© 2021. Published by The Company of Biologists Ltd | Journal of Experimental Biology (2021) 224, jeb225847. doi:10.1242/jeb.225847

REVIEW

Sickness behaviors across vertebrate taxa: proximate and ultimate mechanisms

Patricia C. Lopes[1,*], Susannah S. French[2], Douglas C. Woodhams[3] and Sandra A. Binning[4]

ABSTRACT

There is nothing like a pandemic to get the world thinking about how infectious diseases affect individual behavior. In this respect, sick animals can behave in ways that are dramatically different from healthy animals: altered social interactions and changes to patterns of eating and drinking are all hallmarks of sickness. As a result, behavioral changes associated with inflammatory responses (i.e. sickness behaviors) have important implications for disease spread by affecting contacts with others and with common resources, including water and/or sleeping sites. In this Review, we summarize the behavioral modifications, including changes to thermoregulatory behaviors, known to occur in vertebrates during infection, with an emphasis on non-mammalian taxa, which have historically received less attention. We then outline and discuss our current understanding of the changes in physiology associated with the production of these behaviors and highlight areas where more research is needed, including an exploration of individual and sex differences in the acute phase response and a greater understanding of the ecophysiological implications of sickness behaviors for disease at the population level.

KEY WORDS: Bacteria, Parasite, Pathogen, Infection, Diseases, Sickness behavior, Fever, Cytokines, Inflammation, Prostaglandins, Glucocorticoids, Lipopolysaccharides, Endotoxin

Introduction

The COVID-19 pandemic has renewed both public and research focus on better understanding the intricacies of disease spread in terms of physiology and individual and collective behavior (Arunachalam et al., 2020; Lopes, 2020; Sun et al., 2021; Townsend et al., 2020). Sick animals can behave in ways that are dramatically different from healthy animals. Some of these behavioral changes – for example, lethargy and reduced food and water intake – can affect how hosts interact with others and with shared resources. Simultaneously, altered behaviors can provide cues of disease, which affect how others interact with hosts. Therefore, understanding how diseases change host behavior and social contacts is highly relevant for understanding and predicting patterns of disease spread in populations.

In addition to behaviors associated with disease-specific pathogenesis (e.g. malarial chills; Crutcher and Hoffman, 1996), there are generally two major ways in which pathogens and parasites (see Glossary) can lead to behavioral changes in their hosts: (1) their presence in the body can lead to host immunological responses that affect the nervous system (Dantzer, 2004) and (2) parasites can directly secrete molecules that affect the normal communication or anatomy of the nervous system (Adamo and Shoemaker, 2000; Beckage, 1993; Biron et al., 2005; Cabral et al., 2016; Helluy and Thomas, 2003; Herbison et al., 2018; Jong-Brink et al., 2001; Kavaliers et al., 1999; Klein, 2003; Rojas and Ojeda, 2005; Tain et al., 2006; Thomas et al., 2005). The first one is the focus of our Review.

In this Review, we aim to highlight the diversity of behavioral responses to infection across taxa, while also identifying commonalities in their regulation. We also aim to identify areas where more research is needed and to encourage additional investigation into evolutionary origins of and mechanisms underlying sickness in non-model systems. To address these aims, we first provide a summary of the sickness behaviors (see Glossary) seen across vertebrates. We then describe how, physiologically, sickness behaviors are produced in mammals and assess whether similar mechanisms are observed in other vertebrates. Finally, we discuss different theories for the existence of sickness behaviors and highlight areas of research that deserve more attention in moving the field forward.

What are sickness behaviors?

Infections can dramatically alter the behavior of vertebrates in ways that are not specific to any particular disease. These changes in behavior, known as sickness behaviors, can include decreases in overall activity, exploratory behavior, social and sexual interactions, food and water intake (anorexia and adipsia, respectively; see Glossary), grooming behavior and the ability to feel pain or pleasure. Sickness behaviors are also commonly associated with increases in sleepiness, slow wave sleep, and thermal and pain sensitivity, as well as impairments to learning and memory (reviewed in Dantzer, 2001; Demas et al., 2012). In endotherms, physiological fever typically accompanies sickness behaviors. In animals that cannot produce fever physiologically (i.e. ectotherms and some newborn mammals), sickness behaviors can involve 'behavioral fever', wherein infected individuals move to warmer environments to elevate their core body temperature (Satinoff et al., 1976; reviewed in Rakus et al., 2017b). As discussed below, behavioral thermoregulation upon infection does not always translate into a fever (elevated temperature) but may instead manifest as a hypothermic response (i.e. 'behavioral chill') (Hunt et al., 2016; Landis et al., 2012; Truitt et al., 2019).

Although we will focus here on behaviors that derive from host immune responses to infection, the lines separating host- from pathogen- and parasite-driven responses can be blurry. Experimentally, the most frequently used tools to circumvent this issue are the use of heat-killed microbes, proinflammatory cytokines (see Glossary) or injections of endotoxin such as lipopolysaccharides (LPSs; see Glossary) to elicit sickness

[1]Schmid College of Science and Technology, Chapman University, Orange, CA 92866, USA. [2]Department of Biology and The Ecology Center, Utah State University, Logan, UT 84322, USA. [3]Department of Biology, University of Massachusetts Boston, Boston, MA 02125, USA. [4]Département de Sciences Biologiques, Université de Montréal, Montréal, QC, Canada, H3C 3J7.

*Author for correspondence (lopes@chapman.edu)

P.C.L., 0000-0001-5170-3230

Journal of Experimental Biology (2021) 224, jeb225847. doi:10.1242/jeb.225847

Glossary

Acute phase response
A complex early systemic response to disturbances (such as infection, stress or injury). It involves multiple physiological systems and can result in changes in acute phase proteins, cellular trafficking, fever and overall metabolism.

Adaptive immunity
Immune response triggered after exposure to specific antigens and mediated by lymphocytes (B cells and T cells). B cells produce antibodies that bind to antigens with high specificity. The adaptive immune system therefore includes both cellular and humoral aspects and can form long-term memory to antigens.

Adipsia
A condition characterized by the absence of thirst even when high salt or low bodily water levels are present. Can present as a sickness behavior.

Anorexia
A condition characterized by the absence of hunger and refusal to eat. Can present as a sickness behavior.

Critical thermal maximum
An experimental measure of an animal's upper thermal tolerance limit represented by the temperature at which physiological failure occurs (e.g. loss of performance, muscle spasms, disorganized locomotion) during acute thermal ramping.

Cytokines
Small proteins produced by a wide range of immune cells (and other tissue types) that are important communicators, but also affect cellular interactions and activity.

Damage-associated molecular patterns (DAMPs)
Host biomolecules released from dying or damaged cells; these molecules form part of a host's defense against pathogens by activating the innate immune response through their interaction with pattern recognition receptors.

Innate immunity
Fast-acting, nonspecific response to foreign antigens that generally includes leukocytes, antimicrobial peptides and plasma proteins such as the hemolytic complement pathways.

Lipopolysaccharide (LPS)
A component of the outer membrane of most Gram-negative bacteria consisting of long chains of sugars bound covalently to lipids, that can stimulate a strong immune response when introduced into an animal.

Nucleotide oligomerization domain (NOD)-like receptors
A type of pattern-recognition receptor in the form of intracellular proteins that regulate the host innate immune response.

Parasite
Any organism that lives on a host animal at the expense of the host. This includes both endo- and ecto-parasites, as well as micro-parasites (e.g. microbes, viruses) and macro-parasites (e.g. worms, ticks).

Pathogen/pathogenicity
Any organism or virus that can produce disease within the host or having the ability to induce disease.

Pathogen-associated molecular patterns (PAMPs)
Molecules present on pathogen cells (e.g. LPS) that are recognized by host toll-like or pattern-recognition receptors and activate the host innate immune response.

Pattern recognition receptors
Proteins expressed mainly by cells important in the host innate immune system that can identify both PAMPs and DAMPs.

Sickness behaviors
The set of non-specific behavioral changes that occur when an animal's immune system is stimulated, such as during pathogen infection.

Somatotropic axis (hypothalamic–pituitary–somatotropic axis)
Hormone axis referring to the complex cascade of events beginning with the release of hypothalamic hormones [i.e. growth hormone releasing hormone (somatocrinin)] followed by the secretion of growth hormone (somatotropin) from somatotroph cells in the anterior pituitary gland and culminating in the stimulation of insulin-like growth factors in tissues including the liver.

Toll-like receptors
A class of protein membrane receptors found in many cell types responsible for adaptive and innate immunity that recognize structurally conserved molecules present on many pathogens.

behaviors. LPSs are constituents of the cell wall of Gram-negative bacteria and are recognized by Toll-like receptors (TLRs; see Glossary), activating identical immunological pathways as if whole bacteria had been administered (Zhang and Ghosh, 2000), including neuroinflammation (Lopes, 2016). In addition, peptidoglycan, a different component of the bacterial cell wall, can initiate pro-inflammatory responses across vertebrates through binding of NOD-like receptors (NLRs; see Glossary) (Boyle et al., 2013). Using these tools, one can determine whether behavioral change is driven by the host's response upon parasite detection rather than by additional molecules produced and secreted by the parasite. One research frontier regarding the use of these tools is understanding whether damage-associated molecular patterns (DAMPs; see Glossary) or dietary products in addition to the above pathogen-associated molecular patterns (PAMPs; see Glossary) quantitatively or qualitatively stimulate different sickness behaviors (Rankin and Artis, 2018).

Sickness behaviors throughout vertebrate taxa

Mammals

Mammals, and in particular, rodents, are the most extensively studied vertebrates in terms of sickness behavior. Their behavioral responses to an immune challenge – including reduced activity, reduced food and water intake, and decreased social interactions – are therefore considered the stereotypical sickness behaviors (Dantzer, 2001; Dantzer et al., 2008). Research on livestock has also been of interest given the economic implications of disease outbreaks on farms. This research highlights the difficulty that animals may have in displaying sickness behaviors (such as self-isolation) when maintained at high densities (Proudfoot et al., 2012). Hart (1988) described the presence of sickness behavior responses in several domesticated mammalian species, including dogs, cats, horses, pigs, cattle, sheep and rabbits. Sickness behaviors have also been studied both in laboratory and in natural or semi-natural environments in mammals beyond domesticated and routine laboratory species. Examples include guinea pigs (*Cavia porcellus*; Hennessy et al., 2004), Siberian hamsters (*Phodopus sungorus*; Prendergast et al., 2008), vampire bats (*Desmodus rotundus*; Stockmaier et al., 2018), degus (*Octodon degus*; Ramirez–Otarola et al., 2019) and human (Shattuck and Muehlenbein, 2015; Schedlowski et al., 2014; Lasselin et al., 2018; Sandiego et al., 2015) and non-human primates, such as the red colobus monkey (*Procolobus rufomitratus* ssp. *tephrosceles*; Ghai et al., 2015) and rhesus monkey (*Macaca mulatta*; Friedman et al., 1996). The behavioral responses observed in these species fit the overall picture of sickness behaviors, including anorexia and reduced nest building (Prendergast et al., 2008), decreased activity (Ramirez–Otarola et al., 2019; Stockmaier et al., 2018), reduced allogrooming (Stockmaier et al., 2018) and increased somnolence (Friedman et al., 1996) and resting (Ghai et al., 2015). However, specific symptoms can be species dependent. Contrary to the common social withdrawal response that is described in rodents, rhesus monkeys show increased affiliation during a low-dose LPS challenge (Willette et al., 2007), underscoring the importance of studying diverse species when trying to understand the evolution and adaptive value of sickness behaviors.

Birds

Avian sickness behaviors were first studied in chicken (*Gallus gallus domesticus*) in 1993 (Johnson et al., 1993a,b; Klasing et al., 1987; Macari et al., 1993). Overall, avian manifestations of sickness behaviors are similar to those in mammals, with reduced food and

water intake, increased somnolence and decreased activity (Ashley et al., 2009; Bonneaud et al., 2003; Johnson et al., 1993a,b; Klasing, 1991; Klasing et al., 1987; Lee et al., 2005; Lopes et al., 2012a; Lopes et al., 2014; Owen-Ashley et al., 2006). Not all of these sickness behaviors may manifest within a single species, however. For example, in a study where Pekin ducks (*Anas platyrhynchos domesticus*) were exposed to a variety of immune challenges (viral and bacterial), the birds developed fever and anorexia, but not lethargy (Marais et al., 2013). Avian sickness behaviors may also manifest as changes to social behaviors, including decreases in aggression, vocalizations and parental behavior (Lopes, 2014). Specifically, aggression is reduced during an endotoxin challenge in white-crowned sparrows (*Zonotrichia leucophrys gambelii*; Owen-Ashley et al., 2006), song sparrows (*Melospiza melodia morphna*; Owen-Ashley and Wingfield, 2006) and in dominant, but not subordinate, house finches (*Haemorhous mexicanus*; Moyers et al., 2015). Aggression is also reduced in male, but not female, house finches infected with *Mycoplasma gallisepticum* (Bouwman and Hawley, 2010). The number of vocalizations is reduced in male zebra finches (*Taeniopygia guttata*) and white-crowned sparrows in response to LPS (Lopes et al., 2012a; Owen-Ashley and Wingfield, 2006; Owen-Ashley et al., 2006). House sparrows (*Passer domesticus*) reduce brood feeding rate (Bonneaud et al., 2003) but not egg production (Lee et al., 2005) when exposed to LPS. However, egg production is reduced in immune-challenged tree sparrows (*Passer montanus*; Lee et al., 2005).

Similarly to mammals, fever responses are also observed in birds (reviewed in Gray et al., 2013). Ambient temperature can, however, affect fever responses. Pekin ducks kept at elevated ambient temperatures quickly develop high-magnitude fevers, whereas ducks kept at low ambient temperatures show attenuated febrile responses (Marais et al., 2011). Instead of fever, a hypothermic response to immune challenges is found in small passerines, such as zebra finches and white-crowned sparrows (Lopes et al., 2014; Owen-Ashley et al., 2006). This discrepancy in hypo- and hyperthermic responses between small passerines and other avian taxa cannot be completely explained by body size (Sell et al., 2003) and requires additional investigation.

Reptiles

Reptiles as a whole are not as well studied as other taxonomic groups in the context of the ecological and behavioral consequences of disease. Being largely ectothermic as a group (except for a few examples of heterothermy), reptiles show behaviors when infected that are not found in endotherms, such as those associated with the febrile response. A key example of this is the continually spreading snake fungal disease caused by *Ophidiomyces ophiodiicola*, which has been shown in multiple species to lead to increased basking at unusual times of the year when snakes are often hibernating (Lorch et al., 2015; McBride et al., 2015). Manipulative studies also demonstrate thermoregulatory behavioral adjustments. For instance, gopher tortoises (*Gopherus polyphemus*) show a behavioral fever response via increased basking behavior starting just an hour after injection with LPS (Goessling et al., 2017). Similarly, desert iguanas (*Dipsosaurus dorsalis*) exposed to the inactivated bacterium *Aeromonas hydrophila*, show a long-term behavioral fever (2.3°C elevation for 6–7 days; Bernheim and Kluger, 1976). However, as noted above for birds, not all studies in reptiles have documented a hyperthermic response to infection; instead, some demonstrate hypothermic responses, whereas others show no response at all. For instance, green anole lizards (*Anolis carolinensis*) respond hypothermically following intraperitoneal injection of LPS (Merchant et al., 2008). Diverse factors such as condition, age, life history state or sex can interact with infection status to influence behavioral temperature responses. For example, some juvenile green iguanas (*Iguana iguana*) show behavioral fever responses following an LPS immune challenge, whereas others do not. This difference in behavioral response seems to be related to the condition of the animal, whereby individuals in good condition use behavioral fever, whereas those in poorer condition show a hypothermic response (Deen and Hutchison, 2001). Baseline reproductive condition and hormones may also contribute to variation in sickness behaviors, but this has not been examined in reptiles.

Other than the behavioral fever response, sickness behavior in reptiles can largely be characterized by lethargy and anorexia. These sickness behaviors have been observed both in response to infection (parasites and pathogens) and injury (wounding), perhaps because of the induction of shared immune components (Garrido and Pérez-Mellado, 2014; Martin, 1997). Anorexic behavior is also observed in side-blotched lizards (*Uta stansburiana*) following a cutaneous biopsy (Smith et al., 2017). Moreover, following biopsy, metabolic activity is reduced and is inversely related to healing rate, such that the animals with a greater decrease in metabolism show more healing. These results suggest that, at least in this species, sickness behavior may be beneficial to immune performance.

Finally, multiple studies have investigated the impacts of infection or simulated infection on sprint performance. Sprint speed can be an important survival proxy for both competitive ability and antipredator escape behavior. Therefore, during infection, a reduction in sprint capacity may be a readily characterizable sickness behavior for certain species. For example, male, but not female, Algerian sand racers (*Psammodromus algirus*) treated with LPS show reduced sprint performance (Zamora-Camacho et al., 2014). Similarly, common lizards (*Lacerta vivipara*) parasitized with hemogregarines (intracellular blood parasites) have reduced locomotor speed and oxygen consumption (Oppliger et al., 1996). Moreover, Lilford's wall lizards (*Podarcis lilfordi*) with lower hemogregarine blood parasite loads, but not ectoparasites (i.e. mites), have better body condition and faster sprint speeds (Garrido and Pérez-Mellado, 2014). Whether the reduction in sprint performance under parasitic infection constitutes a sickness behavior or is solely a result of pathology remains unknown.

Amphibians

Amphibian sickness behaviors have been most studied in the context of infection with *Batrachochytrium dendrobatidis* (*Bd*, a fungus in the phylum Chytridiomycota), ranaviruses (from the family Iridoviridae) and trematode parasites. These pathogens can have significant impacts on amphibian populations, physiology and behavior (Gray and Chinchar, 2015; Lips, 2016; Woodhams et al., 2018). The behavioral consequences of disease are often linked to morphological changes associated with infection (Goodman and Johnson, 2011; Venesky et al., 2009), developmental or life-history adjustments (Kohli et al., 2019) and the acute phase response (APR; see Glossary; Blaustein et al., 2012). Amphibian sickness behaviors include reductions in activity, feeding and social interactions, and changes in reproductive behaviors and in habitat use, particularly for behavioral thermoregulation (Rakus et al., 2017b; Rollins-Smith and Woodhams, 2012). For example, cane toads (*Rhinella marina*) injected with LPS show reduced feeding and activity (Llewellyn et al., 2011). Reduced feeding has also been reported as a clinical sign of chytridiomycosis (Voyles et al., 2009).

A recent study provides evidence for behavioral fever in response to ranavirus infection in amphibians: recently metamorphosed

and adult southern toads (*Anaxyrus terrestris*) increase baseline temperature 2 days after ranavirus inoculation (Sauer et al., 2019). Furthermore, during a *Bd* epizootic, Panama golden frogs (*Atelopus zeteki*) increased body temperatures above ambient air temperatures and often above the thermal optimum for fungal growth (Richards-Zawacki, 2010). In midwife toads (*Alytes obstetricans*), *Bd* infection lowers the critical thermal maximum temperature (see Glossary) of tadpoles but not toadlets (Fernández-Loras et al., 2019). Thermoregulation in frogs exposed to *Bd* may reduce chytridiomycosis (Karavlan and Venesky, 2016; Rowley and Alford, 2013), but environmental conditions may constrain the thermoregulatory ability of amphibians, particularly if there is a lag in immune system acclimation (Cohen et al., 2019; Nowakowski et al., 2016; Raffel et al., 2006, 2015; Stevenson et al., 2020).

Fishes

Fishes are, in the vast majority, ectotherms. Thus, as in reptiles and amphibians, most studies examining sickness behaviors in ichthyofauna have tested for thermoregulatory responses to infection. Indeed, some of the foundational studies on behavioral fever as an adaptive response to infection in vertebrates used teleost fishes as model systems. Reynolds et al. (1976) documented a preference for warmer temperatures in bluegill sunfish (*Lepomis macrochirus*) and largemouth bass (*Micropterus salmoides*) injected with heat-killed *Aeromonas hydrophila* bacteria. They further demonstrated that behavioral fever in goldfish (*Carassius auratus*) enhances survival during infection (Covert and Reynolds, 1977). Behavioral fever has also been documented in zebrafish (*Danio rerio*), Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*), carp (*Cyprinus carpio*), Trinidadian guppies (*Poecilia reticulata*) and Nile tilapia (*Oreochromis niloticus*) (Boltaña et al., 2013, 2018a,b; Cabanac and Laberge, 1998; Cerqueira et al., 2016; Gräns et al., 2012; Mohammed et al., 2016; Rakus et al., 2017a; Rey et al., 2017). Changes in teleost fish temperature preference when infected can also include cold-seeking behaviors. Preference for cool temperatures might be beneficial for hosts when the infective agent has strongly temperature-sensitive growth and reproduction rates. For instance, *Vibrio* bacterial growth rates and virulence increase at high temperatures, and it has been found that broad-nose pipefish (*Syngnathus typhle*) experimentally infected either with *Vibrio* or heat-killed *Vibrio* prefer cooler temperatures than uninfected conspecifics (Landis et al., 2012). Despite the long history of these types of studies in teleosts, we are only now beginning to understand the physiological mechanisms underlying behavioral fever and chill in these taxa (Boltaña et al., 2018b). Similarly, although lamprey and many species of sharks and rays can behaviorally thermoregulate (Crawshaw and Hammel, 1973; Hight and Lowe, 2007; Matern et al., 2000; McCauley et al., 1977), we are not aware of studies that have yet explicitly tested this behavior in the context of infection in chondrichthyan or agnathan fishes.

Few studies have explicitly tested for sickness behaviors beyond behavioral thermoregulation in fishes. Indeed, sickness behaviors have only recently been comprehensively characterized and described in zebrafish (Kirsten et al., 2018). The few studies that have examined fish behavior following immune stimulation using endotoxin or inactivated bacterial injection suggest that sickness behaviors in fishes mirror those observed in mammals. For instance, fishes may display altered metabolic rates and social preferences as well as reductions in locomotion, exploratory behavior and food intake during the acute phase immune response (Bonneaud et al., 2016; Kirsten et al., 2018; Volkoff and Peter, 2004). However, more research on a broader range of taxa is needed to fully understand the extent to which fishes modify their behavior following immune activation.

How are sickness behaviors produced?

Above we described characteristics of sickness behaviors across groups of vertebrates, but what mechanisms underlie these behaviors and are they similar across these groups? Here, we identify and summarize parallels between mechanisms in mammals (where these mechanisms are best described) and other vertebrate groups. The ‘acute phase response’ is a term that encompasses not only the behavioral, but also the physiological changes experienced by infected or injured organisms. Several interconnected body systems are involved in the acute phase reaction, including the immune, neuroendocrine and reproductive systems (Fig. 1). The first step in triggering this reaction is the body’s recognition of an invader by the immune system. Innate immune cells are capable of recognizing DAMPs and PAMPs through specific membrane receptors called pattern recognition receptors (PRRs; see Glossary), including TLRs, NLRs, retinoic acid-inducible gene 1 (RIG-1)-like receptors and the C-type lectin receptors (CLRs) (Amarante-Mendes et al., 2018; Walsh et al., 2013). Once activated, these membrane receptors trigger a cascade of intracellular responses that culminates with the production of proinflammatory cytokines. These cytokines [of which the best studied in the context of sickness behaviors are interleukin (IL)-1 beta (IL-1β), IL-6 and tumor necrosis factor alpha (TNF-α)] can act both locally and systemically to activate responses in other cell types, helping to orchestrate the host’s immune response (Parameswaran and Patial, 2010; Sims and Smith, 2010; Tanaka et al., 2014).

The behavioral symptoms of sickness associated with the APR are, in most instances, either a direct or indirect consequence of the production of these proinflammatory cytokines. Proinflammatory cytokines communicate with the central nervous system in two major ways (Dantzer et al., 2008): (1) through activation of the vagus nerve and other afferent neural inputs and (2) by crossing the blood–brain barrier either through diffusion at more ‘porous’ areas of the barrier (the circumventricular organs) or through active transport. It is at the level of the central nervous system that several of the metabolic, hormonal and behavioral responses are initiated. Fever is triggered by production of prostaglandin E2 by brain endothelial cells in response to proinflammatory cytokines (Blomqvist and Engblom, 2018). The binding of proinflammatory cytokines to specific brain regions leads to activation of the hypothalamic–pituitary–adrenal/inter-renal axis (Chesnokova and Melmed, 2002; Turnbull and Rivier, 1995), involving the increased production of glucocorticoids (such as corticosterone and cortisol). Proinflammatory cytokines also downregulate the hypothalamic–pituitary–gonadal axis (Morale et al., 2003; Rivier, 1993), involving reduced production of gonadal steroids (such as testosterone). As steroid hormones have a large number of roles in modulating behavior, changes to the levels of these hormones in circulation also mediate the sickness behavioral responses (e.g. Dantzer et al., 1991; Ashley et al., 2009). Inhibition of the somatotropic and hypothalamic–pituitary–thyroid axes (see Glossary) has also been found under immune challenges (Kondo et al., 1997; Soto et al., 1998; Straub, 2014). Although proinflammatory cytokines play an important role in determining sickness behaviors, they do not underlie all the behavioral symptoms of sickness. Bacterial pathogens are capable of activating nociceptor neurons directly, increasing both mechanical and thermal sensitivity to pain (Chiu et al., 2013). In contrast, a viral protein in SARS-CoV-2 can help

Journal of Experimental Biology (2021) 224, jeb225847. doi:10.1242/jeb.225847

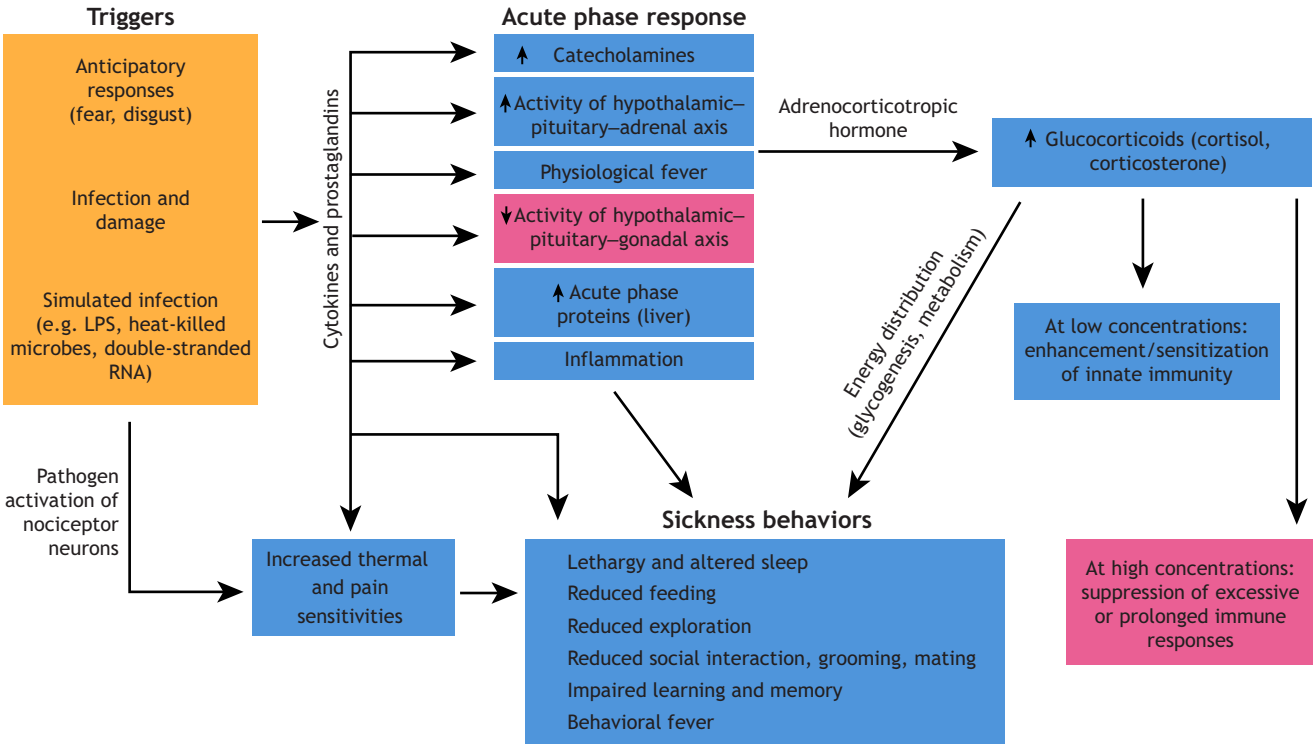

Fig. 1. Well-studied pathways associated with the expression of sickness behaviors. The acute phase response (APR) is activated by various triggers (in orange). Upregulation/activation is shown in blue and downregulation/suppression is shown in pink. The activation of the APR can be anticipatory; for example, uninfected humans and pregnant mice increase cytokine (Schaller et al., 2010) and corticosterone (Curno et al., 2009) levels, respectively, upon exposure to disease cues/symptoms in other individuals; other anticipatory factors are reviewed in O'Connor et al. (2009). Cytokines and prostaglandins are the major drivers of sickness behaviors. Acute or low-concentration exposure to glucocorticoids can enhance inflammatory responses, whereas prolonged or high-concentration exposure is immunosuppressive (Cain and Cidlowski, 2017; Duque and Munhoz, 2016). Not all possible connections and feedback loops are shown, for simplicity. LPS, lipopolysaccharide.

silence pain (Moutal et al., 2020), which could reduce sickness behaviors and favor pathogen spread.

Seasonal and circadian rhythms affect immune function in vertebrates (Baekelandt et al., 2020; Bowden et al., 2007; Esquifino et al., 2004; Esteban et al., 2013; Keller et al., 2009; Logan and Sarkar, 2012; Markowska et al., 2017; Martinez-Bakker and Helm, 2015; Sage et al., 2021; Walton et al., 2011; Weil et al., 2015; Zapata et al., 1992; Zimmerman et al., 2010). As a result, the expression of sickness behaviors is expected to vary throughout the year in seasonal animals. This has been demonstrated, for example, in immune-challenged male Siberian hamsters and white-crowned sparrows, which display reduced sickness behaviors when held under short-day conditions (Bilbo et al., 2002; Owen-Ashley et al., 2006).

Research in rodents has helped determine many of the pathways outlined above. Interestingly, low doses of LPS can also be administered to humans without known long-term consequences. Thus, humans have also been experimentally tested for their sickness behavior and physiological responses to LPS (Shattuck and Muehlenbein, 2015; Schedlowski et al., 2014; Lasselin et al., 2018). For instance, LPS administration to human subjects increases symptoms of fatigue, headache, muscle pain and shivering relative to baseline (before injection), as well as levels of a variety of cytokines in serum, and levels of a marker of microglial activation in several brain regions (Sandiego et al., 2015). The experimental studies in humans highlight that although there are important sex differences in immune responses (with females generally having stronger responses) these do not consistently translate to differences in behavioral responses (Lasselin et al., 2018). Sex differences in sickness behaviors in response to illness have also been studied in other mammals (Avitsur and Yirmiya, 1999). However, little is known about the interplay between sex, infection and sickness behaviors in non-mammalian taxa (but see below for an avian and a reptilian example).

Mechanisms associated with sickness behaviors in non-mammalian taxa

As we summarize in the following paragraphs, physiological pathways involved in the production of sickness behaviors and fever responses generally overlap across vertebrate taxa (Fig. 1; Table 1). This is, perhaps, not surprising, as immune-challenged cephalochordates such as lancelets (amphioxus; close living relatives of vertebrates and considered a basal lineage of chordates) activate innate immune system signaling cascades that overlap with those of vertebrates (Yuan et al., 2009, 2013), even if the majority of cytokines are absent in extant cephalochordates (Huang et al., 2008).

Birds

Studies in chicken and Japanese quail (*Coturnix japonica*) have been crucial in our understanding of the mechanisms involved in avian sickness behaviors and fever responses (Gray et al., 2013; Johnson et al., 1993a,b; Koutsos and Klasing, 2001; Leshchinsky and Klasing, 2001; Macari et al., 1993; Wang et al., 2003). Similarly to mammals, important mediators of these responses in birds are IL-1β, IL-6, TNF-α, glucocorticoids and prostaglandins, and TLRs are involved in the recognition of PAMPs in birds (Gray et al., 2013; Klasing, 1998). For example, in wild house sparrows, an intramuscular LPS injection leads to increased gene expression of

IL-6 and TLR-2 and -4 (measured from blood samples collected at 4 h post-injection) (Martin et al., 2014). In chicken, serum IL-6 is quickly (within 1 h) elevated after an intravenous injection with LPS, and neuro-glial primary cultures of the chicken hypothalamus respond to LPS exposure by producing IL-6, demonstrating that IL-6 is produced both centrally and peripherally in this species (Grabbe et al., 2020). Plasma IL-6 bioactivity is also elevated in zebra finches at 5 h after an intramuscular LPS injection (Lopes et al., 2012b). A different study in zebra finches found that IL-1β gene expression is elevated in the hypothalamus at 4 h post-LPS injection (Lopes et al., 2013). More recent research used RNA-seq to determine differences in global gene expression between LPS- and saline-injected male zebra finches at the level of the hypothalamus, spleen and red blood cells (Scalf et al., 2019). IL-1β is upregulated in response to LPS injection in both the spleen and red blood cells, while the hypothalamus showed a trend in this same direction. The timeframe at which the samples were collected (2 h post-injection) may explain why significant differences in hypothalamic IL-1β were not found here but were found by Lopes et al. (2013), where samples were collected at 4 h post-injection. Dose, route of administration and the timeframe within which samples are collected after LPS administration affect the levels of many physiological responses to this substance (Lopes, 2016). Among the hundreds of genes differentially expressed, TLR-3 is upregulated in red blood cells and IL-6 in spleen (Scalf et al., 2019), further supporting their role in avian responses to endotoxins.

Table 1. Examples of non-mammalian vertebrates where both sickness behaviors and physiological responses known to affect sickness behaviors have been documented

Group	Species studied	Challenge	Behavioral responses	Physiological responses
Birds	Chicken (*Gallus gallus domesticus*)	LPS	Anorexia, lethargy (Johnson et al., 1993b)	Elevation of serum and hypothalamic IL-6 (Grabbe et al., 2020); fever and elevated CORT (Johnson et al., 1993b); increased expression of IL-1β, IFN-γ, TGFβ2 and MGF in spleen (Leshchinsky and Klasing, 2001); indomethacin (inhibitor of PGE2 synthesis) can inhibit LPS-induced fever, drowsiness and anorexia, depending on route of administration (Johnson et al., 1993a)
	Zebra finch (*Taeniopygia guttata*)	LPS	Reduction in hops, calls, flights, increase in time resting (Lopes et al., 2012a)	Elevated plasma CORT, decreased plasma T (Lopes et al., 2012a); high plasma IL-6 (Lopes et al., 2012b); high hypothalamic IL-1β (Lopes et al., 2013); hypothermia (Lopes et al., 2014); high IL-6 expression in spleen and red blood cells (Scalf et al., 2019)
	Japanese quail (*Coturnix japonica*)	LPS	Increase in time resting (Patricia C. Lopes, personal observation)	Increased IL-1β expression in liver and spleen, fever (Koutsos and Klasing, 2001)
	White-crowned sparrow (*Zonotrichia leucophrys gambelii*)	LPS	Decreased activity and food and water intake (Owen-Ashley et al., 2006)	Increase in plasma CORT, decrease in luteinizing hormone, hypothermia (Owen-Ashley et al., 2006)
Reptiles	American alligator (*Alligator mississippiensis*)	LPS	Behavioral fever (Merchant et al., 2008)	Increase in several proteins, including Ubiquitin-activating enzyme 1, which regulates pathways involved in the innate immune response and inflammation (Merchant et al., 2009)
	Western fence lizard (*Sceloporus occidentalis*)	IL-1β	Lethargy (Dunlap and Church, 1996)	This paper documents the behavioral response to IL-1β (Dunlap and Church, 1996)
Amphibians	Cane toad (*Rhinella marina*)	LPS	Lethargy and reduced feeding (Llewellyn et al., 2011)	Upregulated expression of IL-6, IL-1β, TNF-α and other immune genes in the spleen, no increase in plasma CORT (Gardner et al., 2018)
	Salamander (*Necturus maculosus*)	PGE_1 injected in third ventricle of the brain	Behavioral fever (Hutchison and Erskine, 1981)	PGE1 acting in the brain may participate in the production of behavioral fever (Hutchison and Erskine, 1981)
	Frog (*Rana esculenta*)	Killed pathogenic bacteria, brain injection of PGE1	Behavioral fever (Myhre et al., 1977)	PGE1 acting in the brain may participate in the production of behavioral fever (Myhre et al., 1977)
Fishes	Zebrafish (*Danio rerio*)	Double-stranded RNA	Behavioral fever (Boltaña et al., 2013)	Increased plasma PGE2 levels (Boltaña et al., 2013)
		Inactivated bacteria, *Aeromonas hydrophila*	Reduced activity, swimming speeds and social interactions (Kirsten et al., 2018)	IL-1β, IL-6 and TNF-α expression upregulated in brain (Kirsten et al., 2018)
	Atlantic salmon (*Salmo salar*)	Infectious pancreatic necrosis virus	Behavioral fever (Boltaña et al., 2018b)	Elevated plasma IL-1β, IL-6 and PGE2, upregulation in expression of mPGES-1, IL1, IL-6, TNF-α and COX-2 in the head kidney and of IL6 and IFN-γ in the spleen, elevated brain expression of transcripts IL-1r, TNF-R1, IL-6r, EP3 receptor and COX-2 (Boltaña et al., 2018b)

CORT, corticosterone; COX-2, cyclo-oxygenase 2; EP3, prostaglandin E2 receptor, E3 subtype; IFN-γ, interferon gamma; IL, interleukin; LPS, lipopolysaccharide; MGF, mechano growth factor; PGE1, PGE2, prostaglandins E1 and E2; TGFβ2, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TNF-R1, tumor necrosis factor receptor 1; mPGES-1, microsomal prostaglandin E synthase-1.

Several factors have been studied that affect the intensity of sickness behaviors in birds, including early life (*in ovo*) experiences, access to food or certain nutrients, and environmental factors. These factors may provide insights into potential mechanisms underlying the regulation of sickness behaviors. For instance, young chicks exposed to cocaine as embryos do not show sickness behaviors in response to LPS (Schrott et al., 1999), and those embryonically exposed to a potent opiate (*N*-desmethyl-l-α-noracetylmethadol) fail to show fever responses (Schrott and Sparber, 2004). Knowledge of the effects of these substances during early development may provide clues regarding the brain areas or physiological mechanisms involved in the regulation of sickness behaviors and fever. Food restriction of captive red crossbills (*Loxia curvirostra*) does not affect the response to an LPS injection (Schultz et al., 2017), whereas, in European starlings (*Sturnus vulgaris*), access to a carotenoid-enriched diet prevents the decrease in singing rate that is expected during an immune challenge (Casagrande et al., 2015), indicating that, at least in this species, the availability of certain nutrients impacts sickness behaviors. LPS-treated male white-crowned sparrows kept under long-day photoperiods lose more body mass than their counterparts kept under short days, an effect not observed in females, who lose similar amounts of mass in response to LPS under both conditions (Owen-Ashley et al., 2006). This is also one of the few studies that has addressed sex differences in avian sickness behaviors in terms of behavior and physiological responses. The effects of seasonality may be due to availability of energy stores and seasonally varying hormones (Owen-Ashley and Wingfield, 2007). Testosterone levels differ greatly between sexes and vary seasonally: testosterone is typically lower in the winter than in spring in male birds. A study that applied testosterone implants to male white-crowned sparrows found reduced sickness behaviors when the birds were injected with LPS (Ashley et al., 2009) relative to birds with empty implants. However, testosterone-implanted animals also showed elevated corticosterone, which complicates the interpretation of the results, as corticosterone also modulates the immune response. More research is needed to understand the effect of testosterone on avian sickness behaviors.

Reptiles

Most species of reptiles, amphibians and fishes are ectotherms. As highlighted above, ectotherms are special when it comes to fever, because they regulate their fever behaviorally. Nevertheless, similarly to their role in mammals, prostaglandins appear to be important mediators of fever (behavioral, in this case) in ectotherms (Rakus et al., 2017b).

Molecular responses and pathways underlying sickness behaviors in reptiles are generally understudied due to the specificity of detection methods, which have largely been developed in mammalian species. More recent work using reverse-transcriptase quantitative PCR in two chelonian species, the red-eared slider (*Trachemys scripta elegans*) and eastern box turtle (*Terrapene carolina carolina*) has documented IL-1β, TNF-α and IL-10 transcript targets, which are important signaling molecules in the APR (Rayl et al., 2019). Earlier work in Chinese soft-shelled turtle (*Trionyx sinensis*) infected with *Aeromonas hydrophila* revealed that infection results in upregulated expression of IL-8, suggesting that this signaling molecule may play an important role in reptilian inflammatory responses (Zhou et al., 2009). Furthermore, western fence lizards (*Sceloporus occidentalis*) injected with IL-1β show reduced activity levels akin to sickness-induced lethargy in other species (Dunlap and Church, 1996). An LPS injection produces behavioral fever in juvenile American alligators (*Alligator mississippiensis*) (Merchant et al., 2007). A proteomics study in juveniles of this species injected with LPS found several proteins to be upregulated at 24 h post-injection, including Ubiquitin-activating enzyme 1 (Merchant et al., 2009). Ubiquitination is important in the regulation of the nuclear factor-κB (NF-κB) signaling pathway, which, in turn, regulates genes that participate in immune responses, including the innate immune response and inflammation (Sun and Ley, 2008).

However, it should be noted that the effects of proinflammatory cytokines and glucocorticoids on sickness behavior may be more context dependent in ectothermic species than in endotherms, depending particularly on temperature and reproductive status. For example, in the wall lizard (*Hemidactylus flaviviridis*), LPS-induced increases in phagocytosis, nitric oxide production and an IL-1-like molecule are dependent on temperature, such that stimulation of the response only appears to occur in an optimal temperature range (Mondal and Rai, 2001). In the same species, reproductive context seems to influence cytokine release, whereby treatment with reproductive hormones (estradiol and dihydrotestosterone) decreases the production of an IL-1-like molecule, whereas gonadectomy leads to increased IL-1 (Mondal and Rai, 2002).

The context-dependent nature of immune activity and cytokine expression may partially explain the mixed results that are found across reptilian species; whereby some studies find hyperthermic responses to infection, but others find hypothermic or no responses. For example, sex factors into immunological and behavioral responses to infection in reptiles. In African house snakes, *Lamprophis fuliginosus*, no significant body temperature change is noted following inoculation with different strains of UV-killed bacteria (Ryan et al., 2018). Instead, male (but not female) snakes exposed to UV-killed bacterial pathogens (which still act as antigens but are not pathogenic) respond with an increased variance of body (cloacal) temperature that was achieved through behavioral adjustments. This sex-dependent difference in behavioral response could lead to differing exposure and disease dynamics depending on social structure of the species (i.e. solitary, communal) and time of year (e.g. breeding versus non-breeding). Moreover, corticosterone is also likely to play a role in modulating fluctuating immunity across contexts. Corticosterone administered exogenously is immunosuppressive in female ornate tree lizards (*Urosaurus ornatus*) during periods of reproductive investment and also when resources are restricted, but not when non-reproductive females have *ad libitum* access to food (French et al., 2007).

Amphibians

Similarly to other taxa, in amphibians, APRs leading to sickness behaviors correspond to increases in catecholamines and corticosterone, antimicrobial peptides and reallocation of resources toward certain immune defenses and rapid development and away from growth (Rollins-Smith, 2017; Rollins-Smith and Woodhams, 2012; Warne et al., 2011). For example, water-borne corticosterone release rates are higher in ranavirus-infected larval western tiger salamanders (*Ambystoma mavortium*) than in uninfected larvae (Davis et al., 2020). Gabor et al. (2015) found that corticosterone is higher in common midwife toad tadpoles with more aggressive infections of *Bd* and that the frequency of righting reflexes (per minute) of infected metamorphs (which is indicative of the severity of chytridiomycosis) is inversely correlated with corticosterone release rates.

At 24 h after an LPS injection, adult African clawed frogs (*Xenopus laevis*) express IL-1β in several organs (Zou et al., 2000), and the levels of plasma testosterone and melatonin in

bullfrogs (*Lithobates catesbeianus*) are decreased relative to controls (Figueiredo et al., 2021). A transcriptomic approach used to assess gene expression changes upon LPS injection in cane toads found upregulation of transcripts that overlap with responses found in other species (Table 1; Gardner et al., 2018). Also, prostaglandin E1 has been shown to elicit behavioral fever in amphibian species (Table 1; Hutchison and Erskine, 1981; Myhre et al., 1977). Still, better understanding of the molecular underpinnings of the APR in amphibians is needed, including comparative studies on cytokine expression in early and late infection in disease-susceptible and disease-resistant hosts, and in a variety of disease systems (reviewed in Grogan et al., 2018).

Fishes

The majority of fish species spend their early embryonic stages in close contact with the external environment. Thus, there is a longer and heavier reliance on their innate immune system for survival compared with other vertebrate taxa (Uribe et al., 2011). Despite this difference, the immune systems of osteichthian and chondrichthyan fishes remain very similar to those of other vertebrates (Bayne and Gerwick, 2001; Kirsten et al., 2018; Luer et al., 2004; Renshaw and Trede, 2012), and their immune responses include immune gene activation, increased cortisol response and increased antibody production (Balm et al., 1995; Binning et al., 2018; Haukenes and Barton, 2004; Selvaraj et al., 2006; Watzke et al., 2007). Although agnathan fishes lack many aspects of the acquired immune system seen in other vertebrates, they do appear to display an APR similar to that of other fishes following infection (Bayne and Gerwick, 2001).

Despite this understanding, links between the immune system and behavior are not well studied in fishes. Behavioral fever is a notable exception, with several studies dedicated to describing the mechanisms underlying this phenomenon in several different species. When Boltaña et al. (2013) injected zebrafish with double-stranded RNA to simulate a viral infection, they found that immune-stimulated fish shifted their preferred temperature upwards by 3°C compared with sham-injected controls, and thus displayed behavioral fever. These individuals had increased levels of prostaglandin E2 in their plasma compared with immune-stimulated fish that were not permitted to behaviorally thermoregulate. Transcriptome analysis of the brain tissues of immune-challenged fish that displayed behavioral fever found that 39% of transcripts examined showed temperature-dependent up-regulation; the most strongly up-regulated were genes known to be related to the anti-viral response. Individuals expressing behavioral fever were able to rapidly clear the infection. Subsequent studies using Atlantic salmon inoculated with infectious pancreatic necrosis virus (IPNv) have also demonstrated a link between behavioral fever and immune gene expression (Boltaña et al., 2018b). Infected salmon prefer warmer temperatures, and viral loads are higher in individuals that do not engage in behavioral fever. Fish which display fever also experience an upregulation in genes involved in the innate and adaptive immune responses (see Glossary), such as IFNR-γ, IFN-γ, IL4/l3, IL-2, IL1-2, and proinflammatory cytokines mPGES-1, IL1, IL-6, TNF-α and COX-2. Mechanistically, members of the transient receptor potential family of ion receptors (TRPV2 and TRPV4) appear to coordinate temperature sensing during behavioral fever (Boltaña et al., 2018b). Changes in gene expression, cytokine production and lymphocyte proliferation also appear to be the result of epigenetic modifications, including histone methylation, induced by behavioral fever (Boltaña et al., 2018a). These studies have been pivotal in establishing the mechanistic links between behaviorally induced, temperature-dependent gene expression and positive health outcomes in teleosts. Despite these advances, we are still only beginning to understand the molecular, physiological and genetic mechanisms underlying behavioral fever in fishes.

Few other studies have comprehensively described sickness behaviors and their underlying mechanisms in fishes. Kirsten et al. (2018) were the first to formally describe the patterns of sickness-induced behavioral changes following systemic activation of immune cells in zebrafish. After inducing an inflammatory response in zebrafish through injection of formalin-inactivated bacteria, *Aeromonas hydrophila*, Kirsten et al. (2018) tested for differences in fish behavior, cytokine gene expression and neuronal activity compared with sham-injected and handling-control fish. They found that mRNA levels of proinflammatory cytokines IL-1β, IL-6 and TNF-α were upregulated in the brains of immune-stimulated fish. This corresponded to reductions in activity, swimming speed and social interactions in immune-stimulated fish compared to controls, suggesting that behavioral changes in fishes during the APR are mediated by the immune system. Similar responses have since been demonstrated in zebrafish following injection with tilapia lake virus (TiLV), a novel pathogen that has been associated with disease outbreaks in both farmed and wild tilapia and that can lead to mortality rates reaching up to 90% (Rakus et al., 2020). When administered to adult zebrafish in the lab, this virus induces sickness behaviors, characterized by irregular swimming, formation of tight groups at the bottom of the aquarium, anorexia and lethargy. These behaviors are also associated with increased expression of IL-1β in the spleen and kidney. The extent to which these infection-induced behavioral changes occur in other fish species remains to be documented.

Why have sickness behaviors?

For many decades, the pervasive view of the behavioral changes associated with infections was that they were a consequence of a general debilitation of the sick organism and served no major function. This view began changing about 30 years ago, when Hart (1988) first proposed that sickness behaviors constitute a highly coordinated organismal response to help fight the infection and increase host survival. According to his theory, sickness behaviors contribute to self-preservation through a reallocation of energy from activities (e.g. foraging) into components of the immune response and a reduction in the ingestion of nutrients essential for pathogen growth (through anorexia). The best support for Hart's theory comes from studies of altered thermal preference in infected individuals. Several studies in different vertebrate and invertebrate taxa show increased host survival or reduced pathogen growth when animals are allowed to develop behavioral fever (Boltaña et al., 2013; Boorstein and Ewald, 1987; Covert and Reynolds, 1977; Elliot et al., 2002; Kluger et al., 1975; Richards-Zawacki, 2010; Sauer et al., 2019) or behavioral chill (Hunt et al., 2016; Truitt et al., 2019). These effects seem to be partly due to the enhancement of both innate and adaptive immune responses (Boltaña et al., 2013; Evans et al., 2015; Kluger et al., 1996). In endothermic LPS-treated zebra finches, lethargy covaries with the blood's ability to kill bacteria (Lopes et al., 2014). Whereas this study suggests that at least some components of sickness behaviors may support the immune response, as proposed by Hart, other factors could have influenced both the immune response and lethargy. Beyond thermoregulatory behaviors, studying the adaptive value of sickness behaviors is complicated because of the difficulty in preventing their expression. However, one component of sickness behaviors that can be manipulated is anorexia, through use of

force-feeding approaches. When mice infected with *Listeria monocytogenes* are force-fed to a food intake level of uninfected mice, they have higher mortality than infected mice allowed to develop anorexia (Murray and Murray, 1979). The relationship between anorexia and survival is not, however, completely understood, and may be disease specific (Ayres and Schneider, 2009; Rao et al., 2017).

More recently, sickness behaviors have been hypothesized to serve a signaling function (Tiokhin, 2016) or to have evolved to protect kin (i.e. through kin selection, Shakhar and Shakhar, 2015). Some of these new hypotheses were proposed because a host survival theory does not fully explain the costs associated with sickness behaviors such as anorexia: if activating an immune response is energetically costly (Hasselquist and Nilsson, 2012), it appears counterproductive to simultaneously reduce caloric intake during illness. According to the kin protection hypothesis, components of sickness behaviors, including social withdrawal and reduced food and water intake, could be favored through kin selection because these behaviors also reduce the likelihood of disease transmission to kin within a social group. One study aiming at testing this hypothesis using wild mice (*Mus domesticus*) in both a field and laboratory setting found no strong support for it (Lopes et al., 2018). Another way to test the kin protection hypothesis is by comparing across taxonomic groups: one would predict that in species where animals spend very little time close to kin (e.g. territorial or solitary species) sickness behaviors would be reduced or non-existent, whereas the opposite would hold true for group-living species. Contrary to this, our Review contains examples of both solitary/territorial species (e.g. desert iguanas, western fence lizards, rainbow trout) and group-living species (e.g. American alligators, zebrafish, zebra finches) showing sickness behaviors. Using a modeling approach, Iritani and Iwasa (2014) suggested that hosts may disperse from kin at a rate conditional on the level of infection. Whether dispersal rate is a form of sickness behavior developed in response to kin selection, or a trade-off between risk of infection and information transmission (Evans et al., 2020), is unknown, with few experimental studies set up to directly test theory: more evidence is needed.

The extent to which animals engage in the different components of sickness behaviors is flexible and depends on a variety of abiotic (e.g. environmental temperature, time of year; Bilbo et al., 2002; Owen-Ashley and Wingfield, 2006; Prendergast et al., 2016) and biotic factors (e.g. sex differences, and the presence of offspring or potential sexual partners; Avitsur and Yirmiya, 1999; Lopes et al., 2013; Weil et al., 2006; Yirmiya et al., 1995). From a life history or evolutionary perspective, some of this flexibility can be explained rather intuitively (Adelman and Martin, 2009; Ashley and Wingfield, 2011; Lopes, 2014). When animals are faced with deteriorating health conditions, they may also face terminal decisions (Williams, 1966): should they attempt to mate one last time and invest all remaining energy in ensuring hatchlings fledge? If engaging in sickness behaviors allows animals to survive until another reproductive opportunity emerges, then sickness behaviors should occur. Otherwise, individuals might benefit more in terms of their lifetime reproductive fitness by overcoming sickness symptoms and reproducing, even if survival probability decreases. Although there is some empirical evidence for terminal investment or fecundity compensation in a variety of taxa (Bonneaud et al., 2003; Brannelly et al., 2016; Duffield et al., 2017), the proximate mechanisms underlying the decision of whether to engage in sickness behaviors are mostly unknown and urgently need additional investigation (Lopes, 2014).

A deeper understanding of the proximate mechanisms driving sickness behaviors will help uncover the adaptive value of these behaviors. For example, although fever is achieved in different ways in ectotherms and endotherms (behaviorally versus physiologically, respectively), similar molecular pathways are involved in triggering these responses, indicating that fever is likely to be an essential and adaptive component of sickness. Alternatively, finding species or groups where there is a decoupling of cytokine signaling and certain behavioral responses could indicate that the specific behaviors were detrimental to those groups and clarify when and where sickness behaviors are adaptive.

Conclusions

In this Review, we have identified commonalities among the sickness behaviors expressed by diverse vertebrate groups. In all groups, there is evidence of lethargy in some form, changes in social interactions, some degree of anorexia and, across all groups of ectotherms studied, evidence for behavioral thermoregulation. The immune responses to challenges are also similar, an indication that not only the behaviors themselves, but also the mechanisms underlying them, are conserved across taxa. However, the precise connection between those immune responses and the different components of sickness behaviors is not clear in all taxa. A broader exploration of sickness behaviors across non-mammalian taxa is needed.

As highlighted throughout the text, one fascinating aspect of sickness behaviors is that they are not all-or-nothing responses. The expression of sickness behaviors is flexible under certain circumstances (Lopes, 2014); however, very little is known regarding the underlying neuroimmune mechanisms associated with this flexibility. The hormonal milieu is likely to be involved in modulating these responses (reviewed in Ashley and Demas, 2017; Demas et al., 2012; Lopes, 2014). More research uncovering mechanisms that bring about variation in the strength of immune responses may help to clarify individual variation in sickness behavior (Lopes, 2017).

Another topic in need of more research is the mechanistic origin of sex differences in physiological and behavioral responses to infections. Although differences in the levels of sex steroids between sexes are a logical first step, studies in mammals seem to indicate that sex steroid differences do not paint a complete picture (Casimir et al., 2013; Lasselin et al., 2018). Other targets could include genetic components, such as genes related to immune function located on sex chromosomes (Casimir et al., 2013; Klein and Flanagan, 2016).

It has been suggested that the physiological responses of individuals to infection scale up to the population level by exerting influence on pathogen transmission (Blaustein et al., 2012). In this way, disease emergence or fade-out results from ecophysiology. For example, alpine newts (*Ichthyosaura alpestris*) heavily infected with *Bd* spend more time in terrestrial habitats, which helps to clear infection faster (Daversa et al., 2018), but also potentially reduces conspecific exposure. Moving forward, it will therefore be important to use more integrative approaches in the study of neuroendocrine–immune–behavior interactions (Bowden et al., 2017; Demas and Ashley, 2017; Demas and Carlton, 2015; Lopes, 2014; Shattuck et al., 2020; Sylvia and Demas, 2017).

Finally, recent and virulent epizootics point to more research focused on reptiles as an area of increasing importance. For instance, both snake fungal disease (Lorch et al., 2016) and respiratory tract disease in tortoises (Seigel et al., 2003) are having widespread effects on reptile populations worldwide. Changes in behavior in response to infection, such as increased time basking to

elicit behavioral fever, could have important survival and fitness implications for individuals and populations in terms of exposing animals to predators, but they could also affect the spread of the pathogen itself through changes in host social contacts. Knowledge of the precise mechanisms that drive the different components of sickness behaviors, of how malleable these are, and of the relative contributions of physiology and behavior in reducing infectivity and pathogen survival and burden, may help us have predictive power over the impact of these emerging disease outbreaks on populations. To understand how aspects of behavior affect the spread of diseases through populations, especially given current epizootic concerns and rapid global change, there is an urgent need for further work on the mechanisms underlying sickness behaviors.

Acknowledgements
We thank Charlotte Rutledge, Noah Ashley and two anonymous reviewers for their constructive feedback.

Competing interests
The authors declare no competing or financial interests.

Funding
S.A.B. is supported through the Canada Research Chairs program and the Natural Sciences and Engineering Research Council of Canada. D.C.W. is supported by the US National Science Foundation (DEB-1814520 and IOS-1845634). S.S.F. is supported by the US National Science Foundation (IOS-1752908 and IOS-2031420).

References
Adamo, S. A. and Shoemaker, K. L. (2000). Effects of parasitism on the octopamine content of the central nervous system of *Manduca sexta*: a possible mechanism underlying host behavioural change. *Can. J. Zool.* **78**, 1580-1587. doi:10.1139/z00-096

Adelman, J. S. and Martin, L. B. (2009). Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. *Int. Comp. Biol.* **49**, 202-214. doi:10.1093/icb/icp028

Amarante-Mendes, G. P., Adjemian, S., Branco, L. M., Zanetti, L. C., Weinlich, R. and Bortoluci, K. R. (2018). Pattern recognition receptors and the host cell death molecular machinery. *Front. Immunol.* **9**, 2379. doi:10.3389/fimmu.2018.02379

Arunachalam, P. S., Wimmers, F., Mok, C. K. P., Perera, R. A. P. M., Scott, M., Hagan, T., Sigal, N., Feng, Y., Bristow, L., Tsang, O. T.-Y. et al. (2020). Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* **369**, 1210-1220. doi:10.1126/science.abc6261

Ashley, N. T., Demas, G. E. (2017). Neuroendocrine-immune circuits, phenotypes, and interactions. *Horm. Behav.* **87**, 25-34. doi:10.1016/j.yhbeh.2016.10.004

Ashley, N. T. and Wingfield, J. C. (2011). Sickness behavior in vertebrates. In *Ecoimmunology* (ed. G. Demas and R. Nelson), pp. 45-91. Oxford University Press.

Ashley, N. T., Hays, Q. R., Bentley, G. E. and Wingfield, J. C. (2009). Testosterone treatment diminishes sickness behavior in male songbirds. *Horm. Behav.* **56**, 169-176. doi:10.1016/j.yhbeh.2009.04.003

Avitsur, R. and Yirmiya, R. (1999). The Immunobiology of Sexual Behavior: Gender Differences in the Suppression of Sexual Activity During Illness. *Pharmacol. Biochem. Behav.* **64**, 787-796. doi:10.1016/S0091-3057(99)00165-3

Ayres, J. S. and Schneider, D. S. (2009). The role of anorexia in resistance and tolerance to infections in *Drosophila*. *PLoS Biol.* **7**, e1000150. doi:10.1371/journal.pbio.1000150

Baekelandt, S., Milla, S., Cornet, V., Flamion, E., Ledoré, Y., Redivo, B., Antipine, S., Mandiki, S. N. M., Houndji, A., El Kertaoui, N. et al. (2020). Seasonal simulated photoperiods influence melatonin release and immune markers of pike perch Sander lucioperca. *Sci. Rep.* **10**, 2650. doi:10.1038/s41598-020-59568-1

Balm, P. H. M., van Lieshout, E., Lokate, J. and Wendelaar Bonga, S. E. (1995). Bacterial lipopolysaccharide (LPS) and interleukin 1 (IL-1) exert multiple physiological effects in the tilapia *Oreochromis mossambicus* (Teleostei). *J. Comp. Physiol. B* **165**, 85-92. doi:10.1007/BF00301472

Bayne, C. J. and Gerwick, L. (2001). The acute phase response and innate immunity of fish. *Dev. Comp. Immunol.* **25**, 725-743. doi:10.1016/S0145-305X(01)00033-7

Beckage, N. E. (1993). Endocrine and neuroendocrine host-parasite relationships. *Receptor* **3**, 233-245.

Bernheim, H. A. and Kluger, M. J. (1976). Fever and antipyresis in the lizard *Dipsosaurus dorsalis*. *Am. J. Physiol.* **231**, 198-203. doi:10.1152/ajplegacy.1976.231.1.198

Bilbo, S. D., Drazen, D. L., Quan, N., He, L. and Nelson, R. J. (2002). Short day lengths attenuate the symptoms of infection in Siberian hamsters. *Proc. Royal Soc. B* **269**, 447-454. doi:10.1098/rspb.2001.1915

Binning, S. A., Roche, D. G., Grutter, A. S., Colosio, S., Sun, D., Miest, J. and Bshary, R. (2018). Cleaner wrasse indirectly affect the cognitive performance of a damselfish through ectoparasite removal. *Proc. Royal Soc. B* **285**, 20172447. doi:10.1098/rspb.2017.2447

Biron, D., Marché, L., Ponton, F., Loxdale, H., Galéotti, N., Renault, L., Joly, C. and Thomas, F. (2005). Behavioural manipulation in a grasshopper harbouring hairworm: a proteomics approach. *Proc. R. Soc. B* **272**, 2117-2126. doi:10.1098/rspb.2005.3213

Blaustein, A. R., Gervasi, S. S., Johnson, P. T. J., Hoverman, J. T., Belden, L. K., Bradley, P. W. and Xie, G. Y. (2012). Ecophysiology meets conservation: understanding the role of disease in amphibian population declines. *Phil. Trans. R. Soc. B* **367**, 1688-1707. doi:10.1098/rstb.2012.0011

Blomqvist, A. and Engblom, D. (2018). Neural mechanisms of inflammation-induced fever. *Neuroscientist* **24**, 381-399. doi:10.1177/1073858418760481

Boltaña, S., Rey, S., Roher, N., Vargas, R., Huerta, M., Huntingford, F. A., Goetz, F. W., Moore, J., Garcia-Valtanen, P., Estepa, A. et al. (2013). Behavioural fever is a synergic signal amplifying the innate immune response. *Proc. R. Soc. B* **280**, 20131381. doi:10.1098/rspb.2013.1381

Boltaña, S., Aguilar, A., Sanhueza, N., Donoso, A., Mercado, L., Imarai, M. and Mackenzie, S. (2018a). Behavioral fever drives epigenetic modulation of the immune response in fish. *Front. Immunol.* **9**, 1241. doi:10.3389/fimmu.2018.01241

Boltaña, S., Sanhueza, N., Donoso, A., Aguilar, A., Crespo, D., Vergara, D., Arriagada, G., Morales-Lange, B., Mercado, L., Rey, S. et al. (2018b). The expression of TRPV channels, prostaglandin E2 and pro-inflammatory cytokines during behavioural fever in fish. *Brain Behav. Immun.* **71**, 169-181. doi:10.1016/j.bbi.2018.03.023

Bonneaud, C., Mazuc, J., Gonzalez, G., Haussy, C., Chastel, O., Faivre, B. and Sorci, G. (2003). Assessing the cost of mounting an immune response. *Am. Nat.* **161**, 367-379. doi:10.1086/346134

Bonneaud, C., Wilson, R. S. and Seebacher, F. (2016). Immune-challenged fish up-regulate their metabolic scope to support locomotion. *PLoS ONE* **11**, e0166028. doi:10.1371/journal.pone.0166028

Boorstein, S. M. and Ewald, P. W. (1987). Costs and Benefits of Behavioral Fever in *Melanoplus sanguinipes* Infected by *Nosema acridophagus*. *Physiol. Zool.* **60**, 586-595. doi:10.1086/physzool.60.5.30156132

Bouwman, K. M. and Hawley, D. M. (2010). Sickness behaviour acting as an evolutionary trap? Male house finches preferentially feed near diseased conspecifics. *Biol. Lett.* **6**, 462-465. doi:10.1098/rsbl.2010.0020

Bowden, T. J., Thompson, K. D., Morgan, A. L., Gratacap, R. M. L. and Nikoskelainen, S. (2007). Seasonal variation and the immune response: A fish perspective. *Fish Shellfish Immunol.* **22**, 695-706. doi:10.1016/j.fsi.2006.08.016

Bowden, R. M., French, S. S. and Demas, G. E. (2017). Introduction to ecoimmunology: An integrative approach. *J. Exp. Zool. A Ecol. Integr. Physiol.* **327**, 219-221. doi:10.1002/jez.2114

Boyle, J., Mayle, S., Parkhouse, R. and Monie, T. P. (2013). Comparative Genomic and Sequence Analysis Provides Insight into the Molecular Functionality of NOD1 and NOD2. *Front. Immunol.* **4**, 317. doi:10.3389/fimmu.2013.00317

Brannelly, L. A., Webb, R., Skerratt, L. F. and Berger, L. (2016). Amphibians with infectious disease increase their reproductive effort: evidence for the terminal investment hypothesis. *Open Biol.* **6**, 150251. doi:10.1098/rsob.150251

Cabanac, M. and Laberge, F. (1998). Fever in Goldfish Is Induced by Pyrogens But Not by Handling. *Physiol. Behav.* **63**, 377-379. doi:10.1016/S0031-9384(97)00444-7

Cabral, C. M., Tuladhar, S., Dietrich, H. K., Nguyen, E., MacDonald, W. R., Trivedi, T., Devineni, A. and Koshy, A. A. (2016). Neurons are the Primary Target Cell for the Brain-Tropic Intracellular Parasite *Toxoplasma gondii*. *PLoS Pathog.* **12**, e1005447. doi:10.1371/journal.ppat.1005447

Cain, D. W. and Cidlowski, J. A. (2017). Immune regulation by glucocorticoids. *Nat. Rev. Immunol.* **17**, 233-247. doi:10.1038/nri.2017.1

Casagrande, S., Pinxten, R., Zaid, E. and Eens, M. (2015). Birds receiving extra carotenoids keep singing during the sickness phase induced by inflammation. *Behav. Ecol. Sociobiol.* **69**, 1029-1037. doi:10.1007/s00265-015-1916-y

Casimir, G. J., Lefèvre, N., Corazza, F. and Duchateau, J. (2013). Sex and inflammation in respiratory diseases: a clinical viewpoint. *Biol. Sex. Differ.* **4**, 16. doi:10.1186/2042-6410-4-16

Cerqueira, M., Rey, S., Silva, T., Featherstone, Z., Crumlish, M. and MacKenzie, S. (2016). Thermal preference predicts animal personality in Nile tilapia *Oreochromis niloticus*. *J. Anim. Ecol.* **85**, 1389-1400. doi:10.1111/1365-2656.12555

Chesnokova, V. and Melmed, S. (2002). Minireview: Neuro-immuno-endocrine modulation of the hypothalamic-pituitary-adrenal (HPA) axis by gp130 signaling molecules. *Endocrinology* **143**, 1571-1574. doi:10.1210/endo.143.5.8861

Chiu, I. M., Heesters, B. A., Ghasemlou, N., Hehn, C. A. V., Zhao, F., Tran, J., Wainger, B., Strominger, A., Muralidharan, S., Horswill, A. R. et al. (2013).

Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* **501**, 52-57. doi:10.1038/nature12479
Cohen, J. M., McMahon, T. A., Ramsay, C., Roznik, E. A., Sauer, E. L., Bessler, S., Civitello, D. J., Delius, B. K., Halstead, N., Knutie, S. A. et al. (2019). Impacts of thermal mismatches on chytrid fungus *Batrachochytrium dendrobatidis* prevalence are moderated by life stage, body size, elevation and latitude. *Ecol. Lett.* **22**, 817-825. doi:10.1111/ele.13239
Covert, J. B. and Reynolds, W. W. (1977). Survival value of fever in fish. *Nature* **267**, 43-45. doi:10.1038/267043a0
Crawshaw, L. I. and Hammel, H. T. (1973). Behavioral temperature regulation in the California horn shark, *Heterodontus francisci*. *Brain Behav. Evol.* **7**, 447-452. doi:10.1159/000124428
Crutcher, J. M. and Hoffman, S. L. (1996). Malaria. In *Medical Microbiology*, Chapter 83 (ed. S. Baron), Galveston, TX: University of Texas Medical Branch at Galveston.
Curno, O., Behnke, J. M., McElligott, A. G., Reader, T. and Barnard, C. J. (2009). Mothers produce less aggressive sons with altered immunity when there is a threat of disease during pregnancy. *Proc. Roy. Soci. B* **276**, 1047-1054. doi:10.1098/rspb.2008.1612
Dantzer, R. (2001). Cytokine-induced sickness behavior: where do we stand? *Brain Behav. Immun.* **15**, 7-24. doi:10.1006/brbi.2000.0613
Dantzer, R. (2004). Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity. *Eur. J. Pharmacol.* **500**, 399-411. doi:10.1016/j.ejphar.2004.07.040
Dantzer, R., Bluthe, R. M. and Kelley, K. W. (1991). Androgen-dependent vasopressinergic neurotransmission attenuates interleukin-1-induced sickness behavior. *Brain Res.* **557**, 115-120. doi:10.1016/0006-8993(91)90123-D
Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W. and Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Rev. Neurosci.* **9**, 46-56. doi:10.1038/nrn2297
Daversa, D. R., Manica, A., Bosch, J., Jolles, J. W. and Garner, T. W. J. (2018). Routine habitat switching alters the likelihood and persistence of infection with a pathogenic parasite. *Funct. Ecol.* **32**, 1262-1270. doi:10.1111/1365-2435.13038
Davis, D. R., Ferguson, K. J., Schwarz, M. S. and Kerby, J. L. (2020). Effects of Agricultural Pollutants on Stress Hormones and Viral Infection in Larval Salamanders. *Wetlands* **40**, 577-586. doi:10.1007/s13157-019-01207-1
Deen, C. M. and Hutchison, V. H. (2001). Effects of lipopolysaccharide and acclimation temperature on induced behavioral fever in juvenile Iguana iguana. *J. Therm. Biol.* **26**, 55-63. doi:10.1016/S0306-4565(00)00026-7
Demas, G. E. and Ashley, N. T. (2017). Introduction to the Special Issue on Neuroendocrine-Immune Interactions: Implications for Integrative and Comparative Physiologists. *Horm. Behav.* **88**, 1-3. doi:10.1016/j.yhbeh.2017.01.005
Demas, G. E. and Carlton, E. D. (2015). Ecoimmunology for psychoneuroimmunologists: Considering context in neuroendocrine–immune–behavior interactions. *Brain Behav. Immun.* **44**, 9-16. doi:10.1016/j.bbi.2014.09.002
Demas, G., Nelson, R. and Nelson, R. J. (2012). *Ecoimmunology*. USA: Oxford University Press.
Duffield, K. R., Bowers, E. K., Sakaluk, S. K. and Sadd, B. M. (2017). A dynamic threshold model for terminal investment. *Behav. Ecol. Sociobiol.* **71**, 185. doi:10.1007/s00265-017-2416-z
Dunlap, K. D. and Church, D. R. (1996). Interleukin-1β reduces daily activity level in male lizards, *Sceloporus occidentalis*. *Brain Behav. Immun.* **10**, 68-73. doi:10.1006/brbi.1996.0006
Duque, E. de A. and Munhoz, C. D. (2016). The pro-inflammatory effects of glucocorticoids in the brain. *Front Endocrinol (Lausanne)* **7**, 78-78.
Elliot, S. L., Blanford, S. and Thomas, M. B. (2002). Host–pathogen interactions in a varying environment: temperature, behavioural fever and fitness. *Proc. R. Soc. B* **269**, 1599-1607. doi:10.1098/rspb.2002.2067
Esquifino, A. I., Pandi-Perumal, S. R. and Cardinali, D. P. (2004). Circadian organization of the immune response: A role for melatonin. *Clin. App. Immunol. Rev.* **4**, 423-433. doi:10.1016/j.cair.2004.08.002
Esteban, M. Á., Cuesta, A., Chaves-Pozo, E. and Meseguer, J. (2013). Influence of melatonin on the immune system of fish: a review. *Int. J. Mol. Sci.* **14**, 7979-7999. doi:10.3390/ijms14047979
Evans, S. S., Repasky, E. A. and Fisher, D. T. (2015). Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat. Rev. Immunol.* **15**, 335-349. doi:10.1038/nri3843
Evans, J. C., Silk, M. J., Boogert, N. J. and Hodgson, D. J. (2020). Infected or informed? Social structure and the simultaneous transmission of information and infectious disease. *Oikos* **129**, 1271-1288. doi:10.1111/oik.07148
Fernández-Loras, A., Boyero, L., Correa-Araneda, F., Tejedo, M., Hettyey, A. and Bosch, J. (2019). Infection with *Batrachochytrium dendrobatidis* lowers heat tolerance of tadpole hosts and cannot be cleared by brief exposure to CTmax. *PLoS ONE* **14**, e0216090. doi:10.1371/journal.pone.0216090
de Figueiredo, A. C., Titon, S. C. M., Titon, B., , Jr., Vasconcelos-Teixeira, R., Barsotti, A. M. G. and Gomes, F. R. (2021). Systemic hormonal and immune regulation induced by intraperitoneal LPS injection in bullfrogs (*Lithobates catesbeianus*). *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **253**, 110872. doi:10.1016/j.cbpa.2020.110872
French, S. S., McLemore, R., Vernon, B., Johnston, G. I. H. and Moore, M. C. (2007). Corticosterone modulation of reproductive and immune systems trade-offs in female tree lizards: long-term corticosterone manipulations via injectable gelling material. *J. Exp. Biol.* **210**, 2859-2865. doi:10.1242/jeb.005348
Friedman, E. M., Reyes, T. M. and Coe, C. L. (1996). Context-dependent behavioral effects of interleukin-1 in the rhesus monkey (*Macaca mulatta*). *Psychoneuroendocrinology* **21**, 455-468. doi:10.1016/0306-4530(96)00010-8
Gabor, C. R., Fisher, M. C. and Bosch, J. (2015). Elevated Corticosterone Levels and Changes in Amphibian Behavior Are Associated with Batrachochytrium dendrobatidis (Bd) Infection and Bd Lineage. *PLoS ONE* **10**, e0122685.
Gardner, S., Assis, V. R., Zhao, H., Gomes, F. R., Peatman, E. and Mendonça, M. T. (2018). Differential gene expression to an LPS challenge in relation to exogenous corticosterone in the invasive cane toad (*Rhinella marina*). *Dev. Comp. Immunol.* **88**, 114-123. doi:10.1016/j.dci.2018.07.016
Garrido, M. and Pérez-Mellado, V. (2014). Sprint speed is related to blood parasites, but not to ectoparasites, in an insular population of lacertid lizards. *Can. J. Zool.* **92**, 67-72. doi:10.1139/cjz-2013-0092
Ghai, R. R., Fugère, V., Chapman, C. A., Goldberg, T. L. and Davies, T. J. (2015). Sickness behaviour associated with non-lethal infections in wild primates. *Proc. R. Soc. B* **282**, 20151436. doi:10.1098/rspb.2015.1436
Goessling, J. M., Guyer, C. and Mendonça, M. T. (2017). More than Fever: Thermoregulatory Responses to Immunological Stimulation and Consequences of Thermoregulatory Strategy on Innate Immunity in Gopher Tortoises (*Gopherus polyphemus*). *Physiol. Biochem. Zool.* **90**, 484-493. doi:10.1086/692116
Goodman, B. A. and Johnson, P. T. J. (2011). Ecomorphology and disease: cryptic effects of parasitism on host habitat use, thermoregulation, and predator avoidance. *Ecology* **92**, 542-548. doi:10.1890/10-0516.1
Grabbe, N., Kaspers, B., Ott, D., Murgott, J., Gerstberger, R. and Roth, J. (2020). Neurons and astrocytes of the chicken hypothalamus directly respond to lipopolysaccharide and chicken interleukin-6. *J. Comp. Physiol. B* **190**, 75-85. doi:10.1007/s00360-019-01249-1
Gräns, A., Rosengren, M., Niklasson, L. and Axelsson, M. (2012). Behavioural fever boosts the inflammatory response in rainbow trout *Oncorhynchus mykiss*. *J. Fish Biol.* **81**, 1111-1117. doi:10.1111/j.1095-8649.2012.03333.x
Gray, M. J. and Chinchar, V. G. (**ed.**) (2015). *Ranaviruses*, pp. 297-312. Cham: Springer International Publishing.
Gray, D. A., Marais, M. and Maloney, S. K. (2013). A review of the physiology of fever in birds. *J. Comp. Physiol. B* **183**, 297-312. doi:10.1007/s00360-012-0718-z
Grogan, L. F., Robert, J., Berger, L., Skerratt, L. F., Scheele, B. C., Castley, J. G., Newell, D. A. and McCallum, H. I. (2018). Review of the amphibian immune response to chytridiomycosis, and future directions. *Front. Immunol.* **9**, 2536. doi:10.3389/fimmu.2018.02536
Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neurosci. Biobehav. Rev.* **12**, 123-137. doi:10.1016/S0149-7634(88)80004-6
Hasselquist, D. and Nilsson, J.-Å. (2012). Physiological mechanisms mediating costs of immune responses: what can we learn from studies of birds? *Anim. Behav.* **83**, 1303-1312. doi:10.1016/j.anbehav.2012.03.025
Haukenes, A. H. and Barton, B. A. (2004). Characterization of the cortisol response following an acute challenge with lipopolysaccharide in yellow perch and the influence of rearing density. *J. Fish Biol.* **64**, 851-862. doi:10.1111/j.1095-8649.2004.00354.x
Helluy, S. and Thomas, F. (2003). Effects of *Microphallus papillorobustus* (Platyhelminthes: Trematoda) on serotonergic immunoreactivity and neuronal architecture in the brain of *Gammarus insensibilis* (Crustacea: Amphipoda). *Proc. R. Soc. B* **270**, 563-568. doi:10.1098/rspb.2002.2264
Hennessy, M. B., Deak, T., Schiml-Webb, P. A., Wilson, S. E., Greenlee, T. M. and McCall, E. (2004). Responses of guinea pig pups during isolation in a novel environment may represent stress-induced sickness behaviors. *Physiol. Behav.* **81**, 5-13. doi:10.1016/j.physbeh.2003.11.008
Herbison, R., Lagrue, C. and Poulin, R. (2018). The missing link in parasite manipulation of host behaviour. *Parasit. Vectors* **11**, 222. doi:10.1186/s13071-018-2805-9
Hight, B. V. and Lowe, C. G. (2007). Elevated body temperatures of adult female leopard sharks, *Triakis semifasciata*, while aggregating in shallow nearshore embayments: Evidence for behavioral thermoregulation? *J. Exp. Mar. Biol. Ecol.* **352**, 114-128. doi:10.1016/j.jembe.2007.07.021
Huang, S., Yuan, S., Guo, L., Yu, Y., Li, J., Wu, T., Liu, T., Yang, M., Wu, K., Liu, H. et al. (2008). Genomic analysis of the immune gene repertoire of amphioxus reveals extraordinary innate complexity and diversity. *Genome Res.* **18**, 1112-1126. doi:10.1101/gr.069674.107
Hunt, V. L., Zhong, W., McClure, C. D., Mlynski, D. T., Duxbury, E. M. L., Charnley, A. K. and Priest, N. K. (2016). Cold-seeking behaviour mitigates reproductive losses from fungal infection in *Drosophila*. *J. Anim. Ecol.* **85**, 178-186. doi:10.1111/1365-2656.12438
Hutchison, V. H. and Erskine, D. J. (1981). Thermal selection and prostaglandin E1 fever in the salamander necturus maculosus. *Herpetologica* **37**, 195-198.

Iritani, R. and Iwasa, Y. (2014). Parasite infection drives the evolution of state-dependent dispersal of the host. *Theor. Popul. Biol.* **92**, 1-13. doi:10.1016/j.tpb.2013.10.005
Johnson, R., Curtis, S., Dantzer, R. and Kelley, K. (1993a). Central and peripheral prostaglandins are involved in sickness behavior in birds. *Physiol. Behav.* **53**, 127-131. doi:10.1016/0031-9384(93)90020-G
Johnson, R., Curtis, S., Dantzer, R., Bahr, J. and Kelley, K. (1993b). Sickness behavior in birds caused by peripheral or central injection of endotoxin. *Physiol. Behav.* **53**, 343-348. doi:10.1016/0031-9384(93)90215-2
de Jong-Brink, M., Bergamin-Sassen, M. and Soto, M. S. (2001). Multiple strategies of schistosomes to meet their requirements in the intermediate snail host. *Parasitology* **123**, 129-141. doi:10.1017/S0031182001008149
Karavlan, S. and Venesky, M. (2016). Thermoregulatory Behavior of *Anaxyrus americanus* in Response to Infection with *Batrachochytrium dendrobatidis*. *Copeia* **104**, 746-751. doi:10.1643/CH-15-299
Kavaliers, M., Colwell, D. D. and Choleris, E. (1999). Parasites and behavior: an ethopharmacological analysis and biomedical implications. *Neurosci. Biobehav. Rev.* **23**, 1037-1045. doi:10.1016/S0149-7634(99)00035-4
Keller, M., Mazuch, J., Abraham, U., Eom, G. D., Herzog, E. D., Volk, H.-D., Kramer, A. and Maier, B. (2009). A circadian clock in macrophages controls inflammatory immune responses. *PNAS* **106**, 21407-21412. doi:10.1073/pnas.0906361106
Kirsten, K., Soares, S. M., Koakoski, G., Carlos Kreutz, L. and Barcellos, L. J. G. (2018). Characterization of sickness behavior in zebrafish. *Brain Behav. Immun.* **73**, 596-602. doi:10.1016/j.bbi.2018.07.004
Klasing, K. C. (1991). Avian inflammatory response: mediation by macrophages. *Poultry Sci.* **70**, 1176-1186. doi:10.3382/ps.0701176
Klasing, K. C. (1998). Avian macrophages: regulators of local and systemic immune responses. *Poultry Sci.* **77**, 983-989. doi:10.1093/ps/77.7.983
Klasing, K. C., Laurin, D. E., Peng, R. K. and Fry, D. M. (1987). Immunologically mediated growth depression in chicks: influence of feed intake, corticosterone and interleukin-1. *J. Nutr.* **117**, 1629-1637. doi:10.1093/jn/117.9.1629
Klein, S. L. (2003). Parasite manipulation of the proximate mechanisms that mediate social behavior in vertebrates. *Physiol. Behav.* **79**, 441-449. doi:10.1016/S0031-9384(03)00163-X
Klein, S. L. and Flanagan, K. L. (2016). Sex differences in immune responses. *Nat. Rev. Immunol.* **16**, 626-638. doi:10.1038/nri.2016.90
Kluger, M. J., Ringler, D. H. and Anver, M. R. (1975). Fever and survival. *Science* **188**, 166-168. doi:10.1126/science.1114347
Kluger, M. J., Kozak, W., Conn, C. A., Leon, L. R. and Soszynski, D. (1996). The Adaptive Value of Fever. *Infect. Dis. Clin. North Am.* **10**, 1-20. doi:10.1016/S0891-5520(05)70282-8
Kohli, A. K., Lindauer, A. L., Brannelly, L. A., Ohmer, M. E. B., Richards-Zawacki, C., Rollins-Smith, L. and Voyles, J. (2019). Disease and the drying pond: examining possible links among drought, immune function, and disease development in amphibians. *Physiol. Biochem. Zool.* **92**, 339-348. doi:10.1086/703137
Kondo, K., Harbuz, M. S., Levy, A. and Lightman, S. L. (1997). Inhibition of the hypothalamic-pituitary-thyroid axis in response to lipopolysaccharide is independent of changes in circulating corticosteroids. *Neuroimmunomodul.* **4**, 188-194. doi:10.1159/000097337
Koutsos, E. A. and Klasing, K. C. (2001). The acute phase response in Japanese quail (*Coturnix coturnix japonica*). *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **128**, 255-263. doi:10.1016/S1532-0456(00)00199-X
Landis, S. H., Sundin, J., Rosenqvist, G. and Roth, O. (2012). Behavioral adjustments of a pipefish to bacterial Vibrio challenge. *Behav. Ecol. Sociobiol.* **66**, 1399-1405. doi:10.1007/s00265-012-1395-3
Lasselin, J., Lekander, M., Axelsson, J. and Karshikoff, B. (2018). Sex differences in how inflammation affects behavior: what we can learn from experimental inflammatory models in humans. *Front. Neuroendocrinol.* **50**, 91-106. doi:10.1016/j.yfrne.2018.06.005
Lee, K., Martin, L. and Wikelski, M. (2005). Responding to inflammatory challenges is less costly for a successful avian invader, the house sparrow (*Passer domesticus*), than its less-invasive congener. *Oecologia* **145**, 244-251.
Leshchinsky, T. V. and Klasing, K. C. (2001). Divergence of the inflammatory response in two types of chickens. *Dev. Comp. Immunol.* **25**, 629-638. doi:10.1016/S0145-305X(01)00023-4
Lips, K. R. (2016). Overview of chytrid emergence and impacts on amphibians. *Phil. Trans. R. Soc. B* **371**, 20150465. doi:10.1098/rstb.2015.0465
Llewellyn, D., Brown, G. P., Thompson, M. B. and Shine, R. (2011). Behavioral Responses to Immune-System Activation in an Anuran (the Cane Toad, *Bufo marinus*): Field and Laboratory Studies. *Physiol. Biochem. Zool.* **84**, 77-86. doi:10.1086/657609
Logan, R. W. and Sarkar, D. K. (2012). Circadian nature of immune function. *Mol. Cell. Endocrinol.* **349**, 82-90. doi:10.1016/j.mce.2011.06.039
Lopes, P. C. (2014). When is it socially acceptable to feel sick? *Proc. R. Soc. B* **281**, 20140218. doi:10.1098/rspb.2014.0218
Lopes, P. C. (2016). LPS and neuroinflammation: a matter of timing. *Inflammopharmacol.* **24**, 291-293. doi:10.1007/s10787-016-0283-2
Lopes, P. C. (2017). Why are behavioral and immune traits linked? *Horm. Behav.* **88**, 52-59. doi:10.1016/j.yhbeh.2016.09.008
Lopes, P. C. (2020). We are not alone in trying to be alone. *Front. Ecol. Evol.* **8**, 172. doi:10.3389/fevo.2020.00172
Lopes, P. C., Wingfield, J. C. and Bentley, G. E. (2012a). Lipopolysaccharide injection induces rapid decrease of hypothalamic GnRH mRNA and peptide, but does not affect GnIH in zebra finches. *Horm. Behav.* **62**, 173-179. doi:10.1016/j.yhbeh.2012.06.007
Lopes, P. C., Adelman, J., Wingfield, J. C. and Bentley, G. E. (2012b). Social context modulates sickness behavior. *Behav. Ecol. Sociobiol.* **66**, 1421-1428. doi:10.1007/s00265-012-1397-1
Lopes, P. C., Chan, H., Demathieu, S., González-Gómez, P. L., Wingfield, J. C. and Bentley, G. E. (2013). The Impact of Exposure to a Novel Female on Symptoms of Infection and on the Reproductive Axis. *Neuroimmunomodul.* **20**, 348-360. doi:10.1159/000353779
Lopes, P. C., Springthorpe, D. and Bentley, G. E. (2014). Increased activity correlates with reduced ability to mount immune defenses to endotoxin in zebra finches. *J. Exp. Zool. A Ecol. Genet. Physiol.* **321**, 422-431. doi:10.1002/jez.1873
Lopes, P. C., Block, P., Pontiggia, A., Lindholm, A. K. and König, B. (2018). No evidence for kin protection in the expression of sickness behaviors in house mice. *Sci. Rep.* **8**, 16682. doi:10.1038/s41598-018-35174-0
Lorch, J. M., Lankton, J., Werner, K., Falendysz, E. A., McCurley, K. and Blehert, D. S. (2015). Experimental infection of snakes with *Ophidiomyces ophiodiicola* causes pathological changes that typify snake fungal disease. *mBio* **6**, e01534. doi:10.1128/mBio.01534-15
Lorch, J. M., Knowles, S., Lankton, J. S., Michell, K., Edwards, J. L., Kapfer, J. M., Staffen, R. A., Wild, E. R., Schmidt, K. Z., Ballmann, A. E. et al. (2016). Snake fungal disease: an emerging threat to wild snakes. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **371**, 20150457. doi:10.1098/rstb.2015.0457
Luer, C. A., Walsh, C. J. and Bodine, A. B. (2004). The immune system of sharks, skates and rays. In *Biology of Sharks and Their Relatives* (ed. J. C. Carrier, J. A. Musick and M. R. Heithaus), pp. 369-395. New York: CRC Press.
Macari, M., Furlan, R. L., Gregorut, F. P., Secato, E. R. and Guerreiro, J. R. (1993). Effects of endotoxin, interleukin–1/3 and prostaglandin injections on fever response in broilers. *Br. Poult. Sci.* **34**, 1035-1042. doi:10.1080/00071669308417663
Marais, M., Maloney, S. K. and Gray, D. A. (2011). Ambient temperature modulates the magnitude of LPS-induced fevers in Pekin ducks. *J. Therm. Biol.* **36**, 121-127. doi:10.1016/j.jtherbio.2010.12.003
Marais, M., Maloney, S. K. and Gray, D. A. (2013). Sickness behaviours in ducks include anorexia but not lethargy. *Appl Anim Behav Scie* **145**, 102-108. doi:10.1016/j.applanim.2013.02.003
Markowska, M., Majewski, P. M. and Skwarło-Sońta, K. (2017). Avian biological clock – Immune system relationship. *Dev. Comp. Immunol.* **66**, 130-138. doi:10.1016/j.dci.2016.05.017
Martin, P. (1997). Wound healing - Aiming for perfect skin regeneration. *Science* **276**, 75-81. doi:10.1126/science.276.5309.75
Martin, L. B., Coon, C. A. C., Liebl, A. L. and Schrey, A. W. (2014). Surveillance for microbes and range expansion in house sparrows. *Proc. Biol. Sci. B* **281**, 20132690.
Martinez-Bakker, M. and Helm, B. (2015). The influence of biological rhythms on host–parasite interactions. *Trends Ecol. Evol.* **30**, 314-326. doi:10.1016/j.tree.2015.03.012
Matern, S. A., Cech, J. J. and Hopkins, T. E. (2000). Diel movements of bat rays, *Myliobatis californica*, in Tomales Bay, California: evidence for behavioral thermoregulation? *Environ. Biol. Fishes* **58**, 173-182. doi:10.1023/A:1007625212099
McBride, M. P., Wojick, K. B., Georoff, T. A., Kimbro, J., Garner, M. M., Wang, X., Childress, A. L. and Wellehan, J. F. X. (2015). *Ophidiomyces ophiodiicola* dermatitis in eight free-ranging Timber rattlesnakes (*Crotalus Horridus*) from Massachusetts. *J. Zoo Wildlife Med.* **46**, 86-94. doi:10.1638/2012-0248R2.1
McCauley, R. W., Reynolds, W. W. and Huggins, N. H. (1977). Photokinesis and behavioral thermoregulation in adult sea lampreys (*Petromyzon marinus*). *J. Exp. Zool.* **202**, 431-437. doi:10.1002/jez.1402020313
Merchant, M., Williams, S., Trosclair, P. L., Elsey, R. M. and Mills, K. (2007). Febrile response to infection in the American alligator (*Alligator mississippiensis*). *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **148**, 921-925. doi:10.1016/j.cbpa.2007.09.016
Merchant, M., Fleury, L., Rutherford, R. and Paulissen, M. (2008). Effects of bacterial lipopolysaccharide on thermoregulation in green anole lizards (*Anolis carolinensis*). *Vet. Immunol. Immunopathol.* **125**, 176-181. doi:10.1016/j.vetimm.2008.04.014
Merchant, M., Kinney, C. and Sanders, P. (2009). Differential protein expression in alligator leukocytes in response to bacterial lipopolysaccharide injection. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **4**, 300-304. doi:10.1016/j.cbd.2009.08.001
Mohammed, R. S., Reynolds, M., James, J., Williams, C., Mohammed, A., Ramsubhag, A., van Oosterhout, C. and Cable, J. (2016). Getting into hot water: sick guppies frequent warmer thermal conditions. *Oecologia* **181**, 911-917. doi:10.1007/s00442-016-3598-1

Mondal, S. and Rai, U. (2001). In vitro effect of temperature on phagocytic and cytotoxic activities of splenic phagocytes of the wall lizard, *Hemidactylus flaviviridis*. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **129**, 391-398. doi:10.1016/S1095-6433(00)00356-1

Mondal, S. and Rai, U. (2002). In Vitro Effect of Sex Steroids on Cytotoxic Activity of Splenic Macrophages in Wall Lizard (*Hemidactylus flaviviridis*). *Gen. Comp. Endocrinol.* **125**, 264-271. doi:10.1006/gcen.2001.7744

Morale, M. C., Gallo, F., Tirolo, C., L'Episcopo, F., Gennuso, F., Testa, N., Caniglia, S., Spina-Purrello, V., Avola, R., Scoto, G. M. et al. (2003). The reproductive system at the neuroendocrine-immune interface: focus on LHRH, estrogens and growth factors in LHRH neuron-glial interactions. *Domest. Anim. Endocrinol.* **25**, 21-46. doi:10.1016/S0739-7240(03)00043-2

Moutal, A., Martin, L. F., Boinon, L., Gomez, K., Ran, D., Zhou, Y., Stratton, H. J., Cai, S., Luo, S., Gonzalez, K. B. et al. (2020). SARS-CoV-2 Spike protein co-opts VEGF-A/Neuropilin-1 receptor signaling to induce analgesia. *Pain* **162**, 243-252.

Moyers, S. C., Kosarski, K. B., Adelman, J. S. and Hawley, D. M. (2015). Interactions between social behaviour and the acute phase immune response in house finches. *Behav.* **152**, 2039-2058. doi:10.1163/1568539X-00003312

Murray, M. J. and Murray, A. B. (1979). Anorexia of infection as a mechanism of host defense. *Am. J. Clin. Nutr.* **32**, 593-596. doi:10.1093/ajcn/32.3.593

Myhre, K., Cabanac, M. and Myhre, G. (1977). Fever and Behavioural Temperature Regulation in the Frog *Rana esculenta*. *Acta Physiol. Scand.* **101**, 219-229. doi:10.1111/j.1748-1716.1977.tb06001.x

Nowakowski, A. J., Whitfield, S. M., Eskew, E. A., Thompson, M. E., Rose, J. P., Caraballo, B. L., Kerby, J. L., Donnelly, M. A. and Todd, B. D. (2016). Infection risk decreases with increasing mismatch in host and pathogen environmental tolerances. *Ecol. Lett.* **19**, 1051-1061. doi:10.1111/ele.12641

O'Connor, M.-F., Bower, J. E., Cho, H. J., Creswell, J. D., Dimitrov, S., Hamby, M. E., Hoyt, M. A., Martin, J. L., Robles, T. F., Sloan, E. K. et al. (2009). To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav. Immun.* **23**, 887-897. doi:10.1016/j.bbi.2009.04.005

Oppliger, A., Célérier, M. L. and Clobert, J. (1996). Physiological and behaviour changes in common lizards parasitized by haemogregarines. *Parasitology* **113**, 433-438. doi:10.1017/S003118200008149X

Owen-Ashley, N. T. and Wingfield, J. C. (2006). Seasonal modulation of sickness behavior in free-living northwestern song sparrows (*Melospiza melodia morphna*). *J. Exp. Biol.* **209**, 3062-3070. doi:10.1242/jeb.02371

Owen-Ashley, N. T. and Wingfield, J. C. (2007). Acute phase responses of passerine birds: characterization and seasonal variation. *J. Ornithol.* **148**, S583-S591. doi:10.1007/s10336-007-0197-2

Owen-Ashley, N., Turner, M., Hahn, T. and Wingfield, J. (2006). Hormonal, behavioral, and thermoregulatory responses to bacterial lipopolysaccharide in captive and free-living white-crowned sparrows (*Zonotrichia leucophrys gambelii*). *Horm. Behav.* **49**, 15-29. doi:10.1016/j.yhbeh.2005.04.009

Parameswaran, N. and Patial, S. (2010). Tumor necrosis factor-α signaling in macrophages. *Crit. Rev. Eukaryot. Gene Expr.* **20**, 87-103. doi:10.1615/CritRevEukarGeneExpr.v20.i2.10

Prendergast, B. J., Baillie, S. R. and Dhabhar, F. S. (2008). Gonadal hormone-dependent and -independent regulation of immune function by photoperiod in Siberian hamsters. *Am. J. Physiol. Regul.* **294**, R384-R392.

Prendergast, B. J., Hotchkiss, A. K., Bilbo, S. D., Kinsey, S. G. and Nelson, R. J. (2016). Photoperiodic adjustments in immune function protect Siberian hamsters from lethal endotoxemia. *J. Biol. Rhythms* **18**, 51-62. doi:10.1177/0748730402239676

Proudfoot, K. L., Weary, D. M. and von Keyserlingk, M. A. G. (2012). Linking the social environment to illness in farm animals. *Appl. Anim. Behav. Sci.* **138**, 203-215. doi:10.1016/j.applanim.2012.02.008

Raffel, T. R., Rohr, J. R., Kiesecker, J. M. and Hudson, P. J. (2006). Negative effects of changing temperature on amphibian immunity under field conditions. *Funct. Ecol.* **20**, 819-828. doi:10.1111/j.1365-2435.2006.01159.x

Raffel, T. R., Halstead, N. T., McMahon, T. A., Davis, A. K. and Rohr, J. R. (2015). Temperature variability and moisture synergistically interact to exacerbate an epizootic disease. *Proc. R. Soc. B* **282**, 20142039. doi:10.1098/rspb.2014.2039

Rakus, K., Ronsmans, M., Forlenza, M., Boutier, M., Piazzon, M. C., Jazowiecka-Rakus, J., Gatherer, D., Athanasiadis, A., Farnir, F., Davison, A. J. et al. (2017a). Conserved fever pathways across vertebrates: a herpesvirus expressed decoy TNF-α receptor delays behavioral fever in fish. *Cell Host Microbe* **21**, 244-253. doi:10.1016/j.chom.2017.01.010

Rakus, K., Ronsmans, M. and Vanderplasschen, A. (2017b). Behavioral fever in ectothermic vertebrates. *Dev. Comp. Immunol.* **66**, 84-91. doi:10.1016/j.dci.2016.06.027

Rakus, K., Mojzesz, M., Widziolek, M., Pooranachandran, N., Teitge, F., Surachetpong, W., Chadzinska, M., Steinhagen, D. and Adamek, M. (2020). Antiviral response of adult zebrafish (*Danio rerio*) during tilapia lake virus (TiLV) infection. *Fish Shellfish Immunol.* **101**, 1-8. doi:10.1016/j.fsi.2020.03.040

Ramirez–Otarola, N., Espinoza, J., Kalergis, A. M. and Sabat, P. (2019). Response to lipopolysaccharide in *Octodon degus* pups produces age-related sickness behavior but does not have effects in juveniles. *Integr. Zool.* **14**, 235-247. doi:10.1111/1749-4877.12329

Rankin, L. C. and Artis, D. (2018). Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. *Cell* **173**, 554-567. doi:10.1016/j.cell.2018.03.013

Rao, S., Schieber, A. M. P., O'Connor, C. P., Leblanc, M., Michel, D. and Ayres, J. S. (2017). Pathogen-Mediated Inhibition of Anorexia Promotes Host Survival and Transmission. *Cell* **168**, 503-516.e12. doi:10.1016/j.cell.2017.01.006

Rayl, J. M., Wellehan, J. F. X., Bunick, D. and Allender, M. C. (2019). Development of reverse-transcriptase quantitative PCR assays for detection of the cytokines IL-1β, TNF-α, and IL-10 in chelonians. *Cytokine* **119**, 16-23. doi:10.1016/j.cyto.2019.02.011

Renshaw, S. A. and Trede, N. S. (2012). A model 450 million years in the making: zebrafish and vertebrate immunity. *Dis. Model Mech.* **5**, 38. doi:10.1242/dmm.007138

Rey, S., Moiche, V., Boltaña, S., Teles, M. and MacKenzie, S. (2017). Behavioural fever in zebrafish larvae. *Dev. Comp. Immunol.* **67**, 287-292. doi:10.1016/j.dci.2016.09.008

Reynolds, W. W., Casterlin, M. E. and Covert, J. B. (1976). Behavioural fever in teleost fishes. *Nature* **259**, 41-42. doi:10.1038/259041a0

Richards-Zawacki, C. L. (2010). Thermoregulatory behaviour affects prevalence of chytrid fungal infection in a wild population of Panamanian golden frogs. *Proc. R. Soc. B* **277**, 519-528. doi:10.1098/rspb.2009.1656

Rivier, C. (1993). Neuroendocrine effects of cytokines in the rat. *Rev. Neurosci.* **4**, 223-237. doi:10.1515/REVNEURO.1993.4.3.223

Rojas, J. M. and Ojeda, F. P. (2005). Altered dopamine levels induced by the parasite *Profilicollis antarcticus* on its intermediate host, the crab *Hemigrapsus crenulatus*. *Biol. Res.* **38**, 259-266. doi:10.4067/S0716-97602005000200015

Rollins-Smith, L. A. (2017). Amphibian immunity–stress, disease, and climate change. *Dev. Comp. Immunol.* **66**, 111-119. doi:10.1016/j.dci.2016.07.002

Rollins-Smith, L. A. and Woodhams, D. (2012). Amphibian immunity: staying in tune with the environment. In *Ecoimmunology* (ed. G. E. Demas and R. J. Nelson), pp. 92-143. Oxford University Press.

Rowley, J. J. L. and Alford, R. A. (2013). Hot bodies protect amphibians against chytrid infection in nature. *Sci. Rep.* **3**, 1515. doi:10.1038/srep01515

Ryan, M. P., Neuman-Lee, L. A., Durham, S. L., Smith, G. D. and French, S. S. (2018). A sex-dependent change in behavioral temperature regulation in African house snakes (*Lamprophis fuliginosus*) challenged with different pathogens. *J. Therm. Biol.* **73**, 8-13. doi:10.1016/j.jtherbio.2018.02.001

Sage, E. H. L., LaBumbard, B. C., Reinert, L. K., Miller, B. T., Richards-Zawacki, C. L., Woodhams, D. C. and Rollins-Smith, L. A. (2021). Preparatory immunity: Seasonality of mucosal skin defenses and Batrachochytrium infections in Southern leopard frogs. *J. Anim. Ecol.* **90**, 542-554. doi:10.1111/1365-2656.13386

Sandiego, C. M., Gallezot, J.-D., Pittman, B., Nabulsi, N., Lim, K., Lin, S.-F., Matuskey, D., Lee, J.-Y., O'Connor, K. C., Huang, Y. et al. (2015). Imaging robust microglial activation after lipopolysaccharide administration in humans with PET. *Proc. Natl. Acad. Sci. USA* **112**, 12468-12473. doi:10.1073/pnas.1511003112

Satinoff, E., McEwen, G. N. and Williams, B. A. (1976). Behavioral fever in newborn rabbits. *Science* **193**, 1139-1140. doi:10.1126/science.959829

Sauer, E. L., Trejo, N., Hoverman, J. T. and Rohr, J. R. (2019). Behavioural fever reduces ranaviral infection in toads. *Funct. Ecol.* **33**, 2172-2179. doi:10.1111/1365-2435.13427

Scalf, C. S., Chariker, J. H., Rouchka, E. C. and Ashley, N. T. (2019). Transcriptomic analysis of immune response to bacterial lipopolysaccharide in zebra finch (*Taeniopygia guttata*). *BMC Genomics* **20**, 647. doi:10.1186/s12864-019-6016-3

Schaller, M., Miller, G. E., Gervais, W. M., Yager, S. and Chen, E. (2010). Mere visual perception of other people's disease symptoms facilitates a more aggressive immune response. *Psychol. Sci.* **21**, 649-652. doi:10.1177/0956797610368064

Schedlowski, M., Engler, H. and Grigoleit, J.-S. (2014). Endotoxin-induced experimental systemic inflammation in humans: A model to disentangle immune-to-brain communication. *Brain Behav. Immun.* **35**, 1-8. doi:10.1016/j.bbi.2013.09.015

Schrott, L. and Sparber, S. (2004). Suppressed fever and hypersensitivity responses in chicks prenatally exposed to opiates. *Brain Behav. Immun.* **18**, 515-525. doi:10.1016/j.bbi.2003.12.006

Schrott, L., Sweeney, W., Bodensteiner, K. and Sparber, S. (1999). Late embryonic ritanserin exposure fails to alter normal responses to immune system stimulation in young chicks. *Pharmacol. Biochem. Behav.* **64**, 81-88. doi:10.1016/S0091-3057(99)00096-9

Schultz, E. M., Hahn, T. P. and Klasing, K. C. (2017). Photoperiod but not food restriction modulates innate immunity in an opportunistic breeder, *Loxia curvirostra*. *J. Exp. Biol.* **220**, 722-730. doi:10.1242/jeb.149898

Seigel, R. A., Smith, R. B. and Seigel, N. A. (2003). Swine Flu or 1918 Pandemic? upper respiratory tract disease and the sudden mortality of gopher tortoises (*Gopherus polyphemus*) on a protected habitat in Florida. *J. Herpetol.* **37**, 137-144. doi:10.1670/0022-1511(2003)037[0137:SFOPUR]2.0.CO;2

Sell, K., Crowe, S. and Kent, S. (2003). Lipopolysaccharide induces biochemical alterations in chicks trained on the passive avoidance learning task. *Physiol. Behav.* **78**, 679-688. doi:10.1016/S0031-9384(03)00051-9

Selvaraj, V., Sampath, K. and Sekar, V. (2006). Adjuvant and immunostimulatory effects of β-glucan administration in combination with lipopolysaccharide enhances survival and some immune parameters in carp challenged with *Aeromonas hydrophila*. *Vet. Immunol. Immunopathol.* **114**, 15-24. doi:10.1016/j.vetimm.2006.06.011

Shakhar, K. and Shakhar, G. (2015). Why do we feel sick when infected—can altruism play a role? *PLoS Biol.* **13**, e1002276. doi:10.1371/journal.pbio.1002276

Shattuck, E. C. and Muehlenbein, M. P. (2015). Human sickness behavior: ultimate and proximate explanations. *Am. J. Phys. Anthr.* **157**, 1-18. doi:10.1002/ajpa.22698

Shattuck, E. C., Perrotte, J. K., Daniels, C. L., Xu, X. and Sunil, T. S. (2020). The contribution of sociocultural factors in shaping self-reported sickness behavior. *Front. Behav. Neurosci.* **14**, 4. doi:10.3389/fnbeh.2020.00004

Sims, J. E. and Smith, D. E. (2010). The IL-1 family: regulators of immunity. *Nat. Rev. Immunol.* **10**, 89-102. doi:10.1038/nri2691

Smith, G. D., Neuman-Lee, L. A., Webb, A. C., Angilletta, M. J., DeNardo, D. F. and French, S. S. (2017). Metabolic responses to different immune challenges and varying resource availability in the side-blotched lizard (*Uta stansburiana*). *J. Comp. Physiol. B* **187**, 1173-1182. doi:10.1007/s00360-017-1095-4

Soto, L., Martín, A. I., Millán, S., Vara, E. and López-Calderón, A. (1998). Effects of endotoxin lipopolysaccharide administration on the somatotropic axis. *J. Endocrinol.* **159**, 239-246. doi:10.1677/joe.0.1590239

Stevenson, L. A., Roznik, E. A., Greenspan, S. E., Alford, R. A. and Pike, D. A. (2020). Host thermoregulatory constraints predict growth of an amphibian chytrid pathogen (*Batrachochytrium dendrobatidis*). *J. Therm. Biol.* **87**, 102472. doi:10.1016/j.jtherbio.2019.102472

Stockmaier, S., Bolnick, D. I., Page, R. A. and Carter, G. G. (2018). An immune challenge reduces social grooming in vampire bats. *Anim. Behav.* **140**, 141-149. doi:10.1016/j.anbehav.2018.04.021

Straub, R. H. (2014). Interaction of the endocrine system with inflammation: a function of energy and volume regulation. *Arthritis Res. Ther.* **16**, 203. doi:10.1186/ar4484

Sun, S.-C. and Ley, S. C. (2008). New insights into NF-κB regulation and function. *Trends Immunol.* **29**, 469-478. doi:10.1016/j.it.2008.07.003

Sun, K., Wang, W., Gao, L., Wang, Y., Luo, K., Ren, L., Zhan, Z., Chen, X., Zhao, S., Huang, Y. et al. (2021). Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. *Science* **371**, eabe2424. doi:10.1126/science.abe2424

Sylvia, K. E. and Demas, G. E. (2017). A return to wisdom: using sickness behaviors to integrate ecological and translational research. *Integr. Comp. Biol.* **57**, 1204-1213. doi:10.1093/icb/icx051

Tain, L., Perrot-Minnot, M.-J. and Cézilly, F. (2006). Altered host behaviour and brain serotonergic activity caused by acanthocephalans: evidence for specificity. *Proc. R. Soc. B* **273**, 3039-3045. doi:10.1098/rspb.2006.3618

Tanaka, T., Narazaki, M. and Kishimoto, T. (2014). IL-6 in Inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol.* **6**, a016295. doi:10.1101/cshperspect.a016295

Thomas, F., Adamo, S. and Moore, J. (2005). Parasitic manipulation: where are we and where should we go? *Behavi. Process.* **68**, 185-199. doi:10.1016/j.beproc.2004.06.010

Tiokhin, L. (2016). Do symptoms of illness serve signaling functions? (Hint: Yes).*Q. Rev. Biol.* **91**, 177-195. doi:10.1086/686811

Townsend, A. K., Hawley, D. M., Stephenson, J. F. and Williams, K. E. G. (2020). Emerging infectious disease and the challenges of social distancing in human and non-human animals. *Proc. R. Soc. B* **287**, 20201039. doi:10.1098/rspb.2020.1039

Truitt, A. M., Kapun, M., Kaur, R. and Miller, W. J. (2019). Wolbachia modifies thermal preference in *Drosophila melanogaster*. *Environ. Microbiol.* **21**, 3259-3268. doi:10.1111/1462-2920.14347

Turnbull, A. V. and Rivier, C. (1995). Regulation of the HPA axis by cytokines. *Brain Behav. Immun.* **9**, 253-275. doi:10.1006/brbi.1995.1026

Uribe, C., Folch, H., Enriquez, R. and Moran, G. (2011). Innate and adaptive immunity in teleost fish: a review. *Veterinarni Medicina* **56**, 486-503. doi:10.17221/3294-VETMED

Venesky, M. D., Parris, M. J. and Storfer, A. (2009). Impacts of *Batrachochytrium dendrobatidis* Infection on Tadpole Foraging Performance. *EcoHealth* **6**, 565-575. doi:10.1007/s10393-009-0272-7

Volkoff, H. and Peter, R. E. (2004). Effects of lipopolysaccharide treatment on feeding of goldfish: role of appetite-regulating peptides. *Brain Res.* **998**, 139-147. doi:10.1016/j.brainres.2003.11.011

Voyles, J., Young, S., Berger, L., Campbell, C., Voyles, W. F., Dinudom, A., Cook, D., Webb, R., Alford, R. A., Skerratt, L. F. et al. (2009). Pathogenesis of chytridiomycosis, a cause of catastrophic amphibian declines. *Science* **326**, 582-585. doi:10.1126/science.1176765

Walsh, D., McCarthy, J., O'Driscoll, C. and Melgar, S. (2013). Pattern recognition receptors—Molecular orchestrators of inflammation in inflammatory bowel disease. *Cytokine Growth Factor. Rev.* **24**, 91-104. doi:10.1016/j.cytogfr.2012.09.003

Walton, J. C., Weil, Z. M. and Nelson, R. J. (2011). Influence of photoperiod on hormones, behavior, and immune function. *Front. Neuroendocrinol.* **32**, 303-319. doi:10.1016/j.yfrne.2010.12.003

Wang, R., Millam, J. R. and Klasing, K. C. (2003). Distribution of interleukin-1 receptor in chicken and quail brain. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **136**, 663-671. doi:10.1016/S1095-6433(03)00219-8

Warne, R. W., Crespi, E. J. and Brunner, J. L. (2011). Escape from the pond: stress and developmental responses to ranavirus infection in wood frog tadpoles. *Funct. Ecol.* **25**, 139-146. doi:10.1111/j.1365-2435.2010.01793.x

Watzke, J., Schirmer, K. and Scholz, S. (2007). Bacterial lipopolysaccharides induce genes involved in the innate immune response in embryos of the zebrafish (*Danio rerio*). *Fish Shellfish Immunol.* **23**, 901-905. doi:10.1016/j.fsi.2007.03.004

Weil, Z. M., Bowers, S. L., Dow, E. R. and Nelson, R. J. (2006). Maternal aggression persists following lipopolysaccharide-induced activation of the immune system. *Physiol. Behav.* **87**, 694-699. doi:10.1016/j.physbeh.2006.01.005

Weil, Z. M., Borniger, J. C., Cisse, Y. M., Abi Salloum, B. A. and Nelson, R. J. (2015). Neuroendocrine control of photoperiodic changes in immune function. *Front. Neuroendocrinol.* **37**, 108-118. doi:10.1016/j.yfrne.2014.10.001

Willette, A. A., Lubach, G. R. and Coe, C. L. (2007). Environmental context differentially affects behavioral, leukocyte, cortisol, and interleukin-6 responses to low doses of endotoxin in the rhesus monkey. *Brain Behav. Immun.* **21**, 807-815. doi:10.1016/j.bbi.2007.01.007

Williams, G. C. (1966). Natural selection, the costs of reproduction, and a refinement of Lack's principle. *Am. Nat.* **100**, 687-690. doi:10.1086/282461

Woodhams, D. C., Barnhart, K. L., Bletz, M. C., Campos, A. J., Ganem, S. J., Hertz, A., LaBumbard, B. C., Nanjappa, P. and Tokash-Peters, A. G. (2018). Batrachochytrium: biology and management of amphibian chytridiomycosis. In *eLS* (ed. John Wiley & Sons Ltd), pp. 1-18. Chichester, UK: John Wiley & Sons, Ltd.

Yirmiya, R., Avitsur, R., Donchin, O. and Cohen, E. (1995). Interleukin-1 inhibits sexual behavior in female but not in male rats. *Brain Behav. Immun.* **9**, 220-233. doi:10.1006/brbi.1995.1021

Yuan, S., Huang, S., Zhang, W., Wu, T., Dong, M., Yu, Y., Liu, T., Wu, K., Liu, H., Yang, M. et al. (2009). An amphioxus TLR with dynamic embryonic expression pattern responses to pathogens and activates NF-κB pathway via MyD88. *Mol. Immunol.* **46**, 2348-2356. doi:10.1016/j.molimm.2009.03.022

Yuan, S., Zhang, J., Zhang, L., Huang, L., Peng, J., Huang, S., Chen, S. and Xu, A. (2013). The archaic roles of the amphioxus NF-κB/IκB complex in innate immune responses. *J. Immunol.* **191**, 1220-1230. doi:10.4049/jimmunol.1203527

Zamora-Camacho, F. J., Reguera, S., Rubiño-Hispán, M. V. and Moreno-Rueda, G. (2014). Eliciting an immune response reduces sprint speed in a lizard. *Behav. Ecol.* **26**, 115-120. doi:10.1093/beheco/aru170

Zapata, A. G., Varas, A. and Torroba, M. (1992). Seasonal variations in the immune system of lower vertebrates. *Immunol. Today* **13**, 142-147. doi:10.1016/0167-5699(92)90112-K

Zhang, G. and Ghosh, S. (2000). Molecular mechanisms of NF-κB activation induced by bacterial lipopolysaccharide through Toll-like receptors. *J. Endotoxin Res.* **6**, 453-457. doi:10.1179/096805100101532414

Zhou, X., Guo, Q. and Dai, H. (2009). Molecular characterization and expression profiles in response to bacterial infection of Chinese soft-shelled turtle interleukin-8 (IL-8), the first reptilian chemokine gene. *Dev. Comp. Immunol.* **33**, 838-847. doi:10.1016/j.dci.2009.02.002

Zimmerman, L. M., Vogel, L. A. and Bowden, R. M. (2010). Understanding the vertebrate immune system: insights from the reptilian perspective. *J. Exp. Biol.* **213**, 661-671. doi:10.1242/jeb.038315

Zou, J., Bird, S., Minter, R., Horton, J., Cunningham, C. and Secombes, C. J. (2000). Molecular cloning of the gene for interleukin-1β from *Xenopus laevis* and analysis of expression *in vivo* and *in vitro*. *Immunogenetics* **51**, 332-338. doi:10.1007/s002510050627