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Exposure to Prenatal Psychobiological Stress Exerts Programming Influences on the Mother and Her Fetus

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Key Words

Fetal programming · Developmental origins of disease · Cortisol · Stress · CRH · Sex differences · Prenatal stress · Pregnancy · Infant development · Anxiety · Fetal development · Maternal programming · Postpartum depression

Abstract

Background/Aims: Accumulating evidence from a relatively small number of prospective studies indicates that exposure to prenatal stress profoundly influences the developing human fetus with consequences that persist into childhood and very likely forever. ***Methods:*** Maternal/fetal dyads are assessed at ~20, ~25, ~31 and ~36 weeks of gestation. Infant assessments begin 24 h after delivery with the collection of cortisol and behavioral responses to the painful stress of the heel-stick procedure and measures of neonatal neuromuscular maturity. Infant cognitive, neuromotor development, stress and emotional regulation are evaluated at 3, 6 12 and 24 months of age. Maternal psychosocial stress and demographic information is collected in parallel with infant assessments. Child neurodevelopment is assessed with cognitive tests, measures of adjustment and brain imaging between 5 and 8 years of age. ***Results:*** Psychobiological markers of stress during pregnancy, especially early in gestation, result in delayed fetal maturation, disrupted emotional regulation and impaired cognitive performance during infancy and decreased brain volume in areas associated with learning and memory in 6- to 8-year-old children. We review findings from our projects that maternal endocrine alterations that accompany pregnancy and influence fetal/infant/child development are associated with decreased affective responses to stress, altered memory function and increased risk for postpartum depression. ***Conclusions:*** Our findings indicate that the mother and her fetus both are influenced by exposure to psychosocial and biological stress. The findings that fetal and maternal programming occur in parallel may have important implications for long-term child development and mother/child interactions.

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Overview

One central assumption of our program of research is that fetal exposure to maternal signals of stress has a significant (programming) influence on the trajectory of fetal development. Findings from our projects indicate that the human fetus is exquisitely sensitive to the physiological and psychological effects of maternal stress and that these influences can be measured. Moreover, our findings indi-

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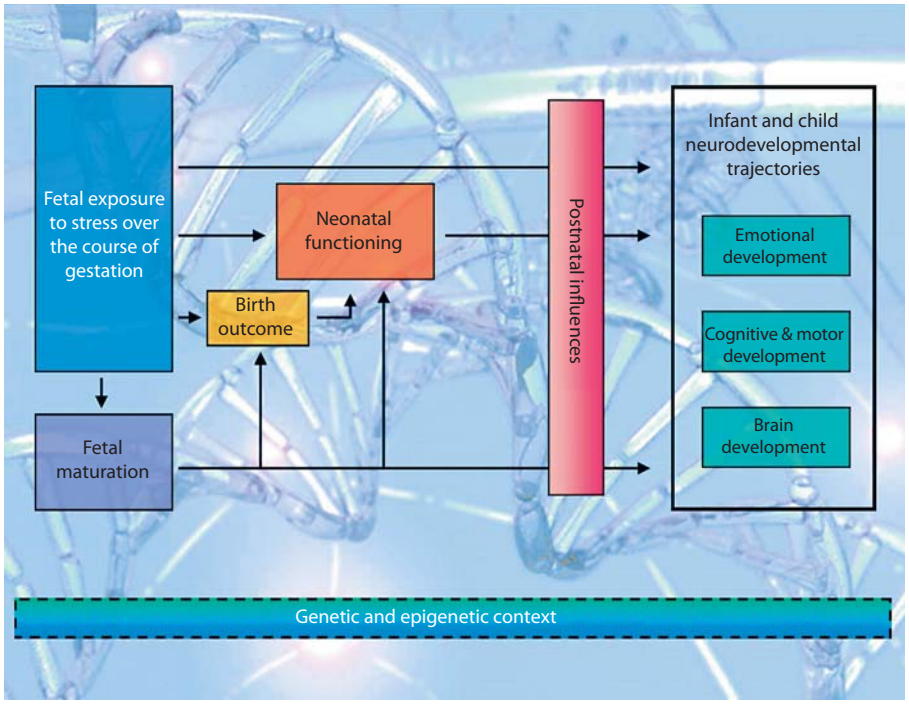

Fig. 1. Schematic representation of the psychobiological stress, fetal programming model that guides our research program. Fetal exposure to stress can influence infant/child development directly or indirectly (though fetal behavior, birth outcomes and neonatal functioning). The consequences of prenatal and very early development on later outcomes can be mediated or moderated by postnatal influences. Genetic and epigenetic influences interact at all stages of the model.

cate that the timing of fetal exposure to maternal psychobiological stress is associated with unique profiles of birth outcomes, fetal reactivity, and infant and child outcomes. We will review here recent findings that both psychosocial and biological markers of stress during pregnancy influence (i) the behavior of the fetus, (ii) the temperament of the neonate and young infant, (iii) the neurobehavioral characteristics of the developing infant/toddler, and (iv) the structure of the nervous system in the child (fig. 1).

A second assumption of our program of research is that the maternal endocrine alterations that accompany pregnancy and influence fetal/infant/child development also have implications for the maternal brain and behavior. Less is known about 'maternal programming'; however, we will review here evidence that (i) maternal behavior is altered during pregnancy, (ii) maternal prenatal exposure to stress hormones influences postpartum adaptation, and (iii) reproductive experience alters the nervous system.

Fetal Programming

The human placenta is both a sensory and effector organ that incorporates information from its maternal host environment into the fetal developmental program. Stress signals detected by the placental/fetal unit may prime or advance the placental clock [1] and activate the promoter region of the corticotropin-releasing hormone (CRH) gene resulting in an increase in placental synthesis of this 'master' stress hormone [2]. The accelerated increase in circulating placental CRH (pCRH) associated with stress initiates a cascade of events initiating parturition and resulting in early departure (i.e. preterm birth) from the inhospitable host.

Preterm birth is one potential outcome of fetal exposure to stress during gestation; however, there are other lifelong consequences of exposure to intrauterine or gestational sources of stress. Because prenatal life is a time of unprecedented growth, the human fetal nervous system is particularly vulnerable both to organizing and disorganizing influences. Fetal exposure to adverse intrauterine events including those associated with maternal anxiety, psychosocial stress and depression result in subsequent risk for cardiovascular disease, hypertension, hyperlipidemia, insulin resistance, non-insulin-dependent diabetes mellitus, obesity, higher serum cholesterol concentrations, shortened lifespan, asthma and other poor health outcomes [3–8]. These influences on the fetus have been described as 'programming'.

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Human Pregnancy and the Stress System

Physiological stress systems change dramatically during human pregnancy [9]. The differences in reproductive and stress physiology, even in very closely related species such as humans and non-human primates, limit the validity of generalizing from animal models to the conditions experienced in humans [10]. The 'fight or flight' stress system is altered during human pregnancy with the growth and development of the placenta. The placenta expresses the genes for CRH (hCRHmRNA) and pro-opiomelanocortin, the precursor for ACTH and β-endorphin. All of these stress hormones increase as pregnancy advances, but the exponential increase in pCRH in maternal plasma is especially dramatic, reaching levels observed only in the hypothalamic portal system during physiological stress [11]. Moreover, in contrast to the well-known negative feedback regulation of hypothalamic CRH, cortisol stimulates the expression of hCRHmRNA in the placenta, establishing a positive feedback loop that allows for the simultaneous increase of pCRH, ACTH, β-endorphin and cortisol over the course of gestation [12, 13]. As pregnancy advances toward term and these stress hormones increase, the positive feedback loop becomes dampened because the hypophyseal corticotrophs are downregulated [14, 15].

The effects of these hormones however are modulated by the activities of binding proteins and enzymes. For example, concurrent with increases in pCRH, maternal CRH-binding protein rises and then falls abruptly around the 36th week of gestation [1]. Maternal plasma cortisol-binding globulin (CBG) levels also change across pregnancy. CBG is stimulated by estrogen and levels increase progressively with advancing gestation until 36 gestational weeks when there is a significant decline in CBG [16]. Variations in CBG may contribute to individual differences in developmental outcomes because levels have been shown to be lower in women with growth-restricted fetuses [16]. Activity of the placental enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD2) also contributes to the influence of cortisol on mother and fetus. This enzyme oxidizes maternal cortisol into its inactive form, cortisone [17, 18]. The levels of placental 11β-HSD2 rise as gestation progresses before falling precipitously near term ensuring maturation of the fetal lungs, central nervous system (CNS) and other organ systems in full-term births [19, 20]. Elevated maternal stress downregulates 11β-HSD2 activity in the placenta allowing a greater proportion of maternal cortisol to cross the placenta [21].

These changes have significant implications for the human fetus and for the mother. First, because of the massive changes in stress hormones (two- to fortyfold) over the course of gestation, pregnancy can be considered a major physiological stressor. Second, because of the positive feedback between cortisol and pCRH that develops during human pregnancy, the fetus will be exposed simultaneously to the increases of both stress hormones. Third, because the receptors in the maternal stress system are downregulated as pregnancy advances, during late gestation environmental stress is less effective in triggering the endocrine axis and women become less responsive to the effects of stress [15, 22–26]. Thus, stressful events early in pregnancy are experienced by the mother as more unpleasant and may exert greater influences on the fetus than events closer to term. The increased exposure to maternal and placental stress hormones and the change in maternal perceptions of stress during gestation play a fundamental role in the organization of the fetal nervous system and in maternal adaptation during pregnancy.

Assessment Protocol for Our Research Program

We have developed a prospective protocol for the assessment of prenatal exposure to maternal stress and stress hormones on fetal, infant and child development (fig. 2). Maternal psychosocial and biological stress measures are collected at five gestational intervals beginning between 14 and 16 weeks. Maternal/fetal dyads are assessed at ~20, ~25, ~31 and ~36 weeks of gestation. At ~25, ~31 and ~36 gestational weeks, fetal neurodevelopment is evaluated with a measure of startle and habituation. At delivery, information on length of gestation and birth weight is abstracted from medical records. Infant assessments begin 24 h after delivery with the collection of cortisol and behavioral responses to the painful stress of the heel-stick procedure and measures of neonatal neuromuscular maturity. Infant cognitive, neuromotor development, stress and emotional regulation are evaluated at 3, 6, 12 and 24 months of age. Maternal psychosocial stress and demographic information is collected in parallel with infant assessments. Child neurodevelopment is assessed with cognitive tests, measures of adjustment and brain imaging between 5 and 8 years of age.

The findings described in all of the studies from our project that are reviewed here were observed in healthy low-risk cohorts of children born at term and remained

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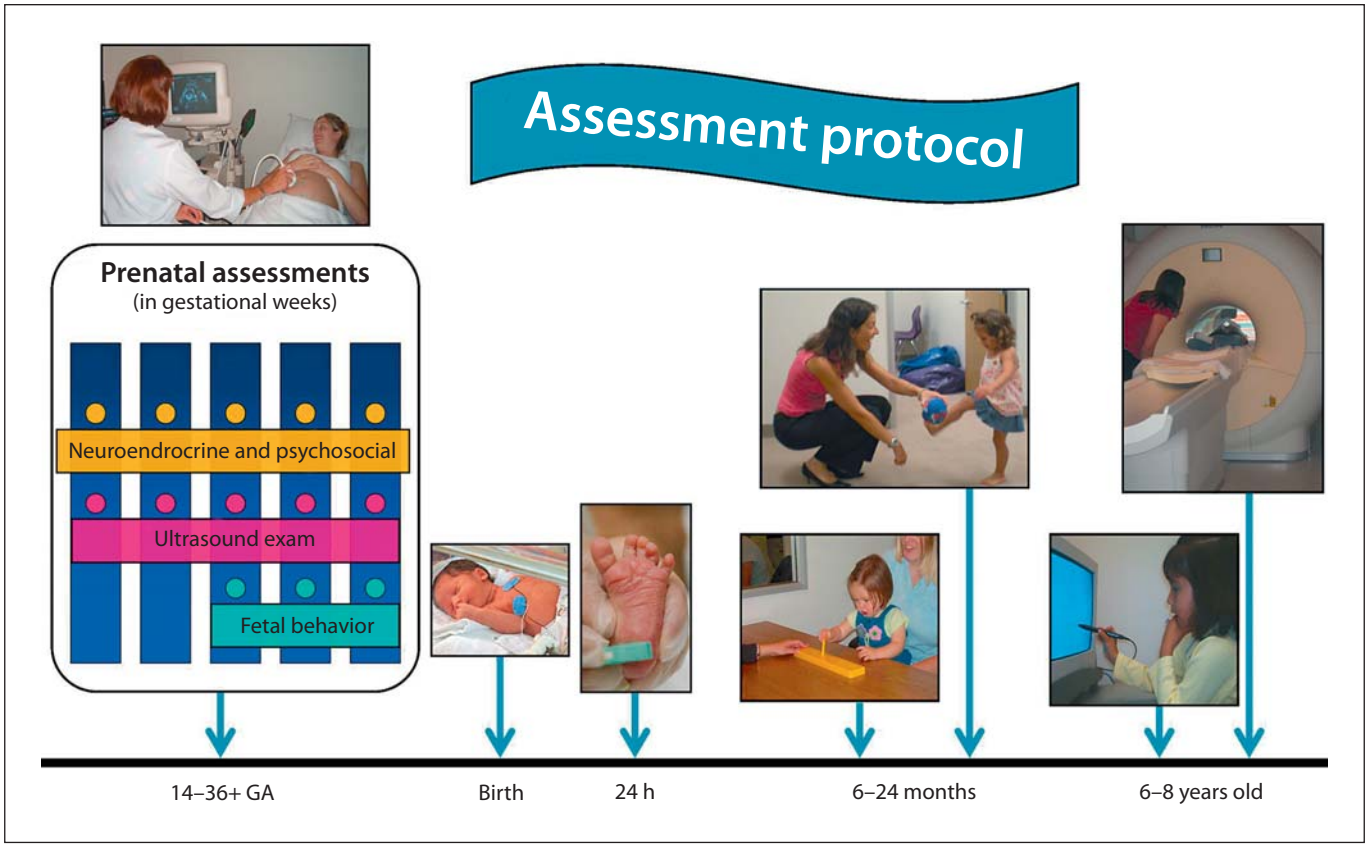

Fig. 2. As described in the text, our prospective, longitudinal assessment protocol is designed to follow fetuses at regular intervals from ~15 weeks' gestation to birth and then to follow the child at regular intervals through 8 years of age. It is important to acknowledge that measures of maternal behavior and self-report also are collected at each child visit.

significant after considering an extensive list of prenatal and postnatal controls (including birth outcome and postnatal maternal stress and depression).

Gestational Stress Influences Human Fetal Behavior

In humans, the most well-documented effects of exposure to maternal stress are on birth outcomes including preterm delivery [24, 27, 28] and the resulting adverse developmental consequences [29]. However, intrauterine exposures to biological and psychosocial stress contribute to developmental impairments independently of preterm birth or growth restriction. The study of human fetal behavior is important because it provides the opportunity to assess the effects of gestational stress on development before the effects of external influences are exerted, such as birth outcome, parenting and socialization.

Several studies reported that increased maternal anxiety or psychosocial stress is associated with hyperactive fetuses and fetal tachycardia [30, 31], a sudden fall in fetal heart rate (FHR) followed by over-swing recovery [32, 33], significant FHR increases [34], increased fetal motor activity [35], more time in quiet sleep [36], and higher pulsatility index in the fetal middle cerebral artery [37]. Conversely, reduced anxiety or positive emotional states result in decreased fetal breathing and increased body movements [38, 39].

Measures of fetal responses to external stimulation have been used in our projects to directly assess the developmental consequences of exposure to biological and psychosocial indices of stress [40]. With measures of FHR we discovered that fetuses of women with elevated pCRH during the third trimester were less responsive to the presence of a novel stimulus [41]. In a subsequent study, we reported that FHR habituation was delayed when fe-

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tuses were exposed to over-expression of maternal endogenous opiates [42]. To evaluate programming influences on the fetus, we assessed the consequences of gestational stress during the early second trimester on fetal behavior in the early third trimester. We found that low pCRH at 15 gestational weeks, but not later, predicted a more mature FHR pattern at 25 gestational weeks [43, 44]. This is evidence of gestational stress exerting programming influences on the developing nervous system that is independent of postnatal experiences.

Gestational Stress Influences Infant Development

Results from animal models have established that fetal exposure to stress is associated with life-long compromised neurodevelopment, enhanced stress reactivity and increased fearful or anxious behavior [45–52]. A small number of human studies have focused primarily on the consequences of prenatal stress for behavioral and emotional regulation. Our studies of the effects of exposure to prenatal stress on infants and children have included measures of both temperament and cognition.

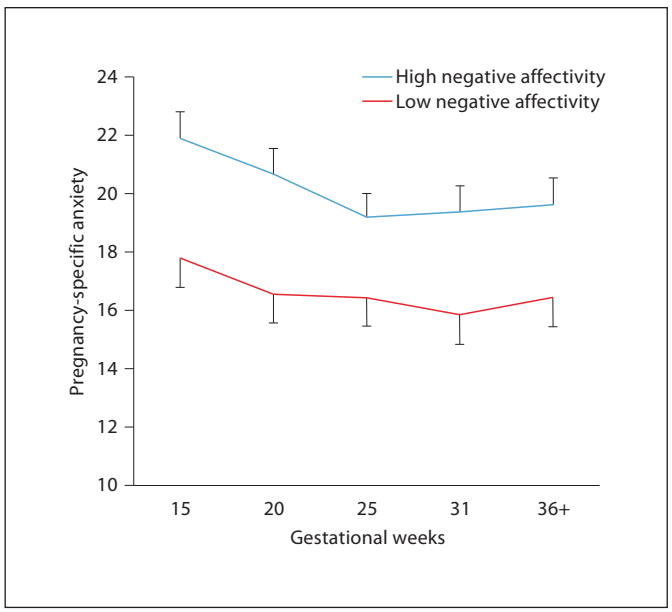

Fig. 3. Maternal reports of high levels of PSA throughout pregnancy are associated with maternal reports of elevated negative affectivity in the infant at 3 months of age independent of the effects of postpartum maternal psychological states.

Prenatal Stress and Temperament

Prenatal exposure to elevated levels of maternal psychosocial stress and stress hormones has been reported to be associated with behavioral and emotional disturbances during infancy and childhood that are independent of birth outcome and postpartum maternal stress or depression [53–61]. Our studies have shown that elevated levels of prenatal maternal anxiety and depression were associated with increased infant fearful temperament after controlling for the influence of postpartum maternal state in both maternal report and laboratory observational measures of temperament [56, 61]. In these same studies, maternal and placental stress-related hormones also were associated with more fearful infant temperament [53, 61]; however, the biological stress associations with infant temperament were independent of the associations between maternal psychosocial stress and infant temperament.

In a second cohort of 179 mothers and their full-term infants, we evaluated the association between prenatal maternal anxiety and infant temperament. Maternal state anxiety and pregnancy-specific anxiety (PSA) were evaluated at five gestational intervals and at 3 months postpartum (fig. 2). Mothers reported their infants' temperament using the Infant Behavior Questionnaire at 3 months. Consistent with our previously published work, elevated maternal state anxiety was associated with increased negative affectivity among healthy 3-month-old infants born at term (*partial r* = 0.15, $p < 0.05$), after controlling for postnatal maternal psychological distress (anxiety and depression). As shown in figure 3, elevated PSA throughout gestation was associated with more negative infant temperament after controlling for postnatal maternal psychological distress (*partial r* ranged from 0.15 to 0.24, $p < 0.05$). A stepwise and hierarchical regression indicated that after accounting for relevant covariates (i) PSA more strongly predicted infant temperament than state anxiety and (ii) the association between state anxiety and infant temperament was not significant after accounting for the effects of PSA. These findings underscore the growing recognition that PSA may be a particularly potent influence on adverse birth and infant outcomes.

In addition to identifying an association between prenatal exposure to maternal psychosocial and biological stress signals and infant temperament, we recently reported [62] in a sample of 116 mothers and their healthy full-term infants assessed at five gestational intervals that prenatal maternal cortisol and psychosocial stress each exerted influences on neonatal stress regulation, independent of baseline functioning, and these influences were

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dependent upon the gestational period during which the fetus was exposed. Specifically we found that elevated maternal cortisol early in gestation was associated with slower behavioral recovery from the painful stress of a heelstick procedure within 24 h of birth. Elevated maternal cortisol during the second half of gestation was associated with a larger and more prolonged neonatal cortisol response to stress. Moreover, higher levels of maternal perceived stress throughout gestation predicted a slower rate of recovery of behavioral stress responses in the newborn. These findings, as with the results of fetal behavior, suggest that the effects of fetal exposures (programming) are observed before the influences of postnatal experiences and exposures are exerted. These data are consistent with evidence that prenatal exposure to synthetic glucocorticoids during the late second and early third trimester is associated with an amplified cortisol response to stress among healthy full-term neonates [63]. Together, these data provide compelling evidence that gestational exposure to excess glucocorticoids alters the developmental trajectory of the fetal hypothalamic-pituitary-adrenal (HPA) axis with consequences for postnatal stress regulation.

Prenatal Stress and Cognition

Few studies have examined the effects of prenatal stress on cognitive development. Although there is evidence that maternal self-report of elevated stress, depression and anxiety during the prenatal period is associated with delayed infant cognitive and neuromotor development [61, 64] and that these deficits may persist into adolescence [65], the findings across studies are not consistent [66, 67].

In the largest study conducted (125 subjects) with repeated evaluations at five prenatal intervals and three intervals during infancy, we reported that the consequences of fetal exposure to maternal cortisol and PSA were dependent upon when during gestation these two indicators of stress were elevated [9]. Fetal exposure to cortisol early in pregnancy resulted in significantly lower scores on measures of mental development. Conversely, elevated maternal cortisol late in gestation was associated with significantly higher scores on measures of mental development. Similar results were observed for levels of maternal PSA. Despite the similar effects of maternal cortisol and anxiety on infant cognition at 1 year of age, these two measures of prenatal stress were not related and exerted independent effects on developmental outcomes. The consequences for the infant were confined to cognitive outcomes. Motor performance was unaffected by either exposure to cortisol or maternal anxiety.

These findings linking cortisol to infant cognitive development are consistent with its function in the maturation of the human fetus. As described above, early in pregnancy the fetus is partially protected from maternal cortisol because it is oxidized and inactivated by 11β-HSD2. However, because 11β-HSD2 is only a partial barrier, excessive synthesis and release of maternal cortisol exposes the fetus to concentrations that may have detrimental neurological consequences. As pregnancy advances toward term, fetal exposure to elevated cortisol is necessary for maturation of the fetal nervous system and lungs [68]. Fetal exposure to cortisol during the third trimester is facilitated by the sharp drop in 11β-HSD2 which allows a greater proportion of maternal cortisol to cross the placental barrier [69, 70].

Gestational Stress Influences the Developing Brain

Low birth weight and preterm birth have been related to reductions in regional brain volumes [71–75]. However, because adverse birth outcomes may be markers of in utero stress exposure, it has been difficult to separate the effects of fetal stress exposures on brain morphology from perinatal complications. Recently, our group published the first study to show that fetal exposure to PSA was related to specific changes in brain morphology at 6–9 years of age independent of birth phenotype [76]. Specifically, PSA early in gestation was associated with gray matter volume reductions in the prefrontal cortex, the premotor cortex, the medial temporal lobe, the lateral temporal cortex, the postcentral gyrus as well as the cerebellum extending to the middle occipital gyrus and the fusiform gyrus (fig. 4). These brain regions are associated with a variety of cognitive functions. Specifically, the prefrontal cortex is involved in executive cognitive functions such as reasoning, planning, attention, working memory, and some aspects of language [77]. Structures in the medial temporal lobe, including areas connected to the hippocampus (entorhinal, perirhinal, parahippocampal cortex), constitute a medial temporal lobe memory system [78]. The temporal polar cortex is involved in social and emotional processing including recognition and semantic memory [79–80]. A network in the temporal-parietal cortex consisting of the middle temporal gyrus, the superior temporal gyrus and the angular gyrus has been shown to be important in processes related to auditory language processing in children [81]. Brain systems involved in language learning including the inferior frontal gyrus, the middle temporal gyrus and the para-

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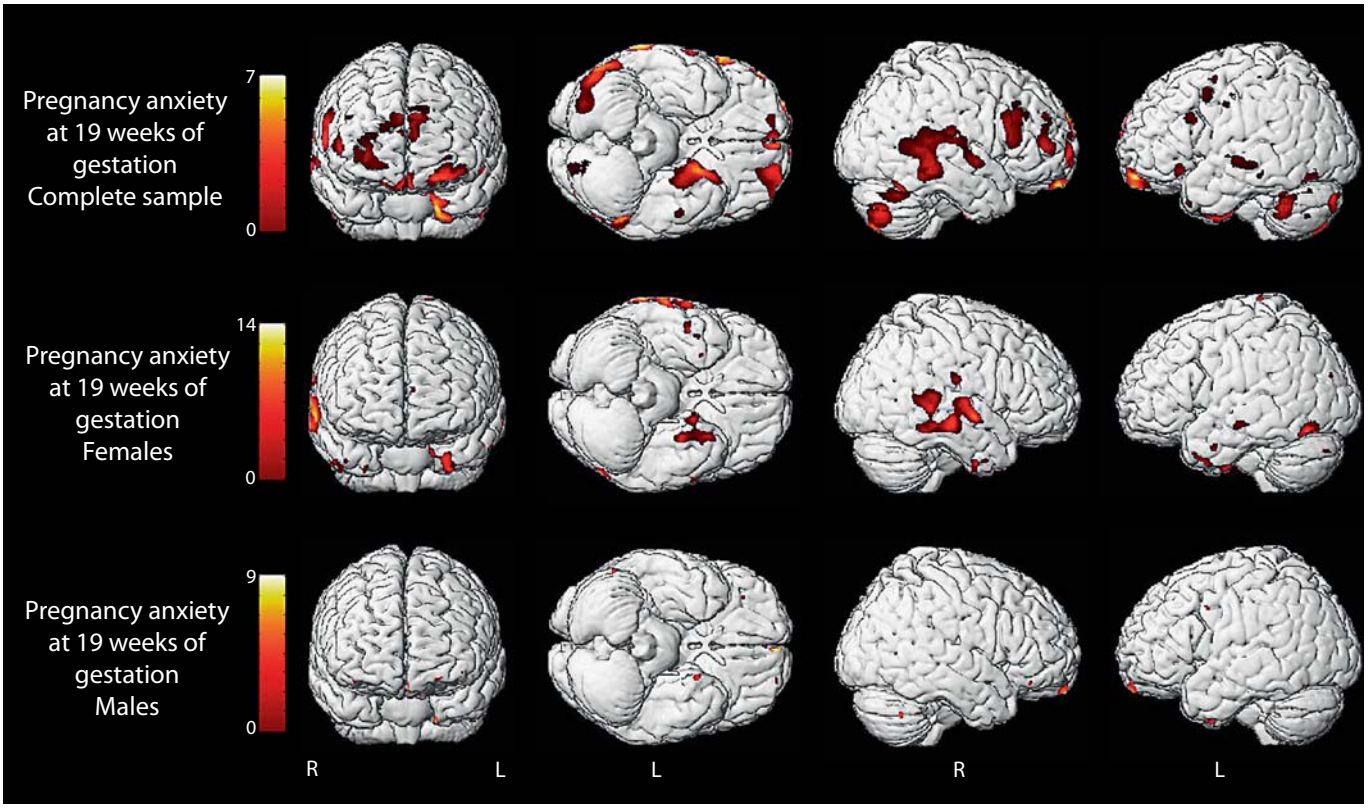

Fig. 4. Areas of reduced gray matter volume in 6- to 8-year-old children in association with elevated PSA at ~19–20 weeks' gestation. The primary effect is observed among girls. Voxels with $p < 0.001$ (uncorrected) are displayed.

hippocampal gyrus also are reduced in children 'exposed' to high levels of PSA [82]. This is the first prospective study in healthy children to show that prenatal maternal anxiety (PSA in this case) is related to distinctive patterns of structural brain development.

Mechanisms of Stress Effects on the Developing Nervous System

Our understanding of the potential mechanisms by which prenatal stress and biological effectors of stress may produce long-lasting changes in brain structure and function come primarily from animal studies. These mechanisms include changes in neurotransmitter levels, adult neurogenesis, as well as cell growth and survival. Pre- and postnatal stress exposure has been associated with changes in N-methyl-D-aspartate (NMDA) receptor expression in the hippocampus and frontal cortex [83–85], reduced adult neurogenesis [52, 86–89] and reduced BDNF mRNA in the hippocampus and prefrontal cortex [84, 90–92].

We described briefly the normal endocrine changes that occur during pregnancy and indicated that they are exacerbated under conditions of stress. We presented evidence that fetal exposure to elevated levels of stress and to stress-related hormones, particularly CRH and cortisol, are associated with abbreviated gestation, disturbed emotional regulation, poorer cognitive performance and reduced brain volume in critical areas. It is possible that fetal exposure to these markers of stress may directly influence the developing nervous system. For instance, elevated concentrations of pCRH may directly affect the developing brain by excessive (upregulation) expression of CRH receptors throughout the brain, including, but not limited to, hippocampus, amygdala and prefrontal cortex [93], and indirectly by stimulating production of fetal cortisol. Exogenously administered CRH has been shown to increase limbic neuronal excitation leading to seizures [93–95] and may participate in mechanisms of

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neuronal injury [96, 97]. CRH has neurotoxic effects on hippocampal neurons [96, 98–101], and these effects seem to be more pronounced in the immature hippocampus [96, 100, 102]. The decline in density of dendritic spines in the hippocampus has been prevented by selective blockade of the CRH_1 receptor [103].

The sources of cortisol in the fetal compartment are from the fetal and maternal adrenals. pCRH is secreted into the fetal circulation and may affect fetal adrenal cortisol production; the CRH_1 receptor is present in human fetal adrenal tissue from mid-gestation onwards [104]. As mentioned above, fetal exposure to maternal cortisol is regulated by 11β-HSD2, but this placental enzyme is only a partial barrier so that a proportion of maternal cortisol passes through the placenta [105, 106]. Glucocorticoid receptors are present throughout the CNS [107–110] and glucocorticoids easily pass through the blood-brain barrier [111] and influence multiple brain regions, including, but not limited to, the hippocampus, amygdala and prefrontal cortex. At high concentrations, cortisol may inhibit growth and differentiation of the developing nervous system; considerable evidence indicates that glucocorticoids are neurotoxic to hippocampal CA3 pyramidal cells [112–114]. Furthermore, in embryonic hippocampal neurons cortiscosterone induces neuronal death, which is mediated by a decrease in BDNF and prevented by BDNF administration [115]. Cortisol also affects myelination in the developing brain because glucocorticoid receptors are expressed in oligodendrocytes, the glia cells that manufacture myelin sheets in the CNS. Specifically, delayed myelination has been reported in the corpus callosum in association with prenatal exogenous glucocorticoid exposure [116], which is consistent with findings that prenatal stress exposure affects the size of the corpus callosum [117].

One remaining question is whether or not the effects of maternal responses to stress on the fetus are related to shared genetic factors. In studies of naturally occurring variations in maternal stress it is difficult to separate the association between the predisposition to respond to stress and the neurodevelopmental patterns observed in the fetus and child, from the consequences of other factors that might contribute to this association, such as shared genes. The programming findings reported here, however, are consistent with animal models where random assignment is possible [118] and with human studies that evaluated the consequences of randomly occurring traumatic events, such as natural disasters [25, 119, 120] and with studies of exogenous administration of GCs. Further, recent human studies have documented developmental consequences of prenatal stress among children conceived by in vitro fertilization who were not genetically related to their mother [121]. Thus, genetic mechanisms cannot be completely ruled out on experimental grounds as a possible explanation for the effects of maternal experience on fetal/child development. There is reasonable evidence, however, to warrant the conclusion that maternal stress is translated into direct effects on the fetal nervous system.

Sex-Specific Programming Effects

There is a rapidly expanding literature in animal models indicating that there are sexually dimorphic responses to stress and adversity [122–124] including and perhaps especially associated with stress during the prenatal period [125–127]. In the study of human FHR responses to external stimulation reported above [44], we discovered that female fetuses displayed more mature responses than males at 31 and 36 gestational weeks. We reported delayed neuromotor development associated with fetal exposure to cortisol early in gestation and CRH late in gestation was confined to male neonates [128]. In this review, we report that the reduction in brain volumes in children exposed to elevated PSA early in gestation [76] primarily were observed in girls (fig. 4). These findings are consistent with findings of sex-specific trajectories of fetal development [129, 130] and the sexually dimorphic risk of neurological impairment associated with neonatal complications [131].

There is evidence that sexually specific patterns are formed very early in development and are reflected in the function and response to stress of the placenta. The female placenta appears to be more responsive to changes in glucocorticoid concentration than the male placenta. Clifton [132] has argued that this sexually dimorphic placental sensitivity to signals of adversity (elevated glucocorticoids) results in different patterns of response and in particular in different patterns of growth. Male fetuses, Clifton suggests, do not alter their patterns of development in response to adversity and continue to grow despite reduced resources. Because the male fetus has not adjusted to the initial adversity and has not conserved its resources, it is more susceptible to later stress with increases in morbidity and mortality. In contrast, the female placenta responds or adjusts to an adverse maternal environment in multiple ways (gene and protein changes) resulting in reduced growth. If exposed to stress that reduces nutrients and resources later in gestation, the

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female fetus has conserved its energy needs which increases the probability of survival. By this mechanism, sexually specific patterns of response to stress may be programmed very early in fetal development.

Maternal Programming

The dramatic maternal endocrine alterations that accompany pregnancy have implications not only for the maintenance of gestation, successful parturition and optimal fetal/infant/child development, but also have ramifications for the maternal brain and behavior. In 1971, Diamond et al. [133] demonstrated that pregnancy in rats resulted in larger cortical size – providing the first empirical evidence that pregnancy is a critical period of development in the female lifespan during which neural architecture is remodeled. More recent studies with rodent models have confirmed that pregnancy and reproduction produce changes in brain structure and function that persist throughout the lifespan [134–139]. These changes are evident in brain regions involved both directly (e.g. recognition of young and attachment) and indirectly in maternal caretaking (e.g. spatial memory and stress responsivity). Our studies have examined the influence of a range of reproductive experience on the structure and function of women's brains – a process we term 'maternal programming' [26].

Affective Programming

Our studies were the first in humans to demonstrate diminished psychological response to major life events during pregnancy [25, 140]. Specifically, we found that events occurring early in pregnancy were experienced as more stressful than those same events occurring later in pregnancy. Our findings were consistent with reports that HPA axis, blood pressure, heart rate and catecholamine responses to stress are dampened as pregnancy progresses [141]. There are several reports in humans that variations in prenatal levels of estrogen, cortisol and oxytocin influence the quality of early postpartum maternal care [142–144]. Further, a recent fMRI study reported that women who had given birth vaginally exhibited greater activation in brain regions involved in the regulation of empathy, arousal, motivation and reward circuits in response to their baby's cries compared to those who had not [145].

The changes in physiological stress responding as gestation advances are adaptive and promote survival [24]. Specifically, downregulated psychological and physiological maternal stress responding provides protection for mother and fetus from the effects of adversity as pregnancy progresses. For instance, stress experienced early in gestation, but not later, is associated with preterm birth [140, 146]. Moreover, women who fail to show the expected decrease in generalized stress and anxiety or dampening in the cortisol awakening response during pregnancy are at increased risk for preterm delivery [24, 147].

Cognitive Programming

Estimates of the percent of women who report impaired cognitive function during pregnancy range from 48 to 81% [148, 149]. A recent meta-analysis of 17 relatively small studies published over the last decade indicated deficits in two components of memory during pregnancy: recall memory (both immediate and delayed) and the executive component of working memory [150]. In the largest longitudinal study of cognitive function during pregnancy (254 pregnant women, 60 non-pregnant women), we assessed memory function and hormones five times during pregnancy and once postpartum. The pregnant women exhibited poorer performance than the non-pregnant women during gestation and these effects were still apparent 3 months after delivery. Further, the diminished memory function during pregnancy and postpartum was associated with prenatal trajectories of both estradiol and cortisol [26]. These findings represent the first demonstration of potential biological mediators of diminished memory associated with pregnancy in humans.

Psychopathology

In the non-pregnant state, CRH is believed to play a role in the etiology of depression. Depressed individuals have an increased number and hypersensitivity of CRH neurons in the paraventricular nucleus of the hypothalamus [16, 17]. Because of the dramatic increase in pCRH during pregnancy and the link between CRH and depression, our group has examined the possible risk pCRH may present for postpartum depression (PPD). In a cohort of 100 women followed prospectively five times beginning early in pregnancy, elevations in pCRH at 25 weeks' gestation were associated with an increased risk of developing symptoms of PPD [18]. These findings add new support to the small but emerging literature indicating that the maternal brain is susceptible to changes associated with normal human pregnancy.

In another large study from our laboratory, plasma levels of β-endorphin in 307 pregnant women with a singleton pregnancy were determined at regular intervals, and again at 9 weeks postpartum. Symptoms of depression were assessed at the last four pregnancy visits and post-

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partum with standardized questionnaires. We found that increased β-endorphin levels at any time point during pregnancy were associated with a more than threefold increase in the risk of developing PPD symptoms among women who were euthymic at 25 weeks' gestation. This relation was not observed among women reporting symptoms of depression during pregnancy. These findings with different biostress markers suggested that 25 weeks' gestation may be a sensitive time period during which endocrine factors may program postnatal maternal mood [151].

Possible Mechanisms

Currently, virtually nothing is known about how reproduction alters human brain structure. It is likely that the dramatic hormonal changes during pregnancy have direct influences on the nervous system. In humans, estrogen alterations due to menopause and the menstrual cycle are associated with transient alterations in brain structure [152, 153]. Moreover, primates who are sensitive to stress-induced amenorrhea exhibit greater evidence of CRH activity in the paraventricular nucleus and thalamus and high CRH fiber density in the central nucleus of the amygdala than resilient animals [154]. These exposures which are of a relatively small magnitude strongly suggest that in humans, as in rodents, the massive hormonal changes of pregnancy alter brain function and morphology. Despite this, only one study has examined the influence of pregnancy on human brain structure. Oatridge et al. [155], using MRI in a small group of women, documented decreased total brain volumes over the course of pregnancy and into the postpartum period. Future work examining maternal programming in humans is essential for a complete understanding of women's mental health and also for a comprehensive understanding of prenatal influences on the health of their offspring.

Conclusions

The results from our research studies indicate that the mother and her fetus both are susceptible to exposure to elevated levels of psychosocial and biological stress. It is important, however, to acknowledge the independent and joint influences of prenatal exposure to psychosocial and biological stress on development. The human placenta integrates numerous sources of maternal stress signals and responds with a dose-dependent release of stress hormones [156]. Because the HPA and placental system is responsive to *both* psychosocial and physiological stress and because these two sources often are independent, the correlation with stress biomarkers often is low. Thus, maternal psychosocial stress does not exclusively determine fetal exposure to biological stress signals and elevated levels of stress hormones do not necessarily reflect the experience of increased maternal stress. The evidence indicates that both biological and psychosocial sources of stress, especially pregnancy-specific stress, have significant influences on the fetus with long-term consequences in the infant, child and perhaps beyond. Moreover, several studies reported in this review found that PSA was a stronger predictor of various outcomes than generalized anxiety. The experience of pregnancy presents unique fears and concerns and these dimensions are captured by items that are included in our measures (e.g., *'I am fearful regarding the health of my baby'; 'I am concerned or worried about losing my baby'; 'I am concerned or worried about developing medical problems during my pregnancy'*).

The finding that fetal and maternal programming may occur in parallel raises interesting possibilities related to long-term consequences. One possibility is that infants/children who are products of pregnancies characterized by elevated stress levels may be subjected to double jeopardy. Fetuses with compromised developmental trajectories by exposures to high stress also are at increased risk for receiving parenting from a depressed mother. Thus, the infant who is already at risk for adverse developmental outcomes, and who has the greatest need of competent mothering, is most likely to receive compromised quality of maternal care. A second possibility involves the adaptive significance of fetal programming. Just as the tadpole adjusts its development to maximize its chances of survival in a hostile environment [157], the human fetus may adjust its development in response to prenatal maternal stress signals in anticipation of a hostile or non-nurturing postnatal environment. The fetus that is stressed in utero and adjusts its development accordingly to prepare for a hostile environment may cope better in the presence of lower quality of maternal care than the fetus that was not exposed to prenatal stress signals and did not make this anticipatory adjustment to its trajectory.

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