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Early adversity, child neglect, and stress neurobiology: From observations of impact to empirical evaluations of mechanisms

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Abstract

Research on the effects of early life adversity, and in particular on the absence of responsive caregiving, has shown long-term impacts on well-being and development. These investigations have been conducted both in human populations and in animal models. The work has demonstrated that neglect experienced in the early years can affect not only behavior but also neurobiological functioning. In particular, studies of children in the foster care system show convergence with research on children adopted following institutional rearing in terms of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which produces the neuroendocrine hormone cortisol. The characteristic pattern that has been most commonly observed involves diminished diurnal cortisol production, particularly in terms of low levels of cortisol upon awakening. Notably, however, a number of evidence-based interventions for infant, toddler, and preschool-aged foster children have been shown to produce more typical patterns of cortisol production, in combination with improved behavioral, socioemotional, and foster care placement outcomes. In this paper, we review the literature on the effects of early disruptions in care on biobehavioral development, and summarize the results of the interventions for young foster children.

Keywords

Early life adversity; Neglect; Neuroendocrine; Cortisol; Foster care; Early intervention

1. A brief historical overview of parallel lines of research on early adversity/child neglect and stress neurobiology

Adverse experiences in the early years of life have long been understood to exert a long-term impact on children's biobehavioral development. Although this work has many historical sources, one of the primary origins of this knowledge base can be traced to research beginning in the 1960s, documenting the harmful effects of child maltreatment on child wellbeing (e.g., Elmer, 1960; Elmer and Gregg, 1967; Kempe et al., 1962). Recognition of the population-level consequences of child maltreatment (e.g., Fontana, 1973) led to the rise

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of the children's rights movement in the United States, and prompted the adoption of mandated reporting laws. These developments paralleled the introduction of "Great Society" early childhood programs such as Head Start, which were designed to serve economically disadvantaged children (Miller-Perrin and Perrin, 2013). In the ensuing decades, investigations have expanded to differentiate between different types of maltreatment, to study children in the child welfare system in particular, and to explicate underlying mechanisms by which early adverse experiences lead to various neurobiological and behavioral outcomes.

Research on child maltreatment and on children in the child welfare system greatly expanded during the 1970s through the 1990s. Initially, child welfare system researchers and others studying early adversity differentiated very little between different types of child maltreatment; the child welfare system included children who had experienced varying levels of severity and types of abuse (e.g., physical, sexual, and emotional) and neglect (e.g., supervisory and medical), all of which were regarded as harmful. Over time, however, researchers began to consider whether specific dimensions (e.g., type, duration, timing, severity) of child maltreatment and related adverse experiences might lead to distinct outcomes (e.g., Allen and Oliver, 1982; Egeland et al., 1983; Manly et al., 1994; Trickett and McBride-Chang, 1995).

Among the insights during this period was an increased understanding of the long-term negative consequences of child neglect (e.g., Widom, 1989, 1999). Specifically, neglected children were observed to perform worse than physically abused children across a number of measures, including academic performance, language development, creativity, and confidence (e.g., Allen and Oliver, 1982; Eckenrode et al., 1993; Egeland et al., 1983). Consequently, researchers came to recognize neglect—and more generally, the absence of responsive care—as a social problem in and of itself warranting investigation and intervention. This understanding was coupled with a growing awareness of the prevalence of neglect within the child welfare system population, in U.S. society in general, and in other international contexts (Fisher et al., 2006). Subsequently, research has continued to validate the deleterious effects of neglect on development, spurring efforts to develop and implement appropriate policies and interventions for children and caregivers (c.f., National Scientific Council on the Developing Child, 2012).

A parallel line of research has simultaneously emerged over the past half century, exploring animal models of early experience on subsequent development. Broadly, these models provide evidence that early stressful experiences affect not only behavioral and socioemotional development, but also neurobiological development (Levine, 2005; Sánchez and Plotsky, 2001). In particular, rodent early life stress models employing paradigms such as maternal separation and handling have documented that disruptions in caregiving can impact stress reactivity in offspring, as indexed by behavioral and endocrine abnormalities, including abnormalities in the neuroendocrine stress response system (Levine, 2005; Zhang et al., 2004).

The hypothalamic-pituitary-adrenal (HPA) axis has been characterized as a final common pathway for stress regulation (Pecoraro et al., 2006) because it helps perform a variety of functions in the presence of stressors, including mobilizing the immune system, metabolizing energy, and even supporting memory formation (McEwen, 2007, 2008; Sapolsky et al., 2000). The HPA axis operates via a cascade of hormones. Specifically, in response to a stressor, the hypothalamus releases corticotropin-releasing factor (CRF). The release of CRF triggers the release of adrenocorticotropic hormone (ACTH) in the pituitary gland, which in turn triggers the release of glucocorticoids in the adrenal gland (e.g., cortisol in primates, corticosterone in rodents). Elevated glucocorticoid levels inhibit the release of hormones in regions with glucocorticoid receptors through a negative feedback process, suppressing HPA axis activation. Importantly, elevations in glucocorticoid levels can occur in response to a real or perceived stressor, but also occur naturally throughout the day, reaching their highest levels about 30 min after waking in the morning. Accordingly, cortisol reactivity (i.e., cortisol levels in response to a stressor) and diurnal cortisol patterns (i.e., normal daytime cortisol levels) can serve as distinct indices of HPA axis functioning in humans.

HPA axis functioning is influenced by developmental experiences. Most research looking at the effects of early adversity on HPA axis development have focused on diurnal cortisol levels in infants and toddlers. Less is known about HPA axis development through adolescence, although some studies suggest that the HPA axis may undergo a second large wave of change or recalibration during puberty among adolescents who have experienced early life stress (e.g., DePasquale et al., 2019; Quevedo et al., 2012). Nevertheless, neurobiological effects of early adversity can and often do persist into adulthood (for review, see Lupien et al., 2009). One potential mechanism by which early adverse experiences may impact later neuroendocrine outcomes is through changes at the level of the epigenome. For example, the presence (or absence) of maternal licking and grooming in the first week postnatally has been found to impact the expression of the glucocorticoid receptor in the rat hippocampus, and in doing so influences the release of hormones such as ACTH and corticosterone in response to stress across the lifespan (Meaney and Szyf, 2005).

Primate studies modeling the effects of early adversity have involved manipulations of caregiving via maternal separation, cross fostering, and peer-rearing (Suomi et al., 1976). As with rodent models, nonhuman primate studies of early life stress reveal an association between disruptions in responsive care during the perinatal period and abnormal behavioral and neuroendocrine stress responses later in life (Levine, 2005; Sánchez and Plotsky, 2001). Taken together, both rodent and primate models have served to support the concept that early experiences can literally “get under the skin” in highly specific ways, influencing biobehavioral development in a pervasive manner (Drury et al., 2016; Sánchez and Plotsky, 2001).

1.1. Social buffering as a moderator of the effects of early life stress on biobehavioral development

Animal models also provide evidence that responsive caregiving can act as a buffer against the negative effects of early adversity. Social buffering refers to the process by which social support (e.g., in the form of responsive caregiving) protects against negative outcomes later in life. One way in which responsive caregiving can serve as a social buffer is by facilitating regulation of the infant's physiological stress response system, which is not fully mature at birth. In both rats and primates, maternal interactions have been found to help moderate infants' physiological responses to stress, inhibiting HPA axis reactivity in the presence of stressors (for review, see Strüber et al., 2014). Similarly, research with humans provides evidence that responsive caregiving can mediate cortisol reactivity in children, promoting healthy development of the HPA axis (for review, see Flannery et al., 2017).

Importantly, research on social buffering has provided impetus for the concept that intervening to improve responsive caregiving early in life could have far-reaching effects, altering the physiological stress response system (Meaney and Szyf, 2005; Sánchez and Plotsky, 2001). Subsequently, the concept of developing interventions focused on the stress buffering role of caregiving has been extended from animal models to human research (Dozier et al., 2002). As discussed later in this paper, this line of research highlights the possibility and value of identifying neurobiological mechanisms by which early adversity affects later outcomes, and using knowledge of these mechanisms to develop targeted interventions.

1.2. Parallel lines connect: Stress neurobiology in child welfare system and other maltreated children

By the early 2000s, child maltreatment researchers began to consider how animal models of neglect might provide insight into mechanisms underlying the effects of early adversity observed among children in the child welfare system. In particular, researchers began to explore HPA axis activity among children in the child welfare system (Fisher et al., 2000). Much of this research focused on diurnal cortisol production, an important component of HPA axis function (Dozier et al., 2002).

Research on daytime cortisol levels in maltreated infants and preschoolers (Gunnar et al., 2006) revealed abnormal patterns of daytime cortisol production among children. The diurnal cortisol pattern is typically established by two to three months of age, characterized by a morning peak that occurs shortly after awakening, and a steep decline throughout the day, with levels close to zero by bedtime (Price et al., 1983; Stalder et al., 2013). In contrast, when Dozier et al. (2006a) examined diurnal cortisol levels among children (ages 20–60 months) who had initially been placed in foster care as infants, they found diminished morning cortisol levels and a smaller change in cortisol levels across the day than among a comparison group of non-maltreated same-aged children. Likewise, Bruce et al. (2009a) observed significantly lower morning cortisol levels among preschool-aged foster children compared to a group of preschool-aged children with no history of maltreatment. Notably, the comparison group in the study by Bruce et al. (2009a, 2009b) comprised a low-income community sample, indicating that diminished cortisol levels were not readily explained by poverty or other structural inequalities affecting low income families.

Somewhat serendipitously, in addition to the stress neurobiology research in the early 2000′s on children in the child welfare system, a separate group of researchers was engaged in studying the effects of early adverse experiences among children who had been adopted after being reared in institutional "orphanages" in other countries (e.g., Carlson and Earls, 1997; Gunnar et al., 2001; Koss et al., 2014). This work similarly revealed cortisol abnormalities. For example, Koss et al. (2014) found that compared to children raised by their birth families, children who were adopted following early institutional rearing exhibited lower morning cortisol and a smaller change in cortisol throughout the day.

Overall, the convergent findings regarding diurnal cortisol patterns in foster and post-institutionalized adopted children provided strong evidence of the connection between early adversity and diminished cortisol production (Fisher and Gunnar, 2010). One proposed mechanism of diminished cortisol levels observed in the absence of responsive care involves a process of HPA downregulation, an adaptive and energy-conserving response (Gunnar and Vazquez, 2001; Koss and Gunnar, 2018; McEwen, 2008). Moreover, the fact that diurnal cortisol abnormalities were observed in both groups prompted researchers to consider whether common early life experiences might provide an explanation. *Specifically, one early life experience shared by many post-institutionalized adopted children and children in foster care was the absence of supportive, responsive care.* To examine this hypothesis (i.e., that alterations in the HPA axis were associated with the absence of a buffering adult), Bruce et al. (2009a, 2009b) coded child welfare case records of a sample of foster preschoolers to investigate whether different types of maltreatment, and particularly neglect, might be associated with different patterns of cortisol production. Using a standardized coding system (Barnett et al., 1993) to obtain a high quality and detailed measure that allowed for differentiation between types of maltreatment, Bruce et al. (2009a, 2009b) found that low morning cortisol was indeed primarily associated with neglect (versus other forms of maltreatment) in their foster preschooler sample. Notably, neglect was the single most common form of maltreatment experienced by foster children in the sample. Thus, Bruce et al.'s (2009a, 2009b) findings provided support for the idea that the absence of responsive care is a key contributor to HPA axis dysregulation.

Neglect has since been recognized as by far the most prevalent form of maltreatment. Recent epidemiological studies estimate that approximately 674,000 children in the United States suffered from child abuse or neglect in 2017, and the majority of these children (74.9%) experienced neglect (U.S. Department of Health and Human Services, 2019). In addition, neglect is by far the most common reason for placement in foster care nationally; preliminary estimates indicate that neglect was associated with 62% of cases in which children were removed from their homes in the United States in 2017 (U.S. Department of Health and Human Services, 2018). Taken together, these statistics document the magnitude of the public health problem represented by neglect.

One important disclaimer is that although the majority of studies examining HPA axis activity among maltreated children have found neglect to be associated with low morning cortisol levels and blunted activity across the day, this finding is not ubiquitous. Several studies have observed elevated cortisol among foster children and maltreated children relative to controls (e.g., Dozier et al., 2006b; Cicchetti and Rogosch, 2001) and at least one study has observed elevated *variability* in cortisol production across time among foster children (Fisher and Stoolmiller, 2008). A possible, but unexplored, explanation for discrepant findings regarding the directionality of cortisol abnormalities (e.g., elevated cortisol vs. blunted cortisol) may be variations in the timing and severity of neglect experiences among different samples. While chronic exposure to stress may initially elicit heightened cortisol production in a child, the evolutionary process of downregulation can prompt the HPA axis system to conserve energy by adjusting to lower cortisol production (Gunnar and Vazquez, 2001; Miller et al., 2007). Consequently, neglected children may experience a stage of elevated cortisol production before exhibiting diminished cortisol production, resulting in mixed findings across studies. The directionality of cortisol abnormalities may also vary among maltreated children based on factors such as whether they are raised in foster care or by their birth parents (Bernard et al., 2015a). In any case, both elevated and blunted cortisol production can be a cause for concern.

Importantly, cortisol abnormalities that have been observed in the context of neglect are concerning because dysregulated HPA axis function is associated with a range of long-term negative consequences. Specifically, chronically dysregulated cortisol levels can affect brain function, especially when dysregulated during sensitive periods of brain development, which can increase individuals' vulnerability to a number of psychological and physical disorders throughout the lifespan (Heim and Nemeroff, 2001; Lupien et al., 2009; McEwen, 2008). In particular, a systematic review and meta-analysis by Adam et al. (2017) found a *flatter diurnal cortisol slope* to be associated with a range of health problems across domains, including immune functioning, cancer, and depression. Consistent with these findings, in addition to being associated with cortisol abnormalities, childhood neglect has been found to be predictive of psychopathology in adolescence and adulthood (Green et al., 2010; Kessler et al., 2010; McLaughlin et al., 2012).

Overall, then, the collective body of research in this area documents the critical role of responsive relationships with caregivers in early childhood in supporting healthy development. As the above review makes clear, neglect—or the absence of such relationships—can seriously impair development, leading to enduring biobehavioral consequences. Taken together, these facts and findings identify neglect as a public health problem that merits continued research and resources directed towards understanding mechanisms and developing targeted interventions to prevent negative outcomes.

2. Interventions to address behavioral and neurobiological functioning following early neglect: the advent of mechanism experiments

Although initial studies examining cortisol levels among children in the child welfare system provided evidence for the hypothesis that early responsive relationships are associated with alterations in HPA axis functioning, these studies established only correlation; they were insufficient to conclude that early responsive relationships might be a *causal mechanism* by which HPA axis regulation occurs. Initial studies described above consistently observed correlations between non-responsive early relationships and abnormal cortisol levels. However, to establish causation, random assignment is necessary.

Because randomly assigning children to either receive responsive or nonresponsive care is ethically and logistically infeasible, an alternative approach was required. One alternative approach is to randomly assign children and caregivers to either receive an intervention that targets early responsive relationships or to be part of a control group (e.g., no intervention, control intervention). The hypothesis that early responsive relationships affect HPA functioning suggests that if an intervention changes the quality of early responsive relationships, these changes will in turn alter regulation of the HPA axis. If the intervention changes the quality of early responsive relationships, but does not change HPA axis regulation, the original correlation observed between early relationship quality and HPA axis functioning is likely attributable to other factors rather than representing a direct causal relationship.

As reviewed below, randomized clinical trials (RCTs) of three different interventions that target responsive caregiving among children who have experienced neglect have generally supported the idea that early responsive relationships are causally linked to HPA axis functioning. Notably, however, as the following review indicates, the hypothesis that improving early responsive relationships through intervention normalizes HPA axis functioning such that healthy HPA axis functioning becomes trait-like is a bit of an oversimplification and overstatement of the evidence base. As such, the relationship between these two variables requires some elaboration.

2.1. The ABC intervention

One intervention that targets early responsive caregiving and has been tested in the context of multiple RCTs is the Attachment and Biobehavioral Catch-Up (ABC) intervention developed by Dozier and colleagues. Based in principles of attachment theory, the ABC intervention targets three parent behaviors that promote responsive caregiving: a) nurturing children when they are distressed, b) following the infant's lead during play, and c) limiting harsh or frightening parent behaviors (Dozier et al., 2006b; Hoye and Dozier, 2018). The intervention is designed to impact child dysregulation by teaching caregivers to appreciate the value of touching and hugging their children and to create environments where children can safely express their emotions. Throughout the 10-week intervention, coaches provide "in the moment" comments to highlight examples of responsive caregiving, connect parent behaviors with intervention targets and child outcomes, and suggest appropriate parent responses to child behaviors (Dozier et al., 2018; Hoye, and Dozier, 2018). Although originally developed for infants in foster care, more recent adaptations of ABC target neglected children who are not in foster care, international adoptees, toddlers in foster care, and neglected toddlers (Dozier et al., 2018; Imrisek et al., 2018).

In a preliminary RCT of the ABC intervention, Dozier et al. (2006b) found evidence to support normalized diurnal cortisol patterns in foster infants following the 10-week intervention period. The sample included children (ages 3–39 months) who had been placed in foster care as infants and comparison children with no history of foster care placement; foster children and their caregivers were randomly assigned to receive either the ABC intervention or an educational control intervention targeting cognitive development. Compared to the educational control group, children whose caregivers completed the ABC intervention exhibited a more normalized diurnal cortisol pattern following the intervention period. This pattern, which reflected lower morning cortisol values and a flatter diurnal slope, was similar to the pattern seen in the comparison group who had never been in foster care. Families who participated in the ABC intervention also reported relatively fewer problem behaviors for older children (< 18 months) than families in the control intervention, providing preliminary evidence of enhanced biobehavioral regulation in response to the ABC intervention. Of note, this data is reported from post-intervention values only, and does not include within-group pre/post change effects. Despite these limitations, these results provide initial evidence that the ABC intervention may improve the self-regulatory capabilities of children in foster care, with downstream biological effects on cortisol (Dozier et al., 2006b).

Expanding on initial evidence supporting the change in daytime cortisol patterns among foster children, Dozier et al. (2008) conducted a follow-up investigation of acute cortisol responses during stressful conditions. Using families from the original 2006 RCT, Dozier et al. (2008) collected cortisol from children (15–24 months) at three time points before and after completing the Strange Situation paradigm (see Ainsworth and Bell, 1970). Although group differences in stress responsivity were not observed, results provided evidence of increased basal cortisol regulation in foster children from the ABC group. Specifically, foster children from the experimental intervention showed significantly lower initial cortisol levels (before the Strange Situation) than those in the control intervention, and did not differ significantly from non-foster care children. These results support the initial findings from the 2006 RCT, suggesting that the ABC intervention impacts the biological regulation of children in foster care.

More recently, research on the ABC intervention has extended beyond the foster care system to include children who are at risk for neglect but still living with their birthparents. Bernard et al. (2015a) conducted an RCT of the ABC intervention with young children (5–34 months) involved with Child Protective Services. Consistent with earlier findings, children in the intervention group showed significant post-intervention differences in cortisol patterns compared to those who received the educational control intervention. Children whose parents had completed the ABC intervention showed similar diurnal cortisol patterns to the (non-CPS-involved) comparison group. Although this study does not report pre-intervention cortisol levels for comparison, Bernard et al. (2015b) were able to confirm the persistence of these post-intervention effects three years later, highlighting the potential of the ABC intervention to impact long-term HPA axis regulation.

Interestingly, the *specific* post-intervention diurnal cortisol pattern observed in the later RCT (Bernard et al., 2015a) differed from the pattern observed in the initial foster care sample (Dozier et al., 2006b, 2008): Bernard and colleagues observed higher morning cortisol levels and a steeper diurnal slope following the ABC intervention, while the foster care infants in Dozier’s 2006 RCT showed lower levels of post-intervention morning cortisol. Findings from the later RCT (Bernard et al., 2015a) are consistent with the broader literature supporting blunted cortisol patterns (“hypocortisolism”) in maltreated children and steeper diurnal cortisol slopes following intervention (Bruce et al., 2009a, 2009b; Fisher et al., 2007; Kertes et al., 2008). However, it should be noted that in *both* RCTs, the diurnal cortisol pattern of children in the ABC condition looked more similar to that of comparison children (i.e. children with no history of maltreatment) than to cortisol patterns of children in the control intervention groups. Given that both hyper- and hypo- cortisolism indicate problematic HPA axis functioning, further research is needed to help differentiate the underlying mechanisms driving differences in these observed hypo- vs. hyper-cortisol activation patterns.

Overall, several randomized controlled trials evaluating the ABC intervention have found evidence suggesting that the intervention promotes a more normalized diurnal cortisol pattern in children who have experienced neglect or maltreatment. Although the specific nature of these post-intervention cortisol patterns (steep vs. blunted diurnal slopes) differs across studies, Dozier and colleagues have consistently found evidence linking early responsive relationships to normalized HPA axis activity.

2.2. The MTFC-P intervention

In a parallel investigation of how responsive caregiving impacts children's biological regulation, Fisher and colleagues developed an intervention called Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) (Fisher and Kim, 2007; Fisher et al., 2009; Fisher, Stoolmiller, et al., 2007). Designed as a comprehensive family-based program, MTFC-P utilizes a team approach to work with foster children, foster parents, birthparents, and other permanent placement resources. Foster parents complete 12 h of intensive training, receive daily support and supervision from consultants, attend weekly foster parent group meetings, and have 24 -h access to support staff. Foster parent coaching includes an emphasis on positive parenting strategies and responsive caregiving. As a part of MTFC-P, foster care children also receive individualized and group therapeutic play sessions that focus on improving behavior at preschool and at home. Throughout the intervention period (typically 6–9 months), family therapists work with foster care children and families to facilitate challenges associated with transitions between placements. An RCT of the MTFC-P intervention found that children (ages 3–6) who received the intervention exhibited increased secure attachments to foster parents (Fisher and Kim, 2007) and improved placement success rates, including increased rates of permanency in foster care homes (Fisher et al., 2009).

In the context of the same RCT described in Fisher and Kim (2007); Fisher et al. (2007) reported on longitudinal analyses of diurnal cortisol samples collected over 12 months from a sample of preschool children who were entering a new foster care placement and a comparison group with no history of foster care or maltreatment. Foster children and their caregivers were randomly assigned to receive the MTFC-P intervention or regular foster care (RFC). Over the course of the intervention period, diurnal cortisol levels of the children in the MTFC-P group normalized to levels comparable to those seen in children with no history of foster care. In contrast, children in the RFC group showed increasingly blunted patterns of diurnal cortisol over time, characterized in particular by diminished morning cortisol levels. These results suggest a strong prevention effect in the MTFC-P group, such that children who received additional support in their transition to a new placement experienced a shorter duration of stress associated with the change. This improved adjustment period is reflected in increasingly normalized AM-PM cortisol patterns over the course of the 12-month follow-up. In contrast, children in the RFC group did not receive the same level of support throughout the disruptive transition to a new placement; consistent with evidence that chronic stress can lead to blunted cortisol patterns, children in the RFC group showed increasingly flattened diurnal cortisol activity. Taken together, these results provide evidence that improving responsive care and support for foster care children can prevent (and possibly reverse) dysregulation in HPA axis functioning (Fisher et al., 2007).

In an effort to better understand this pattern of blunting in the RFC group, Fisher and Stoolmiller (2008) examined the relationship between diurnal cortisol activity, caregiver stress, and child problem behaviors. While parents in the MTFC-P intervention showed significant (and immediate) reductions in stress following the start of the intervention, parents in the RFC group showed increasing stress over the course of the 12-month period. Parents in the RFC group also showed increased self-reported stress in response to child problem behaviors, which in turn predicted lower child cortisol levels the following morning. In other words, children in the RFC group were more likely to exhibit low morning cortisol values if their caregivers had reported high stress the previous day. These results offer further insights into the underlying mechanisms driving HPA axis-regulation, providing evidence that caregiver stress may directly impact diurnal cortisol patterns.

Overall, RCTs testing the MTFC-P intervention provide promising evidence that the MTFC-P model can increase both HPA axis regulation and behavioral outcomes for children in foster care. Beyond the primary findings related to diurnal cortisol regulation following intervention, a subsample of children from this RCT demonstrated group differences on behavioral and electrophysiological measures of cognitive control and response monitoring. Specifically, foster children who received services as usual were less responsive to external feedback, while children who participated in the MTFC-P intervention showed similar ERP response patterns to the non-maltreated children following intervention (Bruce et al., 2009a). Taken together with evidence of HPA-axis regulation following the MTFC-P intervention, these results suggest that MTFC-P may benefit foster care children across multiple cognitive and physiological domains by improving caregiver responsiveness and decreasing caregiver stress.

2.3. The KITS intervention

Building on the evidence that intervention can improve HPA axis regulation in infants and toddlers, Pears et al. (2012) developed an extension of the MTFC-P intervention to target school readiness in older children transitioning to kindergarten. The Kids in Transition to School (KITS) intervention focuses on providing support to both foster children and parents in the 4-month period surrounding children’s transition to kindergarten. Intervention groups for children focus on school readiness, targeting early literacy skills (e.g., letter naming, phonological awareness), prosocial skills (e.g., social problem solving, emotion recognition), and self-regulatory skills (e.g., following multistep directions, handling frustrations) in the context of typical classroom setting. Parent groups receive training to support the academic transition to school (e.g., home practices to help develop early literacy skills) and to promote child regulation (e.g., behavior management strategies). Child groups meet twice weekly during the summer before kindergarten and once weekly for 8 weeks after the start of kindergarten. Parent groups meet every other week throughout the intervention period.

Evidence from an RCT of KITS among foster preschoolers supports growth in both behavior regulation and academic outcomes in children, along with decreased caregiver stress. Specifically, Pears et al. (2012) conducted a large efficacy trial with 192 foster care children split between the KITS intervention and a "regular foster care" comparison group. By the end of kindergarten, children who had received the intervention showed significantly lower levels of parent and teacher reported classroom disruptiveness and oppositional behaviors compared to those in the comparison condition (Pears et al., 2012). Evidence from another efficacy trial of KITS with low-income families outside of foster care supported similarly promising outcomes: children who received the intervention had greater improvements in early literacy skills, increased self-regulation, and decreased aggressive behaviors (Pears et al., 2014). More recent studies have highlighted promising improvements in children with developmental disabilities (McDermott et al., 2017), showing significant differences in the magnitude of feedback-related ERP during the flanker task. These behavioral and electrophysiological results mirror the post-intervention findings seen in foster children who participated in the MTFC-P intervention (Bruce et al., 2009b), suggesting that both interventions may improve self-regulation and self-monitoring via changes in the neurophysiological response to feedback.

Beyond behavioral and neurophysiological changes, recent studies have supported the cost-effectiveness of the KITS intervention in comparison with other programs that provide similar behavioral and academic benefits (Lynch et al., 2017). In their cost-benefit analysis of the original KITS RCT, Lynch et al. (2017) found significant reductions in internalizing symptoms and externalizing behaviors following the KITS intervention, highlighting both the shorter program length (4 months) and lower cost per child ($932) relative to other comparable intervention programs. Shorter intervention periods are particularly relevant to foster care children, who tend to have higher placement transience and may not be able to complete programs with longer requirements. Overall, these analyses have significant implications for policies to support foster care children, demonstrating the feasibility, efficacy, and cost-effectiveness of the KITS program for preschool children in foster care.

Recently, Graham et al. (2018) reported on relationships between behavioral outcomes and HPA axis regulation in the original RCT of KITS with foster children. Results paralleled earlier findings from the MTFC-P and ABC interventions: children in the KITS intervention group had steeper diurnal cortisol slopes on the first day of school, a pattern consistent with the appropriate stress response seen in non-maltreated children. Further, these diurnal cortisol patterns predicted children's adjustment to school as rated by their teachers; steeper cortisol slopes were predictive of higher ratings for engagement, appropriate behaviors, and overall improved academic performance. Evidence of a do-sage effect for KITS – greater exposure to the intervention aligned with increased effects on diurnal cortisol patterns – further clarifies the underlying relationship between this intervention and HPA axis regulation. Graham et al. (2018) proposed a mediational model to explain these effects: the KITS intervention positively influences HPA axis regulation, which predicts behavioral change and school adjustment outcomes. Together with evidence from the ABC and MTFC-P intervention programs, outcomes from KITS provide compelling evidence that HPA axis regulation may play a key role in mediating intervention effects on behavioral and academic outcomes in children.

3. Summary and Conclusions

In this paper, we presented an overview of how research on child maltreatment, beginning in the 1960s and 70 s, converged with animal studies on the effects of early life experiences on development. These two lines of work increased awareness regarding the prevalence and impact of early adversity on well-being and provided documentation that both behavior and neurobiology are altered by disrupted early caregiving. We also described the confluence of investigations on child welfare system children and children adopted following institutional rearing, which led to the insight that the absence of responsive care—i.e., neglect—is capable, even in the absence of physical or sexual abuse, of exerting a lasting impact on development. This collective corpus of empirical research, in combination with epidemiological surveys documenting the prevalence of neglect, have led to changes in policy and support for programs that seek to identify and intervene in cases of non-responsive parental care, in the United States and else-where (Perry et al., 2018).

The three evidence-based interventions we reviewed—ABC, MTFC-P, and KITS—all focus on increasing the predictability and responsiveness of the child's caregiving environment (and in the case of KITS, their pre-kindergarten academic environment as well). These interventions have shown long-term impacts on child behavioral and socioemotional development. In addition, the interventions show that it is possible to impact the regulation of the HPA axis, which is a common pathway of the biological stress response, following early adversity. These interventions further demonstrate that it is possible to mitigate some of the negative effects of neglectful early care, at least in the context of programs that are delivered in the early years of life (Bruce et al., 2013).

There are a number of additional, more nuanced, conclusions to be drawn from the studies that are reviewed in this paper. First, although diminished cortisol production is the most commonly observed marker of dysregulation of the biological stress response system in children who have experienced non-responsive early care, it is specifically the *diurnal pattern of cortisol production* (particularly the level of morning cortisol) that is known to be impacted in the samples that have been investigated to date. Less well understood, in part owing to ethical and methodological challenges, is whether diminished glucocorticoid responses to naturalistic or laboratory psychosocial stressors exist in infants and young children following neglect. There is some indication of diminished HPA activation in response to psychosocial stressors in school-aged foster children (Fisher et al., 2011a, b), but this is an area in which relatively little research has been done relative to the research on diurnal cortisol levels. As such, it is perhaps most accurate to say the evidence supports that the biological stress response system appears to be impacted by early nonresponsive care, rather than that children's stress reactivity is affected.

In addition, although it is the case that diminished cortisol production is the characteristic pattern of altered cortisol production following early non-responsive and neglectful care, these patterns are far from ubiquitous. There are some instances in the literature in which elevated cortisol levels have been observed (e.g., Dozier et al., 2006b) in this population. As noted previously, it may be that differences in the observed patterns of dysregulation are the result of a number of variables, including duration and severity of neglect, age of onset, and age at which children are assessed. While this review has focused on cortisol patterns in early childhood, early adversity can continue to affect HPA development throughout late childhood, adolescence, and adulthood. Interestingly, studies looking at HPA functioning among neglected children have generally not observed differences in diurnal cortisol patterns based on gender (e.g., Bernard et al., 2015a; Bruce et al., 2009a, 2009b; Dozier et al., 2006a); however, more research is needed in this area.

In one attempt to address discrepant cortisol findings, Bernard et al. (2017) conducted a meta-analysis looking at the relationship between child maltreatment and cortisol patterns in childhood and adulthood. The authors found that for studies using agency-referred samples, child maltreatment was associated with low wake-up cortisol levels. They did not find significant main effects for other cortisol patterns, including diurnal cortisol slope; however, the meta-analysis included studies with older children and adults as well as young children and looked at maltreatment broadly rather than neglect in particular. Nevertheless, the meta-analysis did not find age, gender, or type of maltreatment to be significant moderators. Ultimately, there remains a need for more research investigating moderators of cortisol patterns—and other explanations for discrepant findings—among young children who have experienced neglect.

Beyond differential patterns of cortisol dysregulation reported across studies, it is also important to recognize that not all children experiencing non-responsive care exhibit atypical diurnal cortisol levels. Indeed, in the original reports by Dozier et al. (2006a, 2006b) and Fisher et al. (2009), only approximately one-third of each sample of foster children exhibited atypical levels of cortisol, whereas other children in the samples showed typical morning-to-evening decreases (notably, the alterations in diurnal cortisol were of sufficient magnitude among those who showed dysregulation that the overall means for the sample were significantly different than those for non-maltreated comparison groups). Nevertheless, the fact that not all children in the foster care samples under investigation showed alterations in cortisol production following early stress suggests (as with other measures of development) substantial individual differences in response to early adverse experiences.

Somewhat obscured in the results of the intervention studies showing normalization of cortisol levels in foster children who receive intervention services is the fact that for many children who experience early adversity, the temporal stability of their cortisol levels across time is negatively impacted (Doom et al., 2014). Although on average children in the intervention conditions of the above studies did show more typical cortisol production in post-treatment waves of data collection, early adversity appears to increase children's susceptibility to environmental influences, such that subsequent stressors may increase vulnerability for future neuroendocrine dysregulation (Fisher et al., 2011a, 2011b). As such, rather than simply changing cortisol levels to become permanently normalized, improving responsive care among foster children and neglected children may change HPA axis functioning in a less direct way, such as reducing sensitivity to daily perturbations in caregiver stress. Nevertheless, the RCTs reviewed above, as well as a systematic review by Slopen et al. (2014), provide evidence for the general idea that interventions targeting responsive caregiving towards infants and toddlers can promote more typical HPA axis functioning; these findings are consistent with the hypothesis that early responsive relationships are a causal mechanism by which HPA axis regulation occurs.

Although there is a well-established link between responsive caregiving and normalized HPA axis regulation, and in spite of the fact that many improved behavioral, socioemotional, and foster placement outcomes were observed in the above studies (e.g., Bernard et al., 2012, 2015c; Fisher et al., 2006; Fisher and Kim, 2007; Lewis-Morrarty et al., 2012; Lind et al., 2014), the connection between observed cortisol regulation and other child biobehavioral outcomes has been weaker than might be anticipated. The absence of a stronger connection between cortisol and other variables points to the need to evaluate additional biomarkers of stress, which may share a more direct link with child outcomes. While salivary cortisol is a commonly used measure, hair cortisol may provide additional information about the long-term effects of neglect on neurobiological functioning. Biomarkers beyond cortisol that merit further research include measures of oxidative stress, the gut microbiome, and immune activation.

Another important step forward involves establishing ways to translate findings regarding intervention-related neurobiological changes into policy and practice. The studies in this review were designed to be intervention studies of basic mechanisms; accordingly, there is not yet a clear strategy for implementing findings in the health care system. The pediatric primary care system is a particularly important setting for monitoring and addressing public health issues. Finding ways to effectively integrate relevant neurobiological measures and disseminate interventions through the pediatric primary care system could be invaluable in mitigating the effects of early adversity at the population level.

Relatedly, future intervention research with very high adversity samples must address the issue of heterogeneity—both in response to early life stress and in response to the interventions themselves. To date, much of the field has focused on main effects of interventions, in spite of the fact that there is a vast continuum of impact observed on meaningful outcomes. The field should move in the direction of incorporating individual differences in experience and biology to develop a more precise understanding of moderators of intervention effects, and to incorporate more personalized approaches into the design and evaluation of interventions in this area.

Finally, it is important to note that although the above studies provide support for the notion of recovery following early adverse experiences—and more specifically for the potential of responsive caregiving to mitigate the effects of prior neglect—there are limits to the plasticity of biological and behavioral systems. The cumulative effects of adversity, beginning prenatally, combined with a longer latency to an improved caregiving environment, are likely to limit the impact that interventions are likely to have. For these reasons, early identification of risk and the delivery of services with documented efficacy are of utmost importance. In sum, scientific research has the potential to shed light on both the impact of early adversity and the means to minimize its effects, but this knowledge is a means to an end and not an end in itself.

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