

Early-Life Adversity and Physical and Emotional Health Across the Lifespan: A Neuroimmune Network Hypothesis

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ABSTRACT

Children who experience chronic stressors are vulnerable to emotional and physical health problems across the lifespan. This phenomenon raises questions for scientists and clinicians alike. How does adversity get under the skin of the developing child? Through what mechanisms does it confer vulnerability to a heterogeneous set of mental and physical illnesses? And how does it instantiate risk across different life stages, engendering vulnerability to conditions that develop shortly after stressor exposure—like depression—and conditions that manifest decades later, like heart disease? Although answers to these questions have started to emerge, research has typically focused on single diseases or organ systems. To understand the plethora of health problems associated with childhood adversity, we argue that the field needs a second generation of research that recognizes multidirectional transactions among biological systems. To help facilitate this process, we propose a neuroimmune network hypothesis as a heuristic framework for organizing knowledge from disparate literatures and as a springboard for generating integrative research. Drawing on existing data, we argue that early-life adversity amplifies crosstalk between peripheral inflammation and neural circuitries subserving threat-related, reward-related, and executive control-related processes. This crosstalk results in chronic low-grade inflammation, thereby contributing to adiposity, insulin resistance, and other predisease states. In the brain, inflammatory mediators act on cortico-amygdala threat and cortico-basal ganglia reward, circuitries in a manner that predisposes individuals to self-medicating behaviors like smoking, drug use, and consumption of high-fat diets. Acting in concert with inflammation, these behaviors accelerate the pathogenesis of emotional and physical health problems.

Keywords: Depression, Heart disease, Inflammation, Maltreatment, Poverty, Stress

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Children who experience severe chronic stressors are vulnerable to a plethora of health problems across the lifespan (1). These problems span the continuum of what are traditionally understood to be mental and physical illnesses. For example, children maltreated by their parents not only go on to develop psychiatric disorders like unipolar depression and substance abuse at higher than expected rates (2) but also show increased prevalence of metabolic syndrome, coronary heart disease, some cancers, and autoimmune conditions as they age (3,4). Children raised in families of low socioeconomic status (SES) experience disproportionately high rates of many of these same conditions (5,6). Of course, these results derive from observational studies that cannot by themselves distinguish between causes, effects, and confounds. But their results converge with experimental research in animals documenting long-term health consequences of early stressor exposure (7–9). Considered together, these preclinical and observational studies suggest that childhood adversity contributes to subsequent health problems in a causal manner.

This phenomenon raises challenging questions. How does adversity get under the skin to influence the anatomy and physiology of the developing child? Through what mechanisms

does it confer vulnerability to such a heterogeneous set of health problems, spanning the continuum of mental and physical illnesses? And how does it instantiate risk across the lifespan, engendering vulnerability to conditions that develop shortly after stressor exposure—like depression—and those that manifest many decades later, like heart disease?

Answers to these questions have started to emerge. Over the past 10 years, studies have revealed that childhood adversity is associated with subtle differences in multiple aspects of neural, cardiovascular, neuroendocrine, and immune functioning (1,3,4). But nearly all this work has focused on single diseases or organ systems. To understand the plethora of health problems associated with childhood adversity, the field needs a second generation of research that recognizes the multidirectional transactions among these systems (10). Here, we attempt to begin this process, synthesizing knowledge of early adversity with recent discoveries that highlight crosstalk between the nervous and immune systems (11,12) and establish inflammation's role in common health problems (13,14). As a heuristic framework, we propose a neuro-immune network hypothesis (Figure 1). This hypothesis is not a definitive mechanistic account. Indeed, some of

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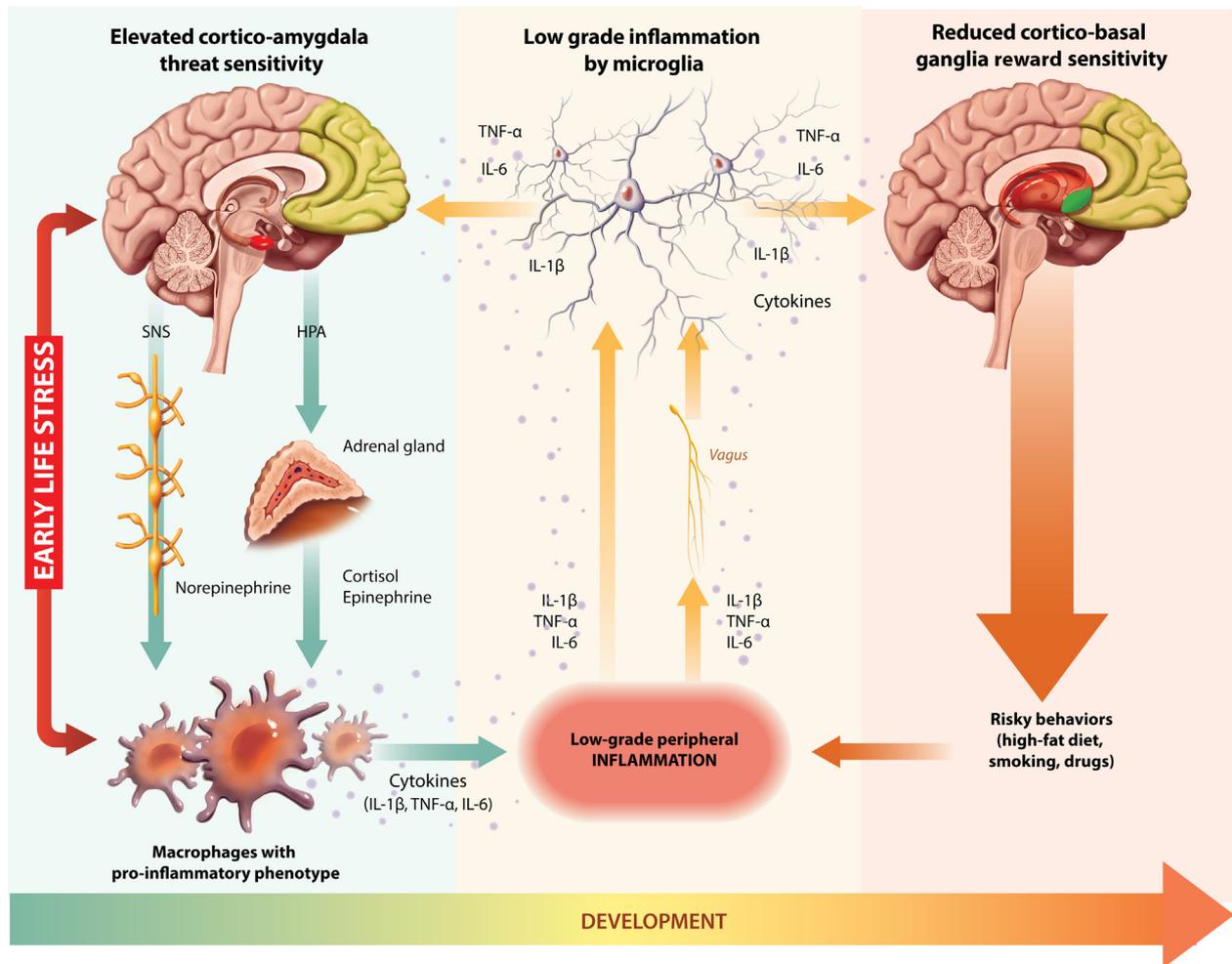


Figure 1. Depiction of neuroimmune network hypothesis. HPA, hypothalamic-pituitary-adrenocortical; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; SNS, sympathetic nervous system; TNF- α , tumor necrosis factor-alpha. (Illustration by Chi-Chun Liu and Qingyang Chen.)

the proposed linkages are quite speculative, based on pre-clinical observations yet to be corroborated in humans. It is offered as a framework to organize knowledge from disparate literatures and as a springboard for generating integrative research.

The article is organized into sections that represent the major tenets of the hypothesis. We begin by describing recent discoveries about stress-related changes in the nervous and immune systems. First, we discuss work showing that early adversity sensitizes the brain's networked cortico-amygdala regions in a manner that heightens vigilance for, and reactions to, threatening stimuli. Second, we describe 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. Next, we review evidence that low-grade inflammation spreads to the brain. The mediators of this inflammation, cytokines, accentuate threat-related processes in the cortico-amygdala circuit and attenuate reward-related processes in the cortico-basal ganglia circuit. Cytokines may also

dampen executive control-related processes linked to regions of the prefrontal cortex. Based on these observations, we postulate the existence of multiple bidirectional pathways linking peripheral inflammation with neural circuitries subserving threat, reward, and executive control. Drawing on recent studies, we suggest that early adversity amplifies bidirectional crosstalk within these neuroimmune pathways. These exchanges result in low-grade, chronic, inflammation, which then acts on neural circuitries to facilitate self-medicating behaviors, like smoking, drug use, and consumption of high-fat and high-sugar diets. Acting in concert with inflammation, these behaviors contribute to common health problems.

Most research we describe focuses on parental maltreatment, early deprivation, or low socioeconomic status. We recognize these are heterogeneous stressors, which likely have somewhat distinct behavioral, neural, and immunologic sequelae. But to date, the limited available evidence suggests that the neural-immune consequences of these stressors are more similar than different (1), so we treat them as such. We also recognize these stressors are not the only adversities that

children face. War, recurrent bullying, and family instability could have similar effects, but presently, little is known about how these stressors affect processes of interest here.

EARLY ADVERSITY SENSITIZES THREAT VIGILANCE AND RESPONSE SYSTEMS

The first proposed neuroimmune pathway centers around the cortico-amygdala neural circuit, which supports vigilance for, and responses to, threatening stimuli. One of the most robust findings about childhood adversity is that it sensitizes cortico-amygdala neural circuitry. Relative to control subjects, physically abused youth develop vigilance for facial cues that connote anger, probably because those faces signal forthcoming aggression (15–18). These proclivities cause abused youth to respond aggressively to provocation, even when it is subtle (19). Similarly, children from low-SES families tend to carefully monitor their environment for danger and maintain a low threshold for judging situations as threatening (20,21). When confronted with ambiguous stimuli, whose threat value is uncertain, low-SES youth exhibit larger cardiovascular responses than higher SES youth (22).

Though multiple brain systems are involved in vigilance for and response to threats, current thinking emphasizes the importance of the amygdala and its regulation by the prefrontal cortex (PFC) (23,24). Consistent with the notion that adversity influences how this circuitry develops, morphometric studies have documented smaller amygdala volumes in maltreated (25) and disadvantaged (26,27) youth. In functional neuroimaging (functional magnetic resonance imaging [fMRI]) studies, maltreated youth show greater amygdala reactivity to emotional stimuli relative to control subjects (28–31) [although, see (32) for contrary findings]. This enhanced reactivity may stem from inadequate recruitment of prefrontal regions that provide top-down regulation. In a study of resting-state activity, previously maltreated adolescents showed less functional coupling of the subgenual anterior cingulate cortex (ACC) and the amygdala (33) relative to control subjects. Similarly, in a study of young adults, childhood SES covaried with cortico-amygdala responsivity during emotion regulation. To the extent they were reared in low-income families, subjects displayed larger amygdala responses and lower activation in both ventrolateral and dorsolateral PFC regions (34), even adjusting for current income. These findings suggest that childhood adversity effects on cortico-amygdala function persist into adulthood.

There are regional variations in the maturational timing of the cortico-amygdala circuit. The amygdala matures during childhood and adolescence, whereas prefrontal regions continue to develop through early adulthood (35,36). Furthermore, prefrontal regulation of the amygdala typically emerges in adolescence (37,38). The development of this functional coupling, however, is accelerated in children exposed to adversity (39), perhaps as a mechanism to compensate for and downregulate the enhanced amygdala reactivity and the downstream threat-response systems it mobilizes, including the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenocortical (HPA) axis. As noted below, the hormonal products of these systems—catecholamines and glucocorticoids—are modulators of inflammation.

EARLY ADVERSITY SENSITIZES CELLS THAT PROPAGATE INFLAMMATION

In a separate literature, research shows that childhood adversity also sensitizes the immune cells that initiate and sustain inflammation. This work shows that maltreated and disadvantaged children are disproportionately exposed to pollutants, second-hand smoke, and high-fat and high-sugar diets, along with psychosocial stressors like family instability, insensitive caregiving, and neighborhood violence (40,41). These exposures prime monocytes and macrophages to respond aggressively to pathogen-associated and danger-associated molecular patterns (1,42). The priming mechanisms are still being established but likely involve some combination of direct influences, e.g., through pollutants, and indirect influences mediated through hormonal products of the SNS and HPA axis. Indeed, to the extent they are from lower SES families, children produce larger volumes of inflammatory cytokines when their cells are stimulated *ex vivo* with microbial products (43,44), and this sensitization remains evident in adulthood (45). The monocytes of low-SES adolescents are also relatively insensitive to inhibition by glucocorticoids, which play a key physiologic role in regulating inflammation (46). Similar patterns are evident in youth reared in harsh family climates. In a longitudinal study, adolescents from harsh families showed an increasingly proinflammatory phenotype over 18 months. This phenotype was marked by progressively larger *ex vivo* cytokine responses to lipopolysaccharide (LPS), a molecule on the surface of gram-negative bacteria. Youth from harsh families also showed declining glucocorticoid sensitivity over time; in *ex vivo* studies, cortisol became progressively less effective at suppressing LPS-evoked cytokine production (47). This insensitivity to glucocorticoids may be adaptive during acute threats but if sustained would facilitate the kind of low-grade chronic inflammation implicated in many emotional and physical health problems (1,48).

Consistent with this notion, maltreated children display higher levels of inflammatory biomarkers relative to control subjects, including C-reactive protein and interleukin-6 (49,50), and so do low-SES youth (51–53). This low-grade inflammation persists into adulthood; multiple studies report that inflammatory biomarkers are elevated in adults exposed to maltreatment and/or disadvantage during childhood (54–58). These associations are typically independent of an adult's concurrent psychosocial and socioeconomic conditions, suggesting that childhood adversity leaves an inflammatory residue.

EARLY ADVERSITY POTENTIATES CROSSTALK BETWEEN THREAT CIRCUITRY AND IMMUNE SYSTEM

The cortico-amygdala and inflammatory sequelae of childhood adversity have been considered in separate literatures. However, growing evidence suggests that both are components of an integrated, bidirectional, network that detects threats to well-being and mobilizes behavioral, physiologic, and inflammatory resources for coping (11,59,60). Next, we draw upon preclinical research to discuss how traffic might flow through

this network in a bidirectional manner and eventually become locked into a self-perpetuating cycle.

Brain-to-Immune Traffic

Research has identified the anatomical basis of brain-to-immune signaling (61). When stimuli are perceived as threatening and uncontrollable, cell groups in the amygdala signal hypothalamic centers that subsequently mobilize fight-or-flight responses mediated by the SNS and HPA axis (62). SNS fibers descend from the brain into organs where leukocytes mature, including bone marrow, the spleen, and thymus, and into organs where pathogen-leukocyte interactions transpire, like the lymph nodes, gut, and lungs (63). Under threat conditions, these fibers release norepinephrine onto resident monocytes and macrophages, activating an inflammatory gene expression program that causes these cells to migrate toward damaged tissue and aggressively release mediators that accelerate pathogen removal and wound healing (11). As this unfolds, neural threat circuits also signal the adrenal gland to boost systemic output of epinephrine and glucocorticoids. These hormones initially reinforce norepinephrine's pro-inflammatory actions, but as the threat subsides, they counter-regulate it (61,64). From an evolutionary perspective, this brain-to-immune signaling is likely adaptive, enabling the organism to mobilize and sensitize cells in anticipation of a forthcoming attack, during which injury and infection are likely. Doing so would presumably speed pathogen eradication and tissue healing.

Immune-to-Brain Traffic

Research shows that network traffic also flows the other direction, from immune to brain. Peripheral inflammation can spread to the brain through multiple mechanisms. Cytokines, like interleukin-1 β , interleukin-6, and tumor necrosis factor- 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 (11,12). This immune-to-brain traffic can modulate cortico-amygdala circuitry involved in threat processing. In rodents, repeated social defeat causes peripheral monocytes to migrate into the parenchyma of multiple brain regions, including the amygdala, hippocampus, and PFC. Stress causes these monocytes, along with tissue-resident microglia, to express pro-inflammatory mediators in the brain. Stress also has a longer-lasting priming effect, sensitizing microglia so the next time they encounter a pathogen, the inflammatory response is larger (65–68). This stress-evoked neuroinflammatory response occurs in parallel with anxiety-like behaviors, including increased light-dark preference and decreased open-field exploration. Notably, mice lacking a functional receptor for interleukin-1 β , a key inflammatory mediator, do not exhibit defeat-evoked microglial activation or anxiety behaviors (68). These results suggest a role for the neuroinflammatory response in threat processing.

One human study suggests similar effects of inflammation on cortico-amygdala functioning. Healthy adults underwent fMRI following administration of low-dose LPS or placebo.

LPS-treated subjects displayed larger amygdala responses to threatening images (69). From an evolutionary perspective, this signaling could be adaptive, enabling peripheral leukocytes to send warning signals to the brain, which act through cortico-amygdala pathways to enhance threat-vigilance. The ensuing behavioral adjustments could prevent or reduce exposure to stimuli likely to cause injury or infection.

Self-perpetuating Cycle?

The findings above indicate that childhood adversity sensitizes cortico-amygdala circuitry that subserve threat processing and the monocytes and macrophages that propagate inflammation. As a result, these systems overshoot threat responses, generating increased traffic through the neuro-immune network. We speculate that over time this traffic takes on a life of its own, creating a positive-feedback circuit where signals flow in both directions, from brain-to-immune and from immune-to-brain. Whether such a positive-feedback circuit actually exists is unknown and is an important question for subsequent research. Even if it does not, the functional connections between these systems are likely to result in cross-sensitization (11,70), wherein larger neural threat responses, acting via the SNS and HPA axis, amplify inflammation and vice-versa. On its own, this cross-sensitization would presumably increase network traffic and, if our broader hypothesis is accurate, heighten risk for later health problems. Next, we expand this discussion to include links between adversity, inflammation, and reward and executive control-related neural circuitries.

EARLY ADVERSITY POTENTIATES CROSSTALK BETWEEN REWARD CIRCUITRY AND IMMUNE SYSTEM

Another potential bidirectional pathway in the neuroimmune network involves the cortico-basal ganglia circuit, which supports reward processing (71). This circuit 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 (71).

Early Adversity and Reward Sensitivity

Similar to the cortico-amygdala circuit, growing evidence indicates that early adversity affects development of the cortico-basal ganglia circuit and the reward-related behaviors it subserves. Animals exposed to early-life stress display weakened preferences for sweet foods, higher thresholds for brain stimulation reward, and blunted responses to amphetamines and dopamine agonists (72–74). Convergent with these findings, research in humans indicates that maltreatment is associated with later reward-processing deficits on behavioral tasks (75,76). Functional MRI studies are elucidating the neural bases of these associations and show that relative to control subjects, previously maltreated individuals have decreased activation in the basal ganglia (ventral striatum, globus pallidus) following monetary gains (76,77). Because

these studies were performed years after maltreatment, they suggest a persistent effect on reward-related brain function. Parallel findings have emerged in those from disadvantaged backgrounds. In an fMRI study of monetary gains, adults from low-SES families showed reduced activation in the dorsal-medial PFC and ACC and less functional connectivity between these areas and striatal regions implicated in reward processing (78). Further research is needed to substantiate these findings and clarify the underlying mechanisms (e.g., dopamine transmission).

Inflammation, Reward, and Depression

Though early adversity undoubtedly influences reward sensitivity through multiple pathways, 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 (79,80). These adaptations are collectively referred to as sickness behaviors and along with anhedonia, include dysphoria, fatigue, psychomotor slowing, and inactivity (81). Sickness behaviors have evolutionary adaptive qualities, maximizing an organism's chances of surviving infection by diverting energetic resources to the immune system and minimizing contact with other pathogens and predators (80).

In line with this perspective, research demonstrates that inflammatory mediators reduce animals' sensitivity to rewarding stimuli, including reinforcers like sex, food, and electrical stimulation (81). Inflammatory products also promote tolerance to the reinforcing properties of many drugs, including opiates, cocaine, alcohol, and amphetamines (82). Experimental studies in humans also suggest a role for inflammation in modulating reward sensitivity. One fMRI study found that low-dose LPS reduced ventral striatal reactivity to monetary gain (83). Another found that a typhoid vaccine, by eliciting peripheral inflammation, affected neural responses to an emotion perception task. Compared with placebo, typhoid-treated subjects showed disrupted functional connections between the subgenual ACC and the ventral striatum, among other subcortical regions involved in reward processing (84). Other research has focused on patients with chronic hepatitis C who are treated with the immune-activating cytokine interferon- α . After 4 to 6 weeks of treatment, these patients displayed reduced ventral striatal activation in response to gambling wins. This deficit was secondary to blunted dopamine transmission in the basal ganglia (85).

Inflammation's effects extend beyond reward sensitivity to depression more generally. Multiple prospective studies have found that inflammatory biomarkers forecast depressive symptoms and episodes (86–88). In patients who receive inflammatory cytokines for treatment of hepatitis C or malignant melanoma, rates of depression are 30% to 50% (89,90). However, the excess depression risks associated with these agents can be ameliorated by pretreatment with paroxetine (89,90). Moreover, a recent clinical trial showed that a cytokine antagonist—infliximab—reduces depressive symptoms in treatment-resistant patients with elevated inflammatory markers (91).

Interestingly, the associations between inflammation and depression are especially strong in persons exposed to childhood adversity. Danese *et al.* (92) stratified young adults into

subgroups based upon a history of childhood maltreatment and past-year major depression. Inflammation was higher among maltreated, depressed subjects, relative to control subjects with neither. Depression alone was not associated with inflammation (92). Similarly, a six-wave study of adolescents found that inflammation presaged the development of syndromal depression. But this association was only present in subjects exposed to relatively high levels of previous adversity (88).

Implications for Poor Health-Related Behaviors

We hypothesize that by dampening reward sensitivity and increasing dysphoric feelings, inflammation facilitates high-risk behaviors with negative health consequences. Across the life course, childhood maltreatment is associated with higher rates of cigarette smoking, excessive alcohol consumption, drug misuse, physical inactivity, and high-fat eating (93). The same trends are seen with low childhood SES (1). Our thinking here is grounded in the reward deficiency model of addiction, which postulates that persons with low reward sensitivity self-medicate negative emotions and/or attempt to elevate positive and reward-related emotions through high-risk behaviors (94–96). Consistent with this model, preclinical research documents that blunted dopamine signaling in the basal ganglia is centrally involved in many addictive behaviors, including food seeking and obesity (95–99). In humans, cause-and-effect relationships are less clear. However, preliminary findings from neurogenetic research indicates that reduced reward-related brain function in the striatum may reflect both a pre-existing vulnerability for, as well as a consequence of, engaging in high-risk behaviors (100), suggesting a bidirectional relationship between dampened reward sensitivity and addictive/poor health behaviors. Future research is needed to more fully unpack these links.

Many high-risk behaviors linked to blunted reward sensitivity have downstream effects on inflammation. Indeed, smoking promotes inflammation (101), as does consumption of high-fat and high-sugar foods (102) and sedentary behavior (103). The latter behaviors contribute to weight gain, which itself is a potent inflammatory stimulus (104). If the inflammation triggered by risky behaviors spreads to the brain, it could modulate cortico-basal ganglia circuitry to further blunt reward sensitivity. This would create a second bidirectional pathway in the neuroimmune network, coupling reward circuitry, risky behavior, and inflammation. Whether a positive-feedback circuit of this nature exists is unknown. But if so, it could help explain why childhood adversity confers vulnerability to the array of inflammation-dependent health problems (see below).

REDUCED PREFRONTAL REGULATION MAINTAINS NEUROIMMUNE NETWORK

As implied, we believe that deficiencies in prefrontal executive control also contribute to neuroimmune network activity. The PFC supports a variety of affective and cognitive processes. Medial PFC regions have been implicated in incentive/risk processing, social cognition, and response inhibition, whereas lateral PFC regions are principally involved in higher executive

functions, impulse control, and voluntary emotion regulation (105). These functions are implemented, in part, through top-down influences on threat and reward circuitries, coordinated via white matter fiber tracts from the medial PFC and ACC to the amygdala and basal ganglia, among other regions (106). As noted, the PFC has a relatively protracted maturational timeline, which renders it particularly vulnerable to early-life adversity. Indeed, structural neuroimaging studies indicate that multiple forms of early adversity (low SES, physical abuse, emotional abuse, neglect, harsh punishment) are associated with reduced gray matter volume, cortical thickness, and white matter tract integrity in both medial and lateral PFC regions (25,26,106–109). Functional MRI studies report that early-life adversity is associated with reduced prefrontal activation during laboratory tasks and atypical connectivity between the amygdala and both the medial PFC and subgenual ACC (33,39,110). Furthermore, prefrontal abnormalities mediate the relationship between early adversity and executive control deficits (107).

Although studied less extensively than the amygdala and basal ganglia, there is growing evidence that inflammation modulates PFC structure, function, and development in a manner that diminishes executive control and self-regulation. Experimental animal models demonstrate that inflammation can slow myelination (111), and in humans, inflammatory biomarkers are associated with smaller medial PFC volume and reduced cortical white matter integrity (112,113). One study found that low-SES adults had reduced whole-brain white matter integrity and that inflammation partially mediated this relationship (106). Functional MRI studies demonstrate that administration of inflammatory stimuli, like cytokines and vaccines, modulate activity of the dorsolateral PFC and both the subgenual and dorsal ACC (84,85). Inflammation also modulates subgenual ACC regulation of threat and reward circuitries discussed above (84). Future research is needed to clarify the mechanisms and boundaries of these associations.

CONSEQUENCES FOR EMOTIONAL AND PHYSICAL HEALTH

As noted, children exposed to severe adversity are prone to a plethora of health problems across the lifespan (1–4). All of these conditions develop through etiologically complex transactions between genetics, lifestyle, and the environment, as mediated via dysregulation of multiple physiological systems. Yet, over the past decade, it has become apparent that chronic, low-grade inflammation is a common soil that helps fertilize the development and progression of many of them (14). These conditions range from traditional psychiatric disorders, like depression and substance misuse, to allergic, metabolic, cardiovascular, neoplastic, and rheumatic diseases (12,13,114,115). Notably, there is much overlap between this list of conditions with a suspected inflammatory etiology and the catalog of health problems disproportionately prevalent among persons who experienced childhood adversity. Noting this overlap, we hypothesize that the proposed neuroimmune network fuels chronic low-grade inflammatory activity, which acts together with genetics, lifestyle, and other exposures to accelerate the pathogenesis of health problems. Because of space limitations, we cannot detail the connections among childhood adversity, inflammation, and disease pathogenesis here, but Table 1 highlights key literature documenting these associations.

LIMITATIONS AND CONCLUDING REMARKS

We argue that understanding how childhood adversity presages health problems across the lifespan requires a fresh, integrated approach to research. Accordingly, we have articulated a neuroimmune network hypothesis and considered evidence for its basic tenets. Although each tenet is grounded in evidence, additional research is needed to determine whether they unfold and interact in the manner the hypothesis specifies. That research will have to combine preclinical studies, which can further elucidate underlying mechanisms, and multiwave

Table 1. Health Problems Across the Lifespan Whose Onset and/or Course May Be Affected by Early Adversity and Subsequent Activation of the Proposed Neuroimmune Network

| Health Problem | Early Adversity and Onset and/or Course | Inflammation's Role in Pathogenesis |
|-------------------------------|---|-------------------------------------|
| Early – Middle Childhood | | |
| Asthma | (21,118,119) | (114) |
| Respiratory infection | (120,121) | (122) |
| Adolescence – Early Adulthood | | |
| Depression | (88,123,124) | (79) |
| Substance misuse | (125–127) | (128,129) |
| Obesity | (130,131) | (104) |
| Insulin resistance | (132–134) | (135) |
| Preclinical atherosclerosis | (136,137) | (138) |
| Middle – Later Adulthood | | |
| Metabolic syndrome | (117,139,140) | (141) |
| Stroke | (142–144) | (141) |
| Coronary heart disease | (138,142,144,145) | (141) |
| Selected cancers | (93,146,147) | (115) |
| Autoimmune conditions | (148,149) | (14) |

Note. Because of space limitations, we are unable to cite many relevant studies here. Instead, we cite exemplar studies and definitive reviews. We apologize to authors whose work was omitted.

longitudinal investigations, which trace children's psychosocial, neural, and inflammatory trajectories across development. As knowledge from these endeavors accumulates, the hypothesis will need to be revised accordingly. Some missing pieces, like genetic influences, are already evident, while others await relevant evidence. For instance, the hypothesis assumes that distinct adversities, like maltreatment and disadvantage, have roughly similar neural and immune repercussions. But as knowledge accrues, we may need to revisit this assumption and formulate adversity-specific pathways. In future research, the issue of resilience will also have to be considered. Even in populations of children who experience severe adversity, only a minority go on to develop any specific health problem (116). Resources like parental nurturance appear to function as stress buffers for these youth (117), and subsequent versions of the hypothesis will have to acknowledge these moderators and clarify how they operate. The network's developmental timeline must also be elucidated. Based on knowledge of how these systems mature (35,36), we suspect that adversity effects on cortico-amygdala and inflammatory functioning manifest in childhood, whereas influences on reward and executive functions come online later, during adolescence and adulthood. But this hypothesis will need to be tested explicitly in longitudinal studies. Despite these limitations, the framework provides a prospectus to guide future research and highlights candidate pathways for interventions with high-risk youth.

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