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Psychoneuroimmunology: An Introduction to Immune-to-Brain Communication and Its Implications for Clinical Psychology

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Abstract

Research conducted over the past several decades has revolutionized our understanding of the role of the immune system in neural and psychological development and function across the life span. Our goal in this review is to introduce this dynamic area of research to a psychological audience and highlight its relevance for clinical psychology. We begin by introducing the basic physiology of immune-to-brain signaling and the neuroimmune network, focusing on inflammation. Drawing from preclinical and clinical research, we then examine effects of immune activation on key psychological domains, including positive and negative valence systems, social processes, cognition, and arousal (fatigue, sleep), as well as links with psychological disorders (depression, posttraumatic stress disorder, anxiety, schizophrenia). We also consider psychosocial stress as a critical modulator of neuroimmune activity and focus on early life adversity. Finally, we highlight psychosocial and mind–body interventions that influence the immune system and may promote neuroimmune resilience.

Contents

1. INTRODUCTION

Inflammation: immune response to infection, tissue damage, or stress, coordinated by proinflammatory cytokines including interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha

Sickness behavior: constellation of behavioral changes induced by inflammation designed to protect the host and promote healing

The field of psychoneuroimmunology (PNI) examines the bidirectional interactions between the brain, behavior, and immunity and the effect of these interactions on mental and physical health. Research on neuroimmune interactions developed in the 1970s, and the term PNI was coined in the 1980s by Robert Ader, who edited the first edition of the classic *Psychoneuroimmunology* textbook and helped to establish the legitimacy of this fledgling discipline (Ader 2000). Initially, research in PNI focused primarily on brain-to-immune signaling, yielding invaluable insights into neural regulation of immunity (Irwin & Cole 2011) and the effects of stress, social relationships, and other psychosocial factors on immune status and physical health (Glaser & Kiecolt-Glaser 2005). The relevance of this work has accelerated in recent years with the discovery that inflammation, a key component of the immune response, plays a prominent role in the onset and progression of many chronic diseases (Furman et al. 2019).

The last several decades have seen a shift in PNI research with more attention on the bottom-up effects of the immune system on the brain and psychological processes. In 1998, Steve Maier and Linda Watkins published an influential paper titled "Cytokines for Psychologists" that provided an accessible introduction to immune-to-brain communication for a psychological audience and raised exciting new questions and ideas about the role of the immune system in mental health and illness (Maier & Watkins 1998). Research in this area initially focused on sickness behavior and depression and has continued to advance our understanding of the intimate connections between

the central nervous system (CNS) and immune system and their role in a range of psychological and neurological symptoms and disorders.

We now know that the immune system plays a central role in how we think, feel, and behave, both in sickness and in health. The goal of this review is to provide an overview of this area of research with a focus on implications for clinical psychologists. We begin with an introduction to the immune system and immune-to-brain signaling pathways that is intended for readers who are new to this area of work. We then consider the following questions, which are motivated in part by our own programs of research:

1. What is the impact of immune activity on key dimensions of psychological functioning, and is this relevant for psychological disorders?
2. What is the effect of psychological stress on the neuroimmune network, and are there risk factors that moderate these effects?
3. How does early life adversity (ELA) become embedded in the immune system, and what are the implications for long-term health?
4. Can psychosocial interventions be used to influence immune activity, and what are the mechanisms through which this occurs?

In reviewing this literature, we hope to convey the excitement of this dynamic field and its potential for understanding and improving health and well-being.

Cytokine: type of protein released by immune (and nonimmune) cells that is responsible for communication between cells

Pathogen: disease-causing microorganism, such as a virus or bacterium

Macrophage: type of immune cell that responds to infection or injury by engulfing pathogens and coordinating the inflammatory response

Monocyte: type of immune cell that responds to infection or injury; monocytes circulate in the blood and develop into macrophages when they move into tissue

Phagocytosis: process through which macrophages ingest large particles (such as bacteria) or other cells (such as those that have sustained damage)

2. INTRODUCTION TO THE IMMUNE SYSTEM

The immune system is designed to detect and protect the body from infection, injury, and damage. It is a complex, multifaceted system encompassing a range of cells, organs, and signaling molecules called cytokines that work together to maintain bodily integrity. For the purposes of this review, we focus on cells and cytokines that are most relevant for immune-to-brain communication.

2.1. Innate and Adaptive Immunity

The immune system can be broadly divided into two arms: innate and adaptive. The innate immune system responds quickly to a wide range of pathogens and danger signals (such as those released by dying or damaged cells). One of the key cell types of the innate immune system is the macrophage, which is found in most tissues in the body. Macrophages are derived in part from monocytes, which are found in the blood. When these cells encounter evidence of infection or damage, they initiate an inflammatory response by releasing specialized proinflammatory cytokines. These cytokines act locally (i.e., in the area where the pathogen or injury is encountered) to facilitate the movement of other immune cells into the infected area and systemically (i.e., throughout the rest of the body) to cause fever and other physiological and behavioral changes (see Section 3). Together, these effects are designed to neutralize and eradicate the threat. Macrophages also help to clear pathogens and damaged cells through phagocytosis.

The adaptive immune system provides a second line of defense for pathogens that cannot be eradicated by the innate immune system alone. This system is more targeted and takes time (i.e., days) to develop and mobilize the cells that are specific to a particular pathogen. The key cell types of the adaptive immune system are T and B cells. There are several types of T cells, each with different functions: CD4 (helper) T cells help coordinate the adaptive immune response, CD8 (cytotoxic) T cells identify and kill infected cells, and CD17 (regulatory) T cells help regulate immune function. B cells are responsible for making antibodies and are essential fighters against pathogens that circulate outside of the cell. One of the distinguishing features of the adaptive immune system is memory; after infection with a particular pathogen, memory cells remain in the body and can respond more rapidly to a second exposure.

2.2. Cytokines

Cytokines are small proteins released by immune and nonimmune cells that are responsible for communication between cells. Typically, cytokines are produced briefly and locally in a self-limiting manner. However, in the context of illness, infection, or other immune challenge, levels can increase dramatically (i.e., 100-fold increase in certain cytokines after administration of endotoxin) and may remain elevated at subclinical levels in certain contexts (e.g., persistent infection, chronic stress). The cytokine network is extremely complex; cytokines are pleiotropic and can act on multiple cell types with different effects depending on the nature of the stimulus and the host. That said, one useful distinction is between cytokines that promote inflammation (proinflammatory cytokines) and those that reduce inflammation (anti-inflammatory cytokines). Canonical proinflammatory cytokines include tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 (although IL-6 also has anti-inflammatory effects in certain contexts). Anti-inflammatory cytokines include IL-4 and IL-10. Importantly, cytokines and other biomarkers are produced by both immune and nonimmune cells in response to a variety of stimuli. Thus, it can be challenging to interpret the origin and function of circulating concentrations of these markers. For example, adipocytes (fat cells) can produce cytokines, which may have little to do with infection. For this reason, it is common to account for participant BMI or central adiposity in analyses involving circulating inflammatory proteins (O'Connor et al. 2009).

Endotoxin: toxin found on the outer membrane of gram-negative bacteria that activates an inflammatory response; also referred to as lipopolysaccharide (LPS)

Microglia: type of immune cell in the brain that plays a critical role in its normal development and function

Blood–brain barrier (BBB): term describing the unique properties of blood vessels in the brain that tightly regulate movement of ions, molecules, and cells

Peripheral immunity: immune processes occurring outside of the central nervous system

2.3. Immune Cells in the Brain

The primary immune cells in the brain are the microglia, which are the macrophages of the CNS. Historically, glial cells (including microglia, astrocytes, and oligodendrocytes) have received little attention from neuroscientists despite constituting half of the cells in the CNS (Azevedo et al. 2009). However, major developments in this field have generated new insight into the critical role of microglia and other immune cells in the adaptive functioning of the brain. Microglia, like other macrophages, survey their environment for threat and respond to infection and injury by eliciting an inflammatory response when necessary. Microglia are also critically important for the normal development and functioning of the brain across the life span (Dziabis & Bilbo 2022, Yirmiya & Goshen 2011). Indeed, alterations in microglia activation have been implicated in neurodevelopmental, psychiatric, and neurodegenerative disorders. In addition to microglia, various nonneuronal cells in the brain are relevant for psychological processes, including other glial cells as well as T cells and other cells of the innate and adaptive immune systems (Cathomas et al. 2022, Korin et al. 2017).

2.4. Blood–Brain Barrier and Brain Borders

The brain has historically been considered immune privileged; that is, cells and molecules of the immune system cannot easily access the brain. This protection comes from the blood–brain barrier (BBB), which is made up of specialized endothelial cells (on the blood side), pericytes, and astrocytes (on the brain side). However, this idea has evolved over time, and the BBB is increasingly understood as a dynamic interface that serves not only to protect the brain but also to regulate the effect of peripheral immune activity on the CNS. The interface functions of the BBB are achieved through transport systems that carry molecules across the BBB, production and secretion of molecules by cells of the BBB that act on the brain, and BBB response to stimuli arising outside and within the brain (Erickson & Banks 2018). The state of the BBB is influenced by both pathological (e.g., traumatic brain injury) and physiological (e.g., inflammation) states.

There are also immune cells in the meninges, the triple-layered membrane that surrounds the brain. Macrophages appear to be the major cell type in this compartment, but various other

immune cell types have been identified, including T cells (Korin et al. 2017). Meningeal immune cells are well positioned to influence the CNS; indeed, meningeal T cells have been shown to affect social behavior, cognitive function, and anxiety through release of specific cytokines (Alves de Lima et al. 2020). The role of immune cells in these border regions of the brain is just beginning to be defined and represents an exciting new frontier in PNI research as major discoveries reshape our understanding of immunity and the brain.

C-reactive protein (CRP): protein produced by the liver in response to IL-6 stimulation; used as a measure of systemic inflammation

Maternal immune activation (MIA): experimental model that involves activating the immune system of a pregnant dam and evaluating effects on her offspring

2.5. Immune Measurement

The primary method for measuring the immune system in humans is through blood collection. Blood samples can be used to assess different types of immune cells, cytokines, and other markers of inflammation [e.g., C-reactive protein (CRP)] and immune activity (e.g., antibodies) as well as genes being expressed by circulating immune cells. Blood is typically collected through venipuncture; however, new techniques allow blood sampling without specialized personnel or equipment, facilitating research in larger and more diverse samples. Other components of the neuroimmune network are more difficult to assess in living humans. In particular, techniques for in vivo imaging of microglia structure and function are currently quite limited, as are approaches to measuring the BBB. The development of new techniques to more directly access immune processes in the brain and brain borders in healthy and clinical populations is critical for advancing our understanding of neuroimmune interactions.

2.6. Neuroimmune Interactions During Development

There is increasing evidence that immune cells, specifically microglia, shape neural development (Reemst et al. 2016). Microglia are long-lived cells that travel to the brain early in fetal development and reside there throughout the life span. One of the primary purposes of microglia is phagocytosis. Throughout human development, the brain undergoes rapid periods of neuronal and synaptic pruning to clear away cells and debris that are decreasing the organism's efficiency or are no longer functioning properly. Microglia and other immune cells are the executors of this critical neurodevelopmental process. Thus, it is hypothesized that immune activation during phases of rapid neurodevelopment can distract microglia from this important activity, with detrimental and long-term effects on the brain and behavior (Dziabis & Bilbo 2022, Reemst et al. 2016).

The periods of human development when immune activation can derail the microglia from their phagocytic responsibilities are the first trimester of human pregnancy, when microglia are first entering what will become the CNS; the first year of human life, when experience-dependent pruning first occurs; and adolescence, when cortical and subcortical neuronal circuits are being pruned, myelinated, and refined for adulthood (Dziabis & Bilbo 2022). One of the earliest phagocytic activities is pruning the neural precursor cell population. Preclinical models have demonstrated that activation of microglia in the developing fetal brain using maternal immune activation (MIA) leads to too few neural precursor cells, whereas pharmacologically blocking microglia activity leads to too many (Cunningham et al. 2013). Importantly, MIA-induced microglia alterations have been linked with development of schizophrenia- and autism-like behaviors (see Section 3.5).

Infection in the early postnatal period is also associated with behavioral changes, particularly in the context of a later immune challenge. In particular, early infection leads to a sensitization or priming of the microglia that manifests as changes in mood, cognition, and neural function following exposure to infection or psychosocial stress in later life (Bilbo & Schwarz 2012, Giovanoli et al. 2013). In addition, immune activation during adolescence appears to have profound effects on cognition and behavior, though research in this area is more limited and primarily focused on substance use. For example, morphine activates microglia in the adolescent rat nucleus

accumbens, leading to the secretion of proinflammatory cytokines and morphine-induced conditioned place preference in adulthood (Schwarz & Bilbo 2013). Further, a single episode of binge alcohol exposure during adolescence can activate microglia in the hippocampus well into early adulthood (McClain et al. 2011).

3. IMMUNE EFFECTS ON THE BRAIN AND BEHAVIOR

3.1. Signaling Pathways from the Periphery to the Brain

How does the brain learn about immune events occurring in the body? To date, three major pathways have been identified: neural, humoral, and cellular. In the neural pathway, immune cells in the periphery release proinflammatory cytokines that are detected by afferent sensory nerves, including the vagus nerve. The vagus transmits these signals to the brain stem and then to higher brain regions, allowing coordination of an overall sickness response (see Section 3.2). In the humoral pathway, cytokines in the blood transmit signals to the brain through more porous regions of the BBB or through active transport mechanisms. Transport of different cytokines varies by brain region, and this variance has implications for effects of specific cytokines on neural activity and behavior. In the cellular pathway, which is the most recently identified, activated microglia recruit monocytes from the peripheral blood into the brain parenchyma. Of note, monocytes appear to traffic to specific regions of the brain, including regions relevant to mood and anxiety (i.e., basal ganglia, amygdala, prefrontal cortex, hippocampus), at least in preclinical models of chronic stress (Reader et al. 2015).

3.2. Effects of Peripheral Immune Activation on the Brain and Behavior

After detection of infection or tissue injury, immune cells produce proinflammatory cytokines that signal the brain to help coordinate a whole-body response (Dantzer & Kelley 2007). This inflammatory signal propagates in the brain, activating microglia and eliciting a range of effects on neurotransmitters and neural processes. These include effects on the availability and activity of monoamines (serotonin, dopamine, noradrenaline) and glutamate as well as effects on neural circuits and regions relevant for mood and cognition (basal ganglia, ventromedial prefrontal cortex, subgenual and dorsal anterior cingulate cortex, amygdala, hippocampus, insula) (Miller & Raison 2016). Inflammatory signaling also influences neurogenesis and neuroendocrine function (Haroon et al. 2012).

What follows from these neuroimmune changes is sickness behavior, a complex syndrome that includes reduced motor activity, social withdrawal, reduced food and water intake, and increased slow wave sleep (Dantzer & Kelley 2007). The parallels between sickness behavior and depressive symptoms were quickly noted (Yirmiya 1997), and subsequent studies have shown that sick animals also exhibit depressive-like behaviors, including increased immobility in forced swim and tail suspension tests and anhedonia-like behaviors such as reduced preference for saccharin solutions and reduced incentive motivation (Lasselin et al. 2021). Importantly, these changes are not simply due to depletion of energy resources; rather, they represent goal-directed behaviors designed to maximize recovery and protect the host. In particular, the lethargy, social avoidance, and anhedonia induced by inflammation help to conserve energy that can be directed toward fighting infection and promoting wound healing (Miller & Raison 2016). These behaviors may also reduce the likelihood of future attack and help reduce the spread of infection.

3.3. Methodological Approaches to Probing Neuroimmune Interactions

The overlap between symptoms and neural correlates of sickness and those of depression and other psychiatric disorders led to the groundbreaking hypothesis that repeated immune activation

or chronic inflammation could play a role in the development of these disorders and in milder alterations in emotion, cognition, and behavior. Below we review the models that have been used to test this hypothesis using immune stimulation in humans, as well as findings from the many studies that have used these models to examine links with neural and behavioral changes in healthy and clinical populations.

Interferon alpha (IFN-α) therapy: antiviral cytokine administered therapeutically for treatment of hepatitis C and certain types of cancer; used to model chronic inflammation

3.3.1. Interferon alpha therapy. Some of the earliest work on inflammation and psychiatric disorders began with the observation that many patients treated with interferon alpha (IFN-α) therapy report depressed mood and other depressive symptoms, which develop into clinically significant depression in up to 40% of patients (Loftis & Hauser 2004). IFN-α elicits a strong inflammatory response and, when administered repeatedly, provides an excellent model for the effects of chronic inflammation on mood, neural function, and behavior.

Studies using IFN-α therapy have clearly demonstrated that cytokines can cause clinically meaningful depressive symptoms and episodes and that inflammation-induced sickness behavior and idiopathic depression share pathophysiological pathways. Indeed, prophylactic treatment of patients undergoing IFN-α therapy with selective serotonin reuptake inhibitors (SSRIs) can prevent increases in depressive symptoms and the occurrence of depressive episodes (Sarkar & Schaefer 2014). Further, studies have demonstrated that specific depressive symptoms emerge in response to IFN-α along different timelines. Fatigue, altered sleep, loss of appetite, and other neurovegetative symptoms emerge within the first 2 weeks of treatment, followed weeks later by mood and cognitive symptoms—a time course that has elucidated distinct neurobiological underpinnings for these symptom dimensions as well as differential responses to treatment (Capuron et al. 2002). This distinction between symptom dimensions is also seen in more recent work on inflammatory correlates of symptoms in depressed patients (see Sections 3.4 and 3.5). Given the chronic nature of immune activation in the IFN-α model, these studies may have the most ecological validity for populations that are exposed to chronic inflammation (e.g., those under chronic stress). However, this model is no longer widely used now that targeted treatments for hepatitis and other disorders are available.

3.3.2. Experimental studies with endotoxin in healthy individuals. Increasing interest in the role of inflammation across a wide range of psychological factors has inspired creative use of experimental immune activation in the laboratory. Common approaches include administering lipopolysaccharide (LPS; also called endotoxin), which elicits a rapid, robust inflammatory response (up to 100-fold increase in circulating concentrations of some cytokines) that peaks at 2 h postinjection and resolves within 5 h (Bahador & Cross 2007). Experimental trials with endotoxin have clearly demonstrated a causal role of inflammatory activation on psychological processes in healthy individuals without the confound of preexisting illness (an issue in IFN-α studies). Additionally, the transient nature of immune activation following experimental endotoxin administration affords a high level of experimental control and an opportunity to observe the effects of acute immune activation, and even specific cytokines, at multiple levels of analysis including self-report, experimenter observations, objective behavioral tasks, and neural reactivity. Of note, endotoxin is also commonly used in preclinical models, maximizing translation of findings across species.

While we continue to learn a great deal from endotoxin administration, results from these studies may have limited generalizability to those most at risk for inflammation-related effects on the brain. Endotoxin studies are typically conducted in healthy adults, and findings may not be applicable to individuals at different stages of the life span (e.g., children, adolescents) or those at risk for chronic disease. Further, the magnitude of immune activation following endotoxin is

large and time-limited and may not capture the level and duration of inflammation most relevant for psychological disorders. Indeed, psychological stress, a potent risk factor for depression, elicits a much smaller inflammatory response (Marsland et al. 2017), and depressed individuals typically evidence much lower levels of inflammation than those triggered by endotoxin (Osimo et al. 2020).

Research Domain Criteria (RDoC): framework designed by the National Institute of Mental Health to facilitate research on the common, transdiagnostic elements of psychiatric disorders

3.3.3. Immune response to vaccination. Vaccines developed for protection against various pathogens have been used by PNI researchers to examine the effect of low-grade inflammatory responses on mood, neural function, and behavior. The typhoid vaccine elicits a mild (approximately twofold) increase in circulating proinflammatory cytokines that peaks within 6–8 h and returns to basal levels at 24 h postvaccination (Paine et al. 2013). This model has been used very productively in healthy adults but has limited use across populations who are unwilling to get an unnecessary vaccine. The annual influenza vaccine is more widely used and has emerged as a promising new model for probing inflammatory effects on psychological processes. The inflammatory response to influenza vaccine is small, peaks approximately 24 h after vaccine administration, and resolves within 3 days (Radin et al. 2021).

Experimental models using vaccines maintain the internal validity needed to demonstrate the causal role of immune activation in different psychological phenomena while also (in the case of influenza vaccine) being feasible for use in vulnerable populations including children, older adults, and pregnant women. In addition, these models provide an opportunity to examine the impact of mild increases in inflammatory cytokines that are more comparable to those observed in the context of psychological disorders or elicited by psychological stress. Further, the time course of the inflammatory response to vaccination differs from that of an endotoxin-induced response; there is a slower peak and longer recovery, which allows examination of effects on daily mood and experience outside of the laboratory (Kuhlman et al. 2018). Of note, some individuals do not demonstrate an inflammatory or psychological response to these vaccines; thus, investigators often examine within-subject associations between changes in particular inflammatory markers and changes in neural and psychological function in vaccine studies.

3.4. Links with Research Domain Criteria Dimensions

The transdiagnostic nature of links between inflammatory activity and psychiatric symptoms lends itself readily to the units-of-analysis approach to understanding underlying psychobiological dimensions of clinical disorders proposed in the Research Domain Criteria (RDoC) framework. **Table 1** summarizes the primary findings from immune challenge studies according to the RDoC matrix and illustrates the transdiagnostic nature of immune activation particularly for positive valence, social, and arousal systems. **Figure 1** provides an overview of immune-to-brain signaling pathways and effects on psychological systems.

3.4.1. Negative valence systems. There has been a great deal of interest in the role of inflammation on negative valence systems. Activation of inflammatory pathways by IFN-α, endotoxin, or vaccination leads to increases in negative mood states, including depressed mood (Eisenberger et al. 2009, Kuhlman et al. 2018) and state anxiety (Lasselin et al. 2016). A scoping review of the literature showed that acute activation of the immune system was linked to increases in the negative affective reactivity endophenotype associated with depression, including greater negative affect in response to stress and increases in attention to negative-mood-congruent stimuli (Dooley et al. 2018). As one compelling example, administration of a single dose of IFN-α led to an acute increase in right amygdala responses to sad (compared with neutral) faces, while a single dose of anti-TNF (a therapeutic antagonist of TNF activity) decreased right amygdala reactivity to

Table 1 Associations between inflammatory activation and Research Domain Criteria (RDoC) systems

Level of analysis	RDoC system				
	Negative valence	Positive valence	Cognitive	Social processes	Arousal and regulatory
Self-report	■ ↑ depressed mood (females are more susceptible) ■ ↑ state anxiety ■ ↑ suicidal ideation ■ ↑ anhedonia	■ ↓ appetite ■ ↓ positive mood	■ ↑ cognitive disturbances	■ ↓ in perceived social status (males) ■ ↑ feelings of social disconnection (females)	■ ↑ sleepiness and fatigue
Behavioral	■ ↓ reaction time to mood-congruent stimuli (specifically sad)	■ Δ reward-motivated behavior	■ ↑ psychomotor slowing ■ ↓ processing speed ■ Δ verbal and nonverbal memory (inconsistent across models)	■ ↑ stranger avoidance, approaching close others ■ ↓ accuracy in identifying strangers' emotions	■ ↓ total sleep time and sleep efficiency
Neural	■ ↑ ventral striatum and anterior insula reactivity to punishment ■ ↓ connectivity between the subgenual anterior cingulate cortex and other regions within the limbic system when viewing emotional faces	■ ↓ ventral striatum and anterior insula reactivity to rewards ■ ↓ ventral striatum reactivity when anticipating rewards (females) ■ ↓ substantia nigra reactivity to novelty	■ ↓ connectivity in default mode network and dorsal attention network (in older adults)	■ ↑ subgenual anterior cingulate cortex reactivity when viewing emotional faces ■ ↑ amygdala reactivity to social threat ■ ↑ neural sensitivity to both positive and negative social feedback ■ ↑ ventral striatum reactivity to social rewards	■ Δ microstructure of insular cortex
Molecular	■ ↓ serotonin	■ ↓ dopamine	■ ↓ decreased glucose metabolism in the medial temporal lobe		

Symbols used in table: ↑, increase; ↓, decrease; Δ, change.

emotional faces (Davies et al. 2021). Observational studies have also demonstrated links between systemic inflammation, depressed mood, and negative attentional bias (Boyle et al. 2017).

These changes in mood and negative affective reactivity may be mediated by the effects of inflammation on neurotransmission, such as a decrease in serotonin and dopamine, as well as an increase in neural sensitivity to threat, punishments, and negative social feedback predominantly within limbic structures and the highly dopaminergic, mesolimbic neural circuit (Kraynak et al. 2018). The common organizing framework for these effects is that acute increases in inflammation are perceived by the brain as danger signals and therefore engage the neural and psychological resources capable of processing and responding to threats. A closer look at the experimental results, however, suggests that the effects of inflammation on negative valence domains are either specific to or more robust using social stimuli (e.g., faces) (Inagaki et al. 2012).

3.4.2. Positive valence systems. Inflammation leads to nuanced changes in positive valence system activity at the self-report, neural, and behavioral levels of analysis. Randomized controlled trials (RCTs) of endotoxin and typhoid vaccination have documented decreases in positive mood (Reichenberg et al. 2001), decreases in ventral striatum activity during monetary reward anticipation (Eisenberger et al. 2010a), and attenuation of substantia nigra reactivity to novelty (Harrison et al. 2015), suggesting a dampening effect of inflammation on reward processes. However, endotoxin also increases ventral striatum activity to social support figures (versus strangers) and increases desire to approach those figures (Inagaki et al. 2015). Effects at the behavioral level are

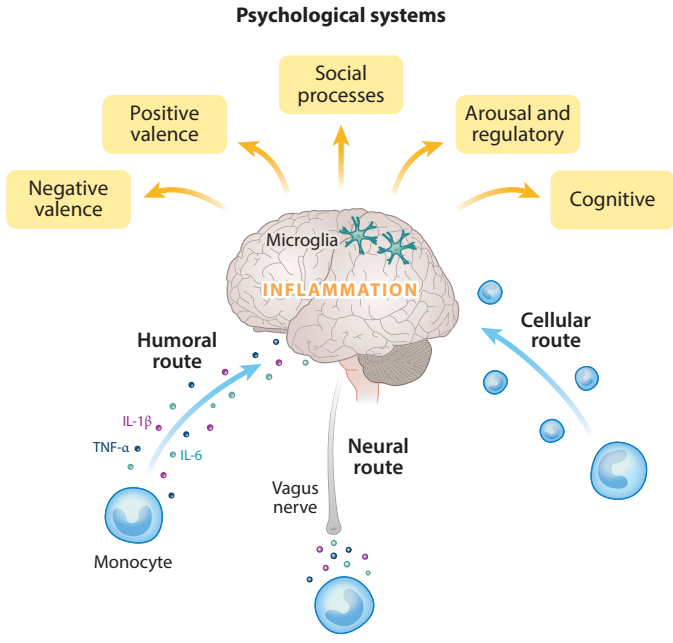

Figure 1

Overview of immune-to-brain signaling pathways and effects on psychological systems.

also complex. For example, there is evidence of both increased (Lasselin et al. 2017) and decreased motivation for monetary rewards (Boyle et al. 2020a, Draper et al. 2018) following endotoxin administration. In one of the few studies of inflammation and reward learning, mild increases in inflammation following vaccination were associated with increases in implicit reward learning (Boyle et al. 2019b). Overall, it seems clear that inflammation leads to changes in reward-related processes, though the nature of that change may depend on the magnitude of the immune challenge, the characteristics of the sample, and the specific reward domain being isolated by the task used in the experiment (e.g., social versus nonsocial, motivation versus sensitivity).

The sickness behavior model provides insight into some of these observations and posits that acute inflammatory activity increases an individual's awareness of the effort involved in the pursuit of rewards such that the individual can calibrate their effort expenditure appropriately (Vichaya & Dantzer 2018). For example, LPS-treated lactating female mice will expend effort to build nests for their pups when exposed to a cold temperature but not in a warm temperature where it is not necessary (Aubert et al. 1997). Similarly, endotoxin administration increases individuals' willingness to engage in high-effort tasks only for high-value rewards (Lasselin et al. 2017). These observations are consistent with findings that inflammatory activity increases interoceptive awareness of the effort involved in a task (Harrison et al. 2009b).

Together, evidence at multiple levels of analysis supports a robust role of inflammatory activity in the modulation of motivation within the positive valence domain. These effects, if chronic, may contribute to anhedonia. Indeed, observational studies with depressed individuals have confirmed that systemic inflammation is associated with decreased activation of and reduced functional connectivity within reward circuits involving the ventral striatum and ventromedial prefrontal cortex in association with anhedonia (Bekhbat et al. 2022). These findings can inform the targeted use of

anti-inflammatory therapies in specific psychiatric populations. For example, in an RCT of infliximab (an anti-TNF agent) for individuals with treatment-resistant depression, the largest clinical effects were observed for symptoms of amotivation (Raison et al. 2013).

3.4.3. Social processes. Some of the most intriguing discoveries in the past decade have pertained to the role of inflammation in social processes (Eisenberger et al. 2017). There is consistent evidence across neural, behavioral, and self-report levels of analysis that immune activation increases sensitivity to social threat. For example, endotoxin increases amygdala reactivity to images involving social, but not nonsocial, threat (Inagaki et al. 2012) and increases neural sensitivity to both positive and negative social feedback (Muscatell et al. 2016). These findings have implications for feelings of social integration and accuracy in interpreting the emotions of others. Indeed, endotoxin induces feelings of social disconnection (Eisenberger et al. 2010b), and individuals who show larger increases in IL-6 following the flu vaccine show implicit tendencies to avoid strangers and approach close others (Jolink et al. 2022). It has been posited that many of the field's findings in positive and negative valence domains may be better accounted for by social processes, such that inflammatory activity increases sensitivity to social, but not necessarily nonsocial, rewards and punishments (Eisenberger et al. 2017).

The role of the immune system in social processes may also go beyond the individual. The faces of individuals who have received endotoxin are rated by strangers as more disgusted, more sad, less happy, and less surprised than those of individuals who received placebo injections (Sarolidou et al. 2019). This observation suggests that emotional expressions differ in perceptible ways among individuals who are or are not experiencing systemic immune activation and that elevated systemic inflammation may contribute in underappreciated ways to the widespread stigmatization of individuals with psychiatric disorders.

3.4.4. Arousal and regulatory systems. Compelling evidence across preclinical, experimental, and clinical studies has demonstrated a role for inflammatory processes in what the RDoC system terms arousal states, including fatigue and sleep (Dooley et al. 2018). Fatigue is one of the first symptoms to emerge after IFN-α therapy (Capuron et al. 2002), and both endotoxin and typhoid vaccination lead to acute increases in fatigue (Harrison et al. 2009a, Lasselin et al. 2020), whereas administration of targeted cytokine antagonists reduces fatigue (Kappelmann et al. 2018). In observational studies, inflammation has been associated with symptoms of fatigue in healthy and clinical populations (Bower 2019). Alterations in the frontostriatal network are hypothesized to underlie inflammation-related fatigue and specifically the motivational component of this symptom, whereas activation of the anterior insula is thought to contribute to the subjective experience of fatigue (Dantzer et al. 2014). Indeed, alterations in the striatal microstructure predict the emergence of fatigue (but not depressed mood) in the context of IFN-α treatment (Dowell et al. 2016).

Inflammation is also closely linked with sleep. Endotoxin increases subjective ratings of sleepiness (Lasselin et al. 2020), and the inflammatory response to typhoid vaccination decreases sleep time and sleep efficiency (Sharpley et al. 2016). These effects are bidirectional, as sleep disturbances also promote and prolong activation of the immune system. For example, experimental sleep deprivation increases inflammatory activity as indicated by increases in the proinflammatory transcription factor NF-κB (Irwin et al. 2008). Further, individuals with clinical sleep disturbance have higher levels of CRP and IL-6, and sleep disturbance predicts increases in inflammation in longitudinal research (Irwin 2019). Thus, behavioral interventions targeting sleep may be a powerful approach to mitigating chronic inflammatory dysregulation (Irwin et al. 2015).

3.4.5. Cognitive systems. Both preclinical and clinical studies have shown reliable effects of acute inflammation on cognitive processes, particularly psychomotor slowing and memory impairment (Felger & Treadway 2017, Goshen & Yirmiya 2007). Indeed, typhoid and influenza vaccination lead to acute increases in subjective cognitive complaints (Harrison et al. 2009b, Kuhlman et al. 2018). However, the evidence that exogenous immune activation consistently impairs cognitive processes measured using clinically validated neuropsychological tasks is weak (Dooley et al. 2018). For example, while an early trial found that endotoxin led to decreases in verbal and nonverbal memory (Reichenberg et al. 2001), this effect has not been replicated in subsequent studies (Handke et al. 2020). The effects of inflammation on cognitive function are likely more nuanced than previously hypothesized and may require tasks that are more sensitive or that tap different domains of cognitive function. For example, using a virtual reality spatial memory task revealed deficits in spatial memory, but not procedural memory, after typhoid vaccination (Harrison et al. 2014).

As we interpret the mixed results from experimental studies of acute inflammation, it is important to contextualize them within the larger literature on chronic inflammation and cognition. Here, there is more compelling evidence that elevated markers of systemic inflammation (e.g., CRP) predict cognitive decline using validated neuropsychological tests, particularly in older adults (Walker et al. 2019). Inflammatory markers are also associated with altered connectivity in large-scale functional brain networks relevant for cognition (and other RDoC dimensions), including the default mode network and the dorsal attention network in older adults (Walker et al. 2020). Of note, different patterns have been observed in younger adults; in this population, systemic inflammation was associated with alterations in emotion-related networks, which may be more susceptible at that stage of development (Nusslock et al. 2019).

3.5. Relevance for Clinical Disorders: Immune Alterations in Individuals with Depression, Posttraumatic Stress Disorder and Anxiety, and Schizophrenia

The inflammatory response and associated changes in mood, cognition, and behavior are believed to be a normal, adaptive response to injury or infection that are time-limited and resolve when the pathogen is eliminated. However, if inflammation is prolonged—for example, in the context of a chronic inflammatory condition, following administration of IFN-α or another inflammatory agent, or with repeated psychosocial stress—these symptoms may endure and develop into a clinically significant syndrome. A large body of observational research, reviewed below, has examined alterations in inflammatory processes among individuals with depression and other psychiatric conditions. Although this work lacks the experimental control of the models described in Section 3.3, it provides converging evidence that inflammation is a likely contributor to psychiatric disorders in a subgroup of patients.

3.5.1. Depression. Meta-analyses of cross-sectional studies comparing individuals with depression and nondepressed controls have documented elevations in peripheral markers of inflammation in depressed patients, including higher levels of IL-6, TNF-α, and CRP (Haapakoski et al. 2015, Osimo et al. 2020). Further, evidence of activated microglia has been observed in postmortem brain samples from suicide victims with depression and in the brains of patients with major depressive disorder (Miller & Raison 2016). The causal role of inflammation in depression is supported by large, longitudinal cohort studies showing that elevated levels of IL-6 and CRP precede the development of depressive symptoms and clinical depression (Khandaker et al. 2014).

Importantly, not all patients with depression show evidence of elevated inflammation. A recent meta-analysis estimated that approximately 30% of patients with depression demonstrate elevated

inflammation (defined as CRP > 3 ng/L; Osimo et al. 2019). This estimate is consistent with results from an RCT of a targeted anti-TNF agent (infliximab) for treatment-resistant depression, which observed beneficial effects only among the subgroup of patients with elevated inflammation (Raison et al. 2013). Characteristics of those with inflammation-associated depression have not been determined, although inflammation appears to be more strongly associated with some symptoms of depression than others. In particular, inflammation is associated with somatic symptoms of depression, including fatigue and sleep disturbance (Frank et al. 2021, Jokela et al. 2016), as also suggested by the literature on experimental immune activation (Section 3.4). In addition, inflammation is associated with symptoms of anhedonia in depressed individuals and associated changes in neural circuitry (Bekhbat et al. 2022).

3.5.2. Posttraumatic stress disorder and anxiety disorders. Meta-analyses of cross-sectional studies have documented elevated concentrations of IL-6, TNF-α, and CRP among individuals with posttraumatic stress disorder (PTSD) relative to healthy controls (Peruzzolo et al. 2022, Renna et al. 2018). Importantly, these elevations were evident in subgroup analyses of patients without comorbid depression (Peruzzolo et al. 2022). However, longitudinal studies examining pretrauma inflammation as a predictor of PTSD have yielded mixed results (Sumner et al. 2020), making it difficult to draw conclusions about the direction of effects. Evidence for links with other anxiety disorders is decidedly mixed. One meta-analysis found no evidence of elevated inflammation in individuals with OCD, panic disorder, social anxiety, or generalized anxiety disorder (GAD) relative to healthy controls (Renna et al. 2018), while another focusing specifically on GAD found elevations in CRP but not in other inflammatory markers (Costello et al. 2019). This is still a developing literature with relatively few studies (particularly outside of PTSD) and variability in the types of inflammatory markers and samples assessed. Of note, surprisingly few studies have examined effects of inflammation on behavioral measures of fear or anxiety in humans, although these are widely used in preclinical and experimental psychopathology research (e.g., fear conditioning). Given links between inflammation and threat-related neural processes in both rodents and humans (Sections 3.4.1 and 4.2.1), this area is ripe for future exploration.

3.5.3. Schizophrenia. Growing evidence supports a role for inflammation in the development of schizophrenia (Khandaker et al. 2015). Consistent with our understanding of schizophrenia as a neurodevelopmental disorder, research in this area is based largely on studies of prenatal exposure to inflammation and its later effects on the brain and behavior. These include ecological and birth cohort studies, which have documented links between maternal infection and increased risk for schizophrenia among offspring (Brown & Derkits 2010). Further, elevated inflammatory markers in childhood predict increased risk for psychosis in young adulthood, supporting a causal role for inflammation (Khandaker et al. 2014). Meta-analyses of cross-sectional studies have also documented elevated levels of CRP and IL-6 among individuals with schizophrenia (Goldsmith et al. 2016, B.J. Miller et al. 2014).

There is a strong mechanistic basis for the link between inflammation and schizophrenia from preclinical studies of MIA. In rodents, activation of the maternal immune system during embryonic development leads to perturbations in neural and behavioral function in the offspring that are consistent with schizophrenia (and other neurodevelopmental disorders) (Meyer et al. 2009). These include, for instance, impairments in attention, learning, and memory; deficits in sensorimotor gating; and altered social exploration (Meyer 2014). Of note, effects of MIA on later behavior may manifest primarily in the context of genetic predisposition or environmental exposures that occur later in life, including immune challenges, exposure to stress, and substance use (Meyer 2014). Microglia have been implicated as key players in this pathway via both early

effects on synaptic pruning and later effects on neural activity. Importantly, the neurodevelopmental effects of early immune activation may not be intractable as evidenced by preclinical studies showing that minocycline, an antibiotic medication that reduces microglia activation, can prevent the development of schizophrenia-like behaviors following an adolescent stressor (Giovanoli et al. 2016).

4. STRESS AS A MODULATOR OF IMMUNITY AND NEUROIMMUNE INTERACTIONS

We have focused thus far on how activation of peripheral inflammatory processes by infection, injury, or illness can influence the brain and behavior. However, infection and injury are not the only stimuli that can activate the immune system; psychological stress also has potent effects on immunity and inflammation. Of course, stress is also a risk factor for depression, anxiety, and other psychological disorders (Hammen 2005). Although the immune system has typically not been seen as a critical player in this process, growing evidence suggests that stress-induced changes in peripheral immunity and the neuroimmune network may have an important role in the psychological and behavioral effects of stress exposure. Indeed, stress-induced activation of peripheral inflammation can lead to changes in neural systems, mood, and behavior that are similar to those observed following direct immune stimulation (e.g., with endotoxin). In addition, stress can influence microglia and the BBB in ways that magnify immune-to-brain signaling and help to instantiate the effects of stress in the brain. The next section reviews the effects of stress on the immune system and other elements of the neuroimmune network and examines moderators of neuroimmune signaling.

4.1. Stress Activates the Peripheral Immune Response

Decades of research in PNI has generated overwhelming evidence that psychological stress can influence immune function (Glaser & Kiecolt-Glaser 2005, Segerstrom & Miller 2004). The nature of these effects depends on the type and timing of the stressor. Acute stressors (lasting minutes to hours) typically lead to increases in measures of innate immunity and inflammation, including increases in circulating concentrations of proinflammatory cytokines (Marsland et al. 2017) and expression of proinflammatory genes that are driven by activation of the sympathetic nervous system (MacCormack et al. 2021). This is considered to be an adaptive response to the physical threats that were prevalent in the ancestral environment, allowing the immune system to proactively prepare for potential infection and tissue damage that might occur following attack.

Chronic stressors also influence the immune system, though the effects here are more nuanced and complex. In general, chronic stress is associated with increases in inflammation and decreases in antiviral and adaptive immunity (Glaser & Kiecolt-Glaser 2005, Segerstrom & Miller 2004). At the genomic level, this profile has been described as the conserved transcriptional response to adversity (CTRA) given its appearance across species and types of stress (e.g., poverty, ELA, social isolation) (Cole 2019). The CTRA is hypothesized to represent a shift in the organism from a predominantly antiviral immune orientation to a more proinflammatory orientation designed to protect against bacterial infection and tissue damage.

4.2. Stress-Induced Inflammation Influences the Brain and Behavior

Research on stress and the immune system has primarily focused on relevance for physical health (Glaser & Kiecolt-Glaser 2005). However, with advances in our understanding of immune regulation of the brain, there is growing interest in how stress-induced inflammation may influence the brain and behavior.

4.2.1. Preclinical models. One of the major preclinical models that have informed this line of research is the repeated social defeat (RSD) paradigm (Reader et al. 2015). In one version of this paradigm, a large, aggressive rodent is placed into a cage of other rodents with an established social hierarchy for 2-h sessions each day. The intruder rodent attacks the residents, which typically develop anxiety-like behavior after several days. Of note, RSD-induced changes in neural activity and behavior may persist for weeks after termination of the stressor and can be reactivated by later stress exposure (Wohleb et al. 2014).

Repeated social defeat (RSD) paradigm: experimental model used in preclinical research to examine effects of chronic social stress on neuroimmune function and behavior

RSD has a number of effects on immune cells in the brain and periphery that are central to these behavioral changes (Weber et al. 2017). In the brain, RSD activates microglia, which enhance neuroinflammation and influence endothelial cells of the BBB to facilitate the recruitment and transport of peripheral monocytes into stress-sensitive neural regions. In the periphery, RSD leads to release of proinflammatory monocytes into the blood that are primed to traffic to the brain in response to microglia signaling; indeed, blocking the transport of these monocytes into the brain abrogates RSD-induced behavioral changes (Reader et al. 2015).

Effects of chronic stress at each level of the neuroimmune network—the brain, the periphery, and the BBB—have also been demonstrated in other preclinical models. Another version of the RSD model led to increases in BBB permeability in the nucleus accumbens, allowing the passage of proinflammatory cytokines into the CNS, which mediated increases in depressive-like behavior (Menard et al. 2017). Of note, these effects were observed only in male animals, demonstrating stark sex differences in stress effects on the neuroimmune network (discussed in Section 4.3.2). In a model of chronic unpredictable stress involving random intermittent stressors over 14 days, microglial activation led to neuronal remodeling in the medial PFC that contributed to synaptic deficits and development of anxiety and depressive-like behavior; again, these effects were more notable in male animals (Wohleb et al. 2018).

4.2.2. Clinical models. The RSD and other chronic stress models nicely illustrate the somewhat surprising role of central and peripheral immune cells in the neural and behavioral effects of stress. Similar models have been proposed to explain the links between stress and the development of psychological disorders in humans. One prominent model is the social signal transduction theory of depression, which proposes that stress-induced increases in peripheral inflammation signal the brain to induce depressed mood and other symptoms of depression (Slavich & Irwin 2014). Also relevant are neuroimmune models of ELA, which posit that the well-documented association between ELA and the development of depression and other psychiatric disorders is driven in part by increased inflammatory reactivity in peripheral immune cells and enhanced neuroimmune signaling (Miller et al. 2011, Nusslock & Miller 2016).

Although these influential models have highlighted the role of stress as a driver of immune effects on the brain and behavior, surprisingly few experimental studies have directly tested these pathways in humans. One recent study used the Trier Social Stress Task (TSST) to examine how stress-induced changes in inflammation influenced dimensions of reward (Boyle et al. 2020b). Healthy young women were exposed to the TSST or a placebo task and completed behavioral measures of reward 90 min after task completion (when IL-6 concentrations tend to peak post-stress). The TSST led to significant increases in IL-6, which were associated with increased response bias during reward learning and increased motivation when probability of receiving a reward was low. Given the importance of stress as a potential driver of immune activation and subsequent effects on the brain, it is critical to test these hypotheses in humans.

4.3. Moderators of Neuroimmune Signaling

A given stressor, or even a given pathogen, can evoke different inflammatory responses depending on characteristics of the host. Further, the same level of peripheral inflammation can have different

neural and behavioral effects in different individuals. These individual differences in inflammatory reactivity and sensitivity to inflammatory signaling have important implications for understanding risk and resilience in the context of immune activation. The next sections review psychological and other individual difference factors that moderate responses to immune signaling.

4.3.1. Psychological factors. Studies using the endotoxin, IFN-α, and vaccine models have typically focused on the main effect of peripheral inflammatory reactivity on the brain and behavior. However, there is compelling evidence of individual variability in the inflammatory and psychological response to these standardized stimuli. For example, individuals who are more sensitive to social isolation or disconnection evidence a larger inflammatory response to endotoxin (Moieni et al. 2015a). In addition, higher perceived stress, trait sensitivity to social disconnection, and more severe depressive or anxiety symptoms increase risk for endotoxin-induced depressed mood, whereas ELA, social status, social support, neuroticism, and sleep disturbance do not (Irwin et al. 2019). Similarly, individuals with higher levels of depressive symptoms before initiation of IFN-α therapy are at increased risk for developing more severe depressive symptoms during treatment; this is particularly true for symptoms of sadness, pessimistic thoughts, and sleep disturbance (Capuron et al. 2004).

Observational studies have begun to extend these observations into real-life settings. In two longitudinal samples of women with breast cancer, perceived stress was shown to moderate the association between inflammation and depressive symptoms, such that peripheral inflammatory markers were associated with elevated depressive symptoms only among women who reported higher levels of stress (Manigault et al. 2021a,b). Similar results were observed for anxiety and sleep disturbance, though not for ELA. Of course, ELA increases risk for later-life stress, anxiety, and depression, which may then influence neuroimmune signaling in the context of psychological or immune challenges in adulthood.

4.3.2. Biological sex. One of the most marked and important moderators of neuroimmune signaling is biological sex. Research in preclinical models has demonstrated sex differences in microglia and the BBB that manifest in neuroimmune responses to inflammatory and psychological stressors (Bordt et al. 2020, Cathomas et al. 2022). Indeed, as mentioned in Section 4.2, effects of chronic stress on neuroimmune communication and resulting changes in behavior are noted primarily in male animals. These effects are observed early in development and may help to account for sex differences in prevalence of neurodevelopmental and psychiatric disorders (Hanamsagar & Bilbo 2016). For example, prenatal exposure to maternal stress and air pollution led to persistent changes in the function of microglia and the development of autism-like behaviors in male but not female offspring (Bilbo et al. 2018). In contrast, neonatal treatment with LPS led to changes in social behavior in adult female, but not male, mice (Smith et al. 2020).

In research with humans, males and females also differ in their susceptibility to the psychological effects of endotoxin and the nature of those effects. For example, while both male and female participants show increases in IL-6 and TNF-α following endotoxin, females are more susceptible to increases in depressed mood and feelings of social disconnection (Moieni et al. 2015b) and reduced neural sensitivity to anticipation of monetary reward (Moieni et al. 2019b). In contrast, for males, endotoxin leads to a decrease in perceived social status (Moieni et al. 2019a).

4.3.3. Aging. The immune system develops and changes over the life span and generally becomes more proinflammatory as one ages. This is evident in the periphery and also in the brain, where microglia shift toward a more proinflammatory phenotype with age. These sensitized microglia are primed to mount a more robust and prolonged neuroimmune response after stimulation; this occurs across a range of stimuli, including bacterial and viral infections, surgery, brain

injury, high-fat diet, and psychological stress (Muscat & Barrientos 2021). The BBB also becomes more permeable with age (Erdő et al. 2017). Together, these changes in the neuroimmune network may account for the exaggerated neuroimmune responses and associated declines in cognitive function observed in aged rodents following immune challenge.

Although there is ample evidence for elevated peripheral inflammation in older adults, whether aging modulates sensitivity to the effects of inflammatory signaling on the brain and behavior in humans has received little attention. In one study conducted in a community sample, older adults (i.e., those over age 50) were more susceptible to inflammation-associated depressive symptoms, particularly somatic symptoms (Straka et al. 2021). However, in some circumstances younger individuals may be at elevated risk. In research with breast cancer survivors, we found that younger women (i.e., those aged 50 or younger) showed increased susceptibility to inflammation-related depressive symptoms (Kuhlman et al. 2022b, Manigault et al. 2021a). This finding highlights the importance of context. Women diagnosed with breast cancer are under significant stress, particularly if they receive this diagnosis at a younger age, which could potentially increase neural sensitivity to inflammation (see Section 4.3.1).

4.4. Early Life Adversity as an Elicitor and Moderator of Inflammation

The importance of ELA in long-term mental and physical health is well established. ELA reliably predicts increased risk for a variety of psychological disorders in adulthood; for example, a global study conducted in 21 countries found that ELA accounted for almost 30% of DSM-IV disorders, and family dysfunction emerged as the strongest predictor (Kessler et al. 2010). The immune system is hypothesized to be a key mediator of these effects as early adversity can shape the inflammatory phenotype and homeostatic regulation of immune cells throughout the life span. For example, being reared under adverse social conditions leads to upregulation of inflammatory gene transcripts and signaling in nonhuman primates (Cole et al. 2012), children (Marie-Mitchell & Cole 2022), and adults (Bower et al. 2020, Miller et al. 2008). In addition, experiences of adversity and maltreatment during childhood are associated with circulating markers of inflammation in both pediatric (Kuhlman et al. 2020a) and adult populations (Baumeister et al. 2016). Further, following acute stress, individuals exposed to more childhood adversity demonstrate larger increases in inflammatory gene expression (Kuhlman et al. 2022a, Schwaiger et al. 2016) and circulating IL-6 (Carpenter et al. 2010) than their less exposed peers.

Though less often the focus, ELA can also moderate the communication between the CNS and the immune system as posited by the neuroimmune network hypothesis (Nusslock & Miller 2016). Indeed, young adults with exposure to more ELA demonstrated larger increases in depressed mood and cognitive difficulties following the flu vaccine than their low-exposure peers (Kuhlman et al. 2020b). Further, among adolescents, inflammation and depressive symptoms correlated most strongly within individuals over time if they had a history of early social adversity (Miller & Cole 2012). Of note, studies with adult populations have not always found moderating effects of ELA (Irwin et al. 2019, Manigault et al. 2021b) (see Section 4.3.1). More research on this hypothesis that considers the role of type and timing of adversity as well as the age of participants would help to clarify the potential neuroimmune mechanisms involved in life-span health disparities observed among individuals with this background.

Importantly, the long-term effects of ELA may not be intractable. In preclinical research, some of the effects of ELA on dopaminergic circuits can be rescued by minocycline (Catale et al. 2022). Further, susceptibility to morphine-induced conditioned place preference during adolescence can be mitigated by enriched maternal care during early development in a rodent model (Schwarz et al. 2011). Similar findings have emerged in studies with humans. For example, maternal warmth

buffered the impact of low childhood socioeconomic status (SES) on proinflammatory signaling in healthy adults (Chen et al. 2011), and a family-focused intervention for low-SES African American youth led to lower inflammation in early adulthood (G.E. Miller et al. 2014). Thus, the family environment can serve as both a risk and a resilience factor for neuroimmune development and function throughout the life course.

Immunopsychiatry: field of clinical and translational science focusing on immune dysregulation as a key mechanism and therapeutic target for psychiatric disorders

Eudaimonic well-being: positive psychological state that encompasses a sense of purpose and meaning in life, social embeddedness, and potential for personal growth

5. INTERVENTIONS TO ENHANCE NEUROIMMUNE RESILIENCE

Given the detrimental effects of exaggerated or prolonged inflammation on mental health, interventions that reduce inflammation in the periphery and the brain and that facilitate adaptive communication between these compartments are clearly needed. The field of immunopsychiatry is exploring pharmacologic approaches that target inflammation and associated changes in neural function that contribute to depression and other mental disorders. In this section, we consider how psychologists can use the techniques of psychological science to reduce inflammation and enhance neuroimmune resilience. We focus on peripheral inflammation as those markers are most readily and reliably accessible in living humans. However, we also describe preclinical studies that suggest effects of behavioral interventions on immune cells in the brain and the BBB.

Various psychological and mind–body interventions have been examined in relation to the immune system in humans. A systematic review and meta-analysis of 56 psychosocial interventions found an overall beneficial effect on immune function, including reductions in peripheral markers of inflammation (Shields et al. 2020). The majority of trials included in this review used cognitive behavioral therapy (CBT), which led to significant reductions in proinflammatory cytokines and other markers of inflammation. Mind–body therapies have also shown beneficial effects on immunity and inflammation (Bower & Irwin 2016, Morgan et al. 2014). In particular, mindfulness-based interventions have been shown to decrease inflammatory activity, particularly at the level of gene expression (Bower et al. 2015).

CBT and mind–body interventions are multifaceted and typically have effects on a range of psychological outcomes. Which of these effects might be driving changes in the immune system? Mindfulness and CBT approaches have been shown to reduce negative psychological states including stress, anxiety, and depression (Butler et al. 2006, Goyal et al. 2014), which are closely linked with inflammatory processes (Antoni et al. 2012). Mindfulness interventions also decrease loneliness, a potent driver of inflammation (Creswell et al. 2012). Thus, it is plausible that reductions in these negative states may be one pathway for intervention effects on inflammation.

However, another plausible mechanism for intervention effects on immunity is through effects on well-being. There is growing evidence that aspects of well-being, including positive affect and eudaimonic well-being, are associated with immunity and inflammation (Bower et al. 2019). For example, positive affect is associated with lower levels of proinflammatory cytokines and circulating markers of inflammation, lower stimulated production of inflammatory cytokines by immune cells (a measure of inflammatory potential), and reduced inflammatory reactivity to psychosocial stress (Pressman et al. 2019). Eudaimonic well-being, which encompasses a sense of meaning and purpose in life, social connection, and the opportunity for personal growth, has also been linked to lower levels of inflammation (Cole et al. 2015; Fredrickson et al. 2013, 2015). Of note, both mindfulness-based and CBT approaches lead to positive changes in well-being, including eudaimonic well-being (Antoni et al. 2001, Garland et al. 2015).

We conducted a single-arm trial of mindfulness for breast cancer survivors designed to probe the psychological and neural mechanisms of intervention effects on inflammation. Results showed that a 6-week mindfulness intervention led to decreases in stress and depression, increases in well-being, and decreases in inflammatory gene expression (Boyle et al. 2019a). However, only changes

in eudaimonic well-being were significantly associated with the changes in gene expression. We also examined neural activity in threat- and reward-related neural regions and links with inflammation (Dutcher et al. 2021). Participants showed significant reductions in amygdala activity in response to threatening images and significant increases in ventral striatum activity in response to rewarding images from pre- to postintervention. Consistent with results for subjective well-being, only the changes in ventral striatum activity were correlated with changes in circulating inflammatory markers. Of note, preclinical work has demonstrated that direct activation of the ventral striatum has beneficial effects on antibacterial and antitumor immune responses (Ben-Shaanan et al. 2016, 2018).

These findings, although preliminary, highlight the importance of positive psychological processes as drivers of inflammatory biology. Other positive psychological approaches have also demonstrated beneficial effects on peripheral inflammation, particularly prosocial interventions. For example, in an intergenerational helping intervention, older adults who acted as volunteers in school classrooms (grades K–3) showed decreases in CTRA gene expression that were correlated with increases in eudaimonic well-being (Seeman et al. 2020). Further, doing kind acts for others decreased CTRA gene expression in healthy adults (Nelson-Coffey et al. 2017), and a volunteering intervention decreased circulating markers of inflammation in adolescents (Schreier et al. 2013). The focus of these interventions on enhancing positive psychological processes is consistent with recent neuroscience-informed interventions for depression and anxiety that have targeted increases in positive affect using positive psychological techniques and found robust effects on both positive and negative affective outcomes (Craske et al. 2019).

Interventions that reduce neuroinflammation and BBB permeability should also have beneficial effects on mental health. Preclinical studies suggest promising behavioral approaches for targeting these aspects of the neuroimmune network. In particular, physical exercise, dietary strategies (i.e., caloric restriction, intermittent fasting, and dietary composition), and environmental enrichment (i.e., conditions that promote increased social, cognitive, and physical engagement) lead to reductions in neuroinflammation and associated improvements in cognition in preclinical models (Bower et al. 2019, Muscat & Barrientos 2020). These interventions also have beneficial effects on the BBB in preclinical studies, particularly in the context of illness or injury (Bower et al. 2019). Of note, similar interventions have demonstrated beneficial effects on peripheral inflammation and measures of mood and cognitive function in humans (Kvam et al. 2016, Muscat & Barrientos 2020).

6. CONCLUSIONS AND FUTURE DIRECTIONS

The field of PNI has grown dramatically over the past 50 years along with our understanding of the critical role of the immune system and inflammation in the body and brain. Research in this area has elucidated previously unrecognized pathways through which the immune system can influence psychological function and has identified new targets for intervention. In closing, we consider several exciting challenges that face the field with direct relevance for advances in clinical psychology.

The present review has considered three approaches to experimentally activating the immune system in humans: IFN-α, endotoxin, and vaccines. Each of these models has led to advances in the field in its own right and has also provided converging evidence for a causal role of inflammatory signaling in clinically meaningful symptoms. The relevance of these models can be extended by including sophisticated, theory-based tasks and measures that provide deeper insight into underlying psychological processes. This approach has been used creatively to elucidate the nuanced effects of inflammation on reward and social function (e.g., Eisenberger et al. 2017) and can be

further developed to interrogate these and other psychological domains. In addition, continuing to develop behavioral assays and tasks that translate the wealth of preclinical findings to clinically meaningful outcomes is essential.

Experimental immune activation informs our understanding of what the immune system *can* do to the brain and psychological processes. However, we also need PNI models that get closer to real-world exposures relevant for psychopathology. Acute stress, which has been highly standardized with the TSST and other tasks, reliably activates the innate immune system but has seldom been used to model the effects of inflammation on psychological phenomena in humans (Boyle et al. 2020b). Outside of the laboratory, longitudinal research with individuals undergoing chronic stress will provide critical insight into neuroimmune pathways relevant for stress-related psychopathology. Also important are studies that model environmental stressors linked to poor health. A compelling example is a preclinical model in which pregnant rodents are exposed to restricted nesting material (a model of resource deprivation) and diesel exhaust particles (a common and toxic type of air pollution), both of which have been linked with autism spectrum disorders (Bilbo et al. 2018). Bringing a PNI lens to research on social determinants of health can shed new light on pathways and identify targets for intervention (Robles et al. 2022).

For many PNI researchers, improving the quality of life, well-being, and longevity of patients is a primary motivation. Despite all of the inflammatory mechanisms involved in the onset and maintenance of psychological symptoms, targeting inflammation with pharmacological interventions has not (yet) yielded transformative effects on mental health. Yet, there is a great deal of promise in the role of immune processes in precision medicine. For example, anti-inflammatory agents do appear to be effective in treating depression in subgroups of patients (Raison et al. 2013), and proinflammatory cytokines have been shown to predict treatment response and nonresponse to existing pharmacological treatments (e.g., SSRIs, serotonin–norepinephrine reuptake inhibitors) (Roman & Irwin 2020). Integrating immune measures into studies of psychosocial, behavioral, and mind–body interventions may identify novel mediators or moderators of effects that can potentially be targeted with more precision treatments.

Another important question is whether immune-modulating therapies have the potential to prevent the *onset* of psychological symptoms in domains associated with inflammation. In older adults, treating sleep disturbance with CBT-I (CBT for insomnia) decreases inflammation (Irwin et al. 2014) and prevents incident and recurrent major depression (Irwin et al. 2022). These findings support the provocative hypothesis that psychological interventions could potentially work through inflammatory pathways to decrease risk for psychological disorders. This preventive approach might be particularly effective in younger populations who are at greatest risk for development of psychopathology. To date, there has been minimal examination of intervention effects on immunity in children and adolescents (Shields et al. 2020), although family interventions have shown preliminary efficacy as long-term modulators of inflammatory activity in low-SES African American youth (G.E. Miller et al. 2014). Whether interventions targeting neuroimmune pathways can mitigate the long-term effects of ELA and improve developmental trajectories in high-risk children and adolescents is an important question for future research.

The field of PNI continues to reveal new facets of the close relationship between the CNS and the immune system. The immune system was described by early PNI researchers as a "seventh sense," a concept that has been further developed by a new generation of scientists (Kipnis 2018). The large and growing body of research on immune regulation of neural activity and behavior reviewed here suggests that the immune system could also be considered to "subjugate the brain," at least in certain circumstances (Dantzer et al. 2008). From either perspective, research in this exciting area continues to push disciplinary boundaries and provide vital insight into mental and physical health across the life span.

SUMMARY POINTS

1. The immune system, which comprises immune cells in the body and brain, plays a critical role in the development and functioning of the central nervous system with profound effects on emotion, cognition, and behavior across the life span.
2. Activation of immune cells by infection or injury leads to release of proinflammatory cytokines, which signal the brain and induce changes in mood, energy, and behavior. At a systems level, inflammation is associated with changes in negative valence, positive valence, and arousal/regulatory systems as well as social processes; effects on cognitive systems are more mixed. In addition, clinical disorders including depression, schizophrenia, and posttraumatic stress disorder are associated with alterations in immune function.
3. Psychological stress also activates inflammatory activity and can influence immune-to-brain signaling in ways that magnify stress effects on mood and behavior. These changes help to instantiate the effects of stress in the body and brain, particularly when stress occurs early in development.
4. Psychological interventions can regulate immune activity and may also influence immune-to-brain signaling, promoting neuroimmune resilience.

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