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Review article

Pathogens, odors, and disgust in rodents

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ABSTRACT

All animals are under the constant threat of attack by parasites. The mere presence of parasite threat can alter behavior before infection takes place. These effects involve pathogen disgust, an evolutionarily conserved affective/emotional system that functions to detect cues associated with parasites and infection and facilitate avoidance behaviors. Animals gauge the infection status of conspecific and the salience of the threat they represent on the basis of various sensory cues. Odors in particular are a major source of social information about conspecifics and the infection threat they present. Here we briefly consider the origins, expression, and regulation of the fundamental features of odor mediated pathogen disgust in rodents. We briefly review aspects of: (1) the expression of affective states and emotions and in particular, disgust, in rodents; (2) olfactory mediated recognition and avoidance of potentially infected conspecifics and the impact of pathogen disgust and its' fundamental features on behavior; (3) pathogen disgust associated trade-offs; (4) the neurobiological mechanisms, and in particular the roles of the nonapeptide, oxytocin, and steroidal hormones, in the expression of pathogen disgust and the regulation of avoidance behaviors and concomitant trade-offs. Understanding the roles of pathogen disgust in rodents can provide insights into the regulation and expression of responses to pathogens and infection in humans.

1. Introduction

Parasites and the threat of infection elicit disgust, fear, and revulsion. However, before examining the expression and neurobiology of pathogen disgust it is necessary to consider the concept of disgust. In humans there have been a variety of categorizations of the possible functions and origins of disgust (reviewed in Stevenson et al., 2019). It is now generally agreed that basic human disgust is a continuation of pathogen and toxin/contamination avoidance behaviors that are ubiquitous in non-human animals (Curtis, 2014; Kavaliers et al., 2018; Stevenson et al., 2019). From an evolutionary perspective disgust responses have a key and conserved role in the avoidance of parasites and infection, contaminants, and toxins across species. Pathogen disgust can be thought of as an affective/emotional system that evolved to detect signs of parasites (which includes viruses and bacteria (including shifts in microbiome components), fungi, protozoa, helminth worms, arthropods and social parasites), as well as to stimulate behaviors that reduce the risk of their acquisition (Curtis, 2014; Kavaliers and Choleris, 2018). Parasite and infection threat posed by others has been shown to be detected by, and elicit, a variety of aversive and avoidance behavioral responses in a diverse range of species from worms, ants, bees, snails, crustaceans, fish, birds, rodents, non-human primates, to humans (e.g., Behringer et al., 2006; Beltran-Bech and Richard, 2014; Case et al., 2019; Kavaliers and Choleris, 2018; Olsson et al., 2014; Poirotte et al., 2017; Sarabian et al., 2017) (in this review we use the terms parasite and pathogen interchangeably, although we are aware that conflation of these terms may be criticized).

Animals can use information provided by conspecifics to guide their own behavior and emotions. Animals, humans included, can gauge the infection and health status of conspecifics on the basis of perceptual and sensory cues. Odor in particular has been associated with the elicitation and expression of pathogen disgust. Evidence from nematodes to fish, rodents, and humans indicates that odors and chemosensory cues associated with parasites, infection, inflammation, and reduced fitness are detected and recognized by conspecifics (see references in Kavaliers and Choleris, 2018; Sarolidou et al., 2020a;, 2020b). As such odors provide an index of potential infection risk and can function as a salient cues for the elicitation of pathogen disgust.

We recently reviewed parasite detection and avoidance in relation to mate-choice (Kavaliers and Choleris, 2018; Kavaliers, Ossenkopp, and

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Choleris, 2019), and there are other reviews that have examined the topic (Beltran-Bech and Richards, 2014). In the present review we address a number of basic features of odor based pathogen disgust in rodents. In particular, we consider what are the fundamental features of pathogen disgust? What are the elicitors of pathogen disgust and how is it expressed and regulated? Is pathogen disgust the same in humans and rodents and other non-humans? How is pathogen disgust related to sensory cues (odors), social information, and the transmission of infection? What trade-offs are involved in the expression of pathogen disgust? A general description of the neurobiological mechanisms involved in the regulation of odor detection and pathogen disgust is also presented.

2. Disgust and affective states and emotions in non-humans

Although investigations of emotions and affect have until relatively recently been limited to humans, rodents and other non-human animals display various cognitive, behavioral, physiological, and neurobiological responses that indicate internal states reminiscent of what in humans are considered to be emotions and affective states (Anderson and Adolphs, 2014; Berridge, 2018; Dolensek et al., 2020; Panksepp and Lahvis, 2011 Panksepp et al., 2017; Paul et al., 2020). For example, mice, similar to humans, display stereotypic facial expressions in response to emotionally salient events including those associated with toxin disgust (Dolensek et al., 2020). Across taxa animals face similar kinds of challenges and opportunities which lend themselves to the elicitation and expression of comparable motivational states and emotional or affective responses. It has been further suggested that the processing of valence labeled sensory signals provided the foundation for evolutionarily conserved affective and emotional systems (Kryklywy et al., 2020). Emotions encompass a number of fundamental properties including; valence (positive or negative), scalability (salience and graded nature of emotional interest), flexibility (context dependence and ability to flexibly regulate emotions), and persistence (Adolphs and Anderson, 2018; Anderson and Adolphs, 2014). The roles of these basic features of emotions and affective states in the expression and regulation of pathogen disgust are considered here.

Affect refers to valenced states that incorporate approach/withdrawal and reward/punishment associated responses while emotion refers to the whole constellation of the observed aspects of emotional or emotion-like expression and processing. It is important to distinguish between subjective emotional "feelings" and objective emotional reactions and affective states. The behavioral expression of emotion-like responses such as disgust and fear by rodents and other non-human animals neither implies nor necessitates a "conscious" affective state as proposed for humans (Anderson and Adolphs, 2014). For a discussion of putative evidence for conscious "felt" emotions in non-humans see Weary et al. (2017) Whether or not pathogen disgust falls into the category of "felt" or "conscious" emotions in non-humans remains to be determined.

3. Pathogen disgust defense mechanisms

3.1. Disgust and the behavioral immune system

Animals have evolved a variety of ways to counter and reduce the impact of pathogens: behavioral avoidance (disgust) and related responses; resistance to reduce parasite load during or after establishment; and tolerance to infection and the presence of pathogens by limiting their harmful effects (Rivas et al., 2014). From an evolutionary perspective the ultimate causes of pathogen disgust address the evolutionary advantages of the avoidance behaviors that are expressed. The proximate causes correspond to the immediate environmental/social contexts, sensory cues, and concomitant neurobiological mechanisms that trigger disgust. Disgust stimulates reactive and preemptive anticipatory avoidance behaviors that reduce the risk of the acquisition of, and contact with, the parasites and other contaminants in the environment. This includes reductions of both social motivation and the incentive salience of social cues and interactions.

In humans the various protective and proactive biological defense responses have been coined as the "behavioral immune system" and are associated with the detection of sickness and infection and the elicitation of anticipatory behavioral avoidance responses, as well as appropriate affective, cognitive, neurobiological, immunological, and cognitive responses (Schaller and Park, 2011). For example, humans not only recognize olfactory and visual cues of disease (photograph of person coughing), but they respond to those cues physiologically by priming their immune system (Schaller et al., 2010).

Comparable behavioral and neurobiological responses to sickness exposure and actual and potential parasite threat (both symptomatic and asymptomatic (i.e. non-sick)) are evident in non-human animals and can be interpreted as reflecting pathogen disgust and by extension perhaps the expression of a behavioral immune system (Hamasato et al., 2017; Kavaliers and Choleris, 2018; Poirotte et al., 2017). The behavioral immune system is characterized by functional flexibility according to the environmental cues present (Schaller and Park, 2011), consistent with the flexibility in the display of disgust. It should be noted that some investigators have indicated that human pathogen disgust and infection/disease avoidance are interchangeable (e.g. Curtis, 2014; Lieberman and Patrick, 2014), while others have suggested that disgust is not necessarily the sole cause of avoidance behavior (e.g. fear, anxiety) (Schaller, 2014). Avoidance can be displayed either as disgust associated direct avoidance in response to threats of, and/or cues associated with, infected individuals, or a more general avoidance of, and reduction of social interactions with, other individuals. The latter in humans is now termed "social distancing" (Van Bavel., 2020).

3.2. Indirect "non-consumptive" effects

All animals are under threat of attack by parasites facing a so-called "landscape of disgust". Parasites are proposed to affect animal behavior and ecology through both direct consumptive (i.e. killing the host) and indirect non-consumptive effects (non-lethal "risk effects") (Buck, 2019; Buck et al., 2018). The indirect non-consumptive effects are the physiological and neurobiological costs associated with the expression of disgust and the detection of parasites and avoidance of infection (Buck et al., 2018; Kavaliers et al., 2019a). Without even infecting their hosts parasites can have a diverse range of motivational, behavioral (social and non-social), and neurobiological actions. These indirect effects eclipse the direct effects of parasites having major impacts on animal, including human, behavior, motivation, ecology, and neurobiology.

Writing this we are struck by how just the threat of infection by the SARS-CoV2 virus responsible for the COVID-19 is impacting on our emotional, psychological, and social behavior and having major repercussions on all aspects of our daily lives. This parallels the diverse disgust associated behavioral effects (e.g. social avoidance, altered social interactions, augmented vigilance) of pathogen threat evident in non-human primates (Poirotte et al., 2017; Sarabian et al., 2017) and rodents (Kavaliers and Choleris, 2018)

Pathogen disgust is considered as an adaptive system that functions to both detect signs of, and sensory cues associated with, pathogens and to facilitate proactive behavioral mechanisms that reduce the risk of their acquisition (Kavaliers et al., 2018). For parasites that complete their entire life cycle within a single species, transmission between host individuals can occur directly (e.g. contact between individuals as in the case of ectoparasites (e.g. Kavaliers et al., 2013; Kavaliers et al., 2005) or indirectly (e.g. Kavaliers et al., 1998; Poirotte et al., 2017). Many parasites however have more complex life cycles involving multiple hosts. Here the implications for parasite transmission depend on whether the altered condition of an infected individual is perceived by hetrospecifics or conspecifics. Although direct transmission is not a risk here proximity to infected conspecifics increases the likelihood of encountering infected

vectors (e.g. mosquitoes, (Kavaliers et al., 2005)).

Parasite and infection avoidance can be either direct by avoiding or removing parasites themselves, or more indirect through the avoidance of conspecifics with either signs of infection or risky fecally and otherwise contaminated areas associated with infection (e.g. Hart, 1990, 2011; Hou et al., 2016; Sarabian et al., 2018; Weinstein et al., 2018). Susceptible individuals that detect infective and threatening parasites may be able to avoid them directly (e.g. herbivores, small mammals go into cover to avoid biting insects (Hart, 2011; Kavaliers et al., 2005). If the infective stages are less detectable infection can be avoided by using cues that are reliably associated with parasites. For example, mandrills use vision and olfaction to avoid grooming conspecifics infected with intestinal protozoa that can be transmitted through social contact (Poirotte et al., 2017; Sarbian et al., 2017), while mice use odors to reduce interactions with individuals harboring lice (Kavaliers et al., 2014). Selective foraging to avoid contaminated grazing areas has been demonstrated across species from the nematode, *C. elegans,* to bonobos (Anderson and McMullan, 2018; Sarabian and MacIntosh, 2015). When infective stages are directly detectable the behavioral responses may be driven in part by fear but when they are less detectable the responses are motivated by disgust. Disgust and its' behavioral consequences can be considered as a key mediator of the non-consumptive effects of pathogen threat.

3.3. Disgust and fear

Other physical (e.g. predator risk) and psychological threats can further affect exposure to parasites via both lethal removal of parasite carrying individuals and stress, fear, and anxiety elicited changes in behavior and neurobiology facilitating avoidance of infection. Although disgust and fear are both negatively valenced affective states associated with survival optimization they are qualitatively different in their behavioral and motivational underpinnings, and have distinct (though partly overlapping) neural mechanisms (Berridge, 2018). Disgust incorporates both the induction of negatively valenced behaviors and a reduction in positively valenced behaviors. In general fear defends against external dangers (e.g. predators) while disgust defends against oral and internal threats (parasites, toxins, contaminants). However, disgust is also elicited by a variety of external threats (e.g. ectoparasites, contaminated feces) and fear (and associated anxiety and stress) can contribute to the behavioral and neurobiological responses to parasite and infection threat (Kavaliers et al., 2019a). Intrinsic to both disgust and fear is also neophobia and the avoidance of novel and unfamiliar environmental and social situations under what are perceived as threat conditions. Neophobia has also been proposed to be a basic form of anticipatory disgust (Stevenson et al., 2019). However, the term anticipatory disgust has been specifically used to describe the disgust responses evident upon exposure to a context that has been previously associated with a toxin or illness (e.g. Cloutier et al., 2019a, b).

4. Pathogen disgust and social information

4.1. Cognition and the transmission of social information

The expression of pathogen disgust involves the acquisition of information to regulate, anticipate, and avoid exposure to parasites. Animals obtain information either by interacting directly with the physical environment and acquiring "asocial' information or from the behavior or products of other individuals, a process termed social information use. Social cognition entails the acquisition of social information both about others and from others (Choleris et al., 2009). Host cognition may change the probability of exposure to parasites by either altering relationships with the environment and, or influencing risk based decision making to avoid infected conspecifics. use. Individuals with reliable information about resources and threats (i.e. parasites, predators, threatening conspecifics) in their environment, as well as about the immediate social and ecological conditions, can make strategic decisions and responses. As parasites exploit the social and sexual behaviors of the host to increase the likelihood of their survival and transmission, organisms have evolved diverse pathogen avoidance behaviors. Through the judicious use of social avoidance and vigilance strategies individuals can evade and respond to threatening situations while monitoring the social and physical environment to rapidly identify favorable changes. Social decision making and its' underlying neural substrates enables animals to respond to their social environment with flexible, context appropriate, behaviors (O'Connell and Hoffman, 2011, 2012).

Social factors and social information have a major role in the expression of disgust elicited by conspecifics. In social animals affiliative behaviors bring many benefits (e.g. lowered stress levels, enhanced immune function, and maintenance of social bonds) but they also have costs. Infection by contagious parasites is a cost of sociality with social interactions between individuals increasing the probability of parasite exposure and transmission (Alexander, 1974; Altizier et al., 2003). Natural populations of animals exhibit complex social interactions and contact patterns and are not simple dyadic (e.g. male-female) interactions (Altizier et al., 2003; Ezenwa et al., 2016; Kavaliers et al., 2019b; Lopes et al., 2016). Across a wide range of taxa individuals that are well connected or highly central in their social networks are more likely to be infected by gastrointestinal and other parasites (Altizier et al., 2003; Ezenwa et al., 2016; Kappeler et al., 2015). However, being social may also provide tolerance benefits by reducing the damage caused by parasites rather than affecting parasite numbers (Ezenwa and Worsley-Tonks, 2018). Social living may simultaneously increase infection risk and decrease the cost of infection.

4.2. Trade-offs between information acquisition and pathogen transmission

Animal sociality reflects the interplay between opportunities for reproduction, cooperation and information acquisition counterbalanced by competition and vulnerability to predators and pathogens. Decision making here depends on sensory cues that convey information about resources, predation risk, hetrospecifics, conspecifics and pathogen risk. Sociality and social interactions present opportunities for both the transmission of social information and the acquisition of socially transmitted pathogens. This can lead to trade-offs between the acquisition of information and the avoidance of pathogens (Evans et al., 2020; Romano et al., 2020). This likely incorporates motivational trade-offs between the expression of positively (social reward, rewarding value of positively salient information) and negatively (pathogen disgust, fear, anxiety) valenced affective states. Pathogen disgust may affect the acquisition of information, it's reward value, the interpretation of the incentive salience value of a potential social/sexual partner and the cues presented by them. This can then influence the subsequent expression of social motivation, social approach and avoidance behaviors. These trade-offs between pathogen risk and social behaviors are likely cross modal incorporating a variety of perceptual and sensory cues.

Current and previous social relationships (e.g. familiarity, kinship) of an individual as well as their infection status per se, and social context can impact the probability of using information through social interactions. The propensity for pathogen disgust has been shown to influence the expression of a range of socially related behaviors including; social partner and mate choice, social groups adhered to and supported (concept of in-group vs out-group), as well as social learning and empathy.

4.3. Disgust and ecological costs and trade-offs

Investments in pathogen avoidance often impose costs on other fitness-promoting behaviors (Oaten et al., 2009; Tybur and Liberman, 2016). The expression of disgust results in ecological costs, which are a combination of energetic costs (e.g. costs of defensive avoidance

behaviors and immune and metabolic costs) and missed opportunity costs (not feeding, mating, or engaging in positive social interactions). As most free-living animals are infected at some point in their life it has been proposed that the optimal level of defense includes accepting some risk of infection which is traded of by the cost of defense (Jokela et al., 2002). The various costs can differentially influence the behavioral and neurobiological responses according to the nature of the infection, degree of susceptibility and other threats that are present. The latter may necessitate trade-offs between distinct avoidance behaviors imposed by different types of threats. Animals, humans included, may through the evocation of disgust, evaluate the level of pathogen risk when deciding what to eat, whom and what to touch, and with whom to have social and sexual interactions with. In decisions related to parasite exposure positive information about nutritive or social interaction and sexual benefits may out-weigh the costs associated with parasite infection. For example, mandrills groom parasitized maternal kin but avoid grooming other parasitized conspecifics (Poirotte and Charpentier, 2020).

Every time a susceptible individual mates with a potentially infectious partner it increases the likelihood of exposure to parasites and a subsequent loss of fitness. However, the overall benefit(s) of disgust and avoidance behavior might be counterbalanced by the cost of missed mating opportunities. These trade-offs in approach-avoidance may be particularly relevant when considering social connectedness and dispersal patterns of the more susceptible males (Habig et al., 2019).

In a similar vein, there are nutritional–parasite/toxin and contaminant exposure related trade-offs. Herbivores and non-human primates adjust their choice of food, and frequency with which they consume food items contaminated with feces based on the nutritional quality of the food items and degree of their hunger, and information available regarding infection risk (Sarabian and MacIntosh, 2015; Sarabian et al., 2020). In general, as the costs of pathogen avoidance behavior increase disgust and fear expression and sensitivity decreases. These trade-offs illustrate the valence dependence, scalability, and flexibility properties of pathogen disgust. They also support the contention that pathogen disgust in non-humans, including rodents, is not just a simple reflex like response, but rather that it reflects components of emotions and affective states.

Animals may also be exposed to a continuous background of pathogen and parasite threat akin to the background of predator threat (Apfelbach et al., 2005; Clinchy et al., 2013). Chronic background threat has been shown to affect both human and non-human affective and cognitive processes including the strengthening of fear memory and trade-offs with other functions (Apfelbach et al., 2005; Taylor et al., 2020). It is conceivable that a background of pathogen threat and elevated disgust may elicit comparable effects in both humans and non-humans. However, the degree of disgust sensitivity in humans is not necessarily always associated with the level of pathogen threat and as such the possible role of background pathogen threat requires further evaluation.

4.4. *Social buffering*

Social interactions can also attenuate aversive and stress responses through a process known as social buffering (Kikusui et al., 2006). Positive social relationships can increase resistance to, and tolerance of, infection in group-living species (Ezenwa et al., 2016). Studies in a wide range of species, including rodents, have found that the presence of non-threatening conspecifics results in reductions in autonomic, neural and behavioral responses to threats (Kiyokawa et al., 2009; Morozov and Ito, 2019). The aversive and avoidance responses to infection and threat per se can be affected by the social presence of other individuals. For instance, isolated mice display greater avoidance responses to infection threat than when in social groups with other uninfected and infected individuals (unpublished, in prep.). These effects of social buffering are of particular relevance when considering the affiliative responses and social distancing of humans and other animals under infection threat as well as the level of pathogen disgust displayed in natural populations of interacting individuals.

5. Pathogen disgust and odors

How one responds to another individual is affected by social cues present at an initial appraisal rather than by direct interactions with, and detailed knowledge of, that individual. Animals are exposed to a range of cues providing information about the current state of their physical and social environment. What cues individuals pay attention to depends on the costs, timeliness, precision and redundancy of the cues.

Odor (chemosignal, “pheromone”) cues and olfactory communication play a crucial role in the expression of social and sexual behaviors (Wyatt, 2014). Odor cues provide complex blends of socially salient information that are important drivers of behavioral interactions in many species. In rodents odors can contain information about species identity, sex, age, and reproductive status (e.g. estrous phase, potentially testosterone levels)), physiological state, social hierarchy (e.g. dominant, subordinate, level of aggression)), genetic relatedness, familiarity, dietary factors, condition and quality (e.g. infection and immune status, microbiome composition) through to true individual recognition (Choleris et al., 2009; Ferkin, 2019; Ferkin and Li, 2005; Hurst, 2009; Johnston, 1993). Pathogens affect the quality and quantity of urine and fecal components, along with chemosignals from other sources (e.g. tears, saliva, male preputial gland, surface sebaceous glands, external and internal microbiome components, excreted steroids) thereby influencing the expression of disgust. In particular, gut and surface microbiota produce a variety of compounds and metabolites that are implicated in social odor production and are influenced by infection status (Sherwin et al., 2019).

Odors are important for the recognition and assessment of condition and infection status in many species (Gordon et al., 2018; Johnston, 2003; Kavaliers and Choleris, 2018; Olsson et al., 2014). Hamilton and Zuk (1982) directly hypothesized that animals should inspect a potential mate’s urine and fecal odors to select for parasite free/resistant status. Olfactory information can provide an indication of the current condition and infection status of another individual before social or sexual attraction and any interactions. Odor based recognition of infection status and degree of pathogen disgust elicited is important for determining whether to engage in behavioral interactions (i.e. approach or avoidance) and the nature of the subsequent social behaviors and interactions, (e.g. aggression, social vigilance, social partner choice, mate choice and sexual behavior) (Kavaliers and Choleris, 2018). Depending on their characteristics and salience, conspecific odors can elicit either positively or negatively valenced behavioral, motivational, and emotional responses.

Rodents recognize and avoid the volatile and non-volatile odors of individuals infected with a variety of parasites and infectious components. This includes both sickness odors and odors from asymptomatic individuals with sub-clinical infections and no evident signs of sickness. For example, rats and mice can recognize and avoid the odors of individuals infected with influenza virus, encephalitis virus, *Salmonella*, gastrointestinal helminth nematodes (e.g. *Heligmosomoides polygyrus*) and protozoan parasites (coccidia, e.g. *Eimeria vermiformis*), ectoparasites such as lice (*Polyplax serrata*), bacterial endotoxin (lipopolyssacharide (LPS) the cell wall of Gram-negative bacteria), the viral analogue, polyinosinic polyctidylic acid (poly I:C) and, specific immune factors (for reviews and list of references see Beltran-Bech and Richards (2014); Kavaliers and Choleris, 2018; for the absence of evidence also see Beltran-Bech and Richards (2014) ; Fairbanks et al., 2015). The majority of these studies have used either fresh urine (sometimes with fecal components) or bedding odors. LeMoene and Agmo (2018) have argued that preputial and surface gland odors are critical for distant sexual attraction in mice and rats with urine and fecal odors having minimal involvement. The roles of volatile odors from the male preputial gland and sebaceous and other surface glands in conveying infection

status need more detailed examination.

It should be noted that in general viruses are species specific and cannot survive for long outside their host environment. As such viral infection is facilitated by direct and positive social contact with conspecifics. In contrast many bacteria can survive for relatively long periods in the external environment and their transmission is less dependent on positive social interactions (Cole et al., 2011). This raises the possibility of differences in the avoidance and aversive responses to low level viral and bacterial infections as well as in the behavior of the infected individuals.

An important caveat here is that poly I:C and LPS mimic selective aspects of a viral or bacterial response (ie. toll like receptor 3 or 4 activation, respectively) whereas actual pathogen recognition and responses occur via a diverse set or receptors and signaling mechanisms in the immune system. Infection with influenza virus neutralized the attractiveness of male odor to female mice (Penn et al., 1998) while that of tick borne encephalitis virus enhanced preference (Moshkin et al., 2002). As such further investigations with actual viral and bacterial infections rather than just their mimetics are necessary.

Behaviors associated with olfactory communication can also be a direct conduit for infectious disease transmission when olfactory secretions (feces, urine, and scent marks) contain pathogens. Environmental transmission occurs when interactions with olfactory secretions provide the primary exposure and transmission of the pathogens between infected and susceptible conspecifics within and between social groups (e.g. Alexander et al., 2016; Hughes et al., 2014; Beauchamp, 2017). Pathogen disgust related behaviors heighten sensitivity to pathogen threat with the elicited avoidance responses limiting direct interactions with infectious products. This further reflects the trade-offs between the transmission of information and that of pathogens.

6. Pathogen disgust, odors and social responses

6.1. Disgust responses to infected individuals

Odors are particularly salient cues of infection and parasite threat and are considered as universal triggers of disgust (Kavaliers and Choleris, 2018; Stevenson et al., 2019). The odors produced by rodents are a complex mixture of volatile and non-volatile peptides, proteins, and steroids. Volatile components permit individuals to quickly identify infected individuals from a distance while non-volatile components necessitate more intimate contact raising the risk of possible infection.

Odors are important for the expression of the appetitive (i.e. pre-sexual, pre-copulatory) motivational aspects of mate choice. These appetitive responses are part of the mechanism whereby females (and males) detect and minimize social and sexual contact with infected individuals, thereby reducing the likelihood of the transmission of infection to themselves. Fresh urine and associated odors of infected males may both increase arousal and the sensitivity of females to, and augment the saliency of, male infection status. This could lead to disgust mediated behavioral avoidance and reduction of sexual attraction via volatile non-urinary and urinary odor cues. Although this avoidance does not directly equal to sexual preference it can still lead to biased mating if the initial choices removes the female from the vicinity of a less preferred male and limits sexual attraction.

Choice can, however, appear to be non-existent or random when there are either minimal differences and benefits in choosing, the costs for discrimination are high with only partial information available, and small variations in mate condition and cues elicited by infection do not translate into meaningful differences in choice (Edward, 2015). These factors can result in an apparent passive acceptance of the first individual encountered without either active sampling or discrimination, or as such, modulation by disgust. This is consistent with the evidence for the absence of odor based avoidance of infected individuals (see references in Kavaliers and Choleris, 2018). Multimodal sensory cues and assessments of trade-offs with other costs may be required for full choice to be expressed.

Prior familiarity with infected individuals and their odors, social context, and previous sexual and experience and history (e.g. status, stressor exposure, infection exposure) can affect infection avoidance and degree of pathogen disgust evident (Kavaliers and Choleris, 2018). The presence of infected conspecifics, or their odor cues, can result in the display of disgust-like responses to uninfected individuals. Likewise, sexually experienced and previously mated female mice who are also less willing to take risks than sexually naïve females display augmented pathogen disgust and avoidance responses (Kavaliers and Choleris, 2018). However, tolerance and resistance to parasitic infection can also influence the aversive and avoidance disgust responses that are displayed. Indeed, it has been suggested that males that are resistant to pathogens through prior exposure may in certain cases be more attractive to females (Adamo and Spiteri, 2009; Joye and Kawecki, 2019).

There are also suggestions of bidirectional relationships between disgust and mate and sexual responses. Bolder and sexually aroused individuals display reduced neophobia and disgust, enhanced risk taking and reduced responses to predator and pathogen threat (Kavaliers, et al., 2005; Kavaliers et al., 2001; Kavaliers and Choleris, 2018; Stevenson et al., 2019). However, as indicated, prior elicitation of pathogen disgust can also inhibit sexual arousal and responses. Hence the immediate social context may “fine tune” the sensitivity to pathogen threat and level of disgust and avoidance behaviors that are expressed. Whether or not these adjustments reflect arousal, motivational, and sensory or perceptual shifts and accompanying changes in the features of affective states remains to be determined.

6.2. Disgust and parasite transmission risk

Parasite transmission risk also affects the degree of disgust expressed and the avoidance of infected individuals, with the degree of infectiveness being particularly important. For example, the odors of male mice infected with a directly transmitted protozoan (coccidian) parasite, *E. vermiformis*, at an early non-infective stage, elicited lower avoidance responses than did the odors from the same males at a later infective stage (Kavaliers et al., 1997). These responses were in part due to changes in opioid mediated responses in females, possibly reflecting shifts in the reward and incentive salience value of the males (for a review of opioids and sexual reward see Paredes, 2004). In a similar vein the likelihood of parasite transmission has been shown to predict avoidance of infected conspecifics in Trinadian guppies (Stephenson et al., 2018). These findings indicate that infection avoidance behaviors and the level of disgust expressed is flexible and sensitive to the context and salience of, and propensity for, infection.

6.3. Behavioral changes in infected individuals

There is evidence that the avoidance of parasitized conspecifics can be diminished when the test subjects themselves are parasitized with the degree and stage of infection affecting host behavior. Infection stage affected the behavior and sexual interest of the coccidia infected males such that they displayed the greatest sexual interest and motivation when most infective (Kavaliers et al., 1997). Male rodents treated with LPS and displaying sickness behavior displayed either reduced social approach or ambivalent approach-avoidance responses to other individuals resulting in “self social isolation” (Lopes et al., 2016; Yee and Pendergast, 2012). In this regard infections such as *Toxoplama gondi* and encephalitis virus that are associated with elevated testosterone enhanced male odor attractiveness (Moshkin et al., 2002; Vyas, 2013). These findings show that not only do the responses to infected individuals, but also the motivational states and responses of the infected hosts need to be considered when examining responses to sensory cues and the expression of pathogen disgust.

6.4. Effects of social context

Context also needs to be considered, there being evidence that infected individuals in a social setting may mask or overcome behavioral symptoms of infection and sickness presenting a greater risk of infection to others (Lopes, 2014). As such reciprocal interactions between the effects of parasites on host behavior and the propensity for infection have to be considered in relation to the expression of pathogen disgust. Since the majority of organisms host multiple parasite species these interactions can affect how individuals react to other infected and uninfected individuals and the level of disgust expressed. There is evidence that helminth parasites increase susceptibility to infection by other parasites (e.g. Ezenawa et al., 2010) and that infected individuals show reduced aversion and avoidance to the odors of individuals infected with the same parasite (Kavaliers and Choleris, 2018).

6.5. Relevance of laboratory studies of odors and pathogen disgust to natural settings

Although, the majority of investigations described here have been limited to the laboratory, the results of odor preference tests are consistent with what occurs in semi-natural environmental settings and reflect the appetitive and consummatory components of actual mating (e.g. Drickamer et al., 2000; Raveh et al., 2014). However, it also has been shown that odor avoidance may only moderately translate into avoidance of potential partners and sexual behavior (e.g. Klein et al., 1999). The salience of social cues may vary according to the social context. One needs to consider multi-modal responses and roles of other sensory stimuli present in natural and semi-natural environments (e.g. Agmo and Snoeren, 2017; Lopes and Konig, 2016). In the wild, odors combined with other sensory cues (e.g. ultrasonic vocalizations), result in female mice being more likely to locate uninfected healthy males (Lopes and Konig, 2016). Similarly, olfactory and visual cues elicit a significantly greater disgust and aversive response to LPS treated humans that either cue by itself (Sarolidou et al., 2020a).

7. Pathogen disgust and unfamiliar individuals

Social information conveying pathogen threat, disgust, and fear influences reactions to familiar and unfamiliar individuals. Social cognition is crucial for recognizing and remembering familiar ("in-group") and distinguishing them from unfamiliar ("out-group") individuals (De Dreu and Kert, 2016; Faulkner et al., 2004; Kavaliers and Choleris, 2018). Humans exposed to pathogen threat show a reduced interest in unfamiliar individuals and a propensity for heightened disgust, though there are also suggestions that disgust is primarily attenuated by in-group relations (De Dreu and Kert, 2016). In particular, odor based disgust was shown to be attenuated by in-group relations (Reicher et al., 2016). In addition, there are likely trade-offs between benefits of social interactions with symptomatic and asymptomatic individuals and the costs of infection (Tybur et al., 2020a). Similarly the presence of unfamiliar individuals can result in a heightened perception of pathogen threat (Navarette and Fessler, 2006; Schaller and Murray, 2008; Curtis et al. 2011; Fincher et al., 2011; Tybur and Gangestad, 2011). In humans this can encompass "social distancing" and reduced social interactions with, and avoidance of, unfamiliar individuals.

Similar patterns of responses to the odors of unfamiliar and familar individuals and pathogen threat are evident in mice with the presence of infection threat biasing preferences for, approaches to, and interactions with familiar individuals and increasing the avoidance of unfamiliar individuals (Kavaliers et al., 2019b).). However, the nature of the infection threat and whether or not sickness behaviors are present needs to be examined before any definite conclusions can be drawn.

8. Individual and social learning of pathogen disgust

8.1. Social learning of pathogen disgust

Learning also affects the expression of pathogen elicited disgust. Animals can learn to recognize and respond to negative, dangerous, and threatening factors through either individual or social learning (Choleris et al., 2009; Debiec and Olsson (2017); Olsson et al., 2020). Social learning here can be broadly defined as learning from, or in interaction with other individuals and, or their cues. This type of learning is often adaptive because it allows learning about the environment through access to others' information with minimal exposure to threats. Social learning of parasite detection and proper avoidance behavior depends on the information content of the observed behavior, as well as how this information is used by the observer. There is suggestive evidence from mice for social learning of the affective states of others, encompassing emotional contagion and potentially empathy for disgust and fear (Kavaliers et., 2017; Keum and Shin, 2019; Panskepp, 2011).

Individual and social learning influence subsequent decisions regarding the salience and valence of various sensory cues including that of odors. Both individual and social learning contributed to the recognition and behavioral avoidance of biting and blood feeding flies, ubiquitous parts of the natural landscape of disgust. The socially acquired responses were biased, being greatest when the demonstrator was either kin or a familiar individual (Kavaliers et al., 2017). This relationship dependent social transmission of disgust through various sensory cues is consistent with the social learning of fear and empathy for fear (Keum and Shin, 2019). Vicarious social learning may, thus, contribute to the population spread of disgust associated avoidance responses to ongoing and potential parasite threats.

8.2. Pathogen disgust, mate choice and social learning

Social partner and mate choice is also influenced by social learning. Individuals can capitalize on the mating choices of others to reduce the risks and uncertainty associated with their own choice (Galef et al., 2008; Kavaliers et al., 2009, 2017). Female mate-choice copying (mate copying) is a form of social learning that occurs when a female's likelihood of mating with a male is influenced by the apparent direct or indirect choice of another female. Mate copying may be a strategy for mitigating neophobia in inexperienced individuals and providing social safety cues leading an increase in the incentive salience and copying of a less desirable including that of an infected male (Kavaliers et al., 2009). This further displays the flexibility of pathogen disgust and avoidance responses.

Although using the choice of another female and minimizing disgust may under certain circumstances be adaptive (e.g. low availability of males; males of low quality) it may also increase the risk of infection. Indeed, the incidence of socially contagious and sexually transmitted diseases in non-human primates has been shown to be positively associated with social learning (McCabe et al., 2015).

Copying of the avoidance of infected males displayed by other females is also evident. Female mice avoid males that are associated with the odor cues of either infected females or infected males (Kavaliers et al., 2003; Kavaliers et al., 2019). Male mice housed with a sick (LPS treated) individual take on aspects of the sick animal's odor and odorant profile, reducing their own social attractiveness (Gervasi et al., 2018). Being associated with an infected individual likely reduces the reward value, incentive salience, and perceived quality of a male, rendering him "disgusting". This odor based avoidance is suggestive of the copying of disgust and is similar to the "stigmatization by association" and disgust responses proposed in humans (Oaten et al., 2011). Accordingly, social learning influences disgust and pathogen avoidance in a flexible manner according to the prevailing social context.

9. Sex differences in pathogen disgust

Male – female differences in pathogen avoidance and disgust need to be considered. Sex differences in disease susceptibility are evident with these differences being compounded when sexual dimorphism increases the risk more for one sex (Klein, 2000; Klein and Flanagan, 2016). Female-biased disease risk avoidance is widespread across species and as noted infections can significantly influence female mate choice (Beltran-Beck and Richard, 2017; Kavaliers and Choleris, 2018). For many pathogens and diseases males and females differ in infection risk and severity of disease symptoms. In many cases males are more susceptible to parasitic infection than females, an effect that can be exacerbated by differential exposure to pathogens via sex differences in behaviors such as space use, aggression and sexual behavior (Keiser et al., 2020). In polygynous mammals males face higher susceptibility and, or exposure to parasites as a result of high energetic costs of male-male competition for mates, high rates of contact between males and females, and higher levels of potentially immunosuppressive steroids.

Sex differences in pathogen avoidance behaviors may vary across modes of pathogen exposure. Females may be more susceptible to exposure to direct sexually acquired infection, exhibiting stronger avoidance/aversive behaviors and hygenic behaviors and greater disgust when confronted with infectious conspecifics (Kavaliers et al., 2019a; Poirotte and Kappeler, 2019; Poirotte et al., 2017). Superimposed on this is a lower risk taking by females with females prioritizing the avoidance of negative outcomes over seeking positive. Females tend to display greater disgust related avoidance/aversive behaviors and caution in their interactions with males and other individuals. A similar sex difference is evident for toxin related disgust with females displaying greater levels of disgust and anticipatory disgust (anticipatory nausea) (Cloutier et al., 2018a, 2018b). Similar sex differences in the propensity for disgust have also been reported in humans (Al-Shawaf et al., 2017; Olatunji et al., 2020; Sparks et al., 2018). However, the nature of the pathogen threat and specific context of infection exposure needs to be considered before drawing definite conclusions. In particular, the roles of sex differences in the use and processing of sensory information including trade-offs with infection threat, as well as bidirectional interactions between the microbiota, hormone levels, immune responses and disease susceptibility need examination.

10. Neurobiology of pathogen disgust

Emotions and their expression are proposed to result from evolutionarily conserved neurobiological processes that reflect the dynamic integration of sensory information, internal signals, and cognitive processes (Kavaliers et al., 2019; Kryklywy et al., 2020). Disgust can impact on pathogen avoidance at a number of levels. These include: (i) sensory inputs and the perception and receipt of sensory cues; (ii) multipath integration and processing of sensory inputs; (iii) discriminating between various individuals and; (iv) turning pathogen cue induced arousal and motivation into behavioral avoidance and deciding (including risk-based decision making and trade-offs) who to either approach and interact with or who to avoid (Kavaliers and Choleris, 2018).

11. Olfactory mechanisms

Two highly polymorphic gene complexes, the major histocompatibility complex (MHC) and the major urinary protein (MUP) cluster (Hurst, 2009; Stowers and Tsung-Han, 2015) are particularly important for urinary odor based recognition and condition assessment. The MHC class I gene complex is directly related to infection through its' linkage to both immune function and volatile odor composition and production. Non-volatile MUPs are carriers of volatile ligands that provide information about condition and individual identity (Stowers and Tsung-Han, 2015). In male mice the non-volatile major urinary protein, darcin, elicits innate attraction and serves as an unconditioned stimulus allowing females to recognize and assess individual males on the basis of their odors and scent marks (Demir et al., 2020; Roberts et al. 2014). Sick LPS treated male mice whose odors were unattractive to females had reduced levels of darcin in their urine (Lopes and Konig, 2016). However, females also avoided the urinary odors of males infected with the nematode, *Aspiculuris tetraptrea*, whose darcin levels were unchanged (Lanuza et al., 2014). It was speculated that the responses to darcin are dependent on a female's internal state (Demir et al., 2020) which could potentially be affected by the elicitation of disgust and by other odor components associated with infection threat. In this regard female mice displayed similar aversive responses to just the volatile odor components (non-volatile components were effectively stopped by a nitrocellulsoe membrane, (Nevison et al., 2003)) as they did to volatile + nonvolatile components of the fresh urine of nematode infected males (Kavaliers et al., 2009).

The chemosignals are detected by the complementary but distinct main and accessory olfactory systems (MOS, AOS, respectively) (Wyatt, 2014). Within the MOS sensory neurons in the main olfactory epithelium (MOE) detect volatile odorants and relay this information to the main olfactory bulb (Baum and Bakker, 2013). As such, the MOS is thought to be particularly important for initial approach-avoidance behavior and inherent social attraction. In contrast, within the AOS sensory neurons of the vomeronasal organ (VNO) detect odors through close contact.

In mice vomeronasal sensory neurons ((VSNrs) detect non-volatile chemostimuli that are indicative of infection and health status, immunological fitness, and genetic compatibility (Boillat et al., 2015). The VSNrs include formyl peptide chemoreceptors that respond to specific bacterial cues as well as other receptors and mechanisms for detecting bacterial toxins, quorum-sensing molecules, and lipopolysaccharides (Bufe et al., 2019; Chiu et al., 2013). Less is known regarding the detection of non-volatile viral associated cues.

The MOS is primarily involved in the detection and processing of volatile odors. In the MOE odors interact with G-protein coupled odorant receptor molecules (ORs) in the cilia of olfactory sensory neurons (OSNs). Although the OSNs that express ORS are primarily involved in the detection of various environmental odors there are populations of OSNs that have selective roles in the detection of volatile and non-volatile social odors. In mice OSNs expressing transient receptor potential receptors respond to urinary volatiles, several putative volatiles, and peptide ligands of the MHC. As well there are trace amine- associated receptors that respond to amines, various gases (carbon dioxide and carbon disulfide) and other volatile and non-volatile odors.

It is likely that in rodents cues signaling infection are detected by multiple types of chemoreceptors and olfactory subsystems. However, for recognition and sexual attraction at a distance the MOS is the primary olfactory system (Le Moene and Agmo, 2018). As well, in humans the MOS is the primary, if not the only, olfactory system for the detection of social and non-social odors. As such the MOS may also have a key role in the detection of infection associated odors and the expression of olfactory mediated pathogen disgust. In addition, there are sex differences in these pathways, and in particular the MOS, that could potentially contribute to the male female differences in the detection of sensory cues and possibly the expression of disgust (Cherry and Baum, 2020).

11.1. Neural substrates

The elicitation and expression of pathogen elicited disgust involves a variety of neural mechanisms. These evolutionarily conserved mechanisms involve a number of central brain networks including the social decision making network (SDMN). This encompasses the social brain network as proposed by Newman (1999) which was merged with mesolimbic reward network to form the SDMN (O'Connell and Hofmann, 2011, 2012). This includes a number of brain areas including the medial amygdala and cortical and sub-cortical substrates such as; nucleus

accumbens, ventral tegmental area, anterior cingulate cortex, insular cortex, pre-frontal cortex, dorsal hippocampus, thalamus, paraventricular nucleus of the hypothalamus, piriform cortex and other olfactory regions. These various brain areas are associated with encoding and processing the positive and negative valence and incentive salience of social and sensory cues including odors (Goodson, 2013; Johnson et al., 2017; Marlin and Fromeke, 2017; Mitre et al., 2017). Detection and avoidance of pathogen threat likely involves coordinated neuronal activity across these networks that integrate sensory input, salience and reward values, threat, and vigilance to elicit relevant behavioral responses.

Both the prefrontal and insular cortex are involved in mediating responses to sensory information. The insular cortex in particular is thought to be integral to the expression of disgust in humans and rodents. The insular cortex is associated with the processing of aversive sensory stimuli and bodily states and exerts top down control on ongoing avoidance/aversive behaviors and has intimate connections with the social brain network and mesolimbic reward structures (Gehrlach et al., 2019; Rogers-Carter and Christianson, 2019). The disgust responses of humans exposed to LPS subjects (including their odors) were associated with increased activity in the orbitofrontal cortex, pyriform cortex, amygdala, and in particular the insular cortex (Regenbogen et al., 2011). In mice toxin disgust elicited facial expression was associated with neuronal activity in the anterior insular cortex (aIC) and could be elicited by optogenetic manipulation of the activity of the aIC (Dolensek et al., 2020). This disgust expression involved neural pathways from the aIC to the medial amygdala (MeA) with an additional insula to basolateral amygdala pathway being involved in the expression of conditioned disgust responses (Kayyal et al., 2019).

Olfactory information from the AOS and MOS is conveyed to the MeA where non-volatile olfactory information from the vomeronasal pathway is integrated with volatile cues from the main olfactory epithelium to elicit appropriate behavioral responses (Cherry and Baum, 2020; Holy, 2018). In addition, the anterior and posterolateral cortical amygdala regions respond to information conveyed about both attractive and aversive urinary volatiles (Root et al., 2014). Efferents from the MeA travel primarily to subdivisions of the bed nucleus of the stria terminalis (BNST), the ventromedial hypothalamus and medial preoptic area, structures that regulate many of the motivated behaviors associated with disgust. The BNST in particular contains spatially and genetically segregated neuronal subpopulations capable of eliciting aversive or appetitive behaviors. The posterolateral amygdala also has projections to the nucleus accumbens whereby the reward value of a conspecific and the likelihood of approach may be determined.

The anterior cingulate (ACC) and its extended neural connections are emerging as an important network for the detection, encoding, and interpretation of social signals during social learning (Burgos-Robles et al., 2019). The ACC has been implicated in the modulation of the social learning of, and empathy for, fear (Jeon et al., 2010; Keum and Shin, 2019) raising the possibility that the ACC is also involved in the social learning of parasite disgust and fear.

11.2. Disgust, nociception, and pathogen avoidance

Shifts in pain sensitivity have also been associated with the expression of disgust and the aversive responses to infected conspecifics. Exposure of mice to the odors of infected individuals affects nociceptive (pain) sensitivity resulting in the induction of a decrease in pain sensitivity (antinociception, analgesia) followed by an increase in pain sensitivity (hypoalgesia) (Kavaliers et al., 1998, 2000). Humans exposed to disgusting images showed a similar initial analgesic responses followed by an increased pain sensitivity (Oaten et al., 2015). In parallel exposure of mice to fearful/threatening stimuli, including that of predator odors, also elicits changes in pain sensitivity and the induction of analgesia (Kavaliers and Choleris, 2011). These alterations in pain sensitivity and their neurobiological correlates can facilitate the expression of disgust responses, shifting the motivational state and enhancing the avoidance of pathogen threat and infected individuals. In addition, there is suggestive evidence from rodents that pain elicits a hypervigilance to threatening stimuli (Lister and Bouchard, 2020). Hypervigilance is consistent with the increased aversion to, and avoidance of, unfamiliar and a corresponding preference for familiar individuals. In addition there are sex differences in nociceptive sensitivity and regulation. As such changes in pain sensitivity may be a component of odor based pathogen detection, avoidance, and the expression of disgust.

11.3. Neuromodulatory substrates

Behavioral disgust responses involve various neurotransmitters; sex steroid hormones (testosterone and, in particular, estrogens (ERs) and progesterone); other steroid hormones (e.g. corticosteroids, neurosteroids); and nonapeptide systems (oxytocin (OT), arginine-vasopressin (AVP) and related peptides and their receptors), as well as immune factors and microbiome components, and possibly rapid neurogenomic (transcriptional) responses in specific gene networks (Choleris et al., 2009, 2012; Gabor et al., 2012; Goodson, 2013; Marlin and Fromeke, 2017; O'Connell and Hoffman, 2011). These various neuromodulatory systems and associated neural regions allow individuals to rapidly evaluate, integrate, and respond to environmental and social information derived from pathogen threats into adaptive emotional responses and appropriate aversive and avoidance behaviors.

11.4. Oxytocin and disgust

The mammalian nonapeptide, OT, has a major role in the processing of social information. OT is synthesized in the supraoptic and paraventricular nucleus of the hypothalamus with neurons projecting to various parts of the brain associated with social cognition and modulating behavior in sex-, brain-region, and context dependent manners (Mitre et al., 2016). The impacts of OT on social behavior are complex and differ based on context. OT has been implicated in a number of social domains including: processing of salient social stimuli; social recognition, social interactions (including social vigilance and social approach/avoidance), social learning and social memory, social reward; and sexual behaviors (e.g., Choleris et al., 2009; De Dreu and Kert, 2016; Grinevich and Stoop, 2018; Marlin and Fomeke, 2017; Jurek and Neumann, 2018; Shamay-Tsoory and Abu-Adel, 2016). OT receptors (OTR) are proposed to modulate the activity of the SDMN and related cortical and subcortical structures. An additional layer of complexity comes from the distinct signaling and cellular pathways that can be activated by OTRs coupling with either excitatory or inhibitory G-protein subunits in different brain areas (Jurek and Neumann, 2018; Williams et al., 2020).

OT mediates both approach and avoidance behavioral responses to positive and negative salient social information, respectively. The type of behavior observed depends on the nature of the social stimulus, social context, and sex of the individual (De Dreu and Kert, 2016; Shamay-Tsoory and Abu-Akel, 2016). This is of relevance to the trade-offs associated with pathogen avoidance and the expression of pathogen disgust. Sex differences are also evident here with OT enhancing social avoidance and aversive response to threatening social stimuli to a greater extent in female than in male rodents (Johnson et al., 2017).

OT affects the activity of the IC in its' mediation of approach vs avoidance behaviors. Inhibition of the aIC or blockade of insular OT receptors disrupts social affective behavior in rats (Rogers-Carter et al., 2018). Oxytocin is also associated with the expression of toxin elicited disgust with treatment with an OT antagonist attenuating the expression of socially determined anticipatory disgust (anticipatory nausea) in male rats (Boulet et al., 2016). These central effects of OT also likely involve the IC with the ICa being associated with the expression of anticipatory disgust in both humans and rats (Wicker al., 2003; Tuerke et al., 2012).

OTergic projections from the paraventricular nucleus to the central

amygdala are also involved in the discrimination of positively and negatively valenced emotional states expressed through a variety of sensory systems (Ferretti et al., 2019). In addition, OT and OT receptors in the medial amygdala are critical for social recognition (Choleris et al., 2003, 2007; Ferguson et al., 2001) and as such are an additional target for altered behavioral responses to infected individuals. These observations suggest that OT may convey social salience in a variety of sensory modalities leading to a broadly based pathogen perception and expression of disgust and avoidance behaviors. There are also oronasal receptors for OT (Greenwood and Hammock, 2017), raising the possibility of peripheral effects of OT that may interact with central actions in the expression of disgust.

OTR activation appears to inhibit social approach by increasing social vigilance towards unfamiliar and possibly threatening individuals and their cues, consistent with the facilitation of disgust responses (Duque-Wilckens et al., 2017). Social approach and avoidance involves different neural circuits and categories of OTRs. OT acting in the nucleus accumbens and ventral tegmental area facilitates social approach and reward, while aversive contexts which elicit social vigilance recruit the BNST (Steinman et al., 2019; Williams et al., 2020). This is of particular interest in that the BNST is a target for MeA integrated olfactory information. It is suggested that stress may link the OT circuits between sociability, social approach and social vigilance. It has also been proposed that OT may increase responses more to threat associated cues than positive social cues (Shamay-Tsory and Abu-Akel, 2016). This raises a mechanism whereby immediate pathogen disgust/fear could elicit social vigilance and minimize social attraction and interactions. However, the roles of OT mediated social buffering and affiliation also need to be considered when reconciling OT mediated vigilance and avoidance of pathogen threat with social approach. In addition the potential involvement of OT in the modulation of risk based decision making and interactions with reward systems needs consideration. These factors are particularly important when trying to reconcile general avoidance and specific avoidance of infection and the various trade-offs therein.

OT has been shown to be directly involved in the recognition and avoidance of infected individuals and their odors. Treatment with an OTR antagonist, attenuated the avoidance responses of mice and rats to the sickness odors of LPS treated conspecifics (Arakawa et al., 2010, 2011; Kavaliers and Choleris, 2018; Kavaliers et al., 2019). However, the extent of the effects was dependent on the age and sex of the individual providing, as well as receiving, the odors associated with sickness.

Female mice with either deletions of the OT gene (OT knockout, OTKO mice), or treated with the selective OT antagonist, L-368,899, were also impaired in their avoidance and aversive responses of the odors of parasitized individuals, though interestingly not in their fear responses to predator odors (Kavaliers et al., 2006, 2019). This suggests a dissociation between fear and disgust responses to pathogen threat. However, the roles of the stress axis and corticosteroids in pathogen avoidance require further consideration.

Oxytocin receptor gene deleted female mice and females treated with an OTR antagonist displayed reduced use of social information and did not copy either the mate choices or avoidances, of other females (Kavaliers et al., 2006). Though it should be noted that this OTR antagonist has also been shown to reduce sexual approach (Blitzer et al., 2017). OT has also been implicated in the mediations of empathy in humans and empathy like behaviors in rats and mice and was found to enhance vicarious socially acquired fear responses in mice though effects at the anterior cingulate cortex (Keum and Shin, 2019; Pisansky et al., 2018).

There is also evidence for the involvement of AVP in the mediation of social recognition particularly in males (Dumais and Veenema, 2016). However, the specific roles of AVP in social cognition and expression of pathogen disgust, especially in males, remain undefined. As OTRs also bind AVP, the roles of AVP in modulation of disgust and pathogen detection and avoidance remain to be determined.

OT is also associated with the mediation of the in-group bias and out-group avoidance displayed after exposure to pathogen threat (De Dreu and Kert, 2016). Treatment with an OTR antagonist attenuated the aversive and avoidance responses to unfamiliar males seen in female mice after exposure to infected individuals, suggesting the possible involvement of OT (Kavaliers et al., 2019). Through its modulation of cortico-amygdala circuits OT also permits the expression of disgust and the display of behavioral avoidance responses to unfamiliar individuals (Mitre et al., 2016). In humans intranasal OT augmented positive responses to members of in-groups and negative responses to out-group members promoting intergroup discrimination (De Dreu and Kert, 2016). OT also amplified intergroup recognition and discrimination leading to enhanced social vigilance/anxiety towards out-groups. It should, though, be noted that not all studies show a consistent in-group favoritism effect of OT. Recent investigations in mice using optogenetic stimulations of OT have shown that although the effects of OT are dependent on social context and may not impact on familiar vs unfamiliar responses (Anpilov et al., 2020).

A variety of other modulatory and neurotransmitter systems have been implicated in the modulation of disgust with these systems having interactions with OT (Jurek and Neumann, 2018). Opioid systems in particular has been implicated in regulating social behaviors and sexual responses (Paredes, 2004). Differential alterations in opioid activity have been linked to shifts in mate choice and the expression of pathogen avoidance by female mice (Kavaliers et al., 1997). In addition to the opioid system, the OT system interacts with the serotonin (5-HT) and dopamine (DA) systems to support social behavior (Jurek and Neumann, 2018). Administration of a 5-HT3 antagonist to female mice attenuated their avoidance of the odors of parasitized males raising the possibility of 5 H T involvement in pathogen disgust (Kavaliers et al., 2000). Manipulations of 5-HT activity also influence toxin disgust. In rats 5-HT3 receptors in the aIC are involved in the mediation of anticipatory disgust (Tureke et al. 2012) with OT modulating 5-HT3 activity.

Shifts in DA activity and decreases in reward and social/sexual incentive salience are also associated with the decreased responses to positively valenced stimuli associated with disgust. In addition, there is evidence linking the nucleus accumbens to the expression of toxin elicited disgust (Berridge, 2018). This may encompass shifts in dopaminergic systems and a reduction in DA mediated reward responses (i.e. reduction of positive valence and incentive).

Endocannabinoid involvement also needs to be considered. Endocannabinoid signaling has been shown to be involved in the mediation of oxytocin-driven social reward (Wei et al., 2015). In addition, endocannabinoid systems per se have been implicated in the modulation of the expression of toxin elicited disgust and anticipatory disgust (Limebeer et al., 2018). However, to date the roles of endocannabinoid systems in the expression pathogen disgust remain to be determined

11.5. Immune systems and disgust

The vertebrate immune system is composed to two main systems, the innate and the adaptive immune system with the former critical for the initial response against pathogens while the latter is involved in long-term protection against pathogens. Depending on parasite abundance in the environment the host can invest in different degrees into the adaptive or innate system (Mayer et al., 2016). Accordingly, these different immune investment strategies result in specific differences in immune responses and potentially the degree of disgust and avoidance behaviors expressed (McDade et al., 2016).

It has further been proposed that the increased threat of exposure to infection with sociability may be counterbalanced by increased microbiota diversity and immune function to counter infection (Sherwin et al., 2019). Even in the absence of infection mice with less effective physiological defenses (e.g. lower adaptive immunity) show diminished sociability and likely enhanced disgust responses that could reduce their likelihood of infection (Filiano et al., 2016).

Exposure to disgusting images in humans and sickness (LPS) odors in

rats has been reported to enhance immune activity (Hamasato et al., 2017; Stevenson et al., 2012). In parallel there are suggestions that a decreased immune function and ability to resist infection leads to greater investment in avoiding infection and likely expression of disgust (Oaten et al., 2009; Miller and Maner, 2011; for negative evidence see Tybur et al., 2020b). Social interactions can also enhance immune activity while immune components (cytokines) can affect social behavior in non-infected individuals (Hennessy et al., 2014). Augmented immune activity associated with inflammation increases neural sensitivity to negative social factors and threats, which can facilitate the avoidance of unfamiliar individuals (Eisenberger et al., 2017). In a parallel fashion augmented immune activity enhances sensitivity to positive social experiences, presumably to increase approach to positive safe situations (in-groups). OT has been shown to influence immune activity while the immune cell marker, CD38, is important for the central release of OT (Jurek and Neumann, 2018). As well, there are prominent sex differences in immune function that likely have important ramifications for the expression of disgust (Klein and Flanagan, 2016).

11.6. Estrogens and disgust

Estrogenic systems are widespread throughout the SDMN and are involved in the regulation of affective states and the utilization of social information in both females and males (Choleris et al., 2009, 2012). Estrogens exert their actions through a number of estrogen receptors (ERs); ERα, ERβ and the G protein coupled, GPER1, which can mediate both rapid non-genomic and the more delayed and lasting classical genomic effects (Paletta et al., 2019).

ERα and ERβ have been implicated in the expression of odor based pathogen disgust. ERα and ERβ gene deleted male mice (ERαKO and ERβKO mice) displayed minimal avoidance of both the volatile and volatile + non-volatile urine and associated odors of infected males with no significant effects on olfactory sensitivity and fear responses to predator odors (Choleris et al., 2012; Kavaliers et al., 2009). The roles of testosterone and aromatase here need examination. As well, how estrogenic systems may contribute to the enhanced pathogen disgust seen in females where ERα and GPER1 have been shown to rapidly facilitate social recognition and social learning (Dey et al., 2015; Lymer et al., 2018; Paletta et al., 2019) remains to be determined. Estrogens are also associated with the greater immune responses evident in females (Klein and Flanagan, 2015). How this may contribute to disgust also requires further examination

There are sex differences in the conditioned disgust in rats with females showing markedly greater responses than males. Estrous phase further affects the expression of conditioned disgust with the greatest levels of conditioned disgust seen in proestrous when elevated levels of estrogens and progesterone are present (Cloutier et al., 2018a). These effects may in part be related to estrogen enhancement of hippocampal memory formation (Paletta et al., 2019). The sexually dimorphic effects may also be associated with a more specific involvement of estrogenic mechanisms in the elicitation of disgust. In addition, these male-female differences in anticipatory disgust may incorporate some the mechanisms that been associated with sex differences in fear learning and memory.

The effects of ERs on disgust may also be related to their association with OT. Oxytocin has been implicated in the expression of the effects of ERs on social recognition and the display of the disgust and avoidance responses to pathogen threat. Both ERβ and GPER are involved in the regulation of the synthesis and release of OT at the level of the hypothalamus (Ervin et al., 2015). All three receptors are expressed at the level of the MeA where they enhance social recognition (Lymer et al., 2018) and likely are associated with the functioning of the OTR (reviewed in Gabor et al., 2012). Estrogens may influence social recognition by mediating both OT and OTR receptor levels via ERα and ERβ (Choleris et al., 2003). It is conceivable that such interactive mechanisms between OT and ERs are associated with the expression of pathogen and toxin disgust.

11.7. Progesterone and disgust

Progesterone has also been suggested to the be involved in the expression of disgust. Progesterone has been implicated in the enhancement of pathogen and toxin avoidance in women (Compensatory Prophylaxis Hypothesis (CPH) (Fessler et al., 2005; Fleischman and Fessler, 2011)). According to the CPH hypothesis progesterone-linked immunosuppression is associated with increased disgust towards pathogen cues. In women disgust responses have been reported to vary across the menstrual cycle being their greatest when progesterone is elevated (Milkowaska et al., 2019; Olatunji et al., 2020; Pilarczyk et al., 2019; Sparks et al., 2018). In addition, the salience of emotional displays of contagion in women's faces is enhanced when progesterone levels are elevated (Conway et al., 2007). However, alternative and negative findings are also present (Jones et al., 2017).

Progesterone is selectively associated with the indifference shown by diestrous female mice to MUP associated male odors (Dey et al., 2015). As well acute administration of progesterone has been shown to elicit a negative affective bias in rats (Hinchciffe et al., 2020). However, peripheral administration progesterone, and the neurosteroid, allopregnalone, had minimal effects on the avoidance of the odors of infected males by female males, consistent with the negative effects in women (accepted). Rather progesterone had inhibitory effects on social recognition in both rodents and humans. How this may relate to immune function, estrogens, and OT involvement in the modulation of disgust remains to be determined.

12. Conclusions

Deciding who to approach and who to avoid is integral to avoiding exposure to pathogens. Social information provides information about pathogen threat while at the same time enhancing the likelihood of the acquisition of parasites. Pathogen disgust is an adaptive affective/emotional state that functions to both detect cues associated with parasitic infection (both asymptomatic and symptomatic expressing "sickness") and facilitate reactive and proactive responses that reduce the risk of infection. In rodents odor based pathogen disgust elicits adaptive modifications of social and non-social behaviors to limit the threat of both actual and potential infection. This likely incorporates shifts in social motivation and social incentive salience. The fundamental features of emotions (valence, scalability, flexibility, and persistence) determine the likelihood and characteristics of the disgust associated avoidance and aversive responses that are expressed. These responses also incorporate disgust modulated trade-offs between the acquisition of odor based social information and the transmission of parasites and infection.

The expression of disgust involves various evolutionarily conserved brain circuits including the social decision making network (O'Connell and Hofman, 2011; 2012). This involves coordinated activity across various brain regions, such as the insular cortex and amygdala, that integrate sensory inputs, reward, threat, and vigilance to elicit relevant pathogen disgust associated avoidance behaviors. The expression of pathogen disgust further involves various neuromodulatory systems. In particular, there is suggestive evidence implicating the nonapeptide, oxytocin, as well as estrogen mechanisms in the mediation of the social and affective aspects of pathogen disgust and the regulation of approach and avoidance and various trade-offs. Understanding the mechanisms underlying the display of disgust and how pathogen recognition and avoidance is expressed and regulated is critical for our understanding of human and non-human animal behavior in the face of pathogen and infection threat.

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