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Consequences of Inadequate Caregiving for Children's Attachment, Neurobiological Development, and Adaptive Functioning

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Abstract

Given that human infants are almost fully reliant on caregivers for survival, the presence of parents who provide sensitive, responsive care support infants and young children in developing the foundation for optimal biological functioning. Conversely, when parents are unavailable or insensitive, there are consequences for infants' and children's attachment and neurobiological development. In this paper, we describe effects of inadequate parenting on children's neurobiological and behavioral development, with a focus on developing capacities for executive functioning, emotion regulation, and other important cognitive-affective processes. Most prior research has examined correlational associations among these constructs. Given that interventions tested through randomized clinical trials allow for causal inferences, we review longitudinal intervention effects on children's biobehavioral and cognitive-affective outcomes. In particular, we provide an overview of the Bucharest Early Intervention Project, a study in which children were randomized to continue in orphanage care (typically the most extreme condition of privation) or were placed into the homes of trained, supported foster parents. We also discuss findings regarding Attachment and Biobehavioral Catch-up, an intervention enhancing sensitivity among high-risk parents. We conclude by suggesting future directions for research in this area.

Keywords Maltreatment · Brain development · HPA axis · Autonomic nervous system · Parenting intervention · Cognitive-affective processes

Introduction

As an altricial species, human infants are almost fully reliant on caregivers for survival and depend on them for even some of the most basic regulatory functions (Hofer, 1994, 2006; Winberg, 2005). The presence of parents who provide sensitive, responsive care helps infants and young children develop the foundation for optimal biological development. As we discuss in this paper, optimal brain and physiological development support children's developing social-affective processes (e.g., acquiring adequate inhibitory control, interpreting ambiguous intentions as benign). Because infants are so dependent on their parents for help with regulation, inadequate caregiving can undermine children's brain development and biological regulation, hence interfering with their cognitive-affective functioning.

In this paper, we consider how inadequate caregiving in infancy and early childhood alters the quality of children's attachments and the development of several key neurobiological systems, which, in turn, affects the development of cognitive-affective processes across childhood and adolescence. Caregiving quality ranges from extreme forms of maltreatment (inadequate caregiving) to consistently nurturing and sensitive care (adequate caregiving or better). In this paper, we focus on the neurobiological consequences of inadequate parenting. Although most research examining these links is correlational, randomized clinical trials (RCTs) of interventions allow for causal inferences. Intervention science is important because it reveals the ways in which children are—and in some cases, are not—resilient to the effects of early life adversity when parenting is enhanced. We therefore discuss two relevant parenting interventions that have been tested in RCTs, the Bucharest

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Early Intervention Project (BEIP) and the Attachment and Biobehavioral Catch-up (ABC) intervention. We conclude the paper with recommendations for future work.

Neurobiological systems highlighted in the paper include the hypothalamic–pituitary–adrenal (HPA) axis, which is involved in mounting a stress response and maintaining a diurnal rhythm; the autonomic nervous system, which is involved in physiological and emotional regulation; the amygdala, which is involved in threat detection and emotional reactivity; the prefrontal cortex, which is involved in higher order cognitive functioning and which can exert control over the amygdala; and electrophysiological spectral power profiles, which reflect neural maturation and cognitive processing. We consider affective-cognitive processes associated with each system's functioning. Given that many neurobiological systems show rapid growth in early life, we focus primarily on early childhood research. However, development of these systems continues across childhood, adolescence, and beyond. Bidirectional and recursive links among constructs are also likely.

The Importance of Parenting

Parents and other caregivers have several critical roles that affect their infants' brain development and nascent regulatory capabilities. Most importantly, infants are dependent on parents and other caregivers for responsive input, as well as for protection from threat. When parents behave in sensitive and responsive ways to infants' verbal or behavioral cues, infants experience a responsive interpersonal world. Parental sensitivity has been described by different scholars as reflecting "serve and return" (Shonkoff & Bales, 2011), "following the lead" (Dozier & Bernard, 2019), or "contingently responsive" interactions (Bigelow & Rochat, 2006). When such interactions occur over and over again in various forms, children develop confident expectations that parents will be available when needed. Over time, these interactions affect the formation of simple and eventually complex neural circuits.

A second important function of parents and other caregivers is protecting the infant from threatening input. When the parent shields the child from harsh or frightening experiences, the child experiences a range of stimuli that is tolerable, rather than a range that would result in feelings of uncontrollable and overwhelming threat. When an infant has a trusted caregiver, he or she is able to withstand a physically painful experience (e.g., heel stick) or a potentially threatening situation (e.g., separation) without mounting a stress response, suggesting that the parent buffers the infant from threat effectively (Gunnar et al., 2009). Parental buffering is especially potent in the context of a secure attachment.

Inadequate care typically takes the form of parents being unresponsive to children's needs (i.e., depriving/neglecting), or parents behaving in overwhelming or frightening ways (i.e., threatening/abusing). Deprivation or neglect can range from mild forms in which parents are inattentive to children to extreme forms in which parents or caregivers are fully neglecting of children. A parent with a mental health or substance abuse disorder who may have difficulty being attentive to their children's cues could serve as an example of a mild form of neglect. At the extreme end of the inadequate care continuum, we see institutional or orphanage care where children do not have dedicated caregivers. The staff to child ratio is often high in such facilities, and attention to individual child needs is minimal (Smyke et al., 2007). Threat or abuse likewise can range from mild forms in which parents make threatening comments or gestures (e.g., threatening that someone will take child away, or suggesting that child will be smacked if he or she touches electrical outlet) to extreme forms in which the child is beaten, shaken, or otherwise physically harmed. McLaughlin et al., (2014a) have argued that threat (associated with abuse) and deprivation (associated with neglect) have different effects on developing regulatory systems. On the other hand, Callaghan and Tottenham (2016) have made the argument that neglect and abuse may not be so distinct in their neurobiological effects because children are vulnerable and hence threatened without an effective protector. Evidence exists to support each of these perspectives.

Attachment

Conditions of deprivation and threat are particularly problematic for the young infant because the infant lacks a trusted attachment figure. Forming an attachment is a key biologically based developmental task. A protracted period of brain and regulatory system development is supported by the availability of parents (or other caregivers) who serve as co-regulators for the young child. As the human species evolved to be characterized by a protracted period of brain and regulatory system development, the attachment system likely evolved to support the child's reliance on the parent for protection. By the age at which infants are capable of locomotor activity (e.g., crawling or walking), they have a strong drive to seek out and maintain proximity to caregivers when they feel threatened or vulnerable (Bretherton, 1985). From an evolutionary perspective, this drive enhances survival by ensuring that infants maintain proximity when they need the protection of parents or other caregivers.

Whether infants become attached to parents or other adults is therefore universal for the most part. Even children reared by maltreating parents tend to develop clear attachments to their parents (although these attachments are likely neither secure nor organized). Only if children have no consistent caregiver available to them, as seen in some orphanage settings, do they appear to fail to develop clear attachments. Indeed, among children from orphanages in Romania that were characterized by grossly inadequate care, only 3.2% showed clear, classifiable attachments to parents, whereas 100% of children raised by birth parents showed clear attachments (Zeanah et al., 2005).

What differentiates the vast majority of infants, therefore, is not whether they form attachments but rather the quality of the attachment. When parents sensitively respond to their infants' bids for reassurance, infants tend to develop secure attachments (Ainsworth et al., 1979). Infants with secure attachments make direct bids for reassurance and are generally easy to soothe when distressed. When parents are rejecting of infants' bids for reassurance, infants often develop avoidant attachments. Avoidant attachments are characterized by infants turning away from parents when distressed. When parents are inconsistent in their availability, infants often develop resistant attachments, characterized by a combination of comfort seeking and ambivalent pushing away. Although avoidant and resistant attachments are not optimal in terms of developmental outcomes, they are seen as organized attachments because they represent coherent strategies that are well suited to their parents' availability. When parents behave in frightening ways, infants often develop disorganized attachments (Jacobvitz et al., 2006; Schuengel et al., 1999). Disorganized attachments are characterized by odd, anomalous behaviors (such as turning in circles or freezing) that do not appear to serve a function. Hesse and Main (1999) have suggested that infants develop disorganized attachments when they experience "fright without solution" (p. 484). Consistent with the premise that children need responsive, available caregivers if they are to develop adequate self-regulatory strategies and optimal brain development, disorganized attachments are most predictive of problems regulating behavior and physiology (Carlson, 1998; Fearon et al., 2010; Luijk et al., 2010). Figure 1 illustrates both the direct links between parental caregiving quality and neurobiological regulatory systems, as well as the mediated path through attachment quality. The sections below explicate these developmental pathways and expand the model by describing cognitive-affective processes associated with disruptions in these neurobiological systems.

HPA Axis

The hypothalamic-pituitary adrenocortical (HPA) axis has two primary functions: mounting a stress response and maintaining a diurnal pattern. Glucocorticoids (cortisol in humans and other primates) are an end product of the cascade of biochemical reactions that are set in motion by exposure to a stressor. After about 4–6 months of age, infants do not typically mount a cortisol response in response to a stressor (Gunnar et al., 2009; Hostinar et al., 2014) unless the parent does not function effectively as a trusted protector.

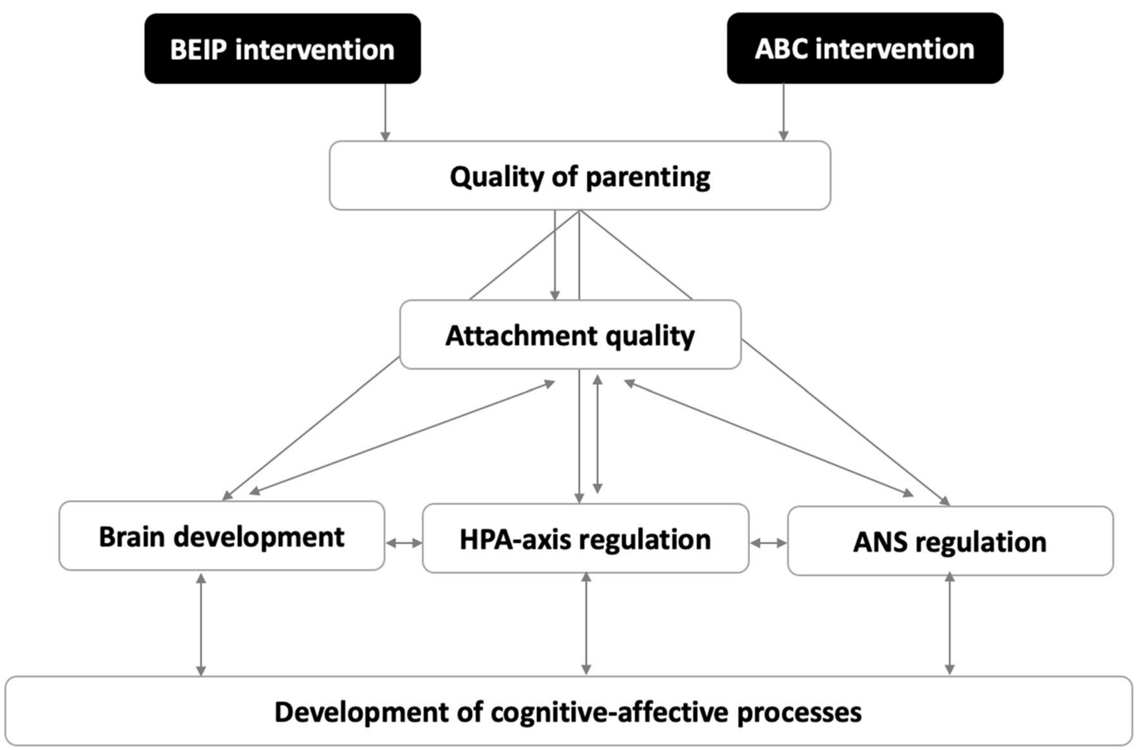

Fig. 1 Conceptual model of links between parenting, attachment, neurobiological regulatory systems, and cognitive-affective processes

This "parental buffering" (Gunnar et al., 2016, p. 474) may be adaptive in protecting the developing brain from high levels of circulating glucocorticoids.

Individual differences in cortisol reactivity among infants and young children are difficult to detect. Unlike rodents and other non-human primates, for whom stressful experiences lead to elevated levels of circulating glucocorticoids and associated neural atrophy (McEwen et al., 2016), human infants often do not mount a cortisol response unless they have disorganized or insecure attachments to parents (Bernard & Dozier, 2010; Gunnar et al., 1996). Even in studies that report differential reactivity, the more reactive infants are sometimes only returning to baseline cortisol levels rather than showing elevated levels of cortisol (Gunnar et al., 2009). Despite the lack of reliable evidence with humans, some theorize that inadequate care leads to high levels of circulating cortisol which are, in turn, responsible for alterations in human brain development (Lupien et al., 2009). We are cautious in making claims that support this theory due to limited evidence of elevated cortisol in research with human infants and young children. The role that the HPA axis plays in deficits seen in key brain regions is an important question for future research.

Whereas individual differences in cortisol reactivity often do not emerge, differences in diurnal patterning between children who have experienced differing levels of caregiving adversity appear robust. Fisher et al. (2000) and Bernard et al. (2010) found that children who had experienced adversity showed a blunted diurnal pattern relative to children who had not experienced adversity. For example, Bernard et al. found that children living under low-risk conditions showed the steepest slope from wake-up to bedtime and children living with child protective services-involved families showed the most blunted slope, with foster children intermediate between these two groups. Blunted diurnal cortisol slopes are predictive of regulatory difficulties and related emotional disorders later in life, as well as inflammatory immune responses (Adam et al., 2017), and callous-unemotional traits (Shirtcliff et al., 2009).

Autonomic Nervous System

The development of the autonomic nervous system, a second arm of the human stress system, is also impaired in the context of early life adversity, with downstream effects on children's cognitive-affective functioning. The autonomic nervous system (ANS) includes the parasympathetic nervous system and the sympathetic nervous system. The parasympathetic nervous system works to conserve and store energy, slowing heart and respiratory rates. Parasympathetic nervous system activity is commonly indexed by respiratory sinus arrythmia (RSA), which refers to the rhythmic fluctuation of heart rate during inhalation and exhalation. Higher levels of resting RSA reflect longer cardiac intervals between inhalation and exhalation, whereas lower levels of resting RSA reflect shorter intervals. RSA reactivity consists of decreases (vagal withdrawal or suppression) or increases (vagal augmentation) in RSA from baseline levels.

The sympathetic nervous system is activated when the body requires energy and alertness, increasing the heart and respiratory rates, and releasing stored energy. Sympathetic nervous system activity is generally indexed by skin conductance level (SCL; also known as electrodermal activity) or by pre-ejection period (PEP). SCL reflects the extent to which sweat glands in the electrodermal system are innervated by the sympathetic nervous system, with higher SCL values corresponding to elevated sympathetic activity. PEP represents the amount of time it takes from the beginning of ventricular depolarization to when the aortic valve opens, with lower PEP values corresponding to elevated sympathetic activity. Coordinated responding between the parasympathetic and sympathetic branches maintain homeostasis during periods of rest and mobilize physiological resources to respond to environmental demands.

Recent reviews of the literature suggest that maltreatment may lead to low resting RSA and blunted RSA reactivity (Holochwost et al., 2021; Young-Southward et al., 2020). Skowron et al. (2011) found maltreated preschoolers had lower resting RSA than those who were not maltreated. McLaughlin and colleagues (2015) found that 12-year-old children who were previously institutionalized showed blunted vagal withdrawal (i.e., smaller decreases from baseline) to a nonsocial stressor, relative to never institutionalized children. However, researchers do not always find that maltreated children show more blunted vagal withdrawal relative to comparison children during challenge tasks (e.g., Shenk et al., 2012). Mixed results in RSA could stem from various types of challenge tasks administered across studies, as well as from differences in the developmental timing, duration, and severity of maltreatment.

In terms of sympathetic nervous system functioning, evidence suggests that maltreatment may lead to blunted sympathetic reactivity over time (Holochwost et al., 2021; Young-Southward et al., 2020). By examining changes in PEP, McLaughlin et al. (2015) found that young adolescents who had been previously institutionalized had blunted sympathetic nervous system responses to a social stressor (i.e., the Trier Social Stress Test) compared to those who were never institutionalized. They suggested that inadequate caregiving might lead to heightened ANS reactivity to environmental demands in early childhood, but ultimately to reduce ANS reactivity later in life.

RSA is hypothesized to index an individual's readiness to engage with the physical and social environment and capacity for emotion regulation (Porges, 2007, 2011; Thayer &

Lane, 2000). Empirically, high resting RSA tends to be associated with healthy self-regulation (e.g., effortful control, executive functions, emotion regulation) and socioemotional competence, while low resting RSA has been associated with psychopathology (particularly externalizing disorders) among children, adolescents, and adults (Beauchaine, 2001, 2015; Butler et al., 2006; Eisenberg et al., 1995; Holzman & Bridgett, 2017). For low-risk children, vagal withdrawal during challenges (i.e., decreases in RSA from baseline levels) is generally associated with healthy outcomes, such as low internalizing and externalizing problems (El-Sheikh & Erath, 2011). Excessive vagal withdrawal, particularly during emotionally evocative tasks, is found among children at risk for psychopathology, relative to comparison children (Beauchaine, 2015), however. Taken together, moderate (but not excessive) levels of RSA reactivity in response to moderately challenging tasks are thought to be adaptive (Beauchaine, 2015). Findings are mixed, but most studies have found that lower resting sympathetic activity (lower SCL or higher PEP at baseline) and smaller increases in sympathetic activity in response to challenges are related to conduct disorders and externalizing problems (El-Sheikh & Erath, 2011; Lorber, 2004), whereas high sympathetic activity at rest and increased activity in response to challenges are related to anxiety, internalizing problems, and fearfulness (El-Sheikh & Erath, 2011).

Brain Regions and Networks

The regulatory efficiency and success of the HPA and ANS systems are highly dependent on adequate central nervous system functioning due to shared neurobiology. Key brain regions implicated in a variety of cognitive-affective processes include the amygdala and the prefrontal cortex, both of which are sensitive to the quality of early care. Using magnetic resonance imaging (MRI), researchers can study the structural and functional development of these regions, and using electroencephalography (EEG), they can examine the maturation of electrophysiological spectral power profiles of cortical brain activity. Other brain structures (e.g., the corpus callosum, uncinate fasciculus, and hippocampus) are also linked to inadequate caregiving and later adaptive functioning in childhood. In this paper we focus solely on research about the amygdala, prefrontal cortex, and spectral power. We first consider the amygdala, an early developing region with important links to processing emotions.

Amygdala

The amygdala plays a role in how people react to and process emotions (Davis & Whalen, 2001). The amygdala undergoes rapid changes early in development and is particularly dependent on environmental input, making it susceptible to the effects of early adversity (Tottenham et al., 2009). Even normative variation in early maternal sensitivity has measurable short- and long-term effects on amygdala development, with insensitive care leading to larger amygdala and hippocampus volumes during infancy (Rifkin-Graboi et al., 2015) and smaller hippocampal volume and total brain volume during middle childhood, adolescence, and adulthood (Kok et al., 2015; VanTieghem et al., 2021). Findings regarding associations between maltreatment and amygdala volume have been mixed (see Paquola et al., 2016 and Teicher et al., 2016 for a meta-analysis and systematic review, respectively), with psychosocial risk associated with reductions, increases, or no differences in volume. In a recent paper, VanTieghem et al. (2021) reported age-dependent volumetric alterations in a longitudinal sample of previously institutionalized children. In particular, the growth of the amygdala of previously institutionalized children reached its volumetric maximum earlier in development than was seen among comparison children. These results are in line with the stress acceleration hypothesis (Callaghan & Tottenham, 2016), which suggests that inadequate care early in life facilitates the early maturation of the brain so that the maltreated child, who does not have the protection of the parent, could reach regulatory independence sooner in development. Enlarged amygdala early in life may also be indicative of an earlier opening and closing of the amygdala's developmentally sensitive period among previously institutionalized youth. The conflicting findings of smaller, larger, or no differences in amygdala volume following early adversity could therefore be due to differences in age sampling or analytic decisions (i.e., controlling versus not controlling for age).

Volumetric differences between children with a history of institutional care and those raised by birth parents have been found years after children were adopted, suggesting that the amygdala fails to recover fully from the effects of early adversity. A dose–response association between early adversity and volume has been documented, but the direction of the effect differs among studies. For instance, Tottenham and colleagues (2010) reported positive associations between amygdala volume and length of institutional rearing, whereas Mehta and colleagues (2009) found negative associations. These inconsistencies may be driven by age-related differences in amygdala volume development (VanTieghem et al., 2021), variability in the operationalization of adversity (McLaughlin et al., 2019), severity (Hodel et al., 2015) and timing of adversity (Ho & King, 2021), or spurious effects.

Functional MRI (fMRI) data indicate that exposure to early adversity is associated with a sensitized amygdala. Two meta-analyses have shown that maltreatment history is linked with heightened amygdala reactivity to threat cues among children and adults (Heany et al., 2018; Hein &

Monk, 2017). A study that compared children who had experienced adversity, either in foster care in the United States or institutional care internationally, showed heightened amygdala sensitivity to emotionally charged facial expressions relative to children from low-risk conditions (Maheu et al., 2010). Tottenham and colleagues (2011) found that children who were previously institutionalized showed more elevated amygdala activation than never institutionalized children when viewing fearful faces on an Emotional Face Go/Nogo task. Increased amygdala reactivity during the processing of fearful faces among institutionalized children as compared to low-risk children follows a similar pattern to that observed among anxious versus non-anxious children and adults without a history of adversity (Hare et al., 2008; Stein et al., 2007), suggesting increased vulnerability to developing emotional disorders among previously institutionalized youth.

Children with a history of inadequate caregiving show problems regulating emotions that are associated with amygdala dysfunction. For example, children who have been maltreated have greater emotional reactivity, more deficits in emotional processing, and more internalizing symptoms (e.g., anxiety) than those without a history of maltreatment (Dalgleish et al., 2001; Ellis et al., 2004, Juffer & van IJzendoorn, 2005; Kaplow & Widom, 2007; Pollak et al., 2000; Tottenham et al., 2009; Vorria et al., 2006; Zeanah et al., 2009). Greater amygdala activation has been associated with deficits in social competence and eye contact (Tottenham et al., 2011). Findings related to amygdala volume and childhood emotional disorders are mixed, with both increases and decreases in amygdala volume showing associations with negative outcomes. For instance, larger amygdala volume has been linked with greater childhood anxiety and internalizing symptoms among both previously institutionalized (Tottenham et al., 2010) and non-institutionalized children (De Bellis et al., 2000; Etkin & Wager, 2007; Thomas et al., 2001). At the same time, reduced amygdala volume has been linked with heightened depression in maltreated groups of children and adolescence (Weissman et al., 2020) and those without a history of maltreatment (Rosso et al., 2005). Again, variations in the participants' ages across samples might be key to understanding discrepancies between amygdala volume and outcomes (VanTieghem et al., 2021).

Altogether, these studies suggest that potential mechanisms for the increased risk of anxiety disorders among maltreated children include alterations in amygdala volume, enhanced amygdala activation, and altered processing of emotional information (Barros-Loscertales et al., 2006; De Bellis et al., 2000; Derryberry & Reed, 2002; Vasey et al., 1996). This mediational pathway is represented in our conceptual model (see Fig. 1). Associations between maltreatment and enhanced amygdala sensitivity and differential neurological processing of emotional information are more consistent than those for amygdala volume. Although more research is needed to disentangle the complex ways in which type and timing of maltreatment are related to amygdala volume, altered amygdala neurodevelopment is likely a key factor in adversity-exposed children's precocial development. A sensitized amygdala that is more reactive to threats (Hein & Monk, 2017) and shows an accelerated structural development in high-risk contexts (Callaghan & Tottenham, 2016; VanTieghem et al., 2021) puts children at elevated risk for affective dysregulation and the onset of affective disorders. We consider the prefrontal cortex next because it plays such a key role in regulating the amygdala.

Prefrontal Cortex

The development of the prefrontal cortex is protracted relative to many other brain regions, continuing into the third decade of life (Gogtay et al., 2004; Rubia et al., 2006; Sowell et al., 2003). The prefrontal cortex's structural and functional development is highly susceptible to the quality of early experiences (Hart & Rubia, 2012; McLaughlin et al., 2016). Children who have been abused or exposed to violence show reduced prefrontal cortex volume. For example, relative to comparison children, physically abused children demonstrate reduced volumes of the right orbitofrontal cortex, right ventral-medial prefrontal cortex, and dorsolateral prefrontal cortex (Hanson et al., 2010). Additionally, decreased gray matter volume in the prefrontal cortex is found among adults who were maltreated in childhood (Andersen et al., 2008; Tomoda et al., 2009; van Harmelen et al., 2010; see also a meta-analysis by Paquola et al., 2016). Nonetheless, some studies suggest an opposite effect. For example, children who were maltreated and developed PTSD showed larger gray matter volume in prefrontal cortex areas than comparison children (Carrion et al., 2009; Richert et al., 2006). Considering that internalizing and externalizing psychopathologies also affect cortical development, inconsistencies in prefrontal cortex outcomes may be the consequence of early onset psychopathologies or may represent differential vulnerability to mental health problems (Whittle et al., 2014).

Whereas evidence is mixed regarding structural changes in the prefrontal cortex, maltreatment is more consistently associated with functional changes in the prefrontal cortex and related brain regions, particularly during tasks requiring inhibitory control. Using fMRI, Carrion et al. (2008) compared the neural activation of maltreated children with PTSD and non-maltreated children during a Go/Nogo task. Non-maltreated children demonstrated increased activation in the middle frontal gyrus, a region involved in response inhibition, relative to maltreated children. Maltreated children showed increased activation in the medial frontal gyrus and anterior cingulate cortex, relative to comparison children.

Previously institutionalized children also showed disruptions in the prefrontal network that are similar to the disruptions found for maltreated children during tasks requiring response inhibition (e.g., Mueller et al., 2010). Finally, Gee et al. (2013) found more adult-like functional connectivity patterns between the prefronal cortex and the amygdala in previously institutionalized children than in low-risk youth, further supporting Callaghan and Tottenham's (2016) stress acceleration hypothesis.

The prefrontal cortex is involved with emotion regulation and executive functions, such as higher order cognition (e.g., planning, inhibitory control, memory, and allocating attention; Miller & Cohen, 2001). Children who have experienced adversity show higher rates of problems that are frontally mediated, including problems with executive functions and ADHD, compared to children without a history of maltreatment or institutionalization (Kreppner et al, 2001; Nolin & Ethier, 2007; Pechtel & Pizzagalli, 2011; Stevens et al., 2008). ADHD is associated with reduced cortical gray matter volume, typically in prefrontal cortex regions (Ellison-Wright et al., 2008; Shaw et al., 2006), and with diminished middle frontal activity and enhanced medial frontal activity (Booth et al., 2005; Schulz et al., 2004). Emerging evidence also suggests that children's cortical morphology directly mediates the association between early adversity and self-regulation. For instance, McLaughlin et al., (2014b) found that widespread cortical thinning in the lateral orbitofrontal cortex (as well as the insula, inferior parietal cortex, precuneus, superior temporal cortex, and lingual gyrus) mediated the association between history of institutionalization and inattention/impulsivity. Moreover, Demers et al. (2019) found that adult frontal lobe volume mediated the association between adolescent relationship quality with the parent (but not maltreatment status) and adult adaptive functioning. Finally, Valadez et al. (2020) found that mean brain activation to parental cues across temporo-parieto-occipital areas, including the anterior and posterior cingulate cortex, mediated the association between the quality of care during infancy and internalizing symptoms during middle childhood. These results suggest that early caregiving adversity is associated with disruptions in prefrontal region function and structure, which then predispose children to problems of attentional control, impulsivity, and regulatory difficulties.

Electrophysiological Spectral Power Profiles

The process of brain maturation and the adverse effects of insensitive care can also be captured by studying the electrophysiological signatures of cortical development. Using electroencephalography (EEG), we can measure children's electrophysiological spectral power profiles that are associated with neuromaturation. Greater EEG power at rest in high-frequency bands (e.g., high alpha and beta bands) and lower power in low-frequency bands (e.g., theta band) are linked to cortical maturation (Stamoulis et al., 2015). Children with a history of early institutional care or risk for abuse have lower spectral power in high-frequency alpha and beta bands and greater spectral power in low-frequency theta bands than children without such histories (e.g., Marshall et al., 2004). These profiles of resting spectral power may indicate delays in cortical maturation and regulatory efficiency.

Marshall et al. (2004) found that children institutionalized in Romania (ages 6 to 30 months) showed different patterns of EEG activity than comparison children. Specifically, institutionalized children showed higher levels of theta power and lower levels of alpha and beta power compared to children who were not in institutions. This pattern of brain activity may suggest a deficit in cortical development or a maturational delay (Marshall et al., 2004), since the proportion of alpha and beta power relative to theta power is expected to increase as the brain matures (Marshall et al., 2002; Stamoulis et al., 2015). The increased low-frequency activity and reduced high-frequency activity among these institutionalized children was longitudinally sustained, appearing at an assessment when these children were 42 months old (Marshall et al., 2008), as well as when they were 12 and 16 years old (Debnath et al., 2020; Vanderwert et al., 2016). Finally, in a sample of institutionalized children, baseline EEG activity early in life characterized by increased low-frequency activity and reduced high-frequency activity predicted elevated hyperactivity and impulsivity symptoms years later (McLaughlin et al., 2010). Similarly, having a resting EEG profile of increased low-frequency activity and reduced high-frequency is associated with ADHD in children (Barry et al., 2003). Taken together, EEG markers of cortical development may contribute to our understanding of maturational processes following adversity exposure. Given the measure's impressive temporal resolution, it is also a robust measure for the study of cognitive-affective processes.

Intervening to Ameliorate the Effects of Early Inadequate Care

The effects of parental care on children's brain and behavioral development are compelling. Children who experience inadequate care in the form of deprivation or threat are less likely than other children to develop secure attachments to parents such that they can rely on parents confidently when distressed. They are less likely than other children to develop healthy HPA axis functioning which supports a typical sleep–wake cycle; they are more likely to have ANS functioning indicative of problems with emotional reactivity and regulation; they are more likely to have a sensitized amygdala, with greater propensity to sense threat; their prefrontal cortex is likely to be less well suited to delaying gratification or making wise choices; and they are more likely to have profiles of brain activity consistent with hyperactivity and impulsivity. But we argue here that such outcomes are almost entirely preventable. Parental sensitivity can be enhanced with effects on children's brain and behavioral outcomes.

Evidence from observational studies and from randomized clinical trials (RCTs) demonstrates there can be at least partial, and in some cases remarkable, recovery from the deleterious effects of early adversity on children's biological regulation and brain development. We review two examples of randomized clinical trials of interventions with adversity-exposed children. These interventions (depicted at the top of Fig. 1) were implemented during infancy or early childhood and were designed to alter risky developmental pathways. Studies followed children's outcomes at least into middle childhood. The first intervention example is rare indeed. The investigators were able to randomize children from orphanage care (typically the most extreme condition of deprivation) to care as usual or to foster care, thus allowing the only experimental test of the effects of orphanage care ever conducted. In the second example, the investigators examined the effectiveness of an early parenting intervention designed to enhance sensitivity among parents of infants who had experienced challenges. Given that participants are randomized to condition in RCTs, causal claims regarding the effects of different caregiving conditions can be made.

The Bucharest Early Intervention Project (BEIP)

Findings from observational studies suggest that when children are adopted out of institutional care into advantaged families, they show impressive recovery in many domains of functioning (van IJzendoorn et al., 2005; van IJzendoorn & Juffer, 2006). However, such evidence from observational studies could potentially be influenced by factors such as selection bias and expectancy effects. For instance, more competent children may be more likely to be adopted than those who are less competent, which would lead to overestimates of children's recovery when examining functioning of children in institutions relative to those who have exited institutions.

Beginning in 2001, the BEIP intervention study was conducted with children who had been living in orphanages in Romania. Charles Nelson, Nathan Fox, and Charles Zeanah were invited to conduct a randomized clinical trial in Romania not long after the fall of Ceausescu when about 100,000 children were found in orphanages in deplorable conditions. Children were randomly assigned to either continue in orphanage care (care as usual group) or were placed into the homes of trained, supported foster parents (foster care group). The foster care program, based on Zeanah's New Orleans model, drew from attachment theory, encouraging parents to psychologically invest in and be responsive to their foster children. Foster parents were also trained to establish consistent routines and manage behavior appropriately. Children in the care as usual group typically stayed in orphanage care for some period of time, although many were ultimately placed into state run foster care or returned to birth parents. Follow-up assessments were conducted to compare cognitive, affective, and neural outcomes between children in the two groups. In addition to the care as usual and foster care groups, the BEIP enrolled a group of demographically matched children who had never been institutionalized (never institutionalized group) to allow for comparisons between children with a history of institutionalization and those without.

When children in the BEIP were between 12 and 31 months of age, their attachment quality was assessed in the Strange Situation Procedure (Ainsworth et al., 1978). Zeanah and colleagues (2005) examined differences in attachment between children who had been institutionalized—those who would later be assigned to either the care as usual or foster care groups—and children with no history of institutionalization. As predicted, most institutionalized children failed to develop an organized attachment to their caregivers. In the few cases of organized attachments among institutionalized children, these were rated as not fully formed, according to a continuous rating of attachment formation. By contrast, the majority of children in the never institutionalized group had secure attachments to their parents, and all of them were rated as having a fully formed attachment relationship.

The preschool attachment classifications of these children were assessed again a few years later by Smyke and colleagues (2010). More children in the foster care group had secure attachments and higher ratings of security than children in the care as usual group. Significantly fewer children in the foster care group had disorganized-controlling or insecure-other classifications than children in the care as usual group. The distribution of attachment classifications was not significantly different between children in foster care and never institutionalized groups. These findings suggest that children may experience marked recovery in their attachment relationships when they are placed with trained and supported foster parents at a young age. The age at which children were placed into foster care predicted recovery, with secure attachments more likely for those who were placed at younger ages (i.e., before 24 months of age).

McLaughlin and colleagues (2015) administered the Trier Social Stress Test—a psychosocial stress task that reliably triggers a stress response in typically developing children—to youth in the BEIP when the children were approximately 12 years old. They found blunted cortisol responses to the stress task for the care as usual group relative to children who were placed in enhanced foster care. At age 12, children's autonomic nervous system (ANS) activity was also assessed (McLaughlin et al., 2015). Children in the care as usual group showed elevated sympathetic nervous system activity at rest (i.e., lower PEP) than children in the foster care group. Parallel to their finding of hyporeactivity of cortisol responses for those in the care as usual group, they found blunted sympathetic nervous system reactivity to a stressor among children in the care as usual group, relative to children in the foster care intervention group.

BEIP researchers also examined children's structural brain development during middle childhood. Although children in the foster care and the care as usual groups did not differ from each other in total gray matter or amygdala volume, the foster care group showed some catch up in white matter growth; those in the foster care group fell between the care as usual and never institutionalized groups in total cortical white matter volume (Sheridan et al., 2012). Given that myelination supports efficient communication between cortical and subcortical structures (Nunez et al., 2015), disruption of white matter development may be one mechanism through which institutionalization leads to worse adaptive functioning among children with a history of institutional care (see the mediational pathway through brain development in Fig. 1).

The BEIP team also studied children's brain electrical activity through EEG. As expected, 8-year-old children who had been randomized to foster care had greater alpha band power and lower theta band power in specific regions of the left hemisphere than children randomized to care as usual (Vanderwert et al., 2010). Interestingly, this intervention effect on high-frequency alpha power was partially mediated by greater total white matter volume (Sheridan et al., 2012). In addition to these intervention effects, robust effects emerged related to the age at which children left institutional care, with higher frequency alpha and beta power seen among children placed into foster care before 2 years of age than among children placed after 2 years of age (Stamoulis et al., 2015; Vanderwert et al., 2010, 2016).

Attachment and Biobehavioral Catch-up (ABC)

Attachment and Biobehavioral Catch-up is designed to help parents behave in nurturing ways when children are distressed, to follow children's lead, and to avoid frightening or harsh behavior. Dozier and colleagues (Dozier & Bernard, 2019) developed the ABC intervention to support parents of infants who experienced adversity, with the expectation that children's outcomes would be improved. The efficacy of ABC has been tested through randomized clinical trials with child protective services-involved birth parents, foster parents, and parents adopting internationally (Dozier & Bernard, 2019).

ABC is a home-visiting intervention consisting of 10 sessions that are delivered by parent coaches. To ensure that the ABC intervention is implemented with fidelity, parent coaches are screened, trained, and supported by supervisors. While delivering the manualized content, parent coaches also make frequent in-the-moment comments (once per minute) about parents' behavior. Comments draw parents' attention to specific behaviors that are linked with the intervention targets (e.g., following the child's lead) and point out the effects that those behaviors have on children's concurrent and long-term outcomes.

To test the efficacy of ABC, families with infants who were involved with the child protective services (CPS) system were recruited. Parental sensitivity was assessed at baseline, and families were randomly assigned to receive either the ABC intervention or a control intervention similar in duration and delivery. We limit this review to findings from the longitudinal follow-up assessments of the RCT conducted with CPS-involved birth parents. Assessments were completed when children were in early childhood and middle childhood, and an adolescent wave of data collection is currently in progress.

Bernard and colleagues (2012) examined whether the quality of children's attachments differed for children whose parents had received the ABC intervention compared to those whose parents received the control intervention. Parents in both groups were involved with child protective services because they were at risk of maltreating their children. They were randomized to an intervention group when children were an average of 10 months old. Attachment classifications were assessed using the Strange Situation Procedure (SSP) after the intervention was completed. At the time of the Strange Situation, children were on average 19 months old. Children in the ABC intervention group were more likely to have secure attachments and less likely to have disorganized attachments than children in the control intervention group (Bernard et al., 2012).

In middle childhood, children rated their perceived attachment security using the Kerns Security Scale (Zajac et al., 2020). Children whose parents were randomized to receive the ABC intervention during infancy reported higher levels of attachment security than children whose parents were randomized to receive the control intervention. Thus, the 10-session ABC intervention influenced the quality of children's attachments over the course of at least eight years. The results of both the BEIP and ABC underscore the importance of intervening early to foster vulnerable children's attachment security and promote their adaptive functioning through high-quality caregiving.

Children whose parents received the ABC intervention showed more normative patterns of diurnal cortisol production than children whose parents received the control intervention. Specifically, three months and three years post-intervention, and during an early childhood follow-up assessment, children in the ABC group showed steeper diurnal patterns of change in cortisol (i.e., from morning to evening) than children in the control intervention group (Bernard et al., 2015a, 2015b). In middle childhood, intervention effects on diurnal cortisol production were mediated by parental sensitivity. Specifically, receiving the ABC intervention led to enhanced parental sensitivity, which in turn led to children having steeper declines in cortisol from wake-up to bedtime (Garnett et al., 2020). Given that children in this CPS-referred sample are now in adolescence, current follow-up assessments are examining whether the intervention effect on diurnal cortisol slope is sustained through adolescence.

Autonomic regulation was also assessed during middle childhood (Tabachnick et al., 2019). When children were 9 years old (i.e., approximately 8 years after receiving an intervention), parent–child dyads participated in baseline resting tasks and interaction tasks. Children's heart rates, RSA, and SCL were measured during the tasks. As compared to children in the control group, children in the ABC group had higher average resting RSA and lower average resting heart rates. These findings suggest that the ABC intervention leads to children having enhanced autonomic regulation.

Bick and colleagues (2019) examined whether children's EEG patterns differed as a function of whether their parents had received the ABC intervention or the control intervention, attempting to replicate the BEIP findings. They also examined EEG among children whose parents did not have a history of CPS involvement (i.e., a low-risk comparison group). Consistent with the pattern of findings from the BEIP (Stamoulis et al., 2015; Vanderwert et al., 2010, 2016), children whose parents received the ABC intervention had greater power in the high-frequency beta band than children whose parents received the control intervention. Whereas children whose parents received the control intervention differed significantly from the low-risk comparison group in beta power, children whose parents received ABC did not differ significantly from this low-risk group, supporting the assumption that greater power in the high-frequency band reflects a more optimal outcome than lower power.

ABC's long-term intervention effects on children's brain development were examined in fMRI tasks when children were about 9 years old (Valadez et al., 2020). In a first task, children viewed pictures of their mothers and strangers to assess neural activation related to maternal cues. Relative to children in the control condition, children in the ABC group showed increased activation in the precuneus, middle temporal gyrus, temporal fusiform cortex, lateral occipital cortex, and the hippocampus when they were looking at their mothers versus strangers. These brain regions are implicated in social cognition (e.g., theory of mind) and social representations. Increased neural reactivity to viewing mother versus stranger also predicted fewer parent-reported problem behaviors on the Child Behavior Checklist (CBCL). In a second task, children viewed scared and neutral faces of adults—stimuli that reliably activate the amygdala and the prefrontal cortex. Children in the ABC group showed increased prefrontal cortex activation, an indicator of better regulatory capacity, relative to children in the control intervention group (Valadez et al., 2021).

These experimental findings from the BEIP and ABC studies demonstrate the power of enhancing sensitive care for children who experienced adversity. Both interventions have had impressive effects on children's physiological and brain development. In addition, these studies allow causal inferences regarding the role of sensitive parenting on children's developing brain and regulatory systems.

Future Directions

In this paper we focused primarily on the effects of inadequate care on children's brain and behavioral development. The BEIP and ABC interventions were both implemented in early childhood, with children who has experienced adversity early in their development. These are first steps in understanding what leads to recovery following early inadequate care, but many questions remain and these early findings should be replicated.

A related question is whether these associations persist across adolescence and beyond. During adolescence neurobiological regulatory systems undergo recalibration, attachment relationships with parents change, and attachments to peers increase in importance (Ainsworth, 1989; Dow-Edwards et al., 2019). Some adolescent outcomes of the BEIP intervention have now been published (e.g., Mukerji et al., 2021; Tang et al., 2020), and ABC intervention researchers will have results in the next couple years from their adolescent wave of data collection. These studies will shed light on some developmental continuities and discontinuities, but many questions remain unexplored.

Mixed findings emerging from prior research may possibly be clarified by a careful analysis of factors related to inadequate caregiving, such as the developmental timing of onset of maltreatment (or timing of removal from institutional care), the frequency, duration, and severity of maltreatment, and the nature of maltreatment (e.g., deprivation versus threat, McLaughlin et al., 2014a). Neurobiological development may also be influenced by risk factors that frequently co-occur with inadequate care but are not adequately modeled. For example, poverty, prenatal substance use, postnatal substance exposure, and neighborhood quality may differ among samples who have similar adversity exposure. Differences in these other variables (holding maltreatment constant) may explain mixed findings, given that such variables play a role in the development of children's neurobiology and cognitive-affective processing.

We highlighted research from two randomized clinical trials partially to allow considerations of *causal* associations, particularly the links between quality of parental caregiving, attachment, and neurobiological development. More experimental and longitudinal work is needed to clarify the nature of associations in the model. A systems approach would allow researchers to examine mediational pathways and bidirectional interactions that become more elaborated over time. But we also highlighted the BEIP and ABC research to demonstrate the power of early intervention in altering developmental trajectories.

Conclusion

Infants and young children need a parent who can serve as a partner in interaction and protect them from threat. Although infants can adapt to a range of caregiver responsiveness, optimally parents are sensitive to infants' cues and responsive to bids for reassurance. In such cases, parents serve effectively as buffers from otherwise overwhelming or frightening stimuli. These conditions support the development of secure, organized attachments and neurobiological regulatory systems that are sensitive to environmental input. We have presented evidence that the HPA axis and the autonomic nervous system are affected by early caregiving experience, and that alterations in the stress response system are associated with social-affective processes that underlie the development of psychopathology. We also reviewed research showing that inadequate caregiving leads to changes in brain development, including changes in the structure and functioning of the amygdala, prefrontal cortex, and spectral power profiles. Such changes are linked with inhibitory control, emotional processing and regulation, and higher order cognition—processes critical for adaptive functioning. Although complete recovery from maladaptive developmental trajectories initiated early in life may not always be possible, evidence from randomized clinical trials suggests that interventions can alter the downstream effects of early childhood adversity to enhance resilience. Developmental pathways tend to become somewhat canalized over time. Nonetheless, evidence from intervention studies suggests that altering or enhancing parental quality of care can alter children's developmental pathways. When the quality of care is improved, changes in brain and regulatory systems, as well as in accompanying cognitive and emotional functioning, may be seen.

Declarations

Conflict of interest Mary Dozier is the developer of the Attachment and Biobehavioral Catch-up Intervention. She works on a non-profit basis.

Ethical Approval The research was approved by the University of Delaware Institutional Review Board.

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