

Loss of Alternative Non-Drug Reinforcement Induces Relapse of Cocaine-Seeking in Rats: Role of Dopamine D₁ Receptors

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Animal models of relapse to drug seeking have focused primarily on relapse induced by exposure to drugs, drug-associated cues or contexts, and foot-shock stress. However, relapse in human drug abusers is often precipitated by loss of alternative non-drug reinforcement. The present experiment used a novel 'resurgence' paradigm to examine relapse to cocaine seeking of rats as a result of loss of an alternative source of non-drug reinforcement. Rats were first trained to press a lever for intravenous infusions of cocaine. Next, cocaine deliveries were omitted and food pellets were provided for an alternative nose-poke response. Once cocaine seeking was reduced to low levels, food pellets for the alternative response were also omitted. Cocaine seeking increased with the loss of the alternative non-drug reinforcer (ie, resurgence occurred) despite continued extinction conditions. The increase in cocaine seeking did not occur in another group of rats injected with SCH 23390 before the loss of the alternative reinforcer. These results suggest that removal of an alternative source of reinforcement may induce relapse of cocaine seeking and that the dopamine D₁ receptor may have a role in this effect.

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INTRODUCTION

The propensity to relapse after a period of abstinence is one of the defining features of drug addiction (American Psychiatric Association, 1994). The goal of drug abuse treatment is to encourage abstinence from drug use and decrease the propensity to relapse. Relapse may be triggered by a variety of events including exposure to drug-related cues (Carter and Tiffany, 1999) or stress (Sinha, 2001). Behavioral theories of addiction suggest that drug use is critically dependent on the value of drug reinforcers relative to other non-drug sources of reinforcement (Vuchinich and Tucker, 1988; Bickel *et al*, 1998). In the laboratory, drug self-administration of both humans and non-humans decreases when an alternative non-drug reinforcer is available (eg, Shahan *et al*, 2001; see Carroll, 1996 for review). Furthermore, the availability of more frequent or larger non-drug reinforcers produces greater shifts in choice away from drug taking in animal models of drug self-administration (eg, Anderson *et al*, 2002; Nader and Woolverton, 1991, 1992). Consistent with such findings, treatments for substance abuse designed explicitly to

decrease the value of drug use by arranging alternative sources of reinforcement have been quite successful (ie, contingency management; see Higgins *et al*, 2004; Petry, 2000). However, when such treatment ends, discontinuation of the alternative reinforcers may result in an increase in the relative value of drug reinforcement, and consequently relapse to drug use (see Silverman *et al*, 1998).

In animal models, examination of environmental and neural mechanisms of relapse have focused almost exclusively on exposure to drug, drug cues, or physical stressors using the reinstatement and renewal paradigms. In the reinstatement paradigm, animals learn to make a response for access to a drug and this response is subsequently extinguished by withholding access to the drug. Responding is then reinstated by exposure to drug, drug-cues, or foot-shock stress (see Shaham *et al* 2003, for review). In the renewal model, animals are trained to respond for a drug in one context, and subsequently that response is extinguished in another context by withholding the drug. A return to the original self-administration context produces relapse to drug seeking, even though drug remains unavailable, (see Crombag *et al*, 2008, for review). Although the reinstatement and renewal models allow assessment of several events that trigger relapse in humans, they do not allow assessment of the impact of losing an alternative source of non-drug reinforcement on relapse.

Both the reinstatement and renewal paradigms have their origins in the basic conditioning and learning literature.

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Another such phenomenon from the conditioning literature called 'resurgence' might provide an animal model of relapse following loss of an alternative non-drug reinforcer. In a resurgence paradigm, animals are trained to make a target response for a reinforcer, and that response is subsequently extinguished by withholding the reinforcer. During extinction of the target response, an alternative reinforcer is made available for a second, different response. When the reinforcer for the second response is subsequently withheld, the target response reappears (eg, Leitenberg *et al*, 1970; Winterbauer and Bouton, 2010; see Shahan and Sweeney, 2011, for review).

Although both reinstatement and renewal of drug seeking have been widely investigated, just one previous study has used the resurgence paradigm to study relapse of drug seeking (Podlesnik *et al*, 2006). Podlesnik *et al* (2006) examined resurgence of extinguished oral alcohol self-administration when an alternative food reinforcer produced by pulling a chain was also removed. However, because both the alcohol and the alternative food reinforcer provided calories, it is possible that resurgence occurred because the food reinforcer was a substitute for the calories provided by the alcohol solution. Thus, at present it is not known if the resurgence model can provide a more general model of relapse induced by loss of alternative non-drug reinforcement.

The purpose of the present experiment was to determine if the loss of an alternative non-drug reinforcer induces relapse to intravenous cocaine seeking in a resurgence paradigm. In addition, previous research has found that activity at dopamine (DA) D₁ receptors has a role in relapse to drug seeking produced by drug priming or exposure to drug cues (Shalev *et al*, 2002). The DA D₁ antagonist SCH 23390 attenuates both reinstatement and renewal of extinguished cocaine seeking (Norman *et al*, 1999; Crombag *et al*, 2002; Alleweireldt *et al*, 2002). Thus, in order to begin an examination of whether resurgence might share neurobiological mechanisms with reinstatement and renewal of cocaine seeking, we also examined whether SCH 23390 would attenuate resurgence of extinguished cocaine seeking.

MATERIALS AND METHODS

Animals and Housing

Subjects. Twelve experimentally naïve male Long-Evans rats obtained from Charles River (Portage, Michigan, USA) were used. Rats were randomly assigned to the control group or the SCH 23390 group. Rats were individually housed in a climate controlled room with a 12:12 light:dark cycle and water was continuously available. Food was continuously available before surgery. Following recovery from surgery, the amount of food the animals received after daily sessions was adjusted to maintain their 85% weights, despite variations in the availability of food in the different phases of the experiment. Care and use of these rats was approved by the Utah State University Institutional Animal Care and Use Committee.

Apparatus. Experimental sessions were conducted in four Med Associates operant self-administration chambers. Each chamber measured 30 cm long, 24 cm wide and 21 cm high,

and was housed in a sound-attenuating cubicle. A 4 cm diameter hole in the roof of the chamber allowed a lead made of Tygon tubing encased in a metal spring to be attached to a connector attached to a rat's head and extend to a swivel (Med Associates) hanging ~15 cm above the chamber. Another 60 cm length of Tygon tubing extended from the swivel to a 60 ml syringe in a Razel infusion pump located outside of the sound-attenuating chamber.

Each chamber contained a response panel with two levers positioned equidistant on either side of a food delivery aperture with an interior light and a tray for collection of 45 mg dustless precision food pellets (Bio-Serv, Frenchtown, New Jersey, USA). A houselight and a Sonalert (2900 ± 500 Hz, 75–85 dB) were located above the food aperture. Three light emitting diodes (LEDs) were located above each lever on the response panel. The opposite side of the chamber contained five apertures evenly spaced horizontally across the bottom of the panel. Each of these apertures contained an interior light and a photobeam to record head entries. Only the left-most aperture and light were used in the present experiment. Med Associates interfacing and software was used for control of experimental events and recording of responses.

Surgery. Before training, each rat was implanted with an intravenous jugular catheter. Surgery was preceded by an injection of antibiotic solution (gentamicin, 2.0 mg/kg, IM) and an anticholinergic drug (atropine sulfate, 0.6 mg/ml, SC, 0.2 ml per rat). Rats were then anesthetized with sodium pentobarbital (65 mg/kg, IP) and prepared for surgery. During surgery, a silastic catheter was inserted into the right jugular vein through an incision made in the right ventral surface of the neck. The catheter was fed subcutaneous dorsally through the neck to the top of the head where it was attached to a 22-gauge metal cannula (PlasticsOne) secured to the skull using skull screws and dental cement. Following surgery, rats were given a non-steroidal anti-inflammatory drug (flunixin meglumine, 1.1 mg/kg, IM) approximately every 12 h for the first 2 days following surgery to minimize pain from the surgical procedures. Rats were allowed to recover at least 5 days after surgery before beginning behavioral training. Food restriction was not implemented until a rat exceeded its pre-surgical weight. Catheter patency was maintained by twice daily infusions of gentamicin heparinized saline solution.

Drug. Cocaine hydrochloride (NIDA/USA) was dissolved in sterile 0.9% saline solution to a concentration of 2.56 mg/ml. Individual infusion doses of cocaine were adjusted by changing the duration of a syringe pump administering 0.0527 ml/s of solution (ie, ~1 s per 0.32 mg/kg infusion depending upon the rat's weight). SCH 23390 HCl was dissolved to a concentration of 10 µg/ml in 0.9% saline solution.

Methods. The experiment was divided into six phases: training, baseline, extinction + food, resurgence, extinction + food 2, and resurgence 2. Sessions were conducted 7 days per week at approximately the same time each day. Sessions lasted 60 min excluding reinforcer delivery time. Rats in the SCH 23390 group received SCH 23390 (10 µg/kg, SC) 15 min before each session in resurgence and resurgence 2 phases.

This dose of SCH 23390 appears to suppress the renewal of extinguished sucrose and cocaine seeking but has little impact on operant responding maintained by food reinforcers (Hamlin *et al*, 2006; Crombag *et al*, 2002; Weissenborn *et al*, 1996).

Training. Rats were first exposed to four daily sessions of magazine training in which a food pellet was delivered approximately every 60 s on a variable time (VT) 60-s schedule. Pellet deliveries were accompanied by the lighting of the food aperture and darkening of other stimuli for 3 s. Following magazine training, rats were trained to press the right lever for infusions of cocaine solution (1.0 mg/kg per infusion) on a fixed ratio (FR) 1 schedule. The number of presses required for each cocaine infusion was increased by increasing the FR value across sessions to an FR 20. The dose of each infusion was then decreased from 1.0 to 0.5, and finally 0.32 across sessions. Rats were limited to obtaining 40 cocaine infusions per session at the 0.32 mg/kg per infusion dose. During training sessions, the light above the right lever was illuminated except during cocaine infusions.

Baseline. Baseline conditions were identical to training with the exception of the cocaine delivery schedule. The baseline schedule arranged a cocaine infusion for an average of 20 responses (ie, a variable ratio (VR) 20 schedule) on the right lever. Responses to the left lever were also recorded but had no other programmed effect. Rats remained in the baseline phase for at least 20 sessions and up to 25 sessions to obtain stability in response rates (ie, coefficient of variation < 25% and absence of consistent increasing or decreasing response rates across 5 days).

Extinction + food phase. Following a stable baseline of responding on the cocaine lever, conditions were changed such that lever presses no longer produced cocaine deliveries (ie, extinction was in effect). With the start of extinction of lever pressing for cocaine, the light in the left aperture on the back wall of the chamber was illuminated and nose pokes produced food pellets. Initially, nose pokes were reinforced on a FR 1 schedule, but the schedule was gradually increased across four sessions to an FR 9. On the fifth session, the schedule of food delivery for nose poking was changed to a VR 10. This gradual escalation of the response requirement for food was used to ensure that nose poking for food was initially well trained but not resulting in excessive numbers of food pellets during the session. This phase lasted at least 10 sessions, or until response rates on the cocaine lever for an individual rat decreased to below 10% of baseline response rates. This phase never exceeded 25 sessions.

Resurgence phase. Resurgence of responding was tested by withholding food deliveries for nose pokes while extinction conditions associated with the cocaine lever remained in effect. The light within the nose-poke aperture remained lighted during this condition. This phase lasted at least 10 sessions and until response rates on the cocaine lever for individual rats returned to below 10% of baseline. This criterion was used in order to ensure that responding returned to low levels before the replication conditions to follow.

Extinction + food 2 and resurgence 2 phases. These replication phases were conducted in order to determine whether resurgence could be examined more than once in a sequence of conditions while cocaine-lever pressing remained on extinction. Immediately following the initial resurgence phase, food pellets were again made available contingent on nose pokes in the lighted aperture for 10 sessions. Food was again subsequently removed in the resurgence 2 phase while the aperture remained lighted. Extinction of responding on the cocaine lever remained in effect throughout these conditions. One rat from each group was euthanized because of catheter failure before these replication conditions. An additional rat from the SCH 23390 group was euthanized due to catheter following three sessions of exposure to the resurgence 2 phase. Thus, analyses of the resurgence 2 phase are limited to three sessions.

Statistical Methods

Total mg/kg per session cocaine delivered and responses per min in the last 5 days of baseline were compared for the control and SCH 23390 using 2 (group) \times (session) mixed factor ANOVAs. Resurgence of extinguished cocaine-lever pressing with the loss of the alternative reinforcer was analyzed using a 2 (extinction + food versus resurgence) \times 5 (session) \times 2 (group) mixed factor ANOVA. This analysis focused on the first five sessions of the resurgence condition in order to permit comparison with low-rate responding during the previous extinction phase for the same number of sessions. A similar analysis was conducted on the food nose-poking response. Given the loss of one rat per group, separate mixed ANOVAs with the same factors were used to compare the last three sessions of the extinction + food 2 phase and the resurgence 2 phase. The magnitude of the resurgence effect obtained for the control group in the resurgence and resurgence 2 tests was compared using a 2 (Phase) \times 3 (session) repeated measures ANOVA based on the first three sessions of each phase. Statistical significance was determined using $\alpha = 0.05$.

RESULTS

Figure 1 shows rates of lever pressing (cocaine) and nose poking (food) for the control and SCH 23390 groups across experimental phases. Data for the last five sessions are presented for the baseline and the two extinction + food phases. Data are presented for the first five sessions of the resurgence phase and the first three sessions of the resurgence 2 phase. There were no significant differences between the two groups in terms of response rates or total mg/kg per session cocaine earned across the last five sessions of the baseline phase.

Examination of cocaine-lever pressing rates during the extinction + food and resurgence phases in Figure 1 reveals that lever pressing increased with the removal of food reinforcement in the resurgence phase for the control group, but not for the SCH 23390 group. In addition, the initially increased rates of lever pressing for the control group in the resurgence phase decreased across sessions. These conclusions are supported by a significant phase \times session \times group interaction ($F(4,40) = 5.99$, $p = 0.007$), a significant phase \times group interaction ($F(1,10) = 14.78$,

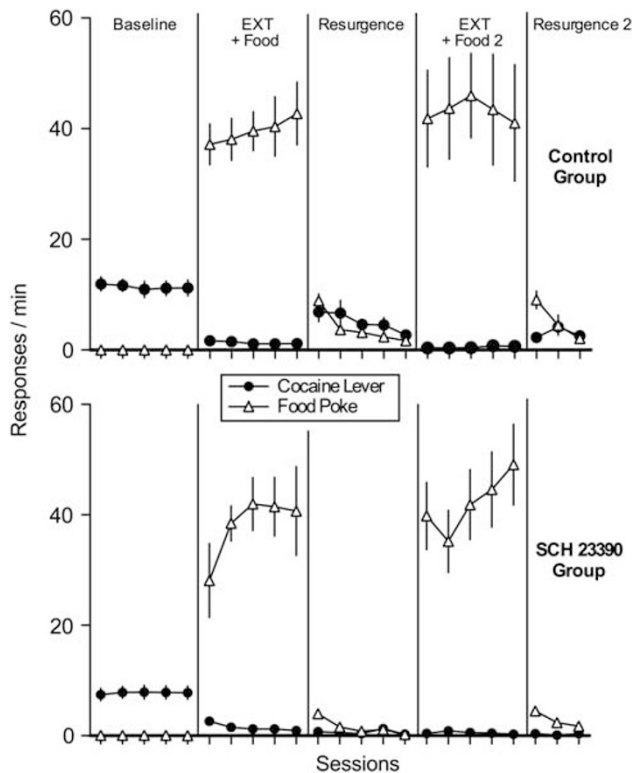


Figure 1 Resurgence of cocaine seeking. Lever pressing (cocaine) and nose poking (food) for the control and SCH 23390 groups across experimental phases. When an alternative source of food reinforcement was removed during the resurgence and resurgence 2 conditions, rates of extinguished lever pressing for cocaine increased for the control group, but not for the SCH 23390 group. Data are from the last five sessions of the baseline and the two extinction + food phases and from the first five and three sessions of the resurgence and resurgence 2 phases, respectively.

$p < 0.003$), and main effects of phase ($F(1,10) = 5.82$, $p = 0.036$), session ($F(4,40) = 5.07$, $p < 0.002$), and group ($F(1,10) = 8.92$, $p = 0.014$). Irrelevant-lever pressing remained low across all phases (ie, < 1 response per min) and showed no significant increase in the resurgence phase for either group. Nose-poking rates decreased for both groups when the pokes no longer produced food in the resurgence phase. This conclusion is supported by a significant phase \times session interaction ($F(1,10) = 5.95$, $p < 0.001$) and a significant main effect of phase ($F(1,10) = 5.95$, $p < 0.001$). There were no significant differences between the control and SCH 23390 groups in terms of nose poking across the extinction + food and resurgence phases (ie, no main effect of group and no significant interactions involving group). Thus, although SCH 23390 blocked the increase in extinguished lever pressing for cocaine when the food reinforcer was removed, it did not affect rates of nose poking.

Figure 1 also shows that cocaine-lever pressing again increased for the control group but not the SCH 23390 group with the transition from extinction + food 2 to resurgence 2 in the replication phases, as evidenced by a significant phase \times group interaction ($F(1,8) = 75.38$, $p < 0.0001$), and significant main effects of phase ($F(1,8) = 59.53$, $p < 0.0001$) and group ($F(1,8) = 31.30$, $p < 0.001$). Again, irrelevant-lever pressing remained low (ie, < 1 response per min) and showed no significant

increase in the resurgence 2 phase for either group. A direct comparison of the first three sessions of the two replications of the resurgence phase reveals that the obtained increase in cocaine-lever responding was larger for the control group in the resurgence than in the resurgence 2 phase ($F(1,8) = 5.51$, $p = 0.047$). Thus, although cocaine-lever responding again increased when the food reinforcer was removed in the replication phase, the magnitude of the resurgence effect decreased. Finally, nose poking also decreased when pokes no longer produced food, as evidenced by a main effect of phase ($F(1,8) = 48.61$, $p < 0.0001$). As in the initial resurgence phase, overall nose-poking rates did not differ for the control and SCH 23390 groups, and there was no interaction of phase and group. However, there was a significant session \times group interaction ($F(2,16) = 8.24$, $p = 0.003$) resulting from the fact that nose-poking rates for the SCH 23390 group tended to increase in the last three sessions of extinction + food 2, but decreased during the first three resurgence 2 conditions.

DISCUSSION

Extinguished lever pressing previously maintained by cocaine increased (ie, showed resurgence) when non-drug reinforcement for an alternative response was removed from the situation. This effect was replicable across a second set of phases in which food was again made available and then removed, but the magnitude of the effect was smaller. In addition, rats that received the DA D_1 antagonist SCH 23390 before resurgence tests did not exhibit an increase in cocaine seeking in either phase in which food was removed.

The present finding that extinguished lever pressing for cocaine increased with the loss of an alternative source of reinforcement is consistent with a larger literature on such resurgence effects in the basic learning literature (Leitenberg *et al*, 1970; Winterbauer and Bouton, 2010; see Shahan and Sweeney, 2011, for review). Like other similar relapse-like effects (ie, reinstatement, renewal, spontaneous recovery), the resurgence effect is consistent with contemporary theories suggesting that extinction does not involve unlearning (see Bouton, 2004, for review). One notable finding of the present experiment was that the magnitude of the resurgence effect was smaller when the alternative reinforcer was reintroduced and then again removed under continued extinction of cocaine-lever pressing. This effect is consistent with a recently proposed quantitative model of resurgence based on behavioral momentum theory (Shahan and Sweeney, 2011). In short, the model suggests that extinction involves the disruption (rather than unlearning) of previously learned behavior and that resurgence occurs because of the removal of the additional disruptive impact of having an alternative reinforcer present during extinction. The effects of repeated resurgence tests are predicted to be smaller because the disruptive impact of extinction continues to grow with time, and thus, the relative release from disruption associated with removing the alternative reinforcer is lessened (see Shahan and Sweeney, in press, for simulations). Regardless of the details of the model, the present findings suggest that the basic conditioning literature on extinction might continue to provide a rich source of ideas about behavioral processes involved in relapse to drug taking.

One potential complication with interpreting the neurobiological significance of the finding that SCH 23390 prevented resurgence of extinguished cocaine seeking is that the drug might have reduced responding via non-specific motor effects. Although more generally dissociating potential motor effects from motivational effects of SCH 23390 in relapse is difficult (see Crombag *et al*, 2002), several lines of evidence suggest that the prevention of resurgence in the present experiment likely was not due to motor impairment alone. First, rates of nose poking did not differ significantly for the SCH 23390 and control groups during the resurgence tests. Obviously, the failure to detect any such difference might have been due to the relatively small sample size. Nonetheless, in some cases, nose poking of the SCH 23390 group in the resurgence tests occurred at rates near those of cocaine-lever pressing in the control group. Second, Alleweireldt *et al* 2002 suggested that evidence against non-specific motor effects of SCH 23390 can be provided by showing that the drug affects persistence across the session, rather than the tendency to begin responding during the session. To examine this possibility, Figure 2 shows the pattern of responding across 2-min bins of the first session of the resurgence phase in the present experiment. Responding across the last day of the extinction + food condition did not differ significantly for the two groups and was thus combined for the analysis. A mixed ANOVA revealed a significant phase \times group \times bin interaction ($F(29, 290) = 7.85, p < 0.0001$), with all other two way interactions and main effects being significant (all $F_s > 7, p < 0.002$). Importantly, cumulative responses increased across time in extinction + food and resurgence phases for the SCH 23390 group ($F(29, 145) = 7.59, p < 0.0001$), and the pattern of the increase across the session did not differ for the two phases (ie, no main effect of phase or interaction). Finally, a significant difference in responding between the SCH 23390 and control groups did not emerge until the 4th 2-min bin into the session ($t(10) = 2.67, p = 0.023$). Thus, SCH 23390 appears not to have impacted the tendency to

initiate responding in the session during resurgence. Combined with the nose-poke data above, these findings are consistent with the suggestion that SCH 23390 likely did not prevent resurgence due to motor impairment alone.

Previous research has also implicated the DA D₁ receptor in drug- and cue-induced reinstatement (Norman *et al*, 1999; Alleweireldt *et al*, 2002), and in context-induced renewal of drug seeking (Crombag *et al*, 2002). On the contrary, DA D₁ receptors are not believed to mediate stress-induced relapse (Shaham *et al*, 2000). This trigger-specific role of DA D₁ receptors is potentially important because the loss of alternative reinforcement that induced relapse in the present experiment could be likened to a stressful event. Indeed, many potentially stress-related sources of relapse like job loss or divorce (eg, Temple *et al*, 1991; Gallo *et al*, 2001; Falba *et al*, 2005) could be characterized as involving reinforcement loss. However, considerable uncertainty remains about potentially shared mechanisms in stress-induced relapse and resurgence induced by reinforcement loss. On one hand, it is true that both extinction of operant behavior (De Boer *et al*, 1990) and exposure to footshock stress (Friedman *et al*, 1967) are associated with increases in the stress hormone corticosterone. On the other hand, although minimal basal levels of corticosterone are necessary for footshock or food-deprivation stress-induced reinstatement of cocaine seeking, increases in corticosterone do not appear to be crucial (Erb *et al*, 1998; Shalev *et al*, 2003). Rather, extrahypothalamic corticotropin-releasing factor appears to have the critical role (see Shalev *et al*, 2010, for review). At present, the respective roles of corticosterone and corticotropin-releasing factor in extinction of even simple food-maintained operant behavior appear to be unknown. In addition, despite renewed interest in resurgence as a relapse phenomenon (eg, Winterbauer and Bouton, 2010; Shahan and Sweeney, 2011) the relevant neurobiological mechanisms have never been examined—even with food maintained behavior.

Regardless of the specific behavioral or neurobiological mechanisms involved in resurgence, the present experiment suggests that the resurgence paradigm may hold promise as an animal model of relapse induced by loss of an alternative non-drug source of reward. The availability of such an animal model is important because, as noted above, treatments that provide alternative sources of reinforcement have been quite effective. Nonetheless, the long-term efficacy of such treatments in reducing relapse is less clear (Prendergast *et al*, 2006). Despite reports of greater abstinence following contingency management treatment than control therapies (see Higgins *et al*, 2000), cessation of treatment is often associated with increased levels of drug use relative to treatment (Silverman *et al*, 1998). The resurgence model appears to provide a novel way to examine the behavioral and neurobiological mechanisms of such relapse, and to perhaps understand it within the context of existing accounts of relapse.

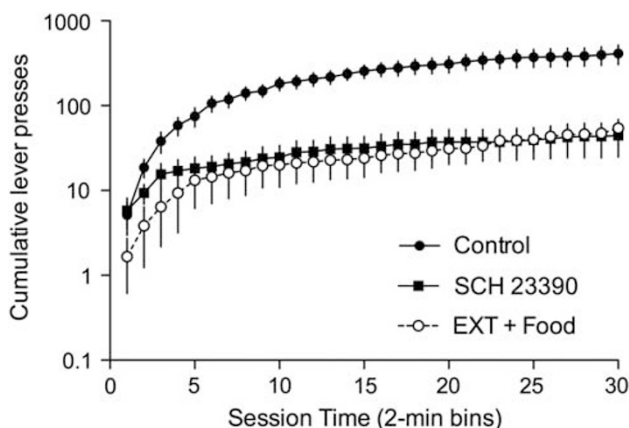


Figure 2 Within-session patterns of responding. Cumulative lever presses across successive 2-min bins of the first resurgence session for the control and SCH 23390 groups. Similar data for the last session of exposure to the extinction + food phase (combined across groups) are provided for comparison. Lever pressing for the control and SCH 23390 groups did not differ until the 4th 2-min bin. In addition, lever pressing for the SCH 23390 continued to occur at a low rate throughout the session, as was true for the last extinction + food session.

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