RESURGENCE OF COCAINE-SEEKING IN RATS FOLLOWING LONG ACCESS AND PUNISHMENT

by

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ABSTRACT

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Alternative-reinforcement-based treatments effectively reduce drug use for individuals with substance use disorders while in effect. However, relapse often occurs when alternative reinforcement ends, an effect called resurgence. Animal models have been used to study factors that may reduce resurgence, but two issues limit their translation to human treatments for drug abuse. First, the models use drug unavailability (i.e., extinction) to reduce drug seeking. However, in humans, abstinence is due to the aversive consequences of drug use. The experiments in Chapter 2 were designed to address this concern by using aversive consequences (i.e. foot shock in rats) to suppress cocaine seeking. Resurgence occurred when cocaine, punishment, and alternative reinforcement were removed, but not when alternative reinforcement was removed and cocaine and punishment remained available. The second concern with animal models of

resurgence is that they fail to capture the uncontrolled drug use characteristic of individuals with substance use disorders. Long access procedures have been shown to produce behavior in animals that reflects uncontrolled drug use in individuals with substance use disorders. Thus, the experiment in Chapter 3 was designed to incorporate aversive consequences and also included a long access procedure to simulate uncontrolled drug seeking. In Chapter 3, groups of rats earned cocaine infusions in either long access (6-hr) or short access (1-hr) sessions before exposure to punishment of cocaine seeking with or without alternative reinforcement. When all consequences were removed, relapse occurred similarly for all groups regardless of access duration or presence of alternative reinforcement. These results suggest that parametric changes between the Chapter 2 and Chapter 3 may have reduced resurgence or increased the chance that removing punishment alone produced relapse. Thus, further investigations into the effects of parameters of reinforcement and punishment under conditions similar to those used in Chapter 3 are warranted. Overall, these changes to the animal model of resurgence of drug seeking should increase the translational utility model by more closely resembling the environmental and neurobiological factors underlying resurgence of drug seeking in humans. Thus, the models developed herein could be useful for evaluating potential treatments and mechanisms of resurgence of drug seeking.

(112 pages)

PUBLIC ABSTRACT

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Strategies that provide access to alternative non-drug rewards are among the most effective at reducing substance use in individuals with substance use disorders, but relapse often occurs when alternative rewards are removed. Relapse induced by the loss of alternative rewards is called resurgence, and represents a challenge to otherwise effective strategies for reducing drug use. An animal model has been useful for studying resurgence, but the extant model has two limitations. First, humans usually refer to the negative consequences of drug use as the reason they stop taking drugs, but the extant model uses drug unavailability to reduce drug seeking. Second, individuals with substance use disorders display behaviors that can be summarized as uncontrolled drug seeking, but the extant model does not simulate uncontrolled drug seeking. Chapter 2 addressed the first concern by studying resurgence of previously-punished cocaine seeking. Chapter 3 addressed the second concern by using procedures shown to simulate uncontrolled drug seeking in rats to study resurgence of previously-punished cocaine seeking. Chapter 2 showed that resurgence of cocaine seeking can occur following suppression by punishment, and Chapter 3 showed that resurgence may be unaffected following procedures shown to increase relapse in other models. The models developed herein should contribute to future research into resurgence by better simulating the conditions under which individuals with substance use disorders experience relapse.

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CHAPTER I

INTRODUCTION

Substance abuse is a significant and widespread burden on public and private health, incurring an estimated annual cost of $740 billion in drug-related crime, productivity-loss, health care, and affecting over 20 million Americans annually [1]. Treatment strategies that provide alternative reinforcement to reduce problematic substance use are among the most successful at reducing drug use in individuals with Substance Use Disorders (SUDs). For example, in contingency management, patients earn vouchers for retail items by providing evidence of drug abstinence [2]. In community reinforcement, reinforcement is explicitly provided for participation in prosocial non-drug related activities such as recreation, job procurement, and spending time with family [3,4]. These alternative-reinforcement-based strategies are effective at reducing substance use during treatment [5], but relapse often occurs when treatment is interrupted or concluded [6–8]. Chronic episodes of relapse are characteristic of SUDs [9] and even alternative-reinforcement-based treatments have demonstrated relapse in as many as 60% of patients following treatment [6]. Despite the relative efficacy of alternative-reinforcement-based treatments for SUD while in effect, relapse rates are similar to other forms of treatment [e.g. up to 60% of individuals, 10]. Thus, relapse following the loss of alternative reinforcement presents a challenge to otherwise effective strategies for reducing substance use. A better understanding of the mechanisms underlying relapse should lead to improvements in existing treatments and to the development of novel treatment approaches.

Relapse can be induced by a variety of environmental events, including re-exposure to drugs, stimuli associated with drugs, or contexts in which drugs were previously available [see, 11]. The loss of non-drug alternative reinforcement can also induce relapse of drug use, an effect called resurgence [e.g., 12,13]. Animal models have been extensively used to study relapse of drug seeking induced by these different environmental events, and most traditional models share similar procedures. First, animals are trained to perform a response to earn access to drug reinforcement. Next, drug seeking is extinguished such that the response no longer produces drug access. After responding has decreased to low levels, an environmental change occurs that induces relapse. What differs between models is the environmental event used to induce relapse. In the reinstatement model, relapse is induced by exposing the animal to non-continent drug delivery, delivery of cues previously paired with the drug, or to stress [e.g., 11]. In the renewal model, responding is trained and extinguished in separate distinct contexts and relapse is induced by returning the animal to the training context or transitioning to a novel context [e.g., 14]. Finally, in the resurgence model, relapse is induced by the loss of alternative reinforcement that was previously available during extinction of drug seeking [e.g., 12,13,15]. The animal model of resurgence may be particularly relevant for relapse of drug use in humans because alternative reinforcement is often effectively used as treatment, as discussed above, and is also influential in successful attempts at remission without treatment [16].

While traditional animal models, including the resurgence model, have been useful for identifying factors that can modulate relapse, they have some limitations that make translation to treatment of SUDs in humans difficult. First, traditional models most

commonly use extinction to reduce drug seeking. That is, the behavior that once produced access to the drug is no longer followed by drug access. Extinction is not generally a part of treatment programs for SUDs. Further, the unavailability of drug effects following drug-related behaviors is unrealistic in typical human environments, making it unlikely that extinction is the factor driving abstinence from drug use in humans [17,18]. Instead, drug abstinence is generally thought to be the product of aversive consequences of drug use [e.g., adverse health, family problems, financial trouble, etc., 16,19,20]. To address the issues associated with using extinction, some researchers have begun to reduce drug seeking by incorporating aversive consequences into animal models. For example, many models have used mild foot shock to reduce drug seeking in rats [e.g., 17,21,22]. In addition to better representing human environmental pressures, punishment models have been useful for observing persistence of drug seeking despite aversive consequences, which is a characteristic of SUDs in humans [23]. Punishment models may also be important given relatively new evidence that the neurobiological processes underlying relapse might depend on whether punishment or extinction was used to suppress drug seeking [24,25]. Because resurgence may be of particular relevance for relapse following treatment for SUDs, and because punishment models are advantageous for the reasons discussed above, examining resurgence of drug seeking following suppression by punishment may be important.

The second limitation of the resurgence model and other traditional animal models of relapse is that they do not capture the characteristic loss of control over drug use seen in humans with SUDs [e.g., 26]. Substance use disorder is diagnosed by the presence of a number of behavioral symptoms that can be summarized as a loss of control

over drug-related behaviors [23]. To address this concern, procedures have emerged that produce behaviors in animals resembling those used to diagnose SUDs in humans. Perhaps the most common example is the long access procedure [e.g., 26,27]. As previously discussed, resurgence may be of particular importance for relapse following treatment for SUDs, but to date, long access procedures have not been used to study resurgence.

The overarching purpose of this dissertation was to develop a model for studying resurgence in the animal laboratory using a procedure designed to simulate key aspects of drug-related behaviors in individuals with SUDs. The experiments described in Chapter 2 developed a model of resurgence in which cocaine seeking was suppressed by aversive consequences. This model better simulates the environmental and potentially neurobiological processes involved in the suppression of drug seeking by aversive consequences in humans and addresses a criticism of the traditional model for studying resurgence of drug seeking in animals. The experiment described in Chapter 3 built upon the model developed in Chapter 2 by first using a long access procedure to simulate loss of control over drug seeking and then evaluating resurgence of previously-punished cocaine seeking. This model includes the advantages of the model developed in Chapter 2, and furthers it by simulating the loss of control over drug-related behaviors seen in humans with SUDs. Better simulating the environmental and potentially neurobiological factors involved in relapse of drug use following alternative-reinforcement-based treatments for SUDs should improve efforts to understand the mechanisms of resurgence of drug seeking, efforts to mitigate resurgence of drug seeking, and development of novel treatments. Chapter 4 provides a summary of the findings of these experiments and

discusses the implications of these models for future studies of resurgence of drug seeking.

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CHAPTER 2

RESURGENCE OF PUNISHMENT-SUPPRESSED COCAINE SEEKING IN RATS[1]

Abstract

Alternative-reinforcement-based treatments are among the most effective for reducing substance abuse. However, relapse often occurs when alternative reinforcement ends. Relapse following the loss of alternative reinforcement is called resurgence. An animal model has been used to study basic factors that may ultimately reduce resurgence, but uses drug unavailability (i.e., extinction) to reduce drug seeking. In humans, drug abstinence is thought to be a product of aversive consequences associated with drug use rather than extinction. This discrepancy is important because the environmental and neurobiological factors involved in relapse may differ between punished and extinguished behavior. Experiment 1 evaluated resurgence of previously-punished cocaine seeking. In Phase 1, rats earned cocaine for pressing levers. In Phase 2, cocaine remained available, but lever pressing also produced mild foot shocks while an alternative response produced food pellets for one group but not for another group. In Phase 3, alternative reinforcement and punishment were removed and resurgence of cocaine seeking occurred only in rats previously exposed to alternative reinforcement. In Experiment 2, resurgence was evaluated similarly, except that consequences of cocaine seeking (i.e. punishment and cocaine) remained available during Phase 3. Resurgence did

[1] [1] Chapter 2 of this dissertation was adapted from "Resurgence of Punishment-Suppressed Cocaine Seeking in Rats," by Rusty W. Nall & Timothy A. Shahan, Submitted, *Experimental and Clinical Psychopharmacology*.

not occur in either group during Experiment 2. The animal models of resurgence developed herein could increase translational utility and improve examination of the environmental and neurobiological factors underlying resurgence of drug seeking.

1. Introduction

Alternative reinforcement techniques are among the most successful for the treatment of substance use disorders (SUDs; Prendergast, Podus, Finney, Greenwell, & Roll, 2006). In such therapies, alternative reinforcers may be provided for maintaining abstinence and/or for engaging in behaviors unrelated to substance use. For example, in Contingency Management, patients earn vouchers for retail items by providing evidence of drug abstinence (e.g. drug-free urine specimen; Higgins & Silverman, 1999). In Community Reinforcement, participation in pro-social, non-drug related activities such as recreation, job procurement, and spending time with family are explicitly reinforced (Hunt & Azrin, 1973a; Miller, Meyers, & Hiller-Sturmhöfel, 2003). Previous work has also noted that alternative reinforcement is a common factor in successful abstinence from drug use in non-treatment environments (i.e. spontaneous autoremission; Burman, 1997; Klingemann, 1991). Alternative-reinforcement based strategies effectively reduce substance use while contingencies remain in place, but relapse often occurs when treatment is interrupted or concluded (McLellan, Lewis, O'Brien, & Kleber, 2000; Secades-Villa et al., 2011; Silverman, Chutuape, Bigelow, & Stitzer, 1999). Relapse induced by the loss of alternative reinforcement has been termed resurgence (Epstein, 1985) and represents a threat to otherwise effective strategies for reducing substance use. As such, a better understanding of the factors contributing to resurgence may be useful in designing more resilient alternative-reinforcement-based treatments for SUDs.

Resurgence of drug seeking is often studied in animals using a three-phase procedure (Craig, Nall, Madden, & Shahan, 2016; Frye et al., 2018; Nall, Craig, Browning, & Shahan, 2018; Quick, Pyszczynski, Colston, & Shahan, 2011; Shahan,

Craig, & Sweeney., 2015). In Phase 1, animals are trained to perform a target response to earn drug reinforcement. Next, in Phase 2, drug seeking is extinguished such that target responses no longer produce drug access. At the same time, an alternative response is made available and produces access to an alternative non-drug reinforcer. Finally, in Phase 3, the alternative response is extinguished while the target response remains on extinction. Resurgence is evidenced by an increase in target responding following the removal of alternative reinforcement in Phase 3 (i.e. resurgence of drug seeking). This procedure has been previously used to demonstrate resurgence of cocaine (Nall et al., 2018; Quick et al., 2011; Shahan et al., 2015) and alcohol (Frye et al., 2018; Nall et al., 2018; Podlesnik, Jimenez-Gomez, & Shahan, 2006) seeking in rats, leading some to suggest that the animal model of resurgence may be useful for studying relapse following the loss of alternative reinforcement in human treatment settings (Nathan J. Marchant, Li, & Shaham, 2013; Peck & Ranaldi, 2014; Winterbauer & Bouton, 2010).

While traditional resurgence procedures have been useful for identifying factors that can modulate relapse, they most commonly use extinction to reduce drug seeking. The use of extinction in animal models of drug relapse has been criticized because it does not accurately reflect the reasons humans with SUDs pursue drug abstinence (Nathan J. Marchant, Li, et al., 2013; Leigh V. Panlilio, Thorndike, & Schindler, 2003). Individuals with SUDs most often refer to the aversive consequences of drug use as their reason for pursuing abstinence. This is true for individuals that stop taking drugs without treatment (e.g., Burman, 1997), and is often influential in the decision to enter treatment (e.g., Laudet, Savage, & Mahmood, 2002). Examples of aversive consequences of drug use might include loss of employment, family problems, financial strain, detriments to

physical and mental health, and legal trouble (Burman, 1997; Laudet et al., 2002). Because aversive consequences play an important role in drug abstinence in humans, it may be important to simulate aversive consequences in animal models of relapse as well.

To more accurately simulate the suppression of drug seeking by aversive consequences in humans, more recent animal models of relapse have employed aversive consequences (i.e., most commonly using mild foot shock in rats) to suppress drug seeking. In these procedures, shock is delivered contingent upon drug seeking responses and ultimately results in a decrease in drug seeking behavior. For example, Marchant and et al. (2013) demonstrated relapse (i.e. contextual renewal) of alcohol seeking in rats following suppression by punishment. First, rats pressed levers to earn alcohol in Context A. Next, in Context B, lever pressing produced alcohol + foot shock or no consequence (i.e., extinction) across groups. Finally, all rats were tested for relapse under extinction conditions (i.e., no alcohol or foot shock) in Contexts A and B. Rats exposed to extinction or punishment demonstrated similar reductions of alcohol seeking in Context B, and similar renewal in Context A. These data demonstrate that relapse can be obtained following suppression of drug seeking by aversive consequences. Similar studies have used punishment to suppress drug seeking and observed relapse induced by contextual change (N. J. Marchant et al., 2016, 2014; Nathan J Marchant & Kaganovsky, 2015; Pelloux, Minier-Toribio, Hoots, Bossert, & Shaham, 2018), drug priming (Ducret et al., 2016; Leigh V. Panlilio et al., 2003; Leigh V. Panlilio, Thorndike, & Schindler, 2005), exposure to drug cues (Campbell et al., 2017; Economidou, Pelloux, Robbins, Dalley, & Everitt, 2009; Torres et al., 2017), and forced abstinence (Gancarz-Kausch, Adank, & Dietz, 2014; Krasnova et al., 2014; Pelloux, Murray, & Everitt, 2013), across a range of

substances of abuse.

Relapse outcomes are not always similar following suppression by punishment and suppression by extinction. Panlilio, Thorndike, & Schindler (2005) found that administration of the benzodiazepine lorazepam reinstated remifentanil seeking (a short acting μ-opioid agonist with reinforcing properties similar to heroin; see L V Panlilio & Schindler, 2000) in rats whose responding was suppressed by punishment, but not by extinction. Further, Pelloux et al. (2018) investigated the neurobiological correlates of relapse of cocaine seeking after extinction and after punishment. They found that inactivation of different sub-regions of the amygdala had opposite effects on relapse depending on the method used for response suppression. For instance, inactivation of the basolateral amygdala decreased relapse after extinction, but increased relapse after punishment. Thus, because punishment may better represent both the environmental and neurobiological conditions under which humans with SUDs reduce drug use, it is important to study relapse of drug seeking following suppression by punishment.

Resurgence effects following suppression by punishment may be of particular interest when investigating relapse of drug seeking, as alternative reinforcement is often used for treatment and plays an important role in spontaneous autoremission, as discussed above. Two recent studies have investigated resurgence of food seeking under punishment conditions. Nall, Rung, and Shahan (2019) examined resurgence of food seeking that was previously suppressed by punishment. In Phase 1, rats pressed levers to earn food pellets. Next, in Phase 2, lever pressing continued to produce food pellets but also resulted in mild foot shock. Also during Phase 2, food pellets were made available for an alternative response. Finally, both responses were placed on extinction and

punishment was discontinued. Resurgence was noted in animals previously exposed to alternative reinforcement (Nall et al., 2019). Another recent study by Fontes et al. (2018) found resurgence of a previously-extinguished target behavior following punishment of an alternative behavior. These findings suggest that resurgence of previously suppressed target behavior may occur more generally when conditions of alternative reinforcement are worsened and that resurgence effects are not inherently extinction-based. While these studies are certainly useful for demonstrating the generality of resurgence effects beyond extinction conditions, their use of non-drug reinforcers limits their extension to relapse following treatment for SUDs.

Taken together, current evidence suggests that relapse of drug seeking can occur following suppression by punishment, and that the factors driving relapse may differ between procedures that use extinction or punishment to suppress drug seeking. Because of these potential differences in mechanism, and because aversive consequences are important for drug abstinence in humans, it is important to study relapse following punishment. Further, it may be particularly important to study resurgence of previously-punished drug seeking because of the prevalence and efficacy of alternative-reinforcement based treatments for SUDs. Thus, the goal of the present experiments was to develop a model for studying resurgence of cocaine seeking following punishment.

2. Experiment 1

Experiment 1 was designed to incorporate aversive consequences of drug use into the animal model of resurgence of drug seeking. In Phase 1, rats were trained to press a target lever to earn infusions of cocaine. In Phase 2, target responding continued to produce cocaine, but also produced intermittent foot shocks. Also during Phase 2, for an

Alternative + Punishment group, food pellets could be earned for performing an alternative response. Finally, to test for resurgence of cocaine seeking, food pellet reinforcement was made unavailable for the alternative response. As Marchant and et al.'s (2013) examination of renewal of punishment-suppressed alcohol seeking, all consequences on the cocaine lever were also removed (i.e., cocaine infusions and foot shocks). Because both alternative reinforcement and target punishment were removed during Phase 3, any increase in target responding could be due to the removal of punishment alone. Thus, the experiment also included a *Punishment Control* group for which target responding was reinforced and punished during Phase 2 as in the *Alternative + Punishment* group, but no alternative reinforcement was available. For the *Punishment Control* group in Phase 3, target reinforcement and punishment were discontinued. Thus, any difference between groups in target responding during Phase 3 should be due to the previous availability and then removal of alternative reinforcement for the *Alternative + Punishment* group (i.e. resurgence).

2.1. Materials and methods

2.1.1. Subjects

Ten experimentally naïve male Long-Evans rats (Charles River, Portage, MI) served as subjects. Rats were 71-80 days old upon arrival and were restricted to 80% of their free-feeding weights following surgery (detailed below). Animal housing, care, and all procedures reported below were conducted in accordance with Utah State University's Intuitional Animal Care and Use Committee and have been described in detail elsewhere (Nall et al., 2018).

2.1.2. Surgery

Prior to the start of the experiment, rats underwent jugular-catheterization surgery, described in detail elsewhere (Craig et al., 2016; Nall et al., 2018). In short, rats were anesthetized and an indwelling, back-mounted cannula (Plastics One, Roanoke, VA) was implanted and an attached silastic catheter (SAI-Infusions, Lake Villa, IL) was inserted into the right jugular vein. Following surgery, rats recovered for 5 days before undergoing food restriction.

2.1.3. Apparatus

Ten modular Med-Associates (St. Albans, VT) operant chambers measuring 30 cm x 24 cm x 21 cm were used. Chambers consisted of Plexiglas side walls, ceilings, and doors and were housed in sound- and light-attenuating cubicles. An aluminum response panel in the rear of the chamber contained 5 nose poke apertures that could be lighted yellow and were equipped to detect head entries. An aluminum response panel on the front wall contained two retractable levers with stimulus lights above them. A food aperture was centered on the front wall between the levers and was illuminated when delivering food (45-mg dustless pellets; Bio Serv, Flemington NJ). A house light near the ceiling on the front wall was used for general chamber illumination.

Chambers were also equipped for intravenous drug self-administration. A 60ml syringe was placed in a fixed-speed infusion pump (Med Associates) outside of the sound attenuating cubicle. Tygon tubing attached to the syringe was run inside the cubicle and attached to a swivel (Instech, Plymouth Meeting, PA) suspended above the ceiling of the chamber. From the swivel, another section of Tygon tubing was passed into the chamber inside a metal spring tether and attached to the rat's back-mounted cannula. Rats were connected to the infusion apparatus at all times while in the chamber.

2.1.4. Drugs

Surgery was preceded by injections of an antibiotic (gentamicin, 2.0mg/kg, intraperitoneal) and an analgesic/anti-inflammatory (flunixin meglumine, 1.1mg/kg, subcutaneous), and anesthesia was induced and maintained using isoflurane. Cocaine hydrochloride (NIDA, USA) was dissolved in sterile 0.9% saline solution to a concentration of 2.56mg/ml. The dose of each infusion was determined daily based on individual body weights and achieved by changing the activation duration of a fixed-speed (0.0527ml/s) syringe pump. During the 5 days of recovery from surgery, subcutaneous injections of an analgesic/anti-inflammatory (flunixin meglumine, 1.1mg/kg, subcutaneous) were provided twice daily. Catheter patency was maintained by daily 0.2ml infusions of gentamicin heparinized saline solution (4mg/ml gentamicin, .04mg/ml heparin) throughout the experiment.

2.2. Procedure

2.2.1. Pellet training

Rats were first trained to consume food pellets from the food aperture. Levers were retracted and lights were not illuminated during pellet training except for the illumination of the food aperture when pellets were delivered response-independently every 60s, on average (Variable Time 60s schedule). Each food delivery was accompanied by a 3s chamber blackout during which responses produced no consequences and all lights were extinguished except for the food aperture, which was illuminated for 3s. This reinforcement schedule and all variable schedules below were constructed from Fleshler and Hoffman's (1962) constant-probability distribution. All

sessions throughout were 45min excluding chamber blackouts and reinforcer delivery times. Pellet training lasted 4 sessions.

2.2.2. Cocaine self-administration training

During Cocaine self-administration training and throughout the remainder of the experiment, target and inactive levers were inserted at the beginning of each session and the stimulus light above the active lever was illuminated throughout the session except during chamber blackouts. Initially, each target lever press produced a 1mg/kg infusion of cocaine (Fixed Ratio [FR] 1 schedule). Each cocaine infusion throughout the experiment was followed by a tone and a 45s chamber blackout, during which all lights were extinguished and responses produced no consequences. As described previously (Nall et al., 2018), the reinforcement schedule was gradually thinned across sessions until rats were earning a cocaine infusion for every 20 responses, on average (Variable Ratio [VR] 20 schedule), and then the cocaine dose was gradually reduced across sessions to 0.32mg/kg/infusion. Throughout the experiment, responses to the inactive lever were recorded but had no consequence. Cocaine self-administration training lasted approximately 50 sessions.

2.2.3. Phase 1: Baseline

Once rats reached the 0.32mg/kg/infusion condition, Phase 1 began. Reinforcement contingencies were identical to those at the end of the cocaine self-administration training phase described above. This phase lasted at least 5 sessions and until rats showed no downward trend in cocaine consumption over the last 3 sessions.

2.2.4. Phase 2: Punishment

Rats were divided into two groups matched on target response rate and cocaine

consumption across the last 3 sessions of Phase 1. For both groups in Phase 2, target responding continued to produce cocaine infusions according to a VR 20 schedule, but each lever press also intermittently produced mild foot shock (probability = 0.5, 50ms, 0.5mA). For the *Alternative + Punishment* group (N = 5), the left-most nose poke aperture was illuminated, and entries into the aperture produced a food pellet according to a VI 15s schedule (the first response after an average of 15s was reinforced). Target and alternative responses were concurrently available throughout the punishment sessions and cocaine or food could be earned at any time except for during the timeout following cocaine infusions or food delivery. No alternative reinforcement was available for the *Punishment Control* group (N = 5). Phase 2 lasted 10 sessions.

2.2.5. Phase 3: Resurgence Test

All consequences were removed for all responses in both groups (i.e. no reinforcement or punishment was delivered) and resurgence of target responding was evaluated. Phase 3 lasted 5 sessions.

2.3. Experiment 1 data analysis

Time for reinforcer deliveries and chamber blackouts were excluded from session time in all rate measures reported below. All analyses were deemed significant at an α level of .05.

2.4 Experiment 1 results and summary

2.4.1. Phase 1: Baseline

Target response rates were similar between groups during the final three sessions of Phase 1 (see Table 2-1). This finding was confirmed by a one-way ANOVA conducted on the average of target response rates across the final three sessions of Phase 1 that

revealed no significant effect of Group $F(1,8) = .485$, $p = .506$, $\eta^2 = .057$. The amount of cocaine consumed was also similar between groups across the final three sessions of Phase 1 (see Table 2-1), as confirmed by a one-way ANOVA conducted on the average of obtained mg/kg across the final three sessions, $F(1,8) = .336$, $p = .578$, $\eta^2 = .040$). Table 2-1 includes a summary of response rates, reinforcer rates, and cocaine consumption for both groups across phases of Experiment 1.

2.4.2. Phase 2: Punishment of Cocaine Seeking

Figure 2-1A shows that target response rates decreased similarly across Phase 2 for both groups. A 2 x 10 (Group x Session) mixed-model ANOVA conducted on target response rates across all session of Phase 2 revealed a significant main effect of Session $F(9,72) = 7.033$, $p < .001$, $\eta_p^2 = .468$, but no significant main effect of Group $F(1,8) = .648$, $p = .444$, $\eta_p^2 = .075$, and no significant Group x Session interaction $F(9,72) = 1.127$, $p = .356$, $\eta_p^2 = .123$, confirming that target responding decreased similarly across Phase 2 for both groups.

Figure 2-1B shows that alternative responding increased across Phase 2 in the *Alternative + Punishment* group, but not in the *Punishment Control* group. This finding was confirmed by a 2 x 10 (Group x Session) mixed-model ANOVA conducted on alternative response rates across all sessions of Phase 2 which revealed a significant Group x Session interaction $F(9,72) = 12.169$, $p < .001$, $\eta_p^2 = .603$, a significant main effect of Session $F(9,72) = 12.122$, $p < .001$, $\eta_p^2 = .602$, and a significant main effect of Group $F(1,8) = 51.911$, $p < .001$, $\eta_p^2 = .866$.

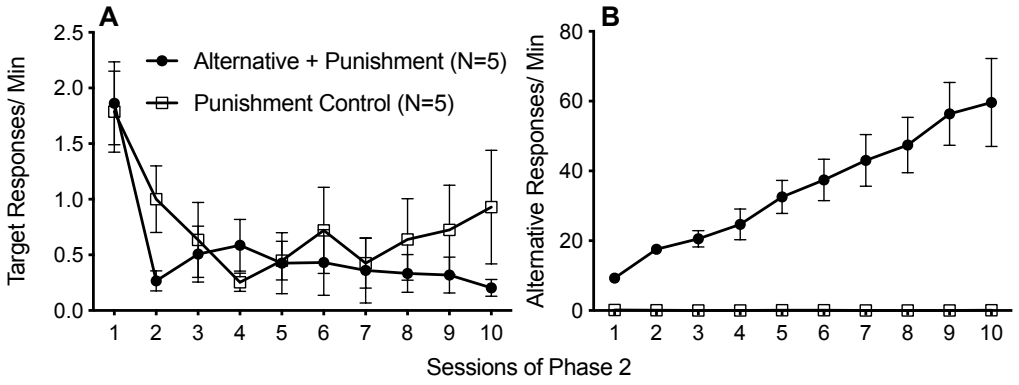

Figure 2-1. Target (A) and alternative (B) response rates across Phase 2 of Experiment 1. Error bars represent standard errors of the mean. Note difference in y-axes between panels A and B.

2.4.3. Phase 3: Resurgence Test

The dotted data paths in Figure 2-2A show that target response rates increased (i.e., resurgence occurred) between the last session of Phase 2 and the first session of Phase 3 for only the *Alternative + Punishment* group. To confirm this finding, a 2 x 2 (Group x Phase) mixed-model ANOVA was conducted on target response rates during the last session of Phase 2 and the first session of Phase 3 and revealed a significant Group x Session interaction $F(1,8) = 17.966$, $p = .003$, $\eta_p^2 = .692$, and a significant main effect of Session $F(1,8) = 15.643$, $p = .004$, $\eta_p^2 = .662$, but no significant main effect of Group $F(1,8) = .014$, $p = .909$, $\eta_p^2 = .002$. The solid data paths in Figure 2-2A show that target responding did not differ between groups across all sessions of Phase 3. A 2 x 5 (Group x Session) mixed-model ANOVA conducted on target response rates across all of Phase 3 revealed a significant main effect of Session $F(4,32) = 3.343$, $p = .021$, $\eta_p^2 = .295$, but no significant Group x Session interaction $F(4,32) = .154$, $p = .960$, $\eta_p^2 = .019$, and no significant main effect of Group $F(1,8) = 1.201$, $p = .305$, $\eta_p^2 = .131$. Thus, target responding increased between Phases 2 and 3 for the *Alternative + Punishment* group

alone, and then decreased across Phase 3 similarly for both groups.

Figure 2-2B shows that alternative responding decreased across Phase 3 for the *Alternative + Punishment* group, and remained low for the *Punishment control* group. These findings were verified by a 2 x 5 (Group x Session) mixed-model ANOVA revealing a significant Group x Session interaction $F(4,32) = 248.135$, $p < .001$, $\eta_p^2 = .969$, and significant main effects of Session $F(4,32) = 246.580$, $p < .001$, $\eta_p^2 = .969$ and Group $F(1,8) = 557.178$, $p < .001$, $\eta_p^2 = .986$.

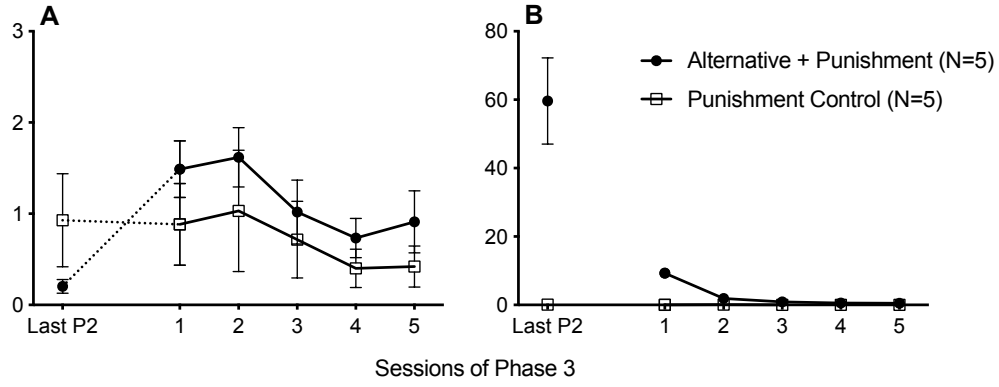

Figure 2-2. Target (A) and alternative (B) response rates across the last session of Phase 2 and all sessions of Phase 3 of Experiment 1. Error bars represent standard errors of the mean. Note difference in y-axes between panels A and B.

Inactive lever response rates did not increase between the last session of Phase 2 and the first session of Phase 3 for either group, indicating that resurgence was the result of responding directed toward the lever that previously produced cocaine rather than a general increase in lever pressing (see Table 2-1). This result was verified by a 2 x 2 (Group x Phase) mixed-model ANOVA conducted on inactive responding on the last session of Phase 2 and the first session of Phase 3, which revealed no significant main

effect of Session $F(1,8) = .070$, $p = .798$, $\eta_p^2 = .009$, no significant main effect of Group $F(1,8) = .961$, $p = .356$, $\eta_p^2 = .107$, and no significant Group x Session interaction $F(1,8) = .419$, $p = .536$, $\eta_p^2 = .050$.

Table 2-1.
Mean (SEM) Response and Reinforcer Rates from each Phase of Experiment 1.

	Group					
	Alternative + Punishment			Punishment Control		
	Phase 1[a]	Phase 2[b]	Phase 3[c]	Phase 1[a]	Phase 2[b]	Phase 3[c]
Target/Min	4.44	0.20	1.49	4.89	0.93	0.88
	(1.35)	(0.08)	(0.31)	(1.31)	(0.51)	(0.45)
Alt./Min	-	59.63	9.30	-	0.10	0.03
	-	(12.57)	(0.43)	-	(0.04)	(0.01)
Inactive/Min	0.19	0.57	0.48	0.39	1.27	1.49
	(0.09)	(0.24)	(0.04)	(0.11)	(0.69)	(1.06)
Infusions/Min	0.26	0.004	-	0.24	0.05	-
	(0.06)	(0.004)	-	(0.06)	(0.03)	-
Cocaine mg/kg	3.20	0.06	-	3.95	0.70	-
	(0.91)	(0.06)	-	(0.91)	(0.46)	-
Foods/Min	-	3.44	-	-	-	-
	-	(0.22)	-	-	-	-
Shocks/Min	-	0.11	-	-	0.43	-
	-	(0.04)	-	-	(0.24)	-

[a] Data averaged across the last three sessions of Phase 1 are shown, [b] Data from the last session of Phase 2 are shown, [c] Data from the first session of Phase 3 are shown.

2.4.4 Summary

Resurgence of cocaine seeking following suppression by punishment occurred when alternative reinforcement was removed for the *Alternative + Punishment* group in Experiment 1. No increase in target responding was observed when the punishment and reinforcement contingencies were discontinued for the *Punishment Control* group during resurgence testing. Thus, the increase in drug seeking (i.e., target responding) between Phases 2 and 3 was due to the loss of alternative reinforcement and not the removal of the

punishment contingency.

3. Experiment 2

The procedure developed in Experiment 1 evaluated resurgence induced by loss of alternative reinforcement under conditions where cocaine-seeking responses had no consequences in Phase 3. This is advantageous for making comparisons to other resurgence procedures (Frye et al., 2018; Nall et al., 2018, 2019; Quick et al., 2011; Shahan et al., 2015) as well as other procedures that have examined relapse of previously-punished drug seeking (Nathan J. Marchant, Khuc, et al., 2013; Nall et al., 2019; Leigh V. Panlilio et al., 2003; Pelloux et al., 2018). However, humans are not likely to experience extinction of drug seeking following treatment with alternative reinforcement (Nathan J. Marchant, Li, et al., 2013; Leigh V. Panlilio et al., 2005). Rather, when treatment ends, the individual retains the option to seek drugs and produce both the positive and negative consequences of doing so. Previous work has examined relapse of previously-punished behavior when either the positive (e.g., Leigh V. Panlilio et al., 2005) or negative (e.g., Cooper, Barnea-Ygael, Levy, Shaham, & Zangen, 2007) consequences of drug seeking remained in place, but not both. Thus, Experiment 2 was designed to assess resurgence of previously-punished cocaine seeking in rats while both reinforcement and punishment of drug seeking remained available during the Phase 3 test.

3.1. Material and method

3.2.1. Subjects. Thirteen experimentally naïve male Long-Evans rats served as subjects in Experiment 2. Housing, care, surgical procedures, apparatus, and drugs were identical to those detailed in Experiment 1. One rat in the *Alternative + Punishment*

group with extremely high rates of target responding was identified as an outlier using Grubbs' method (Grubbs, 1969) with α=.05, and thus was removed from all analyses.

3.2. Procedure

Procedures for pellet training, cocaine self-administration training, and Phase 1: Baseline, were all identical to those described in Experiment 1 (see Section 2.2 above for details).

3.2.1. Phase 2: Punishment of Cocaine Seeking

Rats were divided into two groups matched on target response rate and cocaine consumption across the last 3 sessions of Phase 1. For the *Alternative + Punishment* group (N = 6), alternative responses produced food as described in Experiment 1 and target responses produced cocaine and shock as described in Experiment 1. For the *Punishment Control* group (N = 7), as described in Experiment 1, the target responding produced cocaine and shock but no alternative reinforcement was available. Phase 2 lasted 10 sessions.

3.2.2. Phase 3: Resurgence test

During Phase 3, alternative reinforcement was removed for the *Alternative + Punishment* group. All consequences for target responding remained in place for both groups. That is, target responding was reinforced with 0.32mg/kg infusions of cocaine according to a VR 20 schedule. Target responding also continued to produce intermittent mild foot shock as in Phase 2. Phase 3 lasted for 5 sessions.

3.3. Experiment 2 data analysis

Primary data analyses were conducted as in Experiment 1.

3.4 Experiment 2 results and summary

3.4.1. Phase 1: Baseline

Target response rates were similar between groups during the final three sessions of Phase 1 (see Table 2-2). This finding was confirmed by a one-way ANOVA conducted on the average of target response rates across the final three sessions of Phase 1 that revealed no significant effect of Group $F(1,12) = .011$, $p = .917$, $\eta^2 = .001$. The amount of cocaine consumed was also similar between groups across the final three sessions of Phase 1 (see Table 2-2), as confirmed by a one-way ANOVA conducted on the average of obtained mg/kg across the final three sessions which found no significant effect of Group $F(1,12) = .063$, $p = .806$, $\eta^2 = .006$). Table 2-2 includes a summary of response rates, reinforcer rates, and cocaine consumption for both groups across phases of Experiment 2.

3.4.2. Phase 2: Punishment

Figure 2-3A shows that target response rates decreased across Phase 2 for both groups and were lower for the *Alternative + Punishment* group than for the *Punishment Control* Group. A 2 x 10 (Group x Session) mixed-model ANOVA conducted on target response rates across all session of Phase 2 revealed a significant main effect of Session $F(9,99) = 2.264$, $p = .024$, $\eta_p^2 = .171$, and a significant main effect of Group $F(1,11) = 7.130$, $p = .022$, $\eta_p^2 = .393$, but no significant Group x Session interaction $F(9,99) = .252$, $p = .985$, $\eta_p^2 = .022$. Thus, target response rates decreased at a similar rate across Phase 2 for both groups and target response rates were lower for the *Alternative + Punishment* group than for the *Punishment Control* group.

Figure 2-3B shows that alternative responding increased across Phase 2 in the *Alternative + Punishment* group, but not in the *Punishment Control* group. This finding was confirmed by a 2 x 10 (Group x Session) mixed-model ANOVA conducted on alternative response rates across all sessions of Phase 2 which revealed a significant Group x Session interaction $F(9,99) = 7.289$, $p < .001$, $\eta_p^2 = .399$, a significant main effect of Session $F(9,99) = 7.254$, $p < .001$, $\eta_p^2 = .397$, and a significant main effect of Group $F(1,11) = 11.685$, $p = .006$, $\eta_p^2 = .515$.

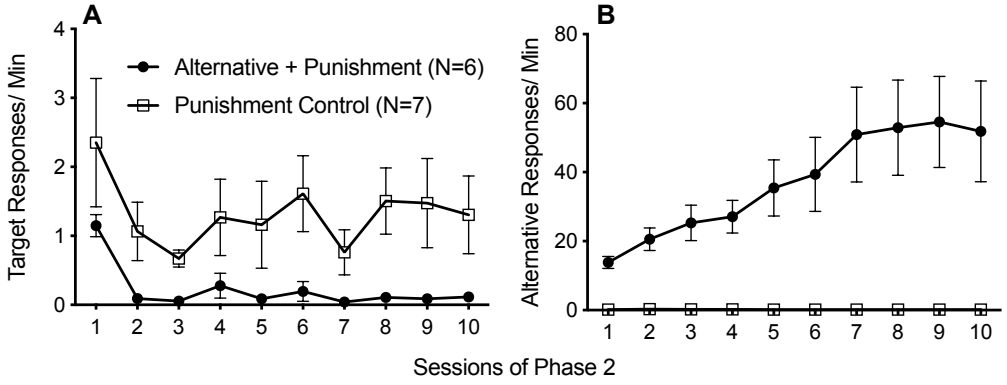

Figure 2-3. Target (A) and alternative (B) response rates across Phase 2 of Experiment 2. Error bars represent standard errors of the mean. Note difference in y-axes between panels A and B.

Because target response rates were lower during Punishment for the *Alternative + Punishment* group than in the *Punishment Control* group during Experiment 2 but not Experiment 1, but all conditions were identical between experiments, a comparison of target response rates combined across experiments was warranted. A 2 x 10 mixed model ANOVA conducted on target response rates during Punishment combined across Experiments 1 and 2 revealed a significant main effects of Session $F(9,189) = 6.184$, $p < .001$, $\eta_p^2 = .227$ and Group $F(1,21) = 7.102$, $p = .014$, $\eta_p^2 = .253$, but no significant Group

x Session interaction $F(9,189) = .559$, $p = .829$, $\eta_p^2 = .026$. Thus, when target response rates during Punishment were combined across experiments, target response rates decreased at a similar rate for both groups, and were lower for the *Alternative + Punishment* group than for the *Punishment Control* group.

3.4.3. Phase 3: Resurgence Test

Mean target response rates increased slightly only for the *Alternative + Punishment* group between the last session of Phase 2 and first session of Phase 3, but that effect was not statistically robust (see dotted data paths in Figure 2-4A). A 2 x 2 (Group x Phase) mixed-model ANOVA was conducted on target response rates during the last session of Phase 2 and the first session of Phase 3 and found no significant Group x Session interaction $F(1,11) = 1.686$, $p = .221$, $\eta_p^2 = .133$, no significant main effect of Session $F(1,11) = .824$, $p = .383$, $\eta_p^2 = .070$, and no significant main effect of Group $F(1,11) = 1.399$, $p = .262$, $\eta_p^2 = .113$. The solid data paths in Figure 2-4A show that target responding did not differ between groups across all sessions of Phase 3. A 2 x 5 (Group x Session) mixed-model ANOVA conducted on target response rates across all of Phase 3 revealed no significant main effect of Session $F(4,44) = .559$, $p = .694$, $\eta_p^2 = .048$, no significant main effect of Group $F(1,12) = .006$, $p = .939$, $\eta_p^2 = .001$, and no significant Group x Session interaction $F(4,44) = .579$, $p = .680$, $\eta_p^2 = .050$. Thus, target responding did not increase significantly for either group with the change from Phases 2 to Phase 3, and responding remained stable across Phase 3 for both groups.

Figure 2-4B shows that alternative responding decreased across Phase 3 for the *Alternative + Punishment* group, and remained low for the *Punishment Control* group. These findings were verified by a 2 x 5 (Group x Session) mixed-model ANOVA

revealing a significant Group x Session interaction $F(4,44) = 12.545$, $p < .001$, $\eta_p^2 = .533$, and significant main effects of Session $F(4,44) = 12.285$, $p < .001$, $\eta_p^2 = .528$ and Group $F(1,11) = 19.888$, $p = .001$, $\eta_p^2 = .644$.

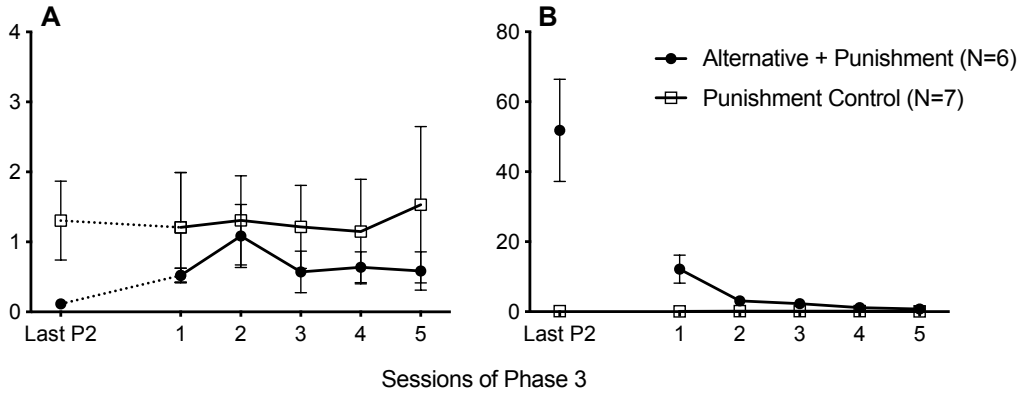

Figure 2-4. Target (A) and alternative (B) response rates across the last session of Phase 2 and all sessions of Phase 3 of Experiment 2. Error bars represent standard errors of the mean. Note difference in y-axes between panels A and B.

Inactive response rates did not increase between the last session of Phase 2 and the first session of Phase 3 for either group (see Table 2-2). This result was verified by a 2 x 2 (Group x Phase) mixed-model ANOVA conducted on inactive responding on the last session of Phase 2 and the first session of Phase 3, which revealed no significant main effect of Session $F(1,11) = 2.961$, $p = .113$, $\eta_p^2 = .212$, no significant main effect of Group $F(1,11) = 2.212$, $p = .165$, $\eta_p^2 = .167$, and no significant Group x Session interaction $F(1,11) = .657$, $p = .435$, $\eta_p^2 = .056$.

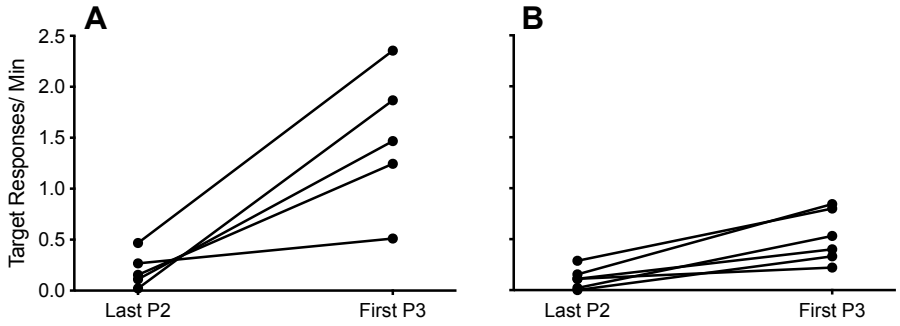

Figure 2-5. Target response rates for each individual in the Alternative + Punishment groups of Experiment 1 (A) and Experiment 2 (B) during the last session of Phase 2 (last P2) and first session of Phase 3 (First P3).

Because resurgence appeared to be blunted in Experiment 2, and all other aspects of the experiments were similar to Experiment 1 except the testing conditions in Phase 3, a comparison with the effect in Experiment 1 was warranted. Figure 2-5 shows target response rates during the last session of Phase 2 and first session of Phase 3 for each individual rat in the *Alternative + Punishment* groups from Experiment 1 (A) and Experiment 2 (B). Target responding increased for every rat in the *Alternative + Punishment* groups in both experiments when alternative reinforcement was discontinued during Phase 3, but the increases were generally much larger in Experiment 1. A 2 x 2 (Experiment x Phase) mixed-model ANOVA conducted on target response rates in the last session of Phase 2 and the first session of Phase 3 for the *Alternative + Punishment* groups in Experiment 1 and Experiment 2. The ANOVA revealed a significant Experiment x Phase interaction $F(1,8) = 9.787$, $p = .014$, $\eta_p^2 = .550$, and significant main effects of Experiment $F(1,8) = 15.966$, $p = .004$, $\eta_p^2 = .666$, and Phase $F(1,8) = 19.258$, $p = .002$, $\eta_p^2 = .707$. Follow up paired-sample t-tests indicated that target response rates increased between the last session of punishment and first session of resurgence testing in

both experiments (Experiment 1, t = 4.277, p = .013; Experiment 2, t = 5.740, p = .002). Thus, mean target response rate increased between phases 2 and 3 of both experiments (i.e. resurgence occurred), and the increase in target responding was larger in Experiment 1 than in Experiment 2.

Table 2-2.
Mean (SEM) Response and Reinforcer Rates from each Phase of Experiment 2.

	Group					
	Alternative + Punishment			Punishment Control		
	Phase 1[a]	Phase 2[b]	Phase 3[c]	Phase 1[a]	Phase 2[b]	Phase 3[c]
Target/Min	6.65	0.11	0.52	6.77	1.30	1.21
	(0.84)	(0.04)	(0.10)	(0.93)	(0.56)	(0.78)
Alt./Min	-	51.84	12.17	-	0.17	0.07
	-	(14.58)	(4.04)	-	(0.10)	(0.04)
Inactive/Min	0.18	0.88	1.11	0.19	0.16	0.24
	(0.07)	(0.62)	(0.53)	(0.05)	(0.04)	(0.12)
Infusions/Min	0.33	0.00	0.02	0.34	0.07	0.06
	(0.04)	(0.00)	(0.01)	(0.05)	(0.03)	(0.04)
Cocaine mg/kg	4.73	0.00	0.27	4.93	1.01	0.82
	(0.60)	(0.00)	(0.10)	(0.70)	(0.50)	(0.57)
Foods/Min	-	3.34	-	-	-	-
	-	(0.21)	-	-	-	-
Shocks/Min	-	0.07	0.27	-	0.60	0.56
	-	(0.03)	(0.06)	-	(0.24)	(0.36)

[a] Data averaged across the last three sessions of Phase 1 are shown, [b] Data from the last session of Phase 2 are shown, [c] Data from the first session of Phase 3 are shown.

3.4.4 Summary

The goal of Experiment 2 was to evaluate resurgence while cocaine reinforcement and punishment remained available for the target behavior, as these conditions may be more analogous to the conditions present when humans with SUDs end alternative-reinforcement-based treatment. Though the dotted data paths in Figure 2-4A hint at a

possible resurgence effect, the continued presence of punishment for cocaine seeking in Phase 3 considerably reduced the magnitude of the effect. Thus, the results indicate that under the current conditions, resurgence effects appear to be smaller when reinforcement and punishment remain in place for the target response during the resurgence test compared to the conditions for resurgence testing in Experiment 1 (i.e., target and alternative extinction, removal of punishment). Further implications will be discussed below.

4. General Discussion

The goal of the present experiments was to develop a model of resurgence of drug seeking following suppression by aversive consequences. In the first phase of Experiment 1, rats pressed levers to earn infusions of cocaine. In Phase 2, cocaine remained available, but lever pressing also produced mild intermittent foot shock. For the *Alternative + Punishment* group in Phase 2, nose poking produced food pellets (i.e. alternative reinforcement). No alternative reinforcement was available for the *Punishment Control* group. Finally, in Phase 3, all consequences were removed for both responses in both groups. That is, lever presses no longer produced shock or cocaine in either group and nose poking no longer produced food for the *Alternative + Punishment* group.

Resurgence of cocaine seeking was observed following the removal of alternative reinforcement for the *Alternative + Punishment* group in Experiment 1. Importantly, the removal of punishment alone in the *Punishment Control* group was not sufficient to produce relapse. Thus, the increase in cocaine seeking in the *Alternative + Punishment* group was due to the history of exposure to and then removal of alternative reinforcement (i.e. resurgence) and not the removal of punishment alone. These data are consistent with

previous studies demonstrating a variety of relapse effects following suppression by punishment (Campbell et al., 2017; Ducret et al., 2016; Economidou et al., 2009; Krasnova et al., 2014; N. J. Marchant et al., 2016; Leigh V. Panlilio et al., 2003; Pelloux et al., 2018), with previous studies showing that the removal of non-drug alternative reinforcement can induce relapse of drug seeking following extinction (Craig et al., 2016; Nall et al., 2018; Podlesnik et al., 2006), and with previous studies demonstrating resurgence of food seeking following suppression by punishment (Nall et al., 2019). The procedures developed in Experiment 1 represent an improvement in the face validity of the animal model of resurgence, better represent the environmental (and potentially neurobiological) factors involved in resurgence of drug seeking in humans, and allow for comparisons between extinction-based resurgence models and other punishment-based models of relapse that test under extinction conditions.

Previous work has examined relapse of previously-punished drug seeking when reinforcement or punishment was continued, but not both. For example, Panlilio et al. (2005) found greater reinstatement by drug-priming injections when remifentanil remained available than when it was unavailable following punishment of the remifentanil-seeking response. However, punishment was discontinued for both groups during the reinstatement test. Cooper et al. (2007) found greater reinstatement by noncontingent exposure to drug-paired cues when punishment was discontinued than when it remained in effect. However, reinforcement was discontinued for both groups during the reinstatement test. Thus, Experiment 2 was designed to assess resurgence while both the positive and negative consequences of drug seeking remained available following suppression of the drug-seeking response by punishment. Rats earned cocaine

infusions during Phase 1 of Experiment 2. Next, cocaine seeking was reinforced and punished, and alternative reinforcement was made available for the *Alternative + Punishment* group but not the *Punishment Control* group. Finally, alternative reinforcement was removed for the *Alternative + Punishment* group and cocaine seeking continued to produce cocaine and punishment for both groups. A small, non-statistically significant increase in target responding occurred following the removal of alternative reinforcement for rats in the *Alternative + Punishment* group, and no change in responding was observed for the *Punishment Control* group.

On the one hand, it is unsurprising that resurgence did not occur for rats in the *Alternative + Punishment* group during Experiment 2, as the continued presence of punishment should serve to reduce drug seeking compared to the extinction conditions present during testing in Experiment 1 (Cooper et al., 2007). On the other hand, one might have expected some resurgence as continued cocaine reinforcement should have served to increase target responding relative to the extinction conditions during testing in Experiment 1 (Leigh V. Panlilio et al., 2005). Thus, the reduced resurgence in Experiment 2 suggests that continued punishment was more effective at suppressing responding than continued reinforcement was at increasing responding. However, rates of target responding (and thus, shock) were higher for the *Punishment Control* group across Phases 2 and 3 (see Table 2-2), indicating that the parameters of shock used in Experiment 2 could permit higher rates of responding that those observed in the *Alternative + Punishment* group. Further, target responding remained stable during Phase 3 for both groups in Experiment 2, but decreased across Phase 3 for both groups in Experiment 1. This finding suggests that even though punishment suppressed resurgence

in Experiment 2, the punishment schedule was permissive enough to allow relatively low and stable rates of cocaine self-administration to continue across 5 further sessions of punishment. Finally, target response rate did increase for the *Alternative + Punishment* group when alternative reinforcement was removed, albeit not too a level significantly different to the *Punishment* Control group (see Figures 2-4A and 2-5B). Taken together, these observations suggest that continued punishment of cocaine seeking reduced resurgence in Experiment 2 relative to the extinction conditions in place in Experiment 1, but that continued reinforcement maintained relatively low and stable rates of cocaine seeking for at least 5 sessions. These results indicate that continuation of both the positive and negative effects of drug seeking may play an important role in determining abstinence from drug use following treatment with alternative reinforcement.

While the removal of alternative reinforcement did not result in a significant resurgence effect in Experiment 2, rates of drug seeking were lower during Phase 2 punishment when alternative reinforcement was available. These findings are consistent with previous work demonstrating increased suppression of drug seeking (e.g. Pelloux, Murray, & Everitt, 2015) and food seeking (e.g. Nall et al., 2019) by punishment when alternative reinforcement is concurrently available. This effect was not statistically significant during Experiment 1, but data for the *Punishment Control* group showed an increasing trend across the last 6 sessions of Phase 2 (see Figure 2-2A). While the effect was non-significant, the obtained effect size was relatively large ($\eta_p^2 = .123$). Further, an analysis of target response rates during punishment combined across both experiments indicated that alternative reinforcement increased sensitivity to punishment. Finally, the results of Experiment 2 and prior studies (e.g. Nall et al., 2019; Pelloux, Everitt, &

Dickinson, 2007; Pelloux et al., 2015) provide evidence for the consistency of this effect. Thus, the reason alternative reinforcement further suppressed punished cocaine seeking in Experiment 2 but did not in Experiment 1 is most possibly due to individual differences in sensitivity to foot shock.

The finding that availability of alternative reinforcement increases the efficacy of punishment may also be relevant for treatment of SUDs in humans. As discussed above, aversive consequences of substance use are thought to reduce drug seeking in natural environments and are often influential in decisions to enter treatment. Thus, treatments that include alternative reinforcement components or are based on alternative reinforcement should increase the efficacy of the natural punishment contingencies for substance use. Indeed, including alternative reinforcement in existing treatment approaches can increase treatment outcomes (e.g. García-Fernández et al., 2011) and alternative-reinforcement-based treatments are among the most effective for substance use disorders (Prendergast et al., 2006). Thus, the models developed here may be beneficial for investigations into the additional suppressive effects that alternative reinforcement may provide when available during punishment.

The models developed here are designed to assess relapse following the removal of alternative reinforcement, which is often used in the treatment of SUDs. Perhaps the most popular form of alternative-reinforcement-based treatment for SUDs is contingency management (Prendergast et al., 2006). It is important to note that the models developed here differ from contingency management by allowing alternative reinforcers to be consumed despite continued drug taking. In contingency management, drug use results in a loss or reduction of the therapeutic alternative reinforcer. The recently developed

voluntary abstinence procedure has sought to model contingency management more directly in animals by first training rats to respond for drugs, and then presenting alternative non-drug reinforcers in a mutually exclusive choice task before examining cue-induced reinstatement under extinction conditions (e.g., Caprioli, Zeric, Thorndike, & Venniro, 2015; Venniro et al., 2018). This model is advantageous because it simulates the suppression of drug seeking by mutually exclusive alternative reinforcement in contingency management and because it is capable of modeling suppression by social stimuli (Venniro et al., 2018). However, the role of aversive consequences of drug use has not been simulated in the voluntary abstinence model to date. Further, studies using the voluntary abstinence model have not included groups that undergo extinction tests without exposure to drug-paired cues. Thus, it is impossible to differentiate the effects of re-exposure to drug-paired cues (i.e. cue-induced reinstatement) and the removal of alternative reinforcement (i.e. resurgence) in this paradigm. Finally, alternative-reinforcement-based treatments other than contingency management do not provide alternative reinforcement contingent upon abstinence. For example, in the community reinforcement approach (e.g., Godley et al., 2017; Hunt & Azrin, 1973b) and behavioral self-control training (e.g., Miller, Leckman, Delaney, & Tinkcom, 1992) individuals undergo counseling which includes strategies to obtain alternative reinforcement in the natural environment without requirements of drug abstinence. In fact, one of the goals of behavioral self-control training is to achieve non-problematic levels of alcohol consumption (Miller & Baca, 1983). Thus, the exclusive choice programmed in the voluntary abstinence model may be a more direct model of contingency management, but it does not simulate all forms of alternative-reinforcement-based treatment. Given the

relative strengths of the voluntary abstinence model and the resurgence model developed here, various combinations of the two models may be better suited to simulating the effects of particular treatment approaches.

Future neurobiological and pharmacological studies similar to those conducted by Pelloux et al. (2018) and Panlilio et al. (2005) are necessary to determine if different underlying mechanisms are involved in relapse tested during extinction and relapse tested during continued reinforcement and punishment. The outcomes of these future studies could be instrumental in furthering a mechanistic understanding of relapse effects and for developing novel treatments to reduce relapse of drug seeking following treatment. Further, evidence suggests that individuals who spontaneously abstain from drug use often attribute their abstinence to the negative effects associated with drug use and the procurement of alternative reinforcement (Burman, 1997). Thus, the models developed herein could also contribute to a better understanding of abstinence and relapse outside of treatment.

Two contemporary theories of resurgence may explain the results of the present results. Context Theory (Trask, Schepers, & Bouton, 2015) suggests that resurgence may be a special case of ABC renewal where the reinforcement conditions of each phase represent contextual stimuli. That is, reinforcement of target behavior during Phase 1 represents Context A. Reinforcement and punishment of the target response, plus reinforcement of the alternative response during Phase 2 represents Context B. And, extinction of target and alternative responding (Experiment 1) or extinction of alternative responding (Experiment 2) represent Context C. Bouton et al. have suggested that inhibitory learning generated by punishment (Schepers & Bouton, 2015) or extinction

(Trask et al., 2015) is highly context-specific. Thus, according to Context Theory, increases in target response rate during Phase 3 are the product of inhibitory learning specific to Context B failing to generalize to the novel Context C (i.e. operant renewal of drug seeking).

The present findings are generally consistent with Context Theory. Response inhibition learned during punishment may have failed to generalize when target and alternative responses were extinguished (Experiment 1) or the alternative response alone was extinguished (Experiment 2) during resurgence testing. Further, the difference in resurgence magnitude between experiments may be explained by the relatively small context change in Experiment 2 relative to Experiment 1. That is, continuing to reinforce and punish target responding during Experiment 2 may have made the context during Phase 3 more similar to that of Phase 2. Indeed, prior work has demonstrated that retaining aspects of the context in which responding was suppressed can reduce resurgence (Podlesnik et al., 2019). However, a quantitative measure for the magnitude of contextual changes and how they influence resurgence has yet to be proposed, making specific predictions about resurgence effects based on the similarity or difference of contexts difficult to generate. For example, during Experiment 1, the removal of target reinforcement and punishment during resurgence testing for rats in the *Punishment Control* group was not sufficient to induce relapse. In Experiment 2, removal of alternative reinforcement alone did produce a small relapse effect. Presumably, the removal of only alternative reinforcement in Experiment 2 should represent a smaller contextual change than the removal of both target punishment and reinforcement in Experiment 1. Thus, while some of the data here align with a Context Theory

interpretation, others are difficult to reconcile. This lack of specificity and the flexibility of Context Theory have led some to question the utility of the approach for making a priori predictions regarding relapse effects (Craig & Shahan, 2016; McConnell & Miller, 2014; Nall et al., 2018, 2019; Podlesnik & Kelley, 2014; Shahan & Craig, 2017).

Resurgence as Choice (RaC; Shahan & Craig, 2017) is an alternative theory of resurgence based on the concatenated matching law (Baum & Rachlin, 1969). According to RaC, the conditional probability of target responding is determined by:

$$\mathrm{pT} = \frac{V_T}{V_T + V_{Alt}} \quad (1)$$

Where *p*T is the conditional probability of a target response, and V_T and V_{Alt} are the values of target and alternative options, respectively (see, Shahan & Craig, 2017 for details on how conditional probability can be converted to response rates). By using a version of the Temporal Weighting Rule (Devenport, Hill, Wilson, & Ogden, 1997), RaC provides a quantitative measure of values of target and alternative responses over time. When alternative reinforcement is removed during resurgence testing, the value of the alternative options decreases, producing an increase in target responding via Equation 1.

According to Equation 1, RaC would suggest that decreases in the value of alternative reinforcement should produce an increase in the conditional probability of target responding (i.e. resurgence). This would explain increases in target response rates during resurgence testing in Experiments 1 and 2. Further, recent studies have discussed that punishment should result in decreases in the value of the punished response within this framework (Fontes et al., 2018; Nall et al., 2019). Thus, the continued punishment of target responding during Phase 3 of Experiment 2 might reduce resurgence relative to the

extinction conditions present during resurgence testing in Experiment 1. However, continued reinforcement of the target response should increase the value of target option, increasing resurgence in Experiment 2. Thus, RaC might serve as a quantitative means for investigating how the reductions in value via punishment and increases in value via reinforcement might interact to influence resurgence under the conditions of resurgence testing in Experiment 2. However, to date, there is no effective means for incorporating punishment into matching-based models (Klapes, Riley, & McDowell, 2018). Thus, formal predictions from RaC about resurgence under punishment conditions await effective quantitative methods for predicting punishment effects. As such, predictions from RaC for the present study remain speculative and subject to the same criticisms as Context Theory discussed above, and further quantitative development is required to formally compare the two theories with respect to punishment-based studies on resurgence.

5. Conclusion

The results of Experiment 1 suggest that loss of alternative reinforcement can induce relapse (i.e., resurgence) of cocaine seeking previously suppressed by punishment. The results of Experiment 2 showed that expected resurgence effects were suppressed when both punishment and cocaine reinforcement were produced by cocaine seeking during the resurgence test. Further manipulations of parameters of punishment, reinforcement, or both are necessary to determine if more robust resurgence can occur when both the positive and negative effects of drug seeking remain during testing. The models developed here improve the face validity of the animal model of resurgence of drug seeking and provide a basis for examining the factors underlying resurgence as well

as those underlying relapse during continued reinforcement and punishment. As such, future work with these models should provide insights for a better mechanistic understanding of relapse effects and for development of novel treatments.

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CHAPTER 3

RESURGENCE OF PUNISHMENT-SUPPRESSED COCAINE SEEKING FOLLOWING LONG ACCESS IN RATS

Abstract

Alternative-reinforcer based treatments are among the most successful for reducing drug use in individuals with substance use disorders. However, relapse often occurs when alternative reinforcers are removed following treatment. Relapse following the loss of alternative reinforcement has been termed resurgence and represents a challenge to otherwise effective treatments for substance use disorders. An animal model has been useful for investigating resurgence, but the current procedure does not simulate the uncontrolled nature of drug-related behaviors seen in humans with substance use disorders. The current experiment was designed to do so by incorporating a long access procedure to simulate uncontrolled cocaine seeking in rats. Rats were first trained to press levers to earn infusions of cocaine. Next, rats were divided into two groups and continued to earn cocaine in either 1hr or 6hr self-administration sessions. Then, half of the rats from each access condition received food pellets for performing an alternative response while cocaine responses continued to be reinforced but also produced intermittent mild foot shock. For the other half of the rats from each access condition, lever pressing produced cocaine and shock but no alternative reinforcement was available. Finally, all consequences were removed from all responses and similar relapse was observed across all four groups. These data suggest that the duration of access during training did not

influence resurgence of drug seeking and that resurgence effects may be unique in their sensitivity to the effects of long access.

1. Introduction

Treatment techniques that provide reinforcement for non-drug-related behaviors are among the most effective at reducing drug use in individuals with substance use disorder (SUD). Popular treatment methods such as voucher-based contingency management and community reinforcement provide alternative reinforcement to reduce problematic substance use. In contingency management, patients earn vouchers for retail items by providing evidence of drug abstinence [e.g. 1]. In community reinforcement, participation in prosocial non-drug related activities such as recreation, job procurement, and spending time with family are explicitly reinforced [e.g. 2,3]. These alternative-reinforcement-based strategies are among the most effective for reducing substance use during treatment [4]. However, relapse occurs in as many as 60% of patients following alternative-reinforcement-based treatment [5–7]. Relapse induced by the loss of alternative reinforcement has been termed resurgence [8], and represents a challenge to otherwise effective strategies for treating SUDs. Thus, a better understanding of resurgence should lead to improvements in existing treatments and to the development of novel strategies to reduce relapse after treatment with alternative reinforcement.

Resurgence of drug seeking has been studied in the animal laboratory using a three-phase procedure [9–13]. In Phase 1, animals earn access to drug reinforcers by performing a target response. In Phase 2, performing the target response no longer produces drug (i.e. target responding is extinguished). Also during Phase 2, non-drug alternative reinforcers can be earned by performing an alternative response. In Phase 3, the target response remains on extinction and the alternative response is extinguished. Typically, an increase in target responding is observed between the end of Phase 2, where

alternative reinforcers are available, and the beginning of Phase 3, where alternative reinforcers are unavailable. That is, the removal of alternative reinforcement induces resurgence of drug seeking. Previous work has demonstrated resurgence of cocaine [9–11] and alcohol [9,13,14] seeking in rats following the loss of alternative reinforcement. These findings have led researchers to suggest that the resurgence procedure might be useful for evaluating resurgence following alternative-reinforcement-based treatments for SUDs in humans [15–17].

Resurgence procedures, as most traditional animal models of relapse, have received criticism for using extinction of drug seeking to study relapse effects [e.g., 17]. There are two reasons for this criticism. First, individuals with SUDs most often refer to the aversive consequences of drug-related behaviors as the reason for seeking drug abstinence with [18] or without [19] formal treatment. Second, it is unlikely that drug seeking and taking behaviors would not be followed by drug effects in the human environment. Thus, researchers have developed methods for reducing drug seeking using aversive consequences in animal models [e.g., 20–23]. This technology was recently applied to the animal model of resurgence of drug seeking. Nall and Shahan [24] first trained animals to press levers to earn infusions of cocaine. Next, lever pressing continued to produce cocaine, but also produced mild foot shock. Alternative reinforcement was available during punishment for one group, but not the other. Finally, alternative reinforcement was discontinued. When target consequences were also removed during the resurgence testing phase, resurgence of cocaine seeking occurred only for rats that previously received alternative reinforcement. When target consequences remained and only alternative reinforcement was discontinued during

testing, resurgence was suppressed. These results indicate that resurgence of cocaine seeking can occur after suppression by punishment, but that continued punishment of the drug seeking response may suppress the effect.

Another criticism of traditional animal models of relapse, including resurgence models, is that they do not capture the loss of control over drug-related behaviors seen in individuals with SUDs [25]. According to the Diagnostic and Statistical Manual of Mental Disorders [26], SUDs are diagnosed by the presence of several behavioral symptoms. Some have argued that models designed to evaluate relapse should produce behavior that simulates these diagnostic criteria [see, 27]. One widely-used example is the long access model, which simply allows animals to consume relatively unlimited amounts of drug in relatively long sessions [28]. Typically, the effects of long access (e.g. 6-hr or longer sessions) are compared to short access conditions (e.g. 2-hr or shorter sessions) with all factors other than session duration held constant. Table 3-1 presents the diagnostic criteria for SUDs and findings from animal models of long access that reflect those criteria. Briefly, rats exposed to long access tend to consume more drug than short access counter parts [29], show an increased propensity for relapse [29], respond more during punishment [30], choose drug over non-drug options more [31], and show increased motivation for drugs [32]. These findings mimic several of the diagnostic criteria for SUDs in humans detailed in Table 3-1, and can be broadly summarized as evidence of uncontrolled drug seeking.

To date, long access procedures have been used to examine relapse induced by re-exposure to drugs [28,33,42,34–41], drug cues [34,41,43,44], and stress [45,46], but not the loss of alternative reinforcement (i.e. resurgence). Because long access procedures

produce behavior in animals that better represents the behavior of individuals with SUDs, and because resurgence procedures better model the use of alternative reinforcement to treat SUDs, it may be important to investigate the effects of long access on resurgence of drug seeking. Some of the behavioral effects produced by long access may also be particularly relevant to the study of resurgence. First, evidence indicates that long access procedures can increase choice of drug over non-drug alternatives [47]. This is especially relevant for resurgence, as some have concluded that this shift in preference indicates a change in the relative value of drug and non-drug reinforcers [31], and differences in relative value have been shown to influence response suppression and relapse in resurgence paradigms [12,16,48]. Further, a contemporary theoretical and quantitative approach to explaining resurgence is based on changes in relative value associated with different response options across conditions [49]. Thus, any changes in relative value of drug and non-drug reinforcement induced by long access may influence responding in the resurgence paradigm. Second, ample evidence shows that long access can increase relapse effects relative to short access [e.g., 33,42,43,46,50]. If this finding generalizes to resurgence effects, it may be important to simulate this increased resurgence effect in studies designed to evaluate potential strategies to mitigate resurgence of drug seeking following treatment for SUDs. Finally, previous work indicates that long access conditions can increase resistance to punishment relative to short access conditions [30,32,51]. As discussed above, a recent study has developed an animal model for studying resurgence of previously-punished cocaine seeking to better simulate the role of aversive consequences in suppressing drug-related behaviors in individuals with SUDs [24]. Because the increased resistance to punishment produced by long access better

simulates the compulsive nature of drug-related behaviors in individuals with SUDs, it may be important to evaluate resurgence of previously-punished drug seeking following long access in animals.

Taken together, the evidence discussed above suggests that humans with SUDs display drug-related behavior that is uncontrolled, generally abstain from drug seeking due to the aversive consequences of drug-related behaviors, and often relapse following treatment with alternative reinforcement. Thus, the goal of the present experiment was to incorporate all of those factors into an animal model of relapse that may be used to evaluate existing treatment strategies and design novel treatments for SUDs. In Phase 1, animals were trained to earn cocaine infusions by pressing a target lever in 1hr sessions. In Phase 2, animals were divided into two groups. For the Long Access group, target responses continued to produce cocaine, but session durations were extended to 6hrs. For the Short Access group, target responding continued to produce cocaine in 1hr sessions. In Phase 3, rats from the Long Access and Short Access groups were further subdivided into 4 total groups and sessions returned to 1hr for all groups. Target responding continued to produce cocaine, but also produced intermittent mild foot shock in all groups. For the Long Access + Alternative and Short Access + Alternative groups, food pellets could be earned by performing an alternative nose poke response. No alternative reinforcement was available for the Long Access Control and Short Access Control groups. In Phase 4, all consequences were removed for all groups to evaluate resurgence. That is, target responding no longer produced cocaine or punishment and alternative responses no longer produced food. The Long Access Control and Short Access Control groups were included because resurgence testing included the removal of punishment,

which could increase target response rates and obscure potential resurgence effects. Thus, any differences between the control groups and Long Access + Alternative and Short Access + Alternative groups during resurgence testing would be due to the history of reinforcement for and subsequent removal of alternative reinforcement (i.e. resurgence).

Table 3-1.
Criteria for substance use disorder and examples of analogues from animal models.

Criterion	Description	Animal Analogue
1	Taking the drug in larger amounts and for longer than intended	Escalation of drug intake[1]
2	Wanting to cut down or quit, but not being able to do so	Increased relapse[2]
3	Spending a lot of time obtaining the drug	
4	Craving or a strong desire to use the drug	Increased motivation[3] and relapse[1]
5	Repeatedly unable to carry out major obligations at work, school, or home due to drug use	
6	Continued use despite persistent or recurring social or interpersonal problems caused by or made worse by drug use	Resistance to punishment[3]
7	Stopping or reducing important social, occupational, or recreational activities due to drug use	Choosing drug over non-drug options[4]
8	Recurrent use of drugs in physically hazardous environments	Resistance to punishment[3]
9	Consistent use of drugs despite acknowledgement of persistent or recurrent physical or psychological difficulties from using drugs	Resistance to punishment[3]
10	Tolerance defined by either a need for markedly increased amounts to achieve intoxication or markedly diminished effect with use of the same amount	
11	Withdrawal manifesting as either characteristic syndrome or increases in the amount of the substance used to avoid withdrawal	

[1]Ahmed (2005); [2]Ahmed & Cador (2006); [3]Ahmed (2011); [4] Lenoir et al. (2013)

Materials and methods

Subjects

Twenty-four experimentally naïve male Long-Evans rats (Charles River, Portage, MI) served as subjects. Rats were 71-80 days old upon arrival to the facility. Following catheter implantation surgery (detailed below), rats were restricted to 80% of their free-feeding weights. All sessions were conducted in the rats' dark cycle (i.e. after 19:00). Animal housing, care, and all procedures reported below were conducted in accordance with Utah State University's Intuitional Animal Care and Use Committee and have been described in detail elsewhere [9].

Apparatus

Ten modular Med-Associates (St. Albans, VT) operant chambers measuring 30 cm x 24 cm x 21 cm were used. Chambers consisted of Plexiglas side walls, ceilings, and doors and were housed in sound- and light-attenuating cubicles. An aluminum response panel in the rear of the chamber contained 5 nose poke apertures that could be lighted yellow and were equipped to detect head entries. An aluminum response panel on the front wall housed two retractable levers with stimulus lights above them. A food aperture was centered on the front wall between the levers and was illuminated when delivering food (45-mg dustless pellets; Bio Serv, Flemington NJ). Chambers were equipped to deliver scrambled foot shock via the floor grid (detailed below).

Chambers were also equipped for intravenous drug self-administration. A 60ml syringe was placed in a fixed-speed infusion pump (Med Associates) outside of the sound attenuating cubicle. Tygon tubing attached to the syringe was run inside the cubicle and attached to a swivel (Instech, Plymouth Meeting, PA) suspended above the ceiling before

passing into the chamber inside a metal spring tether attached to the rat's back-mounted cannula. Rats were connected to the infusion apparatus at all times while in the chamber.

Surgery

Prior to the start of the experiment, rats underwent jugular-catheterization surgery, as previously described [9,12]. In short, rats were anesthetized and an indwelling, back-mounted cannula (Plastics One, Roanoke, VA) was implanted and an attached silastic catheter (SAI-Infusions, Lake Villa, IL) was inserted into the right jugular vein. Following surgery, rats recovered for 5 days before undergoing food restriction.

Drugs

Surgery was preceded by injections of an antibiotic (gentamicin, 2.0mg/kg, intraperitoneal) and an analgesic/anti-inflammatory (flunixin meglumine, 1.1mg/kg, subcutaneous). Anesthesia was induced and maintained using isoflurane. Cocaine hydrochloride (NIDA, USA) was dissolved in sterile 0.9% saline solution to a concentration of 2.56mg/ml. The dose of each infusion was determined daily based on individual body weights and achieved by changing the activation duration of a fixed-speed (0.0527ml/s) syringe pump. During the 5 days of recovery from surgery, subcutaneous injections of flunixin meglumine (1.1mg/kg) were provided twice daily. Catheter patency was maintained by daily 0.2ml infusions of gentamicin heparinized saline solution (4mg/ml gentamicin, .04mg/ml heparin) throughout the experiment.

Procedure

Pellet training

Rats were first trained to consume food from the food aperture. During pellet training, rats were placed in the chamber with levers retracted and all lights off except for

the illumination of the food aperture when a food pellet was delivered. Food was delivered response independently every 60s, on average (Variable Time [VT] schedule of reinforcement). Pellet training and all sessions were 1hr in duration except where otherwise noted. Pellet training lasted for 4 sessions.

Cocaine self-administration training

Immediately following pellet training, sessions began with the insertion of both response levers. One lever served as the target response and was indicated by the illumination of the stimulus light above the lever throughout the experiment except during cocaine or food delivery. The other lever was extended, but the stimulus light was never illuminated. This inactive lever served as a reference for non-specific increases in responding and presses on this lever were recorded but had no consequences throughout. Initially, each target lever press produced a 0.75mg/kg infusion of cocaine accompanied by a tone and a 20s blackout of the chamber. After three sessions without a decreasing trend of cocaine consumption, the response requirement was increased to 2 presses, and then to 3 after three more sessions without a downward trend. Thus, rats terminally earned 0.75mg/kg infusions of cocaine for every third response (Fixed Ratio [FR] 3 schedule of reinforcement). Cocaine self-administration training lasted until rats had progressed to the FR3 condition.

Phase 1: Baseline

During baseline, rats continued to earn 0.75mg/kg infusions according to an FR3. Baseline lasted until a rat completed a minimum of 3 sessions without a downward trend in cocaine consumption under FR3 conditions.

Phase 2: Differential Access

Following baseline, rats were divided into 2 groups matched on baseline target response rates and cocaine consumption. For the Long Access group (N=11), session duration was increased to 6hrs. For the Short Access group (N=13), sessions remained 1hr. For all rats during Differential Access, target responding continued to produce 0.75 mg/kg cocaine infusions according to an FR3. The only limit to cocaine consumption during this phase was the 20s blackout that followed each infusion. Differential Access lasted 12 sessions.

Phase 3: Punishment

Following Differential Access, all sessions were returned to 1hr for the remainder of the experiment, and the Long Access and Short Access groups were further subdivided into 2 groups each, for a total of 4 groups. The Long Access + Alternative (N=6) and Long Access Control (N=5) groups were matched on target response rates and cocaine consumption during Differential Access, as were the Short Access + Alternative (N=6) and Short Access Control (N=7) groups. During Punishment, target responding continued to produce 0.75 mg/kg cocaine infusions according to an FR3 for all groups. In addition, each target response also produced intermittent mild foot shock (probability = .5, 50ms) for all groups. For the first 5 sessions of Punishment, the punishment intensity was fixed at 0.5mA. From sessions 6-15, intensity was increased 0.1mA daily, such that the intensity was 1.5mA on session 15. The intensity remained at 1.5mA for 4 additional sessions. That is, punishment was fixed at 0.5mA for 5 sessions, increased by 0.1mA daily for 9 sessions, and was then fixed at 1.5mA for 5 sessions. Thus, Punishment lasted a total of 19 sessions. Also during Punishment, alternative reinforcement was available

for responses to the left-most nose poke in the Long Access + Alternative and Short Access + Alternative groups. The first nose poke after an average of 15 seconds was reinforced with a single food pellet (Variable Interval [VI] 15s schedule of reinforcement). No alternative reinforcement was available for the Long Access Control and Short Access Control groups.

Phase 4: Resurgence Testing

Following Punishment, all consequences were removed for all responses in all groups. That is, target responding no longer produced cocaine or shock and alternative responding no longer produced food. Resurgence testing lasted 5 sessions.

Data analysis

Time for reinforcer deliveries and chamber blackouts were excluded from session time in all rate measures reported below. Analyses were deemed significant at an α level of .05. Greenhouse-Geisser corrections to degrees of freedom were used when assumptions of sphericity were violated.

Results and summary

Phase 1: Baseline

Figure 3-1 shows that cocaine consumption was similar between the Long Access and Short Access groups across the final 3 sessions of Baseline. This finding was confirmed by one-way ANOVA conducted on the average mg/kg of cocaine consumed across the last 3 sessions of Baseline which revealed no significant effect of group $F(1,23)= .099$, $p=.756$, $\eta^2 = .004$. See Table 3-2 for a summary of response rates, reinforcer rates, and cocaine consumption across all phases of the experiment.

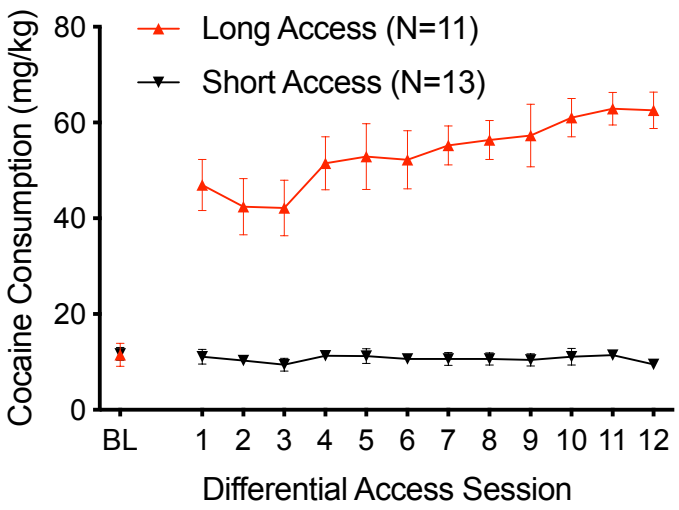

Figure 3-1. Cocaine consumption during the last session of Baseline (BL) and all sessions of Differential Access. Error bars represent standard errors of the mean.

Phase 2: Differential Access

Figure 3-1 shows that cocaine consumption was higher and increased for the Long Access group and remained stable and lower for rats in the Short Access group during Differential Access. These findings were confirmed by a 2 x 12 (Group x Session) mixed-model ANOVA conducted on mg/kg of cocaine consumed across all sessions of Differential Access which revealed a significant Group x Session interaction $F(5.011, 110.246)= 4.320$, $p= .001$, $\eta^2 = .164$, and significant main effects of Session $F(5.011, 110.246)= 4.751$, $p= .001$, $\eta^2 = .178$ and Group $F(1, 22)= 124.735$, $p< .001$, $\eta^2 = .850$. Thus, cocaine consumption increased across Differential Access for the Long Access group, and remained lower and stable for the Short Access group.

Phase 3: Punishment

Figure 3-2 shows that target response rates decreased across sessions of Punishment for all groups similarly. This finding was confirmed by a 4 x 19 (Group x Session) mixed-model ANOVA conducted on target response rates across all sessions of

Punishment, which revealed a significant main effect of Session F(18, 360)= 5.037, p< .001, η^2 = .201, but no significant main effect of Group F(3, 20)= .652, p= .593, η^2 = .109, and no significant Group x Session interaction F(54, 360) = 1.276, p= .103, η^2 = .161. Thus, target responding decreased across Punishment sessions for all groups at a similar rate.

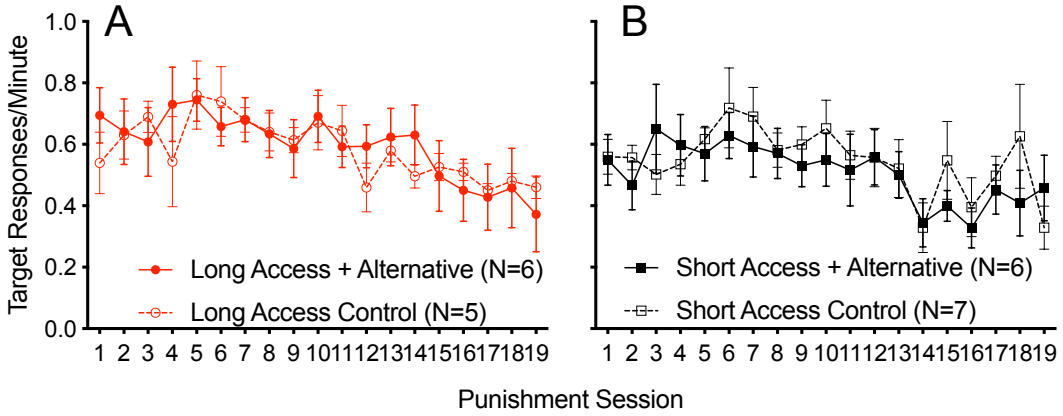

Figure 3-2. Target response rates for each Long Access (A) and Short Access (B) group across all sessions of Punishment. Error bars represent standard errors of the

Cocaine Consumption also decreased similarly across sessions of Punishment for all groups (see Table 3-2). This finding was confirmed by a 4 x 19 (Group x Session) mixed-model ANOVA conducted on mg/kg of cocaine earned across all sessions of Differential Access which revealed a significant main effect of Session F(18, 360)= 5.062, p< .001, η^2 = .202, but no significant main effect of Group F(3, 20)= .432, p= .732, η^2 = .061, and no significant Group x Session interaction F(54, 360) = 1.161, p= .215, η^2 = .148. Thus, cocaine consumption decreased across Punishment sessions for all groups at a similar rate.

Figure 3-3 shows that alternative response rates increased across sessions of punishment only for rats in the Long Access + Alternative and Short Access + Alternative groups. This finding was confirmed by a 4 x 19 (Group x Session) mixed-model ANOVA conducted on alternative response rates across all sessions of Punishment, which revealed a significant Group x Session interaction $F(54, 360) = 1.951$, $p < .001$, $\eta^2 = .226$, as well as significant main effects of Session $F(18, 360) = 4.243$, $p < .001$, $\eta^2 = .175$ and Group $F(3, 20) = .652$, $p = .593$, $\eta^2 = .109$. To determine the source of the Group x Session interaction, pairwise comparisons were made between each group across all sessions of Punishment. The interaction term remained significant when the Long Access + Alternative group was compared to the Long Access Control group ($F(18, 162) = 2.060$, $p = .009$, $\eta^2 = .186$) and the Short Access Control group ($F(18, 198) = 2.972$, $p < .001$, $\eta^2 = .213$) and when the Short Access + Alternative group was compared to the Long Access Control group ($F(18,162) = 2.075$, $p = .009$, $\eta^2 = .187$) and the Short Access Control group ($F(18, 198) = 3.005$, $p < .001$, $\eta^2 = .215$). Notably, there was no significant main effect of Group when comparing alternative response rates across Punishment in the Long Access + Alternative group to the Short Access + Alternative group ($F(1, 10) = 1.040$, $p = .332$, $\eta^2 = .094$. Thus, alternative response rates increased at similar rates for the Long Access + Alternative and Short Access + Alternative groups, and remained low and stable in the Long Access Control and Short Access Control groups.

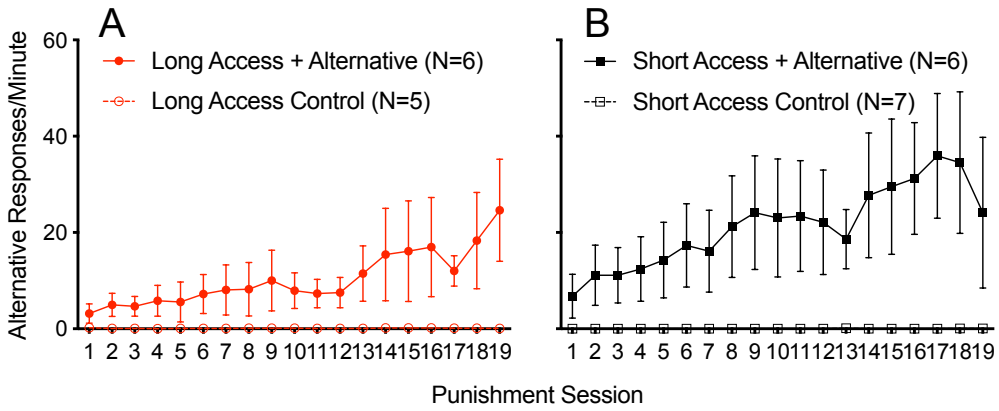

Figure 3-3. Alternative response rates for each Long Access (A) and Short Access (B) group across all sessions of Punishment. Error bars represent standard errors of the mean.

Alternative reinforcer rates were similar between the Long Access + Alternative and Short Access + Alternative groups across all sessions of Punishment and remained low for the Long Access Control and Short Access Control groups (see Table 3-2). Because the Long Access Control groups and Short Access Control groups did not have access to alternative reinforcement, they were excluded from the analysis of alternative reinforcer rates. A 2 x 19 (Group x Session) mixed-model ANOVA conducted on alternative reinforcer rates across all sessions of Punishment for the Long Access + Alternative and Short Access + Alternative groups revealed a significant main effect of Session $F(18, 180) = 5.575$, $p < .001$, $\eta^2 = .358$, but no significant main effect of Group $F(1, 10) = .554$, $p = .474$, $\eta^2 = .053$, and no significant Group x Session interaction $F(18, 180) = .368$, $p = .992$, $\eta^2 = .036$. Thus, alternative reinforcer rates increased at similar rates across sessions of Punishment in the Long Access + Alternative and Short Access + Alternative groups.

Rates of shock decreased for all groups similarly across sessions of Punishment

(see Table 3-2). This finding was confirmed by a 4 x 19 (Group x Session) mixed-model ANOVA conducted on rates of shock for all groups across all sessions of Punishment, which revealed a significant main effect of Session $F(5.730, 114.593) = 3.668$, $p = .003$, $\eta^2 = .155$, but no significant main effect of Group $F(3, 20) = .120$, $p = .947$, $\eta^2 = 0.18$ and no significant Group x Session interaction $F(17.189, 114.593) = 1.081$, $p = .381$, $\eta^2 = .139$. Thus, shock decreased at a similar rate across sessions of Punishment for all groups.

Suppression ratios were calculated to determine if any subgroups of punishment-resistant rats existed within each group. Suppression ratios were calculated by dividing the target response rate from each session of Punishment for each rat by their target response rate during the final session of Baseline. Thus, a suppression ratio was calculated for each session of Punishment for every individual. Mean suppression ratios for each individual were obtained and tested for normality [30,51]. Results indicated a non-normal distribution only for the Long Access + Alternative group (Shapiro-Wilk's, $W = .559$, $p < .001$). Mean suppression ratios for each group are presented in Figure 3-4. These results suggest that a single rat in the Long Access + Alternative group was particularly resistant to punishment.

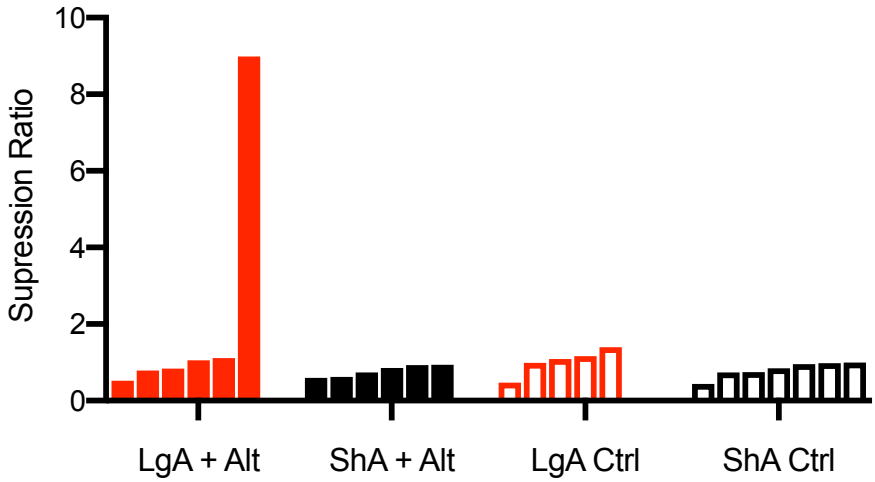

Figure 3-4. Individual subject suppression ratios for Long Access + Alternative (LgA + Alt) Short Access + Alternative (ShA + Alt) Long Access Control (LgA Ctrl) and Short Access Control (ShA Ctrl) groups.

Phase 4: Resurgence Testing

Figure 3-5 shows target responses rates for each individual in all groups during the last session of Punishment and first Session of Resurgence Testing. Increases in target response rate were similar for all groups between these sessions. This finding was confirmed by a 4 x 2 (Group x Session) mixed-model ANOVA conducted on target response rates during the last session of Punishment and first session of Resurgence Testing which revealed a significant main effect of Session $F(1, 20) = 35.070$, $p < .001$, $\eta^2 = .637$, but no significant main effect of Group $F(1, 20) = 1.558$, $p = .305$, $\eta^2 = .162$ and no significant Group x Session interaction $F(3, 20) = 2.565$, $p = .083$, $\eta^2 = .278$. Thus, target response rates increased for all groups to a similar level between the last session of Punishment and first session of Resurgence Testing.

Target response rates decreased across all sessions of Resurgence Testing similarly for all groups (see Figure 3-6A & B). This finding was confirmed by a 4 x 5

(Group x Session) mixed-Model ANOVA conducted on target response rates across all sessions of Resurgence Testing which revealed a significant main effect of Session $F(1.621, 32.418) = 17.395$, $p < .001$, $\eta^2 = .465$, but no significant main effect of Group $F(1, 20) = .992$, $p = .417$, $\eta^2 = .130$ and no significant Group x Session interaction $F(4.863, 32.418) = 2.178$, $p = .083$, $\eta^2 = .246$. Thus, target response rates decreased across sessions of Resurgence Testing similarly between groups.

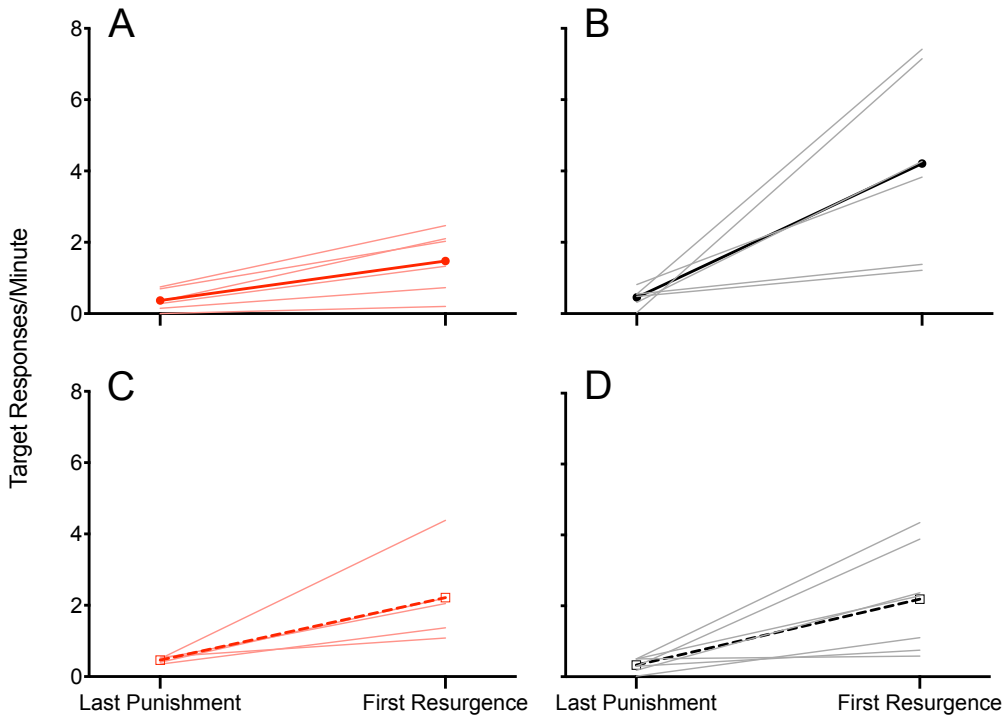

Figure 3-5. Target response rates during the last session of punishment and first session of reinforcement for each individual in the Long Access + Alternative (A), Short Access + Alternative (B), Long Access Control (C), and Short Access Control (D) groups. Heavy lines with symbols represent the group mean.

Alternative response rates decreased across all sessions of Resurgence Testing for the Long Access + Alternative and Short Access + Alternative groups, and remained low

for the Long Access Control and Short Access Control groups (see Figure 3-6C & D). Because responding was near-zero across all sessions of Resurgence Testing for rats in the Long Access Control groups and Short Access Control groups, analyses were performed only on data for the Long Access + Alternative and Short Access + Alternative groups. A 2 x 5 (Group x Session) mixed-model ANOVA performed on alternative response rates for rats in the Long Access + Alternative and Short Access + Alternative groups across all sessions of Resurgence Testing revealed a significant main effect of Session $F(1.164, 11.636) = 14.733$, $p = .002$, $\eta^2 = .596$, but no significant main effect of Group $F(1, 10) = .014$, $p = .910$, $\eta^2 = .001$, and no significant Group x Session interaction $F(1.164, 11.636) = .617$, $p = .472$, $\eta^2 = .058$. Thus, alternative responding decreased across sessions of Resurgence Testing similarly for the Long Access + Alternative and Short Access + Alternative groups.

Inactive response rates did not increase between the last session of Punishment and first session of Resurgence testing (see table 3-2). This finding was confirmed by a 2 x 2 (Group x Session) mixed-model ANOVA conducted on inactive response rates during the last session of Punishment and first session of Resurgence testing, which revealed no significant main effect of Session $F(1, 20) = .002$, $p = .966$, $\eta^2 < .001$ or Group $F(3, 20) = 2.008$, $p = .145$, $\eta^2 = .231$, and no significant Group x Session interaction $F(3, 20) = .340$, $p = .797$, $\eta^2 = .048$. Thus, inactive lever responding did not change between the last session of Punishment and first session of Resurgence Testing. This result indicates that increases in target responding were not likely the product of general increases in responding, but the product of responding on the lever that previously produced cocaine.

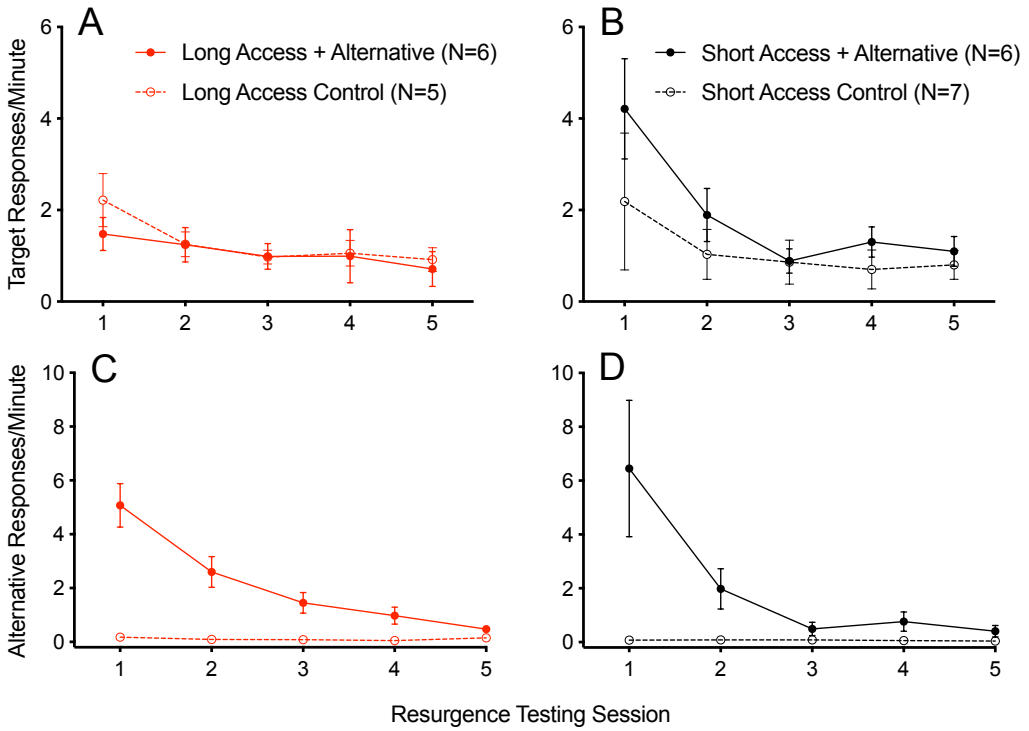

Figure 3-6. Target response rates (A & B) and alternative response rates (C & D) during all sessions of Resurgence Testing for each Long Access (A & C) and Short Access (B & D) group. Error bars represent standard errors of the mean.

Table 3-2.
Mean and SEM Response and Reinforcer Rates from each Phase.

	Group															
	Long Access + Alternative				Short Access + Alternative				Long Access Control				Short Access Control			
	Ph 1[a]	Ph 2[b]	Ph 3[c]	Ph 4[d]	Ph 1[a]	Ph 2[b]	Ph 3[c]	Ph 4[d]	Ph 1[a]	Ph 2[b]	Ph 3[c]	Ph 4[d]	Ph 1[a]	Ph 2[b]	Ph 3[c]	Ph 4[d]
Target/min	0.69	0.67	0.37	1.48	0.76	0.78	0.46	4.21	0.87	0.73	0.46	2.22	0.75	0.72	0.33	2.19
SEM	*0.16*	*0.04*	*0.12*	*0.36*	*0.14*	*0.09*	*0.11*	*1.10*	*0.31*	*0.09*	*0.04*	*0.58*	*0.12*	*0.09*	*0.07*	*0.57*
Alternative/min	-	-	24.61	5.08	-	-	24.11	6.45	-	-	0.07	0.18	-	-	0.07	0.08
SEM	-	-	*10.60*	*0.81*	-	-	*15.68*	*2.54*	-	-	*0.04*	*0.06*	-	-	*0.05*	*0.03*
Inactive/min	0.09	0.01	0.14	0.32	0.02	0.02	2.17	1.60	0.10	0.01	0.54	0.76	0.11	0.08	0.22	0.35
SEM	*0.06*	*0.01*	*0.08*	*0.12*	*0.01*	*0.01*	*1.66*	*0.65*	*0.05*	*0.01*	*0.18*	*0.11*	*0.04*	*0.08*	*0.09*	*0.11*
Infusions/min	13.66	79.83	7.33	-	16.33	10.83	5.50	-	17.4	87.8	9.2	-	15.00	14.29	6.43	-
SEM	*3.22*	*4.14*	*2.46*	-	*2.91*	*2.41*	*2.78*	-	*6.25*	*10.37*	*0.73*	-	*2.33*	*1.86*	*1.48*	-
Cocaine mg/kg	10.25	59.88	5.50	-	12.25	8.13	4.13	-	13.05	65.85	6.90	-	11.25	10.71	4.82	-
SEM	*2.42*	*3.11*	*1.84*	-	*2.18*	*1.81*	*2.08*	-	*4.69*	*7.78*	*0.55*	-	*1.75*	*1.40*	*1.11*	-
Foods/min	-	-	2.21	-	-		1.91	-	-	-	-	-	-	-	-	-
SEM	-	-	*0.44*	-	-		*0.49*	-	-	-	-	-	-	-	-	-
Shocks/min	-	-	0.20	-	-	-	0.22	-	-	-	0.24	-	-	-	0.16	-
SEM	-	-	*0.06*	-	-	-	*0.05*	-	-	-	*0.03*	-	-	-	*0.03*	-

[a] Data from the last session of Phase 1 are shown, [b] Data from the last session of Phase 2 are shown, [c] Data from the last session of Phase 3 are shown. [c] Data from the first session of Phase 4 are shown.

Discussion

The purpose of the current experiment was to develop a model of resurgence of drug seeking that included key aspects of SUD in humans. Thus, the model developed here involved training rats in a long access paradigm, as previous work has shown that long access produces behaviors in rats that resemble those used to diagnose SUDs in humans [27]. Cocaine seeking was then suppressed using aversive consequences (i.e. foot shock) because the aversive outcomes associated with substance use are likely the reason humans with SUDs abstain from drug use [17]. Finally, resurgence was examined because treatments that provide alternative reinforcement are effective at reducing substance abuse, but when treatment ends and alternative reinforcers are removed, relapse often occurs [52]. Rats first pressed levers to earn infusions of cocaine in 1hr sessions during Phase 1. Next, in Phase 2, sessions remained at 1hr for a Short Access group and were extended to 6hrs (i.e. the long access manipulation) for a Long Access group. In Phase 3, all sessions returned to 1hr and lever pressing produced both cocaine and intermittent mild foot shock for all rats. Also during Phase 3, alternative reinforcement was available for rats in the Long Access + Alternative and Short Access + Alternative groups, but not for rats in the Long Access Control and Short Access Control groups. In Phase 4, all consequences were removed for all responses to assess resurgence of cocaine seeking. That is, target responses no longer produced cocaine or foot shock and alternative responses no longer produced food.

During Phase 2 (Differential Access), target response rates and cocaine consumption increased for the Long Access group but not the Short Access group. This finding is consistent with a large body of literature showing escalation of drug

consumption under long access conditions [e.g., 39,43,45,53–55], and has been said to reflect the SUD diagnostic criterion “Taking the drug in larger amounts and for longer than intended.” Researchers have suggested that escalation of drug intake under long access conditions may better model uncontrolled drug use in humans with SUDs than the relatively stable drug intake exhibited by rats under short access conditions [e.g., 27]. Prior research has also demonstrated that escalation of drug intake is paralleled by both transient and persistent neurobiological changes that are also present in individuals with SUDs [56]. Thus, the procedure used in the present experiment may better represent the behavioral and neural states of individuals diagnosed with SUDs. Escalation of cocaine intake in the present experiment demonstrates that the long access procedure used here was effective at simulating one key aspect of uncontrolled drug use.

The current study failed to replicate the finding from prior studies that long access can increase resistance to punishment in rats responding for drugs [57]. However, this increased resistance for punishment is generally observed only in relatively small subgroups of rats following long access [30,51,58]. Analyses similar to those used to determine such subgroups in prior studies identified only a single punishment-resistant rat in the Long Access + Alternative group of the present study. Thus, the percentage of punishment-resistant rats produced by long access in the present study (9.09%) was smaller than what is generally observed [e.g. 30%, 51,58]. However, this discrepancy could also be due to the relatively low N in the present study. Methodological differences could also explain why increased resistance to punishment was not observed following long access in the present study. Prior studies have used a longer duration of punishment than was used in the current study. The duration used here (50ms) has previously been

shown to reduce food [59] and cocaine seeking [24] in resurgence paradigms. However, other studies have used durations of shock ranging from 0.5s - 1.2s to suppress cocaine seeking following long access [32,51]. Thus, longer durations of shock may be more effective at suppressing cocaine seeking under the current conditions and using a longer duration in future studies may allow for better observation of differential sensitivity to punishment. Prior studies of long access also typically use non-food restricted rats to examine resistance to punishment following long access [e.g., 30,32]. The rats in the present study were restricted to 80% of their free-feeding weights to maintain constant motivation for the food used as alternative reinforcement. Future studies may be able to avoid using food restriction by providing sucrose as the alternative reinforcer for non-food-restricted rats [e.g., 11]. These parametric differences could explain discrepancies between some findings in the current experiment and extant literature, and thus, should be considered when designing future studies of resurgence after long access and punishment.

No effect of alternative reinforcement on resistance to punishment was observed in the current experiment (see Figure 3-2). To our knowledge, only one prior study has directly examined the effects of alternative reinforcement on drug seeking under punishment following long access. Pelloux, Murray, and Everitt [30] trained non-food restricted male Lister rats to earn 0.25mg/kg infusions of cocaine according to a seeking-taking chain schedule. Pressing the seeking lever produced access to the taking lever according to a random interval 120s schedule (the first response after an average of 120s produced the taking lever; RI120s). Once access to the taking lever was earned, one press on it produced a cocaine infusion. Next, rats earned cocaine infusions in 6hr sessions

according to an FR1 schedule for 14 sessions. Then, rats were returned to the seeking-taking schedule during which an alternative response produced 20% sucrose solution according to an RI60s schedule for 3 additional sessions. Finally, rats were exposed to punishment. During punishment, completion of the initial RI link of the seeking-taking chain resulted in either access to the taking lever or foot shock followed by timeout and no access to the taking lever (probability =.5, 0.5s shock duration, 0.5mA). They observed a reduction in the number of seeking-taking chains completed when alternative reinforcement was present relative to conditions without alternative reinforcement. The different effects of alternative reinforcement on punishment of cocaine seeking between the current study and that of Pelloux et. al. [30] could be due to the large number of methodological differences between the studies, and thus an integration of the two studies awaits future research into the impact of those methodological differences on suppression by combined alternative reinforcement and punishment.

The finding that alternative reinforcement did not further reduce cocaine seeking during punishment also differs from a prior study on resurgence of previously-punished cocaine seeking. Nall and Shahan [24] trained rats to press levers for 0.32mg/kg infusions of cocaine according to a VR20 schedule (cocaine was delivered following an average of 20 presses). Next, lever pressing continued to produce cocaine as before, but each lever press intermittently produced foot shock (probability = .5, .5mA, 50ms). For one group, a nose poke response produced food pellets according to a VI15s schedule. No alternative reinforcement was available for the second group. During the punishment phase, responding was suppressed to a greater degree by the combination of alternative reinforcement and punishment than by punishment alone. Finally, when all consequences

were removed during resurgence testing, relapse occurred in only the group that had previously received alternative reinforcement. There are several procedural differences between the study by Nall and Shahan [24] and the current study. Notably, the schedule of reinforcement was leaner (VR20 vs FR3) and magnitude of cocaine was smaller (0.32 vs 0.75 mg/kg/infusion) than in the present study. This may be important, as richer schedules [60] and greater magnitudes [61] of reinforcement have previously been shown to increase resistance to punishment. Further, schedules associated with a greater number of non-reinforced responses (e.g. VI schedules) may be more susceptible to punishment effects than schedules with a lesser number of unreinforced responses (e.g. rich FR schedules; [62]). Finally, prior research indicates that punishment reduces response rates in FR schedules by increasing the latency to respond following reinforcement while local rates of responding remain unchanged [62]. However, in VI schedules, punishment generally reduces response rates across the entire session [62]. No prior work has directly examined whether punishment reduces responding via increases in pausing or general decreases in response rates under VR schedules, but evidence indicates that response patterns under VR schedules resemble those of VI schedules. That is, responding under VR schedules tends to occur at high constant rates with no pausing after reinforcement [63]. Each of the differences in reinforcement parameters between the prior study by Nall and Shahan [24] and the present study could have led to the increased resistance to punishment observed here. Thus, the schedule and magnitude of reinforcement used in the present study may have resulted in increased resistance to punishment across all groups, obscuring any potential effects of alternative reinforcement on punished cocaine seeking.

Relapse effects were also similar between all groups following the removal of punishment and alternative reinforcement. To date, no research has examined resurgence effects following long access. However, there is a large body of literature showing that other relapse effects are increased by training in long access procedures [e.g., 33,43,46]. Though the statistical effect was not significant, the obtained effect size was relatively large ($\eta^2 = .162$), and mean differences indicated that relapse was larger in the Short Access + Alternative group than in the Long Access + Alternative group in the present study. One finding from previous long access studies might explain this visual difference in resurgence effects following long and short access. It has been suggested that long access conditions may increase the value of drug reinforcers and reduce the value of non-drug reinforcers [e.g., 47]. For example, responding for drug in progressive ratio schedules reaches higher breakpoints following long access than for the same subjects prior to long access training [64] and relative to short access controls [65]. Preference for drug over non-drug reinforcers in choice tasks is also higher following long access than short access [31]. This could explain the slightly smaller resurgence effect in the Long Access + Alternative group in the current study, as removal of lower valued alternative reinforcement has been shown to reduce resurgence in prior studies [66]. Further, a contemporary quantitative model of resurgence suggests that resurgence may be a product of changes in target and alternative reinforcer values across experimental conditions [49]. Thus, resurgence effects may be unique in the study of relapse, as they are directly tied to the value of the alternative reinforcer that is removed, making them unique in their sensitivity to long access procedures.

The removal of punishment in the Long Access Control and Short Access Control

groups also produced a relapse effect in the present study. Prior work has noted that increases in responding can occur following the removal of punishment [67,68]. However, Nall & Shahan found no increase in cocaine seeking [24] following the removal of punishment alone in a recent study examining resurgence of previously-punished behavior. The most likely explanation of this discrepancy is that the rich schedule and high magnitude of reinforcement used in the present study, relative to the study by Nall and Shahan [24] detailed above, are responsible for the relapse effect observed when punishment alone was removed. Other prior examinations of relapse of drug seeking following suppression by punishment have not included control groups to assess the effects of only removing punishment contingencies. Thus, it is difficult to determine if the increase in responding following the removal of punishment in the present study is anomalous or should be expected.

Conclusion

The present study examined resurgence of cocaine seeking after training in a long access paradigm and subsequent suppression of cocaine seeking by punishment. The goal of including long access was to simulate the characteristic loss of control over drug-related behaviors exhibited by individuals with SUDs. The goal of including punishment was to simulate the aversive consequences of drug-related behaviors that are thought to be responsible for suppressing drug seeking in humans. Thus the model developed herein should better represent the conditions under which humans with SUDs relapse following the loss of alternative reinforcement. Resurgence, in particular was examined because alternative reinforcement is often involved in successful attempts at drug abstinence with and without treatment. Some findings from prior long access studies were replicated in

the present experiment, while others were not. Rats' cocaine seeking escalated across long access simulating the loss of control over drug seeking seen in humans with SUDs. No differences were noted during punishment of cocaine seeking with or without alternative reinforcement. Finally, relapse did not significantly differ across all groups during resurgence testing. That is, the removal of punishment produced a relapse effect similar to that of removing alternative reinforcement (i.e. resurgence) and no significant differences were noted between groups with a history of long or short access. Parametric differences between the present study and previous studies of relapse and punishment following long access may explain the difference in outcomes observed. Though the effect was not statistically different, mean differences suggested a slightly greater relapse effect in the group exposed to short access relative to the group exposed to long access when alternative reinforcement was removed. This finding might indicate that resurgence of cocaine seeking is reduced following long access due to a reduction in the relative value of non-drug reinforcers following exposure to long access. Taken together, the data from the present experiment indicate a need for a better understanding of how parameters of reinforcement and punishment influence suppression and resurgence in long access and resurgence paradigms. Improvements in understanding the role of these parameters should lead to improvements in extant treatment approaches and to development of novel approaches for reducing relapse following treatment for SUDs.

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intracerebroventricular infusion of the competitive NMDA receptor antagonist, LY235959, facilitates escalation of cocaine self-administration and increases break point for cocaine in Sprague-Dawley rats, Pharmacol. Biochem. Behav. 88 (2007) 82–88. doi:10.1016/j.pbb.2007.07.009.

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CHAPTER 4

GENERAL DISCUSSION

Alternative reinforcement strategies are often successful at reducing drug use in individuals with SUDs. However, relapse often occurs when alternative reinforcement is removed, an effect called resurgence. A better understanding of the factors underlying resurgence of drug seeking should lead to the improvement of existing treatments and to the development of novel treatment approaches. The purpose of this dissertation was to develop an animal model of resurgence of drug seeking that included two key factors absent in previous models: the use of aversive consequences to suppress drug seeking, and the development of uncontrolled drug-seeking behaviors. The translational utility of the model should be improved by simulating these key aspects. Thus, the models developed in this dissertation should lead to greater understanding of the environmental and neurobiological factors influencing resurgence and to the development of more resurgence-resistance approaches to treating SUDs.

The experiments in Chapter 2 developed a resurgence model for using aversive consequences to suppress drug seeking. As discussed above, aversive consequences are likely the factor driving reductions in drug use in individuals with SUDs [1] and neurobiological mechanisms differ when relapse is preceded by punishment or extinction [2]. Thus, the inclusion of aversive consequences into the animal model of resurgence of drug seeking should better simulate the environmental and neurobiological factors involved in resurgence of drug seeking in humans with SUDs. In Chapter 2, resurgence was observed following the removal of alternative reinforcement when cocaine and

punishment were also removed during testing (Experiment 1) but not when they remained available (Experiment 2). However, there was a mean increase in drug seeking during resurgence testing following the loss of alternative reinforcement even when cocaine and punishment remained. This suggests that, with some methodological manipulations, resurgence may be obtainable during testing with continued reinforcement and punishment for cocaine seeking.

The experiment in Chapter 3 developed a model for examining resurgence of previously-punished cocaine seeking following training in a long access paradigm. Long access procedures have been shown to produce behaviors in animals that simulate many of the criteria used to diagnose SUD in humans [3]. Further, long access procedures produce neural changes that simulate those seen in humans with SUDs [4]. Thus, many have suggested that the long access procedure may be an effective model to study relapse under conditions similar to those facing humans with SUDs. In Chapter 3, rates of cocaine seeking increased across sessions of long access and remained low and stable across sessions of short access. Thus, the long access procedure was successful at generating what some have interpreted as uncontrolled drug seeking in animals [5]. However, other effects sometimes observed in long access procedures were not replicated in Chapter 3. Responding during punishment was similar between groups with a history of long and short access, and the inclusion of alternative reinforcement also failed to reduce responding during punishment. Similar resistance to punishment following long and short access is inconsistent with a previous study [6], but this discrepancy may be explained by substantial differences in methodology. Finally, relapse was similar between groups exposed to long and short access with and without alternative reinforcement.

Removal of punishment did not generate relapse in the experiments reported in Chapter 2. Thus, differences in parameters between the studies in Chapter 2 and Chapter 3 must be investigated further to understand this discrepancy. Taken together, the experiment in Chapter 3 replicated some findings from prior long access studies, and failed to replicate others.

One potential explanation for the discrepancies between prior research and the results of Chapter 3 might be that resurgence experiments are particularly sensitive to the parameters of reinforcement and punishment. This could also explain why Experiment 2 in Chapter 2 produced such a small, statistically undetectable resurgence effect. There is some precedent for parametric changes influencing responding in resurgence procedures. For example, differences in baseline reinforcer rates [7] and alternative reinforcer magnitudes [8] have been shown to influence suppression of responding during extinction and subsequent resurgence effects. However, it is difficult to estimate the appropriate parameters when designing prospective studies on resurgence of punished behavior because there are few relevant studies [9–11] and no parametric examinations of the effects of different parameters of punishment and reinforcement on suppression and resurgence. Thus, future research could benefit from an examination of the effects of variations in punishment and reinforcement parameters on suppression and resurgence in a punishment-based resurgence paradigm.

Regardless of these limitations, this dissertation was designed to evaluate resurgence of drug seeking under conditions similar to those facing humans with SUDs. These experiments should serve as a foundation upon which future studies could be developed. Some findings from the experiments in Chapter 2 are worth building upon.

First, reinforcement of alternative behavior reduced cocaine seeking during punishment. This finding simulates the effectiveness of alternative-reinforcement based interventions at reducing drug seeking during treatment. A better understanding of the mechanisms leading to reduced drug seeking with alternative reinforcement could guide changes to currently established methods for treating substance abuse. Second, the presence of aversive consequences reduced relapse of cocaine seeking despite continued availability of drug reinforcement. This finding simulates the effectiveness of continued aversive consequences following treatment, which is one aspect of treatment approaches like the therapeutic workplace. In the Therapeutic Workplace, individuals with SUDs provide evidence of drug abstinence (e.g. drug-free urine samples) daily to gain access to employment. Thus, drug use is punished by removing access to gainful employment. This procedure has been used to successfully maintain abstinence for long periods of time [12]. Thus, the procedures used in Chapter 2 may be useful for simulating procedures in which aversive consequences of drug use remain in effect.

Some findings from the experiment in Chapter 3 also merit future attention. First, though the difference did not reach statistical significance, mean differences indicated that resurgence was reduced following long access. If this finding were to be replicated, it could imply that reductions in value of non-drug alternative reinforcers does indeed reduce resurgence. If this is true, then changes to extant alternative-reinforcement based treatments may be necessary. This finding would also indicate that resurgence may have unique neural mechanisms and encourage investigations into how the mechanisms underlying resurgence might differ from relapse induced by other means. Reduced resurgence following long access might also provide support for value-based theories of

resurgence [13], clarifying the environmental factors that influence resurgence. Thus, further investigations into the effects of long access procedures on resurgence could prove fruitful in several ways. Another interesting finding from Chapter 3 is that availability of alternative reinforcement did not reduce cocaine seeking during punishment. To our knowledge, only one other previous study has directly examined the effects of alternative reinforcement on punished drug seeking following training in a long access paradigm, finding that alternative reinforcement did reduce cocaine seeking [6]. Thus, future work is necessary to determine if alternative reinforcement has an any effect on punishment following long access, or to determine the methods necessary for demonstrating that effect.

The results of the experiments presented in this dissertation suggest that some aspects of SUD can be simulated in an animal model of resurgence. Other aspects of SUD may not occur in resurgence paradigms. However, interesting questions about why some effects found in prior studies were replicated and others were not lead to interesting questions about the mechanisms of resurgence and other forms of relapse. Thus, these procedures should serve a base for investigations into environmental factors that might influence resurgence in long access paradigms, the neural mechanisms underlying resurgence, and theoretical investigations about how changes in value of drug and non-drug reinforcers induced by long access might influence resurgence.

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CURRICULUM VITAE

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EDUCATION

Utah State University, Logan, UT

PhD in Experimental Psychology (Behavior Analysis) — **2019**
Major Advisor: Timothy A. Shahan
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Jacksonville State University, Jacksonville, AL

B.S. in Psychology — **2013**
Minor in Mathematics
Major advisors: William L. Palya & Todd L. McKerchar

PROFESSIONAL INTERESTS

Animal models of relapse and addiction
Environmental and Neurobiological mechanisms of relapse and addiction
Effects of reinforcer quality, rate, and magnitude on relapse
Effects of alternative reinforcement and punishment on relapse
Quantitative models of behavior
Extension of quantitative models of relapse to humans
Dissemination of Behavioral Psychology and Behavioral Neuroscience

TEACHING EXPERIENCE

Instructor – *Utah State University: Analysis of Behavior: Basic Principles (IVC)* — **2017**

This course introduces students to the concepts of behavior analytic psychology including positive and negative reinforcement and punishment, shaping, schedules of reinforcement, differential reinforcement paradigms, discrimination training, and a variety of other applied and theoretical concepts. Included in the course is a lab component in which students train an organism to perform a behavior using the principles learned in class. This particular section of the course was offered via Interactive Video Conference, which involves lecturing to students both in-person and remotely at satellite locations. Because of the nature of the course, a large technology component is involved.

Instructor – *Utah State University: University Connections* — **2016-2018**

This course provides an environment of challenge and support to help new students make a successful transition to Utah State University. Class curriculum and activities provide an environment wherein students become familiar with the broad academic, social, and cultural opportunities offered by USU and the surrounding community. Required texts: *How We Got to Now: Six Inventions that Shaped the Modern World* by Steven Johnson, and *Becoming a Learner* by Matthew Sanders

Teaching Assistant – for C. Renee Renda in *Analysis of Behavior: Basic* — **2013-2014**

Gave multiple guest lectures. Provided in-class instruction to students. Graded all submitted work, including quizzes and exams. Managed electronic course features including iGrader wireless polling software and Canvas online course correspondence. Course involved lectures pertaining to, and required reading of *Principles of Everyday Behavior Analysis* by L. Keith Miller and *Let Me Hear Your Voice*: *A Family's Triumph Over Autism* by Catherine Maurice.

Teaching Assistant – for Dr. William Palya in *Intro to Behavior Analysis Lab* — **2012-2013**

	Provided in-class instruction to students. Graded all submitted work, including quizzes and lab reports. Prepared and maintained lab subjects (pigeons) and all research equipment. Managed online course correspondence. Course consisted of six hands-on experiments involving simple and multiple schedules of reinforcement. Each experiment was followed by a full-length APA formatted lab report. Course is rated highest in student preference for the department.

RESEARCH EXPERIENCE

	Utah State University Department of Psychology - USU, Logan, UT – Advisor Dr. Timothy Shahan	
	Research Assistant and Head of Self-administration Team (Psychology) Collaborated with Dr. Timothy Shahan and other researchers and students to design, prepare, and execute research programs. Performed and provided training for surgical procedures related to drug self-administration, including back mount cannula, vascular access harness, and subcutaneous osmotic mini-pump implantation procedures in rats. Performed and provided training for behavioral procedures related to cocaine, alcohol, and nicotine self-administration. Performed and provided training for collection and assay of blood ethanol concentrations. Presented data at academic conferences. Maintained subjects, equipment, and lab facilities. Purchased lab related equipment and perishables. Trained fellow graduate and undergraduate research assistants in the aforementioned duties. *Currently funded under NIAAA 1R21AA025604-01A1 & NICHD R01HD093734-01*	**2013 - 2019t**
	Utah State University Department of Psychology - USU, Logan, UT – Advisor Dr. Gregory Madden	
	Research Assistant (Psychology) Collaborated with Dr. Greg Madden on a meta-analysis comparing length of academic papers and yearly citation rate. Reviewed all publications in popular experimental psychology publications spanning ten years. Collected and analyzed rates of citation and page number for each publication, and presented and discussed these data with Dr. Madden.	**2013**
	SouthEastern Behavior Analysis Center - JSU, Jacksonville, AL – Advisors Drs. William Palya & Todd McKerchar	
	Research Assistant (Psychology) Collaborated with Dr. William Palya and Dr. Todd McKerchar as well as other researchers and students to design, prepare, and execute research programs. Presented data at academic conferences. Constructed, evaluated, and tested program codes for experimental application and analysis. Analyzed and graphed computer-based data. Maintenance of subjects, equipment, and lab facilities. Trained fellow research assistants in the aforementioned duties.	**2010 - 2013**
	Jacksonville State University Department of Biology, Jacksonville, AL – Advisor Dr. Robert Carter	
	Research Assistant (Ecology) Collaborated with Dr. Robert Carter and other students on projects related to public health and Lyme disease. Collected, identified, organized, and dissected research specimen (Amblyomma Americanum). Designed, constructed, and implemented multiple methods of specimen collection. Evaluated the efficacy of different methods of collection. Isolated and computer tested DNA using PCR protocol.	**2007 - 2010**
	NASA DEVELOP, Marshall Space Flight Center- UAB, Birmingham, AL – Advisor Dr. Jeffery Luvall	
	Research Consultant (Ecology) Specified viable sites for collection of research specimen (Amblyomma Americanum). Provided GPS information to aid in satellite imaging of collection sites. Collected and dissected research specimen. Isolated and computer tested DNA strands using PCR protocol. Reported results to researchers at the University of Alabama at Birmingham for the initiation of a public health awareness campaign.	**2008 - 2010**
	Society for the Quantitative Analysis of Behavior (SQAB)	
	Audio-Visual Assistant for SQAB preeminent tutorials Transported and set up audio and video equipment. Filmed presentations. Recorded audio tracks for presentations. Provided technical assistance to presenters. Organized media for post-production team.	**2010 - 2017**

GRANTS AND AWARDS

	FUNDED: *Graduate Research and Creative Opportunities Grant*	**2018**

	Resurgence of Cocaine Seeking in Rats Following Long Access and Punishment. Principal Investigator. Award Amount: $1000	
	FUNDED: *Utah State University College of Education and Human Services Dissertation Award*	**2018**
	Resurgence of Cocaine Seeking in Rats Following Long Access and Punishment. Principal Investigator. Award Amount: $1500	
	FUNDED: *Utah State University Department of Psychology Dissertation Award*	**2018**
	Resurgence of Cocaine Seeking in Rats Following Long Access and Punishment. Principal Investigator. Award Amount: $1000	
	FUNDED: *Four Corners Association for Behavior Analysis Student Poster Presentation Competition Award*	**2018**
	Awarded best student presentation for: *Nall, R.W., & Shahan, T.A. (2018). Resurgence Following Alternative Reinforcement and Punishment. 11th annual conference of Four Corners Association for Behavior Analysis, Park City, UT.* Award Amount: Free Association Membership and Conference Registration	
	FUNDED: *Society for the Advancement of Behavior Analysis Innovative Student Research Dissertation Grant.*	**2016**
	Reductions in Resurgence by Multiple Sources of Alternative Reinforcement: Effects of Response Competition on Suppression and Resurgence of Target Behavior. Principal Investigator. Award Amount: $2500	
PUBLICATIONS		
PUBLISHED PAPERS		
	Nall, R. W., Rung, J. M., & Shahan, T. A. (2019). *Resurgence of a target behaviors suppressed by a combination of punishment and alternative reinforcement.* Behavioral Processes, 162, 177-183.	**2019**
	Nall, R. W., Craig, A. R., Browning, K. O., & Shahan, T. A. (2018). *Effects of treatment duration on resurgence of cocaine- and alcohol-seeking in rats.* Behavioral Brain Research, 341, 54-62.	**2018**
	Frye, C. C. J., Rung, J. M., **Nall, R. W**., Galizio, A., Haynes, J. M., & Odum, A. L. (2018). *The Effect of Nicotine on Resurgence of Alcohol Seeking in Rats.* PLOS ONE, In Press.	**2018**
	Craig, A. R., Browning, K. **Nall, R. W.**, Marshall, C., & Shahan, T. A. (2016). *Resurgence and alternative-reinforcer magnitude.* Journal of the Experimental Analysis of Behavior, 107(2), 218-233.	**2017**
	Craig, A. R., **Nall, R. W.**, Madden, G. J., & Shahan, T. A. (2016). *Higher rate alternative non-drug reinforcement produces faster suppression of cocaine seeking but more resurgence when removed*. Behavioural Brain Research, 306, 48-51.	**2016**
PAPERS IN PREPARATION		
	Nall, R. W., & Shahan, T. A. (2019). *Resurgence of punishment-suppressed cocaine seeking in rats.* Experimental and Clinical Psychopharmacology. Submitted Manuscript.	**Submitted**
PAPER PRESENTATIONS AND SYMPOSIA		
	Nall, R. W. & Shahan, T. A. (2019). *The Effects of Multiple Concurrent Schedules on Resurgence of Food Seeking in Rats*. In Y. Shaham (Chair), Research Examining Strategies to Mitigate Resurgence. Symposium conducted at the 45th annual meeting of the Association for Behavior Analysis, International, Chicago, IL.	**2019**
	Browning, K. O., **Nall, R. W.**, & Shahan, T. A. (2019). *The Effects of Treatment Duration on Resurgence Using Resurgence as Choice Theory.* In A. Furhman (Chair), Treatment Duration and Resurgence. Symposium conducted at the 45th annual meeting of the Association for Behavior Analysis, International, Chicago, IL.	**2019**
	Nall, R.W., & Shahan, T. A. (2018). *Resurgence of Punishment Suppressed Cocaine Seeking*. Winter Conference on Animal Learning and Behavior, Logan, UT.	**2018**

	Nall, R. W. & Shahan, T. A. (2016). *Resurgence of Punishment Suppressed behavior*. In T. Nighbor (Chair), From the Lab to Practice: Variations on Resurgence Procedures and Their Implications. Symposium conducted at the 42nd annual meeting of the Association for Behavior Analysis, International, Chicago, IL.	**2016**
	Nall, R. W., Craig, A. R., Marshall, C., & Shahan, T. A. (2015). *Do shifts in the magnitude or quality of alternative reinforcement produce resurgence?* In C. St. Peter (Chair), Factors Affecting Response Relapse and Resurgence. Symposium conducted at the 41st annual meeting of the Association for Behavior Analysis, International, San Antonio, TX.	**2015**
	Nall, R.W., Guinn. S.M., & Palya, W.L. (2013). *Interresponse Time Schedules.* 39th Annual Convention of the Association for Behavior Analysis, Minneapolis, MN USA.	**2013**
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POSTERS		
	Nall, R. W., & Shahan, T. A. (2018) *Resurgence of Cocaine Seeking in Rats Following Suppression by Negative Consequences*. 41st annual conference of the Society for the Quantitative Analysis of Behavior, San Diego, CA.	**2018**
	Nall, R.W., & Shahan, T.A. (2018). *Resurgence Following Alternative Reinforcement and Punishment*. 11th annual conference of Four Corners Association for Behavior Analysis, Park City, UT.	**2018**
	Nall, R. W., Craig, A. C., Browning, K. O., & Shahan, T. A. (2017). *The Effects of Treatment Duration on Cocaine Seeking*. 40th annual conference of Society for the Quantitative Analysis of Behavior, Denver, CO.	**2017**
	Nelson, S. A., Craig, A. R., **Nall, R. W.**, Cunningham, P. J., Frye, C. C. J., & Shahan, T. A. (2015). *Resurgence of alcohol seeking: Effects of length of exposure to extinction plus alternative reinforcement*. 38th annual conference of Society for the Quantitative Analysis of Behavior, San Antonio, TX.	**2015**
	Nall, R.W., Craig, A.R., & Shahan, T.A. (2014). *Loss of Alternative Non-Drug Reinforcement Produces Resurgence of Cocaine Seeking in Non-Food-Restricted Rats.* 37th annual conference of Society for Quantitative Analysis of Behavior, Chicago, IL.	**2014**
	Nall, R.W., Craig, A.R., Cunningham, P.A., Marshall, C., & Shahan, T.A. (2014). *Duration of Extinction is Negatively Related to Resurgence of Ethanol Seeking Following Loss of Non-Drug reinforcement in Rats*. 7th annual conference of Four Corners Association for Behavior Analysis, Park City, UT.	**2014**
	Guinn, S.W., **Nall, R. W.**, & Palya, W. L. (2013). *Evaluating Initial CFT Negativity with a Multiple Ply Observing Response Procedure.* 36th annual conference of Society for Quantitative Analysis of Behavior, Minneapolis, MN.	**2013**
	Guinn, S.W., **Nall, R. W.**, & Palya, W. L. (2012). *Assessing the Nature of Control Across a Clock Fixed Interval Schedule*. 35th annual conference of Society for Quantitative Analysis of Behavior, Seattle, WA.	**2012**
	Nall, R.W., Guinn. S.M., & Palya, W.L. (2012). *Conceptualizations for Behavior Maintained by Fixed-Interval Schedules.* 29th annual conference of Southeastern Association for Behavior Analysis, Columbia, SC.	**2012**
	Burt, C.R., **Nall, R.W.**, & Palya, W.L. (2011). *Evaluating the Bipolar Effect with a Concomitant CFT/VI Schedule*. 34th annual conference of Society for Quantitative Analysis of Behavior, Denver, CO.	**2011**
	Nall, R.W., Guinn. S.M., & Palya, W.L. (2011). *Rate Modulation in a Concomitant CFT VI schedule.* 28th annual conference of Southeastern Association for Behavior Analysis, Charlotte, NC.	**2011**
EDITORIAL ACTIVITIES		
	AD HOC REVIEWER FOR JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR	**2018**
PROFESSIONAL MEMBERSHIPS		

	SOCIETY FOR NEUROSCIENCE	**2018-PRESENT**
	ASSOCIATION FOR BEHAVIOR ANALYSIS	**2011-PRESENT**
	SOCIETY FOR THE QUANTITATIVE ANALYSIS OF BEHAVIOR	**2011-PRESENT**
	FOUR CORNERS ASSOCIATION FOR BEHAVIOR ANALYSIS	**2014-PRESENT**
	SOUTH EASTERN ASSOCIATION FOR BEHAVIOR ANALYSIS	**2010-2013**