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The Effects of Social Contact on Cocaine Intake Under Extended-Access Conditions In Male Rats

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Abstract

Social learning theories of drug use propose that drug use is influenced by the behavior of peers. We previously reported that cocaine self-administration under limited-access conditions can either be facilitated or inhibited by social contact depending on the behavior of a peer. The purpose of this study was to determine if social contact influences cocaine self-administration under conditions that are more representative of problematic patterns of drug use. Male rats were assigned to either isolated or pair-housed conditions in which a social partner either had access to cocaine or did not have access to cocaine. Pair-housed rats were tested in custom-built operant conditioning chambers that allowed both rats to be tested simultaneously in the same chamber. In Experiment 1, rats were tested for 14 consecutive days during daily 6-hr test sessions. In Experiment 2, different doses of cocaine were tested in 23-hr test sessions conducted every three days. All groups of rats escalated their cocaine intake in Experiment 1; however, pair-housed rats with a partner without access to cocaine had lower levels of intake throughout the 14 days of testing. In Experiment 2, pair-housed rats with a partner without access to cocaine had lower levels of cocaine intake than rats with a partner with access to cocaine, and this effect was observed at all doses of cocaine tested. These data indicate that the behavior of a social partner (i.e., whether or not that partner is also self-administering cocaine) influences cocaine self-administration under conditions that model problematic patterns of drug use.

Keywords

binge; cocaine; escalation; rat; self-administration; social; social behavior; social learning

Peter Dews first systematically examined environmental influences on drug effects in a series of seminal studies beginning in the 1950's (Dews, 1955a, 1955b, 1958), and Division 28 of the American Psychological Association was created in the following decade. The influence of social contact on drug effects has always been a central component of the field, and it may be argued that early studies on aggregate toxicity (i.e., the influence of social contact on drug-induced lethality) laid the groundwork for the establishment of behavioral pharmacology as an independent discipline (e.g., Chance, 1946; Davis & Brister, 1971; Greenblatt & Osterberg, 1961). Over the ensuing decades, the role of social contact on

measures of drug self-administration became a growing focus of psychopharmacological research. Beginning with the work of Bruce Alexander showing that group housing decreases the oral consumption of morphine (Alexander, Beyerstein, Hadaway, & Coombs, 1981; Alexander, Coombs, & Hadaway, 1978; Hadaway, Alexander, Coombs, & Beyerstein, 1979), and continuing with the work of Michael Bardo showing that environmental enrichment decreases amphetamine self-administration (Bardo, Klebaur, Valone, & Deaton, 2001; Green, Gehrke, Bardo, 2002), psychopharmacologists have demonstrated that the social environment plays a critical role in drug-seeking behavior. This line of research continues to evolve today with studies examining the effects of social learning, including imitation and modeling, on substance use within peer groups (see reviews by Neisewander, Peartree, & Pentkowski, 2012; Strickland & Smith, 2014)

Peer influence is generally believed to be a major cause of adolescent drug use (Bahr, Hoffmann, Yang, 2005; Simons-Morton & Chen, 2006). Through social learning, adolescents learn to take drugs in small, informal groups where they are taught, through imitation and reinforcement, to hold attitudes that are favorable or unfavorable to drug use (see reviews by Andrews & Hops, 2010; Kandel, 1986; Pandina, Johnson, & White, 2010). Indeed, experimental studies have shown the initiation and maintenance of alcohol and tobacco use is influenced by modeling and imitation of peer behavior (Harakeh, Engels, Van Baaren, & Scholte, 2007; Larsen, Engels, Granic, & Overbeek, 2009; Quigley & Collins, 1999). Ethical constraints limit the degree to which drug use, particularly illicit drug use, can be modeled and reinforced in human participants. Therefore, in order to understand the behavioral mechanisms mediating social influence on drug use, animal models are needed that allow subjects to observe and mimic the behavior of another subject.

Our laboratory recently developed custom-built, operant conditioning chambers that permit intravenous drug self-administration in two animals at the same time and in the same chamber. These chambers allow rats to be tested simultaneously, side-by-side, separated only by a wire screen, and provide rats with full visual, auditory, olfactory, and limited tactile contact with one another while self-administering drugs. Using this paradigm, we showed that drug self-administration under limited-access conditions could either be facilitated or inhibited by social contact depending on the behavior of a partner. Specifically, cocaine self-administration was increased in rats with a social partner that also self-administered cocaine, but drug self-administration was decreased in rats with a partner that did not have access to cocaine (Smith, 2012). Similarly, we showed that the acquisition of cocaine self-administration was facilitated if an experimentally naïve rat was paired with a cocaine-experienced partner (Smith, Lacy, & Strickland, 2014). Taken together, these data emphasize the critical role of social learning in the acquisition and maintenance of drug-reinforced behavior.

An essential feature of substance use disorders is the loss of control of drug use over time (American Psychiatric Association, 2013). The clinical literature indicates that cocaine use disorder begins with casual, recreational use, but escalates to uncontrolled and binge patterns of use over time (Gawin, 1991). These patterns of escalating and excessive drug intake can be modeled in the laboratory by giving animals extended access to a drug during test sessions lasting 6 hr or longer. For example, Ahmed and Koob (1998, 1999) found that when

animals were given 6 hr of access to cocaine they increased their total cocaine intake across 21 days, while animals given just 1 hr of access maintained stable levels of intake. Similarly, animals given 24-hr access to cocaine exhibited high levels of drug intake that were accompanied by diminished regulation of autonomic functions, loss of circadian patterns of activity, and acute withdrawal symptoms upon cessation of drug use (Mutschler & Miczek, 1998; Tornatzky & Miczek, 2000). The patterns of behavior observed in animals under extended-access conditions are similar to those observed in human laboratory studies (Foltin & Fischman, 1997; Pace-Schott et al., 2005; Reed et al., 2009). Thus, the dysregulated patterns of drug intake in these extended-access procedures are thought to model the uncontrolled drug use displayed by humans with substance use disorders.

The primary aim of this study was to determine if social contact influences cocaine self-administration in procedures designed to model problematic patterns of drug intake. In Experiment 1, the escalation of cocaine intake was examined during daily 6-hr test sessions; in Experiment 2, excessive drug intake was examined during 23-hr “binges” of cocaine self-administration. These procedures model different and distinct transitional phases of a substance use disorder, with the former modeling the “switch” from regulated to dysregulated patterns of use that is characteristic of early stages of a substance use disorder (e.g., Ahmed & Koob, 1998, 1999), and the latter modeling the excessive, “binge-like” patterns of drug intake that are characteristic of latter stages (e.g., Mutschler, Covington III, & Miczek, 2001; Tornatzky & Miczek, 2000). Rats were assigned to either isolated or pair-housed conditions in which a social partner either had access to cocaine or did not have access to cocaine. In both experiments, we predicted that the greatest amount of cocaine intake would be observed in rats with a partner with access to cocaine, and the lowest amount of cocaine intake would be observed in rats with a partner without access to cocaine. Isolated rats were included for comparison to determine the directionality of the effect (i.e., an increase or decrease in cocaine intake) relative to a reference control group. To determine the manner in which social contact influences drug intake we examined both the relative rate of responding and the duration of responding, computed from both lever presses and inter-response intervals.

Methods

General Methods

Animals—Male, Long-Evans rats were obtained at weaning (~21 days) and randomly assigned to isolated or pair-housed conditions in polycarbonate cages (interior dimensions: 50 × 28 × 20 cm) for six weeks. After six weeks, rats were transferred to custom-built, operant conditioning chambers that served as home cages for the remainder of the study (see below). At this time, pair-housed rats were randomly assigned to their treatment group: in one group, only one rat of the pair had access to cocaine (partner no access); in the other group, both rats of the pair had access to cocaine (partner with access). Food and water were freely available in the home cages except during the brief period of lever-press training (see below). All subjects were continuously maintained on a 12-hr light/dark cycle (lights on: 0500) in a temperature- and humidity-controlled colony room. All subjects were used 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—Rats were trained to lever press using food reinforcement in commercially available operant conditioning chambers from Med Associates, Inc. (St Albans, VT). These chambers were equipped with a houselight, two response levers, and a food hopper. Experimental events were programmed and data were collected with software and interfacing from Med Associates, Inc.

All drug self-administration sessions took place in operant conditioning chambers custom made by Faircloth Machine Shop (Winston-Salem, NC). These chambers are IACUC-approved for the long-term housing of rats and served as home cages throughout the period of behavioral testing. Chambers were stainless steel, modular in construction, and cubic in design (interior dimensions: 30 × 30 × 30 cm). Each chamber had a solid rear wall and 14-gauge (1.6 mm) wire sidewalls for ventilation. Each chamber was equipped with one 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. Response levers, syringe pumps, interfacing, and computer software were obtained from Med Associates, Inc.

Chambers for isolated rats consisted of one 30 × 30 × 30 cm chamber. Chambers for pair-housed rats were constructed from two isolated chambers, each with one sidewall removed, and connected with a 14-gauge wire screen panel at existing corner supports. The wire screen permitted rats full visual, auditory, olfactory, and limited tactile contact, but prevented one rat from accessing the response lever and infusion lines of its partner. Response levers were offset from center and located 6 cm from the interior wall. For pair-housed rats, response levers were located 13 cm away from one another. The operant chambers were open to the colony room and were not contained within sound-attenuating cubicles; however, foam insulation panels (2.5 cm thickness) were placed between chambers to attenuate extraneous sounds and prevent a direct line of sight to adjacent chambers (for further description and images, see Smith, 2012; Lacy, Strickland, & Smith, 2014).

Lever-Press Training—Five weeks after arrival and one week prior to catheter implantation, rats were lightly food restricted to no less than 90% of their free-feeding body weight and trained to press a response lever on a fixed ratio (FR1) schedule of food reinforcement. On this schedule, each response produced a 45 mg food pellet delivered to a food hopper located between the two response levers. Sessions terminated automatically once 40 reinforcers were delivered or two hr elapsed, whichever occurred first. Training continued in this manner until a rat earned the maximum number of reinforcers over four days.

Catheter Implantation—Six weeks after arrival, all rats were anesthetized with a combination of ketamine (100 mg/kg) and xylazine (8.0 mg/kg, ip) and surgically implanted with intravenous catheters in the right jugular vein. Ketoprofen (3.0 mg/kg, sc) was given immediately after surgery as a post-operative analgesic and again 24 hr later. Beginning on the day of surgery, a solution of heparinized saline and ticarcillin (20 mg/kg, iv) was infused

through the catheter daily to prevent infection and maintain patency. After seven days, ticarcillin was discontinued and only heparinized saline was used to maintain catheter patency. Wounds were treated with a topical antibiotic ointment for two days after surgery. All animals were transferred to the custom-built operant conditioning chambers immediately after surgery and allowed to recover for at least three days before beginning self-administration training.

Cocaine-Reinforced Responding—Following recovery from surgery, self-administration sessions were conducted daily for all rats with access to cocaine. Each session began promptly at the start of the dark cycle (1700) with insertion of the retractable lever into the chamber and a noncontingent infusion of the dose of cocaine available during that session. Each infusion delivered cocaine over a duration of 2.0 to 2.4 s (based on body weight), representing volumes of 0.036 to 0.043 ml/infusion. Coincident with each infusion, the response lever retracted for 20 s to signal a post-infusion timeout in which cocaine was not available. After 20 s, the lever extended back into the chamber and cocaine was once again available. Pair-housed rats assigned to no-access conditions had an inactive response lever during their partner's self-administration sessions. Presses on this lever had no programmed consequences.

Experiment 1

Self-administration training—Self-administration training sessions were conducted daily for seven days. During these sessions, responding was reinforced on an FR1 schedule of reinforcement with 0.5 mg/kg/infusion cocaine. All sessions terminated automatically after 1 hr.

Self-administration testing—After 7 days of training, daily self-administration sessions were extended to 6 hr with no limit placed on the number of infusions that could be earned. Each session began at the start of the dark phase of the daily light/dark cycle (star time: 1700) and ended 6 hr later (end time: 2300). All other experimental events were identical to those used during training. The dose of cocaine was maintained at 0.5 mg/kg/infusion in all test sessions. Testing continued in this manner for 14 consecutive days.

Data Analysis—Drug self-administration data were expressed as the number of infusions obtained and analyzed via two-way mixed-factor ANOVA, with group serving as a between-subjects factor and session serving as the repeated measure. Preplanned analyses comparing the first versus last 1, 3, 5 and 7 days of testing were also conducted using similar two-way, mixed-factor ANOVA. Group effects were further analyzed under conditions in which the omnibus test was significant using Fisher's Least Significant Differences Test. Cumulative records taken from the first (Day 1) and last (Day 14) test session were also analyzed to determine relative response rates and the duration of responding over the 6-hr test session. Relative response rates were calculated for each rat by determining the slope of a regression line fitted to the data for the duration of responding. The duration of responding was operationally defined as the elapsed time between the beginning of the session and the occurrence of the final lever press emitted during the session, and thus included the time allocated to lever pressing and the inter-response intervals. These data were analyzed via

two-way, mixed-factor ANOVA, with group serving as a between-subjects factor and session serving as the repeated measure. Inactive lever responding from rats without access to cocaine was examined via repeated-measures ANOVA, with session serving as the repeated measure.

Experiment 2

Self-administration training—Self-administration training sessions were conducted daily for 10 days, with the FR value increasing from FR 1 to FR 5 according to the following schedule: days 1–4 (FR1), day 5 (FR2), day 6 (FR3), day 7 (FR4), days 8–10 (FR 5). During these sessions, responding was reinforced with 0.5 mg/kg/infusion cocaine. All sessions terminated automatically after 2 hr.

Self-administration testing—Beginning two days after the conclusion of self-administration training, 23-hr test sessions were conducted at three-day intervals. During these sessions, lever presses produced an infusion of cocaine on an FR5 schedule of reinforcement. Each session began at the start of the dark phase of the daily light/dark cycle (start time: 1700) and ended the following day, 60 min before the start of the next dark phase (end time: 1600). Three doses of cocaine (0.5, 1.0, and 2.0 mg/kg/infusion) and saline were each tested once in an irregular order 73 hr apart.

Data Analysis—Drug self-administration data were expressed as cocaine intake (mg/kg) and analyzed via two-way, mixed-factor ANOVA, with group serving as a between-subjects factor and dose serving as the repeated measure. Area under the curve values were determined via the trapezoidal rule, and these data were analyzed via one-way ANOVA with group as the factor. Group effects were further analyzed under conditions in which the omnibus test was significant using Fisher's Least Significant Differences Test. Data from each 23-hr session were also analyzed by examining the cumulative record of each rat to determine relative response rates and duration of responding over the 23-hr test period. Relative response rates were calculated for each individual rat by determining the slope of the regression line fitted to the data for the duration of responding. The duration of responding was operationally defined as the elapsed time between the beginning of the session and occurrence of the lever press representing the 99th percentile of total lever presses emitted during the session, and thus included the time allocated to lever pressing and the inter-response intervals. We defined the termination of lever pressing as the response representing the 99th percentile of total lever presses to prevent a mischaracterization of this time point under those few instances in which a single (likely inadvertent) lever press occurred hours after the cumulative record revealed that self-administration had ceased. These data were analyzed via two-way, mixed-factor ANOVA, with group serving as a between-subjects factor and dose serving as the repeated measure. Inactive lever responding from rats without access to cocaine was examined via repeated-measures ANOVA, with dose of cocaine (based on the dose available to their self-administering partner) serving as the repeated measure.

Results

Experiment 1

A total of 73 rats completed Experiment 1 (partner no access group: $n = 20$; isolated group: $n = 29$; partner w/access group: $n = 24$).

Rats from all three groups escalated their cocaine intake over the 14 days of testing [main effect of session: $F(13, 910) = 14.721, p < .001$]. The rate of escalation was similar across groups, as indicated by parallel increases in cocaine intake over the 14-day period (Figure 1A) and the lack of a significant group $\times$ session interaction. Large differences were observed across groups in total cocaine intake [main effect of group: $F(2, 70) = 3.237, p = .045$], and post-hoc comparisons revealed that rats with a partner without access to cocaine self-administered significantly less cocaine than isolated rats ($p = .028$) and rats with a partner with access to cocaine ($p = .027$). Isolated rats did not differ from rats with a partner with access to cocaine. Planned comparisons of responding between the first and last 1, 3, 5, and 7 days of testing revealed a similar pattern of effects (Figure 1B). In all cases, cocaine intake was less during the first 1, 3, 5, and 7 days than the last 1, 3, 5, and 7 days (main effects of day in all cases), and significant differences in cocaine intake were observed across groups (main effects of group in all cases). Differences across groups were attributed to rats with partners without access to cocaine responding less than isolated rats (all cases) and less than rats with partners with access to cocaine (all but one case).

Cumulative records revealed patterns of responding that are characteristic of cocaine-maintained responding on an FR1 schedule of reinforcement (Figure 2). Generally, rats displayed a “load up” phase during the first 10 min of the session, followed by a consistent rate of responding for the remainder of the 360-min session. Analysis of these cumulative records (Table 1) revealed that relative response rates increased in all groups from the first (Day 1) to last (Day 14) day of testing [main effect of session: $F(1, 70) = 44.750, p < .001$]. Significant differences were observed across groups [main effect of group: $F(2, 70) = 4.370, p = .016$], and this effect was attributed to rats with a partner without access to cocaine responding at a slower rate than isolated rats ($p = .016$) and rats with a partner with access to cocaine ($p = .008$). The relative response rates of isolated rats did not differ from rats with a partner with access to cocaine. Almost all rats responded for the full duration of the 360-min session, and no differences in the duration of responding were observed between the first and last day of testing or across the three groups.

For rats without access to cocaine, inactive lever responding was low and did not vary as a function of session (Figure 3). Responses from these rats remained steady over the 14-day period and did not track the responding of their partners.

Experiment 2

A total of 47 rats completed Experiment 2 (partner no access group: $n = 14$; isolated group: $n = 15$; partner w/access group: $n = 18$).

The number of infusions decreased monotonically as a function of dose in all groups (data not shown). Cocaine intake (defined in mg/kg) varied in a biphasic fashion [main effect of

dose: $F(2, 88) = 24.302, p < .001$], with the lowest intake occurring when responding was reinforced with 1.0 mg/kg/infusion (Figure 4A). Cocaine intake also varied across group [main effect of group: $F(2, 44) = 3.689, p = .033$], and this effect was consistent across the three doses of cocaine. Post-hoc analyses revealed that rats with partners without access to cocaine self-administered less cocaine than rats with partners with access to cocaine ($p = .009$). Cocaine intake for isolated rats was intermediate between the other two groups, but isolated rats did not differ significantly from either other group. Similar effects were also observed in an AUC analysis (Figure 4B). Specifically, significant differences were observed across groups [$F(2, 44) = 4.551, p = .016$], with rats with a partner without access to cocaine generating lower AUC values than rats with a partner with access to cocaine ($p = .004$).

Cumulative records revealed patterns of responding typical of cocaine-maintained responding on an FR5 schedule of reinforcement (Figure 5). Specifically, responding was characterized by a “step-like” pattern, in which a rapid series of five responses was followed by a post-reinforcement pause, the duration of which was generally consistent within a test session. Analyses of these cumulative records (Table 2) revealed that relative response rates decreased as a function of dose [main effect of dose: $F(2, 88) = 104.992, p < .001$] and differed across the three groups [main effect of group: $F(2, 44) = 3.518, p = .038$]. Post-hoc tests revealed that rats with a partner without access to cocaine had lower response rates than rats with a partner with access to cocaine ($p = .013$). Response rates of isolated rats were intermediate between the other two groups, but isolated rats did not differ significantly from either other group. The majority of rats in all three groups responded for the full duration of the 23-hr test sessions. The duration of responding increased as a function of dose [main effect of dose: $F(2, 88) = 10.401, p < .001$], but no main effect of group or group x dose interaction was observed.

For rats without access to cocaine, inactive lever responding was low and did not vary across sessions (Figure 6). Responses from these rats were not related to the dose of cocaine available to their partners.

Discussion

The goal of the present study was to examine the effects of social contact on cocaine self-administration in extended-access test sessions that model problematic drug use. To this end, rats were assigned to either isolated or pair-housed conditions in which a social partner either had access to cocaine or did not have access to cocaine. In Experiment 1, rats with a partner without access to cocaine self-administered less cocaine across 14 consecutive days of 6-hr test sessions. In Experiment 2, rats with a partner without access to cocaine self-administered less cocaine across a range of doses during 23-hr test sessions. These data suggest that the behavior of a peer, as opposed to merely the presence of a peer, influences how social contact influences cocaine intake under extended-access conditions. In both experiments, exposure to a partner that was not self-administering cocaine (i.e., an abstaining partner) was protective, limiting cocaine intake under conditions that model the escalating and excessive patterns of cocaine intake characteristic of substance use disorders.

In Experiment 1, we examined the escalation of cocaine intake during daily 6-hr test sessions. Typically, daily, 6-hr test sessions produce an acceleration of drug self-administration within each session and an escalation of drug intake across sessions (Ahmed & Cador, 2006; Ahmed & Koob, 1998; Liu, Roberts, & Morgan, 2005; Mantsch, Yuferov, Matthieu-Kia, Ho, & Kreek, 2004). Escalated drug intake with extended access is a robust phenomenon that promotes long-term behavioral and neurobiological changes, which have been proposed to contribute to the transition to an addiction-like state (Ahmed, Kenny, Koob, & Markou, 2002; Ferrario et al., 2005; Mantsch et al., 2004; Oleson et al., 2009; Zernig et al., 2007). In the current study, all rats escalated their responding across 14 days of testing, suggesting a transition from a controlled and stable pattern of intake towards an escalated and dysregulated pattern of intake. The behavioral mechanisms responsible for escalation may be due to a combination of changes in reward allostasis (Ahmed & Koob, 2005), tolerance (Oleson & Roberts, 2009), incentive sensitization (Berridge, 2007), habit formation (Everitt & Robbins, 2005), and discrimination learning (Beckmann, Gipson, Marusich, & Bardo, 2012). Neuroadaptations in mesolimbic dopamine and glutamate systems are possible neurobiological mechanisms underlying these changes (Koob et al., 2004; Madayag et al., 2010) and are posited to account for the persistence of drug addiction and relapse (Kalivas & O'Brien, 2008).

All groups escalated their cocaine intake at a similar rate, suggesting that social contact neither accelerates nor slows the progressive behavioral and neurobiological changes that lead to the escalation of cocaine intake over time. Analysis of cumulative records indicated that all rats responded for the full duration of the 6 hr sessions on both the first and last day of testing, and that changes in cocaine intake were due to an increase in the relative rate for responding from the first to the last day of testing. Significant differences were observed in overall cocaine intake across the three groups, which were attributed to rats with partners without access to cocaine self-administering less cocaine and responding at a slower pace than isolated rats and rats with partners with access to cocaine. The lower levels of cocaine intake in rats with a partner without access to cocaine is significant because overall cocaine use in humans is associated with a number of negative consequences, including exposure to violence, criminal activity, and sexually transmitted diseases (Carvalho & Seibel, 2009; Kramer et al., 2012; Nuttbrock, Rosenblum, Magura, McQuiston, & Joseph, 2000). Moreover, interventions that reduce or prevent escalating patterns of intake protect individuals from the problems of abuse and addiction (U.S. Congress Office of Technology Assessment, 1994). Although our data suggest that the presence of an abstaining partner will not prevent the development of dysregulated patterns of cocaine intake, they do suggest that the presence of an abstaining partner will limit overall cocaine intake, thus limiting the harmful consequences of drug exposure during both early and late stages of a cocaine use disorder. These findings are consistent with a recent behavioral economic study in which rats with a social partner without access to cocaine self-administered less cocaine than isolated rats and rats with a social partner with access to cocaine (Peitz et al., 2013). In that study, isolated rats did not differ from rats with a partner with access to cocaine, similar to that observed in Experiment 1. The reasons these two groups did not differ are not known, but the behavioral mechanisms that contribute to the facilitation of cocaine self-administration

may be less robust than those that contribute to the inhibition of cocaine self-administration (for examples and discussion, see Strickland & Smith, 2014).

In Experiment 2, drug intake was examined during 23-hr test sessions designed to model “binges” of excessive cocaine self-administration (Mutschler et al., 2001; Tornatzky & Miczek, 2000). Results from this experiment indicate that social contact influenced cocaine intake and that this effect was consistent across all doses of cocaine tested. Specifically, pair-housed rats with a social partner without access to cocaine self-administered significantly less cocaine than pair-housed rats with a partner with access to cocaine. These findings are similar to those we’ve reported previously in rats responding on FR and PR schedules of reinforcement under limited-access conditions (Smith, 2012; Smith et al., 2014).

Analysis of cumulative records from Experiment 2 indicated that differences across the three groups were due to differences in the rate of responding over the 23-hr test sessions. It is important to note that the final 11 hr of each session overlapped the light (i.e., inactive) phase of the daily light/dark cycle, and that the majority of rats in all three groups responded during the entire session. Responding that extends into the inactive phase reflects a disruption of circadian patterns of activity and suggests a loss of behavioral regulation regarding drug intake (Roberts, Brebner, Vincler, & Lynch, 2002; Tornatzky & Miczek, 2000). It is significant that the three groups did not differ in the duration of responding because it suggests that social contact does not influence the loss of circadian control of drug intake that might emerge during an extended binge of cocaine use. Rather, social contact influences the overall amount of cocaine consumed during a binge, which directly impacts the likelihood of an overdose related to stroke, seizure, or myocardial infarction (Chang, Kowalski, Carhuapoma, Tamargo, & Naval, 2016; Klonoff, Andrews, & Obana, 1989; Minor, Scott, Brown & Winniford, 1991; Ritz & George, 1993). We previously reported that physical activity (i.e., wheel running) reduces cocaine intake during 23-hr test sessions by significantly decreasing the duration of responding and thus preserving the circadian control of behavior (Smith, Walker, Cole, & Lang, 2011). When considered in conjunction with the present data, such findings suggest that the controlling variables mediating cocaine intake under extend-access conditions differ across behavioral manipulations.

We note that the effects reported in these two experiments are not necessarily applicable to females. Males were selected for this project in order to directly compare data collected under extended-access conditions to those collected previously in males responding under short-access conditions (Smith, 2012). We are currently conducting studies examining the effects of social contact on measures of drug self-administration in females, with the added manipulation of including mixed-sex dyads in our experiment design. Such studies are particularly relevant for public health research, given the ubiquitous nature of male-female dyads in human relationships. We also note that these effects do not necessarily apply to unfamiliar partners. We chose to use familiar dyads to better approximate the social bonds that exist within established peer groups. Gipson and colleagues (2011) reported that exposure to an unfamiliar partner without access to a drug facilitated amphetamine self-administration, suggesting that the effects of an unfamiliar partner may differ from those of a familiar partner. However, this effect was transient and only observed at a single dose of amphetamine.

It is unlikely that the effects of social contact observed in these experiments are limited to cocaine specifically or to psychoactive drugs in general. Studies of social learning using other positive (e.g., food, water) and negative (e.g., electric shock avoidance, candle flame avoidance) reinforcers are consistent with the effects reported in this study (for examples, see Bunch & Zentall, 1980; John, Chesler, Bartlett, & Victor, 1968; Strobel, 1972). Moreover, previous studies using nondrug reinforcers have described how social contact can both increase and decrease responding maintained by food. For instance, if responding by a demonstrator monkey signals the availability of food for an observing monkey, then manipulations that increase or decrease responding in the demonstrator produce corresponding increases or decreases in responding by the observer (Danson & Creed, 1970). Although previous studies examining social learning using nondrug reinforcers have not employed procedures that lead to “binge” patterns of responding, the same social-learning processes would likely be at play (for review, see Strickland & Smith, 2014).

A growing number of studies have shown that drug self-administration can be moderated by the behavior of a peer. For example, monkeys increased consumption of phencyclidine (PCP) when tested in the presence of another monkey with access to PCP, suggesting the presence of a drug-using peer enhances the reinforcing strength of PCP (Newman, Perry, & Carroll, 2007). Anacker, Loftis, and Ryabinin (2011) found that isolated prairie voles classified as high drinkers decreased their alcohol consumption when partnered with a low drinking vole; however, high-drinking voles maintained high levels of consumption when partnered with another high-drinking vole. Numerous human studies have also demonstrated that subjects imitate the drinking behavior of a confederate, with subjects exposed to a heavy-drinking partner consuming more alcohol throughout the session (Caudill & Kong, 2001; Caudill & Marlatt, 1975; Lied & Marlatt, 1979). Furthermore, in studies using a naturalistic bar setting, social partners showed similar rates of sip initiation of alcoholic beverages. Specifically, subjects were more likely to take a sip of a beverage following a confederate’s sip, and this probability was greatest when both subjects were drinking alcohol (Larsen, Engels, Souren, Granic, & Overbeek, 2010). Together, these findings demonstrate that a social peer can influence both total drug intake and individual patterns of drug self-administration.

It is notable that the non-reinforced responding of rats without access to cocaine was not influenced by the responding of their self-administering partners, or by the presumed level of intoxication of their partners. Inactive lever responding in these rats was uniformly low and did not vary across test sessions. We previously reported that inactive lever pressing of rats without access to cocaine varied as a function of the dose available to their partner with access to cocaine under limited-access conditions (Smith, 2012). It is not known why similar effects were not observed in these experiments, but it may be a consequence of the extended test sessions. Cumulative records from subjects without access to cocaine revealed small bouts of responses that occurred at irregular intervals, but with decreasing frequency as the sessions continued. Consequently, periods of mutual lever pressing between social partners were very limited, and confined mostly to the early portions of the sessions.

From a translational perspective, these findings suggest an individual’s social environment can influence patterns of behavior relevant to substance use disorders. Increasing social

contact with nondrug-using peers may decrease an individual's use of cocaine or other drugs, even after the transition has been made from regulated to uncontrolled, compulsive patterns of use. Furthermore, these findings indicate that the presence of a nondrug-using peer may be more influential than the presence of a drug-using peer. Thus, treating any one member of a peer group, or introducing a new nondrug-using peer, could have positive effects on other members of the group. More broadly, these findings extend a long history of research in psychopharmacology on the effects of environmental factors on drug effects by showing that an individual's social environment must be considered in the management of substance use disorders.

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Public Health Significance

Social contact with peers influences the likelihood that an adolescent or young adult will use drugs. Using an animal model, we show that maladaptive patterns of escalating and excessive drug use can either be enhanced or inhibited by social contact, depending on whether a social peer also has access to drugs.

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Figure 1.

Escalation of cocaine intake over 14 daily test sessions in pair-housed rats with a partner without access to cocaine ($n = 20$), isolated rats ($n = 29$), and pair-housed rats with a partner with access to cocaine ($n = 24$). **A.** Data from all 14 days of testing. Vertical axes depict number of infusions obtained during 6-hr test sessions (left axis) and cocaine intake in mg/kg (right axis). Horizontal axis indicate session number relative to the beginning of extended-access conditions. Vertical lines extending from data points represent the SEM. **B.** Data averaged over the first and last 1 day (upper left), 3 days (upper right), 5 days (lower left), and 7 days (lower right) of testing. Vertical axes depict number of infusions obtained during 6-hr test sessions. Vertical lines extending from bars represent the SEM. Horizontal lines indicate significant differences between groups.

Figure 2.

Cumulative records from one pair-housed rat with a partner without access to cocaine (Rat 2771; left panel), one isolated rat (Rat 2566; middle panel), and one pair-housed rat with a partner with access to cocaine (Rat 2573; right panel). Data are shown from the first (Day 1) and last (Day 14) day of testing during 6-hr test sessions. Vertical axes depict cumulative number of responses; horizontal axes depict time expressed in hr. Inset graphs depict a magnified view of the cumulative record during the first 60 min of the session.

Figure 3.

Non-reinforced responding of rats without access to cocaine compared to their self-administering partners over 14 daily test sessions. Data are shown for rats without access to cocaine ($n = 20$) and their partner with access to cocaine ($n = 20$; data redrawn from Figure 1). Vertical axis depicts number of lever presses during 6-hr test sessions. Horizontal axis indicates session number relative to the beginning of extended-access conditions. Vertical lines extending from data points represent the SEM.

Figure 4.

Cocaine self-administration during 23-hr test sessions in pair-housed rats with a partner without access to cocaine ($n = 14$), isolated rats ($n = 15$), and pair-housed rats with a partner with access to cocaine ($n = 18$). **A.** Dose-response analysis. Vertical axis depict cocaine intake in mg/kg; horizontal axis depict dose of cocaine in mg/kg/infusion. Vertical lines extending from data points represent the SEM. **B.** Area Under the Curve (AUC) analysis. Vertical axis depict AUC values of the dose-response data as determined by the trapezoidal rule. Vertical lines extending from bars represent the SEM. Horizontal line indicates significant difference between rats with a partner without access to cocaine and rats with a partner with access to cocaine.

Figure 5.

Cumulative records from one pair-housed rat with a partner without access to cocaine (Rat 2606; left panel), one isolated rat (Rat 2622; middle panel), and one pair-housed rat with a partner with access to cocaine (Rat 7370; right panel). Curves are shown for all three doses of cocaine tested (0.5, 1.0, and 2.0 mg/kg/infusion) during 23-hr test sessions. Vertical axes depict cumulative number of responses; horizontal axes depict time expressed in hr. Inset graphs depict a magnified view of the cumulative record during the first 60 min of the session.

Figure 6.

Non-reinforced responding of rats without access to cocaine compared to their self-administering partners as a function of cocaine dose. Data are shown for rats without access to cocaine ($n = 14$) and their partner with access to cocaine ($n = 14$). Vertical axis depicts number of lever presses during 23-hr test sessions. Horizontal axis indicates dose of cocaine available to the self-administering partner. Vertical lines extending from data points represent the SEM.

Table 1Relative response rate and duration of responding across conditions in Experiment 1^a

Group	<u>Relative Response Rate^b</u>		<u>Duration of Responding^c</u>	
	Day 1	Day 14	Day 1	Day 14
Partner no Access	0.17 (0.02)	0.26 (0.03)	355.25 (0.98)	356.30 (0.60)
Isolated	0.23 (0.02)	0.32 (0.02)	356.24 (0.70)	356.79 (0.68)
Partner w/Access	0.23 (0.02)	0.33 (0.02)	356.08 (0.98)	356.58 (0.96)

^a data reflect the mean (SEM)^b relative response rate was calculated as the slope of the regression line fitted to the portion of the cumulative record covering the period of active responding^c duration of responding was defined as the time in minutes between the beginning of the session and the occurrence of the final lever press

Table 2Relative response rate and duration of responding across conditions in Experiment 2^a

Group	Relative Response Rate ^b			Duration of Responding ^c		
	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg
Partner no Access	1.39 (0.22)	0.51 (0.06)	0.37 (0.04)	1116.6 (83.8)	1156.4 (90.1)	1205.8 (93.3)
Isolated	1.56 (0.17)	0.61 (0.05)	0.43 (0.02)	1171.4 (61.8)	1198.5 (71.7)	1349.2 (22.8)
Partner w/Access	1.99 (0.21)	0.75 (0.04)	0.43 (0.02)	1198.3 (43.9)	1282.6 (44.1)	1352.0 (15.6)

^a data reflect the mean (SEM)^b relative response rate was calculated as the slope of the regression line fitted to the portion of the cumulative record covering the period of lever pressing^c duration of responding was defined as the time in minutes between the beginning of the session and the occurrence of the lever press representing the 99th percentile of total lever presses emitted