Human Sickness Behavior: Ultimate and Proximate Explanations

Eric C. Shattuck* and Michael P. Muehlenbein

Evolutionary Physiology and Ecology Laboratory, Department of Anthropology, Indiana University, Bloomington, IN

KEY WORDS sickness behavior; cytokines; evolutionary endocrinology; testosterone; cortisol; oxytocin; leptin; melatonin; psychoneuroimmunology; sex; gender; social norms

ABSTRACT Sickness behavior, a coordinated set of behavioral changes in response to infection, lies at the intersection of immunology, endocrinology, and evolutionary biology. Sickness behavior is elicited by pro-inflammatory cytokines, is thought to be an adaptive means of redirecting energy away from disadvantageous behaviors and toward mounting an effective immune response, and may be modulated by hormones, including testosterone and oxytocin. Research on sickness behavior in humans has lagged behind non-human animal research due to methodological complexities. Here we review what is known about sickness behavior in humans, the effects of various hormones on sickness behavior, the possible role of cytokine gene variation in influencing sickness behavior responses, and the ways in which culture and gender norms could similarly influence these behavioral changes. We also propose methodologies for advancing further studies of sickness behavior in humans. Am J Phys Anthropol 000:000–000, 2015. © 2015 Wiley Periodicals, Inc.

Over the past few decades, research has delineated a bi-directional influence of immune system activation on mood and behavior in humans and other animals (Maier and Watkins, 1998; Kiecolt-Glaser et al., 2002). For example, experimental stress, both physical and psychological, can result in an increase in immune system effector molecules (e.g., pro-inflammatory cytokines). These same molecules, whether produced by natural infection or experimental activation of the immune system, have been shown to induce a constellation of behavioral changes, collectively known as sickness behavior (Larson and Dunn, 2001). Sickness behavior is comprised of increased sleep, decreased appetite, reduced social behaviors, reduced mobility, decreased libido, cognitive disturbances, weight loss, hypersensitivity to pain, and depression (Miller et al., 2005), and likely represents a change in motivational states (Aubert, 1999). Hormones associated with immune function and social behavior and mood (e.g., testosterone, oxytocin, and cortisol; Muehlenbein and Bribiescas, 2005; Adelman et al., 2010) may play a role in modulating sickness behavior. This paper discusses sickness behavior in humans, the roles of pro-inflammatory cytokines and hormones in eliciting and/or modulating sickness behavior, and offers suggestions for future lines of research.

WHAT IS SICKNESS BEHAVIOR?

The concept of sickness behavior owes its existence to an evolutionary approach to infectious disease. Kluger and coworkers (1975) conducted several fundamental experiments demonstrating that fever has positive effects on host survivability. Rather than being a simple byproduct of infection, Kluger's group showed that fever could be an adaptive host response to fight infection. This point was expanded upon by Ewald (1980), who further suggested that host signs of infection could function to benefit the host or the pathogen, benefit both, or benefit neither. For instance, sneezing can benefit the pathogen by helping it spread to other hosts and can benefit the host by clearing mucus and pathogens. In this adaptationist perspective, a benefit to neither organism remains the null hypothesis (Ewald, 1980). Hart (1988) next collated both the physiological and behavioral symptoms of sick animals, and endeavored to show that this pattern of behavioral change could have adaptive benefits for the sick animal in terms of recovery and survivability. Thus, lethargy and reduced activity are thought to represent a shift in energetic priorities away from foraging or mating and toward fighting infection or avoiding predators that might single out the infirm animal (ibid). Later research further defined sickness behavior as an organized suite of behavioral changes exhibited by animals subsequent to infection; to the original list of lethargy, anorexia, and depression was added appetite disturbances, changes in cognition (including effects on memory and reaction time) decreased libido, anhedonia, sleeping disorders, hyperalgesia, and social

Abbreviations: APR, acute phase response; ARH, arcuate nucleus of the hypothalamus; BBB, blood-brain barrier; CRP, C reactive protein; CVO, circumventricular organs; HPA, hypothalamic-pituitary-adrenal; IL-1β, interleukin-1β; LPS, lipopolysaccharide; PVN, paraventricular nucleus; RRV, residual reproductive value; SNP, single nucleotide polymorphism; SON, supraoptic nucleus; TMJ, temporomandibular joint disorder; TNF-α, tumor necrosis factor-α; VEEV, Venezuelan Equine Encephalitis virus

*Correspondence to: Eric Shattuck, Evolutionary Physiology and Ecology Laboratory, Department of Anthropology, Indiana University, 701 E. Kirkwood Ave. Student Building 130, Bloomington, IN 47405. E-mail: eshattuc@indiana.edu

Received 16 September 2014; revised 27 December 2014; accepted 28 December 2014

DOI: 10.1002/ajpa.22698
Published online 00 Month 2015 in Wiley Online Library (wileyonlinelibrary.com).

TABLE 1. Documented sickness behavior in various species

Sickness behavior	Rodents	Birds	Humans	Other animals	Citations
Lethargy/Fatigue	X	X	X	X (*Macaca mulatta; Sus domesticus; Tragelaphus strepsiceros; Bos taurus)*	Johnson et al., 1993; Friedman et al., 1996; Späth-Schwalbe et al., 1998; Vollmer-Conna et al., 2004; Owen-Ashley, 2006; Owen-Ashley et al., 2006; Escobar et al., 2007; Hetem et al., 2007; Borderas et al., 2008; Ashley et al., 2009; Harrison et al., 2009; Skinner et al., 2009; Adelman et al., 2010; Burness et al., 2010; MacDonald et al., 2014
Anorexia	X	X			Owen-Ashley et al., 2006, 2008; Ashley et al., 2009; Adelman et al., 2010; Nascimento et al., 2013; MacDonald et al., 2014
Depression	X		X		Vollmer-Conna et al., 2004; Wright et al., 2005; Stone et al., 2006; Janicki-Deverts et al., 2007; O'Connor et al., 2008; Phillips et al., 2008; Brydon et al., 2009; Eisenberger et al., 2009, 2010; Grigoleit et al., 2011; Wegner et al., 2014
Cognitive Disturbances	X		X		Vollmer-Conna et al., 2004; Krabbe et al., 2005; Brydon et al., 2008; Bucks et al., 2008; Harrison et al., 2009; Grigoleit et al., 2011; Smith, 2012, 2013, reviewed in Cunningham and Sanderson, 2008
Appetite changes	X	X	X	X (*Carassius auratus auratus; Bos taurus; Sus domesticus)*	Johnson et al., 1993; Reichenberg et al., 2002; Volkoff and Peter, 2004; Escobar et al., 2007; Borderas et al., 2008; Owen-Ashley et al., 2008; Burness et al., 2010; Nascimento et al., 2013; MacDonald et al., 2014
Decreased libido/ Altered sexual behavior	X				Avitsur et al., 1997
Anhedonia	X		X		Kent et al., 1992; Hayley et al., 1999; Vollmer-Conna et al., 2004; Henry et al., 2008; Loftis et al., 2008; Moreau et al., 2008; Prendergast et al., 2009; Salazar et al., 2012
Sleeping disorders	X		X		Hermann et al., 1998; Späth-Schwalbe et al., 1998; Mathias et al., 2000; Haack et al., 2001; Majde et al., 2010; Clevenger et al., 2012; Alt et al., 2013
Hyperalgesia	X		X		Watkins et al., 1995; Vollmer-Conna et al., 2004; Wegner et al., 2014
Social withdrawal	X		X		Henry et al., 2008; Eisenberger et al., 2010

withdrawal and isolation (Miller et al., 2005). As shown in Table 1, various aspects of sickness behavior have been found in a number of diverse genera and species, from humans to goldfish (Volkoff and Peter, 2004).

It is generally thought that the behavioral changes in this expanded definition still function to benefit the sick host by reorganizing energetic priorities, though some changes (like cognitive and sleep disturbances) may be adaptively neutral and merely reflect the impact of immune activation. It is important to note that there are as yet no empirical studies demonstrating either increases in the convalescent period (time to recovery following infection) or decreases in survivorship in hosts somehow deprived of the ability to exhibit sickness behavior as a whole. While it is somewhat easier to experimentally manipulate individual aspects of sickness behavior and demonstrate changes in survivorship (e.g., anorexia and mortality, Murray and Murray, 1979), not every arm of sickness behavior has been so studied. Therefore, sickness behavior remains incompletely understood.

Another defining feature of sickness behavior is its plasticity in response to environmental and social conditions. For instance, mouse dams exhibit typical sickness behavior after treatment with lipopolysaccharide (LPS; a component of Gram-negative bacteria cell walls and a potent inflammatory agent), including diminished nest building and pup retrieval when compared to controls (Aubert et al., 1997). However, when the ambient temperature is decreased from 22°C to 6°C, thus threatening pup safety, LPS-treated dams increase their nest-building and pup retrieval to levels seen in control animals. Whereas moderate doses of LPS affect some maternal and social behaviors in mice, maternal aggression to intruder males is only affected at the highest doses of LPS tested (Weil et al., 2006). In male Gambel's white crowned sparrows (*Zonotrichia leucophrys gambelii*), administration of exogenous testosterone at levels generally seen during bouts of male-male competition leads to decreased levels of experimentally induced sickness behavior (Ashley et al., 2009). Male zebra finches (*Taeniopygia guttata*) exposed to LPS show different behavioral responses when housed individually or in social groups; activity is significantly reduced in animals housed alone, whereas no such change is found in treated animals housed in groups (Lopes et al., 2012). When presented with a novel female for 30 minutes, male zebra finches treated with LPS show no significant differences in behavior relative to control animals, whereas sickness behavior is expressed normally in LPS-treated males kept in isolation (Lopes et al., 2013). Similarly, male song sparrows (*Melospiza melodia morphna*) are relatively insensitive to the behavioral effects of LPS treatment (e.g., reduced activity) only during the breeding season (Owen-Ashley, 2006). Additionally, the lethargy associated with sickness behavior can be counteracted in rhesus macaques (*Macaca mulatta*) when exposed to the "threatening" presence of a human researcher (Willette et al., 2007). There is additional evidence that patterns of inflammation differ between industrialized and developing countries based on factors such as pathogen and parasite exposure and birth weight (McDade et al., 2007, 2012), which may have downstream effects on sickness behavior. Taken together, these results indicate trade-offs between competing life history stages/traits, namely reproduction and somatic maintenance, such that sickness behavior is suppressed when an individual's evolutionary fitness is threatened.

CYTOKINES IN SICKNESS BEHAVIOR

The predominant physiological mediators of sickness behavior are pro-inflammatory cytokines. These regulatory proteins are secreted by macrophages, Th2 T-cells, and other immune cells during immune activation, and serve to regulate inflammation and recruit additional immune cells to the site of injury or infection. Characteristic features of cytokines include transient production induced by stimuli, autocrine/paracrine/endocrine actions, redundancy, and multiple effects (Vilček, 2003). In contrast to hormones, which can be produced by limited types of cells and tissues, cytokines are produced by a variety of cells, and often several unrelated cell types can produce the same cytokine (Vilček, 2003).

Although they can have many effects, cytokines have generally been considered pro-inflammatory or anti-inflammatory based on their actions. Whereas the former group induces the physical components of inflammation (e.g., vasodilation, fever etc.), anti-inflammatory cytokines act to block the inflammatory cascade rather than acting on the relevant tissues themselves (Dinarello, 2000). A well-regulated balance between pro- and anti-inflammatory cytokines is crucial for maintaining a proper immune response. For instance, while pro-inflammatory cytokines are crucial for clearing infections, over-exuberant production or an insufficient production of anti-inflammatory cytokines can lead to a potentially fatal "cytokine storm," a systemic inflammatory response (Clark, 2007).

It is important to note that cytokine actions are context-dependent; under normal conditions, cells do not encounter a single cytokine, but rather a milieu of various cytokines and other biologically active agents with the potential to produce different synergies or antagonisms (Vilček, 2003). Thus, exposure to this blend of biological compounds may lead to qualitatively different cell responses (Vilček, 2003). This has bearing on the study of sickness behavior, as the majority of research has focused on one or two particular cytokines within a laboratory setting; a consideration of all active, circulating cytokines could serve to challenge conclusions about the effects of a single cytokine both when administered exogenously and when studied *in vivo*.

Several pro-inflammatory cytokines have been strongly and consistently linked with sickness behavior in humans and other animals. These cytokines are interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), which are synthesized and released early in infection, during the acute phase response (APR). The APR is a coordinated sequence that begins at the site of injury or infection, and results in the release of a variety of immunological mediators that serve to direct the organism's immune response (Baumann and Gauldie, 1994). Briefly, macrophages, activated by their recognition of a pathogen, release a variety of mediating factors, including IL-1β and TNF-α. These "early" cytokines drive the development of the APR, and act both distally and locally. TNF-α is an important inducer of IL-6 release (Fong et al., 1989; Sundgren-Andersson et al., 1998; Zetterström et al., 1998; Ghezzi et al., 2000). During the APR, endothelial cells are induced to express a variety of adhesion molecules, including intercellular adhesion molecules (ICAMs), which act to slow circulating leukocytes and allow transendothelial passage into tissues (Gearing and Newman, 1993). Fever is generated via an alteration of the temperature set point in the hypothalamus through the actions of IL-1β, IL-6, and TNF-α on prostaglandin E2 (Baumann and Gauldie, 1994). Other APR effects occur in the liver, where IL-6 and other pro-inflammatory cytokines induce release of acute phase proteins, including C reactive protein (CRP) and complement C3, that serve to increase resistance to infection and repair of damaged tissue (Heinrich et al., 1990).

Administration of IL-1β in healthy humans results in fever, joint and muscle pain, and headache, results that are characteristic of the effects of pro-inflammatory cytokines in general (Dinarello, 2000). Furthermore, patients receiving cytokine therapy often report symptoms akin to sickness behavior (Larson, 2002). The role of anti-inflammatory cytokines in down-regulating or "turning off" sickness behavior has been less studied, but we can assume a priori that these compounds play a role in normalizing this behavior, considering their effects on pro-inflammatory cytokines in general.

While the associations between the three aforementioned pro-inflammatory cytokines and sickness behavior appear convincing, precisely how these molecules are able to exert their effects upon the brain remains equivocal. The most obvious explanation is that secreted cytokines accumulate in the bloodstream and make their way to the brain after passing through the blood-brain barrier (BBB). Evidence supporting this notion includes the fact that there are discretely distributed receptors for IL-1β, IL-6, and TNF-α in the brain (Maier and Watkins, 1998). Blocking these receptors can diminish the sickness behavior response to peripherally administered pro-inflammatory cytokines or other immunostimulatory substances, and administration of pro-inflammatory cytokines directly to the brain elicits sickness behavior (Rothwell and Hopkins, 1995). However, the large size of these cytokines makes passive migration through the BBB unlikely without some mediating mechanism. There are currently several proposed mechanisms. First, cytokines could make entry at locations where the barrier is weak or non-existent: the circumventricular organs (CVO; Fig. 1), including the pineal glad and posterior pituitary, among others (Larson and Dunn, 2001; Dantzer et al., 2008).

However, the CVO are isolated from other brain regions by tanycytes, a specialized form of the BBB (Banks and Erickson, 2010). Cytokines may still interact

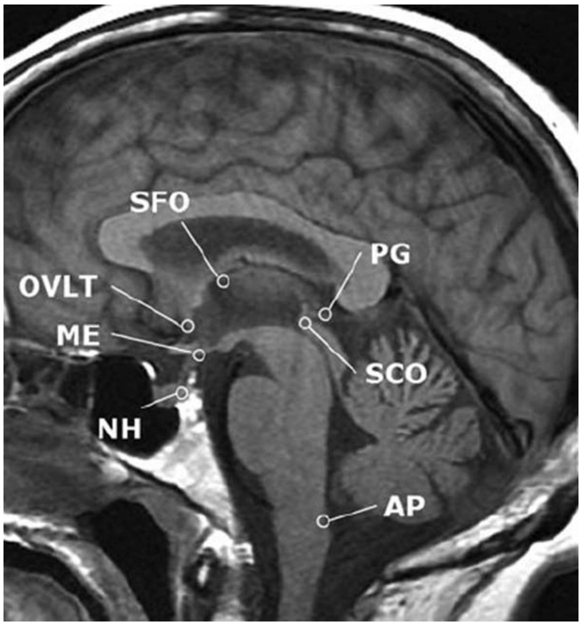

Fig. 1. Mid-sagittal MRI showing positions of the CVO. *NH*, neurohypophysis, *ME* median eminence, *OVLT* organum vasculosum of the lamina terminalis, *SFO* subfornical organ, *PG* pineal gland, *SCO* subcommissural organ, and *AP* area postrema. Image from Horsburgh and Massoud (2012). Reprinted with authors' permission.

with those neurons that connect the CVO to the rest of the brain, however. It is also possible that there are active transport mechanisms that allow cytokines to diffuse through the BBB. These include cytokine specific receptors and other receptors that induce secondary messenger molecules to act as intermediaries between cytokines in the bloodstream and receptors in the brain (Maier and Watkins, 1998; Dantzer et al., 2008; Banks and Erickson, 2010). Finally, LPS and TNF-α have been shown to disrupt the integrity of the BBB, though this may only occur during drastic, systemic immune activation and/or when the BBB's repair mechanisms have been exhausted (Banks and Erickson, 2010).

Because administration of pro-inflammatory cytokines in levels too small to be detected in blood is still able to elicit sickness behavior, an alternative to diffusion through the BBB must be considered (Maier and Watkins, 1998). It is known that sensory organs communicate with the brain via peripheral nerves, and the immune system may be thought of as a diffuse sensory organ (Maier and Watkins, 1998). In the case of the immune system, the vagus nerve (cranial nerve X) enervates immunologically relevant anatomical areas (e.g., spleen, gut, thymus, lymph nodes, etc.), and dense IL-1 binding sites are found on paraganglia that synapse onto the vagus nerve (Maier and Watkins, 1998; Dantzer et al., 2008). Furthermore, experimental removal of this nerve (vagotomy) prevents many aspects of sickness behavior following immunological challenge (Maier et al., 1998).

On the other hand, while vagal communication with the brain appears to be the main mechanism of peripheral cytokine communication based on experiments with vagotomy, it does not explain the presence of cytokine receptors within the brain itself. This shortcoming may be addressed by the fact that certain brain cell types are able to synthesize pro-inflammatory cytokines themselves (Maier and Watkins, 1998). TNF-α, IL-6, and IL-1β are produced by microglia and astrocytes following peripheral infection, stimulation with endotoxin, brain injury, and CNS infection with agents such as HIV, malaria, and cytomegalovirus (Hopkins and Rothwell, 1995). Additionally, these three cytokines are expressed in CNS neurons of healthy, non-inflamed humans, mice, and rats (Schöbitz et al., 1994a) and may be important for normal memory, learning, and brain development (reviewed in Bilbo and Schwarz, 2012). The location of cytokine production varies by stimulus, with peripheral infection inducing production largely in the hypothalamus, while brain injury leads to production around the site of insult (Hopkins and Rothwell, 1995). On the whole, however, the largest increases in cytokine production are in the hypothalamus, including the peri- and paraventricular nuclei, arcuate nucleus, median eminence, and supraoptic nucleus (SON) (Schöbitz et al., 1994b) and hippocampus, with lower amounts found in the brain stem and cortex. The hypothalamus and hippocampus display the greatest amount of cytokine receptors in the brain (Hopkins and Rothwell, 1995). It should be noted that most of this information is derived from animals, particularly rodents (Hopkins and Rothwell, 1995). This overview of cytokine production in the brain and their possible effects on behavior is certainly not definitive. Contrary to predictions, ablation and lesioning of the arcuate nucleus of the hypothalamus (ARH; which contains type 1 IL-1 receptors) does not prevent cytokine-mediated anorexia in rats (Reyes and Sawchenko, 2002). Rather, experimental animals show a higher reduction in food intake than controls, suggesting that the ARH normally acts to counter this anorexia (Reyes and Sawchenko, 2002). Thus, it may be that the effects of CNS cytokines on sickness behavior vary based on the region of brain in question.

On the whole, however, the weight of evidence suggests that peripherally produced pro-inflammatory cytokines communicate with the brain via the vagus nerve, the end result of which is the production of the same cytokines within the brain, and it is these, rather than peripheral cytokines, that induce sickness behavior (Maier and Watkins, 1998; Dantzer et al., 2008).

HORMONES IN SICKNESS BEHAVIOR

The effects of changes in hormone levels on the immune system function were demonstrated long ago, when Hans Selye (1936) showed that physical and psychological stressors activated the hypothalamic-pituitary-adrenal (HPA) axis, leading to shrinkage of the thymus and other lymphoid organs. The impacts of hormones on the immune system are many and varied, and most hormones now appear to have some immunological effect, whether direct or indirect (see Butts and Sternberg, 2008 and Blalock, 1989 for reviews). These relationships are also bidirectional, such that immune activation and immune system molecules (including cytokines) have effects upon the endocrine system. However, the role of hormones in sickness behavior is less well known. We have chosen to review several hormones that may be relevant, having both immunological and behavioral effects.

Testosterone

Sex steroids are known to have modulatory effects on the immune system (Grossman, 1984). Testosterone is present in both men and women, is produced primarily in the testes in men and the ovaries and placenta in women, and is secreted from the adrenal cortex in both sexes. Testosterone is important in regulating energy allocation, particularly with regard to muscle anabolism (Muehlenbein and Bribiescas, 2005). Changes in testosterone levels are associated with immune responses, which likely reflect the hormone's contribution to balancing energetic investment between competing somatic systems, particularly skeletal muscle, secondary sexual characteristics, and the immune system. Lower levels of testosterone are found following myocardial infarction, respiratory illness, burns, and sepsis in men (Spratt et al., 1993). Serum testosterone typically falls at the onset of illness, and increase during recovery. In addition, those patients with greater disease severity typically have lower testosterone than patients with milder disease (Spratt et al., 1993). Testosterone levels show a similar pattern in Honduran men infected with *Plasmodium vivax* malaria, with levels lowest during peak infection and increased during convalescence (Muehlenbein et al., 2005). Higher levels of testosterone are also associated with higher parasitemia, suggesting that high levels of the hormone may predispose individuals toward a compromised immune response (ibid). Studies utilizing macaques (*Macaca fasicularis*) infected with Venezuelan Equine Encephalitis virus (VEEV) show similar results: higher baseline testosterone levels are positively associated with VEEV viremia after exposure, and testosterone levels also decrease during infection (Muehlenbein et al., 2006). Human immunodeficiency virus, African trypanosomiasis (*Trypanosoma brucei*), toxoplasmosis (*Toxoplasma gondii*), schistosomiasis (*Schistosoma mansoni*), and filariasis (*Loa loa* and *Mansonella perstans*) have all been shown to reduce testosterone levels in human males, while infection with *Wucheria bancrofti* or *Onchocerca volvulus* can cause testicular pathology, a common finding in AIDS patients as well (Muehlenbein, 2008).

Testosterone is commonly associated with aggression and sexual behavior/libido. However, it is better described as associated with a general repertoire of social behaviors, including the achievement and maintenance of social status (reviewed in Booth et al., 2006). Some behaviors associated with changes in testosterone include competition, recognition of emotion in others, and expressions of dominance (Booth et al., 2006; Eisenegger et al., 2011). Interestingly, testosterone is also linked with mood, showing a parabolic association with depression: in a sample of over 4,000 military veterans, men with either above- or below-average testosterone levels reported more symptoms of depression (Booth et al., 1999). A recent meta-analysis found that exogenous testosterone administration alleviates depression in hypogonadal males, although this relationship was not found in males over 60 years of age (Amanatkar et al., 2014). It should be noted that relationships between testosterone and depression may not be solely due to any physiological effects of the hormone. Testosterone levels can also be associated with behaviors (e.g., increased risk-taking and antisocial behaviors) that contribute to depression themselves (Booth et al., 1999).

Testosterone is also associated with signs of classic sickness behavior. For example, testosterone levels higher than those required for breeding behavior and physiology suppress sickness behavior in male Gambrel's white-crowned sparrows (*Zonotrichia leucophrys gambelii*) (Ashley et al., 2009). Gonadectomized males treated with testosterone implants also show a smaller reduction in food intake and activity than intact males following LPS inoculation. Castrated male rats are more sensitive to the behavioral effects (a reduction in social investigations of a juvenile conspecific) of both acute injections and chronic infusions of peripheral IL-1β than are intact males (Dantzer et al., 1991). These data suggest that testosterone can attenuate sickness behavior. Furthermore, the overlap between behaviors known to be influenced by testosterone and some of the behaviors known to change during sickness suggests that decreases in circulating levels of testosterone may contribute to sickness behavior expression.

Cortisol

Cortisol is produced in the adrenal cortex in response to physical and psychosocial stressors. For instance, increased urinary cortisol was found in a group of Australian Aborigines on days when many were involved in high-stakes gambling (Schmitt et al., 1998) and in Dominican men playing competitive dominoes (Wagner et al., 2002). Long held to be immunosuppressive (Adelman and Martin, 2009), cortisol's actions on immunity may be more "redistributive" whereby activity of the HPA axis and increased release of cortisol in response to stimuli and stressors drive the migration of leukocytes into various immune tissues (e.g., lymph nodes, skin, mucosa etc.) or sites of infection where they will be more likely to encounter a challenge (Dhabhar et al., 1994). Glucocorticoids have also been shown to switch immune responses from a pro-inflammatory, cell-mediated paradigm (the Th1 response) to an antibody-driven response (Th2) characterized by the production of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 (Elenkov, 2004). These are generally antagonistic toward pro-inflammatory cytokines, and can function to down-regulate their synthesis and release; indeed, glucocorticoids suppress the production of IL-12, a potent pro-inflammatory cytokine and a prime inducer of the Th1 response, which in turn disinhibits the production of IL-4 (Elenkov, 2004).

As with testosterone, cortisol shows a parabolic association with mood. Excessive cortisol production has been reported in a large proportion of depressed patients (Carpenter and Gruen, 1982). Depression is also associated with both Addison and Cushing diseases, which are characterized by below and above normal cortisol production (Musselman and Nemeroff, 1996), though euphoria sometimes approaching mania has been occasionally reported with hypercortisolism (Carpenter and Gruen, 1982). In addition, emotional disturbances are often associated with altered cortisol secretion patterns. Glucocorticoids may also affect neurotransmission and sensory stimuli processing, and hypothalamic implants of cortisol elevate serotonin (Carpenter and Gruen, 1982), suggesting an intermediate mechanism through which glucocorticoids could affect behavior.

Glucocorticoids could function to down-regulate sickness behavior through immune modulation. For example, adrenalectomized animals, or those treated with receptor antagonists, display increased levels of sickness behavior and increased sensitivity to experimental immune challenges (Adelman and Martin, 2009). Adrenalectomized rats also develop adipsia, and corticosterone treatment inhibits development of both fever and anorexia (Pezeshki et al., 1996). Similar results are found with in adrenalectomized mice infected with murine cytomegalovirus (Silverman et al., 2006).

Oxytocin and vasopressin

Oxytocin stimulates smooth muscle contractions during labor and lactation, lowers blood pressure and slows heart rate, and suppresses cortisol, among other things (Sanchez et al., 2009). Vasopressin is a strong vasoconstrictor that has additional effects on water reabsorption (ibid). Both hormones have roles in reproductive and social behaviors. For example, oxytocin typically decreases anxiety whereas vasopressin promotes anxiety (Sanchez et al., 2009). Oxytocin is also associated with pair bonding, parental behavior, and affiliative behavior, while vasopressin is associated with aggression, courtship, male pair-bonding, and social recognition (Lim and Young, 2006; Sanchez et al., 2009; Campbell, 2010). Both hormones are synthesized in the SON and paraventricular nucleus (PVN) of the hypothalamus, and are secreted by the posterior pituitary (Sanchez et al., 2009). This latter area is one of the CVO where cytokine entry into the brain is most likely.

Oxytocin and vasopressin may both contribute to sickness behavior by modulating cytokine activity and production (Landgraf et al., 1995; Clodi et al., 2008). IL-1β stimulates the release of vasopressin and oxytocin both *in vitro* and *in vivo* (Kasting, 1986; Naito et al., 1991; Landgraf et al., 1995). In rats, intracerebroventricular injection of IL-1β increases circulating vasopressin levels by nearly 300%, while oxytocin raises approximately 150% (Landgraf et al., 1995). Direct injection of even smaller doses of IL-1β into the SON do not increase peripheral release of vasopressin or oxytocin, perhaps indicating the primacy of the central nervous system's effects of these hormones in relation to pro-inflammatory cytokines (Landgraf et al., 1995). Elevated oxytocin and vasopressin during illness may function to limit fever via suppression of these cytokines within the brain. Indeed, evidence points to vasopressin being a significant limiter of pyrogens, or substances (including pro-inflammatory cytokines) that elicit fever (Dantzer et al., 1991). In a sample of ten healthy males, oxytocin treatment during administration of bacterial endotoxin leads to reductions in levels of TNF-α and IL-6 (Clodi et al., 2008).

Leptin and ghrelin

Interactions between leptin and ghrelin, two hormones involved in satiety and hunger, may further play important roles in the appetite changes, anorexia, and lethargy of sickness behavior (Adelman and Martin, 2009; Carlton et al., 2012). Leptin is primarily produced in white adipose tissue, and high levels of the hormone indicate a positive energy balance, or adequate energy reserves, whereas a deficit is associated with inadequate energy, and may serve to partition available energetic resources towards different physiological systems and processes (Friedman and Halaas, 1998). Leptin has certain immunological effects as well, namely increasing delayed-type hypersensitivity and enhancing proliferation of T cells in response to mitogen stimulation (Adelman and Martin, 2009). Leptin receptors have recently been found on various leukocytes, including monocytes, natural killer cells, and T and B lymphocytes (Martín-Romero et al., 2000; Zhao et al., 2003; Papathanassoglou et al., 2006). Injections of IL-1β and TNF-α increase circulating leptin levels during the APR in rodents (Adelman and Martin, 2009; Harden et al., 2006). Circulating leptin can then act on the hypothalamus to increase the release of these cytokines via positive feedback. Interestingly, peripheral leptin induces IL-1β receptor antagonist expression on monocytes, which serves to downregulate further production of pro-inflammatory cytokines (Adelman and Martin, 2009). Harden et al. (2006) and Sachot et al. (2004) found that leptin was associated with changes in food intake and fever during LPS immunostimulation in male rats. Administration of anti-leptin serum reversed declines in food intake and abolished fever.

Ghrelin is a potent inducer of food intake, is primarily released into circulation from the stomach, and acts upon the hypothalamus to induce hunger (Baatar et al., 2011). Exogenous ghrelin has been found to suppress IL-6, TNF-α, and IL-1β production and/or expression in rodent studies, though administration of TNF-α and endotoxin has been found to both increase and suppress ghrelin in humans and rodents (Baatar et al., 2011). Furthermore, ghrelin appears to exert its effects on cytokine expression via the vagus nerve, the hypothesized route by which peripheral cytokines exert their influence on the brain. Ghrelin reduces levels of TNF-α and IL-6 during sepsis in sham-operated control rats, but not in vagotomized animals (Baatar et al., 2011).

Melatonin

Melatonin is related to circadian and seasonal rhythms, and is secreted from the pineal gland, another of the CVO (Larson and Dunn, 2001). In addition to up-regulating IL-1β, TNF-α, and IL-6 signaling, melatonin appears to modulate severity of sickness behavior with regard to day length. Hamsters kept under long day conditions and subjected to immunological challenge show more severe sickness behavior (e.g., larger decreases in nest building, foraging etc.) than do hamsters kept under short days (Adelman and Martin, 2009). As day length varies with season, this might suggest that animals are able to devote more time and energy to healing and fighting infection during the warmer months, when resources are likely to be abundant. During the colder months, characterized by shorter days, the immediate needs of food and shelter take precedence over sickness behavior.

In sum, sickness behavior is a highly complex and phylogenetically widespread phenomenon, and is better understood in animal models than in humans. While pro-inflammatory cytokines are certainly the strongest drivers of this behavioral suite, changes in hormones such as the ones discussed above may function to either elicit the characteristic behavioral changes (e.g., hypothesized links between leptin, ghrelin, and reduced food intake) or attenuate sickness behavior (e.g., testosterone).

EXPLAINING VARIATION IN SICKNESS BEHAVIOR

Life history theory

Relatively little research has been conducted on variation in sickness behavior (e.g., strength, duration etc.), though we know from previous work, discussed above, that sickness behavior can be modulated by social stimuli and environmental context, such as male-male competition (Ashley et al., 2009) and temperature threats to offspring survival (Aubert et al., 1997). What is currently known about variable sickness behavior responses, therefore, suggests a life history approach in which sickness behavior is seen as a component of overall somatic maintenance. Life history theory predicts that organisms will allocate limited resources (e.g., time, energy) between biological processes related to reproduction, growth, and maintenance in such a way as to maximize reproductive fitness. In general, therefore, we should expect that sick individuals would modulate their sickness behavior response depending on the value of the activities that would otherwise be sacrificed, with this value varying based on ecological condition (Ashley and Wingfield, 2012).

In addition to these two examples of trade-offs between reproduction and sickness behavior, we can list others discussed above (Owen-Ashley, 2006; Weil et al., 2006; Lopes et al., 2013). Notably, these trade-offs between reproductive effort and sickness behavior are currently only found in species with relatively fast life histories (i.e., rodents and small birds). Because of this quick tempo, time and energy devoted to recovery from injury and infection may be more costly in terms of lifetime reproductive output when compared with larger, longer-lived organisms. Sickness behavior that is more sensitive to reproductive effort could be beneficial for these former species, and the same trade-offs may not be found in species with slower life histories.

However, based on findings of reduced sexual behavior in female, but not male, rats following pro-inflammatory cytokine treatment (Avitsur et al., 1997), Avitsur and Yirmiya (1999) suggest that male responses function to maximize reproductive potential while female responses act to maximize maternal recovery and survival while simultaneously minimizing the possibility of vertical transmission of pathogens to the fetus. At the individual level, we can also expect sickness behavior to be variably expressed depending on residual reproductive value (RRV; Ashley and Wingfield, 2012). Because of the costs of sickness behavior in terms of time lost to recovery, individuals with a lower RRV (i.e., fewer future opportunities to reproduce) would be expected to devote more time and energy to reproduction at the expense of sickness behavior, while the opposite would be true for individuals with high RRV (ibid.). We have already noted a similar phenomenon among seasonal breeding male song sparrows, which do not reduce their territorial defensive behaviors during their breeding season when treated with LPS, although these same behaviors decline following treatment during the non-breeding season (Owen-Ashley, 2006).

Little, if anything, is known about trade-offs between sickness behavior and growth or development. Immune activation, generally speaking, results in reduced height in Tsimané children, particularly younger children and those with lower energy stores (McDade et al., 2008). Higher levels of immunoglobulin E (IgE), a marker of helminth infection, were associated with lower stature in Shuar children and adults (Blackwell et al., 2010), and similar results have been found in the Gambia (Campbell et al., 2003) and Peru (Checkley et al., 1998). It should be noted, however, that these populations are generally energy restricted in comparison to populations in developed countries. Similar studies in these latter countries may not find these trade-offs, as children would have sufficient resources to fuel both immune responses and growth. In populations that exhibit these trade-offs, and if sickness behavior does contribute to reduced convalescent times, then it may be possible that still-growing individuals who regularly sublimate the effects of sickness behavior (e.g., fatigue) and continue their normal activities show reduced growth and development compared to individuals who are more responsive to sickness behavior as their time to clearance of infections is longer, leaving less energy available for growth.

Age and pathogen exposure

As with all biological processes, immune function varies throughout the lifespan, reflecting the competing demands of somatic maintenance and growth (McDade, 2003). Following peaks in function during infancy, many aspects of immune function plateau and even decline at or around puberty (reviewed in McDade, 2003 and Graham et al., 2006). Early investment in immunity theoretically ensures survival to reproductive years, at which point gonadal hormone production is markedly upregulated, corresponding to a prioritization of reproduction at the expense of some degree of growth and maintenance (McDade, 2003). Immune function continues to decline with age in a phenomenon known as immunosenescence (Gomez et al., 2005; Graham et al., 2006). However, this immune dysregulation in the elderly appears to be combined with hyperactive inflammatory processes, including elevated circulating levels of pro-inflammatory cytokines (Gomez et al., 2005). Whether this inflammatory state is due to the ageing process, pre-existing conditions, or some combination of both remains to be seen (ibid.).

We should therefore expect to see heightened sickness behavior responses in both the young and the elderly. In the first instance, more severe behavioral changes are likely reflective of the prioritization of survival, while this phenomenon may only be a byproduct of a stronger inflammatory state in the aged. It may be possible, however, that stronger sickness behavior responses help to offset an imperfectly functioning immune system. Experimental data from animal models generally show more severe sickness behavior in older animals (Godbout, 2005; Kohman et al., 2009; Palacios et al., 2011; McLinden et al., 2012). These findings await replication in humans, and sickness behavior in children and adolescents should be explicitly researched.

Finally, social and environmental conditions during infancy and childhood could shape sickness behavior during adulthood. Exposure to pathogens, nutrition, and psychosocial stress have all been shown to affect immune function in later life (reviewed in McDade, 2012). For instance, longitudinal data from the Philippines indicate that some proxy measures of childhood pathogen exposure are negatively associated with adult inflammation status (McDade et al., 2010). Conversely, childhood stress has been associated with higher CRP levels in adults (Danese et al., 2007; McDade et al., 2013). There is evidence from animal models that juvenile stress affects both the severity and timing of sickness behavior in adult animals (Avitsur and Sheridan, 2009). These results may have bearing on population- and individual-level differences in sickness behavior.

Sex, gender, and cultural factors

Sex (genetic/gonadal typology) and gender identity (personal, subjective experience as masculine, feminine, or other) may also play important roles in the expression of sickness behavior within and between human populations. Unfortunately, we are aware of only a single study specifically addressing mechanisms underlying sex differences in sickness behavior in humans. In a small sample ($N = 20$) of participants receiving LPS, increases in IL-6 levels were significantly associated with increases in depressed mood in females but not males (Eisenberger et al., 2009). Interestingly, IL-6 increases in females were also associated with increased activity in brain areas (assessed via fMRI) associated with social pain (dorsal anterior cingulate cortex and right anterior insula under conditions of social exclusion) (ibid).

There is also evidence for female bias in symptom severity across a variety of cultural contexts (Torsheim et al., 2006). Typically, women report more illnesses and/or symptoms, take more sick days, and have more frequent hospital trips than men, even after accounting for reproductive health concerns (Hinkle et al., 1960; Gove and Hughes, 1979; Verbrugge, 1985; Arber and Lahelma, 1993; Macran et al., 1996). Men are significantly less likely than women to have contact with a physician, regardless of income and ethnicity (Courtenay, 2000). Women report more chronic conditions, including kidney/liver trouble, urinary infections, and allergies, and days confined to bed due to disability than men (Cleary et al., 1982). Women with chronic pain conditions report more severe pain, more frequent pain bouts, and longer-lasting pain than men (Goodin et al., 2013). Migraine, irritable bowel syndrome, temporomandibular joint disorder (TMJ), and pain associated with rheumatic diseases are all more frequent in women than men (Goodin et al., 2013), and Ruau et al. (2012) find that women report increased pain intensities for acute inflammatory conditions, including sinusitis and arthropathies. Women report more angina-related chest pain than men, as well as more symptoms, including dyspnea, irritability, nausea, and dizziness (Granot et al., 2004). Women also show lower pain thresholds and tolerances to experimentally induced pain than do men (Goodin et al., 2013). Another consistent finding is greater female absence from work due to sickness, though there are a variety of factors, including gender composition of the workforce, that appear to affect these absences (Laaksonen et al., 2012). In general, these results suggest that women typically experience their illnesses differently than men.

A mechanistic explanation of this bias in symptomology may be variation in endocrine and immune functions. Clearly, estrogens and progestins influence immune functions (Weinberg, 1984), with estrogens stimulating both cellular (Th1) and humoral (Th2) immune responses (Butts and Sternberg, 2008; Loram et al., 2012). Women have higher serum levels of IgM and IgG, and estrogen has been shown to increase the production of both antibodies from white blood cells *in vitro* (Bouman, 2005).

Another very plausible mechanism for differences in symptomology, health-seeking behaviors, and conceptions of sickness is variation in gender roles (culturally expected norms of behavior). These social norms often associate seeking help or "complaining" with women, or femininity more generally, while males and "masculine" individuals are assumed to maintain a stereotypical stoicism, and interestingly, men and women who self identify as less masculine/more feminine experience more symptoms of illness monthly (Annandale and Hunt, 1990).

Men who report being more masculine may be less likely to seek out preventative health care (Springer and Mouzon, 2011). However, this also likely depends upon different cultural conceptions of sickness and responsibility. Among African-American men there has been reported a relative lack of negative health effects of typical adherence to masculine beliefs (Springer and Mouzon, 2011). For example, self-reliant attitudes were associated with personal wellness (as well as health awareness, motivation to maintain good health, and the belief that one can influence one's health for good or ill) in a sample of African-American men, age 18–71 years (Wade, 2009). This may be a function of how self-reliance is perceived in different ethnic groups, with this group of participants possibly associating self-reliance with responsibility, discipline, and confidence. An individual may associate each of these with maintaining good health, contrary to previous results in which self-reliance was associated with risky health behaviors in Australian men (Mahalik et al., 2007).

There is also a considerable literature covering the cultural context of illness, which often overlaps with gendered experiences of illness, as described above. For instance, *machismo* refers to Latin American conceptions of masculinity, both negative and positive (Arciniega et al., 2008). Positive aspects can include dignity, wisdom, defense of family and its honor, and hard work, while negative aspects include violence, aggression, and highly sexualized behavior (Arciniega et al., 2008), as well as fetishism of women's bodies and a hypersensitivity towards an idealized view of women as virgins or mothers (the concept of *Guadalupismo*) (Sternberg, 2000). Machismo has been identified as a barrier to both health seeking in general in a sample of Mexican American men (Hunter et al., 2007), as well as to HIV prevention in Chile (Cianelli et al., 2008).

Researchers have also reported significant differences in measures of self-perceived health between populations. For instance, Hispanic American children reported more health concerns than did their European American counterparts in a non-clinical sample (Silverman et al., 1995). This finding is in accord with other results showing that Mexican American adults report more symptoms and somatization (i.e., a preoccupation with physical symptoms that likely have a psychological, rather than physical cause) than do Caucasian adults (Escobar, 1987). Similarly, there are data suggesting that Chinese individuals (both living in Asia and as immigrants in Western countries) report more somatic symptoms of depression than do Caucasians (Ryder et al., 2008).

Cultural factors like ethnomedical beliefs, the value placed on family, collectivism, and religiosity may all mediate some of the differences in symptom reporting and perceived health between populations. For example, illness severity in Mexican Americans is often measured by two factors, pain and the appearance of blood, as well as from the basis of family members' and acquaintances' experiences, with illnesses "common" to this group being perceived as relatively "normal" and inconsequential (Gonzalez-Swafford and Gutierrez, 1983). This emphasis on community, family, and interdependence stands in contrast to the Anglo-American valuation of autonomy and individualism which contributes to self-control over pain and illness, as well as a reduced number of protective social factors in comparison to other ethnic groups that might otherwise assist in buffering the effects of stress and disease (Sharp and Koopman, 2013; but see Voronov and Singer, 2002 for a critique of the individualism-collectivism construct). Other personality traits, such as stoicism and religiosity, may help shape individual or even group-level interpretations and experiences of sickness. The ability to endure pain and illness is a valued sign of strength in Mexicans and Mexican Americans (Calvillo, 2013), and high rates of self-reported stoicism in the face of pain have been reported in Andean Quichuas (Incayawar and Maldonado-Bouchard, 2013). A similar phenomenon has been reported in Chinese men (Hong-Gu and Vehviläinen-Julkunen, 2013). Confucianism, as practiced in China, is possibly associated with stoical attitudes towards pain and illness, particularly in males (Hong-Gu and Vehviläinen-Julkunen, 2013). A belief that illness is an act of God may predispose individuals against reporting the condition and/or seeking treatment, as has been observed in Mexican Americans (Gonzalez-Swafford and Gutierrez, 1983). It has also been reported that Anglo-Americans are less likely to use religion as a coping mechanism during chronic pain, in comparison with African-Americans (Sharp and Koopman, 2013).

Based on the findings that socially appropriate behaviors during illness (e.g., complaining of symptoms, seeking health care or other assistance, suspending economic or other social obligations to rest or recuperate etc.) vary by sex, gender, cultural context, and individual personality, it is a reasonable assumption that sickness behavior expression is also modulated by the same factors. For instance, sick individuals scoring higher on a measure of collectivism might downplay the effects of sickness behavior for relatively minor complaints (e.g., a cold, minor influenza), to avoid "becoming a burden," but to actively seek support for a more serious health problem. Similarly, more individualistic people could sublimate the effects of sickness behaviors and avoid soliciting social support at all times, perhaps preferring medical consultation to social support. Males, or individuals who exhibit more "masculine" behavioral and psychological traits, would under-report sickness behavior symptoms (lethargy, depression, and so forth) in cultural contexts that associate "male-ness" and masculinity with stoicism, dismissal of pain, etc., and the opposite may be true for females or highly feminine individuals. Finally, it should be noted that the evidence presented above is predominantly derived from industrialized, Western populations. Similar research in societies with different medical practices, gender roles etc., would be highly illuminating, and a welcome contribution to the field.

Genetic variation

There are a number of polymorphisms in the promoter regions of IL-1β, IL-6, and TNF-α that are associated with varying production of these cytokines [Allen, 1999; see Gallagher et al. (2003) for an exhaustive list of known cytokine polymorphisms, effects on expression, disease associations etc.], and it seems logical to conclude that these polymorphisms would be associated with sickness behavior. Given the strong relationships between IL-6, TNF-α, and sickness behavior, perhaps the two best candidates for initial research are IL6–174 and TNF-308.

The IL6–174 single nucleotide polymorphism (SNP) is characterized by a guanine (G) to cytosine (C) transition, and has been associated with a variety of clinical conditions, including sepsis and juvenile rheumatoid arthritis (Rivera-Chavez et al., 2003). This SNP has been reported to affect gene transcription, and is associated with baseline plasma IL-6 concentrations, such that GG homozygotes have circulating IL-6 levels approximately twice as high as CC homozygotes (Fishman et al., 1998). Endotoxin stimulated leukocytes from healthy individuals carrying the G allele produce greater amounts of IL-6 than their C counterparts (Rivera-Chavez et al., 2003). Similarly, healthy GG individuals vaccinated with *Salmonella typhii* vaccine show significantly higher plasma IL-6 concentrations than CC individuals following inoculation (Bennermo, 2004), and these latter individuals also have greater symptoms following inoculation with respiratory syncytial virus (Doyle et al., 2010). The low-producing CC genotype is associated with significantly fewer symptoms of depression in individuals receiving interferon-α and ribavirin treatment for chronic hepatitis C infection (Bull et al., 2008).

The TNFA-308 SNP is characterized by both a high (A) and low (G) cytokine producing allele, with AA individuals having higher circulating TNF than GG homozygotes (Abraham and Kroeger, 1999); GA individuals may have as 40% higher TNFα levels than GG individuals (Allen, 1999). This variation is likely heavily dependent on the type of immune stimulus applied (Waterer and Wunderink, 2003).

While the precise global geographic distribution of these alleles has not yet been determined, some broad patterns are evident. In general, non-Caucasian populations exhibit a much higher frequency (80–100%) of the IL6–174G allele than do Caucasians (30–45%) (Berger, 2004). The opposite is true for TNF-308, with the high producing A allele being more prevalent in European and Asian populations. Tables 2 and 3 outline allele frequencies from a variety of populations across the globe.

The adaptive nature and evolutionary history of these SNPs and their distribution throughout human populations remain to be studied. The IL6–174 G allele has been associated with greater mood disturbance in humans during viral infection (Piraino et al., 2012), and future research can expand on this result to determine the extent of any associations between these (and other) polymorphisms and sickness behavior, and establish polymorphism frequencies in more populations across the globe. Clarification of these frequencies may say much about the adaptive nature of sickness behavior if it does indeed have a variable genetic component.

Finally, intra- or inter-populational variation in those hormones associated with sickness behavior could have effects on sickness behavior expression and severity. Age may account for some of this variation, as levels of many hormones varies throughout the lifespan (e.g., the pubertal increase in testosterone and declines in older age for some populations) (Bribiescas, 2010). There is also substantial inter-populational variation in hormone levels (Ellison et al., 2002). Precisely what this inter-populational hormonal variation means in terms of sickness behavior (or, indeed, immune responses more generally) is not known.

FUTURE DIRECTIONS

A complete understanding of sickness behavior in humans should address variation in the proximate mechanisms (e.g., cytokine polymorphisms and hormone levels) as well as any possible cultural moderators (on

TABLE 2. Global IL6–174 allele frequencies

Study population	IL6–174 G/G	IL6–174 C/G	IL6–174 C/C	Source
USA				
Caucasian	40%	42%	18%	Ivanova et al., 2010
Caucasian	38.1%	41.9%	20%	Girnita et al., 2006
Caucasian (women only)	36.3%	44.8%	18.8%	Ness et al., 2004
African–American	72%	26%	2.1%	Ivanova et al. 2010
African–American	82.9%	17.1%	–	Girnita et al. 2006
African–American	80%	18%	2%	Hoffmann et al., 2002
African–American (women only)	82.5%	16.4%	1.2%	Ness et al., 2004
African–American (women only)	86%	12%	2%	Hassan et al., 2003
Hispanic	61.5%	32.3%	6.3%	Ivanova et al., 2010
Hispanic	65.4%	32.1%	2.6%	Girnita et al., 2006
First-generation Cuban Americans	49.3%	39.9%	10.8%	Delaney et al., 2004
Japanese	100%	–	–	Ivanova et al., 2010
Caribbean, Central and South America				
Jamaican children	95%	6%	0.7%	Tseng et al., 2006
Brazilian	49.3%	40.8%	9.9%	Visentainer et al., 2008
Brazilians w/German ancestry	45.75%	35.1%	19.15%	Gadelha et al., 2005
Mixed Portuguese/African ancestry (Brazil)	71%	25%	4%	Gadelha et al., 2005
Indigenous Tiriyó (Brazil)	94.9%	5.1%	–	Gadelha et al., 2005
Bolivian Tsimane	100%	–	–	Vasunilashorn et al., 2011
Europe				
Caucasian males	23.5%	46.9%	29.6%	Taudorf et al., 2008
Caucasian (France)	36.1%	48.3%	13.2%	Haddy et al., 2004
Macedonian	47.8%	43.9%	8.3%	Trajkov et al., 2009
Greek Cypriot	67%	29%	4%	Costeas et al., 2003
Near and Middle East				
Iranians	40%	52.5%	7.5%	Bagheri et al., 2006
Asia, S.E. Asia, and Southern Asia				
North Indian	50.1%	35%	14.9%	Kesarwani et al., 2008
Han Chinese	99.57%	0.43%	–	Pan et al., 2011
Japanese	100%	–	–	Watanabe et al., 2005

TABLE 3. Global TNF-308 allele frequencies

Study population	TNF-308 A/A	TNF-308 G/A	TNF-308 G/G	Source
USA				
Caucasian	4%	15%	81%	Hassan et al., 2003
Caucasian	2.4%	25.2%	72.4%	Girnita et al., 2006
Caucasian	2%	25%	73%	Ferdinands et al., 2011
African–American	2%	24%	74%	Hassan et al., 2003
African–American	1.7%	25.4%	72.9%	Kuffner et al., 2003
African–American	2.9%	31.4%	65.7%	Girnita et al., 2006
African–American	–	44%	56%	Ferdinands et al., 2011
Hispanic	3.8%	15.2%	81%	Girnita et al., 2006
Asian	–	14%	86%	Ferdinands et al., 2011
Caribbean, Central and South America				
Brazilians	–	26.2%	73.8%	Visentainer et al., 2008
Brazilians (healthy controls)	1.6%	15.2%	83.2%	Hounie et al., 2008
Brazilians (OCD patients)	2.7%	27.9%	69.4%	Hounie et al., 2008
Europe				
European Caucasian	1%	28.2%	70.7%	Taudorf et al., 2008
Caucasian (France)	1.03%	18.67%	80.5%	Haddy et al., 2004
Macedonians	1.3%	21.9%	76.8%	Trajkov et al., 2009
Greek Cypriot	–	15%	85%	Costeas et al., 2003
Near and Middle East				
Iranians	2.5%	32.5%	65%	Bagheri et al., 2006
Asia, S.E. Asia, and Southern Asia				
Japanese	–	1.3%	98.7%	Watanabe et al., 2005
Ethnic Sulawesi	2%	3.2%	94.7%	Lamsis et al., 2002
Asian Indians	–	14.3%	85.7%	Gupta et al., 2009
Bhutia (Indian tribe)	0.14%	7.3%	92.5%	Sengupta et al., 2007
Kadar (Indian tribe)	0.1%	6.3%	93.5%	Sengupta et al., 2007
Iyer (Indian caste)	0.08%	5.6%	94.3%	Sengupta et al., 2007
Brahmin (Indian caste)	0.3%	8.7%	92.5%	Sengupta et al., 2007

an individual and societal level) that can influence the expression of these behavioral changes. Figure 2 presents this model graphically. Some factors, such as cytokine polymorphisms and hormone levels, influence sickness behavior severity and duration directly, while others, including gender roles and cultural conceptions of appropriate behavior while sick, affect sickness behavior expression. Still other factors, such as life history stage, may influence both.

The study of sickness behavior bridges a variety of disciplines, including immunology, behavioral ecology, and endocrinology. As such, biological anthropologists are poised to make significant contributions to the study of sickness behavior within the framework that we have outlined. Much research within biological anthropology is conducted in non-Western populations, and comparative studies are frequently done. Additionally, biological anthropologists often have the training to critically explore and explain sociocultural factors that may influence sickness behavior, as well as abiding interests in ecology and evolutionary theory to understand better the proximate and ultimate causes of this behavioral suite. Indeed, a focus on life history theory, which underlies many works of biological anthropology, is readily applicable to sickness behavior, as explored above. What remains is first to optimize human sickness behavior study designs to best capture as many of the "symptoms" of sickness behavior as possible while simultaneously measuring these changes throughout the course of illness or immune stimulation. Following this, it will be far easier to turn attention to the larger, holistic picture of human sickness behavior.

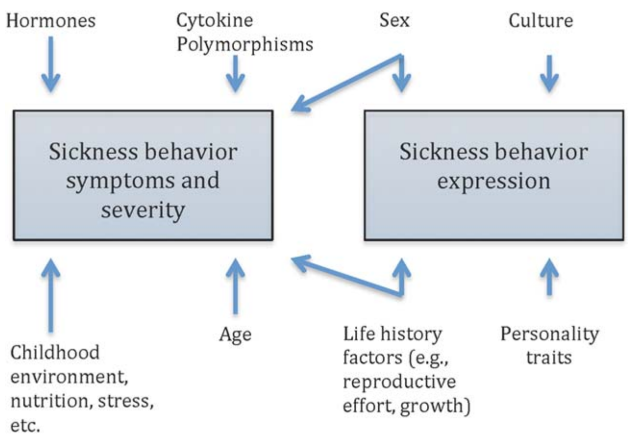

Fig. 2. Conceptual model of biological and social mediators of sickness behavior and its expression. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Unanswered methodological and theoretical questions

Throughout this review, we have raised several theoretical and methodological questions, which are listed in Table 4. These are, of course, not the only remaining questions in this field of enquiry. There are many methodological constraints in studying human sickness behavior. Because sickness behavior is so intertwined with the APR, it is best to begin data collection prior to the onset of signs or symptoms (i.e., during the prodromal phase). However, symptoms, by definition, signify the presence of a disease, and individuals will not seek treatment or self-identify as sick if asymptomatic. Utilizing a study design based on naturally acquired infections is therefore difficult. Furthermore, studies may be confounded immunologically by the use of different treatments for infection, which are of course ethically required when a standard of care is available.

Vollmer-Conna and coworkers (2004) examined sickness behavior in three cohorts of individuals who were infected with Q fever, Epstein-Barr virus, or Ross River virus. Patients in all three groups reported symptoms of sickness behavior, including anhedonia, fatigue, malaise, and depression (Vollmer-Conna et al., 2004). Levels of IL-6 and IL-1β released from LPS-stimulated peripheral blood mononuclear cells (PBMCs) collected from participants were found to correlate strongly with these symptoms (Vollmer-Conna et al., 2004). Imboden et al. (1961) found a similar pattern of behavioral symptoms following acute influenza infection. Individuals sick with the common cold reported lower alertness, increased negative mood, psychomotor slowing, and performed verbal reasoning and semantic processing tasks more slowly compared to healthy controls (Smith, 2012). However, these data were collected several weeks after symptom onset, on average, and it is possible that self-treatment and/or the actions of other immune molecules could confound results. Data collection should begin shortly after infection or immune stimulus exposure to capture the

TABLE 4. Remaining methodological and theoretical questions

Remaining methodological points and questions
1. Assessment of full cytokine context (i.e., interactions between, and subsequent effects of, multiple endogenous cytokines) during sickness behavior.
2. In what ways do the TNF-308 and IL6–174 alleles affect sickness behavior, and do other relevant cytokine polymorphisms show similar effects?
3. What roles do anti-inflammatory cytokines (e.g., IL-4, IL-10) play in regulating sickness behavior responses?
4. How do hormones (e.g., oxytocin, cortisol) affect sickness behavior responses?
5. What effects does inhibition of individual components of sickness behavior have on survivorship and/or time to recovery?
6. Clarification of depression "phenotype" (e.g., depression due to cytokine activity, depression due to neurotransmitter activity, etc.) and their interconnections.
7. Does sickness behavior differ meaningfully between the developed and developing world?
8. In what ways does childhood stress affect sickness behavior severity and duration during adulthood?
9. What effect does childhood pathogen exposure have on sickness behavior severity and duration in adulthood? What contribution, if any, do local disease ecologies have on variation in sickness behavior responses?
Remaining theoretical questions
1. Is sickness behavior truly evolutionarily adaptive?
2. Does sickness behavior vary predictably throughout the lifespan, and if so, how?
3. Do humans show similar trade-offs between sickness behavior and other life history traits (e.g., reproduction), and what variables do these trade-offs depend on?
4. What role, if any, does individual embodiment of cultural/social values play in sickness behavior responses?

physiological and behavioral changes associated with the APR.

Experimental inoculation with a pathogen permits researchers to trace the effects of a known pathogenic organism from a known point of exposure as well as known inoculation dose. In one such study, approximately 200 subjects were experimentally exposed to either rhinovirus or influenza A. Both positive and negative affect and levels of IL-1β, IL-6, and TNF-α were assessed daily for six days (Janicki-Deverts et al., 2007). In those participants that progressed to active infection, expression of all three cytokines was correlated with lower daily positive affect, which was reduced for up to 6 days after infection. Interestingly, there was no relationship between cytokine levels and negative affect (ibid). Ethical considerations dictate that experimentally infected individuals be quarantined (in this case, in a hotel) so as to not infect other people, so it is possible that an unfamiliar environment contributed to participants' negative mood.

In other studies, LPS has been used to activate immune responses. For example, food consumption decreased for up to four hours following LPS administration in 20 male volunteers, and was inversely associated with levels of both IL-6 and TNF-α (Reichenberg et al., 2002). Eisenberger and coworkers (2010) treated thirty-nine participants with either LPS or placebo, and hourly blood draws assessed circulating IL-6 and TNF-α levels through the course of the experiment (6 h). Hourly assessments of symptoms, depression, and feelings of social disconnection (arguably a better measure of the social withdrawal characteristic of sickness behavior than depression) were also collected (Eisenberger et al., 2010). LPS treatment led to significant increases in feelings of social disconnection at 2, 3, and 4 h post-injection, and this increase occurred independent of symptom severity, but was instead associated with cytokine levels (ibid). Interestingly, females showed a larger increase in feelings of social disconnection within two hours after the injection, but the same feelings lasted longer in men (up to 6 h post-injection) (ibid). This last finding continues to suggest the possibility of sex/gender differences in sickness behavior, as discussed above.

Vaccines can also be used to elicit sickness behavior, provided they generate a strong enough inflammatory response. Brydon and coworkers (2009) found that negative mood and IL-6 increased in male subjects following administration of typhoid vaccine, and the effect was more pronounced if subjects were given stressful behavioral tasks (e.g., public speaking). It should be noted that both Brydon et al. (2009) and Eisenberger et al. (2010) were restricted to clinical settings. As with Janicki-Deverts et al. (2007), it is possible that results were influenced by this unfamiliar setting. Isolation also prevents objective measurement of some aspects of sickness behavior, namely changes in social and sexual behavior. Similarly, the brief duration of these studies, which are often completed after several hours, does not lend itself to an examination of detailed changes in diet or sleep patterns. We believe that clinical settings are ill suited to answering questions of both behavior and mood.

We suggest that the most appropriate paradigm for the study of sickness behavior is one that allows participants to go about their day-to-day lives during immune activation after a known point of exposure to an antigen. As such, the use of common vaccines may be the best solution currently available. Vaccines do not require monitoring patients for adverse reactions, as does LPS. However, vaccine responses will vary based on age (Weinberger et al., 2008), sex, (Cook, 2008) and it is possible that genetic factors (Yucesoy et al., 2009; Thomas and Moridani, 2010) or even an individual's mood (Glaser et al., 2003) will affect responses. Interested researchers should remain mindful of these sources of variation. The use of non-invasive biological specimen collection methods (e.g., urine collection for quantification of IL-6) further eliminates the need for clinical settings and minimizes the possibility of stress effects on hormones and mood due to blood draws.

Longitudinal studies could provide a better understanding of mood, behavior, hormonal, and immunological responses through the course of the illness. This perspective is largely missing in the current literature. Some vaccines, such as oral typhoid and rabies, are administered multiple times throughout multiple days or weeks and could be utilized in a longitudinal study design. Researchers studying similar outcomes (e.g., stress) or biomarkers (e.g., CRP) may wish to include some of the immunological or behavioral measures we have outlined above to gain a clearer understanding of these mechanisms. It is also possible to integrate measures of energy balance and availability, diet, and body composition to provide a more accurate picture of this hormone-health-behavior axis in humans. Finally, a validated survey that addresses all aspects of sickness behavior, rather than just mood or cognitive function, for example, would be most welcome.

There has been much recent interest in behavioral components of human immunity and disease avoidance (e.g., Schaller and Park, 2011), and other alternative hypotheses of the role of depression's associations with immunity have been put forth (Raison and Miller, 2012; Anders et al., 2013). Although no small task, a better conceptualization of depression and understanding of its diverse causes and intersecting pathways would likely help to clarify competing hypotheses and experimental findings (Blume et al., 2011). Behavior, mood, inflammation, and immunity are, individually, complex phenomena in humans and other animals; together they form a far more nuanced web of connections, which we are only just beginning to fully appreciate and understand. Sickness behavior is a universal biological phenomenon situated at the intersection of behavior, culture, endocrinology, and immunology. Sickness behavior research and, more broadly, investigations into relationships among pro-inflammatory cytokines, mood, and behavior, have the potential for practical, therapeutic outcomes. For instance, it is possible that some affective disorders may be the result of chronically elevated pro-inflammatory cytokines (reviewed in Maes, 1995 and Raison et al., 2006), which suggests that therapies targeted at these cytokines may be an effective alternative to traditional anti-depressants (Tyring et al., 2006). We feel that biological anthropologists are well positioned to add to the minimal research that has been done on sickness behavior in humans, and we look forward to these contributions.

ACKNOWLEDGMENTS

The authors thank Greg Demas for providing helpful comments on an earlier draft of this article, and the two anonymous reviewers for their constructive and encouraging guidance.

LITERATURE CITED

Abraham LJ, Kroeger KM. 1999. Impact of the-308 TNF promoter polymorphism on the transcriptional regulation of the TNF gene: relevance to disease. J Leukoc Biol 66:562–566.

Adelman JS, Bentley GE, Wingfield JC, Martin LB, Hau M. 2010. Population differences in fever and sickness behaviors in a wild passerine: a role for cytokines. J Exp Biol 213:4099–4109.

Adelman JS, Martin LB. 2009. Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. Integr Comp Biol 49:202–214.

Allen RD. 1999. Polymorphism of the human TNF-alpha promoter–random variation or functional diversity? Mol Immunol 36:1017–1027.

Alt JA, Sautter NB, Mace JC, Detwiller KY, Smith TL. 2013. Antisomnogenic cytokines, quality of life, and chronic rhinosinusitis: a pilot study. Laryngoscope 124:E107–E114.

Amanatkar HR, Chibnall JT, Seo B-W, Manepalli JN, Grossberg GT. 2014. Impact of exogenous testosterone on mood: a systematic review and meta-analysis of randomized placebo-controlled trials. Ann Clin Psychiatry 26:19–32.

Anders S, Tanaka M, Kinney DK. 2013. Depression as an evolutionary strategy for defense against infection. Brain Behav Immun 31:9–22.

Anisman H, Merali Z, Poulter MO, Hayley S. 2005. Cytokines as a precipitant of depressive illness: animal and human studies. Curr Pharm Des 11:963–972.

Anisman H. 2009. Cascading effects of stressors and inflammatory immune system activation: implications for major depressive disorder. J Psychiatry Neurosci 34:4–20.

Annandale E, Hunt K. 1990. Masculinity, femininity and sex: an exploration of their relative contribution to explaining gender differences in health. Sociol Health Illn 12:24–46.

Arber S, Lahelma E. 1993. Inequalities in women's and men's ill-health: Britain and Finland compared. Soc Sci Med 37: 1055–1068.

Arciniega GM, Anderson TC, Tovar-Blank ZG, Tracey TJG. 2008. Toward a fuller conception of Machismo: development of a traditional Machismo and Caballerismo Scale. J Couns Psychol 55:19–33.

Ashley NT, Hays QR, Bentley GE, Wingfield JC. 2009. Testosterone treatment diminishes sickness behavior in male songbirds. Horm Behav 56:169–176.

Aubert A, Goodall G, Dantzer R, Gheusi G. 1997. Differential effects of lipopolysaccharide on pup retrieving and nest building in lactating mice. Brain Behav Immun 11:107–118.

Aubert A. 1999. Sickness and behaviour in animals: a motivational perspective. Neurosci Biobehav Rev 23:1029–1036.

Avitsur R, Donchin O, Barak O, Cohen E, Yirmiya R. 1995. Behavioral effects of interleukin-1 beta: modulation by gender, estrus cycle, and progesterone. Brain Behav Immun 9: 234–241.

Avitsur R, Cohen E, Yirmiya R. 1997. Effects of interleukin-1 on sexual attractivity in a model of sickness behavior. Physiol Behav 63:25–30.

Avitsur R, Pollak Y, Yirmiya R. 1997. Different receptor mechanisms mediate the effects of endotoxin and interleukin-1 on female sexual behavior. Brain Res 773:149–161.

Avitsur R, Yirmiya R. 1999. The immunobiology of sexual behavior: gender differences in the suppression of sexual activity during illness. Pharmacol Biochem Behav 64:787–796.

Avitsur R, Sheridan JF. 2009. Neonatal stress modulates sickness behavior. Brain Behav Immun 23:977–985.

Baatar D, Patel K, Taub DD. 2011. The effects of ghrelin on inflammation and the immune system. Mol Cell Endocrinol 340:44–58.

Bagheri M, Omrani D, Abdi-Rad I. 2006. Cytokine single nucleotide polymorphisms in Iran. J Interferon Cytokine Res 26: 414–420.

Banks WA, Erickson MA. 2010. The blood-brain barrier and immune function and dysfunction. Neurobiol Dis 37:26–32.

Baumann H, Gauldie J. 1994. The acute phase response. Immunol Today 15:74–80.

Bennermo M. 2004. Genetic predisposition of the interleukin-6 response to inflammation: implications for a variety of major diseases? Clin Chem 50:2136–2140.

Berger FG. 2004. The interleukin-6 gene: a susceptibility factor that may contribute to racial and ethnic disparities in breast cancer mortality. Breast Cancer Res Treat 88:281–285.

Bilbo SD, Schwarz JM. 2012. The immune system and developmental programming of brain and behavior. Front Neuroendocrinol 33:267–286.

Blalock JE. 1989. A molecular basis for bidirectional communication between the immune and neuroendocrine systems. Physiol Rev 69:1–32.

Blackwell AD, Snodgrass JJ, Madimenos FC, Sugiyama LS. 2010. Life history, immune function, and intestinal helminths: trade-offs among immunoglobulin E, C-reactive protein, and growth in an Amazonian population. Am J Hum Biol 22:836–848.

Blume J, Douglas SD, Evans DL. 2011. Immune suppression and immune activation in depression. Brain Behav Immun 25:221–229.

Booth A, Johnson DR, Granger DA. 1999. Testosterone and men's depression: the role of social behavior. J Health Soc Behav 40:130–140.

Booth A, Granger DA, Mazur A, Kivlighan KT. 2006. Testosterone and social behavior. Soc Forces 85:167–191.

Borderas TF, de Passille AM, Rushen J. 2008. Behavior of dairy calves after a low dose of bacterial endotoxin. J Anim Sci 86: 2920–2927.

Bouman A. 2005. Sex hormones and the immune response in humans. Hum Reprod Update 11:411–423.

Bribiescas RG. 2005. Serum leptin levels in Ache Amerindian females with normal adiposity are not significantly different from American anorexia nervosa patients. Am J Hum Biol 17: 207–210.

Bribiescas RG. 2010. An evolutionary and life history perspective on human male reproductive senescence. Ann NY Acad Sci 1204:54–64.

Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol Psychiatry 63:1022–1029.

Brydon L, Walker C, Wawrzyniak A, Whitehead D, Okamura H, Yajima J, Tsuda A, Steptoe A. 2009. Synergistic effects of psychological and immune stressors on inflammatory cytokine and sickness responses in humans. Brain Behav Immun 23: 217–224.

Bucks RS, Gidron Y, Harris P, Teeling J, Wesnes KA, Perry VH. 2008. Selective effects of upper respiratory tract infection on cognition, mood and emotion processing: a prospective study. Brain Behav Immun 22:399–407.

Bull SJ, Huezo-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, Miyazaki C, Alexander N, Hotopf M, Cleare AJ, Norris S, Cassidy E, Aitchison KJ, Miller AH, Pariante CM. 2008. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-α and ribavirin treatment. Mol Psychiatry 14:1095–1104.

Burness G, Armstrong C, Fee T, Tilman-Schindel E. 2010. Is there an energetic-based trade-off between thermoregulation and the acute phase response in zebra finches? J Exp Biol 213:1386–1394.

Butts CL, Sternberg EM. 2008. Neuroendocrine factors alter host defense by modulating immune function. Cell Immunol 25:27–15.

Calvillo ER. 2013. Insights on the pain experience in Mexican Americans. In: Incayawar M, Todd K, editors. Culture, brain, and analgesia. New York: Oxford University Press. p 49–61.

Campbell A. 2010. Oxytocin and human social behavior. Pers Soc Psychol Rev 14:281–295.

Campbell DI, Elia M, Lunn PG. 2003. Growth faltering in rural Gambian infants is associated with impaired small intestinal

barrier function, leading to endotoxemia and systemic inflammation. J Nutr 133:1332–1338.
Carlton ED, Demas GE, French SS. 2012. Leptin, a neuroendocrine mediator of immune responses, inflammation, and sickness behaviors. Horm Behav 62:272–279.
Carpenter WT, Gruen PH. 1982. Cortisol's effects on human mental functioning. J Clin Psychopharmacol 2:91–101.
Carroll JE, Low CA, Prather AA, Cohen S, Fury JM, Ross DC, Marsland AL. 2011. Negative affective responses to a speech task predict changes in interleukin (IL)-6. Brain Behav Immun 25:232–238.
Checkley W, Epstein LD, Gilman RH, Black RE, Cabrera L, Sterling CR. 1998. Effects of Cryptosporidium parvum infection in Peruvian children: growth faltering and subsequent catch-up growth. Am J Epidemiol 148:497–506.
Cianelli R, Ferrer L, McElmurry BJ. 2008. HIV prevention and low-income Chilean women: machismo, marianismo and HIV misconceptions. Cult Health Sex 10:297–306.
Clark IA. 2007. The advent of the cytokine storm. Immunol Cell Biol 85:271–273.
Cleary PD, Mechanic D, Greenley JR. 1982. Sex differences in medical care utilization: an empirical investigation. J Health Soc Behav 23:106–119.
Clevenger L, Schrepf A, Christensen D, DeGeest K, Bender D, Ahmed A, Goodheart MJ, Penedo F, Lubaroff DM, Sood AK, Lutgendorf SK. 2012. Sleep disturbance, cytokines, and fatigue in women with ovarian cancer. Brain Behav Immun 26:1037–1044.
Clodi M, Vila G, Geyeregger R, Riedl M, Stulnig TM, Struck J, Luger TA, Luger A. 2008. Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. Am J Physiol Endocrinol Metab 295:E686–E691.
Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, Manuck SB. 2002. Reactivity and vulnerability to stress-associated risk for upper respiratory illness. Psychosom Med 64:302–310.
Cook IF. 2008. Sexual dimorphism of humoral immunity with human vaccines. Vaccine 26:3551–3555.
Costeas PA, Koumas L, Koumouli A, Kyriakou-Giantsiou A, Papaloizou A. 2003. Cytokine polymorphism frequencies in the Greek Cypriot population. Eur J Immunogenet 30:341–343.
Courtenay WH. 2000. Constructions of masculinity and their influence on men's well-being: a theory of gender and health. Soc Sci Med 50:1385–1401.
Cunningham C, Sanderson DJ. 2008. Malaise in the water maze: untangling the effects of LPS and IL-1β on learning and memory. Brain Behav Immun 22:1117–1127.
Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc Natl Acad Sci USA 104:1319–1324.
Dantzer R. 2001. Cytokine-induced sickness behavior: mechanisms and implications. Ann NY Acad Sci 933:222–234.
Dantzer R, Bluthe RM, Kelley KW. 1991. Androgen-dependent vasopressinergic neurotransmission attenuates interleukin-1-induced sickness behavior. Brain Res 557:115–120.
Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9:46–56.
Defrin R, Shramm L, Eli I. 2009. Gender role expectations of pain is associated with pain tolerance limit but not with pain threshold. Pain 145:230–236.
Delaney NL, Esquenazi V, Lucas DP, Zachary AA, Leffell MS. 2004. TNF-α, TGF-β, IL-10, IL-6, and INF-γ alleles among African Americans and Cuban Americans: report of the ASHI minority workshops: Part IV. Hum Immunol 65: 1413–1419.
Dhabhar FS, Miller AH, Stein M, McEwen BS, Spencer RL. 1994. Diurnal and acute stress-induced changes in distribution of peripheral blood leukocyte subpopulations. Brain Behav Immun 8:66–79.
Dinarello CA. 2000. Proinflammatory cytokines. Chest 118, 503–508.
Doyle WJ, Casselbrant ML, Li-Korotky H-S, Doyle APC, Lo C-Y, Turner R, Cohen S. 2010. The interleukin 6-174 C/C genotype predicts greater rhinovirus illness. J Infect Dis 201:199–206.
Eisenberger NI, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. 2009. An fMRI study of cytokine-induced depressed mood and social pain: the role of sex differences. Neuroimage 47:881–890.
Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. 2010. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. Brain Behav Immun 24:558–563.
Eisenegger C, Haushofer J, Fehr E. 2011. The role of testosterone in social interaction. Trend Cogn Sci 15:263–271.
Elenkov IJ. 2004. Glucocorticoids and the Th1/Th2 Balance. Ann NY Acad Sci 1024:138–146.
Ellison PT, Bribiescas RG, Bentley GR, Campbell BC, Lipson SF, Panter-Brick C, Hill K. 2002. Population variation in age-related decline in male salivary testosterone. Hum Reprod 17: 3251–3253.
Escobar JI. 1987. Cross-cultural aspects of the somatization trait. Hosp Commun Psychiatry 38:174–180.
Escobar J, Van Alstine WG, Baker DH, Johnson RW. 2007. Behaviour of pigs with viral and bacterial pneumonia. Appl Anim Behav Sci 105:42–50.
Ewald PW. 1980. Evolutionary biology and the treatment of signs and symptoms of infectious disease. J Theor Biol 86: 169–176.
Ferdinands JM, Denison AM, Dowling NF, Jost HA, Gwinn ML, Liu L, Zaki SR, Shay DK. 2011. A pilot study of host genetic variants associated with influenza-associated deaths among children and young adults. Emerg Infect Dis 17:2294–2302.
Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. 1998. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest 102:1369–1376.
Fong Y, Tracey KJ, Moldawer LL, Hesse DG, Manogue KB, Kenney JS, Lee AT, Kuo GC, Allison AC, Lowry SF. 1989. Antibodies to cachectin/tumor necrosis factor reduce interleukin 1 beta and interleukin 6 appearance during lethal bacteremia. J Exp Med 170:1627–1633.
Friedman EM, Reyes TM, Coe CL. 1996. Context-dependent behavioral effects of interleukin-1 in the rhesus monkey (*Macaca mulatta*). Psychoneuroendocrinol 21:455–468.
Friedman JM, Halaas JL. 1998. Leptin and the regulation of body weight in mammals. Nature 395:763–770.
Gadelha SR, Alcantara LC, Costa GCS, Rios DL, Galvão-Castro B. 2005. Ethnic differences in the distribution of interleukin-6 polymorphisms among three Brazilian ethnic groups. Hum Biol 77:509–514.
Gallagher G, Eskdale J, Bidwell JL. 2003. Cytokine genetics: polymorphisms, functional variations, and disease associations. In: Thomson AW, Lotze MT, editors. The cytokine handbook. London: Academic Press. p 19–57.
Gearing A, Newman W. 1993. Circulating adhesion molecules in disease. Immunol Today 14:506–512.
Ghezzi P, Sacco S, Agnello D, Marullo A, Caselli G, Bertini R. 2000. LPS induced IL-6 in the brain and in serum largely through TNF production. Cytokine 12:1205–1210.
Girnita DM, Webber SA, Ferrell R, Burckart GJ, Brooks MM, McDade KK, Chinnock R, Canter C, Addonizio L, Bernstein D, Kirklin JK, Girnita AL, Zeevi A. 2006. Disparate distribution of 16 candidate single nucleotide polymorphisms among racial and ethnic groups of pediatric heart transplant patients. Transplantation 82:1774–1780.
Glaser R, Robles TF, Sheridan J, Malarkey WB, Kiecolt-Glaser JK. 2003. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. Arch Gen Psychiatry 60:1009–1014.
Godbout, JP, Chen, J, Abraham, J, Richwine, AF, Berg, BM, Kelley KW, Johnson, RW. 2005. Exaggerated neuroinflammation and sickness behavior in aged mice following activation

of the peripheral innate immune system. FASEB J 19:1329–1331.
Gomez CR, Boehmer ED, Kovacs EJ. 2005. The aging innate immune system. Curr Opin Immunol 17:457–462.
Gonzalez-Swafford MJ, Gutierrez MG. 1983. Ethno-medical beliefs and practices of Mexican-Americans. Nurse Pract 8: 29–34.
Goodin BR, Sibille K, Fillingim RB. 2013. Gender and ethnic differences in responses to pain and its treatment. In: Incayawar M, Todd K, editors. Culture, brain, and analgesia. New York: Oxford University Press. p 240–258.
Gove WR, Hughes M. 1979. Possible causes of the apparent sex differences in physical health: an empirical investigation. Am Sociol Rev 44:126–146.
Graham JE, Christian LM, Kiecolt-Glaser JK. 2006. Stress, age, and immune function: toward a lifespan approach. J Behav Med 29:389–400.
Granot M, Goldstein-Ferber S, Azzam ZS. 2004. Gender differences in the perception of chest pain. J Pain Symptom Manage 27:149–155.
Grigoleit J-S, Kullmann JS, Wolf OT, Hammes F, Wegner A, Jablonowski S, Engler H, Gizewski E, Oberbeck R, Schedlowski M. 2011. Dose-dependent effects of endotoxin on neurobehavioral functions in humans. PLoS ONE 6:e28330.
Grossman CJ. 1984. Regulation of the immune system by sex steroids. Endocrine Rev 5:435–455.
Gupta R, Kapuria V, Das SN. 2009. Single nucleotide polymorphisms in TNF-α, TNFR2 gene and TNF-α production in Asian Indians. Immunol Invest 38:240–254.
Haack M, Schuld A, Kraus T, Pollmächer T. 2001. Effects of sleep on endotoxin-induced host responses in healthy men. Psychosom Med 63:568–578.
Haddy N, Sass C, Maumus S, Marie B, Droesch S, Siest G, Lambert D, Visvikis S. 2004. Biological variations, genetic polymorphisms and familial resemblance of TNF-α and IL-6 concentrations: STANISLAS cohort. Eur J Hum Genet 13: 109–117.
Hart BL. 1988. Biological basis of the behavior of sick animals. Neurosci Biobehav Rev 12, 123–137.
Harden LM, Plessis du I, Poole S, Laburn HP. 2006. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. Physiol Behav 89:146–155.
Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, Critchley HD. 2009. Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry 66: 415–422.
Hassan MI, Aschner Y, Manning CH, Xu J, Aschner JL. 2003. Racial differences in selected cytokine allelic and genotypic frequencies among healthy, pregnant women in North Carolina. Cytokine 21:10–16.
Hayley S, Brebner K, Lacosta S, Merali Z, Anisman H. 1999. Sensitization to the effects of tumor necrosis factor-alpha: neuroendocrine, central monoamine, and behavioral variations. J Neurosci 19:5654–5665.
Heinrich PC, Castell JV, Andus T. 1990. Interleukin-6 and the acute phase response. Biochem J 265:621–636.
Henry CJ, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, Sheridan JF, Godbout JP. 2008. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. J Neuroinflammation 5:15.
Hermann DM, Mullington J, Hinze Selch D, Schreiber W, Galanos C, Pollmächer T. 1998. Endotoxin-induced changes in sleep and sleepiness during the day. Psychoneuroendocrinol 23:427–437.
Hetem RS, Mitchell D, Maloney SK, Meyer LCR, Fick LG, Kerley GIH, Fuller A. 2007. Fever and sickness behavior during an opportunistic infection in a free-living antelope, the greater kudu (Tragelaphus strepsiceros). Am J Physiol Regul Integr Comp Physiol 294:R246–R254.
Hinkle LE Jr, Redmont R, Plummer N, Wolff HG. 1960. An examination of the relation between symptoms, disability, and serious illness, in two homogeneous groups of men and women. Am J Public Health Nations Health 50: 1327–1336.
Hinton DE, Lewis-Fernández R. 2010. The cross-cultural validity of posttraumatic stress disorder: implications for DSM-5. Depress Anxiety 28:783–801.
Hoffmann SC, Stanley EM, Cox ED, DiMercurio BS, Koziol DE, Harlan DM, Kirk AD, Blair PJ. 2002. Ethnicity greatly influences cytokine gene polymorphism distribution. Am J Transplant 2:560–567.
Hong-Gu H, Vehviläinen-Julkunen KM. 2013. Allying with Chinese parents for enhanced control of pediatric postoperative pain. In: Incayawar M, Todd K, editors. Culture, brain, and analgesia. New York: Oxford University Press. p 75–89.
Hopkins SJ, Rothwell NJ. 1995. Cytokines and the nervous system. I: expression and recognition. Trends Neurosci 18:83–88.
Horsburgh A, Massoud TF. 2012. The circumventricular organs of the brain: conspicuity on clinical 3T MRI and a review of functional anatomy. Surg Radiol Anat 35:343–349.
Hounie AG, Cappi C, Cordeiro Q, Sampaio AS, Moraes I, Rosário MCD, Palácios SA, Goldberg AC, Vallada HP, Machado-Lima A, Nakano E, Kalil J, Pauls D, Pereira CAB, Guilherme L, Miguel EC. 2008. TNF-alpha polymorphisms are associated with obsessive-compulsive disorder. Neurosci Lett 442:86–90.
Hunter JB, Fernandez ML, Lacy-Martinez CR, Dunne-Sosa AM, Coe MK. 2007. Male preventive health behaviors: perceptions from men, women, and clinical staff along the U.S. Mexico border. Am J Mens Health 1:242–249.
Imboden JB, Canter A, Cluff L. 1961. Convalescence from influenza: a study of the psychological and clinical determinants. Arch Intern Med 108:393–399.
Incayawar M, Maldonado-Bouchard S. 2013. We feel pain too: asserting the pain experience of the Quichua people. In: Incayawar M, Todd K, editors. Culture, brain, and analgesia. New York: Oxford University Press. p 61–75.
Ivanova M, Ruiqing J, Kawai S, Matsushita M, Ochiai N, Maruya E, Saji H. 2010. IL-6 SNP diversity among four ethnic groups as revealed by bead-based liquid array profiling. Int J Immunogenet 38:17–20.
Janicki-Deverts D, Cohen S, Doyle WJ, Turner RB, Treanor JJ. 2007. Infection-induced proinflammatory cytokines are associated with decreases in positive affect, but not increases in negative affect. Brain Behav Immun 21:301–307.
Johnson RW, Curtis SE, Dantzer R, Bahr JM, Kelley KW. 1993. Sickness behavior in birds caused by peripheral or central injection of endotoxin. Physiol Behav 53:343–348.
Kasting NW. 1986. Characteristics of body temperature, vasopressin, and oxytocin responses to endotoxin in the rat. Can J Physiol Pharmacol 64:1575–1578.
Kent S, Kelley KW, Dantzer R. 1992. Effects of lipopolysaccharide on food-motivated behavior in the rat are not blocked by an interleukin-1 receptor antagonist. Neurosci Lett 145:83–86.
Kesarwani P, Ahirwar D, Singh R, Manchanda PK, Mittal RD. 2008. Do IL-4 intron 3 VNTR and -6 (-174) G/C variants reflect ethnic variation? A comparative study between the global and North Indian populations. Asian Pac J Cancer Prev 9:76–80.
Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. 2002. Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. Ann Rev Psychol 53:83–107.
Kluger MJ, Ringler DH, Anver MR. 1975. Fever and survival. Science 188:166–168.
Kluger MJ. 1986. Is fever beneficial? Yale J Biol Med 59:89–95.
Kohman RA, Crowell B, Urbach-Ross D, Kusnecov AW. 2009. Influence of age on behavioral, immune and endocrine responses to the T-cell superantigen staphylococcal enterotoxin A. Eur J Neurosci 30:1329–1338.
Krabbe KS, Reichenberg A, Yirmiya R, Smed A, Pedersen BK, Bruunsgaard H. 2005. Low-dose endotoxemia and human neuropsychological functions. Brain Behav Immun 19:453–460.
Kuffner T, Whitworth W, Jairam M, McNicholl J. 2003. HLA class II and TNF genes in African Americans from the Southeastern United States: regional differences in allele frequencies. Hum Immunol 64:639–647.

Laaksonen M, Martikainen P, Rahkonen O, Lahelma E. 2012. The effect of occupational and workplace gender composition on sickness absence. J Occup Environ Med 54: 224–230.
Lamsis F, Flannery GR, White NG, Muratore R, Kaelan C, Mitchell RJ. 2002. Alleles and haplotypes of tumor necrosis factor (TNF) alpha and beta genes in three ethnic populations of Sulawesi Indonesia. Hum Biol 74:381–396.
Landgraf R, Neumann I, Holsboer F, Pittman QJ. 1995. Interleukin-1 beta stimulates both central and peripheral release of vasopressin and oxytocin in the rat. Eur J Neurosci 7:592–598.
Larson SJ. 2002. Behavioral and motivational effects of immune-system activation. J Gen Psychol 129:401–414.
Larson SJ, Dunn AJ. 2001. Behavioral effects of cytokines. Brain Behav Immun 15:371–387.
Lilja M, Rolandsson O, Shaw JE, Pauvaday V, Cameron AJ, Tuomilehto J, Alberti KGMM, Zimmet PZ, Söderberg S. 2010. Higher leptin levels in Asian Indians than Creoles and Europids: a potential explanation for increased metabolic risk. Int J Obes Relat Metab Disord 34:878–885.
Lim MM, Young LJ. 2006. Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav 50:506–517.
Loftis JM, Huckans M, Ruimy S, Hinrichs DJ, Hauser P. 2008. Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1β and tumor necrosis factor-α. Neurosci Lett 430:264–268.
Lopes PC, Adelman J, Wingfield JC, Bentley GE. 2012. Social context modulates sickness behavior. Behav Ecol Sociobiol 66: 1421–1428.
Lopes PC, Chan H, Demathieu S, González-Gómez PL, Wingfield JC, Bentley GE. 2013. The Impact of Exposure to a Novel Female on Symptoms of Infection and on the Reproductive Axis. Neuroimmunomodulation 20:348–360.
Loram LC, Sholar PW, Taylor FR, Wiesler JL, Babb JA, Strand KA, Berkelhammer D, Day HEW, Maier SF, Watkins LR. 2012. Sex and estradiol influence glial pro-inflammatory responses to lipopolysaccharide in rats. Psychoneuroendocrinol 37:1688–1699.
MacDonald L, Hazi A, Paolini AG, Kent S. 2014. Calorie restriction dose-dependently abates lipopolysaccharide-induced fever, sickness behavior, and circulating interleukin-6 while increasing corticosterone. Brain Behav Immun 40:18–26.
Macintyre S. 1993. Gender differences in the perceptions of common cold symptoms. Soc Sci Med 36:15–20.
Macran S, Clarke L, Joshi H. 1996. Women's health: dimensions and differentials. Soc Sci Med 42:1203–1216.
Madan I, Reading I, Palmer KT, Coggon D. 2008. Cultural differences in musculoskeletal symptoms and disability. Int J Epidemiol 37:1181–1189.
Maes M. 1995. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 19:11–38.
Mahalik JR, Levi-Minzi M, Walker G. 2007. Masculinity and health behaviors in Australian men. Psychol Men Masc 8: 240–249.
Maier SF, Watkins LR. 1998. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev 105:83–107.
Maier SF, Goehler LE, Fleshner M, Watkins LR. 1998. The role of the vagus nerve in cytokine-to-brain communication. Ann NY Acad Sci 840:289–300.
Majde JA, Kapás L, Bohnet SG, De A, Krueger JM. 2010. Attenuation of the influenza virus sickness behavior in mice deficient in Toll-like receptor 3. Brain Behav Immun 24:306–315.
Martín-Romero C, Santos-Alvarez J, Goberna R, Sánchez-Margalet V. 2000. Human leptin enhances activation and proliferation of human circulating T lymphocytes. Cell Immunol 199:15–24.
Mathias S, Schiffelholz T, Linthorst AC, Pollmächer T, Lancel M. 2000. Diurnal variations in lipopolysaccharide-induced sleep, sickness behavior and changes in corticosterone levels in the rat. Neuroendocrinology 71:375–385.
McDade TW. 2003. Life history theory and the immune system: steps toward a human ecological immunology. Am J Phys Anthropol 122:100–125.
McDade TW, Reyes García V, Tanner S, Huanca T, Leonard WR. 2008. Maintenance versus growth: investigating the costs of immune activation among children in lowland Bolivia. Am J Phys Anthropol 136:478–484.
McDade TW, Rutherford J, Adair L, Kuzawa CW. 2010. Early origins of inflammation: microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. Proc Biol Sci 277:1129–1137.
McDade TW. 2012. Early environments and the ecology of inflammation. Proc Natl Acad Sci USA 109:17281–17288.
McDade TW, Hoke M, Borja JB, Adair LS, Kuzawa C. 2013. Do environments in infancy moderate the association between stress and inflammation in adulthood? Initial evidence from a birth cohort in the Philippines. Brain Behav Immun 31:23–30.
McLinden KA, Kranjac D, Deodati LE, Kahn M, Chumley MJ, Boehm GW. 2012. Age exacerbates sickness behavior following exposure to a viral mimetic. Physiol Behav 105:1219–1225.
Miller A, Capuron L, Raison C. 2005. Immunologic influences on emotion regulation. Clin Neurosci Res 4:325–333.
Miller AH, Maletic V, Raison CL. 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 65:732–741.
Moreau M, André C, O'Connor JC, Dumich SA, Woods JA, Kelley KW, Dantzer R, Lestage J, Castanon N. 2008. Inoculation of Bacillus Calmette-Guerin to mice induces an acute episode of sickness behavior followed by chronic depressive-like behavior. Brain Behav Immun 22:1087–1095.
Muehlenbein MP, Bribiescas RG. 2005. Testosterone-mediated immune functions and male life histories. Am J Hum Biol 17: 527–558.
Muehlenbein MP, Alger J, Cogswell F, James M, Krogstad D. 2005. The reproductive endocrine response to Plasmodium vivax infection in Hondurans. Am J Trop Med Hyg 73:178–187.
Muehlenbein MP, Cogswell FB, James MA, Koterski J, Ludwig GV. 2006. Testosterone correlates with Venezuelan equine encephalitis virus infection in macaques. Virol J 3:19.
Muehlenbein MP. 2008. Adaptive variation in testosterone levels in response to immune activation: empirical and theoretical perspectives. Soc Biol 53:13–23.
Murray MJ, Murray AB. 1979. Anorexia of infection as a mechanism of host defense. Am J Clin Nutr 32:593–596.
Musselman DL, Nemeroff CB. 1996. Depression and endocrine disorders: focus on the thyroid and adrenal system. Br J Psychiatry Suppl 30:123–128.
Naito Y, Fukata J, Shindo K, Ebisui O, Murakami N, Tominaga T, Nakai Y, Mori K, Kasting NW, Imura H. 1991. Effects of interleukins on plasma arginine vasopressin and oxytocin levels in conscious, freely moving rats. Biochem Biophys Res Commun 174:1189–1195.
Nascimento A, Bernardi M, Pecorari V, Massoco C, Felicio L. 2013. Temporal analysis of lipopolysaccharide-induced sickness behavior in virgin and lactating female rats. Neuroimmunomodulation 20:305–312.
Ness RB, Haggerty CL, Harger G, Ferrell R. 2004. Differential distribution of allelic variants in cytokine genes among African Americans and White Americans. Am J Epidemiol 160: 1033–1038.
O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R. 2008. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 14: 511–522.
Salazar A, Gonzalez-Rivera BL, Redus L, Parrott JM, O'Connor JC. 2012. Indoleamine 2,3-dioxygenase mediates anhedonia and anxiety-like behaviors caused by peripheral lipopolysaccharide immune challenge. Horm Behav 62:202–209.

Owen-Ashley NT. 2006. Seasonal modulation of sickness behavior in free-living northwestern song sparrows (Melospiza melodia morphna). J Exp Biol 209:3062–3070.
Owen-Ashley NT, Hasselquist D, Råberg L, Wingfield JC. 2008. Latitudinal variation of immune defense and sickness behavior in the white-crowned sparrow (*Zonotrichia leucophrys*). Brain Behav Immun 22:614–625.
Owen-Ashley NT, Turner M, Hahn TP, Wingfield JC. 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.
Palacios MG, Winkler DW, Klasing KC, Hasselquist D, Vleck CM. 2011. Consequences of immune system aging in nature: a study of immunosenescence costs in free-living tree swallows. Ecology 92:952–966.
Pan M, Gao S-P, Jiang M-H, Guo J, Zheng J-G, Zhu J-H. 2011. Interleukin 6 promoter polymorphisms in normal Han Chinese population: frequencies and effects on inflammatory markers. J Investig Med 59:272–276.
Papathanassoglou E, El-Haschimi K, Li XC, Matarese G, Strom T, Mantzoros C. 2006. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. J Immunol 176:7745–7752.
Pezeshki G, Pohl T, Schöbitz B. 1996. Corticosterone controls interleukin-1β expression and sickness behavior in the rat. J Neuroendocrinol 8:129–135.
Phillips AC, Carroll D, Khan N, Moss P. 2008. Cytomegalovirus is associated with depression and anxiety in older adults. Brain Behav Immun 22:52–55.
Piraino B, Vollmer-Conna U, Lloyd AR. 2012. Genetic associations of fatigue and other symptom domains of the acute sickness response to infection. Brain Behav Immun 26: 552–558.
Prendergast BJ, Galang J, Kay LM, Pyter LM. 2009. Influence of the olfactory bulbs on blood leukocytes and behavioral responses to infection in Siberian hamsters. Brain Res 1268: 48–57.
Raison CL, Capuron L, Miller AH. 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27:24–31.
Raison CL, Miller AH. 2012. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol Psychiatry 18:15–37.
Reichenberg A, Kraus T, Haack M, Schuld A, Pollmächer T, Yirmiya R. 2002. Endotoxin-induced changes in food consumption in healthy volunteers are associated with TNF-alpha and IL-6 secretion. Psychoneuroendocrinol 27:945–956.
Reyes TM, Sawchenko PE. 2002. Involvement of the arcuate nucleus of the hypothalamus in interleukin-1-induced anorexia. J Neurosci 22:5091–5099.
Rivera-Chavez FA, Peters-Hybki DL, Barber RC, O'Keefe GE. 2003. Interleukin-6 promoter haplotypes and interleukin-6 cytokine responses. Shock 20:218–223.
Rothwell NJ, Hopkins SJ. 1995. Cytokines and the nervous system II: actions and mechanisms of action. Trend Neurosci 18: 130–136.
Ruau D, Liu LY, Clark JD, Angst MS, Butte AJ. 2012. Sex differences in reported pain across 11,000 patients captured in electronic medical records. J Pain 13:228–234.
Ryder AG, Yang J, Zhu X, Yao S, Yi J, Heine SJ, Bagby RM. 2008. The cultural shaping of depression: somatic symptoms in China, psychological symptoms in North America? J Abnorm Psychol 117:300–313.
Sachot, C, Poole, S, Luheshi, GN. 2004. Circulating leptin mediates lipopolysaccharide-induced anorexia and fever in rats. J Physiol 561:263–272.
Sanchez R, Parkin JC, Chen JY, Gray PB. 2009. Oxytocin, vasopressin, and human social behavior. In: Ellison PT, Gray PB, editors. Endocrinology of social relationships. Cambridge: Harvard University Press. p 319–339.
Schaller M, Park JH. 2011. The behavioral immune system (and why it matters). Curr Dir Psychol Sci 20:99–103.
Schmitt LH, Harrison GA, Spargo RM. 1998. Variation in epinephrine and cortisol excretion rates associated with behavior in an Australian Aboriginal community. Am J Phys Anthropol 106:249–253.
Schöbitz B, Holsboer F, Ron de Kloet E. 1994a. Cytokines in the healthy and diseased brain. Physiol 9:138–141.
Schöbitz B, De Kloet ER, Holsboer F. 1994b. Gene expression and function of interleukin 1, interleukin 6 and tumor necrosis factor in the brain. Prog Neurobiol 44:397–432.
Segerstrom SC, Miller GE. 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull 130:601–630.
Selye, H. 1936. A syndrome produced by diverse nocuous agents. Nature 138:32–35.
Sengupta S, Farheen S, Mukherjee N, Majumder PP. 2007. Patterns of nucleotide sequence variation in ICAM1 and TNF genes in twelve ethnic groups of India: roles of demographic history and natural selection. J Genet 86:225–239.
Sharp S, Koopman C. 2013. Understanding Anglo-Americans' culture, pain, and suffering. In: Incayawar M, Todd K, editors. Culture, brain, and analgesia. New York: Oxford University Press. p 89–105.
Silverman MN, Macdougall MG, Hu F, Pace TWW, Raison CL, Miller AH. 2006. Endogenous glucocorticoids protect against TNF-alpha-induced increases in anxiety-like behavior in virally infected mice. Mol Psychiatry 12:408–417.
Silverman WK, Greca AM, Wasserstein S. 1995. What do children worry about? Worries and their relation to anxiety. Child Dev 66:671–686.
Skinner GW, Mitchell D, Harden LM. 2009. Avoidance of physical activity is a sensitive indicator of illness. Physiol Behav 96:421–427.
Smith AP. 2012. Effects of the common cold on mood, psychomotor performance, the encoding of new information, speed of working memory and semantic processing. Brain Behav Immun 26:1072–1076.
Smith AP. 2013. Effects of upper respiratory tract illnesses and stress on alertness and reaction time. Psychoneuroendocrinol 38:2003–2009.
Späth-Schwalbe E, Hansen K, Schmidt F, Schrezenmeier H, Marshall L, Burger K, Fehm HL, Born J. 1998. Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. J Clin Endocrinol Metab 83:1573–1579.
Spratt DI, Cox P, Orav J, Moloney J, Bigos T. 1993. Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab 76:1548–1554.
Springer KW, Mouzon DM. 2011. "Macho Men" and preventive health care: implications for older men in different social classes. J Health Soc Behav 52:212–227.
Sternberg P. 2000. Challenging machismo: promoting sexual and reproductive health with Nicaraguan men. Gend Dev 8: 89–99.
Stone EA, Lehmann ML, Lin Y, Quartermain D. 2006. Depressive behavior in mice due to immune stimulation is accompanied by reduced neural activity in brain regions involved in positively motivated behavior. Biol Psychiatry 60: 803–811.
Sundgren-Andersson AK, Ostlund P, Bartfai T. 1998. IL-6 is essential in TNF-alpha-induced fever. Am J Physiol Regul Integr Comp Physiol 275:R2028–R2034.
Taudorf S, Krabbe KS, Berg RMG, Møller K, Pedersen BK, Bruunsgaard H. 2008. Common studied polymorphisms do not affect plasma cytokine levels upon endotoxin exposure in humans. Clin Exp Immunol 152:147–152.
Taylor SE, Welch WT, Kim HS, Sherman DK. 2007. Cultural differences in the impact of social support on psychological and biological stress responses. Psychol Sci 18:831–837.
Thomas C, Moridani M. 2010. Interindividual variations in the efficacy and toxicity of vaccines. Toxicology 278:204–210.
Torsheim T, Ravens-Sieberer U, Hetland J, Välimaa R, Danielson M, Overpeck M. 2006. Cross-national variation of gender differences in adolescent subjective health in Europe and North America. Soc Sci Med 62:815–827.

Trajkov D, Arsov T, Petlichkovski A, Strezova A, Efinska-Mladenovska O, Gogusev J, Spiroski M. 2009. Distribution of the 22 cytokine gene polymorphisms in healthy Macedonian population. Bratisl Lek Listy 110:7–17.

Tseng F-C, Brown EE, Maiese EM, Yeager M, Welch R, Gold BD, Owens M, Cranston B, Hanchard B, El-Omar E, Hisada M. 2006. Polymorphisms in cytokine genes and risk of Helicobacter pylori infection among Jamaican children. Helicobacter 11:425–430.

Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, Lalla D, Woolley M, Jahreis A, Zitnik R, Cella D, Krishnan R. 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. Lancet 367:29–35.

Vasunilashorn S, Finch C, Crimmins E, Vikman S, Stieglitz J, Gurven M, Kaplan H, Allayee H. 2011. Inflammatory gene variants in the Tsimane, an Indigenous Bolivian population with a high infectious load. Biodemography Soc Biol 57:33–52.

Verbrugge LM. 1985. Gender and health: an update on hypotheses and evidence. J Health Soc Behav 26:156–182.

Vilček J. 2003. The cytokines: an overview. In: Thomson AW, Lotze MT, editors. The cytokine handbook. London: Academic Press. p 3–18.

Visentainer JEL, Sell AM, da Silva GC, Cavichioli ADG, Franceschi DSA, Lieber SR, de Souza CA. 2008. TNF, IFN-G, IL-6, IL-10 and TGF-B1gene polymorphisms in South and Southeast Brazil. Int J Immunogenet 35:287–293.

Volkoff H, Peter RE. 2004. Effects of lipopolysaccharide treatment on feeding of goldfish: role of appetite-regulating peptides. Brain Res 998:139–147.

Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, Davenport T, Wakefield D, Hickie I, Lloyd A. 2004. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychol Med 34: 1289–1297.

Voronov M, Singer JA. 2002. The myth of individualism-collectivism: a critical review. J Soc Psychol 142:461–480.

Wade JC. 2009. Traditional masculinity and African American men's health-related attitudes and behaviors. Am J Mens Health 3:165–172.

Wagner JD, Flinn MV, England BG. 2002. Hormonal response to competition among male coalitions. Evol Hum Behav 23: 437–442.

Watanabe E, Hirasawa H, Oda S, Matsuda K, Hatano M, Tokuhisa T. 2005. Extremely high interleukin-6 blood levels and outcome in the critically ill are associated with tumor necrosis factor alpha and interleukin-1 beta related gene polymorphisms. Crit Care Med 33:89–97.

Waterer GW, Wunderink RG. 2003. Genetic variability in the systemic inflammatory response. Crit Care 7:308–314.

Watkins LR, Goehler LE, Relton J, Brewer MT. 1995. Mechanisms of tumor necrosis factor-α (TNF-α) hyperalgesia. Brain Res 692:244–250.

Wegner A, Elsenbruch S, Maluck J, Grigoleit J-S, Engler H, Jäger M, Spreitzer I, Schedlowski M, Benson S. 2014. Inflammation-induced hyperalgesia: effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. Brain Behav Immun 41:46–54.

Weil ZM, Bowers SL, Dow ER, Nelson RJ. 2006. Maternal aggression persists following lipopolysaccharide-induced activation of the immune system. Physiol Behav 87: 694–699.

Weinberg ED. 1984. Pregnancy-associated depression of cell-mediated immunity. Rev Infect Dis 6:814–831.

Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstein B. 2008. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis 46: 1078–1084.

Willette AA, Lubach GR, Coe CL. 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.

Wingfield JC, Maney DL, Breuner CW, Jacobs JD, Lynn S, Ramenofsky M, Richardson RD. 1998. Ecological Bases of Hormone—Behavior Interactions: the "Emergency Life History Stage." Am Zool 38:191–206.

Wright CE, Strike PC, Brydon L, Steptoe A. 2005. Acute inflammation and negative mood: mediation by cytokine activation. Brain Behav Immun 19:345–350.

Yucesoy B, Johnson VJ, Fluharty K, Kashon ML, Slaven JE, Wilson NW, Weissman DN, Biagini RE, Germolec DR, Luster MI. 2009. Influence of cytokine gene variations on immunization to childhood vaccines. Vaccine 27:6991–6997.

Zetterström M, Sundgren-Andersson AK, Ostlund P, Bartfai T. 1998. Delineation of the proinflammatory cytokine cascade in fever induction. Ann NY Acad Sci 856:48–52.

Zhao Y, Sun R, You L, Gao C, Tian Z. 2003. Expression of leptin receptors and response to leptin stimulation of human natural killer cell lines. Biochem Biophys Res Commun 300: 247–252.