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## Reduction of extinction and reinstatement of cocaine seeking by wheel running in female rats

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### Abstract

**Rationale and objectives**—Previous work has shown that wheel running reduced the maintenance of cocaine self-administration in rats. In the present study, the effect of wheel running on extinction and reinstatement of cocaine seeking was examined. Female rats were trained to run in a wheel during 6-h sessions, and they were then catheterized and placed in an operant conditioning chamber where they did not have access to the wheel but were allowed to self-administer iv cocaine. Subsequently, rats were divided into four groups and were tested on the extinction and reinstatement of cocaine seeking while they had varying access to a wheel in an adjoining compartment. The four groups were assigned to the following wheel access conditions: (1) wheel running during extinction and reinstatement (WER), (2) wheel running during extinction and a locked wheel during reinstatement (WE), (3) locked wheel during extinction and wheel running during reinstatement (WR), and (4) locked wheel during extinction and reinstatement (WL). WE and WR were retested later to examine the effect of one session of wheel access on cocaine-primed reinstatement.

**Results**—There were no group differences in wheel revolutions, in rate of acquisition of cocaine self-administration, or in responding during maintenance when there was no wheel access. However, during extinction, WE and WER responded less than WR and WL. WR and WER had lower cocaine-primed reinstatement than WE and WL. One session of wheel exposure in WE also suppressed cocaine-primed reinstatement.

**Conclusions**—Wheel running immediately and effectively reduced cocaine-seeking behavior, but concurrent access to running was necessary. Thus, exercise is a useful and self-sustaining intervention to reduce cocaine-seeking behavior.

### Keywords

Alternative reinforcement; Cocaine; Environmental enrichment; Extinction; Rats; Reinstatement; Self-administration; Wheel running

### Introduction

Environmental enrichment with dietary (Carroll et al. 2001), social (Bardo et al. 2001; Schenk et al. 1987), and novel (Bardo et al. 2001; Cosgrove et al. 2002; Klebaur et al. 2001; Smith et al. 2008) stimuli, as well as opportunities for physical activity (Cosgrove et al. 2002; Smith et al. 2008), reduce amphetamine and cocaine self-administration in animals, possibly by a reward substitution mechanism at the behavioral and/or neurochemical level (Bossert et al. 2005; Kalivas and McFarland 2003; Shalev et al. 2002; Solinas et al. 2008). Most of these studies were conducted during a short-access maintenance phase under fixed-

ratio (FR) or progressive-ratio (PR) schedules. Except for the use of preferred dietary substances (see Carroll et al. 2001), little is known about how environmental enrichment affects critical transition phases of drug abuse such as acquisition, escalation, extinction, and reinstatement (see review by Carroll et al. 2009a). In one study, Solinas et al. (2008) showed that housing mice in an enriched environment after developing a cocaine-induced conditioned place preference (CPP) prevented cocaine-primed reinstatement of the CPP and reduced activation of corresponding brain circuitry.

In animal studies, access to exercise in a running wheel is a positive reinforcer. For example, rats lever-pressed to gain access to a running wheel (Belke et al. 2005, Belke and Wagner 2005), and they escalated running during unlimited wheel access (Lattanzio and Eikelboom 2003). Conditioned rewarding effects of the wheel were reflected in a study showing CPP for an environment associated with wheel running (Belke and Wagner 2005; Lett et al. 2000). Initial studies indicated that access to a running wheel reduced the maintenance levels of low dose (0.2 mg/kg) cocaine self-administration in female (but not male) rats under a FR 1 schedule (Cosgrove et al. 2002) and for low (0.3 mg/kg) and high (10 mg/kg) doses of cocaine under a PR schedule in female rats (Smith et al. 2008). The present experiment extended these findings of reduced cocaine-seeking behavior due to wheel running to the extinction and reinstatement phases of drug abuse.

Behavioral studies of exercise, drug self-administration, and other rewarding activities have revealed commonalities, interactions, and substitutions among the various behaviors (see Carroll et al. 2009a for a review). That an increasing number of findings from animal research indicated that exercise and other nondrug rewards interfere with drug self-administration suggests common neurobiological mechanisms. For example, brief exposure to exercise increases central dopamine concentrations (Meeusen 2005; Petzinger et al. 2007), and regular exercise increases dopamine concentration and dopamine-binding proteins (Fisher et al. 2004). These changes are similar to the effects of drugs such as cocaine on the mesolimbic and mesocortical pathways (Caine and Koob 1994; Wise et al. 1995; Pich et al. 1997). Recent imaging in human runners also indicates that release of endogenous opioids occurs in frontolimbic brain regions after sustained physical exercise and was correlated with perceived euphoria (Boecker et al. 2008). Since exercise, preferred foods, and other forms of environmental enrichment activate reward mechanisms similar to those activated by drugs of abuse, it is useful to consider physical activity as a substitute for the rewarding effects of cocaine and other drugs as well as a prevention for reinstatement or relapse of drug seeking after a drug-free period.

The purpose of this study was to examine the effect of access to a running wheel during extinction and/or cocaine-primed reinstatement in rats previously trained to self-administer iv cocaine. Cocaine-primed reinstatement is considered to be an animal model of relapse, and understanding and preventing relapse is a major challenge to the successful treatment of drug abuse. Initial results with dietary substances indicated that environmental enrichment interfered with reinstatement of drug-seeking behavior (Comer et al. 1995; Solinas et al. 2008). In the present study, rats were trained to self-administer iv cocaine (0.4 mg/kg) and then were subsequently divided into four groups according to the following 2x2 design in which access to wheel running or a locked wheel was given during extinction and/or reinstatement: (1) access to wheel running during extinction from cocaine self-administration and reinstatement of cocaine seeking (WER), (2) access to wheel running during extinction and a locked wheel (did not rotate) during reinstatement (WE), (3) access to the locked wheel during extinction and to wheel running during reinstatement (WR), and (4) access to a locked wheel during extinction and reinstatement (WL; i.e., no opportunity to run). It was hypothesized that the groups with access to running during extinction (WER,

WE) and reinstatement (WR, WER) would show reduced responding during these phases compared with the group with locked wheel access (WL).

## Materials and methods

### Subjects

Thirty-seven female 90-day-old Wistar rats weighing 250–300 g at the start of the experiment served as subjects (Harlan Sprague-Dawley, Madison, WI, USA). Females were used, as they readily acquire wheel running (Jones et al. 1990), they run more than males (Boakes et al. 1999; Cosgrove et al. 2002; Eikelboom and Mills 1988; Lambert and Kinsley 1993), and they are more sensitive than males to the attenuating effects of wheel running on cocaine self-administration (Cosgrove et al. 2002). Estrous cycle was not monitored and was allowed to vary randomly in order to generalize findings across all cycle phases. In addition, the animals were housed in their operant chambers during the experiment, and testing for cycle phase may have disrupted the cycle as well as the cocaine and wheel-reinforced behavior. After arrival, rats were pair-housed in plastic cages and allowed at least 3 days to acclimate before testing. They had free access to pellet food (Rodent Diet 2018, Harlan Laboratories, Madison, WI, USA) and water. Subsequently, rats were removed from the plastic cages and placed in individual operant chambers where they remained for the duration of the study. While in the chambers, rats continued to have free access to water and they were fed 16 g of ground food (LabDiet 5001, Purina Laboratory Chow, Minneapolis, MN, USA) at 3:00 p.m. daily to maintain them at 85% of their free-feeding body weight. All rodent holding rooms were maintained at 24°C and at 40–50% humidity under a light/dark cycle of 12:12 h with room lights on at 6:00 a.m. The experimental protocol (0708A15263) was approved by the University of Minnesota Institutional Animal Care and Use Committee. The experiment was conducted in accordance with the Principles of Laboratory Animal Care (National Research Council 2003), and all laboratory facilities were accredited by the American Association for the Accreditation of Laboratory Animal Care.

### Apparatus

Octagonally shaped operant conditioning chambers consisting of alternating stainless steel and Plexiglas walls were used for housing and testing in the present study. Custom-made, sound-attenuating, wooden boxes equipped with a ventilation fan enclosed each operant conditioning chamber. Operant chambers contained slots that allowed for the insertion of stainless steel panels, a drinking bottle holder, a food receptacle, two response levers, two sets of stimulus lights, and a house light. The stimulus lights consisted of three multicolored light-emitting diode lights (red, yellow, and green) located above each response lever, and a single white house light (4.76 W) positioned in the upper corner illuminated each operant chamber. A guillotine-style door, when opened, allowed access to a free-spinning 35.6-cm-diameter running wheel (Med Associates Inc., St. Albans, VT, USA) that was fitted on the left side of each operant chamber. A microswitch recorded quarter-wheel turns and a lock could be put in place to allow entry but prevent rotation.

During self-administration sessions, a syringe pump (model PHM-100, MedAssociates Inc., St. Albans, VT, USA) was used to deliver response-contingent iv infusions and was located on the outside of the wooden sound-attenuating enclosure. During self-administration sessions, responding on the left lever delivered cocaine infusions through a segment of Tygon tubing (1.52 mm o.d., 0.51 mm i.d., Fisher Scientific, Springfield, NJ, USA) that extended from the 35-ml syringe to a plastic swivel (050–022, Alice King Chatham, Hawthorne, CA, USA) secured to the top center of the operant chamber. An additional segment of tubing, protected by a metal spring-covered tether (C313CS, PlasticsOne, Roanoke, VA, USA), was connected to the opposite end of the swivel and extended into the

operant conditioning chamber. Inside the chamber it attached to an infusion harness (Instech, Laboratories, Plymouth Meeting, PA, USA) that was fitted to each rat following catheter implantation. The swivel and tether allowed free movement within the operant chamber and easy access to the adjoining running wheel. Data collection and programming were conducted using PC computers with a Med-PC interface (MedAssociates, Inc., St. Albans, VT, USA).

## Drugs

Cocaine HCl was supplied by the National Institute of Drug Abuse (Research Triangle Institute, Research Triangle Park, NC, USA), dissolved in 0.9% NaCl at a concentration of 1.6 mg cocaine HCl/1 ml saline, and refrigerated. Heparin (1 ml/200 ml saline) was added to the cocaine solution to prevent catheter occlusion from thrombin accumulation. The flow rate of each cocaine infusion was 0.025 ml/s, and the duration of pump activation (1 s/100 g of body weight) was adjusted to provide a 0.4-mg/kg cocaine dose throughout self-administration testing.

## Procedure

**Wheel training**—Table 1 shows the six phases of the procedure. In the first phase, rats were fitted with the infusion harness and tether and fed 16 g of ground food daily. They were allowed access to the wheel during 6-h sessions (9:00 a.m. to 3:00 p.m.) for approximately 8 days to acclimate subjects to running when connected to the harness/tether system. During training, the house light was illuminated and the door to the wheel was opened. Response levers were present during wheel training. Acquisition of wheel running was defined as 400 full wheel revolutions in a single session or 100 revolutions per session for three consecutive sessions. If an animal failed to reach either criterion within 2 weeks, it was not included in the study.

**Surgical procedure**—One to 3 days after achieving wheel-running behavior, rats were surgically implanted with an indwelling catheter in the right jugular vein following the procedure outlined by Carroll and Boe (1982). Briefly, rats were anesthetized with a combination of ketamine (60 mg/kg, ip) and xylazine (10 mg/kg, ip) and administered doxapram (5 mg/kg, ip) and atropine (0.4 mg/ml, 0.15 ml, sc) to facilitate respiration. An incision was made lateral to the trachea, the right jugular was exposed, and a small incision was made perpendicular to the vein. The beveled end of a polyurethane catheter (MRE-040, Braintree Scientific, Inc., Braintree, MA, USA) was inserted and then secured to the vein with silk sutures. The free end of the catheter was guided subcutaneously to the midscapular region of the neck where it exited via a small incision and attached to a metal cannula (C3236, PlasticsOne, Roanoke, VA, USA) that was embedded in the infusion harness.

Following the surgical procedure, doors to the wheels remained closed, and rats were allowed a 3-day recovery period during which antibiotic (gentamicin) and analgesic (buprenorphine) medications were administered. Each rat was fitted with an infusion harness and tether that was worn throughout the remainder of the study. After the recovery period, catheters were flushed with a heparinized saline solution at 8:00 a.m. daily to prevent catheter blockage. Every 7 days at 3:00 p.m. body weights were recorded, and catheter patency was checked by injecting a 0.1-ml solution containing ketamine (60 mg/kg), midazolam (3 mg/kg), and saline (KMS). If a loss of the righting reflex was not manifest upon a KMS catheter patency check, a second catheter was implanted in the left jugular vein following the methods described above, and the experiment resumed in 3 days.

**Cocaine self-administration training and maintenance**—In the third phase, rats were trained to lever press for iv infusions of cocaine (0.4 mg/kg) under a FR 1 schedule of

reinforcement during daily 6-h sessions (9:00 a.m. to 3:00 p.m.) that were signaled by illumination of the house light. During sessions, a response on the active/drug-paired lever started the infusion pump and illuminated the stimulus lights located directly above the lever for the duration of the infusion. Responses on the active lever during the length of the infusion (2.5–3.0 s) were recorded but had no programmed consequences. Responses on the inactive/activity lever illuminated the stimulus lights above that lever but did not activate the pump. Initially, three experimenter-delivered priming infusions of 0.4 mg/kg cocaine were administered at the beginning of each training session (9:00 a.m.) followed by the placement of a small amount of peanut butter on the active/drug-paired lever. This training procedure continued until rats earned at least 60 infusions during a single session. Once rats achieved acquisition of cocaine self-administration, they were allowed to self-administer for ten additional 6-h sessions (maintenance). The door leading to the wheel remained closed throughout self-administration training and maintenance (no wheel access).

**Extinction**—Following day 10 of maintenance, the cocaine solution was replaced with saline, and responding produced a saline infusion (FR 1) along with the stimuli described above for maintenance. Based on total cocaine intake during maintenance, rats were separated into four groups with the following conditions: (1) access to a running wheel during extinction and reinstatement (WER), (2) access to a wheel during extinction and a locked wheel (unable to rotate) during reinstatement (WE), (3) access to the locked wheel during extinction and to wheel running during reinstatement (WR), and (4) access to a locked wheel during extinction and reinstatement (WL). Groups were compared during the extinction phase for 14, 6-h extinction sessions.

**Reinstatement**—In the reinstatement phase, the stimulus lights, house light, and pump were unplugged to ensure that reinstatement responding was due to ip priming injections and not to drug-associated cues (Larson and Carroll 2007). Initially, groups were compared in a *between-subjects* design, and subsequently, the WE and WR groups were tested in a *within-subjects* design to evaluate the effect of brief wheel exposure or removal during single reinstatement sessions.

**Between subjects:** Each of the four groups were administered saline (S)- or cocaine (C)-priming injections at session onset (9:00 a.m.), and their subsequent cocaine-seeking behavior was tested for the next 6 h (9:00 a.m. to 3:00 p.m.) for seven consecutive days. During the first two reinstatement sessions, rats were treated with a single S injection, and for the next 5 days, they were treated with a single C or S injection on alternating days (i.e., S S C S C S C). Response-contingent drug-paired cues and the house light were deactivated during this time. On the C days, rats received priming injections of one of three randomly assigned doses of C (5, 10, and 15 mg/kg). Doors to the adjoining wheel remained open during reinstatement testing, but only groups WR and WER could run; the WE and WL groups could enter the wheel, but it did not rotate.

**Within subjects:** For the rats in groups WE and WR, three S and three 15 mg/kg C-priming injections (alternating) were administered over 6 days. On the second C-priming day, rats in group WE were allowed access to wheel running (C+W) during the 6-h reinstatement session to determine whether acute exposure to the wheel produced the same effect as chronic exposure in the between-subjects condition for group WER. Similarly, group WR was given cocaine-priming injections on the second and sixth day to determine whether reinstatement would occur without wheel access. Thus, in the within-subjects condition, groups WE and WR received the following priming sequence over six consecutive days: S, C, S, C + W, S, C.

## Data analysis

Responses, infusions, and full wheel revolutions during extinction and responses and wheel revolutions during reinstatement were the primary dependent measures. These measures were analyzed with two-factor mixed analyses of variance (ANOVA) with group as the between-subjects factor and blocks of days as the repeated measure. Data were grouped in 2-day blocks to reduce daily variability and the number of post-hoc contrasts. Separate two-factor ANOVAs were used to compare infusion lever and active lever presses during reinstatement with group as the between-subjects factor and the priming injection (e.g., S vs C) as the repeated measure. Infusion lever and inactive lever presses during reinstatement were also examined using a three-factor ANOVA with group and lever type (e.g., active vs inactive) as a between-subjects factor and dose as the repeated measure. A mixed ANOVA was used to compare priming conditions by group for groups WE and WR in the within-subject study. Post-hoc tests were performed with Fisher's least significant difference protected *t* tests, and results were considered significant if  $p < 0.05$ . Statistical analyses were performed using GB Stat (Dynamic Microsystems, Inc., Silver Spring, MD, USA).

## Results

All rats consumed the daily 16-g food allotment and did not differ in mean water intake or body weight during the study. Groups also did not differ in number of wheel training days, wheel revolutions during training, or days to acquire cocaine self-administration (Table 2).

## Maintenance

Figure 1 shows mean responses (a) and infusions (b), respectively, across the 10-day maintenance period. Separately, responses and infusions were averaged across five 2-day blocks, and there was not a significant main effect of group for either responses or infusions. However, there was a significant main effect of session block for both responses ( $F_{4,184}=4.81$ ,  $p < 0.01$ ) and infusions ( $F_{4,184}=7.61$ ,  $p < 0.0001$ ). Data were collapsed and analyzed across groups, and a significant effect of session block was found when averaging responses ( $F_{4,184}=4.86$ ,  $p < 0.01$ ) and infusions ( $F_{4,184}=7.53$ ,  $p < 0.0001$ ) over five 2-day blocks. Post-hoc comparisons showed a significant increase in both responses and infusions during sessions 7 to 8 ( $p < 0.05$ ) and 9 to 10 ( $p < 0.01$ ) compared with those during sessions 1 to 2. There were no significant differences in inactive lever presses (data not shown) among groups or across blocks.

## Extinction

Extinction responses (a) and infusions (b) are shown in Fig. 2. When data were averaged in 2-day blocks, a significant reduction in responding occurred on both active and inactive levers and in saline infusions in rats with wheel access (WER and WE combined) compared with rats without wheel access (WL and WR combined). Since WER and WE did not have significantly different responses or infusions during maintenance (see above) or extinction (data not shown), and both groups underwent the same condition during extinction (i.e., wheel access), their data were collapsed and compared to WL and WR, whose data were similarly combined. There was a significant main effect of group ( $F_{1,258}=9.64$ ,  $p < 0.01$ ) and session block ( $F_{6,258}=42.83$ ,  $p < 0.0001$ ) and a group  $\times$  session block interaction ( $F_{6,258}=9.82$ ,  $p < 0.0001$ ) for responses. Post-hoc tests revealed significantly higher responding on extinction sessions 1 to 2 and 3 to 4 ( $p < 0.01$ ) and sessions 5 to 6 and 7 to 8 ( $p < 0.05$ ) for WL and WR combined vs WER and WE combined (Fig. 2a). A similar analysis was conducted for infusions revealing a significant main effect of group ( $F_{1,258}=9.24$ ,  $p < 0.01$ ) and session block ( $F_{6,258}=41.92$ ,  $p < 0.0001$ ) and a significant interaction ( $F_{6,258}=7.85$ ,  $p < 0.0001$ ). Post-hoc comparisons indicated more saline infusions for WL and WR vs WER and WE during sessions 1 to 2, 3 to 4, and 5 to 6 ( $p < 0.01$ ; Fig. 2b). Inactive

lever presses were compared revealing significant main effects of group ( $F_{1,258}=24.05$ ,  $p<0.0001$ ) and session block ( $F_{6,258}=10.29$ ,  $p<0.0001$ ) and a significant group  $\times$  session block interaction ( $F_{6,258}=3.68$ ,  $p<0.01$ ; data not shown). Post-hoc tests revealed that groups with wheel access (WER and WE) made significantly fewer responses on the inactive lever during sessions 1 to 2, 3 to 4, 5 to 6, 7 to 8, and 11 to 12 ( $p<0.01$ ) and sessions 9 to 10 ( $p<0.05$ ) than groups with locked wheel access (WL and WR). To assess whether groups WL and WR combined (locked wheel access) showed preference for the previously drug-paired lever during extinction, active and inactive lever responses were compared ( $F_{6,265}=15.16$ ,  $p<0.0001$ ), with post hoc tests indicating that significantly more responses were made on the active lever during sessions 1 to 2, 3 to 4, 5 to 6, and 7 to 8 ( $p<0.01$ ).

Wheel revolutions during extinction were averaged in seven 2-day blocks to reduce variability across days, and they were compared between groups WER and WE (Fig. 3). There was a significant main effect of session block ( $F_{6,125}=5.21$ ,  $p<0.01$ ), but there was no effect of group or a group  $\times$  session block interaction. This indicates that a similar increase in revolutions occurred over the 14 days in both groups. To test the hypothesis that removal of cocaine increased extinction responding on the first day, wheel revolutions were compared with a paired  $t$  test on the last day of training and the first day of extinction in groups WER and WE combined, as the groups did not differ, and revolutions were significantly higher on the first day of extinction ( $t_{17}=2.61$ ,  $p<0.05$ ). A comparison of revolutions during training (Table 2) and on the first day of extinction (Fig. 3) for these groups showed that revolutions were nearly twice as high during extinction than training in groups that had wheel access (WE and WER).

## Reinstatement

**Between subjects**—Figure 4a shows responding on the previously active lever following ip priming injections of S or C during the reinstatement period. Reinstatement began with two S-priming injections, and responding following the first priming injection was analyzed to determine the effect of discontinuing unlocked wheel access for group WE after extinction. Group differences were revealed ( $F_{3,39}=11.85$ ,  $p<0.0001$ ), and post hoc tests showed significantly greater responding for group WE (striped bar) on the first S day vs WR, WER, and WL ( $p$ 's  $< 0.01$ ). No significant differences were found in inactive lever responding for the first S-priming injection.

Responses averaged over the remaining three S-priming days were compared to responses on the 5-, 10-, and 15-mg/kg dose C-priming days (Fig. 4a), and there were significant main effects of priming condition ( $F_{3,147}=15.02$ ,  $p<0.0001$ ), group ( $F_{3,147}=6.58$ ,  $p<0.01$ ), and a significant priming condition  $\times$  group interaction ( $F_{9,147}=2.81$ ,  $p<0.01$ ). Post-hoc analyses indicated that the 10- and 15-mg/kg C-priming injections resulted in significantly more responding than S-priming injections for both groups WL and WE ( $p$ 's  $< 0.01$ ). In contrast, responding on S- and C-priming days did not differ for WR and WER. Groups WE and WL did not significantly differ in responding after 10- and 15-mg/kg C-priming injections, but both groups responded significantly more than WER ( $p$ 's  $< 0.01$ ) at these doses. Compared to WR, WE and WL responded significantly more following the 10 ( $p$ 's  $< 0.01$ )- and 15 ( $p$ 's  $< 0.01$  vs WE;  $p$ 's  $< 0.05$  vs WL)-mg/kg priming injections, while WE responded more after the 5 ( $p$ 's  $< 0.05$ )-mg/kg priming dose as well. No significant group  $\times$  priming condition interaction was found for inactive lever responses (not shown), although there were main effects of group ( $F_{3,147}=4.96$ ,  $p<0.01$ ) and priming condition ( $F_{3,147}=3.95$ ,  $p<0.05$ ) similar to responding on the previously active lever.

Inactive and previously-active lever responses during reinstatement were compared in a three-factor mixed ANOVA. This analysis revealed significant main effects of group ( $F_{3,295}=12.19$ ,  $p<0.0001$ ), lever type (e.g., previously active  $>$  inactive;  $F_{1,295}=18.73$ ,

$p < 0.0001$ ), and priming condition ( $F_{3,295} = 15.55$ ,  $p < 0.0001$ ) as well as significant group  $\times$  priming condition ( $F_{9,295} = 3.09$ ,  $p < 0.01$ ) and lever type  $\times$  priming condition ( $F_{3,295} = 4.04$ ,  $p < 0.01$ ) interactions (not shown). However, no significant group  $\times$  lever type  $\times$  priming condition interaction was found. Finally, when comparing wheel revolutions for WER and WR over the 7-day reinstatement period, there was a near-significant effect of group ( $F_{1,71} = 3.67$ ,  $p = 0.0735$ ), probably due to heterogeneity of variance. This suggested that running escalated over time in the WER group. Otherwise, there were no significant effects of interactions (see Fig. 3).

**Within subjects**—Figure 4b shows results for six rats in WE and all nine rats in WR for which a subsequent within-subject reinstatement procedure was implemented after the between-groups data were collected. The mean of three S-priming sessions was compared to corresponding C-priming sessions (C) and to the C + W (C priming + wheel running access) session in a two-factor ANOVA. There was a near-significant effect of group ( $F_{1,59} = 3.78$ ,  $p = 0.0738$ ), a significant effect of priming condition ( $F_{3,59} = 12.05$ ,  $p < 0.0001$ ), and a significant group  $\times$  priming condition interaction ( $F_{3,59} = 2.92$ ,  $p < 0.05$ ). WR did not respond differently for S than on any of the C-priming days. In WE, responding did not differ between C + W and S, but there was significantly higher responding for C1 and C2 vs S ( $p < 0.01$ ) and vs C + W ( $p < 0.01$  vs C1;  $p < 0.05$  vs C2). Comparing WE and WR, WR responded significantly more following C1 and C2 ( $p < 0.01$ ) and C + W ( $p < 0.05$ ). Analysis of inactive lever responding did not reveal significant differences (data not shown).

## Discussion

In the present study, there were no differences among the four experimental groups in initial exposure to the running wheel (revolutions), in the rate of acquisition of cocaine self-administration, or in the level of cocaine maintenance responding. However, during the subsequent extinction phase, wheel running significantly reduced extinction responding in WER and WE compared to WL and WR. This finding suggests that wheel exposure reduced elevated drug seeking during this critical phase. Previous studies have shown that access to another type of reinforcer, sweet substances, decreased the extinction of cocaine (Liu and Grigson 2005)- and amphetamine (Ping and Kruzich 2008)-seeking behavior in rats. Similarly, extinction of behavior maintained by a sucrose reinforcer was reduced by an enriched environment that included more space, greater social contact, novel objects, and opportunity for exercise (Grimm et al. 2008; Stairs et al. 2006).

In the subsequent reinstatement phase, rats without wheel running access (groups WE and WL) reliably reinstated responding on the previously active lever. This was in contrast to groups WER and WR that were allowed to run during reinstatement and consequently showed a suppression of cocaine-primed reinstatement. That group WE did not have suppressed reinstatement indicated that recent running access during extinction did not carry-forward into the reinstatement phase. A consistent finding was that the subsequent within-subjects manipulation in group WE revealed that wheel access effectively reduced reinstatement when it was concurrently available during only one cocaine-priming session; however, there was not a carry-forward suppressive effect after wheel running access ended and the second C-priming condition occurred. The within-subjects reinstatement study also revealed significantly lower drug seeking in the WR group vs WE. This could have been due to the more recent exposure to the wheel in the WR group vs more distant exposure in WE or that exposure during the between-subjects reinstatement more readily generalized to subsequent within-subjects reinstatement testing in the WR vs the WE group.

The lack of an enduring suppressant effect of wheel running on reinstatement of cocaine seeking was consistent with the effects of recent but not previous environmental enrichment



on sucrose seeking during extinction and reinstatement in rats (Grimm et al. 2008). However, these and the present results were not consistent with findings of earlier studies examining the effects of previous and chronic wheel running on the rewarding effects of drugs of abuse (Chen et al. 2008; Smith et al. 2008). Several methodological and procedural differences between the present and previous studies may account for the discrepant findings. The most important difference concerns the duration of wheel access between studies. In previous work, rats were allowed to run on the wheel for extended periods of time (Chen et al. 2008; Smith et al. 2008).

In rats, wheel running upregulates the opioid neuropeptide dynorphin (Werme et al. 2000), dopamine neurons (Ahmad et al. 2009), delta FosB (Werme et al. 2002), and brain-derived neurotrophic factor (Khabour et al. 2009; Macias et al. 2007; Neeper et al. 1996; Widenfalk et al. 1999) in areas of the brain associated with reward only after extended periods of free access to a running wheel. Additionally, increases in these neurosubstrates, through pharmacological manipulations, led to alterations in cocaine-primed reinstatement in rats (Berglind et al. 2007; Gyertyan et al. 2007; Mantsch et al. 2004; Micheli et al. 2007; Schmidt and Pierce 2006). Although these neural correlates were not analyzed in the present study, it may be assumed that the duration of exposure to wheel running may not have been sufficient to increase these measures to the point where they would produce enduring decreases in subsequent cocaine seeking.

The present investigation is consistent with previous results demonstrating that wheel running decreased concurrent cocaine (Cosgrove et al. 2002), amphetamine (Kanarek et al. 1995), and alcohol (McMillan et al. 1995) self-administration as well as MDMA-induced CPP (Chen et al. 2008) in rats. It also supported findings demonstrating suppression of acquisition of cocaine (Carroll and Lac 1992) and phencyclidine self-administration (Campbell et al. 1998) in rats and monkeys, respectively, using sweetened liquids as alternative reinforcers. While both sweetened liquids (Carroll and Lac 1992; Campbell et al. 1998; Carroll and Campbell 2000; Cosgrove and Carroll 2003; Rodefer and Carroll 1997; Carroll 1985; Kanarek and Marks-Kaufman 1988; Ping and Kruzich 2008) and food (Carroll and Lac 1992; Carroll 1996; Carroll et al. 2001) have been highly effective at interfering with drug self-administration, dietary substances can have adverse consequences if consumed in excess (Avena 2007; Avena et al. 2008; Corwin and Wojnicki 2006). The present results and recent work (Cosgrove et al. 2002) to the extinction and reinstatement phases of drug abuse, and indicate that exercise may be an effective and healthier nondrug alternative.

The present results extended the generality of wheel running, as a nondrug alternative reward. Another explanation for the attenuating effects of wheel running on extinction in the WER and WE groups is that cocaine seeking and wheel running were mutually exclusive, and time spent doing one resulted in less time for the other. However, analysis of the time course of wheel- and infusion-maintained behavior indicated that much of the 6-h session was spent on neither activity. For example, the average total during extinction was 50 responses or less, occupying only a small amount of time during the total 6-h session. Thus, the behaviors did not compete for limited time, and this was consistent with previous findings (Cosgrove et al. 2002).

The present findings suggest that rather than the actual behaviors competing, the reinforcing value of the wheel and cocaine reward competed. This interaction was also revealed by the increase in wheel running in group WER and WE from precocaine wheel training (Table 2) to extinction (Fig. 3) when cocaine access had been removed. Another indication of a possible substitution effect of wheel running with cocaine reward was the resurgence of cocaine seeking (e.g., lever responding) in the WE group on the first day of reinstatement

when wheel running was prohibited. That this resurgence did not occur in the group that was reintroduced to wheel running (WR), the group that continued running in the reinstatement phase (WER) or in the locked wheel (WL) group suggests a reward interaction (wheel  $\times$  cocaine) effect. When considering nondrug alternatives as a means of reducing drug-seeking behavior, it is important to consider that they may substitute for the drug and trigger reinstatement of behavior that was previously rewarded by the drug. Thus, extending access to the nondrug alternative (e.g., wheel) during extinction is a preventive strategy that could be employed.

Behavioral analysis of resurgence, or the elevation in previously reinforced behavior following the removal of an alternative reinforcer, has been documented (Leitenberg et al. 1970; Mulick et al. 1976; Carroll 1985; Carroll et al. 1989). For example, a study by Podlesnik et al. (2006) reported that rats that previously self-administered alcohol showed a resurgence in lever pressing following the removal of a food alternative reinforcer. Others have demonstrated a resurgence of lever pressing for a primary reinforcer following the removal of a secondary reinforcer (Epstein 1983; Leitenberg et al. 1970; Mulick et al. 1976; Wilson and Hayes 1996). The magnitude of resurgence is also dependent on extinction experience, with higher levels of resurgence occurring when there is less of an opportunity to extinguish (Cleland et al. 2000). Thus, the resurgence in responding for the primary reinforcer (drug) in the WE group may have resulted from a lack of extinction experience (Marlatt 1990) due to a greater amount of time being dedicated to wheel running during extinction testing.

Another explanation of the present findings may involve the attenuation of drug-related withdrawal effects by wheel running. Drug withdrawal effects are a primary contributor to elevated extinction responding in animal models (Carroll et al. 2009b; Kelamangalath and Wagner 2009; O'Dell et al. 2007), and reduction of withdrawal effects is integral to the implementation of effective treatment strategies in cocaine addiction (Ahmadi et al. 2006; Kampman et al. 2001a, b). Results from animal and human studies (Alaei et al. 2006; Daniel et al. 2007; Taylor and Katomeri 2007; Taylor et al. 2007; Ussher et al. 2001) indicate that withdrawal signs and symptoms are reduced following bouts of exercise. This effect may be attributed, in part, to exercise-induced increases of monoamines in brain areas associated with reward. For example, cocaine withdrawal is associated with decreases in dopamine and serotonin in the striatum (Parsons et al. 1995; Rossetti et al. 1992), and continued drug use may be related to avoidance of these negative effects (Koob 2009). Physical activity, on the other hand, increases several monoamines, including dopamine, within the striatum of rats and humans (Dishman 1997; Fulk et al. 2004; Hattori et al. 1994; Meeusen 2005; Petzinger et al. 2007), and it decreases stress, anxiety, and depression (Dishman 1997; Fulk et al. 2004; Sarbadhikari and Saha 2006). Recent work extended these findings to show that voluntary exercise and sucrose consumption enhanced cannabinoid CB1 receptor sensitivity in the striatum (Di Chiara et al. 2009). Higher vs lower levels of physical activity were also associated with higher self-reported measures of well-being among adolescents (Ussher et al. 2007). Thus, extinction responding in the present study may be described as an attempt to reestablish homeostatic equilibrium following a withdrawal-induced disruption in neural mechanisms that regulate hedonic motivation. Wheel running may have helped to restore this equilibrium thereby decreasing extinction responding.

The present findings offer useful applications for preventing and reducing drug abuse in humans. As mentioned previously, physical activity decreases nicotine craving and withdrawal symptoms (Ussher et al. 2006, 2009; Taylor et al. 2007). A recent investigation using physically active and inactive twin cohorts showed that the physically active cohort was less likely to smoke cigarettes than the inactive cohort (Kujala et al. 2007), and the presence of regular physical activity during adolescence decreased the risk of smoking in

early adulthood (Charilaou et al. 2009; Korhonen et al. 2009). Adolescents participating in drug intervention programs that include physical exercise demonstrate lower risk factors for drug abuse and decreased drug use (Collingwood et al. 1991, 2000). Physical activity has also been useful in combating alcohol abuse in inpatient treatment programs (Palmer et al. 1988; Sinyor et al. 1982) and in improving the probability of abstinence up to 3 months after program release (Sinyor et al. 1982).

Exercise has also been used as a supplement to contingency management (CM), a type of substance abuse treatment that rewards periodically verified abstinence with nondrug alternative reinforcers (e.g., money or vouchers for retail items). Patients who participated in physical activity in addition to CM intervention had higher drug abstinence rates than those who had CM alone (Weinstock et al. 2008). While CM is highly effective in maintaining abstinence (Pendergast et al. 2006; Lussier et al. 2006), it can be costly (Olmstead and Petry 2009; Sindelar et al. 2007; Higgins 1997). In contrast, exercise, by itself or in addition to CM, is an inexpensive and self-maintained behavior that may potentially have greater long-term consequences.

In summary, the present results indicated that access to wheel running decreased the extinction and reinstatement of cocaine-seeking behavior. Reinstatement was reduced by chronic, concurrent wheel running in a between-subjects study and by a single concurrent exposure during a within-subjects procedure. A comparison of four groups with differing wheel-running exposure indicated that concurrent wheel running was a key factor, and recent wheel access did not have a carry-forward effect on cocaine-primed reinstatement. The present findings, along with previous reports, suggest that access to wheel running reduces drug-seeking behavior during maintenance, extinction, and reinstatement.

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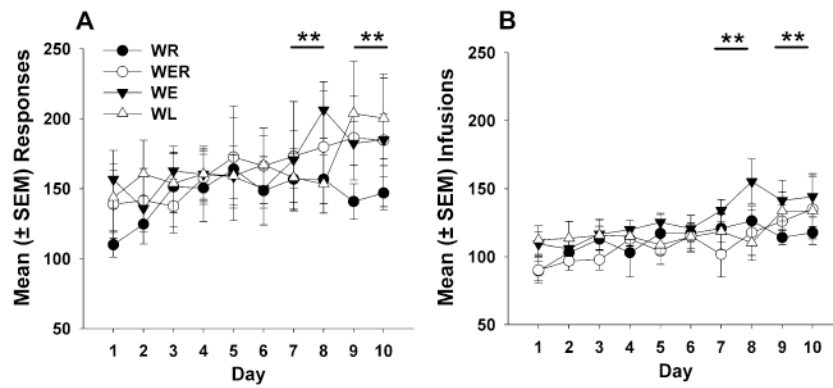
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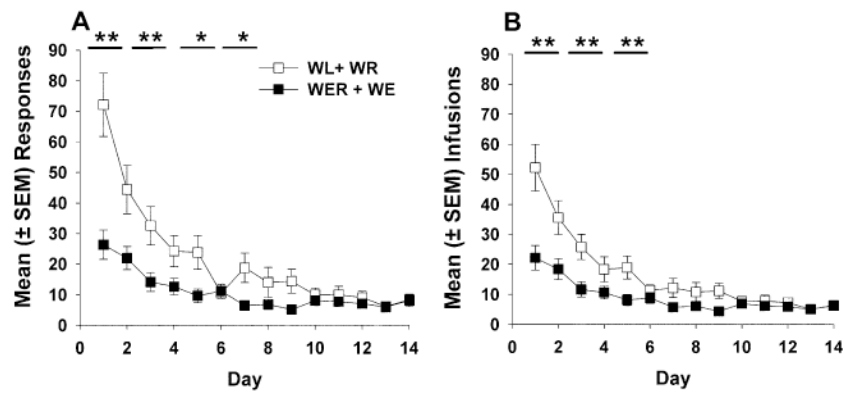
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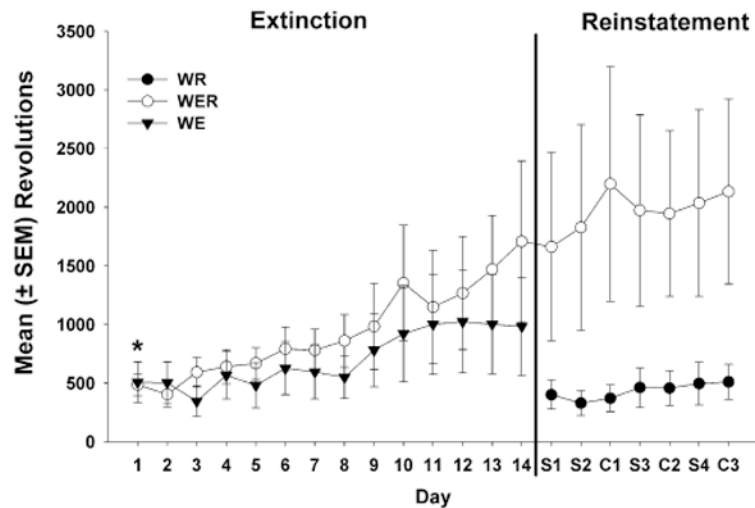


**Fig. 1.** Mean ( $\pm$  SEM) responses (**a**) and iv 0.4 mg/kg cocaine infusions (**b**) in groups WR, WER, WE, and WL during daily 6-h self-administration sessions over the 10-day maintenance period. Session blocks 7 to 8 and 9 to 10 (\*\* $p < 0.01$ ) had significantly more responses (**a**) and infusions (**b**) than session blocks 1 to 2 when group data were collapsed and analyzed across five two-session blocks

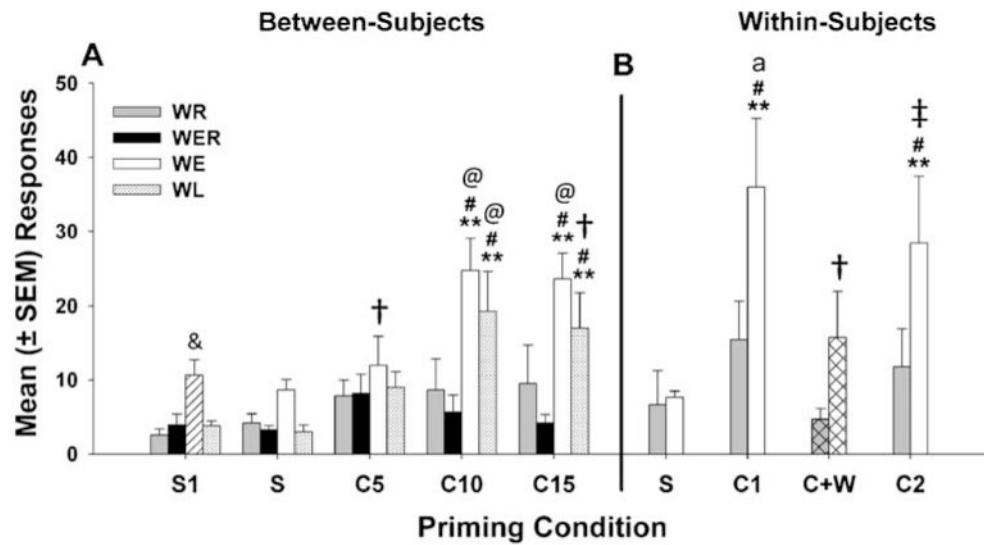


**Fig. 2.**

Mean (± SEM) responses (a) and iv saline infusions (b) during daily 6-h self-administration sessions over the 14-day extinction period. Groups WL and WR were combined and then, separately, WER and WE were combined, as they showed no significant differences. Following introduction of the wheel on day 1 of extinction, combined Groups WL+WR exceeded combined Groups WER+WE in responses (a) and infusions (b) on session blocks 1 to 2 (\*\* $p < 0.01$ ), 3 to 4 (\*\* $p < 0.01$ ), and 7 to 8, (\* $p < 0.05$ ). The combined groups also differed on responses on sessions 5 to 6 and 7 to 8 ( $p < 0.05$ ) and on infusions on session 5 to 6 ( $p < 0.01$ )



**Fig. 3.** Mean ( $\pm$  SEM) wheel revolutions over the 14-day extinction period for groups WR (*filled circles*), WER (*open circles*), and WE (*filled triangles*) and during the reinstatement period for each saline (S) or cocaine (C) priming injection for groups WR and WER. During analysis, groups WE and WER were combined, as they did not significantly differ during cocaine extinction, and when wheel revolutions were compared on the first day of extinction vs the last day of training (see Table 2), they were significantly higher during extinction ( $*p < 0.05$ )



**Fig. 4.** Mean ( $\pm$  SEM) responses on the previously active lever (**a**) following priming injections during reinstatement testing in the *between-subjects* design with ip saline (*S*) or 5-, 10-, and 15-mg/kg ip injections of cocaine (*C*), # $p < 0.01$  vs WER, \*\* $p < 0.01$  vs *S*, @ $p < 0.01$  vs WR, † $p < 0.05$  vs WR. The *striped bar* indicates the first day after termination of wheel running in WE, and & $p < 0.01$  vs all other groups. Mean ( $\pm$  SEM) responses on the previously active lever (**b**) following priming injections of saline (*S*) or two 15-mg/kg cocaine (*C1*, *C2*) during a *within-subjects* reinstatement procedure in groups WE and WR (cocaine and wheel access-*cross-hatched bar*), \*\* $p < 0.01$  vs *S*, # $p < 0.01$  vs WR, † $p < 0.05$  vs WR, ‡ = 0.05 vs WR, ‡ $p < 0.05$  vs *C + W*, *a* =  $p < 0.01$  vs *C + W*

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**Table 1**

## Experimental procedure

Phase (days)	Wheel training (~8)	Surgery/recovery (~3)	S-A training (~5)	Maintenance (10)	Extinction (14)	Between-subjects reinstatement S S C S C C (7)	Within-subjects reinstatement S C S C+W S C (6)
Group	Dose	0.4 mg/kg, iv			Saline, iv	5, 10, 15 mg/kg, ip	15 mg/kg, ip
WER	Wheel	No Wheel			Wheel		-
WE	Wheel	No Wheel			Wheel	Wheel locked	Wheel (C + W)
WR	Wheel	No Wheel			Wheel locked		-
WL	Wheel	No Wheel			Wheel Locked	Wheel	Wheel (C + W)

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**Table 2**

Summary of group data

Group	Number	Mean H <sub>2</sub> O consumption (ml ± SEM)	Mean weight (g ± SEM)	Wheel training days (± SEM)	Training revolutions (± SEM)	Mean days to acquire (± SEM)
WER	9	35.59 (±2.23)	271.82 (±3.51)	8.11 (±2.04)	242.54 (±40.34)	5.22 (±0.70)
WE	9	35.22 (±2.35)	269.46 (±7.58)	3.89 (±1.14)	298.07 (±44.17)	4.00 (±0.17)
WR	9	34.13 (±2.93)	284.04 (±4.78)	6.00 (±1.44)	295.75 (±95.58)	5.00 (±1.16)
WL	10	31.76 (±2.78)	271.06 (±4.63)	4.44 (±0.75)	234.01 (±47.60)	4.44 (±0.53)