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Neuro-, Cardio-, and Immunoplasticity: Effects of Early Adversity

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Abstract

The relationship between early adversity and outcomes across the lifespan is apparent in a striking range of measures. Evidence suggests that many of these outcomes can be traced to the impacts of early adversity on multiple and integrated biological systems mediated by the brain. In this review, we integrate empirical and theoretical advances in the understanding of relationships among the brain and the functions of the endocrine, autonomic, and immune systems. We emphasize the effects of environmental experiences related to caregiver relationships because it is these experiences, in particular, that shape regulatory and threat response systems in ways that increase vulnerability and may underlie the wide range of poor outcomes associated with early adversity. Thus, we metaphorically extend the concept of plasticity to highlight our goal of a broader consideration of these interconnected mechanisms. We conclude by discussing implications for neurobiologically informed interventions that can potentially ameliorate the broad and costly effects of early adversity.

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INTRODUCTION

Levels of societal inequality are rising in many developed and developing countries, including the United States (e.g., Hoffmann et al. 2016, Saez & Zucman 2016). At the same time, awareness of the costs of inequality—including those related to health outcomes, economic productivity, and crime victimization—is also increasing, both among the general public and within political circles (Caspi et al. 2016, Holzer et al. 2008). However, beyond identifying probabilistic relationships between early experience and later life outcomes, research across multiple disciplines is increasingly making progress toward identifying the mechanisms that underlie the long-term, biological embedding of early adversity (e.g., Brito & Noble 2014, Bruce et al. 2013, Fisher et al. 2016, Hackman et al. 2010, Lipina & Posner 2012, Loman & Gunnar 2010, McEwen & Gianaros 2010, Nusslock & Miller 2016, Propper & Holochwost 2013, Shonkoff et al. 2012, Ursache & Noble 2016). By providing mechanistic links between early experiences and distal outcomes, this research is identifying how early experiences get under the skin in ways that have lasting impacts. Such research has begun to address the complex interplay among biological and environmental factors in development and spans a wide range of disciplines.

Although the term early adversity encompasses a range of negative early experiences, our focus in this review is primarily on socioeconomic background, with an emphasis on the adverse effects of growing up in poverty or in households with lower socioeconomic status (SES). We seek to broaden the scope of previous reviews by integrating recent empirical and theoretical advances in several overlapping literatures. Specifically, we focus on the association between early adversity and brain function for self-regulation and attention, stress regulation via both the endocrine and autonomic nervous systems, and immune system function. In taking this approach, we join other recent calls for continued and increased interdisciplinary collaboration and novel approaches to the identification of neurobiological targets for interventions that can potentially ameliorate the broad and costly effects of early adversity.

The relationship between early adversity and outcomes throughout the lifespan is apparent across a striking range of outcome measures. Among the longest-studied effects of early adversity are those that span physical and mental health problems and that can occur immediately following or decades after adverse experiences, even in the absence of subsequent risky behaviors. These

effects include greater risks of mortality, cardiovascular disease, asthma, obesity, pulmonary disease, and autoimmune disease, as well as dysregulation in immune, metabolic, cardiovascular, and behavioral functions and heightened risk for a range of mental illnesses, including anxiety, depression, and substance abuse (for reviews, see e.g., McEwen & Gianaros 2010, Miller et al. 2011a, Sapolsky 2004, Schickedanz et al. 2015, Shonkoff et al. 2012). Beyond health outcomes, early adversity is also associated with poorer cognitive and educational outcomes, and, as in the case of health, these disparities begin early, widen with age, and are evident across the educational trajectory and into adulthood (e.g., Bradbury et al. 2015, Hackman et al. 2010, Ursache & Noble 2016).

These gradient relationships are also evident across an increasingly wide range of societies and cultures. Relationships between early adversity and numerous health and life outcomes have been documented across a wide range of countries (Marmot 2015), and gradient relationships with early adversity have also been documented in specific cognitive and socioemotional domains of early childhood development in a wide range of cultural contexts. Recent examples of these contexts include Vietnam (Duc 2016); Turkey (Baydar & Akcinar 2015); Colombia (Rubio-Codina et al. 2015); Bangladesh (Hamadani et al. 2014); Chile, Colombia, Ecuador, Nicaragua, and Peru (Schady et al. 2015); Madagascar (Fernald et al. 2011); and India, Indonesia, Peru, and Senegal (Fernald et al. 2012).

Because these gradient patterns between early adversity and life outcomes are observed in both poorer and richer societies, the associations likely reflect effects that result not from absolute or material deprivation but, rather, from relative deprivation. As Marmot (2015) notes, whereas a poor person in Glasgow is rich compared to an average person in India, that individual's health is nonetheless worse. Such relative differences also have broader implications, as a wide range of socially relevant outcomes, particularly social and health problems, vary as a function of the level of economic inequality across developed countries, as well as across states in the United States (Wilkinson & Pickett 2009). Across multiple disciplines studying gradient relationships, including pediatrics, epidemiology, economics, and public health, there is an increasing recognition of the importance of social and psychosocial factors in explaining these relationships and a recognition that an increased understanding of the biological mechanisms underlying such patterns is crucial to ameliorating the effects of early adversity (Heckman 2006, Marmot 2015, Schickedanz et al. 2015, Shonkoff 2012, Wilkinson & Pickett 2009). In this review, we limit our focus to specific aspects of neurocognitive function and environmental experience that are common themes across literatures and are central to theoretical discussions of early adversity and outcomes (e.g., Loman & Gunnar 2010, McEwen & Gianaros 2010, Nusslock & Miller 2016, Propper & Holochwost 2013, Shonkoff et al. 2012, Ursache & Noble 2016). We focus on neural systems that support self-regulation and attention as well as threat appraisal, specifically the prefrontal cortex (PFC), amygdala, and hippocampus. These systems are among those most affected by early adversity and, because of their central role in the regulation of endocrine, autonomic, and immune systems, are also key to the theoretical advances we discuss.

Early adversity also has profound effects on multiple neurocognitive systems, in particular those important for language; however, these are beyond the scope of the current review. In addition, numerous factors contribute to differential outcomes associated with early adversity, including genetic factors important to individual differences in trait characteristics such as temperament, as well as a myriad of environmental factors, e.g., exposure to toxins and pollutants, poor nutrition, and lack of exercise. We limit our focus to environmental experiences related to caregiver relationships, parenting, and parental nurturance because these experiences, in particular, shape regulatory and threat response systems in ways that increase vulnerability and underlie the wide range of poor outcomes associated with early adversity. Thus, we metaphorically extend the concept of plasticity to highlight our goal of a broader consideration of these interconnected mechanisms.

We have characterized the unique sensitivity of the brain to experience, i.e., neuroplasticity, as a double-edged sword (e.g., Stevens & Neville 2006) because the systems that are most vulnerable to environmental differences, such as those associated with poverty, are also likely to be the most amenable to enhancement under different environmental conditions. Although our focus is on mechanisms underlying vulnerability, one primary goal of research on these mechanisms is to provide and inform evidence-based approaches to targeting environments that give rise to these effects, so we conclude by highlighting several among the many promising directions in this effort.

This article begins with a brief review of evidence on environmental experiences related to caregiver relationships, after which we discuss the brain systems central to self-regulation and threat appraisal and the effects of early adversity on these systems. We then turn to relationships between these brain systems and systems important for stress regulation, particularly endocrine and autonomic systems, and the effects of early adversity. Next, we discuss interactions between the brain and the immune system, how early adversity affects these interactions, and a model that emphasizes multiple pathways by which early adversity might affect these interacting systems in ways that potentially underlie associated poor health outcomes. Finally, we discuss implications for neurobiologically informed interventions that can potentially ameliorate effects of early adversity and consider future directions in this research.

CAREGIVING, PARENTAL NURTURANCE, AND EARLY ADVERSITY

Abundant evidence from animal and human studies indicates that early caregiving experience influences the development of systems important for stress regulation and threat appraisal and that developmental shaping of these systems can, in turn, impact the function of systems important for self-regulation and attention. Important to the development of regulatory and appraisal systems is the establishment of a relationship, early in development, with a consistently responsive caregiver (Loman & Gunnar 2010). As discussed in the section titled Stress Regulation, studies of rodents demonstrate how differences in early parental nurturance (i.e., licking and grooming behavior) influence the developing brain and, in particular, brain regions important for stress regulation and threat appraisal in ways that shape the way an animal interacts with potential threats in the environment. In humans, parental sensitivity and responsiveness are critical for the development of a secure attachment relationship, which is, in turn, important for the development of regulatory and appraisal function (e.g., Gunnar et al. 1996). A high level of caregiver nurturance is a potential buffer against the long-term health problems associated with early adversity (Miller et al. 2011b); as discussed throughout this review, parenting behavior interacts with multiple systems to confer both vulnerability and potential resilience.

Early experiences with caregivers interact with individual differences in physiological sensitivity to environmental stimulation in important ways to shape development (Blair & Raver 2012). Depending upon a child's natural tendency to be more or less reactive, these profiles can respond differently to variation in the caregiving environment in ways that lead to recursive feedback processes. For example, the development of self-regulation is shaped by this feedback between the environment and differences in emotional reactivity, higher-order attention, and executive control processes; in contexts of early adversity, this relationship can result in the development of reactivity profiles that have consequences for school readiness and broader effects (Blair & Raver 2012, 2015). Individual differences in reactivity also interact with the degree of environmental adversity such that biological sensitivity to context can be adaptive in more supportive caregiving environments but less so in more adverse environments (Ellis & Boyce 2008).

In this review, we primarily focus on early adversity associated with differences in SES, typically measured as parental education, occupation, and/or income during a child's early development.

There are many important considerations in the measurement of SES, including which components to measure, how and whether to aggregate them, and to what degree they might assess different aspects of the environment, as well as the need to consider duration of exposure (e.g., Raver et al. 2013, Ursache & Noble 2016); however, a detailed discussion of these considerations is beyond the scope of this review. Relevant to the current discussion, SES as a proxy variable broadly captures aspects of the environment associated with differences in caregiving. For example, lower SES environments are more likely to be characterized by more chaotic living conditions (e.g., crowding, noise, family instability), inconsistent parenting, lack of routines, and higher levels of unpredictability; such characteristics have been shown to account for up to half of the disparities in academic outcomes associated with SES (Brooks-Gunn & Duncan 1997, Evans 2004, Evans et al. 2005, Farah et al. 2008). As discussed in the next section, these factors impact the development of neurobiological systems important for regulatory and threat appraisal functions.

BRAIN SYSTEMS SUPPORTING REGULATION AND THREAT APPRAISAL

Neurobiological pathways supporting self-regulation and attention, stress regulation, and threat appraisal constitute a distributed network of cortical and subcortical regions with different profiles of development and neuroplasticity. The PFC, amygdala, and hippocampus are neural structures at the heart of this network and, therefore, are also key to characterizations of how early adversity gets under the skin (for more extensive reviews, see e.g., Arnsten 2009, Brito & Noble 2014, Hertzman & Boyce 2010, McEwen & Gianaros 2010). We begin with an overview of these neural structures before considering the effects of early adversity on their development and function.

The PFC is important for many aspects of top-down regulation, including the inhibition of inappropriate responses and the promotion of task-relevant actions, and, as such, is crucial for the flexible regulation of behavior and adaptation in an ever-changing environment (e.g., Arnsten 2009). The PFC has functional subdivisions, organized in a topographical manner, with extensive connections to cortical and subcortical areas. More dorsal and lateral regions of the PFC are involved in the regulation of attention, thought, and action and have extensive connections to sensory and motor cortices, whereas more ventral and medial regions mediate emotional regulation and have extensive connections to subcortical areas including the amygdala, striatum, and hypothalamus. In addition, the PFC has connections to areas in the brainstem that produce catecholamines, such as dopamine, epinephrine, and norepinephrine, that underlie physiological changes associated with the stress response, particularly the fight-or-flight response mediated by the sympathetic nervous system (SNS). Also important for top-down regulation is the anterior cingulate cortex (ACC), involved in error monitoring (dorsal ACC) and assessment of emotional salience and motivation (ventral ACC).

The amygdala, located deep in the medial temporal lobe, is involved in the detection of biologically relevant stimuli with both positive and negative valence; however, amygdala reactivity appears biased toward negatively valenced information in the environment. This is consistent with the general tendency of the brain to prioritize negative information, known as the negativity bias (Cacioppo et al. 1999), which is hypothesized to relate to the mobilization of the SNS as a default response to uncertainty and novelty and, thus, to a potential threat in the environment (e.g., Thayer & Lane 2009). The amygdala is thought to be central to this response, serving as a rapid detector of potential threats and mediator of adaptive responses to them. Upon encountering a potential threat, the amygdala, via connections to the brainstem and hypothalamus, stimulates the release of the catecholamines and glucocorticoids that underlie the SNS and neuroendocrine responses to stress.

Crucial to the relationship between early adversity and poor outcomes is the regulation of the amygdala by the PFC, particularly the ventromedial PFC (vmPFC). Default inhibition of amygdala activity by the vmPFC is thought to reflect an integration of the external context (potential threat) with the internal context (perceptions of control over the potential threat) (e.g., Maier et al. 2006, Thayer et al. 2012). Under conditions of uncertainty and potential threat, the vmPFC becomes hypoactive, and this disinhibition leads to increased amygdala activity and energy mobilization in response to the potential threat and a shift from slower, more thoughtful PFC-regulated action to more reflexive and rapid emotional action (e.g., Arnsten 2009). As discussed in the section titled Threat Appraisal, early adversity influences the development of both the PFC and the amygdala in ways that can lead to more reactive physiological profiles.

The hippocampus, also located in the medial temporal lobe, is closely connected to the amygdala as well as to the PFC. The hippocampus is important for many aspects of learning and memory, particularly the consolidation of information into long-term episodic, declarative, and spatial memory. Although less involved in self-regulation than the PFC, the hippocampus also plays an important regulatory role in the stress response. The hippocampus contributes to the perception of potential threats via contextual memory of the environmental conditions associated with events related to potential threat. This connectivity is adaptive, as events with more emotional salience are better remembered.

Finally, connections between these brain systems and subcortical areas, including the hypothalamus and brainstem, are important for stress regulation, as well as the regulation of cardiac function via both parasympathetic nervous system (PNS) and SNS afferents (e.g., Thayer & Lane 2009). The PFC, amygdala, and hippocampus are all connected to the ventral striatum in the basal ganglia, which is important for sensitivity to rewarding environmental stimuli and motivation, including aspects of drug sensitivity and risky behavior (Haber & Knutson 2010). The degrees to which these systems are interconnected, sensitive to glucocorticoids and catecholamines associated with stress, and connected to more peripheral physiological systems are central to theories that provide a more mechanistic understanding of the effects of early adversity.

VULNERABILITY OF BRAIN SYSTEMS FOR SELF-REGULATION AND STRESS REGULATION

Self-Regulation

Consistent with the effects on brain systems discussed below, the relationship between early adversity and behavioral outcomes associated with self-regulation constitutes one of the more reliably documented relationships between early adversity and cognitive outcomes. Several studies have shown that early adversity is associated with poorer performance on specific aspects of executive function (EF), including working memory, inhibitory control, and attention shifting (e.g., Blair et al. 2011; Farah et al. 2006; Noble et al. 2005, 2007; Sarsour et al. 2011). For systems such as working memory and inhibitory control, these differences emerge as early as infancy (Lipina et al. 2005). Children with higher temperamental reactivity exhibit lower EF in families facing greater economic adversity but higher EF in families facing less adversity (Raver et al. 2013). This is consistent with the theory that children with more reactive profiles display more sensitivity to context, for better or worse (Ellis & Boyce 2008). These effects of early adversity on self-regulation persist into early adolescence (Farah et al. 2006), and some evidence suggests that they endure into adulthood (Evans & Schamberg 2009). Longer exposure to poverty is also associated with greater deficits in EF in both children and young adults (Evans & Schamberg 2009, Raver et al. 2013).

Brain systems underlying aspects of self-regulation are also vulnerable to early adversity. Neuroimaging studies of EF suggest that early adversity is associated with poorer performance and less efficient recruitment of PFC resources during a novel rule-learning task (Sheridan et al. 2012), as well as reduced PFC activation during EF tasks (Bruce et al. 2013). These effects are evident in adults after as little as one month of chronic psychosocial stress, which results in poorer performance on an attention-shifting task and disrupted functional connectivity between the PFC and a frontoparietal network underlying attention; interestingly, these effects were reversed after one month of reduced stress (Liston et al. 2009). Several event-related potential (ERP) studies also suggest that neural systems important for specific aspects of attention are particularly vulnerable to early adversity. In performance-monitoring tasks, children who had experienced institutionalized or foster care early in development show a reduced brain response to errors and feedback (Bruce et al. 2009b, McDermott et al. 2012). Differences have also been found in selective attention, with children from lower SES backgrounds showing differential early responses associated with selectively attending visual and auditory stimuli (e.g., D'Angiulli et al. 2008, Kishiyama et al. 2009, Stevens et al. 2009). We have further documented specific deficits in mechanisms related to suppressing distracting information, as opposed to enhancing task-relevant information, in the environment (Hampton Wray et al. 2017, Stevens et al. 2009). This is consistent with the hypothesis that differences in self-regulation associated with early adversity may be one of the primary mechanisms by which poverty affects academic outcomes, as reduced suppression of environmental information might be adaptive in more chaotic environments associated with early adversity but maladaptive in a classroom environment (Blair & Raver 2012, 2015).

Early adversity is also associated with other aspects of prefrontal regulatory function. Adults from lower SES backgrounds show atypical behavioral responses to reward and reduced activation to reward cues in regions of the basal ganglia important for reward and motivation (Dillon et al. 2009), as well as reduced dorsomedial PFC and ACC activation and decreased functional connectivity between prefrontal and striatal regions important for reward processing and impulse control (Gianaros et al. 2011). In addition, as discussed below, sickness behaviors associated with blunted reward sensitivity may interact with biomarkers of inflammation to affect the functioning of this system in ways that impact health.

Stress Regulation

The brain is the central organ of the stress response, making it key to understanding how early adversity is associated with lifespan outcomes. It is the brain that decides what is threatening to the organism and regulates the response to stressors. The same brain systems that are important for self-regulation are also the primary neural components of the stress regulation system, which involves neuroendocrine, autonomic, metabolic, and immune systems with diverse biomediators. These systems interact spatially and temporally on multiple timescales as a nonlinear and interactive network that enables a coordinated, adaptive response to a diverse range of stressors (for more comprehensive reviews, see, e.g., Lupien et al. 2009, McEwen & Gianaros 2010). Given this complexity, the stress response system has aptly been characterized as a neuro-symphony (Joëls & Baram 2009). Although a detailed overview is beyond the scope of this paper, we focus in this section on two interconnected systems that operate on different timescales and are vulnerable to experiences associated with early adversity: the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). Whereas the HPA axis is the most well-studied stress response system in the context of early adversity, the ANS is one focus of studies of neurobiological flexibility related to multiple outcomes, as well as of models of reactivity and sensitivity to the environment in the context of early adversity.

An important concept with regard to outcomes associated with early adversity, particularly health outcomes, is allostatic load. Allostasis is an active process of dynamic adaptation to changing environmental demands as an organism encounters physical and behavioral stressors; this adaptation is mediated by changes in the physiological responses of multiple neurobiological systems involved in stress regulation, including both the HPA axis and the ANS, as well as immune systems (McEwen & Gianaros 2010). In the context of adversity, this adaptation can be costly, and McEwen & Stellar (1993) have called this cost allostatic load. Allostatic load refers to the wear and tear on the brain and peripheral systems as a consequence of chronic exposure to stress, as well as to changes in lifestyle that can result from this exposure, such as substance use and abuse and changes to diet, sleep, and level of exercise. Within this framework, four types of physiological response are associated with allostatic load: the frequency and intensity of stressors; the failure to habituate to repetition of stressors, leading to persistently elevated levels of biomediators such as cortisol; the failure to effectively terminate otherwise adaptive regulatory responses to stress; and the failure to mount an adequate response to acute stressors.

The hypothalamic-pituitary-adrenal axis. In conjunction with the SNS, the HPA axis plays a key role in mounting and coordinating the physiological response to stressors. Whereas the SNS initiates a faster, fight-or-flight response via the release of catecholamines, the HPA axis mounts a slower response. When a potential stressor is detected or perceived, the hypothalamus releases corticotrophin-releasing hormone (CRH), which, in turn, stimulates the release of adrenocorticotrophin hormone (ACTH) in the pituitary gland; ACTH then stimulates the release of cortisol from the adrenal cortex. Cortisol can be measured in saliva approximately 20 minutes after the perception of an acute stressor, which is one reason why this system has been better studied in the context of early adversity. Cortisol acts via corticosteroid receptors in the peripheral nervous system and in the brain, with corticosteroid receptors in the PFC, amygdala, and hippocampus mediating both fast and slow effects of this system on brain function. Importantly, there are two types of corticosteroid receptors that have different levels of affinity for cortisol: glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs), with the latter exhibiting a higher affinity for cortisol. In areas of the brain with both types of receptors, such as the amygdala and hippocampus, GRs are only occupied with higher levels of cortisol. Because the PFC has much higher concentrations of GRs, it is more sensitive to even mild stress that can improve amygdala and hippocampus function (Arnsten 2009). Whereas acute elevation of glucocorticoids helps terminate physiological and behavioral responses to stress, chronic elevation can adversely impact the structure and function of brain regions important for stress regulation and have longer-term effects (e.g., Loman & Gunnar 2010).

The development of the HPA axis is highly dependent on experience and, therefore, vulnerable to early adversity. Studies using animal models provided some of the first evidence of this vulnerability (for reviews, see Gunnar & Quevedo 2007, Hackman et al. 2010, Lupien et al. 2009), including epigenetic mechanisms mediating these effects. Rats who experience lower levels of maternal sensitivity early in development (e.g., reduced licking and grooming following a stressor such as brief separation) exhibit elevated levels of corticosterone accompanied by elevated levels of anxiety in response to a stressor as adults. This programmed response of the HPA axis is mediated by epigenetic alterations of GR expression in the hippocampus.

Studies in humans also reveal that early adversity is associated with dysregulation of the HPA axis, although there is some inconsistency to date in the results concerning directionality of effects. Several studies have found that early adversity is associated with higher levels of diurnal (daytime variability in) cortisol (Blair et al. 2011, Cicchetti & Rogosch 2001) or higher cortisol levels either in the morning (e.g., Lupien et al. 2001) or overnight (Evans & English 2002). Other studies have

reported that early adversity is associated with lower levels of cortisol (e.g., Badanes et al. 2011, Chen & Paterson 2006), and studies of children experiencing early adversity that is more extreme than that typically associated with socioeconomic differences also report a blunted HPA response. Institutionalized children raised in orphanages show lower levels of diurnal cortisol (for a review, see Gunnar & Vazquez 2001), and the degree to which this response is blunted is associated with both longer time in institutional care (Gunnar et al. 2001) and lower levels of social care and more problem behaviors postadoption (Koss et al. 2014). Children from lower SES backgrounds in foster care are more likely to have low morning cortisol levels than their peers who are not in foster care (Bruce et al. 2009a), and other studies of children in foster care have also reported reduced diurnal cortisol levels (Dozier et al. 2006). This inconsistency with regard to cortisol and dysregulation is likely related to multiple factors, including the age of the participants; the type, degree, and timing of the stressor(s) experienced; and the length of time since the occurrence of the stressor (e.g., Bruce et al. 2013, Miller et al. 2007, Ursache et al. 2015).

In addition to dysregulation of HPA activity, early and chronic exposure to stress is also associated with structural differences in the neural network involved in stress regulation. Evidence from studies using animal models shows that chronic stress is associated with structural differences, including in volume, neurogenesis, and dendritic branching, in the PFC, hippocampus, and amygdala, and that these structural differences are associated with differences in behavior, such as fear responses and learning (McEwen & Gianaros 2010). Studies of humans show a similar pattern of results for macrostructure: Structural differences, including differences in both cortical volume and cortical surface area, have been found in the PFC (Noble et al. 2012, 2015; Raizada et al. 2008), hippocampus (Hanson et al. 2011; Jednoróg et al. 2012; Noble et al. 2012, 2015), and amygdala (Gianaros et al. 2008, Luby et al. 2013, Noble et al. 2012; for an extensive review, see Brito & Noble 2014). In results underscoring the importance of caregiver relationships, parental nurturance at age four has been found to predict hippocampal volume in a sample of adolescents from lower SES backgrounds (Rao et al. 2010), and caregiver support has been shown to mediate the effects of early adversity on hippocampal volume (Luby et al. 2013). Although there is some degree of inconsistency in the results, which likely depends both on the timing of the stressor and on the time of measurement (for a discussion, see Tottenham & Sheridan 2010), there is generally convergence between human studies and animal studies in that early adversity is associated with structural atrophy in the PFC and hippocampus but hypertrophy of the amygdala structure. As discussed in the next section, this pattern is likely associated with heightened threat sensitivity via increased amygdala reactivity and reduced inhibition of the amygdala by the vmPFC.

Threat appraisal. An important function of the stress regulation system is the identification and processing of socially relevant stimuli that are potentially threatening. Importantly for allostatic effects, it is the brain that decides what is perceived as threatening, and therefore stressful, to an individual (McEwen & Gianaros 2010). This decision making initially involves rapid assignment of the emotional salience of environmental events by the amygdala, which can initiate a rapid response with little cortical processing (Loman & Gunnar 2010, Phelps & LeDoux 2005). The amygdala has bidirectional connections with the PFC and ACC, which play important roles in both the regulation of the response to threat and aspects of self-regulation and attention that are sensitive to early adversity.

Differences in the functioning of the threat appraisal system are thought to play a major role in the effects of early adversity on health, particularly mental health outcomes such as depression and anxiety. In addition, as discussed in the section titled Vulnerability of Immune System Function, this system is a major part of emerging theories linking early adversity to diverse poor health outcomes via compromised neuroimmune function. Importantly, anticipatory responses

to perceived threat (e.g., including perceptions related to social standing and status) can lead to activation of allostatic biomediators such as ACTH and cortisol. This activation can contribute to wear and tear associated with prolonged anxiety resulting from dysregulation of systems important for sensing and responding to potential threats in the environment (McEwen & Gianaros 2010). Thus, perceptions of threat shaped by the environment can lead to prolonged states of vigilance, with deleterious effects on health.

Relationships among early adversity, threat sensitivity, and related aspects of socioemotional processing, as well as the corticoamygdala network underlying this sensitivity, represent another of the more robust findings in the literature. Children from lower SES backgrounds show higher rates of internalizing and externalizing behaviors and conduct disorders, as well as higher rates of depression and anxiety (e.g., Duncan et al. 1994, Goodman et al. 2003, McLoyd 1998, Merikangas et al. 2010, Tracy et al. 2008) and lower self- and parent-reported psychological well-being (Evans & English 2002). Adolescents from lower SES backgrounds are also more likely to judge ambiguous scenarios as threatening (Chen & Matthews 2003). Moreover, heightened threat perception mediates relationships between childhood SES and immune processes in children with asthma (Chen et al. 2006) and partially mediates the relationship between childhood SES and increases in daily cortisol output over a 2-year period (Chen et al. 2010). As discussed in the section titled Vulnerability of Immune System Function, this suggests that threat sensitivity is one mechanism by which early adversity has broader effects on health.

In addition to the amygdala's critical role in the perception of and response to potential threat, the vmPFC also plays an important role in the regulation of the HPA axis via connections to the hypothalamus and the SNS response. The PFC has connections to areas in the brainstem that produce catecholamines, such as dopamine, epinephrine, and norepinephrine, that underlie physiological changes associated with the stress response, particularly the fight-or-flight response mediated by the sympathetic nervous system. Under conditions of moderate stress, the sensitivity of the PFC to catecholamines and cortisol leads to arousal and improved attention and effortful regulation (Blair & Raver 2015). However, at higher levels of stress, PFC activity is reduced as amygdala activity increases, resulting in a shift from more reflective, top-down processing to more reactive, bottom-up processing (Arnsten 2009). As discussed in the section titled Vulnerability of Immune System Function, the balance between PFC regulation and amygdala reactivity interacts with experiences associated with early adversity in ways that contribute to increased allostatic load, as activity from enhanced reactivity mobilizes downstream stress systems (the SNS, the HPA axis) that contribute to allostatic load and modulate inflammation.

Increasingly, evidence suggests that chronic stress associated with early adversity affects PFC and amygdala function across development. Adolescents who have faced more extreme early adversity in the form of institutionalization show greater amygdala reactivity to emotional stimuli (Gee et al. 2013, Tottenham et al. 2011), and young adults from lower SES backgrounds show greater amygdala activity in response to threatening facial expressions (Gianaros et al. 2008). This increased reactivity may result from insufficient top-down regulation by the PFC. Young adults from lower SES backgrounds show both greater amygdala activity and reduced PFC activity during effortful regulation of negative emotion, and chronic stress exposure across development mediates the relationship between early adversity and PFC activation (Kim et al. 2013).

Systems important for both self-regulation and reactivity to threat are shaped by interactions with the environment in a complex and dynamic process characterized as canalization, or channeling, of development (Blair & Raver 2012, 2015; Raver et al. 2013). In contexts of early adversity, this may not result in consistent levels of arousal over time, which are important for more reflective self-regulation processes that facilitate learning. As Blair & Raver (2012, 2015) have noted, heightened vigilance to emotionally negative stimuli (e.g., Cicchetti & Rogosch 2009, Pollak et al. 2005)

may lead to a response profile that is more reactive to experience, which may be beneficial in the short term in certain environments associated with early adversity but maladaptive in educational environments (Blair & Raver 2012). These interactions thus shape individual differences in self-regulation at least in part via the stress response system, and evidence suggests that early adversity affects self-regulation via both emotional regulation and dysregulation of the HPA axis. Emotional regulation profiles in infancy predict self-regulation skills later in development such that children from lower SES backgrounds with high levels of emotional reactivity in a fear-eliciting task and low levels of emotional regulation have poor EF performance; however, children with high reactivity but also high levels of emotional regulation have better EF performance, and positive parenting is associated with better emotional regulation (Ursache et al. 2013). Early adversity is associated with poorer EF, and this relationship is mediated by caregiving and HPA function such that lower parental sensitivity is associated with higher basal cortisol levels that, in turn, predict poorer EF performance in 3-year-olds (Blair et al. 2011). In adults, poorer EF performance is associated with a greater amount of time spent in childhood poverty, and this relationship is mediated by allostatic load associated with elevated chronic stress during childhood (Evans & Schamberg 2009). Thus, a more reactive response profile is associated with several poor outcomes related to early adversity. In the next section, we consider another stress response system that may index the prefrontal hypoactivity and amygdala hyperreactivity associated with this profile.

Autonomic nervous system function. The dynamic interaction between the heart and brain in response to changing environmental demands constitutes another important aspect of stress regulation that is also shaped by early adversity in ways that likely increase allostatic load (e.g., Porges 2007, Thayer & Lane 2009). Central to this interaction is the autonomic nervous system (ANS), which plays a prominent role in the determination of heart rate via inputs from the brainstem from both SNS and PNS branches. Whereas the SNS initiates physiological arousal when a real or perceived threat arises, the PNS modulates SNS input to the heart and other peripheral systems, serving a regulatory function that restores and contributes to the maintenance of homeostasis. Because the cardiovascular system is one of the systems most vulnerable to stress (McEwen & Gianaros 2010), and because of the important role of the ANS in aspects of self-regulation, the ANS is also central to theories of how early adversity gets under the skin. In addition, responses to stress take place at different timescales ranging from milliseconds to days (Joëls & Baram 2009), and examinations of the ANS provide the opportunity to examine stress at the timescale of milliseconds. Recent methodological developments also present the opportunity to integrate measures of brain function and stress regulation on a trial-by-trial basis at this timescale (e.g., Mueller et al. 2010), which could prove fruitful in future investigations of early adversity and neurobiology.

One influential model of adaptation to environmental stressors emphasizes the importance of flexibility in the face of changing environmental demands to successful adaptation and proposes that this flexibility is achieved via a system that integrates input from internal and external systems to generate adaptive responses (Thayer & Lane 2009). In this model of neurovisceral integration, Thayer & Lane propose that high-frequency heart rate variability (HRV) may index this system. High-frequency HRV (0.15 to 0.4 Hz) reflects the influence of the vagus nerve, a cranial nerve that provides a bidirectional link between the heart and brain structures (Thayer & Lane 2009) and that is thought to be analogous to a central executive in the PNS that lowers heart rate and overall levels of arousal. There are ongoing methodological issues surrounding the measurement of vagal function (e.g., Graziano & Derefinko 2013) and, thus, varying methods and terminology used in the literature (e.g., vagal tone, respiratory sinus arrhythmia); however, this debate is beyond the

scope of this review, and, following Thayer & Lane (2009), we use HRV for ease of comparison across studies.

Increases in HRV reflect increased activation of the vagus nerve, often co-occurring with decreased heart rate and arousal akin to a vagal brake (Berntson et al. 1993). Because the vagally mediated PNS provides a more rapid and flexible response, resting cardiac balance is characterized by PNS dominance over SNS influences. When a stressor is encountered, the vagal brake is withdrawn to facilitate an increase in heart rate, and this brake can then be reengaged to facilitate a return to a calm state after a stressor. A large body of literature has found associations between vagal function (lower baseline HRV) and poor cardiovascular health outcomes (e.g., Thayer & Lane 2007), as well as a broader range of poor physical and mental health outcomes across development and into adulthood that include many outcomes associated with early adversity. This has led Beauchaine & Thayer (2015) to identify HRV as a transdiagnostic biomarker of psychopathology such that lower HRV may index vulnerability to a wide range of disorders.

Interestingly, vagally mediated cardiac activity is modulated by the same prefrontal systems that are involved in the regulation of the HPA axis. Evidence suggests a preferential role for the right PFC in aspects of inhibitory control of both cognition and affective behavior (e.g., Aron et al. 2004), as well as for modulation of cardiac activity via the vagus nerve (Thayer & Lane 2009). Central to this role is the tonic inhibition of the amygdala by the PFC, most prominently the medial and orbitofrontal PFC (Thayer et al. 2012). Tonic default inhibition of amygdala activity by the vmPFC is thought to reflect an integration of the external context (potential threat) with the internal context (perceptions of control over the potential threat) (Maier et al. 2006, Thayer et al. 2012). As discussed above, PFC hypoactivity leads to increased amygdala activation and SNS- and HPA-mediated mobilization of resources in response to a potential threat. Thayer and colleagues (2012) hypothesized that a prolonged state of PFC hypoactivity associated with chronic stress, as indexed by HRV, produces increases in allostatic load that likely contribute to the range of poor health outcomes associated with HRV. Moreover, some longitudinal evidence suggests that chronic stress associated with exposure to parents' marital conflict in childhood results in lower resting HRV in adolescence (El-Sheikh et al. 2011) and that lower educational attainment in young adulthood is associated with lower resting HRV (Sloan et al. 2005).

As discussed above, early adversity is associated with a more reactive response profile characterized by heightened vigilance to emotionally negative stimuli, and the neurovisceral integration model posits that both tonic and reactive HRV provide an index of this prefrontal hypoactive state associated with disinhibition of SNS activity. Consistent with this hypothesis, neuroimaging studies document a consistent association between HRV and both vmPFC and amygdala activity (Thayer et al. 2012). Differences in PNS function, as assessed by HRV, are related to emotional regulation and threat sensitivity, as well as cognition. Both higher levels of resting HRV and increases in HRV during emotional regulation tasks (i.e., removal of the vagal brake) are associated with more effective emotional regulation across development, from early childhood (Porges 1996) into adulthood (e.g., Park & Thayer 2014, Thayer & Brosschot 2005), as well as less sensitivity to potential threats (Shook et al. 2007) and inhibition of threat responses to nonthreatening stimuli (Thayer & Friedman 2002). Although less evidence exists of a link between HRV and aspects of cognition, a similar pattern is emerging, suggesting that higher levels of baseline HRV and HRV withdrawal are associated with better performance on self-regulation and EF tasks in children (e.g., Chapman et al. 2010, Marcovitch et al. 2010) and adults (e.g., Hansen et al. 2003, Kimhy et al. 2013). Taken together, these results suggest that higher resting HRV and HRV withdrawal are associated with more flexible and adaptive regulatory behavior and that lower resting HRV and lower HRV withdrawal are associated with hypervigilance and impaired prefrontal regulation of the response to emotional stimuli (Park & Thayer 2014, Thayer & Lane 2009).

Increasingly, evidence suggests that early adversity is associated with dysregulation of both PNS and SNS function, although most evidence comes from studies of forms of early adversity that are more extreme than differences in SES. Overall, the pattern is characterized by lower resting HRV and HRV withdrawal and, to a lesser degree, by increased sympathetic activity, consistent with heightened vigilance and prefrontal hypoactivity. More evidence exists on the role of the PNS, likely because nonintrusive measures of SNS function, such as measures of salivary α-amylase (sAA) and pre-ejection period (PEP), have only recently become more common in developmental studies (for a review, see Propper & Holochwost 2013). Effects of early adversity on the ANS have been documented as early as the prenatal period, as fetuses of mothers reporting higher levels of perceived stress have lower resting levels of HRV (Allister et al. 2001, DiPietro et al. 1996), and greater socioeconomic adversity during pregnancy is associated with heightened SNS reactivity across development to age five (Alkon et al. 2014). In addition, maternal depression and substance abuse during pregnancy is associated in infants with lower resting levels of HRV, HRV withdrawal, and elevated heart rate, which likely reflects a combination of PNS and SNS activity (e.g., Field et al. 1995, Schuetze et al. 2011). Consistent with the evidence reviewed above, differences in interactions with caregivers are also associated with differences in regulation of the ANS. Lower resting HRV in infants is associated with poorer parent–child joint communication (Porter 2003) and higher levels of parental marital conflict (Porter et al. 2003), and increased parental marital conflict is also associated with lower HRV withdrawal in response to maternal disengagement (e.g., Moore 2010). In addition, higher levels of sAA in response to challenge are associated with irregular profiles of attachment associated with early adversity (Oosterman et al. 2010).

Other studies extend the findings associating early adversity and dysregulation of ANS function and, like the pattern of results in studies of early adversity and cortisol, present a somewhat inconsistent pattern of results that highlights the need to consider the interaction between physiological profiles of reactivity and context. Although higher resting HRV and increased HRV withdrawal have been found to be associated with adaptive behavior, recent evidence suggests that this may not always be the case in children from lower SES backgrounds. Children from lower SES backgrounds who receive insensitive caregiving have higher levels of problem behavior, but only if they also have higher levels of resting HRV (Conradt et al. 2013). Similarly, children from lower SES backgrounds with higher HRV withdrawal at one month of age exhibit more behavioral dysregulation at age three, but only if they were exposed to higher levels of caregiver stress (Conradt et al. 2016). Higher HRV withdrawal in response to challenge tasks is also associated with poorer behavioral and academic outcomes in kindergartners, but only in the context of higher family adversity, whereas children with higher HRV withdrawal but with lower levels of family adversity have higher levels of educational engagement and academic competence (Obradovic et al. 2010). Similar patterns have been reported in studies of more extreme forms of early adversity. For example, Skowron and colleagues (2014) found that HRV withdrawal predicts better inhibitory control in children who had not experienced child maltreatment but that, in children who had experienced child maltreatment, better inhibitory control was instead predicted by HRV augmentation, with stronger effects occurring in tasks in which children were engaged with the maltreating caregiver. Taken together, these results are consistent with the theory of biological sensitivity to context (Ellis & Boyce 2008) and a recent extension of this theory, the adaptive calibration model (Del Giudice et al. 2011). Both models suggest that the stress response system interacts with environmental context such that high reactivity may be adaptive in more supportive environments but less adaptive in more negative and potentially threatening environments associated with early adversity. The adaptive calibration model describes a wider range of stress response profiles that potentially interact with the severity and duration of stressors related to early adversity, providing testable hypotheses for future studies.

Although less evidence exists on the effects of early adversity on the interaction between the PNS and SNS (Propper & Holochwost 2013), some researchers have suggested that more reactive and vigilant profiles associated with early adversity might be characterized, in some contexts, by SNS dominance and blunted PNS activity (e.g., Del Giudice et al. 2011). Some evidence suggests that a pattern of PNS activation and SNS inhibition may represent a profile of resilience (e.g., El-Sheikh et al. 2009). Response strategies to mild stressors may be dictated, first, by the evolutionarily newer PNS system, followed by a shift to the evolutionarily older SNS system if the PNS system is ineffective (Beauchaine et al. 2007). If this is the case, the ability of children from backgrounds of adversity to mount a PNS response to challenge may be limited by a less flexible PNS system, which could result in a greater relative reliance on SNS resources, imposing, in turn, greater allostatic load. Because research on this model is limited and comes mostly from studies of infants, it is necessarily speculative at this time. Future research on the effects of early adversity that incorporates independent measures of PNS and SNS function in the same participants will shed valuable light on this question (Propper & Holochwost 2013).

THE IMMUNE SYSTEM

As discussed above, early adversity is associated with a wide range of poor health outcomes across the lifespan, including both infectious and inflammation-related diseases (Irwin & Cole 2011, McEwen & Gianaros 2010). Importantly, adult behavior alone does not explain these patterns, and evidence suggests that early adversity leaves a biological residue (Chen & Miller 2013) that may operate independently of subsequent experience and behavior. For example, even in a sample of well-educated and affluent physicians, rates of coronary heart disease were more than twice as high at age 50 for those raised in lower SES households (Kittleson et al. 2006). Increasingly, evidence suggests that these enduring effects are likely mediated by the immune system and its interactions with the neural and stress regulation systems discussed above. Central to emerging hypotheses on the role of the immune system is the role of the HPA axis and SNS, as well as related brain systems, in the regulation of broad patterns of gene expression in immune cells.

Key to the function of the immune system is the activation of immune response genes that encode antibodies, as well as regulatory molecules such as cytokines. This activation is triggered by different types of internal signals (for a detailed review, see Irwin & Cole 2011). Two broad classes of internal signals have been found: extracellular pathogens (e.g., bacteria), which activate proinflammatory programming, and intracellular pathogens (e.g., viruses), which activate antiviral programming. Both responses come at an energetic cost to the organism.

More recently, the brain has emerged as a third class of stimulus that plays a vital role in the modulation of the immune response. This neural modulation is beneficial for adaptation and survival because it allows for the suppression of the effects of inflammation and sickness behavior when the broader environmental context presents more immediate threats. Neural suppression of the transcription of both proinflammatory and antiviral genetic programming occurs via multiple mechanisms. The first involves the release of glucocorticoids from the HPA axis, a mechanism that is protective against hyperinflammatory disease. The second involves the SNS, which simultaneously inhibits antiviral genes and activates proinflammatory genes via multiple pathways, including the production of proinflammatory cytokines, with a net effect of increased expression of proinflammatory immune response genes. This occurs even when glucocorticoid levels are stable or elevated, which appears to be the result of a functional desensitization of the GR (Pace et al. 2007) that is related to chronic stress and threat in animal models (e.g., Powell et al. 2011), as well as early adversity in humans (G.E. Miller et al. 2009). These cytokines also work within the brain, in part via receptors in the hippocampus and hypothalamus, to activate a broad array of

sickness behaviors, including anhedonia and fatigue, reductions in exploratory and reward-seeking behavior, altered cognitive and motor function, sleep alterations, and reduced social functioning (e.g., Dantzer et al. 2008). Neuroimaging studies have found that this cytokine-induced pattern of sickness behaviors is associated with altered connectivity among the ACC, medial PFC, and amygdala and reduced ventral striatum activation to reward (e.g., Eisenberger et al. 2010, Harrison et al. 2009).

Reductions in glucocorticoid-mediated feedback inhibition have the effect of increasing proinflammatory gene expression, even at baseline levels. Allostatic theories (McEwen & Gianaros 2010) propose that physiological systems survive best if they are prepared to actively anticipate challenges and proactively alter their functioning in preparation, leading to the idea of a forward-looking immune system programmed by the environment. Thus, an environment characterized by chronic exposure to real or perceived threats to survival might program a more proinflammatory phenotype that is beneficial for shorter-term survival but confers adverse longer-term consequences for a range of health outcomes.

VULNERABILITY OF IMMUNE SYSTEM FUNCTION

Early adversity is also associated with altered immune system function at different stages of development. Increased levels of circulating biomarkers of inflammation, such as the cytokines C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor α (TNFα), provide a reliable index of systemic inflammation in studies of humans. Increased production of proinflammatory cytokines is found in newborns experiencing greater prenatal maternal stress (Wright et al. 2010) and in children from lower SES backgrounds (e.g., Azad et al. 2012, Broyles et al. 2012). This altered function may endure into adolescence and adulthood, as adolescents exposed to early family adversity show increasingly greater production of proinflammatory cytokines over time (Miller & Chen 2010). Furthermore, young adults from lower SES backgrounds show increased proinflammatory cytokine production compared to adults from higher SES backgrounds, even in the absence of differences in adult SES (G.E. Miller et al. 2009). In addition, early adversity is associated with higher rates of inflammation-related diseases typical of older age in adults in their thirties, with stronger effects when adversity occurred earlier in development (Ziol-Guest et al. 2012). Consistent with the mechanisms discussed above, several of these studies also found an association between early adversity and decreased sensitivity to glucocorticoids. One specific mechanism that appears to underlie chronic proinflammatory gene expression is sleep, as elevated levels of proinflammatory biomarkers have been consistently found in people suffering sleep disturbances (for a review, see Irwin et al. 2016). Disruptions of sleep are associated with both early adversity and chronic stress, and poor sleep habits have been linked to poor academic outcomes in children from lower SES backgrounds, with family stress and inconsistency in the home environment hypothesized to be moderating factors in this relationship (for a review, see Buckhalt 2011).

The neuroimmune network hypothesis of Nusslock & Miller (2016) builds on and integrates much of the evidence discussed above. This hypothesis notes the large overlap between health outcomes with a suspected inflammatory etiology and those associated with early adversity. The network hypothesis proposes that early adversity amplifies crosstalk between multiple systems in a manner that leads to chronic low-grade inflammation that contributes to this wide range of poor health outcomes. Given the evidence that early adversity may lead both to a more reactive, hypervigilant profile mediated by corticoamygdala circuitry and HPA and SNS mechanisms and to a proinflammatory phenotype, the neuroimmune network hypothesis posits that this combination of effects leads to increased bidirectional traffic between the brain and immune system, creating a

positive feedback loop that heightens risk over time. The hypothesis further posits an additional bidirectional pathway involving the corticostriatal pathway, which supports reward processing. Given the evidence that early adversity is associated with blunted reward sensitivity and that this sensitivity is mediated in part by inflammatory cytokines (e.g., A.H. Miller et al. 2009), the hypothesis posits that a more proinflammatory phenotype leads to higher rates of high-risk and addictive behavior. Such high-risk behaviors (e.g., smoking, poor nutrition) in turn have proinflammatory effects (e.g., Kiecolt-Glaser 2010, Yanbaeva et al. 2007), thereby potentially creating another positive feedback loop. Finally, given the evidence that early adversity is associated with differences in PFC structure and function and emerging evidence that inflammation may also affect the structure, function, and connectivity of the PFC and other brain areas (e.g., Gianaros et al. 2012, Marsland et al. 2008), the model posits that these differences in self-regulation and inhibition of amygdala reactivity may further contribute to a self-perpetuating cycle driven by increased neuroimmune crosstalk. As Nusslock & Miller (2016) note, several aspects of this hypothesis are speculative but provide fruitful directions for future research. Although this is not part of the hypothesis and is also speculative, it is interesting to note that lower HRV has also been associated with higher levels of proinflammatory cytokines (for a review, see Thayer & Sternberg 2006), raising the possibility that an autonomic profile of SNS dominance and blunted PNS activity may also contribute to a proinflammatory phenotype and associated chronic low-grade inflammation.

CONCLUSION

The effects of early adversity are evident across numerous levels of analysis and at multiple levels of society, and the costs to society are great. The costs of growing up in poverty are estimated to be equivalent to almost 4% of gross domestic product, or approximately $500 billion per year, distributed across costs associated with increases in direct and indirect health expenditures and the values of life expectancy, economic output, and crime victimization (Holzer et al. 2008). A recent study estimates that the 20% of society that is most vulnerable to effects associated with early adversity incur as much as 80% of the costs to society associated with social welfare, health, and crime (Caspi et al. 2016). Thus, there is a degree of urgency in the need for a more mechanistic understanding of early adversity that can inform efforts to ameliorate these costly effects.

Neurobiological Targets for Intervention

Although the studies reviewed in this article represent great progress in understanding the relationships between early adversity and multiple integrated neurobiological systems, because they are correlational, they are necessarily limited in the degree to which causation can be inferred from them. However, studies that employ experimental designs provide the opportunity to build on correlational studies in ways that inform both theories regarding the causal pathways and policies that seek to ameliorate the costly effects of early adversity. Building on the work described above, translational researchers are designing, implementing, and assessing interventions that include consideration of the multiple integrated biological systems affected by adversity. A well-informed intervention should also target the proximal pathways through which adversity operates and incorporate these pathways into theory-of-change models (e.g., Fisher et al. 2016); consistent with the research above, evidence from experimental studies suggests that interventions addressing the caregiving environment may yield particularly high dividends. Some of these studies include one or more of the neurobiological systems described as outcome measures, providing valuable evidence on the potential for intervention to alter the adverse developmental trajectory of these vulnerable systems. In this section, we briefly highlight a subset of interventions targeting early adversity.

Consistent with our framework emphasizing the two sides of plasticity (Stevens & Neville 2006), we consider whether the same neural systems that are vulnerable in the face of early adversity might also, under different conditions, be capable of enhancement. We focus specifically on interventions that have included assessment of one or more of the integrated biological systems identified above and that specifically target an aspect of the early caregiving environment, thereby examining the second side of plasticity, namely the capacity for vulnerable subsystems to be modified for the better.

Several studies document the responsiveness of the neurobiological systems reviewed in this article to interventions targeting the early caregiving environment, ranging from adoption out of institutional rearing (Tottenham et al. 2010) to targeted interventions (Neville et al. 2013). As an example, in our own research, we have examined the effects of an 8-week, two-generation intervention for families of preschool children living in poverty. The program combined direct work with small groups of children on attention and self-regulation activities with small-group training for parents, providing tools and strategies for the home focused, in part, on reducing family stress. Children randomly assigned to receive the intervention showed an increase in the effects of selective attention on neural processing from before to after the training relative to children in both active and passive control groups, and parents randomly assigned to the intervention reported less parenting stress compared to parents from both control groups (Neville et al. 2013). In addition to underscoring the importance of targeting caregiving, this result also highlights the potential of two-generation interventions that simultaneously target attention and self-regulation in children and family stress in parents.

Stress is another neurobiological target for intervention. Increasingly, intervention studies are examining cortisol: One review reported that, of 19 studies incorporating cortisol into rigorous experimental designs, more than half were published after 2008 (Slopen et al. 2014). This review found that 18 of the 19 studies published found at least one significant change in cortisol with interventions, many of which targeted caregiving in some way. Importantly, all eight studies that included a comparison group from lower-risk backgrounds reported evidence that patterns of cortisol activity in intervention groups from higher-risk backgrounds changed with intervention to more closely resemble patterns of children from lower-risk backgrounds. Although there was inconsistency in how interventions affected cortisol, this pattern nonetheless illustrates the plasticity of the HPA system and suggests that interventions can alter the developmental trajectory of stress regulation systems in ways that may lead to better health outcomes. For example, in seminal studies of an intervention targeting stress in foster parents and preschool-aged foster children, Fisher and colleagues (Fisher & Stoolmiller 2008, Fisher et al. 2007) demonstrated that the intervention reduces stress in foster parents and normalizes diurnal cortisol patterns in foster children to levels more comparable with community controls relative to foster families who did not receive the intervention. Another study also found that a classroom-based program targeting self-regulation in kindergarten children had positive effects on multiple self-regulation and academic measures, as well as effects on cortisol specific to children from high-poverty schools, illustrating that classroom-based approaches targeting self-regulation can also impact stress physiology in children from backgrounds of adversity (Blair & Raver 2014).

Although considerably less evidence exists regarding the response of the ANS to intervention, one study suggests that this system exhibits considerable plasticity and also underscores the importance of caregiving, particularly early caregiving. McLaughlin and colleagues (2015) found that institutionalized children show blunted cortisol and SNS reactivity in response to psychosocial stressors compared to children randomly assigned to adoption into high-quality foster care. They also found that earlier age of placement into foster care is associated with normalization of cortisol reactivity, as well as greater HRV withdrawal during a social task, suggesting sensitive

periods underlying the plasticity of these systems and some specificity with regard to the timing of caregiving changes and the development of more flexible PNS function. Although more study is necessary, this result demonstrates that the ANS may be amenable to early intervention.

Finally, some evidence suggests that the immune system is responsive to early interventions focused on the caregiving environment. Miller and colleagues (2014) demonstrated that African American adolescents from lower SES backgrounds who were randomly assigned as children to receive an intervention designed to strengthen parenting, family relationships, and youth competencies had lower levels of inflammation across six cytokines 8 years after receiving the intervention. These effects were mediated by improvements in parenting, again highlighting the importance of targeting the caregiving environment. The authors hypothesize that changes in parenting may have led children to adopt an adaptive shift and persist strategy. This strategy entails a combination of acceptance and endurance in the face of adversity and has been shown to moderate the relationships between SES and both glucocorticoid sensitivity and systemic inflammation in adolescents and their parents (Chen et al. 2015). The identification of adaptive psychosocial characteristics that can be targeted in interventions and that have the potential to mitigate the effects of early adversity via physiological and inflammatory processes represents a promising future direction of research in this area.

FUTURE DIRECTIONS

Although considerable progress has been made to understand the ways in which early adversity gets under the skin to affect multiple neurobiological systems, much important work remains. We close by briefly highlighting multiple ongoing and future directions in this research, many of which have been discussed by researchers whose work is the focus of this review. Although our review has emphasized the importance of caregiving, there are multiple additional influences on the development and plasticity of the systems discussed above. These include both genetic and epigenetic effects, as well as other environmental influences such as pollution, exposure to toxins, nutrition, and exercise, among many others. With regard to stress, it is particularly important to consider other psychosocial factors with implications for health, including the degree to which an individual feels control in life and, relatedly, subjective social status. It is also important to consider factors that confer resilience because, despite the profound effects reviewed in this article, a substantial proportion of children who experience early adversity avoid many of these poor outcomes. Research that identifies mediators or moderators that may confer vulnerability as well as resilience, as does some of the evidence on caregiving discussed above, is important in this regard.

Future research should also employ more longitudinal designs that include a greater consideration of interactions between early adversity and the developmental trajectories of different neurobiological systems in a life-course perspective. Employment of these designs involves careful consideration of both how and when adversity is measured, as well as differential contributions of different aspects of adversity at different points in development and the integration of measures of multiple neurobiological systems. This will, in turn, provide more specificity to inform the development of theoretically driven interventions and theory-based evaluations of the efficacy of interventions on targeted systems. We have highlighted interventions targeting the systems that are the focus of this review; however, other intervention approaches, including behavioral programs that target physical activity and social integration, as well as pharmacological and therapeutic programs, show promise in ameliorating the effects of early adversity (McEwen & Gianaros 2010). In addition, promising work in developing countries illustrates how evidence-based interventions can be designed in ways that address challenges to large-scale implementation (Neville et al. 2015).

Future work should also continue the ongoing focus on efforts to use scientific evidence to inform public policy. Central to these efforts is the need to continue to improve public as well as professional (e.g., education, health care) understanding of this research and the profound relationships between early adversity and neurobiological development. A good example is the work of the National Scientific Council on the Developing Child, the Center on the Developing Child, and the FrameWorks Institute in taking an evidence-based approach to the iterative development of metaphors to communicate complex scientific concepts to nonscientists; these metaphors have, in turn, been used successfully to promote a broader understanding of concepts such as brain architecture and toxic stress (Shonkoff & Bales 2011). It is crucial for scientists to be closely involved in their communities and to make efforts to share their work directly with the public when possible. Increased public understanding can potentially lead to greater public support for evidence-based public policies, such as investments in early education and caregiver support, that have the potential to more broadly address issues related to early adversity.

Finally, as we have tried to highlight in this review, progress in this area requires continued and increased consideration of findings from different disciplines, as well as interdisciplinary collaborations. It is increasingly evident that these collaborations should include neuroscientists, cognitive neuroscientists, social and developmental psychologists, geneticists, epidemiologists, prevention and intervention scientists, educators, economists, and policy makers. Such collaborative efforts will lead to more progress in understanding the complex interplay among the biological and environmental factors that underlie the broad and costly effects of early adversity, as well as the plasticity that provides hope for the amelioration of these effects.

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