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The effects of social learning on the acquisition of cocaine self-administration

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ABSTRACT

Background: Social learning models of substance use propose that drug-use behaviors are learned by observing and mimicking the behavior of others. The aim of this study was to examine the acquisition of cocaine self-administration in three groups of experimentally naïve rats: rats that were tested in isolation, rats that were tested in the presence of another rat that had access to cocaine and had previously been trained to self-administer cocaine, and rats that were tested in the presence of another rat that did not have access to cocaine.
Methods: Male rats were reared in isolated or pair-housed conditions and implanted with intravenous catheters. Pair-housed rats were then assigned to drug-experienced or drug-naïve conditions. In the drug-experienced condition, one rat of each pair was trained to self-administer cocaine in isolation before the reintroduction of its partner. In the drug-naïve condition, one rat of each pair did not have access to cocaine for the duration of the study. For each group, the acquisition of cocaine self-administration was measured over 15 days in rats with access to cocaine but no prior operant training.
Results: Rats tested with a drug-experienced partner were faster to acquire cocaine self-administration and emitted more active lever presses than rats tested with a cocaine-naïve partner. Data for the isolated control group fell between the other two groups on these measures.
Conclusion: These data indicate that the acquisition of cocaine self-administration can either be facilitated or inhibited by social contact. Collectively, these results support a social learning model of substance use.

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1. Introduction

Social learning models of substance use propose that drug use is learned, in part, by observing and mimicking the behavior of others (see reviews by Andrews and Hops, 2010; Kandel, 1986; Pandina et al., 2010). Despite the popularity of these models, very few experimental studies have examined the role of social learning in drug use, possibly due to a lack of animal models that allow subjects to observe and mimic the drug use behavior of another subject. We recently described the use of custom-built, operant conditioning chambers that permit two rats to be tested simultaneously during periods of intravenous, drug self-administration (Smith, 2012). Using these chambers, we reported that cocaine self-administration could either be increased or decreased based on the behavior of a partner. Specifically, we reported that cocaine self-administration was facilitated when a rat was paired with another rat with simultaneous access to cocaine, but cocaine self-administration was inhibited when a rat was paired with another rat without access to cocaine. Such data support a social learning model by showing that the behavior of a peer, as opposed to merely the presence of a peer, determines whether social contact increases or decreases drug self-administration.

In our previous study, all rats received lever-press training using food reinforcement before self-administration testing, and this prevented us from examining the role of social learning on the acquisition of drug self-administration. This is relevant because a rapid transition from initial drug exposure to regular patterns of use is an important prognosticator of whether an individual will later develop problems with substance use (U.S. Congress, Office of Technology Assessment, 1994). The acquisition of regular patterns of intake after initial drug exposure is often modeled in the laboratory by exposing a subject to noncontingent drug infusions and then permitting the subject to self-administer that drug during free-operant test sessions. Importantly, factors that increase the rate of acquisition in the laboratory are considered to be risk factors

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for developing problems with substance use in humans, whereas factors that decrease the rate of acquisition in the laboratory are considered to be protective against substance abuse in humans. For example, social isolation (Kosten et al., 2000) and social stress (Tidey and Miczek, 1997) reliably increase the rate of acquisition in laboratory animals and serve as risk factors in human populations (Chartier et al., 2010; Dube et al., 2006). In contrast, access to alternative, nondrug reinforcers decreases the rate of acquisition in laboratory animals (Carroll and Lac, 1993; Cosgrove et al., 2002), and access to nondrug social activities decreases the acquisition of drug and alcohol use in human adolescents (D'Amico et al., 2012; St. Pierre et al., 1992; for similar studies using the conditioned place preference procedure, see Bahi, 2013; Geuzaine and Tirelli, 2014; Ribeiro Do Couto et al., 2009). To date, the role of social learning in the acquisition of drug self-administration, at least in regard to intravenous drug self-administration, has not been examined.

The purpose of the present study was to examine the contribution of social learning to the establishment of stable patterns of drug intake after initial drug exposure. To this end, the acquisition of cocaine self-administration was examined in three groups of experimentally naïve rats: (1) rats that were tested in isolation, (2) rats that were tested in the presence of another rat that had access to cocaine and had previously been trained to self-administer cocaine (drug-experienced), and (3) rats that were tested in the presence of another rat that did not have access to cocaine (drug-naïve). Behavioral testing advanced through three stages designed to systematically increase the probability that self-administration would be acquired. In phase 1 (days 1–5), responding was reinforced with 0.25 mg/kg cocaine; in phase 2 (days 6–10), responding was reinforced with 0.75 mg/kg cocaine; and in phase 3 (days 11–15), responding was reinforced with 1.5 mg/kg cocaine. Our previous data (Smith, 2012) suggested that cocaine self-administration is enhanced in socially housed rats if both members of the pair have access to cocaine, but cocaine self-administration is inhibited if only one member of the pair has access to cocaine. Consequently, we hypothesized that the rate of acquisition would occur most rapidly in the drug-experienced group and most slowly in the drug-naïve group.

2. Methods

2.1. Animals and apparatus

Male, Long-Evans rats were obtained at weaning (~21 days) from Charles River Laboratories and assigned to isolated or pair-housed conditions. Both isolated and pair-housed rats were housed in standard laboratory cages (interior dimensions: 50 × 28 × 20 cm) until the beginning of self-administration testing. At that time, all rats were transferred to custom-built, operant conditioning chambers that served as home cages for the remainder of the study. All rats were kept in a temperature- and humidity-controlled colony room on a 12 h light/dark cycle (lights on: 0500) for the duration of the study. All animals were maintained in accordance with The Guide for Care of Laboratory Animals (Institute of Laboratory Animal Resources, 2011).

All drug self-administration sessions were conducted in custom-built, operant conditioning chambers described previously (Smith, 2012). Briefly, chambers for isolated rats were cubic in design with two response levers on the rear wall. Chambers for pair-housed rats were constructed from 2 isolated chambers separated by a 14-gauge wire-screen panel. The wire screen allowed pair-housed rats visual, auditory, olfactory, and limited tactile contact with each other, but prevented one rat from accessing the tethering system of its companion. Each rat had individual access to two response levers mounted on the rear wall. The response levers were positioned 13 cm apart and 6 cm from each sidewall. For pair-housed rats with access to cocaine, the inner lever (i.e., the lever in closest physical proximity to the partner) was designated the active lever, whereas the outer lever was designated the inactive lever. Drug infusions were delivered via Tygon tubing protected by a stainless steel spring and connected to a counter balanced swivel suspended above the chamber. An infusion pump (3.33 rpm) was mounted behind the cage and connected to interfacing equipment provided by Med Associates, Inc. (St Albans, VT, USA). Fresh food was placed inside the cages daily, and water dispensers were continuously available inside the cage.

Lever-press training for cocaine-experienced rats (see below) was conducted in standard, commercially available, operant conditioning chambers from Med Associates, Inc. These chambers were equipped with two response levers, two white stimulus lights above the response levers, a house light, and a food pellet receptacle located between the two response levers.

2.2. Group assignments

Isolated rats were housed individually and tested in individual test chambers with no visual contact with other rats. Pair-housed rats were randomly assigned to cocaine-experienced and cocaine-naïve groups approximately 5 weeks after arrival. Rats in the isolated and cocaine-naïve groups remained undisturbed in their home cage until surgery and catheter implantation.

For rats in the cocaine-experienced group, one rat of each pair (the cocaine-experienced rat) was trained to press a lever using food reinforcement. Approximately 5 weeks after arrival, these rats were food restricted to no less than 90% of their free-feeding body weight, placed in operant conditioning chambers, and trained to press a response lever on a fixed ratio (FR1) schedule of reinforcement. Training sessions lasted 2 h or until 40 reinforcers were delivered, whichever occurred first. Daily training sessions continued in this manner until a rat received the maximum number of 40 reinforcers during any 4 training sessions. Once this criterion was met, training was discontinued and the rat was placed back on unrestricted feed. The experimentally naïve partners of the cocaine-experienced rats were left undisturbed in the home cage throughout this time period.

Cocaine-experienced rats were surgically implanted with intravenous catheters 6 weeks after arrival and 5 days before their experimentally naïve partners (see below). Three days after surgery, cocaine-experienced rats were placed in custom-built, operant conditioning chambers (in isolation and without their experimentally naïve partner) during daily training sessions. Each session began with a priming infusion of cocaine, and the insertion of two retractable levers into the home cage. Each response on the inner (active) lever produced an infusion of cocaine and retraction of the lever for 20 s. All infusions, including the priming infusion, delivered 0.5 mg/kg cocaine over a duration of 2.5–3.0 s (based on body weight). Each session lasted 2 h with no limit placed on the maximum number of infusions that could be earned. Training continued in this manner for five consecutive days, at which time the cocaine-experienced rats were joined by their experimentally naïve partners during daily test sessions (see below).

Rats that lost catheter patency before the end of testing were removed from the study and not included in the statistical analysis. For socially housed rats, if one member of the pair lost catheter patency before the end of testing, then both members of the pair were removed from the study and not included in the statistical analysis. This practice led to the removal of a greater number of socially housed rats than isolated rats from the study (rats removed: $n = 1$ experimentally naïve isolated rat; $n = 5$ cocaine-experienced rats and their five experimentally naïve partners; $n = 3$ cocaine-naïve rats and their three experimentally naïve partners). A total of 62 rats completed all phases of testing ($n = 24$ experimentally naïve isolated rats; $n = 9$ cocaine-experienced rats and their 9 experimentally naïve partners; $n = 10$ cocaine-naïve rats and their 10 experimentally naïve partners). All data (e.g., % of rats meeting the acquisition criterion) reflect only those animals that completed all phases of the study.

2.3. Surgery

All rats were surgically implanted with intravenous catheters between 6 and 7 weeks after arrival. Rats were deeply anesthetized with a combination of ketamine HCl (100 mg/kg, ip) and xylazine HCl (8.0 mg/kg, ip). An intravenous catheter was implanted into the right jugular vein and exited the body via a port implanted on the dorsal surface of the scapulae. Ketoprofen (3.0 mg/kg, sc) was given immediately after surgery as an analgesic, and a solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused through the catheter daily for 7 days to maintain patency and prevent infection. After 7 days, ticarcillin was discontinued and only heparinized saline was used to maintain catheter patency. All rats were allowed to recover for 3 days before beginning acquisition testing. We employ a 3-day recovery period because general indices of health and behavioral activity (e.g., feeding, drinking, wheel running) return to pre-surgical levels within 3 days using our surgical protocol.

2.4. Acquisition of cocaine self-administration

Immediately prior to the beginning of acquisition testing, all rats were transferred to the custom-built, operant conditioning chambers, which served as home cages for the remainder of the study. All cocaine self-administration sessions began promptly at the beginning of the dark phase of the light/dark cycle (lights off: 1700).

All rats in the isolated group, all experimentally naïve rats in the cocaine-experienced group, and one member of each pair of the cocaine-naïve group were tested for the acquisition of cocaine self-administration. Each session began with the insertion of two retractable levers into the chamber and a noncontingent infusion of cocaine. During all sessions, responding was reinforced on a FR1 schedule of reinforcement. On this schedule, each response on the active (inner) lever produced an infusion of cocaine and retraction of the response lever for 20 s to signal a timeout during which cocaine was not available. For all sessions, responses on the inactive (outer) lever were recorded but had no programmed consequences. Sessions lasted

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