Stress and the Immune System

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The association between stress and immune function has received considerable attention in the past several decades (Irwin 2008; Kemeny and Schedlowski 2007; Kiecolt-Glaser et al. 2002). Dysregulation of the neuroendocrine and immune systems, due to chronic stress, is associated with psychological and physiological disorders, including depression, atherosclerosis, asthma, cardiovascular disease, cancers, and the progression of HIV to AIDS (Antoni et al. 2006; Cohen et al. 2007; Dantzer et al. 2008; Irwin 2008). Furthermore, chronic inflammation and other forms of immune dysregulation increase risk for premature all-cause mortality and a variety of diseases including cardiovascular disease, cancer, and metabolic syndrome (Ershler and Keller 2000; Hansson 2005; Hotamisligil 2006; Nabipour et al. 2006; Parkin 2006). Given these significant health outcomes, it therefore seems essential to understand the complex ways in which stress influences immune functioning, as well as the intrapersonal and interpersonal factors that may exacerbate or buffer the effects of stress on immunity.

In this chapter, we provide an overview of how stress affects immune functioning and examine evidence in the literature of various intrapersonal and interpersonal factors that may exacerbate or buffer the health effects of stress. We first review some basic information concerning the immune system to provide the reader with necessary background. We then present the primary pathways by which stress impacts the immune system, including the sympathetic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and vagal withdrawal. Next, we discuss how the immune response varies and even goes awry, depending on the nature of the stress (acute versus chronic). Additionally, we discuss how the immune response varies depending upon the individual within whom the stress is occurring. Specifically, we focus on various intrapersonal and interpersonal factors associated with immune functioning. Intrapersonal factors reviewed include rumination, emotion regulation, alexithymia, psychological stress, optimism, and positive affect. Interpersonal factors reviewed include close relationship and family processes such as negative and positive behaviors, ambivalence towards a relationship partner, social rejection and social isolation, and early life adversity. To conclude, we highlight some substantive and methodological considerations relevant to future research on the effects of stress on immunity.

5.1 What Is Stress?

We conceptualize stress to be a constellation of events, beginning with a stressor (stimulus), which precipitates a reaction in the brain (stress perception) that in turn activates a physiological or biological stress response to allow the organism to deal

with the threat or opportunity (Dhabhar and McEwen 1997). Psychological stress occurs when events or environmental demands exceed an individual's ability or willingness to cope (Lazarus and Folkman 1984). Being laid off from work, experiencing an argument with a loved one, being diagnosed and living with cancer, or giving a presentation in class are just a few examples of the unexpected obstacles, overwhelming challenges, and uncontrollable events that may be stressful experiences of everyday life. Stress exists on a spectrum—from short-term or acute stress, lasting minutes to hours, to long-term or chronic stress, lasting weeks, months, or years, and the intensity of the stressor is generally linked to its relevance to the survival and reproduction of the organism.

5.2 Overview of the Immune System

Before examining the mechanisms by which psychosocial stressors affect the immune system, we present a brief overview of the immune system as background. The immune system is critical for human health and well-being, as it helps coordinate the body's response to physical injuries and infections that, if left unaddressed, could cause illness or death (Slavich and Irwin 2014). The immune system is composed of two interconnected branches: innate or nonspecific immunity and acquired or specific immunity. Depending on the type of immune response, different components of the immune system may be activated.

The innate response acts immediately (within minutes to hours) when the body is subjected to tissue damage or microbial infection (Medzhitov 2007). The "first line of defense" of innate immunity includes physical barriers such as the skin and mucosal membranes. If these physical barriers are not enough to keep pathogens out, the innate immune response includes neutrophils, monocytes (found in the circulating peripheral blood), and macrophages (found in the tissue) that circulate through the body and use invariant receptors to detect a wide array of pathogens. Upon detecting a pathogen, the cells phagocytize them by engulfing and ingesting them. Additionally, a signaling cascade is activated that results in the activation of nuclear factor-κB (NF-κB) and interferon (IFN) regulatory factors, which are transcription factors that in turn drive the expression of proinflammatory immune-response genes including interleukin (IL)-1 and tumor necrosis factor-α (TNF-α). These genes then produce small protein molecules called cytokines, which are the main actors of the inflammatory response (Raison et al. 2006). Proinflammatory cytokines (e.g., IL-1, IL-6, TNF-α) are those that increase or upregulate inflammation, whereas anti-inflammatory cytokines (e.g., IL-4, IL-10) decrease or downregulate inflammation. The cumulative activities/effects of proinflammatory cytokines are referred to as inflammation. These cytokines initiate a "call to action" and attract other immune cells to the infected area. Another cell involved in innate immunity is the natural killer (NK) cell. NK cells recognize the lack of a self-tissue molecule on the surface of cells (characteristic of many kinds of virally infected cells and some cancerous cells) and lyse the cells by releasing toxic substances on them. The innate immune response is also referred to as a nonspecific response because these

mechanisms are not specific to any antigen; rather, this immune response is programmed to recognize features that are shared by groups of foreign substances and will take action to eliminate anything and everything that it deems "foreign" or "not-self."

If a pathogen survives or evades the actions of the innate immune response, then the acquired immune response becomes activated. In contrast to innate immunity, which is nonspecific and does not provide long-lasting protection to the host, acquired immunity involves the proliferation of microbial-specific white blood cells (lymphocytes) that attempt to neutralize or eliminate microbes based on a memory response of having responded to a specific pathogen in the past. The primary cells of the acquired immune response are lymphocytes, including T cells and B cells. T cells include helper T cells (T_H) and cytotoxic T cells (T_C). Helper T cells recognize and interact with an antigen, "raise the alarm" by producing cytokines that call more immune cells to the area, and activate B cells, which produce soluble antibodies. Antibodies are proteins that can neutralize bacterial toxins and bind to free viruses, "tagging" them for elimination and preventing their entry into cells. Cytotoxic T cells recognize antigen expressed by cells that are infected with viruses or otherwise comprised cells (e.g., cancer cells) and lyse those cells. Whereas the innate immune response is rapid, the acquired immune response takes days to fully develop (Barton 2008).

Importantly, acquired immunity in humans is composed of cellular and humoral responses (Elenkov 2008). Cellular immune responses are mounted against intracellular pathogens (e.g., viruses) and are coordinated by a subset of T-helper lymphocytes called *Th1* cells. In the Th1 response, helper T cells produce cytokines, including IL-2, TNF-β, and IFN-γ. These cytokines are associated with the promotion of excessive inflammation and activate macrophages and cytotoxic T cells, which lyse the infected cells. Humoral immune responses are mounted against extracellular pathogens (e.g., parasites, bacteria) and are coordinated by a subset of T-helper lymphocytes called *Th2* cells. In the Th2 response, helper T cells produce different cytokines including IL-4, which stimulate the growth and activation of mast cells and eosinophils, as well as the differentiation of B cells into antibody-secreting B cells. These cytokines also inhibit macrophage activation, T-cell proliferation, and the production of proinflammatory cytokines (Elenkov 2008).

Regulatory T cells (Treg) also play an important role in mediating immune suppression in numerous settings, including, for example, autoimmune disease, allergy, and microbial infection. Treg cells are in the CD4, helper T-cell lineage. They form a subset of cells that also express the cell-surface activation marker CD25, but are best distinguished by the intracellular expression of forkhead box P3 (FOXP3), an important T-cell immunoregulatory transcription factor. Treg cells are an important source of IL-10, once considered a Th2 cytokine but now recognized as being more generally immunoregulatory and anti-inflammatory. Tregs also produce transforming growth factor (TGF)-beta, a cytokine with complex and somewhat contradictory actions but a profile that is generally anti-inflammatory.

Given the general rule that physiological systems in the body have built-in restraining mechanisms, it should perhaps not be surprising that the discovery of

Tregs has prompted the search for regulatory cells in other immune lineages. And indeed, although not as well characterized as Tregs, it is now clear that such cells exist and are important for proper immune functioning. Such cells include regulatory dendritic and B cells and M2-type macrophages. It is increasingly recognized that inflammatory and autoimmune conditions are promoted when these regulatory cells function suboptimally. On the other hand, increasing data suggest that these cells can also pose a risk of inducing patterns of immune suppression that are not always health promoting. For example, regulatory cells have been implicated in vulnerability to cancer development. Increasing evidence also suggests, however, that suboptimal immunoregulatory functioning may be a common feature of major depression and may, in fact, contribute to the proinflammatory state often observed in major depressive disorder.

5.3 Pathways Connecting Stress to Immune Function

Stress can modulate the immune system through various pathways (Fig. 5.1). The first pathway involves the sympathetic nervous system (SNS; adrenergic activation), and the second pathway involves the hypothalamic-pituitary-adrenal (HPA) axis. Both pathways are presented below, and we also discuss evidence suggesting that the parasympathetic nervous system (PNS), specifically vagal withdrawal, affects immune functioning.

5.3.1 Sympathetic Nervous System

Running from a tiger or moving in for a first kiss are various stressful situations, as perceived by the brain, which result in the rapid activation of the autonomic nervous system (ANS). The ANS can be separated into two divisions: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS.)

Activation of the SNS rapidly produces many physiological effects evolved to help cope with threat, including increased blood flow to essential organs, such as the brain, heart and lungs, and to skeletal muscles, dilation of lung bronchioles, increased heart rate and contraction strength, and dilation of the pupils to allow more light to enter the eye and enhance far vision. At the same time, SNS activation diverts blood flow away from the gastrointestinal (GI) tract and skin by stimulating vasoconstriction and inhibits GI peristalsis.

The SNS, also referred to as the "fight-or-flight" system, releases mainly norepinephrine (noradrenalin) and epinephrine (adrenaline) from the cells of the adrenal medulla. Once released, these catecholamines act through α- and β-adrenergic receptors to increase production of circulating proinflammatory cytokines including IL-1, IL-6, and TNF-α (Black 2002; Steptoe et al. 2007). In addition, norepinephrine promotes NF-κβ activation, which regulates and increases the gene expression of several proinflammatory mediators, including IL-6 and IL-8 (Fig. 5.1e). These inflammatory mediators, in turn, enhance inflammation.

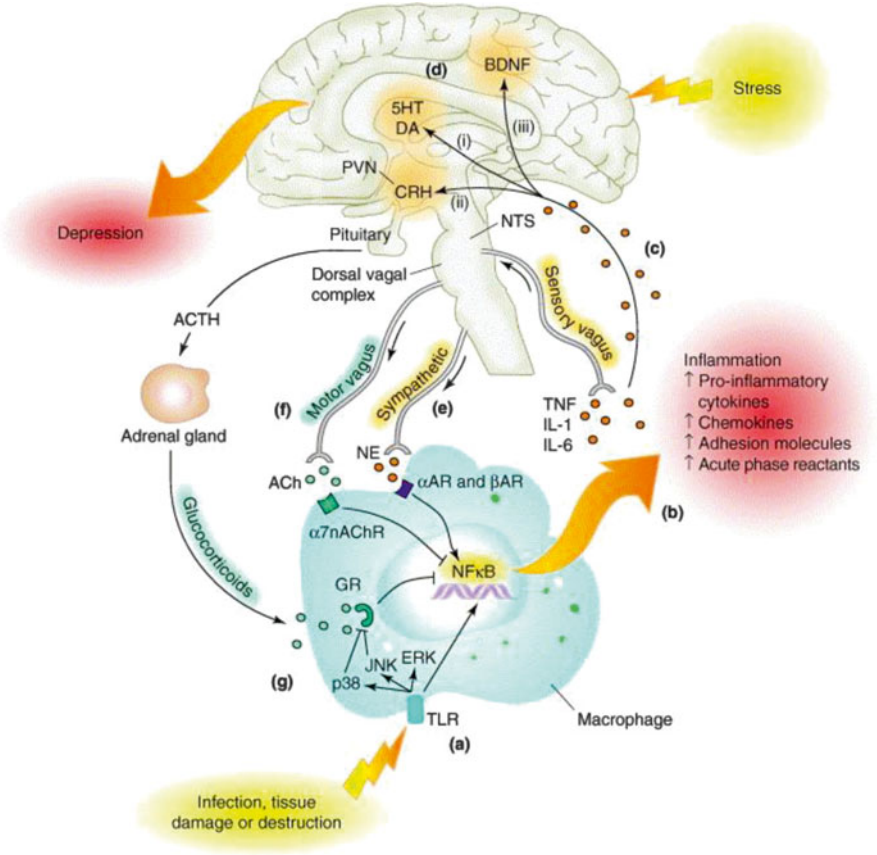

Fig. 5.1 Stress-immune interactions. (*a*) Activation of NF-kB through Toll-like receptors (*TLR*) during immune challenge leads to an inflammatory response including (*b*) the release of proinflammatory cytokines TNF-α, IL-1, and IL-6. (*c*) These cytokines, in turn, access the brain via leaky regions in the blood-brain barrier, active transport molecules, and afferent nerve fibers (e.g., sensory vagus), which relay information through the nucleus tractus solitaries (*NTS*). (*d*) Once in the brain, cytokines participate in various pathways (i, ii, iii) known to be involved in the development of depression [not focused on in this chapter—see Raison et al. 2006]. (*e*) Exposure to environmental stressors promotes activation of inflammatory signaling (NF-κβ) through increased outflow of proinflammatory-sympathetic nervous system responses, including the release of norepinephrine (*NE*), which binds to α- and β-adrenoceptors (αAR and βAR). (*f*) Stressors also induce withdrawal of inhibitory motor vagal input, including the release of acetylcholine (*Ach*), which binds to the α7 subunit of the nicotinic acetylcholine receptor (*α7nAChR*). (*g*) Concurrently with activation of the ANS, stressors induce the production of corticotropin-releasing hormone (*CRH*) in the paraventricular nucleus (*PVN*), which serves to turn on the HPA axis. CRH stimulates the release of adrenocorticotropic hormone (*ACTH*), which then stimulates the release of glucocorticoids (cortisol in humans). Typically, cortisol exerts major suppressive effects on the immune system. However, activation of the mitogen-activated protein kinase pathways (including p38 and Juan amino-terminal kinase [*JNK*]—not discussed here) inhibits the function of glucocorticoid receptors (*GR*), thereby releasing NF-κB from negative regulation by glucocorticoids released as a result of the HPA axis in response to stress (From Raison et al. (2006), with permission)

Neuropeptide Y (NPY) is a co-transmitter of sympathetic nervous innervation and potentiates the actions of norepinephrine. It is considered a stress hormone and mediates many of the cardiovascular effects of stress, including controlling blood pressure and blood flow (Elenkov et al. 2000). NPY can also enhance leukocyte adhesion and together with catecholamines, platelet aggregation, and macrophage activation (Black 2002).

5.3.2 Hypothalamic-Pituitary-Adrenal (HPA) Axis

Concurrently with activation of the ANS, the brain stimulates the production of two closely related neuropeptides in the paraventricular nucleus (PVN) of the hypothalamus via multiple pathways: corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). Together, these chemicals serve to turn on the HPA axis. CRH is the primary activator of the HPA axis. From the PVN, CRH is transported by a specialized portal circulatory system to the anterior portion of the pituitary gland where it stimulates the release of adrenocorticotropic hormone (ACTH). Importantly, arginine vasopressin (AVP) is a potent synergistic factor with CRH in stimulating ACTH secretion; furthermore, there is a reciprocal positive interaction between CRH and AVP at the level of the hypothalamus, with each neuropeptide stimulating the secretion of the other. ACTH then circulates in the bloodstream and stimulates the outer portion of the adrenal glands (i.e., the zona fasciculate of the adrenal cortex) to release glucocorticoids, mainly cortisol in humans and corticosterone in rats (Fig. 5.1g).

Cortisol is the quintessential stress hormone with multiple effects that enhance the fight-or-flight response. It stimulates the breakdown of amino acids in muscles to be converted into glucose for rapid energy utilization by the body and simultaneously promotes insulin resistance to leave glucose in the bloodstream. It increases blood pressure and enhances the ability of stress-released catecholamines to increase cardiac output, which also increases energy available to the organism for coping with stress. The effects of glucocorticoids on the brain are complex, but in response to acute stress, they narrow and focus attention and enhance memory formation for the circumstances that promoted their release.

Importantly, under normal conditions, cortisol exerts major suppressive effects on the immune system. Cortisol does this by reducing the number and activity of circulating inflammatory cells (including lymphocytes, monocytes, macrophages, neutrophils, eosinophils, mast cells), inhibiting production of proinflammatory mediators (including NF-κβ transcription pathway) and cytokines (IL-1, 2, 3, 6, TNF, interferon gamma), and inhibiting macrophage-antigen presentation and lymphocyte proliferation. Cortisol exerts its effects through cytoplasmic receptors. Activated receptors inhibit, through protein-protein interactions, other transcription factors including NF-κβ.

Additionally, cortisol plays an important negative feedback role on the HPA axis: cortisol binds to glucocorticoid receptors in the hippocampus, which inhibits the production of CRH and ACTH, as well as cortisol, to ultimately turn down or off the

activated system. CRH is also negatively regulated by ACTH and itself, as well as by other neuropeptides and neurotransmitters in the brain, such as γ-aminobutyric acid-benzodiazepines (GABA-BDZ) and opioid peptide systems. These mechanisms are critical to ensure that the inflammatory response is appropriately elevated but does not exceed concentrations that would be dangerous for the organism.

5.3.3 How the Immune System "Hears" Changes in the SNS and HPA Axis

Primary and secondary lymphoid organs are innervated by sympathetic noradrenergic nerve fibers (Nance and Sanders 2007). Immune modulation can occur directly through the binding of the hormone to its related receptor at the surface of a cell. Almost all immune cells express receptors for one or more of the stress hormones that are associated with the sympathetic/adrenergic activation and HPA axis (Glaser and Kiecolt-Glaser 2005; Sanders and Kavelaars 2007; Webster et al. 2002). Specifically, T cells, B cells, monocytes, and macrophages express receptors for glucocorticoids, substance P, neuropeptide Y, prolactin, growth hormones, catecholamines (including adrenaline and noradrenaline), and serotonin. T cells also express receptors for corticotropin-releasing hormone. Ultimately, the binding of a stress hormone to a cell-surface receptor triggers a cascade of signals within the cell that can rapidly lead to changes in cell function.

Stress hormones also modulate immune responses indirectly, by altering the production of cytokines, such as IL-1, IL-2, IL-6, and TNF (Glaser and Kiecolt-Glaser 2005). These cytokines have many functions and affect different target cells; thus, dysregulation of these cytokines can cause later downstream effects. Importantly, although not discussed in detail here, these interactions are bidirectional such that cytokines produced by immune cells can feedback and modulate the brain (Fig. 5.1c)—including the SNS and HPA axis (Dantzer et al. 2008; Irwin and Cole 2011; Miller et al. 2009a).

5.3.4 Parasympathetic Activity: Vagal Withdrawal

The sympathetic and parasympathetic nervous systems (PNS) act in tandem to change the state of the body, often by promoting one system and actively withdrawing the other system. The PNS uses primarily the vagus nerve and acetylcholine (cholinergic receptors) as its primary effectors. There is emerging evidence that PNS activity modulates immune responses at the local level to prevent excessive inflammation through both the efferent and afferent fibers of the vagus nerve (Borovikova et al. 2000; Sternberg 2006; Tracey 2009).

The cholinergic anti-inflammatory pathway is the efferent arc of the inflammatory reflex, meaning that its purpose is to send signals down to the periphery to change the response and progression of inflammation. This neural mechanism inhibits macrophage activation through parasympathetic outflow (Borovikova et al. 2000; Tracey

2002, 2009). Specifically, messages sent via action potentials are transmitted by efferent vagus nerve activity to the periphery, including the liver, heart, spleen, and gastrointestinal track, which leads to acetylcholine release. Acetylcholine then interacts with α-bungarotoxin-sensitive nicotinic receptors (ACh receptors) on tissue macrophages and effectively downregulates inflammation by inhibiting the release of TNF, IL-1, and other cytokines (Fig. 5.1f) (Tracey 2002, 2009).

Although the inflammatory reflex is typically described as rapid response to localized inflammation, it may also induce systemic humoral anti-inflammatory response; vagus nerve activity can be relayed to the medullary reticular formation, locus coeruleus, and hypothalamus, leading to increased release of acetylcholine from the anterior pituitary and ultimately a systemic effect to downregulate inflammation (Tracey 2002). Interestingly, based on both in vivo and in vitro experiments, the vagus nerve is selective in that it downregulates the production of proinflammatory cytokines, but not anti-inflammatory cytokines (Tracey 2009). In fact, one abundant peptide, vasoactive intestinal polypeptide (VIP), inhibits TNF-α and IL-12 production and stimulates the secretion of the anti-inflammatory cytokine IL-10, primarily through VPAC1 receptors on immune cells (Ganea and Delgado 2001). Because lymphoid organs receive peptidergic/sensory innervation, this could be one method by which there is a systemic anti-inflammatory effect.

Vagal withdrawal in response to stress might therefore promote inflammation, given the evidence that vagal activity inhibits NF-κB activation (and the release of TNF-alpha from macrophages) via cholinergic signaling through the alpha-7 subunit of the nicotinic acetylcholine receptor (Pavlov and Tracey 2005). Indeed, decreased vagal tone, as manifested by reduced heart rate variability, has been associated with increased inflammatory markers in women with coronary-artery disease (Janszky et al. 2004), healthy controls (Thayer and Fischer 2009), and those with cardiovascular diseases (Haensel et al. 2008).

5.4 When the System Goes Awry: Adaptive and Maladaptive Responses to Stress

The stress response can vary and even go awry, depending on the nature of the stress. In the following section, we discuss how the stress response is typically adaptive in acute stress situations but maladaptive when faced with chronic stressors.

5.4.1 Acute Stress

Psychological acute stressors, such as giving a public speech, and physical acute stressors, such as receiving a cut from a sharp knife, employ the same pathway to activate the stress response system (Maier and Watkins 1998). In both of these hypothetical acute stress situations, the stress response (including activation of the sympathetic nervous system and effects on the immune system) is typically healthy and adaptive for survival.

Acute or short-term stress induces a large-scale redistribution of immune cells in the body. Typically, immune cells stay in certain compartments of the body, including the marginated pool, spleen, bone marrow, and lymph nodes; when acute stressors occur, stress hormones initiate a cascade of events and induce the trafficking of immune cells (e.g., lymphocytes) out of these compartments and into the blood, to ultimately reside in target organs where an individual is most likely to be injured (e.g., skin, gastrointestinal track, urogenital tract, lungs) (Dhabhar et al. 2012). In doing so, the body has increased the immune cell's ability to do defensive maneuvers.

In sum, the body's activation of the sympathetic nervous system and the immune system and concomitant reduction in PNS activity is its way of appropriately responding to the stressor and preparing the body for survival. In the example of public speaking, the brain perceives a stressor, which then warns the body of danger. To promote survival, the body then mounts an immune response to "prepare" for anticipated activation of the immune system (wounding or infection). Although in reality, we do not expect to be physically wounded, for example, when giving a presentation, across evolutionary time stress was a reliable enough signal of impending physical danger that it was adaptive to respond to all fight-or-flight situations (both psychological and physical stressors) by mounting an appropriate biological response, to ultimately ensure survival. Similarly, in the example of receiving a cut, especially prior to modern medicine and hygiene, the immune-enhancement effect of activating the stress response system is advantageous to mount a response against any pathogens that may have entered the wound, as well as to begin the recovery process.

All stress is not necessarily harmful, and all stress is not immunosuppressive. One caveat to this adaptive response to acute stress is that a stress-induced enhancement of the immune system could be harmful if it exacerbates existing inflammatory or autoimmune diseases (Dhabhar and McEwen 2007), possibly due to chronic stress, which we turn to next.

5.4.2 Chronic Stress

Chronic stressors, such as caring for a spouse with dementia, concealing a sexual identity, or coping with childhood physical, or sexual abuse, tell a different story for the stress response system. These types of stressors are considered to be the most toxic because they so often result in long-term changes in the emotional, behavioral, and physiological responses that lead to the risk, development, or progression of diseases (Cohen et al. 2007). In addition to emotional and behavioral changes due to the stressor, such as difficulty in coping with the stressor or changes in health behaviors such as sleeping, physiological changes also occur.

Prolonged or repeated activation of the HPA and SAM axes can disrupt the regulation of other body processes, including the immune system. Individuals experiencing chronic stressors have less effective immune functioning, as demonstrated by their increased susceptibility to the common cold (Cohen et al. 1998), impaired

immune response to vaccination, and delayed healing after standardized wound inductions (Glaser et al. 1998, 1999). Additionally, they also experience low-grade, nonspecific inflammation (Segerstrom and Miller 2004). This increase in inflammation is likely due to decreased anti-inflammatory feedback. As previously mentioned, the HPA axis plays an important negative feedback role in suppressing the immune response when it is no longer needed. However, in chronic stress situations, glucocorticoid resistance or insufficient glucocorticoid signaling may occur, which lead to HPA axis-related increases (as opposed to decreases) in inflammation. Possible effects include (1) the adrenal gland can get exhausted and therefore produce less cortisol, which corresponds to decreased anti-inflammatory feedback, or (2) the HPA axis is hyperactivated and the adrenal gland pumps out so much cortisol that the cells' receptors, which typically recognize the cortisol and shut down, become resistant and do not "hear" the cortisol as well (i.e., they are less sensitive) (Hänsel et al. 2010).

In sum, autonomic and neuroendocrine activation in response to stressors is beneficial up to a point, but excessive activation may also have long-term costs. The metabolic requirements posed by psychological stressors to which people are typically exposed in contemporary society are often minimal (Cacioppo 1998). As such, strong autonomic and neuroendocrine activation to psychological stressors is often not needed for effective coping and instead may contribute to chronic diseases over time (Miller et al. 2009b; Robles et al. 2005).

5.5 Intrapersonal Processes and Immune Functioning

How individuals view the world and appraise their own situations and stressors can influence their physiological response to stress. Certain patterns of thought or appraisal of emotions are intrapersonal (i.e., within person) processes that can generate a chronic perception that the world is dangerous, which can create an immune response that "runs hot" and is extra vigilant. Other intrapersonal processes may buffer the effects of stress on immune functioning. In the following section, we discuss various intrapersonal factors that may be associated with, or moderate, the effects of stress on immunity.

5.5.1 Rumination

Rumination is defined as conscious, spontaneous, and recurrent thoughts or images or both about past negative information. For those who ruminate, stress responses may last longer (i.e., slower recovery), based on the Perseverative Cognition Hypothesis (Brosschot et al. 2006). In one study that experimentally induced either rumination or distraction after a public speaking task, the participants in the rumination condition demonstrated sustained increases in inflammation (measured in plasma CRP) that did not return to prestressor levels by the end of the visit. Conversely, participants' CRP in the distraction group increased post-stressor and

then returned to prestressor levels by the end of the visit (Zoccola et al. 2014). Additionally, in a cross-sectional study, older adults who reported being highly ruminative also had greater numbers of leukocytes, lymphocytes, and B cells than those who reported lower rumination (Thomsen et al. 2004), suggesting that rumination may be related to an activation of the acquired immune system and thus may be associated with a more prolonged immune response to stress.

5.5.2 Emotion Regulation

Emotion regulation refers to the processes by which individuals influence which emotions to have, when to have them, and how to experience and express them (Gross 1998). Two common emotion regulation strategies include cognitive reappraisal and expressive suppression. *Cognitive reappraisal*, considered an adaptive strategy, involves altering how to think about an emotion-eliciting situation in order to change its emotional impact. In contrast, *expressive suppression*, generally considered a maladaptive emotion regulatory strategy, involves inhibiting emotional expression in response to an emotion-eliciting event (Gross and John 2003).

To date two studies have examined these emotion regulation strategies in relation to immune functioning and cardiovascular disease (CVD). In one study, CRP levels (a known marker of CVD risk) and reappraisal and suppression were assessed in 379 adults. Reappraisal was associated with lower CRP, and suppression was associated with higher CRP after controlling for demographics, suggesting that adaptive emotion regulation strategies may promote healthy outcomes by lowering inflammatory mechanisms (Appleton et al. 2013). In the second study, IL-6 mediated the association between reappraisal-related engagement of the dorsal anterior cingulate cortex (dACC, a brain region involved in governing the release of neurohormones and neurotransmitters of the HPA axis, SNS, and PNS) and atherosclerosis (Gianaros et al. 2014). One interpretation offered was that elevated inflammation, as reflected by increased IL-6, might have upregulated negative affect or arousal processes that consequently increased the cognitive demands required for the regulation of emotion at the neural level (e.g., there might have been more negative affect to regulate). However, this was a cross-sectional design and so additional research is needed to examine the directionality and pathways linking emotion regulatory processes and immune functioning in clinically relevant populations.

Another emotion regulation strategy, emotional approach coping (EAC), has also been examined in relation to inflammation. EAC is comprised of emotional processing (purposive attempts to acknowledge, explore, and understand one's emotions) and emotional expression (active verbal and nonverbal efforts to communicate emotional experiences) (Stanton et al. 1994). In a sample of 41 men who had undergone prostatectomy or radiation therapy for localized prostate cancer, emotional processing at baseline predicted lower IL-6, sTNF-RII, and CRP 4 months later, whereas emotional expression was associated with higher levels of sTNF-RII (Hoyt et al. 2013). Interestingly, the interaction of emotional processing and expression

suggested that expression of emotion is associated with higher inflammation (CRP and sTNF-RII) only in the context of low emotional processing. The expression of emotions without efforts to understand them might promote emotion dysregulation and higher inflammation.

Master et al. (2009) examined emotional approach coping and inflammation before and after a standardized laboratory stressor, the Trier Social Stress Test (TSST). Participants in the TSST paradigm were asked to prepare and give an impromptu public speech and to perform difficult mental arithmetic to a nonresponsive, socially rejecting panel of raters. Findings revealed that, in response to the stressor, higher levels of emotional approach coping, particularly emotional processing, were associated with a less pronounced increases in soluble tumor necrosis factor receptor type-II (sTNF-RII) in oral mucosal transudate. These findings suggest that people who are more likely to cognitively reappraise and cope with stressors by approaching their emotions, particularly through emotional processing and related emotional expression, may demonstrate lower inflammatory outcomes, which could promote more optimal health.

5.5.3 Alexithymia

Alexithymia is a personality trait characterized by impairments in cognitive processing and regulation of emotions that is typically measured using the 20-item Toronto Alexithymia Scale (TAS-20). It is hypothesized that this deficit in affective and cognitive-emotional processing leads to prolonged and amplified physiological arousal to stress thus disturbing the autonomic system and HPA axis and ultimately the immune system (Guilbaud et al. 2003). Rather than there being a clear shift towards either pro- or anti-inflammatory mediators in alexithymic individuals, circulating cytokine profiles and Th1/Th2 responses may be affected (Guilbaud et al. 2003; Mandarelli et al. 2011).

Alexithymia has been linked to lower circulating levels of IL-2R and IL-4α in somatoform disorders (Pedrosa Gil et al. 2007) and IL-6 in healthy participants (Mandarelli et al. 2011). Others have found significant positive correlations between alexithymia and serum levels of TNF-α in patients suffering from rheumatoid arthritis (Bruni et al. 2006), as well as serum levels of IL-4 (a type 2 cytokine) in healthy female participants (Corcos et al. 2004). Alexithymia has also been linked to decreased in vitro production of IL-1β, IL-2, and IL-4, and a skewed Th1/Th2 (IL-2/IL-10) response towards Th2 response (Guilbaud et al. 2009). In addition, various lymphocytes have been found in very low levels in alexithymic men (for the natural killer subset: CD57 – CD16+ and killer effective T-cell CD8+CD11a+cells) (Dewaraja et al. 1997) and women (CD2, CD3, CD4, and CD19) (Todarello et al. 1994, 1997). Lastly, alexithymic patients with HIV exhibited increased norepinephrine-to-cortisol ratio and viral load (McIntosh et al. 2014), suggesting a greater vulnerability to disease progression in these patients. Taken together, these findings suggest that alexithymia may be associated with lower cell-mediated

immunity and a skewed Th1/Th2 ratio towards Th2 response. Thus, it has been suggested that the neuroendocrine and immune responses of alexithymics may follow a similar pattern as in persons with chronic stress (Guilbaud et al. 2003).

5.5.4 Psychological Stress

Across a number of studies over the years, psychological stress has been found to be associated with changes in physiological functioning, including changes in immunity. Measures of psychological stress include the Perceived Stress Scale (PSS) (Cohen et al. 1983) and the Life Events and Difficulties Schedule (LEDS) (Brown and Harris 1978). Higher levels of perceived psychological stress have been associated with reduced control of latent herpesviruses, blunted humoral responses to immunization, greater susceptibility to infectious disease, and poorer wound healing (Cohen et al. 2001; Dyck et al. 1999; Glaser and Kiecolt-Glaser 2005; Glaser et al. 1998, 1999; Kiecolt-Glaser et al. 1996a). Interestingly, measures of objective stress do not always yield the same health findings. For example, Cohen and colleagues reported that both perceived stress and stressful live events (objective measure of stress) predicted greater risk for developing the common cold. However, these two measures produced different associations with illness and were mediated by different biological processes (Cohen et al. 1993). Thus, measures of stress based upon the objective environment versus those based upon subjective appraisal relate to different biological mechanisms, predict different aspects of illness, and may ultimately be associated with different disorders and disease (Monroe 2008).

5.5.5 Positive Psychological Well-Being: Optimism and Positive Affect

Positive psychological well-being, including dispositional optimism and positive affect, has also been associated with immune functioning. Evidence suggests that higher levels of optimism and positive affect are generally associated with better immune functioning and may ultimately be protective for health during times of heighted stress, whereas lower levels of these are generally associated with poorer immune functioning.

5.5.5.1 Dispositional Optimism

Dispositional optimism reflects the extent to which individuals hold generalized favorable expectancies for their future and is most often assessed by the Life Orientation Test (LOT (Scheier and Carver 1985)). Greater optimism has been associated with lower levels of IL-6 cross-sectionally (Roy et al. 2010) and IL-6 and soluble intercellular adherence molecule pooled across multiple time points (Ikeda et al. 2011). In a double-blind placebo-controlled study in which men underwent either a placebo or real vaccine and then completed two mental stress tasks, those

who reported high levels of dispositional optimism had smaller IL-6 responses to the stress task (independent of age, BMI, trait depression and baseline IL-6) (Brydon et al. 2009). Additionally, in the vaccine/stress group, there was a strong positive association between optimism and antibody responses, indicating that stress accentuated the antibody response to vaccine in optimists (Brydon et al. 2009). Another interesting study examined immune functioning and telomeres, a biological marker of immunosenescence, as related to optimism in men. Men who had shorter telomeres with high telomerase activity (indicative of active cell stress) were less optimistic and showed blunted post-stress recovery in autonomic measures as well as monocyte chemoattractant protein-1 in comparison to men with longer telomeres or men with shorter telomeres and low telomerase activity (Zalli et al. 2014). Together these findings provide support for the stress-buffering hypothesis: optimism may help to buffer the negative effects of stress on immune functioning.

A growing number of studies, however, have demonstrated that difficult stressors have more potentially detrimental effects on the immune systems of more optimistic people (Cohen et al. 1999; Segerstrom 2001, 2005, 2006; Segerstrom et al. 2003). For example, during stressors that are complex, persistent, and uncontrollable, more optimistic people had smaller delayed-type hypersensitivity responses, indicative of less robust in vivo cellular immunity (Segerstrom 2006). This effect may be due to optimists' greater engagement, fatigue, and ultimately physiological stress during difficult stressors. The relation between optimism and immunity is complex and dependent on the duration and type of stressor involved, as well as the individual dealing with the stressor.

5.5.5.2 Positive Affect

There is contention in the field of emotion about how to precisely define positive affect. However, positive affect is broadly defined as reflecting pleasant engagement with the environment (Pressman and Black 2012). Overall, results from investigations into naturally occurring positive affect indicate an association between positive affect and immune function, where higher levels of positive affect are generally associated with enhanced immune function (Pressman and Black 2012). In cross-sectional studies, greater trait positive affect was related to lower levels of circulating IL-6 in the Whitehall study, a large-scale population based study on health (Steptoe et al. 2008), as well as lower levels of stimulated IL-6 in adults after accounting for age, gender, race, BMI, and white blood cell count (Prather et al. 2007). Additionally, the presence of low-grade inflammation (as measured by higher levels of IL-6) and the absence of positive affect were independently predictive of worse subjective health in 347 women of the general population aged 45–90 years (Andreasson et al. 2013).

In other studies, researchers have examined positive affect in the context of an immune challenge and laboratory stressor. In individuals who were experimentally infected with rhino virus, those who had a higher positive emotional style (assessed before infection) demonstrated less symptoms and signs of rhinovirus infection (Doyle et al. 2006); specifically, higher positive emotional style was associated with lower IL-6 levels and lesser symptom and sign responses. Another study examined

the maintenance of a positive outlook in the midst of an acute laboratory stress (the Trier Social Stress Test; TSST) in 35 postmenopausal women. Greater acute stress-induced declines in positive outlook were significantly associated with increased IL-1β reactivity, which significantly predicted increases in depressive symptoms over the following year, controlling for age, body mass index, chronic stress, antidepressant use, and baseline depressive symptoms (Aschbacher et al. 2012). In sum, difficulty maintaining positivity under stress and heightened proinflammatory reactivity may be markers and/or mechanisms of risk for future increases in physical and mental disorders.

5.5.6 Summary

In this section, we identified key intrapersonal factors that are directly or indirectly associated with stress effects on individuals' immune functioning. See Table 5.1 for a summary of intrapersonal factors and their effects on immune parameters. Rumination, the emotion regulation technique of suppression, alexithymia, and perceived psychological stress are generally associated with poorer immune functioning. Interestingly, objective psychological stress may not be associated with the same immune outcomes, or immune pathways. Conversely, the emotion regulation technique of reappraisal and emotional approach coping (particularly emotional processing), optimism, and positive affect are generally associated with better immune functioning and may ultimately be protective for health during times of heightened stress.

5.6 Interpersonal Processes and Immune Functioning

An important extension to the study of relationships between intrapersonal processes and stress and immune functioning acknowledges that individuals live in a social environment and continually interact with others. Individuals' health and emotions influence, and are influenced by, significant others, including, for example, spouses, partners, parents, and children, as well as the broader social ecological contexts in which they live. The following section focuses on how interpersonal processes relate to stress and immune regulation and functioning.

5.6.1 Close Relationships

Broadly, the strength and quality of a person's social connection to other people can predict risk for mortality: stronger social bonds (i.e., better social integration and/or social support) decrease risk for morality by up to 50 % (Holt-Lunstad et al. 2010). Results from another meta-analytic review of 126 published empirical articles over the past 50 years indicate that greater marital quality is related to better health, including lower risk of mortality and lower cardiovascular reactivity during marital

Table 5.1 Summary of intrapersonal factors and effects on immune parameters

Intrapersonal factors	Associated effects on immune parameters and functioning
Rumination	↑ CRP, leukocytes, lymphocytes, and B cells (Thomsen et al. 2004; Zoccola et al. 2014)
Emotion regulation	
Reappraisal	↓ CRP (Appleton et al. 2013)
Suppression	↑ CRP (Appleton et al. 2013)
Emotional approach coping	
Emotional processing	↓ IL-6, sTNF-RII, CRP (Hoyt et al. 2013; Master et al. 2009)
Emotional expression	↑ sTNF-RII (Hoyt et al. 2013)
Alexithymia	↓ IL-2R, IL-4α, IL-6, in vitro production of IL-1β, IL-2, and IL-4, lymphocytes (Dewaraja et al. 1997; Guilbaud et al. 2009; Mandarelli et al. 2011; Pedrosa Gil et al. 2007; Todarello et al. 1994, 1997) ↑ TNF-α, IL-4, in vitro production of IL-1β, IL-2, and IL-4, and Th2 response (Bruni et al. 2006; Corcos et al. 2004; Guilbaud et al. 2009)
Perceived psychological stress	↓ control of latent herpesviruses, blunted humoral responses to immunization, poorer wound healing ↑ susceptibility to infectious disease (Cohen et al. 2001; Dyck et al. 1999; Glaser and Kiecolt-Glaser 2005; Glaser et al. 1998, 1999; Kiecolt-Glaser et al. 1996a)
Dispositional optimism	↓ IL-6, soluble intercellular adherence molecule (Brydon et al. 2009; Ikeda et al. 2011; Roy et al. 2010) ↑ antibody response to vaccine (Brydon et al. 2009)
Positive affect	↓ circulating and stimulated IL-6, ↓ symptoms and signs of rhinovirus infection (Steptoe et al. 2008; Doyle et al. 2006) Declines in positive affect: ↑ IL-1β (Aschbacher et al. 2012)

CRP C-reactive protein, *IL* interleukin, *TNF* tumor necrosis factor, *sTNF-RII* soluble tumor necrosis factor (receptor II), *Th2* T-helper cell type 2

conflict (Robles et al. 2014). Findings from Whisman and Sbarra (2012) suggest that lower marital satisfaction is related to elevated inflammation. It is apparent that close relationships influence health outcomes, and recent growing evidence suggests that immune functioning may be one potential pathway linking close relationships and health (Robles and Kiecolt-Glaser 2003).

5.6.2 Negative Relationship Processes: Anger, Hostility, and Conflict

Negative close relationship processes involving stressful encounters, such as marital strain, conflict, or abuse, can affect immune functioning (Robles and Kiecolt-Glaser 2003). Specifically, how we interact with our close relationship partners (e.g., showing anger, hostility, conflict, blaming or interrupting our partner) may be particularly detrimental and increase both circulating proinflammatory cytokines and stimulated immune inflammatory responses.

For example, couples who displayed higher levels of hostile behaviors during marital conflict showed larger increases in circulating markers of inflammation, including IL-6 and TNF-α, and slower wound healing at 60 % the rate of low-hostile couples (Kiecolt-Glaser et al. 2005). Additionally, high-hostile partners had greater decrements in 24 h immune cell functioning than participants who exhibited fewer negative behaviors (Kiecolt-Glaser et al. 1993). These effects are beginning to be examined longitudinally: Couples who were in more distressful marriages at baseline had larger declines in cellular immune function (proliferative responses to two mitogens, concanavalin A and phytohemagglutinin) 2 years later when compared to spouses in less distressful marriages (Jaremka et al. 2013b). Looking specifically at adaptive immunity, low marital satisfaction and greater hostility during marital conflict were associated with higher Epstein-Barr virus (EBV) antibody titers, indicating poorer ability to control this latent herpesvirus that infects most adults (Kiecolt-Glaser et al. 1987, 1988, 1993, 1997).

There are interesting gender effects in this literature: When comparing a functional measure of the immune system (proliferative response to mitogen) of men and women over the course of a conflict induction, one study found that men's immune functioning increased and women's immune functioning decreased from pre- compared to post-conflict induction (Mayne et al. 1997). These results are corroborated by other findings with similar gender effects, especially for women (Kiecolt-Glaser et al. 1996b, 1998; Malarkey et al. 1994). Taken together, these findings suggest that women may be more sensitive to negative marital interactions than men.

5.6.3 Supportive Relationship Processes

Just as distressing relationships can dysregulate immune function, supportive relationship processes may be immunoprotective. For example, increased positive behaviors exhibited by couples during a social support interaction task predicted faster wound repair from suction blisters (Gouin et al. 2010); positive behaviors were behaviorally indexed by aggregating measures of acceptance, relationship-enhancing attribution, self-disclosure, and humor exhibited during the interaction task. Other behaviors, including warm physical contact, may also be immune enhancing; circulating levels of interferon (IFN)-γ decreased significantly in couples after an hour-long experimental induction of warm physical contact (hugging and kissing), whereas levels did not change in the control condition (couples who read books in separate rooms) (Matsunaga et al. 2009). In other work on HPA and ANS responses to stress, which have important implications on immune functioning, women who received positive physical partner contact (standardized neck and shoulder massage) before undergoing a TSST exhibited significantly reduced subsequent cortisol responses to stress, as well as reduced heart rate increase in response to the stressor (Ditzen et al. 2007).

Supportive communication patterns also promote healthy immune functioning and may be one way to mitigate the stressful effects of martial conflict—or other every-day stressors—on inflammation. Couples who displayed more cognitive

engagement, assessed by the number of cognitive processing words used, during a marital conflict discussion had lower systemic IL-6 responses 24 h after the discussion than did those displaying less cognitive engagement (Graham et al. 2009). In another study, researchers examined the effect of communal orientation, which is marked by first-person pronoun use (*we* talk)—as opposed to singular first-person pronoun (*I* talk)—on the trajectory of congestive heart failure, an immune-related disease. Specifically, in couples in which one partner had congestive heart failure, *we* talk by the spouse, but not by the patient (with congestive heart failure), independently predicted positive change in the patient's heart failure symptoms and general health over the next 6 months (Rohrbaugh et al. 2008). Thus, supportive and positive relationship processes, including warm contact and supportive communication patterns within couples, may prove to be a significant area of research for generating interventions to improve partners' health by mitigating inflammatory responses.

5.6.4 Ambivalence

Much research focuses on how the positive or negative aspects of relationships influence health. However, a small but growing area of research examines the effect of ambivalence on health outcomes. Ambivalence is described as simultaneously feeling positive and negative emotions towards a close relationship partner (Uchino et al. 2001). Perceiving ambivalence towards one's spouse in a support context was linked to greater inflammation (higher IL-6 and fibrinogen and marginally higher CRP levels) even when considering health behaviors, relationship-specific romantic attachment style, spouse negativity/positivity ratings, and overall marital satisfaction (Uchino et al. 2013). Perceptions of ambivalence during support may be a particularly important relational context in which close relationship ties influence health. Further work is needed to examine ambivalence in other contexts (e.g., in response to daily stressors and longitudinal assessments of ambivalence ratings, which may change over time), as well its relation to other indicators of immune functioning.

In related work, coronary-artery calcification scores were highest for individuals who both viewed and were viewed by their spouse in an ambivalent manner (Uchino et al. 2014). Importantly, coronary-artery calcification is correlated with the extent of plaque buildup in the coronary arteries and is a robust predictor of cardiovascular disease and stroke—both of which are associated with chronic inflammation (Danesh et al. 2004). Future work that examines inflammatory mediators associated with ambivalence and other clinically relevant diseases may provide insight on possible interventions to improve health outcomes by fostering interpersonal relationship functioning.

5.6.5 Social Rejection and Social Isolation/Loneliness

Social rejection is a major life event that is related to immune functioning. This interpersonal process is often studied in the context of depression due to the sustained inflammatory process that may elicit sickness behaviors and precipitate

depression for vulnerable individuals (Slavich et al. 2010). In a longitudinal study of 147 adolescent girls at elevated risk for depression, participants had significantly higher levels of mRNA for both proinflammatory transcription factor NF-κB and inhibitor of κB (I-κB), which regulates the effects of NF-κB, at visits when they had experienced a recent targeted rejection life event compared to visits when no such event had occurred (Murphy et al. 2013). A growing body of research suggests that stressors involving social rejection and exclusion activate neural regions involved in processing negative affect, including the dorsal anterior cingulate cortex (dACC) and anterior insula (Slavich et al. 2010). These neural regions activate multiple biological systems, including, in particular, the HPA axis and sympathetic-adrenal-medullary axis, which produce cortisol and catecholamines that can bind to receptors on immune cells, which then modulate the release of proinflammatory cytokines. Thus, social stress-related implications on the neurocognitive pathway involving the dACC and anterior insula may be one mechanism linking social threat and rejection with elevated inflammation and risk for depression (Slavich et al. 2010).

Social isolation, or loneliness, is another interpersonally distressing state that dysregulates immune function (Jaremka et al. 2013c). Interestingly, social isolation is not broadly immunosuppressive but instead selectively suppresses some groups of immune-response genes (e.g., type I interferons and specific immunoglobulin genes) while simultaneously activating others (e.g., proinflammatory cytokines); social isolation has been related to a downregulation of genes involved in antibody production and an upregulation of expressed genes involved in proinflammatory immune response (Cole et al. 2011). Indeed, lonelier people had smaller antibody responses to an influenza virus vaccine than those who were less lonely (Pressman et al. 2005). Additionally, among healthy adults and posttreatment breast cancer survivors, stimulated TNF-α, IL-6, and IL-1β were higher after laboratory stress tasks (including the TSST and Stroop task) among those experiencing greater loneliness compared with those who were less lonely (Hackett et al. 2012; Jaremka et al. 2013a). Thus, social isolation/loneliness has immune consequences that may be especially relevant to clinical populations, such as women undergoing breast cancer treatment.

5.6.6 Early Life Environment and Adversity

A very well-developed area of research has focused on inflammation and early life adversity. Early life adversity is a term ranging in meaning from poverty and abuse to parental loss and is characterized by unpredictability and interpersonal stress (Slavich and Irwin 2014). Childhood adversity can cause long-term alterations in HPA axis functioning that ultimately affects the immune system. In this context, early life adversity programs the brain and body to run inflammation "hot," likely as a result of evolutionary pressure linking stress to danger of wounding and tissue damage (Raison and Miller 2013). This results in chronically elevated inflammation that, although modest, contributes to shaping the brains and bodies of these individuals to be especially vulnerable to mental and physical health problems, including major depressive disorder, cardiovascular disease, and dementia.

Results from research have demonstrated that adults who experienced early life adversity show exaggerated inflammatory responses to stress (Carpenter et al. 2010; Danese et al. 2007, 2008; Pace et al. 2006). Maltreated children develop higher levels of IL-6 in response to a standardized social stressor (TSST) when tested as adults in comparison to a non-maltreated control group (Carpenter et al. 2010; Pace et al. 2006). Additionally, findings from longitudinal studies showed that greater cumulative stress exposure before age 8 predicted higher levels of IL-6 and CRP at age 10 and higher levels of CRP at age 15 in a sample of 4600 children (Slopen et al. 2013). Additionally, maltreated children tended to have higher levels of CRP 20 years later (Danese et al. 2007).

Interestingly, exposure to coevolved microorganisms in childhood may play an important role in how early life adversity affects immune functioning. Recently, researchers in the Philippines have found that even a childhood trauma as severe as maternal deprivation can fail to result in a raised background CRP in adulthood in those individuals who were heavily exposed to a microbe-rich environment and animal feces in childhood (McDade et al. 2013), whereas individuals raised in clean childhood environments in the Philippines showed strong correlations between early life adversity and elevated CRP in adulthood. In the USA, such adverse childhood events tend to have serious consequences for later health, as previously discussed. These findings suggest that exposure to animal-derived microbes might improve regulation of inflammation and so increase stress resilience, though this observation needs to be confirmed in other populations (Rook et al. 2014). We return to this issue in the Future Considerations below.

5.6.7 Summary

In this section, we have attempted to elucidate interpersonal and interdependent factors that may influence health and immune functioning. See Table 5.2 for a summary of interpersonal factors and their effects on immune parameters. Negative relationship processes, including behaviors such as anger, hostility, and conflict, ambivalence, social rejection, social isolation/loneliness, and early life adversity, are generally associated with poorer immune functioning. Importantly, microbial exposure in childhood may play an important role in moderating the effects of early life adversity on inflammation such that it minimizes the effects of adversity and lessens inflammation. On the other hand, supportive relationship processes, including positive behaviors, supportive communication patterns, and warm touch, are generally associated with better immune functioning and may provide insight on possible interventions to improve health outcomes.

5.7 Conclusions and Future Directions

Immune functioning is essential to health and well-being. Understanding how stress influences the immune system requires knowledge of not only the biological pathways and mechanisms by which stress can "get under the skin" but also the multiple

Table 5.2 Summary of interpersonal factors and effects on immune parameters

Interpersonal factors	Associated effects on immune parameters and functioning
Negative relationship processes	↑ IL-6, TNF-α, EBV-titers (Kiecolt-Glaser et al. 1987, 1988, 1993, 1997, 2005) ↓ wound healing, cellular immune functioning (Kiecolt-Glaser et al. 1993, 2005; Jaremka et al. 2013b) Cellular immune functioning: men >females (Mayne et al. 1997)
Supportive relationship processes	↑ wound repair (Gouin et al. 2010) ↓ IFN-γ, IL-6 (Graham et al. 2009; Matsunaga et al. 2009)
Ambivalence	↑ IL-6, fibrinogen, CRP (Uchino et al. 2013)
Social rejection	↑ mRNA for NF-κB and I-κB (Murphy et al. 2013)
Social Isolation/loneliness	↓ antibody response to influenza; downregulation of genes involved in antibody response (Cole et al. 2011; Pressman et al. 2005); ↑ stimulated TNF-α, IL-6, and IL-1β; upregulation of genes involved in proinflammatory immune response (Cole et al. 2011; Hackett et al. 2012; Jaremka et al. 2013a)
Early life environment and adversity	↑ IL-6, CRP (Carpenter et al. 2010; Danese et al. 2007, 2008; Pace et al. 2006)

IL interleukin, *TNF* tumor necrosis factor, *EBV* Epstein-Barr virus, *IFN* interferon, *CRP* C-reactive protein, *mRNA* messenger ribonucleic acid, *NF* nuclear factor, *I* inhibitor

intrapersonal and interpersonal factors that may exacerbate or buffer the effects of stress on immune functioning. Certain factors may prolong or exacerbate the effects of stress, including rumination, emotional suppression, alexithymia, psychological distress, negative relationships processes, ambivalence, social rejection, social isolation/loneliness, and early life adversity. Other factors may mitigate the effects of stress, including emotional reappraisal, emotional approach coping, dispositional optimism, positive affect, and supportive relationship processes. More research is needed in these areas to further uncover the biological and behavioral mechanisms by which these intrapersonal and interpersonal factors exert their effects on the immune system and ultimately overall health and well-being. In the following sections, we highlight some new substantive and methodological considerations relevant to future research on the effects of stress on immunity.

Research findings on stress and immunity may benefit from being understood and approached from an evolutionary perspective. Evolution can provide a guiding framework to help answer *why* individuals have certain behavioral and immunological responses. For example, Raison and colleagues have put forward the Pathogen Host Defense (PATHOS-D) hypothesis, which suggests that the constellation of behaviors observed in major depression (i.e., symptoms associated with elevated levels of inflammatory cytokines or sickness behavior) should be viewed as having been adaptive, rather than socially maladaptive, across human evolution because they allowed the organism to utilize limited metabolic resources for immune activation and recovery (Raison and Miller 2013). The lens of human evolution can be applied to related work on stress and immune functioning, particularly in the

context of interpersonal and group processes. Using this framework, we can begin to address various questions, including, for example, what is the evolved immunology of group processes? In other words, what is advantageous about how couples respond to a conflict? Why might it be advantageous (in an evolutionary sense) that women are seemingly more sensitive to negative social interactions than men? Much of the research reviewed here addresses the "what" (e.g., what factors are associated with altered immune functioning) and "how" (e.g., how does positive social interactions moderate the effects of stress on immune function). The theory of evolution can clarify the underlying logic connecting these issues by beginning to address *why* variables are associated with each other the way that they are. Furthermore, evolution allows us to see stress in a new light—that is, the coordinated stress response is not only a risk factor and source of physiological and behavioral dysregulation but also serves an adaptive and evolutionary function to aid survival. Using this perspective will allow us to continue to move the field forward and examine how and why stress affects immune functioning in individuals, couples, families, and communities.

Future research on stress and immunity may also benefit from accounting for ecological factors, such as exposure, or lack of exposure, to an array of microbes and helminths with which we coevolved and which—while lacking to a large degree in the industrialized world—are still relevant to immune/stress interactions in other geographical and cultural contexts. Much of the present research on stress and inflammation has been conducted exclusively in higher-income, industrialized populations with regimes of sanitation and hygiene that have reduced the frequency and diversity of microbial exposures and burdens of infectious disease (McDade et al. 2013). In other words, we have been studying humans in environments quite different from that in which humans evolved, due to our reconfigured relationship with the microbial and parasitic world. Exposure to these "Old Friend" immunoregulatory organisms may play a paramount role in optimal immune function and should therefore be studied from developmental and life-span perspectives to further advance our knowledge of stress and the immune system.

These "Old Friends" include elements of the gut microbiota, as well as certain pseudocommensal environmental bacterial and helminthes. Exposure to certain ancient viruses at appropriate stages of development also likely programmed appropriate immune function (Rook et al. 2013). Individuals from high-income countries, including the USA, may receive inadequate exposure to immunoregulation-inducting Old Friends. Importantly, infectious exposures in infancy may have lasting effects on the regulation on inflammation in adulthood; to the extent that these pathways become established and carried forward, inflammatory stressors in adulthood may be handled in a similar manner (McDade 2012). Lack of exposure to Old Friends may increase the likelihood of immunoregulatory deficits and uncontrolled inflammation, which, in concert with psychosocial stressors, could contribute to chronic inflammatory and psychiatric diseases (Raison et al. 2010; Rook et al. 2013). As previously discussed, empirical evidence suggested that recent psychosocial stress did not cause detectable increases in CRP in adults who received heavy microbial exposures as infants (McDade et al. 2013). Future research is needed that

explores how other ecological factors (including exposure to Old Friends) may help buffer the negative health effects of stress, with possible implications for intervention and prevention in the US and other Westernized cultures.

Lastly, there are a variety of key methodological considerations that can be incorporated into future research on stress and immune functioning. In the current chapter, we focused mostly on one piece of the puzzle—mainly stress effects on *immune functioning*. However, as shown in some of the research findings reviewed here, changes in immune functioning are mediated by bidirectional and interacting effects of the central nervous system (CNS) and endocrine system. Thus, to further tease apart the mechanisms of action and gain a more complete understanding of the physiological and health impacts of stress, advanced computational modeling that accounts for stress-related changes in multiple, dynamic systems (CNS, immune, and endocrine systems) within and between individuals and ecological contexts, over time, should be employed (Reed et al. 2013; Sturmberg and Martin 2013). Ultimately, these methodological advances may allow us to better understand the mechanisms by which intrapersonal and interpersonal factors may moderate and mediate the regulatory effects of stress on immune functioning. Application of these statistical and design methods can help inform future research and practice regarding optimal, targeted ways to improve immune functioning and treat immune-related conditions to improve health.

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