The Influence of Maternal Stress and Child Maltreatment on Offspring

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Abstract and Keywords

Child maltreatment has significant impacts on developmental trajectories and is one of the most preventable early-life adversities. It shapes the development of many biological systems, with most research concentrating on its influence on stress response systems like the hypothalamic-pituitary-adrenal (HPA) axis. This chapter reviews associations between child maltreatment and HPA axis activity across development. One emerging pattern is that of flattened diurnal cortisol slopes in children, adolescents, and adults with childhood maltreatment histories. This effect was moderated by psychiatric diagnosis, maltreatment subtype, and genetic vulnerability in some studies. Effects on cortisol reactivity are more mixed, including reports of higher reactivity, lower reactivity, or no differences compared to nonmaltreated samples. Interventions that focus on enhancing the quality of parent–child relationships early in life may reverse some of the effects of maltreatment. This chapter discusses implications of maltreatment-related alterations in HPA axis function for mental and physical health and concludes with suggested future research directions.

Keywords: maltreatment, HPA axis, cortisol, early-life adversity, maternal stress, intervention

Child maltreatment can have a profound impact on developmental trajectories and is one of the most preventable early-life adversities that children face (Bruce, Gunnar, Pears, & Fisher, 2013; Cicchetti, 2016). Maltreatment during childhood is associated with increased risk of later psychopathology, especially posttraumatic stress disorder (PTSD) and depression (Kaufman & Charney, 2001; Pratchett & Yehuda, 2011; Teicher & Samson, 2013). It also forecasts poorer adult physical health, including greater odds of developing cardiovascular disease and diabetes (Ehrlich, Miller, & Chen, 2016; Gilbert et al., 2015), obesity (Danese & Tan, 2014), fibromyalgia, and chronic fatigue syndrome (Borsini, Hepgul, Mondelli, Chalder, & Pariante, 2014; Lee, 2010). It is theorized that one common

pathway leading to the development of these diverse mental and physical health problems involves the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Burke, Finn, McGuire, & Roche, 2016; Chrousos, 2009; Lee, 2010; Pratchett & Yehuda, 2011). The goal of the present review is to examine the evidence that child maltreatment shapes the development of the HPA axis and reveal the nature of the associations between maltreatment and several aspects of HPA functioning: basal activity, reactivity to stressors, and responses to pharmacological challenges. We describe the existing human literature on associations between child maltreatment and indices of HPA activity in childhood, adolescence, and adulthood. We begin by discussing the influence of maternal stress and other risk factors for maltreatment. This is followed by brief overviews of the HPA axis and animal models of maltreatment and its effects on the HPA axis. Then, we summarize the existing human literature on maltreatment and the HPA axis. We conclude by discussing some of the implications of maltreatment-related alterations in HPA functioning for mental and physical health and providing some suggested future directions for this area of research.

Child Maltreatment: Definition, Prevalence, and Risk Factors

Although definitions of maltreatment vary based on factors such as culture or purpose (e.g., legal vs. research), maltreatment can be broadly defined as aberrant caregiving behaviors that threaten a child's well-being and capacity for psychobiological adaptation (Cicchetti, 2016). Maltreatment can be divided into behaviors that reflect abuse (i.e., physical abuse, sexual abuse, emotional abuse) or neglect (i.e., physical neglect, emotional neglect; Barnett, Manly, & Cicchetti, 1993). Physical abuse involves the nonaccidental infliction of physical injury on a child and can range from a temporary injury to a permanent disfigurement. Sexual abuse involves an attempted or actual sexual act between a child and a family member or caretaker for purposes of that person's sexual enjoyment or financial benefit. Emotional abuse involves threatening behavior that thwarts a child's basic emotional needs for psychological safety and security, acceptance and self-esteem, and age-appropriate autonomy; emotional neglect similarly conveys to a child that he or she is unloved, unwanted, or unworthy but involves the lack of appropriate emotional responsiveness, rather than threatening emotional input. Physical neglect can be divided into two different subtypes: failure to provide, which involves the failure to meet the child's nutritional, medical, or hygiene needs, and lack of supervision, which includes either leaving a child unattended or with an inadequate caregiver. Severity, frequency, and chronicity, as well as the developmental period in which the abuse occurred, are also essential parameters to take into account when assessing child maltreatment (Barnett et al., 1993).

The majority of research on the sequelae of child maltreatment has been conducted on samples from the United States and Europe, with comparatively fewer studies reporting results from other regions of the world (Stoltenborgh, Bakermans-Kranenburg, Alink, &

van IJzendoorn, (p. 162) 2015). More recent research has begun examining the prevalence and risk factors for child maltreatment in developing countries (Antai, Braithwaite, & Clerk, 2016; Singhi, Saini, & Malhi, 2013). The official prevalence estimate in the United States was of 702,000 abused or neglected children in 2014, or 9.4 victims per 1,000 children, with rates of abuse decreasing with age and neglect being the most common subtype of abuse (U.S. Department of Health & Human Services, Administration on Children, Youth and Families, Children's Bureau, 2016). However, statistics based on officially documented cases likely underestimate the overall prevalence of maltreatment, which is 10 times higher according to victim and parent reports (Gilbert et al., 2009). Official records in the United States show that rates of child maltreatment have declined since the early 1990s (Jud, Fegert, & Finkelhor, 2016). However, it is unclear whether these statistics represent real change or differences in how these incidents are reported or investigated. For obvious reasons, much less is known about the rate of change over the past two decades among unreported cases. Despite the encouraging indication of improvement over time, child maltreatment remains all too prevalent and is a significant societal concern.

Maltreatment is thought to be caused by a complex interplay of factors and systems (Garbarino, 1977; Howze & Kotch, 1984; Thompson, 2015). Studies have focused on maternal factors because many of the families where child maltreatment is observed tend to be single-parent families where the mother is the parent, and mothers tend to spend the most time with their children (Taylor, Guterman, Lee, & Rathouz, 2009). The most commonly studied risk factor is maternal stress, which can stem from multiple sources, including intimate partner violence (Antai et al., 2016; Taylor et al., 2009); having an insecure attachment with their own parents or being maltreated as a child (Cicchetti, Rogosch, & Toth, 2006; De Bellis et al., 2001; Widom, Czaja, & DuMont, 2015); having many children (Cicchetti et al., 2006; Kotch et al., 1995); being a single parent or having unstable relationships (Cicchetti et al., 2006; Taylor et al., 2009); receiving low levels of family support (Cicchetti et al., 2006; Cowen, 2001); suffering from psychopathology such as substance abuse, depression, and PTSD (De Bellis et al., 2001; Kotch et al., 1995; Taylor et al., 2009); having a child with conduct disorder, which can create a vicious cycle of escalating maltreatment and worsening conduct problems (Cowen, 2001; Dodge, Bates, & Pettit, 1990); and certain maternal personality attributes, such as poor impulse control (Cowen, 2001; De Bellis et al., 2001). Low socioeconomic status and being from an area where there is large income inequality are other risk factors (Cicchetti et al., 2006; Cowen, 2001; De Bellis et al., 2001; Eckenrode, Smith, McCarthy, & Dineen, 2014; Kotch et al., 1995). Residence with a stepparent has also been noted as a (p. 163) significant epidemiologic risk factor for child abuse, neglect, and murder (Daly & Wilson, 1988, 2005), which predicts outcomes independently of the other risk factors mentioned previously. Naturalistic studies also note that children living with stepparents exhibit elevated levels of basal cortisol compared to biological children living in the same families, perhaps suggesting greater exposure of stepchildren to adverse events in the home (Flinn, Ward, & Noone, 2005). Evolutionary explanations for these phenomena highlight the reproductive fitness benefits of suppressing violent or conflictual tendencies

toward genetically related offspring (Daly & Wilson, 1988). These are some of the predictors that have been linked to higher likelihood of child maltreatment. For the remainder of the chapter we focus on the outcomes of child maltreatment, with a primary emphasis on alterations in the functioning of stress response physiology and possible consequences for mental and physical health. Before proceeding, a brief introduction to the activity of the HPA axis is necessary.

Overview of the Hypothalamic-Pituitary-Adrenal Axis

When confronted with physical or psychological challenges that overwhelm the individual's capacity to cope, the body initiates a number of physiological and behavioral responses through the endocrine, nervous, and immune systems (Gunnar, Doom, & Esposito, 2015). The hypothalamic-pituitary-adrenal (HPA) axis plays an integral role in these processes by mobilizing energy for coping with stressors and modifying the individual's responses to similar stressors in the future (Gunnar et al., 2015; Sapolsky, Romero, & Munck, 2000; Smith & Vale, 2006).

The activity of the HPA axis can be studied along two basic dimensions: basal functioning and reactivity to stressors (Joëls & Baram, 2009). Basal HPA functioning follows a diurnal rhythm whereby cortisol, the end product of the HPA axis, is secreted in a pulsatile fashion across the day, reaching peak levels in the morning approximately 30 minutes after awakening, and declining gradually across the day to reach minimum levels at night (Joëls & Baram, 2009). Superimposed on this basal rhythm is the reactivity of the HPA axis to physical or psychological threats to well-being (i.e., stressors). Stress-induced cortisol production begins when corticolimbic regions relay threat signals to the paraventricular nucleus (PVN) of the hypothalamus, which releases corticotropin-releasing hormone (CRH) and arginine vasopressin onto the anterior pituitary gland (Joëls & Baram, 2009; Levy & Tasker, 2012). The pituitary responds by releasing adrenocorticotropic hormone (ACTH) into circulation, which binds to its receptors in the cortex of the adrenal gland. This stimulates the production of the steroid hormone cortisol by the adrenal (Gunnar et al., 2015; Smith & Vale, 2006).

Cortisol has pervasive effects across the body (Sapolsky et al., 2000). Acutely, cortisol facilitates the mobilization of energy to the muscles, increases cardiovascular output, sharpens cognition and alertness, and stimulates immune function, while inhibiting other bodily functions that are not as immediately necessary, such as reproductive physiology and appetite (Sapolsky et al., 2000). When cortisol is released into the circulation, it acts upon its receptors throughout the body, of which there are two main types: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs; Gunnar et al., 2015; Joëls & Baram, 2009). MRs have higher binding affinity for cortisol than GRs and regulate the basal activity of the HPA across the day (Herman et al., 2016). The lower affinity GRs become activated at higher levels of cortisol, including at the peak of the

diurnal cycle and during stressors, mediating the effects of these stressors on many organs and systems including the brain (Herman et al., 2016).

In the past two decades there has been burgeoning interest in characterizing how early-life experiences shape both the basal activity and the reactivity of the HPA axis to stressors or under pharmacological challenge. Dysregulation of the HPA axis is frequently noted in children and adolescents experiencing psychosocial adversity (Ehlert, 2013; Fisher et al., 2016; Tarullo & Gunnar, 2006) and has been increasingly linked to deleterious physical and mental health outcomes (Bruce et al., 2013; De Bellis, Spratt, & Hooper, 2011; Ehlert, 2013; Gunnar et al., 2015), as we discuss in more depth in subsequent sections.

Animal Models of Early-Life Maltreatment

Animal models have been critical in substantiating the causal role of maltreatment on neurodevelopmental trajectories (Drury, Sanchez, & Gonzalez, 2016; Sanchez, 2006; Parker & Maestripieri, 2011). Rodent models provided some of the earliest mechanistic data on the effects of low- versus high-quality maternal care on the HPA axis (Meaney & Szyf, 2005; Plotsky & Meaney, 1993). Nonhuman primate models have greatly added to these insights, particularly since there are several important similarities between them and humans (e.g., the importance (p. 164) of maternal care for primate development, the prolonged period of postnatal maturation and growth; Sanchez, 2006). As nonhuman primate models are the most similar to human development, we focus on them in this section.

Research on early-life adversity in nonhuman primates has primarily focused on maternal stress and its effects on the mother's HPA system, the offspring's HPA system, and the dyad's relationship (Sanchez, 2006; Sanchez, McCormack, & Howell, 2015). Maltreatment tends to occur in 5 to 10 percent of rhesus macaques and other related primate species and occurs primarily in infancy, similar to humans (Maestripieri & Carroll, 1998; Sanchez et al., 2010). Additionally, primates who abuse their offspring tend to have been abused themselves by their mothers, even if they were cross-fostered (i.e., not genetically related to their abusive mothers; Maestripieri, 2005). They also tend to abuse all of their subsequent offspring, irrespective of whether they are adoptive or biological offspring (Maestripieri, Megna, & Jovanovic, 2000). This suggests that the abuse has little to do with the infant and is environmentally transmitted (Maestripieri, Lindell, Ayala, Gold, & Higley, 2005).

The variable foraging demand (VFD) model has been used as an ecologically valid way to study the effects of maternal stress on the mother–infant dyad (Andrews & Rosenblum, 1991; Rosenblum & Paully, 1984; Sanchez, 2006). This experimental paradigm disrupts the mothers' feeding pattern and makes the usual pattern of foraging for food unpredictable. This results in elevated levels of corticotropin-releasing factor (CRF) in the cerebrospinal fluid of the mothers (Coplan et al., 2005) and in more rejecting maternal behavior (e.g., mothers break contact with the infants more often; Rosenblum & Andrews,

1994), compared to mothers maintained under normal feeding conditions. The effects of being randomly assigned to live in a VFD environment are profound on the offspring as well, with infants showing hyperresponsiveness to stressful stimuli and elevated levels of CRF in cerebrospinal fluid (Coplan et al., 2001, 2005). Dysregulation of the HPA system has also been found to persist through the juvenile period, into young adulthood, and in the offspring of the infants raised in VFD conditions (Coplan et al., 2001, 2011; Kinnally et al., 2013; Rosenblum, Forger, Noland, Trost, & Coplan, 2001). These experimental studies indicate that induced maternal stress can not only affect the way that dyads interact but also shape the long-term neurobiological development of the offspring. Despite these average trends, there is variability in outcomes, such that some animals are more vulnerable than others to this experimental disruption (Coplan et al., 2001). More research is needed to uncover the genetic and experiential bases for these individual differences in reactions to VFD conditions in mothers and their offspring.

Other studies have focused on the effect of naturally occurring maltreatment on the offspring's HPA axis. As in humans, the quality of maternal care alters infants' HPA axis and their reaction to stress (Drury et al., 2016), as well as their mothers' ability to buffer their stress response (Sanchez et al., 2015). Maltreated primates exhibit heightened basal cortisol levels in infancy, which appear to normalize at later ages (Howell et al., 2013; Koch, McCormack, Sanchez, & Maestripieri, 2014). Despite this apparent normalization of basal levels, abnormalities in cortisol reactivity persist, including heightened cortisol reactivity to stressors and CRH challenge, and decreased ACTH response to CRH challenge (Drury et al., 2016; Sanchez et al., 2010). In studies of repeated maternal separation, animals similarly show an initial pattern of increased basal cortisol, which is followed by a flattened diurnal cortisol rhythm during the juvenile period, consistent with many studies in humans (Drury et al., 2016). The mechanisms underlying this transition from hypercortisolism early in life to hypocortisolism later in development have yet to be revealed, but down-regulation of CRH receptors and epigenetic alterations are thought to be at play (Drury et al., 2016).

Maltreatment and Hypothalamic-Pituitary-Adrenal Functioning in Children and Adolescents

The human literature on associations between early-life maltreatment and indices of HPA axis activity in youth is quite heterogeneous (Tarullo & Gunnar, 2006). As we review in more depth in this section, some studies reveal that maltreated youth exhibit heightened cortisol levels, while others show lower cortisol levels or no differences compared to nonmaltreated groups. There are several reasons for these varying effects. First, these effects depend on the HPA axis indices used (basal levels vs. cortisol reactivity vs. pharmacological challenge). Second, the evidence suggests that effects vary based on features of the maltreatment experience, such as subtype (physical, emotional, or sexual abuse; physical or emotional neglect) or developmental timing. Lastly, there are

individual differences based on gender, genetics, and the type of psychopathology (p. 165) that individuals develop (e.g., internalizing or externalizing, posttraumatic stress disorder [PTSD], depression). We discuss findings regarding the association between maltreatment and HPA activity in children and adolescents next and highlight how the overall pattern of results differs in light of these factors.

Most of the prior studies in youth have examined diurnal cortisol production (e.g., diurnal slope, the typically steep decline in basal cortisol from morning to evening) or cortisol levels at one point during the day. Based on our review of these studies, the emerging pattern was that maltreated children tended to exhibit flattened diurnal cortisol slopes compared to nonmaltreated comparison groups—that is, lower morning cortisol levels and a less steep decline across the day (Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010; Bernard, Zwerling, & Dozier, 2015; Dozier et al., 2006; Fisher, Van Ryzin, & Gunnar, 2011). Consistent with this pattern of flatter slopes, some studies found that girls who had experienced sexual abuse had lower levels of morning cortisol than nonmaltreated girls (King, Mandansky, King, Fletcher, & Brewer, 2001), and this effect appears particularly pronounced for girls with PTSD (Keeshin, Strawn, Out, Granger, & Putnam, 2014). Two other studies found that maltreated children were more likely to exhibit flatter cortisol slopes, but in these studies the flatter slopes were more characteristic of maltreated children if they were also depressed (Hart, Gunnar, & Cicchetti, 1996; Kaufman, 1991). Another study found that lower morning cortisol levels and flatter diurnal slopes were more likely among maltreated children exhibiting both internalizing and externalizing symptoms, with a particularly prominent effect in maltreated boys with elevated levels of externalizing symptoms (Cicchetti & Rogosch, 2001b). Both maltreatment subtype and developmental timing appear to matter, as one study found flatter diurnal cortisol slopes among those experiencing early physical or sexual abuse (before age 5), but not for those exposed to abuse later in development or those experiencing other types of maltreatment (Cicchetti, Rogosch, Gunnar, & Toth, 2010). In another study suggesting a role for maltreatment subtype, Bick et al. (2015) reported that adolescents with moderate to severe neglect showed higher levels of afternoon cortisol than adolescents with little to no experience of physical neglect, with no effects of other maltreatment types. Finally, one investigation focusing on the role of genes regulating HPA function among maltreated children reported that flatter slopes were specific to children with two copies of the TAT haplotype of the CRH receptor 1 (CRHR1) gene, a gene encoding a receptor that binds CRH, a major player in the activation of the HPA axis (Cicchetti, Rogosch, & Oshri, 2011). In conclusion, the basal cortisol literature suggests that maltreated children and adolescents are more likely to evince flatter cortisol slopes across the day compared to nonaffected groups, with some studies finding a main effect of maltreatment and others reporting this effect only in subgroups with psychopathology, greater severity, earlier onset of maltreatment, or a genetic vulnerability.

A few studies reported results that at least partially contradict this overall pattern. A recent report showed that girls who had been sexually abused exhibited heightened morning cortisol levels compared to those without a trauma history (Simsek, Yuksel,

Kaplan, Uysal, & Alaca, 2015). However, there was a negative correlation between morning cortisol and time since abuse, suggesting decreasing levels of morning cortisol as the time interval from the abuse increased. Furthermore, in this study children who had experienced multiple sexual assaults exhibited *lower* cortisol levels than the nonmaltreated group. A study with preschool-aged children found that even though children who experienced neglect exhibited the common lowering of morning cortisol compared to a nonmaltreated sample, children who experienced emotional abuse exhibited heightened levels of morning cortisol (Bruce, Fisher, Pears, & Levine, 2009). In a study of school-aged children, those experiencing multiple types of abuse (physical and sexual abuse) showed elevated morning cortisol levels compared to the nonmaltreated group, though children exposed only to physical abuse showed lower levels of morning cortisol than the nonmaltreated group (Cicchetti & Rogosch, 2001a). Finally, a longitudinal study of sexually abused females reported higher morning cortisol in 6- to 16-year-olds recruited within six months of disclosure of the abuse, but this pattern changed across development such that the abused females showed decreasing morning cortisol levels over time and exhibited lower morning cortisol in young adulthood (ages 20 to 32 years) compared to the nonabused control group (Trickett, Noll, Susman, Shenk, & Putnam, 2010). The conclusion emerging from some of these studies (Simsek et al., 2015; Trickett et al., 2010) is that morning cortisol levels can be elevated in some instances in the aftermath of the maltreatment experience, but may lower below normative levels over time. This pattern is (p. 166) consistent with meta-analytic findings suggesting that the HPA axis may hypersecrete cortisol soon after an adverse event, but may down-regulate and switch to a pattern of hyposecretion if the stressor becomes chronic or is distant in time (Miller, Chen, & Zhou, 2007). Indeed, naturalistic studies of children in their home environments suggest that cortisol levels are elevated immediately after being reprimanded or punished by a caregiver, then decrease below normal levels in subsequent days and appear below normal in children chronically exposed to stressful situations (for a review, see Flinn et al., 2005). Finally, two studies found no difference in cortisol levels between maltreated children and nonmaltreated comparison groups (Doom, Cicchetti, & Rogosch, 2014; Fisher, Gunnar, Chamberlain, & Reid, 2000). This may be due to small sample sizes (Fisher et al., 2000) or because of greater variability in cortisol levels among the maltreated youth, which can make it difficult to capture group-level mean differences (Doom et al., 2014).

In the literature examining cortisol reactivity to a stressor, findings were mixed. Some studies reported that maltreated children and adolescents showed a blunted cortisol response to the stressor compared to nonmaltreated youth (Fisher, Kim, Bruce, & Pears, 2012; Gordis, Granger, Susman, & Trickett, 2008; Hart, Gunnar, & Cicchetti, 1995; MacMillan et al., 2009; Peckins, Susman, Negriff, Noll, & Trickett, 2015; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014). Others reported a heightened response (Bugental, Martorell, & Barraza, 2003; Harkness, Stewart, & Wynne-Edwards, 2011) or no differences in cortisol reactivity by maltreatment status (Cook, Chaplin, Sinha, Tebes, & Mayes, 2012; Eisen, Goodman, Qin, Davis, & Crayton, 2007).

To illustrate some of these findings, one of the earliest studies of cortisol reactivity was on reactions to social conflict in the classroom in preschool boys who had been maltreated, who showed a blunted response to this social stressor (Hart et al., 1995). Another widely used paradigm for eliciting a stress response is the Trier Social Stress Test (TSST), a social-evaluative stressor involving public speaking and mental arithmetic components (Kirschbaum, Pirke, & Hellhammer, 1993). In one experiment using the TSST, foster children who had endured physical abuse, and children exposed to physical abuse along with prenatal substance exposure, displayed a blunted cortisol response over time when compared to children who had endured other abuse subtypes and nonmaltreated children (Fisher et al., 2012). In another study, maltreated female adolescents showed a blunted cortisol response to the TSST when compared with nonmaltreated females (MacMillan et al., 2009). In another analysis of adolescents using the TSST, adolescents with a history of child maltreatment showed a blunted cortisol response to the TSST, and this effect was more pronounced for adolescents who were carriers of one or two G alleles for the *rs110402* polymorphism of the CRHR1 gene (Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014). As already discussed, the CRHR1 gene plays important roles in regulating HPA function, and this study suggests that variation in the CRHR1 gene may shape the effect of maltreatment on cortisol reactivity (Sumner et al., 2014). In one of only a few longitudinal studies in this area of research, maltreated adolescents were more likely to have a blunted cortisol response to the TSST than the nonmaltreated comparison group when they were 12 and 13 years old, but no differences emerged at age 18 (Peckins et al., 2015). This was interpreted as a form of adaptive calibration to the environment over time, meaning that the stress response may adapt to meet the changing demands of the environment across development. Adaptation is presumed to be a lengthy process, and thus HPA functioning at any point in time likely reflects longer periods of cumulative life experiences (Peckins et al., 2015).

Some studies reported mixed results within the same sample based on maltreatment subtype or psychiatric diagnosis. For instance, adolescents who had experienced physical and/or sexual abuse exhibited a blunted cortisol response to the TSST in comparison to nonmaltreated adolescents, whereas adolescents who had experienced neglect or emotional abuse did not differ from the nonaffected comparison group (Trickett, Gordis, Peckins, & Susman, 2014). Moreover, adolescents who have a history of maltreatment along with mild to moderate levels of depression show a heightened and prolonged cortisol response to the TSST (Harkness et al., 2011), whereas those with moderate or severe depression evince a blunted cortisol response whether they were maltreated or not.

Another approach to understanding the effect of maltreatment on the HPA axis is to use pharmacological challenges. In these studies, exogenous CRH, ACTH, or dexamethasone (Dex, a synthetic glucocorticoid) is administered. These studies are quite rare in pediatric populations, and sample sizes are small, which may explain why findings are quite mixed. For instance, one study reported lower ACTH response to CRH challenge in sexually abused youth (p. 167) (De Bellis et al., 1994), whereas another reported higher ACTH

response to CRH challenge in depressed abused children currently living in adverse situations (Kaufman et al., 1997). Both investigations reported no difference in CRH-stimulated cortisol levels. These findings suggest different abnormalities in pituitary responses to CRH (perhaps due to depressed versus nondepressed status), and possible compensatory mechanisms at the adrenal level allowing similar cortisol levels compared to controls despite differing ACTH levels. Two Dex challenge studies have also reported no differences in post-Dex cortisol levels, but lower ACTH responses (Bicanic et al., 2013; Duval et al., 2004). In contrast, one study reported that children who scored higher on the Child Trauma Questionnaire exhibited lower cortisol levels after Dex challenge than children who had lower scores (Lipschitz et al., 2003), suggesting a more robust negative feedback mechanism among these children. More research is needed to examine the role of psychiatric symptoms and duration and severity of maltreatment in explaining these somewhat inconsistent findings, as well as the extent to which these presumed alterations in pituitary and adrenal function are long-lasting.

Child Maltreatment and Hypothalamic-Pituitary-Adrenal Functioning in Adulthood

There have been few studies examining diurnal cortisol slopes in adults with maltreatment histories. However, the few extant studies reveal some evidence consistent with the presence of flatter diurnal slopes, similar to the literature on youth. For instance, participants who had been adopted in childhood after experiencing neglect or abuse were more likely to exhibit flatter cortisol slopes in adulthood, especially if they suffered from anxiety and had a history of severe neglect (vs. abuse; van der Vegt, van der Ende, Huizink, Verhulst, & Tiemeier, 2010; van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Consistent with the possibility of flatter slopes, adults who were maltreated as children also tended to show lower morning cortisol levels (Power, Thomas, Li, & Hertzman, 2012) and higher afternoon levels (Bremner et al., 2003).

Most empirical investigations with adults maltreated as children have focused on cortisol reactivity, but the findings in these studies using experimental reactivity paradigms are mixed. The most widely used paradigm was the TSST, but a few studies employed other psychosocial stressors (e.g., cognitive challenge: Bremner et al., 2003; conflict role-play: Hagan, Roubinov, Mistler, & Luecken, 2014). In one study on cortisol reactivity using the TSST, adults who retrospectively reported childhood maltreatment showed a blunted cortisol response to the stressor compared to adults without childhood maltreatment exposure (Carpenter et al., 2007). Another study found that women who experienced childhood physical abuse exhibited a blunted cortisol response to the TSST when compared to women who had experienced other subtypes of abuse and nonmaltreated women (Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011). A third study (Buchmann et al., 2014) used the TSST as a stress elicitor to look at the interaction between child maltreatment and the FKBP5 *rs1360780* genotype in explaining cortisol reactivity in emerging adults (mean age 19). FKBP5 is a glucocorticoid receptor–regulating

cochaperone (i.e., proteins that assist in protein folding and other functions) that has been implicated in the negative feedback inhibition of the HPA axis. Analyses revealed that adults who reported high levels of maltreatment in childhood and were carriers of the *rs1360780* CC genotype exhibited a lower cortisol response to the TSST when compared to nonmaltreated adults, whereas carriers of the T allele did not show this difference (Buchmann et al., 2014). In contrast to these reports of lower reactivity, one study found higher cortisol responses to the TSST in women who had experienced child maltreatment if they were also depressed compared to three groups: nondepressed maltreated, depressed nonmaltreated, and nondepressed nonmaltreated women (Heim et al., 2000, 2002). These findings suggest that genetic differences and concurrent psychopathology moderate the effect of childhood maltreatment on adult cortisol reactivity.

Among the studies using psychosocial stress tests other than the TSST, null results predominated. For instance, a study of adults meeting criteria for PTSD related to child abuse showed no group differences in reaction to a series of cognitive challenges (Bremner et al., 2003), though the study reported higher anticipatory cortisol levels pretask in the PTSD group. Another study with young adults (aged 18 to 22) found a null effect of maltreatment on cortisol reactivity (Hagan et al., 2014). This experiment used a conflict role-play challenge with a confederate in the lab acting as a peer and found that there was no difference in cortisol reactivity between the maltreated and nonmaltreated group of emerging adults (Hagan et al., 2014). It is difficult to interpret these null results with any confidence. (p. 168) They may be due to the fact that these protocols did not elicit robust enough cortisol responses to reveal individual differences in the samples. Alternatively, lack of main effects at the group level may be the result of averaging across subgroups with opposite profiles (i.e., blunted and heightened reactivity). Indeed, when Hagan et al. (2014) probed their results further, maltreatment was associated with lower reactivity in those with high levels of externalizing symptoms, and higher reactivity in those with internalizing symptoms.

Pharmacological challenge tests have been conducted much more frequently in adults compared to children or adolescents. Two Dex suppression studies revealed enhanced negative feedback (or “super suppression” of the HPA axis) as indicated by lower ACTH or lower cortisol responses in adults with abuse or neglect histories compared to controls, especially if they had a diagnosis of depression or PTSD (Newport, Heim, Bonsall, Miller, & Nemeroff, 2004; Stein, Yehuda, Koverola, & Hanna, 1997; Watson et al., 2007). Clinical studies using a CRH or Dex/CRH challenge have predominantly reported hyporesponsiveness of the HPA axis (lower ACTH and/or lower cortisol) following these challenges in abused patients, especially if they were also suffering from depression or PTSD (Carpenter et al., 2009; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Klaassens et al., 2009; Rinne et al., 2002; Stein et al., 1997). In contrast, chronically abused women with borderline personality disorder (BPD) exhibited a heightened ACTH and cortisol response to a Dex/CRH test (Rinne et al., 2002), and adults with the GG genotype for two single-nucleotide polymorphisms (SNPs) in the CRHR1 gene (*rs110402* and *rs242924*) also exhibited higher cortisol responses to the Dex/CRH challenge than

never-maltreated adults and maltreated adults with the other alleles (Tyrka et al., 2009). The pharmacological findings add to the mixed patterns emerging from reactivity studies to underscore the importance of considering psychiatric diagnosis and variations in genes regulating the HPA axis in future studies, given that these two factors may explain the widespread heterogeneity in the associations between maltreatment and the activity of the HPA axis.

Intervention Studies

Most of the human literature on maltreatment and the HPA axis has been correlational, making it difficult to infer whether the effects described previously are causal in nature. A growing number of intervention studies have provided important evidence that HPA alterations observed in maltreatment can be causal and also reversible. We summarize these studies here.

A number of interventions have been developed to improve parent–child relationships in high-risk families (e.g., families referred to Child Protective Services). We review some of the most commonly used interventions in studies that specifically assessed effects on children's cortisol regulation.

The Attachment and Biobehavioral Catch-up (ABC) intervention is a parent-coaching program that aims to enhance the quality of attachment between the caregiver and the child and support children's self-regulatory capabilities. Parent coaches provide in-the-moment feedback in response to parent–child interactions as they occur to promote nurturing, responsive, and nonfrightening care. In randomized controlled trials, ABC has been compared with an active control condition that is meant to enhance motor, cognitive, and language skills (Bernard, Dozier, Bick, & Gordon, 2015; Bernard, Hostinar, & Dozier, 2015; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008). In a study of infants and toddlers who had been involved with Child Protective Services, infants who received ABC showed more typical diurnal cortisol production than the infants who received the control intervention at a follow-up assessment within several months of the intervention (Bernard, Dozier, et al., 2015). At a preschool follow-up assessment of the same children, at approximately three years postintervention, young children who had received the ABC intervention still showed a more normalized diurnal rhythm than the control group, who showed a flattened diurnal rhythm (Bernard, Hostinar, & Dozier, 2015). In a study of infants in foster care, children randomly assigned to receive ABC showed a lower cortisol response during the Strange Situation, an assessment of attachment that involves brief separations from caregivers, than children in the control intervention (Dozier et al., 2008). Taken together, these studies suggest that the ABC intervention was effective in helping children to regulate both diurnal production and stress reactivity responses of the HPA system.

The Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) is a caregiver-based preventative intervention that aims to address the developmental and socioemotional needs of preschool-aged foster children by providing additional support to

foster parents, such as parenting skills that promote responsiveness and consistency (Fisher & Stoolmiller, 2008; Fisher, Stoolmiller, Gunnar, & Burraston, 2007; (p. 169) Fisher et al., 2011; Graham et al., 2012). In one study, children who received MTFC-P did not show the increasingly flattened diurnal rhythm over time, whereas foster children in regular foster care did (Fisher et al., 2007). Following foster care placement changes, which were found to be associated with dysregulation in cortisol rhythms among children in regular foster care, children who received MTFC-P continued to show the typical cortisol decline from morning to evening (Fisher et al., 2011). In a study aimed to identify potential mechanisms leading to changes in cortisol reactivity, Fisher and Stoolmiller (2008) examined changes in foster parent stress as a result of MTFC-P. Indeed, foster parents who received MTFC-P demonstrated lower stress than foster parents in the comparison group. Further, in the regular foster care comparison group, higher foster parent stress was associated with a more blunted diurnal rhythm and lower morning cortisol levels (Fisher & Stoolmiller, 2008). Finally, in a study examining the potentially challenging transition to school, foster children who received the MTFC-P showed a similar response to a community sample of children, whereas children in regular foster care showed elevated morning cortisol levels on the fifth day of the transition (Graham et al., 2012).

A study that investigated the effects of Promoting First Relationships (PFR), an intervention aimed at improving attachment quality in children who had a recent caregiver change, found no effects on basal morning cortisol levels after the intervention. However, older children who received the intervention exhibited higher cortisol reactivity postintervention compared to children who did not receive the intervention and younger children receiving the intervention (Nelson & Spieker, 2013). This finding was interpreted as a restoration of typical physiological stress reactivity as a result of the intervention, given that most of these at-risk children showed a flat cortisol production pattern during a challenging situation at baseline.

Child–Parent Psychotherapy (CPP) is a dyadic intervention that aims to enhance the quality of the relationship between a parent and child by increasing parents' reflective capacity and sensitivity to child cues; the approach is supportive and nondirective. Over time, maltreated children whose parents received CPP, as well as maltreated children whose parents received a psychoeducational parenting intervention, displayed morning cortisol levels that were similar to nonmaltreated children; in contrast, maltreated children who did not receive an intervention showed decreasing cortisol levels over time (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011).

Collectively, these results indicate that the effects of child maltreatment on the HPA axis can be prevented or reversed with interventions that focus on enhancing parenting and parent–child relationships, which can inform future intervention strategies and policymaking (Slopen, McLaughlin, & Shonkoff, 2014).

Child Maltreatment and Mental Health

Child maltreatment is associated with increased vulnerability to mental health disorders across the lifespan. This includes higher risk of developing depression, PTSD, anxiety disorders, conduct disorder, substance abuse, and personality disorders (Edwards, Holden, Felitti, & Anda, 2003; Scott, McLaughlin, Smith, & Ellis, 2012; Teicher & Samson, 2013). However, not everyone who experiences maltreatment suffers from mental health issues later in life (Cicchetti, 2016). It has been proposed that alterations in the HPA axis following early trauma may have an effect on whether psychopathology develops, and what form it takes (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Susman, 2006).

PTSD is one of the most prevalent mental health outcomes linked to child maltreatment. There is a high rate of PTSD among adults who were exposed to maltreatment during childhood (estimated to be as high as 72 to 100 percent in some studies), and there are higher rates of child maltreatment among adult patients diagnosed with PTSD than among those without PTSD (Pratchett & Yehuda, 2011). The current literature on links between childhood maltreatment and adult PTSD offers the hypothesis that one of the mediating pathways for this vulnerability may involve the sensitization of the HPA axis by early maltreatment, which may be a particularly potent risk factor for those exposed to revictimization in adulthood (Brewin, Andrews, & Valentine, 2000; Pratchett & Yehuda, 2011). PTSD that develops after various types of adult trauma has tended to be associated with lower basal cortisol levels and enhanced negative feedback of the HPA axis (Pratchett & Yehuda, 2011). There are only a few examinations of adults with PTSD secondary to childhood maltreatment, and results are somewhat inconsistent. For instance, one study assessed 24-hour plasma cortisol samples in adult women with a history of child abuse and concurrent PTSD and revealed lower basal cortisol levels in the afternoon in these women compared to abused women without PTSD and women without abuse or PTSD (p. 170) (Bremner, Vermetten, & Kelley, 2007). Another study reported higher levels of 24-hour urinary cortisol in women with PTSD related to childhood sexual abuse (Lemieux & Coe, 1995). This latter sample also exhibited a tendency toward obesity, which may explain the elevated cortisol output. Although childhood abuse appears to create a vulnerability for later PTSD especially in those who are re-exposed to trauma in adulthood (Brewin et al., 2000), more research is clearly needed to test the hypothesis that this vulnerability is mediated by dysregulation of the HPA axis.

Depression is another prevalent condition in those exposed to childhood maltreatment (Batten, Aslan, Maciejewski, & Mazure, 2004; Heim et al., 2008). Two recent reviews of more than four decades of research on depression and the HPA axis have reported a predominant pattern of hyperactivity of the HPA axis in depression (Pariante & Lightman, 2008; Stetler & Miller, 2011), with the strongest effects being noted in older inpatients with melancholic or psychotic depressive features (Stetler & Miller, 2011). Early-life stress is thought to affect the functioning of glucocorticoid receptors in the brain and the periphery, which results in impaired negative feedback mechanisms and elevated levels of basal or reactive cortisol in many depressed patients (Pariante & Lightman, 2008). Results become less consistent when considering HPA functioning in the context of child

maltreatment and concurrent depression, which can manifest with hypo- or hyperreactivity of the HPA axis depending on comorbidity with PTSD, duration of early-life stress exposure, and ongoing stress in adulthood (Penza, Heim, & Nemeroff, 2003).

Conduct disorder, callous-unemotional behavior, aggression, and externalizing symptoms are also more prevalent among individuals who experience child maltreatment than in the general population (Dackis, Rogosch, & Cicchetti, 2015; Gowin et al., 2013; Maniglio, 2015). A growing literature has reported physiological hypoarousal (e.g., low basal cortisol levels and low sympathetic reactivity) in those with antisocial behavior (Alink et al., 2008; Susman, 2006), though effect sizes are smaller than once thought. Hypoarousal of stress systems is thought to be linked to fearlessness, lack of empathy, and seeking stimulation from the environment through disruptive or aggressive behavior. There is increasing evidence that among children exposed to interpersonal violence, blunted cortisol patterns are associated with externalizing behavior (Bernard, Zwerling, & Dozier, 2015; Busso, McLaughlin, & Sheridan, 2016). Some have proposed that the effects of early-life trauma on later conduct problems may be, at least in part, mediated by attenuated HPA responses (Susman, 2006), though a subgroup of those who exhibit antisocial behavior and HPA axis hypoactivity show these behaviors independently of environmental adversity (Hawes, Brennan, & Dadds, 2009). Furthermore, some children show disruptive behavior in the context of HPA hyperreactivity (Hawes et al., 2009). More research is needed to test whether HPA activity plays a causal role in the development of aggressive and antisocial behavior in general and for those exposed to maltreatment in particular.

In sum, heterogeneity seems to be the norm rather than the exception when examining patterns of HPA activity linked to psychopathology in those exposed to maltreatment. Several types of psychopathology appear to be associated with hypercortisolism in some studies and hypocortisolism in others. These complex patterns may be, at least in part, explained by a recent meta-analysis of studies on chronic stress and HPA activity (Miller et al., 2007), which revealed that HPA activity increases acutely after stressor onset but reduces over time as stressors become more chronic. Incorporating detailed assessments of recent stressful life events and lifetime patterns of acute and chronic stress exposure in future studies may add clarity to this literature.

Child Maltreatment and Physical Health

Child maltreatment has also been connected to an increased number of hospital visits in adulthood and greater morbidity due to multiple causes, including cardiovascular disease and diabetes (Ehrlich et al., 2016; Gilbert et al., 2015), obesity (Danese & Tan, 2014), fibromyalgia, and chronic fatigue syndrome (Borsini et al., 2014; Lee, 2010). As with the effects of child maltreatment on the development of psychopathology, maltreatment does not always ensure physical health problems, but these conditions are more common in maltreated individuals. Importantly, most theoretical accounts of how maltreatment instantiates these health risks have hypothesized that the activity of the HPA axis plays a

central role (Chrousos, 2009). Cortisol has widespread effects throughout the body, including effects on metabolism, immunity, and brain development (Sapolsky et al., 2000). Thus, it is biologically plausible that chronic activation of the HPA axis during abuse or neglect might foster the development of numerous physical health problems. However, few studies have directly tested mediational models (p. 171) linking child maltreatment to altered HPA functioning and, in turn, physical health symptoms.

Accumulating evidence suggests that links between HPA activity and inflammation may play a key role in this mediational pathway. Childhood maltreatment is associated with elevated inflammatory biomarkers (Coelho, Viola, Walss-Bass, Brietzke, & Grassi-Oliveira, 2014), which have been implicated in the development of many conditions with inflammatory underpinnings, such as coronary heart disease, diabetes, and obesity (Hotamisligil, 2006). Cortisol is known to play an important role in countering the proinflammatory activity of monocytes and macrophages (Irwin & Cole, 2011), and there is evidence that dysregulated cortisol levels (either abnormally low or chronically high) can impair the control of inflammatory responses (Raison & Miller, 2003; Sapolsky et al., 2000). Thus, dysregulation of the HPA axis may be one pathway through which maltreatment may lead to excessive inflammation and chronic diseases of aging precipitated by inflammation (Glaser & Kiecolt-Glaser, 2005). Despite the important role likely played by the HPA axis and inflammation, we must recognize other pathways through which maltreatment might impair health, such as the adoption of health-compromising behaviors that are occasioned or exacerbated by stress, such as smoking, overeating, or sedentary lifestyles (Kiecolt-Glaser & Glaser, 1988; Raposa, Bower, Hammen, Najman, & Brennan, 2014).

In conclusion, there is accumulating evidence to provide piecemeal support for associations between maltreatment and HPA dysregulation, HPA activity and inflammation, and inflammation and multiple disease endpoints. However, testing these full, multistep pathways within the same participants followed longitudinally will be necessary to explicitly examine the mediating role of the HPA axis in the development of many of these health conditions.

Future Directions

Recent literature has brought a greater understanding of the range of possible effects of child maltreatment on the HPA system and its implications for mental and physical health, but many questions remain unanswered. One such question is whether the effects of maltreatment on the HPA axis are transient or persistent across the lifespan, and how they may change with development. A frequently noted gap in the literature has been the scarcity of longitudinal studies to address this question (Bernard et al., 2015; Cicchetti et al., 2011; Heim et al., 2008). The few existing longitudinal investigations suggest a potential switch from cortisol hypersecretion in the aftermath of trauma to a pattern of hyposecretion later in development (e.g., Trickett et al., 2010), but more studies are needed to corroborate this pattern.

Intervention studies that follow participants over time are especially needed to examine the persistence of intervention effects, and to compare interventions to each other (Fisher et al., 2011, 2016; Slopen et al., 2014). There is also a dearth of intervention studies attempting to ameliorate or normalize HPA functioning in adults with childhood trauma exposure. As summarized previously, interventions with children have shown that there is some plasticity in children's HPA activity, but it is unclear whether this plasticity extends into adulthood.

There is also a lack of cortisol reactivity studies in younger maltreated children. The majority of the existing research with these younger participants has focused on diurnal cortisol, whereas studies that incorporated paradigms to test cortisol reactivity have mostly been conducted with preteenagers, teenagers, and adults. This makes it difficult to draw conclusions about developmental changes that may occur across the lifespan, and provides an incomplete characterization of HPA functioning within each life stage.

There is some emerging evidence supporting the role of maltreatment subtypes and varying levels of chronicity in shaping HPA outcomes, but this evidence base needs to be expanded (McCrory, De Brito, & Viding, 2010). Furthermore, the role of interactions between genetic variation and maltreatment experiences in influencing psychiatric outcomes is only beginning to be explored. Current results in these areas are relatively mixed, and the number of studies conducted is quite limited. This research could lead to more targeted intervention programs and a greater understanding of the development of individual differences in HPA and mental health outcomes following child maltreatment. More evidence is also needed to test the mediating role of HPA alterations in the relation between child maltreatment and mental or physical health. This research has only recently begun to gain traction (e.g., Bernard, Zwerling, & Dozier, 2015; Hagan et al., 2014), but it is critical for testing many contemporary theories of how early-life stress leads to later psychopathology and chronic disease.

There are also a few methodological limitations that have been noted in this literature (McCrory et al., 2010; Pollak, 2015). These limitations include (p. 172) inconsistencies in how HPA function and maltreatment are assessed across studies, the widespread use of retrospective designs in adult studies, and small sample sizes. Cortisol sampling occurs in multiple settings (e.g., laboratory, home, clinic), and there is little consistency in the timing of sample collection. This makes the results incomparable to each other in some respects, and makes it difficult to quantitatively summarize this literature to determine how robust the effects are. Differences in how maltreatment is classified may also lead to heterogeneous patterns of results. Some researchers have used a classification system such as the Maltreatment Classification System (Barnett et al., 1993). Other studies use records from Childhood Protective Services and other similar agencies, whereas others collect parental report or retrospective self-report measures. Retrospective and prospective assessments of maltreatment both relate to negative outcomes; however, these different measurement strategies seem to identify only partially overlapping populations, and more research is needed to understand their relationship. Additionally, the prevalence of small sample sizes in this literature (McCrory et al., 2010) is not

surprising given the difficulty of recruiting from this vulnerable population, but it can also lower the statistical power to detect effects. Although it may be difficult to address these issues, it is vital to take them into consideration to move this research agenda forward and improve the evidence base.

In conclusion, it is clear that child maltreatment is associated with altered patterns of HPA activity, which may end up explaining the development of several deleterious mental and physical health outcomes. Intervention studies with children provide hope that these effects can be prevented or mitigated, but more research is needed before concluding that these benefits are long-lasting into adulthood.

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