The Effects of Stress on Early Brain and Behavioral Development

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Synopsis
Over a half century of research using animal models has documented the impact of early life stress on neurobehavioral development. In this chapter we review research on the impact of pre- and postnatal stress in human development. We consider questions of whether the findings are consistent with the concept of fetal programming and whether programming or predictive adaptation in response to harsh conditions extends into the postnatal period in human ontogeny. Consistent with prior research, we maintain a focus on the hypothalamic-pituitary-adrenocortical (HPA) system as a potential mediator of pre- and postnatal stress.

INTRODUCTION

Over a half century of research using animal models has documented the impact of early life stress on neurobehavioral development (Sanchez, Ladd, & Plotsky, 2001). Both stress to the mother or more directly to the fetus during prenatal development and stressors that affect mother and infant during postnatal development impact circuits that are developing during the period of stressor exposure, including the development of stress-mediating systems. Alterations in stress-mediating systems, in turn, influence responses to stressors throughout development, producing cascading effects that can produce significant physical and mental health problems later in life. Research on the neurobiological sequelae of stress during human pre- and postnatal development has a much shorter history. However, inroads are being made in understanding how exposure to stress early in life influences neurobehavioral development and lifelong health (Koss & Gunnar, 2018).

Activity of the hypothalamic-pituitary-adrenocortical (HPA) axis, a stress-sensitive neuroendocrine system, has figured prominently in animal studies of early life stress since the 1950's when it was noted that early experiences permanently altered HPA reactivity and regulation (Levine & Wiener, 1988). Because the HPA axis produces hormones that function as gene transcription factors in numerous organs and tissues and because experience alters its activity as well as the activity of its receptors, research on early life stress has continued to include a focus on this neuroendocrine system. Attention to activity of this system in studies of human development has been promoted by the availability of assays that allow non-invasive measurement of cortisol, its end hormone, in small samples of saliva (Kirschbaum & Hellhammer, 1989). Consistent with the history of research in this area, we will maintain a focus, though not exclusively, on the HPA axis in reviewing the

research on early life stress and human neurobehavioral development.

This chapter consists of four parts: (1) a brief review of the anatomy and physiology of the mature HPA axis and related stress-mediating system; (2) a discussion of prenatal stress and fetal programming; (3) a discussion of the postnatal development of the HPA system, the importance of social regulation of HPA axis in early human development, and what is currently known about long-term impacts of early life stress on later physical and mental health; and (4) issues that need to be addressed as this field moves forward.

THE ANATOMY AND PHYSIOLOGY OF STRESS

Stressors are real or perceived threats to psychological or physical viability that are responded to by stressor-specific release of molecules termed stress mediators. These molecules bind to their receptor targets and orchestrate integrated responses that have evolved to increase survival in the immediate face of threat (Joëls & Baram, 2009). Glucocorticoids (cortisol in humans) are steroid hormones that serve as a major mediator of the mammalian stress response. Glucocorticoids are produced by the cortex of the adrenal glands; the medulla of the adrenals produces adrenaline, a hormone that is central to the fight/flight response. Glucocorticoids serve multiple roles in defensive responding (Sapolsky, Romero, & Munck, 2000). At basal levels they are permissive, in the sense that they maintain organs and tissues in a state that permits rapid and sustained mobilization by other neurotransmitters or hormones. At elevated levels they suppress the actions of other stress-mediating systems and, through negative feedback, return the HPA system to basal levels of activity. Via effects on gene transcription, glucocorticoids also can have long-term effects on neural systems mediating perception and response to threat, both up- and downregulating reactions to subsequent stressors. Critically, the effects of acute activations of the HPA

system and those of chronic activation are markedly different, with chronic activation resulting in progressive changes in the expression of stress-mediating genes, alteration in neuronal systems that process signals of threat, and changes in neuronal firing patterns throughout the brain.

The cascade of events that produce changes in cortisol release by the adrenals begins with the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) by cells in the paraventricular nuclei of the hypothalamus (see figure 1, reviewed in (Gunnar & Vazquez, 2006)). CRH and AVP are released through small blood vessels to the anterior pituitary where

<figure 1>

they stimulate the release of adrenocorticotropic (ACTH) hormone into the blood stream. Cells on the cortex of the adrenal glands respond to ACTH and start a cascade of enzymatic actions that convert cholesterol to cortisol (corticosterone in rodents). Activation of the adrenal cortex by ACTH also results in production of dehydroepiandrosterone (DHEA) an adrenal androgen that because of its anabolic effects has anti-stress properties. Once released into circulation, because of its lipid solubility, cortisol enters the cytoplasm of cells throughout the body and brain where it interacts with its receptors if they are present.

Cortisol has affinity to two receptors, mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Its affinity with MRs is many times greater than to GRs; hence, if both are present, MRs will be occupied and activated first, followed by GRs. In most areas of the body, however, cortisol cannot access MRs because an enzyme is present (11 beta hydroxysteroid dehydrogenase or 11β-HSD) that converts cortisol to a form with low MR affinity. As will be discussed, this enzyme is also present in the placenta where it serves to regulate impacts of maternal cortisol on the placenta and fetus. In the brain, however, the

enzyme is not present, allowing the levels of cortisol in circulation to determine the balance between MR and GR activation. Under basal levels MR tend to be almost wholly occupied; while when cortisol rises to stress levels and also at the peak of the diurnal rhythm, GR become occupied as well. MRs tend to mediate many of the permissive effects of cortisol; while GRs mediate many of the more catabolic stress effects. GRs are also involved in negative feedback of the axis, functioning at the level of the pituitary, hypothalamus, hippocampus, and likely also the medial frontal cortex, to contain the HPA response and help return the axis to basal levels of activity.

While there is increasing evidence that under conditions of stress, rapid cell membrane-mediated effects of cortisol occur, most effects of cortisol involve translocation of the cortisol-receptor complex from the cytoplasm to the cell nucleus where cortisol interacts with glucocorticoid response elements (GREs) in the promotor region of many genes. Activation of GREs increase or decrease gene transcription in interaction with other gene transcription factors. When cortisol operates as a gene transcription factor, its effects on organs and tissues take minutes to hours to be produced. This means that while acute threat may stimulate increases in cortisol production, cortisol itself is not a major factor in fight/flight responses that proceed on the basis of seconds to minutes.

Activation of the HPA axis is regulated by complex signals derived across a number of pathways that carry information about the state of the internal and external milieu (see figure 2).

<figure 2>

Activation of the system in response to threats to internal homeostasis (e.g. blood volume loss), travel to the CRH-producing cells in the hypothalamus through brainstem

pathways. Psychological threats that require integration of information about external events are mediated through pathways involving the amygdala and bed nucleus of the stria terminalis (BNST). Notably, neural systems involve in activating the axis in response to psychosocial threats either produce CRH or have receptors for CRH. The central nucleus of the amygdala is one region rich in CRH-producing neurons, activation of which plays a role not only on activating the HPA axis, but also in stimulating increases in central norepinephrine and peripheral activation of the sympathetic nervous system. The extra-hypothalamic CRH system is part of the fight/flight system and a key orchestrator of fear behavior (McCall et al., 2015). The expression of CRH and its receptors in the various brain regions involved in emotion and cognition is age-dependent and regulated by stress throughout the lifespan. Recent evidence indicates that effects of stress on neurodevelopment are mediated by CRH, as well as cortisol (Korosi & Baram, 2008).

The activity of the HPA axis is closely related to the sympathetic and parasympathetic nervous systems. The sympathetic nervous system governs the fight-flight response, which is a critical component of our response to threat. Immediately following the perception of threat, preganglionic sympathetic nerves are activated in the spinal cord, which then leads directly to organs involved in responding to stress. The most important of these organs in the adrenal medulla, which produces epinephrine that travels throughout the body to influence cardiovascular function and energy metabolism (Ulrich-Lai & Herman, 2009). In concert with norepinephrine release from nerve terminals, these neurotransmitters coordinate responses to stress in the periphery, although norepinephrine is also produced in the central nervous system. The sympathetic-adrenal medullary (SAM) system is a component of the sympathetic nervous system involving hormones, and it supports arousal and attention in addition to stress responses.

Thus, the SAM system will respond to effortful tasks that do not involve threats to the physical or social self, even though the sympathetic nervous system and HPA axis do not respond.

The parasympathetic nervous system (PNS) helps to restore the body to baseline following a stressor, assisting with rest and repair (Porges, 2009). Activation of the PNS is more targeted, with projection between the body and brain to relay information about the body's state. The nucleus tractus solitarius relays these inputs to the amygdala and other neural systems that detect and respond to threat. One of the main effectors of the PNS is the vagus nerve, which provides tonic inhibitory input to the heart. In children performing negative emotional tasks, it is primarily changes in vagal tone that are responsible for changes in heart rate. Notably, the PNS provides important input not only to the amygdala, as noted, but also to the HPA axis as this is the primary mode through which systemic (physical) as opposed to psychological stressors impact the regulation of CRH, ACTH and thus cortisol (Herman, 2017).

PRENATAL STRESS AND NEUROBEHAVIORAL DEVELOPMENT

Fetal Programming

Fetal development proceeds at a more rapid pace than any later developmental stage (Barker, 1998). For this reason, the human fetus is particularly vulnerable to both organizing and disorganizing influences, which have been described as programming. Programming is the process by which a stimulus or insult during a vulnerable developmental period has a long-lasting or permanent effect (Barker, 1998; Kuzawa, 2005). The trajectory of fetal development adjusts, in response to cues in utero, to optimize adaptability to the environment and ultimately survival of the organism. Such adaptations, however, can have long-term negative consequences postnatally, particularly if there is significant mismatch between prenatal and postnatal

environments (Sandman, Davis, & Glynn, 2012). The effects of programming are dependent on the timing (i.e. the developmental stage of organ systems and the changes in maternal and placental physiology) and the duration of exposure (Davis & Sandman, 2010; Nathanielsz, 1999), as well as the dosage of prenatal stress (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). Programming also has differential effects by fetal sex (Glover & Hill, 2012) and genotype (Buss, Entringer, & Wadhwa, 2012). There is convincing support for fetal programming of adult health outcomes including heart disease, diabetes, and obesity; however, the evidence comes primarily from studies that rely on birth phenotype (e.g., small size at birth or preterm delivery) as an index of fetal development (e.g., Barker, 1998). It is unlikely that birth phenotype alone is the cause of subsequent health outcomes. Birth phenotype, instead, likely is a marker of fetal adaptations that shape the structure and function of those physiological systems that are part of the causal pathway to health outcomes (Gluckman & Hanson, 2004).

Prenatal exposure to maternal stress signals is one of the primary pathways for programming of later health and development. The HPA axis participates in a surveillance and response system for stress that is present in many species, from the desert-dwelling Western Spadefoot tadpole to the human fetus, and allows for the detection of threat so that development can be adjusted accordingly. For instance, rapidly evaporating pools of desert water result in elevation of CRH in the tadpole, accelerating metamorphosis and increasing the likelihood of survival. If the CRH response is blocked during environmental desiccation, then development is not accelerated and the tadpole's survival is compromised. There are, however, long-term consequences for the tadpole that survives this early life stress because its growth is stunted, and it is at a disadvantage in the competition for food and reproduction (Denver, 1997).

It has been argued that a similar signaling pathway participates in the regulation of human fetal development. Detection by the fetal/placental unit of stress signals from the maternal environment (e.g. cortisol) informs the fetus that there may be a threat to survival. This information may prime or advance the placental clock (McLean et al., 1995) by activating the promoter region of the CRH gene and increasing the placental synthesis of CRH (Sandman et al., 2006). Trajectories of CRH levels affect fetal growth and development; early increases or rapidly rising levels of placental CRH lead to shorter gestation and preterm birth (McGrath et al., 2002). Early departure from an inhospitable host environment may be essential for survival, but it also may have long-term consequences for the human fetus just as it does for the tadpole. The developmental trajectory of the fetus, whether born early or at term, is influenced by the maternal environment, and adaptation of the developmental program to maternal stress signals may prepare the fetus for postnatal survival. The goal of the second section is to discuss the various pathways through which prenatal maternal stress signals may prepare the fetus for adaptation to the postnatal world.

Stress Regulation and Pregnancy

Changes in the maternal HPA and placental axis over the course of pregnancy

Regulation of the HPA axis is altered dramatically during pregnancy. The maternal pituitary gland doubles in size and the production of maternal HPA axis hormones increases several-fold. The growth and development of the placenta is primarily responsible for the profound changes in the HPA axis throughout gestation. The placenta expresses the genes for CRH (hCRHmRNA) and the precursor for ACTH and betaendorphin (proopiomelanocortin) (see figure 3). All of these stress responsive hormones increase as

<figure 3>

pregnancy advances, but the exponential increase in placental CRH (pCRH) in maternal plasma is especially dramatic, reaching levels observed only in the hypothalamic portal system during physiological stress. Placental CRH (pCRH) is identical to hypothalamic CRH in structure, immunoreactivity, and bioactivity. There is, however, one crucial difference in its regulation. In contrast to the negative feedback regulation of hypothalamic CRH, cortisol stimulates the expression of hCRHmRNA in the placenta, establishing a positive feedback loop that allows for the simultaneous increase of pCRH, ACTH, and cortisol over the course of gestation (see for review (Sandman & Davis, 2010). The normative increase in stress responsive hormones such as cortisol and pCRH plays an important role in the regulation of pregnancy as well as facilitating maturation of the fetus. However, because of the positive feedback between cortisol and pCRH, the effects of maternal stress on the fetus may be amplified with potentially negative consequences for the developing fetus.

The effects of CRH and cortisol are modulated by the activities of binding proteins and enzymes, including CRH binding protein, cortisol binding globulin (CBG), and 11β-HSD2. Levels of these proteins and enzymes increase progressively with advancing gestation, to protect the fetus from over-exposure to cortisol. Prior to term, levels decline to ensure maturation of the fetal lungs, CNS and other organ systems in full term births (Murphy & Clifton, 2003). Levels of binding protein have been associated with birth outcome (Hobel, Arora, & Korst, 1999), and variations in CBG may contribute to individual differences in developmental outcomes because levels have been shown to be lower in women with growth restricted fetuses (Ho et al., 2007). In addition, despite the presence of 11β-HSD2 early in gestation, maternal cortisol does reach the fetus and the amount varies with circulating maternal levels (Gitau, Cameron, Fisk, & Glover, 1998). Maternal stress down-regulates 11β-HSD2 activity in the placenta allowing a greater

proportion of maternal cortisol to cross the placenta to reach the fetus (Mairesse et al., 2007), impacting fetal growth and development (Baibazarova et al., 2013; Reinisch, Simon, Karow, & Gandelman, 1978). This is another mechanism through which the consequences of maternal stress for the developing fetus may be amplified. Because of the time table of fetal development and the changes in maternal and placental physiology, the consequences of stress exposures will vary based on the gestational period of exposure.

Although findings regarding the nature of prenatal influence on postnatal functioning are well established in animal models, it is critical to acknowledge that the differences in reproductive and stress physiology, even in very closely related species such as humans and non-human primates, limit the validity of generalizing from animal models (Smith & Nicholson, 2007). For these reasons, this chapter primarily focuses on studies of gestational stress in humans.

Fetal adrenal development

The fetal adrenals make unique contributions to both the regulation of fetal development and the timing of parturition. Cortisol is thought to play critical roles in the promotion of fetal maturation in preparation for extra-uterine life. Further, dehydroepiandrosterone sulfate (DHEAS) produced by the fetal adrenal is an obligate precursor for placental estrogen and is also thought to contribute to the initiation of parturition.

Morphologically, the fetal adrenal gland is comprised of two zones: the outer, definitive zone, and the large, inner fetal zone. Between these two zones is the transitional zone. The fetal and definitive zones can be recognized after the 8th gestational week. The fetal adrenals grow rapidly until the third trimester so that at term the fetal adrenals are significantly larger, relative to body weight, than the adult adrenals. At the end of human pregnancy, the fetal zone begins to

atrophy. The human fetal adrenal has steroidogenic enzymes as early as the seventh gestational week and cortisol secretion can be detected as early as eighth week. Cortisol production from the fetal adrenal is regulated by ACTH and ACTH containing cells can be seen in the pituitary by eight gestational weeks (Jaffe et al., 1998; Kempná & Flück, 2008). There is evidence that the fetus responds to pain with an increase in cortisol during the latter half of gestation (Gitau, Fisk, Teixeira, Cameron, & Glover, 2001).

Fetal brain development and susceptibility to stress and stress hormones

The rapid changes in the developing fetal brain render it particularly susceptible to influences of stress responsive hormones such as cortisol and pCRH. Neurodevelopmental processes including neurogenesis, migration, neuronal differentiation, dendritic arborization, axonal elongation, synapse formation and collateralization, and myelination proceed at an exceptionally rapid pace throughout the fetal period (Bourgeois, 1997; Sidman & Rakic, 1973). We specifically discuss regions of the brain that are both integral to the regulation of stress responses and vulnerable to exposure to stress hormones, including the hippocampus and amygdala. Both are identifiable between 6 and 8 gestational weeks and by term the basic neuroanatomical architecture of these regions is present. Limited information exists regarding the time course of prenatal development of cortisol receptors in humans. There is evidence that both types of cortisol receptors are present in the human hippocampus by 24 gestational weeks (Noorlander, De Graan, Middeldorp, Van Beers, & Visser, 2006).

Exposure to prenatal maternal biological and psychosocial stress influences the developing fetal brain and endocrine systems producing long term effects on cognition, emotion, and physiology in the offspring (Kapoor, Petropoulos, & Matthews, 2008). Evidence for persistent organizational changes or programming influences on the nervous system has been

growing and may include changes in neurotransmitter levels, cell growth and survival and adult neurogenesis.

For instance, high concentrations of glucocorticoids (e.g., cortisol) and CRH may inhibit growth and differentiation of the developing nervous system. In a human study of over 400 pregnant women, maternal gestational cortisol secretion was found to be inversely related to ultrasound measures of fetal brain size in early, middle, and late pregnancy (Li et al., 2012). Prenatally, elevated prenatal placental CRH predicted cortical thinning in childhood (Sandman et al., 2018). Experimental animal studies similarly show that high levels of CRH causes dendritic atrophy in cortical neurons (Curran, Sandman, Davis, Glynn, & Baram, 2017). Lastly, glucocorticoids may be especially neurotoxic to hippocampal CA3 pyramidal cells; fetal exposure to high levels of glucocorticoids produces irreversible damage to the hippocampus (Liston & Gan, 2011). These data from human and animal models suggest endocrine and brain mechanisms by which early-life stress may provoke long-term effects on stress, emotional regulation and cognition [see Joëls & Baram, 2009; Seckl, 2007; for reviews].

Gestational Stress Influences the Human Fetus

In humans, a compelling body of work has documented that both maternal report of elevated maternal stress or anxiety and exposure to traumatic events during pregnancy are associated with increased risk for preterm birth. Sociodemographic stressors, including low socioeconomic status, experiences of discrimination, and residing in unsafe neighborhoods, increase risk for preterm birth (Giurgescu et al., 2012). However, studies that have controlled for these key sociodemographic factors as well as obstetric risk factors continue to find a correlation between maternal stress and preterm birth, suggesting that psychological functioning over and above contextual stress affects birth outcomes. There are several pathways by which maternal

stress may lead to preterm birth including accelerated production of pCRH and altered vascular and immune functioning (Dunkel-Schetter & Glynn, 2011). Preterm birth is associated with pervasive developmental delays (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009); however, intrauterine exposures, including stress, likely contribute to these impairments independently from birth outcomes. Further, fetal brain development differs between fetuses who go on to be delivered preterm and their counterparts who go on to be delivered at term, suggesting that the neurodevelopmental correlates of preterm birth begin in utero (Thomason et al., 2017). The study of human fetal development is important because it provides a direct test of the fetal programming hypothesis with the opportunity to assess the effects of gestational stress on development before the effects of external forces, such as birth outcome, parenting and socialization, are exerted.

More direct tests of the effect of maternal stress on the fetus come from studies manipulating maternal stress and evaluating the consequences for fetal behavior and studies measuring fetal responses to external stimulation. Fetuses display a consistent response profile (e.g., suppression of motor activity) during maternal exposures to moderate laboratory challenges such as the Stroop color-word test or viewing videos of labor and delivery (DiPietro, 2004). The nature of these responses appears to be moderated by maternal psychological state (Kinsella & Monk, 2009).

Direct measures of fetal responses to external stimulation provide an index of fetal nervous system development and have been used to assess the developmental consequences of exposure to physical or maternal psychological stress. The response to a vibroacoustic stimulus (VAS) is an indication of fetal maturity reflecting maturation and integrity of neural pathways through the cerebral cortex, midbrain, brainstem, vagus nerve and the cardiac conduction system.

Using the fetal response to VAS, it has been shown that stress signals, most clearly pCRH trajectories, influence the developing fetal nervous system. Low pCRH is associated with more mature or earlier development of the fetus' ability to mount a response to the VAS and with a more mature profile to a classic habituation/dishabituation paradigm (Sandman, Wadhwa, Chicz-DeMet, Porto, & Garite, 1999). Other maternal stress signals including over-expression of betaendorphin and under-expression of ACTH have additionally been linked to the fetal response to VAS (Sandman et al., 2003). Fetal responses may be linked to brain development, as one study found that fetal heart rate variability was correlated with connectivity between the dACC and mPFC (Spann, Monk, Scheinost, & Peterson, 2018).

These studies raise the possibility that repeated exposures over the course of gestation may influence the developing fetal nervous system. They also provide evidence that signals of maternal stress during gestation exert programming influences on the nervous system that cannot be explained by postnatal experiences. Continuity between the fetal and infant periods in assessments of movement and heart rate indicate that maternal influences that shape developmental trajectories during the prenatal period will continue to influence functioning postnatally (DiPietro, 2004).

Prenatal Maternal Psychosocial Stress and Infant and Child Development

Socioemotional development

Prenatal exposure to elevated levels of maternal psychosocial stress is associated with behavioral and emotional disturbances during infancy and childhood among healthy full-term infants that is independent of postpartum maternal psychosocial stress (Bergman, Sarkar, O'connor, Modi, & Glover, 2007; Davis et al., 2007; Davis et al., 2004). Both maternal report of psychosocial stress and stressful life events are associated with more fearful and reactive

behaviors during infancy and toddlerhood. Effects on social and emotional development continue to be observed during childhood and adolescence. Maternal antenatal stress, anxiety and depression predict childhood behavioral and emotional problems, including attention deficit/hyperactivity disorder (ADHD) and both internalizing and externalizing problems, after controlling for birth outcomes and postnatal maternal psychological state (Barker, 1998; Bergman et al., 2007; Van den Bergh & Marcoen, 2004). Recent evidence suggests that lack of predictability in maternal mood additionally predicts internalizing problems in childhood beyond the effects of level of maternal distress (Glynn et al., 2018).

Maternal distress may impact the development of limbic and prefrontal brain regions and changes in these regions may be a mechanism underlying the observed behavioral findings. Recent studies have shown that elevated prenatal maternal distress predicts microstructure of the right and left amygdala (lower fractional anisotropy and axial diffusivity; Rifkin-Graboi et al., 2013) as well as connectivity between prefrontal and limbic regions in the newborn (Posner et al., 2016). Prenatal maternal distress further predicts elevated amygdala response to negative emotional stimuli and cortical thinning, primarily in the right frontal cortex during childhood (Lebel et al., 2016; Sandman, Buss, Head, & Davis, 2015). Thus, maternal distress shapes the trajectory of brain development, and developing prefrontal and limbic regions may be particularly susceptible.

HPA axis functioning

Alterations to the fetal HPA axis are frequently proposed as the primary biological pathway underlying fetal programming of later health and development. Animal studies suggest that the fetal HPA axis may be particularly vulnerable to prenatal exposure to maternal stress (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006); however, relatively little is known about

the consequences of prenatal maternal psychosocial stress for HPA axis functioning among humans. One study found that infants of women with higher economic strain during pregnancy had elevated cortisol response to vaccination (Thayer & Kuzawa, 2014). Prenatal psychosocial stress is also associated with altered circadian regulation during childhood and adolescence on typical days (O'Connor et al., 2005; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). Prenatal exposure to maternal psychosocial stress may influence the developing fetal HPA axis in ways that implicate the regulation of cortisol production during infancy, childhood and adolescence.

Cognitive Development

The influence of gestational exposure to maternal psychosocial stress on cognitive and motor development is less clear. There is evidence that maternal self-report of elevated stress and anxiety, as well as exposure to traumatic life events, such as severe ice storms, during pregnancy are associated with delayed infant and child cognitive, language and neuromotor development and that these deficits may persist into adolescence. However, a recent meta-analysis found only a small relation (r = -.05) between maternal stress and child cognitive development as assessed using the Bayley Scales or general measures of IQ in children under 5 years (Tarabulsy et al., 2014). The impact of prenatal stress on cognitive outcome may vary based on the aspect of functioning considering. For example, it may be the case that executive functions are particularly susceptible to the impact of gestational stress (Buss, Davis, Hobel, & Sandman, 2011).

It is also plausible, however, that generalized self-report measures of psychological distress do not adequately characterize stress that is unique during pregnancy. As reviewed in Davis & Sandman (2010), measures of pregnancy specific stress (e.g., *"I am fearful regarding the health of my baby," "I am concerned or worried about losing my baby")* are better than

measures of generalized psychological distress for predicting neurodevelopmental outcomes. It is important to note that these associations are not explained by actual medical risk associated with pregnancy and birth outcome. Further, pregnancy specific stress is linked to trajectories of gestational stress hormones (Kane, Schetter, Glynn, Hobel, & Sandman, 2014). Support for the importance of pregnancy specific stress for developmental outcomes comes from a recent study documenting associations between elevated pregnancy-specific anxiety and decreased gray matter density in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus as well as the cerebellum extending to the middle occipital gyrus and the fusiform gyrus at 6 to 10 years of age (Davis & Sandman, 2010). These brain regions are associated with a variety of cognitive processes including reasoning, planning, attention, memory and language and raise the possibility that developmental alterations to these regions may underlie associations between elevated pregnancy specific anxiety and cognitive performance observed in prior studies (Buss, Davis, Muftuler, Head, & Sandman, 2010).

Prenatal Maternal Biological Stress Signals and Infant and Child Development

Given the accumulating evidence that prenatal psychosocial stress affects the developing offspring, evaluation of the underlying biological mechanisms will elucidate critical mediators of this relationship. Alterations to the maternal HPA and placental axis are most frequently cited as the mechanism that underlies fetal programming of later health and developmental outcomes.

Social/emotional development

Prenatal exposure to elevated maternal cortisol and placental CRH predict increased fussiness, negative behavior and fearfulness during infancy (Davis et al., 2005, 2007; de Weerth, van Hees, & Buitelaar, 2003) and toddlerhood (Bergman et al., 2007). Further, both maternal cortisol and placental CRH predict childhood anxiety symptoms (Davis & Sandman, 2012;

Howland, Sandman, Glynn, Crippen, & Davis, 2016). Prenatal stress hormones may impact development of internalizing problems via alterations to development of limbic regions. Prenatal maternal cortisol predicts greater right amygdala volume among girls (Buss, Davis, et al., 2012), which mediated the relation between prenatal maternal cortisol and child anxiety. Recent work indicates that prenatal stress hormones may also shape the connectivity of the human brain. Fetal exposure to elevated maternal cortisol predicts network segregation in girls. Specifically, girls generated more connections than boys to maintain topologically capable and efficient neural circuits, and this increase in neural cost was associated with higher levels of internalizing problems (Kim et al., 2016).

HPA axis functioning

Prenatal elevations in maternal cortisol production may impact the development of the fetal HPA axis with consequences for postnatal HPA axis regulation. Higher levels of prenatal cortisol have been associated with elevated cortisol reactivity following a blood draw in infants (Davis, Glynn, Waffarn, & Sandman, 2011) and with higher levels of cortisol on the day of inoculation and the first day of school in preschoolers (Gutteling, de Weerth, & Buitelaar, 2005). Amniotic fluid cortisol also predicted infant cortisol response patterns to separation-reunion stress at age 17 months, after controlling for key covariates, including prenatal and obstetric factors and parent-child attachment (O'Connor, Bergman, Sarkar, & Glover, 2013). These studies provide evidence for effects of prenatal maternal cortisol on HPA axis functioning although interpretation is limited by modest sample sizes and varied methodologies (e.g., type of stressor, mode and timing of maternal cortisol measurement). Complementary lines of evidence from animal research (Henry, Kabbaj, Simon, Le Moal, & Maccari, 1994; Mustoe, Taylor, Birnie, Huffman, & French, 2014) and evaluation of prenatal synthetic glucocorticoid

administration (Davis, Waffarn, & Sandman, 2011) substantiate the likely role of prenatal cortisol in HPA axis development.

Cognitive Development

Evidence suggests that the trajectory of maternal cortisol across gestation is a strong predictor of child neurodevelopment, and the effects likely vary by timing of the exposure. Elevated maternal cortisol during early and mid-gestation has been associated with decreased neuromuscular maturity in the newborn (Ellman et al., 2008) and delayed cognitive development during toddlerhood (Bergman, Sarkar, Glover, & O'Connor, 2010). Conversely, elevated maternal cortisol late in gestation has been associated with significantly higher scores on measures of mental development at one year (Davis & Sandman, 2010) and during middle childhood (Davis, Head, Buss, & Sandman, 2017), as well as greater cortical thickness during childhood (Davis et al., 2017).

These findings linking cortisol exposure in late gestation to neurodevelopment are remarkably consistent with its function in the maturation of the human fetus. As pregnancy advances toward term, exposure to cortisol is necessary and beneficial for fetal maturation and exposure to increased cortisol is facilitated by the sharp drop in 11β-HSD2 activity allowing a greater proportion of maternal cortisol to cross the placental barrier (Murphy & Clifton, 2003). The beneficial effects of modestly elevated cortisol during late gestation are consistent with animal models demonstrating that modest cortisol increases during the early postnatal period are associated with persisting beneficial effects for the developing brain (Catalani et al., 2000).

Sex differences

There is clear evidence that the male and female fetus respond differentially to prenatal stress. Clifton and colleagues have shown that male fetuses respond to an adverse maternal

environment with minimal placental adaptation, to ensure increased or continued growth. Female fetuses, on the other hand respond with multiple changes involving placental genes and proteins to ensure survival in the case of additional adverse events in utero (Clifton, 2010). These differences in fetal adaptation may explain why male fetuses are more vulnerable to threats to morbidity and mortality (DiPietro & Voegtline, 2017). In contrast, the more subtle adaptations made by female fetuses in response to stress may underlie sex-specific vulnerabilities to subsequent psychopathology (Sandman, Glynn, & Davis, 2013). For example, females exposed to prenatal stress are more likely to show elevations in symptoms of anxiety and depression and have heightened stress responses (Davis & Pfaff, 2014; Sandman et al., 2013), while males are more likely to show deficits in memory and learning and exhibit increased aggression (Glover & Hill, 2012).

Epigenetics

Researchers are in the early stages of examining specific biological pathways through which maternal stress produces changes in offspring development. Because the placenta regulates the prenatal environment, including cortisol levels, an important area of study involves effects of maternal stress on the expression of genes in the placental glucocorticoid-pathway. Prenatal anxiety and depression predict the downregulation of placental 11β-HSD2 (O'Donnell et al., 2012). Experimental work with rats has supported the hypothesis that maternal stress altered HSD11B2 gene expression and fetal brain development (Peña, Monk, & Champagne, 2012). Human studies have similarly found that prenatal stress was associated with the methylation of glucocorticoid pathway genes in the placenta (i.e., HSD11B2, NR3C1, and FKBP5). Maternal stress and methylation in the placenta have been correlated with fetal CNS

development (Monk et al., 2016) and infant neurodevelopment and behavior (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013).

Methylation of genes related to HPA axis functioning is also impacted by prenatal stress. In a sample of 24 mother-infant dyads residing in the conflict-ridden region of the Democratic Republic of Congo, Kertes and colleagues (2016) found that chronic stress and war trauma significantly affected the methylation of HPA axis genes, particularly at transcription factor binding sites. Further, gene methylation levels were related to birth weight outcomes, collectively explaining over half of birth weight's variance. Maternal prenatal stress (i.e., material deprivation, daily psychosocial stressors, war stress) was also related to newborn methylation of the glucocorticoid receptor NR3C1 (Mulligan, D'Errico, Stees, & Hughes, 2012). These findings provide promising preliminary support for possible biological mechanisms underlying the link between maternal stress and infant HPA functioning and highlight the need for further research to understand the nature of this relation.

Interactions with the postnatal environment

The next section of this chapter will extensively cover postnatal influences on brain and behavioral development; however, it is important to note that prenatal and postnatal influences likely interact with and/or build upon each other. It is unlikely that the programming window closes at birth (O'Connor, Monk, & Fitelson, 2014). Interestingly, breastmilk may serve as one pathway through which mothers continue to shape the development of their children, as biologically active components in breastmilk, including maternal cortisol, have been associated with infant behavior (Grey, Davis, Sandman, & Glynn, 2013). Adverse childhood experiences, when paired with a history of prenatal stress exposure, may exacerbate negative developmental outcomes. Pawlby et al. (2011) found that children exposed to prenatal stress *and* childhood

maltreatment were at almost 12 times greater risk of developing psychopathology compared to children exposed to either prenatal stress or childhood maltreatment.

On the other hand, positive postnatal experiences may buffer the negative impact of prenatal stress. Rat pups exposed to prenatal stress have improved outcomes when postnatal rearing is enriched, such as when they are cross-fostered to unstressed mothers (Del Cerro et al., 2010; Maccari et al., 1995) or when subjected to "neonatal handling" (removed from mother and placed in an individual compartment for a brief period of time; Wakshlak & Marta, 1990). In humans, high levels of positive parenting act as a buffer against the negative effects of prenatal stress on cognitive functioning in early childhood (Schechter et al., 2017). Similarly, maternal sensitivity quells infant distress, and this association is strengthened for infants exposed to maternal prenatal anxiety (Grant, McMahon, Reilly, & Austin, 2010).

Is this Fetal Programming?

One concern that challenges research with humans is whether associations between maternal stress and fetal outcomes should be interpreted as fetal programming, or alternatively as a reflection of shared genetic factors or as continuity between the prenatal and postnatal environment. In the studies of naturally occurring variations in maternal cortisol or maternal self-reported stress, it is difficult to differentiate between these alternative explanations. The programming findings reported here, however, are consistent with animal models where random assignment is possible (Kapoor et al., 2006) and with human studies of randomly occurring traumatic events, such as natural disasters (Laplante et al., 2004; Yehuda et al., 2005) and with prenatal exposure to synthetic glucocorticoids (Davis et al., 2006; French, Hagan, Evans, Godfrey, & Newnham, 1999). Further, in studies involving measurement of prenatal and postnatal stress, prenatal effects generally hold when postnatal effects are statistically controlled

(O'Connor, Heron, Glover, & Team, 2002; Van den Bergh & Marcoen, 2004). More convincingly, similar effects of prenatal stress on child outcomes were documented among children conceived by in vitro fertilization, and thus in a model where mother and fetus were genetically unrelated (Rice et al., 2010). Thus, while in most human studies of prenatal stress, genetic and postnatal mechanisms cannot be ruled out as a possible explanation, there is reasonable evidence to warrant the conclusion that maternal stress has effects on the neurodevelopment of her fetus. Future research can examine the impact of experimental manipulations of prenatal stress using a randomized controlled design (Davis, Hankin, Swales, & Hoffman, 2018).

Summary

Both psychosocial and biological maternal stress signals are associated with developmental consequences for the fetus. Further, these effects cannot be accounted for by birth outcome or postnatal maternal psychological distress. However, it is important to acknowledge that although there is some evidence that psychosocial and biological stress signals converge (Hoffman, Mazzoni, Wagner, & Laudenslager, 2016), others have suggested that these signals may not be correlated during pregnancy and may exert independent influences on developmental outcomes (Sandman & Davis, 2010). Future research will have to examine vascular or immune pathways that could be mechanisms by which increases in maternal psychosocial stress might also affect the fetus.

The studies discussed in this section of the chapter emphasize the importance of performing prospective longitudinal studies in order to evaluate the trajectory of maternal stress signals across gestation and its association with infant and child developmental outcomes. Data indicate that the trajectory or profile of biological and psychosocial stress signals may be more

critical for determining developmental outcomes as compared to level at a given gestational interval (Davis & Sandman, 2010; Glynn, Schetter, Hobel, & Sandman, 2008). Both severity and timing of exposure, as well as the sex of the fetus, must be considered in order to evaluate associations between prenatal stress measures and infant outcomes. The adaptive significance of these associations is yet to be determined and requires long term follow-up evaluating the interaction between the prenatal and the postnatal environment.

POSTNATAL STRESS AND NEUROBEHAVIORAL DEVELOPMENT

The HPA axis is not yet mature at birth (Gunnar & Herrera, 2013). The fetal zone of the adrenal cortex involutes over the first six postnatal months. As it involutes, the structure of the mature adrenal cortex becomes more distinct. Cortisol binding globulin (CBG) is low in the newborn but gradually increases during the first postnatal months. Thus, even small increases in plasma cortisol in response to stress may result in large increases of biologically active unbound cortisol as CBG binding sites become filled. Adrenal sensitivity to ACTH also appears to decrease over these first postnatal months as sensitivity is higher in the first four months than later in development. For the first few months of postnatal life there is higher HPA reactivity to stimuli than in later development, which is consistent with evidence than mild stimuli such as being undressed or undergoing a physical exam provokes elevations in cortisol in the first 3-4 postnatal months but not later.

Diurnal cortisol patterning changes dramatically in the first few years of life. Basal cortisol levels are not related to time-of-day at birth; rather cortisol is associated with behavioral arousal. As early as 6 weeks postnatal, a morning cortisol peak and a nadir in the evening can be observed. However, there is a great deal of variability in the diurnal rhythm at this age. The morning peak and evening nadir become more distinct across the next few months, but the more

mature adult-like pattern with consistent cortisol decreases from mid-morning to late afternoon is not observed until around age 4 years, when children give up their daily naps. Napping in young children has been associated with decreases in cortisol during sleep and increases in cortisol to pre-nap levels around 30-45 minutes after awakening. The cortisol awakening response (CAR), or the increase in cortisol levels soon after awakening that precedes decreases in cortisol throughout the day, can be detected already in young infants and is reliably detected through adulthood (Bäumler, Kirschbaum, Kliegel, Alexander, & Stalder, 2013). These developmental considerations make measurement of the HPA axis more difficult in infants and young children.

There are few developmental changes in cortisol reactivity and regulation from age 5 until puberty, when basal cortisol levels and cortisol reactivity both show increases (Netherton, Goodyer, Tamplin, & Herbert, 2004; Stroud et al., 2009). This increase in HPA reactivity and greater reactivity of neural systems underlying emotion have been hypothesized to increase risk for psychiatric disorders in adolescence (Spear, 2000). Shifts in neurodevelopment and stress system functioning across puberty may make this developmental period a time during which the impacts of early experiences—both positive and negative—may be fully realized. Alternatively, the peripubertal period may be a time of heightened plasticity of the HPA axis and the neuroaffective circuits that stimulate its activation, thus allowing the system to calibrate to current life conditions, for better or for worse (DePasquale, Donzella, & Gunnar, under review; Romeo, 2010).

The HPA axis is regulated by multiple factors (Herman et al., 2016), so understanding developmental changes in multiple systems with inputs to the HPA axis are important to consider. For example, neural systems including the amygdala and BNST are involved with activation of the HPA axis, while the medial prefrontal cortex (mPFC) and hippocampus are

involved in inhibition of the axis. Interestingly, the human hippocampus does not show developmental increases in GR, which suggests that the hippocampus may have a relatively mature ability to terminate the HPA response to stress at birth (Pryce, 2008). However, GR mRNA expression levels in the prefrontal cortex do increase into adolescence, and GR expression appears to be as high or even higher in the human neocortex as in the hippocampus (Pryce, 2008). Thus, the protracted development of the prefrontal cortex continues to impact—and is impacted by—the development of the HPA axis well beyond infancy. The complex stress-mediating circuitry that unfolds over time in response to environmental signals, such as early caregiving, has been termed the "neurosymphony of stress" (Joëls & Baram, 2009).

Receptors for CRH outside the HPA axis have been detected in the basolateral and medial nuclei of the amygdala, prefrontal cortex, hippocampus, reticular formation and cerebellum, suggesting broad effects in many parts of the brain following the release of CRH. Interestingly cortisol in the PVN down-regulates CRH, while in the amygdala, chronic elevations of cortisol upregulate CRH and increase fear behavior. In order for the HPA axis to react to psychological stressors, the central nucleus of the amygdala activates a pathway that crosses multiple synapses and involves the bed nucleus of the stria terminalis, which then converges on the PVN to release CRH (Ulrich-Lai & Herman, 2009). Threats to the social self, especially when uncontrollable or unpredictable, are one of the most reliable and relatively common triggers of HPA activation (Dickerson & Kemeny, 2004).

Cortisol regulates its own release through negative feedback mechanisms in the hypothalamus, pituitary, medial prefrontal cortex (mPFC), and hippocampus (Tasker & Herman, 2011). GABA-producing cells surrounding the PVN have tonic inhibition on the HPA axis, and downregulation of GABA input due to chronic stress reduces the tonic inhibition on the system.

CRH and ACTH can also regulate their own production. Negative feedback of cortisol can act quickly through the endocannabinoid system in the PVN or slowly through genomic mechanisms in the mPFC and hippocampus (Joëls & Baram, 2009). Chronic stress may also reduce GR expression in the mPFC and hippocampus as a result of negative feedback mechanisms in order to protect the brain from chronic HPA activation (Joëls & Baram, 2009). These adaptations to stress occurring early in life may have implications for neurodevelopment years later. There is evidence that early adversity speeds up certain aspects of neurodevelopment, including connectivity of the amygdala and mPFC, which is important for emotion regulation (Gee et al., 2013). In both human and animal models, these changes are mediated by altered HPA activity (Gee et al., 2013), which suggests that the HPA axis may facilitate faster neurodevelopment in the context of adversity in order to promote adaptation to the current environment. Overall, the HPA axis is a complex system involving multiple inputs from various physiological systems that is sensitive to the physical and social environment to coordinate basal regulation and reactivity to and recovery from stress.

Social Regulation of the HPA Axis and the Role of Caregivers

Across rodents, nonhuman primates, and humans, there is a wealth of evidence that both caregiver proximity and contact are critical to regulation of the HPA axis in early postnatal development (Gunnar, Doom, & Esposito, 2015; Sanchez et al., 2001). Sensitive and responsive caregiving in the first few months of life is associated with a more rapid recovery of the HPA axis following activation (Blair, Granger, Willoughby, & Kivlighan, 2006), while insensitive care is associated with increases in cortisol during infant-parent play (Spanglar, Schieche, Ilg, Maier, & Ackermann, 1994). These findings extend to non-parent caregivers including childcare providers (Vermeer & van IJzendoorn, 2006), as young children in out-of-home care with less

sensitive and/or more intrusive care providers show larger increases in cortisol across the child care day than do those with more sensitive caregivers.

Sensitive and responsive caregiving is an important component in the development of secure attachment, which characterizes the relationship between the child and their caregiver and not a trait of the child. Children may be securely attached to some caregivers while being insecurely attached to others. Nearly all studies on attachment security have centered on the mother-child relationship and these studies suggest that the presence and availability of the mother in secure attachment relationships provides a powerful buffer for HPA axis activity, while the presence of the mother in insecure relationships is less capable of buffering HPA responses when infants are frightened and distressed (Gunnar & Donzella, 2002). While the exact mechanism behind social buffering in humans is unknown, neurobiological and developmental work suggests that neural priming in areas of the brain associated with fear and emotion and the use of attachment figures as safety signals likely contribute (Hostinar, Sullivan, & Gunnar, 2014). Oxytocin, a neuropeptide associated with social behaviors, is thought to be one of the proposed mediators of social buffering (Smith & Wang, 2014). Intranasal oxytocin infusions have been shown to enhance social support's stress-buffering effects (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), but negative early care experiences may influence oxytocin's role in social behavior (Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005).

The actual presence of the attachment figure is needed to buffer HPA axis activity early in life, although secure attachment relationships are associated with better regulated anxiety and stress responses across development. When mothers and toddlers have a secure attachment relationships, toddlers show lower cortisol levels on days when the mother is present at a new child care arrangement than when she is absent (Ahnert, Gunnar, Lamb, & Barthel, 2004). These

elevations in cortisol decreased over several weeks, but did not dissipate after 5 months in child care, suggesting the importance of parental presence early in life.

Parents are capable of buffering increases in cortisol in response to stressors throughout childhood but less so during adolescence (Hostinar, Johnson, & Gunnar, 2015). The decrease in effectiveness of parents as a social buffer appears to track pubertal development more than age (Doom, Hostinar, VanZomeren-Dohm, & Gunnar, 2015). In addition, friends do not take over the buffering role in adolescence at least when the stressor involves social evaluation; indeed, for these stressors their presence actually increases cortisol responses relative to responses when parents serve as stress buffers (Doom, Doyle, & Gunnar, 2017). This loss of social buffering effectiveness may be one potential contributor to the increase in psychopathology during early adolescence. At this point it is unclear whether the reduction in social buffering effectiveness extends beyond threats to the social self as only these stressors have been studied. Nor is it clear how long a period of reduced social buffering effectiveness youth experience.

It is clear that by adulthood, the presence of one's spouse is a powerful social buffer, particularly if the relationship is supportive and secure (Beckes & Coan, 2011). In addition, social support figures in adulthood appear to serve as prepared safety stimuli (Hornstein, Fanselow, & Eisenberger, 2016). Finally, the HPA axis is powerfully regulated by spousal attachment figures in adulthood (Heinrichs et al., 2003). There are variations in buffering ability by sex, physical touch, and relationship to the buffering figure (e.g., friend vs. romantic partner), though emotional intimacy does appear to be a key element of social buffering effects as strangers will generally not buffer the HPA axis. Whether parents again become powerful stress buffers for their adult children is not known. We are also unsure what qualities of friend and parent relationships beyond infancy and toddlerhood lead to the most effective social buffering

and if more effective social buffering of the HPA axis prevents the onset of psychopathology in the face of stress.

Early adversity

Children's early care histories shape the development of the HPA axis, with both normal variations (e.g., sensitive versus harsh parenting) and extreme variations (e.g., abuse or neglect) in care associated with HPA regulation across development. Individual differences in genetics, as well as risk and protective factors play a large role in the effects of these early care experiences on development (Koss & Gunnar, 2018). Stressors that are particularly potent involve either *threat*, such as physical or sexual abuse, interparental conflict, and community violence, or *deprivation*, such as neglect, institutional care, or parental loss. Many children experience stressors that involve both threat and deprivation, such as extreme poverty, and there is evidence that the effects of these early stressors are cumulative (Doan, Dich, & Evans, 2014). These conditions of early stress are typically chronic, with the rare exceptions (e.g., children adopted out of institutions), which makes it challenging to understand the effects of stressor timing on development.

Diurnal cortisol following postnatal stress

The diurnal HPA rhythm that is maturing during the first postnatal years appears to be sensitive to immediate contexts of care. In a study of 46 2- and 3-year-olds living in an institution in Romania, no child exhibited the typical diurnal pattern that would be expected at this age. In addition, the institutionalized children showed lower cortisol than home-reared Romanian children in the morning and slightly higher cortisol in the later afternoon hours (Carlson & Earls, 1997). However, institutions are quite heterogeneous, and the flatter diurnal rhythm is not always found (Dobrova-Krol, van IJzendoorn, Bakermans-Kranenburg, Cyr, &

Juffer, 2008). Nonetheless, similar findings have been reported for children recently placed in foster care after being removed from maltreating homes (Bruce, Fisher, Pears, & Levine, 2009).

It is still not clear what factors are associated with the flatter diurnal rhythm in young children when it is found; however, there are several findings that point to neglect rather than abuse as an important factor. Bruce and colleagues (2009) found that it was the severity of neglect that predicted low early morning and a flatter diurnal slope in children entering a new foster placement. Similarly, in toddlers and preschoolers adopted from institutions, those who experienced less supportive social care (i.e., fewer caregivers to children, less interaction) produced the lower and flatter cortisol diurnal activity (Koss, Hostinar, Donzella, & Gunnar, 2014) although see also (Kertes, Gunnar, Madsen, & Long, 2008). Adults adopted as children from maltreating homes also show a lower morning cortisol than adoptees without this history, and the main predictor of a flatter diurnal slope appeared again to be the severity of neglect (van der Vegt, Van Der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). Notably, the altered pattern of diurnal activity was persistent for several years post adoption in one study (Koss et al., 2014) or from childhood to adulthood in another (van der Vegt et al., 2009). Thus at least in some cases, removing the child from conditions of neglect does not appear to normalize the diurnal rhythm. In other cases, no differences in rhythm have been noted between those with abuse and neglect histories and individuals without such histories, particularly for children with later onset abuse and low levels of internalizing symptoms (Cicchetti, Rogosch, Gunnar, & Toth, 2010). While it is as yet uncertain whether these differences reflect the type or severity of adversity, there is some evidence that the age of removal from adversity may affect the HPA axis.

Effects of early care on cortisol set points and reactivity

In rodent models, poor quality postnatal care shapes development in a unidirectional manner, increasing both behavioral and physiological reactivity to stress. However, in primates, including humans, adverse early life care does not always result in hyper-activity of the HPA axis. For example, rhesus infants reared on non-animate surrogates exhibit hypoactivity of the axis in terms of basal levels, response to psychosocial stressors and in response to pharmacological challenge (Capitanio, Mendoza, Mason, & Maninger, 2005). Similarly, squirrel monkeys separated repeatedly from their mothers exhibit a more regulated HPA axis (Lyons, Parker, & Schatzberg, 2010). Thus, several researchers have proposed that the relationship between early adversity and stress system functioning may be a J-shaped curve, with modest amounts of adversity leading to a better regulated system, while high amounts result in hyper-activity of stress systems (Boyce & Ellis, 2005; Del Giudice, Ellis, & Shirtcliff, 2011). The problem with these models is that, as noted for infant rhesus, complete removal of the mother and other potential caregivers, which must be viewed as extreme adversity, results in hypocortisolism. This also appears to be true for children reared in institutions. Not only, as noted, are flatter diurnal rhythms observed, but for those who remain in institutional care for their first two years of life or more, the HPA and SNS response to stressors also appears to be blunted (McLaughlin et al., 2015). In addition, we have noted a blunted cortisol awakening response for children adopted internationally from institutional care if they were over 16 months at removal, but not if they were 16 months or younger (Leneman, Donzella, Desjardins, Miller, & Gunnar, 2018). Likewise, adults adopted as young children from Romanian orphanages still exhibit a blunted CAR in adulthood (Kumsta et al., 2017).

Evidence that low care or neglect is associated with low cortisol reactivity has also been found in family-reared children. Thus both low and very high maternal care has been associated with low cortisol reactivity (Engert et al., 2010). Note that the association of high maternal care with low reactivity argues against the J-shaped model described earlier. Similarly, again in contrast to that model, children who have been bullied were found to have blunted cortisol responses compared to their non-bullied twin and that these differences were not attributable to genetics or shared environments (Ouellet-Morin et al., 2011). Likewise, a study of teenage girls who had been maltreated showed blunted cortisol but not cardiac responses to a social evaluative stressor, suggesting a block on the HPA axis (MacMillan et al., 2009).

While these studies would seem to argue that extreme early adversity shapes a hyporesponsive HPA axis, other studies do tend to support the more J-shaped model, at least with regards to higher levels of adversity predicting hyper-activity of the axis. Many of these studies, however, have involved children of depressed mothers, raising the possibility that the genetics of depression may also play a role. Thus, children whose mothers reported high depressive symptoms during infancy showed higher afternoon cortisol levels at age 4 (Essex, Klein, Cho, & Kalin, 2002). A cash transfer program for extremely poor families in Mexico resulted in lower cortisol levels for children aged 2-6 years, but this effect was only noted for the children of mothers with high depressive symptoms (Fernald & Gunnar, 2009). This finding, then, indicates that poverty was associated with elevated cortisol for children of depressed, but not non-depressed mothers. Children of women who experienced postnatal depression showed higher and more variable morning cortisol concentrations at 13 years (Halligan, Herbert, Goodyer, & Murray, 2007).

Other studies also support the idea that psychiatric disorders moderate the association between childhood adversity and HPA axis functioning. For example, survivors of child maltreatment have been found to exhibit higher cortisol levels and greater reactivity, but primarily if they have also developed major depression (e.g., Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). For adults without a psychiatric diagnosis, those with histories of adversity often show a lower HPA axis set point and more blunted cortisol responses to psychosocial stress (Carpenter et al., 2007). In children, those who were physically or sexually abused before age 5 showed altered diurnal cortisol production only if they were also high in internalizing problems (Cicchetti et al., 2010). One of the challenges of determining trait-like HPA activity is that both child extremes in temperament (Gunnar, Tout, de Haan, Pierce, & Stanbury, 1997) and life conditions (Doom, Cicchetti, & Rogosch, 2014) have been shown to be associated with day-to-day variability in basal cortisol activity, and likely also in reactivity.

Importantly, maltreatment that leads to Post-Traumatic Stress Disorder (PTSD) is not associated with hyper-activity of the HPA axis, even though it is often comorbid with depression. Instead, in adults it is associated with normal to low levels of cortisol activity (Yehuda, 2001). PTSD before puberty appears to be related to elevated cortisol production (Carrion et al., 2002). Longitudinal work on sexually abused girls showed that elevated cortisol levels decreased beginning in adolescence with lower cortisol levels by adulthood, with at least this study supporting time-since-trauma as the critical factor over pubertal onset (Trickett, Noll, Susman, Shenk, & Putnam, 2010).

Individual differences in sensitivity to experience

Not every child exposed to chronic or severe stress goes on to develop emotional or behavioral problems, and developmental science has been attempting to understand the wide

variation in outcomes following early stress. For example, two children who have experienced maltreatment from a caregiver may have vastly different emotional and behavioral outcomes if there are variations in social support, the environment, genetics, and previous early experiences that influence risk and resilience processes. One theory about variation in responses to early experiences is the *biological sensitivity to context* theory (Boyce & Ellis, 2005). This theory argues that individuals whose biology is more reactive to context are more likely to have outcomes that vary by the contexts they encountered during development. Similarly, the *differential susceptibility framework* argues that there are genetic polymorphisms that result in greater plasticity and reactions to contextual variations (Belsky & Pluess, 2009). Both of these theories are distinct from the diathesis-stress framework that frequently guides work on early stress, which only frames individual variation as vulnerability to adversity. Both biological sensitivity to context and differential susceptibility theories argue that the same individual difference fact that may make one vulnerable to adverse conditions may allow superlative developmental outcomes under supportive conditions. Thus, with regards to genes, those referred to as "risk alleles" might be better named "plasticity genes" in reference to their vulnerability to risky environments and enhanced outcomes in enriched environments.

There are a number of factors that influence susceptibility to effects on both the fear- and stress-responsive systems, including temperament, sex differences and genetics. One dimension of temperament closely tied to the fear and stress systems is behavioral inhibition, which includes greater behavioral reactivity and less approaching of novel or unpredictable stimuli. Infants who are behaviorally inhibited often go on to be shy and more likely to have social anxiety (Henderson, Pine, & Fox, 2015). These infants do not always have higher cortisol levels and reactivity, as stress system functioning in behaviorally inhibited infants likely depends on

factors such as support from the attachment figure or whether avoidance is an effective way to regulate stress. In the absence of supportive care, higher cortisol reactivity in inhibited children could mediate their greater vulnerability to adverse early caregiving (Phillips, Fox, & Gunnar, 2011). Their sensitivity to the environment could help them to excel in high-quality care (biological sensitivity to context, discussed above; Boyce & Ellis, 2005).

Animal models of early stress document sex-specific changes as a result of postnatal stress and stress hormone exposure (Bale & Epperson, 2015). Increasing evidence points to sex differences in neurological development that begin prenatally, with developmental hormone exposure largely guiding the organization of the sexually dimorphic brain (Bale & Epperson, 2015). Hormonal effects on cell migration early in life may program stress-regulatory brain regions, including the hypothalamus and limbic circuitry, which contribute to sex differences in stress responses throughout the lifespan (Bale & Epperson, 2015). Sex-specific developmental trajectories observed postnatally are likely a continuation of prenatal changes in neurodevelopment, which may lead to sex differences in psychiatric disorders. There is evidence that females may be at greater risk for early postnatal and peripubertal stressors leading to affective disorders later in life. Sex differences postnatally may be due to biological differences, including interactions between sex chromosome genes and hormonal changes, as well as differences in the effects of parents on developing fear and stress-responsive systems between males and females. Sex is a major factor in guiding prenatal and early postnatal brain development, and it also contributes to brain development across puberty. Limbic brain regions, such as the amygdala and hippocampus, express many androgen and estrogen steroid hormone receptors and increase in volume in rodents and humans (Bale & Epperson, 2015). Sex-specific

changes in brain development across puberty influence functioning of fear- and stress-responsive systems across the lifespan.

Genetics play a role in one's sensitivity to the environment and the likelihood of significant alterations in cognitive and socioemotional development following early stress. The CRHR1 gene, for example, has been shown to mediate both behavioral and physiological stress responses, and variants in this gene have been shown to interact with early abuse to increase depression risk (Gillespie, Phifer, Bradley, & Ressler, 2009). In the context of childhood stress, genes regulating GR and the HPA axis are of particular interest, as these have been associated with risk and resilience in the context of early stress (DeRijk & de Kloet, 2008; Gillespie et al., 2009). The same genetic polymorphism associated with risk in the context of early harsh caregiving could be associated with enhanced outcomes in the context of sensitive, responsive caregiving (Belsky & Pluess, 2009).

More recently, genetic work has shifted to understanding how early caregiving may "get under the skin" to influence children's health and development through the study of epigenetics. Epigenetics involves modifications to the genome that alter the accessibility of DNA and may alter gene expression but do not change the base-pair sequence. Epigenetic changes are thought to be one of the primary pathways by which early experiences—both positive and negative—may be embedded to influence later cognitions, emotions, and behavior. A growing body of literature has begun to document associations between early stress and epigenetic modifications, including DNA methylation. A study of adolescents adopted during early childhood from institutions in Eastern Europe showed altered DNA methylation patterns in genes associated with neurodevelopment compared to adolescents raised in their birth families (Esposito et al., 2016). Even less extreme variation in early life stressors have been shown to be associated with

adolescent DNA methylation (Essex et al., 2013). Evidence in twins demonstrate that the twin who was bullied showed higher serotonin transporter methylation at 10 years compared to their non-bullied co-twin, which could not be attributed to genetic make-up or shared environments, and this higher methylation was associated with blunted cortisol reactivity to stress (Ouellet-Morin et al., 2013). A recent systematic review identified that 89% of publications in humans on early parental stress and methylation of the promoter of the GR gene (*NR3C1*) showed greater methylation with increased stress at this site (Turecki & Meaney, 2016). Epigenetics could be one way by which experiences are transmitted intergenerationally (Champagne, 2008). Further work must be done on investigating the type and timing of early experiences that impact epigenetics, understanding who are the most sensitive to epigenetic alterations in response to the environment, and delineating the pathway by which epigenetic changes could lead to downstream effects on health and behavior.

Summary

Accumulating research is illuminating the impact of early postnatal experiences on neurodevelopment and the development of stress-mediating systems. In humans, the HPA axis develops significantly over the first 6 months of postnatal life. The fear and stress-response systems are strongly regulated by caregivers, and sensitive, responsive caregiving has been associated with better regulation of these systems and the ability to return to baseline quickly following challenges. Adverse early care, including maltreatment and institutional care, have been associated with disruptions in the HPA axis that can persist for years and may partially mediate cognitive, behavioral, and emotional outcomes following stress. More normative variations in early care are also associated with HPA profiles. The timing and type of stressor and the age at assessment are important moderators, as developmental changes like puberty may

play an important role in the functioning of the HPA axis post-stressor. In addition, current psychiatric status, including experiencing depression or PTSD, are associated with unique HPA profiles. Factors such as genetics and temperament are important moderators of HPA functioning and behavior, and specific genetic profiles or temperamental characteristics may act as a vulnerability factor in certain contexts and a resilience factor in others. Thus, developmental timing and individual differences are vital to consider when understanding the development of the HPA axis and the brain, particularly in the context of postnatal stress.

FUTURE DIRECTIONS

The study of pre- and postnatal stress and its impact on neurodevelopment and health has thus far proceeded largely independently. It is time for this work to become integrated, both empirically and theoretically. While researchers studying prenatal stress have sometimes obtained measures of outcomes later in life, it is rare that postnatal experiences are examined as anything other than potential confounds to be controlled statistically. Yet, postnatal experiences have the potential to either ameliorate or exacerbate prenatal effects. In addition, alterations in infant functioning related to prenatal experiences may result in differential sensitivity to variations in early care experiences and/or behaviors, which elicit different responses from caregivers. As noted, some researchers are beginning to address how postnatal care interacts with prenatal stress exposure to influence cognitive, behavioral and health outcomes. More of this work is needed.

From a fetal programming perspective, it is especially critical that conceptual models are examined via longitudinal studies that track postnatal development. If, as some models posit, fetal programming via stress mediators prepares the fetus to survive in a harsh postnatal world (Gluckman & Hanson, 2004), then we need to design studies to directly test

such hypotheses. With regards to nutrition, there is evidence that concordance in pre- and postnatal nutrition leads to more functional health outcomes than discordance (Cleal et al., 2007). Within the socioemotional domain, infant developmental outcomes appear to be improved when mothers experience similar levels of depression during and after pregnancy (Sandman, Davis, & Glynn, 2012). Replication and extension of these findings is essential to identify the prenatal stressors and postnatal outcomes for which adaptive advantage exists.

Consistent with the early literature on outcomes for premature infants, it is also possible that a supportive postnatal environment may ameliorate and a harsh environment may exacerbate the neurobehavioral sequelae of prenatal stress. In this case, discordance in the harshness of pre- and postnatal experience may predict better outcomes as long as the later environment is supportive. Recent human studies have provided support for this possibility demonstrating that high quality maternal care can compensate for the negative effects of prenatal stress exposures (Bergman, Sarkar, Glover, & O'Connor, 2010; Schechter et al., 2017). It remains likely that the effects of stress during the prenatal and postnatal period will differ by developmental outcome and there is a clear need for prospective studies with multiple prenatal and postnatal assessments.

A more compelling reason to study prenatal stress in the context of postnatal stress is if prenatal experiences alter the individual's susceptibility to postnatal experiences. This would be the case if, as it has been argued, prenatal stress programs postnatal plasticity (Pluess & Belsky, 2011) or if prenatal stress increases suitability to certain types of postnatal environments. If true, this might mean that postnatal experiences might not only exacerbate or reduce the negative impacts of prenatal stress, which is more a diathesis-stress

model, prenatal stress might result in more positive outcomes if postnatal conditions are favorable, and more negative if they are not, as has been shown in at least one study of voles (Hartman, Freeman, Bales, & Belsky, 2018). This argument, of course, completely contradicts the Barker hypothesis, which argues that adaptations to harsh conditions during fetal development increase survival advantage if the postnatal environment is harsh and poor in resources, but impairs outcomes if it is a mismatch (supportive, well-resourced) with the prenatal environment. Strong support for this survival advantage of a match between the prenatal and postnatal environment comes from both animal and human studies looking at nutrition (Cleal et al., 2007; Gluckman & Hanson, 2004; Gluckman, Hanson, & Spencer, 2005). Few studies, however, have looked at the impact of a mismatch between the prenatal and postnatal environments in the psychosocial domain (Sandman et al., 2012). Which predictions turn out to be accurate requires the longitudinal studies, beginning before birth that we have been calling for in this future directions section. They also likely require a range of outcome to be assessed, as the predictive utility of the model may be a function of the outcomes we study. That is, psychological functioning might follow a sensitivity to context/susceptibility model as prenatally stress and emotionally sensitivity and physiological reactive children blossom under supportive parenting, while body mass and cardiovascular health suffer when a harsh and low nutrient fetal environment is followed by a nutrient rich and high calorie postnatal context.

Thus far we have only focused these future direction comments on the value of incorporating research and theory on postnatal stress into models and research on prenatal stress. Perhaps a more critical need is for those studying postnatal stress to consider the role that prenatal stress may be playing in their findings. Certainly it seems likely that children

who are abused, neglected, or abandoned to orphanage care may be the product of stressed pregnancies. It also is likely that they are the products of pregnancies complicated by poor nutrition and exposure to alcohol and drugs. Unfortunately, in many studies of postnatal stress there is meager information about prenatal conditions or even birth outcomes. Retrospective reports obtained from parents in studies, for example, of child maltreatment must be suspect. For children abandoned to orphanage care even the child's age at abandonment is often unknown, let alone their gestational age, health at birth, and prenatal conditions. Nonetheless, despite the challenge of obtaining accurate information on prenatal conditions for children identified because of their poor postnatal care, we need studies where such information can be or has been obtained. This is particularly important in studies examining interventions to improve outcomes as prenatal conditions may moderate how the child responds.

Finally, one area that would seem ripe for integration into research on pre- and postnatal stress is the role that the dramatic hormonal changes that accompany pregnancy contribute to the quality of postnatal caregiving. Stress and reproductive hormones during pregnancy are associated with maternal cognitive functioning (Glynn, 2010), the development of postpartum depression (Yim et al., 2009) and the quality of maternal care (Feldman & Eidelman, 2007; Glynn, Davis, Sandman, & Goldberg, 2016). The maternal hormonal milieu also impacts the developing fetus, as was discussed. Thus, to close the loop on our understanding of the ways in which stress impacts the developing fetus and young child, we need studies that incorporate the impacts of stress and maternal hormonal changes on the mother, her caregiving, and her response to her infant. This research will directly inform prenatal interventions through considering the intervention's effects in the

context of the anticipated postnatal environment. Likewise, postnatal interventions may be adapted based on knowledge of the infant's prenatal environment.

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