# Chapter 6
# Developmental Origins of Self-regulation: Prenatal Maternal Stress and Psychobiological Development During Childhood

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## Introduction: Setting the Scene

Even before birth, a mother's psychological state is shaping her child's subsequent development of self-regulation. The premise that fetal development sets pathways for health and well-being as well as risk and challenge across the life span is generally referred to as *fetal programming* (cf. Developmental Origins of Health and Disease, Barker, 2003). The notion of fetal programming implies that fetal development is altered in a way that prepares the offspring for the particular environment in which it will find itself (cf. predictive adaptive response, Gluckman & Hanson, 2005). Thus, not all outcomes reflect conditions of risk or disease. Some fetal adaptations that increase vigilance to the environment or alter one's capacity to respond to stress could be maladaptive in one context but quite adaptive in another (Glover, 2011), thus shaping the developmental outcomes for better *and* worse (Belsky & Pluess, 2009).

The period of intrauterine life represents one of the most sensitive windows during which the effects of stress may be transmitted inter-generationally from a mother to her as-yet-unborn child. The fact that maternal mood disturbances (e.g., negative emotions and perceived stress) during pregnancy are linked with later child behavior, even after controlling for effects of postnatal maternal mood and other relevant prenatal and postnatal confounders, suggests that, as in animal models, some of the risk is conferred prenatally via changes in women's mood-based physiology affecting fetal neurobehavioral development (M. Weinstock, 2008). While multiple underlying mechanisms and systems are involved in fetal programming (Talge, Neal, & Glover, 2007), the

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stress regulatory system in general and the hypothalamic pituitary adrenal (HPA) axis in particular may play a significant role in mediating the effects of maternal stress/anxiety and child outcomes (Glover, O'Connor, & O'Donnell, 2010). Despite the popularity of the fetal programming model, it is also important to acknowledge that such effects are not necessarily permanent as research has shown that young animals show remarkable neuronal resilience if the stress is discontinued (McEwen & Morrison, 2013). Thus, while in this chapter we will focus on prenatal maternal mood exposure and its associations with child self-regulatory abilities, it is important to bear in mind that postnatal factors (e.g., parenting, secure attachment, and socioeconomic status) matter as well and will be the main focus of the other chapters in this book (e.g., Chap. 8 by Finegood & Blair; Chap. 11 by Crnic & Ross in this volume).

A key assumption underlying the fetal programming hypothesis is that biological systems undergoing rapid developmental changes are especially vulnerable to organizing and disorganizing influences (Seckl & Meaney, 1993). Stress early in life, and specifically prenatal maternal stress, may have a particularly large effect on prefrontal cortex (PFC) structure and function because of its rapid growth during gestation and its high density of glucocorticoid receptors (Arnsten, 2009; Fuster, 2008; Sanchez, Young, Plotsky, & Insel, 2000). In particular, executive function (EF)—a set of higher order cognitive processes, such as working memory, inhibition, and attention shifting, associated with PFC and integral to emerging self-regulatory behavior (Blair, 2002)—is the first to suffer and suffer disproportionately, if we are stressed (Arnsten, 2009; Diamond & Ling, 2016). Here we will examine the possiblity that prenatal maternal stress may have a similarly strong impact on children's emerging EF.

Several independent prospective longitudinal studies using behavioral questionnaires and clinical scales administered at varying time points during development have established an association between prenatal maternal mood and child self-regulatory abilities. Specifically, children of mothers who were stressed during pregnancy (high anxiety/depression) had more difficulties than children not exposed to prenatal maternal stress with cognitive, behavioral, and emotional self-regulation as reflected in difficult temperament, attention regulation problems, hyperactivity, clinical diagnosis of ADHD, ADHD symptoms, conduct disorders, and emotional problems (after controlling for possible confounding factors such as prenatal maternal smoking or alcohol consumption, maternal education, birthweight, gestational age, and postnatal maternal mood; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, Heron, Golding, Glover, & Team, 2003; Oberlander et al., 2007; Van den Bergh & Marcoen, 2004). More recently, human studies have begun to examine the neurodevelopmental consequences in children exposed to maternal stress during gestation in more depth and more specifically (e.g., Entringer, Buss, & Wadhwa, 2015; Van den Bergh, Mulder, Mennes, & Glover, 2005). In this chapter, we will specifically focus on current studies using laboratory-based measurement of child EF or neurophysiological measures indexing PFC activity to examine the long-term consequences of maternal stress during pregnancy on emerging

regulatory mechanisms in children. These findings provide a unique opportunity to elucidate which specific aspects of children's self-regulation (including underlying structure–function relations) may be altered following exposure to prenatal maternal stress.

Increasingly, research has focused on how fetal programming models explain variations in psychiatric outcomes (Glover, 2011). A case in point is illustrated by the role the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) plays in shaping developmental risk and resiliency. Increased use of selective serotonin reuptake inhibitor (SSRI) antidepressants to manage mood disorders during pregnancy highlights the role psychotropic medication exposure during critical prenatal periods has in shaping children's development. We will review how exposure to prenatal antidepressants shape—possibly via altered central 5-HT levels—the development of systems that regulate attention, cognition, emotion, and stress responses (Hanley & Oberlander, 2012).

In this chapter, we focus on empirical evidence examining associations between prenatal maternal stress (i.e., pregnancy-specific anxiety, stress exposure, depression, and antidepressants) and child self-regulatory capacities reflected in neurobiological processes such as EF and stress regulation spanning fetal periods to early adulthood. We take the view that psychobiological processes comprising EF and stress regulation are shaped by early exposures related to maternal mood during gestation that influence the developing central nervous system (CNS) and autonomic nervous system (ANS). Furthermore, we will review current evidence within a conceptual perspective whereby prenatal maternal mood during sensitive periods of fetal development may act as a "plasticity factor" rather than "risk factor" associated with vulnerability that predicts disordered development and behavior. With this perspective in mind, we will critically review empirical studies examining the association of maternal mood during gestation on stress regulation and higher order cognitive abilities (behavioral measures of EF and neurophysiological measures indexing PFC) during childhood and adolescence, as well as the role of altered 5-HT signaling (i.e., antidepressant exposure). Understanding the role of maternal stress during gestation for child development offers critical insights that may explain why variations in early typical environment are associated with shaping both developmental risk *and* resilience.

## Developmental Origins of Self-regulation

The development of self-regulation is central to a child's emerging ability to adaptively respond to environmental demands and to engage in goal-directed behavior (Baumeister & Vohs, 2004; Calkins & Howse, 2004). It is marked by the acquisition of an integrated set of domain specific (biological, attentional, emotional, behavioral, and cognitive) self-regulatory mechanisms that are hierarchical in nature and that build upon each other (Calkins & Williford, 2009). Biological components of self-regulation include serotonin and dopamine neurotransmitter system genes

and central and peripheral nervous system connectivity (Bell & Deater-Deckard, 2007). Cognitive components are generally referred to as EF representing a complex and interrelated set of higher order cognitive processes associated with the PFC, including the maintenance and manipulation of relevant information (working memory), inhibition of predominant responses (inhibition), and mental set shifting (shifting, Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). EF serves a critical higher level or top-down role in behavior regulation, such as directing attention and organizing cognitive resources (Miller & Cohen, 2001) and/or regulating emotions (Ochsner & Gross, 2005). Over the past two decades, a strong body of developmental research has established that EFs are crucial for social, emotional, and academic success during childhood (e.g., Blair & Razza, 2007; Hughes & Ensor, 2011; Neuenschwander, Röthlisberger, Cimeli, & Roebers, 2012) and self-regulation has been shown to shape physical and mental health risk trajectories across the life span (Moffitt et al., 2011). Importantly, EFs are malleable based on context-specific experiences both at home and at school (for reviews see Diamond & Lee, 2011; Hughes, 2011; see also Chap. 8 by Finegood & Blair).

Various aspects of parenting, including parenting stress, have been shown to be associated with child EF. For instance, sensitive parents that engage in age-appropriate scaffolding act as external regulators of child behavior and in these terms gradually facilitate children's ability to regulate their own emotions and behaviors (e.g., Bernier, Carlson, & Whipple, 2010). These parenting aspects also reflect the parent's ability to regulate their own emotions and behaviors, and suggest that parental EF is an important part of sensitive parenting (Barrett & Fleming, 2011) (see also Chap. 10 by Mileva-Seitz & Fleming in this volume). Specifically, parental EF may moderate the association between parental risk and child outcomes, such that the negative effects of parental risk are mostly evident when, for instance, mothers show low EF (Deater-Deckard, Wang, Chen, & Bell, 2012). In general, parenting stress may be one crucial mechanism through which stressors in a family's environment affect parent–child interactions and ultimately children and their neurocognitive development (see Chap. 8 by Finegood & Blair).

The PFC is the brain region that is most sensitive to the detrimental effects of stress exposure (Arnsten, 2009; McEwen & Morrison, 2013). Phylogenetically, the PFC is among the brain regions that evolved most recently or were most recently altered in the course of human evolution. In line with this, the PFC shows a protracted ontogenetic development into early adulthood and displays remarkable structural and functional plasticity over the life course (Fuster, 2008). Chief external landmarks of the PFC (i.e., its primary sulci) develop during gestational weeks 25–26 (Stiles & Jernigan, 2010). Importantly, the PFC intelligently regulates our thoughts, actions, and emotions through extensive connections with other more posterior and subcortical areas of the brain. Therefore, it is likely that a dysfunction of the PFC can be associated with a dysfunction in one or more of the related systems.

Chronic stress early in life may have a particularly large effect on PFC structure and function in adulthood because of its rapid growth during fetal life. This rapid growth rate and the high density of glucocorticoid receptors (Fuster, 2008; Sanchez et al., 2000) make the fetal PFC especially vulnerable to stress hormones that reach

it in excess amounts as a result of *maternal* stress. Such hormones may impede the formation of correct neural connections and reduce plasticity and neurotransmitter activity, which in turn can induce subtle changes in subsequent cognitive function and behavior (Weinstock, 2008). For instance, in animal models, dendritic changes in fetuses have been documented in utero when the rat mother was exposed to stress (Murmu et al., 2006). In humans, growing up under social or economic disadvantage has been shown to increase young toddlers' cortisol levels which in turn mediated the effects of poverty and parenting on EF at the age of three (Blair et al., 2011). In adults, acute psychosocial stress exposure has been found to impair EF (e.g., Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Lupien, Gillin, & Hauger, 1999). To some extent, these effects are believed to reflect the fact that glucocorticoid levels (i.e., cortisol) modulate synaptic activity in the neural circuitry of the PFC. Importantly, the functional relation between cortisol levels and PFC activity or EF performance is curvilinear (Arnsten, 2009; de Kloet, Oitzl, & Joëls, 1999; Lupien, Maheu, Tu, Fiocco, & Schramek, 2007), such that very high or very low levels of stress impair EF performance, whereas moderate stress/cortisol levels lead to optimal EF performance. This inverted U-shape relation may have important implications for beneficial effects of prenatal exposure to mild and moderate levels of maternal stress on certain child outcomes (cf. DiPietro, Novak, Costigan, Atella, & Reusing, 2006). Taken together, it can be concluded that prenatal stress may have a particularly strong effect on EF; however, the relationship between EF and stress is complex and appears to be context dependent.

## Prenatal Maternal Mood and Stress

Pregnancy is a dramatic biological and psychological period in a woman's life. The woman's transition to motherhood not only does transform her physical landscape including the internal hormonal milieu but also has significant implications for her relationships and her societal role. Furthermore, for many women, the stereotypical image of pregnancy as a happy and joyful time in life when a mother and her partner are expecting a child they planned to have and that they are well prepared to love and care for does not apply. For many women, pregnancy is an experience characterized by a lack of adequate resources, both socioeconomic and psychosocial, and the presence of many stressors such as work responsibilities and conflict with the partner makes pregnancy a distant reflection of the ideal prototype (Dunkel Schetter, 2011). It is thus not surprising that pregnancy and the postpartum period tend to heighten risk for development or recurrence of mood disorders (Leight, Fitelson, Weston, & Wisner, 2010).

Prevalence estimates of antenatal depression vary greatly depending on the criteria used and may usually represent rather conservative estimates, because cases of maternal depression are underreported and underdiagnosed (Howard et al., 2014). A systematic review (Bennett, Einarson, Taddio, Koren, & Einarson, 2004) of studies conducted mostly in Europe and Northern America examining the prevalence of

depression during pregnancy found the following estimates by trimester: 7.4% in the first, 12.8% in the second, and 12% in the third. For women of low socioeconomic status, in contrast, meta-analytic estimates, although based on few studies, were much higher: for the second and third trimesters 47% and 39%, respectively, when obtained by self-report, and 28% and 25% when determined by structured clinical interviews. Estimates for prenatal anxiety, in contrast, are scarce, probably because the interplay between the perinatal period and anxiety disorders remains poorly studied (Leight et al., 2010). Some of the stressors that commonly affect women in pregnancy around the globe are low material resources, unfavorable employment conditions, heavy family and household responsibilities, strain in intimate relationships, and pregnancy complications (Dunkel Schetter & Tanner, 2012).

Antenatal maternal mood disturbances have been characterized on multiple dimensions, including measures reflecting stress-related disorders such as anxiety and/or depression. These outcomes are often used interchangeably, often implying similar constructs. Indeed, differentiating symptoms reflecting anxiety from depression remains challenging, and many of these symptoms may lie along a continuum of a maternal stress regulatory disorder. Stress is typically regarded as a physiological and psychological condition that is beyond the capacity of an individual's ability to cope, often leading to symptoms such as anxiety or depression. If severe enough, these symptoms may meet a clinical threshold and constitute a major affective disorder. Notwithstanding this perspective, while maternal symptoms of anxiety and depression often imply a common metric for stress, a distinction between these two dimensions can be drawn (DiPietro, 2012) and the differential impact of distinct types of maternal stress on developmental outcomes has been established in some studies.

Definitions and measurements of prenatal maternal stress have evolved over time. Whereas older studies often relied solely on a checklist of retrospectively assessed stressful life events (e.g., death of a family member or catastrophic community-wide disasters such as earthquakes), more recent studies have shifted toward considering prenatal maternal stress as a multi-dimensional concept. Given that an event or situation can be perceived differently by various individuals, it is really that subjective perception or interpretation of an external stressor rather than its objective nature that has the power to trigger an emotional response (Lazarus, 1991) and hence possibly influence health outcomes. Thus, more recent studies combine measures of acute (life events) and chronic (daily hassles) stress stimuli with more subjective measures including resources (personality and social support), stress perception, and mood outcomes (anxiety and depression) that reflect emotional responses to stressful stimuli (Dunkel Schetter, 2011). It is still unclear which types of prenatal emotional disturbances or stress are most harmful for fetal and child development. Interestingly, there is some evidence that levels of maternal self-reported pregnancy-specific anxiety are superior to general measures of distress (such as state anxiety or symptoms of depression) for predicting the developmental outcomes (e.g., Buss, Davis, Hobel, & Sandman, 2011; DiPietro et al., 2006). We will emphasize which types of maternal stress were assessed and most predictive for developmental outcomes in the studies that we review below.

## Prenatal Maternal Stress Shaping Child Self-regulation

Accumulating research indicates that a mother's stress and related affective states experienced in pregnancy can have significant negative consequences for her child's long-term learning, stress physiology, motor, cognitive, and emotional development, behavior, and health (reviewed in, Beydoun & Saftlas, 2008; Dunkel Schetter & Tanner, 2012; Entringer et al., 2015; Glover, 2011; Kinsella & Monk, 2009; Mennes, Stiers, Lagae, & Van den Bergh, 2006; Talge et al., 2007; Van den Bergh, Mulder, et al., 2005; M. Weinstock, 2008)—even when accounting for postnatal maternal psychological state. Specifically, with regard to developmental origins of self-regulation, antenatal maternal stress disrupts fetal neurobehavioral development (DiPietro et al., 1996; Tronick & Weinberg, 1997), alters behavioral reactivity in utero (Allister et al., 2001; Monk et al., 2000), and in the newborn period is reflected in reduced birthweight and increased risk of prematurity (Glover, 2011; Talge et al., 2007). The exact mechanisms by which antenatal anxiety and stress influence fetal brain development remain unclear, yet the magnitude of their effects is clinically significant, with approximately 15% of emotional and behavioral problems in childhood attributable to antenatal stress/anxiety (Talge et al., 2007). Furthermore, emerging evidence suggests that the combination of early life stress, genetics, and ongoing stress may ultimately determine individual responsiveness to stress and the vulnerability to psychiatric disorders, such as depression (Charney & Manji, 2004). Importantly, not all outcomes following stressful early life events reflect adversity. Antenatal exposure to mild-to-moderate levels of psychological distress may actually advance motor and mental development in a healthy population (DiPietro et al., 2006), suggesting that early stress exposure shapes developmental outcomes for better *and* worse.

Laboratory-based measures of child neurocognitive development (behavioral measures of EF and neurophysiological measures indexing PFC structure and activity) offer a key insight into the neural correlates (i.e., specific aspects of children's EF including underlying structure–function relations) that may be affected by prenatal maternal stress. The first study that measured cognitive functioning (or cognitive regulation problems) with computerized and standardized tasks placing a load on PFC functions comes from the prospective study of the Van den Bergh and Marcoen group in the Netherlands (e.g., Van den Bergh & Marcoen, 2004). Van den Bergh and colleagues (Van den Bergh, Mennes, et al., 2005) reported that adolescents of mothers who experienced high levels of anxiety (state subscale of the State-Trait Anxiety Inventory, Spielberger, Gorsuch, & Lushene, 1970) during the second trimester of their pregnancy were reported to be more impulsive on visual attention control tasks compared to adolescents exposed to low to average levels of prenatal maternal anxiety. Specifically, adolescents of mothers who were highly anxious during the 12–22 weeks of pregnancy, but not later, responded faster and made more errors in the target present condition of the "endcoding" task compared to the low-average group, reflecting an impulsive response pattern. Importantly, this impulsive response pattern did not disappear

when controlling for performance on two subtests of the Wechsler Intelligence Scale for Children (WISC-R), suggesting a specific cognitive regulation impairment. Furthermore, as anxiety did not interact with memory load, this specific pattern of cognitive regulation impairment did not appear to be related to a working memory problem, nor to an impairment in a stop signal task tapping exogenous response control processes. Therefore, the authors concluded that the cognitive regulation problem of adolescents of mothers who were highly anxious at 12–22 weeks of pregnancy was related to altered endogenous response control processes. This control deficit, for instance, is expressed when individuals are required to continue the inhibition of a response for a longer time without external signals encouraging the inhibition.

Support for this interpretation was provided by a second study with the same group of adolescents (Van den Bergh et al., 2006). Performance on a computerized continuous performance task measuring sustained attention declined as the task progressed in 15-year-old boys of mothers with high levels of state anxiety during 12–22 weeks of their pregnancy, but not at later points in gestation. Specifically, these adolescent boys' processing speeds became slower and their reaction times became more variable as the task progressed compared to a group of adolescents of mothers with low to moderate levels of prenatal anxiety. These results indicated that boys, but not girls, of highly anxious mothers were less able than boys of low to moderate anxious mothers to sustain their attention and stay focused on the task at hand, thus showing impaired endogenous attention control (e.g., resisting thinking about other things; resisting looking away). Of note, no significant associations with antenatal maternal anxiety were found in the number of errors (neither commission nor omission errors) made. The fact, however, that these results held when controlling for two subtests of the WISC-R indicates that maternal anxiety was uniquely associated with sustained attention/endogenous response inhibition.

To further delineate the cognitive sequelae associated with antenatal maternal anxiety, Van den Bergh and colleagues (Mennes et al., 2006) reviewed recent neuroimaging studies to create a cortical map of regions commonly and selectively activated by well-known EF tasks. The pragmatic value of this cortical map was tested in a subsample of the previous reported adolescents who were now 17-years-old. Adolescents of mothers with high levels of anxiety during 12–22 weeks of their pregnancy performed significantly lower in tasks that required integration and control of different task parameters compared to adolescents of mothers with normal levels of antenatal anxiety. Specifically, the percentage of correct answers in a response-shifting task was lower overall—and especially during the incompatible trials—in the high maternal anxiety group as compared to the normal maternal anxiety group. Moreover, a decrease in performance when the cognitive load of dual tasks increased was observed in adolescents in the high maternal anxiety group. Together these results suggest that the adolescents in the high anxiety group experienced difficulties organizing their cognitive resources in order to handle two tasks at the same time. In contrast, working memory (N-back task), inhibition of a prepotent response (Go/NoGo task), and visual orienting of attention (visual cued-attention orientation task) were not impaired, suggesting that

adolescents of mothers experiencing high levels of anxiety during the second trimester performed selectively poorer in tasks that require subjects to perform two tasks simultaneously and switch between different task rules. This conclusion was based on the established cortical map found to be linked to a part of, or in cortical and subcortical regions linked to, the orbitofrontal cortex. Importantly, although several other areas were activated by dual- and response-shifting tasks, this part of the orbitofrontal cortex was found to respond exclusively during performance on these two tasks (and not during performance on the other EF tasks).

Further evidence of neurodevelopmental consequences in the offspring of maternal stress during pregnancy comes from the prospective study of the multi-investigator research program at the University of California, Irvine. The first study examined links between pregnancy-specific anxiety (a self-developed measure by Glynn, Schetter, Hobel, & Sandman, 2008) and prefrontal cortical volumes in 6- to 9-year-old children (Buss, Davis, Muftuler, Head, & Sandman, 2010). Pregnancy-specific anxiety at 19 weeks' gestation, but not at 25 and 31 weeks' gestation, was associated with diffuse cortical volume reductions (in gray matter) in the PFC, the premotor and temporal cortices, as well as the postcentral gyrus and the cerebellum extending to the middle occipital gyrus and the fusiform gyrus. Interestingly, the prefrontal regions that were found to be associated with high anxiety during pregnancy have been shown to be involved in the regulation of stress hormone secretion (Pruessner et al., 2008). These same brain regions appear to be particularly vulnerable to conditions of chronic stress due to their high density of glucocorticoid receptors (Sapolsky, Uno, Rebert, & Finch, 1990). Thus, high prenatal anxiety in mothers may increase the risk of higher stress susceptibility and reactivity in their developing children, rendering the children more vulnerable to neurodevelopmental and psychiatric disorders as well as cognitive and intellectual impairment.

In a second study, Buss and colleagues (2011) examined the association of pregnancy-specific anxiety with EF in a larger subset of the same cohort of 6–9 year-old children. High levels of maternal pregnancy-specific anxiety over the course of gestation were associated with lower inhibitory control (Flanker task), in girls only, and lower visuospatial working memory performance (Corsi block-tapping test), both in boys and girls. Specifically, girls showed slower reaction times as a function of maternal anxiety, and this difference was most pronounced in the incongruent trials. Of note, higher state anxiety and depression were also associated with lower visuospatial working memory performance. However, neither state anxiety nor depression explained any additional variance after accounting for pregnancy-specific anxiety. These results are especially interesting in light of the gray matter reductions in PFC regions in association with pregnancy-specific anxiety reported above (cf. Buss et al., 2010). A lack of power, though, prevented the authors from testing if PFC volume reductions mediated the association between pregnancy-specific anxiety and EF. Nevertheless, the fact that these associations between pregnancy-specific anxiety and child EF were observed among a group of low-risk women that did not smoke or consume alcohol during pregnancy and had a slightly higher than average socioeconomic status strengthens the results of the study.

A third study from the same cohort examined the associations of cortical changes and child externalizing behavior in 7-year-olds exposed to maternal depressive symptoms during pregnancy (Sandman, Buss, Head, & Davis, 2015). Using MRI, changes in cortical thickness were analyzed by measuring the width of the cortical gray matter layer that covers the surface of the brain. Significant cortical thinning (i.e., selective diminishment of gray matter brain regions which implies reduced synaptic density) primarily in children's right frontal lobes (right superior, medial orbital, and frontal pole regions of the PFC) was associated with exposure to prenatal maternal depression across gestation, with the strongest associations found at 25 weeks' gestation (compared to 19 and 31 weeks). This pattern of cortical thinning seems to be similar to patterns in depressed patients and individuals with risk of depression (Lagopoulos, Hermens, Naismith, Scott, & Hickie, 2012). Interestingly, the significant association between prenatal maternal depression and child externalizing behavior (assessed with the Child Behavior Checklist) was mediated by cortical thinning in prefrontal areas of the right hemisphere.

Further evidence of differential prenatal stress-dependent effects on neurodevelopmental consequences in the offspring comes from a retrospective study in Germany (Entringer, Buss et al., 2009). These authors hypothesized that if there is only a subtle vulnerability in subjects exposed to prenatal psychosocial stress, small differences between groups may not emerge under basal conditions but will emerge when a substantial challenge is imposed on the system. Indeed, young women whose mothers experienced a major negative life event during their pregnancy did not differ from a matched non-exposed comparison group in their working memory performance (item-recognition task). However, after hydrocortisone (cortisol) administration, women in the prenatal stress group showed significantly longer reaction times compared to women in the control group. These findings provide support for the potential modulatory effect of acute stress exposure (cortisol) on the association between prenatal stress exposure and subsequent working memory performance in young adults.

Finally, Pearson and colleagues (Pearson et al., 2016) examined prospective observational data from a large UK population cohort (Avon Longitudinal Study of Parents and Children, ALSPAC) looking at associations between prenatal maternal anxiety (anxiety items from the Crown-Crisp Index, Birtchnell, Evans, & Kennard, 1988), several EF measures at age 8, and academic achievement at the end of compulsory school at age 16. Prenatal anxiety (not specified at what time point) was neither associated with attentional control (basic form of a Stroop task), selective attention (baseline of Sky search task), nor attentional switching (Sky search task) after controlling for postnatal depression. However, there was evidence that prenatal anxiety was associated with impaired working memory (digit span and non-word memory). Interestingly, impaired working memory mediated the effect of prenatal anxiety to math grades at age 16, with 17% of the total association between prenatal anxiety and math being explained by indirect paths through working memory. A similar pattern was seen for language grades, but associations were confounded by maternal education. This is the first study to demonstrate that EF mediates the association between prenatal stress and later academic outcomes.

Taken together, these studies indicate that prenatal maternal stress (mostly anxiety in the second trimester) is associated with subtle changes in EF and the PFC in middle childhood, adolescence, and early adulthood. The specific findings, however, are not always consistent, and in some cases, they are sex-specific. For example, Buss and colleagues (2011) only found an association between maternal pregnancy-specific anxiety and inhibitory control in girls but not in boys, whereas Van den Bergh and colleagues (2006) detected impaired endogenous response inhibition in adolescent boys but not in girls. To date, few human studies have addressed sex-specific differences in child outcomes following prenatal stress exposure. Future research needs to further explore the possibility that differences in the effects of timing in boys and girls may be based on the differences in the amount of sex hormones in the developing fetus (de Bruijn, van Bakel, & van Baar, 2009).

With regard to which specific types of prenatal maternal emotional disturbances or stress have the strongest impact on child development, the reviewed studies indicate that maternal anxiety may be especially predictive for developmental outcomes. Whereas the Van den Bergh and Marcoen group as well as the Pearson study only included or analyzed anxiety measures during pregnancy, the multi-investigator research group from California assessed multiple measures of maternal stress during pregnancy, possibly allowing to draw conclusions about the most sensitive measure for developmental outcomes. This, however, was only possible in one of their studies (Buss et al., 2011), since selection of prenatal stress measures was reduced to only include one of the available measures in the two other studies reviewed above.

An important question with regard to fetal programming is the time period of pregnancy during which the fetus is most vulnerable to maternal stress. The finding of a specific time window makes it unlikely that the associations found can be explained by shared genetic variance only, as this does not explain why effects only involve prenatal maternal anxiety at a specific time period (here mostly in the second trimester) and not earlier in pregnancy or after birth. In most of the reviewed studies, the relationship seems to be more evident when stress by mothers is experienced in the second trimester (12–27 weeks)—although some studies did only find specific associations with some time points in the second trimester and not others (Buss et al., 2010; Sandman et al., 2015). In humans, key external markers of the PFC develop during gestational weeks 25–26 (Stiles & Jernigan, 2010) and key brain developmental processes such as neuron proliferation, migration, and differentiation take place between gestational weeks 8 and 24 in brain areas connected to the PFC (e.g., amygdala, ACC, brain stem, and basal ganglia) (Levitt, 2003). Therefore, it is plausible that in the reviewed studies, physiological factors related to maternal anxiety interfered with some of the complex neurodevelopmental processes taking place at that gestation period. However, the level of antenatal maternal anxiety before 12 weeks of gestation and its association with child EF remains unknown. Moreover, the effect of timing may be due to the fact that pregnancy anxiety is highest at 19 weeks' gestation and decreases over the course of gestation, which is in line with previous observations of reduced physiological

and psychological stress reactivity as pregnancy advances (de Weerth & Buitelaar, 2005; Glynn et al., 2008). In general, there is currently little agreement about the gestational age most sensitive to maternal prenatal stress, and the fact that several gestational ages have been reported to be critical for the long-term effects of antenatal anxiety/stress may indicate that different mechanisms are operating at different stages (Van den Bergh, Mulder, et al., 2005).

There is now ample evidence suggesting that prenatal maternal stress is associated with long-term neurodevelopmental alterations in the offspring: Across all studies, prenatal stress was associated with each one of the EF components—inhibition, shifting, and working memory. These findings, however, lack robustness as in several studies multiple EF tasks tapping various EF components have been administered, but associations with prenatal maternal stress were only found for selected EF tasks (Mennes et al., 2006; Pearson et al., 2016; Van den Bergh, Mennes, et al., 2005). Therefore, it is too early to draw firm conclusions as to which specific aspects of children's EF including underlying PFC structures and functions may be altered following exposure to prenatal maternal stress. For instance, some authors report impaired performance on working memory tasks (Buss et al., 2011; Pearson et al., 2016), others do not (Mennes et al., 2006; Van den Bergh, Mennes, et al., 2005), and still others only find a difference between prenatally stress exposed individuals and non-exposed individuals after hydrocortisone administration (Entringer, Kumsta, et al. 2009). A way to reconcile these seeming inconsistencies rests in the idea that earlier in development (early-to-middle childhood), prenatal stress effects on working memory are more pervasive, whereas later in development (adolescence and early adulthood), the subtle vulnerability in these subjects can only be detected when a challenge is imposed on the system. This interpretation, however, is speculative at best and requires further investigation in future studies. Nevertheless, of particular interest are the studies (Buss et al., 2010; Entringer, Buss, et al., 2009) that provide indirect evidence that prenatal maternal stress affects brain development in a way that may also affect the regulation of stress (HPA axis) in subsequent offspring.

## Prenatal Maternal Stress Shaping Child Stress Regulation

The HPA axis may play a significant role in mediating the effects of maternal stress/anxiety on child EF. Animal models have helped illustrate a central role for the HPA axis in mediating prenatal stress effects on behavioral or cognitive alterations in the offspring (M. Weinstock, 2008). Emerging evidence shows that prenatal maternal stress also affects the HPA axis in humans (Glover et al., 2010). Thus, evaluating how children's stress regulation is affected by prenatal stress exposure should help elucidate our understanding of potential pathways through which the development of EF may be affected by prenatal maternal stress.

Two main systems comprise the psychobiology of stress: the HPA axis with its end product cortisol and the adrenal medullary system (SAM, which is part of the autonomic nervous system or ANS) with its end products epinephrine and norepinephrine. The acute secretion of glucocorticoids (called corticosterone in animals and cortisol in humans) and catecholamines (epinephrine and norepinephrine, also known as adrenaline) constitutes the primary agents in the chain of hormonal events triggered in response to stress. In response to stress, these neurochemicals act to give rise to the "fight-or-flight response" reflected in increased heart rate and blood pressure. In this way, stress responses serve an adaptive survival mechanism consisting of a carefully orchestrated yet near-instantaneous sequence of hormonal changes and physiological responses enabling an individual to react quickly to threat. However, frequent activation can result in a permanent dysregulation of the HPA axis, particularly when experienced during phases of rapid brain development such as the prenatal period and infancy (Gunnar & Quevedo, 2007). Moreover, chronic stress exposure has long-term effects on physical and psychological health such as high blood pressure, increased risk of infection, arterial disease, and brain changes that may contribute to anxiety, depression, and addiction (for a general review, see McEwen, 2000).

A series of developmental studies in animals, both rodent and non-human primate, established the central role of the HPA axis in mediating prenatal stress effects in both mother and offspring (M. Weinstock, 2008), although other neurocircuits, such as the dopaminergic and serotonergic systems, are also likely to be involved. In rodents, many studies have found that prenatal stress causes both an increase in basal levels and an increase in corticosterone response in the offspring (although variability of the findings is high). In humans, equivalent work is only just starting, but there is suggestive evidence that there may be similar reprogramming effects (Glover et al., 2010). Whereas maternal stress could affect fetal development by exposure to stress hormones that are transported through the placenta, noradrenaline does not appear to cross from mother to fetus (Giannakoulopoulos, Teixeira, Fisk, & Glover, 1999) but may have an indirect effect via changes in the maternal muscular or vascular tone which in turn may cause stress to the fetus and raise cortisol levels (Van den Bergh, Mulder, et al., 2005). We will now review recent studies examining long-term effects of prenatal maternal stress on basal cortisol levels and cortisol responses to stress in the offspring.

Glover and colleagues' (2010) review of the literature revealed 11 studies in the last 10 years that have examined the association between prenatal maternal mood or stress and the function of the HPA axis in human offspring. The method of measuring the outcome varied from diurnal saliva cortisol to single basal samples, or saliva or plasma cortisol and ACTH response to a stressor. The age of the subjects ranged from 1 week up to young adulthood. All studies found that there were associations between prenatal maternal stress and some aspect of HPA axis function in the child. However, perhaps unsurprisingly, the nature of this association varied and solid replications seem to be missing. Nevertheless, the authors concluded that the reviewed studies mostly suggested that prenatal stress or anxiety is associated

with raised basal cortisol or raised cortisol reactivity in the offspring. Furthermore, the effect was particularly apparent in the children of mothers exposed in their third, rather than earlier trimesters. Note that for the relationship between prenatal maternal stress and EF/PFC, the second trimester seems to be the most sensitive period, indicating that a different—yet to be established—mechanism may underlie the association between prenatal maternal stress and child stress regulation as opposed to prenatal maternal stress and EF. Most importantly, though, as mentioned before, the finding of a specific time window supports the possibility of fetal programming, rather than a shared genetic vulnerability. Finally, in their review, there was only one study (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008) that provided evidence that an altered diurnal cortisol profile associated with prenatal anxiety was mediating an altered behavioral phenotype (i.e., depressive symptoms) in adolescent girls (but not in boys).

Recently published studies that were not part of Glover and colleague's review expand on their conclusions and provide some interesting new insights. O'Donnell and colleagues (2013), for instance, followed 889 mother–child dyads and found that high levels of mother's anxiety in the third trimester predicted both a reduced cortisol awakening response (CAR) and a reduced diurnal cortisol decline (DCD) among 15-year-old males and females. Interestingly and in contrast, an earlier study (that was part of Glover's review) based on a smaller selection ($n$ = 74) of this sample showed that higher maternal prenatal anxiety in the third trimester predicted higher morning cortisol levels (single assessment after awakening) among 10-year-olds (O'Connor et al., 2005). The reduced CAR and DCD in adolescents, however, are in line with Van den Bergh and colleagues' (2008) findings, indicating that maternal anxiety during the second trimester predicted a combination of a low morning cortisol level (single assessment after awakening) and a reduced DCD among 14- to 15-year-olds. These findings provide preliminary evidence that early stress exposure may be associated with elevated or hyperactivation of the HPA axis that, over time, leads to adrenocortical counter-regulation and hypo-activation (Miller, Chen, & Zhou, 2007). More research, however, is needed to confirm this longitudinal pattern of the HPA axis following prenatal stress exposure, possibly getting exhausted over time, resulting in long-term dampened stress responses. To date, very few studies have assessed diurnal cortisol patterns in middle childhood and adolescence in the offspring of maternal stress during pregnancy, and findings are not always consistent (see Vänskä et al., 2015 for an intensified CAR but non-affected DCD in 10- to 12-year-olds) or applied analytical approaches prevent to compare specific findings with regard to CAR and DCD (Simons, Beijers, Cillessen, & de Weerth, 2015).

Furthermore, dysregulation of the HPA axis following prenatal stress exposure may not be detectable in diurnal cortisol patterns, but in stress reactivity. For instance, Entringer and colleagues (2009) did not find differences in the diurnal patterns of young adults whose mothers experienced severe stress during their pregnancy compared to an age-matched comparison group, but in stress responses to the Trier Social Stress Test (TSST). In particular, pre-TSST cortisol levels were lower (possibly reflecting hypo-activation), whereas the increase in cortisol in

response to the TSST was higher in exposed subjects compared to subjects from the comparison group. This pattern of raised cortisol reactivity to a stressor as noted in Glover's review has also been confirmed by recent studies in infants (Davis, Glynn, Waffarn, & Sandman, 2011) although some found that the direction of the effect depends on infant age and/or the nature of the stressor (Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011).

Additionally, not all children or adolescents are equally affected by prenatal maternal stress. A recent study (Buchmann et al., 2014) shows that in 19 year-old adolescents exposed to prenatal maternal stress, only carriers of the DRD4 seven-repeat allele were found to have an altered (i.e., attenuated) cortisol secretion during the TSST. These results suggest that prenatal maternal stress may only affect the HPA axis of carriers of certain "risk alleles" (the DRD4 7r allele has been shown to be a "risk allele" for externalizing problems, particularly in the presence of environmental adversity; Bakermans-Kranenburg & van IJzendoorn, 2006). Importantly, the notion of a "biological sensitivity to context" (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011) illustrates how an allelic variation in the context of both early (i.e., fetal) and ongoing (i.e., postnatal/childhood) life experience shapes adaptation and diversity of child developmental outcomes. In this context, allelic variations may confer advantages for some children in supportive environments, but disadvantages when facing social adversity in the context of maternal depression (Boyce & Ellis, 2005). Intriguingly, the biological sensitivity to context concept offers a critical perspective that allows us to move our thinking about fetal programming from "invariant" developmental outcomes associated with early adverse exposure to a perspective that outcomes in childhood represent interactions between biological (a child's genotype) and contextual (maternal mood) variables enabling both positive and negative outcomes. Further, DNA methylation—an epigenetic mechanism—may be a crucial component of genetic differential susceptibility/biological sensitivity to context (see Chap. 7 by Mulder, Rijlaarsdam & Van IJzendoorn).

Taken together, emerging evidence suggests that prenatal maternal stress affects both diurnal profiles and reactivity patterns of the HPA axis in the offspring. Studies providing evidence that an altered HPA axis mediates the association of prenatal maternal stress and neurodevelopmental outcomes, however, are still missing and needed (Glover et al., 2010). Detecting these relationships, though, may be quite challenging as studies have shown that the relation between HPA axis reactivity and measures of EF is of a complex nature (e.g., Blair, Granger, & Peters Razza, 2005; see also Chap. 8 by Finegood & Blair).

Whether or not prenatal maternal stress is initially associated with a hyperactivation of the HPA axis and later in development with a hypo-activation needs to be determined. Hyperactivation is in general suggested to be indicative of a currently stressed, hyperactive HPA axis (e.g., McEwen & Wingfield, 2003), whereas hypo-activation reflects reduced cortisol production, possibly due to more chronic stress that has caused "exhaustment" of the mechanisms underlying the HPA axis (e.g., Doom, Cicchetti, & Rogosch, 2014). In line with this, a recent meta-analysis on chronic stress in adults (G. E. Miller et al., 2007) found that the more months

that had elapsed since the stress first emerged, the lower a person's morning cortisol, daily cortisol volume, and ACTH levels. In contrast, when chronic stressors were still present in a person's life (e.g., unemployment), morning, afternoon, evening, and daily cortisol outputs were significantly higher. Importantly though, exposure to chronic stress in the early years of life, when the nervous system is still developing, may result in a distinct pattern of dysregulation.

## Molecules Matter Too: In Utero Exposure to Antidepressants

With increased understanding that prenatal maternal stress and related mood disturbances have consequences for child behavior and development, antenatal mood disorders are treated with selective serotonin reuptake inhibitor (SSRI) antidepressants. This is raising critical and unanswered questions about the long-term impact of serotonin exposure in combination with maternal mood disturbances on the developing brain. Importantly, both exposures (i.e., maternal mood and SSRIs) are increasingly common and the developmental impact of SSRIs is often indistinguishable from the impact of antenatal maternal mood disturbances (Oberlander, Gingrich, & Ansorge, 2009). Maternal mood disturbances during gestation occur in 10–20% of pregnancies, and up to a third of all depressed mothers have been reported to be treated with an SSRI during pregnancy (Oberlander, Warburton, Misri, Aghajanian, & Hertzman, 2006). SSRIs primarily act by blocking the serotonin transporter (5-HTT) leading to increased intrasynaptic 5-HT levels, thereby potentiating 5-HT neural transmission. SSRIs readily cross the placenta and the blood–brain barrier (Laine, Heikkinen, Ekblad, & Kero, 2003), thereby altering fetal central 5-HT signaling. Such exposure adds a new dimension to how maternal mood disturbances including their treatment by antidepressants during pregnancy potentially shape early human development, possibly via changes in levels of the central neurotransmitter 5-HT during critical periods of neurodevelopment. Maternal mood symptoms, however, do not have to reach clinical levels to have an impact on development (Dunkel Schetter & Tanner, 2012). Our current understanding of negative affective states in pregnancy is based largely on studies—such as reviewed above—of symptomatology (i.e., symptoms of anxiety and depression during pregnancy, as measured with screening tools such as the Edinburgh Postpartum Depression Scale (EPDS)) as opposed to confirmed diagnoses of mental disorders. Further, even in the presence of prenatal SSRI antidepressant treatment, maternal mood disturbances can still have an impact on infant development (Weikum, Oberlander, Hensch, & Werker, 2012). Clearly, regardless of SSRI treatment, maternal mood during pregnancy can affect infant and child development for better *and* worse.

Because prenatal SSRI exposure has not been associated with gross structural teratogenic effects, they are often considered for antenatal therapy (Misri et al., 2006), with the expectation that they confer benefit to mothers (improved prenatal

mood) and by extension to her offspring (i.e., via improved prenatal and possibly postnatal maternal mood). However, a substantial number of pregnant women with depression and anxiety remain partially or fully symptomatic even after treatment (Cohen et al., 2006). Failure to achieve remission leaves mothers' mood disturbances (and inherent confounding factors, such as smoking, alcohol, and socioeconomic status) and antenatal SSRI exposure to continue incurring consequences for mothers, and cognitive and emotional child development. Thus, mothers and clinicians must balance the potential consequences of untreated or poorly treated mental illness against risks of antenatal psychopharmacotherapy.

Central to our understanding of how in utero SSRI exposure influences early brain development is the diverse role played by the neurotransmitter 5-HT and its role as a mediator between early life experience and subsequent development. Serotonin is a phylogenetically ancient neurotransmitter widely distributed throughout the entire brain. As early as 5 weeks of gestation, serotonergic neurons are already evident in the human brain (Sundstrom et al., 1993), and by 15 weeks, the raphe nuclei already contain 5-HT neurons (Takahashi, Nakashima, Ohama, Takeda, & Ikuta, 1986). Serotonin plays two critical roles: First, during early developmental periods, 5-HT acts as a growth factor, regulating the development of its own and related neural systems (Whitaker-Azmitia, Druse, Walker, & Lauder, 1996). As a trophic factor, 5-HT also regulates cell division, differentiation, migration, myelination, synaptogenesis, and dendritic pruning (Gaspar, Cases, & Maroteaux, 2003). Then in the mature brain, 5-HT acts as a modulatory neurotransmitter regulating cognition, attention, emotion, learning, sleep, arousal, and stress responsivity. Given these dual roles (i.e., growth and nurturance), it is conceivable that altering 5-HT levels during early sensitive periods might have developmentally lasting consequences for stress and self-regulation.

Effects are evident even before SSRI exposure ends during gestation. Changes in fetal neurobehavioral disturbances include disrupted non-rapid eye movement sleep (Mulder, Ververs, de Heus, & Visser, 2011), reduced brain flow indices (Rurak et al., 2011), and reduced fetal heart rate variability (Rurak et al., 2011). Importantly, such effects are apparent before and following a typical daily maternal SSRI dose, possibly reflecting an early and sustained effect on brain function beyond an acute medication-related effect. Soon after the introduction of SSRI antidepressants in 1988 to manage mood disorders during pregnancy, reports emerged of newborn neurobehavioral disturbances (irritability, weak or absent cry, increased motor activity) or "withdrawal" symptoms, shorter mean gestational age, and lower birthweight (Moses-Kolko et al., 2005). SSRI-exposed neonates have been reported to be more motorically active and tremulous, and had lower heart rate variability and state regulation (Zeskind & Stephens, 2004). Some of these behaviors may be predictors of altered behavior in childhood (Oberlander et al., 2007), and these effects may be mediated through the pharmacological variables (Laine et al., 2003; Oberlander et al., 2004).

## Prenatal SSRI Exposure Shaping Child Stress Regulation

Serotonin plays central roles in the early development and function of the two key stress response systems—the HPA axis and the ANS system. Both systems are highly interrelated, and possibly via 5-HT, they are exquisitely sensitive to the effects of early adverse experience (Laplante, Diorio, & Meaney, 2002). Alterations in HPA function that frequently characterize anxiety and depressive disorders (Lowry, 2002) may link altered serotonin levels to neuroendocrine stress regulation and psychopathology (Chrousos, 2000; Homberg & Contet, 2009; McEwen, 2005). In animal models, changing prenatal serotonergic tone affects neurodevelopmental processes associated with stress regulation (Ansorge, Hen, & Gingrich, 2007). Importantly, the relationship between 5-HT and stress reactivity is bidirectional. That is, stressors may alter 5-HT metabolism as well as bias how an individual copes with subsequent stressful challenges (L. Weinstock, Cohen, Bailey, Blatman, & Rosenbaum, 2001; M. Weinstock, 2001). Chronic unpredictable stress during pregnancy alters 5-HT levels that have lasting effects on monoaminergic system function and behavior in rodent offspring (Schneider, Roughton, Koehler, & Lubach, 1999; Weinberg & Tronick, 1998). Prenatal stress lowers plasma and hippocampal serotonergic activity (Peters, 1990) leading to reduced HPA adaptation to stressors reflecting 5-HT's role in HPA function (Firk & Markus, 2007). Serotonin and cardiovascular/autonomic stress regulation are also highly interrelated via links between reflex control of parasympathetic outflow to the heart that involve regulation of central sympathetic and parasympathetic autonomic tone (Ramage, 2001). Given these relationships, it is conceivable that early manipulation of 5-HT levels (i.e., in utero or early life in animal models) alters subsequent stress regulation (Ishiwata, Shiga, & Okado, 2005).

In human newborns, prenatal SSRI exposure is associated with altered stress regulation. A case in point is the duration of facial action and cardiac responses in response to an acute painful event—particularly, parasympathetic cardiac activity is shorter and less intense in SSRI-exposed compared to non-exposed neonates (Oberlander et al., 2002). Altered pain reactivity persists at 2 months of age, after controlling for postnatal drug level and maternal mood (Oberlander et al., 2005). Neurobehavioral changes have been associated with measures of central serotonergic levels in utero and levels of the serotonin metabolite 5-HIAA specifically (Laine et al., 2003). Further, SSRI-exposed neonates exhibit lower cord blood levels of a biomarker of early brain maturation and central serotonergic function (i.e., the astroglial-specific calcium-binding protein, S100B, Hilli et al., 2009; Pawluski, Galea, Brain, Papsdorf, & Oberlander, 2009) and increased norepinephrine metabolite levels (Davidson et al., 2009).

SSRIs are thought to act via increased central 5-HT activity to "normalize" the hypercortisolism and stress dysregulation (Barden, Reul, & Holsboer, 1995) that characterizes depression (Gillespie & Nemeroff, 2005). In an animal model, Ishiwata and colleagues (2005) observed that early SSRI treatment of prenatally stressed mice "normalized" corticosterone responses to a subsequent stressor,

increased 5-HT turnover in the hippocampus, and restored the ability to learn spatial information compared with the effects of exposure to prenatal stress alone. In human infants, effects of SSRI exposure on stress regulation may only became evident in the presence of a specific postnatal environment (Oberlander et al., 2008). That is, in response to a non-noxious challenge, SSRI-exposed and non-exposed infants exhibited similar salivary cortisol levels. However, when infant feeding status was considered, differences associated with SSRI exposure emerged. Specifically, compared with breastfed SSRI-exposed and breastfed non-exposed infants, the latter showed a blunted post-stress cortisol response. These findings suggest an SSRI-related effect on the HPA stress system that only becomes apparent in a particular postnatal maternal caregiving context.

Importantly, altered HPA function is characteristic of mood disorders such as anxiety and depression (Fuller, 1996; Lowry, 2002) and links stress regulation with altered serotonergic tone as a key related risk factor for psychopathology (Chrousos, 2000; Homberg & Contet, 2009; McEwen, 2005). Moreover, disruption of 5-HT signaling is considered a key developmental component underlying a number of neuropsychiatric disorders, such as schizophrenia, affective disorders, anxiety, and autism (Bonnin & Levitt, 2011; Chugani et al., 1999; Sodhi & Sanders-Bush, 2004; Whitaker-Azmitia, 2001). With this perspective, the importance of understanding the implications of changing 5-HT signaling during critical periods and altered stress regulation in the emergence of neurodevelopment disorders becomes particularly evident. These concerns have been further raised by recent studies linking in utero SSRI exposure to an increased risk of complex development disorders such as autism spectrum disorders (Boukhris, Sheehy, Mottron, & Berard, 2016; Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Man et al., 2015; Rai et al., 2013), anxiety (Hanley, Brain, & Oberlander, 2015), depression (Malm et al., 2016), and ADHD (Clements et al., 2015) during childhood. Whether these developmental outcomes reflect a long-term impact of increased serotonin signaling associated with prenatal SSRI exposure, maternal mood disturbances, or a genetic predisposition for these developmental disorders remains a focus for future research.

In summarizing our current knowledge about whether SSRI treatment can potentially have advantages or disadvantages for development, three key themes emerge: First, while prenatal SSRIs alter central 5-HT levels, developmental outcomes do not necessarily reflect a "main effects" story that can be easily attributed to one causal factor (i.e., maternal mood, genetics, or the drug itself). Rather, outcomes in this setting represent an interplay between maternal mood, pharmacological, genetic, and contextual factors related to both mother and her developing child. Second, while SSRIs are typically prescribed during pregnancy with the expectation of optimizing maternal mood and by extension infant developmental health, children may continue to be at risk as maternal pharmacotherapy might not "buffer" or protect them from antenatal maternal mood disturbances (i.e., a lack of drug efficacy). Finally, this is a context of developmental vulnerability *and* plasticity. Therefore, identifying settings whereby individuals might benefit from prenatal maternal pharmacotherapy remains a key and pressing question. Longitudinal

study designs that integrate a maternal and infant/child developmental perspective should help us move away from characterizing prenatal SSRI exposure, maternal mood, or even genetic variations as "bad" or "harmful" and rather look at these as adversity- or risk-related factors that heighten or lessen vulnerability associated with early development.

## Putting It All Together

The notion that a mother's mood during pregnancy shapes the developing fetal brain and influences risks of mental and physical health across the life span has been a part of popular beliefs for millennia (Murphy, 2010). More than six decades of empirical research has shed light onto the role a mother's psychological state in pregnancy plays for her offspring, although the underlying specific mechanisms remain unclear. In this chapter, we have provided an overview of more recent studies examining the role of prenatal maternal stress (stress exposure, anxiety, depression, and antidepressants) on developmental origins of self-regulation reflected by neurobiological processes such as EF and HPA axis functioning in the offspring spanning from early childhood to early adulthood. These findings highlight the importance of incorporating the prenatal period into our models of parent–child interactions. Some of the stressors that commonly affect women in pregnancy (e.g., low material resources, employment conditions, and strain in intimate relationships) are the same that underlie parenting stress, as discussed in several other chapters of this book.

Understanding the role of maternal stress during gestation in shaping child development offers important insights that may explain why variations in early typical environment are associated with shaping both developmental risk *and* resilience. Importantly, not all gestational stress associated with maternal mood disorders results in negative developmental outcomes; ultimately, understanding the complex relation between maternal stress during pregnancy and effects on children after birth requires the systematic unpacking of interrelations between micro-level factors (e.g., genes), macro-level factors (e.g., medications), and niche (e.g., where the child lives), all couched within time and timing.

Given the central role of EF for child developmental health and the fact that stress early in life may have a particularly large impact on PFC structure and function, this chapter reviewed evidence linking prenatal maternal stress to long-term neurocognitive alterations in the offspring. Across all studies, evidence was found that prenatal stress is associated with each one of the EF components: inhibition (Buss et al., 2011; Van den Bergh, Mennes, et al., 2005), shifting (Mennes et al., 2006), and working memory (Buss et al., 2011; Entringer, Buss, et al., 2009; Pearson et al., 2016), as well as with cortical reductions in the PFC (Buss et al., 2010) and cortical thinning in the right frontal lobes (Sandman et al., 2015). However, no conclusions can be firmly drawn as to which specific aspects of children's EF including underlying PFC structures and functions may be most

strongly or consistently altered following exposure to prenatal maternal stress. Future research is needed to examine how prenatal stress shapes EF during childhood and determine whether the functional relation between early stress exposure and EF performance is curvilinear (Arnsten, 2009; de Kloet et al., 1999; Lupien et al., 2007), such that moderate levels of stress exposure may actually enhance EF performance. Evidence that the relationship between prenatal stress exposure and child outcomes may not be necessarily linear is supported by DiPietro and colleagues' (2006) findings, showing that exposure to moderate levels of prenatal stress may actually advance motor and mental development. Critical insight may also be gained by investigating whether child EF mediates the association between prenatal stress exposure and later emotional and behavioral outcomes. Such findings may allow us to understand how exposure to prenatal stress affects children's functioning *across* different developmental domains.

One of the most studied mechanisms involved in fetal programming is the HPA axis, which may play a significant role in mediating the effects of prenatal maternal stress on child EF. We reviewed emerging evidence linking prenatal stress to diurnal and reactivity patterns of the HPA axis in the offspring. Whereas variability in the findings is high, many studies have found that prenatal stress is associated with raised basal and reactivity cortisol levels in infancy (Davis et al., 2011; Glover et al., 2010; Tollenaar et al., 2011), and early-to-middle childhood (Glover et al., 2010; O'Connor et al., 2005; Simons et al., 2015). Later in development, some studies have found either reduced CAR and DCD in adolescents (O'Donnell et al., 2013; Van den Bergh et al., 2008) or no detectable differences in diurnal patterns among young adults exposed to early stress vs. an age-matched comparison group (Entringer, Kumsta, et al., 2009). In this later sample, however, differences between the two groups were found in stress reactivity with raised cortisol reactivity during the TSST for the early stress group. Another study (Buchmann et al., 2014), however, only found attenuated cortisol secretion during the TSST for a subgroup of adolescents (DRD4 7r allele carriers) following prenatal stress exposure. Future research may clarify for whom, in which domain/situation, and during which developmental stage prenatal stress exposure is associated with dysregulation of the HPA axis.

Whether alterations in HPA axis function mediate the association between early stress exposure and altered behavioral outcomes (Van den Bergh et al., 2008) remains a critical question. Alternatively, a child's stress regulation may moderate the association between prenatal stress exposure and later child outcomes. As Entringer and colleagues (2009) have shown, acute stress exposure can have a modulatory effect on the association between prenatal stress exposure and subsequent working memory performance in young adults. Thus, subtle vulnerabilities in the offspring of prenatal stress may be found in the intricate interplay between stress regulation and EF.

Importantly, not all children are affected in the same fashion by prenatal maternal stress and some may even be positively affected, raising questions about the role of genetic and epigenetic influences that shape interactions between early experience and developmental outcomes. As brain development is a product of the

dynamic, bidirectional interplay between the individual's genotype and the nature of the early environment, a number of genetic factors (DRD4r, SERT, and COMT) have been identified that determine how children respond to various exposures. While this chapter did not specifically review studies examining the idea of "biological sensitivity to context" (Ellis et al., 2011), there is supporting evidence for it (Buchmann et al., 2014; Weikum et al., 2013). For instance, Pluess and colleagues (2011) have shown that the association between maternal anxiety during pregnancy and negative emotionality in early infancy was only significant in infants carrying one or more copies of the 5-HTTLPR short allele but not in those homozygous for the long allele. In this way, the 5-HTTLPR allelic variations might increase vulnerability to adverse environmental influences as early as the fetal period for some, while in other settings, 5-HTTLPR allelic variations may be associated with resiliency for other infants (Weikum et al., 2013).

The combination of early life stress, genetics, and ongoing challenge may ultimately shape or calibrate individual responsiveness to subsequent stress and vulnerability for behavioral or psychiatric disorders (Charney & Manji, 2004). Recent work with rodents suggests that long-term behavioral outcomes are determined by characteristics of both the pre- and postnatal environment (Francis, Szegda, Campbell, Martin, & Insel, 2003). The interactive effects of pre- and postnatal environmental influences represent an important area for future investigation. In fact, the congruence between prenatal and postnatal environments may be crucial. For instance, Sandman and colleagues (2012) found increased motor and mental development during the first year of life among infants whose mothers experienced congruent levels of depressive symptoms during and after pregnancy, even when the levels of symptoms were relatively high and the prenatal and postnatal environments were unfavorable. In this sense, prenatal environments prepare the fetus for postnatal life and confer an adaptive advantage for critical survival functions during early development. Furthermore, maternal prenatal and postnatal mental health problems may be differentially associated with later outcomes in the offspring. For instance, Vänskä et al., (2015) showed that both maternal prenatal and postnatal mental health problems predicted children's later stress regulation, but in unique ways.

In conclusion, we presented evidence that perinatal maternal stress shapes key elements of self-regulatory abilities during childhood. Conceptualization of these associations has drawn on the concept of fetal programming (Barker, 2003) which implies that changes in the fetal environment may shape a "predictive adaptive response" in which fetal development sets a forecast for a place in the world ahead (Gluckman & Hanson, 2005). Altered PFC function and stress regulation are not inevitably associated with dysfunctional outcomes. Increasingly, research is pointing to the possibility that early stress exposure works to "calibrate" developmental systems that only become "vulnerable" or "resilent" in particular childhood contexts (Glover, 2011). In this way, whether via developmental alterations in serotonin signaling or altered levels of cortisol, maternal mood during gestation may shape a sensitivity to negative and positive life experiences that predicts variations in long-term behavioral and psychiatric health and illness (Homberg, Schubert, & Gaspar, 2010).

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## References

Alexander, J. K., Hillier, A., Smith, R. M., Tivarus, M. E., & Beversdorf, D. Q. (2007). Beta-adrenergic modulation of cognitive flexibility during stress. *Journal of Cognitive Neuroscience, 19,* 468–478.

Allister, L., Lester, B. M., Carr, S., & Liu, J. (2001). The effects of maternal depression on fetal heart rate response to vibroacoustic stimulation. *Developmental Neuropsychology, 20*, 639–651.

Ansorge, M. S., Hen, R., & Gingrich, J. A. (2007). Neurodevelopmental origins of depressive disorders. *Current Opinion in Pharmacology, 7,* 8–17.

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Review Neuroscience, 10,* 410–422.

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48,* 406–409.

Barden, N., Reul, J. M., & Holsboer, F. (1995). Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? *Trends in Neuroscience, 18,* 6–11.

Barker, D. J. (2003). The developmental origins of adult disease. *European Journal of Epidemiology, 18,* 733–736.

Barrett, J., & Fleming, A. (2011). Annual research review: All mothers are not created equal: Neural and psychobiological perspectives on mothering and the importance of individual differences. *Journal of Child Psychology and Psychiatry, 52,* 368–397.

Baumeister, R. F., & Vohs, K. D. (Eds.). (2004). *Handbook of self-regulation: Research, theory, and applications*. New York: Guilford Press.

Bell, M. A., & Deater-Deckard, K. (2007). Biological systems and the development of self-regulation: Integrating behavior, genetics, and psychophysiology. *Journal of Developmental and Behavioral Pediatrics, 28,* 409–420.

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135,* 885–908.

Bennett, H. A., Einarson, A., Taddio, A., Koren, G., & Einarson, T. R. (2004). Prevalence of depression during pregnancy: Systematic review. *Obstetrics and Gynecology, 103,* 698–709.

Bernier, A., Carlson, S. M., & Whipple, N. (2010). From external regulation to self-regulation: Early parenting precursors of young children's executive functioning. *Child Development, 81,* 326–339.

Beydoun, H., & Saftlas, A. F. (2008). Physical and mental health outcomes of prenatal maternal stress in human and animal studies: A review of recent evidence. *Paediatric and Perinatal Epidemiology, 290,* 595–596.

Birtchnell, J., Evans, C., & Kennard, J. (1988). The total score of the crown-crisp experiential index: A useful and valid measure of psychoneurotic pathology. *British Journal of Medical Psychology, 61,* 255–266.

Blair, C. (2002). School readiness: Integrating cognition and emotion in a neurobiological conceptualization of children's functioning at school entry. *American Psychologist, 57,* 111–127.

Blair, C., Granger, D., & Peters Razza, R. (2005). Cortisol reactivity is positively related to executive function in preschool children attending head start. *Child Development, 76,* 554–567.

Blair, C., Granger, D. A., Willoughby, M., Mills-Koonce, R., Cox, M., Greenberg, M. T., … & F. L. P. I. (2011). Salivary cortisol mediates effects of poverty and parenting on executive functions in early childhood. *Child Development, 82*, 1970–1984.

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in Kindergarten. *Child Development, 78,* 647–663.

Bonnin, A., & Levitt, P. (2011). Fetal, maternal, and placental sources of serotonin and new implications for developmental programming of the brain. *Neuroscience, 197,* 1–7.

Boukhris, T., Sheehy, O., Mottron, L., & Berard, A. (2016). Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. *JAMA Pediatrics, 170,* 117–124.

Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: An evolutionary-developmental theory of the origins and functions of stress reactivity. *Developmental Psychopathology, 17,* 271–301.

Buchmann, A. F., Zohsel, K., Blomeyer, D., Hohm, E., Hohmann, S., Jennen-Steinmetz, C., et al. (2014). Interaction between prenatal stress and dopamine D4 receptor genotype in predicting aggression and cortisol levels in young adults. *Psychopharmacology (Berl), 231,* 3089–3097.

Buss, C., Davis, E. P., Hobel, C. J., & Sandman, C. A. (2011). Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. *Stress, 14,* 665–676.

Buss, C., Davis, E. P., Muftuler, L. T., Head, K., & Sandman, C. A. (2010). High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6–9-year-old children. *Psychoneuroendocrinology, 35,* 141–153.

Calkins, S. D., & Howse, R. B. (2004). Individual differences in self-regulation: Implications for childhood adjustment. In P. Philippot & R. S. Feldman (Eds.), *The regulation of emotion* (pp. 307–332). Mahwah, NJ: Lawrence Erlbaum.

Calkins, S. D., & Williford, A. P. (2009). Taming the terrible twos: Self-regulation and school readiness. In O. A. Barbarin & B. H. Wasik (Eds.), *Handbook of child development and early education: Research to practice* (pp. 172–198). New York: Guilford Press.

Charney, D. S., & Manji, H. K. (2004). Life stress, genes, and depression: Multiple pathways lead to increased risk and new opportunities for intervention. *Science Signaling, 2004*, 5.

Chrousos, G. P. (2000). The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: Neuro-endocrine and target tissue-related causes. *International Journal of Obesity Related Metabolic Disorders, 24*(Suppl 2), S50–S55.

Chugani, D. C., Niimura, K., Chaturvedi, S., Muzik, O., Fakhouri, M., Lee, M. L., et al. (1999). Increased brain serotonin synthesis in migraine. *Neurology, 53,* 1473–1479.

Clements, C. C., Castro, V. M., Blumenthal, S. R., Rosenfield, H. R., Murphy, S. N., Fava, M., et al. (2015). Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Molecular Psychiatry, 20,* 727–734.

Cohen, L. S., Altshuler, L. L., Harlow, B. L., Nonacs, R., Newport, D. J., Viguera, A. C., et al. (2006). Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA, 295,* 499–507.

Croen, L. A., Grether, J. K., Yoshida, C. K., Odouli, R., & Hendrick, V. (2011). Antidepressant use during pregnancy and childhood autism spectrum disorders. *Archives of General Psychiatry, 68,* 1104–1112.

Davidson, S., Prokonov, D., Taler, M., Maayan, R., Harell, D., Gil-Ad, I., et al. (2009). Effect of exposure to selective serotonin reuptake inhibitors in utero on fetal growth: Potential role for the IGF-I and HPA axes. *Pediatric Research, 65,* 236–241.

Davis, E. P., Glynn, L. M., Waffarn, F., & Sandman, C. A. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry, 52,* 119–129.

de Bruijn, A. T., van Bakel, H. J., & van Baar, A. L. (2009). Sex differences in the relation between prenatal maternal emotional complaints and child outcome. *Early Human Development, 85,* 319–324.

de Kloet, E. R., Oitzl, M. S., & Joëls, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neurosciences, 22,* 422–426.

de Weerth, C., & Buitelaar, J. K. (2005). Physiological stress reactivity in human pregnancy: A review. *Neuroscience and Biobehavioral Reviews, 29,* 295–312.

Deater-Deckard, K., Wang, Z., Chen, N., & Bell, M. A. (2012). Maternal executive function, harsh parenting, and child conduct problems. *Journal of Child Psychology and Psychiatry, 53,* 1084–1091.

Diamond, A., & Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science, 333,* 959–964.

Diamond, A., & Ling, D. S. (2016). Conclusions about interventions, programs, and approaches for improving executive functions that appear justified and those that, despite much hype, do not. *Developmental Cognitive Neuroscience, xx*, xx.

DiPietro, J. A. (2012). Maternal stress in pregnancy: Considerations for fetal development. *Journal of Adolescent Health, 51,* S3–8.

DiPietro, J. A., Hodgson, D. M., Costigan, K. A., & Johnson, T. R. (1996). Fetal antecedents of infant temperament. *Child Development, 67*, 2568–2583.

DiPietro, J. A., Novak, M. F., Costigan, K. A., Atella, L. D., & Reusing, S. P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development, 77,* 573–587.

Doom, J. R., Cicchetti, D., & Rogosch, F. A. (2014). Longitudinal patterns of cortisol regulation differ in maltreated and nonmaltreated children. *Journal of the American Academy of Child and Adolescent Psychiatry, 53,* 1206–1215.

Dunkel Schetter, C. (2011). Psychological science on pregnancy: Stress processes, biopsychosocial models, and emerging research issues. *Annual Review of Psychology, 62,* 531–558.

Dunkel Schetter, C., & Tanner, L. (2012). Anxiety, depression and stress in pregnancy: Implications for mothers, children, research, and practice. *Current Opinion in Psychiatry, 25,* 141–148.

Ellis, B. J., Boyce, W. T., Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Differential susceptibility to the environment: An evolutionary–neurodevelopmental theory. *Development and Psychopathology, 23*, 7–28.

Entringer, S., Buss, C., Kumsta, R., Hellhammer, D. H., Wadhwa, P. D., & Wuest, S. (2009a). Prenatal psychosocial stress exposure is associated with subsequent working memory performance in young women. *Behavioral Neuroscience, 123,* 886–893.

Entringer, S., Buss, C., & Wadhwa, P. D. (2015). Prenatal stress, development, health and disease risk: A psychobiological perspective—2015 Curt Richter Award Paper. *Psychoneuroendocrinology, 62,* 366–375.

Entringer, S., Kumsta, R., Hellhammer, D. H., Wadhwa, P. D., & Wust, S. (2009b). Prenatal exposure to maternal psychosocial stress and HPA axis regulation in young adults. *Hormones and Behavior, 55,* 292–298.

Firk, C., & Markus, C. R. (2007). Serotonin by stress interaction: A susceptibility factor for the development of depression? *Journal of Psychopharmacology, 21,* 538–544.

Francis, D. D., Szegda, K., Campbell, G., Martin, W. D., & Insel, T. R. (2003). Epigenetic sources of behavioral differences in mice. *Nature Neuroscience, 6,* 445–446.

Fuller, R. W. (1996). Mechanisms and functions of serotonin neuronal systems: Opportunities for neuropeptide interactions. *Annals of the New York Academy of Sciences, 780,* 176–184.

Fuster, J. M. (2008). *The prefrontal cortex* (4th ed.). London: Academic Press.

Gaspar, P., Cases, O., & Maroteaux, L. (2003). The developmental role of serotonin: News from mouse molecular genetics. *Nature Review Neuroscience, 4,* 1002–1012.

Giannakoulopoulos, X., Teixeira, J., Fisk, N., & Glover, V. (1999). Human fetal and maternal noradrenaline responses to invasive procedures. *Pediatric Research, 45,* 494–499.

Gillespie, C. F., & Nemeroff, C. B. (2005). Hypercortisolemia and depression. *Psychosomatic Medicine, 67*(Suppl 1), S26–28.

Glover, V. (2011). Annual research review: Prenatal stress and the origins of psychopathology: An evolutionary perspectiv. *Journal of Child Psychology and Psychiatry, 52,* 356–367.

Glover, V., O'Connor, T. G., & O'Donnell, K. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews, 35,* 17–22.

Gluckman, P., & Hanson, M. (2005). *The fetal matrix: Evolution, development and disease*. New York: Cambridge University Press.

Glynn, L. M., Schetter, C. D., Hobel, C. J., & Sandman, C. A. (2008). Pattern of perceived stress and anxiety in pregnancy predicts preterm birth. *Health Psychology, 27,* 43–51.

Gunnar, M. R., & Quevedo, L. (2007). The neurobiology of stress and development. *Annual Review of Psychology, 58,* 145–173.

Hanley, G. E., Brain, U., & Oberlander, T. F. (2015). Prenatal exposure to serotonin reuptake inhibitor antidepressants and childhood behavior. *Pediatric Research, 78,* 174–180.

Hanley, G. E., & Oberlander, T. F. (2012). Neurodevelopmental outcomes following prenatal exposure to serotonin reuptake inhibitor antidepressants: A "social teratogen" or moderator of developmental risk? *Birth Defects Research (Part A), 94,* 651–659.

Hilli, J., Heikkinen, T., Rontu, R., Lehtimaki, T., Kishida, I., Aklillu, E., et al. (2009). MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. *European Neuropsychopharmacology, 19,* 363–370.

Homberg, J. R., & Contet, C. (2009). Deciphering the interaction of the corticotropin-releasing factor and serotonin brain systems in anxiety-related disorders. *Journal of Neuroscience, 29,* 13743–13745.

Homberg, J. R., Schubert, D., & Gaspar, P. (2010). New perspectives on the neurodevelopmental effects of SSRIs. *Trends in Pharmacological Sciencies, 31,* 60–65.

Howard, L. M., Molyneaux, E., Dennis, C.-L., Rochat, T., Stein, A., & Milgrom, J. (2014). Non-psychotic mental disorders in the perinatal period. *The Lancet, 384,* 1775–1788.

Hughes, C. (2011). Changes and challenges in 20 years of research into the development of executive functions. *Infant and Child Development, 20,* 251–271.

Hughes, C., & Ensor, R. (2011). Individual differences in growth in executive function across the transition to school predict externalizing and internalizing behaviors and self-perceived academic success at 6 years of age. *Journal of Experimental Child Psychology, 108,* 663–676.

Huizink, A. C., Robles de Medina, P. G., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2003). Stress during pregnancy is associated with developmental outcome in infancy. *Journal of Child Psychology and Psychiatry, 44,* 810–818.

Ishiwata, H., Shiga, T., & Okado, N. (2005). Selective serotonin reuptake inhibitor treatment of early postnatal mice reverses their prenatal stress-induced brain dysfunction. *Neuroscience, 133,* 893–901.

Kinsella, M. T., & Monk, C. (2009). Impact of maternal stress, depression & anxiety on fetal neurobehavioral development. *Clinical Obstetrics and Gynecology, 52,* 425–440.

Lagopoulos, J., Hermens, D. F., Naismith, S. L., Scott, E. M., & Hickie, I. B. (2012). Frontal lobe changes occur early in the course of affective disorders in young people. *BMC Psychiatry, 12,* 1–7.

Laine, K., Heikkinen, T., Ekblad, U., & Kero, P. (2003). Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Archives of General Psychiatry, 60,* 720–726.

Laplante, P., Diorio, J., & Meaney, M. J. (2002). Serotonin regulates hippocampal glucocorticoid receptor expression via a 5-HT7 receptor. *Brain Research. Developmental Brain Research, 139,* 199–203.

Lazarus, R. S. (1991). Progress on a cognitive-motivational-relational theory of emotion. *American Psychologist, 46,* 819–834.

Leight, K. L., Fitelson, E. M., Weston, C. A., & Wisner, K. L. (2010). Childbirth and mental disorders. *International Review of Psychiatry, 22,* 453–471.

Levitt, P. (2003). Structural and functional maturation of the developing primate brain. *Journal of Pediatrics, 143,* 35–45.

Lowry, C. A. (2002). Functional subsets of serotonergic neurones: Implications for control of the hypothalamic-pituitary-adrenal axis. *Journal of Neuroendocrinology, 14,* 911–923.

Lupien, S. J., Gillin, C. J., & Hauger, R. L. (1999). Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: A dose-response study in humans. *Behavioral Neuroscience, 113,* 420–430.

Lupien, S. J., Maheu, F., Tu, M., Fiocco, A., & Schramek, T. E. (2007). The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. *Brain and Cognition, 65,* 209–237.

Malm, H., Brown, A. S., Gissler, M., Gyllenberg, D., Hinkka-Yli-Salomäki, S., McKeague, I. W., et al. (2016). Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: A national register-based study. *Journal of the American Academy of Child and Adolescent Psychiatry, 55,* 359–366.

Man, K. K., Tong, H. H., Wong, L. Y., Chan, E. W., Simonoff, E., & Wong, I. C. (2015). Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: A systematic review and meta-analysis of observational studies. *Neuroscience and Biobehavioral Reviews, 49,* 82–89.

McEwen, B. S. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsychopharmacology, 22,* 108–124.

McEwen, B. S. (2005). Glucocorticoids, depression, and mood disorders: Structural remodeling in the brain. *Metabolism, 54*(5 Suppl 1), 20–23.

McEwen, B. S., & Morrison, J. H. (2013). The brain on stress: Vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron, 79,* 16–29.

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior, 43,* 2–16.

Mennes, M., Stiers, P., Lagae, L., & Van den Bergh, B. R. H. (2006). Long-term cognitive sequelae of antenatal maternal anxiety: Involvement of the orbitofrontal cortex. *Neuroscience and Biobehavioral Reviews, 30,* 1078–1086.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24,* 167–202.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological Bulletin, 133,* 25–45.

Misri, S., Reebye, P., Kendrick, K., Carter, D., Ryan, D., Grunau, R. E., et al. (2006). Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. *American Journal of Psychiatry, 163,* 1026–1032.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., & Howerter, A. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49–100.

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., et al. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences of the United States of America, 108,* 2693–2698.

Monk, C., Fifer, W. P., Myers, M. M., Sloan, R. P., Trien, L., & Hurtado, A. (2000). Maternal stress responses and anxiety during pregnancy: Effects on fetal heart rate. *Developmental Psychobiology, 36*, 67–77.

Moses-Kolko, E. L., Bogen, D., Perel, J., Bregar, A., Uhl, K., Levin, B., et al. (2005). Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: Literature review and implications for clinical applications. *JAMA, 293,* 2372–2383.

Mulder, E. J., Ververs, F. F., de Heus, R., & Visser, G. H. (2011). Selective serotonin reuptake inhibitors affect neurobehavioral development in the human fetus. *Neuropsychopharmacology, 36,* 1961–1971.

Murmu, M. S., Salomon, S., Biala, Y., Weinstock, M., Braun, K., & Bock, J. (2006). Changes of spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy. *European Journal of Neuroscience, 24,* 1477–1487.

Murphy, P. A. (2010). *Origins: How the nine months before birth shape the rest of our lives*. New York: Free Press.

Neuenschwander, R., Röthlisberger, M., Cimeli, P., & Roebers, C. M. (2012). How do different aspects of self-regulation predict successful adaptation to school? *Journal of Experimental Child Psychology, 113,* 353–371.

O'Connor, T. G., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover, V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry, 58,* 211–217.

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years: Report from the Avon longitudinal study of parents and children. *British Journal of Psychiatry, 180,* 502–508.

O'Connor, T. G., Heron, J., Golding, J., Glover, V., & Team, T. A. S. (2003). Maternal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry, 44,* 1025–1036.

O'Donnell, K. J., Glover, V., Jenkins, J., Browne, D., Ben-Shlomo, Y., Golding, J., et al. (2013). Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology, 38,* 1630–1638.

Oberlander, T. F., Gingrich, J. A., & Ansorge, M. S. (2009). Sustained neurobehavioral effects of exposure to SSRI antidepressants during development: Molecular to clinical evidence. *Clinical Pharmacology and Therapeutics, 86,* 672–677.

Oberlander, T. F., Grunau, R., Mayes, L., Riggs, W., Rurak, D., Papsdorf, M., et al. (2008). Hypothalamicpituitary-adrenal (HPA) axis function in 3-month old infants with prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure. *Early Human Development, 84,* 689–697.

Oberlander, T. F., Grunau, R. E., Fitzgerald, C., Ellwood, A. L., Misri, S., Rurak, D., et al. (2002). Prolonged prenatal psychotropic medication exposure alters neonatal acute pain response. *Pediatric Research, 51,* 443–453.

Oberlander, T. F., Grunau, R. E., Fitzgerald, C., Papsdorf, M., Rurak, D., & Riggs, W. (2005). Pain reactivity in 2-month-old infants after prenatal and postnatal serotonin reuptake inhibitor medication exposure. *Pediatrics, 115,* 411–425.

Oberlander, T. F., Misri, S., Fitzgerald, C. E., Kostaras, X., Rurak, D., & Riggs, W. (2004). Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *Journal of Clinical Psychiatry, 65,* 230–237.

Oberlander, T. F., Reebye, P., Misri, S., Papsdorf, M., Kim, J., & Grunau, R. (2007). Externalizing and attentional behaviors in children of depressed mothers treated with a selective serotonin reuptake inhibitor antidepressant during pregnancy. *Archives of Pediatrics and Adolescent Medicine, 161,* 22–29.

Oberlander, T. F., Warburton, W., Misri, S., Aghajanian, J., & Hertzman, C. (2006). Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Archives of General Psychiatry, 63,* 898–906.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends in Cognitive Sciences, 9,* 242–249.

Pawluski, J. L., Galea, L. A. M., Brain, U., Papsdorf, M., & Oberlander, T. F. (2009). Neonatal S100B protein levels after prenatal exposure to selective serotonin reuptake inhibitors. *Pediatrics, 124,* e662–e670.

Pearson, R. M., Bornstein, M. H., Cordero, M., Scerif, G., Mahedy, L., Evans, J., et al. (2016). Maternal perinatal mental health and offspring academic achievement at age 16: The mediating role of childhood executive function. *Journal of Child Psychology and Psychiatry, 57,* 491–501.

Peters, D. A. (1990). Maternal stress increases fetal brain and neonatal cerebral cortex 5-hydroxytryptamine synthesis in rats: A possible mechanism by which stress influences brain development. *Pharmacology, Biochemestry, and Behavior, 35,* 943–947.

Pluess, M., Velders, F. P., Belsky, J., van IJzendoorn, M. H., Bakermans-Kranenburg, M. J., Jaddoe, V. W., … Tiemeier, H. (2011). Serotonin transporter polymorphism moderates effects of prenatal maternal anxiety on infant negative emotionality. *Biological Psychiatry, 69*, 520–525.

Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., et al. (2008). Deactivation of the limbic system during acute psycho-social stress: Evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological Psychiatry, 63,* 234–240.

Rai, D., Lee, B. K., Dalman, C., Golding, J., Lewis, G., & Magnusson, C. (2013). Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: Population based case-control study. *British Medical Journal, 349,* f2059.

Ramage, A. G. (2001). Central cardiovascular regulation and 5-hydroxytryptamine receptors. *Brain Research Bulletin, 56,* 425–439.

Rurak, D., Lim, K., Sanders, A., Brain, U., Riggs, W., & Oberlander, T. F. (2011). Third trimester fetal heart rate and Doppler middle cerebral artery blood flow velocity characteristics during prenatal selective serotonin reuptake inhibitor exposure. *Pediatric Research, 70,* 96–101.

Sanchez, M. M., Young, L. J., Plotsky, P. M., & Insel, T. R. (2000). Distribution of corticosteroid receptors in the rhesus brain. *The Journal of Neuroscience, 20,* 4657–4568.

Sandman, C. A., Buss, C., Head, K., & Davis, E. P. (2015). Fetal exposure to maternal depressive symptoms is associated with cortical thickness in late childhood. *Biological Psychiatry, 77,* 324–334.

Sandman, C. A., Davis, E., & Glynn, L. (2012). Prescient human fetuses thrive. *Psychological Science, 23,* 93–100.

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *Journal of Neuroscience, 10,* 2897–2902.

Schneider, M. L., Roughton, E. C., Koehler, A. J., & Lubach, G. R. (1999). Growth and development following prenatal stress exposure in primates: An examination of ontogenetic vulnerability. *Child Development, 70,* 263–274.

Seckl, J. R., & Meaney, M. J. (1993). Early life events and later development of ischaemic heart disease. *Lancet, 342,* 1236.

Simons, S. S. H., Beijers, R., Cillessen, A. H. N., & de Weerth, C. (2015). Development of the cortisol circadian rhythm in the light of stress early in life. *Psychoneuroendocrinology, 62,* 292–300.

Sodhi, M. S., & Sanders-Bush, E. (2004). Serotonin and brain development. *International Revue of Neurobiology, 59,* 111–174.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *STAI manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.

Stiles, J., & Jernigan, T. L. (2010). The basics of brain development. *Neuropsychology Review, 20,* 327–348.

Sundstrom, E., Kolare, S., Souverbie, F., Samuelsson, E. B., Pschera, H., Lunell, N. O., et al. (1993). Neurochemical differentiation of human bulbospinal monoaminergic neurons during the first trimester. *Brain Research. Developmental Brain Research, 75,* 1–12.

Takahashi, H., Nakashima, S., Ohama, E., Takeda, S., & Ikuta, F. (1986). Distribution of serotonin-containing cell bodies in the brainstem of the human fetus determined with immunohistochemistry using antiserotonin serum. *Brain Development, 8,* 355–365.

Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry and Allied Disciplines, 48,* 245–261.

Tollenaar, M. S., Beijers, R., Jansen, J., Riksen-Walraven, J. M. A., & de Weerth, C. (2011). Maternal prenatal stress and cortisol reactivity to stressors in human infants. *Stress, 14,* 53–65.

Tronick, E. Z., & Weinberg, M. K. (1997). Depressed mothers and infants: Failure to form dyadic states of consciousness. In: L. Murray & P. J. Cooper (Eds.), *Postpartum depression and child development* (pp. 54–81). New York: Guilford Press.

Van den Bergh, B. R. H., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Development, 75,* 1085–1097.

Van den Bergh, B. R. H., Mennes, M., Oosterlaan, J., Stevens, V., Stiers, P., Marcoen, A., & Lagae, L. (2005). High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. *Neuroscience and Biobehavioral Reviews, 29*, 259–269.

Van den Bergh, B. R. H., Mennes, M., Stevens, V., Van der Meere, J., Börger, N., Stiers, P., et al. (2006). ADHD deficit as measured in adolescent boys with a continuous performance task is related to antenatal maternal anxiety. *Pediatric Research, 59,* 78–82.

Van den Bergh, B. R. H., Mulder, E. J., Mennes, M., & Glover, V. (2005b). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms: A review. *Neuroscience and Biobehavioral Reviews, 29,* 237–258.

Van den Bergh, B. R. H., Van Calster, B., Smits, T., Van Huffel, S., & Lagae, L. (2008). Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: A prospective study on the fetal origins of depressed mood. *Neuropsychopharmacology, 33,* 536–535.

Vänskä, M., Punamäki, R.-L., Lindblom, J. K., Tolvanen, A., Flykt, M., Unkila-Kallio, L., … Tiitinen, A. (2015). Timing of early maternal mental health and child cortisol regulation. *Infant and Child Development, (early view- online version), 25,* 461–483. doi:10.1002/icd.194

Weikum, W. M., Brain, U., Chau, C. M. Y., Grunau, R. E., Boyce, T., Diamond, A., et al. (2013). Prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and serotonin transporter promoter genotype (SLC6A4) influence executive functions at 6 years of age. *Frontiers in Cellular Neuroscience, 7,* 1–12.

Weikum, W. M., Oberlander, T. F., Hensch, T. K., & Werker, J. F. (2012). Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception. *Proceedings of the National Academy of Sciences, 109,* 17221–17227.

Weinberg, M. K., & Tronick, E. Z. (1998). The impact of maternal psychiatric illness on infant development. *Journal of Clinical Psychiatry, 59*(Suppl 2), 53–61.

Weinstock, L., Cohen, L. S., Bailey, J. W., Blatman, R., & Rosenbaum, J. F. (2001). Obstetrical and neonatal outcome following clonazepam use during pregnancy: A case series. *Psychotherapy and Psychosomatics, 70,* 158–162.

Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Progress in Neurobiology, 65,* 427–451.

Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience and Biobehavioral Reviews, 32,* 1073–1086.

Whitaker-Azmitia, P. M. (2001). Serotonin and brain development: Role in human developmental diseases. *Brain Research Bulletin, 56,* 479–485.

Whitaker-Azmitia, P. M., Druse, M., Walker, P., & Lauder, J. M. (1996). Serotonin as a developmental signal. *Behavioral Brain Research, 73,* 19–29.

Zeskind, P. S., & Stephens, L. E. (2004). Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics, 113,* 368–375.