CHAPTER 5

The Neurobiology of Stress and Adversity in Infancy

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Stress from a neurobiological perspective relates to the activation of biological systems that respond to changes in the environment and that maintain allostasis. Adversity, in turn, reflects negative experiences that are likely to require significant neurobiological adaptation by an average child and that represent deviations from the expectable environment (McLaughlin, 2016). Biomarkers of stress response systems can reveal how neurobiological stress systems respond to stressful environments in infancy, contributing to greater understanding of what constitutes adversity in infancy.

This chapter is organized into three sections. In the first, we broadly outline component systems of the neurobiological stress response systems. These systems include endocrine pathways hallmarked by the hypothalamic–pituitary–adrenal (HPA) axis and the biomarker cortisol, autonomic pathways including the sympathetic nervous system (SNS) and the biomarker galvanic skin response (GSR), as well as the parasympathetic nervous system (PNS) and the biomarker respiratory sinus arrhythmia (RSA). We focus our discussion on these peripheral systems. We explore in the second section infants' neurobiological responses to normative, circumscribed, laboratory stressors spanning fear, frustration, surprise and mild pain paradigms, building on a well-established literature indicating that stress vulnerability, reactivity, and regulation in infancy are predictive of later cognitive, socioemotional, and physical health (Gunnar & Quevedo, 2007; Heim & Nemeroff, 2001). In the third section, we discuss the neurobiological reflections of adversity in infancy, or experiences that represent a deviation from the expectable environment and require adaptation. This literature is best contextualized within epidemiological evidence that childhood adversity is common and strongly associated with the onset of psychopathology (McLaughlin, 2016). We conclude with a discussion of the themes of the neurobiology of stress and adversity in infancy, which include developmental changes, evidence of individual differences or protective effects, potential for buffering or mitigating effects, and key directions for future research.

Neurobiology of the Stress Response in Infants

Endocrine Pathways

The infant stress response is in part regulated by the HPA axis. Activation of the HPA axis involves downward influence via pathways beginning in the amygdala and projecting to the adrenal glands through connections with the hypothalamus and pituitary. More specifically, amygdala projections to the paraventricular nucleus in the hypothalamus stimulate the produc-

tion of corticotropin-releasing hormone (CRH) following amygdala activation. Upon release, CRH travels to the pituitary and prompts the release of adrenocorticotropic hormone (ACTH), which travels via the bloodstream to the adrenal glands and stimulates the production and release of cortisol into the bloodstream (Gunnar & Cheatham, 2003). Under normative conditions, most of the circulating cortisol binds to corticotropin-binding globulin (CBG) and exerts inhibitory influence to stop the production of CRH in the hypothalamus through a negative feedback loop involving the hippocampus. Thus, this negative feedback loop, in which circulating cortisol serves to regulate the production of CRH, works to stop the stress response and limit the amount of cortisol released into the bloodstream (Gunnar & Vazquez, 2001).

In adults, cortisol production occurs at basal levels and operates in a diurnal rhythm, with a predictable circadian rhythm that rises to peak levels within 30 minutes of waking and shows a gradual decline across the rest of the day until bedtime. At basal levels, about 10% of cortisol circulates unbound to CBG, whereby it exerts metabolic influence on the body (Gunnar & Cheatham, 2003). However, in response to stress, levels of circulating cortisol exceed this threshold and bind with cell receptors throughout the body to influence gene expression and ultimately metabolic processes that regulate the functioning of organs, muscles, digestion, and the nervous system.

In newborns, unlike in adults, cortisol is usually unbound or free, as opposed to bound to proteins (e.g., CBG). Only free (unbound) cortisol binds to receptors and prompts stress responding. Free cortisol is greatest in infants immediately following birth, drops dramatically in postnatal days 3–5, then gradually rises to adult levels at around 3 months of age (Rokicki, Forest, Loras, Bonnet & Bertrand, 1990). CBG levels increase over the first 6 months (Gunnar, Talge, & Herrera, 2009).

Across infancy, cortisol rhythms are variable and do not map onto patterns observed in adulthood. In adults, cortisol follows a diurnal rhythm, with steep rises immediately after waking, followed by a sharp decline that becomes more gradual across the day, with the lowest levels of cortisol in the evening before bedtime. In contrast, newborns show two diurnal peaks, 12 hours apart, which do not correspond to a time of day (Gunnar & Quevedo, 2007). It is not until the infant is 3 months old that the early morning peak and evening nadir are established (Gunnar & Quevedo, 2007). The decrease from midmorning to midafternoon is not seen until beyond infancy, when children stop daytime napping, whereupon the pattern matches adult diurnal cortisol patterns.

The HPA axis responds to environmental and physical stressors as early as birth (Gunnar, 1992). For example, higher cortisol is observed in infants born vaginally versus through cesarean section (Kaplan, Grumbach, & Aubert, 1976). Moreover, birth process and timing also appear to impact cortisol, as premature infants show higher cortisol in the first week of life than do full-term newborns (Rokicki et al., 1990).

The HPA axis in infancy regulates normative responses to daily stressors, as well as acute stressors. For example, infants in full-day center-based child care settings show increases in cortisol across the day when in child care, whereas the majority of infants do not show increases in cortisol from midmorning to midafternoon, when cared for at home (Watamura, Donzella, Alwin, & Gunnar, 2003). On balance, 3-month-old infants demonstrate significant increases in cortisol when taken out of their bath, though there is a large variability in this cortisol increase, suggestive of individual differences in stress responding (Albers, Rikesen-Walraven, Sweep, & de Weerth, 2008). Of note, infants whose mothers were observed to be more sensitive and less intrusive in the bathing study demonstrated heightened cortisol levels for shorter periods of time, suggesting that these parental behaviors encourage stress recovery. There is no evidence that small increases in cortisol, such as those observed in these two studies, are harmful to infants. It is, nevertheless, useful to understand the sensitivity of this system even to normal daily stressors, which suggests meaningful individual differences in infants' stress responding even to minor, routine stressors. This has relevance for considering HPA axis responses in the context of stress paradigms and adversity discussed below.

Autonomic Pathways

The infant stress response systems also involve autonomic pathways that encompass peripheral influences of the SNS and PNS. Very broadly speaking, the SNS can be thought of as a fast-responding, mobilizing system, accelerating heart rate and respiration, among other body functions, in response to changes in the envi-

ronment, while the PNS promotes long-term growth and restoration, and facilitates a return to homeostasis following activation of the SNS.

Sympathetic Pathways

Sympathetic influences are often measured through peripheral indicators. In infants, the primary measure of SNS activation is the GSR, which reflects activity of the palmar and plantar eccrine sweat glands that release sweat to the skin surface through a process mediated by the postganglionic cholinergic fibers of the SNS. Increases in electrodermal activity, in turn, produce measurable waves of increased skin conductance (Storm, 2000). Other common measures of SNS activation (e.g., preejection period) and salivary alpha-amylase are rarely used in infants (for additional reading and information, see Buss, Goldsmith, & Davidson, 2005; Davis & Granger, 2009).

SNS reactivity varies developmentally in infancy. An early study of skin conductance and arousal in newborns noted that infants less than 40 weeks old had lower median skin conductance levels and lower skin conductance reactivity when compared to infants 40–43 weeks of age. In response to a heel prick, 95% of infants 40–43 weeks, whereas only 30% of infants 36–39 weeks and 0% of infants under 36 weeks, exhibited significant change in skin conductance (Gladman & Chiswick, 1990). These results suggest that measures of skin conductance may not capture infant SNS response until around 36 postnatal weeks. One study detected a significant skin conductance response to heel lance but not routine nursing care among hospitalized infants under 6 months of age (Harrison et al., 2006). The maturational development of skin conductance may be related to gestational age (Munsters, Wallström, Ågren, Norsted, & Sindelar, 2012). Premature infants show skin conductance response to heel stick from at least 29 weeks gestational age (Storm, 2000) and additionally exhibit skin conductance response to nonpainful sensory stimulation such as routine nursing handling (Hellerud & Storm, 2002).

Parasympathetic Pathways

Vagal tone reflects parasympathetic influence on heart rate variability via the vagus nerve (Bernston, Quigley, & Lozano, 2007). Measured noninvasively, heart rate variability and RSA are indices of vagal tone and reflect parasympathetic influence on cardiac variability (Porges, 1995). Parasympathetic activity influences variation in heart rate as a result of innervations of the sinoatrial node by the vagus nerve, which originates in the nucleus ambiguus and contains efferent and afferent fibers projecting to multiple organs in the body, including the heart (Porges, 1995). Importantly, the nucleus ambiguus directly communicates with the amgydala, linking efferent activity from the brainstem to changes in cardiac activity (LeDoux, 2000; Porges, 1995). Polyvagal theory hypothesizes that the "vagal brake" is a mammalian mechanism that facilitates rapid changes in heart rate to environmental demands, thereby mobilizing metabolic resources and facilitating changes in social behavior (Beauchaine, 2001; Porges, 2007). At rest, the vagal brake has tonic inhibitory influences on cardiac chronotropy, which results in a resting heart rate lower than the basal firing rate of the sinoatrial node. However, in response to social and environmental stressors, withdrawal of the vagal break facilitates sympathetic activation and metabolic mobilization to support rapid response to environmental demands. Conversely, in response to social engagement and communication, the vagal break is activated (Porges, 2007), facilitating homeostasis. Transitory vagal withdrawal is common in response to internal or external stressors (Porges, 1995).

Basal vagal tone and vagal reactivity vary with age during infancy. Resting vagal tone increases beginning around the first month postpartum through age 6 months (Harper, Schechtman, & Kluge, 1987; Porges, Doussard-Roosevelt, Portales, & Suess, 1994). The most pronounced changes occur from birth to 1 month of age, suggesting biological reorganization occurring during the first month of life or the residual stress of birth on the ANS. The system becomes gradually more stable. For example, multiple groups have found low correlations between vagal tone measured in the first month of life and vagal tone measured between 3 and 6 months of age (Fox, 1989; Porter, Bryan & Hsu, 1995); however, vagal tone measurements at 3 and 6 months are correlated, as well as measurements take at 6 months and 9 months (Izard et al., 1991; Porter et al., 1995).

Vagal tone and vagal reactivity have often been linked with affective and cognitive functioning. In general, higher heart rate relative to baseline is thought to index cardiac arousal in response to stress. Importantly, there are indi-

vidual differences in heart rate variability in infants by 3 months of age (Porter et al., 1995), suggestive of individual differences in infants' RSA. In infancy, vagal tone is a marker of positive engagement and attention (Bazhenova, Plonskaia, & Porges, 2001). Vagal withdrawal in response to stress reflects emotion regulation and self-soothing (Beauchaine, 2001; DeGangi, DiPietro, Greenspan, & Porges, 1991; Huffman et al., 1998). High levels of vagal tone in combination with a lack of vagal suppression during challenge are thought to be indicators of poorly regulated emotional reactivity (Porges, Doussard-Roosevelt, & Maiti, 1994). Participant movement is a consideration in infant RSA research, as infants tend to show distress with increased movement (Bazhenova, Plonskaia, & Porges, 2001) and may pull on heart rate leads, resulting in movement to a degree that renders the data unusable (e.g., Calkins, Dedmon, Gill, Lomax, & Johnson, 2002).

Normative Neurobiological Responses to Stress in Infancy

Laboratory studies offer insights into how the stress systems reviewed earlier respond to relatively benign stressors in generally normative settings. Application of noninvasive measurement techniques in developmental stress research has identified reliable patterns of neurobiological response to environmental stress in infants. Individual differences in neurobiological stress responding are also evident in early infancy. Individual differences in stress vulnerability and reactivity in these paradigms have relevance for later cognitive, socioemotional, and physical health (Gunnar & Quevedo, 2007; Heim & Nemeroff, 2001).

Endocrine Responses to Normative Stressors

There is a substantial literature examining the effectiveness of laboratory or controlled stressors in eliciting a cortisol reaction among infants (reviewed in Gunnar et al., 2009; Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). Stressor domains include fear paradigms, frustration paradigms, reactivity in the context of mild pain, and reactivity to maternal separation. Such tasks do not uniformly produce significant group-level cortisol responses across infancy. Gunnar and colleagues (2009) note 23 studies of laboratory-based stressors in infants ≤ 3 months, with 91% showing mean increase in cortisol, 20 studies of infants ages 4–9 months, with 55% showing a mean increase in cortisol, and 15 studies of 12- to 24-month-old infants, with 20% showing mean increase in cortisol. Beyond the apparent developmental trend for nonsignificant mean reactivity with age, there is some specificity in reactivity patterns across stressor domains.

Fear-Based Responses

Fear/behavioral inhibition paradigms commonly employ a stranger approaching the infant or use of a scary novel object (e.g., a scary gorilla mask) with the infant. Such studies fairly uniformly fail to elicit a significant mean cortisol response. Gunnar and colleagues (2009) highlight that the failure of these tasks to produce significant mean-level increases in cortisol among infants may also be attributed to the fact that (1) protocols generally dictate the task be terminated if the child shows intense negative reactivity; (2) fear-eliciting tasks are often sequenced between pleasant or calming tasks; (3) response samples are poorly timed; (4) stimuli are only mildly provoking; and (5) often parents are present and available during these paradigms, and emerging evidence documents maternal buffering of fear responses early in development (Gee et al., 2014; van Rooij et al., 2017).

Frustration-Based Responses

Anger/frustration paradigms are often adaptations from the Laboratory Temperament Assessment Battery (LAB-TAB; Goldsmith & Rothbart, 1996) frustration tasks. In such tasks an infant's mother may be instructed to hold the infant's arm firmly at the infant's side in arm restraint or a desirable toy may be placed out of reach but in sight of the infant. Other researchers employ the Still-Face Procedure to study infant frustration. Classically, the paradigm has three episodes, beginning with an episode in which a mother has a "normal" face-to-face social interaction, followed by a "still-face" episode, during which the mother adopts a neutral, unresponsive face and does not smile, touch or talk to her infant, and concluding with a "reunion" episode, during which the mother resumes normal social interaction with her infant. Conceptually, the infant is frustrated, as his or her goal is to get the mother to respond. Of the limited number of frustration studies, most fail to elicit a significant mean cortisol response (Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007;

Lewis & Ramsay, 2005), though some detect significant mean increases (Blair, Granger, Willoughby, & Kivlighan, 2006; Haley, 2011; Haley & Stansbury, 2003). The absence of cortisol reactivity, on average, to anger, fear, and frustration tasks does not appear to vary by infant age (Jansen et al., 2010).

Responses to Physical Stressors

Infant's cortisol responses have been examined in numerous studies in the context of handling. Most commonly, infants' cortisol is collected before and after physical exams. Newborns to infants 3 months of age consistently show increases in cortisol in response to physical exam (Gunnar et al., 2009; Jansen et al., 2010). Infants in this age group also show cortisol increases in response to more minor forms of handling, such as having their diaper changed (Mörelius, Nelson, & Gustafsson, 2007) or bathing (Albers et al., 2008). Interestingly, infants 4 months of age and older do not show significant mean change in cortisol in response to a physical exam (Gunnar et al., 2009; Jansen et al., 2010). Taken together, handling appears to increase cortisol in children 3 months of age and younger. There is a marked developmental change in this reactivity to handling when infants are around 3–4 months of age, suggesting that, on balance, the effect of mild physical stressors on cortisol reactivity decreases with age (Jansen et al., 2010).

Infants' cortisol reactivity to mild pain has often been assessed within the context of blood draws and inoculations, which produce significant increases in cortisol in response across early but not late infancy (Gunnar et al., 2009; Jansen et al., 2010). For example, Gunnar, Brodersen, Krueger, and Rigatuso (1996) reported that unlike infants at ages 2, 4, and 6 months, 15-month-old infants did not show changes in cortisol in response to inoculation. Jansen and colleagues (2010) note that the average effect size of cortisol reactivity to mild pain decreases from 0.5 in newborns to 0.3 in infants age 26 weeks. Only a few studies have examined cortisol reactivity in infants beyond 26 weeks, with varying outcomes.

Responses to Parental Behaviors

Infant's cortisol response to maternal separation changes across early development. Infants begin resisting maternal separation at around 6–7 months of age and also begin to exhibit significant increases in cortisol in response to such separations in the 6- to 9-month developmental window (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992; Larson, Gunnar, & Hertsgaard, 1991). At around 1 year of age and onward, infants generally do not show significant increases in cortisol in response to short-term maternal separation (Gunnar & Nelson, 1994; Spangler & Grossman, 1993; Spangler & Schieche, 1998; for an exception, see Van Bakel & Riksen-Walraven, 2004). Across studies that report mean increases in cortisol in response to separation, the size is small (Jansen et al., 2010).

Taken together, some laboratory paradigms (e.g., common fear and frustration tasks) appear not to elicit a cortisol response in infants. Other stressors (handling, mild pain, maternal separation) appear to prompt a cortisol response that tends to decrease with age. On balance, these laboratory stimuli do not provoke a cortisol reaction in infants, especially in later infancy. Of note, most studies have been conducted with low-risk samples, and it is unknown whether infants exposed to chronic environmental stress show increased or altered reactivity to the previously reviewed stress paradigms.

Individual Differences in Cortisol Reactivity to Laboratory Stressors

Although fear-based paradigms do not elicit significant cortisol reactivity in infants on average, group-level analyses may obscure individual differences in cortisol reactivity for subgroups of infants. For example, temperamentally fearful children and insecurely attached infants demonstrate greater cortisol responses to fear paradigms than do nonfearful or securely attached infants (Buss, Davidson, Kalin, & Goldsmith, 2004). Similarly, while maternal separation, on balance, does not prompt a cortisol response past the first postnatal year, maternal separation continues to elicit cortisol increases in insecurely attached and highly fearful infants beyond this developmental period (Gunnar et al., 1996; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Spangler & Grossmann, 1993). These findings suggest that fearful infants and infants with insecure attachment have more reactive endocrine systems. Gunnar and colleagues (1996) found that attachment security moderates the physiological consequences of fearful, inhibited temperament, as measured by cortisol response to the Strange Situation Procedure (Ainsworth, Blehar, Waters, & Wall, 1978), which involves maternal separation. This suggests that maternal responsiveness, which is

associated with secure attachment, may buffer the magnitude of stress reactivity, even among fearful infants.

Autonomic Responses to Normative Stressors

SNS Responses

A relatively smaller literature has used skin conductance, a measure of the electrodermal activity, to measure infant response to stress noninvasively. Storm and her colleagues (Hernes et al., 2002) used a startle clap (i.e., a loud and unexpected auditory stimulus) to assess skin conductance responses in infants. The percentage of infants who showed skin conductance response to the stimulus was just 8.3% at 1 day of age, 52% at 10 weeks of age, and 62% at 6 and 12 months of age. These data suggest that skin conductance reactivity matures from birth, and that the amplitude and mean skin conductance levels reach mature levels at 10 weeks (Hernes et al., 2002). Ham and Tronick (2008) built on the startle clap research, finding unconditioned as well as anticipatory conditioned skin conductance responses to startle claps in a small sample of 5-month old infants. In a study in neonatal intensive care settings, infants showed increased skin conductance when the unit was at high sound levels compared to baseline sound levels (Salavitabar et al., 2010). Finally, one study used measures of skin conductance with the Still-Face Procedure. Infants showed a general pattern of increasing skin conductance across episodes. The group of infants that recovered in the reunion episode showed the lowest mean skin conductance levels during all episodes (Ham & Tronick, 2006).

PNS Responses

By 3 months of age (Porter et al., 1995) there is individual variability in resting vagal tone. Resting vagal tone (typically measured with RSA) has been shown to correlate with response to laboratory and acute stressors. Infants with high RSA show greater negative reactivity in response to a pacifier withdrawal procedure (Stifter, Fox, & Porges, 1986), to arm restraint (Fox, 1989; Stifter & Fox, 1990), to the onset of a stimulus tone (Porges, Arnold, & Forbes, 1973), to heelstick (Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995), to tube feeding (DiPietro & Porges, 1991), and to circumcision (Porter, Porges, & Marshall, 1988) than do infants with low RSA. Of note, these studies measured vagal tone at baseline and assessed infant reactivity through observational measures.

Most studies that assess RSA reactivity use the Still-Face Procedure. As indicated previously, the episodes are social play, "still-face," and then a reunion episode in which the mother resumes social play. Conradt and Ablow (2010) found a significant increase in RSA from baseline to the play episode, perhaps reflecting increased attention among infant. Infants' RSA decreased significantly between the play and still-face episodes, suggestive of parasympathetic withdrawal during distress. Finally, there was no significant difference in RSA between the still-face and reunion episodes, suggesting that infants had not recovered physiologically from the still-face episode. Of note, another study found vagal recovery of infants during the reunion period of the Still-Face Procedure (Weinberg & Tronick, 1996). Across studies, the Still-Face Procedure appears to elicit a PNS response in infants (Conradt & Ablow, 2010; Ham & Tronick, 2006; Moore et al., 2009). In support of the regulatory role of RSA in stress responding, infants who exhibit behavioral recovery from the still-face episode also tend to have the largest RSA recovery from still-face to reunion (Ham & Tronick, 2006, Moore et al., 2009).

In addition to research suggesting RSA recovery after challenge relates to behavioral recovery, suppression of RSA during challenge also relates to better regulation and greater self-soothing (DeGangi et al., 1991; Huffman et al., 1998) in infancy. Suppression of RSA may facilitate sustained attention and active coping, as mediated by the PNS. Ability to suppress RSA among infants may relate to baseline RSA. Calkins and colleagues (2002) found that easily frustrated infants had higher baseline RSA. These infants also had difficulty with the suppression of RSA during an attention-demanding task. DeGangi and colleagues (1991) examined infants in a normal control group in comparison with infants in the "regulatory disordered" group (who exhibited disturbances in sleep, feeding, state control, self-calming, etc.). There was a trend for regulatory disordered infants to have higher baseline vagal tone. Normal infants with high vagal tone consistently suppressed vagal tone when completing the Mental scale of the Bayley Scales of Infant Development. In contrast, regulatory disordered infants exhibited changes in vagal tone unrelated to baseline and inconsistent vagal reactivity, reflecting difficulty in regulating the ANS to support the attention state required for the task.

Sensitive Parenting and RSA

Infants are reliant on external sources of regulation in response to stress vis-à-vis parental support. "Sensitivity," or a parent's ability to respond accurately and effectively to their infant, is thought to be integral to a caregiver's support of an infant's ability to regulate emotion (e.g., Crockenberg & Leerkes, 2000). Sensitive parenting behaviors appear to influence infant PNS reactivity. Infants of mothers observed to be insensitive were more likely to fail to recover from the still-face episode, as indexed by RSA and infant behaviors in the reunion episode (Ham & Tronick, 2006). More recently, maternal sensitivity during the reunion episode of the Still-Face Procedure was associated with infant RSA recovery (Conradt & Ablow, 2010; Moore et al., 2009). Together these studies suggest that maternal sensitivity may offer protective or buffering effects to infants experiencing stress.

Adverse Environments and Stress Neurobiology in Infancy

Studies of infants facing adversity suggest that chronic and severe negative experiences in infancy produce enduring alterations in stress biology. In turn, these alterations may increase vulnerability to stress later in life. "Adversity during childhood" has been defined as experiences associated with disruption, danger, and stress, which deviate from the normative and expected environment (Felitti & Anda, 1997; Gest, Reed, & Masten, 1999; McLaughlin, 2016). Three common forms of adversity that have been studied in relation to stress biology in infants are low socioeconomic status (SES), maternal depression, and child maltreatment. Experiences of adversity are hypothesized to tax stress response systems through repeated and frequent activation, which is thought to exhaust endocrine and autonomic response systems (Loman & Gunnar, 2011). Research examining the impact of adverse contexts in shaping infant neurobiological stress responses is reviewed below.

Poverty

Poverty has detrimental and lasting effects, predicting psychopathology and disability well into adulthood (Brooks-Gunn & Duncan, 1997; Evans, 2003; Kohn, Dohrenwend, & Mirotznik, 1998; Wadsworth & Achenbach, 2005). The impact of poverty may be greater for young children (Brooks-Gunn & Duncan, 1997; Gilman, Kawachi, Fitzmaurice, & Buka, 2002), as developing systems are susceptible to environmental experience and exposure during sensitive and critical periods of development (see Murray, Halligan, & Cooper, Chapter 10, this volume). Poverty is hypothesized *to get under the skin* and shape infant neurobiology through allostasis (Evans, Chen, Miller, & Seeman, 2012), in which taxation of physiological systems results in long-term alterations of the threshold for activation (McEwen, 2000). Increasingly, researchers posit that poverty shapes children's socioemotional, physical, and cognitive development through its impact on the developing stress response systems (see Malhomes & King, 2012, for review). Evidence for how poverty alters and shapes infant endocrine and autonomic stress responses is reviewed briefly below. For a comprehensive review on poverty and stress neurobiology, see Evans and colleagues (2012).

Poverty and Endocrine Systems

Several studies from the Family Life Project speak to the role of poverty in infancy on children's developing HPA system. This study oversampled low-income and African American families with infant children in rural Pennsylvania and North Carolina. Aside from the epidemiological design, which oversampled for socioeconomic risk, the study also included a sizable sample ($N = 1{,}292$) and longitudinal data from infancy through early childhood. In one report, Blair, Granger, and colleagues (2011) demonstrated that infants living in poverty exhibited higher levels of salivary cortisol from age 7 months through the second year of life. This suggests that poverty is concurrently associated with patterns of hypercortisolism during infancy. In another study using the same sample, parents' perceptions of poverty, or economic insufficiency, predicted higher basal cortisol at 7 months of age, with steeper declines across early childhood (Blair, Raver, et al., 2011). Together these studies support HPA levels and rhythms as a mechanism by which poverty shapes infant's developing neurobiological stress systems.

Few studies have considered the impact of familial SES on the development of the ANS in infants. This is in part related to measurement considerations, as peripheral measures of parasympathetic and sympathetic activity are challenging in small children. The lack of research

is concerning, as findings in related biological stress systems highlight the role of early life stress, and poverty in particular, in shaping organisms' adaptive response patterns in a meaningful and long-standing manner (Gunnar, 2016; Propper, 2012). Additional study into the relations of poverty and infant autonomic stress reactivity is clearly warranted.

Maternal Depression

Although not all cases of parental psychopathology result in significant adversity to children, psychopathology may result in changes to parenting behavior that deviate from expectable care environments. Maternal depression has long been linked to differences in parenting behavior, particularly intrusive and withdrawn behaviors (Lovejoy, Graczyk, O'Hare, & Neuman, 2000).

Endocrine Responses

The timing and course of maternal depressive symptoms appears particularly relevant to the study of infant cortisol levels and reactivity (Laurent, Ablow, & Measelle, 2011). With regard to basal levels, a growing body of work suggests that a history of depression in mothers *prior* to pregnancy is associated with higher basal cortisol levels in infants (Brennan et al., 2008; Diego et al., 2004). These relations are observed in infants of mothers with a lifetime history of depression (Brennan et al., 2008) or continuing depression through the prepartum and postpartum period (Diego et al., 2004) but are not observed in mothers of infants who endorse depressive symptoms with onset exclusively in the postnatal period (Azak, Murison, Wentzel-Larsen, Smith, & Gunnar, 2013; Brennan et al., 2008). A history of depression prior to pregnancy (but not during pregnancy) does not appear to be related to infant cortisol reactivity (Brennan et al., 2008; Luijk et al., 2010). Rather, infant cortisol reactivity to stress appears to be related to *post*partum depressive symptoms, as observed in cortisol reactivity across frustration and fear paradigms in one study (Brennan et al., 2008) and a fear paradigm in another study (Feldman et al., 2009).

PNS Responses

Very few studies have examined maternal depression and infant RSA. One research group found that postnatal depression is associated with lower vagal tone in infants, including when infants engage in face-to-face interaction with their mothers (Field, Pickens, Fox, Nawrocki, & Gonzalez, 1995; Pickens & Field, 1995). Of note, these infant differences are attributed to infants of depressed mothers failing to show normative developmental increases in vagal tone. Specifically, although maternal depression was unrelated to infant vagal tone at 3 months, infants of mothers with depression had lower vagal tone compared to control infants at 6 months, with infants of mothers with depression failing to show the developmental increase in vagal tone that occurred between 3 and 6 months for control infants (Field et al., 1995). In contrast to these findings, one study indicated no differences in vagal tone in infants as a function of maternal depression (Johnson, Brennan, Stowe, Leibenluft, & Newport, 2014). Johnson and colleagues (2014) also found no differences in infant RSA reactivity to frustration tasks based on maternal depression.

Individual Differences in Consequences of Maternal Depression for Stress Reactivity

Infant characteristics appear to interact with maternal depression to predict infant cortisol reactivity. Luijk and colleagues (2010) found a stronger effect of maternal lifetime depression on cortisol reactivity among insecure–resistant infants compared to insecure–avoidant and secure infants. Khoury and colleagues (2016) found that infants who had mothers with higher current levels of depressive symptoms had the highest total cortisol output and cortisol reactivity during a frustration task when infants also exhibited a greater duration of independent emotion regulation strategies. This finding is consistent with research suggesting that negative coordination or lower degrees of coordination between mother and child are associated with higher cortisol levels (Laurent et al., 2011). With regard to social buffering effects, few studies have examined parenting in the context of maternal depression and infants' stress reactivity (Feldman et al., 2009). In one study, greater maternal sensitivity predicted less cortisol stress reactivity among 9-month-old infants to a fear paradigm, although maternal sensitivity operated as a main effect rather than an interaction effect with maternal depression, suggesting that sensitive parenting is useful in mitigating infant cortisol reactivity independent of ma-

ternal depressive symptoms (Feldman et al., 2009). In contrast, Kaplan, Evans, and Monk (2008) found that cortisol was significantly higher for infants of mothers with depression if mothers were also low in sensitivity. With regard to RSA, Waters, Boyce, Eskenazi, and Alkon (2015) found that infant vagal regulation interacted with maternal depression to predict behavior problems well into childhood. Specifically, infants exhibiting low levels of RSA reactivity to laboratory stress in infancy, in the presence of chronic maternal depression, had the highest levels of externalizing behaviors at age 7 years.

Child Maltreatment

Animal models demonstrate rich support for the importance of parental caregiving and responsiveness across early life (e.g., Meaney & Szyf, 2005). Disruptions in maternal presence through infant isolation or prolonged separation produce lasting changes in neurobiological development across a variety of mammalian species, including rodents and primates (see Levine, 2005, for a full review; Meaney & Szyf, 2005). Applying these findings to infant development, disruptions in the development of physiological stress response systems are posited as potential mechanisms linking child maltreatment to adverse developmental outcomes. Child maltreatment (i.e., physical, sexual, and emotional abuse and neglect) predicts an array of adverse health outcomes across development, including increased risk for psychiatric problems (Cohen, Brown, & Smailes, 2001; Green et al., 2010; McLaughlin et al., 2012) and chronic health conditions, including asthma, hypertension, diabetes, and cardiovascular disease (Batten, Aslan, Maciejewski, & Mazure, 2004; Bentley & Widom, 2009; Dong et al., 2004; Felitti et al., 1998; Rich-Edwards et al., 2010; Shin & Miller, 2012). Neurobiologically, environments characterized by threats, such as child abuse, and environments characterized by a lack of sensitive and responsive caregiving and an absence of protection from harm, as in child neglect, are posited to disrupt developing systems through allostatic load—or the repeated activation of stress physiological, biological, and endocrine stress response systems (McEwen, 2012). Researchers have largely examined the impact of maltreatment in infancy on the young child's developing HPA axis. This is in line with existing theories indicating that the endocrine system aids in responding to physical and social experiences of threat. However, additional work is needed to understand how experiences of early maltreatment impact human infants' developing CNS and PNS.

Maltreatment and Endocrine Responsiveness

As noted earlier, the HPA axis is highly sensitive to experiential influences across the first year of life. Research has begun to document how experiences of social, physical, and emotional assault may shape endocrine reactivity and responsiveness into early childhood (Tarullo & Gunnar, 2006). As infancy is a circumscribed time in development, many studies have documented the impact of infant maltreatment on the later functioning of the HPA axis. Such work consistently demonstrates the prolonged impact of abuse and neglect in infancy on patterns of endocrine responsiveness and rhythms into toddlerhood (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011) and beyond (see Gunnar & Vasquez, 2001, for a review). Evidence consistently supports that experiences of maltreatment in infancy disrupt the diurnal rhythm and reactivity of the HPA axis. Most studies indicate that maltreatment is associated with blunted HPA axis activity, or "hypocortisolism." This pattern is characterized by low morning levels and a shallow decline across the day and/or blunted reactivity to stress (Carlson & Earls, 1997; Fisher et al., 2016; Gunnar & Vasquez, 2001).

A relatively flat pattern has been found across multiple types of maltreatment, including abuse, neglect, and institutional rearing. More specifically, in studies examining infant orphanage placements (Carlson & Earls, 1997), experiences of abuse/neglect in the first year of life (Cicchetti et al., 2011) and infant foster care placement (Dozier et al., 2006) were associated with blunted HPA axis activity across the first 2 years of life. Furthermore, these disrupted patterns of glucocorticoid production appear to endure beyond the first 2 years of life (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). Although most studies suggest a long-term and marked blunting in later basal cortisol levels of infants who experienced early deprivation and maltreatment, the direction of effects on HPA axis activity is mixed across studies, with some researchers finding blunted and others finding exaggerated responses across childhood. This is exemplified

by a study that followed infants placed in foster care who exhibited altered cortisol rhythms (i.e., high and low diurnal rhythms) into early childhood as compared with normative controls (Dozier et al., 2006). Hypocortisolism may be unique to extreme experiences of maltreatment, as researchers examining more subtle patterns of parental maltreatment, such as spanking or corporal punishment, have found a relation with higher basal cortisol in infancy (Bugental, Martorell, & Barraza, 2003).

Emerging work suggests that the impact of maltreatment and deprivation on HPA axis responses may be mitigated, at least in the short term, with prompt social interventions. One study demonstrated that parental intervention during the transition from infancy to toddlerhood was associated with no observable difference in the trajectory of morning cortisol between maltreated infants and controls (Cicchetti et al., 2011). In addition, temporal distance from the experience of maltreatment combined with early placement into supportive environments may ameliorate hypocortisol patterns later in childhood (Gunnar & Cheatham, 2003). Finally, in a randomized controlled trial of foster care as an alternative to institutional rearing for abandoned infants, McLaughlin and colleagues (2015) found that infants randomized into family care exhibited HPA axis reactivity that more closely resembled that of typically developing children than children who remained in institutional care; critically, intervention effects were most pronounced for infants placed into families before 2 years of age. In a systematic review of 19 studies, Slopen, McLaughlin, and Shonkoff (2014) found good evidence for an impact of psychosocial interventions on cortisol diurnal rhythms and reactivity. These findings are promising, as they indicate malleability in HPA axis functioning, even after severe adversity, and suggest that early intervention can prevent long-term disruptions in this system.

Conclusions

Taken together, existing evidence provides insight into how neurobiological stress systems respond to stress and adversity in infancy. Controlled laboratory studies provide insights into what constitutes stress (and during which developmental windows within infancy) in normative samples. Given that this research is nearly exclusively conducted with low-risk samples, further study is needed to understand how infants exposed to adversity respond to stress paradigms. This is particularly important given strong evidence for individual differences in stress vulnerability and reactivity within infancy, many of which are related to parent–child relationships, maternal sensitivity and responsiveness, as well as environmental experience. Adverse experiences such as maltreatment and poverty influence both the "set point" of the HPA axis and reactivity to environmental challenges; less is known about how these adverse experiences relate to infants' autonomic functioning. Sensitive parenting appears to buffer infant stress responding in adverse contexts. Studies testing complex, bioecological moderators and mediators of infants' experiences of stress and adversity represent an important direction for future research.

The research reviewed in this chapter is a growing literature that offers insights into the maturation and function of infant stress response systems. Extant research suggests not only a potent role of adversity in altering core regulatory systems but also plasticity of these systems following intervention. Future studies are needed to identify buffering effects to adverse experiences and the multilevel mechanisms underlying individual risk and resilience. Taken together, these literatures would serve to inform preventive and targeted early interventions aimed at bolstering stress hardiness of infants in adverse contexts and promoting healthy stress neurobiology across the lifespan.

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