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Cocaine self-administration in social dyads using custom-built operant conditioning chambers

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HIGHLIGHTS

- We used custom-built chambers to assess social cocaine self-administration.
- Dyads exhibited reliable responding on fixed interval schedules with a limited hold.
- Dyadic responding became more similar across testing days.
- We characterized a preclinical model of social drug taking behavior in dyads.

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ABSTRACT

Background: Traditionally, the analysis of intravenous drug self-administration is limited to conditions in which subjects are tested in isolation. This limits the translational appeal of these studies because drug use in humans often occurs in the presence of others.
New method: We used custom-built operant conditioning chambers that allowed social dyads visual, olfactory, auditory, and limited tactile contact while concurrently self-administering cocaine. Male rats were trained to respond according to a fixed interval schedule of reinforcement (with a limited hold) in order to determine if patterns of cocaine (0.75 mg/kg/infusion) self-administration became more similar over time in social pairs. Cocaine self-administration was tested across five days according to a 10-min fixed interval schedule (with a 5-min limited hold). Quarter-life values (time at which 25% of responses were emitted per interval) were analyzed using intraclass correlations.
Results: The total number of reinforcers obtained did not vary across the five days of testing; however, quarter-life values became progressively more similar between individuals within the social dyads.
Comparison with existing methods: Standard operant conditioning chambers are unable to assess responding in multiple animals due to their small size, the need to prevent subjects from responding on the lever of their partner, and the need to prevent infusion lines from entangling. By using custom-built social operant conditioning chambers, we assessed the effects of social contact on cocaine self-administration.
Conclusion: Social operant conditioning chambers can be used as a preclinical method to examine social influences on drug self-administration under conditions that approximate human substance use.

1. Introduction

Substance use is typically modeled in laboratory animals using the drug self-administration procedure. In this procedure, operant responding is reinforced by the contingent delivery of a drug according to a schedule of reinforcement programmed by the experimenter. Most studies that employ intravenous drug self-administration (i.e., the delivery of drug to a peripheral vein) use commercially available operant conditioning chambers distributed by established manufacturers (e.g., Med Associates, Lafayette Instruments, Harvard Apparatus). These chambers allow the experimenter to record responses (e.g., lever presses) and program experimental events (e.g., drug infusions) according to a theoretically infinite number of schedule parameters. One limitation of commercially available chambers is that only one animal may be tested in a chamber at a time. This limitation is due to (1) the small size of commercially available chambers, (2) the need to prevent

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infusion lines from becoming tangled, and (3) the need to prevent one animal from pressing the response lever of another animal. This also limits the translational appeal of studies that employ intravenous drug self-administration because drug use in humans often occurs in the presence of others.

Several investigators have recently described innovative approaches to overcome this limitation by using modified operant conditioning chambers. For instance, Gipson et al. (2011) and Chen et al. (2011) examined amphetamine and nicotine self-administration, respectively, in laboratory rats using customized chambers that permitted a social partner (without access to drugs) to be present during experimental sessions. Similarly, we recently developed custom-built chambers that permit two rats to be tested in a single experimental session, with the caveat that both rats have access to drugs and data can be collected from both rats simultaneously (Smith, 2012). One novel aspect of this arrangement is that it allows for comparison of individual response patterns from each subject within a social pair. Comparisons of this nature are relevant because social learning models of substance use predict that individual patterns of drug self-administration should become progressively more similar over time within a social group (see reviews by Andrews and Hops, 2010; Kandel, 1986; Pandina et al., 2010).

Most drug self-administration studies use schedules of reinforcement that engender stable rates of responding prior to each reinforcer, interspersed with periods of non-responding after each reinforcer (e.g., fixed ratio schedules, progressive ratio schedules). Inter-subject differences in responding on these schedules are typically limited to overall rates of responding, total number of responses, and total number of reinforcers (Panlilio and Goldberg, 2007; Richardson and Roberts, 1996). In contrast, in a fixed interval (FI) schedule, the first response after a fixed period of time has elapsed is reinforced. This schedule engenders a particular pattern of responding characterized by low rates of responding early in the interval, moderate rates of responding in the middle of the interval, and high rates of responding late in the interval (Balster and Schuster, 1973; Dougherty and Pickens, 1973; Ferster and Skinner, 1957; Guilhardi and Church, 2004; Schneider, 1969). Individual response patterns on this schedule can be summarized and quantified by quarter-life values, which correspond to the time point within an interval at which one quarter of the responses occur (Herrnstein and Morse, 1957).

In the present study, we describe the use of custom-built operant conditioning chambers to examine cocaine self-administration within social dyads in which both subjects have simultaneous access to cocaine. To this end, pair-housed rats were surgically implanted with intravenous catheters and trained to self-administer cocaine on a FI schedule of reinforcement. Once training was completed, intraclass correlations were determined for each dyad using quarter-life values obtained from both rats. Unlike most other correlations (e.g., Pearson Product–Moment), intraclass correlations operate on data structured as groups rather than as paired observations. Consequently, they may be used to determine the degree to which individuals within a dyad resemble one another (Griffin and Gonzalez, 1995; Shrout and Fleiss, 1979). Intraclass correlation coefficients were determined over five consecutive days, with the prediction that responding would become progressively more similar over time within each dyad.

2. Materials and methods

2.1. Animals

Male, Long–Evans rats were obtained at weaning (~21 days) from Charles River Laboratories and immediately assigned to pair-housed conditions. Rats were housed together in standard laboratory cages (interior dimensions: 50 cm × 28 cm × 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 (see below). All rats were kept in a temperature- and humidity-controlled colony room on a normal 12-h light/dark cycle with lights on at 0500 (5:00 am) for the duration of the study. Fresh food and water were continuously available in home cages throughout the study except during lever-press training (see below). All rats were maintained in accordance with *The Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animal and Resources, 2011).

2.2. Apparatus

All drug self-administration sessions were conducted in custom-built, operant conditioning chambers specifically designed to allow visual, auditory, olfactory, and limited tactile contact for pair-housed rats (Faircloth Machine Shop, Winston-Salem, NC; see Fig. 1). Chambers were cubic in design (30 cm × 30 cm × 30 cm) and separated by a 14-gauge wire-screen panel. The wire screen restricted each subject's access to the tethering system and response lever of its partner. Each rat had access to a single active response lever mounted on the rear wall of the chamber. The distance between the response levers was 13 cm, 6.5 cm from the wire screen. Drug infusions were delivered via Tygon tubing protected by a stainless steel spring and connected to a counter-balanced swivel above the chamber. An infusion pump (3.33 rpm) was mounted behind the cage and connected to interfacing equipment from Med Associates, Inc. (St Albans, VT, USA). In contrast to standard operant conditioning chambers, our custom-designed chambers allow for within-session, social contact manipulations (Fig. 1).

Lever-press training 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.

2.3. Lever-press training

One goal of this project was to establish responding reinforced by cocaine on a FI schedule of reinforcement. There are very few studies describing the use of FI schedules in drug self-administration studies, and there is no standardized protocol for training laboratory rats in this procedure. Given the limited lifespan of jugular catheters (~30 days in our laboratory), it was necessary to expedite self-administration training as much as possible by initially training rats to respond on a FI schedule using food reinforcement. This was done through a series of sessions in which responding was initially reinforced on a fixed ratio schedule (to establish the response), then on a variable ratio (VR) schedule (to establish responding under conditions of intermittent reinforcement), and finally on a FI schedule (to establish responding on an interval schedule in which reinforcement is not a direct function of response rate). Later, once catheters were implanted, self-administration training advanced through these same three schedules using cocaine as the reinforcer.

Prior to beginning lever-press training, rats were left undisturbed in their home cages to mature. Approximately four weeks after arrival (~7 weeks of age), subjects were restricted to 90% of their free-feeding body weight and trained to press a response lever using food reinforcement. Rats were handled daily by the experimenters from this day forward. During initial lever-press training,