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Cocaine self-administration and reinstatement in female rats selectively bred for high and low voluntary running

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Abstract

Background—Previous research has found that rats behaviorally screened for high (vs. low) wheel running were more vulnerable to cocaine abuse. To assess the extent to which a genetic component is involved in this drug-abuse vulnerability, rats selectively bred for high or low voluntary running (HVR or LVR, respectively) were examined for differences in cocaine seeking in the present study.

Methods—Female rats were trained to lever press for food and then were assessed for differences in acquisition of cocaine (0.4 mg/kg; i.v.) self-administration across 10 sessions. Once acquired, rats self-administered cocaine for a 14-day maintenance phase, followed by a 14-day extinction phase when cocaine was no longer available. Subsequently, reinstatement of cocaine seeking was examined with priming injections of cocaine (5, 10 & 15 mg/kg), caffeine (30 mg/kg), yohimbine (2.5 mg/kg) and cocaine-paired cues.

Results—A greater percentage of LVR rats met the acquisition criteria for cocaine self-administration and in fewer sessions than HVR rats. No differences in responding for cocaine were observed between phenotypes during maintenance. However, during extinction LVR rats initially responded at higher rates and persisted in cocaine seeking for a greater number of sessions. No

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Contributions

JS, NZ, DM, MW, FB and MC participated in study concept and design. JS, NZ and MC oversaw collection of data. JS, NZ, DM, FB and MC assisted in analyzing the data and interpreting the findings. JS, NZ and MC initially drafted the manuscript. JS, NZ, DM, MW, FB and MC contributed to the final revisions of the document.

Declaration of Interest

Conflict of Interest

No conflict declared.

phenotype differences were observed following drug and cue-primed reinstatement of cocaine seeking.

Conclusions—In general, LVR rats were more sensitive to the reinforcing effects of cocaine than HVR rats during periods of transition into and out of cocaine self-administration. Thus, LVR rats showed a greater vulnerability cocaine seeking than HVR rats.

Keywords

Acquisition; Cocaine Self-administration; Extinction; Wheel Running; Phenotype; Rats

1. INTRODUCTION

Recent evidence suggests that exercise is an effective treatment for drug abuse (see reviews by Bardo and Compton, 2015; Zhou et al., 2016). One potential explanation for this interrelationship is that exercise serves as a competing reinforcer for drug use. In both humans and animals, exercise is a reinforcing activity (e.g., Iverson, 1993; Raichlen et al., 2012; Ussher et al., 2012) that stimulates the same mesolimbic reward pathway as drugs of abuse (e.g., Fienberg et al., 1998; Raichlen et al., 2012). The strong interrelationship, however, is presumably bidirectional and suggests that greater reinforcing efficacy of exercise in certain individuals may indicate a vulnerability to drug abuse.

Larson and Carroll (2005) conducted the initial work on how the proclivity for exercise indicates a potential vulnerability to drug abuse. In this study, they screened (not selectively bred) wild-type rats into high and low wheel-running (HiR and LoR, respectively) groups using a median split, and then assessed cocaine seeking and the motoric effects of cocaine. Results indicated HiR rats self-administered more cocaine and showed more cocaine-primed reinstatement of drug seeking than LoR rats. However, when cocaine-induced locomotor activity was examined, LoR rats showed a relatively greater sensitivity to cocaine's motoric effects than HiR rats. These inconsistent results may have been a byproduct of prescreening rats into the high and low wheel running groups. One issue is that rats screened into the high wheel running group may have co-selected for rats that also engaged more in other reinforcing activities, such as cocaine seeking. Another issue is that allowing rats to run prior to testing may have resulted in neurobiological changes that dampened the motoric effects of cocaine (see Greenwood et al., 2011; Werme et al., 2000). To address the extent to which these drug effects are genetically mediated, researchers have turned to naïve rats selectively bred for high and low running.

Roberts and Colleagues (2012, 2013, 2014) recently developed rat strains that are selectively bred for high and low voluntary running (HVR and LVR, respectively), which is a heritable trait in both rodents (Roberts et al., 2012) and humans (e.g., De Moor et al., 2011). Brown et al. (2015) conducted the first investigation that used naïve HVR and LVR rat strains to determine if the motoric effects of cocaine in Larson and Carroll (2005) were genetically mediated. In this study, they found that LVR rats showed relatively greater cocaine-induced locomotor activity compared to HVR rats (see also Rhodes et al., 2001). Although LVRs were more sensitive than HVRs to the locomotor stimulating effects of cocaine, such motoric effects are not a reliable predictor of cocaine self-administration (Mitchell et al.,

2005). Thus, it is difficult to predict how HVR and LVR rats will differ in cocaine self-administration. However, if these findings parallel Larson and Carroll (2005), who found HiR rats were more vulnerable to heightened levels of cocaine self-administration, one would predict that HVRs would show greater cocaine seeking than LVRs.

The present study examined HVRs and LVRs across all phases of the drug self-administration process. Rats were assessed in the acquisition, maintenance, extinction and reinstatement phases of cocaine seeking. Following completion of the study, expression of the HVR and LVR phenotype was assessed by allowing access to a running wheel. It was hypothesized based on the findings of Brown et al. (2015) and Larson and Carroll (2005) that HVR rats would display a genetically-mediated vulnerability to cocaine self-administration during maintenance and cocaine-primed reinstatement compared to LVR rats.

2. MATERIALS AND METHODS

2.1. Animals

Outbred female Wistar rat (generations 12–14) strains selected for high ($n = 22$) or low ($n = 32$) voluntary running were bred at the University of Missouri (Columbus, MO) and were tested at the University of Minnesota beginning on postnatal day (PND) 50. All rats were naïve and were not assessed for voluntary running prior to the study. Briefly, the HVR and LVR lines were bred using rats that were selected for high (e.g., > 30 km/day) and low (e.g., < 10 km/day), respectively, voluntary treadmill running from PND 28–34 (see Roberts et al., 2012 for additional breeding details). Female rats were used as they were used in Larson and Carroll (2005) to examine wheel running as a vulnerability factor for cocaine abuse. Additionally, females are more active in running wheels (e.g., Krasnoff and Weston, 1976) and are more vulnerable to developing cocaine-seeking behavior (see a review by Anker and Carroll, 2010b). Estrous cycle was not sampled since the primary interest of this study was to characterize HVR and LVR female rats across all reproductive phases. Rats were initially housed in rooms maintained at 24 °C (40 – 50% humidity) under a 12/12-hr light/dark cycle (lights on at 0600) in polycarbonate cages with free access to water. At the beginning of the study, rats were food restricted to 16 g of chow per day (Harlan Teklad 2018, Madison, WI) to maintain 85% of their free-feeding weight and facilitate drug taking (Carroll et al., 1979; Lynch and Carroll, 1999). During cocaine self-administration, rats were housed in the operant conditioning chamber. The experimental protocol conformed to the Guide for the Care and Use of Animals (National Research Council, 2011) and was approved by the University of Minnesota Institutional Animal Care and Use Committee.

2.2. Operant conditioning chambers

Experimental operant conditioning chambers were custom-built and octagonal, with alternating aluminum and clear plastic panels. For the lever training with food pellets (see below), chambers were equipped with a 45-mg pellet dispenser, two response levers with stimulus lights directly above, and a ceiling light for general illumination. For the cocaine self-administration procedure, chamber levers and lights were arranged identically to Larson and Carroll (2005), and the chamber was equipped with a syringe pump to deliver response-

contingent cocaine infusions based on the weight of the rat (1s/100g) at a rate of 0.025 ml/s. Rat weights were updated weekly.

2.3. Drugs

(–)-Cocaine HCl (National Institute of Drug Abuse, Research Triangle Institute, Research Triangle Park, NC) was dissolved in a mixture of saline and heparin (5 USP/mL) at a concentration of 1.6 mg/ml. Cocaine was delivered at a unit dose of 0.4 mg/kg, which produces reliable self-administration in rats and is the same dose used by Larson and Carroll (2005).

2.4. Procedure

2.4.1. Jugular catheterization surgery—Rats were anesthetized with ketamine (60 mg/kg, intraperitoneally [*ip*]) and xylazine (10 mg/kg, *ip*) and then were given atropine (0.15 ml, subcutaneously [*sc*]) to facilitate respiration. Subsequently, an indwelling polyurethane catheter was inserted into the right jugular vein and sutured in place with silk thread (4-0). The distal end was tunneled subcutaneously to the mid-scapulae area where it exited and attached to a harness and tether system previous described (see Anker et al., 2007). Following recovery, rats were treated with buprenorphine (0.05 mg/kg, *sc*) twice daily for 72 hr. An additional analgesic, ibuprofen (~50 mg/kg, PO), was provided in the drinking water. During the 3 recovery days, catheters were flushed daily with an antibiotic (enflloxacin; 10 mg/kg) and heparinized saline (10 IU/kg). To maintain patency thereafter, catheters were flushed daily with heparinized saline, and patency was verified weekly with a 0.1 ml flush of ketamine (60 mg/ml) and midazolam (3 mg/ml) in saline (KMS). If a loss of righting reflex did not occur within 10 sec of the KMS flush, a second catheter was implanted in the left jugular vein using the aforementioned methods.

2.4.2. Acquisition of IV Cocaine Self-administration—Rats were trained to respond for sucrose pellets (BioServ #F0021, Frenchtown, NJ) on a fixed-ratio 1 schedule of reinforcement until more than 30 reinforcers were earned in 3 consecutive 45-min training sessions. Once lever trained, rats underwent jugular catheterization surgery and commenced housing in the cocaine self-administration chambers at the start of the 3-day recovery period. After recovery, HVR (*n* = 22) and LVR (*n* = 31) rats were allowed to self-administer cocaine (0.4 mg/kg, *iv*) during daily 6-hr sessions (7 days/week). The start of the self-administration session (0900 h) was signaled by the illumination of the overhead light. During the session, cocaine was infused following a response on left (i.e., “infusion”) lever. During the cocaine infusion (1s/100g), the stimulus light above the left lever was illuminated, and additional responses on this lever during the infusion were recorded but produced no consequence. A response on the right (i.e., “activity”) lever illuminated the lights above that lever for the same duration as the infusion lever but produced no other consequence.

Rats were initially limited to 40 infusions/session until they achieved 3 consecutive sessions with 35 or more cocaine infusions and at least a 2:1 infusion to activity response ratio in the final session. Once these criteria were met, the rats were transitioned into the maintenance phase wherein the limit on cocaine infusions was removed. The main dependent measure was the number of sessions to acquire cocaine self-administration from the first session

where a rat responded to earn cocaine. Additionally, to compare cocaine self-administration levels across acquisition, group mean cocaine infusions were calculated across acquisition sessions (note that group sizes decreased over sessions as rats met acquisition criterion). To ensure that only rats that contacted the contingencies associated with the cocaine infusion lever were included during the acquisition phase, two exclusion criteria were in place. Specifically, rats that lost patency or had equipment problems (LVR: $n = 4$; HVR: $n = 1$) and those that did not earn a cocaine infusion during 5 of the 10 acquisition sessions (LVR: $n = 5$; HVR: $n = 4$) were excluded from the acquisition portion of the study. Any rat that did initiate self-administration following the 10 acquisition sessions was provided lever training, which involved placing ground food on the lever and providing 3 experimenter-delivered infusions every 2 hr (9 total over the 6-hr session). Once responding was reliably over 15 infusions per session, ground food and free infusions were discontinued, and rats were required to meet the acquisition criteria outlined above (2 HVR rats requiring this additional training completed study).

2.4.3. Maintenance and Extinction—During maintenance, rats were allowed to self-administer cocaine during 6-hr sessions (0900 – 1500 hr). Longer maintenance sessions were employed since previous research has found this facilitates escalation of cocaine self-administration (Anker et al., 2009). Rats completed 14 sessions of maintenance prior to being placed into the extinction phase (rats were excluded that did not complete 14 sessions). The main dependent measures were the number of infusion responses, cocaine infusions and activity lever responses during the 6-hr sessions. Following maintenance, rats began the extinction phase wherein lever pressing on the infusion and activity lever produced no consequences. Following 14 sessions of extinction, rats were assessed in the reinstatement procedure.

2.4.4. Reinstatement—During reinstatement, rats were administered either saline or priming injections (see below) or response-contingent access to drug-paired stimuli (i.e., infusion lever lights, drug pump activation). Priming injections at the start of the session consisted injections of Saline (S), Cocaine (Coc) at 5, 10 or 15 mg/kg (*i.p.*; respectively, 5 Coc, 10 Coc, 15 Coc), Caffeine at 30 mg/kg (*i.p.*; Caf), and Yohimbine at 2.5 mg/kg (*i.p.*; Yoh). No injections were provided when access was provided to cocaine-related cues (Cue; infusion lever lights, drug pump activation). The following order of priming conditions was administered over 12 sequential daily test sessions: S, 5 Coc, S, 10 Coc, S, 15 Coc, S, Caf, S, Yoh, No Cue, Cue. These conditions were not counterbalanced to assess presumed phenotype differences in initial sensitivity to the acute effects of cocaine (see differences in Acquisition and Extinction below). At the start of the reinstatement sessions (0900 hr) the overhead houselight was illuminated, and during cue-primed reinstatement sessions, the stimulus conditions present during maintenance were also reinstituted (see drug-paired stimuli above). These priming conditions were chosen based on previous work showing they elicited reinstatement of cocaine-seeking behavior (Anker and Carroll, 2010a) and contained the same priming condition (10 Coc) as Larson and Carroll (2005). The main dependent measure was the number of infusion- and activity-lever responses during the 6-hr session.

2.4.5. Wheel Running Phenotype Validation—To validate expression of the voluntary wheel running phenotype, a subset of HVR ($n = 11$) and LVR ($n = 11$) were randomly selected following the self-administration portion of the study and were allowed free (i.e., continuous) access to a 35.6-cm diameter running wheel for 21 days. Rats lived in polycarbonate homecages with free access to food and water in a room with a 12-hr light:dark cycle (lights on at 0600 hr). The running wheel (ENV-046, Med Associates, Inc., St. Albans, VT) was continuously accessible through a 10-cm square opening in the side of the homecage. Wheel revolutions were recorded at the same time each day (1300 hr).

2.5 Data Analysis

Statistical differences in the HVR and LVR phenotype in the number of sessions to meet the acquisition criteria were assessed using a Mantel-Cox log-rank test. During acquisition, the mean daily number of infusions earned across the first 5 sessions of acquisition by the HVR and LVR groups was assessed using a 2-way analysis-of-variance (ANOVA; session $\times$ phenotype). During maintenance, extinction, and wheel running, differences between the HVR and LVR phenotypes in infusion lever responses, infusions self-administered, activity lever presses, and wheel running were assessed using a mixed-model 2-way ANOVA (phenotype $\times$ session). To assess differences across all reinstatement conditions, a mixed-model 3-way ANOVA (phenotype $\times$ reinstatement condition [e.g., C5, Caf, etc.] $\times$ priming injection [e.g., S vs. C5]) was conducted. Two reinstatement data points for an HVR rat were outliers (greater than 2 standard deviations from the mean) and were replaced with the HVR group mean for those priming conditions. To assess phenotype differences in the cocaine dose-response (5, 10 & 15 mg/kg Coc) manipulation during reinstatement, a 2-way ANOVA (dose $\times$ phenotype) across the initial three doses of cocaine was conducted. Post-hoc tests (see below) were used to examine within- and between-group differences across factors.

3. RESULTS

3.1. Lever Training and Acquisition of Cocaine Self-Administration

There were no differences in the sucrose pellet lever training for HVR and LVR rats. On average, both strains met the acquisition criteria for lever pressing after a similar number of sessions (HVR: 9.2; LVR: 9.8) and earned a similar number of sucrose pellets across the three acquisition sessions (HVR: 89.7; LVR: 91.2).

Differences were observed, however, in the percentage of HVR and LVR rats that met the criteria for cocaine self-administration during the 10 acquisition sessions, which is plotted in Figure 1A. Overall, LVR rats required fewer sessions than HVR rats to reach levels of cocaine self-administration that satisfied the acquisition criteria, which was supported by a Mantel-Cox log-rank test, ($\chi^2_{1, 39} = 4.73, p < 0.05$). Figure 1B presents the number of cocaine infusions self-administered by HVR and LVR rats across the 10 acquisition sessions. In general, cocaine infusions were higher in LVR vs. HVR rats across the first 5 sessions when the majority of rats in each group were self-administering cocaine. However, during the last 5 sessions of acquisition, no significant phenotype differences were found, which could be related to the reduction in group-size as subjects met the acquisition criteria. Across phenotypes, a 2-way ANOVA of the mean infusions earned in the first 5 sessions of

acquisition support these conclusions by revealing a main effect of Phenotype ($F_{1, 167} = 14.31, p < 0.001$) and Session ($F_{4, 167} = 3.52, p < 0.01$). A Sidak post-hoc assessment revealed a significant difference ($p < 0.05$) in infusions in the first acquisition session. No significant strain differences in activity lever responses were found across the first 5 sessions of acquisition or during the three sessions that met acquisition criteria.

3.2. Maintenance

Figure 2 presents the mean number of infusion responses (panel A) and cocaine infusions (panel B) during maintenance. There were no significant differences between HVR and LVR rats in mean infusion responses (Fig. 2A), cocaine infusions (Fig. 2B), and activity lever responses (data not shown).

3.3. Extinction

The number of infusion responses across the 14 extinction sessions for the LVR and HVR rats is presented in Figure 3. In general, LVR rats responded at higher rates across the first week of extinction than HVR rats, and this was confirmed by a two-way ANOVA (phenotype $\times$ extinction session) that revealed a main effect of session ($F_{13, 260} = 5.64, p < 0.001$) and an interaction of session and phenotype ($F_{13, 260} = 1.87, p < 0.05$). A Sidak post-hoc assessment revealed a significant difference ($p < 0.05$) in infusion responses in the third extinction session. There were no significant differences in inactive lever responses (data not shown).

3.4. Reinstatement of Cocaine Seeking

Figure 4 shows the results of the reinstatement priming condition (stripped bars), each proceeded by a control condition (open bars). There were no significant between-group differences in cocaine-seeking or activity lever pressing during priming conditions. A 3-way ANOVA revealed no main effect of, or interaction with, phenotype, but there was a main effect of reinstatement condition ($F_{5, 20} = 4.19, p < .01$), priming injection ($F_{1, 20} = 31.64, p < .001$) and an interaction of priming condition and injection ($F_{5, 20} = 3.56, p < .01$), indicating that both HVRs and LVRs reinstated cocaine seeking compared to control conditions and to different degrees across reinstatement conditions. A Fisher's LSD post-hoc assessment revealed that LVR and HVR rats both reinstated ($p < 0.05$) to the 10 Coc, 15 Coc, Caf and Coc Cues when compared to control conditions. However, only the HVR rats showed significant reinstatement to the 5 Coc priming condition, although responding in this condition was not significantly different when compared between HVR and LVR rats. A 2-way ANOVA across doses of Coc did not reveal a main effect of dose, phenotype or an interaction of these factors.

3.5. Wheel Running Phenotype Validation

The number of wheel revolutions for subsets of HVR and LVR rats over the 21 days of wheel access are presented in Figure 5. Overall, HVR rats completed significantly more revolutions across the 21 days of wheel access, which was supported by repeated-measures 2-way ANOVA (phenotype $\times$ access day) that revealed a main effect of phenotype ($F_{1, 20} = 14.20, p < 0.001$), access day ($F_{20, 400} = 2.38, p < 0.001$) and the interaction of phenotype $\times$

access day ($F_{20, 400} = 2.79, p < 0.001$). A Fisher's LSD post-hoc analysis revealed that HVR rats significantly more than LVR rats during access days 6–21. The number of wheel revolutions did not correlate with any measure of cocaine seeking (i.e., days to acquire, cocaine infusions, etc.) for rats within the HVR or LVR groups.

4. DISCUSSION

The most prominent finding of this investigation was the enhanced vulnerability of LVR rats during the transitional phases of the drug abuse process compared to their HVR counterparts. LVR rats self-administered more cocaine initially during acquisition, they acquired cocaine self-administration after fewer sessions and they took a longer amount of time to extinguish cocaine seeking than HVR rats. Inherent strain differences in learning capabilities did not appear to play a role in acquisition of cocaine use as no difference in lever training for food were observed. Collectively, these findings suggest that selection of the LVR phenotype may confer a genetically-mediated vulnerability to develop cocaine abuse.

The present findings are in contrast to Larson and Carroll (2005), who screened wild-type (not selectively bred) rats for high (HiR) and low wheel running (LoR). In this 2005 study, HiR rats self-administered more cocaine during maintenance and displayed more cocaine seeking during reinstatement (10 mg/kg Coc) than LoR rats, but neither group differed in acquisition or extinction of cocaine seeking. In contrast, the present study found no differences between HVR and LVR rats in cocaine intake during maintenance (Figure 2) and limited differences in cocaine seeking during reinstatement (Figure 4), but did find LVR rats were more vulnerable to acquire cocaine self-administration (Figure 1) and more resistant to extinguish cocaine seeking than HVR rats (Figure 4). Collectively, these findings suggest that genetically-mediated neurobiological and behavioral factors could underlie the vulnerability to cocaine seeking in acquisition and extinction in this LVR phenotype.

The percentage of LVR rats that acquired cocaine self-administration was relatively high compared to similar studies from our lab. At the end of 10 sessions, approximately 85% of the LVRs had acquired cocaine self-administration (Figure 1A). In comparison, cocaine studies from our lab that employ female Wistar rats typically report that 20–55% acquire cocaine self-administration following 10 training sessions (e.g., Carroll et al., 2002; Perry et al., 2005, 2008; Swalve et al., 2015); Larson and Carroll (2005) did not report the percentage of HiR and LoR rats that acquired. Thus in comparison to other studies, LVR rats appear more vulnerable to developing cocaine-seeking behaviors than HVR rats, which appear to be more like the typical (i.e., wild-type) out-bred Wistar rats.

In contrast, the HVR and LVR rats responded at similar rates and earned nearly equivalent number of infusions during maintenance (Figure 2). These findings suggest that the strain differences in cocaine seeking may be subtle and are perhaps overshadowed once stable levels of cocaine seeking is established in maintenance. Reinstatement provided another opportunity to assess whether LVR rats were more sensitive to the acute effects of cocaine. The increase in cocaine priming doses across reinstatement test sessions produced no differences in cocaine seeking between HVR and LVR rats with one exception. In the 5 Coc

priming condition, the HVR rats showed a significant increase in cocaine seeking compared to the preceding control condition (see Figure 4), which suggests HVR rats may be slightly more sensitive to this lower dose of cocaine. However, the relative difference between HVR and LVR rats was not significantly different at this dose. Thus, cocaine-primed reinstatement was relatively similar between groups. One explanation for lack of a strain difference is that the change from self- to experimenter-administered cocaine may have dampened the reinforcing effects of cocaine, which has been demonstrated with other stimulants (see Balster et al., 1976).

The present findings are consistent with those of Brown et al. (2015) who used the same strains of rats and found that LVR rats displayed relatively more cocaine-induced locomotor activation than HVR rats. However, the potential cause for the increased sensitivity of LVR rats to the effects of cocaine is complex. For example, drug-naïve HVR and LVR rats express similar levels of dopamine transporter (DAT) protein levels in the nucleus accumbens (NAc; Brown et al., 2015). This suggests the innate neurobiological difference in DAT may not play a causal role. However, it is possible that this or other neurobiological factors underlying this phenotype difference are transient and only observed during transition periods of cocaine exposure (see Everitt and Robbins, 2005; Koob et al., 1998). In the present study, greater sensitivity to the reinforcing effects of cocaine was only observed during acquisition and extinction of cocaine seeking, but not under steady-state conditions such as maintenance.

The lower basal activity level in LVRs compared to HVRs was evident during the three weeks of unrestricted running wheel access (see Figure 5). During the final week of access, HVR rats ran 10 times the distance of LVR rats; however, the increased activity level did not transfer into increased cocaine seeking. LVR rats earned more cocaine infusions than HVR rats during acquisition, and LVR rats persisted in responding more during the first week of extinction. These findings suggest that while the high- or low-running phenotypes were not expressed prior to cocaine use because rats did not have access to running wheels, the underlying neurobiological differences between these phenotypes may have influenced drug seeking during the transitions into and out of cocaine use.

The difference in cocaine abuse vulnerability between HVR and LVR rats may be enhanced if these rats were allowed access to a running wheel prior to cocaine self-administering. Previous research examining the neuromodulatory effects of exercise on responsiveness of brain reward regions to cocaine supports this conclusion. Research by Zlebnik et al. (2014) found that chronic wheel running altered activation in brain reward regions. Following wheel access, the rats in the Zlebnik study were given injections of saline or cocaine (15 mg/kg) and activation of brain reward regions was measured by cFos expression. Rats provided access to a running wheel (vs. sedentary controls) showed lower raw c-Fos expression in brain regions that mediate drug seeking (see also Greenwood et al., 2011). Although complex to interpret, these findings complement the present study by demonstrating that exercise, or the lack thereof, may impart functional changes in brain reward regions that dampen the effects of cocaine.

In conclusion, LVR rats acquired cocaine self-administration more rapidly, and they persisted longer in cocaine seeking during extinction than HVR rats. However, during the maintenance and reinstatement phases, no differences were observed between phenotypes. These results suggest that LVR rats may initially be more sensitive to the reinforcing effects of cocaine, but that these differences are subtle and are only apparent during transition periods in cocaine use. Broadly, these results may suggest that the HVR predisposition to exercise may confer a genetically-mediated defense against the development of drug abuse.

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Highlights

- Rats bred for High and Low Voluntary Running (HVR/LVR) self-administered cocaine
- LVRs acquired cocaine use faster and persisted in drug seeking longer upon extinction
- Once acquired, few differences in cocaine self-administration were observed
- LVRs were more vulnerable to cocaine seeking than HVRs during transition periods

Figure 1.

Acquisition. **(A)** The percentage of HVR ($n = 17$) and LVR ($n = 22$) rats acquiring cocaine self-administration across 10 sessions. LVR rats acquired cocaine self-administration in a shorter number of sessions and to a greater percentage than HVR rats ($\dagger = p < .05$). **(B)** The mean ($\pm$ SEM) number of cocaine infusions (0.4 mg/kg) self-administered by HVR and LVR rats across acquisition session. Numbers above and below data points denote the reduction in group size as rats met the acquisition criteria for cocaine self-administration and were transitioned into the maintenance phase. LVR rats self-administered more cocaine on

average over the first five acquisition sessions ($\dagger = p < 0.05$ main effect of phenotype; $* = p < 0.05$ in post-hoc test of sessions)

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Figure 2. Maintenance. Mean ($\pm$ SEM) total session infusion lever responses during maintenance (**A**) and the mean ($\pm$ SEM) number of cocaine infusions (0.4 mg/kg) produced (**B**) in HVR ($n = 11$) and LVR ($n = 13$) rats during maintenance.

Figure 3.

Extinction. Mean ($\pm$ SEM) infusion lever responses during extinction session for HVR ($n = 11$) and LVR ($n = 11$) rats. LVR rats responded more at the onset of extinction than HVR rats ($\dagger = p < .05$).

Figure 4.

Reinstatement. Mean ($\pm$ SEM) infusion lever responses across different drug priming [Cocaine (Coc); caffeine (Caf); Yohimbine (Yoh); and cocaine-related injections (Cue)] conditions in HVR ($n = 11$) and LVR ($n = 11$) rats (* denotes significant [$p < 0.05$] reinstatement vs. control condition).

Figure 5.

Mean ($\pm$ SEM) wheel revolutions in HVR ($n = 11$) and LVR ($n = 11$) rats across 21 days of continuous wheel access ($\dagger = p < .01$ main effect of phenotype; $* = p < .05$ post-hoc phenotype difference).