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Longer Treatment with Alternative Non-Drug Reinforcement Fails to Reduce Resurgence of Cocaine or Alcohol Seeking in Rats

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1. Introduction

Treatments based on alternative reinforcement are among the most effective for reducing drug use in individuals with substance use disorders [1,2]. In alternative-reinforcement-based therapies for substance use, non-drug alternative reinforcers are arranged for abstinence from drug taking or for engaging in behaviors unrelated to drug use. For example, in Contingency Management [CM; 3,4], individuals with substance use disorders earn vouchers contingently upon proof of abstinence from drugs of abuse (e.g. drug-free urine samples). Similarly, in Community Reinforcement Approach [CRA; 5,6], alternative reinforcers are obtained for engaging in pro-social behaviors that are unrelated to drug use such as job procurement, attending social events, and spending time with family. Alternative-reinforcement based techniques are effective at reducing substance use while treatment is in place, but relapse of drug use often occurs when alternative reinforcers become unavailable following lapses in treatment integrity or upon cessation of treatment [e.g., 7]. Relapse following the loss of alternative reinforcement is known as resurgence [8]. A better understanding of resurgence may provide insights into methods for reducing relapse following alternative-reinforcement based treatments for substance use.

Resurgence is often studied in animals using a procedure consisting of three phases. In Phase 1 (baseline), a target response produces reinforcement. In Phase 2 (treatment), the target response is placed on extinction and an alternative response produces reinforcement. Finally, in Phase 3 (resurgence test), the alternative response is also placed on extinction and resurgence is said to occur if target responding increases relative to terminal responding in the previous phase. Previous studies have used this basic procedure to examine resurgence of both cocaine [9–11] and alcohol seeking [12,13] in rats. These studies have led some to suggest that the resurgence procedure might be useful for modeling relapse of drug seeking induced by loss of alternative reinforcement in clinical settings [10,12,14–16].

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One factor that could influence the magnitude of resurgence of drug seeking is the duration of the treatment phase. Indeed, animal models investigating other types of relapse have demonstrated an increase in drug craving and relapse of drug seeking following longer periods of forced [17] or voluntary abstinence [18]. The effects of treatment duration on resurgence, however, have been examined directly in only two studies, and those studies produced mixed results. Further, the available studies on resurgence have only used non-drug reinforcers for target behavior. Leitenberg, Rawson, and Mulick [19] found that resurgence of food seeking in rats was smaller after 27 sessions of treatment than after 3 or 9 sessions. In contrast, Winterbauer, Lucke, and Bouton [20] obtained similar levels of resurgence of food seeking in rats following 4, 12, or 36 sessions of treatment. One potential complication with interpreting the result of Winterbauer, Lucke, and Bouton, [20] is that the use of a ratio schedule of reinforcement for the alternative behavior resulted in a confound between rates of alternative reinforcement and treatment duration across groups (i.e., alternative reinforcer rates were higher for the 36-session group than for shorter duration groups). Relatively high rates of alternative reinforcement produce greater resurgence than relatively low rates [9,21], and the higher alternative reinforcer rate may have counteracted the effects of longer treatment duration [for discussion see 22]. Thus, the effects of treatment duration on resurgence remain unclear and have never been directly examined with drug-seeking behavior.

Given the uncertainty surrounding the effects of treatment duration on resurgence and the use of only food reinforcers, the goal of the present experiments was to directly examine the effects of treatment duration on resurgence of cocaine and alcohol seeking in rats. Rats were trained to self-administer cocaine (Experiment 1) or alcohol (Experiment 2) and resurgence was measured following either 5 or 20 sessions of extinction and alternative reinforcement.

2. Experiment 1

Experiment 1 evaluated the effects of treatment duration on resurgence of cocaine seeking in rats. In Phase 1, rats pressed levers (i.e., target response) for infusions of cocaine. During Phase 2, rats were divided into three groups and target responding was placed on extinction for all groups. For the 5-Day and 20-Day groups, a non-drug alternative reinforcer (i.e. food pellets) was also made available for nose poke responses (i.e., alternative response). Extinction and alternative reinforcement lasted five sessions for the 5-Day group and 20 sessions for the 20-Day group. For the Extinction Control group, extinction of target responding lasted for 25 sessions. In Phase 3, alternative responding was extinguished while target responding remained on extinction for the 5-Day and 20-Day groups (see Figure 1 for a summary of the phase durations for each group in Experiment 1). Resurgence (i.e., an increase in target responding between the last session of Phase 2 and the first session of Phase 3) was expected in the 5-Day and 20-Day groups, but not the Extinction Control group. If longer duration of treatment does indeed reduce resurgence, the magnitude of resurgence would be expected to be smaller in the 20-Day group than in the 5-Day group.

2.1. Materials and methods

2.1.1. Subjects—Thirty-two experimentally naïve male Long-Evans rats (Charles River, Portage, MI) served as subjects. Rats were 71–80 days old upon arrival and weighed approximately 450 g at the time of jugular-catheterization surgery (detailed below). Rats were individually housed in a temperature-controlled colony room with a 12:12 hr light/dark cycle (lights on at 7:00 am) and had free access to water in their home cages. Rats were allowed ad lib access to rat chow in their home cages until they had recovered from surgery. They were then maintained at 80% of their free-feeding weights. Animal housing and care, and all procedures reported below were conducted in accordance with Utah State University's Institutional Animal Care and Use Committee.

2.1.2. Surgery—Prior to the start of the experiment, rats underwent jugular-catheterization surgery, described in detail elsewhere [9]. 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 during which infusions of an electrolyte solution (Ringer's Solution, 5ml, subcutaneous) and an NSAID analgesic (Flunixin Meglumine, 1ml/kg, subcutaneous) were provided twice daily. Catheter patency was maintained by twice daily 0.1ml infusions of gentamicin heparinized saline solution (4mg/ml gentamicin, .04mg/ml heparin).

2.1.3. Apparatus—Ten modular Med Associates (St. Albans, VT) operant chambers were used. Chambers measured 30 cm × 24 cm × 21 cm and were housed in sound- and light-attenuating cubicles. Each chamber had aluminum panels on the front and back walls, and Plexiglas walls on each side. The front panels were equipped with two retractable levers with stimulus lights above them. Levers were positioned equidistantly on either side of a centered food aperture that was illuminated when delivering 45-mg food pellets (used for all food reinforcement; Bio Serv, Flemington, NJ). A house light above this receptacle was used for general chamber illumination. The back panel housed 5 horizontally arranged nose-poke apertures equipped with photocells to detect entry into each aperture. These receptacles could be illuminated by yellow LEDs.

Chambers were also equipped for intravenous drug self-administration. Tygon tubing encased in a metal-spring tether was inserted through a hole cut in the center of the chamber ceiling. The Tygon tubing and tether were attached to rats' back-mounted cannulae at all times. The other end of the tubing was attached to a stainless-steel swivel (Instech, Plymouth Meeting, PA) suspended above the chamber ceiling. Tygon tubing attached the swivel to a 60-ml syringe mounted on an infusion pump (Med Associates) outside the cubicle. Cocaine hydrochloride was dissolved in a sterile 0.9% saline solution to a concentration of 2.56 mg/ml. Individual doses were determined daily based on body weight and achieved by changing the activation duration of the fixed-speed (0.0527 ml/s) syringe pump. All experimental events and data collection were controlled by Med-PC (Med-Associates) software run on a computer in an adjoining control room.

2.2. Procedure

2.2.1. Pellet Training—Prior to the start of self-administration training, rats were trained to consume food pellets from the food aperture. Levers remained retracted and no stimuli were on during pellet training except for the illumination of the food aperture when pellets were delivered. Food pellets were delivered response-independently according to a variable-time (VT) 60-s schedule for four, 45-min sessions. Session durations for the remainder of the experiment were also 45 min excluding time for reinforcer deliveries and chamber blackouts. Each food delivery consisted of a single pellet and was accompanied by a 3-s blackout of the chamber. The VT schedule and all subsequent VT and variable-interval (VI) schedules reported below were constructed of 10 intervals derived from Fleshler and Hoffman's [23] constant-probability distribution.

2.2.2. Cocaine Self-Administration Training—Sessions during self-administration training (and for the remainder of the experiment) began with illumination of the house light, insertion of both levers, and illumination of the stimulus light above the right (target) lever. Initially, responses to the target lever produced 1mg/kg infusions of cocaine according to a fixed-ratio (FR) 1 schedule. Each cocaine delivery was accompanied by a 45-s blackout of the chamber and timeout from the session. The ratio requirement was then increased in increments of one response across sessions until an FR 4 schedule was reached. Next, a variable-ratio (VR) 2 schedule was implemented and the ratio requirement was increased in increments of two responses until rats reliably self-administered 1 mg/kg infusions of cocaine according to a VR 20 schedule. The values for the VR schedule were obtained using a modified Fleshler-Hoffman [23] distribution. Finally, the cocaine dose was decreased to 0.5 mg/kg then again to 0.32 mg/kg across sessions. During training and for the remainder of the experiment, responses to the left (inactive) lever were recorded but had no consequence. Cocaine self-administration training lasted approximately 30 sessions.

2.2.3. Phase 1: Baseline—Phase 1 began once rats reached the 0.32 mg/kg dose of cocaine. Reinforcement contingencies were identical to those at the end of the self-administration training phase described above. That is, pressing the target lever produced infusions of cocaine according to a VR 20 schedule. This phase lasted at least five sessions and until rats showed no downward trend in responding for the last three sessions. Rats were then divided into three groups such that average mg/kg of cocaine infused across the last three sessions and rates of target responding were equivalent between groups.

2.2.4. Phase 2: Treatment—During Phase 2 for all groups, the target lever no longer produced cocaine infusions, and the left-most nose-poke aperture was illuminated. This phase lasted five sessions for the 5-Day group ($n = 11$), and 20 sessions for the 20-Day group ($n = 11$). For rats in these groups, nose-poke responses to illuminated nose-poke aperture (i.e., alternative responses) produced food according to a VI 15-s schedule. The Extinction Control Group ($n = 10$) did not receive alternative reinforcement and was exposed to target-response extinction for 25 sessions (i.e. Phase 3 conditions; see Figure 1).

2.2.5. Phase 3: Resurgence Test—During Phase 3, target-response extinction continued for all groups. Alternative responding was placed on extinction for the 5-Day and

20-Day groups such that nose pokes no longer produced food. This phase lasted five sessions for the 5-Day and 20-Day groups. Conditions remained unchanged for the Extinction Control group (see Figure 1).

2.3. Data Analyses

Time for reinforcer deliveries and chamber blackouts was excluded from session time in the calculation of all rate measures reported below. Resurgence was defined as a statistically significant increase in target responding between the last session of Phase 2 and the first session of Phase 3. Further, increases in target responding were compared with increases in responding on the inactive lever. The purpose of this comparison was to differentiate focal increases in target responding (i.e. resurgence) from general increases in activity induced by extinction of the alternative response. All statistical analyses were deemed significant at an α level of .05. When Mauchly's test indicated a violation of sphericity for within-subject factors in analyses of variance (ANOVA), Greenhouse-Geisser corrections to degrees of freedom were used.

2.4 Results and Summary

2.4.1. Phase 1: Baseline—Average target response rates for infusions of cocaine were similar for all groups during the final three sessions of Phase 1. A one-way ANOVA conducted on target response rates averaged across these final three sessions of Phase 1 revealed that target responding did not differ between groups, $F(2, 29) < 0.01$, $p = .998$, $\eta_p^2 < .001$. Further, infusions of cocaine per min and obtained mg/kg were similar between groups during these final sessions. See Table 1 for summary of response and reinforcer rates for the three groups for each phase of the experiment.

2.4.2. Phase 2: Treatment—Figure 2A shows average target response across sessions of Phase 2 for all groups. To assess extinction of cocaine-seeking, a 5×3 (Session $\times$ Group) mixed-model ANOVA was conducted on target response rates during the first five sessions of Phase 2 in all three groups. This analysis revealed a significant effect of Session, $F(2.14, 62.15) = 27.22$, $p < .001$, $\eta_p^2 = .484$, but no effect of Group, $F(2, 29) = 1.49$, $p = .24$, $\eta_p^2 = .093$, or Session $\times$ Group interaction, $F(4.29, 62.15) = 2.27$, $p = .068$, $\eta_p^2 = .135$. These results suggest that target responding decreased at similar rates across groups (see Figure 2A). Finally, target responding was comparable between groups at the end of Phase 2 (see Table 1).

Figure 2B shows average alternative response rates across sessions of Phase 2 for all groups. Alternative responding increased across sessions of Phase 2 in the 5-Day and 20-Day groups and remained low for the Extinction Control group. An independent-samples t -test conducted on alternative response rates during the last session of Phase 2 for the 5-Day and 20-Day groups approached significance, $t(20) = 1.93$, $p = .068$, $d = .822$ (see "Last Phase 2" in Figure 3B), suggesting that alternative-response rates were marginally higher at the end of Phase 2 in the 20-Day group than in the 5-Day group.

2.4.3. Phase 3: Resurgence Test—Figure 3A shows target response rates during the last session of Phase 2 and across all sessions of Phase 3 for each group. Target response

rates across two time points in the Extinction Control group (i.e., sessions 5-10 and sessions 20-25) are included to provide relevant comparisons for the resurgence tests for the 5-Day and 20-Day groups. As $2 \times 2 \times 2$ (Phase $\times$ Response $\times$ Group) mixed-model ANOVA was conducted on target and inactive response rates during the last session of Phase 2 and the first session of Phase 3 for the 5-Day and 20-Day groups to examine changes in target and inactive responding between phases for these groups. This analysis revealed significant effects of Phase, $F(1, 20) = 23.05$, $p < .001$, $\eta_p^2 = .535$, and Response, $F(1, 20) = 15.88$, $p = .001$, $\eta_p^2 = .443$, but no effect of Group, $F(1, 20) = 0.33$, $p = .575$, $\eta_p^2 = .016$. The Phase $\times$ Group, $F(1, 20) = 0.69$, $p = .417$, $\eta_p^2 = .033$, Response $\times$ Group, $F(1, 20) = 0.50$, $p = .490$, $\eta_p^2 = .024$, and Response $\times$ Phase $\times$ Group, $F(1, 20) = 0.85$, $p = .369$, $\eta_p^2 = .041$, interactions were not significant. However, the Response $\times$ Phase interaction, $F(1, 20) = 19.82$, $p < .001$, $\eta_p^2 = .498$, was significant. Thus, resurgence of cocaine-seeking occurred in both the 5- and 20-Day groups and was specific to the target response (see Table 1 for inactive responding during these sessions). A planned 2×2 (Phase $\times$ Group) mixed-model ANOVA conducted on target response rates between Phases 2 and 3 for the 5-Day and 20-Day groups revealed a main effect of Phase $F(1, 20) = 21.62$, $p < .001$, $\eta_p^2 = .519$, but no significant effect of group $F(1, 20) < 0.01$, $p = .983$, $\eta_p^2 < .001$, or Phase $\times$ Group interaction $F(1, 20) = 0.77$, $p = .392$, $\eta_p^2 = .037$. These statistical findings are also consistent with the data from individual subjects, which are shown in Figure 4. Together, these results suggest that the magnitude of resurgence of target responding was comparable between the 5-Day and 20-Day groups (see dotted data paths in Figure 3A and individual subject data in Figure 4).

A 5×2 (Session $\times$ Group) mixed-model ANOVA was conducted on target response rates across sessions of Phase 3 (i.e., solid data paths in Figure 3A) to assess target responding during resurgence testing in the 5-Day and 20-Day groups. Target responding in the Extinction Control group was not analyzed because it remained low during this phase at the comparable time points (see Figure 3A). This analysis revealed a significant effect of Session, $F(2.42, 48.48) = 4.18$, $p = .015$, $\eta_p^2 = .173$, but no effect of Group, $F(1, 20) = 0.17$, $p = .684$, $\eta_p^2 = .008$, or Session $\times$ Group interaction, $F(2.42, 48.48) = 0.07$, $p = .954$, $\eta_p^2 = .004$. Thus, target responding decreased at similar rates across sessions of Phase 3 in the 5-Day and 20-Day groups.

Figure 3B shows alternative response rates during the last session of Phase 2 (i.e., sessions 5 and 20 for the 5-Day and 20-Day groups, respectively) and across all sessions of Phase 3 for the 5-Day and 20-Day groups. Alternative responding for the Extinction Control group was not included in the figure or in the below analysis as it occurred at near-zero levels during this phase (see Table 1). To assess between-group differences in alternative responding during Phase 3, a 5×2 (Session $\times$ Group) mixed-model ANOVA was conducted on alternative response rates across sessions of Phase 3 for the 5-Day and 20-Day groups. This analysis revealed significant effects of Session, $F(1.33, 26.52) = 38.82$, $p < .001$, $\eta_p^2 = .660$, Group, $F(1, 20) = 17.20$, $p < .001$, $\eta_p^2 = .462$, and the interaction between these terms, $F(1.33, 26.52) = 10.85$, $p = .001$, $\eta_p^2 = .352$. Thus, alternative responding was relatively high in the 20-Day group and decreased across sessions of Phase 3. Alternative responding was lower in the 5-Day group and decreased less steeply across sessions of Phase 3 (see Figure 3B).

2.4.4 Summary—The goal of Experiment 1 was to determine if different durations (i.e., 5 or 20 sessions) of Phase 2 treatment differentially impacted the magnitude of resurgence of rats' cocaine seeking. Resurgence occurred for both groups that received alternative reinforcement, but not for the Extinction Control group. The duration of Phase 2 treatment had no differential effect on resurgence of target responding in the 5-Day and 20-Day groups. Another noteworthy finding is that alternative responding was more resistant to extinction during Phase 3 (see Figure 3B) for the 20-Day group than for the 5-Day group. This may be important for extensions to applied treatment of substance use disorders, which will be discussed in the General Discussion below.

3. Experiment 2

The goal of Experiment 2 was to systematically replicate and extend the findings of the 5-Day and 20-Day groups from Experiment 1 by examining the effects of Phase 2 treatment duration on resurgence of alcohol seeking.

3.1. Materials and methods

3.1.1. Subjects—Eighteen experimentally naïve male Long-Evans rats (Charles River, Portage, MI) served as subjects. Rats were 71-90 days old upon arrival and were housed as in Experiment 1.

3.1.2. Apparatus—Four modular Med Associates (St. Albans, VT) operant chambers were used. Chambers measured 30 cm × 24 cm × 21 cm and were housed in sound-and light-attenuating cubicles. Each chamber had aluminum panels on the front and back walls, and Plexiglas walls on each side. The front panels were equipped with two retractable levers and stimulus lights above them. Levers were positioned equidistantly on either side of a centered food aperture that was illuminated when delivering 45-mg food pellets (Bio Serv, Flemington, NJ). A house light above this receptacle was used for general chamber illumination. A third retractable lever and stimulus light were positioned on the center of the back wall. A dipper aperture was positioned to the right of this lever and was illuminated when delivering 0.10 ml dippers of ethanol solution. Each chamber was also equipped with a chain attached to a micro switch that could be inserted through a hole in the center of the ceiling. Distilled water, table sugar (w/vol), and 95% stock ethanol (vol/vol) were used to prepare solutions. All solutions were stored at room temperature and were prepared at least every two days to maintain freshness. All experimental events and data collection were controlled by Med-PC (Med-Associates) software run on a computer in an adjoining control room.

3.2. Procedure

3.2.1. Pellet and Dipper Training—Rats were first trained to consume food pellets and ethanol solution from the food and dipper apertures, respectively. Levers remained retracted and no stimuli were on during pellet and dipper training except for the illumination of the food/dipper apertures when food/ethanol was delivered. First, food pellets were delivered response-independently according to a VT 60-s schedule for three, 30 min sessions. Session durations for the remainder of the experiment were also 30 min excluding time for reinforcer

deliveries and chamber blackouts. Each food delivery consisted of a single pellet and was accompanied by a 3-s blackout of the chamber. Rats were then trained to consume a 2% ethanol/10% sucrose solution from the dipper aperture. Ethanol dippers were raised for 4 s and were delivered response-independently according to a VT 60-s schedule for four sessions. Each dipper delivery was accompanied by a 4-s blackout of the chamber. Following dipper training, alcohol self-administration training commenced.

3.2.2. Alcohol Self-Administration Training—Sessions during self-administration training (and for the remainder of the experiment) began with illumination of the house light, insertion of the front-left and back-center levers, and illumination of the light above the center (target) lever. Responses to the target lever produced dippers of ethanol solution and rats were trained to self-administer alcohol according to a modified sucrose fading procedure [24], as described by Shahan [25]. Alcohol self-administration training lasted until rats responded reliably on a VR 20 schedule for 10% ethanol solution. During self-administration training and for the remainder of the experiment, responses to the front-left (inactive) lever were recorded but had no consequence. Alcohol Self-Administration Training lasted approximately 50 sessions.

3.2.3. Phase 1: Baseline—Phase 1 began once rats responded for the 10% ethanol solution. Reinforcement contingencies were identical to those at the end of the self-administration training phase described above. This phase lasted a minimum of 20 sessions and until rats showed no downward trend in responding for the last three sessions. Rats were then divided into two groups such that average g/kg of ethanol consumed across the last three sessions and target response rates were equivalent between groups.

3.2.4. Phase 2: Treatment—During Phase 2, target lever pressing no longer produced ethanol dippers, and a chain was inserted into the chamber from a hole in the ceiling. For both groups, chain pull responses (i.e., alternative responses) produced food according to a VI 15-s schedule. This phase lasted five sessions for the 5-Day group ($n = 9$), and 20 sessions for the 20-Day group ($n = 9$).

3.2.5. Phase 3: Resurgence Test—During Phase 3, target responding remained on extinction and alternative responding was also placed on extinction for both groups. This phase lasted five sessions.

3.3. Data Analyses

Same as described for Experiment 1.

3.4. Results and Summary

3.4.1. Phase 1: Baseline—Target response rates for dippers of ethanol were similar for both groups during the final three sessions of Phase 1. An independent-samples *t*-test conducted on target response rates averaged across these final sessions of Phase 1 revealed that target responding did not differ between groups, $t(16) = 0.66$, $p = .519$, $d = .311$. Further, dippers of ethanol per min and obtained g/kg were similar between groups during these final sessions. Inactive responding occurred at low rates for both groups. See Table 2

for summary of response and reinforcer rates for both groups for each phase of the experiment.

3.4.2. Phase 2: Treatment—Figure 5A shows target response rates across sessions of Phase 2 for both groups. Target responding decreased similarly for both groups across Phase 2. To assess extinction of alcohol seeking, a 3×2 (Session $\times$ Group) mixed-model ANOVA was conducted on target response rates during the first five sessions of Phase 2 for both groups. This analysis revealed a significant effect of Session, $F(1.22, 19.52) = 14.94$, $p = .001$, $\eta_p^2 = .483$, but no effect of Group, $F(1, 16) = 0.04$, $p = .839$, $\eta_p^2 = .003$, or Session $\times$ Group interaction, $F(1.22, 19.52) = 0.37$, $p = .594$, $\eta_p^2 = .022$. Thus, target responding decreased at similar rates for both groups across sessions of Phase 2 (see Figure 5A). Finally, target responding was comparable between groups at the end of Phase 2 (see Table 2).

Figure 5B shows alternative response rates across sessions of Phase 2 for both groups. Alternative responding increased across sessions of Phase 2 for both groups. Though alternative response rates were visually larger for the 20-Day group, an independent-samples t -test conducted on alternative response rates during the last session of Phase 2 revealed that alternative responding was not statistically different between groups, $t(16) = 1.55$, $p = .140$, $d = .733$ (see “Last Phase 2 in Figure 6B). Inactive responding remained at low levels in both groups (see Table 2).

3.4.3 Phase 3: Resurgence Test—Figure 6A shows target responding during the last session of Phase 2 and across all sessions of Phase 3 for both groups. To assess resurgence, a $2 \times 2 \times 2$ (Phase $\times$ Response $\times$ Group) mixed-model ANOVA was conducted on target and inactive response rates during the last session of Phase 2 and the first session of Phase 3. This analysis revealed a significant effect of Phase, $F(1, 16) = 17.95$, $p = .001$, $\eta_p^2 = .529$, but no effects of Response, $F(1, 16) = 3.05$, $p = .100$, $\eta_p^2 = .160$, or Group, $F(1, 16) = 0.06$, $p = .804$, $\eta_p^2 = .004$. The Phase $\times$ Group, $F(1, 16) = 0.33$, $p = .572$, $\eta_p^2 = .020$, Response $\times$ Group, $F(1, 16) = 2.14$, $p = .163$, $\eta_p^2 = .118$, and Response $\times$ Phase $\times$ Group, $F(1, 16) = 0.32$, $p = .577$, $\eta_p^2 = .030$, interactions were not significant. However, the Response $\times$ Phase interaction, $F(1, 16) = 4.70$, $p = .045$, $\eta_p^2 = .227$, was significant. These results suggest that resurgence was specific to the target response (see Table 2 for inactive responding during these sessions) and that the magnitude of resurgence was similar between groups (see dotted data paths in Figure 6A). Figure 7 shows target responding resurged similarly for individual subjects in the 5-Day and 20-Day groups during the last day of Phase 2 and first day of Phase 3.

Target responding initially increased during Phase 3 for both groups, and then decreased across sessions (see solid data paths in Figure 6A). A 5×2 (Sessions $\times$ Group) mixed-model ANOVA conducted on target response rates across sessions of Phase 3 revealed a significant effect of Session, $F(4, 64) = 2.89$, $p = .029$, $\eta_p^2 = .153$, but no effect of Group, $F(1, 16) = 3.34$, $p = .086$, $\eta_p^2 = .173$, and no Session $\times$ Group interaction, $F(4, 64) = 0.29$, $p = .826$, $\eta_p^2 = .018$. Further, the bitonic shape of the target response function across Phase 3 was confirmed by a significant quadratic trend for session, $F(1, 16) = 5.86$, $p = .028$, $\eta_p^2 = .268$. The quadratic trend for the Session $\times$ Group was not significant, $F(1, 16) = 0.28$, $p = .603$,

$\eta_p^2 = .017$. These results suggest that target responding increased early in Phase 3, and then decreased for both groups similarly. Together, these results indicate that resurgence occurred and was similar for both groups (see dotted data paths in Figure 6A and individual subject data in Figure 7).

Figure 6B shows alternative response rates during the last session of Phase 2 (i.e., sessions 5 and 20) and across all sessions of Phase 3 for both groups. To assess alternative-response extinction during Phase 3, a 5×2 (Session $\times$ Group) mixed-model ANOVA was conducted on alternative response rates across sessions of Phase 3 for both groups. This analysis revealed significant effects of Session, $F(2.59, 41.39) = 45.30, p < .001, \eta_p^2 = .739$, and Group, $F(1, 16) = 15.09, p = .001, \eta_p^2 = .485$, and a significant Session $\times$ Group interaction, $F(2.59, 41.39) = 5.02, p = .007, \eta_p^2 = .239$. These results suggest that alternative responding decreased faster in the 5-Day group compared to the 20-Day group (see Figure 6B).

3.4.4 Summary—Resurgence of alcohol seeking occurred following 5 and 20 sessions of treatment in Phase 2, and the duration of treatment did not differentially impact resurgence. These findings are consistent with Experiment 1, in which Phase 2 duration failed to differentially impact resurgence of cocaine seeking. As in Experiment 1, alternative responding was more resistant to extinction during Phase 3 in the 20-Day group relative to the 5-Day group. One difference between Experiment 1 and Experiment 2 is the shape of the target response function across sessions of Phase 3 (see Figures 3A & 6A). The monotonically decreasing function in Experiment 1 is more common in the literature [e.g., 11,12,15], but the bitonic function in Experiment 2 has also been noted on occasion [e.g., 26]. The bitonic response function in Experiment 2 presents a challenge for some theoretical approaches to resurgence, which will be discussed below.

4. General Discussion

The goal of the present experiments was to evaluate the effects of treatment duration on resurgence of cocaine and alcohol seeking in rats. Resurgence of both cocaine and alcohol seeking occurred following removal of non-drug alternative reinforcement. This finding is consistent with previous work demonstrating resurgence of cocaine seeking [9–11] and alcohol seeking [12,13] following suspension of alternative non-drug reinforcement. Importantly, the current data demonstrate a similar magnitude of resurgence of drug seeking following 5 and 20 sessions of treatment.

Previous work from forced or voluntary abstinence models suggests that relapse is greater following longer periods of abstinence. For example, Grimm, Hope, Wise, and Shaham [27] found that cue-induced reinstatement increased with increases in the number of forced abstinence sessions. The failure to find increased resurgence following longer duration of treatment in the current experiments could indicate that the impact of removing alternative reinforcement does not increase over time. Indeed, the lack of evidence for a treatment duration effect on resurgence is consistent with the findings of Winterbauer, Lucke, and Bouton [20], who found no difference in resurgence following 4, 12, or 36 sessions of treatment with alternative reinforcement. Leitenberg Rawson and Mulick [19] found no difference in resurgence after 3 or 9 sessions of treatment, but smaller resurgence following

27 sessions. It is unclear why resurgence was smaller after 27 sessions of treatment, as Leitenberg, Rawson, and Mulick [19] failed to report schedule types and reinforcer rates used for alternative reinforcement. Regardless, taken together, the current and previous findings suggest that longer durations of treatment with alternative reinforcement generally fail to significantly reduce resurgence.

Theoretical accounts of resurgence may be useful for understanding the effects of treatment duration on resurgence. Three common, contemporary accounts of resurgence include Shahan and Sweeney's [28] extension of Behavioral Momentum Theory [BMT; 28], Context Theory [30,31], and Resurgence as Choice [RaC; 31]. These accounts differ in the mechanisms purported to govern resurgence. Shahan and Sweeney's [28] BMT account of resurgence suggests that both extinction of target behavior and reinforcement of an alternative behavior contribute to disruption of target behavior. Thus, when alternative reinforcement is removed, target behavior is partially released from disruption, resulting in an increase in target behaviour (i.e. resurgence). Because target behavior is increasingly disrupted each session during which it is extinguished, BMT predicts substantially more resurgence following short than following long treatment durations [28]. Thus, the current finding that varying treatment duration has no differential effect on resurgence is inconsistent with the BMT-based account. Further, this model suggests that target behavior is increasingly disrupted across sessions of the resurgence test phase because it remains on extinction. This necessarily results in a monotonically decreasing function of target behavior across sessions of the resurgence test phase. Thus, the bitonic target response function demonstrated in Phase 3 of Experiment 2 (see Figure 6A) is also inconsistent with the BMT-based account of resurgence.

Context Theory suggests that resurgence is a special case of ABC renewal [33]. In ABC renewal preparations, a target behavior is reinforced in Context A and extinguished in a different Context B. Then, transition to a novel Context C induces relapse (i.e. renewal) of target responding. Thus, resurgence can be viewed as a case of ABC renewal in which the availability of target reinforcers in Phase 1 serves as Context A, extinction of target behavior and the availability of alternative reinforcement denotes Context B, and the unavailability of target or alternative reinforcers in Phase 3 represents a novel Context C [33]. From this perspective, resurgence is the result of the change to the novel Phase-3 context. For present purposes, the magnitude of the context change between Phases 2 and 3 should not differ following different durations of Phase 2. Thus, resurgence might be expected to be similar following 5 or 20 sessions of treatment, and the results from the present experiments are consistent with this prediction. However, the bitonic shape of the target response function during Phase 3 of Experiment 2 (see Figure 6A) presents a challenge for Context Theory. Because there is no change in context between sessions one and two of Phase 3, there should be no reason to expect any further increase in target behavior. Thus, while the obtained results are generally consistent with Context Theory, it does not fully capture the dynamics of target behavior over the course of resurgence testing. Further, the imprecise and potentially unfalsifiable nature of Context Theory has led some to question its utility in general [21,26,32,34].

Finally, RaC suggests that resurgence is governed by the same processes thought to govern choice. The basic framework of the model is based on the concatenated matching law [35], which suggests that the probability of target behavior is a function of the relative reinforcer rates associated with the response options over time (i.e. target and alternative behaviors in a typical resurgence experiment). According to RaC, value is a function of temporally weighted reinforcement histories for each behavior [32]. The value of the target behavior decreases during treatment with alternative reinforcement and extinction of target behavior, resulting in a decrease in target behavior. When alternative reinforcers are removed during the resurgence test, the value of the alternative behavior drops precipitously. This results in a *relative* increase in value for the target option, which produces an increase in target behavior (i.e. resurgence). Importantly, due to the hyperbolic nature of the weighting function applied to the reinforcement history used to calculate value, very short durations of treatment are predicted to produce slightly more resurgence than longer durations, but such differences would likely be difficult to detect statistically [see for full discussion, 31]. This prediction is generally consistent with the results from previous work [19,20] as well as the current data. That is, when hints of length of treatment effects are found, they generally trend toward larger resurgence effects following short durations of treatments. However, the size of the differences predicted by RaC are considerably smaller than those predicted by the BMT-based approach. Thus, the current data are generally consistent with RaC. Further, RaC can produce non-monotonic functions of target behavior across resurgence test sessions [32], and suggests that the exact shape of such functions depends upon the overall level of invigoration induced by appetitive stimuli (i.e. arousal). In sum, the current experiments present a challenge for the BMT-based model of resurgence, as well as Context Theory, but are generally consistent with the predictions of RaC.

In addition to theoretical implications, the results of the present experiments may also have implications for clinical treatment of substance use disorders. The fact that extended treatment did not reliably reduce resurgence suggests that other methods will need to be developed to prevent relapse induced by loss of alternative non-drug reinforcers—even following extensive treatment. This is reflected in the clinic where extending treatment also fails to increase duration of abstinence in CM treatment programs [2]. Though resurgence of target behavior may not have been affected by duration of treatment, alternative behavior was more resistant to extinction following longer treatment duration in both experiments (see Figures 3B & 6B). This could be important for clinical application, as increasing engagement with alternative reinforcement and producing behavior that is more resistant to disruption may, in turn, increase abstinence periods during treatment which is the best predictor for successful treatment outcomes [36]. Indeed, some types of CM have sought to lengthen treatment duration as a means to establish robust alternatives to drug seeking and use (e.g. 35). Thus, further studies should directly examine the effects of treatment duration on resilience of appropriate alternative behavior in humans and work to develop more effective means to reduce resurgence following the loss of alternative non-drug sources of reinforcement.

4.1 Conclusions

The major finding of the present experiments is that relatively long durations of treatment do not reduce resurgence of cocaine and alcohol seeking in rats compared to relatively short durations. The current findings add to a growing literature challenging Shahan and Sweeney's [28] BMT-based theory of resurgence [see 20,21,31,36], as well as the Context Theory of resurgence [see 21,31,37]. These data provide support for Resurgence as Choice [32] as an alternative theory of resurgence. To the extent that the findings from this animal model of drug seeking are generalizable to humans with substance use disorders, they suggest that reducing the duration of alternative-reinforcement-based treatments may not reduce resurgence following treatment. However, the current finding that alternative behavior was more resistant to extinction following treatment may be promising for clinical applications. It is also important to note that the resurgence phenomenon is not limited to relapse of drug use. Resurgence has also been noted in treatment of other problem behaviors, including inappropriate communication [e.g., 38], self-injury [e.g., 39], and other destructive behaviors [42] in individuals with intellectual and developmental disabilities. Thus, the current data may have potential implications for a wide variety of problem behaviors.

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Figure 1.
Summary of phase durations for each group in Experiment 1.

Figure 2.

A. Average target responses per min across sessions of Phase 2 for each group in Experiment 1. **B.** Average alternative responses per min across sessions of Phase 2 for each group in Experiment 1. Error bars represent standard error of the mean. Note the difference in y-axes.

Figure 3.

A. Average target responses per min during the last session of Phase 2 and across all sessions of Phase 3 for each group in Experiment 1. Target responding across two time points in the Extinction Control group (i.e., between sessions 5-10 and sessions 20-25) is included to provide relevant comparisons to the 5-Day and 20-Day groups. Dotted lines represent resurgence. **B.** Average alternative responses per min during the last session of Phase 2 and across all sessions of Phase 3 for the 5-Day and 20-Day groups in Experiment 1. Error bars represent standard error of the mean. Note the difference in y-axes.

Figure 4.

A. Target responses per min for each subject in the 5-Day group during the last session of Phase 2 and first session of Phase 3 in Experiment 1. **B.** Target responses per min for each subject in the 20-Day group during the last session of Phase 2 and first session of Phase 3 in Experiment 1.

Figure 5.

A. Average target responses per min across sessions of Phase 2 for both groups in Experiment 2. **B.** Average alternative responses per min across sessions of Phase 2 for both groups in Experiment 2. Error bars represent standard error of the mean. Note the difference in y-axes.

Figure 6.

A. Average target responses per min during the last session of Phase 2 and across all sessions of Phase 3 for both groups in Experiment 2. Dotted lines represent resurgence. **B.** Average alternative responses per min during the last session of Phase 2 and across all sessions of Phase 3 for both groups in Experiment 2. Error bars represent standard error of the mean. Note the difference in y-axes.

Figure 7.

A. Target responses per min for each subject in the 5-Day group during the last session of Phase 2 and first session of Phase 3 in Experiment 2. **B.** Target responses per min for each subject in the 20-Day group during the last session of Phase 2 and first session of Phase 3 in Experiment 2.

Table 1

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

	Group											
	5-Day			20-Day			Extinction Control ^f					
	Phase 1 ^a	Phase 2 ^b	Phase 3 ^c	Phase 1 ^a	Phase 2 ^b	Phase 3 ^c	Phase 1 ^a	Phase 2 ^b	Phase 3 ^c	Phase 2 ^b	Phase 3 ^c	Phase 3 ^c
Target/Min	7.37 (0.68)	1.89 (0.44)	3.64 (0.66)	7.34 (0.53)	1.50 (0.41)	4.06 (1.08)	7.40 (0.60)	1.59 (0.34)	1.17 (0.26)	0.92 (0.27)	0.72 (0.26)	
Alt./Min	–	38.94 (7.25)	5.87 (0.67)	–	62.20 (9.66)	18.21 (3.25)	–	0.12 (0.03)	0.11 (0.02)	0.10 (0.09)	0.09 (0.04)	
Inactive/Min	0.38 (0.22)	0.30 (0.09)	0.47 (0.09)	0.24 (0.06)	1.03 (0.79)	1.02 (0.77)	0.15 (0.04)	0.18 (0.03)	0.12 (0.04)	0.21 (0.06)	0.31 (0.06)	
SR/Min	0.37 ^d (0.04)	3.36 ^e (0.06)	–	0.37 ^d (0.02)	3.35 ^e (0.11)	–	0.36 ^d (0.03)	–	–	–	–	
mg/kg	5.30 (0.48)	–	–	5.35 (0.36)	–	–	5.22 (0.42)	–	–	–	–	

^aData averaged across the last three sessions of Phase 1 are shown.^bData from the last session of Phase 2 are shown.^cData from the first session of Phase 3 are shown.^dCocaine infusions per min.^eFood deliveries per min.^fData for the Extinction Control group was evaluated at two time point to provide relevant comparisons between this group and the 5-Day and 20-Day groups.

Table 2

Mean (SEM) Response and Reinforcer Rates for each Phase of Experiment 2.

	Group					
	5-Day			20-Day		
	Phase 1 ^a	Phase 2 ^b	Phase 3 ^c	Phase 1 ^a	Phase 2 ^b	Phase 3 ^c
Target/Min	34.88 (5.27)	0.87 (0.25)	4.08 (1.32)	39.41 (5.64)	0.62 (0.18)	2.79 (1.13)
Alt./Min	–	15.06 (1.42)	6.00 (0.59)	–	20.19 (2.98)	11.98 (1.18)
Inactive/Min	1.16 (0.48)	1.14 (0.70)	1.27 (0.60)	1.38 (0.51)	1.41 (0.60)	1.18 (0.65)
SR/Min	1.68 ^d (0.27)	2.89 ^e (0.24)	–	1.95 ^d (0.28)	3.23 ^e (0.15)	–
g/kg	1.28 (0.19)	–	–	1.83 (0.21)	–	–

^aData averaged across the last five sessions of Phase 1 are shown.^bData from the last session of Phase 2 are shown.^cData from the first session of Phase 3 are shown.^dAlcohol dippers per min.^eFood.