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.

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 allele (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 symptomology 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-