Infant Stress Reactivity: Associations with Exposures to Perinatal Depressive Symptoms and Prenatal Cortisol

Meaghan E. McCallum, B.A.

Advisor: Sherryl H. Goodman, Ph.D.

Emory University

Abstract

Recent findings have revealed associations between perinatal depressive symptoms and cortisol in mothers and infant stress reactivity. The current study improved upon previous work by including multiple assessments of maternal depressive symptoms and cortisol in order to parse out the relative contributions of pre- versus post-natal depressive symptoms in women with increased risk for a perinatal depressive episode. The trajectory of depressive symptoms across both the pre- and postnatal periods and maternal sensitivity, rated at 3, 6, and 12 months, were also examined in relation to infants' behavioral and cortisol reactivity. At 12 months, mother-infant dyads (n=71) completed a laboratory visit where infant cortisol reactivity was measured in response to the Strange Situation. Infant behavioral reactivity was rated during two stressful interactions with mothers, one mild (mothers filling out paperwork while face-to-face with the infants) and one moderate (mothers turning around and ignoring the infant). Results indicated that infant cortisol was associated with the trajectory of maternal depressive symptoms, such that infants exposed to high levels of prenatal depressive symptoms and low levels of postnatal symptoms exhibited higher cortisol (both the initial sampling and the overall level) in comparison to infants exposed to high depressive symptoms during both the pre- and postnatal periods. This finding lends support to the fetal programming hypothesis, whereby infant cortisol reactivity may be dysregulated when the fetal expectancy of postnatal environment is not met. In addition, results indicated that sensitive parenting may buffer the adverse effects of perinatal depression. Implications of these findings are discussed.

Keywords: perinatal depression, cortisol, stress reactivity

Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

_____ _____

Meaghan E. McCallum Date

Infant Stress Reactivity: Associations with Exposures to Perinatal Depressive Symptoms and Prenatal Cortisol

By

Meaghan E. McCallum
Master of Arts

Clinical Psychology

_____
Sherryl H. Goodman, Ph.D.
Advisor

_____
Jocelyne Bachevalier, Ph.D.
Committee Member

_____
Kim Wallen, Ph.D.
Committee Member

_____
Elaine F. Walker, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

Infant Stress Reactivity: Associations with Exposures to Perinatal Depressive Symptoms and Prenatal Cortisol

By

Meaghan E. McCallum
B.A., Emory University, 2008

Advisor: Sherryl H. Goodman, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Arts
in Clinical Psychology
2013

Abstract

Infant Stress Reactivity: Associations with Exposures to Perinatal Depressive Symptoms and Prenatal Cortisol

By Meaghan E. McCallum

Recent findings have revealed associations between perinatal depressive symptoms and cortisol in mothers and infant stress reactivity. The current study improved upon previous work by including multiple assessments of maternal depressive symptoms and cortisol in order to parse out the relative contributions of pre- versus post-natal depressive symptoms in women with increased risk for a perinatal depressive episode. The trajectory of depressive symptoms across both the pre- and postnatal periods and maternal sensitivity, rated at 3, 6, and 12 months, were also examined in relation to infants' behavioral and cortisol reactivity. At 12 months, mother-infant dyads (n=71) completed a laboratory visit where infant cortisol reactivity was measured in response to the Strange Situation. Infant behavioral reactivity was rated during two stressful interactions with mothers, one mild (mothers filling out paperwork while face-to-face with the infants) and one moderate (mothers turning around and ignoring the infant). Results indicated that infant cortisol was associated with the trajectory of maternal depressive symptoms, such that infants exposed to high levels of prenatal depressive symptoms and low levels of postnatal symptoms exhibited higher cortisol (both the initial sampling and the overall level) in comparison to infants exposed to high depressive symptoms during both the pre- and postnatal periods. This finding lends support to the fetal programming hypothesis, whereby infant cortisol reactivity may be dysregulated when the fetal expectancy of postnatal environment is not met. In addition, results indicated that sensitive parenting may buffer the adverse effects of perinatal depression. Implications of these findings are discussed.

Keywords: perinatal depression, cortisol, stress reactivity

Table of Contents

List of Figures and Tables

Introduction

Women experience depression during the perinatal period at rates similar to non-childbearing years, with current estimates suggesting 12.7% of women experience a major depressive episode (MDE) during pregnancy (Gavin et al., 2005). Similarly, postnatal depression, defined as depression occurring within one year of delivery, is estimated to affect 9-13% of women (Banti et al., 2011; Cox, Murray, & Chapman, 1993; O'Hara & Swain, 1996). Women with a lifetime history of depression are at an even higher risk of suffering from a recurrent episode during the perinatal period compared to women without history of depression. Women who have experienced a MDE prior to pregnancy have been shown to exhibit clinically significant symptoms of depression at rates three to five times higher than those found in women without a history of depression (Goodman & Tully, 2009; Marcus, Flynn, Blow, & Barry, 2003; Rich-Edwards et al., 2006), and rates of postnatal depression are higher among women who experience elevated symptoms of depression during pregnancy (Beck, 1996; O'Hara & Swain, 1996). Thus, women with a history of depression are at increased risk of experiencing depression during the development of their fetuses or infants. Additionally, a subgroup of postnatally depressed women experience the onset of depressive symptoms during pregnancy, resulting in a group of infants exposed to both maternal prenatal and postnatal depression (Stowe, Hostetter, & Newport, 2005).

Maternal depression has been consistently associated with negative long-term child outcomes, including greater risk for later child psychopathology (for review see Goodman et al., 2011) as well as deficits in cognitive development (for review see Grace, Evindar, & Stewart, 2003). However, the underlying mechanisms of these outcomes still

remain largely unknown. The dysregulation of the child's stress response, namely via the hypothalamic-pituitary-adrenocortical (HPA) axis, has been proposed as a potential mechanism underlying these associations (Goodman & Gotlib, 1999). Researchers have hypothesized that depression during pregnancy is associated with alterations in maternal HPA axis activity (Kammerer, Taylor, & Glover, 2006), and that fetal exposure to these alterations may underlie the relationship between prenatal depression and infant HPA dysregulation (Goodman & Gotlib, 1999). The current study seeks to further explore the relationships among perinatal exposures to mothers' depression and cortisol, and infant stress reactivity using a longitudinal, prospective design.

The HPA Axis

The HPA axis is responsible for regulating neuroendocrine responses to stress. A cascade of events is initiated following an autonomic signal at the hypothalamus, which activates secretion of corticotropin-releasing hormone (CRH) from neurons in the paraventricular nucleus. This peptide stimulates secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which in turn stimulates the production of glucocorticoids, primarily cortisol, in the adrenal cortices. Glucocorticoids circulate the bloodstream and are then involved in a negative feedback cycle, suppressing CRH production by binding to glucocorticoid receptors in the hippocampus and elsewhere in the central nervous system. The major processes regulated by glucocorticoids include digestion, aiding in fat, protein, and carbohydrate metabolism, suppression of the immune system, and increasing blood sugar. These processes mobilize resources necessary to adequately respond to environmental stressors. The HPA axis has been conceptualized as

the long-acting component of stress reactivity, since it takes minutes after encountering a stressor before peak cortisol concentrations are found in the bloodstream.

In the context of pregnancy, it is also important to consider the role of the placenta in HPA axis activity. In humans, the placenta expresses CRH messenger RNA (mRNA) as early as seven weeks gestational age (Petraglia, Sawchenko, Rivier, & Vale, 1987). Fetal CRH is an active peptide, that when released into maternal circulation, stimulates further production of ACTH and cortisol (Goland, 1988). Regulation of placental CRH levels differs in one crucial aspect, however. Whereas glucocorticoids are part of a negative feedback loop in the maternal central nervous system, they actually promote CRH gene expression in the placenta, establishing a positive feedback loop that leads to increases in levels of maternal plasma CRH and cortisol over gestation (for review of CRH regulation in placenta see King, Smith, & Nicholson, 2001). This normative increase in cortisol over the course of pregnancy has been demonstrated in several studies, with cortisol levels rising more rapidly in early pregnancy and smaller increases or a plateau observed in later pregnancy (Carr, Parker, Madden, MacDonald, & Porter, 1981; Sandman et al., 2006).

Researchers have tested a model in which maternal prenatal stress hormones mediate associations between maternal depression and infant HPA activity. A first step in testing this mediational model is to establish associations between mothers' prenatal levels of both depression and cortisol. Although some studies found support for associations between depression and cortisol levels during pregnancy (Diego et al., 2004; Field, Diego, Hernandez-Reif, et al., 2004; Field, Hernandezreif, Diego, Schanberg, & Kuhn, 2006; Lundy et al., 1999), several other studies have failed to show differences in

maternal cortisol related to depressive symptoms alone (Davis & Sandman, 2010; Davis et. al., 2007; Evans, Myers, & Monk, 2008; McCool, Susman, & Susman, 1994; Petraglia et al., 2001). However, even in the absence of consistent support for associations between depression and cortisol during pregnancy, there are reasons to be concerned about infants born to women with prenatal depression as well as infants born to women with elevated prenatal cortisol levels. Both prenatal cortisol levels and maternal depressive symptoms have been independently linked to adverse outcomes in offspring, as outlined in the next two sections of this paper.

Fetal Exposure to Elevated Maternal Cortisol Levels

Studies of fetal environmental exposures provide compelling evidence for the prenatal origins of many illnesses (Barker, 1998, 2002). Maternal levels of prenatal cortisol have been associated with negative long-term outcomes, including lower verbal IQ scores in children (LeWinn et al., 2009).

Experimental designs with animals have also shown that adverse fetal environments influence offspring development and HPA axis regulation in later life. Preclinical studies examining prenatal exposure to high levels of synthetic glucocorticoids have demonstrated influences on neonatal outcomes, including reductions in fetal growth, altered immune functioning, and altered metabolism (for review, see Coe & Lubach, 2005). Prenatal exposure to synthetic glucocorticoids has also been associated with profound and long-lasting changes in offspring development, including increased basal and challenge induced HPA axis activity (Shoener, Baig, & Page, 2006), worse performance on cognitive tasks (Brabham et al., 2000), and reduced hippocampal

development (Bruschettini, van den Hove, Gazzolo, Steinbusch, & Blanco, 2006; Coe & Lubach, 2005; Uno et al., 1994).

In addition to these offspring outcomes associated with prenatal synthetic glucocorticoids, the HPA axis of offspring also seems to be dysregulated following prenatal exposure to endogenous maternal glucocorticoids. In animal studies, increased exposure has been associated with more rapid, severe, and prolonged HPA responses to novel or challenging tasks in offspring (Henry, Kabbaj, Simon, Le Moal, & Maccari, 1994; Maccari et al., 1995; Vallee et al., 1997; Weinstock, Matlina, Maor, Rosen, & McEwen, 1992). Alterations in stress reactivity are still apparent in adult animals, indicating that prenatal glucocorticoid exposure programs long-term changes in the functioning of HPA axis in offspring.

Animal studies have also begun to delineate the role of placental functioning in fetal exposure to maternal glucocorticoids. The barrier enzyme 11beta-hydroxysteroid dehydrogenase type 2 (11β-HSD2) protects the developing fetus from excessive glucocorticoid exposure by converting active glucocorticoids into their inactive form (in humans cortisol is converted into cortisone, in rats corticosterone is converted into 11-dehydrocorticosterone). When pregnant rats were exposed to chronic stress, however, placental 11β-HSD2 activity was greatly reduced (Mairesse et al., 2007), even when presented with an acute stressor (Welberg, Thrivikraman, & Plotsky, 2005). Thus, it seems that innate biological mechanisms may protect the developing offspring of mothers who face acute stress, but leave offspring of mothers experiencing chronic stress particularly vulnerable to exposure to active maternal glucocorticoids, which easily pass

through the fetal blood brain barrier (Jacobson & Sapolsky, 1991; Sanchez, Young, Plotsky, & Insel, 2000).

There is also evidence of fetal programming effects in humans. Although fetal and maternal HPA axes are regulated independently during pregnancy, by mid-pregnancy maternal cortisol concentrations are significantly associated with levels of placental CRH, which stimulates the synthesis of fetal cortisol (O'Keane et al., 2011; Wadhwa, Porto, Garite, Chicz-DeMet, & Sandman, 1998). Studies of pregnant women undergoing intrauterine needling have examined relationships between maternal and fetal plasma cortisol concentrations and have estimated that 34-40% of the variance in fetal cortisol is attributable to maternal levels (Gitau, Cameron, Fisk, & Glover, 1998; Gitau, Fisk, Teixeira, Cameron, & Glover, 2001). Additionally, even small increases in maternal cortisol in response to needling resulted in doubling of fetal plasma cortisol concentrations (Gitau et al., 2001).

In human infants, elevated maternal prenatal cortisol is associated with poor obstetrical outcomes, including restricted fetal growth, low birth weight, and preterm delivery (Diego et al., Diego et al., 2009; 2006; Field, Hernandez-Reif, et al., 2006; Sandman et al., 2006). In addition, maternal cortisol levels in late pregnancy predict infants' greater negative temperament (de Weerth, van Hees, & Buitelaar, 2003) and predict worse psychomotor development over and above cortisol levels earlier in pregnancy (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003). In contrast, exposure to high concentrations of maternal cortisol in early pregnancy predicts worse performance on a test of mental development (Davis & Sandman, 2006).

Fetal exposure to elevated maternal cortisol during pregnancy has also been associated with infant HPA dysregulation. Maternal cortisol levels in the second and third trimesters predicted neonatal cortisol in first urine samples (Field et al., 2004), as well as exaggerated cortisol in response to a heel stick in the first 24 hours of life (Davis, Glynn, Waffarn, & Sandman, 2011). It remains unknown whether or not fetal exposure to maternal cortisol during pregnancy predicts infant HPA reactivity beyond the neonatal period. One study reported no significant association between prenatal cortisol levels and infant cortisol reactivity to stressors over the first year of life (Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011), but relied solely on a nonclinical sample and measured maternal cortisol at only one time point, which was during the late third trimester. It is possible that maternal cortisol levels in nonclinical samples are not dysregulated enough to influence the developing fetus. As Peeters, Nicolson, and Berkhof demonstrated, HPA axis dysregulation is not associated with depressive symptoms in community samples of nonpregnant adults (2004). Instead, elevated cortisol levels have been associated with recurrent, severe episodes of depression (Knorr, Vinberg, Kessing, & Wetterslev, 2010). It remains unknown whether or not HPA dysregulation is associated only with recurrent, severe depression in pregnant women. Further research with women with histories of depression who are, thus, at high-risk for perinatal depression is needed to elucidate the potential associations between maternal depression and the maternal and fetal HPA axes.

In addition to concerns about sample characteristics, the dramatic normative changes in cortisol levels across gestation suggest that multiple measures of cortisol sampled across pregnancy would illustrate a more complete picture of fetal exposures

relative to the approach taken in much of the published literature, which is only one or two samples collected late in pregnancy. Furthermore, researchers have hypothesized that maternal cortisol levels early in pregnancy may be more likely to affect fetal development than cortisol levels late in pregnancy (Gutteling, Weerth, & Buitelaar, 2005; Vrijkotte, van der Wal, van Eijsden, & Bonsel, 2009). These hypotheses are consistent with the buffering influence of the placenta. In early pregnancy, the fetus is partially protected from maternal cortisol by placental 11β-HSD2 activity. As parturition approaches, however, 11β-HSD2 activity decreases, allowing a greater proportion of maternal cortisol to cross the placental barrier (Giannopoulos, Jackson, & Tulchinsky, 1982; Murphy, 2006). This exposure to elevated cortisol in late pregnancy is beneficial for maturation of fetal organ systems, especially the lungs (Hacking, Watkins, Fraser, Wolfe, & Nolan, 2001). Additionally, exposures during early pregnancy may be especially harmful because rapid neurogenesis takes place during this time, with the majority of neuroblasts formed between 5 and 25 weeks of gestation (Mrzljak, Uylings, Kostovic, & van Eden, 1992; Rakic, 2002). Researchers examining associations between timing of a natural disaster, considered a major prenatal stressor, and child outcomes have found that exposure to prenatal stress during the first or second trimester led to worse performance on a test of mental development at two years of age (Laplante et al., 2004). Taken together, these studies suggest that exposure to stressors early in pregnancy may have more profound effects on offspring relative to later exposure. Research studies with multiple measures of maternal cortisol beginning early in pregnancy and assessments of infant outcomes are needed to further explore the influence of timing of exposure.

Fetal Exposure to Maternal Depression and Infant HPA

In addition to the accumulating evidence of lasting alterations of infant stress regulation associated with fetal exposure to glucocorticoids, researchers have also begun to explore the relationships between maternal depression and infant stress regulation. Previous findings support the idea that HPA dysregulation in children may be a risk factor for poor social and emotional functioning, with a positive association observed between cortisol levels in preschoolers and behavioral problems (Essex, Klein, Cho, & Kalin, 2002). Research examining influences of prenatal and postnatal depression on HPA axis regulation are presented in the following two sections.

Role of exposure to prenatal depression. The results of numerous studies have yielded support for associations between prenatal depressive symptoms and elevated basal cortisol levels in infants (Brennan et al., 2008; Diego et al., 2004; Field, Diego, Dieter, et al., 2004; Field, Hernandezreif, et al., 2006; Lundy et al., 1999) and prepubescent children (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002). Moreover, elevated or increasing symptoms of depression over the course of pregnancy have been associated with increased ACTH in cord blood (Marcus et al., 2011). Cortisol alterations associated with prenatal depression are evident in the neonate as early as one day postpartum, suggesting that prenatal exposures exert influences on the developing HPA axis independent of further postnatal exposures (Lundy et al., 1999).

Role of exposure to postnatal depression. Beyond the neonatal period, it is unclear to what extent infants' dysregulated HPA axis stress reactivity is linked to exposures to prenatal depression alone, postnatal depression alone, both prenatal and postnatal (indicating additive or interactive effects), or either period (indicating that a

sensitive period of development does not exist), or even a mother with a lifetime history of depression (indicating that a history of depression prior to the child's lifetime may be associated with other risk factors and/or genetic influences may be at play). Most published studies focus on prenatal or postnatal maternal mood in isolation, rather than investigating outcomes related to the timing or trajectories of perinatal exposures. The small body of evidence exploring the effects of timing of maternal depression is presented below.

Researchers examining the role of lifetime depression in a high-risk, teenage sample reported that 4 month-old infants of mothers who had two or more major depressive episodes during their lifetimes had greater cortisol responses to an arm restraint relative to women who had experienced one or no major depressive episodes (Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007). However, the infants' cortisol reactivity was not related to mothers' diagnosis of a major depressive episode during pregnancy or levels of postnatal depressive symptoms. That is, the history of recurrent depression predicted infant cortisol reactivity, whereas pre- and postnatal depression did not. Other researchers have observed heightened cortisol reactivity in 6-month-old infants in response to an arm restraint and sound burst regardless of whether the maternal depression occurred during pregnancy, the postpartum period, or both periods (Brennan et al., 2008). This finding suggests that timing of maternal depressive symptoms is equally toxic during pre- and postnatal development. Yet another study reported that exposure to both prenatal and postnatal depressive symptoms related to neonate HPA dysregulation, indicating additive effects of depression exposures (Diego et al., 2004). This study, however, measured postnatal depressive symptoms only during the first week

following delivery. Further, there were not significant differences between cortisol levels of infants of mothers who experienced depression during the prenatal and postnatal period in comparison to those of mothers who experienced elevated depressive symptoms during pregnancy only or postpartum only. It should also be noted that neither of the previous studies was firmly rooted in a theoretical model that explained why a difference (or lack thereof) would be expected in infant outcomes.

One theoretical perspective that is highly relevant to questions about the role of postnatal exposure is differential susceptibility to environment. Consistent with this theory, discontinuity of depressive symptoms between the pre- and postnatal environments was found to be predictive of the greatest alterations in infant HPA reactivity, with low prenatal depressive symptoms and high postnatal depressive symptoms predicting the highest cortisol reactivity in 18-month-old infants (Laurent, Ablow, & Measelle, 2011). These results suggest fetal development in preparation for a healthy postnatal environment may result in negative outcomes when the postnatal environment expectancy is not met. According to this environmental expectancy and fit model (Oitzl, Champagne, van der Veen, & de Kloet, 2010), infants of mothers with low prenatal depressive symptoms develop an evolutionarily adaptive heightened stress response in preparation for a presumably nonthreatening environment. These infants would not be physiologically prepared for the highly stressful environment associated with a mother with postnatal depression, and the infants' HPA axis would be driven into a state of hyperarousal. Conversely, high levels of prenatal depressive symptoms followed by low postnatal depressive symptoms would be expected to predict blunted

HPA reactivity, where infant HPA axes would be down-regulated in anticipation of a highly stressful postnatal environment.

Moderating effects of maternal caregiving behaviors. Further complicating an understanding of predictors of infant cortisol reactivity is consideration of the possible role of postnatal exposures in addition to maternal depression, and particularly correlates of maternal depression, which may moderate associations between maternal depression and infant stress reactivity. In particular, in addition to exposure to maternal depression, infants may also be exposed to stressful caregiving interactions, which may moderate the relationship between maternal depression and infant HPA dysregulation. Evidence suggesting the importance of maternal caregiving behaviors, which frequently differ among women with and without depression, is presented below.

Preclinical studies also suggest that offspring of low licking and grooming mothers display disordered behavioral responses to stress as adults, including increased startle responses, decreased open-field exploration, and longer latencies to eat food in a novel environment (Caldji et al., 1998; Francis, Caldji, Champagne, Plotsky, & Meaney, 1999; Francis, Diorio, Liu, & Meaney, 1999; Francis & Meaney, 1999). The results of animal studies suggest that maternal care behaviors toward offspring can program both neuroendocrine and behavioral stress reactivity, leading to stable individual differences lasting into adulthood.

Research with rodents and non-human primates shows a link between prenatal stress, quality of parenting behaviors and offspring phenotypic development. In Bonnet macaques, stress during pregnancy has been shown to impair mother-infant interactions, with mothers exhibiting increased rates of rejection toward offspring (Coplan et al.,

1996). Offspring of prenatally stressed mothers also exhibited increased fearfulness and stress reactivity. In rodents, chronic prenatal stress results in diminished maternal pup licking and grooming levels (Champagne & Meaney, 2006; Roth, Lubin, Funk, & Sweatt, 2009; Smith, 2004). Differences in rodent licking and grooming behaviors have been shown to influence development of the HPA axis of offspring (Caldji et al., 1998; Liu et al., 1997; Weaver et al., 2004). The offspring of high licking and grooming dams show increased glucocorticoid receptor (GR) expression, enhanced negative-feedback sensitivity to glucocorticoids, reduced corticotropin releasing factor (CRF) expression in the hypothalamus, and more modest hormonal stress responses (for review see Caldji, Hellstrom, Zhang, Diorio, & Meaney, 2011).

In human studies, research has indicated that mothers with depression differ in interaction styles with their infants, exhibiting poorer interactive behavior (Beck, 1995), less positivity (Campbell, Cohn, & Meyers, 1995), and less sensitivity (Frankel & Harmon, 1996; Zeanah, Boris, & Larrieu, 1997) relative to nondepressed mothers or mothers low in depressive symptom levels. In a meta-analysis of maternal depression and parenting behavior, depression in mothers was found to be associated with higher levels of negative parenting behaviors, lower levels of engagement, and lower levels of positive social interactions (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Importantly, these observed differences were strongest in mothers of infants as compared to older children.

Quality of maternal-infant interactions has also been identified as a predictor of infant stress dysregulation. Low maternal sensitivity, measured by a global rating of maternal behavioral responsiveness to infant signals, has been shown to predict higher

infant cortisol reactivity in response to a free-play session in both 3- and 6-month-olds (Spangler, Schieche, Ilg, Maier, & Ackermann, 1994). Additionally, infants' cortisol reactivity to lab stressors, including the strange situation (Ainsworth, Blehar, Waters, & Wall, 1978), differs based on maternal-infant attachment style, with securely attached infants showing no significant change in cortisol levels and infants characterized as disorganized (Hertsgaard, Gunnar, Erickson, & Nachmias, 1995; Spangler & Schieche, 1998) or avoidant (Spangler & Schieche, 1998) showing the greatest cortisol reactivity.

A limited number of studies have also shown that aspects of maternal-infant interactions moderate the relationship between maternal psychopathology and infant HPA dysregulation. Kaplan, Evans, and Monk investigated the role of maternal sensitivity, measured by a global rating of mothers' emotional quality of interactions and successful repairs of dyssynchronies, as a moderator between the associations between prenatal psychiatric status and infant HPA dysregulation at 4 months of age (2008). Maternal insensitivity moderated this relationship, such that prenatal psychiatric status and infant basal cortisol were significantly associated only if mothers were rated as highly insensitive during a free-play session. This study included a range of Axis I maternal psychiatric disorders, and did not investigate effects specific to maternal depression, however. In a larger study of maternal mood and infant stress response, however, postnatal maternal depression and insensitivity each independently predicted 9 month-old infants' increased cortisol reactivity, with no support for an interaction or moderation (Feldman et al., 2009). These authors defined sensitivity more broadly, as a composite score of several maternal behaviors, including acknowledgement of child communications, warm vocal quality, and an appropriate range of affect. Further, the

study differed from Monk et al. in that maternal depression was studied in the postpartum rather than prenatal and infants were older (9- relative to 4-months old) and focused specifically on maternal depression instead of various forms of psychopathology. Although these results differ in their suggestion of a main effect or a moderating effect, both sets of findings are consistent with maternal depression and caregiving behaviors both influencing the infant's HPA regulatory capability. The current study seeks to explore these relationships further, using multiple measures of maternal depression and sensitive parenting behaviors over the infant's first year of life.

Infant Behavioral Stress Reactivity

In addition to this extensive body of research on infant cortisol reactivity, infant behavioral reactivity, another indicator of an infant's stress reactivity, has also been studied in relation to maternal depression and interactive qualities. Few studies have included both behavioral and neuroendocrine measures of infant stress reactivity, and these studies have yielded inconsistent results with regards to the independence vs. co-regulation of the functioning of these two indices of stress reactivity. Researchers have shown that infant cortisol reactivity is not related to infant observed negative affect in response to a heel stick at day one of life (Davis, Waffarn, & Sandman, 2011; Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995) or in response to an inoculation in six-month-old infants (Ramsay & Lewis, 2003). However, others have demonstrated that behavioral reactivity to inoculations, including increased latency to quieting and higher levels of negative affect, is positively associated with cortisol reactivity to inoculations from infant ages 2 to 6 months (Lewis & Ramsay, 1995; Ramsay & Lewis, 1994). Cortisol reactivity has also been associated with affective and behavioral distress to limitations, including

sitting in a car seat and having a toy out of reach (Gunnar, Hertsgaard, Larson, & Rigatuso, 1991). Additionally, negative affect in response to a physical exam and inoculation were associated with increased cortisol reactivity in 2- and 6-month-old infants, but not in 15-month-old infants (Gunnar, Brodersen, Krueger, & Rigatuso, 1996). Based on this evidence, behavioral measures of stress reactivity are considered here as a potential independent measure of infant stress reactivity, and associations between indices of behavioral and cortisol reactivity are explored.

Maternal depression during pregnancy has been associated with measures of infant behavioral reactivity. Elevated prenatal depressive symptoms were associated with increased infant negative reactivity at two months, indicated by higher scores on the fear subscale of the Infant Behavior Questionnaire which assesses the extent to which infants startle or show distress in response to sudden changes or novel stimuli (Davis et al., 2007). These researchers also demonstrated that maternal cortisol levels during pregnancy independently predicted report of infant negative behavioral reactivity, with higher levels of maternal cortisol associated with increased infant reactivity.

Maternal depression during pregnancy has also been associated with infant behavioral reactivity during laboratory assessments. Specifically, maternal depressive symptoms during the third trimester of pregnancy, but not postnatal symptoms, predicted infant negative behavioral reactivity at four months of age (Davis et al., 2004), where elevated depressive symptoms predicted increased infant motor activity and crying in response to presentations of novel stimuli.

Researchers have also identified associations between characteristics of maternal-infant interactions and infant behavioral stress reactivity. Five to six-month-old infants of

responsive parents, i.e. parents who more often responded to infant vocalizations or facial expressions, spent a lower proportion of time exhibiting negative affect following a series of separations from their parents (Haley & Stansbury, 2003). Six-month-old infants whose mothers engaged their infants contingently have also been shown to express less distress during presentation of novel stimuli (Crockenberg & Leerkes, 2004). Similarly, infants of mothers rated high in sensitivity, or responsiveness to infant cues and ability to regulate her own and her infant's affect, showed greater engagement during the reunion following the still-face procedure, while infants of less sensitive mothers showed more gaze aversion and negative affect (Kogan & Carter, 1996). A meta-analysis of maternal behavior during the still-face paradigm revealed that maternal sensitivity was positively associated with infant positive affect (Mesman, van Ijzendoorn, & Bakermans-Kranenburg, 2009), which has been shown to be a predictor of secure attachment at one year of life (Cohn, Campbell, & Ross, 1991). Thus, it seems that higher levels of maternal engagement and sensitivity are associated with infants' greater abilities to regulate affect during physical or social stressors.

Current Study

We examined associations between maternal pre- and postnatal depression, prenatal cortisol, and infant cortisol and behavioral stress reactivity at 12 months of age. We sampled women who all had at least one major depressive episode according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (*DSM-IV*) criteria (American Psychiatric Association, 1994a) prior to pregnancy. This sampling strategy yields a higher percentage of women who have an episode of perinatal depression than does sampling the general population of pregnant women. To examine influences of both

the prenatal and postnatal environments on infant stress regulation, women were assessed at multiple time points throughout pregnancy and the postnatal period in this prospective, longitudinal study. Infant outcomes were evaluated at twelve months based on several considerations: (1) infant negative affect, an index of behavioral stress reactivity, at 12 months has been shown to predict early childhood depressive symptoms (O'Connor, 2001); (2) by 12 months of age, infants are more attentive to their social environment, and have more highly developed cognitive processes and capacity for self-regulation relative to younger infants (e.g. self-soothing; Cicchetti, 1991). We observed infants in two contexts, one intended to be a mild stressor and one a more moderate stressor in order to assess stress reactivity across multiple contexts and examine the consistency of the behavioral stress response. We define behavioral reactivity to a stressor by examining multiple indices of stress, including proportion time spent in negative affect, time until distress, and intensity of distress. We examine multiple aspects of infant cortisol response as well, including initial cortisol levels upon infants' arrival to the laboratory, overall cortisol levels, and cortisol reactivity (by computing difference and percent change scores). Additionally, we improve upon previous studies by measuring other prenatal exposures, including maternal smoking status, known to be associated with infant cortisol (Ramsay, Bendersky, & Lewis, 1996; Schuetze, Lopez, Granger, & Eiden, 2008).

Based on the literature reviewed, we predicted that exposure to higher symptom levels of (1) prenatal maternal cortisol would be associated with heightened infant cortisol reactivity. We also tested exploratory hypotheses regarding the timing of exposures. We predicted (2) heightened cortisol early in pregnancy and infants'

heightened cortisol reactivity. Additionally, we expected that higher levels of both (3) pre- and (4) postnatal depression would be associated with higher infant cortisol and behavioral reactivity to a stressor. Exploratory hypotheses investigating the timing and interactions among exposures will also be addressed. More specifically, consistent with the differential susceptibility to the environment theory, we expect (5) increasing depressive symptoms from the pre- to postnatal period to be associated with higher infant cortisol reactivity. Additionally, we investigated the role of maternal sensitivity as a potential independent predictor (6) or moderator (7) of the relationship between perinatal depression and infant cortisol and behavioral stress reactivity.

Method

Participants

This research was part of a larger longitudinal research study, *Maternal Depression: Implications for Infant Development (Pregnancy, Postpartum and Newborn Development Analysis [PANDA] Project).* Participants were pregnant women and, later, their infants through 12 months of age. In order to be considered eligible to participate, women must have met criteria for one or more major depressive episodes according to the *DSM-IV* criteria (American Psychiatric Association, 1994a) prior to pregnancy. Additionally, women were required to be in the first 27 weeks of pregnancy at the time of enrollment, be at least 19 years old, primiparous, married or cohabiting, and either Caucasian and non-Hispanic, or African-American (the primary ethnic/racial groups in the geographic area from which women were recruited). Women age 19 and above were included in order to reduce the risk of pregnancy complications associated with teen-aged mothers (Abu-Heija, 2002; Fraser, Brockert, & Ward, 1995; Jolly, 2000), as well as

poorer quality of mother-infant interactions associated with teen-aged mothers (Barratt & Roach, 1995; Landy, 1983; Levine, Garcia Coil, & Oh, 1985; Pomerleau, Scuccimarri, & Malcuit, 2003). In order to further reduce the variability in quality of parenting associated with multiparity (Fish & Stifter, 1993) or single parents (Cheadle & Amato, 2011), only primiparous women who were married or cohabitating with a partner were included in this study.

Women were excluded from the current study if they expressed active suicidality, tested positive on a urine toxicology screen, had a medical condition which was stable for less than six months, or if they met criteria for the following *DSM-IV* diagnoses: organic mental disorders, substance abuse within the last six months, schizophrenia, delusional disorder, psychotic disorders, bipolar disorder, antisocial personality disorder, or presence of psychotic features. These inclusion and exclusion criteria were selected in order to examine the influences on infant stress reactivity specific to maternal depression.

Pregnant women were recruited from community obstetrical/gynecologists' offices and media announcements. Eligibility was determined using a two-stage process. First, women were interviewed by phone to evaluate inclusion/exclusion criteria. A brief depression screen was used to reveal whether they were likely to have ever experienced a depression episode. The depression screen consisted of two questions from the Diagnostic Interview Schedule (Robins, Helzer, Croughan, & Ratcliff, 1981), asking about lifetime depressed mood and anhedonia. These two items have high sensitivity as screeners for depression, from .83 to .94 across samples (Rost, Burnam, & Smith, 1993). Second, following informed consent, eligible women were administered the Structured Clinical Interview for DSM-IV (SCID; First, 2007) to determine that they met diagnostic

criteria for at least one lifetime episode of major depression. In this manner, we avoided the inherent biases of recruiting women who self-identify as being depressed, self-selection biases in terms of identifying oneself as having been depressed and biases of access to care, if one recruits a sample being treated for depression, given that only a minority of people with depression seek treatment (Sheila M Marcus, Heather A Flynn, Frederic C Blow, & Kristen L Barry, 2003). A total of 116 women were enrolled in the study. Of these women, 38 dropped out of the study during pregnancy and 2 dropped out within 4 months postpartum. Of the remaining 78 women, 70 completed a 12-month postpartum laboratory visit with their infants. One mother participated in two separate laboratory visits with each of her twin infants, resulting in a final sample of 71 mother-infant dyads in the current study (37 female; 52%).

Women in the final sample were, on average, 30 years old (SD= 5.4), 69% were Caucasian, 71% married, and 70% had college education or higher. Participants reported a median annual household income of 71,000-75,000 dollars. Self-reports indicated that 8 women (11%) were smoking cigarettes or using tobacco products when they became pregnant and 10 women (14%) took psychotropic medications for one or more months during pregnancy. Infants in the final sample were, on average, born at 39.1 weeks gestational age (SD= 2.1), with an average birth weight of 3280 grams (SD= 657).

Procedure

Women were enrolled between 4 and 27 weeks gestation. At their first visit, participants completed the *Structured Clinical Interview fir DSM-IV-TR Axis I Disorders* (SCID; Michael B First, 2007) to verify that they had experienced at least one previous major depressive episode and rule out exclusionary diagnoses. At that time, women were

also interviewed in order to ascertain background and medical history information, including smoking status at the time they became pregnant, and use of psychotropic medications. Additionally, following enrollment, women completed the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996) once per month during pregnancy. On the same day, women collected first void at home with a urine collection kit, which they refrigerated until the time of their lab visit. During the postnatal period, women completed self-report measures of depressive symptoms at 5-7 days, 1, 2, 3, 4, 5, 6, and 12 months postpartum.

At twelve months postpartum, women and their infants were invited to the laboratory to complete the strange situation and a series of face-to-face interactions. All twelve month laboratory visits were completed within 9 weeks of the child's first birthday (*M*= 12.20 months, *SD*= .44, range=11- 14). Upon arrival to the lab, infant saliva was collected using rolled cotton, which the infant sucked on. All saliva samples were immediately frozen until thawed for assay.

Next, mothers, infants, and a lab volunteer completed the strange situation procedure (Ainsworth et. al, 1978), consisting of a series of separations and reunions, which most infants find at least mildly distressing (Ainsworth, Blehar, Waters, & Wall, 1978). The strange situation mimics developmentally relevant stressors, namely separation from mothers, being left alone, and interacting with a stranger, and is moderately stressful for 12-month-olds. It consists of eight 3-minute segments during which the infant is alone, with his/her mother, a female stranger, or with both the mother and stranger in an unfamiliar setting. The infant is separated from his/her mother two times during the procedure. Segments are shortened if the infant is extremely distressed

for at least 20 seconds. Previous studies have documented individual differences among infants' cortisol response to the strange situation (Hertsgaard et al., 1995; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Spangler, 1998; Spangler & Grossmann, 1993). A second saliva sample was taken twenty minutes following the conclusion of the strange situation procedure. Infants were consoled as necessary before completing the rest of the laboratory visit protocol.

Next, mothers and infants were videotaped during a series of face to face interactions. Infants were seated in a high chair with mothers seated directly in front of them. Participants completed a series of interactive segments, including peek-a-boo (2 minutes), unavailable (2 minutes), during which mothers were instructed to turn around in their chairs and ignore their infant, free-play (5 minutes), during which mothers were given a set of toys and instructed to play with their infants just as they normally would at home, feeding (5 minutes), and distract (5 minutes), during which mothers were asked to fill out paperwork while face-to-face with their infant. To examine stress reactivity, we focused on the unavailable and distract segments, which were intended to be moderate and mild stressors, respectively.

Measures

Maternal Depression. The SCID (First, Spitzer, Gibbon, & Williams, 1995) is a semi-structured diagnostic interview designed to assess Axis I disorders of the DSM-IV (American Psychiatric Association, 1994b). The SCID was used to assess for a past history of any psychological disorders, in order to confirm that women met diagnostic criteria for at least one MDE. Trained clinicians administered the SCID, with reliability

determined by a senior clinical psychologist who listened to the audiotapes of each interview and independently assigned diagnoses.

The BDI-II (Beck, Steer, & Brown, 1997) is a self-report measure with 21 items. Respondents are instructed to base their answers on the past two weeks, paralleling the DSM-IV criteria of duration for a major depressive episode. Each item on this instrument is rated on a 4-point scale, ranging from 0 to 3. A total score is computed by adding the ratings across items. BDI-II scores above 13 indicate at least mild depression (Beck et. al, 1997). The BDI-II has been found to be both a valid and reliable measure of depression severity, with an especially high degree of content validity, construct validity, and internal consistency (Beck et. al, 1997). The BDI-II has been shown to have good concurrent validity with measures of both antenatal and postpartum depression (Boyd, Le, & Somberg, 2005; Steer, Scholl, & Beck, 1990). Women completed an average of 5 self-report assessments (*SD*= 1.47, range= 1-9). Depressive symptom scores were highly intercorrelated across time points (see Table 3). In order to test our hypotheses about mothers' depressive symptoms over the pre- and postnatal periods, mean BDI-II scores were calculated to capture dose of exposure separately for each time period (for descriptive statistics, see Table 4).

In order to address our hypotheses involving the patterns of BDI-II trajectories from the prenatal to postnatal periods, nonhierarchical clustering, a descriptive statistical technique, was used to identify groups of women with similar patterns of depressive symptoms. First, a "distance" was calculated to represent the dissimilarity between each pair of cases, on the basis of their BDI-II scores. In the first step of nonhierarchical clustering procedures, the two cases with the smallest distance or dissimilarity were

joined to form a group. In subsequent steps, cases or groups of cases were combined according to a systematic principle (Johnson, 1992). FASTCLUS is a SAS procedure that implements nonhierarchical clustering, where we specified a squared Euclidean distance metric to measure the dissimilarity between each pair of cases (SAS, 1990). The goal of the analysis is to maximize the differentiation of the sample while retaining sufficient cluster size to permit meaningful statistical analysis (Morral, Iguchi, Belding, & Lamb, 1997).

Our analysis included all 107 participants enrolled with BDI-II scores across the perinatal period. Therefore, each cluster was required to include at least 11 subjects to meet the 10% of the effective sample size requirement described per Morral et al. (1997). This requirement was satisfied, as the smallest cluster from our analyses with the entire sample included 18 women. Of the original 107 women included in the clustering analysis, 67 participants had outcome data at 12 months postpartum and are included the current analyses.

Nonhierarchical clustering yielded four clusters of BDI-II trajectories. The first group identified included 14 women with consistently high scores, who met or exceeded the BDI-II cut-off at nearly every time point (*hi/hi group*; see Figure 1). The second group included 22 women with consistently low scores (*lo/lo*). The third group identified included 20 women with scores that indicated consistent sub-threshold levels of depression (*mod/mod*). The final group included 11 women who exceeded the BDI-II cut-off early in pregnancy, followed by a decline in symptoms and low scores during the postnatal period (*hi/lo*).

Urinary Free Cortisol. Experienced lab technicians measured urinary free cortisol using the extracted competitive binding immunoenzymatic assay available on the Beckman Coulter Access analyzer (Beckman Coulter Access Immunoassay System Product Insert (1997): Cortisol assay 170157E, 1997). In this assay, the cortisol in urine is extracted with ethyl acetate. A portion of the ethyl acetate supernatant is evaporated to dryness and re-dissolved in assay buffer. Recovery of cortisol from the ethyl acetate extraction averages 99% over a wide range of concentrations. The limit of detection is 0.4 µg/dL of urine. The between run imprecision is 7.9% at 6.0µg/dL and 6.0% at 24.1µg/dL. The within run imprecision is 6.7 and 4.4% at the same levels respectively. The assay has also been compared to the extracted DPC cortisol RIA and yielded a linear regression coefficient (r) of 0.968 (y = 0.988x + -1.10, n=121). Samples are run in duplicate and three levels of quality control are included with each assay run. Duplicates are averaged unless they exceed a 10% difference in which case the analysis is repeated.
Women completed an average of 5 urine collections (SD= 1.37, range= 1 - 8).

For maternal prenatal cortisol samples, overall fetal exposure was summarized by computing a mean value for months 4 through 9 of pregnancy (for descriptive statistics, see Table 4). Mean scores were also calculated for trimesters two, including values from months four through six of pregnancy, and trimester three, including values from months seven through nine of pregnancy. Means were log transformed in order to reduce skewedness. However, raw cortisol values prior to log transformation will be presented in tables and figures for ease of interpretation.

Skilled lab technicians conducted the analysis of infant salivary cortisol. The cotton rolls used to collect saliva samples were first centrifuged in order to obtain the

fluid. Using a syringe, the fluids were collected and frozen within a protective tube. Before analysis could begin, the oral fluids were thawed and centrifuged once again to insure the removal of any protein debris. Salivary cortisol was measured by means of a series of laboratory tests, using a modification of the competitive binding immunoenzymatic assay. Cortisol in the specimen being analyzed competed with a cortisol-alkaline phosphate conjugate for binding sites on a rabbit anti-cortisol antibody. Paramagnetic particles coated with goat anti-rabbit capture antibody were then added. The captured antigen-antibody complexes were separated in a magnetic field and washed to remove any unbound substances. A chemiluminescent phophatase substrate was added to the salivary substance, producing a light that was measured with a luminometer. This light was inversely proportional to the concentration of cortisol. In some cases, the quantity of saliva was insufficient to be able to measure cortisol and thus was coded as "quantity not sufficient," reducing the sample size for analyses with these variables. Infant saliva samples were assayed in duplicate. Samples were reassayed if they varied by 20% or more.

Infant Affect Coding. Infant affect was rated continuously on a 7-point scale. A neutral affect code was added to the scale Dawson *et al.* (1999) adapted from Osofsky (1987). Scores ranged from -4 = marked distress or cry to +4= laughter or squeal. Infant affect scores were based on infant facial expressions, vocalizations, and body movements (see Appendix A). Additional codes were used to account for various errors, such as if the infant was out of the view of the camera, protocol was broken, or if a researcher entered the room. All raters were unaware of other data collected on the mothers and babies, including maternal depression status.

This system yielded several different measures of infant distress for each segment: (1) *Time until Distress,* calculated by counting the number of seconds until the infant demonstrated negative affect; (2) *Proportion Time Negative*, calculated as the proportion of codeable time the infant spent in negative affect[1]; (3) *Peak Distress*, coded as the most negative affect level an infant displayed. For infants that never displayed a negative affective state (unavailable: n= 2, distract: n=1), *Peak Distress* was coded as missing and was not included in the analyses. Descriptive statistics for each variable are presented in Table 1.

The distract segment was intended to be a mild intensity stressor for the infants, whereas the unavailable segment was intended to be a moderate intensity stressor. Consistent with this intent, infants exhibited higher *proportion time negative* during the unavailable segment relative to the distract segment, $t(54)= 3.16$, $p = .003$, and a shorter *time until distress* during the unavailable segment relative to the distract segment, $t(52)= -3.90$, $p < .001$. There were not significantly different proportions of infants reaching various levels of *peak distress*, $\chi^2= 7.53$, $p = .11$. Thus, for ease of interpretation, the distract segment is hereafter referred to as the mild stressor and the unavailable segment is hereafter referred to as the moderate stressor.

For each segment, a subset of video files [41% (n = 28) for distract; 42% (n = 24) for unavailable] was randomly selected for weekly reliability checks on the infant stress reactivity variables. Inter rater reliability, assessed by intraclass correlations and Cohen's kappa coefficients, indicated moderate agreement or better. Specifically, for the

[1] The proportion of time the infant spent in a positive affective state was not included in the analyses. This variable was not included because of its high correlation with the proportion of time spent in a negative affective state within both the unavailable (r= -.96, p< .001) and distract (r= -.99, p< .001) segments. These high correlations were due to the infants spending very little time in a neutral affective state during the unavailable (M= 4.5% of coded time) and distract (M= 1.8% of coded time) segments.

mild stressor, obtained reliabilities were: time until distress (r= .85), proportion of time spent in a negative affective state (r= .92), and peak distress (mean κ= .84). For the *moderate stressor* segment, obtained reliabilities were: time until distress (r= .59), proportion of time spent in a negative affective state (r= .92), and peak distress variable (mean κ= .73).

As shown in Table 2, infant stress reactivity variables were highly intercorrelated within segments. Principal components analysis (PCA) was conducted in order to reduce variable redundancy. In order to be included in the PCA analyses, participants needed to have infant behavioral data during both the mild and moderate stressor (n= 52). PCA yielded two interpretable factors, one factor including variables calculated for the unavailable segment (moderate stressor), and one factor related including those calculated for the distract segment (mild stressor). These two factors explained a total of 72% of the variance in infant behavioral reactivity scores. Factors were rotated using the Oblimin with Kaiser Normalization. Variable loadings on the factors ranged from .76 to .94. Factor scores were not significantly correlated with one another (r= -.01, p= .97). The resulting factor scores, infant observed distress during the mild stressor (distract) (M= -.03, SD= .92, range= -1.31 to 2.02) and infant observed distress during the moderate stressor (M= -.002, SD= .97, range = -.99 to 3.29) were used in subsequent analyses. Higher scores indicate more time until the infant displayed a negative affective state, less time spent in a negative affective state, and less intense peak distress.

Maternal Behavior Rating. Following previous studies (Feldman et al., 2009; Spangler et al., 1994), maternal parenting behaviors were rated from video recordings of free-play segments. Maternal parenting behaviors were rated for 3, 6, and 12 month

visits using the *Maternal Interactive Quality Ratings*, 12 rating scales taken from the standardized rating scales of Ainsworth (Ainsworth et al., 1978), Clark (1985), and Campbell (1991). This set of scales was selected to assess the quality of the mother's interactive behavior with her infant, and specifically, to assess behaviors that may reflect insensitive parenting, intrusiveness, withdrawal, positive affect, and negative affect. For a full description of the scales, see Appendix B. Scores for each of the scales were rated using either a 4- or 5-point Likert scale, and took into consideration both the quality and quantity or intensity of the behavior measured in the scale. Generally, most of the scale scores indicated whether the behavior was 'characteristic' or 'not characteristic' of the mother (or some gradient in between). Raters were blind to the past and current depression status of the mothers they observed. A subset of video files (39% of all videos for 3 months, 15% for 6 months, 17% for 12 months) was randomly selected for weekly reliability checks of parenting behavior scores. Inter rater reliability was examined by calculating the percentage of exact score agreements and the percentage of scores within one point of each other. Percent exact agreement ranged from 33-100% and percent agreement within one point ranged from 73-100%. See Table 5 for reliability statistics.

Prior to analyzing maternal parenting scores, PCA was conducted in order to reduce variable redundancy. Since the sensitivity to distress scale was missing for many infants (49% at 3 months, 61% at 6 months, 46% at 12 months), as they did not show distress during the free-play segment, this scale was not included in PCA. PCA yielded 3 interpretable factors at each time point. Factors were rotated using the Oblimin with Kaiser Normalization. The factor scores accounted for 75, 75, and 76% of the variance in

maternal parenting behavior ratings at 3, 6, and 12 months, respectively. At each time point, one factor reflected parenting behaviors we characterized as sensitive parenting. At 3 months, these items included sensitivity to nondistress, low intrusiveness, cooperation, low detachment/disengagement, and stimulation of development. At 6 and 12 months, items included sensitivity to nondistress, low detachment/disengagement, positive affect, positive regard for the infant, warmth, and stimulation of development. At each age, higher sensitivity factor scores indicate that these sensitive parenting behaviors are more characteristic of mothers. Sensitivity factor score descriptive statistics are presented in Table 6. Sensitivity scores were significantly associated with one another over time (see Table 7).

Approach to analyses

Prior to testing our hypotheses, we examined associations among predictor variables, outcome variables, and potentially confounding variables. First, in order to test the prediction that elevated prenatal cortisol exposure is associated with heightened infant stress reactivity (Hypothesis 1), we tested multiple linear regression models with mean prenatal cortisol predicting infant cortisol and behavioral stress reactivity. Significant covariates were included in the model in the first step of the model and prenatal cortisol values were entered in the second step. Next, to test the predicted associations between heightened cortisol early in pregnancy and infants' heightened stress reactivity (Hypothesis 2), we tested a multiple linear regression model controlling for (entering in the model prior to) third trimester maternal cortisol, and then entering second trimester maternal cortisol, predicting infant cortisol and behavioral reactivity.

To test the prediction that exposure to higher symptom levels of both pre- (Hypothesis 3) and postnatal depression (Hypothesis 4), independently, will be associated with increased infant cortisol and behavioral reactivity to a stressor, we tested this by testing multiple linear regression models, with covariates in the first step of the model and pre- or postnatal depression entered in the second step. To test the extent to which pre- and postnatal depression are uniquely predictive of infant stress reactivity, we tested two multiple regression models. In the first model, covariates were entered in the first step, prenatal depression was entered in the second step, and postnatal depression in the third step. In the second model, the order of entry of pre- and postnatal depression was reversed.

In order to test our prediction that patterns of depressive symptoms across the perinatal period would be associated with infant cortisol and behavioral reactivity scores (Hypothesis 5), analysis of variance (ANOVA) models were tested. Groups were defined using membership to the four trajectory clusters derived from the nonhierarchical clustering analysis. Pairwise comparisons were then tested in order to follow up the omnibus ANOVA.

In order to test the prediction that insensitive maternal interactive styles will independently predict infant outcome variables (Hypothesis 6), we tested multiple linear regression models with the inclusion of covariates. Last, multiple linear regression models were tested to determine whether or not maternal sensitivity scores were significant moderators of the relationship between perinatal depression and infant outcomes (Hypothesis 7). Separate regressions were tested to examine sensitivity at each time point. Covariates were entered in the first step of the model, followed by centered

prenatal depression and sensitivity scores, and last an interaction (product) term of the two. Similarly, regression models examining sensitivity as a moderator between postnatal depression scores and infant outcomes were tested using the same approach.

Results

Preliminary Analyses

Missing Data. Of the 71 mother-infant dyads who participated in 12 month lab visits, 52 (73%) completed both the mild and moderate stressors and thus were included in PCA and hypothesis testing related to behavioral stress reactivity. Dyads who completed free-play segments at 3 (n= 63), 6 (n=55), and 12 (n=66) months were rated for maternal sensitivity and were included in related hypothesis testing. Further, of the infants who participated in the lab visit, 62 (87%) of infants who participated in the 12 month lab had sufficient initial saliva sample volumes for cortisol assays. Sixty (97%) of the infants who had the initial sample also had sufficient post-stressor saliva sample volumes so that cortisol reactivity scores (level, difference, percent change) could be analyzed.

Associations among Predictors. Mean prenatal cortisol values were not significantly associated with mean prenatal depressive symptom scores , $r(68)= -.07$, p= .55). Mean prenatal cortisol values, however, were significantly associated with mean postnatal depressive symptom scores, $r(68)= -.25$, $p= .04$.

Mean depressive symptoms during pregnancy were not significantly associated with maternal sensitivity at 3 months postpartum, $r(59)= -.20$, $p= .13$, but were significantly associated with less sensitive parenting at 6, $r(52)= -.29$, $p= .03$ and 12 months, $r(62)= -.45$, $p < .001$. Postnatal depressive symptoms were significantly

associated with less sensitive parenting at 6 months, $r(53)= -.28$, $p= .04$. Postnatal depressive symptoms were not associated with maternal sensitivity when infants were 3 [$r(61)= -.04$, $p= .74$], or 12, [$r(64)= -.20$, $p= .10$] months old.

Associations among Infant Outcomes. There were no significant associations between infant behavioral reactivity scores and cortisol measures (see Table 8).

Potential Control Variables. Based on previous studies (Ramsay et al., 1996; Schuetze et al., 2008), we examined relationships between maternal prenatal smoking status and infant outcomes in order to determine whether or not it should be included as a control variable. Indeed, infants of mothers who reported smoking during pregnancy (n = 8) had significantly lower initial cortisol values, $t(58)= -2.48$, $p = .02$, Cohen's $d= 1.2$, and cortisol level values, $t(56)= -2.37$, $p = .02$, Cohen's $d= 1.2$ (see Figure 1), in comparison to infants of mothers who did not report smoking during pregnancy (n = 63), with large effect sizes. Maternal smoking status was not significantly related to infant behavioral reactivity scores, cortisol percent change, or cortisol difference scores. Maternal smoking status was not associated with any significant differences in maternal prenatal or postnatal depressive symptom scores, infant gestational age, or infant birthweight. In order to control for the possible effects of maternal smoking on infant cortisol initial values and level values, additional analyses were conducted with smoking status as a covariate when infant cortisol initial values or levels were considered the dependent variable.

Infant exposure to maternal antidepressant medication use (yes/no) during pregnancy was not associated with any differences in infant outcome variables. Additionally, infant birthweight was not associated with infant outcome variables. No

significant sex differences in infant outcome measures were found. Of the six infant outcome measures, infant gestational age at birth was significantly associated with only the behavioral stress reactivity score in response to the mild stressor, $r(49) = .28$, $p = .04$. Given the large number of tests run and the possibility that this association was only due to chance, we did not include gestational age as a covariate in analyses.

Prenatal Maternal Cortisol

First, in order to test our first hypothesis, that maternal prenatal cortisol would predict infant stress reactivity at 12 months, we tested simple linear regression models. Contrary to our hypothesis, maternal prenatal cortisol values did not predict infant behavioral reactivity scores for either the mild or moderate stressors (ps > .10). Also contrary to our hypotheses, maternal prenatal cortisol did not predict infant cortisol initial, level, percent change, or difference values (ps > .10). Prenatal maternal cortisol did not predict infant initial cortisol or level values even after controlling for maternal smoking status (ps > .10).

In order to test our second hypothesis, that trimester 2 maternal cortisol would predict infant stress reactivity over and above trimester 3 maternal cortisol, hierarchical linear regression models were tested. Results showed that trimester 2 cortisol levels did not predict infant behavioral reactivity to mild or moderate stressors when controlling for trimester 3 cortisol levels (ps > .10). Also contrary to our hypotheses, trimester 2 cortisol levels did not predict infant cortisol initial, level, percent change, or difference scores when controlling for trimester 3 cortisol levels (ps > .10). Again, prenatal maternal cortisol did not predict infant initial cortisol or level values even after controlling for maternal smoking status (ps > .10).

Prenatal Maternal Depressive Symptoms

In order to test our third hypothesis, that prenatal depressive symptoms would predict infant stress reactivity, we conducted several simple linear regressions. Contrary to our hypothesis, prenatal depression scores did not predict infant behavioral reactivity scores during the mild stressor (*p*s > .10). Contrary to our hypothesis, elevated maternal prenatal depression scores significantly predicted less behavioral reactivity scores during the moderate stressor, $\beta = .40$, $t(49) = 3.02$, $p = .004$, indicating that higher levels of prenatal depression were associated with less behavioral reactivity. Prenatal depression scores explained a significant proportion of the variance in behavioral reactivity scores, $R^2 = .16$, $F(2, 49) = 9.11$, $p = .004$, indicating a medium effect size.

Prenatal depression scores were not significant predictors of initial cortisol values, cortisol levels, or cortisol reactivity scores (*p*s > .10). Prenatal depression scores were not significant predictors of initial cortisol or level values even after controlling for maternal smoking status (*p*s > .10).

Postnatal Maternal Depression

Next, we conducted simple linear regressions in order to test our fourth hypothesis, that postnatal maternal depressive symptoms would predict infant stress reactivity scores. Contrary to our hypothesis, maternal postnatal depression scores did not predict infant behavioral reactivity scores during the mild or moderate stressors (*p*s > .10).

Maternal postnatal depression scores were a marginally significant predictor of infant initial cortisol values in the predicted direction, $\beta = -.22$, $t(58) = -1.77$, $p = .08$, with higher postnatal depression scores associated with lower initial cortisol values.

Postnatal depressive symptoms explained a marginally significant proportion of the variance in initial cortisol values, $R^2 = .05$, $F(1, 60) = 3.13$, $p = .08$, indicating a small size. After controlling for maternal smoking status, postnatal depressive symptoms were a statistically significant predictor of infant initial sample cortisol values, $\beta = -.25$, $t(57) = -2.07$, $p = .04$, and significantly predicted additional variance in the initial sample cortisol values over and above maternal smoking status, $\Delta R^2 = .05$, $\Delta F(2, 57) = 4.30$, $p = .01$, again indicating a negative association and a small effect size.

Contrary to our hypothesis, postnatal depression scores did not significantly predict infant cortisol level, percent change, or difference scores (ps > .10). After controlling for maternal smoking status, postnatal depression still was not a significant predictor of infant cortisol level values (ps > .10).

Unique Influences of Pre- and Postnatal Depressive Symptoms

Role of Prenatal Depressive Symptoms Independent of Postnatal Symptoms. Next, in order to examine the unique variance in infant stress reactivity scores predicted by prenatal and postnatal depressive symptoms, we tested multiple linear regression models, including both pre- and postnatal depressive symptoms as predictors.

After controlling for postnatal depression scores, prenatal depression scores still did not predict infant behavioral reactivity scores during the mild stressor ($p > .10$). Prenatal depressive symptoms remained a significant predictor of behavioral reactivity scores during the moderate stressor, even after controlling for the influence of postnatal depressive symptoms, $\beta = .42$, $t(48) = 2.70$, $p = .01$, indicating that higher prenatal depression scores were associated with less behavioral reactivity. Prenatal depression scores significantly predicted additional variance in the behavioral reactivity scores

during the moderate stressor over and above postnatal depression scores, $\Delta R^2 = .13$, $\Delta F(2, 57) = 7.31$, $p = .01$, indicating a medium effect size.

After controlling for postnatal depression scores, prenatal depression scores were a marginally significant predictor of infants' initial cortisol values, $\beta = .27$, $t(57) = 1.87$, $p = .07$, indicating that higher prenatal depressive symptoms were associated with increased infant cortisol values. The overall model explained a significant proportion of the variance in initial cortisol values, $R^2 = .11$, $F(2, 57) = 3.40$, $p = .04$, indicating a medium effect size. After controlling for both postnatal depression scores and maternal smoking status, prenatal depression scores remained a marginally significant predictor of infants' initial cortisol values, $\beta = .26$, $t(56) = 1.84$, $p = .07$, and the overall model explained a significant proportion of the variance in initial cortisol values, $R^2 = .21$, $F(3, 56) = 4.87$, $p = .004$, again indicating a medium effect size.

Role of Postnatal Depressive Symptoms Independent of Prenatal Symptoms. After controlling for the prenatal depression scores, postnatal depression scores remained a significant predictor of initial infant cortisol values, $\beta = -.37$, $t(57) = -2.51$, $p = .02$, indicating that higher postnatal depression scores were associated with lower initial infant cortisol values. Results also indicated a significant incremental contribution of postnatal depression scores over and above the variance accounted for by prenatal depression scores, $\Delta R^2 = .10$, $\Delta F(2, 57) = 6.32$, $p = .02$, indicating a small effect size. These results remained significant when maternal smoking status and prenatal depression were included as control variables, with postnatal scores predicting a significant proportion of the variance in infant initial sample cortisol values, $\beta = -.38$, $t(56) = -2.76$, $p = .01$, and adding a significant improvement in the overall model's prediction of variance, $\Delta R^2 =$

.11, $\Delta F(3, 56) = 7.60$, $p = .01$. Thus, both prenatal and postnatal depressive symptoms were associated with initial infant cortisol values, although the directions of associations were opposite. The association between prenatal depressive symptoms and initial infant cortisol values did not reach significance beyond a trend level, however.

After controlling for prenatal depression scores, postnatal depression scores were a marginally significant predictor of infant cortisol level values, $\beta = -.26$, $t(55) = -1.75$, $p = .09$, indicating that higher postnatal depressive symptoms were associated with lower infant cortisol values. The overall model did not predict a significant proportion of the variance in infant cortisol level scores, however ($p > .10$). After controlling for both maternal smoking status and prenatal depression scores, postnatal depression scores were a marginally significant predictor of infant cortisol level values, $\beta = -.28$, $t(54) = -1.95$, $p = .06$, and was a marginally significant predictor of the variance in infant cortisol levels over and above maternal smoking status and prenatal depression, $\Delta R^2 = .06$, $\Delta F(3, 54) = 3.79$, $p = .06$, with a small effect size.

Perinatal Depression Symptom Trajectory Profiles

Next, we conducted ANOVAs to test our fifth hypothesis, that maternal depressive symptom trajectory profiles would be associated with differences in infant outcome variables.

No significant differences among depressive symptom trajectories were observed in relation to infant behavioral reactivity scores (ps $> .10$).

The omnibus ANOVA indicated significant differences in initial infant cortisol values among maternal depressive symptom trajectory clusters, $F(3, 53) = 4.06$, $p = .01$, partial $\eta^2 = .19$, indicating a medium effect size. Results remained significant when

maternal smoking status was included as a covariate, $F(3, 53)= 4.71$, $p< .01$, partial $\eta^2= .22$. Posthoc Tukey pairwise comparisons revealed significant differences between infants of *hi/lo* and *hi/hi* groups ($p = .01$, Cohen's $d= 1.42$), such that infants within the *hi*/*lo* group showed significantly higher initial cortisol values compared to the *hi/hi* group, with a large effect size. Posthoc Tukey comparisons showed that infants of the *hi/lo* group had marginally significantly higher initial cortisol values compared to the *lo/lo* group ($p = .09$, Cohen's $d= 1.14$; see Figure 3), with a large effect size.

Marginally significant differences were also observed among depressive symptom trajectory clusters in relation to infant cortisol level values, $F(3, 51)= 2.33$, $p = .09$, partial $\eta^2= .15$, indicating a medium effect size. Results became statistically significant when maternal smoking status was included as a covariate, $F(3, 51)= 2.82$, $p = .049$, partial $\eta^2= .15$. Tukey pairwise comparisons revealed marginally significant differences between infants of *hi/lo* and *hi/hi* groups ($p = .05$, Cohen's $d= 1.02$; see Figure 4), such that infants in the *hi*/*lo* group showed significantly higher cortisol level values compared to the *hi/hi* group, indicating a large effect size.

No significant differences among depressive symptom trajectories were observed in relation to infant cortisol difference or percent change values ($ps > .10$).

Maternal Sensitivity

Next, in order to test our sixth hypothesis, that maternal sensitivity at 3, 6, and 12 months would predict infant stress reactivity at 12 months of age, we tested simple linear regression models for each time point.

Maternal Sensitivity at 3 months. Contrary to our hypothesis, maternal sensitivity at 3 months of age did not significantly predict infant behavioral stress

reactivity to the mild or moderate stressors, infant cortisol initial, level, percent change, or difference scores (*p*s > .10).

Maternal Sensitivity at 6 months. Contrary to our hypothesis, maternal sensitivity at 6 months of age did not significantly predict infant behavioral stress reactivity to the mild or moderate stressors (*p*s > .10). Sensitivity at 6 months also did not predict infant cortisol initial values or infant cortisol difference scores (*p*s > .10). Maternal sensitivity at 6 months was a statistically significant predictor of infant cortisol percent change scores, $\beta = .31$, $t(46) = 2.22$, $p = .06$, with higher sensitivity scores associated with higher infant cortisol reactivity. Sensitivity at 6 months significantly predicted variance in infant percent change scores, $R^2 = .10$, $F(1, 46) = 4.92$, $p = .03$, indicating a medium effect size. The direction of this association was not in the hypothesized direction, however. Similarly, maternal sensitivity at 6 months was also a significant predictor of infant cortisol level scores, $\beta = .29$, $t(46) = 2.08$, $p = .04$, with higher maternal sensitivity predicting higher infant cortisol levels. Sensitivity at 6 months significantly predicted variance in infant percent change scores, $R^2 = .09$, $F(1, 46) = 4.33$, $p = .04$, indicating a medium effect size. Sensitivity at 6 months remained a significant predictor of infant cortisol level scores even after controlling for maternal smoking status, $\beta = .33$, $t(44) = 2.45$, $p = .02$, and significantly predicted variance in infant cortisol levels over and above maternal smoking status, $\Delta R^2 = .10$, $\Delta F(2, 44) = 5.93$, $p = .02$.

Maternal Sensitivity at 12 months. Inconsistent with our hypothesis, sensitivity at 12 months was not a significant predictor of infant behavioral reactivity to the mild stressor ($p > .10$). Consistent with our hypothesis, sensitivity at 12 months was a

marginally significant predictor of infant behavioral reactivity during the moderate stressor, $\beta = -.27$, $t(47) = -1.94$, $p = .06$, and explained a marginally significant proportion of the variance in behavioral reactivity scores, $R^2 = .07$, $F(1, 47) = 3.76$, $p = .06$, indicating a small effect size. Sensitivity at 12 months of age did not significantly predict infant cortisol initial, level, percent change, or difference scores (ps > .10).

Next, in order to test the seventh hypothesis, that maternal sensitivity scores at 3, 6, and 12 months were significant moderators of the relationship between perinatal depression scores and infant outcomes, we tested hierarchical linear regression models at each time point. Given the number of regression models were tested, interactions that were significant at a trend level were not probed further.

Moderation by Maternal Sensitivity at 3 months. Sensitivity at 3 months was a marginally significant moderator of the relationship between prenatal depressive symptoms and infant behavioral reactivity during the mild stressor, $\beta = .29$, $t(42) = 1.88$, $p = .07$, although the overall model was not a significant predictor of variance in behavioral reactivity to the mild stressor, $R^2 = .09$, $F(3, 42) = 1.31$, $p = .29$. Sensitivity at 3 months was also a marginally significant moderator of the relationship between prenatal depressive symptoms and infant behavioral reactivity during the moderate stressor, $\beta = .29$, $t(42) = 1.95$, $p = .06$, although the overall model was not a significant predictor of variance in behavioral reactivity during the moderate stressor, $R^2 = .13$, $F(3, 42) = 2.07$, $p = .19$.

Maternal sensitivity at 3 months was not a significant moderator of the relationship between prenatal depressive symptoms and infant cortisol initial, level, difference, or percent change values (ps > .10).

Sensitivity at 3 months was a significant moderator of the relationship between mean postnatal depressive symptoms and infant behavioral reactivity during the mild stressor, $\beta = .37$, $t(42) = 2.54$, $p = .02$, and the interaction of postnatal depressive symptoms and sensitivity predicted a significant proportion of the variance in reactivity, $R^2 = .17$, $F(3, 42) = 2.86$, $p = .048$. Further analyses revealed that postnatal depressive symptoms did not predict behavioral reactivity to the mild stressor at low levels of sensitivity, $\beta = .004$, $t(22) = .02$, $p = .98$. At high levels of sensitivity, however, postnatal depression scores predicted behavioral reactivity, $\beta = .53$, $t(21) = 2.87$, $p = .01$ (see Figure 5), such that higher depressive symptoms were associated with less behavioral reactivity.

Maternal sensitivity at 3 months was not a significant moderator of the relationship between postnatal depression and infant behavioral reactivity during the moderate stressor, infant cortisol initial, level, difference, or percent change values.

Moderation by Maternal Sensitivity at 6 months. There was no evidence that sensitivity at 6 months moderated the relationship between prenatal depression and infant behavioral stress reactivity scores (*p*s > .10). Similarly, sensitivity at 6 months did not moderate the relationship between postnatal depressive symptoms and infant cortisol scores, with the exception of one trend, where the interaction between postnatal depression and sensitivity was a marginally significant predictor of infant cortisol percent change scores, $\beta = .37$, $t(44) = 1.79$, $p = .08$.

Moderation by Maternal Sensitivity at 12 months. There was no evidence that sensitivity at 12 months moderated the relationship between prenatal depressive symptoms and infant behavioral reactivity scores (*p*s > .10). Similarly, sensitivity at 12

months did not moderate the relationship between postnatal depressive symptoms and infant stress reactivity scores (*p*s > .10).

Discussion

Our findings contribute support for a model of perinatal depressive symptoms playing a role in the development of infant stress regulation. Additionally, our findings suggest that the influence of maternal depressive symptoms varies as a function of the timing of exposures as well as the trajectory of depressive symptoms across the perinatal period. Further, we found that maternal sensitivity is associated with infant cortisol reactivity and may moderate the association between postnatal depression and infant behavioral reactivity.

Prenatal Maternal Cortisol

The results of this study indicate that prenatal cortisol levels are not significantly associated with infant stress reactivity. Furthermore, the specific timing of exposure to maternal cortisol levels also was not associated with infant stress reactivity. These results were inconsistent with our hypotheses and with published studies which found that exposure to maternal prenatal cortisol was associated with infants' first void cortisol (Field et al., 2004), and cortisol reactivity (Davis et al., 2011). Both of the latter two studies were conducted with neonates, however, and it is possible that effects of prenatal exposures are not maintained beyond the neonatal period. Our results are consistent with another published study, however, which found no significant association between maternal prenatal cortisol and infant stress reactivity over the first year of life (Tollenaar et al., 2011). Combined with our finding, this pattern of findings suggests that the influences of prenatal cortisol exposure may be limited to early infancy, when the HPA

axis is extremely sensitive and labile, and that HPA reactivity later in infancy may be buffered by quality of parental care, as suggested by Gunnar (1998).

Perinatal Depression

Our results indicate that maternal prenatal depression is associated with behavioral reactivity to a moderate stressor. Unexpectedly, we found that increased levels of depressive symptoms are associated with lower levels of behavioral reactivity. This finding is inconsistent with previous studies (Davis et al., 2007; Davis et al., 2004), which found that increased prenatal depressive symptoms were associated with higher infant reactivity. These studies, however, assessed infant reactivity using measures more similar to infant temperament, by using either maternal reports or behavioral ratings of infants' startle or distress in response to novel stimuli. It is possible, especially given our findings that infant behavioral responses are inconsistent across stressors, that these measures may not be associated with infant behavior observed during a stressor.

Also inconsistent with prior work, we did not find statistically significant associations between prenatal depression and infant basal cortisol levels (Brennan et al., 2008; Diego et al., 2004; Field, Diego, Dieter, et al., 2004; Field, Hernandezreif, et al., 2006; Lundy et al., 1999) or reactivity (Brennan et al., 2008). Once again, however, none of these studies examined infant cortisol beyond the age of 6 months, and it is possible that the associations between perinatal depression and infant HPA regulation may not be maintained at 12 months.

Somewhat surprisingly, postnatal depressive symptoms were negatively associated with infant initial cortisol values, such that higher symptom levels were associated with lower infant cortisol values. Previous studies have yielded inconsistent

findings related to postnatal depression and infant cortisol levels, with no relationship observed between postnatal depressive symptoms and infant baseline cortisol (Azar & Brennan), or elevations evident only in infants of women with elevated depressive symptoms during both pre and postnatal periods (Diego).

In studies of adults with chronic stress-related disorders, which co-occur with depressive symptoms such as posttraumatic stress disorder, a well-documented pattern of blunted HPA functioning has been observed (Heim, Ehlert, & Hellhammer, 2000). This pattern of low cortisol levels has been suggested to be an adaptive response to a chronically stressful environment, which arises over time as a measure to protect the individual from deleterious effects of increase cortisol and conserve resources (Fries, Hesse, Hellhammer, & Hellhammer, 2005). Furthermore, blunted cortisol reactivity has been observed in children who have experienced maltreatment or neglect (Gunnar & Vazquez, 2001; Hart, Gunnar, & Cicchetti, 1995). Our results are consistent with these findings. It is possible that over the first year of life, infants of mothers with chronically elevated levels of postnatal depressive symptoms experience down-regulation in HPA activity in as a means of self-preservation.

Our results also provide evidence that the trajectory of depressive symptoms over the perinatal is associated with infant HPA regulation. We found that infants of mothers with high levels of depression early in pregnancy and low levels of depression following delivery have increased levels of initial cortisol and overall cortisol levels in response to a stressor. Additionally, these infants had higher cortisol in relation to infants of women with high levels of both pre- and postnatal depression, indicating that the consistency of

perinatal environments may be of highest importance and that the developing HPA axis may be programmed by fetal exposures.

Laurent, Ablow, and Measelle, also found dysregulated cortisol reactivity among infants exposed to elevated depressive symptoms either during the prenatal or postnatal period compared to those exposed during both or neither period (2011). In this study, however, they found that infants exposed to high levels of prenatal depressive symptoms and low levels of postnatal symptoms had the lowest cortisol levels and responses, whereas infants exposed to low levels of prenatal depressive symptoms and high levels of postnatal symptoms had the most exaggerated cortisol responses. This study relied on a single measure of prenatal depressive symptoms late in pregnancy, however, indicating that the trajectory of depressive symptoms in the subgroup of women with high prenatal symptoms and low postnatal symptoms differed from the women in the *hi/lo* group identified in the current study, since these women exhibited high levels of depressive symptoms early in pregnancy, with low levels by late pregnancy and postpartum. Thus, these two groups of women cannot be directly compared to one another. While our results are similar in that the inconsistency of depressive symptoms across the perinatal period was associated with infant HPA dysregulation, the direction of these effects was inconsistent and may differ based on the timing or chronicity of exposure.

Our results are also consistent with the predictive adaption hypothesis, introduced by Oitzl et al. (2010). This theory asserts that environmental cues allow the organism to prepare for a specific environment, and that this is plasticity is generally adaptive. When the expectation of the future environment or the degree of match is not met, however, organisms may exhibit a dysregulated stress response. Therefore, in the context of

prenatal depression, a fetus may develop an adaptive response to the stress of prenatal depression that is no longer adaptive when the postnatal environment expectancy is not met. Additionally, an increased biological sensitivity to the environment has been proposed as an adaptive response such that high cortisol reactivity may reflect a more plastic and responsive organism, which may do well in a nurturing, positive environment (Ellis & Boyce, 2008). Further research is needed to identify long-term outcomes of infants with increased cortisol reactivity, in order to determine whether or not more reactive infants are at risk for future psychopathology only in the context of adverse environments. If our findings are replicated, may suggest an additional way to interpret this theory, such that the mismatch between pre- and postnatal environments may be associated with poor infant outcomes regardless of postnatal exposure.

Maternal Sensitivity

We found a significant interaction between maternal sensitivity at 3 months and postnatal depression in the prediction of infant behavioral reactivity to a mild stressor, such that postnatal depression predicted lower infant behavioral reactivity only in the context of more sensitive parenting. Thus, maternal sensitivity may be a protective influence for infants of depressed mothers. Since we also observed that increased postnatal depressive symptoms are associated with less sensitive parenting, this interaction appears to be driven by a subgroup of women with high postnatal depressive symptoms who manage to be high in sensitivity.

We also found evidence that sensitivity at 6 months predicted higher infant cortisol percent change and overall level values. Thus, maternal sensitivity seems to play a role in both domains of infant stress reactivity, and is associated with greater reactivity

in both behavioral and HPA reactivity. These results were inconsistent with previous studies which found that higher maternal sensitivity was associated with decreased infant cortisol reactivity at 3, 6, and 9 months (Feldman et al., 2009; Spangler et al., 1994). These studies employed free-play (Spangler et al., 1994) and fear provoking masks (Feldman et al., 2009) in order to elicit a stress response. As our results indicate, inconsistency among research studies examining reactivity to stressors may be further complicated by the nature of the stressor. Our findings suggest that infant behavioral stress reactivity is not related across a mild and more severe stressor. Further, it is unknown whether infant cortisol responses vary across levels of a stressor when stressors are delivered on the same day, as most studies administer just stressors during a single visit without a full recovery between stressors or have allowed two months to lapse between stressors. Thus, infant reactivity to a stressor may not generalize across various stressors and each study may require individual interpretation.

Implications

Alterations in infants' cortisol in response to a stressor may be indicative of a dysfunctional response to stress. Our findings highlight the potential to identify infants who are at-risk for dysfunctional HPA regulation, whose families may benefit from intervention. Given the patterns of depressive symptoms observed in the current study, we suggest early and repeated screening for maternal depression, perhaps within an obstetrics-gynecology setting when women first find out they are pregnant. Children of families participating in psychotherapy have shown altered HPA functioning over participation in treatment (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011), suggesting

that the HPA axis is sensitive to the environment and its regulation may improve following intervention.

Our study also provides several implications for future research. First, our findings highlight the importance of repeated measures of depressive symptoms across both the prenatal and postnatal period. Studies including a single assessment of depressive symptoms, or measures of depressive symptoms capturing only the prenatal or postnatal period may be missing a crucial piece of information related to infant development. Future research should include multiple, prospective assessments of depressive symptoms across the perinatal period and examine whether or not similar associations with infant stress reactivity are observed. Second, our results indicate that infant behavioral stress reactivity may not be consistent across stressors of varying intensity and duration. Future studies should examine infant stress reactivity across various contexts in typically developing infants, so that generalizability of our findings may be more clear. Finally, our findings did not provide evidence that maternal prenatal cortisol levels are associated with infant stress reactivity at 12 months. Future research should examine the biological mechanisms underlying fetal cortisol exposure. In particular, potential associations between maternal psychopathology and the functioning of the placenta and the barrier enzyme 11β-HSD2 have been suggested as a potential mechanism (O'donnell, O'connor, & Glover, 2009). Further, associations between maternal depression and epigenetic regulation of DNA expression have also been suggested (Oberlander et al., 2008) and should be explored further.

Limitations

There are several limitations of the current study that may be improved upon in future research studies. First, because this study relied on naturally occurring variations in maternal depression, cortisol, and parenting behaviors, it is difficult to parse apart the effects of these variables from the effects of alternative factors, such as shared genes. Second, our measures of maternal cortisol are not a direct measure of fetal cortisol exposure. Metabolism of cortisol during pregnancy, especially in the placenta, likely influences the levels of maternal cortisol that fetuses are exposed to. There is evidence, however, that maternal and fetal cortisol levels are significantly correlated, which suggests that maternal cortisol is a valid measure of fetal exposure (Gitau et al., 1998). Third, we did not examine all possible mechanisms underlying the intergenerational transmission of risk. Other prenatal influences, such as maternal health practices (Lindgren, 2001), epigenetic programming and functioning of the placenta (Oberlander et al., 2008), as well as other sensitive systems including the immune and vascular systems (Schetter & Glynn, 2010), may also play a role in the effects of maternal depression on fetal development. Other postnatal influences, including comorbid psychiatric disorders, and the role of fathering, should also be explored in future research. Last, because we were interested in women likely to have a depressive episode during the perinatal period, our study did not include women without a history of at least one major depressive episode. Even when depressive episodes are in remission, continued deficits in parenting have been observed among mothers (DeMulder, Tarullo, Klimes-Dougan, Free, & Radke-Yarrow, 1995; Seifer, Dickstein, Sameroff, Magee, & Hayden, 2001). Thus, it is possible that the mothers in our sample exhibit parenting behaviors that are less sensitive

in comparison to women without a history of depression. Therefore, our results may be generalizable only to infants of women with a history of depression.

Conclusion

Infant HPA reactivity appears to be associated with maternal depressive symptoms. More specifically, infant cortisol levels are associated with the trajectory of maternal depressive symptoms, such that infants exposed to high levels of depressive symptoms show increased cortisol, both at the initial sampling as well as overall levels in response to a stressor, when mothers exhibit low levels of depressive symptoms during the postnatal period. Infant HPA functioning seems to be associated with fetal exposures, with dysregulation observed when the fetal expectancy of postnatal environment is not met, consistent with the fetal programming hypothesis (Barker, 1998). Further, sensitive parenting may buffer the adverse effects of perinatal depression.

References

Abu-Heija, A., Ali, A. M., & Al-Dakheil, S. (2002). Obstetric and perinatal outcome of adolescent nulliparous pregnant women. *Gynecologic and Obstetric Investigation, 53*, 90-92.

Ainsworth, Mary DS, Blehar, Mary C, Waters, Everett, & Wall, Sally. (1978). Patterns of attachment: Assessed in the strange situation and at home: Hillsdale, NJ: Erlbaum.

Ainsworth, Mary S., Blehar, Mary C., Waters, Everett, & Wall, Sally. (1978). *Patterns of attachment: A psychological study of the strange situation*. Oxford England: Lawrence Erlbaum.

American Psychiatric Association. (1994a). *Diagnostic and statistical manual of mental disorders (4th ed.)*. Arlington, VA US: American Psychiatric Publishing, Inc.

American Psychiatric Association. (1994b). *Diagnostic and Statistical Manual of Mental Disorders (4th Ed.)*. Washington, DC: Author.

Ashman, S. B., Dawson, G., Panagiotides, H., Yamada, E., & Wilkinson, C. W. (2002). Stress hormone levels of children of depressed mothers. *Development and Psychopathology, 14*(02), 333-349. doi: doi:10.1017/S0954579402002080

Banti, Susanna, Mauri, Mauro, Oppo, Annalisa, Borri, Chiara, Rambelli, Cristina, Ramacciotti, Daniele, . . . Cassano, Giovanni B. (2011). From the third month of pregnancy to 1 year postpartum. Prevalence, incidence, recurrence, and new onset of depression. Results from the Perinatal Depression,ÄìResearch & Screening Unit study. *Comprehensive Psychiatry, 52*(4), 343-351. doi: 10.1016/j.comppsych.2010.08.003

Barker, D. J. (1998). In utero programming of chronic disease. *Clinical Science, 95*(2), 115-128.

Barker, D. J. (2002). Fetal programming of coronary heart disease. *Trends in Endocrinology & Metabolism, 13*(9), 364-368.

Barratt, Marguerite Stevenson, & Roach, Mary A. (1995). Early interactive processes: Parenting by adolescent and adult single mothers. *Infant Behavior and Development, 18*(1), 97-109. doi: 10.1016/0163-6383(95)90011-x

Beck, A.T., Steer, R.A., & Brown, G.K. (1997). *Beck Depression Inventory: Second edition*. San Antonio: Texas: The Psychological Corporation.

Beck, A.T., Steer, R.A., & Brown, G. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Beck, Cheryl Tatano. (1995). The effects of postpartum depression on maternal-infant interaction: A meta-analysis. *Nursing Research, 44*(5), 298-304. doi: 10.1097/00006199-199509000-00007

Beck, Cheryl Tatano. (1996). A meta-analysis of predictors of postpartum depression. *Nursing Research, 45*(5), 297-303. doi: 10.1097/00006199-199609000-00008

Boyd, Rhonda C., Le, H., & Somberg, R. (2005). Review of screening instruments for postpartum depression. *Archives of Women's Mental Health, 8*(3), 141-153.

Brabham, T., Phelka, A., Zimmer, C., Nash, A., Lopez, J. F., & Vazquez, D. M. (2000). Effects of prenatal dexamethasone on spatial learning and response to stress is influenced by maternal factors. *American Journal of Physiology - Regulatory Integrative & Comparative Physiology, 279*(5), R1899-1909.

Brennan, Patricia A., Pargas, Rebecca, Walker, Elaine F., Green, Paula, Jeffrey Newport, D., & Stowe, Zachary. (2008). Maternal depression and infant cortisol: influences of timing, comorbidity and treatment. *Journal of Child Psychology and Psychiatry, 49*(10), 1099-1107. doi: 10.1111/j.1469-7610.2008.01914.x

Bruschettini, Matteo, van den Hove, Daniel L. A., Gazzolo, Diego, Steinbusch, Harry W. M., & Blanco, Carlos E. (2006). Lowering the dose of antenatal steroids: the effects of a single course of betamethasone on somatic growth and brain cell proliferation in the rat. *American Journal of Obstetrics & Gynecology, 194*(5), 1341-1346.

Caldji, Christian, Hellstrom, Ian C., Zhang, Tie-Yuan, Diorio, Josie, & Meaney, Michael J. (2011). Environmental regulation of the neural epigenome. *FEBS Letters, 585*(13), 2049-2058. doi: 10.1016/j.febslet.2011.03.032

Caldji, Christian, Tannenbaum, Beth, Sharma, Shakti, Francis, Darlene, Plotsky, Paul M., & Meaney, Michael 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 of the United States of America, 95*(9), 5335-5340.

Campbell, Susan B. (1991). *Coding manual for videotaped mother-infant interaction*. [Manuscript]. In NICHD Study of Early Child Care.

Campbell, Susan B, Cohn, Jeffrey F, & Meyers, Teri. (1995). Depression in first-time mothers: mother-infant interaction and depression chronicity. *Developmental Psychology, 31*(3), 349.

Carr, B. R., Parker, C. R., Madden, J. D., MacDonald, P. C., & Porter, J. C. (1981). Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. *American Journal of Obstetrics and Gynecology, 139*(4), 416-422.

Champagne, Frances A., & Meaney, Michael J. (2006). Stress During Gestation Alters Postpartum Maternal Care and the Development of the Offspring in a Rodent Model. *Biological Psychiatry, 59*(12), 1227-1235. doi: 10.1016/j.biopsych.2005.10.016

Cheadle, Jacob E., & Amato, Paul R. (2011). A quantitative assessment of lareau's qualitative conclusions about class, race, and parenting. *Journal of Family Issues, 32*(5), 679-706. doi: 10.1177/0192513x10386305

Cicchetti, Dante. (1991). Fractures in the crystal: Developmental psychopathology and the emergence of self. *Developmental Review, 11*(3), 271-287.

Cicchetti, Dante, Rogosch, Fred A., Toth, Sheree L., & Sturge-Apple, Melissa L. (2011). Normalizing the development of cortisol regulation in maltreated infants through preventive interventions. *Development and Psychopathology, 23*(3), 789-800. doi: 10.1017/S0954579411000307

Clark, R. (1985). The parent-child early relational assessment. Instrument and manual. *Madison, WI: Department of Psychiatry, University of Wisconsin Medical School*.

Coe, C. L., & Lubach, G. R. (2005). Developmental consequences of antenatal dexamethasone treatment in nonhuman primates. *Neurosci Biobehav Rev, 29*(2), 227-235. doi: S0149-7634(04)00118-6 [pii] 10.1016/j.neubiorev.2004.10.003

Cohn, Jeffrey F, Campbell, Susan B, & Ross, Shelley. (1991). Infant response in the still-face paradigm at 6 months predicts avoidant and secure attachment at 12 months. *Development and Psychopathology, 3*(04), 367-376.

Coplan, Jeremy D., Andrews, Michael W., Rosenblum, Leonard A., Owens, Michael J., Friedman, Steven, Gorman, Jack M., & Nemeroff, Charles B. (1996). Persistent Elevations of Cerebrospinal Fluid Concentrations of Corticotropin-Releasing Factor in Adult Nonhuman Primates Exposed to Early-Life Stressors: Implications for the Pathophysiology of Mood and Anxiety Disorders. *Proceedings of the National Academy of Sciences of the United States of America, 93*(4), 1619-1623.

Cox, J. L., Murray, D., & Chapman, G. (1993). A controlled study of the onset, duration and prevalence of postnatal depression. *The British Journal of Psychiatry, 163*(1), 27-31. doi: 10.1192/bjp.163.1.27

Crockenberg, Susan C., & Leerkes, Esther M. (2004). Infant and Maternal Behaviors Regulate Infant Reactivity to Novelty at 6 Months. *Developmental Psychology, 40*(6), 1123-1132. doi: 10.1037/0012-1649.40.6.1123

Davis, E. P. , & Sandman, C. A. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Dev, 81*(1), 131-148. doi: CDEV1385 [pii] 10.1111/j.1467-8624.2009.01385.x

Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-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*(6), 737-746. doi: 10.1097/chi.0b013e318047b775

Davis, E. P., & Sandman, C. A. (2006). Prenatal exposure to stress and stress hormones influences child development. *Infants & Young Children, 19*(3), 246-259. doi: 10.1097/00001163-200607000-00008

Davis, Elysia Poggi, Glynn, Laura M., Waffarn, Feizal, & Sandman, Curt A. (2011). Prenatal maternal stress programs infant stress regulation. *Journal of Child Psychology and Psychiatry, 52*(2), 119-129. doi: 10.1111/j.1469-7610.2010.02314.x

Davis, Elysia Poggi, Snidman, Nancy, Wadhwa, Pathik D., Glynn, Laura M., Schetter, Chris Dunkel, & Sandman, Curt A. (2004). Prenatal Maternal Anxiety and Depression Predict Negative Behavioral Reactivity in Infancy. *Infancy, 6*(3), 319-331. doi: 10.1207/s15327078in0603_1

Davis, Elysia Poggi, Waffarn, Feizal, & Sandman, Curt A. (2011). Prenatal treatment with glucocorticoids sensitizes the hpa axis response to stress among full-term infants. *Developmental Psychobiology, 53*(2), 175-183. doi: 10.1002/dev.20510

Dawson, G., Frey, K., Self, J., Panagiotides, H., Hessl, D., Yamada, E., & Rinaldi, J. (1999). Frontal brain electrical activity in infants of depressed and nondepressed mothers: Relation to variations in infant behavior. *Development and Psychopathology, 11*(03), 589-605. doi: doi:null

DeMulder, Elizabeth K, Tarullo, Louisa B, Klimes-Dougan, Bonnie, Free, Kathleen, & Radke-Yarrow, Marian. (1995). Personality disorders of affectively ill mothers: Links to maternal behavior. *Journal of personality disorders, 9*(3), 199-212.

Diego, M. A., Field, T., Hernandez-Reif, M., Cullen, C., Schanberg, S., & Kuhn, C. (2004). Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry, 67*(1), 63-80.

Diego, M. A., Field, Tiffany, Hernandez-Reif, Maria, Schanberg, Saul, Kuhn, Cynthia, & Gonzalez-Quintero, Victor Hugo. (2009). Prenatal depression restricts fetal growth. *Early Human Development, 85*(1), 65-70. doi: 10.1016/j.earlhumdev.2008.07.002

Diego, M. A., Jones, N. A., Field, T., Hernandez-Reif, M., Schanberg, S., Kuhn, C., & Gonzalez-Garcia, A. (2006). Maternal psychological distress, prenatal cortisol, and fetal weight. *Psychosom Med, 68*(5), 747-753. doi: 68/5/747 [pii] 10.1097/01.psy.0000238212.21598.7b

Ellis, Bruce J, & Boyce, W Thomas. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17*(3), 183-187.

Essex, Marilyn J, Klein, Marjorie H, Cho, Eunsuk, & Kalin, Ned H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biological psychiatry, 52*(8), 776-784.

Evans, Lynn M., Myers, Michael M., & Monk, Catherine. (2008). Pregnant women's cortisol is elevated with anxiety and depression — but only when comorbid. *Archives of Women's Mental Health, 11*(3), 239-248. doi: 10.1007/s00737-008-0019-4

Feldman, Ruth, Granat, Adi, Pariente, Clara, Kanety, Hannah, Kuint, Jacob, & Gilboa-Schechtman, Eva. (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(9), 919-927. doi: 10.1097/CHI.0b013e3181b21651

Field, T., Diego, Miguel, Dieter, John, Hernandez-Reif, Maria, Schanberg, Saul, Kuhn, Cynthia, . . . Bendell, Debra. (2004). Prenatal depression effects on the fetus and the newborn. *Infant Behavior and Development, 27*(2), 216-229. doi: 10.1016/j.infbeh.2003.09.010

Field, T., Diego, Miguel, Hernandez-Reif, Maria, Vera, Yanexy, Gil, Karla, Schanberg, Saul, . . . Gonzalez-Garcia, Adolfo. (2004). Prenatal maternal biochemistry predicts neonatal biochemistry. *International Journal of Neuroscience, 114*(8), 933-945. doi: 10.1080/00207450490461305

Field, T., Hernandez-Reif, M., Diego, M., Figueiredo, B., Schanberg, S., & Kuhn, C. (2006). Prenatal cortisol, prematurity and low birthweight. *Infant Behav Dev, 29*(2), 268-275. doi: S0163-6383(06)00011-7 [pii] 10.1016/j.infbeh.2005.12.010

Field, T., Hernandezreif, M., Diego, M., Schanberg, S., & Kuhn, C. (2006). Stability of mood states and biochemistry across pregnancy. *Infant Behavior and Development, 29*(2), 262-267. doi: 10.1016/j.infbeh.2005.12.009

First, M.B. , Spitzer, R.L. , Gibbon, M., & Williams, J.B.W. (1995). *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, D.C.: American Psychiatric Press.

First, Michael B. (2007). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders: SCID-I*: Biometrics Research Department, New York State Psychiatric Institutute.

Fish, Margaret, & Stifter, Cynthia A. (1993). Mother parity as a main and moderating influence on early mother-infant interaction. *Journal of Applied Developmental Psychology, 14*(4), 557-572. doi: 10.1016/0193-3973(93)90007-i

Francis, D. D., Caldji, Christian, Champagne, Frances, Plotsky, Paul M., & Meaney, Michael J. (1999). The role of corticotropin-releasing factor-norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. *Biological Psychiatry, 46*(9), 1153-1166. doi: 10.1016/s0006-3223(99)00237-1

Francis, D. D., Diorio, Josie, Liu, Dong, & Meaney, Michael J. (1999). Nongenomic Transmission Across Generations of Maternal Behavior and Stress Responses in the Rat. *Science, 286*(5442), 1155.

Francis, D. D., & Meaney, Michael J. (1999). Maternal care and the development of stress responses. *Current Opinion in Neurobiology, 9*(1), 128-134. doi: 10.1016/s0959-4388(99)80016-6

Frankel, K. A., & Harmon, R. J. (1996). Depressed mothers: they don't always look as bad as they feel. *Journal of the American Academy of Child & Adolescent Psychiatry, 35*(3), 289-298.

Fraser, Alison M., Brockert, John E., & Ward, R.H. (1995). Association of Young Maternal Age with Adverse Reproductive Outcomes. *New England Journal of Medicine, 332*(17), 1113-1118. doi: doi:10.1056/NEJM199504273321701

Fries, Eva, Hesse, Judith, Hellhammer, Juliane, & Hellhammer, Dirk H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*(10), 1010-1016.

Gavin, N. I., Gaynes, B. N., Lohr, K. N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol, 106*(5 Pt 1), 1071-1083. doi: 106/5/1071 [pii] 10.1097/01.AOG.0000183597.31630.db

Giannopoulos, George, Jackson, Katharine, & Tulchinsky, Dan. (1982). Glucocorticoid metabolism in human placenta, decidua, myometrium and fetal membranes. *Journal of Steroid Biochemistry, 17*(4), 371-374. doi: 10.1016/0022-4731(82)90628-8

Gitau, R., Cameron, A., Fisk, N. M., & Glover, V. (1998). Fetal exposure to maternal cortisol. *The Lancet, 352*(9129), 707-708. doi: 10.1016/s0140-6736(05)60824-0

Gitau, R., Fisk, N. M., Teixeira, J. M., Cameron, A., & Glover, V. (2001). Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. *J Clin Endocrinol Metab, 86*(1), 104-109.

Goland, R. S. (1988). Biologically active corticotropin-releasng hormone in maternal and fetal plasma during pregnancy. *American Journal of Obstetrics & Gynecology, 159*, 884-890.

Goodman, Sherryl H., & Gotlib, Ian H. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review, 106*(3), 458-490. doi: 10.1037/0033-295x.106.3.458

Goodman, Sherryl H., Rouse, Matthew H., Connell, Arin M., Broth, Michelle Robbins, Hall, Christine M., & Heyward, Devin. (2011). Maternal depression and child

psychopathology: A meta-analytic review. *Clinical Child and Family Psychology Review, 14*(1), 1-27. doi: 10.1007/s10567-010-0080-1

Goodman, Sherryl H., & Tully, Erin C. (2009). Recurrence of depression during pregnancy: psychosocial and personal functioning correlates. *Depression and Anxiety*, n/a-n/a. doi: 10.1002/da.20421

Grace, Sherry L., Evindar, A., & Stewart, D. E. (2003). The effect of postpartum depression on child cognitive development and behavior: A review and critical analysis of the literature. *Archives of Women's Mental Health, 6*(4), 263-274. doi: 10.1007/s00737-003-0024-6

Gunnar, Megan R. (1998). Quality of early care and buffering of neuroendocrine stress reactions: Potential effects on the developing human brain. *Preventive medicine, 27*(2), 208-211.

Gunnar, Megan R, Porter, Fran L, Wolf, Cynthia M, Rigatuso, Joseph, & Larson, Mary C. (1995). Neonatal stress reactivity: Predictions to later emotional temperament. *Child Development, 66*(1), 1-13.

Gunnar, Megan R, & Vazquez, Delia M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Development and psychopathology, 13*(03), 515-538.

Gunnar, Megan R., Brodersen, Laurie, Krueger, Kent, & Rigatuso, Joseph. (1996). Dampening of Adrenocortical Responses during Infancy: Normative Changes and Individual Differences. *Child Development, 67*(3), 877-889. doi: 10.1111/j.1467-8624.1996.tb01770.x

Gunnar, Megan R., Hertsgaard, Louise, Larson, Mary C., & Rigatuso, Joseph. (1991). Cortisol and behavioral responses to repeated stressors in the human newborn. *Developmental Psychobiology, 24*(7), 487-505. doi: 10.1002/dev.420240704

Gutteling, Barbara M., Weerth, Carolina de, & Buitelaar, Jan K. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology, 30*(6), 541-549. doi: 10.1016/j.psyneuen.2005.01.002

Hacking, Doug, Watkins, Andrew, Fraser, Simon, Wolfe, Rory, & Nolan, Terry. (2001). Respiratory distress syndrome and antenatal corticosteroid treatment in premature twins. *Archives of Disease in Childhood - Fetal and Neonatal Edition, 85*(1), F75. doi: 10.1136/fn.85.1.F75g

Haley, David W., & Stansbury, Kathy. (2003). Infant Stress and Parent Responsiveness: Regulation of Physiology and Behavior During Still-Face and Reunion. *Child Development, 74*(5), 1534-1546. doi: 10.1111/1467-8624.00621

Hart, Jordan, Gunnar, Megan, & Cicchetti, Dante. (1995). Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. *Development and Psychopathology, 7*, 11-11.

Heim, Christine, Ehlert, Ulrike, & Hellhammer, Dirk H. (2000). The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology, 25*(1), 1-35.

Henry, C., Kabbaj, M., Simon, H., Le Moal, M., & Maccari, S. (1994). Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. *Journal of Neuroendocrinology, 6*(3), 341-345.

Hertsgaard, L., Gunnar, M., Erickson, M.F., & Nachmias, M. (1995). Adrenocortical responses to the strange situation in infants with disorganized/disoriented attachment relationships. *Child development, 66*(4), 1100-1106.

Huizink, A. C., Robles de Medina, P. G., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2003). Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry, 44*(6), 810-818.

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews, 12*(2), 118-134.

Johnson, Norman Lloyd. (1992). *Breakthroughs in Statistics: Foundations and basic theory* (Vol. 1): Springer.

Jolly, M. C., Sebire, N., Harris, J., Robinson, S., & Regan, L. (2000). Obstetric risks of pregnancy in women less than 18 years old. *Obstetrics & Gynecology, 96*(6), 962 - 966.

Kammerer, M., Taylor, A., & Glover, V. (2006). The HPA axis and perinatal depression: a hypothesis. *Archives of Women's Mental Health, 9*(4), 187-196. doi: 10.1007/s00737-006-0131-2

Kaplan, Lauren A., Evans, Lynn, & Monk, Catherine. (2008). Effects of mothers' prenatal psychiatric status and postnatal caregiving on infant biobehavioral regulation: Can prenatal programming be modified? *Early Human Development, 84*(4), 249-256. doi: 10.1016/j.earlhumdev.2007.06.004

King, Bruce R., Smith, Roger, & Nicholson, Richard C. (2001). The regulation of human corticotrophin-releasing hormone gene expression in the placenta. *Peptides, 22*(11), 1941-1947. doi: 10.1016/s0196-9781(01)00486-7

Knorr, Ulla, Vinberg, Maj, Kessing, Lars V., & Wetterslev, J√∏rn. (2010). Salivary cortisol in depressed patients versus control persons: A systematic review and meta-analysis. *Psychoneuroendocrinology, 35*(9), 1275-1286. doi: 10.1016/j.psyneuen.2010.04.001

Kogan, Nina, & Carter, Alice S. (1996). Mother-infant reengagement following the still-face: The role of maternal emotional availability an infant affect regulation. *Infant Behavior and Development, 19*(3), 359-370. doi: 10.1016/s0163-6383(96)90034-x

Landy, Sarah. (1983). Mother‚Äìinfant interaction of teenage mothers and the effect of experience in the observational sessions on the development of their infants. *Early Child Development and Care, 10*(2-3), 165-185. doi: 10.1080/0300443830100203

Laplante, David P., Barr, Ronald G., Brunet, Alain, Du Fort, Guillaume Galbaud, Meaney, Michael L., Saucier, Jean-Francois, . . . King, Suzanne. (2004). Stress During Pregnancy Affects General Intellectual and Language Functioning in Human Toddlers. *Pediatr Res, 56*(3), 400-410.

Laurent, Heidemarie K., Ablow, Jennifer C., & Measelle, Jeffrey. (2011). Risky shifts: How the timing and course of mothers' depressive symptoms across the perinatal period shape their own and infant's stress response profiles. *Development and Psychopathology, 23*(02), 521-538. doi: 10.1017/s0954579411000083

Levine, Lauren, Garcia Coil, Cynthia T., & Oh, William. (1985). Determinants of Mother-Infant Interaction in Adolescent Mothers. *Pediatrics, 75*(1), 23.

LeWinn, K.Z., Stroud, L.R., Molnar, B.E., Ware, J.H., Koenen, K.C., & Buka, S.L. (2009). Elevated maternal cortisol levels during pregnancy are associated with reduced childhood IQ. *International journal of epidemiology, 38*(6), 1700-1710.

Lewis, Michael, & Ramsay, Douglas S. (1995). Developmental change in infants' responses to stress. *Child Development, 66*(3), 657-670.

Lindgren, Kelly. (2001). Relationships among maternal–fetal attachment, prenatal depression, and health practices in pregnancy. *Research in Nursing & Health, 24*(3), 203-217. doi: 10.1002/nur.1023

Liu, Dong, Diorio, Josie, Tannenbaum, Beth, Caldji, Christian, Francis, Darlene, Alison, Freedman, . . . Meaney, Michael J. (1997). Maternal Care, Hippocampal Glucocorticoid Receptors, and Hypothalamic- Pituitary-Adrenal Responses to Stress. *Science, 277*(5332), 1659-1662.

Lovejoy, M. Christine, Graczyk, Patricia A., O'Hare, Elizabeth, & Neuman, George. (2000). Maternal depression and parenting behavior: A meta-analytic review. *Clinical Psychology Review, 20*(5), 561-592. doi: 10.1016/s0272-7358(98)00100-7

Lundy, Brenda L., Jones, Nancy Aaron, Field, Tiffany, Nearing, Graciela, Davalos, Marisabel, Pietro, Paul A., . . . Kuhn, Cynthia. (1999). Prenatal depression effects on neonates. *Infant Behavior and Development, 22*(1), 119-129. doi: 10.1016/s0163-6383(99)80009-5

Maccari, S., Piazza, P. V., Kabbaj, M., Barbazanges, A., Simon, H., & Le Moal, M. (1995). Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *Journal of Neuroscience, 15*(1 Pt 1), 110-116.

Mairesse, J., Lesage, J., Breton, C., Breant, B., Hahn, T., Darnaudery, M., . . . Viltart, O. (2007). Maternal stress alters endocrine function of the feto-placental unit in rats. *Am J Physiol Endocrinol Metab, 292*(6), E1526-1533. doi: 00574.2006 [pii] 10.1152/ajpendo.00574.2006

Marcus, S., Lopez, Juan F., McDonough, Susan, MacKenzie, Michael J., Flynn, Heather, Neal Jr, Charles R., . . . Vazquez, Delia M. (2011). Depressive symptoms during pregnancy: Impact on neuroendocrine and neonatal outcomes. *Infant Behavior and Development, 34*(1), 26-34. doi: 10.1016/j.infbeh.2010.07.002

Marcus, S. M., Flynn, H. A., Blow, F. C., & Barry, K. L. (2003). Depressive symptoms among pregnant women screened in obstetrics settings. *J Womens Health (Larchmt), 12*(4), 373-380. doi: 10.1089/154099903765448880

Marcus, Sheila M, Flynn, Heather A, Blow, Frederic C, & Barry, Kristen L. (2003). Depressive symptoms among pregnant women screened in obstetrics settings. *Journal of Women's Health, 12*(4), 373-380.

McCool, W. F., Susman, E. J., & Susman, E. J. (1994). Cortisol reactivity and self-report anxiety in the antepartum: predictors of maternal intrapartal outcomes in gravid adolescents. *Journal of Psychosomatic Obstetrics & Gynecology, 15*(1), 9-18.

Mesman, Judi, van Ijzendoorn, Marinus H., & Bakermans-Kranenburg, Marian J. (2009). The many faces of the Still-Face Paradigm: A review and meta-analysis. *Developmental Review, 29*(2), 120-162. doi: 10.1016/j.dr.2009.02.001

Morral, Andrew R, Iguchi, Martin Y, Belding, Mark A, & Lamb, Richard J. (1997). Natural classes of treatment response. *Journal of consulting and clinical psychology, 65*(4), 673.

Mrzljak, Ladislav, Uylings, Harry B. M., Kostovic, Ivica, & van Eden, Corbert G. (1992). Prenatal development of neurons in the human prefrontal cortex. II. A quantitative Golgi study. *The Journal of Comparative Neurology, 316*(4), 485-496. doi: 10.1002/cne.903160408

Murphy, V. E. (2006). Endocrine Regulation of Human Fetal Growth: The Role of the Mother, Placenta, and Fetus. *Endocrine Reviews, 27*(2), 141-169. doi: 10.1210/er.2005-0011

Nachmias, M., Gunnar, M., Mangelsdorf, S., Parritz, R.H., & Buss, K. (1996). Behavioral inhibition and stress reactivity: The moderating role of attachment security. *Child development, 67*(2), 508-522.

O'Connor, Mary J. (2001). Prenatal alcohol exposure and infant negative affect as precursors of depressive features in children. *Infant Mental Health Journal, 22*(3), 291-299.

O'Hara, Michael W., & Swain, Annette M. (1996). Rates and risk of postpartum depression--a meta-analysis. *International Review of Psychiatry, 8*(1), 37.

O'Keane, V., Lightman, S., Marsh, M., Pawlby, S., Papadopoulos, A. S., Taylor, A., . . . Patrick, K. (2011). Increased pituitary–adrenal activation and shortened gestation in a sample of depressed pregnant women: A pilot study. *Journal of Affective Disorders, 130*(1-2), 300-305. doi: 10.1016/j.jad.2010.10.004

O'donnell, K, O'connor, TG, & Glover, V. (2009). Prenatal stress and neurodevelopment of the child: focus on the HPA axis and role of the placenta. *Developmental Neuroscience, 31*(4), 285-292.

Oberlander, Tim F, Weinberg, Joanne, Papsdorf, Michael, Grunau, Ruth, Misri, Shaila, & Devlin, Angela M. (2008). Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. *Epigenetics, 3*(2), 97-106.

Oitzl, Melly S., Champagne, Danielle L., van der Veen, Rixt, & de Kloet, E. Ronald. (2010). Brain development under stress: Hypotheses of glucocorticoid actions revisited. *Neuroscience & Biobehavioral Reviews, 34*(6), 853-866. doi: 10.1016/j.neubiorev.2009.07.006

Osofsky, J. . (1987). *Manual for coding maternal and infant global affect*. Unpublished work. Louisiana State University. New Orleans.

Peeters, Frenk, Nicolson, Nancy A., & Berkhof, Johannes. (2004). Levels and variability of daily life cortisol secretion in major depression. *Psychiatry Research, 126*(1), 1-13. doi: 10.1016/j.psychres.2003.12.010

Petraglia, F., Hatch, M. C., Lapinski, R., Stomati, M., Reis, F. M., Cobellis, L., & Berkowitz, G. S. (2001). Lack of Effect of Psychosocial Stress on Maternal Corticotropin-Releasing Factor and Catecholamine Levels at 28 Weeks' Gestation. *Journal of the Society for Gynecologic Investigation, 8*(2), 83-88. doi: 10.1177/107155760100800204

Petraglia, F., Sawchenko, P.E., Rivier, J., & Vale, W. (1987). Evidence for local stimulation of ACTH secretion by corticotropin-releasing factor in human placenta. *Nature, 328*, 717-719.

Pomerleau, Andr√©e, Scuccimarri, Connie, & Malcuit, G√©rard. (2003). Mother-infant behavioral interactions in teenage and adult mothers during the first six months

postpartum: Relations with infant development. *Infant Mental Health Journal, 24*(5), 495-509. doi: 10.1002/imhj.10073

Rakic, Pasko. (2002). Pre- and post-developmental neurogenesis in primates. *Clinical Neuroscience Research, 2*(1,Äì2), 29-39. doi: 10.1016/s1566-2772(02)00005-1

Ramsay, Douglas, & Lewis, Michael. (2003). Reactivity and regulation in cortisol and behavioral responses to stress. *Child Development, 74*(2), 456-464. doi: 10.1111/1467-8624.7402009

Ramsay, Douglas S, & Lewis, Michael. (1994). Developmental change in infant cortisol and behavioral response to inoculation. *Child Development, 65*(5), 1491-1502.

Ramsay, Douglas S., Bendersky, Margaret I., & Lewis, Michael. (1996). Effect of prenatal alcohol and cigarette exposure on two- and six-month-old infants' adrenocortical reactivity to stress. *Journal of Pediatric Psychology, 21*(6), 833-840. doi: 10.1093/jpepsy/21.6.833

Rich-Edwards, J. W., Kleinman, K., Abrams, A., Harlow, B. L., McLaughlin, T. J., Joffe, H., & Gillman, M. W. (2006). Sociodemographic predictors of antenatal and postpartum depressive symptoms among women in a medical group practice. *J Epidemiol Community Health, 60*(3), 221-227. doi: 60/3/221 [pii] 10.1136/jech.2005.039370

Robins, Lee N, Helzer, John E, Croughan, Jack, & Ratcliff, Kathryn S. (1981). National Institute of Mental Health diagnostic interview schedule: its history, characteristics, and validity. *Archives of general psychiatry, 38*(4), 381.

Rost, Kathryn, Burnam, M. Audrey, & Smith, G. Richard. (1993). Development of Screeners for Depressive Disorders and Substance Disorder History. *Medical Care, 31*(3), 189-200. doi: 10.2307/3765814

Roth, Tania L., Lubin, Farah D., Funk, Adam J., & Sweatt, J. David. (2009). Lasting Epigenetic Influence of Early-Life Adversity on the BDNF Gene. *Biological Psychiatry, 65*(9), 760-769. doi: 10.1016/j.biopsych.2008.11.028

Sanchez, M. M., Young, L. J., Plotsky, P. M., & Insel, T. R. (2000). Distribution of corticosteroid receptors in the rhesus brain: relative absence of glucocorticoid receptors in the hippocampal formation. *Journal of Neuroscience, 20*(12), 4657-4668.

Sandman, C. A., Glynn, L., Schetter, C. D., Wadhwa, P., Garite, T., Chicz-DeMet, A., & Hobel, C. (2006). Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental corticotropin releasing hormone (CRH): priming the placental clock. *Peptides, 27*(6), 1457-1463. doi: S0196-9781(05)00470-5 [pii] 10.1016/j.peptides.2005.10.002

Schetter, Christine Dunkel, & Glynn, Laura M. (2010). Stress in pregnancy: Empirical evidence and theoretical issues to guild interdisciplinary research. *The Handbook of Stress Science: Biology, Psychology, and Health*, 321.

Schuetze, Pamela, Lopez, Francisco A., Granger, Douglas A., & Eiden, Rina D. (2008). The association between prenatal exposure to cigarettes and cortisol reactivity and regulation in 7 month-old infants. *Developmental Psychobiology, 50*(8), 819-834. doi: 10.1002/dev.20334

Seifer, Ronald, Dickstein, Susan, Sameroff, Arnold J, Magee, Karin D, & Hayden, Lisa C. (2001). Infant mental health and variability of parental depression symptoms. *Journal of the American Academy of Child & Adolescent Psychiatry, 40*(12), 1375-1382.

Shoener, J.A., Baig, R., & Page, K.C. (2006). Prenatal exposure to dexamethasone alters hippocampal drive on hypothalamic-pituitary-adrenal axis activity in adult male rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 290*(5), R1366-R1373.

Smith, J. (2004). Gestational stress induces post-partum depression-like behaviour and alters maternal care in rats. *Psychoneuroendocrinology, 29*(2), 227-244. doi: 10.1016/s0306-4530(03)00025-8

Spangler, G. (1998). Emotional and adrenocortical responses of infants to the strange situation: The differential function of emotional expression. *International Journal of Behavioral Development, 22*(4), 681-706.

Spangler, G., & Grossmann, KE. (1993). Biobehavioral organization in securely and insecurely attached infants. *Child development, 64*(5), 1439-1450.

Spangler, Gottfried, & Schieche, Michael. (1998). Emotional and Adrenocortical Responses of Infants to the Strange Situation:The Differential Function of Emotional Expression. *International Journal of Behavioral Development, 22*(4), 681-706. doi: 10.1080/016502598384126

Spangler, Gottfried, Schieche, Michael, Ilg, Ursula, Maier, Ursula, & Ackermann, Claudia. (1994). Maternal sensitivity as an external organizer for biobehavioral

regulation in infancy. *Developmental Psychobiology, 27*(7), 425-437. doi: 10.1002/dev.420270702

Steer, Robert A., Scholl, Theresa O., & Beck, Aaron T. (1990). Revised Beck Depression Inventory scores of inner-city adolescents: Pre- and postpartum. *Psychological Reports, 66*(1), 315-320.

Stowe, Zachary N., Hostetter, Amy L., & Newport, D. Jeffrey. (2005). The onset of postpartum depression: Implications for clinical screening in obstetrical and primary care. *American Journal of Obstetrics and Gynecology, 192*(2), 522-526. doi: 10.1016/j.ajog.2004.07.054

Tollenaar, M. S., Beijers, R., Jansen, J., Riksen-Walraven, J. M. A., & de Weerth, C. (2011). Maternal prenatal stress and cortisol reactivity to stressors in human infants. *Stress: The International Journal on the Biology of Stress, 14*(1), 53-65.

Uno, H., Eisele, S., Sakai, A., Shelton, S., Baker, E., DeJesus, O., & Holden, J. (1994). Neurotoxicity of glucocorticoids in the primate brain. *Hormones & Behavior, 28*(4), 336-348.

Vallee, M., Mayo, W., Dellu, F., Le Moal, M., Simon, H., & Maccari, S. (1997). Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. *Journal of Neuroscience, 17*(7), 2626-2636.

Vrijkotte, Tanja G. M., van der Wal, Marcel F., van Eijsden, Manon, & Bonsel, Gouke J. (2009). First-Trimester Working Conditions and Birthweight: A Prospective Cohort Study. *American Journal of Public Health, 99*(8), 1409-1416. doi: 10.2105/ajph.2008.138412

Wadhwa, P. D., Porto, M., Garite, T. J., Chicz-DeMet, A., & Sandman, C. A. (1998). Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. *American Journal of Obstetrics & Gynecology, 179*(4), 1079-1085.

Weaver, Ian C. G., Cervoni, Nadia, Champagne, Frances A., D'Alessio, Ana C., Sharma, Shakti, Seckl, Jonathan R., . . . Meaney, Michael J. (2004). Epigenetic programming by maternal behavior. *Nat Neurosci, 7*(8), 847-854.

Weinstock, M., Matlina, E., Maor, G. I., Rosen, H., & McEwen, B. S. (1992). Prenatal stress selectively alters the reactivity of the hypothalamic-pituitary adrenal system in the female rat. *Brain Research, 595*(2), 195-200.

Welberg, L. A., Thrivikraman, K. V., & Plotsky, P. M. (2005). Chronic maternal stress inhibits the capacity to up-regulate placental 11beta-hydroxysteroid dehydrogenase type 2 activity. *J Endocrinol, 186*(3), R7-R12. doi: 186/3/R7 [pii] 10.1677/joe.1.06374

Zeanah, C. H., Boris, N. W., & Larrieu, J. A. (1997). Infant development and developmental risk: a review of the past 10 years. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(2), 165-178.

Appendix A

Infant Affect Coding System

Laughter/ Squeal	+ 4	High intensity, high-pitched positive sounds with simultaneous smiling. Vigorous smiles with either: 1. Laughter 2. Smiles with excited body movement, or 3. Clearly high pleasurable vocalizations (i.e. happy gurgling, pleasure screeches, or laughter)
Excitement or Smile	+ 3	-Fleeting smiles w/ or w/o eye involvement or vocalization -Excitement in body movements or vocalizations
Positive interest	+2	-Any large body movements showing positive interest and attentiveness (to people or toys) -Smiles with raised eyebrows, or leaning forward (i.e. facial expression not blunt). -Visual tracking -Slight smile with interest
None	1	-None of the above or below (no clearly positive or negative affect). --May have blunt affect. -No raised eye-brows or large body movements which show interest.
Negative Interest	-2	-Negative concentration. -Facial expressions may include wrinkled or furrowed brow in concentration (distress). -Smile with furrowed brow also included, as well as withdrawal movements. -Mild negative vocal
Frown/Protest Fuss/Whimper	-3	-Pouting, pre-cry face, disgust, or clearly distinguishable distress frown -Negative vocalizations (i.e. grunt, protest or frustration sounds – these tend to be in single bursts with a strident tone or vocal tensions). -Whimpering, fussing w/ frown - Negative vocal w/ strident tones -Crying distress, but no continuous cry
Marked distress/cry	- 4	-Marked distress in face and voice. Cry accompanied by appropriate facial expressions (i.e. screwing up face, closed eyes, maybe tears) - High intensity, high-pitched distress sounds simultaneous frown face (mouth turned downward; brow and forehead may be wrinkled), temporary cessation of breathing, kicking, flailing of body.

Appendix B

Maternal Interactive Quality Ratings

I. Insensitive Parenting

1. *Sensitivity/responsiveness to distress*

- Proportion of distress signals responded to. Responds to all signals.
- Latency of response. Responds promptly. Mild fussiness does not require as quick a response than acute distress.
- Appropriateness of response. Effective in soothing the child. For example, speaking to the child, switching positions, offering or changing toys, patting, holding close, etc. All attempts to soothe should be acknowledged.
- The decision of a 2 vs. a 3 would be made on the basis of the overall percentage of signals (greater than 1/2 responded to being given a 3; fewer than 1/2 given a 2) and the relation between degree of distress and responsiveness.
- If the mother's first response to the distressed infant does not soothe the child, the episode should be judged as insensitive/unresponsive (even if the response was immediate) unless the mother proceeds to offer a "fuller" response (i.e., more proximal soothing behaviors).

1 = **Not at all characteristic.** Mother's behavior is extremely insensitive. Either no response or only responds when infant becomes very demanding. A rating of 1 should be given for those mothers who are so unresponsive, delayed, and inappropriate in their responding that it could be considered problematic.

2 = **Minimally characteristic.** Mother displays infrequent/weak response. Responds slowly and ineffectively. If the clear majority of responses were inappropriate/ineffective even though immediate, the rating should be a 2.

3 = **Moderately characteristic.** Mother is predominantly sensitive/responsive, but there is some time in which the infant's signal does not receive a response or the response is delayed. If only the milder fusses are the ignored signals, even if fussing represents more than half of the distress signals emitted, then the observation would be coded 3.

4 = **Highly characteristic.** Mother is exceptionally sensitive and responsive to distress. A rating of 4 should be given to those mothers who exhibit immediate and exceptionally sensitive appropriate responses.

9 = **No opportunity to observe (NR).** No instances of child distress were observed.

2. ***Sensitivity/responsiveness to nondistress***

- The mother is tuned to the child and manifests awareness of the child's needs, moods, interests, and capabilities, and allows this awareness to guide his/her interaction.
- The mother provides stimulation that is situationally appropriate and takes an active interest in the child's activities (i.e. makes comments and embellishments when child loses interests).
- The mother is not overstimulating/intrusive and the interactions are well timed and paced to the child's responses.

1 = **Not at all characteristic.** Mother is predominately intrusive or detached. No signs of sensitivity.

2 = **Minimally characteristic.** Mother displays infrequent or weak sensitivity/responsiveness

3 = **Moderately characteristic.** Mother is predominately sensitive/responsive. Sometimes (at least twice)
neglects to give a fuller response or a well-timed or appropriate response.

4 = **Highly characteristic.** Mother is exceptionally sensitive and responsive.

II. Intrusiveness

3. ***Intrusiveness***

- The mother imposes her agenda on the child despite signals that a different activity, level, or pace of interaction is needed.
- If the child responds positively with sustained interest and is not engaging in defensive behaviors then intrusiveness is not occurring; however, intrusiveness is evident when the child averts his/her gaze, turns away, or expresses negative affect and the mother continues or escalates his/her activity.
- For example, (a) speaking too loudly or being extremely close to the child physically or with a toy; (b) offering a continuous barrage of stimulation, food, or toys; (c) persisting to demonstrate toys long after the child's interest has been

gained and he/she wants to manipulate the toy him/herself; (d) overwhelming the child with a rapid succession of toys or approaches and not allowing him/her time to react to one before another occurs.

1 = **Not at all characteristic.** This rating should be given to mothers who display almost no sign of intrusive behavior. A mother may show two instances of mildly intrusive behavior and still receive a 1 if the baby does not respond defensively in any way.

2 = **Minimally characteristic**. This rating should be given to mothers who display minimal intrusiveness. There is some evidence of intrusiveness, but it is not typical. The mother may initiate interactions with and offer suggestions to the child which occasionally are not welcomed. The mother sometimes continues his/her activity after the child engages in defensive behavior, but does not escalate the activity.

3 = **Moderately characteristic.** This rating should be given to mothers who are regularly intrusive. Mother intrusiveness occurs with moderate frequency.

4 = **Highly characteristic**. This rating should be given to mothers who are so intrusive that it is worrisome. The mother is consistently and typically intrusive. Most of the observation period is marked by the mother completely controlling the interaction, allowing the child little self-direction in his/her activities.

4. Cooperation vs. Interference

- This scale is concerned with the extent to which the mother's interactions interrupt the baby's ongoing activity rather than being concerned with the timing and the baby's state, mood, and current interests.
- Some examples of interference are: (a) not allowing the child to influence the pace or focus of play, interaction, or feeding; (b) taking away objects or food while the child still appears interested; (c) not allowing the child to handle toys he/she reaches for; (d) insisting that the child do something (play, eat, interact) in which he/she is not interested; and (e) not allowing the child to make choices.
- Some examples of cooperation are: (a) delaying interference until a natural break in the child's activity occurs; (b) gradually diverting the child from what he or she is doing to move toward a more desirable activity; (c) responding to the child's vocalizations and/or initiations of play; (d) shifting an approach when the child does

not respond; and (e) being spontaneous according to the child's mood and the situation (i.e. talking softly when the baby appears tired and irritable).

1 = **Highly interfering**. This rating should be given to mothers who "are conspicuous for the direct, physical, forcefulness of their interruptions or restraints. Others are conspicuous for the extreme frequency of interruption of the baby's activity-in-progress so that they seem 'at' the baby most of the time – instructing, training, eliciting, directing, and controlling. But the "1" mother tends to combine both types of interference, even though she may emphasize one type more than the other. Regardless of the balance between physical man-handling and milder interruptions, these mothers have in common an extreme lack of respect for the baby's autonomy, and an obtrusiveness which permits them to break into what the baby is doing without any need to explain to others or even to justify to themselves the reason for the interruption."

2 = **Interfering.** Like "1" mothers, these mothers display either direct, forceful, physical interference or frequent milder interference or both. But the "2" mother "has some kind of rationale for her actions which is perceivable to the observer (even though it may seem far from desirable); the interference is not obviously arbitrary. For example, the mother may be more focused on attempting to "shape the baby" to her way of doing things or she may be trying to focus on a specific routine.

3 = **Mildly interfering**. The "3" mother tends to issue more verbal commands and prohibitions to control the baby from a distance rather than being direct, abrupt, and physically forceful, making her interference milder than mothers with lower ratings. Compared to mothers with higher ratings, the "3" mother "pays less attention to mood-setting and to other techniques which aid smooth transitions from one activity to another". She tends to switch to certain activities (nap, feeding, etc.) without regard to the baby's ongoing activity.

4 = **Cooperative.** The mother is predominately cooperative and non-interfering. The "4" mother tends to give more verbal commands and prohibitions that the "5" mother; however she attempts to avoid interference and "rarely, if ever, intervenes in direct, abrupt, physical ways."

5 = **Conspicuously cooperative**. This mother "avoids interrupting an activity the baby has in progress. When it is desirable to intervene for a routine or to shift she truly

engages his cooperation, by mood-setting, by inviting him, by diverting him, and by engaging him in reciprocal activity of some sort, often enough vocalization or play." Except in emergency situations, the mother never interferes abruptly.

III. Withdrawal

5. Detachment/disengagement

- The mother appears emotionally uninvolved or disengaged, and unaware of the child's needs for appropriate interaction to facilitate involvement with objects or people.
- Detachment can be marked by (a) putting the child so he/she faces away from the mother, without attempts to visually "check in"; (b) presenting toys without first engaging the child or showing him/her how to manipulate them;(c) rarely making eye contact or rarely talking to the child; (d) not responding to the child's vocalizations. smiles, or reaches for toys; (e) an unawareness of the child's capabilities and appropriate activities; (f) positioning the child so that he/she cannot reach or manipulate a toy; (g) cleaning the child, rocking, diapering, or feeding in a mechanical, detached, distant way (h) ignoring the interesting things the child does; (i) letting the child play unsupervised without checking in; and (j) continually calling the child "baby" instead of using his/her name.
- The mother is more focused on the toy than the child.

1 = **Not at all characteristic.** This rating should be given to mothers who display almost no signs of detachment or under-involvement. When interacting with the child. The mother is clearly emotionally involved. These mothers can be sensitive or intrusive.

2 = **Minimally characteristic.** This rating should be given to mothers who display minimal detachment. While the mother is sometimes noninvolved, he/she is clearly more involved than not.

3 = **Moderately characteristic.** This rating should be given to mothers who are predominantly detached. The mother is relatively more noninvolved than involved, but the detachment is not so prevalent that it is problematic.

4 = **Highly characteristic.** This rating should be given to mothers who are so detached that it is worrisome. In the minimal instances of involvement, the mother's behaviors are

simple, mechanical, stereotyped, repetitive, and perfunctory. The mother is clearly not emotionally involved with the child, and appears to be "just going through the motions."

6. ***Flatness of affect***

- This scale measures how animated the mother is. Flat affect may reflect boredom, depression, fatigue, or distraction.
- Flatness is exhibited by blank, impassive facial expression, and flat tone in vocal expression. It is marked by a lack of animation. If the mother is watching the child with interest (eyes "bright"), it is a sign that the mother's affect is not flat.

1 = **Not at all characteristic.** This rating should be given to mothers who exhibit almost no flatness. There is consistent animation in the mother's demeanor and behavior

2 = **Minimally characteristic.** This rating should be given to mothers who exhibit some flatness. The mother is usually animated, but there is some time when facial expression is blank and impassive.

3 = **Moderately characteristic.** This rating should be given to mothers who are predominantly flat. Some periods of animation alternate with more clear periods of flatness than observed for a score of 2. Flat affect predominates.

4 = **Highly characteristic**. This rating should be given to mothers who are so flat that it is worrisome. There is consistent absence of animation.

IV. Positive Affect

7. Positive Regard for the child

- Ratings on this scale are based on both quality and quantity of positive regard.
- Positive feelings are shown by (a) speaking in a warm tone of voice; (b) hugging or other expressions of physical affection; (c) an expressive face; (d) smiling; (e) laughing with the child; (f) enthusiasm about the child; (g) praising the child; and (h) general enjoyment of the child. Positive regard is evident when the mother listens, watches attentively, looks into the child's face when talking to him/her, has affectionate physical contact, and is playful.

1 = **Not at all characteristic**. This rating should be given to mothers who display so little positive regard that it is worrisome. This rating can also be used for positive expressions

(laughing, smiling) that appear to be inappropriate to the situation or an inaccurate reflection of the mother's feelings. The mother may be expressionless or flat, or negative.
2 = **Minimally characteristic.** This rating should be given to mothers who display infrequent or weak signals of positive regard. The intensity and frequency of behavioral indicators are both low.
3 = **Moderately characteristic.** This rating should be given to mothers who predominantly display positive regard. More frequent and intense positive affect is shown than in the 2 rating, but the mother is not as strongly or consistently positive as those scored as a 4.
4 = **Very characteristic.** This rating should be given to mothers who are exceptionally positive in terms of facial and vocal expressiveness and behavior. Affect is positive and spontaneous.
The mother shows a range of expressions and behaviors, which are all clearly positive. He/she clearly “delights" in the child.

8. Warmth

- This scale reflects the quality of Mother’s affection toward Baby; it includes the extent to which Mother expresses affection toward Baby in a pleasurable way. Warmth may be apparent in vocal affect or content, expression, or handling.

1 = **None.** M’s behavior consistently fails to convey warmth; interactions generally lack tenderness, caring and affection
2 = **Little**
3 = **Some**. M’s behavior usually expresses some warmth, but on some or many occasions, her behavior lacks tenderness, caring, and affection.
4 = **Much**
5 = **Very much.** M’s behavior always expresses warmth. Her behavior is very tender, caring and affectionate.

9. Stimulation of Development

- This scale focuses on the amount and quality of activities that may ultimately enhance perceptual, cognitive, linguistic, and physical development. All qualitative judgments must be considered in relation to the quantity of stimulation

provided by the mother: How many of the available opportunities for stimulation were taken advantage of?

- Behaviors characterizing stimulation include (a) attempting to focus the child on an object or task; (b) focusing the child's attention on the perceptual qualities (sounds, colors, movement, etc.) of objects; (c) verbally responding to or expanding on the child's verbalizations or vocalizations; and (d) encouraging the child to actively participate in activities.
- Higher scores should be reserved for those mothers who (a) describe or label toys or objects, or demonstrate how they work; (b) read or recite to the child; (c) challenge the child to try something new; (d) present activities in an organized sequence of steps; (e) teach the child or give him/her an opportunity to experiment with materials that illustrate or teach concepts; (f) label and interpret the child's experiences, (e.g. "you think that's funny"); and so on.

1= Not at all characteristic. This rating should be given to mothers who provide so little stimulation that it is worrisome. The mother makes almost no attempts to teach the child anything. The mother may ignore the child's activities and never does more than offer toys in a perfunctory, mechanical manner. She is typically silent.

2= Minimally characteristic. This rating should be given to mothers who provide infrequent or weak stimulation. The mother's conscious and purposeful attempts to engage the child in development fostering experiences are limited. He/she may label or demonstrate materials, but does so perfunctorily and with minimal elaboration. If a mother spends a very brief portion of the time in high-quality interactions with a child and provides that child with no stimulation for the remainder of the time, he/she would receive a rating of 2. A mother might also receive a 2 if stimulation is continuous but minimally advantageous.

3= Moderately characteristic. This rating should be given to mothers who provide adequate stimulation but could reasonably be expected to provide more and higher-quality stimulation. The mother does make some effort to provide stimulation, but does not consistently take advantage of opportunities to do so. Stimulation is not the main agenda. The mother may find some new ways to engage the child with toys, for example, but, actions are likely to be simply repeated rather than thoughtfully varied**.** Mothers who

provide a rich linguistic environment but do not demonstrate the potential of toys or objects would receive this rating as well as mothers who demonstrate toys in a stimulating but non-vocal manner.

4= Very characteristic. This rating should be given to the mother who is consistently stimulating and takes advantage of many activities to stimulate. The mother provides frequent stimulation through "lessons," explanations, activities, or toys. Teaching or fostering development is a primary intent. The mother thoughtfully varies and elaborates on these activities, providing numerous opportunities, which are exceptionally advantageous to the child.

V. Negative Affect

10. Quality and Amount of Physical Contact: Negative

- This variable assesses the quality and amount of negative physical contact experienced by child. This may range from awkward, abrupt, disruptive and/or insensitive handling to intense tickling and/or rough-and-tumble play to physical restraint, slapping, pinching, and/or hitting.

1 = Characteristic; frequent negative contact or restraint of child.

2 = Considerable. Not characteristic.

3 = Moderate amount of negative contact or restraint of child.

4 = Slight instances.

5 = No instances of negative contact or restraint of child.

11. Angry, Hostile Mood

- This may be reflected in hostile, irritable or angry *behavior* and/or *facial expressions*; annoyance or irritability; *tone of voice*; *content* of vocalizations; *posture*. Consider intensity and duration of expressed affect over the five-minute segment.

1 = Extremely or characteristically hostile or angry mood, i.e. attitude and affect

2 = Marked expression of anger and hostility; some modulation in intensity and duration. Angry mood not quite characteristic.

3 = Moderately angry, irritable or hostile. Quality of anger, irritability or hostility is not intense.

4 = Slight annoyance, irritability, hostility or brief, fleeting episode of anger. Pervasive mood w/o anger.

5 = No anger displayed.

12. Displeasure, Disapproval, Criticism

- This may be evidenced in mild expressions of displeasure to extreme amounts of criticism and/or negativity including harsh tone of voice, cynical, nasty and/or taunting remarks.
- Criticism may be expressed vocally, facially, or through gestures toward the child. Does not need to be blatant displeasure; could be cynical or sarcastic. Examples of criticism: "You can't do that" "No, don't do it that way" "Why are you doing this" "You ain't paying attention."

1 = Characteristically negative; critical; may include attributing negative characteristics to child; abusive remarks or behavior.

2 = Considerable negativity; critical much of the time

3 = Moderately displeased, disapproving and/or critical.

4 = Slight displeasure, disapproval, and/or criticism

5 = No evidence of displeasure, disapproval, or criticism.

Table 1

Descriptive Statistics of Infant Behavioral Stress Reactivity Variables

	Mean/ Median	Standard Deviation	Range
Mild Stressor			
Time until distress (seconds)	35.31	47.14	0 - 254
Proportion time negative	.54	.29	0 - 1
Peak distress	-3.00		-2 - -4
Moderate Stressor			
Time until distress (seconds)	8.87	19.55	0 - 124
Proportion time negative	.70	.30	0 - 1
Peak distress	-3.00		-2 - -4

Note: Means are reported for time until distress and proportion time negative variables, medians are reported for peak distress variables.

Table 2

Intercorrelations among Infant Behavioral Stress Reactivity Variables

	1	2	3	4	5	6
1. Unavailable time until distress	__					
2. Unavailable proportion time negative	-.65**	__				
3. Unavailable peak distress	.32*	-.67**	__			
4. Distract time until distress	-.002	-.11	-.14	__		
5. Distract proportion time negative	.06	.12	-.10	-.60**	__	
6. Distract peak distress	-.11	-.15	.07	.48**	-.72**	__

** $p < .01$ level (2-tailed). * $p < .05$ level (2-tailed).

Table 3

Intercorrelations among Maternal Depression Scores

	1	2	3
1. Pregnancy	__		
2. Delivery through six months postpartum	.63***	__	
3. Concurrent score at twelve months postpartum	.39**	.72***	__

** $p < .01$ level (2-tailed). *** $p < .001$ level (2-tailed).

Table 4

Descriptive Statistics for Maternal Depression and Cortisol Variables

Variables	*M*	*SD*	Minimum	Maximum
BDI-II				
Pregnancy	9.43	5.23	0.60	22.00
Postpartum through 12 mos.	21.54	6.64	0.33	21.54
Cortisol (raw values)	2.05	6.35	2.05	38.85

Table 5

Maternal Parenting Behavior Rating Reliability: Percent Agreement

	3 months		6 months		12 months	
	Exact agreement	Agreement within 1	Exact agreement	Agreement within 1	Exact agreement	Agreement within 1
Sensitivity	61	96	36	100	42	83
Intrusiveness	75	96	82	100	58	92
Cooperation	43	86	64	73	42	92
Detachment	75	96	73	100	58	100
Flatness of Affect	71	96	100	100	75	100
Positive regard	61	100	73	100	58	92
Warmth	68	89	64	91	33	92
Stimulation of development	68	96	55	91	67	100
Negative physical contact	71	100	91	100	92	100
Angry, hostile mood	75	100	100	100	58	100
Displeasure, disapproval, criticism	79	100	100	100	75	100

Note: All values reported are percentages.

Table 6

Maternal Sensitivity Score Descriptive Statistics

Time point	*M*	*SD*	Minimum	Maximum
3 months	-.02	1.01	-2.25	1.17
6 months	.03	1.04	-3.51	1.35
12 months	.01	.99	-2.99	1.82

Table 7

Intercorrelations among Maternal Sensitivity Scores

	1	2	3
4. 3 months	__		
5. 6 months	.41**	__	
6. 12 months	.33*	.35*	__

** $p < .01$ level (2-tailed). * $p < .05$ level (2-tailed).

Table 8

Intercorrelations among Infant Behavioral Stress Reactivity & Infant Cortisol Variables

	1	2	3	4	5	6
1. Unavailable behavioral reactivity score	__					
2. Distract behavioral reactivity score	-.01	__				
3. Initial cortisol value	.11	-.22	__			
4. Cortisol difference score	-.02	-.09	.44*	__		
5. Cortisol percent change score	-.03	.05	-.45**	.81**	__	
6. Cortisol level	.09	-.24	.73**	.39**	-.27*	__

** $p < .01$ level (2-tailed). * $p < .05$ level (2-tailed).

Figure 1. Depressive Symptom Trajectory Cluster Profiles over Entire course of Pregnancy and Postpartum.

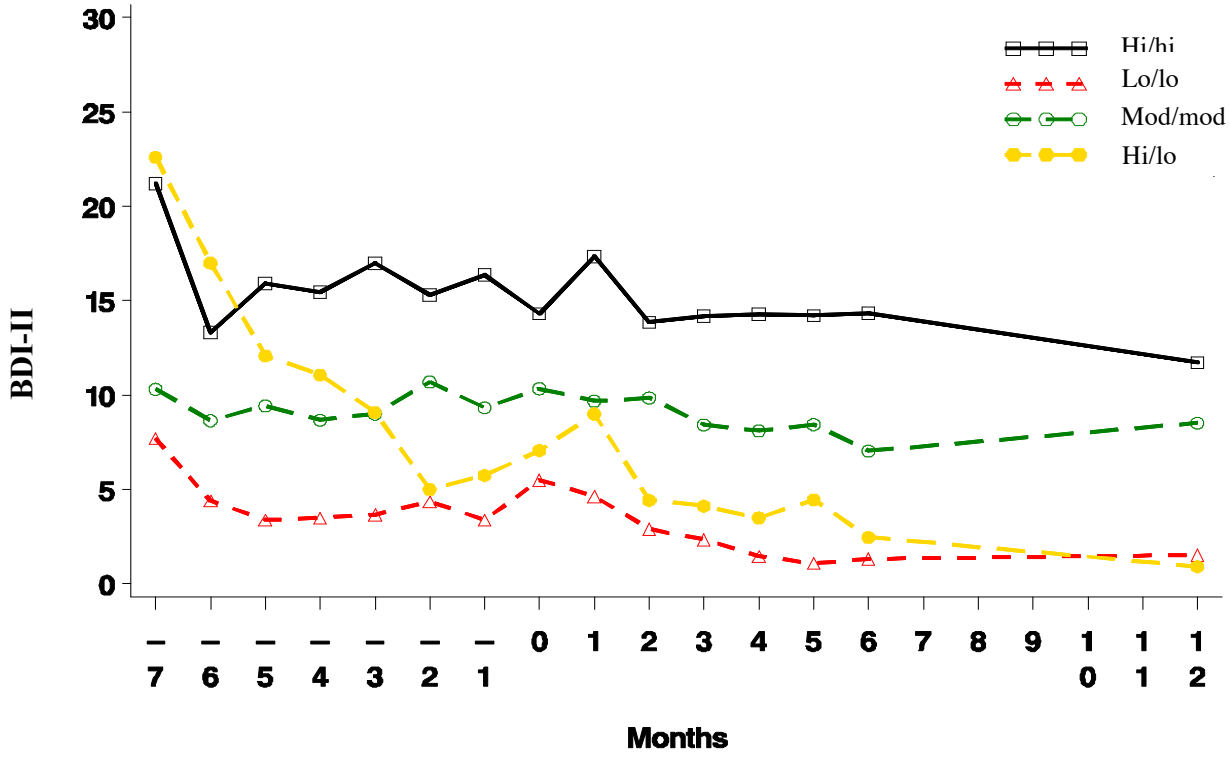


Figure 2. Infant Cortisol Values Differ Based on Exposure to Maternal Smoking During Pregnancy.

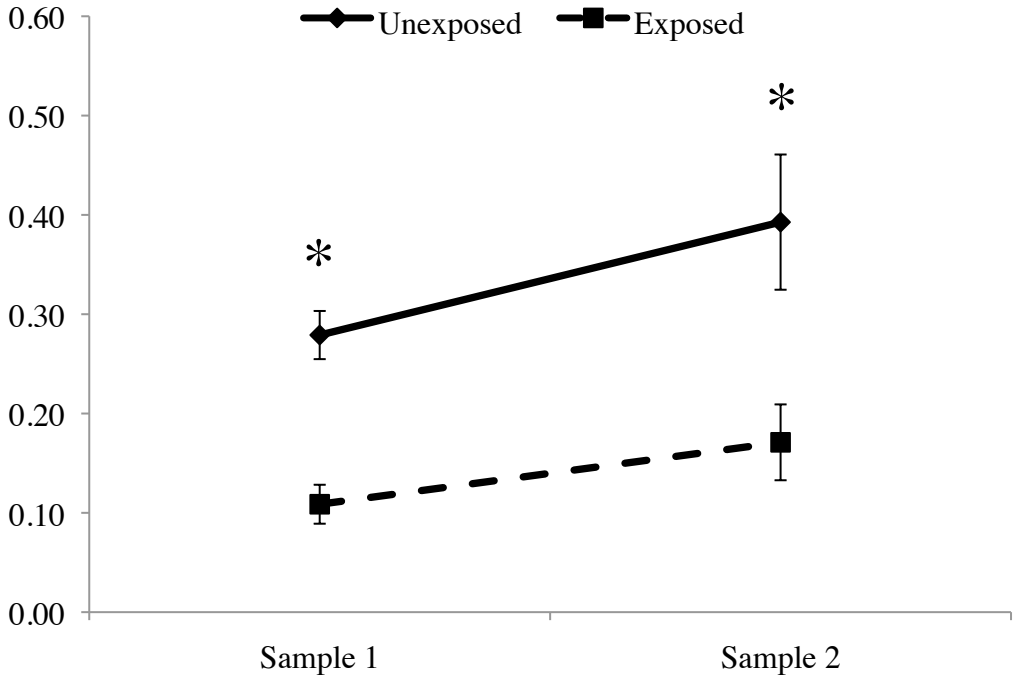
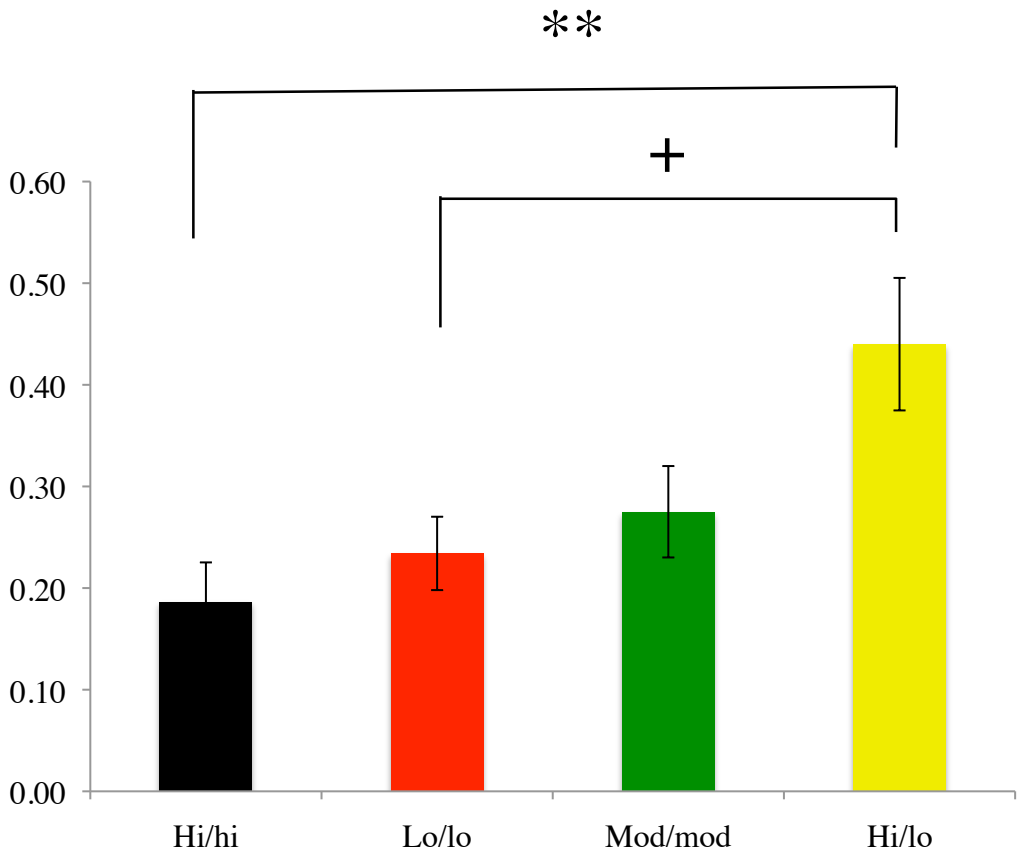
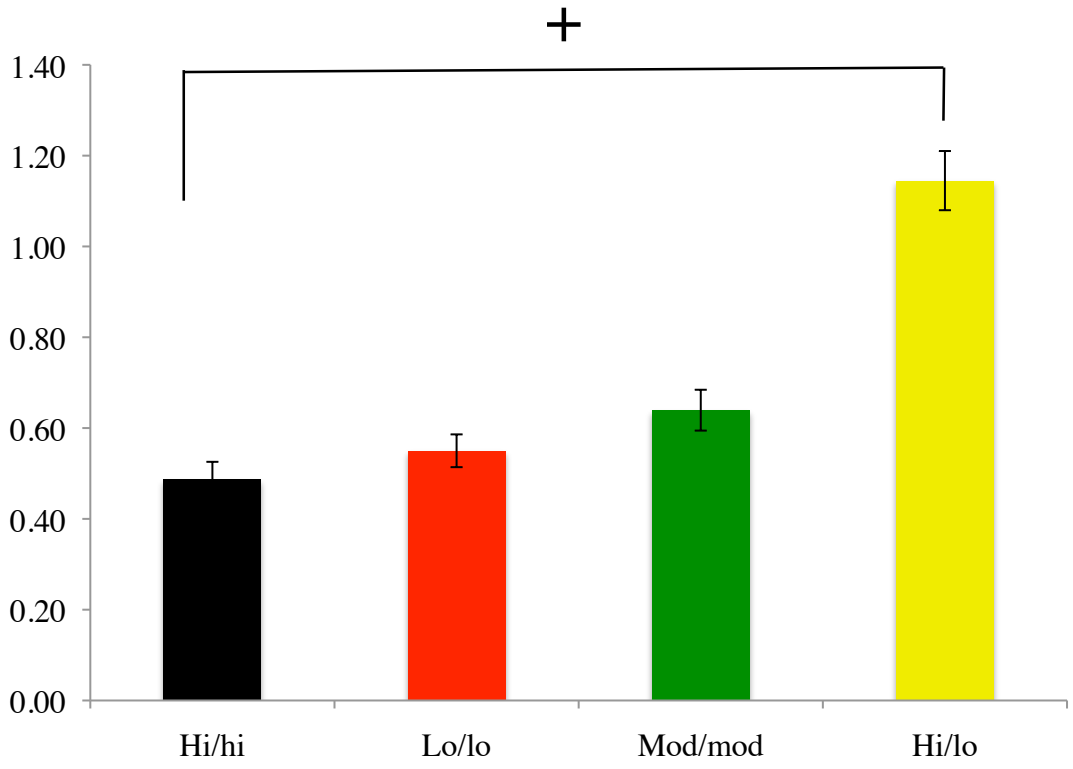


Figure 3. Infant Initial Cortisol Values Differ Based on Depressive Symptom Cluster Profiles.



** $p < .01$ level (2-tailed). + $p < .10$ level (2-tailed).

Figure 4. Infant Cortisol Level Values Differ Based on Depressive Symptom Cluster Profiles.



+ $p < .10$ level (2-tailed).

Figure 5. Maternal Sensitivity at 3 months Moderates the Relationship between Postnatal Depression and Infant Behavioral Reactivity during the Distract Segment.