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Peer Influences on Drug Self-Administration: An Econometric Analysis in Socially Housed Rats

Geoffrey W. Peitz¹, Justin C. Strickland², Elizabeth G. Pitts², Mark Foley^{1,3}, Scott Tonidandel², and Mark A. Smith^{1,2}

¹Center for Interdisciplinary Studies, Davidson College

²Department of Psychology, Davidson College

³Department of Economics, Davidson College

Abstract

Social-learning theories of substance use propose that members of peer groups influence the drug use of other members by selectively modeling, reinforcing, and punishing either abstinence-related or drug-related behaviors. The objective of the present study was to examine social influences on cocaine self-administration in isolated and socially housed rats, with the caveat that the socially housed rats were tested simultaneously with their partner in the same chamber. To this end, male rats were obtained at weaning and housed in isolated or pair-housed conditions for 6 weeks. Rats were then implanted with intravenous catheters and cocaine self-administration was examined in custom-built operant conditioning chambers that allowed two rats to be tested simultaneously. For some socially housed subjects, both rats had simultaneous access to cocaine; for others, only one rat of the pair had access to cocaine. An econometric analysis was applied to the data, and the reinforcing strength of cocaine was measured by examining consumption (i.e., quantity demanded) and elasticity of demand as a function of price, which was manipulated by varying the dose and ratio requirements on a fixed ratio schedule of reinforcement. Cocaine consumption decreased as a function of price in all groups. Elasticity of demand did not vary across groups, but consumption was significantly lower in socially housed rats paired with a rat without access to cocaine. These data suggest that the presence of an abstaining peer decreases the reinforcing strength of cocaine, thus supporting the development of social interventions in drug abuse prevention and treatment programs.

Keywords

cocaine; consumption; demand; elasticity; rat; reinforcing strength; self-administration; social; social learning; unit price

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Epidemiological studies consistently report that one of the strongest predictors of adolescent and young adult substance use is whether an individual's peers also use alcohol, tobacco, and illicit drugs (Bahr et al., 2005; Picotte et al., 2006; Simons-Morton and Chen, 2006; Fowler et al., 2007). Social-learning theories of substance use posit that members of peer groups influence the substance use of other members by selectively modeling, reinforcing, and punishing either abstinence-related or drug-related behaviors (see reviews by Kandel, 1986; Andrews and Hops, 2010; Pandina et al., 2010). Evidence supporting the role of

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

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social-learning theories in substance use is limited – ethical constraints limit the degree to which substance use can be modeled and/or reinforced in human populations, and very few preclinical models permit animals to model and/or reinforce the substance use behavior of peers. However, human laboratory studies report that individuals will often imitate the drinking behavior of a model consuming alcohol (Caudill and Marlatt, 1975; Lied and Marlatt, 1979; Larsen et al., 2009), and animal studies report that responding maintained by nondrug reinforcers (e.g., food, water, escape from shock) is facilitated if a subject is allowed to observe an experienced model (John et al., 1968; Strobel, 1972; Bunch and Zentall, 1980; Henning and Zentall, 1981; Hake et al., 1983). To date, very few studies have extended these findings to responding maintained by intravenous drug administration, the most common method by which drug reinforcement is examined in the laboratory.

In a recent study, we described the use of custom-built, operant conditioning chambers to examine intravenous drug self-administration in two animals simultaneously in the same chamber (Smith, 2012). In that study, all socially housed rats remained in the chambers for the duration of testing and were separated from one another by a wire screen. For some socially housed rats, both members of the pair had simultaneous access to cocaine, but for others, only one member of the pair had access to cocaine. Relative to individually housed control rats, 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 member of the pair had access to cocaine. Thus, it was the self-administration behavior of a peer (as opposed to simply the presence of a peer) that determined whether cocaine intake was facilitated or inhibited by social contact. Such findings suggest that socially housed rats influence the drug self-administration of their partners, and that these effects can either enhance or attenuate the reinforcing effects of a drug.

The purpose of the present study was to further examine the role of social influence on cocaine self-administration by performing a more comprehensive analysis of the reinforcing strength of cocaine in isolated and socially housed rats. This was accomplished by manipulating the unit price of cocaine by varying the dose and the ratio requirement on a fixed ratio (FR) schedule of reinforcement. Cocaine intake was measured at each price and then an econometric analysis was performed on the resulting demand curve. An econometric analysis offers some advantages over traditional measures of drug self-administration (e.g., response rate, total number of infusions) because it allows multiple dimensions of reinforcing strength to be measured at each unit price. For instance, both consumption (i.e., the quantity demanded) and point elasticity (i.e., the responsiveness of demand to an infinitesimally small change in price) can be determined at each point of a demand curve to determine how different manipulations influence the reinforcing strength of a drug across an infinite number of unit prices. Such information can then be used to determine the efficacy of potential interventions to change the reinforcing effects of cocaine across a wide range of economic conditions.

One limitation of our previous study was that the socially housed animals were never removed from the operant chambers once self-administration training was initiated, and thus were continually separated from their cagemates by a wire screen throughout the period of behavioral testing. In the present study, all rats were returned to their home cage after each experimental session, thus permitting full species-typical social contact (e.g., pinning, chasing, rolling, grooming) in the pair-housed rats for 21 hours each day. This change was made to improve the ecological validity of the model by allowing dyadic social interactions to unfold naturally in the pair-housed animals. Similar to our previous study, for some socially housed rats, both members of the pair had access to cocaine, whereas for the other socially housed rats, only one member of the pair had access to cocaine. Data from both

groups were compared to a control group, which remained under isolated conditions for the entirety of the study. Finally, locomotor activity was examined in all groups following self-administration testing to determine whether any group differences in cocaine self-administration could be attributed to differences in general drug sensitivity.

Methods

Subjects

Male, Long-Evans rats were obtained at weaning (~21 days) and assigned randomly to isolated and pair-housed conditions 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. Pair-housed rats were kept in polycarbonate cages of equal dimensions, but with two rats assigned to each cage. At the beginning of self-administration training (see below), pair-housed rats were further subdivided randomly into two-access and one-access groups. In the two-access groups, both members of the pair were trained to self-administer cocaine, and self-administration tests were conducted in both rats. In the 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 pair-housed rats remained with their partner from weaning until the end of study and were never exposed to other rats inside or outside the home cage. Five cohorts of rats (n = 9–12 rats per cohort) were tested over a 15-month period at 2–4 month intervals. Each cohort had approximately equal numbers of subjects in each of the three experimental groups. Throughout the study, all rats were kept in a temperature- and humidity-controlled colony room maintained on a 12-hr light/dark cycle (lights on: 05:00). Food and water were available freely in the home cage, except during the brief period of lever-press training (see below). 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

Lever-press training using food reinforcement (45 mg Noyes grain pellets) was conducted in commercially available operant conditioning chambers from Med Associates, Inc. (St Albans, VT). Each chamber was equipped with two retractable response levers, one houselight, and one 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 were conducted in custom-built, operant conditioning chambers (Faircloth Machine Shop, Winston-Salem, NC). Chambers for isolated rats were cubic in design (interior dimensions: 30 cm × 30 cm × 30 cm) and constructed from stainless steel with a solid rear wall and 14-gauge (1.6 mm) wire sidewalls for ventilation (Fig. 1). Each chamber contained one retractable response lever and an infusion pump mounted outside the chamber. Drug infusions were delivered through plastic tubing protected by a stainless-steel spring and attached to a counterbalanced swivel at the top of the chamber. Chambers for pair-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 a response lever beyond the reach of its companion. 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. Software and interfacing for the chambers were obtained from Med Associates, Inc.

Locomotor activity tests were conducted in open-field, locomotor-activity chambers (interior dimensions: 43 × 43 × 30 cm) obtained from Med Associates, Inc. The chamber consisted of a PVC floor and acrylic sidewalls with aluminum corner supports. Two circuit boards were located on opposite sidewalls 2.5 cm above the floor of the chamber. One board contained 16 infrared photocells spaced 2.5 cm apart; the opposite board contained 16 infrared detectors with identical spacing. Software and interfacing for the chambers were obtained from Med Associates, Inc.

Lever-Press Training

Five weeks after arrival and one week prior to catheter implantation, all rats were lightly food restricted to no less than 90% of their free-feeding body weights and trained to lever press using food reinforcement. During these initial training sessions, each lever press was reinforced on a fixed ratio (FR1) schedule of reinforcement. All sessions terminated automatically once 40 reinforcers were delivered or 2 hr elapsed. If any rat had not acquired by the third day of training, one shaping session was conducted in which a technician shaped the lever press response using manually delivered food pellets. Once a rat earned 40 reinforcers during any four training sessions, training was discontinued and the rat was placed back on free feed. All rats met this criterion within 7 days and no differences were observed across groups.

Surgery

Six weeks after arrival and following the completion of lever-press training, 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 was then surgically implanted into the right jugular vein, routed subcutaneously over the shoulder, 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.

Self-Administration Training and Testing

All training and testing sessions were conducted in the custom-built operant conditioning chambers. Self-administration training began three days after surgery and each session started promptly at the beginning of the dark phase of the light-dark cycle (17:00). Each session began with the insertion of a retractable lever into the cage and a noncontingent priming infusion of 0.5 mg/kg cocaine HCl. For the remainder of the session, lever pressing was reinforced on an FR1 schedule of reinforcement. On this schedule, each response activated an infusion pump that delivered 0.5 mg/kg/infusion cocaine over 2.5 – 4.0 s duration (based on body weight). Simultaneous with each infusion, the lever retracted to signal a 20 s post-infusion timeout. After 20 s, the lever extended back in 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 maximum number of infusions that could be earned, other than those set by the session length and post-infusion timeout. All sessions terminated automatically after 180 min. Training continued in this manner for four days, at which time behavioral testing commenced. No-access rats (i.e., nonuser rats) in the one-access group were tethered to the infusion line by the counterbalanced spring, and the lever

extended into the chamber for 180 min. Lever presses were recorded for these rats, but responses had no programmed consequences.

Behavioral testing commenced on the day immediately following the final training session. Testing lasted 12 consecutive days, during which the unit price of cocaine was systematically varied across sessions. Unit price was manipulated by varying the dose of cocaine (0.1, 0.3, 1.0 mg/kg) and FR value (1, 3, 7, 15) in each session. All unit prices were tested in a defined order with the stipulation that neither dose nor ratio value could increase or decrease for more than two consecutive sessions. Using this stipulation, each dose was tested in four-day blocks in the following order: 1.0, 0.1, and 0.3 mg/kg cocaine; within each block, each ratio value was tested once in the following order: 1, 7, 3, and 15. Similar to training sessions, each session started promptly at the beginning of the dark phase of the light-dark cycle with the insertion of the retractable lever in the cage and a priming infusion of the dose of cocaine available during that session. Each response activated the infusion pump and retracted the lever for 20 s to signal a post-infusion timeout. No limit was placed on the maximum number of infusions that could be earned and all sessions terminated automatically after 180 min. No-access rats (i.e., nonuser rats) in the one-access group were tethered to the infusion line by the counterbalanced spring, and the lever extended into the chamber for 180 min. Lever presses were recorded for these rats, but responses had no programmed consequences.

Locomotor Activity Testing

Locomotor activity was examined in a majority of rats following the conclusion of self-administration testing (note: a subset of rats ended testing immediately before a major holiday and could not be tested at a time point that was congruent with the other rats). One day following the conclusion of self-administration testing, rats were habituated to the locomotor activity chambers for one 60-min session. Over the next three consecutive days, locomotor activity tests were conducted with two doses of cocaine (3.0 and 10 mg/kg, ip) and saline. In all three tests, cocaine or saline was administered via intraperitoneal injection and each rat was placed individually into a locomotor activity chamber. Locomotor activity (operationally defined as distance traveled in cm) was measured over the next 60 min in the presence of white noise to mask extraneous sounds.

Data Analysis

In the self-administration experiment, cocaine intake at each price was applied to the following demand equation:

$$\ln Q = \beta_0 + \beta_1 P + \beta_2 ONE + \beta_3 TWO + \beta_4 P * ONE + \beta_5 P * TWO + \varepsilon \quad (1)$$

The dependent variable Q represents the amount of cocaine in mg/kg consumed at each dose and FR schedule combination (i.e., price). Each data point for Q came from a single rat during a single 3-hour self-administration session. Log transformation of these data yielded data for the dependent variable lnQ with units depicted as ln(mg/kg). β_0 , the intercept, indicates consumption at price zero for the isolated comparison group. P, price, represents the number of lever presses required to obtain 1 mg/kg cocaine. The variables ONE and TWO are dummy variables for rats in the one-access and two-access groups, respectively. The isolated group was defined *a priori* as the reference control group against which the other two groups were compared. The terms P*ONE and P*TWO were included to analyze potential price $\times$ group interactions. Finally, the error term ε represents variance in the data not explained by the independent variables. This log-linear equation allowed for elasticity to vary at different prices, thus providing additional opportunities to test for differences across groups.

Regression coefficients, marginal effects, and R^2 values were calculated for Equation 1 (Table 1). The White test (White, 1980) revealed evidence of possible heteroskedasticity in the estimated regression, $\chi^2(28) = 66.27$, $p = .0001$; consequently, heteroskedasticity-robust standard errors are reported. Although heteroskedasticity-robust standard errors differed slightly from the unadjusted standard errors, correcting for heteroskedasticity did not change the significance level of any coefficient or marginal effect.

Not shown but present in the equation are dummy variables for cohorts. As noted above (see Animals), there were five cohorts of rats that were tested over a 15-month period. We often see differences in cocaine intake in cohorts of rats that arrive at different time points, even when they come from the same breeder. Consequently, cohort variables were included to control for cohort fixed effects. Cohort 3 was defined *a priori* as the reference comparison group because it represented both the middle cohort and the midpoint of the period of data collection. We emphasize that the reference group is chosen arbitrarily because the choice does not change the coefficients for the other variables (e.g., P, ONE, TWO, P*ONE, P*TWO), and thus does not fundamentally change the results. The choice of the reference group also does not influence heteroskedasticity because both the data and the specification of the regression equation (i.e., Equation 1) remain constant.

Estimated coefficients were used to calculate the average marginal effect of price (ME_P), the average marginal effect of group (ME_{ONE} and ME_{TWO}), and the point elasticity of demand (η , the elasticity at a specific price-quantity combination) for each group, as shown in the following equations:

$$ME_P = \frac{\partial(\ln Q)}{\partial(P)} = \beta_1 + \beta_4 ONE + \beta_5 TWO \quad (2)$$

$$ME_{ONE} = \frac{\partial(\ln Q)}{\partial(ONE)} = \beta_2 + \beta_4 P \quad (3)$$

$$ME_{TWO} = \frac{\partial(\ln Q)}{\partial(TWO)} = \beta_3 + \beta_5 P \quad (4)$$

$$\eta = \frac{\partial(\ln Q)}{\partial(P)/P} = (\beta_1 + \beta_4 ONE + \beta_5 TWO)P \quad (5)$$

Marginal effects were analyzed via z-tests; coefficients on independent variables (e.g., β_1) were analyzed via Student t-tests. A statistically significant marginal effect for a certain group meant that consumption for that group was different from consumption for the isolated comparison group. Average elasticity was the average of the point elasticity values for each data point in a given group. Unpaired, two-sample, t-tests were used to compare the average elasticity between groups. Wald tests were used to compare the elasticity between groups at each specific price. The alpha level was set at .05 for all analyses.

Raw data from the cocaine self-administration experiments were analyzed via three-way, mixed-factor ANOVA, with group serving as a between-subjects factor and with dose and ratio value serving as within-subjects factors. Data from the locomotor activity tests were analyzed via two-way, mixed-factor ANOVA, with group serving as a between-subjects factor and dose serving as a within-subjects factor. Data obtained with saline were analyzed separately via one-way ANOVA, using group as a between-subjects factor.

Results

All rats responded on the first day of cocaine self-administration training, and 51 out of 53 rats (96%) received the maximum number of 21 infusions. Cocaine intake did not differ across the three groups over the remaining three days of training when responding was reinforced with 0.5 mg/kg/infusion. On the final day of training, the mean (SE) cocaine intake was 13.72 (1.45), 12.97 (1.43), and 13.94 (1.29) mg/kg in the isolated, one-access, and two-access groups, respectively.

Cocaine intake varied as a function of group, dose, and ratio value (Fig. 2). A three-way, mixed-factor ANOVA revealed a main effect of group, $F(2, 50) = 4.695$, $p = .014$, dose, $F(2, 100) = 114.723$, $p < .001$, ratio value, $F(3, 150) = 89.273$, $p < .001$, a group $\times$ ratio interaction, $F(6, 150) = 4.586$, $p < .001$, a dose $\times$ ratio interaction, $F(6, 300) = 4.463$, $p < .001$, and a trend for a group $\times$ dose $\times$ ratio interaction, $F(12, 300) = 37.679$, $p = .057$. In general, cocaine consumption decreased with decreases in dose and increases in ratio value. Additionally, rats in the one-access condition consumed less cocaine than the other two groups, and this effect was most apparent at higher doses and lower ratio values.

When the self-administration data were applied to Equation 1, the intercept prediction and the marginal effect of price were both statistically significant ($p < .05$; Table 1). As expected, consumption decreased systematically with increases in unit price. On average, an increase in price of 1 lever press per mg/kg decreased the quantity of cocaine consumed by approximately 2%, $z = -19.10$, $p < .001$ (Fig. 3).

The marginal effect of the one-access group indicated that rats in this group consumed significantly less cocaine than rats in the isolated group, $z = -2.88$, $p = .004$. On average, the one-access group consumed approximately 30% less cocaine than the isolated group, regardless of price. In contrast, the marginal effect of the two-access group was not significant, indicating that cocaine consumption in this group did not differ from that of the isolated group.

The marginal effects for the one-access and two-access groups differed by a magnitude of 0.347. In other words, rats in the one-access group consumed approximately 29% less cocaine than rats in the two-access group. Equation 1 does not allow for the calculation of the standard error for this difference; however, by omitting the dummy variable for the two-access condition instead of the isolated condition, the standard error for the marginal effect of the one-access group compared to the two-access group may be calculated. In this scenario, the standard error is 0.146, which reflects a statistically significant difference ($p = 0.017$). Given that the two-access group was not defined *a priori* as the reference comparison group, this finding must be considered exploratory.

Interactions between price and group were measured by the coefficients for the P*ONE and P*TWO variables (Table 1). The interaction between price and the two-access group and the interaction between price and the one-access group were both nonsignificant. Thus, the marginal effect of each group was consistent across all unit prices examined.

As noted above (see Methods), cohort dummy variables were included in the econometric analysis to control for cohort fixed effects. The third cohort was tested in the middle of the 15-month period of data collection and served as the reference comparison group for this analysis. Rats in the first cohort consumed 83% more cocaine than rats in the third cohort, $t(626) = 3.62$, $p < .001$, and rats in the fifth cohort consumed 107% more cocaine on average than rats in the third cohort, $t(626) = 4.46$, $p < .001$. In contrast, rats in the second cohort, $t(626) = -1.39$, $p = .166$, and fourth cohort, $t(626) = 1.44$, $p = .150$, did not differ from those in the third cohort. To determine the impact of the cohort dummy analysis on the

econometric measures, we removed the cohort variable from the regression analysis and reanalyzed the cocaine self-administration data. Although the magnitude and standard errors for some of the marginal effects changed slightly when cohort fixed effects were left uncontrolled (data not shown), it did not fundamentally change the significance of any of the effects described above.

The magnitude of point elasticity increased as a function of unit price (Fig. 4). Wald tests indicated that point elasticity did not differ as a function of group. The average elasticity of demand was -0.691 , -0.682 , and -0.572 for the two-access, one-access, and isolated groups, respectively.

The responses of the no-access rats in the one-access group were recorded but had no programmed consequences. The mean (SE) number of lever presses emitted by this group ranged from 13.24 (2.28) to 17.29 (4.39) across the 12 days of testing. No significant differences were observed across the 12 test sessions, indicating that the responding of these rats did not vary as a function of the responding of their self-administering companions.

In the locomotor activity test, cocaine produced dose-dependent increases in distance traveled in all three groups [main effect of dose: $F(1, 35) = 21.644$, $p < .001$] (Fig. 5). Importantly, no differences were observed across the three groups at either dose of cocaine tested. Similarly, no differences were observed across the groups following saline administration.

Discussion

The principal finding of this study is that the presence of a peer without access to a drug decreases the reinforcing strength of cocaine as measured by reductions in cocaine consumption. The effects of this social manipulation were specific to the maintaining event (i.e., the contingent delivery of cocaine), because no differences were observed to the effects of cocaine on locomotor activity. The study also revealed that increases in the unit price of cocaine decreases the consumption of cocaine and increases the point elasticity of cocaine, regardless of social condition. Finally, the findings revealed that the presence of a companion self-administering cocaine does not alter the reinforcing strength of the drug as measured by either consumption or demand elasticity, at least in comparison to an isolated control group.

The econometric analysis used in the present study provided two measures of reinforcing strength: consumption and point elasticity. Each of these measures provides unique and useful information for understanding the reinforcing effects of cocaine. For instance, consumption reveals the quantity of drug used, which frequently serves as the primary outcome measure of animal, human laboratory, and human clinical studies examining the abuse liability of cocaine and other drugs of abuse. Point elasticity, a term borrowed from the economic literature, measures the sensitivity of demand to infinitesimally small changes in price. The unit price of cocaine was manipulated by varying both the dose and ratio requirement of cocaine, resulting in a 150-fold range of prices tested. As expected, consumption decreased and point elasticity increased as a function of unit price, indicating that cocaine loses its reinforcing strength as the price of cocaine systematically increases. These findings are consistent with a large number of studies reporting that measures of drug intake decrease as the dose of cocaine decreases or as the response requirement of cocaine increases (e.g., Pickens et al., 1981; Files et al., 1993; Nader et al., 1993; Wee et al., 2007; Christensen et al., 2009).

We previously reported that cocaine self-administration was facilitated in pair-housed rats with simultaneous access to cocaine (Smith, 2012), and we predicted that the reinforcing

strength of cocaine would be greatest in pair-housed rats with simultaneous access to cocaine in the present study. Although this group differed from the pair-housed group in which only one rat of the pair had access to cocaine, it did not differ from the isolated comparison group at any unit price. One critical difference between the two studies is in the schedules of reinforcement that were used to characterize the reinforcing effects of cocaine. Our previous study used only a ratio value of 1 on the FR schedule, whereas the present study used a range of ratio values across three doses of cocaine. Interestingly, numeric differences can be observed across the three groups in the present study if only data from the FR1 sessions are considered, and these differences are consistent with those reported in our previous study (Two-Access > Isolated > One-Access). As noted above (see Introduction), we also changed another important experimental parameter in the present study in order to increase the ecological validity of the model. In our prior study, rats remained in the self-administration chambers continuously (i.e., 24 hr/day) throughout the period of behavioral testing, thus limiting the social interactions between companion animals. In contrast, rats in the present study were able to engage in unrestricted species-typical social behavior for 21 hr/day in the home cage, such as pinning, chasing, and rolling, as well complex behavioral sequences of deception and surprise attacks (Panksepp et al., 1984). These behaviors play a critical role in the development of normal social relationships in socially housed rats (Hol et al., 1999; Van den Berg et al., 1999; Von Frijtag et al., 2002), and likely play a modulatory role in social learning tasks in which responding depends on the degree of familiarity between the subjects (see, for example, Choleris et al., 1998; Galef et al., 1998; Kavaliers et al., 2005).

Previous studies have reported that rats living under conditions of environmental enrichment, conditions in which multiple rats are housed together in the same cage, exhibit less drug-seeking behavior than rats living in isolation (Green et al., 2002; Thiel et al., 2009; Gipson et al., 2011; Ranaldi et al., 2011). It is thus notable that the pair-housed rats with simultaneous access to cocaine administered at least as much as the isolated rats in the present study. Such findings suggest that the presence of a self-administering peer can “block” the protective effects of an enriched environment on measures of drug-seeking behavior, and may carry a “risk” that is similar in magnitude to that of prolonged social isolation. These findings further suggest that proximal social factors at the time of drug taking may be as important, and possibly more important, than factors in an individual’s home environment in determining the likelihood that drug use will occur.

Consistent with our predictions, the reinforcing strength of cocaine was lowest in pair-housed rats with a no-access companion. Interestingly, this effect was apparent on measures of cocaine consumption but not on measures of cocaine elasticity. It is important to note that consumption and elasticity are independent measures of reinforcement strength, and it is not surprising that the two measures were differentially responsive to the experimental manipulation. Indeed, drug self-administration studies have long used different schedules of reinforcement to tease apart these different aspects of drug reinforcement. For instance, FR1 schedules of reinforcement are believed to be models of intake regulation, whereas progressive ratio schedules of reinforcement are believed to be models of demand elasticity (Arnold and Roberts, 1997; Solinas et al., 2004; Oleson et al., 2009). Thus, reinforcing strength can be conceptualized as possessing both satiety factors (measured by consumption) and motivational factors (measured by elasticity). The present study indicates that these two components are functionally independent, and that social manipulations may influence drug satiety without influencing motivational factors related to the drug. This is not to suggest that motivational factors are not sensitive to environmental manipulations, as previous studies have reported changes in drug demand following experimental manipulations of the external, albeit not social, environment (Carroll et al., 1991; Carroll, 1993; Lenoir and Ahmed, 2008).

It is important to note that the differences between the one-access group and the other two groups cannot be attributed to traditional pharmacological explanations based on differences in the pharmacokinetics or pharmacodynamics of cocaine across the three groups. No differences were observed in sensitivity to the effects of either a low (3.0 mg/kg) or high (10 mg/kg) dose of cocaine on locomotor activity. This is relevant because both the locomotor and reinforcing effects of cocaine are mediated by similar neuroanatomical substrates, and both are consequences of cocaine's action at the dopamine transporter (Mead et al., 2002; Chen et al., 2006; Thomsen et al., 2009). Such findings support the proposition that the effects observed in the self-administration test were specific to the testing environment.

Social-learning models of substance use posit that social factors related to modeling, imitation, reinforcement, and punishment have a causal influence on substance use behaviors (see Introduction). The present study offers some support for a social-learning model in that the self-administration behavior of a peer, as opposed to merely the presence of a peer, determined the reinforcing strength of cocaine. Findings such as these are consistent with a large body of literature indicating that modeling and social reinforcement influence responding maintained by nondrug reinforcers (see Angermeier, 1960; Heyes et al., 1992; Evans et al., 1994; Akins and Zentall, 1996; Akins et al., 2002). These findings also extend those from several recent studies examining proximal social factors (i.e., those present at the time of testing) on measures of drug reinforcement. For instance, Newman et al. (2007) reported that oral phencyclidine consumption was facilitated in monkeys presented with a familiar peer also consuming phencyclidine, and Gipson et al. (2011) reported that intravenous amphetamine consumption was facilitated in rats presented with an unfamiliar peer not consuming amphetamine (but this effect was not observed at a low dose of amphetamine and dissipated with repeated presentations). Consistent with the present findings, Anacker et al. (2011) reported that prairie voles that exhibited high levels of alcohol intake significantly reduced their alcohol consumption when paired with a low-drinking peer over four days during which alcohol and water were continuously available.

Evidence of proximal social factors on measures of drug reward has also been reported in several studies employing the conditioned place preference procedure. For instance, a low dose of cocaine (2 mg/kg, ip) and a low number of social pairings (2 pairings with an unfamiliar peer) failed to produce a place preference when administered alone, but produced a robust place preference when administered together (Thiel et al., 2008). Social interaction also reversed a previously established place preference for cocaine, and blocked the reinstatement of a cocaine-induced place preference after a priming injection (Fritz et al., 2011; El Rawas et al., 2012). It is important to note that species-typical social play is not necessary for social contact to produce rewarding effects, because social pairing establishes a place preference even when subjects are separated by a wire or mesh partition (Kummer et al., 2011; Peartree et al., 2012). This latter finding is relevant to the present investigation, because all rats assigned to the two social conditions were separated during the self-administration tests (but not in the home cage) by a wire screen to prevent the tethering systems from becoming entangled.

From a translational perspective, these findings suggest that changing an individual's social environment may serve to decrease substance use and abuse. Specifically, extensive social contact with a nonusing peer may decrease an individual's use of cocaine and similar drugs. The present findings also suggest that these protective effects would be observed under a wide range of economic conditions – under conditions in which cocaine is readily available and the unit price is low, and under conditions in which cocaine availability is limited and the unit price is high. Perhaps more importantly, these findings suggest that treating any one individual of a peer group may have positive effects on other group members by setting up a positive feedback loop in which abstinence-related behaviors are spread from one individual

to another. Finally, in terms of public policy, these results suggest that social programs that use positive role models to demonstrate and reinforce abstinence-related behaviors might be a cost-effective approach to reduce illicit drug consumption in adolescent and young adult populations.

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Figure 1.

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 $30 \times 30 \times 30$ 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 or response lever of its companion. 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.

Figure 2.

Cocaine self-administration in the three groups of rats. Data are shown for 1.0 mg/kg/infusion (left), 0.3 mg/kg/infusion (center) and 0.1 mg/kg/infusion (right) cocaine. Vertical axes depict cocaine consumption (mg/kg) during 3-hr session. Horizontal axes depict ratio values (1, 3, 7, and 15). Vertical lines represent the SEM; where not indicated, the SEM fell within the data point.

Figure 3.

Demand curves showing regression-predicted log consumption of cocaine as a function of price in the three groups of rats. Vertical axis depicts consumption expressed as ln[mg/kg]; horizontal axis depicts unit price of cocaine expressed as lever presses per mg/kg.

Figure 4.

Point elasticity of demand as a function of price in the three groups of rats. Vertical axis depicts point elasticity expressed as $\% \Delta \text{Quantity} / \% \Delta \text{Price}$; horizontal axis depicts unit price of cocaine expressed as lever presses per mg/kg. Vertical lines represent the SEM.

Figure 5.

Locomotor activity in the three groups of rats. Vertical axis depicts distance traveled expressed in cm ($\times 1000$); horizontal axis depicts dose of cocaine in mg/kg. Points above 0.0 depict the effects of saline. Vertical lines represent the SEM; where not indicated, the SEM fell within the data point

Table 1

Variable Effects for Equation 1.

Variable	Estimate (standard error)	
	EQ1	EQ1 (robust)
Intercept	1.539 [*] (0.146)	1.539 [*] (0.151)
Price	−0.018 [*] (0.002)	−0.018 [*] (0.002)
ONE	−0.267 (0.151)	−0.267 (0.153)
TWO	0.069 (0.154)	0.069 (0.145)
Price * ONE	−0.003 (0.003)	−0.003 (0.003)
Price * TWO	−0.003 (0.003)	−0.003 (0.003)
Cohort 1	0.606 [*] (0.161)	0.606 [*] (0.167)
Cohort 2	−0.234 (0.161)	−0.234 (0.169)
Cohort 4	0.221 (0.158)	0.221 (0.153)
Cohort 5	0.725 [*] (0.156)	0.725 [*] (0.163)
Marginal effect of price	−0.020 [*] (0.001)	−0.020 [*] (0.001)
Marginal effect of one	−0.358 [*] (0.122)	−0.358 [*] (0.124)
Marginal effect of two	−0.012 (0.127)	−0.012 (0.128)
<i>n</i>	636	636
<i>R</i> ²	.382	.382
Adjusted <i>R</i> ²	.373	.373

Values depict regression coefficient estimates, marginal effects, and goodness of fit measures for Equation 1. Both unadjusted and heteroskedasticity-robust standard errors are reported. Dependent variable is log of quantity of cocaine consumed.

Asterisks indicate statistical significance ($p < .05$).