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Conspecific infection threat rapidly biases the social responses of female mice: Involvement of oxytocin

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ABSTRACT

Pathogen threat affects social preferences and responses across species. Here we examined the effects of social context and the infection status of conspecific females and males on the social and mate responses of female mice. The responses of female mice to males were rapidly affected by the presence of infected female conspecifics and infected males. In mice odor cues drive appetitive and aversive social and mate responses. Brief (1 min) exposure to the fresh urinary odors of females infected with the murine nematode parasite, *Heligmosomoides polygyrus*, attenuated the responses of other uninfected females to the odors of naturally preferred unfamiliar males and enhanced their preferences for familiar males. Likewise exposure to the odors of a male either infected with *H. polygyrus* or treated with the bacterial endotoxin, lipopolysaccharide, reduced the responses of females to the odors of unfamiliar males. In addition, females displayed an avoidance of, and discrimination against, male mice whose odors had been associated with that of an infected female ("guilt by association") and a preference for the odors associated with an uninfected female ("mate copying"). These shifts in preferences for female associated male odors were attenuated in a dose-related manner by pre-treatment with the oxytocin receptor antagonist, L-368,899. These findings show that social information associated with the infection status of conspecifics can rapidly bias the mate preferences of female mice in an oxytocin receptor dependent manner.

1. Introduction

Animals are under constant risk from parasites and pathogens facing a so-called "landscape of disgust" (Buck et al., 2018; Kavaliers et al., 2018). Infection and pathogen threat directly posed by others has been shown to influence social and sexual preferences and responses in a variety of species including humans (e.g., Beltran-Bech and Richard, 2014; Hamilton and Zuk, 1982; Kavaliers and Choleris, 2018; Olsson et al., 2014; Poirotte et al., 2017; Regenbogen et al., 2011; Vyas, 2013). In many cases the responses to infected conspecifics involve olfactory mechanisms. In rodents, where odor cues are of major importance in determining social responses and mate choice (Arakawa et al., 2011; Hurst, 2009; Hurst and Beynon, 2004; Kavaliers and Choleris, 2017a), females can distinguish between the odors of infected and uninfected males, avoiding and displaying aversive responses to the odors of parasitized males (e.g., Beltran-Bech and Richard, 2014; Ehman and Scott, 2002; Kavaliers and Colwell, 1995; Kavaliers et al., 2005; Penn et al., 1998; Zala et al., 2004).

The effects of pathogen threat on female mate responses have been primarily considered in terms of male-female interactions and responses. However, natural populations of animals experience complex social interactions, contact patterns, and networks and are not simply dyadic male-female interactions (Altizer et al., 2003; Ezenwa et al., 2016; Lopes et al., 2016). In female mice this entails interactions not only with males, but also with both uninfected and infected female conspecifics and their odor cues. Social information about potential pathogen threat in the absence of any behavioral interactions has significant emotional, motivational and neurobiological responses affecting the expression of disgust and subsequent avoidance and aversive behaviors (Kavaliers and Choleris, 2018; Kavaliers et al., 2018). Chemical and other sensory signals from nearby conspecifics have been shown to both positively and negatively influence sexually and

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reproductively related responses in mice and other rodents (Osakada et al., 2018; Petrulis, 2013 and references therein). In particular, in female mice brief exposure to the odors of an infected male can inhibit a female's natural responses to unfamiliar males (Kavaliers et al., 2003, 2014). Whether or not this bias in mate response also extends to the odors of infected conspecific females is unclear. Here, we investigated how female social preferences and mate choice are influenced by the infection status of conspecific females and males.

Firstly, we examined whether or not exposure to the odors of either an infected or uninfected female and male affects the subsequent social responses and mate choice of other females. Secondly, in view of the evidence for "mate-choice copying" in which females prefer males that have been associated with other estrous females and, or their odors (Galef et al., 2008; Kavaliers et al., 2006, 2017) we considered how association with the odors of an infected female affects subsequent female preferences for those uninfected males. Thirdly we addressed the neurobiological correlates of these effects. Specifically, we considered the roles of the nonapetide, oxytocin (OT) receptor (OTR) in mediating the effects of joint female/male exposure on subsequent female preferences. OT is linked to mammalian communication and social recognition. Oxytocin has been implicated in the modulation of social partner choice and social reward, sexual motivation as well as the olfactory mediated recognition and avoidance of infected males and the expression of "disgust" (Arakawa et al., 2010a, 2010b; Blitzer et al., 2017; De Dreu and Kret, 2016; Kavaliers and Choleris, 2018; Wei et al., 2015). OT is proposed to modulate social discrimination based on social salience and stimulus valence (Shamay-Tsoory and Abu-Akel, 2016).

Using an odor preference test, the results of which are considered to be consistent with social and sexual preference (Ehman and Scott, 2002; Krackow and Matuschak, 1991), we examined the effects of: (i) brief exposure to the odors of an uninfected estrous female or female subclinically infected with the murine nematode parasite, *Heligmosomoides polygyrus*, on the subsequent responses of other uninfected female mice to male odors; (ii) brief exposure to the odors of either a *H. polygrus* infected or a sick (but non-infectious) male treated with a non-replicating bacterial endotoxin, lipopolysaccharide (LPS), on the responses of females to male odors; (iii) brief exposure to the odors of either an infected or uninfected female associated with the odors of an uninfected male on the subsequent responses to the odors of that male; and (iv) treatment with the brain permeant OT receptor antagonist, L-368,8999 (Blitzer et al., 2017; Boccia et al., 2007; Olszewski et al., 2015; Wei et al., 2015), on the effects of pre-exposure to the odors of either an infected or uninfected female that were associated with an uninfected male on the subsequent responses to that male.

2. Materials and methods

2.1. Animals

Outbred male and female mice (CD-1, Charles River, Canada) were individually housed in clear Plexiglas cages (25 cm × 5 cm × 20 cm) under a 12:12 h dark light/dark cycle (lights 0800–2000 h) with wood shavings bedding and food (Pro-Lab Chow, St. Louis, MO) and tap water available ad libitum. Infected (parasitized) and non-infected (non-parasitized) mice were kept in separate rooms throughout the experiments. All procedures were conducted in accordance with the Institutional Animal Care Committees (University of Western Ontario protocol number 2008-058-05; Agriculture and Agri-Food (Lethbridge) protocol no. LRC 172) and the guidelines of the Canadian Council for Animal Care.

2.2. Parasite infection

Male and female mice were orally infected with approximately 400 infective (L3 stage) of *Heligmosomoides polygyrus*. Their bedding was collected and frozen at −18 °C for 20 days after infection. This subclinical infection elicits no evident malaise, including disruptions of the estrous cycle, alterations in testosterone levels, or pathology, though it is considered sufficient to elicit immune alterations (Barnard et al., 1998; Kavaliers et al., 2003). Resistant stages of *H. polygyrus* are shed in the faeces of infected hosts. After a short development period they become infective to other mice that acquire them during feeding, grooming and other social interactions (Herandez and Sukhedo, 1995). Detailed descriptions of infection with *H. polygyrus*, collection of odors, along with the results of previous determinations of the responses of females to the odors of infected males, and control uninfected males are provided elsewhere. Briefly, urine was obtained by palpation from single males and females as previously described (Kavaliers et al., 2003) and frozen at −18 °C until its use. At the end of the study mice were euthanized and infection confirmed by necropsy.

2.3. Experimental apparatus

Odor preferences of individual estrous female mice (n = 10, per group) were determined in the light period in a clean cage (25 cm × 5 cm × 20 cm) into which a vented Plexiglas tube (10 cm in length, 3 cm in diameter, divided in the middle and sealed at each end with fine plastic mesh) was placed (see Fig. 1 in Kavaliers et al. (2014)). The mesh was sufficiently open to permit diffusion of the odors and to allow the female to have nasal contact with both volatile and non-volatile odor components but prevented direct contact with, and chewing of, the odor sources. This eliminated the possibility of female infection while allowing for full olfactory exposure.

2.4. General experimental procedures

2.4.1. Odor pre-exposures

15 min prior to odor preference determinations estrous females were exposed to either female and, or male odors. Different females were used for each of the experiments and tests. During the odor pre-exposure conditions individual female mice were placed briefly for 1 min in clean cages in a sealed Plexiglas partitioned area (12.5 × 15 × 10 cm) of the cage that was provided with the vented Plexiglas tube in which an odor source was placed. This small space ensured that the female was in very close proximity and exposed to the odors. To minimize novelty responses and to allow for habituation to the apparatus, female mice were exposed to the empty tubes in clean cages for 30 min on 3 consecutive days prior to pre-exposures and testing.

2.4.2. Odor preference tests

15 min after the various odor pre-exposures the odor preferences of individual females were determined in the Plexiglas partitioned cage. The 15 min was based on the results of prior studies (Kavaliers et al., 2003, 2014). During the odor preference test each end of a vented Plexiglas tube contained filter paper with a different odor source. During the 5 min test the times spent investigating each odor source (head/nose oriented towards and within 2 cm of the odor source) were recorded. Each female was tested only once.

Experiment 1. Effects of pre-exposure to the odors of either infected females or males on the subsequent responses of females to male odors.

The odor sources (n = 10, for each condition) for pre-exposure were bedding (50 g) of either an: (i) uninfected estrous female; (ii) estrous female infected for 20 day with the nematode parasite, *H. polygyrus*; (iii) uninfected non-estrous female; (iv) uninfected male; (v) male infected with *H. polygyrus*; (vi) sick (as confirmed by body weight loss) male that received 100 μg/kg of the bacterial endotoxin lipopolysaccharide (LPS) (derived from *Escherichia coli* serotype 0111:B4, Sigma Chemical, St. Louis MO) dissolved in 0.9% isotonic saline (bedding collected 24 h post-injection); (vii) uninfected vehicle (isotonic saline, 0.50 ml/kg) treated male; (vii) clean bedding containing no male or female odor

components. At least 10 days before testing isolated females were primed with the bedding of uninfected males not used in the present study to facilitate estrous cycling. Daily wet vaginal smears were used to determine the estrous state of the females during the test period (Rugh, 1968).

The male stimulus odors for the preference tests were unfamiliar male – familiar male (both uninfected). The tubes contained filter paper spotted with urine and associated anogenital odorous secretions of the male. Immediately before each days testing a fixed aliquot of urine (5 μl) was thawed, diluted 1:5 with deionized water and spotted on the filter paper (1.0 cm diameter spot, Whatman No. 5 filter paper, London, UK). Males whose bedding (200 g in fine plastic mesh to prevent any direct contact and infection) was placed in the home cage of a female for 3 days before the test were considered as being familiar.

Experiment 2. Effects of pre-exposure to joint female and male odors on the responses of females to male odors.

The odor sources (n = 10, for each condition) for pre-exposure were bedding (50 g) of either an: (i) uninfected male (A) + uninfected estrous female; (ii) male (A) + *H. polygyrus* infected estrous female; (iii) male (A) + uninfected non-estrous female; (iv) male (A) + restraint stressed female. Females were restraint stressed by being placed in a sealed vented tube (10 cm × 3 cm) that included bedding that was used as the odor source for exposures.

The male stimulus odors for the preference tests were the odors of a familiar male (familiar male A) associated with female odor versus unfamiliar uninfected male (unfamiliar male B), with the natural expected preference being for unfamiliar males (Choleris et al., 2009). Urine was collected and presented as described in Experiment 1. In control studies determination were made of the effects of pre exposure to the odors of: (i) Male A alone; (ii) Uninfected estrous female alone; (ii) Infected estrous female alone on familiar Male A - unfamiliar Male B preferences.

Experiment 3. Effects of an oxytocin receptor antagonist on female responses to male odor pre-exposure

The oxytocin receptor antagonist, L-368,899 (L-368,899 hydrochloride Tocris Bioscience, Minneapolis MN) (1.0 and 5.0 mg/kg) and the control isotonic saline vehicle (0.50 ml/kg) were administered 30 min before the odor pre-exposures. Previous studies have shown that L-368,8999 at 5.0 mg/kg is an effective OT receptor antagonist in rats and mice, crossing the blood brain barrier with a half-life of approximately 2 h (Blitzer et al., 2017; Boccia et al., 2007; Olszewski et al., 2015; Wei et al., 2015).

The male stimulus odors for the preference tests were the male (familiar male A) associated with female odor versus an unfamiliar uninfected male (unfamiliar male B). The tubes contained filter paper spotted with urine and associated anogenital odorous secretions of the males and females. Immediately before each testing day a fixed aliquot of urine (5 μl) was thawed, diluted 1:5 with deionized water and spotted on the filter paper (1.0 cm diameter spot, Whatman No. 5 filter paper, London, UK).

2.5. Data analysis

For experiment 1 preference for an 'Unfamiliar Male' odor, was calculated by dividing the time spent investigating the unfamiliar male's odor by the total time spent investigating both odors (i.e. [unfamiliar male] / [unfamiliar male + familiar male]). For Experiments 2 and 3 preference rations were calculated as [male A] / [male A + male B], with male A being that associated with the female (familiar) and male B that has not been associated with the female (unfamiliar). One sample *t*-tests were used to test whether or not the odor preferences of the females differed from random (0.5). For each preference ratio the effects of pre-exposure to various odors were assessed with separate one-way analyses of variance (ANOVA). Post hoc tests were performed using Tukey's Honestly Significant Difference test, and all tests used a significance criterion of $\alpha = 0.05$. All statistical analyses were performed in IBM SPSS Statistics 23.

Table 1
Effects of a 1 min pre-exposure to infected and uninfected male or female odors on the subsequent preferences of females for the odors of unfamiliar males.

Exposure condition	*t*	*p*-Value	Effect size (*d*)	Direction of effect
No female or male	3.44	0.007	1.09	>
Uninfected estrous female	6.63	0.0001	2.10	>
Uninfected non-estrous female	5.15	0.0006	1.63	>
Infected estrous female	−4.05	0.0029	−1.28	<
Uninfected male	5.43	0.0004	1.72	>
Infected male	−2.29	0.0478	−0.72	<
Uninfected male + Vh	6.12	0.0002	1.94	>
Uninfected male + LPS	−3.302	0.0092	−1.04	<

3. Results

3.1. Preference for the odors of unfamiliar males

Experiment 1. Effects of pre-exposure to either infected female or male odors on the subsequent responses of females to male odors (Table 1).

3.1.1. Pre-exposure to female odors

The ANOVA revealed a significant effect of female odor pre-exposure on subsequent preferences for the odors of unfamiliar males, ($F(3,36) = 22.960$, $p < 0.001$, $\eta^2 = .66$). As expected females that had no female odor pre-exposure displayed a significant preference ($p = 0.007$) for the odors of an unfamiliar males. Pre-exposure to the odors of either an uninfected estrous ($p < 0.01$) or non-estrous ($p = 0.01$) female significantly enhanced the preferences for the odors of unfamiliar males (Fig. 1; Table 1). In contrast, pre-exposure to the odors of an estrous infected female significantly reduced ($p < 0.001$) female preference for the odors of unfamiliar males such that females now displayed a significant avoidance of the odors of an unfamiliar male and preferences for odors of the familiar male ($p = 0.03$).

3.1.2. Pre-exposure to male odor

The ANOVA revealed a significant effect of male odor pre-exposure on the subsequent preferences for the odors of unfamiliar males ($F(4,45) = 22.051$, $p < 0.001$, $\eta^2 = .662$) (Fig. 2). Post hoc analysis revealed that pre-exposure to the odors of an uninfected male significantly ($p = 0.010$) enhanced the preferences for uninfected males ($p < 0.001$) (Table 1). In contrast exposure to the odors of *H. polygyrus* infected males significantly ($p = 0.024$) reduced female odor preferences for unfamiliar males such that females now preferred the odors of the familiar males ($p = 0.048$). Similarly, pre-exposure to the odors of an LPS treated male significantly ($p < 0.001$) reduced the preference for the odors of unfamiliar males such that they now preferred the odors of familiar males ($p = 0.009$). This was not significantly different ($p = 0.935$) from that seen after exposure to the odors of *H. polygyrus* infected males. Females pre-exposed to the odors of vehicle treated males displayed the expected significant preference for the odors of unfamiliar males ($p < 0.001$) that was not significantly different from that seen after exposure to the odors of uninjected and uninfected males.

Thus, preference for the odors of an unfamiliar male was affected by prior exposure to either a female or male odor. Preference for the odors of an unfamiliar male was specifically inhibited by prior exposure to the odors of either an infected conspecific female or infected male.

Experiment 2. Effects of pre-exposure to joint female and male odors on the responses to male odors (Table 2).

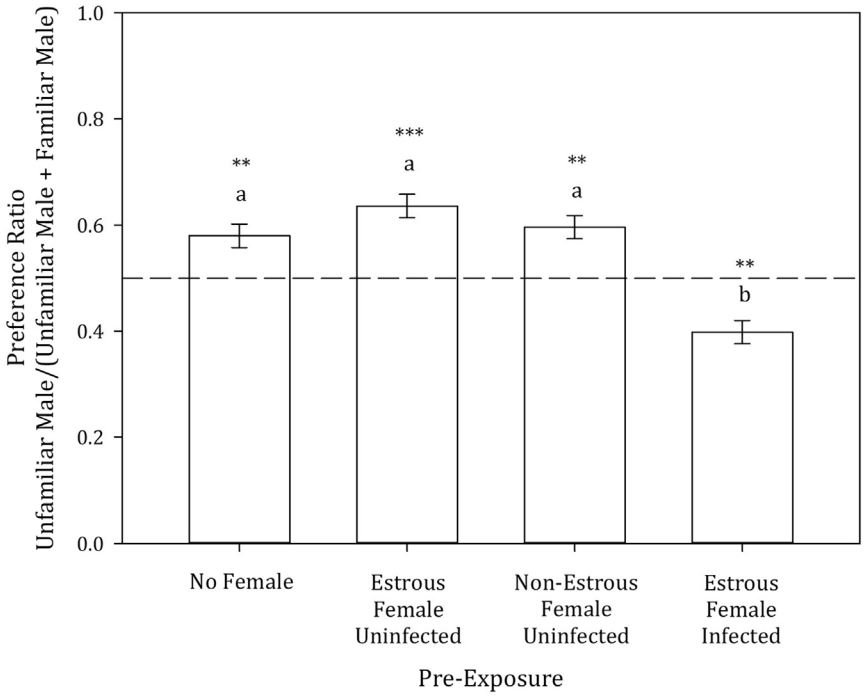

Fig. 1. Effects of a 1 min pre-exposure to the odors of: (i) Uninfected Estrous Female; (ii) Uninfected Non-estrous Female; (iii) Infected Estrous Female; (iv) or clean bedding (No Female) on female preferences for the odors of unfamiliar uninfected and familiar uninfected males. Responses are given as preference ratios (i.e. time spent in the vicinity of the odor of the unfamiliar uninfected male/time spent in the vicinity of the odor of the familiar uninfected male + time spent in the vicinity of the odor of the unfamiliar uninfected male). Preferences were determined over a 5 min period. N = 10, in all cases. Vertical lines denote a standard error of the mean. Means with different letters are significantly different (**$p < 0.01$, ***$p < 0.001$) when compared to a random preference (0.5).

The ANOVA revealed a significant effect of prior male (A) and female odor association on the subsequent preference for the odor of male A ($F(3,36) = 52.119$, $p < 0.001$, $\eta^2 = 0.81$) (Fig. 3). Females that were pre-exposed to the odors of male A + an uninfected estrous female subsequently displayed a significant preference for the odors of male A ($p < 0.001$) (Table 2). In contrast females that were pre-exposed to the odors of male A + an infected estrous female, subsequently displayed a decreased preference for male A odor and a significant increased preference for the odor of the alternative male B ($p = 0.009$). Females that were pre-exposed to odors of male A + an uninfected non-estrous female, showed no particular preference for male A odor with their odor preferences being not significantly different from random ($p < 0.275$). Females that were pre-exposed to the odors of male A + a stressed estrous female, also showed a significant preference for male A odor ($p = 0.023$).

Females pre-exposed to male A + estrous uninfected female odors displayed a significantly higher preference for male A than all of the other pre-exposure groups ($ps < 0.001$). Females pre-exposed to male A + non-estrous uninfected female odors were not significantly different in their preference for male A from that of the estrous infected and estrous stressed pre-exposure conditions. Finally, females pre-exposed to male A + estrous infected female odors had a significantly lower preference for male A than female mice pre-exposed to male A + stressed estrus female odor, ($p = 0.001$).

Exposure to the odors of either; Male A alone ($t_9 = -1.121$, $p = 0.291$), uninfected estrous female alone ($t_9 = 0.383$, $p = 0.710$) or

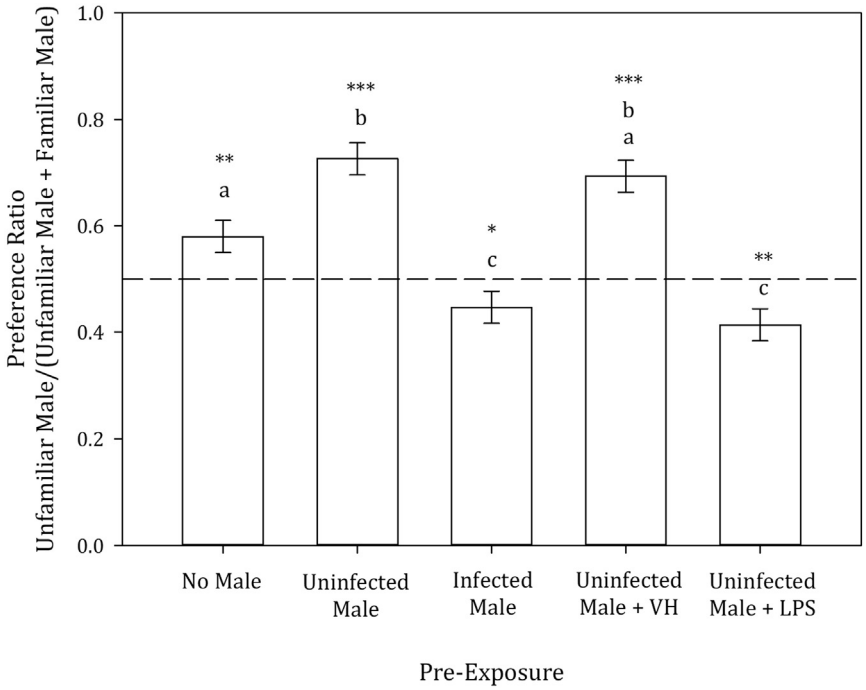

Fig. 2. Effects of a 1 min pre-exposure to the odors of: (i) Uninfected Male; (ii) Infected Male; (iii) LPS treated male (Uninfected Male + LPS); (iv) Vehicle treated male (Uninfected Male + Vh); (iv) or clean bedding (No Male) on female preferences for the odors of unfamiliar uninfected and familiar uninfected males. Responses are given as preference ratios (i.e. time spent in the vicinity of the odor of the unfamiliar uninfected male/time spent in the vicinity of the odor of the familiar uninfected male + time spent in the vicinity of the odor of the unfamiliar uninfected male). Preferences were determined over a 5 min period. N = 10, in all cases. Vertical lines denote a standard error of the mean. Means with different letters are significantly different (**$p < 0.01$, ***$p < 0.001$) when compared to a random preference (0.5).

Table 2
Effects of a 1 min pre-exposure to joint male (Male A) and female odors on subsequent female preference for the odors of Male A.

Exposure condition	*t*	*p*-Value	Effect size (*d*)	Direction of effect
Male A + uninfected estrous female	12.62	0.00001	3.99	>
Male A + uninfected non-estrous female	−1.16	0.275	−0.37	<
Male A + infected estrous female	−3.35	0.008503	−1.06	<
Male A + stressed estrous female	2.73	0.023396	0.86	>

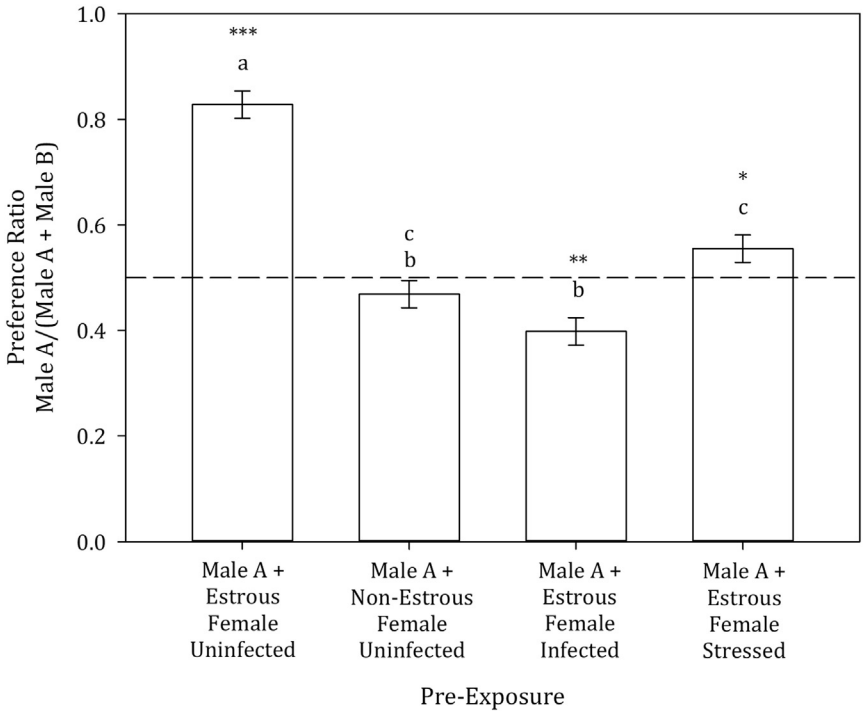

Fig. 3. Effects of a 1 min pre-exposure to the odors of: (i) Male A + Estrous Uninfected; (ii) Male A + Non-Estrous Uninfected Female; (iii) Male A + Estrous Infected Female; (iv) Male A + Estrous Female Stressed (restraint stressed for 30 min) on female preferences for the odors of the same male (Male A) and a different male (Male B). Responses are given as preference ratios (i.e. time spent in the vicinity of the odor of Male A/time spent in the vicinity of the odor of Male A + time spent in the vicinity of the odor of Male B). Preferences were determined over a 5 min period. N = 10, in all cases. Vertical lines denote a standard error of the mean. Means with different letters are significantly different (**$p < 0.01$, ***$p < 0.001$) when compared to a random preference (0.5).

estrous infected female alone ($t_9 = 0.092$, $p = 0.928$) had no significant effect on the preference for the odor of either Male A or Male B.

Thus, the presence of the odors of an uninfected estrous female in conjunction with that of male A enhanced the subsequent preference for that particular male (Male A). In contrast the presence of the odors of an infected female with that of male A led to subsequent avoidance of male A and preference for the odors the alternative male B.

Experiment 3. Effects of an oxytocin receptor antagonist on female responses to male odor pre-exposure (Table 3).

The ANOVA revealed a significant effect of treatment with the OT receptor antagonist on the effects of prior male (A) + female association on the subsequent preferences for male A ($F(5,64) = 19.245$, $p < 0.001$, $\eta^2 = .601$) (Fig. 4, Table 3). Vehicle treated females pre-exposed to male A + infected estrous female odors showed a significantly decreased preference for the odors of male A and a preference for those of the alternative male B ($p < 0.001$). Females that were pre-exposed to the odors of male A + infected estrous females and had received the oxytocin receptor antagonist at 1.0 mg/kg ($p = 0.471$) and 5.0 mg/kg ($p = 0.056$) showed no significant preference for either male A or B odor (Table 3).

Females pre-exposed to the odors of male A + uninfected estrous female, and receiving a vehicle injection (n = 20), showed an enhanced preference for male A odor ($p < 0.001$). Females that were pre-exposed to the odors of male A + uninfected estrous female, and receiving the oxytocin receptor antagonist at 1.0 mg/kg, showed a reduced preference for male A odor ($p < 0.001$). Finally, females treated with the OT receptor antagonist at 5.0 mg/kg, and pre-exposed to the odors of Male A + uninfected estrous female showed no preference for male A odor, such that there was no significant difference in their preference from random ($p = 0.284$) (Table 3).

Vehicle injected female mice pre-exposed to male A + estrous infected female odor, preferred male A significantly less ($p < 0.05$) than females receiving all of the other treatments ($ps < 0.05$). Similarly,

Table 3
Effects pre-treatment with the oxytocin receptor antagonist, L-368,899, (L 1.0 and 5.0 mg/kg) on the effects of a 1 min pre-exposure to joint male (Male A) and female odors on the subsequent female preference for the odors of Male A.

Treatment group	*t*	*p*-Value	Effect size (*d*)	Direction of effect
Pre VH + Male A + infected estrous female	−7.05	0.000001	−1.58	<
Pre L 1.0 + Male A + infected estrous female	0.75	0.47	0.24	>
Pre L 5.0 + Male A + infected estrous female	2.19	0.056	0.69	>
Pre VH + Male A + uninfected estrous female	10.57	0.000002	3.34	>
Pre L 1.0 + Male A + uninfected estrous female	5.29	0.0005	1.674	>
Pre L 5.0 + Male A + uninfected estrous female	1.14	0.284	0.36	>

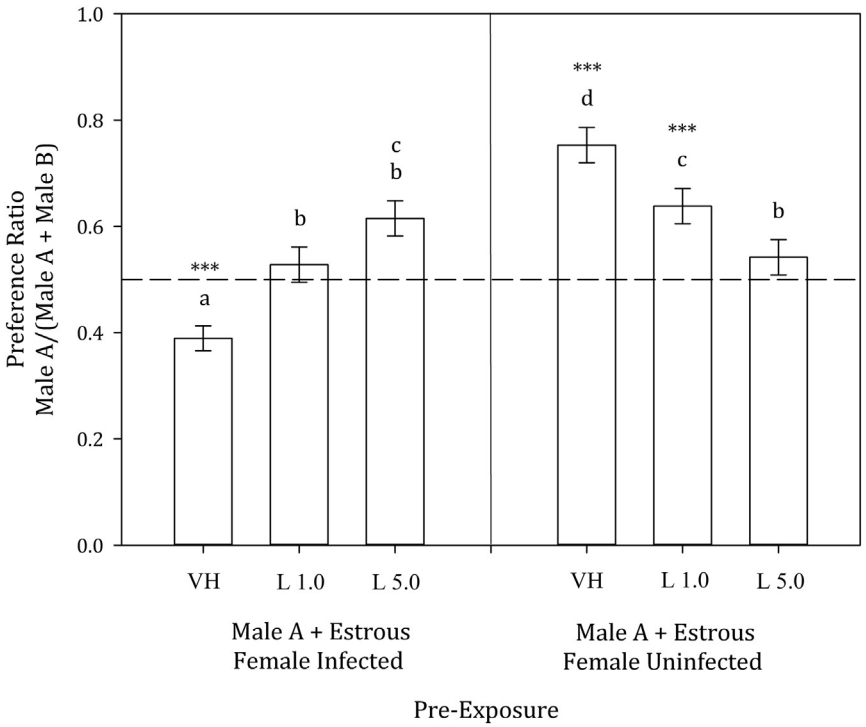

Fig. 4. Effects of a 1 min pre-exposure to the odors of either Male A + Estrous Uninfected or Male A + Non-Estrous Uninfected Female on female preferences for the odors of the same male (Male A) and a different male (Male B). Thirty minutes before the pre-exposure females were treated with either the oxytocin receptor antagonist, L-368,899, at 1.0 or 5.0 mg/kg (L 1.0, L 50). Responses are given as preference ratios (i.e. time spent in the vicinity of the odor of Male A/time spent in the vicinity of the odor of Male A + time spent in the vicinity of the odor of Male B). Preferences were determined over a 5 min period. N = 10, in all cases. Vertical lines denote a standard error of the mean. Means with different letters are significantly different (**$p < 0.01$, ***$p < 0.001$) when compared to a random preference (0.5).

vehicle treated females pre-exposed to estrous uninfected female odor + Male A and vehicle preferred male A significantly more ($p < 0.05$) than females exposed to the odors of estrous infected females ($p < 0.05$). Females treated with the OT receptor antagonist (5.0 mg/kg), pre-exposed to the odors of either infected or uninfected female odors did not significantly differ, $p = 0.673$ in their preferences for male A.

Thus, treatment with the OT receptor antagonist attenuated both the enhanced preference for, and avoidance of, the odors of a male that was associated with the odors of either the uninfected or infected estrous females, respectively.

4. Discussion

Social and mate responses are context dependent and affected by pathogen threat and the risk of infection (Ezenwa et al., 2016; Jordan and Brooks, 2011; Kavaliers and Choleris, 2018; Martinez-Padilla et al., 2012; Qvarnstrom, 2001; Rodriguez et al., 2013). Our results show that female mice are sensitive to the social information regarding pathogen threat conveyed by their immediate environment, with their social and mate preferences being affected by the infection status of nearby conspecifics. We showed here that the infection status of conspecific females and males influences the subsequent responses of females to male odors and as such the appetitive components of mate choice. Brief exposure to the odors of infected females or infected males inhibited the natural preference of estrous female mice for unfamiliar males. Likewise, females displayed an avoidance of, and discrimination against, male mice whose odor had been associated with that of an infected female and a preference for those associated with an uninfected female.

These social cognitive responses involve the acquisition of information about others (i.e. social recognition) and information from others (i.e. social learning) providing rapid and flexible mechanisms to deal with the ongoing social context and pathogen threat (Choleris et al., 2009; Kavaliers and Choleris, 2017a). Here female mice were able to recognize and distinguish between the odors of infected and uninfected individuals as well as to learn, remember, and utilize the association that a specific male odor had with either an infected or uninfected female.

The shifts in preferences for female-associated male odors were blocked in a dose-related manner by pre-treatment with the OTR antagonist, L368,899, supporting the involvement of OTRs in the modulation of socially associated pathogen detection and avoidance (Kavaliers et al., 2005, 2006). Results of previous studies have also shown that peripheral treatment with the OTR antagonist L368,899, attenuates social reward in mice (Wei et al., 2015) and aspects of sexual motivation in rats (Blitzer et al., 2017). OT is intimately associated with various aspects of sociality (Goodson, 2013). OT mechanisms are involved in the rapid modulation of social decision making and approach/avoidance responses to both positively and negatively valenced socially salient stimuli and threats, including, as shown here, that of parasitic infection (De Dreu and Kret, 2016; De Dreu et al., 2010a, 2010b; Shamay-Tsoory and Abu-Akel, 2016). As OTRs also bind AVP, these findings with the OTR antagonist indicate that most likely OT and not AVP is involved in the modulation of pathogen detection and avoidance described here.

Pre-exposure to either cat odor (Kavaliers et al., 2003) or the odor of a restraint stressed female or male had no significant comparable effects on the subsequent responses of females to male odors. This shows that the altered social responses displayed after exposure to the odors of infected conspecifics arise from various motivational, neural, hormonal and physiological responses associated with olfactory mediated pathogen detection and the expression of disgust (reviewed in Kavaliers et al., 2018).

Individuals pay attention to the cues associated with the mate choice decisions of others, thereby reducing the risks and uncertainty associated with their own decisions. Such non-independent mate choice, where individuals gain information and socially learn about potential mates by observing conspecifics or their cues, is termed “mate-choice copying” or “mate copying” (Dugatkin, 1996; Galef et al., 2008; Kavaliers et al., 2017). Male mice deposit urine which females investigate, thereby leaving their own odors as a source of information regarding their mate interests (Zala et al., 2004). The odors of a female that are associated with that of a male can be used to guide the mate choice and subsequent sexual interests of another female. As shown here estrous female mice recognized and subsequently preferred and approached the odors of a male that was associated with the odors of

another uninfected estrous female. In contrast males that were associated with the odors of an infected female displayed "guilt by association" and were actively discriminated against and avoided. Both the approach and avoidance responses to males were blocked by the OTR antagonist consistent with OTR involvement in the modulation of responses to both positively and negatively valenced salient social stimuli and the social salience hypothesis of OT. In prior studies it was shown that female mice with deletions of the OT gene (OT knockout mice) were impaired in their recognition of the odors of infected mice as well as the copying of the odor based positive mate choices of other females (Kavaliers et al., 2005, 2006). The present results identify the specific involvement of OT and OTRs in odor based mate copying by estrous female mice and rats.

Although mate preferences are often regarded as the outcomes of dyadic interactions between males and females our results show that these preferences can be influenced by the social context and infection status of nearby conspecific females and males. The present results extend to conspecific females previous findings that the odors of parasitized males rapidly biased the social responses and mate preferences of female mice (Kavaliers et al., 2003, 2014). The aversive effects of pre-exposure to the odors of LPS treated males extend prior findings of the modulatory effects of the odors of parasitized individuals to that of sickness odors. These findings are in agreement with the results of studies showing that rodents can detect and avoid either LPS treated individuals or their odors (Arakawa et al., 2010a, 2010b; Boillat et al., 2015; Lopes and Konig, 2013; Renault et al., 2008). The present results are also consistent with the findings that sharing an environment with sick, LPS treated mice, can affect the odors and behavior of healthy conspecifics (Gervais et al., 2018), thus, rendering an immediate detection and avoidance adaptive. Similar protective detection and preparatory avoidance responses to sickness and infection cues have also been observed in humans and have been termed the “behavioral immune system” (Schaller and Park, 2011; Schaller et al., 2015). The behavioral immune system is assumed to consist of cognitive, affective and behavioral processes that facilitate the detection and avoidance of potential pathogen/infection sources. For example, the odors and faces of individuals treated with LPS were rated by women as less desirable and to be avoided (Regenbogen et al., 2011; Olsson et al., 2014). These responses have also been associated with anticipatory immune activation (Schaller et al., 2010) with suggestions that a similar immune response may also occur in mice (Hamasato et al., 2017).

The detection of pathogen threat incorporates rapid modulation of various aspects of social behavior, motivation and responses including the social and sexual incentive value of conspecifics (Kavaliers and Choleris, 2018). Being associated with an infected female likely reduces the hedonic and reward value, incentive salience, and perceived quality of a male. These labile social preferences allow for female mice to rapidly adjust their social and mate preferences to the infection status of conspecific females and males and the infection risk they present. Hence, the immediate social context may “fine tune” the sensitivity and vigilance to pathogen threat. In a complex interplay, the immediate social conditions and infection threat presented by conspecific females and males can affect and bias the social responses and mate preferences of female mice. The possible implications of these rapid biased responses to social networks and group dynamics of populations in the wild need to be considered.

These results with female mice also support the concept of in-group assortative sociality in humans, whereby, the presence of pathogen threat conveyed by either female or male conspecifics biases preferences for, and approaches towards, familiar individuals (in group preference and “ethnocentrism”) and increases the avoidance of unfamiliar individuals (out-group avoidance and “xenophobia”) as well as leading to stigmatization by association (“guilt by association”) with “disgusting” infected individuals (Faulkner et al., 2004; Fincher and Thornhill, 2012; Fincher et al., 2011; Kavaliers and Choleris, 2017b; Murray et al., 2013; Navarette and Fessler, 2006; Oaten et al., 2011), with the preferential responses to in groups being modulated by OTRs (De Dreu et al., 2010a, 2010b; De Dreu and Kret, 2016).

In mice freshly produced odors provide an index of current infection status and quality prior to any direct social interactions and are crucial for the expression of the appetitive (i.e. presexual, precopulatory) components of mate choice. These appetitive responses are likely part of the mechanisms whereby females detect and reduce social and sexual contact with infected individuals, reducing the likelihood of transmission of infection to themselves. The presence of the odors of an infected female or male may by itself both increase the sensitivity of females to, and augment the saliency of, male infection condition. This may also increase or sensitize a female's responsiveness to potential infection threat that may be posed by an unfamiliar individual leading to the avoidance of that individual. Emotional responses including that of disgust are driven by social cues associated with the initial appraisal, rather than by a direct interaction with, and detailed knowledge of, that individual (Moshkin et al., 2012; Olsson et al., 2014; Tybur and Gangestad, 2011).

In nature parasites/pathogens can have far reaching implications for population dynamics and overall behavior (Buck et al., 2018). Under natural conditions odor and other sensory cues may result in disgust associated avoidance of less preferred infected males and bias mate choice. Infected individuals in the immediate vicinity, as suggested by the presence of their odor cues, likely can influence the attractivity and incentive salience value of others. In this regard nearby conspecifics have been shown in certain cases to negatively influence the sexual behavior of female mice (Petrulis, 2013). There is also recent evidence that specific neural circuits and olfactory signals and receptors can either evoke of inhibit the sexual behavior of female mice (Osakada et al., 2018).

There is mounting evidence for a very quick detection and neurohumoral mediation of the behavioral responses to conspecifics through a variety of volatile and non-volatile odor cues in rodents (Baum and Kelliher, 2009; Hurst and Beynon, 2004; Stowers and Tsuang-Han, 2015). This allows the social environment to rapidly control the appetitive aspects of social and sexual behavior through a variety of regulatory mechanisms that include various neurotransmitters, sex steroid hormones and the nonapeptides, oxytocin and arginine vasopressin and their receptors (Choleris et al., 2009; Kavaliers and Choleris, 2018).

In rodents OTRs are proposed to modulate a social salience network, a set of interconnected brain nuclei, including the social behavior network (Goodson, 2013; Johnson et al., 2017; Marlin and Froemke, 2017; Mitre et al., 2016). These areas encode the valence and incentive salience of social and sensory cues that are relevant to the expression of disgust associated responses. OT is implicated in the mediation of social learning, including mate copying and observational learning of fear (Allsop et al., 2018; Kavaliers et al., 2006; Keum et al., 2018; Pisansky et al., 2017). OT increases negative social judgements, heightens outgroup bias and amplifies anxiety to unpredictable threats (De Dreu and Kret, 2016; Shamay-Tsoory and Abu-Akel, 2016). The present findings with an OTR antagonist support OT involvement in the modulation of both the positive and negative effects of pre-exposure to uninfected and infected conspecifics on the responses to unfamiliar males by female mice. The insular cortex, which is implicated in the expression of disgust, mediates approach and avoidance responses through OT signaling (Rogers-Carter et al., 2018). In females, OTR activation appears to inhibit social approach, not by reducing social motivation, but by increasing vigilance towards unfamiliar and possibly threatening contexts, including as suggested here those associated with pathogens and parasites (Duque-Wilckens et al., 2018). The exact nature of the behavior seen depends on the social context and sex of the individual being examined. In this regard the roles of vasopressin systems, with which OTR has interactions, (Dumais and Veenema, 2016) as well as sex specific responses and effects of OTR system (Duque-Wilckens et al., 2018; Steinman et al., 2019) need to be further considered. In addition

to exploring the specific neural mechanisms underlying OT's role an examination of diurnal rhythms and nocturnal responses under natural and semi-natural conditions requires consideration. Studies with laboratory and wild mice have indicated that mating and other social interactions do occur outside predicted nocturnal patterns (Berry, 1970; Latham and Mason, 2004). Results of previous studies (Ehman and Scott, 2002) and pilot studies here have indicated that females display equivalent responses to *H.polygyrus* infected males under light and dark conditions. Further studies explicitly examining nocturnal responses under naturalistic conditions are warranted.

Conspecifics are a major environmental factor and are key components of the social context and the landscape of disgust. The present findings show that brief exposure to the odor cues of infected and uninfected male and female conspecifics influences the mate preferences of female mice and that this involves, at least in part, OT systems. These findings reinforce the importance of the social context and social information in determining mate and social preferences. This includes both the information provided by conspecifics and how this information is perceived and utilized by the recipient. These findings have implications for our understanding of the dynamics of social/sexual responses and plasticity and biases in individual interactions.

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