Biological Psychiatry: Celebrating 50 Years

Archival Report

Operant Social Reward Decreases Incubation of Heroin Craving in Male and Female Rats

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ABSTRACT

BACKGROUND: We recently reported that operant social choice–induced voluntary abstinence prevents incubation of methamphetamine craving. Here, we determined whether social choice–induced voluntary abstinence would prevent incubation of heroin craving. We also introduce a fully automatic social reward self-administration model that eliminates the intense workload and rat–human interaction of the original semiautomatic model.

METHODS: In experiment 1, we trained male and female rats for social self-administration (6 days) and then for heroin self-administration (12 days). Next, we assessed relapse to heroin seeking after 1 and 15 abstinence days. Between tests, the rats underwent either forced or social choice–induced abstinence. In experiment 2, we developed a fully automatic social self-administration procedure by introducing a screen between the self-administration chamber and the social-peer chamber; the screen allows physical contact but prevents rats from crossing chambers. Next, we compared incubation of craving in rats with a history of standard (no-screen) or automatic (screen) social self-administration and social choice–induced abstinence.

RESULTS: The time-dependent increase in heroin seeking after cessation of drug self-administration (incubation of craving) was lower after social choice–induced abstinence than after forced abstinence. There were no differences in social self-administration, social choice–induced abstinence, and incubation of craving in rats trained in the standard semiautomatic procedure versus the novel fully automatic procedure.

CONCLUSIONS: Our study demonstrates the protective effect of rewarding social interaction on heroin self-administration and incubation of heroin craving and introduces a fully automatic social self-administration and choice procedure to investigate the role of volitional social interaction in drug addiction and other psychiatric disorders.

Keywords: Addiction, Animal models, Choice, Incubation, Motivation, Operant, Opioid, Rats, Reward, Self-administration, Social, Voluntary abstinence

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Research on neural substrates of drug reward, withdrawal, and relapse has yet to be translated into an advancement in addiction treatment (1,2). The reasons for the limited translational success of studies using rodent addiction models are complex and multifactorial (2–4). This state of affairs has led us to change the classic translational approach involved in identifying unique mechanisms of relapse-provoking stimuli (stress, discrete and contextual cues, and drug priming) (5,6) to a different reverse-translational approach (7,8). The goal of the reverse-translational approach is to develop animal models that mimic successful behavioral treatments in humans—contingency management (9) and community reinforcement approach (10)—to improve mechanistic understanding of abstinence and relapse.

Contingency management maintains prolonged abstinence by giving nondrug rewards (monetary vouchers) in exchange for negative drug tests (11–13). However, when contingency management discontinues, former drug users relapse to drug use (14,15). The community reinforcement approach employs similar learning principles, and its goal is to substitute drug use with alternative nondrug social rewards (e.g., family support, employment) contingent, at least in part, on cessation of drug use (10,16). However, as with contingency management, when the treatment discontinues, former drug users relapse to drug use (13,15). We recently developed rat models of voluntary abstinence and relapse based on these human behavioral treatments.

In the rat contingency management model, we first trained rats to self-administer palatable food (the alternative nondrug reward) and then to self-administer a drug (heroin or methamphetamine) for several weeks. We then assessed relapse to drug seeking during early and late abstinence days in the absence of the food reward. Between tests, we exposed rats to mutually exclusive choice sessions between drug and food (8,17). Under these contingency management conditions, rats voluntarily abstain from drug self-administration when the alternative nondrug reward is available, but they relapse when the food reward is removed (7,18–20).

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In the rat community reinforcement model, our goal was to improve the translational utility of the voluntary abstinence model by using social interaction as the alternative nondrug reward (8) because in humans the rewards that compete with drugs are primarily social (e.g., family, friends, employment) (16,21–23). We found that the availability of a mutually exclusive operant social reward prevented methamphetamine and heroin self-administration in the escalation model of addiction (24) and prevented methamphetamine self-administration in the DSM IV–based (25) and intermittent access (26) addiction models. Social choice–induced abstinence also prevented incubation of methamphetamine craving (8), the progressive increase in drug seeking after cessation of drug self-administration (27,28).

Here, based on studies showing behavioral and mechanistic differences between opiate and psychostimulant drugs (29–33), we determined whether the inhibitory effect of social choice–induced abstinence on incubation of methamphetamine craving generalizes to incubation of heroin craving. In addition, we developed a fully automatic social self-administration procedure by introducing a screen between the self-administration chamber and the social-peer chamber; the screen allows physical contact and prevents rats from crossing chambers (see Supplement for details). Next, we compared incubation of heroin craving in rats with a history of standard (no-screen) or automatic (screen) social self-administration and social choice–induced abstinence. We developed the screen model to eliminate limitations of the original model—intense workload and repeated physical interaction between the experimenter and rats, which can introduce experimenter-related confounds and induce rodent-related allergies.

METHODS AND MATERIALS

Subjects

We used male and female Sprague Dawley rats (Charles River Laboratories, Kingston, NY) (N = 192 rats: 96 resident [48 male and 48 female] and 96 social partners [48 male and 48 female]) weighing 150 to 175 g on arrival. We housed the rats 2 per cage by sex for 2 to 3 weeks and then individually starting 1 week prior to social self-administration. We randomly assigned rats to resident (drug user) and social partner (drug naïve) conditions. We maintained rats on a reverse 12-hour light/dark cycle (lights off at 8:00 AM) with free access to laboratory chow and water. The study followed the guidelines outlined in the Guide for the Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf) and was approved by the National Institute on Drug Abuse Intramural Research Program Animal Care and Use Committee. We excluded 8 rats (3 male and 5 female) because of catheter failure.

Surgery

We anesthetized the rats with isoflurane (5% induction and 2%–3% maintenance) and inserted into the jugular vein (Silastic Silicone Laboratory Tubing, 0.020 × 0.037 "wall 0.009"; VWR, Radnor, PA), which passed subcutaneously to the midscapular region, and attached to a modified 22-gauge cannula cemented to polypropylene mesh (Small Parts, Amazon.com). We injected ketoprofen (2.5 mg/kg, subcutaneous; Butler Schein, Dublin, OH) after surgery to relieve pain. We allowed the rats to recover from surgery for 3 to 4 days. We flushed the catheters daily with sterile saline containing gentamicin (4.25 mg/mL; Fresenius Kabi, Lake Zurich, IL) (8,19,34).

Procedures

Social Self-administration. We trained rats to self-administer for access to their social partner during daily 40-minute sessions (20 trials/session, 60 seconds, experiments 1 and 2) or 120-minute sessions (60 trials/session, 60 seconds, experiment 1) using a discrete trial design. We housed resident rats with their social partner (cage mate) until 1 week prior to social interaction self-administration, and each resident rat lever pressed for its previously paired partner. As previously described (8), the trials started with illumination of the social-paired houselight followed 10 seconds later by insertion of the social-paired lever; we allowed resident rats 60 seconds to press the active lever (fixed-ratio-1 reinforcement schedule) before lever retraction and houselight turning off. Successful lever presses caused the retraction of the active lever, a discrete 20-second tone cue, and opening of the guillotine-style sliding door. Resident rats were subsequently allowed to interact with their social partner for 60 seconds until the houselight turned off, at which point the guillotine door closed. We manually removed the social partner rats in experiments 1 and 2 for the standard group rats.

Drug Self-administration. We trained rats to self-administer heroin (fixed-ratio-1 20-second time-out reinforcement schedule, 0.1 mg/kg/infusion) (8,19,34) during six 1-hour sessions that were separated by 10-minute off periods. We limited the number of infusions to 15 per hour. We started the self-administration sessions at the onset of the dark cycle, and sessions began with the presentation of the red light and 10 seconds later with the insertion of the drug-paired lever; the red light remained on for the duration of the session and served as a discriminative cue for drug availability. At the end of each 1-hour session, the red light was turned off and the active lever was retracted (8,19).

Discrete Choice Procedure. We conducted the discrete choice sessions using the same parameters used during social and heroin self-administration training. We allowed the rats to choose between the social- and drug-paired levers in a discrete trial choice procedure. We divided each 120-minute choice session into 15 discrete trials that were separated by 8 minutes (8). Each trial began with presentations of the discriminative stimuli for social interaction and heroin, followed 10 seconds later by insertion of the levers paired with the rewards. Rats could then select one of the 2 levers. If rats responded within 6 minutes, they received only the reward corresponding with the selected lever. Each reward delivery was signaled by the social- or drug-associated cue, retraction of both levers, and turning off the discriminative cues. If rats failed to respond on either active lever within 6 minutes, both levers were retracted and the discriminative stimuli were turned

off with no reward delivery. We manually replaced both resident rats and social partner rats in their appropriate chambers after 60 seconds of social interaction (experiments 1 and 2, standard group rats).

Social Choice–Induced Abstinence. After the training phase, we allowed the rats to choose between the drug-paired lever (delivering one infusion) and social interaction (60 seconds) during 15 discrete choice trials (8 minutes apart) for 10 sessions over 14 days.

Forced Abstinence. After the day 1 relapse test, we returned the rats to their home cage for 14 days and then assessed relapse to heroin seeking on abstinence day 15. We handled the rats twice each week.

Relapse Tests. The 30-minute relapse tests were conducted in the presence of the heroin-associated cues. The sessions began with presenting the heroin-paired discriminative cue, followed 10 seconds later by insertion of the heroin-paired lever; the red light remained on for the session duration. Active lever presses during testing, the operational measure of drug seeking in incubation of craving and relapse studies (8,35), caused contingent presentations of the light cue previously paired with heroin infusions but not heroin.

Experiment 1: Incubation of Heroin Craving After Social Choice–Induced Abstinence

We previously reported that operant social reward prevented incubation of methamphetamine craving (8). In experiment 1, we tested whether social choice–induced abstinence would prevent incubation of heroin craving. We used 2 groups of rats (34 male and 32 female) in an experimental design that included the between-subjects factors of abstinence condition (forced or voluntary) and sex (male or female) and the within-subjects factor of abstinence day (1 or 15).

Training. We first trained rats to self-administer social interaction (6 sessions, 20 trials/session [23 female and 23 male] or 60 trials/session [9 female and 11 male]) and then trained them to self-administer heroin (12 sessions, 6 hours/session). We used the standard (semiautomatic) social self-administration and choice procedure.

Discrete Choice Tests. We determined social interaction versus heroin preference for 10 sessions in the voluntary abstinence group.

Relapse Tests. We tested the forced and voluntary abstinence rats for heroin seeking under extinction conditions on abstinence days 1 and 15. The duration of the test session was 30 minutes to minimize carryover effect of extinction learning, which may decrease drug seeking on day 15 testing.

Experiment 2: Incubation of Heroin Craving After Social Choice–Induced Abstinence Using the Automatic Procedure

In experiment 2, we compared social self-administration, social choice–induced abstinence, and incubation of heroin craving in rats trained in the semiautomatic standard (no-screen) procedure with those in rats trained in the new automatic (screen) procedure (Supplement). We used 2 groups of rats (4 male and 3 female in the no-screen group; 7 male and 8 female in the screen group) in an experimental design that included the between-subjects factor of voluntary abstinence condition (standard or screen) and the within-subjects factor of abstinence day (1 or 15).

Training. We first trained rats to self-administer social interaction (6 sessions, 20 trials/session) and then trained them to self-administer heroin (12 sessions, 6 hours/session).

Discrete Choice Tests. We determined social interaction versus heroin preference during training, after every 3 drug self-administration sessions, and for 10 sessions to achieve voluntary abstinence after heroin self-administration training.

Relapse Tests. We tested the screen and no-screen voluntary abstinence groups for heroin seeking under extinction conditions on abstinence days 1 and 15. The session duration was 30 minutes.

Statistical Analysis

We used factorial analyses of variance and *t* tests using SPSS (version 25, general linear model procedure) (IBM Corp., Armonk, NY). We followed significant main and interaction effects ($p < .05$, 2-tailed) with post hoc tests (Fisher's protected least significant difference). We report only significant effects critical for data interpretation and indicate results of post hoc analyses in the figures. For choice data, the statistical analyses were performed on a social preference ratio score (number of social rewards/[number of social rewards + number of heroin infusions]). In experiment 2, we combined the male and female rats in each group for the statistical analysis because we did not observe sex differences in experiment 1. We indicate *p* values for those less than .001 as $p < .001$ and report exact *p* values for values $< .05$ and $< .001$. In Supplemental Table S1 we report the full statistical results of the experiments, and in Supplemental Table S2 we provide results of inactive lever presses during the relapse tests.

RESULTS

Incubation of Heroin Craving After Social Choice–Induced Abstinence

In experiment 1, we determined whether social choice–induced abstinence would decrease incubation of heroin craving. The experiment consisted of 3 phases (Figure 1A): self-administration training (3 weeks), relapse test 1 day after the last self-administration session, and relapse test after 15 days of either social choice–induced abstinence or home-cage forced abstinence.

Training. The male and female rats lever pressed for social interaction, and no sex differences were observed (Figure 1B). The analysis of number of operant social interactions showed a significant main effect of session (60-trials group: $F_{5,80} = 68.2$, $p < .001$; 20-trials group: $F_{5,210} = 133.2$, $p < .001$) but not of

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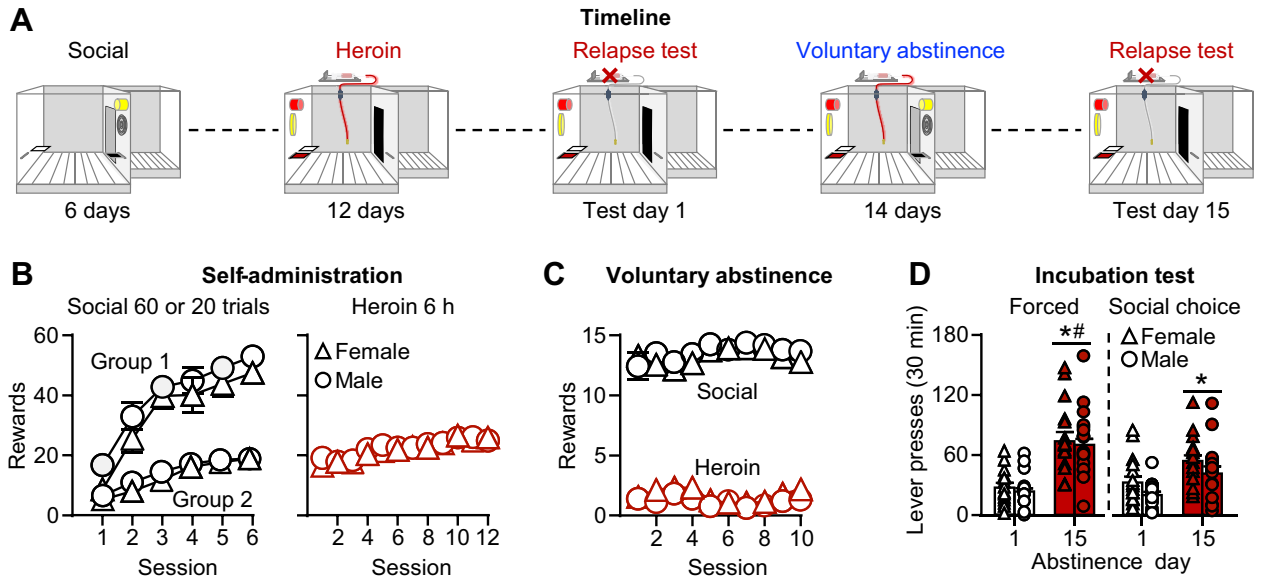

Figure 1. Social choice–induced voluntary abstinence decreases incubation of heroin craving. **(A)** Timeline of the experiments. **(B)** Self-administration training (rewards: social interaction or heroin infusion). Number of social rewards (60 or 20 trials) or heroin infusions (6 hours) in male and female rats is shown. **(C)** Voluntary abstinence. Social rewards and heroin infusions earned during 10 discrete choice sessions (15 trials/session) are shown. **(D)** Incubation (relapse) test. Active lever presses during the 30-minute test sessions (including individual data) for both forced (left panel) and social choice (right panel) groups are shown. During testing, active lever presses led to contingent presentation of the discrete light cue previously paired with heroin infusions during training but not heroin (extinction conditions). *Different from test day 1, $p < .05$. #Different from the social choice voluntary abstinence group on test day 15, $p < .05$. Forced abstinence condition: 16 male/16 female rats; social choice abstinence condition: 18 male/16 female rats. Data are mean ± SEM.

sex or session × sex interaction (p values > .05). The male and female rats also reliably lever pressed for heroin infusions, and no sex differences were observed (Figure 1B). The analysis of number of infusions showed a significant effect of session ($F_{11,682} = 15.4$, $p < .001$) but not of session × sex interaction (p values > .05).

Abstinence Phase. The male and female rats in the voluntary abstinence groups showed strong preference for social interaction over heroin, and no sex differences were observed (Figure 1C). The analysis of the social preference score showed a significant effect of session ($F_{9,270} = 3.1$, $p = .001$) but not of sex or session × sex interaction (p values > .05).

Relapse Tests. Active lever presses during testing were higher after 15 abstinence days than after 1 day (Figure 1D), demonstrating incubation of heroin craving after either forced abstinence or social choice–induced abstinence. However, the latter condition decreased this incubation effect. There were no sex differences in incubation after either voluntary or forced abstinence. The analysis, which included the between-subjects factors of sex and abstinence condition (forced or voluntary) and the within-subjects factor of abstinence day (1 or 15), showed significant effects of abstinence condition ($F_{1,62} = 6.2$, $p = .02$) and abstinence condition × abstinence day interaction ($F_{1,62} = 9.8$, $p = .003$) but no other interactions (p values > .05). Inactive lever presses were very low (Supplemental Table S2) and did not differ among abstinence days, access conditions, and sex.

Experiment 1 demonstrated that social choice–induced voluntary abstinence decreased but did not completely prevent incubation of heroin craving.

Incubation of Heroin Craving After Social Choice–Induced Abstinence Using the Automatic Procedure

In experiment 2, we determined whether the automatic (screen) (see Figure 2) procedure could be used to study social self-administration, social choice–induced abstinence, and incubation of heroin craving after voluntary abstinence. The experiment consisted of 3 phases (Figure 3A and Supplemental Figure S1A): self-administration training (3 weeks) that also included 3 discrete choice sessions, voluntary abstinence (14 days), and relapse tests. (Note that we combined male and female rats in each group [standard and screen] for the statistical analysis because we did not observe sex differences in experiment 1. In addition, the n for the no-screen group was too low for meaningful analysis of sex differences; for a male versus female comparison of the screen group, see Supplemental Figure S1.)

Training. The rats in the semiautomatic (no-screen) and automatic (screen) procedure lever pressed for a social peer, and there were no group differences. The analysis showed a significant effect of session ($F_{5,100} = 72.1$, $p < .001$) but not of access condition or session × access condition (standard or screen) interaction (p values > .05). During training for heroin self-administration, the rats increased their drug intake over time (Figure 3B). The analysis showed a main

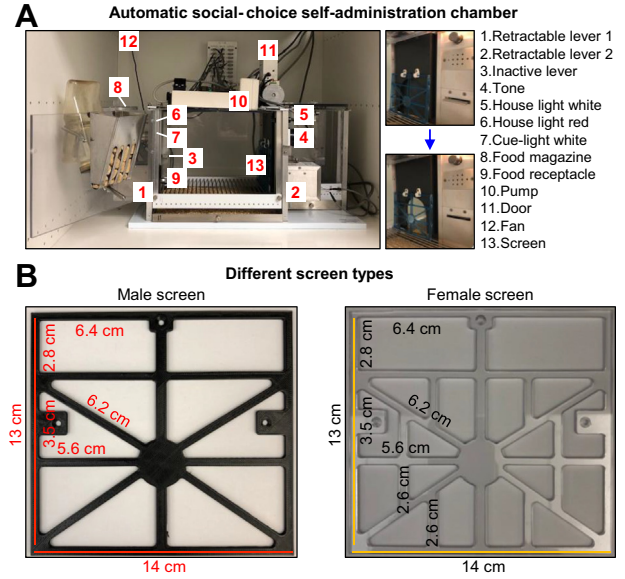

Figure 2. Automatic social choice self-administration chamber. **(A)** Picture of the chamber. The chamber has two active levers (drug paired and social paired), one inactive lever, two discriminative cues (red light for drug and white light for social), two discrete cues (white light for drug and tone for social), a food magazine and receptacle, a pump, a fan, a social-peer chamber separated by a sliding door, and a plastic grid barrier (termed screen) with triangular openings. **(B)** Different screen types. Left panel: Screen for male rats. Right panel: Screen for light- to medium-weight (mean weight, 237 g) female rats. Chamber dimensions: length, 58.5 cm; width, 35.6 cm; height, 44.5 cm. This chamber fits into the standard sound-attenuating Med Associates chambers.

effect of session ($F_{11,220}$ = 25.7, $p < .001$) but not of access condition or the session × access condition interaction (p values > .05).

Discrete Choice Sessions During Training. During the 3 discrete choice sessions, the rats in both access conditions showed a strong preference for social interaction (Figure 3C). The analysis of the social preference score showed a significant effect of session ($F_{2,40}$ = 5.0, p = .01) but no effect of access condition or the interaction between the two factors (p values > .05).

Abstinence Phase. The rats showed strong preference for social interaction, an effect that was independent of the access condition (Figure 3D). The analysis of the social preference scores showed no significant effects of access condition, session, or the interaction between the two factors (p values > .05).

Relapse Tests. Active lever presses during the tests were higher after 15 abstinence days than after 1 day in both the standard and screen conditions (Figure 3E), demonstrating incubation of heroin craving after social choice–induced abstinence under both access conditions. The analysis, which included the between-subjects factor of access condition and the within-subjects factor of abstinence day, showed a significant effect of abstinence day ($F_{1,20}$ = 5.5, p = .03) but no significant effects of abstinence condition or an interaction between the two factors (p values > .05). Inactive lever presses were very low (Supplemental Table S2) and did not differ between abstinence days and access conditions.

Experiment 2 confirmed that incubation of heroin craving occurs after social choice–induced voluntary abstinence. More important, this experiment demonstrated that the automatic social self-administration and choice procedure can replace the original semiautomatic labor-intensive social self-administration procedure.

DISCUSSION

There are two main findings in our study. First, independent of sex, social choice-induced abstinence decreased incubation of heroin craving. Second, there were minimal differences in social self-administration, social choice–induced abstinence, and incubation of heroin craving in rats trained in the semiautomatic procedure (8) and those trained in the fully automatic screen procedure. The fully automatic procedure overcomes two main limitations of the semiautomatic procedure (8)—intense workload and rat–human interaction—and can facilitate the study of social factors in addiction and other psychiatric disorders.

Incubation of Drug Craving After Voluntary Abstinence

As in previous studies using both sexes of rats (19) or male rats (36–39), we report incubation of heroin craving after forced abstinence. More important, we found reliable, albeit reduced (compared with forced abstinence), incubation of heroin craving after social choice–induced abstinence. This pattern of results is different from that seen in our recent studies using choice-induced abstinence with social interaction or palatable food. Specifically, social choice–induced abstinence prevented incubation of methamphetamine craving (8), and food choice–induced abstinence prevented incubation of heroin craving (19). Below we discuss these different results across drug classes and voluntary abstinence conditions. We caution that our conclusions and speculations are based on comparisons across studies.

The different effect of social choice on incubation of methamphetamine versus heroin craving may be due to the differential impact of social interaction on dissociable behavioral and brain mechanisms controlling opioid versus psychostimulant reward (29,30,32,33,40,41) and relapse (31,42,43). Relevant here are data indicating that different mechanisms control incubation of psychostimulant versus opiate craving (44). Specifically, inhibition of glial cell–derived neutrotrophic factor signaling in the ventral tegmental area decreases incubation of cocaine but not heroin craving (39,45). In contrast, chronic delivery of the toll-like receptor 4 antagonist (+)-naltrexone decreases incubation of heroin but not methamphetamine craving (38). In addition, reversible inactivation of orbitofrontal cortex decreases incubation of heroin but not methamphetamine craving (37,46).

A more challenging task is explaining the different effects of social choice–induced abstinence (partial inhibition) versus palatable food choice–induced abstinence (complete

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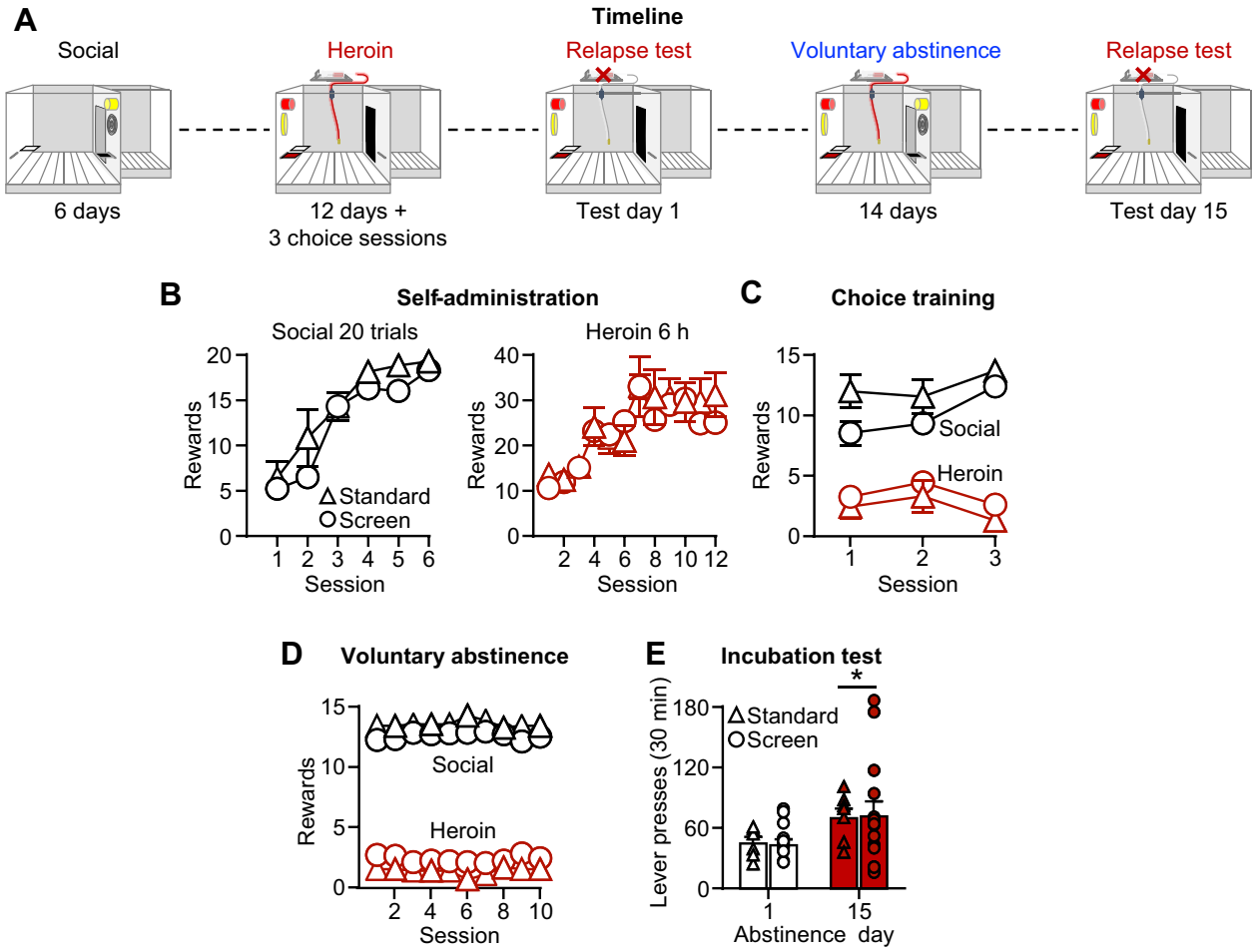

Figure 3. Automatic social choice self-administration procedure to study social choice–induced voluntary abstinence and incubation of heroin craving. **(A)** Timeline of the experiments. **(B)** Self-administration training (rewards: social interaction or heroin). Number of social rewards (20 trials) or heroin infusions (6 hours) is shown. **(C)** Choice trials during training. Social rewards and heroin infusions earned during 3 discrete choice sessions performed after every 3 days of heroin self-administration training (15 trials/session) are shown. **(D)** Voluntary abstinence. Social rewards and heroin infusions earned during the 10 discrete choice sessions (15 trials/session) are shown. **(E)** Incubation (relapse) test. Active lever presses during the 30-minute test sessions (including individual data) for both the standard and screen groups are shown. *Different from test day 1, $p < .05$. Standard (no-screen) condition: $n = 7$ (4 male/3 female rats). Screen condition: $n = 15$ (7 male/8 female rats). Data are mean ± SEM.

inhibition) (19) on incubation of heroin craving. We expected similar effects of the voluntary abstinence conditions because endogenous opioids are critical for heroin (29,33,40,47) and palatable food (48–51) reward and also contribute to social reward (52–54). We previously proposed that in the food choice–induced abstinence procedure, the palatable food acts as a substitute for heroin in a manner akin to agonist substitution therapy (55), leading to decreased heroin seeking 1 day after the removal of the food substitute. A similar mechanism may account for the partial inhibitory effect of social choice–induced abstinence, but to a lesser degree, potentially owing to a more prominent role of endogenous opioids in palatable food reward than in social reward, which is critically dependent on other neuromodulators such as oxytocin and vasopressin (56,57).

Finally, a main finding in our study is the lack of sex differences in heroin self-administration, preference for social interaction over heroin, and relapse after social choice–induced abstinence or forced abstinence. These results confirm and extend our previous study on lack of sex differences in heroin self-administration, food choice–induced abstinence, and relapse after food choice–induced abstinence or forced abstinence (19).

Methodological Considerations

An alternative explanation for the lower incubation in the voluntary abstinence condition in experiment 1 is that unlike in the forced abstinence condition, during social choice–induced abstinence the rats were exposed to low amounts of heroin (mean of 1.5 ± 0.2 infusions/day [male rats] and 1.9 ± 0.2 infusions/day [female rats]). While we cannot rule out this explanation, we believe that it is unlikely because we found no correlation between heroin intake during the 10 sessions of

voluntary abstinence and active lever presses during the day 15 relapse test in experiment 1 (Pearson's $r = .30$, $p = .10$) and found a positive (rather than negative) correlation between the 2 measures in experiment 2 (Pearson's $r = .55$, $p = .01$).

Another issue to consider is that the rats in the home-cage forced abstinence condition were not exposed to the self-administration chambers between the day 1 and day 15 relapse tests. However, it is unlikely that exposing them to the self-administration chambers without access to their social partners would decrease incubation of drug craving because in previous studies we found that incubation of heroin or cocaine craving reliably occurs after forced abstinence in either the self-administration chambers or the home cage (27,36,39,58). However, we cannot rule out the possibility that forced abstinence plus operant social interaction in the self-administration chambers without choice will decrease incubation of drug craving. In this regard, previous studies have shown that home cage environmental enrichment, which includes a social interaction component, decreases incubation of cocaine and sucrose craving (59–61).

From the perspective of the translation of results from studies on incubation of craving in rat models [which primarily have used forced abstinence (28,44,62,63)] to the human condition, it should be noted that this phenomenon is less robust and more variable in human studies than in rat studies (64–66). There are many reasons for this state of affairs, but based on our current study and previous study (8) on the inhibitory effect of volitional social interaction on incubation of drug craving, one reason might be different degrees of positive (and negative) social interaction of the subjects in the human studies.

Automatic Social Self-administration and Choice Procedure

In our original social self-administration and choice procedure, we manually removed the social partner rats after each social interaction (8). The intense experimenter workload is a limiting factor for timely data collection and is a potential experimental confound owing to extensive human–rat physical interaction. These two limitations decrease the likelihood that other researchers will use our operant social interaction procedure (8). Here, we introduced an automatic social self-administration and choice procedure by adding a custom-made screen to separate the self-administration chambers from the social partner chambers. This modification was partially inspired by an early study showing that rhesus monkeys prefer to open a window for visual access to a room containing another monkey rather than food (67). In pilot studies, we tested different screen designs with different shapes and hole sizes (circles vs. rectangles). We excluded the circle design because rats did not reliably perform the operant task with small holes that prevented extensive physical social interaction or they became stuck in larger holes that allowed social interaction but not chamber crossing. We chose the current rectangle design with smaller holes for low- to medium-weight (mean weight, 237 g; $n = 8$ in the present study) female rats because they were able to cross to the other chambers with the male-size screen (Figure 2). The new automatic screen procedure allows the rats to physically interact with their peers, which is a critical component of social reward in rodents (53) and eliminates procedural limitations of the semiautomatic procedure (8).

Conclusions

We showed that the protective effect of social interaction on drug relapse (8) generalizes to male and female rats with a history of heroin self-administration. More broadly, the results from our study and our previous choice-induced voluntary abstinence studies with palatable food and social rewards (68) highlight the notion that incorporating choice procedures and social factors into rodent models is critical for a more complete behavioral and mechanistic understanding of drug addiction (2,4,69–72). From a clinical perspective and within the context of the current opioid crisis (73,74), our findings highlight the importance of combining social-based behavioral treatments (16,23) with opioid agonist maintenance treatments (1). Finally, beyond addiction, the automatic social self-administration and choice procedure provides an ideal tool to study the mechanisms of social reward and its disruption in animal models of autism, depression, posttraumatic stress disorder, and schizophrenia.

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MV, TIR, MZ, and YS contributed to different aspects of the study, including the design and performance of the research, the data analysis, and the writeup of the manuscript.

Materials, datasets, protocols, and chamber details are available on request to Marco Venniro (venniro.marco@nih.gov) or Yavin Shaham (yshaham@intra.nida.nih.gov).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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