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Role of oxytocin in the ventral tegmental area in social reinforcement

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Abstract

The rewarding properties of social interactions play a critical role in the development and maintenance of social relationships, and deficits in social reward are associated with various psychiatric disorders. In the present study, we used a novel Operant Social Preference (OSP) task to investigate the reinforcing properties of social interactions under conditions of high or low reward value, and high or low behavioral effort in male Syrian hamsters. Further, we investigated the role of oxytocin (OT) in a key structure of the mesolimbic reward system, the ventral tegmental area (VTA), in mediating the reinforcing properties of social interaction. Adult male hamsters were placed in a three-chambered apparatus, and allowed access to either a social chamber containing an unrestrained conspecific or a non-social chamber, by pushing through a one-way entry, vertical-swing door. Increasing the duration of social interaction (reward value) decreased the frequency of entering the social interaction chambers, whereas decreasing the duration of social interaction conversely increased the frequency of entries. Moreover, increasing behavioral effort required to access social interaction decreased the frequency of entries, especially under conditions when the duration of social interaction was only 5 s. OT injected into the VTA decreased the frequency of entering social interaction chambers in a manner similar to that observed when duration was increased, whereas injection of an OT receptor antagonist in the VTA increased the frequency of seeking social interaction. Taken together, these data support the hypothesis that activation of OT receptors in the VTA are critical for the reinforcing properties of social interactions. Furthermore, social interactions may exhibit duration and cost dependent reinforcing effects on behavior similar to those observed with food and drugs of abuse.

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Contributors

Borland designed and conducted all experiments, analyzed the data, and also wrote the first draft of this manuscript. Aiani and Grantham participated in conducting the experiments and scored behavior. Albers and Frantz supervised all aspects of the study, especially experimental design, data analysis, and preparation of the submission.

Conflict of interest

The authors declare no conflicts of interest.

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/ S0306-4530(18)30086-6

Keywords

Social behavior; Social interaction; Social motivation; Social salience; Social cognition; Social reward; Dopamine; Mesolimbic dopamine system; Neuropeptides; Vasopressin; Operant

1. Introduction

Social reward is a critical element in the development, expression, and maintenance of social behaviors and relationships (Suomi et al., 1971; Krach et al., 2010; Trezza et al., 2011). Despite the importance of social reward in adaptive and maladaptive behaviors, much remains to be learned about the reinforcing properties of social interaction and the neurobiological mechanisms underlying its rewarding properties. Various types of social interactions can serve as behavioral reinforcers (Everitt et al., 1987; Lee et al., 2000; Matthews et al., 2005; Trezza et al., 2011). To extend our ability to investigate social reward and reinforcement, we developed a new operant social preference (OSP) task for Syrian hamsters (Borland et al., 2017), a species in which social interactions are highly rewarding (Meisel and Joppa, 1994; Gil et al., 2013) and which serves as an important model for pre-clinical studies of psychiatric disease (Terranova et al., 2016). Hamsters are provided the choice to push through a vertical swing door into a chamber for brief social interaction, push into an empty chamber, or remain in a start chamber. As in other new operant social tasks (Cummings and Becker, 2012; Achterberg et al., 2016; Golden et al., 2017), animals demonstrated a preference for the social chamber within 2–3 test sessions, in a manner similar to preference for access to reward of a different modality, palatable food (sunflower seeds) (Borland et al., 2017). With this novel method, the parameters and neural underpinnings for behavioral reinforcement by social reward can be examined in great depth.

In the present study, we aimed to test the effects of both reward *value* and behavioral *cost* on the reinforcing effects of social interactions. Specifically, we investigated whether the duration of social interactions between adult males alters the motivating and reinforcing properties of those interactions. Because studies investigating the rewarding properties of other stimuli (e.g., drugs) have found that increasing reward value (e.g., dose) decreases the number of rewards obtained in a test session (Maldonado et al., 1993; Doherty et al., 2013), we predicted that increasing the duration of social interaction would decrease the frequency of seeking social interaction. Conversely, decreasing the duration of social interaction would increase the frequency of seeking social interaction. Moreover, based on behavioral economics and progressive ratio schedules of reinforcement in drug and food reinforcement studies (e.g. (Rowlett, 2011; Beeler et al., 2012; Doherty and Frantz, 2012; Bentzley et al., 2014), we also predicted that increasing the behavioral cost (i.e., weight of an access door) to gain access to social interaction would decrease the frequency of seeking social interactions in a test session, especially when the duration of social interaction was relatively short. As such, the present study investigates whether the relationships between reward value (i.e. duration of interaction) and the effort required (i.e. weight on the vertical swing door) to obtain rewards are similar to those reported for other rewarding stimuli (e.g., drugs of abuse).

In a second set of experiments, we investigated the role of oxytocin (OT) in mediating the reinforcing properties of social interactions. OT is a neuropeptide that influences many different social processes and behaviors (Caldwell and Albers, 2016; Johnson and Young, 2017), including play behavior (Bredewold et al., 2014), social recognition (Albers, 2012; Wacker and Ludwig, 2012), and aggression (Harmon et al., 2002; Kelly and Goodson, 2014). Studies in humans also support a role for OT in regulating social behavior (Groppe et al., 2013; Rilling et al., 2014), and OT has been proposed as a potential treatment for a range of psychiatric disorders including autism spectrum disorder (Dichter et al., 2012; Stavropoulos and Carver, 2013; Young and Barrett, 2015). Because of the strong link between deficits in social reward and psychiatric disorders, understanding how OT contributes to the neural mechanisms controlling social reward is a critical gap in current knowledge.

OT administered peripherally or in the cerebroventricular system can increase reward in the context of conditioned place preference models (CPP) (Liberzon et al., 1997; Kent et al., 2013; Kosaki and Watanabe, 2016). These effects may be mediated by OT in the mesolimbic reward system. Activation of oxytocin receptors (OTRs) in the nucleus accumbens appears necessary for social reward in male mice (Dolen et al., 2013), and activation of OTRs in the ventral tegmental area (VTA) also appears necessary for social reward in male hamsters and mice (Song et al., 2016; Hung et al., 2017). Yet in these studies, the possibility that activation of OTRs influences the memory of the reward stimulus instead of the reward value itself cannot be excluded (Bardo and Bevins, 2000). Indeed, OT can influence memory processes in general and social memory in particular (de Wied and Versteeg, 1979; Albers, 2012; Gabor et al., 2012). Therefore, we used a direct test of social reinforcement, per se, with the operant social preference task, focusing on the role of OTRs in the VTA. We predicted that if activation of OTRs in the VTA mediates the reinforcing properties of social interactions, then injection of OT into the VTA will decrease the frequency of seeking social encounters, whereas injection of an OTR antagonist will increase the frequency of seeking social encounters.

2. Materials and methods

2.1. Subjects

Male Syrian hamsters (N = 73, 11 wks of age; 120–140 g) were purchased from Charles River Laboratory (Wilmington, MA) and housed singly, in solid-bottom, Plexiglas cages (43 × 22 × 20 cm), containing corncob bedding and cotton nesting material (Neslets; Ancare, Bellmore, NY) in a humidity and temperature controlled (22 °C) vivarium. Hamsters were provided food and water *ad libitum*, and housed on a reverse light-dark (LD) cycle (14L: 10D; lights off at 13:00) for 4 weeks before experiments. All behavioral tests were performed under red light during the first 3 h of the dark phase. All procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and approved by the Georgia State University Institutional Animal Care and Use Committee.

2.2. Operant social preference (OSP) apparatus

For a detailed description of the OSP apparatus, see (Borland et al., 2017). Briefly, the test apparatus consisted of three chambers: a main chamber, and two smaller chambers, each separated from the main chamber by one-way entry vertical-swing doors equipped with buckets that can hold weights (Fig. 1). Test and stimulus hamsters can be placed in any of the chambers. The entire apparatus is made of clear Plexiglas with an open top, allowing detection of visual, olfactory and auditory cues among the chambers, thereby reducing memory requirements in the choice of whether or not to enter through the swing doors, e.g. to interact with a conspecific.

2.3. Operant social preference (OSP) conditioning

For a detailed description of conditioning sessions, see (Borland et al., 2017). Briefly, male test hamsters (120–140 g) were allowed to move throughout the apparatus, while a smaller (100–120 g) male stimulus hamster was confined to one of the small chambers. Stimulus hamsters were group-housed five per cage, and subjects were paired with a different stimulus hamster every test session. If a subject chose to enter a small chamber, time allowed in that chamber was either 20 s (baseline), 5 s, or 60 s. After the designated time course expired, the subject hamster was removed from the small chamber by the experimenter and placed back into the main chamber, facing the back wall, equidistant from the two small chambers. All test sessions were 10 min in total length. To assess chamber entries under higher effort requirements after conditioning sessions, door weights were progressively increased over consecutive days, from baseline at 113 g (4oz), to 227 g (8oz), 340 g (12oz), 454 g (16oz) and 624 g (22oz). Only subjects that met acquisition criteria (at least 2 entries into chambers containing stimulus hamsters per session and more entries into social chambers vs. non-social chambers, for at least 2 consecutive test sessions) were included in the analysis.

2.4. Behavioral scoring

All behavioral tests were video recorded (Panasonic-WVCP294) and analyzed using the Noldus Observer system (11.5, Leesburg, VA). A scorer blind to treatments scored each videotape for the following measures: the number of entries into chambers, latency to enter chambers (first latency and subsequent latencies, i.e. post reinforcement pause), social preference score (entries into chambers containing stimulus hamsters – entries into non-social chambers), and social entries per minute (number of social entries divided by the total time spent in the main chamber). Post reinforcement pause was calculated as the time to re-enter chambers containing stimulus hamsters or non-social chambers respectively once subjects are returned to the main chamber. The quality of social interaction was also scored: duration of aggression, social investigation, submission (e.g. fleeing, avoidance), grooming, and non-social behavior were considered mutually exclusive, and the proportions of time spent in each were calculated. The frequency of attacks was calculated based on point events during displays of aggression, and flank marks were scored as point events during non-social behavior. Flank marks were scored due to their strong link to dominance status and territoriality in rodents (Ferris et al., 1987; Terranova et al., 2017). For operational definitions of these behaviors, see (Drickamer et al., 1973; Gray et al., 2015). Locomotor

activity was also scored as the number of entries into any of the six equal-sized squares (16.9 × 16.5 cm) into which the OSP apparatus was subdivided for analysis.

2.5. Stereotaxic surgery

Hamsters were anesthetized with isofluorane (induced at 5% and maintained at 2–4%), a 4 mm 26-gauge cannula was implanted unilaterally and was aimed at the VTA (from bregma; anteroposterior (AP) −3.80 mm; mediolateral (ML) + 0.55 mm; dorsoventral (DV) −3.20 mm; 0° angle). Previous studies investigating the effects of OT in the VTA on social reward have also used unilateral injections (Song et al., 2016; Hung et al., 2017). All hamsters were injected subcutaneously with the anti-inflammatory agent, ketoprofen (5 mg/kg), and were allowed to recover for at least 4–6 days prior to behavioral testing.

2.6. Intra-VTA drug treatment

Microinjections were administered using a 12 mm, 32-gauge needle attached to a 1 μl Hamilton syringe that extended an additional 4.2 mm beyond the cannula to a final depth of 7.4 mm below the skull surface. Drug was delivered in a volume of 200 nl at a rate of 0.400 μl per min using an infusion pump (Harvard Apparatus, Holliston, MA). The needle was left in place for an additional 30 s to allow diffusion away from the tip of the injection needle. Approximately 5 min after micro-injection, hamsters were tested in the OSP apparatus. The drugs used were oxytocin (Bachem, CA, USA) dissolved in sterile saline to a final concentration of 9 μM or 90 μM; and desGly-NH_2-d$(CH_2)_5$[DTyr2,Thr4]OVT, a highly selective OTR antagonist (Manning et al., 2012; gift from Dr. Maurice Manning), dissolved in sterile saline to a final concentration of 0.9 μM or 9 μM. Drug doses were based on previous studies indicating effects on social CPP in Syrian hamsters (Song et al., 2014, 2016).

2.7. Histology

Within 24 h of the final behavioral tests, hamsters were euthanized with a lethal dose of sodium pentobarbital (0.25 ml, i.p. Henry Schein Animal Health, Dublin, OH), and 200 nl of India Ink was microinjected through the guide cannula to mark the injection site. Hits were categorized if ink was seen within the caudal VTA, referenced to the hamster stereotaxic atlas (Morin and Wood, 2001).

2.8. Experimental design and statistical analysis

Data were analyzed using SPSS software (SAS Institute, 23.0 for Windows). All data were examined to determine if the assumptions of parametric statistical tests were met (normality, equal variance, sphericity). When assumptions were violated, data were cube-root transformed (Exp. 1 the latency to re-enter chambers, Exp. 2 the number of entries into chambers, social preference score, social entries per minute in main chamber score, Exp. 3 the duration of grooming and the number of flank marks). All tests were two-tailed, and results considered statistically significant if $p \leq 0.05$. All data are presented as mean ± standard error of the mean.

2.8.1. Experiment 1: effect of the duration of social interactions on social preference—

After stable acquisition of a social preference (more entries into the chamber containing a social stimulus vs. the non-social chamber) at 113 g door weights and 20 s per entry, subjects (n = 11) experienced different duration conditions: 5, 20 (baseline) or 60 s in chambers per entry. Door weights were maintained at 113 g. Assignment of duration was counter-balanced within-subjects, such that each subject experienced each duration for one session. A repeated measures one-way ANOVA was carried out to examine effect of the duration of social interaction on behavior. Two subjects failed to meet acquisition criteria.

2.8.2. Experiment 2: interaction between duration of chamber exposure and door weights on social preference—

After stable acquisition of a social preference at baseline duration (20 s) and door weights (113 g), subjects were assigned to experience 5 (n = 9) or 60 (n = 8) sec in chambers after every entry into social interaction and non-social chambers. The weights on doors were progressively increased over 5 consecutive days to 113 g (4 oz), 227 g (8 oz), 340 g (12 oz), 454 g (16 oz) and 624 g (22 oz). A 2 × 5 mixed measures, between-within ANOVA was carried out to test the effects of the duration of social interaction and the weights of the doors on behavior. Binomial distributions were also carried out to test for the effects of the duration of social interaction on the ability to successfully achieve entries into chambers versus not during a test session. Binomial distributions were compared by calculating z scores (test statistic). All subjects met acquisition criteria.

2.8.3. Experiment 3: effect of OT or OTR antagonist in the VTA on social preference—

After stable acquisition of a social chamber preference, subjects were surgically implanted with a guide cannula aimed at the caudal VTA. Subjects received injections of saline, 9 μM OT (n = 18), and 90 μM OT (n = 14) in a counter-balanced order: other subjects received saline, 0.9 μM OTR antagonist, and 9 μM OTR antagonist (n = 14) in a counter-balanced order. Injections and behavior testing occurred over 3 consecutive days. Since the high dose of OT (90 μM) resulted in secondary behavioral effects (flank marking and grooming), subjects received injections of only saline or the low dose of OT (9 μM) in subsequent experiments. In this experiment, subjects experienced 20 s in small chambers per entry and door weights were 113 g. Paired sample t-tests were carried out to examine drug effects on behavior (saline versus specific drug treatments). Nine subjects had cannulas outside the caudal VTA and were not included in the analysis. Four subjects did not meet acquisition criteria.

3. Results

3.1. Experiment 1: effect of duration of social interactions on social preference

The duration of social interactions influenced the number of entries into the social chambers (i.e., chambers containing a stimulus hamster), according to a main effect of duration ($p < 0.001$, $F(220) = 25.278$) (Fig. 2a). Specifically, 20 s of social interactions following entry decreased the number of entries into chambers containing stimulus hamsters, compared to 5 s of social interaction ($p = 0.050$; 5 s 6.227 +/−0.740; 20 s 5.091 +/−0.653). Furthermore, 60 s of social interaction decreased the social chamber entries, compared to 20 s ($p = 0.001$; 60

sec 1.909 +/−0.241). On the other hand, the duration in stimulus chambers had no effect on the number of entries into the non-social chambers ($p = 0.525$, $F(220) = 0.665$; Fig. 2a). As expected, there were no differences in the latency to the first entry into chambers in groups assigned to different durations of time in the chambers containing a social stimulus ($p = 0.482$; $F(220) = 0.600$) or to groups assigned to different durations of time in non-social chambers ($p = 0.398$; $F(220) = 0.966$) (Fig. 2b). There was, however, a significantly shorter latency to the first entry into chambers containing a stimulus hamster compared to the latency to the first entry into non-social chambers ($p = 0.002$; $F(120) = 16.667$) (Fig. 2b inset).

The duration of social interactions influenced the social preference score, according to a main effect ($p = 0.001$, $F(220) = 11.347$) (Fig. 2c). Pairwise comparisons revealed that 60 s interactions decreased social preference scores compared to 20 s interactions ($p = 0.010$: 60 s 1.045 +/−0.396; 20 s 4.000 +/−0.874) or 5 s interactions ($p < 0.001$; 5 s 4.773 +/−0.651), but no difference in social preference scores occurred between 5 s and 20 s social interactions ($p = 0.385$). An important caveat to the design of this experiment is that although the test session was 10 min in length for all subjects, subjects that spent 60 s in chambers per entry spent less time in the main chamber, and thus had fewer opportunities to enter small chambers compared to subjects that spent 5 s in chambers per entry. To control for differences in time spent in the main chamber, social entries per minute in the main chamber scores were calculated. The number of entries into chambers with stimulus hamsters a subject made during the test session was divided by the time over which each subject had to choose to enter one or the other small chamber, i.e. time spent in the main chamber. Results were the same as the raw frequency scores, such that the duration of social interaction had a main effect on social entries per minute score ($p < 0.001$, $F(220) = 13.444$; Fig. 2d). Pairwise comparisons revealed that when subjects spent 60 s in chambers there was a slower rate of entering chambers containing stimulus hamsters (i.e., number of entries per minute) compared to when subjects had social interactions for 20 s ($p = 0.005$; 60 s 0.278 +/−0.044) or 5 s ($p = 0.001$). However, there was no difference in rate of entry into chambers containing stimulus hamsters between conditions in which subjects experienced 5 s and 20 s in chambers ($p = 0.895$; 5 s 0.672 +/−0.085; 20 s 0.663 +/−0.102).

Next, we examined whether the duration of time spent in the chambers had an effect on the latency to re-enter chambers following the first and second entries (first and second post reinforcement pauses). Spending 60 s in the chambers containing stimulus hamsters increased the latency to re-enter the social chambers ($p = 0.003$, $F(220) = 8.080$) compared to spending 20 s ($p = 0.033$) and 5 s ($p = 0.007$) in the chambers (Fig. 3a). Spending 60 s in the chambers containing stimulus hamsters also increased the second post reinforcement pause ($p = 0.012$, $F(212) = 6.484$) compared to spending 20 s ($p = 0.010$) in the chambers. The duration of time in the chambers had no effect on the latency to re-enter the non-social chambers ($p > 0.05$). Overall, increasing the duration of time spent in social stimulus chambers to 60 s increased the latency to enter those chambers, compared to 5 or 20 s durations in the social chambers.

Finally, we explored the quality of social interactions in the social chambers, specifically by considering whether the duration of the time spent in the social chambers per entry

influenced the nature of the interaction. The duration in the social chambers did affect the proportion of time spent in social investigation ($p = 0.014$, $F(220) = 5.327$); such that the proportion of time spent in social investigation was lower in the 60 s condition group compared to the 20 s condition group ($p < 0.001$) (Fig. 3b). On the other hand, time in the social chambers had no effect on the proportion of time displaying aggression ($p = 0.294$, $F(220) = 1.301$) nor the frequency of attacks ($p = 0.166$, $F(220) = 1.966$). The 60 s condition group did spend more time grooming ($p = 0.032$) and displayed a higher rate of flank marking ($p = 0.017$) (Fig. 3c) compared to the 20 s condition group when in the main chamber.

3.2. Experiment 2: interaction between duration of social interaction and behavioral cost on social preference

Because a decrease in the frequency of the number of rewards obtained could be interpreted as either an increase in reward value (fewer rewards needed to reach satiety) or a decrease (less motivation for reward), we investigated the effects of varying the behavioral cost of obtaining the reward on social preference between the two reward durations (i.e., 5 or 60 s of social interaction) to help discriminate between these alternative interpretions. While all hamsters entered the chambers containing stimulus hamsters when the door weighed 113 g or 227 g, significantly fewer hamsters entered the social chambers at least once as the door weights increased (z score = 4.246, $p < 0.001$) (Fig. 4a). Interestingly, however, and consistent with the possibility that a longer duration in the social chambers is more rewarding, significantly more hamsters in the 60 s group entered the social chamber at least once in the session compared to the 5 s duration group (z score = 1.917, $p = 0.027$) (Fig. 4a). An interaction between the duration of social interaction and the weight of the entry door (i.e., behavioral cost) on the total number of entries into social chambers was also observed ($p = 0.005$, $F(460) = 4.132$) (Table S1). Progressively increasing the weight of the door decreased social entries when the duration in the chambers was 5 s, such that 227 g ($p = 0.002$), 340 g ($p = 0.002$), 454 g ($p < 0.001$), and 624 g ($p < 0.001$) all resulted in fewer entries than at baseline (113 g). However, when the duration in stimulus chambers was 60 s, only the three heaviest weights (i.e., 340 g ($p = 0.030$), 454 g ($p = 0.019$) and 624 g ($p < 0.001$)) significantly decreased the number of social chamber entries below baseline (113 g) (Fig. 4b). The duration of social interaction interacted with weight of the door to influence social preference score as well ($p = 0.006$, $F(460) = 3.996$) (Fig. 4c) (Table S2). For subjects that experienced 5 s in chambers, all door weights decreased social preference score (227 g ($p = 0.028$), 340 g ($p = 0.003$), 454 g ($p < 0.001$), and 624 g ($p < 0.001$)). However, for subjects that received 60 s in chambers, only the heaviest door weight (624 g) was effective ($p = 0.021$) in decreasing the social preference score (Fig. 4c). With regard to social chamber entries per minute in the main chamber, duration of social interaction and door weight also interacted to influence outcomes ($p = 0.049$, $F(460) = 2.540$). For subjects that were allowed 5 s social interactions, all heavier weights decreased the social chamber entries per minute: 227 g ($p = 0.003$), 340 g ($p = 0.001$), 454 g ($p < 0.001$), 624 g ($p < 0.001$). However, for subjects that received 60 s social interactions, only 340 g ($p = 0.030$), 454 g ($p = 0.018$) and 624 g ($p = 0.001$) door weights decreased the social chamber entries per minute (Fig. 4d).

To examine the relationship between the number of entries into social chambers and door weights, simple linear regressions were calculated. Social entries correlated negatively with door weights, both for subjects allowed 5 s social interactions ($F(1,3) = 22.516$, $p = 0.018$; R^2 of 0.882) and those allowed 60 s social interactions ($F(1,3) = 29.727$, $p = 0.012$; R^2 of 0.908). Comparison of slopes between the 5 and 60 s condition correlations revealed a z score of 3.638 ($p < 0.001$). Thus, the rate at which increasing the weight of the chamber doors (behavioral cost) decreased the number of entries (rewards acquired) was greater in 5 s social interaction conditions, compared with 60 s interaction conditions (Fig. 4e). There was no correlation between door weights and entries into the non-social chambers for 5 s group ($p = 0.229$, $R^2 = 0.430$) nor the 60 s group ($p = 0.413$, $R^2 = 0.069$).

3.3. Experiment 3: effect of OT and OTR antagonist injected into the VTA on social preference

OT (9 μM or 90 μM) injected into the caudal VTA decreased the number of entries into chambers containing stimulus hamsters, compared to saline ($p < 0.001$, $t(17) = -4.389$; 9 μM OT 3.11 +/−0.411, saline 4.67 +/−0.524; $p = 0.041$, $t(13) = -2.271$; 90 μM OT 2.21 +/−0.793, saline 3.86 +/−0.443; Fig. 5a). Conversely, injections of 0.9 μM or 9.0 μM OTR antagonist into the VTA increased the number of entries into chambers containing stimulus hamsters ($p = 0.006$, $t(13) = 3.214$; 0.9 μM OTR antagonist 5.33 +/−0.52, saline 3.87 +/−0.60; $p = 0.119$, $t(13) = 1.669$; 9.0 μM OTR antagonist 5.00 +/−0.94; Fig. 5b). Neither OT nor the OTR antagonist affected the number of entries into non-social chambers ($p > 0.050$; Table S3). Although not statistically significant, comparisons of the latency to re-enter the chamber containing the stimulus hamsters tended to be longer for hamsters given 9 or 90 μM OT compared to saline controls $p = 0.132$, $t(7) = 1.706$; Fig. 6a), whereas hamsters given the OTA at 0.9 and 9 μM trended towards shorter re-entrance latencies than saline controls ($p = 0.096$, $t(11) = -1.822$; Fig. 6b).

Neither OT nor the OTR antagonist affected social investigation or aggression (proportion of time displaying social investigation and aggression (Fig. 7a and b)) nor the rate of attacks per minute (Fig. 7c, e). There was a trend for the 90 μM concentration of OT to increase the duration of grooming ($p = 0.066$, $t(11) = 2.042$; OT 80.8 +/−34.5, saline 32.5 +/−11.8), but there was no effect of the OTR antagonist on these behavioral measures compared to saline (Fig. 7d and f). The 90 μM concentration of OT increased the number of flank marks observed ($p = 0.043$, $t(11) = 2.288$; OT 12.17 +/−4.78, saline 2.25 +/−0.94), although the OTR antagonist had no effect compared to saline (Fig. 7g, and i). The 0.9 μM concentration of the OTR antagonist significantly increased the amount of locomotor activity ($p = 0.021$, $t(13) = 2.595$; OTR antagonist 120 +/−7, saline 102 +/−7) compared to saline. There was also a trend for the 9 μM concentration of the OTR antagonist to increase the amount of locomotor activity ($p = 0.061$, $t(13) = 2.047$; OTR antagonist 118 +/−11) compared to saline (Fig. 7h).

Histological analysis of injection sites, which can be seen in Fig. 8, revealed 9 subjects for which injections were outside the caudal VTA. No drug effects were observed among the nine hamsters for which injection sites were found to be outside of borders of the caudal VTA (data not shown).

4. Discussion

From the present findings that increasing the duration of time allowed in the stimulus chambers decreases the number of entries and increases the latency to re-enter those chambers (post reinforcement pause), we infer a more general conclusion that this operant social preference task reveals the expected relationship that increasing reward value decreases the number of rewards obtained. We interpret the findings that increasing the weights on the doors decreases the number of entries into chambers containing a stimulus hamster, as an indicator that increasing behavioral effort required to obtain rewards will decrease the number of rewards obtained. Moreover, reward value and behavioral effort interacted in predictable ways, such that the influence of behavioral cost was greater in conditions of lower reward value than higher reward value. Finally, the present results also supported a role for OT within the VTA in these relationships. OT injected into the caudal VTA decreased the number of entries into chambers containing stimulus hamsters, and did so in the same manner as increasing the duration of time in the stimulus chambers. Conversely, an OTR antagonist injected into the VTA increased the number of entries into chambers containing stimulus hamsters, in the same manner as decreasing the time in the stimulus chambers. There was also a trend that OT increased the latency to re-enter social chambers and that the OTR antagonist reduced the latency to re-enter chambers.

In general, none of the manipulations of reward value, behavioral effort, or neural activity affected entries into non-social chambers. The effects of OT and the OTR antagonist on other behaviors were not statistically significant except that the high concentration of OT induced flank marking and increased the duration of grooming; an effect that may be due to the activation of arginine-vasopressin V1a receptors (Song and Albers, 2017). This is particularly interesting considering that there was also an increase in the proportion of time spent flank marking and grooming in the main chamber for subjects that experienced 60 s of interaction per entry. There was also a decrease in the proportion of time spent socially investigating the stimulus hamster for subjects that experienced 60 s of interaction. However, these effects may be due to differences in the total time in the main chamber versus social interaction chamber between the different duration conditions. In other words, although there was a decrease in the proportion of time spent per entry socially investigating for subjects that experienced 60 s of interaction, the total time spent socially investigating was greater compared to subjects that experienced 20 s and 5 s. Subjects that experienced 60 s in the chambers per entry spent on average 120 s in the social interaction chambers per test session, while subjects that experienced 20 s spent on average 60 s in the social chambers, and the 5 s group spent on average only 30 s in the social chambers. Likewise, the increase in the proportion of time spent grooming and flank marking may be due to a decrease in the total time.

We also found that OTR inactivation in the VTA increases locomotor activity. Previous studies have reported similar effects of OTR activation and inactivation in the substantia nigra in male and female rats (Angioni et al., 2016; Leong et al., 2016). However, the OTR antagonist did not increase the number of entries into the non-social chamber. To our knowledge, this is the first study to show that OT injected into the VTA is sufficient to modulate the value of social reward in a behavioral reinforcement paradigm, or that OTR

activation in the VTA is critical for normal expression of such behaviors. Furthermore, OT's effects on social reward are likely due to activation of OTRs and not V1aRs in the VTA (Song et al., 2016). Taken together, these data support the hypothesis that OT in the VTA regulates social reward and reinforcement.

The operant task used in the present study provides a rich set of dependent measures of reward and motivation including the number of entries into chambers, the first latency to enter chambers, subsequent latencies to re-enter chambers and chamber preference score (Borland et al., 2017). Also unique to this operant task, adding weights to the doors provides a powerful approach for increasing the behavioral cost to access a social stimulus. Finally, the simplicity of the apparatus and utility of the two small chambers can support a myriad of economic decision models for the study of social motivation or other rewarding modalities.

A main goal of this study was to determine whether the same experimental parameters regulate social reinforcement in this operant social preference task, as influence drug and food reinforcement in classic drug and food self-administration studies. Both our prior report and the present results suggest that they do. In (Borland et al., 2017), we noted palatable food (sunflower seeds) reinforces entries into chambers to a similar intensity as social interactions, and removal of the social stimulus decreases entries into chambers. Here, we demonstrate further that when the social stimulus is present, there is an inverse relationship between duration of social interaction and frequency of entries into social chambers. Indeed, substantial evidence demonstrates an inverse relationship between reward value and reward consumption (e.g. cocaine dose and cocaine infusions) (Maldonado et al., 1993; Veeneman et al., 2012; Doherty et al., 2013). We also report a direct relationship between duration of social interaction and post reinforcement pause (latency to re-enter social interaction chamber). Additional studies over many decades have demonstrated the inverse relationship between behavioral cost and reward consumption as well (Salamone et al., 2009; Bentzley et al., 2013). Furthermore, we demonstrate that the correlation between behavioral cost and reward consumption interacts with reward value, such that reward consumption declines at faster rates with increased behavioral cost if the reward value is relatively low. These outcomes fit well with models of behavioral elasticity (Salamone et al., 2009; Rowlett, 2011), all of which stem from interpretations based in behavioral economics.

Finally, injections of OT or OTR antagonist into the VTA produce results similar to classic manipulations of dopamine signaling in the mesolimbic circuitry. For example, administration of a dopamine antagonist (SCH 23,390) into the nucleus accumbens, amygdala or striatum increased cocaine self-administration (Maldonado et al., 1993; Caine et al., 1995). At certain concentrations, dopamine perfusate in the nucleus accumbens decreases cocaine self-administration (Hurd and Ponten, 2000). Enhancement of OT signaling by direct OT administration to VTA appears similar to enhancing dopamine transmission, whereas blocking OT receptors produced results similar to blocking dopamine transmission. For example, OT injected into the caudal VTA decreased sucrose consumption, while an OTR antagonist injected into the caudal VTA increased sucrose consumption in rats (Mullis et al., 2013). Notably, experimental conditions that decrease the number of rewards obtained in an operant task can be interpreted as an increase or a decrease in reward value, and various schedules of reinforcement are often used to

differentiate between these possibilities. Although in the present study we provide evidence that the reduction in operant responding resulting from OT administion in the VTA is consistent with an increase in social reward value, others have interpreted similar effects of OT as reducing reward value (Peters et al., 2017). Future studies using various schedules of reinforcement could be used to help discriminate between these interpretations. Together, our results suggest that activation of OTRs in the VTA modulates reward value to influence reinforced behavior in this social preference task.

Although beyond the scope of the present experiment, circuit analyses suggests that inputs from OT-containing neurons in the paraventricular nucleus into the VTA may be critical for social reward in adult male mice (Hung et al., 2017). Furthermore, projections from the VTA to the nucleus accumbens regulate social behavior (Gunaydin et al., 2014). In terms of mechanisms by which OT influences dopamine transmission in this pathway, OT receptors are located on dopamine and glutamate-containing neurons in mice (Peris et al., 2017) and injections of OT in the caudal VTA increased extracellular dopamine in the nucleus accumbens (Melis et al., 2007).

In conclusion, these data support the hypothesis that OT can enhance social reward (Groppe et al., 2013; Feng et al., 2015; Chen et al., 2017) via activity in the mesolimbic dopamine system (Melis et al., 2007), consistent with clinical research. Furthermore, economic demand models of motivation can serve as important tools for identifying promising addiction treatments (Bentzley et al., 2014), such as OT administration (Cox et al., 2017). As such, drugs that activate OTRs and thereby modulate social motivation may represent an approach that will contribute to the development of new treatments for psychiatric and mental health disorders (Meyer-Lindenberg et al., 2011; McGregor and Bowen, 2012; Caldwell and Albers, 2016), such as Autism Spectrum Disorder (Stavropoulos and Carver, 2013; Gordon et al., 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Achterberg EJ, van Kerkhof LW, Servadio M, van Swieten MM, Houwing DJ, Aalderink M, Driel NV, Trezza V, Vanderschuren LJ, 2016 Contrasting roles of dopamine and noradrenaline in the motivational properties of social play behavior in rats. Neuropsychopharmacology 41, 858–868. [PubMed: 26174597]

Albers HE, 2012 The regulation of social recognition, social communication and aggression: vasopressin in the social behavior neural network. Horm. Behav 61, 283–292. [PubMed: 22079778]

Angioni L, Cocco C, Ferri GL, Argiolas A, Melis MR, Sanna F, 2016 Involvement of nigral oxytocin in locomotor activity: a behavioral, immunohistochemical and lesion study in male rats. Horm. Behav 83, 23–38. [PubMed: 27189764]

Bardo MT, Bevins RA, 2000 Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology 153 (3), 1–43. [PubMed: 11255919]

Beeler JA, Frazier CR, Zhuang X, 2012 Putting desire on a budget: dopamine and energy expenditure, reconciling reward and resources. Front. Integr. Neurosci 6 (49).

Bentzley BS, Fender KM, Aston-Jones G, 2013 The behavioral economics of drug self-administration: a review and new analytical approach for within-session procedures. Psychopharmacology 226, 113–125. [PubMed: 23086021]

Bentzley BS, Jhou TC, Aston-Jones G, 2014 Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat. Proc. Natl. Acad. Sci. U.S. A 111, 11822–11827. [PubMed: 25071176]

Borland JM, Frantz KJ, Aiani LM, Grantham KN, Song Z, Albers HE, 2017 A novel operant task to assess social reward and motivation in rodents. J. Neurosci. Methods 287, 80–88. [PubMed: 28587895]

Bredewold R, Smith CJ, Dumais KM, Veenema AH, 2014 Sex-specific modulation of juvenile social play behavior by vasopressin and oxytocin depends on social context. Front Behav Neurosci 8 (216).

Caine SB, Heinrichs SC, Coffin VL, Koob GF, 1995 Effects of the dopamine d-1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. Brain Res 692, 47–56. [PubMed: 8548319]

Caldwell HK, Albers HE, 2016 vasopressin, and the motivational forces that Drive social behaviors. Curr. Topics Behav. Neurosci 27 (5), 1–103.

Chen X, Gautam P, Haroon E, Rilling JK, 2017 Within vs. Between-subject effects of intranasal oxytocin on the neural response to cooperative and non-cooperative social interactions. Psychoneuroendocrinology 78, 22–30. [PubMed: 28142074]

Cox BM, Bentzley BS, Regen-Tuero H, See RE, Reichel CM, Aston-Jones G, 2017 Oxytocin acts in nucleus accumbens to attenuate methamphetamine seeking and demand. Biol. Psychiatry 81, 949–958. [PubMed: 28110822]

Cummings JA, Becker JB, 2012 Quantitative assessment of female sexual motivation in the rat: hormonal control of motivation. J. Neurosci. Methods 204, 227–233. [PubMed: 22120688]

de Wied D, Versteeg DH, 1979 Neurohypophyseal principles and memory. Fed. Proc 38, 2348–2354. [PubMed: 110623]

Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, Bodfish JW, 2012 Reward circuitry function in autism spectrum disorders. Soc. Cogn. Affect Neurosci 7, 160–172. [PubMed: 21148176]

Doherty JM, Cooke BM, Frantz KJ, 2013 A role for the prefrontal cortex in heroin-seeking after forced abstinence by adult male rats but not adolescents. Neuropsychopharmacology 38, 446–454. [PubMed: 23072838]

Doherty JM, Frantz KJ, 2012 Heroin self-administration and reinstatement of heroin-seeking in adolescent vs. adult male rats. Psychopharmacology 219, 763–773. [PubMed: 21773722]

Dolen G, Darvishzadeh A, Huang KW, Malenka RC, 2013 Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. Nature 501, 179–184. [PubMed: 24025838]

Drickamer LC, Vandenbergh JG, Colby DR, 1973 Predictors of dominance in the male golden hamster (Mesocricetus auratus). Anim. behav 21, 557–563. [PubMed: 4795935]

Everitt BJ, Fray P, Kostarczyk E, Taylor S, Stacey P, 1987 Studies of instrumental behavior with sexual reinforcement in male rats (Rattus norvegicus): I. Control by brief visual stimuli paired with a receptive female. J. Comp. Psychol 101, 395–406. [PubMed: 3691062]

Feng C, Hackett PD, DeMarco AC, Chen X, Stair S, Haroon E, Ditzen B, Pagnoni G, Rilling JK, 2015 Oxytocin and vasopressin effects on the neural response to social cooperation are modulated by sex in humans. Brain Imaging Behav 9, 754–764. [PubMed: 25416642]

Ferris CF, Axelson JF, Shinto LH, Albers HE, 1987 Scent marking and the maintenance of dominant/subordinate status in male golden hamsters. Physiol. Behav 40, 661–664. [PubMed: 3671532]

Gabor CS, Phan A, Clipperton-Allen AE, Kavaliers M, Choleris E, 2012 Interplay of oxytocin, vasopressin, and sex hormones in the regulation of social recognition. Behav. Neurosci 126, 97–109. [PubMed: 22141469]

Gil M, Nguyen NT, McDonald M, Albers HE, 2013 Social reward: interactions with social status, social communication, aggression, and associated neural activation in the ventral tegmental area. Eur. J. Neurosci 38, 2308–2318. [PubMed: 23607682]

Golden SA, Heins C, Venniro M, Caprioli D, Zhang M, Epstein DH, Shaham Y, 2017 Compulsive addiction-like aggressive behavior in mice. Biol. Psychiatry 82, 239–248. [PubMed: 28434654]

Gordon I, Jack A, Pretzsch CM, Vander Wyk B, Leckman JF, Feldman R, Pelphrey KA, 2016 Intranasal oxytocin enhances connectivity in the neural circuitry supporting social motivation and social perception in children with autism. Sci. Rep 6, 35054. [PubMed: 27845765]

Gray CL, Norvelle A, Larkin T, Huhman KL, 2015 Dopamine in the nucleus accumbens modulates the memory of social defeat in Syrian hamsters (Mesocricetus auratus). Behav. Brain Res 286, 22–28. [PubMed: 25721736]

Groppe SE, Gossen A, Rademacher L, Hahn A, Westphal L, Grunder G, Spreckelmeyer KN, 2013 Oxytocin influences processing of socially relevant cues in the ventral tegmental area of the human brain. Biol. Psychiatry 74, 172–179. [PubMed: 23419544]

Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RD, Zalocusky KA, Tye KM, Anikeeva P, Malenka RC, Deisseroth K, 2014 Natural neural projection dynamics underlying social behavior. Cell 157, 1535–1551. [PubMed: 24949967]

Harmon AC, Huhman KL, Moore TO, Albers HE, 2002 Oxytocin inhibits aggression in female Syrian hamsters. J. Neuroendocrinol 14, 963–969. [PubMed: 12472877]

Hung LW, Neuner S, Polepalli JS, Beier KT, Wright M, Walsh JJ, Lewis EM, Luo L, Deisseroth K, Dolen G, Malenka RC, 2017 Gating of social reward by oxytocin in the ventral tegmental area. Science 357, 1406–1411. [PubMed: 28963257]

Hurd YL, Ponten M, 2000 Cocaine self-administration behavior can be reduced or potentiated by the addition of specific dopamine concentrations in the nucleus accumbens and amygdala using in vivo microdialysis. Behav. Brain Res 116, 177–186. [PubMed: 11080549]

Johnson ZV, Young LJ, 2017 Oxytocin and vasopressin neural networks: implications for social behavioral diversity and translational neuroscience. Neurosci. Biobehav. Rev 76, 87–98. [PubMed: 28434591]

Kelly AM, Goodson JL, 2014 Hypothalamic oxytocin and vasopressin neurons exert sex-specific effects on pair bonding, gregariousness, and aggression in finches. Proc. Natl. Acad. Sci. U. S. A 111, 6069–6074. [PubMed: 24711411]

Kent K, Arientyl V, Khachatryan MM, Wood RI, 2013 Oxytocin induces a conditioned social preference in female mice. J. Neuroendocrinol 25, 803–810. [PubMed: 23841518]

Kosaki Y, Watanabe S, 2016 Conditioned social preference, but not place preference, produced by intranasal oxytocin in female mice. Behav. Neurosci 130, 182–195. [PubMed: 26890248]

Krach S, Paulus FM, Bodden M, Kircher T, 2010 The rewarding nature of social interactions. Front. Behav. Neurosci 4 (22).

Lee A, Clancy S, Fleming AS, 2000 Mother rats bar-press for pups: effects of lesions of the mpoa and limbic sites on maternal behavior and operant responding for pup-reinforcement. Behav. Brain Res 108, 215–231. [PubMed: 10701665]

Leong KC, Zhou L, Ghee SM, See RE, Reichel CM, 2016 Oxytocin decreases cocaine taking, cocaine seeking, and locomotor activity in female rats. Exp. Clin. Psychopharmacol 24, 55–64. [PubMed: 26523890]

Liberzon I, Trujillo KA, Akil H, Young EA, 1997 Motivational properties of oxytocin in the conditioned place preference paradigm. Neuropsychopharmacology 17, 353–359. [PubMed: 9397423]

Maldonado R, Robledo P, Chover AJ, Caine SB, Koob GF, 1993 D1 dopamine receptors in the nucleus accumbens modulate cocaine self-administration in the rat. Pharmacol. Biochem. Behav 45, 239–242. [PubMed: 8516365]

Manning M, Misicka A, Olma A, Bankowski K, Stoev S, Chini B, Durroux T, Mouillac B, Carbani M, Guillon G, 2012 Oxytocin and vasopressin agonists and antagonists as research tools and potential therapeutics. J. Neuroendcrinol 24, 609–628.

Matthews TJ, Abdelbaky P, Pfaff DW, 2005 Social and sexual motivation in the mouse. Behav. Neurosci 119, 1628–1639. [PubMed: 16420165]

McGregor IS, Bowen MT, 2012 Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm. Behav 61, 331–339. [PubMed: 22198308]

Meisel RL, Joppa MA, 1994 Conditioned place preference in female hamsters following aggressive or sexual encounters. Physiol. Behav 56, 1115–1118. [PubMed: 7824580]

Melis MR, Melis T, Cocco C, Succu S, Sanna F, Pillolla G, Boi A, Ferri GL, Argiolas A, 2007 Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. Eur. J. Neurosci 26, 1026–1035. [PubMed: 17672853]

Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M, 2011 Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. Nat. Rev. Neurosci 12, 524–538. [PubMed: 21852800]

Morin LP, Wood RI, 2001 A Stereotaxic Atlas of the Golden Hamster Brain. Academic Press, San Diego, Calif.; London.

Mullis K, Kay K, Williams DL, 2013 Oxytocin action in the ventral tegmental area affects sucrose intake. Brain Res 1513, 85–91. [PubMed: 23548602]

Peris J, MacFadyen K, Smith JA, de Kloet AD, Wang L, Krause EG, 2017 Oxytocin receptors are expressed on dopamine and glutamate neurons in the mouse ventral tegmental area that project to nucleus accumbens and other mesolimbic targets. J. Comp. Neurol 525, 1094–1108. [PubMed: 27615433]

Peters ST, Bowen MT, Bohrer K, McGregor IS, Neumann ID, 2017 Oxytocin inhibits ethanol consumption and ethanol-induced dopamine release in the nucleus accumbens. Addict. Biol 22, 702–711. [PubMed: 26810371]

Rilling JK, Demarco AC, Hackett PD, Chen X, Gautam P, Stair S, Haroon E, Thompson R, Ditzen B, Patel R, Pagnoni G, 2014 Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology 39, 237–248. [PubMed: 24157401]

Rowlett P, 2011 The unplanned impact of mathematics. Nature 475, 166–169. [PubMed: 21753831]

Salamone JD, Correa M, Farrar AM, Nunes EJ, Pardo M, 2009 Dopamine, behavioral economics, and effort. Front. Behav. Neurosci 3, 13. [PubMed: 19826615]

Song Z, Albers HE, 2017 Cross-talk among oxytocin and arginine-vasopressin receptors: relevance for basic and clinical studies of the brain and periphery. Front. Neuroendocrinol

Song Z, Borland JM, Larkin TE, O'Malley M, Albers HE, 2016 Activation of oxytocin receptors, but not arginine-vasopressin V1a receptors, in the ventral teg-mental area of male Syrian hamsters is essential for the reward-like properties of social interactions. Psychoneuroendocrinology 74, 164–172. [PubMed: 27632574]

Song Z, McCann KE, McNeill JK, Larkin TE, Huhman KL, Albers HE, 2014 Oxytocin induces social communication by activating arginine-vasopressin V1a receptors and not oxytocin receptors. Psychoneuroendocrinology 50C, 14–19.

Stavropoulos KK, Carver LJ, 2013 Research review: social motivation and oxytocin in autism–implications for joint attention development and intervention. J. Child Psychol. Psychiatry 54, 603–618. [PubMed: 23451765]

Suomi SJ, Harlow HF, Kimball SD, 1971 Behavioral effects of prolonged partial social isolation in the rhesus monkey. Psychol. Rep 29 (117), 1–1177.

Terranova JI, Ferris CF, Albers HE, 2017 Sex differences in the regulation of offensive aggression and dominance by arginine-vasopressin. Front. Endocrinol 8 (308).

Terranova JI, Song Z, Larkin TE, 2nd, Hardcastle N, Norvelle A, Riaz A, Albers HE, 2016 Serotonin and arginine-vasopressin mediate sex differences in the regulation of dominance and aggression by the social brain. Proc. Natl. Acad. Sci. U. S. A 113, 13233–13238. [PubMed: 27807133]

Trezza V, Campolongo P, Vanderschuren LJ, 2011 Evaluating the rewarding nature of social interactions in laboratory animals. Dev. Cognit. Neurosci 1, 444–458. [PubMed: 22436566]

Veeneman MM, Broekhoven MH, Damsteegt R, Vanderschuren LJ, 2012 Distinct contributions of dopamine in the dorsolateral striatum and nucleus accumbens shell to the reinforcing properties of cocaine. Neuropsychopharmacology 37, 487–498. [PubMed: 21918505]

Wacker DW, Ludwig M, 2012 Vasopressin, oxytocin, and social odor recognition. Horm Behav 61, 259–265. [PubMed: 21920364]

Young LJ, Barrett CE, 2015 Neuroscience. Can oxytocin treat autism? Science 347, 825–826. [PubMed: 25700501]

Fig. 1.

Operant Social Preference Apparatus: schematic (left) and vertical view (right). The main chamber contains an experimental subject whereas, one of the side chambers is occupied by a stimulus hamster; the subject and stimulus hamster are separated by a vertical-swing door. Visual, auditory and olfactory cues are shared between the chambers through the open top and holes in the door. An acrylic bucket positioned on the stimulus hamster side of the doors serves to hold weights.

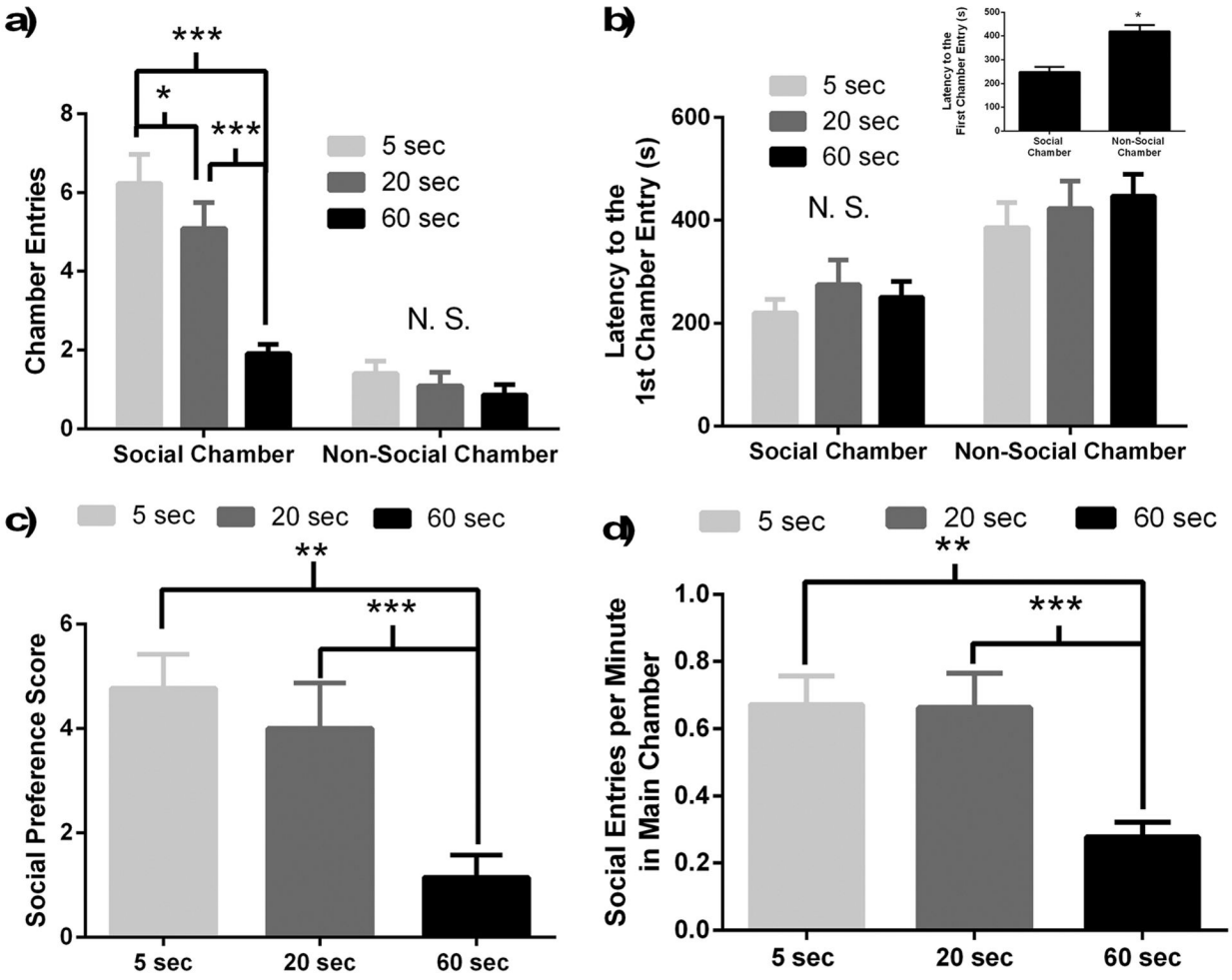

Fig. 2.

Effect of Time Allowed in Chambers Containing a Stimulus Hamster (Social Chamber) and Time Allowed in Non-Social Chambers on Social Preference. a) More time allowed in chambers decreased number of entries into social chambers, but had no effect on entries into non-social chambers (n = 11; * $p \leq 0.050$; *** $p \leq 0.001$). b) There were no differences in the latency to the first entry into chambers in groups assigned to different durations of time in the chambers containing a social stimulus or to groups assigned to different durations of time in non-social chambers. There was, however, a significantly shorter latency to the first entry into chambers containing a stimulus hamster compared to the latency to the first entry into non-social chambers (* $p = 0.002$; inset). c) More time in chambers decreased social preference score (** $p \leq 0.010$). d) More time in chambers decreased the rate of social chamber entries as a proportion of time in the main chamber.

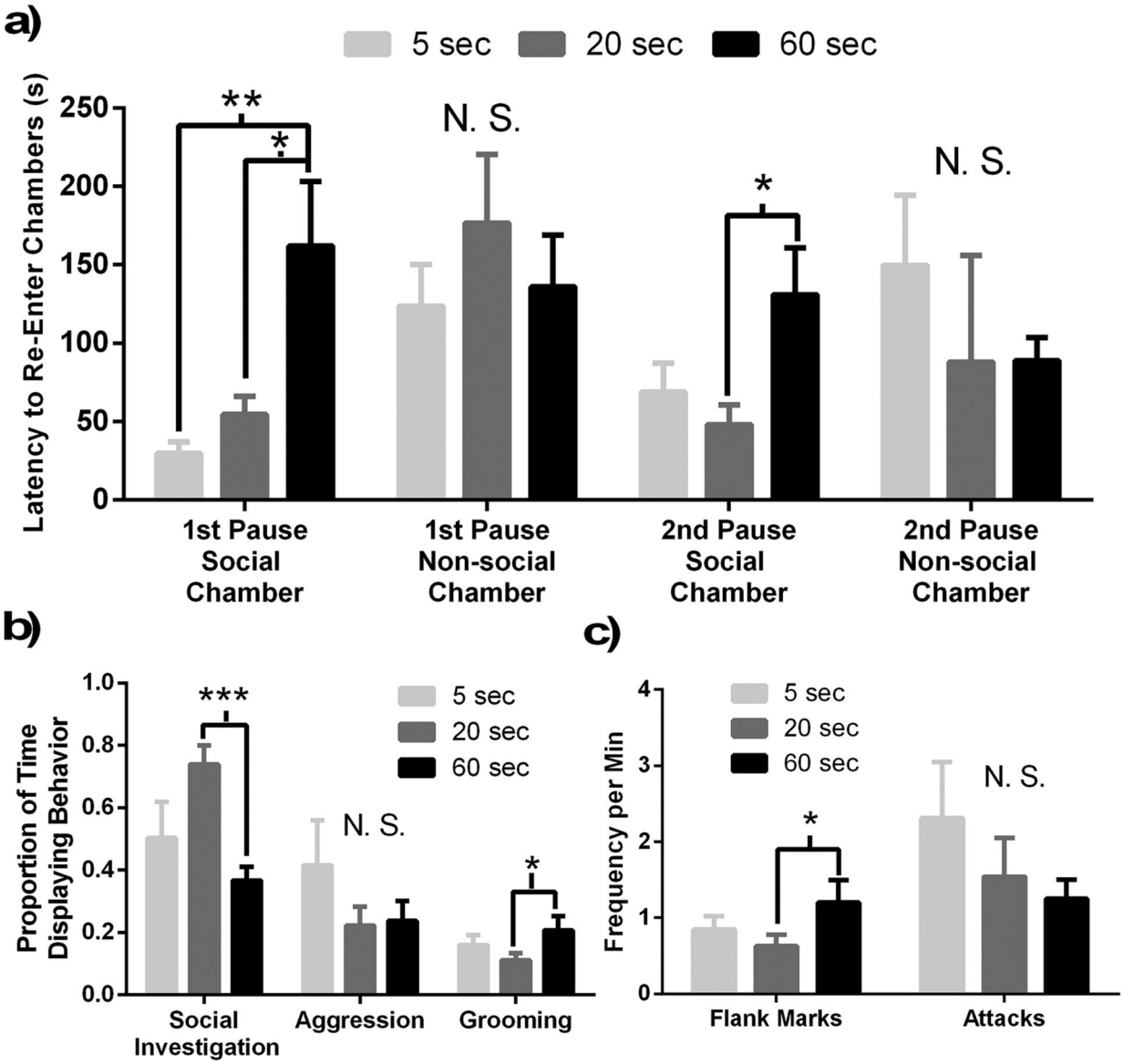

Fig. 3.

Effect of Time Allowed in Social and Non-Social Chambers on the Post Reinforcement Pause and Social Behavior. a) More time in the chambers increased the latency to re-enter the chambers containing stimulus hamsters, but had no effect on the latency to re-enter the non-social chambers, an effect observed on both the first and second post reinforcement interval (n = 11; * $p \leq 0.050$; ** $p \leq 0.010$). b) More time allowed in the chambers decreased the proportion of time spent socially investigating stimulus hamsters when in the social interaction chambers, but an increase in the proportion of time spent grooming when in the main chamber (*** $p \leq 0.001$). c) More time allowed in the social interaction chambers also increased the rate of flank marking when in the main chamber.

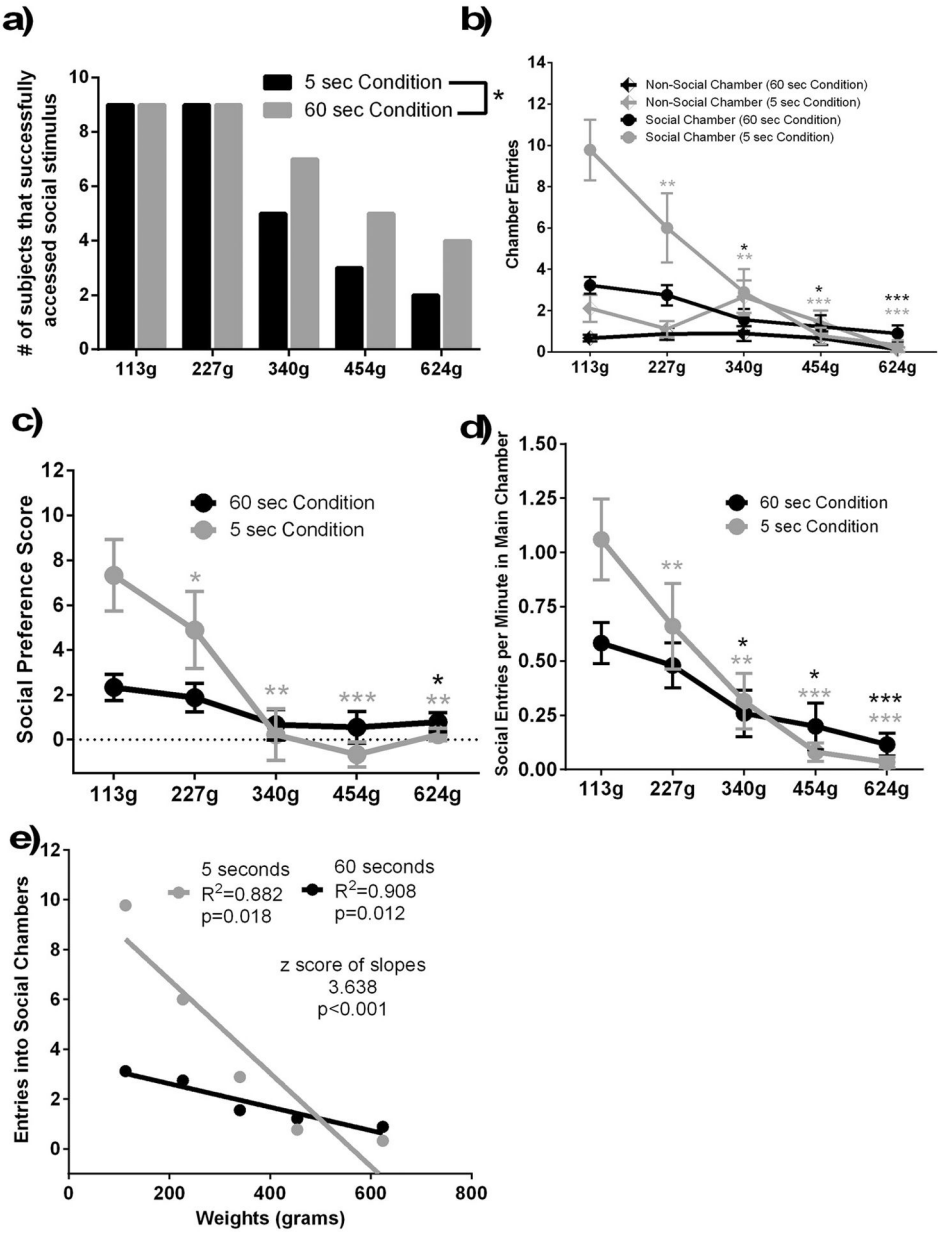

Fig. 4.

Effect of the Duration of Social Interaction on Social Preference under Conditions Requiring Increasing Effort. a) While all hamsters (n = 9) entered the chambers containing stimulus hamsters when the door weighed 113 g or 227 g, significantly fewer hamsters entered the social chambers at least once as the door weights increased (n = 9; * $p < 0.05$). Significantly more hamsters in the 60 s group entered the social chamber at least once in the session compared to the 5 s duration group ($p = 0.05$). b) All door weights (compared to 113 g) decreased the number of entries into chambers containing stimulus hamsters for subjects that were allowed 5 s of social interaction. Only the heaviest three door weights decreased the number of entries into chambers containing stimulus hamsters for subjects that were allowed 60 s of social interaction. c) Compared to a door weight of 113 g, all door weights decreased

the social preference score for subjects that were allowed 5 s of social interaction. Only the heaviest door weight decreased social preference score for subjects that were allowed 60 s of social interaction. d) Compared to a door weight of 113 g, all door weights decreased the number of entries per minute for subjects allowed 5 s of social interaction. Only the heaviest 3 door weights decreased social entries per minute in the main chamber for subjects that were allowed 60 s of social interaction. e) Correlation between door weights and the number of entries into chambers containing stimulus hamsters revealed that both 5 s and 60 s treatment conditions show a linear decrease in number of entries with increasing door weights. The slope is greater in the 5 s condition than the 60 s condition. Asterisks in graphs (b, c, d) indicate a significant difference from the door weight of 113 g, with asterisks and lines color-coded (gray 5 s Condition; black 60 s Condition) (* $p \leq 0.050$; ** $p \leq 0.010$; *** $p \leq 0.001$).

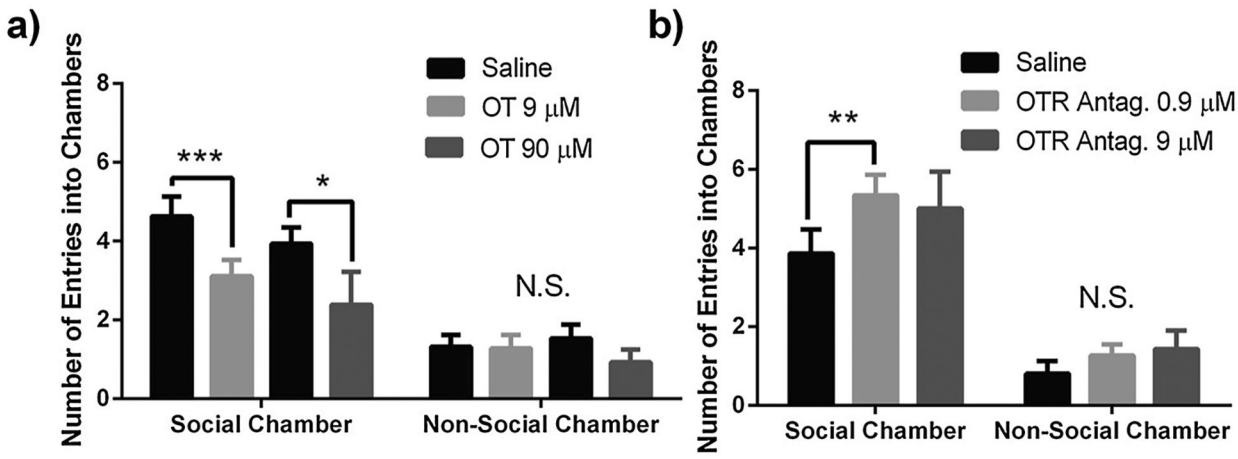

Fig. 5.

Effect of injection of OT and an OTR Antagonist in the VTA on Social Preference. a) OT (9 μM n = 18; 90 μM n = 14) injected in the VTA 5 min before the test decreased the number of entries into chambers containing a stimulus hamsters (i.e., Social Chamber), but had no effect on the number of entries into non-social chambers (i.e., non-social chamber; * $p \leq 0.050$; *** $p \leq 0.001$). b) Injection of the OTR antagonist at 0.9 μM (n = 14) but not 9 μM (n = 14) increased the number of entries into the Social Chamber, but neither dose affected the number of entries into the non-social chamber (** $p \leq 0.010$).

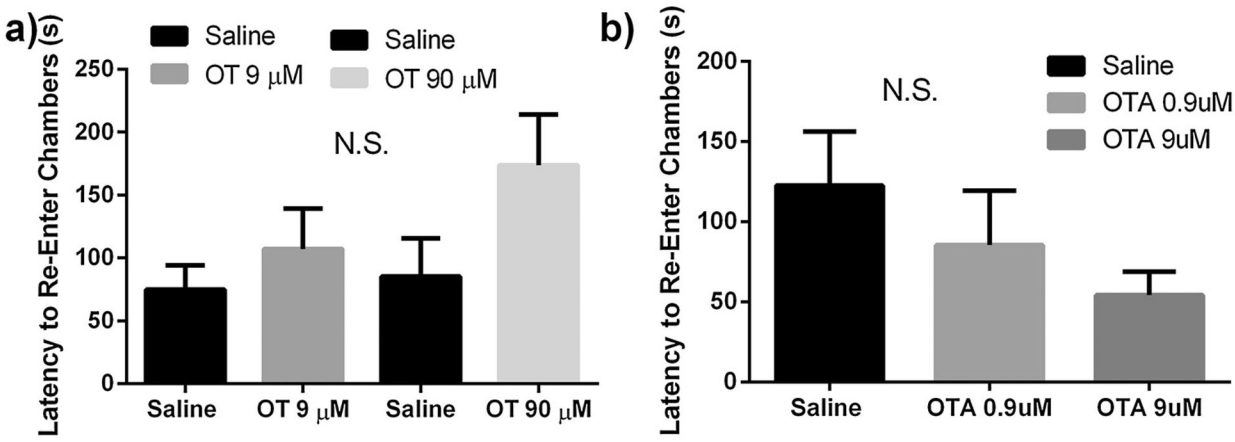

Fig. 6.

Effect of Injections of OT and an OTR Antagonist in the VTA on the latency to reenter chambers containing stimulus hamsters (post reinforcement pause). a) OT (90 μM) injected into the VTA increased the latency to reenter chambers containing stimulus hamsters trended towards significance ($p = 0.132$). b) Likewise, injections of the OTR antagonist (9 μM) decreased the latency to re-enter chambers containing stimulus hamsters also just missed significance ($p = 0.096$).

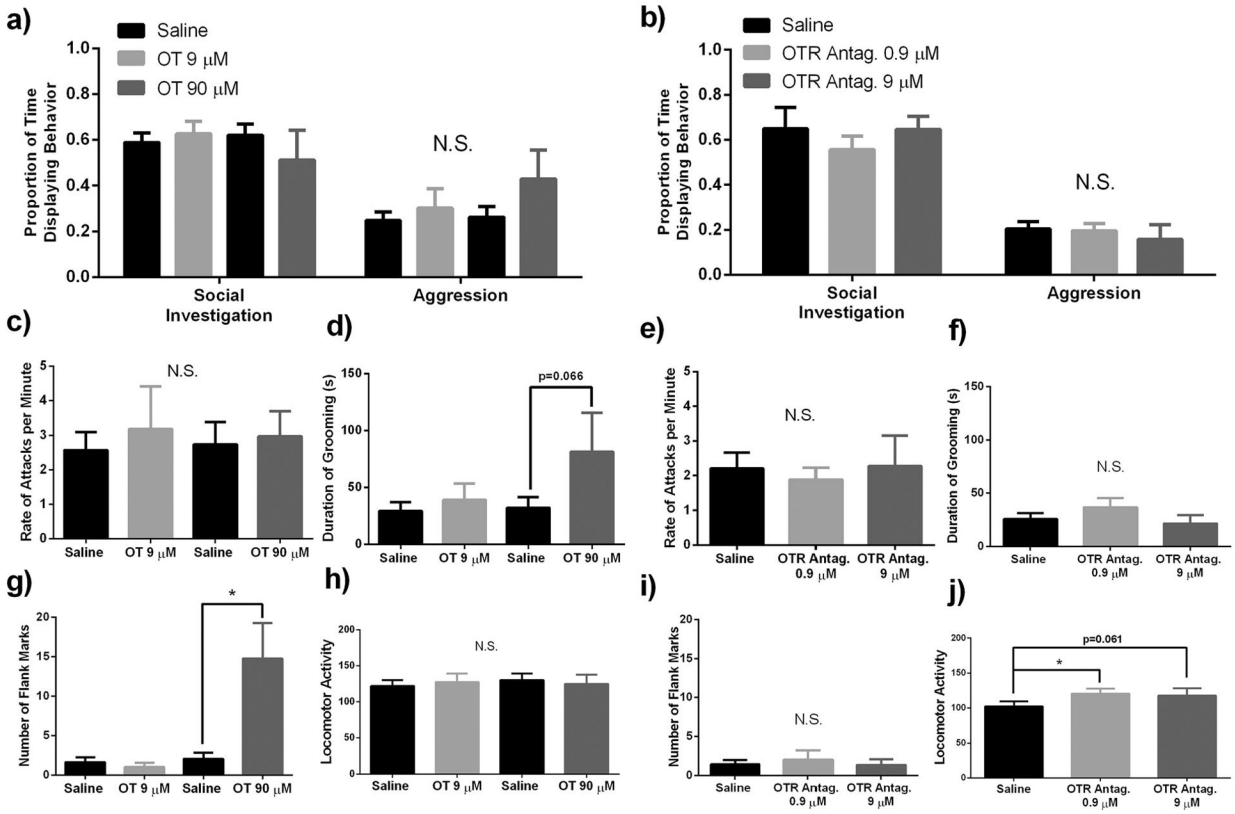

Fig. 7.

Effect of injection of OT and an OTR Antagonist in the VTA on Social Investigation, Aggression, Grooming and Flank Marking, and Locomotor Activity. a) OT (9 μM n = 18; 90 μM n = 12) injected into the VTA had no effect on social investigation, aggression or c) attacks per minute. b) Injection of the OTR antagonist (0.9 μM n = 14) had no effect on social investigation, aggression or e) attacks. d) A trend for the 90 μM concentration of OT to increase the duration of grooming that just missed significance (p = 0.066) was observed. f) Injections of the OTR antagonist had no effect on grooming. g) The 90 μM concentration of OT increased the number of flank marks (* p ≤ 0.050). i) The OTR antagonist injected into the VTA had no effect on the number of flank marks observed. *h*) Injection of OT had no effect on the amount of locomotor activity. *j*) Injection of 0.9 μM OTR antagonist increased locomotor activity (p ≤ 0.050) and a trend for 9 μM OTR antagonist to increase locomotor activity just missed significance (p = 0.061).

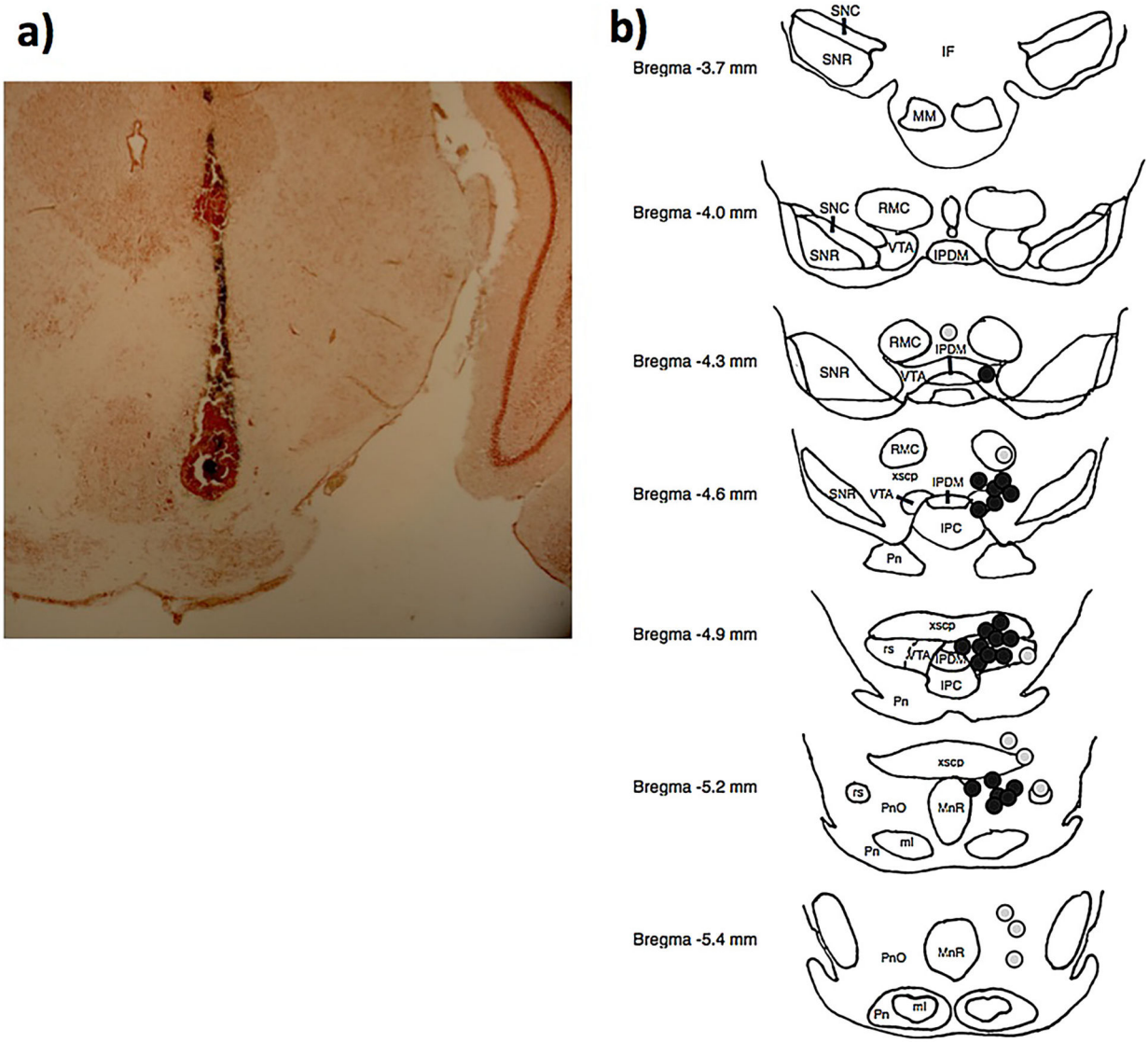

Fig. 8.

Localization of Drug Injections. a) Representative injection site in the caudal VTA. b) Localization of the sites of injection of oxytocin (OT) and OT receptor antagonist. Subjects with ink found within the caudal VTA were classified as hits (black circle), while subjects with ink found outside the caudal VTA were classified as misses (gray circle). IF: interfascicular nucleus IPC: interpeduncular nucleus caudal IPDM: interpeduncular nucleus dorsomedial ml: medial lemniscus MM: medial mammillary nucleus MnR: median raphe nucleus Pn: pontine nucleus PnO: pontine reticular nucleus oral RMC: red nucleus rs: rubrospinal tract SNC: substantia nigra compact SNR: substantia nigra reticular VTA: ventral tegmental area xscp: decussation of the superior cerebellar penduncle (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).