

# Linking prenatal maternal adversity to developmental outcomes in infants: The role of epigenetic pathways

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## Abstract

Prenatal exposure to maternal stress, anxiety, and depression can have lasting effects on infant development with risk of psychopathology. Although the impact of prenatal maternal distress has been well documented, the potential mechanisms through which maternal psychosocial variables shape development have yet to be fully elucidated. Advances in molecular biology have highlighted the role of epigenetic mechanisms in regulating gene activity, neurobiology, and behavior and the potential role of environmentally induced epigenetic variation in linking early life exposures to long-term biobehavioral outcomes. In this article, we discuss evidence illustrating the association between maternal prenatal distress and both fetal and infant developmental trajectories and the potential role of epigenetic mechanisms in mediating these effects. Postnatal experiences may have a critical moderating influence on prenatal effects, and we review findings illustrating prenatal–postnatal interplay and the developmental and epigenetic consequences of postnatal mother–infant interactions. The in utero environment is regulated by placental function and there is emerging evidence that the placenta is highly susceptible to maternal distress and a target of epigenetic dysregulation. Integrating studies of prenatal exposures, placental function, and postnatal maternal care with the exploration of epigenetic mechanisms may provide novel insights into the pathophysiology induced by maternal distress.

The developmental origins of disease risk have been established through epidemiological studies in humans and illustrate the profound impact of early life adversity. During prenatal development, the fetus is particularly vulnerable to the effects of a broad range of environmental exposures, with consequences that can persist into infancy, adolescence, and adulthood. In particular, maternal distress during pregnancy, in the form of exposure to chronic or acute stressors, depression, and/or anxiety, can influence both fetal and infant behavioral and physiological outcome measures. For example, antenatal depression and anxiety symptoms predict increased behavioral reactivity and cortisol in response to novelty in infants (Kaplan, Evans, & Monk, 2007; O'Connor, Heron, Glover, & The ALSPAC Study Team, 2002), higher resting cortisol throughout the day among adolescents (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008), and a reduction in gray matter density in the prefrontal cortex (Buss, Davis, Muftuler, Head, & Sandman, 2010; Pruessner et al., 2008). These human studies parallel the findings from decades of animal research that indicate that prenatal stress can induce long-term neurobiological and behavioral effects with particular consequences for the hypothalamus–pituitary–adrenal (HPA) response to stress

(Weinstock, 2005). The stress vulnerability that is established in utero in response to exposure to maternal prenatal stress, depression, and anxiety may ultimately lead to increased risk of psychopathology (O'Connor, Heron, Golding, Beveridge, & Gover, 2002; Pawlby, Hay, Sharp, Waters, & O'Keane, 2009; Talge, Neal, & Glover, 2007).

A critical question within these studies concerns the mechanism through which maternal distress shapes development. An emerging theme within developmental studies is the dynamic interactions between environmental experiences and gene activity achieved through epigenetic mechanisms, which are molecular modifications to gene activity that do not involve changes to the underlying DNA sequence. Although these mechanisms were once thought to be limited in their plasticity to the very early stages of embryonic development, more recent evidence indicates that epigenetic variation can be induced across the life span in response to a broad range of environmental exposures (Champagne, 2010; Jirtle & Skinner, 2007). These epigenetic pathways can give rise to altered gene expression levels in multiple tissues, including the brain, with consequences for the functioning and connectivity of neural circuits, which can confer risk for physical and psychiatric disorders in later life. Thus, the exploration of epigenetic mechanisms in the context of studies of prenatal maternal distress may provide insight into the biological pathways linking fetal exposure to maternal distress and both acute and long-term outcomes.

In this article, we highlight evidence for the impact of human maternal distress on fetal and infant outcomes, and research exploring the role of epigenetic mechanisms in linking

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this form of prenatal adversity to neurobiological and behavioral outcomes. Within the study of prenatal effects, a critical consideration is the continued influence of prenatal maternal adversity during the postnatal period mediated through variations in mother–infant interactions. The quality of interactions between mothers and infants during postnatal development can have a profound impact on development, and these effects may also involve epigenetic pathways. Thus, to compliment the findings from studies of prenatal adversity, here we describe the evidence for shifts in developmental trajectories associated with postnatal maternal care in humans and illustrate evidence from both human and animal studies that these postnatal effects are associated with epigenetic modifications. Finally, during fetal development the placenta serves as a critical interface between the mother and fetus, and dynamic changes in gene regulation within this temporary endocrine structure can have significant implications for growth and development. Epigenetic regulation of gene activity within the placenta can alter functioning of this tissue; in this article, we will describe the evidence suggesting that prenatal distress may act through the placenta to alter fetal development. Overall, these studies provide growing support for the hypothesis that epigenetic pathways may serve as a biological link between maternal psychosocial states during and after pregnancy and psychological, physiological, and neurobiological changes in infants that may increase risk of psychopathology in later life.

### **Prenatal Consequences of Maternal Stress, Depression, and Anxiety in Humans**

There is considerable evidence demonstrating that fetal exposure to maternal psychosocial experiences contributes to the determination of children's neurodevelopmental trajectories (Bale et al., 2010). Data generated largely over the last two decades shows that when pregnant women experience significant stress, anxiety, or depression (each of which are frequently indexed by cortisol levels), their children are at increased risk for biobehavioral characteristics conceptualized as potential precursors to psychopathology (Beydoun & Saftlas, 2008; Charil, Laplante, Vaillancourt, & King, 2010; Talge et al., 2007). The specific findings generated from these studies can vary considerably, however, depending on the methodological approach used to explore the link between maternal adversity and developmental outcomes. Despite wide-ranging methodological approaches, it is evident that maternal psychosocial variables assessed during pregnancy can predict developmental outcomes and that this "transmission of risk" probably occurs independent of the inheritance-specific gene variants. Thus, the quality of the fetal environment, shaped by maternal adversity, can lead to divergent developmental pathways.

#### *Epidemiological studies*

Nearly 40 years ago, seminal epidemiological research on birth cohorts from the Dutch Hunger Winter of 1944 showed

associations between characteristics of pregnant women's lives and offspring's long-term cognitive and mental health development (Stein, Susser, Saenger, & Marolla, 1972; Susser & Lin, 1992). Based on data on adult children of women who were pregnant when food intake was reduced to 500–1000 kcal per day due to the wartime blockade, these studies showed that fetal development during the blockade was associated with a twofold increased risk for neurodevelopmental disorders (Susser, Hoek, & Brown, 1998). Two interpretations regarding the causal mechanisms of these effects have been suggested: (a) deficiency in many micro- and macronutrients or (b) maternal distress, secondary to famine, each having neurotoxic effects on the developing brain. Several subsequent studies, each based on the Dutch Famine, found similar elevated risk for adult psychopathology in relation to fetal exposure to this maternal experience. Overall, these studies suggest that exposure to this event in the first trimester increases the offspring's risk for future schizophrenia, whereas exposure in the second or third trimester is associated with elevated risk for affective disorders (Brown, Van Os, Driessens, Hoek, & Susser, 2000; Hoek, Brown, & Susser, 1998; Susser et al., 1998; Susser, Brown, & Matte, 1999). It is important to note, however, that these findings are based on a population's experience of the Dutch Famine and do not measure individual exposure.

The impact of prenatal exposures, and, in particular, maternal distress, on an individual level has been explored in several cohort studies. In a Danish cohort of 1.38 million births, traumatic events occurring during pregnancy were documented and used to predict risk of psychopathology among offspring (Khashan et al., 2008). In this cohort, the death of a relative during the first trimester was associated with an increased risk of schizophrenia, although this did not hold for those who had a family history of mental illness (Khashan et al., 2008). There has been some evidence linking prenatal distress to autism (Beverdors et al., 2005; Kinney, Miller, Crowley, Huang, & Gerber, 2008), although a recent population-based cohort study (1.49 million births) also using individual exposure assessment found no association between maternal distress due to the death of a relative and risk of autism (Li et al., 2009). These studies, based on archived health records, point to links between maternal prenatal distress and children's risk for psychopathology.

#### *Prospective, event-based studies of prenatal distress effects: Natural disasters*

Consistent with the Dutch Famine studies, population exposure to events such as wars (Malaspina et al., 2008; Seltzer et al., 2003) and earthquakes (Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001) as a proxy for prenatal distress have been associated with negative effects on child outcomes. One series of studies, based on the 1998 ice storm in Quebec, Canada, prospectively followed a cohort of women pregnant during the ice storm up until the children were 8 years of age (Charil et al., 2010; King & Laplante,

2005; Laplante et al., 2004; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). This work differentiated “objective distress” (i.e., what events the woman experienced related to the storm, e.g., loss of electrical power) from “subjective distress” (i.e., women’s self-reported psychological reaction to the ice storm); the former is randomly distributed and independent of potentially heritable personality traits whereas the latter is not. Children prenatally exposed to high versus low levels of objective distress, particularly during the first or second trimester, exhibited poorer cognitive, linguistic, and play abilities at 2, 5, and 8 years of age (Charil et al., 2010; King & Laplante, 2005; Laplante et al., 2004, 2008).

#### *Longitudinal, observational infant and child research*

Spanning infancy through adolescence, numerous reports of prospective, observational studies indicate that prenatal distress exposure predicts an increased likelihood of poor emotion regulation, as evidenced with the difficult temperament and symptoms of attention-deficit/hyperactivity disorder (ADHD). Maternal prenatal anxiety and depression across pregnancy, assessed via self-report, and higher cortisol in the third trimester, were found associated with fearful behavior in infants at 2 months of age (Davis et al., 2007), and, during the third trimester, greater motor and cry responses to novelty at 4 months of age (Davis et al., 2004). In a prospective study of 179 women, elevated pregnancy-specific anxiety throughout gestation (in contrast to more global state/trait anxiety) predicted a more negative infant temperament at 3 months, after controlling for maternal postnatal distress (Sandman, Davis, Buss, & Glynn, 2011). Among 4-month-old infants, symptoms of maternal depression and anxiety during the third trimester were associated with greater cry responses to novelty. Infants categorized by calm reactions to novel stimuli were, in contrast, 8.4 times as likely as other infants to have a mother free of psychiatric symptoms (Werner et al., 2007).

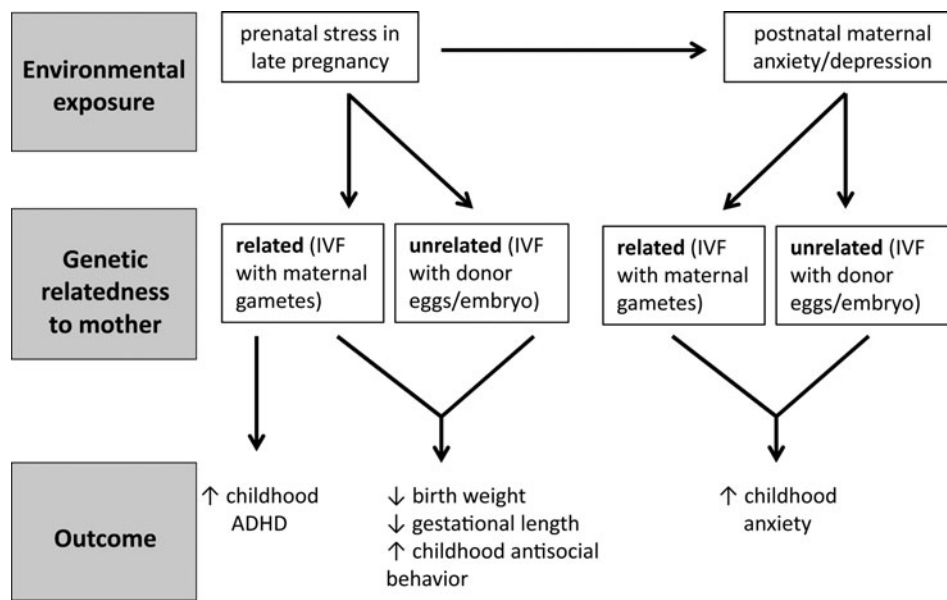
Following children to 2 years of age, higher pregnancy-specific anxiety in the second trimester predicts greater likelihood of increased negative temperament (Blair, Glynn, Sandman, & Davis, 2011) and fear behavior (Bergman, Sarkar, O’Connor, Modi, & Glover, 2007). Prenatal anxiety exposure in the third trimester has been associated with behavioral/emotional problems among 4-year-olds (O’Connor, Heron, Bolding, et al., 2002) and ADHD symptoms among 6-year-olds (O’Connor, Heron, Golding, & Glover, 2003). For 8- and 9-year-old children, elevated prenatal anxiety in the first and second trimester accounted for 22% and 15% of the variance in teacher- and parent-rated ADHD and externalizing symptoms, respectively (Van den Bergh & Marcoen, 2004). Follow-up studies of this same cohort to 15 years of age showed that prenatal anxiety predicted poorer performance on a continuous performance task for boys (a validated instrument for detection of ADHD symptoms (Van den Bergh et al., 2006) and greater impulsivity for both boys and girls (Van den Bergh et al., 2005). Finally, depression

during pregnancy has been linked to risk for depression in adolescents independent of the impact of the mothers’ subsequent depressions throughout the child’s life (Pawlby et al., 2009). What emerges from these studies is a risk profile associated with prenatal exposure to maternal distress: less adaptive emotion regulation, evidenced in particular by greater reactivity to stimuli, which may be an early marker of stress-linked psychopathology, as well as ADHD symptoms. Animal studies of prenatal stress exposure (which largely control for genetic transmission) produce similar results, in other words, offspring who are more distractible and “anxious” (Clarke & Schneider, 1997; Schneider, 1992; Schneider, Roughton, Koehler, & Lubach, 1999; Takahashi, Baker, & Kalin, 1990; Takahashi, Haglin, & Kalin, 1992). In an attempt to tease apart genetic from environmental influence on infant/childhood outcomes in humans, a comparison of children conceived through donor eggs (i.e., having maternal genetic dissimilarity) versus IVF (i.e., having maternal genetic similarity) suggests that the emergence of ADHD was based on shared genetic factors, whereas exposure to prenatal distress could increase the risk of antisocial behavior in children (Rice et al., 2009; see Figure 1).

It is important to note that, with some exceptions (Bergman et al., 2007; Davis et al., 2004; Pawlby et al., 2009; Van den Bergh & Marcoen, 2004; Van den Bergh et al., 2005, 2006; Werner et al., 2007), these studies rely on maternal reports for the predictive variable (prenatal distress) and dependent variable (child behavior). Although some researchers argue that parents are the best source of descriptions of their children (Rettew & McKee, 2005), others have questioned whether maternal reports of infant behavior are sufficiently unbiased, or reflective of, and, therefore, highly correlated with maternal distress, which often is maintained from the pregnancy to the postnatal period (DiPietro, Hodgson, Costigan, & Johnson, 1996a; Pesonen, Raikkonen, Strandberg, & Jarvenpaa, 2005; Zeanah, Keener, Stewart, & Anders, 1985). Moreover, although these studies control for maternal postnatal distress proximal to the child’s birth and still identify prenatal effects, the question of whether the prenatal maternal distress is a marker for compromised maternal care throughout development, which itself is an agent of influence, is only rarely considered (see Bergman, Sarkar, Glover, & O’Connor, 2010; Grant et al., 2009; Kaplan et al., 2007).

#### *Infant and child biological outcomes*

The biological impact of prenatal exposure to maternal distress has also been explored and dysregulation of HPA function has been implicated as a primary outcome. At birth, infants exposed to higher levels of maternal plasma cortisol in the second and third trimesters had a larger cortisol response to a heel-stick procedure (Davis, Glynn, Waffarn, & Sandman, 2011). In a study of 4-month-old infants, exposure to third trimester prenatal depression and anxiety, based on psychiatric interviews, predicted higher cortisol levels upon entering a laboratory setting (Kaplan et al., 2007). Among



**Figure 1.** The prenatal cross-fostering design in the study of the effects of human maternal distress. Although differentiating the impact of genetic and environmental factors in predicting childhood outcomes associated with maternal distress is challenging in humans, studies examining mothers who have used in vitro fertilization (IVF) may provide a useful experimental design. Rice et al. (2009) examined birth outcomes and childhood psychopathology among infants who were genetically related (IVF using mother's own gametes) or genetically unrelated (IVF with donor eggs/embryo) to their mother. Prenatal stress in late pregnancy was found to predict reduced birth weight and gestational length and a higher incidence of childhood antisocial behavior regardless of genetic relatedness to the mother. Prenatal stress was likewise found to predict increased childhood anxiety regardless of maternal genetic relatedness, although this effect was found to be mediated in part by maternal postnatal anxiety/depression. In contrast, increased risk of attention-deficit/hyperactivity disorder was observed only in response to prenatal stress when there was genetic relatedness between mother and infant, which suggests a significant genetic contribution to this outcome.

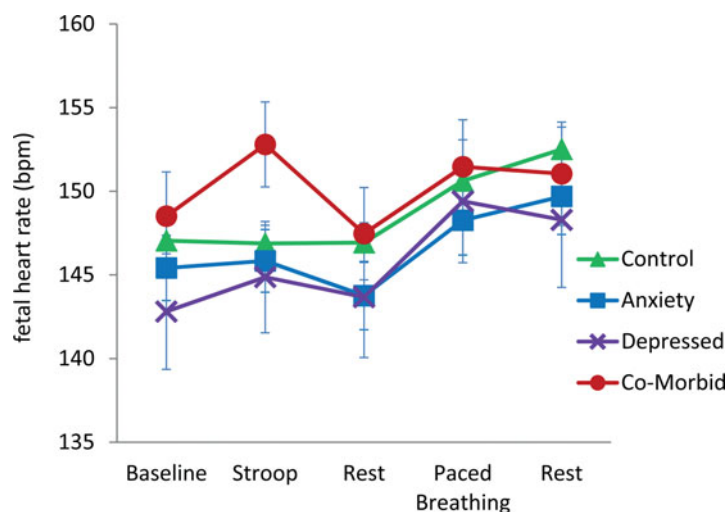
7-month-old infants exposed prenatally to maternal anxiety, heightened cortisol activation was observed even after the experimental procedures were completed (Grant et al., 2009). A high-flattened, daytime cortisol profile (Van den Bergh et al., 2008) and higher cortisol levels upon awakening (O'Connor et al., 2005) have been observed in preadolescents and adolescents and are related to prenatal distress exposure. Neurobiological correlates of exposure to prenatal maternal distress have also been identified. In a prospective report, children exposed to maternal prenatal anxiety in the second trimester were found to have reduced gray matter volume in the prefrontal cortex, premotor cortex, the medial temporal lobe, and other areas involved with learning and memory (Buss et al., 2010). Although these studies of the biological impact of maternal prenatal stress provide promising insights into the pathophysiology of these early life exposures, the issues of the moderating or mediating effects of postnatal factors are typically not explored within these approaches.

#### *Fetal neurobehavior related to maternal distress*

Assessment of fetal neurobehavioral outcomes within the study of prenatal exposures provides an opportunity to examine prenatal effects prior to the potential influence of the postnatal period. During baseline assessments, heightened maternal stress was found to be associated with reduced fetal

heart-rate variability (DiPietro, Hodgson, Costigan, & Johnson, 1996b) as well as increased fetal movement (DiPietro et al., 2002). Maternal prenatal depression was also associated with increased motor activity (Dieter et al., 2001; Emory & Dieter, 2006). Higher levels of maternal cortisol have been positively associated with greater amplitude of fetal movement, as well as the amount of time spent moving (DiPietro, Kivighan, Costigan, Laudenslager, 2009). In contrast, women who endorsed greater trait anxiety had fetuses that spent more time in quiet sleep and showed less gross body movement in active sleep (Groome, Swiber, Bentz, Holland, & Atterbury, 1995). Differences in fetal assessment may account for this seemingly conflicting finding (i.e., ultrasound vs. Doppler actigraphy).

Additional approaches to fetal assessments involve exposing mothers to psychological challenge (e.g., using the Stroop task) or directly stimulating the fetus via a vibroacoustic probe. It has been shown that although fetuses of nonanxious and psychiatrically healthy women do not show a heart-rate change during the Stroop task, fetuses of anxious and depressed women show a significant heart-rate increase (Monk et al., 2000, 2004, 2011; see Figure 2). In the most recent results, maternal cortisol levels were marginally positively associated with fetal heart-rate activity (Monk et al., 2010). When stimulated directly with a vibroacoustic probe, fetuses of women with elevated levels of corticotropin releas-



**Figure 2.** Fetal heart rate during the laboratory protocol by women's diagnostic status. In a sample of third trimester pregnant women (Monk et al., 2011), fetuses of women with diagnosed depression and anxiety showed greater heart rate reactivity during Stroop compared to those in the other groups. There was a trend for maternal salivary cortisol to be positively associated with fetal heart rate. [A color version of this figure can be viewed online at <http://journals.cambridge.org/dpp>]

ing hormone (CRH; which, during pregnancy, is predominantly of placental origin, and can be increased by maternal cortisol) failed to respond to a novel stimulus in a habituation/dishabituation paradigm. In addition, higher CRH has been related to higher overall fetal heart-rate reactivity to stimulus (Sandman, Wadhwa, Chicz-DeMet, Proto, & Garite, 1999). Taken together, these findings suggest a similar biobehavioral profile to that of a child exposed to maternal prenatal distress: greater activity and reactivity, and a possible decrement in a rudimentary form of discrimination (e.g., during the habituation studies). Thus, these approaches may provide a valuable new strategy for exploring the early origins of maternal adversity-induced risk of psychopathology.

### Effects of Stress, Depression, and Anxiety on Mother–Infant Interactions During the Postpartum Period

Exposure to maternal distress during fetal development is highly correlated with continued exposure during postnatal development, which highlights the importance of considering postnatal factors within the study of prenatal effects. Maternal prenatal depression is strongly associated with risk for postpartum depression (PPD) and one-third of pregnant women with depressive symptomatology have been reported to experience depression during the postpartum period (Beck, 1996; Gotlib, Whiffen, Mount, Milnes, Cordy, 1989; O'Hara & Swain, 1996). Distress during pregnancy is also associated with increased risk for PPD. For example, distress-related risk factors in the prenatal period that predict PPD symptoms include anxiety (Beck, 1996; O'Hara & Swain, 1996; Sutter-Dallay, Giaccone-Marcésche, Glatigny-Dallay, & Verdoux, 2004), recent intimate partner violence (Valentine, Rodriguez, Lapeyrouse, & Zhang, 2011), marital adjustment, over-

all low social support, inadequate support from the baby's father (O'Hara & Swain, 1996), and low socioeconomic status (Goyal, Gay, & Lee, 2010). When pregnant women were divided into high- and low-risk groups based on depression-related risk factors, 25% of those in the high-risk group (versus 6% in the low-risk group) developed PPD, and depressive symptomatology during pregnancy independently predicted PPD (Verkerk, Pop, Van Son, & Van Heck, 2003). It seems that when a child experiences an altered in utero environment linked to maternal mood, there likely is continuity to the postpartum environment in the form of maternal PPD or depressive symptoms. This continuity has significant implications for the quality of the postnatal environment, particularly the quality of maternal care.

Healthy mother–infant interactions are critical to the development of healthy children and adults. Specifically, the quality of maternal caregiving behavior (MCB) during infancy has been linked to outcomes such as emotion regulation, social adjustment, stress reactivity, cognitive abilities, and risk for psychopathology. Maternal adversity, in the form of psychosocial distress, negatively affects MCB, and, therefore, results in poor outcomes for children and adolescents. Maternal depression during infancy (or since birth) predicts higher waking cortisol levels during adolescence (Murray, Halligan, Goodyer, & Herbert, 2010), larger amygdala (but not hippocampal) volume and higher cortisol level at 10 years (Lupien et al., 2011), greater childhood internalizing and total behavior problems (Bagner, Pettit, Lewinsohn, & Seeley, 2010), and greater childhood and adolescent depressive symptoms (Bureau, Easterbrooks, & Lyons-Ruth, 2009). Moreover, adverse outcomes can emerge as early as infancy (Kikkert, Middelburg, & Hadders-Algra, 2010). Maternal, but not paternal, trait anxiety has been related to less optimal neurological de-

velopment of the infant as measured by the Towne Infant Neurological Examination at 10 months of age. Even typical variations in MCB predicts differences in infant emotion regulation (Hane & Fox, 2006). Variations in the quality of MCB, assessed in terms of maternal sensitivity and responsiveness during multiple mother–infant interactions, were found to predict infant stress reactivity as indexed by right frontal EEG asymmetry, fear reactivity, and positive sociability with a stranger. Relative to high MCB, low MCB was associated with greater right frontal EEG asymmetry and fear reactivity and less positive sociability, and these findings have been extended to stress reactivity outcomes at 2 and 3 years of age (Hane, Henderson, Reeb-Sutherland, & Fox, 2010).

#### *Maternal distress and MCB*

Assessment of the quality of postnatal mother–infant interactions with a focus on the mother typically measures variables such as maternal sensitivity and responsivity during dyadic interactions such as free play, diaper changing, and feeding. Postnatal maternal depression has been shown to reduce maternal responsivity to infants 6 months of age (Forman et al., 2007) and increase maternal hostility–intrusiveness to infants 18 months of age (Bureau et al., 2009). Mothers with anxiety show hyperarousal during free play with infants 6 months of age (Kaitz, Maytal, Devor, Bergman, & Mankuta, 2010), less sensitivity and reduced emotional tone during free play with infants 10–14 months of age (Nicol-Harper, Harvey, & Stein, 2007), less maternal sensitivity during free play with infants 9 months of age (Feldman et al., 2009), and exaggerated behavior during free play and teaching with infants 6 months of age (Kaitz et al., 2010). Finally, maternal stress has been associated with less maternal sensitivity to infant cues in a vocal elicitation paradigm (Crnic, Greenberg, Schetter, Hobel, & Chicz-Demet, 1984).

#### *Maternal distress and infant behavior*

Maternal distress can also lead to altered behavioral reactions to mothers. One assessment approach is the use of the Still Face paradigm, during which mothers are asked to become unresponsive to their infants for a brief period of time, and infant reactivity is measured. In a study that compared responses to the Still Face paradigm in 5-month-old infants of depressed versus nondepressed mothers, infants of depressed mothers were found to engage in a self-soothing strategy, whereas infants of nondepressed mothers engaged in an attention strategy (Manian & Bornstein, 2009). This finding suggests that infants use varying emotion regulation strategies as a function of maternal depression, and is consistent with earlier work showing that infants of depressed mothers first attempt to use external regulation, and then engage in self-directed regulatory behavior (Gianino & Tronick, 1985; Tronick & Gianino, 1986). Infants have also been observed to display negative affect when interacting with mothers who have depression or with healthy mothers who simulate de-

pression (Gianino & Tronick, 1985; Tronick & Gianino, 1986). Depressed mood in healthy women reduces infant responsivity and infant positive responses (Zekoski, O'Hara, & Wills, 1987): infants look less at depressed mothers and appear distressed (Cohn, Matias, Tronick, Connell, & Lyons-Ruth, 1986; Tronick, 1989), and infants of depressed mothers show low social engagement (Feldman et al., 2009). Likewise, maternal anxiety was found to be associated with reduced social engagement among infants (Feldman et al., 2009), although less negative affect in the Still Face paradigm was observed (Kaitz et al., 2010), and maternal stress was found to be associated with less infant responsivity (Crnic et al., 1984). Infant attachment, as measured by the Strange Situation task, also varies significantly in association with maternal distress. Infants of depressed mothers are more likely to show insecure attachment (Martins & Gaffan, 2000; McMahon, Barnett, Kowalenko, & Tennant, 2006; Teti, Felfand, Messinger, & Isabella, 1995), and a disorganized attachment style has been linked to the chronicity of maternal depression (Teti et al., 1995). Maternal trauma has likewise been found to predict insecure infant attachment (Lyons-Ruth & Block, 1996).

#### *Maternal distress and mother–child interactions*

The coordination of behavior between mother and infant may also be sensitive to the effects of maternal distress. For example, dyadic gaze rhythm can be measured to assess the level of predictability and expectancy between a mother and infant when they look at and away from one another's faces. In a study that compared mother–infant dyads with either low- or high-distressed mothers, maternal distress related to less efficient gaze rhythm, suggesting that establishing predictable patterns of eye gaze may be more difficult for dyads of infants and high-distress mothers (Beebe et al., 2008). Predictability of behavioral responses can also be assessed through the observed contingency of behavior between dyads (interactive contingency) or within an individual (self-contingency). Anxious mothers have been found to exhibit heightened (vigilant) interactive and self-contingencies in some modalities and lowered (withdrawn) interactive and self-contingencies in others, whereas infants of anxious mothers exhibited lowered self-contingency (Beebe et al., 2011). Anxious mothers were found to engage in heightened visual monitoring, but lowered emotional coordination with their infants. Taken together, these studies suggest that maternal adversity may lead to aberrant forms of social coordination/communication between mothers and infants.

#### *Potential underlying mechanisms*

It has been suggested that the primary parenting demands during infancy are (a) to establish a secure attachment with the infant and (b) to foster development of emotion regulation in the infant (Goodman & Gotlib, 1999). In the case of distressed mothers, it appears likely that there is reduced attain-

ment of these goals. Infants of distressed mothers exhibit insecure attachment styles (Martins & Gaffan, 2000; McMahon et al., 2006; Teti et al., 1995) and increased fear reactivity (Feldman et al., 2009), whereas in healthy participants, the quality of MCB has been linked to reduced fear reactivity (Hane & Fox, 2006). It may also be the case that exposure to maternal depression-associated negative cognition, affect, and behavior affects the infant through social learning or modeling (Goodman & Gotlib, 1999). Infants of depressed mothers tend to show more negative affect, flatter affect, and less positive responsivity (Dawson, Klinger, Panagiotides, Hill, & Spieker, 1992; Gianino & Tronick, 1985; Tronick, 1989; Zekoski et al., 1987). Infants of depressed mothers may also experience inadequate arousal and stimulation (Field, 1998). Depressed mothers have been found to be less responsive to verbal utterances (Bettes, 1989) and to provide less tactile stimulation (gentle touching, stroking; Field, 2002). Tactile experiences during the postnatal period have been demonstrated to influence pain sensitivity, affect, and growth in neonates (Field, 2010), and the reciprocal tactile stimulation between mother and infant may contribute to increased maternal responsiveness and infant attachment (Bystrova et al., 2009; Field, 2010). Thus, mood/stress-induced reductions in this form of MCB may serve as a critical mechanism for shifting psychological and physical development in infants.

### Epigenetic Perspectives on the Impact of Prenatal Adversity

Studies of the impact of prenatal maternal distress suggest that this form of early life adversity can lead to neurobiological, behavioral, and psychological consequences for infants. Moreover, this distress can also lead to altered mother–infant interactions during the postpartum period, which has been demonstrated to shift developmental trajectories. Thus, it is evident that development is a dynamic process during which shifts in the experiences of the fetus and infant can have profound consequences. In the case of maternal distress, the psychosocial characteristics of the mother can induce these effects, raising the question of how these effects are achieved. An evolving approach that has been applied to address this question involves exploring the biological mechanisms through which environmental exposures shape the activity of genes within the developing organism. This epigenetic perspective has been a significant breakthrough in linking the psychological and physiological experiences of an individual to mechanistic pathways within cells that either enhance or reduce gene expression with consequences for multiple biological and behavioral outcomes.

#### *Epigenetic mechanisms and gene regulation*

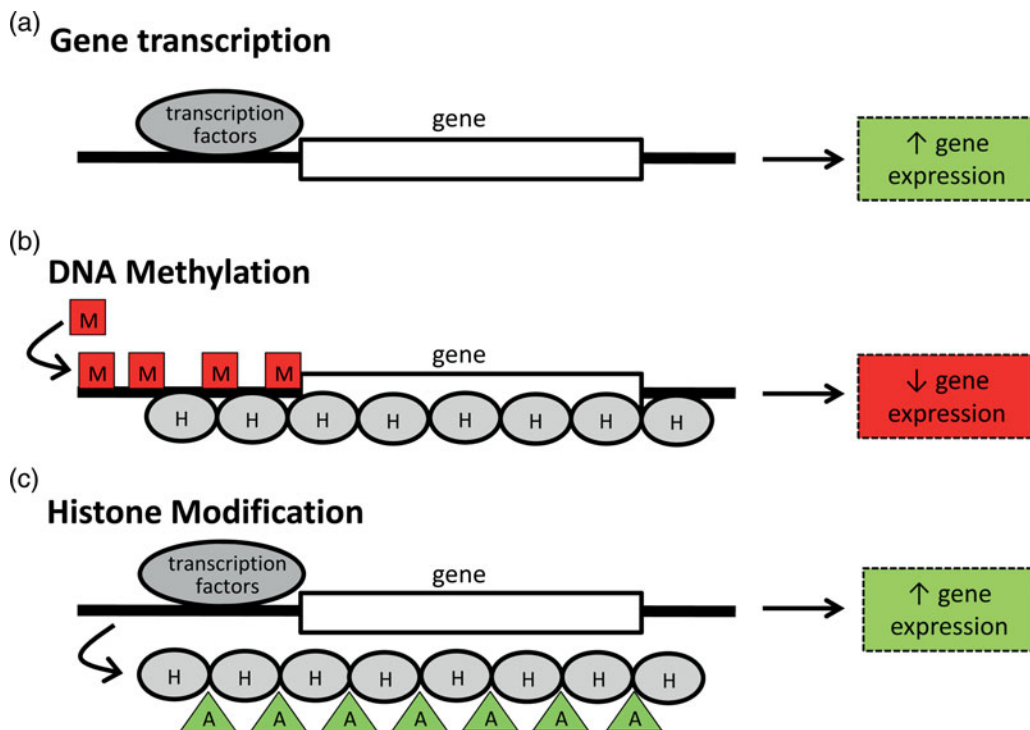
The term *epigenetic* is attributed to the developmental biologist Conrad Waddington, who, in the 1940s and 1950s, posited that interactions between genes and their products lead to

the diverging characteristics of cells in an organism (Jablonka & Lamb, 2002). This epigenesis of cellular “phenotypes” emphasized the dynamic process of development and the stable maintenance of characteristics once they had emerged. Advances in molecular biology have led to the identification of specific molecular mechanisms through which this process is achieved, and thus the more modern applications of epigenetic refer to those mechanisms. Gene regulation is a complex process and is dependent on a cascade of protein–protein, protein–DNA, and enzymatic interactions that ultimately determine the accessibility of DNA to the process of gene transcription (Turner, 2001). DNA methylation and posttranslational histone modifications (Peterson & Laniel, 2004; Razin, 1998; Umlauf, Goto, & Feil, 2004) are two mechanisms through which this accessibility can be altered (see Figure 3) and have been explored within the context of environmentally induced changes in gene activity that may be relevant to our understanding of the pathways by which prenatal adversity can lead to altered infant and childhood outcomes.

#### *DNA methylation and histone modifications*

Within DNA, cytosine nucleotides can undergo the process of methylation, which is the addition of a methyl chemical group to the cytosine. This modification is not a mutation and is potentially reversible. When cytosines become methylated, there is generally less accessibility to the DNA (although the location of the methylated cytosine within the gene sequence is an important predictor of this accessibility), so, as a result, DNA methylation is thought to be a process leading to gene silencing (Razin, 1998). Methylated cytosines can also attract methyl-binding proteins, which cluster around the DNA and attract enzymes that can shift the state of the histone proteins around which the DNA is wrapped, a process that can further reduce access to the DNA (Fan & Hutnick, 2005). The addition of methyl groups to DNA is accomplished via a class of enzymes called DNA methyltransferases (e.g., *DNMT1* and *DNMT3a/b*; Turek-Plewa & Jagodzinski, 2005). Disrupting these enzymes, using targeted gene-deletion techniques, results in genome-wide hypomethylation, impairments in growth, and embryonic or postnatal lethality (Li, Bestor, & Jaenisch, 1992; Okano, Bell, Haber, & Li, 1999), which highlights the critical role of DNA methylation in development. In particular, DNA methylation is a process that maintains cellular differentiation. As cells become more specialized, taking on the characteristics of a specific cell type (i.e., muscle cells, neurons, skin cells), DNA methylation patterns must be reliably copied during the process of cell division or the unique characteristics of the cell will be lost when the cell divides. Thus, DNA methylation patterns are heritable during cell division and are also potentially very stable, generating cellular diversity among genetically identical cells (Jones & Taylor, 1980).

Modification to histone proteins is another critical epigenetic process that can either increase and decrease accessibility to DNA. In order to compact DNA within the cell nucleus,



**Figure 3.** A schematic illustrating epigenetic regulation of gene expression. (a) Gene expression (production of mRNA from DNA) is dependent on the binding of transcription factors to the region upstream of the coding region of the gene. (b) DNA methylation involves the addition of methyl chemical groups (M) to the DNA. This modification reduces accessibility of the DNA to transcription factors, increases the interactions between histone proteins (H) and DNA, and generally leads to decreased gene expression. (c) Modification of histone proteins, such as addition of acetyl chemicals (A), can reduce the interactions between histones and DNA, increase the access of DNA to transcription factors, and lead to increased gene expression. [A color version of this figure can be viewed online at <http://journals.cambridge.org/dpp>].

the DNA is wrapped around a core of histone proteins (Turner, 2001). The “tails” of these histone proteins can undergo multiple posttranslational modifications that will alter the dynamic interactions between these proteins and the DNA. For example, histone acetylation is a process whereby an acetyl chemical is added to the histone protein tail and is typically associated with increased gene expression due to a looser interaction between the histones and the DNA (Peterson & Laniel, 2004; Umlauf et al., 2004). Histone methylation can result in either enhanced or reduced gene expression, depending on the location within the histone tail of the methyl group (Barski et al., 2007; Koch et al., 2007). There are many chemicals that can be added or removed from the histone tails, resulting in histone phosphorylation, methylation, and ubiquitination and various other chemical modifications. Taken as a group, these modifications result in a “histone code,” which is a dynamic and complex strategy for reducing or enhancing gene expression (Jenuwein & Allis, 2001). As is the case for DNA methylation, there are specific enzymes that facilitate these epigenetic modifications (Legube & Trouche, 2003), and disrupting these enzymes can result in significant impairments in development. For example, targeted deletion of a histone acetyltransferase gene can be lethal and induce deficits in neural tube closing (Xu et al., 2000; Yao et al., 1998); in addition, mutation of the histone methyltransferase euchromatic histone-lysine *N*-methyl-

transferase 1 has been found to be associated with severe developmental delay in humans (Kleefstra et al., 2006).

#### *Epigenetic effects of prenatal adversity*

Although epigenetic modifications (particularly DNA methylation) were once thought to be limited in plasticity to early embryonic development, it is becoming evident that both DNA methylation and histone modifications are dynamic and changeable across the life span (Champagne, 2010). Given this plasticity, epigenetic variation may be induced by experiences occurring during prenatal and postnatal development and therefore may be a mechanistic link between maternal adversity and infant outcomes. In humans, the epidemiological studies involving the Dutch Hunger Winter birth cohort have explored whether DNA methylation is altered as a function of this early-life exposure. Analysis of whole blood samples from exposed versus nonexposed sibling pairs has indicated that periconceptual exposure to conditions of famine/stress are associated with differential methylation of several genes among adults (Heijmans et al., 2008; Tobi et al., 2009). In particular, decreased DNA methylation was found within the insulin-like growth factor II (*IGF2*) gene among exposed compared to nonexposed siblings (Heijmans et al., 2008). *IGF2* plays a significant role in growth and development (Smith, Garfield, & Ward, 2006) and is likely a key factor in regulating

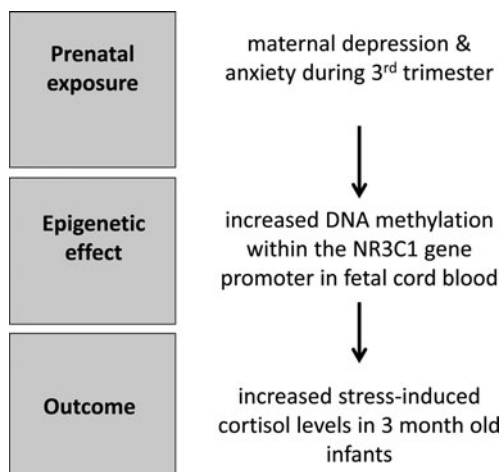


many of the outcomes associated with prenatal adversity. Within this cohort, several other genes, including insulin/insulin-like growth factor-1, interleukin-10, leptin, ATP-binding cassette transporter 1, guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1 antisense RNA 1, and maternally expressed 3 were found to have altered DNA methylation levels (Tobi et al., 2009), suggesting widespread epigenetic effects of this early life exposure. These effects appear to be timing specific, with differential DNA methylation most evident when exposure occurred during the periconceptual period rather than in late gestation.

Although sibling studies within the Dutch Hunger Winter cohort did not find significant effects on genes associated primarily with the HPA axis, such as *CRH* and the glucocorticoid receptor (nuclear receptor subfamily 3, group C, member 1 [*NR3C1*]), studies of prenatal maternal stress and depression have provided evidence of epigenetic dysregulation within HPA pathways. Analysis of cord blood samples from infants born to mothers with elevated ratings of depression (using the Hamilton Depression Scale) during the third trimester of pregnancy indicated elevated levels of DNA methylation within the *NR3C1* gene (Oberlander et al., 2008). These epigenetic effects were observed in fetal but not maternal blood samples. At 3 months of age, infant HPA reactivity was assessed using a habituation information processing task during which salivary cortisol levels were measured. Levels of *NR3C1* DNA methylation in fetal cord blood were found to predict infant cortisol response to stress, suggesting a functional consequence of this epigenetic variation (see Figure 4). The persistence of these prenatal effects on *NR3C1* DNA methylation beyond infancy has also been demonstrated. Children and adolescents (age 10–19 years) born to women who had experienced stress in the form of intimate partner

violence during pregnancy were found to have elevated *NR3C1* DNA methylation levels in whole blood samples (Radtke et al., 2011). As was observed in the case of prenatal maternal depression, these epigenetic effects were present in offspring blood samples, but were not evident in maternal blood samples. Methylation within the gene encoding the serotonin transporter (solute carrier family C6 member 4 [*SLC6A4*]) gene, has been found to be reduced in cord blood samples in response to increased maternal depressed mood during the second trimester, whereas no effects on brain-derived neurotrophic factor (*BDNF*) were observed (Devlin, Brain, Austin, & Oberlander, 2010).

Although there has been increasing exploration of epigenetic effects in human cohort studies, the meaning of these epigenetic changes in blood is unclear. However, animal models have demonstrated that, under controlled laboratory conditions, exposure to prenatal stress can induce epigenetic variation within brain regions involved in the behavioral characteristics associated with this form of prenatal adversity. In mice, chronic variable stress exposure during the first gestational week (first trimester) results in increased corticosterone response to stress and increased depressive-like behavior (Mueller & Bale, 2008). In adult male offspring, prenatal stress is associated with decreased DNA methylation of the *CRH* gene and increased methylation of the *NR3C1* gene in hypothalamic tissue of adult male offspring. Moreover, there is altered expression of these genes (increased *CRH* expression and decreased glucocorticoid receptor expression) in response to prenatal stress, which probably induces increased HPA reactivity in offspring. Thus, animal studies can be used to provide support for the validity of target genes identified in human studies using peripheral blood samples, which enable us to explore the mechanistic pathways through which prenatal adversity alters the brain and behavior.



**Figure 4.** The impact of prenatal maternal depression/anxiety on DNA methylation and infant stress response. Oberlander et al. (2008) found that maternal depression and anxiety assessed during pregnancy (third trimester) was significantly correlated with the degree of DNA methylation within the glucocorticoid receptor gene (nuclear receptor subfamily 3, group C, member 1 [*NR3C1*]) measured in fetal cord blood. At 3 months of age, this epigenetic effect was found to predict increased infant cortisol response to stress.

### Epigenetic Effects During Postnatal Development

The epigenetic impact of postnatal mother–infant interactions has also been explored in both humans and animals and, as has been previously described, may be an important consideration in studies of prenatal adversity. Deprivation of parental care, such as that observed in institutionalized infants, has been found to have broad epigenetic consequences. Among institution reared (since birth) children aged 7–10 years, analysis of blood samples indicates increased DNA methylation throughout the genome when compared to age-matched children reared by their biological parents (Naumova et al., 2012). Among the differentially methylated genes are those implicated in brain development, including genes within vasopressinergic, serotonergic, glutamatergic, and GABAergic pathways. The epigenetic effects of childhood abuse have also been observed in human brain tissue (McGowan et al., 2009). Analysis of gene expression and DNA methylation levels in postmortem hippocampal tissue from adults with or without a documented history of childhood abuse has indicated decreased expression of the *NR3C1* gene and increased DNA methylation

within the regulatory region of the *NR3C1* gene associated with a history of childhood abuse. Decreased levels of glucocorticoid receptors within the hippocampus can lead to a heightened HPA response to stress and, in particular, a decreased capacity to regulate the stress response. As such, the epigenetic effects on *NR3C1* induced by postnatal adversity may account for the increased risk of psychopathology and poorer emotional regulation among individuals with a history of abuse.

#### *Variation in maternal care in rodents*

Although there is certainly emerging data from human cohorts indicating the impact of postnatal experiences on epigenetic pathways, it is animal studies that have provided a significant basis for this exploration. In particular, studies of laboratory rodents illustrate the neurobiological and behavioral consequences of variations in maternal care within the normal range, and the role of epigenetic mechanisms in the long-term consequences of maternal care on offspring outcomes (Meaney, 2001; Meaney & Szyf, 2005). Rodents provide tactile stimulation to offspring through licking/grooming (LG) of pups and this form of maternal care has been found to influence HPA reactivity, cognition, and the reproductive behavior of offspring (Caldji et al., 1998; Cameron et al., 2008a; Champagne et al., 2008; Champagne, Francis, Mar, & Meaney, 2003; Liu, Diorio, Day, Francis & Meaney, 2000; Liu et al., 1997). Gene expression within the hippocampus and hypothalamus has been found to be altered in adult offspring that experienced low versus high levels of LG during the postnatal period, and may account for the behavioral and physiological effects of LG. Males that have experienced low versus high LG are observed to have reduced levels of hippocampal glucocorticoid receptors within the hippocampus, which probably accounts for the increased HPA reactivity of these offspring (Liu et al., 1997). Analysis of DNA methylation within the *NR3C1* gene indicates that experiencing low levels of LG is associated with increased DNA methylation at several sites within this gene (Weaver et al., 2004). These adult patterns of DNA methylation are not observed prenatally or at the time of birth, but instead emerge during the first postnatal week. Histone acetylation (histone H3 lysine 9) is also reduced within the *NR3C1* gene in low-LG compared to high-LG offspring. It is worth noting that these early life effects on *NR3C1* can be modified in adulthood through pharmacological manipulations that increase histone acetylation or increase the potential for DNA methylation, which suggests a high degree of plasticity within these epigenetic pathways (Weaver et al., 2004, 2005). Maternal LG also leads to altered levels of *DNMT1* in the hippocampus, so that male offspring that receive low levels of LG have elevated levels of *DNMT1* mRNA (Zhang et al., 2010). In addition to hippocampal glucocorticoid receptors, maternal LG has been found to alter expression of the enzyme glutamic acid decarboxylase gene, and analysis of DNA methylation within the glutamic acid decarboxylase gene indicates that there is heightened DNA methylation and reduced

histone acetylation of this gene that can be observed to persist into adulthood among offspring that experience low levels of postnatal LG (Zhang et al., 2010). Genome-wide analysis of gene-expression profiles in the hippocampus of male offspring that have received low versus high levels of maternal care indicate that over 900 genes are differentially expressed in the hippocampus as a function of maternal LG, and that, overall, there is increased gene expression among adult offspring of high LG compared to low LG dams (Weaver, Meaney, & Szyf, 2006). These findings suggest widespread epigenetic consequences of maternal care.

The effects of maternal LG on female offspring have primarily focused on reproductive outcomes such as sexual and maternal behavior (Cameron et al., 2008a; Cameron, Fish, & Meaney, 2008b; Champagne, Francis, et al., 2003), although it should be noted that females display similar stress responsiveness profiles to their male siblings as a function of maternal LG (e.g., low LG associated with behavioral inhibition to novelty; Champagne & Meaney, 2007). Among female offspring that received low levels of LG during the postnatal period, there is decreased mRNA and protein levels of estrogen receptor alpha ( $ER\alpha$ ) in the medial preoptic are (MPOA), which may account for the reduced estrogen sensitivity and maternal care evident in these offspring (Champagne, Diorio, Sharma, & Meaney, 2001; Champagne, Weaver, Diorio, Sharma, & Meaney, 2003). Analysis of levels of DNA methylation within the  $ER\alpha$  gene (*ESR1*) in MPOA tissue indicates that offspring that experience low LG have elevated *ESR1* DNA methylation in adulthood (Champagne et al., 2006). This persistent epigenetic effect may account for the transmission of maternal LG behavior across generations (Champagne, 2008), and illustrates the profound effect of early rearing experiences on the neurobiological circuits involved in reproductive behavior. Experience-driven epigenetic effects on *ESR1* may also lead to sexual dimorphism. Within the MPOA there are sex differences in *ESR1* DNA methylation such that males have higher levels of *ESR1* DNA methylation in this brain region compared to that of females (Kurian, Olesen, & Auger, 2010). If females are provided with additional tactile stimulation during postnatal days 5–7, however, there are increases in *ESR1* DNA methylation, such that females become indistinguishable from males. Previous studies have indicated that male pups receive elevated levels of maternal LG compared to females (Moore, 1984; Moore & Morelli, 1979), so that it may be the case that differential levels of LG can trigger epigenetic pathways that enhance sex differences in the brain. Moreover, the frequency of LG may be an important consideration in studies of prenatal adversity because this form of maternal care has been found to be reduced among females that experienced stress during gestation (Champagne & Meaney, 2006).

#### *Epigenetic effects of neglect and abuse in animal models*

Maternal separation studies with laboratory primates and rodents have been used as a strategy to model early maternal

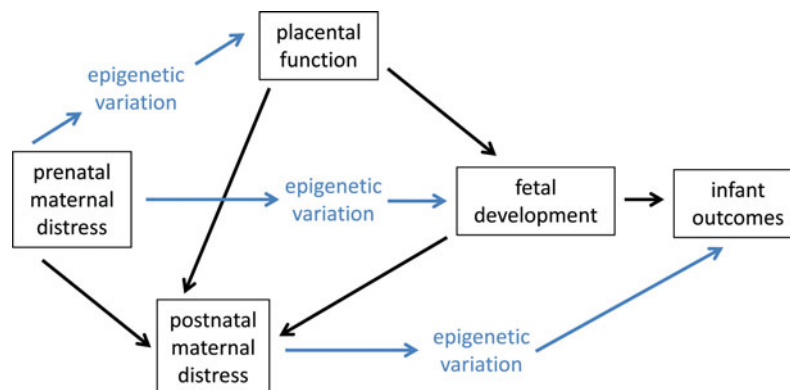
deprivation/neglect and have demonstrated the impact of this form of postnatal adversity on neurobiological and behavioral outcomes (Lehmann et al., 2002; Spinelli et al., 2009; Suomi, Eisele, Grady, & Harlow, 1975; Suomi, Harlow, & Kimball, 1971). Rhesus macaques reared under conditions of maternal separation and possess the risk allele of the *SLC6A4* gene (the short version which has been associated with increased anxiety-like behavior) were found to have increased DNA methylation of *SLC6A4* gene in blood samples (Kinnally et al., 2010). These findings highlight the interaction between genetic variation and epigenetic effects in response to early life adversity, which is likely an important consideration in human studies. In mice, maternal separation occurring daily during the postnatal period leads to increased stress sensitivity and an upregulation in the expression of hypothalamic vasopressin (*AVP*) that can be observed in adulthood (Murgatroyd et al., 2009). DNA methylation levels within key regulatory regions of the *AVP* gene have been found to vary as a function of exposure to postnatal maternal separation, such that maternally separated offspring have decreased hypothalamic *AVP* DNA methylation compared to normally reared offspring. This separation-induced hypomethylation of *AVP* was also associated with reduced levels of binding of MeCP2 (a methyl-binding protein) to the *AVP* gene (Murgatroyd et al., 2009).

Maternal abuse of offspring can also be modeled in laboratory rodents and has illustrated the role of epigenetic modifications in maintaining the effects of abuse across the life span. In laboratory rats, aggressive behavior toward pups (such as stepping on pups, aggressive grooming, or transporting of pups by a limb) can be induced by reducing the nesting materials provided to lactating dams during the postnatal period (Roth & Sullivan, 2005). This manipulation also reduces the frequency of nurturing behaviors such as maternal LG. When pups are exposed to caregivers (nonbiological mothers) that are provided with limited nesting materials and placed in an unfamiliar environment, there is increased exposure of pups to aggressive encounters (Roth, Lubin, Funk, & Sweatt, 2009). Within the prefrontal cortex of abuse-exposed offspring, there

is a downregulation of the expression of *BDNF*. Analysis of DNA methylation within the regulatory regions of the *BDNF* gene indicates that there are very low levels of DNA methylation among nonabused offspring whereas abused offspring have elevated levels of this repressive epigenetic modification (Roth et al., 2009). These epigenetic effects of abuse are also observed in the offspring of abused versus nonabused females, possibly suggesting an epigenetic basis to the multi-generational transmission of abuse and its consequences for neurobiological and behavioral functioning.

### Gene Regulation in the Placenta and Fetal Development

The mechanistic pathways linking prenatal adversity to infant development are likely to be very complex, varying by the timing of exposure, the type of exposure, and underlying genetic and environmental risk factors. However, the functioning of the placenta will probably be of critical importance within these diverse pathways. This temporary endocrine structure regulates the transfer of nutrients to the developing fetus, buffers the fetus from toxins and maternal glucocorticoids, and, by altering maternal hormone levels, can influence maternal mood and the priming of the maternal brain with consequences for the quality of postnatal mother–infant interactions (Cottrell & Seckl, 2009; Desforges & Sibley, 2010; Levy, 1981; Mann & Bridges, 2001; see Figure 5). Thus, gene regulation within the placenta can have functional consequences for both fetal and infant development. Gene transcription within the placenta varies during the course of gestation and it is likely that epigenetic mechanisms, such as variation in the levels of placental DNA methyltransferase levels, account for the temporal shifts in placental gene expression profiles (Novakovic et al., 2010). Altered gene expression within the placenta has also been associated with adverse birth outcomes, such as intrauterine growth retardation (Angiolini et al., 2006; Lee et al., 2010; McCarthy et al., 2007; McMinn et al., 2006; Sitras, Paulssen, Leirvik, Vartun,



**Figure 5.** Pathways linking prenatal maternal distress to infant outcomes. There are both direct and indirect pathways through which epigenetic modifications may shape infant outcomes associated with prenatal maternal distress. Within these pathways, postnatal maternal distress and placental function are critical factors. [A color version of this figure can be viewed online at <http://journals.cambridge.org/dpp>]

& Acharya, 2009). Many of the genes identified as differentially expressed in these studies are imprinted genes (McMinn et al., 2006; Tycko, 2006), that is, genes subject to epigenetic silencing mechanisms to achieve parent of origin expression patterns, and there is emerging evidence for altered DNA methylation levels both genome wide and within specific target genes that may account for this altered transcriptional profile (Lambertini et al., 2011; Nelissen, Van Montfort, Dumoulin, & Evers, 2011; Tabano et al., 2010).

It is interesting that there is significant overlap among genes identified as differentially methylated in the placenta in studies of fetal growth retardation and those genes identified as differentially methylated in blood samples from famine-exposed individuals in the Dutch Famine cohort (e.g., *IGF2*; guanine nucleotide binding protein, alpha stimulating activity polypeptide 1; leptin; maternally expressed 3; Heijmans et al., 2008; McMinn et al., 2006; Tobi et al., 2009). Thus, it is likely that maternal distress can lead to altered gene expression and epigenetic profiles in placental tissues. In mice, chronic variable stress during the first trimester is associated with altered placental gene expression, including altered mRNA levels of *DNMT1* (Mueller & Bale, 2008). One gene target of particular importance in linking maternal distress to fetal outcomes (particularly the HPA reactivity that is often observed) is the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase 2 gene (*11 $\beta$ -HSD2*) encoding the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase 2. *11 $\beta$ -HSD2* is highly expressed in the placenta and functions to inactivate glucocorticoids (Cottrell & Seckl, 2009). Thus, the degree of expression of *11 $\beta$ -HSD2* in the placenta is predicted to influence the exposure of the fetus to circulating maternal stress hormones. In humans, heightened maternal anxiety during pregnancy has been found to be negatively correlated with placental *11 $\beta$ -HSD2* mRNA levels (O'Donnell et al., 2011), and reduced placental *11 $\beta$ -HSD2* mRNA levels have also been found to be associated with intrauterine growth retardation and preterm birth (Borzsonyi et al., 2012; Dy, Guan, Sampath-Kumar, & Richardson, & Yang, 2008). In rats, chronic restraint stress during gestational days 11–20 was found to decrease placental *11 $\beta$ -HSD2* mRNA levels of this gene (Mairesse et al., 2007) and increased DNA methylation within the *11 $\beta$ -HSD2* gene may account for this downregulation of gene expression. Thus, it is likely that the placenta is a central target of maternal distress effects and a key mechanistic link between maternal distress and infant outcomes.

### Future Directions

Although both the acute and long-term consequences of prenatal exposure to maternal distress are evident in humans, the

biological mechanisms through which these effects are achieved have yet to be fully elucidated. Exploration of epigenetic factors within the study of maternal distress may provide a promising strategy for identifying the pathways through which development is altered as a function of prenatal adversity, and there is increasing evidence in humans for the epigenetic consequences of the early life environment. From this emerging literature, it is clear that there are critical methodological issues and empirical questions that must be addressed if we are to advance our understanding of the mechanisms of prenatal effects. First, the moderating and mediating influence of postnatal experiences following prenatal adversity must be carefully considered, because prenatal adversity is highly predictive of postnatal adversity and postnatal experiences, particularly those involving variations in mother–infant interactions, which can have significant epigenetic, neurobiological, and behavioral consequences. The investigation of prenatal–postnatal interplay in shaping development may provide insights into the pathways through which fetal exposures lead to childhood and adolescent outcomes, as well as identifying potential interventions by which the long-term consequences of fetal adversity can be attenuated. Second, the validity and interpretation of human peripheral tissue samples in the study of epigenetic effects must be carefully considered. Unlike genetic markers, epigenetic variation is likely to occur within and across tissue types. Although fetal exposures will likely have system-wide consequences for epigenetic modifications and gene expression, the nature of this consequence may differ in brain cells compared to blood cells, thus limiting our capacity to explore the pathophysiology of psychological and behavioral outcomes linked to fetal adversity based exclusively on peripheral tissue samples. To address this issue, animal models in which both brain and blood epigenetic profiles can be compared and responsiveness to environmental exposures assessed, could provide an essential methodological tool. Finally, from both a neuroendocrine and epigenetic perspective, the placenta is a critical interface between maternal adversity and fetal/infant outcomes (see Figure 5). Continued investigation of the impact of prenatal adversity on placental function and gene regulation may contribute significantly to our understanding of the routes through which maternal psychosocial characteristics induce biological effects in the developing fetus. Future studies addressing these issues and incorporating an epigenetic perspective in the study of prenatal maternal distress have the potential to illustrate the complex interplay between genes and environments in shaping infant outcomes and to determine the mechanisms, both genetic and epigenetic, through which the transmission of risk of psychopathology from mothers to infants is achieved.

### References

- Angiolini, E., Fowden, A., Coan, P., Sandovici, I., Smith, P., Dean, W., et al. (2006). Regulation of placental efficiency for nutrient transport by imprinted genes. *Placenta*, 27(Suppl. A), S98–S102.
- Bagner, D. M., Pettit, J. W., Lewinsohn, P. M., & Seeley, J. R. (2010). Effect of maternal depression on child behavior: A sensitive period? *Journal of the American Academy of Child & Adolescent Psychiatry*, 49, 699–707.

- Bale, T. L., Baram, T. Z., Brown, A. S., Goldstein, J. M., Insel, T. R., McCarthy, M. M., et al. (2010). Early life programming and neurodevelopmental disorders. *Biological Psychiatry*, *68*, 314–319.
- Barski, A., Cuddapah, S., Cui, K., Roh, T. Y., Schones, D. E., Wang, Z., et al. (2007). High-resolution profiling of histone methylations in the human genome. *Cell*, *129*, 823–837.
- Beck, C. T. (1996). A meta-analysis of predictors of postpartum depression. *Nursing Research*, *45*, 297–303.
- Beebe, B., Badalamenti, A., Jaffe, J., Feldstein, S., Marquette, L., Helbraun, E., et al. (2008). Distressed mothers and their infants use a less efficient timing mechanism in creating expectancies of each other's looking patterns. *Journal of Psycholinguistic Research*, *37*, 293–307.
- Beebe, B., Steele, M., Jaffe, J., Buck, K., Chen, H., Cohen, P., et al. (2011). Maternal anxiety symptoms and mother–infant self- and interactive contingency. *Infant Mental Health Journal*, *32*, 174–206.
- Bergman, K., Sarkar, P., Glover, V., & O'Connor, T. G. (2010). Maternal prenatal cortisol and infant cognitive development: Moderation by infant–mother attachment. *Biological Psychiatry*, *67*, 1026–1032.
- Bergman, K., Sarkar, P., O'Connor, T. G., Modi, N., & Glover, V. (2007). Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*, 1454–1463.
- Bettes, B. A. (1989). Maternal depression and motherese: Temporal and intonational features. *Child Development*, *59*, 1089–1096.
- Beversdorf, D. Q., Manning, S. E., Hillier, A., Anderson, S. L., Nordgren, R. E., Walters, S. E., et al. (2005). Timing of prenatal stressors and autism. *Journal of Autism & Developmental Disorders*, *35*, 471–478.
- 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 & Perinatal Epidemiology*, *22*, 438–466.
- Blair, M. M., Glynn, L. M., Sandman, C. A., & Davis, E. P. (2011). Prenatal maternal anxiety and early childhood temperament. *Stress*, *14*, 644–651.
- Borzsonyi, B., Demendi, C., Pajor, A., Rigo, J. Jr., Marosi, K., Agota, A., et al. (2012). Gene expression patterns of the 11beta-hydroxysteroid dehydrogenase 2 enzyme in human placenta from intrauterine growth restriction: The role of impaired fetomaternal glucocorticoid metabolism. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, *161*, 12–17.
- Brown, A. S., Van Os, J., Driessens, C., Hoek, H. W., & Susser, E. S. (2000). Further evidence of relation between prenatal famine and major affective disorder. *American Journal of Psychiatry*, *157*, 190–195.
- Bureau, J. F., Easterbrooks, M. A., & Lyons-Ruth, K. (2009). Maternal depressive symptoms in infancy: Unique contribution to children's depressive symptoms in childhood and adolescence? *Development and Psychopathology*, *21*, 519–537.
- 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.
- Bystrova, K., Ivanova, V., Edhborg, M., Matthiesen, A. S., Ransjo-Arvidson, A. B., Mukhamedrahimov, R., et al. (2009). Early contact versus separation: Effects on mother–infant interaction one year later. *Birth*, *36*, 97–109.
- Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M., & Meaney, M. J. (1998). Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proceedings of the National Academy of Sciences*, *95*, 5335–5340.
- Cameron, N., Del Corpo, A., Diorio, J., McAllister, K., Sharma, S., & Meaney, M. J. (2008a). Maternal programming of sexual behavior and hypothalamic–pituitary–gonadal function in the female rat. *PLoS ONE*, *3*, e2210.
- Cameron, N. M., Fish, E. W., & Meaney, M. J. (2008b). Maternal influences on the sexual behavior and reproductive success of the female rat. *Hormones & Behavior*, *54*, 178–184.
- Champagne, D. L., Bagot, R. C., van Hasselt, F., Ramakers, G., Meaney, M. J., de Kloet, E. R., et al. (2008). Maternal care and hippocampal plasticity: Evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *Journal of Neuroscience*, *28*, 6037–6045.
- Champagne, F., Diorio, J., Sharma, S., & Meaney, M. J. (2001). Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proceedings of the National Academy of Sciences*, *98*, 12736–12741.
- Champagne, F. A. (2008). Epigenetic mechanisms and the transgenerational effects of maternal care. *Frontiers in Neuroendocrinology*, *29*, 386–397.
- Champagne, F. A. (2010). Epigenetic influence of social experiences across the lifespan. *Developmental Psychobiology*, *52*, 299–311.
- Champagne, F. A., Francis, D. D., Mar, A., & Meaney, M. J. (2003). Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiology & Behavior*, *79*, 359–371.
- Champagne, F. A., & Meaney, M. J. (2006). Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. *Biological Psychiatry*, *59*, 1227–1235.
- Champagne, F. A., & Meaney, M. J. (2007). Transgenerational effects of social environment on variations in maternal care and behavioral response to novelty. *Behavioral Neuroscience*, *121*, 1353–1363.
- Champagne, F. A., Weaver, I. C., Diorio, J., Dymov, S., Szyf, M., & Meaney, M. J. (2006). Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. *Endocrinology*, *147*, 2909–2915.
- Champagne, F. A., Weaver, I. C., Diorio, J., Sharma, S., & Meaney, M. J. (2003). Natural variations in maternal care are associated with estrogen receptor alpha expression and estrogen sensitivity in the medial preoptic area. *Endocrinology*, *144*, 4720–4724.
- Charil, A., Laplante, D. P., Vaillancourt, C., & King, S. (2010). Prenatal stress and brain development. *Brain Research Reviews*, *65*, 56–79.
- Clarke, A. S., & Schneider, M. L. (1997). Effects of prenatal stress on behavior in adolescent rhesus monkeys. *Annals of the New York Academy of Sciences*, *807*, 490–491.
- Cohn, J. F., Matias, R., Tronick, E. Z., Connell, D., & Lyons-Ruth, K. (1986). Face-to-face interactions of depressed mothers and their infants. *New Directions for Child Development*, *34*, 31–45.
- Cottrell, E. C., & Seckl, J. R. (2009). Prenatal stress, glucocorticoids and the programming of adult disease. *Frontiers in Behavioral Neuroscience*, *3*, 19.
- Crnic, K. A., Greenberg, M. T., Robinson, N. M., & Ragozin, A. S. (1984). Maternal stress and social support: Effects on the infant–mother relationship from birth to eighteen months. *American Journal of Orthopsychiatry*, *54*, 224–235.
- Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicx-Demet, A., & Sandman, C. A. (2007). Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*, 737–746.
- 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.
- Davis, P. E., Snidman, N., Wadhwa, P., Glynn, L. M., Schetter, C. D., & Sandman, C. A. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy*, *6*, 319–331.
- Dawson, G., Klinger, L. G., Panagiotides, H., Hill, D., & Spieker, S. (1992). Frontal lobe activity and affective behavior of infants of mothers with depressive symptoms. *Child Development*, *63*, 725–737.
- Desforges, M., & Sibley, C. P. (2010). Placental nutrient supply and fetal growth. *International Journal of Developmental Biology*, *54*(2–3), 377–390.
- Devlin, A. M., Brain, U., Austin, J., & Oberlander, T. F. (2010). Prenatal exposure to maternal depressed mood and the *MTHFR C677T* variant affect *SLC6A4* methylation in infants at birth. *PLoS ONE*, *5*, e12201.
- Dieter, J. N. I., Field, T., Hernandez-Reif, M., Jones, N. A., Lecanuet, J. P., Salman, F. A., et al. (2001). Maternal depression and increased fetal activity. *Journal of Obstetrics and Gynaecology*, *21*, 468–473.
- DiPietro, J. A., Bornstein, M. H., Costigan, K. A., Pressman, E. K., Hahn, C. S., Painter, K., et al. (2002). What does fetal movement predict about behavior during the first two years of life? *Developmental Psychobiology*, *40*, 358–371.
- DiPietro, J. A., Hodgson, D. M., Costigan, K. A., & Johnson, T. R. B. (1996a). Fetal antecedents of infant temperament. *Child Development*, *67*, 2568–2583.
- DiPietro, J. A., Hodgson, K. A., Costigan, S. C., & Johnson, T. R. B. (1996b). Developmental of fetal movement–fetal heart rate coupling from 20 weeks through term. *Early Human Development*, *44*, 139–151.
- DiPietro, J. A., Kivlighan, K. T., Costigan, K. A., & Laudenslager, M. L. (2009). Fetal motor activity and maternal cortisol. *Developmental Psychobiology*, *51*, 505–512.
- Dy, J., Guan, H., Sampath-Kumar, R., Richardson, B. S., & Yang, K. (2008). Placental 11beta-hydroxysteroid dehydrogenase type 2 is reduced in pregnancies complicated with idiopathic intrauterine growth restriction: Evidence that this is associated with an attenuated ratio of cortisone to cortisol in the umbilical artery. *Placenta*, *29*, 193–200.

- Emory, E. K., & Dieter, J. N. (2006). Maternal depression and psychotropic medication effects on the human fetus. *Annals of the New York Academy of Sciences*, 1094, 287–291.
- Fan, G., & Hutnick, L. (2005). Methyl-CpG binding proteins in the nervous system. *Cell Research*, 15, 255–261.
- Feldman, R., Granat, A., Pariente, C., Kanety, H., Kuint, J., & Gilboa-Schechtman, E. (2009). Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48, 919–927.
- Field, T. (1998). Maternal depression effects on infants and early interventions. *Preventive Medicine*, 27, 200–203.
- Field, T. (2002). Early interactions between infants and their postpartum depressed mothers. *Infant Behavior and Development*, 25, 25–29.
- Field, T. (2010). Touch for socioemotional and physical well-being: A review. *Developmental Review*, 30, 367–383.
- Forman, D. R., O'Hara, M. W., Stuart, S., Gorman, L. L., Larsen, K. E., & Coy, K. C. (2007). Effective treatment for postpartum depression is not sufficient to improve the developing mother-child relationship. *Development and Psychopathology*, 19, 585–602.
- Gianino, A., & Tronick, E. (1985). The mutual regulation model: The infant's self and interactive regulation and coping and defensive capacities. In T. Field, P. McCabe, & N. Schneiderman (Eds.), *Stress and coping* (pp. 47–68). Hillsdale, NJ: Erlbaum.
- Glynn, L. M., Wadhwa, P. D., Dunkel-Schetter, C., Chiciz-Demet, A., & Sandman, C. A. (2001). When stress happens matters: Effects of earthquake timing on stress reactivity in pregnancy. *American Journal of Obstetrics & Gynecology*, 184, 637–642.
- Goodman, S. H., & Gotlib, I. H. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review*, 106, 458–490.
- Gotlib, I. H., Whiffen, V. E., Mount, J. H., Milne, K., & Cordy, N. I. (1989). Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. *Journal of Consulting and Clinical Psychology*, 57, 269–274.
- Goyal, D., Gay, C., & Lee, K. A. (2010). How much does low socioeconomic status increase the risk of prenatal and postpartum depressive symptoms in first-time mothers? *Womens Health Issues*, 20, 96–104.
- Grant, K. A., McMahon, C., Austin, M. P., Reilly, N., Leader, L., & Ali, S. (2009). Maternal prenatal anxiety, postnatal caregiving and infants' cortisol responses to the still-face procedure. *Developmental Psychobiology*, 51, 625–637.
- Groome, L. J., Swiber, M. J., Bentz, L. S., Holland, S. B., & Atterbury, J. L. (1995). Maternal anxiety during pregnancy: Effect on fetal behavior at 38 to 40 weeks of gestation. *Developmental and Behavioral Pediatrics*, 16, 391–396.
- Hane, A. A., & Fox, N. A. (2006). Ordinary variations in maternal caregiving influence human infants' stress reactivity. *Psychological Science*, 17, 550–556.
- Hane, A. A., Henderson, H. A., Reeb-Sutherland, B. C., & Fox, N. A. (2010). Ordinary variations in human maternal caregiving in infancy and biobehavioral development in early childhood: A follow-up study. *Developmental Psychobiology*, 52, 558–567.
- Heijmans, B. T., Tobi, E. W., Stein, A. D., Putter, H., Blauw, G. J., Susser, E. S., et al. (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences*, 105, 17046–17049.
- Hoek, H. W., Brown, A. S., & Susser, E. (1998). The Dutch famine and schizophrenia spectrum disorders. *Social Psychiatry and Psychiatric Epidemiology*, 33, 373–379.
- Jablonka, E., & Lamb, M. J. (2002). The changing concept of epigenetics. *Annals of the New York Academy of Sciences*, 981, 82–96.
- Jenuwein, T., & Allis, C. D. (2001). Translating the histone code. *Science*, 293(5532), 1074–1080.
- Jirtle, R. L., & Skinner, M. K. (2007). Environmental epigenomics and disease susceptibility. *Nature Reviews in Genetics*, 8, 253–262.
- Jones, P. A., & Taylor, S. M. (1980). Cellular differentiation, cytidine analogs and DNA methylation. *Cell*, 20, 85–93.
- Kaitz, M., Maytal, H. R., Devor, N., Bergman, L., & Mankuta, D. (2010). Maternal anxiety, mother-infant interactions, and infants' response to challenge. *Infant Behavior & Development*, 33, 136–148.
- Kaplan, L. A., Evans, L., & Monk, C. (2007). Effects of mothers' prenatal psychiatric status and postnatal caregiving on infant biobehavioral regulation: Can prenatal programming be modified? *Early Human Development*, 84, 249–256.
- Khashan, A. S., Abel, K. M., McNamee, R., Pedersen, M. G., Webb, R. T., Baker, P. N., et al. (2008). Higher risk of offspring schizophrenia following antenatal maternal exposure to severe adverse life events. *Archives of General Psychiatry*, 65, 146–152.
- Kikkert, H. K., Middelburg, K. J., & Hadders-Algra, M. (2010). Maternal anxiety is related to infant neurological condition, paternal anxiety is not. *Early Human Development*, 86, 171–177.
- King, S., & Laplante, D. P. (2005). The effects of prenatal maternal stress on children's cognitive development: Project Ice Storm. *Stress*, 8, 35–45.
- Kinnally, E. L., Capitanio, J. P., Leibel, R., Deng, L., LeDuc, C., Haghghi, F., et al. (2010). Epigenetic regulation of serotonin transporter expression and behavior in infant rhesus macaques. *Genes, Brain, and Behavior*, 9, 575–582.
- Kinney, D. K., Miller, A. M., Crowley, D. J., Huang, E., & Gerber, E. (2008). Autism prevalence following prenatal exposure to hurricanes and tropical storms in Louisiana. *Journal of Autism & Developmental Disorders*, 38, 481–488.
- Kleefstra, T., Brunner, H. G., Amiel, J., Oudakker, A. R., Nillesen, W. M., Magee, A., et al. (2006). Loss-of-function mutations in euchromatin histone methyl transferase 1 (EHMT1) cause the 9q34 subtelomeric deletion syndrome. *American Journal of Human Genetics*, 79, 370–377.
- Koch, C. M., Andrews, R. M., Flicek, P., Dillon, S. C., Karaoz, U., Clelland, G. K., et al. (2007). The landscape of histone modifications across 1% of the human genome in five human cell lines. *Genome Research*, 17, 691–707.
- Kurian, J. R., Olesen, K. M., & Auger, A. P. (2010). Sex differences in epigenetic regulation of the estrogen receptor- $\alpha$  promoter within the developing preoptic area. *Endocrinology*, 151, 2297–2305.
- Lambertini, L., Lee, T. L., Chan, W. Y., Lee, M. J., Diplas, A., Wetmur, J., et al. (2011). Differential methylation of imprinted genes in growth-restricted placentas. *Reproductive Sciences*, 18, 1111–1117.
- Laplante, D. P., Barr, R. G., Brunet, A., Galbaud du Fort, G., Meaney, M. L., Saucier, J. F., et al. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research*, 56, 400–410.
- Laplante, D. P., Brunet, A., Schmitz, N., Ciampi, A., & King, S. (2008). Project Ice Storm: Prenatal maternal stress affects cognitive and linguistic functioning in 5½-year-old children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47, 1063–1072.
- Lee, M. H., Jeon, Y. J., Lee, S. M., Park, M. H., Jung, S. C., & Kim, Y. J. (2010). Placental gene expression is related to glucose metabolism and fetal cord blood levels of insulin and insulin-like growth factors in intrauterine growth restriction. *Early Human Development*, 86, 45–50.
- Legube, G., & Trouche, D. (2003). Regulating histone acetyltransferases and deacetylases. *EMBO Reports*, 4, 944–947.
- Lehmann, J., Pryce, C. R., Jongen-Relo, A. L., Stohr, T., Pothuizen, H. H., & Feldon, J. (2002). Comparison of maternal separation and early handling in terms of their neurobehavioral effects in aged rats. *Neurobiology of Aging*, 23, 457–466.
- Levy, G. (1981). Pharmacokinetics of fetal and neonatal exposure to drugs. *Obstetrics and Gynecology*, 58(Suppl. 5), 9S–16S.
- Li, E., Bestor, T. H., & Jaenisch, R. (1992). Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. *Cell*, 69, 915–926.
- Li, J., Vestergaard, M., Obel, C., Christensen, J., Precht, D. H., Lu, M., et al. (2009). A nationwide study on the risk of autism after prenatal stress exposure to maternal bereavement. *Pediatrics*, 123, 1102–1107.
- Liu, D., Diorio, J., Day, J. C., Francis, D. D., & Meaney, M. J. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience*, 3, 799–806.
- Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., et al. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science*, 277(5332), 1659–1662.
- Lupien, S. J., Parent, S., Evans, A. C., Tremblay, R. E., Zelazo, P. D., Corbo, V., et al. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences*, 108, 14324–14329.
- Lyons-Ruth, K., & Block, D. (1996). The disturbed caregiving system: Relations among childhood trauma, maternal caregiving, and infant affect and attachment. *Infant Mental Health Journal*, 17, 257–275.
- Mairesse, J., Lesage, J., Breton, C., Breat, B., Hahn, T., Darnaudery, M., et al. (2007). Maternal stress alters endocrine function of the fetoplacental

- tal unit in rats. *American Journal of Physiology, Endocrinology, and Metabolism*, 292, E1526–E1533.
- Malaspina, D., Corcoran, C., Kleinhaus, K. R., Perrin, M. C., Fennig, S., Nahon, D., et al. (2008). Acute maternal stress in pregnancy and schizophrenia in offspring: A cohort prospective study. *BMC Psychiatry*, 8, 71.
- Manian, N., & Bornstein, M. H. (2009). Dynamics of emotion regulation in infants of clinically depressed and nondepressed mothers. *Journal of Child Psychology and Psychiatry* 50, 1410–1418.
- Mann, P. E., & Bridges, R. S. (2001). Lactogenic hormone regulation of maternal behavior. *Progress in Brain Research*, 133, 251–262.
- Martins, C., & Gaffan, E. A. (2000). Effects of early maternal depression on patterns of infant–mother attachment: A meta-analytic investigation. *Journal of Child Psychology and Psychiatry*, 41, 737–746.
- McCarthy, C., Cotter, F. E., McElwaine, S., Twomey, A., Mooney, E. E., Ryan, F., et al. (2007). Altered gene expression patterns in intrauterine growth restriction: potential role of hypoxia. *American Journal of Obstetrics and Gynecology*, 196, 70e1–e6.
- McGowan, P. O., Sasaki, A., D'Alessio, A. C., Dymov, S., Labonte, B., Szyf, M., et al. (2009). Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nature Neuroscience*, 12, 342–348.
- McMahon, C. A., Barnett, B., Kowalenko, N. M., & Tennant, C. C. (2006). Maternal attachment state of mind moderates the impact of postnatal depression on infant attachment. *Journal of Child Psychology and Psychiatry*, 47, 660–669.
- McMinn, J., Wei, M., Schupf, N., Cusmai, J., Johnson, E. B., Smith, A. C., et al. (2006). Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. *Placenta*, 27, 540–549.
- Meaney, M. J. (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Reviews in Neuroscience*, 24, 1161–1192.
- Meaney, M. J., & Szyf, M. (2005). Maternal care as a model for experience-dependent chromatin plasticity? *Trends in Neuroscience*, 28, 456–463.
- Monk, C., Fifer, W. P., Myers, M. M., Babiella, E., Duong, J. K., Chen, I. S., et al. (2011). Effects of maternal breathing rate, psychiatric status, and cortisol on fetal heart rate. *Developmental Psychobiology*, 53, 221–233.
- Monk, C., Fifer, W. P., Sloan, R. P., Myers, M. M., Trien, L., & Hurtado, A. (2000). Maternal stress responses and anxiety during pregnancy: Effects on fetal heart rate. *Developmental Psychobiology*, 36, 67–77.
- Monk, C., Myers, M. M., Sloan, R. P., Werner, L., Jeon, J., Tager, F., et al. (2004). Fetal heart rate reactivity differs by women's psychiatric status: An early marker for developmental risk? *Journal of the American Academy of Child & Adolescent Psychiatry*, 43, 283–290.
- Moore, C. L. (1984). Maternal contributions to the development of masculine sexual behavior in laboratory rats. *Developmental Psychobiology*, 17, 347–356.
- Moore, C. L., & Morelli, G. A. (1979). Mother rats interact differently with male and female offspring. *Journal of Comparative Physiological Psychology*, 93, 677–684.
- Mueller, B. R., & Bale, T. L. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience*, 28, 9055–9065.
- Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmuhl, Y., Fischer, D., et al. (2009). Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nature Neuroscience*, 12, 1559–1566.
- Murray, L., Halligan, S. L., Goodyer, I., & Herbert, J. (2010). Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: A preliminary study. *Journal of Affective Disorders*, 122, 218–223.
- Naumova, O. Y., Lee, M., Kuposov, R., Szyf, M., Dozier, M., & Grigorenko, E. L. (2012). Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. *Development and Psychopathology*, 24, 143–155.
- Nelissen, E. C., van Montfoort, A. P., Dumoulin, J. C., & Evers, J. L. (2011). Epigenetics and the placenta. *Human Reproduction Update*, 17, 397–417.
- Nicol-Harper, R., Harvey, A. G., & Stein, A. (2007). Interactions between mothers and infants: Impact of maternal anxiety. *Infant Behavior and Development*, 30, 161–167.
- Novakovic, B., Wong, N. C., Sibson, M., Ng, H. K., Morley, R., Manuelpillai, U., et al. (2010). DNA methylation-mediated down-regulation of DNA methyltransferase-1 (*DNMT1*) is coincident with, but not essential for, global hypomethylation in human placenta. *Journal of Biological Chemistry*, 285, 9583–9593.
- Oberlander, T. F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., & Devlin, A. M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (*NR3C1*) and infant cortisol stress responses. *Epigenetics*, 3, 97–106.
- 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., Glover, V., & the ALSPAC Study Team. (2002). Antenatal anxiety predicts child behavior/emotional problems independently of postnatal depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41, 1470–1477.
- O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioral/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. (2003). Maternal antenatal 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., Bugge Jensen, A., Freeman, L., Khalife, N., O'Connor, T. G., & Glover, V. (2011). Maternal prenatal anxiety and downregulation of placental 11beta-HSD2. *Psychoneuroendocrinology*, 109, E1312–E1319.
- O'Hara, M. W., & Swain, A. M. (1996). Rates and risk of postpartum depression: A meta-analysis. *International Review of Psychiatry*, 8, 37–54.
- Okano, M., Bell, D. W., Haber, D. A., & Li, E. (1999). DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*, 99, 247–257.
- Pawlyb, S., Hay, D. F., Sharp, D., Waters, C. S., & O'Keane, V. (2009). Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study. *Journal of Affective Disorders*, 113, 236–243.
- Pesonen, A. K., Raikkonen, K., Strandberg, T. E., & Jarvenpaa, A.-L. (2005). Continuity of maternal stress from the pre- to the postnatal period: Associations with infant's positive, negative, and overall temperamental reactivity. *Infant Behavior and Development*, 28, 36–47.
- Peterson, C. L., & Laniel, M. A. (2004). Histones and histone modifications. *Current Biology*, 14, R546–R551.
- Pruessner, J. C., Dedovic, K., Khalili-Mahani, N., Engert, V., Pruessner, M., Buss, C., et al. (2008). Deactivation of the limbic system during acute psychosocial stress: Evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biological Psychiatry*, 63, 234–240.
- Radtke, K. M., Ruf, M., Gunter, H. M., Dohrmann, K., Schauer, M., & Elbert, T. (2011). Transgenerational impact of intimate partner violence on methylation in the promoter of the glucocorticoid receptor. *Translational Psychiatry*, 1, e21.
- Razin, A. (1998). CpG methylation, chromatin structure and gene silencing: A three-way connection. *EMBO Journal*, 17, 4905–4908.
- Rettew, D. C., & McKee, L. (2005). Temperament and its role in developmental psychopathology. *Harvard Review of Psychiatry*, 13, 14–27.
- Rice, F., Harold, G. T., Boivin, J., Van den Bree, M., Hay, D. F., & Thapar, A. (2009). The links between prenatal stress and offspring development and psychopathology: Disentangling environmental and inherited influences. *Psychological Medicine*, 40, 335–345.
- Roth, T. L., Lubin, F. D., Funk, A. J., & Sweatt, J. D. (2009). Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biological Psychiatry*, 65, 760–769.
- Roth, T. L., & Sullivan, R. M. (2005). Memory of early maltreatment: Neonatal behavioral and neural correlates of maternal maltreatment within the context of classical conditioning. *Biological Psychiatry*, 57, 823–831.
- Sandman, C. A., Davis, E. P., Buss, C., & Glynn, L. M. (2011). Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology*, 95, 8–21.
- Sandman, C. A., Wadhwa, P. D., Chic-DeMet, A., Porto, M., & Garite, T. J. (1999). Maternal corticotropin-releasing hormone and habituation in the human fetus. *Developmental Psychobiology*, 34, 163–173.
- Schneider, M. L. (1992). The effect of mild stress during pregnancy on birth-weight and neuromotor maturation in rhesus monkey infants (*Macaca mulatta*). *Infant Behavior and Development*, 15, 389–403.
- 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.

- Selten, J. P., Cantor-Graae, E., Nahon, D., Levav, I., Aleman, A., & Kahn, R. S. (2003). No relationship between risk of schizophrenia and prenatal exposure to stress during the Six-Day War or Yom Kippur War in Israel. *Schizophrenia Research, 63*, 131–135.
- Sitras, V., Paulssen, R., Leirvik, J., Vartun, A., & Acharya, G. (2009). Placental gene expression profile in intrauterine growth restriction due to placental insufficiency. *Reproductive Sciences, 16*, 701–711.
- Smith, F. M., Garfield, A. S., & Ward, A. (2006). Regulation of growth and metabolism by imprinted genes. *Cytogenetic Genome Research, 113*, 279–291.
- Spinelli, S., Chefer, S., Suomi, S. J., Higley, J. D., Barr, C. S., & Stein, E. (2009). Early-life stress induces long-term morphologic changes in primate brain. *Archives of General Psychiatry, 66*, 658–665.
- Stein, Z., Susser, M., Saenger, G., & Marolla, F. (1972). Nutrition and mental performance. *Science, 178*, 708–713.
- Suomi, S. J., Eisele, C. D., Grady, S. A., & Harlow, H. F. (1975). Depressive behavior in adult monkeys following separation from family environment. *Journal of Abnormal Psychology, 84*, 576–578.
- Suomi, S. J., Harlow, H. F., & Kimball, S. D. (1971). Behavioral effects of prolonged partial social isolation in the rhesus monkey. *Psychological Reports, 29*, 1171–1177.
- Susser, E., Hoek, H. W., & Brown, A. (1998). Neurodevelopmental disorders after prenatal famine: The story of the Dutch Famine Study. *American Journal of Epidemiology, 147*, 213–216.
- Susser, E. B., Brown, A., & Matte, T. D. (1999). Prenatal factors and adult mental and physical health. *Canadian Journal of Psychiatry, 44*, 326–334.
- Susser, E. S., & Lin, S. P. (1992). Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Archives of General Psychiatry, 49*, 983–988.
- Sutter-Dallay, A. L., Giaccone-Marcésche, V., Glatigny-Dallay, E., & Verdoux, H. (2004). Women with anxiety disorders during pregnancy are at increased risk of intense postnatal depressive symptoms: A prospective survey of the MATQUID cohort. *European Psychiatry, 19*, 459–463.
- Tabano, S., Colapietro, P., Cetin, I., Grati, F. R., Zanutto, S., Mando, C., et al. (2010). Epigenetic modulation of the IGF2/H19 imprinted domain in human embryonic and extra-embryonic compartments and its possible role in fetal growth restriction. *Epigenetics, 5*, 313–324.
- Takahashi, L. K., Baker, E. W., & Kalin, N. H. (1990). Ontogeny of behavioral and hormonal responses to stress in prenatally stressed male rat pups. *Physiology and Behavior, 47*, 357–364.
- Takahashi, L. K., Haglin, C., & Kalin, N. H. (1992). Prenatal stress potentiates stress-induced behavior and reduces the propensity to play in juvenile rats. *Physiology and Behavior, 51*, 319–323.
- 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, 48*, 245–261.
- Teti, D. M., Felfand, D. M., Messinger, D. S., & Isabella, R. (1995). Maternal depression and the quality of early attachment: An examination of infants, preschoolers, and their mothers. *Developmental Psychobiology, 31*, 364–376.
- Tobi, E. W., Lumey, L. H., Talens, R. P., Kremer, D., Putter, H., Stein, A. D., et al. (2009). DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Human Molecular Genetics, 18*, 4046–4053.
- Tronick, E., & Gianino, A. (1986). The transmission of maternal disturbance to the infant. In E. Tronick & T. Field (Eds.), *Maternal depression and infant disturbance* (pp. 5–12). San Francisco, CA: Jossey-Bass.
- Tronick, E. Z. (1989). Emotions and emotional communication in infants. *American Psychologist, 44*, 112–119.
- Turek-Plewa, J., & Jagodzinski, P. P. (2005). The role of mammalian DNA methyltransferases in the regulation of gene expression. *Cellular and Molecular Biology Letters, 10*, 631–647.
- Turner, B. (2001). *Chromatin and gene regulation*. Oxford: Blackwell Science.
- Tycko, B. (2006). Imprinted genes in placental growth and obstetric disorders. *Cytogenetic and Genome Research, 113*, 271–278.
- Umlauf, D., Goto, Y., & Feil, R. (2004). Site-specific analysis of histone methylation and acetylation. *Methods in Molecular Biology, 287*, 99–120.
- Valentine, J. M., Rodriguez, M. A., Lapeyrouse, L. M., & Zhang, M. (2011). Recent intimate partner violence as a prenatal predictor of maternal depression in the first year postpartum among Latinas. *Archives of Women's Mental Health, 14*, 135–143.
- Van den Bergh, B. R., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems and anxiety in 8–9 year olds. *Child Development, 75*, 1085–1097.
- Van den Bergh, B. R., Mennes, M., Oosterlaan, J., Stevens, V., Stiers, P., Marcoen, A., et al. (2005). High antenatal maternal anxiety is related to impulsivity during performance on cognitive tasks in 14- and 15-year-olds. *Neuroscience & Biobehavioral Reviews, 29*, 259–269.
- Van den Bergh, B. R., Mennes, M., Stevens, V., Van der Meere, J., Borger, 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., 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*, 536–545.
- Verkerk, G. J., Pop, V. J., Van Son, M. J., & Van Heck, G. L. (2003). Prediction of depression in the postpartum period: A longitudinal follow-up study in high-risk and low-risk women. *Journal of Affective Disorders, 77*, 159–166.
- Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*, 847–854.
- Weaver, I. C., Champagne, F. A., Brown, S. E., Dymov, S., Sharma, S., Meaney, M. J., et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking later in life. *Journal of Neuroscience, 25*, 11045–11054.
- Weaver, I. C., Meaney, M. J., & Szyf, M. (2006). Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. *Proceedings of the National Academy of Sciences, 103*, 3480–3485.
- Weinstock, M. (2005). The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain, Behavior, and Immunity, 19*, 296–308.
- Werner, A., Myers, M. M., Fifer, W. P., Cheng, B., Fang, Y., Allen, R., et al. (2007). Prenatal predictors of infant temperament. *Developmental Psychobiology, 49*, 474–484.
- Xu, W., Edmondson, D. G., Evrard, Y. A., Wakamiya, M., Behringer, R. R., & Roth, S. Y. (2000). Loss of Gcn5l2 leads to increased apoptosis and mesodermal defects during mouse development. *Nature Genetics, 26*, 229–232.
- Yao, T. P., Oh, S. P., Fuchs, M., Zhou, N. D., Ch'ng, L. E., Newsome, D., et al. (1998). Gene dosage-dependent embryonic development and proliferation defects in mice lacking the transcriptional integrator p300. *Cell, 93*, 361–372.
- Zeanah, C. H., Keener, M. A., Stewart, L., & Anders, T. F. (1985). Prenatal perception of infant personality: A preliminary investigation. *Journal of the American Academy of Child & Adolescent Psychiatry, 24*, 204–210.
- Zekoski, E. M., O'Hara, M. W., & Wills, K. E. (1987). The effects of maternal mood on mother–infant interaction. *Journal of Abnormal Child Psychology, 15*, 361–378.
- Zhang, T. Y., Hellstrom, I. C., Bagot, R. C., Wen, X., Diorio, J., & Meaney, M. J. (2010). Maternal care and DNA methylation of a glutamic acid decarboxylase 1 promoter in rat hippocampus. *Journal of Neuroscience, 30*, 13130–13137.