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Ainara Turnes
Facultad de Ciencias, Universidad de la República
Natalia Uriarte
Facultad de Ciencias, Universidad de la República
Daniella Agrati
dagrati@fcien.edu.uy

Facultad de Ciencias, Universidad de la República

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Effect of antagonizing D1-like and D2-like receptors in the Nucleus Accumbens shell on the expression of sexually motivated behaviors in female rats

Ainara Turnes[1], Natalia Uriarte[2], Daniella Agrati[1]

1 Physiology and Nutrition Department, Facultad de Ciencias, Universidad de la República, Montevideo, Uruguay

2 Neuroscience Laboratory, Facultad de Ciencias, Universidad de la República, Montevideo, Uruguay

Corresponding author: Dr. Daniella Agrati

Sección Fisiología y Nutrición, Facultad de Ciencias

Igua 4225, ZP 11400, Montevideo, Uruguay

dagrati@fcien.edu.uy

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Abstract

Rationale: In female rats, sexual behavior is strongly motivated, and the mesolimbic dopaminergic system plays a regulatory role. Although the action of dopamine on its D1 (D1R) and D2 (D2R) receptors in the nucleus accumbens (NAcc) has been implicated in general motivation, its role in the expression of sexual motivation and behavior in female rats remains unknown. *Objectives:* To determine whether activation of D1R or D2R receptors in the shell of the NAcc of sexually active, cycling female rats is necessary for the expression of sexual motivation in the presence of a male. *Methods:* With this aim, we compared the behavior of adult females in the late proestrus phase of the estrous cycle in a sexual preference test—male vs. female—followed by a sexual behavior test in a bilevel chamber after local administration into the NAcc shell of the selective D1R antagonist SCH 23390 (0.0, 0.5, 1.0, 2.5, or 5.0 μg/0.5 μl/side) or the selective D2R antagonist raclopride (0.0, 2.5 or 5.0 μg/0.5 μl/side). *Results:* Selective blockade of D1R or D2R in the NAcc shell did not affect preference for the male or sexual receptivity. However, antagonizing D1R, but not D2R, reduced attempts to access the male in the preference test and proceptive behaviors during sexual interaction—indicators of female sexual motivation. *Conclusion:* Our findings suggest that dopamine exerts a specific role in this mesolimbic structure in female sexual motivation, predominantly through its D1R.

Keywords

sexual behavior; sexual motivation; female rat; dopamine receptors; nucleus accumbens; SCH 23390; raclopride

Introduction

The sexual behavior of female rats is strongly motivated, as demonstrated in tests designed to assess the incentive value of males (Guarraci and Frohardt 2019; Agrati 2022). Thus, sexually active females prefer intact males over females or castrated males (Clark et al. 2004; Agrati et al. 2008), emit more ultrasonic vocalizations after exposure to a male in comparison to a female (McGinnis and Vakulenko 2003; Armas et al. 2021), learn to press a lever to gain access to a male (Bermant 1961), and develop a conditioned place preference for a context associated with sexual interaction (Paredes and Vazquez 1999; Coria-Avila et al. 2016).

The mesolimbic dopaminergic (DAergic) system, which mainly includes DAergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) (Melis and Argiolas 1995), has been identified as a key neural system involved in the regulation of motivated behaviors (Kelley and Berridge 2002; Kringelbach and Berridge 2009; Berridge and Kringelbach 2011; Ventura-Aquino et al. 2018). Specifically, recent theories propose that dopamine (DA) release in the NAcc regulates the activational aspects of motivated behaviors and allows individuals to overcome work-related obstacles and limitations that separate them from motivationally significant stimuli (Aberman and Salamone 1999; Berridge 2007; Salamone and Correa 2012; Salamone et al. 2016b).

The motivational effects of DA acting on the NAcc have been attributed to its action on D1-like and D2-like receptors (D1R and D2R) families in its two main subregions, the shell and core (Ikemoto et al. 1997; Nowend et al. 2001; Baldo et al. 2002; Schmidt et al. 2006). These subregions are characterized by differential and specific afferent-efferent relationships and by different functional roles (Heimer et al. 1991, 1997; Zahm 1999, 2000). In particular, the DAergic activity in the NAcc shell has been associated with the incentive value of stimuli and responses to novelty (Bassareo et al. 2002), participating in the encoding of predictive signals and rewarding stimuli (Cacciapaglia et al. 2012).

DAergic neurotransmission in the NAcc has been implicated in the regulation of sexual motivation, primarily in male rats (Everitt 1990; Robinson et al. 2001; Pfaus 2009; Bialy et al. 2010; Coria-Avila et al. 2018; Guadarrama-Bazante and Rodríguez-Manzo 2019; Melis et al. 2022), whereas evidence regarding its role in female sexual behavior is controversial. Pfaus et al. (1995) observed increased DA levels in the NAcc of sexually active females, both in the presence of a male and during copulation. Moreover, extracellular DA levels in the NAcc increase during mating only when copulation occurs at the female's preferred pacing interval (Mermelstein and Becker 1995; Jenkins and Becker 2003). Lesions of the NAcc have also been shown to alter the copulatory behavior pattern of females, increasing rejections of mounts and eliminating preference for the

male (Rivas and Mir 1990, 1991). Similarly, Jenkins and Becker (2001) found that lesions of the medial portion of the NAcc shell affect the female's latency to approach a male rat and engage or re-engage in sexual interaction, indicating an affectation of the motivational aspects of sexual behavior. In contrast, Guarraci et al. (2002) found no effect of NAcc shell lesion on sexual receptivity and pacing behavior of females. Also, depleting DA in the NAcc does not eliminate the expression of hops and darts (Hansen et al. 1991a), although these authors did not assess the intensity of proceptive displays. Thus, the contribution of DAergic neurotransmission in the NAcc to female sexual motivation remains unclear, and its relevance has been questioned by some authors (Paredes and Agmo 2004).

Interestingly, Meisel et al. (1996) noted that the systemic administration of D2R antagonists, raclopride and sulpiride, prevented the establishment of a copulation-induced conditioned place preference in females. Likewise, in ovariectomized, hormonally primed rats the systemic administration of the DAergic antagonist haloperidol reduced the expression of proceptive behaviors (Ismail et al. 2010). Together, these findings suggest a potential role for the D2R subtype signaling in the motivational aspects of female sexual behavior. Moreover, a substantial body of evidence supports a role of D1R in mediating the incentive value of motivationally significant stimuli (Self and Nestler 1995; Ikemoto et al. 1997; Beninger and Miller 1998; Sutton and Beninger 1999), including stimuli involved in other affiliative behaviors, such as maternal behavior (Keer and Stern 1999; Miller and Lonstein 2005; Numan et al. 2005; Parada et al. 2008; Numan and Stolzenberg 2009; Stolzenberg et al. 2010; Mileva-Seitz et al. 2012). However, to our knowledge, the effect of antagonizing D1R on female sexual motivation and behavior have not been examined.

Based on evidence of the involvement of D1R and D2R in the expression of motivated behaviors mediated by the NAcc shell (for a review see Salamone and Correa 2024), and particularly in maternal behavior (Numan et al. 2005), we hypothesized that local antagonism of D1R and D2R within the NAcc shell would affect the expression of the motivational components of sexual behavior in sexually active female rats.

Most studies examining the role of the DAergic system in female sexual behavior have used ovariectomized rats subjected to different hormonal priming treatments and have had prior sexual experience. Different schedules of sexual steroid administration modulate the mesolimbic DAergic activity and influence the incentive value of females for males (Becker 1999; Meisel and Mullins 2006; Meerts et al. 2014; Guarraci and Meerts 2017; Yoest et al. 2018; Zachry et al. 2021). Furthermore, although estradiol and progesterone treatment can induce sexual behavior resembling that observed during late proestrus, the underlying hormonal milieu differs between hormonally primed ovariectomized rats and cycling females. Therefore, as a first approach to assessing the role

of NAcc dopamine in the unconditional incentive value of the male and in the execution of sexual behavior under natural physiological conditions, we examined the effect of the local D1R and D2R antagonism in the NAcc shell in cycling virgin females during the late proestrus stage of their estrous cycle. To distinguish motivational components of sexual behavior from copulatory performance, females were first evaluated in a male vs. female preference test (Agrati et al. 2016; Ferreño et al. 2018) followed by a sexual behavior test in a bilevel chamber (Mendelson and Gorzalka 1987; Pfaus et al. 1999). Male vs. female preference tests are widely used to assess sexual motivation (Ventura-Aquino and Paredes 2017). In the Y-maze model without contact used it is possible to measure the attempts to access the stimuli, which can additionally be quantified as an index of effort directed towards obtaining the incentive stimulus (Agrati et al. 2016; Ferreño et al. 2018).

Material and Methods

Animals

Female and male adult rats (*Rattus norvegicus*, Wistar strain) were housed in temperature- and humidity-controlled conditions (21 ± 1°C and 50–70%) under a 12-h light–dark cycle (lights on at 03:00), with food and water *ad libitum.* The estrous cycle of sexually naive females was followed through the inspection of daily vaginal smears performed during the light phase of the cycle (Marcondes et al. 2002). All animal care and experimental procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH) and the Uruguayan law (No. 18 611) for the Care and Use of Laboratory Animals (number of protocol: 24001-000941-17).

Stereotaxic surgery

Diestrus females, that have shown at least two regular cycles, were anesthetized with 2 ml/kg intraperitoneal injection of a solution containing 75.0 mg/ml ketamine HCl, 7.5mg/ml xylazine, and 1.5mg/ml acepromazine maleate. Rats were then secured in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at 3.2 mm (flat skull). Females were bilaterally implanted with 28-gauge stainless steel guide cannulae (Plastics One) aimed at above of the NAcc shell anterior-posterior from bregma 2.5 mm, medial-lateral from the midline ± 0.8 mm, and dorso-ventral from the skull surface 7.8 mm. Cannulae were secured to the skull with stainless steel screws and cranioplastic cement. Dummy stylets were inserted in the guide cannulae to maintain patency until infusions were made.

Once the surgery was completed, analgesic was administered (Meloxicam, 1 mg/kg/ml s.c.) and a local antibiotic and anti-inflammatory was applied. After surgery, the females were housed individually and once daily to habituate them to the experimenter handling associated with the intracranial drug administration.

Drug administration

After undergoing surgery, the females' estrous cycle was followed so they could be tested during the subsequent proestrus phase. As shown in Figure 1, on the second proestrus day following surgery, females were gently hand-held while their stylets were removed and replaced by 28-gauge stainless steel injectors that extended 1 mm past the tip of the guide cannulae. Injectors were connected by PE-10 tubing to 10- µl Hamilton syringes, and bilateral infusions were driven simultaneously by a two-syringe infusion pump (Harvard 22 syringe pump; Harvard Apparatus). The infusion rate was 0.25 µl/min, and the injectors remained in place for an additional minute to allow adequate diffusion, according to Nowend et al. (2001) and Baldo et al. (2002).
SCH 23390 (D1R antagonist) and raclopride (D2R antagonist) were obtained from Sigma-Aldrich. For intracranial injection, both drugs were dissolved in 0.9% saline solution. For Experiment 1, five drug doses were used (0.0, 0.5, 1.0, 2.5, or 5.0 µg/0.5 µl/side of SCH 23390), while for Experiment 2, three drug doses (0.0, 2.5, or 5.0 µg/0.5 µl/side of raclopride) were used. The doses of both drugs were within the range used by other researchers (Nowend et al. 2001; Baldo et al. 2002; Numan et al. 2005). The D1R experiment has two additional dose groups compared to the D2R experiment due to significant motor effects observed when higher doses of SCH 23390 were administered. These effects could mask motivational ones.

Verification of injection sites

After completion of behavioral testing, females were overdosed with sodium thiopental (120 mg/kg, i.p.), and perfused transcardially with 0.9% saline followed by 4 % formalin. Brains were removed and postfixed in the same solution for 48 h before being stored in a 30% sucrose solution. The brains were sliced on a cryostat at 50µm thickness, and cross-sections were mounted on glass slides and stained with cresyl violet. Figure 2 presents schematic cross-sections of the rat brain, showing injector tip placements within the NAcc of the rats included in the analyses.

Behavioral Tests

Sexual preference test

The sexual incentive value of the male was evaluated through a sexual preference test conducted between a sexually active male and a sexually active female in a Y-maze apparatus comprising three equal-sized chambers (25 cm wide x 30 cm long x 18 cm high) at the end of each arm (10 cm wide x 30 cm long x 10 cm high) (Agrati et al. 2016; Armas et al. 2021). Two of the chambers contained the stimuli: either a sexually active male (trained to perform one ejaculation in less than 15 minutes) or a sexually active cycling female, while the third chamber was designated as a neutral chamber and remained empty. The locations of the stimulus animals were randomly assigned in a counter balanced manner. Each chamber is divided into two sections by a perforated acrylic transparent partition. The perforated division enables experimental females to see, hear, and smell the stimulus animals while preventing direct contact.

The experimental females were situated in the center of the maze and permitted to explore the apparatus for a 10-minute acclimatization period. Subsequent to this interval, the female was removed from the model, and intracranial microinjection was conducted. Once the injection was complete, the female was returned to the model, the stimulus animals were introduced to the chambers, and the experimental females' behavior was documented over a 15-minute testing period according to Agrati et al. (2016) and Ferreño et al. (2018). The variables that were measured included the number of entries to each arm and chamber, the cumulative time spent in each chamber, the olfactory exploration of stimuli through the perforated division and the number of attempts to access each stimulus animal (defined as the act of biting or scratching the inner chamber wall). Locomotor activity, measured as the total number of entries into each chamber and each arm, were also evaluated. The entire maze was cleaned with a 50% ethanol solution and allowed to dry thoroughly between test sessions.

Sexual behavior test in a bilevel chamber

The assessment of sexual behavior was conducted in accordance with the methodology described by Mondino et al. (2019) within a transparent acrylic bilevel chamber (70 cm long x 60 cm high x 20 cm wide) during the dark phase of the light cycle (between 17:00 and 21:00 h) under a dim red light. The animals (both females and males), were habituated to the model three times a week for two weeks prior to the start of the experiment, for 15 minutes each time.

At the time of the test, the female was placed on the upper level of the chamber. After a 2-minute habituation period, a sexually active male (trained to perform one ejaculation in less than 15 minutes) was introduced, and the number of the following behaviors of the female was recorded for 15 minutes: hops and darts (short distance

hopping and running near by the male, usually with a “rigid” body posture), sexual solicitations (approach toward or orientation of the head to the male, followed by a rapid run away from it to another level; or jumping after an anogenital sniff of the male and running to the other level, both scenarios may conclude in a hop and dart or a presentation posture; in this case the entire action was deemed a sexual solicitation and the concluding hop and dart was not counted as a separate component) and lordosis postures in response to male mounting. The latency to the first proceptive behavior and lordosis was also recorded (Pfaus et al. 1999, 2000; Mondino et al. 2019). The duration of each lordosis posture was recorded and the mean duration of lordosis per female was calculated (sum of the duration of all lordosis postures/total number of lordosis postures). The assessment of the male's sexual behavior included the measurement of the number of mounts (including those with and without intromission) and ejaculations, as well as the respective latencies (Fernández-Guasti et al. 1990). Female sexual receptivity was assessed by the lordosis quotient (LQ) —female sexual receptivity index— calculated as the ratio between the number of lordosis and the total number of mounts and ejaculations (Hardy and DeBold 1973).

Ambulatory activity test

Since microinjections of DAergic antagonists into the NAcc have been shown to alter spontaneous motor activity by significantly decreasing ambulatory activity and rearing posture display (Baldo et al. 2002), the ambulatory activity of females was evaluated over a 10-minute period in an open field comprising a rectangular arena (36 cm wide x 53 cm long x 25 cm high) with transparent polycarbonate walls and a floor divided into 12 squares. According to Delgado et al. (2019), the number of crosses (crossing gridlines with all four paws) and rearings (standing on both hind paws in an upright position) were recorded

Experimental procedure

To determine the effect of selective blockade of D1R (Experiment 1) and D2R (Experiment 2) in the NAcc shell on the sexual motivation and execution of sexually naive females (90-120 days of life), rats underwent stereotaxic surgery for the implantation of bilateral cannulas in diestrus, after showing two regular estrous cycles. As shown in Figure 1, on the night of the first proestrus following a complete estrous cycle post-surgery, females were placed with a male for one minute to confirm whether they were sexually active. Immediately after, they were allowed to acclimate to the Y-maze for 10 minutes, and afterwards, the intracranial injection was performed. After the injection, the females were returned to the Y-maze, where a 15 min sexual preference

test was conducted, followed by a sexual behavior test in the bilevel chamber (15 min). Finally, locomotor activity was evaluated during a 10 min test. The following day, the females were anesthetized (sodium thiopental, 120 mg/kg, i.p.) and perfused with heparinized saline followed by 4% formalin. The brains were processed for histological verification of the injection sites.

The following experimental groups were formed: for Experiment 1 females treated with saline/0.5.µl/side (0.0, n=13), 0.5/0.5µl/side (n=12), 1.0/0.5µl/side (n=12), 2.5/0.5µl/side (n=12) or 5.0µg/0.5µl/side (n=8) of the D1R antagonist SCH 23390, and for Experiment 2 females treated with saline/0.5µl/side (0.0, n=9), 2.5µg/0.5µl/side (n=10) or 5.0µg/0.5µl/side (n=10) of D2R antagonist raclopride.

Statistical analysis

Data were expressed as medians and interquartile ranges (quartile 1, Q1-quartile 3, Q3) and analyzed using non-parametric tests (Gibbons and Chakraborti 2020). Comparisons between groups of independent data were made using the Kruskal–Wallis ANOVA, followed by Dunn's post hoc test (Dinno 2015). The Friedman ANOVA test and the Wilcoxon matched-pairs test were employed to analyze the dependent data (Siegel and Castellan 1988).

Results

Experiment 1: Effect of D1R antagonism in the NAcc shell on the behavior of proestrous females

Sexual Preference Test

As shown in Figure 3A, four of the five groups of females exhibited a preference for the male, spending significantly more time in the male than in the female compartment (SCH-0.0µg: $T_{(13)}$=0, p<0.001; SCH-0.5µg: $T_{(12)}$=12, p=0.034; SCH-1.0µg: $T_{(12)}$=5, p=0.005 and SCH-2.5µg: $T_{(12)}$=12, p=0.034, Wilcoxon matched-pairs test). Although, time spent across compartments differed in the SCH-5.0µg group ($\chi^{2(2)}$=7, p=0,030), the Wilcoxon matched-pair test did not detect differences between chambers (male vs. neutral: $T_{(8)}$=5, p=0.078; female vs. neutral: $T_{(8)}$=8, p=0.195; male vs. female: $T_{(8)}$=15, p=0.711). In addition, females in all groups except for SCH-5.0µg group spent significantly more time in both stimuli compartments (male or female), than in the neutral compartment (p<0.05 for all comparisons).

Females from all groups sniffed the male significantly more than the female (Figure 3B, SCH-0.0µg: $T_{(13)}$=0, p<0.001; SCH-0.5µg: $T_{(12)}$=4.5, p=0.004; SCH-1.0µg: $T_{(12)}$=6.5, p=0.009; SCH-2.5µg: $T_{(12)}$=2, p=0.004 and SCH-5.0µg: $T_{(8)}$=0, p=0.031). However, females treated with 2.5µg or 5.0µg of SCH 23390 sniffed the male

significantly less than those treated with 0.0µg (0.0µg vs 2.5µg: $Z_{(13, 12)}$=4.762, p<0.001 and 0.0µg vs 5.0µg: $Z_{(13, 8)}$=4.354, p<0.001, Dunn's test between dose groups). In contrast, only females treated with saline or 0.5µg of SCH 23390 made significantly more attempts to access the male compared to the female (Figure 3C, SCH-0.0µg: $T_{(13)}$=0, p<0.001; SCH-0.5µg: $T_{(12)}$=2, p=0.006; SCH-1.0µg: $T_{(12)}$=22, p=0.633; SCH-2.5µg: $T_{(12)}$=0, p=0.091 and SCH-5.0µg: $T_{(8)}$=0, p=0.125). In accordance, the number of attempts to access the male decreased in SCH-1.0µg, 2.5µg and 5.0µg groups when compared to saline-treated rats (0.0µg vs 1.0µg: $Z_{(13, 12)}$=3.606, p=0.003; 0.0µg vs 2.5µg: $Z_{(13, 12)}$=3.670, p=0.002 and 0.0µg vs 5.0µg: $Z_{(13, 8)}$=3.418, p=0.006). The attempts to access the female were reduced by SCH 23390 treatment ($H_{(5)}$=11.66, p=0.020), however no significant difference between groups were detected with the Dunn test.

Female locomotor activity (Table 1) decreased following SCH 23390 administration in a dose-dependent manner ($H_{(5)}$=38.17, p<0.001). Locomotion was significantly lower in females treated with SCH-1.0µg, 2.5µg, and 5.0µg than in saline-treated females (0.0µg vs 1.0µg: $Z_{(13, 12)}$=2.793, p=0.005; 0.0µg vs 2.5µg: $Z_{(13, 12)}$=5.026, p<0.001 and 0.0µg vs 5.0µg: $Z_{(13, 8)}$=5.053, p<0.001), whereas a trend toward reduced locomotion was observed at the 0.5µg dose (0.0µg vs 0.5µg: $Z_{(13, 12)}$=1.846, p=0.065). In addition, females receiving 2.5µg and 5.0µg doses of SCH 23390 exhibited reduced locomotor activity than those receiving 0.5µg and 1.0µg doses (0.5µg vs 2.5µg: $Z_{(12, 12)}$=3.118, p=0.002; 0.5µg vs 5.0µg: $Z_{(12, 8)}$=3.355, p<0.001; 1.0µg vs 2.5µg: $Z_{(12, 12)}$=2.189, p=0.029 and 1.0µg vs 5.0µg: $Z_{(12, 8)}$=2.525, p=0.012). Although SCH 23390 reduced the total number of entries to the three choice chambers (Table 1, $H_{(5)}$=38.43, p<0.001), this treatment did not affect the total time that females spent in the compartments (Table 1, $H_{(5)}$=5.536, p=0.237).

Sexual behavior test

Females' behavior

The records of five females from the sexual behavior test in a bilevel chamber were lost: two treated with a dose of 1.0 µg, two treated 2.5 µg, and one treated with 5.0 µg of SCH 23390. Consequently, the analyses presented below were performed using reduced sample sizes for the aforementioned groups.

Female sexual receptivity, assessed by the LQ, was maximal in all groups and did not differ according to the pharmacological treatment received (Figure 4A, $H_{(5)}$=1.622, p=0.805). In contrast, lordosis duration differed among groups, being significantly longer in females treated with 2.5µg and 5.0µg doses of SCH 23390 than in saline treated females and those receiving the 0.5µg dose of the drug (Figure 4B, 0.0µg vs 2.5µg: $Z_{(13, 10)}$=4.041, p<0.001; 0.0µg vs 5.0µg: $Z_{(13, 7)}$=4.044, p<0.001; 0.5µg vs 2.5µg: $Z_{(12, 10)}$=3.111, p=0.002 and 0.5µg vs 5.0µg:

$Z_{(12, 7)}$=3.213, p=0.001). Lordosis duration was also significantly longer in females receiving the 5.0µg dose than in those receiving the 1.0µg dose of SCH 23390, and this last group differed from saline group (0.0µg vs 1.0µg: $Z_{(13, 10)}$=2.080, p=0.038; 1.0µg vs 5.0µg: $Z_{(10, 7)}$=2.072, p=0.038).

The administration of SCH 23390 also impacted the expression of proceptive behaviors. Thus, females that received the two highest doses of SCH 23390 (2.5µg and 5.0µg) displayed fewer hops and darts than females that received 0.0µg and 0.5µg (Figure 4C, 0.0µg vs 2.5µg: $Z_{(13, 10)}$=2.917, p=0.004; 0.0µg vs 5.0µg: $Z_{(13, 7)}$=3.092, p=0.002; 0.5µg vs 2.5µg: $Z_{(12, 10)}$=2.781, p=0.005 and 0.5µg vs 5.0µg: $Z_{(12, 7)}$=2.972, p=0.003). The SCH-1.0µg group showed a statistical tendency to express fewer hops and darts than the saline-treated group (0.0µg vs 1.0µg: $Z_{(13, 10)}$=1.818, p=0.07). As shown in Figure 4D, active sexual solicitations decreased in all groups treated with SCH 23390 when compared to the control group (0.0µg vs 0.5µg: $Z_{(13, 12)}$=2.116, p=0.034; vs 1.0µg: $Z_{(13, 10)}$=2.790, p=0.005; vs 2.5µg: $Z_{(13, 12)}$=4.169, p<0.001 and vs 5.0µg: $Z_{(13, 12)}$=3.830, p<0.001). This effect of SCH 23390 was more pronounced in the 2.5µg and 5.0µg groups, that also differed from the SCH-0.5µg group (0.5µg vs 2.5µg: $Z_{(12, 10)}$=2.116, p=0.034 and 0.5µg vs 5.0µg: $Z_{(12, 7)}$=1.993, p=0.046). The olfactory exploration of the male (as determined by the sum of anogenital and corporal sniffs performed by females on the male) decreased in groups of females that received the highest doses of SCH 23390 (as described in Supplementary Materials).

As shown in Table 1, SCH 23390 treatment did not affect the latency to display proceptive behaviors ($H_{(5)}$=3.899, p=0.420) or the latency to perform lordosis ($H_{(5)}$=4.833, p=0.305).

Male behavior

As shown in Table 1, the number of mounts (with and without intromission) and ejaculations displayed by males did not differ among treatment groups (mounts: $H_{(5)}$=1.462, p=0.833; ejaculations: $H_{(5)}$=0.676, p=0.954). Similarly, treatment did not affect the latencies to mounting ($H_{(5)}$=4.502, p=0.342) or ejaculation ($H_{(5)}$=1.130, p=0.889).

Ambulatory test

Treatment with SCH 23390 decreased horizontal ($H_{(5)}$=38.81, p<0.001) and vertical ($H_{(5)}$=26.81, p<0.001) exploration in the open field. As shown in Figure 5, the number of crosses and rearing postures was lower in the groups treated with SCH-1.0µg, 2.5µg, and 5.0µg compared to the saline group (number of crosses: vs 1.0µg: $Z_{(13, 12)}$=2.818, p=0.005; vs 2.5µg: $Z_{(13, 12)}$=4.631, p<0.001 and vs 5.0µg: $Z_{(13, 8)}$=5.372, p<0.001; number of rearing postures: vs 1.0µg: $Z_{(13, 12)}$ =2.698, p=0.007; vs 2.5µg: $Z_{(13, 12)}$=3.890, p<0.001 and vs 5.0µg: $Z_{(13,}$

$_{8)}$=4.580, p<0.001). The groups that received the two highest doses also differed from SCH-0.5µg dose (crosses: vs 2.5µg: $Z_{(12, 12)}$=2.952, p=0.003 and vs 5.0µg: $Z_{(12 , 12)}$=3.867, p<0.001; rearing postures: vs 2.5µg: $Z_{(12, 12)}$=2.091, p=0.037 and vs 5.0µg: $Z_{(12, 12)}$=2.968, p=0.003). SCH-5.0µg also exhibited a reduced number of crosses ($Z_{(12, 8)}$=2.816, p=0.005) and rearings ($Z_{(12, 8)}$=2.143, p=0.032) compared to SCH-1.0µg groups.

Experiment 2: Effect of antagonising D2R in NAcc shell on the behavior of proestrous females

Sexual preference test

All groups showed a preference for the male, spending significantly more time in the male compared than in the female compartment (Figure 6A, raclopride 0.0µg: $T_{(9)}$=3, p=0.021; raclopride 2.5µg: $T_{(10)}$=4, p=0.016 and raclopride 5.0µg: $T_{(10)}$=8, p=0.047). Similarly, females in all groups spent significantly more time in the compartments with both stimuli, male or female, than in the neutral compartment (p<0.05 for all comparisons). Females in all groups sniffed the male more than the female (Figure 6B, raclopride 0.0µg: $T_{(9)}$=0, p=0.008; raclopride 2.5µg: $T_{(10)}$=4, p=0.017; raclopride 5.0µg: $T_{(10)}$=1, p=0.007). However, females treated with 5.0µg of raclopride sniffed the female less than those treated with 0.0µg (0.0µg vs. 2.5µg: $Z_{(9,10)}$=1.751, p=0.08 and 00.0µg vs. 5.0µg: $Z_{(9,10)}$=2.842, p=0.005). As in Experiment 1, females in the saline group and those that received the lowest dose of raclopride made more attempts to access the male compartment than the female compartment (Figure 6C, raclopride 0.0µg: $T_{(9)}$=0, p=0.012 and raclopride 2.5µg: $T_{(10)}$=0, p=0.018), while females receiving the highest dose of this drug tended to make more attempts to access the male than the female compartment ($T_{(10)}$=7, p=0.066). Additionally, attempts to gain access to the male ($H_{(3)}$=4.449, p=0.106) or the female ($H_{(3)}$= 0.939, p=0.626) did not differ between groups according to treatment.

As shown in Table 2, female locomotion in the model was lower in both experimental groups than in the saline group (0.0µg vs. 2.5µg: $Z_{(9,10)}$=2.169, p=0.030 and 0.0µg vs. 5.0µg: $Z_{(9,10)}$=2.527, p=0.012). Although the total number of entries to the three choice chambers was reduced by this D2R antagonist (Table 2, $H_{(3)}$=7,924, p=0,019), this treatment did not affect the total time that females spent in the compartments (Table 2, $H_{(3)}$=1.969, p=0.374).

Sexual behavior

Females' behavior

The LQ was maximal in females from all groups and was not affected by the administration of raclopride (Figure 7A, $H_{(3)}$=0.847, p=0.655). Also, no differences were observed in the duration of the lordosis posture between the three groups (Figure 7B, $H_{(3)}$=1.940, p=0.379).

Neither the expression of hops and darts, nor the display of active sexual solicitations were affected with raclopride administration (hops and darts: $H_{(3)}$=0.222, p=0.895 and sexual solicitations: $H_{(3)}$=3.940, p=0.140, Figure 7C and D). Accordingly, the latencies to display these behaviors (Table 2, $H_{(3)}$=0.900, p=0.638) or to perform lordosis (Table 2, $H_{(3)}$=0.157, p=0.924) were not affected.

Males behavior

The number of mounts ($H_{(3)}$=1.112, p=0.574) and ejaculations ($H_{(3)}$=1.741, p=0.419) performed by the males, as well as the latencies to express these behaviors, did not differ between groups (mounting: $H_{(3)}$=0.137, p=0.934; ejaculation: $H_{(3)}$=3.497, p=0.174, Table 2).

Ambulatory test

As shown in Figure 5, no differences were detected between the experimental groups for any of the recorded variables (number of crosses: $H_{(3)}$= 1.941, p=0.379 and number of rearing postures: $H_{(3)}$= 0.228, p=0.892).

Discussion

This study shows that the selective blockade of either D1R or D2R in the NAcc shell does not affect the lordosis quotient or male over female preference displayed by late proestrous females, independently of its motor effects. These findings suggest that DAergic signaling in the NAcc shell does not play a major role in female sexual receptivity nor in the directional component of sexual motivation. Moreover, the clear reduction in the expression of sexual solicitations following administration of SCH 23390 at doses that did not affect or only moderately affected locomotion, together with the absence of a comparable effect of raclopride, supports a more relevant role for D1R than D2R activity in the NAcc shell in the expression of sexually motivated behaviors in females.

Lack of effect of antagonizing DAergic receptors in NAcc shell on sexual receptivity and male preference

The present results showing maximal sexually receptivity of late proestrous females after blocking D1R or D2R in the NAcc are in agreement with previous studies in ovariectomized fully hormonal-primed rats reporting that the systemic administration of DAergic antagonists do not affect lordosis quotient (Ellingsen and Ågmo 2004; García Horsman and Paredes 2004; Ismail et al. 2010). Furthermore, the administration of amphetamine, a nonselective indirect-acting DA agonist (Dayne Mayfield et al. 1993), in the NAcc (Guarraci et al. 2008) or the depletion of DA in the NAcc (Hansen et al. 1991a) does not affect female receptivity. Although other studies

have proposed an inhibitory role for DA on female receptivity via D2R (Everitt et al. 1974; Everitt and Fuxe 1977; Foreman and Hall 1987; Fernández-Guasti et al. 1987; Grierson et al. 1988; Mani et al. 1994), these effects vary depending on the females' hormonal priming and the DAergic drug and dose used. The differences between our results and those of these studies on systemic effects may be due to the action of these DAergic drugs in other areas that regulate the lordosis posture, such as the medial preoptic area (mPOA) and other hypothalamic areas (Powers and Valenstein 1972; Foreman and Moss 1979; Takeo et al. 1993; Apostolakis et al. 1996; Shimogawa et al. 2015), or locomotion such as the dorsal striatum (Beninger 1983; Robbins and Everitt 1992; Dunnett 2005).

Although DAergic transmission within the NAcc shell did not impact the sexual responsiveness of females to male mounts, the highest doses of SCH-23390 increased the duration of the lordosis posture performed by females, suggesting a role in the sensory-motor control of this reflexive posture. Indeed, these doses had the most pronounced effect on locomotion. These results are in line with prior research by Ellingsten & Ågmo (2004), which demonstrated an increase of lordosis duration after the systemic administration of 0.5 mg/kg of the DAergic antagonist cis(Z)-flupenthixol, a dose that also affected rats' locomotion.

Consistent with the lack of effect on sexual responsiveness, most female groups treated with D1R and D2R antagonists exhibited a clear preference for males. This heightened interest in males of rats regardless of DAergic manipulation was also evidenced by a greater olfactory exploration of males compared to females in the preference test. In a similar vein, Ellingsten & Ågmo (2004) found no difference in preference for an intact male vs. a castrated male when using fully hormonal-primed ovariectomized females treated systemically with different DAergic agents, apomorphine, amphetamine or cis(Z)-flupenthixol. Likewise, Ferreño et al. (2018) found that preference for a male against a sexually receptive female of postpartum estrous rats was not affected by systemic haloperidol administration.

According to current theories of motivation (Salamone and Correa 2002, 2012, 2024; Salamone et al. 2017), motivational processes encompass directional and activational aspects. The directional aspect is reflected in the fact that motivated behaviors are directed toward goals or outcomes; in this context, the goal is the male. The activational aspect is related to the effort and physical work individuals are willing to invest to reach a goal and interact with it. Studies employing behavioral tests designed to dissect these two aspects determined that DA in the NAcc does not mediate the direction of behavior but rather the activational aspects—the effort required to reach a certain goal. Under this conceptual framework, we do not expect male preference of sexually active females to change due to D1R or D2R antagonism. Instead, we expect to observe an effect on behavioral

displays involving greater energy expenditure by females in their search for proximity, as well as attempts to access the male (Ferreño et al. 2018) or sexual solicitations (Pfaus et al. 1999; Ismail et al. 2010).

Differential effect of DAergic receptors antagonism in NAcc shell on the expression of sexually motivated behaviors

As expected, the attempts made to access the male in the preference test, considered an index of effort (Ferreño Vázquez 2014; Ferreño et al. 2018), were reduced in females receiving medium and high doses of SCH 23390, and in those receiving the highest dose of raclopride. However, as attempts to obtain stimuli are complex motor acts, this effect may be, at least, partially reflecting motor impairment rather than reduced sexual motivation. Consistent with the notion that the D1R selective blockade in the NAcc shell affected females' motivation, SCH 23390, but not raclopride, reduced the display of proceptive behaviors. While the expression of hops and darts decreased only with the highest doses of SCH 23390, which caused greater motor impairment, solicitations decreased markedly with all doses of the antagonist, including those that did not affect or only moderately affected locomotion. The more pronounced effect of antagonizing the D1R on solicitations than on hops and darts could be related to differences in the characteristics of these two types of proceptive behaviors. Both are voluntary behaviors displayed by the female that promote approach and mounting by males (Beach 1976; Blaustein and Erskine 2002; Heijkoop et al. 2018; Guarraci and Frohardt 2019; Agrati 2022), however, hops and darts are more stereotyped behaviors and are displayed in a stimulus-response fashion in response to male stimulation. For example, they can be elicited by stimulation of the hind flanks, either in a reproductive context—by male mounting—(Beach 1976; Bergheim et al. 2015; Mondino et al. 2019) or even in a non-reproductive context, by manual stroking (Hansen et al. 1991a, b; Cummings and Becker 2012). In contrast, solicitations are more dependent on the female's motivational state, been more sensitive to manipulations that decrease or increase sexual motivation (Pfaus 2009; Pfaus et al. 1999; Gelez et al. 2013; Kim et al. 2013; Mondino et al. 2019). Therefore, the clear effect of the D1R antagonist on solicitation behavior at all doses supports the hypothesis that the D1R activation in the NAcc shell is involved in sexual motivation of late proestrus rats.

Consistent with the proposed role of the DAergic system in the sexual motivation of females, repeated, intermittent, systemic administration of amphetamine in a manner that induces changes in the mesolimbic dopaminergic system mediating behavioral sensitization (Robinson and Becker 1986), enhances the expression of sexual motivation behaviors in ovariectomized, fully hormonal-primed rats in both the bilevel chamber

(Afonso et al. 2009) and the paced-mating test (Guarraci and Clark 2003). Similarly, systemic administration of cocaine at low doses to fully hormonally-primed ovariectomized females, increases the display of solicitations and hops and darts (Pfaus et al. 2010). Together with present results, these studies support the idea that DA plays a role in mediating sexually motivated behaviors in female rats, particularly via D1R in the NAc shell.

The lack of effect of D2R blockade in the NAcc on the expression of proceptive behaviors contrasts with previous studies showing that systemic administration of the D2R antagonist haloperidol reduces the performance of solicitations and hops and darts (Ismail et al. 2010; Ferreño Vázquez 2014). This discrepancy may be due to the different administration routes, systemic versus local. Systemic administration involves several DAergic pathways, such as the nigrostriatal pathway, which is strongly involved in motor control (Dunnett 2005). Therefore, its alteration will produce a greater motor impact than altering NAcc shell signaling.

As with the effects observed in the sexual behavior of proestrus females, local antagonism of DAreceptors in the NAcc of postpartum female rats with the nonspecific antagonists cis-z-flupenthixol reduces pups´retrieval, active component of maternal behavior, but leaving nursing unchanged or even increasing its duration (Keer and Stern 1999). These effects are replicated by depressing the release of DA in the NAcc by means of inhibiting (Numan et al. 2009) or destroying (Hansen et al. 1991a, b) the DAergic neurons of the VTA. Interestingly, in line with present results, Numan et al. (2005) found that blocking D1R with SCH 23390 in the NAcc, but not antagonizing D2R with eticlopride, disrupted the active components of postpartum rats' maternal behavior. Moreover, as observed in sexual behavior (Ismail et al. 2010; Ferreño Vázquez 2014), the systemic administration of a D2R antagonist, unlike local injection in the NAcc, affects pups' retrieval of lactating rats Hansen et al. (1991b). The similar effect of antagonizing DAergic receptors in the NAcc on sexual and maternal behaviors of the female rat could be related to the fact that both are strongly motivated affiliative behaviors that share common characteristics and neural circuits (Hansen, 1994; Numan, 2007; Numan & Stolzenberg, 2009; Stolzenberg & Numan, 2011; Numan, 2012). Under this framework DA acting on the NAcc, primarily through D1R, seems to have a main role on the expression of the most active voluntary components of these affiliative behaviors in females.

The greater impact of the D1R antagonist compared to the D2R antagonist on the sexual and maternal behavior of females contrasts with the study by Baldo et al. (2002) on the feeding behavior of male rats, which showed that equivalent doses of D1R and D2R antagonists had a similar impact on feeding. Therefore, the reduced or absent effect of blocking D2R in the NAcc shell of female rats (present results, Numan et al. 2005), could be due to differences in DAergic control of feeding and affiliative behaviors. It could also be due to sex-dependent

differences in sensitivity to D2R antagonists. Accordingly, the function of DAergic receptors is modulated by sex and gonadal steroid background (Becker 1999; Yoest et al. 2018; Kokane and Perrotti 2020; Zachry et al. 2021). Furthermore, Baldo et al. (2002) and other studies (Nowend et al. 2001; Lex and Hauber 2008; Farrar et al. 2010) have reported that antagonizing D2R in the core subregion of the NAcc disrupts motivated behaviors. Several studies have attributed a primary role to DA increases in the NAcc core in signaling the activational or energizing aspects of these behaviors (Sokolowski and Salamone 1998; Ghods-Sharifi and Floresco 2010; Saddoris et al. 2015; Ko and Wanat 2016; Dai et al. 2022). Therefore, future research should examine the differential contributions of the two families of DAergic receptors in both NAcc subregions to female sexual motivation.

The DAergic mesolimbic pathway plays a role in more than just behavioral activation. It has also been associated with effort-related decision-making between rewarding activities (Salamone et al. 2007, 2016a, b; Ghods-Sharifi and Floresco 2010; Salamone and Correa 2012). For instance, Nowend et al. (2001) showed that blocking D1R or D2R in the core and shell regions of the NAcc decreased lever pressing to obtain a preferred, highly reinforcing food when a less reinforcing food was available. These findings, along with those of Koch et al. (2000) and Baldo et al. (2002), support the theory that activation of D1R and D2R in the NAcc plays a significant role in allocating behavioral resources to override the effort associated with obtaining a preferred reward. Therefore, rather than influencing the execution of sexual behavior, it is possible that activation of D2R in the NAcc shell of females could mediate a preference for sexual interaction over other rewarding activities. It would be interesting to evaluate the role of DAergic receptors in the NAcc in regulating behavioral choices between sexual interaction and other rewarding activities when both are available simultaneously.

Effect of antagonizing DAergic receptors in NAcc shell on female locomotion

The reduction of the locomotor exploration observed in late proestrous females after the administration of SCH 23390 or raclopride in the NAcc shell is in accordance with previous studies employing male rats locally injected D1R or D2R antagonists or agonists in this nucleus (Nowend et al. 2001; Baldo et al. 2002; Guadarrama-Bazante and Rodríguez-Manzo 2019). However, the locomotor effects of the D2R antagonist raclopride observed in the present study were less intense than those expected based on these studies. In fact, doses of 2.5µg or greater were employed in the present study because we did not observe behavioral effects in females in late proestrus with 1.0µg doses in a pilot study. This dose of raclopride produces motor (Nowend et al. 2001; Baldo et al. 2002) and motivational effects (Lex and Hauber 2008) when administered in the NAc shell

of male rats. Interestingly, in accordance with the present study, Numan et al. (2005) found that the administration of 1µg or 3µg of the D2R antagonist etoclopride in the NAcc shell of postpartum female rats does not affect locomotion. As previously mentioned, the low sensitivity of female rats to D2R antagonists administered in the NAcc shell (present results and Numan et al. 2005) could be related to sex-dependent differences in DAergic mesolimbic function. It could also be related to the particular stages of the female rats' reproductive cycles in these studies: the late proestrus and postpartum periods, which are characterized by significant changes in circulating ovarian steroid levels (Bazzett and Becker 1994; Becker 1999; Yoest et al. 2018; Kokane and Perrotti 2020).

In summary, the present study shows that activation of either the D1R or the D2R in the NAcc shell is not required for sexually active female rats to display sexual receptivity or interest toward a male. However, our findings suggest that D1R signaling in this nucleus contributes to the expression of female sexual motivation, while suggesting a more limited role of the D2R. Further studies examining D2R function over a broader dose range, comparing the NAcc shell and core, and incorporating behavioral tests that consider effort-based decision-making will help clarify the respective contributions of D1R and D2R signaling to female sexual motivation in more challenging and ecological contexts.

Table 1. Behavior of females in the preference test and of females and of both, males in the sexual behavior test after administration of SCH 23390

Preference test					
	0.0	0.5	1.0	2.5	5.0
Locomotion	125 (112-161)	96.5 (77-119)	69.5 (50.5-89.3)**	36.5 (9.3-52.8)****ǂǂ†	17.5 (8.5-41.5)****ǂǂ†
Total number of visits	42 (35-53)	30 (25.5-37.3)	21.5 (16.3-29.3)**	12.5 (2.5-17)****ǂǂ†	5.5 (3-12.8)****ǂǂ†
Total time spent in compartments (s)	650 (610-690.5)	574.5 (519-691.3)	681 (623.8-747.8)	636 (523.3-782.3)	758.5 (617.5-809.3)
Sexual behavior test					
Female					
proceptive latency (s)	30.3 (21.1-46)	28.2 (10.8-51.7)	21.1 (13.4-75.9)	13.2 (11.6-28.2)	30.7 (18.5-52.9)
receptive latency (s)	36.6 (28.4-49.6)	22.85 (12.9-36.8)	51.75 (16.5-83.3)	21.9 (13.8-35.6)	36.1 (21.7-61.6)
Male					
mount latency (s)	37.8 (28.2-49.4)	22.7 (12.7-36.6)	51.5 (16.3-83.1)	23.3 (13.5-35.4)	35.9 (21.6-61.2)
ejaculation latency (s)	579.8 (296-773.5)	449.3 (243.4-745.6)	640.1 (308.6-783.5)	591.6 (249.5-900)	403.9 (279-510.9)
n° mounts	22 (14.5-27)	19 (14.3-30.5)	23 (16.5-30.5)	24 (17.5-28.8)	22 (15-24)
n° ejaculation	1 (1-2)	1 (1-2)	1 (1-2)	1.5 (0.8-2)	1 (1-2)

Data is expressed as median (Q1-Q3). ****p<0.0001 and **p<0.01 vs 0.0µg of SCH 23390; ǂǂp<0.001 and ǂǂp<0.01 vs 0.5µg of SCH 23390; †p<0.05 vs 1.0µg of SCH 23390, Dunn's test between dose groups.

Table 2. Behavior of females in the preference test and of females and of both, males in the sexual behavior test, after administration of raclopride

Preference test			
	0.0	2.5	5.0
Locomotion	120 (111.5-147)	89 (56.3-110.5)*	67 (34.8-122.5)*
Total number of visits	41 (36-48.5)	30 (20-37.3)	17 (11-39)**
Total time spent in compartments (s)	697 (646.5-734.5)	778.5 (662.8-816.3)	721 (658.5-793.8)
Sexual behavior test			
Female			
proceptive latency (s)	41.6 (33.6-86)	56.9 (43.8-75.6)	50.7 (41-96)
receptive latency (s)	47.8 (40.5-153.7)	68.7 (39-92.3)	56.4 (42.4-103.7)
Male			
mount latency (s)	47.5 (40.7-153.5)	68.4 (38.6-92)	55.9 (42-103.4)
ejaculation latency (s)	449.7 (264.8-702.4)	516.5 (347.9-696.7)	34.6 (290.4-458.4)
n° mounts	24 (17.5-28.5)	20.5 (14.8-23.3)	21 (18.3-26.3)
n° ejaculation	1 (1-2)	1 (1-2)	2 (1-2)

Data is expressed as median (Q1-Q3). **p<0.01 and *p<0.05 vs 0.0µg of raclopride, Dunn's test between dose groups.

Figure 1

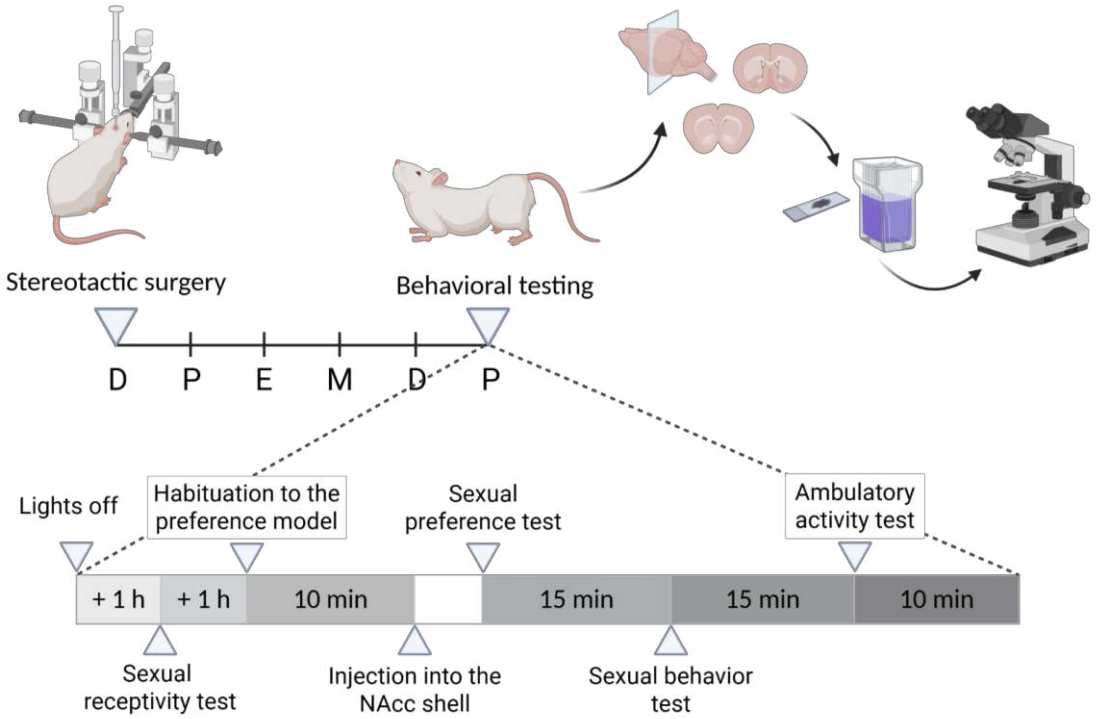
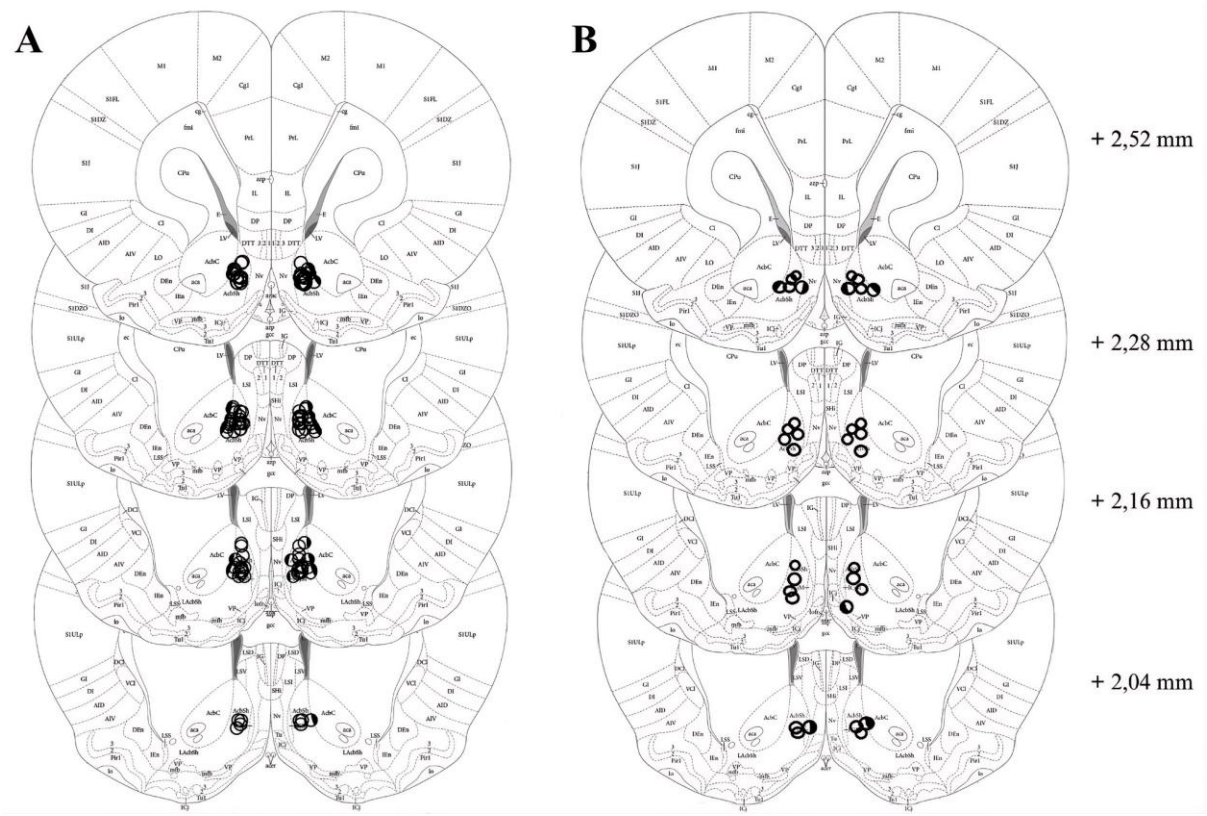

Stereotactic surgery
Behavioral testing
D
P
E
M
D
P
Lights off
Habituation to the preference model
Sexual preference test
Ambulatory activity test
+ 1 h
+ 1 h
10 min
15 min
15 min
10 min
Sexual receptivity test
Injection into the NAcc shell
Sexual behavior test

Figure 2



1 **Figure 3**

2

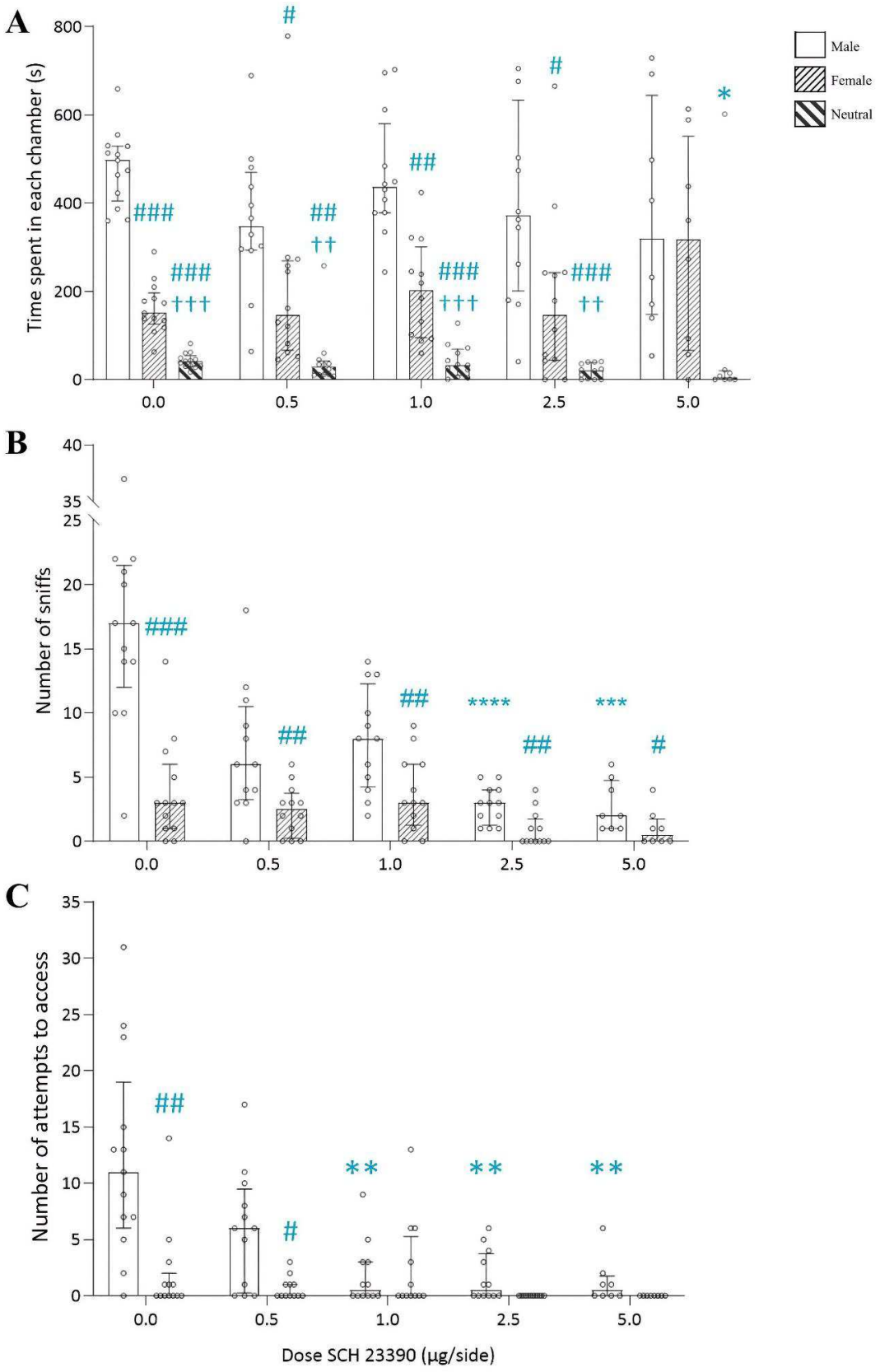

A
Time spent in each chamber (s)
800
600
400
200
0
0.0
0.5
1.0
2.5
5.0
Male
Female
Neutral
B
Number of sniffs
40
35
25
20
15
10
5
0
C
Number of attempts to access
30
Dose SCH 23390 (µg/side)

Figure 4.

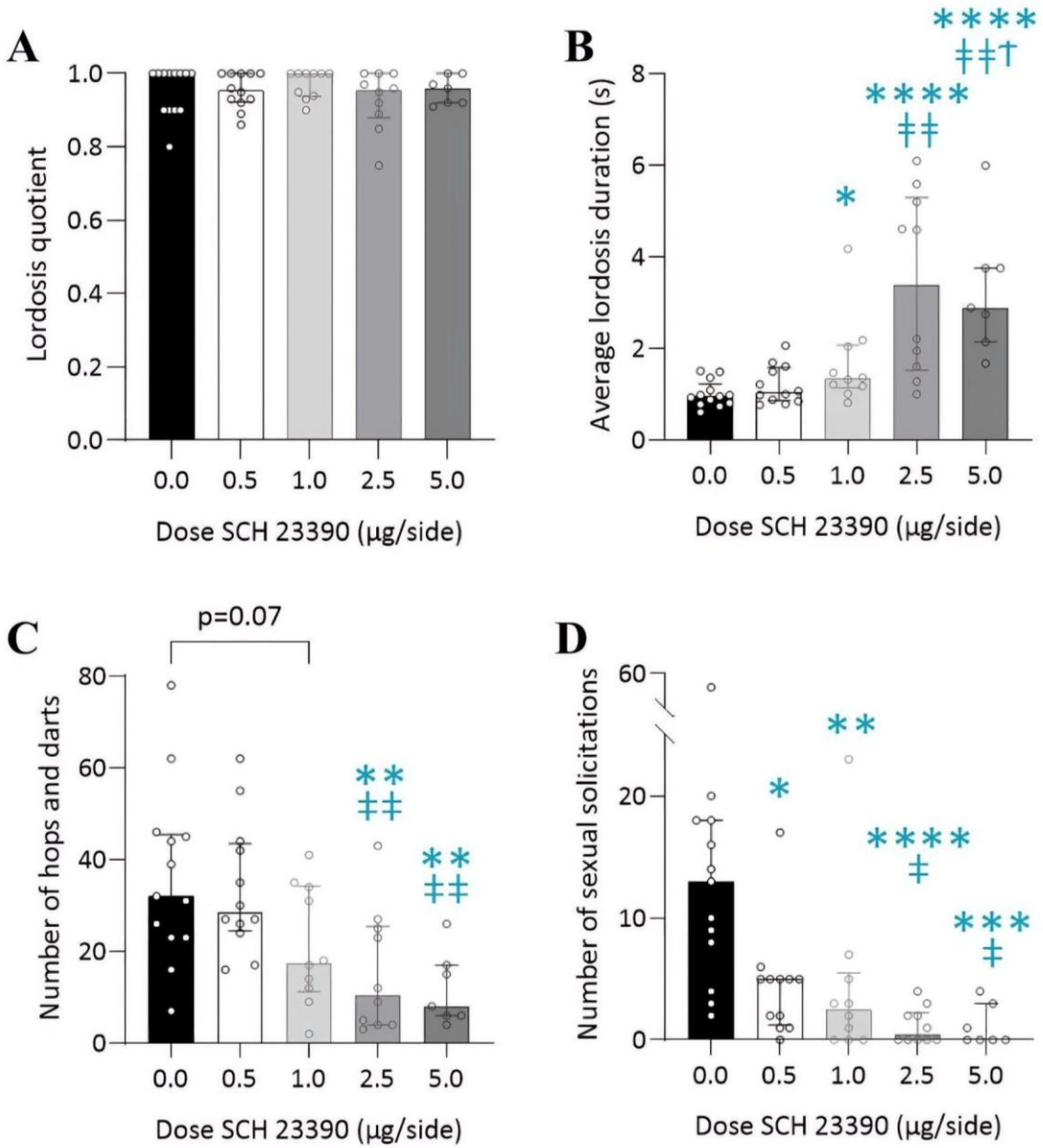

A
Lordosis quotient
1.0
0.8
0.6
0.4
0.2
0.0
0.0 0.5 1.0 2.5 5.0
Dose SCH 23390 (µg/side)
B
Average lordosis duration (s)
8
6
4
2
0
* **** ‡‡ **** ‡‡†
0.0 0.5 1.0 2.5 5.0
Dose SCH 23390 (µg/side)
C
p=0.07
Number of hops and darts
80
60
40
20
0
** ‡‡ ** ‡‡
0.0 0.5 1.0 2.5 5.0
Dose SCH 23390 (µg/side)
D
Number of sexual solicitations
60
20
10
0
* ** **** ‡ *** ‡
0.0 0.5 1.0 2.5 5.0
Dose SCH 23390 (µg/side)

Figure 5.

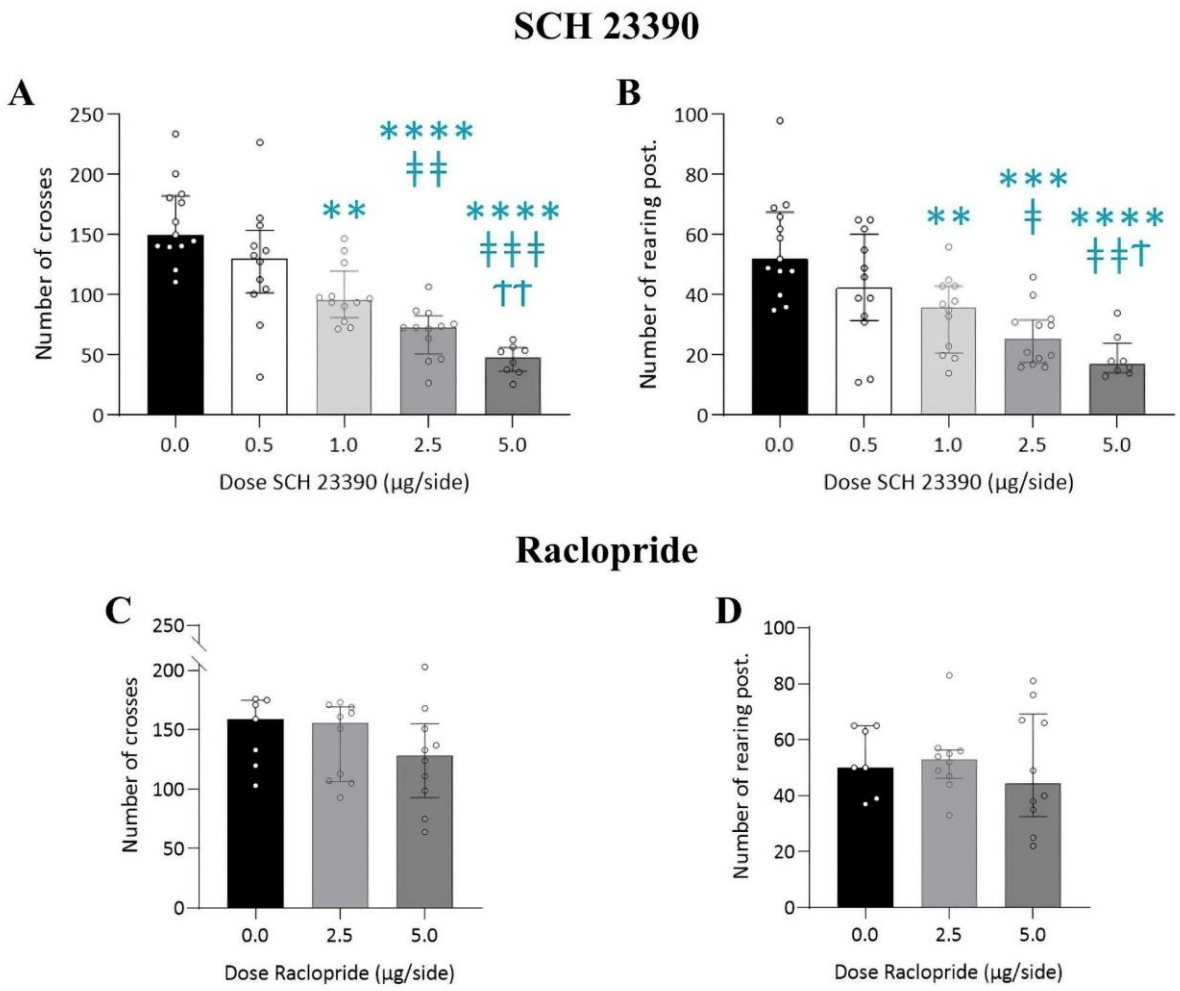

SCH 23390
A
Number of crosses
250
200
150
100
50
0
0.0
0.5
1.0
2.5
5.0
Dose SCH 23390 (µg/side)
****
‡‡
**
****
‡‡‡
††
B
Number of rearing post.
100
80
60
40
20
0
0.0
0.5
1.0
2.5
5.0
Dose SCH 23390 (µg/side)
***
‡
**
****
‡‡†
Raclopride
C
Number of crosses
250
200
150
100
50
0
0.0
2.5
5.0
Dose Raclopride (µg/side)
D
Number of rearing post.
100
80
60
40
20
0
0.0
2.5
5.0
Dose Raclopride (µg/side)

Figure 6.

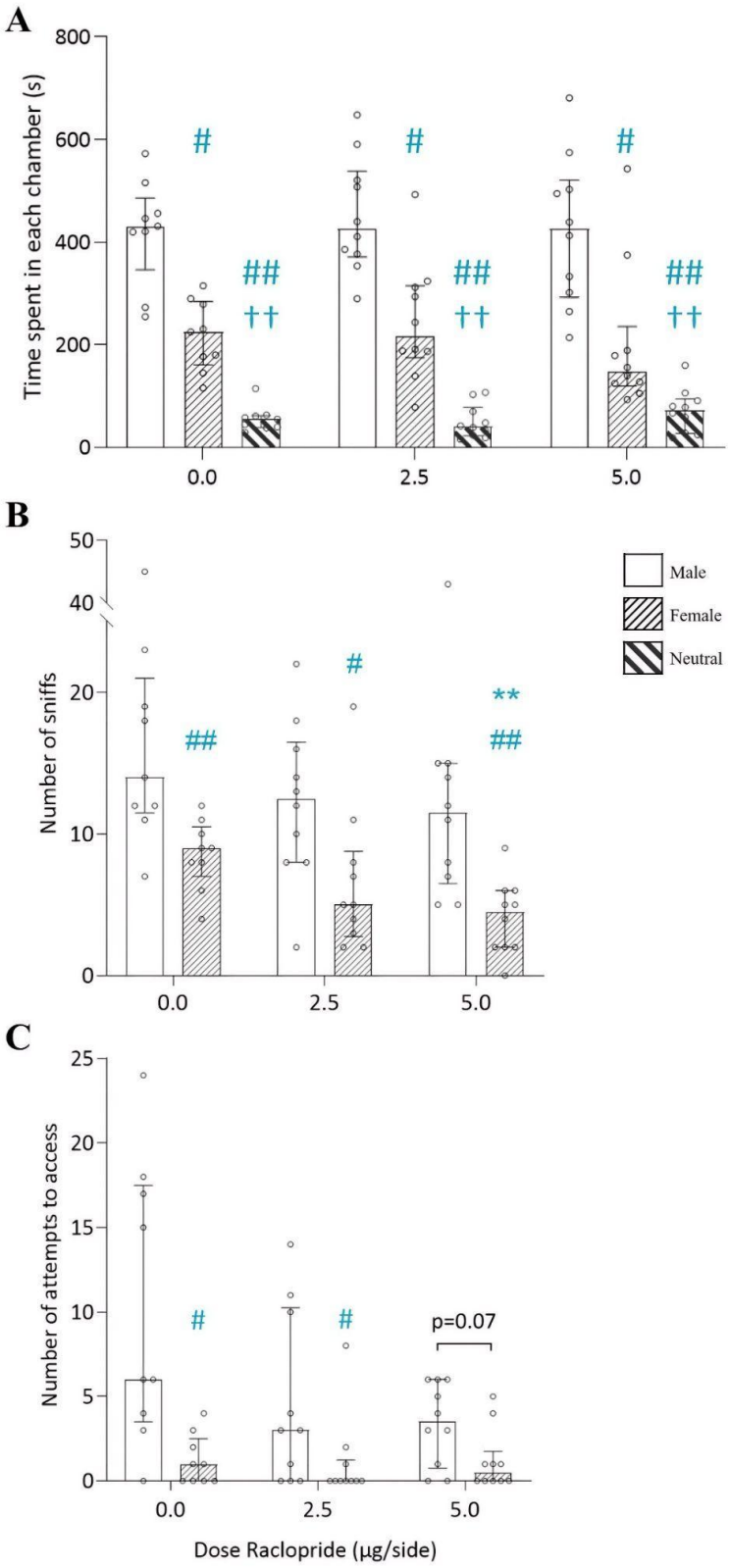
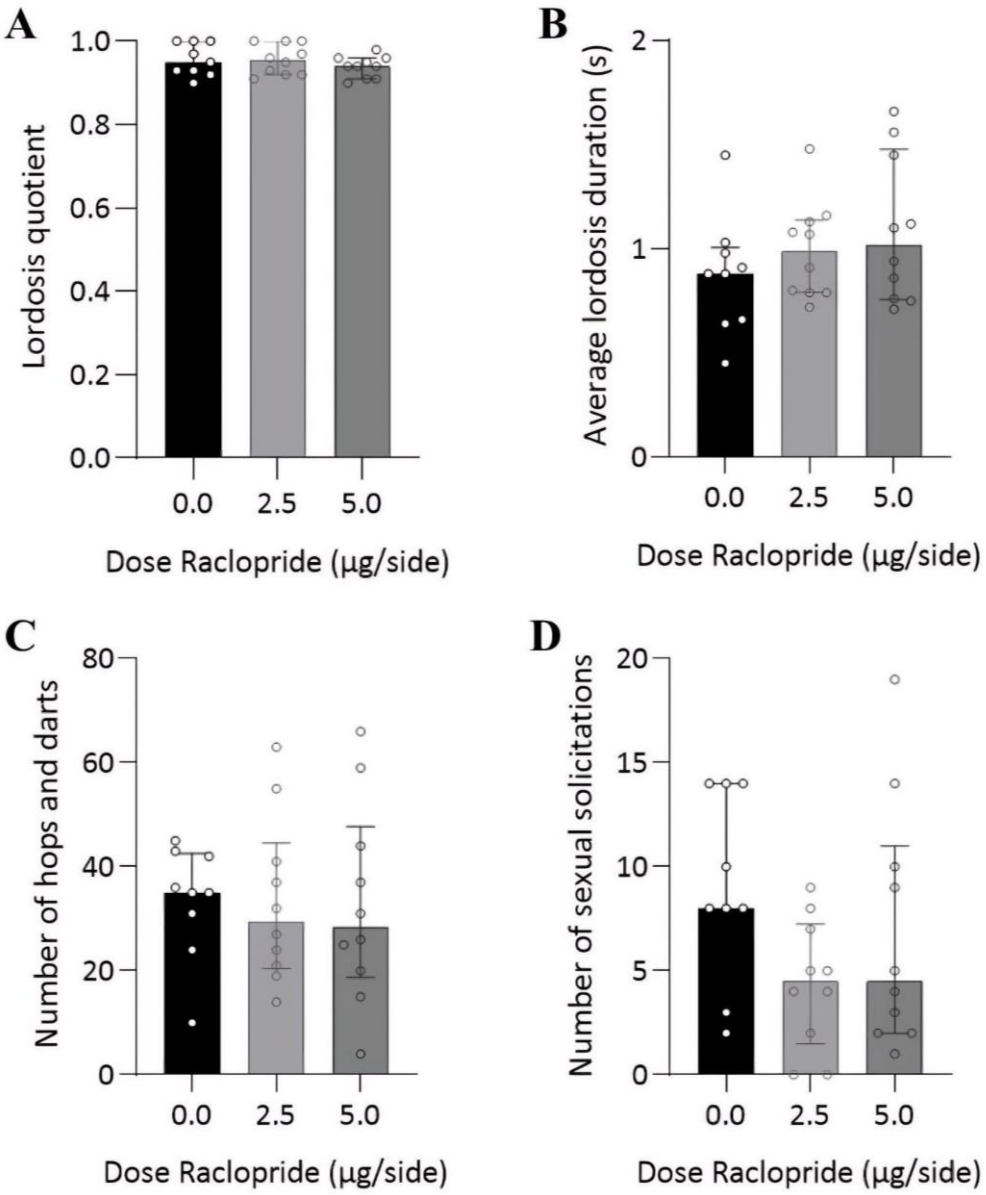

A
Time spent in each chamber (s)
800
600
400
200
0
0.0
2.5
5.0
#
##
††
B
Number of sniffs
50
40
20
10
0
**
Male
Female
Neutral
C
Number of attempts to access
25
20
15
10
5
0
p=0.07
Dose Raclopride (µg/side)

Figure 7.


A
Lordosis quotient
1.0
0.8
0.6
0.4
0.2
0.0
0.0
2.5
5.0
Dose Raclopride (µg/side)
B
Average lordosis duration (s)
2
1
0
0.0
2.5
5.0
Dose Raclopride (µg/side)
C
Number of hops and darts
80
60
40
20
0
0.0
2.5
5.0
Dose Raclopride (µg/side)
D
Number of sexual solicitations
20
15
10
5
0
0.0
2.5
5.0
Dose Raclopride (µg/side)

Figures Legends

Figure 1. Schematic representation of the experimental procedure. Stereotaxic surgery for bilateral cannula implantation was performed during diestrus (D). Behavioral testing was conducted during late proestrus (P), after the animals had completed one full postoperative estrous cycle. The timeline shows the sequence of procedures performed on the test day. On the following day, females were transcardially perfused, and their brains were collected and processed for histological verification of the injection sites. D: diestrus; P: proestrus; E: estrus; M: metestrus. Created in BioRender. Uriarte, N. (2026) https://BioRender.com/9w05n11

Figure 2. Histological verification of microinjection sites in the dorsomedial NAcc shell. The locations of the microinjection sites in animals included in the behavioral analyses for those receiving (A) SCH 23390 or (B) raclopride. Injection sites were determined by microscopic examination of cresyl violet stained sections. Open circles indicate injections into the Nacc shell, whereas half-filled circles indicate injections that extend into adjacent regions. Anteroposterior coordinates are expressed in millimeters relative to Bregma (0.0 mm). Coronal brain section diagrams were adapted from Paxinos and Watson (6th edition, 2007).

Figure 3 | Behavior of late proestrous females in the male vs. female preference test. Cumulative time spent in each chamber (male, female and neutral, Panel A), number of male and female sniffs (Panel B) and number of attempts to access the male and the female (Panel C) made by late proestrous rats after the administration of 0.0, 0.5, 1.0, 2.5 or 5.0µg/0.5µl/side of SCH 23390. The data are presented as median (interquartile range) and circles represent individual values per group. ###$p<0.001$, ##$p<0.01$ and #$p<0.05$ vs male; †††$p<0.001$ and ††$p<0.01$ vs female; within a group, Wilcoxon matched-pairs test. ****$p<0.0001$, ***$p<0.001$, **$p<0.01$ and *$p<0.05$ vs 0.0µg, Dunn's test between dose groups.

Figure 4 | Behavior of late proestrous female rats in the sexual behavior test in the bilevel chamber. Lordosis quotient (number of lordosis/(total number of mounts + ejaculations)) (Panel A), average duration (s) of lordosis posture (Panel B), number of hops and darts (Panel C) and number of sexual solicitations (Panel D)

displayed by late proestrous females after the administration of 0.0, 0.5, 1.0, 2.5 or 5.0µg/0.5µl/side of SCH 23390. The data are presented as median (interquartile range) and circles represent individual values per group. ****p<0.0001, ***p<0.001, **p<0.01 and *p<0.05 vs 0.0µg; ǂp<0.01 and ǂp<0.05 vs 0.5µg; ŧp<0.05 vs 1.0µg, Dunn's test between dose groups.

Figure 5 | Behavior of females in the ambulatory test in Experiment 1 (SCH 23390 administration) and Experiment 2 (raclopride administration). Number of crosses (panels A and C) and number of rearing postures (panels B and D) performed by late proestrous female rats following the administration of 0.0, 0.5, 1.0, 2.5 or 5.0µg/0.5µl/side of SCH 23390 (panels A and B) or 0.0, 2.5 or 5,0µg/0.5µl/side of raclopride (panels C and D). The data are presented as median (interquartile range) and circles represent individual values per group. ****p≤0.0001, ***p<0.001 and **p<0.01 vs control group, ǂǂp<0.001, ǂp<0.01 and ǂp<0.05 vs 0.5µg, ŧŧp<0.01 and ŧp<0.05 vs 1.0µg, Dunn's test between dose groups.

Figure 6 | Behavior of late proestrous female rats in the male vs. female preference test. Cumulative time spent in each chamber (male, female and neutral, Panel A), number of male and female sniffs (Panel B) and number of attempts to access the male and the female (Panel C) made by late proestrous female rats after the administration of 0.0, 2.5 or 5,0µg/0.5µl/side of raclopride. The data are presented as median (interquartile range) and circles represent individual values per group. ##p<0.01 and #p<0.05 vs male; ††p<0.01 vs female, within a group, Wilcoxon matched-pairs test. **p<0.01 vs 0.0µg, Dunn's test between dose groups.

Figure 7 | Behavior of late proestrous female rats in the sexual behavior test in the bilevel chamber. Lordosis quotient (number of lordosis/(total number of mounts + ejaculations), Panel A), average duration (s) of lordosis posture (Panel B), number of hops and darts (Panel C) and number of sexual solicitations (Panel D) displayed by late proestrous female rats after the administration of 0.0, 2.5 or 5.0µg/0.5µl/side of raclopride. The data are presented as median (interquartile range) and circles represent individual values per group. p=ns, Kruskal-Wallis test.

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