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Neurodevelopmental Optimization after Early Life Adversity: Cross Species Studies to Elucidate Sensitive Periods and Brain Mechanisms to Inform Early Intervention

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Abstract

Human brain development is influenced by early-life experiences, particularly during sensitive periods, with impact on cognitive and emotional outcomes. Understanding how the timing and the nature of such experiences (including adversity, trauma and enrichment) governs their influence on brain organization is crucial for harnessing key environmental factors early in life to enhance brain development. Here we synthesize findings from human and animal studies focusing on sensitive periods and their regional and circuit specificity, and highlight the challenge and power of such cross-species approaches for informing the 'next steps' in optimizing cognitive and emotional health in developing children. We propose designs for neurodevelopmental optimization research programs utilizing randomized enhancement trials in early childhood to inform public health strategies on prevention and early intervention.

Keywords

sensitive periods; developmental enhancement

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Early Experiences and Vulnerability to or Protection from Mental Illness

The finding that human brain development is strongly influenced by the environment, particularly during early-life sensitive periods, has important global mental and public health implications. An increasing body of empirical data from human and animal studies demonstrates strong associations (in humans) and causal relations (in animals) between early environmental factors and brain maturation [1–7]. Early-life experiences are known to play an important role in influencing cognitive and emotional outcomes in humans through their impact on neurodevelopment. There is also robust evidence for the strong effects of early adversity on risk for psychopathology [8]. Conversely, a large body of work demonstrates the central importance of early-life nurturance for healthy social and emotional development [9, 10]. Building on this work, we address how empirically informed timing of preventive or developmentally enhancing interventions, may be used to achieve larger and more sustained neuroprotective effects from the negative consequences of adversity. To accomplish this, a more comprehensive understanding of how environmental factors influence specific aspects of the complex machinery of brain development is required. Data informing these processes from animal, human and cross-species studies would facilitate harnessing of modifiable factors early in life to support healthier brain development as part of a proactive practice of optimizing child development [11, 12].

We propose here a program of research as the foundation for a new science of neurodevelopmental optimization. Building on causal inferences and mechanistic data from the animal-models literature, we posit that there is a need to obtain a nuanced empirical picture of how the timing and type of adverse exposures impacts specific aspects of neurodevelopment and the correlated cognitive and emotional capabilities in young children. We highlight the potential of caregiving interventions that enhance warmth, sensitivity and predictability as well as child cognitive and emotional skill building programs delivered at key sensitive periods. These strategies carry a promise to nourish neurodevelopment, mitigate the risk for psychopathology, and enhance human potential.

Key Considerations for Neurodevelopmental Optimization: Timing and Specificity

Information about the nature, timing, regional specificity, and mechanisms of environmental factors that influence the trajectory of brain maturation is necessary to enable neurodevelopmental optimization programs. Timing relates to whether there are sensitive periods in the development of specific brain regions and circuits subserving specific emotional and cognitive functions, during which children might be either particularly vulnerable to environmental adversity or receptive to enhancement. Regional specificity refers to whether environmental effects are broad, related to general factors that influence brain development as a whole, or more specific to particular brain regions and circuits. Identifying regional specificity will inform the nature of enhancements targeting specific regions or circuits and their cognate functions. Specificity of environmental factors refers to the degree to which different types of early adversity (e.g., trauma/abuse, deprivation, unpredictability/chaos, poverty, etc.) and/or enhancement (caregiver support, cognitive stimulation, enriched diet or sleep) have similar or different effects on brain development

both globally and regionally. Empirical mapping of these patterns is necessary to inform the type and timing of the most effective optimization strategies.

Sensitive Periods across Species

Whereas the brain is influenced by the environment through experience-dependent processes throughout the lifespan, sensitive periods are windows of time during which the brain is especially susceptible to these influences [13–15]. Sensitive periods allow brain architecture to be maximally informed by experience to optimize function for events expected later in life, and are well documented in both the basic neuroscience and child development literatures [13–16]. Notably, the timing and duration of sensitive periods are themselves experience-dependent [14–17].

Importantly, it is becoming evident that different brain regions and circuits have distinct trajectories of development and sensitive periods [16–19]. This information is critical to enable the translation of ground-breaking experimental studies in animals to human interventions. Whereas older work compares phases of total brain growth across species, newer studies avoid assigning a global brain age to rodents that is then equated with human age. Rather, maturation of specific brain circuits and regions is compared [18, 19]. For example, for hippocampal formation development, the developmental state of a human full-term neonate might be equated with that of a 5–7 day Sprague Dawley rat, with infancy encompassing the second week of life in the rodent [18]. A similar approach to identifying homologues in brain age across humans and rodents has been recently employed for the reward circuit, including ventral striatum / nucleus accumbens, ventral tegmental area and interconnected amygdala nuclei and cortical regions, again suggesting homology between the middle first postnatal week in the rodent and the human neonate (for details see Table 1 in ref [19]).

Sensitive periods for specific regions and circuits in animals and to a lesser extent in humans are being delineated. Such studies attest to the importance of timing of early life experiences, because the ages of sensitive periods for distinct regions or circuits differ [15–17, 20]. For example, the sensitive period for the effects of light signals on visual system organization in the kitten spans the first postnatal weeks [20]. In humans, “lazy” or otherwise deprived eye during the first postnatal months provokes enduring loss of normal function in primary visual cortex and life-long deficits in vision (amblyopia), suggesting homologous timing-sensitive plasticity processes during sensitive periods across species [14].

The sensitive period for the patterns of tones on tonotopic organization of the auditory cortex in the mouse involves postnatal days 7–14. In rodents, the sensitive period for early-life adversity seems to include the first two postnatal weeks influencing both the maturation of specific brain circuits and functional outcomes [6, 21–29]. Deprivation from maternal signals [30, 31] or chaotic unpredictable patterns of care [23–28] promote vulnerability to memory and emotional deficits.

Whereas it is not possible to directly translate sensitive periods across species, it is helpful to consider that at least some of the neurobiological mechanisms that generate sensitive periods

are likely common across mammals [14–16, 20]: The organization of brain circuits involves the generation of synaptic connections, followed by their strengthening and persistence or their pruning and elimination. It is generally believed that the first step, the recognition by pre- and post-synaptic elements of their future ‘partners’ is genetically encoded and relatively insensitive to the environment. The second stage, involving activity-dependent processes and molecular triggers such as the maturation of specific neurotransmitter systems, influence persistent versus eliminated synapses and constitutes the sensitive period. Because the timing of this second phase can be estimated in humans and rodent from the developmental trajectory of each circuit in each species, the relative timing of sensitive periods can be estimated across species [32, 33].

Artificially augmenting maternal care via ‘handling’ has been widely shown to enhance cognitive and emotional outcomes in rodents. Daily brief separations predictably promote recurrent intense barrages of maternal care behavior upon returning the pups to the cage [34], and this enrichment has consistently been shown to lead to a well-regulated response to stress, as well as enhanced memory functions [35–37], as found in other enrichment studies in animals [34, 38–41]. Accordingly, natural variation in the quantity and quality of maternal care behaviors correlates with pups’ outcomes, supporting the positive effects of extensive and consistent maternal-derived sensory input to developing rat pups on cognitive and social behaviors [22, 42].

In humans, the landmark Bucharest Early Intervention Project (BEIP) randomized institutionalized children to therapeutic foster homes and compared them to those remaining in institutional care [15]. Results suggested that the first two years of life might be the developmental period most sensitive to the negative effects of primary caregiver deprivation on later cognitive and emotional outcomes, a finding augmented by a second sample that suggests that different brain circuits have different sensitive periods, emphasizing the amygdala-prefrontal cortex circuitry [11]. However, much more work is needed to address sensitive periods in human development, and we propose the use of randomized controlled trials of discrete and targeted enhancements in early childhood that is informed by animal studies as the next most feasible and important scientific step.

Specificity of Experience Type on Neurodevelopment

Evidence of some neural specificity of types of adversity in both animals and humans is available. These types of adversity include abuse, neglect, deprivation, poverty, and unpredictability and fragmentation of parental care and environmental signals. The broader construct of adverse childhood experiences (ACEs) includes many of these factors as well as exposure to parental mental disorder and criminal behavior [43]. Notably, these forms of early adversity often co-occur, and share enhanced risk for poor neurodevelopmental outcomes, and psychiatric disorders [18, 23, 44–47]. A critical issue is whether forms of early adversity converge on the same aspects of brain structure and function, or alternatively, whether there is evidence of neural specificity to particular forms of adversity. The challenge in dissociating these diverse components of adversity in human studies, led to assessing the issue in experimental animals where paradigms have been designed to simulate distinct aspects of early-life adversity. These include separation from the dam once or chronically

[30, 31, 48–50] (for review see [24]) and simulated poverty/resource scarcity [6, 23, 25–29]. Notably, as is the case in human adversity, most of these paradigms intermingle, generating maternal stress which disrupts maternal care patterns rendering them unpredictable or abusive [6, 21, 23, 26] (for reviews see [24, 29]. Thus, assessing the selective contribution of different components of adversity on cognitive and emotional outcomes remains a significant challenge in both human and animal studies.

Specificity: which brain regions are impacted and when?

The functional consequences of early-life adversity are a result of disruption of the development of the underlying brain regions and circuits. To date, much of the literature has focused on particular brain regions, but future work will need to more clearly embed such regions in the larger networks in which they function. Many studies converge on a relation between distinct types of early adversity and hippocampal structure and function, including reductions in hippocampal volume associated with poverty [51–59], reduced maternal support [60, 61] and abuse/adverse childhood experience (ACE) [1, 4, 62]. There is also evidence for reduced amygdala volume associated with poverty [52, 53, 55, 56, 63] which may vary by age [64]. Alterations in striatum structure in relation to early adversity, often associated with deficits in reward processing, have also been reported [65, 66]. Controlled animal work supports the causal nature of such associations [11, 21, 25, 28, 30, 49, 67].

A longitudinal neuroimaging study in humans found more complex developmentally-specific interactions between the timing of experience (preschool, school age, adolescence) and both positive and negative and regional brain effects [44]. Specifically, interactions between preschool ACEs and school age maternal support were found for both hippocampus and amygdala volumes, such that school age maternal support was associated with greater volumes, only in the context of low preschool ACEs. However, for the caudate, a pattern suggesting early emerging additive reductions in caudate volume were associated independently with preschool maternal support and ACEs that were stable over time. These findings suggest that there is regional, and likely circuit, specificity to the timing of adversity and support as they influence brain maturation, providing clues for the design of future neurodevelopmental optimization strategies.

Neurodevelopmental Enhancement Programs Informed by Timing and Specificity

We aim to employ this empiric knowledge of distinct sensitive periods and generate additional information to achieve larger and more sustained neuroprotective effects from the negative consequences of adversity. To achieve this, we propose the use of focused enrichment paradigms in randomized controlled trials in early childhood. These studies should design enhancement interventions building on known sensitive periods in animal models and emerging human work and apply them to young child samples. The use of environmental enhancement that targets parenting more broadly is an important and feasible strategy that could test the importance of protections or enhancements during sensitive periods at varying ages, and most importantly targeting birth to age 5. In addition, application of enhancement that directly targets the child and augments specific emotional or cognitive skill building at different ages will elucidate sensitive periods for human cognitive and emotional development. Specifically, infants/young children facing a variety of forms of

adversity can be randomized to usual care versus enriched or stimulating settings for periods of time or enhanced parenting, at certain age periods, ideally those shown to be sensitive to particular inputs (e.g., before age two compared to later in preschool for enhanced parenting, etc.). Another design would be to expose young children to intensive training for specific cognitive and emotion skills (e.g. emotion recognition, executive function) also at specific developmental periods, and then compare them to those who do not receive the training. We suggest targeting interventions for children living in poverty or facing adversity who have primary caregivers whose support can be harnessed for such interventions as a first step. We propose to employ empirically validated early mental health interventions. One such example with large effect sizes and enduring efficacy and high feasibility is Attachment and Biobehavioral Catch Up (ABC, [68]) that is focused on enhancing early attachment. Other effective programs include child parent psychotherapy (CPP) [69], video based intervention to promote positive parenting (VIPP) [70], as well as several forms of preschool intervention Parent Child Interaction Therapy (PCIT) that have also demonstrated large effect sizes and enduring efficacy [71, 72]. These interventions can be tested at different age periods and varying “doses” with effects on brain structure and function pre and post intervention assessed. For assessing effects on brain network organization, one could employ for instance resting-state neuroimaging during sleep, and this could be augmented (or replaced) by feasible and less costly measures of neural function such as task-based EEG or Event Related Potentials. The proposed studies will inform and provide the building blocks of a new neurodevelopmental optimization approach that is pragmatic and cost-effective that could be applied broadly in public health settings.

Other broad and overall underexplored targets for enhancement of child neurodevelopment include sleep, diet and the gut microbiome. Early life adversity may disrupt these targets, which may contribute to suboptimal brain development. For example, the role of the developmental timing and quality of sleep and circadian rhythms during neurodevelopment should be further studied, as well as the possible effects of their disruption. Diet acting on brain development either directly or via alterations of the gut microbiome has increasingly been a focus of research, and emerging evidence in animal models suggests that replenishing specific micro- and macronutrient early in life may mitigate the cognitive consequences of experimentally imposed early-life adversity [73–75]. The effects of all of these modifiable environmental factors on neurodevelopment should be further clarified in terms of the nature and timing of exposures, as they represent potential pathways for timing- and context-dependent neurodevelopmental optimization.

Concluding Remarks

We propose a concept and data-driven approach to neurodevelopmental optimization to enable enhancement programs promoting optimal cognitive and emotional outcomes in early childhood. Given the greater focus to date on risk factors, relatively little attention has been given to the notion of optimization, which can be useful to those at both high and low risk. For these programs to be effective, they need to incorporate basic principles of brain development and build on experimental animal models that enable establishing causality and mechanisms (see Outstanding Questions). The proposed interventional studies in humans

could provide the foundation for large-scale, cost effective preventative approaches to mental illness.

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Outstanding Questions

1. When--during development--are the key sensitive periods for social, emotional and cognitive skills?
2. Are there specific sensitive periods and regional specificities for the effects of different types of adversity and nurturance on neurodevelopment?
3. In order to apply neurobiological information from experimental animal-models to humans, focused and concerted trans-disciplinary cross-species studies are needed. Can research programs be designed to enhance productive and cutting-edge cross-species research?
4. How can findings from both experimental models and human research be harnessed to design a neurodevelopmental enhancement program to protect children from adversities at key time periods and inform the timing of developmental enhancement in specific domains?
5. Can insights from such research efforts be applied on a broad, public- health level for prevention and early intervention strategies?

Highlights

1. Human brain development is influenced by exposure to early-life experiences, including enrichment and adversity, with cognitive and emotional consequences including vulnerability to or protection from mental illness.
2. The timing of the exposure is critical, because there are sensitive periods when vulnerability is augmented; sensitive periods may pertain also to the timing of enrichment or mitigation efforts.
3. Animal studies indicate that sensitive periods are specific for distinct brain regions and circuits, providing a timing framework for selective and insult-specific interventions.
4. Capitalizing on findings gleaned from animal-model studies and human imaging in childhood, we propose the ‘next steps’ in cross-species research towards the goal of optimizing cognitive and emotional health in developing children.
5. Neurodevelopmental optimization research should address issues including deprivation, unpredictability and insecure attachment, as well as potentially sleep, diet and gut microbiome via carefully timed randomized enhancement trials.

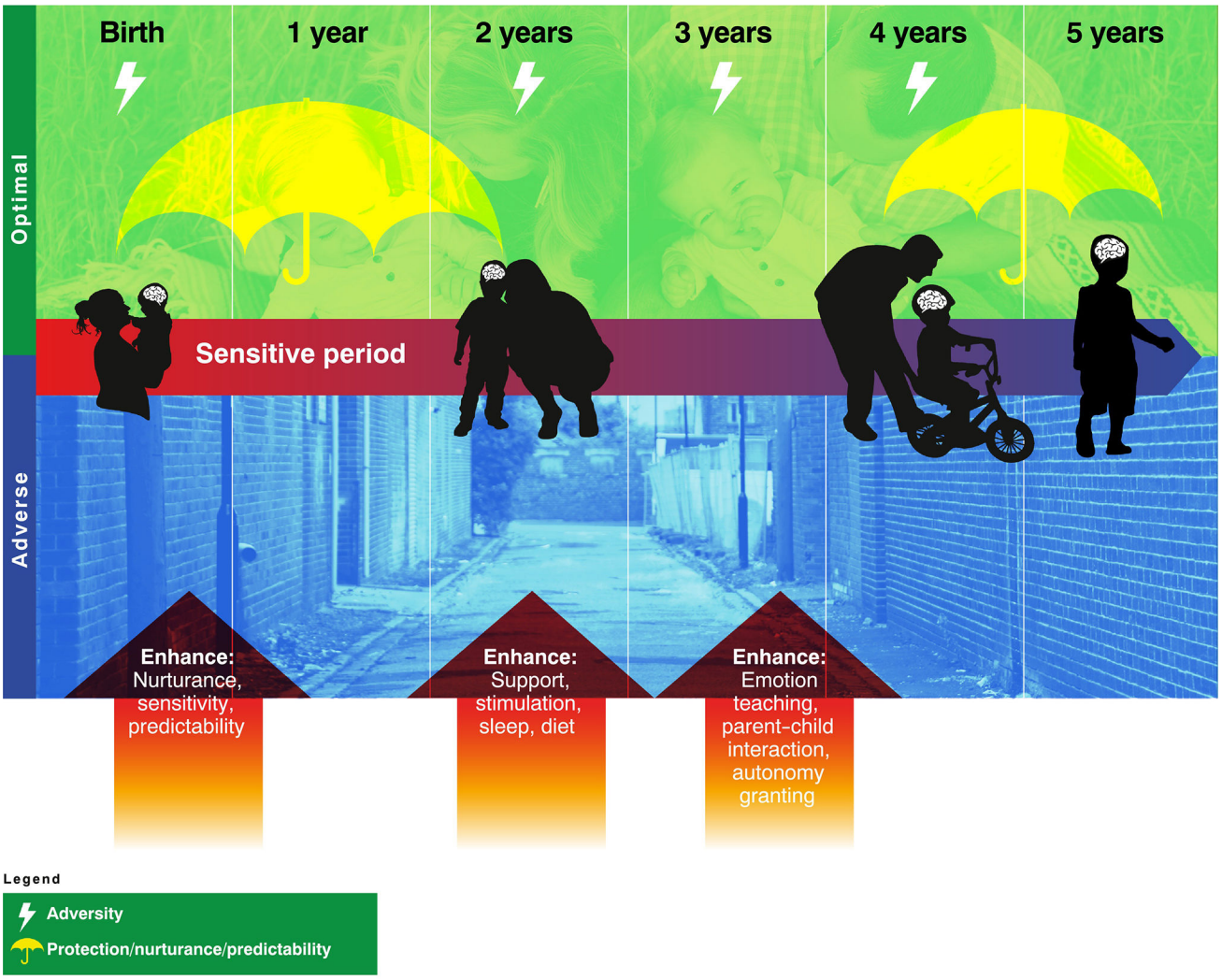

Figure 1: Factors in the Optimization of Early Childhood Neurodevelopment.

The schematic illustrates the theoretical optimization model, where umbrellas represent the specific need for protection from adversity at key timepoints (to be empirically determined) based on sensitive periods. Enhancement is applied during phases of development also based on these empirically determined periods and child's individual needs. Lightning bolts represent adversity that developing children may face. Placement of these icons in the figure are currently speculative awaiting empirical anchoring based on animal and human enhancement trials to inform the timing of sensitive periods.