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Annual Research Review: Neuroimmune network model of depression: a developmental perspective

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Depression is a serious public health problem, and adolescence is an 'age of risk' for the onset of Major Depressive Disorder. Recently, we and others have proposed neuroimmune network models that highlight bidirectional communication between the brain and the immune system in both mental and physical health, including depression. These models draw on research indicating that the cellular actors (particularly monocytes) and signaling molecules (particularly cytokines) that orchestrate inflammation in the periphery can directly modulate the structure and function of the brain. In the brain, inflammatory activity heightens sensitivity to threats in the cortico-amygdala circuit, lowers sensitivity to rewards in the cortico-striatal circuit, and alters executive control and emotion regulation in the prefrontal cortex. When dysregulated, and particularly under conditions of chronic stress, inflammation can generate feelings of dysphoria, distress, and anhedonia. This is proposed to initiate unhealthy, self-medicating behaviors (e.g. substance use, poor diet) to manage the dysphoria, which further heighten inflammation. Over time, dysregulation in these brain circuits and the inflammatory response may compound each other to form a positive feedback loop, whereby dysregulation in one organ system exacerbates the other. We and others suggest that this neuroimmune dysregulation is a dynamic joint vulnerability for depression, particularly during adolescence. We have three goals for the present paper. First, we extend neuroimmune network models of mental and physical health to generate a developmental framework of risk for the onset of depression during adolescence. Second, we examine how a neuroimmune network perspective can help explain the high rates of comorbidity between depression and other psychiatric disorders across development, and multimorbidity between depression and stress-related medical illnesses. Finally, we consider how identifying neuroimmune pathways to depression can facilitate a 'next generation' of behavioral and biological interventions that target neuroimmune signaling to treat, and ideally prevent, depression in youth and adolescents. **Keywords:** Depression; Neurobiology; Immune disorders; Development.

Introduction

According to the World Health Organization (WHO), depression is the leading cause of disability worldwide, and a major contributor to the global burden of disease across the planet (Murray et al., 1996; World Health Organization, 2017). Depression affects over 300 million people globally each year (World Health Organization, 2017), and approximately 40% of depressed individuals will experience another episode within 2 years, and 70% within 5 years (Birmaher, Arbelaez, & Brent, 2002; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Even symptoms of depression in the absence of a diagnosis are associated with significant functional impairment, increased suicide risk, and can progress to a Major Depressive Disorder (MDD) over time (Balázs et al., 2013; van Lang, Ferdinand, & Verhulst, 2007). Furthermore, depression rarely occurs in a vacuum, and instead tends to co-occur with other mental and physical health problems. Over 70% of individuals with MDD have a comorbid psychiatric disorder at some point in their life (Kessler et al., 2003), and a history of depression puts individuals at risk for numerous stress-related medical conditions, including coronary heart disease, metabolic syndrome, and autoimmune illnesses (Gold et al., 2020).

Despite this great public health and scientific significance, the mechanisms responsible for generating risk for depression are not fully understood. Yet, knowledge of these mechanisms is important for understanding pathways to MDD and for developing interventions that prevent or treat the epidemic of depression (Holmes, Craske, & Graybiel, 2014; Insel & Cuthbert, 2015). Growing evidence implicates brain systems involved in detecting threats in the environment, evaluating rewards, and regulating one's emotions and behaviors in the pathophysiology of depression (Hamilton et al., 2012). In a separate literature, heightened inflammation in both the periphery and the central nervous system has been documented in MDD (Dowlati et al., 2010; Goldsmith, Rapaport, & Miller, 2016; Setiawan et al., 2015). Furthermore, the 'sickness syndrome' (e.g. fatigue, anhedonia, inactivity) triggered by inflammation shares many features with depression, and MDD frequently co-occurs with inflammation-related medical disorders (Irwin & Miller, 2007). To date, however, research on neural and inflammatory processes in depression mostly has occurred in parallel. Recently, we (Nusslock & Miller, 2016) and others (Eisenberger, Moieni, Inagaki, Muscatell, &

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Irwin, 2017; Felger & Treadway, 2017; Raison & Miller, 2013; Slavich & Irwin, 2014) have proposed neuroimmune network models that highlight bidirectional communication between the brain and the immune system in both mental and physical health. These models argue that a next generation of research that recognizes signaling between multiple organ systems may provide a more comprehensive and holistic understanding of health and illness than single organ perspectives alone. The goal of the present paper is to refine and extend these models to generate a developmental framework of risk for neuroimmune dysregulation and the onset of depression during adolescence.

Neuroimmune models draw on research indicating that the cellular actors (particularly monocytes) and signaling molecules (particularly cytokines) that orchestrate inflammation in the periphery can directly modulate the structure and function of the brain (Schiller, Ben-Shaanan, & Rolls, 2021; Weber, Godbout, & Sheridan, 2017; Figure 1). More specifically, inflammatory activity in periphery can 'spread' to the brain, where it heightens sensitivity to threatening stimuli, lowers sensitivity to rewarding stimuli, and alters executive control and emotion regulation in both the medial and lateral prefrontal cortex (Nusslock & Miller, 2016). When regulated, this immune-to-brain signaling is highly adaptive. It coordinates a defensive mindset and sickness behaviors (e.g. inactivity) that help remove pathogens and heal wounds by diverting resources to the immune system. When dysregulated, however, particularly under conditions of chronic stress, inflammation can lead to sustained alterations in brain systems involved in generating and regulating emotions, which is reflected in dysphoria and anhedonia (Nusslock & Miller, 2016). This is proposed to initiate unhealthy, self-medicating behaviors (substance use, poor diet) to manage the dysphoria, which further heighten inflammation. Over time, dysregulation in threat, reward, and executive control brain systems and the heightened inflammatory response

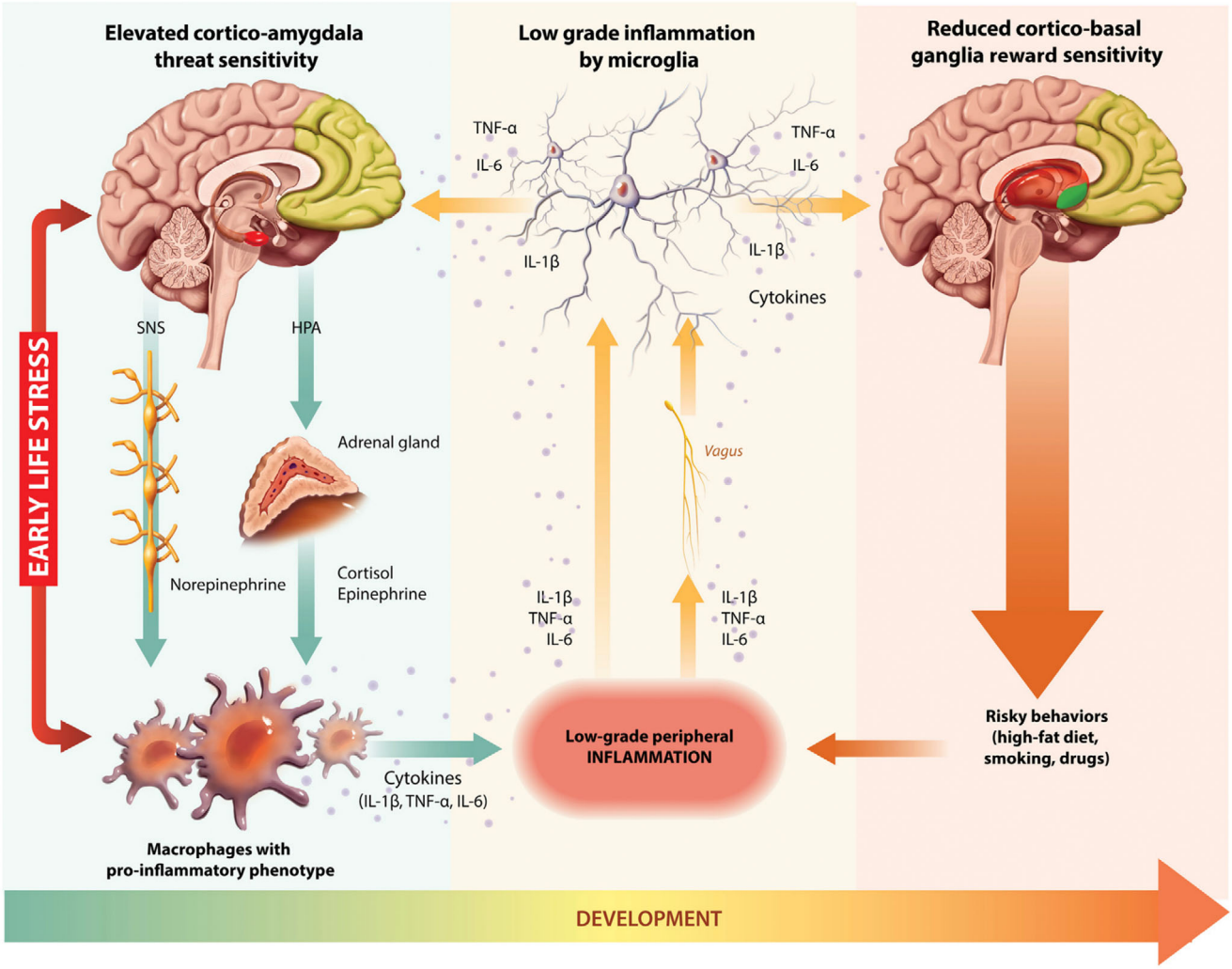

Figure 1 Depiction of neuroimmune network model. HPA, hypothalamic–pituitary–adrenocortical; IL-1β, interleukin-1β; IL-6, interleukin-6; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-alpha. Illustration by Chi-Chun Liu and Qingyang Chen. Reproduced with permission from Nusslock and Miller (2016). Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. Biological Psychiatry, 80, 23–32

may compound each other to form a positive feedback loop, whereby dysregulation in one organ system exacerbates the other. We (Nusslock & Miller, 2016) and others (Eisenberger et al., 2017; Felger & Treadway, 2017; Raison & Miller, 2013; Slavich & Irwin, 2014) argue below that this profile of neuroimmune dysregulation is a dynamic joint vulnerability for depression, particularly during adolescence.

Adolescence is a developmental period that is considered an 'age of risk' for the onset of MDD. Rates of depression rise from adolescence through early adulthood, with the steepest increase occurring between ages 15 and 18 (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015; Breslau et al., 2017). This rise in depression has been linked to normative increases in brain activity that occur during adolescence in neural systems involved in generating threatening, rewarding, and self-conscious emotions (Forbes & Dahl, 2012; Scherf, Smyth, & Delgado, 2013; Somerville et al., 2013; Somerville & Casey, 2010), as well as hormonal changes associated with puberty (Forbes et al., 2010; Urošević, Collins, Muetzel, Lim, & Luciana, 2014). As we argue below, these normative changes in brain activity can heighten responses to stress during adolescence, thus increasing risk for depression (Casement, Shaw, Sitnick, Musselman, & Forbes, 2015; Duffy, McLaughlin, & Green, 2018). In addition, normative changes in peripheral and central immune function and blood–brain barrier permeability occur in adolescence (Bilbo & Schwarz, 2012; Brenhouse & Schwarz, 2016). These normative changes in immune function may cause the immune system to be particularly sensitive to stress and adversity during adolescence, increasing risk for chronic low-grade inflammation and depression (Kuhlman, Chiang, Horn, & Bower, 2017; Lam, Chiang, Chen, & Miller, 2021). Adolescence also is characterized by an increase in social rewards and stressors, and interpersonal stressors during adolescence are particularly likely to precipitate depression (Ge, Lorenz, Conger, Elder, & Simons, 1994; Hammen, 2009; Vrshek-Schallhorn et al., 2015). Thus, adolescence involves a confluence of maturing neural, biological, and social processes that when dysregulated can generate risk for depression. Yet, as discussed below, we argue that early-life adversity from infancy to childhood sets the initial foundation for neuroimmune dysregulation that is then amplified by subsequent stress during adolescence. Thus, the present paper takes a developmental perspective and examines the mechanisms through which stress 'gets under the skin' to heighten risk for depression across multiple sensitive periods of development. This developmental perspective is an important extension of existing models of neuroinflammatory activity in both mental and physical health. Such a developmental perspective can help us better understand whether abnormalities in neuroinflammatory activity predate the onset of depression, reflecting a preexisting vulnerability, or emerge because of the disorder. This is important for understanding etiological pathways to depression, identifying biobehavioral markers of risk, and facilitating treatment development.

We have three goals for the present paper. First, we extend neuroimmune network models of mental and physical health to generate a developmental framework of risk for the onset of depression during adolescence. Many of the constituent parts and pathways of this framework have been discussed elsewhere, and what is unique to the present paper is our attempt to contextualize these pathways in a developmental framework. Furthermore, many of the proposed causal linkages in this developmental framework are speculative at the moment, and the framework is meant to stimulate developmental research in the context of neuroimmune models, rather than provide a definitive mechanistic account. Second, we examine how a neuroimmune network perspective can help explain the high rates of comorbidity between depression and other psychiatric disorders across development, and multimorbidity between depression and stress-related medical illnesses. We will draw on the work and suggestions of others (Dooley et al., 2018; Lucido et al., 2021; Majd, Saunders, & Engeland, 2020) to argue that it will be important to move beyond examining the relationship between inflammation and depression as a homogenous construct, and to instead examine the relationship between inflammation and specific symptom dimensions, particularly anhedonia. Finally, we consider how identifying neuroimmune pathways to depression and motivational deficits can facilitate a 'next generation' of behavioral and biological interventions that target neuroimmune signaling to treat, and ideally prevent, depression during both childhood and adolescence.

Threat, reward, and executive-control neural circuitry in depression

Threat circuitry

Individuals prone to experience more frequent negative emotions, dysphoria, and distress are at an increased risk for MDD and depressive symptoms (Dooley et al., 2018; Jeronimus, Kotov, Riese, & Ormel, 2016; Lucido et al., 2021; Majd et al., 2020; Shackman et al., 2016). This temperament, sometimes referred to as dispositional negativity or negative emotionality, emerges early in development and persists into adulthood (Hur, Stockbridge, Fox, & Shackman, 2019). Among individuals with a history of depression or other internalizing disorders, higher levels of dispositional negativity are associated with a greater number of lifetime episodes and a more pessimistic diagnosis (Buckman et al., 2018; Struijs et al., 2018).

Animal and human research indicate that both a negative disposition and clinical depression are associated with excessive responses to threats in a number of brain regions, including the amygdala, anterior insula, bed nucleus of the stria terminalis, hippocampus, and midcingulate cortex (Kalin, 2017; Shackman et al., 2011; Shackman, Tromp, et al., 2016). Although all of these regions are important, we focus here on the amygdala for three reasons. First, of the brain regions involved in processing threats, the amygdala is the most scrutinized (Freese & Amaral, 2009). Second, the developmental trajectory of the amygdala is well established, which is important given the developmental focus of the present paper (Casey, Heller, Gee, & Cohen, 2019; Gilmore et al., 2012; Payne, Machado, Bliwise, & Bachevalier, 2010). And third, preclinical, animal, and human research indicate that the amygdala is a primary target of immune-to-brain signaling, which is a central mechanistic pathway in neuroimmune models of mental and physical health (see Weber, Godbout, and Sheridan, 2017). However, despite this focus, it is important to recognize that the amygdala is one of multiple brain regions implicated in threat processing and dysphoric emotions, and thus where appropriate we will discuss threat-sensitive brain areas in the present paper rather than focusing exclusively on the amygdala.

Anatomically, the amygdala is positioned to use information from sensory, contextual, and regulatory brain regions to facilitate defensive reactions to a wide variety of threatening or salient stimuli. This literature teaches us that the amygdala is not a fear or dysphoria center, per se, but instead plays a central role in assembling reactions to threats in the environment (Hur et al., 2019; Shackman, Tromp, et al., 2016). These reactions include behavioral responses (e.g. freezing behaviors), physiological responses (cardiovascular, immune, and endocrine activity), and cognitive processes (e.g. attention and vigilance; Davis & Whalen, 2001; Fox, Oler, Tromp, Fudge, & Kalin, 2015). For example, activating the amygdala enhances attentional biases to threat-related stimuli, and humans and animals with amygdala damage fail to show these attentional biases (Hadj-Bouziane et al., 2012; Herry et al., 2007; Hur et al., 2019). Activating the amygdala also creates dysphoria and fear, although newer work suggests that the subjective experience of these emotions also involves the cortex (Fox & Shackman, 2019; LeDoux & Pine, 2016). Converging lines of mechanistic, imaging, and clinical evidence suggest that populations of neurons in the amygdala underlie core features of dispositional negativity in humans and other mammals and causally contribute to feelings of distress and dysphoria that individuals with internalizing disorders experience, including depression (Hamilton et al., 2012; Hur et al., 2019; Shackman, Tromp, et al., 2016). For example, momentary fluctuations in negative mood are reliably associated with functional connectivity between the amygdala and hippocampus, and this association is only evident among individuals with a more negative disposition (Kirkby et al., 2018). Children, adolescents, and adults with internalizing disorders such as depression display elevated amygdala activation to threatening stimuli, and so do individuals with a positive family history of such disorders (Shackman et al., 2016). Higher amygdala activation tends to be associated with more severe symptoms of distress (Thomas et al., 2001; van den Bulk et al., 2014), and this activation is reduced by psychotherapeutic and pharmacological treatments (Månsson et al., 2016; Shackman, Stockbridge, et al., 2016).

Both structurally and functionally, the amygdala goes through a normative and critical period of development from infancy through early childhood (Gilmore et al., 2012; Payne et al., 2010). This early development, together with its sensitivity to environmental stimuli, and its massive connections to the rest of the brain, position the amygdala to inform later developing brain regions about the emotional world, particularly the prefrontal cortex (Tottenham & Gabard-Durnam, 2017). For example, tract tracing in rodents shows that ascending projections from subcortical to cortical regions, and specifically from the amygdala to the prefrontal cortex, emerge earlier than descending projections from the prefrontal cortex to the amygdala (Bouwmeester, Smits, & Van Ree, 2002). This early development makes the amygdala vulnerable to stress and adversity during the early days and years of life (Leppänen & Nelson, 2009). Studies involving mice, monkeys, and humans indicate that early-life adversity sensitizes cells in the amygdala to be highly responsive to threatening stimuli (Nusslock & Miller, 2016). Youth who have been physically abused are vigilant for angry facial cues, probably because they signal forthcoming aggression, and children from low-SES families have a low threshold for judging situations as threatening (Pollak & Kistler, 2002; Pollak & Tolley-Schell, 2003). In the brain, individuals with a history of childhood maltreatment or those who grew up in poverty display structural alterations in the amygdala and show heightened amygdala reactivity to threatening stimuli (Edmiston et al., 2011; Luby et al., 2013; Noble, Houston, Kan, & Sowell, 2012).

Adolescence is another important window of development for threat-related brain systems, including the amygdala. During adolescence, individuals begin to prioritize peer interactions and social relationships and individuate from their parents (Crone & Dahl, 2012; Nelson, Leibenluft, McClure, & Pine, 2005; Scherf et al., 2013). Some studies suggest (Scherf et al., 2013) that the amygdala is at the heart of this reorganization given: (a) its critical role in ascribing salience to stimuli (Adolphs, 2010), (b) its extensive connections with

both cortical and subcortical brain regions (Pessoa, 2008), and (c) the fact that it is one of the few brain regions with both estrogen and androgen receptors, which are critical for pubertal development (Roselli, Klosterman, & Resko, 2001). The amygdala continues to grow in volume throughout childhood and adolescence (Uematsu et al., 2012), and recent longitudinal studies report a normative quadratic pattern whereby both amygdala volume and activity are heightened in adolescents relative to both children and adults (Hu, Pruessner, Coupé, & Collins, 2013; Pfeifer et al., 2011). This, combined with the fact that the amygdala is normatively very responsive to social stressors during adolescence (Scherf et al., 2013), which dramatically increase during this time period (Ge et al., 1994; Larson & Ham, 1993), may help explain why adolescence is 'an age of risk' for depression. Finally, McLaughlin and colleagues reported that individuals with a highly reactive amygdala to negative stimuli at an initial assessment experienced higher internalizing symptoms following a subsequent traumatic event during adolescence (McLaughlin et al., 2014). This is consistent with the idea that prior adversity may incubate in the body and brain and then be amplified by subsequent stress during a period of risk for the onset of a particular disorder.

Reward circuitry

Decreased positive emotions and a reduced sensitivity to rewarding stimuli have long been considered core features of depression (Lewinsohn & Graf, 1973; Meehl, 1975). Indeed, anhedonia, characterized by a diminished interest or pleasure in activities (American Psychiatric Association, 1994), is a cardinal symptom of MDD. Both adults and youth in a current depressive episode self-report reduced reward sensitivity, extraversion, and pleasure sensitivity, and engage less frequently in goal directed behaviors (Alloy, Olino, Freed, & Nusslock, 2016; Forbes, 2009; Kasch, Rottenberg, Arnow, & Gotlib, 2002; Kazdin, 1989; Kotov, Gamez, Schmidt, & Watson, 2010). This reduced sensitivity to rewarding stimuli appears to be a trait-like vulnerability for depression, as opposed to simply a correlate of depressive symptoms. For example, individuals with a lifetime history of depression, but who are in remission, also report lower levels of reward sensitivity (Pinto-Meza et al., 2006), and offspring of depressed parents, who themselves are at heightened risk for depression (Goodman et al., 2011), display deficits in goal-directed behaviors (Mannie, Williams, Browning, & Cowen, 2015) [although see Kasch et al. (2002) and Morris, Bylsma, Yaroslavsky, Kovacs, and Rottenberg (2015) for conflicting results]. In prospective studies, reduced reward sensitivity, as measured by behavioral tasks and scalp recorded neurophysiological data, predicts depressive symptoms and the first onset of MDD, suggesting that a blunted sensitivity to rewards may predate the onset of the illness (Alloy et al., 2016; Bress, Foti, Kotov, Klein, & Hajcak, 2013; Nelson, Perlman, Klein, Kotov, & Hajcak, 2016; Nusslock et al., 2011).

Although many regions in the brain respond to rewards, the cortico-striatal neural circuit is at the heart of the brain's reward system (Berridge, Robinson, & Aldridge, 2009; Haber & Knutson, 2010; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Kringelbach & Berridge, 2010; Schultz, 2000). This circuit involves dopaminergic projections from midbrain nuclei (e.g. the ventral tegmental area) to subcortical regions that assess the value of stimuli (e.g. the ventral striatum) to cortical target regions, including the orbitofrontal cortex. Both animal and human research highlight the role that this circuit plays in processing rewards, determining the probability of receiving a reward, and in facilitating goal-directed behaviors. The cortico-striatal circuit responds to both primary (e.g. food) and secondary (e.g. money) rewards and both social and non-social rewards, suggesting that many different types of rewards share a 'common neural currency' in the brain (Berridge et al., 2009; Gu et al., 2019; Haber & Knutson, 2010). Human neuroimaging studies show that individuals with MDD display reduced activation in the ventral striatum during both the anticipation and receipt of both monetary and social rewards (Keren et al., 2018; Ng, Alloy, & Smith, 2019; Zhang, Chang, Guo, Zhang, & Wang, 2013). More recent work suggests that reduced striatal activation relates to a specific variant of anhedonia characterized by motivational deficits and a disinterest in pursuing pleasurable rewards (Treadway, 2016; Treadway & Zald, 2011). Low striatal activation is present among individuals with MDD during remission (Dichter, Kozink, McClernon, & Smoski, 2012), suggesting that reduced reward-related brain function is trait-like, and is present among offspring of depressed individuals who have yet to develop a depressive episode (Gotlib et al., 2010; Olino et al., 2014; Sharp et al., 2014). The reward hyposensitivity model of major depression argues that individuals with this profile of low trait reward-related brain function do not tend to experience the typical increase in positive emotion following rewarding life events (Alloy et al., 2016; Nusslock & Alloy, 2017). This model also proposes that individuals vulnerable to depression experience an even further reduction in reward-related brain function following negative life events such as certain loss or failure, which can lead to depressive symptoms, particularly anhedonia.

Like threat circuitry, adversity in childhood affects the development of the cortico-striatal reward circuit and is associated with later deficits in reward processing. Animals exposed to early adversity display less interest in sweet foods and blunted responses to dopamine agonists designed to increase

positive emotions (Matthews & Robbins, 2003; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994). Humans exposed to maltreatment during childhood display later deficits while processing rewards on behavioral tasks and lower activation in the ventral striatum following monetary gains (Dillon et al., 2009; Guyer et al., 2006; Mehta et al., 2010).[1] Like the amygdala, the ventral striatum undergoes a normative, but rapid maturation during adolescence that generates a developmental period characterized by a heightened sensitivity to and motivation for rewards (Somerville & Casey, 2010). For example, Steinberg and colleagues used behavioral tasks to show that sensitivity to monetary rewards peaks during adolescence, with a steady increase from late childhood to adolescence and a subsequent decline from late adolescence to adulthood (Cauffman et al., 2010; Steinberg et al., 2009). Thus, adolescence may be a period during which the brain's reward systems are particularly sensitive to stress, and stress exposure during adolescence may compound the effects of early adversity on reward-related brain function. In line with this view, individuals exposed to adversity during adolescence often fail to show the normative increase in reward sensitivity during this time period and are at increased risk for depression (Casement et al., 2015; Duffy et al., 2018). Also like the amygdala, the striatum is very responsive to social rewards and stressors during adolescence (Crone & Dahl, 2012; Nelson et al., 2005). In fact, neural responses to social rewards during adolescence may distinguish depressed from non-depressed individuals as well as or better than neural responses to other classes of rewards (He, Zhang, Muhlert, & Elliott, 2019; Sankar et al., 2019). Finally, early-life adversity increases risk for disruptive behaviors that are a common precursor for mental health problems during adolescence, including depression (Broidy et al., 2003; Copeland, Shanahan, Costello, & Angold, 2011; Jaffee, 2017). Thus, one pathway through which early-life adversity might increase risk for depression is through generating disruptive behaviors that themselves are stress-generating across childhood and into adolescence.

Executive control circuitry

The prefrontal cortex (PFC) is another brain system implicated in both risk and resilience for depression (Pizzagalli & Roberts, 2022). The PFC supports executive control, which is a set of processes that regulate one's thoughts, emotions, and behaviors to accomplish goals in the face of competing inputs and demands (Casey, Giedd, & Thomas, 2000; Miyake et al., 2000; Miyake & Friedman, 2012). The PFC is frequently divided into medial (i.e. toward the midline) versus lateral (i.e. toward the side) and dorsal (i.e. toward the top) versus ventral (i.e. toward the bottom) regions (Phillips, Ladouceur, & Drevets, 2008). Dorsal portions of the medial PFC (dmPFC) help process information about the self, others, and social situations, or what is referred to as social cognition (Amodio & Frith, 2006; Hiser & Koenigs, 2018), and are implicated in self-mentalizing processes linked to the default mode network (Bressler & Menon, 2010). The ventral medial PFC (vmPFC) is more involved in assessing the risks versus rewards of engaging in behaviors, inhibiting behaviors and unlearning fears (i.e. extinction), and automatic or involuntary emotion regulation (Etkin, Büchel, & Gross, 2015; Haber & Knutson, 2010; Schultz, Tremblay, & Hollerman, 2000). Lateral portions of the PFC, particularly in the dorsal lateral PFC (dlPFC), are involved in higher order cognitive functions, impulse control, working memory, and voluntary or conscious emotion regulation (Barbey, Koenigs, & Grafman, 2013; Bressler & Menon, 2010; Etkin et al., 2015).

Depression is associated with structural and functional alterations in both the medial and lateral PFC, as well as deficits in executive control and self-regulation, that typically emerge during adolescence (Altamirano, Miyake, & Whitmer, 2010; Arnone et al., 2016; Hamilton et al., 2012; Wise et al., 2017). The development of the PFC may yield important information as to why adolescence is an age-of-risk for the onset of depression. For example, depression frequently involves negative or hopeless thoughts about the self, world, and future (Abramson, Metalsky, & Alloy, 1989; Nusslock et al., 2011). The ability to generate these thoughts may depend on the normative development of portions of the dmPFC during adolescence that facilitate social cognition, mentalizing, and the ability to think about the future and reflect on the past (Rankin, Lane, Gibbons, & Gerrard, 2004; Shaw et al., 2008). On this topic, Somerville and colleagues report that adolescents report higher levels of self-conscious emotions during laboratory tasks involving social evaluation compared to both children and adults, which is reflected in a normative increase in dmPFC activation (Somerville et al., 2013). Thus, adolescence involves the confluence of a normative increase in threat processing in the amygdala (Hu et al., 2013; Pfeifer et al., 2011), reward processing in the striatum (Somerville & Casey, 2010; Steinberg et al., 2009), and self-conscious emotions facilitated by the dmPFC. This is adaptive when regulated, and can set the foundation for behavioral exploration, and self-awareness (Somerville & Casey, 2010). When dysregulated, however, we argue that this can set the stage for cognitive vulnerability, dysphoria, and the onset of depression.

Researchers have begun to underscore the importance of examining integrated neural circuits and networks rather than focusing only on brain regions in isolation of each other (Bassett, Xia, &

Satterthwaite, 2018; Somerville & Casey, 2010). In line with this logic is an emerging body of work suggesting that threat, reward, and executive control processes are intimately related and reciprocally interact (Swartz, Carrasco, Wiggins, Thomason, & Monk, 2014; Tillman et al., 2018). For example, starting in adolescence, the vmPFC sends projections via white matter tracks to inhibitory cells in threat-sensitive brain areas in the sub-cortex, including the amygdala (Casey et al., 2019; Cressman et al., 2010). This 'top-down' communication via the vmPFC forms the basis of automatic or involuntary emotion regulation and the ability of executive control systems to bias lower level threat processes to optimize emotion and behavior to the circumstances (Delgado, Nearing, LeDoux, & Phelps, 2008; Stevens, Skudlarski, Pearlson, & Calhoun, 2009; Swartz et al., 2014). The development of automatic emotion regulation strategies during adolescence is complimented by the subsequent development of more conscious, deliberate, and voluntary emotion regulation strategies during early adulthood, including cognitive reappraisal (Casey et al., 2019; Denny, Inhoff, Zerubavel, Davachi, & Ochsner, 2015). These processes are supported by that maturation of dorsolateral portions of the PFC that continue to develop via cortico-cortical connections into the late twenties (see Casey et al. for review; Casey et al., 2019). For example, recent evidence suggests that the dlPFC mediates the association between increasing age and diminished amygdala responses to emotionally evocative stimuli (Silvers et al., 2017). Yet individuals with, and at risk for depression and dysphoria often engage the PFC in a manner that increases or amplifies threat related brain activity, even when the situation does not call for it (i.e. the person is safe and not facing threat; Birn et al., 2014; Fowler, Miernicki, Rudolph, & Telzer, 2017; Johnstone, Van Reekum, Urry, Kalin, & Davidson, 2007). To quote Shakespeare, 'thinking makes it so' (Shakespeare, 2008), and the propensity towards negative or hopeless thoughts in depressed individuals tends to amplify amygdala reactivity, and thus, distress and dysphoria. In line with this perspective, depression is associated with weakened connections within large scale brain networks anchored in the dlPFC that support the cognitive regulation of emotion, behavior, and thought, including the frontoparietal central executive network (Bressler & Menon, 2010; Schultz et al., 2018). The dlPFC also has been implicated in cognitive vulnerability for depression, which has been shown to predict the onset, course, and severity of depression over the life span (Abramson et al., 2002; Nusslock et al., 2011).

Negative or depressive thoughts not only increase threat processing and dysphoria, they also tend to dampen positive and rewarding emotions, and individuals with, and at risk for, depression may engage the PFC in a manner that decreases ventral striatal activity to rewarding stimuli (Anderson et al., 2023; Walsh et al., 2017). Growing evidence highlights the role that glutamate, the brain's primary excitatory neurotransmitter, plays in providing 'top-down' regulation of reward processing and goal-directed behavior (Belleau, Treadway, & Pizzagalli, 2019; Sesack, Carr, Omelchenko, & Pinto, 2003). Glutamatergic neurons descend from the vmPFC to the ventral striatum where they modulate dopamine transmission to facilitate motivation and goal-directed behaviors to pursue rewards in the environment (Britt et al., 2012; Carr & Sesack, 2000; Sesack & Grace, 2010). Animal studies report that disrupted glutamate signaling between the vmPFC and striatum impairs motivation for rewards and reward-based decision making (Kelley, Andrzejewski, Baldwin, Hernandez, & Pratt, 2003; Stanton, Holmes, Chang, & Joormann, 2019). In humans, multiple meta-analyses of studies using magnetic resonance spectroscopy report that individuals with MDD have altered glutamate in the mPFC (Belleau et al., 2019; Portella et al., 2011), which specifically has been linked to anhedonia and motivational deficits (John et al., 2012; Stanton et al., 2019).

The PFC is particularly vulnerable to life stress and adversity given its protracted development into early adulthood. Both early-life adversity and chronic stress are associated with structural and functional alterations in both medial and lateral portions of the PFC (Edmiston et al., 2011; Luby et al., 2013; Sheridan et al., 2022). Thus, one mechanism through which stress may get under the skin to generate risk for depression is by affecting the developmental arc of the PFC. Stress and adversity also affect structural and functional connectivity between the PFC and both the amygdala and ventral striatum. With respect to cortico-amygdala threat circuitry, early-life adversity (e.g. maltreatment, poverty) is associated with less functional connectivity between the mPFC and amygdala at rest and during an emotion regulation task, and less structural integrity in the uncinate fasciculus, which is the white matter axonal tract that connects the mPFC and amygdala (Herringa et al., 2013; Kim et al., 2013; McCarthy-Jones et al., 2018). Adversity also affects the developmental timing of when the vmPFC begins to regulate the amygdala. Typically, this coupling emerges during adolescence, but appears to be accelerated in children exposed to adversity (Gee et al., 2013). This may reflect the need for children living in adverse environments to 'grow up too soon' and hyper-regulate their amygdala reactivity and stress physiology to survive in unpredictable settings. Children who display this accelerated vmPFC-amygdala connectivity are at elevated risk for depression later in life (Gee et al., 2013). Adversity also affects connections in the cortico-striatal reward circuit. Individuals who grew up in a low SES household display less functional connectivity between the mPFC and ventral striatum as

adults and less structural connectivity in the corticostriatal circuit (Gianaros et al., 2011; Kennedy et al., 2021; Marshall et al., 2018). These findings may be mediated through stress's effect on glutamatergic neurons in the mPFC which, as noted above, modulate dopamine transmission and reward signaling in the striatum (Belleau et al., 2019). Future research is needed to test this hypothesis. Finally, another way that stress and adversity may affect the PFC and generate risk for depression is through 'bottom-up' signaling from the subcortex. As noted, threat-sensitive brain regions, including the amygdala, develop early and then influence the subsequent development of the PFC, particularly the vmPFC, during adolescence (Tottenham & Gabard-Durnam, 2017). For example, Tye and colleagues report that amygdala–prefrontal inputs guide behavior amid conflicting cues of reward and punishment (Burgos-Robles et al., 2017). Under conditions of adversity, threat-sensitive brain regions, such as the amygdala, could become wired to the PFC in a way that facilitates chronic vigilance, a negative disposition, and ultimately depression. Future research is needed to test this perspective as well.

Inflammation in depression

A parallel and growing literature highlights the role of other organ systems in the pathogenesis of depression, including the immune system. Inflammation is one of the first responses of the immune system to infection and injury and attempts to eradicate invading pathogens and promote tissue healing in the short term. Inflammation begins when circulating immune cells, including neutrophils, monocytes, and dendritic cells, detect microbial invasion or damaged tissue and release communication molecules known as inflammatory cytokines (Bartekova, Radosinska, Jelemensky, & Dhalla, 2018). These cytokines coordinate a series of immunologic events that typically remove the pathogen or repair the tissue, upon which the inflammation subsides (Barton, 2008; Nathan, 2002). However, if this response becomes prolonged and disseminated, because either the evoking stimulus remains or the system is dysregulated and cannot dampen the inflammatory response, a low-grade, chronic inflammation can develop. Depending on where in the body this nonresolving inflammation develops, different immune cells and signaling molecules become involved. Despite the biological diversity of these 'nonresolving inflammatory responses' (Nathan & Ding, 2010) their presence forecasts morbidity and mortality from multiple physical and mental health problems, including depression (Miller & Raison, 2016; Nusslock & Miller, 2016; Tottenham & Gabard-Durnam, 2017).

One of the early insights into inflammation's role in depression came from observing the 'sickness syndrome', which is a state of anhedonia, fatigue, and inactivity that is triggered by inflammation during the early stages of an illness (Charlton, 2000; Kent, Bluthé, Kelley, & Dantzer, 1992). It was observed that this syndrome shares many features with depression, particularly the symptom of anhedonia (Irwin & Miller, 2007; Raison & Miller, 2003). It also was noted that depression frequently co-occurs with medical illnesses (e.g. heart disease, autoimmune disorders) and treatments (e.g. radiation therapy for cancers, interferon therapy for hepatitis) that provoke inflammation (Benros et al., 2013; Pryce & Fontana, 2017). Corroborating these clinical observations, multiple lines of evidence indicate that depression is associated with heightened inflammation in both the periphery and the central nervous system. With respect to the periphery, numerous studies report that individuals with depression, compared to controls, exhibit higher circulating levels of biomarkers thought to reflect non-resolving inflammation, including signaling molecules like cytokines and chemokines, acute phase proteins released by the liver, and adhesion molecules that help cells migrate into tissue (Lucido et al., 2021; Miller & Raison, 2016). Meta-analytic research suggests that the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 and the acute phase protein C-reactive protein (CRP) are the most reliably elevated inflammatory biomarkers in depression (Dowlati et al., 2010; Köhler et al., 2017; Osimo, Baxter, Lewis, Jones, & Khandaker, 2019). A number of studies, including meta-analyses, report that heightened biomarkers including CRP and IL-6 prospectively predict the onset of depression, raising the possibility that nonresolving inflammation is a pre-existent risk factor for depression, rather than merely a corollary or consequence of the illness (Mac Giollabhui, Ng, Ellman, & Alloy, 2021; Moriarity et al., 2020; Osimo et al., 2019; Valkanova, Ebmeier, & Allan, 2013). However, these findings on specific inflammatory biomarkers elevated in depression should be interpreted with caution. Immunopsychiatry studies typically do not measure all the inflammatory biomarkers in general circulation, and related, some inflammatory proteins involved in immune-to-brain signaling (e.g. IL-1) are hard to access and measure in general circulation (Maes, Song, & Yirmiya, 2012). Thus, the inflammatory biomarkers reported in human studies may not be the most mechanistically important mediators of immune-to-brain signaling. Furthermore, inflammatory cytokines frequently have redundant and synergistic effects on target cells, and focusing exclusively on individual cytokines may not capture the dynamic activity among inflammatory markers and the cascading manner in which they are released.

In the central nervous system, individuals with depression exhibit increased inflammatory biomarkers in the cerebrospinal fluid, which flows in and around the hollow spaces of the brain and spinal

cord (Felger et al., 2020; Franzen et al., 2020). Postmortem studies of individuals with depression who died by suicide demonstrate increased inflammatory cytokines in brain tissue compared to non-psychiatric controls, as well as increased activation of the microglia, which are the immune cells of the brain (Enache, Pariante, & Mondelli, 2019; Pandey, 2017; Torres-Platas, Cruceanu, Chen, Turecki, & Mechawar, 2014). Findings from postmortem studies, however, should be interpreted with caution given that it can be difficult to differentiate whether such inflammation is a consequence of depression or the tissue damage and stress reactivity associated with suicidal behavior. Increased microglial activation in depression also has been reported in positron emission tomography (PET) studies that use ligands that attach to the translocator protein (TSPO), whose expression is increased in activated microglia (Enache et al., 2019; Setiawan et al., 2015). This latter finding should also be interpreted with caution, however, as PET studies of TSPO are unable to distinguish the many states and functions of microglia, which include synaptic pruning and dendritic arborization that are unrelated to inflammation (Notter et al., 2021).

These studies on peripheral and CNS inflammation in depression are limited by their correlational designs, making it difficult for them to establish causality. Complimenting this literature are studies that directly examine the effect of inflammatory and anti-inflammatory stimuli on symptoms of depression. Much of this work comes from treatment trials that administered the proinflammatory cytokine interferon-α (IFN-α) to patients with certain cancers or infectious diseases (e.g. hepatitis C). Depending on the dose of IFN-α, approximately 30%–50% of patients receiving the treatment develop a major depressive episode, and IFN-α is particularly likely to induce motivational deficits characterized by anhedonia, psychomotor slowing, and fatigue (Capuron et al., 2002, 2009; Capuron & Miller, 2004). Similar patterns, although less severe in nature, are seen in healthy individuals administered mildly inflammatory stimuli, for example, a typhoid vaccine or low-dose endotoxin (Brydon, Harrison, Walker, Steptoe, & Critchley, 2008; Moieni et al., 2019). Furthermore, an emerging literature indicates that blocking inflammation via anticytokine therapies reduces depression in patients with autoimmune and inflammatory disorders (Kappelmann, Lewis, Dantzer, Jones, & Khandaker, 2017; Wittenberg et al., 2020). These therapies also reduce depression, and particularly lower anhedonia, in individuals with major depression who have heightened inflammation, but who were otherwise medically healthy (Lee et al., 2020; Raison et al., 2013). Collectively, these studies support a cause-and-effect relationship between inflammation and depressive symptoms, particularly anhedonia and motivational deficits (Musselman et al., 2001).

These findings are qualified, however, by other studies that do not support a role for inflammation in depression (Brambilla & Maggioni, 1998; Köhler et al., 2017; Marques-Deak et al., 2007), and the relationship between inflammation and depression is now recognized to be more nuanced (Lucido et al., 2021). Recent (Glassman & Miller, 2007) meta-analytic research indicates that only about 30% of individuals with depression display heightened inflammation, as defined by a CRP level greater than 3 mg/L (Osimo et al., 2019). This implies that inflammation may be involved in the pathogenesis of depression for only a subgroup of individuals, rather than for individuals with depression in general. This begs the question, what characterizes this subgroup? Some have suggested that comorbid medical conditions are important for driving a relationship between inflammation and depression, including obesity, metabolic syndrome, and coronary heart disease (Shelton et al., 2015; Xiao et al., 2017). We agree, and we will discuss this topic below. Others have suggested that inflammation may be more strongly associated with specific dimensions and symptoms of depression, rather than depression as a general or homogenous construct (Dooley et al., 2018; Lucido et al., 2021; Majd et al., 2020). In line with this view, heightened inflammation is associated with exaggerated reactivity to negative information, blunted responsivity to rewarding information, and neurovegetative symptoms (Dooley et al., 2018; Majd et al., 2020). Furthermore, there is growing evidence from animal and human research to suggest that heightened inflammation is particularly associated with motivational deficits and the symptom of anhedonia (Lucido et al., 2021). In this context, anhedonia appears to be generated by inflammation decreasing the synthesis and release of dopamine and altering glutamate signaling in the ventral striatum (Lucido et al., 2021; Miller, Haroon, Raison, & Felger, 2013). Supporting this perspective, immunotherapy with interferon alpha (IFN-α) in humans induced anhedonia and the immune activator lipopolysaccharide induced motivational deficits, as measured by behavioral responses to reward (Capuron & Miller, 2004; Lasselin et al., 2017). Some studies report no differences between individuals with depression and healthy controls on mean levels of inflammation, but report that, among individuals with a psychiatric condition, heightened inflammation is associated with anhedonia (Freed et al., 2019). Thus, studies that do not examine the relationship between inflammation and specific symptom dimensions of depression may be vulnerable to false negatives and contributing inconsistencies to the literature. We will discuss this topic in more detail below in the comorbid and transdiagnostic section.

Finally, we suggest that exposure to severe life stress and adversity, particularly during the early years of life, is also important for enhancing the link

between inflammation and depression, and studies that do not account for life stress may be vulnerable to false negatives. On this topic, a large body of literature suggests that early-life adversity is associated with chronic and nonresolving low-grade inflammation that persists, and even worsens, into adulthood (Chiang, Lam, Chen, & Miller, 2022; Kautz et al., 2023; Segerstrom & Miller, 2004). Researchers define adversity in different ways, with some focusing on toxicants and allergens (Furman et al., 2019; Yang et al., 2014), and others on psychosocial stressors, including poverty, parental maltreatment (e.g. abuse), and early deprivation (Ehrlich, Miller, & Chen, 2016; McLaughlin, Weissman, & Bitrán, 2019). We focus here on psychosocial stressors given their relevance to both depression and neuroimmune signaling (Hammen, 2005; Nusslock & Miller, 2016). Childhood adversity is proposed to sensitize youth's immune cells that initiate and propagate inflammation, programming them to mount exaggerated cytokine responses to infection and injuries (Miller, Chen, & Parker, 2011). Recent preclinical studies suggest that classical monocytes facilitate this process. When mice are subjected to chronic social stress, classical monocytes are mobilized from the bone marrow into circulation. These cells are functionally immature but highly aggressive and mount excessive inflammatory responses that, when chronic, can damage cells and tissue (Weber et al., 2017; Wohleb, McKim, Sheridan, & Godbout, 2015). In humans, children raised in poverty or in a harsh family climate produce larger volumes of inflammatory cytokines when their cells are stimulated ex vivo with microbial products (Azad et al., 2012; Miller & Chen, 2010; Wright et al., 2010), and this sensitization persists into adulthood (Miller et al., 2009). The monocytes of children living in adversity also become less sensitive to inhibitory signals, such as glucocorticoids and primarily anti-inflammatory cytokines (e.g. IL-10), which further dysregulates the inflammatory response (Lam, Chen, Chiang, & Miller, 2022; Schreier, Roy, Frimer, & Chen, 2014). This insensitivity may be adaptive during acute threats but under conditions of chronic stress could facilitate low-grade and nonresolving chronic inflammation (Miller et al., 2011). In line with this view, children living in adversity display higher levels of inflammatory biomarkers (e.g. IL-6, CRP) that persist into adolescence or adulthood (Broyles et al., 2012; Danese et al., 2009, 2011; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Kautz et al., 2023).

Given early-life adversity predicts both inflammation and depression, the association between inflammation and depression may be especially strong in individuals exposed to adversity. In line with this perspective, Danese et al. (2008) stratified young adults into subgroups based upon a history of childhood maltreatment and past-year major depression. Inflammation was higher among maltreated, depressed participants, relative to control participants with neither. Depression alone was not associated with inflammation (Danese et al., 2008). Similarly, a six-wave study of adolescents found that inflammation presaged the development of syndromal depression. But this association only was present in individuals exposed to relatively high levels of previous adversity (Miller & Cole, 2012). Collectively, this work suggests that life adversity may be an important mechanism for driving heightened inflammation among a subgroup of depressed individuals with a proinflammatory phenotype. Future research is needed to test this claim.

Recent work suggests that the association between early-life stress and nonresolving inflammation strengthens with time, becoming larger in magnitude through adolescence and adulthood (Chiang et al., 2022). One explanation for this phenomenon is that it simply takes time for the residue of increased monocyte reactivity to accumulate, or more specifically manifest in a sustained elevation of circulating biomarkers like CRP and IL-6 (Hostinar, Nusslock, & Miller, 2018; Lam et al., 2021). Another, although not mutually exclusive possibility, is that adolescent stress and development strengthen the association between early-life adversity and monocyte responsivity. Biologically, both the innate and adaptive immune system continue to develop into adolescence, and some have suggested that adolescence is when the immune system 'hits its stride' (Simon, Hollander, & McMichael, 2015). This is facilitated, in part, by pubertal increases in gonadal hormones, including estrogens and androgens, that modulate the peripheral immune system and predict cytokine levels (Brenhouse & Schwarz, 2016; Stumper et al., 2020). Gonadal hormones affect the function of immune cells either directly by binding to hormone receptors or indirectly via their effects on other hormone-responsive target tissues such as the hypothalamic pituitary axis that in turn influence immune responses (Shames, 2002). Psychosocially, adolescence, as discussed earlier, is characterized by a heightened sensitivity to stress (Pfeifer et al., 2011; Somerville et al., 2013), and adolescent adversity can heighten inflammation in its own right (Kuhlman, Horn, Chiang, & Bower, 2020). Adolescent adversity also can compound the effect of early-life adversity on the immune system (Kautz et al., 2023). For example, adolescent life stress forecasted exaggerated inflammatory responses to bacterial products among those raised in a harsh family climate, but not for those raised in warmer family climates (Miller & Chen, 2010). This provides further evidence that early-life adversity may incubate in the developing brain and body and be exacerbated by stress at a subsequent developmental stage. Finally, adolescence is associated with the onset of behaviors that can contribute to, or mediate, heightened

inflammation, including substance use, alcohol, cigarettes, and certain diets (Kuhlman et al., 2017; Paavola, Vartiainen, & Haukkala, 2004). To date, however, far fewer studies have examined the effect of adversity on the immune system during adolescence, as compared to early-life adversity (Kuhlman et al., 2020). Given adolescence is an age of risk for the onset of depression (Avenevoli et al., 2015), future research should investigate adversity-inflammation associations during adolescence, and the extent to which adversity across the developmental spectrum is important for understanding the subgroup of depressed individuals with heightened inflammation.

Crosstalk between the brain and immune system

How does life adversity during development 'get under the skin' to alter brain structure and function, heighten inflammation, and generate risk for mental and physical health problems? Historically, researchers have focused separately on either the brain or the immune system to examine this question. Recently, however, researchers have begun to take a multiorgan perspective, drawing on work highlighting bidirectional signaling between the brain and immune system in both health and disease (Felger & Treadway, 2017; Miller & Raison, 2016; Nusslock & Miller, 2016; Slavich & Irwin, 2014; Treadway, Cooper, & Miller, 2019). In these next sections, we discuss this work on the anatomical and behavioral pathways underlying neuroimmune signaling and extend it to propose an integrative and developmental neuroimmune network model of depression.

Brain-to-immune traffic

All three of the brain systems discussed thus far – threat, reward, and executive control-neural circuitry – influence the immune system, either directly or indirectly (Schiller et al., 2021; Weber et al., 2017). Under conditions of stress or threat, cell groups in the amygdala, insula, and other stress-sensitive brain areas signal centers in the hypothalamus and brainstem to mobilize fight-or-flight responses. These responses are mediated, in part, by the sympathetic nervous system (SNS) and neuroendocrine pathways, including the hypothalamic–pituitary–adrenal (HPA) axis (Irwin & Cole, 2011; see left panel in Figure 1). SNS fibers descend from the brain into peripheral lymphoid organs where leukocytes (i.e. white blood cells) mature, including the bone marrow, thymus, and spleen, and release norepinephrine onto developing immune cells, which can amplify inflammatory activity. This can be compounded by stress-related dysregulation of the HPA axis. Typically, glucocorticoids released by the HPA axis (e.g. cortisol) inhibit the inflammatory response, serving as a brake on the immune system. But during chronic stress and depressive episodes, cortisol's regulatory influences on inflammation is attenuated (Sternberg, 2006).

Apart from these direct brain-immune pathways, adversity and depression can generate inflammation via behavioral mechanisms (see right panel in Figure 1; Nusslock & Miller, 2016). Living in adversity or in a sustained state of fight-or-flight is unpleasant, and people may seek strategies to manage their pain and dysphoria (Koob et al., 2014; Volkow, Koob, & McLellan, 2016). These strategies can involve behaviors with downstream effects on the brain and body. For example, growing up in adversity (i.e. childhood maltreatment) is associated with higher rates of cigarette smoking, excessive alcohol consumption, drug misuse, physical inactivity, weight gain, and intake of calorically dense foods (Felitti et al., 1998). All these behaviors promote inflammation (Hotamisligil, 2006). Many of these behaviors emerge or increase during adolescence, which is a developmentally sensitive period for the immune system and an age-of-risk for the onset of depression (Avenevoli et al., 2015; Simon et al., 2015).

Taken together, these observations imply that both direct physiological (e.g. SNS and HPA signaling) and indirect behavioral responses to stress and threat can contribute to inflammation over the life course. As we will discuss below, these two pathways may compound each other to drive a self-perpetuating cycle that has implications for mental and physical health.

Most of the research on the anatomical pathways mediating brain-to-immune signaling has focused on threat and defensive neural circuitry. There is growing interest, however, in the influence of positive emotions and reward-related neural circuity on inflammation (see right panel in Figure 1). This work has focused on the nucleus accumbens and the ventral tegmental area in the cortico-striatal reward circuit. A recent study tested this hypothesis in a particularly elegant manner: Ben-Shaanan and colleagues (Ben-Shaanan et al., 2016) used chemogenetics to directly activate dopaminergic neurons in the mouse ventral tegmental area, and this manipulation increased innate and adaptive immune responses during a bacterial challenge in the periphery. By chemically ablating the SNS, they further showed these effects were, at least in part, mediated by the SNS.

Complimenting these findings is evidence that reward-related brain activity also affects peripheral inflammation via behavioral pathways (see right panel in Figure 1). This work is grounded in the reward deficiency model of addiction, which postulates that persons with a blunted sensitivity to rewards will attempt to elevate positive and reward-related emotions through high-risk and proinflammatory behaviors (Blum et al., 2000). Consistent

with this view, animal work reports that reduced dopamine signaling in the cortico-striatal reward circuit, including the ventral striatum and ventral tegmental area, is centrally involved in many addictive and proinflammatory behaviors, including substance dependence, food seeking, and obesity (Volkow, Wise, & Baler, 2017). In humans, preliminary data suggest that low reward-related brain function precedes, and potentially motivates, proinflammatory behaviors, rather than simply being a consequence of these behaviors. For example, we and others report that low activation in the ventral striatum to rewarding stimuli, as measured by fMRI, prospectively predicts substance use in adolescents and early adults (Bart et al., 2021; Büchel et al., 2017). Furthermore, recent life stress strengthens the association between reward-related brain function and inflammation (Treadway et al., 2017). This may reflect individuals self-regulating and medicating their emotional responses to these stressors through high-risk, proinflammatory behaviors. Thus, both high threat- and low reward-related brain activity can generate behaviors that heighten inflammation: the former to regulate general distress and dysphoria caused by stress and/or depression, the latter to regulate anhedonia and low positive emotions.

Regarding executive control neural circuitry, we recently reported that lower functional connectivity in the brain's frontoparietal central executive network was associated with heightened inflammation in the periphery, as measured by both proinflammatory cytokines and classical monocytes (Nusslock et al., 2019). These associations were observed in both adolescents (ages 13–14) and young adults (age 25), indicating that a relationship between executive control neural circuitry and inflammation is present across development. To the best of our knowledge, there are no animal or human studies that examine direct anatomical pathways from the PFC to the immune system, like there are with threat and reward neural circuitry. We suggest that executive control influences peripheral inflammation, in part, through its regulatory influence on subcortical brain systems involved in threat and reward. These subcortical systems then have a more direct impact on the immune system via the SNS and HPA axis (Schiller et al., 2021; Weber et al., 2017). As noted, there is a functional and structural coupling between the PFC and both threat- and reward-sensitive brain areas in the subcortex that have important implications for mental and physical health (Anderson et al., 2023; Tillman et al., 2018). Stress, depression, and, as we will discuss below, inflammation can affect the integrity of this coupling (Herringa et al., 2013; Kim et al., 2013). If a person engages the cortex in a manner that consistently amplifies threat-sensitive brain areas and attenuates reward-sensitive brain areas, they may dysregulate the SNS and HPA axis, putting them at risk for heightened inflammation. Future research testing the associations between inflammation and connectivity between the PFC and both threat- and reward-sensitive brain regions is needed to test this prediction. Both medial and lateral portions of the PFC also play an important role in regulating behavior (Miyake & Friedman, 2012). When confronted with addictive, unhealthy, or proinflammatory substances, individuals with poor executive control may have difficulty inhibiting the urge to consume the substances (Nusslock & Miller, 2016). This is particularly true during periods of stress and depression when the urge to self-medicate dysphoria and/or accentuate positive emotions may be particularly strong (Koob et al., 2014; Volkow et al., 2016). Thus, the executive control systems may be a final arbiter of whether a person regulates stress, dysphoria, or low positive emotions through high-risk, unhealthy behaviors, or less inflammatory behaviors.

Immune-to-brain traffic

Given that inflammation in the periphery is associated with depression, there has been growing interest in how immune products access the brain (Miller, Maletic, & Raison, 2009) (see middle panel in Figure 1). For most of the molecules traveling through circulation, access to the brain parenchyma is limited by the blood–brain barrier (Schiller et al., 2021). This semipermeable membrane lines the interior of capillaries that supply the brain, and allows a limited range of molecules to cross into the parenchyma. Cytokines like TNF-α and IL-6 are too large to cross the blood–brain barrier (BBB), however, they are still able to gain access at leaky regions such as the circumventricular organs, and via active transport through cytokine specific saturable transporters (Schiller et al., 2021). Peripheral cytokines also can engage receptors on afferent vagal fibers that are widely dispersed in the periphery, and project to limbic structures in the brain via the nucleus of the solitary tract (Haroon, Raison, & Miller, 2012; Irwin & Miller, 2007). When activated, these fibers stimulate the production of primarily proinflammatory cytokines in brain tissue by microglia, the primary innate immune cell in the central nervous system. Numerous studies report increased microglial activation and neuroinflammatory signaling in stress-reactive brain regions during stress exposure, including the frontal cortex, hypothalamus, amygdala, and hippocampus (Hinwood, Morandini, Day, & Walker, 2012; Wohleb et al., 2011). This stress-evoked microglial activity elevates threat and reduces reward-related behaviors in rodents, and pharmacologically inhibiting microglia during stress exposure protects rodents against the development of depressive and anxiety-like behaviors (Frank et al., 2016; Kreisel et al., 2014; Wohleb et al., 2012).

Another immune-to-brain pathway involves classical monocytes, which as noted above are primary drivers of inflammation in the periphery (Weber et al., 2017; Wohleb et al., 2015). During stress, activated microglia in the brain release chemokines into general circulation (Weber et al., 2017). These chemokines travel throughout the body and bind to classical monocytes in the periphery and actively recruit them to the blood vessels that supply the brain. There, classical monocytes bind to adhesion molecules on the endothelium of the blood–brain barrier, and acting in concert with microglia, increase inflammatory signaling in resident brain tissue. (It is unclear whether these monocytes migrate into brain tissue, or just signal microglia to express inflammatory mediators in the brain.) This inflammatory signaling then directly affects brain activity through targeting the synthesis, release, and reuptake of neurotransmitters including glutamate and the monoamines (i.e. serotonin, norepinephrine, and dopamine; Miller et al., 2013).

Importantly, classical monocytes are not recruited to all parts of the brain equally, but rather target brain systems specified in the neuroimmune network model, including regions that process threatening stimuli and facilitate defensive and anxious behaviors (Weber et al., 2017; see left panel in Figure 1). For example, stress-evoked neuroinflammation increases anxiety-like behaviors in rodents, including increased light–dark preference and decreased open-field exploration (Weber et al., 2017). Blocking monocyte trafficking to the brain inhibits this stress-induced inflammation and lowers these anxiety-like behaviors (Wohleb et al., 2011; Wohleb, Powell, Godbout, & Sheridan, 2013). fMRI studies suggest similar effects of inflammation on threat-related brain function in humans. Exposing individuals to endotoxins that generate peripheral inflammation increases threat-related brain activity in both the amygdala and dorsal ACC to negative social feedback and cues of social rejection (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012; Muscatell et al., 2016), although these findings need to be corroborated in youth and adolescents. Collectively, this highlights the potential causal role of peripheral inflammation, and particularly classical monocytes, in elevating threat-related brain activity, which increases vigilance and anxiety-like behaviors. When dysregulated, particularly under conditions of chronic stress, immune-to-threat signaling could lead to sustained states of dysphoria, distress, and anxiety. Furthermore, some work suggests that the mobilization of classical monocytes to threat-sensitive brain regions is particularly elevated during social stressors (Weber et al., 2017). This raises the possibility that adolescence is a sensitive period for establishing heightened and dysregulated immune-to-threat signaling. We propose this given that adolescence is (a) characterized by an increase in social stressors (Hammen, 2009), (b) characterized by hypersensitivity in threat-sensitive brain regions to social rejection (Scherf et al., 2013), and (c) associated with important developments in both the innate and adaptive immune system (Simon et al., 2015). Future research is needed to test this prediction.

The cortico-striatal reward circuit is another primary target of inflammation in the brain (Lucido et al., 2021; Miller et al., 2013; Schiller et al., 2021; see right panel in Figure 1). This immune-to-brain pathway reduces the motivation to pursue rewards in the environment and induces the 'sickness syndrome' mentioned above. This syndrome involves fatigue, inactivity, and decreased motivation in order to conserve metabolic resources for fighting pathogens and to facilitate wound healing (Dantzer, O'connor, Freund, Johnson, & Kelley, 2008). Decades of research demonstrate that once in the brain, inflammation reduces motivation and decreases one's sensitivity to rewards by modulating glutamate and decreasing levels of dopamine in the ventral striatum (Miller et al., 2013). With respect to glutamate, inflammatory cytokines both stimulate the release and decrease the reuptake (i.e. removal) of glutamate in the ventral striatum in animals (Haroon, Miller, & Sanacora, 2017; Miller & Raison, 2016). This can lead to structural changes in striatal synapses and cells, which has been demonstrated to reduce motivation and goal-directed behaviors (Bechtholt-Gompf et al., 2010). In humans, administering the pro-inflammatory cytokine IFN-α generates acute structural changes in the striatum, which predate symptoms of fatigue and demotivation (Haroon et al., 2017). With respect to dopamine, rodents and rhesus monkeys exposed to pro-inflammatory cytokines (e.g. IFN-α) display reduced synthesis and release of dopamine in the striatum, as measured by microdialysis and PET (Lucido et al., 2021). These effects are reversed when the animals are administered a dopamine agonist (i.e. methylphenidate) or levodopa (the precursor to dopamine) directly into the striatum (Felger, Hernandez, & Miller, 2015; Yohn et al., 2016). Experimental studies in humans report that exposing individuals to proinflammatory stimuli, such as cytokines, endotoxins, or vaccines, reduces brain activity in the ventral striatum to monetary rewards, as measured by fMRI (Capuron et al., 2012; Eisenberger et al., 2010; Harrison et al., 2009). PET studies indicate that this reduction in reward-related brain activity in humans also is associated with lower dopamine transmission in the ventral striatum (Capuron et al., 2012). In both animals and humans, inflammation-induced reductions in striatal dopamine are associated with decreases in motivation and a reduced willingness to expend effort for monetary rewards (Boyle et al., 2019; Vichaya & Dantzer, 2018). Interestingly, inflammation does not lower the consumption of rewards when they are

freely available (Draper et al., 2018). This suggests that inflammation specifically targets brain systems involved in the motivational pursuit of rewards (i.e. wanting), rather than pleasure of consuming a reward (i.e. liking).[2]

When chronic or dysregulated, immune-to-reward signaling can lead to sustained deficits in motivation and anhedonia (Lucido et al., 2021). This may be more likely to occur during adversity, given that stress exposure strengthens the association between peripheral inflammation and reward-related brain function (Treadway et al., 2017). This heightened immune-to-reward signaling appears to be facilitated by selective disruptions in the BBB during stress in brain regions involved in motivation, including the ventral striatum. For example, stress-sensitive mice exhibit disruptions in the BBB in the ventral striatum that increase permeability to cytokines compared to stress-resilient control mice (Dudek et al., 2020). Importantly, this enhanced BBB permeability in stress-sensitive mice is unique to the ventral striatum, highlighting the precision of immune-to-brain signaling during stress. Similar decreases in the integrity of the BBB have been observed in the ventral striatum of postmortem brain samples of individuals with depression, with some evidence that this effect may be mitigated by antidepressants (Menard et al., 2017). The fact that adolescence is characterized by heightened stress (Hammen, 2009), increased BBB permeability (Brenhouse & Schwarz, 2016), and important developments in both reward-related brain activity (Somerville & Casey, 2010) and the immune system (Brenhouse & Schwarz, 2016) suggests that it may be a developmentally sensitive period for establishing immune-to-reward signaling. Future research is needed to test this claim.

Although studied less extensively, there is growing evidence that inflammation modulates the structure, function, and development of the PFC in a manner that diminishes executive control and self-regulation. Higher inflammatory activity in the periphery is associated with a smaller volume of the medial PFC and administering inflammatory stimuli, like cytokines and vaccines, modulates activity in the dorsolateral PFC in humans, as measured by fMRI (Meyer, 2013). As noted, an important role of the PFC in the neuroimmune network model is providing 'top-down' regulation of subcortical brain systems involved in processing threats and rewards, including the amygdala and ventral striatum (Delgado et al., 2008; Swartz et al., 2014). Growing evidence suggests that inflammation weakens these regulatory pathways, particularly in the cortico-striatal reward circuit. For example, healthy individuals exposed to a proinflammatory stimulus (typhoid vaccine) displayed decreased functional connectivity to emotional faces between the cortex and the ventral striatum, as well as other subcortical brain regions involved in processing rewards (Harrison et al., 2009). Other studies report that, among individuals with depression, heightened inflammatory biomarkers in the periphery are associated with decreased functional connectivity at rest between the ventromedial PFC and the ventral striatum (Felger et al., 2016; Mehta et al., 2013). Importantly, these inflammation-induced deficits in cortico-striatal connectivity are associated with motivational and self-regulatory changes, including reduced reward anticipation, decreased willingness to work for rewards, anhedonia, and a heightened sensitivity to aversive stimuli (Lucido et al., 2021). These deficits may emerge from inflammation targeting glutamate activity in neurons that descend from the mPFC to the ventral striatum which, as noted above, play an important role in modulating subcortical dopamine transmission involved in motivation and goal-directed behaviors (Haroon et al., 2017; Sesack et al., 2003). They also may emerge from inflammation targeting the structural integrity of the myelin sheath that insulates the axons of these glutamatergic neurons connecting the cortex and striatum. In support of this latter prediction, preclinical studies suggest that chronic inflammation inhibits the maturation of oligodendrocytes, which are the glial cells that produce myelin in the central nervous system (Meyer, 2013). Human studies suggest that inflammation partially mediates the relationship between chronic stress and the integrity of white matter (i.e. myelin) in the cortex (Gianaros, Marsland, Sheu, Erickson, & Verstynen, 2013). Future research is needed to test these mechanistic predictions. Finally, microglia play a critical role in the normative development of the PFC during late adolescence and early adulthood. They are the primary drivers of synaptic pruning and dendritic arborization in the PFC, and via their effect on oligodendrocytes, influence the myelination of neurons in the PFC during development (Lenz & Nelson, 2018). Most of the research on the effect of stress on microglia has focused on the inflammatory functions of these cells. Future research should examine whether adversity also affects these developmental functions of microglia, as this could have important effects on the maturation of executive control and top-down regulation of subcortical threat and reward processing.

Developmental neuroimmune network model of depression

Having discussed the relationships between peripheral inflammation and threat, reward, and executive control neural circuitries separately, we next outline a developmental framework of risk for depression that integrates these multiple pathways (Figure 2). This developmental framework involves a series of proposed causal linkages that occur across development to generate risk for neuroimmune dysregulation and subsequent depression. Many of these

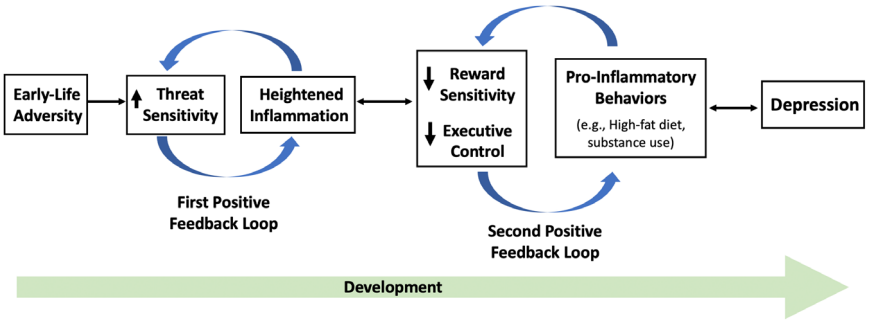

Figure 2 A developmental neuroimmune network model of depression

proposed causal linkages are speculative, and perhaps oversimplified, and based on preclinical and developmental findings yet to be corroborated in humans. We offer this framework to help organize developmental knowledge from disparate literature and as a springboard for generating developmental research in the context of neuroimmune models.

We suggest that brain regions involved in processing threatening stimuli in the environment, including the amygdala, are among the earliest targets of psychosocial adversity in the brain and body. We base this prediction on the fact that threat-sensitive brain regions go through a critical and normative period of development from infancy through early childhood in which they are highly sensitive to, and influenced by, environmental stimuli and experiences (Gilmore et al., 2012). During stress or adversity, threat-sensitive brain regions enhance the inflammatory activity of classical monocytes in the periphery via the SNS and HPA axis (Schiller et al., 2021). As noted, when this threat-to-immune signaling is dysregulated or sustained, it can evolve into nonresolving inflammation. Thus, signaling between threat-sensitive brain regions, such as the amygdala, and the immune system via the SNS and HPA axis is an anatomical pathway through which psychosocial adversity in the environment can embed itself in monocytes to generate chronic inflammation during the early years of life. This perspective suggests that over the course of development, heightened threat processing in the brain precedes heightened inflammation in the body, although future research is needed to test this claim.[3] During stress and adversity, inflammatory cytokines and classical monocytes are recruited back to the brain in a coordinated manner where they further accentuate threat processing and vigilance and modulate the structure and function of threat-sensitive brain regions (Weber et al., 2017; Wohleb et al., 2015). We speculate that over time, this traffic between threat-sensitive brain areas and the immune system takes on a life of its own, creating a positive feedback circuit wherein heightened threat activity in the brain amplifies inflammation in the periphery, and vice versa (Nusslock & Miller, 2016). We further speculate that this feedback circuit is more likely to emerge if early-life adversity is compounded by stress during adolescence. As noted, adolescence is characterized by a normative increase in threat-sensitivity (Hu et al., 2013; Pfeifer et al., 2011), important pubertal developments in the innate and adaptive immune system (Simon et al., 2015), and increased psychosocial stressors (Hammen, 2009). Thus, a central tenet of our developmental framework is that life adversity over the course of development amplifies crosstalk between threat-sensitive brain areas and peripheral inflammation in a manner that heightens threat processing and vigilance in the brain and inflammation in both the brain and body.

A second immune-to-brain pathway involves the cortico-striatal reward circuit. Here, inflammation reduces motivation to pursue rewards and induces anhedonia through altering glutamate and decreasing dopamine transmission in reward-sensitive brain areas, including the ventral striatum (Lucido et al., 2021; Miller et al., 2013). We speculate that stress may have a particularly strong effect on immune-to-reward pathways during the teenage years. We base this prediction on the fact that adolescence involves important and normative developments in the cortico-striatal neural circuit, which may make it more sensitive to stress during this time (Somerville & Casey, 2010). Furthermore, stress may selectively increase the permeability of the BBB in reward-sensitive brain areas, including the ventral striatum, during adolescence, which should modulate immune-to-reward signaling (Dudek et al., 2020). The PFC is likely the last area of the brain to be targeted by inflammation given its protracted development into early adulthood (Swartz et al., 2014). Inflammation lowers executive control and weakens the regulatory influence that both the medial and lateral PFC have on limbic structures, which further heightens threat activity and reduces reward activity in the brain (Harrison et al., 2009; Meyer, 2013). Furthermore, the normative development of portions of the dmPFC during adolescence involved in social cognition and mentalizing may cause certain individuals to be particularly affected by stress and inflammatory activity, and at heightened risk for negative thoughts about the self, world,

and future (Nusslock et al., 2011; Rankin et al., 2004; Somerville et al., 2013).

Taken together, we propose that the developmental arc toward neuroimmune dysregulation is first set in motion by early-life adversity affecting the development of threat-sensitive brain areas. Given how early threat-sensitive brain areas like the amygdala develop, their massive connections to the rest of the brain, and the anatomical pathways through which they can affect inflammatory activity, they are positioned to subsequently inform the developing brain and body about the extent to which the world is safe and trustworthy (Schiller et al., 2021; Tottenham & Gabard-Durnam, 2017). Thus, heightened and dysregulated activity in threat-sensitive brain areas during early life should (a) foster a highly reactive phenotype in monocytes, (b) influence the maturation of the ventral striatum and the prefrontal cortex during adolescence and early adulthood in a manner that reduces sensitivity to rewards and weakens executive control, and (c) amplify crosstalk between these brain circuits and peripheral monocytes over the course of development. This crosstalk is likely compounded by subsequent adversity and disruptive behaviors during adolescence, which amplifies and accelerates dysregulated brain-immune signaling.

We next argue that these linkages and pathways should drive the brain toward a neural phenotype of depression that has been documented in multiple studies and meta-analyses (Hamilton et al., 2012; Ng et al., 2019). This profile is characterized by heightened activity in threat-sensitive brain areas like the amygdala, insula, bed nucleus of the stria terminalis, and anterior cingulate cortex, decreased activity in reward-sensitive brain areas like the ventral striatum, and weakened executive control in both medial and lateral portions of the PFC. This profile of brain activity then is suggested, particularly under conditions of stress, to predispose individuals to high-risk, unhealthy behaviors like smoking, excessive alcohol use, drug misuse, and high-fat diets to self-medicate the distress, dysphoria, and anhedonia associated with this neural phenotype (Blum et al., 2000; Nusslock & Miller, 2016). Increased substance use further blunts reward-related brain activity and deteriorates portions of the PFC implicated in executive control, which makes it even more difficult to inhibit the urge to use substances and eat unhealthy foods (Volkow et al., 2016). Substance use may be especially harmful during adolescence and the transition to adulthood, given these time periods are associated with critical and normative developments in reward-sensitive brain areas and ventromedial portions of the PFC involved in emotion regulation (Somerville & Casey, 2010). As noted, these behaviors also increase inflammation, in part through contributing to weight gain (Hotamisligil, 2006). If the inflammation triggered by these behaviors spreads back to the brain, it could establish a second positive feedback circuit driven by behavior, whereby heightened threat and low reward and executive control neural activity facilitate proinflammatory behaviors, which, in turn, further amplify this neural phenotype, and so on. Over time, this neuroimmune dysregulation could drive the brain and body toward depression.

Neuroimmune dysregulation in comorbid symptoms and disorders: a transdiagnostic perspective

Above, we discussed research indicating that only about 30% of individuals with depression display heightened inflammation, suggesting that inflammation may not be sufficient on its own for understanding risk for depression (Osimo et al., 2019). This work is complemented, however, by studies indicating that inflammation is heightened in numerous other psychiatric disorders, including bipolar disorder, schizophrenia, anxiety disorders, posttraumatic stress disorders, and personality disorders (Costello, Gould, Abrol, & Howard, 2019; Goldsmith et al., 2016). These findings have pushed the field to move beyond a singular focus on inflammation's relationship with depression and to instead take a transdiagnostic perspective that examines the relationship between a mechanism (in this case inflammation) and specific psychiatric symptoms in a manner that is agnostic to psychiatric diagnosis (Lucido et al., 2021). Several alternative classification models have been proposed to help catalyze this research, many of which rely on dimensional, rather than categorical, frameworks [e.g. the Research Domain Criteria (RDoC), the Hierarchical Taxonomy of Psychopathology (HiTOP)] (Insel et al., 2010; Kotov et al., 2017). We speculate that the tri-level model may be particularly well-suited for analyses of neuroimmune dysregulation. This is a well-established model that examines symptoms that are shared or common across multiple disorders (i.e. General Distress) versus relatively specific to anxiety (i.e. Fears) or depression (i.e. Anhedonia; Prenoveau et al., 2011). We predict that heightened inflammation will be associated with heightened General Distress and Fears across depression and anxiety through heightened activation of threat-sensitive brain areas (Figure 3). We base this prediction on the research summarized thus far indicating that inflammatory proteins and cells alter the structure and function of threat-sensitive brain areas, and in particular the amygdala, in a manner that increases threat processing, vigilance, dysphoria, and distress (Inagaki et al., 2012; Muscatell et al., 2016; Weber et al., 2017). We next predict that heightened inflammation will be associated with heightened anhedonia through reduced activation in reward-sensitive brain areas, and in particular the ventral striatum, to rewarding stimuli (Figure 3). As noted earlier, animal and human research indicate

that anhedonia and motivational deficits are a cardinal symptom of heightened inflammation, and that this is driven by reduced dopamine and altered glutamate signaling in the ventral striatum (Lucido et al., 2021; Miller et al., 2013; Miller & Raison, 2016). Furthermore, decreased reward-related brain function in depressed individuals has been uniquely associated with anhedonia above and beyond other symptoms of depression (Nusslock & Alloy, 2017). Importantly, however, inflammation has been shown to induce motivational deficits in multiple other psychiatric disorders as well, including negative symptoms in schizophrenia and anhedonia in PTSD (Lucido et al., 2021). Taken together, these data suggest that immune-to-brain signaling defies conventional categories and contributes to common symptom clusters across disorders. Future research is needed to test this prediction and examine the relationship between specific immune-to-brain pathways and specific symptom clusters.

Future research also is needed to examine the developmental arc of the relationships between immune-to-brain pathways and specific symptom clusters. We predict that the association between immune-to-threat pathways with General Distress and Fears will develop earlier in childhood, whereas the association between immune-to-reward pathways with anhedonia will develop during adolescence. We base these predictions on two bodies of literature. The first indicates that threat-sensitive brain areas and the immune system go through a normative and critical period of development early in life and symptoms of anxiety and distress tend to emerge during childhood (Gilmore et al., 2012; Lee et al., 2014; Payne et al., 2010). The second indicates that reward-sensitive brain areas go through a normative and critical period of development during adolescence, and depression-specific symptoms such as anhedonia tend to emerge during adolescence (Lee et al., 2014; Somerville & Casey, 2010). These predictions, however, are qualified by the fact that the association between early-life stress and nonresolving inflammation strengthens with time (Chiang et al., 2022). Thus, it remains to be seen when exactly immune-to-brain pathways become activated in a manner that generates risk for depressive symptoms.

Neuroimmune network models also may help us understand the high rates of comorbid substance abuse and dependence among individuals with depression and other psychiatric disorders. Over 50% of individuals with depression report a lifetime comorbid substance use problem, and inflammation increases one's risk for substance use and comorbid substance use and depression (Hunt, Malhi, Lai, & Cleary, 2020; Hutchinson & Watkins, 2014). There are multiple pathways through which inflammation can generate these high rates of comorbidity. First, risk for depression and substance use are associated with an identical profile of brain activity characterized by heightened activity in threat-sensitive brain areas, decreased activity in reward-sensitive brain areas, and weakened executive control in both the medial and lateral PFC (Hamilton et al., 2012; Ng et al., 2019; Volkow et al., 2016). Thus, by driving the brain toward this neural phenotype, inflammation may increase one's risk for both depression and substance use. Second, and as outlined throughout this paper, a central tenet of our neuroimmune network model is that this profile of brain activity drives people to engage in high-risk, proinflammatory behaviors to self-medicate their distress, dysphoria, and anhedonia (Nusslock & Miller, 2016). When used extensively, these substances can generate neuroadaptive changes in the brain (e.g. blunting of ventral stratal activity and alterations in PFC executive control), which further elevates risk for abuse and dependence (Volkow et al., 2016). One mechanism through which substances may induce neuroadaptive changes is through the inflammation that they generate. Recent animal studies suggest that inflammation affects the brain's reward centers in a way that increases tolerance to, and dependence on, addictive stimuli (Coller & Hutchinson, 2012). For example, multiple addictive substances stimulate the production of inflammatory cytokines in the

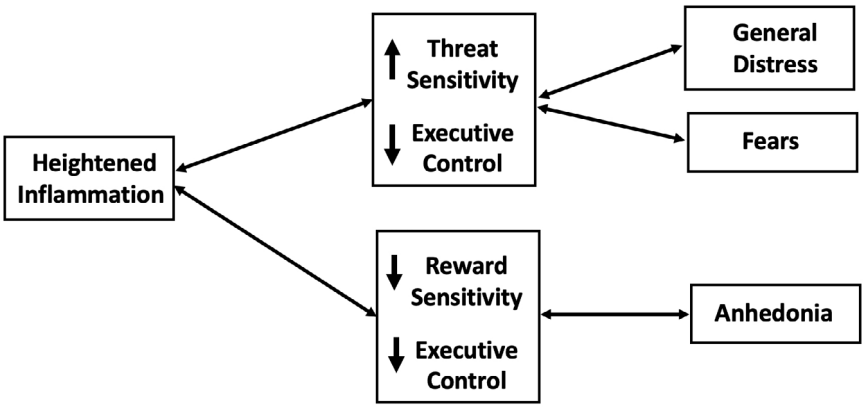

Figure 3 A transdiagnostic perspective of the relationship between neuroimmune dysregulation and psychiatric symptoms

brain, which affect dopamine release in reward-sensitive regions such as the ventral striatum (Wang et al., 2012). This cascade affects the rewarding properties of drugs, promoting tolerance to the drug (Volkow et al., 2016, 2017). In fact, some studies of mice indicate that the onset of addiction is, in part, dependent on the substance eliciting an inflammatory response in the ventral striatum (Liu, Coller, Watkins, Somogyi, & Hutchinson, 2011). These risk factors often begin to take shape during adolescence. Adolescence is characterized by significant developments in the brain and immune system that heighten risk for neuroimmune dysregulation and depression (Brenhouse & Schwarz, 2016; Scherf et al., 2013; Somerville & Casey, 2010), and it is a period in which people are first beginning to consume proinflammatory substances like drugs and alcohol (Pfeifer et al., 2011). Thus, adolescence involves the confluence of multiple risk factors for the onset of comorbid depression and substance use over the life span.

Finally, psychiatric disorders, including depression, frequently co-occur with numerous physical illnesses. For example, individuals with lifetime depression are at increased risk for autoimmune conditions and various cardiometabolic diseases, including coronary heart disease, diabetes, metabolic syndrome, and stroke (Gold et al., 2020; Kessler et al., 2003). Importantly, each of these mental and physical health problems have been shown to be elevated among individuals with a history of early-life adversity (Nusslock & Miller, 2016). Furthermore, chronic low-grade inflammation is implicated in the pathophysiology of each of these conditions, suggesting that inflammation is a common thread that links mental and physical illness (Nusslock & Miller, 2016). For example, inflammation is an important contributor to the clinical manifestations of cardiometabolic disease, including fat accumulation, high blood pressure, glucose intolerance, lipid dysregulation, and insulin resistance (Lackey & Olefsky, 2016). Chronic inflammation in the arterial wall also is implicated in coronary heart disease, and the early stages of this atherosclerotic process is largely driven by classical monocytes (Schloss, Swirski, & Nahrendorf, 2020). We argue that integrative neuroimmune network models will be helpful for identifying common mechanistic pathways underlying various illnesses, and for understanding how early-life stress heightens risk for a plethora of comorbid mental and physical health problems. We also speculate that the anatomical positive feedback circuit between threat-sensitive brain systems and the immune system and the behaviorally driven positive feedback circuit proposed above will both be important for understanding comorbidity between depression and physical illnesses. In support of this perspective, Tawakol et al. reported that elevated amygdala activity predicted cardiovascular disease through increased inflammatory signaling in the bone marrow and aortic lesions (Tawakol et al., 2017). This neuroimmune dysregulation should also precipitate proinflammatory behaviors to self-medicate distress and dysphoria (Pfeifer et al., 2011), which should further elevate risk for both depression and physical health problems, including cardiometabolic and coronary heart disease. Future research is needed to test these predictions and the extent to which neuroimmune dysregulation is a common etiological pathway to comorbid mental and physical health problems. It will be particularly important to test these predictions in youth and adolescents given that chronic stress and adversity have already begun to lay the foundation for autoimmune conditions, cardiometabolic diseases, and coronary heart disease in youth as young as 12 years old (Juhola et al., 2011; Strong, 1999). Furthermore, a developmental perspective can lay the foundation for early interventions, and ideally prevention programs, a topic to which we turn next.

Treatment implications

Historically, psychology and psychiatry have focused on treating a single disorder (e.g. depression) through targeting a single mechanism (e.g. serotonin, cognition). Neuroimmune network models may facilitate a more holistic framework that can identify numerous targets across multiple organ systems to treat, and ideally prevent, mental and physical health problems, such as depression. Furthermore, these models speculate that there are multiple ways to break the vicious cycle between dysregulated neural and inflammatory activity, and that therapeutic change in one system (e.g. reducing inflammation) should have cascading benefits for other systems (e.g. reducing threat processing; Nusslock & Miller, 2016). Here we briefly discuss the implications of our neuroimmune network model for pharmacological, behavioral, familial, and societal interventions depression.

Depression is difficult to treat pharmacologically. One-third of depressed individuals fail to respond to traditional antidepressant medications (Rush et al., 2006), and inflammation is a mechanism hypothesized to contribute to some cases of treatment resistance (Jha et al., 2017). Our growing understanding of how inflammation affects the brain could facilitate the development and refinement of anti-inflammatory drugs as primary or adjunctive treatments for depression. These drugs could target inflammation itself, including inflammatory cells and mediators (e.g. cytokines), their signaling and metabolic pathways, or the impact of inflammation on neurotransmitter systems like dopamine and glutamate (Lucido et al., 2021). Consistent with this logic are studies reporting that medications that antagonize the action of inflammatory cytokines (e.g. infliximab) also reduce depressive symptoms, even

among individuals with treatment-resistant depression (Raison et al., 2013). The catch, however, is that current anticytokine therapies appear to only reduce depression among individuals with elevated inflammation (CRP ≥3 mg/L) or a comorbid autoimmune or inflammatory disorder (Raison et al., 2013). And even among those patients, these medications pose a non-trivial health risk, as they block immune responses that are critical for defending against infection. Finally, current anticytokine therapies are most effective for reducing anhedonia and motivational deficits in psychiatric disorders, rather than distress or dysphoria (Lucido et al., 2021). However, research and drug development on anti-inflammatory-based treatments for depression are in their early days, and it is reasonable to expect that new drugs will more precisely target inflammation in the brain with benefits for a broader range of symptoms and fewer off-target effects. One development to watch out for is the use of ultrasound to modify the blood–brain barrier permeability in specific brain regions (Rabut et al., 2020). This technique could help anti-inflammatory medications selectively access brain regions specified in our neuroimmune network model and increase their efficacy in treating anhedonia, as well as perhaps distress and dysphoria.

Our neuroimmune network model not only specifies anatomical connections between the brain and immune system, it also highlights the role of behavior in driving inflammation (Nusslock & Miller, 2016). Identifying behavioral mediators of neuroimmune dysregulation can help identify modifiable targets for behavioral interventions. Strong candidates for such interventions include regularizing sleep schedules, exercise, stress reduction, and nutrition, all of which have been shown to have anti-inflammatory benefits (Santos, Tufik, & De Mello, 2007). These interventions should not only help manage depression but also highly comorbid conditions including substance abuse and dependence and physical health problems like coronary heart disease and cardiometabolic conditions. Cognitive therapies that enhance executive control should also help mitigate neuroimmune dysregulation. These therapies can engage the prefrontal cortex in a manner that helps individuals regulate limbic reactivity during stress and inhibit the momentum to self-medicate dysphoria and distress through proinflammatory behaviors (Siegle, Ghinassi, & Thase, 2007). Support for this perspective comes from a series of studies that we conducted showing that individuals with strong connectivity in the central executive network, which is anchored in the dorsolateral prefrontal cortex, were largely protected from the effects of stress on inflammatory and cardiometabolic activity (Miller et al., 2018, 2021). Thus, the central executive network may be a good target for enhancing resilience and treating neuroimmune dysregulation.

Finally, a central tenet of the neuroimmune network model is that stress and adversity amplify crosstalk between the brain and peripheral inflammation in a manner that heightens risk for mental and physical health problems, including depression (Nusslock & Miller, 2016). Thus, interventions and policies that reduce chronic stress exposure should minimize neuroimmune dysregulation and corresponding health problems. For example, family-based interventions that improve parenting and parent–child relationship quality have positive effects on children's stress-reactivity and reduce inflammatory activity. For example, a randomized controlled trial showed that a family-strengthening intervention implemented with low-income 11-year-old youth and their mothers resulted in lower levels of inflammation in the youth at age 19 (Miller, Brody, Yu, & Chen, 2014). On a broader scale, there is preliminary evidence that providing individuals or families with a guaranteed basic income reduces family stress and helps support parent, family, and child development. For example, studies that examine state-level variation in earned income tax credits and/or unconditional cash transfers of meaningful amounts of money show that increased financial resources is associated with increases in children's physical and emotional health, and positive effects on brain development (Akee, Copeland, Costello, & Simeonova, 2018; Troller-Renfree et al., 2022). Our hope is that collectively this work might help facilitate policies that target structural inequities in our society that contribute to experiences of early-life adversity and chronic stress exposure.

As noted above, neuroimmune signaling appears to defy conventional diagnostic categories and instead generates risk for psychiatric symptoms that cut across disorders (Costello et al., 2019; Dooley et al., 2018; Goldsmith et al., 2016; Majd et al., 2020). We and others (Lucido et al., 2021; Miller & Raison, 2023) extend this logic by proposing transdiagnostic perspectives where inflammation predicts general distress and fears through threat-sensitive brain areas and anhedonia and motivational deficits through reward-sensitive brain areas. These transdiagnostic perspectives have important treatment implications (Miller & Raison, 2023). They can help us move beyond 'one size fits all' therapeutics and develop and refine more personalized interventions that target specific pathophysiological pathways that impact specific symptom clusters (Insel et al., 2010). This approach also can help us identify subgroups of individuals who are likely to respond to a specific set of psychosocial, behavioral, or pharmacological interventions (Insel et al., 2010). An important component of developing and evaluating more targeted interventions will be the development of psychological, behavioral, and biological outcome variables that are sensitive to the pathophysiological pathways of interest (Miller & Raison, 2023). The goal of such a translational

research program is to move from treating outdated and overly inclusive diagnostic categories (e.g. depression) to develop personalized, holistic, and mechanistically precise interventions.

Finally, a goal of this paper is to extend neuroimmune network models of mental and physical health to generate a developmental framework of risk for the onset of depressive symptoms in youth and adolescents. Collectively, this work suggests that risk for depression does not happen by chance, but rather, for some, is set in motion during the early years of life through exposure to life adversity and a series of causal linkages between the brain and immune system that occur across development. Basic, clinical and epidemiological research all suggest that the earlier the intervention the better (Brody et al., 2017; Chetty, Hendren, & Katz, 2016; Nusslock & Miller, 2016). The developmental framework proposed here strongly aligns with this perspective and highlights how the foundations of risk for depression are established very early in life. Our hope is that this framework can help highlight candidate pathways that can be targeted in early intervention and prevention programs with high-risk youth and adolescents.

Limitations and concluding remarks

We argue that understanding how childhood adversity heightens risk for depression during adolescence requires a fresh, integrated approach to research. Accordingly, in this paper we extend neuroimmune network models of mental and physical health to generate a developmental framework of risk for the onset of depression in adolescence. This model is not a definitive mechanistic account and many of the proposed pathways will need to be examined and corroborated in subsequent animal and human research. First, the developmental timeline of the model and its causal claims will need to be tested in longitudinal studies, including our hypothesis that early-life stress incubates in the developing brain and body and is exacerbated by subsequent stress during adolescence. Second, stress is a complex construct and different types of stress may be more associated with neuroimmune dysregulation. Preliminary evidence suggests that stressors involving threat (e.g. presence of a threat) versus deprivation (e.g. absence of expected environmental inputs) affect the brain differently but have comparable effects on the immune system (Chiang et al., 2022; McLaughlin et al., 2019). Third, it will be important to examine whether there are sex differences in the effect of early-life stress on neuroimmune signaling and risk for depression. Animal and human studies highlight sex differences in response to stress across all stages of life (Bale & Epperson, 2015), and females have higher rates of immune disorders and depression (Fairweather, Frisancho-Kiss, & Rose, 2008). Despite this, sex differences in neuroimmune signaling have not been a focus of study. Finally, it will be important to examine which specific symptom clusters of depression, and psychiatric disorders more broadly, are affected by neuroimmune dysregulation. Despite these limitations, our model provides a roadmap for future research and identifies biological and behavioral pathways that can be addressed to treat, and ideally prevent, depression across development.

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Key points

- Growing evidence implicates brain systems involved in detecting threats in the environment, evaluating rewards, and regulating one's emotions and behaviors in the pathophysiology of depression.
- In a separate literature, heightened inflammation in both the periphery and the central nervous system has been documented in MDD.
- Recently, we and others have proposed neuroimmune networks models suggesting that neuroimmune dysregulation is a dynamic joint vulnerability for depression.
- Here we extend neuroimmune network models to generate a developmental framework of neuroimmune dysregulation and risk for the onset of depression during adolescence.
- This work can facilitate a 'next generation' of behavioral and biological interventions that target neuroimmune signaling to treat, and ideally prevent, depression in youth and adolescents.

Endnotes

1. In certain contexts, early-life adversity may be associated with heightened, as opposed to blunted, reward-related brain activity. For example, we have reported that growing up in poverty is associated with greater activation in brain regions involved in attention to both rewards and loss cues and reduced differentiation in the brain between reward and loss feedback (White, Nusslock, & Miller, 2022). Both of these results are consistent with the concept of the 'scarcity mindset,' which suggests that individuals living with minimal resources are sensitive to cues of both gain and loss and that the metabolic demand of this hypersensitivity can generate health problems overtime (Shah, Shafir, & Mullainathan, 2015). This finding is also consistent with the fact that early-life adversity can increase risk for disruptive or externalizing behaviors which are frequently characterized by a heightened sensitivity to rewards (McLaughlin, Costello, Leblanc, Sampson, & Kessler, 2012; Murray, Waller, & Hyde, 2018). The present paper, however, primarily focuses on the linkage between early-life adversity and decreased reward-related brain activity given our focus on depression and the fact that chronic inflammation typically lowers, rather than enhances, reward-related brain activity (Lucido et al., 2021). Future research should examine the relevance of neuroimmune models to disruptive disorders and the comorbidity between internalizing and externalizing symptoms.
2. Under certain conditions, inflammation may enhance sensitivity to rewards. For example, inflammation has been shown to increase reward-related brain activity to rewarding social stimuli, presumably to increase connection and approach behaviors toward people who provide support or care during sickness (Eisenberger et al., 2017).
3. It is important to recognize that there are multiple mechanisms through which stress and adversity can heighten inflammation outside the influence of neuroimmune signaling. These include, but are not limited to, exposure to toxins and particulate matter in the environment, lack of nutritional resources and food insecurity during development, and inadequate access to and use of medical care (Yang et al., 2014). Thus, we propose that heightened threat processing in the brain precedes heightened inflammation in the body in the context of intrapersonal stress-related pathways. Future research is needed to integrate research on intrapersonal stress-related pathways with family investment and societal pathways to inflammation.

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