Dimensions of Early Experience and Neural Development: Deprivation and Threat

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Abstract

Over the past decade, a growing area of research has focused on adverse childhood experiences (ACEs) and their impacts on neural and developmental outcomes. Work in the field to-date has generally conceptualized ACEs in terms of exposure to stress while overlooking the underlying dimensions of environmental experience that may distinctly impact neural development. We propose a novel framework that differentiates between deprivation (absence of expected cognitive and social input) and threat (presence of a threat to one’s physical integrity). We draw support for the neural basis of this distinction from studies on fear learning and sensory deprivation in animals to highlight potential mechanisms through which experiences of threat and deprivation could come to effect neural structure and function in humans.
research. We highlight pathways beyond the most commonly hypothesized mechanism of stress exposure to suggest additional ways in which ACEs influence brain development. Our aim is not to comprehensively review existing evidence on ACEs and neural development in humans or animals, but to provide a conceptual framework to guide future research.

The long-term negative effects of ACEs on developmental outcomes have been documented for decades. This research historically focused on single types of adversity, such as abuse and neglect. Recent studies have examined associations between number of ACEs and developmental outcomes,\(^4\) based on evidence that different types of ACEs frequently co-occur.\(^1\) An unintended consequence of this approach has been an oversimplification of the boundaries between distinct types of environmental experience. One example of this problem involves use of the term “early-life stress” (ELS), which is used to refer to disparate experiences ranging from institutionalization to maternal depression and marital conflict,\(^5\),\(^6\) and obscures differences between these experiences that are likely to have important implications for understanding their impact on neural development. Characterizing underlying dimensions of environmental experience associated with diverse forms of adversity is critical for identifying their distinct effects on neural development, an essential first step in identifying mechanisms linking ACEs to developmental outcomes.

Here we propose a novel conceptual framework for studying the effects of ACEs on neural development. The central distinction we make is between experiences of deprivation and threat (Table 1). We suggest that these dimensions differentially influence neurodevelopment. We do not propose that exposure to deprivation and threat occur independently for children, as many ACEs co-occur. Instead we propose that they can be measured separately (Figure 1) and have unique effects on neurodevelopment. Below we separately describe deprivation and threat. Within each section, we first review mechanisms of neural development from animal neuroscience and describe how deprivation and threat influence these mechanisms. Next, we highlight emerging work in humans examining the neural consequences of ACEs. We end by proposing directions for future research that will help to determine the utility of our proposed framework.

The contribution of this perspective within the larger literature on ACEs and neurodevelopment is to highlight the importance of conceptualizing and measuring underlying dimensions of environmental experience reflected in frequently studied exposures, such as abuse, neglect, and poverty, because those dimensions may differentially influence neural outcomes. Critically, because fine-grained measurement of these dimensions has not been undertaken in human studies of neurodevelopment and because prior studies have focused on specific types of exposure (e.g., abuse) often without measuring or reporting co-occurring exposures (e.g., neglect), any conclusions regarding the consistency of existing human work with our proposed framework are necessarily tentative. Moreover, some exposures inherently involve high degrees of both deprivation and threat. For example, institutionalization involves the complete absence of an attachment figure in early development,\(^7\) an experience that involves not only deprivation in expected inputs but also can represent a significant threat to survival for an infant. Importantly, we do not suggest that deprivation and threat are the only dimensions of experience that are important or that all ACEs can be conceptualized solely along these dimensions. Rather, we propose...
that these are two dimensions of experience that have not previously been differentiated with regard to their distinct influences on neural development.

**Deprivation**

The dimension of deprivation refers to the absence of species- or age-expectant environmental inputs, specifically a lack of expected cognitive and social inputs. We argue that the animal neuroscience literature examining the effects of sensory deprivation on sensory cortex development can be used as a model for understanding the neural consequences of deprivation in complex cognitive and social inputs in humans. Specifically, we suggest that an early environment without cognitive enrichment will yield a neural structure designed to deal with low complexity environments. Thus exposure to cognitive and social deprivation in children would result in: a) age-specific reductions in thickness and volume of association cortex, due in part to early over-pruning of synaptic connections, lower numbers of synaptic connections, and reduced dendritic branching; and b) reduced performance on tasks that depend on these areas (e.g., complex cognitive tasks). Reductions in cortical thickness should be most pronounced in regions of association cortex that are recruited for processing complex cognitive and social inputs, including prefrontal cortex (PFC), superior and inferior parietal cortex, and superior temporal cortex.

**Insights from animal models**

A central principal of neuroscience, developed and elaborated over the last half century, is that early experience shapes brain structure and function through pruning of synaptic connections in the central nervous system (CNS). Decades of work have documented that CNS development contains two distinct phases of synaptic growth: proliferation and pruning. Synaptic proliferation occurs in a period beginning during the third trimester, peaking three months after birth, and ending before the second year of life.\(^8,9\) During this period, there are rapid increases in the ratio of asymmetrical to symmetrical synapses, synaptic density, and total number of synapses.\(^10,11\) Following proliferation, a period of pruning of synaptic connections occurs and continues for an extended period through childhood and adolescence. In humans, synaptic elimination occurs earlier for primary sensory cortex and later for association cortex, although the final density of synapses in adulthood across cortical areas is not different.\(^8,10\) Pruning is dependent on co-activation: as two cells co-activate, the association between them strengthens, trophic factors are transmitted, and it becomes more likely that the connection will persist. The emergent system reflects the relative effectiveness of various pathways, theoretically yielding the most efficient system for the environment in it developed.

Early work on the effect of experience on neural development examined the effect of visual deprivation on visual cortex structure and function through direct manipulation of visual input. This work documents that visual deprivation early in development leads to irreversible changes in the structure and function of primary visual cortex resulting from a radical reduction in synapses (see Figure 2 for details). A second literature has investigated the impact of more general deprivation exposure. Global deprivation due to single rodent housing early in development—associated with decreased visual, auditory, and social inputs—results in widespread decreases in dendritic arborization, spines, neuronal depth and
cortical thickness. These changes are at least partially reversible through exposure to enriching, cognitively-stimulating environments following deprivation. In sum, there is evidence from the animal literature that decreases in environmental input during development within a single modality (e.g., vision) decreases dendritic arborization and number of synapses in corresponding sensory cortex and across multiple modalities (e.g., global deprivation) results in similar changes that are widespread throughout the cortex.

Insights from human studies

Given observed changes in cortical structure following sensory deprivation in rodents, cognitive and social deprivation in humans is likely to result in reductions in cortical thickness. These reductions are likely to be most pronounced in association cortex, because these regions develop and are influenced by environmental inputs for the longest period of time, and result in deficits in cognitive and social functions reliant on these regions of association cortex (e.g., language, executive function, spatial navigation, social cognition). As noted above, it is difficult to garner conclusive evidence for this hypothesis from the current literature given the way that ACEs have been measured and reported in existing studies. However, studies of children reared in institutional settings or exposed to neglect provide an opportunity to examine patterns of neural structure and function following exposure to environments that are clearly characterized by deprivation. In these environments most children will experience reduced and low quality cognitive (e.g., language exposure) and social (e.g., caregiver interactions) inputs. Studies examining neural structure in children exposed to these types of deprived environments observe reductions in cortical thickness in association cortex, disruptions in PFC function, and declines in associated cognitive functions. Other environments, such as poverty, are not inherently characterized by deprivation, (i.e., it is possible to be poor and to have typical exposure to cognitive and social inputs) but serve as a marker for a greater likelihood of deprivation in exposure to enriching and cognitively complex environments. Poverty has also been associated with reductions in cortical thickness in PFC, disruptions in PFC function, and declines in associated cognitive functions.

Threat

In contrast to the proposed impact of deprivation, we suggest that early threat exposure is associated with changes in neural circuits that underlie emotional learning, including the hippocampus, amygdala, and ventromedial PFC (vmPFC). Specifically, early threat exposure is associated with: a) changes in adult hippocampal morphology and function, including reduced dendritic spines and arborization and poor hippocampal function in learning and memory tasks; b) changes in amygdala function due to novel pairing of threat cues with previously neutral stimuli and heightened salience of emotional information, resulting in elevated amygdala activation to emotional stimuli and increased vigilance and attention to threat-related cues; and c) under-recruitment of vmPFC due to stronger representation of conditioned fear than extinction memories, resulting in reduced vmPFC thickness, low vmPFC recruitment during extinction recall and other types of emotional processing, and low structural and functional connectivity of vmPFC with amygdala and hippocampus.
Insights from Animal Models

Fear is a defensive mechanism that promotes survival. The neural circuitry underlying fear learning is well-characterized in animals; detailed reviews can be found elsewhere.\textsuperscript{30,31} Fear learning occurs when a previously innocuous stimulus is paired with an aversive stimulus, such that the neutral stimulus comes to elicit the behavioral and neurobiological responses associated with the aversive stimulus. This learning happens automatically, allowing threats to quickly elicit defensive responses. The amygdala is necessary for acquisition and expression of conditioned fear, and the hippocampus is involved in fear acquisition for complex stimuli.\textsuperscript{32} Learned fear generally abates with the passage of time as a result of extinction learning, although extinguished fear can be re-activated through a variety of processes, including exposure to novel threats.\textsuperscript{33} Successful fear extinction involves recruitment of the vmPFC, which is required for retrieval of extinction learning, resulting in inhibition of the amygdala and dampened fear expression.\textsuperscript{34}

Exposure to threats early in development alters neural circuitry underlying fear learning. Here we focus on fear-eliciting paradigms, including shock, restraint, predator odor, and minimal bedding, which results in erratic, rough maternal care.\textsuperscript{35} We do not review maternal separation paradigms, because they conflate dimensions of threat and deprivation. Early threat exposure results in lasting changes in hippocampus and amygdala structure and function. Specifically, early threat leads to reduced dendritic length and branching in adulthood, blunted long-term potentiation in the hippocampus, and impairments in hippocampus-dependent learning and memory,\textsuperscript{36-40} including impaired contextual fear learning and extinction of context-dependent fear.\textsuperscript{41-43} Early threat also predicts dendritic atrophy in vmPFC and poor synaptic transmission between vmPFC and hippocampus.\textsuperscript{43} In the amygdala, early threat is associated with increased dendritic spines, elevated basal activity and response to novel or stressful tasks, deficits in inhibitory pathways regulating amygdala activity, and widespread changes in gene expression.\textsuperscript{43-46}

Insights from human studies

In rodents, early exposure to threat results in stable changes in the neural systems underlying fear learning. Thus, in humans, we expect that early threat exposure will be associated with parallel changes in fear learning and in the structure and function of the neural systems that support emotional learning: the hippocampus, amygdala, and vmPFC. Existing studies of children exposed to threatening environments, including physical and sexual abuse, domestic violence, and other violent trauma—which share the characteristic of being significant threats to survival—provide an opportunity to evaluate associations of threat with neural circuits underlying fear learning. Consistent with animal findings, early threat exposure is associated with: a) reduced hippocampal volume in adulthood but not childhood;\textsuperscript{47,48} b) poor hippocampal function on learning and memory tasks;\textsuperscript{49} c) elevated amygdala reactivity to threatening stimuli (e.g., angry faces);\textsuperscript{50,51} d) attention biases that facilitate the identification of threats;\textsuperscript{52} e) reduced vmPFC volume,\textsuperscript{53,54} and f) reduced resting-state amygdala-vmPFC connectivity.\textsuperscript{55} Importantly, threat exposure often co-occurs with deprivation (e.g., neglect), making it impossible to conclude that these patterns are specifically the result of threat.

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**Recommendations for Future Research**

The exposures that give rise to experiences of deprivation and threat co-occur at high rates in children and adolescents.\(^1\) This co-occurrence has generated many of the methodological and conceptual challenges in identifying dimensions of experience that influence specific aspects of neural development. One way of testing the pathways proposed here is to identify children who experience only one form of adversity. However, finding such a sample is not only difficult, but also would not accurately represent the population of children exposed to ACEs. Instead, we propose that future studies examining neural development in children exposed to ACEs should measure these underlying dimensions of experience, in addition to the traditional categories of exposure, to determine whether deprivation and threat are indeed uniquely associated with the patterns of neural development proposed here. We have focused on two dimensions of experience that are particularly likely to impact neural development, but there are undoubtedly others (e.g., chaos or unpredictability and loss). Future studies should identify other key dimensions of experience and characterize their impact on the developing brain.

Despite consistencies in the neural circuitry underlying fear learning in animals and humans, there is also a surprising lack of human research on how early threat influences fear learning across development. This represents a critical area for future research. Future studies should also attempt experimental manipulation of specific aspects of experience (e.g., increasing enriching cognitive experiences for institutionalized children) to identify the causal pathways through which environmental experience shapes neurodevelopment.

**Concluding Remarks**

We propose a novel conceptual framework for understanding the impact of ACEs on neural development. Our approach argues that the field must move beyond the prevailing approach of examining the impact of complex and co-occurring exposures on brain development to distilling those complex experiences into their core underlying dimensions. Two important dimensions that appear to have distinct effects on neural development are deprivation and threat. Existing evidence from human studies is consistent with animal work examining how deprivation and threat influence neural development, although additional work is needed to determine the utility of our proposed framework. We believe that such an approach will improve our understanding of how atypical experience influences the developing brain and, ultimately, confers risk for adverse developmental outcomes.

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Highlights

- New framework differentiates between depriving and threatening adverse childhood experiences
- Deprivation, or the absence of expected inputs, impacts proliferation and pruning
- Threat, or the presence of atypical trauma experiences, impacts fear learning
- These patterns can be observed in humans and animals
Importantly, we argue that threat and deprivation are dimensions of experience that can be measured among children exposed to a wide range of ACEs, both those that occur in isolation (e.g., a single incident of community violence exposure) and those that are co-occurring (e.g., physical abuse and physical neglect). We use the term complex exposures to refer to experiences that in most cases involve aspects of both threat and deprivation.

Figure 1. Dimensions of threat and deprivation associated with commonly occurring adverse childhood experiences (ACEs)

1 Importantly, we argue that threat and deprivation are dimensions of experience that can be measured among children exposed to a wide range of ACEs, both those that occur in isolation (e.g., a single incident of community violence exposure) and those that are co-occurring (e.g., physical abuse and physical neglect). We use the term complex exposures to refer to experiences that in most cases involve aspects of both threat and deprivation.
Figure 2. The effects of early visual deprivation on cortical structure in animals and humans

Early work identifying the effect of deprivation on neural structure and function comes from investigations of the effect of sensory deprivation. **A.** This figure shows decreased synapses visual cortex of kittens raised in complete visual deprivation, or “dark rearing” (DR220) from post-natal day 70 – 220. This decrease in synapses is accompanied by a decrease in thickness compared to typically reared kittens (N220; reproduced with permission from O’Kusky, 1985a). **B.** Similarly, in humans, congenital blindness is associated with less volume in visual cortex compared to sighted or late-blind participants (reproduced with permission from Leporé et al., 2010).
Table 1

Definitions of Threat and Deprivation

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<th>Threat</th>
<th>Deprivation</th>
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<td>Experiences of threat involve the presence of an atypical (i.e., unexpected) experience characterized by actual or threatened death, injury, sexual violation, or other harm to one’s physical integrity. Our definition of threat is consistent with the definition of a traumatic event in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5).</td>
<td>Experiences of deprivation involve the absence of expected environmental inputs in cognitive (e.g., language) and social domains as well as the absence of species- and age-typical complexity in environmental stimulation.</td>
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