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Peer Influences on Drug Self-Administration: Social Facilitation and Social Inhibition of Cocaine Intake in Male Rats

Mark A. Smith
Department of Psychology, Program in Neuroscience, Davidson College, Davidson, NC 28035-7037, USA

Abstract

Rationale—One problem facing animal models of intravenous drug self-administration, particularly those examining social manipulations, is that subjects must be removed from the home environment and separated from cagemates during testing. This represents a limitation of animal models, because it fails to capture the complex social environments in which drug use often occurs.

Objectives—The aim of this study was to examine intravenous cocaine self-administration in isolated and socially housed rats, with the caveat that the socially housed subjects lived together 24 hr/day, including during daily self-administration sessions. As a secondary aim, the study examined the impact of a companion that also self-administered cocaine versus a companion without access to cocaine.

Methods—Male rats were obtained at weaning and reared in isolated or pair-housed conditions for 6 weeks. Rats were then implanted with intravenous catheters and transferred to custom-built operant conditioning chambers that served as home cages for the remainder of the study. For some socially housed subjects, both rats had simultaneous access to cocaine; for others, only one rat of the pair had access to cocaine.

Results—Cocaine self-administration was facilitated in socially housed rats if both members of the pair had access to cocaine; however, cocaine self-administration was inhibited if only one rat of the pair had access to cocaine.

Conclusions—These data indicate that the self-administration behavior of a peer, not merely the presence of a peer, determines whether cocaine self-administration is facilitated or inhibited by social contact.

Keywords

cocaine; fixed ratio; isolated; peer; progressive ratio; rat; self-administration; social; socialization; social-learning theory

Epidemiological studies consistently report that one of the most reliable predictors of whether an adolescent or young adult will use drugs is whether his or her friends use drugs (Bahr et al. 2005; Simons-Morton and Chen 2006). The reasons for the high concordance rate of substance use among members of peer groups are not fully known, but two types of theories have received the most attention. Selection theories suggest that adolescents and young adults self-select into social groups that are similar to themselves. In these models, an

Corresponding Author: Mark A. Smith, Department of Psychology, Box 7037, Davidson College, Davidson, NC 28035-7037, USA, Phone: 704-894-2470, Fax: 704-894-2512, masmith@davidson.edu.

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individual chooses peers who share similar substance use beliefs, attitudes, and behaviors. In contrast, socialization (or social-learning) theories propose that members of a group model substance use behaviors, and other members imitate those behaviors. In addition, members of the social group selectively reinforce and/or punish the substance use behavior of other members depending on the norms established by that group (see reviews by Kandel 1986; Andrews and Hops 2010; Pandina et al. 2010 for further discussion of selection and socialization theories). These two models are not mutually exclusive of one another, but the relative contribution of selection and socialization in substance use behaviors is not currently known.

Experimental studies examining the roles of selection and socialization in substance use behaviors are limited. Experimental studies are difficult to conduct in human populations because ethical constraints limit the degree to which substance use can be modeled and reinforced. Most animal studies examining social influences on drug self-administration limit their experimental manipulations to distal (i.e., home-cage) variables. In these types of studies, animals experience a social manipulation in the home cage (e.g., social stress, social enrichment) and are then compared to control animals on measures of intravenous drug self-administration, the most common method for evaluating drug-seeking behavior in the laboratory (see reviews by Miczek et al. 2008; Stairs and Bardo 2009). One aspect of these studies is that subjects are typically removed from their home environment and separated from their cagemates during testing, thus preventing an examination of proximal (i.e., within-session) social influences on drug-seeking behavior. This has traditionally been a practical limitation of intravenous drug self-administration studies, due in part to the small size of commercially available operant conditioning chambers and in part to the need to keep one animal from accessing the tethering system of another animal. This has also limited the translational appeal of these studies, because it fails to take into consideration the complex social environment in which drug use often occurs. Although social patterns of drug use differ across drugs (Hanson et al. 2011), instances of drug consumption often involve the presence of multiple individuals, some or all of whom may be using that substance. Importantly, the drug-taking behavior of these other individuals (i.e., whether or not they are also using drugs) may influence the drug-taking behavior of the user (Quigley and Collins 1999; Larsen et al. 2009).

Recent studies using the conditioned place preference (CPP) procedure suggest that proximal social influences can impact measures of drug reward. For instance, a low dose of cocaine (2 mg/kg, ip) and a low number of social pairing (2 pairings with a gender- and weight-matched conspecific) failed to produce CPP when examined alone, but produced robust CPP when combined, suggesting a possible synergistic interaction between the two rewards (Thiel et al. 2008). Interestingly, the dose of cocaine tested reduced social play, indicating that aspects of the social interaction other than play contributed to the effects. Using a similar paradigm, social interaction reversed a previously established cocaine-induced CPP and blocked the reinstatement of CPP after a priming injection of cocaine (Fritz et al. 2011; El Rawas et al. 2012). Again, play behavior was not necessary for its rewarding effects, because social pairing established a CPP even when rats were separated by wire or mesh patricians (Kummer et al. 2011; Peartree et al. 2012). Collectively, these studies indicate that immediate and proximal social factors can modulate drug reward in the CPP procedure.

In the present study, we used custom-built, operant-conditioning chambers to examine intravenous drug self-administration in two animals at the same time and in the same chamber. The principal scientific aim of this study was to examine the effects of social housing on intravenous cocaine self-administration under conditions in which a companion animal was continuously present during the self-administration sessions. As an important

and novel secondary aim, the study examined the impact of a companion animal that also self-administered cocaine (i.e., a co-user) versus the impact of a companion animal that did not self-administer cocaine (i.e., a nonuser). As suggested by socialization theories of peer influence and drug self-administration, our central hypothesis was that cocaine self-administration would be facilitated in rats paired with a companion with access to cocaine and inhibited in rats paired with a companion without access to cocaine. Finally, in order to examine the influence of modeling and imitation on measures on drug-seeking behavior in the absence of drug reinforcement, nonreinforced lever pressing was examined in rats without access to cocaine that were housed with a companion with access to cocaine.

Methods

Subjects

Male, Long-Evans rats were obtained at weaning (~21 days) and randomly assigned to isolated or socially housed conditions immediately upon arrival. Isolated rats were housed individually in opaque polycarbonate cages (interior dimensions: 50 × 28 × 20 cm) that permitted no visual or tactile contact with other rats. Socially housed rats were kept in polycarbonate cages of equal dimensions, but with two rats assigned to each cage. All rats remained under these conditions until the beginning of self-administration training, at which time they were transferred to custom-built, operant-conditioning chambers that also served as home cages for the remainder of the study. At that time, socially housed rats were subdivided randomly into both-access and one-access groups. In both-access groups, both rats of the pair were trained to self-administer cocaine, and self-administration tests were conducted in both rats. In one-access groups, one rat was designated randomly as the “user”, whereas the other rat was designated as the “nonuser”. In this group, only one rat was trained to self-administer cocaine, and self-administration tests were conducted only in that rat. The other rat never had access to cocaine, and lever presses had no programmed consequences. All socially housed rats remained with their companion from weaning until the end of the study and were never exposed to other rats inside or outside the home cage. Food and water were freely available in the home cages, except during the brief period of lever-press training (see below). Throughout the study, subjects were maintained on a 12-hr light/dark cycle (lights on: 5:00 a.m.) in a temperature- and humidity-controlled colony room. All subjects were maintained in accordance with the guidelines of the Animal Care and Use Committee of Davidson College and the *Guide for the Care and Use of Laboratory Animals* (Institute of Laboratory Animals Resources 2011).

Apparatus

One week prior to surgery, all rats were trained to lever press using food reinforcement in commercially available operant conditioning chambers from Med Associates, Inc. (St Albans, VT). Each chamber was equipped with a single houselight, two retractable response levers, and a food hopper. Experimental events were programmed and data were collected through software and interfacing supplied by Med Associates, Inc.

All drug self-administration training and testing sessions took place in custom-built, operant-conditioning chambers (Faircloth Machine Shop, Winston-Salem, NC) that also served as home cages (Fig 1). Chambers were constructed from stainless steel and had a solid rear wall and 14-gauge (1.6 mm) wire side walls for ventilation. All chambers were equipped with a retractable response lever and an infusion pump mounted outside the chamber. Drug infusions were delivered through a Tygon® tube protected by a stainless-steel spring and attached to a counterbalanced swivel at the top of the chamber. Food and water were freely available in ports mounted to one sidewall of the chamber. Software and interfacing for the chambers were obtained from Med Associates, Inc.

All chambers were modular in construction and could easily be altered to house isolated or socially housed rats. Chambers for isolated rats were cubic in design (interior dimensions: 30 cm × 30 cm × 30 cm) with one response lever on the rear wall. Chambers for socially housed rats were constructed from two isolated chambers, each with one side wall removed, and connected with a 14-gauge wire-screen panel at existing corner supports. The wire screen allowed each rat visual, auditory, olfactory, and limited tactile contact with its partner, but prevented one rat from accessing the tethering system of its companion. Each rat of the pair had individual access to food, water, and a response lever beyond the reach of its companion. For each socially housed rat, the response lever was placed 6 cm from the wire screen, 13 cm away from the response lever of its partner.

Foam insulation panels (2.5 cm thickness) were placed between all chambers to attenuate extraneous sounds and prevent a direct line of sight to all other rats in the colony.

Lever-Press Training

Five weeks after arrival and one week prior to catheter implantation, all rats were food restricted to 90% of their free-feeding weight and trained to lever press during daily 2-hr training sessions. During these sessions, responding was reinforced on a fixed ratio (FR1) schedule of food reinforcement. All sessions terminated automatically once 40 reinforcers were delivered or 2 hr elapsed. For any rat that failed to acquire the lever-press response by the third session, the response was shaped by the experimenter using the method of successive approximations. Once a rat earned 40 reinforcers during any four training sessions, training was discontinued and the rat was placed back on unrestricted feed. All rats met this criterion within 7 days.

Surgery

Six weeks after arrival, all rats were anesthetized with a combination of ketamine HCl (100 mg/kg, ip) and xylazine HCl (8.0 mg/kg, ip). An intravenous catheter (CamCaths, Cambridge, UK) was surgically implanted into the right jugular vein and exited the body on the dorsal surface of the scapulae. Butorphanol HCl (1.0 mg/kg, sc) was given 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 administration was discontinued and only heparinized saline was used to maintain catheter patency. All animals received 3 days of recovery before beginning self-administration training.

Self-Administration Training

All training and testing sessions were conducted in the custom-built, operant-conditioning chambers and began promptly at the beginning of the dark phase of the light/dark cycle (5:00 p.m.). At the start of behavioral training, a retractable lever extended into the chamber and lever pressing was reinforced on an FR1 schedule of reinforcement. On this schedule, each lever press activated an infusion pump that administered 0.5 mg/kg/infusion cocaine HCl over a 2.5 – 4.0 s duration (based on body weight). Concurrent with the start of each infusion, the lever retracted to signal a 20 s post-infusion time-out. After 20 s, the lever extended back into the chamber and cocaine was again available on an FR1 schedule of reinforcement. To prevent overdose, the maximum number of infusions was limited to 21 during the first session; during all subsequent sessions, no limit was placed on the number of infusions that could be earned, and no signs of toxicity were observed. All sessions terminated after 120 min. At that time, the lever retracted and no further infusions were available until the beginning of the next session on the following day. After 4 days, training was discontinued and behavioral testing commenced. For no-access rats in the one-access

group, the lever extended into the chamber for 120 min each day, but responding had no programmed consequences.

Self-Administration Testing

After 4 days of training, operant contingencies changed and responding was reinforced on a progressive ratio (PR) schedule of reinforcement. On the PR schedule, the number of responses required for an infusion incremented through the following progression: 1, 2, 4, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 323, 402, 492 and 603 (Richardson and Roberts 1996). Each session continued until a breakpoint was reached, with breakpoint defined as the number of infusions obtained before one hour elapsed with no infusions. Breakpoints were obtained for 0.1, 0.3, and 1.0 mg/kg/infusion cocaine, as well as for saline. Doses were tested in an irregular order with the stipulation that no more than two ascending or descending doses could be tested in a row. Each dose was tested once in each rat. For rats in the both-access group, both rats always received the same dose during a given session, and data from both rats were used for the statistical analysis. If catheter patency was lost in one rat of the pair, then both rats were removed from the study, and data from that pair were not used in the statistical analysis. For no-access rats in the one-access group, the lever extended into the chamber for 240 min each session, but responding had no programmed consequences. Data were not collected on the temporal distribution of responding within individual sessions.

After the conclusion of PR testing, operant contingencies changed again and responding was reinforced on an FR1 schedule of reinforcement. On this schedule, contingencies were identical to those used during training, with no limit placed on the number of infusions that could be earned. All sessions terminated after 120 min. Tests were conducted with 0.03, 0.1, 0.3, and 1.0 mg/kg/infusion cocaine, as well as with saline. Doses were tested in an irregular order with the stipulation that no more than two ascending or descending doses could be tested in a row. Each dose was tested once in each rat. For rats in the both-access group, both rats always received the same dose during a given test session, and data from both rats were used for the statistical analysis. If catheter patency was lost in one rat of the pair, then both rats were removed from the study, and data from that pair were not used in the statistical analysis. For no-access rats in the one-access group, the lever extended into the chamber for 120 min each session, but responding had no programmed consequences.

Data Analysis

All self-administration data were analyzed via repeated measures ANOVA, with group serving as the between-subjects factor and dose serving as the within-subjects factor. As a secondary analysis, area under the curve (AUC) estimates were calculated for each rat by applying the Trapezoidal Rule to the dose-response data. AUC estimates provide a dimensionless measure of reinforcing efficacy in drug self-administration procedures, and are helpful when a dose-effect curve has both an ascending and descending limb (see Cooper et al. 2008). These AUC estimates were then analyzed via one-way ANOVA using group as a factor. Data obtained during the saline substitution tests were analyzed separately via one-way ANOVA, using group as a between-subject factor. Under conditions in which a main effect was observed for group, post-hoc tests were conducted using Tukey's HSD (Honestly Significant Difference) test for multiple comparisons. An alpha level of 0.05 was used for all statistical tests. The experimental design did not allow sufficient power to determine whether responding was mutually correlated in pair-housed animals with simultaneous access to cocaine (i.e., only 4 pairs of 8 rats were tested). Effect sizes were determined using Cohen's *d*.

Results

All rats responded on the first day of self-administration training. The three groups did not differ on the first day of training in which the maximum number of reinforcers was limited to 21 infusions. Differences between groups were observed over the next three days of training during which no limit was placed on the number of infusions that could be earned [main effect of group: $F(2, 19) = 3.824$, $p = .040$], and post-hoc tests revealed that the both-access group responded to a significantly greater degree than the no-access group ($p = .032$). Across all groups, responding decreased significantly by the final day of training [main effect of day: $F(2, 38) = 15.033$, $p < .001$]. Analysis of individual event records revealed stable patterns of responding were apparent in all animals by the third day of testing, with an initial "load-up" phase followed by a steady rate of responding characterized by regular post-reinforcement responses. This pattern of responding did not differ across groups (data not shown).

Responding on the Progressive Ratio Schedule of Reinforcement

Breakpoints maintained by cocaine differed significantly across doses and across groups on the PR schedule (Fig 2, left panel). Responding increased linearly, albeit modestly, across the three doses of cocaine [main effect of dose: $F(2, 38) = 8.347$, $p = .001$]. Importantly, breakpoints maintained by cocaine differed significantly across the three groups of rats [main effect of group: $F(2, 19) = 4.063$, $p = .034$]. Rats assigned to the both-access group, in which both rats self-administered cocaine, had the highest breakpoints; rats assigned to the one-access group, in which only one rat had access to cocaine, had the lowest breakpoints. Post-hoc tests revealed that the both-access group differed significantly from the one-access group ($p = .031$). No differences were observed between groups when saline was tested ($p > .05$). As a secondary analysis, AUC estimates were determined for each dose-effect curve (Fig 2, right panel). Similar to that seen with the dose-response analysis, significant differences were observed across the three groups [$F(2, 19) = 3.804$, $p = .041$], with the both-access group differing significantly from the one-access group ($p = .035$). Effect sizes between groups ranged from moderate ($d = 0.43$) to very large ($d = 1.31$). Session lengths were positively, but not significantly, related to breakpoints at each dose ($r = 0.336–0.442$). An analysis of session lengths on the PR schedule revealed a main effect of dose [$F(2, 38) = 23.310$, $p < .000$]. Numeric differences in session lengths were observed across groups (both-access > isolated > one-access), but these differences were not statistically significance (data not shown).

Responding on the Fixed Ratio Schedule of Reinforcement

Responding differed significantly across doses and across groups on the FR1 schedule (Fig 3, left panel). On this schedule, cocaine self-administration was characterized by an inverted U-shaped dose-effect curve [main effect of dose: $F(3, 57) = 33.570$, $p < .001$]. Responding on the FR1 schedule differed significantly across the three groups [main effect of group: $F(2, 19) = 5.999$, $p = .010$], and this effect was most apparent at intermediate doses of cocaine [dose × group interaction: $F(6, 57) = 2.755$, $p = .020$]. Across all doses, responding was highest in the both-access group and lowest in the one-access group, and post-hoc tests revealed that these two groups differed significantly from one another ($p = .008$). No significant differences were observed between groups when saline was tested ($p > .05$). Data obtained in the AUC analysis mirrored those obtained in the dose-response analysis (Fig 3, right panel). Significant differences were observed across the three groups [$F(2, 19) = 5.630$, $p = .012$], with the both-access group differing significantly from the one-access group ($p = .010$). Effect sizes between groups ranged from moderate ($d = 0.62$) to very large ($d = 1.62$).

Responding in No-Access Companions in the Absence of Drug Reinforcement

No-access companion animals had an inactive response lever on which responses were recorded but had no programmed consequences. Lever presses were measured in these rats under each dose condition, and their responding was compared to that of their self-administering companions. Interestingly, the lever pressing of no-access animals mimicked that of their self-administering companion on both FR1 and PR schedules of reinforcement (Fig 4), even though responding was never reinforced in these animals by any programmed consequence. In both groups, responding increased linearly across the three dose conditions on the PR schedule [main effect of dose: $F(2, 28) = 4.179$, $p = .026$] and followed a U-shaped dose-effect curve on the FR1 schedule [main effect of dose: $F(3, 42) = 8.030$, $p < .001$]. Although the absolute number of lever presses was modest under all conditions, the dose-response function of no-access rats mimicked the dose-response function of their self-administering companions on both schedules of reinforcement.

Discussion

The principal finding of this study is that the self-administration behavior of a peer (i.e., whether or not that peer is self-administering cocaine) influences intravenous cocaine self-administration in laboratory rats housed together 24 hr/day, including during daily self-administration sessions. Specifically, cocaine self-administration was facilitated in socially housed rats if both members of the pair had access to cocaine, whereas cocaine self-administration was inhibited if only one rat of the pair had access to cocaine. These effects were observed on both FR1 and PR schedules of reinforcement, and were consistent across a wide range of doses. Differences between groups were evident as early as the second day of training and persisted until the end of the study, approximately 2 weeks later. Importantly, the three groups did not differ during sessions in which saline was substituted for cocaine, suggesting that the differences in drug self-administration were not due to differences in baseline rates of operant behavior.

Although statistical significance was obtained between the two social groups, no significant differences were observed between either of these groups and the individually housed group. This lack of statistical significance was likely due to insufficient power for testing all possible comparisons. Using an alternative analysis, effect sizes between the both-access group and the isolated group were very large ($d = 1.03–1.04$). Although effect sizes between the one-access group and the isolated group were markedly smaller ($d = 0.43–0.62$), they were still within the range considered “moderate” in the behavioral sciences (Cohen 1988).

Proximal Social Influences on Drug Self-Administration

Previous studies examining proximal (i.e., within-session) social influences on drug self-administration have typically measured the oral consumption of drugs in liquid drinking solutions. Early studies reported that socially housed rats consumed less of a liquid morphine solution than isolated control rats (Hadaway et al. 1979; Alexander et al. 1981). In a more recent study, Newman et al. (2007) reported that the oral consumption of phencyclidine was greater in rhesus monkeys when presented with a cagemate (also with access to phencyclidine) than when the monkeys were tested alone. In one of the few studies that examined intravenous drug self-administration, Gipson et al. (2011) reported that the presentation of an unfamiliar, same-sex conspecific (without access to a drug) facilitated responding maintained by a high dose of amphetamine in rats; however, this effect was not apparent at a lower dose and dissipated with repeated presentations. In all of these studies, the behavior of the peer (i.e., whether or not the peer was also self-administering the drug) was not experimentally manipulated. Consequently, it was not clear whether the behavior of

the peer or merely the presence of the peer was responsible for the observed effects on drug self-administration.

Socialization theories of substance use hypothesize that proximal social contact with companions who use drugs directly influences an individual's drug consumption. Accordingly, peer groups reinforce and punish the substance use behavior of individual members to facilitate or inhibit drug intake. In the present study, the ability of one rat to reinforce and/or punish the behavior of its companion was limited by the presence of a wire screen that restricted tactile contact between the two rats; however, social signals could still be relayed via visual, auditory, and olfactory routes of communication. Technical limitations prevented us from directly measuring these forms of social communication, but positive and negative social cues were likely relayed between rats throughout the experimental sessions.

Theories of substance use that emphasize social factors are derived from basic learning theories on social facilitation, observational learning, and imitation (e.g., Allport 1924; Bandura 1962; 1977). These theories, in turn, were developed primary from animal studies in which responding was maintained by nondrug reinforcers. Early studies using pair-housed animals reported social facilitation of lever pressing maintained by food (Strobel, 1972) and water (Henning and Zentall 1981) reinforcement. In a similar line of research, social learning was used to explain the facilitation of responding in a "follow-the-leader" task in which food delivery was contingent on successfully imitating the behavior of a companion behind a transparent partition (Hake et al. 1983). Social facilitation has also been observed in cats using a shock-avoidance procedure (John et al. 1968) and rats using a candle-flame avoidance procedure (Bunch and Zentall 1980). In the latter study, facilitation was significantly diminished when the observer was blocked from viewing the demonstrator's interaction with the candle, indicating that observation of the operant response was critical for facilitation to occur. The present study represents an extension of this research by showing that social factors also influence drug self-administration in pair-housed animals, and that social learning may have either excitatory or inhibitory effects on drug-maintained responding.

Socialization theories do not explicitly state that substance use behaviors have to be naturally reinforcing; rather, some substance use behaviors are merely imitations of behaviors performed by a peer. Although true imitation is difficult to determine in laboratory animals (see Zentall and Akins 2001), we measured imitation-like behavior in our no-access rats by comparing their responding to that of their self-administering companions. Interestingly, the lever pressing of no-access rats mimicked that of their self-administering companion on both FR1 and PR schedules of reinforcement. It is important to note that the responding of no-access rats was more closely related to the *responding* (i.e., lever pressing) of their companion than to the companion's level of *cocaine intake* (i.e., level of intoxication). On an FR1 schedule, cocaine intake is a *monotonic* function of dose (i.e., a linear curve with a positive slope), whereas responding is a *biphasic* function of dose (i.e., an inverted U-shaped dose-effect curve). Although these data suggests that the companion rats were imitating the behavior of their peers, other explanations cannot be ruled out. For instance, because the response levers were positioned close to one another (see Figure 1), the no-access rats may have pressed the lever inadvertently while attempting to interact with their companions while they were self-administering cocaine. Alternatively, a rat with access to cocaine that repeatedly approached the lever, and hence the companion's side of the chamber, may have produced a general activation effect in its companion, which would again be reflected by nonreinforced lever presses that varied as a function of dose. Future design modifications, such as the inclusion of additional response levers or a reconfiguration of existing levers, may resolve these issues.

Limitations of the Current Study and Possibilities for Future Studies

One of the aims of this study was to demonstrate the feasibility of conducting intravenous self-administration studies in socially housed rats with simultaneous access to cocaine. Now that this has been established, a number of issues can be addressed in follow-up studies. For instance, we did not examine how social behavior is influenced by cocaine self-administration. Noncontingent cocaine administration is associated with increases in defensive behavior (Rademacher et al. 2002), decreases in social affiliation (Rademacher et al. 1999), and reductions in play behavior (Ferguson et al. 2000), but less is known about the effects of contingent (i.e., self-administered) cocaine. The wire screen limited the amount of physical contact between pair-housed subjects because pilot testing revealed that the screen was necessary to prevent the tethering systems from tangling. Future design modifications that allow for more social contact will permit a more thorough investigation of the relationship between cocaine self-administration and social behavior. We also do not know the nature of the social interactions during the self-administration sessions (the experimental sessions were neither directly observed or video recorded). Rats self-administering cocaine emit a variety of ultrasonic vocalizations that reveal both positive and negative affective states (Barker et al. 2010). Ultrasonic vocalizations might be particularly relevant for the present study, because they would provide a means by which information regarding the interoceptive drug stimulus (i.e., the reinforcing event) could be relayed between two animals separated by a wire screen.

All subjects were young adult male rats, and future studies will need to determine whether these findings extend to other populations. The experimental chambers might also be ideal for studying male-female dyads. It is well-established that responding maintained by cocaine is heavily influenced by the estrous cycle in females, with responding peaking on the day of estrous (Roberts et al. 1989). Based on the present data, one could hypothesize that cocaine self-administration would also “cycle” in males paired with females, mirroring the cycle of the female. In the present study, all rats were trained to lever press for food reinforcement prior to the introduction of cocaine, and thus there was no acquisition period that is common to many self-administration studies. Subjects learn a response faster if they are first allowed to view a model performing the behavior (Herbert and Harsh 1944), and it is likely that acquisition would be facilitated in pair-housed rats with simultaneous access to cocaine. Furthermore, no data were collected on the temporal distribution of responses on the PR schedule of reinforcement. Responding on a PR schedule is characterized by long response runs followed by post-reinforcement pauses of several minutes. Information about the timing of these events would reveal the degree to which self-administration was synchronized in the pair-housed animals. Alternatively, schedules of reinforcement that lead to high rates of responding over extended periods of time (e.g., second-order schedules) may be particularly helpful in these types of within-session analyses.

Implications for the Epidemiology and Treatment of Substance Use Disorders

The present findings provide empirical support for socialization theories of substance use and offer evidence that the self-administration behavior of a peer has a causal influence on the drug-seeking and drug-taking behavior of the individual. Epidemiological studies report that one of the best predictors of adolescent substance use is whether an individual’s friends use psychoactive substances (Bahr et al. 2005; Simons-Morton and Chen 2006; Picotte et al. 2006; Fowler et al. 2007). Although self-selection contributes to the formation of peer groups, particularly those that share common interests, social stimuli provided by the group serve to shape, maintain, facilitate, and inhibit the behavior of individual members. In regard to the use of illicit drugs, the present findings suggest that these social stimuli facilitate or inhibit drug self-administration by individual group members, thereby setting up positive or

negative feedback loops by which modeling and imitation further facilitate or inhibit drug self-administration.

From a translational perspective, one of the most promising implications of these findings is that changing an individual's social environment might be the most effective way to reduce substance use. This is by no means a novel proposition, and changing an individual's social environment is easier said than done, but the current data provide some guidance regarding how change might occur. Peer-group members could model behaviors that are incompatible with drug use, social reinforcers could be delivered for abstaining from drug use (i.e., other behaviors could be differentially reinforced), and aversive consequences could be used to punish lapses to drug use (see Lerman and Vorndran 2002 for a discussion of punishment in applied settings). Moreover, the present findings suggest that if one member of a group is treated effectively and exhibits a corresponding decrease in drug self-administration, then his or her behavior will likely have positive consequences for other group members. Thus, the costs of treating any single individual might be outweighed by the benefits experienced by the entire group.

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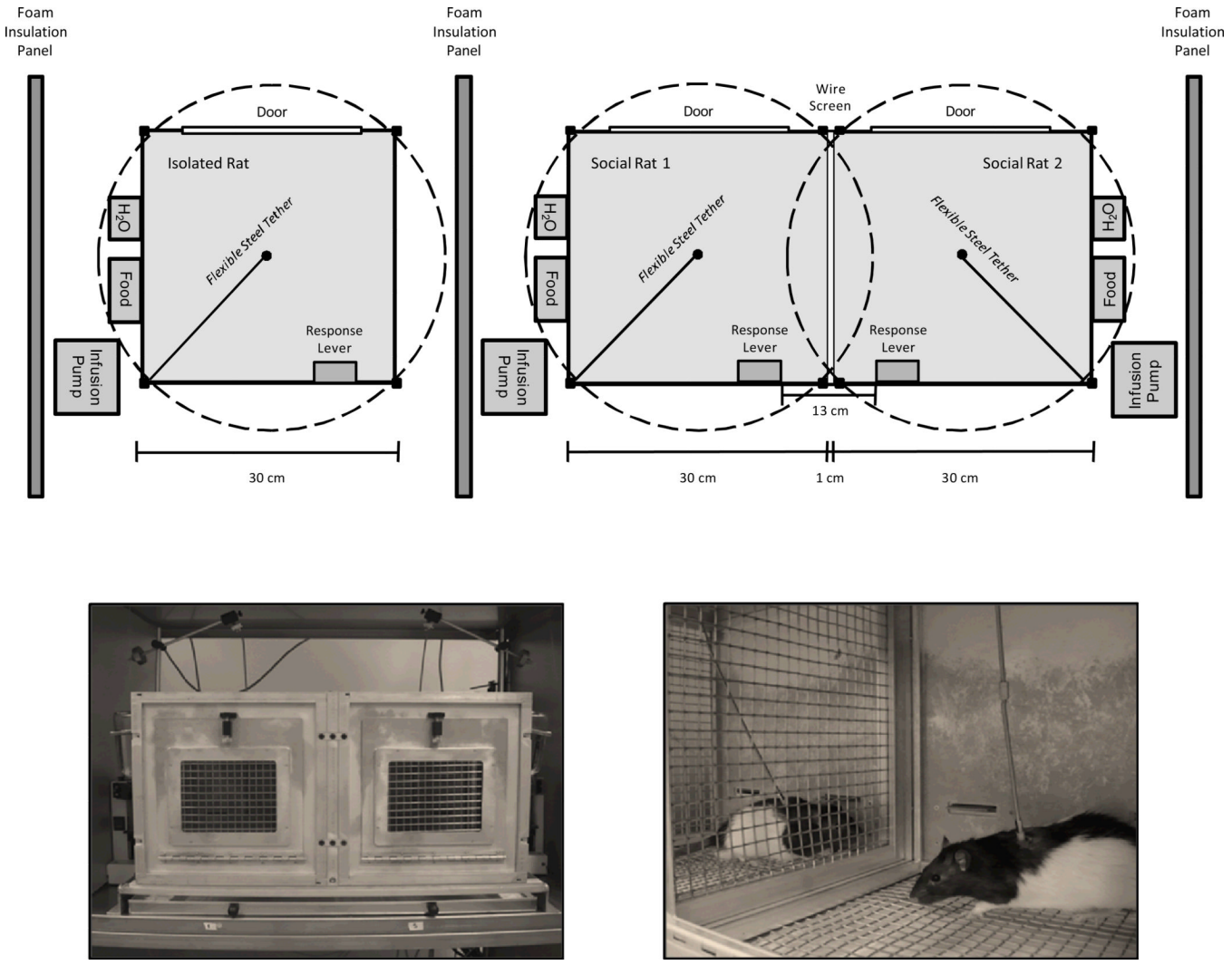

Fig. 1.

Top Panel: Overhead schematic of operant conditioning chambers for isolated (left) and social (right) rats. All cages are constructed from stainless steel and are modular in construction. Cages for isolated rats are comprised of one individual chamber measuring 30 × 30 × 30 cm. Cages for social rats are constructed from two individual chambers, each with one sidewall removed, and with a screen panel installed at existing corner supports. The wire screen allows each rat visual, auditory, olfactory, and limited tactile contact with its partner, but prevents one rat from accessing the tethering system of its companion. Both cages allow a rat individual access to food, water, and one response lever controlling intravenous drug infusions. A flexible, stainless-steel spring protects the infusion line and allows full movement within the cage (dotted lines indicate hypothetical range of movement permitted by tether). Foam insulation panels located on both sides of each cage attenuate extraneous sounds and prevent a rat from having a direct line of sight to other rats in the colony room. For social rats, response levers controlling drug infusions are positioned 13 cm apart. Bottom Panels: Photographs depicting front (left) and inside (right) views of the chamber

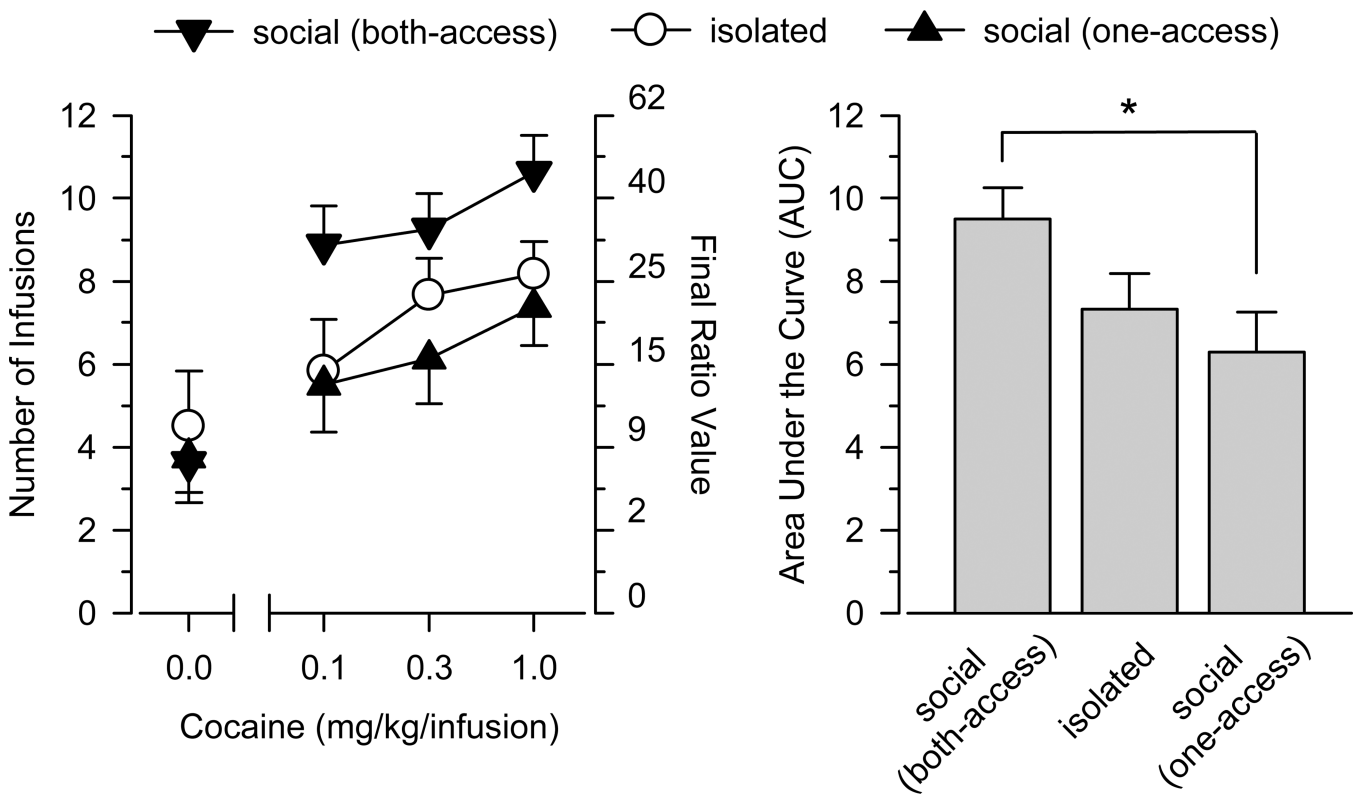

Fig. 2.

Left Panel: Breakpoints maintained by cocaine on a PR schedule of reinforcement. Data are shown for socially housed rats in which both members of the pair have access to cocaine [social (both-access); n = 8], isolated rats [isolated; n = 6], and socially housed rats in which only one member of the pair has access to cocaine [social (one-access); n = 8]. Left axis depicts breakpoints expressed as number of infusions obtained; right axis depicts breakpoints expressed as final ratio value completed. Horizontal axis depicts dose of cocaine in mg/kg/infusion. Points above 0.0 depict the effects of saline. Significant main effects ($p < .05$) were obtained for both dose and group. Post-hoc tests revealed that the both-access group differed significantly from the one-access group ($p = .031$). Right Panel: Area under the curve (AUC) estimates for cocaine in rats responding on a PR schedule of reinforcement. Significant difference is indicated by an asterisk (*)

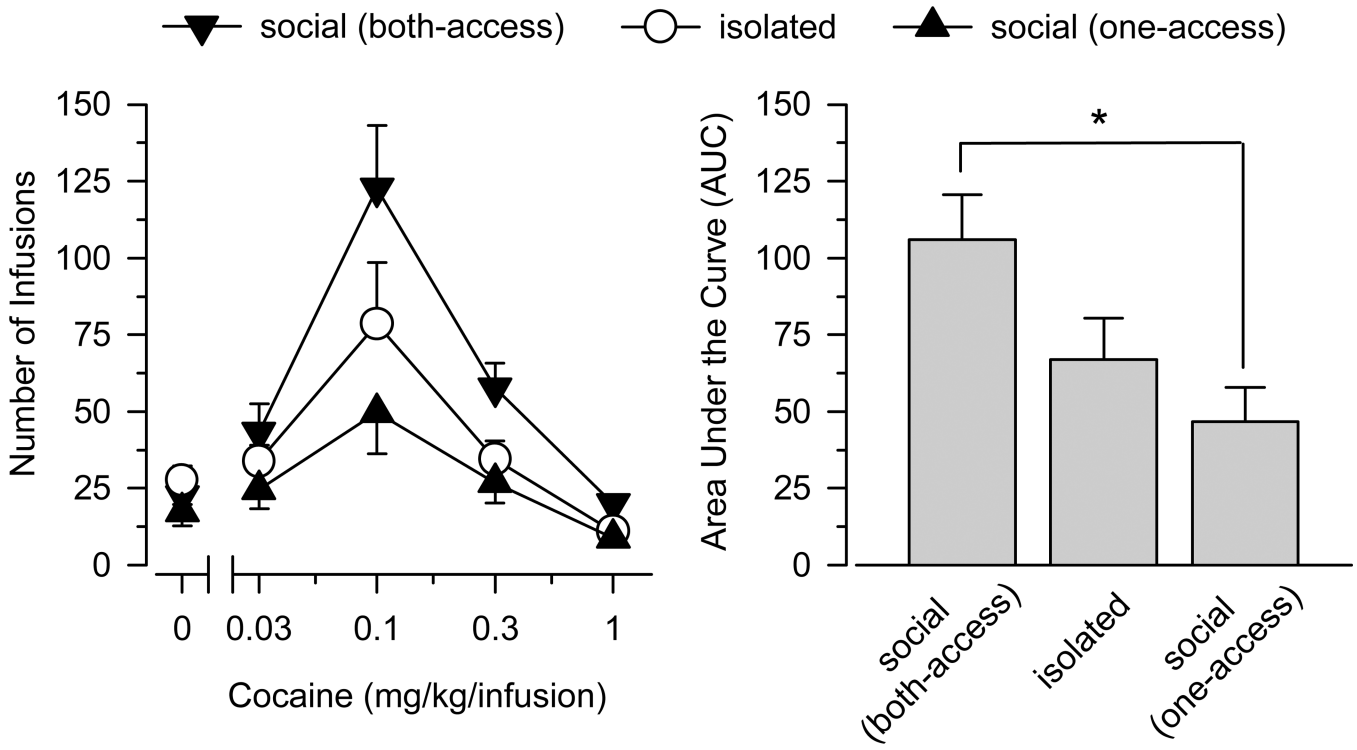

Fig. 3.

Left Panel: Responding maintained by cocaine on an FR1 schedule of reinforcement. Data are shown for socially housed rats in which both members of the pair have access to cocaine [social (both-access); n = 8], isolated rats [isolated; n = 6], and socially housed rats in which only one member of the pair has access to cocaine [social (one-access); n = 8]. Vertical axis depicts number of infusions during 2-hr test session. Horizontal axis depicts dose of cocaine in mg/kg/infusion. Points above 0.0 depict the effects of saline. Significant main effects ($p < .05$) and a significant interaction ($p < .05$) were obtained for both dose and group. Post-hoc tests revealed that the both-access group differed significantly from the one-access group ($p = .008$). Right Panel: Area under the curve (AUC) estimates for cocaine in rats responding on an FR1 schedule of reinforcement. Significant difference is indicated by an asterisk (*)

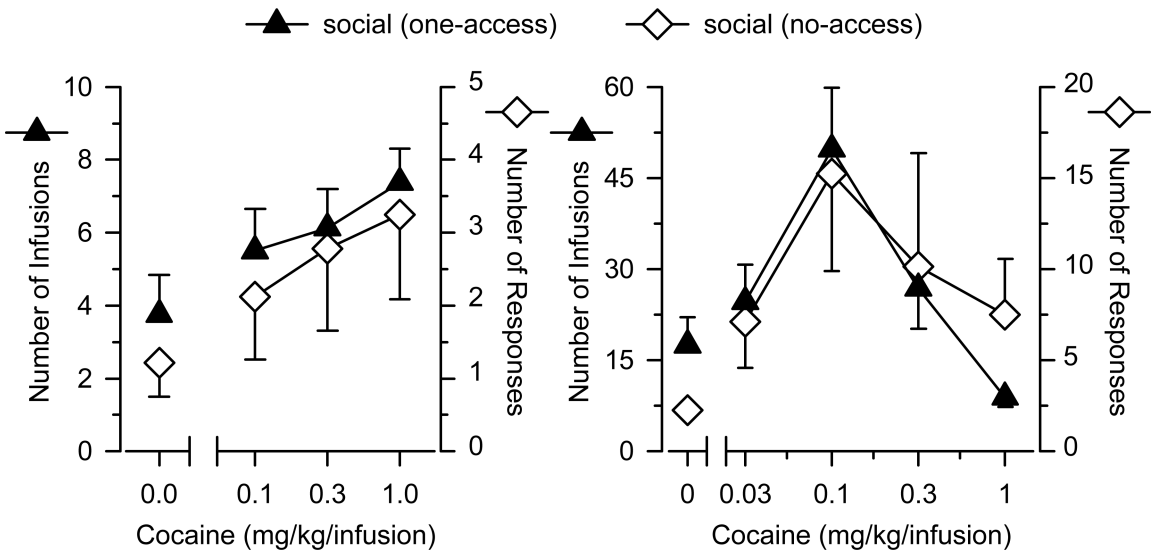

Fig. 4.

Nonreinforced responding of no-access rats compared to their self-administering companions. Data are shown for socially housed rats paired with a companion without access to cocaine [social (one-access); n = 8] and their no-access companions [social (no-access); n = 8]. Left axes depicts number of infusions obtained by self-administering rats when responding was reinforced on PR (left panel) and FR1 (right panel) schedules of reinforcement. Right axes depict nonreinforced responding of no-access rats during test sessions in which their companion was self-administering cocaine on PR and FR1 schedules of reinforcement. Horizontal axes depict dose of cocaine in mg/kg/infusion. Points above 0.0 depict the effects of saline. Significant dose effects ($p < .05$) were obtained on each schedule