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ARTICLE

# Social odor choice buffers drug craving

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Social interactions are rewarding and protective against substance use disorders, but it is unclear which specific aspect of the complex sensory social experience drives these effects. Here, we investigated the role of olfactory sensory experience on social interaction, social preference over cocaine, and cocaine craving in rats. First, we conducted bulbectomy on both male and female rats to evaluate the necessity of olfactory system experience on the acquisition and maintenance of volitional social interaction. Next, we assessed the effect of bulbectomy on rats given a choice between social interaction and cocaine. Finally, we evaluated the influence of olfactory sensory experience by training rats on volitional partner-associated odors, assessing their preference for partner odors over cocaine to achieve voluntary abstinence and assessing its effect on the incubation of cocaine craving. Bulbectomy impaired operant social interaction without affecting food and cocaine self-administration. Rats with intact olfactory systems preferred social interaction over cocaine, while rats with impaired olfactory sense showed a preference for cocaine. Providing access to a partner odor in a choice procedure led to cocaine abstinence, preventing incubation of cocaine craving, in contrast to forced abstinence or non-contingent exposure to cocaine and partner odors. Our data suggests the olfactory sensory experience is necessary and sufficient for volitional social reward. Furthermore, the active preference for partner odors over cocaine buffers drug craving. Based on these findings, translational research should explore the use of social sensory-based treatments utilizing odor-focused foundations for individuals with substance use disorders.

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## INTRODUCTION

How much can the sensory information we experience from vision, sound, or smell rival what we experience through social interactions? Although physical touch is often involved in social interaction, such as hugging a friend, many forms of social interaction are highly rewarding and involve multiple senses [1, 2]. The sense of smell plays a crucial role in facilitating healthy social interactions in both humans and laboratory animals. People tend to subconsciously smell each other during social interactions and develop friendships with those who smell similar to them highlighting the significant impact the sense of smell on human behavior [3–8]. In rodents, the ability to detect social olfactory cues is critical for social approach and recognition [9–11]. Additionally, exposure to the odor of a conspecific activates dopaminergic neurons in a similar way to exposure to a conspecific [11]. When rats are exposed to olfactory cues from a partner rat that is engaged in cooperative behavior, it increases the likelihood of the observing rat engaging in similar behavior [12]. These studies highlight the critical role of olfactory neurons in social behaviors [13]. The direct olfactory bulb connections with subcortical and amygdala regions may explain how smell contributes to the reinforcing nature of social interaction [1, 14, 15].

Odor-based associative learning can lead to specific odors triggering strong emotional memories, which can alter behavior [14, 16]. Impaired olfaction is a disabling condition that can lower the quality of life due to impaired social relationships [14, 16, 17]. Conversely, positive social interactions and the ability to communicate emotions via sensory systems can protect against several neuropsychiatric disorders [18–20]. Individuals with higher psychopathic traits show less efficient functioning in brain areas that are responsible for higher olfactory processes, including identification and discrimination [21]. Exposure to the social chemosignal hexadecanal reduces aggression in men while triggering aggression in women [22]. Substance use disorders have also been linked to taste and smell dysfunction [23–26]. Exposure to pleasant olfactory distractor cues has been shown to reduce craving in abstinent cigarette smokers [27]. In rodents, social odors mitigate stress responses [28] and olfaction is critical for both morphine-induced behavioral sensitization and conditioned place preference [29].

Recent evidence has revealed that rats display a preference for interacting with a social partner instead of receiving an injection of an abused drug [30]. Notably, the active preference for social interaction serves as a protective mechanism, effectively preventing drug craving [30–33]. A plausible and straightforward explanation for this phenomenon lies in the cognitive complexity associated with volitional social interaction. However, it remains unknown whether there is a specific aspect within the complex

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sensory social experience that is required for volitional social interaction to produce its reinforcing and protective effects. Here, we address this gap using a translational relevant social-choice self-administration model [30]. We found that, independent of sex or training conditions, olfactory sensory experience is necessary both for the acquisition and maintenance of social reward self-administration and for the rats' social preference over cocaine. Furthermore, rats exhibited a preference for the odor of their partner rats over cocaine. This active social-odor preference, in turn, prevented the incubation of cocaine craving compared to conditions of home-cage forced abstinence or non-contingent exposure to cocaine and partner odors in the self-administration social context. Our findings highlight the significance of the olfactory sensory aspect in social experiences. The active preference for social odors over abused drugs offers a potential mechanism against drug craving.

## MATERIALS AND METHODS

### Subjects

We used male and female Sprague-Dawley rats (Charles River, total $n = 240$ [136 "Resident" (75 males and 61 females) and 104 "Social partners" (52 males and 52 females)], weighing 150–175 g upon arrival. For all experiments we always matched rats for age and sex. We housed the rats two per cage by sex for 2–3 weeks prior to the experiments and then individually housed them starting 1 week prior to self-administration for the duration of the experiment. We randomly assigned the rats to the "Resident" and "Social partner" groups. In Exp. 4-5, the social partners were rats of the same age and sex, but they were not previously housed with the resident drug-experienced rats, and we used them to generate the social odor. We maintained the rats on a reverse 12-h light/dark cycle (lights off at 9:00 AM) with free access to standard laboratory chow and water. Our procedures followed the guidelines outlined in the Guide for the Care and Use of Laboratory Animals (8th edition; http://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf). This study was approved by UMB School of Medicine Animal Care and Use Committee. We excluded 18 resident rats (8 male and 10 females) due to sickness and 10 partner rats (3 males and 7 female) due to the exclusion of their resident partner.

### Surgery

We anesthetized the rats with isoflurane (5% induction; 2–3% maintenance). During bulbectomies, we fixed the rats in a stereotaxic apparatus and performed a craniotomy to expose and ablate the olfactory bulbs. We removed the olfactory bulbs by suction using a glass pipette connected to a vacuum apparatus. We filled the ablation cavity with Gelfoam to prevent regeneration of olfactory axons. During sham surgeries we performed the craniotomy without removing the olfactory bulbs. At the end of each experiment, we removed the brains to verify the degree of lesion. During intravenous catheter implantation, we inserted Silastic catheters into the jugular vein, which we passed subcutaneously to the mid-scapular region and attached to a modified 22-gauge cannula cemented to polypropylene mesh. We injected Rimadyl (2.5 mg/kg, s.c., Butler Schein) after surgery to relieve pain and decrease inflammation. We flushed the catheters daily with sterile saline containing gentamicin (4.25 mg/ml, APP Pharmaceuticals) during the recovery, training, and choice phases. Rats were administered post-surgery care for 5–6 days before training.

### Drug

We received cocaine HCl (cocaine) from Sigma Aldrich and dissolved the powder in sterile saline. In Experiment (Exp.) 3–4 we used a dose of 0.75 mg/kg/infusion and in Exp. 5 we used a dose of 0.5 mg/kg/infusion for self-administration training and choice. Unit doses are based on previous studies [33].

*Experimental model*

Self-administration chambers: We trained the rats to self-administer palatable food, cocaine, and to gain access to a social peer (termed herein 'social self-administration' [34–36]) or social odor (termed herein 'odor self-administration') in social-choice self-administration chambers [30–34].

Procedures: Food self-administration: We trained the rats to lever press for food during two 1-h daily sessions separated by 10 min under a fixed ratio 1 (FR1) – 20-s timeout reinforcement schedule, which led to the delivery of one 45-mg palatable food pellet (TestDiet, Catalogue # 1811155). Prior to the first self-administration training sessions, we gave the rats a 40 min magazine session, during which one pellet was delivered noncontingently every 5 min. The self-administration sessions began with the presentation of the red house-light, followed 10 s later by the insertion of the food-paired active lever; the red house-light remained on for the duration of the session and served as a discriminative stimulus. Successful lever presses on the food-paired lever activated the pellet dispenser and a discrete white cue light for 20 s; palatable food pellets were delivered to a pellet dispenser located near the food-paired lever. At the end of the session, the red house-light was turned off and the active lever was retracted. We recorded the number of food rewards, active and inactive lever presses.

Social self-administration: We trained rats to self-administer for access to the social partner sex and age matched during two 1-h daily sessions separated by 10 min under a fixed ratio 1 (FR1) – 20-s timeout reinforcement schedule. The session started with the illumination of the social-paired white houselight followed 10 s later by the insertion of the social-paired active lever; the house-light remained on for the duration of the session and served as a discriminative stimulus. Successful lever presses on the social-paired lever resulted in a discrete 20-s tone cue and the opening of the guillotine door. We allowed the resident rat to subsequently interact with the social partner through the perforated screen for 60 s, at which point the guillotine door closed. We recorded the number of social rewards, active and inactive lever presses.

Odor self-administration: The self-administration procedure is identical to the one reported for social self-administration with the exception that, upon lever pressing, we allowed rats to gain access to a social partner's odor and not physical social interaction. Urine procedure: We collected urine samples from the partner rats by placing trays without bedding on the social partner side of the operant chamber and stored the samples in 1.5 ml centrifuge tubes in a refrigerator. Using a cotton swab, we deposited drops of the samples onto the frame of the guillotine door and inside the partner chamber. We repeated this procedure every day before the session. Odor loading: We allowed the partner rat to stay in the partner side of the operant chamber for a period of 90 min prior to the start of the session. After removing the partner, we placed the resident rat in the chamber and initiated the session within 5 min. We recorded the number of odor rewards, active and inactive lever presses. After every odor self-administration procedure, we cleaned both the resident and partner sides of the chamber. We used a solution of 70% ethanol, Clorox wipes, and replace the resident's bedding to maintain a clean environment for the next session.

Drug self-administration: In Exp. 3-4, we trained rats to self-administer cocaine (0.75 mg/kg/infusion) during six 1-h sessions that were separated by a 10-min off period, under an FR1 20-s timeout reinforcement schedule (10 sessions). To prevent overdose, we limited the number of infusions to 15 per h [33]. In Exp. 5, we trained rats to self-administer cocaine (0.5 mg/kg/infusion) during one 6-h session, under an FR1 20-s timeout reinforcement schedule (12 sessions). To prevent overdose, we limited the number of infusions to 150 per 6 h. The sessions began with the presentation of the red light and 10 s later by the insertion of the drug-paired active lever; the red light remained on for the duration of the session and served as a discriminative stimulus for drug availability. At the end of each session, the red light was turned off, and the active lever was retracted.

Discrete choice procedure: We conducted the discrete choice sessions using the same parameters (cocaine dose, length of social interaction, stimuli associated with either social-, odor, or cocaine-paired levers) that we used during the social and cocaine self-administration training [33]. We allowed the rats to choose between the social- or odor- and cocaine-paired levers in a discrete-trial choice procedure. We divided each 120-min choice session into 15 discrete trials that were separated by 8 min [30, 34]. Each choice trial began with the presentation of the discriminative stimuli for social interaction and cocaine, followed 10 s later by the insertion of the levers paired with both rewards. Rats could then select one of the two levers. If the rats responded within 6 min, they only received the reward corresponding with the selected lever. Thus, on a given trial, the rat can earn either reward, but not both [37, 38]. Each reward delivery was signaled by the social- or odor- or cocaine-associated discrete cue, the retraction of both levers, and turning off both discriminative cues. If a rat failed to respond on either active lever within 6 min, both levers were

retracted, and their related discriminative cues were turned off with no reward delivery. We assessed the rats' preference during cocaine self-administration for two sessions. An inactive lever remained stationary throughout the session, allowing the rats to press it during the inter-trial intervals without consequences.

Active choice abstinence: After the relapse test on day 1, we allowed the rats from the voluntary abstinence (active choice) group to choose between the or odor-paired lever (delivering 60-s odor exposure) and cocaine-paired lever (delivering one infusion) during 15 discrete-choice trials (separated by 8 min) for 10 sessions over 14 days, and then assessed relapse to cocaine seeking on abstinence day 15 [33, 39].

Non-contingent abstinence: After the relapse test on day 1, we exposed one group of rats (non-contingent) to non-contingent cocaine infusions and exposure to odors associated with a peer in the self-administration social context. To replicate the patterns of drug infusions and odor exposures observed in the active social group, we used a yoked design. This design aimed to mimic the active social group's behaviors, administering a mix of non-contingent odor or drug presentations across each session based on the responding patterns of a yoked choice rat. As with the active choice group, we conducted this procedure for 10 sessions over 14 days, and then assessed relapse to cocaine seeking on abstinence day 15.

Forced abstinence: After the relapse test on day 1, we returned a group of rats to their home-cage for 14 days of forced abstinence, and then assessed relapse to cocaine seeking on abstinence day 15. We handled the rats twice per week [33].

Relapse test: The relapse test in the presence of cocaine cues consisted of a 30-min session. The test session began with the presentation of the cocaine-paired red discriminative cue light followed 10 s later by the insertion of the cocaine-paired lever; the red light remained on for the duration of the session. Active lever presses during testing, the operational measure of drug seeking in incubation of drug craving (the progressive increase of drug seeking over time [40]) and relapse studies [40, 41], resulted in contingent presentations of the discrete light cue previously paired with cocaine infusions, but not cocaine delivery. At the end of the session, the active lever retracted, and the house light was turned off.

### Statistical analyses

We used factorial ANOVAs and t-tests using SPSS (IBM, version 25, GLM procedure). When we obtained significant main effects and interaction effects ($p < 0.05$, two-tailed), we followed them with post-hoc tests (Fisher PLSD). Because our multifactorial ANOVAs yielded multiple main and interaction effects, we only report significant effects that are critical for data interpretation. We indicate results of post-hoc analyses in the figures but do not describe them in the Results section. In Supplementary Table S1 we provide a complete report of the statistical results for the data described in the manuscript. We did not include inactive lever data in the figures due to consistently low response rates. However, we provided statistical analyses for both active and inactive responses in Supplementary Table S1. In the choice/voluntary abstinence procedure, active lever presses correspond to rewards, while the inactive lever remains stationary, allowing for presses during inter-trial intervals. Nevertheless, the responding on the inactive lever was minimal during the choice experiments, averaging ~0.7 and ~1.3 presses/session across all experiments.

## RESULTS

### Olfaction mediates acquisition and maintenance of volitional social interaction

Humans and laboratory animals, through sensory systems, actively react to the affective state of others during interactions and share information about the surrounding environment [42]. Classically, the studies exploring the role of sensory mechanisms on social behaviors rely on passive (or experimenter-imposed) social interactions [43]. However, it is unknown whether sensory systems play a role in rats' motivation to engage in volitional social interaction, which more closely models the human scenario [44]. In Exp. 1 (Fig. 1A), we used our established rodent social self-administration model [30, 34–36] to investigate the impact of the olfactory sensory system on rats' motivation for social reward. First, we trained male and female rats for reliable palatable food self-administration (Fig. 1B – Session: $F_{4,60} = 4.0$, $p = 0.006$). Next, we removed both olfactory bulbs (Supplementary Fig. S1A – sham $n = 10$ (5 males, 5 females); bulbectomy $n = 9$ (5 males, 4 females)) before training rats for social self-administration. We observed that, independently of sex ($p > 0.05$), bulbectomy impaired acquisition of social self-administration relative to sham controls (Fig. 1C – Session x Group: $F_{9,135} = 2.4$, $p = 0.02$). The effect of bulbectomy was selective to social interaction, as it did not impair food self-administration in two additional sessions conducted during the training for social self-administration (Fig. 1D – $p > 0.05$).

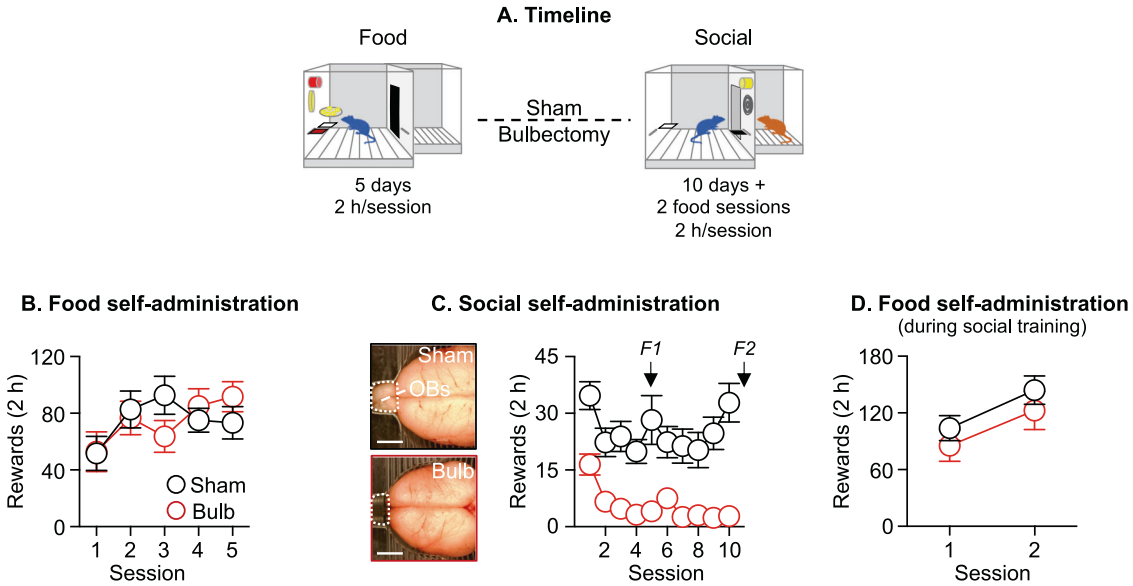


**Fig. 1 Olfactory sensory system is critical for acquisition of volitional social interaction. A** Timeline of the experiment. **B** Food self-administration. Number of food (2 h) rewards over 5 sessions. **C** Social self-administration. Left: Representative pictures of sham and bulbectomy surgery; scale bar = 5 mm. Right: Number of social (2 h) rewards over 10 sessions. **D** Food self-administration during social training. Number of food (2 h) rewards over 2 additional food sessions during social self-administration. Sham group (black) $n = 10$ (5 males, 5 females); bulbectomy group (red) $n = 9$ (5 males, 4 females). Data are mean ± SEM. F = food session during social self-administration training. See also Supplementary S1A.

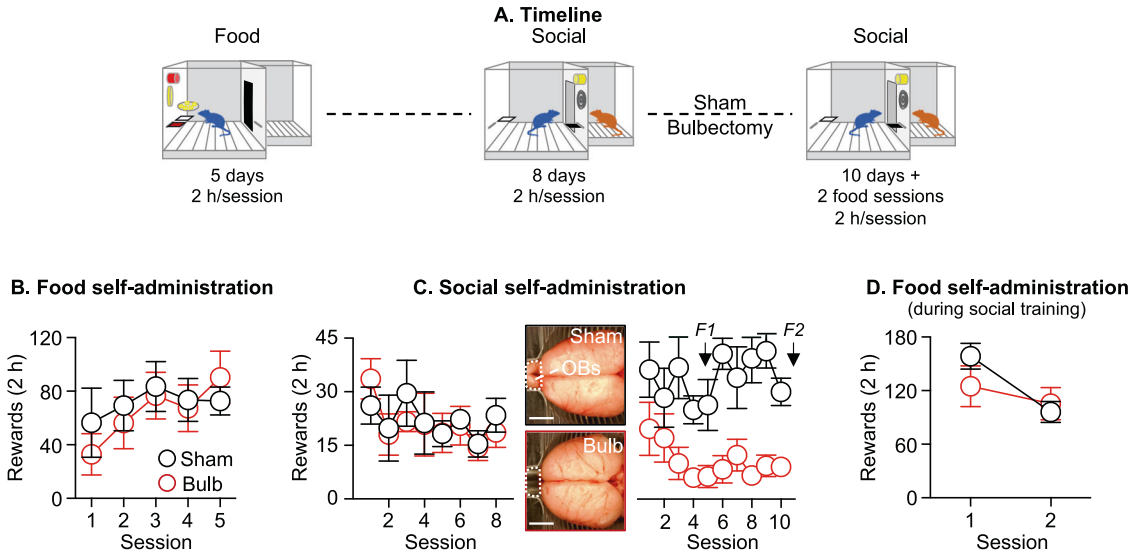


**Fig. 2 Olfactory sensory system is critical for maintenance of volitional social interaction. A** Timeline of the experiment. **B** Food self-administration. Number of food (2 h) rewards over 5 sessions. **C** Social self-administration. Left: Number of social (2 h) rewards over 8 sessions prior surgery. Middle: Representative pictures of sham and bulbectomy surgery; scale bar = 5 mm. Right: Number of social (2 h) rewards over 10 sessions after surgery. **D** Food self-administration during social training. Number of food (2 h) rewards over 2 additional food sessions during social self-administration. Sham group (black) $n = 7$ (4 males, 3 females); bulbectomy group (red) $n = 6$ (4 males, 2 females). Data are mean ± SEM. F = food session during social self-administration training. See also Supplementary S1B.

In Exp. 1, we showed that the olfactory sensory system is critical and selective for the acquisition of social reward self-administration. However, the question of whether olfaction is necessary for maintaining volitional social interaction once the behavior is learned and acquired remained open. Thus, in Exp. 2 (Fig. 2A) we investigated the role of the olfactory sensory system in the maintenance of social self-administration. First, we trained male and female rats for reliable food (Fig. 2B – Session: $F_{4,36} = 2.7$, $p = 0.05$) and stable social self-administration (Fig. 2C, left – Session: $F_{7,63} = 2.1$, $p = 0.06$). Next, we removed the olfactory bulbs (Supplementary Fig. S1B – sham $n = 7$ (4 males, 3 females); bulbectomy $n = 6$ (4 males, 2 females)) before re-exposing the rats to social self-administration. We observed that, independently of sex ($p > 0.05$), bulbectomy also impaired the maintenance of social self-administration (Fig. 2C, right – Session × Group: $F_{9,81} = 2.4$, $p = 0.02$). The effect on maintenance was also selective to social reward as food self-administration in two additional sessions conducted during social self-administration was not impaired (Fig. 2D – $p > 0.05$).

The key finding from this series of experiments is that the olfactory sensory system plays a critical role in both the acquisition and maintenance of volitional social reward. Importantly, this effect is specific to social reward and does not generalize to other natural rewards, such as food. These results highlight the importance of olfaction in social behavior and emphasize its unique role in facilitating and sustaining volitional social interactions.

## Olfaction is critical for social preference over cocaine

While we established the essential role of the olfactory sensory system in volitional social interaction, it remains unknown whether olfaction mediates the protective effect of volitional social interaction against abused drugs. In Exp. 3 (Fig. 3A), we used our established social-choice self-administration model [30] to investigate the effect of bulbectomy on the rats' preference between social interaction and cocaine. First, we trained male and female rats for reliable food self-administration (Fig. 3B – Session: $F_{4,88} = 22.0$, $p < 0.001$). Next, we removed the olfactory bulbs (Supplementary Fig. S1C – sham $n = 17$ (10 males, 7 females); bulbectomy $n = 9$ (4 males, 5 females)) before training rats for social self-administration. We replicated and extended the finding from Exp. 1 showing that independently of sex ($p > 0.05$), bulbectomy impaired acquisition of social self-administration relative to sham controls (Fig. 3C – Session × Group: $F_{7,154} = 2.9$, $p = 0.007$). Then, we used the established extended-access self-administration model to determine whether bulbectomy would prevent drug self-administration. Over the sessions, sham and bulbectomized rats maintained stable and similar patterns of cocaine self-administration (Fig. 3D – $p > 0.05$), indicating that the involvement of the olfactory sensory system does not extend to the reinforcing effects of cocaine self-administration. Finally, we gave the rats a mutually exclusive choice between social interaction and cocaine. Rats with an intact olfactory system preferred social interaction over cocaine, whereas rats with rats who lacked olfactory experience preferred cocaine self-administration (Fig. 3E – Session × Group: $F_{9,198} = 9.8$, $p < 0.001$).

In Exp. 3, we provide evidence that the olfactory sensory system plays a crucial role in the preference for social interaction over cocaine self-administration. Importantly, this effect is specific to motivated social interaction and does not generalize to cocaine self-administration.

## Active preference for conspecific odor prevents cocaine craving

Exp. 3 showed that the olfactory system is necessary for social preference over cocaine self-administration in rats. However, it is unclear whether conspecific odor alone is reinforcing and can prevent drug-seeking behavior. In Exp. 4 (Fig. 4A), we conducted a more stringent test to determine the effect of conspecific odors on volitional social reward in the absence of a social partner (No odor $n = 8$ (4 males, 4 females); odor $n = 8$ (4 males, 4 females). First, we trained male and female rats for reliable food self-administration (Fig. 4B – Session: $F_{4,48} = 13.0$, $p < 0.001$). Next, we exposed the rats to different odors, specifically, either urine or social odors, both derived from previously associated social partners, and trained them for both forms of odor self-administration. Notably, both male and female rats did not engage in self-administration of the odor associated with the urine of a social partner. The number of rewards earned during the session did not significantly differ from rats that were lever

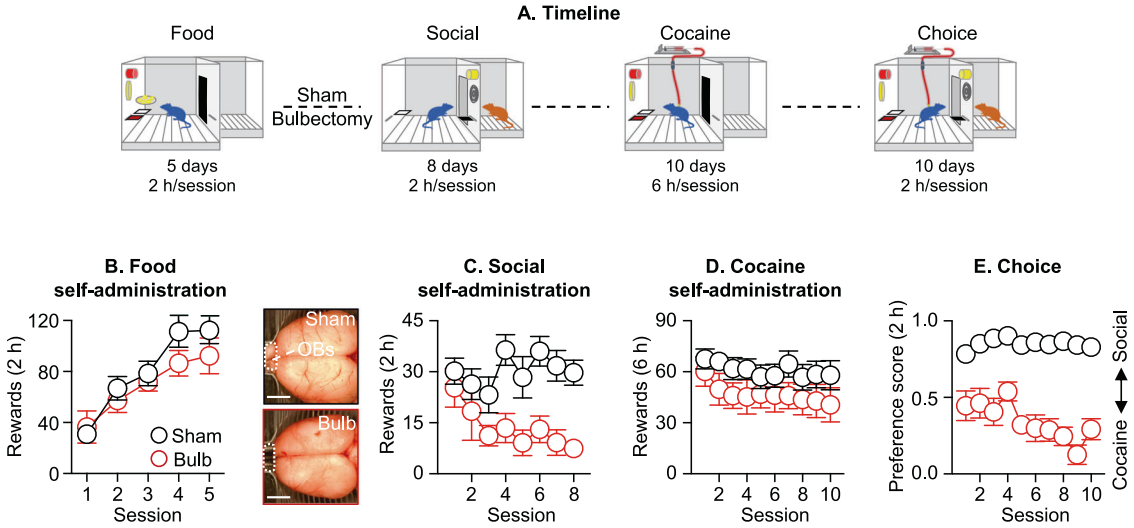


**Fig. 3 Olfactory sensory system is critical for social preference. A** Timeline of the experiment. **B** Food self-administration. Number of food (2 h) rewards over 5 sessions. **C** Social self-administration. Left: Representative pictures of sham and bulbectomy surgery; scale bar = 5 mm. Right: Number of social (2 h) rewards over 8 sessions. **D** Cocaine self-administration. Number of cocaine (6 h) infusions over 10 sessions. **E** Choice. Average preference score (number of social rewards/[number of social reward + number of drug infusions]). 0 indicates preference for cocaine; 1 indicates preference for social reward. Sham group (black) $n = 17$ (10 males, 7 females); bulbectomy group (red) $n = 9$ (4 males, 5 females). Data are mean ± SEM. See also Supplementary S1C.

pressing for an empty, clean chamber (Fig. 4C, left – $p > 0.05$). However, the rats successfully acquired and maintained self-administration when the odor was released by a social partner prior to the session (Fig. 4C, right – Group: $F_{1,12} = 12.0$, $p = 0.005$). Additionally, rats self-administered their own odor in a similar pattern to when the odor was from a social partner, although it remained stable over time (Fig. 4D – $n = 6$ (4 males, 2 females)). Moreover, rats self-administered an opposite-sex social odor (Fig. 4E – $n = 5$ (3 males, 2 females)), although not consistently over the five sessions (Session: $F_{4,16} = 4.2$, $p = 0.02$). This variability could be related to the estrous cycle stage of either the resident rat or the odor of the partner rat.

Given the importance of social odors in facilitating volitional social interactions (Exp. 4), our next question was whether rats would prefer social odors over cocaine without physical interaction, and if this preference would, in turn, prevent cocaine craving [39–41]. Exp. 5 had 3 phases (Fig. 5A): odor and cocaine self-administration training, abstinence, and relapse tests 1 d after the last self-administration session and 1 d after the last abstinence session. We compared three different conditions: home-cage forced abstinence (rats not exposed to either social odors or cocaine – $n = 12$ (10 males, 2 females)); active social (voluntary abstinence – rats making a choice between odors and cocaine to achieve abstinence – $n = 14$ (12 males, 2 females)); non-contingent (yoked – rats non-contingently exposed to odors and cocaine based on the voluntary abstinence rats' preference – $n = 7$ (4 males, 3 females)). we replicated and extended the finding from Exp. 4 on the ability of rats to reliably self-administer an odor of a social partner in the absence of a social partner (Fig. 5B, left – Session: $F_{5,155} = 7.6$, $p < 0.001$; no interactions with Sex). Over subsequent sessions, both sexes increased their number of cocaine rewards (Fig. 5B, right – Session: $F_{11,341} = 2.3$, $p = 0.01$). During active choice abstinence, both sexes strongly and stably preferred social odor over cocaine achieving voluntary abstinence (Fig. 5C). In 30-min relapse tests, the active preference for odors over cocaine effectively prevented the incubation of cocaine craving in contrast to the notable incubation observed after home-cage forced abstinence (Fig. 5D – $p = 0.005$), or after non-contingent (Fig. 5C) exposure to social odors and cocaine infusion in the self-administration context (Fig. 5D – $p = 0.02$), in both male and female rats. This highlights that the active preference for the social partner's odor over cocaine was sufficient for rats to voluntarily abstain from cocaine, and that it plays a pivotal role in the protective effect against cocaine craving. Importantly, these results demonstrate that non-contingent exposure to cocaine (~3-4 infusions per day on average or ~1.5–2 mg/kg/day on average) and social odor in the same self-administration context is insufficient to prevent cocaine craving.

## DISCUSSION

In this study, we demonstrate the critical role of olfactory sensory experience in mediating volitional social reward and social preference. We also demonstrate that rats prefer odors associated with a partner over cocaine. Furthermore, our findings demonstrate that the active preference for social odors effectively inhibits the incubation of cocaine craving. Depriving rats of their ability to rely on the olfactory sensory system through bulbectomy impairs social self-administration, as intact olfactory bulbs are required for both the acquisition and maintenance of volitional social reward learning. Critically, our findings highlight the importance of the olfactory system in mediating social preference and its role in modulating drug-seeking behavior. Rats with intact olfactory systems showed strong social preference over cocaine whereas bulbectomized rats preferred cocaine self-administration. Surprisingly, odors associated with a social partner are sufficient to maintain odor self-administration and to achieve voluntary abstinence from cocaine self-administration, a procedure that prevents the incubation of cocaine craving. Our results highlight the significance of smell in shaping social behavior and are suggestive of a possible mechanism to prevent drug craving in substance abuse disorders.

### How does the olfactory sensory system mediate volitional social interaction?

Our data demonstrates that bulbectomy produced impairments in the acquisition of volitional social reward. This effect could be attributed to either a deficit in social motivation or social learning. It is possible that rats without an intact olfactory system were not motivated to engage in lever pressing because the presence of

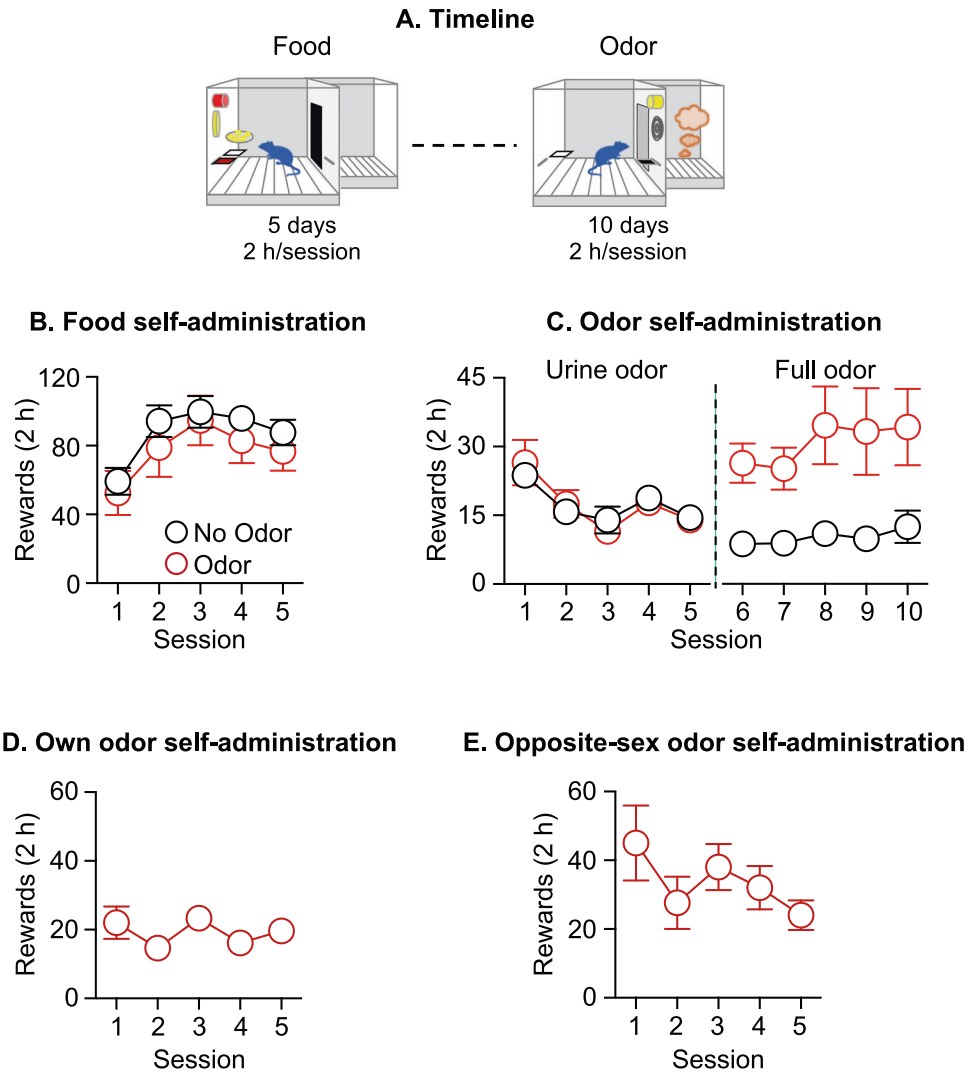


**Fig. 4 Social odors mediate volitional social reward. A** Timeline of the experiment. **B** Food self-administration. Number of food (2 h) rewards over 5 sessions. **C** Odor self-administration. Left: Number of urine odor (2 h) rewards over 5 sessions. Right: Number of full odor (2 h) rewards over 5 sessions. No odor group (black) $n = 8$ (4 males, 4 females); odor group (red) $n = 8$ (4 males, 4 females). **D** Own odor self-administration. Number of odor (2 h) rewards over 5 sessions; $n = 6$ (4 males, 2 females). **E** Opposite-sex odor self-administration. Number of odor (2 h) rewards over 5 sessions; $n = 5$ (3 males, 2 females). Data are mean ± SEM.

their partner without the associated odor was no longer reinforcing. Alternatively, the deficits could stem from a difficulty in social learning, as rats may require an intact olfactory system and sensory input to successfully associate lever pressing with social reward. To test these possibilities, we removed the olfactory bulbs after the rats had acquired stable social self-administration, because cues associated with social self-administration could potentially acquire incentive salience after operant training such that the cues alone become sufficient to drive operant behavior [45]. Our findings indicate that the removal of olfactory bulbs significantly reduced rats' behavioral response to a social partner, despite previously acquiring stable social self-administration. This suggests that the impairment caused by olfactory bulbectomy is related to social motivation rather than social learning.

Bilateral bulbectomy is a widely used rodent model of depression-like behaviors producing anosmia [46, 47]. Although we did not explicitly test for canonical signs of depression-like behaviors in our bulbectomized rats, notably, the behavioral motivational deficits were specific to the social domain, as bulbectomized rats continued to display operant responding for a different natural reward (food) and a drug reward (cocaine).

Rats self-administered social partner odors in the absence of a social partner. Interestingly, the number of rewards earned during social self-administration was similar to the number earned during social partner odor self-administration, showing the strong reinforcing value of partner odor alone in driving the behavior. Rodents possess exceptional olfactory capabilities, enabling them to efficiently detect and distinguish smells. Olfactory neurons in rodents are remarkably sensitive and selectively attuned to pheromonal signatures [48]. Our findings revealed that the reinforcing value of social odor is contingent upon the odor profile released by a social partner in the environment. Importantly, in Exp. 4-5, the social partners were rats of the same age and sex, but they had not been previously housed with the resident drug-experienced rats. We used them to generate the social odor, demonstrating that the behavior is consistent even with non-familiar conspecifics. Furthermore, while natural predators' urine odor alone can trigger fear responses and contribute to the development of post-traumatic stress disorder-like behaviors in rodents [49, 50], conspecific social partners' urine odor alone is not sufficient to promote positive affiliative social reward which requires the full spectrum of odors from the conspecific social partner.

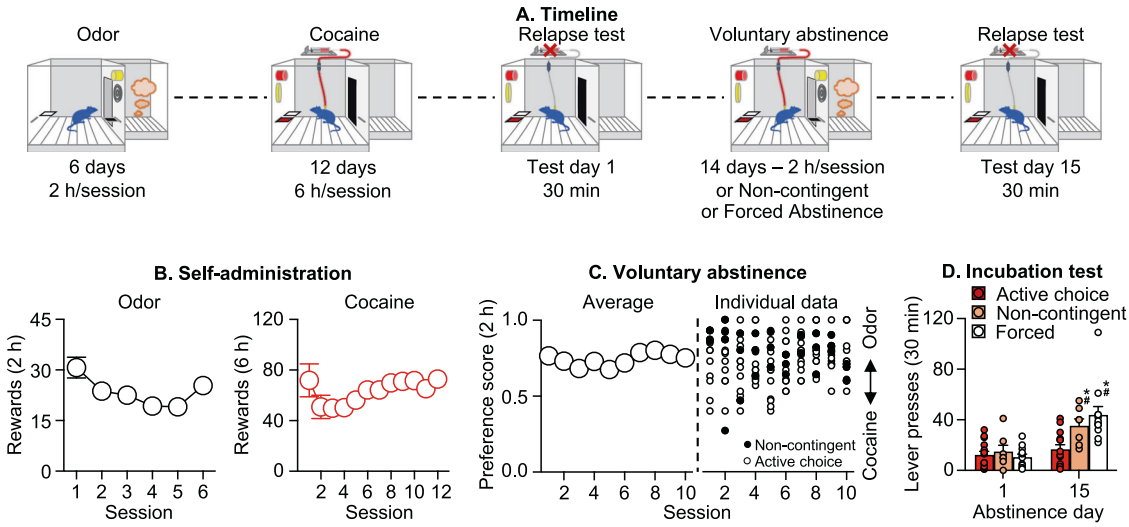


**Fig. 5 Active odor preference prevents incubation of cocaine craving. A** Timeline of the experiment. **B** Left: Odor self-administration. Number of odor (2 h) rewards over 5 sessions. Right: Cocaine self-administration. Number of cocaine (6 h) rewards over 12 sessions. **C** Voluntary abstinence. Left: Average preference score (number of odor rewards / [number of odor reward + number of cocaine infusions]). Right: Individual data for preference scores: closed circles depict rats' behavior used to yoke the deliveries of cocaine and odors for the non-contingent group, while open circles represent preference scores for the active choice group. 0 indicates preference for cocaine; 1 indicates preference for odor reward over 10 sessions. **D** Incubation test. Active-lever presses during the 30-min test sessions. During testing, active-lever presses led to contingent presentation of the light cue previously paired with cocaine infusions during training, but not cocaine or odor delivery or exposure (extinction conditions). * Different from active lever on test day 1. # Different from active lever from the active-choice voluntary abstinence group on test day 15. Active-choice voluntary abstinence $n = 14$ (12 males, 2 females); non-contingent abstinence $n = 7$ (4 males, 3 females); Forced abstinence $n = 12$ (10 males, 2 females). Data are mean ± SEM.

### How does the preference for social odors prevents cocaine choice and craving?

Both olfactory sensory modalities and social odors play a crucial role in promoting voluntary abstinence from cocaine self-administration and the active preference for social odors over cocaine prevents incubation of cocaine craving. We brought to light the overlooked impact of olfaction and social olfactory cues, which may have played a significant role in the limited applicability of classical animal models for translation to human studies [44]. The specific effects observed regarding cocaine highlight the distinct and targeted influence of social odors on the relationship between social reward and drug-seeking behaviors. We have previously demonstrated that preference for a social partner prevents drug craving [30]. Notably, our findings challenge this notion by revealing that a two-week period of volitional odor-mediated voluntary abstinence effectively prevented cocaine craving in the absence of any direct physical social interaction.

An alternative explanation for these results is that the inhibition of the incubation of cocaine craving is a result of some drug exposure during voluntary abstinence. We believe that this alternative is unlikely for several reasons. Our previous findings indicate that even a small drug dose alongside an alternative reward like food sustains high craving during late abstinence, similar to forced abstinence controls [51–53]. When given a choice between heroin and social interaction, exposure to small amount of heroin did not prevent craving, but it was reduced compared to forced abstinence [31]. In line with these points, in Exp. 5 we determine the importance of the odor-based choice procedure in preventing cocaine craving. Specifically, we compared the incubation of cocaine craving under three different conditions: forced abstinence, active choice, and non-contingent. Our results indicate that non-contingent exposure to cocaine and social odor is insufficient to prevent cocaine craving. Thus, by recognizing the intricate interplay between the olfactory sensory system, social odors, and the motivation underlying drug-seeking behaviors, we provided a deeper understanding of the mechanisms involved in the protective effect of social interactions on substance use disorders.

### Could the effects of active odor preference inhibiting drug craving provide insights for human disorders?

It is widely recognized that positive social support, such as the community reinforcement approach or contingency management, can be beneficial in the treatment of substance use disorders [54, 55]. However, concerns have been raised regarding the long-term sustainability of these approaches. Additionally, social support may lack relapse prevention immediacy in situations where one experiences craving without the ability to obtain social support in that moment. The notion that social-based behavioral treatments may not be effective for every patient [56–58] emphasizes the need for new treatments targeting individuals who exhibit lower responsiveness. In this regard, our findings represent a significant potential step toward a novel treatment discovery strategy, as they provide compelling evidence regarding the importance of the active preference for a social odor over cocaine for relapse prevention. The strategy of exposure to pleasant smells has been used successfully to mitigate cigarette cravings in abstinent smokers [27]. Positive social odors competing against abused drugs provide a promising avenue for personalized interventions that establish an association between positive odors and supportive experiences. Therapies such as pairing a specific odor with a positive social support experience group, may allow an immediacy of use of odor, as a proxy for social support by association, by individuals during craving episodes [59, 60].

Our findings have broader implications and can be generalized to several other neuropsychiatric conditions characterized by social and olfactory impairments [18, 61–66]. While the role of olfaction in social recognition and learning in rodents is well-established [67, 68], as well as its facilitation of human perception and behavior [3–8], the potential connection between olfactory and social dysfunction in neuropsychiatric disorders remains understudied. Exploring the motivation to engage in odor-mediated social interactions and neuropsychiatric disorders through translational research could help identify olfactory-based biomarkers for social dysfunction.

## Concluding remarks

We identified the olfactory system and the preference for social odors as critical components contributing to the protective effect of social and odor active preference against drug seeking. We demonstrated the role of the olfactory system in mediating volitional social interaction, cocaine choice and craving in rats. Olfaction represents a potential avenue for using odor-based therapies in the treatment of substance use disorders, and for the discovery of biomarkers for other neuropsychiatric disorders with a component of social dysfunction.

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## AUTHOR CONTRIBUTIONS
KMP, ACP, and MV conceptualized the project; KMP, CAL, and MV designed the experiments and collected the behavioral data; KMP, and MV analyzed the data; KMP, CAL, DC, HP, ACP, LAR, and MV contributed to different aspects of the write-up of the paper.

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## COMPETING INTERESTS
The authors declare no competing interests.

## ADDITIONAL INFORMATION
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