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Social Preference and Drug Self-Administration: A Preclinical Model of Social Choice Within Peer Groups

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Abstract

Background—Selection models of substance use propose that individuals choose or self-select into peer groups based on shared substance use histories. Few experimental studies have examined the role of selection in substance use, possibly because few preclinical models allow subjects to choose or select individuals based on a shared self-administration history.

Methods—In the present study, we used custom-built, three-compartment, operant conditioning chambers that permitted multiple rats to self-administer cocaine simultaneously in the same session. Rats assigned to the center compartment had access to two response levers, each in close physical proximity to one of its partners. In one group, a rat with access to cocaine was assigned to the center compartment and flanked by one rat with access to cocaine and one rat without access. In a second group, a rat without access to cocaine was assigned to the center compartment and flanked by one rat with access to cocaine and one rat without access.

Results—In the first group, rats with access to cocaine emitted more responses on the lever in close proximity to the other rat with access to cocaine; in the second group, rats without access to cocaine emitted more responses on the lever in close proximity to the other rat without access. These preferences were not apparent immediately, but developed gradually over the course of several days of testing.

Conclusion—These data suggest that rats prefer to be in close physical proximity to another rat with a shared behavioral history during periods of drug self-administration.

Keywords

cocaine; choice; rat; selection; self-administration; social

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Contributors

Mark Smith conceived of the study and wrote the manuscript. Elizabeth Pitts contributed to the experimental design, was responsible for collecting all data, and edited the final draft of the manuscript. Both authors read and approved the final draft of the manuscript.

Conflict of Interest

The authors have no financial conflicts of interest in regard to this research.

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1. INTRODUCTION

One of the most reliable predictors of an individual's substance use is the prevalence of substance use among his or her social peers (Walden et al., 2004; Bahr et al., 2005; Simons-Morton and Chen, 2006). Explanations for the high concordance rate of substance use among members of peer groups are typically derived from either selection or social-learning theories of behavior (Kandel, 1986; Andrews and Hops, 2010; Pandina et al., 2010). Selection theories propose that individuals self-select into social groups that are similar to themselves. In these models, an individual chooses peers who share similar substance use beliefs, attitudes, and histories. In contrast, social-learning theories posit that members of a social group model substance use and other members imitate that use. Furthermore, members of the group reinforce the substance use of other members based on the norms established by that group. These models are not mutually exclusive of one another, but their relative contributions to substance use are not known.

Very few experimental studies have examined the role of selection and social learning in substance use. Such studies are difficult to conduct in humans 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 variables (i.e., variables outside the testing environment). For instance, animals experience a social manipulation in the home cage and are then compared to control animals on measures of intravenous drug self-administration. These studies have been critical in helping us understand how factors such as social stress, social isolation, social dominance, and social subordination impact drug-seeking and drug-taking behavior (Miczek et al., 2004, 2008; Stairs and Bardo, 2009; Nader et al., 2012). One criticism of these studies is that subjects must be removed from their social environment and separated from their cagemates during testing, thus preventing an examination of proximal social variables (i.e., variables present at the time of testing) on measures of drug self-administration. A number of practical issues must be addressed to overcome these limitations, such as the small size of commercially available testing chambers, the need to keep one animal from accessing the response lever of another animal, and the need to keep intravenous lines from becoming tangled.

We recently developed custom-built, operant conditioning chambers that permit two animals to be tested simultaneously during drug self-administration studies. These chambers allow two rats to have visual, auditory, olfactory, and limited tactile contact with one another through a wire screen, but they prevent one rat from accessing the response lever or intravenous lines of its partner. Using these chambers, we reported that cocaine self-administration is facilitated in pair-housed rats if both rats have access to cocaine; however, cocaine self-administration is inhibited if one member of the pair does not have access to cocaine (Smith, 2012). Such findings suggest that a partner's behavior (i.e., whether or not that partner is also self-administering a drug) determines whether drug self-administration is increased or decreased by social contact, and suggests that social learning may play a role in these effects.

To our knowledge, experimental studies addressing the role of selection in drug self-administration have not been conducted, possibly because of a lack of experimental models that allow a subject to "choose" or "select" a peer on the basis of a shared self-administration history. Recently, we further modified our operant conditioning chambers to permit three rats to be tested simultaneously. In the present study, rats were housed in triads and placed into three-compartment, operant conditioning chambers, with the center rat flanked by one rat with access to cocaine and one rat without access to cocaine. The chamber of the center compartment was partially divided by a solid partition that

functionally divided the compartment into two equal halves, each with one response lever. We tested the hypothesis that a rat would emit more responses on the lever in close physical proximity to the rat with a shared self-administration history. Consequently, the relative allocation of responses to the two levers was used as a proxy to measure “preference” or “choice” for one partner over another.

2. METHOD

2.1 Animals

Male Long-Evans rats were obtained at weaning (~21 days) and housed in triads in polycarbonate cages for the duration of the study. Cages were kept in a temperature- and humidity-controlled colony room maintained on a 12-hour light/dark cycle. Except during the period of lever-press training (see below), rats had free access to food and water in the home cage. All rats that were housed together were also tested together. Rats exhibited species-typical social behavior throughout the study (e.g., chasing, pinning, boxing), but no evidence of aggressive behavior resulting in injury was observed (e.g., scratches, bites). Dominance hierarchies, if present, were not determined. A total of 45 rats (15 triads) were used.

2.2 Apparatus

Rats were trained to press a response lever using food reinforcement in commercially available operant conditioning chambers from Med Associates, Inc. (St Albans, VT). Food training was conducted in chambers that were different from those used for cocaine self-administration because our custom-built, drug self-administration chambers do not have a food delivery device that permits an examination of food-maintained responding.

Drug self-administration sessions were conducted in custom-built, three-compartment, operant conditioning chambers (Faircloth Machine Shop, Winston-Salem, NC). Each of the three compartments was cubic in design and constructed from stainless steel with a solid rear wall and wire-screen sidewalls that separated each compartment (Figure 1). The wire screens allowed each rat visual, auditory, olfactory, and limited tactile contact with its partners, but prevented one rat from accessing the tethering system of its companions. Each chamber contained two retractable levers and an infusion pump mounted outside the chamber. Drug infusions were delivered through tubing protected by a flexible steel tether and attached to a counterbalanced swivel at the top of the chamber. The levers were placed 13 cm apart and 6 cm from each sidewall. Software and interfacing for the chambers were obtained from Med Associates, Inc.

The center compartment of each chamber contained a solid, stainless steel partition located midway between the two levers and extending 14 cm into the center of the chamber. Whenever a rat in the center compartment was responding on one lever, the partition occluded the view of the rat in the opposite compartment, no matter where in its compartment that rat was located; however, the rat in the center compartment could see the rat in the proximal compartment, no matter where in its compartment that rat was located. Consequently, the rat in the center compartment was forced to choose a response lever that was in close physical proximity to one companion but that occluded the view of the other companion.

2.3 Food Training

Five weeks after arrival, all rats were food restricted to no less than 90% of their free-feeding body weight and trained to lever press using food reinforcement during daily training sessions on a fixed ratio (FR1) schedule of reinforcement. Once a rat earned 40

reinforcers during any four training sessions, training was discontinued and the rat was placed back on unrestricted feed. Lever-press training with food increases the rate of acquisition of cocaine self-administration, such that rats respond on the first day of cocaine availability, and stable patterns of cocaine self-administration are obtained within 2–3 days (personal observations). Lever-press training was necessary in the present study because all three rats from each triad were tested in cocaine self-administration sessions simultaneously, and all experimental events were synchronized across the three subjects.

2.4 Surgery

Six weeks after arrival, rats were anesthetized with a combination of ketamine (100 mg/kg, ip) and xylazine (8.0 mg/kg, ip). An intravenous catheter was implanted into the right jugular vein and exited the body on the dorsal surface of the scapulae. Butorphanol (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 to maintain patency and prevent infection. After 7 days, ticarcillin administration was discontinued and only heparinized saline was used to maintain catheter patency.

2.5 Subject and Group Assignments

Self-administration sessions were conducted in the custom-built, three-compartment, operant conditioning chambers. Triads assigned to Group 1 (8 triads) consisted of two rats that had access to cocaine and one rat that never had access. Triads assigned to Group 2 (7 triads) consisted of one rat that had access to cocaine and two rats that never had access. For both groups, one side compartment contained a rat with access to cocaine and the other side compartment contained a rat that did not have access. These assignments were counter-balanced across triads. The critical difference between the two groups was that the rat in the center compartment had access to cocaine in Group 1 but did not have access to cocaine in Group 2.

Rats that did not have access to cocaine experienced all other experimental manipulations of the study, including lever-press training, catheter surgery, and daily catheter flushes. These procedures were followed to insure that any expression of social preference for one rat over another was due to a similar history with cocaine, and not due to any superficial aspect of the study. Access to cocaine was withheld from these rats by setting the FR value on their response levers to 9999.

2.6 Self-Administration Training

Immediately prior to each session, rats from each triad were placed into their assigned compartment. For rats with access to cocaine, each session began with the insertion of two levers into the chamber and a priming infusion of cocaine. All cocaine infusions (including the priming infusion) delivered 0.5 mg/kg cocaine hydrochloride in sterile saline. For rats with access to cocaine, cocaine was available on an FR1 schedule of reinforcement. On this schedule, each lever press on either lever resulted in an infusion of cocaine and retraction of both levers for 20 seconds. After 20 seconds, the levers extended back into the chamber and cocaine was again available on the FR1 schedule. Each session lasted 4 hours, with no limit placed on the number of infusions that could be earned. For rats without access to cocaine, each session began with the insertion of two levers into the chamber, but lever presses had no programmed consequences. Training continued in this manner for five consecutive days.

Rats assigned to the center compartment followed a slightly different training schedule than that described above. On the second and fourth day of training, only the left lever extended into the cage, and responses could only be made on this lever. On the third and fifth day of training, only the right lever extended into the cage, and responses could only be made on

that lever. The purpose of this manipulation was to force the rat in the center compartment to learn the contingencies operating on both levers prior to the beginning of testing. All rats were returned to their home cage after each session. To minimize the likelihood that cocaine was still behaviorally active, rats remained in the self-administration chambers for 60 minutes following all sessions.

2.7 Self-Administration Testing

Self-administration testing began on the day immediately following the fifth and final training session and lasted seven days. All conditions during the test sessions were identical to those described for the training sessions, with the exception that both levers in the center compartment extended into the cage, and the rat in this compartment was free to respond on either lever. All lever presses were recorded, regardless of whether the rat had access to cocaine.

2.8 Data Analysis

The primary dependent measures of this study were (1) the mean number of responses per session on each of the two levers, and (2) the mean percentage of total responses allocated to a given lever during each session. The mean number of responses on the two levers were compared via Student's *t*-tests. A significant preference for one lever over the other was assumed when the 95% confidence limits of the mean percentage of total responses for that lever did not overlap the 50% indifference point (i.e., the point in which an equal number of responses occurred on both levers). Data on the total number of responses was compared across rats via one-way ANOVA, followed by post hoc tests using the Bonferroni adjustment.

3. RESULTS

All rats responded during all five days of training, including those rats without access to cocaine in which responding had no programmed consequences (data not shown). All rats assigned to the center compartment alternated between the left and right levers during the final four days of training. All rats that began training completed all phases of the study.

3.1. Group 1 (No Access, Cocaine Access, Cocaine Access)

Within each triad, responding differed significantly across the three rats [$F(2, 23) = 8.741$, $p = .002$]. As shown in Figure 2 (upper panels), both rats with access to cocaine emitted more lever presses per session than the rat without access to cocaine ($p < .05$). The two rats in the side compartments did not exhibit a preference for one lever over the other; however, the rat in the center compartment with access to cocaine made a significantly greater number of responses on the lever in close proximity to its peer that also self-administered cocaine [$t(14) = 2.893$, $p = .012$]. This preference was not apparent immediately but developed over the course of several days. The percentage of responses allocated to the lever in proximity to the self-administering peer was not significant until the fourth day of testing, and remained significant every day thereafter (lower panels). On the final day of testing, rats in the center compartment made a mean (SEM) number of 62.3 (17.5) responses on the lever in close proximity to the self-administering peer versus 21.5 (9.49) responses on the other lever. No lever preference was observed in the two rats in the outer compartments on any day of testing.

3.2. Group 2 (No Access, No Access, Cocaine Access)

Within each triad, responding differed significantly across the three rats [$F(2, 20) = 11.594$, $p = .001$]. As shown in Figure 3 (upper panels), the rat with access to cocaine emitted more

lever presses per session than both rats without access to cocaine ($p < .05$). The two rats in the side compartments did not exhibit a preference for one lever over the other; however, the rat in the center compartment without access to cocaine made a significantly greater number of responses on the lever in close proximity to its peer that also did not have access to cocaine [$t(12) = 2.996, p = .011$]. Similar to that observed in Group 1, this preference was not apparent immediately but developed over the course of several days. The percentage of responses allocated to the lever in proximity to its peer without access to cocaine was not significant until the fifth day of testing, and remained significant every day thereafter (lower panels). On the final day of testing, rats in the center compartment made a mean (SEM) number of 13.1 (3.1) responses on the lever in close proximity to the peer without access to cocaine versus 3.9 (1.8) responses on the other lever. No lever preference was observed in the two rats in the outer compartments on any day of testing.

4. Discussion

The primary finding of this study is that rats in the center compartment self-administering cocaine emitted a greater number of responses on an active lever in close physical proximity to a peer that also self-administered cocaine. Similarly, rats in the center compartment without access to cocaine emitted a greater number of responses on an inactive lever in close physical proximity to a peer that also did not have access to cocaine. These preferences were not apparent immediately, but developed after several days; however, once established, the preference was maintained over the remainder of testing. In contrast, rats in the side compartments, which did not have a solid partition dividing the cage, never developed a preference for one lever over the other. Collectively, these data suggest that rats prefer to be in close physical proximity to another rat with a similar self-administration history, at least during times in which an operant response and subsequent drug infusion occurs.

4.1. Behavioral Mechanisms of Social Choice

Selection models of substance use propose that individuals “self-select” or “choose” social peers in terms of shared attitudes, beliefs, and histories of substance use. The center compartment of our experimental chambers forces a rat to choose a lever that is in close physical proximity to one partner and occludes the view of and prevents physical contact with the other partner. Rats with access to cocaine in the present study clearly developed a preference for a lever in close proximity to a peer that also self-administered cocaine. Although these data appear to support a selection model, several alternative explanations could also account for the observed findings.

For rats in Group 1, a rat in the center compartment could be imitating the behavior of its partners. In this scenario, when a rat was in close proximity to its partner with access to cocaine, it pressed the lever at high rates because that partner also pressed the lever at high rates. Alternatively, data obtained in Group 1 could be explained by social facilitation, a process by which a behavior is increased in the presence of others. Importantly, social facilitation is most pronounced if both individuals are performing the same action (Hake and Laws, 1967). In the present study, lever pressing of the rat in the center compartment was greatest when in proximity to the self-administering partner, possibly because that partner was pressing the lever at a high rate and social facilitation was greatest under these conditions. Furthermore, data obtained in Group 1 could be explained by stimulus enhancement, a process by which an individual draws attention to a stimulus in the environment that is associated with reinforcement (Fritz et al., 2000). In this scenario, rats in the center compartment would be more likely to make contact with a lever in close proximity to another rat that is pressing the lever at a high rate, presumably due to an increase in the stimulus control exerted by that lever. Finally, data from Group 1 could be explained by non-associative mechanisms. For instance, seeing a cocaine-intoxicated peer

may have produced anxiety that was manifested as nonspecific increases in behavior. Consequently, the apparent preference for one lever over the other could be an artifact of nonspecific rates of behavior between the two sides of the compartment.

We believe that data collected in Group 2 refute the possibilities described above. In this group, the rat in the center compartment never had access to cocaine, and lever presses had no programmed consequences. Traditional social-learning explanations of behavior would predict that greater responding, even in the absence of programmed reinforcement, would occur at a higher rate on the lever in close proximity to its self-administering partner. Indeed, explanations based on imitation, social facilitation, and stimulus enhancement would all predict that the rat would respond more when in proximity to a partner that is pressing the lever at a high rate. Similarly, non-associative explanations based on nonspecific increases in motor activity elicited by seeing a cocaine-intoxicated peer would also predict greater responding on the lever in close proximity to that peer. Instead, rats in the center compartment allocated more responses on the lever in close proximity to its partner without access to cocaine, even though that rat emitted relatively few lever presses. It was thus a shared behavioral history, at least as it pertains to a shared set of environmental contingencies during testing, that was predictive of how behavior was allocated between the two levers.

It is notable that rats without access to cocaine responded throughout the 7 days of testing when there was no stimulus change, saline infusion, or programmed consequence when the lever was pressed. We believe that prior food training, coupled with the presence of another rat self-administering cocaine, is responsible for sustained lever pressing over extended periods of time. Indeed, similar patterns of non-reinforced responding were obtained in rats with a similar behavioral history in a previous study (Smith, 2012).

4.2. Limitations of the Model

One goal of the present study was to evaluate the procedure as a model of social preference when subjects are actively self-administering cocaine. Given this goal, the primary limitation of the model is that preference for a response lever was used as a proxy to infer preference for a particular individual. Although the only relevant feature of the environmental context that differed from one side of the compartment to the other was proximity to a rat with or without access to cocaine, it must be acknowledged that all sessions took place in the dark in the absence of human observers or video recording equipment. It is possible that allocation of responses is not a reliable indicator of how time is spent over the course of the session, and instead reflects only episodes of time in which a response and subsequent drug infusion occurs. We emphasize, however, that an analysis of how behavior is allocated in the seconds surrounding a response is important for understanding how proximal social factors impact drug self-administration.

A second limitation of the model is that the available data do not distinguish between an affinity for (i.e., “an approach to”) one partner versus an aversion to (i.e., “a retreat from”) the other partner. This is relevant for a central tenet of selection theory, which states that similarities between individuals are critical for the formation of affiliative relationships (Kandel, 1985). Further design modifications to the chambers could potentially resolve this issue. For instance, a third lever located in a position that occluded the view of both partners could determine if a shift in responding away from one partner necessarily resulted in a shift toward the other partner.

A final limitation of the model is that it does not allow one to determine what aspect of the shared behavioral history is responsible for the expressed preference. At the broadest level, rats developed a preference depending upon whether it and one of its partners self-

administered cocaine. It is not known, however, whether it was the shared history of experiencing the unconditioned effects of cocaine, the shared history of experiencing response-contingent reinforcement, or the shared history of high rates of operant responding that was responsible for the development of this preference. Future studies using food-maintained behavior should be able to determine whether cocaine exposure is necessary for the development of a preference, or whether a preference may develop with only a shared history of operant training. Unfortunately, our current chambers are not equipped to examine food-maintained responding, and further design modifications will be needed to conduct these studies.

4.3. Conclusions

One of the principal limitations of examining proximal social influences on drug self-administration is a paucity of preclinical models that allow social manipulations to be performed during periods of active self-administration. We believe the current procedure models a relevant feature of the social environment as it pertains to a preference for one individual over another based on a shared history of drug self-administration. It is notable that this preference was observed in rats with access to cocaine and without access to cocaine. Such findings suggest that selection plays a role in the establishment and maintenance of groups in which substance use is a norm and in which abstinence is a norm. It is also notable that preference was not apparent initially in either group, but developed gradually over the course of several days. This finding suggests that selection-related processes may be malleable early in the establishment of social preferences, and that interventions to reduce or prevent substance use may be particularly effective during a critical period of group formation. In other words, groups may be more susceptible to outside influences before social preferences develop and before group norms that promote substance use are established.

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Figure 1.

Overhead view of a three-compartment operant-conditioning chamber allowing intravenous drug self-administration for three rats. 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). Wire screens between each compartment allow each rat visual, auditory, olfactory, and limited tactile contact with its partners, but prevent one rat from accessing the tethering system of its companions. All three compartments have two response levers positioned 13 cm apart and equidistant between the two side walls. The two response levers of the center compartment are separated by a solid partition that extends 14 cm into the chamber, thus preventing a direct line of sight to the opposite compartment when a rat is pressing a lever. This layout allows the center rat to “choose” a lever based on its proximal distance to another self-administering rat.

Figure 2.

Responding of two rats self-administering cocaine and one rat without access to cocaine. Left panels (No Cocaine Access): Mean (SEM) number of non-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the inner response lever on each of 7 daily test sessions (bottom panel). Center panels (Access to Cocaine): Mean (SEM) number of cocaine-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the lever adjacent to the self-administering peer (SA-peer Lever) on each of 7 daily test sessions (bottom panel). Asterisks (*) indicate significant difference between levers (top panel) and significant difference from the 50% indifference point (bottom panel). Right panels (Access to Cocaine): Mean (SEM) number of cocaine-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the inner response lever on each of 7 daily test sessions (bottom panel).

Figure 3.

Responding of two rats without access to cocaine and one rat self-administering cocaine. Left panels (No Cocaine Access): Mean (SEM) number of non-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the inner response lever on each of 7 daily test sessions (bottom panel). Center panels (No Cocaine Access): Mean (SEM) number of non-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the lever adjacent to the self-administering peer (SA-peer Lever) on each of 7 daily test sessions (bottom panel). Asterisks (*) indicate significant difference between levers (top panel) and significant difference from the 50% indifference point (bottom panel). Right panels (Access to Cocaine): Mean (SEM) number of cocaine-reinforced lever presses per session on each of two response levers over 7 consecutive days (top panel) and mean (95% CL) percentage of total responses on the inner response lever on each of 7 daily test sessions (bottom panel).