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Research report

# Sign-tracking predicts increased choice of cocaine over food in rats

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## HIGHLIGHTS

- Sign-trackers compared to goal-trackers had a higher preference for cocaine over food.
- Sign-tracking is the first known behavioral predictor of increased cocaine choice in rats.
- Results provide further evidence sign-tracking is a biobehavioral marker for addiction proneness.

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## ABSTRACT

The purpose of this study was to determine whether the tendency to sign-track to a food cue was predictive of rats' choice of cocaine over food. First, rats were trained on a procedure where insertion of a retractable lever was paired with food. A sub-group of rats – sign-trackers – primarily approached and contacted the lever, while another sub-group – goal-trackers – approached the site of food delivery. Rats were then trained on a choice task where they could choose between an infusion of cocaine (1.0 mg/kg) and a food pellet (45 mg). Sign-trackers chose cocaine over food significantly more often than did goal-trackers. These results support the incentive-salience theory of addiction and add to a growing number of studies which suggest that sign-trackers may model an addiction-prone phenotype.



## 1. Introduction

Sign-tracking – also called autoshaping or Pavlovian conditioned approach – describes animals' approach and contact behavior directed toward a conditioned stimulus (CS) that has been paired with an appetitive unconditioned stimulus (US; for reviews, see [1,2]). For example, when insertion of a retractable lever precedes delivery of a food pellet, rats often come to bite, gnaw, and touch the lever (e.g., [3,4]). Importantly, these lever-directed behaviors occur even though delivery of food is not dependent on them – the conditioning procedure is a purely Pavlovian one. Rats will even touch the lever when doing so results in the omission of food [5,6]. That sign-tracking occurs despite being unnecessary for the receipt of food has led to the suggestion that it is a form of maladaptive cue-focused behavior [7]. Given the central role that drug cues play in addiction, it has been hypothesized that sign-tracking importantly contributes to the disorder [7–11].

There are large individual differences in the extent to which subjects engage in sign-tracking [12–18]. Some rats approach the location of reward delivery (e.g., the food receptacle) during presentation of the CS rather than approaching and contacting the CS itself. These rats are called goal-trackers (GTs) instead of sign-trackers (STs). It has been argued that STs approach the cue predictive of reward because they attribute incentive salience to the cue itself, while GTs do not [12,16]. According to the incentive-salience theory of addiction [19–21], an increased tendency to attribute incentive salience to cues is a characteristic of individuals prone to addiction. Thus, in animal models, STs should show greater addiction-like behavior than GTs.

Recent experiments have shown that STs do in fact engage in many addiction-like behaviors to a greater extent than do GTs. For example, STs work harder than GTs for cocaine on a progressive ratio schedule [22]. STs also display more cocaine seeking than GTs despite electric footshock punishment, when "goaded" by a cocaine cue [62]. STs display more cue- and cocaine-induced reinstatement than GTs [22–24]. Cocaine cues elicit more approach behavior in STs than in GTs and also serve as more effective conditioned reinforcers [14,15,24]. Tomie et al. [25] have also found that sign-tracking is associated with increased alcohol drinking. Contrasting this trend, Saunders et al. [26] recently found that GTs demonstrate greater

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contextual renewal of cocaine seeking than STs. With the exception of their response to contextual cues, these studies show that STs generally display more addiction-like behaviors than GTs on a variety of measures.

It has been argued that a critical symptom of addiction is the choice of the drug over non-drug alternatives [27,28]. A growing number of rat studies have recently appeared that have modeled this behavior by having rats make mutually exclusive choices between drug and a non-drug alternative reinforcer (e.g., [29–36]). To date, there are no known behavioral predictors of increased choice of the drug over the non-drug alternative. The goal of the present experiment was to determine whether a predisposition to sign-track to a food cue would predict increased choice of the drug. That is, would STs be more inclined than GTs to choose cocaine over food? Such an outcome would further cement the case for STs being a model of an addiction-prone phenotype.

## 2. Materials and methods

### 2.1. Subjects

Twenty-one adult male Long-Evans rats were initially screened for ST vs. GT behavior. Five rats eventually dropped out of the experiment due to non-patent catheters. Rats were individually housed in plastic cages with wood-chip bedding and metal wire tops. They were maintained at 85% of their free-feeding weights (approximately 300–400 g) throughout the experiment by feeding them approximately 15–20 g of rat chow following training sessions. Rats had unlimited access to water in their home cages. The colony room where the rats were housed had a 12-h light:dark cycle with lights on at 08:00 h. Training sessions were conducted 5–7 days per week during the light phase of the light:dark cycle. Throughout the experiment, rats were treated in accordance with the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 2011) and all procedures were approved by American University's Institutional Animal Care and Use Committee (IACUC).

### 2.2. Apparatus

Training took place in 10 Med-Associates (St. Albans, VT) or Coulbourn Instruments (Whitehall Township, PA) modular test chambers (30.5 cm × 24 cm × 29 cm and 30 cm × 25.5 cm × 29 cm, respectively) enclosed in sound attenuation chests. Each chamber had aluminum front and rear walls, a grid floor, and two clear plexiglass side walls. Two Med-Associates retractable levers (model ENV-112CM) were positioned 5 cm from the floor and located on the front wall of the chamber, equidistant from the center where a food trough was located. A photobeam horizontally spanned the food trough opening and would record a nosepoke if the rat inserted its nose 1.0 cm into the trough. Tone (4000 Hz and 70 dB) and white noise (65 dB) stimuli were delivered through a speaker mounted on top of the chamber. A shielded 100-mA houselight mounted to the ceiling at the front of the chamber was used to signal the start and end of sessions. Two 100-mA cue lights were also mounted to the front wall, located approximately 10 cm above the floor and directly above each lever. Experimental events were controlled by a Med-Associates computer system located in an adjacent room.

Cocaine (National Institute on Drug Abuse) in a saline solution at a concentration of 2.56 mg/ml was infused at a rate of 3.19 ml/min by 10-ml syringes driven by Med-Associates syringe pumps located outside of the sound attenuation chests. Tygon tubing extended from the 10-ml syringes to a 22-gauge rodent single-channel fluid swivel and tether apparatus (Alice King Chatham Medical Arts, Hawthorne, CA) that descended through the ceiling of the chamber. Cocaine was delivered to the subject through Tygon tubing that passed through the metal spring of the tether apparatus. This metal spring was attached to a plastic screw cemented to the rat's head to reduce tension on the catheter.

### 2.3. Procedure

#### 2.3.1. Phase 1: screening for ST vs. GT behavior

Rats were screened for ST vs. GT behavior using an autoshaping procedure previously developed by others [22]. Each training session in this phase began with the illumination of the houselight. Rats were first habituated to pellet delivery (45-mg dustless precision grain pellet, Bio-serv, New Brunswick, NJ) for two sessions, in the absence of predictive stimuli. During these sessions, 50 pellets were delivered according to a variable-time (VT) 90-s schedule (sessions lasted approximately 75 min). Next, autoshaping training began. The left lever was used as a CS, with lever insertion signaling impending delivery of the food pellet US. Each autoshaping trial consisted of insertion of the lever CS for 8 s, then simultaneous lever retraction and pellet delivery. Trials were separated by inter-trial intervals lasting 60 s on average (range: 30–90 s). There were 25 trials per each session (sessions lasted approximately 25 min), with five such sessions making up the screening phase [22]. The behavior of interest during the 8-s CS periods was lever deflections, used as a measure of sign-tracking (i.e., CS contact). Nosepoking in the food trough was taken as a measure of goal-tracking (i.e., contacting the site of US delivery). The Pavlovian Conditioned Approach (PCA) index [22] was used to assess the degree to which a rat engaged in ST vs. GT behavior. The PCA index is the average of three ratios: (1) the probability of a lever contact vs. nosepoke being made on a trial, (2) the ratio of lever contacts vs. nosepokes made in a session, (3) the ratio of average latency to lever contact vs. average latency to nosepoke in a session. As each of these ratios yields a value between −1.0 (exclusively GT behavior) and +1.0 (exclusively ST behavior), the average of these ratios yielded for each rat on each session a value between −1.0 (all GT behavior, every trial) and +1.0 (all ST behavior, every trial). The average of the last two sessions was used as the final PCA score for each rat. Rats that predominantly sign-tracked (i.e., positive PCA scores) were defined as STs, while rats that predominantly goal-tracked (i.e., negative PCA scores) were defined as GTs.

#### 2.3.2. Surgery

Following ST vs. GT screening, all rats were surgically prepared with chronic indwelling jugular vein catheters, using a modification of the procedure originally developed by Weeks [63] and described in detail elsewhere [35]. Rats were given 5–7 days to recovery from surgery. Catheters were flushed daily with 0.1 ml of a saline solution containing 1.25 μg/ml heparin and 0.08 mg/ml gentamycin.

#### 2.3.3. Phase 2: operant response acquisition

For half of the rats, the left lever was the cocaine lever and the right lever was the food lever. For the other half, this arrangement was reversed. This was done to ensure that previous autoshaping experience did not have carry-over effects which systematically enhanced response acquisition with either reinforcer. To further ensure that both responses would be similarly acquired, only one lever was inserted into the chamber per session, with the lever inserted alternating over sessions (i.e., cocaine or food lever). The start of each session was signaled by illumination of the houselight and insertion of the designated lever. A response on the food lever was reinforced with a food pellet (45-mg grain pellet, see Phase 1) and a response on the cocaine lever was reinforced with a 1.0 mg/kg cocaine infusion. The selected cocaine dose was based on previous studies from this lab [35,36]. A press on either lever also initiated a 10-s time-out (TO) period signaled by a distinct audiovisual cue.