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Cassandra Lei Hendrix Date

Physiological Attunement in Mother-Infant Dyads at Clinical High Risk: The Influence of Maternal Depression and Positive Parenting

By

Cassandra Lei Hendrix

Master of Arts

Psychology

_____

Patricia Brennan, PhD

Advisor

_____

Nancy Bliwise, PhD

Committee Member

_____

Jocelyne Bachevalier

Committee Member

Accepted:

_____

Lisa A. Tedesco, Ph.D.

Dean of the James T. Laney School of Graduate Studies

_____

Date

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Cassandra Lei Hendrix

B.S., Oglethorpe University, 2012

Advisor: Patricia Brennan, PhD

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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 Psychology

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Abstract

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By Cassandra Lei Hendrix

A growing number of research studies have examined the intra-dyadic co-regulation (attunement) of psychobiological stress responses, such as hypothalamic-pituitary-adrenal axis functioning, in mothers and their children. However, it is unclear how early this co-regulation may be present in dyads at clinical high risk and whether certain factors, such as maternal depression or positive parenting, are associated with the strength of this co-regulation. The present study used Hierarchical Linear Modeling to examine physiological attunement within mother-infant dyads in a high risk sample of 233 mothers who received treatment for psychiatric illness during pregnancy and whose infants were 6 months old at the study visit. Results showed that maternal and infant cortisol co-varied across 4 time points that included a stressor paradigm and a mother infant interaction task. Maternal positive affect, but not depression, predicted stronger cortisol attunement. In addition, infants' cortisol response to maternal separation predicted mothers' cortisol response at the next time point. Mothers' cortisol responses to separation and the laboratory stress paradigm predicted infants' cortisol responses at each successive time point, over and above infants' own cortisol at the previous time point. These findings suggest that maternal and infant cortisol levels may influence one another in a bidirectional fashion in a stressful context. Theoretical and clinical implications are discussed.

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The hypothalamic-pituitary-adrenal (HPA) axis is one of the main biological systems associated with the human stress response. Heightened stress reactivity (Bale, 2006) and slowed recovery from stressors (Burke, Davis, Otte, & Mohr, 2005) has repeatedly been linked to depression and may even confer risk for depression across generations. External factors that regulate the development of the HPA axis are still being identified. One promising avenue explores the role of positive parenting behaviors, as well as the parent-child relationship more broadly, in the regulation of child stress responses. The present study employs a multi-modal approach to examine an intersection of social (parenting) and biological (activity of the HPA axis) mechanisms that may contribute to the intergenerational transmission of psychiatric illness from mothers to their children.

Early development of the HPA axis

In humans, HPA axis activity is typically measured via cortisol, which is the final hormonal output of the cascading adrenocortical system. Although some researchers measure cortisol via blood or plasma samples, it is more common to measure salivary cortisol levels (especially in child research) because saliva collections are much less invasive than blood draws (Jessop & Turner-Cobb, 2008).

When the HPA axis is activated (either by a stressor or an internal, diurnal circadian rhythm), neurons in the paraventricular nucleus (PVN) release corticotrophin releasing hormone (CRH). CRH signals the anterior pituitary to release adrenocorticotrophic hormone (ACTH), which then binds to the adrenal cortex, leading to the release of glucocorticoids such as cortisol. However, extended exposure to these glucocorticoids can have deleterious effects because of their catabolic nature. To prevent

prolonged exposure to glucocorticoids, the HPA axis is partially regulated by a negative feedback loop, such that the presence of glucocorticoids signals the PVN to stop the release of CRH, which disrupts the adrenocortical cascade. Changes in heart rate and respiration as well as pain or cytokine changes associated with inflammation or infection may also send signals to the PVN to initiate the HPA axis cascade (Herman, Ostrander, Mueller, & Figueiredo, 2005).

Stressful events often lead to an increase in cortisol levels (known as cortisol reactivity), followed by a subsequent down-regulation of cortisol after the stressful event has ended (often referred to as cortisol recovery). However, HPA axis activity changes drastically throughout early childhood. Newborns exhibit significant increases in salivary cortisol in response to stressful events such as physical examinations (Gunnar, 1989), but the magnitude of this response is attenuated over time (Davis & Granger, 2009; Jansen, Beijers, Riksen-Walraven, & de Weerth, 2010). By the end of the first year postpartum, some researchers claim that infants enter into a hyporesponsive period (Gunnar & Vazquez, 2006) during which it is difficult to elevate cortisol levels using behavioral stress paradigms. Theoretically, a hyporesponsive period may provide benefit by protecting the brain from exposure to high levels of catabolic cortisol during a sensitive developmental period. However, this claim is largely based on work completed in rodents and has not yet been definitively shown in humans or non-human primates (Larson, White, Cochran, Donzella, & Gunnar, 1998). The current study examines cortisol responses in infants at six months postpartum, a developmental time period in which the HPA axis should still be reactive to behavioral stressors in a laboratory context.

Parental regulation of child stress responses

Positive parenting behaviors model appropriate actions and down-regulate fear and stress responses in infants. Attachment theory suggests that the mother may act as an external regulator of her infant's states – particularly attenuating infant fearfulness – by responding to infant cries, providing nourishment, and otherwise attending to her child's needs (Ainsworth, Blehar, Waters, & Wall, 1978; Bowlby, 1998). In a secure attachment relationship, infant behavior (e.g., crying, smiling) evokes appropriate maternal behavior (e.g., soothing, feeding, vocalizing), and it is this cause-effect relationship that allows the infant to develop a cognitive model regarding the safety of the surrounding environment. According to this theory, the mother-infant relationship further serves as the primary model for future social interactions during the first few years of life, and disturbances in the attachment relationship are associated with maladaptive child development (Bowlby, 1958).

The quality of caregiving infants receive early in life is closely tied to later stress reactivity across multiple species (Gunnar & Donzella, 2002). Although this research is purely correlational in human studies, animal research enables the use of experimental manipulation and invasive procedures, which are unethical in human populations. This manipulation can provide improved understanding of causality, identify potential neurobiological mechanisms of risk transmission, and inform researchers about the effects of developmental timing. Non-human primate studies are particularly useful in achieving these goals because the parenting and postnatal early development of certain non-human primates, such as the rhesus macaque, closely resembles that of humans.

When macaque mothers are repeatedly separated from their infants for short periods of time, their infants show an initial hyperactive response to stress, followed by

blunting of the cortisol stress response later in life (Sanchez, 2006). Moreover, macaque infants who are physically abused by their mothers show increased cortisol secretion in response to stressors up to 3 years later (Sanchez et al., 2010). These findings suggest that experimental disruption to the mother-infant relationship is associated with hormonal alterations in offspring that persist into adulthood. Moreover, these alterations can impact the caregiving behaviors of these offspring, further perpetuating risk for adverse development across generations (Cirulli, Berry, & Alleva, 2003). These findings are consistent with correlational research in humans that shows exposure to adversity or negative parenting behaviors before the age of 5 years is associated with elevated, rather than attenuated, cortisol reactivity over time (Hunter, Minnis, & Wilson, 2011). Additional human research has shown that attachment disruption early in life is correlated with heightened stress reactivity in infancy (Luijk et al., 2010) and internalizing and externalizing psychopathology in later childhood (Lyons-Ruth & Jacobvitz, 2008).

Conversely, in a strong mother-infant relationship, the mother may serve as an external regulator of infant stress responses. Research in rats (Levine, Stanton, & Gutierrez, 1988) and humans (Feldman, Singer, & Zagoory, 2010) indicates that an action as simple as maternal touch helps infants attenuate their physiological responses to stress. In macaques, immediate and prolonged contact between mother and infant following separation is related to greater attenuation of the infant stress response (Hinde & McGinnis, 1977; Sanchez, 2006). Positive maternal caregiving behaviors (such as maternal sensitivity) are further associated with more adaptive stress regulation in human infants at 6 months (Blair, Granger, Willoughby, & Kivlighan, 2006) and 9 months (Hane & Fox, 2006) postpartum as measured by infant HPA axis activity and

electroencephalogram symmetry, respectively. Taken together, this research suggests that maternal responsiveness and strong mother-infant relationships contribute to more adaptive stress regulation early in life. Caregiving, therefore, may be an important vehicle through which environmental factors influence early development of the stress response.

It is unclear whether there is a critical period during which responsive and sensitive caregiving is most effective at shaping infant stress reactivity and recovery. Infants of mothers who positively engage them at 7 months postpartum are more likely to show adaptive HPA axis functioning even into toddlerhood, but maternal positive engagement assessed at 15 months postpartum is not associated with HPA axis responses (Blair et al., 2008). The developmental specificity of this finding indicates that early infancy may be a sensitive, but not necessarily critical, period in which caregiving behaviors have a more profound impact on children's stress regulatory abilities, perhaps due to the plasticity of biological stress systems during this period of development.

It is also possible that early exposure to positive caregiving must be maintained in order to have lasting effects. Following Nicolae Ceausescu's regime in Romania, tens of thousands of infants were raised in state-operated orphanages where they received little touch or caregiver attention. This unfortunate situation provided a naturalistic setting for research on the effects of early caregiving deprivation. One study enrolled a random selection of these infants in an early intervention where they received greater caregiver attention starting at 6 months postpartum. Compared to control infants who remained in their original deprived conditions, infants in this intervention showed significant gains in physical and cognitive growth for the duration of the intervention. However, when the project lost funding after 13 months, the infants in the intervention condition were

returned to an environment of caregiving deprivation and showed rapid deterioration of their physical and cognitive growth. In addition to regression of physical and cognitive development by 2-3 years of age, these children did not show the steady decrease in diurnal cortisol levels shown by same-age children raised by a family (Carlson & Earls, 1997). This study suggests that consistent receipt of adequate caregiving early in life may be an essential component of typical biological stress systems development.

Co-regulation of the human stress response

Behavioral mimicry is a natural human tendency that begins in infancy (Meltzoff & Moore, 1977) and extends into adulthood (McGuigan, Makinson, & Whiten, 2011). Emotional contagion, which involves the spread of emotions from one person to another, has recently become a popular research topic, especially among social psychologists. These researchers have examined the spread of happiness (Fowler & Christakis, 2008), depression (Rosenquist, Fowler, & Christakis, 2011), loneliness (Cacioppo, Fowler, & Christakis, 2009), sleep habits (Mednick, Christakis, & Fowler, 2010), and anxiety (Eisenberg, Golberstein, Whitlock, & Downs, 2013) among interconnected social networks. The possibility that this "contagion" or spread of states may be detected on a physiological level among dyads is an exciting and interesting extension of such research. In fact, co-regulation (or attunement) of biological stress systems has been observed in parent-child dyads during infancy, childhood, and adolescence (Papp, Pendry, & Adam, 2009; Sethre-Hofstad, Stansbury, & Rice, 2002; Thompson & Trevathan, 2008; van Bakel & Riksen-Walraven, 2008) and has even been detected in unrelated romantic partners (Brandtstädter, Baltes-Götz, Kirschbaum, & Hellhammer, 1991; Powers, Pietromonaco, Gunlicks, & Sayer, 2006).

The mechanism by which this attunement occurs, and its adaptive function, is thus far unknown. Biological attunement may be one physiological process that underlies a strong attachment relationship as an empathic mother/partner may be more sensitive to micro-cues that signal her child's/partner's distress, which then results in heightening of her own stress response. Early studies on mother-infant attunement conceptualized this physiological co-regulation as a function of maternal sensitivity. Specifically, more sensitive mothers were expected to be attuned to their child's feelings of distress and thus demonstrate elevations in cortisol when their children's cortisol levels increased. To test this theory, Sethre-Hofstad, Stansbury, and Rice (2002) asked two to four year old children and their mothers to complete a teaching task that was behaviorally coded for maternal sensitivity. Next, children completed a mild stressor task in which they walked across a balance beam while the mother watched from a monitor in a nearby room. Salivary cortisol was collected from both the mother and child before and after the balance beam task. Results revealed that mother and child cortisol reactivity to the balance beam task was positively correlated, but only for mothers who showed high levels of sensitivity during the original teaching task. Mother-child cortisol levels were not correlated if mothers showed low levels of sensitivity during the teaching task. These results were later replicated in 15-month old infants using a different stressor task that involved the infant interacting with a stranger and a novel robot (van Bakel & Riksen-Walraven, 2008). These studies provide preliminary support for the notion that physiological attunement may reflect (or be influenced by) maternal sensitivity.

Later studies expanded on the original Sethre-Hofstad et al. (2002) findings by including more saliva samples (3 on average) and examining whether physiological

attunement is present in the context of other types of stressors and/or over the course of a typical day. However, the results of these studies are mixed. At 3 months of age, infant and mother basal (or baseline) cortisol is correlated when they are in physical contact with one another, but mother-infant cortisol reactivity is uncorrelated following an infant learning paradigm in which infants were physically separated from their mothers (Thompson & Trevathan, 2008). A cross-sectional study examining mother-infant attunement at 2, 6, 12, and 24 months found that mother and infant cortisol reactivity following infant inoculation was uncorrelated at all ages, as was their basal cortisol (Davis & Granger, 2009). Research conducted by other groups shows adrenocortical attunement between mothers and their infants as early as 5 months postpartum (Fuchs, Möhler, Resch, & Kaess, 2016), at 16 months postpartum (Khoury et al., 2016), and only when the infants show emotional distress (Middlemiss, Granger, Goldberg, & Nathans, 2012). Some research has found attunement only when mother-infant dyads are of high socioeconomic status (SES; Clearfield, Carter-Rodriguez, Merali, & Shober, 2014), while other research has identified attunement in a primarily low SES sample (Laurent, Ablow, & Measelle, 2011). An additional study identified attunement of cortisol reactivity in 18-month-old infants and their mothers following a separation stressor, but not in the context of a challenge stressor in which mothers and infants worked together to clean up a mess, suggesting that the type of stressor may play a role in attunement of stress responses (Laurent, Ablow, & Measelle, 2012). Although adrenocortical attunement has recently gained interest from a variety of investigators, the field is predominated by mixed, and sometimes contradictory, findings.

Differences in these findings may in part reflect different responses by mothers and infants to particular stressors. For instance, a mother may not experience stress during an inoculation procedure because she knows the benefits of vaccination outweigh the temporary distress her infant will feel during the inoculation. The infant, of course, has no such knowledge and may therefore experience cortisol elevations following the pain of inoculation. Meta-analysis reveals that infants consistently produce cortisol elevations to physical stressors (e.g., vaccinations) and separation from their mothers, but rarely show cortisol elevations to anger, fear, or novelty stressors (Jansen et al., 2010). Adults, however, often produce cortisol in response to emotional stressors (Dickerson & Kemeny, 2004).

Taken together, these studies suggest that moderators of attunement are present, but few have been consistently identified. Moreover, the vast majority of studies examining adrenocortical attunement have been conducted in healthy community samples. Given that dysregulated stress responsivity has repeatedly been implicated in the development of depression, attunement of stress systems may be particularly important to study within mother-infant dyads at clinical high risk for depression.

Potential disruptors of attunement

Two prime disruptors of attunement may be insensitive caregiving and by extension, maternal depression. To date, no research has examined whether maternal depression, and the altered parenting practices that often accompany depression, impact the development of physiological attunement in mother-infant dyads within the first year postpartum. This is an important gap in the literature that the current study addresses. Behaviorally, maternal depression may hinder women from engaging their infants in

dyadic, synchronous exchanges and thus interfere with the development of strong attachment bonds (Lundy, 2002; Murray, Fiori-Cowley, Hooper, & Cooper, 1996). Even mild depressive symptoms in the first 4 months postpartum have been associated with impaired mother-child bonding at least a year and a half later (Moehler, Brunner, Wiebel, Reck, & Resch, 2006), which could hold implications for physiological attunement. A few studies have begun to examine mother-infant behavioral attunement in the context of maternal depression and have found that decreased behavioral (Lundy, 2002) and affective attunement (Moore & Calkins, 2004) is present in mother-infant dyads where the mother is depressed.

When affective attunement is present, infants of mothers who suffer from depression tend to match their mothers more on negative affect and less on positive affect when compared to healthy controls (Field, Healy, Goldstein, & Guthertz, 1990). The increased negative affectivity within dyads in which the mother is depressed may foster negative emotion in infants, which could bias their interactions with other adults and exacerbate any preexisting emotion regulatory issues. Even more concerning is the fact that these effects are seen not only in infants of severely depressed mothers, but also in infants whose mothers have subthreshold levels of depression (Tronick & Reck, 2009).

In addition to being more likely to engage their infants in negative interactions, mothers diagnosed with depression are less likely to show sensitive caregiving behaviors (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Among other reasons, this finding is significant to the present study because maternal sensitivity mediates the relationship between maternal depression and infant attachment. Specifically, the presence of maternal depression predicts less sensitive parenting behaviors, and this decreased

maternal sensitivity predicts insecure attachment styles in infants (Huang, Lewin, Mitchell, & Zhang, 2012). Other research has shown that caregiver depression has both a direct effect on toddler attachment style and an indirect effect on attachment via parenting behaviors (Hopkins, Gouze, & Lavigne, 2013). A lifetime history of maternal depression and hostile, intrusive parenting behaviors are both associated with heightened reactivity to a stressor in 4-month-old infants (Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007). This particular finding highlights the importance of maternal mental health, and specifically its influence on parenting, in shaping how children respond to stressful events, even during infancy.

Importantly, not all mothers who struggle with depression exhibit negative or withdrawn parenting behaviors. As with all human behaviors, parenting exists on a continuum and this holds true among women suffering from mental illness. Moreover, the presence of positive parenting behaviors – particularly maternal sensitivity – in the context of maternal illness, may buffer children from the effects of maternal psychopathology (Feldman et al., 2009; McMahon, Barnett, Kowalenko, & Tennant, 2006). For example, children (Laucht, Esser, & Schmidt, 2001) and adolescents (Brennan, Le Brocque, & Hammen, 2003) at heightened environmental risk for psychopathology are less likely to develop behavior problems if their mothers exhibit warmth and sensitivity early in life.

One reason for this buffering effect could be that maternal sensitivity creates an environment in which the infant can build a secure attachment with his/her caregiver. Maternal sensitivity during the first few months postpartum is a strong predictor of mother-infant attachment in the toddler years (Bigelow et al., 2010; Gunnar, Brodersen,

Nachmias, Buss, & Rigatuso, 1996) and appears to protect the parent-child attachment relationship in the context of maternal depression (Campbell et al., 2004). These studies provide support for the notion that positive, responsive caregiving behaviors during the first year of life protect children from the potentially negative impact of maternal depression, possibly by improving attunement within mother-infant dyads and ultimately strengthening the attachment relationship.

The present study

A better understanding of the avenues through which vulnerability for depression is passed from mothers to their children could aid in interrupting the cycle of risk transmission from one generation to another. Although mother-infant attunement is a promising line of research that combines both social and biological mechanisms of risk transmission, no studies have examined the impact of maternal psychiatric illness on physiological attunement in a clinical sample of mothers and their infants. Furthermore, no studies have examined whether specific parenting behaviors aside from sensitivity differentially influence mother-infant cortisol attunement.

The present study aims to fill these gaps in the literature by examining attunement of a major biological stress system, the HPA axis, in a high-risk sample of psychiatrically ill women and their infants. Severity of maternal depression (measured using both self-report and clinician ratings) will be examined as a predictor of mother-infant cortisol attunement. An additional aim of the present study is to examine whether specific parenting behaviors (eye gaze, positive affect) predict mother-infant attunement. The final aim of the present study is to explore the directionality of physiological attunement. The specific hypotheses to be tested are as follows:

Hypothesis 1: Mother cortisol levels will be correlated with infant cortisol levels (respectively) over time.

Hypothesis 2a: The number of months mothers meet criteria for a depressive disorder during the child's life and the number of current maternal depressive symptoms will be negatively associated with attunement.

Hypothesis 2b: Increased mother positive affect and a greater length of time spent gazing at her infant after an infant stressor task will be positively associated with attunement.

Hypothesis 3 (Exploratory): Mother and infant cortisol levels measured at an earlier time point will influence those measured at the next time point, suggesting a bidirectional relationship between mother and infant physiology.

Methods

Participants

This study utilizes a prospective, longitudinal sample of 233 women and their infants. Mothers' ages ranged from 20-44 years (M =34.08, SD=4.16) and 92.3% of mothers were married or cohabitating (see Table 1 for additional demographic information). Mothers were primarily Caucasian (91.4%) with a median education level of college graduate. Mothers were recruited during pregnancy from the Emory Women's Mental Health Program (WMHP), a tertiary care center for women with psychiatric disorders. A majority of women experienced at least one psychiatric illness across their lifetime, with the most common diagnosis being depression (n=195, 83.7%). The primary diagnoses for all mothers in the sample are shown in Table 2. In addition, most of the women received psychopharmacologic treatment during pregnancy (n=204, 87.6%) and were taking psychotropic medication at the study visit (n=192, 82.4%). Women meeting criteria for substance abuse or dependence during pregnancy or within 6

months of becoming pregnant were excluded from the current study. Women meeting criteria for a psychotic disorder were also excluded. Additionally, infants with major congenital malformations (e.g., spina bifida) were excluded. Women were seen during pregnancy and once postpartum as part of a longitudinal study on perinatal mood disorders. The current set of analyses focused on data collected at the 6-month postnatal visit and from birth records.

Procedure

Women and their infants completed a single 3-hour laboratory visit when infants were 6 months old. All study procedures began between 1:00-1:30 PM and were completed by 4:00PM to control for known diurnal variations in cortisol levels (Jessop & Turner-Cobb, 2008; Kirschbaum & Hellhammer, 1989). Following maternal informed consent, a laboratory stressor paradigm was employed in which four salivary cortisol samples were collected as follows.

The first baseline maternal and infant salivary cortisol samples were obtained (T0 – baseline) in a quiet room with the mother and infant seated together. The second set of salivary samples (T1 – post-separation stressor) were obtained after a 20 minute mother infant separation during which the mother completed questionnaires while her infant was held by a research assistant (RA) across the room. Next, the infant was exposed to two laboratory stressor tasks, including a brief arm restraint and noise burst, while the mother monitored her infant's behavior on a computer screen. These stressor tasks were followed by a semi-structured 3-minute videotaped interaction between the mother and infant (details below). The third maternal and infant salivary cortisol samples were obtained immediately following the completion of the mother infant interaction and approximately

15 to 20 minutes after the noise burst and arm restraint stressor tasks (T2 – post laboratory stressor I). The fourth saliva samples were collected from the mother and infant an additional 15-20 minutes later (T3 – post laboratory stressor II) to capture the full window of cortisol response to the stressors (Ramsay & Lewis, 2003).

Measures

Maternal Psychopathology. Maternal psychiatric illness since delivery was retrospectively evaluated using multiple measures as detailed below.

Structured Clinical Interview for DSM-IV (*SCID;* First, Spitzer, Gibbon, Williams, & Biometrics Research, 2002). The current sample was recruited from a psychiatric clinic. The SCID is a clinical interview based on Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) diagnostic criteria that was administered by Masters-level clinicians at the 6-month visit to assess current and lifetime psychiatric status. Following data collection, a reliability analysis performed by an independent judge on 10% of the sample yielded *kappas* over .75 for all mood disorder diagnoses. The number of months postpartum in which mothers met diagnostic criteria for Major Depressive Disorder was used as one measure of maternal depression.

Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996). Mothers completed the BDI at the 6-month visit as an additional assessment of current depression. This measure is a 21-item self-report scale that evaluates depressive symptoms experienced in the last two weeks. The symptoms listed on the measure and the two-week time frame are consistent with diagnostic criteria for Major Depressive Disorder in the DSM-IV. The BDI has been shown to have good test-retest reliability, high internal consistency, and good construct, concurrent, and discriminative validity in clinical and

nonclinical samples (Steer, Ball, Raneeri, & Beck, 1997). BDI scores were used in analyses as a measure of current maternal depressive symptomology.

HPA axis functioning. Saliva samples were used to measure cortisol levels of mothers and infants. The mother provided each saliva sample by swabbing a dental cotton roll inside her mouth. Infant saliva samples were collected using a similar methodology, with the RA swabbing the infant's mouth using a dental cotton roll. Saliva was then transferred from the cotton roll to a 15cc polypropylene tube via syringe. Saliva samples were frozen at -20°C within 15 minutes of collection.

Samples were assayed using a commercially available radioimmunoassay kit (DiaSorin GammaCoat, Stillwater, Minnesota) with a cortisol sensitivity of .05 µg/dL. Inter and intraassay coefficients of variation for this kit are 6.0% and 3.5% respectively. An RA blind to maternal psychiatric status and the time point at which each sample was collected assayed all standards and samples in duplicate.

Maternal Affective Parenting Style. The mother-child interaction occurred after the infant stressors and was videotaped for later scoring. Mothers were instructed to interact normally with their infants for three minutes, but asked not to physically touch their infants. Maternal affect (positive, negative, and neutral) and time spent looking at infant was rated by trained coders and inter-rater reliability analyses were conducted to ensure adequate reliability (kappas > .70). The percentage of time mothers exhibited each type of affect was calculated using MANgold INTERACT software. Mother positive affect was defined as a broad smile with cheeks raised, making funny or positive faces at the infant, half smiling, and when whole eyebrows were raised and eyes were wide open while talking with infant. Mother negative affect was identified as

anger/disgust/contempt/sadness/fear/pain or a turned down mouth, furrowed brow, raised inner corners of brow, and wincing/scrunched up face with mouth turned down. Mother neutral affect was defined as the absence of observable positive or negative affect as defined above. Because mother negative affect showed little variability in this sample and the focus of the study was on positive parenting behaviors, only positive affect and time spent gazing at infant were used in the following analyses.

Data Analysis Plan

Variables that have been previously associated with cortisol levels (e.g., maternal age, infant age, delivery complications, infant gender, infant food intake, current maternal tobacco use, maternal menstruation, hours of sleep, aerobic activity, etc.) were examined as potential covariates prior to the primary analyses. The amount of time infants and mothers spent away from one another each week was additionally examined as a possible covariate. Because this was a treatment sample, psychotropic medication use was also explored as a potential covariate. Variables that were significantly associated with maternal or infant cortisol, or the association between mother-infant cortisol, were included as covariates in the appropriate analyses. Infant sex, maternal tobacco use, and whether the infant was fed during the lab visit were significantly associated with both infant and maternal cortisol. Maternal psychotropic medication use was additionally associated with infant cortisol and current menstruation was associated with maternal cortisol. Maternal tobacco use and infant food intake during the lab visit were the only covariates associated with mother-infant cortisol attunement.

Multilevel modeling was conducted using Hierarchical Linear Modeling 7 (HLM-7) software to test the association between maternal and infant cortisol levels across time

points as well as to explore predictors of this time-varying association. HLM-7 allows for the use of nested models, which enabled the researcher to examine changes in cortisol within mother-infant dyads across multiple time points rather than collapsing measures of cortisol across all mothers and all infants within a sample, the latter of which may obscure analyses of dyadic attunement.

Results

Since the primary aim of this study was to examine adrenocortical attunement in a clinically at-risk sample, dyads that were recruited from the community to serve as healthy controls (N=36) were excluded from the present analyses. Dyads were also excluded if maternal cortisol levels were more than 3 standard deviations above the mean (N=12) or if mothers only had one cortisol sample (N=5). There were 4 sets of twins in the original sample, so one twin was randomly chosen from each set to be retained for data analysis. The other twin was excluded from analyses to maintain statistical assumptions of independence. The final sample included 233 mother-infant dyads. Of the infants, approximately half were male (N=121, 51.9%) and all were between 4.7 and 7.9 months old (M=6.3, SD=0.6).

Linear, quadratic, and cubic relationships between time and maternal cortisol, as well as between time and infant cortisol were examined. Maternal cortisol decreased linearly over the course of the visit (β=-0.07, 95CI: -0.08, -0.003, p=0.04) while infant cortisol increased linearly over the visit (β=0.09, 95CI: 0.02, 0.10, p=0.005). Neither maternal nor infant cortisol showed a quadratic or cubic association with time (see Table 3 for cortisol means and standard deviations).

Hierarchical Linear Modeling was used to examine maternal and infant cortisol across all study time points. Infant cortisol (grand mean centered) and collection time point (uncentered) were entered as Level 1 predictors of maternal cortisol in the following model:

a. $Maternal\ Cortisol = \beta_0 + \beta_1\ (infant\ cortisol) + \beta_2\ (time\ point) + error$

Attunement between mothers and their infants was assessed using significance testing of Level 1 time-varying covariates (see equation a). Infant cortisol levels significantly predicted maternal cortisol, beyond any shared association between them due to timing of the sample collection. There was not a significant amount of variance remaining in maternal cortisol scores once the impact of infant cortisol was accounted for (σ^2=0.04, χ^2 (*df*=161)=175.74, *p*=0.20). This lack of variance suggests that levels of infant cortisol consistently predicted maternal cortisol levels across dyads, and that no moderators were present for this association.

Next, maternal cortisol (grand mean centered) was examined as a predictor of infant cortisol, over and above saliva collection time point (uncentered), to provide information about effect directionality:

b. $Infant\ Cortisol = \beta_0 + \beta_1\ (maternal\ cortisol) + \beta_2\ (time\ point) + error$

Maternal cortisol levels significantly predicted infant cortisol, above any shared association between them due to timing of the sample (see Table 4). Moreover, there was significant variance remaining after accounting for this association (σ^2=0.15, χ^2 (*df*=161)=219.29, *p*=.002), suggesting that moderators could be tested at Level 2.

Next, current maternal depression, history of maternal depression since birth of infant, maternal gaze toward infant, and maternal positive affect were individually

examined as Level 2 predictors of the slope of the relationship between mother and infant cortisol in the following model:

c. $\beta_{10j} = \gamma_{10} + \gamma_{11}$ *(predictors)* + *error*

In these predictor models, maternal cortisol was group mean centered and infant cortisol was the dependent measure at Level 1. Neither maternal depression nor length of time mothers spent gazing at their infants was associated with mother-infant cortisol attunement. Conversely, the percent of time mothers showed positive affect while interacting with their infants predicted infant hormonal attunement to his/her mother's cortisol (see Table 5).[1,2]

Time-Lagged Model

Time-lagged analyses provide additional insight into directionality of adrenocortical attunement. Hierarchical linear regressions were conducted in SPSS to examine whether maternal cortisol from the previous time point predicted infant cortisol at the subsequent time point, above and beyond infant's own cortisol from the previous time point. These analyses were also conducted with infant cortisol predicting maternal cortisol at subsequent time points. Results from these analyses are graphically depicted in Figure 1.

Mothers and infants showed positive autocorrelations between their own cortisol samples, such that one's prior cortisol level was associated with cortisol sampled at the subsequent time point. Maternal cortisol level at T1 (reflecting response to the initial

[1] This association held even after including covariates that predicted mother-infant attunement (i.e., current tobacco use and infant food intake during lab visit).
[2] Exploratory analyses examining gender as a moderator were also conducted. Gender did not interact with mothers' current depression, months of postpartum depression, positive affect, or gaze to predict cortisol attunement.

mother-infant separation) positively predicted infant cortisol level at T2 (reflecting response to the stressor tasks), above and beyond infant cortisol level at T1. Maternal cortisol response to the stressor tasks (T2) also predicted infant cortisol response at the subsequent post-stressor time point (T3), above and beyond infants' own cortisol response at the earlier time point (T2). In other words, if a mother showed an attenuated cortisol response to a stressor (separation from her infant or the laboratory stressor task), her infant showed a more attenuated cortisol response at the subsequent time point. Interestingly, infant cortisol response to separation (T1) predicted maternal cortisol response to the laboratory stressor (T2), which in turn predicted infant cortisol response at the next time point. Overall these findings suggest a bi-directional relationship such that infant adrenocortical response and maternal adrenocortical response influence one another within the context of a stressful event.[3] No other significant time-lagged associations were detected.

Discussion

This is the first study to examine mother-infant adrenocortical attunement in a clinical sample of women that received psychiatric care during pregnancy. We found a moderate, bi-directional relationship between maternal and infant cortisol across 4 time points that was not influenced by maternal gaze during a parent-child interaction task or by maternal depression. Infant cortisol strongly predicted mother cortisol, over and above any shared variance due to time at which the sample was collected. There was no variance in this association, suggesting that the cortisol of mothers in this clinical high-

[3] Given the strong correlations between infant and maternal cortisol at all time points, tolerance statistics were examined in these regressions to assess for multicollinearity. All tolerance statistics were above 0.75, suggesting that multicollinearity was not a significant issue in these analyses.

risk sample consistently mirrors that of their infants in the context of an infant stressor paradigm. This is contrary to literature suggesting impaired attachment and sensitivity in mothers with depression, but fits with a recent study that identified mother-infant cortisol attunement only in dyads where the mother showed heightened depressive symptomology (Khoury et al., 2016). The present results suggest that mothers diagnosed with and at clinical high risk for depression are physiologically linked with their infants in the context of a stressor paradigm, and show sensitivity in that regard.

We also found that mother cortisol predicted infant cortisol at all time points and that maternal positive affect moderated this association, such that greater maternal positive affect was associated with stronger mother-infant physiological attunement. This is inconsistent with one study that found high and low levels of negative affect, but not positive affect, to predict stronger adrenocortical attunement between mothers and their adolescent children (Papp et al., 2009). These differences may reflect a shift in development between infants and adolescents or may be residuals of the different interaction tasks used in the two studies. The present study required a mother to interact with her infant following a stressor task. She was therefore most likely to show positive affect during this interaction in an attempt to soothe her infant. In fact, there was virtually no negative affect displayed by mothers in our study. In contrast, Papp, Pendry, and Adam (2009) measured emotion during a family discussion about a current conflict. Positive affect may be less likely to occur during conflict discussions, so there may have been a restricted range in the amount of time that positive affect was shown in that scenario.

Research on emotional and behavioral contagion, or the spread of emotions and behaviors among social networks, shows that both positive and negative emotions spread across interconnected people (Coviello et al., 2014; Fowler & Christakis, 2008; Rosenquist, Fowler, & Christakis, 2011). Certain emotional states and health behaviors may even be transmitted between people who are randomly assigned to spend time together, suggesting that being predisposed to spend time with similar people does not fully explain this emotional attunement (Centola, 2010; Golberstein, Whitlock, & Downs, 2013). The present study extends such research by showing physiological attunement among mother-infant dyads and showing that emotional expression is one factor associated with the strength of adrenocortical attunement. A hopeful avenue for future research may be to examine whether parenting interventions that increase maternal positive affect (e.g., Landry, Smith, Swank, & Guttentag, 2008) also improve mother-infant physiological attunement.

Maternal cortisol predicted infant cortisol at subsequent time points of measurement, but only when the infant was responding to or recovering from the stressor tasks. These findings suggest that more well-regulated mothers may be better able to regulate their infants' response to stressful events, and that maternal regulation may be impacted by infant response to separation. Conversely, maternal cortisol dysregulation following stressful events may contribute to a positive feedback cycle in which maternal distress contributes to infant distress, and infant distress then heightens or maintains maternal distress. Such a cycle could increase the negative emotion expressed within a household, which may have deleterious consequences for pre-existing maternal psychopathology, such as increased risk of disease relapse (Butzlaff & Hooley, 1998).

Mother/infant baseline cortisol did not predict partner's cortisol levels at subsequent time points. Therefore, the observed time-lagged associations between mother and infant cortisol were specific to the context of the stressor paradigm in this study. This is consistent with research that has found mother-child attunement to be stronger in the context of a challenge (Ruttle, Serbin, Stack, Schwartzman, & Shirtcliff, 2011).

Although the present study identifies a bi-directional influence of maternal and infant cortisol on each other, the directionality of this relationship may change with child maturation. One study has found adolescents' cortisol before, during, and after a family conflict discussion to be predicted by father cortisol at the previous time point, above and beyond adolescents' own cortisol. Adolescent cortisol was not predicted by mother cortisol at the previous time point, but mother cortisol at subsequent time points was predicted by adolescent cortisol (Saxbe et al., 2014). This change may occur as children become increasingly independent from their mothers with age. Infancy is a time when children are entirely dependent upon their caregivers, which may explain why the present study found infant physiology to be more strongly connected with maternal physiology.

It is important to note that our sample consists of highly educated mothers, many of whom received psychiatric treatment at the time of their study visit. Despite the receipt of treatment, mothers in our sample displayed a wide range of BDI scores (see Table 1) with quite a few scores above the clinical cut-off (which is 21 for moderate depression), suggesting that many women continued to experience clinically significant depression in the two weeks leading up to their study visit. Although possible, it therefore seems unlikely that the receipt of treatment interfered with our ability to examine the influence of maternal depression on physiological attunement. However, mother-infant attunement

may not occur, or may occur to a lesser extent, in untreated dyads who experience additional stressors, such as those living below the poverty line (Clearfield et al., 2014; Laurent et al., 2011). Future research should therefore examine whether our findings replicate in clinical samples of women who face additional environmental stressors such as poverty.

The attunement identified in the present study may not generalize in the same way to all biological markers of stress reactivity. For example, salivary alpha amylase (SAA) – a marker of sympathetic nervous system activity – and cortisol attunement may occur differentially under different circumstances and at different ages. One study found mother and infant cortisol to be uncorrelated before and after a stressor at 2, 6, 12, and 24 months. Unlike cortisol, mother-infant SAA basal levels were correlated before, but not after, an inoculation stressor when infants were at least 6 months old (Davis & Granger, 2009). These results suggest that mother-infant attunement of SAA and cortisol occurs differentially in certain contexts.

This explanation is further supported by research that shows a double dissociation between cortisol and SAA attunement with different stressors. Specifically, cortisol attunement was present in 18-month-old infants and their mothers in the context of a separation stressor, but not in the context of a challenge stressor in which mothers and infants worked together to clean up a mess. Mother-infant SAA attunement, on the other hand, was present in the context of the aforementioned challenge stressor, but was not detected in response to the separation stressor (Laurent et al., 2012). Future research should examine multiple markers of stress reactivity in the same research study to further identify converging and differential patterns of within-dyad physiological attunement.

Causal conclusions cannot be drawn from the current study due to its correlational design. To date, there have been no experimental studies on the spread of physiological stress responses within mother-child dyads. Comparison of experimental manipulation of mother and child cortisol using stressors or a pharmacological agent and an un-manipulated control group may provide greater insight into causality in this relationship. Moreover, studies have not examined the specificity of adrenocortical attunement by examining whether it exists between strangers. Determining whether physiological attunement occurs only within intimate dyads or not would provide information that could drive future research on the mechanisms by which this physiological phenomenon occurs. For instance, if attunement only occurs within intimate dyads, it may be related to secure attachment within that dyad. However, if attunement readily occurs between strangers, then it may reflect general empathy instead of attachment.

Research and theory are beginning to provide some insight into the adaptive benefit of emotional and physiological attunement. For instance, matching conspecifics who show a fear response may activate biological stress response systems, better preparing an animal for a fight or flight response to a threat. Experiencing an emotion that a conspecific displays may also create a connection that lays the groundwork for empathy (de Waal, 2008), which could further the propagation of a species as a whole. In human research, parents whose cortisol changes are driven by changes in their children's cortisol show lower overall cortisol output during short-term family conflict. This lowered cortisol output may represent better parental physiological regulation in the context of a social stressor. Adolescents whose cortisol levels change in response to changes in maternal cortisol show *higher* overall cortisol output during family conflict,

suggesting this mother-child cortisol linkage may not similarly help adolescents self-regulate (Saxbe et al., 2014). Future research should examine whether physiological attunement between mothers and their children is associated with future child outcomes, such as child stress reactivity.

The current study has several strengths, including the use of HLM to examine time-varying and non-time-varying predictors of attunement in a high-risk clinical sample. Mothers who have experienced psychopathology are an especially important group in which to study attunement as their infants are at increased risk of developing mental illness as they age (Goodman et al., 2011) and are more likely to be exposed to negative or disengaged parenting (Lovejoy et al., 2000). An additional strength of the study design is the use of multiple cortisol samples and control for variation in diurnal cortisol by only allowing lab visits to occur between 1 and 4pm.

Mother and infant cortisol levels exert a bi-directional influence on one another by 6 months postpartum in a sample of mothers who sought psychiatric treatment during pregnancy. These results suggest that many mothers who experience mental illness maintain a close physiological linkage with their infants, particularly in the context of stressors. The present study extends stress research conducted with healthy mother-child dyads by being the first to identify adrenocortical attunement in a clinical sample of mothers and their infants. This is an integral step in advancing theory regarding the development of the human stress response and the influence of social factors on HPA axis functioning.

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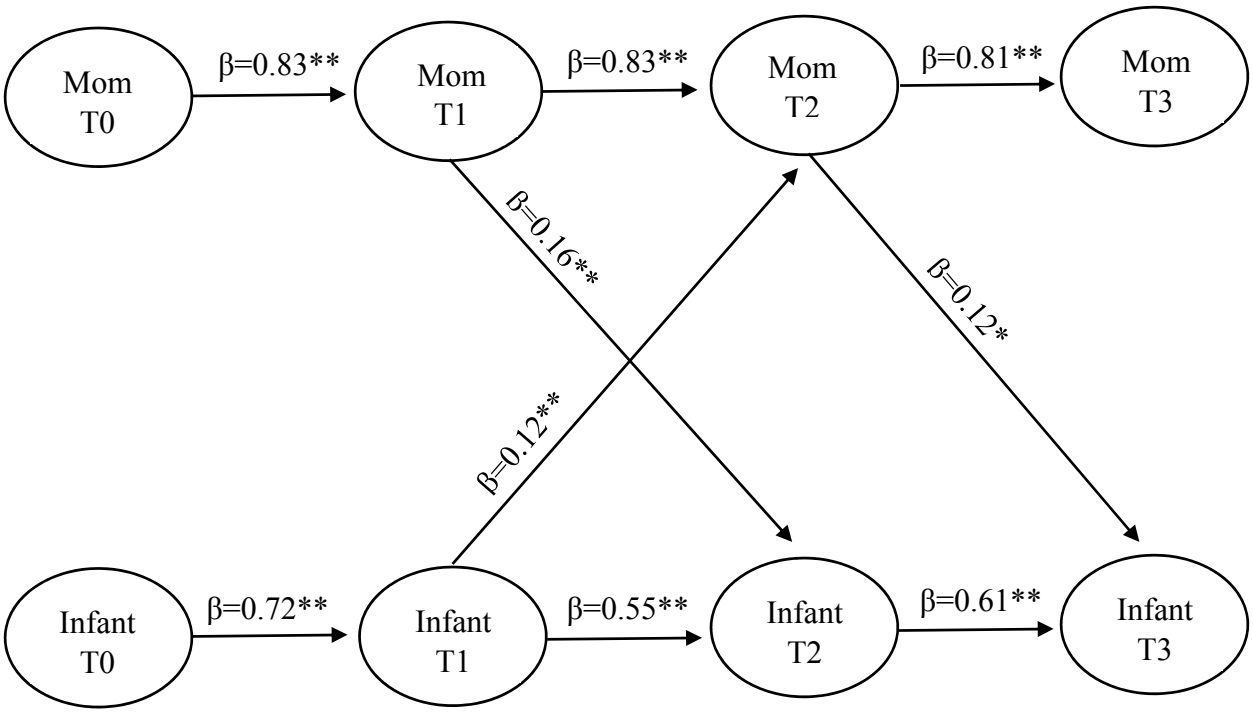
Figure 1. Results from time-lagged analyses.



Note: Only significant associations are shown. All relationships control for own cortisol at the previous time point. *p<0.05, **p<0.01

Table 1. Sample Demographics.

Variable	M (SD)	Range
Maternal Age	34 years (4)	20 - 44
Maternal Ethnicity, % (N)	91.4 (213) Caucasian	-
Married/Cohabitating, % (N)	92.3 (215) yes	-
Education, % (N)	73.4 (171) college graduate	-
History of MDE, % (N)	87.6 (204) yes	-
Current BDI	9.6 (9.0)	0 - 51
No. Months Depressed Postpartum	0.8 (1.5)	0 - 6
Current Psychotropic Medication, % (N)	82.4 (192) yes	-
Current Tobacco Use, % (N)	9.4 (22) yes	-
Current Menstruation, % (N)	5.2 (12) yes	-
No. Pregnancy Complications	1.7 (1.4)	0 - 7
% Time Gaze at Infant	96.1 (4.8)	73.6 - 100
% Time Positive Affect	27.3 (23.7)	0 – 95.7
Currently Breastfeeding, % (N)	51.9 (121) yes	-
Infant Age	6.3 (0.6) months	4.7 – 7.9
Infant Sex, % (N)	48.1 (112) female	-
Infant Ethnicity, % (N)	91.4 (213) Caucasian	-
Birth Weight	3.3 (0.5) kg	1.6 – 4.8
No. Siblings	0.8 (0.9)	0 - 4

Note: % time gaze at infant and % time positive affect were coded during the mother-child interaction.

Table 2. Primary Maternal Diagnosis.

Diagnosis	**N (%)**
No Axis I Psychopathology	11 (4.7)
Bipolar I Disorder	24 (10.3)
Bipolar II Disorder	6 (2.6)
Bipolar Disorder, Other	1 (0.4)
Major Depressive Disorder	137 (58.8)
Dysthymic Disorder	7 (3.0)
Depressive Disorder, Not Otherwise Specified	2 (0.9)
Mood Disorder due to a General Medical Condition	1 (0.4)
Schizoaffective Disorder	1 (0.4)
Brief Psychotic Disorder	1 (0.4)
Alcohol Use Disorder	2 (0.9)
Panic Disorder	11 (4.7)
Obsessive Compulsive Disorder	3 (1.3)
Posttraumatic Stress Disorder	6 (2.6)
Generalized Anxiety Disorder	10 (4.3)
Anxiety Disorder Not Otherwise Specified	1 (0.4)
Binge Eating Disorder	1 (0.4)
Adjustment Disorder	2 (0.9)

Table 3. Cortisol Means and Standard Deviations.

Collection Time Point	Maternal Cortisol, M(SD)	Infant Cortisol, M(SD)
0 *(Baseline)*	-1.13 (0.68)	-0.92 (0.73)
1 *(Post Separation)*	-1.16 (0.64)	-0.77 (0.74)
2 *(Post Lab Stressors I)*	-1.24 (0.69)	-0.85 (0.68)
3 *(Post Lab Stressors II)*	-1.24 (0.69)	-0.69 (0.66)

Note: All cortisol values are log transformed.

Table 4. Hierarchical Linear Models of Physiological Attunement.

Fixed effect	**Coefficient**	***SE***	***t-ratio***
Maternal Cortisol			
Infant Cortisol slope (attunement)	0.09	0.03	2.83*
Time Point slope	-0.04	0.01	-4.00**
Infant Cortisol			
Maternal Cortisol slope (attunement)	0.25	0.06	3.93**
Time Point slope	0.08	0.02	3.50**

Note: *p<0.05, **p<0.001; n = 230

Table 5. Parental Characteristics and Behaviors as Moderators of Physiological Attunement.

Fixed effect	**Coefficient**	***SE***	***t***	***p***	***Variance Explained***
Current Maternal Depression	0.01	0.01	0.64	0.53	16.7%
No. Months of Maternal Depression	-0.06	0.09	-0.68	0.50	13.6%
Maternal Gaze	-0.01	0.02	-0.70	0.49	16.1%
*Maternal Positive Affect	0.006	0.003	2.10	0.03	21.9%

Note: Infant Cortisol was entered as the dependent variable for the above analyses. Variance explained refers to the percentage of variance in mother-infant cortisol slope accounted for by each variable.
*$p < 0.05$