

## Oxford Handbooks Online

### **Psychoneuroimmunology of Stress and Mental Health**

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The Oxford Handbook of Stress and Mental Health

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Subject: Psychology, Clinical Psychology Online Publication Date: Mar 2019

DOI: 10.1093/oxfordhb/9780190681777.013.24

Cite as: Slavich, G. M. (in press). Psychoneuroimmunology of stress and mental health. In K. Harkness & E. P. Hayden (Eds.), *The Oxford handbook of stress and mental health*. New York: Oxford University Press.

### **Abstract and Keywords**

Psychoneuroimmunology (PNI) is the study of how psychological, neural, and immunologic processes interact and affect human health and behavior. Although once a relatively small field, some of the most exciting discoveries in psychopathology and mental health research have recently involved ideas and methods from PNI. In reviewing this work, I first summarize the structure and function of the human immune system, focusing primarily on inflammation. Second, I describe neural and physiologic pathways that link the brain and immune system, which give neurocognitive processes the ability to regulate the immune system and immunologic processes the ability to affect neural, cognitive-emotional, and behavioral outcomes. Third, I review studies examining associations between life stress and inflammation, and inflammation and mental health. Finally, I highlight several promising avenues for future research. Overall, despite the notable impact that PNI has already had on our understanding of mental and physical health, many important questions remain unanswered.

Keywords: stress, cytokines, inflammation, anxiety, depression, posttraumatic stress disorder, schizophrenia, suicide, health, disease

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The question of how mental health problems originate goes back centuries. In the early days before Christ, the Greeks viewed mental disorders as arising out of imbalances in bodily fluids. Many years later, Plato proposed that imbalances in the mind, body, and spirit could cause emotional distress; and then in the 18th and 19th centuries, the idea emerged that adverse life experiences—especially during childhood—could have negative effects on the human psyche that persist well into adulthood and potentially touch every aspect of a person's social and emotional life (Maddux & Winstead, 2015). Indeed, historical perspectives on the fundamental origins of mental illness have been as varied and as creative as the human imagination itself.

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The modern field of psychopathology has made substantial progress in terms of focusing researchers' attention on more biologically plausible mechanisms that may underlie mental illness, but even so, a wide variety of pathways are still considered, including those that involve social, psychological, neural, immunologic, genetic, and genomic processes. Integrating across these different complex systems and levels of analysis to achieve a more sensible and coherent perspective on the underlying pathophysiology of mental illness is no small task. Yet a relatively small group of scientists have been doing just this for decades, having started years before the Research Domain Criteria (RDoC) initiative made interdisciplinary research on psychopathology popular. They call themselves *psychoneuroimmunologists*.

Psychoneuroimmunologists' area of study, called *psychoneuroimmunology* (or *PNI* for short), is a highly integrative field that examines how psychological, neural, and immunologic processes influence each other and shape human health and behavior (Irwin & Slavich, 2017). Using a variety of different *in vivo*, *in situ*, and *in vitro* techniques in both human and animal model system, PNI has yielded numerous discoveries that have helped to greatly clarify how social, psychological, and behavioral factors influence the activity of the immune system; how the immune system affects cognition, emotion, neural processes, and behavior; and how these bidirectional interactions shape risk for a variety of mental and physical health problems, including anxiety disorders, depression, posttraumatic stress disorder (PTSD), cardiovascular disease, chronic pain, certain cancers, and neurodegeneration. A complete overview of this very large literature work is beyond the scope of the present review, but thankfully, many excellent summaries of PNI and the allied field of health psychology have been written over the years (e.g., Ader, Cohen, & Felten, 1995; Cohen & Herbert, 1996; Haroon, Raison, & Miller, 2012; Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Maier & Watkins, 1998; Miller, Chen, & Cole, 2009).

One of the most basic and fundamental cornerstones of PNI involves the discovery that components of the immune system involved in inflammation are influenced not just by factors such as viruses and bacteria that are present inside the body, but also by cues, signals, and events occurring in the external social and physical environment (Glaser & Kiecolt-Glaser, 2005). Such effects do not comport with classic models of the immune system, which suggest that inflammation is regulated largely by internal interactions that occur below the shoulders and that do not involve the brain. However, it is now widely recognized that social-environmental processes, including psychological stress, can substantially upregulate inflammatory activity (e.g., Denson, Spanovic, & Miller, 2009; Irwin & Cole, 2011; Segerstrom & Miller, 2004; Steptoe, Hamer, & Chida, 2007), and that inflammation can in turn increase a person's risk for a variety of health problems and related adverse outcomes (Couzin-Frankel, 2010; Fagundes & Way, 2014; Shields, Moons, & Slavich, 2017; Slavich, 2015). As a result, PNI has provided the much-needed empirical basis for several new theories of stress and mental health that are notable in large part because they identify specific mechanisms that have a high likelihood of being directly

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involved in disease onset, maintenance, and/or progression (e.g., Kinney et al., 2010; O'Donovan, Slavich, Epel, & Neylan, 2013; Raison & Miller, 2013; Slavich & Irwin, 2014).

The purpose of the present review is to provide an overview of recent thinking and research on stress and mental health from the perspective of PNI. First, I briefly summarize the main structure and function of the human immune system, with a primary focus on inflammatory biology. Second, I describe neural and physiologic pathways that link the brain and immune system, which in turn give neurocognitive processes the ability to regulate the immune system and immunologic processes the ability to affect the brain, cognition, emotion, and behavior. Third, I review recent studies examining associations between stress and inflammation, and inflammation and mental health. Finally, I highlight some possible avenues for future research on stress and health from a PNI perspective.

## The Immune System

The fundamental goal of the human immune system is to keep the body biologically safe and protected from foreign pathogens. It thus plays a critical role in promoting health and survival, especially during times of physical injury or infection. The system has two interconnected branches that are referred to as *innate immunity* and *adaptive immunity*, and these branches work together to provide humans with short- and long-term protection against pathogens that could enter the body through open body cavities (e.g., the nose or mouth) or through wounds created during fighting or social conflict (Medzhitov, 2007; Takeda, Kaisho, & Akira 2003). The systems are described in greater detail in the following sections.

### Innate Immunity

Innate immunity represents the body's highly conserved, rapid, first-line defense against tissue damage and microbial infection. The innate immune system response is mediated by innate immune cells (e.g., monocytes/macrophages and dendritic cells) that circulate throughout the body and use invariant receptors to detect a wide variety of pathogens that have the potential to cause biological harm if left unaddressed. Once these cells identify an injury or infection, they initiate a complex cascade of inflammatory processes that help contain an infection and promote healing and recovery (Medzhitov, 2007).

Activation of the innate immune system frequently begins when receptors located on immune cells recognize highly conserved features of microbes or *pathogen-associated molecular patterns* (PAMPs), such as lipopolysaccharide (LPS), unmethylated cytosine-guanine dinucleotide or CpG sequences in bacterial and viral genomes, and double-stranded RNA viruses. This recognition strategy is termed *pattern recognition*, and innate immune receptors that use this strategy are called *pattern recognition receptors*. One of the most well-characterized families of pattern recognition receptors are *toll-like receptors* (TLRs). TLRs are present on macrophages, neutrophils, and dendritic cells, and they recognize conserved components of a wide variety of microbes, including bacteria, viruses, and fungi (Akira, Takeda, & Kaisho, 2001; Medzhitov, 2001). Examples of this

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family of TLRs include types that bind to, and become activated by, specific ligands such as LPS (TLR4), double-stranded RNA (TLR3), and single-stranded RNA (TLR7 and TLR8; Barton, 2008).

When any of these TLRs are activated, a conserved signaling cascade is initiated that results in the activation of two principal intracellular transcription factors—namely, nuclear factor- $\kappa$ B (NF- $\kappa$ B) and interferon regulatory factors (Karin, 2006; Kawai & Akira, 2007). These transcription factors in turn drive the expression of pro-inflammatory immune response genes, such as tumor necrosis factor- $\alpha$  (*TNF- $\alpha$* ) and interleukin-1 (*IL-1*), which results in the synthesis and secretion of small, soluble proteins called *cytokines*. As I describe in more detail later, cytokines act mainly on leukocytes and endothelial cells to upregulate and control the body's inflammatory response during times of pathogenic threat, and they are frequently assessed in biobehavioral and clinical studies as indices of individuals' immune-related stress reactivity or disease risk (Karin, 2006; Raison, Capuron, & Miller, 2006). Together, this complex biological reaction is referred to as the *acute-phase response*, and it is characterized by substantial increases in inflammatory activity that can occur both locally (i.e., at the site of a specific injury or infection) or systemically (i.e., throughout the body; Hennessy, Schiml-Webb, & Deak, 2009).

### Adaptive Immunity

When innate immune system defenses are insufficient for addressing a biological threat, the second branch of the immune system, *adaptive immunity*, is called into action. In contrast to innate immunity, which is nonspecific and does not confer long-term protection for the host, adaptive immunity involves the proliferation of microbial-specific white blood cells (i.e., *lymphocytes*) that attempt to neutralize or eliminate microbes based on an *immunological memory* of having previously responded to a specific pathogen or antigen (Gruys, Toussaint, Niewold, & Koopmans, 2005; Murphy, 2011). Whereas the innate immune response is rapid, occurring over minutes or hours, the adaptive immune response takes days to develop (Slavich & Irwin, 2014).

In contrast to innate immunity, adaptive immunity is initiated by antigen-presenting cells (APCs), such as macrophages or dendritic cells, which help the immune system differentiate between the host's own cells (i.e., "self") and those of invading bacteria or viruses (i.e., "nonself" or "foreign"). These APCs are attracted to sites in the body where they ingest, or *endocytose*, invading antigen. Once the foreign antigen has been ingested and processed, APCs then migrate from the infection site to local lymph nodes, where they present antigen peptides to T helper ( $T_h$ ) cells, resulting in the release of different cytokines, including interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), and interferon gamma (IFN- $\gamma$ ), which help promote and control the adaptive immune response (Murphy, 2011).

As described later, the cytokines produced during this process can have wide-ranging effects on mood, cognition, and behavior. In addition, on an immunologic level, these inflammatory mediators induce  $T_h$  cells to become activated, to proliferate, and to then

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differentiate into one of two cell types. One type of resulting  $T_H$  B cells become antibody-producing cells (i.e., plasma cells), and another type leaves the lymph node to coordinate cytotoxic cell responses that eliminate foreign pathogens and help return the body to biological safety. What primarily differentiates this response from the innate immune system response is its capacity to remember past threats. It does this by keeping a part of antigen-specific  $T_H$  cells, cytotoxic T cells, and B cells around after the adaptive immune response has effectively ended, thereby forming an *immunological memory* of the pathogen that enables the adaptive immune system to respond more quickly and more effectively when the same foreign invader returns in the future (Murphy, 2011).

### Inflammatory Cytokines

We have already discussed the fact that cytokines are a key mediator of the inflammatory response and briefly reviewed how they coordinate innate and adaptive immune system reactions to pathogens. Given their central role in stress physiology and in shaping mental health, however, cytokines deserve a bit more attention and description. This is especially true because, as alluded to earlier, cytokines are the primary biological endpoint of immune system activity that presently gets assessed in biobehavioral studies of stress and mental health.

Cytokines are released from several different types of immune cells, including monocytes/macrophages, dendritic cells, and neutrophils, and their primary function is to coordinate cell-to-cell communication during times of physical injury or infection. However, they can also alter neurochemical and neuroendocrine processes that have wide-ranging effects on human physiology and behavior (Curfs, Meis, & Hoogkamp-Korstanje, 1997). Cytokines may thus be thought to function in a manner similar to neurotransmitters and hormones insofar as they mediate physiologic responses, rely on receptor-ligand interactions, and have self (autocrine), local (paracrine), and distal (endocrine) effects (Jain & Mills, 2007). Broadly speaking, cytokines can be categorized as those that are primarily involved in innate immunity (e.g., tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], interleukin-1 [IL-1], interleukin-6 [IL-6], interleukin-8 [IL-8], and interleukin-10 [IL-10]) versus adaptive immunity (e.g., IFN- $\gamma$ , IL-2, IL-4, and IL-5), and those that increase (i.e., *upregulate*) inflammatory activity, which are called *pro-inflammatory cytokines*, versus those that decrease (i.e., *downregulate*) inflammatory activity, which are called *anti-inflammatory* cytokines.

Literally hundreds of cytokines have been identified to date (Dinarello, 2007), some of which have been studied extensively by immunologists and others of which remain relatively unexplored. In the context of psychology and psychiatry, however, the situation is very different. Indeed, as of today, only a small number of cytokines have been consistently examined across studies of stress and mental health. Those cytokines are, primarily, IL-1, IL-6, and TNF- $\alpha$ .

Collectively, these cytokines coordinate a variety of cell functions that stimulate and enhance a complex set of immunologic processes that help to locate, identify, and kill pathogens. One of their main purposes is to orchestrate the deployment of the body's

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biological “soldiers” (i.e., immune cells) to sites of injury or infection during times of stress. In this model, the stress hormones epinephrine and norepinephrine call immune cells out of the spleen, bone marrow, and lymph nodes (i.e., the “barracks”) and into the bloodstream (i.e., the “boulevards”); then, cytokines help promote vascular permeability and cellular adhesion, which allows immune cells to leave the bloodstream and migrate to affected tissue (i.e., “battlefields”), where they can neutralize or eliminate foreign pathogens (Dhabhar, Malarkey, Neri, & McEwen, 2012). Each cytokine plays a slightly different role in this process. For example, IL-1 activates the expression of the endothelial adhesion molecule intercellular adhesion molecule-1 (ICAM-1), which promotes firm adhesion to endothelial cells for eventual extravasation (i.e., migration of cells from circulation to tissue; Smith, Marlin, Rothlein, Toman, & Anderson, 1989). TNF- $\alpha$ , in turn, stimulates the production of the adhesion molecule E-selectin on the endothelium, which binds to adhesion molecules on neutrophils (Hubbard & Rothlein, 2000). Small polypeptides called *chemokines*, which are activated by TNF- $\alpha$ , IL-6, and IL-1, play an important role in this process, as they continually survey the body to screen for pathogens in a process called *immunosurveillance*. Once a pathogen or infection has been identified, chemokines can act as *chemoattractants* that recruit other immune cells to the site of inflammatory activity (Murphy, 2011). Finally, these cytokines help promote the differentiation of lymphocytes called *cytotoxic T cells*, which ultimately assist in killing pathogens, especially viruses.

In addition to helping coordinate the mobilization and distribution of immune cells throughout the body, cytokines play a critical role in promoting and regulating the most commonly recognized signs of inflammation. These biobehavioral effects are briefly described in Table 1. At specific sites of infection, for example, cytokines promote redness, heat, swelling, and pain that combine to accelerate wound healing, limit the spread of infection, and heighten the host’s awareness of the injury (Murphy, 2011). At a more systemic level, cytokines induce the production of the acute-phase protein *C-reactive protein* (CRP), which is a robust biomarker of inflammation that is frequently measured in both biomedical research and in clinical settings (e.g., as an indicator of cardiovascular disease risk). CRP, in turn, acts with cytokines to promote increased body temperature, fever, heart rate, and respiratory rate, which combine to help kill off pathogens and conserve vital energy during times of injury (Poon, Ho, Chiu, & Chang, 2013; Ricciotti & FitzGerald, 2011).

Finally, on a neurocognitive and behavioral level, cytokines communicate with the central nervous system to induce a constellation of behaviors known as *sickness behaviors* (Hart, 1988). These behaviors include increased pain and threat sensitivity, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal. These behaviors have several functions and are intended, for example, to draw attention to potential injuries (i.e., pain sensitivity), heighten an individual’s awareness of potential threats in the surrounding social and physical environment (i.e., threat sensitivity), help an individual recuperate and recover from possible injury (i.e., anhedonia, fatigue), and reduce the likelihood that an infected individual will spread an infection to nearby conspecifics (i.e., psychomotor retardation, social-behavioral withdrawal). When combined, these effects help increase

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an individual's ultimate likelihood of survival during times of physical injury or threat. At the same time, it should be noted that these neurocognitive and behavioral outcomes are very similar—if not identical in some instances—to several symptoms of anxiety and depression, which is what provided some of the first indications that inflammation may play a role in anxiety disorders and depression (Slavich & Irwin, 2014).

Table 1 Inflammatory Cytokines and Their Key Characteristics

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<b>Cytokine</b>	<b>Family</b>	<b>Producer Cells</b>	<b>Function</b>
Pro-inflammatory cytokines			
Interleukin-1 $\beta$ (IL-1 $\beta$ )	Unassigned	Macrophages	Key mediator of sickness behavior; promotes fever and pain hypersensitivity; involved in HPA axis activation, lymphocyte activation, macrophage and neutrophil activation, endothelial activation, prostanoid synthesis, and IL-6 synthesis
Interleukin-2 (IL-2)	Hematopoietins	T cells	Facilitates immunoglobulin production by B cells, and differentiation and proliferation of NK cells
Interleukin-6 (IL-6) <sup>a</sup>	Hematopoietins	Macrophages, T cells	Key mediator of acute phase response; promotes fever, and T and B cell differentiation and activation; can downregulate inflammation by inhibiting TNF- $\alpha$ and IL-1 production
Interleukin-8 (IL-8)	Chemokines	Macrophages	Key mediator of inflammation; recruits neutrophils to the site of inflammation and induces chemotaxis in target cells
Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ )	TNF family	Macrophages, NK cells	Key mediator of sickness behavior; promotes fever and suppresses appetite; stimulates HPA axis, endothelial activation, and

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			neutrophil activation; induces apoptotic cell death
Anti-inflammatory cytokines			
Interleukin-4 (IL-4)	Hematopoietins	T cells	Inhibits production of the pro-inflammatory cytokines TNF- $\alpha$ and IL-1; stimulates B and T cell proliferation
Interleukin-10 (IL-10)	Unassigned	Macrophages, T cells	Inhibits production of the pro-inflammatory cytokines IL-1, IL-6, and TNF- $\alpha$ ; Enhances B cell proliferation and antibody production

*Note.*

(<sup>a</sup>) Although IL-6 is listed as a pro-inflammatory cytokine, as described, it can also have anti-inflammatory effects. NK cells = natural killer cells; HPA axis = hypothalamic-pituitary-adrenal axis. Reprinted with permission from Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, 140, 774–815. Washington, DC: American Psychological Association.

### Inflammation: A Double-Edged Sword

From this brief description of the immune system, it should be clear that mounting a rapid and effective inflammatory response to physical injury or the first signs of a pathogen is critical for resolving infection, repairing tissue damage, and promoting survival (Kushner, 1982; Medzhitov, 2008). Unfortunately, though, what can save us in the short run can also kill us in the long run. This is because persistent elevations in inflammatory activity can cause *oxidative stress*, driven in part by cytokine-related increases in the production of free radical species derived from oxygen (i.e., ROI), which can directly oxidize DNA and also interfere with mechanisms of DNA repair. For example, whereas the pro-inflammatory cytokine TNF- $\alpha$  enhances the formation of ROI by neutrophils and other cells in the body, TNF- $\alpha$ , IFN- $\gamma$ , and interleukin-1 $\beta$  (IL-1 $\beta$ ) stimulate the expression of inducible nitric oxide synthase in inflammatory and epithelial cells (Federico et al., 2007). These interactions in turn lead to DNA mutations, genomic instability, and ultimately increased risk for numerous health problems that have an inflammatory component. As a result, although inflammation was once thought of as being involved in only a few disorders, such as cardiovascular disease and certain

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cancers, it is now recognized that chronic inflammation is present in several psychiatric disorders, such as PTSD and depression, and that it plays a role in the development, exacerbation, or progression of numerous physical disease conditions, including asthma, rheumatoid arthritis, diabetes, obesity, atherosclerosis, ovarian and breast cancer, and Alzheimer's disease (Couzin-Frankel, 2010; Slavich, 2015; see also Bower, Crosswell, & Slavich, 2014; Schrepf et al., 2013).

Understanding when inflammation is beneficial for health and when it is harmful largely comes down to the question of how the inflammatory response is regulated (Slavich, 2015). In this context, a beneficial inflammatory response is one that occurs quickly and in response to an actual physical or biological threat, and that then dissipates once the threat has passed. One factor that can substantially alter immune system responding and prolong inflammation is psychological stress (Segerstrom & Miller, 2004; Steptoe et al., 2007). In the next section, therefore, we review the primary neurobiological and physiologic pathways that give experiences of stress the ability to affect inflammatory activity.

### Central Regulation of Inflammatory Activity

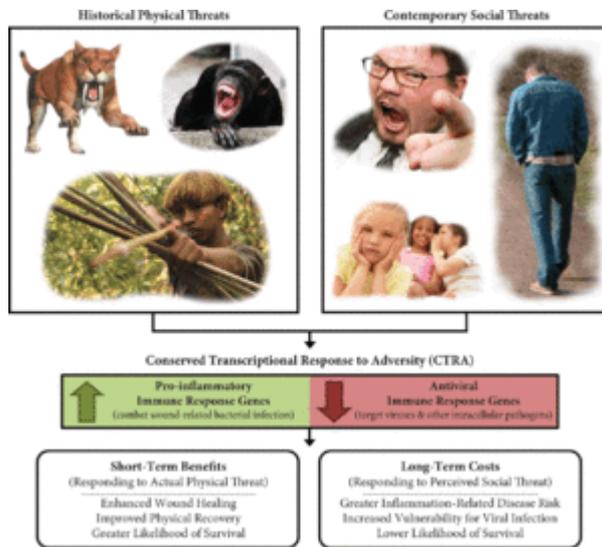
As alluded to already, the human inflammatory response is a highly complex, tightly regulated process that is influenced by numerous physiologic events occurring throughout the periphery of the body. However, systemic inflammatory activity is also regulated by processes occurring in the brain, including by neurocognitive representations of the surrounding social and physical environment (Irwin & Cole, 2011). This neuro-inflammatory link is critical for survival because it enables the immune system to mobilize and redistribute immune cells not just *after* a physical injury or infection has occurred, but *in advance* of a physical assault that could increase an individual's risk for a pathogen-related infection (Dhabhar et al., 2009; Rosenberger et al., 2009). An anticipatory immunologic response such as this is helpful for wound healing and recovery, but most important, it can be critical for survival in instances where a quick biological response is needed to limit the spread of infection, which likely explains why it was highly conserved.

Several excellent reviews have described the specific mechanisms linking neural and immunologic processes (e.g., Dantzer et al., 2008; Irwin & Cole, 2011; Maier & Watkins, 1998; Pavlov & Tracey, 2004; Radtke, Macdonald, & Tacchini-Cottier, 2013; Rivest, 2009; Sternberg, 2006). For the present discussion, however, it is perhaps most important to understand that immunologic responses to social-environmental adversity represent the body's attempt to deploy its resources to best handle the specific biological threats that are most likely to be present in different environments. Because psychological stressors, such as those involving social conflict or rejection, historically increased a person's risk for physical wounding, the types of psychological stressors that individuals experience in the present-day environment are most likely to upregulate expression of pro-inflammatory immune response genes, which combat bacteria and other extracellular pathogens that

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an individual could be exposed to during physical injury. This response is accompanied by a reciprocal downregulation of antiviral immune response genes, which target intracellular pathogens such as viruses that are spread in social situations. We have referred to this increased pro-inflammatory/reduced antiviral skewing of the human basal gene expression profile (i.e., the *basal transcriptome*) as the *conserved transcriptional response to adversity* (CTRA; Slavich & Cole, 2013; Slavich & Irwin, 2014), and it is depicted in Figure 1.



*Figure 1* Conserved transcriptional response to adversity (CTRA) (see Slavich & Cole, 2013; Slavich & Irwin, 2014). The innate immune system developed to counter physical threats from predatory animals and hostile conspecifics that dominated our ancestral environment. Exposure to these threats activates a conserved transcriptional response to adversity (CTRA) that involves upregulation of pro-inflammatory immune response genes, which combat extracellular pathogens and wound-related bacterial infections, and downregulation of antiviral immune response genes, which target intracellular pathogens such as viruses. This redeployment of the leukocyte basal transcriptome is adaptive in the context of actual physical threat because it enhances wound healing and recovery from injury and infection. However, the CTRA can also be activated by modern-day social, symbolic, anticipated, and imagined threats, leading to increased risk for several mental and physical health conditions that involve inflammation. Reprinted with permission from Slavich, G. M., & Irwin, M. R. (2014).

From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, 140, 774-815. Washington, DC: American Psychological Association.

A fundamental principal of the CTRA involves the ability for the immune system to activate ancestral host defense programs in response to present-day social-environmental adversity. The immune system cannot directly detect social threats in the surrounding environment, though, so it relies on the brain, which can alert the peripheral immune system to the presence of a threat via multiple non-mutually exclusive pathways. Two of the main pathways are the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis (Irwin & Cole, 2011; Slavich & Irwin, 2014). Additionally, a third pathway was recently discovered that involves a direct physical connection between the brain and peripheral immune system via meningeal lymphatic vessels, which were previously not known to exist. We briefly discuss

each of these neural-immune pathways next.

## Sympathetic Nervous System

The SNS can influence the production of pro-inflammatory cytokines by releasing the neurotransmitter norepinephrine into peripheral tissues, primary and secondary lymphoid organs, and all other major organ systems, including the vasculature and perivascular tissues. Once released, norepinephrine modulates immune response gene transcription via stimulation of  $\beta$ -adrenergic receptors and, possibly,  $\alpha$ -adrenergic signaling (Grisanti et al., 2011; Huang et al., 2012; Nance & Sanders, 2007). This adrenergic signaling cascade suppresses transcription of antiviral type I interferon genes (Cole, Korin, Fahey, & Zack, 1998; Lee et al., 2000), and it upregulates transcription of the pro-inflammatory immune response genes *IL1*, *TNF*, and *IL6*, leading to increased systemic inflammatory activity and decreased antiviral activity (Cole et al., 2010; Grebe et al., 2010). Ultimately, therefore, the SNS plays a central role in coordinating the CTRA, which involves “steering” innate immune system responses between pro-inflammatory and antiviral phenotypes (Slavich & Cole, 2013).

## Hypothalamic-Pituitary-Adrenal Axis

The HPA axis also regulates pro-inflammatory cytokine activity in the periphery of the body. It is typically thought that activation of the HPA axis suppresses transcription of both pro-inflammatory and antiviral immune response genes by stimulating the release of the glucocorticoid cortisol, which is one of the body’s most potent anti-inflammatory substances. However, cortisol can also enhance inflammation. As described in detail elsewhere (e.g., Sorrells, Caso, Munhoz, & Sapolsky, 2009), cortisol enables the catecholamines epinephrine and norepinephrine to upregulate immune system activity, facilitates the mobilization of immune cells to injured tissues, and can also augment inflammatory responses to immunologic challenges. In addition, prolonged elevations in cortisol can lead to a phenomenon called *glucocorticoid insensitivity*, or *glucocorticoid resistance*, which occurs when immune cells become less sensitive to the anti-inflammatory effects of glucocorticoids, thus leading to HPA axis-related increases (as opposed to decreases) in inflammation (Avitsur, Stark, & Sheridan, 2001; Miller, Cohen, & Ritchey, 2002). Glucocorticoid resistance has been associated with exposure to both early life adversity and chronic stress (Miller, Cohen, & Ritchey, 2002; Miller et al., 2009), and it also occurs following acute stressors that involve elements of social evaluation and rejection (Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009; Rohleder, Schommer, Hellhammer, Engel, & Kirschbaum, 2001).

## Meningeal Lymphatic Vessels

Finally, although the brain and immune system have historically been thought of as physically separate systems, which has required researchers to consider *indirect* pathways by which the brain may communicate with the peripheral immune system and vice versa, two landmark studies recently revealed that the brain is directly connected to the periphery via meningeal lymphatic vessels that were previously not known to exist (Aspelund et al., 2015; Louveau et al., 2015). Although these lymphatic vessels are

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primarily responsible for draining excess fluid from the central nervous system in order to help maintain fluid homeostasis, these vessels also serve as a physical path along which immune cells can travel from the brain to the peripheral immune system and back again. As a result, neural and immunologic signals originating in the central nervous system have the ability to *directly influence* inflammatory activity in the periphery, and vice versa, via immune cell trafficking (Slavich & Auerbach, 2018).

### **Summary: The Immune System, Cytokines, and Inflammation**

To summarize, the immune system plays a critical role in promoting human health and survival, especially during times of physical injury, wounding, and infection. A key component of this system is the inflammatory response, which is mediated by cytokines that identify, neutralize, and eliminate foreign pathogens, such as bacteria and viruses. Individuals always possess some basal risk of developing a bacterial infection that requires a quick and effective inflammatory response to contain. However, this risk is substantially increased when a person is exposed to situations involving potential physical danger. To detect such situations *before* they occur, I have hypothesized that the immune system relies on the brain to identify environmental cues that indicate an increased risk of physical or social threat. Then, in such circumstances, the brain can initiate a systemic inflammatory response via the SNS and HPA axis, and potentially via meningeal lymphatic vessels. Collectively, this increase in pro-inflammatory activity and decrease in antiviral activity in response to social threat has been referred to as the CTRA (Slavich & Cole, 2013; Slavich & Irwin, 2014).

Although bidirectional communication between the central nervous system and peripheral immune system is beneficial because it enables activation of the CTRA before a physical injury has occurred, this connection also has a downside, which is that it gives mere perceptions or symbolic representations of social-environmental threat the ability to activate the CTRA in the absence of actual physical threat. Therefore, threats that are purely imagined—including those that have not yet happened or that may never actually occur—can lead to substantial increases in inflammatory activity when such a response is not necessary to support survival. This reactivity pattern may not be problematic if it occurs infrequently or if increases in inflammation are quickly resolved. As discussed earlier, however, sustained increases in inflammatory activity can occur via several mechanisms, including neuroinflammatory sensitization and glucocorticoid resistance, and prolonged elevations in inflammation in turn increase a person's risk for several mental and physical health problems (Slavich & Irwin, 2014). Psychological stress is a key factor that can induce and sustain inflammatory activity, so we examine links between stress and inflammation next, with a focus on the specific types of stressors that are most strongly associated with inflammatory activity.

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### Stress and Inflammation

Research on associations between stress and inflammation has been conducted both in the laboratory and in the context of naturalistic cross-sectional and longitudinal studies. Whereas studies conducted in the laboratory have the advantage of being able to standardize and control the stress exposure that participants experience (e.g., using an experimental stress-induction task), the external validity of such studies is limited. On the other hand, studies involving the assessment of naturally occurring stressors in a person's life have the benefit of high external validity, but obtaining a comprehensive assessment of individuals' life stress exposure is both complicated and costly, as has been discussed elsewhere (see Monroe, 2008; Monroe, Slavich, & Georgiades, 2014; Slavich, 2016; Slavich & Auerbach, 2018). An overview of both naturalistic and laboratory-based studies of stress and inflammation is provided next, with a focus on the specific types of stressors that are most strongly associated with elevated inflammatory activity.

### Early Adversity and Inflammation

Numerous studies have examined associations between early life adversity (i.e., stressful experiences generally occurring before age 18) and inflammatory activity. These studies have characterized early life stress in several different ways, but they converge to yield remarkably similar findings linking early life stress with heightened inflammatory activity (Fagundes & Way, 2014). In one recent prospective population-based study, for example, investigators followed more than 4,600 children for nearly 10 years and assessed their acute life event exposure at seven time points between 1.5 and 8 years of age. Levels of inflammatory activity were, in turn, assessed at age 10 and at age 15. Consistent with the formulation that stressors involving social and physical threat are strongly associated with heightened inflammatory activity, the investigators found that greater exposure to physical or sexual abuse, being separated from a mother or father, and being taken into foster care prior to age 8 prospectively predicted higher basal levels of IL-6 and CRP at age 10, as well as higher levels of CRP at age 15 (Slopen, Kubzansky, McLaughlin, & Koenen, 2013). In a second study that assessed both prenatal stressors (i.e., family structure, parental education, parental occupation, and family income) and early life stressors (e.g., parental occupation, changes in parental marital status, changes in family environment, death of a sibling, unemployment, housing problems, financial difficulties, etc.), prenatal stressors were strongly associated with higher CRP levels in adulthood ( $M_{age} = 42.2$  years old), and these effects were independent of childhood adversity and potential confounding factors, including maternal health problems reported during pregnancy (Slopen et al., 2015). Converging results have been provided by other studies showing that growing up in a risky early environment, characterized in part by chronic unpredictability, harsh discipline, a lack of parental love and/or close supervision, and verbal, physical, and/or sexual abuse, is associated with elevated levels of CRP in young adulthood (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Taylor, Lehman, Kiefe, & Seeman, 2006), and by studies showing that a socially tumultuous early environment predicts elevated levels of IL-6 in young adulthood (Cho, Bower, Kiefe, Seeman, & Irwin,

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2012; Slopen et al., 2010) and higher levels of IL-6 and TNF- $\alpha$  in older adulthood (Kiecolt-Glaser, Gouin et al., 2011; cf. Carpenter, Gawuga, Tyrka, & Price, 2012).

Several studies have also examined associations between socioeconomic status in childhood and levels of inflammatory activity in adulthood. Consistent with the studies described earlier, this literature has provided evidence that lower socioeconomic status in childhood is associated with greater inflammatory activity in adulthood. In a recent multisite, community-based, prospective study of more than 1,000 women, for example, women raised in low socioeconomic status families had higher levels of CRP than their high-status counterparts. These effects were robust to several potential demographic and clinical confounds (e.g., ethnicity, study site, age, health problems, smoking status, medication use, etc.), and they appeared to be mediated by individuals' body mass index (BMI) and education level in adulthood (Matthews et al., 2016). Similar findings have been reported for circulating levels of IL-6 and CRP in mixed samples of adult men and women (e.g., Appleton et al., 2012; Carroll, Cohen, & Marsland, 2011; Taylor et al., 2006), and also in studies of ethnically diverse adolescents (Miller & Chen, 2007). Interestingly, in this latter study, inflammatory activity was measured at the molecular level by assessing levels of mRNA for glucocorticoid receptor and toll-like receptor 4. Results revealed that adolescents who grew up in low socioeconomic status households exhibited increased expression of genes that code for TLR4, which is involved in activating the innate immune system response, and decreased expression of genes that code for the glucocorticoid receptor, which is typically responsible for downregulating inflammation in response to cortisol (Miller & Chen, 2007). These findings are noteworthy because they suggest that early life stress may reach deep inside the body to affect inflammatory activity at the level of gene expression.

Finally, there is substantial evidence that childhood bullying, abuse, and trauma strongly predict levels of inflammatory activity in adulthood. In a large prospective longitudinal cohort study that followed all individuals born in Britain during 1 week in 1958 ( $N = 7,102$ ), exposure to childhood bullying occurring between 7 and 11 years old was found to predict heightened levels of CRP in midlife, even when controlling for several potential confounding factors, including psychopathology in childhood, childhood BMI, and parental social class during childhood, as well as social class, smoking behavior, diet, and exercise in adulthood (Takizawa, Danese, Maughan, & Arseneault, 2015). In contrast, with respect to childhood abuse and trauma, a recent meta-analytic review of 25 studies revealed that these early life adversities are associated with heightened levels of CRP, IL-6, and TNF- $\alpha$ , and that the effects are not influenced by several potential confounding factors, including individuals' age, BMI, or gender (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016). In subgroup analyses that tested for differential effects as a function of type of early life stress experienced, the authors found that physical and sexual abuse occurring during childhood were associated with elevations in TNF- $\alpha$  and IL-6, but not CRP. Conversely, parental absence during childhood was primarily associated with significant elevations in CRP, whereas emotional abuse occurring during childhood was not related to any of the inflammatory markers examined (Baumeister et al., 2016). Considered together, these studies provide substantial evidence that early life

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stress exposure is associated with elevations in several inflammatory markers, and some evidence that these stress-inflammation effects may differ as a function of the specific type of early adversity experienced.

### **Adulthood Life Stress and Inflammation**

Paralleling results from the studies of childhood adversity described earlier, there is also a relatively large and consistent body of work linking naturally occurring social stressors in adolescence and adulthood with elevated levels of inflammatory activity. Interestingly, these results also seem to be particularly strong for social stressors that involve elements of social devaluation, conflict, threat, isolation, or rejection (for reviews, see Herbert & Cohen, 1993; Kiecolt-Glaser, Gouin, & Hantsoo, 2010; Segerstrom & Miller, 2004; Slavich & Irwin, 2014). In a recent analysis of more than 1,100 adults in the United States, for example, low socioeconomic status (i.e., indexed as poorer education, income, and occupational prestige) predicted higher levels of CRP, and this effect was partially attenuated for men possessing more psychological resources (e.g., optimism, perceived mastery and control, purpose in life) but not for women possessing such resources (Elliot & Chapman, 2016). At least two other studies have shown similar associations between lower socioeconomic status and elevated levels of CRP in adulthood (Gimeno et al., 2007; Janicki-Deverts, Cohen, Kalrab, & Matthews, 2012), and there is also evidence that IL-6 is elevated in individuals with lower socioeconomic status (Gruenewald, Cohen, Matthews, Tracy, & Seeman, 2009; see also Petersen et al., 2008; Pollitt et al., 2007).

Consistent with the CTRA model presented earlier, there is also evidence that negative interpersonal interactions involving friends, peers, and family members influence systemic inflammatory activity. In one study that assessed daily experiences of negative interpersonal interactions in the domains of family, peers, and school, for example, more daily experiences of social conflict, harassment, and punishment were associated with higher levels of CRP (Fuligni et al., 2009). In a second longitudinal study that assessed levels of acute and chronic stress exposure, as well as inflammatory levels, every 6 months for 2 years, experiencing a recent acute stressful life event was associated with within-person increases in the inflammatory cytokines IL-4, IL-5, and IFN- $\gamma$  for individuals who were also exposed to high levels of chronic family stress, but not for those exposed to low levels of chronic family stress (Marin, Chen, Munch, & Miller, 2009), thus highlighting potential interactive effects between acute and chronic stress exposure in structuring inflammatory levels (see also Chiang, Eisenberger, Seeman, & Taylor, 2012).

In addition to socioeconomic status and interpersonal relationships, numerous studies have examined how inflammatory levels differ among people reporting various levels of social isolation and connection. Consistent with an abundance of research showing that social isolation substantially increases risk for all-cause mortality (Holt-Lunstad, Robles, & Sbarra, 2017), a community based case-cohort study and a nationally representative cohort study both revealed that individuals who are socially isolated are approximately 2.0–2.5 times more likely to have clinically high levels of CRP as compared to those who

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are socially well integrated (Ford, Loucks, & Berkman, 2006; Heffner, Waring, Roberts, Eaton, & Gramling, 2011). Again, consistent with the CTRA model presented earlier, high levels of social isolation have also been found to be associated with a systematic upregulation of pro-inflammatory immune response genes and a reciprocal downregulation of genes involved in antibody production (Cole, Hawkley, Arevalo, & Cacioppo, 2011), thus providing evidence that social isolation has relatively broad effects on immunologic processes that are relevant for health (for a review, see Slavich & Cole, 2013).

Collectively, these studies provide evidence that different forms of chronic social stress are associated with elevated inflammatory activity at both the gene expression and protein level. In addition, we have conducted several studies examining how experiencing just one recent, socially stressful major life event is sufficient for upregulating inflammation. To model these effects, we have identified specific major life events that involve a combination of interpersonal loss and social rejection, which we have called *targeted rejection*. These stressors, which we have defined as “social rejection that is directed at, and meant to affect, a single person, and that involves an active and intentional severing of relational ties with that person,” occur most frequently in the context of intimate relationships (e.g., getting broken-up with) or work (e.g., getting fired), and they have been found to precipitate the development of depression three times faster than other major life events of the same objectively rated severity (Slavich, Thornton, Torres, Monroe, & Gotlib, 2009). In one study that examined the effects of these acute life events on inflammatory biology, we followed participants at elevated risk for depression for 2.5 years and assessed their recent acute life event exposure and current inflammatory levels every 6 months. Consistent with the CTRA model, individuals exhibited significantly higher levels of inflammatory gene expression at study visits when they had experienced a recent targeted rejection major life event as compared to study visits when no such life event had recently occurred (Murphy, Slavich, Rohleder, & Miller, 2013).

In a second independent longitudinal study in which we assessed participants at elevated risk for asthma every 6 months for 2 years, we found the exact same pattern of effects, but this time for *anti*-inflammatory gene expression. Namely, individuals exhibited significantly lower levels of anti-inflammatory gene expression during study visits when they had experienced a recent targeted rejection life event as compared to study visits when no such stressor had occurred (Murphy, Slavich, Chen, & Miller, 2015). Importantly, these effects were not found for other types of similarly severe stressors, including other interpersonal and noninterpersonal stressors, and they were especially strong for individuals who self-reported having higher levels of subjective social status, suggesting that perceptions of social standing may moderate the effects of targeted rejection on inflammatory gene expression (Murphy et al., 2015). More broadly, these studies provide evidence that experiencing even one major life event is sufficient for increasing pro-inflammatory gene expression and reducing anti-inflammatory gene expression, so long as the life event involves the seemingly critical “ingredient” of targeted rejection.

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### Laboratory-Based Social Stressors and Inflammation

Finally, numerous studies have attempted to manipulate experiences of stress in the laboratory to model how social stressors affect inflammatory activity (Marsland, Walsh, Lockwood, & John-Henderson, 2017). These studies have the arguable limitation that they utilize laboratory-based stressors that have differing degrees of external validity, but they possess the notable advantage of being able to standardize the stress exposure and, in addition, assess inflammatory activity in a relatively controlled environment. The main take-away message from this body of work is that even relatively brief laboratory stressors (e.g., lasting 5–15 minutes) can induce increases in inflammatory activity, and this is especially true when the stressors (a) involve elements of social evaluation, conflict, rejection, or exclusion, or (b) trigger emotions that are frequently associated with these experiences, such as shame and humiliation (Slavich & Auerbach, 2018; Slavich & Irwin, 2014; Slavich, O'Donovan, et al., 2010).

In one prototypic laboratory-based study, married couples were asked to take part in a social support interaction during a first study visit and a hostile marital interaction during a subsequent visit. Whereas couples who were independently judged to be low in hostility were relatively unaffected by these tasks, those who were high in hostility exhibited significantly greater increases in plasma IL-6 and TNF- $\alpha$  following the hostile marital interaction than following the social support interaction (Kiecolt-Glaser et al., 2005). In another study, participants were randomly assigned to write about either a traumatic experience in which they blamed themselves or a neutral experience. Writing about the stressful experience involving self-blame led to significant increases in a soluble receptor for TNF- $\alpha$  (i.e., sTNF-RII); in addition, participants who experienced the greatest increases in self-reported shame during this stressor exhibited the greatest stress-induced increases in pro-inflammatory cytokine activity (Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004).

One of the most commonly used tasks for inducing an experience of stress in the laboratory is the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993; for a review, see Shields & Slavich, 2017). In this social stress-inducing paradigm, participants are first asked to prepare and then give an impromptu speech in front of a panel of nonresponsive, socially rejecting “expert” raters wearing white lab coats. Sometimes they are also audiotaped or videotaped and told that the tapes will be carefully reviewed by another expert who specializes in behavioral coding and analysis. Afterward, participants are asked to perform difficult mental arithmetic out loud in front of the expert raters (e.g., start at 1,022 and count backward by 7s, and then by 13s).

In one prototypic study that used the TSST, participants who completed the TSST in the presence of socially rejecting raters exhibited greater *in vitro* LPS-stimulated production of TNF- $\alpha$  and greater glucocorticoid resistance than those who performed the TSST in the absence of these raters, thus indicating the importance of social evaluation for inducing an heightened inflammatory response (Dickerson, Gable, et al., 2009). Perhaps most interesting is the fact that although participants judged these two experimental

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conditions to be equally challenging, controllable, and difficult, those who perceived more social evaluation in both conditions of the TSST exhibited greater increases in TNF- $\alpha$ . Moreover, these effects were robust even while adjusting for participants' perceived levels of TSST-related challenge, controllability, and difficulty.

### **Individual Differences in Inflammatory Reactivity to Laboratory-Based Stressors**

Although a complete summary of psychological processes and clinical factors that predict differences in inflammatory responding to the TSST and similar laboratory-based stressors is beyond the scope of this discussion (for reviews, see Campbell & Ehlert, 2012; Slavich & Irwin, 2014), a few example studies are useful for describing the wide variety of factors that have been found to predict stress-induced inflammatory reactivity in the laboratory. For example, in one report of two separate studies, participants reporting higher levels of trait loneliness exhibited greater LPS-stimulated production of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in response to the TSST as compared to their less lonely counterparts (Jaremka et al., 2013; see also Hackett, Hamer, Endrighi, Brydon, & Steptoe, 2012). In a second study, individuals reporting greater experiences of fear to the TSST exhibited more pronounced TSST-related increases in sTNF-RII (Moons, Eisenberger, & Taylor, 2010). In a third study, a public speaking task similar to the TSST induced significant feelings of anxiety, depression, and anger, and greater increases in anxiety and anger were, in turn, independently related to greater increases in circulating levels of IL-6 (Carroll, Low, et al., 2011). Finally, a fourth study found that individuals who had more difficulty maintaining a positive cognitive-affective state during the TSST had the greatest TSST-induced IL-1 $\beta$  reactivity, which in turn predicted their levels of depression over the following year (Aschbacher et al., 2012).

Different forms of life stress exposure and perceived stress burden have also been associated with inflammatory reactivity to stress in the laboratory. In one study, for example, greater levels of TSST-induced perceived stress predicted greater increases in TSST-induced IL-1 $\beta$  (Yamakawa et al., 2009; see also Prather et al., 2009). In a second study, more moderate-to-severe early life stress was unrelated to baseline levels of IL-6, but strongly related to participants' IL-6 reactivity to the TSST (Carpenter et al., 2010). Finally, in a third study that sampled adolescent girls at elevated risk for psychopathology, greater exposure to peer victimization predicted greater TSST-induced increases in the pro-inflammatory cytokines IL-6 and IL-1 $\beta$ ; moreover, these effects were strongest for girls reporting high levels of hopelessness (Giletta et al., 2018).

Finally, given substantial interest in the role of inflammation in depression, several studies have examined how depression levels moderate the effects of acute social stressors on inflammatory reactivity in the laboratory (for a review, see Slavich & Irwin, 2014). In one early study, depressed and nondepressed women completed a variant of the TSST, which increased levels of anxiety and shame and led to greater LPS-stimulated production of the pro-inflammatory cytokines TNF- $\alpha$  and IL-6 for both depressed and nondepressed women. As compared to nondepressed women, however, depressed women exhibited elevations in CRP that persisted following the TSST (Miller, Rohleder, Stetler, &

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Kirschbaum, 2005). In a second study that examined associations between stress-induced inflammatory activity and depression in adult males with both depression and early life stress exposure, depressed individuals with early life stress exhibited greater TSST-induced increases in IL-6 and NF- $\kappa$ B, as well as higher levels of IL-6 during the post-TSST recovery period, as compared to nondepressed males; moreover, greater depression severity was an independent predictor of participants' TSST-induced increases in both IL-6 and NF- $\kappa$ B (Pace et al., 2006). Finally, in a more recent study of adult men and women with depression, a variant of the TSST induced relatively greater increases in TNF- $\alpha$ , IL-6, and CRP in depressed versus nondepressed men and women (Weinstein et al., 2010).

### **Neural Processes Associated With Inflammatory Reactivity to Laboratory-Based Social Stress**

One of the more important frontiers in this area of research involves the examination of how neural processes regulate peripheral inflammatory activity and vice versa. Research along these lines is critical for advancing our basic mechanistic understanding of pathways that underlie inflammatory reactivity, but also for shedding light on neurocognitive processes that could potentially be modified to reduce persistent neuroimmune responses to stress and, therefore, disease risk. As a result, my lab has spent considerable time pioneering the integration of ideas and methods from psychology, neuroscience, immunology, genetics, and genomics to elucidate how psychological and neural processes regulate the immune system, and how the immune system in turn affects human behavior and disease risk.

In the first study to ever examine neurocognitive processes underlying inflammatory responding to social stress, for example, we had healthy young adults complete the TSST while we assessed their levels of IL-6 and sTNF-RII. Then, we exposed a subset of these participants to a brief experience of social rejection (i.e., using Cyberball) while we assessed their neural activity using functional magnetic resonance imaging (fMRI). Three findings were noteworthy. First, consistent with the studies described earlier, the TSST triggered significant increases in IL-6 and sTNF-RII, even though participants were relatively young and healthy. Second, the brief experience of social rejection engaged specific brain regions that prior research has shown are implicated in processing the affective component of physical pain—namely, the bilateral anterior insula and dorsal anterior cingulate cortex (dACC). Finally, greater neural activity in these particular brain regions during social rejection (vs. inclusion) was related to greater inflammatory reactivity to the TSST, thus identifying for the first time specific neurocognitive processes that are associated with inflammatory responding to acute social stress (Slavich, Way, Eisenberger, & Taylor, 2010).

We have since explored these dynamics using other types of laboratory-based social stressors. In one study, for example, we interviewed healthy young participants about their upbringing, likes and dislikes, hopes and aspirations, and personal beliefs. Then, in a subsequent study visit, participants were led to believe that another participant

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(actually a confederate) was watching their video and judging how they were coming across using a grid of characteristics that included words such as “interesting,” “friendly,” “caring,” “insecure,” “lazy,” and “arrogant.” Consistent with the neuroimaging study described above, this relatively brief, 10-minute experience of social evaluation led to significant increases in IL-6; moreover, these effects were strongest for individuals who exhibited the greatest neural activity in the left amygdala in response to negative versus neutral feedback words (Muscatell et al., 2015). In a subsequent analysis of these same participants, we found that individuals who were lower in subjective social status exhibited greater IL-6 responses to the social evaluation task, and that these effects were mediated by neural activity in the dorsomedial prefrontal cortex, which plays a role in *mentalizing*, or thinking about the thoughts and feelings of others (Muscatell et al., 2016; see also Dedovic, Slavich, Muscatell, Irwin, & Eisenberger, 2016).

Likewise, some studies have examined how experimentally induced changes in immune system function affect neural responses to social stress. In one early study, for example, healthy adults were randomized to receive either an inflammatory challenge (i.e., bacterial endotoxin) or placebo (i.e., saline) via intravenous injection. Then, participants had their brains scanned while they were socially excluded (i.e., using Cyberball). Consistent with the basic dynamics of the innate immune system described earlier, administration of bacterial endotoxin triggered significant increases in circulating levels of IL-6, in addition to physical sickness symptoms and depressive mood, and increases in IL-6 were in turn associated with greater neural activity in the anterior insula and dACC. Further confirming the likely relevance of these brain regions for inflammatory responding, activity in these specific brain areas mediated the association between endotoxin-induced increases in IL-6 and depressive mood in female (but not male) participants (Eisenberger, Inagaki, Rameson, Mashal, & Irwin, 2009).

Collectively, these neuroimmune studies provide evidence of a bidirectional link between neural and inflammatory processes that has important implications for understanding the biological bases of mental and physical health problems. Namely, whereas the former studies demonstrated that neural activity in brain regions that process experiences of physical pain is associated with inflammatory responding to acute social stress, the latter study revealed that greater endotoxin-induced increases in inflammatory activity are associated with greater activity in physical pain-related neural circuitry. I have hypothesized that this bidirectional link between neural and inflammatory processes may be critical for survival during times of physical danger to the extent that it heightens threat sensitivity and increases the production of immune factors that help accelerate wound healing and recovery. As illustrated in Figure 2, however, if this neural-immune response becomes self-promoting—for example, because of persistent neural responding to actual or perceived threat, or because of an illness or infection that prolongs the inflammatory response—then this neuro-immune dynamic could become engaged in self-promoting, recursive loop that leads to hypervigilance, threat sensitivity, and anxiety symptoms in the short term, and increases a person’s risk for potentially serious mental

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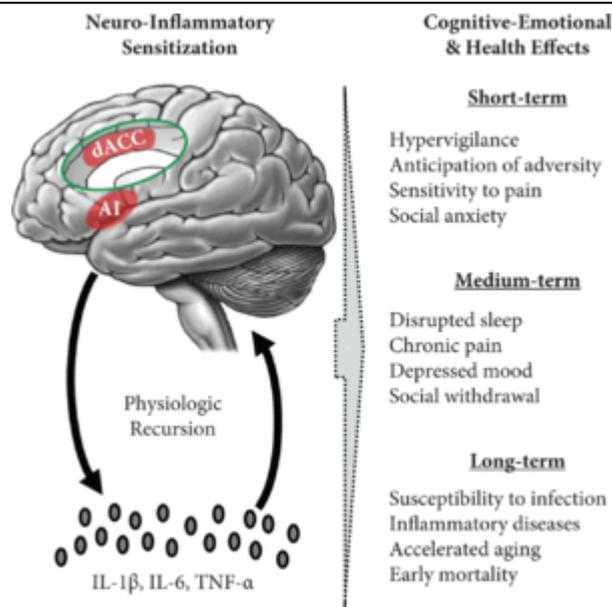
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and physical health problems over the long run (Slavich & Cole, 2013; Slavich & Irwin, 2014).

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*Figure 2* Neuro-inflammatory sensitization to adversity (see Slavich & Cole, 2013; Slavich & Irwin, 2014). Bidirectional links between the brain and periphery allow the brain to regulate inflammatory activity, and inflammatory activity to in turn influence neural processes in the brain. This dynamic is initiated by experiences of early life stress or chronic adversity, which promote a pro-inflammatory skewing of the leukocyte basal transcriptome (i.e., the CTRA) that feeds back on pain-related neural systems to perpetuate subjective perceptions of threat. Brain regions involved in this process include the anterior insula (AI) and dorsal anterior cingulate cortex (dACC, shown in the insert). As a result of this physiologic recursion, experiences of social-environmental adversity can become “biologically embedded” and sustain perceptions of threat for months or years after the original social-environmental impetus has passed. The consequences of these dynamics are multifold and start with increased hypervigilance, chronic anticipation of adversity, sensitivity to pain, and symptoms of social anxiety. As activation of the CTRA persists, somatic and affective symptoms of depression may develop. Finally, after years of sustained engagement, these dynamics may confer increased risk for inflammation-related disorders, infection, accelerated biological aging, and early mortality. Abbreviations: IL-1 $\beta$  = interleukin-1 $\beta$ , IL-6 = interleukin-6, and TNF- $\alpha$  = tumor necrosis factor- $\alpha$ . Reprinted with permission from Slavich, G. M., & Irwin, M. R. (2014).

From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, 140, 774–815. Washington, DC: American Psychological Association.

# Inflammation and Mental Health

So far, we have reviewed the basic purpose and function of the immune system, as well as some of the key neural and physiologic processes that influence immune system activity. We have also discussed how components of the immune system involved in inflammation are influenced by psychological stress. Now, we turn to the important question of how inflammatory processes are altered in the context of several major psychiatric disorders and related mental health condition—specifically, major depression, PTSD, schizophrenia, and self-harm and suicide. Finally, we examine a few recent studies that have performed comparative analyses across these disorders. The main take-home message from this body of work is that although there is substantial evidence that mental illness is associated with aberrations in immune system function, there is notable variability in these effects. In addition, we presently know very little about how mental illness-related aberrations in immune system function initially come about and how immunologic processes that are associated with these disorders give rise to specific symptoms.

## Major Depression

The most systematic evidence linking aberrant immune system function with psychiatric status is in the context of major depression (Slavich & Auerbach, 2018; Slavich & Irwin, 2014). Early on, Sigmund Freud wrote that “The complex of melancholia behaves like an open wound” (1917/1957, p. 253), but it was not until the 1960s that sickness behaviors were conceptualized as a strategy for conserving energy (Miller, 1964) and not until the 1980s that this biobehavioral response was recognized as a highly conserved, adaptive reaction to physical injury and infection (Hart, 1988). Then in the early 1990s, Ronald Smith (1991) proposed a “Macrophage Theory of Depression,” which hypothesized that cytokines might affect neural function to cause depression.

Today, five major lines of research converge to suggest that inflammation plays a prominent role in at least some forms of depression (for a review, see Slavich & Irwin, 2014). First, doctors have long noticed that depression frequently co-occurs with several physical diseases that have an inflammatory basis (Barton, 2008; Calder, 2006). These conditions include rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, coronary heart disease, and chronic pain. For example, individuals with rheumatoid arthritis and inflammatory bowel disease are two-to-three times more likely to have major depression than the general population (Graff, Walker, & Bernstein, 2009; Katz & Yelin, 1993; Regier et al., 1988), and the prevalence of depression in individuals experiencing chronic pain is as high as 86% (Poole, White, Blake, Murphy, & Bramwell, 2009; see also Bair et al., 2004). Second, depression is consistently associated with elevations in several markers of inflammatory activity, including IL-1, IL-6, TNF- $\alpha$ , and CRP (Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012; Howren, Lamkin, & Suls, 2009), and elevations in these biomarkers appear to precede the development of depression in many cases (Gimeno et al., 2009; van den Biggelaar et al., 2007).

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These lines of research provide data that are largely correlational, but a third line of work has shown that immunologic challenges that upregulate inflammatory activity, such as IFN- $\alpha$  administration, typhoid vaccination, and endotoxin administration, frequently trigger depressive-like behaviors in animal model systems of depression and diagnosable forms of major depressive disorder (MDD) in humans. For example, up to 50% of patients receiving IFN- $\alpha$  for the treatment of hepatitis C and cancer have been observed to subsequently develop MDD (Capuron & Miller, 2004; Raison et al., 2006). Likewise, typhoid vaccination has been found to induce increases in negative mood, confusion, and fatigue, which are mediated by increases in IL-6 (Harrison et al., 2009; Strike, Wardle, & Steptoe, 2004; Wright, Strike, Brydon, & Steptoe, 2005), and bacterial endotoxin has been found to elicit heightened anxiety, as well as sad mood, anhedonia, cognitive impairment, fatigue, reduced food intake, altered sleep, and social-behavioral withdrawal (for a review, see DellaGioia & Hannestad, 2010). Fourth, each of these three inflammatory challenges has been shown to alter metabolic or neural activity in brain regions that have been implicated in depression, including the basal ganglia, cerebellum, ACC, and ventral striatum. In one study, for example, long-term administration of IFN- $\alpha$  was associated with reduced neural responses to a hedonic reward task in the bilateral ventral striatum, which is involved in reward-related responding, and this reduced activity was in turn correlated with greater symptoms of anhedonia, depression, and fatigue (Capuron et al., 2012). Similar neural changes have been reported following bacterial endotoxin administration as well (Eisenberger, Berkman, et al., 2010).

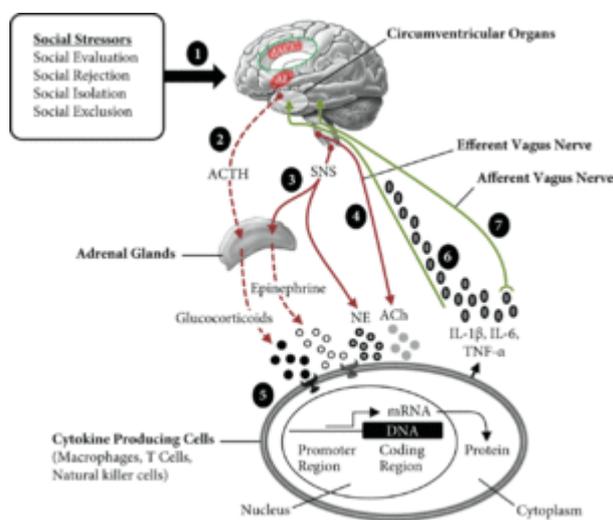
Finally, at least three anti-inflammatory agents have been found to alleviate depressive symptoms in double-blind, randomized, placebo-controlled studies. These agents include celecoxib, which is a cyclooxygenase (COX)-2 inhibitor commonly used for treating excessive inflammation and pain, and the TNF- $\alpha$  antagonists etanercept and infliximab, which are used to treat rheumatoid arthritis, psoriasis, and other inflammatory conditions. In one recent double-blind, placebo-controlled study, for example, 60 outpatients with treatment-resistant depression were randomly assigned to receive either three infusions of the TNF- $\alpha$  antagonist infliximab or placebo at baseline, week 2, and week 6 of a 12-week clinical trial (Raison et al., 2013). Although no overall differences in depression severity were found between the two groups over the trial, 62% of infliximab-treated patients with starting CRP levels above 5 mg/L exhibited a treatment response (i.e.,  $\geq 50\%$  reduction in depressive symptoms during the trial) as compared to only 33% of placebo-treated patients. Interestingly, clinical improvements were seen across a variety of symptoms, including anxiety and depressive symptoms, psychomotor retardation, suicidal ideation, and behavioral motivation and performance. Consistent with the possibility that these improvements were mediated by changes in inflammatory activity, infliximab-treated responders showed significantly greater decreases in levels of CRP from baseline to week 12 as compared to placebo-treated responders (Raison et al., 2013).

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## Social Signal Transduction Theory of Depression

Collectively, this research has provided the empirical basis for the first fully integrated, multilevel theory of depression, called *social signal transduction theory of depression*, which describes the full set of social, psychological, and biological mechanisms linking experiences of social stress with risk for depression (see Figure 3; Slavich & Irwin, 2014). According to this theory, social stressors that historically increased an organism's risk for physical threat, such as those involving social conflict, isolation, rejection, and exclusion, are represented by neural systems that process the affective and interoceptive aspects of physical and social pain, including the anterior insula and dACC. These regions in turn project to lower level brain regions, including the hypothalamus and brainstem autonomic control nuclei, which modulate the activity of the HPA axis and SNS—and therefore the production of cortisol, epinephrine, norepinephrine, and acetylcholine—which in turn influence systemic inflammatory activity. Whereas cortisol and acetylcholine typically suppress (but can also increase) inflammatory activity, epinephrine and norepinephrine both promote inflammation by inducing the activation of the intracellular transcription factors NF- $\kappa$ B and AP-1, which upregulate the expression of pro-inflammatory immune response genes, including *IL1B*, *IL6*, *IL8*, and *TNF*. Expression of these genes ultimately leads to the production of pro-inflammatory cytokines that induce depressive symptoms such as sad mood, anhedonia, fatigue, psychomotor retardation, and social-behavioral withdrawal, in addition to other cognitive, affective, and somatic phenomena that often co-occur with depression—namely, increased hypervigilance, anxiety, and pain sensitivity. The central nervous system can also influence peripheral inflammation via efferent vagus nerve activity, which downregulates inflammation by strongly suppressing *TNF* gene transcription.



*Figure 3* Social signal transduction theory of depression (see Slavich & Irwin, 2014). Social signal transduction theory of depression describes mechanisms that convert, or *transduce*, experiences of the external social environment into the internal biological environment of depression pathogenesis. (1) Social-environmental experiences indicating possible social threat or adversity (e.g., social conflict,

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evaluation, rejection, isolation, or exclusion) are represented neurally, especially in brain systems that process experiences of social and physical pain. Key nodes in this neural network include the anterior insula (AI) and dorsal anterior cingulate cortex (dACC, shown in the insert). These regions project to lower level brain areas (e.g., hypothalamus, brainstem autonomic control nuclei) that have the ability to initiate and modulate inflammatory activity via three pathways that involve (2) the hypothalamic-pituitary-adrenal axis, (3) sympathetic nervous system, and (4) efferent vagus nerve. (5) Activation of these pathways leads to the production of glucocorticoids, epinephrine, norepinephrine, and acetylcholine, which interact with receptors on cytokine producing cells. Whereas glucocorticoids and acetylcholine have anti-inflammatory effects, epinephrine and norepinephrine activate intracellular transcription factors (e.g., nuclear factor- $\kappa$ B and activator protein 1) that bind to *cis*-regulatory DNA sequences to upregulate inflammatory gene expression. When this occurs and immune response genes are expressed, DNA is transcribed into RNA and then translated into protein. The resulting change in cell function leads to the production of pro-inflammatory cytokines (e.g., interleukin-1 $\beta$ , interleukin-6, tumor necrosis factor- $\alpha$ ) that signal the brain to induce cognitive, emotional, and behavioral alterations that include several hallmark symptoms of depression (e.g., sad mood, anhedonia, fatigue, psychomotor retardation, altered appetite and sleep, and social-behavioral withdrawal). Cytokines can exert these effects on the central nervous system by (6) passing through "leaky" or incomplete regions of the blood-brain barrier (e.g., circumventricular organs, organum vasculosum of the lamina terminalis) and by (7) stimulating primary afferent nerve fibers in the vagus nerve, which relays information to brain systems that regulate mood, motor activity, motivation, sensitivity to social threat, and arousal. Bidirectional communication between the brain and peripheral immune system may also occur via meningeal lymphatic vessels, along which cytokines have been shown to travel (not shown). Although these neurocognitive and behavioral responses are adaptive during times of actual threat, these social signal transduction pathways can also be initiated by purely symbolic, anticipated, or imagined threats—that is, situations that have not yet happened or that may never actually occur. Moreover, activation of these pathways can become self-promoting over time due to neuro-inflammatory sensitization and, as a result, remain engaged long after an actual threat has passed. In such instances, these dynamics can increase risk for depression in the short term, and possibly promote physical disease, accelerate biological aging, and hasten mortality over the long run. Abbreviations: ACTH = adrenocorticotropic hormone, SNS = sympathetic nervous system, NE = norepinephrine, ACh = acetylcholine, mRNA = messenger ribonucleic acid, IL-1 $\beta$  = interleukin-1 $\beta$ ,

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IL-6 = interleukin-6, and TNF- $\alpha$  = tumor necrosis factor- $\alpha$ . Reprinted with permission from Slavich, G. M., & Irwin, M. R. (2014).

From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, 140, 774–815. Washington, DC: American Psychological Association.

Ultimately, this highly conserved, biological response to adversity is critical for survival during times of actual physical threat insofar as it prepares the body to deal

with physical wounding and infection, should they occur. In the present-day social environment, however, these social signal transduction pathways are most frequently activated not by impending *physical danger*, but by contemporary *social threats*, including those that are purely symbolic, anticipated, or imagined. It is under these social-environmental conditions, therefore, that this biological response can lead to an increasingly pro-inflammatory phenotype that is hypothesized to be a key phenomenon driving depression pathogenesis and recurrence, as well as the overlap of depression with several somatic conditions including asthma, rheumatoid arthritis, chronic pain, metabolic syndrome, cardiovascular disease, obesity, and neurodegeneration (for a complete overview, see Slavich & Irwin, 2014).

### Posttraumatic Stress Disorder

The second largest literature on inflammation and mental health involves PTSD. There are several reasons for this, including the fact that (a) life stress exposure, which is known to increase inflammation, is the main psychosocial precipitant of the disorder; (b) cytokines are known to induce hypervigilance, which is a cardinal symptom of PTSD; and (c) many individuals with PTSD develop somatic health problems that have an inflammatory basis, including chronic pain, heart disease, diabetes, and neurodegeneration (O'Donovan & Neylan, 2017). Overall, studies examining associations between inflammation and PTSD have yielded mixed findings. At the same time, recent meta-analyses have found that, on average, concentrations of inflammatory markers are substantially higher in patients with PTSD compared to psychiatrically healthy controls.

In one recent meta-analytic review and metaregression that examined 20 different studies, levels of IL-1 $\beta$ , IL-6, and IFN- $\gamma$  were found to each be significantly elevated in patients with PTSD versus psychiatrically healthy individuals. Follow-up analyses revealed several interesting findings. For example, longer duration of PTSD symptoms was associated with higher levels of IL-1 $\beta$ ; greater PTSD severity was associated with higher IL-6 levels; and levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  were significantly elevated in PTSD patients even when those with comorbid MDD were excluded from analyses. Finally, in the metaregression analysis, four factors that are known to influence levels of inflammatory activity—namely, presence of comorbid MDD, psychotropic medication use, type of immunologic assay used, and time of blood collection—explained substantial proportions of the heterogeneity across studies. Impressively, these four factors alone explained 100% of the heterogeneity for studies assessing IL-1 $\beta$ , 100% for studies assessing CRP, and 79.9% for studies assessing IL-6. In sum, therefore, inflammatory activity appears to be elevated in PTSD in a manner that is at least somewhat

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independent of depression, and the heterogeneity that has been observed in these effects across studies of PTSD (and possibly other disorders) may be attributable to a relatively few clinical and technical factors (Passos et al., 2015).

### **Schizophrenia**

Schizophrenia is a particularly complicated disorder from a pathophysiology standpoint. One of the most widely reported findings, though, is that risk for the disorder is associated with pre- and perinatal exposure to several adverse events that substantially upregulate inflammatory activity, including exposure to infections (Brown, 2006; Mednick, Huttunen, & Machon, 1994) and to prenatal life stressors, such as the loss of a father during pregnancy (Huttunen & Niskanen, 1978; see also Malaspina et al., 2008). Several other findings also argue for a potentially important role of cytokines in risk for schizophrenia. For example, life stressors that are known to trigger increased pro-inflammatory cytokine activity frequently precipitate symptom exacerbation in schizophrenia (Kinney et al., 2010), and prenatal maternal stress is associated with levels of cytokine activity that equal to those seen in persons experiencing chronic stress (Entringer et al., 2008). Perhaps more directly, genetic studies have shown that alleles that are associated with increased risk for schizophrenia also affect the structure of receptors for pro-inflammatory cytokines in addition to the expression of those cytokines (Lencz et al., 2007). Finally, neurobiological mechanisms have been described that link excessive inflammatory responding with an imbalance of glutamatergic and dopaminergic neurotransmission that may in turn promote both psychotic symptoms (Müller & Schwarz, 2006) and a progressive loss of brain tissue that in turn contributes to cognitive deficits evident in individuals with the disorder (Monji, Kato, & Kanba, 2009).

Finally, evidence from postmortem studies also supports a role for inflammation in schizophrenia. In a recent meta-analytic review of 41 postmortem studies that included brains from 783 patients with schizophrenia and 762 psychiatric controls, for example, analyses revealed significantly higher density of microglia in the brains of patients with schizophrenia as compared to healthy control participants, with these neurobiological alterations most frequently being seen in the temporal cortex. Moreover, patients with schizophrenia were found to exhibit significantly greater pro-inflammatory gene expression and higher pro-inflammatory cytokine levels, as compared to their nonaffected counterparts (Van Kesteren et al., 2017). Ultimately, although we are still far from having a comprehensive, biologically grounded theory of schizophrenia that describes exactly how the immune system is involved in this complex disorder, some promising integrative models have been proposed that help explain several features of the disorder (e.g., Kinney et al., 2010).

### **Self-Harm and Suicide**

Research has also examined associations between inflammation and suicidal behavior. As with all psychiatric conditions other than major depression, the specific inflammatory mechanisms that might give rise to self-harm and suicide remain poorly understood.

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Nevertheless, in one recent meta-analysis that examined associations between suicidality and cytokine levels in blood, cerebrospinal fluid (CSF), and postmortem tissue across 18 studies ( $N = 583$ ), levels of IL-1 $\beta$  and IL-6 were elevated in both blood and in the postmortem brain samples of individuals with suicidality as compared with both patients without suicidality and healthy controls. Moreover, individuals' inflammatory levels were able to distinguish psychiatric patients with suicidality from psychiatric patients without suicidality and healthy controls. The meta-analysis also found that CSF levels of IL-8 were lower in individuals exhibiting suicidal behavior (Black & Miller, 2015).

Given these associations between inflammation and suicide, some researchers have recently begun examining pathways underlying these links. In one recent study, investigators quantified levels of TNF- $\alpha$  gene expression and related factors in the dorsolateral prefrontal cortex of the postmortem brains of individuals who died by suicide with depression versus with other psychiatric disorders (cohort 1), and of those with depression who died of suicide versus non-suicide-related causes (cohort 2). Consistent with a potential role for inflammation in suicide, TNF- $\alpha$  expression was greater in the dorsolateral prefrontal cortex of individuals who died by suicide than of those who died of non-suicide-related causes, regardless of their psychiatric diagnosis (i.e., depressed or other psychiatric disorder). Furthermore, in a separate cohort, the authors found that TNF- $\alpha$  expression was elevated in persons diagnosed with MDD regardless of how they died (i.e., suicide or non-suicide-related causes), as compared to nondepressed individuals who passed away. Finally, the authors found that expression of a microRNA involved in pro-inflammatory cytokine regulation (i.e., miR-19a-3p) was specifically upregulated in individuals who died by suicide (Wang, Roy, Turecki, Shelton, & Dwivedi, 2018).

Given the fact that suicide is presently the second leading cause of death in young adults worldwide (WHO, 2012), there is clearly a pressing need to better understand the biological basis of this phenomenon. Several interesting conceptual and integrative reviews have recently attempted to clarify this pathophysiologic picture (e.g., Brundin, Bryleva, & Rajamani, 2017; Serafinia et al., 2013; Slavich & Auerbach, 2018). At present, however, the number of studies is relatively limited, the results are somewhat mixed, and it remains unclear to what extent cytokine activity can specifically induce suicidal behavior.

### Comparative Reviews

Finally, at least two studies have compared inflammatory marker levels across different psychiatric disorders. The first meta-analysis examined 28 studies that assessed CSF cytokine and tryptophan catabolites in patients with MDD, bipolar disorder, and schizophrenia. CSF levels of IL-1 $\beta$  and kynurenic acid were significantly higher in patients with bipolar disorder and schizophrenia compared to healthy controls. In addition, CSF levels of IL-6 and IL-8 were found to be significantly higher in patients with schizophrenia and MDD compared to healthy controls (Wang & Miller, 2017). The second meta-analysis examined 115 studies that assessed cytokine levels in blood in acutely and

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chronically ill patients with MDD, bipolar disorder, and schizophrenia. Levels of IL-6, TNF- $\alpha$ , a soluble receptor for IL-2 (sIL-2R), and a cytokine receptor antagonist (IL-1RA) were significantly higher in acutely ill patients with MDD, bipolar mania, and schizophrenia compared to healthy controls. Moreover, treatment was associated with significant reductions in levels of IL-6 in both MDD and schizophrenia, significant reductions in levels of IL-1RA in bipolar mania, and significant increases in levels of sIL-2R in schizophrenia. In chronically ill patients, levels of IL-6 were significantly elevated in patients with MDD, euthymic (but not depressed) bipolar disorder, and schizophrenia as compared with controls, as were levels of IL-1 $\beta$  and sIL-2R in patients with both chronic schizophrenia and euthymic bipolar disorder (Goldsmith, Rapaport, & Miller, 2016).

Although theoretical perspectives on how and why immune markers are altered across different psychiatric disorders is presently limited, one possibility is that it occurs as a result of stress-induced activation of central and peripheral immune cells, which in turn synthesize and release cytokines into circulation (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017). This possibility is consistent with the social signal transduction theory of depression described earlier, and also with the finding that some disorders—especially those involving anxiety and fear—are associated with increased sympathetic tone and decreased parasympathetic activity, which is known to upregulate inflammation. However, much more research is needed to fully understand these issues.

## Future Directions

Considered together, the literatures reviewed here provide substantial evidence that stress alters immune system activity, and that several immune markers are altered in persons with mental health problems. At the same time, numerous issues remain unresolved, thus highlighting several avenues for future research on stress, the immune system, and mental health. I summarize some of the main avenues next.

1. As reviewed here, there is growing evidence that not all stressors have the same impact on inflammatory biology or health (Monroe, Slavich, Torres, & Gotlib, 2007; Slavich, Monroe, & Gotlib, 2011; Slavich, O'Donovan, et al., 2010; Slavich & Irwin, 2014; Slavich, 2016). Moreover, there is great variability in how “stress” is defined and assessed (Epel et al., 2018; Harkness & Monroe, 2016). One critical avenue for future research, therefore, is to better standardize assessment procedures and to examine what types of stress are most strongly related to different aspects of immune system function and health. Such studies could examine the effects of acute versus chronic stressors, as well as those occurring during different periods of life, across different life domains (e.g., work, finances, intimate relationships), and involving different social-psychological characteristics (e.g., interpersonal loss, physical danger, humiliation, entrapment) (Slavich, in press).
  2. Relatedly, although numerous theoretical papers have discussed how lifetime stress exposure might impact biological functioning and health, the number of
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studies that have actually assessed acute and chronic stress exposure over the entire life course is extremely small (Malat, Jacquez, & Slavich, 2017; Shields & Slavich, 2017). Therefore, much more research is required to understand how stressors occurring over the life course exert a cumulative impact on immune system function. Such work could examine important questions concerning whether there are sensitive or critical periods for damaging effects, as well as whether there are specific periods during which time reversibility is possible. I have developed the Stress and Adversity Inventory (STRAIN) to allow investigators to quickly assess lifetime stress exposure in an efficient and reliable manner in both adolescents (Slavich, Stewart, Esposito, Shields, & Auerbach, in press) and adults (Slavich & Shields, 2018), and the resulting lifetime stress exposure scores have been shown to predict several cognitive, biological, and health-related outcomes (e.g., Cuneo et al., 2017; Goldfarb, Shields, Daw, Slavich, & Phelps, 2017; Toussaint, Shields, Dorn, & Slavich, 2016). However, more work is needed to link these scores to the specific immune markers and disorders describe here.

**3.** Despite the main finding that levels of inflammation are elevated in the context of psychiatric illness, there is substantial variability in these levels across individuals. Therefore, more research is needed to elucidate factors that are associated with elevated inflammatory activity in both psychiatrically healthy and psychiatrically ill individuals. Given the multitude of biobehavioral factors that can affect immune system function, such work could assess some combination of individuals' life stress exposure and subjective experience, diet, sleep, exercise, pollution exposure, vaccination and illness history, and genetic profile, to name a few. This research will be important for understanding factors that moderate individuals' inflammatory levels, but it will also be critical for shedding light on the extent to which aberrant immune system function is an inherent biological feature of some disorders, or certain disorder subtypes, versus merely a concomitant of those disorders.

**4.** Given the involvement of stress in increasing inflammatory activity and the role that inflammation plays in several major chronic diseases, additional research is sorely needed to identify neurocognitive processes that influence inflammatory reactivity to stress that could be potentially targeted to reduce inflammation and improve human health. We have identified neural responsivity to social threat and exclusion as one such process (Slavich, Way, et al., 2010), as well as cognitive control of emotional information (Shields, Young Kuchenbecker, Pressman, Sumida, & Slavich, 2016). However, other cognitive-emotional process that are involved in stress reactivity might also play a role, including those involved in attention and memory for social- and stress-related information, as well as negative affective responding and emotion regulation.

**5.** Finally, despite the possibility that targeting inflammatory processes could help reduce chronic disease risk, relatively little is presently known about different psychosocial and psychopharmacological interventions that could have a salutary effect on immune system function and mental and physical health. As we have reviewed elsewhere (e.g., Black & Slavich, 2016; Slavich & Irwin, 2014), reduced inflammation has been associated with the administration of at least three

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psychosocial interventions, including cognitive-behavioral stress management, mindfulness-based stress reduction, and Kirtan Kriya meditation, as well as with several psychopharmacological interventions, including the TNF- $\alpha$  antagonists etanercept and infliximab, the COX-2 inhibitor celecoxib, and omega-3 fatty acid supplementation. However, the total number of intervention studies that have been conducted to date is still relatively small, and the findings across these studies are not wholly consistent. Therefore, several important questions remain unanswered, including, for example, which patients benefit most from targeting inflammatory pathways and which do not see any improvement (and why)? What are the specific multilevel mechanisms of action? And do these interventions have effects on symptom severity, clinical course, or likelihood of recurrence in a manner that is mediated by intervention-related reductions in inflammatory activity?

## Conclusion

In conclusion, we are presently experiencing a watershed moment in the search for processes that underlie several major psychiatric disorders, and many of the most exciting discoveries on this topic are employing ideas and methods from PNI. This research has already elucidated entirely new bodily structures that link the brain and peripheral immune system, revealed the broad extent to which stress alters immune system activity, and highlighted the role the immune system plays in promoting certain psychiatric symptoms. This work has also led to the identification of immune mediators that could potentially be targeted to reduce disease burden and improve human health. However, numerous questions remain unanswered, and many of the most important and clinically relevant discoveries still lie ahead. Addressing these issues will not be easy, and it will require individuals who possess the desire and training needed to combine methods from psychology, neuroscience, immunology, genetics, and genomics. However, the upside potential is huge, as this work will undoubtedly contribute greatly to our understanding of the social, psychological, and biological bases of mental and physical health.

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