INDIVIDUAL DIFFERENCES IN COCAINE'S LOCOMOTOR ACTIVATING EFFECTS PREDICTS REWARD-DIRECTED BEHAVIOR

BY

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THESIS

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Abstract

Humans exhibit marked individual differences in susceptibility to develop drug dependence. Addiction-like behaviors have been modeled in rodents as well with similar individual variability in the development of addiction-like behaviors. One potential mechanism that could differentiate addiction-vulnerable from addiction-resistant individuals is sensitivity to reward-paired cues. Pavlovian-instrumental transfer (PIT) is a paradigm that assesses the extent to which reward cues can initiate previously unpaired instrumental responding for a common reward. To examine the potential that sensitivity to reward-paired cues is a mechanism differentiating individuals with a propensity to develop addiction-like behaviors, we used a rodent model known to differ in initial responsiveness to cocaine as well as in behaviors implicated in 'addiction-vulnerability'. We hypothesize that rodents displaying the 'addiction-vulnerable' phenotype will initiate instrumental responding to a greater degree when presented with cues associated with reward than their counterparts.

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Chapter 1: Introduction

Although nearly 15% of the US population tries cocaine at some time in their life, only a fraction of those individuals eventually meet criterion for dependence (Schramm-Sapyta et al., 2009). This suggests that individual differences play an important role in predicting vulnerability for drug dependence. Rodent models of addiction have demonstrated that, like humans, a subpopulation of rats (about 17%) will develop addiction-like behaviors in an extended self-administration paradigm (Deroche-Gamonet et al., 2004; Kasanetz et al., 2010). These rats demonstrate addiction-like behaviors similar to humans in that they will progressively increase intake of the drug over time, continue self-administering despite adverse consequences, and work harder than other rats under progressive ratio schedules of reinforcement for the drug (Deroche-Gamonet et al., 2004). Given the compelling evidence for individual differences in the development of addiction-like behaviors, it is important to understand the factors that contribute to a heightened vulnerability.

Sensitivity to the incentive properties of reward-paired cues is a potential mechanism that might differentiate individuals with a propensity towards addictive behavior from their non-addiction prone counterparts. Clinical imaging studies have demonstrated that drug cues, such as videos of subjects purchasing, preparing, and using cocaine, increase activation of the mesolimbic dopamine (DA) system and increase self-reported cocaine craving in individuals with a history of cocaine dependence (Childress et al., 1999; Volkow et al., 2006). This likely contributes to the chronic relapsing nature of drug dependence even after prolonged abstinence, a hallmark of addiction (Deroche-Gamonet et al, 2004). The incentive-sensitization theory of drug-dependence reconciles these two prominent factors, dopaminergic neuroadaptations and cue-induced craving, in the drug dependence equation. Specifically, the theory postulates that drug-

induced neuroadaptations in DA systems sensitize the association between drug cues and reward, thereby giving the cues increased incentive salience and ultimately leading to increased drug 'wanting' in response to drug cues (Robinson & Berridge, 1993).

Another rodent model that is useful for investigating the neural basis of addiction vulnerability is one developed by Zahniser and colleagues that focuses on individual differences in sensitivity to the hyperactivity-inducing effects of cocaine. Specifically, rats that have a reduced locomotor response to cocaine (low cocaine responders, LCRs) discriminate cocaine at lower doses (Klein and Gulley, 2009), exhibit higher progressive ratio breakpoints during cocaine self-administration (Mandt et al., 2008) and develop enhanced cocaine conditioned place preference (Allen et al., 2007) compared to rats with a heightened locomotor response to the drug (high cocaine responders, HCRs). Additionally, LCRs, but not HCRs, readily exhibit sensitization to the locomotor activating effects of cocaine (Gulley et al., 2003; Sabeti et al., 2003; Briegleb et al., 2004; Nelson et al., 2009, 2010) that appears due to a wide range of neuroadaptations that are unique in LCRs compared to HCRs (Sabeti et al., 2003; Nelson et al., 2009). Thus, LCRs exhibit characteristics of an "addiction-vulnerable" phenotype, compared to HCRs.

Pavlovian-instrumental transfer (PIT) is a paradigm that examines the ability of a previously reward-paired cue to initiate instrumental responding for the reward. Two key advantages of PIT are the ability to examine animals in a drug-free state and the ability to dissociate cue-induced instrumental responding from competing explanations of enhanced responding, such as conditioned instrumental responding to the reward cue (Wyvell & Berridge, 2001). Although the rats in this paradigm respond for food rather than a drug reward, Saunders and Robinson (2009) demonstrated that rats with a propensity to attend to cues associated with a

food reward (sign-trackers) also have an increased propensity to reinstate drug-seeking in response to drug-paired cues. In the current study, we used the PIT paradigm to assess whether sensitivity to reward-related cues is enhanced in the "addiction-vulnerable" LCRs compared to HCRs. Given the known role of reward-cues in addiction, we hypothesized that LCRs would be more sensitive to the behavioral-activating effects of reward-paired cues relative to HCRs.

Chapter 2: Methods

Subjects

Sixty-two male Sprague-Dawley rats were born in our facility from breeders obtained from Harlan (Indianapolis, IN, USA). Animals were kept on a 12-hour light/dark cycle (lights on 8 AM) and were housed in groups of 2-3 until ~2.5 months of age when they were housed individually. Rats were allowed *ad libitum* access to water but were food restricted to 85% of their free feeding body weight beginning at 1 week before the start of experiments (at 3-4 months of age). Experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Illinois, Champaign-Urbana, and were consistent with the Principles of Laboratory Animal Care (NIH Publication no. 85-23).

Apparatus

Instrumental and Pavlovian conditioning sessions occurred in standard operant chambers (Coulbourn Instruments; Whitehall, PA, USA) that were housed inside sound-attenuating boxes. The boxes were equipped with fans that provided ventilation and masked extraneous noise. On one wall of each chamber there were two retractable levers mounted on either side of a centrally located food trough. White cue lights were located above each lever and a tone-emitting speaker (2.9 kHz Sonalert) was located directly above the food trough. Entries into the food trough were monitored by infrared detectors. A white house-light (4 W), which was illuminated during all training and test sessions, was located near the top of the chamber on the opposite wall from the food trough. Graphic State (v3.1; Coulbourn Instruments) was used for automated chamber control and data collection.

Locomotor activity was assessed in an open-field activity apparatus (Coulbourn Instruments) consisting of a clear acrylic box (41 x 41 x 41 cm) and fitted with a photobeam

frame located 2.5 cm above the arena floor (16 beams/dimension; 2.5 cm between beams). The activity chamber was located inside a 76 x 80 x 63 cm sound attenuating cubicle that had a 76 mm speaker mounted on the inside of one wall and two ceiling-mounted white lights (4 W each) that provided dim illumination. White noise (70 dB) was played continuously through the speakers when rats were in the testing room. Each open-field apparatus was connected to a nearby computer running software (TruScan, v 2.01; Coulbourn Instruments) that recorded beam breaks with a 500 ms sampling rate and converted this to locomotor distance (m).

Instrumental training

On the first training day, rats were familiarized with the operant chambers and the process of retrieving food (45 mg pellets; Bioserv; Frenchtown, NJ, USA) from the trough in one 30-min magazine training session. Over the next 10 days, they underwent instrumental training for 60 min/day. During these sessions, both levers were extended into the chamber, but only one was active. Assignment of the active lever to the left or right side of the food trough was counterbalanced across rats. Responses on the active lever were reinforced with food pellet delivery using the following schedule: continuous reinforcement (sessions 1, 2 and 3), random ratio (RR) 2 (sessions 4, 5 and 6), RR5 (sessions 7 and 8), and RR10 (sessions 9 and 10). During these sessions, responses on the inactive lever were recorded but had no programmed consequences. The first two continuous reinforcement sessions were done during the rat's dark cycle to facilitate response acquisition.

Pavlovian approach training

Following instrumental training, two groups of rats were given once daily sessions of Pavlovian approach training during which a conditioned stimulus (CS; 2.9 kHz tone and illumination of the two cue lights) was presented in association with the delivery of food pellets.

These sessions occurred in the same operant chambers that were used in instrumental training, but the levers remained retracted. In the first group of rats (CS-30), the CS was presented a total of 10 times for 30 sec/presentation, with pellet delivery occurring every 10 sec throughout the CS (i.e., 3 pellets/CS presentation). CS presentations were separated by a random time inter-stimulus interval (ISI) that varied between 90 and 210 sec. In the second group of rats (CS-120), the number of training sessions was increased to 8, CS duration was increased to 120 sec, and 6 CS presentations were given per session. During CS presentation, food pellets were delivered with a 33% probability every 10 sec. Thus, an average of 4 pellets was delivered per CS presentation. In this group, the ISI varied randomly from 120 to 240 sec.

Saline or cocaine exposure

The day after the last Pavlovian approach training session, rats from both training groups were randomly assigned to receive once daily injections (i.p.) of saline or 10 mg/kg cocaine for a period of 7 days. On the 1st and 7th day of exposure, rats were brought to a testing room with open field chambers and allowed to habituate for 30 min. Following habituation, the rats were placed in the open-fields for 90 min to assess their novelty response and allow them to habituate to the chamber. After this time, they were briefly removed and injected with either saline or 10 mg/kg cocaine and returned to the chamber for an additional 60 min. On exposure days 2-6, rats were taken to a separate testing room, given their assigned injection, and placed for 60 min in an acrylic tub (46×25×22 cm) lined with hardwood bedding. These tubs and bedding were distinct to those used for the rat's home cage in the animal colony. Following the 7^{th} exposure, animals remained in the colony room undisturbed (aside from daily weighing and feeding) in home cages for 10 days during which no treatment or testing occurred.

Instrumental reminder session and PIT test

On the 11th day after the last injection with saline or cocaine, rats received one 30 min instrumental training "reminder" session (RR 10). On the following day, they were given a test for PIT. During these sessions, rats were placed in the test chambers with both levers extended. For rats in the CS-30 group, the 30-sec CS was then presented three separate times with each presentation followed by a randomly varying ISI of 90-210 sec. In addition to the lever press reminder session, rats in the CS-120 group received a 30 min lever press extinction session, during which both levers were extended but no reinforcement was available. For rats in the CS-120 group, the 120-sec CS was presented four times with each presentation followed by a randomly varying ISI of 120-240 sec. For both groups of rats, the PIT test was administered under extinction conditions (i.e., no food pellet delivery).

Cocaine Challenge

Two days after PIT testing, which corresponded to a 14 to 15-day withdrawal period from the last injection of saline or cocaine for the CS-30 and CS-120 groups, respectively, all rats were given a challenge injection of 10 mg/kg cocaine (i.p.) in the open field using the same procedures described previously.

Data Analysis

Cocaine-induced locomotor activity in the open-field was assessed by determining the cumulative activity during the first 30 min following injection. As in previous studies (Gulley et al., 2003; Gulley, 2007; Klein and Gulley, 2009) rats with activity scores in the lower half of the population distribution were designated LCRs and those in the upper half were designated HCRs. For rats repeatedly exposed to saline, data for this analysis were obtained from the cocaine challenge; data for those repeatedly exposed to cocaine were from the first treatment. The

statistical significance of group differences in cocaine-induced activity was determined using two-way, mixed factor ANOVA, with group (saline, LCRs and HCRs) as the between-subjects factor and treatment (1, 7, and challenge) as the repeated measure.

Behavior during Pavlovian approach training was evaluated by calculating an approach index: CS trough entries – pre-CS trough entries/total trough entries during the session x 100. The pre-CS period corresponded to the time period immediately preceding CS onset that was of equal duration to the CS (30 or 120 sec). These data were analyzed using two-way, mixed factor ANOVA with group and training session as the between- and within-subjects factors, respectively. For the PIT test, the dependent measures of interest were rate of trough entries and rate of lever presses during the CS and pre-CS periods. These were analyzed with mixed factor ANOVAs, with group and time period as the between- and within-subjects factors, respectively. To examine extinction of Pavlovian approach during the PIT test, the approach index (described above for Pavlovian performance) from each trial during the PIT test was subtracted from the approach index on the final day of Pavlovian training. These data were analyzed with two-way mixed factor ANOVA with group and trial as the between- and within-subjects factors, respectively. For all of the analyses, main effects and interactions were followed up with Holm-Sidak post-hoc tests where appropriate. Data from four rats were excluded from the PIT analyses because these rats failed to respond during the PIT test. This included 2 saline pre-exposed rats and 2 cocaine pre-exposed rats (1 HCR and 1 LCR).

Chapter 3: Results

Locomotor activity

Tests of the locomotor response to the first injection of 10 mg/kg cocaine, which occurred after Pavlovian approach training for rats exposed repeatedly to cocaine and after the PIT test for rats exposed repeatedly to saline, revealed a wide variation of activity levels that ranged from 16.3 to 188 m for the 60 min test period. Using the median level of activity for the first 30 min post-injection (94.3 m), rats were characterized as LCRs and HCRs if their scores fell below or above the median, respectively. A repeated measures ANOVA of activity following the 1stand 7th treatments and the cocaine challenge revealed significant main effects of group ($F_{2,118} = 36.67$, $p < 0.001$) and treatment ($F_{2,118} = 16.43$, $p < 0.001$), along with a significant group x treatment interaction ($F_{4,118} = 10.54$, $p < 0.001$). Compared to saline-treated rats, both LCRs and HCRs had significant increases in locomotor activity following the 1st and 7th treatment with cocaine (Fig. 1). Moreover, HCRs had significantly greater responses after both of these treatments compared to LCRs. Neither group had significant changes in their response to cocaine on the 1st compared to the 7th treatment. However, in LCRs, there was evidence of sensitization following the cocaine challenge, which occurred between 14 and 15 days following the 7th treatment (Fig. 1). This relatively enhanced locomotor response to cocaine in LCRs was evident when comparing their response during the challenge to that seen after their first exposure. The magnitude of this response was not different from that observed in rats pre-exposed to saline or in HCRs pre-exposed to cocaine.

Pavlovian approach behavior

Analysis of behavior during Pavlovian approach training, which occurred prior to the 1st treatment with saline or cocaine, revealed differences in the development of approach behavior

between rats that would later be characterized as LCRs and HCRs (Fig. 2A). A two-way repeated measures ANOVA of the Approach Index for rats trained with a 30-sec CS revealed significant main effects of group ($F_{1,150} = 7.20$, $p < 0.05$) and session ($F_{5,150} = 22.80$, $p < 0.001$), but a non-significant interaction. As shown in Fig. 2, LCRs and HCRs had significant increases in approach behavior during sessions 2 through 6 compared to session 1. Moreover, LCRs exhibited more approach behavior, compared to HCRs, during each of the training sessions. Regression analysis of the relationship between cocaine-induced activity and approach behavior revealed a significant, negative correlation between these two measures (Fig. 3).

When CS duration was increased to 120-sec, the difference in conditioned behavior between LCRs and HCRs was not observed (Fig. 2B). ANOVA revealed that the only significant effect was a main effect of session ($F_{7,196} = 13.87$, $p < 0.001$). When the data were collapsed across group, the increases in trough entries during the CS in sessions 2 through 8 compared to session 1 were significant. In addition, there was no significant relationship between cocaine-induced activity and approach behavior (Fig. 3).

PIT test

As shown in Fig. 4A, there was no evidence of a transfer effect in the CS-30 or CS-120 groups. In fact, rather than the expected increase in lever pressing during the CS, we observed reduced responding relative to the pre-CS period. This effect was especially robust in the group trained with the 30-sec CS. In these rats, a mixed factor ANOVA revealed a significant main effect of time bin ($F_{1,28} = 23.08$, $p < 0.001$). As shown in Fig. 4B, the lack of a transfer effect was likely influenced by response competition with Pavlovian approach behavior, as both groups exhibited significantly higher trough entries during the CS compared to the pre-CS period.

ANOVA of these data revealed a significant main effect of time bin for the CS-30 ($F_{1,29}$ = 131.83, $p < 0.001$) and CS-120 ($F_{1,29} = 25.17$, $p < 0.001$) groups.

Approach behavior during the PIT test extinguished rapidly, however, and differed as a function of CS duration (Fig. 5). ANOVA of the approach index during successive trials in the PIT test revealed a significant main effect of trial ($F_{1,28} = 7.97$, $p < 0.01$) for rats trained with a 30-sec CS (Fig. 5A). There was no main effect of group and no group x trial interaction in these rats. Approach extinction during PIT testing was not as consistent for rats trained with a 2-min CS (Fig. 5B). Trough entries during CS presentation relative to the pre-CS reduced across trials in both groups, but ANOVA of the approach index revealed no main effects and no interaction.

Chapter 4: Discussion

In this experiment, we demonstrated that LCR and HCR rats exhibit differences in reward-directed behavior that can be measured prior to their first exposure to cocaine. Specifically, LCRs acquired Pavlovian conditioning to a greater degree than HCRs when training occurred with a short duration CS (30 sec). These findings are consistent with others who examine addiction-vulnerability within the framework of another phenotype, sign-trackers and goal-trackers. In these studies sign-trackers, rats that attend primarily to tangible cues associated with reward delivery instead of the goal, also exhibit more cue-induced cocaine-seeking reinstatement (Saunders & Robinson, 2009), sensitization to cocaine with repeated exposure (Flagel et al., 2008), and different patterns of dopamine activation in response to reward cues (Flagel et al., 2011) than goal-trackers. This supports the notion that one important indicator of addiction-vulnerability may be an enhanced tendency to attend to reward cues.

This study, in addition to contributing to the burgeoning literature on the behavioral differences that distinguish the LCRs and HCRs, provides the first evidence of *a priori* differences between the phenotypes. Previously, it was suggested that the initial exposure to cocaine induced the neurobiological and behavioral differences that had been observed between the two phenotypes (Mandt et al., 2010). The current study instead suggests that individual differences in Pavlovian reward-directed behavior are not induced by drug exposure. This is important because it opens up opportunities for behavioral and neurochemical assays to be done prior to phenotype characterization (drug exposure). This would permit investigating characteristics of an 'addiction-vulnerable' phenotype prior to drug exposure using a model that requires minimal time to identify and offers considerable consistency across addiction-like behaviors.

In spite of the differences in Pavlovian approach we observed between the phenotypes, we did not find significant differences in the PIT task. In fact, most of the rats did not display a transfer effect at all. The reason for this is not entirely clear, but it is noteworthy that the PIT procedure is very sensitive to subtle methodological changes (Holmes et al., 2010). For example, it has been noted that the order in which instrumental and Pavlovian training occur, using a variable interval (VI) schedule for lever press training, and instituting a Pavlovian approach extinction session, as well as a lever press extinction session prior to PIT, all contribute to the development of the transfer effect. In the current experiment, we based our procedures largely on those of Wyvell & Berridge (2001), who successfully demonstrated that amphetamine sensitization enhanced PIT. As such, we used a 30-sec CS for Pavlovian training and trained our rats in lever pressing prior to Pavlovian approach, both of which likely diminished our chances of getting a transfer effect. Shifting to a longer duration CS (2-min) and instituting a lever press extinction session prior to PIT testing, also proved insufficient for observing the transfer effect. It may be the case that in the current experiments, Pavlovian approach behavior was too intrusive to allow the transfer to occur. This is evidenced by the fact that as Pavlovian approach behavior extinguished over CS presentations, there was some indication of an increase in lever pressing behavior (data not shown). This suggests that during the CS periods, the propensity to 'seek' reward from the trough was greater than the propensity to 'seek' the reward by pressing the lever. Given our data, it seems likely that a Pavlovian approach extinction session would have facilitated a more robust transfer effect by reducing competition between Pavlovian and instrumental responses.

The locomotor data obtained from our rats replicates several other accounts of behavioral sensitization unique to the LCR phenotype following repeated cocaine exposure (Gulley et al.,

2003; Sabeti et al., 2003; Nelson et al., 2009, 2010). However, in contrast to reports from Sabeti et al. (2003), we did not observe reduced behavioral activation in saline versus cocaine pretreated groups in response to the cocaine challenge. Instead, we found that locomotor activation following a cocaine challenge in saline and cocaine pretreated groups did not differ significantly. There are several possible explanations for this difference, likely due to slight methodological differences. Several studies emphasize the importance of context in the development of sensitization (Carey & Damianopoulos, 2006; Janak et al., 1997; Mattson et al., 2008; Wise et al., 1996). The saline group in the Sabeti et al. (2003) paper had extensive pre-exposure in the testing apparatus that occurred as recently as 1 day prior to the cocaine challenge. Our saline rats had only 2 prior exposures in the testing apparatus, which occurred two weeks prior to the cocaine challenge. The differences in familiarity with the testing context could contribute to the differences in locomotor response magnitude observed between the two studies. Additionally, we could be observing residual effects of food deprivation in our saline rats, which has also been shown to effect the development of sensitization (Marinelli et al., 1996).

Up to this time, the differences implicating LCRs as the addiction-vulnerable phenotype have been primarily in tasks that require associative learning. The current study adds to the literature indicating the LCRs acquire Pavlovian conditioning to a greater extent than HCRs, which is what has been demonstrated up to this time with drug-discrimination and CPP (Klein and Gulley, 2009; Allen et al., 2007). While this study does reveal that differences in LCRs and HCRS exist prior to drug exposure, it does not conclusively demonstrate whether LCRs are more sensitive than HCRs to the behavioral activating effects of reward-paired cues. However, the Pavlovian findings are congruent with other reports of addiction-vulnerability. Further studies are required to determine if reward-paired cues enhance responding in the LCR, ‘addiction-

vulnerable' phenotype, regardless of whether or not the reward-cue has been previously paired with the instrumental response.

Figures

Figure 1

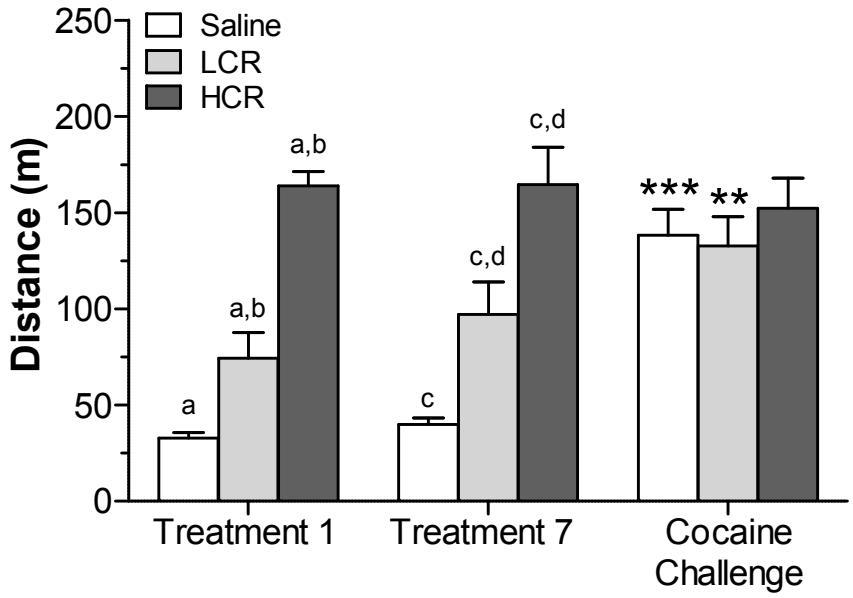

Figure 1: Total locomotor activity during the 60 min following injection of saline or 10 mg/kg cocaine on treatment 1 or 7 and following a 10 mg/kg cocaine challenge given 14-15 days after treatment 7. Rats in the saline pre-treatment group (n = 31) were exposed repeatedly to saline prior to cocaine challenge. Rats repeatedly exposed to cocaine were characterized as LCRs or HCRs (n = 13 and 18, respectively) based on their response following injection 1 (see Methods for details). Matching letters indicate significant differences between groups ($p < 0.05$); ** $p < 0.01$ and *** $p < 0.001$, compared to treatment 1 within group.

Figure 2

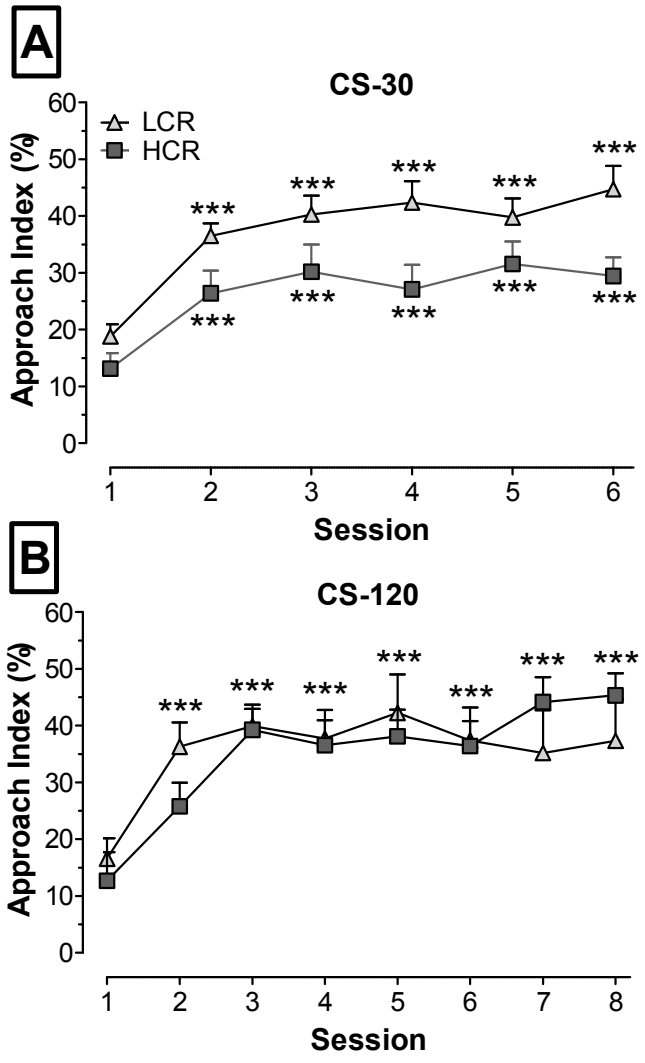

Figure 2: Pavlovian approach behavior during training sessions for rats trained with a 30-sec (CS-30; n = 16 LCR and 16 HCR) or 120-sec CS (CS-120; n = 13 LCR and 15 HCR). Approach index was calculated for each rat as follows: CS trough entries – pre-CS trough entries/total trough entries during the session x 100. ***$p < 0.001$, compared to session 1 collapsed across group.

Figure 3

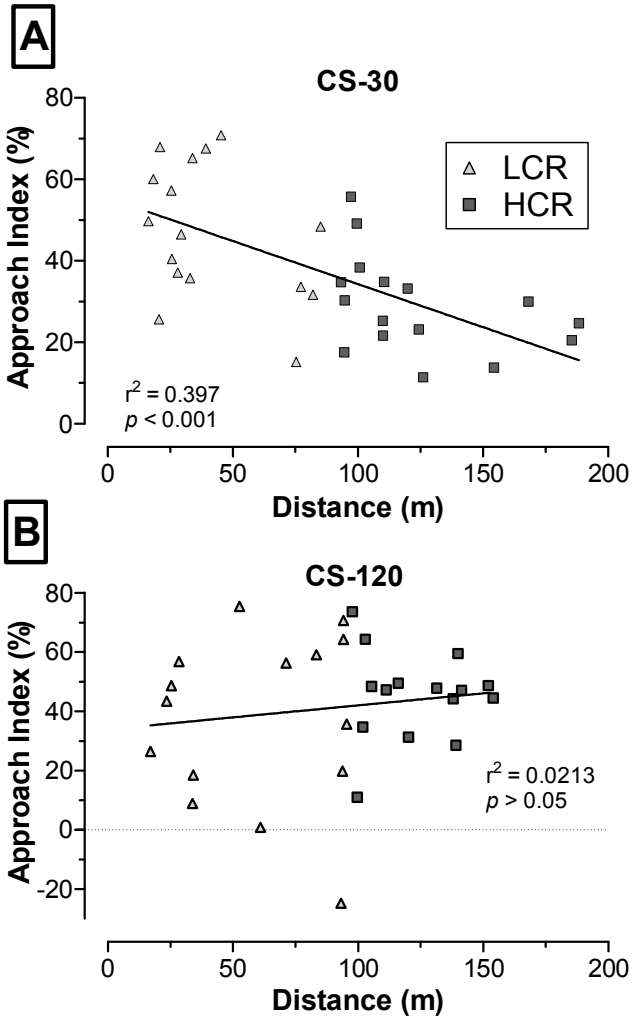

Figure 3: Relationship between cocaine-induced locomotor activity (first 30 min post-injection) and Pavlovian approach behavior during the last training session for rats trained with a 30-sec (CS-30; n = 32) or 120-sec CS (CS-120; n = 28). Statistical analysis revealed that the slope of the regression line was significantly different from zero in the CS-30 group ($F_{1,32} = 19.7$, $p < 0.001$), but not in the CS-120 ($F_{1,28} = 0.61$) group.

Figure 4

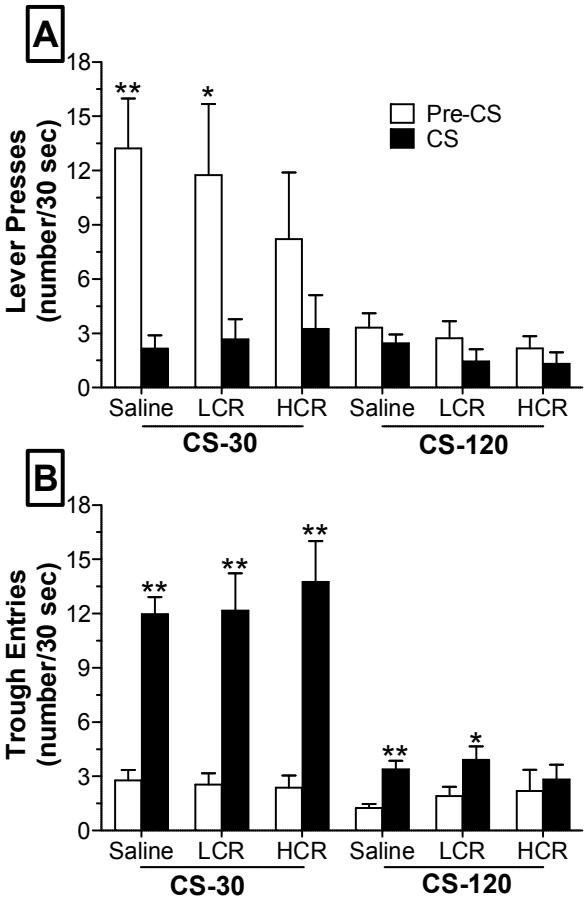

Figure 4: Activity during the PIT test (n= 6-16 rats/group). **(A)** The rate of lever pressing (number/30 sec) during the CS and pre-CS periods for the CS-30 and CS-120 groups * $p < .01$, ** $p < .001$ vs. CS within group. **(B)** The rate of trough entries (number/30 sec) during the CS and pre-CS periods for the CS-30 and CS-120 groups. ** $p < .001$, * $p < .01$ vs. pre-CS within group.

Figure 5

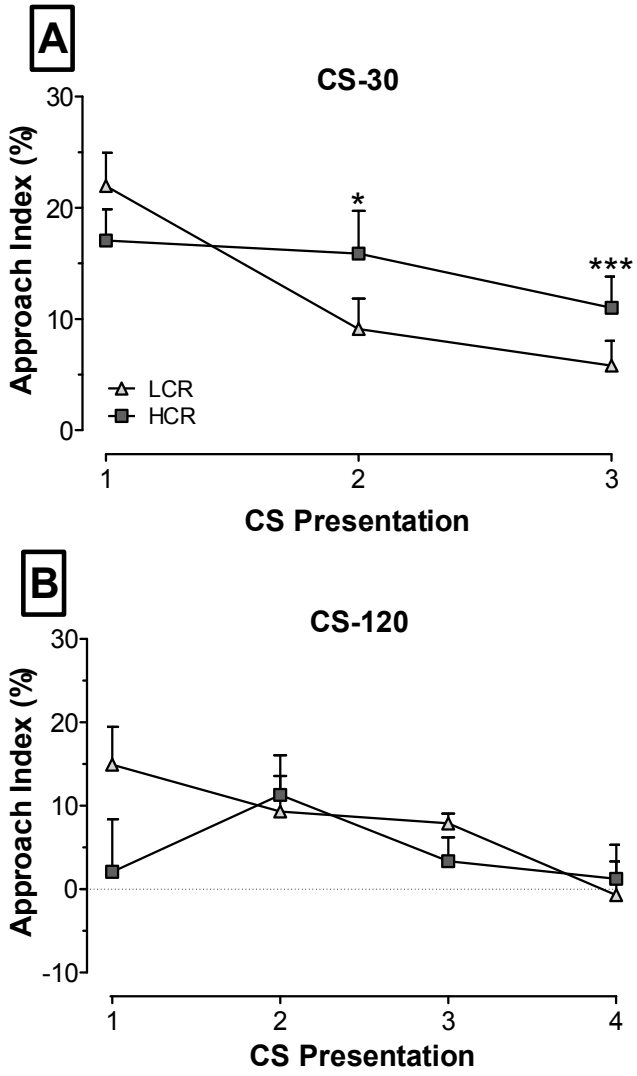

Figure 5: Approach index across PIT trials for the CS-30 **(A)** and the CS-120 **(B)** groups (n=7-8 rats/group). Performance was calculated the same as for Pavlovian approach training sessions. * $p < 0.05$ and *** $p < 0.001$ versus trial 1 with data collapsed across group.

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