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Stress, Development, and Well-being

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Abstract:

Typically, when we experience stress, our physiological and social resources allow us to regulate and adapt effectively, which tends to prevent maladaptive outcomes associated with those experiences. A complex network of stress response systems maintains physiological and behavioral allostasis, or stability through change in their activity. The social relationships we have, particularly those with attachment figures, allow us to maintain this balance even if the stress would otherwise be outside our regulatory capacity. This is particularly critical early in life when we cannot regulate on our own. When these social relationships are absent, inconsistent, or of low quality, chronic activation of stress response systems can result in dysregulated stress reactivity and regulation. This puts children at increased risk for poor physiological and psychological outcomes and overall lower well-being across the life span.

Keywords: Stress Response, Physiology, Social Relationships, Regulation, Development

The experience of stress is a normal part of life. Therefore, humans possess mechanisms both "under the skin" and in the environment that function to support processing, responding to, and recovering from stressors while preserving physical and psychological well-being. During development, these stress systems are adapted to our individual context based on personal characteristics, early experiences, and social relationships. When faced with chronic stressors, the body makes continuous adjustments that may come at a cost to future well-being. When stressors become too intense or overwhelming, or when one of these mechanisms breaks down and can no longer function properly, there can be detrimental effects on physiological, behavioral, and emotional health. Up to a point, it is not the presence of stressors in your life, but the capacity to regulate reactions to them, that influences their impact on physical and psychological well-being. These impacts vary over time as the stress systems develop from infancy into adulthood.

Throughout this chapter, the 'stress response' is defined as the body's network of physiological and behavioral processes that are activated in order to restore homeostasis following an encounter with a real or imagined threat to our well-being. Stress responses are moderated by actual and/or perceived controllability and predictability of the stressor, the presence of social support, and the extent to which the stressor threatens physiological or behavioral stability (Koolhaas et al., 2011). It is important to note that stress is neither always negative nor does it always have negative consequences. Stressors within the regulatory capacity of the individual that result in moderate activation of stress response systems can actually aid in learning (Lucas, Chen, & Richter-Levin, 2013). We experience stress at all stages of life, for example after separation from a caregiver, when there is a physical or emotional threat to the self, or during the anticipation of social evaluation. By mobilizing available physiological and social resources when necessary, humans have an incredible capacity to regulate in response to stress. In fact, even in the face of severe, chronic stress, a sizable portion of individuals show resilient functioning. This may be due in large part to the buffering effect of stable, high-quality caregiving and social relationships.

Physiological Building Blocks of Well-being

There is a complex array of physiological systems involved in the stress response. This neuro-symphony of stress mobilizes particular resources in order to deal with stressors. While these systems work in concert, they do not all respond the same way to the same stressors. Perhaps the most critical, and most

frequently studied, system involved in the stress response is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis response begins in the paraventricular nuclei (PVN) of the hypothalamus, a brain region that is a central regulator of a wide range of homeostatic, autonomic and neuroendocrine processes. Multiple neural signals regulate the activity of these PVN neurons according to signals from higher brain regions, including the amygdala, hippocampus and prefrontal cortex (PFC; Ulrich-Lai & Herman, 2009). The hypothalamus secretes corticotropin-releasing hormone (CRH) which activates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH travels to the adrenal cortex, which sends the HPA axis end-product cortisol throughout the body (Charmandari, Tsigos, & Chrousos, 2005). Circulating cortisol binds to its receptors that reside in most cells, facilitating its wide-ranging influence on multiple systems. Once bound to its receptor, this glucocorticoid hormone is transported to the cell nucleus where it regulates protein synthesis for various genes. Peak cortisol levels are achieved 20-40 minutes after activation of the system. Cortisol operates by regulating the transcription of genes into protein, processes that take minutes to hours to be achieved and whose effects may last days (Kirschbaum & Hellhammer, 1994). The HPA axis is reliably activated by psychosocial stressors, but not necessarily to stimuli like exercise, which results in non-social homeostatic disruption (Ulrich-Lai & Herman, 2009).

Circulating cortisol is regulated by its own negative feedback loop, reducing activity at all levels of the HPA axis, to prevent excess amounts of cortisol that may have detrimental effects on physical and mental health (Chrousos, 2009). However, in the context of severe, prolonged stressors, activating signals override negative feedback and elevated levels of cortisol continue which may result in poorer well-being (Strüber, Strüber, & Roth, 2014). Even in healthy individuals, increases in cortisol production seen approximately 30 minutes following wake-up (cortisol awakening response), have been negatively associated with trait well-being when they get too large (Smyth et al., 2015). In some cases, after a long period of elevated cortisol, negative feedback mechanisms can overcompensate and result in lower than normal cortisol production (i.e. hypocortisolism), which is also associated with poorer health and behavior outcomes (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Strüber et al., 2014).

The effects of the HPA axis are generally slow and long lasting. In contrast, the sympathetic-adrenomedullary (SAM) system responds rapidly and supports fight/flight. This system is a component of the sympathetic nervous system (SNS) and is more reliably activated by any (internal or external) environmental stimulus that disrupts the body's physiological homeostatic balance and, to a lesser extent, psychosocial stressors (Ulrich-Lai & Herman, 2009). The SAM system involves innervation of chromaffin tissue in the adrenal medulla via the splanchnic nerve, which then releases epinephrine (Epi) and some norepinephrine (NE) into circulation to act on systems throughout the body (Gunnar & Quevedo, 2007). SAM activity amplifies the effect of the SNS which releases NE at synapses on many of the same target organs (e.g. heart, lungs, pupils, blood vessels; Charmandari et al., 2005; Gunnar & Quevedo, 2007). In a matter of seconds, heart rate and respiration increase to prepare the body for an immediate stress response.

The SNS is also influenced by the opposing branch of the autonomic nervous system, the parasympathetic nervous system (PNS), which operates synergistically with the SNS and promotes 'rest and repair' functions like digestion and bodily maintenance. Typically, the PNS suppresses or inhibits the activity of organs involved in fight/flight, for example causing the heart to beat slower, or the pupils to be less dilated. Upon detection of a stressor, the PNS usually releases its influence (i.e., 'lifting the vagal brake'), allowing organs under tonic inhibition (e.g., the heart) to rapidly increase their activity. This is enhanced seconds later as the actions of the SNS take effect, resulting in large increases in heart rate and blood pressure (Porges, 2007). Epi and the CRH produced outside of the hypothalamus act as positive feedback mechanisms for the SNS (Chrousos, 2009); however, PNS activation dampens the effects of SNS activity and returns the body to its resting state (Quas et al., 2014). In the context of chronic stress, the SNS tends to be hyperreactive, and autonomic regulation shifts away from balanced activation of SNS and PNS to an SNS-dominant system (Del Giudice, Ellis, & Shirtcliff, 2011).

These peripheral systems have upstream influences by widespread brain regions involved in detecting and responding to real or imagined threats in the environment. The HPA axis is regulated by CRH released by the hypothalamus, which is in turn regulated by the PFC, hippocampus, and amygdala (McEwen, 2007; Ulrich-Lai & Herman, 2009). Given that the hypothalamus also plays a role in autonomic functioning (Porges, 2007), neural regulation of the hypothalamus can have wide-ranging effects on the stress response. Generally, the medial PFC and hippocampus have inhibitory effects on the hypothalamus and are involved in the reduction or termination of the stress response (Ulrich-Lai & Herman, 2009), while the amygdala has excitatory effects (McEwen, 2007). Cortisol alters the activity of the structures that regulate its own production and, in doing so, alters thresholds for perceiving and responding to threat. Large and/or chronic increases in cortisol reduce hippocampal and medial PFC functioning, weakening their ability to terminate the HPA axis stress response and inhibiting learning and memory. Chronic cortisol production also increases the activity of the amygdala, which may lower the threshold for responding to

threats and increase HPA axis activation (McEwen, 2007; Ulrich-Lai & Herman, 2009). All of these consequences may result in impaired well-being across domains (Davidson & McEwen, 2012).

There are a number of hormones and neuropeptides that are neuromodulators of stress, beyond CRH and NE. Oxytocin tends to reduce the HPA stress response, potentially through reduced expression of hypothalamic CRH (Jurek et al., 2015; Zheng et al., 2010). CRH produced in the central nucleus of the amygdala has widespread influence on neural systems that orchestrate fear responses and fear learning (Gafford & Ressler, 2015). Serotonin has been shown to reduce the sensitivity of the adrenal cortex to ACTH (Chen & Miller, 2012). Similarly, direct activation of serotonin receptors (5-HT_{1A}) in the rat hypothalamus reduces the amount of corticosterone (the rodent equivalent of cortisol) produced in response to restraint stress, a common rodent stressor that involves extended immobilization and restricted limb movement (Stamper et al., 2017). Additionally, serotonin transporters in the adrenal medulla function to reduce the SAM response in rats (Brindley, Bauer, Blakely, & Currie, 2017). These patterns may partially explain why selective-serotonin reuptake inhibitors are a common treatment for anxiety and depression (Hirschfeld, 2001). Dopamine may also be a critical modulator of the stress response. When activated, CRH receptors in the ventral tegmental area release dopamine throughout the brain (Wanat, Hopf, Stuber, Phillips, & Bonci, 2008). The ventral tegmental area has bidirectional connections with the PFC, and increased levels of circulating dopamine produced by the nucleus accumbens are seen following acute (i.e., short-lived) stressors. However, exposure to chronic stress in infancy has been found to downregulate dopamine expression (Gatzke-Kopp, 2011). Additionally, rats exposed to restraint stress showed an increase in prefrontal NE followed by an increase in dopamine in the nucleus accumbens and PFC that does not occur in the absence of increased NE (Pascucci, Ventura, Latagliata, Cabib, & Puglisi-Allegra, 2007).

Coordination Between Stress Systems

Clearly, these systems are highly interdependent and each system responds based on activity of other systems. Additionally, genes influence the rate and amount of production of neuromodulators, their receptors, and other molecules involved in the transmission of neural signals (Charmandari et al., 2005). Every person has two copies of each gene (termed 'alleles') that may be identical to or different from each other and those of another person. Particular alleles influence stress system regulation; for example, alleles of the glucocorticoid receptor gene *NR3C1* confer differential sensitivity to HPA axis negative feedback (McEwen, 2007). Similarly, allelic variation impacts psychiatric outcomes associated with these stress systems; for example, an allele of the monoamine oxidase A (*MAOA*) gene that produces inefficient MAOA functioning increases the risk for antisocial behavior following abuse (Caspi et al., 2002).

While the genes a person possesses are permanent, the capacity of genes in a specific cell to be transcribed into protein (i.e., gene expression) is subject to change via numerous processes, including epigenetic modifications. Epigenetic modifications are alterations to chromatin structure that do not change the DNA sequence, but still can influence gene expression. Chromatin is comprised of the genes and their packaging proteins (called 'histones'). The more tightly the histones "package" the genes, which is influenced by epigenetic modifications, the less likely that gene will be transcribed into protein. These modifications are a key mechanism through which the environment and experiences produce lasting changes on gene function (Boyce & Kobor, 2015). Rodent studies have found that epigenetic alterations of the glucocorticoid receptor gene, *NR3C1,* are a function of the quality of early maternal care, and mediates early care's impact on stress responsivity in adulthood (Zannas & West, 2014). In humans, epigenetic processes are mechanisms through which children who have experienced maltreatment are at higher risk for various types of psychopathology (Lutz & Turecki, 2014). While epigenetic changes can be long-lasting and even transgenerational, they can also be reversible (Boyce & Kobor, 2015). This is promising for the success of interventions and treatment following adverse early experiences.

Although there is a wide range of stress systems and neuromodulators that allow the body to respond to diverse challenges, they tend to overlap in their functions (Joëls & Baram, 2009). There is extensive cross-talk and coordination between systems, such that each system cannot truly be understood except in the context of the rest. Countless studies have explored the link between HPA and sympathetic activity in rodents, primates, and humans (for a review, see Schumacher, Kirschbaum, Fydrich, & Ströhle, 2013). Petrullo et al. (2016) found attenuated cortisol reactivity, but unchanged salivary a-amylase reactivity (a peripheral marker of SNS activity), in juvenile rhesus macaques exposed to maternal abuse. Gordis and colleagues (2006) found that attenuated cortisol reactivity was associated with increased aggressive behavior in the context of lower, but not higher, a-amylase reactivity. Thus, it seems that attenuated cortisol reactivity is associated with aggression; however, it is still unclear whether and how SNS activity plays a role in this association. More research into the biological mechanisms underlying these associations is also needed to investigate whether this is a causal relationship. Coordination between these systems may also be associated with subjective stress and anxiety when discussing a conflict with a

romantic partner (Laurent, Powers, & Granger, 2013). Other studies have explored SNS/PNS activity patterns (Blechert, Michael, Grossman, Lajtman, & Wilhelm, 2007; Winzeler et al., 2016), and their relation to HPA activity (Quas et al., 2014). El-Sheikh and Erath (2011) found that coactivation or coinhibition of the SNS and PNS, diverging from their typical asymmetry, presents greater susceptibility to externalizing problems for children experiencing marital conflict. Rash et al. (2016) suggest that maternal stress response profiles of HPA, SNS, and PNS activity may predict their child's dysregulation of the same systems. They propose that children with asymmetrical SNS/PNS activity and SNS/HPA activity are at the lowest risk for behavioral problems and psychological well-being.

With the emergence of cross-system research, some have put forth theories that include activity of multiple systems (Del Giudice et al., 2011; Joëls & Baram, 2009; Korte, Koolhaas, Wingfield, & McEwen, 2005; Porges, 2007). However, many questions remain unanswered. These systems operate on different time scales, and thus it is difficult to assess multiple systems within the same study. Similarly, while we are often interested in brain activation of these systems, practical and technological limitations sometimes force us to measure peripheral endpoints in blood, saliva, or activity of downstream systems (i.e. heart rate, skin conductance). These measures may only be modestly correlated with activity of the brain regions orchestrating the stress response. Moreover, responses are highly context-dependent and small manipulations such as the presence of a caregiver can alter the stress response (Conner et al., 2012). Finally, many studies have sought to find linear relationships between stress response systems. However, some systems, the HPA axis in particular, have non-linear relationships with well-being, such that both too much and too little activity are associated with poor outcomes (Chrousos, 2009). There is also reason to believe that relationships between stress systems are non-linear. Future studies should address the coordination between multiple systems using the most direct measures as possible, and acknowledge that their interactions are likely complex and non-linear.

Developmental Processes in Well-being

In addition to interrelations between stress systems, there are many changes occurring with development. Again, the most studied stress system in this regard is the HPA axis. Beginning in the prenatal period, a child's HPA axis develops in the context of the mother's cortisol production which impacts activity in the placenta (Gunnar, Doom, & Esposito, 2015). While the majority of the mother's cortisol is broken down by the enzyme 11b-HSD2, some cortisol still reaches the fetus intact and this prenatal exposure may influence the child's future HPA axis regulation (Oberlander et al., 2008). Moreover, maternal cortisol stimulates the placenta to produce CRH which may activate the fetus' own HPA axis. Infants exposed to higher levels of cortisol *in utero* were less able to mount a sufficient cortisol response to the Strange Situation, a maternal separation stressor paradigm, which may signify that fetal programming of the HPA axis can have maladaptive effects on later stress regulation (O'Connor, Bergman, Sarkar, & Glover, 2013). In the first few months after birth, infants typically start to develop a stable diurnal rhythm. During the preschool period, with the end of regular daily naps, this rhythm starts to resemble an adult-like pattern (Gunnar & Quevedo, 2007). There is some evidence to suggest that the cortisol awakening response tends to increase across the entire lifespan (Miller et al., 2016).

The other stress response systems have much less research delineating normative developmental changes. There is some evidence that heart rate, a measure of SNS activity, decreases with age and vagal tone, a measure of PNS activity, increases with age (Alkon et al., 2003; Gunnar & Quevedo, 2007). An increase in PNS activity may be associated with the development of emotion regulation, via the increased ability to modulate physiological and behavioral responses to a stimulus (Gunnar & Quevedo, 2007). Neuromodulators like serotonin are present at relatively high levels very early in fetal development, and during this period serve as neurotrophic (i.e., nerve growth) factors that stimulate brain development. Serotonin levels remain high for the first two years of life before gradually declining in childhood (Whitaker-Azimitia, 2001). Further research should address developmental changes in all stress response systems and their interactions in more detail.

The normative development of stress regulatory systems may vary by sex. These differences, particularly in the HPA axis, tend not to be present until puberty (Doom & Gunnar, 2013). When differences are found, males tend to have lower diurnal cortisol levels compared to females of the same age (Miller et al., 2016). With puberty, differences in gonadal hormone production tends to facilitate differential neural and HPA axis regulation (Del Giudice et al., 2011; Ordaz & Luna, 2012). Adolescent females begin to have larger cortisol awakening responses that peak at 45, rather than 30, minutes following wake-up (Schlotz, Hellhammer, Schulz, & Stone, 2004). Males begin to react to stressors more strongly than females, however not all studies have found these sex differences (Doom, Hostinar, VanZomeren-Dohm, & Gunnar, 2015; Ordaz & Luna, 2012). This inconsistency may depend on the type of stressor (e.g. social evaluation, pain, performance, Del Giudice et al., 2011). Studies assessing sex differences in autonomic reactivity have not always shown consistent effects either (Kelly, Tyrka,

Anderson, Price, & Carpenter, 2008); however, some studies have found that females tend to have increased autonomic reactivity (Ordaz & Luna, 2012). Cortisol reactivity patterns may be a mechanism through which females, particularly adolescents, are at heightened risk for depression and anxiety, however the direction of these effects has been inconsistent (Natsuaki et al., 2009; Powers, Laurent, Gunlicks-Stoessel, Balaban, & Bent, 2016). For males, on the other hand, suppressed HPA and autonomic reactivity may be associated with substance abuse (Fox et al., 2009).

Temperament is associated with stress regulation and reactivity and affects how children respond to stressors. Temperamental fearfulness is associated with increased HPA axis activity to unavoidable social challenges in non-human primates and preschool children (Kalin, Shelton, & Davidson, 2000; Talge, Donzella, & Gunnar, 2008). Talge et al. (2008) also examined associations between fearfulness and autonomic activity but found no consistent relation. Infant surgency (low fearfulness, high impulsivity) is also associated with elevated HPA and sympathetic reactivity (Laurent, Ablow, & Measelle, 2012); however, this may be dependent on the social context (Gunnar, Sebanc, Tout, Donzella, & van Dulmen, 2003). In fact, several studies have shown that associations between temperament and stress reactivity depend on the quality of the parent-child relationship or the child's attachment to their primary caregiver (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Smeekens, Riksen-Walraven, & Van Bakel, 2007) with similar patterns emerging when predicting behavioral and emotion regulation (Kim & Kochanska, 2012; Thomas et al., 2017). Interestingly, the effect seems to be bidirectional – one study found that low parent-child relationship quality predicted increases in negative emotionality across childhood but only when the child also exhibited higher cortisol reactivity (Kopala-Sibley et al., 2015).

Social Relationships and Well-being

The parental figure is a primary example of how powerfully social relationships regulate stress response systems. Better parenting quality has been consistently associated with healthier HPA axis regulation (Albers et al., 2008; Martin, Kim, Bruce, & Fisher, 2014) and parasympathetic tone (Hinnant, Erath, & El-Sheikh, 2015). Secure attachment relationships and higher quality parenting are effective buffers from maladaptive stress outcomes for young children experiencing a wide variety of adversities (poverty: Blair, Raver, Granger, Mills-Koonce, & Hibel, 2011; foster care, Fisher, Gunnar, Chamberlain, & Reid, 2000, Oosterman, De Schipper, Fisher, Dozier, & Schuengel, 2010; maltreatment, Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; international adoption, Pitula, DePasquale, Mliner, & Gunnar, *in press*). Parenting quality may sometimes moderate the association between physiological regulation and maladaptive behavioral outcomes, such that the poor outcomes only occur when the child also experiences lower quality parenting (Barrios, Bufferd, Klein, & Dougherty, 2017; Bubier, Drabick, & Breiner, 2009). Furthermore, the dysregulation of a parent's own stress response systems may hinder their ability to provide high quality parenting (Skowron, Cipriano-Essel, Benjamin, Pincus, & Van Ryzin, 2013).

The presence of a sensitive caregiver often reduces the reactivity of a child's stress response systems, particularly the HPA axis (i.e. parental social buffering, Gunnar & Quevedo, 2007). In rat pups, by about 10 days of age the stress-hyporesponsive period ends and their HPA axis responds to aversive stimuli, except (for approximately the next 10 days) in the presence of the mother (Sullivan & Perry, 2015). This is similar to the capacity of the parent to buffer HPA axis responses by the end of the first year of life in humans and is most prominent in secure attachment relationships (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996). Oxytocin, a critical neuromodulator involved in attachment and affiliative behavior, may play a role in this phenomenon (Strüber et al., 2014). In one study, children who completed the Trier Social Stress Test (TSST), a common social-evaluative stressor, and had full contact with their parent immediately after showed both the lowest cortisol reactivity and the highest spike in oxytocin (Seltzer, Ziegler, & Pollack, 2010). Even for adult males, having a best friend provide social support during TSST preparation resulted in a smaller cortisol response, a larger increase in oxytocin, and less subjective stress and anxiety (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003).

Still, there are developmental changes in the social buffering of stress reactivity. Parents essentially block the entire stress response in infants (Gunnar et al., 1996). They are also more effective buffers for children compared to adolescents. The loss of parental effectiveness as a stress buffer likely corresponds to pubertal maturation (Gunnar & Hostinar, 2015). Who, then, takes over as the primary source of social support? It turns out, it is not friends – at least not for social-evaluative stressors (Doom, Doyle, & Gunnar, 2016). In this study by Doom and colleagues, adolescents ages 15-16 showed a larger cortisol response to the TSST when preparing with their caregiver compared to that of younger children ages 8-9. Adolescents showed an even larger response when preparing with their best friend. Whether friends can be social buffers under other conditions during this developmental period or whether the quality of the friendship matters is not yet known. Certainly, by adulthood social partners can be effective buffers (Heinrichs et al., 2003). The ability to utilize social partners to buffer the stress response in early development is likely important for healthy physiological and brain development. It is possible that the apparent loss of this

ability in adolescence helps the body learn to independently self-regulate and develop more mature patterns of stress system activity, however more research is needed to directly test this claim. Additionally, a limitation to this body of research is the disproportionate use of decontextualized stressors. The TSST, while a reliable way to activate the HPA axis, is one of many laboratory stressors that may not reflect how a person would respond in the real world. Future research should delve further into the developmental patterns of parental social buffering in more naturalistic contexts.

Nevertheless, it seems clear that the presence of a sensitive caregiver at particular points in development is critically important for physical and psychological well-being. Positive parenting in childhood can influence future HPA axis regulation and how children react to stressors years later (Hagan et al., 2011; Shirtcliff, Skinner, Obasi, & Haggerty, 2017). Early parenting, over and above later parenting, is especially important for healthy physiological development (Loman & Gunnar, 2010; Sroufe, 1979). During early development, rapid changes in neurological and physiological systems are the building blocks for healthy functioning. The environment a child experiences during this time of heightened plasticity is highly influential for how those systems develop (Luecken & Lemery, 2004). Early experiences set the stage for physical, physiological, and psychological well-being across the lifespan.

Impact of Absent, Low Quality, and Inconsistent Relationships

Because early caregiving relationships have the potential to be a strong positive influence on children's development, they can also cause great harm when those relationships are absent, of low quality, or inconsistent. The negative influence of early caregiving has been powerfully demonstrated in "natural experiments" where children were exposed to extremely stressful or deprived environments early in life but were later removed from those environments. For example, children who have been adopted from or fostered out of orphanages/institutions have typically experienced unstable, inadequate care. In institutional care children have multiple rotating caregivers with whom they have no real opportunity to form relationships and little developmentally appropriate stimulation (Gunnar, Bruce, & Grotevant, 2000). However, once adopted or fostered into families, their environments drastically change. Still, many post-institutionalized children have lingering physiological and behavioral deficits for several years following adoption (Koss, Mliner, Donzella, & Gunnar, 2016; McLaughlin et al., 2015) and these deficits increase their risk for psychopathological outcomes (Slopen, McLaughlin, Fox, Zeanah, & Nelson, 2012). Increased caregiving quality following institutionalization has been shown to improve outcomes, however, particularly in the HPA axis (DePasquale, Raby, Hoye, & Dozier, *under review*; McLaughlin et al., 2015).

Even in more typical circumstances, breakdowns in early caregiving are detrimental to a child's well-being. Children who have experienced maltreatment exhibit dysregulated HPA and autonomic stress response systems and poorer socioemotional outcomes (McLaughlin, Sheridan, Alves, & Mendes, 2014). Children in foster care, particularly those placed several times, also show HPA axis dysregulation (Fisher, Van Ryzin, & Gunnar, 2011). Maternal depression and cumulative risk associated with poverty have been associated with more negative parenting and thus dysregulated HPA axis and autonomic functioning (Evans & Kim, 2007; Oberlander et al., 2008; Zalewski, Lengua, Kiff, & Fisher, 2012). In all of these instances – maltreatment, foster care, and poverty – the very people who should be a child's primary source of support and positive experiences may become the source of extreme stress and neglect. This may enhance the maladaptive consequences of those experiences, and significantly impact children's ability to adapt effectively over time. What remains to be studied in sufficient detail are the bidirectional effects between the parent and child on child physiological development, and the dyad's relationship quality and physiological, behavioral, and emotional well-being over time.

Because of the powerful role of caregivers in children's development, it is not necessarily the presence of stressors, but the capacity of the parents to buffer and regulate stress that affects a child's physical and psychological well-being. Depending on the developmental time period, when buffering systems fail stressors can have profound impacts on the entire network of stress response systems, which drastically reduces a person's ability to effectively adapt despite adverse experiences. Some stressors, like early institutionalization, are powerful enough to offset the protective effect of a sensitive caregiver encountered after adoption or foster placement. Institutionalization also highlights the specific importance of experiences during the first few years of life when the stress response systems are developing rapidly. Caregivers can affect well-being for better or for worse, and there are critical neurobiological mediators involved in the experience of stress and the impact of caregiving throughout development. The timing and nature of caregiving influences and adverse experiences may affect how these factors impact physiological reactivity and regulation and, as a result, psychological well-being. While timing is central to understanding development, it is precisely this area where we lack definitive answers. The question of sensitive periods and periods of opportunity to recalibrate stress-responsive systems is at the cutting-edge of research on stress reactivity, regulation and well-being.

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