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Pathogen–Host Defense in the Evolution of Depression: Insights into Epidemiology, Genetics, Bioregional Differences and Female Preponderance

Charles L Raison*[,1,2,3] and Andrew H Miller[4,5]

[1]Department of Human Development and Family Studies, School of Human Ecology, University of Wisconsin-Madison, Madison, WI, USA; [2]Department of Psychiatry, School of Medicine and Public Health, University of Wisconsin-Madison, Madison, WI, USA; [3]School of Pharmacy, University of Wisconsin-Madison, Madison, WI, USA; [4]Department of Psychiatry and Behavioral Sciences, School of Medicine, Emory University, Atlanta, GA, USA; [5]The Winship Cancer Institute, Emory University, Atlanta, GA, USA

Significant attention has been paid to the potential adaptive value of depression as it relates to interactions with people in the social world. However, in this review, we outline the rationale of why certain features of depression including its environmental and genetic risk factors, its association with the acute phase response and its age of onset and female preponderance appear to have evolved from human interactions with pathogens in the microbial world. Approaching the relationship between inflammation and depression from this evolutionary perspective yields a number of insights that may reveal important clues regarding the origin and epidemiology of the disorder as well as the persistence of its risk alleles in the modern human genome.
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"…when diseases have been common in human populations for many generations and still have a substantial negative impact on fitness, they are likely to have infectious causes....These infectious causes may be causes in the proximate sense (e.g., Mycobacterium tuberculosis causes tuberculosis) or in an evolutionary sense (Plasmodium falciparum is an evolutionary cause of sickle cell anemia).…The only such compensating fitness benefit that has been documented for major human genetic diseases is resistance to infection." — (*Cochran et al, 2000*) Cochran, Ewald & Cochra.

INTRODUCTION

Major depressive disorder (MDD) is about relationships. Or so one would think based on an extensive literature that seeks to explain how a condition with genetic underpinnings could be so widespread when it is so apparently inimical to the Darwinian mandates of survival and reproduction. This literature on adaptive theory bifurcates over whether depression is adaptive in and of itself or whether the genes that increase the risk of depression also promote other types of social behavior (ie, avoiding conflict with more powerful individuals) that promoted survival and reproduction sufficiently to have been retained in the human genome (Supplementary Table S1). Despite differences, however, these theories all share in common the notion that the adaptive value of MDD is to be found in its effects on our relationships with other people.

We agree that the adaptive value of MDD is to be found in our relationships, but not primarily in our relationships with other humans. Rather, in this review we argue that MDD, and the genes that subserve it, evolved to help us manage relationships with the wide range of pathogens with which humans co-evolved. Specifically, at least some of the genes that promote MDD evolved and have been retained in the human genome because—on average—they helped hominids avoid death from infection. Importantly, we are not suggesting that these genes promoted host defense against pathogens at the cost of inducing depression. Rather, the tendency of these genes to induce depression and other related behavioral changes including arousal, anxiety and alarm is integral to their anti-pathogen benefits, because—like sickness from which it evolved—depression conferred protection from pathogens in the environments in which humans evolved. Said differently, depression may itself be an anti-pathogen defense strategy, one that is both activated by

*Correspondence: Dr CL Raison, School of Human Ecology, University of Wisconsin-Madison, 1300 Linden Drive, Room 4174, Madison, WI 53706, USA, Tel: 678 429 9870, E-mail: charles.raison@wisc.edu
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inflammation and, somewhat paradoxically, one that across evolutionary time may have made inflammatory activation less necessary, as we shall see in our discussion of sex differences in the prevalence of MDD. From this perspective, even environmental risk factors for depression, such as psychosocial stress, promote MDD primarily because across evolutionary time these adversities reliably served as warnings that an individual's risk for infectious morbidity/mortality were heightened. Although this perspective may be most relevant to sub-types of depression associated with increased inflammation, we highlight in this review the possibility that other immune and/or behavioral responses relevant to pathogen–host defense may also be associated with MDD in ways that extend the role of microbial–human interactions in the evolution of depression beyond its now well-recognized associations with inflammation.

Consistent with earlier publications from our group (Raison and Miller, 2012, 2013; Miller and Raison, 2015), we refer to this constellation of ideas as the pathogen–host defense theory of depression, or PATHOS-D. This position overlaps, but has significant differences from a pathogen defense theory of depression first articulated by Kinney and Tanaka, (2009) (Anders *et al*, 2013). Table 1 situates PATHOS-D within other possible explanatory frameworks for understanding why MDD and alterations in immune function should be related. Supplementary Table S1 provides a comparison of different adaptive explanations for the persistence of MDD and its risk alleles in human populations. As with all theories, the value of PATHOS-D will eventually be determined by its ability to make novel predictions and to provide coherent and parsimonious explanations for a wider range of variables than are accounted for by competing hypotheses. Our aim in this review is to evaluate PATHOS-D by these criteria. To do this, we list a series of concepts consistent with PATHOS-D theory, in each case evaluating the evidence for and against the theory's explanatory and predictive potential. In addition, we explore the theory's possible explanations for sex differences in the prevalence of MDD. In all these areas, we are careful to note the degree of data in support of each idea, and which ideas are frankly speculative. Figure 1 provides a graphic representation of epidemiological, biological, and genetic domains relevant to MDD that are addressed by PATHOS-D.

DEPRESSION IS ASSOCIATED WITH IMMUNE CHANGES AND THESE SAME CHANGES SHOULD BE CAPABLE OF INDUCING DEPRESSION

Of all the predictions of PATHOS-D, this one is the best established. Indeed, it was the effort to provide an evolutionary perspective on the association between inflammation and depression that provided the initial impetus for the theory. Taken as a whole, studies suggest that MDD is associated with all the cardinal features of an inflammatory response including increased proinflammatory cytokines and their receptors and increased acute phase reactants, chemokines, and soluble adhesion molecules in peripheral blood (Lieb *et al*, 1983; Calabrese *et al*, 1986; Sluzewska *et al*, 1996; Song *et al*, 1998; Howren *et al*, 2009; Dowlati *et al*, 2010; Liu *et al*, 2012b; Valkanova *et al*, 2013; Black and Miller, 2015; Haapakoski *et al*, 2015; Eyre *et al*, 2016; Goldsmith *et al*, 2016b; van Dooren *et al*, 2016). Several studies provide evidence of increased inflammatory activity in the central nervous system of depressed individuals as well, as indexed by increased cerebrospinal fluid (CSF) concentrations of interleukin (IL)-1-β and neural adhesion molecules, as well as by increased prefrontal cortex gene expression of IL-1-α, IL-2, IL-3, IL-5, IL-8, IL-9, IL-10, IL-12A, IL-13, IL-15, IL-18, interferon (IFN)-γ, and lymphotoxin alpha (TNF superfamily member 1; Poltorak *et al*, 1996, Levine *et al*, 1999; Shelton *et al*, 2010). Perhaps suggesting a link between inflammation and symptom acuity, and/or reflecting the association between inflammation and heightened anxiety (a known suicide risk), a recent meta-analysis found that levels of IL-1-β and IL-6 were significantly increased in blood and postmortem brain samples of patients with suicidality compared with both non-suicidal depressed patients and healthy control subjects (Black and Miller, 2015). Given their centrality in activating innate immune responses to pathogens, it is striking that

TABLE 1 Possible Evolutionary Understandings of the Association Between Depression and Inflammation/Immune Activation

No adaptive relationship exists between immune changes and depressive symptoms. Immune changes observed in major depressive disorder (MDD) may be beneficial or detrimental to pathogen–host defense and adaptive benefits of depression exist in non-pathogen/immune-related domains (multiple adaptive theories, eg, social navigation hypothesis)
Depressive symptoms extract a cost to survival and reproduction but this cost is offset by the direct anti-pathogen benefits of heightened inflammation/immune activation (antagonistic pleiotropy)
In individuals with reduced immune competence for any number of reasons, depressive symptoms serve pathogen–host defense by inducing social avoidance/energy conservation and behaviors that provide protection from becoming infected and/or energy for immune activity once infection has occurred (Kinney and Tanaka)
Genetic alleles that promote an inflammatory bias have undergone positive selection because in ancestral environments they provided direct pathogen defense and because they promoted the development of depressive symptoms in response to immune activation. Like sickness behavior, depression in response to immune activation aided in host defense both directly (ie, raised body temperature and energy conservation behaviors) and indirectly (social avoidance, energy conservation, and hypervigilance; Raison and Miller, pathogen–host defense theory of depression [PATHOS-D])
Adaptive explanations for associations between MDD and altered immune functioning are not considered (frequent unexamined assumption of researchers working on proximal mechanisms)

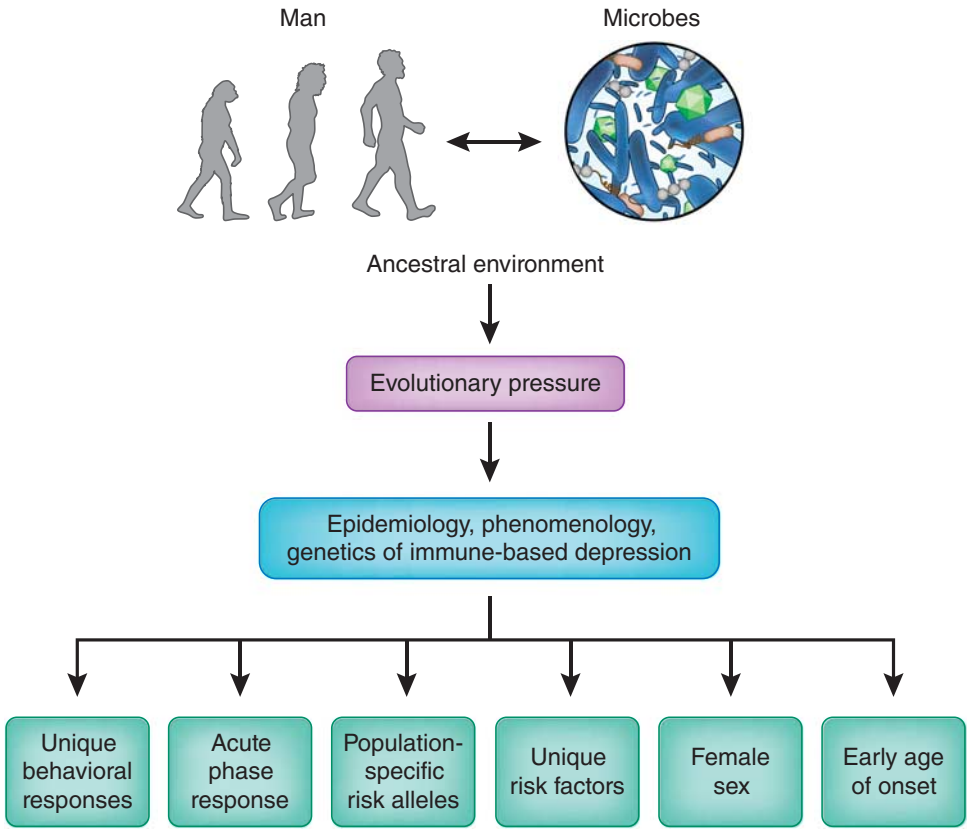

Figure 1. Man meets microbes. In ancestral environments, heavy pathogen loads applied significant evolutionary pressure on human survival that ultimately entailed a host of adaptations that, according to the pathogen–host theory of depression, shaped interactions between the immune system (inflammation in particular) and the brain, leading to a unique set of behaviors. These behaviors, including anhedonia, fatigue, and psychomotor slowing as well as anxiety, arousal and alarm supported energy conservation for fighting infection and wound healing and hypervigilance to prevent future attack. In addition, these evolutionary forces instantiated a coupling of these behavioral responses with the acute phase response including not only increases in acute phase reactants such as c-reactive protein but also hypoferremia and zinc deficiency, as well as fever, which are better suited for interactions with pathogens than people. In addition, evolutionary pressures from human interactions with the microbial world can explain risk alleles that are specific to the pathogens to which given populations were exposed as well as epidemiologic features of depression such as female sex preponderance, an early age of onset, and occurrence in the postpartum period that supported reproductive success. Finally, the pathogen–host theory of depression is consistent with modern risk factors for depressive symptoms, including obesity, processed-food-based diets, sedentary lifestyle, and sleep deprivation, all of which serve to exacerbate the inflammatory bias that is the legacy of our evolutionary past.

Toll-like receptor (TLR) mRNA and protein have been reported to be elevated in both the periphery and CNS of individuals with MDD (Hung *et al*, 2014, 2015; Keri *et al*, 2014; van Dooren *et al*, 2016), with some evidence suggesting that successful pharmaco- or psychotherapy reduces peripheral TLR activity (Keri *et al*, 2014; Hung *et al*, 2015). Of these various findings, meta-analyses suggest that the best replicated associations between depression and inflammatory biomarkers are increases in circulating levels of c-reactive protein (CRP) and IL-6 (Howren *et al*, 2009; Dowlati *et al*, 2010; Liu *et al*, 2012b; Valkanova *et al*, 2013; Black and Miller, 2015; Haapakoski *et al*, 2015). Taken as a whole, the meta-analytic literature also supports an association with circulating levels of tumor necrosis factor (TNF) and IL-1-β, although with more variability. Because IL-1-β features so prominently in both the inflammatory response and in animal studies of stress, and depression-like behavior, it is curious that meta-analyses split on whether it is elevated in the blood of patients with MDD (Dowlati *et al*, 2010; Black and Miller, 2015). One possible explanation that would be consistent with the animal literature is that IL-1-β has a larger role in the CNS than the periphery in terms of depressogenesis. Consistent with this, some evidence suggests that IL-1-β is elevated in the CSF of depressed individuals (Levine *et al*, 1999). Alternately, evidence linking IL-1-β to MDD may not be robust because of limitations in assay methods in detecting levels of IL-1 in human studies. Although increases in inflammatory biomarkers in depressed patients compared with controls are modest when compared with acute infections or autoimmune conditions, recent animal data demonstrate that these types of low-level inflammatory stimulation are sufficient to induce depressive-like behavior and associated brain changes when such stimulation is chronic (Tarr *et al*, 2012a), such as appears to be the case in many individuals with MDD.

Nonetheless, cross-sectional associations between MDD and inflammation do not establish that immune system activity is capable of producing depression, as would be predicted by PATHOS-D theory. It might well be that depression is associated with brain states that through their impact on neuroendocrine function secondarily increase inflammatory biomarkers that themselves have no impact on the disorder. However, a wealth of data demonstrate that although it is true that mental states can increase inflammation, it is equally true that activation of the body's inflammatory response system can induce depression, as well as many of the CNS and neuroendocrine changes that have been repeatedly associated with MDD. This has been shown in studies examining the acute behavioral and CNS responses to a single exposure to endotoxin or typhoid vaccine and even more convincingly by the many studies examining the biological and behavioral effects of chronic immune activation secondary to treatment with the cytokine IFN-α for either cancer or hepatitis C virus infection (Capuron *et al*, 2002, 2003a, 2003b, 2005, 2007, 2009; Wichers and Maes, 2004; Wichers *et al*, 2005b, 2006, 2007; Majer *et al*, 2008; Harrison *et al*, 2009a, 2009b; Lotrich, 2009; Lotrich *et al*, 2009; Prather *et al*, 2009; Raison *et al*, 2009, 2010a, 2010b, 2010d; Eisenberger *et al*, 2010a, b; Franzen *et al*, 2010; Felger *et al*, 2011, 2012). Importantly, the induction of depressed mood in response to both acute (ie, typhoid vaccine) and chronic (ie, IFN-α) immune stimulation has been associated with increased concentrations of circulating inflammatory cytokines (Wright *et al*, 2005; Raison *et al*, 2010a). Also consistent with the ability of immune activation/inflammation to negatively impact mood is the fact that the risk of developing MDD, increases following significant infections (Benros *et al*, 2013; Gunaratne *et al*, 2013; Bornand *et al*, 2016). Finally, a recent meta-analysis confirms findings from a number of individual studies that elevated levels of circulating inflammatory biomarkers predict the future development of depression in currently non-depressed individuals, even when controlling for other depressive risk factors (Valkanova *et al*, 2013).

Increased inflammatory activity has been the most replicated immune change associated with MDD, but there is no *a priori* reason why this should be the only adaptive immune pattern associated with depression that enhanced pathogen–host defense. A clear prediction of PATHOS-D theory is that as novel innate immune antipathogenic mechanisms are identified, they will be found to be enhanced in depressed individuals. For example, recent studies indicate that antimicrobial peptides upregulated by inflammatory cytokines (eg, ribonuclease 7, psoriasin, and human β-defensin-2 and 3; Harder *et al*, 2007) are increased in the skin of patients with inflammatory skin conditions, such as atopic dermatitis and psoriasis (Harder and Schroder, 2005; Harder *et al*, 2010), that are comorbid with MDD (Gili *et al*, 2010; Yang *et al*, 2010). One would expect a similar increase in these peptides—although perhaps to a lesser degree—in medically healthy individuals with MDD.

RISK FACTORS FOR DEPRESSION SHOULD INDUCE THE SAME PATTERNS OF IMMUNE ACTIVITY SEEN IN MDD

The best replicated risk factors for MDD in the modern world have been repeatedly associated with the same changes in immune functioning that are observed in MDD (Raison, *et al*, 2010c). This is especially apparent in relation to associations between these risk factors and increased inflammation; however, stress—which has been the most extensively studied—has also been repeatedly associated with other immune changes seen in MDD (Herbert and Cohen, 1993a, b). Taken at face value, these associations appear to provide strong support for PATHOS-D. However, it is important to note that a number of these factors—such as obesity, sedentary lifestyle and processed foods—are artifacts of modern lifestyles, and therefore are unlikely to have evolved to activate depression as a result of being 'early warning signs' of impending infectious morbidity/mortality in the environment of evolutionary adaptiveness (EEA), as would be predicted by PATHOS-D.

However, at least two proinflammatory risk factors for MDD—medical illness and psychosocial stress—are certainly ancient and may well have evolved an association with depression as a result of inducing immune changes that enhanced survival in the EEA. PATHOS-D proposes that depression evolved out of sickness, so it is no surprise that robust associations have been seen between medical illness and increased rates of depression in all cultures examined (Moussavi *et al*, 2007). Because cytokines are primary drivers of sickness, it is also no surprise that medical illnesses are typically characterized by increased inflammation, nor that increased levels of inflammatory cytokines in medically ill patients are associated with an increased risk for depression (Musselman, 2001).

On the other hand, it is not immediately apparent why psychosocial stressors should so reliably activate inflammatory pathways in animals and humans when these types of adversities are not in and of themselves associated with either an infectious challenge or an immune stimulus. Indeed, it has become so commonplace to say that stress increases inflammation that it is easy to lose track of what a remarkable thing this is. Consider the Trier Social Stress Test (TSST) in which study participants are charged with giving a personally meaningful speech and doing mental arithmetic in the presence of a judgmental panel. Predictably, the threatened subject experiences a classic fight or flight response characterized by an increased heart rate and blood pressure and an increased release of cortisol and catecholamines. However, the TSST also activates key intracellular inflammatory transcription pathways (eg, nuclear factor-kappa β (NF-κB)) within peripheral blood mononuclear cells and dramatically increases circulating levels of inflammatory cytokines, such as interleukin (IL)-6 (Bierhaus *et al*, 2003; Pace *et al*, 2006a; Carpenter *et al*, 2010). Moreover, individuals with known risk factors for developing depression (eg, early-life adversity) show larger

inflammatory responses to laboratory psychosocial stressors than do others (Pace *et al*, 2006a; Carpenter *et al*, 2010), and the larger the inflammatory response to the stressor, the more likely the subject is to develop depression over the ensuing months (Aschbacher *et al*, 2012). In essence, the body mounts an immune response, not against a pathogen, but against a threat to the subject's self-esteem.

Theories that view depression as having evolved to serve adaptive social purposes do not yield easy explanations for why non-infectious stressors should activate peripheral inflammatory pathways. On the other hand, PATHOS-D suggests a straightforward and parsimonious explanation. Because the vast majority of stressors in mammals over evolutionary time boiled down to risks inherent in hunting, being hunted or fighting conspecifics in dominance hierarchies for reproductive access/status, it is not surprising that these states are also circumstances in which the risk of pathogen invasion—and subsequent death from infection—was greatly increased as a result of traumatic opening of the protective skin barrier from wounding (DiPietro, 1995). Such wounding is common in social species and was a significant source of morbidity and mortality among humans in the ancestral environment, and indeed well into the historical period (Ross *et al*, 2009; Eshed *et al*, 2010; Pinker, 2011). In ancestral environments, the association between stress perception and risk of subsequent wounding was reliable enough that evolution, operating by the so-called 'smoke detector' principle, favored organisms that prepotently activated inflammatory systems in response to a wide array of environmental threats and challenges (including psychosocial stressors), even if this activation was often a 'false alarm.' As noted by Dhabhar—'stress perception by the brain may serve as an early warning signal to activate the immune system in preparation for a markedly increased likelihood of subsequent infection' (Dhabhar, 2009). And while chronic stress is best known to suppress certain aspects of immune function (ie, natural killer cell activity, circulating T-cell subsets; Herbert and Cohen, 1993c), the types of acute and/or psychosocial stressors most likely to be associated with immediate risk of wounding and hence infection activate both innate and adaptive immunity (Quan *et al*, 2001; Bierhaus *et al*, 2003; Avitsur *et al*, 2005; Viswanathan *et al*, 2005; Pace *et al*, 2006b; Steptoe *et al*, 2007; Joachim *et al*, 2008; Bailey *et al*, 2009; Rosenberger *et al*, 2009; Mays *et al*, 2010; Powell *et al*, 2010).

That non-immune stressors can activate inflammation—and do so via multiple mechanisms including activation of the intracellular inflammasomes—is now firmly established (Miller and Raison, 2015). However, PATHOS-D also predicts that stress-induced immune changes should produce an overall enhancement of pathogen–host defense and especially anti-bacterial defense given that these organisms are the chief cause of wound-related infections. This has yet to be proven or disproven, but significant animal data suggest that psychosocial stressors—even when recurrent—can enhance host defense mechanisms and improve immune function. Using a repeated social defeat stress paradigm (SDR), Sheridan and colleagues have shown that stress primes multiple aspects of the rodent host defense repertoire. SDR increases the bactericidal activity of splenic macrophages through a Toll-like receptor-dependent pathway; (Bailey *et al*, 2007) enhances the innate immune response to a primary HSV-1 infection in the cornea and trigeminal ganglia; (Dong-Newsom *et al*, 2010) primes dendritic cells and augments clonal expansion of CD8(+)T cells during primary influenza A viral infection with a resultant enhancement of adaptive immunity and viral clearance; (Powell *et al*, 2010; Mays *et al*, 2012) and activates natural killer cells (Tarr *et al*, 2012b). To our knowledge, none of these effects have been directly examined in humans, but it is intriguing to note that improved functional recovery following knee surgery has been associated with an increase in the type of immune cell redistribution effects that are known to be induced by acute stress in animals (Rosenberger *et al*, 2009).

Also relevant to the hypothesis that stress-induced activation of inflammation provides pre-potent protection against pathogens is work by Cole and colleagues demonstrating that social isolation is associated with an immune signature well-tailored to the types of infectious challenges that would most likely have resulted from ostracism in ancestral environments. Individuals who perceive themselves as chronically socially isolated (ie. lonely) show a pattern of gene transcription in leukocytes characterized by increased expression of inflammatory pathways crucial for protection against bacteria with a concomitant decrease in the expression of genes important for antiviral immunity, especially interferon response genes (Slavich and Cole, 2013). Consistent with these findings, individuals with high trait sensitivity to social disconnection produce greater blood levels of proinflammatory cytokines (TNF and IL-6) and increased expression of inflammatory genes in response to an endotoxin stimulus (Moieni *et al*, 2015a). Similarly, study participants who responded to an fMRI-based social exclusion paradigm with greater activity in the dorsal anterior cingulate cortex and anterior insula—brain regions that have previously been associated with processing rejection-related distress and negative affect—also responded to a laboratory psychosocial stress test with increased salivary production of the inflammatory biomarker soluble TNF-α type II receptor (Slavich *et al*, 2010).

As Slavich and Cole, (2013) have observed, this pattern of findings in response to social isolation (ie, increased inflammation/reduced antiviral immunity) may well have evolved to optimize immune responses to threats from environmental pathogens associated with wounding/starvation that would have been the primary risk for infectious morbidity/mortality in the EEA for individuals with diminished human-to-human contact. Because ostracism was an almost certain death sentence in ancestral environments, the inflammatory response induced by social isolation/exclusion can be seen as a modern vestige of what once served as an immunological ostracism detection system that worked in concert with other ostracism detection systems described in

the literature (Spoor and Williams, 2011) to encourage individuals to endure the costs of group existence during the long years of human evolution. This hypothesis might help explain the recent finding that cytokine activation via exposure to endotoxin induces feelings of social disconnection, especially in females. (Moieni *et al*, 2015) This phenomenon might reflect an evolved and adaptive feed-forward mechanism whereby the risk of social exclusion induced a prepotent inflammatory response that then fostered a further sensitivity to the risk of ostracism. And this mechanism may be more apparent in modern females because the offspring of ostracized mothers would have been less likely to survive than those of ostracized fathers (Sear and Mace, 2008). On the other hand, the increased balance of antiviral to anti-bacterial/inflammatory gene expression seen in more socially integrated individuals would have been more optimal for providing protection against more recent viral infections that spread from person to person but that only became widely lethal (and thereby exerted greater selection pressure) with the increased population density that became the norm after the development of agriculture in the first epidemiological transition.

THE ASSOCIATION BETWEEN DEPRESSION AND INFLAMMATION SHOULD BE ANCIENT

If we assume that a chronic inflammatory response is the most common immune profile associated with MDD, then PATHOS-D predicts that this association should be ancient, because it is this immune response and its associated depressive symptoms that enhanced survival and reproduction via reduced pathogen-related mortality. Strong evidence for this comes from innumerable studies in mice and rats showing that inflammatory cytokines and their stimulators induce depressive and anxiety-like behavior (Dantzer *et al*, 2008a), as well as studies indicating that even when induced by psychological stress, these behavioral responses are dependent upon cytokine activation—especially the induction of IL-1-β in the CNS (Goshen and Yirmiya, 2009). The fact that primate and rodent lineages separated from each other in the time of the dinosaurs strongly suggests that the rudiments of the immune-depression link were laid down early in mammalian evolution, if not earlier.

However, not all data support an ancient or universal link between inflammation and depression, nor is PATHOS-D the only evolutionary theory that might account for such a link if it in fact exists. Indeed, it is increasingly clear that numerous conditions in the modern world have dysregulated immune functioning in ways that promote autoimmunity and chronic inflammation, while simultaneously reducing any adaptive advantage that might be inherent in either the inflammatory response or MDD (Raison *et al*, 2010c). This scenario opens the possibility that the association between inflammation and depression is a non-adaptive by-product of first world environmental and social conditions, rather than something inherent in either our genetic or behavioral make-up. Said differently, the link between chronic inflammation and MDD may not reflect an evolved adaption, but rather represents an example of non-adaptive environmental mismatch, defined as a state of disequilibrium whereby a trait that enhanced reproductive fitness in the environment in which it evolved becomes maladaptive in another environment.

Of all the modern environmental conditions that have altered associations between immune function and behavior, none has received more attention than our changed relationships with a huge range of microorganisms that were ubiquitous in the EEA, but that are largely missing from the industrialized world. Unlike potentially lethal pathogens, most of which produced either immunity or death, many of the now-absent organisms were best dealt with via the development of immune tolerance, either because the organisms were beneficial (eg, the microbiota), harmless (eg, many environmental organisms), infectious but not lethal (eg, hepatitis A virus) or potentially harmful but not easily cleared by the immune system without excessive tissue damage (eg, many helminths). The central insight of recent iterations of the 'hygiene hypothesis' (such as the 'Old Friends' Hypothesis of Rook) is that because the immune system had to learn to tolerate these organisms (as opposed to clearing them from the body), they became 'teachers of tolerance,' especially during childhood development when their absence predisposes individuals in industrialized societies to develop a host of allergic, asthmatic, autoimmune, and psychiatric pathologies (Raison *et al*, 2010c).

In a way that seems more than metaphorical, this notion points toward another way that depression may be about relationships. We need to look no further than the impact of bereavement on mood or the strong association between the death of a parent in childhood and the development of MDD in adulthood to see that human relationships characterized by loss can be profoundly depressogenic (Berg *et al*, 2016). Increasing evidence suggests the same is true of our relationships with the microbial world. Via dysregulated inflammatory activity, our moods are haunted by the loss of 'old friend' organisms of which most of us have no conscious knowledge. Again, like our relationships with other humans, our relationships with bacteria, viruses, and parasites can be understood as comprising various degrees of competition and cooperation/collaboration. PATHOS-D suggests that the link between depression and immune activation primarily reflects the competitive element in these relationships. The evolutionary mismatch model suggests the opposite: that the link between depression and immune activation reflects the failure of the modern world to honor many ancient and mutually beneficial collaborations. So, can available data help us determine which theory is better supported?

To our minds, the strongest data that support evolutionary mismatch, while simultaneously arguing against PATHOS-D, come from the ground-breaking work of McDade and colleagues who have examined associations between stress, mood and inflammation in non-industrialized environments. Working in the Philippines and lowland Ecuador,

they have shown that patterns of inflammation observed in the West do not necessarily translate to less-developed environments with significantly higher pathogen exposure and infectious mortality. In industrialized contexts, the concentrations of peripheral inflammatory biomarkers show significant intra-individual stability, with some individuals demonstrating chronically elevated levels of these biomarkers (Macy *et al*, 1997; Ockene *et al*, 2001). Moreover, factors other than pathogen exposure (especially obesity) have been repeatedly shown to upregulate inflammation. McDade *et al*, (2009) found that neither of these pertain in more traditional societies. In the Philippines levels of CRP were significantly lower, and levels of the anti-inflammatory cytokine IL-10 significantly higher, than are typically observed in Western contexts, and these associations were not accounted for by differences in body mass index between the populations (McDade *et al*, 2009). In lowland Ecuador among the indigenous Shuar people, levels of CRP were found to vary widely within the same individuals, showing a pattern of rapid rise to high levels in response to acute infection and then dropping to often undetectable levels upon infection resolution (McDade *et al*, 2012b). An even more direct challenge to PATHOS-D predictions came from findings that depression was not associated with elevated CRP in the Philippines and that associations between both current and childhood stressors (ie, death of a parent) and inflammation were only apparent in the sub-population in the Cebu region that had been raised in more hygienic environments (McDade *et al*, 2012a). Individuals with high levels of microbial exposure in infancy showed no such associations. Taken together, these data suggest that high microbial exposure early in life—such as would have been normative across human evolution—may hone the immune response to be more specific for pathogen exposure and less generalized to the types of psychosocial stress that so reliably induce depression. Under these evolutionarily normative environments, the links between inflammation and MDD that are so apparent in the West would not exist.

However, these findings must be balanced against more recent work conducted in the lowland jungle of Bolivia among the Tsimane Amerindians, a small-scale society composed of lean forager-horticulturalists with a short average lifespan who live in a high-pathogen environment and thus have significant microbial priming in infancy (Stieglitz *et al*, 2015b). In all these ways the Tsimane represent a reasonable approximation of environmental and social conditions prototypically confronted by humans in the EEA. Working among these people, Stieglitz *et al.* (2015b) examined whether a syndrome recognizable as MDD exists, and if it exists, whether it is associated with increased inflammatory biomarkers. Results indicated that a depressive syndrome identical to that seen in the industrialized world exists among the Tsimane, and is associated with the same risk factors that have been observed everywhere else in the world: reduced health (indexed as functional disability) and psychosocial stress (indexed by social conflict, especially with non-kin; Stieglitz *et al*, 2015a). When examined as a binary construct based on a median split in symptom scores, depression was also associated with significantly increased serum concentrations of IL-6, TNF, and CRP but not IL-1-β (Stieglitz *et al*, 2015b), replicating the overall pattern of meta-analytic findings from studies conducted in industrialized societies. These associations remained after adjustment for age, body mass index, and high leukocyte count (likely indicative of current infection), and associations were observed across a wide range of depressive symptoms.

As our discussion of this prediction suggests, currently available data provide a split decision on whether associations between depression and inflammation are ancient and hence potentially adaptive, or are of recent origin and thus likely a result of non-adaptive evolutionary mismatch. One can only mourn the fact that the theoretical perspectives and technology necessary to resolve this issue were not available in the middle years of the 20th Century when a range of hunter–gatherer groups on several continents had yet to be driven to extinction by the inexorable onrush of the modern world. PATHOS-D theory engenders a sense of urgency to examine this issue in the remnant small-scale societies that remain. Two types of studies would be especially relevant. First, it would be of great interest to conduct the equivalent of Trier Social Stress Tests in these societies to examine whether objectively induced psychosocial stress activates inflammatory pathways as it does in the West. Second, it would be important to examine whether the administration of cytokine activators (ie, endotoxin, typhoid vaccine or longer-term treatment with IFN-α) produce depressive symptoms as they do in the industrialized world. If individuals living in environments more closely aligned with prototypical conditions in the EEA showed inflammatory responses to psychosocial stress and if they responded to immune stimulation with depression, strong evidence in support of PATHOS-D would have been obtained.

THE TYPES OF IMMUNE CHANGES SEEN COMMONLY IN MDD SHOULD HAVE PROMOTED SURVIVAL IN THE HIGH-PATHOGEN ENVIRONMENTS IN WHICH HUMANS AND THEIR ANCESTORS EVOLVED

From a PATHOS-D perspective there is no *a priori* reason that MDD should be associated with increased inflammation, only that MDD be associated with genes, physiology and behavior that—on average—decreased infectious mortality across human evolution. The fact that a subset of patients with MDD demonstrate increased inflammation implies the hypothesis that if depression is associated with increased inflammation, and if depression evolved as an adaptive pathogen–host defense strategy, then increased inflammatory activity should have produced an overall survival benefit in high-pathogen ancient environments, if indeed the association between depression and inflammation was adaptive in the EEA. For this idea to be credible two things are required: first depression should enhance host defense,

and second inflammation should enhance host defense. On the face of it, neither appears to be true, given significant evidence that both depression and inflammation appear to increase—rather than decrease—vulnerability to infection (Zorrilla *et al*, 1996; Evans *et al*, 2002; Cruess *et al*, 2003; Raison *et al*, 2005; Doering *et al*, 2008; Faulkner and Smith, 2008; Leserman, 2008; Leutscher *et al*, 2010; Andersson *et al*, 2016; Doran *et al*, 2002). Here we consider the question of whether inflammatory activity provided protection against infectious mortality.

For at least 2000 years it has been recognized that inflammation is essential for human health and a necessary ingredient of our ability to adequately fight infections. We now know that the larger innate immune response—of which inflammation is a core component—provides both direct and rapid protection against all classes of pathogens and has a crucial role in activating slower, but more definitive acquired immune responses. However, studies in recent years have found that the relationship between the innate and acquired immune systems follows the laws of cooperation and competition that define all evolved relationships. Especially under conditions of limited energy availability or simultaneous infectious risk from multiple pathogens, immune function can become characterized by trade-offs between these two branches of immunity, such that resources invested in one, mean reduced functionality of the other (McDade *et al*, 2016). Consistent with this notion, chronic inflammation can actually suppress T- and B-cell function through various mechanisms (Cope *et al*, 1997; Moraska *et al*, 2002; Cope, 2003; Clark *et al*, 2005; Muller *et al*, 2008; Vaknin *et al*, 2008; Eleftheriadis *et al*, 2009; Blume *et al*, 2011), and rates of infection are often increased —not decreased—in autoimmune conditions characterized by chronic inflammation (Doran *et al*, 2002). However, PATHOS-D theory requires only that across evolutionary time the patterns of enhanced inflammatory activity characteristic of depression provided overall survival benefits that outweighed any costs imposed by associated reductions in other aspects of immune functioning.

Some evidence for this possibility comes from studies conducted by Westendorp and colleagues in Ghana and the Netherlands. These researchers observed that cytokine-stimulated production of TNF-α declines with age in the Netherlands, a country with a low infectious burden, but does not decline with age in Ghana, a country with high rates of infection (ie, 85% of Ghanan study participants were infected with malaria; May *et al*, 2009), suggesting that increased proinflammatory cytokine production—as observed in MDD—promotes survival under conditions of high-pathogen burden (Drenos *et al*, 2006). More definitive evidence for this possibility comes from a second Ghanian study that more directly examined the impact of pathogen exposure on the association between inflammation and survival. Ghana is a country in which some regions have pure water available from boreholes, whereas other regions must rely on heavily contaminated rivers for drinking water. As would be expected, death rates from infection are far higher in regions that utilize rivers than in areas where borehole-obtained water is available. Consistent with the prediction that increased inflammatory signaling is protective in the high-infection environments that were common during human evolution (and especially common since the origin of agriculture and the rise of cities; Armelagos *et al*, 2005), a haplotype of the IL-10 gene associated with increased inflammation was found to be significantly more prevalent in populations that relied on river water than in populations that drank from boreholes—suggesting positive selection driven by enhanced pathogen protection (Kuningas *et al*, 2009). Consistent with this possibility, during a five-year follow-up period, the high-inflammation IL-10 haplotype was associated with reduced survival in individuals who drank clean water from boreholes, but increased survival in populations exposed to high levels of pathogens as a result of drinking river water (Kuningas *et al*, 2009).

We have already noted that depression is associated with increased circulating inflammatory biomarkers in the forager-horticulturist Tsimane people of lowland Bolivia (see Prediction 3). Researchers also conducted *ex vivo* stimulation studies with endotoxin and phytohemagglutinin (PHA; to assess response capacity of both the innate and acquired immune systems, respectively) and found that Tsimane individuals with high levels of depression produced greater levels of IL-1-β, IL-6, and TNF in response to both endotoxin and PHA, even when excluding individuals with leukocyte counts suggestive of current infection (Stieglitz *et al*, 2015b). Interestingly, this pattern is different from the suppression of mitogen-stimulated immune responses commonly observed in depressed patients in the Western world (Herbert and Cohen, 1993a), which may point to yet another way in which modern conditions have disabled previously adaptive associations between depression, immune function, and pathogen–host defense. Nonetheless, whether the increased mitogen-stimulated inflammatory cytokine response observed among depressed members of Tsimane society would translate to enhanced protection against pathogens remains unknown.

Multiple facets of the modern world, from antibiotics to refrigeration and paved surfaces have profoundly reconfigured our relationship with the microbial world in ways that have reduced the benefits of inflammation and increased its costs (Drenos *et al*, 2006; Raison *et al*, 2010c). Nonetheless, even in an environment so radically different from that in which humans evolved, data link increased inflammation with improved outcome in the context of at least some infections. For example, in a large study of consecutive patients admitted to hospital with fever, elevations in plasma concentrations of the anti-inflammatory cytokine IL-10—as well as the ratio of IL-10/TNF-α—were associated with increased mortality (van Dissel *et al*, 1998) and increased IL-10 production late in the disease course predicted reduced survival following infection with the pandemic A/H1N1-/2009 influenza virus (Bermejo-Martin *et al*, 2010). As these findings would predict, alleles of the IL-10 gene—such as -1082G—associated with higher IL-10 production appear to

promulgate poor infectious outcomes. For example, the −1082G allele predicts increased symptom severity and mortality in the context of community acquired pneumonia (Gallagher *et al*, 2003) and is associated with reduced antibody responses to tetanus, influenza and hepatitis B virus (HBV) vaccines (Hohler *et al*, 2005; Corsini *et al*, 2006; Li *et al*, 2007). Families with a member who died from meningococcal disease were characterized by increased production of IL-10 and reduced production of TNF-α when compared with families with a member who had bacterial meningitis but survived (Westendorp *et al*, 1997) and elevated CRP has been associated with increased survival in children with meningococcal sepsis (Joosten *et al*, 2000). The IFN-γ +874T allele increases production of this Th1 inflammatory cytokine via enhanced binding of NFKB (Pravica *et al*, 1999, 2000) and protects against Mediterranean Spotted fever (Forte *et al*, 2009). Multiple studies and a large meta-analysis find that the T allele also protects against the development of tuberculosis on the individual (Pacheco *et al*, 2008) and population levels (Larcombe *et al*, 2008). In individuals with active tuberculosis, the T allele reduces severity and risk of disseminated disease (Ansari *et al*, 2009). The T allele also reduces the risk of leprosy (Cardoso *et al*, 2010), severe acute respiratory syndrome (SARS; Chong *et al*, 2006), and Chagas disease (Torres *et al*, 2010). Conversely, the low-producing +825A allele predisposes for hepatitis B and C persistence and negatively impacts clinical course of the disease (Gao *et al*, 2009). Consistent with these findings, reduced peripheral blood mononuclear cell production of IFN-γ and IL-12 is associated with increased severity of respiratory syncytial virus symptoms in infants under one year of age (Pinto *et al*, 2006).

THE SIGNS AND SYMPTOMS OF MDD SHOULD SERVE PATHOGEN DEFENSE FUNCTIONS

The association of depression with increased circulating levels of proinflammatory cytokines and CRP does not easily lend itself to social explanations for the high prevalence of either MDD or putative depressogenic risk alleles. On the other hand, this association is foundational to the proposal that depression evolved to serve pathogen–host defense functions. However, if this is indeed the case, why should we expect the immune changes seen in depression to be limited to circulating cytokines or CRP? In the context of innate immune activation, cytokine stimulation forms only part of a larger phenomenon that comprises the acute phase response (APR). As noted in a recent review (LeGrand and Alcock, 2012), the APR is a somewhat paradoxical phenomenon, given that many of its features inflict significant energetic costs (eg, fever), hamstring immune responses (eg, iron sequestration, zinc, and tryptophan depletion), or produce behaviors likely to reduce attractiveness to potential mates, induce loss of social status or increase the risk for predation (eg, lethargy, psychomotor slowing, and social withdrawal), all of which would be expected to impair, rather than enhance, host survival, and reproduction. And while fever has been shown to enhance immune function while simultaneously contributing directly to pathogen killing, no direct immune benefits have been shown for many other APR features. A potential resolution to this enigma has been offered recently under the rubric of 'immune brinksmanship', which suggests that many APR features—such as iron sequestration and reduced zinc availability—have evolved to make the host environment less optimal for invading organisms, given that these minerals are essential nutrients for microorganisms, without which they can neither replicate nor survive (LeGrand and Alcock, 2012). From this perspective the APR can be seen as being, in part, a strategy that risks damage to the self, but that is likely to kill the offending agent before it kills the host. A comprehensive vision of the APR sees some of its elements as serving direct anti-pathogen functions (eg, leukocytosis), some as serving to reallocate energy to the immune system (eg, psychomotor slowing, somnolence) and some as serving 'immune brinkmanship' functions.

Studies suggest that, as a group, medically healthy individuals with depression demonstrate multiple biological and behavioral stigmata of an APR (Jimenez-Fernandez *et al*, 2015). For a full listing of elements of the APR that have been associated with MDD in medically healthy individuals, see Supplementary Table S2. Importantly, at least one group has found that the APR in medically healthy adults with MDD is associated with increased levels of IL-6, suggesting that the APR is indeed part of a larger pathogen–host defense immune response (Maes *et al*, 1995; Sluzewska *et al*, 1996).

Moreover, if psychosocial stress serves as an 'early warning system' for increased danger of impending wounding and subsequent infection, PATHOS-D would predict that psychosocial adversity should also be associated with an APR over and above activation of cytokines. Consistent with this possibility, stress in animals reduces gastrointestinal absorption and blood levels of iron (Zhao *et al*, 2008; Chen *et al*, 2009) and in human males a 5-day intense psychological stressor ('Hell Week') reduced blood levels of iron, zinc, and albumin (Singh *et al*, 1991), as would be predicted if stress induces an APR. Psychological stress has also been reported to elevate core body temperature in animals and humans (Soszynski *et al*, 1996; Kaneda *et al*, 2009; Hayashida *et al*, 2010), an anti-pathogen defense mechanism that is most effective in conditions of low host iron availability (Kluger and Rothenburg, 1979). That these changes serve immune purposes is suggested by findings that in animals, stress-induced hypoferremia and hyperthermia are associated with stress-induced increases in IL-6 (Soszynski *et al*, 1996; Zhao *et al*, 2008); however, other mechanisms may also be active, including hypothalamic activation of brown fat (Kataoka *et al*, 2014). Because at least some biological changes associated with the APR have been shown to have important roles in pathogen–host defense, their presence in depression would be strongly predicted by PATHOS-D, and their

absence would strongly argue against the validity of this approach. On the other hand, their presence in MDD is not parsimoniously explained by theories that focus on potential social benefits of depression. In what ways would elevated body temperature or reduced iron availability aid in negotiating relationships with other humans? Similarly, if depression is simply a non-adaptive phenomenon, why would such ancient, highly conserved and highly complex physiological responses be associated with the disorder?

Inseparable from the physiological aspects of the APR, immune activation also produces a suite of behavioral responses known as sickness behavior that has been retained across vertebrate evolution and that shares many features in common with the symptoms of MDD (Dantzer, 2006; Dantzer *et al*, 2008b). These symptoms include lethargy/fatigue, psychomotor slowing, altered sleep, loss of appetite, anhedonia, and social withdrawal. Although it is clear that the symptoms of depression can arise from a wide variety of divergent causes—including internally generated thought patterns—PATHOS-D proposes that MDD initially evolved out of sickness behavior. Circumstantial evidence for this type of close relationship between sickness and MDD come from several sources. For example, data suggest that many people cannot accurately identify whether they are developing depression or an infectious illness early in the course of either condition (Ratcliffe, 2013). Similarly, sickness in the first week of treatment with the cytokine IFN-α strongly predicts the development of cognitive/emotional symptoms of depression over the ensuing 6 months of therapy (Wichers *et al*, 2005a). Finally, if inflammation induces sickness and if depression evolved out of sickness, inflammation might be expected to be more strongly associated with the symptoms most often shared by sickness and depression, rather than symptoms such as sadness and guilt/feelings of worthlessness that are more specific to MDD. Supporting this possibility, an early report found that the acute phase protein haptoglobin correlated with psychomotor retardation, sleep disturbance, anorexia/weight loss, and anhedonia (Maes *et al*, 1993). More recently, a large population-based study ($N = 15\,071$) reported that CRP was more strongly associated with sleep abnormalities, fatigue, and appetite changes than with MDD symptoms less common in the context of sickness (Jokela *et al*, 2016). In a group of patients with MDD, increased circulating levels of IL-6 and monocyte chemoattractant protein-1 were positively associated (and levels of IL-10 were negatively associated) with objectively measured psychomotor slowing (Goldsmith *et al*, 2016a), and elevated plasma CRP was associated with reduced functional connectivity between the ventromedial prefrontal cortex and ventral striatum. These changes in functional connectivity mediated associations between increased CRP and anhedonia and psychomotor slowing (Felger *et al*, 2015).

Evolutionary processes do not produce perfect products, and all evolved adaptive mechanisms come with associated costs and trade-offs. If indeed MDD is conceptualized as a condition evolved from, and 'designed' to serve the same purposes as, sickness, the obvious question is what pathogen-related survival and reproductive benefits accrue from depressive symptoms that offset their costs. That depression reduces fitness in modern environments has often been remarked upon; however, the costs across evolutionary time of the types of prolonged sickness behaviors that comprise MDD have also likely been substantial. As part of the APR, sickness exacts significant metabolic costs that limit energy available to other tasks essential for survival and reproduction. In many species, including humans, even subtle signs of sickness promote avoidance behavior from conspecifics (Schaller, 2011). Over and above the suppressive effect of inflammation on sexual functioning, individuals who appear sick are judged to be less attractive and hence are less likely to find high-quality mates. In hierarchical social groups the display of sickness risks loss of social status, with associated reductions in survival and reproductive access. Finally, sickness increases the risk of predation (Schaller, 2011).

One possibility is that the PATHOS-D perspective is exactly backwards, and in fact depression is a maladaptive consequence of the benefits of acute sickness. Perhaps depression is akin to other chronic conditions, such as HIV and autoimmune diseases, in which ongoing inflammation, rather than providing benefit, actually increases the risk of infection and/or infectious mortality. Many studies associating MDD with increased infectious morbidity in the modern world would support this possibility (Zorrilla *et al*, 1996; Evans *et al*, 2002; Cruess *et al*, 2003; Raison *et al*, 2005; Doering *et al*, 2008; Faulkner and Smith, 2008; Leserman, 2008; Leutscher *et al*, 2010; Andersson *et al*, 2016). If true, this removes pathogen–host defense as an explanation for the conundrum of why genes that contribute to MDD have been retained across hominid evolution.

Or it may be that by inducing social withdrawal, depression provides an adaptive advantage for individuals at increased risk of infection as a result of immune functioning that for one reason or other is sub-optimal. This is the position taken by Kinney and Tanaka (2009) in proposing that depression evolved as an adaptive response to cope with pathogens (Anders *et al*, 2013). In contradistinction, PATHOS-D suggests that—whatever its costs in relation to specific pathogens—depression was not primarily a compensation for immune inadequacy, but rather enhanced overall survival in the EEA via its association with physiological and behavioral changes that reduced the impact of infectious agents on reproductive success. Said differently, in conditions characterized by a heightened risk for infectious mortality, such as occur during active infection or when environmental adversity signals an increased risk for wounding or other processes that increase the risk of infection (ie, starvation secondary to ostracism), the generalized innate immune activation and symptoms associated with depression provided a net survival benefit, whatever their other costs in terms of immune or social trade-offs. Importantly, this perspective does not require that depression be the only way for humans to adaptively cope with infectious risk only that it was adaptive enough for its genetic

underpinnings to be retained in the human genome at a level significant enough for MDD to be with us today.

From a PATHOS-D perspective, MDD in response to infection or tissue trauma provides the same types of survival benefits as does sickness behavior. In response to stress, depression can be seen as proactive physiological/behavioral sickness behavior—a type of 'just in case' condition that keeps an individual in a state of pathogen defense readiness. Proinflammatory cytokine activation in response to either infection or stress induces a behavioral state of conservation-withdrawal (Engel and Schmale, 1972; Eisenberger *et al*, 2010b; Hannestad *et al*, 2011) characterized by depressed mood, anhedonia, psychomotor retardation, fatigue, social avoidance, and anorexia (Capuron *et al*, 2002; Dantzer *et al*, 2008b; Majer *et al*, 2008; Irwin and Cole, 2011). This state is an integral component of depressive disorders and has been widely considered to develop in the context of infection and/or tissue injury as a means of marshalling limited metabolic resources for the expensive tasks of immune activation, fever generation and tissue repair (Hanff *et al*, 2010).

In addition to energy allocation, conservation-withdrawal symptoms may have also proved adaptive by reducing interpersonal contact and thereby limiting infectious exposure (Kinney and Tanaka, 2009). In the paradigm proposed by Kinney and Tanaka (2009) this is seen as an evolved compensatory mechanism to cope with immunodeficiency. However, it is equally possible that the infection-avoidance benefits of social withdrawal evolved as a complement to its metabolically valuable infection-fighting benefits. Indeed, the more survival and reproductive benefits accrue for any one trait the more likely its genetic antecedents are to be retained and to spread in the population. Because humans in the EEA lived in small coalitional groups of genetically related individuals, the logic of inclusive fitness suggests that social withdrawal might have been adaptive for an individual's genes by reducing the risk of infection in kin, even if such withdrawal limited the provision of much needed care from others and thus reduced individual survival (Cole, 2006; Schaller and Murray, 2008). Indeed, given evidence that merely viewing pictures of a sick individual activates the viewer's innate immune system (Schaller *et al*, 2010), it may be that by prepotently activating the innate immune responses in one's kin, depression served as an early warning system for increased infectious risk. In this regard, it is interesting to note that associating with depressed individuals increases the risk of developing depression oneself (Fowler and Christakis, 2008), exactly as would be predicted if depression served as an early warning signal to others of infectious risk and if depression enhanced host pathogen defense by priming the innate immune system. A clear prediction of this line of reasoning that awaits testing is that viewing images of depressed individuals should activate the immune system.

In addition to potential inclusive fitness benefits, any decrement in survival from depression-induced loss of social aid might have been more than offset by reduced risk of exposure to other pathogens while in a vulnerable state due to a pre-existing infection, given that viral infections promote aggressive immune responses to bacterial super-infections that can greatly increase mortality (Degre and Glasgow, 1968; Jakab and Dick, 1973; Jones *et al*, 1983; Nguyen and Biron, 1999; Molyneux *et al*, 2003; Beadling and Slifka, 2004; McCullers *et al*, 2010). Moreover, social withdrawal and reduced environmental exploration might also have promoted individual survival by limiting a depressed individual's contact with immunologically dissimilar out-group members who potentially harbored pathogens against which the depressed person would have had reduced immunity compared to pathogens endemic in the home group (Schaller and Murray, 2008; Thornhill *et al*, 2009). This idea suggests a hypothesis that to our knowledge has never been tested that MDD should be associated with increased xenophobia. It is intriguing to note, however, that endotoxin administration increased the desire of healthy volunteers to be around individuals they had previously identified as 'support figures' (Inagaki *et al*, 2015), consistent with the possibility that immune changes associated with depression might have promoted an in-group bias that reduced exposure to more potentially lethal pathogens harbored by members of other social groups. How such an increased desire to associate with in-group members would square with the potential selective advantages of withdrawing from kin to prevent the spread of infection is unknown. Moreover, given that sterile psychosocial stressors also activate inflammation, it is intriguing to speculate that the benefits of seeking support/proximity with kin/in-group members in response to psychosocial dangers may have offset the potential risks of contagion spread as a result of inflammation enhancing prosocial behavior with trusted in-group members.

With the exception of asthma and allergies, inflammatory conditions typically strike after the age of reproduction, and thus alleles that promote them are subject to minimal selective pressure, even in modern environments (Beekman *et al*, 2010). Almost certainly, the association between chronic inflammation and these disease states (eg, dementia and cardiovascular disease) serves no adaptive purpose and likely results in large measure from environmental conditions unique to the modern world. However, the relationship between inflammation and depression is quite different, given that the incidence of MDD peaks in the 20–30 s (Eaton *et al*, 1997; Patten *et al*, 2006; Kessler *et al*, 2010), an age of primary reproductive/childrearing responsibilities. In this, MDD is not alone. Schizophrenia and bipolar disorder—conditions with which MDD is genetically linked—are also characterized by increased inflammation and by an average age of onset early in life when the costs of these disease states to survival and reproduction are (and were) likely to be maximal.

Although the current article focuses on unipolar depression, there is no reason to think that depressive symptoms occurring in the context of bipolar disorder would be any less efficacious for pathogen–host defense than the same symptoms when they occur in other contexts, and indeed

multiple studies demonstrate that bipolar depression is associated with the same types of inflammatory activation that are observed in unipolar MDD (Goldstein *et al*, 2009). However, what should we make of the fact that multiple studies show that inflammatory markers are at least as elevated—and maybe more elevated—in manic episodes as they are during bipolar depressions (Goldstein *et al*, 2009)? A proximal answer might point to the fact that mania is associated with many of the same neuroendocrine abnormalities as depression, especially glucocorticoid resistance (Schmider *et al*, 1995), which is known to release inflammatory pathways from inhibitory control and which has been associated with increased proinflammatory cytokine levels in MDD (Maes, 1999). Moreover, although far less common than depression, full manic episodes have been reported during IFN-α therapy, which produces chronic immune activation, and combinations of depressive and manic symptoms during IFN-α treatment are common (Constant *et al*, 2005).

However, this type of answer provides no insight into why mania should be associated with increased inflammation. Might the association serve adaptive purposes or is it better considered as an example of antagonistic pleiotropy? Here PATHOS-D offers a novel perspective. Until it becomes disabling, mania increases the types of social and sexual extroversion that may provide direct Darwinian benefits as a result of increased opportunities for reproduction (Berry and Miller, 2001). However, increased social and sexual activity also increase the risk for reduced survival as a result of increased pathogen exposure (Hamrick *et al*, 2002). In this context, might genes linking inflammation with mania have undergone positive selection by conferring increased protection against the wide range of infections to which manic behavior would have exposed an individual in the EEA? Although highly speculative, this hypothesis produces the clear prediction that the increased inflammation observed in mania should be associated with the symptom of hypersexuality, especially in males, who across evolutionary time would have been more likely than females to benefit in terms of reproductive success from sexual activity with multiple partners. Interestingly, animal data provide some evidence for this possibility, given that cytokine activation suppresses sexual activity in female, but not male, rats (Avitsur and Yirmiya, 1999). However, this hypothesis would be strengthened by evidence that manic behavior itself can elevate inflammation and to our knowledge this type of causal connection has not been investigated.

WHATEVER THEIR OTHER FUNCTIONS, RISK GENES FOR MDD SHOULD SERVE PATHOGEN–HOST DEFENSE

In a previous publication we provided an exhaustive enumeration of known immune and/or pathogen defense functions for the best-supported risk alleles for MDD derived from genome-wide association studies (GWAS) and meta-analyses of candidate gene studies (Raison and Miller, 2012). These GWAS findings are presented in Supplementary Table S3. In the time since our prior publication, an additional study utilized sparse whole-genome sequencing in a population of Han Chinese females to identify and replicate two novel depression risk loci on chromosome 10, one 5′ to the suirtuin 1 (*SIRT1*) gene (rs12415800) and one in an intron of the phospholysine phospho-histadine inorganic pyrophosphate phosphatase (*LHPP*) gene (consortium C (2015)). As with previously identified 'genes of interest,' PATHOS-D predicts that these genes should impact immune function in ways that provided adaptive advantages for pathogen–host defense. In this regard, nothing is known regarding LHPP, but an extensive database attests to multiple immune functions of sirtuin 1, a class III histone deacetylase enzyme that serves as an important sensor of cellular energy and redox states (Supplementary Table S3; Michan and Sinclair, 2007).

In particular, sirtuin 1 has been shown via epigenetic mechanisms to have a key role in limiting the extent and duration of acute inflammation by promoting a shift from inflammation-driven glycolytic activity to 'adaptation-phase' fatty acid metabolism. Sirtuin 1 suppresses nuclear factor-kappa B RelA/p65 activity, represses cyclooxygenase 2 gene expression (Zhang *et al*, 2010b), and induces gene silencing facultative heterochomatin formation at the promotors of proinflammatory genes, including TNF and IL-1-β, as well as the promotor for hypoxia-inducible factor-1-α, a signaling factor important for maintenance of proinflammatory glycolytic activity (Vachharajani *et al*, 2016). In addition, sirtuin 1, in dependence on NAD+, increases levels of peroxisome proliferator-activated receptor gamma coactivator 1 (PCG-1)-α and β, which promotes the fatty acid metabolism essential for resolution of the inflammatory response (Fernandez-Marcos and Auwerx, 2011). The end result of these activities is that sirtuin 1 inhibits the transformation of monocytes to macrophages and promotes anti-inflammatory M2 macrophages and regulatory T cells (Treg) at the expense of proinflammatory M1-type macrophages and effector T cells (Liu *et al*, 2012a; Park *et al*, 2016). However, conflicting data suggest that in at least some contexts sirtuin 1 may have inflammatory and adaptive immune stimulating effects. For example, sirtuin 1 inhibition has been reported to stimulate Foxp3 expression in Treg (Akimova *et al*, 2014).

Despite these complexities, evidence of diminished sirtuin 1 activity in medical conditions characterized by chronic inflammation suggest that its function might also be reduced in MDD, especially in patients with elevated peripheral inflammatory biomarkers. However, to our knowledge, no data are available to support or disprove this idea. Similarly, given the association of MDD with chronic inflammation, one would predict that the depression risk allele near the *SIRT1* gene should reduce sirtuin 1 activity, if it is found to have a functional effect, which is currently unknown. However, these predictions should be tempered by findings suggesting a complex and contradictory role for sirtuin 1 in

pathogen defense. In certain contexts, such as the hypoinflammatory phase of sepsis, sirtuin 1 blockade has been reported to reduce bacterial load and enhance survival. Sirtuin 1 blockade has also been shown to inhibit hepatitis B replication in hepatocytes (Ren *et al*, 2014). Similarly, sirtuin-deficient mice have been shown to demonstrate improved intestinal anti-bacterial defense mechanisms (Lo Sasso *et al*, 2014). On the other hand, the use of celecoxib to stimulate sirtuin 1 within macrophages resulted in an enhanced ability of ampicillin to clear *Staphylococcus aureus* from these cells (Annamanedi and Kalle, 2014), consistent with the observation that low levels of sirtuin 1 within macrophages associates with bacterial infection in these cells (Zhang *et al*, 2010a, 2010b). Sirtuin 1 also appears to be essential for optimal immune clearance of respiratory syncytial virus and has been shown to suppress human T-cell leukemia virus type 1 transcription (Owczarczyk *et al*, 2015; Tang *et al*, 2015).

Although a perusal of Supplementary Table S3 highlights the remarkable degree to which *SIRT1* and many other potential depression risk alleles impact both immune function and pathogen defense, it should be noted that there is another pathway whereby these risk alleles might enhance pathogen–host defense without directly modulating immune function. If the PATHOS-D proposal that depressive symptoms themselves serve pathogen defense functions is correct, genes that promote these symptoms might have served adaptive purposes in fighting infection via this mechanism alone. For example, in addition to multiple immune effects, sirtuin 1 signaling in the hippocampus appears to have antidepressant effects, given animal data that pharmacologic and genetic inhibition of hippocampal SIRT1 function increases depression-like behaviors in response to stress, whereas SIRT1 activation blocks both the development of depression-related phenotypes and aberrant dendritic structures elicited by chronic stress exposure (Abe-Higuchi *et al*, 2016). *CACNA1C* is another putative depression risk gene known to both enhance and impair pathogen–host defense depending on the microorganisms involved (Raison and Miller, 2012). Carriers of the rs1006737 A risk allele have also been shown in several studies to demonstrate changes in brain function and morphology relevant to MDD (Bigos *et al*, 2010; Erk *et al*, 2010; Perrier *et al*, 2011), again raising the possibility that even genes with known immune effects might enhance pathogen defense either primarily, or synergistically, via the direct induction of depression in response to environmental adversities known to increase the risk for pathogen-induced morbidity/mortality (ie, stress signaling an increased risk of wounding, active infection; Bigos *et al*, 2010; Erk *et al*, 2010; Perrier *et al*, 2011). Understanding the impact of putative risk genes like *SIRT1* or *CACNA1C* on inflammatory and behavioral responses to psychosocial stress would provide invaluable insight into the question of whether they promote depression and pathogen–host defense via the type of inflammatory activation that is a hallmark of MDD in the modern world.

RISK ALLELES FOR MDD SHOULD NOT BE CONSTANT ACROSS RACIAL/ETHNIC/CULTURAL GROUPS AS A RESULT OF DIFFERENTIAL EXPOSURE TO PATHOGENS AND ADAPTIVE INTROGRESSION WITH ARCHAIC HUMAN SPECIES

PATHOS-D proposes that depression risk alleles have been maintained in the human genome primarily because, by enhancing pathogen–host defense, they provided a net survival and reproductive advantage. A primary problem that this theory shares with other adaptive explanations for depression is that to date no incontrovertible risk alleles for MDD have been identified. Indeed, most large GWAS have failed to find SNPs that meet genome-wide significance and when such SNPs are found (ie, rs12520799 in *DCNP1* and rs76917 in *TNF*) they are not replicated in GWAS conducted in other populations (Raison and Miller, 2012).

Multiple explanations have been offered for this case of 'missing depression genes,' most often that MDD is heterogeneous in relation to its environmental antecedents, the nature and severity of its symptoms and its disease course; and that therefore it is likely that the condition is a concatenation of numerous as-yet-unidentified more etiologically homogeneous sub-conditions that are likely to be more genetically consistent. Although not dismissing disease heterogeneity as a cause for failure to replicate depressive risk alleles, PATHOS-D offers an additional novel explanation for at least some cases of replication failure. Because pathogens can develop resistance to host immune defenses, or in many cases actually evolve to benefit from these defenses via pathogen manipulation strategies, not all genetically programmed physiological or behavioral pathogen–host defense strategies will be equally effective against all microbes. Because of this, in cultures/societies exposed to different mixtures of pathogens across time, different immune mechanisms will be adaptive, and therefore likely to become linked to depression. Said differently, because of geographic and historical differences in pathogen exposure, we should not expect all human ethnic/racial groups to have benefitted from the same genetically driven pathogen defense strategies and therefore to show the same risk alleles for MDD. Thus, a PATHOS-D perspective suggests that understanding the specific histories of shared and unique co-evolved pathogen–host interactions within and across human societies will be essential for enhancing our understanding of why genotype–phenotype associations observed in one population do or do not replicate across other populations, as well as why certain genetic variants drive physiological processes that induce depression in certain individuals but not in others.

These insights may help account for the intriguing finding that the association between *SIR1* nor *LHPP* SNPs and MDD identified in Han Chinese females was not replicated in European populations (Consortium C (2015)). PATHOS-D would predict that this finding might be accounted for by the fact that *SIRT1* and *LHPP* conferred specific anti-pathogen

defenses in the Chinese environment that were not relevant in Europe. If so, one would expect the prevalence of the *SIRT1* and *LHPP* risk alleles to be significantly higher in Han populations than in Europeans as a result of positive selection, and this is indeed the case (Consortium C (2015).

Many genes have been replicated across a range of ethnic/racial groups as risk factors for schizophrenia, suggesting that at least certain pathways for the disorder are ancient and arose prior to the first migrations of modern humans out of Africa. From a PATHOS-D perspective, the fact that no such replicated risk alleles have been found for MDD may suggest that the condition is more environmentally based than are conditions with more universally established genetic risk genes, but not in the way that this environmental primacy is usually understood. Instead, MDD may have no universal risk genes because pathogen pressures in local environments over the last 60 000 years have been pre-eminent in determining which specific immune mechanisms were most adaptively linked to the generation of depressive symptoms in any given environment. If it turns out that the association between depression and increased inflammation is a human universal (not universal in terms of all depressed individuals showing increased inflammation, but rather that groups of depressed individuals demonstrate increased inflammation across all ethnicities/cultures), then the clear prediction of PATHOS-D would be that alleles that confer depression risk in one population but not another should either (1) increase inflammatory signaling more in the population in which they confer risk; or (2) more powerfully increase the prevalence/severity of depressive symptoms in response to any given degree of inflammatory activity in the population in which they confer risk.

Similarly, because present-day human societies/cultural groups have historically experienced widely different degrees of exposure to bacterial and viral pandemics that exerted extreme selective pressure (Fincher *et al*, 2008), PATHOS-D predicts that the types of immunity that best cope with these different types of pathogens should have different relationships with depression across human cultures. So, for example, because interferon signaling is especially essential for host defense against viruses, a PATHOS-D perspective would predict that individuals from cultures with higher rates of historical exposure to lethal viral pandemics should respond to treatment with IFN-α with increased rates of depression development, if indeed depressive symptoms aid in pathogen defense. Were it possible to assess, this effect should be largest in hunter–gatherer populations that have evolved in the types of low population density environments that work against widespread viral infections. In such populations, viruses provided little positive selection pressure that would link antiviral defenses with depression, whereas such populations would have benefitted from optimal protection against environmental pathogens (eg, protozoa, bacteria, and fungi) that would have increased mortality under these conditions. Were such a population available, the prediction is that they would show enhanced depressive symptoms in response to a bacterial stimulant such as endotoxin, while showing a muted depressive response to IFN-α. Alas, given the escalating loss of isolated indigenous cultures, the time for such a definitive study may have passed.

Adaptive introgression provides another fascinating example of why pathogen–host defense processes may ensure that no universal genes for MDD will ever be found. Research over the last several years indicates that ~2% of the DNA of non-African humans derives from multiple bouts of interbreeding with Neanderthals, with current Melanesian populations also showing a Denisovan genetic inheritance from ancestral interbreeding with that group of now-extinct archaic humans (Vernot *et al*, 2016). In general, the results of this interbreeding were deleterious, as attested to by multiple 'desert' regions of human DNA depleted of archaic genetic material. Against this backdrop, it is striking that other Neanderthal and Denisovan sequences appear to have undergone positive selection. From a PATHOS-D perspective it is even more striking that these archaic alleles are associated with both immune function and with an increased risk of depression (Mendez *et al*, 2012; Segurel and Quintana-Murci, 2014; Simonti *et al*, 2016). Although it does not yet appear that the same Neanderthal allelic variants code for both immunity and mood, anyone concerned with adaptive explanations for MDD cannot help but be struck by this association, especially given that negative selection appears to have removed archaic human DNA from areas of the genome involved with other aspects of CNS morphology and function. Researchers tend to assume that retained archaic immune alleles provided an adaptive benefit for coping with novel Eurasian pathogens; PATHOS-D would suggest that their proclivity to induce depression provided additional advantages in our endless struggles with microbes and parasites.

UNEXPLAINED EPIDEMIOLOGICAL FEATURES OF MDD SUCH AS THOSE RELATED TO SEX SHOULD HAVE PROVIDED PROTECTION FROM INFECTIOUS MORTALITY IN HIGH-PATHOGEN ENVIRONMENTS

Here we consider ways in which PATHOS-D might provide adaptive explanations (as opposed to mere proximal/mechanistic explanations) for three epidemiological features of MDD that are striking characteristics of the disorder and relate directly to sex: (1) the 2:1 female preponderance of the disorder; (2) the impact of age and sex on the disorder's phenotypic presentation; and (3) the significant risk of the postpartum period for MDD development.

Why is Female Sex a Risk for MDD?

Females are approximately twice as likely as males to suffer from MDD (Seedat *et al*, 2009), with this imbalance being most pronounced during the reproductive years, exactly

when the manifold negative social and biological effects of depression would be expected to impact evolutionary fitness most adversely (Fiske *et al*, 2009). While many answers for the female preponderance of depression have been proposed over the years (eg, females are more sensitive than males to the social environment), none have successfully identified an adaptive advantage that would outweigh the costs of female depression to survival and reproduction. In contrast, PATHOS-D suggests a testable explanation for why depression is so common in females of reproductive age. Females are more likely to develop depression during the reproductive years because across evolutionary time depressive symptoms—having evolved out of sickness—promoted behaviors that decreased the risk of pathogen exposure and provided increased protection from pathogens for any given level of inflammatory activation once an infection had occurred (eg, by increasing energy available to immune processes by inducing conservation-withdrawal behavior, maintaining elevated body temperature, and so on). Said differently, by inducing social and biological behaviors that promoted host defense against pathogens, depressive symptoms allowed females of reproductive age to 'get by' with less inflammation. The unique importance of this for reproductive success in females is highlighted by the fact that inflammation reduces fertility, impairs lactation and directs metabolic resources away from the multiple energetically-costly aspects of female biology that were required for successful reproduction in ancestral environments (Van Bodegom *et al*, 2007; Schaller, 2011; Kobayashi *et al*, 2013). Interestingly MDD has also been associated with reduced fertility (Williams *et al*, 2007; Nillni *et al*, 2016). PATHOS-D theory predicts that this association should less prominent in females who have effectively 'replaced' inflammation with depression-based behavioral pathogen avoidance in the absence of elevated levels of inflammatory biomarkers.

Although most implications of this idea remain to be tested, some data support the first prediction of this hypothesis, which is that females should develop increased levels of depression for any given amount of inflammatory exposure. Indeed, when compared with men, females respond to an injection of lipopolysaccharide (LPS) with an increase in depression and feelings of social isolation, both of which are correlated with amount of cytokine response to the LPS in females, but not males (Moieni *et al*, 2015b). Similarly, females are more likely than males to develop depression in response to chronic inflammatory stimulation resulting from treatment with the cytokine IFN-α (Udina *et al*, 2012). Finally, given the pre-eminent role of psychosocial stress as an environmental risk factor for MDD, as well as evidence that hyperthermia enhances host defense, it is intriguing that reproductive aged females appear to be most vulnerable to developing psychogenic fever (Kaneda *et al*, 2009). However, these findings need to be balanced against results from a small recent study indicating that females mounted an enhanced proinflammatory cytokine response to low-dose endotoxin when compared with men, while showing no difference in inflammation-induced mood or anxiety symptoms—a pattern of findings opposite to this PATHOS-D prediction (Engler *et al*, 2016). If confirmed in larger studies, these findings might support an alternative immune-based mechanism for the female/male preponderance of depression and anxiety, specifically that females respond to immune challenges with greater immune activation which subsequently increases the risk for depression/anxiety.

Why is the Depressive Phenotype Affected by Sex and Age?

MDD is most commonly characterized by impaired sleep and reduced appetite (Smith *et al*, 2008), but a significant minority of depressed individuals manifest hypersomnia and hyperphagia instead (Thase, 2009). These symptoms are most frequent in females between adolescence and middle-age (Carter *et al*, 2000; Posternak and Zimmerman, 2001; Matza *et al*, 2003; Blanco *et al*, 2012). How might PATHOS-D theory seek to account for the existence of these reversed neurovegative symptoms, as well as their age and sex distribution? A first step is to establish that cytokine pathways known to be activated by infection are capable of producing both hypersomnia and hyperphagia. Hypersomnia has been recognized for years as a primary behavioral manifestation of proinflammatory cytokines (Krueger and Majde, 1994; Krueger and Toth, 1994; Krueger and Majde, 2003; Opp, 2004, 2009), and studies in healthy adolescents and adults indicate that chronically increased sleep is associated with increased saliva and blood concentrations of IL-6 and CRP (El-Sheikh *et al*, 2007; Patel *et al*, 2009; Prather *et al*, 2015). In terms of feeding behavior, animal models demonstrate that inflammation promotes carbohydrate preference (Aubert *et al*, 1995), such as is typical in depressive hyperphagia. Less well known are data that high-fat diets induce leptin and insulin resistance, as well as obesity, dependent upon activation of inflammatory mediators in the hypothalamus (Zhang *et al*, 2008; Kleinridders *et al*, 2009). Conversely, blocking hypothalamic inflammation prevents obesity and other stigmata of the metabolic syndrome, even in the context of high-fat consumption (Zhang *et al*, 2008; Milanski *et al*, 2009; Posey *et al*, 2009). In rodents, exposure to either TNF or IL-6 *in utero* results in adulthood obesity (Dahlgren *et al*, 2001), again suggesting that cytokines can induce hyperphagia/weight gain under certain circumstances. Although we know of no data showing that females are more likely than males to respond to inflammatory signaling with hyperphagia, female rodents have less anorexia than males in response to influenza infection (Avitsur *et al*, 2010).

Because the presence of widespread obesity is recent, the question arises as to whether more ancient signals for inflammatory activation might also promote hyperphagia, instead of anorexia. We know of no data that directly address this issue in terms of infection, but note that certain adenoviruses have been associated with weight gain

(Atkinson, 2008; Mitra and Clarke, 2010). In terms of psychosocial factors, preclinical studies suggest that stressors associated with a high degree of wounding—such as chronic social defeat—induce hypothalamic resistance to leptin (Kleinridders *et al*, 2009; Chuang *et al*, 2010), consistent with their known ability to activate inflammatory pathways (Avitsur *et al*, 2005; Bailey *et al*, 2007, 2009; Powell *et al*, 2010). As in depression, where hyperphagia and weight gain are associated with disease chronicity (Posternak and Zimmerman, 2001), chronic social defeat leads initially to weight loss but to weight gain over time (Chuang *et al*, 2010). Given the role of leptin resistance in hyperphagia, it is intriguing that increased peripheral leptin levels (consistent with leptin resistance) have been observed more consistently in females than in males with MDD (Rubin *et al*, 2002; Yang *et al*, 2007; Pasco *et al*, 2008; Zeman *et al*, 2009; Cizza *et al*, 2010), and are more common in atypical than non-atypical depression (Gecici *et al*, 2005).

Why might younger individuals in general, and females in particular, be more likely to develop depressive conditions characterized by hypersomnia and hyperphagia? From a PATHOS-D perspective, the simplest answer may be: because they can. In hunter-gatherer societies youth and females are frequently more protected from predation and to have food supplied to them by others (Kaplan and Gurven, 2005), raising the possibility that in ancestral environments these individuals enjoyed sufficient security to partake of the recuperative effects of sleep and to eat without having to expend energy searching for food.

Given evidence that anorexia may confer anti-pathogen effects (Raison and Miller, 2012), might similar benefits accrue to hyperphagia, especially in youth and females, under at least some evolutionarily relevant situations? Although admittedly speculative, several lines of evidence suggest that by promoting hypothalamic resistance to leptin, genes associated with increased inflammatory signaling might enhance host defense by driving ongoing leptin production despite malnutrition in conditions of food scarcity. This increased leptin production would both augment the drive to seek and consume food and would lower the set point at which food consumption initiated the types of inflammatory responses that are all too common in the obese, but that appear to be life-saving in the face of an infection such as tuberculosis, that was (and is) most lethal for females of reproductive age and for which low body weight and reduced leptin are deadly (van Crevel *et al*, 2002; Wieland *et al*, 2005; Buyukoglan *et al*, 2007; Leung *et al*, 2007; Pednekar *et al*, 2008; Roth, 2009).

Depression and anxiety are highly comorbid, and in both animals and humans, activation of the inflammatory response produces both types of symptoms. In a previous publication, we devoted significant space to providing a PATHOS-D perspective on why inflammation produces changes in brain function that subserve not just conservation-withdrawal symptoms likely to aid in defense against pathogens, but that also have been associated with hypervigilance symptoms (eg, anxiety/agitation, insomnia, anger/irritability (Association AP, 2013)) that across human evolution would have presumably siphoned metabolic resources away from the life-or-death task of immune protection (Raison and Miller, 2012). We suggested that sickness behavior—while of benefit for surviving infection—carries its own survival and reproduction costs as a result of increased risk for predation and reduced ability to care for one's young, as well as potential loss of status in a social species and/or loss of breeding territory (Miller and Cohen, 2005), all of which were relevant to humans in the EEA. Given these competing challenges to survival and reproduction, evolutionary logic may have dictated that inflammatory processes—especially when chronic—might have promoted hypervigilant behavior, which, while shunting energy away from fighting infection, would nonetheless have served adaptive purposes by protecting against environmental dangers engendered by sickness.

Given that human females and youth likely received more protection in the EEA than did adult males (who therefore on average would have more to lose from sickness behavior), a clear prediction from PATHOS-D is that males should respond to immune challenges/inflammatory activation with an increased ratio of hypervigilant to conservation-withdrawal symptoms, as well as an increase in cytokine effects on brain areas such as the dorsal anterior cingulate that subserve hypervigilance when compared with cytokine effects on areas such as the ventral striatum, which have been linked to inflammatory effects on anhedonia (Felger *et al*, 2015), which would be expected to promote social withdrawal. Available data provide mixed support for this hypothesis. On the one hand. a recent study found no difference between males and females in the severity of anxiety symptoms induced by low-dose endotoxin (Engler *et al*, 2016). On the other hand, a recent large cohort study reported that peripheral inflammatory biomarkers were more strongly associated with anxiety symptoms and anxiety disorders in males than in females (Duivis *et al*, 2013, Vogelzangs *et al*, 2013). More definitive confirmation or refutation of the possibility that males respond to inflammation with increased hypervigilance await studies specifically designed to assess the modulating effect of sex on the impact of cytokines on hypervigilant-specific behaviors and on neural pathways known to mediate this type of behavior.

Why is The Postpartum Period a Risk Factor for MDD?

Given significant evidence that maternal depression in the postpartum period is associated with numerous short- and long-term adverse consequences for the affected offspring (Ghodsian *et al*, 1984; Stein *et al*, 1991; Beardslee *et al*, 1998; Beck, 1999; Halligan *et al*, 2007; Kersten-Alvarez *et al*, 2012), the question of why the condition is so common is especially pressing. As with all evolutionary considerations, the first question to consider is whether risk genes that promote postpartum depression (PPD) confer an adaptive benefit, at least in part, via benefits resulting from the

condition itself or whether PPD is pleiotropically linked to non-related effects of these genes that benefitted survival and/or reproduction across evolution in ways that outweighed the cost of PPD. From a PATHOS-D perspective, the question might be framed by asking whether PPD enhanced maternal survival and/or reproduction via an overall net benefit in pathogen–host defense.

In terms of maternal survival, PPD would be expected to serve the same pathogen defense purposes as MDD in general. However, what about the survival of the newborn, which reflects a significant investment on the mother's part in her long-term reproductive success? Might maternal depression contribute to the child's pathogen–host defense prospects? An interesting twist on this theme might be provided by Parental Investment Theory, which postulates that parents reduce their care for, and involvement with, offspring when the costs of such care and involvement outweigh the benefits (Trivers, 1972). Building on this theory, it has been argued that PPD is an evolved mechanism that aids mothers in disengaging from infants with a low chance of surviving (Hagen, 1999; Bottino *et al*, 2012). Because infection was the primary cause of infant mortality across human evolution, one might predict that PPD would be more likely to develop in response to giving birth to an unhealthy infant, and data from hunter-horticulturalists in the Amazon basin are consistent with this prediction (Hagen and Barrett, 2007). Under this scenario, PPD, rather than helping the infant survive pathogen challenge, would actually serve as a 'warning signal' to the mother that the infant's likelihood of surviving postnatal pathogen exposure was not high enough to warrant significant resource investments.

Although consistent with a PATHOS-D focus on the primacy of pathogen–host interactions in selecting for depression-promoting genetic variants, the notion that PPD functions as a type of immunological abandonment strategy goes against the general tenor of the theory, which sees the link between depression and immunity as providing overall advantages in the face of infectious morbidity and mortality, whatever their costs in other domains. Whether PPD is associated with behavioral or immune changes that might actually help infant survival—especially in conditions such as high environmental pathogen exposure, reduced metabolic resources or increased infant vulnerability to infection—is a question that to our knowledge has never been examined. Certainly it is possible that PPD-induced maternal withdrawal might have decreased the risk of infant infection in circumstances when the maternal depression resulted from pathogen-induced cytokine activation. It is also intriguing to speculate that PPD might influence the composition of breast milk in ways that might aid nursing infants in avoiding or surviving infection. Intriguingly, a Japanese study found PPD to be associated with increased breast milk concentrations of the cytokine transforming growth factor (TGF)-β2. TGF-β2 has complex pro- and anti-inflammatory effects (Kondo *et al*, 2011), but in the context of the newborn immune system, it has been shown to have a key role in establishing the mucosal immune response, including production of secretory immunoglobulin A (Ogawa *et al*, 2004; Oddy and Rosales, 2010). Also of potential relevance, reduced levels of TGF-β have been associated with increased symptom severity in children infected with Plasmodium falciparum (Chaiyaroj *et al*, 2004; Rovira-Vallbona *et al*, 2012), suggesting that the provision of increased TGF-β2 in breast milk from depressed mothers might confer some protection against malaria, which has been a primary source of pathogen-induced mortality across human evolution. Importantly, TGF-β and other immune factors in breast milk remain biologically active after passage through the infant stomach as a result of its higher pH (Hennet and Borsig, 2016).

CONCLUSION

In essence, PATHOS-D does nothing more than attempt to instantiate and provide specifics to the observation from the quote that started this article, that '*the only…compensating fitness benefit that has been documented for major human genetic diseases is resistance to infection*' (Cochran *et al*, 2000). We have argued that depression and its relationship with inflammation and in particular the acute phase response is yet another example of this evolutionary reality, providing insights into the puzzling lack of consistency of risk alleles across populations as well as the epidemiology of the disorder including its risk factors in ancient and modern times and its age of onset and female preponderance.

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