Biological Psychiatry

Review

Neglect as a Violation of Species-Expectant Experience: Neurodevelopmental Consequences

Katie A. McLaughlin, Margaret A. Sheridan, and Charles A. Nelson

ABSTRACT

The human brain requires a wide variety of experiences and environmental inputs in order to develop normally. Children who are neglected by caregivers or raised in institutional environments are deprived of numerous types of species-expectant environmental experiences. In this review, we articulate a model of how the absence of cognitive stimulation and sensory, motor, linguistic, and social experiences common among children raised in deprived early environments constrains early forms of learning, producing long-term deficits in complex cognitive function and associative learning. Building on evidence from animal models, we propose that deprivation accelerates the neurodevelopmental process of synaptic pruning and limits myelination, resulting in age-specific reductions in cortical thickness and white matter integrity among children raised in deprived early environments. We review evidence linking early experiences of psychosocial deprivation to reductions in cognitive ability, associative and implicit learning, language skills, and executive functions as well as atypical patterns of cortical and white matter development—domains that should be profoundly influenced by deprivation through the learning and neural mechanisms we propose. These patterns of atypical development are difficult to explain with existing models that emphasize stress pathways and accelerated limbic system development. A learning account of how deprived early environments influence cognitive and neural development provides a complementary perspective to stress models and highlights novel pathways through which deprivation might confer risk for internalizing and externalizing psychopathology. We end by reviewing evidence for plasticity in cognitive and neural development among children raised in deprived environments following interventions that improve caregiving quality.

Keywords: Brain development, Childhood adversity, Deprivation, Early life stress, Learning, Neglect

http://dx.doi.org/10.1016/j.biopsych.2017.02.1096

The human brain requires a wide variety of experiences and environmental inputs, some during sensitive periods, in order to develop normally. The simplest demonstration of this principle can be observed in sensory systems; access to patterned light and complex sounds during the first months of life is required for normal visual and auditory function to develop. Similar sensitive periods exist for the development of more complex behaviors and competencies, including language and the formation of an attachment to a caregiver. The wide-ranging domains of functioning that require environmental input for normal development are referred to as experience expectant (1). In this review article, we examine what happens when these expected environmental inputs are absent. We present a conceptual model of how an absence of expected inputs from the environment influences learning and neurodevelopmental processes in children, and we review existing literature on youths raised in deprived early environments in light of this model. We highlight how atypical cognitive and neural development might serve as a mechanism linking environmental deprivation to psychopathology, and we end by reviewing evidence for plasticity in cognitive and neural outcomes among children raised in deprived environments following interventions that improve caregiving quality.

SCOPE OF THE PROBLEM

Neglect involves failure of a caregiver to act in ways that are necessary to meet the basic needs of a child (2–4). Neglect encompasses inadequate provision for physical needs, poor protection from harm, and failure to provide for emotional or educational needs (see Table 1) (2–4). Neglect is the most common form of maltreatment reported to child protective services in the United States (2,5). Worldwide, millions of children have lost their parents due to armed conflict, forced migration, or infectious diseases; a common response is to raise these children in institutions. Although most institutions provide for physical needs, institutional care is often characterized by limited interaction with caregivers, resulting in a failure to provide for children's emotional and developmental needs. Despite the high prevalence of neglectful early environments, the developmental consequences of neglect are understudied as compared with other forms of adversity (6).

NEGLECT AS ENVIRONMENTAL DEPRIVATION

Environmental deprivation is a central feature of child neglect and institutional rearing. This deprivation spans numerous inputs the human brain expects, often at particular points in

SEE COMMENTARY ON PAGE e49

 ISSN: 0006-3223

Table 1. Key Domains and Examples of Child Neglect

Neglect Involves Failure of a Caregiver to Provide for:	Examples
Physical Needs	Nutrition, clothing, shelter, access to medical care
Protection From Harm	Inadequate supervision
Emotional Needs	Presence of a stable caregiver, sensitive and responsive caregiving, emotional nurturance
Educational Needs	School attendance

development. Deprivation is the core feature of neglect that distinguishes it from other forms of adversity, such as trauma and abuse, where the most prominent feature is harm or threat of harm to the child. Although experiences of deprivation often co-occur with experiences of threat (i.e., abuse), the developmental consequences of deprivation and threat are at least partially distinct (7–9). Here, we focus specifically on neurodevelopmental consequences of deprivation resulting from neglect and institutional rearing.

At the most fundamental level, neglected children are deprived of a stable, sensitive, and responsive caregiver, which is a species-expectant experience. Caregivers are necessary to ensure survival in early human development by providing nutrition and ensuring safety from threats (10). Infants are born with a behavioral repertoire designed to ensure caregiver protection and proximity (e.g., crying) (11). Children develop a secure attachment when caregiving is sensitive, responsive, and predictable (12–15). Caregivers impose regularity onto children's environment by regulating sleep–wake cycles and feeding and by responding contingently to distress with physical proximity and nurturance. Neglected children are not afforded sensitive, supportive, and stable caregiving on a consistent basis. Parents with documented histories of neglect generally show low levels of emotional warmth, positive behaviors, and empathy (16–18). Neglectful families also exhibit caregiving that is irregular and unstable (17). A similar absence of emotionally supportive caregiving occurs in institutional environments, where caregiver interactions with children are infrequent and contingent responding is low (19).

Early in life, most forms of learning occur in the context of caregiver interactions. The sensory, motoric, linguistic, and social experiences provided by caregivers determine the complexity of children's environment and the degree of cognitive stimulation children receive. Caregivers regulate exposure to environmental inputs of numerous kinds, including language and auditory stimulation in the form of caregiver vocalizations, social interaction through play, and sensory and motor stimulation through physical contact and the provision of objects for children to manipulate. In some domains (e.g., language), exposure to environmental input must occur in the context of social interaction to generate learning (20,21). The absence or unavailability of a primary caregiver results in gross reductions in sensory, cognitive, and social stimulation. Indeed, reductions in cognitive stimulation, provision of learning opportunities, supervision by adults, and parent–child interactions have been observed among children who are neglected (16,18,22). Similarly, children raised in institutions experience dramatic reductions in exposure to language, less frequent and predictable interactions with adults, limited variation in daily routines and experiences, and less access to novel and age-appropriate enriching cognitive stimuli than do children raised in families (19,23,24).

Importantly, the severity of deprivation experienced by neglected children exists along a continuum. Most studies do not measure specific types of deprivation directly (e.g., degree and complexity of linguistic experiences) but rather assess the presence of neglect or institutional rearing. Determining how the neurodevelopmental mechanisms outlined below vary as a function of the severity of deprivation is a critical goal for future research.

EXISTING PERSPECTIVES

A variety of brain regions and circuits are influenced by early deprivation. The absence of a caregiver to provide protection from harm and to regulate arousal and distress represents a pervasive stressor that can produce lasting changes in emotional development. Most existing models emphasize atypical limbic system development resulting from prolonged early-life stress as a central mechanism underlying developmental outcomes associated with caregiver deprivation (25–31). Strong evidence supports this view. Children deprived of a stable and responsive caregiver exhibit high levels of insecure and disorganized attachment and atypical affective development characterized by heightened emotional reactivity, accelerated functional development of the amygdala, poor emotion regulation, and atypical stress reactivity (25,32–37). These disruptions in attachment and affective development contribute to high levels of internalizing psychopathology among children raised in deprived early environments (31,38–40).

But is this the only mechanism involved in neglect? One of the most consistent observations of neglected children is that they exhibit deficits in numerous areas of cognitive development (27,28), and these deficits are more extreme than those observed in other forms of adversity (e.g., abuse) (41). Are disruptions in limbic system development sufficient to explain these widespread cognitive effects? We argue that additional mechanisms are involved.

Deprivation as an Absence of Learning

Environmental deprivation that characterizes child neglect and institutional rearing has a pervasive and lasting influence on development. Disruptions in early learning may underlie the far-reaching developmental consequences of neglect, including those not readily explained by atypical limbic development (e.g., low cognitive ability). Children who experience neglect are raised in an environment characterized by the absence or limited availability of a caregiver, which curtails the complexity of their sensory, motor, and linguistic experiences and reduces learning opportunities.

Early deprivation constrains basic forms of learning that depend on rich sensory and social inputs early in development, including associative and implicit learning. Caregivers play a critical role in the development of these learning

processes by directing children's attention to relevant stimuli in the environment through repetitive vocalizations, facial displays, and tactile stimulation (42). Child-directed language has unique acoustic properties (43–45) that shape early learning by increasing infant attention to external stimuli and enhancing associative learning (46–48). In the absence of caregiver speech directed to the child—a feature of neglectful environments (17,19)—associative learning and implicit learning are likely to be constrained. Indeed, child-directed speech produced by caregivers with depression fails to promote infant associative learning (49) due to reduced perceptual salience of caregiver vocalizations that lack the typical acoustic properties of child-directed speech (50).

Associative and implicit learning processes are the foundation on which more complex forms of cognition and learning are built. Atypical early development of these types of learning may propagate throughout myriad domains of development, producing deficits in general cognitive abilities, language, and executive functioning. Language development relies on implicit learning of regularities in speech and their pairing with visual cues in the environment (51–56). Associative learning also provides the scaffolding for executive functioning, including conflict adaptation, response inhibition, cognitive flexibility, and attentional control (57). Early disruptions in associative learning may produce difficulties in multiple domains of executive functioning by reducing associations between goal representations and relevant environmental stimuli in a particular context.

Neglect involves reduced inputs in sensory, linguistic, cognitive, and social domains. Here we propose a common learning mechanism—constrained associative learning—that might explain the consequences of deprivation in each of these domains on cognitive development, although it is important to highlight that other forms of learning are also reduced for children who have inconsistent interactions with caregivers (e.g., imitation) and that domain-specific mechanisms (e.g., visual input producing columnar organization of visual cortex) also influence developmental outcomes. Altogether, a learning account of deprivation predicts that neglect will be associated with atypical cognitive development in many domains, including poor associative and implicit learning, global declines in cognitive functioning, and deficits in language and executive functioning.

Neurodevelopmental Mechanism of Environmental Deprivation

Early deprivation exerts profound influences on neurodevelopmental processes that are shaped by learning and experience, particularly experience-expectant processes (1). Experience-expectant refers to processes whereby the human brain expects certain inputs to acquire a skill or competency, typically during sensitive periods in development. If such inputs are present, development proceeds in a typical fashion. When a child passes through the sensitive period without such inputs, development will be compromised in those domains (58).

An overproduction of synaptic connections early in development that are pruned as a function of experience provides the biological basis for experience-expectant learning (1). Pruning is an activity-dependent developmental process that selectively eliminates synaptic connections that are used infrequently (59–61). When two cells coactivate frequently, the synaptic connection between them strengthens and becomes more efficient, resulting in long-term potentiation and increases in the density and number of dendritic spines on postsynaptic neurons. Long-term potentiation underlies numerous forms of learning, including experience-expectant learning (62,63). In contrast, when two cells coactivate infrequently, dendritic spines shrink or disappear and the synaptic connection weakens and is likely to be eliminated (64,65). Synaptic pruning is a central force in the remodeling of the brain across development in response to experience (60).

We propose that environmental deprivation hijacks the developmental process of synaptic pruning, resulting in accelerated and extreme synapse elimination (see Figure 1). Animals deprived of visual input early in development exhibit dramatic reductions in synapses, dendritic branching, and the number and density of dendritic spines in visual cortex (66–70). These changes produce measurable reductions in the thickness of visual cortex in animals deprived of visual input (70).

What about environmental deprivation that is more global? The environment of neglected and institutionally reared children is characterized by an absence of inputs and complexity across multiple domains. Animal models of global deprivation compare animals raised in isolation in an empty cage with those reared in a complex environment with access to conspecifics, toys, and novel stimuli; this type of deprivation leads to dramatic changes in synaptic organization similar to those observed in sensory deprivation but that are more widespread across the cortex. Animals raised in a deprived environment exhibit reductions in the number of synapses per neuron (71), the density of cortical dendritic spines (72), the branching and length of dendrites (73,74), and cortical thickness (75,76). These neural changes are accompanied by deficits in numerous forms of learning and memory (77–81).

Although synaptic changes are a primary mechanism of experience-dependent plasticity, poor white matter integrity resulting from reduced myelination and axon sprouting also occurs in animals exposed to early environmental deprivation, particularly in the posterior corpus callosum (82) and prefrontal cortex (PFC) (83). Other mechanisms are also involved, including changes in epigenetic regulation (84), although we do not review those mechanisms here.

Animal models of global deprivation resemble neglect in that they reflect an environment characterized by a lack of complexity and an absence of sensory, cognitive, and social stimulation. Findings from animal models provide clues about how deprivation will influence learning and neural development in children. Specifically, we expect deprivation to be associated with exaggerated synapse elimination, reduced dendritic branching and density throughout the cortex, and reduced myelination in the corpus callosum and PFC; although these molecular processes cannot be studied directly in humans, they should produce reductions in cortical thickness (see Figure 2) and fractional anisotropy measurable by magnetic resonance imaging.

NEURODEVELOPMENTAL CONSEQUENCES OF ENVIRONMENTAL DEPRIVATION

Does existing evidence support a learning model of environmental deprivation? In this section, we review evidence on the association of environmental deprivation with domains of

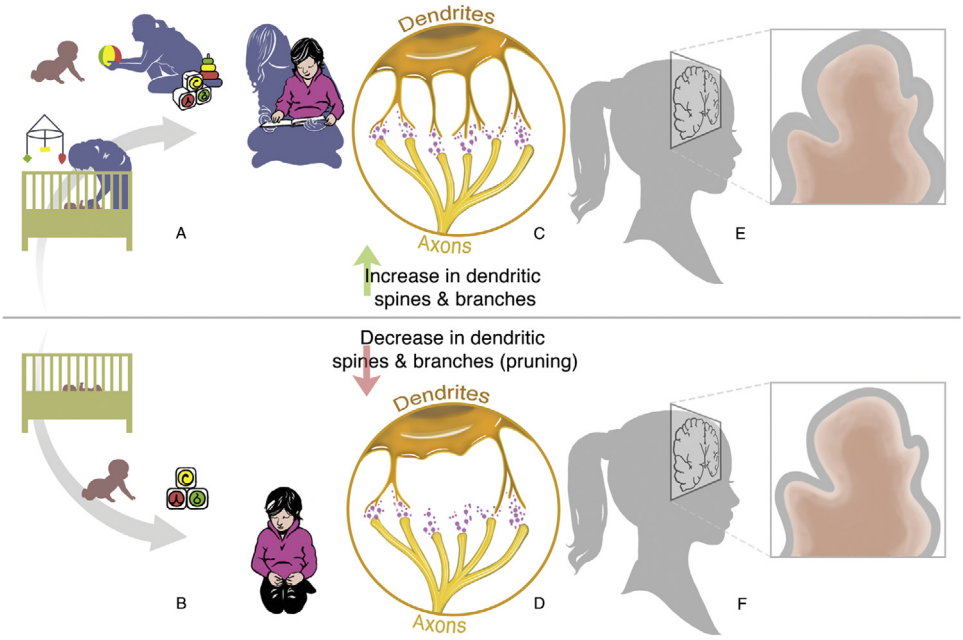

Figure 1. A neurodevelopmental mechanism of early deprivation. **(A)** A typical early environment is rich in sensory, linguistic, and social experiences that occur in the context of interactions with a caregiver and that provide a rich source of cognitive stimulation. Caregivers foster cognitive stimulation and shape early learning by directing children's attention to important cues in the environment through vocalizations, facial displays, and tactile stimulation. **(B)** Child neglect and institutional rearing constitute a deprived environment with dramatic reductions in the quantity and quality of caregiver interactions. This type of deprived environment constrains cognitive and social stimulation as well as learning opportunities. **(C)** Coactivation of presynaptic and postsynaptic neurons promotes postsynaptic dendritic branching, dendritic spine formation, and stabilization and strengthening of existing synaptic connections. **(D)** Limited coactivation of presynaptic and postsynaptic neurons ultimately leads to pruning of the synaptic connection. **(E)** A typical early environment should produce a pattern of greater cortical thickness throughout both primary sensory and association cortices as compared with children in a deprived environment. **(F)** Accelerated synaptic pruning that occurs as a result of deprived sensory, linguistic, cognitive, and social stimulation will lead to age-specific reductions in cortical thickness for children raised in deprived environments that are widespread across the cortex.

development that should be strongly influenced by the learning and neural mechanisms outlined in our model and that are difficult to explain based solely on stress and limbic system pathways. Specifically, we examine the associations of deprivation with global cognitive ability, associative and implicit learning, language, executive functioning, cortical structure, and white matter integrity. Our model predicts that children exposed to deprivation will exhibit poor performance in these cognitive domains, widespread reductions in cortical thickness, and reduced white matter integrity, particularly in the corpus callosum and PFC. We constrain this review to studies of children with documented histories of a) neglect or b) institutional rearing beginning early in life (i.e., where children were institutionalized from birth or shortly thereafter). We exclude studies that assess neglect or developmental outcomes in adults, that assess neglect based on retrospective appraisals (85,86), or that focus on children institutionalized later in development.

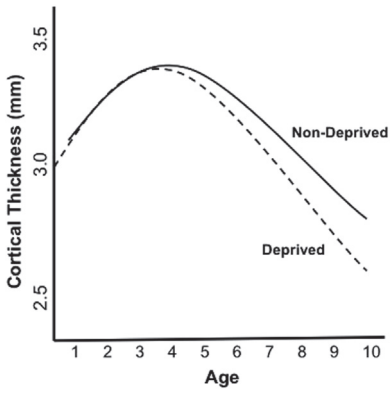

Figure 2. Predicted patterns of cortical thickness across development for children raised in typical and deprived early environments. Exaggerated synaptic pruning occurring throughout the cortex among children from deprived environments will produce a pattern of accelerated cortical thinning as compared with children from nondeprived environments. This pattern will produce age-specific reductions in cortical thickness in both primary sensory cortex and association cortex.

Cognitive Ability

If environmental deprivation produces learning deficits, global cognitive ability should be affected. Indeed, children exposed to neglect and institutional rearing experience dramatic reductions in cognitive ability. Neglected children have lower IQ and academic performance than children raised in typical caregiving environments (41,87–91). A similar pattern has been observed among children reared in institutional settings. Tizard and Rees's seminal study of children raised in institutions characterized by relatively mild deprivation nonetheless demonstrated that these children had lower IQ than children raised in families (92). Critically, the degree of environmental stimulation children received—including literary experiences, interactions with adults, and experiences outside the institution—was positively associated with cognitive ability (92). Dramatic reductions in IQ among children reared in deprived institutional settings have been widely replicated and are associated with the duration of institutional care (93–95). These findings are consistent with a learning account of

deprivation in which the degree and duration of cognitive and social stimulation in the early environment are strongly associated with global cognitive abilities.

Associative Learning

Associative learning creates connections between co-occurring stimuli or between a stimulus and a response, mediated by coordinated cell assemblies whose synaptic connections are strengthened on coactivation (96,97). Although we expect environmental deprivation to be associated with broad impairments in associative learning, existing research has focused primarily on stimulus–response learning. Children raised by responsive caregivers learn that exhibiting signs of distress will produce caregiver proximity, soothing behaviors, food, or removal of a source of distress. Through contingent responding, children learn that certain behaviors elicit reward (e.g., food, soothing). An absence of contingent responding teaches children that their behaviors are unlikely to produce reinforcement, creating weak stimulus–reward associations that may shape the neural circuits underlying reward learning, producing lasting alterations in reward-directed behavior.

Growing evidence supports these predictions. Poor stimulus–response learning has been observed in children raised in institutions and is associated with the duration of institutional care (98). Children reared in institutions do not alter behavioral responses to stimuli as a function of reward value, whereas typically developing children are faster and more accurate in responding to rewarded versus nonrewarded stimuli (99; see also M.A. Sheridan, Ph.D., *et al.*, unpublished data, 2017). Institutionally reared children also exhibit reduced activation in the ventral striatum—a region centrally involved in reward processing—during reward anticipation and in response to positive cues (100,101). Existing evidence supports the prediction that early deprivation is associated with atypical stimulus–response associative learning.

Implicit Learning

Implicit learning is an unconscious learning process that creates abstract knowledge through detection of structure in a complex sensory environment (102–105). Implicit learning depends on a rich sensory environment and observable regularities in the environment. Infants rapidly learn about statistical regularities in the environment across multiple sensory domains (51,106,107) that form lasting representations of the environment that facilitate skill development, problem solving, and predictions about the future (102,105). Implicit learning is likely to be constrained in environments lacking sensory and linguistic complexity.

Two studies have examined implicit learning in neglected children. The first examined children adopted into the United States internationally who performed no worse than nonadopted children on an implicit learning task (108). These children displayed cognitive abilities that were no different from those of comparison children, suggesting a less deprived institutional experience. In contrast, a recent study documents poor implicit learning in children raised in deprived institutions. Children exposed to institutional deprivation were less likely to learn a pattern of numbers embedded in a serial reaction time task, as indicated by slower reaction time and lower accuracy than comparison children on patterned trials relative to nonpatterned trials (M.A. Sheridan, Ph.D., *et al.*, unpublished data, 2017). More research on implicit learning following early deprivation is clearly needed.

Language Development

Extensive evidence supports the prediction that language development is influenced by environmental deprivation. Poor language skills are likely influenced directly by inconsistent exposure to caregiver language—common in neglected children—and indirectly through poor associative and implicit learning. In nondeprived family environments, the degree of environmental stimulation in the home as well as the amount and quality of maternal language predicts children's language skills (109,110). Poor expressive language and receptive language have been consistently observed in neglected children, who exhibit language difficulties that are more pronounced than those associated with abuse (87,111,112). Children raised in institutional settings also exhibit meaningful reductions in language ability that are associated with the duration of institutional care (108,113–115).

Executive Functioning

Executive functions (EFs) comprise a set of cognitive processes that support the ability to learn new knowledge and skills, hold in mind goals and information, and create and execute complex, future-oriented plans. EFs encompass working memory, inhibition, and switching/cognitive flexibility (116,117). These skills, and the frontoparietal networks that support them, exhibit a protracted developmental trajectory that extends throughout adolescence (118,119), suggesting ongoing plasticity in EFs across development. Yet, one of the most consistently observed patterns in children exposed to early deprivation is lasting and intractable EF deficits. Children raised in institutions exhibit poor performance on tests of working memory, inhibition, planning, sustained attention, and cognitive flexibility (98,108,120–126) and exhibit a less efficient pattern of dorsolateral PFC recruitment in tasks requiring executive control (126). EF performance is worse in children with more severe and longer-lasting deprivation (98,108,123,124). EF deficits often persist after removal from a deprived environment, which is surprising given the extended development of brain regions that support these functions. Associative learning is thought to play a central role in the development of EFs by facilitating the association of goal representations with relevant environmental stimuli in a particular context (57). Early problems in associative learning may explain, in part, these lasting difficulties with EFs, although future research is needed to evaluate this possibility.

Neural Structure and Function

Consistent with the first proposed neurodevelopmental mechanism of deprivation—accelerated synaptic pruning, leading to age-specific reductions in cortical thickness—children reared in deprived institutions exhibit smaller total brain volume (127), pronounced reductions in cortical gray matter (128), and widespread cortical thinning throughout both primary sensory and association cortices in the parietal, temporal, and frontal lobes (129). Reduced cerebellum volume was also reported in one study of children raised in institutions (130). Smaller left

amygdala volume and larger right amygdala volume were reported in a small study of previously institutionalized children (127), but these patterns have not been replicated in larger studies (33,128).

Institutionally reared children exhibit patterns of neural function that reflect tonic cortical hypoactivation consistent with these structural findings, including reduced power in high-frequency electroencephalogram bands (alpha) and increased power in low-frequency bands (theta), increased short-distance electroencephalogram coherence, and reduced gamma cross-frequency coupling, each of which is associated with duration of institutional care (131–134).

White matter changes have also been observed, consistent with evidence from animal models, including reduced volume of the posterior corpus callosum (128,135) and reduced fractional anisotropy in white matter tracts linking the PFC with the temporal lobe (e.g., uncinate fasiculus, superior longitudinal fasciculus) and the striatum (e.g., internal and external capsules) (135–137).

NEURODEVELOPMENTAL MECHANISMS LINKING DEPRIVATION TO PSYCHOPATHOLOGY

Children raised in deprived environments exhibit elevations in many forms of psychopathology, including anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), aggression, and substance abuse (38,40,138). What role do disruptions in cognitive and neural development play in the etiology of deprivation-related psychopathology? One domain for which these mechanisms appear to be particularly important is externalizing psychopathology, including ADHD—a disorder characterized by impulsivity, inattention, and poor EF. ADHD is strongly associated with institutional rearing and persists following removal from institutional care after the age of 6 months (38,40,139). EF deficits (particularly in working memory and inhibition), reductions in cortical thickness, and patterns of neural function reflecting tonic cortical hypoactivation are mechanisms that explain the association of early deprivation with ADHD (121,129,140). Changes in neural structure and cognitive function related to early deprivation may be a core mechanism underlying the development of externalizing psychopathology in children exposed to early deprivation.

In contrast, internalizing psychopathology following early deprivation improves following removal from a deprived environment (38,40) and involves mechanisms consistent with stress models focusing on atypical affective development. Improvements in anxiety and depression following early deprivation are explained, in part, by the development of secure attachment to new caregivers among adopted children (39).

Future research is needed to evaluate whether atypical associative learning is a mechanism in the link between early deprivation and psychopathology. Both depression and externalizing problems have been associated with poor reward learning and atypical neural response to reward (141,142), patterns also observed among children exposed to early deprivation. It seems plausible that disruptions in reward learning are an additional pathway explaining the link between deprivation and multiple forms of psychopathology.

PLASTICITY

Are the neural and behavioral consequences of deprivation reversible? Understanding ongoing plasticity is essential for preventing the onset of psychopathology in children raised in deprived environments. Although numerous methods exist in animal models for examining plasticity and critical periods, there are obvious constraints on what one can do with human children. One approach that has yielded important insights into neural plasticity is intervention, where the aim is to manipulate a system at different points in development and examine the impact on developmental processes. One example is the Bucharest Early Intervention Project, the first randomized controlled trial of foster care as an intervention for early institutionalization (23,143). After screening for developmental and neurological issues, 136 infants aged 6 to 30 months were randomly assigned to a high-quality foster care intervention or to care as usual—continued institutional care (23). These children have been followed through age 12 years, and a 16-year assessment is ongoing.

Relevant to our proposed model of deprivation, of the developmental domains reviewed here, intervention effects have been found for IQ, language development, reward learning, neural function assessed with electroencephalogram, and white matter volume and integrity (93,113,128,132,134,135; see also M.A. Sheridan, Ph.D., *et al.*, unpublished data, 2017); similar effects on cognitive development have also been observed in intervention studies designed to improve caregiving quality in institutions (144). Additional domains that improved in children randomized out of institutional care include physical growth, attachment, stress reactivity, and internalizing symptoms (34,38,40,145). Earlier removal from the institution led to more dramatic improvements in IQ, language, neural function, stress reactivity, and attachment. No intervention effects were found for EFs, ADHD, and cortical thinning, which are affected by institutionalization but not by foster care intervention.

CONCLUSIONS

Child neglect and institutional rearing deprive children of numerous environmental experiences the human brain expects to develop normally. This deprivation produces lasting alterations in many domains of cognitive development, including general cognitive ability, associative and implicit learning, language, and EFs as well as reductions in cortical gray matter volume and thickness and white matter integrity. We propose that deprived environments constrain early forms of experience-expectant learning, accelerate the neurodevelopmental process of synaptic pruning, and limit myelination, ultimately producing these atypical patterns of cognitive and brain development. These developmental disruptions, in turn, may confer risk for psychopathology, which is common among neglected and institutionally reared children. Interventions aimed at improving developmental outcomes in children raised in deprived environments would benefit from increased attention to the importance of cognitive and social stimulation.

ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported by the National Institute of Mental Health (Grant Nos. R01-MH103291 [to KAM], R01-MH106482 [to KAM], and

R01-MH091363 [to CAN]), a Jacobs Foundation Early Career Research Fellowship to KAM, and a Jacobs Foundation research grant to CAN.

All authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychology (KAM), University of Washington, Seattle, Washington; Department of Psychology and Neuroscience (MAS), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Division of Developmental Medicine and Department of Psychiatry (CAN), Boston Children's Hospital, Harvard Medical School, Boston, and Harvard Graduate School of Education (CAN), Harvard University, Cambridge, Massachusetts.

Address correspondence to Katie McLaughlin, Ph.D., Department of Psychology, University of Washington, Box 351525, Seattle, WA 98195; E-mail: mclaughk@uw.edu.

Received Oct 13, 2016; revised Feb 03, 2017; accepted Feb 21, 2017.

REFERENCES

1. Greenough WT, Black JE, Wallace CS (1987): Experience and brain development. Child Dev 58:539–559.
2. Gilbert D, Widom CS, Browne K, Fergusson DM, Webb E, Staffan J (2009): Burden and consequences of child maltreatment in high-income countries. Lancet 373:68–81.
3. Leeb RT, Paulozzi LJ, Melanson C, Simon TR, Arias I (2008): Child Maltreatment Surveillance: Uniform Definitions for Public Health and Recommended Data Elements. Atlanta, GA: Centers for Disease Control and Prevention.
4. Straus MA, Kaufman Kantor G (2005): Definition and measurement of neglectful behavior: Some principles and guidelines. Child Abuse Negl 29:19–29.
5. Sedlak AJ, Mettenburg J, Basena M, Petta I, McPherson K, Greene A, *et al*. (2010): Fourth National Incidence Study of Child Abuse and Neglect (NIS-4): Report to Congress, Executive Summary. Washington, DC: Office of Planning, Research and Evaluation.
6. Stoltenborgh M, Bakermans-Kranenburg MJ, Van Ijzendoorn MH (2013): The neglect of child neglect: A meta-analytic review of the prevalence of neglect. Soc Psychiatry Psychiatr Epidemiol 48:345–355.
7. McLaughlin KA, Sheridan MA, Lambert HK (2014): Childhood adversity and neural development: Deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 47:578–591.
8. McLaughlin KA, Sheridan MA (2016): Beyond cumulative risk: A dimensional approach to childhood adversity. Curr Dir Psychol Sci 25:239–245.
9. Sheridan MA, McLaughlin KA (2014): Dimensions of early experience and neural development: Deprivation and threat. Trends Cogn Sci 18:580–585.
10. Nelson CA (1999): Neural plasticity and human development. Curr Dir Psychol Sci 8:42–45.
11. Ainsworth MD (1985): Patterns of infant–mother attachments: Antecedents and effects on development. Bull N Y Acad Med 61:771–791.
12. Bowlby J (1969): Attachment and Loss, vol. 1: Attachment. New York: Basic Books.
13. Ainsworth MDS, Blehar MC, Waters E, Wall S (1978): Patterns of Attachment. Hillsdale, NJ: Lawrence Erlbaum.
14. Egeland B, Farber EA (1984): Infant–mother attachment: Factors related to its development and changes over time. Child Dev 55:753–771.
15. Sroufe LA (1979): The coherence of individual development: Early care, attachment, and subsequent developmental issues. Am Psychol 34:834–841.
16. Kaufman Kantor G, Holt MK, Mebert CJ, Straus MA, Drach KM, Ricci LR, *et al*. (2004): Development and preliminary psychometric properties of the Multidimensional Neglectful Behavior Scale–Child Report. Child Maltreat 9:409–428.
17. Gaudin JM, Polansky NA, Kilpatrick AC, Shilton P (1996): Family functioning in neglectful families. Child Abuse Negl 20:363–377.
18. Bousha DM, Twentyman CT (1984): Mother–child interactional style in abuse, neglect, and control groups: Naturalistic observations in the home. J Abnorm Psychol 93:106–114.
19. Smyke AT, Koga S, Johnson DE, Fox NA, Marshall PJ, Nelson CA, *et al*. (2007): The caregiving context in institution-reared and family-reared infants and toddlers in Romania. J Child Psychol Psychiatry 48:210–218.
20. Kuhl PK, Tsao FM, Liu HM (2003): Foreign-language experience in infancy: Effects of short-term exposure and social interaction on phonetic learning. Proc Natl Acad Sci U S A 100:9096–9101.
21. Thiessen ED, Hill EA, Saffran JR (2005): Infant-directed speech facilitates word segmentation. Infancy 7:53–71.
22. Hines DA, Kaufman Kantor G, Holt MK (2006): Similarities in siblings' experiences of neglectful parenting behaviors. Child Abuse Negl 30:619–637.
23. Zeanah CH, Nelson CB, Fox NA, Smyke AT, Marshall PJ, Parker SW, *et al*. (2003): Designing research to study the effects of institutionalization on brain and behavioral development: The Bucharest Early Intervention Project. Dev Psychopathol 15:885–907.
24. Nelson CA, Furtado EA, Fox NA, Zeanah CH (2009): The deprived human brain. Am Sci 97:222–229.
25. Tottenham N (2012): Human amygdala development in the absence of species-typical expected caregiving. Dev Psychobiol 54:598–611.
26. Callaghan BL, Tottenham N (2016): The neuro-environmental loop of plasticity: A cross-species analysis of parental effects on emotion circuitry development following typical and adverse caregiving. Neuropsychopharmacology 41:163–176.
27. Pechtel P, Pizzagalli DA (2011): Effects of early life stress on cognitive and affective function: An integrated review of human literature. Psychopharmacology 214:55–70.
28. De Bellis MD (2005): The psychobiology of neglect. Child Maltreat 10:150–172.
29. Shonkoff JP, Garner AS (2012): The lifelong effects of early childhood adversity and toxic stress. Pediatrics 129:232–246.
30. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009): Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci 10:434–445.
31. Teicher MH, Samson JA (2016): Annual research review: Enduring neurobiological effects of childhood abuse and neglect. J Child Psychol Psychiatry 57:241–266.
32. Tottenham N, Hare T, Millner A, Gilhooly T, Zevin JD, Casey BJ (2011): Elevated amygdala response to faces following early deprivation. Dev Sci 14:190–204.
33. Tottenham N, Hare T, Quinn BT, McCarry TW, Nurse M, Gilhooly T, *et al*. (2010): Prolonged institutional rearing is associated with atypically larger amygdala volume and difficulties in emotion regulation. Dev Sci 13:46–61.
34. McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA (2015): Causal effects of the early caregiving environment on stress response system development in children. Proc Natl Acad Sci U S A 112:5637–5642.
35. Gunnar MR, Frenn K, Wewerka S, Van Ryzin MJ (2009): Moderate versus severe early life stress: Associations with stress reactivity and regulation in 10-12 year-old children. Psychoneuroendocrinology 34:62–75.
36. Zeanah CH, Smyke AT, Koga SF, Carlson E, The Bucharest Early Intervention Project Core Group (2005): Attachment in institutionalized and community children in Romania. Child Dev 76:1015–1028.
37. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, *et al*. (2013): Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci U S A 110:15638–15643.
38. Zeanah CH, Egger HL, Smyke AT, Nelson CA, Fox NA, Marshall PJ, *et al*. (2009): Institutional rearing and psychiatric disorders in Romanian preschool children. Am J Psychiatry 166:777–785.
39. McLaughlin KA, Zeanah CH, Fox NA, Nelson CA (2012): Attachment security as a mechanism linking foster care placement to improved mental health outcomes in previously institutionalized children. J Child Psychol Psychiatry 53:46–55.
40. Humphreys KL, Gleason MM, Drury SS, Miron D, Nelson CA, Fox NA, *et al*. (2015): Effects of institutional rearing and foster care on psychopathology at age 12 years in Romania: Follow-up of an open, randomised controlled trial. Lancet Psychiatry 2:625–634.

41. Hildyard KL, Wolfe DA (2002): Child neglect: Developmental issues and outcomes. Child Abuse Negl 26:679–695.
42. Stern DN, Beebe B, Jaffe J, Bennett SL (1977): The infant's stimulus world during social interaction: A study of caregiver behaviors with particular reference to repetition and timing. In: Schaffer H, editor. Studies in Mother–Infant Interaction. New York: Academic Press, 177–202.
43. Kuhl PK, Andruski JE, Chistovich IA, Chistovich LA, Kozhevnikova EV, Ryskina VL, *et al*. (1997): Cross-language analysis of phonetic units in language addressed to infants. Science 277:684–686.
44. Papoušek M, Papoušek H, Symmes D (1991): The meanings of melodies in motherese in tone and stress languages. Infant Behav Dev 14:415–440.
45. Fernald A, Simon T (1984): Expanded intonation contours in mothers' speech to newborns. Dev Psychol 20:104–113.
46. Cooper RP, Aslin RN (1990): Preference for infant-directed speech in the first month after birth. Child Dev 61:1584–1595.
47. Werker JF, McLeod PJ (1989): Infant preference for both male and female infant-directed talk: A developmental study of attentional and affective responsiveness. Can J Psychol 43:230–246.
48. Kaplan PS, Jung PC, Ryther JS, Zarlengo-Strouse P (1996): Infant-directed versus adult-directed speech as signals for faces. Dev Psychol 32:880–891.
49. Kaplan PS, Bachorowski J, Zarlengo-Strouse P (1999): Child-directed speech produced by mothers with symptoms of depression fails to promote associative learning in 4-month old infants. Child Dev 70:560–570.
50. Kaplan PS, Bachorowski JA, Smoski MJ, Hudenko WJ (2002): Infants of depressed mothers, although competent learners, fail to learn in response to their own mothers' infant-directed speech. Psychol Sci 13:268–271.
51. Saffran JR, Aslin RN, Newport EL (1996): Statistical learning by 8-month-old infants. Science 274:1926–1928.
52. Saffran JR (2003): Statistical language learning: Mechanisms and constraints. Curr Dir Psychol Sci 12:110–114.
53. Maye J, Werker JF, Gerken L (2002): Infant sensitivity to distributional information can affect phonetic discrimination. Cognition 82: B101–B111.
54. Roy DK, Pentland AP (2002): Learning words from sights and sounds: A computational model. Cogn Sci 26:113–145.
55. Misyak JB, Christiansen MH, Tomblin JB (2010): On-line individual differences in statistical learning predict language processing. Front Psychol 14:31.
56. Kidd E (2012): Implicit statistical learning is directly associated with the acquisition of syntax. Dev Psychol 48:171–184.
57. Abrahamse E, Braem S, Notebaert W, Verguts T (2016): Grounding cognitive control in associative learning. Psychol Bull 142:693–728.
58. Nelson CA (2007): A neurobiological perspective on early human deprivation. Child Dev Perspect 1:13–18.
59. Changeux J-P, Danchin A (1976): Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. Nature 264:705–712.
60. Petanjek Z, Judas M, Simic G, Rasin MR, Uylings HBM, Rakic P, *et al*. (2011): Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A 108:13281–13286.
61. Purves D, Lichtman JW (1980): Elimination of synapses in the developing nervous system. Science 210:153–157.
62. Segal M (2005): Dendritic spines and long-term plasticity. Nat Rev Neurosci 6:277–284.
63. Whitlock JR, Heynen AJ, Shuler MG, Bear MF (2006): Learning induces long-term potentiation in the hippocampus. Science 313:1093–1097.
64. Zhou Q, Homma KJ, Poo MM (2004): Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 44:749–757.
65. Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS (1986): Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 232:232–235.
66. O'Kusky JR (1985): Synapse elimination in the developing visual cortex: A morphometric analysis in normal and dark-reared cats. Brain Res 354:81–91.
67. Rothblat LA, Schwartz ML (1979): The effect of monocular deprivation on dendritic spines in visual cortex of young and adult albino rats: Evidence for a sensitive period. Brain Res 161: 156–161.
68. Valverde F (1971): Rate and extent of recovery from dark rearing in the visual cortex of the mouse. Brain Res 33:1–11.
69. Valverde F (1967): Apical dendritic spines of the visual cortex and light deprivation in the mouse. Exp Brain Res 3:337–352.
70. Fifkova E (1970): The effect of unilateral deprivation on visual centers in rats. J Comp Neurol 140:431–438.
71. Turner AM, Greenough WT (1985): Differential rearing effects on rat visual cortex synapses: I. Synaptic and neuronal density and synapses per neuron. Brain Res 329:195–203.
72. Globus A, Rosenzweig MR, Bennett EL, Diamond MC (1973): Effects of differential experience on dendritic spine counts in rat cerebral cortex. J Comp Physiol Psychol 82:175–181.
73. Greenough WT, Volkmar FR (1973): Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Exp Neurol 40:491–504.
74. Volkmar FR, Greenough WT (1972): Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science 176: 1445–1447.
75. Diamond MC, Law F, Rhodes H, Lindner B, Rosenzweig MR, Krech D, *et al*. (1966): Increases in cortical depth and glia numbers in rats subjected to enriched environment. J Comp Neurol 128: 117–126.
76. Diamond MC, Lindner B, Raymond A (1967): Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. J Comp Neurol 131:357–364.
77. Rosenzweig MR, Bennett EL (1996): Psychobiology of plasticity: Effects of training and experience on brain and behavior. Behav Brain Res 78:57–65.
78. Schrijver NC, Bahr NI, Weiss IC, Würbel H (2002): Dissociable effects of isolation rearing and environmental enrichment on exploration, spatial learning and HPA activity in adult rats. Pharmacol Biochem Behav 73:209–224.
79. Martínez-Cué C, Baamonde C, Lumbreras M, Paz J, Davisson MT, Schmidt C, *et al*. (2002): Differential effects of environmental enrichment on behavior and learning of male and female Ts65Dn mice, a model for Down syndrome. Behav Brain Res 134:185–200.
80. Hebb DO (1947): The effects of early experience on problem solving at maturity. Am Psychol 2:306–307.
81. Renner MJ, Rosenzweig MR (1987): Enriched and Impoverished Environments: Effects on Brain and Behavior. New York: Springer-Verlag.
82. Juraska JM, Kopcik JR (1988): Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. Brain Res 450:1–8.
83. Makinodan M, Rosen KM, Ito S, Corfas G (2012): A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science 337:1357–1360.
84. Baroncelli L, Scali M, Sansevero G, Olimpico F, Manno I, Costa M, *et al*. (2016): Experience affects critical period plasticity in the visual cortex through an epigenetic regulation of histone post-translational modifications. J Neurosci 36:3430–3440.
85. Hanson JL, Hariri AR, Williamson DE (2015): Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. Biol Psychiatry 78:598–605.
86. Bogdan R, Williamson DE, Hariri AR (2012): Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. Am J Psychiatry 169:515–522.
87. Spratt EG, Friedenberg SL, Swenson CC, Larosa A, De Bellis MD, Macias MM, *et al*. (2012): The effects of early neglect on cognitive, language, and behavioral functioning in childhood. Psychology 3: 175–182.
88. Erickson MF, Egeland B, Planta R (1989): The effects of maltreatment on the development of young children. In: Cicchetti D, Carlson V, editors. Child Maltreatment. New York: Cambridge University Press, 647–684.

89. Eckenrode J, Laird M, Doris J (1993): School performance and disciplinary problems among abused and neglected children. Dev Psychol 29:53–62.
90. Wodarski JS, Kurtz PD, Gaudin JM, Howing PT (1990): Maltreatment and the school-aged child: Major academic, socioemotional, and adaptive outcomes. Soc Work 35:506–513.
91. Perez CM, Widom CS (1994): Childhood victimization and long-term intellectual and academic outcomes. Child Abuse Negl 18:617–633.
92. Tizard B, Rees J (1974): A comparison of the effects of adoption, restoration to the natural mother, and continued institutionalization on the cognitive development of four-year-old children. Child Dev 45:92–99.
93. Nelson CA, Zeanah CH, Fox NA, Marshall PJ, Smyke AT, Guthrie D (2007): Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. Science 318:1937–1940.
94. Fox NA, Almas AN, Degnan KA, Nelson CA, Zeanah CH (2011): The effects of severe psychosocial deprivation and foster care intervention on cognitive development at 8 years of age: Findings from the Bucharest Early Intervention Project. J Child Psychol Psychiatry 52: 919–928.
95. O'Connor TG, Rutter M, Beckett C, Keaveney L, Kreppner JM (2000): The effects of global severe privation on cognitive competence: Extension and longitudinal follow-up—English and Romanian Adoptees Study Team. Child Dev 71:376–390.
96. Pearce JM, Bouton ME (2001): Theories of associative learning in animals. Annu Rev Psychol 52:111–139.
97. Rescorla RA, Wagner AR (197): A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black AH, Prokasy WF, editors. Classical Conditioning II: Current Research and Theory. New York: Appleton–Century–Crofts, 64–99.
98. Pollak SD, Nelson CA, Schlaak MF, Roeber BJ, Wewerka S, Wiik KL, *et al*. (2010): Neurodevelopmental effects of early deprivation in postinstitutionalized children. Child Dev 81:224–236.
99. Wismer Fries AB, Pollak SD (2017): The role of learning in social development: Illustrations from neglected children. Dev Sci 20(2).
100. Goff B, Gee DG, Telzer EH, Humphreys KL, Gabard-Durnam LJ, Flannery DJ, *et al*. (2013): : Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. Neuroscience 249:129–138.
101. Mehta MA, Gore-Langton E, Golembo N, Colvert E, Williams SCR, Sonuga-Barke E (2010): Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. J Cogn Neurosci 22:2316–2325.
102. Reber AS (1989): Implicit learning and tacit knowledge. J Exp Psychol Gen 118:219–235.
103. Perruchet P, Pacton S (2006): Implicit learning and statistical learning: One phenomenon, two approaches. Trends Cogn Sci 10: 233–238.
104. Turk-Browne NB, Scholl BJ, Chun MM, Johnson MK (2009): Neural evidence of statistical learning: Efficient detection of visual regularities without awareness. J Cogn Neurosci 21:1934–1945.
105. Seger CA (1994): Implicit learning. Psychol Bull 115:163–196.
106. Kirkham NZ, Slemmer JA, Johnson SP (2002): Visual statistical learning in infancy: Evidence for a domain general learning mechanism. Cognition 83:B35–B42.
107. Saffran JR, Johnson EK, Aslin RN, Newport EL (1999): Statistical learning of tone sequences by human infants and adults. Cognition 70:27–52.
108. Eigsti I-M, Weitzman C, Schuh J, de Marchena A, Casey BJ (2011): Language and cognitive outcomes in internationally adopted children. Dev Psychopathol 23:629–646.
109. Farah MJ, Betancourt L, Shera DM, Savage JH, Giannetta JM, Brodsky NL, *et al*. (2008): Environmental stimulation, parental nurturance and cognitive development in humans. Dev Sci 11: 793–801.
110. Hoff E (2003): The specificity of environmental influence: Socioeconomic status affects early vocabulary development via maternal speech. Child Dev 74:1368–1378.
111. Allen RE, Oliver JM (1982): The effects of child maltreatment on language development. Child Abuse Negl 6:299–305.
112. Culp RE, Watkins RV, Lawrence H, Letts D, Kelly DJ, Rice ML (1991): Maltreated children's language and speech development: Abused, neglected, and abused and neglected. First Lang 11: 377–389.
113. Windsor J, Benigno JP, Wing CA, Carroll PJ, Koga SF, Nelson CA, *et al*. (2011): Effect of foster care on young children's language learning. Child Dev 82:1040–1046.
114. Rakhlin N, Hein S, Doyle N, Hart L, Macomber D, Ruchkin V, *et al*. (2015): Language development of internationally adopted children: Adverse early experiences outweigh the age of acquisition effect. J Commun Disord 57:66–80.
115. Albers LH, Johnson DE, Hostetter MK, Iverson S, Miller LC (1997): Health of children adopted from the former Soviet Union and Eastern Europe. Comparison with preadoptive medical records. JAMA 278: 922–924.
116. Miyake A, Friedman NP, Rettinger DA, Shah P, Hegarty M (2001): How are visuospatial working memory, executive functioning, and spatial abilities related? A latent-variable analysis. J Exp Psychol Gen 130:621–640.
117. Miyake A, Friedman NP (2012): The nature and organization of individual differences in executive functions: Four general conclusions. Curr Dir Psychol Sci 21:8–14.
118. Best JR, Miller PH (2010): A developmental perspective on executive function. Child Dev 81:1641–1660.
119. Blakemore SJ, Choudhury S (2006): Development of the adolescent brain: Implications for executive function and social cognition. J Child Psychol Psychiatry 47:296–312.
120. Bos KJ, Fox NA, Zeanah CH, Nelson CA (2009): Effects of early psychosocial deprivation on the development of memory and executive function. Front Behav Neurosci 3:16.
121. Tibu F, Sheridan MA, McLaughlin KA, Fox NA, Zeanah CH, Nelson CA (2016): Disruptions of working memory and inhibition mediate the association between exposure to institutionalization and symptoms of attention-deficit/hyperactivity disorder. Psychol Med 46: 529–541.
122. McDermott JM, Troller-Renfree S, Vanderwert R, Nelson CA, Zeanah CH, Fox NA (2013): Psychosocial deprivation, executive functions and the emergence of socio-emotional behavior problems. Front Hum Neurosci 7:167.
123. Colvert E, Rutter M, Kreppner JM, Beckett C, Castle J, Groothues C (2008): Do theory of mind and executive functioning deficits underlie the adverse outcomes associated with profound early deprivation? Findings from the English and Romanian Adoptees Study. J Abnorm Child Psychol 36:1057–1068.
124. Hostinar CE, Stellern SA, Schaefer C, Carlson SM, Gunnar MR (2012): Associations between early life adversity and executive function in children adopted internationally from orphanages. Proc Natl Acad Sci U S A 109:17208–17212.
125. Loman MM, Johnson AE, Westerlund A, Pollak SD, Nelson CA, Gunnar M (2013): The effect of early deprivation on executive attention in middle childhood. J Child Psychol Psychiatry 54:37–45.
126. Mueller SC, Maheu FS, Dozier M, Peloso E, Mandell D, Leibenluft E, *et al*. (2010): Early-life stress is associated with impairment in cognitive control in adolescence: An fMRI study. Neuropsychologia 48:3037–3044.
127. Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, *et al*. (2009): Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian Adoptees Study pilot. J Child Psychol Psychiatry 50:943–951.
128. Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA (2012): Variation in neural development as a result of exposure to institutionalization early in childhood. Proc Natl Acad Sci U S A 109: 12927–12932.
129. McLaughlin KA, Sheridan MA, Winter W, Fox NA, Zeanah CH, Nelson CA (2014): Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to ADHD. Biol Psychiatry 76:629–638.

130. Bauer PM, Hanson JL, Pierson RK, Davidson RJ, Pollak SD (2009): Cerebellar volume and cognitive functioning in children who experienced early deprivation. Biol Psychiatry 66:1100–1106.
131. Marshall PJ, Fox NA, Bucharest Early Intervention Project Core Group (2004): A comparison of the electroencephalogram between institutionalized and community children. J Cogn Neurosci 16: 1327–1338.
132. Vanderwert RE, Marshall PJ, Nelson CA, Zeanah CH, Fox NA (2011): Timing of intervention affects brain electrical activity in children exposed to severe psychosocial neglect. PLoS One 5:e11415.
133. Stamoulis C, Vanderwert RE, Zeanah CH, Fox NA, Nelson CA (2015): Early psychosocial neglect adversely impacts developmental trajectories of brain oscillations and their interactions. J Cogn Neurosci 27: 2512–2528.
134. Marshall PJ, Reeb BC, Fox NA, Nelson CA, Zeanah CH (2008): Effects of early intervention on EEG power and coherence in previously institutionalized children in Romania. Dev Psychopathol 20:861–880.
135. Bick J, Zhu T, Stamoulis C, Fox NA, Zeanah C, Nelson CA (2015): Effect of early institutionalization and foster care on long-term white matter development: A randomized clinical trial. JAMA Pediatr 169: 211–219.
136. Govindan RM, Behen ME, Helder E, Makki MI, Chugani HT (2010): Altered water diffusivity in cortical association tracts in children with early deprivation identified with tract-based spatial statistics (TBSS). Cereb Cortex 20:561–569.
137. Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M (2006): Abnormal brain connectivity in children after early severe socioemotional deprivation: A diffusion tensor imaging study. Pediatrics 117:2093–2100.
138. McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky A, Kessler RC (2012): Childhood adversities and first onset of psychiatric disorders in a national sample of adolescents. Arch Gen Psychiatry 69:1151–1160.
139. Kreppner JM, O'Connor TG, Rutter M (2001): Can inattention/overactivity be an institutional deprivation syndrome? J Abnorm Child Psychol 29:513–528.
140. McLaughlin KA, Fox NA, Zeanah CH, Sheridan MA, Marshall PJ, Nelson CA (2010): Delayed maturation in brain electrical activity explains the association between early environmental deprivation and symptoms of attention-deficit/hyperactivity disorder (ADHD). Biol Psychiatry 68:329–336.
141. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al*. (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry 166:702–710.
142. Gatzke-Kopp LM, Beauchaine TP, Shannon KE, Chipman J, Fleming AP, Crowell SE, *et al*. (2009): Neurological correlates of reward responding in adolescents with and without externalizing behavior disorders. J Abnorm Psychol 118:203–213.
143. Nelson CA (2014): Romania's Abandoned Children. Cambridge, MA: Harvard University Press.
144. Hermenau K, Goessman K, Rygaard NP, Landolt MA, Hecker T (2016): Fostering child develpment by improving care quality: A systematic review of the effectiveness of structural interventions and caregiver trainings in institutional care [published online ahead of print Apr 12]. Trauma Violence Abuse.
145. Smyke AT, Zeanah CH, Fox NA, Nelson CA, Guthrie D (2010): Placement in foster care enhances quality of attachment among young institutionalized children. Child Dev 81:212–223.