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Post-training cocaine administration facilitates habit learning and requires the infralimbic cortex and dorsolateral striatum

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ABSTRACT

Human drug addiction is a complex disorder, in which exogenous substances are able to recruit and maintain behaviors involved in drug taking. Many drugs that are addictive in humans are able to act on natural brain systems for learning and memory, and while many memory systems may be affected by addictive drugs, work with operant tasks has shown that addictive drugs (e.g. cocaine and alcohol) are particularly effective in recruiting habit learning systems, compared to natural rewards. It is currently unknown if the ability of addictive drugs to facilitate habit learning depends on a direct action on habit learning systems in the brain, versus the rewarding properties of drug administration. To differentiate between these options, rats were trained to perform two actions (lever pressing), each of which was rewarded with a different natural reward. After acquiring the behavior, rats received three training sessions which were followed by post-training injections of saline or cocaine (5 or 10 mg/kg, i.p.). Using sensory-specific satiety, extinction tests revealed that lever pressing for actions which were paired with saline were sensitive to devaluation (typical of goal-directed behaviors) while actions which were paired with cocaine were not sensitive to devaluation (typical of habitual behaviors). Lesions of the infralimbic or dorsolateral striatum were able to block the action of post-training cocaine injections. These data indicate that, within individual rats, cocaine injections facilitate the transition of behavior to habitual control for actions that have been recently performed, without a general facilitation of habit learning, and that this action of cocaine requires brain areas that are critical for learning natural habits.

1. Introduction

Humans self-administer a wide variety of drugs for recreational purposes, and individuals who transition from recreational use to drug addiction incur substantial costs to both themselves and society. To better intervene in drug addiction, many research studies today focus on the mechanisms by which drugs are able to recruit and sustain self-administration. Several studies have shown that experience with addictive drugs can bias rats to use habitual behaviors (in which responses are driven by stimulus-response associations) over goal-directed behaviors (in which responses are guided by action-outcome associations, and the motivation to obtain an outcome, Dickinson, 1985). For instance, Dickinson and colleagues have shown that actions reinforced with alcohol (Dickinson, Wood, & Smith, 2002) or cocaine (Miles, Everitt, & Dickinson, 2003) become resistant to devaluation of the outcomes, an index of the development of habitual behaviors. In these same animals, actions which were reinforced with natural rewards (such as sucrose) remained sensitive to outcome devaluation, an indication that these actions were goal-directed. Similarly, a study by Gabriele, Setlow, and Packard (2009) demonstrated that in extinction training in a straight alley maze, training that had been reinforced with oral cocaine led to more habitual behavior during extinction, compared to training that had been reinforced with a sucrose solution. As proposed by White (1996), these drug effects may be produced in several ways, either through the reinforcing properties of the drugs themselves, through the action of the drugs on memory systems in the brain which support habitual behavior, or by the incentive learning effects of the drugs. Both amphetamine sensitization (Nelson & Killcross, 2006; Nordquist et al., 2007) and exposure to cocaine (LeBlanc, Maidment, & Ostlund, 2013) has been demonstrated to bias rats to perform habitually actions which were learned subsequently (in a drug free state). Similarly, alcohol dependent humans also show accelerated development of habitual behavior (Sjoerds et al., 2013). Together, these studies show that in nonhuman animals, drugs which are addictive in

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humans can selectively facilitate the transition to habitual control when behaviors are reinforced with drugs, and can more globally facilitate habit learning (or suppress goal-directed learning) after drug exposure. And, correlational studies suggest that these results may be observed in human drug dependence.

Currently, it is unclear if selective facilitation of habit learning depends on the action of drugs on the habit learning system, or in the reinforcing properties of the drug. To address this question, the present study used post-training (non-contingent) injections to test the ability of cocaine to selectively facilitate habit learning for a recently trained action, without causing a global facilitation of habit learning. Post-training injection of addictive drugs (such as cocaine and amphetamine) as well as dopaminergic agonists and antagonists can facilitate learning in a wide variety of tasks, including inhibitory avoidance (Introini-Collison & McGaugh, 1989), active avoidance (Janak, Keppel, & Martinez, 1992; Janak & Martinez, 1992), Pavlovian conditioning (Leri et al., 2013; Simon & Setlow, 2006), and win-stay learning (Leri et al., 2013), presumably by impacting post-training consolidation of learning. Rather than facilitating task acquisition, our goal was to use post-training drug administration to test the ability of cocaine to shift rats from goal-directed to habitual behavior.

2. Experiment 1

Rats were trained to perform two actions, each reinforced with a different natural reward. Once rats had acquired each behavior, post-training injections of either saline or cocaine were given immediately after each training session for three days. After training, rats were tested in extinction after devaluing one of the rewards, using sensory-specific satiety (Berridge, 1991; Rolls, Rolls, Rowe, & Sweeney, 1981), to differentiate between goal-directed and habitual behavior. In the extinction tests, actions that were paired with cocaine injections were not sensitive to devaluation of the outcome, while actions paired with saline injections remained sensitive to devaluation, indicating that post-training cocaine injections facilitated the transition to habitual lever pressing.

2.1. Methods

2.1.1. Animals

Twenty male four Sprague–Dawley rats (Harlan, Indianapolis, IN, USA, mean ad lib weight = 437 g, SD = 26 g) were used in the experiment. Rats were placed on food-restriction approximately 1 week before training began, and maintained at approximately 80% of their ad lib weight throughout the experiment. Rats were either pair-housed ($n = 4$) or individually housed ($n = 20$) in plastic cages in a vivarium (pair housing was discontinued after the initial set of four rats, in order to conduct prefeeding in the home cage for the satiety tests described below). The vivarium was on a 12:12 light/dark schedule, and rats were tested in the light phase.

2.1.2. Training

Training was conducted using a set of four standard operant chambers (Med-Associates, St. Albans, VA) controlled by a computer running Med-PC IV. Each operant chamber was equipped with a magazine for food and liquid delivery, two retractable levers (one on either side of the magazine), a stimulus light over each lever, and a house light on the chamber wall opposite the magazine and levers. Each chamber was placed in a sound-attenuating cubicle equipped with a fan for ventilation. Rats were trained to perform two actions, each in a separate chamber. To make each chamber more discriminable, two of the chambers had white backgrounds and paper in the removable tray at the bottom of the chamber. The other two chambers had a black background and cage bedding in the removable tray at the bottom of the chamber.

Behavioral training followed the procedures described by Nelson and Killcross (2006), with the following modifications. Rats were trained to perform two actions, each of which was paired with a different reinforcer. Throughout training, rats received two sessions per day, one in each type of operant chamber (described above). Training sessions were separated by several hours, and the order of training (which chamber rats began in each day) was constant throughout training. For each type of operant chamber, rats were assigned at the start of training one action (left or right lever) and one reinforcer (a 30% sucrose solution or chocolate flavored pellets). Levers, reinforcers and contexts were counterbalanced across rats.

Training began with two days of magazine training, with one session for each reinforcer (see Table 1). Magazine training sessions lasted 30 min, during which 30 reinforcers were given on a random-time 60 s schedule (RT-60 s), with the restriction that after each delivery of a reinforcer, the next random interval did not begin until the rat had made an entry into the magazine. If rats did not obtain 30 reinforcers within 30 min, the session continued for a maximum of 90 min. After the first day of training, rats typically completed magazine training in 30 min. After completing magazine training, instrumental training began with a single day of continuous reinforcement. For all instrumental training sessions, rats received 40 reinforcers in each session. At the start of each session, one lever (left or right) was extended and the stimulus light over that lever was illuminated at the same time that the house light was illuminated. Rats that failed to acquire the lever press in the first session were given additional sessions of continuous reinforcement.

Rats then received one day of random interval training on a 10 s schedule (RI-10 s). As in magazine training, after the delivery of a reinforcer, the next random interval did not begin until rats had made an entry into the magazine. After these training sessions on the RI-10 s schedule, rats received an intraperitoneal (i.p.) saline injection (1 ml/kg). Rats then completed three days of training on a RI-30 s schedule. After each training session, rats received an i.p. injection of either saline or cocaine (5 or 10 mg/kg cocaine HCl, Sigma–Aldrich, dissolved in saline, injected at volumes of 1 ml/kg) and were returned to their home cages. For half of the rats, the morning session was followed by cocaine, for the other half, the afternoon session was followed by cocaine.

After finishing the final day of training on the RI-30 s schedule, rats began extinction tests on the following day. Rats were pre-fed for one hour with one of the reinforcers. Then, rats received two 10 min extinction tests (one for each action, in the appropriate operant chamber, in the same order as the training sessions) conducted back-to-back. After the first extinction test, rats were returned to the animal colony briefly while the second extinction test was prepared. The tests were conducted in the same order as was done in acquisition: the first extinction test was conducted for the lever trained in the morning, and the second extinction test was conducted for the lever trained in the afternoon. The following day, rats were retrained in both chambers, reinforced on the RI-30 s schedule, trained in the morning and afternoon, as was done during acquisition. No injections were given following the retraining sessions. On the day after retraining, rats were pre-fed with the alternate reinforcer (not used in the first extinction test) and the extinction tests were repeated.

2.2. Results

2.2.1. Acquisition

Rats readily acquired both the lever press followed by saline injections (the Saline-paired action) and the lever press followed