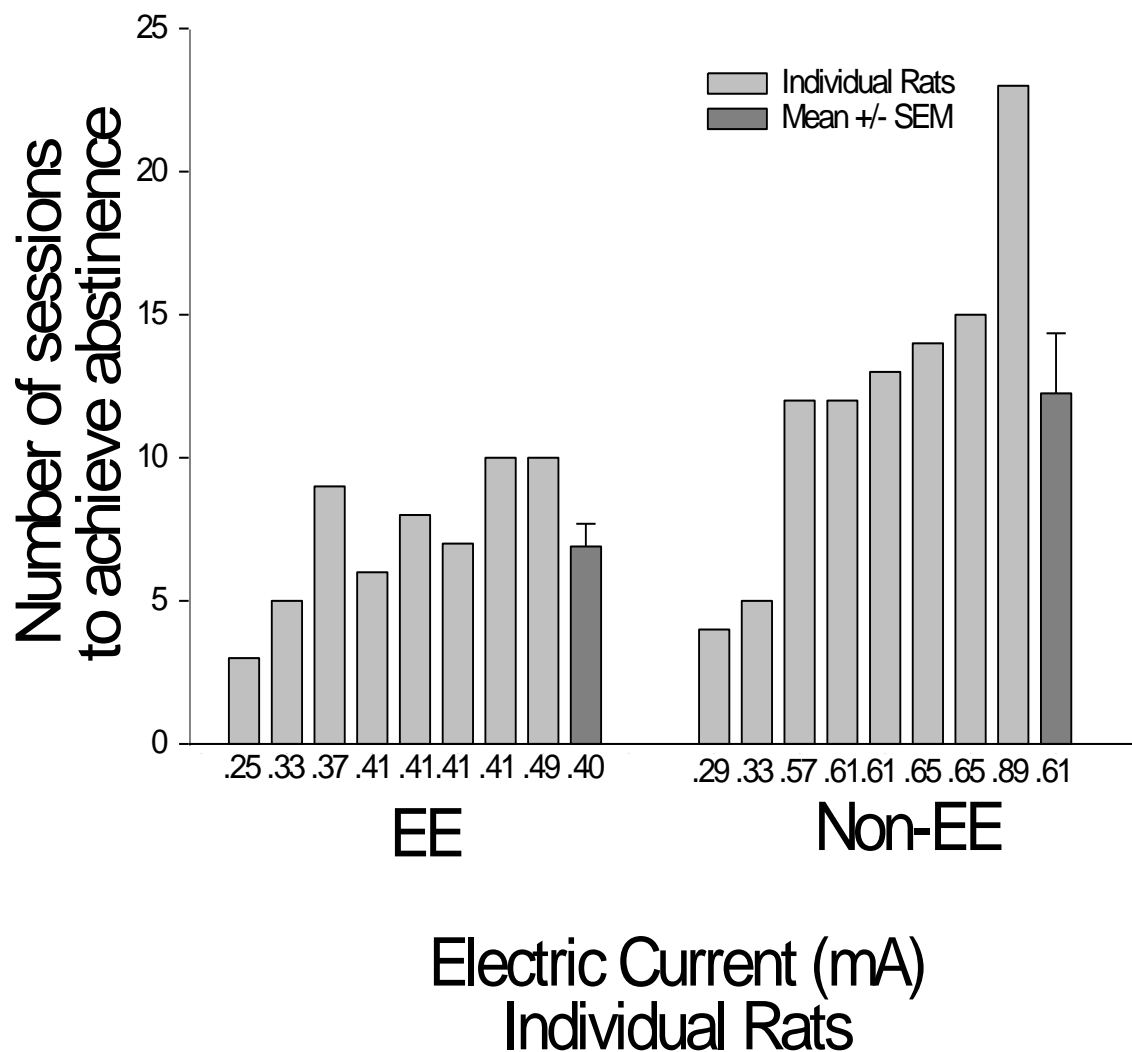


Figure 1. The final shock intensities for individual rats that led to 3 consecutive sessions of zero presses on the active lever during abstinence and mean (\pm SEM) number of abstinence sessions for both EE and NEE heroin groups ($n = 8$).

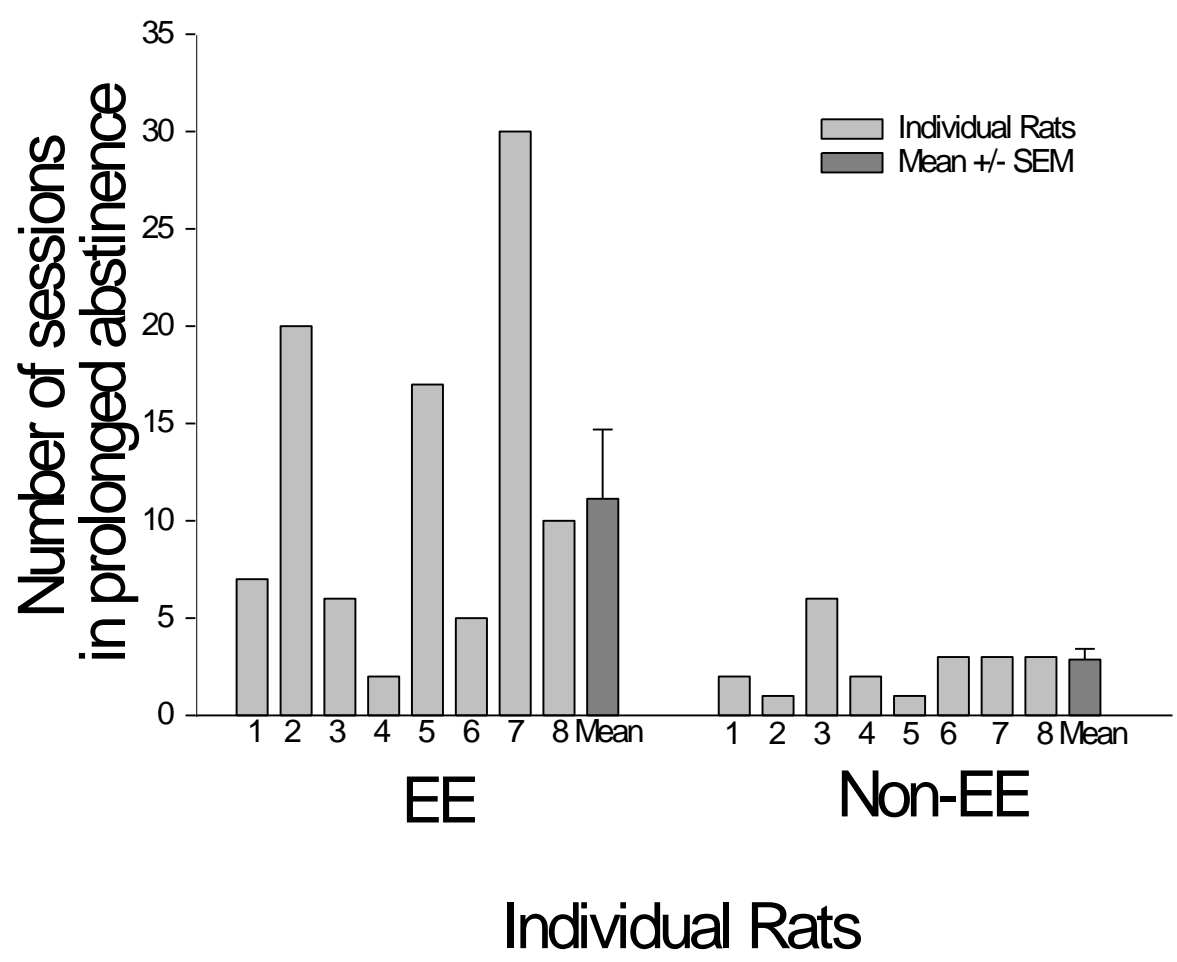


Figure 2. The number and mean (\pm SEM) of sessions for individual EE and NEE rats presented in the same order as their final shock intensities during the prolonged abstinence phase (n = 8).

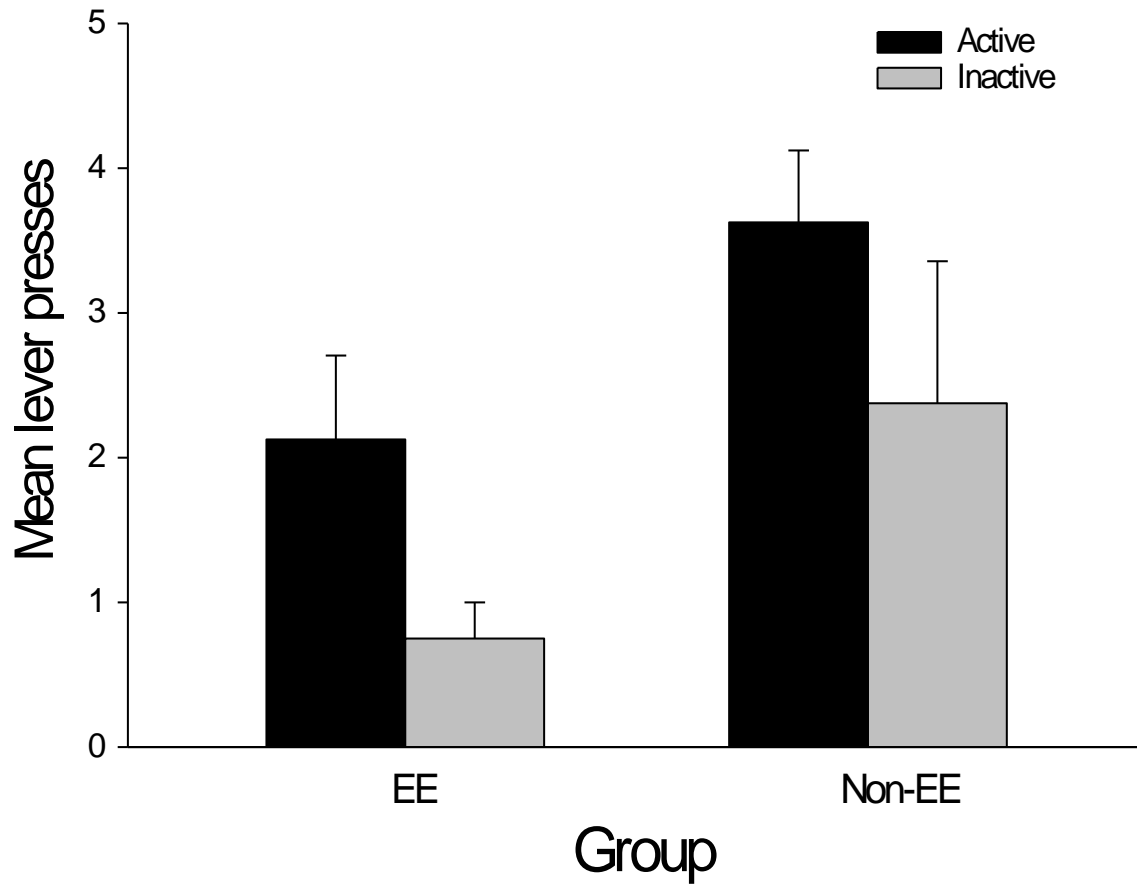


Figure 3. Mean (\pm SEM) total active and inactive lever presses for EE and NEE rats during the last session of prolong abstinence.

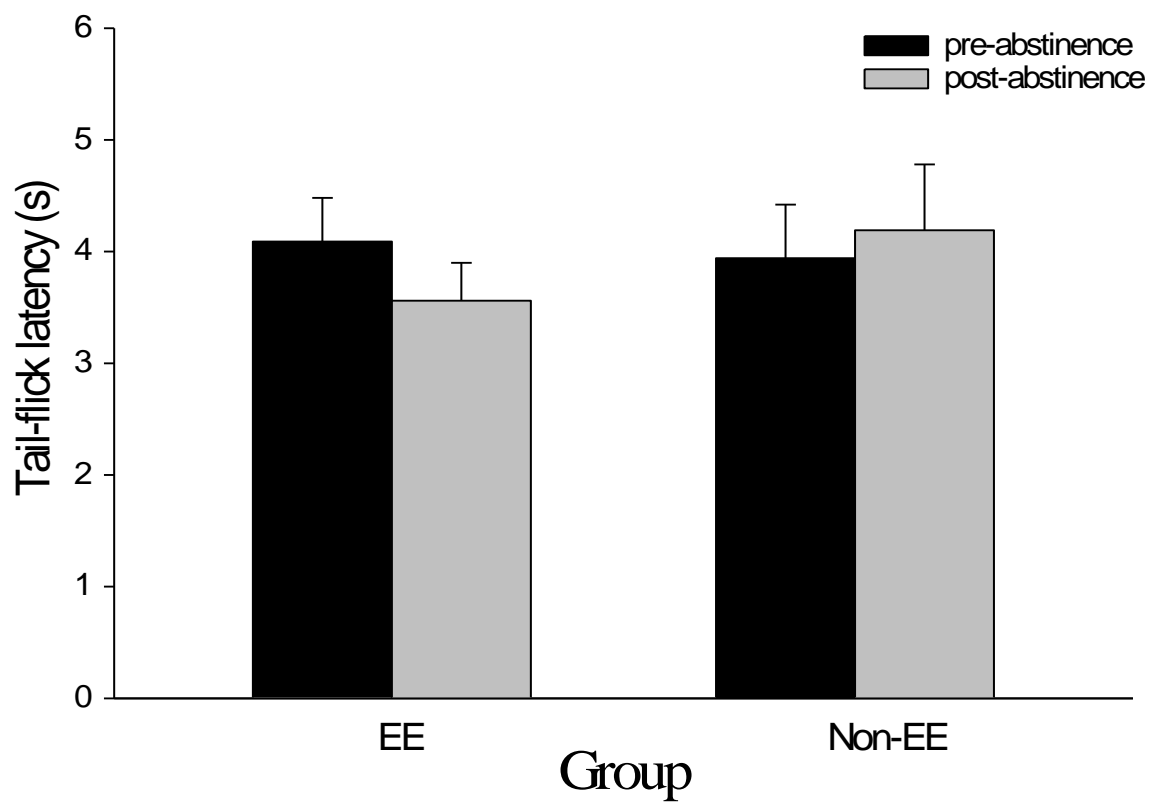


Figure 4. Mean (\pm SEM) tail-flick latency measure for both individual EE and NEE heroin rats before the first session of the abstinence phase and after the last session of the prolonged abstinence phase ($n = 8$).

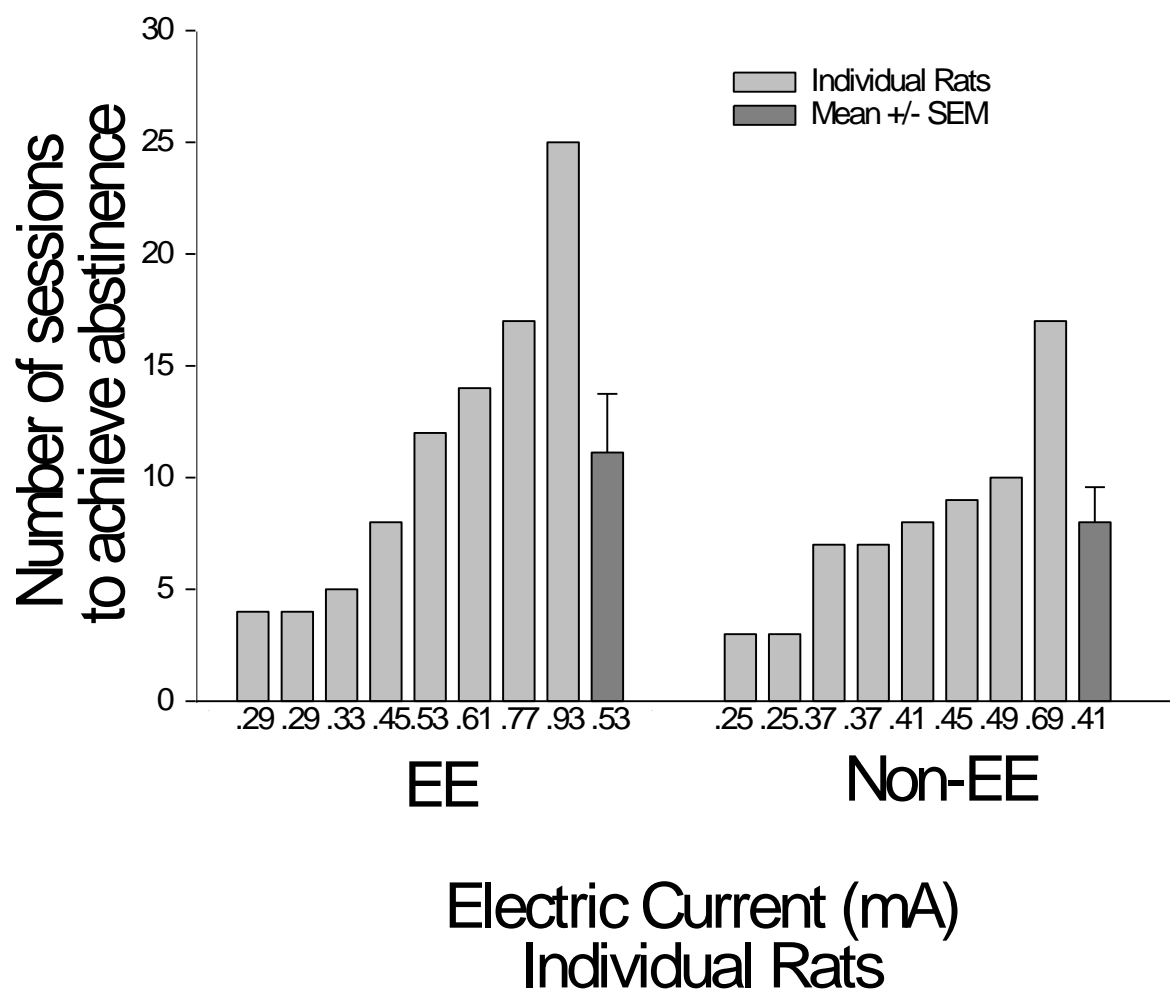


Figure 5. The final shock intensities for individual rats that led to 3 consecutive sessions of zero presses on the active lever during abstinence and mean (\pm SEM) number of abstinence sessions for both EE and NEE heroin groups ($n = 8$).

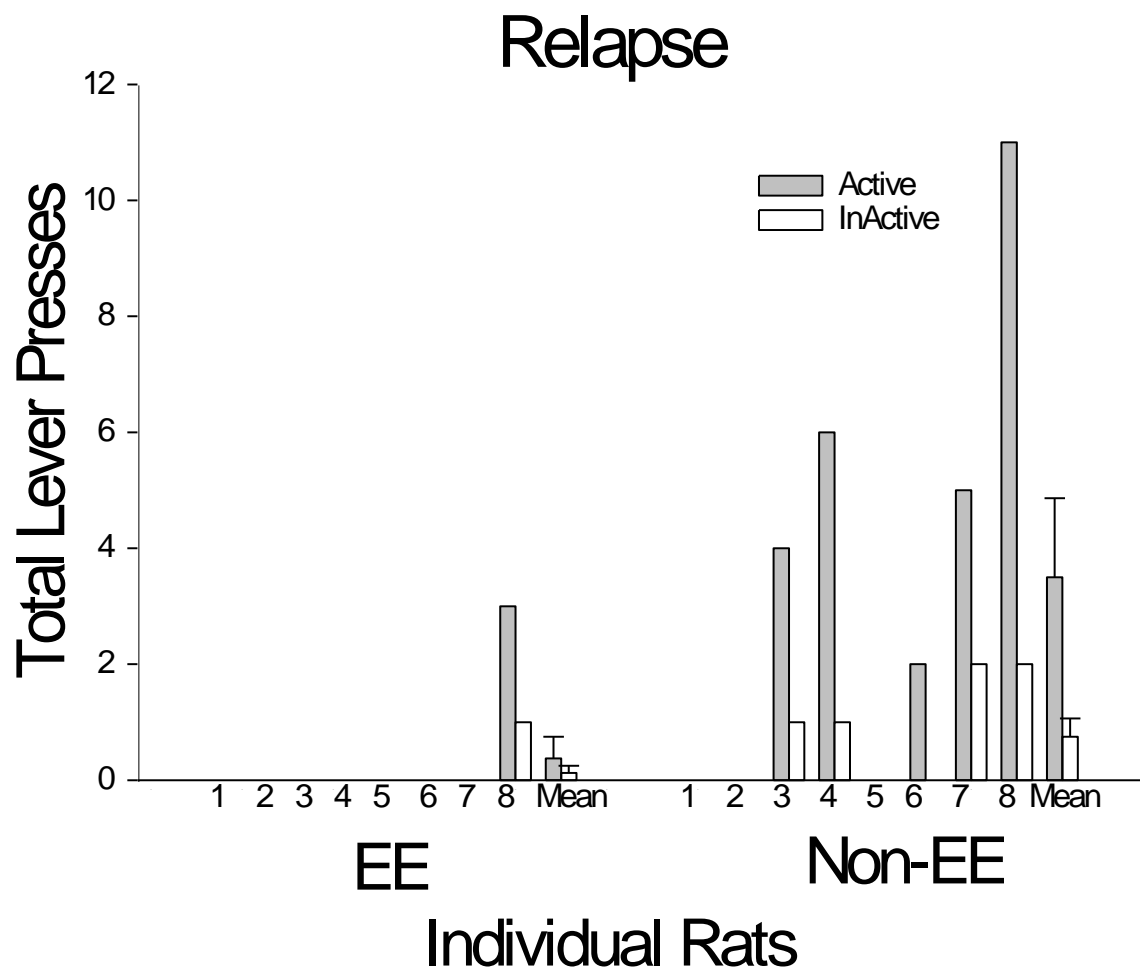


Figure 6. Individual and mean (\pm SEM) active and inactive lever presses for individual EE and NEE heroin rats presented in the same order as their final shock intensities during the 30-min relapse test ($n = 8$).

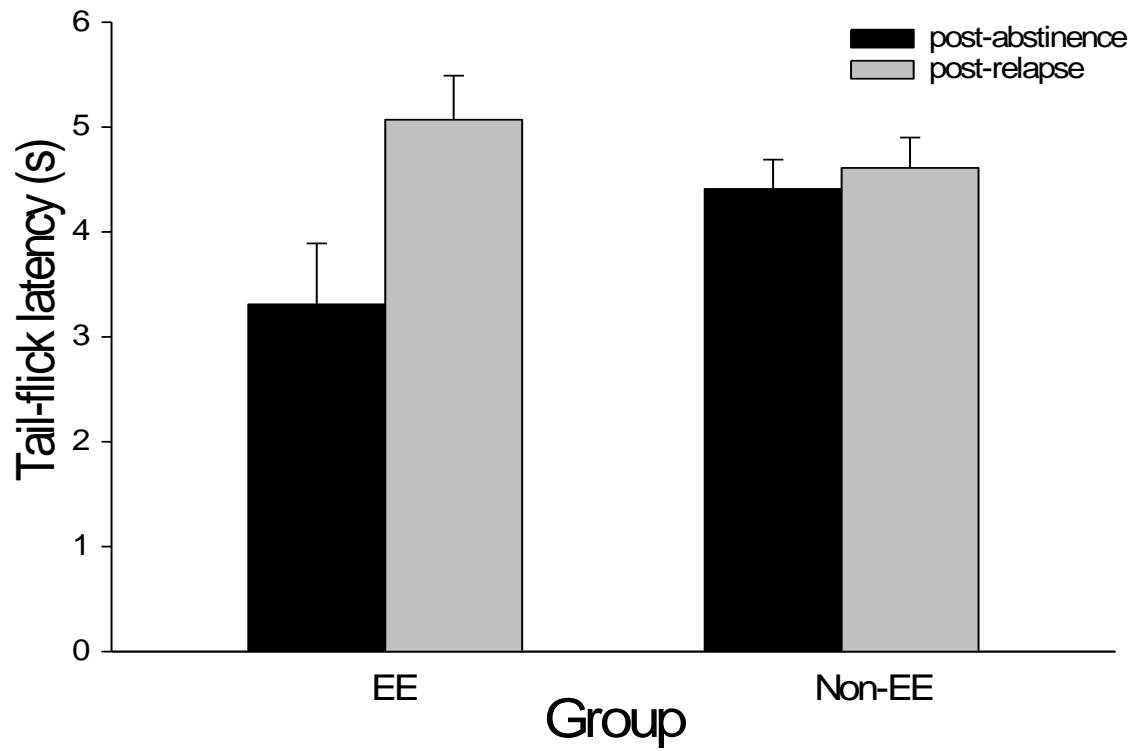


Figure 7. Mean (\pm SEM) tail-flick latency measure active for both individual EE and NEE heroin rats after the last session of the abstinence phase and after the 30-min relapse test ($n = 8$).

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