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Research report

Individual differences in the attribution of incentive salience to a reward-related cue: Influence on cocaine sensitization

Shelly B. Flagel [a,*], Stanley J. Watson [a], Huda Akil [a], Terry E. Robinson [b]

[a] *Molecular and Behavioral Neuroscience Institute, The University of Michigan, 205 Zina Pitcher Place, Ann Arbor, MI 48109, United States*
[b] *Department of Psychology, The University of Michigan, 525 E. University, Ann Arbor, MI 48109, United States*

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Abstract

When a discrete cue (a "sign") is presented repeatedly in anticipation of a food reward the cue can become imbued with incentive salience, leading some animals to approach and engage it, a phenomenon known as "sign-tracking" (the animals are sign-trackers; STs). In contrast, other animals do not approach the cue, but upon cue presentation go to the location where food will be delivered (the goal). These animals are known as goal-trackers (GTs). It has been hypothesized that individuals who attribute excessive incentive salience to reward-related cues may be especially vulnerable to develop compulsive behavioral disorders, including addiction. We were interested, therefore, in whether individual differences in the propensity to sign-track are associated with differences in responsivity to cocaine. Using an autoshaping procedure in which lever (conditioned stimulus) presentation was immediately followed by the response-independent delivery of a food pellet (unconditioned stimulus), rats were first characterized as STs or GTs and subsequently studied for the acute psychomotor response to cocaine and the propensity for cocaine-induced psychomotor sensitization. We found that GTs were more sensitive than STs to the acute locomotor activating effects of cocaine, but STs showed a greater propensity for psychomotor sensitization upon repeated treatment. These data suggest that individual differences in the tendency to attribute incentive salience to a discrete reward-related cue, and to approach and engage it, are associated with susceptibility to a form of cocaine-induced plasticity that may contribute to the development of addiction.

Keywords: Cocaine; Sensitization; Addiction; Stereotypy; Locomotion; Sign-tracking; Goal-tracking; Individual differences; Autoshaping; Pavlovian learning

1. Introduction

When a discrete cue (conditioned stimulus, CS) is repeatedly presented in anticipation of a food reward (unconditioned stimulus, US) many different conditioned responses (CR) emerge, including changes in emotional and motivational states that are manifested by complex changes in behavior. Zener (1937) first described individual differences in complex skeletal CRs in dogs trained using a classic Pavlovian conditioning procedure (i.e., a bell paired with food reward). He reported that some dogs responded to the CS with "an initial glance at the bell" followed by "a constant fixation. . .to the food-pan . . .", whereas a few dogs exhibited a "small but definite movement of approach toward the conditioned stimulus . . . followed by a backing up later to a position to eat", a sequence described by Zener as a "striking phenomenon" [56, p. 391]. These two different CRs to a food-related CS were later characterized in rats by Boakes (1977), who called CS-elicited approach to the cue "sign-tracking" (note that the procedure is sometimes called "autoshaping") and CS-elicited approach to the location where the food would be delivered "goal-tracking" [5]. In rats the sign-tracking response not only consists of approach, but often includes a repertoire of behaviors similar to those involved in consuming the US [16,31]. For example, if presentation of a lever is followed by the *response-independent* delivery of a food pellet, animals not only begin to approach the lever but often grasp and gnaw the lever [30,50]. Whether an individual develops a sign-tracking CR or a goal-tracking CR may reflect individual differences in the degree to which incentive salience is attributed to the reward-associated cue.

Incentive salience refers to a motivational component of reward, one that "transforms mere sensory information about rewards and their cues (sights, sounds, and smells) into attractive, desired, riveting incentives" [4, p. 510]. That is, incentive

* Corresponding author. Tel.: +1 734 615 2995; fax: +1 734 647 4130.
E-mail address: sflagel@umich.edu (S.B. Flagel).

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stimuli become "motivational magnets" [3], eliciting approach towards them, as in the case of Pavlovian conditioned approach behavior towards rewards and their signals [12]. Reward-related cues in the environment not only guide and energize normal behavior, but can also lead to pathological and apparently compulsive behavior [23,50]. Thus, the way individuals respond to signals associated with rewards may confer vulnerability to psychopathology, such as substance abuse.

We recently reported that sign-trackers (STs) and goal-trackers (GTs) show different experience-dependent changes in dopaminergic gene expression [27] and others have implicated the dopamine system in sign-tracking behavior. For example, Tomie et al. [51] reported increased levels of dopamine and DOPAC in the nucleus accumbens of STs and found a positive correlation between accumbens dopamine levels and the vigor with which rats engaged the cue. In addition, Dalley et al. [15] demonstrated that dopamine D1 receptors in the nucleus accumbens are necessary for the acquisition of a sign-tracking response and Phillips et al. [40], using electrical brain-stimulation as the US, reported disruption of sign-tracking following the administration of neuroleptic drugs. Finally, it is well known that the presentation of reward-related cues alters the activity of dopamine and striatal neurons [for review see 17]. Taken together, these studies highlight the involvement of the mesolimbic dopamine system in the emergence of Pavlovian conditioned approach behavior. We hypothesized, therefore, that individual differences in the propensity to sign-track may also be related to differences in responsivity to drugs that increase dopamine neurotransmission, such as cocaine. Thus, in the current study we investigated both the acute psychomotor response to cocaine and the ability of repeated injections of cocaine to induce psychomotor sensitization in STs and GTs.

2. Methods

2.1. Subjects

Forty-two adult male Sprague–Dawley rats from Charles River (Wilmington, MA, USA) weighing 250–300 g upon arrival were used. Rats were housed in pairs and kept on a 12-h light/12-h dark cycle (lights on 06:00 h) with controlled temperature and humidity. Food and water were available ad libitum throughout the study. The experiments followed the "Principles of Laboratory Animal Care" (http://www.nap.edu/readingroom/books/labrats/) and the "Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National Research Council 2003), and the procedures were approved by the University Committee on the Use and Care of Animals.

2.2. Pavlovian conditioned approach

2.2.1. Conditioning chambers

Fifteen MED Associates test chambers (21.6 cm × 17.8 cm floor area, 12.7 cm high; MED Associates, St. Albans, VT) were used for Pavlovian training. Each chamber was equipped with a food receptacle, which was located in the center of the 21.6-cm-wide wall, 3 cm above the stainless steel grid floor. An illuminated retractable lever (Med Associates) was located approximately 2.5 cm to the left or right of the food receptacle, 3 cm above the floor. The side of the lever with respect to the food receptacle was counter-balanced across boxes to eliminate any side bias. A red house light was located on the wall opposite the food receptacle and remained on throughout the training sessions. Two nose-poke ports were located approximately 3 cm above the grid floor on either side of the house light. Responses in the nose-poke ports were without consequence and served as an index of general exploratory behavior. A white LED was flush-mounted on the inside of the retractable lever and could be used to illuminate the slot through which the lever protruded. The lever required only a 10-gram force to operate, such that most contacts with the lever were recorded as a "lever press." Operation of the pellet dispenser (Med Associates) delivered one 45-mg banana-flavored food pellet (Bio-Serv®, #F0059, Frenchtown, NJ) into the food receptacle. Head entry into the food receptacle was recorded each time a rat broke the infrared photobeam located inside the receptacle (approximately 1.5 cm above the base of the food cup). Each conditioning chamber was located in a sound-attenuating enclosure and white noise was supplied by a ventilating fan to mask outside noise.

2.2.2. Pavlovian conditioning procedures

All training sessions were conducted between the hours of 13:00 and 17:00. Three waves of rats (14 animals per wave) were tested per day. For 2 days prior to the start of training 45-mg banana-flavored food pellets were placed into the rats' home cages to familiarize the animals with this food. After 1 week of acclimation to the colony room rats were placed into the testing chambers for pre-training sessions during which the red house-light remained on but the lever was retracted. Fifty food pellets were delivered on a variable interval (VI) 90-s schedule, and it was determined whether the rats were reliably retrieving the pellets from the food receptacle. The pre-training sessions lasted approximately 25 min. By the end of the 2nd pre-training session all of the rats consumed all of the food pellets. Thus, after 2 days of pretraining Pavlovian training commenced using procedures similar to those described previously [27]. During a Pavlovian training session each individual trial consisted of presentation of the illuminated lever (CS) into the chamber for 8 s, and immediately following retraction of the lever the pellet dispenser was activated and one 45-mg food pellet (US) was delivered into the food receptacle. The beginning of the next inter-trial interval (ITI) commenced immediately after pellet delivery. The CS was presented on a random interval 90 s schedule (i.e., one presentation of the CS occurred on average every 90 s, but the actual time between CS presentations varied randomly between 30 and 150 s). Each Pavlovian training session consisted of 25 trials, resulting in a 35–40 min session, and training was conducted over 5 consecutive days. We recorded the following events: (1) the number of lever presses, (2) the latency to the first lever press, (3) the number of receptacle entries during presentation of the CS, (4) the latency to the first receptacle entry following CS presentation, (5) the number of receptacle entries during the ITI, and (6) the number of nose-pokes (as an index of general exploratory behavior). These data were recorded using Med Associates software (St. Albans, VT). The number of food pellets consumed was also recorded following each session.

2.3. Psychomotor activating effects of cocaine

2.3.1. Activity chambers and video recording devices

In-house custom made activity chambers were used. Each chamber was made from expanded PVC (33.02 cm × 68.58 cm × 60.96 cm tall) with a stainless woven wire cloth grid floor (30.48 cm × 60.96 cm, 7.62 cm × 7.62 cm), complete with a catch tray. Directly above each activity chamber was a camera (CCTV Specialty Bullet Cameras, Lake Worth, FL) used to record behavior during the drug testing sessions. A Pelco (Clovis, CA) DX9100 digital video recorder (DVR) was used to transfer the videos to a computer for automated analysis (see below).

2.3.2. Cocaine treatment

Cocaine treatment began 1 day following the last day of Pavlovian training. Animals were transferred from the colony room and placed into the activity chambers on the 1st day of testing. Rats were allowed to habituate to the activity chambers for 45 min before they received a vehicle (0.9% saline) injection. After this, the animals received escalating doses of cocaine (7.5, 15, 30 mg/kg, i.p.). A 45-min period elapsed between injections, during which time behavior was video-recorded. After the first day of testing rats were returned to their home cages where they received 15 mg/kg cocaine once a day for 6 days. On day 7, the rats returned to the activity chambers where they again were allowed to habituate and then received escalating doses of cocaine (starting with vehicle, as on day 1). This procedure generates within-subjects dose-effect information, allowing us to compare the day 7 to the day 1 response to assess sensitization.