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Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat

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Abstract

It has been suggested that incentive salience plays a major role in drug abuse and the development of addiction. Additionally, novelty seeking has been identified as a significant risk factor for drug abuse. However, how differences in the readiness to attribute incentive salience relate to novelty seeking and drug abuse vulnerability has not been explored. The present experiments examined how individual differences in incentive salience attribution relate to novelty seeking and acquisition of cocaine self-administration in a preclinical model. Rats were first assessed in an inescapable novelty task and a novelty place preference task (measures of novelty seeking), followed by a Pavlovian conditioned approach task for food (a measure of incentive salience attribution). Rats then were trained to self-administer cocaine (0.3 or 1.0 mg/kg/infusion) using an autoshaping procedure. The results demonstrate that animals that attributed incentive salience to a food-associated cue were higher novelty seekers and acquired cocaine self-administration more quickly at the lower dose. The results suggest that novelty-seeking behavior may be a mediator of incentive salience attribution and that incentive salience magnitude may be an indicator of drug reward.

Keywords

novelty; sign tracking; goal tracking; incentive salience; autoshaping

1. INTRODUCTION

Although many people experiment with drugs at some point in their lives, far fewer develop subsequent substance use disorders. These apparent differences in abuse vulnerability are of great interest in identifying risk factors and physiological processes that underlie drug abuse and addiction [17,22,28]. For example, impulsivity is a well-established predictor of drug self-administration in laboratory animals and is related to abuse vulnerability in humans [30]. Furthermore, individual differences in response to novelty have been repeatedly linked to drug abuse [6]. People who score higher on the Zuckerman sensation-seeking questionnaire or the Cloninger novelty-seeking questionnaire also report more frequent drug use [43,44,47] and are more sensitive to the subjective and reinforcing effects of drugs [19,20,38]. Thus, individuals categorized as high sensation or novelty seekers may be more vulnerable to drug abuse.

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In animal models of drug reward, individual differences in response to novelty have been linked to enhanced vulnerability. For example, rats that demonstrate an increased locomotor response to a novel environment show enhanced drug self-administration [15], including amphetamine [6,21,31,32] and cocaine [24]. In addition, using a large sample size, animals that show a preference for a novel environment in a novelty place preference task show enhanced self-administration of amphetamine [6]. Interestingly, although these two measures of response to novelty predict drug self-administration, they are not correlated with each other [5,6], suggesting that these two measures may be measuring different aspects of novelty seeking that are mediated by different neurobiological processes [5]. For example, elevated corticosterone secretion co-occurs with elevated locomotor responses to novelty [32], suggesting that locomotor responses to a novel environment may be mediated by a stress response.

More recently, individual differences in incentive salience attribution using animal models have been linked to drug abuse-like behavior [10,41]. The bulk of this work has focused on appetitive approach responses within a Pavlovian conditioned approach task. With this procedure, a discrete cue serves as a predictive stimulus of a subsequent biologically significant event, like food or drug infusion. For example, in the rat model, the predictive cue is often insertion of a response lever, with food following soon after. Reliable and contiguous pairings of the lever with food come to elicit appetitive responses directed at the lever, even though these responses have no consequence on the occurrence of food (i.e., food follows lever insertion whether or not an animal responds on the lever). These appetitive responses directed at the lever are referred to as sign tracking [4]. With sign tracking, stimulus incentive properties are measured through appetitive approach and contact with the lever *without* establishing a contingency between responses and reward, helping to separate Pavlovian from operant influences on responding [10].

When a lever predicts food, some animals approach the lever, while others react to the insertion of the lever by approaching the receptacle into which the food is dispensed. Animals that approach the lever are referred to as sign trackers and those that approach the receptacle are called goal trackers [3]. These individual differences in sign/goal tracking have been linked to abuse-like behavior [10,41], with sign trackers exhibiting increased cocaine-induced locomotor sensitization [12] and greater susceptibility to relapse in the cue-induced reinstatement model compared to goal trackers [36]. Sign trackers also share some overlap with neurobiological changes known to accompany repeated drug exposure, such as decreased dopamine transporter (DAT) expression and dopamine D2 receptor mRNA [12], as well as elevated corticosterone levels [10,42].

Although the relationship between individual differences in sign tracking and drug use is becoming increasingly clear, their relationship to existing predictors of vulnerability is largely unknown. In the only study that explicitly explored the relationship between impulsivity and sign tracking, Tomie and colleagues [39] demonstrated that choices for a smaller, sooner reward in an impulsive choice task were correlated with elevated sign tracking responses. Additionally, there is tangential genetic evidence of a relationship between impulsivity and sign tracking, as Lewis rats, a strain shown to be relatively impulsive [1,23], exhibit elevated sign tracking compared to Fischer rats [18]. Also, Flagel and colleagues [11] reported that rats selectively bred to be high responders in an inescapable novel environment were more likely to be sign trackers and exhibited elevated behavioral disinhibition in an impulsive action task.

There is little information on the relationship between individual differences in sign tracking and response to novelty among outbred rats. To date, the only studies that have investigated this relationship demonstrated that individual differences in locomotor responding within an inescapable novel environment were uncorrelated with sign tracking [35]. However, those studies did not assess novelty seeking in a free-choice preference test. Thus, the purpose of the

current study was to determine if novelty place preference would serve as a useful predictor of sign tracking and whether sign tracking would serve as a useful predictor of cocaine self-administration.

2. METHODS AND MATERIALS

2.1. Animals

Twenty-four adult male Sprague Dawley rats (Harlan Inc., Indianapolis, IN), weighing 250-275 g at the beginning of experimentation were housed individually in a temperature and humidity controlled environment with a 14:10 hr light/dark cycle (lights on at 0600 hr). All experimentation was conducted during the light phase. The rats were first acclimated to the colony environment and handled daily for one week prior to experimentation. Following acclimation, rats were food deprived to 85% of their free-feeding weights and sufficient food was given post-session to maintain this weight percentage. All experimental protocols were in accordance with the 1996 NIH *Guide for the Care and Use of Laboratory Animals* and were approved the Institutional Animal Care and Use Committee at the University of Kentucky.

2.2. Apparatus

Locomotor activity was measured using the Digiscan and Versamax activity monitoring systems (AccuScan Instruments, Columbus, OH, USA). Twelve clear Plexiglass chambers (42 × 42 × 30 cm) incorporated a horizontal 16 × 16 grid of photo beam sensors spaced 2.5 cm apart and 7.0 cm above the chamber floor. Locomotor activity was measured and recorded using Digipro and Versamax System software (v. 1.40, AccuScan Instruments) operated by a PC. Activity was recorded as photo beam breaks and expressed as total distance traveled (cm).

Novelty place preference was conducted in conditioned place preference chambers (MED-CPP-RS, MED Associates) enclosed within sound-attenuating compartments (ENV-018M, MED Associates). Each chamber contained 3 compartments: two 28-cm long compartments (one black with steel rod flooring and one white with wire mesh flooring) separated by one 12-cm long compartment (gray with smooth plastic flooring). All compartments were separated by manual guillotine doors and illuminated with white incandescent lights.

Sign tracking and cocaine self-administration experiments were conducted within operant conditioning chambers (ENV-008, MED Associates, St. Albans, VT,) that were enclosed within sound-attenuating compartments (ENV-018M, MED Associates). Each chamber was connected to a personal computer interface (SG-502, MED Associates), and all chambers were operated using MED-PC™. Within each chamber, a 5 × 4.2 cm recessed food receptacle was located on the response panel of the chamber, 2 retractable response levers were mounted on either side of the food receptacle (7.3 cm above metal rod floor), and a 28 V, 3-cm diameter, white cue light was mounted 6 cm above each response lever. Food pellets (45-mg Noyes Precision Pellets; Research Diets, Inc., New Brunswick, NJ) were delivered via a dispenser (ENV-203, MED Associates). Drug infusions (0.1 ml over 5.9 sec) were administered via a syringe pump (PHM-100, MED Associates) through a water-tight swivel attached to a 10 ml syringe via tygon tubing that was attached to a head-mounted cannula.

2.3. Drugs

Cocaine HCl was acquired from the National Institute on Drug Abuse (Bethesda, MD) and mixed in sterile saline (0.9% NaCl).

2.4. Locomotor activity in an inescapable novel environment

Following a one-week acclimation period, 24 rats were placed within locomotor activity monitoring chambers for a 30-min period. During this period, total distance traveled was recorded.

2.5. Novelty place preference

Novelty place preference proceeded according to the methods described in Cain et al. [6]. One day following locomotor testing, the same 24 rats were habituated to either the black or white place preference compartment (counterbalanced across individuals) for 30 min across 2 consecutive days. On the third day, rats were placed in the central, gray compartment and allowed free access to all place preference compartments for 15 min. The percentage of time spent in the novel and familiar (habituated) compartments was recorded. A preference ratio was calculated as the time in the novel compartment divided by the time spent in both the novel and familiar compartments; the ratio was then multiplied by 100 to calculate a preference percentage score.

2.7. Pavlovian conditioned approach

The day after novelty place preference testing, the same 24 animals were trained under a Pavlovian conditioned approach task carried out according to the procedure described in Flagel et al. [12], with few alterations. Briefly, animals were shaped initially to retrieve food pellets from the receptacle for two consecutive days. During Pavlovian training, a response lever (lever side was counterbalanced across individuals) was inserted into the chamber for 8 s, and following lever retraction, a food pellet was non-contingently delivered into the receptacle. Lever insertion trials were spaced by a 90-s variable time schedule that began immediately after pellet delivery. Each session consisted of 25 lever insertion trials, and rats were trained for 5 consecutive sessions. Sign-tracking responses were recorded as lever presses, while goal-tracking responses were recorded as breaks of a photo beam inserted within the food receptacle. Sign tracking and goal tracking were expressed as the percentage of trials on which at least one sign- or goal-tracking response occurred over the 5 sessions of training.

2.8. Cocaine self-administration

Approximately 3 days following Pavlovian conditioned approach training, the same 24 rats were anesthetized (100 mg/kg ketamine and 5 mg/kg diazepam, i.p.), and while under anesthesia, catheters were implanted into the right jugular vein and exited through a dental acrylic head mount that was affixed to the skull via jeweler screws. After a one-week post-surgery recovery period, one group of rats ($n = 12$) was trained to acquire cocaine self-administration at a low unit dose (0.3 mg/kg/infusion) according to a modified drug autoshaping procedure described by Carroll and Lac [8], which measures acquisition of drug reinforced responding without a prior history of operant training. This autoshaping procedure was chosen because it is sensitive to individual differences in acquisition [29], and thus might be expected to differentiate between sign and goal trackers. A second group of rats ($n = 12$) was trained with a high unit dose of cocaine (1.0 mg/kg/infusion), using the same autoshaping method. Training consisted of two 1-hr sessions each day over 7 consecutive days. During the first session, the active lever (assigned as the lever opposite to that used in Pavlovian training) was extended for 15 s; following the retraction of the active lever, a non-contingent infusion of cocaine was delivered, or if animals responded on the lever while it was inserted the infusion was delivered immediately. The inactive lever (i.e., responses had no programmed consequence) was extended throughout the session. During the first 15 min of this session, animals received 10 active lever-cocaine infusion pairings, while only the inactive lever was extended during the final 45 min. Following a 1-hr rest period spent in the home cage, rats were returned to the operant chambers for an additional 1-hr session of cocaine self-

administration on an FR 1 schedule of reinforcement. Responses on the active and inactive lever were recorded during both daily cocaine sessions.

2.9. Analysis

Correlations were calculated using Pearson's r ($\alpha = 0.05$). Acquisition of sign and goal tracking responses was determined using one-way ANOVA, with session as a within subject factor; post hoc tests were conducted using Tukey HSD. The impact of sign tracking on the acquisition of cocaine self-administration was determined using linear mixed-effects modeling [46], with FR1 cocaine self-administration session as a continuous within-subject variable and sign tracking score (i.e., percentage of trials on which at least one sign-tracking response occurred over the 5 training sessions) as a continuous between-subject variable. Given that each variable in the linear mixed-effects analyses was specified as a continuous variable, they each have a single degree of freedom.

3.0. RESULTS

3.1. Relations among response to novelty, sign tracking and goal tracking

Figure 1 illustrates the relationship between sign tracking and goal tracking collapsed across sessions (panel A), as well as the acquisition of each response as a function of training session (panels B and C). Sign-tracking behavior significantly increased with training ($F(4, 92) = 34.64, p < 0.01$; panel B); post hoc comparisons revealed that sign tracking during sessions 2-5 was significantly higher than that during session 1. Goal-tracking behavior also changed significantly with training ($F(4, 92) = 3.63, p < 0.01$; panel C); post hoc comparisons revealed that goal-tracking behavior during session 5 was significantly lower than that during sessions 2 and 3. In addition, when sign tracking and goal tracking were averaged for each rat across the 5 days of training, there was a significant negative correlation between sign tracking and goal tracking ($r = -0.77, p < 0.01$; panel A).

Figure 2 illustrates the relationship between locomotor responding in an inescapable novel environment and novelty place preference (panel A), as well as the relationship between sign tracking and either locomotor activity in a novel environment (panel B) or novelty place preference (panel C). Locomotor activity in a novel environment was negatively correlated with novelty place preference ($r = -0.59, p < 0.01$; panel A). In addition, while locomotor activity in a novel environment was unrelated to sign tracking ($r = -0.05, \text{NS}$; panel B), novelty preference was significantly correlated with sign tracking ($r = 0.59, p < 0.01$; panel C).

3.2. Sign tracking and acquisition of cocaine self-administration at a low unit dose (0.3 mg/kg/infusion)

Due to faulty head mounts, 2 animals were dropped from the experiment, leaving a total of 10 animals. There were no significant correlations between sign tracking and active ($r = 0.47, \text{NS}$) or inactive ($r = 0.15, \text{NS}$) responding over the 7 cocaine autoshaping sessions (results not shown). However, there was a significant relationship between sign tracking and the average number of cocaine infusions (0.3 mg/kg/infusion) earned across the 7 FR1 response-contingent sessions during acquisition ($r = 0.75, p < 0.01$; top panel of Figure 3). Interestingly, consistent with the increase in sign tracking with continued training, sign-tracking responses from the 1st training day were unrelated to infusions earned, while sign tracking responses from the final training day were significantly correlated with infusions earned (see Table 1). To further probe this relationship, linear mixed-effects modeling was used to analyze the impact of sign tracking on cocaine infusions earned over the course of the 7 FR1 sessions. Linear mixed-effects analysis revealed that animals earned more cocaine infusions as a function of session ($F(1, 58) = 14.14, p < 0.01$) and they earned more cocaine infusions as a function of sign tracking ($F(1,$

8) = 10.43, $p < 0.01$), but the change in cocaine infusions across sessions was not affected by sign tracking ($F(1, 58) = 0.08$, $p > 0.05$).

To determine if the increase in cocaine infusions earned during FR1 acquisition was due to a simple psychomotor effect of cocaine or response generalization from previous Pavlovian conditioned approach training, the impact of session and sign tracking on inactive lever pressing was also investigated. There was no relationship between sign tracking and inactive lever presses collapsed across the 7 FR1 sessions ($r = -0.03$, NS; bottom panel of Figure 3). Furthermore, linear mixed-effects analysis revealed that inactive lever pressing did not change across session ($F(1, 58) = 0.32$, $p > 0.05$), inactive lever pressing did not change as a function of sign tracking ($F(1, 8) = 1.77$, $p > 0.05$), and inactive lever pressing over the course of acquisition was not affected by sign tracking ($F(1, 58) = 2.25$, $p > 0.05$).

Finally, there was no significant relationship between locomotor activity in a novel environment and 0.3 mg/kg cocaine infusions earned across the 7 FR1 sessions during acquisition (see Table 1). However, the relationship between novelty place preference and infusions earned tended toward significance (see Table 1).

3.3. Sign tracking and acquisition of cocaine self-administration at a high unit dose (1.0 mg/kg/infusion)

Due to a faulty head mount, 1 animal was dropped from the experiment, leaving a total of 11 animals. There were no significant correlations between sign tracking and either active ($r = 0.43$, NS) or inactive ($r = 0.11$, NS) responding over the course of the 7 cocaine autoshaping sessions (results not shown). Further, there was also no significant relationship between sign tracking and average number of cocaine infusions earned across 7 FR1 sessions during acquisition at the 1.0 mg/kg/infusion unit dose ($r = .11$, NS; top panel of Figure 4), nor was there a relationship between sign tracking from the 1st or 5th training session and infusions earned (see Table 1). A linear mixed-effects analysis of the impact of sign tracking on cocaine infusions earned over the course of the 7 FR1 sessions revealed a trend toward more cocaine infusions earned as a function of session ($F(1, 64) = 2.82$, $p = 0.09$); cocaine infusions earned were not affected by sign tracking ($F(1, 9) = 0.27$, $p > 0.05$), and cocaine infusions earned across sessions were not affected by sign tracking ($F(1, 64) = 0.22$, $p > 0.05$).

The bottom panel of Figure 4 illustrates the relationship between sign tracking and average inactive lever presses earned across the 7 FR1 sessions using the higher unit dose (1.0 mg/kg/infusion). There was no relationship between sign tracking and inactive lever presses ($r = 0.12$, NS). Furthermore, linear mixed-effects analysis revealed that inactive lever pressing did not change across session ($F(1, 64) = 0.64$, $p > 0.05$), inactive lever pressing did not change as a function of sign tracking ($F(1, 9) = 0.15$, $p > 0.05$), and inactive lever pressing over the course of acquisition was not affected by sign tracking ($F(1, 64) = 0.03$, $p > 0.05$).

Finally, there was no significant relationship between novelty place preference or locomotor activity in a novel environment and 1.0 mg/kg cocaine infusions collapsed across the 7 FR1 sessions during acquisition (see Table 1).

4. DISCUSSION

The present study investigated how individual differences in sign tracking relate to novelty seeking, a well-established risk factor for drug abuse in humans. The results suggest that sign tracking is related to novelty seeking, as measured by novelty place preference, and that animals exhibiting more sign tracking behavior also self-administer more cocaine during acquisition. Thus, sign tracking appears to predict vulnerability to initiate drug use in rats, and this may be mediated by its relationship to novelty seeking.

Although both inescapable novelty and novelty preference are thought to reflect novelty seeking, unlike novelty preference [27], responses to inescapable novelty have been shown to elevate corticosterone levels, suggesting that this response is associated with activation of the stress axis. Tomie et al. [42] demonstrated that sign tracking also elevates corticosterone, and Flagel et al. [10] demonstrated that this elevation is evident after a single training session. Hence, based on their common ability to increase corticosterone, it might be expected that sign tracking and activity in inescapable novelty would be related. However, the present results show that sign tracking was unrelated to locomotor activity in an inescapable novel environment, which replicates the finding of Robinson and Flagel [35]. Thus, although they both may be stress-related, sign tracking and locomotor activity in an inescapable environment are not isomorphic measures.

There have been mixed findings in the literature about the relation between locomotor activity in inescapable novelty and free-choice novelty place preference. Although there is evidence to suggest that animals with an elevated locomotor response to inescapable novelty also prefer novel environments [9,16], this relationship has not always been replicated [7,21]. In the present study, there was a significant negative relationship between these measures, consistent with the results of Cain et al. [7].

The lack of a relationship between locomotor activity in inescapable novelty and cocaine infusions during acquisition contrasts with previous literature [7,21,31,32,33]. With few exceptions [6], the vast majority of experiments investigating individual differences in response to novelty have relied on a categorical split procedure. The pitfalls of the median split are well known [26]. For example, using a large sample, Cain et al. [6] demonstrated that locomotor activity in a novel environment is normally distributed, suggesting that a median split may not be the most appropriate analytic method. When these scores were regressed onto amphetamine self-administration, Cain et al. [6] found a weak relationship at a single ratio value, leaving open the possibility that previous effects reported with median splits may depend on placing a small number of animals into discrete binomial categories. When we divided animals into 'high' and 'low' responders to inescapable novelty based on a median split, a one-way ANOVA revealed that 'low' responders earned significantly more cocaine infusions over the 7 FR 1 cocaine self-administration sessions at the 0.3 mg/kg dose ($F(1, 68) = 7.24, p < 0.01$), and there were no differences between the groups at the 1.0 mg/kg dose ($F(1, 75) = 0.18, p > 0.05$). There are a number of procedural differences between the present study and previous studies that may account for this discrepancy. For example, previous studies pretrained lever pressing for food pellets on FR schedules prior to self-administration training and then subsequently elevated the fixed ratio requirement during self-administration acquisition. In contrast, the present study pretrained rats in a Pavlovian, not operant, food task, followed by an acquisition procedure in which daily autoshaping and response-contingent FR1 training sessions occurred in sequence on each of 7 days. The active lever was opposite to the stimulus used as the Pavlovian conditioned stimulus during both autoshaping and FR1 training sessions. Thus, in the current experiment, operant acquisition occurred only during cocaine self-administration using a continuous reinforcement schedule, and this procedure may be less sensitive to individual differences in inescapable novelty.

Recently, Saunders and Robinson [36] demonstrated that there were no differences in acquisition of cocaine self-administration between animals that exhibited primarily sign tracking or goal tracking behavior during Pavlovian approach training. The current results using a low unit dose of cocaine (0.3 mg/kg/infusion) contrast with this previous report; however, there are a number of procedural differences between studies. In particular, Saunders and Robinson [36] used nose pokes rather lever presses as the operant response during cocaine acquisition and it is likely that the topography of the operant response affected intake. For example, Goeders et al. [13] demonstrated that escalation of sucrose intake does not occur in

mice when using a nose-poke operant response but is robust when using a lever-press response. Thus, the nose-poke response could hinder the detection of differences between sign trackers and goal trackers. Furthermore, the unit dose used by Saunders and Robinson was relatively high (0.5 mg/kg/infusion) and delivered over a short duration (1.6 sec). Schindler et al. [37] demonstrated that 0.3 mg/kg/infusion of cocaine delivered over 1.7 s yielded rapid acquisition of cocaine self-administration using the nose poke operant response. The majority of past research on individual differences in drug use vulnerability has demonstrated differences primarily using low unit doses [6,7,21,25], presumably because higher doses are well above reward thresholds for all animals and consequently may obscure individual differences. Thus, the 0.5 mg/kg/infusion dose of cocaine delivered over 1.6 s in Saunders and Robinson [36] could have yielded a reinforcing stimulus similar to the 1.0 mg/kg/infusion dose delivered over 5.9 s in the present experiment, negating any individual differences during acquisition. Perhaps most important, sessions in Saunders and Robinson [36] were bound by the number of infusions earned, not by time. This was designed to match the number of infusions delivered across groups and thereby control for differences in acquisition. Finally, as mentioned previously, Saunders and Robinson [36] did not utilize the drug autoshaping procedure described here. Thus, these various procedural differences could contribute to the discrepancy in results.

At present, the underlying neural mechanisms that govern sign tracking and goal tracking are largely unknown. Like drug reward, the mesocorticolimbic dopamine (DA) system seems to be critically involved in the individual differences governing sign tracking and goal tracking. Flagel et al., [12] reported that sign trackers have reduced mRNA expression for DA transporter and tyrosine hydroxylase in the ventral tegmental area (VTA), and reduced D2 receptor mRNA in the nucleus accumbens (Nac). Tomie et al. [42] reported elevated DA and 3,4-dihydroxyphenylacetic acid (DOPAC) tissue levels in the Nac of animals that demonstrated elevated sign tracking. These results suggest that sign trackers have elevated DA turnover in the mesolimbic DA system and this enhanced turnover results in a downregulation of accumbal D2 receptors. In addition, individual differences in activity in an inescapable novel environment and novelty preference are both mediated by mesolimbic DA [2,14,15]. Furthermore, animals selectively bred for high locomotor activity in an inescapable novel environment show elevated sign tracking to both a food- and cocaine-associated cues, as well as elevated striatal DA tone and more phasic DA release in the Nac core [11]. Moreover, the increased phasic DA release in sign trackers could be related to the observed increased excitation of DA neurons in the Nac core during approach to the novel side during novelty place preference [34,45]. This relationship suggests that the overlap between novelty place preference and sign tracking observed here may be mediated by differences in DA tone in the Nac core and may be suggestive of differential sensitivity to conditioned reinforcement. Indeed, food-associated cues during Pavlovian approach serve as conditioned reinforcers only in sign trackers [35].

In conclusion, individual differences in incentive salience attribution are proving to be important risk factors for drug use vulnerability. As shown in the present study, animals that attribute incentive salience to a food-associated cue are more vulnerable to the initiation of cocaine use. Furthermore, there is also recent evidence to suggest that animals that attribute incentive salience to a food-associated cue are also more vulnerable to relapse of cocaine seeking behavior [36]. Further research is necessary to determine if individual differences in incentive salience are also related to the maintenance of drug use and the escalation of drug intake that characterizes addiction.

Research Highlights

- Novelty preference was negatively related to activity in a novel environment
- Sign tracking was positively related to novelty preference

- Sign tracking was unrelated to activity in a novel environment
- Sign tracking predicted acquisition of cocaine self-administration at a low dose

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Fig 1.

A.) Relationship between sign tracking and goal tracking during conditioned Pavlovian approach. Data are expressed as the percentage of trials on which a sign tracking or goal tracking response occurred averaged over all 5 training sessions. B.) Sign tracking as a function of training session. C.) Goal tracking as a function of training session. Asterisk (*) represents significant difference from session 1 for sign tracking and session 5 for goal tracking at $p < .05$; $n = 24$.

Fig 2.

A.) Relationship between locomotor activity in an inescapable novel environment and novelty place preference. B.) Relationship between sign tracking and locomotor activity in an inescapable novel environment. C.) Relationship between sign tracking and novelty preference. Locomotor activity is presented as the total distance traveled, measured in centimeters; novelty place preference is measured as the percentage of time spent in the novel environment during the novelty place preference task; sign tracking is presented as the percentage of trials on which a sign tracking response occurred; NS = not significant; $n = 24$.

Fig 3.

Top panel: Relationship between sign tracking and cocaine infusions during acquisition of cocaine self-administration at a low dose (0.3 mg/kg/infusion). Sign tracking responses are presented as the percentage of trials on which a sign-tracking response occurred and cocaine infusions are expressed as the average number of infusions earned over the 7 days of FR1 acquisition. *Bottom panel:* Relationship between sign tracking responses and inactive lever presses during acquisition of cocaine self-administration at a low dose (0.3 mg/kg/infusion). Sign tracking responses are presented as the percentage of trials on which a sign tracking response occurred and inactive lever presses are expressed as the average number of responses emitted over the 7 days of FR1 acquisition. NS = not significant; $n = 10$.

Fig 4.

Top panel: Relationship between sign tracking and cocaine infusions during acquisition of cocaine self-administration at a high dose (1.0 mg/kg/infusion). Sign tracking responses are presented as the percentage of trials on which a sign tracking response occurred and cocaine infusions are expressed as the average number of infusions earned over the 7 days of FR1 acquisition. *Bottom panel:* Relationship between sign tracking responses and inactive lever presses during acquisition of cocaine self-administration at a high dose (1.0 mg/kg/infusion). Sign tracking responses are presented as the percentage of trials on which a sign tracking response occurred and inactive lever presses are expressed as the average number of responses emitted over the 7 days of FR1 acquisition. NS = not significant; $n = 11$.

Table 1

Correlation analysis of average sign tracking (ST) percentage from the 1st and 5th training session and average cocaine infusions earned during FR1 acquisition (0.3 and 1.0 mg/kg); correlation analysis of average novelty place preference (NPP) percentage and average cocaine infusions earned during FR1 acquisition (0.3 and 1.0 mg/kg); and correlation analysis of average total distance traveled in locomotor (LOCO) and average cocaine infusions earned during FR1 acquisition (0.3 and 1.0 mg/kg)

Comparison	R-value	R ² -value	p-value
ST-Cocaine (0.3 mg/kg - Session 1)	0.44	0.19	NS
ST-Cocaine (0.3 mg/kg - Session 5)	0.64	0.41	$p < .05^*$
ST-Cocaine (1.0 mg/kg - Session 1)	0.44	0.19	NS
ST-Cocaine (1.0 mg/kg - Session 5)	0.28	0.08	NS
NPP-Cocaine (0.3 mg/kg)	0.58	0.33	$p = .07$
NPP-Cocaine (1.0 mg/kg)	0.26	0.07	NS
LOCO-Cocaine (0.3 mg/kg)	-0.30	0.09	NS
LOCO-Cocaine (1.0 mg/kg)	0.09	0.01	NS

NS = not significant

* Asterisk = $p < .05$