# Operant social reward in animal models: behavior, brain mechanisms, and implications to neurodevelopment and psychiatric disorders, stress, and pain

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## Abstract

Social connection is a fundamental animal need, and its maintenance primarily depends on the rewarding nature of positive social interactions. A central feature of several medical conditions, including neuropsychiatric disorders, is decreased interest in positive social interactions and a tendency toward social isolation, which can in turn worsen these conditions.

Numerous studies using animal models have identified brain mechanisms underlying both unconditioned and conditioned (using conditioned place preference) social interactions, where the interaction is imposed by the experimenter. In contrast, much less is known about the brain mechanisms involved in volitional, rewarding social interactions that are initiated by the animals themselves. This is critical as social interactions between humans are often voluntary. Early studies showed that rats will perform a volitional operant response to gain access to social interaction with a peer. More recently, the operant social self-administration procedure has been used to investigate the brain mechanisms of rewarding social interaction in mice, rats, prairie voles, and hamsters.

In this review, we summarize behavioral and neurobiological studies that have used the operant social self-administration procedure. We then discuss how this model has been used to study the effect of volitional social interaction across neurodevelopmental disorders, addiction, stress, pain, and inflammation, including its role in drug self-administration and relapse in rats, the identification of heroin-addiction–vulnerable individuals, and to study how pain and social stress disrupt volitional social interaction. We conclude by briefly discussing future research directions and potential clinical applications.

**Keywords:** social connections, social reward, operant social-interaction, social self-administration, rodents, neurobiology of social reward

## 1. Introduction

Social connection is a fundamental need shared across most species. Both humans and most non-human animals form social groups, which enhance survival and overall fitness [1]. Affiliative bonds have been shown to improve health outcomes, reduce mortality risk, and extend lifespan [2]. In contrast, social isolation is associated with adverse effects, including an elevated risk of developing neuropsychiatry disorders, immune dysfunction, cardiovascular disease, and cancer [3].

The rewarding nature of social interaction plays a key role in promoting group cohesion and resilience, serving as a protection against both physical health issues and neuropsychiatric disorders [4,5]. Animal models provide the opportunity to investigate the molecular and neural mechanisms involved in social behavior [6]. Yet, selecting the most appropriate behavioral procedure for each specific research question is important for the translational relevance of the study.

Previous preclinical studies have used approaches in which the social interaction was experimenter-controlled. These methods include reciprocal social interaction tests or three-chamber tasks and unconditioned measures, such as the number of contacts made and the time spent near a social partner [7,8], or social conditioned place preference (CPP) and conditioned measures, such as time spent in a location previously paired with a social partner [9-11]. Using these unconditioned and conditioned measures of social interaction, many studies have characterized neuropharmacological and circuit mechanisms of social interaction [6,12]. However, while these procedures are useful for measuring different behaviors reflecting social interactions – which include, but not limited to, huddling, pinning, and pouncing – and for assessing conditioned response to social interactions (in the case of social conditioned place preference), they do not capture the volitional and actively engaging components of social interaction that is essential for the formation and reinforcement of social connections [13].

Early studies demonstrated that rats readily learn to press a lever to gain access to a peer [14,15], indicating that the volitional component of social interaction can be captured and effectively modeled in rodents using operant procedures. Similarly, recent studies have used social operant reinforcement procedures to investigate how social interaction serves as a reinforcer and have begun to characterize the neurobiological mechanisms underlying volitional social interaction [16-19].

In this review, we provide an overview of behavioral and neurobiological studies that have used operant social reinforcement procedures to investigate the volitional aspects of social interaction in rodents. Additionally, we will discuss how this model has been used to examine the impact of social reward on drug self-administration and relapse in rats, to identify individuals vulnerable to heroin addiction, to explore circuit-level mechanisms underlying autism-related behaviors in genetic mouse models, and to understand how pain and stress interfere with volitional social interaction.

Due to space limitations, we will not cover studies that have used operant procedures to investigate appetitive aggression reward [20-23]; see Golden et al. [24] and Miczek et al. [25] for reviews.

## 2. Rat studies

Behavioral studies

In the 1930s, Skinner showed that rats can be trained to press a lever by reinforcing the lever press with food delivery; since then, food has been the predominate non-drug reinforcer in operant conditioning studies [26,27]. Although the rewarding effects of social interaction are well-known, it was not until the 1960s that Angermeier [14,28] showed that rats can also be trained to press a lever by reinforcing the lever press with access to another rat. Subsequent studies investigated factors influencing operant social self-administration. These include (i) factors related to the experimental subject and the social partner, such as rearing conditions, social contact type, strain, familiarity, housing conditions, and sex; and (ii) variables related to the reinforcement schedules such as duration of access to the social partner and effort required to obtain access (Table 1).

Regarding factors related to the experimental subject, Angermeier [14] showed that both socially housed and isolated rats (post-weaning) can acquire social self-administration when given full contact access to the social partner. However, in socially isolated rats, social self-administration is impaired when social interaction is limited to visual or partial contact via a screen, suggesting that physical (tactile) contact is critical to the reinforcing effects of social interaction. However, while socially housed rats can acquire operant responding with visual, partial, or full social access [14], as well as for social olfactory cues such as bedding odor [29], these different social contact types likely involve distinct sensory and motivational processes [30], potentially influencing both operant behavior and the specific dimensions of

social motivation under investigation. A systematic comparison of these different types of social contact under operant conditions remains lacking.

Several studies used rats reared together and partial contact interaction via a screen. Under these conditions, rats of different strains, age and sex, learn to lever-press for social interaction (Table 1). Among these factors, age effects have been observed, with adolescent rats (around P30–P50) having higher breakpoints for social interaction than adults [31]. Similarly, sex influences responding: males often have higher breakpoints and response rates than females [32], particularly for opposite-sex partners [18,32]. These sex differences are likely mediated, at least in part, by variations in arginine-vasopressin levels, which have been shown to differentially affect social behavior in male and female rats [33].

Single housing (of more than 24h) during adulthood generally increases social self-administration and play behaviors [34-37]. Additionally, when single housed, rats prefer a familiar over a novel social partner [35]. In contrast, when socially housed, rats tend to prefer novel partners [35,38], indicating that housing conditions and novelty can influence operant social reinforcement. In this regard, Angermeier [28] showed that socially housed rats will also lever press for access to a novel social stimulus, a baby chick.

Regarding factors related to procedural variables, studies showed that partner-access durations ranging from 3.75 s to 2 min and FRs ranging from FR1 to FR5 reliably maintain social self-administration (Table 1). However, Chow et al. [35] systematically investigated the effect of access time and effort, showing that high FRs, but not short time of access, generally decrease responding. Similarly, Schulingkamp et al. [39], in an economic demand assessment, showed that motivation to lever press for social rewards decreases with increasing response requirements. This effect is independent of both social access duration and familiarity of the social partner.

Chow et al. [35], found that rats learned to press a lever for food and social interaction at similar rates, but they earn more food rewards at comparable fixed ratios (FR) and strongly prefer food over partial-contact social interaction in choice procedures. However, Hiura et al. [37], using a trial-by-trial microstructural analysis of behavior, observed that rats show a time-dependent shift in preference, choosing social reward earlier in the session and food reward later.

Finally, in a recent study Lis et al. [19] adapted the social self-administration procedure to a volitional, mutual social interaction procedure, in which the partner rat also engaged in operant responding. They showed that rats will lever press when social access depends on the operant response of both rats.

Mechanistic studies

Several studies identified a role of dopaminergic and noradrenergic systems in operant social self-administration (Table 1).

At a correlational level, using fiber photometry, Chow et al. [18] showed that in single-housed rats dopamine release in the nucleus accumbens (NAc) and dorsomedial striatum (DMS) is involved in social self-administration. They found that in male rats, dopamine peaks to a greater extent at lever extension for a female partner than a male partner; this effect was associated with increased responding for a female partner. Whereas in females, dopamine peaks at lever extension regardless of the partner's sex, indicating sex- and behavior-specific temporal dynamics in dopamine signaling during social self-administration. Additional evidence for a role of NAc in social self-administration comes from findings that in single-housed rats, social seeking is associated with increased expression of the neuronal activity marker Fos [34].

Causal evidence further supports the involvement of the dopaminergic system. Achterberg et al. [36] showed that dopamine reuptake inhibitors increase social self-administration, whereas noradrenaline reuptake inhibitors decrease it. Lis et al. [19], using the mutual social self-administration procedure, showed that antagonism of dopamine D1 and D2 receptors decreases mutual responding. Similarly, inhibition of noradrenergic transmission, using clonidine (an α2-adrenoceptor agonist) or lesions of locus coeruleus noradrenergic projection neurons, decreased mutual social interaction. The latter results are opposite from those of Achterberg et al. [36] who showed that increased noradrenaline transmission decreases standard social self-administration, potentially suggesting partially dissociable mechanisms of standard versus mutual social interaction.

Conclusions

Studies show that social interaction is an operant reinforcer across a wide range of conditions. Operant procedures with social rewards are robust and flexible, sensitive to both subject-related factors

(age, sex, housing conditions, partner familiarity, etc.) and procedural variables (partner access type, duration, and response requirements), and can therefore be adjusted to address specific experimental questions about motivational aspects of social interaction. Moreover, Lis et al. [19] recently showed that this procedure can be adapted to investigate volitional mutual social interaction, offering a valuable tool to dissect more complex dimensions of social behavior.

At the mechanistic level, correlational and pharmacological studies indicate a key role for dopamine and noradrenaline in social reinforcement. However, to date, with one exception [19], no study has causally examined neural circuits underlying operant social reinforcement.

## 3. Mouse studies

Behavioral studies

Mice, like rats, are social animals that show typical social behaviors such as group living and affiliative interactions. However, compared to rats, mice show greater inter-strain variability in sociability and aggression, particularly among males and in interactions with unfamiliar conspecifics [40]. This variability makes strain selection a critical factor in the experimental design and results interpretation in operant social self-administration studies (Table 2).

Martin et al. [41] were the first to show that mice will lever press to gain access to a social partner. To assess the utility of the social self-administration procedure for investigating social motivation deficits, their study compared two strains: C57BL/6J mice, a widely used strain in neuroscience research, and BTBR mice, a strain used in autism research due to its documented social deficits [42]. When given concurrent access to food and social rewards, both C57BL/6J and BTBR responded more for food, indicating relatively low social motivation in both strains. However, BTBR mice showed reduced responding overall for both food and social rewards, with only 53% successfully meeting the operant task acquisition criteria, indicating potential learning deficits this strain. Subsequently, Hu et al. [16] showed that adult C57BL/6J mice will nosepoke for social interaction with novel juvenile mice (novel mice were used as partners for each session). These results, however, may reflect operant responding for a novel stimulus and may not be relevant within the context of rewarding effects of peer interaction.

Ramsey et al. [13] carried out a systematic comparison of social self-administration and food-vs-social choice in female C57BL/6J and female CD1 mice. Notably, CD1 is an outbred strain whose males

have been used in studies on aggressive behavior, including appetitive operant self-administration where the rewarding stimulus for male CD1 mice is the opportunity to attack a smaller C57BL/6J male [24]. Unlike Martin et al. [41], they found little evidence that social interaction with a peer is an operant reinforcer in adolescent and adult female C57BL/6J mice. Specifically, lever pressing was similar when the guillotine door opening resulted in a social peer or an empty partner chamber, and they strongly preferred food over social interaction. Additionally, the female C57BL/6J mice did not show CPP for a social peer. In contrast, adolescent and adult female CD1 mice reliably lever-press for social interaction, preferred it over food, and formed CPP for social interaction [13]. More recently, Lee et al. [43] extended these results to male CD1 mice that were grouped housed after weaning.

In contrast, Isaac et al. [44] recently reported similar social self-administration and choice between social interaction between CD1 and C57BL/6J mice.

The reasons for the discrepant results between the study of Ramsey et al. [13] and the other studies using C57BL/6J mice are unclear. Unlike Ramsey et al. [13], Isaac et al. [44] trained mice directly in a two-choice procedure, without first establishing operant social self-administration using a single-poke setup. Additionally, two recent studies have reported substantial individual variability within the C57BL/6J strain, with only 70–80% of mice acquiring the task when trained exclusively in the social condition, without prior conditioning using food or sucrose rewards [45,46]. These differences in training protocols may have contributed to the inconsistent results across studies (Table 2).

Another important procedural variable is the familiarity of the social partner. Studies reporting high success rates in social self-administration in C57BL/6J mice have predominantly used unfamiliar conspecifics (or novel partners) as social partners [16,17,41]. This suggests that operant responding in mice is controlled by the rewarding effects of the novel stimulus [47] rather than the rewarding social peer interaction (but see [46]).

The age of the social partner also appears to play a role. Hu et al. [16] showed that using novel juvenile conspecifics as social partners results in reliable operant responding in C57BL/6J mice. Juvenile partners may elicit stronger social motivation while minimizing confounds such as aggression or sexual behavior [48]. However, as mentioned above, data from studies using novel juveniles as the rewarding stimulus are likely irrelevant to the study of the rewarding effects of familiar or even novel social peer.

Mechanistic studies

Mechanistic studies in mice have identified multiple brain regions involved in regulating social self-administration with distinct cell-type and sex-specific dynamics. Overall, consistent with findings in rats (see Mechanistic Studies, Section 2), studies support a role of dopamine in operant social reward (Table 2).

Solié et al. [17] showed that dopaminergic neurons in the ventral tegmental area (VTA) are dynamically activated during different phases of social self-administration and potentially encode social reward prediction errors. VTA dopamine neurons activity, in the early stages of training, increases during social interaction. However, as the training progresses, the increase in activity shifts to the moment of lever pressing. Additionally, activity of VTA DA neurons decreased immediately after lever pressing when the social reward is unexpectedly omitted. This dynamic resembles reward prediction error signaling [49]. At the causal level, Solié et al. [17] confirmed the role of VTA dopamine neurons in social self-administration showing that optogenetic inhibition of these neurons reduces operant behavior for social interaction.

Hu et al. [16] provided additional support for dopamine's role in social self-administration. Using social self-administration with a juvenile partner, they showed that nucleus accumbens (NAc) dopamine release increases during the interval between the door opening and the start of social interaction. At the circuit level, they proposed that this dopaminergic signal is driven by activation of $Vgat^+$ GABAergic neurons in posteriodorsal medial amygdala (MeApd), a region implicated in social cue processing, aggression, and mating [50,51]. They showed that activating MeApd $Vgat^+$ neurons increase NAc dopaminergic release. Additionally, optogenetic activation of MeApd $Vgat^+$ increases nose poking for social interaction while optogenetic inhibition decreases it. Finally, they also identified a MeApd→medial preoptic area (MPOA) circuit whose activation similarly increases social self-administration.

Isaac et al. [44] focused their investigation on another aspect of operant social behavior: its interaction and differences with other natural rewards. Using a choice procedure between social interaction and sucrose rewards, they measured neuronal activity in medial prefrontal cortex (mPFC). They identified non-overlapping mPFC neuronal populations that are selectively activated during social and sucrose rewards. Notably, overall calcium activity in mPFC neurons was stronger during social

rewards than sucrose in females, whereas in males, activity was comparable across conditions, suggesting sex-specific encoding of reward value in mPFC. At a causal level, Isaac et al. [44] used broad optogenetic activation and inhibition of mPFC, both manipulations increased latency and omission rates for both social and sucrose rewards in both sexes. While this manipulation suggests a general role for the mPFC in choice, these results do not isolate the specific causal contribution of the mPFC's social- or sucrose-responsive neuronal subpopulations. Cell-type–specific approaches are necessary to identify their precise roles. For example, outside of operant conditioning, Jennings et al. [52] showed that distinct neuronal subpopulations in orbitofrontal cortex selectively respond to food or social stimuli. Using a cell-type specific activation, they showed that activation of social-responsive neurons suppresses feeding.

Conclusions

Taken together, studies showed that social self-administration can be implemented in mice, and it is highly sensitive to strain, sex, training protocols, and the characteristics of the social partner. Despite being the most widely used strain in neuroscience, C57BL/6J mice have relatively weak and variable behavior under operant procedures involving social rewards, suggesting that other strains such as CD1 or FVB may be more suitable for investigating the neurobiological bases of social interaction. At the mechanistic level, studies showed a central role for dopamine signaling, within the VTA and NAc, in mediating social self-administration, with some evidence suggesting interactions between these regions, dopamine signaling and broader brain circuits, involving medial amygdala and prefrontal cortex.

## 4. Hamster studies

Behavioral studies

Borland et al. [53] demonstrate that Syrian hamsters can be trained to make an operant response to gain access to social interaction, by reinforcing door-sliding with physical access to a social partner (Table 3) [53]. As a control, they showed that hamsters are more likely to open a door when it leads to a social partner or sunflower seeds, than to an empty chamber. In hamsters, as in rats [35], responding for food and social interaction is comparable. Both male and female hamsters prefer a same-sex partner over an empty chamber; females show higher responding that is not influenced by the estrous cycle. The estrous cycle exclusively affects the quality of interactions where social bouts are longer, and aggression is lower during estrus vs. diestrus [54].

To assess motivation, the authors developed a progressive ratio-like procedure adapted to the apparatus, named progressive weights schedule. In this procedures, the door's weight is increased overtime, and the hamsters remain motivated to access the social partner despite increased effort to open the door [53].

Mechanistic studies

At the neurobiological level, Borland et al. [55] showed that oxytocin signaling in VTA is critical to social motivation (Table 3). Oxytocin injections into caudal VTA reduces responding for social interaction, whereas blocking oxytocin receptors increases lever pressing for social interaction. These manipulations do not alter non-social responding, suggesting a selective role of caudal VTA oxytocin in social self-administration.

Conclusions

Syrian hamsters can be trained in operant social self-administration tasks. Using this model, studies have identified oxytocin signaling in VTA as a key region for social self-administration in this species.

## 5. Voles studies

Behavioral studies

Mice, rats, and hamsters are social species that readily learn operant responses for access to a social partner. However, they do not form stable bonds, whereas voles form selective social relationships. Prairie voles and meadow voles are two rodent species widely used in neuroscience to investigate behavioral and neural bases of social behavior, bond formation, and mating [56]. Prairie voles are socially monogamous and establish long-term selective male-female bonds [57]; while meadow voles are promiscuous, but live in communal groups during winter months [58]. Thus, vole species are used as a model for comparing peer bonds *between* species and different relationship types *within* the same species and explore how bonding influences motivation for social interaction [59].

Beery et al [59] first showed that both male and female prairie voles, and female meadow voles learn to lever press for social interaction (Table 4). They showed that both social self-administration and quality of social interactions are influenced by partner familiarity and sex. Male and female prairie and meadow voles show more affiliative behaviors, such as huddling, with familiar partners, and more aggression toward novel partners [59-61]. Similarly, Pierce et al. [62] observed that after a period of separation from

a familiar partner, prairie voles show reduced huddling, suggesting decreased pair bond. At the operant level, in female prairie voles, under progressive ratio schedules, motivation is higher for familiar partners [59-61], and in choice procedures, female prairie voles prefer familiar over novel partners or novel objects [60,63]. In males prairie voles, lever pressing for a novel partner is positively correlated with aggression [59]. However, aggression, but not lever pressing, diminishes with repeated exposure and thus does not explain overall motivation for social interaction with the partner [59]. Together, these findings indicate that in voles, the motivation to lever press is primarily linked to affiliative behaviors and mating, rather than aggression.

Mechanistic studies

Neurobiological studies in prairie voles indicate roles for dopamine and oxytocin systems in social self-administration, partner preference, and quality of social interaction (Table 4).

At the correlational level, Pierce et al. [62] showed that dopamine release in the NAc during social self-administration training increases during lever pressing and door opening, but not during the social interaction itself. This supports the idea that dopamine encodes for the anticipation of social interaction rather than the interaction per se [17,18,62]. Pierce et al. [62] also showed that dopamine release, at door opening and lever press, is enhanced when the partner is familiar vs. novel, suggesting that dopamine encodes familiarity. Further supporting this notion, they showed that following social isolation, when the pair bonding is disrupted, dopamine release is reduced for a familiar partner, while responses to a novel partner remain unchanged [62].

Other correlational studies reported a contribution of the oxytocinergic system in affiliative behaviors with differences between sexes. Prairie voles lacking the oxytocin receptor ($Oxtr1^{-/-}$) do not develop a preference for familiar same-sex partners over novel partner or for opposite-sex partners over non-social rewards; these transgenic vole show increased responding for non-social rewards [63]. Knockout of Oxtr1 reduces oxytocin release (without affecting its clearance) and impairs dopamine clearance, suggesting an interaction between oxytocin and dopamine systems in regulating operant social reinforcement [63]. Additionally, oxytocin receptor density in NAc correlates with lever pressing for same-sex partners in females [59], but with aggressive behaviors during social interaction in males [61]. In contrast, in females, aggression is associated with oxytocin receptor density in BNST [59].

Causal studies using pharmacological manipulations, showed differential contributions of dopamine receptor subtypes: D1 receptor antagonists reduce operant responding for social interaction regardless of partner familiarity, whereas D2 receptor antagonists increase affiliative huddling but do not alter partner preference [62].

Conclusions

Studies in male and female prairie voles and female meadow voles show that operant social procedures can be adapted to investigate social reward in this species. Studies show that both sex and partner familiarity influence social self-administration in prairie and meadow voles, likely reflecting their unique affiliative bonding system. Importantly, unlike most studies in other rodents, studies in voles have investigated the quality of social interaction and how this is connected to operant responding and neurobiological basis of social interaction.

At the neurobiological level, studies in prairie voles, consistent with findings in mice and rats, suggest a central role of the dopaminergic system in operant social interaction and sustaining operant responding. In voles, however, dopamine is not only involved in motivation and reward, but also in partner familiarity and bond formation [62]. Additionally, as showed for hamsters, oxytocin plays a critical role, influencing partner preference, affiliative behaviors, and aggression. Black et al. [63] showed evidence for an interaction between the oxytocin and dopamine systems, suggesting that oxytocin can regulate upstream dopamine release.

## 6. Summary of mechanistic studies on across species

Mechanistic studies using operant social self-administration procedures show a key role of dopamine transmission across species [17, Hu, 2021 #3209,18,19,36,62] (Figure 1). Correlational studies from rats, mice, and voles show that NAc dopamine release and activity of VTA dopamine neurons encode anticipation of social reward: dopamine release peaks during lever-pressing and immediately before social interaction onset (e.g., door opening) [16-18,62]. Additionally, high Fos expression in NAc was observed during social seeking [34]. Furthermore, in voles, NAc dopamine release is higher prior to interactions with a familiar vs a novel partner, suggesting a role for dopamine in social selectivity [62]. Finally, causal manipulations showed that optogenetic inhibition of VTA dopamine neurons reduces social self-administration [17].

Oxytocin has also been implicated in social self-administration [59,61,63]. In voles, NAc Oxtr density positively correlates with social self-administration in females [59]. In hamsters, VTA injections of oxytocin or Oxtr antagonist further implicates oxytocin in social self-administration [55]. In voles, $Oxtr^{-/-}$ knockout voles show impaired development of preference for a familiar partner. Finally, *in vitro* experiments indicate a potential oxytocin–dopamine interaction, showing that Oxtr knockout reduces NAc dopamine clearance [63].

Other studies in mice suggest additional brain regions contributing to social reinforcement. Both activation of MeA GABAergic neurons and selective activation of MeA GABAergic neurons projecting to MPOA increase social self-administration [16]. Moreover, activation of MeA GABAergic neurons (which projects to NAc) increases NAc dopamine release. Finally, mPFC is active during social self-administration and, in females, specifically encodes the relative value of social versus non-social rewards [44].

Finally, noradrenaline has been implicated in reciprocal social interaction [19]. In rats, lesions of locus coeruleus noradrenergic projections or decreased noradrenaline transmission with the alpha-2 adrenoceptor agonist reduce mutual social self-administration [19].

## 7. Application of the operant social model to study neuropsychiatric disorders, stress and pain

Social factors play a central role in the onset, recovery, and maintenance of both physical and mental health, and are widely recognized as key determinants of overall health outcomes [64-66]. Animal models are critical to disentangle whether alterations in the social domain are intrinsic to specific conditions, act as vulnerability or protective factors, or instead emerge because of the mental or physical illness [67,68]. Within this framework, the operant social self-administration model provides a unique tool to examine (1) how disease states disrupt social reward processing and vice versa, and (2) how access to social interaction can promote resilience and recovery. Below, we summarize how the model has been applied across different domains of mental and physical health.

### Neurodevelopment disorders

Martin et al. [69] used the social self-administration model to study changes in social reward in a genetic model of Williams syndrome and autism, associated with mutations on the Gtf2i gene. Deletion of this gene causes Williams syndrome characterized by hyper-sociability, while duplication of the gene is

frequently associated with autism [70,71]. They showed that Gtf2i+/− mice have higher breakpoints for social rewards and stronger preference for social over food reward, replicating the hyper-sociability phenotype of the William syndrome. In contrast, duplication the Gtf2i gene had no effect on social reward breakpoint and choice [69].

More recent work extended the social self-administration model to other neurodevelopmental disorders. Maloney et al. [46] showed that Shank3B knockout mice, a model of autism spectrum disorder (ASD) [72], showed lower social self-administration than wildtype littermates. However, they observed sex differences, with male heterozygous and homozygous Shank3b mutants showing lower social self-administration, while females were unaffected [46]. Chaturvedi et al. [73] further investigated sex differences using the four-core genotypes (FCG) mouse model, which allows for dissociation of the effects of gonadal hormones from those of sex chromosomes [74]. In this model, mice can carry sex chromosomes that do not correspond to their gonadal type. The authors combined the FCG with a mutation in the MYT1L gene. In humans, MYT1L haploinsufficiency leads to behavioral abnormalities such as hyperactivity, and social impairments, with more severe phenotypes in males [75]. Chaturvedi et al. [73] found that the presence of ovaries increased time spent in the interaction zone and number of social rewards, highlighting a central role for ovarian hormones in the interaction component of social self-administration. In contrast, sex chromosome did not influence social behavior. MYT1L haploinsufficiency selectively increased social self-administration in females but not in males.

The Shank3B knockout and MYT1L haploinsufficiency mouse models only partially recapitulate the human condition [75,76]. In these animal models, the manipulation of a single gene was sufficient to alter aspects of social behavior. However, in humans, autism is a polygenic condition, and social deficits are unlikely to be attributable to mutations in Shank3 or MYT1L alone. Rather, variations in multiple genes, or in specific gene networks, or additional contributing factors, such as environment, hormonal influences, or other neurodevelopmental processes might interact and contribute to the social impairments observed in autism and related neurodevelopmental disorders and social impairments [77,78].

**Drug addiction**

Venniro et al. [79] introduced the operant social self-administration and choice procedure in animal models of addiction, adapting it to mimic the community reinforcement approach (CRA), which uses

operant principles to reduce drug use and promote long-term abstinence through positive social and environmental reinforcers [80]. In the original rat version, rats are trained to lever press for social interaction and then to lever press for methamphetamine infusions. Next, the rats are given a choice between immediate access to methamphetamine versus social interaction. Under these conditions, all rats strongly prefer social interaction and achieve 'voluntary abstinence.' This effect is independent of methamphetamine dose, abstinence duration, the type of addiction model (escalation model, intermittent access model, DSM-IV model). However, delay or punishment of the social reward shift preference toward methamphetamine [79]. Social-choice-induced abstinence also prevents incubation of methamphetamine craving [79], the time-dependent increase in drug seeking during abstinence [81].

Mechanistic studies further showed that this protective effect on methamphetamine craving is mediated by PKCδ neurons in the CeL and inhibition of CeM output [79,82]. More recently, Papastrat et al. [83] showed a critical role in the model for olfactory processing: bulbectomy prevents social self-administration and shifts preference toward the drug, while contingent presentation of social odors decreases incubation of craving.

Follow-up studies applied the social self-administration model across drugs and explored individual differences in drug-vs-social preference. With cocaine, social rewards are typically preferred over the drug [83-85], although preference is dose-dependent [85] and can be influenced by FR requirements or delays of social reward [84]. With alcohol, rats generally prefer drinking over social reward [86,87], and this preference can be reduced with high FR requirements, alcohol pre-exposure, or substitution with water. For opioids, Venniro et al. [79] showed rats prefer social over heroin rewards, independent of the contact type (full contact, contact via a screen) [88]; additionally social interaction decreases, but does not prevent, incubation of craving [88]. More recently, Pilz et al. [89] found that opioid dependence (induced by different regimens of non-contingent exposure to morphine) decreases lever pressing for social interaction, and that morphine pre-treatment fails to restore pre-opioid dependence social self-administration. In choice procedures between low doses of opioids (fentanyl or remifentanil) and social reward, rats are largely indifferent, but preference for opioids increases with higher doses [35,90]. More recently, we showed that allowing rats to self-select their heroin dose during choice reveals stable individual differences: while many rats prefer social rewards, a subset consistently chooses heroin

regardless of partner access condition (full contract, screen contract), FR requirements, or abstinence duration [91].

Overall, these findings show that drug-vs-social choice in the operant model is sensitive to variables such as drug type and dose, relative reward value, cost of access, and adverse consequences of social self-administration (punishment) [84,85,90-93].

**Stress**

The operant social self-administration model has also been applied to stress research. Both preclinical and human studies indicate that early-life adversity and stress reduce social connectedness [94-96]. Using the social self-administration model, Williams et al. [97] showed that early-life stress 'paradoxically' increases social self-administration in male, but not female, Long-Evans rats. Navarrete et al. [45] showed that social-defeat stress produces individual and sex differences in social self-administration, with stressed male, but not female C57BL/6J mice, showing the strongest decrease in social self-administration.

Pain and inflammation

Pain and inflammation impair social engagement, reflecting a reduced ability or motivation to interact under conditions of physical and psychological discomfort. In rodents, inflammatory challenges (lipopolysaccharide injections) [98] and nociceptive stimuli (lactic acid) [99] decrease social self-administration, suggesting that immune and nociceptive signaling directly modulate social motivation circuits. Notably, Baldwin et al. [99] found that morphine reverses pain-induced suppression of food self-administration but fails to restore social self-administration. This finding highlights a critical distinction in how analgesic treatment modulates motivated behaviors for food versus social interaction.

**Conclusion**

Studies using the operant social self-administration procedure in animal models of neuropsychiatric disorders, stress, inflammation, and pain show that the procedure is highly flexible and suitable to investigate social motivation across different conditions. However, the model has been used predominantly in addiction research, and most of the behavioral and mechanistic information we currently have stems from this field. This leaves gaps in our understanding of how operant social reward is altered in other preclinical models of neuropsychiatric disorders, such as depression, anxiety, and post-traumatic

stress disorder. Notably, Venniro et al. [79] showed that providing access to social reward promotes long-term abstinence, paralleling clinical findings in humans [5], and suggesting that the procedure has translational potential. Extending this approach beyond addiction may therefore provide valuable insights into the role of social reward processing in resilience and recovery across a broader range of mental or physical conditions.

## 8. Future directions and clinical applications

Social behaviors are complex and multidimensional, representing challenges for identifying the neural circuits that regulate them [100]. Operant social self-administration in rodents allows the study of the motivational and appetitive components of social interaction, with strong translational relevance as it models the volitional nature of social behavior seen in humans [101,102]. In this review, we summarized behavioral, pharmacological, and circuit mechanisms of the operant social self-administration across rodent species.

Behavioral evidence show that social interaction is a operant reinforcer across rodent species, and it is modulated by subject-specific factors (e.g., age, sex, housing, strain, familiarity) and procedural variables (e.g., partner type, access duration, response effort, delay of access to social interaction). Of note, conditions known to influence human social behavior, such as social isolation (single housing) [103], also alter lever pressing for social interaction in rodents [35,36,43], highlighting the potential validity, flexibility, and adaptability of this procedure. The model has also been extended to rodent models of neuropsychiatric disorders, demonstrating its capacity to mirror human conditions. For example, the model has been shown to replicate in rodents the hyper-sociability phenotype associated with Williams syndrome [69], capture vulnerability to drug addiction as reflected by reduced motivation for social interaction [89,91,104], demonstrate the protective effects of social interaction in addiction [79], and reveal reduction in social motivation following stress [45,97] and pain states [99].

However, further extension of this model to neurodegenerative disorders is warranted, given that both social impairments and age-related changes in social behavior characterize these conditions [105-107]. Another future direction concerns the role of inflammation and neuroinflammation in shaping social behavior. Growing evidence links immune signaling to neuropsychiatric disorders and motivational processes, often reducing motivation and effort for natural rewards, including social interaction [108,109].

However, some studies indicate that systemic inflammation, such as during fever, can transiently improve behavioral symptoms in autism [110,111]. Yet, as highlighted in this review, only two studies have directly examined the impact of inflammation and pain on social interaction [98,99], limiting our understanding of how inflammation influences the motivation for social interaction.

At the mechanistic level, across rats, mice, hamsters, and voles, dopaminergic transmission in the mesolimbic system emerges as a central regulator of operant social self-administration. These findings support the idea that neural responses to social and non-social rewards share common pathways [112]. For example, Isaac et al. reported that both social and sucrose rewards are represented in the mPFC [44]. However, other work shows that certain brain regions respond selectively to social rewards: MeApd Vgat+ neurons are active during social interaction, but not by non-social rewards such as chocolate or sucrose [16]. These findings suggest a partial dissociation between social and food reward processing. While the mesolimbic system may serve as a common downstream pathway, future studies should investigate projection-specific circuits within this system that are differentially engaged by social versus food or drug rewards, to better define the unique neural representations of social self-administration. Furthermore, other studies using pharmacological approaches have shown that, in rodents, social self-administration is modulated by oxytocin, a neuropeptide that regulates affiliative behavior and social bonding in humans [113,114].

Nevertheless, most evidence remains correlational, with relatively few studies using causal circuit-level approaches. Strain- and species-specific variability has been consistently reported, offering an opportunity to investigate individual differences in social motivation that may parallel vulnerability and resilience factors in psychiatric and neurological disorders. Importantly, the translational value of the model has already been demonstrated in models of autism, stress, pain, and addiction.

In conclusion, by integrating modern causal neuroscience tools, expanding across disease models, and incorporating immune and aging dimensions, operant social self-administration can provide a richer understanding of the interplay between social reward, brain function, and mental health. Ultimately, these insights may guide the development of interventions that leverage social reward as a therapeutic strategy for a wide range of disorders.

**Figure legends**

**Figure 1. Brain regions and circuits underlying social self-administration across different rodent species.** (**A**) Rodent species: rats, mice, hamsters, and voles (color-coded). (**B**) An artistic representation of a rodent brain with brain regions implicated in social self-administration. Circles indicate the brain regions and arrows represent projections between regions. (**C**) Colored boxes summarize the neurochemical mechanisms of social self-administration, with each box color-coded by signaling molecules: **red** = dopamine; **yellow** = oxytocin; **blue** = GABA. (**D**) Neurochemical mechanisms of reciprocal social lever pressing. (**E**) Neurobiological mechanisms of social seeking. (**F**) Neurobiological mechanisms of social versus non-social choice. Abbreviations: LC, locus coeruleus; MeA, medial amygdala; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; NAc, nucleus accumbens; SA, self-administration; VTA, ventral tegmental area.

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**Figure 1**

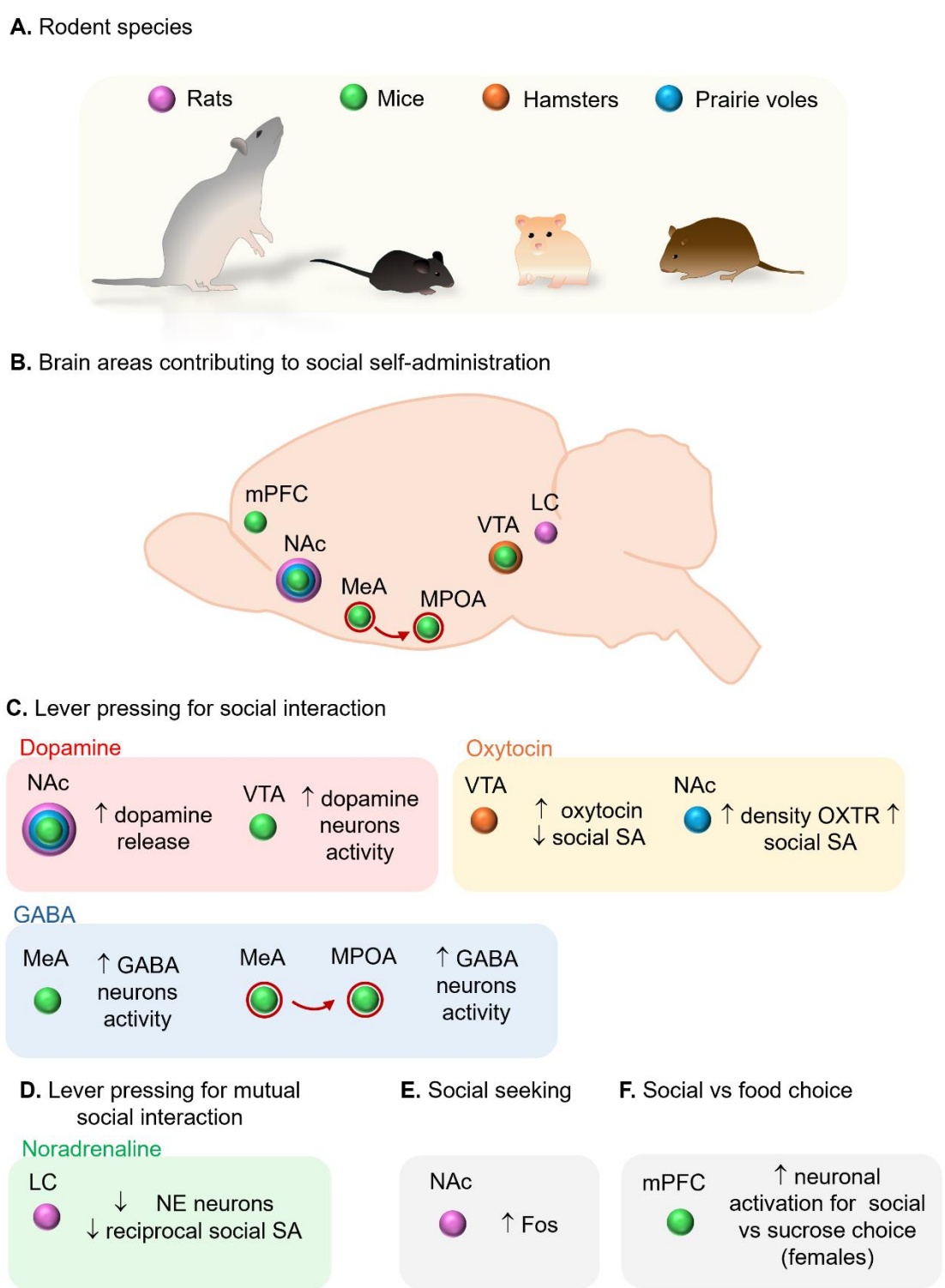
A. Rodent species
Rats
Mice
Hamsters
Prairie voles
B. Brain areas contributing to social self-administration
mPFC
NAc
MeA
MPOA
VTA
LC
C. Lever pressing for social interaction
Dopamine
NAc
↑ dopamine release
VTA
↑ dopamine neurons activity
Oxytocin
VTA
↑ oxytocin
↓ social SA
NAc
↑ density OXTR ↑ social SA
GABA
MeA
↑ GABA neurons activity
MeA
MPOA
↑ GABA neurons activity
D. Lever pressing for mutual social interaction
Noradrenaline
LC
↓ NE neurons
↓ reciprocal social SA
E. Social seeking
NAc
↑ Fos
F. Social vs food choice
mPFC
↑ neuronal activation for social vs sucrose choice (females)

**Table 1:** *Behavior and mechanistic studies of operant social self-administration in **rats**.* Abbreviations: AVP, arginine vasopressin; FR, fixed ratio; HET, heterozygous; HOM, homozygous; PR, progressive ratio; WT, wildtype.

| Reference | Experimental rat sex & Schedule | Social contact type & access time | Social partner sex | Strain | Main finding |
|---|---|---|---|---|---|
| (Angermeier 1960) | Male<br>FR1 | Full contact, partial contact (via perforated screen), visual contact only<br>10s | Male & female | Wistar | • Rats reared together learn to lever press for social reinforcers, regardless of partner sex and contact type (visual, partial and full contact)<br>• Post-weaning social isolation decreases acquisition of social self-administration, regardless of partner sex, under visual and partial contact, but not full contact conditions |
| (Angermeier 1962) | Male<br>FR1 | Visual contact<br>10 s | Male & female | Albino | • Responding increases when a rat partner is substituted with a baby chick (novel social stimulus)<br>• Responding decreases when a bright light is paired with social interaction |
| (Evans et al. 1994) | Female<br>FR3 | Full contact<br>45 s | Male (castrated) | Long-Evans | • Operant behavior is reinforced by social contact |
| (Achterberg et al. 2016) | Male<br>FR1<br>PR 1,5 | Full contact<br>2 min | Male | Wistar | • Single housing for 24 h, prior to training, increases social self-administration compared to single housing for 2 h of prior to training<br>• Dopamine reuptake inhibitors increase responding<br>• Noradrenaline reuptake inhibitors decrease responding |
| (Hiura et al. 2018) | Male<br>FR1<br>PR | Full contact<br>10 s | Male<br>Familiar | Long-Evans | • Responding for social rewards is higher when both food and social interactions were restricted, compared to when only one is restricted<br>• Responding followed the pattern: combined restriction > food restriction > social restriction, consistent across both social and food rewards<br>• Rats respond more for food rewards than for social rewards, regardless of restriction condition<br>• In choice task, rats show time-dependent preference: more social reward early in the session and more food reward later in the session |
| (Schatz et al. 2019) | Male & Female<br>FR1 | Partial contact<br>1 min | Male & female<br>Familiar | Brattleboro rats (WT, HET and HOM) | • Females WT and HET rats respond less for social rewards compare to male WT and HET rats<br>• HOM rats animals lever press for social interaction with no sex differences<br>• AVP levels determine sex differences in operant social interaction |
| (Hackenberg et al. 2021) | Female<br>FR5 | Full contact<br>45 s | Female<br>Familiar & novel | Long Evans, Sprague-Dawley | • Rats prefer a familiar partner over an empty chamber<br>• Rats prefer a novel over a familiar partner, but are indifferent when presented with two novel partners |
| (Chow et al. 2022) | Male & Female<br>FR1-to-32, PR | Partial contact<br>3.75, 7.5, 15, 30, 60, 120, and 240 s | Male & Female<br>Familiar & novel | Sprague-Dawley, Long-Evans | • Peer access had minimal effect on response rate<br>• Rats showed no preference between short and long access durations.<br>• Higher responding for social interaction in single-housed compared to paired-housed<br>• Single-housed rats preferred familiar over unfamiliar partners; paired-housed rats showed no preference. |

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| | | | | | • Rats prefer palatable food over social interaction.<br>• Preference for social interaction over remifentanil is dose-dependent |
| (Schulingkamp et al. 2023) | Female<br>Demand curve for social interaction | Full contact<br>10 s, 30 s, & 60 s | Female<br>Familiar & novel | Sprague-Dawley | • Responding for social reward decreases as FR increases, regardless of familiarity of social partner<br>• Demand curve and response rate are independent of social access time or familiarity of social partner |
| (Murray et al. 2024) | Male & female; P30 to P70<br>FR1, PR | Partial contact<br>5 s | Male & female<br>novel | Long Evans | • Responding to social reward was highest at P30 and P50 with no sex differences.<br>• P30 rats achieved the higher breakpoints than the other age groups.<br>• P30 rats and P50 rats responded the highest during extinction test<br>. |
| (Raymond et al. 2024) | Male & female<br>FR1, PR | Partial contact<br>60 s | Male & female (Opposite & same sex) | Wistar | • Males achieve higher breakpoints for social reward than females<br>• Females interact more than males during social access<br>• Estrous cycle has no effect on social self-administration |
| (Chow et al. 2024) | Male & female<br>FR1, economic demand, food-vs-social interaction choice | Partial contact<br>15 s | Male & female, (Opposite & same sex) | Sprague-Dawley | • In males, responding is higher for the opposite sex than in females, and demand elasticity is lower when pressing for the opposite sex<br>• Estrous cycle has no effect on social self-administration<br>• Dopamine release increases in NAc and DMS during social self-administration<br>• In males, dopamine release in NAc and DMS increases after lever extension; in females it increases at lever press<br>• Dopamine release in NAc increases at lever extension in males for a female partner, whereas in females, dopamine release increases at lever press for a female partner |
| (Lis et al. 2025) | Male & Female,<br>FR1-to-16, PR | Partial contact<br>60 s | Male & female; the partner rat also lever-press for social interaction | Sprague-Dawley | • Rats lever press for mutual social interaction where the interaction occurs after both rats lever press in tandem<br>• Lesions of locus coeruleus noradrenergic projection neurons and clonidine (an alpha2-adrenoceptor agonist) decreases mutual social interaction<br>• Selective antagonists of dopamine D1 and D2 receptor have a similar effect |
| (Hinnenkamp et al. 2025) | Female<br>FR1 | Social odor<br>0.3 s | Female bedding odors<br>Familiar & novel | Not Provided | • Rats prefer social and nonsocial scents over control scents<br>• Rats are indifferent when presented with social and nonsocial scents |
| (Olaniran et al. 2025) | Male & female either pair-or single-housed<br>FR1 | Partial contact<br>30 s | Male & female novel partner either pair- or single-housed | Sprague-Dawley | • Higher responding for social interaction in single-housed vs. pair-housed<br>• Incubation of social seeking from single housing day 1 to 12 was not reliably observed<br>• Fos expression in the NAc shell after social seeking is higher in single-housed than in pair-housed rats |

**Table 2:** *Behavior and mechanistic studies of operant social self-administration in **mice***. Abbreviations: DA, dopamine; FR, fixed ratio; MeApd, post dorsal subdivision of medial amygdala; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; NAc, nucleus accumbens; PR, progressive ratio; VTA, ventral tegmental area.

| Reference | Experimental mice sex & Schedule | Social contact type & access time | Social partner sex | Strain | Main finding |
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| (Martin et al. 2014) | Male<br>PR, food-vs-social interaction choice | Partial contact<br>15 s | Male<br>Novel | BTBR & C57Bl/6J | • BTBR have lower breakpoints than C57BL/6J<br>• Only 53% (9/17) of BTBR mice acquired the operant response for social interaction<br>• In a concurrent access to food and social, both strains have higher responding for food than social reward<br>• In a concurrent access to food and social, responding for social, but not food, is similar in BTBR and C57Bl/6J<br>• Higher percentage of social rewards in BTBR compared to C57Bl/6J |
| (Hu et al. 2021) | Male & Female<br>FR1 | Partial contact<br>7 s | Male & female<br>Novel juvenile | C57Bl/6J | • Adult mice nose-poke for social interaction with a juvenile mouse.<br>• Inhibition of Vgat+ neurons in MeApd decreases nose-poke for social interaction<br>• Activation MeApd Vgat+ neurons increases nose-poke for social interaction<br>• NAc DA increases during social interaction in both sexes and independent of social partner novelty<br>• Activation of MeApd GABAergic neurons (Vgat+) projecting to MPOA increases operant social interaction, while inhibition of these neurons has an opposite effect |
| (Ramsey et al. 2022) | Female<br>FR1-6, PR | Partial contact<br>60 s | Female<br>Familiar | C57Bl/6J and CD1 | • Reliable social self-administration in female CD1 mice but not female C57Bl/6J mice<br>• CD1 female mice prefer social reward over food<br>• C57Bl/6J mice prefer food over social reward |
| (Solié et al. 2022) | Male & Female<br>FR1 | Partial contact<br>7 s | Male & female<br>Novel | C57Bl/6J | • Mice learn to lever press for an unfamiliar mouse<br>• In early phases of operant training, activity of VTA DA neurons increases during social interaction<br>• In late phases of operant training, activity of VTA DA neurons increases at the onset of lever pressing<br>• Activity of VTA DA neurons decreases during interaction window and when the social partner was not presented after lever pressing<br>• Optogenetic inhibition of the VTA DA neurons decreases social self-administration<br>• VTA DA neurons encode social reward prediction error |
| (Lee et al. 2025) | Male & Female<br>FR1-6, PR | Partial contact<br>60 s | Male & female<br>Familiar | CD1 | • Male CD1 mice reared together lever press for social interaction with a male partner<br>• Male and female mice learn to lever press for a social partner and seek social cues after isolation, with no sex differences<br>• Social contact and attacks are higher in single-housed mice and group-house mice<br>• Single-housed mice and group-house mice learn to lever press for a social partner at similar rate |
| (Isaac et al. 2024) | Male & Female<br>FR1, food-vs-social | Partial contact<br>20 s | Male & female (Familiar, Same sex) | C57Bl/6J and CD1 (CD1 | • Female C57 mice prefer social interaction over sucrose, male C57 mice are indifferent<br>• CD1 and C57 females do not differ in preference for social interaction over sucrose |

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| | interaction choice | | | only females) | • Choice between sucrose and social interaction is not affected by estrous cycle in females<br>• Non-overlapping populations of neurons in mPFC encode social interaction and sucrose<br>• mPFC neurons mostly respond during choice and reward<br>• Calcium activity in mPFC neurons increases during both social and sucrose rewards with sex differences: in females, mPFC neurons have higher activation during social choices than sucrose choices; in males mPFC neurons have similar activation during social and sucrose choices<br>• mPFC neurons are predominantly activated during social interaction and inhibited during sucrose rewards<br>• Optogenetic activation and inhibition of mPFC neurons increase latency and omissions for both reward in both sexes<br>• Social isolation increases preference for social interaction in males, whereas it decreases preference for social interaction in females<br>• Social isolation decreases social reward mPFC neuron calcium activity amplitude in males, whereas it increases in females |

**Table 3:** *Behavior and mechanistic studies of operant social self-administration in* ***hamsters****.* Abbreviations: FWR, fixed weight ratio; PWR, progressive weight ratio

| Reference | Experimental hamster sex & Schedule | Social contact type & access time | Social partner sex | Strain | Main finding |
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| (Borland et al. 2017) | Males<br>FWR 85 g,113 g, &170 g<br>PWR | Full Contact<br>20 s | Males<br>Novel | Syrian | • Hamsters prefer a chamber associated with a social partner over an empty chamber<br>• Responding for social interaction is similar to responding for sunflower seeds<br>• Increasing effort required to open partner's door decreases number of entries<br>• Reinstatement and extinction responding are comparable for social and sunflower rewards |
| (Borland et al. 2018) | Males<br>FWR113 g<br>PWR | Full Contact<br>5, 20, & 60 s | Males<br>Novel | Syrian | • Responding for social interaction decreases with increasing social interaction times: 5 s > 20 s > 60 s<br>• Responding decreases for 5-s social interaction as effort to open the door increases, whereas responding decrease for 60-s social interaction at the highest effort required<br>• Oxytocin injections into caudal VTA decreases responding for social interaction but has no effect on responding for the nonsocial chamber<br>• Oxytocin receptor antagonist in caudal VTA increases responding for social interaction and has no effect on responding for the nonsocial chamber |
| (Borland et al. 2019) | Male & Female | Full Contact<br>20 s | Male & female<br>(Novel, Same sex) | Syrian | • Both males and females prefer a chamber associated with a same-sex social partner to an empty chamber<br>• Responding is higher in females compared to males<br>• Estrous cycle has no effect on responding for social interaction<br>• Estrous cycle influences social interaction quality: duration of social interaction is higher during estrous than diestrus, while aggression is lower during estrus than diestrus |

**Table 4:** *Behavior and mechanistic studies of operant social self-administration in* ***voles****.* Abbreviations: BNST, bed of the nucleus of the stria terminalis; D1, dopamine receptor type 1; D2, dopamine receptor type 2; FR, fixed ratio; LS, lateral septum; NAc, nucleus accumbens; $Oxtr^{1-/-}$, lacking functional oxytocin receptor gene;PR, progressive ratio; WT, Wildtype; $Oxtr^{1-/-}$, lacking functional oxytocin receptor gene

| Reference | Experimental vole sex & Schedule | Social contact type & access time | Social partner sex | Strain | Main finding |
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| (Beery et al. 2021) | Male & Female PR1 | Full contact 60 s | Male & female (Familiar & novel, Opposite & same sex) | Prairie and Meadow | • Female prairie voles press more for social interaction than female meadow voles<br>• Female prairie voles have higher breakpoints for familiar over novel partner; while male prairie voles have higher breakpoints for females over males, regardless of familiarity<br>• Familiarity influences social interaction quality: males and females prairie voles have more aggressive bouts for a novel partner, but more time huddling with a familiar partner<br>• Female meadow voles display less aggressive behaviors compared to female prairie voles<br>• Female meadow voles have higher breakpoints for familiar same-sex conspecifics than for a novel partner<br>• In male, but not in female prairie voles, lever pressing for a novel partner is correlated with aggression<br>• In females prairie voles, oxytocin receptor density in NAc correlates with lever pressing for same-sex partners, while oxytocin receptor density in the BNST correlates with aggression toward novel partners |
| (Brusman et al. 2022) | Male & Female FR1 | Full contact 60 s | Male & female (familiar & novel, opposite sex) | Prairie | • Both male and female prairie voles learn to lever press for social interaction regardless of familiarity<br>• In a social choice task, females prefer familiar over novel partners, whereas males show no such preference<br>• Familiarity influences social interaction quality: males and females spend more time huddling with a familiar partner than a novel partner |
| (Vahaba et al. 2022) | Male & Female FR1-FR4 | Full contact 60 s | Male & female (Familiar & novel, opposite sex) | Prairie | • In a social choice task, females prefer familiar over novel partners, whereas males show no such preference<br>• Familiarity influences social interaction quality: males and females have more aggressive bouts for a novel partner, but more time huddling with a familiar partner<br>• In males, oxytocin receptor density in the NAc correlates with aggressive behavior |
| (Pierce et al. 2024) | Male & Female FR1 | Partial contact 30 s | Male & female (familiar & novel opposite sex) | Prairie | • Voles learn to lever press for both novel partner and familiar partner; lever pressing is equal for both (not in choice conditions)<br>• D1 and D2 receptor antagonists do not affect preference for a familiar partner over novel partner<br>• D2 antagonists increase huddling<br>• D1 antagonists decrease responding for social interaction regardless of partner familiarity<br>• Dopamine release in the NAc increases over sessions during lever press and door opening, but not during social interaction<br>• Dopamine release is in the NAc higher for familiar over novel partner |

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| | | | | | • Social isolation decreases dopamine release during both lever pressing and social interaction for a familiar partner, but not for a novel partner |
| (Black et al. 2025) | Male & Female FR1-4 | Full contact 60 s | Male & female (familiar & novel Same & opposite sex) | Prairie (WT, $Oxtr^{1-/-}$) | • WT females prefer same-sex familiar partner over novel same-sex partner, $Oxtr^{1-/-}$ do not show a preference<br>• WT and $Oxtr^{1-/-}$ females prefer opposite-sex familiar partner over a novel partner<br>• WT females prefer opposite-sex familiar partner over non-social reward, $Oxtr^{1-/-}$ do not show a preference and have higher responding than WT for non-social rewards<br>• Lacking Oxtr1 reduces oxytocin release, but not clearance<br>• Lacking Oxtr1 reduces dopamine clearance |

**Table 5.** *Behavioral and mechanistic studies using the operant model in neuropsychiatric disorders, stress and pain.* Abbreviations: CeL, lateral central amygdala; CeM, medial central amygdala; FR, fixed ratio; KO, knockout; LPS, lipopolysaccharide; meth, methamphetamine; SA, self-administration; SIA, self-initiated aggression; SOM, somatostatin; WT, wild type

| Reference | Area of investigation | Experimental sex & Schedule | Social contact type & access time | Social partner sex | Strain | Main finding |
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| Neurodevelopment disorders | | | | | | |
| (Martin et al. 2018) | Williams syndrome & autism | Male<br>FR 1-3<br>PR | Partial contact<br>15s | Male (novel) | Gtf2i+/−, *Gtf2i*+/+, Gtf2i+/dup, *Gtf2i*+/+ dup, C57BL/6J | • All genotypes acquire lever pressing for social rewards, but all prefer food over social rewards<br>• Loss-of-function (Gtf2i+/-) increases breakpoint for social rewards and preference for social over food rewards<br>• Duplication (Gtf2i+/dup) increases motivation, but does not change preference for social over food reward |
| (Maloney et al. 2023) | Autism | Male & Female<br>FR1-3<br>PR | Partial contact<br>12 s | Male & Female (novel, same sex) | Shank3B WT, Shank3B Het, Shank3B KO, C57BL/6J | • 85% (6/10 females, 9/10 males) of mice learned to nose poke for social rewards<br>• Non-learners mice spend less time attempting interactions, whereas control mice that only open the door show more general activity<br>• Increasing FR requirement increases responding for social interaction<br>• Males show higher responding and breakpoints for social interaction than females and spend more time in the interaction zone<br>• Shank3B KO male mice show lower responding for social interaction than WT; Het mice respond at intermediate levels (KO < Het < WT); females were unaffected<br>• WT vs KO and Het mice spend more time attempting interactions and have higher breakpoints<br>• Oxtr antagonist decreases responding and lowers breakpoints for social rewards<br>• Oxtr antagonist does not affect social orienting and time in interaction zone, but decreases locomotion |
| (Chaturvedi et al. 2025) | MYT1L Syndrome | Male & Female<br>FR1<br>PR | Partial contact<br>12s | Male & Female (novel, same sex) | Four-core genotypes (FCG), MYT1L Het, MYT1L WT | • Greater interaction time in mice with ovaries compared to testes; while sex chromosome does not affect social behavior<br>• Learning to nose poke for social rewards is independent of sex, gonads, or MYT1L genotype<br>• MYT1L Het mice show greater locomotion in the social operant task compared to WT<br>• Female Myt1L Het mice show higher responding than male Myt1L Het mice and female WT mice<br>• Cohort is the strongest factor influencing social reward, social interactions, and locomotion; however, number of rewards are similar across sexes within cohorts |

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| | | | | | | • Older mice (90–110 days) show greater locomotion than younger mice (44–62 days) across cohorts |
| (Venniro et al. 2021) | Addiction | Male & Female FR1-16 cocaine-vs-social interaction choice | Partial contact 60s | Male & female (familiar, same sex) | Sprague-Dawley | • Rats prefer social over cocaine reward, independent of the training schedule (intermittent or continues access)<br>• Operant social interaction inhibits cocaine self-administration and prevents incubation of cocaine craving<br>• Delay of both social and cocaine rewards or only social reward, increases cocaine preference with individual differences<br>• Increase of FR requirements for social reward increases cocaine preference with individual differences |
| (Chow et al. 2022) | Addiction | Male & Female | Partial contact 15 s | Familiar | Sprague-Dawley | • Preference for social interaction over remifentanil is dose-dependent |
| (Marcus et al. 2022) | Addiction | Male & Female FR1-3 PR, cocaine-vs-social interaction choice | Partial contact 30s, 60s | Male & female (familiar, same sex) | Sprague-Dawley | • Rats prefer social over cocaine reward<br>• Social over cocaine preference is dose dependent<br>• Increasing social interaction time does not change social preference<br>• Preference for social interaction is not influenced by presentation of non-contingent reinforcers |
| (St Onge et al. 2022) | Addiction | Male & Female FR1-320 fentanyl-vs-social interaction choice | Partial contact 30s | Male & female (familiar, same sex) | Sprague-Dawley | • Rats are indifferent to social and fentanyl rewards<br>• Fentanyl over social preference is dose dependent<br>• Fentanyl over social preference is not affected by partner's presence in the box<br>• Fentanyl choices are higher in males compared to females<br>• Opioid withdrawal does not affect fentanyl over social preference<br>• Increased FR requirements decrease fentanyl choice<br>• Naltrexone modestly decreases fentanyl preference |
| (Marchant et al. 2023) | Addiction | Male & Female FR1-30 alcohol -vs-social interaction choice | Partial contact 60s | Male & female (familiar, same sex) | Long-Evans | • During operant social SA, females spend more time interacting with the social partner, whereas males spend more time in the lever area during social self-administration<br>• Rats prefer alcohol over social rewards, with sex differences: males have a greater preference for alcohol compared to females<br>• Preference for social reward increases with increasing FR requirements for alcohol<br>• Pre-exposure to alcohol increases preference for social rewards in males, but not females<br>• Preference for social rewards remains unchanged with reduced alcohol doses, but shifts to social only when alcohol is replaced with water |

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| (Augier et al. 2023) | Addiction | Male & Female<br>FR1-32<br>PR<br>alcohol -vs-social interaction choice | Partial contact 15-45s | Male & female (familiar & novel, same sex) | Wistar | • Rats prefer alcohol over social reward<br>• Preference for alcohol over social rewards is not affected by partner novelty, and social isolation time<br>• Social isolation increases responding for social rewards and breakpoints for alcohol and social, but not preference for social over alcohol rewards<br>• During sampling pre-choice, rats take more alcohol than social reward<br>• Preference for alcohol was decreased only at high FR requirement for alcohol<br>• Partner housing does not alter responding for social reward<br>• Preference for social rewards remains unchanged with reduced alcohol doses, but shifts to social only when alcohol is replaced with water |
| (Papastrat et al. 2024) | Addiction | Male & Female<br>FR1<br>cocaine -vs-social interaction choice | Partial contact 20 | Male & female (familiar, same sex) | Sprague-Dawley | • Removal of olfactory bulb (bulbectomy) prevents acquisition of social SA, but not cocaine SA<br>• Bulbectomy decreases responding for social rewards in rats pre-trained for social SA<br>• Rats with intact olfactory bulb prefer social rewards over cocaine, whereas rats with a bulbectomy prefer cocaine<br>• Rats press more to access a chamber containing social full odor (but not social urine odor alone) compared to an empty chamber<br>• Rats prefer social odor vs cocaine<br>• Social odor SA inhibits cocaine self-administration and decreases incubation of cocaine craving<br>• Non-contingent presentation of social odor does not prevent incubation of cocaine craving |
| (Bird et al. 2024) | Addiction | Male & Female<br>FR6-24<br>Cocaine/ heroin -vs-social interaction choice | Partial contact 60s | Male & Female (familiar, same sex) | Long-Evans | • In discrete choice between two social rewards, rats established as indifferent are sensitive to price changes and prefer the cheaper FR option<br>• Rats show individual differences in the FR requirement at which heroin and social rewards are valued equally<br>• In discrete choice between heroin and social rewards, rats established as indifferent show limited sensitivity to price changes, and only slightly shift toward the cheaper option<br>• In discrete choice between cocaine and social rewards, rats established as indifferent show sensitivity to price changes and prefer cheaper option<br>• Cocaine–Social rats often start the sessions with social reinforcers before shifting mainly to cocaine, whereas Heroin–Social rats do not display this switching pattern |

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| (D'Ottavio et al. 2025) | Addiction | Male & Female<br>FR1-32<br>PR<br>heroin -vs- social interaction choice | Full and partial contact<br>60 s | Male & female (familiar & same sex) | Sprague-Dawley | • In discrete choice between 1 infusion of heroin vs 1 min of social interaction, rats prefer social rewards<br>• In discrete choice between 5 min of heroin access (= several infusions) vs 5 min of social interaction, rats show individual differences in heroin preference<br>• In the 5 vs 5 choice preference remains stable regardless of partner access time, FR requirement on the heroin lever and after 4 weeks abstinence<br>• Higher heroin preference with screen-based contact vs physical contact<br>• Addiction severity index (heroin intake, number of bursts and lever presses during seeking test) is strongly correlated with heroin over social rewards preference<br>• Social SA is not correlated to addiction severity |
| (Pilz et al. 2025) | Addiction | Male & Female<br>FR 1 | Partial contact<br>15s | Male & female (familiar & same sex) | Sprague-Dawley | • Morphine dependence (daily injections) decreases lever pressing for social interaction<br>• Morphine, fluoxetine (serotonin reuptake inhibitor), LY2456302 (KOR antagonist), GVR12909, (dopamine uptake inhibitor) did not restore lever pressing for social interaction |
| Stress | | | | | | |
| (Williams et al. 2022) | Early life stress | Male & Female<br>FR1<br>PR | Full Contact<br>40s | Male & Female (familiar, novel, same sex) | Long-Evans | • Early life stress increases responding for social rewards in male, but not females<br>• Early life stress increases motivation (PR) for social rewards in male, but not females |
| (Navarrete et al. 2024) | Social defeat stress | Male & Female<br>FR1<br>PR | Full Contact<br>10s | Male & Female (familiar, novel, same sex) | C57BL/6 J, CD-1, CFW | • 75% (69/89 males and 43/61 males) of mice learned to press for social reward<br>• Responding for social reward decreases when the social partner is removed or randomly delivered<br>• Responding for social interaction is similar regardless of partner coat color, partner novelty, and prior experience<br>• In males, but not females, social-defeat stress decreases responding for social reward and breakpoints<br>• Witnessing social defeat does not affect responding for social rewards, but it increases breakpoints in females<br>• Social defeat produces individual differences in responding to social reward, with males exposed to social-defeat stress showing the greatest effects |
| Pain & Inflammation | | | | | | |
| (Baldwin et al. 2022) | Pain (Lactic acid) | Male & Female<br>FR 1-16 | Partial contact<br>15-60s | Male & Female (familiar, same sex) | Sprague-Dawley | • Responding for social rewards decreases if the social partner is removed, but does not decrease if the social partner is present, regardless of door opening<br>• Time of access has a minimal effect on response rate (15s, 30s, 60s) |

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| | | | | | | • Increasing FR requirements decreases social self-administration<br>• Lactic acid dose-dependently decrease responding for social and food rewards<br>• Morphine dose-dependently decrease responding for social and food rewards<br>• Morphine reverses pain-induced suppression of food but not social self-administration<br>• Ketoprofen has no effect on responding for social and food rewards<br>• Lactic acid and morphine more strongly affect responding for social vs food reward<br>• Ketoprofen, but not morphine, reverses lactic acid-induced inhibition of social self-administration |
| (Young et al. 2024) | Inflammation (LPS) | Male & Female FR1-4 | Full contact 60s | Male & female (familiar & novel, same sex) | Prairie vole | • LPS inflammation decreases social self-administration<br>• LPS inflammation increases preference for social interaction with familiar over an empty chamber<br>• LPS inflammation does not affect preference for a familiar vs novel partner<br>• LPS inflammation increases huddling time with for both familiar and novel partners<br>• LPS inflammation does not affect extinction responding |

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