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Review

Depression as an evolutionary strategy for defense against infection

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ABSTRACT

Recent discoveries relating depression to inflammation and immune function may help to solve an important evolutionary puzzle: If depression carries with it so many negative consequences, including notable costs to survival and reproduction, then why is it common and heritable? What countervailing force or compensatory advantage has allowed susceptibility genes for depression to persist in the population at such high rates? A priori, compensatory advantages in combating infection are a promising candidate, given that infection has been the major cause of mortality throughout human history. Emerging evidence on deeply rooted bidirectional pathways of communication between the nervous and immune systems further supports this notion. Here we present an updated review of the "infection-defense hypothesis" of depression, which proposes that moods—with their ability to orchestrate a wide array of physical and behavioral responses—have played an adaptive role throughout human history by helping individuals fight existing infections, as well as helping both individuals and their kin avoid new ones. We discuss new evidence that supports several key predictions derived from the hypothesis, and compare it with other major evolutionary theories of depression. Specifically, we discuss how the infection-defense hypothesis helps to explain emerging data on psychoimmunological features of depression, as well as depression's associations with a diverse array of conditions and illnesses—including nutritional deficiencies, seasonal changes, hormonal fluctuations, and chronic diseases—that previous evolutionary theories of depression have not accounted for. Finally, we note the potential implications of the hypothesis for the treatment and prevention of depression.

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1. Introduction: rationale for an "infection-defense" hypothesis of depression

Infection has been the leading cause of mortality throughout human history (Cairns, 1997; Finch, 2010). It has been estimated that prior to the industrial period, the average life expectancy was 25, and it was not uncommon for half of the siblings in a family to die before reaching adulthood (Cairns, 1997; Casanova and Abel, 2005). Particularly virulent pathogens could wipe out an entire family or village, such as the English "sweating sickness" known to have wiped out one-half to two-thirds of the population in many English towns during the late 1400s and early 1500s (Thwaites et al., 1997). With such stark capabilities, infection has been a critical and potent driving force in natural selection (Dobson and Carper, 1996). Specific alleles have evolved in response to common pathogens in an environment; however, pathogens are ubiquitous and wide-ranging, with new forms continually evolving, leaving individuals intrinsically vulnerable (Casanova and Abel, 2005; Dobson and Carper, 1996). The ideal system of defense against this inherent vulnerability to infection requires a generalized response that is proactive in reducing infection risk during times of increased vulnerability, as well as both flexible and adaptive enough to provide resistance to a wide range of pathogens.

Here, and in several recent papers (Kinney and Tanaka, 2009; Tanaka and Kinney, 2011a,b; Tanaka et al., 2012), we propose that moods—with their ability to orchestrate a wide array of physical and behavioral responses—have evolved as part of a complex system of immune defense that helps counteract our inherent vulnerability to the diversity of environmental pathogens. The "infection-defense hypothesis" offers a novel evolutionary framework for understanding how many of the social and behavioral features of depression may help individuals fight existing infections, as well as help both individuals and their family members avoid new ones. In contrast to many previous evolutionary theories of depression, it takes into account and helps to integrate a large and growing body of evidence linking depression to inflammation and immune function, and helps to explain depression's association with a vast array

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of conditions and illnesses such as nutritional deficiencies, seasonal changes, hormonal fluctuations, and chronic diseases. The infection-defense hypothesis may also help to resolve a baffling evolutionary puzzle—why major psychological depression is so prevalent and heritable, despite its high costs for survival and reproduction, including suicide (Tanaka and Kinney, 2011a).

We begin the paper with an overview of the epidemiology and neurobiology of depression, including recent updates linking depression to immune factors. This is followed by a discussion of the infection-defense hypothesis (Kinney and Tanaka, 2009), in which we propose that depressive features provide advantages in combating infectious diseases—advantages that offset many known disadvantages of depression. We also briefly review other hypotheses and evidence that have related changes in immune function to depression. We then describe several testable predictions of the "infection-defense hypothesis" and discuss empirical evidence that bears on each prediction. We conclude by comparing the hypothesis with other evolutionary theories of depression and by discussing some potential implications of the hypothesis for better treatment and prevention of depression.

2. Depression: an evolutionary puzzle

While depression can occur at any point during the lifespan, its most frequent onset occurs during the peak years of work and reproduction—and both depressed individuals and their family members often endure serious physical, social, and economic burdens as a result (Broadhead et al., 1990; Eaton et al., 1997; Klerman, 1989). Depression negatively impacts productivity, as well as psychosocial functioning, and is associated with increased rates of unemployment and divorce (Weissman et al., 1996). Depression is associated with lower rates of fertility (Tondo et al., 2011; Williams et al., 2007; Yates et al., 2010), and children of depressed mothers show poorer average outcomes on a wide range of developmental indices (Cummings and Davies, 1994), with adverse consequences noted even in cases where there has only been prenatal exposure to maternal depression (Davis et al., 2007). Increased mortality rates are also associated with depression, as depression is a risk-factor for many disease-related causes of death as well as for suicide (Mykletun et al., 2007). From a global perspective, the World Health Organization (WHO) has made the projection that, by the year 2020, depression will be the 2nd leading cause of disease burden worldwide (Murray and Lopez, 1996).

Depression thus poses a baffling evolutionary puzzle; despite the serious consequences of depression for individuals and their family members, including decreased fertility and increased mortality rates, depression remains both common and heritable. The estimated lifetime risk of a major depressive episode has risen to 23% in the United States (Kessler et al., 2005), and there is evidence to suggest that the incidence of major depressive disorder may actually be increasing (e.g., Compton et al., 2006). Moreover, the heritability of depression is well-established, with estimates based on twin, adoption, and genetic molecular studies consistently falling at about 40% (Kendler et al., 1995; McGuffin et al., 1996; Shyn and Hamilton, 2010; Sullivan et al., 2000; Wender et al., 1986). Genetic association and linkage studies have begun to discover specific alleles that increase risk for depression (see review by Goldberg, 2006), such the CYP2C9*3 allelle (LLerená et al., 2003) and the 5-HTTLPR short allele of the serotonin transporter gene (Eley et al., 2004; Kendler et al., 2005).

For more than half a century, efforts to understand the neurobiological underpinnings of depression have been dominated by the view that depression is caused by a deficiency in synaptic concentrations of monoaminergic neurotransmitters including serotonin and norepinephrine (Hirschfeld, 2000; Schildkraut and Kety, 1967). This idea, known as the monoamine hypothesis, has stimulated a wealth of research and has been the major driving force behind antidepressant drug development. Over time, however, the initial promise of the monoamine hypothesis has been tempered by the fact that attempts to find direct links between monoaminergic transmission and mood have yielded equivocal results (Delgado, 2000; Heninger et al., 1996). In addition, the efficacy of antidepressant drugs based on the fundamental premise of the monoamine hypothesis has been limited, with estimates that between 30% and 50% of individuals treated with antidepressant medication do not show adequate response (Schatzberg, 2000). The insufficiency of the monoamine hypothesis to explain critical aspects of mood regulation and the desire for more favorable treatment outcomes have resulted in an expanded search for the neurobiological underpinnings of depression.

Research on the neuroimmune system and its role in the etiology of depression has emerged as an especially promising area for study. In particular, the role of immune-activated inflammatory cytokines has been identified as a key area of focus in understanding the neurobiological pathways that trigger depressive states, by way of direct and indirect effects on hypothalamic–pituitary–adrenal (HPA) axis, and by altering monoamine neurotransmitters in multiple regions of the brain (Dantzer et al., 2008; Loftis et al., 2010; Raison et al., 2006). In addition, a recent review of risk alleles for depression has revealed that in a striking majority of cases the depression alleles were associated with known effects on immune function (Raison and Miller, 2012). These new lines of research—which show wide ranging links between depressive symptomatology and immune function—not only have the potential to lead to novel treatment strategies for the prevention and treatment of depression, but may also provide important clues as to the reasons for depression's prevalence and persistence throughout human history.

3. Immune alterations, mood, and the macrophage and cytokine theories of depression

Numerous associations between depression and immune function have been observed in recent years. Early studies investigating immune alterations during depression focused almost exclusively on markers of suppressed cellular immunity—such as decreased lymphocyte proliferation and natural killer (NK) cell activity (Reiche et al., 2004; Schleifer et al., 1989; Zorilla et al., 2001). More recently, however, there has been a shift toward understanding the role of inflammation in depression, with a particular focus on the role of proinflammatory cytokines (Zorilla et al., 2001; Irwin and Miller, 2007). Increased levels of proinflammatory cytokines—such as interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ)—have been repeatedly observed in depressed individuals, prompting formulation of the 'macrophage theory of depression' (Smith, 1991), and its successive formulation as the 'cytokine hypothesis of depression' (Maes et al., 1995; Maes, 1999; Raison et al., 2006; Schiepers et al., 2005). According to the cytokine hypothesis, proinflammatory cytokines produced by macrophages during the acute phase of an immune response act as neuromodulators that mediate the behavioral and neurobiological features of depression.

3.1. Cytokine-induced changes in somatic experience, cognition, and behavior

When infection or injury occurs, proinflammatory cytokines are responsible for orchestrating the early immune response, including sickness behavior. Sickness behavior—characterized by somatic, cognitive, and behavioral changes, such as fever, weakness, mal-

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aise, listlessness, hyperalgesia, and impaired concentration (Hart, 1988)—represents an organized strategy for fighting infection by conserving metabolic resources and helping an individual avoid further stressors (Hart, 1988; Kluger, 1991; Segerstrom, 2010; Yirmiya et al., 2000). Dantzer (2001, 2009) has extended this notion to suggest that sickness behavior is an expression of a biologically-mediated motivational state triggered by the innate immune system that resets an organism's priorities to adaptively cope with the threat of bodily insult. The costs of shifting resources and priorities during this state are purportedly offset by the critical advantages offered for fighting infection.

A portion of individuals who experience sickness behavior go on to develop major depressive disorder. There is evidence that secondary development of depression following sickness behavior occurs in individuals who have an exaggerated vulnerability to infection (Dantzer, 2009; Wichers et al., 2006). For example, the therapeutic administration of cytokines such as interferon-α (IFN-α) and interleukin-2 (IL-2)—used to treat patients with cancer and a number of infectious diseases—has been found to induce a two-phase response. First, a few days following cytokine administration, many patients experience sickness behavior, marked by neurovegetative and somatic symptoms (fatigue, aches, loss of appetite, sleep disturbance). Second, up to 50% of those treated go on to develop symptoms of major depression, including depressed mood, feelings of worthlessness, guilt, and even suicidal ideation (Capuron et al., 2002; Capuron and Miller, 2004). Individuals who are most likely to develop depression during the course of cytokine therapy have been found to show increased baseline levels of proinflammatory cytokines prior to treatment (Wichers et al., 2006), and more severe levels of sickness-type behavior following initial administration of treatment (Robaeys et al., 2007; Wichers et al., 2005). Notably, cytokine-induced symptoms of depression are attenuated by pretreatment with antidepressant therapy (Capuron et al., 2002).

3.2. Sickness behavior and depression compared

There are many parallels between sickness behavior and depression, although the two conditions are not equivalent (see Table 1). For example, similar to sickness behavior, symptoms of depression such as anhedonia, fatigue, hypersomnia, and psychomotor retardation (i.e., slowed speech, thinking, and body movements) all tend to reduce activity and encourage rest, thereby conserving energy. Some studies have found that depression is associated with mild elevations in body temperature (e.g., Avery et al., 1999; Rausch et al., 2003), and there is suggestive evidence that milder temperature elevations, particularly when combined with reduced bodily iron stores, may be inhibitive to pathogen growth (Ismael and Bedell, 1986; Kluger and Rothenburg, 1979). Nevertheless, a major difference between sickness behavior and depression is that the costly antibiotic strategy of fever is notably subverted during depression (Maier and Watkins, 1998). Depression also differs from sickness behavior in that its symptoms are more variable and include behavioral and cognitive features that discourage social contact and activity. Several authors have suggested that depressive symptoms, like sickness behavior, may not just be a spurious byproduct of cytokine-induced inflammation, but may constitute an adaptive longer-term strategy for fighting infection (Raison et al., 2006; Kinney and Tanaka, 2009).

3.3. Neuromodulatory mechanisms of cytokines

Multiple pathways have been identified by which cytokines exert neuromodulatory effects, and these have been covered extensively in a number of recent reviews (e.g., Capuron and Miller, 2011; Dantzer et al., 2008; Maes et al., 2009; Miller et al., 2009; Loftis et al., 2010). Proinflammatory cytokines have been noted, for example, to exert both direct and indirect effects on monoamine neurotransmitter availability and metabolism (Dunn and Wang, 1995), as well as to increase activation of the hypothalamic–pituitary–adrenal (HPA) axis (Holsboer, 2000; Pace et al., 2007). A number of recent studies have also demonstrated links between inflammatory activation and brain changes that underlie depression (e.g., Brydon et al., 2008; Eisenberger et al., 2010; Harrison et al., 2009).

Cytokines administered to laboratory animals and humans have been shown to alter the metabolism of the neurotransmitters serotonin, norepinephrine, and dopamine in areas of the brain that are associated with mood regulation (Rivier et al., 1989; Shuto et al., 1997; Capuron et al., 2003). A number of studies suggest that cytokines may decrease the amount of serotonin available for neurotransmission by up-regulating the expression and activity of the serotonin transporter (SERT) (Katafuchi et al., 2006; Zhu et al., 2006). One of the most studied pathways by which cytokines may influence neurotransmitter metabolism, however, involves degradation of tryptophan by activation of the enzyme, indoleamine 2,3-dioxygenase (IDO) (Capuron et al., 2003; Dantzer et al., 2008). IDO is activated by proinflammatory cytokines released during the acute-phase immune response, including IFN-α, IL-6, and TNF. Serotonin levels are reduced due to the

Table 1
A comparison of sickness behavior and depression based on the "infection-defense hypothesis".

	Sickness behavior	Depression
Eliciting Conditions	Infection, trauma, injury	Immune vulnerability, immune compromise
Mode of Action	Reactive	Proactive and/or complementary; may act preemptively to avoid infection during times of increased immune vulnerability, or help combat existing infections
Symptoms	Circumscribed, including fever, malaise, muscle and joint aches, impaired concentration, fatigue, loss of appetite	Variable, including sadness, loss of interest and pleasure, low motivation, withdrawal, impaired concentration, fatigue, decreased sex drive, decreased speech, psychomotor slowing, appetite disturbance, sleep disturbance, low self- esteem, hopelessness, guilt, suicidal ideation, and somatic changes such as increased pain sensitivity, aches, and mild hyperthermia. Depressive symptoms are diverse and vary across patients and subtypes (e.g., melancholia may involve hypervigilance with agitation and insomnia that is less common in atypical, postpartum, or seasonal subtypes); however, nearly all symptoms appear to help fight or avoid infection in some way.
Duration	Acute; sustained activation is biologically costly and harmful to host	Sustainable for indefinite periods of time
Inflammatory Response	Sickness behavior always involves inflammation	Depression commonly, but not necessarily, involves inflammation
Adaptive Function	Acute mobilization of resources to combat infection and promote healing	Help combat existing infections, help avoid new immune-compromising stressors, and help individuals and their kin avoid new infections

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breakdown of tryptophan by IDO, resulting in the production of several neurotoxic compounds that may further mediate a depressive response (Dantzer et al., 2008). IDO activity diverts tryptophan metabolism from the production of serotonin to the synthesis of its primary metabolite kynurenine, which is further metabolized into several neuroactive compounds that include 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN) or kynurenic acid (KA). These compounds, in turn, generate free radicals that cause neuronal damage due to oxidative stress (Wichers and Maes, 2004). The potential importance of kynurenine metabolites in inflammatory-mediated depression is underscored by the results of a recent study in which Raison et al. (2010) found that individuals receiving IFN-α for treatment of Hepatitis C were found to have higher cerebrospinal fluid (CSF) levels of kynurenine and its metabolites QUIN and KA, and that these increases were correlated with increased inflammatory biomarkers as well as depression.

Depression also has well-established links with hyperactivity of the HPA-axis (Pariante and Lightman, 2008). Cytokines may contribute to depression either directly, via activation of the HPA-axis, or indirectly, through cytokine-induced glucocorticoid-receptor resistance (Holsboer, 2000; Pace et al., 2007). Cytokines activate the HPA-axis by inducing corticotropin-releasing hormone (CRH) and vasopressin (AVP)—key regulators of the HPA-axis that are found at increased levels in depressed individuals (see Owens and Nemeroff, 1991; Holsboer, 2000; Scott and Dinan, 2002). Cytokines may contribute to HPA-axis hyperactivity indirectly, as well, through their effects on the glucocorticoid receptor. Cytokines increase glucocorticoid receptor resistance by way of several signaling pathways, including activation of the p38 MAPK, and by stimulating changes in the expression of glucocorticoid receptor isoforms (Pace et al., 2007). These changes, in turn, create a dysregulation of the CRH feedback system and result in a feed-forward cascade that decreases the inhibitory effect of glucocorticoids on CRH and stimulates increased cytokine production.

Further evidence on the neuromeodulatory effects of cytokines comes from studies using functional magnetic resonance imaging (fMRI) techniques. A number of studies have shown that inflammatory activation can stimulate changes in key areas of the brain that underlie depression. For example, following experimental induction of an immune-inflammatory response, Eisenberger et al. (2010) found that research participants showed increased symptoms of depression, and reduced activity in the ventral striatum (VS)—the neural correlate of anhedonia—in response to reward cues. In another study investigating the neural correlates of psychomotor slowing, neural activity in the substantia nigra was found to correspond to increased levels of IL-6 and decreased reaction times following immune stimulation (Brydon et al., 2008). The same research group has also reported findings that depressed mood and increased circulating levels of IL-6 following immune stimulation correspond to changes in areas of the brain highly involved in emotional processing. Specifically, they found increased subgenual anterior cingulate cortex (sACC) activity and reduced connectivity of sACC to mesolimbic regions of the brain including the amygdala, medial prefrontal cortex, nucleus accumbens, and superior temporal sulcus (Harrison et al., 2009).

4. The "infection-defense hypothesis" of depression

Advances in understanding the ways in which immune function, inflammation, and depression are related potentially provide clues as to why genes that increase vulnerability to depression have persisted at relatively high levels in the gene pool, despite depression's significant costs to reproduction and survival. The infection-defense hypothesis of depression (Kinney and Tanaka, 2009) offers an integrative view of these findings, based on the idea that depression confers a critical compensatory advantage in immune protection that has offset notable disadvantages of depression for evolutionary fitness. More specifically, the infection-defense hypothesis proposes that immune vulnerability to infection elicits depressed mood, which in turn stimulates behaviors that help protect vulnerable individuals and their kin against infectious diseases (see Table 2).

The immune system is an amazingly sophisticated system involving multiple, layered, and complementary strategies and mechanisms for helping individuals combat infections, second only in complexity to the nervous system. That natural selection has sculpted this incredibly complex system is testament to what a powerful role infection has played in natural selection. What we are hypothesizing here is that natural selection may have also sculpted coordinated pathways between the nervous and immune systems so as to evolve behavioral response mechanisms that help prevent and combat infections. Others, including Hart, have noted the potential for such mechanisms: "It is quite logical to expect animals and people to also have evolved nonimmunologic disease-fighting strategies including behavioral patterns, that might serve as a first line of defense before the nonspecific and specific immunologic systems are activated and that would complement or potentiate immunological processes" (Hart, 1988 (p. 123)). As Hart notes, behavioral responses, in principle, offer a valuable potential advantage for combating infection—which is to avoid becoming infected in the first place. There are numerous examples of preventive immune strategies including, for example, human aversion to noxious odors, which helps to prevent contact with high-pathogen sources such as human waste and decaying flesh.

Although at first glance it may seem counter-intuitive, from an evolutionary perspective, it is precisely the high costs associated with depression, combined with the fact that it is common and heritable, that argues for some adaptive advantage to depression. That is, given such negative consequences, there must be some critical countervailing force or compensatory advantage that has allowed susceptibility genes for depression to remain in the population at high rates. Compensatory advantages in combating infection are a promising candidate, given that infection has had strong associations with morbidity and mortality throughout evolutionary history. Increasing evidence that complex, deeply rooted mechanisms have evolved, by which the nervous and immune systems can communicate and influence one another, also points in this direction.

Examples whereby costly adaptations have evolved because they offer compensatory advantages in defending against infection are numerous and widespread. Classic examples in humans in-

Table 2
Key postulates of the infection-defense hypothesis of depression.

1. Immune vulnerability to infection elicits depressed mood, which in turn stimulates behaviors that help protect vulnerable individuals and their kin against infectious diseases.
2. Depressive signs and symptoms offer individuals advantages for fighting existing infections by helping to conserve energy and avoid environmental stressors and insults that could provide further immune-compromising challenge.
3. By inhibiting social contact, depression also prevents individuals and their biological relatives from contracting new infections.
4. Moods orchestrate—in a timely, titrated, and strategic manner—an array of behavioral and immunological responses to infections and immune vulnerability, which can in turn be affected by a wide range of factors, including, e.g., genetic and seasonal variables, physical illness or injury, nutritional status, hormonal fluctuations, exposure to environmental toxins, sleep disturbance, and stress.

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clude sickle cell anemia and other hereditary hemoglobinopathies, such as thallasemia. Sickle cell anemia, for example, is a hereditary disease that is typically fatal, yet it is very prevalent in tropical regions. People who inherit only one copy of the sickle-cell gene have increased resistance to malaria, allowing the gene to persist despite its severe costs (Kwiatkowski, 2005). An example from non-human species involves the evolution of eye-catching plumage and courtship dances that peacocks and the males of many other avian species use to woo females. At first glance—from an evolutionary perspective—this is a rather puzzling phenomenon; after all, it takes significant energy and metabolic resources for the birds to produce those ostentatious feathers and dances, and increases visibility to predators. So why do it? Field studies indicate that it is adaptive because showy feathers and skillful dance signal to the females that the male carries fewer parasites. When the female chooses the visually more attractive males, she reduces her own exposure (and that of her offspring) to infection, and increases the likelihood that the male (and her offspring) will have better genetic resistance to infections in that ecological niche (see Kempenaers, 2007).

Behavioral strategies that defend kin against risk of infection can also be noted in species such as honey bees and African naked mole rats (see Preti, 2007). These species are like humans in that they are social and live together in large, complex communities, and have been known to display altruistic self-sacrifice, often leaving the hive or burrow to die when they are ill—reducing the risk that they will expose others within their community to the infection.

From an evolutionary perspective, moods potentially provide an attractive system for behavioral defense against infection, as they have the ability to (1) orchestrate a wide range of behaviors; (2) create responses that are generalizable to a variety of environmental challenges—a variety that reflects the inherent mutability and variability of environmental pathogens; (3) respond to immune vulnerability in a way that is both timely and titrated; and (4) act preemptively, based on both endogenous and environmental signals of increased infection risk. Depression's overlapping features with sickness behavior appear to help conserve energy and avoid further immune challenges, while depressive states are more sustainable than sickness behavior over longer periods of time by reducing the high cost of fever. This may allow depression to serve as a complementary line of defense when the early immune response to infection cannot be sustained during extended periods of infection or immune vulnerability.

What we propose is even broader, however. A key aspect that distinguishes the infection-defense hypothesis from many other evolutionary theories of depression is that it proposes that depressive signs and symptoms not only offer individuals advantages for fighting existing infections, but also for preventing individuals and their biological relatives from contracting new infections. Social withdrawal, low energy, irritability, and blunted affect, for example, may greatly reduce the spread of infections by discouraging mobility and/or social contact with others.

5. Some testable predictions of the infection-defense hypothesis

A number of testable predictions follow from the infection-defense hypothesis. These predictions include the following:

1. Most signs and symptoms of depression will aid the immune system's ability to fight infections, by performing one or more of the following functions:
   (a) conserving metabolic resources for use by the immune system in fighting infection;
   (b) directly enhancing immune function through antimicrobial action or by stimulating an increase in NK cell activity;
   (c) reducing the risk of further environmental stresses that impair immune function; and/or
   (d) helping individuals and their kin to avoid transmitting or contracting new infections.
2. Many types of infectious diseases will be associated with depressive symptoms.
3. Depressed individuals will tend to have elevated rates of infection and/or immune alteration.
4. Medical, environmental, and physiological conditions that increase immune vulnerability, or that increase exposure to infection, will also be associated with increased rates of depression.
5. There are bidirectional processes that communicate between the nervous and immune systems and provide mechanisms for infections, immune processes, and mood to influence one another.
6. Moods provide an implicit mechanism for cost-benefit analysis of an individual's optimal responses to environmental challenges and the organisms' immune status, helping to regulate the timing and intensity of infection-defense responses.

Considerable evidence exists to support each of these predictions. Evidence relevant to the respective predictions is discussed in the following six sections.

6. Evidence for prediction # 1: most signs and symptoms of depression appear to aid the immune system's ability to fight infections

As the infection-defense hypothesis predicts, there is evidence that most features of depression appear to aid defense against infections. Depressive signs and symptoms do this in four ways: (a) conserving energy; (b) directly enhancing immune function through antimicrobial action or by stimulating an increase in NK cell activity; (c) reducing the risk of further immune-compromising challenges; and/or (d) by helping individuals and their kin avoid contracting new infections (see Fig. 1).

Akin to the symptoms of sickness behavior present during an acute immune response to infection, depressive symptoms—such as increased bodily aches and fatigue, hypersomnia, and psychomotor retardation—also reduce physical activity and encourage rest, thereby conserving metabolic resources for use by the immune system. In addition to these somatic and behavioral changes that occur during depression, anhedonia and cognitive features of depression—such as decreased self-esteem and feelings of hopelessness (American Psychiatric Association, 2000)—also discourage exploration and risk-taking, thereby reducing exposure to new pathogens or to accidents, conflicts, or injuries that can exacerbate existing immune system compromise. A number of studies have found, for example, that depressed individuals exhibit state-dependent increases in harm-avoidance behavior (e.g., de Winter et al., 2007; Nery et al., 2009). Moreover, the degree of harm-avoidance behavior endorsed by depressed individuals increases along with increases in depression severity and the number of depressive episodes (Nery et al., 2009).

Moods help to regulate social behavior. Social withdrawal and decreased sexual drive, as well as cues that discourage social contact from others—such as decreased speech, irritability, and changes in body language and facial expression (blunted affect)—can reduce the risk for contracting or transmitting infections, including sexually transmitted ones. Thus, the changes in social interest and demeanor associated with depression not only reduce an individual's risk for contracting new infections by discouraging close contact with others, but also reduce the risk of transmitting infection to relatives. The importance of reducing the spread of

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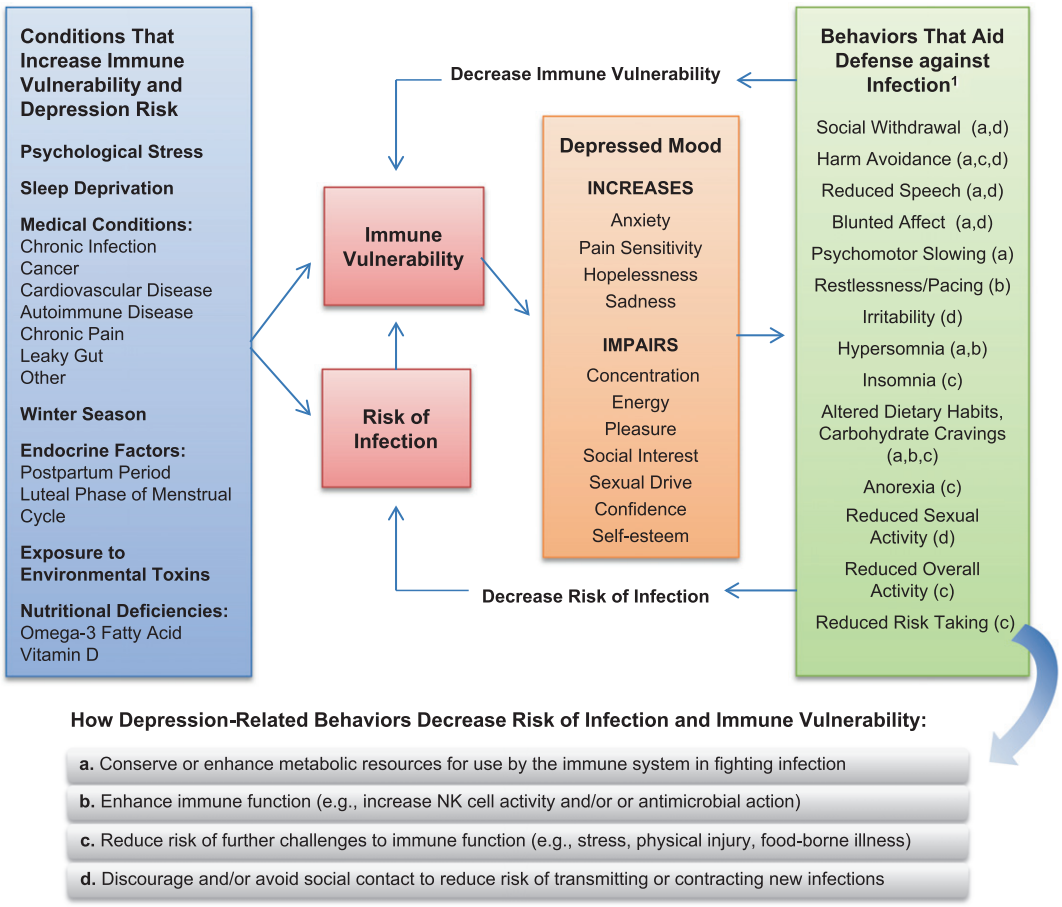

Fig. 1. A neuro-immune feedback system regulates the timing and intensity of behaviors that aid defense against infection. Immune vulnerability is influenced by acute risk of infection, as well as by a number of other known immune-compromising factors that include stress, sleep deprivation, chronic infection and disease, winter season, hormonal fluctuations, exposure to toxins, and nutritional deficiencies. According to the infection-defense hypothesis, depression and related behaviors that aid against infection are activated by immune status, which in turn reduce immune vulnerability and risk of infection by (a) conserving or enhancing metabolic resources for fighting infection, (b) directly aiding immune defenses through antimicrobial action and/or by increasing NK cell activity, (c) reducing risk of further immune challenge, such as avoiding danger or conflict to reduce the risk of physical injury, or restricting patterns of eating to avoid food-borne illness, and/or (d) by reducing the spread of infection through decreased social contact. [1]Depressive symptoms vary by subtype, accounting for seemingly paradoxical symptoms involving energy and appetite. For example, seasonal affective disorder (SAD) and other atypical forms of depression often include symptoms of psychomotor slowing, hypersomnia, and increased appetite/carbohydrate cravings, while other forms of depression – such as melancholia – include symptoms of restless agitation, anorexia, and insomnia.

infection to others is highlighted by many examples throughout human history whereby infectious diseases were known to wipe out entire families or villages (e.g., Thwaites et al., 1997). The nascent immune system of infants and young children render them especially vulnerable to infections. Consistent with the notion of a heightened need to protect the young, depression among human mothers, as well as sickness behavior among murine animal models, is associated with disengagement—and sometimes even rejection—of offspring (Burke, 2003; Dantzer, 2009).

Reduced mobility and reduced sociability associated with depression, as noted by Raison and Miller (2012), may also have the effect of minimizing exposure to out-group members. Contact with individuals from different groups or environments who are immunologically dissimilar increases the risk of exposure to pathogens to which an individual has not developed specific immunity in their home environment.

Appetite changes are extremely common in depression. Depressed individuals can vary in whether they tend to increase or decrease overall intake of food (American Psychiatric Association, 2000). However, the specific forms that these appetite changes take in depression may constitute alternative strategies that help defend against infection. Proinflammatory cytokines, for example, have a number of known anorectic effects, including increased stimulation of the peptide leptin, which plays a key regulatory role in balancing food intake and energy expenditure (Andréasson et al., 2007; Wong and Pinkney, 2004). Reduced appetite can reduce the risk of food–borne parasites, a major source of infection throughout history and the present (Mead et al., 1999). By contrast, some forms of depression, including seasonal affective disorder (SAD), are associated with increased carbohydrate cravings. Carbohydrates and carbohydrate-based foods, such as sugar and baked bread, offer high metabolic and caloric resources, while at the same time being less likely to cause illness due to spoiling than many other foods, such as meat, fish, or fruits and vegetables. In addition, increased intake of carbohydrates influences immune function by triggering changes in proinflammatory cytokines and an increase in NK cell activity (see Braun and Von Duvillard, 2004). It has also been noted that high intake of carbohydrates can promote defense against infection by decreasing the relative intake of lipids, as lipid consumption has been associated with worse outcomes for infectious illness (Heyland et al., 1998).

Some individuals with depression develop paradoxical symptoms that include notable anxiety, agitation, and insomnia, constituting a state of hypervigilance. In spite of high metabolic costs, heightened vigilance is likely to have been an extremely adaptive response to stress throughout human evolution, where the threat

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of predators and other physical dangers to self and family was high (Marks and Nesse, 1994). Hypervigilance may contribute to harm-avoidance behaviors that, as noted earlier, reduce risk of exposure to new infections or immune-compromising injuries and stressors. Furthermore, although speculative, restless pacing or hand-wringing, which can occur during agitated forms of depression, may offer some benefits to immune function just as other forms of moderate physical activity do. For example, moderate physical activity can increase NK cell activity (Nieman et al., 2005) and elevate core body temperature, which may have additional immune effects (Mestre-Alfaro et al., 2012). An agitated state tends to occur in the context of patients' increased anxiety about their personal safety and that of their family, thereby discouraging them from adventurous activity outside the home, so that the increased exercise occurs in a way that reduces the risk of injury and contact with new infections that would otherwise tend to occur as a result of increased exercise.

7. Evidence for prediction # 2: many types of infection are associated with depression

Increased rates of depressive symptoms have been observed following an individual's contracting a number of acute or subacute infections (Fazekas et al., 2006; Murray et al., 2007), as well as following chronic infections (Cohen et al., 2002; Lipkin and Hornig, 2004; O'Connor et al., 2009; Yates and Gleason, 1998), and immunization with live virus vaccines (Afsar et al., 2009; Glaser et al., 2003; Yirmiya et al., 2000). For example, increased depressive symptoms have been found in patients with herpes simplex encephalitis (Fazekas et al., 2006) and West Nile virus (WNV) (Murray et al., 2007). Murray et al. (2007) found that over 31% of WNV patients in their study experienced the onset of a depressive episode within one year of their becoming infected. Those who had been diagnosed with the more severe form of WNV, neuroinvasive disease, showed an even greater risk for developing depression.

Evidence for an increased risk of depression among those who suffer from chronic infections comes from a variety of studies involving both humans and laboratory animals. Depression-like behavior has been observed, for example, in mice infected with Bacille Calmette Guerin (BCG), a bacterium related to the one that causes tuberculosis (O'Connor et al., 2009). Humans suffering from chronic infections, such as human immunodeficiency virus (HIV), hepatitis C (HCV), and genital herpes (HSV-2), have also been found to have an increased risk for depression (Yates and Gleason, 1998; Lipkin and Hornig, 2004). Among HIV patients, high viral loads are associated with higher depression scores on the Hamilton Rating Scale for Depression (Cohen et al., 2002).

Vaccines containing live viruses can also cause depressive symptoms. For example, in a prospective double-blind study (Yirmiya et al., 2000), vaccination with live attenuated rubella virus resulted in depressive symptoms that lasted up to 10 weeks. In another study, Afsar et al. (2009) found increases in symptoms of depression related to antibody response following Hepatitis B vaccination in hemodialysis patients. Among certain sub-groups of older adults, influenza vaccination has also been linked to increased depressive symptoms, accompanied by a rise in serum levels of IL-6 (Glaser et al., 2003).

8. Evidence for prediction # 3: elevated rates of infection and/or immune alteration are found in depressed patients

Just as elevated rates of infection would be expected among individuals with fever, elevated rates of infection and/or immune alteration are expected in depressed patients, given our proposal that depression is elicited as an immune defense during conditions of infection or immune-compromise.

Accordingly, depressed individuals show marked evidence of immune suppression and excessive inflammation (Dowlati et al., 2010; Irwin and Miller, 2007; Zorilla et al., 2001), as well as greater vulnerability to infection (Cohen, 1995; Irwin, 2002b; Zorilla et al., 1996). For example, a robust association has been found between depressive symptoms and reduced NK cell activity (Zorilla et al., 2001; Reiche et al., 2004). Depression has also been associated with decreased lymphocyte proliferation, although the results are less consistent, and appear to depend on moderating factors such as age (Schleifer et al., 1989).

Increased levels of proinflammatory cytokines and chronic inflammatory response have been found repeatedly in depressed individuals (Dowlati et al., 2010; Irwin and Miller, 2007; Zorilla et al., 2001). Depressed individuals most often show evidence for increased levels of the proinflammatory cytokines IL-1β, IL-6, TNF-α, and INF-γ (Maes et al., 2009). Other inflammatory biomarkers that have shown regular associations with depressive symptoms include changes in acute-phase-response protein, C-reactive protein (CRP), haptoglobin, nitric oxide, and glucocorticoids (Loftis et al., 2010; Maes et al., 2009; Zorilla et al., 2001).

A number of studies indicate that depressed individuals show increased vulnerability to contracting infections, such as upper respiratory tract infections (Cohen, 1995). Among HIV-infected patients, depressive symptoms are associated with higher viral load and lower NK cell activity (see review by Kopinsky et al., 2004). Depressive symptoms are also significantly associated with recurrence of herpes simplex infection (Zorilla et al., 1996) and reduced cellular immunity to varicella-zoster (Irwin, 2002b).

9. Evidence for prediction # 4: many conditions associated with immune vulnerability are also associated with depression

The list of conditions that show associations both with increased vulnerability to infection and with elevated risk for depression is long and varied, and includes seasonal factors, nutritional deficiencies, hormonal fluctuations, toxin exposure, cancer, cardiovascular disease, autoimmune diseases, and chronic pain (see Tanaka et al., 2012, for a review). Two widely-studied factors linked both to immune vulnerability and to depression include stress and sleep deprivation. Stress, for example, which has a clear and well-established role in the etiology of depression (Brown et al., 1986; Hammen, 2005; Kendler et al., 1999; Sillaber et al., 2009), is also associated with increased numbers of circulating proinflammatory cytokines (Bierhaus et al., 2003; Wolf et al., 2009). Increased cytokines sensitize the HPA-axis, contributing to the hypersecretion of cortisol (Turnbull and Rivier, 1995), which has been identified as a critical pathway in central nervous system (CNS) dysregulation. Cortisol can suppress cellular immune response that is critical in defending the body against viral infections (Maes et al., 1994). Accordingly, there is evidence that chronic stress significantly increases vulnerability to infection (e.g., Cohen, 1995; Cohen et al., 1999; Horesh et al., 2008; Kiecolt-Glaser et al., 2002; Mundt et al., 2000). For example, it has been found that stressed caretakers are more vulnerable to infectious diseases (Kiecolt-Glaser et al., 2002), and populations that experience higher levels of social stress tend to have higher rates of mortality and morbidity from infectious disease (Weiss and McMichael, 2004).

Another major risk factor for depression is chronic insomnia (Lustberg and Reynolds, 2000). Chronic sleep deprivation is associated with increased immune vulnerability (Irwin, 2002a), and the severity of insomnia is negatively correlated with NK cell activity in both depressed and non-depressed groups (Zorilla et al., 2001; Irwin, 2002a). Poor sleep quality and insomnia can precipitate

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inflammatory processes, raising plasma cortisol, C-reactive protein (CRP), and proinflammatory cytokines (Motivala et al., 2005). In experiments with rats, chronic restriction of sleep causes depression-like changes in both the sensitivity of neurotransmitter receptors and neuroendocrine reactivity to stress (Novati et al., 2008).

In addition to stress and sleep deprivation, the list of conditions that are associated both with immune vulnerability and with depression is staggering and diverse. They include seasonal factors such as reduced daylight hours and colder temperatures during the winter months (Lam et al., 2004; Magnusson, 2000), nutritional factors such as deficiencies of Vitamin D or Omega-3 fatty acids (Borges et al., 2011; Ganji et al., 2010; Hibbeln, 2009; McNamara et al., 2010; Parker et al., 2006), hormonal fluctuations associated with the menstrual cycle and post-partum period (Groër and Morgan, 2007; Rubinow et al., 2009), exposure to environmental toxins such as toxigenic mold and pesticides (Anyanwu et al., 2003; Beseler and Stallones, 2008; Corsini et al., 2008; Udoji et al., 2010), and a number of medical or physiological conditions such as cancer (Miller et al., 2008), cardiovascular disease (Cesari et al., 2003; Kling et al., 2007), autoimmune diseases (Gold and Irwin, 2006; Nery et al., 2008), and chronic pain (Watkins and Maier, 2000). That such a wide array of conditions has well-established links with both depression and immune alteration is consistent with the notion that depression evolved as a generalized immune response that can offer broad defense against a range of immune challenges. A preponderance of cross-sectional research in these areas limits causal interpretations and highlights the need for more longitudinal investigations; however, a number of experimental studies have reliably demonstrated that conditions associated with sources of immune vulnerability such as stress and sleep deprivation increase risk of depression-like behavior in animal models (e.g., Ardayfio and Kim, 2006; Novati et al., 2008; Sillaber et al., 2009).

10. Evidence for prediction # 5: bidirectional links between the nervous and immune systems allow moods and immune vulnerability to influence each other

Multiple pathways have been identified by which immune system activation may lead to depression, including activation of the HPA-axis by proinflammatory cytokines (Holsboer, 2000; Pace et al., 2007) and degradation of tryptophan by activation of the IDO (Capuron et al., 2003; Dantzer et al., 2008). There is now well-established evidence to suggest that bidirectional communication between the immune system and nervous system also occurs (Maier and Watkins, 1998).

Bidirectional communication between the immune and nervous systems is suggested by the immune-enhancing effects of antidepressant interventions, such as electroconvulsive therapy (ECT) (Fischler et al., 1992; Kronfol et al., 2002; Hestad et al., 2003), a variety of psychosocial interventions (Fang et al., 2010; Robinson et al., 2003; Witek-Janusek et al., 2008), and meditation practice (Lavretsky et al., 2012; Pace et al., 2009). For example, while ECT—known for its rapid amelioration of depressive symptoms—shows no evidence of changes in monoamine metabolism or neuroplasticity following a single ECT session, augmented NK cell activity is found after a single session (Fischler et al., 1992; Kronfol et al., 2002), with a gradual and significant decline in TNF-α levels over the course of repeated sessions (Hestad et al., 2003).

There is evidence that NK cell activity is significantly elevated after experimental exposure to pleasurable conditions (Berk et al., 2001; Matsunaga et al., 2008), and that psychological interventions for the treatment of depression and emotional distress, such as mindfulness training and cognitive behavior therapy (CBT), also enhance NK cell activity (Masuda et al., 2002; Robinson et al., 2003; Witek-Janusek et al., 2008). Notably, among participants in a mindfulness-based stress reduction program, Fang et al. (2010) found that NK cell activity was significantly enhanced only in patients who reported improved well-being following the intervention.

Studies of meditation practice also show notable effects on stress and immune responses. For example, Pace et al. (2009) found that among individuals undergoing training for compassion meditation, the amount of time spent in meditation practice was associated with decreased IL-6 concentrations and decreased levels of distress following exposure to a laboratory stressor. In another study (Lavretsky et al., 2012), dementia caregivers who practiced daily yogic meditation experienced a reduction in depressive symptoms and reduced signs of stress-induced aging, measured by telomerase activity.

Several types of antidepressants and mood stabilizers are also noted to have antibiotic effects. In a recent review, Lieb (2007) cites a number of *in vivo* and *in vitro* studies demonstrating that antidepressant drugs and lithium have significant antimicrobial and immune-potentiating effects. These effects include the ability to reverse resistance of bacteria to antibiotics (e.g., Kristiansen et al., 2010). It has been proposed that psychotropic medications derive their antimicrobial properties by acting as bacterial efflux pump inhibitors (EPIs) (Munoz-Bellido et al., 2000). Lieb (2007) also notes that several antibiotics have been found to have mood-enhancing effects.

11. Evidence for prediction # 6: moods orchestrate the timing and intensity of infection-defense behaviors

There is evidence that moods also provide a mechanism for regulating the timing and intensity of immune-related behaviors based on an implicit cost-benefit analysis of what is most adaptive for survival and reproduction. Depressive behaviors are biologically costly, interfering with work and social functioning, and especially in pre-modern times would likely interfere with efforts to acquire and compete for food, territory, and mates. Therefore, the benefits would outweigh the costs only when initial efforts to cope with an immune challenge are ineffective, or when an individual suffers from chronic infection or stress. Sickness behavior and depression (and perhaps various sub-types of depression) are elicited—and vary in timing and intensity—based on feedback from the immune system. An extension of this is that mood elevation can stimulate more adventurous or gregarious behavior when an individual is in a more robust immune state.

Evidence from a number of studies indicates that risk for depression and depression severity varies in relation to immune-compromise. For example, as mentioned above, Murray et al. (2007) found a heightened risk for depression among a group of individuals who had contracted WNV disease, while those who had been diagnosed with the more severe form of WNV, neuroinvasive disease, demonstrated an even greater risk for depression. In a study of HIV patients, high viral loads were associated with higher depression scores on the Hamilton Rating Scale for Depression (Cohen et al., 2002). Maes et al. (1994, 1995) have also found depression severity to correlate with circulating numbers of proinflammatory cytokines, including IL-1 and IL-6, as well as with measures of HPA-axis hyperactivity.

There is also evidence that the timing of mood response to antidepressant interventions parallels changes in immune function (Lieb, 2007; Tanaka and Kinney, 2011b). In a recent paper, Tanaka and Kinney (2011b) reviewed studies that provided information about the time course of mood response and NK cell activity following a number of mood-enhancing interventions such as exercise, therapeutic administration of ketamine, and antidepressant

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treatments. Notable parallels in the time course of mood improvement and immune response were observed across all modalities. For example, both mood and NKCA are rapidly enhanced in response to exercise, and both of these effects tend to dissipate within several hours after the conclusion of exercise, following a similar time course. In a separate review, Lieb (2007) described evidence that antidepressant drugs and lithium demonstrate concomitant increases in mood-response and immune-potentiating effects.

12. Comparison of the infection-defense hypothesis with other evolutionary theories of depression

Although the proliferation of recent evidence linking depression to inflammation and immune function has led some to speculate about the potentially adaptive role of depression in helping fight infections, there is currently little in the way of systematic attempts to help explain depression from an evolutionary infection-defense point of view. An exception to this is Raison and Miller's (2012) recent hypothesis of pathogen host defense (PATHOS-D). Drawing on evidence that many genes identified as risk alleles for depression are also associated with immune factors related to pathogen host defense—such as hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance, and anorexia—PATHOS-D, like the infection-defense hypothesis, suggests that the advantages in pathogen host defense conferred by depression risk alleles offset depression's notable costs to reproduction and survival. The two hypotheses differ, however, in their explanations of how depression relates to immune activation. According to PATHOS-D, genes that are involved in immune response and depression are one in the same, and depression is intrinsically tied to immune activation. The infection-defense hypothesis, on the other hand, can be theoretically de-coupled from immune activation, suggesting that well-established mechanisms for communication between the immune system and the nervous system provide pathways for depression to be triggered and modulated by infections as well as other signals of vulnerability, which is consistent with evidence that depression is commonly—but not always—associated with an immune-inflammatory response (Raison and Miller, 2011).

More traditional attempts to explain the persistence of depression from an evolutionary standpoint have focused on socially adaptive mechanisms. Evolutionary theorists have often drawn upon key features of depression—such as sadness and withdrawal—as part of a subversive, "second-line" posture that offers protective advantages in response to defeat, and helps to explain many of depression's puzzling, self-limiting features. For example, according to 'rank theory,' depression signals yielding behavior following an unsuccessful struggle for dominance in order to avoid unnecessary harm (Gilbert, 1992). Similarly, 'social risk theory' describes depression as a signal of submissiveness in response to social failure, as a way to maintain social ties critical for survival and reproduction (Allen and Badcock, 2006; Price et al., 1994). The 'psychic pain hypothesis,' offers a more general model of depressed mood, suggesting that it provides affective feedback that discourages continued investment in adverse or unreachable goals (Thornhill and Thornhill, 1989). Other theories describe ways in which behavioral changes and nonverbal cues associated with depression function as distress signals to elicit help during adversity (Hagen, 2003). Each theory hones in on selection pressures that have likely shaped affective responses throughout evolution; sadness, for example, heightening attention to adversity, provides important feedback to self and others about social and environmental sources of stress, and can promote adaptive behavior in response to the types of losses or conflicts described above. From our infection-defense perspective, the immune system co-opts this affective response so that the deep, pervasive sense of sadness that often occurs in the context of clinical depression may help to promote withdrawal behaviors that conserve energy and reduce exposure to new sources of stress or infection.

Traditional evolutionary theories of depression, while offering potentially useful explanations for understanding changes in affect and behavior under a circumscribed set of conditions, on the whole remain limited (1) in their ability to offer predictions that can be submitted to rigorous testing; (2) in their ability to explain the full range of signs and symptoms of depression, including apparently paradoxical features such as hypervigilance vs. conservation/withdrawal states; (3) in their ability to explain depression's association with a diverse array of conditions and illnesses such as nutritional deficiencies, seasonal changes, hormonal fluctuations, and chronic diseases; and (4) in their failure to account for evidence that depression is linked to immune-inflammatory factors, mediated by a variety of neuroimmune processes. The infection-defense hypothesis, by contrast, helps to integrate a large and growing body of research that depression is intimately linked with immune function, and offers insight into the mechanisms by which many known risk factors for depression, such as stress and sleep deprivation, contribute to the etiology of depression.

13. Potential challenges to the infection-defense hypothesis

Depression's associations with higher morbidity and mortality rates for a number of diseases appear to contradict the notion that depression provides an evolutionary advantage. From the infection-defense point of view, however, we would expect depression to be elicited more often in the context of illness and disease; thus, there would be extremely high rates of morbidity and mortality associated with it. There is some evidence to suggest that depression not only follows, but also presages worse outcomes for a number of illnesses, including HIV (Leserman, 2008) and cancer (Reiche et al. 2004). More longitudinal data is needed to provide an accurate account of the progression and relative contributions of depression, inflammation, and potential "third variables" that may be influencing immune response. It is important to note, however, that our hypothesis only requires that the relative advantages of depression outweigh its costs. Throughout human history, the impact of infection on survival and reproduction has been staggering, and life expectancy throughout most of human history was less than half of what it is today; thus, immune responses are likely to be biased toward surviving acute or relatively short-term immune challenges, while the long-term effects of chronic immune-activation or inflammation only become more relevant as life expectancy gradually increases over time. Moreover, from a Darwinian perspective, the fact that depression has persisted despite these costs only strengthens the case that it must have offered a powerful adaptive advantage for risk alleles to have remained so high in the population.

There may be other ways to understand depression's persistence from an immune standpoint. For example, might depression simply be an epiphenomenon of a prolonged or severe inflammatory response? Or is it possible that depression is a maladaptive expression of genes that confer immune advantages to the host under some circumstances, and confer risk in others? Just as fever, a key asset in combatting infections, can be harmful or even lethal at high levels, an adaptive view of depression does not imply that depression can't sometimes be harmful. However, the view that depression is a fundamentally maladaptive state is again refuted by the notably high prevalence rates of depression risk alleles in the population.

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14. A comprehensive view of depression

A comprehensive view of depression takes into account its multi-faceted nature that manifests in a variety of clinical presentations. For example, as noted above, some depressed individuals experience hypervigilant states that include agitation and restlessness, while others experience low energy and psychomotor slowing (American Psychiatric Association, 2000). At any given point in time, the specific features of depression that are evoked likely depend on the interaction of genetic factors (Raison and Miller, 2012), early experience (Bradley et al., 2008; Chapman et al., 2004; Garnefski et al., 1990), immune vulnerability (Dantzer et al., 2008; Kinney and Tanaka, 2009), physiological vulnerabilities (Maes et al., 2009; Raison and Miller, 2011), and situational triggers (Keller and Nesse, 2006). For example, grief-related depression following the loss of a loved one is more likely to elicit crying, whereas depression that follows from stress or seasonal factors is more likely to involve pessimism and fatigue (Keller and Nesse, 2006). While not all individuals who experience depression show evidence of increased inflammation (Raison and Miller, 2011), it remains to be seen whether some forms of depression are better explained from alternate bio-behavioral frameworks. For example, grief reactions to separation and loss, rooted in survival strategies employed during the vulnerable state of infancy, may be better explained from an ethological attachment framework (Bowlby, 1982; Mikulincer and Shaver, 2007).

Gene-environment interactions have been found to exert influence on depression risk, as in the case of the 5-HTTLPR short allele of the serotonin transporter gene. Numerous studies have shown, for example, that carriers of the 5-HTTLPR short allele demonstrate an elevated risk for depression that is further increased in relation to levels of environmental stress (Eley et al., 2004; Kendler et al., 2005).

Evidence from studies using both human and laboratory animals suggest that early life experiences can influence susceptibility to inflammation and depression. Early adverse experiences such as neglect and trauma are related to increased risk for depression and disease across the lifespan (Chapman et al., 2004; Garnefski et al., 1990). Childhood maltreatment is also associated with increased inflammation (Danese et al., 2007), and adults with a history of childhood maltreatment have been found to respond to acute stress with increased IL-6 concentrations compared to controls (Carpenter et al., 2010). Laboratory studies using rats have found that impaired maternal contact and milk quality can induce significant changes in stress response and inflammation in offspring (Walker, 2010). Increased CRH concentrations and HPA-axis activity are found in both humans and laboratory animals who have experienced early life stress, and have been implicated as key factors mediating the associations between early experience, inflammation, and depression (Bradley et al., 2008; Gillespie et al., 2009; Walker, 2010).

Given the complex interplay of multiple systems involved in a depressive response, immune response may also interact with other physiological vulnerabilities to increase risk for depression. Maes and colleagues (Maes et al., 2009), for example, have outlined factors related to the condition of increased gut permeability, known as "leaky gut," that may contribute to inflammation-associated depression, such as increased translocation of lipopolysaccharide (LPS) from gram-bacteria.

While the infection-defense hypothesis posits a protective role for depression in humans' environment of evolutionary adaptedness, the role of increased hygiene and availability of antimicrobial treatments in modern society have reduced mortality rates associated with infection, and suggests the possibility that depression's relative advantages in infection-defense may be decreasing. The fact that rates of depression are increasing does not necessarily counter this, as the increasing rates may not be due to increased genetic risk per se, but rather to the increased presence of immune-compromising factors such as environmental toxins.

It is also of note that, from a clinical perspective, psychological interpretations of depression—including psychodynamic or schema-based interpretations—insofar as they help to identify and alleviate sources of psychological stress, including classically-conditioned stress responses to situational triggers, complement an infection-defense view of depression. The infection-defense view of depression not only helps to provide an evolutionary explanation for the prevalence and persistence of depression throughout human history, but also supports an integrative framework for understanding the etiology of depression from multiple levels of influence.

15. Summary and further clinical implications of the infection-defense hypothesis

Converging evidence suggests that depression is often an inflammatory/immune-mediated response to infection, vulnerability to infection, and/or chronic activation of the innate immune system. This inflammatory response is stimulated by increased production of proinflammatory cytokines, which have wide-ranging effects on both neuroendocrine and neuronal systems, including an inhibitory influence on serotonergic transmission. This emergent model of depression helps to explain: (1) why depression is associated with immune alterations such as decreased NKCA, (2) why depression is associated with increased rates of infection and disease, and (3) why a wide range of environmental and physiological factors associated with increased vulnerability to infection are also associated with increased risk for depression.

In addition, the discovery of inflammatory-immune factors in the physiology of depression helps to explain an important psychiatric puzzle as to why genes associated with major depression have persisted, despite depression's association with increased morbidity and mortality. As outlined in the infection-defense hypothesis, signs and symptoms of depression such as anhedonia, social withdrawal, reduced energy and psychomotor retardation—and the genes that contribute to them—may be explained as adaptive responses to infection vulnerability that serve to: (1) conserve metabolic resources for fighting infection, (2) reduce exposure to further infections or environmental stressors, and (3) reduce social contact to prevent the spread of infection to kin.

Unlike many other evolutionary theories of depression, key tenets derived from the infection-defense hypothesis can be submitted to rigorous testing. For example, using a double-blind placebo-controlled experimental design, a stringent test of the hypothesis that interventions reducing infection and/or immune compromise will lead to a reduction in depressive symptoms could be made. Future studies using longitudinal and epidemiological data will also be important in helping to establish the relative progression of immune-inflammatory factors and depression following exposure to infection or immune-compromising conditions.

15.1. Clinical Implications

Associations between immune function and depression, and in particular, the notion that moods may serve as a behavioral defense against infection, carry important implications for understanding the causes, treatment, and prevention of depression. Some of these implications pose a challenge to conventional wisdom; for example, if symptoms of depression are serving a protective function in the face of immune challenge, then the goal of reducing depressive symptoms to ease emotional distress should be balanced against the need to first identify and treat possible

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underlying immune factors. Some factors that influence immune vulnerability, such as stress and sleep disturbances, are commonly addressed in mental health treatment settings and can be alleviated with traditional forms of therapy including CBT and mind–body relaxation techniques, as well as pharmacological interventions; however, the potential role of underlying infections and immune disorders warrants greater attention. Underlying infections or immune disorders may be under-diagnosed, and should routinely be ruled out as potential causative factors. This need is underscored by the findings of Rabinowitz et al. (1997) that psychiatric patients tend to have higher rates of unrecognized and untreated physical illness than the rest of the population.

The notion that depressed individuals may have increased immune vulnerability, an underlying infection, or other source of immune compromise leads to several further implications. First, increased attention to hygiene in clinical settings such as waiting rooms, shared bedrooms on inpatient units, or other shared spaces may help to reduce the spread of pathogens that contribute to depression. Relatedly, depressed individuals may benefit from taking heightened precautionary measures to reduce the risk of incurring further immune challenge, such as more thorough and frequent handwashing, or by avoiding crowded public places where there is greater exposure to pathogens. Finally, engaging in strategies to enhance immune function could potentially complement traditional anti-depressant therapies. The reduction of immune-compromising factors—such as sleep disorders, chronic pain, stress, dietary deficiencies, and insufficient exercise—deserves more investigation as a possible approach to treating and preventing depression. For example, moderate exercise, meditation practice, and nutritional supplementation to correct for deficiencies in omega-3 fatty acids and vitamin D, may be simple and economical ways to help alleviate depressive symptoms.

Environmental pathogens that trigger immune impairment and inflammation, such as toxigenic molds, pesticides, and other pollutants, also deserve greater attention for their potential role in the etiology of depression. For example, exposure to toxigenic mold is associated both with alterations in both NK cell activity and various neuropsychiatric symptoms, including depression (Anyanwu et al., 2003). Increasing levels of environmental toxins that contribute to inflammation and depression may potentially help to explain recent increases in rates of depression (Compton et al., 2006).

Pharmacologic interventions that have established antimicrobial, immune-enhancing, or anti-inflammatory properties also merit more study for their potential antidepressant effects. For example, minocycline, a second-generation tetracycline antibiotic, has demonstrated anti-inflammatory and anti-depressant effects in both human and animal studies (Pae et al., 2008). Preliminary findings suggest that non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, celecoxib, and naproxen may have antidepressant effects by way of their action as cyclooxygenase (COX)-2 inhibitors (Müller, 2010). For example, celecoxib has been found to block COX-2 enzymes as well as to reduce depression-like behaviors in laboratory animals (Guo et al., 2009). In at least one human study, celecoxib has been found to augment the antidepressant effects of fluoxetine (Akhondzadeh et al., 2009). This latter finding, in particular, points to the possibility that COX-2 inhibitors may be effective adjunct therapies to traditional antidepressants.

Another promising line of research in the search for improved pharmacologic treatments of depression involves anti-inflammatory cytokine antagonists. For example, in animal studies, the use of the IL-1β receptor antagonist IL-1ra prevented the development of depression-like behavioral and neurochemical changes in response to chronic stress exposure (Koo and Duman, 2008; Norman et al., 2010). The anti-inflammatory cytokine IL-10 has also been identified as a potential target for antidepressant action. In studies with laboratory animals there is evidence that IL-10 modulates numerous features associated with depression including sleep, helplessness, and pain perception (Roque et al., 2009). Moreover, increased levels of circulating IL-10 have been found in both humans and animals receiving anti-depressant treatment (Kenis and Maes, 2002).

TNF-α inhibitors have shown promise in clinical trials for decreasing symptoms of depression. Patients with treatment-resistant depression who had high baseline levels of inflammatory biomarkers showed improvement following several infusions of the TNF antagonist Infliximab over a 12-week trial (Raison et al., 2012). Another TNF inhibitor, Etanercept, administered to psoriasis patients over a 12-week period, resulted in a greater decrease of depressive symptoms from baseline when compared with placebo (Tyring et al., 2006).

Of note, a potential risk of using anti-inflammatory agents in the treatment of depression is that the suppression of immune function may mask existing infections or increase susceptibility to new ones. This again underscores the need to rule out infection or immune-related causes of depression prior to treatment, and to weigh the potential risks of anti-inflammatory/immunosuppressant agents against the need to alleviate depressive symptoms.

In summary, the infection-defense hypothesis bears important clinical implications for the treatment and prevention of depression. Its basic premise that depression is an adaptive immune strategy (1) indicates that many behavioral features of depression may serve an adaptive purpose to help fight existing infections and avoid new ones; and (2) points to the need for a fundamental shift in depression treatment that favors the primacy of investigating and remedying underlying infections or immune-compromising factors (both environmental and endogenous) that may be contributing to depression. In addition, interventions that aid the body's natural ability to fight infections, such as correcting nutritional deficiencies or engaging in stress-reduction activities like meditation, would be expected, as numerous studies show, to help temper symptoms of depression. Finally, the proliferation of new discoveries over the past several decades that link depression to immune-inflammatory processes, and that have identified bidirectional pathways by which the nervous and immune systems communicate, also opens the door for a wide range of novel pharmacologic interventions in the clinical management of depression.

Conflict of interest

All authors declare that there are no conflicts of interest.

References

Afsar, B., Elsurer, R., Eyileten, T., Yilmaz, M.I., Caglar, K., 2009. Antibody response following hepatitis B vaccination in dialysis patients: does depression and quality of life matter? Vaccine 27, 5865–5869.

Akhondzadeh, S., Jafari, S., Raisi, F., Nasehi, A.A., Ghoreishi, A., Salehi, B., Mohebbi-Rasa, S., Raznahan, M., Kamalipour, A., 2009. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress. Anxiety 26, 607–611.

Allen, N.B., Badcock, P.B., 2006. Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 30, 815–826.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders text revision (4th ed.). American Psychiatric Association, Washington, DC.

Andréasson, A., Arborelius, L., Erlanson-Albertsson, C., Lekander, M., 2007. A putative role for cytokines in the impaired appetite in depression. Brain Behav. Immun. 21, 147–152.

Anyanwu, E., Campbell, A.W., Jones, J., Ehiri, J.E., Akpan, A.I., 2003. The neurological significance of abnormal natural killer cell activity in chronic toxigenic mold exposures. Sci. World J. 3, 1128–1137.

Ardayfio, P., Kim, K., 2006. Anxiogenic-like effect of chronic corticosterone in the light-dark emergence task in mice. Behav. Neurosci. 120, 249–256.

Avery, D.H., Shah, S.H., Eder, D.N., Wildschiødtz, G., 1999. Nocturnal sweating and temperature in depression. Acta Psychiatr. Scand. 100, 295–301.

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Berk, L.S., Felten, D.L., Tan, S.A., Bittman, B.B., Westengard, J., 2001. Modulation of neuroimmune parameters during the eustress of humorassociated mirthful laughter. Alter. Ther. Health Med. 7 (62–72), 74–76.
Beseler, C.L., Stallones, L., 2008. A cohort study of pesticide poisoning and depression in Colorado farm residents. Ann. Epidemiol. 18, 768–774.
Bierhaus, A., Wolf, J., Andrassy, M., Rohleder, N., Humpert, P.M., Petrov, D., Ferstl, R., von Eynatten, M., Wendt, T., Rudofsky, G., Joswig, M., Morcos, M., Schwaninger, M., McEwen, B., Kirschbaum, C., Nawroth, P.P., 2003. A mechanism converting psychosocial stress into mononuclear cell activation. Proc. Natl. Acad. Sci. USA 100, 1920–1925.
Borges, M.C., Martini, L.A., Rogero, M.M., 2011. Current perspectives on vitamin D, immune system, and chronic diseases. Nutrition 27, 399–404.
Bowlby, J., 1982. Attachment and loss, . Attachment, 2nd ed., Vol. 1. Basic Books, New York.
Bradley, R.G., Binder, E.B., Epstein, M.P., Tang, Y., Nair, H.P., Liu, W., Gillepsie, C.F., Berg, T., Evces, M., Newport, J., Stowe, Z., Heim, C.M., Nemeroff, C.B., Schwartz, A., Cubells, J.F., Ressler, K.J., 2008. Influence of child abuse on adult depression: moderation by the corticotropin-releasing hormone receptor gene. Arch. Gen. Psychiatry 65, 190–200.
Braun, W.A., Von Duvillard, S.P., 2004. Influence of carbohydrate delivery on the immune response during exercise and recovery from exercise. Nutrition 20, 645–650.
Broadhead, W., Blazer, D., George, L., Tse, C.K., 1990. Depression, disability days and days lost from work in a prospective epidemiological study. JAMA 264, 2524–2528.
Brown, G.W., Bifulco, A., Harris, T., Bridge, L., 1986. Life stress, chronic subclinical symptoms and vulnerability to clinical depression. J. Affect. Disord. 11, 1–19.
Brydon, L., Harrison, N.A., Walker, C., Steptoe, A., Critchley, H.D., 2008. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. Biol. Psychiatry 63, 1022–1029.
Burke, L., 2003. The impact of maternal depression on familial relationships. Int. Rev. Psychiatry 15, 243–255.
Cairns, J., 1997. Matters of Life and Death. Princeton University Press, Princeton, NJ.
Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A.H., 2002. Neurobehavioral effects of interferon-alpha in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. Neuropsychopharmacology 26, 643–652.
Capuron, L., Miller, A.H., 2004. Cytokines and psychopathology: lessons from interferon-alpha. Biol. Psychiatry 56, 819–824.
Capuron, L., Miller, A.H., 2011. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol. Ther. 130, 226–238.
Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H., 2003. Interferon-α-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. Biol. Psychiatry 54, 906–914.
Carpenter, L.L., Gawuga, C.E., Tyrka, A.R., Lee, J.K., Anderson, G.M., Price, L.H., 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology 35, 2617–2623.
Casanova, J.L., Abel, L., 2005. Inborn errors of immunity to infection: the rule rather than the exception. J. Exp. Med. 202, 197–201.
Cesari, M., Penninx, B.W., Newman, A.B., Kritchevsky, S.B., Nicklas, B.J., Sutton-Tyrrell, K., Rubin, S.M., Ding, J., Simonsick, E.M., Harris, T.B., Pahor, M., 2003. Inflammatory markers and onset of cardiovascular events: results from the health ABC study. Circulation 108, 2317–2322.
Chapman, D.P., Whitfield, C.L., Felitti, V.J., Dube, S.R., Edwards, V.J., Anda, R.F., 2004. Adverse childhood experiences and the risk of depressive disorders in adulthood. J. Affect. Dis. 82, 217–225.
Cohen, S., 1995. Psychological stress and susceptibility to upper respiratory infections. Am. J. Respir. Crit. Care Med. 152, S53–S58.
Cohen, M., Hoffman, R.G., Cromwell, C., Schmeidler, J., Ebrahim, F., Carrera, G., Endorf, F., Alfonso, C.A., Jacobson, J.M., 2002. The prevalence of distress in persons with human immunodeficiency virus infection. Psychosomatics 43, 10–15.
Cohen, S., Kemeny, M.E., Kearney, K.A., Zegans, L.S., Neuhaus, J.M., Conant, M.A., 1999. Persistent stress as predictor of genital herpes recurrence. Arch. Int. Med. 159, 2430–2436.
Compton, W.M., Conway, K.P., Stinson, F.S., Grant, B.F., 2006. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991–1992 and 2001–2002. Am. J. Psychiatry 163, 2141–2147.
Corsini, E., Liesivuori, J., Vergieva, T., Van Loveren, H., Colosio, C., 2008. Effects of pesticide exposure on the human immune system. Hum. Exp. Toxicol. 27, 671–680.
Cummings, E.M., Davies, P.T., 1994. Maternal depression and child development. J. Child Psychol. Psychiatry 35, 73–112.
Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult Inflammation in a life-course study. Proc. Natl. Acad. Sci. USA 104, 1319–1324.
Dantzer, R., 2001. Cytokine-induced sickness behavior: where do we stand? Brain Behav. Immun. 15, 7–24.
Dantzer, R., 2009. Cytokines, sickness behavior, and depression. Immunol. Allergy Clin. North Am. 29, 247–264.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Neuroscience 9, 46–57.
Davis, E.P., Glynn, L.M., Schetter, C.D., Hobel, C., Chicz-Demet, A., Sandman, C.A., 2007. Prenatal exposure to maternal depression and cortisol influences infant temperament. J. Am. Acad. Child Adolesc. Psychiatry 46, 737–746.
de Winter, R.F., Wolterbeek, R., Spinhoven, P., Zitman, F.G., Goekoop, J.G., 2007. Character and temperament in major depressive disorder and a highly anxious-retarded subtype derived from melancholia. Compr. Psychiatry 48, 426–435.
Delgado, P.L., 2000. Depression: the case for a monoamine deficiency. J. Clin. Psychiatry 61 (Suppl 6), 7–11.
Dobson, A.P., Carper, E.R., 1996. Infectious diseases and human population history. Bioscience 46, 115–126.
Dowlati, Y., Herman, N., Swardfager, W., Sham, L., Reim, E.K., Lanotôt, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatry 67, 446–457.
Dunn, A.J., Wang, J., 1995. Cytokine effects on CNS biogenic amines. Neuroimmunomodulation 2, 319.
Eaton, W.W., Anthony, J.C., Gallo, J., 1997. Natural history of diagnostic interview schedule/DSM-IV and major depression. The Baltimore Epidemiologic Catchment Area follow-up. Arch. Gen. Psychiatry 54, 993–999.
Eisenberger, N.I., Berkman, E.T., Inagaki, T.K., Rameson, L.T., Mashal, N.M., Irwin, M.R., 2010. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol. Psychiatry 68, 748–754.
Eley, T.C., Sugden, K., Corsico, A., Gregory, A.M., Sham, P., McGuffin, P., Plomin, R., Craig, I.W., 2004. Gene-environment interaction analysis of serotonin system markers with adolescent depression. Mol. Psychiatry 9, 908–915.
Fang, C.Y., Reibel, D.K., Longacre, M.L., Rosenzweig, S., Campbell, D.E., Douglas, S.D., 2010. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural cell activity. J. Alter. Complement. Med. 16, 531–538.
Fazekas, C., Enzinger, C., Wallner, M., Kischka, U., Greimel, E., Kapeller, P., Stix, P., Pieringer, W., Fazekas, F., 2006. Depressive symptoms following herpes simplex encephalitis – an underestimated phenomenon? Gen. Hosp. Psychiatry 28, 403–407.
Finch, C.E., 2010. Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. Proc. Natl. Acad. Sci. USA 107 (Suppl. 1), 1718–1724.
Fischler, B., Bocken, R., Schneider, I., De Waele, M., Thielemans, K., Derde, M.P., 1992. Immune changes induced by electroconvulsive therapy (ECT). Ann. N. Y. Acad. Sci. 650, 326–330.
Ganji, V., Milone, C., Cody, M.M., McCarty, F., Wang, Y.T., 2010. Serum vitamin D Concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. Int. Arch. Med. 11, 3–29.
Garnefski, N., van Egmond, M., Straatman, A., 1990. The influence of early and recent life stress on severity of depression. Acta Psychiatr. Scand. 81, 295–301.
Gilbert, P., 1992. Depression: The Evolution of Powerlessness. Lawrence Erlbaum, East Sussex, UK.
Gillespie, C.F., Phifer, J., Bradley, Bekh, Ressler, K.J., 2009. Risk and resilience: genetic and environmental influences on development of the stress response. Depress. Anxiety 26, 984–992.
Glaser, R., Robles, T.F., Sheridan, J., Malarkey, W.B., Kiecolt-Glaser, J.K., 2003. Mild depressive symptoms are associated with amplified and prolonged inflammatory responses after influenza virus vaccination in older adults. Arch. Gen. Psychiatry 60, 1009–1014.
Gold, S.M., Irwin, M.R., 2006. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. Neurol. Clin. 24, 507–519.
Goldberg, D., 2006. The aetiology of depression. Psychol. Med. 36, 1341–1347.
Groër, M.W., Morgan, K., 2007. Immune, health and endocrine characteristics of depressed postpartum mothers. Psychoneuroendocrinology 32, 133–139.
Guo, J.Y., Li, C.Y., Ruan, Y.P., Sun, M., Qi, X.L., Zhao, B.S., Luo, F., 2009. Chronic treatment with celecoxib reverses chronic unpredictable stress-induced depressive-like behavior via reducing cyclooxygenase-2 expression in rat brain. Eur. J. Pharmacol. 612, 54–60.
Hagen, E.H., 2003. The bargaining model of depression. In: Hammerstein, P. (Ed.), Genetic and Cultural Evolution of Cooperation. MIT Press, pp. 95–123.
Hammen, C., 2005. Stress and depression. Annu. Rev. Clin. Psychol. 1, 293–319.
Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Critchley, H.D., 2009. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol. Psychiatry 66, 407–414.
Hart, B.L., 1988. Biological basis of the behavior of sick animals. Neurosci. Biobehav. Immun. 12, 123–137.
Heninger, G.R., Delgado, P.L., Charney, D.S., 1996. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. Pharmacopsychiatry 29, 2–11.
Hestad, K.A., Tønseth, S., Stoen, C.D., Ueland, T., Aukrust, P., 2003. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. JECT 19, 183–188.
Heyland, D.K., MacDonald, S., Keefe, L., Drover, J.W., 1998. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA 280, 2013–2019.
Hibbeln, J.R., 2009. Depression, suicide and deficiencies of omega-3 essential fatty acids in modern diets. World Rev. Nutr. Diet 99, 17–30.
Hirschfeld, R.M., 2000. History and evolution of the monoamine hypothesis of depression. J. Clin. Psychiatry 61 (Suppl. 6), 4–6.
Holsboer, F., 2000. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 23, 477–501.
Horesh, N., Klomek, A.B., Apter, A., 2008. Stressful life events and major depressive disorders. Psychiatry Res. 160, 192–199.

Please cite this article in press as: Anders, S., et al. Depression as an evolutionary strategy for defense against infection. Brain Behav. Immun. (2013), http://dx.doi.org/10.1016/j.bbi.2012.12.002

Irwin, M., 2002a. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav. Immun. 16, 503–512.
Irwin, M., 2002b. Psychoneuroimmunology of depression: clinical implications. Brain Behav. Immun. 16, 1–16.
Irwin, M.R., Miller, A.H., 2007. Depressive disorders and immunity: 20 years of progress and discovery. Brain Behav. Immun. 21, 374–383.
Ismael, A., Bedell, G.W., 1986. Effect elevated temperatures and low levels of trace metals on the growth and phenotypic development of *Candida albicans*. Mycopathologicia 94, 45–51.
Katafuchi, T., Kondo, T., Take, S., Yoshimura, M., 2006. Brain cytokines and the 5-HT system during poly 1: C-induced fatigue. Ann. N. Y. Acad. Sci. 1088, 230–237.
Keller, M.C., Nesse, R.M., 2006. The evolutionary significance of depressive symptoms: different adverse situations lead to different depressive symptom patterns. J. Pers. Soc. Psychol. 91, 316–330.
Kempenaers, B., 2007. Mate choice and genetic quality: a review of the heterozygosity theory. Adv. Study Behav. 37, 189–278.
Kendler, K.S., Karkowski, L.M., Prescott, C.A., 1999. Causal relationship between stressful life events and the onset of major depression. Am. J. Psychiatry 156, 837–841.
Kendler, K.S., Kuhn, J.W., Vittum, J., Prescott, C.A., Riley, B., 2005. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. Arch. Gen. Psychiatry 62, 529–535.
Kendler, K.S., Pedersen, N.L., Neale, M.C., Mathé, A., 1995. A pilot Swedish twin study of affective illness including hospital- and population-ascertained subsamples: results of model fitting. Behav. Genet. 25, 217–232.
Kenis, G., Maes, M., 2002. Effects of antidepressants on the production of cytokines. Int. J. Neuropsychopharmacol. 5, 401–412.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence of age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 62, 593–602.
Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Psychoneuroimmunology: psychological influences on immune function and health. J. Consult. Clin. Psychol. 70, 537–547.
Kinney, D.K., Tanaka, M., 2009. An evolutionary hypothesis of depression and its symptoms, adaptive value, and risk factors. J. Nerv. Ment. Dis. 197, 561–567.
Klerman, G.L., 1989. Depressive disorders. Further evidence for increased medical morbidity and impairment of social functioning. Arch. Gen. Psychiatry 46, 856–858.
Kling, M.A., Alesci, S., Csako, G., Costello, R., Luckenbaugh, D.A., Bonne, O., Duncko, R., Drevets, W.C., Manji, H.K., Charney, D.S., Gold, P.W., Neumeister, A., 2007. Sustained low grade pro-inflammatory state in unmedicated, remitted women with major depressive disorder as evidenced by elevated serum levels of the acute phase proteins C-reactive protein and serum amyloid A. Biol. Psychiatry 62, 309–313.
Kluger, M.J., 1991. Fever: role of pyrogens and cryogens. Physiol. Rev. 71, 93–127.
Kluger, M.H., Rothenburg, B.A., 1979. Fever and reduced iron: their interaction as a host defense response to bacterial infection. Science 203, 374–376.
Koo, J.W., Duman, R.S., 2008. IL-1beta is an essential mediator of the antineurogenic and anhedonic effects of stress. Proc. Natl. Acad. Sci. USA 105, 751–756.
Kopinsky, K.L., Stoff, D.M., Rausch, D.M., 2004. Workshop report: the effects of psychological variables on the progression of HIV-1 disease. Brain Behav. Immun. 18, 246–261.
Kristiansen, J.E., Thomsen, V.F., Martins, A., Viveiros, M., Amaral, L., 2010. Non-antibiotic reverse resistance of bacteria to antibiotics. In Vivo 24, 751–754.
Kronfol, Z., Nair, M.P., Weinberg, V., Young, E.A., Aziz, M., 2002. Acute effects of electroconvulsive therapy on lymphocyte natural killer cell activity in patients with major depression. J. Affect. Disord. 71, 211–215.
Kwiatkowski, D.P., 2005. How malaria has affected the genome and what human genetics can teach us about malaria. Am. J. Hum. Genet. 77, 171–192.
Lam, R.W., Song, C., Yatham, L.N., 2004. Does neuroimmune dysfunction mediate seasonal mood changes in winter depression? Med. Hypotheses 63, 567–573.
Lavretsky, H., Epel, E.S., Siddarth, P., Nazarian, N., Cyr, N.S., Khalsa, D.S., Lin, J., Blackburn, E., Irwin, M.R., 2012. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. Int. J. Geriatr. Psychiatry. http://dx.doi.org/10.1002/gps.3790 [Epub ahead of print].
Leserman, J., 2008. Role of depression, stress, and trauma in HIV disease progression. Psychosom. Med. 70, 539–545.
Lieb, J., 2007. Lithium and antidepressants: stimulating immune function and preventing and reversing infection. Med. Hypotheses 69, 8–11.
Lipkin, W.I., Hornig, M., 2004. Psychotropic viruses. Curr. Opin. Microbiol. 7, 420–425.
LLerená, A., Berecz, R., Dorado, P., González, A.P., Peñas-LLedó, E.M., De La Rubia, A., 2003. CYP2C9 gene and susceptibility to major depressive disorder. Pharmacogenomics 3, 300–302.
Loftis, J.M., Huckans, M., Morasco, B.J., 2010. Neuroimmune mechanisms of cytokine-induced depression: current theories and novel treatment strategies. Neurobiol. Dis. 37, 519–533.
Lustberg, L., Reynolds, C.F., 2000. Depression and insomnia: questions of cause and effect. Sleep Med. Rev. 4, 253–262.
Maes, M., 1999. Major depression and activation of the inflammatory response system. Adv. Exp. Med. Biol. 461, 25–46.
Maes, M., Meltzer, H.Y., Stevens, W., Cosyns, P., Blockx, P., 1994. Multiple reciprocal relationships between in vivo cellular immunity and hypothalamic-pituitary-adrenal axis in depression. Psychol. Med. 24, 167–177.
Maes, M., Smith, R., Scharpe, S., 1995. The monocyte- T-lymphocyte hypothesis of major depression. Psychoneuroendocrinology 20, 111–116.
Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., Kubera, M., Bob, P., Lerer, B., Maj, M., 2009. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab. Brain Dis. 24, 27–53.
Magnusson, A., 2000. An overview of epidemiological studies on seasonal affective disorder. Acta Psychatr. Scand. 101, 176–184.
Maier, S.F., Watkins, L.R., 1998. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol. Rev. 105, 83–107.
Marks, I.M., Nesse, R.M., 1994. Fear and fitness: an evolutionary analysis of anxiety disorders. Ethol. Sociobiol. 15, 247–261.
Masuda, A., Nakayama, T., Yamanaka, T., Koga, Y., Tei, C., 2002. The prognosis after multidisciplinary treatment for patients with postinfectious chronic fatigue syndrome and noninfectious chronic fatigue syndrome. J. Behav. Med. 25, 487–497.
Matsunaga, M., Isowa, T., Kimura, K., Miyakoshi, M., Kanayama, N., Murakami, H., Sato, S., Konagaya, T., Nogimori, T., Fukuyama, S., Shinoda, J., Yamada, J., Ohira, H., 2008. Associations among central nervous, endocrine, and immune activities when positive emotions are elicited by looking at a favorite person. Brain Behav. Immun. 22, 408–417.
McGuffin, P., Katz, R., Watkins, S., Rutherford, J., 1996. A hospital-based twin register of the heritability of DSM-IV unipolar depression. Arch. Gen. Psychiatry 53, 129–136.
McNamara, R.K., Jandacek, R., Rider, T., Tso, P., Cole-Strauss, A., Lipton, J.W., 2010. Omega-3 fatty acid deficiency increases constitutive proinflammatory cytokine production in rats: relationship with central serotonin turnover. Prostaglandins Leukot. Essent. Fatty Acids 83, 185–191.
Mead, P.S., Slutsker, L., Dietz, V., McCraig, L.F., Bresee, J.S., Shapiro, C., Griffin, P.M., Tauxe, R.V., 1999. Food-related illness and death in the United States. Emerg. Infect. Dis. 5, 607–625.
Mestre-Alfaro, A., Ferrer, M.D., Banquells, M., Riera, J., Drobnic, F., Sureda, A., Tur, J.A., Pons, A., 2012. Body temperature modulates the antioxidant and acute immune response to exercise. Free Radic. Res. 46, 799–808.
Mikulincer, M., Shaver, P.R., 2007. Attachment in adulthood: structure, dynamics, and change. Guilford, New York.
Miller, A.H., Ancoli-Israel, S., Bower, J.E., Capuron, L., Irwin, M.R., 2008. Neuroendocrine immune mechanisms of behavioral comorbidities in patients with cancer. J. Clin. Oncol. 26, 971–982.
Miller, A.H., Maletic, V., Raison, C., 2009. Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol. Psychiatry 65, 732–741.
Motivala, S.J., Sarfatti, A., Olmos, L., Irwin, M.R., 2005. Inflammatory markers and sleep disturbance in major depression. Psychosom. Med. 67, 187–194.
Müller, N., 2010. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. Curr. Opin. Invest. Drugs 11, 31–42.
Mundt, C., Reck, C., Backenstrass, M., Kronmuller, K., Fiedler, P., 2000. Reconfirming the role of life events for the timing of depressive episodes. A two-year prospective follow-up study. J. Affect. Disord. 59, 23–30.
Munoz-Bellido, J.L., Munoz-Criado, S., Garcìa-Rodrìguez, J.A., 2000. Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors. Int. J. Antimicrob. Agents 14, 177–180.
Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease. World Health Organization, Geneva.
Murray, K.O., Resnick, M., Miller, V., 2007. Depression after infection with West Nile virus. Emerg. Infect. Dis. 13, 479–481.
Mykletun, A., Bjerkeset, O., Dewey, M., Prince, M., Overland, S., Stewart, R., 2007. Anxiety, depression and cause-specific mortality: the HUNT study. Psychosom. Med. 69, 323–331.
Nery, F.G., Borba, E.F., Viana, V.S., Hatch, J.P., Soares, J.C., Bonfá, E., Neto, F.L., 2008. Prevalence of depressive and anxiety disorders in systemic lupus erythematosus and their association with antiribosomal P antibodies. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 695–700.
Nery, F.G., Hatch, J.P., Nicoletti, M.A.m Monkul, E.S., Najt, P., Matsuo, K., Cloninger, C.R., Soares, J.C., 2009. Temperament and character traits in major depressive disorder: Influence of mood state and recurrence of episodes. Depress. Anxiety 26, 382–388.
Nieman, D.C., Henson, D.A., Austin, M.D., Brown, V.A., 2005. Immune response to a 30-minute walk. Med. Sci. Sports Exerc. 37, 57–62.
Norman, G.J., Karelina, K., Zhang, N., Walton, J.C., Morris, J.S., Devries, A.C., 2010. Stress and IL-1beta contribute to the development of depressive-like behavior following peripheral nerve injury. Mol. Psychiatry 15, 404–414.
Novati, A., Roman, V., Cetin, T., Hagewoud, R., den Boer, J.A., Luiten, P.G., Meerlo, P., 2008. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. Sleep 31, 1579–1585.
O'Connor, J.C., Lawson, M.A., André, C., Briley, E.M., Szegedi, S.S., Lestage, J., Castanon, N., Herkenham, M., Dantzer, R., Kelley, K.W., 2009. Induction of IDO by Bacillus Calmette–Guérin is responsible for development of murine depressive-like behavior. J. Immunol. 182, 3202–3212.
Owens, M.J., Nemeroff, C.B., 1991. Physiology and pharmacology of corticotropin-releasing factor. Pharmacol. Rev. 43, 425–473.
Pace, T.W., Hu, F., Miller, A.H., 2007. Cytokine-effects on glucocorticoid receptor function: relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. Brain Behav. Immun. 21, 9–19.

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Pace, T.W., Negi, L.T., Adame, D.D., Cole, S.P., Sivilli, T.I., Brown, T.D., Issa, M.J., Raison, C.L., 2009. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. Psychoneuroendocrinology 34, 87–98.

Pae, C.U., Marks, D.M., Han, C., Patkar, A.A., 2008. Does minocycline have antidepressant effect? Biomed. Pharmacother. 62, 308–311.

Pariante, C.M., Lightman, S.L., 2008. The HPA-axis in major depression: classical theories and new developments. Trends Neurosci. 31, 458–464.

Parker, G., Gibson, N.A., Brotchie, H., Heruc, G., Rees, A.M., Hadzi-Pavlovic, D., 2006. Omega-3 fatty acids and mood disorders. Am. J. Psychiatry 163, 969–978, Erratum in Am. J. Psychiatry 163, 1842.

Preti, A., 2007. Suicide among animals: a review of evidence. Psychol. Rep. 101, 831–848.

Price, J., Sloman, L., Gardner Jr., R., Rohde, P., 1994. The social competition hypothesis of depression. Br. J. Psychiatry 164, 309–315.

Rabinowitz, J., Mark, M., Popper, M., Feldman, D., 1997. Physical illness among all discharged psychiatric inpatients in a national case register. J. Ment. Health Adm. 24, 82–89.

Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27, 24–31.

Raison, C.L., Dantzer, R., Kelly, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., Miller, A.H., 2010. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. Mol. Psychiatry 15, 393–403.

Raison, C.L., Miller, A.H., 2011. Is depression an inflammatory disorder? Curr. Psychiatry Rep. 13, 467–475.

Raison, C.L., Miller, A.H., 2012. The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). Mol. Psychiatry. http://dx.doi.org/10.1038/mp.2012.2 [Epub ahead of print].

Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2012. A randomized controlled trial of the tumor necrosis factor antagonist Infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. Arch. Gen. Psychiatry 3, 1–11.

Rausch, J.L., Johnson, M.E., Corley, K.M., Hobby, H.M., Shendarkar, N., Fei, Y., Ganapathy, V., Leibach, F.H., 2003. Depressed patients have higher body temperature: 5-HT transporter long promoter region effects. Neuropsychobiology 47, 120–127.

Reiche, E.M., Nunes, S.O., Morimoto, H.K., 2004. Stress, depression, the immune system, and cancer. Lancet Oncol. 5, 617–625.

Rivier, C., Vale, W., Brown, M., 1989. In the rat, interleukin-1α and -β stimulate adrenocorticotropin and catecholamine release. Endocrinology 125, 3096–3102.

Robaeys, G., De Bie, J., Wichers, M.C., Bruckers, L., Nevens, F., Michielsen, P., Van Ranst, M., Buntinx, F., 2007. Early prediction of major depression in chronic hepatitis C patients during peginterferon alpha-2b treatment by assessment of vegetative depressive symptoms after four weeks. World J. Gastroenterol. 13, 5736–5740.

Robinson, F.P., Mathews, H.L., Witek-Janusek, L., 2003. Psycho-endocrineimmune response to mindfulness-based stress reduction in individuals infected with the human immunodeficiency virus: a quasiexperimental study. J. Alter. Complement. Med. 9, 683–694.

Roque, S., Correia-Neves, M., Mesquita, A.R., Palha, J.A., Sousa, N., 2009. Interleukin-10: a key cytokine in depression? Cardiovasc. Psychiatry Neurol., 2009:187894. Epub 2009 Aug 16.

Rubinow, D.R., Schmidt, P.J., Meltzer-Brody, S., Harsh, V., 2009. The neurobiology of menstrual cycle-related mood disorders. In: Charney, D.S., Nestler, E.J. (Eds.), Neurobiology of Mental Illness, 3rd ed. Oxford University Press, New York.

Segerstrom, S.C., 2010. Resources, stress, and immunity: an ecological perspective on human psychoneuroimmunology. Ann. Behav. Med. 40, 114–125.

Schatzberg, A.F., 2000. Current status of managing depression: is there a need for new treatment strategies? Program and abstracts of the 153rd Annual Meeting of the American Psychiatric Association, Chicago.

Schiepers, O.J.G., Wichers, M.C., Maes, M., 2005. Cytokines and major depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 201–217.

Schildkraut, J.J., Kety, S.S., 1967. Biogenic amines and emotion. Science 156, 21–37.

Schleifer, S.J., Keller, S.E., Bond, R.N., Cohen, J., Stein, M., 1989. Major depressive disorder and immunity. Role of age, sex, severity, and hospitalization. Arch. Gen. Psychiatry 46, 81–87.

Scott, L.V., Dinan, T.G., 2002. Vasopressin as a target for antidepressant development: an assessment of the available evidence. J. Affect. Disord. 72, 113–124.

Shyn, S.I., Hamilton, S.P., 2010. The genetics of major depression: moving beyond the monoamine hypothesis. Psychiatr. Clin. North Am. 33, 125–140.

Shuto, H., Kataoka, Y., Horikawa, T., Fujihara, N., Oishi, R., 1997. Repeated interferon-α administration inhibits dopaminergic neural activity in the mouse brain. Brain Res. 747, 348–351.

Sillaber, I., Holsboer, F., Wotjak, C.T., 2009. Animal Models of Mood Disorders. In: Charney, D.S., Nestler, E.J. (Eds.), Neurobiology of Mental Illness, 3rd ed. Oxford University Press, New York.

Smith, R.S., 1991. The macrophage theory of depression. Med. Hypotheses 35, 298–306, Erratum in Med. Hypotheses 36, 178.

Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatry 157, 1552–1562.

Tanaka, M., Anders, S., Kinney, D.K., 2012. Environment, the immune system, and depression: an integrative review and discussion of the infection-defense hypothesis. In: Dietert, R.R., Luebke, R.W. (Eds.), Immunotoxicity, Immune Dysfunction, and Chronic Disease. Springer, New York.

Tanaka, M., Kinney, D.K., 2011a. An evolutionary hypothesis of suicide: why it could be biologically adaptive and is so prevalent in certain occupations. Psychol. Rep. 108, 977–992.

Tanaka, M., Kinney, D.K., 2011b. Does the immune system regulate mood to defend against infection? Evidence from studies of immune factors, depression, and antidepressants. Curr. Psychiatry Rev. 7, 57–66.

Thornhill, R., Thornhill, N.W., 1989. The evolution of psychological pain. In: Bell, R.W., Bell, N.J. (Eds.), Sociobiology and the Social Sciences. Texas Tech University Press, Lubbock, pp. 73–103.

Thwaites, G., Taviner, M., Gant, V., 1997. The English sweating sickness, 1485 to 1551. N. Engl. J. Med. 336, 580–582.

Tondo, L., Lepri, B., Baldessarini, R.J., 2011. Reproduction among 1975 Sardinian women and men diagnosed with major mood disorders. Acta Psychiatr. Scand. 123, 283–289.

Turnbull, A.V., Rivier, C., 1995. Regulation of the HPA-axis by cytokines. Brain Behav. Immun. 9, 253–275.

Tyring, S., Gottlieb, A., Papp, K., Gordon, K., Leonardi, C., Wang, A., Lalla, D., Woolley, M., Jahreis, A., Zitnik, R., Cella, D., Krishnan, R., 2006. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomized phase III trial. Lancet 367 (9504), 29–35.

Udoji, F., Martin, T., Etherton, R., Whalen, M.M., 2010. Immunosuppressive effects of triclosan, nonylphenol, and DDT on human natural killer cells in vitro. J. Immunotoxicol. 7, 205–212.

Walker, C.D., 2010. Maternal touch and feed as critical regulators of behavioral and stress responses in the offspring. Dev. Psychobiol. 52, 638–650.

Watkins, L.R., Maier, S.F., 2000. The pain of being sick: implications of immune-to-brain communication for understanding pain. Annu. Rev. Psychol. 51, 29–57.

Weiss, R.A., McMichael, A.J., 2004. Social and environmental risk factors in the emergence of infectious diseases. Nat. Med. 10, S70–S76.

Weissman, M.M., Bland, R.C., Canino, G.J., Faravelli, C., Greenwald, S., Hwu, H.G., Joyce, P.R., Karam, E.G., Lee, C.K., Lellouch, J., Lepine, J.P., Newman, S.C., Rubio-Stipec, M., Wells, J.E., Wickramaratne, P.J., Wittchen, H., Yeh, E.K., 1996. Cross-national epidemiology of major depression and bipolar disorder. JAMA 276, 293–299.

Wender, P.H., Kety, S.S., Rosenthal, D., Schulsinger, F., Ortmann, J., Lunde, I., 1986. Psychiatric disorders in the biological and adoptive families of adopted individuals with affective disorders. Arch. Gen. Psychiatry 43, 923–929.

Wichers, M.C., Kenis, G., Leue, C., Koek, G., Robaeys, G., Maes, M., 2006. Baseline immune activation as a risk factor for the onset of depression during interferon-alpha treatment. Biol. Psychiatry 60, 77–79.

Wichers, M.C., Koek, G.H., Robaeys, G., Praamstra, A.J., Maes, M., 2005. Early increase in vegetative symptoms predicts IFN-alpha-induced cognitive depressive changes. Psychol. Med. 35, 433–441.

Wichers, M.C., Maes, M., 2004. The role of indoleamine 2,3-dioxygenase (IDO) in the pathophysiology of interferon-α-induced depression. J. Psychiatry Neurosci. 29, 11–17.

Williams, K.E., Marsh, W.K., Rasgon, N.L., 2007. Mood disorders and fertility in women: a critical review of the literature and implications for future research. Hum. Reprod. Update 13, 607–616.

Witek-Janusek, L., Albuquerque, K., Chroniak, K.R., Chroniak, C., Durazo-Aryizu, R., Mathews, H.L., 2008. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. Brain Behav. Immun. 22, 969–981.

Wolf, J.M., Rohleder, N., Bierhaus, A., Nawroth, P.P., Kirschbaum, C., 2009. Determinants of the NF-kappa B response to acute psychosocial stress in humans. Brain Behav. Immun. 23, 742–749.

Wong, S., Pinkney, J., 2004. Role of cytokines in regulating feeding behavior. Curr. Drug Targets 5, 251–263.

Yates, W.R., Gleason, O., 1998. Hepatitis C and depression. Depress. Anxiety 7, 188–193.

Yates, W.R., Meller, W.H., Lund, B.C., Thurber, S., Grambsch, P.L., 2010. Early-onset Major Depressive Disorder in men is associated with childlessness. J. Affect. Disord. 124, 187–190.

Yirmiya, R., Pollak, Y., Morag, M., Reichenberg, A., Barak, O., Avitsur, R., Shavit, Y., Ovadia, H., Weidenfeld, J., Morag, A., Newman, M.E., Pollmacher, T., 2000. Illness, cytokines and depression. Ann. N. Y. Acad. Sci. 917, 478–487.

Zhu, C.B., Blakely, R.D., Hewlett, W.A., 2006. The proinflammatory cytokines interleukin 1beta and tumor necrosis factor-alpha active serotonin transporters. Neuropsychopharmacology 31, 2121–2131.

Zorilla, E.P., Luborsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkle, R., Seligman, D.A., Schmidt, K., 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav. Immun. 15, 199–226.

Zorilla, E.P., McKay, J.R., Luborsky, L., Schmidt, K., 1996. Relation of stressors and depressive symptoms to clinical progression of viral illness. Am. J. Psychiatry 153, 626–635.

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