

Long-lasting Impact of Early-Life Stress and Adversity

Review

Early Adversity and Critical Periods:
Neurodevelopmental Consequences of
Violating the Expectable EnvironmentCharles A. Nelson III^{1,2,3,4,*} and Laurel J. Gabard-Durnam^{1,3}

It is now widely recognized that children exposed to adverse life events in the first years of life are at increased risk for a variety of neural, behavioral, and psychological sequelae. As we discuss in this paper, adverse events represent a violation of the expectable environment. If such violations occur during a critical period of brain development, the detrimental effects of early adversity are likely to be long lasting. Here we discuss the various ways adversity becomes neurobiologically embedded, and how the timing of such adversity plays an important role in determining outcomes. We conclude our paper by offering recommendations for how to elucidate the neural mechanisms responsible for the behavioral sequelae and how best to model the effects of early adversity.

A Conceptual Framework for Considering the Effects of Early Adversity on Brain Development

There is growing evidence that children exposed to **adversity** (see [Glossary](#)) early in life are at increased risk for atypical variations in brain development that in turn are associated with a variety of psychological, behavioral, and physical health sequelae [1–3]. Adversity generally involves exposure to **biological hazards** (e.g., malnutrition, environmental toxins, chronic infection), psychological hazards (e.g., maltreatment, neighborhood or domestic violence), or both; and, although one can be exposed to adversity at any point in the lifespan, here we argue that exposure to adversity during **critical periods** of brain development – many of which occur within the first years of life – can be particularly hazardous to development.

We begin our article by arguing that adversity is best considered through the lens of violations in the expectable environment. These violations include experiences that are atypical (e.g., patterned light is diffused through a cataract; a caregiver is physically or emotionally abusive) or experiences that are entirely absent (e.g., a child born deaf or a child deprived of adequate caregiving). Critical periods of brain development exist to encode the expectable environment, with enduring effects on brain and behavior. Thus, it is vital to consider critical periods in the context of how adversity exerts such deleterious effects. Indeed, adversity disrupts both critical period substrates and critical period mechanisms themselves. Thus, adversity that occurs during a critical period of brain development is far more likely to have enduring rather than transient effects on development. We summarize these enduring effects of early adversity on human development, and we offer suggestions for advancing progress on this complex topic. We make the point that it is rare for children to be exposed to a single form of adversity at a single time point; rather, a majority of children are exposed to multiple forms of adversity simultaneously, and in many cases, such adversity extends over time rather than occurring at a single time point. This makes it difficult to disentangle the differential effects of any specific adverse experience on brain development; indeed, one might ask if it makes more sense to develop models that reflect

Highlights

Adversity might best be thought of as a violation of the expectable environment.

Adversity can take many forms, including exposure to biological and psychosocial hazards, which often coexist as complex exposures.

Many forms of early adversity are not time limited, making it difficult to tease apart the cumulative effects of adversity from the effects of early life adversity.

Exposure to various forms of adversity early in life is associated with alterations in brain development, which in turn is associated with psychological, behavioral, and physical health consequences.

Exposure to adversity during critical periods of development is more likely to lead to permanent rather than transient effects on the brain.

Parallel studies across humans and animal models of early adversity will prove essential to understanding how adversity becomes neurobiologically embedded.

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the aggregate and interactive effects of adversity exposures. Finally, because of limitations in the spatial and temporal resolution of human neuroimaging tools, and because of ethical constraints on the kinds of studies that can be performed with human children, understanding how adversity becomes neurobiologically embedded will require the continued development of animal models that closely parallel the human condition.

What Do We Mean by ‘Adversity’?

Adversity has been used in a variety of ways. Some investigators have drawn analogies between early life stress and adversity [4–6]. However, this can be misleading, as not all forms of adversity will be interpreted and/or encoded as stressful, depending on brain maturity and developmental history (e.g., an impoverished language environment, where a child is exposed to fewer words and less complex language, is likely a form of adversity but it is in and of itself not stressful and does not activate the stress response system); and conversely, not all stressful experiences are adverse (e.g., a child may experience preparation for an exam as stressful, but this would not be considered a form of adversity).

There are also conflicting views about the dimensions of adversity that are most impactful on development. For example, the long-running Adverse Childhood Experiences study (ACEs) [2,7–10] has argued that it is the number of adverse life events that most influence development, not the nature of these events. However, not all adhere to this view of adversity; for example, McLaughlin and Sheridan [11–13] have offered persuasive evidence that threatening events (e.g., physical abuse) impact the brain differently than neglect does (e.g., absence of caregiving). Moreover, the type of threat (e.g., physical abuse vs. verbal abuse) or the type of deprivation (e.g., lack of caregiving vs. lack of visual or auditory input) likely impacts development differently. Thus, simply considering the number of adverse events without also considering the nature of the adversity and the timing of the adversity (as we discuss in some detail later) likely captures only part of the story.

Adversity as a Violation of the Expectable Environment

For the purposes of this paper, we argue that adversity should be taken to reflect deviations in or disruptions of the expectable environment [22,23]; that is, experiences that are expected to occur (in order to confer survival and adaptation to the environment) either do not occur (e.g., lack of caregiving; lack of nutrition) or are atypical in some way (e.g., physical abuse). The reason an absence of an expected experience or the presence of an atypical experience matter can be attributed to the experience-driven nature of brain development [20,21]. When cortical specialization is driven by experience, atypical experiences or the lack of experiences during those windows should lead to atypical patterns of brain development [24,25]. This, of course, is well established in sensory systems [26], and increasingly well established in higher cognitive and emotional systems [27,28]. Thus, any deviation in or disruption of an expectable experience should be considered to have potentially adverse consequences (Figure 1 provides a conceptual representation of adverse experiences compared with stress experiences in development).

The Role of Critical Periods

Recently, Gabard-Durnam and McLaughlin [14] summarized several conceptual models that attempt to explain how adversity impacts neurodevelopment (Figure 2). These models emphasize different dimensions of adversity (e.g., timing, duration, type, number) or focus on how individual-level traits moderate the impact of an adverse experience [12,15–19]. The conceptual models make assumptions not only about the most relevant features of environmental experience but also the underlying neurobiological mechanisms involved. The majority of the models assume experience-dependent neural mechanisms; essentially processes that facilitate learning across

Glossary

Adversity: a violation of the expectable environment that takes the form of biological hazards, psychosocial hazards, or complex exposures of both hazard types, with negative effects on development.

Biological embedding: the mechanisms through which environmental experiences impact neurobiology such that these experiences have enduring consequences on brain structure and function.

Biological hazard: adverse biological factors in the environment that have negative effects on development, such as insufficient nutrients, environmental toxins, and pathogens that induce chronic infection and inflammation.

Critical period: window of heightened brain plasticity for encoding specific environmental inputs through experience-expectant mechanisms that results in irreversible changes in brain function with permanent effects on behavior, for example, as in filial imprinting.

Experience-dependent mechanism: neural plasticity mechanism facilitating learning in response to experiences across the lifespan without developmental constraints, for example, strengthening or weakening neural synapse connections.

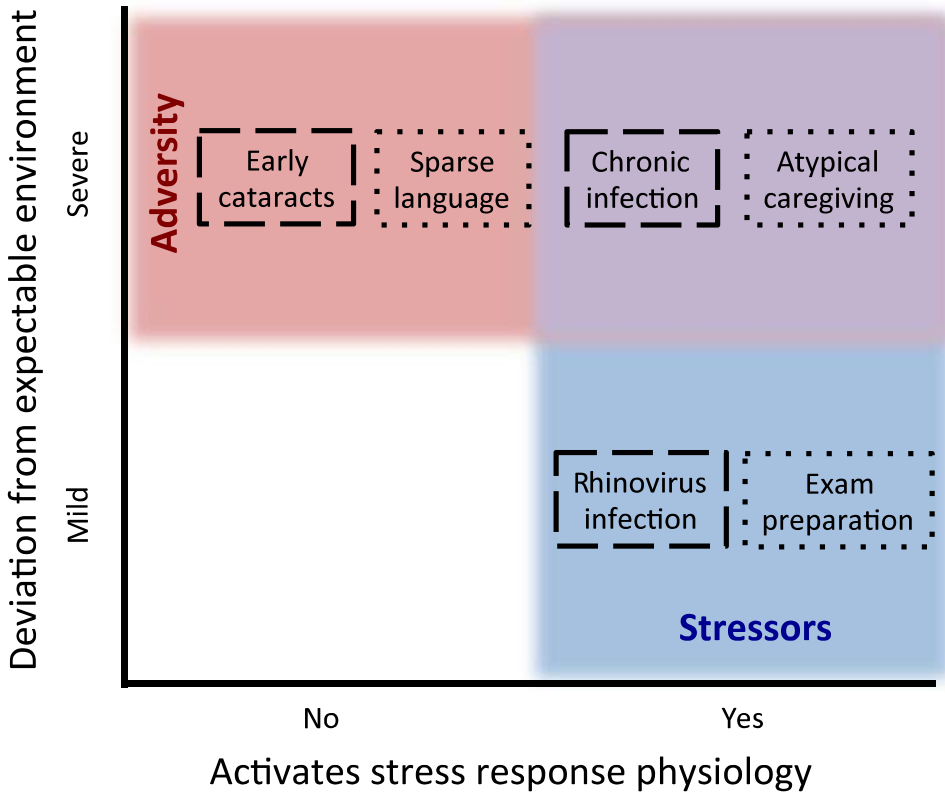
Experience-expectant mechanism: neural plasticity mechanism facilitating the encoding of specific, expectable environmental stimuli, such as patterned light or auditory tones, during constrained developmental windows; underlies critical and sensitive period phenomena.

Mixture model: a conceptual and statistical framework for complex adversity exposures that accounts for how different types of adversity interact and generate synergistic effects on development, for example, implemented with toxin mixtures.

Psychosocial hazard: adverse cognitive, affective, or social experiences that negatively impact development, such as poverty, inadequate caregiving, and maltreatment.

Sensitive period: constrained window of time when the environment most impacts brain function via experience-expectant mechanisms; similar to a critical period but with residual plasticity after the period ends such that experiences may continue to affect brain function, for example, as in caregiver attachment formation.

Negative experience matrix



Biological hazard
Psychosocial hazard

Trends in Neurosciences

Figure 1. Relation between Adversity and Stress Experiences in Development. This diagram illustrates the conceptual differences and overlap between experiences of adversity and stress in development. We define adverse experience to be a significant deviation from the expectable environment, independent of whether that experience triggers a response in the stress system (adverse exposures highlighted in red). Similarly, early stressors all impact the stress response system, independent of whether the experience reflects a severe deviation from the expectable environment (stress exposures highlighted in blue). Some experiences may be considered both stressful and adverse experiences (highlighted in purple). We provide examples of biological hazards (broken outline) and psychosocial hazards (dotted outline) in each category of adverse and stress experiences.

the lifespan without ontogenetic constraints (e.g., synaptogenesis/pruning [20,21]). However, sensitive and critical period models (see later) rely on **experience-expectant mechanisms** that facilitate biological encoding of expectable environmental stimuli (e.g., patterned light, speech) during constrained developmental windows of heightened plasticity [20,21]. These neurobiological mechanisms have distinct implications for the impact of adversity. That is, adversity occurring during experience-expectant development, such as during sensitive/critical periods, is more likely to have significant, persistent effects on neural function into adulthood.

Thus, the timing of exposure is essential in considering the effects of early adversity on brain development, which brings us to the role of sensitive or critical periods. Although these terms

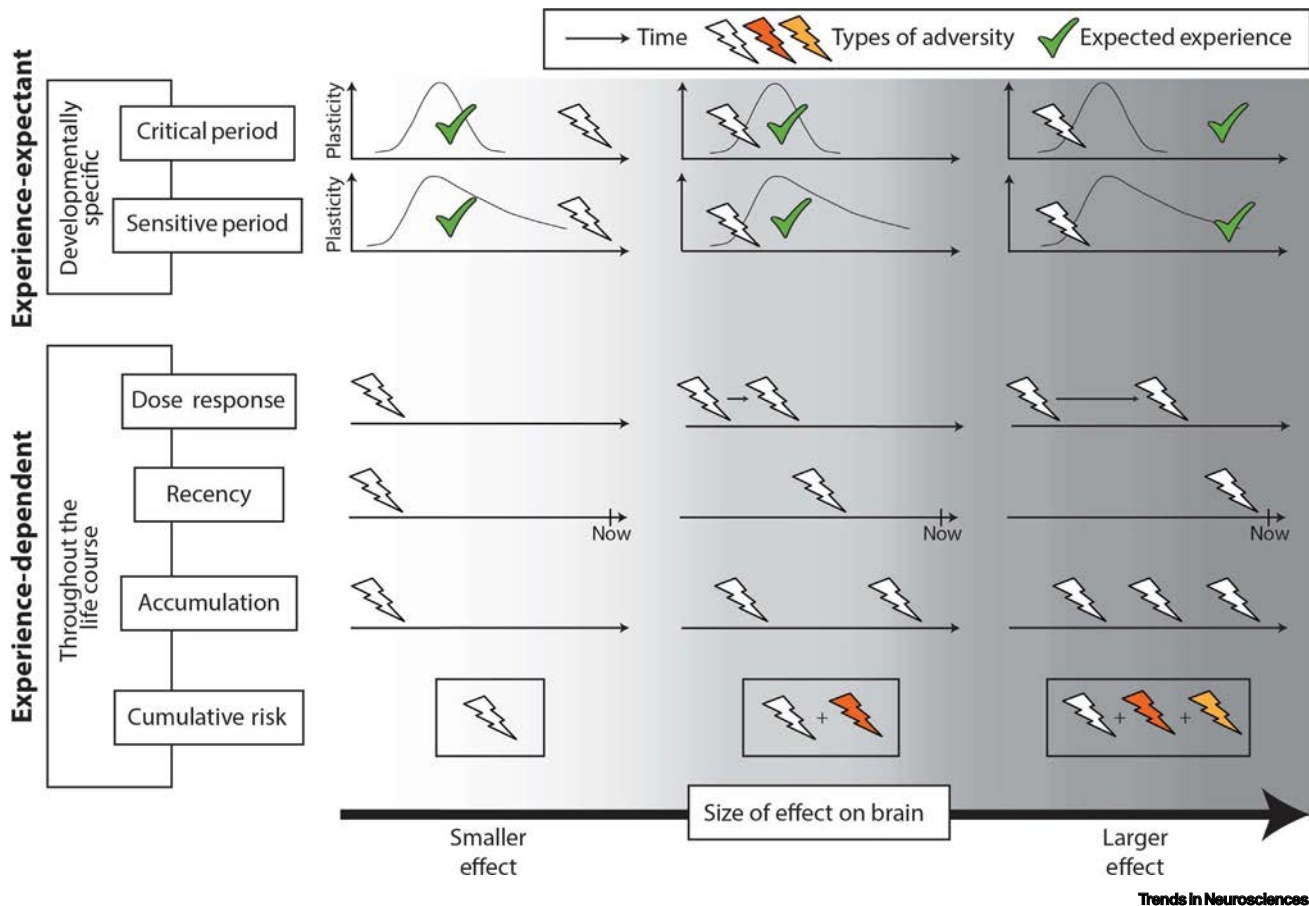


Figure 2. Conceptual Models of Environmental Influence on Neurodevelopment. These models differ in the dimensions of adversity they account for (e.g., duration, timing, number) and the underlying neurobiological mechanisms (i.e., experience-expectant or **experience-dependent mechanisms**). Adversity may have the most significant, long-lasting effects on the brain when it disrupts or abolishes expected experiences during critical or sensitive periods of development for encoding those experiences (cases at top right of figure). Adapted from [14].

are often used interchangeably, they differ in fundamental ways. Knudsen [65], for example, has argued that **sensitive period** is a more general term used to describe the effects experience has on the brain during narrow windows of time. If experiences essential to cortical specialization fail to occur during this time (e.g., access to patterned light or linguistic input), it may be difficult to redirect development along a typical trajectory; even then, function in the affected domain (e.g., vision, language) may not fully recover. As Nelson *et al.* [28] argue, the formation of a secure attachment to a caregiver may reflect a sensitive period. Importantly, Knudsen [65] has argued that whatever plasticity exists beyond a sensitive period is constrained by what transpired during a sensitive period; that is, one can reshape existing circuits only to a limited degree. If there is no residual plasticity after the experience-expectant window, however, then this period is deemed a critical period. Therefore, critical periods result in irreversible changes in brain function. If a key experience fails to occur during a critical period, behavior will be permanently impacted, with little recovery possible. Filial imprinting in animals likely represents a critical period (e.g., [66]).

Several additional points about critical/sensitive periods are worth noting. First, there is not just one critical/sensitive period but rather, cascading critical and sensitive periods for different neural circuits and for different complex phenomena, such as caregiving and language (Figure 3).

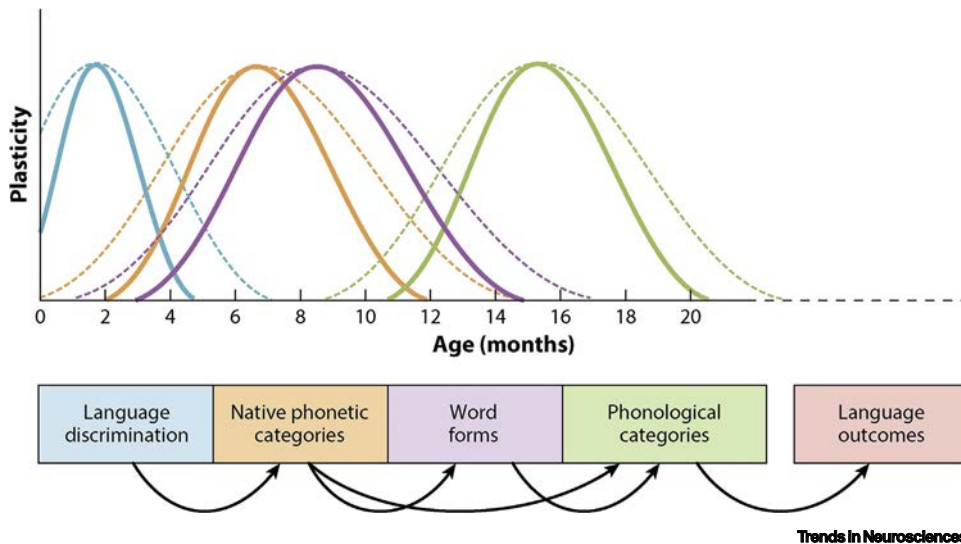


Figure 3. Multiple Critical and Sensitive Periods Occur in the First Years of Life. Sensitive and critical periods in early brain development exist across sensory, cognitive, and affective domains. There are multiple critical and sensitive periods both across and within domains, as illustrated here for language development. Adversity in early life may have particularly significant, lasting consequences if it disrupts these early critical and sensitive periods of brain development. Reproduced, with permission, from [26].

Second, even within a domain there will be different critical and sensitive periods. For example, there are multiple critical/sensitive periods for language [26].

Considering Critical Period Plasticity in the Context of Adversity

We wish to make several points to clarify the association between adversity and critical period plasticity. First, adversity is not itself an expectable experience that the brain prepares for. For example, the brain does not expect exposure to domestic violence. Adversity reflecting absent or impoverished specific expectable experiences clearly influences critical period inputs, but the adversity is not the expected substrate. Moreover, critical periods are inherently specific to particular types of experience and particular neural circuits [26,67]. However, many types of adversity reflect complex exposures (e.g., poverty, malnutrition) that can impact multiple critical periods across multiple domains (e.g., co-occurring language and attachment critical periods) and across development (hierarchical language critical periods). Thus, there is unlikely to be one narrow window when these adverse experiences affect a single neural target. Indeed, the ability to exert widespread effects on the brain (and multiple critical periods) is part of what makes adversity, such as poverty or malnutrition, so deleterious to development.

Second, adversity acts on critical period processes. The extent to which adverse experiences activate biological mediators, like glucocorticoids or oxidative stress, reduces plasticity during critical periods or prolongs plasticity afterwards, respectively (e.g., [68–70]). Other changes are adversity specific. For example, threat experiences appear to accelerate critical period timing, whereas deprivation in certain domains (e.g., vision, such as cataracts in newborns) causes timing delays [17,71,72]. Thus, adversity exerts powerful effects on development, in part because it impacts both the expectable experience substrates of critical periods and the critical period mechanisms themselves.

Third, adversity that occurs in the context of critical periods is also potent because it is more likely to have lasting effects on brain function and behavior than adversity following critical periods.

Indeed, critical periods 'close' via molecular brakes (e.g., perineuronal nets, myelin) that actively dampen plasticity to stabilize and protect experience-driven learning from future insults like adversity [67]. That is, in the context of healthy development, these protective brakes reduce future vulnerability to adversity, as experiences of any kind may only minimally impact brain circuitry. However, in the context of adversity that occurs during critical periods, deleterious effects are similarly preserved and 'locked in' brain circuit function. Plasticity brakes then prevent future experience from rescuing function effectively. This shift in developmental priorities from plasticity to stability is thus a double-edged sword with regard to adversity experiences.

A High-Level Summary of the Effects of Adversity

We now consider the empirical evidence that early adversity can have enduring effects on human development. Countless studies have demonstrated an association between exposure to early, adverse life events and later maladaptive outcomes, with sequelae spanning a broad number of developmental domains. What follows is a cursory summary of some of the main findings.

Biological Hazards

There is a host of biological hazards that can disrupt healthy development. Examples of two hazards that are particularly problematic among children growing up in many parts of the world include malnutrition (from an insufficient nutritional environment) and inflammation (e.g., from unsanitary environments, for review, see [29]). The literature regarding the effects of malnutrition is ample, and the following are intended just as illustrative examples. There is evidence from human postmortem studies that 3- to 4-month-old infants who are malnourished show reduced dendritic growth in the primary motor cortex [30]. In addition, adults who experienced famine during gestation exhibit white matter (WM) hyperintensities over the entire cerebrum. One hypothesis regarding the underpinnings of such changes is that famine may lead to an inadequate supply of the nutrients required to sustain and replace catabolized myelin and gliosis after myelin loss [31]. There is histological evidence from malnourished juvenile rodents of an association between undernutrition and reduced cortical synaptic density and neuronal loss and alterations in callosal connections, likely caused by reduced neuron proliferation and changes in myelination and synaptic pruning [32–34]. The neuronal and volumetric changes in the brain associated with undernutrition may lead to poor cognitive outcomes [35].

Turning specifically to macronutrient deficiencies in children (for review, see [36]), even viewed through the coarse lens of body mass index (BMI), deleterious effects on brain development have been observed. For example, using functional magnetic resonance imaging (fMRI), van Meer *et al.* [37] have reported that as BMI increases, activation in the dorsolateral prefrontal cortex decreases. In terms of micronutrients, deficiencies in a large number of vitamins and minerals have been found to lead to perturbations across multiple levels of brain development (for review, see [38]). An extensively studied single nutrient deficiency is iron, which is known to influence myelination early in life (e.g., [39]) and impact the functioning of the default mode brain network in adults [40].

Inflammatory processes brought about by hazards, such as poor sanitation and unclean water, have also been linked to poor developmental outcomes. For example, higher levels of inflammation in the first few years of life are associated with reduced scores on the Bayley Scales of Infant Development (e.g., [41]). At the level of the brain, both increased inflammation and adversity generally are associated with decreases in the amplitude of the visual evoked potential [42] and changes in functional networks, derived from the electroencephalography (EEG), that underpin social information processing [43].

Psychosocial Hazards

Psychosocial hazards include a plethora of events, such as lack of adequate caregiving, poverty, and maltreatment. A great deal of work has reported associations between psychosocial hazards and a variety of developmental outcomes. At the behavioral level, for example, higher levels of adversity are associated with problems in learning and memory, which in turn may be related to higher rates of academic failure (see [8,22,44–49]). Similarly, higher levels of adversity (particularly neglect) are associated with atypical patterns of social-emotional development and higher rates of psychopathology [45,50], and in stress reactivity [4]. Many of these behavioral sequelae appear to be mediated by a variety of changes in the brain, such as increased/decreased cortical volume [51,52], increased/decreased cortical thinning [12,53], perturbations in WM integrity [54–56], and increased/decreased brain activity [57,58].

The Intersection of Biological and Psychosocial Hazards

Although there is a long history of attempting to examine the differential effects of different types of adversity, the reality is the vast majority of children are exposed to multiple and concurrent forms of adversity [23,59,60]. A case in point is work our lab is conducting in an urban slum in Dhaka, Bangladesh (see [61]). These children are often exposed to very high levels of both biological and psychosocial hazards, including chronic inflammation, diarrheal disease, malnutrition, maltreatment, poverty, and exposure to domestic violence. Across a series of studies we have demonstrated that this constellation of factors is associated with reduced brain volume [62], reduced functional activation of various resting state networks [62], reductions in the amplitude of the visual evoked potential [42], an increase in the functional brain networks associated with social information processing [43], and reductions in brain metabolism in response to social and nonsocial events [90].

Strategies to Parse the Effects of Adversity on Development

Given this robust literature linking early adversity with lasting impacts on development, a question that is currently receiving considerable attention empirically is how early adversity becomes neurobiologically embedded. Figure 4 complements the mechanisms highlighted in Figure 2 by illustrating a potential general model of **biological embedding** and sequelae across the lifespan. How may these conceptual models of biological embedding be translated into productive empirical strategies? At the level of the brain, it is well established that certain regions and circuits are targets for different types of adversity and have different maturation trajectories; so empirical studies must carefully consider adversity type and timing in the context of specific brain targets' development. For example, receptors for circulating glucocorticoids in the hippocampus make this particular structure vulnerable to chronic early stress [73,74]; as a result, there are now multiple studies that indicate that children who are maltreated [75,76] or adults with a history of maltreatment in childhood [77–79] show reductions in hippocampal volume and perform more poorly on tests of declarative and working memory [80,81]. We suggest two additional empirical approaches to parse the complex ways that adversity becomes biologically embedded in brain development.

New Statistical Frameworks

First, given the prevalence of co-occurring types of adversity in development, it may be advantageous in future research to take an approach that accounts for these multiple exposures as environmental mixtures. **Mixture models** facilitate identifying how different types of adversity interact and generate synergistic effects on development. Such an approach has already been successfully implemented in the context of environmental toxicology, to model complex effects of toxin mixtures [63,64]. A broadening of the mixture framework for combinations of adverse experiences across biological and psychosocial hazards may thus provide additional insight into the effects of adversity under the conditions most frequently experienced in development.

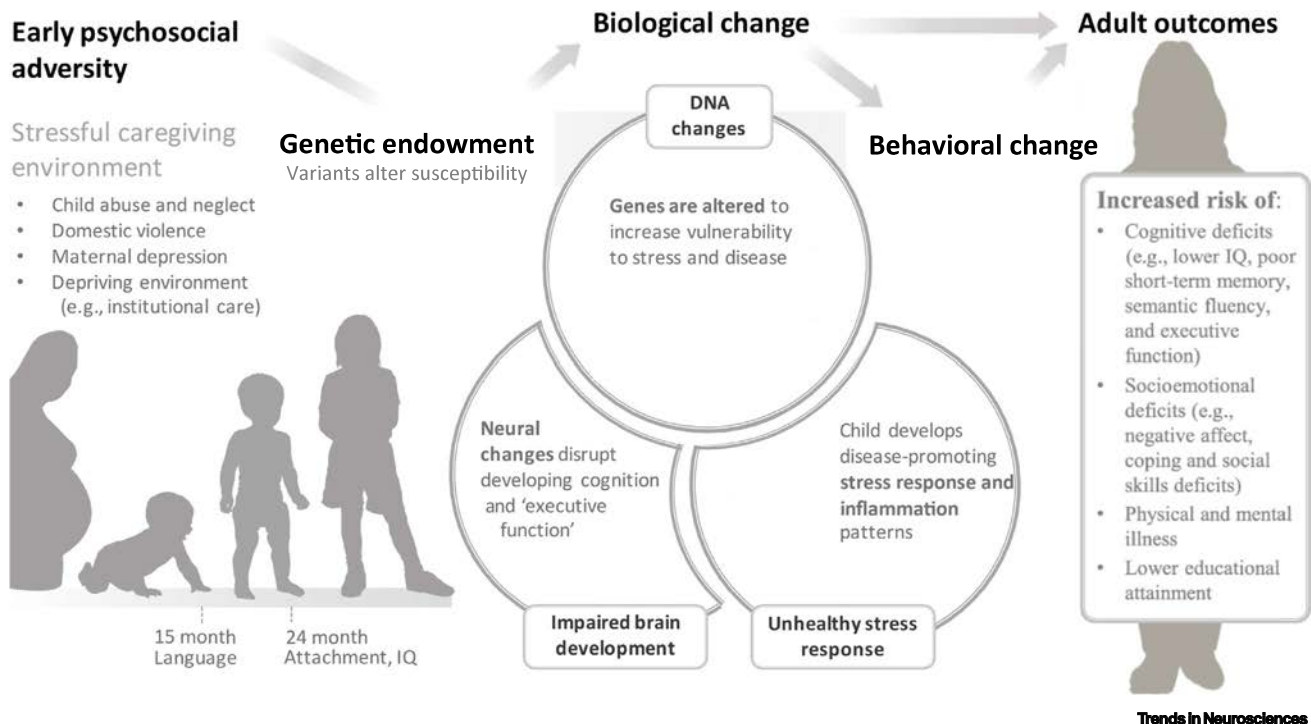


Figure 4. Sequelae of Adverse Experiences. Illustration of the consequences of early adverse experience across development (here for the psychosocial hazard type of adversity). Adverse psychosocial hazards in early life co-occurring with critical and sensitive periods to encode psychosocial experiences (e.g., language and caregiver attachment) interact with genetic profiles to produce biological and behavioral changes across development that together lead to a variety of detrimental outcomes persisting into adulthood. Adapted from [1].

Coordinated Cross-Species Approaches

Second, given the significant, enduring effects of adversity that occurs during critical periods, we advocate that future research addressing the question of neurobiological embedding of adversity would benefit from a central focus on critical period processes via coordinated cross-species studies (such as has been done in the context of autism, where the visual evoked potential has been used in human children with Rett syndrome and in MECP2 mice [91]). Importantly, critical periods are carefully orchestrated processes at the molecular level. For example, critical period initiation is regulated by both molecular pacers, which inhibit critical period initiation to prevent precocious plasticity [e.g., polysialylated neural cell adhesion molecule (PSA-NCAM)], and triggers that promote critical period plasticity [e.g., brain-derived neurotrophic factor (BDNF), γ -aminobutyric acid (GABA)-ergic development] (see [67]). Moreover, manipulations (including adversity-related changes) of these molecular regulators are so powerful that they can shift critical period timing, prevent critical periods from opening, and even reopen critical periods in the adult brain [67,82–84]. However, these molecular-level processes are difficult to observe in human neurodevelopment. Thus, to fully understand how adversity becomes biologically embedded, it is necessary to coordinate human behavioral and neuroimaging studies with those in animal models.

Parallel studies across species, to examine the biological embedding of adversity, offer several advantages. Insights from molecular-level studies in animal models may identify new neural targets (e.g., a prefrontal cortex critical period [85]) or critical period modulators [e.g., selective serotonin reuptake inhibitors (SSRIs), opioids, general anesthetic drugs] that can be studied in human development [83,84,86]. Animal model experiments may also offer therapeutic solutions

for adverse experiences in humans, as with the treatment for amblyopia in the visual domain [87]. Lastly, the timing and nature of adversity in animal models can be manipulated in a controlled manner to complement the natural experiments of adversity exposure in humans [88,89].

Concluding Remarks

Epidemiological studies dating back several decades advanced the idea that early adversity is associated with compromised neural and psychological outcomes. Recent work in neuroscience has begun to shed light on how a violation in experience-expected development during critical periods of brain development accounts for altered developmental outcomes. Not surprisingly, many questions remain unanswered (see Outstanding Questions). Moving forward, we advocate that this critical period approach will be just as important for an interventionist agenda. Specifically, interventions informed by our knowledge of how and when critical periods unfold in the context of adversity may leverage that critical period plasticity to redirect development along a typical trajectory. Moreover, these interventions, which can often be seen by themselves as enriched experiences, can shed additional light on developmental plasticity and critical period mechanisms. Thus, critical periods provide a framework for the synthesis of basic neuroscience and translational interventions in the context of early life adversity, and for development of new interventional strategies that are urgently needed to address the clinical and public health repercussions of adversity.

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Outstanding Questions

How do genetic variants interact with environments and developmental timing to influence critical periods, and in so doing confer risk/protection from adversity?

Which critical period mechanisms, in the context of adversity, generalize or differ between animal models and human neurodevelopment, and across different circuits within the human brain (e.g., sensory vs. associative cortex)?

How may simulations of the effects of adversity using computational approaches, without the constraints of human and animal studies, improve our understanding of how adversity becomes neurobiologically embedded?

In considering the development of new interventions for individuals exposed to early adversity, the question arises as to the most beneficial approach – targeting specific behaviors or trying to manipulate brain circuitry itself?

Is it possible to lift the molecular brakes that impact critical period closure noninvasively to target specific circuitry and behaviors, or are the tools too coarse such that the entire brain is impacted? Under what conditions, if any, would it be advisable to lift these molecular brakes?

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