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Effects of Heroin on Rat Prosocial Behavior

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Abstract

Opioid use disorders are characterized in part by impairments in social functioning. Previous research indicates that laboratory rats, which are frequently used as animal models of addiction-related behaviors, are capable of prosocial behavior. For example, under normal conditions, when a “free” rat is placed in the vicinity of rat trapped in a plastic restrainer, the rat will release or “rescue” the other rat from confinement. The present study was conducted to determine the effects of heroin on prosocial behavior in rats. For two weeks, rats were given the opportunity to rescue their cagemate from confinement, and the occurrence of and latency to free the confined rat was recorded. After baseline rescuing behavior was established, rats were randomly selected to self-administer heroin (0.06 mg/kg/infusion i.v.) or sucrose pellets (orally) for 14 days. Next, rats were retested for rescuing behavior once daily for 3 days, during which they were provided with a choice between freeing the trapped cagemate or continuing to self-administer their respective reinforcer. Our results indicate that rats self-administering sucrose continued to rescue their cagemate, whereas heroin rats chose to self-administer heroin and not rescue their cagemate. These findings suggest that rats with a history of heroin self-administration show deficits in prosocial behavior, consistent with specific diagnostic criteria for opioid use disorder. Behavioral paradigms providing a choice between engaging in prosocial behavior and continuing drug use may be useful in modeling and investigating the neural basis of social functioning deficits in opioid addiction.

Keywords

opioid; heroin; sucrose; prosocial behavior; self-administration; operant

Introduction

Rates of heroin use have dramatically climbed over the last 15 years. Opioid overdose rates have also reached an all-time high, increasing threefold between 2010 and 2015, with 12,989 heroin-related deaths in 2015 alone (Rudd et al., 2016). A major factor that has led to increased heroin use is the over-prescription of opioid analgesics, which can lead to opioid dependency and transitioning to heroin use. Also contributing to this problem is the

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Author Contributions

SET and MFO were responsible for the study concept and design. SET acquired all data experimental data. SET and GMS performed data analyses. All authors contributed to the writing and review of the manuscript, and approved the final version for publication.

increasing amount of inexpensive and readily available heroin, which often contains fentanyl or other opioids to increase potency (Ciccarone et al., 2017)

Opioid use disorder is characterized in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)* by symptoms and behaviors that include impaired control over drug use, continued drug use despite harm, craving for the drug, withdrawal symptoms during abstinence, and persistent or recurrent social or interpersonal problems caused by or resulting from opioid use (APA, 2013). These social and interpersonal problems are the focus of the current study. Many clinical studies have aimed to evaluate interpersonal problems and their role in substance use disorders; however, this has proved to be difficult due to the fact that such problems in the context of addiction are dynamic and underpinned by a conglomerate of physiological, psychosocial, environmental, and motivational dysfunctions. Despite this, it has been shown that among heroin-dependent individuals, undergraduate marijuana users, psychiatric patients, incarcerated inmates, and police officers, empathy and socialization are the particularly deficient in heroin-dependent individuals (Kurtines et al., 1975). Therefore, loss of prosocial function may be an important feature of heroin addiction.

Previous research indicates that laboratory rats, which are frequently used as animal models of addiction and related behaviors, are capable of pro-social or empathy-like behaviors. Under normal conditions, when a "free" rat is placed in the vicinity of a "trapped" rat in a plastic restrainer (see Fig. 1), the rat will release the other rat from confinement, even if it has to give up food to do so (Ben-Ami Bartal et al., 2011). Further, the free rat will share its food with the trapped rat after it has been released (Ben-Ami Bartal et al., 2011). A subsequent study found that rats will continue to rescue "stranger" rats (i.e., non-cagemates), but not "stranger" rats of a different strain. However, once rescuer rats were acclimated to the different strain, they would release it from confinement (Ben-Ami Bartal et al., 2014). Ultimately, this indicates that previous social experience is a factor in pro-social behavior in rats. In another study, Sato et al. (2015) used a water-based paradigm, whereby a rescuer rat was allowed to release a soaked conspecific, and showed that rats previously soaked in water learned to rescue the soaked rat more quickly than those who had not been previously soaked.

The current study was designed to examine the effects of heroin on prosocial behavior in rats. Specifically, we examined whether a history of heroin self-administration would affect rats' willingness to aid a conspecific by releasing it from confinement. Unlike previous research using passive administration of a particular drug (Ben-Ami Bartal et al., 2016), in the present study rats were given the choice of rescuing their cage mate from the restrainer and/or self-administering either a drug (heroin) or non-drug (sucrose) reinforcer. We hypothesized that rats with a history of heroin self-administration would choose to continue to self-administer the drug instead of freeing the trapped rat, whereas rats with a history of sucrose self-administration would continue rescue their cagemate.

Methods

All experimental procedures were conducted with the approval of the Institutional Animal Care and Use Committee at Arizona State University and in accordance with the Guide for Care and Use of Laboratory Animals as adopted by the National Institutes of Health.

Animals

Sixty-four male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA), weighing ~250 g, were pair-housed upon arrival on a 12-hour reversed light–dark cycle (lights off at 0700 hr), and given ad libitum access to food and water during all experimental procedures except during behavioral testing. All experimental sessions took place during the dark phase of the light-dark cycle. Upon arrival, one rat from each pair was randomly selected and its tail was marked with a permanent marker. This rat was designated the rescuer rat while the other rat was designated the trapped rat. Thus, a total of $n=32$ rats were randomly selected to be rescuer rats, and $n=32$ cagemates were designated to be trapped rats. Animals were handled and weighed individually for 5 minutes daily for three weeks to allow them to acclimate to handling procedures (Fig. 2A).

Assessment of Baseline Prosocial Behavior

Following handling, animals underwent baseline assessment of prosocial behavior. Testing occurred at the same time of day every day for 2 weeks (Fig. 2A). In this procedure, each designated trapped rat was placed in a plastic restrainer (Harvard Apparatus, Holliston, MA; modified to 13.3 cm $\times$ 8 cm $\times$ 8.9 cm;) with a removable door, and the restrainer was placed in an operant conditioning chamber (Med Associates, St. Albans, VT; model ENV-008, custom modified to 43.2 cm $\times$ 20.3 cm $\times$ 22.9 cm). All self-administration chambers were located inside sound attenuating cubicles equipped with a house light and exhaust fan designed to mask external noise and odors, and were interfaced to a PC computer. Chambers were equipped with two nosepoke response holes on one wall, and a 4.2 $\times$ 5 cm pellet receptacle equipped with head entry detector between the response holes. Each response hole was located approximately 7 cm above a stainless steel grid floor, and positioned above each was a 2.5-cm diameter white stimulus light. Located near the top of the self-administration chambers was a Sonalert speaker that provided an auditory stimulus during reinforcer delivery. Located outside each chamber were a computer-interfaced syringe pump and pellet dispenser. For rats assigned to self-administer heroin, the syringe pump delivered the drug solution via a single-channel liquid swivel mounted atop the chamber via polyethylene tubing. For rats assigned to self-administer sucrose, the pellet dispenser delivered sucrose pellets into the receptacle. All rescuing and self-administration sessions were video recorded. Following placement of the trapped rat inside the restrainer into the operant chamber, the rescuer rat was then placed in the chamber, followed by illumination of a house light. The occurrence of and latency to rescue the trapped rat was recorded for each session. The maximum amount of time allowed in the operant chamber for each session was initially 1 hr, which was then reduced to 45 min and ultimately 30 min over the course of the 2 weeks of testing. In order to reduce the possibility that removal from the testing apparatus was a motivating factor for rescuing behavior, upon freeing of the trapped rat, rats remained

in the chambers for the duration of the session. Rats failing to release the trapped rat across the two weeks of baseline testing were removed from the study.

Surgical Procedures

After establishment of baseline rescuing behavior, rescuer rats were randomly assigned to self-administer heroin or sucrose as a non-drug reinforcer. Animals assigned to the heroin group were then surgically implanted with intravenous catheters into the jugular vein according to our previously published procedures (Watterson et al., 2014). Rats were anesthetized with isoflurane (2% v/v) vaporized oxygen at a flow rate of 2 l/min. Rats received pre-incision injections of buprenorphine (0.05 mg/kg, s.c., Henry Schein Animal Health, Dublin, OH) and meloxicam (1 mg/kg, s.c., Henry Schein Animal Health.). Surgical sites were shaved and disinfected with 1% povidone-iodine. A 2 cm incision was made in order to locate and isolate the right or left jugular vein. A sterile silastic catheter filled with 100 U/ml heparin was inserted 2.5 cm into the vein. The catheter was secured to the surrounding tissue with silk sutures, and the opposite end of the catheter was tunneled subcutaneously to the dorsum where it exited the skin between the scapulae. The catheter was secured to a vascular access port (Plastics One, Roanoke, VA or Instech Laboratories, Plymouth Meeting, MA – see note below), then sutured to the surrounding tissue. The wound was then closed with Ethicon nylon sutures and topically treated with topical lidocaine and triple antibiotic ointment. The access port was covered with an aluminum cap to prevent damage from cagemate chewing. All rats were allowed to recover from surgery for 5 days prior to the initiation of self-administration procedures (Fig. 2A). During this time, rats were single housed and received daily intravenous infusions of Timentin (66 mg/ml, dissolved in sterile saline containing 70 U/ml heparin, 0.1 ml volume) to maintain catheter patency and protect against infection. Meloxicam (2.5 mg/kg, s.c.) was administered once daily for 5 days following surgical procedures to provide additional relief of post-surgical discomfort, and buprenorphine (0.03 mg/kg s.c. was administered once daily for 3 days. To minimize any potential influence of peri- and post-operative analgesics (i.e., buprenorphine) on prosocial behavior, rats assigned to the sucrose control group did not undergo sham surgical procedures, but were separated from their cagemate during this time to maintain the same social conditions across groups. After recovery from surgery, all rats were returned to their respective pair-housing conditions.

Self-Administration Procedures

Following post-surgical recovery, rats underwent 6 hr daily self-administration sessions (Fig. 2A). For animals assigned to self-administer heroin, nosepoke entries into the designated active response hole resulted in delivery of heroin (Cayman Chemical, Ann Arbor, MI) at a dose of 0.06 mg/kg per infusion. Heroin was dissolved in sterile saline and delivered in a volume of 0.06 ml over a 2 sec period. For rats assigned to self-administer sucrose, nosepoke entries into the designated active response hole resulted in delivery of a 45 mg sucrose pellet (BioServ, Frenchtown, NJ). Self-administration was conducted on a fixed ratio 1 (FR1) schedule of reinforcement. Each heroin infusion or sucrose pellet delivery was followed by a 20-sec timeout period, during which additional active nosepokes were recorded but produced no drug infusions. Each reinforcer delivery was accompanied by concurrent illumination of a stimulus light located directly above the active response hole, and simultaneous presentation

of an auditory tone (2900 Hz, ~65 dB) for 2 sec. Nosepokes into a separate inactive hole had no programmed consequences at any time during the experiment. Self-administration sessions were conducted 7 days per week for 14 consecutive days. To verify catheter patency, rats were periodically administered sodium methohexital (10 mg/ml i.v., 0.2 ml volume) and observed for brief periods of immobility. Rats failing to demonstrate catheter patency continued to undergo testing throughout all experimental phases to serve as a non-patent reference group.

Since larger, customized operant conditioning chambers were required to accommodate the restrainer while allowing simultaneous self-administration behavior, extended length stainless steel tethers were utilized for intravenous infusions. However, in initial pilot studies, we found that extended length tethers increased tension on the vascular access ports and compromised catheter patency in many of the first cohort of animals. As a result, tethers made of a lighter material and vascular access ports with lower vertical profiles were used for all subsequent cohorts of animals. All other conditions detailed above were identical to those described above, and data from the rats that lost catheter patency during the experiment were included in the analyses as a non-patent surgitized control group. Analysis of video recordings (see below) revealed that neither the tether nor vascular access port type hindered the rats' ability to open the restrainer door.

Re-assessment of Prosocial Behaviors

Starting on the day following the last day of heroin or sucrose self-administration, the rescue paradigm was repeated as described above, with the exception of rats in the heroin group were attached to the infusion tethers as during the self-administration phase. Animals were tested for prosocial behaviors in 30-min sessions for 3 consecutive days, while being allowed concurrent access to their respective reinforcer (i.v. heroin or sucrose pellets, Fig. 2A). All post self-administration test sessions were video recorded.

Assessment of Opioid-Induced Behaviors

To address the possibility that heroin intoxication might interfere with the ability to perform the rescuing task, video recordings of the last three rescue test sessions in heroin self-administering rats were analyzed by three investigators blind to experimental condition. Opioid-induced behaviors were quantified using a rating scale developed by Seip and colleagues (2012), where stupor, pica, stereotypy, aberrant grooming, hyperactivity, and non-specific swallowing behaviors were rated on a scale of 0 to 4, with 0 representing an absence of the behavior and 4 representing severe or high frequency of occurrence. Scores for each measure were then averaged across all observers.

Data Analyses

Primary dependent measures were observation of rescuing the trapped rat, latency to rescue, number of active/inactive nose-pokes emitted, and number of heroin or sucrose reinforcers delivered. Observation of rescuing behavior on at least 3 days was required in order to establish baseline behavior and progress to the self-administration phase. Following heroin or sucrose self-administration, rescuing behavior was again measured three times in order to determine post self-administration rates of rescue, which was defined as the proportion of

rats completing the rescue task across the test session in 1 minute intervals. Self-administration data (number of infusions earned) were analyzed using a two-way ANOVA, with self-administration session and number of reinforcers delivered in each group as main factors. However, for repeated measures analysis of rescuing behavior in combination with heroin or sucrose self-administration, a multilevel model was used, where individual observations were nested within each individual rat. In order to account for observation of rescuing behavior as well as the latency to rescue, we conducted a survival analysis using the accelerated failure time (AFT) model in order to model the rate of rescue as predicted by the treatment condition (sucrose vs. heroin), the stage in the study (pre vs. post self-administration), and the interaction between these two variables (for details on survival analysis and the AFT model, see Allison, 2010). The primary measure of interest was a potential interaction between reinforcer group (heroin or sucrose) the stage of the study (pre or post self-administration), which would indicate whether the change of rate in rescue from the pre- to post self-administration stages differed across reinforcer type. Due to the lack of variability of the rescue rate in the heroin group after the self-administration, in which none of the rats rescued their cagemate, we imposed a penalty in order to obtain conservative but stable parameter estimates (Gart, 1966, adapted for survival analysis; see Agresti, 2002 for methods regarding handling of monotonic responses). All analyses were conducted in SAS Version 9.4. Statistical significance was considered to be reached for p -values < 0.05 .

Results

A total of $n=7$ rats were excluded from the study due to failure to demonstrate baseline rescuing behavior, and $n=2$ were excluded for failure to acquire heroin self-administration (>10 infusions per session). An additional $n=3$ animals were removed from the study due to surgical complications. Therefore, the final sample size consisted of $n=13$ rats ($n=6$ in the heroin group and $n=7$ in the sucrose group). An additional $n=7$ animals lost catheter patency during the experiment as demonstrated by lack of behavioral response to sodium methohexital. However, data from these animals were included in the analyses to control for the possibility that catheter implantation procedures and/or limited heroin intake influenced prosocial behavior.

During the self-administration phase (Fig. 2B), we observed a significant effect of self-administration session [$F_{13,198} = 6.69$, $P < 0.001$] and reinforcer group [$F_{2,198} = 7.68$, $P < 0.001$], with the number of reinforcers earned being increased as compared to the first self-administration session, and the number of sucrose reinforcers obtained being greater than that of the number of heroin reinforcers. In addition, the number of heroin reinforcers obtained was greater in the patent vs. non-patent groups (Fig 2A).

Table 1 shows the descriptive statistics for each condition including the proportion of rescues, the median latency to rescue, and the mean and standard deviation of the time until rescue among rats that demonstrated rescuing behavior for each reinforcer group and phase of the experiment. On average, prior to self-administration of heroin or sucrose, rescue rates were 78–91% (Fig. 2C). After the self-administration phase, rats self-administering sucrose rescued 76% of the time, and non-patent heroin rats rescued 81% of the time, whereas the rats receiving heroin stopped rescuing completely (0% rescue rate, Fig. 2C).

The main interest of the study was to determine whether the reinforcer condition had a significant effect on the change in rescuing behavior from pre- to post- self-administration phases, and it was found that this effect was significant. Table 2 shows the maximum likelihood parameter estimates of the multilevel survival analysis for the reinforcer condition, phase of the study, and their interaction, as well as the confidence intervals for each parameter estimate. The main parameter of interest was the treatment by stage interaction, which was statistically significant ($t_{12} = 3.57$, $P < 0.005$). These results indicate that after self-administration, rats receiving heroin significantly reduced their rescuing rate in comparison to rats receiving sucrose. These results are also reflected on Figs. 2C and 2D, which show that rats in the sucrose group consistently rescued before and after self-administration.

We further compared data from the group of $n=7$ rats that lost patency during the experiment to the sucrose group (Figure 2C) in order to rule out the possibility that the catheter implantation (rather than self-administration of heroin) was the reason for the change in rescue rates. A multilevel survival analysis was conducted comparing the non-patent and the sucrose rats. The results indicated that none of the parameter estimates were significantly different from 0 (see Table 3 for statistical values), indicating that rats in the sucrose and non-patent heroin groups did not differ from each other in their rescuing rate across reinforcer conditions or phase of the experiment.

Figure 2D shows the number of sucrose or heroin reinforcers obtained during each of the three sessions when concurrent self-administration and rescuing behavior was assessed. We observed neither an effect of session ($F_{2,24} = 2.24$, $P = 0.13$) or reinforcer group [$F_{1,24} = 0.32$, $P = 0.58$], indicating no differences in reinforcers obtained across the three sessions. Due to the loss of catheter patency, reinforcers obtained by rats in the non-patent heroin group were excluded from this analysis. Fig. 2E shows the total proportion of rescues during the 30-min (1800 sec) rescue sessions for each reinforcer condition before and after the self-administration phase. The line representing heroin self-administration is flat line at $y=0$, indicating that no rescues were observed.

To control for the possibility that the lack of observation of rescuing behavior in the heroin group was due to drug intoxication, we performed an assessment of opioid-induced behaviors during each of the final three test sessions using a rating scale developed by Seip and colleagues (2012). On a scale of 0 to 4, with 0 representing an absence of the behavior and 4 representing high levels of the behavior, the following scores were obtained (mean $\pm$ SEM): stupor (0.99 ± 0.21), pica (0.22 ± 0.03), stereotypy (1.53 ± 0.18), aberrant grooming (0.15 ± 0.15), hyperactivity (0.58 ± 0.22), and non-specific swallowing (0.44 ± 0.44). These values are lower than those observed by Seip and colleagues (2012) following non-contingent heroin exposure, where values of 2–4 were typically observed for these behaviors. In addition, although not quantified, such behaviors were not generally observed in animals in the non-patent of sucrose groups. These observations suggest that a lack of performance of the rescuing task in heroin self-administering rats was not likely a result of inability to do so due to heroin intoxication.

Discussion

The current study confirms previous findings that rats will exhibit prosocial behavior by releasing their cagemate from a plastic restrainer (Ben-Ami Bartal et al. 2011; Sato et al. 2015). We demonstrate that rats with a history of sucrose self-administration continue to rescue their cagemate, while rats with a history of heroin self-administration choose to continue heroin intake and do not rescue their cagemate. Further, rats that lost catheter patency during the experiment, and thus had a history of heroin intake but were unable to receive heroin during the final test, continued to rescue their cagemates. Thus, heroin intake appears to reduce the likelihood of prosocial behavior, particularly in the continued presence of drug access, which is reflective of the loss of social motivation and functioning in opioid-dependent individuals (APA, 2013).

One possible interpretation of our findings is that the intoxicating effects of heroin might have inhibited the ability of rats to perform the rescuing task when provided simultaneous access. However, we assert that this is unlikely for several reasons. First, using a opioid-induced behavioral rating scale developed by Seip and colleagues (2012), we did not observe evidence of significant heroin-induced stupor or other opioid-induced behaviors during these test sessions. In addition, the amount of heroin intake during these sessions (~9–10 infusions per 30 min session) were much lower than the amount of intake during longer access self-administration sessions (40–50 infusions per 6 hr session). Thirdly, a recent study by Ben-Ami Bartal et al. (2016) using a similar paradigm showed that rats receiving an acute administration of the benzodiazepine midazolam were still able to open the restrainer to obtain a palatable reward. Thus, heroin intoxication was not likely a factor in inhibiting rescuing behavior in the present study, although it is of interest for future studies to determine what level of heroin intake reduces the ability to perform the rescue task.

Some critics of this animal models of prosocial behavior, particularly the notion that it represents an expression of “empathy”-like behavior, argue that the willingness to release the trapped rat is primarily motivated by seeking social contact and interaction (Silberberg et al., 2014; Schwartz et al., 2017). In an attempt to address this issue, Ben-Ami Bartal and colleagues (2014) utilized a novel paradigm to demonstrate that rats would continue to release their cagemate from a restrainer even when the trapped rat was released into a separate chamber away from the rescuer rat, thus removing any subsequent social contact. Still, there is no universal agreement as to whether these behaviors are expression of empathy-like or social contact motivated behaviors. Regardless, we assert that such behaviors can be viewed as representative of prosocial functioning.

Prior research examining social behavior of rats with a history of opioid exposure has shown that rats that maintained in isolation vs. group housing more rapidly acquire heroin self-administration; however, over time, isolated rats do not self-administer more heroin overall than rats maintained in group housing conditions (Bozarth et al., 1987). Another study showed that group housed rats showed increased conditioned rewarding effects of heroin (0, 20, 40, and 80 µg/kg, s.c.) as compared to isolated rats (Schenk et al., 1982). Together these results suggest that housing conditions and social interaction may influence the rewarding and reinforcing effects of opioids.

The precise mechanisms and brain regions underlying heroin-induced deficits in social functioning and motivation are unknown. One likely substrate are cortico-limbic circuits that involve the dorsal anterior cingulate cortex, anterior mid-cingulate cortex, supplementary motor area, and bilateral insula, which can be considered a core neural network involved in social information processing and empathy-related behaviors (Fan et al. 2011; Namkung et al., 2017). In addition, a relationship between substance abuse and the insula was supported by a recent fMRI study that identified a positive association between activity in the posterior insula, substance abuse, and general disinhibition (Abram et al., 2015). In rodents, inhibition of protein synthesis in the insula disrupts drug-related contextual memories (Contreras et al., 2012), and this region also plays a role in drug seeking when alternative goals or competing contingencies are available (Naqvi, Gaznick, Tranel & Bechara 2014). Given the role of the insula in both drug-seeking and prosocial behaviors, future studies are needed to attempt to restore prosocial behavior following heroin intake using chemogenetic activation or other neuromodulatory approaches in one or more of these brain regions.

A potential limitation of the present study is the attrition of some subjects due to loss of catheter patency. However, rats that lost catheter patency during the experiment, and therefore had more limited heroin intake, continued to demonstrate prosocial behavior, suggesting that impaired social function may be a function of amount of prior drug intake. Additional studies are needed to examine other factors such as heroin dose, length of self-administration history, repeated cycles of intoxication and withdrawal, acute vs. protracted stage of abstinence, and whether these findings extend to other abused opioids (e.g., oxycodone or fentanyl) or other drugs of abuse (e.g., psychostimulants). Finally, it should also be noted that despite engaging in rescuing behavior following the self-administration phase, rats in the sucrose group also continued to self-administer sucrose (see Fig. 2D). These observations suggest that rats are capable of both prosocial and appetitive behaviors when both are available simultaneously, and are therefore not mutually exclusive of each other. It is therefore of interest to further explore potential influences of the presence of a trapped conspecific on the acquisition of heroin self-administration, since trapped cagemates were not present during this portion of the present study.

Overall, our findings also suggest that the rescue paradigm may represent a novel rodent model of impaired social function in opioid use disorders. Utilization of this model may give insight into the neural mechanisms of impaired social function in opioid addiction, and may lead to improved target strategies in facilitating recovery and treatment. As mentioned previously, a diagnostic criterion for opioid use disorder is persistent use despite interpersonal problems due to opioid use. Thus, if prosocial behavior can be restored in opioid addicted individuals via a specifically developed therapy and/or targeted medications, this may allow successfully rebuilding of social support systems and relationships affected by previous drug use, with the ultimate goal of having greater chances of reaching and maintaining sobriety. Finally, as mentioned previously, heroin use is often initiated as a result of prior dependence on prescription opioids as a result of pain management, future studies could explore the propensity to disengage from prosocial behaviors as a result of opioid self-medication to alleviate pain.

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Figure 1.
Photograph of a rescuer rat releasing a trapped rat from a plastic restraint.

Figure 2.

(A) Timeline of different phases of the current study. (B) Number of reinforcers earned during the self-administration phase across the three experimental groups (heroin, $n=6$), heroin non-patent ($n=7$), and sucrose ($n=7$). (C) Rescue rate (defined as the percent of sessions where rescuing behavior was observed) in the each experimental groups during the final 3 test sessions days prior to commencement of self-administration (baseline), and the final 3 tests sessions following the self-administration phase (post self-admin). (D) Number of reinforcers earned by rats in the heroin ($n=6$) and sucrose ($n=7$) groups across the 3 test sessions in which animals had simultaneous access to both their respective reinforcer and the trapped rat. (E) Total proportion of rescues across the 30 min in the test chamber for each of the reinforcer conditions ($n=6$ heroin, $n=7$ heroin non-patent, and $n=7$ sucrose) before and after the self-administration phases of the experiment.

Table 1

Proportion of rescues, median latency (in sec) to rescue, mean and standard deviation of latency to rescue (in sec) for each reinforcer group and experimental phase.

Treatment condition	Stage Pre or post self admin	Proportion of rescues	Median latency to rescue (in sec)	Mean (SD) of latency to rescue (in sec)
Sucrose	Pre	90.5%	60	78.83 (69.02)
	Post	76.2%	74	88.88 (153.20)
Heroin	Pre	77.8%	344	430.57 (464.91)
	Post	0%	N/A	N/A
Heroin non-patent	Pre	90.5%	146	362.11 (451.73)
	Post	80.7%	123	129.00 (96.85)

N/A, not applicable due to failure to demonstrate rescuing behavior.

SD, standard deviation

Table 2

Analysis of maximum likelihood estimates for each variable for the multilevel survival analysis comparing heroin and sucrose rats

Variable	<i>df</i>	Parameter Estimate Mean (SD)	<i>t</i> Statistic	<i>p</i> -value	95% C.I. Lower Bound	95% C.I. Upper Bound
Reinforcer condition	12	1.71 (0.81)	2.1	0.06	−0.06	3.47
Phase	12	0.41 (0.43)	0.94	0.37	−0.54	1.36
Treatment by Phase interaction	12	3.26 (0.91)	3.57	<0.05	1.27	5.26

Table 3

Analysis of maximum likelihood estimates for each variable for the multilevel survival analysis comparing sucrose rats and the rats that lost catheter patency during the experiment.

Variable	<i>df</i>	Parameter Estimate Mean (SD)	<i>t</i> Statistic	<i>p</i> -value	95% C.I. Lower Bound	95% C.I. Upper Bound
Reinforcer condition	13	1.02 (0.52)	1.96	0.07	−0.10	2.14
Phase	13	0.40 (0.52)	0.75	0.45	−0.72	1.52
Reinforcer by stage interaction	13	−0.38 (0.37)	−1.02	0.31	−1.18	0.42