Viewpoints

# The Protective Effect of Social Reward on Opioid and Psychostimulant Reward and Relapse: Behavior, Pharmacology, and Brain Regions

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**Until recently, most modern neuroscience research on addiction using animal models did not incorporate manipulations of social factors. Social factors play a critical role in human addiction: social isolation and exclusion can promote drug use and relapse, while social connections and inclusion tend to be protective. Here, we discuss the state of the literature on social factors in animal models of opioid and psychostimulant preference, self-administration, and relapse. We first summarize results from rodent studies on behavioral, pharmacological, and circuit mechanisms of the protective effect of traditional experimenter-controlled social interaction procedures on opioid and psychostimulant conditioned place preference, self-administration, and relapse. Next, we summarize behavioral and brain-mechanism results from studies using newer operant social-interaction procedures that inhibit opioid and psychostimulant self-administration and relapse. We conclude by discussing how the reviewed studies point to future directions for the addiction field and other neuroscience and psychiatric fields, and their implications for mechanistic understanding of addiction and development of new treatments.**

*Key words:* **addiction; animal models; craving; opioids; psychostimulants; social behavior**

**Significance Statement**

**In this review, we propose that incorporating social factors into modern neuroscience research on addiction could improve mechanistic accounts of addiction and help close gaps in translating discovery to treatment. We first summarize rodent studies on behavioral, pharmacological, and circuit mechanisms of the protective effect of both traditional experimenter-controlled and newer operant social-interaction procedures. We then discuss potential future directions and clinical implications.**

## Introduction

In both humans and laboratory animals, adverse social interactions and social isolation promote drug use (including, in humans, the transition to addiction) and relapse, while positive social interactions tend to be protective (Marlatt et al., 1988; Miczek et al., 2008; Bardo et al., 2013; Nader and Banks, 2014). Manipulation of social factors is being increasingly reintroduced to the laboratory-animal procedures used in addiction neuroscience. This resurgence has been inspired in part from the development of ethologically relevant procedures (Morgan et al., 2002; Miczek et al., 2004; Smith, 2012; Vanderschuren et al., 2016) that allow researchers to better capture the impact of complex social behaviors on drug addiction in humans (Hunt and Azrin, 1973; Azrin et al., 1996; Silverman et al., 2012). In this regard, we recently proposed a reverse translational approach to develop and understand models that mimic successful treatments (Venniro et al., 2020a), such as contingency management (Higgins et al., 1991), the community-reinforcement approach (Hunt and Azrin, 1973), and the therapeutic workplace (Silverman et al., 2012). Contingency management is a learning-based treatment in which abstinence is maintained by providing nondrug rewards (monetary vouchers, prizes, or other incentives) in exchange for negative drug tests. The community-reinforcement approach is a learning-based treatment whose goal is to substitute drug use with nondrug social rewards (family support, employment) contingent on decrease or cessation of drug use.

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These treatments harness operant principles by increasing volitional contact with social reinforcers, such as support groups and positive work environments (Stitzer et al., 2011). We have proposed that reverse-translation "treatment" models provide an ethologically relevant platform from which we can improve forward translation by identifying rats that are comparatively unresponsive to generally successful behavioral treatments for drug self-administration, drug choice, and drug relapse (Venniro et al., 2020a).

In this review, we first review rodent studies on behavioral and neuropharmacological mechanisms of the effect of traditional experimenter-controlled positive social interaction procedures. These include the effect of social peer on opioid and psychostimulant conditioned place preference (CPP), drug self-administration, relapse or reinstatement (Smith, 2012; Bardo et al., 2013; Zernig et al., 2013), the effect of sexual social interaction on opioid and psychostimulant CPP and self-administration (Beloate and Coolen, 2017), and the effect of maternal behavior on cocaine CPP in lactating dams (Mattson et al., 2001). CPP is a conditioning procedure in which one distinct context is paired with the effects of a drug (given noncontingently) while another context is paired with vehicle; during subsequent drug-free tests, increased preference for the drug-paired context serves as a measure of a drug's rewarding effects (Bardo and Bevins, 2000). Drug self-administration is an operant procedure in which laboratory animals lever press (or nose poke) for drug injections or oral drug delivery (Schuster and Thompson, 1969). Relapse, as we use the term here, refers to the resumption of drug-taking behavior during self-imposed (voluntary) or forced abstinence in humans and laboratory animals (Wikler, 1973). Reinstatement refers to the resumption of drug seeking after extinction of the drug-reinforced responding induced by exposure to priming drug injections, drug-associated cues, drug-associated contexts, or stressors (Shaham et al., 2003).

Next, we summarize results from recent rat studies on behavioral and brain mechanisms of the protective effect of operant social interaction on opioid and psychostimulant self-administration and incubation of drug craving (Venniro et al., 2018, 2020b). Incubation of drug craving refers to a hypothetical motivational process inferred from the findings of time-dependent increases in nonreinforced operant responding (e.g., lever pressing) during abstinence from drug self-administration in laboratory animals (Grimm et al., 2001). We conclude by discussing potential future directions of the studies reviewed to the addiction field and other fields, and their implications to treatment of drug addiction in humans.

In the "rat park" study (Alexander et al., 1978; Alexander and Hadaway, 1982), rats living in large housing colony, but not isolated rats, preferred drinking water over a sweetened morphine solution. This study is often cited as the seminal introduction of social factors into preclinical addiction research, although it has had a legacy more interesting than is generally known: the investigator's graduate student was unable to replicate the specific "rat park" findings using the same procedure (Petrie, 1985, 1996), but many subsequent studies have provided ample conceptual replication (Khoo, 2020). It is beyond the scope of our review to summarize this extant literature. Except for rat studies on sexual social interaction, our review is limited to the effect of different forms of positive social interactions on opioid and psychostimulant CPP, self-administration, and relapse or reinstatement under conditions in which social interaction occurs in the drug exposure (CPP studies) or drug self-administration (drug self-administration and relapse/reinstatement studies) environment. We refer readers to excellent reviews on the effect of homecage housing conditions (single vs group-housing with or without environmental enrichment) on drug CPP, self-administration, reinstatement, and incubation of drug craving (Solinas et al., 2010, 2021; Neisewander et al., 2012; Bardo et al., 2013; Malone et al., 2022). We also refer readers to excellent reviews on the effect of negative social interactions (e.g., social defeat, early life stress, and other social stressors) and social hierarchy on addiction-related behaviors in animal models (Lu et al., 2003; Miczek et al., 2008; Bardo et al., 2013; Nader and Banks, 2014; Levis et al., 2021; Nader, 2021). Finally, our review is limited to opioid and psychostimulant drugs; we do not cover the large literature on the effect of social peers on homecage alcohol intake and nonoperant alcohol drinking outside the homecage (Tomie et al., 2004, 2014; Ryabinin and Fulenwider, 2021; Walcott and Ryabinin, 2021).

## Experimenter-controlled social reward

### *Effect of social peer on drug CPP*

*Behavioral studies.* The CPP procedure has been used for many years to measure the rewarding effects of drugs (Mucha and Iversen, 1984; Bardo and Bevins, 2000). Investigators have used CPP to examine how responses to drugs are affected by acute exposure to social interaction, showing that social interaction enhanced the drug's rewarding effects (e.g., nicotine) (Thiel et al., 2009). Additionally, it has been shown that social isolation increased the rewarding effects of social interaction in adolescent rats and the rewarding effects of a drug (D-amphetamine) in adult rats (Yates et al., 2013). Additionally, independent of age, social interaction (experienced during CPP) prevented the acquisition of D-amphetamine CPP (Yates et al., 2013) (for experimental details of each study, see Table 1).

In a series of studies, Zernig et al. (2013) examined the effect of social interaction on cocaine CPP in rats and mice using two experimental procedures (Fig. 1*A*). In the first setup (termed concurrent social and cocaine CPP), they paired, on different days, one context with cocaine and the other context with social interaction during acquisition of CPP, and then tested for expression of CPP for cocaine or social interaction. In the second setup, the investigators trained the subjects for acquisition of cocaine CPP (cocaine vs saline) and tested for its expression. Next, during the extinction phase, they paired, on different days, the previously cocaine-paired context with saline and the saline-paired context with social interaction (a counterconditioning manipulation). Subsequently, the investigators tested the rats for either cocaine CPP or reacquisition of cocaine CPP (single cocaine injection before exposure to the cocaine-paired context and 24 h later retest for cocaine CPP) (Fig. 1*A*). Extinction refers to a decrease in the frequency or intensity of learned responses after the removal of the unconditioned stimulus (e.g., food, drug) that has reinforced the learning. Counterconditioning is an experimental procedure in which a subject, already conditioned to respond to a stimulus in a particular way, is trained to produce a different response to the same stimulus that is incompatible with the original response (Catania, 1992). Reacquisition refers to the resumption of the original learned response when the reinforcer (operant or classical) is reintroduced after extinction (Bouton and Swartzentruber, 1991).

Using these procedures, the authors showed that behaviorally (1) social interaction during CPP acquisition prevented the expression of cocaine CPP (Fritz et al., 2011a), (2) exposure to

**Table 1. Effect of social peer on drug CPP[a]**

| | Reference | Drug and subjects | Major finding |
|---|---|---|---|
| 1 | Thiel et al., 2009 | Nicotine<br>Male SD rats | • CPP expression after acquisition with nicotine + peer > CPP expression after acquisition with nicotine alone or peer alone |
| 2 | Yates et al., 2013 | D-amphetamine<br>Male SD rats | • Social interaction CPP only occurs in isolated adolescents but not group-housed adolescents or isolated or group-housed adults<br>• D-amphetamine (1 mg/kg) CPP was observed in adolescents independent of the housing condition, and in isolated but not group-housed adults<br>• In a concurrent CPP procedure (D-amphetamine vs social interaction), isolated adolescents preferred social interaction and group-housed adolescents preferred D-amphetamine; adult rats showed no preference for either reward independent of the housing conditions<br>• Social interaction prevented acquisition of D-amphetamine CPP in isolated adolescent and adult rats |
| 3 | Fritz et al., 2011b | Cocaine<br>Male SD rats | • Exposure to social peer prevents acquisition of cocaine CPP<br>• Exposure to social peer during extinction of cocaine CPP prevents reacquisition of cocaine CPP<br>• The inhibitory effect of social peer on reacquisition is associated with decreased Zif268 expression in NAc shell, CeA, BLA, and VTA |
| 4-5 | El Rawas et al., 2012; Prast et al., 2014 | Cocaine<br>Male SD rats | • The inhibitory effect of social peer on reacquisition of cocaine CPP is associated with decreased Zif268 expression in NAc core & shell, medial & lateral septum, and DS<br>• Striatal Zif268 is primarily colabeled with dynorphin-containing (presumably Drd1-expressing) neurons |
| 6 | El Rawas et al., 2012 | Cocaine<br>Male SD rats | • The inhibitory effect of social peer on reacquisition is associated with decreased FosB/$\delta$FosB expression in NAc shell & core, and increased pCREB expression in NAc shell & cingulate cortex |
| 7 | Fritz et al., 2011a | Cocaine<br>Male SD rats | • Exposure to social peer prevents acquisition of cocaine CPP<br>• This effect is increased by pretraining excitotoxic lesions of NAc core and BLA decreased by pretraining lesions of NAc shell |
| 8 | El Rawas et al., 2012 | Cocaine<br>Male SD rats | • Expression of cocaine and social peer CPP is associated with similar Zif268 expression in cortical (PrL, IL, orbitofrontal, cingulate), striatal (NAc core, shell, DS), amygdala (CeA, BLA), and VTA<br>• Expression of social peer CPP is associated with lower Zif268 expression in AI and GI |
| 9 | Kummer et al., 2014 | Cocaine<br>Male SD rats & male C57 mice | • Acquisition of social interaction CPP in mice is less robust in than in rats<br>• Exposure to social peer prevents acquisition of cocaine CPP in rats but not in mice |

[a]Summary of main findings on the effect of social interaction on drug CPP. AI, Agranular insular cortex; BLA, basolateral amygdala; CeA, central amygdala; CPP, conditioned place preference; DS, dorsal striatum; GI, granular insular cortex; PrL and IL, prelimbic and infralimbic cortex; NAc, nucleus accumbens; SD, Sprague Dawley; VTA, ventral tegmental area.

social interaction during extinction accelerated extinction of cocaine CPP and also prevented its reacquisition (Fritz et al., 2011a), and (3) the protective effect of social interaction on drug CPP generalized to C57BL/6 male mice, although acquisition of social interaction CPP was less robust in mice than in rats. However, a clearer species difference was that concurrent acquisition of cocaine and social interaction prevented cocaine CPP in rats but not in mice (Kummer et al., 2014; Pinheiro et al., 2016; Bregolin et al., 2017).

Together, results from the studies of Zernig et al. (2013) show that rewarding social interaction has a strong inhibitory/protective effect on cocaine CPP in rats.

*Brain mechanisms.* Mechanistically, at the correlational level, Zernig et al. (2013) reported that exposure to social interaction during extinction of CPP (1) decreased the expression of the immediate early gene Zif268 (an activity marker) in NAc core and shell, medial and lateral septum, dorsal striatum, predominately colabeled with dynorphin-containing (presumably Drd1-expressing) striatal neurons (Prast et al., 2014), central amygdala (CeA), BLA, and VTA (Fritz et al., 2011b; El Rawas et al., 2012; Prast et al., 2014); and (2) decreased expression of the transcription factor FosB/$\delta$FosB in NAc shell and core but increased expression of pCREB in NAc shell and cingulate cortex (El Rawas et al., 2012) (Fig. 3*A*).

At the causal level, the authors reported that (1) BD1047 (a sigma1 receptor antagonist) increased the reversal of preference from the cocaine-paired context to the social-paired context after extinction of cocaine CPP (Fritz et al., 2011a); and (2) in rats trained for concurrent cocaine versus social interaction CPP, excitotoxic lesions of NAc core and BLA before acquisition increased CPP for the social-interaction-paired context during testing. In contrast, lesions of NAc shell before acquisition increased CPP for the cocaine-paired context (Fritz et al., 2011a) (Fig. 3*A*).

*Conclusions.* To date, mechanistic studies are limited to a single study using permanent excitotoxic lesions before training. The results of this study suggest opposite roles for NAc shell versus NAc core and BLA in the protective effect of social interaction on cocaine CPP. An important conclusion from the studies reviewed is that the protective effect of social peer does not appear to generalize to C57BL/6 mice, the background strain used in most transgenic mice lines.

From a human addiction perspective, the studies reviewed have some limitations. The studies on concurrent drug and social interaction CPP exclusively used male rats and mice, and exclusively used cocaine. The generality of the findings to females and to other addictive drugs is unknown. Thus, the lack of causal studies, together with no investigations using female rodents and drugs other than cocaine, represents unique opportunities for future investigations. Finally, the drug CPP model does not mimic human addiction because it relies on noncontingent exposure to low drug doses for several days, not resembling human drug-use patterns of long-term voluntary drug self-administration that often increases over time.

### Effect of social peer on drug self-administration and reinstatement

Social interactions can contribute positively or negatively to human initiation and maintenance of drug use, and to relapse to drug use (Kandel and Kandel, 2015). To model this in rats, investigators have used customized operant chambers with connecting

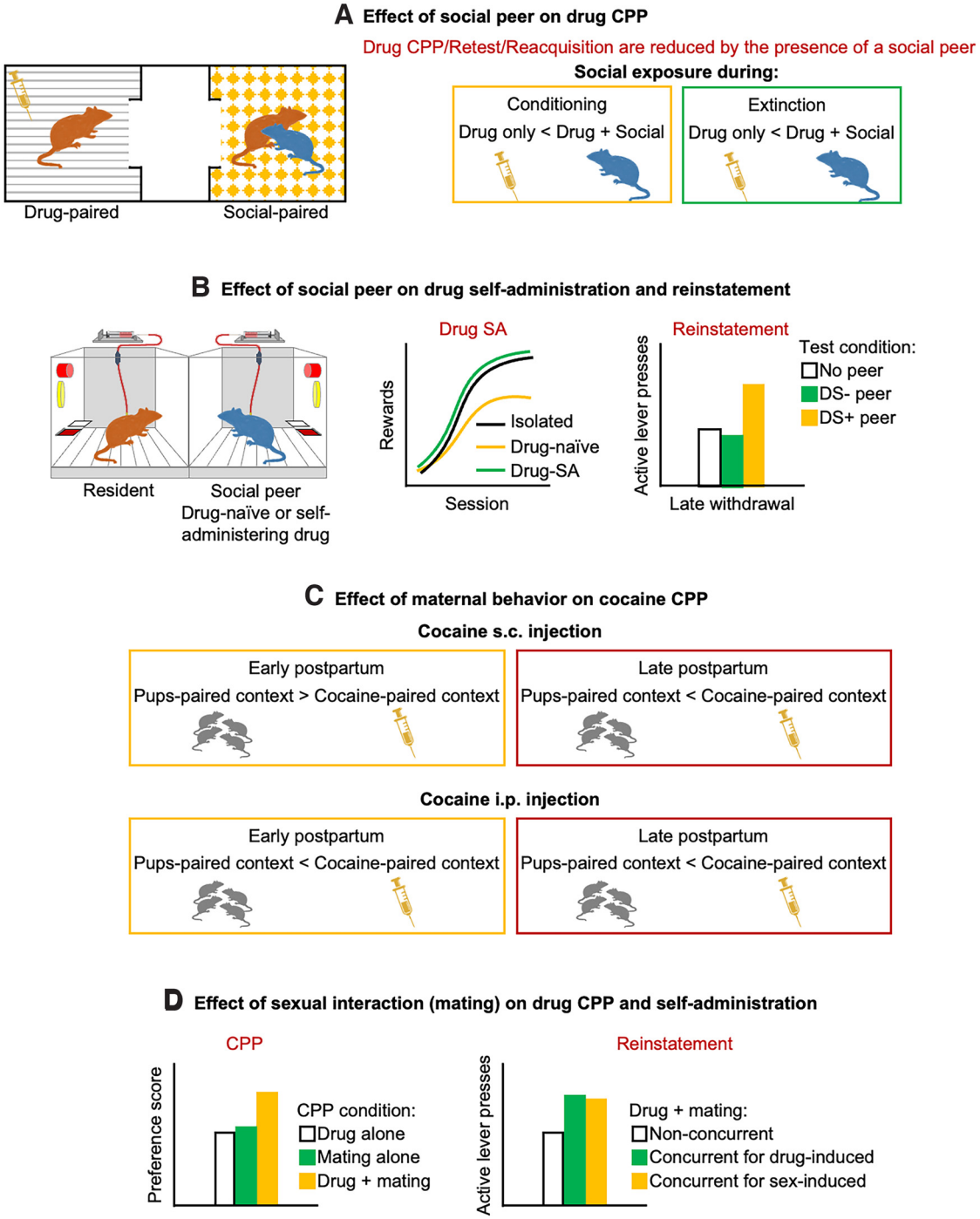


**Figure 1.** Experimenter-controlled positive social interaction models. ***A***, Effect of social peer on drug CPP: Left, Schematic of the behavioral model. One distinct context is paired with noncontingent drug injections (drug-paired) while another context is paired with social interaction (social-paired – orange rodent: resident; blue rodent: social partner). Drug- and Social-paired contexts are distinguished by different cues (colors and wall shapes). Right, Behavioral outcomes. Drug CPP, Retest and Reacquisition are reduced by the presence of social peer for both conditioning (yellow box) and extinction (green box). Panel represents a qualitative description of the data described in Table 1. ***B***, Effect of social peer on drug self-administration: Left, Schematic of the behavioral model. Two operant chambers are positioned side by side. The resident rodent (orange) self-administers a drug while observing a social peer (blue) who is either drug-naive or self-administering the drug at the same time. Right, Behavioral outcomes. Relative to drug self-administration either in isolation (black line) or in the presence of a social peer self-administering a drug (green line), the presence of a drug-naive social peer decreases drug self-administration and reinstatement of drug seeking. Panel represents a qualitative description of the data described in Table 2. ***C***, Effect of maternal behavior on cocaine CPP: Top, During early postpartum period (yellow box), the rats prefer the previously pup-paired context; while during late postpartum period (red box), they prefer the previously cocaine-paired context, when cocaine is injected subcutaneously. In contrast, when cocaine is injected intraperitoneally, rats prefer the cocaine-paired context during both early postpartum (yellow box) and late (red box) postpartum. Panel represents a qualitative description of the data described in Table 3. ***D***, Effect of social sexual interaction (mating) on drug CPP and self-administration: Left, In a CPP setup, rats prefer the side associated with drug plus mating relative to drug or mating alone. Right, Concurrent (solid square) drug plus mating during self-administration increases subsequent drug-induced (green) and mating-induced (blue) reinstatement of drug seeking, relative to a non-concurrent mating experience during drug self-administration (white square). DS, Discriminative stimulus; DS- peer, a peer that signals saline (no drug) availability during self-administration training; DS+ peer, a peer that signals drug availability during self-administration training. Panel represents a qualitative description of the data described in Table 3.

**Table 2. Effect of social peer on drug self-administration and reinstatement of drug seeking**[a]

| | Reference | Drug and subjects | Major finding |
|---|---|---|---|
| 1 | Gipson et al., 2011 | D-amphetamine<br>Male SD rats | • The presence of a drug-naive social peer increased SA of a high but not low D-amphetamine dose |
| 2 | Smith, 2012 | Cocaine<br>Male LE rats | • The presence of a cocaine-naive social peer decreased cocaine SA (FR1 and PR reinforcement schedules)<br>• The presence of a social peer that self-administers cocaine (termed herein cocaine SA peer) increased cocaine SA |
| 3 | Peitz et al., 2013 | Cocaine<br>Male LE rats | • The presence of a cocaine-naive or cocaine-experienced peer had no effect on the behavioral economic measure of demand elasticity<br>• The presence of the cocaine-naive but not cocaine-experienced peer decreased the behavioral economic measure of consumption |
| 4 | Robinson et al., 2017 | Cocaine<br>Female LE rats | • The presence of a cocaine SA peer increased the behavioral economic measure of consumption and FR responding for a low but not high cocaine dose<br>• The presence of a cocaine-naive peer had no effect on these measures |
| 5 | Smith et al., 2014 | Cocaine<br>Male LE rats | • Exposure to a peer with a prior history of cocaine SA (cocaine-experienced peer) increased acquisition of cocaine SA<br>• Exposure to a cocaine-naive peer had no effect |
| 6 | Smith and Pitts, 2014 | Cocaine<br>Male Long-Evans rats | • In a 3-chamber compartment, the cocaine SA rats preferred a cocaine-paired lever near a chamber of another cocaine SA rat over a cocaine-paired lever near a chamber of a drug-naive rat |
| 7 | Lacy et al., 2014 | Cocaine<br>Male LE rats | • The presence of a cocaine SA peer had no effect on cocaine SA under an FI reinforcement schedule |
| 8 | Lacy et al., 2016 | Cocaine and heroin<br>Male and female LE rats | • In the mixed-sex condition with cocaine, PR responding was lower in proestrus in females but not males<br>• In the mixed-sex condition with heroin, females showed a shift-to-the-right in proestrus and males shift-to-the-right in proestrus and met/diestrus<br>• In the same-sex condition with heroin, females showed lower responding during proestrus |
| 9 | Robinson et al., 2016 | Cocaine<br>Male LE rats | • Under extended access conditions (6 or 23 h/d), cocaine self-administration was lower in the presence of a drug-naive than in the presence of a cocaine SA peer or no peer<br>• Cocaine SA was similar in the presence of the cocaine SA peer vs no peer |
| 10 | Smith et al., 2021 | Cocaine and MDMA<br>Male and female LE rats | • The presence of the drug SA peer or the drug-naive peer had no effect on MDMA SA |
| 11 | Smith et al., 2016 | Cocaine<br>Male and female LE rats | • In rats trained for cocaine SA in the presence of a cocaine SA peer and for saline SA in the presence of drug-naive peer, exposure to the peers predicting cocaine availability or nonavailability after extinction without the peers had no effect on reinstatement of cocaine seeking |
| 12 | Weiss et al., 2018 | Cocaine<br>Male LE rats | • In rats trained for cocaine SA in the presence of a drug-naive peer and for saline SA in the presence of another drug-naive peer, exposure to the cocaine-predictive but not saline-predictive peer after extinction without the peers, reinstated cocaine seeking |
| 13 | Hofford et al., 2020 | Remifentanil<br>Male SD rats | • The presence of a social peer enhanced acquisition of remifentanil SA |
| 14 | Montanari et al., 2020 | Cocaine<br>Male LH rats | • Exposure to positive USV (50 kHz) from a nonfamiliar rat during 5 daily sessions decreased cocaine SA<br>• Exposure to negative USV (22 kHz) from a nonfamiliar rat during 5 daily sessions increased cocaine SA for the first day but not the other days<br>• STN lesions prevented the effects of positive and negative USV on cocaine SA |
| 15 | Vielle et al., 2021 | Cocaine<br>Male LH rats | • Exposure to positive or negative USVs from a familiar rat had no effect on cocaine SA<br>• Exposure to positive but not negative USVs from a nonfamiliar rat decreased cocaine SA, an effect prevented by STN lesions |
| 16 | Giorla et al., 2022 | Cocaine<br>Male LH rats | • The presence of abstinent or cocaine SA peer decreased cocaine SA<br>• The presence of nonfamiliar but not familiar peer decreased cocaine SA<br>• Familiar dominant or subordinate peer had no effect on cocaine SA<br>• STN lesions had inconsistent and variable effects on the effect of social peer under the different peer conditions (see text) |

[a]Summary of main findings on the effect of social interaction on drug self-administration and reinstatement. FR, Fixed ratio; FI, fixed interval; LE, Long-Evans; LH, Lister-Hooded; PR, progressive ratio; SA, self-administration; SD, Sprague Dawley.

walls (clear Plexiglas or wire mesh) that provide visual, olfactory, auditory, and limited tactile interaction with a peer (typically same sex and age) during drug self-administration or reinstatement testing (Fig. 1*B*). Below, we discuss these studies (for experimental details of each study, see Table 2).

*Effect of social peer on drug self-administration*

*Behavioral studies.* Studies assessing the effect of the presence of social peers during drug self-administration have shown a bidirectional effect based on the drug exposure of the social partner (drug-naive vs drug self-administering). The presence of a social peer increased drug self-administration of a high unit dose of D-amphetamine (Gipson et al., 2011) and remifentanil (Hofford et al., 2020). However, in other studies, the presence of a drug-naive peer decreased cocaine self-administration under either fixed ratio and progressive ratio reinforcement schedules and extended access (6 h or 23 h per day) training conditions (Smith, 2012; Robinson et al., 2016). In contrast, the presence of drug self-administering social partners increased cocaine self-administration (Smith, 2012). In the progressive ratio schedule, the number of required responses increases after each presented reinforcement (Richardson and Roberts, 1996).

Studies using an economic-demand behavioral model (applying microeconomic principles to drug self-administration) for cocaine in male and female rats showed that the peer conditions had no effect on elasticity (how quickly demand shifts from inelastic to elastic with increases in price, e.g., increasing response requirements or decreasing drug dose in self-administration

studies) but that male rats paired with cocaine-naive partners had lower consumption, while female rats paired with cocaine-experienced partners had greater consumption (Peitz et al., 2013; Robinson et al., 2017). Additionally, rats trained with a cocaine-experienced peer acquired cocaine self-administration faster than rats trained with a drug-naive peer or no peer (Smith et al., 2014) and rats self-administering cocaine together developed patterns of fixed interval responding similar to each other (Lacy et al., 2014).

Lacy et al. (2016) also examined whether the estrous cycles of female rats influence cocaine and heroin self-administration in the presence of a peer. In the same-sex condition with heroin, progressive-ratio responding was lower during proestrus. In the mixed-sex condition with cocaine, progressive-ratio responding was also lower in females during proestrus (but showed no concurrent changes in males). In the mixed-sex condition with heroin, responding was lower in females during proestrus, and higher in males during met/diestrus. Finally, rats trained to self-administer cocaine in the presence of two peers (3-chamber apparatus) preferred a cocaine-paired lever near the chamber of another cocaine self-administering rat over a cocaine-paired lever near the chamber of a cocaine-naive rat (Smith and Pitts, 2014).

*Brain mechanisms.* Baunez and colleagues examined the role of subthalamic nucleus (STN) in rats' cocaine self-administration during exposure to either a peer or to a peer's recorded ultrasonic vocalizations (USVs) (Pelloux et al., 2019). To do this, they used "positive" USVs (50 kHz range, emitted from a nonfamiliar rats during social play and other positive social interactions) and "negative" USVs (22 kHz range, emitted from a nonfamiliar rats during negative social interactions, such as social defeat or during exposure to other stressful stimuli (Vivian and Miczek, 1999; Knutson et al., 2002). Montanari et al. (2020) reported that positive USVs induced CPP, while negative USVs induced conditioned place aversion; both effects were prevented by lesions of the STN. Rats also self-administered audio recordings of positive USVs from a nonfamiliar rat; this effect was also reversed by STN lesions (Vielle et al., 2021).

Similar findings generalize to rats trained to self-administer cocaine. Positive USVs from a nonfamiliar rat decreased acquisition of cocaine self-administration, whereas negative USVs from a nonfamiliar rat increased acquisition. In contrast, after STN lesion, positive and negative USVs from a nonfamiliar rat had no effect on cocaine self-administration (Montanari et al., 2020). Using familiar versus nonfamiliar partners, Vielle et al. (2021) showed that positive USVs, but not negative USVs, from a nonfamiliar peer decreased cocaine self-administration, while positive and negative USVs from a familiar rat had no effect. After STN lesion, positive and negative USVs from a nonfamiliar rat had no effect on cocaine self-administration. This set of results generalized to rats trained to self-administer cocaine in the presence of social peers (not USVs). The presence of a cocaine-naive peer decreased cocaine self-administration to a greater degree in STN-lesioned rats than in sham rats. Additionally, in STN-lesioned rats, both familiar and nonfamiliar cocaine-naive peers decreased cocaine self-administration to a similar degree (Giorla et al., 2022) (Fig. 3*A*).

Together, the results of the studies above indicate a role for STN in the inhibitory effect of positive USVs on cocaine self-administration, but no clear role for STN in the effect of negative USVs or nonfamiliar social peers. An interpretational limitation is the use of a single cocaine unit dose, which makes it difficult to determine whether the observed behavioral effects of the manipulations were because of decreased sensitivity to cocaine or increased sensitivity to cocaine. Another limitation to consider for future investigations is the very limited cocaine self-administration experience (five 1-h sessions), which results in both high variability before the behavioral tests and low drug intake.

*Effect of social peer on reinstatement of drug seeking*

Researchers have also explored the effect of a social peer on reinstatement of drug seeking. Smith et al. (2016) examined the effect of peer presence on reinstatement of cocaine seeking after extinction (a potential model of social cue-induced relapse). They reported that reinstatement of cocaine responding was higher for the cue previously associated with cocaine self-administration in the presence of a social peer than for the cue associated with cocaine self-administration alone, but neither condition was significantly different from the isolated extinction condition. Weiss et al. (2018) also using male rats, under different experimental conditions (single-lever vs two-lever discrimination), showed that the social peer predicting cocaine availability but not the social peer predicting saline modestly reinstated cocaine seeking (Fig. 1*B*).

*Conclusions.* The results of the studies reviewed indicate a complex and often variable effect of the presence of social peer on drug self-administration and reinstatement of drug seeking. In an initial study, the presence of a self-administering social peer increased cocaine self-administration, whereas the presence of a drug-naive peer had an opposite effect (Smith, 2012). This general pattern has been observed in some but not all subsequent studies (see Giorla et al., 2022), and appears to vary by procedure, behavioral measure, and drug (Fig. 1*B*). Similarly, the presence of a social peer predictive of cocaine availability had either a modest effect on reinstatement or no effect. Two questions for future research are whether there are sex differences in the influence of same-sex social peer on drug self-administration and reinstatement, and the neurobiological mechanisms of the effect of the presence of a social peer on drug self-administration and reinstatement/relapse. As mentioned above, recent studies suggest a role of STN in the inhibitory effect of positive USVs on cocaine self-administration, but the role of STN in the effect of nonfamiliar social peer on cocaine self-administration has yet to be established.

*Effect of maternal behavior on cocaine CPP*

Pregnancy and lactation in humans have been associated with decreased drug use and increased willingness to undergo addiction treatment (Richardson and Day, 1991; Cornelius et al., 1994). These reports suggest that pregnancy and early maternal behavior protect against drug use. Preclinical studies have shown that pups function as rewarding stimuli: mothers choose pups over food and prefer contexts associated with pups (Fleming et al., 1989; Lee et al., 2000). Below, we describe CPP studies in lactating dams where during CPP training one context was paired with pups and the other context with cocaine (typically four pairings for each reward). The test for expression of cocaine CPP was preference for the cocaine-paired context versus the pup-paired context (for experimental details of each study, see Table 3).

*Behavioral studies.* Mattson et al. (2001, 2003) determined pup versus cocaine preference at different postpartum time points. During the early postpartum period, rats preferred the context previously paired with pups; during the late postpartum period, they preferred the context previously paired with cocaine (10 mg/kg, s.c.) (Mattson et al., 2001, 2003) (Fig. 1*C*). In contrast, Seip and Morrell (2007) reported that, during both early and late postpartum, the rats preferred the previously cocaine-paired context when the same drug dose was injected intraperitoneally.

**Table 3. Effect of maternal behavior and sexual interaction with a peer on drug CPP and self-administration[a]**

| | Reference | Drug and subjects | Major finding |
|---|---|---|---|
| 1 | Mattson et al., 2001 | Cocaine<br>Female SD rats | • Rats prefer the pup-paired context during early postpartum period (day 8)<br>• Rats prefer the cocaine-paired context during middle and late postpartum periods (day 10 and 16) |
| 2 | Mattson et al., 2003 | Cocaine<br>Female SD rats | • At postpartum day 10, some rats prefer the pup-paired context while others prefer the cocaine-paired context |
| 3 | Mattson and Morrell, 2005 | Cocaine<br>Female SD rats | • High Fos and CART expression in PrL, NAc, and BLA correlates with preference for the cocaine-paired context<br>• High Fos and CART expression in mPOA correlates with preference for the pup-paired context |
| 4 | Seip and Morrell, 2007 | Cocaine<br>Female SD rats | • Rats prefer the pup-paired context during early postpartum period<br>• Preference for the cocaine-paired context resumes after prolonged postpartum period |
| 5 | Pereira and Morrell, 2010 | Cocaine<br>Female SD rats | • Inactivation of mPOA (via bupivacaine) decreased preference for the pup-paired context |
| 6 | Pereira and Morrell, 2020 | Cocaine<br>Female SD rats | • Bupivacaine inactivation of IL increased preference for the cocaine-paired context<br>• Bupivacaine inactivation of PrL increased preference for the pup-paired context |
| 7 | Frohmader et al., 2011 | Meth<br>Male SD rats | • Concurrent Meth + mating is preferred over Meth alone or mating alone<br>• Meth CPP was only observed after prior exposure to concurrent Meth + mating but not Meth alone or saline alone |
| 8 | Pitchers et al., 2010 | D-amphetamine<br>Male SD rats | • Repeated mating experience increased sensitivity to D-amphetamine CPP 10 d but not 1 d after the last mating session<br>• Repeated mating experience in drug-naive rats increased number of dendrites and spines in NAc 7 d but not 1 d after the last mating session |
| 9 | Pitchers et al., 2013 | D-amphetamine<br>Male SD rats | • Repeated mating experience increased sensitivity to D-amphetamine CPP 7 and 28 d after the last mating session<br>• Mating in drug-naive rats increased expression $\delta$-FosB in NAc for up to 28 d after the last mating session, while the effect of mating on dendritic spines only lasted for 7 d<br>• Inhibition of NAc $\delta$-FosB reversed the effect of mating on D-amphetamine CPP<br>• Pharmacological blockade of NAc Drd1 but not Drd2 decreased mating-induced increases in D-amphetamine CPP and NAc $\delta$-FosB expression, but not dendritic spines |
| 10 | Beloate et al., 2016b | D-amphetamine<br>Male SD rats | • NAc injections of high but not low volume of the NMDAR antagonist MK-801 reversed mating-induced sensitization of D-amphetamine CPP<br>• NAc injections of both the high and low volume MK-801 reversed the effect of mating on NAc $\delta$-FosB expression |
| 11 | Pitchers et al., 2016 | D-amphetamine<br>Male SD rats | • NAc injections of the mGluR5 antagonists MPEP and MTEP had no effect on mating-induced sensitization of D-amphetamine CPP<br>• In sexually naive rats, these injections induced sensitization of D-amphetamine CPP |
| 12 | Beloate et al., 2016a | D-amphetamine<br>Male SD rats | • In TH-Cre rats injected with inhibitory DREADD (DIO-hM4Di) into the VTA, systemic CNO injections during mating prevented mating-induced sensitization of D-amphetamine CPP<br>• CNO injections during mating reversed the effect of mating on $\delta$-FosB expression in NAc and mPFC, and VTA dopamine neurons' soma size |
| 13 | Pitchers et al., 2014 | Morphine<br>Male SD rats | • Mating induced tolerance to morphine CPP<br>• Mating decreased VTA dopamine soma size 1 and 7 d but not 31 d after the last mating session |
| 14 | Kuiper et al., 2019 | Meth<br>Male SD rats | • Concurrent Meth SA + mating induced higher extinction responding and Meth priming-induced reinstatement than nonconcurrent Meth SA + mating (see text for description of the two conditions)<br>• Sex-induced reinstatement was only observed when mating in the concurrent group had occurred in the Meth SA context but not in a nondrug context |
| 15 | Kuiper et al., 2020 | Meth<br>Male SD rats | • Mating and Meth coactivate CaMKII neurons in ACC<br>• Chemogenetic inhibition of these neurons decreased the effect of concurrent Meth SA + mating on Meth priming-induced reinstatement but not extinction responding<br>• The effect of chemogenetic inhibition on the potentiation effect of the concurrent condition on cue-induced reinstatement is mixed |

[a]Summary of main findings on the effect of maternal behavior or social sexual interaction on drug CPP and self-administration. ACC, Anterior cingulate cortex; CART, cocaine and amphetamine-regulated transcript; CNO, clozapine N-oxide; Meth, methamphetamine; SA, self-administration; SD, Sprague Dawley.

These conflicting results are difficult to interpret in the absence of dose–response curves with subcutaneous versus intraperitoneal cocaine injections.

*Brain mechanisms.* Mattson and Morrell (2005) determined the effect of exposure to pup-paired and cocaine-paired contexts during a CPP test on c-Fos and cocaine and amphetamine-regulated transcript peptide immunocytochemistry in several brain regions. They tested for CPP on day 10 postpartum, a midpoint in which some dams prefer the pup-paired context and other dams prefer the cocaine-paired context. They reported that cocaine preference is associated with activation of NAc, mPFC, and BLA, while pup preference is associated with activation of medial preoptic area (mPOA). In a follow-up study, Pereira and Morrell (2010) reported that reversible inactivation of the mPOA with the local anesthetic bupivacaine shifted preference from the pup-paired context to the cocaine-paired context. The same manipulation also blocked pup-induced CPP (pups vs no pups during CPP training) but not cocaine CPP (cocaine vs saline during training) (Fig. 3*B*).

In another study, Pereira and Morrell (2020) tested how pup versus cocaine preference is affected by bupivacaine injections into dorsal anterior cingulate, prelimbic (PrL), and infralimbic (IL) cortex. Inactivation of IL increased preference for the cocaine-paired context. In contrast, inactivation of PrL cortex increased preference for the pup-paired context (Fig. 3*B*). Cingulate inactivation had no effect. A barrier to interpretation is that bupivacaine inhibits the activity of both local cell bodies and fiber of passage.

*Conclusions.* Maternal interaction with pups can be protective against cocaine CPP during early but not late postpartum. Mechanistic studies suggest that the mPOA and mPFC subregions contribute to this protective effect.

*Effect of sexual interaction on drug CPP and self-administration*

Social interactions with peers can be sexual in nature, and sexual experience can be used as an experimental manipulation to study the relationship between rewarding social interactions and behavioral responses to addictive drugs (Frohmader et al., 2010) (Fig. 1*D*). In several studies, Coolen and colleagues (Frohmader et al., 2010) exposed male rats to sexual experiences (3-5 mating sessions) with receptive females and measured the effect of these experiences on drug CPP or drug self-administration at different time points after the last sexual experience. Below, we describe these studies (for experimental details of each study, see Table 3).

*Effect of sexual interaction (mating) on psychostimulant and opioid CPP*

*Behavioral studies.* Frohmader et al. (2011) reported that methamphetamine + mating was preferred over methamphetamine alone or mating alone. They also reported that prior concurrent methamphetamine and sexual experience increased methamphetamine CPP. The results of this study suggest that sexual experience in the presence of methamphetamine is more rewarding than each reward alone, and that concurrent exposure to the two rewards increases sensitivity to subsequent methamphetamine CPP. An interpretational limitation of these single-dose results is that it is unknown whether preference changes are because of shift-to-the-right or shift-to-the left in the methamphetamine dose response curve.

This limitation was addressed in the studies described below in which Coolen's group (Frohmader et al., 2010) examined whether repeated mating experience increases sensitivity to D-amphetamine CPP. They reported that sexual experience had no effect on expression of D-amphetamine CPP when acquisition of drug CPP occurred concurrently with the mating experience. In contrast, sensitization of D-amphetamine CPP occurred 10 d after the last mating experience (Fig. 1*D*).

*Brain mechanisms.* Mating experience increased the number of dendrites and spines in NAc core and shell 7 d, but not 1 d, after the last mating experience (Pitchers et al., 2010) (Fig. 3*C*). Mating experience in drug-naive rats increased the expression of the transcription factor $\delta$-FosB in NAc and shell for up to 28 d. A viral vector expressing $\delta$-JunD (a dominant-negative binding partner of FosB that suppresses $\delta$-FosB transcription) reversed the effect of mating experience plus 7 d of "sexual abstinence" on both enhanced D-amphetamine CPP and NAc dendritic spines. Finally, pharmacological blockade of Drd1, but not Drd2, in NAc (using the receptor antagonists SCH-23390 and eticlopride) before each mating session decreased mating experience-induced increases in D-amphetamine CPP and NAc $\delta$-FosB expression, but not dendritic spines (Pitchers et al., 2013) (Fig. 3*C*).

In another study, Beloate et al. (2016b) showed that high but not low volume of MK-801 (noncompetitive NMDAR antagonist) reversed mating-experience-induced sensitization of D-amphetamine CPP, and both volumes reversed the effect of mating experience on NAc $\delta$-FosB expression. MK-801 had no effect on sexual behavior and mating-induced CPP. But unexpectedly, prior injections of the higher MK-801 volume induced CPP to the low dose of D-amphetamine in sexually naive rats that typically do not show CPP at that dose. An interpretational issue is the site of action of MK-801 because drugs injected at high volume into NAc can diffuse to the nearby ventricles and can act at other brain areas (Wise and Hoffman, 1992).

Pitchers et al. (2016) reported that NAc injections of the mGluR5 antagonists 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) and 2-methyl-6-(phenylethynyl)-pyridine before the mating sessions had no effect on mating experience-induced sensitization of D-amphetamine CPP. In contrast, in sexually naive rats, prior MTEP injections mimicked the effect of mating experience on sensitization of D-amphetamine CPP. The authors also reported decreased NAc mGluR5 expression 7 and 28 d after the last mating session. Still unknown is the mechanistic connection between decreased NAc mGluR5 expression and sensitization of D-amphetamine CPP.

Beloate et al. (2016b), using TH-Cre rats and inhibitory DREADDs, showed that dopamine neurons in VTA are critical for mating-experience-induced sensitization of D-amphetamine CPP, and that inhibition of these neurons reversed or decreased the effect of mating experience on $\delta$-FosB expression in NAc and mPFC, and VTA dopamine neurons' soma size. Finally, Pitchers et al. (2014) reported that, unlike D-amphetamine CPP, morphine CPP showed tolerance after mating experience when acquisition of morphine CPP occurred 1 d after the last mating session. Mating-experience-induced tolerance to morphine CPP was associated with decreased soma size of dopamine neurons in the VTA but not substantia nigra.

*Effects of sexual interaction on methamphetamine self-administration*

*Behavioral studies.* Kuiper et al. (2019) reported that rats trained for methamphetamine self-administration immediately followed by a mating session (concurrent) show higher lever presses during the extinction sessions than rats trained for methamphetamine self-administration nonconcurrently to mating sessions. Additionally, sex-induced reinstatement was observed only when mating in the concurrent group had occurred in the methamphetamine self-administration context, not in a nondrug context. Sex-induced reinstatement was not observed in the nonconcurrent group (Fig. 1*D*); this result agrees with results from an early study using a similar nonconcurrent design in heroin-trained rats (Shaham et al., 1997).

*Brain mechanisms.* Kuiper et al. (2020), using immunohistochemistry and chemogenetic approaches, showed that noncontingent methamphetamine injections and mating coactivated CaMKII-expressing neurons in anterior insular cortex (ACC). Additionally, inhibition of CaMKII-expressing ACC neurons decreased the potentiation effect of concurrent methamphetamine self-administration + mating on drug cue- and drug priming-induced reinstatement but not extinction responding. However, in another experiment, the same manipulation had no effect on either extinction responding or cue-induced reinstatement. Chemogenomic inhibition of ACC neurons had no independent effect on methamphetamine self-administration or sexual behavior (Fig. 3*C*).

Together, the results of this study confirm that concurrent methamphetamine self-administration plus mating induce higher extinction responding and reinstatement than nonconcurrent mating that follows methamphetamine self-administration, but the role of ACC in this effect has not been clearly established.

*Conclusions.* The results of the CPP studies of Coolen and colleagues (Frohmader et al., 2010) provide reproducible evidence that prior exposure to repeated mating plus prolonged "sexual abstinence" induces sensitization of D-amphetamine CPP. This effect is mediated by $\delta$-FosB-expressing neurons in NAc and Drd1 but not Drd2. There is also some evidence for a potential role of NAc NMDARs, but not mGluR5 receptors. Additionally, prior concurrent methamphetamine + mating induces sensitization of methamphetamine CPP (Fig. 3*C*). In contrast, mating experience appears to induce tolerance to

morphine CPP. However, this tolerance-related effect was only shown when morphine CPP was tested after 1 d of "sexual abstinence." A question for future research is whether repeated mating will induce sensitization of morphine CPP after longer abstinence periods, as is the case with D-amphetamine.

The results of the methamphetamine self-administration studies indicate that concurrent drug self-administration + mating results in higher extinction responding and cue- and drug-induced reinstatement than nonconcurrent experience (mating that follows drug self-administration). Additionally, when concurrent drug self-administration + mating occurs in the drug self-administration context, mating can induce reinstatement of drug seeking. In contrast, sex-induced reinstatement is not observed when mating in the concurrent condition occurs in a nondrug context. Finally, a mechanistic study suggested a role for ACC in the potentiating effect of the concurrent-mating condition on drug-priming-induced reinstatement but not extinction responding, and results are inconclusive about ACC's role in potentiation of cue-induced reinstatement.

Sexual social interaction appears to have an effect opposite what might have been expected from studies of nonsexual exposure to same-sex peers, in which drug CPP and self-administration were typically decreased. A question for future research is whether these apparently opposite effects are because of the nature of the social interaction or some other procedural variables. For example, we predict that sexual social interaction will mimic the inhibitory effect of a same-sex peer on extinction, reinstatement, and reacquisition of cocaine CPP, as assessed in the counterconditioning procedure of Zernig et al. (2013) (see above), and that sexual social interaction will mimic the inhibitory effect of same-sex social interaction on drug self-administration in the operant discrete-choice procedure described in the next section.

## Operant social reward

We recently developed a social-choice self-administration model whose goal is to reduce the translational gap between preclinical animal models of drug choice and relapse and the human condition (Heilig et al., 2016; Venniro et al., 2020a). In most choice studies in rats and monkeys, the alternative reward is food (Caprioli et al., 2015; Banks and Negus, 2017; Venniro et al., 2017b); and in most reinstatement/relapse studies, abstinence is experimenter-imposed by either extinction procedures or by keeping the laboratory animals in their homecage (Venniro et al., 2020a). In contrast, in most human drug users, the rewards that compete with drugs are primarily social (family and employment) (Stitzer et al., 2011), and abstinence is typically chosen because of significant loss of these nondrug social rewards (Epstein and Preston, 2003). From a translational perspective, the social choice model attempts to mimic some aspects of human behavioral treatments, such as the community reinforcement approach and the therapeutic workplace, which promote prolonged abstinence by offering volitional social interactions with social reinforcers, such as support groups and positive work environments (Hunt and Azrin, 1973; Silverman et al., 2012).

We have used the operant social self-administration and choice model to determine the effect of rewarding social interaction on drug self-administration in rats that have undergone procedures intended to mimic critical aspects of human addiction (see below), as assessed in the extended-access escalation model (Ahmed and Koob, 1998), the three-criteria DSM-IV model (Deroche-Gamonet et al., 2004), and the intermittent-access model (Zimmer et al., 2012). We also used the social self-administration and choice model to determine the effect of voluntary abstinence induced by providing rats a choice between a drug and rewarding social interaction on incubation of drug craving (Venniro et al., 2018; Venniro and Shaham, 2020). We use the term "voluntary abstinence" to refer to experimental conditions in which the self-administered drug is available in the self-administration chamber but the laboratory animal either stops or significantly decreases self-administration in favor of the nondrug alternative (Fredriksson et al., 2021; Venniro et al., 2021b).

### *Effect of operant social interaction on drug self-administration*

*Behavioral studies.* In the study in which we introduced the social self-administration and choice model (Venniro et al., 2018), we first used the established extended-access escalation model of drug addiction (Ahmed and Koob, 1998) in which drug intake increases over time to determine whether methamphetamine or heroin self-administration would be prevented by operant access to social interaction with same-sex peer. We then devalued the social reward by either increasing the delay after social-lever press or by punishment of 50% of social-lever presses with footshock of increasing intensity. We found that social interaction prevented methamphetamine and heroin self-administration independent of drug unit dose (Venniro et al., 2018) (Fig. 2). Methamphetamine or heroin self-administration resumed only if there was a long delay before social reward or if lever presses for social interaction were punished. These data extend a surprising recent observation from Canchy et al. (2021) that delaying access to both cocaine and the alternative nondrug reward (sweet solution) increases preference for cocaine. In our recent study, we found that preference for social interaction was decreased by the delay of both rewards or social interaction alone, or by increased response requirements for social reward, with notable individual differences (Venniro et al., 2021a).

We also performed a more stringent test of the effect of social reward using rats identified as "addicted" in the three-criteria DSM-IV–based model (Deroche-Gamonet et al., 2004). This model evaluates three behaviors based on DSM-IV criteria: persistent drug seeking during periods when drug is not available, high motivation to self-administer the drug (progressive ratio responding), and willingness to take drug despite adverse consequences (footshock punishment). An "addiction" score (0-3) is calculated based on the subjects' percentile on each measure's distribution (Deroche-Gamonet et al., 2004). In our experiment, we determined the rats' addiction score by measuring (1) total nonreinforced lever presses during nondrug periods, (2) number of drug rewards earned under a progressive-ratio schedule, and (3) punishment responding. We classified the rats based on their $Z$ score as highly "addicted" (High, ~19% of the rat sample), moderately addicted (Medium, ~21% of the rat sample), and mildly addicted (Low, ~60% of the rat sample). Finally, we trained some or all rats from each group (High, Medium, Low) for social self-administration, and then determined choice of methamphetamine versus social interaction. The main finding was that the rats strongly preferred social interaction over methamphetamine, independent of addiction-score group (Venniro et al., 2018).

We replicated these findings using the intermittent-access drug-self-administration model of addiction (Zimmer et al., 2012). In this model, rats are given intermittent access to drug intake; in each daily session, drug availability is cycled on and off (typically 5 min ON, 25 min OFF for 6-12 h per day). Under these conditions, drug intake and brain levels fluctuate between peaks and troughs during the daily sessions, which more closely mimics human drug intake (Zimmer et al., 2012). We showed

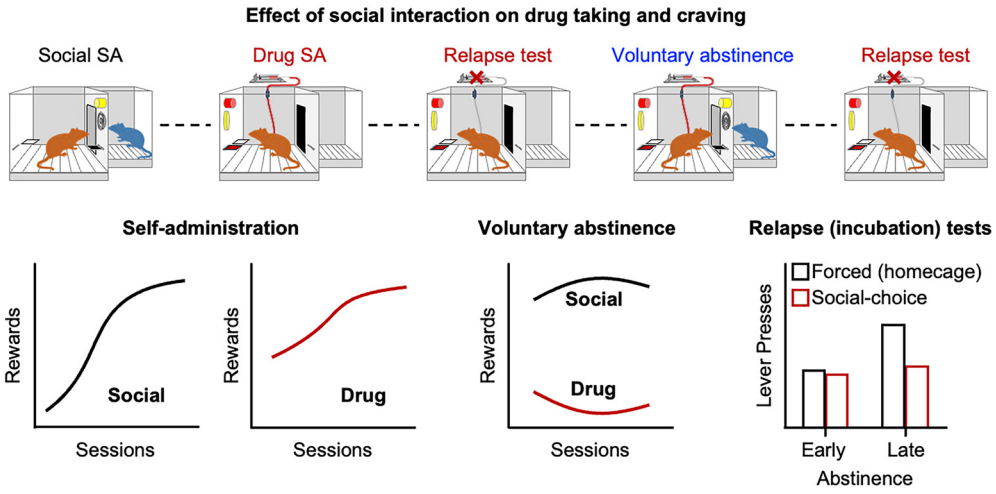


**Figure 2.** Operant social interaction voluntary abstinence models. Top, Schematic of the behavioral model. Timeline of the behavioral experiment: the resident rat (orange) is first trained to self-administer for access to a social peer (blue) and then for drug infusions. The rat is then tested for relapse to drug seeking during early and/or late abstinence. The test is in extinction condition with neither the drug nor the social peer available. In between tests, the rat is provided with a mutually exclusive choice between the drug or social interaction with a peer. Bottom, Behavioral outcomes. Rats learn to reliably self-administer both social reward (black) and drug (red line). The rats achieve voluntary abstinence because they prefer the social reward over the drug. Social choice-induced voluntary abstinence reduces or prevents incubation of drug craving (red square), relative to the reliable incubation observed during the period of homecage forced abstinence (white square). Panel represents a qualitative description of the data described in in Table 4.

that rats strongly preferred social interaction over methamphetamine, and this effect was independent of the addiction-score group; this score was derived from the individual rats' behavior during tests for progressive ratio and punishment. Additionally, high addiction scores did not predict lower social preference (Venniro et al., 2018). In follow-up studies, we showed that the protective effect of social interaction on drug self-administration generalizes to heroin and cocaine using a fully automatic social-choice self-administration procedure (Venniro et al., 2019, 2021a). We developed this procedure 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 (Venniro and Shaham, 2020).

We had not expected social interaction to be chosen over drug by rats classified as "highly addicted" in established models. The robustness of the finding may reflect higher valuation of social reward because of its more rapid availability than the rewarding effects of drugs. We have found, for example, that increasing access duration to a peer decreased social self-administration under a fixed-ratio reinforcement schedule (though not a progressive-ratio schedule) (Chow et al., 2022). Other parametric considerations include housing conditions: social self-administration under different fixed-ratio requirements was higher in single-housed than in paired-housed rats, and higher for a familiar versus unfamiliar partner in single-housed but not paired-housed rats (Chow et al., 2022). Dose of drug may sometimes play a role: with heroin and methamphetamine, the robust preference for social interaction was dose-independent; but with the short-acting opioid remifentanil, the rats preferred a high (but not a low) dose over social interaction (Venniro and Shaham, 2020; Chow et al., 2022).

Our working hypothesis is that these parametric manipulations, whose effects uncover individual differences in what might otherwise be an unvarying choice of social reward over drug reward (Venniro et al., 2021a), could be key to identifying a subpopulation of rats that is not identified by established models of addiction. The established models would continue to be useful for identifying rats that are most vulnerable to the transition toward and initial maintenance of addiction, but social-interaction models might be more relevant for identifying intractability to situational changes (which, in humans, might include provision of psychosocial treatment).

*Conclusions.* We proposed that the social choice procedure could identify mechanisms of individual differences and could thereby help screen medications for people who are relatively unresponsive to treatments based on rewarding social interaction (Venniro et al., 2021a). Questions for future research are the neuronal mechanisms of the strong protective effect of immediate operant social interaction and the decrease in this effect after delay or punishment of rewarding social interaction. Another future research question is the generality of the findings to oral drug self-administration. In this regard, in a very recent study, Marchant et al. (2022) reported that rats prefer oral alcohol solution over social interaction. The reasons for this unexpected finding are currently unknown.

### *Effect of operant social interaction on incubation of drug craving*

*Behavioral studies.* In our studies of the effect of social interaction on incubation, the procedure is composed of four phases: social interaction and drug self-administration, an early-abstinence relapse test, social-choice-induced voluntary abstinence, and a late-abstinence relapse test (Venniro et al., 2018; Venniro and Shaham, 2020). During the relapse tests, the rats do not have access to the social-interaction-paired lever (Venniro and Shaham, 2020).

In the first study, we found that incubation of methamphetamine seeking, which is reliably observed after homecage forced abstinence or food-choice-induced voluntary abstinence (Caprioli et al., 2015; Li et al., 2015; Venniro et al., 2017a), was prevented by social-choice-induced voluntary abstinence; this inhibitory effect persisted for additional 15-30 d of forced abstinence (Venniro et al., 2018). Subsequently, we determined the generality of these behavioral findings to heroin and cocaine. For heroin, social-choice-induced voluntary abstinence decreased (but did not prevent) incubation compared with homecage forced abstinence (Venniro et al., 2019). For cocaine, social-choice-induced voluntary abstinence did prevent incubation, independent of cocaine-access

**Table 4. Effect of operant social interaction on drug self-administration and incubation of drug craving[a]**

| Year | Reference | Drug and subjects | Major finding |
|---|---|---|---|
| 1 | Venniro et al., 2018 | Meth and heroin<br>Male and female SD rats | • In a discrete choice procedure, operant social reward eliminated Meth and heroin SA in established addiction models (escalation, DSM-IV–based, and intermittent access)<br>• The inhibitory effect of social choice on drug SA in decreased by delay or punishment of the social reward<br>• Social choice-induced voluntary abstinence prevented incubation of Meth craving<br>• The protective effect on incubation was associated with activation (index by Fos) of CeA PKC$\delta$-expressing neurons and decreased activity in AIC |
| 2 | Venniro et al., 2019 | Heroin<br>Male and female SD rats | • In a discrete choice procedure, operant social reward (either full contact or limited contact via a screen) decreased extended access (6 h/d) heroin SA<br>• Social choice-induced abstinence decreased (but not prevented) incubation of heroin craving<br>• There were no sex differences in the effect of social choice on heroin SA or incubation of heroin craving |
| 3 | Venniro et al., 2020b | Heroin<br>Male SD rats | • shRNA knockdown of CeL PKC$\delta$ reversed the inhibitory effect of social choice-induced voluntary abstinence on incubation of Meth craving<br>• shRNA knockdown of CeL SOM decreased incubation of Meth craving after homecage forced abstinence |
| 4 | Venniro et al., 2021a | Heroin<br>Male and female SD rats | • In a discrete choice procedure, operant social reward decreased extended access (12 h/d) intermittent or continuous cocaine SA<br>• Social choice-induced abstinence prevented incubation of cocaine craving<br>• Delay of social reward increased cocaine preference, with considerable individual differences<br>• There were no sex differences in the effect of social choice on cocaine SA or incubation of cocaine craving |
| 5 | Marchant et al., 2022 | Alcohol<br>Male and female LE rats | • In a discrete choice procedure, male and female rats preferred oral alcohol over operant social reward (contact via a screen)<br>• The choice for alcohol was decreased by increased response requirement for alcohol, prechoice alcohol exposure, or decreased alcohol concentration |

[a]AIC, anterior insular cortex; CeA, central nucleus of the amygdala; CeL, lateral part of CeA; FR1, fixed ratio 1; LE, Long-Evans; Meth, methamphetamine; SA, Self-administration; shRNA, short-hairpin RNA; SD, Sprague Dawley; PKC, protein kinase C.

conditions and sex (Venniro et al., 2021a) (for experimental details of each study, see Table 4).

*Brain mechanisms.* We have begun to explore the mechanisms of the protective effect of social interaction on incubation of methamphetamine craving. We have focused on the CeA because of its role in incubation of drug craving after forced abstinence across drug classes (Pickens et al., 2011; Dong et al., 2017; Roura-Martinez et al., 2020). We initially used double/triple immunohistochemistry and RNAscope in situ hybridization and found that the protective effect of social choice-induced abstinence on incubation of methamphetamine seeking is associated with activation (assessed by Fos) of inhibitory protein kinase-C$\delta$ (PKC$\delta$)-expressing neurons in the lateral part of CeA (CeL) and decreased activity of output neurons in the medial part (CeM). In contrast, incubation of methamphetamine seeking after forced abstinence was associated with activation of CeL-expressing somatostatin (SOM) neurons and CeM output neurons (Fig. 3*D*). The protective effect of social choice-induced abstinence on incubation was also associated with decreased activity (Fos expression) of anterior insula cortex, but not anterior cingulate, dorsal and ventral mPFC, and BLA (Venniro et al., 2018).

We have also examined the causal role of CeL PKC$\delta$ and SOM in inhibition of incubation of methamphetamine seeking after social choice-induced abstinence and expression of incubation of drug seeking after forced abstinence. We developed and validated short-hairpin RNAs against PKC$\delta$ (shPKC$\delta$) and SOM (shSOM) (Venniro et al., 2020b). We found that CeL injections of shPKC$\delta$ decreased Fos in CeL PKC$\delta$-expressing neurons, increased Fos in CeM output neurons, decreased CeL PKC$\delta$ neuronal excitability (assessed by whole-cell current-clamp recordings), and reversed the inhibitory effect of social-choice-induced abstinence on incubation of methamphetamine seeking. In contrast, CeL injections of shSOM decreased Fos in CeL SOM-expressing neurons, decreased Fos in CeM output neurons, decreased CeL SOM neuronal excitability, and decreased incubation after forced abstinence (Venniro et al., 2020b) (Fig. 3*D*).

*Conclusions.* The results from our studies indicate that operant social interaction prevents incubation of methamphetamine and cocaine craving and reduces incubation of heroin craving (Fig. 2). In our first mechanistic study, we found that the protective effect of social reward on incubation of methamphetamine craving is mediated by activation of CeL PKC$\delta$, leading to inhibition of CeM neurons. In contrast, incubation after forced abstinence was mediated by activation of CeL SOM, leading to activation of CeM neurons. A question for future research is which CeA-related circuits (and potentially other regions and circuits) contribute to these protective effects, and likely other relapse-related behaviors.

## Concluding remarks, future directions, and clinical implications

We summarized results from rodent studies on behavioral, pharmacological, and circuit mechanisms of the effect of experimenter-controlled and operant social interaction on opioid and psychostimulant CPP, self-administration, reinstatement, and incubation of drug craving.

At the behavioral level, the first major conclusion is that rewarding social interaction with a same-sex peer decreases drug CPP, self-administration, reinstatement, and incubation of craving when social interaction "competes" with the drug in a choice setup (either CPP or self-administration). A second major conclusion is that a more complex picture emerges when other types of social interaction/exposure occur concurrently with or just before drug exposure or drug self-administration. For example, drug self-administration may increase after mating or when a peer is a discriminative stimulus for drug availability; drug self-administration may be unaffected in the presence of a drug-self-administering peer (or sometimes a drug-naive peer); and drug self-administration may decrease in the presence of a drug-naive peer.

These two major conclusions from rodent studies are primarily based on data from males. Thus, a question for future research is the generality of the findings to females. We suspect that some of the findings will not generalize to females because, in nonhuman primates, social hierarchy (presumably rewarding

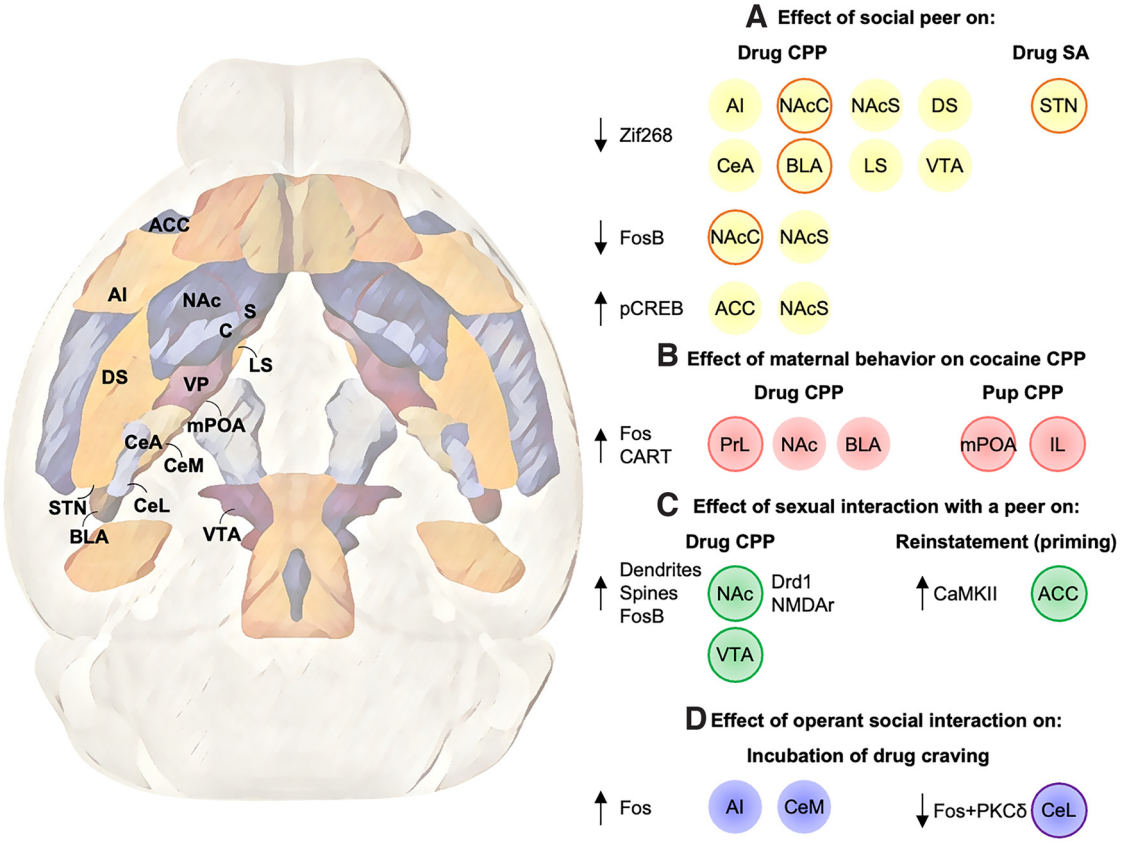


**Figure 3.** Neuropharmacological findings. Left, Representation of a horizontal section of a rat brain. Left hemisphere represents each brain region and its label. Right, Brain regions with increased (arrow up) or decreased (arrow down) activity associated with the (***A***) effect of a social peer on drug CPP (left) and drug self-administration (right). ***B***, Effect of maternal behavior on cocaine (left) and pup (right) CPP. ***C***, Effect of social sexual interaction with a peer on drug CPP. ***D***, Effect of operant social interaction on incubation of drug craving. Circles with solid outlines represent brain regions critical for the behavior. Each color represents a different animal model of social interaction. ACC, Anterior cingulate cortex; AI, anterior insula cortex; BLA, basolateral amygdala; CART, cocaine and amphetamine-regulated transcript; CeA, central nucleus of amygdala; CeL, lateral part of CeA; CeM, medial part of CeA; DS, dorsal striatum; IL, inframlimbic area; LS, lateral septum (S, shell; C, core); PrL, prelimbic area; STN, subthalamic nucleus; VTA, ventral tegmental area. Conceptual visualization derived from the data described in Tables 1–4.

for the dominant monkeys and aversive for the submissive monkeys) has a major sex-dependent effect on cocaine self-administration: dominant status decreases self-administration in males and increases it in females, while submissive status has an opposite effect (Morgan et al., 2002; Nader et al., 2012). The generality of behavioral findings across factors, such as sex, dominance status, and age, should be systematically investigated because, as we note below, studies of neural mechanisms of behavior are only as informative as the behaviors themselves.

For the behaviors characterized to date, the neurobiological and circuit data suggest that, in rats, rewarding social interactions can either increase or decrease the effects of opioids and psychostimulants on the activity of different brain areas involved in the rewarding effects of these drugs and conditioned drug effects (VTA, NAc, amygdala subregions, and mPFC subregions) (Fig. 3). However, with few exceptions (e.g., role of NAc $\delta$FosB in sexual interaction-induced sensitization of methamphetamine CPP or role of PKC$\delta$ CeL in inhibition of incubation of methamphetamine craving by operant social choice), the brain mechanisms of the protective (or facilitatory), effects of rewarding social interactions are largely unknown. The reason for this state-of-affairs is that most of the studies reviewed were either purely behavioral or used correlational neuroscience methods (e.g., expression of immediate early genes). Correlational methods are informative as an initial screen to identify potential circuits and brain regions, but their results should be interpreted with caution because they can reflect either causes or consequences of the behavior under study (Cruz et al., 2013). Below, we discuss several future directions and their implications.

*Future directions*

*A mouse model of social self-administration and choice.* The addiction-related rodent studies we reviewed used rats (primarily males) almost exclusively. In contrast, most current studies on circuit mechanisms of social reward use C57Bl/6-based transgenic mice, which enable investigators to use diverse genetic tools for identification and manipulation of specific cell types and circuits for social behavior (Yizhar et al., 2011; Felix-Ortiz and Tye, 2014; Hu et al., 2021). To facilitate the identification of mechanisms underlying the effects we see in our studies of operant social interaction (Venniro et al., 2018; Venniro and Shaham, 2020), we recently developed an operant model of social self-administration and choice in adolescent and adult female mice (Ramsey et al., 2022). We examined operant self-administration under different fixed-ratio schedules (FR1-FR6) and a progressive-ratio schedule, along with nonreinforced social seeking during isolation, and choice between social interaction and highly palatable food. The same palatable food induces "voluntary abstinence" for opioid and psychostimulant drugs in a choice setup (Caprioli et al., 2017; Reiner et al., 2020; Fredriksson et al., 2021) in rats, and strongly inhibits highly rewarding operant aggression self-administration in innately aggressive male CD1 mice (Golden et al., 2017a, 2019a).

The main finding from our study was that, independent of age, social interaction with a same-sex and age-matched peer serves as a strong operant reinforcer in CD1 female mice, but not C57BL/6J mice (Ramsey et al., 2022). CD1 mice showed significantly stronger social self-administration than C57BL/6J mice under both reinforcement schedules. CD1 but not C57BL/6J mice showed robust social seeking after social isolation. In the choice task, CD1 mice preferred social interaction under low FR requirements, while C57 mice preferred the palatable food. Finally, to further confirm that social interaction with a same-sex peer is rewarding to CD1 but not C57BL/6J female mice, we showed that CD1 mice developed robust social CPP while C57BL/6J did not (Ramsey et al., 2022).

Our study suggests that C57BL/6-based transgenic mice are not suitable for the study of operant-based learned rewarding social interaction with same-sex peer (we also found that operant responding for social reward is not reliable in male C57BL/6 mice) (Ramsey et al., 2022). A potential strategy to combine the operant model with CD1 female mice with existing transgenic tools, while still maintaining the social phenotype, is to breed outbred female CD1 mice with transgenic C57BL/6J male mice and then use hybrid F1 female offspring, which maintain the phenotype of operant social self-administration (L.A.R., unpublished data). This breeding scheme has been used successfully to maintain the aggressive phenotype of outbred CD1 males (Golden et al., 2017b, 2019b; Aleyasin et al., 2018).

*The social-choice model to study social factors in drug reward and relapse in adolescent rats and monkeys*

Social experience during adolescence is an important factor in subsequent drug use (Sinha, 2008; Burke et al., 2017). Within the context of our review, social interaction with a peer is highly rewarding during adolescence for rats; they engage in social play most frequently during juvenile and adolescent stages (Trezza et al., 2011, 2014). Social-play deprivation in adolescence increases cocaine and alcohol self-administration in rats (Baarendse et al., 2014; Lesscher et al., 2015), and isolation during adolescence (resulting in lack of opportunity for social play) increases CPP for cocaine, amphetamine, and alcohol in adulthood (Whitaker et al., 2013; Walker et al., 2022). The relationship between social play and subsequent drug self-administration is not straightforward. Lesscher et al. (2021) reported that adolescent rats that played more also drank more alcohol during adulthood. However, the high-play rats showed stronger conditioned suppression of alcohol intake (decreased operant responding in the presence of a cue paired with shock), suggesting that they are more responsive to contingencies that should moderate alcohol intake, even if their baseline drinking levels are higher (Lesscher et al., 2021).

Based on these studies, a future research question is whether social play in an operant choice setup will inhibit drug self-administration in adolescents and whether voluntary abstinence induced by social play during adolescence will prevent relapse during adulthood. Rewarding social play can also be incorporated into drug CPP studies in the manner described above for the studies by Zernig et al. (2013), to prevent reinstatement of drug CPP in adolescent rats.

Another potential application of the operant social-choice model is to expand it to monkey choice studies, where for many years the alternative nondrug reward has been food (Spragg, 1940; Nader et al., 1993; Banks and Negus, 2017). In an early study, Mason et al. (1963) showed that young chimpanzees prefer to play with the experimenter when given a choice between social play and food. But we have not found any published studies on choice between drug reward versus social interaction with a peer (or the experimenter). A question for future research is the extent to which the findings we have discussed from studies with rats and mice will generalize to nonhuman primates (Morgan et al., 2002; Porrino et al., 2004; Nader et al., 2012).

*The application of the operant social self-administration and choice model to other psychiatric and medical conditions*

Decreased positive social interaction with peers, family, and society at large is not unique to drug addiction; it is a common feature of psychiatric disorders, including depression (Seligman, 1972), autism (Hyman et al., 2020), PTSD and anxiety disorders (St-Jean-Trudel et al., 2009; Guay et al., 2017), and schizophrenia (van Os and Kapur, 2009), as well as medical conditions, such as chronic pain (Nazarian et al., 2021). In animal models of those conditions, investigators have almost exclusively assessed decreased social interaction by using different forms of unconditioned social interaction among familiar or naive peers (Berton and Nestler, 2006; Silverman et al., 2010). These measures fail to assess either volitional (operant) rewarding social interaction or learned social interactions because the interaction is both experimenter-imposed and innate in nature. This significantly diverges from the human condition, where social interactions are primarily volitional in nature and learned. Our operant-based social interaction and choice model in rats and mice can overcome this apparent preclinical-to-clinical "disconnect."

As a first attempt toward this goal, in collaboration with the Negus laboratory, we compared the effect of intraperitoneal injection of lactic acid (a visceral noxious stimulus) on social interaction versus food self-administration in male and female rats (many studies have shown that pain states reliably decrease food-reinforced responding in rodents) (Negus, 2019). We found that, compared with food self-administration, social interaction self-administration was significantly more sensitive to pain-related disruption of operant responding, and surprisingly unresponsive to rescue by an opioid analgesic (morphine) (Baldwin et al., 2022). These results indicate that learned operant social behavior may be especially vulnerable to depression by pain-related states. We hope that this study will inspire other investigators to incorporate the social self-administration and choice model in basic studies on mechanisms of disruption of learned operant social behavior in psychiatric disorders, chronic pain, and potentially other medical disorders.

*A note on clinical implications and ethological/human relevance*

In some of the models reviewed here, investigators are trying to situate the drug-related behavior of laboratory animals in a multioperant environment, incorporating choices that might be relevant in a more naturalistic setting. That endeavor raises more issues than we can address in this review, which is intended mostly as an update on procedures and findings. We will note some of the issues briefly.

We see a twofold justification for the use of social models in addiction research. First, as we have noted, screening of new biomedical treatments for addiction might have greater predictive validity for human use if the screening were done only in subsets of laboratory animals identified as comparatively nonresponsive to social rewards (Venniro et al., 2021a). This would be labor intensive at the preclinical end (because most of the laboratory animals initially trained and tested would have to be excluded), but it might be the most rapid route to identification of new

treatments that can be readily disseminated, which, for the most part, would be medications administered systemically and chronically.

Second, studies on the specific neurocircuitry and neuropharmacology of drug choice might have greater construct validity if the drug choice occurred in social situations. This justification may be the more appealing one to neuroscientists because it concerns inquiries into mechanism and theory. But we think both justifications are important. Neurocircuit-specific mechanisms are not yet translatable into treatments to which most people would have access, although neurocircuit-specific discovery could lead to greater revolutions in treatment in the long run (dependent on yet-unrealized feats in bioengineering, or the adequate approximation of a neurocircuit-specific manipulation by an orally taken medication in humans). At the same time, rapidly translatable treatments (which, in rodents, would be most appropriately tested via systemic drug administration, not in more mechanistically informative ways) are needed to address crises in public health that cannot wait for unspecified technological breakthroughs.

Both of these justifications rest on assumptions that the animal models discussed here are indeed more ethologically relevant for the laboratory animals, and more relevant to humans, than models in which laboratory animals are socially isolated and/or not offered choices among reinforcers. These are open questions, most of which hinge on the functional significance of the behaviors under study. For example, we do not know what attributes of the drug experience/behavior of a peer (or the act of mating or maternal behavior) account for effects on drug reward or drug choice in rats. Without that knowledge, it is difficult to know what aspects of human psychology are being modeled. Clarification of those questions would require in-depth behavioral studies with considerable input from ethologists, and that is not common practice in the neuroscience of addiction. Even pending such work, however, we think that the reintroduction of social factors into laboratory-animal research is a promising development, in part because it has already led to reconsideration of what was becoming entrenched conclusions, such as the intractability of drug reward relative to other rewards.

## References


Ahmed SH, Koob GF (1998) Transition from moderate to excessive drug intake: change in hedonic set point. Science 282:298–300.

Alexander BK, Hadaway PF (1982) Opiate addiction: the case of an adaptive orientation. Psychol Bull 92:367–381.

Alexander BK, Coambs RB, Hadaway PF (1978) The effect of housing and gender on morphine self-administration in rats. Psychopharmacology (Berl) 58:175–179.

Aleyasin H, Flanigan ME, Golden SA, Takahashi A, Menard C, Pfau ML, Multer J, Pina J, McCabe KA, Bhatti N, Hodes GE, Heshmati M, Neve RL, Nestler EJ, Heller EA, Russo SJ (2018) Cell-type-specific role of deltaFosB in nucleus accumbens In modulating intermale aggression. J Neurosci 38:5913–5924.

Azrin NH, Acierno R, Kogan ES, Donohue B, Besalel VA, McMahon PT (1996) Follow-up results of supportive versus behavioral therapy for illicit drug use. Behav Res Ther 34:41–46.

Baarendse PJ, Limpens JH, Vanderschuren LJ (2014) Disrupted social development enhances the motivation for cocaine in rats. Psychopharmacology (Berl) 231:1695–1704.

Baldwin AN, Banks ML, Marsh SA, Townsend EA, Venniro M, Shaham Y, Negus SS (2022) Acute pain-related depression of operant responding maintained by social interaction or food in male and female rats. Psychopharmacology (Berl) 239:561–572.

Banks ML, Negus SS (2017) Insights from preclinical choice models on treating drug addiction. Trends Pharmacol Sci 38:181–194.

Bardo MT, Bevins RA (2000) Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology (Berl) 153:31–43.

Bardo MT, Neisewander JL, Kelly TH (2013) Individual differences and social influences on the neurobehavioral pharmacology of abused drugs. Pharmacol Rev 65:255–290.

Beloate LN, Omrani A, Adan RA, Webb IC, Coolen LM (2016a) Ventral tegmental area dopamine cell activation during male rat sexual behavior regulates neuroplasticity and d-amphetamine cross-sensitization following sex abstinence. J Neurosci 36:9949–9961.

Beloate LN, Weems PW, Casey GR, Webb IC, Coolen LM (2016b) Nucleus accumbens NMDA receptor activation regulates amphetamine cross-sensitization and deltaFosB expression following sexual experience in male rats. Neuropharmacology 101:154–164.

Beloate LN, Coolen LM (2017) Influences of social reward experience on behavioral responses to drugs of abuse: review of shared and divergent neural plasticity mechanisms for sexual reward and drugs of abuse. Neurosci Biobehav Rev 83:356–372.

Berton O, Nestler EJ (2006) New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci 7:137–151.

Bouton ME, Swartzentruber D (1991) Sources of relapse after extinction in Pavlovian and instrumental learning. Clin Psychol Rev 11:123–140.

Bregolin T, Pinheiro BS, El Rawas R, Zernig G (2017) Preventive strength of dyadic social interaction against reacquisition/reexpression of cocaine conditioned place preference. Front Behav Neurosci 11:225.

Burke AR, McCormick CM, Pellis SM, Lukkes JL (2017) Impact of adolescent social experiences on behavior and neural circuits implicated in mental illnesses. Neurosci Biobehav Rev 76:280–300.

Canchy L, Girardeau P, Durand A, Vouillac-Mendoza C, Ahmed SH (2021) Pharmacokinetics trumps pharmacodynamics during cocaine choice: a reconciliation with the dopamine hypothesis of addiction. Neuropsychopharmacology 46:288–296.

Caprioli D, Venniro M, Zeric T, Li X, Adhikary S, Madangopal R, Marchant NJ, Lucantonio F, Schoenbaum G, Bossert JM, Shaham Y (2015) Effect of the novel positive allosteric modulator of metabotropic glutamate receptor 2 AZD8529 on incubation of methamphetamine craving after prolonged voluntary abstinence in a rat model. Biol Psychiatry 78:463–473.

Caprioli D, Venniro M, Zhang M, Bossert JM, Warren BL, Hope BT, Shaham Y (2017) Role of dorsomedial striatum neuronal ensembles in incubation of methamphetamine craving after voluntary abstinence. J Neurosci 37:1014–1027.

Catania CA (1992) Learning. Englewood Cliffs, NJ: Prentice-Hall.

Chow JJ, Beacher N, Chabot JM, Oke M, Venniro M, Lin DT, Shaham Y (2022) Characterization of operant social interaction in rats: effects of access duration, effort, peer familiarity, housing conditions, and choice between social interaction versus food or remifentanil. Psychopharmacology (Berl) 239:2093–2108.

Cornelius MD, Richardson GA, Day NL, Cornelius JR, Geva D, Taylor PM (1994) A comparison of prenatal drinking in two recent samples of adolescents and adults. J Stud Alcohol 55:412–419.

Cruz FC, Koya E, Guez-Barber DH, Bossert JM, Lupica CR, Shaham Y, Hope BT (2013) New technologies for examining the role of neuronal ensembles in drug addiction and fear. Nat Rev Neurosci 14:743–754.

Deroche-Gamonet V, Belin D, Piazza PV (2004) Evidence for addiction-like behavior in the rat. Science 305:1014–1017.

Dong Y, Taylor JR, Wolf ME, Shaham Y (2017) Circuit and synaptic plasticity mechanisms of drug relapse. J Neurosci 37:10867–10876.

El Rawas R, Klement S, Salti A, Fritz M, Dechant G, Saria A, Zernig G (2012) Preventive role of social interaction for cocaine conditioned place preference: correlation with FosB/DeltaFosB and pCREB expression in rat mesocorticolimbic areas. Front Behav Neurosci 6:8.

Epstein DH, Preston KL (2003) The reinstatement model and relapse prevention: a clinical perspective. Psychopharmacology (Berl) 168:31–41.

Felix-Ortiz AC, Tye KM (2014) Amygdala inputs to the ventral hippocampus bidirectionally modulate social behavior. J Neurosci 34:586–595.

Fleming AS, Cheung U, Myhal N, Kessler Z (1989) Effects of maternal hormones on 'timidity' and attraction to pup-related odors in female rats. Physiol Behav 46:449–453.

Fredriksson I, Venniro M, Reiner DJ, Chow JJ, Bossert JM, Shaham Y (2021) Animal models of drug relapse and craving after voluntary abstinence: a review. Pharmacol Rev 73:1050–1083.

Fritz M, El Rawas R, Salti A, Klement S, Bardo MT, Kemmler G, Dechant G, Saria A, Zernig G (2011a) Reversal of cocaine-conditioned place preference and mesocorticolimbic Zif268 expression by social interaction in rats. Addict Biol 16:273–284.

Fritz M, El Rawas R, Klement S, Kummer K, Mayr MJ, Eggart V, Salti A, Bardo MT, Saria A, Zernig G (2011b) Differential effects of accumbens core vs shell lesions in a rat concurrent conditioned place preference paradigm for cocaine vs social interaction. PLoS One 6:e26761.

Frohmader KS, Pitchers KK, Balfour ME, Coolen LM (2010) Mixing pleasures: review of the effects of drugs on sex behavior in humans and animal models. Horm Behav 58:149–162.

Frohmader KS, Lehman MN, Laviolette SR, Coolen LM (2011) Concurrent exposure to methamphetamine and sexual behavior enhances subsequent drug reward and causes compulsive sexual behavior in male rats. J Neurosci 31:16473–16482.

Giorla E, Nordmann S, Vielle C, Pelloux Y, Roux P, Protopopescu C, Manrique C, Davranche K, Montanari C, Giorgi L, Vilotitch A, Huguet P, Carrieri P, Baunez C (2022) Peer presence and familiarity as key factors to reduce cocaine intake in both rats and humans: an effect mediated by the subthalamic nucleus. Psychopharmacology (Berl) 239:1097–1113.

Gipson CD, Yates JR, Beckmann JS, Marusich JA, Zentall TR, Bardo MT (2011) Social facilitation of d-amphetamine self-administration in rats. Exp Clin Psychopharmacol 19:409–419.

Golden SA, Heins C, Venniro M, Caprioli D, Zhang M, Epstein DH, Shaham Y (2017a) Compulsive addiction-like aggressive behavior in mice. Biol Psychiatry 82:239–248.

Golden SA, Aleyasin H, Heins R, Flanigan M, Heshmati M, Takahashi A, Russo SJ, Shaham Y (2017b) Persistent conditioned place preference to aggression experience in adult male sexually-experienced CD-1 mice. Genes Brain Behav 16:44–55.

Golden SA, Jin M, Shaham Y (2019a) Animal models of (or for) aggression reward, addiction, and relapse: behavior and circuits. J Neurosci 39:3996–4008.

Golden SA, Jin M, Heins C, Venniro M, Michaelides M, Shaham Y (2019b) Nucleus accumbens Drd1-expressing neurons control aggression self-administration and aggression seeking in mice. J Neurosci 39:2482–2496.

Grimm J, Hope B, Wise R, Shaham Y (2001) Neuroadaptation: incubation of cocaine craving after withdrawal. Nature 412:141–142.

Guay S, Nachar N, Lavoie ME, Marchand A, O'Connor KP (2017) The buffering power of overt socially supportive and unsupportive behaviors from the significant other on posttraumatic stress disorder individuals' emotional state. Anxiety Stress Coping 30:52–65.

Heilig M, Epstein DH, Nader MA, Shaham Y (2016) Time to connect: bringing social context into addiction neuroscience. Nat Rev Neurosci 17:592–599.

Higgins ST, Delaney DD, Budney AJ, Bickel WK, Hughes JR, Foerg F, Fenwick JW (1991) A behavioral approach to achieving initial cocaine abstinence. Am J Psychiatry 148:1218–1224.

Hofford RS, Bond PN, Chow JJ, Bardo MT (2020) Presence of a social peer enhances acquisition of remifentanil self-administration in male rats. Drug Alcohol Depend 213:108125.

Hu RK, Zuo Y, Ly T, Wang J, Meera P, Wu YE, Hong W (2021) An amygdala-to-hypothalamus circuit for social reward. Nat Neurosci 24:831–842.

Hunt GM, Azrin NH (1973) A community-reinforcement approach to alcoholism. Behav Res Ther 11:91–104.

Hyman SL, et al. (2020) Identification, evaluation, and management of children with autism spectrum disorder. Pediatrics 145:e20193447.

Kandel D, Kandel E (2015) The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr 104:130–137.

Khoo SY (2020) Have we reproduced Rat Park? Conceptual but not direct replication of the protective effects of social and environmental enrichment in addiction. J Reproducibil Neurosci. Advance online publication. Retrieved Aug 13, 2020. https://doi.org/10.31885/jrn.1.2020.1318.

Knutson B, Burgdorf J, Panksepp J (2002) Ultrasonic vocalizations as indices of affective states in rats. Psychol Bull 128:961–977.

Kuiper LB, Beloate LN, Dupuy BM, Coolen LM (2019) Drug-taking in a socio-sexual context enhances vulnerability for addiction in male rats. Neuropsychopharmacology 44:503–513.

Kuiper LB, Lucas KA, Mai V, Coolen LM (2020) Enhancement of drug seeking following drug taking in a sexual context requires anterior cingulate cortex activity in male rats. Front Behav Neurosci 14:87.

Kummer KK, Hofhansel L, Barwitz CM, Schardl A, Prast JM, Salti A, El Rawas R, Zernig G (2014) Differences in social interaction vs cocaine reward in mouse vs rat. Front Behav Neurosci 8:363.

Lacy RT, Strickland JC, Smith MA (2014) Cocaine self-administration in social dyads using custom-built operant conditioning chambers. J Neurosci Methods 236:11–18.

Lacy RT, Strickland JC, Feinstein MA, Robinson AM, Smith MA (2016) The effects of sex, estrous cycle, and social contact on cocaine and heroin self-administration in rats. Psychopharmacology (Berl) 233:3201–3210.

Lee A, Clancy S, Fleming AS (2000) Mother rats bar-press for pups: effects of lesions of the mPOA and limbic sites on maternal behavior and operant responding for pup-reinforcement. Behav Brain Res 108:215–231.

Lesscher HM, Spoelder M, Rotte MD, Janssen MJ, Hesseling P, Lozeman-van't Klooster JG, Baars AM, Vanderschuren LJ (2015) Early social isolation augments alcohol consumption in rats. Behav Pharmacol 26:673–680.

Lesscher HM, Achterberg EJ, Siviy SM, Vanderschuren L (2021) Individual differences in social play behaviour predict alcohol intake and control over alcohol seeking in rats. Psychopharmacology (Berl) 238:3119–3130.

Levis SC, Baram TZ, Mahler SV (2021) Neurodevelopmental origins of substance use disorders: evidence from animal models of early-life adversity and addiction. Eur J Neurosci 55:2170–2195.

Li X, Zeric T, Kambhampati S, Bossert JM, Shaham Y (2015) The central amygdala nucleus is critical for incubation of methamphetamine craving. Neuropsychopharmacology 40:1297–1306.

Lu L, Shepard J, Hall F, Shaham Y (2003) Effect of environmental stressors on opiate and psychostimulant reinforcement, reinstatement and discrimination in rats: a review. Neurosci Biobehav Rev 27:457–491.

Malone SG, Shaykin JD, Stairs DJ, Bardo MT (2022) Neurobehavioral effects of environmental enrichment and drug abuse vulnerability: An updated review. Pharmacol Biochem Behav 221:173471.

Marchant NJ, McDonald AJ, Matsuzaki R, van Mourik Y, Schetters D, De Vries TJ (2022) Rats choose alcohol over social reward in an operant choice procedure. Neuropsychopharmacology. Advance online publication. Retrieved Sep 15, 2022. https://doi.org/10.1038/s41386-022-01447-6.

Marlatt GA, Baer JS, Donovan DM, Kivlahan DR (1988) Addictive behaviors: etiology and treatment. Annu Rev Psychol 39:223–252.

Mason WA, Saxon SV, Sharpe LG (1963) Preferential responses of young chimpanzees to food and social rewards. Psychol Rec 13:341–345.

Mattson BJ, Morrell JI (2005) Preference for cocaine- versus pup-associated cues differentially activates neurons expressing either Fos or cocaine- and amphetamine-regulated transcript in lactating, maternal rodents. Neuroscience 135:315–328.

Mattson BJ, Williams S, Rosenblatt JS, Morrell JI (2001) Comparison of two positive reinforcing stimuli: pups and cocaine throughout the postpartum period. Behav Neurosci 115:683–694.

Mattson BJ, Williams SE, Rosenblatt JS, Morrell JI (2003) Preferences for cocaine- or pup-associated chambers differentiates otherwise behaviorally identical postpartum maternal rats. Psychopharmacology (Berl) 167:1–8.

Miczek KA, Faccidomo S, De Almeida RM, Bannai M, Fish EW, Debold JF (2004) Escalated aggressive behavior: new pharmacotherapeutic approaches and opportunities. Ann NY Acad Sci 1036:336–355.

Miczek KA, Yap JJ, Covington HE 3rd (2008) Social stress, therapeutics and drug abuse: preclinical models of escalated and depressed intake. Pharmacol Ther 120:102–128.

Montanari C, Giorla E, Pelloux Y, Baunez C (2020) Subthalamic nucleus mediates the modulation on cocaine self-administration induced by ultrasonic vocalization playback in rats. Addict Biol 25:e12710.

Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA (2002) Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nat Neurosci 5:169–174.

Mucha RF, Iversen SD (1984) Reinforcing properties of morphine and naloxone revealed by conditioned place preferences: a procedural examination. Psychopharmacology (Berl) 82:241–247.

Nader MA (2021) The impact of social variables in preclinical models of cocaine abuse. Fac Rev 10:76.

Nader MA, Banks ML (2014) Environmental modulation of drug taking: nonhuman primate models of cocaine abuse and PET neuroimaging. Neuropharmacology 76:510–517.
Nader MA, Hedeker D, Woolverton WL (1993) Behavioral economics and drug choice: effects of unit price on cocaine self-administration by monkeys. Drug Alcohol Depend 33:193–199.
Nader MA, Nader SH, Czoty PW, Riddick NV, Gage HD, Gould RW, Blaylock BL, Kaplan JR, Garg PK, Davies HM, Morton D, Garg S, Reboussin BA (2012) Social dominance in female monkeys: dopamine receptor function and cocaine reinforcement. Biol Psychiatry 72:414–421.
Nazarian A, Negus SS, Martin TJ (2021) Factors mediating pain-related risk for opioid use disorder. Neuropharmacology 186:108476.
Negus SS (2019) Core outcome measures in preclinical assessment of candidate analgesics. Pharmacol Rev 71:225–266.
Neisewander JL, Peartree NA, Pentkowski NS (2012) Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. Psychopharmacology (Berl) 224:33–56.
Peitz GW, Strickland JC, Pitts EG, Foley M, Tonidandel S, Smith MA (2013) Peer influences on drug self-administration: an econometric analysis in socially housed rats. Behav Pharmacol 24:114–123.
Pelloux Y, Giorla E, Montanari C, Baunez C (2019) Social modulation of drug use and drug addiction. Neuropharmacology 159:107545.
Pereira M, Morrell JI (2010) The medial preoptic area is necessary for motivated choice of pup- over cocaine-associated environments by early postpartum rats. Neuroscience 167:216–231.
Pereira M, Morrell JI (2020) Infralimbic cortex biases preference decision making for offspring over competing cocaine-associated stimuli in new mother rats. eNeuro 7:ENEURO.0460-19.2020.
Petrie BF (1985) Failure to replicate an environmental effect of morphine hydrochloride consumption: a possible psychopharmacogenetic link. Thesis, Simon Fraser University.
Petrie BF (1996) Environment is not the most important variable in determining oral morphine consumption in Wistar rats. Psychol Rep 78:391–400.
Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y (2011) Neurobiology of the incubation of drug craving. Trends Neurosci 34:411–420.
Pinheiro BS, Seidl SS, Habazettl E, Gruber BE, Bregolin T, Zernig G (2016) Dyadic social interaction of C57BL/6 mice versus interaction with a toy mouse: conditioned place preference/aversion, substrain differences, and no development of a hierarchy. Behav Pharmacol 27:279–288.
Pitchers KK, Balfour ME, Lehman MN, Richtand NM, Yu L, Coolen LM (2010) Neuroplasticity in the mesolimbic system induced by natural reward and subsequent reward abstinence. Biol Psychiatry 67:872–879.
Pitchers KK, Vialou V, Nestler EJ, Laviolette SR, Lehman MN, Coolen LM (2013) Natural and drug rewards act on common neural plasticity mechanisms with ΔFosB as a key mediator. J Neurosci 33:3434–3442.
Pitchers KK, Coppens CM, Beloate LN, Fuller J, Van S, Frohmader KS, Laviolette SR, Lehman MN, Coolen LM (2014) Endogenous opioid-induced neuroplasticity of dopaminergic neurons in the ventral tegmental area influences natural and opiate reward. J Neurosci 34:8825–8836.
Pitchers KK, Di Sebastiano AR, Coolen LM (2016) mGluR5 activation in the nucleus accumbens is not essential for sexual behavior or cross-sensitization of amphetamine responses by sexual experience. Neuropharmacology 107:122–130.
Porrino LJ, Lyons D, Smith HR, Daunais JB, Nader MA (2004) Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. J Neurosci 24:3554–3562.
Prast JM, Schardl A, Sartori SB, Singewald N, Saria A, Zernig G (2014) Increased conditioned place preference for cocaine in high anxiety related behavior (HAB) mice is associated with an increased activation in the accumbens corridor. Front Behav Neurosci 8:441.
Ramsey LA, Holloman FM, Hope BT, Shaham Y, Venniro M (2022) Waving through the window: a model of volitional social interaction in female mice. Biol Psychiatry 91:988–997.
Reiner DJ, Lofaro OM, Applebey SV, Korah H, Venniro M, Cifani C, Bossert JM, Shaham Y (2020) Role of projections between piriform cortex and orbitofrontal cortex in relapse to fentanyl seeking after palatable food choice-induced voluntary abstinence. J Neurosci 40:2485–2497.
Richardson GA, Day NL (1991) Maternal and neonatal effects of moderate cocaine use during pregnancy. Neurotoxicol Teratol 13:455–460.
Richardson NR, Roberts DC (1996) Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J Neurosci Methods 66:1–11.
Robinson AM, Lacy RT, Strickland JC, Magee CP, Smith MA (2016) The effects of social contact on cocaine intake under extended-access conditions in male rats. Exp Clin Psychopharmacol 24:285–296.
Robinson AM, Fronk GE, Zhang H, Tonidandel S, Smith MA (2017) The effects of social contact on cocaine intake in female rats. Drug Alcohol Depend 177:48–53.
Roura-Martinez D, Ucha M, Orihuel J, Ballesteros-Yanez I, Castillo CA, Marcos A, Ambrosio E, Higuera-Matas A (2020) Central nucleus of the amygdala as a common substrate of the incubation of drug and natural reinforcer seeking. Addict Biol 25:e12706.
Ryabinin AE, Fulenwider HD (2021) Alcohol and oxytocin: scrutinizing the relationship. Neurosci Biobehav Rev 127:852–864.
Schuster CR, Thompson T (1969) Self administration of and behavioral dependence on drugs. Annu Rev Pharmacol 9:483–502.
Seip KM, Morrell JI (2007) Increasing the incentive salience of cocaine challenges preference for pup- over cocaine-associated stimuli during early postpartum: place preference and locomotor analyses in the lactating female rat. Psychopharmacology (Berl) 194:309–319.
Seligman ME (1972) Learned helplessness. Annu Rev Med 23:407–412.
Shaham Y, Puddicombe J, Stewart J (1997) Sexually arousing events and relapse to heroin-seeking in sexually experienced male rats. Physiol Behav 61:337–341.
Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003) The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Berl) 168:3–20.
Silverman JL, Yang M, Lord C, Crawley JN (2010) Behavioural phenotyping assays for mouse models of autism. Nat Rev Neurosci 11:490–502.
Silverman K, DeFulio A, Sigurdsson SO (2012) Maintenance of reinforcement to address the chronic nature of drug addiction. Prev Med 55 Suppl:S46–S53.
Sinha R (2008) Chronic stress, drug use, and vulnerability to addiction. Ann NY Acad Sci 1141:105–130.
Smith MA (2012) Peer influences on drug self-administration: social facilitation and social inhibition of cocaine intake in male rats. Psychopharmacology (Berl) 224:81–90.
Smith MA, Pitts EG (2014) Social preference and drug self-administration: a preclinical model of social choice within peer groups. Drug Alcohol Depend 135:140–145.
Smith MA, Lacy RT, Strickland JC (2014) The effects of social learning on the acquisition of cocaine self-administration. Drug Alcohol Depend 141:1–8.
Smith MA, Zhang H, Robinson AM (2016) The effects of excitatory and inhibitory social cues on cocaine-seeking behavior. Front Behav Neurosci 10:217–217.
Smith MA, Schmidt KT, Sharp JL, Pearson T, Davis AL, Gibson AN, Potter KM (2021) Lack of evidence for positive reinforcing and prosocial effects of MDMA in pair-housed male and female rats. Eur J Pharmacol 913:174646.
Solinas M, Thiriet N, Chauvet C, Jaber M (2010) Prevention and treatment of drug addiction by environmental enrichment. Prog Neurobiol 92:572–592.
Solinas M, Chauvet C, Lafay-Chebassier C, Jaafari N, Thiriet N (2021) Environmental enrichment-inspired pharmacological tools for the treatment of addiction. Curr Opin Pharmacol 56:22–28.
Spragg SD (1940) Morphine addiction in chimpanzees. Comp Psychol Mono 15:132.
St-Jean-Trudel E, Guay S, Marchand A (2009) The relationship between social support, psychological stress and the risk of developing anxiety disorders in men and women: results of a national study. Can J Public Health 100:148–152.
Stitzer ML, Jones HE, Tuten M, Wong C (2011) Community reinforcement approach and contingency management interventions for substance abuse. In: Handbook of motivational counseling: goal-based approaches to assessment and intervention with addiction and other problems (Cox WM, Klinger E, eds). Chichester, UK: Wiley.
Thiel KJ, Sanabria F, Neisewander JL (2009) Synergistic interaction between nicotine and social rewards in adolescent male rats. Psychopharmacology (Berl) 204:391–402.

Tomie A, Burger KM, Di Poce J, Pohorecky LA (2004) Social opportunity and ethanol drinking in rats. Prog Neuropsychopharmacol Biol Psychiatry 28:1089–1097.

Tomie A, DeFuria AA, Jones HA, Edwards SD, Yu L (2014) Effects of cagemate gender and the cagemate's access to ethanol on ethanol and water intake of the proximal male or the proximal female CD-1 mouse. Alcohol 48:73–82.

Trezza V, Campolongo P, Vanderschuren LJ (2011) Evaluating the rewarding nature of social interactions in laboratory animals. Dev Cogn Neurosci 1:444–458.

Trezza V, Baarendse PJ, Vanderschuren LJ (2014) On the interaction between drugs of abuse and adolescent social behavior. Psychopharmacology (Berl) 231:1715–1729.

van Os J, Kapur S (2009) Schizophrenia. Lancet 374:635–645.

Vanderschuren LJ, Achterberg EJ, Trezza V (2016) The neurobiology of social play and its rewarding value in rats. Neurosci Biobehav Rev 70:86–105.

Venniro M, Shaham Y (2020) An operant social self-administration and choice model in rats. Nat Protoc 15:1542–1559.

Venniro M, Zhang M, Shaham Y, Caprioli D (2017a) Incubation of methamphetamine but not heroin craving after voluntary abstinence in male and female rats. Neuropsychopharmacology 42:1126–1135.

Venniro M, Caprioli D, Zhang M, Whitaker LR, Zhang S, Warren BL, Cifani C, Marchant NJ, Yizhar O, Bossert JM, Chiamulera C, Morales M, Shaham Y (2017b) The anterior insular cortex→central amygdala glutamatergic pathway is critical to relapse after contingency management. Neuron 96:414–427.e8.

Venniro M, Zhang M, Caprioli D, Hoots JK, Golden SA, Heins C, Morales M, Epstein DH, Shaham Y (2018) Volitional social interaction prevents drug addiction in rat models. Nat Neurosci 21:1520–1529.

Venniro M, Russell TI, Zhang M, Shaham Y (2019) Operant social reward decreases incubation of heroin craving in male and female rats. Biol Psychiatry 86:848–856.

Venniro M, Banks ML, Heilig M, Epstein DH, Shaham Y (2020a) Improving translation of animal models of addiction and relapse by reverse translation. Nat Rev Neurosci 21:625–643.

Venniro M, Russell TI, Ramsey LA, Richie CT, Lesscher HM, Giovanetti SM, Messing RO, Shaham Y (2020b) Abstinence-dependent dissociable central amygdala microcircuits control drug craving. Proc Natl Acad Sci USA 117:8126–8134.

Venniro M, Panlilio LV, Epstein DH, Shaham Y (2021a) The protective effect of operant social reward on cocaine self-administration, choice, and relapse is dependent on delay and effort for the social reward. Neuropsychopharmacology 46:2350–2357.

Venniro M, Reverte I, Ramsey LA, Papastrat KM, D'Ottavio G, Milella MS, Li X, Grimm JW, Caprioli D (2021b) Factors modulating the incubation of drug and non-drug craving and their clinical implications. Neurosci Biobehav Rev 131:847–864.

Vielle C, Montanari C, Pelloux Y, Baunez C (2021) Evidence for a vocal signature in the rat and its reinforcing effects: a key role for the subthalamic nucleus. Proc Biol Sci 288:20212260.

Vivian JA, Miczek KA (1999) Interactions between social stress and morphine in the periaqueductal gray: effects on affective vocal and reflexive pain responses in rats. Psychopharmacology (Berl) 146:153–161.

Walcott AT, Ryabinin AE (2021) Assessing effects of oxytocin on alcohol consumption in socially housed prairie voles using radio frequency tracking. Addict Biol 26:e12893.

Walker DM, Zhou X, Cunningham AM, Lipschultz AP, Ramakrishnan A, Cates HM, Bagot RC, Shen L, Zhang B, Nestler EJ (2022) Sex-specific transcriptional changes in response to adolescent social stress in the brain's reward circuitry. Biol Psychiatry 91:118–128.

Weiss VG, Yates JR, Beckmann JS, Hammerslag LR, Bardo MT (2018) Social reinstatement: a rat model of peer-induced relapse. Psychopharmacology (Berl) 235:3391–3400.

Whitaker LR, Degoulet M, Morikawa H (2013) Social deprivation enhances VTA synaptic plasticity and drug-induced contextual learning. Neuron 77:335–345.

Wikler A (1973) Dynamics of drug dependence: implications of a conditioning theory for research and treatment. Arch Gen Psychiatry 28:611–616.

Wise RA, Hoffman DC (1992) Localization of drug reward mechanisms by intracranial injections. Synapse 10:247–263.

Yates JR, Beckmann JS, Meyer AC, Bardo MT (2013) Concurrent choice for social interaction and amphetamine using conditioned place preference in rats: effects of age and housing condition. Drug Alcohol Depend 129:240–246.

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K (2011) Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477:171–178.

Zernig G, Kummer KK, Prast JM (2013) Dyadic social interaction as an alternative reward to cocaine. Front Psychiatry 4:100.

Zimmer BA, Oleson EB, Roberts DC (2012) The motivation to self-administer is increased after a history of spiking brain levels of cocaine. Neuropsychopharmacology 37:1901–1910.