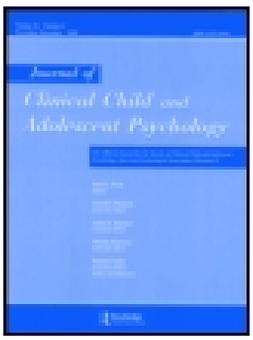

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Future Directions in the Study of Early-Life Stress and Physical and Emotional Health: Implications of the Neuroimmune Network Hypothesis

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Early-life stress is associated with increased vulnerability to physical and emotional health problems across the lifespan. The recently developed neuroimmune network hypothesis proposes that one of the underlying mechanisms for these associations is that early-life stress amplifies bidirectional crosstalk between the brain and the immune system, contributing to several mental and physical health conditions that have inflammatory underpinnings, such as depression and coronary heart disease. Neuroimmune crosstalk is thought to perpetuate inflammation and neural alterations linked to early-life stress exposure, and also foster behaviors that can further compromise health, such as smoking, drug abuse and consumption of high-fat diets. The goal of the present review is to briefly summarize the neuroimmune network hypothesis and use it as a starting point for generating new questions about the role of early-life stress in establishing a dysregulated relationship between neural and immune signaling, with consequences for lifespan physical and emotional health. Specifically, we aim to discuss implications and future directions for theory and empirical research on early-life stress, as well as for interventions that may improve the health and well-being of children and adolescents living in adverse conditions.

Early-life stress is associated with elevated risk of both mental and physical health problems across the lifespan (Danese & McEwen, 2012; Ehlert, 2013; G. E. Miller, Chen, & Parker, 2011). For instance, adults who report four or more adverse childhood experiences (e.g., emotional, physical, or sexual abuse; family dysfunction) are 4.6 times more likely to experience depressed mood and 12.2 times more likely to attempt suicide compared to individuals without any major childhood adversity. In addition to these mental health risks, they are also more likely to develop coronary heart disease (2.2 times), stroke (2.4 times), and diabetes (1.6 times; Felitti et al., 1998).

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Despite these patterns, most prior research on early-life stress has focused on either physical *or* mental health to the exclusion of the other. This is surprising because in many instances the health problems associated with early-life stress have high rates of comorbidity and share common risk factors and etiological pathways. The recently developed *neuroimmune network hypothesis* (Nusslock & Miller, 2016) attempts to integrate these disparate literatures. It proposes that many of the health problems related to early-life stress arise because adversity potentiates bidirectional crosstalk between the neural and immune systems, engendering a positive feedback circuit that links emotional processes, low-grade inflammation, and unhealthy behaviors.

The goal of the present review is to briefly summarize the neuroimmune network hypothesis and to use it as a starting point for generating new questions about the role of early-life stress in shaping bidirectional crosstalk between neural and immune signaling, with implications for the development of physical and mental health conditions. Our goal is not to

conduct a comprehensive overview of the literature (for recent reviews on early-life stress and the development of psychopathology, see Humphreys & Zeanah, 2014; McLaughlin, 2016; Teicher & Samson, 2013; on early-life stress and brain development, see Fareri & Tottenham, 2016; Gee & Casey, 2015; McLaughlin, Sheridan, & Lambert, 2014; on early-life stress and later physical health, see Danese & McEwen, 2012; Ehrlich, Miller, & Chen, 2016; G. E. Miller et al., 2011). Rather, our aim is to discuss implications of the neuroimmune network hypothesis and explore future directions for theory, research, and interventions with children and adolescents that follow from this hypothesis. Specifically, we (a) discuss conceptual implications of the hypothesis (e.g., its use of a systems approach and focus on explaining multimorbidity and on neurobehavioral precursors), (b) suggest empirical studies that would deepen our understanding of neuroimmune regulation and its role in transducing the effects of early-life stress on health, and (c) discuss perspectives on intervention strategies in early life that might be beneficial (e.g., group prenatal care, parenting interventions). We focus on maltreatment (emotional, physical, or sexual abuse, and physical or emotional neglect), low socioeconomic status (SES), and early deprivation as operationalizations of early-life stress, given that most research findings assessing neuroimmune correlates of adversity have concentrated on these experiences. Ideally, future studies should explore other types of early-life stress that may set in motion similar neuroimmune processes (e.g., war, natural disasters, bullying, familial dysfunction, discrimination). Before we proceed with a summary of the neuroimmune network hypothesis, we briefly describe the emerging evidence implicating inflammation in the etiology of numerous emotional and physical disorders.

PSYCHOSOCIAL STRESS AND INFLAMMATION

Emerging findings are increasingly revealing the role of peripheral low-grade inflammation in explaining the associations between early-life stress and various physical or mental health outcomes (Fagundes, Glaser, & Kiecolt-Glaser, 2013; G. E. Miller et al., 2011; Slavich & Irwin, 2014). Inflammation is a response by innate immune cells to injuries and infections, which attempts to eradicate invading pathogens and promote tissue healing in the short term. 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. This "nonresolving inflammation" (Nathan & Ding, 2010) has been linked to multiple health problems across the lifespan (see next for more details). Low-grade inflammation is frequently assessed in population studies using biomarkers, typically C-reactive protein (CRP) and interleukin-6 (IL6), both of which can be measured in blood.

Studies show that these biomarkers of low-grade inflammation are increased in populations who experience chronic psychosocial stress. For instance, there is emerging evidence suggesting that children and adolescents who experience adversity (e.g., maltreatment, low SES) exhibit higher levels of inflammatory biomarkers relative to nonexposed peers (Danese et al., 2011; Dowd, Zajacova, & Aiello, 2010; Pietras & Goodman, 2013; Slopen, Kubzansky, McLaughlin, & Koenen, 2013). There is also evidence to suggest these effects might be long-lasting, given that both prospective and retrospective studies of adults who experienced adversity during childhood report that these adults also display higher levels of inflammatory biomarkers (Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2014; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Fagundes et al., 2013; Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015; Slopen et al., 2013). Finally, chronic stress during adulthood (e.g., low SES, familial caregiving obligations, job burnout, loneliness) is also associated with higher levels of these biomarkers (Hänsel, Hong, Cámara, & Von Känel, 2010; Nazmi & Victora, 2007).

What are the mental and physical health implications of these stress-related increases in low-grade inflammation? Observational studies in humans and experimental studies in both human and nonhuman animals have shown that inflammatory mediators like interleukin-1 and interferon-alpha can trigger a constellation of sickness behaviors that overlaps substantially with major depression (for a comprehensive review, see Slavich & Irwin, 2014). In the physical health realm, biomarkers of low-grade inflammation forecast premature mortality in population-based studies, as well as the onset of frailty, type 2 diabetes, stroke, coronary heart disease, vascular dementia, and some cancers (Black, 2003; Chung et al., 2009; Libby, 2012; Powell, Tarr, & Sheridan, 2013; Ridker, 2007).

THE NEUROIMMUNE NETWORK HYPOTHESIS

Recent studies have highlighted associations between markers of low-grade inflammation and early-life stress, patterns of neural activity, and health-relevant behaviors like smoking, drug use, and obesity (Gianaros & Hackman, 2013; G. E. Miller et al., 2011; Shonkoff, Boyce, & McEwen, 2009). The *neuroimmune network hypothesis* (for a detailed account, see Nusslock & Miller, 2016) organizes and integrates these findings, then proposes a common mechanism underlying these disparate observations. The mechanism is assumed to be an integrated neuroimmune network involving the brain, the immune system, and behavior, which is shaped by early-life stress and creates self-perpetuating cycles of activity that promote disease processes (see Figure 1 and caption for an illustration of the neuroimmune-behavior connections thought to be implicated and a brief description of the cortico-amygdala and cortico-basal ganglia neural circuits).

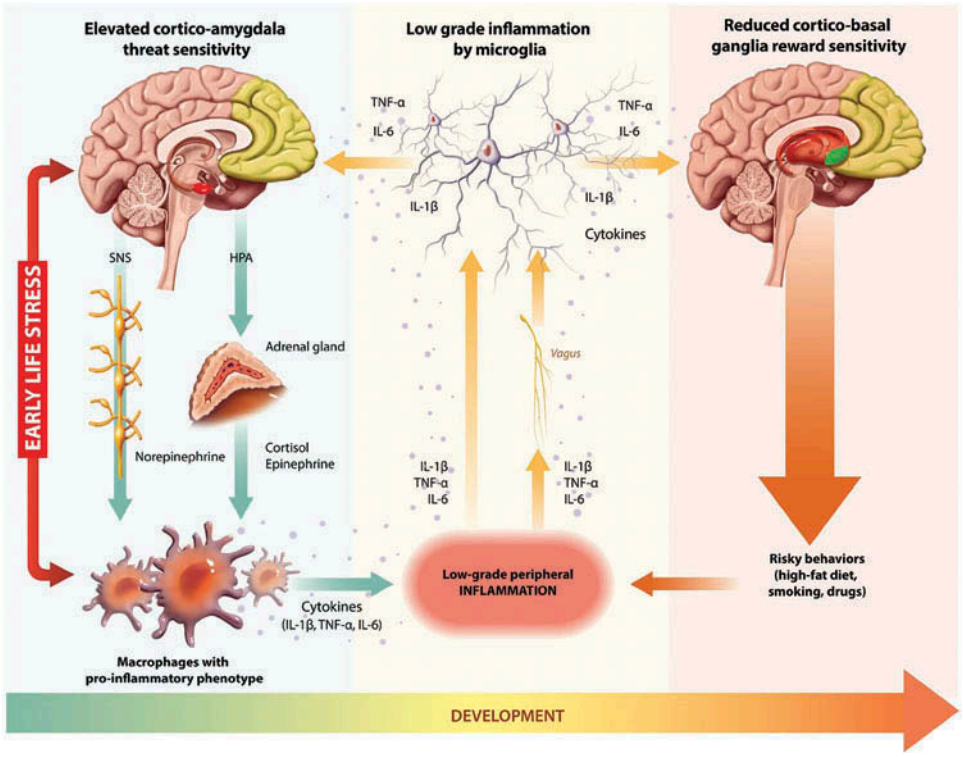

FIGURE 1 Depiction of the neuroimmune network hypothesis. *Note*: The cortico-amygdala neural circuit supports vigilance for and responses to threatening stimuli. This circuit includes the amygdala, a limbic region that has been implicated in emotion perception, learning, and responding, and the prefrontal cortex, which participates in emotion-regulatory processes by exerting inhibitory top-down control over the amygdala and other limbic regions (Callaghan & Tottenham, 2016). The cortico-basal ganglia circuit supports reward processing and involves projections from midbrain nuclei (e.g., substantia nigra) to subcortical areas within the basal ganglia (e.g., ventral striatum) and cortical target regions (e.g., orbitomedial frontal cortex). Dopamine is the neurotransmitter most directly involved in reward processing within this circuit, playing a central role in incentive motivation, reward-based learning, and motor control (Haber & Knutson, 2009). 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*(1), 1–10.

Briefly, the neuroimmune network hypothesis relies on three streams of evidence. First, it builds on research showing that early adversity sensitizes the brain's networked cortico-amygdala regions in a manner that heightens vigilance for, and reactions to, threatening stimuli (for a recent review, see Callaghan & Tottenham, 2016) and attenuates sensitivity to rewards and reward-related brain function in networked cortico-basal ganglia regions (e.g., Mehta et al., 2010). Second, it integrates studies indicating that early adversity also sensitizes the immune cells that propagate inflammation (monocytes and macrophages), programming them to mount exaggerated responses to infections and injuries (G. E. Miller et al., 2011; Rook, Raison, & Lowry, 2014). Next, this hypothesis draws further inferences from evidence that peripheral inflammation can spread to the brain through multiple mechanisms (Irwin & Cole, 2011). Cytokines, like interleukin-1β, IL6, and tumor necrosis factor alpha (TNF-α), can access the brain through active transport or can enter at circumventricular organs or leaky regions of the blood–brain barrier. Peripheral cytokines can also engage receptors on afferent vagal fibers, which project to limbic regions via the nucleus of the solitary tract (Haroon, Raison, & Miller, 2012; Irwin & Cole, 2011). Studies in rodents have shown that this immune-to-brain traffic can modulate cortico-amygdala circuitry involved in threat processing and is linked to heightened anxiety-like behaviors (Frank, Watkins, & Maier, 2011; Wohleb et al., 2011; Wohleb, Powell, Godbout, & Sheridan, 2013). Emerging evidence suggests similar processes in humans, for example, cytokines released in response to an experimental inflammatory paradigm accentuate threat-related processes in the cortico-amygdala circuit (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). Inflammatory mediators can also attenuate reward-related processes in the cortico-basal ganglia circuit, inducing "sickness behaviors" like anhedonia, sleep dysregulation, and fatigue, which are antecedents and components of depression (Dantzer, Connor, Freund, Johnson, & Kelley, 2008). Although early adversity undoubtedly influences reward sensitivity through multiple pathways (e.g., learning mechanisms, Fareri & Tottenham, 2016; McLaughlin & Sheridan, 2016), growing evidence

suggests a possible mechanistic role for inflammation. Blunted reward sensitivity is part of a generalized set of adaptations to infection, mediated by inflammatory cytokines (Maier & Watkins, 1998; A. H. Miller, Maletic, & Raison, 2009). Animal models show that inflammatory mediators reduce animals' sensitivity to rewarding stimuli, including reinforcers like sex, food, and electrical stimulation (for a review, see Dantzer et al., 2008). In humans, there is experimental evidence that inflammation can reduce neural reactivity to rewards, as shown by studies that trigger inflammation by administering low-dose bacterial products (Eisenberger et al., 2010) or examining the effects of immune-activating treatments on neural reward processing (Capuron et al., 2012). These experimental studies in humans support the idea that inflammation is capable of modulating the activity of neural circuits involved in reward independently of other processes (e.g., reinforcement learning) that may be operating in parallel or in concert with inflammation in those exposed to childhood adversity. Nevertheless, studies have yet to directly examine the role of inflammation in reducing reward sensitivity in adverse rearing conditions above and beyond other mechanisms such as learning and heritability in the midbrain dopamine system. This is an important direction for future research.

Cytokines may also dampen executive control-related processes linked to regions of the prefrontal cortex involved in executive control, decision making, and regulating threat- and reward-related tendencies (Harrison et al., 2009; Juengling et al., 2000). Based on these observations, the neuroimmune network hypothesis postulates the existence of multiple bidirectional pathways linking peripheral inflammation with neural circuitries subserving threat, reward, and executive control. Drawing on recent studies, this hypothesis suggests that early adversity amplifies bidirectional crosstalk within these neuroimmune pathways. For example, low-grade, chronic inflammation is hypothesized to act on these neural circuitries in ways that facilitate self-medicating behaviors, like smoking, drug use, and consumption of high-fat and high-sugar diets, which are prevalent among individuals exposed to early-life stress. In turn, these behaviors further propagate inflammation, creating a self-sustaining feedback loop. Across the lifespan, these processes are thought to act in concert with genetic liabilities and other exposures to contribute to common physical and mental health problems (Campbell, Walker, & Egede, 2016; Felitti et al., 1998; G. E. Miller et al., 2011). Thus, a novel feature of the neuroimmune network hypothesis is that it provides a common mechanistic pathway to mental and physical health problems that occur across the lifespan.

Although previous studies on human and nonhuman animals have provided piecemeal support for some of these bidirectional connections among nervous, immune, and behavioral systems, the overall model has yet to be empirically tested in humans, despite its potential to explain a wide range of mental and physical health problems in those affected by early-life adversity. To collect evidence in support of this proposed neuroimmune network, a new theoretical orientation and new empirical research will need to be pursued. We turn our attention to these next.

THEORETICAL IMPLICATIONS OF THE NEUROIMMUNE NETWORK HYPOTHESIS

Systems Approach

The neuroimmune network hypothesis suggests that a systems-oriented generation of research is needed to understand the consequences of early-life stress. Systems biology is increasingly recognizing that diseases arise as a result of perturbations in biological networks and their interactions (Hood, Heath, Phelps, & Lin, 2004) and not simply due to isolated dysfunction in a single organ. For instance, recent neuroscientific efforts to map the human "connectome" (i.e., the network of neural connections in the brain, or the wiring diagram of the brain) are revealing how easy it is for neural dysfunction in one region to become widespread (Fornito, Zalesky, & Breakspear, 2015). Furthermore, dysfunction can spread not only within brain regions but also into other organ systems regulated by the brain. For example, current theorizing regarding irritable bowel syndrome, a gastrointestinal disorder with unknown etiology that affects 15% of the worldwide population and has been associated to early-life stress, suggests that this is a "systems disease" (Mayer, Labus, Tillisch, Cole, & Baldi, 2015). Namely, there is increasing recognition that the disorder likely arises from dysregulated bidirectional interactions among neural, immune, digestive, and gut-microbiota systems, given that correlated patterns of activity across these systems seem to explain more variance in the disorder than activity within any of the systems (Mayer et al., 2015). It has been proposed that a systems approach integrating information across multiple biological systems will lead to more effective treatments by allowing us to discover which disorder features are primary and which are secondary in the unfolding of disease processes (Mayer et al., 2015).

Explaining Multimorbidity

Another implication of the neuroimmune network hypothesis is that identifying common etiological pathways for chronic diseases (e.g., low-grade inflammation) may help explain multimorbidity, which has been defined as "the co-occurrence of multiple physical or psychological illnesses" (Suls, Green, & Davidson, 2016). Epidemiological studies reveal that multimorbidity is increasingly becoming the norm rather than the exception, especially given the growing proportion of the elderly population in the United States (Vogeli et al., 2007; Ward, Schiller, & Goodman, 2014). This stands in stark contrast with the conventional biomedical approach of

conceptualizing diseases as distinct entities with distinct causes. New theoretical models need to be developed to explain the emergence of specific constellations of multimorbidity (e.g., depression and coronary heart disease, which co-occur at greater than chance levels; Lichtman et al., 2008) and test underlying synergistic processes that might lead to these multiple deleterious endpoints. The neuroimmune network hypothesis proposes that alterations in brain-immune traffic leading to chronic low-grade inflammation may explain why early-life stress elevates risk for multiple health problems, and one potential implication may be that studying and ultimately treating clusters of disorders with common inflammatory underpinnings jointly may be more fruitful than a one-disorder-at-a-time approach.

Focusing on Neurobehavioral Precursors

The neuroimmune network hypothesis also rests on the assumption that certain neurobehavioral phenotypes (e.g., high threat responsivity, low sensitivity to reward, diminished executive control) might forecast later dysfunction and explain some of the pathways from early-life stress to adult disorders. This focus on neurobehavioral precursors is consistent with recent efforts in psychiatry to shift from current clinical diagnostic systems to a neuroscience-based understanding of common mechanisms across different disorders as they are currently defined, for example, the Research Domains Criteria project (RDoC; Insel et al., 2010). Briefly, the RDoC initiative describes five major domains of functioning (negative valence systems, positive valence systems, cognitive systems, social processes, and arousal/regulatory systems) and promotes the study of constructs within these domains as they relate to indices measured at multiple levels of analysis: genes, molecules, cells, circuits, physiology, behavior, self-report, and assessment paradigms (Cuthbert & Insel, 2010). The brain is featured prominently across the five domains and all the units of analysis, consistent with the RDoC vision of conceptualizing mental illnesses as "disorders of brain circuits" (Insel et al., 2010). Another goal of RDoC is to identify "biosignatures" that could be used in conjunction with symptoms to improve diagnosis and treatment (Insel et al., 2010). Inflammation may be one such biosignature that could serve as a transdiagnostic marker across multiple disorders. As just reviewed, inflammation has bidirectional interactions with neural circuits involved in threat and reward processing, as well as executive control. These processes are at the core of three of the five RDoC domains: negative valence systems, positive valence systems, and cognitive systems. Not surprisingly, the RDoC matrix recognizes this evidence and has begun incorporating immune measures. For instance, inflammatory molecules are linked to negative valence systems (the construct of loss). Microglia, the primary immune cells in the central nervous system and of the monocyte/macrophage lineage, are also featured as important in the study of negative valence systems (construct of sustained threat). Immune markers are included as physiological markers linked to social processes (affiliation and attachment system), and cytokines are referenced in the context of studying arousal, the organism's sensitivity to internal and external stimuli (National Institute of Mental Health, 2016). The RDoC vision and the neuroimmune network hypothesis both suggest that an important future direction of research will be to develop ways to integrate immune measures like the ones enumerated above with assessments of neural activity and behavior into coherent models that might improve early detection of risk for mental illness and inform efforts to prevent or treat psychopathology. It would be helpful if research in this arena could propose and characterize specific, well-defined neurobehavioral and immune phenotypes (e.g., co-occurrence of heightened amygdala activity, amplified cytokine responses to immune challenge, and depressed affect) that can be tied to early-life stress and that might be precursors to later mental and physical illnesses. If such well-identified phenotypes are closely linked to both adverse exposures and health outcomes, they could be targets for interventions that have the goal of preventing multiple mental and physical health disorders simultaneously. In addition, studying such precursors might facilitate a better tailoring of prevention and treatment efforts, particularly if those precursors are shown to be amenable to intervention (Cicchetti, 2016).

UNRESOLVED EMPIRICAL QUESTIONS

As just mentioned, the neuroimmune network hypothesis is a proposed integration of separate pieces of evidence from neuroscience, immunology, developmental psychology, and public health. However, more research is needed to test this model empirically, as we discuss in more depth next.

Testing the Neuroimmune Network Hypothesis

The challenge in studying biological networks in their dynamic complexity is that, once dysfunction emerges and spreads, it is difficult to tease apart primary from secondary features (Mayer et al., 2015). In the context of the neuroimmune network discussed here, there is insufficient empirical evidence indicating which neural, immune, and behavioral processes play a primary role temporally and causally. The model assumes that elevated cortico-amygdala threat sensitivity and the programming of macrophages to exhibit a proinflammatory phenotype occur first and play a primary role, followed by changes in cortico-basal ganglia reward sensitivity and the adoption of unhealthy behaviors. However, more research is needed to empirically test this proposed developmental sequence. Toward this goal, it will be important for scientists to concurrently assess neural, immune, and behavioral measures at multiple time points and within different developmental stages (e.g., using multiwave panel designs like the one illustrated in Figure 2).

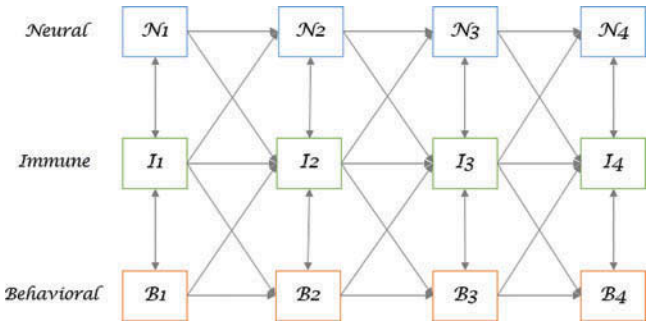

FIGURE 2 Sample illustration of a multiwave panel design collecting neural, immune, and behavioral measures at four time points. *Note*: Arrows represent correlations in a cross-lagged panel correlational design or paths in a structural equation model.

Although a number of studies have provided cross-sectional evidence for the links in the neuroimmune network model, estimates for mediation models can be biased in cross-sectional studies (Cole & Maxwell, 2003; Maxwell & Cole, 2007); additionally, the temporal ordering of effects is ambiguous in these designs. Longitudinal studies would allow for a more detailed mapping of connections between the systems, allow a better understanding of the temporal ordering of the various alterations, and suggest some possibilities for how early-life stress might mechanistically operate to perturb these systems. These initial studies could serve as a snapshot and foundation for later developing a more complex understanding of the bidirectional and perhaps nonlinear dynamics that govern neuroimmune interactions.

One question raised by the neuroimmune network hypothesis is: when do developmental trajectories in neuroimmune functioning of children experiencing adversity start to diverge from those of typically developing children? In other words, when could we first observe evidence that dysregulation across each level of the neuroimmune network has crystallized (i.e., evidence of concomitant heightening of threat responsivity, lowered reward sensitivity, reduced executive function, and elevated levels of inflammation that persist over time)? There are no empirical examinations of this question in humans. Studies within early, middle, or late childhood, as well as during adolescence that assess neural (EEG, MRI), immune and behavioral measures in the same participants will be able to provide an initial answer to this question, with short-term follow-up assessments (e.g., 6–24 months) needed to test whether the patterns are consistent over time.

There are, however, some potential clues regarding the emergence of each component in the neuroimmune network hypothesis. For instance, novel methodologies such as task-based and resting-state fMRI functional connectivity with infants and toddlers during natural sleep (i.e., without sedation) have started to be used successfully (Graham et al., 2015). A recent study using this methodology indicates that higher levels of parental conflict are associated with greater neural responses to angry voice recordings versus neutral speech in infants as young as 6–12 months old (Graham, Fisher, & Pfeifer, 2013). It is unclear whether these neural patterns of responsivity to threat persist across development, but due to novel observational paradigms there is some recent indication that children as young as 4 who have been exposed to family violence show consistent attentional biases to threat that are predictive of anxiety disorders (Briggs-Gowan et al., 2015). Newly developed task-based measures of executive function in early childhood have also revealed reduced executive function in children exposed to early parental deprivation or poverty in samples as young as 2.5–4 years old (Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012; Raver, Blair, & Willoughby, 2013). With respect to reward sensitivity, most prior research has focused on school-age children and adolescents (8–16 years old) and revealed a link between early-life stress and decreased reward sensitivity (Guyer et al., 2006; Mehta et al., 2010). More paradigms need to be developed and research conducted to understand when these alterations in reward processing occur in human development in the context of adversity. Reward sensitivity shows a normative spike during adolescence (Somerville & Casey, 2010); thus, future studies could examine whether this is also a period when reward-processing abnormalities emerge in youth exposed to early-life stress.

Proinflammatory responses have been linked to adversity as early as the neonatal period. For instance, one study reported that prenatal maternal stress was associated with greater stimulated cytokine production (e.g., IL-8 and TNF-α) in newborns' cord blood cells that were cultured with microbial stimuli (Wright et al., 2010). However, it is not known whether this phenotype persists across development. There are now more than 20 studies examining psychosocial adversity and measures of low-grade inflammation in children and adolescents between the ages of 2 and 18 according to a recent meta-analysis (Slopen et al., 2013). The majority of these studies used CRP as an index of inflammation, and most of those conducted with 2- to 9-year-olds reported null or mixed findings, including some well-powered epidemiological studies, whereas among 10- to 18-year-olds there are more studies finding significant associations than null results (Slopen et al., 2013).

There are several potential explanations for these patterns. First, these could be latent effects, which incubate during childhood and don't manifest until early adolescence. Second, the biomarkers of inflammation often studied in this literature, particularly CRP, are expressed at very low concentrations in children, and assays may lack the sensitivity to make fine-grained differentiations. Third, and consistent with the reasoning in the neuroimmune network hypothesis, is that different layers of the inflammatory phenotype come online sequentially across development. The initial layers, which are increased monocyte/macrophage responsivity to

microbial threats and decreased sensitivity to anti-inflammatory signals, appear in childhood. But they have seldom been studied in children as a function of adversity (for some examples, see Azad et al., 2012; Chen et al., 2006; Chen et al., 2016), perhaps because the measurements are of greater complexity. Instead, most research in the literature has focused on circulating CRP and IL6, which are fairly simple to measure, but according to the neuroimmune network hypothesis should not be elevated until well in adulthood. In conclusion, more studies are needed that explicitly measure brain, behavior, and immunity in early, middle, and late childhood in the context of poverty, maltreatment, or early parental deprivation/separation to understand exactly when and if a stable proinflammatory neuroimmune constellation emerges during these developmental stages.

Another major unknown is what occurs to the neuroimmune network during normative developmental transitions, which can be periods of heightened vulnerability as well as an opportunity for neurobehavioral reorganization. For instance, puberty is a relatively stressful life transition that brings about a plethora of neuro-hormonal, bodily, and psychosocial changes (Forbes & Dahl, 2010); a heightening of biological stress reactivity (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Stroud et al., 2009); and the onset of a substantial proportion of mood, anxiety, and substance abuse disorders (Merikangas et al., 2010). There is a paucity of studies in humans on puberty-related developmental changes in immune function, with most developmental work in immunology having primarily focused on the prenatal/perinatal period and senescence (Brenhouse & Schwarz, 2016). This is despite some intriguing recent findings in rodents that animals exposed to early-life maternal separation exhibit lower anti-inflammatory activity during puberty (Grassi-Oliveira, Honeycutt, Holland, Ganguly, & Brenhouse, 2016). This raises the following question in humans: Does early-life stress exposure interact with pubertal onset to amplify risk for neuroimmune dysregulation, and what are the implications of this interaction for neuroimmune interactions and for psychopathology? This question could be answered with cross-sectional studies of pre- and postpubertal adolescents with and without exposure to early-life stress, or in longitudinal cohorts with documented childhood adversity exposure that use repeated measurements across the pubertal transition. This would require triangulating neuroimaging measures of cortico-amygdala or cortico-basal ganglia activity (e.g., fMRI tasks tapping threat responsivity or reward sensitivity) along with measures of inflammation and health behaviors between the ages of 10 and 15, when most girls and boys undergo pubertal changes.

Understanding the signals and mechanisms through which childhood adversity affects neural, immune, and behavioral parameters, as well as their interactions, will also be critical. Social relationships are likely an important conduit. Throughout development, interactions with caregivers modulate children's emotional and physiological reactivity, for better or for worse (Callaghan & Tottenham, 2016; Hostinar, Sullivan, & Gunnar, 2014). This tunes the developing neural circuitry, especially during sensitive developmental periods for structures involved in emotion processing and regulation, such as the cortico-amygdala circuit (Callaghan & Tottenham, 2016). The exact mechanisms through which these effects are instantiated are currently not known, and need further exploration.

In the immune system, it is theorized that childhood adversity programs immune cells to have proinflammatory tendencies via epigenetic markings, posttranslational modifications, and tissue remodeling (G. E. Miller et al., 2011), but more work is needed to examine these processes in humans, during early development, and with long-term follow-up periods. In addition, proinflammatory tendencies are thought to be amplified through altered patterns of hypothalamic-pituitary-adrenocortical (HPA) and sympathetic nervous system activity, and unhealthy behaviors that promote inflammation (G. E. Miller et al., 2011). The burgeoning number of studies that assess hypothalamic-pituitary-adrenocortical or sympathetic nervous system indices in children and adolescents—especially those adopting an experimental/intervention design (Fisher et al., 2016; Slopen, McLaughlin, & Shonkoff, 2014) creates opportunities for the addition of immune measures and assessment of neural activity, which would allow testing of some of the basic tenets of the neuroimmune network model.

Animal models will remain instrumental in probing causal mechanisms, both in terms of the ability to randomly assign animals to various rearing conditions and the opportunities for directly probing brain and immune function through techniques that are too invasive in humans. For instance, pharmacological experiments and gene knockout models in rodents (e.g., cytokine-deficient mice) have proven extremely useful in substantiating the causal role of inflammatory proteins such as IL-1β and TNF-α in producing sickness behaviors, anhedonia, and social withdrawal (Dantzer et al., 2008). These techniques could be used to answer questions derived from the basic neuroimmune network model. For example, would cortico-amygdala and cortico-basal ganglia alterations following early-life stress be attenuated in animals if inflammation were experimentally reduced? Which aspects of brain structure and function are most affected by peripheral and central inflammation (e.g., gray matter, white matter, total brain volume, functional activation)? Which neural alterations happen first, heightened threat responsivity or lowered reward sensitivity? And how does the timing of these effects shape behavioral and immune outcomes?

Another unresolved question that could inform interventions in humans is whether the developmental timing of stress exposure matters in shaping the outcomes specified in the neuroimmune network model. There is emerging evidence that gestation, infancy/early childhood, and adolescence may be periods of heightened neural plasticity in

systems relevant for processing and regulating threat and reward-related emotions (Callaghan & Tottenham, 2016; McEwen & Morrison, 2013; Romeo, 2015), which may mean greater vulnerability if chronic stress is encountered during these periods. With respect to immune development, research has identified sensitive periods during prenatal and early postnatal life (Holladay & Smialowicz, 2000). But nearly all this work has focused on toxicants and allergens, and much less is known about sensitive periods for chronic psychosocial stressors, or how the timing of such exposures shapes immune development (for an exception, see G. E. Miller & Chen, 2007). Furthermore, the possibility that there are sensitive periods in the development of patterns of neuroimmune crosstalk has yet to be investigated. Future studies should explore the possibility that immune–brain and brain–immune traffic may also undergo periods of heightened vulnerability to disruptions, if these disruptions occur during periods of organizational changes in the pipelines through which these two systems signal to each other. This could be accomplished using rodent models, which have begun revealing and manipulating the molecular triggers and brakes for critical periods in the brain, for example, in the visual cortex (Takesian & Hensch, 2013) and the amygdala (Gogolla, Caroni, Lüthi, & Herry, 2009). The maturation of GABA neural circuits, formation of perineuronal nets (structures that envelop neurons and stabilize synapses, ending sensitive periods), myelination and synaptic pruning are some of the mechanisms through which sensitive periods in the brain are modulated (Hartley & Lee, 2015; Takesian & Hensch, 2013). Much less is known about developmental changes and molecular mechanisms governing sensitive periods in the human immune system (Brenhouse & Schwarz, 2016). Immune cells also express receptors for and respond to GABA (Bhat et al., 2009), thus one exploratory strategy for probing sensitive periods in the development of neuroimmune networks might be to experimentally examine developmental changes in immune cell GABA transmission in conjunction with early-life stress exposure to detect possible periods of vulnerability for neuroimmune dysregulation that may be dependent on sensitive periods occurring in each of the systems. Knowledge about opening and closing sensitive periods in the brain and in the immune system will need to mature further to guide these experiments.

In addition, more research is needed in humans to explore the relation between early-life stress and the timing and duration of later reexposure to stress as it affects neuroimmune interactions. Animal models can elegantly characterize various combinations of early exposure and later reexposures to stress and show how different lifespan stress schedules affect neural outcomes (McEwen & Morrison, 2013). In humans, there is increasing interest in and some emerging evidence on how early-life stress and later reexposure to stress may predispose for psychopathology (Hammen, 2005) and interact with sensitive periods in brain development to shape neural outcomes (for recent reviews, see Gee & Casey, 2015; Tottenham & Galván, 2016). For instance, adults who experienced childhood trauma are at greater risk of developing combat-related posttraumatic disorder, and this may be explained by alterations in resting state functional connectivity between the amygdala and the ventromedial prefrontal cortex (Birn, Patriat, Phillips, Germain, & Herringa, 2014). Exposure to multiple stressful life events in early adolescence is also associated with increasing amygdala reactivity from age 12 to age 18, and the increasing slopes over time are even steeper for those with a family history of depression (Swartz, Williamson, & Hariri, 2015). Furthermore, adolescents who show higher amygdala reactivity at baseline are more likely to exhibit posttraumatic stress disorder symptoms after a major negative event (e.g., the Boston Marathon terrorist attack, McLaughlin et al., 2014). The impact of these neural alterations on patterns of neuroimmune communication is not presently known. However, parallel findings suggest that when adolescents experience major life events, the effects on their immune response depend somewhat on early-life family conditions. Among those raised in harsh family climates, adolescent life events forecast exaggerated inflammatory responses to bacterial products. No such stress-related amplification is observed in adolescents raised in warmer family climates (G. E. Miller & Chen, 2010). The neuroimmune hypothesis suggests the stress-related amplifications of inflammatory and amygdala reactivity during adolescence are part of the same phenomenon, part of a bidirectional pipeline through which early-life adversity potentiates responses to stressors later in development. This hypothesis deserves empirical testing in future studies, particularly those employing multiwave panel designs like the ones depicted in Figure 2.

Understanding Equifinality and Multifinality

The greatest challenge confronting research on the sequelae of early-life stress in humans is explaining the heterogeneity of outcomes linked to childhood adversity, which has been noted with both mental and physical health outcomes. Examples of both equifinality (reaching the same outcomes despite differences in initial conditions or intermediary processes) and multifinality (divergent outcomes despite exposure to the same adverse events; Cicchetti & Rogosch, 1996) are abundant in developmental psychopathology, neuroscience, and psychoneuroimmunology. For instance, even though low socioeconomic status is on average associated with poorer physical or mental health, there are numerous individual, familial, and neighborhood risk and protective factors that moderate this association (Chen & Miller, 2013; Evans & Kutcher, 2011; Garmezy, 1991; McLoyd, 1998), as well as diverse mediators and pathways through which low SES individuals may reach resilient or maladaptive outcomes (Chen & Miller, 2013; Conger, Conger, & Martin,

2010; Hertzman & Boyce, 2010; Matthews & Gallo, 2011). In this section, we discuss a few possible strategies for beginning to address this seemingly insurmountable challenge.

Several theoretical perspectives have argued that a more complete taxonomy of stressful exposures during early life in humans would greatly aid research in this area (Humphreys & Zeanah, 2014; McLaughlin, 2016; McLaughlin & Sheridan, 2016). Children experiencing adversity are often exposed to numerous co-occurring risk factors. For instance, low household SES can coincide with harsh and unresponsive parenting, crowded housing conditions, food insecurity and nutrient deficiencies, and so on (Cohen, Janicki-Deverts, Chen, & Matthews, 2010; Conger & Donnellan, 2007; Evans, 2004; Evans, Li, & Whipple, 2013; Johnson, Riis, & Noble, 2016). Recent attempts to improve measurement of adversity and clarify mechanistic pathways to detrimental outcomes have proposed two orthogonal dimensions of adversity: threat and deprivation (McLaughlin et al., 2014). Other researchers have referred to these two dimensions as harmful input (e.g., abuse, trauma) and inadequate input (e.g., neglect/deprivation; Humphreys & Zeanah, 2014). Although many children experience both threat (e.g., physical abuse) and deprivation (e.g., neglect; Fisher et al., 2016), the fact that threat exposure and deprivation have been linked to differentiable outcomes (e.g., posttraumatic stress disorder is more common after threat exposure, whereas attachment disorders are more commonly linked with deprivation; Humphreys & Zeanah, 2014) suggests that this is a viable path forward for early-life stress research aiming to identify the active ingredients of childhood adversity and understand its effects on psychopathology. Much less is known about the differential role of threatening versus depriving experiences in shaping immune outcomes and physical health more broadly. An important future direction in this area would be to empirically examine whether there are distinct neuroimmune signatures related to each of these two dimensions, as well as to explore other potential dimensions of adversity that may be relevant for health (e.g., physical stressors such as exposure to noise and pollutants, which are neither threatening per se nor depriving but may interact with psychological stress to amplify allostatic load processes; McEwen & Tucker, 2011). How much of the effects of childhood psychosocial adversity on physical health are due to a common stress pathway versus due to distinct processes activated by specific ingredients of adversity like threat or deprivation? Moving closer to answering this question will be critical for informing intervention and prevention efforts.

Continued efforts to characterize normative developmental trajectories of neural, immune, and behavioral functioning will also be needed to explain equifinality and multifinality with respect to the outcomes discussed in the neuroimmune network hypothesis. However, it must be emphasized that deviations from the normative trajectory are not always maladaptive. For instance, some recent studies find that alterations in cortico-amygdala connectivity following early-life stress may be an adaptation to adversity that is protective against internalizing symptoms in some individuals (Gee et al., 2013; Herringa et al., 2016), even though as a group, individuals who experience early-life adversity exhibit higher-than-average levels of internalizing symptoms (Gee et al., 2013). More research is need to understand whether these apparent adaptations have trade-offs in socioemotional development that may lead to maladaptive outcomes later in the lifespan. It will also be important to expand these studies to investigate ramifications for immune and physical health to understand whether the legacy of early-life stress persists in immune cells despite these neural adaptations that may prevent internalizing symptoms through the early engagement of the prefrontal cortex in regulating the amygdala. Conducting such studies will inform our understanding of the reversibility of early-life stress effects on physical health and reveal whether successful adaptation occurs at the network level or only in some components of the neuroimmune network.

Incorporating detailed assessments of childhood experiences in studies of adult physical and mental health might also reveal important disorder subtypes with differing etiologies. For instance, depression and inflammation are not always coupled but are more likely to cluster together in those exposed to adverse childhood experiences such as maltreatment (Danese et al., 2008; G. E. Miller & Cole, 2012). Given that the antidepressant properties of anti-inflammatory agents have been increasingly tested in human samples (Kohler et al., 2014), more research is needed to explain the sensitization of the immune system by early-life stress in some depressed individuals and the lack of apparent immune abnormalities in other depressed patients.

A more proactive study of sex differences in the role of early-life stress in shaping neuroimmune and neurobehavioral development would also be welcome. Animal models and human studies consistently point to sex differences in responses to stress across all life stages, from the prenatal period to senescence (Bale & Epperson, 2015; Monk, Spicer, & Champagne, 2012). For instance, in utero exposure to maternal stress is associated with more negative outcomes for males, whereas adversity during childhood is associated with greater expression of affective disorders for females, especially after the onset of puberty (Cyranowski, Frank, Young, & Shear, 2000). Women also show more pronounced neural alterations subsequent to childhood adversity (Burghy et al., 2013; Herringa et al., 2013) and exhibit greater increases in depressed mood during experimental inflammatory challenges compared to men (Moieni et al., 2015). Immune disorders are also more prevalent among women than men (e.g., 78% of patients with autoimmune conditions are women; Fairweather, Frisancho-Kiss, & Rose, 2008). Despite these observations, sex differences in neuroimmune crosstalk have thus far not been a major focus of empirical study but will likely play a major role in accounting for the pervasive heterogeneity of outcomes linked to early-life stress in humans.

IMPLICATIONS FOR INTERVENTIONS WITH CHILDREN AND ADOLESCENTS

One obvious implication of the neuroimmune network hypothesis and of research in this area is that preventing or reducing chronic stress exposure may have cascading benefits for child and adolescent neural, immune, and mental health. It is much less obvious how or when it would be best to intervene to promote these ideal outcomes, and there is limited empirical evidence to provide guidance on these issues. Advancing our knowledge of sensitive periods of brain and immune system development, as well as expanding the evidence base on interventions for children at risk for adversity, will bring us closer to answering these pivotal questions.

Studies documenting the increased risk of psychopathology and health problems in the offspring of mothers who experienced stress, depression, or anxiety during pregnancy (Monk et al., 2012) suggest that intervening in the prenatal period might be beneficial. The group prenatal care model has amassed considerable evidence that group prenatal education improves pregnancy, birth, and delivery outcomes compared to standard care (Thielen, 2012), particularly for low-income minority women and teenage mothers (Thielen, 2012), whose offspring are more likely to experience early-life stress postnatally. For instance, Centering Pregnancy (one of the most widely used group prenatal care programs) invites eight to 12 women with similar due dates to attend ten 90-min group sessions regularly throughout their pregnancy and early postpartum period (Rising, 1998). These sessions are led by facilitators (typically nurse practitioners trained in group processes) and usually include three components: (a) a standard prenatal risk assessment (including assessments of blood pressure, weight, gestational age); (b) a didactic component that educates women about health promotion during pregnancy and the postpartum period (e.g., healthy nutrition, lactation); and (c) a group discussion component designed to elicit peer support where women are given time and encouraged to share and discuss their experiences, pregnancy related or not (Rising, 1998). Notwithstanding the encouraging evidence on the benefits of this program for perinatal outcomes, much less is known about its possible beneficial effects on long-term physical and mental health outcomes of the offspring. Given the rising popularity of these programs since the 1990s, this would be a fertile area for future investigation. For instance, following up on offspring of mothers who were randomly assigned to group prenatal care versus standard care in the 1990s and 2000s would be a useful strategy for examining whether there are notable differences in the prevalence of psychiatric disorders or cardio-metabolic diseases among the offspring during their late adolescence/young adulthood. This could be accomplished either via laboratory-based studies of these offspring that would include comprehensive assessments of physical and mental health outcomes or through linkage of available medical and administrative records of mothers and their children with data on their participation in experimental research studies testing the effects of group prenatal care. It would also be informative to meta-analytically compare the effect sizes in these prenatal prevention programs with those noted in early childhood interventions in order to examine which timing yields greater benefits for each mental and physical health outcome.

Postnatally, family-based interventions that improve parenting and parent–child relationship quality seem not only to benefit children's cognitive outcomes and socioemotional skills (Blair & Raver, 2016; Fisher et al., 2016; Neville et al., 2013) but also to affect the functioning of their stress-response systems (Fisher et al., 2016; Slopen et al., 2014) and reduce inflammatory activity (G. E. Miller, Brody, Yu, & Chen, 2014). For instance, a recent randomized controlled trial showed that a family-strengthening intervention implemented with low-income 11-year-old African American youth and their mothers resulted in lower levels of inflammation at age 19, as indexed by six cytokines (G. E. Miller et al., 2014). However, most parenting interventions do not assess physical health benefits but rather rely solely on assessing behavioral or mental health outcomes. More research is needed to begin tracking the effects of these interventions on neurodevelopment and on the coregulation between the brain and the immune system, or the coregulation between the brain, the immune system, and endocrine stress-response systems.

In addition, interventions that have long-term anti-inflammatory effects in adults might be tested with children to examine whether similar benefits can be achieved. For instance, physical exercise can reduce inflammation, and these effects are strongest in those with high levels of inflammation at baseline (Kasapis & Thompson, 2005; Kiecolt-Glaser, Derry, & Fagundes, 2015). However, many of the extant randomized controlled trials suggesting these effects have been conducted with patient or elderly populations. It is currently unclear whether the same benefits can be replicated with youth, and particularly with youth who experienced early-life stress. Given that physical exercise has corollary benefits for mood, it would be warranted to conduct studies testing its efficacy in preventing or mitigating mental and physical health problems following childhood adversity.

Finally, an important avenue of future research will be to empirically test ways of incorporating neuro-immune measures in clinical assessments of children and adolescents to inform prevention and treatment. The challenges associated with implementing physiological measures in clinical child and adolescent settings have been eloquently discussed elsewhere (De Los Reyes & Aldao, 2015), including numerous considerations such as cost, the need to (re)train personnel, and the possibility of inconsistent findings across various physiological and behavioral measures, which would lead clinicians to divergent conclusions depending on the set of measures they focus on. Some have also noted a "research–practice gap" in child and adolescent mental health

assessments, whereby even well-established, evidence-based recommendations are adopted in practice with delays and at low rates (De Los Reyes & Aldao, 2015). Thus, research that is designed to speak directly to the utility and feasibility of incorporating neural and immune measures in clinical settings with children and adolescents would be extremely beneficial at this stage.

SUMMARY AND CONCLUSIONS

In sum, the neuroimmune network hypothesis (Nusslock & Miller, 2016) proposes that early-life stress sensitizes neuroimmune communication in ways that amplify inflammation and promote physical and mental health problems across the lifespan. Recognizing the frequent co-occurrence of psychiatric and physical disorders (Suls et al., 2016) and the role of inflammation in mediating bidirectional transactions among their causes and symptoms (Figure 1) may boost the efficacy of existing treatments and allow their tailoring to the individual needs of each patient. For instance, addressing obesity in children and adolescents can reduce inflammation (Roth, Kratz, Ralston, & Reinehr, 2011), which may lower risk of depression (Kohler et al., 2014). Conversely, treating depression might prevent obesity (Goodman & Whitaker, 2002) and reduce risk of cardiovascular disease (Lichtman et al., 2008). The current health care model treats psychiatric and physical disorders separately, but emerging evidence from psychoneuroimmunology, developmental science, and public health suggests that preventing or mitigating early-life stress might be a successful strategy for promoting both physical and emotional health.

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