2011

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Published in final edited form as:
Behav Brain Res. 2011 April 15; 218(2): 341–345. doi:10.1016/j.bbr.2010.11.048.

Sign- vs. goal-tracking in a feature positive discrimination task with nicotine: Importance of spatial location of the conditional stimulus

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Abstract

We assessed whether sign-tracking developed along with goal-tracking in a Pavlovian drug discrimination task. Rats had nicotine sessions intermixed with saline sessions. For nicotine sessions, 15-sec illumination of a light near (Experiment 1) or far (Experiment 2) from the dipper receptacle was followed by sucrose. Saline sessions were similar except sucrose was withheld. Regardless of location, the light evoked goal-tracking only on nicotine sessions. Only rats with the light near the dipper developed sign-tracking.

Keywords

appetitive learning; classical conditioning; goal-tracking; interoceptive stimulus; occasion setting; Pavlovian drug discrimination; rats; sign-tracking; smoking; tobacco

The interoceptive effects of a drug can come to acquire control of behavior. For drugs of abuse, this acquired control by an interoceptive drug state is thought to contribute to the tenacity of addictions [e.g., (Bevins & Murray, in press; Porter & Prus, 2009; Stolerman, 1997)]. Of interest in the present report are the interoceptive effects of nicotine, the primary addictive constituent of tobacco [for recent reviews see (Smith & Stolerman, 2009; Wooters et al., 2009)]. Research in our laboratory has shown that interoceptive stimulus effects of nicotine can serve as a positive feature that disambiguates when a cue light conditional stimulus (CS) will be paired with a sucrose unconditional stimulus (US) (Palmatier et al., 2004; Palmatier et al., 2005; Palmatier & Bevins, 2007, 2008). That is, when nicotine was administered to the rat, offset of a 15-sec cue light CS was followed by 4-sec access to sucrose; no sucrose followed the CS when saline was administered. Conditioning was evidenced by increased dipper entries [goal-tracking (Boakes, 1977; Farwell and Ayres, 1979)] during the light CS only on nicotine sessions. In this case, the nicotine stimulus is said to facilitate or modulate responding evoked by the light CS.

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Localized stimuli such as the cue light used in this earlier drug discrimination research may also come to evoke approach and contact to itself [i.e., sign-tracking; Brown & Jenkins (1968)]. In fact, Palmatier and Bevins (2007, 2008) speculated that a sign-tracking conditioned response (CR) had developed alongside the goal-tracking CR. Unfortunately, the apparatus used in these earlier studies on nicotine as a Pavlovian positive feature (Palmatier et al, 2004; Palmatier et al., 2005; Palmatier & Bevins, 2007, 2008) did not allow measures of approach to the incandescent cue light CS mounted on the same wall as the dipper receptacle. In Experiment 1 of the present report, we modified the apparatus to include nose-poke holes that had a yellow liquid emitting diode (LED) mounted inside and could detect nose entries with an infrared emitter/detector unit. This modification allowed us to investigate whether approach to a light CS (i.e., sign-tracking) developed concurrently with the goal-tracking CR when the nicotine stimulus disambiguated when illumination of the nose-poke LED juxtaposed to the dipper receptacle was paired with sucrose. Assessing whether sign-tracking CR evoked by the light CS can also be modulated by the interoceptive effect of nicotine, the addictive constituent in tobacco, is of interest given the increasing focus on sign-tracking as a pro-addictive behavioral phenotype (e.g., Flagel et al., 2009; Tomie, 1995; see Discussion).

In Experiment 1, there were 10 adult male Sprague-Dawley rats obtained from Harlan (Indianapolis, IN, USA). Rats were housed individually in clear polycarbonate cages lined with wood shavings in a temperature- and humidity-controlled colony. Water was continuously available in the home cage. Daily access to chow was restricted such that rats were maintained at 85% of free-feeding body weights. All sessions were conducted during the light portion of a 12 hour light:dark cycle. Protocols were approved by the University of Nebraska-Lincoln Animal Care and Use Committee and followed the `Guide for the Care and Use of Laboratory Animals' (National Research Council, 1996). Before the start of the current experiment, rats were used in a cocaine and novel-object place conditioning experiment; they had 4 or 5 exposures to 7.5 mg/kg cocaine and 4 exposures to novel objects (10 min each).

Four conditioning chambers (ENV-008CT; Med Associates, Inc., St. Albans, VT, USA) measuring 30.5 × 24.1 × 21 cm (l × w × h) were used in this study. Sidewalls were aluminum; the ceiling and front and back walls were clear polycarbonate. Each chamber was equipped with a recessed receptacle (5.2 × 5.2 × 3.8 cm; l × w × d) on one sidewall. A dipper arm raised a 0.1-ml cup of solution into the receptacle. An infrared emitter/detector unit, 1.2 cm into the receptacle and 3 cm from the chamber floor, monitored head entries into the dipper. The nose-poke hole (2.5 cm in diameter) had a yellow LED mounted inside and was mounted on the aluminum sidewall with the dipper receptacle, 5.4 cm from the floor of the chamber and 2.5 cm from the back wall (hereby termed `Near Light CS'). Entry into the nose-poke hole was detected by an infrared beam 0.6 cm into the hole. Each chamber was enclosed in a light- and sound-attenuating cubicle fitted with a fan to provide airflow. A computer with Med Associates interface and software (Med-PC for Windows, version IV) timed sessions, controlled stimulus events (sucrose and CS presentations), and recorded interruptions of the infrared beams for dipper-entries and nose-pokes.

Rats in Experiment 1 were injected subcutaneously (SC) with 1 ml/kg (−)-nicotine hydrogen tartrate (0.4 mg base/kg; pH adjusted to 7.0±0.2 with NaOH; Sigma, St. Louis, MO USA) or 0.9% saline 5 min before placement in the conditioning chamber. On nicotine sessions, the offset of each of eight 15-sec Near Light CS presentations was followed by 4-sec access to sucrose (26% w/v). Intermixed saline sessions were similar except CS offset was not followed by sucrose. All sessions lasted 20 min and timing of sucrose deliveries was varied by using four different computer programs that changed when stimulus events occurred. Comparable programs were written for saline sessions except sucrose was not delivered. The

average time before onset of the first CS was 135 sec (range=90 to 180 sec) with an average of 124 sec between CS offset the next CS onset (range=79 to 169 sec). Acquisition training consisted of 8-day cycles, each including 4 nicotine and 4 saline sessions. Nicotine and saline sessions were intermixed in a unique order for each rat with the restriction that no more than two of the same session type occurred in a row and that all programs were used within the 8-day cycle. Rats received 20 nicotine and 20 saline sessions before an extinction probe was given to assess nicotine modulation of responding in the absence of the US. For this probe, nicotine was administered 5 min before placement in the chamber for a 20-min session. There were 8 presentations of the light CS, however, sucrose was withheld, thus providing a measure of nicotine modulation of responding across an entire session in the absence of the US. The day following extinction, rats resumed the same procedures as described in acquisition for 10 nicotine and 10 saline sessions.

The primary dependent measure of conditioning was the mean elevation score of the 8 trials per session. An elevation score was defined as the number of dipper-entries (or nose-pokes) during the 15-sec CS minus the entries (or pokes) in the 15-sec interval immediately before CS onset (pre-CS period). The elevation score was used because it controls for individual differences in baseline levels of responding, it is a widely used measure in related Pavlovian conditioning research, and it allows for comparison with our previously published research on modulation of conditioned responding by drug features (Bevins et al., 2006; Palmatier et al., 2004, 2005; Reichel et al., 2007; Palmatier & Bevins, 2007, 2008). For the extinction probe, we averaged the elevation scores for the 8 light CS presentations into four 2 trials blocks. Elevation scores from conditioning were analyzed using separate two-way repeated measures analysis of variance (ANOVA) with Drug (nicotine or saline) and Session as the within-subject factors. Results from the extinction probe were analyzed using a one-way repeated measure ANOVA. Pair-wise comparisons prompted by the omnibus ANOVA used Fisher's least significant difference (LSD) tests. Statistical significance was declared at $p < 0.05$.

Figures 1A and 1B show the mean elevation scores for dipper entries and nose pokes, respectively, for Experiment 1 (see Table 1 for pre-CS and CS values for first and last session of each phase). When the light CS was located on the front wall just to the side of the dipper receptacle, the discrimination was readily acquired whether goal-tracking (dipper-entries) or sign-tracking (nose-pokes) was used as the measure of conditioning. For dipper entries, there was a main effect of Drug, $F(1,9)=15.41$, $p=0.003$, and Session, $F(19,171)=6.47$, $p<0.001$. The Drug × Session interaction was also significant, $F(19,171)=7.80$, $p<0.001$, indicating increased dipper-entries during the light on later nicotine sessions (Figure 1A). Post-hoc comparisons revealed that elevation scores were significantly different on sessions 4 through 20 ($LSD_{mmd}=0.892$). For nose-pokes, there was a main effect of Drug, $F(1,9)=25.94$, $p=0.001$, and Session, $F(19,171)=3.38$, $p<0.001$. The Drug × Session interaction was also significant, $F(19,171)=6.40$, $p<0.001$, indicating increased nose-pokes during the light on later nicotine sessions (Figure 1B). Post-hoc comparisons revealed that elevation scores were significantly different on sessions 4 and 6 through 20 ($LSD_{mmd}=0.733$).

For the extinction probe, the ANOVA was significant for dipper-entries, $F(3,27)=4.51$, $p=0.011$; the third trial block was significantly lower than the first block ($LSD_{mmd}=1.393$). The ANOVA on the extinction probe was not significant for nose-pokes, $F(3,27)=2.16$, $p=0.116$. In the re-training phase, there was a significant main effect of Drug for dipper entries, $F(1,9)=16.77$, $p=0.003$, indicating more dipper-entries evoked during the CS on nicotine than saline sessions (Figure 1A). There was no main effect of Session or a Drug × Session interaction, $Fs<1$. For nose-pokes, there was a main effect of Drug, $F(1,9)=27.35$, $p=0.001$, denoting more sign-tracking on nicotine than saline sessions (Figure 1B). There

was also a main effect of Session, $F(1,9)=2.63$, $p=0.01$, but not a Drug × Session interaction, $F(9,81)=1.77$, $p=0.086$.

In Experiment 1, sign-tracking developed alongside goal-tracking to the Near Light CS that was paired with sucrose only when the nicotine stimulus was present. That is, nicotine served as a feature positive modulator that facilitates a sign-tracking, as well as a goal-tracking CR. Both response types persisted in the extinction probe, yet the tendency for a decrease across repeated non-reinforced tests of the light CS suggests some sensitivity to the absence of the US. Overall, the findings from Experiment 1 support the speculations of past researchers that sign-tracking (what they described as `checking behavior') was likely occurring to their visual CS (Farwell & Ayres, 1979; Palmatier & Bevins, 2007, 2008). The finding from Experiment 1 also extends previous research by Troisi and Akins (2004) on drug modulation of sign-tracking to a new drug (nicotine) and a new species (rat). In that study by Troisi and Akins, a set of male Japanese quail had introduction of a wood block serve as a CS for access to a sexually receptive female (i.e., the US) only when administered cocaine. On saline sessions, the wood block CS was presented but there was no access to a female. They found that relative to the saline sessions, quail increased approach and time near the wood block CS (i.e., sign-tracking) on cocaine sessions. Thus, cocaine served as positive drug feature facilitating sign-tracking to the CS (see also [Parker et al., 1994] for related sign-tracking research with pigeons).

Notably, in Experiment 1 the 15-sec illumination of the Near Light CS shared temporal contiguity with the US (i.e., sucrose delivered immediately upon its offset), as well as spatial contiguity (i.e., LED located next to the dipper). Both spatial and temporal contiguity are considered important for conditioning and degrading one can adversely affect learning (Pavlov, 1927). Indeed, Silva et al. (1998) found that a sign-tracking CR in rats varied with spatial and temporal proximity of the lever CS (inserted into chamber for 4 sec) to delivery of food pellets. Whether a similar effect will be seen with nicotine as the drug feature modulating responding to the CS is unclear especially considering that nicotine can enhance learning, memory, and attention (Besheer & Bevins, 2004). Accordingly, in Experiment 2, we sought to investigate whether the same degree of approach to the nose-poke light would develop if we degraded spatial contiguity, while maintaining the temporal contiguity. To do so, illumination of a nose-poke hole in the rear of the chamber (i.e., wall opposite the sucrose receptacle) served as the CS (Far Light CS) in the initial training phase.

For Experiment 2, the pre-experimental treatment of a different set of rats (n=6), as well as materials, drug preparations, etc. were the same as Experiment 1 unless otherwise noted. Initial training and the extinction probe proceeded as described in Experiment 1 except that the CS was the Far Light CS. The day following extinction, rats resumed the same discrimination training procedures for 10 nicotine and 10 saline sessions except that the CS was switched from the Far Light CS to the Near Light CS.

Figures 2A and 2B show the mean elevation scores for dipper-entries and nose-pokes, respectively, for Experiment 2 (see Table 1 for pre-CS and CS values). Rats that had the light CS located on the back wall acquired the discrimination as measured by dipper-entries, but not as indexed by nose-pokes. For dipper-entries, there was a main effect of Drug, $F(1,5)=24.69$, $p=0.004$, and Session, $F(19,95)=3.71$, $p<0.001$. The Drug × Session interaction was also significant, $F(19,95)=3.97$, $p<0.001$, indicating increased dipper-entries during the light on later nicotine sessions (Figure 2A). Post-hoc comparisons revealed that elevation scores were significantly different on sessions 6 through 20 ($LSD_{mmd}=1.527$). For nose-pokes, there was a main effect of Session, $F(19,95)=2.72$, $p=0.001$, and a main effect of Drug, $F(1,5)=22.53$, $p=0.005$. The main effect of drug denoted a slight but consistent tendency for more nose-poking to the light CS on non-reinforced saline sessions (marginal

mean = 0.199±0.037) than nicotine sessions (0.063±0.028). The Drug × Session Interaction was not significant, F=1.36 (Figure 2B). For the extinction probe, the ANOVA was not significant for dipper entries or nose-pokes, Fs≤1.52, p≥0.25.

When the CS was switched to the Near Light CS, the goal-tracking CR evoked by the CS in nicotine sessions was maintained [a significant main effect of Drug, F(1,5)=17.80, p=0.008; Figure 2A]. There was no main effect of Session or Drug × Session interaction, Fs<1. Although nose-pokes appeared to increase slightly when the light CS was moved next to the dipper, the main effect of Drug, F(1,5)=5.78, p=0.061, did not meet the cutoff for significance. The main effect of Session and the Drug × Session interaction were not significant, Fs≤1.03 (Figure 2B).

If the CS was 30.5 cm away from the dipper receptacle, then a nose-poke CR like that seen in Experiment 1 did not develop. Moving the location of the CS from the Far to the Near Light CS position slightly increased the average number of nose-pokes on nicotine session; that level was not significantly different from saline sessions. These findings indicate the importance of spatial location on nicotine modulation of a sign-tracking CR, and extend this conclusion to a very different task and set of procedures than that of Silva et al. (1998). In the Silva et al. studies, they found that a `far' CS did not control sign-tracking (lever contact) when the `far' CS was the more temporally contiguous stimulus. Interestingly, that `far' CS did control sign-tracking when a separate `near' CS intervened between the presentation of the `far' lever CS and the delivery of the food pellet (i.e., temporal proximity degraded). Although having the light CS away from the site of US delivery affected the development of a sign-tracking CR, it did not appear to affect goal-tracking. The discrimination was readily acquired in Experiment 2 with the light CS located on the opposite side of the chamber evoking a robust goal-tracking CR on nicotine sessions; a CR that persisted on the extinction probe.

There has been a recent increase in interest in sign-tracking in the field of drug addiction. For instance, some theories of addiction draw explicit parallels between sign-tracking and addictive behaviors and suggest that a better understanding of sign-tracking CRs imbued by pairing exteroceptive stimuli with drugs of abuse will further our understanding of addiction processes (e.g., Flagel et al., 2009; Krank, 2003; Tomie, 1995; Tomie et al., 2008). Along these lines, Flagel et al. (2008) screened rats for their tendency to develop a sign-tracking CR versus a goal-tracking CR to a CS paired with food. A greater tendency to sign-track was related to an increased sensitivity to the locomotor sensitization effects of repeated administration of cocaine. The authors' proposed that this relation may reflect an enhanced sensitivity of this sign-tracking phenotype to attribute conditioned appetitive value to reward-associated stimuli (see also Flagel et al., 2009). This literature suggests that there may be systematic individual difference in the present report. For example, perhaps rats that goal-track do not necessarily sign-track, or at least show a blunted sign-tracking CR. We did not find much support for this suggestion in Experiment 1. For example, a majority of rats (7 of 10) had stable discrimination performance when using both the sign-tracking and the goal-tracking measure. Of the remaining three rats, one acquired only a sign tracking CR, one acquired only a goal-tracking CR, and one did not display either CR consistently. Further, a Pearson correlation indicated that there was no relation between the magnitude of the two response types on the last day of the acquisition phase, r=0.033, p=0.929, or the last day of the re-training phase, r=−0.029, p=0.937, in Experiment 1. This outcome suggests that a robust sign-tracking CR does not necessarily preclude a strong goal-tracking CR, or vice versa, in this task. Whether a similar outcome would occur with inbred or outbred strains of rats more or less likely to express a sign-tracking phenotype will be of interest in future research.

Acknowledgments

We thank Matthew Palmatier for his thoughtful comments on earlier versions of this manuscript. We would also like to thank Ayako Masuda for her help with the rats during the study. The research and R.A. Bevins were supported by United States Public Health Service Grant DA018114. All MED-PC programs used in the present article are available upon request.

The research and R.A. Bevins were supported by United States Public Health Service Grant DA018114.

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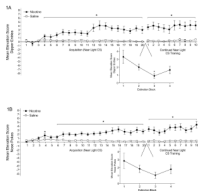

Figure 1.
Experiment 1: Panel A shows the mean (±1 SEM) dipper-entry elevation scores during acquisition, the extinction probe (small inset graph), and continued Near Light CS training. Panel B shows the mean (±1 SEM) nose-poke elevation scores during acquisition, the extinction test (small inset graph), and continued Near Light CS training. * denotes a significant difference ($p<0.05$) from saline. + denotes a significant difference from the first extinction block.

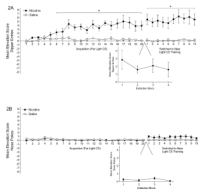

Figure 2.
Experiment 2: Panel A shows the mean (±1 SEM) dipper-entry elevation scores during acquisition, the extinction probe (small inset graph), and the switch to Near Light CS training. Panel B shows the mean (±1 SEM) nose-poke elevation scores during acquisition, the extinction probe (small inset graph), and the switch to Near Light CS training. * denotes a significant difference ($p<0.05$) from saline.

Table 1

Mean (±1 SEM) pre-CS and CS values for select sessions

Experiment 1	**Acquisition Session**		**Continued Training Session**	
Dipper Entries	1	20	1	10
pre-CS nicotine	1.93 (±0.21)	2.45 (±0.39)	1.61 (± 0.28)	2.08 (± 0.28)
CS nicotine	2.16 (±0.45)	5.44 (±0.95)	5.30 (±0.81)	6.21 (±1.17)
pre-CS saline	1.94 (±0.19)	0.73 (±0.13)	0.70 (±0.14)	0.36 (±0.12)
CS saline	2.14 (±0.30)	0.79 (±0.10)	1.05 (±0.15)	0.91 (±0.14)
Nose Pokes				
pre-CS nicotine	0.01 (±0.01)	0.58 (±0.16)	0.35 (±0.15)	0.96 (±0.26)
CS nicotine	0.09 (±0.04)	3.25 (±0.67)	3.64 (±0.63)	5.35 (±0.88)
pre-CS saline	0.04 (±0.02)	0.11 (±0.04)	0.04 (±0.03)	0.08 (±0.08)
CS saline	0.45 (±0.08)	0.30 (±0.09)	0.33 (±0.11)	0.41 (±0.13)

Experiment 2	**Acquisition Session**		**Switch to Near Light CS**	
Dipper Entries	1	20	1	10
pre-CS nicotine	1.94 (±0.37)	2.17 (±0.22)	1.81 (±0.31)	1.94 (±0.22)
CS nicotine	1.85 (±0.40)	6.06 (±1.01)	7.33 (±1.39)	7.46 (±1.65)
pre-CS saline	1.58 (±0.20)	1.06 (±0.17)	0.83 (±0.20)	0.79 (±0.27)
CS saline	1.42 (±0.22)	1.23 (±0.17)	1.10 (±0.23)	0.98 (±0.39)
Nose Pokes				
pre-CS nicotine	0.06 (±0.06)	0.13 (±0.06)	0.10 (±0.06)	0.21 (±0.15)
CS nicotine	0.02 (±0.02)	0.08 (±0.04)	1.06 (±0.41)	0.69 (±0.30)
pre-CS saline	0.00 (±0.00)	0.00 (±0.00)	0.06 (±0.03)	0.06 (±0.04)
CS saline	0.42 (±0.10)	0.08 (±0.04)	0.15 (±0.10)	0.06 (±0.03)