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The role of social cognition in parasite and pathogen avoidance

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The acquisition and use of social information are integral to social behaviour and parasite/pathogen avoidance. This involves social cognition which encompasses mechanisms for acquiring, processing, retaining and acting on social information. Social cognition entails the acquisition of social information about others (i.e. social recognition) and from others (i.e. social learning). Social cognition involves assessing other individuals and their infection status and the pathogen and parasite threat they pose and deciding about when and how to interact with them. Social cognition provides a framework for examining pathogen and parasite avoidance behaviours and their associated neurobiological mechanisms. Here, we briefly consider the relationships between social cognition and olfactory-mediated pathogen and parasite avoidance behaviours. We briefly discuss aspects of (i) social recognition of actual and potentially infected individuals and the impact of parasite/pathogen threat on mate and social partner choice; (ii) the roles of 'out-groups' (strangers, unfamiliar individuals) and 'in-groups' (familiar individuals) in the expression of parasite/pathogen avoidance behaviours; (iii) individual and social learning, i.e. the utilization of the pathogen recognition and avoidance responses of others; and (iv) the neurobiological mechanisms, in particular the roles of the nonapeptide, oxytocin and steroid hormones (oestrogens) associated with social cognition and parasite/pathogen avoidance.

This article is part of the Theo Murphy meeting issue 'Evolution of pathogen and parasite avoidance behaviours'.

1. Introduction

Parasites and pathogens are integral components of animal ecology and evolution. Parasite recognition and avoidance are key facets of animal social behaviour with every individual being infected by one or more parasites (i.e. microparasites, including bacteria and viruses, and macroparasites such as helminths and arthropods) [1–4]. Alexander [5] elegantly hypothesized that parasitism by contagious parasites is a cost of sociality. Various forms of social interactions between individuals can increase the probability of parasite and pathogen exposure and transmission from infected to uninfected individuals. Parasites and pathogens can exploit the mechanisms that are associated with the expression of host social and sexual behaviours to increase the likelihood of their survival and dissemination ([1,6–8], for considerations of the advantages of co-evolved parasites, see [9]). This cost of sociality can result in trade-offs between the benefits of engaging in social interactions and the ability to deal with, and avoid, contamination and infection. The regulation and expression of social behaviour are shaped by pathogen pressure with both social and solitary animals displaying a variety of cognitive processes and adaptive behavioural responses to avoid parasites and pathogens [4,6,7]. In pioneering studies, Freeland [10] proposed that various aspects of primate social behaviour and interactions have evolved to reduce the spread of new and existing parasites and pathogens.

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Who an individual interacts with and what they do underlies social behaviour. Integral to this is the acquisition and use of social information [11–13]. Social information can arise either as direct signals (i.e. personal information) from others, or arise indirectly (inadvertently as 'public information') as cues or by-products of the behaviour and decisions of others with similar needs and requirements [14]. The social information allows individuals to integrate their own behaviour (ranging from the approach to avoidance) with that of another individual in a manner that is appropriate to the social context. Animals require social information to make rapid decisions that determine their interactions with each other in dynamic social environments. This involves social cognition and both learning about others and from others and integrating that information with functional behavioural responses [13,14]. Social cognition entails not only successfully assessing other individuals and their behaviour and condition (i.e. infection status and the risk they present from various cues), but also rapidly deciding whether, when, where and how to interact with them [8,12]. This ability to recognize and avoid individuals and situations presenting actual and potential parasite and pathogen threat is crucial for host defence and pathogen/parasite avoidance [7,8].

Social cognition encompasses a range of neurobiological components and neural mechanisms for the perception, acquisition, processing and use of social information, as well as its use in learning and memory [15]. Neuroendocrine and neuromodulatory systems are integral components of the mechanisms that are involved in the modulation of social cognition [12,15,16]. These systems can quickly respond to fluctuations in the social environment associated with pathogen and parasite threat, mediating rapid changes in cognitive and motivational processes and social behaviour as well as triggering longer-term changes in behaviour.

We argue here that various aspects of sociality including social behaviour *per se* (i.e. social interactions among conspecifics) and mate/partner choice are reliant on adaptive social cognition for effectively coping with the threat of infection and contamination. We briefly describe the relationships between social cognition and pathogen and parasite avoidance. Firstly, we provide an overview of social cognition. Secondly, we consider social cognition and (i) mate and partner choice and parasite avoidance; (ii) the relationships among familiarity, pathogen threat, avoidance responses and disgust; and (iii) learning and responses to parasite and pathogens. Thirdly, we address the associated neuromodulatory mechanisms, focusing on nonapeptides (oxytocin, OT) and steroid hormones (oestrogens), both of which are directly involved in the regulation of social behaviour and social cognition [12,17].

2. Social cognition – social recognition and social learning

Social cognition has been generally considered as the study of social information processing in a social setting [15]. More specifically social cognition refers to the processes by which animals acquire, process, retain and act on various forms of social information [18]. Social cognition incorporates a variety of sensory and neurobiological mechanisms for assessing, evaluating and responding to the broad range of cues and signals associated with social behaviour. Social cognition impinges on various aspects of social motivation that are related to pathogen and parasite avoidance. It incorporates concepts, such as social discrimination and recognition, familiar–unfamiliar categorization, attention, decision-making and social learning [19], that are particularly relevant to host defence and pathogen avoidance.

Social cognition involves both the acquisition of information about others (i.e. social recognition) and information from others (i.e. social learning) combined with the processing and use of that information in decision-making and expression of subsequent behavioural responses [12,13].

(a) Social recognition

Social recognition refers to the ability to distinguish and categorize conspecifics. This includes potential social and mating partners, kin and non-kin, familiar and unfamiliar individuals, and individuals presenting either social rewards or posing threats. Social recognition varies along a continuum from the recognition of different groups of individuals (class-level recognition including that of infected individuals) to specific individuals (true individual recognition). Social recognition is not simply the act of discrimination but also includes information that an individual has accumulated from past social experiences with, or observation of, other individuals and their social networks. The expression of social recognition is affected by both immediate and prior social and environmental conditions and incorporates rapid and flexible learning and memory to deal with the ongoing social environment and the nature of the social information available [12,13]. Social recognition involves the acquisition, processing and recognition of multi-modal (e.g. olfactory, acoustic, tactile and vibrational) distal and proximal salient sensory information, including that related to condition and contamination.

Animals use different types of sensory pathways to gain information about potential social partners, with olfaction being particularly prominent [20]. Olfactory information is especially important for the recognition of social and sexual partners and their condition in rodents as well as other mammals, including humans [21,22]. In rodents olfactory recognition incorporates a variety of potential odour sources (e.g. urine, tears and saliva), their volatile and non-volatile products, and detection mechanisms and receptors in the main and accessory olfactory systems and the vomeronasal organ (VNO) [23,24]. Odours both provide genetically determined information about others and convey that information to others [24]. Some aspects of olfactory information are stable across the lifetime (e.g. sex) while others may vary according to the social environment and an individual's social experience and condition. Olfactory-mediated recognition ranges from category recognition, including sex, age and reproductive status (e.g. oestrous phase, potentially testosterone levels), social hierarchy (e.g. dominant, subordinate and level of aggression), genetic relatedness, familiarity, condition and quality (e.g. infection and immune status, microbiome composition) to true individual recognition [16,21].

(b) Social learning

The ability to use information either directly or indirectly provided by others to guide behaviour is widespread. Social learning is defined here simply as 'learning that is influenced

by observation of, or interaction with, another animal (typically a conspecific) or its products' (such as odour cues) [25–27]. Social learning allows individuals to save energy and mitigate risk without the added cost of acquiring information first-hand. Social learning provides adaptive information that allows individuals to exploit the previous experience of others and to respond to fluctuations in the immediate environment. Social learning entails deciding when to copy the behaviour of others rather than learning asocially, and whose behaviour to copy. In order to maximize the efficacy of social learning, animals should learn from direct experiences and use social learning strategies selectively depending on the circumstances and individuals from whom they learn. Social learning has been reported for a variety of behaviours from where and what to eat (social learning of food preferences), avoidance of aversive situations and individuals (social learning of fear and threat avoidance, including that of parasite threat (e.g. avoidance of biting flies)), to using the mate choice decisions of others to judge infection risk (i.e. 'mate-choice copying' and choosing either infected or uninfected individuals; e.g. [12,13,26–35]). Proficiency in social learning is affected by the perception of, attention to, and motivation to seek social cues. Social recognition is often integral to social learning, with cues such as familiarity, relatedness and social status influencing various forms of social learning [35,36]. The use of social learning may differ between social contexts and species, depending on the opportunities for social interaction, the extent to which behaviour needs to be adjusted to changing spatial and environmental conditions, and how risky or costly it is to obtain personal information.

3. Social cognition and pathogen avoidance

Animals exhibit a range of interacting behavioural, physiological, morphological, immunological and neurobiological responses to parasite and pathogen threat [2–4,7,8]. Social information alone in the absence of overt behavioural interactions can elicit significant emotional, motivational and neurobiological responses (e.g. 'disgust') that can influence subsequent avoidance behaviour and social interactions [7,8,37,38]. While a host's immune system may constitute the primary defence against pathogens, humans and non-humans are proposed to have evolved a set of behavioural avoidance mechanisms (what has been termed as the 'behavioural immune system') that may be the initial defence against pathogens [39]. Human disgust can be considered as an adaptive system that has evolved to detect signs of parasites, pathogens, contamination and toxins, as well as to facilitate the expression of behaviours that reduce the risk of their acquisition (Parasite Avoidance Theory of Disgust) [37,38]. Similar aversive and avoidance responses to parasites, pathogens, contamination and toxins in non-human animals have also been interpreted as reflecting disgust [40–42] and are considered by some as components of the behavioural immune system [43]. These hypothesized systems involve the engagement of efficient cognitive mechanisms and the elicitation of both reactive and predictive preparatory behavioural avoidance in concert with adaptive emotional and motivational responses to actual and potential infection threat.

In nature, behavioural avoidance of infection can take different forms depending on the nature of the host–parasite system. This can range from either directly avoiding or removing parasites or pathogen themselves, avoiding conspecifics with signs of infection, or avoiding contaminants and contaminated areas [4]. Infection avoidance responses incorporating social cognition include (i) social partner and mate choice and, who to interact with and who to avoid [7,8,44]; (ii) recognition and avoidance of strangers (familiar–unfamiliar discrimination) combined with social distancing and territorial behaviour to exclude conspecifics or areas contaminated by them [40]; and (iii) individual and social learning, including the use of the responses to parasite and infection threat shown by others [31–35].

(a) Mate and partner choice and pathogen avoidance

There are suggestions of links between host mating systems and the likelihood of infection [1,5,6,45]. Species with promiscuous mating systems (e.g. mice and rats) may be particularly susceptible to infection due to the close proximity and high contact rate of individuals. Evidence from a variety of species has accumulated supporting the recognition and avoidance of actual and potentially infected individuals during female mate choice [7,8,44,46]. This may benefit females not only directly by reducing their likelihood of parasite infection (contagion indicator hypothesis [47]), but also indirectly by improving genetic disease resistance (parasite-mediated sexual selection hypothesis) [48]. Although preferences for healthy males may function to avoid pathogens and immediate infection, they can also have additional longer-term adaptive functions (e.g. heritable immunity thereby reducing future infection risk).

Mate choice has been considered as a social cognitive process by which one sex selects on the basis of various traits (e.g. signals of attractiveness, condition and importantly here, infection status) and then mates in a preferential manner with members of the opposite sex (for further descriptions of mate choice, see [49–51]). Both preference (order in which an individual ranks potential mates (including just their signals and cues)) and choosiness (responsiveness to potential mates and the amount of effort expended in choice) are important here [49,50]. Even though mate preference may be at the basis of mate choice sampling strategy, various costs and social constraints can influence that choice [50]. Mate choice can be costly in terms of time spent searching, cognitive and neural abilities, and costs to obtain information and discriminate between potential partners and the risk of predation. Indeed, there are suggestions that in certain mating systems (e.g. rodents) mating may occur with the first individual encountered with the minimal apparent choice being exhibited [41,50,52]. Under variable environmental and social conditions, static traits are not necessarily reliable indicators of mate quality. Depending on the social context and degree of infection of individuals in the immediate environment, small variations in mate condition and quality may not translate into meaningful differences in choice [53]. There is a need for flexible, environmentally and contextually dependent mate choice and preferences. This is particularly relevant when considering responses to infected individuals and the reported absence of any evident choice and avoidance responses [44].

Mate choice includes cognitive, sensory, motivational and salience components [13,53]. Mate choice is tuned to an individual's responsiveness (level of arousal and motivational state) and the incentive salience (positive or negative) and reward value of the potential partner's signals and cues. Mate choice ultimately results in turning arousal into sexual behaviour [51,54]. Mate choice incorporates a number of cognitive levels at which the recognition and avoidance of pathogens and parasites can occur. This includes (i) the perception and receipt of sensory cues and signals; (ii) integration and processing of the sensory inputs; (iii) recognizing, searching for and discriminating between various individuals according to the salience and sexual incentive value of their cues and signals; and (iv) deciding to mate with specific individuals [55]. The roles of recent social history, individual experience and cognitive abilities, and various social factors and biases need to be taken into account when considering how the threat of infection may affect these components of mate choice. For example, there is evidence suggesting that just the perception of male olfactory signals without any resultant interactions and sexual behaviour is stressful to oestrous female mice and reduces their overall sexual interest and motivation [56]. Likewise prior sexual and mating experience can influence a female's responsiveness to male odours and her subsequent sexual behaviour [13].

Avoidance of infected and parasitized individuals occurs in a broad social context and necessitates efficient recognition mechanisms. Hamilton & Zuk [48] suggested that animals should benefit from inspecting the odours of a potential mate as a way of gauging condition. Odours can provide an index of current condition (e.g. infection status and level of 'sickness') and quality prior to any direct interactions and are crucial for the expression of the appetitive (i.e. pre-sexual and pre-copulatory) components of mate choice [21,57,58]. This includes both distal and proximal assessments of the odour signals *per se* as well as subsequent investigations of, and approach towards, actual individuals. For example, adult oestrous female mice normally prefer male- to female-derived odours presented as either an entire anaesthetized animal, a small drop of urine or soiled bedding [57]. Likewise, oestrous female mice discriminate between, and prefer the urinary odours of, intact rather than castrated male mice. In a similar manner, odour-based recognition of pathogen and infection status is important for determining ensuing behavioural interactions (i.e. approach or avoidance) and mate choice [7,44].

Vertebrates, in particular rodents, emit odours from a variety of sources that broadcast their internal state. These odours are emitted as complex chemical blends that include volatile and non-volatile constituents, steroids and proteins [24]. Urinary odours are particularly prominent in the determination of social interactions and condition in rodents. Mouse urine is composed of a large number of volatile constituents as well as non-volatile peptides and proteins that function as chemosignals that promote approach/avoidance social behaviours. These odour constituents are related to two highly polymorphic gene complexes: the major histocompatibility complex (MHC) and the major urinary protein (MUP) cluster [24,57]. Non-volatile MUPs act as carriers of volatile ligands, with polymorphisms of MUPs contributing to the diversity of urine constituent that has been linked to individual recognition and assessment of condition [57]. Infection-associated changes in MHC class II gene complex-linked immune function and volatile odour constituents and production have been related to individual condition (e.g. [24,59–61]). Using volatile components, females may be able to quickly identify the infected producer of urine marks from a distance, without having to spend time in the direct investigation of, and contact with, non-volatile cues. Through modifications in the quality and quantity of urine as well as chemical signals from other sources, parasitic infections can directly affect the mating possibilities of the host as well as their social interactions in non-mating contexts.

Rodents have been shown to use urinary odours to recognize, avoid and display aversive responses to males infected with a variety of macroparasites, microparasites, viruses, bacteria and their components (see reviews in [7,8,44,46]). For example, female rats and mice show preferences for the urinary odours of healthy uninfected males versus males experimentally infected with influenza virus [62]; *Salmonella* [63,64]; gastrointestinal (nematode e.g. *Heligmosomoides polygyrus*) and protozoan (coccidian, e.g. *Eimeria vermiformis*) parasites [65,66]; ectoparasites such as lice (*Polyplax serrata*) [67]; or immune-activated males, including males treated with a bacterial endotoxin (lipopolysaccharide, (LPS, a component of the cell wall of Gram-negative bacteria)), specific immune factors or vaccinated with mutant bacteria (e.g. [68–71]). Although these types of studies have been primarily conducted with rodents, there are data indicating that odour cues are used to recognize and socially avoid infected and parasitized same- and opposite-sex conspecifics in humans (e.g. LPS-treated) and non-human primates [43,72].

In the above-described studies with rodents, females discriminated between the odours of infected (both subclinically infected (i.e. non-sick) and sick) and uninfected males, displaying a decreased interest in, and avoidance of, the odours of infected males [7,44]. Female mice and rats not only discriminated against the odours of infected males but also were more attracted to the odours of uninfected males than that of infected males. In simultaneous choice tests (infected versus non-infected), female mice displayed overall preferences for, and initial choice of, the urinary odours of uninfected males. In sequential and binary choice tests, both pro-oestrous and oestrous females recognized and avoided the odours of infected males as well as the actually infected males (for discussion of the details of the experimental designs used in studies of mate choice, see [73]).

An additional consequence of exposure to the odours of infected males is a decrease in nociceptive (pain) sensitivity and the induction of antinociception (analgesia) [30,65,67]. The nature of the analgesia varies as a function of the duration of exposure, with prolonged exposures to the odours of infected males inducing a relatively long-lasting analgesia and brief exposures eliciting a shorter lasting analgesia [30,65]. The levels of analgesia are relatively independent of the intensity of infection and are not simply the result of exposure to stress- or illness-associated odours. The shorter responses and their neurochemical substrates are considered to represent anxiety-related anticipatory defence reactions, while the more protracted analgesia is primarily associated with stress and related responses [7]. Anxiety can induce a sustained apprehension of the environment and elevated vigilance for ongoing and future threats. These analgesic responses and their anxiety/fearfulness/stress-associated behavioural correlates shift the motivational state of the

females, eliciting a reduced interest in, and avoidance of, the aversive cues associated with the parasitized males, thereby facilitating the avoidance of infected and a choice of uninfected males.

Female mice can modulate the levels of aversion and analgesia according to their prior familiarity with a male and his infection status. For example, after a single exposure to the odours of a mouse louse (*Polyax serrata*) infested male, females could discriminate between the odours of this familiar and unfamiliar infested males [67]. Females displayed attenuated aversive analgesic responses towards the familiar male while maintaining their behavioural avoidance. This individual recognition suggests that females can modulate their anxiety/stress responses and associated costs to infection according to their prior experience with infected individuals. This is probably aimed at reducing costs associated with prolonged or persistent stress and anxiety responses. Repeated stress responses can lead to immunosuppression possibly exacerbating infection, whereas brief, acute stress may augment immune functions [67].

Females are also sensitive to the degree of infectiveness and the stage of infection. The urinary odours of males infected with the enteric protozoan (coccidian) parasite, *E. vermiformis*, at an early non-infective stage of infection were less aversive to females than odours from a later infective stage [65]. Interestingly, the stage of infection also affected the males' interest in females, with non-infective males showing a reduced, and infective males an enhanced interest in females and their odours [67]. The shifts in preference probably incorporate infection-related changes in arousal and sexual incentive motivation of the male. This illustrates the need to examine not only the responses to infected individuals, but also the responses of the hosts themselves when considering infection, behavioural avoidance and mate choice.

Evidence from mice and rats suggests that the aversive and avoidance responses to infected males involve both volatile and non-volatile odour constituents and most probably the accessory olfactory systems. In particular, in mice, there are data indicating that the avoidance of an acutely sick (treated with LPS) conspecific requires normal functions of the VNO which is sensitive to both volatile and non-volatile constituents [74]. Whether or not the responses to other infections similarly involve the VNO as well as the relative roles of other olfactory components and receptors remains to be clarified.

A number of low-level infections in rodents have been shown to not only affect the quality and composition of the urine odour components, but also the quantity and extent of male scent marking [63,75]. For example, Zala *et al*. [63] showed that wild-derived male mice infected with *Salmonella enterica* bacteria have both a reduced marking rate and their odours appear less attractive to females. Marking rate is affected by testosterone levels and can be considered as an indicator of the condition, though it should be noted that there are inconsistent relationships between testosterone and social rank [76]. According to the imunocompetence hypothesis, testosterone acts as a mediator of traits important for female choice (i.e. scent marking rate). Testosterone adaptively suppresses immune function, reallocating resources from immunity to reproduction and development ([77]; for limitations of this hypothesis, see [76]). As such the quality and quantity of urinary odour products that are linked to testosterone and are costly to produce may serve as a reliable indicator of male condition and infection status.

Although investigations have focused on parasite avoidance and female mate choice, under certain circumstances males also use odour cues to discriminate and display aversive responses to infected conspecifics, including females (e.g. [78]). Prior sexual experience is important here, with sexually experienced males displaying larger aversive responses than sexually naive males to the odours of parasitized female mice. However, exposure to novel oestrous females or their cues also enhances risk-taking in males (e.g. predators and infected individuals) and reduces male behavioural avoidance of, and aversive responses to, threatening stimuli [79]. In the view of the significant sex differences in various behavioural, immunological and neurobiological responses [80], sex differences in both the effects of the actual infection and responses to infection require further examination.

Most investigations of infection- and odour-related mate choice have been carried out under laboratory conditions where there are limited opportunities for social interactions and the display of sexual behaviour. However, there is evidence suggesting that the laboratory findings with mice are consistent with the results from semi-natural environmental settings and do reflect the appetitive and consummatory components of mating preferences (e.g. [59,81,82]). Under natural conditions, odour and other sensory cues (e.g. ultrasonic vocalizations [75]) may result in female mice being more likely to detect and locate healthy males. Biased mating can result if the initial sensory-based choices lead to rejection of a less preferred male. There are, however, also findings from laboratory and semi-natural conditions, suggesting that odour avoidance only moderately translates into avoidances of sexual behaviours [64]. It is necessary to consider multi-modal responses and the effects of the ecological (e.g. predators, food availability and 'noisy' backgrounds) and social context (e.g. prior experience, degree of motivation, male availability, social networks and interactions, the presence of other females and their choices) on female mate and social partner choice (e.g. [13,44,50,52,55,64]). Decision-making regarding parasite avoidance needs to incorporate both present and future risks and decisions. If the probability of infection is high an individual may forsake avoidance and engage in social contact and mating, whereas if the number of infected individuals is low or ambiguous an immediate avoidance response may be appropriate.

In order to reduce the risks and uncertainty associated with their own choice, individuals pay attention to the mating choices of others [28,31,83]. This non-independent mate choice where individuals gain information and socially learn about potential mates by either directly observing conspecifics or obtaining information from the cues associated with the choices of others is termed 'mate-choice copying'. Females (observers) who witness another female (demonstrator) that was paired with a male are subsequently more likely to prefer the male (target) that was paired with the female over an unpaired male [31,83]. The observer needs to recognize, select and integrate social information from the demonstrator and target and then make appropriate decisions regarding their own mate choice.

According to the original definition of mate-choice copying, an observer does not need to observe actual sexual interactions and mating but only an 'apparent choice' (i.e. appetitive responses) [84]. In nature, females may be exposed to an index of another individual's mate choice rather than

the actual mating. In addition to direct interactions with conspecifics, male mice communicate by proxy, depositing urine odours in the environment to advertise their presence to females and rival males [57]. Female mice that investigate these male scent marks and leave odours in response to male odours [63] provide a potential source of information regarding their mate choice. Sexually naive oestrous female mice recognized and preferred the urinary odours of a male that was associated with the odours of another oestrous female over those of males that either had no association or were with the cues of non-oestrous females. This socially learned odour preference resulted in the choice for the odours and subsequently of the specific male that was the odour source [31,32]. Similar odour-based mate-choice copying has been reported for female Norway rats and deer mice as well as for sexually naive male mice [32,83,85].

Mate choice copying can override a female's initial choice and bias her preference, leading to the copying of what was previously a less preferred male [31,83]. Although oestrus female mice normally prefer the odours of sexually aroused males with elevated testosterone, when the odour of another oestrous female is associated with that of a non-aroused low testosterone male that choice is shifted. In a similar manner, the presence of the odours of an oestrous female paired with that of a nematode (*H. polygyrus*)-infected male attenuated the analgesic and elevated corticosterone and avoidance responses normally shown by sexually naive female mice. This resulted in the subsequent choice for the odours of the specific infected male [31]. Uninfected is not necessarily a male in better condition [86]. Dominant male mice are more susceptible to *H. polygyrus* infection, showing both elevated testosterone levels and reduced parasite clearance and higher parasite levels [87]. Moreover, there are also suggestions that the acquisition of a low-level helminth infection may be adaptive, priming the microbiome and reducing the deleterious effects of subsequent bacterial infections [88]. Importantly, mate-choice copying reduces the costs of mate choice which may outbalance any cost incurred by mating with an infected individual. As such, using the interests and choice of another female for an infected male may under certain circumstances be adaptive.

Mate-choice copying may, however, also increase the risk of infection. Results of comparative investigations with primates have suggested that the incidence of socially contagious and sexually transmitted diseases is positively associated with social learning [89]. On the other hand, there is also preliminary evidence for copying of the avoidance of non-preferred sick (LPS-treated) males [31]. As well, female mice avoid the odours of males that are associated with the cues of infected or sick individuals [85]. This is similar to the disgust and 'stigma by association' proposed in humans [90]. Mate-choice copying most probably influences the expression of parasite and pathogen avoidance in a flexible and plastic manner according to the immediate social context and prior sexual experience.

(b) Familiar–unfamiliar discrimination and pathogen avoidance

Social cognition is integral to recognizing and remembering 'in-group' members (familiar and/or genetically related individuals) and distinguishing them from 'out-group' individuals (strangers, unfamiliar and genetically non-related members of the same species) [8,37,41,90–93]. The ability to distinguish between in- and out-group individuals is essential for the establishment of appropriate intergroup relations and social interactions and dealing with pathogens, parasites and other threats. Although the level of sociality differs across species [94], there are occasions for all animals (e.g. mating, offspring care) where the recognition of strangers and the threats they may pose is critical.

The actual and potential threats posed by individuals from out-groups (unfamiliar individuals, strangers, foreigners and outsiders) are important determinants of social interactions in humans. Out-group individuals can present threats to the territory, resources and, importantly, pose a risk of pathogen exposure (Pathogen Stress Theory of Sociality [91–93]). The threats posed by out-group members bias social preferences and interactions and promote affiliation, interactions and cooperation with in-group individuals. In humans, (i) exposure to, or priming with, pathogen/parasite threat (e.g. facial cues and odours) elicits avoidance of, and leads to more negative and avoidant responses to, out-groups and (ii) the presence of out-groups leads to heightened aversion (disgust) and sensitivity to potential pathogen threat [90–93]. Pathogen threat has been shown to directly affect women's perceptions of male attractiveness by increasing negative attitudes towards, and decreasing interest in, unfamiliar and/or lower quality males [95,96]. This in- and out-group discrimination has promoted the idea of 'assortative sociality' whereby perceived pathogen infection threat favours social interactions between familiar individuals (in-group bias) with an increased sensitivity to, and avoidance of, unfamiliar individuals (out-group avoidance) [91].

In both humans and non-humans, responses to other individuals (out-groups) are often determined by social cues associated with the initial appraisal, rather than by direct interaction with, and detailed knowledge of, that individual [8,13]. This can include olfactory cues, with evidence from humans showing that odour-based disgust responses to conspecifics are attenuated by in-group and enhanced by out-group relations [97]. Similar interactions between olfactory-mediated pathogen threat and social responses are present in non-humans. Brief exposure to the odours of an *H. polygyrus*-infected male rapidly decreased the subsequent responses to, and preferences for, socially unfamiliar males or females in oestrous female mice [40,85]. In social groups of wild mice, infection threat alters social connectivity and interactions in a manner consistent with a greater in-group interaction and out-group avoidance [68]. In parallel, the presence of unfamiliar mice leads to heightened sensitivity to, and avoidance of, nematode-infected individuals and their odours [40]. In phylogenetically distant molluscs (snail, *Cepaea nemoralis*), the presence of the odours of an infected (LPS-treated) snail similarly led to a greater avoidance of unfamiliar individuals, while exposure to unfamiliar snails elicited heightened avoidance and aversive responses to infected individuals [85]. The enhancement of in-group behaviour could be mediated by a variety of factors, including protection against parasites through 'social buffering' and socially mediated amelioration of stress responses, reduced anxiety regarding threats, enhanced resilience to stressors, and the establishment and maintenance of a beneficial microbiome [41,98].

These findings across species show that the immediate social conditions and infection threat can rapidly affect and

bias social preferences and influence female mate choice and social interactions, in general. Pathogen-related amplification of in-group attractiveness, along with enhanced aversive responses to out-groups, may contribute to the expression and evolution of in-group affiliation and social behaviour. This is consistent with assortative sociality and, in human terms, ethnocentrism and xenophobia [8,41,93]. As such, social information conveying pathogen threat can affect how familiar and unfamiliar individuals interact with others, while perceptions of others can affect sensitivity to pathogen threat and influence social behaviour and social interactions.

(c) Learning and pathogen avoidance

Animals can learn to recognize and respond to dangerous, threatening factors through either individual or social learning. While inherently dangerous stimuli provoke avoidance and fear responses, fear is also learned to stimuli associated with the threat. Animals that initially show no fear of predators have been conditioned in both the laboratory and wild to respond to either live or model predators and their cues. Individual learning can, however, place animals in potentially non-adaptive dangerous situations where learning requires that they directly encounter the aversive stimulus. Social learning, on the other hand, allows an individual to use another's expertise, circumventing the disadvantages associated with individual learning [25–27]. Socially learned recognition of ethologically relevant dangerous stimuli (e.g. predators and toxins) as well as laboratory stressors (e.g. electric shock) has been described in a number of species of birds, fish and mammals (reviewed in [31,99]). Similarly, social learning of fear was demonstrated in a number of experimental paradigms in humans [99].

There is evidence for both individually and socially learned recognition and avoidance of ectoparasites [32–35]. Biting and blood feeding flies are among the most prevalent and biologically important ectoparasites and are responsible for many deleterious effects in humans and non-humans. Large ungulates often display defence and avoidance behaviours, indicative of heightened levels of anxiety and fear during fly attacks [3]. Small mammals also display a variety of fly-avoidance behaviours and defensive responses during fly attacks [33,35]. Both individually and socially acquired defensive (i.e. analgesia) and active behavioural avoidance responses (i.e. self-burying into cover) to stable flies, *Stomoxys calcitrans*, were evident in deer mice and laboratory mice. Brief exposure of individual mice to biting flies induced analgesia and self-burying avoidance responses [32–35]. Preparatory analgesia and avoidance responses were subsequently seen when the mice were exposed to biting flies rendered to be incapable of biting but was not displayed to similar sized non-biting house flies [34,35]. These anticipatory avoidance and analgesic responses were also acquired through social learning without direct experience with biting flies. Fly-naive 'observer' mice that witnessed other 'demonstrator' mice being attacked and bitten by biting flies but themselves were not bitten displayed analgesic responses. These analgesic responses can be interpreted as reflecting arousal and possibly 'empathy' to the pain responses of the demonstrator (for a discussion of empathy in rodents, see [100]). Upon subsequent exposure to altered flies without biting mouthparts, the observers displayed socially acquired enhanced analgesic and avoidance responses. There was a selectivity and social recognition in this, with enhanced social learning evident in observers whose demonstrators were kin, familiar or dominant individuals. A similar effect of familiarity with social learning on distress and fear is also evident in humans, with cues from members of in-groups eliciting greater responses [99]. The usefulness of social learning depends on both the informational content of the observed behaviour as well as, if and how, the information is used by the observer. The cues emitted by a related, familiar or dominant individual may be more salient (including eliciting a greater level of empathy) and better recognized, requiring reduced cognitive resources to discriminate the demonstrator.

Learned disgust and avoidance responses to internal toxins/pathogens have also been shown [42,101,102]. Disgust is proposed to have expanded from an internal toxin- and pathogen-based food rejection system to an external pathogen/toxin disease avoidance system [37,38]. Toxin-associated disgust encompasses a typical facial expression, as well as a withdrawal response, which may be associated with vomiting (emesis). These distinct responses are observed in humans as well as a variety of non-human animals, including non-emetic rodents where disgust is inferred from facial expressions such as gaping (a large opening of the mouth revealing the bottom incisors) [102]. Rats as well as humans display conditioned taste avoidance responses and learned disgust upon re-exposure to a taste that has been previously associated with malaise [84,102]. Both humans and rats also display disgust responses upon exposure to a context that has been previously associated with a toxin or illness (anticipatory nausea) [84,102]. Social factors can have a contextual role here, leading to the expression of socially conditioned disgust responses and anticipatory nausea [84]. Social learning and social modulation of parasite and pathogen/toxin behavioural avoidance responses, including that of disgust, may thus occur over a range of situations. Social mediation and transmission of pathogen recognition and avoidance may be particularly relevant for various species, including humans and merits further consideration.

4. Neurobiology of pathogen avoidance

Social cognition and the seeking, acquisition and processing of social information about pathogen threat involves a variety of neurobiological regulatory mechanisms [12]. These mechanisms allow individuals to rapidly evaluate, integrate and respond to social information derived from the potential parasite and pathogen threats into adaptive recognition and avoidance responses. These mechanisms include various evolutionarily conserved neurotransmitters, in particular dopamine (DA) and serotonin in the 'mesolimbic reward system' and 'social behaviour network' as well as other neurotransmitters; opioid peptide systems; sex steroid hormones (testosterone and, in particular, oestrogens (ERs)); other steroid hormones (e.g. corticosteroids, neurosteroids) and nonapeptide systems (OT, arginine-vasopressin (AVP) and related peptides and their receptors) [12,16,17,58,76,103,104]. In addition, immune factors and microbiome components that are implicated in the mediation of social behaviour also impact on pathogen and parasite avoidance [98].

OT, AVP and ERs underlie various aspects of social cognition including both social recognition and social learning

[104]. OT and ERs are integral parts of the neural mechanisms underlying social interactions [12,13,17]. Both of these neuroendocrine mechanisms interact with brain networks associated with the expression and regulation of social behaviour, emotions and learning [17]. These modulatory systems have been associated with the expression of social recognition, social learning, disgust and pathogen avoidance [67,69,102] and memory [104] and are the major focus here.

(a) Oxytocin, social cognition and pathogen avoidance

The hormone-regulated mammalian nonapeptides, OT and AVP, are involved in mediating responses to, and processing of, socially salient information associated with social recognition, social interactions, social learning and social memory [8,12,105,106]. OT is also implicated in sexual motivation and sociosexual behaviours including the recognition and approach of males by females and the facilitation of female and male sexual behaviours [107]. In addition, OT can act as a modulator of anxiety and stress-related behaviours [108].

OT is synthesized in the supraoptic nucleus and paraventricular nucleus (PVN) of the hypothalamus with neurons projecting to various parts of the brain associated with social cognition and modulating behaviour in sex-, brain region- and context-dependent manners [109]. OT receptors (OTR) in rodents are proposed to modulate a social salience network, a set of interconnected brain nuclei, including the social behaviour network (e.g. medial amygdala and cortical and sub-cortical substrates, such as insular cortex, dorsal hippocampus, thalamus, PVN of the hypothalamus, piriform cortex and other olfactory regions) encoding the valence and incentive salience of social and sensory cues, including that of odours [94,110,111].

OT is proposed to facilitate adaptations to the social environment by modifying cognitive processes and emotional and motivation responses [105,106]. OT increases social salience and affects social motivation and emotions through the modulation of attention to, and perception of, social signals [105]. OT mediates approach and avoidance behavioural responses to positive and negative salient social information, respectively. The exact nature of the behaviour exhibited is dependent on the social context, nature of the social stimulus and sex of the individual [105,106]. In humans, OT appears to enhance aversive response to threatening social stimuli (e.g. facial expression), more so in women than in men [112]. Similar sex differences are also evident in rodents. Optogenetic stimulation of OTR interneurons in the prefrontal cortex results in anxiolytic effects and modulation of sociosexual behaviour in male but not female mice [113]. OT also promotes social avoidance in females, but not males, that have been exposed to a prior social stressor. In female California deer mice, OTR activation in the bed nucleus of the stria terminalis induces an anxiogenic response in which individuals avoid an unfamiliar social context (odour or actual individual) [108]. OTR activation appears to inhibit social approach, not by reducing social motivation, but by increasing vigilance towards unfamiliar and possibly dangerous social contexts.

OT is involved in the regulation of the recognition and avoidance of infected (sick (LPS-treated) and non-sick) individuals and their odours in both male and female rats [7,8,69,70]. In a similar manner, female mice with either deletions of the OT gene (OT knockout, OTKO mice), or treated with a selective OT antagonist, were impaired in their recognition and avoidance of the odours of infected individuals, though not of predator odour [7,8,30,67]. Social odour information is detected by the VNO and main olfactory systems and conveyed to the amygdala and other central social network sites. OT and OTR in the medial amygdala are critical for social recognition [114–116] and are a likely target for the altered behavioural responses to infected males. As well, OT in the pyriform cortex and anterior olfactory cortex is involved in the modulation of odour-mediated social recognition and encoding the saliency of social stimuli [111]. It is suggested that OT may convey social salience in different sensory modalities, leading to a more broadly based pathogen/parasite detection and expression of avoidance responses.

OT was also implicated in the mediation of the in-group bias and out-group avoidance associated with pathogen threat. Female mice treated with an OT antagonist displayed attenuated aversive and avoidance responses to unfamiliar males following exposure to infected individuals [85]. These findings are consistent with the observation that exposure to a stressor, such as the odour of an infected individual, elicits OT-mediated social avoidance in female deer mice [108]. In humans, OT and to a lesser extent AVP have been similarly implicated in the mediation of social cues promoting intergroup discrimination [105,106]. OT facilitates positive responses to in-groups and negative responses to out-groups, promotes intergroup discrimination and may heighten the awareness of, and defence against, out-groups. It also amplifies intergroup recognition and discrimination, leading to differential treatment of in- and out-group members, accompanied by enhanced vigilance/anxiety towards out-groups. Through its modulation of corticoamygdala circuits, OT also permits behavioural avoidance responses to out-group threat [109].

In a broader context, OT was also involved in the mediation of the avoidance and aversive responses to unfamiliar individuals in the snail *C. nemoralis* [85]. Orthologues of OT and AVP are involved in the modulation of a broad range of basic behavioural responses across species, with pathogen threat and familiar and unfamiliar discrimination probably being part of this process. A basic role of OT may be to increase vigilance and defensive aggression to protect oneself and in-group members against out-group threat.

OT is also involved in the mediation of social learning [12] and the regulation of the expression of mate-choice copying [31]. OTKO female mice and females treated with an OTR antagonist were impaired in their use of social information and did not copy the odour-based mate choices for infected and lower quality males of other females [30]. This is reminiscent of OT's involvement in increasing the salience of, and attention and approach to, positive social stimuli in humans [105,106]. OT increases trust and information sharing among individuals from the same group [117]. It is conceivable that during mate-choice copying, female mice may be similarly 'trusting' and attributing a greater positive salience to the mate interests of other females, especially those that are familiar and kin. OT is also implicated in the mediation of the social learning of fear and threat avoidance including potentially that of parasite threat [118]. The bi-directional effects of OT on approach/avoidance according to the context and social salience of the sensory inputs [105] could facilitate both pathogen avoidance and mate-choice copying of infected individuals.

OT is implicated in sexual motivation and sociosexual behaviours [113] and the recognition and facilitation of positive sexual reward [107]. OT modulates reward circuits through effects on DA, serotonin as well as opioid and endocannabinoid systems [119,120]. It has been proposed that OT mediates the expression of DA tone at a number of sites within the reward network, resulting in the modulation of social behaviour and social partner reward [121]. As seeking information is by itself considered rewarding and evokes DA release, this may provide a further means by which OT could modulate behavioural approach/avoidance to infected individuals.

Results of recent studies have also indicated that OT and mu opioids can also influence human social interaction [122]. Changes in mu and kappa opioid activity were similarly associated with the altered responses to female odours of males infected with *E. vermiformis* as well as the responses of the females to infected males [65]. However, whether or not these shifts in the behavioural responses to infected males involve alterations in the functioning of OT systems remains to be determined.

OT is also involved in the modulation and expression of socially mediated conditioned disgust (anticipatory nausea) in male rats [102]. This is consistent with findings from humans, suggesting that OT is associated with the expression of disgust, including that which is socially mediated [123]. The anterior insula is associated with the expression of disgust in humans and anticipatory nausea in humans and rats [124,125]. The 5-HT3 receptor in the anterior insula is involved in the mediation of anticipatory nausea [125] and intriguingly OT modulates 5-HT3 activity [126].

Although the emphasis has been on OT, there is evidence that AVP is also involved in the mediation of social recognition, though probably more so in males than females [103]. In general, the effects of OT are primarily modulated by oestrogenic mechanisms while those of AVP are more testosterone-dependent. The roles of AVP in social cognition and responses to social information and sociality need to be further investigated especially in relation to recognition and avoidance of infection threat.

(b) Oestrogens, pathogen avoidance and social cognition

Gonadal steroid hormones play a major role in the regulation of social behaviours and social cognition. Oestrogenic systems, in particular, are involved in the regulation of the expression and utilization of social information [12,16,29,104]. This ranges from social odour production, social recognition, social learning, to the expression of sexual behaviour (reviewed in [104]). Females adjust their responses to male signals according to their oestrogen-dependent prior sexual experience, sexual motivation and neural responsiveness [127].

There are three main oestrogen receptors (ERs), ERα, ERβ and the G-protein-coupled ER 1 (GPER1), through which oestrogens can exert rapid non-genomic and more delayed and lasting genomic effects [104]. ERα and GPER1 have been shown to rapidly facilitate social recognition and social learning, while the effects of ERβ are at present less well defined [128,129]. In regards to pathogen avoidance, ERα and ERβ gene-deleted mice (ERαKO and ERβKO mice) were impaired both in their ability to discriminate between the odours of infected and uninfected individuals and to distinguish between familiar and unfamiliar individuals (reviewed in [12,16,104]). Furthermore, ERαKO and ERβKO mice displayed minimal aversive responses to the odours of infected individuals, and these impairments were not associated with differences in olfactory sensitivity, sexual motivation or stress responses.

OT is thought to be involved in the expression of the effects of ERs on social recognition and the display of the aversive and avoidance responses to infection threat. Both ERβ and GPER are thought to be involved in the regulation of the synthesis and release of OT at the level of the hypothalamus [104]. All three ER receptors are expressed in the medial amygdala where they enhance social recognition [128] and probably are associated with the functioning of the OTR [17,114]. In addition, oestrogens in the PVN rapidly facilitate social recognition, an effect that was blocked by OTR antagonists in the amygdala (P Paletta, J Smit & E Choleris 2018, unpublished data), whereas oestrogens in the medial preoptic area of female mice have been associated with the rewarding effects of male odours, facilitating DA release at the level of the ventral tegmental area [128].

The roles of progesterone, which is selectively associated with the indifference shown by diestrous female mice to MUP-associated male odours, need to be examined [130]. In particular, how this relates to progesterone's proposed enhancement of disease avoidance in human females (Compensatory Prophylaxis Hypothesis [131]; for alternative findings, see [132]) and the potential interaction with OT need consideration.

The roles of other neuromodulators, including immune components that can affect behaviour and are influenced by oestrogens, and pathogen threat also need to be further considered. Results of recent studies have indicated that male rats exposed to LPS-treated conspecifics display avoidance responses and a modest increase in the cytokine tumour necrosis factor α [133]. This avoidance is consistent with activation of the behavioural immune system, the display of disgust and associated cognitive responses.

5. Conclusion and future directions

The acquisition of social information is integral to the adaptive pathogen and parasite avoidance. This necessitates social cognition and involves the use of information about the condition of others (social recognition) and from the responses of others to parasite and pathogen threat (social learning). As outlined here cognitively based pathogen and parasite avoidance involves (i) selective recognition of, and response to, social partners and potential mates; (ii) recognition and context-appropriate avoidance of out-groups (strangers, unfamiliar individuals) and preference for, and social interactions with, in-groups (familiar individuals); (iii) individual and social learning that incorporates the pathogen recognition and behavioural avoidance responses of others. This entails the utilization of multi-modal sensory information and in particular olfactory information.

These findings have a direct bearing on the pathogen avoidance behaviour found in nature. Avoidance of parasitized and diseased conspecifics has been shown in many taxa, though not in all cases [8,9,13,44,64,86,89]. Accumulating field evidence from humans and non-human primate points to olfactory-based detection and avoidance of parasitized conspecifics [72,134]; for the absence of evidence, see

[44,135]. For example, wild mandrills use olfaction to socially avoid parasitized conspecifics [43]. Similarly, captive chimpanzees display avoidance of biological contaminants through tactile, visual and olfactory modalities [136]. Likewise, field studies with LPS-treated wild mice have revealed altered social interactions [68]. Studies of this kind provide important insights into the evolution of behavioural and physiological responses that allow animals to manage pathogenic risks and threats in their natural habitats. Field studies along with laboratory-based studies also point to the need to consider the various social (e.g. prior sexual/social experience, prior infections [113,130,137]) and environmental factors that can influence disease/parasite/pathogen/contamination recognition and avoidance. This necessitates the determination of the conditions under which parasite/pathogen recognition translates into behavioural avoidance.

Social cognition provides a framework for investigating the evolution and expression of pathogen and parasite avoidance and addressing the underlying neurobiological proximal mechanisms. Social cognition entails communication between neural circuits subserving the discrimination and acquisition of socially relevant information and those mediating approach, affiliation and avoidance. As outlined here, there is accumulating evidence that evolutionarily conserved nonapeptide systems (e.g. OT) are associated with the acquisition, utilization and integration of olfactory and other social information as well as the expression of context-appropriate parasite and pathogen avoidance. As OT is often considered to be a modulator of rewarding social contacts [105], understanding its role in the mediation of socially salient pathogen and parasite avoidance and expression of disgust is important. Similarly, the roles that OT has in the social learning of fear [118] and of parasite recognition and avoidance have to be further addressed. These investigations need to be conducted in conjunction with examinations of the roles of other neuromodulators, neuroendocrine systems (e.g. oestrogens and progesterone) as well as immune and microbiome components that are all implicated in the regulation of pathogen recognition and avoidance.

Like most traits, infection avoidance behaviours may vary according to the context. How this impacts on the patterns of social avoidance and interactions needs further consideration. There are also important sexual dimorphisms in infection avoidance and the display of disgust [138,139]. The understanding of how sex differences in social cognition and their neuroendocrine substrates contribute to pathogen recognition and avoidance is essential. Understanding how pathogen recognition and avoidance are achieved is therefore important for our understanding of how the disease will spread in natural populations and more broadly how pathogens might evolve in response to variation in host avoidance strategies.

Ethics. All experiments described were conducted with approval from the University of Western Ontario Animal Care and Use Committee

Data accessibility. This article has no additional data.

Authors' contributions. E.C. and M.K. wrote the paper.

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