# Environmental enrichment, administered after establishment of cocaine self-administration, reduces lever pressing in extinction and during a cocaine context renewal test

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**The objective of this study was to test the hypothesis that environmental enrichment (EE) administered to rats previously trained to self-administer cocaine would reduce responding in extinction and in a cocaine-context renewal test. Long – Evans male rats were trained to press an active lever reinforced by cocaine (1.0 mg/kg/injection) under a fixed-ratio 1 schedule of reinforcement (inactive lever presses produced no consequences). After stable responding was established, all rats were given a 10-day break from the operant chambers followed by random assignment to EE (larger cages equipped with visual and auditory stimuli) or control (standard housing) group conditions in which they lived for the remainder of the experiment. Ten days after this move, rats were exposed to 10 extinction-responding sessions in a context different from the one in which self-administration occurred, followed by a context-renewal session occurring in the original self-administration context. The EE group responded significantly less in both the extinction and context-renewal sessions compared with the control group. These results suggest that EE reduces the ability of cocaine-associated stimuli to control cocaine-related responding.** *Behavioural Pharmacology* **22:347–353**


**Behavioural Pharmacology** 2011, **22**:347–353

**Keywords: addiction, craving, drug abuse, environmental enrichment, psychostimulants, rat**

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**Received** 1 December 2010 **Accepted as revised** 19 April 2011

## Introduction

A serious problem in drug addiction is relapsing, which itself is typically triggered by intense craving for the drug. Drug craving can be elicited by several stimuli including stress, the drug itself or drug-associated contexts and stimuli. Thus, potential strategies to treat cocaine addiction would benefit from including procedures that would lessen the impact of these stimuli on drug craving. Here we focus on environmental enrichment (EE) as a behavioral procedure that may serve as a treatment strategy for cocaine-context induced cocaine seeking (i.e. cocaine craving).

EE may be an effective treatment for cocaine addiction for at least two reasons: (i) it stimulates motivational circuits involved in the behavioral effects of cocaine and (ii) it provides various forms of stimulation that may be perceived as alternate rewards. In adult rats exposed to EE there are increases in cortical weight, dendritic branching, cholinesterase activity (Zolman and Morimoto, 1962; Bennett *et al.*, 1964; Reige, 1971), and cortical RNA (Ferchmin and Eterovic, 1986). In addition, enrichment can induce changes in specific brain regions involved in conditioning and memory: enriched environments lead to increased mRNA (Pinaud *et al.*, 2001) and brain-derived neurotrophic factor (Spires *et al.*, 2004) in striatum, a region important for stimulus-response learning in drug-taking, and in hippocampus (Pinaud *et al.*, 2001), a region critical for contextual learning. Thus, it is conceivable that by altering brain regions important for the learned and motivational aspects of drug addiction, EE may modulate cocaine-seeking (i.e. craving). Several studies have shown that EE, provided either as an alternative to drug or nonconcurrently with drug, may attenuate the motivation to seek the drug. When enrichment was made available concurrently with cocaine, it reduced drug self-administration in rats (Cosgrove *et al.*, 2002). When given earlier access to sucrose reward, rats previously trained to self-administer cocaine responded less in extinction and in cocaine-induced reinstatement tests (Liu and Grigson, 2005).

Recently, the effects of EE on cocaine seeking in rats previously trained to self-administer cocaine were investigated. Chauvet *et al.* (2009) and Thiel *et al.* (2009) found that EE reduced responding in extinction and in reinstatement tests in which reinstatement was induced by phasic, discrete cocaine-paired stimuli. These studies support the idea that enrichment can decrease cocaine-seeking, at least as elicited by phasic, discrete drug-associated cues. However, the effects of enrichment on the ability of nonphasic, long duration cues, such as the cocaine-taking context, to renew responding have not been investigated. Thus, this study was conducted to test the effects of EE on extinction responding and on cocaine context renewal of responding. We hypothesized that EE

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would attenuate responding in extinction and reduce the impact of the cocaine-taking context on the renewal of responding.

## Methods

The protocols used in these experiments were in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Queens College Institutional Animal Care and Use Committee.

### Subjects and surgery

Subjects were 15 male, Long–Evans rats (Charles River, Kingston, New York, USA) weighing between 325 and 375 g at the time of surgery. The rats were kept on a 12 : 12-h light:dark cycle with the dark phase starting at 06 : 00 h. All subjects had access to food (Purina rat chow) and water at all times except during operant conditioning sessions when they had no access to food. While under sodium pentobarbital anesthesia (65 mg/kg, administered intraperitoneally), each rat was fitted with a permanently indwelling jugular catheter. An incision was made in the neck and the jugular vein was isolated and opened. A silastic intravenous catheter (Dow Corning, Midland, Michigan, USA) was inserted into the vein so that the tip penetrated to a position just short of the right atrium. The other end of the catheter was fed subcutaneously to the back of the neck and exited through an opening at the back of the skull. A bent 22-gauge stainless steel tube was inserted into the catheter and secured to the rat's skull with dental cement anchored by stainless steel screws. This tube served as a connector between the intravenous catheter and the drug-infusion line. The catheter was flushed with a heparin–saline solution (200 USP/ml) immediately after surgery and every day thereafter.

### Apparatus

The operant conditioning chambers measured $26 \times 26 \times 30$ cm ($l \times w \times h$). The chambers were equipped with two 2.5 cm levers mounted 16 cm apart and 10 cm from metal rod floors, and a white cue light mounted 3 cm above each lever. Each rat was connected by polyethylene tubing, through a fluid swivel, to a syringe in a syringe pump (Razel, 3.33 rpm). Only the right lever was active, the left lever produced no programmed consequences. A reinforced lever press activated the syringe pump delivering an intravenous infusion of drug and illuminated the white cue light over that lever.

### Procedures

All behavioral sessions (training and test) were conducted during the dark phase of the light:dark cycle and began 3 days after surgery.

#### *Cocaine self-administration training*

For 2 h every day the animals were placed in the operant conditioning chambers and trained to self-administer cocaine under a fixed-ratio 1 (FR1) schedule of reinforcement. One press on the active lever produced an intravenous injection of cocaine and a white cue light as described above, and started a 4.5 s time-out period during which lever presses were counted but had no other consequence. A cocaine injection consisted of 1.0 mg/kg of cocaine in a 0.125 ml volume of saline delivered over 4.5 s. Training began with only the active lever present. When the animal demonstrated acquisition of self-administration, determined by visual inspection of consistency of injection rate across the session, the inactive lever was introduced. Presses on the inactive lever were recorded but had no scheduled consequences.

Rats were maintained on the FR1 schedule of reinforcement until stable responding was established. Stable responding was defined as follows: 10 consecutive sessions in which the total number of rewards obtained per session was greater than 20 and in which the total number of rewards per session for the last three consecutive sessions was within $\pm$ 10% of the mean for these three sessions. The number of sessions to reach this criterion for all rats ranged from 11 to 15; the groups did not differ on this criterion.

#### *Environmental enrichment*

After stable FR1 responding was established, all rats were given a break from the self-administration chambers for 10 days; they were kept in the home cages 24 h per day for this period. At the end of this break, all rats were assigned to an enriched environment ($n = 8$) or non-enriched environment ($n = 7$); the two groups were matched based on the number of active lever presses emitted during the last self-administration training session. Rats in the enriched group were removed from their standard housing cages and placed in enrichment cages measuring $36 \times 66 \times 41$ cm. Each enrichment cage was equipped with β chip bedding, a running wheel, a 10-cm diameter tunnel, and two additional objects that were rotated daily, including a jingly ball, mirrored bowl, glass mug, toy car, and dog chew. The enriched rats remained in an enriched cage for the remainder of the experiment. Rats in the control group were removed from their standard housing cage and placed in another identical standard housing cage in the same room as the enrichment cages.

#### *Extinction and renewal*

Ten days after being moved to the enriched or standard housing cages all rats resumed daily sessions in the operant chambers. This resumption consisted of 10 extinction sessions followed by one drug-context response renewal session.

Each extinction session was 2-h long and occurred in a different environmental context from the one in which self-administration training occurred, as follows. During training, the chambers had the following cues: gray smooth aluminum walls, metal rod floors, one white cue light illuminating concurrently with reward delivery, sound of syringe pump, and proprioceptive cues related to being connected to drug line tether. During extinction,

the cues were as follows: one rough (sandpaper-like) wall and another black and white striped wall, a metal grid floor, the same proprioceptive cues of tether connection, and no syringe pump sound and no cue light. During extinction session responses on the active and inactive levers were counted but produced no programed consequences. After the tenth extinction session each rat was tested in a 2-h drug-context response renewal session in which part of the original cocaine self-administration training environment was restored; this included the original walls and floor. Presses on both levers were counted.

### Data analysis

For each group the data consisted of the number of responses on the active and inactive levers per 30-min segment of the extinction and response renewal sessions. Extinction responding was analyzed using a four-way analysis of variance (ANOVA) with group (enriched or control) as a between-subjects factor and session, time interval, and lever as repeated-measures factors. Significant interactions were followed by tests of simple effects. Responding in the drug-context response renewal test was analyzed using a three-way ANOVA with group (enriched or control) as a between-subjects factor and time interval and lever as repeated-measures factors. In addition, to better understand the impact of drug-context on response renewal the total number of responses made on each lever during the response renewal test was calculated as a percentage of the total number of responses made on each lever during the last extinction session for each group. These percentage values were analyzed using a two-way ANOVA with group (enriched or control) and lever as factors.

## Results

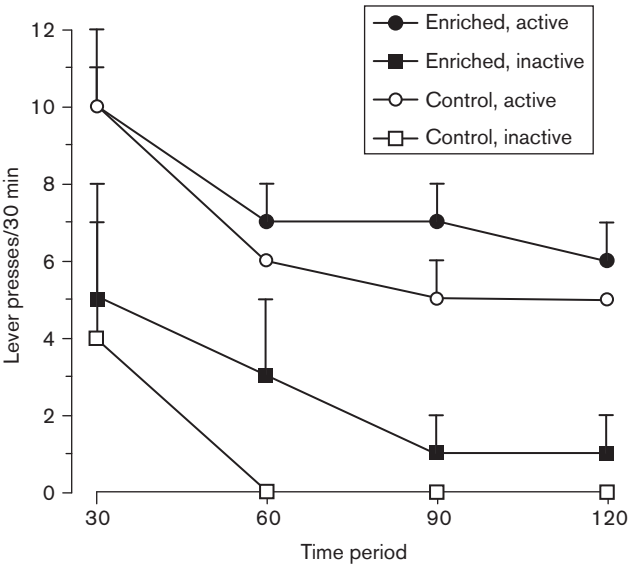
### Self-administration

The mean number of active lever presses during the last five self-administration sessions for all rats was 29 ($\pm$ 3) whereas the mean inactive lever presses over the same period was 9 ($\pm$ 2). A paired samples *t*-test revealed a significant difference between active and inactive lever presses [$t(21) = 5.98$, $P < 0.001$]. Figure 1 shows active and inactive lever presses per 30-min segment on the last self-administration training day for all rats separated by the group condition (control or enrichment) to which these rats would later be assigned. The data show that the two groups had similar patterns and levels of responding on both levers before being assigned to their respective groups. A three-way, mixed-design, ANOVA with group (between-subjects), lever and time (both repeated measures) as factors revealed a significant lever effect [$F(1,13) = 42.02$, $P < 0.001$] but no significant lever by group interaction.

### Extinction

Both the enriched and control groups showed generally greater responding on the active than the inactive lever (see Fig. 2). Both groups also showed similar declines in responding on both levers within and across extinction sessions. In the first extinction session responding on the active and inactive levers was similar between both groups. However, during sessions 2 to 10, the enriched group appeared to respond less than the control group on both levers (see Fig. 2). A four-way ANOVA with group, lever, session, and time interval as factors showed a significant lever $\times$ time interval $\times$ session interaction [$F(27,351) = 1.72$, $P < 0.01$], which did not interact with the group factor. The ANOVA also revealed a significant group $\times$ time interaction [$F(3,39) = 5.26$, $P < 0.005$] that did not further interact with session or lever. To follow-up on the significant group $\times$ time interaction, tests of simple effect of group were conducted at each time interval. These tests revealed significant group differences (all had *P* values less than 0.005) at each time interval except the 60–90 min interval.

**Fig. 1**

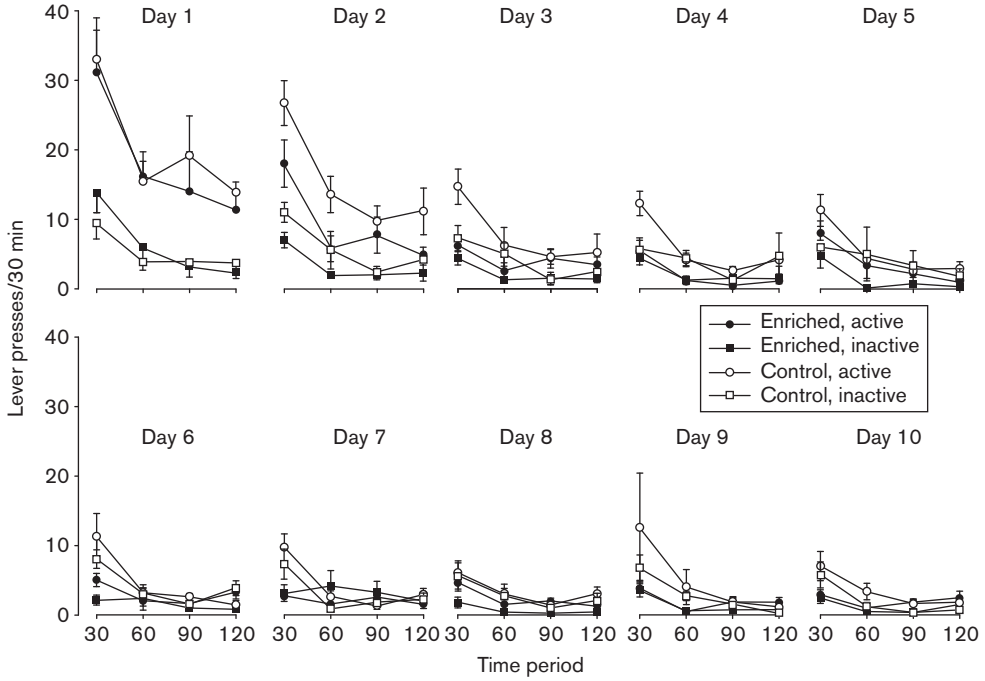



Mean ($\pm$ standard error of the mean) presses on active and inactive levers per 30-min segment for all rats during the last cocaine self-administration training session. Although, at this time all rats have identical treatment histories, their data are separated according to the groups to which these rats were eventually assigned. A three-way analysis of variance revealed no differences between groups.

### Drug-context response renewal

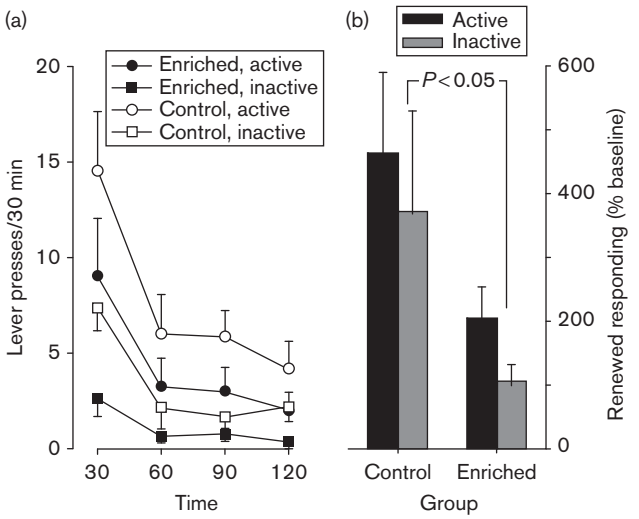
During the drug-context response renewal test both groups showed greater responding on the active than inactive lever and both groups responded more in the first time interval than in the remaining intervals, in which responding on both levers did not change much (see Fig. 3a). However, similar to responding in extinction sessions 2 to 10, responding on both levers in the renewal test was lower in the enriched than in the control group throughout the test session. A three-way ANOVA with

**Fig. 2**




Mean (±standard error of the mean) presses on active and inactive levers per 30-min segment of each extinction session. A four-way analysis of variance revealed a significant group × time interaction ($P<0.005$).

**Fig. 3**




(a) Mean [±standard error of the mean (SEM)] presses on active and inactive levers per 30-min segment of cocaine context renewal test session. A three-way analysis of variance (ANOVA) revealed a significant group effect ($P<0.05$). (b) Mean (±SEM) total presses on active and inactive levers during cocaine context renewal test session expressed as percentage of total responding during the last extinction session. A two-way ANOVA revealed a significant group effect ($P<0.05$).

group, lever, and time interval as factors revealed a significant lever × time interval interaction [$F(3,39) = 5.36$, $P < 0.005$] that did not further interact with group. The same ANOVA also revealed a significant group effect [$F(1,13) = 4.43$, $P < 0.05$] that did not interact with time interval. Figure 3b shows total responding during the drug-context response renewal test as a percentage of total responding during the last extinction session. The drug-context renewed responding on both levers less than half as much in the enriched group than in the control group (see Fig. 3b). A two-way ANOVA with group (between-subjects) and lever (repeated measures) conducted on these data revealed a significant group effect [$F(1,13) = 4.41$, $P < 0.05$].

## Discussion

In this experiment, the enriched group pressed both active and inactive levers significantly less than the control group during the extinction responding period and during the context renewal test. These findings are in agreement with previous studies that have investigated the effects of EE on cocaine seeking. For instance, Thiel *et al.* (2009) found that animals receiving enrichment responded significantly less than a control group during extinction sessions as well as during a reinstatement test where the reinstating stimulus was a phasic, short-duration cocaine-associated stimulus. A similar outcome was reported by Chauvet *et al.* (2009) who demonstrated that enrichment produced significantly less responding during a 6-h extinction session and during a reinstatement session using a phasic, short-duration cocaine-paired cue. Thus, our findings, along with those of these

two studies, strongly suggest that EE can reduce the impact of tonic, long-duration cocaine cues and phasic, short-duration cues on extinction and renewal responding. Interestingly, although Thiel *et al.* (2009) found that enrichment reduced the capacity of a noncontingent cocaine injection to induce reinstatement, Chauvet *et al.* (2009) found that enrichment had no effect on a cocaine prime. Thus, the effects of EE on the capacity of cocaine itself to induce responding remain ambiguous.

The reduced lever pressing in this study can be explained in one of two ways. One is that the enriched group was less motivated for cocaine than the control group and the other is that the enriched group was generally less active than the control group. Had the enriched group shown a significant reduction in lever pressing that was selective for the active lever, with inactive lever presses remaining similar to control group levels, then this would have ruled out the reduction in general activity explanation. Although this was not the case, the reduced activity explanation remains highly unlikely for other reasons. If the enriched group was generally less active than the control group then the reduced lever pressing on both levers, if caused by reduced activity, should have been present on the first day. However, the enriched rats actually had greater combined active and inactive lever presses on the first day than the control group (see Fig. 1, day 1; means of 113 and 95 total presses for enriched and control groups, respectively). Reduced lever pressing in the enriched group began on day 2 and appeared more accelerated, although not significantly so, than in the control group, suggesting, if anything, that the enriched group learned extinction responding quicker than the control group. Furthermore, although we used the inactive lever to measure nonspecific activity (activity not related to motivation for cocaine) the pattern of our results suggests that in fact the inactive lever was not impervious to motivational factors. Considering strictly the control group, the pattern of inactive lever responding resembled that of the active lever; both patterns were characterized by extinction declines during each session and spontaneous recoveries at the start of every session, as well as large increases in response to the reintroduction of the cocaine context. Thus, if we are to explain the pattern of active lever responding in the control group as a result of the learning and motivational factors controlling such responding then it is not reasonable to explain an identical pattern on the inactive lever as a result of different factors. The parsimonious explanation is that both lever response patterns reflect what is to be expected by the learning and motivational factors that control behavior under extinction and response renewal conditions. Thus, it seems that inactive lever responding, because it does not appear to be impervious to motivational factors under the current experimental parameters, cannot shed light on general activity states. Thus, although these results do not allow a strong conclusion that enrichment reduced cocaine seeking *per se* the pattern of results also does not rule out this possibility. The most parsimonious interpretation of these data is that enrichment reduced the behavioral activational effects of cocaine-associated stimuli.

Another explanation for the decreased active and inactive lever pressing observed in the enriched group may be that EE reduced exploration of novelty. Others have shown that rats raised in enriched environments demonstrated significantly less exploration of novel objects than control rats, an effect that is attributable to accelerated habituation to novelty (Zimmermann *et al.*, 2001; Schrijver *et al.*, 2002). It is possible that our enriched rats, when presented with the novel extinction environment, may have experienced less exploratory arousal and responded generally less to novelty, resulting in decreased lever pressing. Although interesting and plausible, this explanation has some drawbacks. We would not expect enrichment-induced habituation to novelty to be directed to the levers themselves because, although the extinction environment was novel, the levers were not. In addition, during the renewal test, the original training environment was restored, removing the novel component that might have been present during extinction. Yet, even in the absence of this novel component, responding on both levers was less in the enriched than in the control groups. Finally, there is at least one study that shows no effects of being raised in an enriched environment on habituation to or exploration of novel objects (De Jong *et al.*, 2000).

Other studies have assessed the impact of EE on behaviors that may be related to cocaine addiction. In a conditioned place preference (CPP) experiment, EE reduced the preference for the cocaine-paired environment (Solinas *et al.*, 2009). Moreover, housing mice in an enriched environment after the development of CPP prevented cocaine-induced reinstatement of CPP (Solinas *et al.*, 2008). These studies add additional support for the notion that EE can reduce the influence of cocaine-associated contexts to control behavior. In addition to effects on drug-associated contexts and cues, enrichment types of experience may affect the primary reinforcing effects of self-administered drugs. For instance, the introduction of novel stimuli in self-administration chambers reduced the rate of acquisition and the maintenance of amphetamine self-administration in rats (Cain *et al.*, 2004, 2006).

There is also an accumulation of evidence showing that enrichment during rearing can impair future acquisition of drug self-administration. Rats reared in an enriched environment demonstrated less self-administration of low doses of amphetamine under both fixed and progressive ratio schedules of reinforcement (Bardo *et al.*, 2001; Green *et al.*, 2002), but self-administration of high doses was similar between groups. Similarly, in a recent study investigating the effects of enriched rearing on escalation of cocaine self-administration, enrichment protected against

escalation at low doses of cocaine but at higher doses the escalation rates were similar between enriched and nonenriched groups (Gipson *et al.*, 2010). In contrast, in one study (Smith *et al.*, 2009) it was found that, when enrichment was administered during rearing, enriched rats showed greater sensitivity to cocaine reward than nonenriched rats. Thus, although it appears that enrichment during rearing can affect sensitivity to drug self-administration, it remains somewhat unclear exactly what the effects are. Finally, rats raised in an enriched environment and later trained to self-administer amphetamine showed greater extinction of the lever press response and less sensitivity to priming-induced reinstatement than nonenriched rats (Stairs *et al.*, 2006). These data are in accord with the present findings and together with the present findings suggest that EE, administered either before or after self-administration training, may reduce drug-seeking types of behaviors.

The mechanisms whereby EE might reduce the effects of cocaine-associated stimuli on responding are not known. However, as indicated earlier, these mechanisms may involve both neurobiological and behavioral pathways. From a neurobiological perspective, the effects of EE include an increase in cortical weight in adult rats, stimulation of dendritic branching and cholinesterase activity (Zolman and Morimoto, 1962; Bennett *et al.*, 1964; Reige, 1971) as well as cortical RNA (Ferchmin and Eterovic, 1986). Moreover, not only can enrichment foster changes in brain regions involved in conditioning and memory, including increased mRNA (Pinaud *et al.*, 2001) and brain-derived neurotrophic factor (Spires *et al.*, 2004) in striatum and in hippocampus (Pinaud *et al.*, 2001), enrichment has been associated with increased plasticity in the hippocampus, frontal cortex, and striatum and pronounced changes in neuroendocrine regulation (Moncek *et al.*, 2004). From a behavioral perspective, it is possible that introducing rewarding stimulation, as would be expected with EE, may have the effect of reducing the significance of drug-related stimuli through a contrast mechanism. This hypothesis is supported by a recent report that in rats previously trained to self-administer cocaine and receiving enrichment after training, the cocaine-associated cues activated cFos in the mesocorticolimbic system to a lesser extent than in nonenriched animals (Thiel *et al.*, 2010). Finally, it has been hypothesized that EE may reduce responding in extinction because it produces an antistress effect by lowering stress-responsive hormones. Animals housed in an enriched environment demonstrated significantly lower baseline adrenocorticotropic hormone and corticosterone concentrations compared with those housed in a nonenriched environment (Belz *et al.*, 2003). Interestingly, it has been shown that stress-induced reinstatement of responding in cocaine-trained animals is preceded by corticotropin-releasing factor release in the ventral tegmental area (Wang *et al.*, 2005) and can be blocked by intra-ventral tegmental area injections of corticotropin-releasing factor antagonists (Wang *et al.*, 2007).

In summary, animals exposed to EE after acquiring the cocaine self-administration habit showed significantly less lever pressing in extinction and in a cocaine context renewal test than control animals not exposed to an enriched environment. These results have significant implications for the development of behavioral strategies to treat cocaine addiction.

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