WHY OUR IMMUNE SYSTEMS MAKE US FEEL SICK: PATHOLOGIES, ADAPTATIONS, AND EVOLUTIONARILY NOVEL CONDITIONS

by

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DISSERTATION ABSTRACT

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Title: Why Our Immune Systems Make Us Feel Sick: Pathologies, Adaptations, and Evolutionarily Novel Conditions.

Three decades of research in neuroimmunology has demonstrated that the state of sickness is generated by the host's immune system when it detects internal indicators of pathology. But *why* do our own immune systems make us feel sick? Chapter I introduces this research question.

Chapter II reviews the evidence that infectious disease has been a selection pressure throughout our evolutionary history. It outlines problems that arise for the host when the immune system is activated to fight infection. It describes how the regulatory changes that occur during sickness can help solve the problems posed by immune activation. For example, fatigue and sadness during infection may help the host prioritize immune function during infection by reducing physical activity, thereby making more metabolic resources available to the immune system.

Experimental studies have demonstrated that acute inflammatory immune activity can induce fatigue and low mood, but studies of associations between inflammation and mood in real-world settings have produced mixed findings, raising questions about the dose and chronicity of inflammation needed to induce fatigue and sadness. Chapter III finds that greater inflammation is associated with stronger feelings of sickness but not fatigue or

sadness in a sample of Shuar forager-horticulturalists in the northern Amazon, who experience frequent acute, but mild, inflammation. This suggests that inflammation may generate internally perceptible cues, even when the dose and chronicity of inflammation are insufficient to increase fatigue or sadness.

Chapter IV finds that greater chronic morbidity is associated with stronger feelings of fatigue in six culturally distinct countries. Chronic disease-induced fatigue may often be a maladaptive response to evolutionarily novel diseases – one that suppresses physical activity in the long term, which is a risk factor for further disease progression and acquisition of additional morbidities.

Chapter V finds that, among diurnal primates, greater relative brain size is strongly associated with less resting time and more active time. Intensive reciprocal helping behavior during sickness in humans may have evolved due in part to high levels of pathogen exposure and the limits on resting time imposed by the nutritional requirements of our large brains.

This dissertation includes previously published co-authored material.

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DEDICATION

In memory of my father, Matthew T. Schrock (1961 – 2015).

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CHAPTER I

INTRODUCTION

Anyone reading this has almost certainly had the experience of being sick. Three decades of research in neuroimmunology has demonstrated that the state of sickness is generated by the host's immune system when it detects indicators that some kind of pathology is present (Dantzer & Kelley, 2007; Hart, 1990; Lasselin et al., 2020; McCusker & Kelley, 2013). Why do our immune systems impose this misery upon us? Does sickness provide functional benefits to a host fighting infection? If so, what are these advantages? Does the experience of sickness vary depending on the environmental context of the host? If so, what are the contextual factors that shape the experience of sickness? If sickness provides some kind of benefit to the host, what happens when it goes wrong? What explains the distinctive features of sickness in humans? In this dissertation, I work towards answering these questions. This chapter provides a brief introduction to the dissertation.

The immune system plays a central role in helping the human body fight infection (Akira et al., 2006; McDade, 2005). But in biological systems, useful solutions sometimes pose additional problems and introduce tradeoffs. In Chapter II, co-authored with Josh Snodgrass and Lawrence Sugiyama, I outline the second-order adaptive problems posed to the host when the immune system is activated to fight infection. These problems include how to fund the high metabolic costs of activating the immune system, how to avoid acquiring additional infections or injuries that would further compound the immune system's workload, how to regulate food consumption in ways that support the fight against infection, how to efficiently maintain an optimal body temperature for

fighting infection, and how to elicit caregiving behavior from social allies.

I then review the existing literature to show how various features of sickness can help the host solve these problems. Lethargy reduces active energy expenditure, leaving more metabolic resources available to fund immune responses. Increased pain sensitivity and susceptibility to nausea reduce the risk of acquiring additional infections or injuries that would compound the immune system's workload. A selective preference for foods with low digestion costs (e.g., sugars) reduces the proportion of the metabolic budget spent on digestion, leaving more metabolic resources available to the immune system. Altered social behavior helps the host obtain care from social allies and avoid agonistic individuals. Increased warmth-seeking behavior reduces the metabolic costs of maintaining an optimal body temperature for immune function.

Taken together, the existing literature suggests that vertebrates possess an evolutionarily conserved internal regulatory system that detects cues of infection or injury and deploys a series of regulatory changes that help the host address the adaptive demands that come with infection or injury. This kind of regulatory system is what some investigators call an "emotion" (Al-Shawaf et al., 2016; Sznycer et al., 2017; Tooby & Cosmides, 2008). For example, Tooby and Cosmides write, "[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" (2008, p. 107). In this dissertation, I use the term "lassitude" to refer to the regulatory state that coordinates useful changes in response to cues of infection or injury. I do this to distinguish between the regulatory state (lassitude) and its behavioral outputs (sickness behavior). This is similar to the distinction between hunger

(regulatory state) and feeding behavior (behavioral outputs). Lassitude also exhibits other features that are often associated with emotions, including specific qualia (i.e., there is a specific subjective experience that comes with being sick) (Andreasson et al., 2018), a distinctive facial expression (Axelsson et al., 2018), distinctive body language (Sundelin et al., 2015), and being phylogenetically conserved (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015). Chapter II also serves as a conceptual introduction to the subsequent chapters of this dissertation, outlining the theoretical framework and lines of evidence that motivated the later chapters.

Most studies of the relationship between immune activation and sickness have been conducted in high-income, industrialized countries (Shattuck & Muehlenbein, 2015, 2016). It has been demonstrated, using samples from these societies, that experimentally induced inflammation can generate feelings of fatigue and depression (DellaGioia & Hannestad, 2010; Lasselin et al., 2020). Along the same lines, chronic low-grade inflammation has been linked to depressive symptoms in clinical and epidemiological studies (Osimo et al., 2020). Depressive symptoms are measured in a variety of different ways but these measures generally include fatigue- and sadness-related items. Evolutionarily novel environments characterized by low microbial diversity and infrequent exposure to ancestrally common pathogens can shape the development and deployment of immune responses in unexpected ways (Gurven & Lieberman, 2020). These changes in immune development and deployment may increase the prevalence of disorders caused by overactivity of the immune system (e.g., inflammatory, autoimmune, and allergic diseases) (Bach, 2018; Fitzsimmons et al., 2014).

In Chapter III, I test whether everyday mild immune activation is associated with

fatigue, sadness, or general feelings of sickness among Shuar forager-horticulturalists, who inhabit environments characterized by substantial requirements for physical work, high reproductive rates, high microbial diversity, and frequent exposure to common macroparasites. I find that greater inflammation (as indexed by C-reactive protein levels, CRP) is associated with stronger feelings of sickness but not fatigue or sadness. The overall levels of CRP in my sample are relatively low (serum equivalent median: 0.38 mg/L, median absolute deviation: 0.47 mg/L, maximum: 11 mg/L).

Previous work in similar Shuar communities has found no evidence for chronic low-grade inflammation (Blackwell et al., 2010; McDade et al., 2012; Urlacher et al., 2018), so the higher end of the distribution in my sample likely reflects mild acute inflammation. These results suggest that mild acute inflammation may generate internally perceptible cues, even when it is too mild or too short-term to increase fatigue or sadness. Previous work suggests that mild acute inflammation is a common occurrence among the Shuar (Blackwell et al., 2010; McDade et al., 2012; Urlacher et al., 2018). In Chapter II, I hypothesize that the deployment of fatigue and sadness during immune activation depends on both the magnitude of the immune challenge and the opportunity costs of deploying fatigue and sadness (Schrock et al., 2020). In a subsistence population where livelihoods require sustained physical work, frequent feelings of fatigue or sadness may interfere with an individual's ability to make a living. It is possible that frequent exposure to mild acute inflammation across the life course, in combination with substantial requirements for physical work, recalibrate the underlying regulatory mechanisms to require higher levels of inflammation to induce fatigue or sadness. Further work is needed to describe the dose dependencies, ecological parameters, and developmental

reaction norms that shape the subjective experience of inflammation.

Chronic diseases that are now the leading global causes of death (e.g., cardiovascular disease, diabetes) were probably rare for most of our evolutionary history (Eaton et al., 1988; Raichlen et al., 2017; Roth et al., 2018). During acute infection or injury, fatigue may facilitate adaptive reductions in physical activity, thereby making more metabolic resources available to fund costly immune responses (Schrock et al., 2020). But in the context of chronic disease, low levels of physical activity are a risk factor for disease progression and the acquisition of additional comorbidities (Booth et al., 2012; Warburton et al., 2006). In fact, the health benefits of physical activity may be due, in part, to its capacity to reduce excessive inflammatory immune activity (Pontzer, 2018). Thus, fatigue may often be counterproductive when deployed in response to chronic disease.

Many of the chronic degenerative conditions that are now leading causes of mortality and morbidity were likely rare throughout most of our evolutionary history (Eaton et al., 1988; Gurven & Lieberman, 2020). Excessive inflammation and fatigue in response to these chronic conditions may be a case of mismatch between contemporary environments and our evolved biology. If increased fatigue is a common response to chronic morbidity, it may generate a feedback loop, with greater chronic morbidity leading to greater fatigue, greater fatigue suppressing physical activity, and reduced physical activity leading to even greater chronic morbidity. If this feedback loop plays out in real-world populations, we should expect to see consistent associations between cumulative chronic morbidity and levels of fatigue. In Chapter IV, I test this prediction using large samples of adults from six culturally distinct countries. I find that greater

cumulative chronic morbidity (i.e., having more chronic conditions) is associated with higher levels of reported fatigue. This finding replicates within each country and is robust to adjustment for key covariates. Further research is needed to test causal pathways running in both directions.

Some aspects of lassitude and sickness behavior appear to be broadly evolutionarily conserved (changes in thermoregulatory behavior, altered patterns of food intake) (Rakus et al., 2017; van Niekerk et al., 2016). Other dimensions of sickness behavior may be present in some species but absent in others. For example, infection will not affect parental effort in species that do not provide parental care (Weil et al., 2006). Still other aspects of sickness behavior may exist in many species but vary in intensity (e.g., degree of social withdrawal) (Lopes, 2014). I am interested in understanding why human lassitude and sickness behavior takes its particular form. One of the common threads running through several different features of sickness behavior is that they seem to play a role, directly or indirectly, in helping the host manage the metabolic costs of activating the immune system (Shattuck & Muehlenbein, 2015). Thus, other competing metabolic demands and the resulting energetic tradeoffs may play a role in shaping what lassitude and sickness behavior look like in a given species.

Humans have very large brains, both in absolute terms and relative to body size (Leonard et al., 2003). Humans spend a substantially greater proportion of their metabolic budgets on brains than do other extant primates (Isler & van Schaik, 2006). The human adaptive complex that manages the metabolic costs of large brains may also play a role in shaping what lassitude and sickness behavior looks like in humans. One of the primary behavioral outputs of lassitude is to increase resting time and reduce engagement in

energetically expensive activities (Schrock et al., 2020). If brain size also shapes time allocation, it may have consequences for the deployment of sickness behavior.

In Chapter V, I test whether brain and body size are associated with patterns of time allocation using a sample of species-level data on non-human primates. I find that, when body size is held constant, larger brain size is strongly associated with less resting time, more foraging time, and more locomotion time. When brain size is held constant, larger body size is strongly associated with more resting time, less subsistence time and less locomotion time. In other words, greater encephalization (relative brain-to-body size) is associated with less resting time and more active time. Diet quality (a measure of the caloric density of the diet) largely accounts for the association between encephalization and subsistence time, which suggests that highly encephalized species spend more time in subsistence activities in part because they are pursuing higher quality food items. Time allocation data from human foragers suggest that humans spend far less time in subsistence and locomotion activities than my model would predict for primate for with our level of encephalization. This is consistent with the hypothesis that human evolution depended on adaptations that enhanced the efficiency of time use (Fonseca-Azevedo & Herculano-Houzel, 2012).

A previous comparative primate study found that higher rates of social learning, innovation, and extractive foraging are associated with greater parasite richness (a measure of the variety of parasites in a species' disease ecology) (McCabe et al., 2015). In particular, higher rates of social learning are associated with greater richness of socially transmitted parasites, and higher rates of exploration are associated with greater richness of environmentally transmitted parasites. Cognitive capacities for exploration

and social learning, which are strongly intensified in humans, may therefore come at a cost of greater infection risk.

My results in Chapter V show that greater encephalization is associated with less resting time. Thus, highly encephalized species that rely heavily on social learning, extractive foraging, and exploration (e.g., our recent hominin ancestors) may face a double bind of greater infection risk and less available resting time to prioritize immune function. I hypothesize that some animals may address this problem via reciprocal helping behavior directed toward sick individuals. Receiving care when sick (e.g., food provisioning, protection, grooming, allocare of offspring) allows the sick individual to temporarily increase resting time in order to prioritize immune function (Hart, 1990). Future comparative studies should test whether greater encephalization and parasite richness are associated with increased reports of helping sick conspecifics.

The ethnographic record demonstrates that human foragers provide care and support for sick conspecifics, which allows the sick person to rest without worrying about feeding themselves or their family, watching out for threats, or keeping up with the group (Bailey, 1991; Gurven et al., 2000; Hill et al., 2007; Sugiyama, 2004; Sugiyama & Chacon, 2000). The bioarchaeological record provides examples of individuals surviving pathologies that would have required care from conspecifics (Dickel & Doran, 1989; Tilley, 2015; Tilley & Oxenham, 2011; Trinkaus & Zimmerman, 1982). The apparent importance of receiving care from social conspecifics in our evolutionary history may help explain why the experience of receiving care alone has such a powerful effect on subjective wellbeing in human sickness (e.g., the placebo effect) (Steinkopf, 2015). The flexibility to facultatively adjust patterns of resting behavior to suit an individual's

immunological circumstances may have played a role in relaxing the joint constraints on brain size posed by high infection risk and limited resting time.

Bridge to Chapter II

Sickness is a common experience in human life, and sickness behavior appears to be highly phylogenetically conserved in vertebrates. In the next chapter, I review the evidence that infectious disease has been a ubiquitous selection pressure throughout our evolutionary history. I then outline the second-order adaptive problems posed to the host when the immune system is activated to fight infection. I describe the regulatory changes that occur during sickness, and explain how these changes help the host solve the problems posed by immune activation. This theoretical account of lassitude and sickness behavior outlined in Chapter II sets the stage for the subsequent empirical chapters of this dissertation.

CHAPTER II

LASSITUDE: THE EMOTION OF BEING SICK

This work was published in Volume 41, Issue 1 (pages 44-57) of the journal Evolution and Human Behavior in January 2020. It was co-authored with J. Josh Snodgrass and Lawrence S. Sugiyama. I planned and drafted the paper. Drs. Snodgrass and Sugiyama participated in many discussions with me about the scope and direction of the paper and provided edits and comments on multiple drafts.

2.1. 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 (Jalasvuori & Bamford, 2008; Koskella & Brockhurst, 2014; Weitz et al., 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 et al., 2006; Lochmiller & Deerenberg, 2000), immune mechanisms that adjust to specific pathogenic organisms (Cooper & Alder, 2006; McDade, 2005), infection-sensitive developmental programs (Georgiev et al., 2016; Urlacher et al., 2018), and, arguably, sexual reproduction, cellular differentiation, and patterns of parent-offspring association (Liow et al., 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 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).

Box 2.1. 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" (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).

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).

2.2. 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, Hurtado, & Walker, 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 pertenue)* in *H. erectus* remains dating to about 1.6 mya (Rothschild et al., 1995), and evidence of brucellosis in *Australopithecus africanus* dating to about 2.4-2.8 mya (D'Anastasio et al., 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 (Jalasvuori & 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.

2.2.1. 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 (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.

2.2.2. 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, & Vanderplasschen, 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 et al., 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:

2.2.2a. 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 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 et al., 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.

Box 2.2. 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

Box 2.2 Cont. Components of an Energy Budget

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 less than 30% to more than 350% of daily RMR, though these high extremes of AEE are not sustainable in the long term (Westerterp, 2001; Westerterp et al., 1986).

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

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; Herman Pontzer et al., 2015, 2016). 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 hours 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 hours (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 less than 30% of RMR in very sedentary individuals (Prentice et al., 1989) to three-week periods of more than 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 more than 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.

2.2.2b. 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 2.2a, 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.

2.2.2c. 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 Sebastian et al., 2013; Kluger et al., 1975) but is energetically expensive and can cause cellular damage (Bois, 1921; Del Bene, 1990; Walter et al., 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.

2.2.2d. 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.

2.2.2e. 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).

2.3. 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).

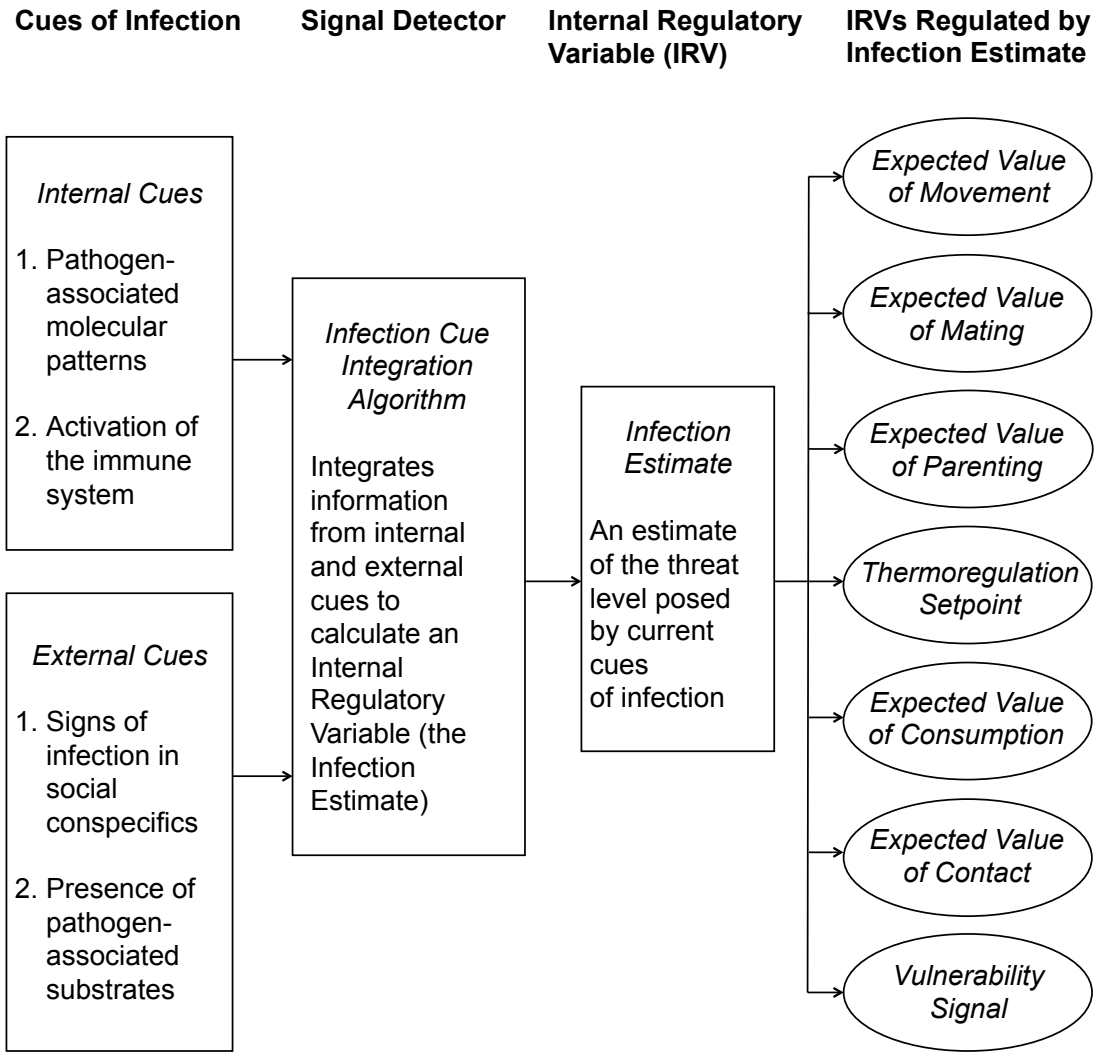
2.4. The Information-Processing Structure Of Lassitude

2.4.1. 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 Figure 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).

Figure 2.1 (next page). 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 the costs (e.g., lost opportunities for foraging, feeding, mating, social interaction, parental investment) of altering its operation.

Notes on Figure 2.1.

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.



2.4.1.1. 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 & Hemmi, 2003). 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 et al., 1997). However, when treated with both LPS and the proinflammatory cytokine IL-1β, 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, Ortiz, Plotkin, & Kastin, 1991; Banks, Kastin, & Gutierrez, 1994; Gutierrez, Banks, & Kastin, 1993). Peripheral cytokine production also increases pro-inflammatory cytokine signaling in brain microglia (van Dam et al., 1992). Studies in which lab animals were vagotomized suggest there is also a pathway mediated by afferent vagal nerves (Bluthe et al., 1996; Goehler et al., 1997, 1999; 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 et al., 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.

2.4.1.2. 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 et al., 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 (TNFα) (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.

2.4.2. 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.

2.4.3. 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.

2.4.3.1. 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 et al., 2011), white-crowned sparrows (*Zonotrichia leucophrys gambelii*) (Owen-Ashley et al., 2006), and laboratory rats (*Rattus norvegicus domestica*) (Pezeshki et al., 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, et al., 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 et al., 1994; Hadju et al., 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 et al., 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.

2.4.3.2. 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)

2.4.3.3. 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 et al., 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 et al., 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).

2.4.3.4. 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 directly 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, Ringler, & Anver, 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 et al., 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.

2.4.3.5. 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 et al., 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, Fugère, 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 et al., 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 (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 et al., 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 hours 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 et al., 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.

2.4.3.6. 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 2.2e, 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.

2.4.3.7. 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 et al., 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.

2.4.4. 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 et al., 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.

2.5. 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" (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 (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 et al., 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 (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.

2.6. Directions For Future Research

2.6.1. Social Support And Immunity. Humans provide care to social allies during illness and injury (see section 2.2e). 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).

2.6.2. 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).

2.6.3. 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 et al., 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).

2.6.4. 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 et al., 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.

2.6.5. 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.

2.7. 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, de Barra, & Aunger, 2011; Lieberman & Patrick, 2018; Murray, Prokosch, & Airington, 2019; Oaten, Stevenson, &

Case, 2009; Schaller, 2015; Tybur, Lieberman, Kurzban, & DeScioli, 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 et al., 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.

2.8. Bridge to Chapter III

In Chapter II, I outlined the adaptive problems that arise for the host when the immune system is activated to fight infection. I reviewed the regulatory changes that occur during sickness and explained how these changes help the host solve the adaptive problems posed by immune activation. But much of what we know about immune activation and the regulation of sickness in humans comes from studies conducted in high-income, industrialized countries. In these societies, many individuals are engaged in sedentary occupations, have ready access to highly processed calorie dense foods, and are rarely exposed to pathogens that were common in ancestral environments. These evolutionarily novel environments may have unexpected consequences for the development and deployment of immune responses. In Chapter III, I test whether greater immune activation is associated with stronger feelings of fatigue, sadness, and sickness in a sample of Shuar forager-horticulturalists. The Shuar have relatively high requirements for energy expenditure, rely primarily on a subsistence diet, and experience relatively frequent parasite exposure.

CHAPTER III

IMMUNE ACTIVATION AND SICKNESS AMONG THE SHUAR

3.1. Introduction

Vertebrates (including humans) often exhibit depression-like behavioral changes during acute infectious disease (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015). These changes, known as *sickness behavior*, include increased lethargy, reduced interest in activities that are usually rewarding, and social withdrawal (Ghai, Fugere, et al., 2015; Henry et al., 2008; Lopes, 2014). In humans, sickness behavior is often accompanied by subjective feelings of fatigue and low mood (DellaGioia & Hannestad, 2010; Lasselin et al., 2020). Sickness behavior is thought to help the host prioritize immune function by reducing active energy expenditure, thereby making more metabolic resources available to fund energetically costly immune responses (Adelman & Martin, 2009; Schrock et al., 2020; Shattuck & Muehlenbein, 2015). Some components of sickness behavior, such as increased pain sensitivity and altered feeding behavior, may also reduce the risk of acquiring additional infections or injuries that would compound the immune system's workload (Kyriazakis et al., 1998; Wegner et al., 2014). In cooperative social environments, visible behavior changes during illness may also help signal the host's vulnerable status to social allies, in order to elicit care and support (Axelsson et al., 2018; Steinkopf, 2015; Sundelin et al., 2015; Tiokhin, 2016).

Three decades of research in neuroimmunology has demonstrated that inflammatory immune responses play a key mechanistic role in generating sickness-related changes in behavior and mood (Dantzer & Kelley, 2007; Hart, 1990; Lasselin et al., 2020; McCusker & Kelley, 2013). Studies in high-income, industrialized societies

have shown that experimentally inducing acute inflammation can generate fatigue and low mood (DellaGioia & Hannestad, 2010; Lasselin et al., 2020). A number of clinical and epidemiological studies have reported that inflammation levels are higher among those with depressive disorders or that greater inflammation is associated with more severe depressive symptoms (Dowlati et al., 2010; Elovainio et al., 2006; Howren et al., 2009; Osimo et al., 2020), while others have reported mixed results or no evidence of an association between inflammation and depression (Danner et al., 2003; Morris et al., 2011; Steptoe et al., 2003).

High-income, industrialized environments are characterized by low microbial diversity and infrequent exposure to parasites that were common throughout most of our evolutionary history (Gurven & Lieberman, 2020; Parker & Ollerton, 2013). Chronic inflammation has been linked to higher levels of adiposity (Cartier et al., 2009; Tilg & Moschen, 2006) and physical inactivity (Abramson & Vaccarino, 2002; Ford, 2002). Obesity and low levels of physical activity are particularly common in high-income, industrialized societies (Caballero, 2007; Eaton et al., 1988; Herman Pontzer, 2018; Raichlen et al., 2017; Wells, 2012). A growing body of evidence suggests that the evolutionarily novel environments of high-income, industrialized societies may modulate the development and deployment of immune responses in unexpected ways (Georgiev et al., 2016; McDade, 2012). Individuals in these societies appear to face greater risks for chronic diseases caused by overactive immune responses (e.g., allergic, autoimmune, and inflammatory disorders) (Bach, 2018; Fitzsimmons et al., 2014). It is possible that inflammation-related fatigue and low mood, in the absence of acute infection, is another example of a maladaptive, overactive immune response.

To date, relatively few studies have examined associations between inflammation and mood outside of high-income, industrialized societies. One exception is a study conducted in the Philippines among participants who experience relatively high levels of microbe exposure and infectious disease (McDade et al., 2013). The authors reported low median levels of inflammation and no evidence for an association between inflammation and depressive symptoms (ibid). Another study was conducted among Amazonian Tsimane forager-horticulturalists who experience high pathogen burdens and rely largely on human-powered subsistence activities to meet their dietary needs (Stieglitz et al., 2015). The authors reported high median levels of inflammation and pronounced associations between inflammation and depressive symptoms (ibid). The apparent heterogeneity of associations between inflammation and mood raises questions about the dose and chronicity of inflammation required to induce low mood.

This study tests whether greater immune activation is associated with stronger feelings of fatigue, sadness, or sickness in a sample of Shuar forager-horticulturalists. Like the Tsimane, the Shuar inhabit a tropical Amazonian environment and rely largely on non-market, human-powered subsistence activities to meet their dietary needs (Liebert et al., 2013). But previous studies suggest that the Tsimane exhibit substantially higher levels of C-reactive protein (a biomarker of inflammation) and Immunoglobulin E (a class of antibodies produced in response to macroparasite exposure) (Blackwell et al., 2011; Gurven et al., 2009). These differences, which appear to be rather large in magnitude, suggest that the Tsimane experience heavier immune burdens. Along these lines, a recent study reported that the Tsimane exhibit lower bone density and greater osteoperosis risk compared to the Shuar, which may reflect the high metabolic costs of

greater immune activation across the lifecourse (Madimenos et al., 2020). Studies collecting repeated measures of CRP suggest that the Shuar exhibit low median levels of inflammation, punctuated by relatively frequent short-term increases (McDade et al., 2012; Urlacher et al., 2018).

3.1.2. Shuar Economy, Reproduction, and Disease Ecology. The Shuar exhibit high levels of total energy expenditure, measured using the doubly labeled water method (Christopher et al., 2019). Most of the calories in the Shuar diet come from manual garden cultivation (primarily manioc, plantains, and taro), husbandry of domesticated fowl, hunting, fishing, and gathering of wild foods (Liebert et al., 2013), and highly processed calorie-dense market foods are not generally dietary staples, due to limited disposable income. In many communities, however, there is increasing engagement in cash economies, and traditional diets are sometimes supplemented with purchased carbohydrates (e.g., rice, wheat products), proteins (e.g., canned tuna and sardines), fats (primarily cooking oil), and salt. The most common cash activities – the sale of forest products, sale of garden produce, cattle husbandry, and manual wage labor – also require substantial physical work. Informal conversations with the participants of this study suggested that the availability of wage labor had sharply declined in recent months, due to difficulties in the broader Ecuadorian economy.

The self-reported use of hormonal contraceptives is rare, and demographic patterns are consistent with what would be expected in a natural fertility population – average age at first parturition of 17.5, an average interbirth interval of 31.5 months, and an average of 8.8 lifetime births reported by post-menopausal women (Madimenos et al., 2012). An accelerometer study among the Shuar found that husbands of women who are

pregnant or lactating exhibit higher levels of estimated active energy expenditure, which may reflect compensation for the metabolic costs of pregnancy and lactation (Madimenos et al., 2011).

Several lines of evidence indicate that infectious disease exposure is relatively common among the Shuar compared to high-income, industrialized populations. Studies of fecal shedding of *Ascaris lumbricoides* (roundworm) and *Trichiuris trichiuris* (whipworm) eggs have found that roughly 50-70% of Shuar individuals exhibit evidence of infection with at least one of the two species, based on microscopic analysis of a single stool sample for each study participant (Cepon-Robins et al., 2014; Gildner et al., 2016). Another study conducted weekly repeat measures of CRP in a sample of 52 Shuar adults and found that 34.6% of individuals exhibited evidence of acute increases in innate immune activity (CRP >3 mg/l) at one time point in the four-week study period, but no evidence of chronic low-grade inflammation (McDade et al., 2012). A study among Shuar children reported substantial variation in immune activation and found that greater immune activation is associated with slowed growth (Urlacher et al., 2018). This study also found that skinfold thickness moderated the association between inflammation and growth at one-week follow-up, suggesting that higher levels of subcutaneous fat can act as a buffer against the growth-slowing effects of acute immune challenges (ibid). The fat-free mass-adjusted resting metabolic rates of Shuar children are higher than those of children in high-income, industrialized societies, and, in a sample of Shuar children, RMRs were higher among those with higher levels of total Immunoglobulin G (IgG; the most common class of antibody) (Urlacher et al., Under review). Compared to high-income, industrialized samples, the Shuar exhibit very high mean levels of

Immunoglobulin E (IgE; a class of antibodies produced in response to macroparasitic antigens) (Blackwell et al., 2011).

Subsistence practices, pathogen exposure, and high reproductive rates appear to generate high requirements for energy expenditure among the Shuar. The rate of calorie intake and body fat deposition among the Shuar is likely limited by a high degree of reliance on garden and forest foods, along with limited access to highly processed calorie-dense market foods. The Shuar may therefore face sharper tradeoffs between alternative investments of metabolic effort compared to individuals in high-income, industrialized societies. These tradeoffs may influence the deployment of psychological responses to immune activation. In this study, we test whether greater inflammation is associated with stronger feelings of fatigue, sadness, or sickness in a sample of Shuar individuals.

3.2. Objectives and Hypotheses

Experimental studies in high-income, industrialized societies have demonstrated that acute inflammation can induce fatigue and low mood. Some clinical and epidemiological studies have reported evidence for associations between inflammation and depressive disorders/symptoms, and others have reported no evidence for these associations or mixed results. The apparent heterogeneity in associations between inflammation and mood raises questions about the dose and chronicity of inflammation required to induce fatigue and sadness. Here we test whether concentrations of C-reactive protein (CRP, a biomarker of inflammation) are associated with feelings of fatigue, sadness, or sickness among Shuar forager-horticulturalists. The Shuar typically

experience low levels of inflammation punctuated by short-term acute increases. We hypothesize that higher levels of CRP are associated with stronger feelings of fatigue (**Hypothesis 1**), stronger feelings of sadness (**Hypothesis 2**), and stronger feelings of sickness (**Hypothesis 3**).

Few previous studies have examined whether longer-term biomarkers of immune activation are associated with measures of mood. In this study, we also include measures of total Immunoglobulin G (IgG, the most common class of antibody) and total Immunoglobulin E (IgE; a class of antibody produced in response to macroparasite exposure) in our statistical models. We include these biomarkers to control for possible confounding effects of past infection and to explore potential associations between longer-term patterns of immune activation and current mood. CRP levels increase within hours of acute antigen exposure and often remain elevated for several days thereafter (Pepys & Hirschfield, 2003). IgG levels peak in the weeks following antigen exposure and gradually decline over the following months (Urlacher et al., 2018; Zhang et al., 2002). IgE concentrations increase in the months following antigen exposure and may remain elevated for years thereafter (Fitzsimmons et al., 2014).

3.3. Methods

Participants were sampled from two clusters of communities in the Morona-Santiago Province in southeastern Ecuador over a five-month time period in 2019. Participants from the first cluster lived in the Andean foothills near the Palora River (elevation ~1800m). Participants from the second cluster lived in the Upano River Valley (elevation ~900m), which runs between the Andes and Cutucú mountain ranges. In each

study community, the details of the study were publicly announced, and all eligible participants were invited to participate. Residents of study communities were eligible to participate if they identified as Shuar and were 15 years of age or older (the local age of majority). Due to the varying degrees of literacy in the study region, all data were collected using face-to-face protocols, and informed consent was obtained verbally from each participant. All study protocols were approved by the University of Oregon IRB and by community leaders in each study community.

Participants in both the mountain and valley communities lived within walking distance of a dirt road. The mountain communities had obtained road access more recently than the valley communities. The valley communities were closer to a regional market town (~30 min by motor vehicle) than the mountain communities (~2 hours by motor vehicle). The valley communities also had access to a bus route that connected rural communities to the regional market town. Most of the houses in the mountain communities were constructed from chainsaw-hewn wood planks, with a few concrete houses. The valley communities had roughly equal numbers of plank houses and government-built concrete houses.

Informal conversations with study participants suggested that the availability of wage work had declined in recent months, due to difficulties in the broader Ecuadorian economy.

3.2.1. Immune Biomarkers. Dried blood spot (DBS) samples were collected on Whatman 903 Proteinsaver cards (Maidstone, UK), using established protocols (McDade et al., 2007). The DBS samples were allowed to dry and then stored in a field freezer at -

15 to -20 C until being shipped on dry ice to the Global Health Biomarker Lab at the University of Oregon, where they were stored at -80 C until analysis.

We measured concentrations of C-reactive protein (CRP), total Immunoglobulin G (IgG), and total Immunoglobulin E (IgE) using enzyme-linked immune assays that have been validated in-house for use with DBS samples via comparison with venipuncture blood samples (Urlacher et al., 2018). All samples were measured in duplicate. Samples with CVs >15% between duplicate wells were rerun unless the absolute difference in readings was less than 0.02. The mean within-assay CVs for the samples included in the final analyses were 5.04% for CRP, 2.43% for IgG, and 5.93% for IgE. We fitted a standard curve using non-parametric four-parameter models with Gen5 software. All standard curves had r^2 values of 0.995 or greater. Biomarker values were natural log transformed prior to analysis. A few participants had concentrations below the lower limit of detection for CRP (n=1) or IgE (n=6). Values below the lower limit of detection were imputed with the lowest detected value divided by two. CRP and IgE were not normally distributed, and we natural log transformed them for analysis. IgG concentrations approximated a normal distribution. In all models, we standardized lnCRP, IgG, and lnIgE (mean=0, SD=1). For the remainder of this paper, we refer to the standardized values of these variables as CRP, IgG, and IgE. To compare the distribution of CRP values in our sample to distributions in other studies, we calculated serum equivalent CRP values using a formula generated using 40 matched DBS and serum samples in our laboratory: $e^{(1.2 * \ln CRP + 0.3405)}$; $r^2 = 0.87$.

3.2.2. Anthropometrics and Grip Strength. Anthropometric measurements were conducted with participants wearing light clothing and without shoes. Height was

measured in cm using a Seca stadiometer (Hamburg, Germany). Weight was measured in kg using a Tanita scale (Tokyo, Japan). Waist circumference was measured in cm using a flexible tape just above the iliac crest. Grip strength was measured using a Jamar hydraulic dynamometer (Performance Health, Warrenville, IL) with the participant seated, their upper arm pointing downward, and their forearm oriented at a right angle relative to the upper arm. Participants were instructed to briefly squeeze the dynamometer with as much force as possible. Two trials were conducted with each hand. To calculate our analytic grip strength variable, we took the mean of the higher value for each hand. Four participants had valid grip strength data for only one hand. For these participants, the higher value of the two trials from the hand with available data was assigned as their value for the analytic grip strength variable.

3.2.3. Fatigue, Sadness, and Sickness. In 2016, we conducted face-to-face structured interviews with 50 individuals (ages 15-69, 23 females, 27 males) in four Shuar communities to collect data to develop four brief, culturally appropriate scales to measure fatigue, vigor, sadness, and happiness. Respondents were read a list of mood-related adjectives and asked to rate on a five-point scale how well each adjective described how they felt that day. These adjectives were drawn from previous Spanish-language studies of mood (Rodríguez & Church, 2003; Sandín et al., 1999; Sanz Fernández et al., 2014). To reinforce the concept of an ordinal scale, participants were shown a graphical representation consisting of horizontal line connecting sequentially larger circles, each of which was labeled with the corresponding value of the scale.

Using these pilot data, we conducted an exploratory factor analysis for each scale using the 'psych' and 'GPArotation' packages in R. In the unrotated solution, principal

factors with eigenvalues greater than or equal to one were considered factors. A single factor was identified for each scale. Visual inspection of scree plots confirmed that a one-factor solution was appropriate for each scale.

Oblique rotation was used to examine standardized factor loadings. We initially piloted seven items for the fatigue scale. One of these was dropped from the final scale due to low familiarity. Two additional items were dropped due to factor loadings less than 0.3. We initially piloted six items for the Vigor Scale. One of these items was dropped due to low familiarity. We initially piloted 5 items for the Sadness scale, two of which were dropped due to low familiarity. We initially piloted 3 items for the Happiness Scale, one of which was removed due to low familiarity. So that each scale had at least three items, we tentatively added a highly familiar item to the Happiness Scale (*feliz*). The data collection protocol for this study consisted of a four-item Fatigue Scale, a five-item Vigor scale, a three-item Sadness scale, and a three-item Happiness Scale.

Based on our experiences with the pilot study, we changed the values of the numerical scale to 0-to-4 (instead of 1-to-5). We also asked participants how they were feeling “right now” instead of “today”.

The numerical values for each response were summed to create a score for each subscale (e.g., a higher score on the Fatigue subscale indicates stronger feelings of fatigue). To generate a continuous bipolar measure of fatigue/vigor, the vigor score was subtracted from the fatigue score, and the resulting value was rescaled to have a mean of 0 and a standard deviation of 1. For the resulting analytic variable, higher values indicate greater net fatigue. The same method was used to create a continuous bipolar measure using the Sadness and Happiness subscales. For the resulting analytic variable, higher

values indicate greater net sadness. When data were collected for this study, these subscales were interspersed with one another and data collection forms alternated between three arbitrarily assigned item orders.

Feelings of sickness were measured by asking participants to rate their feelings of sickness on a single-item ordinal scale ranging from 0 (not sick at all) to 4 (very sick).

3.2.4. Statistical Analysis. Some of the study participants were from the same households, so we included a random intercept term by household (n=88) in all models to account for this non-independence of cases. To facilitate mixed model convergence procedures, all continuous input variables were rescaled (mean=0, SD=1) prior to model estimation. Our fatigue and sadness variables are continuous and approximate a normal distribution. When fatigue and sadness were the output variables, we specified linear mixed models estimated using restricted maximum likelihood in the 'lme4' package in R. Feelings of sickness were measured using an ordinal variable. When sickness was the output variable, we used a cumulative link mixed model estimated using a logit link and a Laplace approximation in the 'ordinal' R package. All models also included fixed effects for age, sex, height, weight, waist circumference, and region.

3.4. Results

Data for this study were collected from 161 participants. Seven participants were not included in the analytic sample because they were missing data for one of the variables used in statistical analyses or because they were suffering from a severely disabling chronic illness. The final analytic sample consisted of 154 participants, ages 15-85. Descriptive statistics for the analytic sample are presented in **Table 3.1**. Standardized

Cronbach's α was α= 0.666 for the fatigue scale, α= 0.667 for the vigor scale, α= 0.554 for the sadness scale, and α= 0.713 for the happiness scale. Grouping all the negatively valenced items into one scale and all the positively valenced items together in another scale (much like the Positive and Negative Affect Schedule; PANAS) yielded two scales with greater reliability (standardized Cronbach's α=0.76 and α=0.779, respectively). The serum equivalent median concentration of CRP was 0.38 mg/L, the median absolute deviation was 0.47 mg/L, and the maximum value was 11 mg/L).

Table 3.1. Descriptive statistics for a sample of Shuar forager-horticulturalists (n=154)

Age in years (mean, SD)	38.5 (15.9)
Sex (n, %)	
Male	60 (38.96)
Female, not pregnant or lactating	66 (42.86)
Female, pregnant or lactating	28 (18.18)
Region (n, %)	
Mountain	75 (48.7)
Valley	79 (51.3)
Height in cm (mean, SD)	153.4 (7.7)
Weight in kg (mean, SD)	61.8 (12.9)
Waist in cm (mean, SD)	87.9 (9.6)
Do you feel sick? (n, %)	
Not at all	44 (28.57)
A little	44 (28.57)
Moderately	20 (12.99)
Quite	36 (23.38)
Very	10 (6.49)

We found no evidence that CRP (β=0.09, SE=0.08, P=0.245), IgG (β=-0.1, SE=0.08, P=0.24), or IgE (β=-0.06, SE=0.08, P=0.494) is associated with fatigue. We found no evidence that CRP (β=0.04, SE=0.08, P=0.665), IgG (β=0.006, SE=0.08, P=0.943), or IgE (β=-0.02, SE=0.09, P=0.818) is associated with sadness. Using the

individual subscales for output variables (instead of the net bipolar variables) did not change the interpretation of the results. Summing standardized values for scale items (instead of raw values) also did not change the interpretation of the results. Along the same lines, there was no evidence that CRP, IgG, or IgE were associated with either of the PANAS-like positive or negative affect scales.

We found that greater CRP is associated with stronger feelings of sickness (β=0.46, SE=0.15, P=0.002). We found no evidence that IgG (β=-0.02, SE=0.15, P=0.882) or IgE (β=-0.12, SE=0.15, P=0.419) is associated with feelings of sickness. Coefficients, standard errors, and P-values for models with fatigue, sadness, and sickness as the output variables are presented in **Table 3.2**.

3.5. Discussion

We found no evidence to support our hypotheses that greater inflammation is associated with stronger feelings of fatigue and sadness among Shuar forager-horticulturalists. We did find that higher levels of C-reactive protein (CRP) are associated with stronger feelings of sickness, measured using a single ordinal scale item.

A previous study conducted repeated weekly measures of CRP in a Shuar sample and found no evidence of chronic low-grade inflammation in any study participants, even though a substantial proportion of participants exhibited CRP >3 mg/L at one or more non-consecutive time point (McDade et al., 2012). This suggests that the CRP values >3 mg/L in our sample likely reflect acute inflammation, rather than chronic inflammation.

Table 3.2. Mixed models with fatigue, sadness, and sickness as output variables using data from a sample of Shuar forager-horticulturalists (n=154)

	Fatigue	Sadness	Sickness
Intercept			
β	-0.13	0.03	--
SE	0.19	0.19	--
P	0.497	0.873	--
Age			
β	0.15	0.13	0.2
SE	0.13	0.14	0.26
P	0.257	0.362	0.437
Sex (Ref=Male)			
Female, not pregnant or lactating			
β	0.37	-0.15	1.11
SE	0.29	0.31	0.59
P	0.211	0.619	0.057
Female, pregnant or lactating			
β	0.52	-0.06	0.43
SE	0.36	0.38	0.72
P	0.154	0.876	0.556
Region (Ref=Mountain)			
Valley			
β	-0.24	0.09	0.41
SE	0.18	0.19	0.36
P	0.185	0.624	0.262
Height			
β	0.15	0.05	0.59
SE	0.14	0.15	0.29
P	0.274	0.732	0.0408
Weight			
β	-0.23	-0.01	-1.4
SE	0.13	0.14	0.5
P	0.088	0.941	0.005
Waist			
β	-0.089	-0.2	0.77
SE	0.14	0.15	0.4
P	0.537	0.179	0.053
ln C-reactive protein			
β	0.09	0.04	0.46
SE	0.08	0.08	0.15
P	0.245	0.665	0.002

Table 3.2 Cont. Mixed models with fatigue, sadness, and sickness as output variables using data from a sample of Shuar forager-horticulturalists (n=154)

Immunoglobulin G			
β	-0.1	0.006	-0.02
SE	0.08	0.08	0.15
P	0.24	0.943	0.882
ln Immunoglobulin E			
β	-0.06	-0.02	-0.12
SE	0.08	0.09	0.15
P	0.494	0.818	0.419
Threshold Coefficients (SE)			
0|1	--	--	-0.3 (0.37)
1|2	--	--	1.13 (0.38)
2|3	--	--	1.79 (0.4)
3|4	--	--	3.84 (0.51)
Household (Random Effect)			
Intercept			
Variance	0.0891	0.0094	$7.592e^{-09}$
Std. Dev.	0.2985	0.0968	$8.713e^{-05}$
Residual			
Variance	0.814	0.9755	--
Std. Dev.	0.9022	0.9877	--

We found no evidence that higher levels of total Immunoglobulin G or total Immunoglobulin E are associated with stronger feelings of sickness. Although the role of innate immune responses in generating sickness behavior in animal models has been studied extensively (see Chapter 2), few previous studies have tested whether antibody concentrations (e.g., IgG or IgE) are associated with psychological features of sickness. The findings of this study are consistent with previous work highlighting the role of the acute phase immune response in generating the psychological and behavioral features of sickness (CRP is an acute phase protein) (McCusker & Kelley, 2013). The fact that a measure of innate immune activity is associated with feelings of sickness, but measures

of acquired immune activity are not, may ultimately reflect the comparatively high metabolic costs of inflammation (McDade et al., 2016). **Figure 3.1** plots standardized natural log-transformed CRP by reported feelings of sickness.

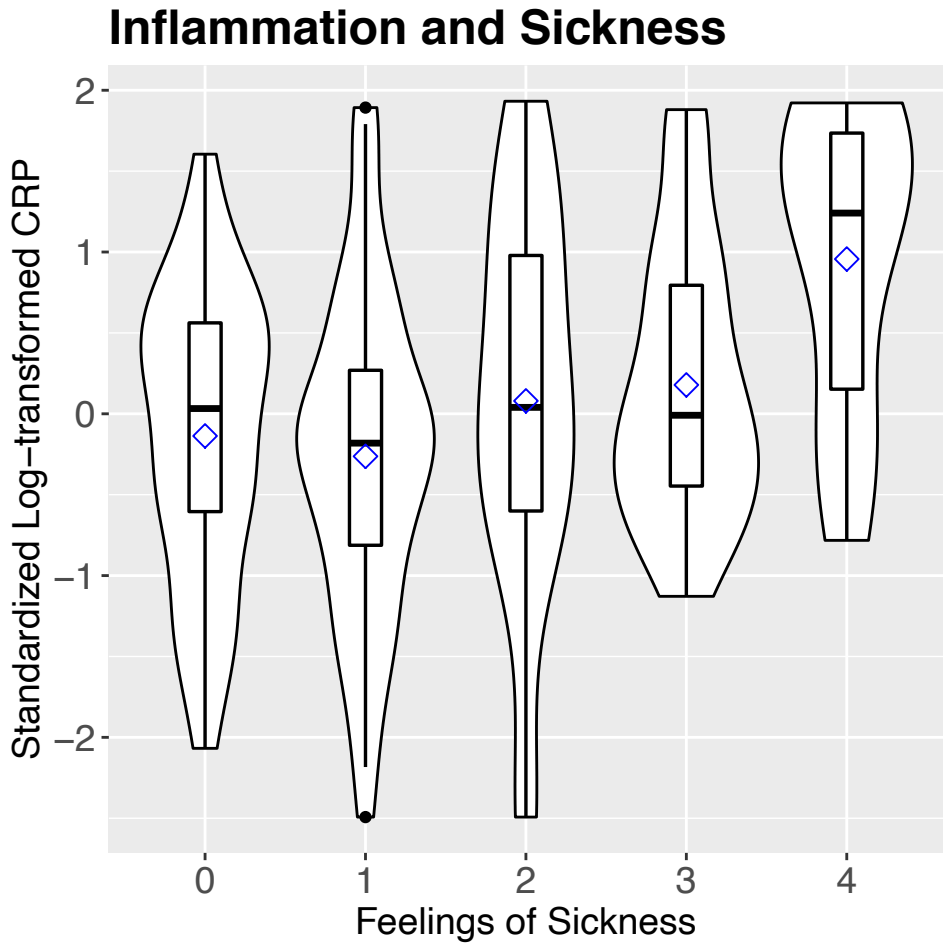


Figure 3.1. Inflammation and reported feelings of sickness. The *y*-axis depicts standardized natural log-transformed C-reactive protein (CRP) levels, with higher values indicating greater inflammation. The *x*-axis depicts responses on an ordinal scale to the question "do you feel sick?" Responses range from 0="not at all" to 4="very". Smoothed kernel density plots are overlaid with boxplots depicting median values and interquartile ranges. The blue diamonds indicate the mean concentration of CRP for each level of the ordinal sickness scale.

Why is CRP associated with feelings of sickness but not fatigue or sadness in this study? A number of studies using samples from western, industrialized societies have reported that greater inflammation is associated with fatigue and low mood, though there have also been studies reporting null results (Lasselin et al., 2020; Lee & Giuliani, 2019; Osimo et al., 2020). These studies have measured both inflammation and psychometric outcome variables in a variety of different ways. A study of Tsimane older adults (an indigenous forager-horticulturalist group in lowland Bolivia) found that higher levels of inflammation, measured using multiple biomarkers, were associated with a greater reported frequency of depressive symptoms (including tiredness and sadness) (Stieglitz et al., 2015). The Tsimane study asked respondents how frequently they experienced each symptom (e.g., never, rarely, often). Thus, their psychometric measures may reflect long-term patterns of affect, rather than the individual's current state. Nonetheless, the authors found that depressive symptoms scores were correlated with observer-ratings of participant joviality during other parts of the data collection protocol, which suggests depression measures were also correlated with contemporaneous mood.

It is worth noting that, in the Tsimane study, the median serum CRP concentration was 5.49 mg/L for those with scores on the depressive symptoms scale and 1.8 mg/L among those with low scores on the depressive symptoms scale. Thus, the median CRP concentration for the total Tsimane sample appears to be more than four times as high as the estimated median serum CRP concentration in our sample (0.38 mg/L). Along the same lines, a previous study found that concentrations of IgE are substantially higher among the Tsimane than the Shuar (Blackwell et al., 2011). These comparisons suggest that average levels of pathogen load and immune activation may be substantially higher

among the Tsimane than the Shuar. Another study was conducted in the Philippines among participants who, much like the Shuar, experience relatively frequent pathogen exposure but low median levels of inflammation (0.2 - 0.8 mg/L). That study reported no evidence of associations between biomarkers of inflammation and depressive symptoms. These comparisons between studies should be interpreted with caution, however, as the measures were obtained using different collection methods and assays.

One possible explanation for the apparent heterogeneity in associations between inflammation and low mood is that certain psychological features of inflammation may only emerge at sufficiently high doses of inflammation. It may be that the levels of acute inflammation necessary to detect increases in fatigue and sadness were not represented in this sample. In previous theoretical work, we hypothesized that the deployment of fatigue and sadness during immune activation depends on both the magnitude of the immune challenge and the opportunity costs of deploying fatigue and sadness (Schrock et al., 2020). The sensitivity of sickness behavior to opportunity costs has been demonstrated in a variety of studies using experimentally induced inflammation in animal models (see Chapter 2). Shuar livelihoods typically depend on demanding physical work. High levels of fatigue and sadness may reduce an individual's ability to allocate effort to physically demanding subsistence work. Thus, the average opportunity costs of upregulating fatigue and sadness may be greater for a Shuar or Tsimane individual than it would be for someone who is employed in a sedentary occupation. A higher dose of inflammation may be necessary to induce fatigue and sadness when opportunity costs are high.

Chronicity may also play a role in shaping the subjective experience of inflammation. In the next chapter of this dissertation, we report that greater cumulative

chronic morbidity is associated with stronger feelings of fatigue in large samples of adults in six culturally distinct countries. Associations between non-experimental inflammation and depressive symptoms in high-income, industrialized samples are generally thought to reflect chronic low-grade inflammation (Lee & Giuliani, 2019; Osimo et al., 2020). The higher end of the distribution of CRP in my sample likely reflects mild acute immune challenges, rather than chronic low-grade inflammation.

This is a cross-sectional study that collected data from each individual at only one time point. The reported associations between CRP and sickness reflect differences between individuals, rather than differences within the same individuals over time. Additional studies using repeated measures are needed to test whether within-person increases in CRP are associated with corresponding increases in feelings of sickness.

The results of this study suggest that mild inflammation may be associated with internally perceptible cues that are experienced as feelings of sickness, even when levels of inflammation are too low or too short-term to increase fatigue or sadness. These findings highlight the importance of investigating immune responses in a wide range of human environments beyond the high-income, industrialized societies where they are typically studied. Further work is needed to describe the dose dependencies, ecological parameters, and developmental reaction norms that shape the subjective experience of inflammation.

3.6. Bridge to Chapter IV

In Chapter III, I found that mild inflammation is associated with feelings of sickness in a sample of Shuar forager-horticulturalists. In contrast to a previous study

among Tsimane forager-horticulturalists, we found no evidence that inflammation is associated with fatigue or sadness. The Tsimane exhibit high pathogen loads and what appears to be high levels of chronic infectious disease-related inflammation. Another study was conducted in the Philippines among participants who, much like the Shuar, experience relatively frequent pathogen exposure but low median levels of inflammation. That study reported no evidence of associations between biomarkers of inflammation and depressive symptoms. These results raise questions about the dose and chronicity of inflammation needed to induce fatigue and sadness in real-world environments. Chronic degenerative diseases are often associated with chronic low-grade inflammation. In Chapter IV, I test whether greater cumulative chronic morbidity is associated with stronger feelings of fatigue in large samples of adults in six culturally distinct countries.

CHAPTER IV

CHRONIC MORBIDITY AND FATIGUE IN SIX COUNTRIES

4.1. Background and Objectives

Chronic degenerative diseases (e.g., heart disease, diabetes, cancer) now jointly account for most of the global burden of death and disability (James et al., 2018; Roth et al., 2018). Many of these chronic diseases, however, have likely been rare throughout most of our evolutionary history (Eaton et al., 1988). Epidemics of chronic degenerative disease tend to emerge in environments where extrinsic mortality rates are relatively low and obesity rates are relatively high (Armelagos et al., 2005).

Obesity-related chronic disease risk factors are rare in contemporary hunter-gatherers and other minimally market-integrated subsistence societies (Eaton et al., 1988; Kaplan et al., 2017; Pontzer et al., 2018). Infectious diseases, on the other hand, account for between 20 and 85 percent of deaths in contemporary and ethnographically known hunter-gatherer groups (Blurton Jones et al., 2002; Early & Headland, 1998; Hill et al., 2007; Hill & Hurtado, 1996; Howell, 1979; Burton Jones et al., 1992). The rise of agriculture (starting ~10,000 BP) likely brought about new sources of infectious disease risk, with dense population centers and proximity to domesticated animals (Houldcroft & Underdown, 2016; Omran, 2005).

In the past 100-200 years, global infectious disease mortality rates have declined (Holmes et al., 2017) and rates of obesity have increased (Caballero, 2007). In many countries, obesity was once associated with high socioeconomic status but is now

prevalent across social strata and disproportionately impacts those of low socioeconomic status (Pampel et al., 2012; Monteiro et al., 2004).

These changes have been accompanied by a dramatic global increase in chronic disease burden (Armelagos et al., 2005; James et al., 2018; Roth et al., 2018). Given the apparently recent rise of chronic degenerative disease as a major source of morbidity and mortality, our brains and bodies may be poorly equipped for dealing with these diseases (Gluckman & Hanson, 2004). Much of our susceptibility to chronic disease may be explained by mismatches between our evolved biology and contemporary environmental conditions (Corbett et al., 2018).

For example, humans have a propensity to generate large fat reserves when it is nutritionally feasible (Kuzawa, 1998). In the environments typical of our evolutionary history, the capacity to form large fat deposits likely helped our ancestors survive fluctuations in food availability (Wells, 2012). In contemporary environments characterized by calorie dense foods and sedentary occupations, our propensity for adiposity makes us vulnerable to obesity (Eaton et al., 1988).

Along the same lines, human immune systems seem to be mismatched with contemporary environments that are low in microbial diversity and feature low rates of exposure to infectious pathogens that were common for most of our evolutionary history (e.g., parasitic worms) (Bach, 2018). This lack of exposure to our long-time microbial and macroparasitic co-evolutionary companions may influence the development of our immune systems, making us vulnerable to allergies, autoimmune diseases, and inflammation-related disorders (Parker & Ollerton, 2013).

In this paper, we consider another feature of our evolved biology that may be mismatched with contemporary environments – disease-induced fatigue. Disease-induced fatigue probably promotes host survival during acute infection (more on this later). Disease-induced fatigue may be counterproductive, however, when it is deployed chronically in response to chronic degenerative disease.

Like other vertebrates, humans exhibit a typical neuropsychological response to internal immunological cues of infection or somatic damage (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015). This response often includes increased lethargy, social withdrawal, reduced appetite, and increased pain sensitivity (Dantzer & Kelley, 2007). Animal behaviorists and psychoneuroimmunologists refer to these changes as *sickness behavior* (Dantzer, 2004; Hart, 1990). These behavioral features of illness may be adaptive adjustments that help organisms fight acute infection and recover from acute somatic damage (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015).

In a recent paper, we reviewed evidence suggesting that humans possess an evolutionarily conserved neurocomputational program that scans for immunological cues of infection or injury (Schrock et al., 2020). When these cues are detected, this program coordinates a series of regulatory changes that help the sick host solve the adaptive problems posed by the detected pathology.

Depending on various contextual cues, these disease-induced changes may include: (a) increased fatigue to reduce physical activity, thereby making more energy available for the immune system; (b) increased sensitivity to nausea and pain to reduce the risk of acquiring additional infections or injuries that would compound the immune system's workload; (c) changes in temperature perception to promote thermoregulatory

behaviors that reduce the cost of maintaining or increasing body temperature; (d) changes in appetite to promote consumption behaviors (or lack thereof) that support the fight against infection; and (e) detectable changes in facial expressions, body language, and social behavior that signal to our social allies that we need help and support.

This kind of superordinate program – one that detects cues of a specific situation and, when the situation is detected, orchestrates other mechanisms to help solve the problems that come with it – is what some psychologists call an emotion (Sznycer et al., 2017; Tooby & Cosmides, 2008). We use the term *lassitude* to refer to this disease-activated emotion program and the regulatory state that it initiates (Schrock et al., 2020).

Acute infection, injury, and chronic degenerative disease are all associated with increases in pro-inflammatory immune activity (Del Giudice & Gangestad, 2018; Maes et al., 2012; McCusker & Kelley, 2013). Studies with human participants and animal models demonstrate that experimentally induced increases in pro-inflammatory cytokine production can initiate the psychological and behavioral changes characteristic of lassitude (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015).

During acute infection or injury, increased fatigue is thought to be a feature of lassitude that helps reduce physical activity, thereby making more energy available to mount an effective immune response (Lasselin et al., 2020; Lopes et al., 2014; Schrock et al., 2020). During chronic disease, however, low levels of physical activity are a risk factor for disease progression and the acquisition of additional morbidities (Booth et al., 2012; Kujala, 2006).

A number of studies have reported associations between higher levels of inflammation and greater fatigue (Lee & Giuliani, 2019). Some cases of chronic disease

appear to induce a chronic version of lassitude (Bower, 2014; Katon, 2011). Thus, chronic morbidity may initiate a vicious self-perpetuating cycle, in which increased chronic morbidity triggers increased chronic fatigue, and greater chronic fatigue leads to even greater chronic morbidity by reducing levels of physical activity.

This feedback loop connecting chronic disease, fatigue, and physical activity may play a role in generating the global pandemic of chronic degenerative disease. If this is the case, we expect greater cumulative chronic morbidity to be associated with higher levels of subjective fatigue. We test this prediction using large cross-sectional samples of adults from six culturally distinct countries.

4.2. Methodology

We utilized data from the World Health Organization's (WHO) Study on global AGEing and adult health (SAGE), Wave 1, which collected cross-sectional data on aging-related health and other selected factors among adults in six middle-income countries. In our analyses, we include all adults (ages 18+) from the SAGE Wave 1 dataset who have complete data for all variables included in our statistical models. Wave 1 data collection spanned 2007 to 2010. Data collection protocols for SAGE are described in detail elsewhere (Kowal et al., 2012). All SAGE study protocols were approved by WHO's Research Ethics Review Committee and by the ethical review organization with jurisdiction in each country.

4.2.1. Cumulative Chronic Morbidity. We created a cumulative chronic morbidity variable by summing the number of chronic conditions that each participant reported. Data were available on seven chronic conditions: arthritis, stroke, angina,

diabetes, chronic lung disease, asthma, and hypertension. For arthritis, angina, chronic lung disease, and asthma, we followed previously published protocols for coding each condition as either present or absent (Arokiasamy et al., 2017). A participant was coded as having the condition if they reported having been diagnosed with it, or if their responses to a diagnostic algorithm questionnaire indicated that they had the condition. Participants were coded as having hypertension if they reported ever having been diagnosed with it or if their measured resting blood pressure (average of three trials, except for the Mexico data, where an average of the two available trials was used) was greater than systolic=140 mmHg or diastolic=90 mmHg. Participants were coded as having diabetes if they reported having been diagnosed with it. Summing the number of chronic conditions for each individual generated a count variable ranging from 0 to 7.

4.2.2. Subjective Fatigue. We calculated a subjective fatigue score by summing responses to four questionnaire items. Question 1 asked, "Overall in the last 30 days, how much difficulty did you have in vigorous activities (vigorous activities require hard physical effort and cause large increases in breathing or heart rate)?" Question 2 asked, "Overall in the last 30 days, how much of a problem did you have due to not feeling rested or refreshed during the day?" Question 3 asked, "Do you have enough energy for everyday life?" Question 4 asked, "During the last 12 months, have you had a period lasting several days when you have been feeling your energy decreased or that you are tired all the time?" Questions 1-3 were answered on a 5-point scale, with higher values indicating greater subjective fatigue. Question 4 was a yes-or-no question, so we coded the response "no" as 1 and the response "yes" as 5 so that this item would have an

influence on the subjective fatigue score equivalent to the other three items. The resulting subjective fatigue score ranged from 5 to 20.

4.2.3. Sociodemographic Covariates. Age was reported as chronological age in years. Sex was reported as male or female. Household wealth was a composite measure based on possession of durable goods, dwelling characteristics, and access to services. Responses to 21 items were coded as "1" (denoting possession or access to the item) or "0" (denoting a lack of possession or access to the item). In a reshaped dataset, each response item was then treated as a separate observation for wealth in a pure random effects model, which produced indicator-specific thresholds for a latent wealth scale. Households were then arranged into a country-specific asset ladder using an empirical Bayes postestimation method. The value of this asset ladder was assigned to individuals as their wealth score.

4.2.4. Physical Covariates. A physical function score was calculated by combining performance on two different timed walk tasks and grip strength for each hand. One timed walk task involved walking four meters at a normal pace. The other timed walk task involved walking four meters as quickly as possible. Grip strength was measured using a dynamometer with two trials for each hand. We averaged the two trials in each hand to create an average for the dominant and non-dominant hands. If no dominant hand was reported, the right hand was coded as dominant. Normal walk time and rapid walk time were each standardized by stature separately for men and women. Dominant grip strength and non-dominant grip strength were each standardized by body weight separately for men and women. These standardized scores were combined to generate an overall physical function score. To remove implausible values and extreme

outliers, we dropped cases for which the physical performance score was more than four standard deviations from the mean.

Following the Global Physical Activity Questionnaire (GPAQ) analysis guide (Armstrong & Bull, 2006), we calculated a habitual physical activity variable that multiplies the minutes per week spent in each category of activity by the metabolic equivalent (MET) for that activity (the estimated ratio of total energy expenditure required to perform the task to the energy expenditure required for just resting). The resulting MET-minutes variable integrates the both the quantity and intensity of an individual's habitual physical activity.

Body mass index (BMI, kg/m^2) was calculated from stature and weight measured using standard protocols.

4.2.5. Statistical Analysis. In analyses with all countries combined, we specified mixed-effects linear models with participants nested in countries (i.e., with a random effect for country) in the R package "lme4" (version 1.1-19). In analyses that considered each country separately, we specified ordinary least squares multiple regression models in base R (version 3.5.0). We created plots using the R package "ggplot2" (version 3.1.0).

In the first set of models, only cumulative chronic morbidity and an intercept term were included as predictors of subjective fatigue. In the second set of models, the sociodemographic covariates (age, sex, wealth) were included, in addition to the terms in the first set of models. In the third set of models, the physical covariates (physical function score, habitual physical activity, BMI, BMI^2) were included, in addition to the terms in the second set of models.

Models with physical covariates included terms for both BMI and BMI^2 because we expected BMI to have both linear effects (greater body mass represents greater energetic reserves and, therefore, less subjective fatigue) and curvilinear effects (those in the underweight and obese extremes of BMI are expected to have greater subjective fatigue).

All variables except age, sex, and cumulative chronic conditions were standardized prior to analysis. Habitual physical activity (MET-minutes) and subjective fatigue scores were positively skewed, and were natural log-transformed prior to standardization.

4.3. Results

The distribution of age, sex, and cumulative chronic morbidity by country is presented in **Table 4.1.** Model 1 included fixed effects for cumulative chronic morbidity, a random effect for country, and the model intercept as predictors of subjective fatigue. Greater cumulative chronic morbidity was associated with greater subjective fatigue (β=0.34, SE=0.005, P<2e-16). Model 2 contained all of the terms in Model 1 as well as fixed effects for age, sex, and wealth. Greater cumulative chronic morbidity was also associated with greater subjective fatigue in Model 2 (β=0.25, SE=0.005, P<2e-16). Model 3 contained all of the terms in Model 2, as well as fixed effects for physical function score, habitual physical activity, BMI, and BMI^2. Greater cumulative chronic morbidity was also associated with greater subjective fatigue in Model 3 (β=0.25, SE=0.005, P<2e-16).

Table 4.1. Sample distribution of sex, age, and cumulative chronic disease burden by country

	China (n=12,319)	Ghana (n=3,792)	India (n=9,271)	Mexico (n=1,888)	Russia (n=2,387)	South Af. (n=2,798)	Total (N=32,455)
Female n(%)	6566(53.3)	1693(44.6)	5603(60.4)	1150(60.9)	1499(62.8)	1564(55.9)	18075(55.7)
Age μ(SD)	60(11.7)	58.7(14)	49.1(16.4)	61.7(13.9)	59.9(12.8)	59.8(12.2)	56.8(14.6)
Number of chronic conditions n(%)							
0	3548(28.8)	1155(30.5)	4353(47)	467(24.7)	533(22.3)	490(17.5)	10546(32.5)
1	5093(41.3)	1762(46.5)	2909(31.4)	796(42.2)	621(26)	1465(52.4)	12646(39)
2	2467(20)	695(18.3)	1269(13.7)	423(22.4)	625(26.2)	574(20.5)	6053(18.7)
3	834(6.8)	149(3.9)	494(5.3)	142(7.5)	348(14.6)	185(6.6)	2152(6.6)
4	280(2.3)	23(0.6)	189(2)	43(2.3)	171(7.2)	60(2.1)	766(2.4)
5	83(0.7)	4(0.1)	49(0.5)	14(0.7)	74(3.1)	20(0.7)	244(0.8)
6	12(0.1)	4(0.1)	6(0.06)	2(0.1)	14(0.6)	4(0.14)	42(0.1)
7	2(0.02)	0(0)	2(0.02)	1(0.05)	1(0.04)	0(0)	6(0.02)

4.3.1. Analyses by Country. Analyses stratified by country included the same set fixed effect terms as the pooled analyses with all countries combined. In Model 1, greater cumulative chronic morbidity was associated with greater subjective fatigue in all countries: China (β=0.29, SE=0.007, P<2e-16), Ghana (β=0.315, SE=0.017, P<2e-16), India (β=0.392, SE=0.01, P<2e-16), Mexico (β=0.323, SE=0.021, P<2e-16), Russia (β=0.394, SE=0.014, P<2e-16), South Africa (β=0. 0.345, SE=0.016, P<2e-16).

In Model 2, greater cumulative chronic morbidity was also associated with greater subjective fatigue in all countries: China (β=0.222, SE=0.007, P<2e-16), Ghana (β=0.217, SE=0.015, P<2e-16), India (β=0.262, SE=0.009, P<2e-16), Mexico (β=0.27, SE=0.021, P<2e-16), Russia (β=0.323, SE=0.014, P<2e-16), South Africa (β=0.315, SE=0.016, P<2e-16).

The same was true in Model 3: China (β=0.228, SE=0.007, P<2e-16), Ghana (β=0.207, SE=0.015, P<2e-16), India (β=0.262, SE=0.009, P<2e-16), Mexico (β=0.271, SE=0.021, P<2e-16), Russia (β=0.31, SE=0.015, P<2e-16), South Africa (β=0.299, SE=0.016, P<2e-16).

In **Table 4.2**, we present coefficients, standard errors, and P-values for all models. In **Figure 4.1**, we use violin plots and plotted lines representing marginal effects to visualize the relationship between cumulative chronic morbidity and subjective fatigue by country.

4.4. Conclusions and Implications

We find that greater cumulative chronic morbidity is consistently associated with greater subjective fatigue. In most models, having approximately three or four additional chronic conditions is associated with a full standard deviation increase in levels of subjective fatigue. This pattern is remarkably consistent across samples from six countries that are culturally and geographically distinct.

Table 4.2. Linear models predicting subjective fatigue scores

	All Countries (N=32,455)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.36	-1.62	-1.47
SE	0.11	0.17	0.15
P	0.0225	0.0002	0.0001
Chronic Conditions			
β	0.34	0.25	0.25
SE	0.005	0.005	0.005
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.23	0.23
SE		0.009	0.009
P		< 2e-16	< 2e-16
Age			
β		0.021	0.019
SE		0.0004	0.0004
P		< 2e-16	< 2e-16
Wealth			
β		-0.204	-0.186
SE		0.006	0.006
P		< 2e-16	< 2e-16
Physical Function			
β			-0.083
SE			0.005
P			< 2e-16
Physical Activity			
β			-0.018
SE			0.005
P			0.0003
BMI			
β			-0.09
SE			0.006
P			< 2e-16
BMI^2			
β			0.061
SE			0.006
P			< 2e-16

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Country (Random Effect)			
Intercept			
Variance	0.07493	0.1616	0.1234
Std. Dev.	0.2737	0.402	0.3513
Residual			
Variance	0.80514	0.6893	0.6791
Std. Dev.	0.8973	0.8302	0.8241
BIC	85155.86	80177.15	79763.3
AIC	85122.31	80118.43	79671.04
Log Likelihood	-42557.2	-40052.2	-39824.5

	China (n=12,319)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.617	-1.70	-1.53
SE	0.012	0.039	0.042
P	< 2e-16	< 2e-16	< 2e-16
Chronic Conditions			
β	0.29	0.222	0.228
SE	0.007	0.007	0.007
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.181	0.181
SE		0.014	0.014
P		< 2e-16	< 2e-16
Age			
β		0.015	0.013
SE		0.0007	0.0007
P		< 2e-16	< 2e-16
Wealth			
β		-0.288	-0.278
SE		0.009	0.009
P		< 2e-16	< 2e-16
Physical Function			
β			-0.076
SE			0.009
P			< 2e-16

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Physical Activity			
β			-0.012
SE			0.007
P			0.103
BMI			
β			-0.106
SE			0.012
P			< 2e-16
BMI^2			
β			0.056
SE			0.013
P			0.00001
BIC	31112.68	29312.67	29194.04
AIC	31090.42	29268.16	29119.85
Log Likelihood	-15542.2	-14628.1	-14549.9

	Ghana (n=3,792)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.084	-1.78	-1.68
SE	0.022	0.056	0.603
P	0.0002	< 2e-16	< 2e-16
Chronic Conditions			
β	0.315	0.217	0.207
SE	0.017	0.015	0.015
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.286	0.323
SE		0.026	0.026
P		< 2e-16	< 2e-16
Age			
β		0.029	0.026
SE		0.0009	0.001
P		< 2e-16	< 2e-16
Wealth			
β		-0.148	-0.123
SE		0.016	0.017
P		< 2e-16	1.38^{-13}

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Physical Function			
β			-0.093
SE			0.013
P			8.86^{-13}
Physical Activity			
β			0.035
SE			0.014
P			0.012
BMI			
β			-0.073
SE			0.017
P			0.00001
BMI^2			
β			0.045
SE			0.018
P			0.0133
BIC	9983.667	8945.119	8904.073
AIC	9964.946	8907.675	8841.666
Log Likelihood	-4979.47	-4447.84	-4410.83

	India (n=9,271)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.063	-1.32	-1.27
SE	0.013	0.035	0.04
P	0.000001	< 2e-16	< 2e-16
Chronic Conditions			
β	0.392	0.262	0.262
SE	0.01	0.009	0.009
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.337	0.326
SE		0.019	0.019
P		< 2e-16	< 2e-16
Age			
β		0.028	0.025
SE		0.0006	0.0007
P		< 2e-16	< 2e-16

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Wealth			
β		-0.226	-0.196
SE		0.01	0.011
P		< 2e-16	< 2e-16
Physical Function			
β			-0.117
SE			0.015
P			5.90^{-15}
Physical Activity			
β			-0.006
SE			0.011
P			0.58
BMI			
β			-0.081
SE			0.012
P			3.08^{-11}
BMI^2			
β			0.063
SE			0.015
P			0.00001
BIC	25515.64	23328.67	23231.41
AIC	25494.24	23285.86	23160.07
Log Likelihood	-12744.1	-11636.9	-11570.03

	Mexico (n=1,888)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.396	-1.23	-0.987
SE	0.033	0.1	0.113
P	< 2e-16	< 2e-16	< 2e-16
Chronic Conditions			
β	0.323	0.27	0.271
SE	0.021	0.021	0.021
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.337	0.319
SE		0.043	0.044
P		8.67^{-15}	3.72^{-13}

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Age			
β		0.011	0.006
SE		0.002	0.002
P		2.06^{-11}	0.0004
Wealth			
β		-0.081	-0.072
SE		0.029	0.029
P		0.005	0.014
Physical Function			
β			-0.114
SE			0.033
P			0.0006
Physical Activity			
β			-0.08
SE			0.019
P			0.00004
BMI			
β			-0.051
SE			0.039
P			0.198
BMI^2			
β			0.014
SE			0.03
P			0.649
BIC	5095.952	5008.227	5004.198
AIC	5079.322	4974.967	4948.765
Log Likelihood	-2536.66	-2481.49	-2464.38

	Russian Federation (n=2,387)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.387	-1.33	-1.1
SE	2.95E-02	8.93E-02	1.01E-01
P	< 2e-16	< 2e-16	< 2e-16
Chronic Conditions			
β	0.394	0.323	0.31
SE	0.014	0.014	0.015
P	< 2e-16	< 2e-16	< 2e-16

Table 4.2 Cont. Linear models predicting subjective fatigue scores

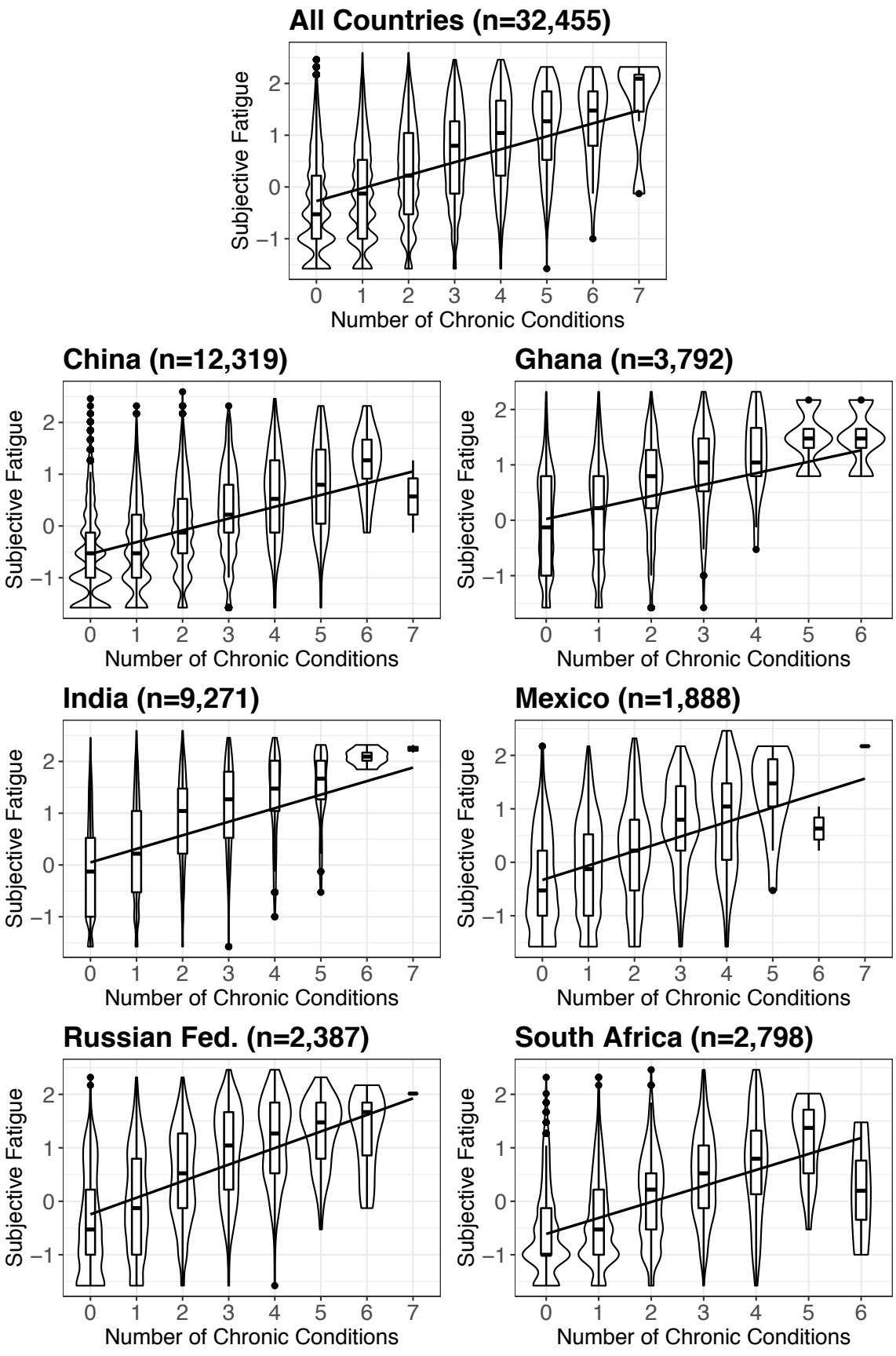
Sex			
β		0.282	0.259
SE		0.038	0.038
P		8.12^{-14}	1.18^{-11}
Age			
β		0.014	0.011
SE		0.002	0.002
P		< 2e-16	1.26^{-10}
Wealth			
β		-0.106	-0.088
SE		0.027	0.027
P		0.00008	0.001
Physical Function			
β			-0.089
SE			0.018
P			0.000001
Physical Activity			
β			-0.016
SE			0.023
P			0.502
BMI			
β			-0.017
SE			0.031
P			0.584
BMI^2			
β			0.03
SE			0.022
P			0.177
BIC	6315.323	6168.611	6170.37
AIC	6297.99	6133.945	6112.592
Log Likelihood	-3146	-3060.97	-3046.3

	South Africa (n=2,798)		
	Model 1	**Model 2**	**Model 3**
Intercept			
β	-0.669	-1.5	-1.28
SE	0.026	0.078	0.079
P	< 2e-16	< 2e-16	< 2e-16

Table 4.2 Cont. Linear models predicting subjective fatigue scores

Chronic Conditions			
β	0.345	0.315	0.299
SE	0.016	0.016	0.016
P	< 2e-16	< 2e-16	< 2e-16
Sex			
β		0.127	0.153
SE		0.031	0.031
P		0.0004	8.07^{-7}
Age			
β		0.014	0.011
SE		0.001	0.001
P		< 2e-16	< 2e-16
Wealth			
β		-0.094	-0.086
SE		0.016	0.016
P		1.20^{-08}	1.28^{-07}
Physical Function			
β			-0.087
SE			0.009
P			< 2e-16
Physical Activity			
β			-0.075
SE			0.012
P			4.60^{-10}
BMI			
β			-0.097
SE			0.021
P			2.51^{-06}
BMI^2			
β			0.05
SE			0.013
P			0.0001
BIC	6929.116	6780.346	6657.881
AIC	6911.306	6744.726	6598.514
Log Likelihood	-3452.65	-3366.36	-3289.26

Figure 4.1 (next page). Cumulative chronic morbidity and subjective fatigue. Plotted lines represent marginal effects from linear models.


All Countries (n=32,455)
China (n=12,319)
Ghana (n=3,792)
India (n=9,271)
Mexico (n=1,888)
Russian Fed. (n=2,387)
South Africa (n=2,798)
Subjective Fatigue
Number of Chronic Conditions

Adding key physical variables to the model (physical function score, habitual physical activity, BMI, BMI^2) does not substantially diminish the association between cumulative chronic morbidity and subjective fatigue in any model, which suggests that this association is not mediated by declines in physical capacity. Plotting subjective fatigue by number of chronic conditions reveals a dose-response pattern – each additional chronic condition is associated with a higher level of subjective fatigue. This pattern suggests that subjective fatigue is actually associated with cumulative chronic morbidity, not just with one or two of the chronic conditions aggregated in the variable.

Our findings suggest that subjective fatigue may be useful as a low-cost, non-invasive marker of cumulative pathology across a variety of physiological systems. Our findings dovetail with a previous study of the general UK population, which found that greater fatigue predicted higher hazards of all-cause and cardiovascular disease-related mortality, even after adjusting for a variety of potential confounders (Basu et al., 2016). Along the same lines, a study of older US adults found that a single-item measure of fatigue at baseline ("do you feel tired most of the time?") predicted mortality rates ten years later (Hardy & Studenski, 2008).

In this study, we utilize relatively low-resolution measures of cumulative chronic morbidity and subjective fatigue. Even so, we find that greater cumulative chronic disease burden exhibits consistent associations with greater subjective fatigue. Using measures that capture a wider range and finer grain of variation in these variables might yield even stronger associations between cumulative chronic morbidity and fatigue.

We hypothesize a bidirectional relationship between chronic morbidity and fatigue – greater morbidity induces greater fatigue, and greater fatigue increases risks for

additional morbidity by reducing long-term levels of physical activity. This study is cross-sectional. Further research is needed to evaluate causal pathways running in both directions. Clinical research is also needed to test whether interventions that reduce chronic disease-related fatigue are also successful in reducing subsequent morbidity and mortality.

There are specific features of many contemporary environments that may contribute to chronic disease-induced fatigue. Low microbial diversity, low rates of exposure to ancestrally common pathogens, and obesity are all thought to play a role in the etiology of chronic inflammation (Bach, 2018; Ellulu et al., 2017; Parker & Ollerton, 2013). Experimental studies have demonstrated that inflammatory processes play a key mechanistic role in inducing disease-related changes in behavior and psychology, including increased fatigue (McCusker & Kelley, 2013). Thus, chronic inflammation may initiate the self-reinforcing feedback cycle of declining physical activity and increasing chronic morbidity, even before the appearance of clinically identifiable chronic disease.

Experimental research with animal models demonstrates that disease-induced behavior changes are regulated in ways that are highly sensitive to the costs and benefits of a given change. For example, a study of rhesus monkeys (*Macaca mulatta*) found that sick monkeys were more somnolent than non-sick monkeys when they were in a quiet environment but not when they were challenged by direct eye contact with a human experimenter (Friedman et al., 1996). In fact, sick monkeys exhibited more agonistic behavior than non-sick monkeys when exposed to the human intruder. The perceived threat from the human intruder seems to have provided an alternative motivation that was strong enough to outweigh sickness-induced somnolence.

For humans who have occupations requiring high levels of physical activity (e.g., subsistence farmers), the economic and social need to engage in the requisite work tasks may provide a motivation to engage in physical activity that counterbalances chronic disease-induced fatigue when it occurs. For those engaged in sedentary occupations (e.g., office workers), there may be few naturally occurring motivations to engage in physical activity that are sufficiently strong to counterbalance chronic disease-induced fatigue. Humans may have an evolved tendency to avoid unnecessary exertion (Lieberman, 2015). Thus, people in sedentary occupations may be particularly susceptible to feedback cycles of declining physical activity and increasing chronic morbidity.

While further work is needed, the results reported here are consistent with the hypothesis that increased fatigue is a common response to chronic degenerative disease. Evolutionary scientists have proposed that certain human traits, such as our propensity for adiposity and our immunological development programs, are mismatched with contemporary environments where diets are calorie-dense, occupations are sedentary, microbial diversity is low, and ancestrally common pathogens are rare. During acute illness, disease-induced fatigue may improve host survival by reducing physical activity, thereby making more energy available to mount an immune response. In many cases of chronic illness, disease-induced reductions in physical activity may increase risks of disease progression and acquisition of additional morbidities. Chronic disease-induced fatigue may be another example of an evolved mechanism that is often mismatched with many of the environments that humans currently inhabit.

4.5. Bridge to Chapter V

Chapter II described the regulatory state of sickness and explained how different dimensions of sickness help the host solve the adaptive problems posed to the host when the immune system is activated. Chapter III reported that mild inflammation is associated with stronger feelings of sickness but not fatigue or sadness among Shuar forager-horticulturalists. Chapter IV reported that greater cumulative chronic morbidity is associated with stronger feelings of fatigue in large samples of adults from six culturally distinct countries. Most of the dissertation up to this point has been concerned with how experiences of sickness might vary as a function of an individual's physiological or ecological context.

Chapter V sets the stage for a different but related question – what explains the distinctive social features of sickness in humans? Humans have very large brains, both in absolute terms and relative to body size. Humans spend a substantially greater proportion of their metabolic budgets on brains than do other extant primates. The human adaptive complex that manages the metabolic costs of large brains may also play a role in shaping what sickness behavior looks like in humans. One of the primary behavioral features of sickness is increase resting time and reduced engagement in energetically expensive activities. If brain size also shapes time allocation, it may have consequences for the deployment of sickness behavior. To begin pursuing this line of inquiry, I compare patterns of brain size, body size, diet quality, and time allocation in a sample of diurnal primate species.

CHAPTER V

BRAIN SIZE, BODY SIZE, AND TIME ALLOCATION IN PRIMATES

5.1. Introduction

Large brains and large bodies are metabolically costly (Leonard et al., 2007; C. R. White & Seymour, 2003). Evolutionary biologists and anthropologists have proposed a number of hypotheses to explain why these traits evolve and how large-brained and large-bodied animals afford these metabolic costs (Aiello & Wheeler, 1995; Blanckenhorn, 2000; DeCasien et al., 2017; Dunbar, 2009; Sailer et al., 1985). Time is a finite resource, and time allocation is a fundamental factor in determining an animal's energy intake and expenditure. Thus, particular time allocation strategies may be useful in helping animals manage the energy costs of large brains and large bodies. Furthermore, brain and body size may shape the relative benefits that can be obtained from investing time in different kinds of activities. Yet, relatively little is known about how brain size and body size relate to patterns of time allocation (but see Fonseca-Azevedo & Herculano-Houzel, 2012).

The primate order exhibits a wide range of variation in brain size and body size (Powell et al., 2017; Sailer et al., 1985). In general, primates tend to be highly encephalized (high relative brain-to-body mass) compared to members of other mammalian orders (Boddy et al., 2012). Human brains are very large compared to other extant primates, roughly 2-3 times the size of the other great apes (Fonseca-Azevedo & Herculano-Houzel, 2012). Adult human body weights, in contrast, are within the range of body weights found in other extant great apes. Identifying the behavioral correlates of

brain size and body size evolution in primates may offer insight on the selection pressures underlying human evolution. Here we test whether brain size and body size are associated with patterns of time allocation in a sample of 42 diurnal primate species.

5.1.1. Why Do Large Brains Evolve? The brain is one of the most energetically expensive organs per unit of mass (Aiello & Wheeler, 1995; Isler & van Schaik, 2006). Given the substantial costs of brain metabolism, it stands to reason that a large brain offers a set of functional benefits that, in some lineages, compensated for its metabolic costs. There are several different candidates for the selection pressures that drive the evolution of large brains in primates. Some have argued that social group size and complexity are major drivers of brain size evolution (Dunbar, 2009). Being a member of a large group may be associated with reduced predation risk (Creel et al., 2014). Large brains may confer cognitive capacities that reduce the conflict-related costs or increase the coordination-related benefits of living in large, complex groups (Cowl & Shultz, 2017; Dunbar & Shultz, 2017). Others have suggested that social learning may play an important role in driving the evolution of large brains (Street et al., 2017).

There is also evidence to suggest that the evolution of large brain size is associated with complex adaptations for foraging (DeCasien et al., 2017; Heldstab et al., 2016). Social and foraging-related explanations are not necessarily mutually exclusive (Dunbar & Shultz, 2017). Social group dynamics may present novel foraging opportunities and challenges that would not otherwise exist. Conversely, a species' foraging ecology may shape the costs and benefits of different group sizes and structures.

5.1.2. How Do Primates Afford Large Brains? Large brain size may provide certain functional benefits, but it also generates substantial metabolic costs (Isler & van

Schaik, 2006; Leonard et al., 2007). Thus, selection pressures that favor large brain size likely arise in tandem with selection pressures that favor adaptations for accommodating the energy costs of large brains.

A variety of hypotheses have been put forward to explain how highly encephalized hominins were able to afford the energy costs of having brains that are much larger than expected relative to body size. One way to make more energy available for brain metabolism is to decrease the energy requirements of the rest of the body. There is some evidence to suggest that reduced investment in non-brain metabolism evolved in the human lineage. While humans spend far more on brain metabolism than other extant primates, our overall resting metabolic rates are not exceptional for a primate of our body weight (Leonard & Robertson, 1997). This apparently reduced investment in non-brain metabolism may be explained in part by reduced muscularity compared to other primates (Leonard et al., 2007). Humans also possess exceptionally large adipose tissue reserves compared to other extant primates, which may serve to buffer brain metabolism during periods of low food availability (Altmann et al., 1993; Kuzawa, 1998; Wells, 2012).

Other scholars have proposed that certain diet-related adaptations increase food quality or foraging efficiency, thereby making more energetic resources available for brain metabolism. The hypothesized adaptations that may have played a role in supporting increased brain size in humans include increases in the consumption of meat (Milton, 1999), cooking (Wrangham et al., 1999), tool use (Ambrose, 2001), cooperative breeding (Isler & van Schaik, 2012), and food sharing (Herman Pontzer, 2012). It has also been proposed that high quality diets allow reduced investment in metabolically costly digestive tissues, freeing up more resources for brain metabolism (the *Expensive*

Tissue Hypothesis) (Aiello & Wheeler, 1995). The empirical predictions of the Expensive Tissue Hypothesis have received mixed support (Fish & Lockwood, 2003; Navarrete et al., 2011).

5.1.3. Why Do Large Bodies Evolve? Competition over mates or resources may drive the evolution of larger body size, as larger bodies likely offer competitive advantages in certain ecological contexts (Blanckenhorn, 2000). For example, intraspecific comparisons have revealed that larger female body size is associated with greater fecundity in Prussian carp (*Carassius gibelio*) (Tarkan et al., 2007), various species of insects (Honěk, 1993), the common frog (*Rana temporaria*) (Cummins, 1986), and moose (*Alces alces*) (Sand, 1996). In species in which males compete directly with one another over mates, larger male body size is often associated with greater mating success in males (Hagelin, 2002; Serrano-Meneses et al., 2007). In a study comparing primate species, greater male-male competition was associated with greater sexual dimorphism in body size (Plavcan & Schaik, 1997). In mating systems that emphasize female mate choice, females are often more likely to select larger-bodied males as mates (Cooper & Vitt, 1993; Howard et al., 1998). Larger body size may also reduce vulnerability to predation in some food webs (Woodward & Hildrew, 2002). Many taxonomic groups exhibit a trend toward larger body size over time, a phenomenon known as *Cope's Rule* (Stanley, 1973). In contrast to studies within species, comparisons between species suggest that larger-bodied species exhibit lower rates of fecundity, which may put large-bodied species at greater risk for extinction (Allainé et al., 1987; Bennett & Owens, 1997). This size-related extinction risk might play a role in shaping the distribution of body sizes represented in extant taxa.

5.1.4. How Do Primates Afford Large Bodies? Metabolic rates increase with body size, but this increase is negatively allometric (C. R. White & Seymour, 2003). While absolute metabolic rates are higher in animals with larger bodies, metabolic rates per unit of weight tend to be lower for larger animals, all else equal. This suggests that larger body size may be associated with gains in energetic efficiency. Larger digestive systems may provide greater relative capacity for processing structural plant matter (e.g., stems and leaves) (Müller et al., 2013). Structural plant matter offers fewer calories per unit of food consumed, but it is generally more readily available. In primates, larger body size is associated with lower diet quality (Sailer et al., 1985). Large body size tends to coevolve with feeding ecologies characterized by low-quality but abundantly available food, a pattern sometimes called the *Jarman-Bell Principle* (Gaulin, 1979). Locomotor efficiency also appears to increase with larger body size (Alexander, 2005).

5.1.5. Brain Size, Body Size, And Time Allocation. Time allocation plays a key role in determining how an individual obtains and expends energy. For example, certain kinds of intensive movement (e.g., rapid locomotion) can dramatically increase an organism's rate of energy expenditure (Hanna & Schmitt, 2011). Time allocation also plays a key role in energy intake. In order to acquire calories from the environment, a primate must spend time foraging, feeding, and moving between patches (McGraw & Daegling, 2012). Optimal subsistence strategies must balance the expected nutritional yield of a given foraging or feeding behavior against its expected time and energy costs.

There are two potential time allocation strategies that an animal could use to make more energy available to support a large brain or body, all else being equal. One potential strategy is to increase the proportion of time spent resting, thereby reducing the calories

spent on physical activity. Another potential strategy is to spend more time pursuing food to increase total energy intake.

With these alternative strategies in mind, there are a few plausible hypotheses about associations between brain size, body size, and time allocation:

1. ***The Resting Hypothesis:*** Species with larger brains and bodies spend a greater proportion of their time resting to compensate for the energy costs of larger brains and larger bodies.
2. ***The Feeding Hypothesis:*** Species with larger brains and larger bodies spend a greater proportion of their time on subsistence and travel, which enables them to obtain more calories from the environment.
3. ***The Idiosyncratic Strategy Hypothesis:*** Time allocation strategies are highly particular to a given context and therefore do not exhibit clear patterns of association with brain size or body size.
4. ***The Divergent Strategy Hypothesis:*** Brain size and body size are associated with contrasting time allocation patterns. In other words, one of the patterns described above holds for brain size but not body size (and vice versa).

To adjudicate between these hypotheses, we test whether brain size and body size are associated with patterns of time allocation using data from 42 diurnal primate species.

5.2. Methods

5.2.1. Time Allocation And Social Group Size. Data on time allocation and social group size for each species were drawn from a published dataset (Pollard & Blumstein, 2008). The authors aggregated data on time budgets in free-living, diurnal primate groups, collected via instantaneous or focal sampling. They did not include time budgets when they represented only one season or sex unless an equal number of studies were available for the other season or sex. Time budgets were divided into percentages of observed time in spent four mutually exclusive and exhaustive categories (Resting, Subsistence, Locomotion, Other). When more than one time budget was available for a species, they averaged the values for each component of the budget and rescaled the values to sum to 100%.

Their group size variable was also generated from studies of free-living groups and included both males and females. For fission-fusion species, they assigned values for group size that reflected "the size of the largest stable exclusive group" (p.1686).

5.2.2. Brain And Body Weight. Data on species-typical brain and body weight (averaged between sexes) in g were drawn from DeCasien et al. (2017). When data sources reported endocranial volume (ECV) as a measure of brain size, the authors multiplied the number of cubic centimeters by 1.036 g cm^{-3}, the specific gravity of brain tissue. When both brain weight and ECV were reported, the authors averaged the values for weight in g and the ECV values converted to g. Values for both weight and ECV were available for a subset of species (n=79): "(1) corrected ECV and weight measurements were highly correlated ($R^2 = 0.99$); (2) the mean difference (corrected ECV – weight) was 0.62 g with a 95% CI including zero (−1.81 to 3.05 g); and (3) there was low

correlation ($R^2 = 0.20$) between the mean value of the two methods and the difference" (p. 4).

The authors (DeCasien et al., 2017) compiled body weight data in g from CRC Handbook of Mammalian Body Masses (Silva-Aliaga & Downing, 1995), the AnAge database (Tacutu et al., 2013), and the PanTHERIA database (K. E. Jones et al., 2009). They used body weight values from other secondary sources when necessary (Harvey et al., 1987; Plavcan & Schaik, 1997; Smith & Jungers, 1997).

5.2.3. Diet Quality. We used an established quantitative index of diet quality that assigns different weights to structural plant foods, reproductive plant foods, and faunal foods based on their putative caloric density. The diet quality index (DQ) is calculated using the following formula:

$$DQ = s + 2r + 3.5a$$

Where *s* is the percentage of the diet composed of structural plant parts, *r* is the percentage of the diet composed of reproductive plant parts, and *a* is the percentage of the diet composed of animal foods. This formula was developed by comparing different weighting schemes in terms of how much of the variance between species in body weight they explained (Sailer et al., 1985). The authors reported that the equation above accounted for the most variance in body weight of the different weighting schemes assessed. It offered a substantial improvement over percent folivory alone – the DQ index explained 43% of the variance in body weight, and percent folivory alone explained less than 28% of the variance in body weight.

We used published secondary compilations of DQ values, calculated using the formula above, where available (Allen & Kay, 2012; Coiner-Collier et al., 2016; Sailer et al., 1985; Snodgrass et al., 2009). For species that were not represented in published complied datasets, we calculated DQ from published primary studies (Hanya et al., 2011; S. M. Holmes et al., 2016; McGraw et al., 2016; Nijman, 2017; Roy et al., 2011; Solanki et al., 2008; F. J. White, 1992). The source of the DQ value for each species is listed in Supplementary File 1.

5.2.4 Statistical Analysis And Phylogeny. A problem inherent in using linear models to evaluate comparative cross-species associations is that, due to phylogenetic relatedness, the residuals of the relationship between the predictors and the outcomes are non-independent, which violates the assumptions of many statistical techniques (e.g., ordinary least squares regression). Therefore, the models we utilized were phylogenetic generalized least squares (PGLS) regression models implemented in the R package "ape" v5.1 (Paradis et al., 2004). Each model included an estimate of Pagel's λ, which accounts for phylogenetic relatedness in the model (Freckleton et al., 2002). The method used to fit all models was restricted maximum likelihood (see Supplementary File 2 for R code). We used a consensus primate phylogenetic tree downloaded from the 10kTrees website v3 (https://10ktrees.nunn-lab.org/) (Arnold et al., 2010). After integrating all of our data sources, complete data on brain weight, body weight, time allocation, social group size, diet quality, and phylogeny were available for 42 species.

We specified a series of PGLS models for each of the four components of the time budget (Resting, Subsistence, Locomotion, Other). Model 1 of each series consisted of only log brain size and the intercept as fixed effects. Model 2 consisted of only log

body size and the intercept as fixed effects. Model 3 consisted of log brain size, log body size, and the intercept as fixed effects. Model 4 consisted of all of the variables in Model 3, plus diet quality and group size as fixed effects.

5.2.5. Encephalization Quotient. To visualize the associations between relative brain-to-body size and percentages of time spent in each category of time allocation, we calculated encephalization quotient for each species using the following equation (Martin, 1981):

$$EQ = \frac{brain}{0.12 \times body^{0.76}}$$

Where *brain* is brain weight in g, and *body* is body weight in g. We then fitted PGLS models with standardized EQ (mean=0; SD=1) as the input variable and time budget percentages as the output variables. We then generated scatterplots of EQ by each time budget variable and plotted lines representing marginal effects using the ggplot2 package in R (Wickham, 2011).

5.2.6. Predicted Values For Fossil Hominins. To evaluate the implications of our findings for hominin evolution, we generated equations that use EQ to predict percentages of time spent in subsistence and locomotion activities. We found that PGLS models (with EQ as the input and Subsistence Time and Locomotion Time as the output variables) estimated Pagel's λ coefficients close to 0. This indicates that the PGLS models are practically equivalent to ordinary least squares (OLS) regression. We therefore utilized OLS regression to generate the following equation for relating Subsistence Time to EQ:

$$ST = 27.5 \times EQ + 11.83$$

Where *ST* is the percentage of the time budget spent in subsistence activities and *EQ* is encephalization quotient calculated using the formula in the previous section. We also generated the following equation for relating Locomotion Time to EQ:

$$LT = 17.37 \times EQ + 4.71$$

Where *LT* is the percentage of the time budget spent in locomotion activities, and *EQ* is encephalization quotient calculated using the formula in the previous section.

To calculate encephalization quotient for selected fossil hominin species, we used published estimates of brain volume (in cubic centimeters) and body weight (Leonard & Robertson, 1994). We multiplied the estimated brain volumes by 1.036 g cm^{-3} so that they are comparable to the brain weights in the primate dataset used in this paper (DeCasien et al., 2017). We also applied the prediction equation to contemporary humans using published values for brain and body weights (Leonard & Robertson, 1994).

5.2.7. Observed time budgets for contemporary humans. We compared predicted percentages of time spent in subsistence and locomotion activities for contemporary *Homo sapiens*, based on EQ, to actual values observed in human hunter-gatherers. Two contemporaneous studies (one focusing on men; the other on women) measured time budgets in mobile groups of Ache hunter-gatherers using behavioral observation methods comparable to those used in contemporary primatology (Kim Hill et al., 1985; Hurtado et

al., 1985). The researchers used a combination of instantaneous and focal sampling to measure time budgets through direct behavioral observation. They spent extended periods of time with the same groups, and group members became accustomed to the researchers' presence in everyday life. For comparison to our primate dataset, we grouped the reported Ache time allocation budgets into categories of resting, subsistence, locomotion, and other activities. Eating and tool work were included in the subsistence category. Percentages of time spent in each of these categories were then averaged between men and women, and the resulting averages rescaled to sum to 100%.

5.3. Results

5.3.1. Phylogenetic Least Squares Regression Models Predicting Resting Time (%). When either brain or body size is the sole fixed effect in the model (along with the intercept), neither is strongly associated with resting time. The association between body size and resting time, however, does approach statistical significance (P=0.0684). When both brain size and body size are in the model, greater brain size is strongly associated with less resting time, and greater body size is strongly associated with more resting time. The effects of brain size and body size remain strong after adjusting for diet quality and group size. Coefficient estimates, along with their standard errors and P-values, for all models are presented in **Table 5.1**.

Table 5.1. Phylogenetic least squares regression models predicting Resting Time (%)

	Model 1	**Model 2**	**Model 3**	**Model 4**
Intercept				
β	42.42	43.6	38.83	67.77
SE	14.47	13.7	10.18	14
P	0.0056	0.0028	0.0005	< 0.00001
Log Brain Size				
β	2.03		-26.53	-20.81
SE	3.94		7.33	7.18
P	0.6096		0.0008	0.0063
Log Body Size				
β		6.86	30.2	21.47
SE		3.66	7.21	7.76
P		0.0684	0.0002	0.0088
Diet Quality				
β				-0.15
SE				0.07
P				0.0253
Group Size				
β				-0.11
SE				0.1
P				0.2955
Pagel's λ	0.94	0.93	0.85	0.69
BIC	339.01	335.97	324.01	331.8
AIC	332.25	329.22	315.69	320.52
Log Likelihood	-162.13	-160.61	-152.85	-153.26

5.3.2. Phylogenetic Least Squares Regression Models Predicting Subsistence Time (%).

When either brain or body size is the sole fixed effect in the model (along with the intercept), neither is associated with subsistence time. When both brain size and body size are in the model, however, greater brain size is strongly associated with more

subsistence time, and greater body size is strongly associated with less subsistence time. In the final model, which includes diet quality and group size, the effects of brain size and body size are substantially reduced. This attenuation appears to be largely driven by the inclusion of diet quality (β=0.2, SE=0.05, P=0.0008), as group size is not associated with subsistence time (β=0.02, SE=0.08, P=0.8035). Coefficient estimates, along with their standard errors and P-values, for all models are presented in **Table 5.2**.

Table 5.2. Phylogenetic least squares regression models predicting Subsistence Time (%)

	Model 1	**Model 2**	**Model 3**	**Model 4**
Intercept				
β	31.87	31.13	35.05	-2.2
SE	9.78	9.54	0.33	9.23
P	0.0023	0.0023	< 0.00001	0.8132
Log Brain Size				
β	-0.69		23.03	10.65
SE	3.09		4.61	4.9
P	0.8242		0.000013	0.0364
Log Body Size				
β		-3.59	-22.89	-6.45
SE		2.99	4.61	5.63
P		0.2369	0.000014	0.2589
Diet Quality				
β				0.2
SE				0.05
P				0.0008
Group Size				
β				0.02
SE				0.08
P				0.8035
Pagel's λ	0.78	0.77	-0.06	-0.09
BIC	334.71	333.37	320.13	322.07
AIC	327.96	326.61	311.81	310.79
Log Likelihood	-159.98	-159.31	-150.91	-148.4

5.3.3. Phylogenetic Least Squares Regression Models Predicting Locomotion Time (%). When either brain or body size is the sole fixed effect in the model (along with the intercept), neither is associated with locomotion time. The association between body size and locomotion time, however, does approach statistical significance (P=0.0718). When both brain size and body size are in the model, greater brain size is strongly associated with more locomotion time, and greater body size is strongly associated with more less locomotion time. The effects of brain size and body size remain strong after adjusting for diet quality and group size. Coefficient estimates, along with their standard errors and P-values, for all models are presented in **Table 5.3**.

5.3.4. Phylogenetic Least Squares Regression Models Predicting Other Time (%). Neither brain size nor body size is associated with other time in any of the models we specified. Coefficient estimates, along with their standard errors and P-values, for all models are presented in **Table 5.4**.

5.3.5. Encephalization Quotient And Time Allocation. To illustrate the association between relative brain-to-body size and time allocation, we specified phylogenetic least squares regression models with EQ predicting time spent in each domain of time allocation. As suggested by previous analyses, greater EQ was associated with less resting, more subsistence time, more locomotion time, and was not associated with other time. Coefficient estimates, along with their standard errors and P-values, for all models are presented in **Table 5.5**.

5.3.6. Prediction Equations For Subsistence Time And Locomotion Time. Phylogenetic least squares regression models predicting subsistence time and locomotion time yielded near-zero estimates of Pagel's λ, which indicates that the models are

practically equivalent to OLS regression models. To generate equations for predicting subsistence time and locomotion time based on EQ, we specified OLS regression models with EQ predicting subsistence time and locomotion time.

Table 5.3. Phylogenetic least squares regression models predicting Locomotion Time (%)

	Model 1	**Model 2**	**Model 3**	**Model 4**
Intercept				
β	18.64	18.16	20.14	16.52
SE	5.82	5.32	2.48	7.57
P	0.0027	0.0015	< .00001	0.0355
Log Brain Size				
β	-1.01		13.59	12.5
SE	1.89		3.27	3.99
P	0.5974		0.0002	0.0034
Log Body Size				
β		-3.27	-15.5	-13.99
SE		1.77	3.27	4.52
P		0.0718	0.000029	0.0038
Diet Quality				
β				0.019
SE				0.04
P				0.6440
Group Size				
β				0.005
SE				0.06
P				0.9396
Pagel's λ	0.74	0.71	0.26	0.2
BIC	298.05	295.11	283.01	298.04
AIC	291.3	288.36	274.69	286.76
Log Likelihood	-141.65	-140.18	-132.35	-136.38

Table 5.4. Phylogenetic least squares regression models predicting Other Time (%)

	Model 1	**Model 2**	**Model 3**	**Model 4**
Intercept				
β	7.9	7.88	7.82	11.65
SE	2.23	2.17	2.28	6.97
P	0.001	0.0008	0.0014	0.1032
Log Brain Size				
β	0.48		-0.72	-0.59
SE	1.17		3.18	3.68
P	0.6858		0.8231	0.8739
Log Body Size				
β		0.63	1.28	-0.54
SE		1.16	3.18	4.18
P		0.5883	0.6895	0.8978
Diet Quality				
β				-0.04
SE				0.04
P				0.3463
Group Size				
β				0.13
SE				0.06
P				0.0339
Pagel's λ	0.22	0.21	0.23	0.16
BIC	282.61	282.49	281.87	292.58
AIC	275.86	275.74	273.55	281.3
Log Likelihood	-133.93	-133.87	-131.78	-133.65

Table 5.5. Models with Encephalization Quotient predicting time allocation

	Resting (%)	Subsistence (%)	Locomotion (%)	Other (%)
Intercept				
β	38.07	35.42	19.55	7.71
SE	10.29	2.11	0.06	2.21
P	0.0006	< 0.00001	< 0.00001	0.0012
Encephalization Quotient				
β	-10.15	7.68	4.8	-0.37
SE	2.56	1.66	1.01	1.07
P	0.0003	0.00004	0.000028	0.73
Pagel's λ	0.85	0.04	-0.05	0.22

Coefficient estimates, their standard errors and P-values, and residual standard errors for these models are presented in **Table 5.6**. Predicted subsistence and locomotion time for fossil hominins and contemporary humans, as well as observed subsistence and locomotion times for contemporary human hunter-gatherers, are presented in **Table 5.7**.

Table 5.6. Ordinary least squares models with Encephalization Quotient as the predictor

	Subsistence (%)	Locomotion (%)
Intercept		
β	11.83	4.71
SE	5.35	3.4
P	0.0328	0.173
Encephalization Quotient		
β	27.5	17.37
SE	5.89	3.74
P	0.0000341	0.0000362
Residual SE	10.5	6.66

Table 5.7. Predicted subsistence and locomotion time for fossil hominins. The prediction equations were derived from regression models using data from diurnal primates with EQ as the input variable and subsistence time and locomotion time as the output variables. For comparison, we also list observed time allocation values for contemporary humans (Ache foragers).

	EQ	Subsistence Time (%)	Locomotion Time (%)	Combined Time (%)
A. afarensis	1.18	44.19	25.15	69.34
A. africanus	1.33	48.28	27.74	76.02
P. robustus/boisei	1.45	51.77	29.94	81.71
H. habilis	1.71	58.73	34.34	93.07
H. erectus	1.94	65.2	38.43	103.63
Early *H. sapiens*	2.34	76.31	45.44	121.75
Contemporary *H. sapiens*	2.75	87.48	52.5	139.98
Observed time allocation values for contemporary *H. sapiens* (Ache foragers)		36.68	24.71	61.39

5.4. Discussion

In a sample of 42 diurnal primate species, we find that greater encephalization is strongly associated with more time spent in subsistence and locomotion activities, and greater relative body size is strongly associated with more resting time. Entering diet quality into the model substantially attenuates the effects of brain size and body size on subsistence time. This suggests that one of the reasons more encephalized primates spend more time in subsistence activities may be that they are pursuing higher quality foods. These results suggest that primates use divergent time allocation strategies for managing the metabolic costs of larger bodies and larger brains. Those with larger relative brain size spend more time active, possibly to obtain more high-quality foods. Those with larger relative body size spend more time resting, possibly to conserve energy and to prioritize the high digestion costs of lower quality foods.

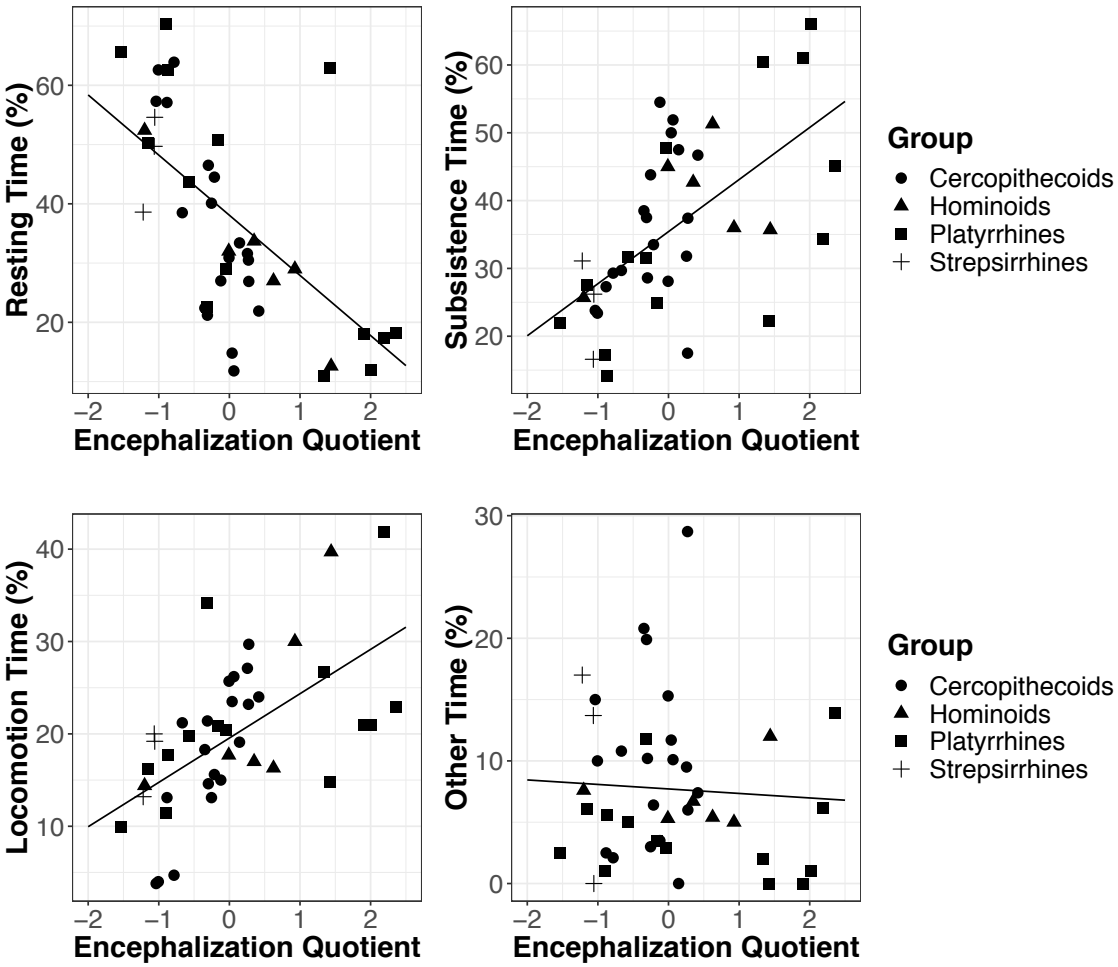


Figure 5.1. Time spent in various activities by encephalization quotient in primates. The plotted lines represent the marginal effects of encephalization quotient on the time use variable, estimated using phylogenetic least squares regression models.

These results highlight the importance of also considering body size when studying the behavioral correlates of brain size. Brain size and body size are strongly positively correlated with one another, but they may be residually associated in opposite directions with behavioral outputs, as was the case in this study.

Humans are outliers among extant primates in terms of both absolute brain size and encephalization quotient (Isler & van Schaik, 2006; Leonard et al., 2007). We therefore did not include them in our statistical models, as their inclusion may have substantially distorted model estimates. Using equations generated from our data, we found that a primate species with the encephalization quotient of contemporary *Homo sapiens* is expected to allocate 87.48% of its time budget to subsistence behaviors and 53.5% of its time budget to locomotion behaviors. These combined values are, of course, jointly impossible in the real world, as they sum to a percentage substantially greater than 100. A pair of previous studies used behavioral observation methods similar to those used in primatology to investigate time allocation in mobile Ache hunter-gatherer camps (Hill et al., 1985; Hurtado et al., 1985). They found that Ache adults spend about 37% of observed time on subsistence activities and about 25% of observed time on locomotion. These values fall well within the range of reported values for other primate species in our dataset.

To evaluate the predictions of our equations for a selection of fossil hominins, we predicted subsistence and locomotion time budget percentages using EQ values calculated from published brain and body size estimates (**Table 5.7**). For earlier fossil hominins, the equations predict combined subsistence/locomotion percentages within the range of observed values for other primate species. However, our equations predicted combined subsistence/locomotion percentages near or above 100% for the three fossil species from the genus Homo. This suggests that the evolutionary origins of the genus *Homo* may have depended upon adaptations that enhanced the efficiency of time use.

A previous comparative primate study found that higher rates of social learning, innovation, and extractive foraging are associated with greater parasite richness (a measure of the variety of parasites in a species' disease ecology) (McCabe et al., 2015). In particular, higher rates of social learning are associated with greater richness of socially transmitted parasites, and higher rates of exploration are associated with greater richness of environmentally transmitted parasites. Thus, the cognitive capacities that underlie the emergence of culture may come at a cost of greater infection risk. In this study, we find that greater encephalization is strongly associated with less resting time and more spent in subsistence and locomotion activities.

Highly encephalized species that rely heavily on social learning and extractive foraging may therefore face an adaptive problem – they experience greater parasite risk but have less time available in which to rest and prioritize immune function. We hypothesize that some animals may address this problem via reciprocal helping behavior directed toward sick individuals. Receiving care when sick (e.g., food provisioning, protection, grooming, allocare of offspring) allows the sick individual to temporarily increase resting time in order to prioritize immune function (Hart, 1990). Apparent helping behavior directed toward sick conspecifics has been documented in a variety of non-human taxa including chimpanzees (*Pan troglodytes*) (Huffman & Seifu, 1989), potto (*Perodicticus potto*) (Cowgill, 1974), African savannah elephants (*Loxodonta africana*) (Byrne et al., 2008), and dwarf mongooses (*Helogale parvula*) (Rasa, 1976). Future comparative studies should test whether greater encephalization and parasite richness are associated with increased reports of helping sick conspecifics.

Compared to other primates, humans spend a very large proportion of their metabolic budget on brain metabolism (Isler & van Schaik, 2006; Leonard et al., 2007). How were ancestral hominins able to afford the metabolic costs of such large brains? Possible explanations include increases in diet quality (Fish & Lockwood, 2003; Milton, 1999); cooking and food processing to further increase the caloric density of the diet (Wrangham et al., 1999); cooperative foraging; large fat reserves to buffer periods of low food availability (Kuzawa, 1998; Wells, 2006); reduced gut size (Aiello & Wheeler, 1995); and low relative muscularity (Leonard & Robertson, 1997). Cooking also reduces pathogen exposure by killing microorganisms. Thermoregulatory innovations (e.g., fire, clothing) may reduce the metabolic costs of maintaining an optimal body temperature.

Humans also provide intensive reciprocal care and support during illness. The ethnographic record demonstrates that human foragers provide care and support for sick conspecifics, which allows the sick person to rest without worrying about feeding themselves or their family, watching out for threats, or keeping up with the group (Bailey, 1991; Gurven et al., 2000; K Hill et al., 2007; Sugiyama, 2004; Sugiyama & Chacon, 2000). The bioarchaeological record provides examples of individuals surviving pathologies that would have required care from conspecifics (Dickel & Doran, 1989; Tilley & Oxenham, 2011; Trinkaus & Zimmerman, 1982). The flexibility to facultatively adjust patterns of resting behavior to suit an individual's immunological circumstances may have played a role in relaxing the joint constraints on brain size posed by high infection risk and limited resting time.

Our findings suggest that activity patterns tend to track relative investment in brain vs. body metabolism. Greater relative investment in brain metabolism may increase the average expected value of foraging and exploration. The leading hypotheses about the evolution of brain size propose that larger brains provide some set of cognitive benefits (DeCasien et al., 2017; Dunbar & Shultz, 2017; Street et al., 2017). However, these enhanced cognitive abilities are only worthwhile when an animal has sufficient opportunities to engage in activities that make use of the enhanced abilities. Thus, relative increases in brain metabolism are likely to evolve only in ecological contexts where such opportunities occur at a sufficient rate to compensate for the increased costs of brain metabolism. Species that are more encephalized may spend more time in subsistence and travel activities because their cognitive capacities, in combination with environmental affordances, offer richer marginal returns for additional time spent in these activities.

Greater relative investment in body metabolism, on the other hand, may increase the average expected value of resting. Larger bodies are more costly to move in absolute terms (Alexander, 2005), and larger guts may provide more relative digestive capacity for lower quality foods, which may require less foraging and exploration time to obtain (Müller et al., 2013). Despite size-related increases in digestive capacity, the absolute metabolic costs of digesting lower quality foods are, by definition, greater (Westerterp, 2004). Relative increases in body size, along with decreases in diet quality, may redistribute the metabolic costs of subsistence by allocating less energy to foraging behavior but more energy to digestive metabolism. Digestion can be done at rest, which may help explain why greater relative body size and lower diet quality are associated

with more resting time. In combination, these findings provide new insights on how the costs and benefits of relative investment brain and body size may shape time allocation strategies in diurnal primates.

5.5. Bridge to Chapter VI

The next chapter concludes this dissertation and outlines directions for future research.

CHAPTER VI

CONCLUSIONS AND FUTURE DIRECTIONS

Chapter I introduced the research questions that motivated this dissertation. Why do our own immune systems make us feel sick? Does sickness provide functional benefits to a host fighting infection? If so, what are these advantages? Does the experience of sickness vary depending on the environmental context of the host? If so, what are the contextual factors that shape the experience of sickness? If sickness provides some kind of benefit to the host, what happens when it goes wrong? What explains the distinctive features of sickness in humans?

Chapter II reviewed the evidence that infectious disease has been a ubiquitous selection pressure throughout our evolutionary history (Schrock et al., 2020). It outlined the second-order adaptive problems posed to the host when the immune system is activated to fight infection. It describes the regulatory changes that occur during sickness, and explains how these changes help the host solve the problems posed by immune activation. It reviews the inflammation-related pathways that play a central role in generating the experience of sickness (McCusker & Kelley, 2013).

Multiple lines of evidence demonstrate that sickness behavior can be suppressed in the face of highly salient alternative motivations (e.g., social competition, starvation, threats to offspring) (Aubert et al., 1997; Lopes et al., 2014; MacDonald et al., 2014). Fatigue and sadness in response to inflammation may diminish an individual's ability and motivation to devote effort to demanding physical work (DellaGioia & Hannestad, 2010; Lasselin et al., 2020). It is possible that mild doses of inflammation are not sufficient to

increase fatigue and sadness in societies in which subsistence requires demanding physical labor.

Chapter III tested whether greater immune activation is associated with stronger feelings of fatigue, sadness, and sickness among Shuar forager-horticulturalists. Experiments in high-income, industrialized societies have demonstrated that acute phase immune activation can induce fatigue and low mood (DellaGioia & Hannestad, 2010; Lasselin et al., 2020). Clinical and epidemiological studies have reported that chronic low-grade inflammation is associated with depressive symptoms, including a lack of energy and persistent sadness (Maes et al., 2012; Osimo et al., 2020). But evolutionarily novel environments characterized by infrequent macroparasite exposure and low microbial diversity may modulate the development and deployment of immune responses in unexpected ways (Bach, 2018; Fitzsimmons et al., 2014). The Shuar have high fertility rates (Madimenos et al., 2012), depend on subsistence activities that require high levels of physical activity (Christopher et al., 2019), and inhabit environments characterized by frequent parasite exposure and high levels of microbial diversity (Cepon-Robins et al., 2014; Gildner et al., 2016; Stagaman et al., 2018). I find that greater inflammation is associated with stronger feelings of sickness but not fatigue or sadness. These findings suggest that mild inflammation may generate internally perceptible cues, even when the dose and chronicity of inflammation are insufficient to increase fatigue or sadness.

In Chapter IV, I proposed that fatigue might often be a maladaptive response in the context of evolutionarily novel chronic diseases. Chronic disease-induced fatigue may lead to long-term reductions in physical activity, which in turn, may increase an individual's subsequent risk of disease progression and risk of acquiring additional

comorbid conditions (Booth et al., 2012; Kujala, 2006; Warburton et al., 2006). Thus, chronic disease-induced fatigue may perpetuate a feedback loop that generates trajectories of deteriorating health across the lifecourse. I find that greater chronic morbidity is associated with stronger feelings of fatigue in large samples of adults from six culturally distinct countries. This association replicates within each country and is robust to adjustment for covariates. Each additional chronic condition is associated with stronger feelings of fatigue in a dose-response manner, which suggests that fatigue is actually associated with cumulative chronic morbidity, rather than just one or two of the conditions aggregated in the variable. Further research is needed to test whether greater chronic morbidity is a longitudinal predictor of greater fatigue and to test whether greater fatigue is a longitudinal predictor of chronic morbidity. It may be possible to test these predictions using existing data resources, such as the Framingham Heart Study (https://framinghamheartstudy.org/).

Taken together, these findings raise questions about the dose and chronicity of inflammation required to induce fatigue and sadness in real-world environments. Future studies should collect repeated measures of inflammation and psychometric outcome variables from the same set of individuals. A broader sampling timeframe and larger sample size may capture higher doses of inflammation that were not represented in my sample. Repeated measures would allow us to test whether long-term between-individual differences in inflammation are associated with fatigue or sadness. For the purpose of evaluating causal arguments, it would also be useful to conduct experimental studies in the field. One promising experimental approach (that would also provide a benefit to participants) would be to use vaccines that trigger an acute but mild inflammatory

response (e.g., the typhoid vaccine) (Harrison et al., 2009). Crossover study designs would allow us to evaluate the behavioral and psychological effects of inflammation in comparison to a placebo control group.

Further work is needed to evaluate the impact of alternative motivations on experiences of sickness in real-world settings. Subsistence farmers who depend on seasonal crops must engage in long days of strenuous physical work during the harvest, but requirements for physical labor are more flexible during other parts of the year (Kashiwazaki et al., 2009). One interesting study would be to test whether inflammation, lassitude, and sickness behavior differ between harvest and non-harvest seasons in these societies.

I am also interested in why sickness behavior takes its particular form in humans. One of the common threads running through several different features of sickness behavior is that they seem to play a role, directly or indirectly, in helping the host manage the metabolic costs of activating the immune system (Adelman & Martin, 2009; Shattuck & Muehlenbein, 2015). Thus, other competing metabolic demands may play a role in shaping what lassitude and sickness behavior look like in a given species. One of the most distinctive features of human metabolic budgets is our very large and metabolically costly brain. One of the primary behavioral outputs of lassitude is that it increases resting time and reduces engagement in energetically expensive activities (Schrock et al., 2020). If brain size also shapes time allocation, it may have consequences for the deployment of sickness behavior.

Chapter V tests whether brain and body size are associated with patterns of time allocation using species-level data from a sample of diurnal primates. I find that species

with larger relative brain size spend more time active, which is explained in part by the pursuit of higher-quality foods. Those with larger relative body size spend more time resting, which may help conserve energy and to prioritize the greater digestion costs of easier-to-obtain but lower-quality foods. Human foragers spend far less time on subsistence and locomotion than expected for a primate with our encephalization quotient. This suggests that human evolution depended on adaptations that enhanced the efficiency of time use.

A previous comparative primate study found that higher rates of social learning, innovation, and extractive foraging are associated with greater parasite richness (a measure of the variety of parasites in a species' disease ecology) (McCabe et al., 2015). In this study, we find that greater encephalization is strongly associated with less resting time and more spent in subsistence and locomotion activities. Highly encephalized species that rely heavily on social learning and extractive foraging (e.g., humans) may therefore face an adaptive problem – they experience greater parasite risk but have less time available in which to rest and prioritize immune function. We hypothesize that some animals may address this problem via reciprocal helping behavior directed toward sick individuals.

The ethnographic record shows that human foragers provide care and support for sick conspecifics, which allows the sick person to rest without worrying about feeding themselves or their family, watching out for threats, or keeping up with the group (Bailey, 1991; Gurven et al., 2000; Hill et al., 2007; Sugiyama, 2004; Sugiyama & Chacon, 2000). The bioarchaeological record provides examples of individuals surviving pathologies that would have required care from conspecifics (Dickel & Doran, 1989;

Tilley & Oxenham, 2011; Trinkaus & Zimmerman, 1982). The flexibility to facultatively adjust patterns of resting behavior to suit an individual's immunological circumstances may have played a role in relaxing the joint constraints on brain size posed by high infection risk and limited resting time.

The search for distinctive features of human sickness behavior is a research topic in its infancy. To my knowledge, no one has yet pursued this research topic in a systematic, comparative manner. Receiving social sickness aid in plays a key role in recovering from disease in humans (Bailey, 1991; Sugiyama, 2004), and humans are unique among primates in the complexity and flexibility of our social systems (Dunbar, 2009; Kaplan et al., 2000). One promising area of research would be to investigate whether humans exhibit distinctive features of sickness behavior that relate to our sociality. One way to begin pursuing this line of inquiry would be to build a comparative database of primate sickness behavior that complements the Global Primate Parasite Database (https://parasites.nunn-lab.org/).

Genomic tools may also prove useful in identifying distinctively human features of sickness. The genes that produce certain pro-inflammatory cytokines (e.g., tumor necrosis factor α, interleukin-1β, interleukin-6) have been described (Ferguson-Smith et al., 1988; Old, 1985; Rogus et al., 2008). These cytokines play key roles in generating and regulating sickness behavior (McCusker & Kelley, 2013). Phylogenetic comparisons could help us identify patterns of similarity and divergence between humans and other species in these genes. Patterns of variation at these loci could be used to test for evidence of positive selection. Incorporating measures of pro-inflammatory cytokine gene expression, in addition to measures of cytokine concentrations, could provide

additional nuance to commonly used study designs. Ultimately, it would be useful to take a systems approach, integrating functional genomics, physiological measures, psychometrics, and behavioral outputs in the same studies.

Future studies should also work towards understanding how sickness behavior varies depending on the type of infecting pathogen. Different pathogens have different modes of transmission, different life histories, and different ways of exploiting the host (Ewald, 1994). Pathogenic species are not static – they have short generation times and are under selection to manipulate hosts in ways that enhance the pathogen's fitness (Hughes et al., 2012). Thus, sickness behavior is likely a battleground in the perpetual co-evolutionary arms race between hosts and pathogens. Taking a "pathogen's-eye view" of host sickness behavior might help us understand why different kinds of infections lead to different patterns of sickness behavior and different experiences of sickness. One way to advance this line of inquiry would be to develop a database that contains data on various features of sickness for different species of infecting pathogens, as well as data on pathogen characteristics. These data could be aggregated from a variety of sources, including de-identified medical records, clinical case reports, surveys of infectious disease clinicians, and surveys of individuals who have previously been infected with the pathogen in question.

Much of what we know about sickness behavior comes from an experimental paradigm (lipopolysaccharide administration) that mimics gram-negative bacterial infection in laboratory animal models (Dantzer & Kelley, 2007). While this body of evidence is useful, complementary approaches are needed to help us understand how the context-dependent regulation of sickness works in humans. The evidence reviewed in this

dissertation makes a case for expanding the scope of research on inflammation and sickness to include a broader range of study designs, ecological settings, pathologies, and host species.

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