

## Lassitude: The emotion of being sick

Joshua M. Schrock<sup>a,b,\*</sup>, J. Josh Snodgrass<sup>a,b</sup>, Lawrence S. Sugiyama<sup>a</sup>

<sup>a</sup> Department of Anthropology, University of Oregon, 1218 University of Oregon, Eugene, OR 97403, United States of America

<sup>b</sup> Global Health Biomarker Lab, University of Oregon, 1218 University of Oregon, Eugene, OR 97403, United States of America

### ARTICLE INFO

#### Keywords:

Disease  
Immunity  
Motivation  
Movement  
Sociality  
Consumption

### ABSTRACT

Our long co-evolutionary history with infectious agents likely began soon after the rise of the first single-celled organisms. This ongoing evolutionary arms race has generated complex host adaptations, many highly conserved, for resisting infection (e.g., innate and acquired immune systems, infection-sensitive developmental programs, sexual reproduction). A large body of evidence suggests that, in humans, pathogen-avoidance disgust is an emotion that motivates avoidance of cues associated with pathogens, thereby reducing infection. However, the question of whether there is an emotion that coordinates resistance to active infection has received less attention. We propose that *lassitude* is such an emotion. It is triggered by cues of active infection and coordinates the fight against infection by: (a) reducing energetically expensive movement to make more energy available to the immune system, (b) reducing exposure to additional infections and injuries that would compound the immune system's workload, (c) promoting thermoregulatory behaviors that facilitate immunity, (d) regulating food consumption to be beneficial for the host but detrimental to pathogens, and (e) deploying strategies that elicit caregiving behavior from social allies. Lassitude exhibits the core features of an emotion – it is triggered by cues of an adaptive problem (i.e., infection), generates a characteristic facial expression (e.g., slack facial muscles, drooping eyelids, slightly parted lips), and has distinct qualia (e.g., profound tiredness, reduced appetite, feelings of vulnerability, altered temperature perception, increased pain sensitivity). We outline the information-processing structure of lassitude, review existing evidence, suggest directions for future research, and discuss implications of lassitude for models of human evolution.

### 1. Introduction

The evolutionary arms race between infectious agents and their hosts probably began soon after the rise of the first living organisms. Even single-celled prokaryotes (i.e., bacteria and archaea) are perpetually co-evolving with the viruses that infect them (Jalasuuri & Bamford, 2008; Koskella & Brockhurst, 2014; Weitz, Hartman, & Levin, 2005). Infection-related selection pressures have generated and maintained multiple adaptations in complex multicellular organisms to reduce the fitness costs of infectious disease, including generalized immune mechanisms that are effective against multiple infection types (Akira, Uematsu, & Takeuchi, 2006; Lochmiller & Deerenberg, 2000), immune mechanisms that adjust to specific pathogenic organisms (Cooper & Alder, 2006; McDade, 2005), infection-sensitive developmental programs (Georgiev, Kuzawa, & McDade, 2016; Urlacher et al., 2018), and, arguably, sexual reproduction, cellular differentiation, and patterns of parent-offspring association (Liow, Van Valen, & Stenseth, 2011; Tooby, 1982). In the human lineage, evidence indicates a long co-evolutionary history with a variety of infectious organisms, including

various kinds of bacteria, viruses, parasitic worms, and protozoans (Brinkworth & Pechenkina, 2013; Deschamps et al., 2016; Houldcroft & Underdown, 2016; Hurtado, Frey, Hurtado, Hill, & Baker, 2008). Infectious disease remains a major cause of morbidity and mortality for humans in contemporary subsistence and industrialized populations (Hill, Hurtado, & Walker, 2007; Holmes et al., 2017; Sugiyama & Chacon, 2000).

The threat of infectious disease poses two major sets of adaptive problems for host organisms: (1) how to prevent infection, and (2) how to fight infection when it occurs. Substantial evidence indicates that, in humans, pathogen-avoidance disgust provides a key solution to the first problem – it appears to limit infection by reducing contact with pathogen-associated substrates, individuals, and situations (Curtis, de Barra, & Aunger, 2011; Murray, Prokosch, & Airington, 2019; Oaten, Stevenson, & Case, 2009; Schaller, 2015; Tybur, Lieberman, Kurzban, & DeScioli, 2012). The innate and acquired immune systems are critical solutions to the second set of problems (Akira et al., 2006; Cooper & Alder, 2006), but the fight against infection poses additional adaptive problems that cannot be solved by innate and acquired immune

\* Corresponding author at: Department of Anthropology, 1218 University of Oregon, Eugene, OR 97403, United States of America.

E-mail addresses: [jschroc2@uoregon.edu](mailto:jschroc2@uoregon.edu) (J.M. Schrock), [jjosh@uoregon.edu](mailto:jjosh@uoregon.edu) (J.J. Snodgrass), [sugiyama@uoregon.edu](mailto:sugiyama@uoregon.edu) (L.S. Sugiyama).

responses alone.

We propose that the emotion *lassitude* (see [Box 1](#)) is triggered by cues of infection and coordinates the fight against infection by: (a) reducing engagement in energetically expensive movement in order to make more energy available for the immune system, (b) reducing exposure to additional pathologies that would compound the immune system's workload (e.g., injuries, poisoning, additional infections), (c) modulating thermoregulatory behaviors in ways that are conducive to effective immune function (e.g., promoting warmth-seeking behavior), (d) regulating food consumption in ways that are beneficial to the host but detrimental to pathogens, and (e) deploying strategies to elicit caregiving behavior from social allies (e.g., preferential contact, signaling of vulnerability). We hypothesize that *lassitude* is an evolutionarily conserved adaptation but also has derived features that evolved in the human lineage, due to distinctive aspects of our life history, sociality, and diet.

We recognize that non-infectious pathologies (e.g., injury, chronic disease, poisoning) probably also activate *lassitude* (or at least an overlapping suite of mechanisms). These non-infectious somatic insults pose many of the same adaptive problems as infectious disease, and they frequently activate some of the mechanistic pathways that trigger *lassitude* during infectious disease ([Del Giudice & Gangestad, 2018](#); [McCusker & Kelley, 2013](#)). However, for the sake of brevity and clarity, we focus our discussion in this paper on *lassitude* triggered by infection with pathogenic organisms (e.g., bacteria, viruses, parasitic worms, protozoans).

## 2. Infectious disease poses a suite of adaptive problems

Infectious disease is a ubiquitous feature of life for most animals ([Hart, 1990](#); [Knoll & Carroll, 1999](#); [Zuk, 1992](#)). Humans are no exception. Infectious disease is a major driver of mortality among extant and ethnographically known human hunter-gatherers, causing between 20% and 85% of deaths in populations for which data are available ([Blurton Jones, Hawkes, & O'Connell, 2002](#); [Early & Headland, 1998](#); [Hill et al., 2007](#); [Hill & Hurtado, 1996](#); [Howell, 1979](#); [Jones, Smith, O'Connell, Hawkes, & Kamuzora, 1992](#)). Non-lethal infections also occur frequently in subsistence populations and often cause substantial morbidity ([Gurven, Allen-Arave, Hill, & Hurtado, 2000](#); [McDade et al., 2012](#); [Sugiyama, 2004](#)). For instance, [Sugiyama and Chacon \(2000\)](#) found that Yora forager men of the Peruvian Amazon were unable to work due to illness or injury on 10.6% of work days, conservatively estimated to include only days on which they would have otherwise gone hunting, fishing, or foraging. Direct behavioral observation of Efe hunter-gatherers of the Ituri Forest, in what is now the Democratic Republic of the Congo, found that men were sick with some recorded ailment 21.4% of the time ([Bailey, 1991](#)) and women 22% of the time ([Peacock, 1985](#)). Infectious disease is also a major cause of morbidity and mortality in industrialized populations ([Holmes et al., 2017](#)).

The available paleopathological, genomic, and phylogenetic evidence suggests that the human lineage shares a long co-evolutionary history with a variety of pathogen types ([Ewald, 1994](#)). Paleopathological discoveries have revealed skeletal evidence of *Mycobacterium tuberculosis* in *Homo erectus* dating to about 0.5 million years ago (mya) ([Kappelman et al., 2008](#)), evidence of yaws infection (*Treponema pallidum pertenu*) in *H. erectus* remains dating to about 1.6 mya ([Rothschild, Hershkovitz, & Rothschild, 1995](#)), and evidence of brucellosis in *Australopithecus africanus* dating to about 2.4–2.8 mya ([D'Anastasio, Zipfel, Moggi-Cecchi, Stanyon, & Capasso, 2009](#)). Many pathogens do not leave skeletal signs, but pathogen genomes, host immune genes, and their respective phylogenies suggest a pre-Holocene origin of a number of other pathogenic bacteria, viruses, and parasitic worms in ancestral hominin populations (e.g., whipworm, pertussis, hepatitis A) ([Brinkworth & Pechenkina, 2013](#); [Deschamps et al., 2016](#); [Houldcroft & Underdown, 2016](#)). Sedentary agriculture, dense population centers, and animal domestication probably introduced a new

array of epidemic diseases (e.g., measles, plague, smallpox), introducing novel sources of infectious disease morbidity and mortality ([Houldcroft & Underdown, 2016](#); [Omran, 2005](#)).

Thus, pathogen-related selection pressures likely began shortly after the rise of the first living organisms ([Jalavsuori & Bamford, 2008](#); [Koskella & Brockhurst, 2014](#); [Weitz et al., 2005](#)), persisted during the emergence of complex multicellular organisms ([Ewald, 1994](#); [Liow et al., 2011](#); [Tooby, 1982](#)), and continues to the present day in extant host species, including humans ([Hill et al., 2007](#); [Holmes et al., 2017](#)). These selection pressures favor adaptations that solve two major sets of adaptive problems: (1) how to prevent infection, and (2) how to fight infection when it occurs.

### 2.1. How to prevent infection

An effective way to avoid infection-related morbidity and mortality is to limit pathogen exposure, thereby keeping pathogen load low. However, efforts at avoiding exposure have opportunity costs (e.g., lost opportunities to mate, travel, work, eat, etc.). There is thus a tradeoff between the health benefits of avoiding pathogen exposure and the opportunity costs of doing so. A large body of evidence suggests that pathogen-avoidance disgust is a system that regulates this tradeoff ([Lieberman, Billingsley, & Patrick, 2018](#); [Oaten et al., 2009](#); [Schaller, 2015](#)). The pathogen-avoidance disgust system monitors cues of situations, individuals, and substrates associated with high pathogen risk, calculates the costs and benefits of avoiding contact with these cues, and calibrates disgust sensitivity to pathogen-associated cues based on these costs and benefits ([Curtis et al., 2011](#); [Murray et al., 2019](#); [Tybur et al., 2012](#)). The evolved structure and function of pathogen-avoidance disgust is covered in detail elsewhere ([Curtis et al., 2011](#); [Lieberman & Patrick, 2018](#); [Murray et al., 2019](#); [Oaten et al., 2009](#); [Schaller, 2015](#); [Tybur et al., 2012](#)). However, the literature on the evolution of the emotions has largely neglected the second set of adaptive problems posed by infectious disease—how to fight infection when it occurs.

### 2.2. How to fight infection when it occurs

The innate and acquired immune systems are complex adaptations that evolved to resist infection. The innate immune system generates an early, non-specific immune response (i.e., one that works against multiple types of pathogens) ([Akira et al., 2006](#)). It is highly evolutionarily conserved—strong homologies in innate immunity exist across animal species ([Kimbrell & Beutler, 2001](#)). In endotherms, activation of the innate immune system often generates fever, and ectothermic species often exhibit behavioral fever when the innate immune system is activated (i.e., they seek out warmer microclimates) ([Kluger, Ringler, & Anver, 1975](#); [Rakus, Ronsmans, & Vanderplassen, 2017](#)). The acquired immune system uses immunological memory to generate immune responses targeted at specific pathogens ([Cooper & Alder, 2006](#)). Acquired immune responses are slower-acting but less metabolically costly than innate immune responses ([McDade, Georgiev, & Kuzawa, 2016](#); [Urlacher et al., 2018](#)). Although these systems clearly play a key role in resistance to infection, the fight against infection poses additional adaptive problems that cannot be solved by innate and acquired immune responses alone.<sup>1</sup>

#### 2.2.1. How to fund the high energetic costs of immune responses

Activating the immune system is energetically costly, due to the energetic costs of generating fever, protein synthesis, and the

<sup>1</sup> Not all of the adaptive problems listed here are *problems* in the negative sense. For example, the value of securing social support during infection presented an adaptive *opportunity*—natural selection would have favored adaptations that helped sick individuals take advantage of opportunities to elicit caregiving behavior from social allies.

**Box 1**

## Why “Lassitude”?

We use the term *lassitude* to refer to the hypothesized emotion of being sick. Lassitude is a term no longer in common use, defined by the *Merriam-Webster Online Dictionary* as “a condition of weariness or debility” or “a condition characterized by lack of interest, energy, or spirit” (Definition of LASSITUDE, 2018) (<https://www.merriam-webster.com/dictionary/lassitude>). We use this term to distinguish the emotion of sickness from related constructs, such as fatigue and depression. Although lassitude often generates profound feelings of tiredness, it also includes qualia that are not typical of everyday fatigue, including feelings of vulnerability, reduced appetite, increased pain sensitivity, increased propensity for nausea, and altered perceptions of ambient temperature. Everyday fatigue often subsides following a period of rest or after switching to a more rewarding activity (Hockey, 2013), but lassitude generally persists until the eliciting immune response has subsided. Lassitude shares some of the symptoms of depression (e.g., reduced motivation to pursue activities that are typically rewarding), but unlike depression, lassitude is initiated by cues of infection and recedes following abatement of immune activity (Maes et al., 2012). In addition to its characteristic qualia and time course, lassitude exhibits other core features of an emotion – it is triggered by cues of an adaptive problem (i.e., infection), it orchestrates other mechanisms (e.g., systems that regulate movement and consumption) to help solve this adaptive problem, and it includes distinctive facial and bodily characteristics (e.g., slack facial muscles, drooping eyelids, altered gait) (Axelsson et al., 2018; Sundelin et al., 2015).

**Box 2**

## Components of an energy budget.

**Total Energy Expenditure (TEE)** is the total energy that an individual spends on all life functions (Snodgrass, 2012). The gold standard for measurement of TEE is doubly labeled water in urine samples, which measures rates of isotope elimination (Schoeller et al., 1986). Total energy expenditure scales proportionally to body size. For example, U.S. adults and Hadza forager adults have similar TEE after adjusting for fat-free body mass, despite the fact that the Hadza on average exhibit much higher levels of moderate-to-vigorous physical activity (Pontzer et al., 2015; Raichlen et al., 2017). For most adults, total daily average energy expenditure is between 1500 and 3500 kcal (Pontzer et al., 2016).

**Resting Metabolic Rate (RMR)** is the energy spent to maintain internal physiological functions including the operation of vital organs and somatic maintenance mechanisms. Infection, injury, gestation, and lactation can cause increases in RMR. Resting metabolic rate is typically measured by indirect calorimetry, which usually involves evaluating oxygen consumption or carbon dioxide production via respirometry (Ferrannini, 1988). Under typical circumstances, RMR accounts for about 60–75% of TEE (Pontzer et al., 2016).

**Diet Induced Thermogenesis (DIT)** is the energy that is spent on physiological processes involved in metabolizing food. In other words, DIT reflects the increase in metabolic rate, compared to resting, that is caused by metabolizing food. In order to maintain viability, an individual must, of course, gain more energy from food than they spend on food, but the internal processing of food requires a significant upfront investment. Under typical circumstances, DIT makes up 5–15% of TEE (Westerterp, 2004). Diet induced thermogenesis is typically measured by comparing metabolic rate between fasting and non-fasting states.

**Active energy expenditure (AEE)** is the amount of energy spent on non-resting activity. The primary component of AEE is physical activity, but it also includes energy expenditure on non-volitional processes that occur during non-resting states (e.g., physiological stress responses). Active energy expenditure can be measured indirectly by subtracting RMR and DIT from TEE. It can also be estimated via use of accelerometers, ambulatory heart rate monitors, behavioral observation, or self-report. Active energy expenditure is the most flexible component of human energy budgets, ranging from < 30% to > 350% of daily RMR, though these high extremes of AEE are not sustainable in the long term (Westerterp, 2001; Westerterp, Saris, van Es, & ten Hoor, 1986).

Commonly used estimating equations assume that RMR, DIT, and AEE make up TEE exhaustively, but sometimes these components are further subdivided (Snodgrass, 2012).

production and use of other immune system components (Lochmiller & Deerenberg, 2000; McDade, 2005). The energetic costs of immune-related processes are often estimated by measuring changes in resting metabolic rate (RMR), the amount of energy the body uses to maintain vital functions while at rest) during infection (Box 2). Fever, which often accompanies the innate immune response to acute infection, increases resting energy requirements substantially; for each 1 °C increase in body temperature, RMR increases by about 13% (Del Bene, 1990) and even mild non-febrile respiratory tract infections (e.g., colds) can increase RMR by 8–14% (Muehlenbein, Hirschtick, Bonner, & Swartz, 2010). Treatment with endotoxin, which stimulates the innate immune response, has been reported to increase RMR by an average of 20%, with increases of up to 40% in some cases (Bois, 1921). Among the Tsimane, a forager-horticulturalist population of lowland Bolivia who experience high pathogen burdens, RMR was 18–47% percent higher than expected using standard prediction equations based on non-subsistence, industrialized populations, and elevated leukocytes and helminth (parasitic worm) infection jointly predicted RMRs 10–15% above expected values (Gurven et al., 2016). Along the same lines, Shuar forager-horticulturalist children who inhabit a high-pathogen environment in the Ecuadorian Amazon, exhibit RMRs 20% greater than children from industrial populations (Urlacher et al., 2019), and immune activation over 1, 4, and 12 week periods is associated with reductions

in growth of up to 49% (Urlacher et al., 2018). These findings may underestimate the actual energetic costs of immunity, because they do not account for possible facultative downregulation of physiological investment in other life functions during infection (e.g., reproductive physiology, level of physiological arousal, production of skeletal muscle tissue). Given these high metabolic costs, it would be impossible to sustain immune responses without some substantial increase in energy expenditure or reconfiguration of energy budgets.

Though perhaps an intuitively logical solution, increasing food intake to fund the high metabolic costs of immunity may often be a suboptimal strategy for several reasons:

1. Increasing food intake requires paying the costs (physical, social, ecological, or economic) of obtaining more food.
2. In many environments, increasing one's own food intake may reduce the food available to family members, thereby incurring inclusive fitness costs.
3. Greater food consumption increases the rate of pathogen intake, which further increases the immune system's workload. In some cases, food consumption may also provide energy and nutrients that fuel the reproduction of pathogenic agents.
4. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are molecules produced as a byproduct of cellular metabolism. At

low/moderate levels, ROS and RNS have beneficial effects, including anti-pathogen properties (Valko et al., 2007). However, at high levels, ROS and RNS generate deleterious effects, including cellular damage (ibid). Therefore, increasing total energy expenditure (TEE) to fund immunity may actually interfere with immune function by increasing the production of ROS and RNS. The costs of excessive ROS and RNS production may help explain why human TEE tends to remain within a relatively narrow range for a given body size and does not tend to scale upwards in environments with greater food availability and higher rates of overnutrition (Dugas et al., 2011; Pontzer et al., 2016, 2015). Due to the dose-dependent effects of ROS and RNS, increasing TEE to fund immune responses may often be a counterproductive strategy.

5. Increasing food intake increases the amount of energy spent on diet induced thermogenesis (DIT), which reflects the increase in metabolic rate caused by food consumption. Consuming food may actually *decrease* the proportion of the energy budget that is immediately available for immune function. While consuming more food increases energy availability in the long term, digesting and metabolizing food imposes a short-term energetic cost (5–15% of non-fasting TEE, or even more when consuming high-protein diets) (Westerterp, 2004). The energy cost of human DIT following a meal temporarily elevates metabolic rate by about 20–30%, returning to near pre-meal levels approximately 4–6 h later (Secor, 2009). Thus, there is a period of a few hours post-ingestion when a substantial proportion of metabolic resources are invested on DIT. During active infection, investment in DIT at the cost of immune function may provide a critical window of opportunity for rapidly replicating pathogens to reach a lethal population size. For example, *Vibrio cholerae* and *Staphylococcus aureus* infections in humans are estimated to double in population size approximately every 1 to 2 h (Gibson, Wilson, Feil, & Eyre-Walker, 2018). Therefore, a few hours of greater differential investment in DIT at the cost of immune function could make a major difference in the trajectory of a rapidly replicating infection.

Given the limited utility of increasing food intake and TEE to fund immune function, how do we fund the high metabolic costs of immunity? One potential strategy is to reduce active energy expenditure (AEE), the amount of energy spent on physical activity, thereby making more energy available for immune function. Active energy expenditure is the most flexible component of human energy budgets, ranging from < 30% of RMR in very sedentary individuals (Prentice et al., 1989) to three-week periods of > 350% of RMR in endurance athletes (Westerterp et al., 1986). Although the extremely high levels seen among endurance athletes are not typical, individuals engaged in vigorous physical work exhibit long term AEE levels that are as much as 100% of RMR (Westerterp, 2001). Subsistence agropastoralists sometimes exhibit seasonal AEE levels > 120% of RMR (Kashiwazaki et al., 2009). A recent study of endurance events of varying lengths suggests that AEE of about 150% of BMR is the upper sustainable long-term limit in humans when high-quality food access is not a limitation (Thurber et al., 2019). Given the flexibility of AEE, temporarily reducing AEE during infection may be a feasible strategy for increasing the metabolic resources available to the immune system.

### 2.2.2. How to avoid compounding the immune system's workload

A related adaptive problem is how to avoid acquiring additional pathologies that would increase the burden on the immune system. As discussed in section 2.2.1, activating the immune system to fight infection strains the body's energy budget. It would therefore be particularly risky, when already infected, to contract additional pathologies that compound the workload of the immune system or activate other metabolically costly somatic maintenance mechanisms. Therefore, a key adaptive problem in the fight against infection is how to modify behavior in ways that reflect the greater cost of contracting additional

pathologies when already fighting infection.

### 2.2.3. How to keep body temperature within an optimal range

Another adaptive problem is how to keep body temperature within a range that balances the costs and benefits of fever. Fever enhances the effectiveness of innate immune responses (Boltaña et al., 2013; Kluger et al., 1975) but is energetically expensive and can cause cellular damage (Bois, 1921; Del Bene, 1990; Walter, Hanna-Jumma, Carraretto, & Forni, 2016). A key adaptive problem in the fight against infection, therefore, is how to maintain a body temperature that supports immunity while also keeping the metabolic costs and cellular damage of fever within a manageable range.

### 2.2.4. What to eat (or not eat) to promote immunity

Regulation of food consumption during infection is a particularly complex adaptive problem. Foods that are energetically costly to digest (e.g., high-protein foods) may reduce the metabolic resources that are immediately available to the immune system. Foods that carry a high pathogen risk (e.g., animal products, uncooked foods) may increase the rate of pathogen ingestion, thereby increasing the risk of compounding the immune system's workload. Conversely, some foods may be toxic to pathogens (e.g., honey, bitter plant components), and ingesting them may thus facilitate pathogen elimination. The optimal foods during infection, in terms of toxicity, are those that have a high *differential* toxicity to pathogens (i.e., they are highly toxic to pathogens but minimally toxic to the host). An evolved mechanism that adaptively modulates consumption during infection would need to integrate cues about all of these costs and benefits when evaluating consumption of a particular food type.

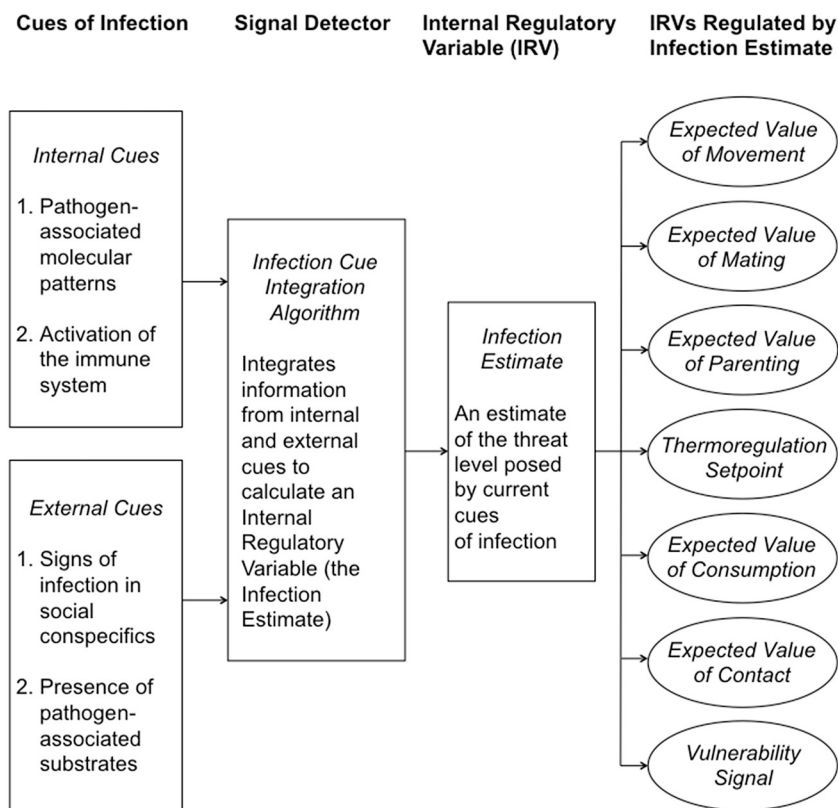
### 2.2.5. How to elicit caregiving behavior from social allies

In addition to adaptations for internally funding the energy required to mount an immune response, another feature that would provide an advantage to those fighting infection would be an ability to secure social support. The ethnographic record shows that human foragers systematically provide care to sick social allies (e.g., providing food to the sick person's household, carrying the sick person when mobile camps move), which is a critical buffer against the fitness costs of illness (Bailey, 1991; Gurven et al., 2000; Hill et al., 2007; Sugiyama, 2004; Sugiyama & Chacon, 2000). The literature on the bioarchaeology of care also provides multiple examples in which there is evidence that individuals survived pathologies that would have been impossible to survive without receiving care from conspecifics (Dickel & Doran, 1989; Tilley & Oxenham, 2011; Trinkaus & Zimmerman, 1982). Thus, an important adaptive problem for humans is how to elicit care from others during infection (see Tooby & Cosmides, 1996 for the logic behind the evolution of systems that cultivate friendships and mutual valuation).

## 3. Lassitude: a coordinating mechanism to fight infection

We propose that lassitude is triggered by cues of active infection and coordinates the fight against infection by initiating a set of strategic regulatory changes that typically include: (a) reducing energetically expensive movement in order to make more energy available to the immune system, (b) reducing the risk of exposure to additional pathologies (infection, injury, poisoning) that would compound the immune system's workload, (c) promoting thermoregulatory behaviors that facilitate immunity, (d) regulating food consumption to be beneficial for the host but detrimental to pathogens, and (e) deploying strategies to elicit caregiving behavior from social allies. These regulatory changes overlap with what has been described as *sickness behavior*, a set of behavioral and psychological phenomena that occur during infection, including reduced locomotion, reduced sexual motivation, altered social behavior, reduced appetite, and increased pain sensitivity (Dantzer & Kelley, 2007; Hart, 2011; Shattuck & Muehlenbein, 2015).





**Fig. 1.** The information-processing structure of lassitude. A signal detector scans for cues of infection and integrates information from internal and external cues to calculate an internal regulatory variable, the Infection Estimate. This internal regulatory variable reflects the threat level posed by current levels of pathogen load. Each motivational system regulated by the Infection Estimate then calibrates its operation to match the current threat level. When threat levels are high, these motivational systems are configured to support the fight against infection. Each motivational system has its own processing algorithm that determines how much to alter its operation in response to the Infection Estimate, based on the estimated benefits (e.g., improved immune function) as well as the costs (e.g., lost opportunities for foraging, feeding, mating, social interaction, parental investment) of altering its operation.

- "Notes"
- 1 Pathogen-associated molecular patterns (PAMPs) and activation of the immune system are not independent cues of infection. When an infection occurs, PAMPs trigger pattern recognition receptors, which, in turn, activate the immune system.
  - 2 External cues of infection risk are not expected to trigger lassitude in the absence of internal cues of infection. Rather, the external cues modify the threshold that internal cues must exceed in order to trigger a given level of lassitude.
  - 3 There are probably relationships between various components of the lassitude system that are not depicted in this figure. For example, the Expected Value of Movement IRV may collect information about the specific locations in

the body where PAMPs are detected in order to avoid particular kinds of movement that would further damage infected or injured tissues

#### 4. The information-processing structure of lassitude

##### 4.1. Cues of infection

For the lassitude program to coordinate the fight against infection, it must be able to detect reliable cues of the threat level posed by current levels of pathogen load (see Fig. 1). These cues fall into two major categories: internal cues (e.g., pathogen-associated molecular patterns, activation of the immune system) and external cues (e.g., signs of infection in social conspecifics, the presence of pathogen-associated substrates).

##### 4.1.1. Internal cues

Pathogen-associated molecular patterns (PAMPs) are molecular characteristics typical of pathogenic organisms (Akira et al., 2006). Specialized immune proteins (e.g., Toll-like receptors) detect PAMPs, and activate different components of the immune system (Akira et al., 2006). Some of these receptors (e.g., Toll-like receptor 4) initiate pro-inflammatory cytokine production when they detect PAMPs (McCusker & Kelley, 2013). Pro-inflammatory cytokines are signaling molecules that are critical mediators of the innate immune response (McCusker & Kelley, 2013). Multiple lines of experimental evidence demonstrate that pro-inflammatory cytokines play a central role in generating behavioral changes during infection (Dantzer, 2004; Johnson, 2002). The causal pathway from PAMPs to pro-inflammatory cytokine production to behavioral change is so reliable that lipopolysaccharides (LPS, molecules found on the outer membranes of gram-negative bacteria) without live bacteria attached are often used in experiments with both human subjects and animal models to study the psychological and behavioral consequences of infection (Dantzer, 2004).

Pro-inflammatory cytokines appear to be necessary for the induction of infection-related behavioral changes (Johnson, 2002). One strain of laboratory mice, C3H/HeJ, has a mutation that prevents them from producing Toll-like receptor 4 in mononuclear phagocytic cells,

which is a pattern recognition receptor that detects several common types of PAMPs and stimulates pro-inflammatory cytokine production (Hoshino et al., 1999). When treated with LPS, these mice do not exhibit infection-related behavioral changes (Segreti, Gheusi, Dantzer, Kelley, & Johnson, 1997). However, when treated with both LPS and the proinflammatory cytokine IL-1 $\beta$ , these mice exhibit infection-related behavior similar to that of wild-type mice with weight loss, reduced food intake, and reduced social exploration (Johnson, Gheusi, Segreti, Dantzer, & Kelley, 1997).

There is evidence of multiple pathways by which the brain detects cytokine production in the body, including active transport of cytokines across the blood-brain barrier, afferent neural signaling, and mediation by circumventricular organs (Dantzer, 2004). For example, a series of studies injected radio-labeled pro-inflammatory cytokines in the peripheral bloodstream and some of the radio-labeled molecules were recovered in the brain, suggesting active transport across the blood brain barrier had occurred (Banks, Kastin, & Gutierrez, 1994; Banks, Ortiz, Plotkin, & Kastin, 1991; Gutierrez, Banks, & Kastin, 1993). Peripheral cytokine production also increases pro-inflammatory cytokine signaling in brain microglia (van Dam, Brouns, Lousse, & Berkenbosch, 1992). Studies in which lab animals were vagotomized suggest there is also a pathway mediated by afferent vagal nerves (Bluthe, Michaud, Kelley, & Dantzer, 1996; Goehler et al., 1999, 1997; Laye et al., 1995). A Fos protein expression mapping study found evidence that circumventricular organs (structures in the brain that are more permeable than the parts of the brain with a blood brain barrier) mediate the effects of peripheral cytokine production on the brain (Konsman, Kelley, & Dantzer, 1999).

This body of evidence suggests that PAMPs and the associated activation of the immune system are good candidates for reliable internal cues of infection that trigger lassitude. All else being equal, higher concentrations of PAMPs indicate greater threats and are therefore expected to trigger stronger lassitude.

#### 4.1.2. External cues

While internal cues are probably the main trigger of lassitude, there are also external cues that provide relevant information about infection-related threats. For example, the presence of sick social conspecifics indicates a greater risk that local pathogen exposures will result in a dangerous infection. For a given level of pathogen load, detecting more cues of infection in others (e.g., sneezing, coughing, vomiting, diarrhea, skin lesions, convalescence, reports of illness) is predicted to trigger stronger lassitude. Consistent with this prediction, one study found that simply seeing cues of infection in images of other people's faces produced more aggressive immune responses when subjects' blood samples were cultured with bacteria (Schaller, Miller, Gervais, Yager, & Chen, 2010). Along the same lines, detecting more cues of pathogen-associated substrates in one's environment is also expected to trigger stronger lassitude. Another study reported that simple exposure to disgust-eliciting images elevated core body temperature and levels of the pro-inflammatory cytokine tumor necrosis factor alpha (TNF $\alpha$ ) (Stevenson et al., 2012). Humans appear to be able to detect cues of illness in the faces, body odors, and gaits of others (Axelsson et al., 2018; Olsson et al., 2014; Sundelin et al., 2015), further supporting the existence of adaptations for assessing the disease risk posed by local exposures. It is worth noting that we do not expect external cues alone to trigger lassitude, as this could be maladaptive, potentially thwarting the active avoidance of infection risks. Rather, external cues modulate the threshold that internal cues must surpass in order to trigger a certain level of lassitude.

#### 4.2. Infection cue integration algorithm

Once various internal and external cues of infection have been detected, an algorithm integrates this information to compute an internal regulatory variable that reflects the threat level posed by current cues of infection (the Infection Estimate). Different cues are assigned different weights – those that are most strongly associated with mortality risk and those that are most reliable are the most heavily weighted. For example, cues of systemic infection are given heavier weights than cues of localized infection, and internal cues are given heavier weights than external cues. The distribution of PAMP recognition receptors throughout the body, along with the multiple pro-inflammatory signaling pathways that operate over different timescales (McCusker & Kelley, 2013), may play a role in helping the brain to determine the location and assess the extent of pathogenic activity.

Evolved signal detection mechanisms are often biased in ways that optimize the tradeoff between false negatives and false positives (Johnson, Blumstein, Fowler, & Haselton, 2013). For defense mechanisms, these tradeoffs are often asymmetrical, with the costs of false negatives being greater than the costs of false positives (Nesse, 2005). In the case of lassitude, the cost of a false negative (failing to activate when an infection is present) is likely much greater than the cost of a false positive (activating when an infection is not present). The former is potentially fatal, whereas the latter inflicts temporary opportunity costs. Thus, it is expected that the infection cue integration algorithm is structured in a way that maintains a low rate of false negatives at the cost of a higher rate of false positives.

#### 4.3. The infection estimate and the parameters it regulates

Once the Infection Estimate is calculated, its computed value is signaled to each of the motivational systems regulated by lassitude. The Infection Estimate does not impose behavioral changes on these systems in an obligate manner. Doing so would result in maladaptive outcomes such as suppressing food intake even though the infected individual is at risk of starvation, suppressing movement even though the infected individual is being pursued by a predator, or signaling vulnerability in the presence of a dangerous, antagonistic individual. To achieve context-sensitive regulation, each motivational system must evaluate the

Infection Estimate in the context of the other information it collects. For example, when the motivational system that regulates hunger detects cues of high starvation risk, a moderate Infection Estimate is expected to have little effect on food consumption. Similarly, a moderate Infection Estimate is predicted to have little effect on the motivational system that regulates movement when this system is also receiving signals of imminent attack by a predator. We therefore hypothesize that each motivational system has its own processing algorithm that determines how much to alter its operation in response to the Infection Estimate, based on the benefits (e.g., improved immune function) as well the costs (e.g., lost opportunities for foraging, feeding, mating, social effort, parental investment) of altering its operation.

##### 4.3.1. Expected value of movement

We hypothesize that one of the primary functions of lassitude is to downregulate engagement in energetically expensive movement in order to make more metabolic resources available to the immune system. We therefore predict that, when values of the Infection Estimate are higher, the average Expected Value of Movement will be lower. We recognize that there is probably not a monolithic motivational system that controls all movement. Rather, movement is likely regulated by multiple hierarchically organized subsystems, many of which draw inputs from other motivational systems (e.g., hunger, sexual desire, injury avoidance). Research has demonstrated that treatment with LPS (which triggers an immune response) reduces locomotion in a variety of species, including cane toads (*Bufo marinus*) (Llewellyn, Brown, Thompson, & Shine, 2011), white-crowned sparrows (*Zonotrichia leucophrys gambelii*) (Owen-Ashley, Turner, Hahn, & Wingfield, 2006), and laboratory rats (*Rattus norvegicus domestica*) (Pezeshki, Pohl, & Schöbitz, 1996). A study of wild red colobus monkeys (*Procolobus rufomitratus tephrosceles*) found that helminth infection was associated with increased resting and reduced engagement in energetically expensive behaviors (Ghai, Fugère, Chapman, Goldberg, & Davies, 2015). Along the same lines, a study of vervet monkeys (*Chlorocebus aethiops*) found that resting time decreased and travel time increased after treatment with deworming medication (Chapman et al., 2016). Bailey reports that, when sick, Efe hunter-gatherer men of the Ituri Forest travel less (0.283 km between half-hour observations vs. 0.423 km) and spend less time hunting (14.4% of observations vs. 22.9%). Experimental studies with schoolchildren who have parasitic infections have found that parasite removal leads to increases in physical activity (Adams, Stephenson, Latham, & Kinoti, 1994; Hadju, Stephenson, Mohammed, Bowman, & Parker, 1998). Other human studies have found that sickness is associated with reports of greater fatigue and subjective low energy (Brydon et al., 2009; Späth-Schwalbe et al., 1998). One study found that, when treated with LPS, zebra finches (*Taeniopygia guttata*) housed in isolation reduced their levels of locomotion but those housed in colonies did not (Lopes, Adelman, Wingfield, & Bentley, 2012). This study illustrates the role of opportunity costs in evaluating whether or not to downregulate movement in response to signals of infection. In this highly social species, it appears that the opportunity costs of downregulating movement in the presence of mates and competitors outweighed the immunological benefits. In a follow-up study, birds in the isolation group (who reduced locomotion) exhibited superior immune function as measured by greater haptoglobin-like activity, improved ability to change body temperature, and improved bacterial killing capacity compared to members of the colony group (who did not reduce locomotion) (Lopes, Springthorpe, & Bentley, 2014). This finding supports the hypothesis that the function of reducing movement during infection is to make more metabolic resources available to the immune system.

The motivation to reduce non-immune energy expenditure during infection may also explain other features of sickness, including increased motivation to sleep (Imeri & Opp, 2009), increased pain sensitivity (Watkins, Goehler, Relton, Brewer, & Maier, 1995; Wegner et al., 2014), and reduced processing on tasks not directly relevant to solving the problem of pathogen elimination (Bucks et al., 2008). Sleep

provides the lowest possible levels of AEE (with the exception of being comatose) and therefore maximizes the amount of energy available for the immune system (Snodgrass, 2012). Increased pain sensitivity may reinforce the motivation to avoid locomotion by making movement more painful than usual. Reduced processing on some tasks may reflect reduced energetic investment in non-critical brain functions in order to prioritize immune function.

#### 4.3.2. Expected value of mating effort

Reproductive effort is a fundamental determinant of an organism's evolutionary fitness, but during infection, energy spent on mating (obtaining mates, retaining them, and having sex) reduces the metabolic resources available for immune function. We expect that, all else being equal, infection downregulates the expected value of mating. All else being equal, female mammals are expected to reduce mating behavior during lassitude to a greater extent than males because female reproductive physiology is much more sensitive to energetic stress and infectious disease increases the risk of spontaneous abortion (Aisemberg et al., 2010; Ellison, 2003). One experiment found that sickness reduced sexual motivation in female, but not male, rats, which supports the prediction of a sex difference in the degree to which mating behavior is sacrificed during infection (Avitsur & Yirmiya, 1999).

The scarcity of mating opportunities is also a relevant variable for determining the opportunity costs of forgoing mating. Signals of infection are predicted to have less effect on the willingness to mate when mating opportunities are rare. In contrast, individuals that have more opportunities to obtain successful matings are expected to exhibit greater reductions in mating behavior during infections. Supporting this prediction, a study found that males of a southern population of a species of wild song sparrow (*Melospiza melodia*), who had a longer breeding season and thus a larger window of time to successfully mate, exhibited less territorial behavior and more lethargy when dosed with LPS compared to two northern populations of the same species, who had shorter breeding seasons (Adelman, Córdoba-Córdoba, Spoelstra, Wikelski, & Hau, 2010). This population difference in sickness behavior was replicated in a study using individuals from the same populations under controlled captive conditions (Adelman, Bentley, Wingfield, Martin, & Hau, 2010). These results suggest that, when mating opportunities are scarce, individuals are less likely to forgo mating opportunities in response to infection. It is worth noting that the Expected Value of Mating Effort that we describe here is very similar to the concept of Expected Sexual Value that has been used in the disgust literature (see Lieberman & Patrick, 2018; Tybur et al., 2012).

#### 4.3.3. Expected value of parenting effort

Another dimension of reproductive effort that conflicts with immunity is parental investment. As with mating, we expect that infection downregulates the average expected value of parenting and that these downregulations are highly sensitive to opportunity costs. One study found that mouse dams (*Mus musculus*) injected with LPS reduced nest-building behaviors at neutral temperatures but did not reduce nest building at critically low temperatures when their offspring's lives were threatened (Aubert, Goodall, Dantzer, & Gheusi, 1997). Another study found that mouse dams exhibited sickness behavior, but it was attenuated by the presence of a virgin male intruder (an individual that poses a threat of infanticide) (Weil, Bowers, Dow, & Nelson, 2006). These findings suggest that the expected value of parental investment responds to signals of infection but is also sensitive to signals of offspring mortality risk. We expect that parenting behaviors with smaller effects on offspring mortality risk (e.g., playing with children) are downregulated to a greater extent during infection than behaviors that have large effects on offspring mortality risk (e.g., protecting children from danger).

#### 4.3.4. Thermoregulation setpoint

During febrile infection in endotherms, the body's thermoregulation setpoint (i.e., target body temperature) is increased and this elevated setpoint is reached through the internal production of pyrogens and other mechanisms such as shivering (Del Bene, 1990; Walter et al., 2016). It is difficult to directly test whether fever in endotherms benefits immunity, because interventions that block fever are also likely to block other key elements of the innate immune response. However, the immunological benefits of fever during infection can be tested in ectotherms by experimentally manipulating ambient temperatures (Kluger, 1979). Many ectotherms exhibit behavioral fever during infection (i.e., they increase body temperature during infection by seeking out warmer locations), which demonstrates that, like endotherms, they have a higher regulatory set point for body temperature during infection (Rakus et al., 2017). Experiments have demonstrated that generating febrile body temperatures during infection reduces mortality rates in multiple species, including desert iguanas (*Dipsosaurus dorsalis*) (Kluger et al., 1975), zebrafish (*Danio rerio*) (Boltaña et al., 2013), and newborn mice, which are practically ectothermic when they are born (Teisner & Haahr, 1974).

Behavioral efforts to increase body temperature during infection are not exclusive to ectotherms. For example, a study of free-living greater kudu (*Tragelaphus strepsiceros*) found that, when infected with bacterial pneumonia, the animals preferentially inhabited warmer microclimates (Hetem et al., 2008). Internal generation of fever is highly energetically costly, so low-cost behaviors that reduce the metabolic costs of fever are likely to be favored. The sensation of chills during febrile infection probably reflects a motivational state that functions to promote warmth-seeking behaviors. Humans have additional strategies at their disposal to reduce the energetic costs of generating and maintaining a higher body temperature such as the use of heat sources (e.g., fire) (Hlubik et al., 2019; James et al., 1989) and insulation technologies (e.g., clothing) (Toups, Kitchen, Light, & Reed, 2010). We predict that, when thermoregulatory setpoints are elevated, humans make use of these thermoregulatory strategies with greater frequency. In addition, we expect that thermoregulatory consequences are taken into account when evaluating other behaviors. For example, a sick individual may be highly motivated to seek contact with close social allies, but if they have to expose themselves to cold in order to pursue this contact, they may be dissuaded from doing so.

#### 4.3.5. Expected value of consumption

One of the central adaptive problems posed by infection is how to regulate food consumption in ways that are good for the host but detrimental to pathogens. We expect that infection decreases the expected value of consuming foods that are energetically expensive to digest because the more energy that is spent on digesting food, the less is available for immune function. Consistent with this prediction, one study found that sick rats increased the proportion of carbohydrates consumed relative to proteins (proteins are more expensive to digest) (Aubert, Goodall, & Dantzer, 1995).

We predict that signals of infection increase the expected value of consuming items that have anti-pathogen qualities (see also Lieberman & Patrick, 2018). In support of this prediction, a study of red colobus monkeys found that parasite infection was associated with a greater frequency of consuming plants that the local human population use for their medicinal effects (Ghai et al., 2015). Medicinal consumption of leaves and bitter pith has been reported among the African great apes (gorillas, chimpanzees, bonobos) (Huffman, 1997). Nicotine has been hypothesized to have anti-parasitic effects (Hagen, Roulette, & Sullivan, 2013), and an experiment among Aka forager men in central Africa found that treatment with an anti-parasitic medication (Albendazole) reduced tobacco use as measured by salivary levels of cotinine, a nicotine metabolite (Roulette et al., 2014). This effect was stronger in those with greater infection burdens at baseline. The antibiotic effects of honey have been demonstrated in vitro, and many cultures around



the world value honey for its medicinal effects (Mandal & Mandal, 2011). It is both ingested to treat internal infections and applied to external wounds to prevent and treat cutaneous infections (Bailey, 1991; Mandal & Mandal, 2011). Honey has the added benefit of being relatively inexpensive to digest because its primary macronutrient is sugar. Bailey reports that Efe hunter-gatherers are highly motivated to obtain honey when infected or wounded (Bailey, 1991). Although sick Efe men spend less time hunting and travel less when sick, they spend more time pursuing honey (13.6% of observations vs. 10.4%).

We hypothesize that infection reduces the overall expected value of calorie intake. The benefits of reduced calorie intake during infection are twofold: (1) reducing DIT increases the metabolic resources available to the immune system, and (2) reducing food intake during infection reduces the risk of acquiring additional pathogens that would compound the immune system's workload. It is worth noting that, in humans, average DIT may be higher in subsistence populations, due to a relative scarcity of highly processed, energy dense foods. Reduced calorie intake and/or a reduced motivation to eat during infection have been reported in a variety of species, including humans (Shattuck & Muehlenbein, 2015). We expect that this effect is strongly conditional upon the energetic state of the body. The regulatory algorithm that controls the expected value of calorie intake must balance the immunological benefits of reduced calorie intake against the risk of starvation. Only individuals that have sufficient energy reserves (e.g., glycogen, fat) to sustain immune function are expected to reduce calorie intake during infection. This effect is illustrated by a study reporting that rats who had been feeding ad libitum exhibited low levels of calorie intake after treatment with LPS, rats that had been calorie-restricted for 28 days exhibited relatively high levels of calorie intake, even after treatment with LPS, and rats that had been calorie restricted for 14 and 21 days exhibited intermediate levels of calorie intake after treatment with LPS (MacDonald, Hazi, Paolini, & Kent, 2014).

In order to test whether reduced food intake during infection provides a benefit to the host, one study infected mice with the bacteria *Listeria monocytogenes* and measured survival and mortality in two experimental groups: one was force-fed to a normal level of energy intake and the other group was allowed to feed ad libitum and therefore exhibited the low levels of food intake typical of infected animals (Murray & Murray, 1979). The force-fed group exhibited substantially higher levels of mortality and shorter survival times.

Even fasting shortly before the onset of infection may improve immunocompetence by upregulating the metabolic resources available for anticipatory immune defenses. One set of experiments found that mice subjected to 24–72 h of food deprivation before inoculation with *Listeria monocytogenes* exhibited lower mortality rates compared to mice that were allowed to feed freely prior to inoculation (Wing & Young, 1980). A study of human participants who were obese at baseline (and therefore had substantial metabolic reserves) found that natural killer cell cytolytic activity and blood monocyte bactericidal activity were enhanced after a 14-day fast (compared to before the fast) which suggests that there is a physiological tradeoff between food metabolism and some aspects of innate immune function (Wing, Stanko, Winkelstein, & Adibi, 1983). Taken together, these findings suggest that reduced food intake during, or even shortly before, infection provides a direct immunological benefit to the host.

Finally, we predict that, in humans, signals of infection reduce the expected value of consuming foods with an elevated risk of carrying pathogens, such as uncooked foods or animal products. Infection may also increase the relative expected value of foods that carry a low risk of transmitting pathogens, such as salted foods or familiar foods that have not caused disease in past experience. We are not aware of any published studies that have tested these predictions.

#### 4.3.6. Expected value of contact

One cost of contact with other individuals during infection is that they may be vectors for additional pathogens that would compound the

immune system's workload. On the other hand, contact with social allies during illness may have certain benefits (e.g., increasing the probability of receiving care, deterring potential predators and antagonists). As reviewed in section 2.2.5, receiving care during illness is a critical buffer against pathology-related mortality in humans. We predict that infection increases the relative expected value of contact with trusted allies that are likely to provide care or protection, and infection decreases the expected value of contact with strangers and antagonists that might take advantage of the sick person's vulnerable state. Within the category of social allies, there may be other variables (e.g., degree of genetic relatedness, the ally's vulnerability to illness) that further modulate the expected value of contact.

#### 4.3.7. Vulnerability signal

We hypothesize that sick individuals boost signals of vulnerability in the presence of social allies that are likely to provide care but mask these signals in the presence of strangers and antagonists (Steinkopf, 2015; Tiokhin, 2016). Potential components of an infection-induced vulnerability signal include overt signs of infection, changes in facial expressions, changes in body language, and behavior indicative of fatigue, sadness, and pain. Experiments with animal models support the hypothesis that sick individuals mask signs of sickness when in the presence of potentially threatening individuals. For example, rhesus macaques (*Macaca mulatta*) exhibit increased somnolence when sick, but this effect is abolished when a human researcher makes eye contact with the sick monkey (Friedman, Reyes, & Coe, 1996). A study of mice found that, when males are housed in dyads, dominant individuals reduce their frequency of social behavior when sick, but subordinate individuals do not (Cohn & de Sá-Rocha, 2006). This suggests that a key variable for determining whether or not to mask signs of sickness is the threat level posed by other individuals. Other dimensions of aid-eliciting strategies may include reminding potential helpers of instances in the past when roles were reversed, extending perceived benefits to the potential helper (e.g., attention, material goods, sexual access), alerting other in-group members about one's illness in order to amplify the reputational effects of helping (or refusing to help), and appealing to the potential helper's sense of social interdependence or kinship.

#### 4.4. Summary

An infection cue integration algorithm detects internal and external cues of infection and integrates this information to compute an internal regulatory variable, the Infection Estimate. The Infection Estimate represents the threat level posed by the current level of pathogen load. The value of the Infection Estimate is signaled to each motivational system that is regulated by lassitude. When the threat level is high, these motivational systems are configured in ways that support the fight against infection. Each motivational system has its own processing algorithm that determines whether and how much to alter its operation, based on the value of the Infection Estimate as well as the other costs and benefits of altering its operation. Some of the motivational changes induced by lassitude have multiple benefits for resisting infection. For example, reduced food intake during infection both reduces DIT (thereby making more energy immediately available to the immune system) and reduces the risk of acquiring additional pathogens that would compound the immune system's workload. Increased pain sensitivity both suppresses energetically expensive movement and reduces the risk of acquiring injuries that would activate energetically costly repair mechanisms.

Cultural contexts likely influence the operation of lassitude. For example, in some cultural contexts it may be particularly socially costly to signal vulnerability, especially for men (Gilmore, 1990). We expect that sick individuals in these cultures will mask infection-induced signals of vulnerability to a greater extent than those in other cultures. We also expect that the brain encodes culturally transmitted information about the medicinal value of particular foods or plants (Eyssartier,



Radio, & Lozada, 2008). When threat levels are high, the stored information about the item's value is retrieved by the motivational system that regulates consumption and the expected value of consuming items encoded as having high medicinal value increases.

The immune system is sensitive to inputs from developmental environments (McDade, 2012; McDade et al., 2016). We expect that lassitude also exhibits developmental reaction norms. We predict that, when individuals are exposed to developmental cues that signal a high risk of pathogen-related mortality, their lassitude response will develop to be triggered more easily and will deploy more intense lassitude for a given level of pathogen load. We expect developmental cues of nutritional stress to have the opposite effects on the calibration of lassitude because one of the major costs of activating lassitude is the increased risk of starvation-related morbidity and mortality.

This paper focuses on lassitude in response to infectious disease. Other pathologies, such as injury, poisoning, and chronic degenerative disease, present many of the same adaptive problems as infection. However, there are important differences that likely influence how lassitude is deployed in response to these other pathologies. For example, in response to localized injuries, additional measures (e.g., increased local pain sensitivity) may be deployed to reduce the risk of further damaging the injured tissues. For pathologies that are caused by particular nutritional deficiencies (e.g., some kinds of anemia), we predict that the expected value of consuming foods that would alleviate the deficiency is strongly upregulated. Future work should include efforts to outline the functional logic and information-processing structure of lassitude in response to non-infectious pathologies.

## 5. Lassitude: a new emotion?

Our approach to characterizing lassitude is informed by Tooby and Cosmides' framework: “[the emotions] are the neurocomputational adaptations that have evolved in response to the adaptive problem of matching arrays of mechanism activation to the specific adaptive demands imposed by alternative situations” (Tooby & Cosmides, 2008, p. 117). Lassitude satisfies this definition of an emotion. It is a coordinating system that functions to orchestrate various mechanisms to solve the adaptive problem of fighting infectious disease.

Other theoretical approaches emphasize the distinctive facial expression and qualia of an emotion (Ekman & Oster, 1979; Frijda, 2005). We propose that lassitude has a distinctive facial expression generated by less muscle tension relative to a neutral facial expression (i.e., slack facial muscles). In particular, it consists of a long crown-to-chin length, drooping eyelids, and slightly parted lips. A recent study showed participants pictures of faces of people who had been injected with LPS or with placebo (Axelsson et al., 2018). Participants correctly identified the faces of sick people at a higher rate than chance, even though individuals in the photos were instructed to exhibit a neutral facial expression, which may have resulted in partial masking of the facial expression of lassitude. The faces of sick people were rated as having droopy corners of the mouth, having hanging eyelids, looking more tired, having redder eyes, and having paler, puffier skin. We propose that lassitude also has distinct qualia – profound tiredness, greater relative preference for close social allies, reduced overall appetite but stronger relative preference for particular food items, greater feelings of vulnerability, increased pain sensitivity, greater susceptibility to nausea, and altered perceptions of ambient temperature. Not all of these qualia are present in all cases of infection – the presence of each component depends on context-sensitive regulation of the underlying motivational system.

Panksepp's account of basic emotions emphasizes universality across species of mammals and conserved neural circuitry (Panksepp, 1982). Lassitude involves specific immune and neural signaling pathways that have been mapped with increasing thoroughness in animal models (McCusker & Kelley, 2013). Lassitude-like regulatory states exist not only in mammals but also birds (Owen-Ashley & Wingfield,

2007), amphibians (Llewellyn et al., 2011), and possibly even fish (Kirsten, Fior, Kreutz, & Barcellos, 2018).

Based on the criteria discussed here, lassitude is an emotion, albeit one that has gone unrecognized. It is worth noting that there are at least two ways in which our account of lassitude is not novel. First, Tooby and Cosmides hypothesized that malaise during infection might be an evolved emotion but did not elaborate (Tooby & Cosmides, 2008). Second, scholars who study sickness behavior, focusing mostly on non-humans, have proposed that many infection-induced behavioral changes are evolutionarily adaptive (Adelman & Martin, 2009; Hart, 1990). However, the sickness behavior literature largely focuses on the description of infection-related behavior and its physiological mechanisms. It has largely neglected to characterize the evolutionary background, information-processing structure, and functional logic of the regulatory system that generates sickness behavior.

## 6. Directions for future research

### 6.1. Social support and immunity

Humans provide care to social allies during illness and injury (see section 2.2.5). This is an important buffer against the opportunity costs of reducing movement when sick. A compelling hypothesis to explain the placebo effect is that one function of visible illness symptoms is to elicit care from others (Steinkopf, 2015). When others provide care, the signaling function of the symptoms is fulfilled and the symptoms become less severe (ibid). We predict that cues of social support (or a lack thereof) are also key inputs for modulating the regulation of lassitude during infection. Infected individuals who are socially isolated may be unable to afford to devote as much energy to fighting infection, and may therefore experience longer-lasting infections and higher mortality risks. In support of this hypothesis, there is evidence to suggest that those who are socially isolated tend to suffer from poorer health (Cacioppo & Cacioppo, 2014).

### 6.2. Lassitude in healthcare settings

We hypothesize that cues of infection increase the relative preference for contact with social allies. Furthermore, we propose that sick individuals boost signals of vulnerability when in the presence of social allies (in order to elicit care) and mask signals of vulnerability in front of strangers and antagonists (in order to reduce the risk of social and physical danger during the vulnerable state of sickness). This suggests that the degree to which a patient sees a healthcare provider as a social ally may have a major influence on a patient's decision to pursue care, and ability to elicit it.

Patients who do not see providers as social allies may be less likely to seek healthcare, and when they do, may have greater difficulty eliciting useful care, due to the fact that they are (perhaps inadvertently) masking signals of vulnerability. This may help explain why many patients highly value good “bedside manner” in healthcare providers (Thompson & Anderson, 1982).

### 6.3. Lassitude and chronic disease

There is evidence to suggest that chronic diseases (e.g., heart disease, diabetes, chronic obstructive pulmonary disorder) may activate a response that resembles a chronic version of lassitude (Swain, 2000). This may be due, in part, to the fact that chronic somatic damage activates some of the same pro-inflammatory immune pathways that trigger lassitude during infection (Del Giudice & Gangestad, 2018; McCusker & Kelley, 2013). This poses a problem because one of most effective interventions for preventing and treating chronic disease is to engage in healthy levels of physical activity (Warburton, Nicol, & Bredin, 2006). The motivational state of lassitude directly opposes this goal. Thus, even sub-clinical levels of chronic morbidity may trigger a

vicious, self-reinforcing cycle in which greater chronic morbidity leads to greater lassitude, and greater lassitude leads to even greater chronic morbidity. This cycle may help explain why chronic disease epidemics emerge when populations transition to economic sectors with a greater proportion of sedentary occupations (Omran, 2005).

#### 6.4. Lassitude in relation to time, reward, and risk preferences

We hypothesize that lassitude modifies the cost-benefit structure of a wide range of decisions. Individuals in a state of lassitude place a lower value on some types of rewards (e.g., food, sex). Higher levels of lassitude may therefore generate a greater willingness to delay some kinds of payoffs in temporal discounting scenarios (Green, Myerson, & Mcfadden, 1997). We also propose that individuals in a state of lassitude place a greater value on avoiding social and physical risks. Thus, lassitude may induce greater risk aversion when the risks are social or physical. On the other hand, lassitude may induce *less* aversion to the risk of losing a potential payoff that has lower value during lassitude (e.g., food, sex). Researchers who study time-, reward-, and risk-related decision-making should therefore consider incorporating lassitude into their studies and theoretical models.

#### 6.5. Approach-avoidance conflict

The fact that humans systematically help social allies during illness suggests that we have cognitive mechanisms for detecting signs of illness in others and deciding how to respond. The occurrence of illness in a social conspecific poses a potential motivational conflict. On one hand, helping the sick individual may induce the target of aid to reciprocate in the future, when the roles are reversed (Gurven et al., 2000; Sugiyama, 2004; Sugiyama & Chacon, 2000). Furthermore, helping sick individuals provides a costly signal of the helper's quality as a social ally (Steinkopf, 2015). On the other hand, the effort required for providing aid is costly, and providing aid to a sick person may increase the helper's risk of getting sick (Tybur et al., 2012). Thus, navigating the motivational conflict between approaching a sick individual (to help them) and avoiding them (to reduce infection risk) is an important adaptive problem for humans. Variables that influence the decision to help or avoid a sick person may include the relationship/kinship of the sick person to the helper, the sick person's reputation as a reciprocator, the helper's vulnerability to illness, and the social audience that would be aware of the helping behavior.

## 7. Conclusions

In this paper, we develop a theoretical account of lassitude as an emotion that coordinates the fight against infection. We review evidence suggesting that a signal detection system monitors cues of infection and integrates this information to estimate the threat level posed by current levels of pathogen load. When threat levels are high, the system sends a signal to various motivational systems, configuring them in ways that facilitate effective immunity and pathogen clearance. Each motivational system has its own processing algorithm that determines how much to alter its operation in response to infection threat signals, based on the direct benefits (e.g., improved immune function) as well the costs (e.g., lost opportunities for foraging, parenting, mating) of altering its operation. The deployment of lassitude typically involves a variety of strategic regulatory changes, including (a) reducing energetically expensive movement in order to make more energy available to the immune system, (b) reducing exposure to additional pathologies that would compound the immune system's workload, (c) promoting thermoregulatory behaviors that facilitate immunity, (d) regulating food consumption to be beneficial for the host but detrimental to pathogens, and (e) deploying strategies to elicit caregiving behavior from social allies. Lassitude exhibits the characteristics often used to define emotions: it is triggered by cues of a particular adaptive

problem, coordinates other mechanisms to address this problem, is phylogenetically conserved, has a distinct facial expression, and has specific qualia.

Most of the existing research on behavioral and psychological changes during infection appears in the literature on sickness behavior (Dantzer, 2004; Dantzer & Kelley, 2007; Hart, 1990; McCusker & Kelley, 2013). This literature, which has mostly focused on non-human animals, has been very effective in demonstrating that sickness behavior is a reliably occurring phenomenon (Dantzer & Kelley, 2007; Shattuck & Muehlenbein, 2015), showing that sickness behavior is regulated in a context-sensitive manner (Adelman & Martin, 2009; Lopes, 2014), and characterizing the physiological mechanisms that generate sickness behavior (Johnson, 2002; McCusker & Kelley, 2013). However, the sickness behavior literature has largely neglected to elaborate the evolutionary background, information-processing structure, and functional logic of the regulatory system that coordinates these changes. The literature on the evolution of the emotions has invested considerable effort on characterizing the psychological architecture of adaptations to prevent infectious disease in humans (i.e., pathogen avoidance-disgust/the behavioral immune system) (Curtis et al., 2011; Lieberman & Patrick, 2018; Murray et al., 2019; Oaten et al., 2009; Schaller, 2015; Tybur et al., 2012) but has largely neglected the question of what we do when infection occurs. In this paper, we extend and integrate these two literatures by developing a theoretical account of the evolved system that coordinates the fight against infection (i.e., the emotion of lassitude) and reviewing the existing evidence. We believe that investigating the information-processing structure of lassitude will contribute to a more complete understanding of sickness behavior, much like the information-processing structure of hunger helps us understand feeding behavior (Al-Shawaf, 2016).

Lassitude is phylogenetically ancient (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015), but we propose that lassitude interacts synergistically with several specific human adaptations in ways that substantially reduce infection-related mortality. Human foragers systematically provide one another with aid during illness (e.g., providing food to the sick person's family, carrying the sick person when mobile camps move) (Gurven et al., 2000; Hill et al., 2007; Sugiyama, 2004). This is a critical buffer against the costs of reducing energetically expensive movement when sick. Humans also possess adipose tissue deposits that are proportionally larger than other primates (Altmann, Schoeller, Altmann, Muruthi, & Sapolsky, 1993; Dittus, 2013; Kuzawa, 1998; Sherry & Marlowe, 2007; Wells, 2012). This allows humans to exhibit greater reductions in food intake for longer periods of time during infection than would otherwise be possible. Human foragers possess sophisticated technologies that allow them to efficiently acquire and process high quality foods (Ambrose, 2001; Wrangham, Jones, Laden, Pilbeam, & Conklin-Brittain, 1999). Our ancestors could therefore acquire enough surplus calories to provide aid to sick individuals and deposit large adipose tissue reserves. Finally, unique thermoregulatory innovations (e.g., control of fire, clothing) (Hlubik et al., 2019; James et al., 1989; Toups et al., 2010) allow humans to reduce the metabolic costs of generating and maintaining fever. Thus, lassitude may dovetail with social sickness aid, large fat reserves, high-quality diets, and thermoregulatory innovations to substantially reduce infection-related mortality in humans. This reduction in mortality may help explain our longevity, demographic success, and ability to thrive in high-pathogen environments.

#### Declarations of Competing Interest

None.

#### Funding

There were no specific grants that supported this research.

## Acknowledgements

We thank Dr. Debra Lieberman for her insightful comments and suggestions on earlier versions of this paper. We are grateful to the reviewers for their thoughtful and detailed reviews.

## References

- Adams, E. J., Stephenson, L. S., Latham, M. C., & Kinoti, S. N. (1994). Physical activity and growth of Kenyan school children with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved after treatment with albendazole. *The Journal of Nutrition*, 124(8), 1199–1206.
- Adelman, J. S., Bentley, G. E., Wingfield, J. C., Martin, L. B., & Hau, M. (2010). Population differences in fever and sickness behaviors in a wild passerine: A role for cytokines. *Journal of Experimental Biology*, 213(23), 4099–4109. <https://doi.org/10.1242/jeb.049528>.
- Adelman, J. S., Córdoba-Córdoba, S., Spoelstra, K., Wikelski, M., & Hau, M. (2010). Radiotelemetry reveals variation in fever and sickness behaviours with latitude in a free-living passerine. *Functional Ecology*, 24(4), 813–823.
- Adelman, J. S., & Martin, L. B. (2009). Vertebrate sickness behaviors: Adaptive and integrated neuroendocrine immune responses. *Integrative and Comparative Biology*, 49(3), 202–214. <https://doi.org/10.1093/icb/0028>.
- Aisemberg, J., Vercelli, C., Wolfson, M., Salazar, A. I., Osycka-Salut, C., Billi, S., ... Franchi, A. M. (2010). Inflammatory agents involved in septic miscarriage. *Neuroimmunomodulation*, 17(3), 150–152. <https://doi.org/10.1159/000258710>.
- Akira, S., Uematsu, S., & Takeuchi, O. (2006). Pathogen recognition and innate immunity. *Cell*, 124(4), 783–801. <https://doi.org/10.1016/j.cell.2006.02.015>.
- Al-Shawaf, L. (2016). The evolutionary psychology of hunger. *Appetite*, 105, 591–595. <https://doi.org/10.1016/j.appet.2016.06.021>.
- Altmann, J., Schoeller, D., Altmann, S. A., Muruthi, P., & Sapolsky, R. M. (1993). Body size and fitness of free-living baboons reflect food availability and activity levels. *American Journal of Primatology*, 30(2), 149–161. <https://doi.org/10.1002/ajp.1350300207>.
- Ambrose, S. H. (2001). Paleolithic technology and human evolution. *Science*, 291(5509), 1748–1753. <https://doi.org/10.1126/science.1059487>.
- Aubert, A., Goodall, G., & Dantzer, R. (1995). Compared effects of cold ambient temperature and cytokines on macronutrient intake in rats. *Physiology & Behavior*, 57(5), 869–873. [https://doi.org/10.1016/0031-9384\(94\)00391-H](https://doi.org/10.1016/0031-9384(94)00391-H).
- Aubert, A., Goodall, G., Dantzer, R., & Gheusi, G. (1997). Differential effects of lipopolysaccharide on pup retrieving and nest building in lactating mice. *Brain, Behavior, and Immunity*, 11(2), 107–118.
- Avitsur, R., & Yirmiya, R. (1999). The immunobiology of sexual behavior: Gender differences in the suppression of sexual activity during illness. *Pharmacology Biochemistry and Behavior*, 64(4), 787–796.
- Axelsson, J., Sundelin, T., Olsson, M. J., Sorjonen, K., Axelsson, C., Lasselin, J., & Lekander, M. (2018). Identification of acutely sick people and facial cues of sickness. *Proceedings of the Royal Society B: Biological Sciences*, 285(1870), 20172430.
- Bailey, R. C. (1991). *The behavioral ecology of Efe pygmy men in the Ituri Forest, Zaire*. Ann Arbor, Mich: Museum of Anthropology, University of Michigan.
- Banks, W. A., Kastin, A. J., & Gutiérrez, E. G. (1994). Penetration of interleukin-6 across the murine blood-brain barrier. *Neuroscience Letters*, 179(1), 53–56. [https://doi.org/10.1016/0304-3940\(94\)90933-4](https://doi.org/10.1016/0304-3940(94)90933-4).
- Banks, W. A., Ortiz, L., Plotkin, S. R., & Kastin, A. J. (1991). Human interleukin (IL) 1 alpha, murine IL-1 alpha and murine IL-1 beta are transported from blood to brain in the mouse by a shared saturable mechanism. *Journal of Pharmacology and Experimental Therapeutics*, 259(3), 988–996.
- Blurton Jones, N. G., Hawkes, K., & O'Connell, J. F. (2002). Antiquity of postreproductive life: Are there modern impacts on hunter-gatherer postreproductive life spans? *American Journal of Human Biology*, 14(2), 184–205. <https://doi.org/10.1002/ajhb.10038>.
- Bluthe, R.-M., Michaud, B., Kelley, K. W., & Dantzer, R. (1996). Vagotomy blocks behavioural effects of interleukin-1 injected via the intraperitoneal route but not via other systemic routes. *NeuroReport*, 7(15), 2823.
- Bois, E. F. (1921). The basal metabolism in fever. *JAMA: The Journal of the American Medical Association*, 77(5), 352–357. <https://doi.org/10.1001/jama.1921.02630310022006>.
- Boltaña, S., Rey, S., Roher, N., Vargas, R., Huerta, Huntingford, F. A., ... MacKenzie, S. (2013). Behavioural fever is a synergistic signal amplifying the innate immune response. *Proceedings of the Royal Society B: Biological Sciences*, 280(1766), 20131381. <https://doi.org/10.1098/rspb.2013.1381>.
- Brinkworth, J. F., & Pechenkina, K. (2013). *Primates, pathogens, and evolution*. Springer Science & Business Media.
- Brydon, L., Walker, C., Wawrzyniak, A., Whitehead, D., Okamura, H., Yajima, J., ... Steptoe, A. (2009). Synergistic effects of psychological and immune stressors on inflammatory cytokine and sickness responses in humans. *Brain, Behavior, and Immunity*, 23(2), 217–224. <https://doi.org/10.1016/j.bbi.2008.09.007>.
- Bucks, R. S., Gidron, Y., Harris, P., Teeling, J., Wesnes, K. A., & Perry, V. H. (2008). Selective effects of upper respiratory tract infection on cognition, mood and emotion processing: A prospective study. *Brain, Behavior, and Immunity*, 22(3), 399–407. <https://doi.org/10.1016/j.bbi.2007.09.005>.
- Cacioppo, J. T., & Cacioppo, S. (2014). Social relationships and health: The toxic effects of perceived social isolation. *Social and Personality Psychology Compass*, 8(2), 58–72.
- Chapman, C. A., Friant, S., Godfrey, K., Liu, C., Sakar, D., Schoof, V. A., ... Goldberg, T. L. (2016). Social behaviours and networks of vervet monkeys are influenced by gastrointestinal parasites. *PLoS One*, 11(8), e0161113.
- Cohn, D. W. H., & de Sá-Rocha, L. C. (2006). Differential effects of lipopolysaccharide in the social behavior of dominant and submissive mice. *Physiology & Behavior*, 87(5), 932–937. <https://doi.org/10.1016/j.physbeh.2006.02.011>.
- Cooper, M. D., & Alder, M. N. (2006). The evolution of adaptive immune systems. *Cell*, 124(4), 815–822. <https://doi.org/10.1016/j.cell.2006.02.001>.
- Curtis, V., de Barra, M., & Aunger, R. (2011). Disgust as an adaptive system for disease avoidance behaviour. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, 366(1563), 389–401. <https://doi.org/10.1098/rstb.2010.0117>.
- D'Anastasio, R., Zipfel, B., Moggi-Cecchi, J., Stanyon, R., & Capasso, L. (2009). Possible brucellosis in an early hominin skeleton from Sterkfontein, South Africa. *PLoS One*, 4(7), e6439. <https://doi.org/10.1371/journal.pone.0006439>.
- Dantzer, R. (2004). Cytokine-induced sickness behaviour: A neuroimmune response to activation of innate immunity. *European Journal of Pharmacology*, 500(1–3), 399–411. <https://doi.org/10.1016/j.ejphar.2004.07.040>.
- Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, 21(2), 153–160.
- Definition of LASSITUDE (2018). Retrieved October 29, 2018, from <https://www.merriam-webster.com/dictionary/lassitude>.
- Del Bene, V. E. (1990). Temperature. In H. K. Walker, W. D. Hall, & J. W. Hurst (Eds.). *Clinical methods: The history, physical, and laboratory examinations* (3rd ed.). Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK331/>.
- Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, Behavior, and Immunity*, 70, 61–75.
- Deschamps, M., Laval, G., Fagny, M., Itan, Y., Abel, L., Casanova, J.-L., ... Quintana-Murci, L. (2016). Genomic signatures of selective pressures and introgression from archaic hominins at human innate immunity genes. *The American Journal of Human Genetics*, 98(1), 5–21. <https://doi.org/10.1016/j.ajhg.2015.11.014>.
- Dickel, D. N., & Doran, G. H. (1989). Severe neural tube defect syndrome from the early archaic of Florida. *American Journal of Physical Anthropology*, 80(3), 325–334. <https://doi.org/10.1002/ajpa.1330800306>.
- Dittus, W. P. J. (2013). Arboreal adaptations of body fat in wild toque macaques (*Macaca sinica*) and the evolution of adiposity in primates. *American Journal of Physical Anthropology*, 152(3), 333–344. <https://doi.org/10.1002/ajpa.22351>.
- Dugas, L. R., Harders, R., Merrill, S., Ebersole, K., Shoham, D. A., Rush, E. C., ... Luke, A. (2011). Energy expenditure in adults living in developing compared with industrialized countries: A meta-analysis of doubly labeled water studies. *The American Journal of Clinical Nutrition*, 93(2), 427–441. <https://doi.org/10.3945/ajcn.110.007278>.
- Early, J. D., & Headland, T. N. (1998). *Population dynamics of a Philippine rain forest people: The San Ildefonso Agta*. University Press of Florida.
- Ekman, P., & Oster, H. (1979). Facial expressions of emotion. *Annual Review of Psychology*, 30(1), 527–554.
- Ellison, P. T. (2003). Energetics and reproductive effort. *American Journal of Human Biology*, 15(3), 342–351. <https://doi.org/10.1002/ajhb.10152>.
- Ewald, P. W. (1994). *Evolution of infectious disease*. Oxford University Press on Demand.
- Eyssartier, C., Ladio, A. H., & Lozada, M. (2008). Cultural transmission of traditional knowledge in two populations of North-Western Patagonia. *Journal of Ethnobiology and Ethnomedicine*, 4(1), 25.
- Ferrannini, E. (1988). The theoretical bases of indirect calorimetry: A review. *Metabolism*, 37(3), 287–301. [https://doi.org/10.1016/0026-0495\(88\)90110-2](https://doi.org/10.1016/0026-0495(88)90110-2).
- Friedman, E. M., Reyes, T. M., & Coe, C. L. (1996). Context-dependent behavioral effects of interleukin-1 in the rhesus monkey (*Macaca mulatta*). *Psychoneuroendocrinology*, 21(5), 455–468. [https://doi.org/10.1016/0306-4530\(96\)00010-8](https://doi.org/10.1016/0306-4530(96)00010-8).
- Frijda, N. (2005). Emotion experience. *Cognition & Emotion*, 19(4), 473–497.
- Georgiev, A. V., Kuzawa, C. W., & McDade, T. W. (2016). Early developmental exposures shape trade-offs between acquired and innate immunity in humans. *Evolution, Medicine, and Public Health*, 2016(1), 256–269. <https://doi.org/10.1093/emph/eow022>.
- Ghai, R. R., Fugère, V., Chapman, C. A., Goldberg, T. L., & Davies, T. J. (2015). Sickness behaviour associated with non-lethal infections in wild primates. *Proceedings of the Royal Society B: Biological Sciences*, 282(1814), <https://doi.org/10.1098/rspb.2015.1436>.
- Gibson, B., Wilson, D. J., Feil, E., & Eyre-Walker, A. (2018). The distribution of bacterial doubling times in the wild. *Proceedings of the Royal Society B: Biological Sciences*, 285(1880), 20180789.
- Gilmore, D. D. (1990). *Manhood in the making: Cultural concepts of masculinity*. Yale University Press.
- Goehler, L. E., Gaykema, R. P. A., Nguyen, K. T., Lee, J. E., Tilders, F. J. H., Maier, S. F., & Watkins, L. R. (1999). Interleukin-1<sup>α</sup> in immune cells of the abdominal vagus nerve: A link between the immune and nervous systems? *Journal of Neuroscience*, 19(7), 2799–2806.
- Goehler, L. E., Relton, J. K., Dripps, D., Kiechle, R., Tartaglia, N., Maier, S. F., & Watkins, L. R. (1997). Vagal parasympathetic bind biotinylated Interleukin-1 receptor antagonist: A possible mechanism for immune-to-brain communication. *Brain Research Bulletin*, 43(3), 357–364. [https://doi.org/10.1016/S0304-3840\(97\)00020-8](https://doi.org/10.1016/S0304-3840(97)00020-8).
- Green, L., Myerson, J., & Mcfadden, E. (1997). Rate of temporal discounting decreases with amount of reward. *Memory & Cognition*, 25(5), 715–723. <https://doi.org/10.3758/BF03211314>.
- Curven, M., Allen-Arave, W., Hill, K., & Hurtado, M. (2000). "It's a Wonderful Life": Signaling generosity among the Ache of Paraguay. *Evolution and Human Behavior*, 20.
- Curven, M. D., Trumble, B. C., Stieglitz, J., Yetish, G., Cummings, D., Blackwell, A. D., ... Pontzer, H. (2016). High resting metabolic rate among Amazonian forager-horticulturalists experiencing high pathogen burden. *American Journal of Physical*



- Anthropology*, 161(3), 414–425. <https://doi.org/10.1002/ajpa.23040>.
- Gutierrez, E. G., Banks, W. A., & Kastin, A. J. (1993). Murine tumor necrosis factor alpha is transported from blood to brain in the mouse. *Journal of Neuroimmunology*, 47(2), 169–176. [https://doi.org/10.1016/0165-5728\(93\)90027-V](https://doi.org/10.1016/0165-5728(93)90027-V).
- Hadju, V., Stephenson, L. S., Mohammed, H. O., Bowman, D. V., & Parker, R. S. (1998). Improvements of growth, Appetite, and physical activity in helminth-infected schoolboys 6 months after single dose of albendazole. *Asia Pacific Journal of Clinical Nutrition*, 7, 170–176.
- Hagen, E. H., Roulette, C. J., & Sullivan, R. J. (2013). Explaining human recreational use of 'pesticides': The neurotoxin regulation model of substance use vs. the hijack model and implications for age and sex differences in drug consumption. *Frontiers in Psychiatry*, 4. <https://doi.org/10.3389/fpsy.2013.00142>.
- Hart, B. L. (1990). Behavioral adaptations to pathogens and parasites: Five strategies. *Neuroscience & Biobehavioral Reviews*, 14(3), 273–294. [https://doi.org/10.1016/S0149-7634\(05\)80038-7](https://doi.org/10.1016/S0149-7634(05)80038-7).
- Hart, B. L. (2011). Behavioural defences in animals against pathogens and parasites: Parallels with the pillars of medicine in humans. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, 366(1583), 3406–3417. <https://doi.org/10.1098/rstb.2011.0092>.
- Hetem, R. S., Mitchell, D., Maloney, S. K., Meyer, L. C., Fick, L. G., Kerley, G. I., & Fuller, A. (2008). Fever and sickness behavior during an opportunistic infection in a free-living antelope, the greater kudu (*Tragelaphus strepsiceros*). *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 294(1), R246–R254.
- Hill, K., Hurtado, A., & Walker, R. (2007). High adult mortality among Hiwi hunter-gatherers: Implications for human evolution. *Journal of Human Evolution*, 52(4), 443–454. <https://doi.org/10.1016/j.jhevol.2006.11.003>.
- Hill, K., & Hurtado, A. M. (1996). *The ecology and demography of a foraging people*. New York: Aldine de Gruyter.
- Hlubik, S., Cutts, R., Braun, D. R., Berna, F., Feibel, C. S., & Harris, J. W. K. (2019). Hominin fire use in the Okote member at Koobi Fora, Kenya: New evidence for the old debate. *Journal of Human Evolution*, 133, 214–229. <https://doi.org/10.1016/j.jhevol.2019.01.010>.
- Hockey, R. (2013). *The psychology of fatigue: Work, effort and control*. Cambridge University Press.
- Holmes, K. K., Bertozzi, S., Bloom, B. R., Jha, P., Gelband, H., DeMaria, L. M., & Horton, S. (2017). Major infectious diseases: Key messages from disease control priorities, third edition. In K. K. Holmes, S. Bertozzi, B. R. Bloom, & P. Jha (Eds.). *Major infectious diseases* (3rd ed.). Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK525197/>.
- Hoshino, K., Takekuchi, O., Kawai, T., Sanjo, H., Ogawa, T., Takeda, Y., ... Akira, S. (1999). Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: evidence for TLR4 as the Lps gene product. *Journal of Immunology*, 162(7), 3749–3752.
- Houlicroft, C. J., & Underdown, S. J. (2016). Neanderthal genomics suggests a pleistocene time frame for the first epidemiological transition. *American Journal of Physical Anthropology*, 160(3), 379–388. <https://doi.org/10.1002/ajpa.22985>.
- Howell, N. (1979). Demography of the Dobe !Kung. Retrieved from <http://ehrafworldcultures.yale.edu/document?id=fx10-019>.
- Huffman, M. A. (1997). Current evidence for self-medication in primates: A multi-disciplinary perspective. *American Journal of Physical Anthropology*, 104(S25), 171–200. [https://doi.org/10.1002/\(SICI\)1096-8644\(1997\)25+<171::AID-AJPA7>3.0.CO;2-7](https://doi.org/10.1002/(SICI)1096-8644(1997)25+<171::AID-AJPA7>3.0.CO;2-7).
- Hurtado, M., Frey, A., Hurtado, I., Hill, K., & Baker, J. (2008). The role of Helminthes in human evolution implications for Global Health in the 21st century. In P. O'Higgins, & S. Elton (Vol. Eds.), *Medicine and evolution. Vol. 20082529. Medicine and evolution* (pp. 153–180). <https://doi.org/10.1201/9781420051377.ch8>.
- Imeri, L., & Opp, M. R. (2009). How (and why) the immune system makes us sleep. *Nature Reviews Neuroscience*, 10(3), 199–210. <https://doi.org/10.1038/nrn2576>.
- Jalasvuori, M., & Bamford, J. K. H. (2008). Structural co-evolution of viruses and cells in the primordial world. *Origins of Life and Evolution of Biospheres*, 38(2), 165–181. <https://doi.org/10.1007/s11084-008-9121-x>.
- James, S. R., Dennell, R., Gilbert, A. S., Lewis, H. T., Gowlett, J., Lynch, T. F., ... Stahl, A. B. (1989). Hominid use of fire in the lower and middle Pleistocene: A review of the evidence. *Current Anthropology*, 30, 1, 1–26.
- Johnson, D. D. P., Blumstein, D. T., Fowler, J. H., & Haselton, M. G. (2013). The evolution of error: Error management, cognitive constraints, and adaptive decision-making biases. *Trends in Ecology & Evolution*, 28(8), 474–481. <https://doi.org/10.1016/j.tree.2013.05.014>.
- Johnson, R. W. (2002). The concept of sickness behavior: A brief chronological account of four key discoveries. *Veterinary Immunology and Immunopathology*, 87(3–4), 443–450. [https://doi.org/10.1016/S0165-2427\(02\)00069-7](https://doi.org/10.1016/S0165-2427(02)00069-7).
- Johnson, R. W., Gheusi, G., Segreti, S., Dantzer, R., & Kelley, K. W. (1997). C3H/HeJ mice are refractory to lipopolysaccharide in the brain. *Brain Research*, 752(1), 219–226. [https://doi.org/10.1016/S0006-8993\(96\)01454-0](https://doi.org/10.1016/S0006-8993(96)01454-0).
- Jones, N. G. B., Smith, L. C., O'Connell, J. F., Hawkes, K., & Kamuzora, C. L. (1992). Demography of the Hadza, an increasing and high density population of savanna foragers. *American Journal of Physical Anthropology*, 89(2), 159–181. <https://doi.org/10.1002/ajpa.1330890204>.
- Kappelman, J., Alçiçek, M. C., Kazanci, N., Schultz, M., Ozkul, M., & Sen, S. (2008). First Homo erectus from Turkey and implications for migrations into temperate Eurasia. *American Journal of Physical Anthropology*, 135(1), 110–116. <https://doi.org/10.1002/ajpa.20739>.
- Kashiwazaki, H., Uenishi, K., Kobayashi, T., Rivera, J. O., Coward, W. A., & Wright, A. (2009). Year-round high physical activity levels in agropastoralists of Bolivian Andes: Results from repeated measurements of DLW method in peak and slack seasons of agricultural activities. *American Journal of Human Biology*, 21(3), 337–345. <https://doi.org/10.1002/ajhb.20864>.
- Kimbrell, D. A., & Beutler, B. (2001). The evolution and genetics of innate immunity. *Nature Reviews Genetics*, 2(4), 256–267. <https://doi.org/10.1038/35066006>.
- Kirsten, K., Fior, D., Kreutz, L. C., & Barcellos, L. J. G. (2018). First description of behavior and immune system relationship in fish. *Scientific Reports*, 8(1), 846. <https://doi.org/10.1038/s41598-018-19276-3>.
- Kluger, M. J. (1979). Fever in ectotherms: Evolutionary implications. *American Zoologist*, 19(1), 295–304 (Retrieved from JSTOR).
- Kluger, M. J., Ringler, D. H., & Anver, M. R. (1975). Fever and survival. *Science*, 188(4184), 166–168.
- Knoll, A. H., & Carroll, S. B. (1999). Early animal evolution: Emerging views from comparative biology and geology. *Science*, 284(5423), 2129–2137. <https://doi.org/10.1126/science.284.5423.2129>.
- Konsman, J. P., Kelley, K., & Dantzer, R. (1999). Temporal and spatial relationships between lipopolysaccharide-induced expression of fos, interleukin-1  $\beta$  and inducible nitric oxide synthase in rat brain. *Neuroscience*, 89(2), 535–548. [https://doi.org/10.1016/S0306-4522\(98\)00368-6](https://doi.org/10.1016/S0306-4522(98)00368-6).
- Koskella, B., & Brockhurst, M. A. (2014). Bacteria–phage coevolution as a driver of ecological and evolutionary processes in microbial communities. *FEMS Microbiology Reviews*, 38(5), 916–931. <https://doi.org/10.1111/1574-6976.12072>.
- Kuzawa, C. W. (1998). Adipose tissue in human infancy and childhood: An evolutionary perspective. *Yearbook of Physical Anthropology*, 41, 33.
- Laye, S., Bluthé, R. M., Kent, S., Combe, C., Medina, C., Parnet, P., ... Dantzer, R. (1995). Subdiaphragmatic vagotomy blocks induction of IL-1 beta mRNA in mice brain in response to peripheral LPS. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 268(5), R1327–R1331. <https://doi.org/10.1152/ajpregu.1995.268.5.R1327>.
- Lieberman, D., Billingsley, J., & Patrick, C. (2018). Consumption, contact, and copulation: How pathogens have shaped human psychological adaptations. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, 373, 20170203.
- Lieberman, D., & Patrick, C. (2018). *Objection: Disgust, morality, and the law*. New York, NY: Oxford University Press.
- Liow, L. H., Van Valen, L., & Stenseth, N. C. (2011). Red queen: From populations to taxa and communities. *Trends in Ecology & Evolution*, 26(7), 349–358. <https://doi.org/10.1016/j.tree.2011.03.016>.
- Llewellyn, D., Brown, G. P., Thompson, M. B., & Shine, R. (2011). Behavioral responses to immune-system activation in an anuran (the cane toad, *Bufo marinus*): Field and laboratory studies. *Physiological and Biochemical Zoology*, 84(1), 77–86. <https://doi.org/10.1086/657609>.
- Lochmiller, R. L., & Deerenberg, C. (2000). Trade-offs in evolutionary immunology: Just what is the cost of immunity? *Oikos*, 88(1), 87–98. <https://doi.org/10.1034/j.1600-0706.2000.880110.x>.
- Lopes, P. C. (2014). When is it socially acceptable to feel sick? *Proceedings of the Royal Society B: Biological Sciences*, 281(1788), <https://doi.org/10.1098/rspb.2014.0218> (20140218–20140218).
- Lopes, P. C., Adelman, J., Wingfield, J. C., & Bentley, G. E. (2012). Social context modulates sickness behavior. *Behavioral Ecology and Sociobiology*, 66(10), 1421–1428. <https://doi.org/10.1007/s00265-012-1397-1>.
- Lopes, P. C., Springthorpe, D., & Bentley, G. E. (2014). Increased activity correlates with reduced ability to mount immune defenses to endotoxin in zebra finches. *Journal of Experimental Zoology Part A: Ecological Genetics and Physiology*, 321(8), 422–431. <https://doi.org/10.1002/jez.1873>.
- MacDonald, L., Hazi, A., Paolini, A. G., & Kent, S. (2014). Calorie restriction dose-dependently abates lipopolysaccharide-induced fever, sickness behavior, and circulating interleukin-6 while increasing corticosterone. *Brain, Behavior, and Immunity*, 40, 18–26. <https://doi.org/10.1016/j.bbi.2014.01.005>.
- Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Galecki, P., & Leonard, B. (2012). Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. *BMC Medicine*, 10(1), <https://doi.org/10.1186/1741-7015-10-66>.
- Mandal, M. D., & Mandal, S. (2011). Honey: Its medicinal property and antibacterial activity. *Asian Pacific Journal of Tropical Biomedicine*, 1(2), 154–160. [https://doi.org/10.1016/S2221-1691\(11\)60016-6](https://doi.org/10.1016/S2221-1691(11)60016-6).
- McCusker, R. H., & Kelley, K. W. (2013). Immune-neural connections: How the immune system's response to infectious agents influences behavior. *Journal of Experimental Biology*, 216(1), 84–98. <https://doi.org/10.1242/jeb.073411>.
- McDade, T. W. (2005). The ecologies of human immune function. *Annual Review of Anthropology*, 34(1), 495–521. <https://doi.org/10.1146/annurev.anthro.34.081804.120348>.
- McDade, T. W. (2012). Early environments and the ecology of inflammation. *Proceedings of the National Academy of Sciences of the United States of America*, 109(Suppl. 2), 17281–17288. <https://doi.org/10.1073/pnas.1202244109>.
- McDade, T. W., Georgiev, A. V., & Kuzawa, C. W. (2016). Trade-offs between acquired and innate immune defenses in humans. *Evolution, Medicine, and Public Health*, 2016(1), 1–16. <https://doi.org/10.1093/emph/eov033>.
- McDade, T. W., Tallman, P. S., Madimenos, F. C., Liebert, M. A., Cepon, T. J., Sugiyama, L. S., & Snodgrass, J. J. (2012). Analysis of variability of high sensitivity C-reactive protein in lowland Ecuador reveals no evidence of chronic low-grade inflammation. *American Journal of Human Biology*, 24(5), 675–681. <https://doi.org/10.1002/ajhb.22296>.
- Muehlenbein, M. P., Hirschtick, J. L., Bonner, J. Z., & Swartz, A. M. (2010). Toward quantifying the usage costs of human immunity: Altered metabolic rates and hormone levels during acute immune activation in men. *American Journal of Human Biology*, 22(4), 546–556. <https://doi.org/10.1002/ajhb.21045>.
- Murray, D. R., Prokosch, M. L., & Airington, Z. (2019). PsychoBehavioroimmunology: Connecting the behavioral immune system to its physiological foundations. *Frontiers in Psychology*, 10. <https://doi.org/10.3389/fpsyg.2019.00200>.
- Murray, M. J., & Murray, A. B. (1979). Anorexia of infection as a mechanism of host

- defense. *The American Journal of Clinical Nutrition*, 32(3), 593–596. <https://doi.org/10.1093/ajcn/32.3.593>.
- Nesse, R. M. (2005). Natural selection and the regulation of defenses: A signal detection analysis of the smoke detector principle. *Evolution and Human Behavior*, 26(1), 88–105. <https://doi.org/10.1016/j.evolhumbehav.2004.08.002>.
- Oaten, M., Stevenson, R. J., & Case, T. I. (2009). Disgust as a disease-avoidance mechanism. *Psychological Bulletin*, 135(2), 303–321. <https://doi.org/10.1037/a0014823>.
- Olsson, M. J., Lundström, J. N., Kimball, B. A., Gordon, A. R., Karshikoff, B., Hosseini, N., ... Lekander, M. (2014). The scent of disease: Human body odor contains an early chemosensory cue of sickness. *Psychological Science*, 25(3), 817–823. <https://doi.org/10.1177/0956797613515681>.
- Omran, A. R. (2005). The epidemiologic transition: A theory of the epidemiology of population change. *The Milbank Quarterly*, 83(4), 731–757. <https://doi.org/10.1111/j.1468-0009.2005.00398.x>.
- Owen-Ashley, N. T., Turner, M., Hahn, T. P., & Wingfield, J. C. (2006). Hormonal, behavioral, and thermoregulatory responses to bacterial lipopolysaccharide in captive and free-living white-crowned sparrows (*Zonotrichia leucophrys gambelii*). *Hormones and Behavior*, 49(1), 15–29.
- Owen-Ashley, N. T., & Wingfield, J. C. (2007). Acute phase responses of passerine birds: Characterization and seasonal variation. *Journal of Ornithology*, 148(S2), 583–591. <https://doi.org/10.1007/s10077-007-0197-2>.
- Panksepp, J. (1982). Toward a general psychobiological theory of emotions. *Behavioral and Brain Sciences*, 5(3), 407–422. <https://doi.org/10.1017/S0140525X00012759>.
- Peacock, N. R. (1985). *Time allocation, work and fertility among Efe pygmy women of Northeast Zaire*. Harvard University.
- Pezeshki, G., Pohl, T., & Schöbitz, B. (1996). Corticosterone controls interleukin-1 beta expression and sickness behavior in the rat. *Journal of Neuroendocrinology*, 8(2), 129–135.
- Pontzer, H., Durazo-Arvizu, R., Dugas, L. R., Plange-Rhule, J., Bovet, P., Forrester, T. E., ... Luke, A. (2016). Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. *Current Biology*, 26(3), 410–417. <https://doi.org/10.1016/j.cub.2015.12.046>.
- Pontzer, H., Raichlen, D. A., Wood, B. M., Emery Thompson, M., Racette, S. B., Mabulla, A. Z. P., & Marlowe, F. W. (2015). Energy expenditure and activity among Hadza hunter-gatherers. *American Journal of Human Biology*, 27(5), 628–637. <https://doi.org/10.1002/ajhb.22711>.
- Prentice, A. M., Leavelle, K., Murgatroyd, P. R., Coward, W. A., Schorah, C. J., Bladon, P. T., & Hullin, R. P. (1989). Is severe wasting in elderly mental patients caused by an excessive energy requirement? *Age and Ageing*, 18(3), 158–167. <https://doi.org/10.1093/ageing/18.3.158>.
- Raichlen, D. A., Pontzer, H., Harris, J. A., Mabulla, A. Z. P., Marlowe, F. W., Josh Snodgrass, J., ... Wood, B. M. (2017). Physical activity patterns and biomarkers of cardiovascular disease risk in hunter-gatherers. *American Journal of Human Biology*, 29(2), e22919. <https://doi.org/10.1002/ajhb.22919>.
- Rakus, K., Ronsmans, M., & Vanderplassen, A. (2017). Behavioral fever in ectothermic vertebrates. *Developmental and Comparative Immunology*, 66, 84–91. <https://doi.org/10.1016/j.dci.2016.06.027>.
- Rothschild, B. M., Hershkovitz, I., & Rothschild, C. (1995). Origin of yaws in the pleistocene. *Nature*, 378(6555), 343–344. <https://doi.org/10.1038/378343b0>.
- Roulette, C. J., Mann, H., Kemp, B. M., Remiker, M., Roulette, J. W., Hewlett, B. S., ... Hagen, E. H. (2014). Tobacco use vs. helminths in Congo basin hunter-gatherers: Self-medication in humans? *Evolution and Human Behavior*, 35(5), 397–407. <https://doi.org/10.1016/j.evolhumbehav.2014.05.005>.
- Schaller, M. (2015). The behavioral immune system. *The handbook of evolutionary psychology* (pp. 1). .
- Schaller, M., Miller, G. E., Gervais, W. M., Yager, S., & Chen, E. (2010). Mere visual perception of other people's disease symptoms facilitates a more aggressive immune response. *Psychological Science*, 21(5), 649–652. <https://doi.org/10.1177/0956797610368064>.
- Schoeller, D. A., Ravussin, E., Schutz, Y., Acheson, K. J., Baertschi, P., & Jequier, E. (1986). Energy expenditure by doubly labeled water: Validation in humans and proposed calculation. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 250(5), R823–R830. <https://doi.org/10.1152/ajpregu.1986.250.5.R823>.
- Secor, S. M. (2009). Specific dynamic action: A review of the postprandial metabolic response. *Journal of Comparative Physiology B*, 179(1), 1–56.
- Segreti, J., Gheusi, G., Dantzer, R., Kelley, K. W., & Johnson, R. W. (1997). Defect in interleukin-1b secretion prevents sickness behavior in C3H/HeJ mice. *Physiology & Behavior*, 61(6), 873–878.
- Shattuck, E. C., & Muehlenbein, M. P. (2015). Human sickness behavior: Ultimate and proximate explanations. *American Journal of Physical Anthropology*, 157(1), 1–18.
- Sherry, D. S., & Marlowe, F. W. (2007). Anthropometric data indicate nutritional homogeneity in Hadza foragers of Tanzania. *American Journal of Human Biology*, 19(1), 107–118. <https://doi.org/10.1002/ajhb.20591>.
- Snodgrass, J. J. (2012). Human energetics. In S. Stinson, B. Bogin, & D. O'Rourke (Eds.), *Human biology* (pp. 325–384). <https://doi.org/10.1002/9781118108062.ch8>.
- Späth-Schwalbe, E. S., Hansen, K., Schmidt, F., Schrezenmeier, H., Marshall, L., Burger, K., ... Born, J. (1998). Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men. *The Journal of Clinical Endocrinology and Metabolism*, 83(5), 1573–1579.
- Steinkopf, L. (2015). The signaling theory of symptoms: An evolutionary explanation of the placebo effect. *Evolutionary Psychology*, 13(3), 1474704915600559. <https://doi.org/10.1177/1474704915600559>.
- Stevenson, R. J., Hodgson, D., Oaten, M. J., Mousavi, M., Langberg, R., Case, T. I., & Barouei, J. (2012). Disgust elevates core body temperature and up-regulates certain oral immune markers. *Brain, Behavior, and Immunity*, 26(7), 1160–1168. <https://doi.org/10.1016/j.bbi.2012.07.010>.
- Sugiyama, L. S. (2004). Illness, injury, and disability among Shiwi forager-horticulturalists: Implications of health-risk buffering for the evolution of human life history. *American Journal of Physical Anthropology*, 123(4), 371–389. <https://doi.org/10.1002/ajpa.10325>.
- Sugiyama, L. S., & Chacon, R. (2000). Effects of illness and injury on foraging among the Yora and Shiwi: Pathology risk as adaptive problem. In N. A. Chagnon, & W. Irons (Eds.), *Human behavior and adaptation: An anthropological perspective* (pp. 371–395). New York, NY, US: Aldine.
- Sundelin, T., Karshikoff, B., Axelsson, E., Höglund, C. O., Lekander, M., & Axelsson, J. (2015). Sick man walking: Perception of health status from body motion. *Brain, Behavior, and Immunity*, 48, 53–56. <https://doi.org/10.1016/j.bbi.2015.03.007>.
- Swain, M. G. (2000). Fatigue in chronic disease. *Clinical Science*, 99(1), 1–8.
- Teisner, B., & Haahr, S. (1974). Poikilothermia and susceptibility of suckling mice to Coxsackie B1 virus. *Nature*, 247(5442), 568.
- Thompson, J., & Anderson, J. (1982). Patient preferences and the bedside manner. *Medical Education*, 16(1), 17–21.
- Thurber, C., Dugas, L. R., Ocobock, C., Carlson, B., Speakman, J. R., & Pontzer, H. (2019). Extreme events reveal an alimentary limit on sustained maximal human energy expenditure. *Science Advances*, 5(6), eaaw0341. <https://doi.org/10.1126/sciadv.aaw0341>.
- Tilley, L., & Oxenham, M. F. (2011). Survival against the odds: Modeling the social implications of care provision to seriously disabled individuals. *International Journal of Paleopathology*, 1(1), 35–42. <https://doi.org/10.1016/j.ijpp.2011.02.003>.
- Tiokhin, L. (2016). Do symptoms of illness serve signaling functions? (hint: Yes). *The Quarterly Review of Biology*, 91(2), 177–195. <https://doi.org/10.1086/686811>.
- Tooby, J. (1982). Pathogens, polymorphism, and the evolution of sex. *Journal of Theoretical Biology*, 97(4), 557–576.
- Tooby, J., & Cosmides, L. (1996). Friendship and the banker's paradox: Other pathways to the evolution of adaptations for altruism. In W. G. Runciman, J. M. Smith, & R. I. M. Dunbar (Vol. Eds.), *Proceedings of the British Academy. Vol. 88. Proceedings of the British Academy* (pp. 119–143). New York, NY, US: Oxford University Press Evolution of social behaviour patterns in primates and man.
- Tooby, J., & Cosmides, L. (2008). The evolutionary psychology of the emotions and their relationship to internal regulatory variables. In M. Lewis, J. M. Haviland-Jones, & L. F. Barrett (Eds.), *Handbook of emotions* (pp. 114–137). New York, NY, US: The Guilford Press.
- Toups, M. A., Kitchen, A., Light, J. E., & Reed, D. L. (2010). Origin of clothing lice indicates early clothing use by anatomically modern humans in Africa. *Molecular Biology and Evolution*, 28(1), 29–32.
- Trinkaus, E., & Zimmerman, M. R. (1982). Trauma among the Shanidar Neandertals. *American Journal of Physical Anthropology*, 57(1), 61–76. <https://doi.org/10.1002/ajpa.1330570108>.
- Tybur, J. M., Lieberman, D., Kurzban, R., & DeScioli, P. (2012). Disgust: Evolved function and structure. *Psychological Review*, 120(1), 65. <https://doi.org/10.1037/a0030778>.
- Urlacher, S. S., Ellison, P. T., Sugiyama, L. S., Pontzer, H., Eick, G., Liebert, M. A., ... Snodgrass, J. J. (2018). Tradeoffs between immune function and childhood growth among Amazonian forager-horticulturalists. *Proceedings of the National Academy of Sciences*, 115(17), E3914–E3921. <https://doi.org/10.1073/pnas.1717522115>.
- Urlacher, S. S., Snodgrass, J. J., Dugas, L. R., Sugiyama, L. S., Liebert, M. A., Joyce, C. J., & Pontzer, H. (2019). *Constraint and tradeoffs regulate energy expenditure during childhood*. Under review.
- Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T. D., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The International Journal of Biochemistry & Cell Biology*, 39(1), 44–84. <https://doi.org/10.1016/j.biocel.2006.07.001>.
- van Dam, A.-M., Brouns, M., Louise, S., & Berkenbosch, F. (1992). Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? *Brain Research*, 588(2), 291–296. [https://doi.org/10.1016/0006-8993\(92\)91588-6](https://doi.org/10.1016/0006-8993(92)91588-6).
- Walter, E. J., Hanna-Jumma, S., Carraretto, M., & Forni, L. (2016). The pathophysiological basis and consequences of fever. *Critical Care*, 20. <https://doi.org/10.1186/s13054-016-1375-5>.
- Warburton, D. E., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: The evidence. *Cmaj*, 174(6), 801–809.
- Watkins, L. R., Goehler, L. E., Relton, J., Brewer, M. T., & Maier, S. F. (1995). Mechanisms of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) hyperalgesia. *Brain Research*, 692(1), 244–250. [https://doi.org/10.1016/0006-8993\(95\)00715-3](https://doi.org/10.1016/0006-8993(95)00715-3).
- Wegner, A., Elsenbruch, S., Maluck, J., Grigoleit, J.-S., Engler, H., Jäger, M., ... Benson, S. (2014). Inflammation-induced hyperalgesia: Effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. *Brain, Behavior, and Immunity*, 41, 46–54. <https://doi.org/10.1016/j.bbi.2014.05.001>.
- Weil, Z. M., Bowers, S. L., Dow, E. R., & Nelson, R. J. (2006). Maternal aggression persists following lipopolysaccharide-induced activation of the immune system. *Physiology & Behavior*, 87(4), 694–699.
- Weitz, J. S., Hartman, H., & Levin, S. A. (2005). Coevolutionary arms races between bacteria and bacteriophage. *Proceedings of the National Academy of Sciences*, 102(27), 9535–9540. <https://doi.org/10.1073/pnas.0504062102>.
- Wells, J. C. K. (2012). The evolution of human adiposity and obesity: Where did it all go wrong? *Disease Models & Mechanisms*, 5(5), 595–607. <https://doi.org/10.1242/dmm.009613>.
- Westertep, K. R. (2001). Limits to sustainable human metabolic rate. *Journal of Experimental Biology*, 204, 3183–3187 Pt 18.
- Westertep, K. R. (2004). Diet induced thermogenesis. *Nutrition and Metabolism*, 1, 5.
- Westertep, K. R., Saris, W. H., van Es, M., & ten Hoor, F. (1986). Use of the doubly

- labeled water technique in humans during heavy sustained exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 61(6), 2162–2167. <https://doi.org/10.1152/jappl.1986.61.6.2162>.
- Wing, E. J., Stanko, R. T., Winkelstein, A., & Adibi, S. A. (1983). Fasting-enhanced immune effector mechanisms in obese subjects. *The American Journal of Medicine*, 75(1), 91–96.
- Wing, E. J., & Young, J. B. (1980). Acute starvation protects mice against *Listeria monocytogenes*. *Infection and Immunity*, 28(3), 771–776.
- Wrangham, R. W., Jones, J. H., Laden, G., Pilbeam, D., & Conklin-Brittain, N. (1999). The raw and the stolen. Cooking and the ecology of human origins. *Current Anthropology*, 40(5), 567–594.
- Zuk, M. (1992). The role of parasites in sexual selection: Current evidence and future directions. *Advances in the Study of Behavior*, 21, 39–68.