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The ability for cocaine and cocaine-associated cues to compete for attention

Kyle K. Pitchers*, Taylor R. Wood, Cari J. Skrzynski, Terry E. Robinson, Martin Sarter

Department of Psychology, University of Michigan, Ann Arbor, MI, USA

HIGHLIGHTS

- A classically conditioned auditory cue elicited cue-induced drug seeking in STs and GTs.
- Intermittent Access cocaine self-admin produced escalation of drug intake.
- Intermittent Access cocaine self-admin produced robust stimulus control over self-admin behavior.
- Auditory cocaine cue elicited cocaine-seeking but did not disrupt performance of a sustained attention task.
- Cocaine availability, contingent on the discriminative stimulus or non-contingently, severely disrupted attention task performance.

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ABSTRACT

In humans, reward cues, including drug cues in individuals experiencing addiction, are especially effective in biasing attention towards them, so much so they can disrupt ongoing task performance. It is not known, however, whether this happens in rats. To address this question, we developed a behavioral paradigm to assess the capacity of an auditory drug (cocaine) cue to evoke cocaine-seeking behavior, thus distracting thirsty rats from performing a well-learned sustained attention task (SAT) to obtain a water reward. First, it was determined that an auditory cocaine cue (tone-CS) reinstated drug-seeking equally in sign-trackers (STs) and goal-trackers (GTs), which otherwise vary in the propensity to attribute incentive salience to a localizable drug cue. Next, we tested the ability of an auditory cocaine cue to disrupt performance on the SAT in STs and GTs. Rats were trained to self-administer cocaine intravenously using an Intermittent Access self-administration procedure known to produce a progressive increase in motivation for cocaine, escalation of intake, and strong discriminative stimulus control over drug-seeking behavior. When presented alone, the auditory discriminative stimulus elicited cocaine-seeking behavior while rats were performing the SAT, but it was not sufficiently disruptive to impair SAT performance. In contrast, if cocaine was available in the presence of the cue, or when administered non-contingently, SAT performance was severely disrupted. We suggest that performance on a relatively automatic, stimulus-driven task, such as the basic version of the SAT used here, may be difficult to disrupt with a drug cue alone. A task that requires more top-down cognitive control may be needed.

1. Introduction

Cues that have been associated with rewards are especially efficacious in drawing attention towards them, to the extent they can disrupt ongoing task performance, and there is considerable individual variation in their ability to do so [4,25]. Indeed, even under conditions in which participants are aware that reward cues are irrelevant to the current task and should be ignored, such cues remain capable of capturing attention, distracting the individual, and consequently, impairing task performance [5,6,25]. In individuals experiencing addiction, drug cues are especially effective in attracting attention relative to other stimuli and the degree to which drug cues produce an attentional bias is predictive of their ability to induce drug craving and of the likelihood of relapse [19,31,53]. One reason reward cues may bias attention towards them is because they become attributed with incentive motivational properties (incentive salience), and as incentive stimuli they become themselves highly desired, capable of attracting indi-

* Corresponding author at: Department of Psychology, University of Michigan, East Hall, 530 Church St., Ann Arbor, Michigan, 48109, USA.
E-mail address: pitchers@umich.edu (K.K. Pitchers).

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viduals towards them and instigating reward-seeking behavior [14,40,41].

The ability of a drug cue to gain attention and thus distract an individual from attending to other stimuli necessary for successful task performance has rarely been studied in animals. One goal of the experiments reported here was to develop a procedure to study potential drug cue-induced disruption of ongoing task performance. To do this, rats were first trained to perform a sustained attention task (SAT) which requires constant monitoring of a stimulus array to report the occurrence, or non-occurrence, of a visual signal to obtain a natural reward [21,32,50]. Rats were then independently trained to self-administer cocaine using an Intermittent Access (IntA) procedure known to produce addiction-like behavior [27,60]. This procedure involves cycles of Drug Available and No-Drug Available periods, signaled by a discriminative stimulus (DS+), such that drug-seeking quickly comes under strong discriminative stimulus control. Discriminative stimuli are known to have potent motivational properties, robustly reinstating drug-seeking behavior even after long periods of abstinence [17,39,54]. Therefore, we examined the ability of the DS+ (a signal for cocaine availability) to interrupt performance on the SAT, with or without the simultaneous availability of cocaine.

There is considerable individual variation in the extent to which reward cues, including drug cues, are attributed with incentive salience [23,24,45,56,58]. Animals prone to attribute incentive salience to reward cues are called sign-trackers (STs) and those less prone to do so are called goal-trackers (GTs) (for review [41]). Furthermore, STs tend to be more prone to impulsive action than GTs, [29] and they have relatively poor attentional control, as indicated by fluctuating levels of attentional performance and attenuated cholinergic neuromodulatory mediation of performance when compared to GTs [38]. Therefore, we further asked whether a cocaine cue would influence task performance differently in STs and GTs.

2. Methods

2.1. Animals

Male Sprague-Dawley rats (Envigo, Indianapolis, IN) weighing 250-274 g upon arrival were individually housed in Plexiglas cages and kept on a 12-h light/12-h dark cycle (lights on at 0800 h) with regulated temperature and humidity. After arrival, rats were given 1 week to acclimate to the colony room before experimentation commenced. Food (Rodent Chow, Laboratory Rodent Diet 5001, LabDiet) and water were available *ad libitum* until either self-administration or SAT training began. At the start of SAT training, animals were water-deprived by restricting water access to a 15 min period after each training session. Water was also provided as a reward during task performance (see below). On days not tested, water access was increased to a total of 60 min. During task training, food was available *ad libitum*. Starting 2 days before the first day of self-administration the animals were mildly food restricted to maintain a stable body weight throughout testing [43] and water was available *ad libitum*. All procedures were approved by the University of Michigan Institutional Animal Care and Use Committee and were conducted in AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care)-accredited laboratories.

2.2. Pavlovian conditioned approach with food as the unconditioned stimulus

2.2.1. Apparatus

Med Associates test chambers (20.5 cm × 24.1 cm floor area, 29.2 cm high; Med Associates, St. Albans, VT) were used for Pavlovian training. Each chamber was equipped with a food receptacle located 2.5 cm above the floor in the center of the wall. A catch tray filled with corn-cob bedding was located underneath the floor, which was constructed from stainless steel rods. A red house light was located on the wall opposite the food receptacle and remained on for the duration of training sessions. An illuminated retractable lever (Med Associates) was located approximately 2.5 cm to the left or right of the food receptacle, 6 cm above the floor. The side of the lever with respect to the food receptacle was counter-balanced across boxes. A white LED was flush-mounted on the inside of the lever and was used to illuminate the slot through which the lever protruded. The lever required a ∼20 g force to deflect, such that most contacts with the lever were recorded as a 'lever press'. The pellet dispenser (Med Associates) delivered one 45 mg banana-flavored food pellet (Bio-Serv®, #F0059, Frenchtown, NJ) into the food receptacle at a time. 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 background noise was supplied by a ventilating fan to mask outside noise. Data collection was controlled by Med-PC software.

2.2.2. Pavlovian conditioned approach

All rats (Experiments 1 and 2) were initially trained using a Pavlovian conditioned approach (PCA) procedure described previously [24]. During a 1 week acclimation to the colony room, rats were handled regularly before training procedures commenced. All training sessions were conducted during the 12 h lights on period. Prior to the start of training, ∼20 banana-flavored food pellets were placed into the rats' home cages to familiarize the animals with this food. For pre-training, rats were placed into the test chamber with a red houselight illuminated, while the lever remained retracted throughout the entire session. Twenty-five food pellets were delivered on a variable interval (30 s) schedule to determine whether rats were reliably retrieving the pellets from the receptacle. If a rat failed to retrieve all of its food pellets, it received a second pre-training session. By the end of pre-training, all rats consumed all food pellets.

During the Pavlovian training sessions, each individual trial consisted of the insertion of the illuminated lever (CS) into the chamber for 8 s, and immediately following retraction of the lever, the pellet dispenser was activated causing the delivery of a single food pellet (unconditioned stimulus, US) into the food receptacle. The inter-trial interval (ITI) started immediately following the retraction of the lever. The CS was presented on a variable interval 90 s schedule (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 35–45 min session. Pavlovian training was conducted over 5 consecutive days. We recorded the following events for each trial: (i) number of lever deflections (contacts), (ii) latency to first lever deflection, (iii) number of head entries into the food receptacle (referred to as magazine entries) during presentation of the CS, (iv) latency to the first receptacle entry following CS presentation and (v) number of magazine entries during the ITI. All animals included in analysis consumed all food pellets during each training session. At the end of each training session the animals were returned to their home cages in the animal colony room.