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Hair Cortisol in Pregnancy Mediates Associations Between Maternal Adversity and Disrupted Maternal Interaction in Early Infancy

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Abstract

Existing literature points to the possibility that cortisol could be one link between maternal adversity and poorer parenting quality, but most studies have examined salivary cortisol concentrations rather than hair cortisol concentrations. The current study examined hair cortisol concentration (HCC) during the third trimester of pregnancy as a mediator between maternal adversity indicators (childhood abuse, severe mental illness, symptomatic functioning) and maternal caregiving behavior at 4 months postpartum. Forty-four women participated in the study: 30 with severe mental disorders, and 14 non-clinical controls. HCC was assessed during the third trimester of pregnancy (HCC-P) and at 4 months postpartum (HCC-4M). Sexual, physical, and emotional abuse were assessed by the Adverse Childhood Experiences Study Questionnaire. Maternal disrupted interaction was reliably coded from mother-infant video interactions during a Still-Face Procedure. Maternal HCC-P and HCC-4M mediated associations between maternal psychopathology and maternal disrupted interaction. Childhood abuse directly predicted maternal withdrawing behavior at 4 months, with no significant mediation by HCC. Our findings indicate that HCC may be a potential early biomarker for future caregiving challenges among mothers with severe mental illness.

Keywords: Disrupted caregiving behavior, hair cortisol, maternal childhood abuse, severe mental illness, perinatal period

Hair Cortisol in Pregnancy Mediates Associations Between Maternal Adversity and Disrupted Maternal Interaction in Early Infancy

Maternal childhood abuse has been identified as a predictor of both maternal disengagement and maternal hostile-intrusive behavior towards the infant (Lyons-Ruth & Block, 1996; Moehler, Biringen, & Poustka, 2007), and cortisol has been suggested as a possible biological mechanism linking maternal adverse experiences to disrupted caregiving behavior (Juul, Hendrix, Robinson, Stowe, Newport, Brennan, & Johnson, 2016). These associations are important because maternal disrupted interaction has been associated with infant disorganized attachment and later child behavior problems (Lyons-Ruth, Bronfman, & Parsons 1999; Madigan, Bakermans-Kranenburg, IJzendoorn, Moran, Pederson, & Benoit, 2006; van IJzendoorn, Schuengel & Bakermans-Kranenburg, 1999).

Maternal psychopathology has also been identified as a risk factor for parenting impairment (Muzik, Morelen, Hruschak, Rosenblum, Bocknek, & Beeghly, 2017; Rigby, Conroy, Miele-Norton, Pawlby, & Happé, 2016), but the role of cortisol in this association has not yet been explored. Furthermore, Muzik et al. (2017) showed that in the context of childhood abuse history and/or current PTSD, maternal depression was the most salient risk factor associated with parenting impairment, i.e. lower behavioral sensitivity, higher negative/lower positive affect, during infancy. Thus, it seems warranted to explore maternal psychopathology alongside childhood abuse in order to understand the potential mediating effect of hypothalamic-pituitary-adrenal (HPA) axis status in the development of disrupted maternal interactions.

Assessing cortisol in the perinatal period

During pregnancy, the corticotropin-releasing hormone (CRH), normally produced in the hypothalamus, is also produced in the placenta. Placenta CRH is identical to the hypothalamic CRH in structure and physiological activity, and thus stimulates the release of

cortisol. While glucocorticoids, such as cortisol, suppress hypothalamic production of CRH, placental CRH production appears to be stimulated by glucocorticoids in a positive feedback loop (reviewed in de Weerth & Buitelaar, 2005). As such, maternal circulating cortisol increases throughout pregnancy (Anna-Hernandez, Ross, Natvig, & Laudenslager, 2011; de Weerth & Buitelaar, 2005), with particular increases in the third trimester.

Regarding the postpartum period, Barret and Fleming (2011) suggested that high maternal cortisol levels in the very early postpartum period (i.e., first postpartum week) might serve to influence maternal responsiveness by enhancing the salience of infant stimuli and attention to it. However, Barret and Fleming (2011) also proposed that increased HPA axis activity may have a negative relation with mothering later in the postpartum period (i.e., five to six months postpartum) or in mothers who are stressed and/or 'at risk'. Thus, the relation between the HPA axis activity and maternal behavior might vary as a function of the pre- or postnatal period being assessed, as well as other factors such as the tool used to assess cortisol.

Associations between maternal childhood trauma and HPA axis dysregulation

Severe stress early in life is associated with persistent sensitization of the pituitary-adrenal and autonomic stress response, and the experience of childhood trauma can alter the functioning of the physiological response to stress later in life (Danese, Moffitt, Harrington, Milne, Polanczyk, Pariante, Poulton, & Caspi, 2009; Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, Nemeroff, 2000). Under stressful conditions, the hormone cortisol is released, and under normal circumstances the negative feedback loop of the HPA axis halts the production of cortisol after the stressful situation has ceased. However, the initiation as well as the termination of the stress response is susceptible to dysregulation. Adverse childhood experiences are hypothesized to disrupt the normal physiological response to stress by chronic over-activation of the stress system leading to allostatic load and consequently

receptor desensitization and tissue damage (Danese et al., 2009; McEwen, 2003). As such, allostatic load is reflected in a chronic dysregulation of the HPA axis.

This dysregulation may be expressed as either chronic activation or as exhaustion of the HPA axis, thus studies have linked early adversity to both *hypercortisolism* (Heim et al., 2000), and *hypocortisolism* (Juul et al., 2016). Possibly, HPA axis activity follows a time line after traumatization with initial hypercortisolism, which over time gradually reverts to hypocortisolism (Miller, Chen, & Zhou, 2007). In any case, the findings from these studies indicate a possible impact of early trauma on the mother's HPA axis functioning, possibly already identifiable during pregnancy (Gonzalez, Jenkins, Steiner, & Fleming, 2009; Heim et al., 2000; Juul et al., 2016).

Associations between psychopathology and HPA axis dysregulation

Psychopathology has also been associated with dysregulation of the HPA axis (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). Major depressive disorder and late age-of-onset bipolar disorder have been related to increased hair cortisol concentration (HCC) (Staufenbiel et al., 2013), and hyper-activity of the HPA axis assessed by plasma, serum, and salivary cortisol has been linked to psychosis and schizophrenia (Borges, Gayer-Anderson, & Mondelli, 2013). Thus, these severe psychiatric diagnoses (depression, bipolar disorder, schizophrenia) have been linked to increased stress sensitivity. In contrast, other forms of psychopathology, such as anxiety disorders and PTSD, have been associated with both blunted activity in the HPA axis (Staufenbiel et al., 2013) and with increased HCC levels (Luo et al., 2012; Steudte et al., 2011).

Cortisol as a possible link between maternal adversity and maternal caregiving behavior postpartum

General life stress and specific parenting stress are strong predictors of parenting behavior (Puff & Renk, 2014). Cortisol levels are very sensitive to social stressors (Gunnar &

Donzella, 2002) and thus have been the focus of research examining the physiological markers of stress in relation to caregiving. Many of the studies on cortisol and caregiving have measured acute cortisol in saliva and have yielded mixed findings. For example, maternal intrusiveness during parent-child interactions has been associated with *higher* maternal salivary cortisol (Mills-Koonce et al., 2009), while overall maternal disrupted interaction has been associated with *lower* maternal salivary cortisol (Crockett et al., 2013; Schechter et al., 2004).

Taken together, the literature suggests that maternal HPA-axis dysregulation is associated with both early-life trauma and with parenting quality. However, findings vary based on the type of parenting behavior assessed, and few studies have explored cortisol as a putative link between early adversity and maternal caregiving behavior in humans (Gonzales, Jenkins, Steiner & Fleming, 2012; Juul et al. 2016). Juul et al. (2016) reported that *lower* salivary cortisol reactivity to a stress test mediated the association between trauma history and maternal affect. In addition, Gonzalez et al. (2012) found that *greater* diurnal cortisol secretion (indicated by a larger area under the curve (AUCg) value) mediated the relation between early-life trauma and lower maternal sensitivity. Thus, both higher basal cortisol levels (i.e., diurnal cortisol secretion) and blunted reactivity may indicate a pattern of cortisol dysregulation which acts as a mechanism linking adversity to maladaptive caregiving (Reijman et al., 2016).

Thus, an important but complex role for cortisol dysregulation emerges in models relating maternal adversity to later caregiving disruptions. As reviewed above, both hyper- and hypo- activation of cortisol have been demonstrated in relation to early adversity and both have been further related to deviations in caregiving. Thus, for some mothers, early adversity may result in hyperresponsiveness to stressful experiences, including the infant's distress and affective cues, and such hyperarousal may fuel excessive intrusiveness in her attentions to the

infant. In contrast, for other mothers, chronically elevated cortisol levels may lead to desensitization of cortisol receptors and blunting of stress responsiveness, with consequent muting of the mother's sensitivity to infant affective cues, as well as to her own affective responses. This is supported by Juul et al.'s findings that lower cortisol levels mediated the relation between maternal trauma and increased neutral affect expression towards infants. The impact of blunted HPA activity on maternal behavior may also be reflected in maternal withdrawal or flatness of affect in relation to the infant's distress and affective cueing in the early months of life.

The neurobiological processes that might underlie such associations between HPA dysregulation and maternal behavior are not adequately understood (Barrett & Fleming, 2011). Barrett and Fleming (2011) propose several neurological mechanisms. One candidate brain region that might account for how HPA activity is related to maternal behavior is the medial preoptic area (MPOA) of the hypothalamus, as this region contains ample HPA receptors and receptors for hormones that are involved in the activation of maternal behavior and affect (Barrett & Fleming, 2011). An alternative model is that early adversity in some cases results in serious psychopathology, characterized in part by affective hyper- or hypo-arousal to stress, and it is the resulting psychopathology and social-emotional dysregulation, rather than cortisol dysregulation per se, that affects maternal behavior.

Previous studies on cortisol as a mechanism linking maternal adversity and caregiving behavior have primarily relied on salivary cortisol. However, measures of salivary cortisol are highly influenced by acute contextual stressors, and most saliva assays do not take the rapid conversion of cortisol to cortisone into account. In contrast, a single hair sample provides an integrated measure of chronic cortisol production, with one cm of hair reflecting one month of cortisol production. Such integrated cortisol levels over an extended time

interval obtained by HCC might be more informative about the effects of previous and current maternal adversity indicators on caregiving behavior.

It is possible that the variability in findings linking cortisol and parenting behavior are related to measurement issues characterizing acute salivary cortisol sampling. The methodological advantages of obtaining a reliable index of hair cortisol over a longer period of time could yield a better understanding of how physiological stress impacts parenting behavior and whether cortisol levels constitute one mechanism linking adversity to parenting. In this study we assessed HCC during the third trimester of pregnancy and at 4 months postpartum and evaluated whether HCC acted as a mediator between maternal adversity indicators (i.e. childhood abuse, severe mental illness, symptomatic functioning) and maternal caregiving behavior in the early postpartum period.

Hypotheses

The main hypothesis was that 1) HCC will mediate the relation between maternal adversity indicators (childhood abuse, severe mental illness, and current symptomatic functioning) and maternal disrupted interaction. Building up to this mediation, we hypothesized the following associations: 2) HCC prenatal (HCC-P) will be related to HCC at 4 months postpartum (HCC-4M); 3) Both cortisol assessments, HCC-P and HCC-4M, will be related to disrupted maternal interaction; 4) The three adversity indicators (childhood abuse, severe mental illness, and current symptomatic functioning) will also be related to HCC-P and HCC-4M; 5) The three adversity indicators (childhood abuse, severe mental illness, and current symptomatic functioning) will also be related to maternal disrupted interaction at 4 months.

2. Method

2.1. Participants

Participants in the current study included 44 women, 12 with Major Depressive Disorder, 10 with Bipolar Disorder, 8 with Schizophrenia Spectrum Diagnosis, and 14 non-clinical controls. Participants represented a sub-sample of Danish participants from the ongoing WARM study (Harder, Davidsen, Macbeth, Lange, Minnis, Andersen, Simonsen, Lundy, Nyström-Hansen, Trier, Røhder, & Gumley, 2015). Participants for the present study were recruited from obstetric wards in the Region of Southern Denmark, Region Zealand, and the Capital Region, Denmark in the period from October 2014 to February 2017. Inclusion criteria were: 1) Pregnant women with a minimum age of 18; and 2) a diagnosis of either a) lifetime Schizophrenia Spectrum Diagnosis, or b) lifetime Bipolar I or II Disorder, or c) current or recurrent moderate to severe Major Depressive Disorder, and d) non-clinical controls. Exclusion criteria were: a) inability to provide informed and written consent to participate, b) inability to speak English or Danish, c) miscarriage, d) maternal diagnosis of Autism Spectrum Disorder, and e) alcohol or drug dependency being the primary diagnosis. Further exclusion criteria for controls were: women describing current psychiatric symptoms not previously identified or treated and likely to require treatment. If an infant was born with a congenital developmental disorder, which could be diagnosed from birth, such as Down's syndrome, the family was excluded from the present study. Because women with depression or without a psychiatric history are more prevalent in services, in order to reduce selection biases, women from these groups were randomly selected using electronic randomization lists.

Fifty-two participants provided informed written consent to participate. Three participants dropped out prior to initial assessments and one participant was excluded. Thus, maternal data on psychiatric diagnosis and childhood maltreatment were available for 48 participants. Three participants dropped out prior to the 4 months postpartum assessments, and one participant did not consent to 4 months data collection, leaving n = 44 participants in

the study. The WARM study was approved by the committees of Health Research Ethics in the Capital Region of Denmark.

2.2. Procedure

Assessments were carried out at two time points: during pregnancy (P), and 4 months post-partum (4M). Sociodemographic characteristics, childhood adversity, and clinical assessments were collected during the second or third trimester shortly after recruitment. Maternal hair was collected in the third trimester (P). Due to scheduling conflicts, exceptions were made in three cases, where hair was collected in the second trimester at gestational ages 18.7, 26.0, and 27.9 weeks respectively. Symptomatic functioning assessment and maternal hair collection were repeated at 4M. For further information on study design, see Harder et al. (2015).

2.3. Measures

2.3.1. Sociodemographics

Age, race/ethnicity, and highest level of education were self-reported (Harder et al., 2015). Education was categorized based on the ISCED-1997. All participants also self-reported as married/living with a partner or never married/not living with a partner, and partner status was dichotomized into "Married/co-habitating" vs. not.

2.3.2. Maternal adversity indicators

Childhood adversity was assessed using the Adverse Childhood Experiences Study Questionnaire (ACE) (Felitti, Anda, Nordenberg, Williamson, Spitz, Edwards, Koss, & Marks, 1998). The ACE has excellent internal reliability (Cronbach's Alpha = 0.88) (Murphy, Steele, Dube, Bate, Bonuck, Meissner, Goldman, & Steele, 2013). While the ACE includes questions about household dysfunction other than abuse, based on previous research linking childhood abuse specifically to adverse outcomes in later life (e.g. psychosis) (Varese, Smeets, Drukker, Lieverse, Lataster, Viechtbauer, Read, Van Os, & Bentall, 2012), we

focused our analyses on abuse experiences only and did not analyze questions regarding household dysfunction. Number of abuse types was computed as the sum of items assessing childhood emotional abuse, physical abuse and sexual abuse (range 0 – 3).

Severe mental illness was assessed by lifetime diagnosis of major depressive disorder, bipolar disorder, or schizophrenia spectrum disorder. Participants were referred to the study based on preexisting diagnoses, and psychiatric diagnoses were further confirmed by structured diagnostic interviews using the psychosis and mood modules of the Structured Clinical Interview (SCID) from the DSM-5 (First, Williams, Karg, & Spitzer, 2016), which was administered during pregnancy. None of the women in the severe mental illness group received recent (within the past several months) diagnoses. All diagnostic assessments were supervised by a SCID trained researcher and all diagnoses were confirmed through consensus discussion with senior researchers (SH, AG, KD, AM). The severe mental illness variable was computed as severe mental illness (1) / control group status (0).

Current symptomatic functioning was assessed using the Global Assessment of Functioning scale, symptomatic functioning subscale (GAF-S) (American Psychiatric Association (APA), 2013), with higher scores indicating better functioning. The interrater reliability was acceptable (ICC(1) = 0.602, N = 8). The GAF-S was assessed at the initial study visit during pregnancy and again at four months postpartum.

2.3.3. Maternal disrupted interaction

Maternal disrupted interaction was coded from the recovery phase of the still-face procedure (5 minutes video interaction) at 4 months infant age by two coders, using the Atypical Maternal Behavior Instrument for Assessment and Classification (AMBIANCE) coding system (Lyons-Ruth et al., 1999). Using extensive itemized examples of disrupted maternal interactions in the coding manual, the coder first tallies the frequency of occurrences of the following five forms of disrupted maternal communication: 1. *Affective*

communication errors, defined as contradictory affective signals to the infant (e.g. using a sweet voice with a derogatory message) or inadequate or inappropriate responses to the infant's signals (e.g. fails to comfort a distressed infant); 2. *Role-confusion*, defined by the mother calling the infant's attention to herself in ways that override or ignore the infant's cues (e.g. asking the infant for a kiss when the infant is distressed); 3. *Frightened/disoriented behavior*, defined by fearful, hesitant, or deferential behavior towards the infant (e.g. hesitating before responding to infant; tense body postures) or by disoriented behavior (e.g. flat or odd affect in interaction; frenetic or uncoordinated overtures toward the infant); 4. *Negative-intrusive behavior*, defined as harsh or critical behavior (e.g. pulling the infant by the wrist; mocking or teasing the infant; attributing negative affect to the infant); 5. *Withdrawing behavior,* defined by creating physical or emotional distance from the infant (e.g. standing across the room while interacting; interacting silently).

Based on the frequency and seriousness of the observed forms of disrupted interaction, a single rating of the overall level of maternal disrupted interaction is assigned on a seven point scale (1 – 7). The manual gives explicit guidelines for judging each level on the rating scale, including specific descriptions of behavior that might satisfy criteria for that level. In addition, separate seven-point ratings for the five contributing aspects of maternal disrupted communication are also assigned, using similar anchored descriptors. Intercoder reliability was excellent on all scales: overall level of disrupted interaction, ICC = .88; (a) affective communication errors ICC = .84, (b) role confusion ICC = .73, (c) negative-intrusive behavior ICC = .84, (d) disorientation ICC = .68, and (e) withdrawal ICC = .75. Stability and validity of the AMBIANCE have been shown by meta-analysis (Madigan et al., 2006).

2.3.4. Hair cortisol

A section of hair strands approximately 3 mm in diameter was cut as close to the scalp as possible from the posterior vertex area. Hair samples were stored in aluminum foil as

previously described (Anna-Hernandez, Ross, Natvig, & Laudenslager, 2011), and analyzed at the Department of Psychology, Technical University of Dresden, Germany using liquid chromatography–tandem mass spectrometry (Gao, Stalder, Foley, Rauh, Deng, & Kirschbaum, 2013). The 4-cm hair segment closest to the scalp was used for analyses. This hair segment is taken to represent cortisol secretion over the most recent 4-month period (Stalder & Kirschbaum, 2012). HCC values were standardized to the weight of the respective sample. Samples with outlying high results were checked in a second analysis.

At sample collection, three participants were in the 2nd trimester (18.71 weeks, 26 weeks, and 27.86 weeks) and the remainder were in the third trimester. Time of collection of the third trimester cases ranged from 28.14 to 38.86 weeks. Therefore, HCC values, other than the sample collected at 18.71 weeks, indexed cortisol levels over a collective time period from 8.67 weeks to 38.86 weeks of pregnancy.

2.3.5. Confounding variables

Potential confounders for HCC were: 1) parity (categorized yes/no for primipara), 2) breastfeeding (3 categories: breastfeeding only; both breastfeeding and formula; formula only), 3) smoking (categorized yes/no for smoking during past week), 4) regular use of medication (categorized yes/no to current use of any prescription medication), 5) body mass index (BMI: weight (kg)/by height squared (meters)), 6) waistline (full cm), and 7) hair treatments (self-reported yes/no to dyeing, bleaching, permanent waves over the past 3 months). Potential confounders for maternal behavioral outcome were infant age and gender.

2.4. Analytic strategy

Descriptive and preliminary analyses were conducted using IBM SPSS Statistics 24. Given the non-normality of data (see 3.1.) and categorical variables, bivariate Spearman's correlations were first run between potential control variables and dependent variables. Several demographic characteristics and characteristics associated with HCC were explored

as potential covariates (see Rippe et al., 2016). Variables with significant correlations to dependent variables were included as covariates in later regression and mediation analyses. The main analyses were conducted in Mplus (Version 8). A series of regression analyses were conducted to examine associations among childhood abuse, mental illness status, current symptomatic functioning, HCC-P, HCC-4M, and maternal disrupted interaction at 4 months, including direct associations and indirect (mediated) effects. FIML and bootstrapping were estimated for all regression and mediation models to account for missing data, non-normality, and small sample size (Fox, 2015). Bias-corrected confidence intervals (CIs) were used to determine significance; CIs that do not contain zero are significant at $p < .05$.

3. Results

3.1. Data transformations and missing data

Cortisol values and the number of types of abuse were log transformed to reduce skewness. After log10 transformations, HCC-P (M = 0.82, SD = 0.35) and abuse variables (M = 0.15, SD = 0.19) were normally distributed but HCC-4M remained skewed. Descriptive analyses identified two cases with extreme HCC values at 4 months. In order to correct for non-normality, HCC-4M values were winsorized, modifying extreme values in order to limit the impact of outliers (Ghosh & Vogt, 2012). All analyses were conducted both with the winsorized HCC-4M variable and with the non-winsorized HCC-4M variable, with the two outliers excluded. Results of the two analyses did not differ, thus winsorized results are reported.

There were no differences between dropouts and participants remaining in the study at 4M on mental illness/control group status, parity, age, education, current symptomatic functioning at pregnancy , or number of abuse types, *p*s > .05. Hair samples were missing from 13.6% of participants (n = 6) at pregnancy and 26.8% (n = 11) at 4 months. Women who *did not* provide hair cortisol at pregnancy were more likely to be in the control group

(Fisher's Exact Test, $p = .009$) and were more likely to report fewer types of abuse ($F(1,42) = 4.45$, $p = .041$. In addition, 13.6% (n = 6) were missing maternal interaction data. Based on Little's Missing Completely at Random (MCAR) test, data were deemed to be missing completely at random (X^2 (155) = 152.75, p = 0.536), and thus are appropriate for the use of FIML. Because FIML does not delete cases with missing data, this statistical procedure avoids biased parameter estimates likely to occur if pairwise or listwise deletion is used for missing data (Graham, 2003; Wolthke, 2000). Therefore, it is recommended to use statistical methods such as FIML to account for missing data when data is MCAR (McCartney, Burchinal, & Bub, 2006).

3.2. Descriptive statistics and analyses of covariates

Sample characteristics are detailed in Table 1. Spearman correlations between maternal interaction variables and potential covariates indicated that overall disrupted maternal interaction was correlated with marital status (*rho* = -.321, $p < .05$). In addition, regarding the five dimensions contributing to disrupted interaction, maternal affective communication was correlated with marital status (*rho* = -.35, $p < .05$) and infant age (*rho* = .438, $p < .01$); maternal disoriented behavior was correlated with marital status (*rho* = -.327, $p < .05$), BMI (4M) (*rho* = .393, $p < .05$), waistline (4M) (*rho* = .380, $p < .05$) and smoking (P) (*rho* = .385, $p < .05$); and maternal withdrawing behavior was correlated with medication use (4M) (*rho* = -.410, $p < .05$).

Regarding the HCC assessments, maternal HCC-4M was correlated with waistline (4M) (*rho* = .403, $p < .05$). Maternal HCC-P was correlated with education level (*rho* = -.437, p < .01), BMI (P) (*rho* = .412, p < .05), and waistline (4M) (*rho* = .474, p < .01). No other covariates were significant. These significant covariates were controlled for in further regression and mediation analyses with the relevant dependent variables.

Insert Table 1 here

3.3. Main analyses

3.3.1. Relations among HCC-P, HCC-4M, and maternal disrupted interaction at 4 months

As shown in Table 2, there was a large and significant association between HCC-P and HCC-4M. A linear regression model, using FIML and bootstrap confidence intervals and controlling for relevant covariates (severe mental illness, symptomatic functioning in pregnancy, waistline (4M)), confirmed that maternal HCC-P strongly predicted maternal HCC-4M (β= .695, SE= .17, CI= .418, .968, p = .000). This large effect size indicates substantial stability in HCC from the third trimester to 4 months after giving birth.

Second, controlling for marital status, both HCC-P (β= .541, SE= .19, CI= .207, .817, p = .004) and HCC-4M (β= .415, SE= .18, CI= .092, .684, p = .020) significantly predicted overall level of disrupted maternal interaction at 4 months. These results indicate that the cortisol levels reflected in both pregnancy and postpartum HCC assessments are associated with the mother's disrupted face-to-face interaction with her infant at 4 months of age. Notably, HCC-P was particularly predictive of both disoriented and negative-intrusive aspects of maternal interaction at 4 months, with similar trends for HCC-4M (Table 2).

Insert Table 2 here

3.3.2. Relations between childhood abuse and maternal disrupted interaction at 4 months

As also shown in Table 2, there were no significant correlations between childhood abuse and maternal disrupted interaction or its subdimensions. However, when linear regression models were run, using FIML with bootstrap confidence intervals and the relevant

covariate (medication use), abuse significantly predicted maternal withdrawing behavior (β = .400, SE = .113, CI = 0.196, 0.568, p = .000), such that women who experienced more abuse demonstrated more withdrawing behavior while interacting with their infants. No other models were significant: overall level of disruption (β = .207, p = .207), affective communication errors (β = .150, p = .356), role-confused behavior (β = .054, p = .744), disoriented behavior (β = .089, p = .655), or negative-intrusive behavior (β = .197, p = .260). Thus, results indicated that abuse had a specific effect on early maternal withdrawal in face-to-face interaction but not on other forms of maternal disrupted interaction.

3.3.3. HCC as mediator between childhood abuse and maternal disrupted interaction at 4 months

Given the significant association between childhood abuse and maternal withdrawal, both HCC-P and HCC-4M were examined as mediators of this association. Contrary to hypotheses, childhood abuse was not significantly positively associated with HCC-P, and, in fact, the direction of the association was negative (β= -.221, SE= .19, CI= -.541, .053, p= ns). In contrast, HCC-P was positively, but not significantly, associated with maternal withdrawal (β= .249, SE = .397, CI= -.536, .743, p= ns). Accordingly, HCC-P did not mediate the relation between childhood abuse and increased maternal withdrawal (indirect effect: β= -.001, SE= .058, CI= -.108, .081, p= ns).

Childhood abuse *was* positively and significantly related to elevated HCC-4M (β= .402, SE = .231, CI= .002, .758, $p < .05$). However, HCC-4M was not related to maternal withdrawal (β= .120, SE = .241, CI= -.345, .445, p =ns), and HCC-4M was not found to be a significant mediator of the relation between abuse and withdrawal (indirect effect: β= .017, SE = .088, CI= -.588, .841, p =ns). Thus, these findings do not support a mediation model of the relations among abuse, HCC, and caregiving. Instead, childhood abuse affected HCC-4M

and also affected maternal withdrawing behavior in face-to-face interaction at 4 months, regardless of HCC levels.

3.3.4. Relations between severe psychopathology and maternal disrupted interaction at 4 months

Bivariate correlations revealed no significant relations between severe mental illness or current symptomatic functioning and any of the maternal interaction variables (Table 2). Linear regressions on overall maternal disrupted interaction, controlling for the relevant covariate (marital status), yielded similar results (severe mental illness: β= .050, SE= .187, CI= -.283, .346, *p* = ns; symptomatic functioning in pregnancy: GAF-S (P): β= -.184, SE= .138, CI= -.383, .076, *p* = ns; symptomatic functioning at 4 months: GAF-S (4M): β= -.167, SE= .169, CI= -.427, .127, *p* = ns).

3.3.5. HCC as mediator between severe mental illness, current symptomatic functioning, and maternal disrupted interaction at 4 months

Bivariate correlations indicated that both HCC-P and HCC-4M were significantly correlated with severe mental illness and symptomatic functioning in pregnancy, but not with symptomatic functioning at 4 months (Table 2). Linear regression models, with relevant covariates, confirmed these associations. Regression results were as follows: severe mental illness and HCC-P (β= .297, SE= .189, CI= .031, .700, p < .05; severe mental illness and HCC-4M (β= .428, SE= .158, CI= .140, .659, *p* <.01)), symptomatic functioning in pregnancy and HCC-P (β= -.225, SE= .145, CI= -.487, -.012, *p* <.05), symptomatic functioning in pregnancy and HCC-4M (β= -.404, SE= .164, CI= -.638, .-.036, *p* <.01)). Relevant covariates for the analyses were as follows: covariates HCC-P: education level, BMI (P), waistline (4M); covariates HCC-4M: waistline (4M)). Also, as reported earlier, both HCC variables were correlated with overall disrupted maternal interaction.

Though there was no direct relation between severe mental illness or current symptomatic functioning and maternal disrupted interaction (see above), indirect effects can occur even in the absence of a direct effect between two variables when both variables are significantly related to a third variable (i.e. HCC) (Hayes, 2009; Hayes, 2013). Because severe mental illness was based on a lifetime diagnosis established prior to participation in the study, HCC-P and HCC-4M were both potential candidates for an indirect effect linking severe mental illness to quality of maternal interaction at 4 months.

The first analysis examined severe mental illness as a predictor of disrupted maternal interaction, with HCC-P as a mediator (Figure 1). The indirect effect was significant (Table 3, Model 1). Although the direct path was not significant, given that both the *a* and *b* paths were significant and the indirect path was significant (Table 3), a significant mediation was confirmed (Hayes, 2013). Therefore, HCC-P mediated the relation between severe mental illness and overall disrupted maternal interaction, as illustrated in Figure 1.

Insert Figure 1 and Table 3 here

In addition, we examined HCC-4M as a mediator linking severe mental illness and disrupted maternal interaction (Table 3, Model 2). The indirect effect for this model was also significant ($\beta = .243$, SE= .118, CI= 077, .466, $p < .05$). These results indicate that maternal cortisol levels, both in pregnancy and at 4 months, mediate the relation between severe mental illness and mothers' disrupted interactions with their infants.

With regard to current symptomatic functioning in pregnancy, this variable was not always assessed temporally prior to the 4-month period indexed by the HCC assay in pregnancy. Therefore, given the lack of temporal priority of the proposed independent variable in relation to the proposed mediator, HCC-P was not assessed as a potential mediator

of the relation between current symptomatic functioning in pregnancy and quality of maternal interaction at 4 months. However, current symptomatic functioning in pregnancy *was* assessed temporally prior to assessment of HCC at 4 months, so HCC-4 was assessed as a mediator of the relation between current symptomatic functioning in pregnancy and disrupted maternal interaction at 4 months. This mediation analysis was also significant (HCC-4M β= -.172, SE= .103, CI= -.368, -.036, $p < .05$). Thus, higher levels of function in pregnancy mediated higher quality maternal interaction at 4 months though lower levels of HCC at 4 months.

4. Discussion

There were several important findings from this study. Most notably, HCC in pregnancy and at 4 months were both robustly related to both severe mental illness and to disrupted maternal interaction with the infant at 4 months. In addition, HCC at 4 months was significantly predicted by a history of childhood abuse. Furthermore, higher maternal HCC acted as one mechanism linking a diagnosis of severe mental illness and poorer current symptomatic functioning to maternal disrupted interaction with her infant. Importantly, this mediation effect of elevated HCC could be identified by the third trimester of pregnancy. Future studies might explore the estimation of a 'risk' range of values for HCC during mid-pregnancy that best predicts later disrupted interaction between mother and infant. Such efforts could contribute further tools for identifying infants and mothers at risk earlier than the first year of life and strengthen our understanding of intergenerational transmission of psychosocial risk.

Regarding our second hypothesis, results also indicated that a strong and stable relation existed between HCC-P and HCC-4M. This strong association suggests that elevated levels of chronic stress may be relatively continuous for the women in this sample. In addition, the strong correlation further suggests that HCC levels in pregnancy do not necessarily reflect

deviating cortisol patterns specific to pregnancy, particularly among women exposed to adversity. However, the intra- individual stability of HCC from pregnancy into the postnatal period, particularly among women experiencing adversity, is still poorly understood across risk groups and warrants further study.

The finding that cortisol levels at both assessments were related to disrupted maternal interaction with the infant at 4 months extends previous work that investigated maternal salivary cortisol basal levels in relation to disrupted maternal interaction. Crockett, Holmes, Granger, and Lyons-Ruth (2013) found that *lower* maternal salivary cortisol concentrations were related to higher levels of maternal disrupted interaction in the same face-to-face paradigm at 4 months, using the same assessment of maternal interaction as in the present study. These differences in direction of effect of salivary versus hair markers of stress in relation to maternal interaction are likely to reflect the fact that they measure different things, with salivary cortisol reflecting stress reactivity at a current time point and hair cortisol thought to reflect cumulative stress over a more extended time period. Mothers with more disrupted interaction seem to have higher levels of chronic stress as reflected in hair cortisol, but lower basal salivary cortisol levels and less reactivity to their infants' stress in the still-face procedure. In addition, sample differences may play a role in the different direction of effects, in that Crockett et al. (2013) were assessing an economically impoverished community sample of women, whereas the present sample consisted of more economically advantaged women with and without severe psychopathology. Possibly chronic poverty and severe psychopathology have different effects on cortisol regulation.

Previous studies on cortisol as a mechanism linking maternal adversity and caregiving behavior have primarily relied on assays from salivary cortisol. The concentration of cortisol in saliva is partly determined by the parotid metabolism of cortisol to cortisone. However, most saliva assays do not take this rapid conversion of cortisol to cortisone into account and

may therefore not yield an accurate estimate of free cortisol (Perogamvros, Keevil, Ray, Trainer, 2010; Perogamvros, Owen, Keevil, Brabant, Trainer, 2010). In addition, acute cortisol levels, as measured by salivary cortisol, fluctuate markedly depending on a wide range of factors, including circadian rhythmicity, acute stress, alcohol consumption, food intake, nicotine, or even exercising (Stalder & Kirschbaum, 2012). Thus, salivary cortisol is strongly affected by the context of the measurement situation and may thus compare poorly to cortisol levels measured in hair (Stalder & Kirschbaum, 2012).

In contrast, the use of HCC is supported by accumulating evidence of the validity of HCC as an index of long-term systemic cortisol levels, its reliability across repeated measurements, and its relative robustness to potential confounding influences (Stalder & Kirschbaum, 2012). A single hair sample provides an integrated measure of chronic cortisol production, with one cm of hair reflecting one month of cortisol production (Stalder & Kirschbaum, 2012). Hair samples in the current study were 4 cm long, thus indexing 4 months of cortisol production. Such integrated cortisol levels over a longer time period obtained via HCC are likely to be more informative regarding effects of chronic maternal adversity on caregiving behavior. Furthermore, studies indicate that HCC can be used as a marker of overall maternal HPA activity during each trimester of pregnancy (Anna-Hernandez et al., 2011).

Our fourth hypothesis was that all three adversity indicators (childhood abuse, severe mental illness, and current symptomatic functioning) would be related to HCC. As noted above, both severe mental illness and symptomatic functioning in pregnancy were significantly related to elevations in HCC-P and HCC-4M, though symptomatic functioning at 4 months was not. In contrast, childhood abuse was significantly positively related to HCC-4M, but not to HCC-P, which trended negatively. This negative direction is consistent with prior work finding both positive and negative relations between childhood abuse and HCC

(Kalmakis, Meyer, Chiodo, & Leung, 2015; Schreier, Bosquet Enlow, Ritz, Gennings, & Wright, 2015) and suggests that abuse may be associated with cortisol hyporeactivity among some mothers during pregnancy. More work with larger samples is needed to explore how type, timing, and severity of abuse predicts hypo- versus hyper-reactivity of the cortisol system in the perinatal period.

In our fifth hypothesis, we expected that all three adversity indicators (childhood abuse, severe mental illness, and current symptomatic functioning) would be related to maternal disrupted interaction at 4 months. Previous research has linked maternal childhood abuse to the mother's caregiving behavior. Specifically, women with a history of sexual abuse displayed more flatness of affect and less maternal involvement with the infant, while mothers with a history of physical abuse were more hostile and intrusive with the infant (Lyons-Ruth & Block, 1996; Moehler et al., 2007). In the present sample, a history of childhood abuse was significantly associated only with early withdrawing behavior in face-to-face interaction and not with other forms of disrupted interaction. Though all studies document caregiving impairment, the differences in types of caregiving impairment across studies may reflect differences in types of abuse represented in the sample, in the ages of the infants at assessment, or in differences in observational formats for observing maternal behavior (e.g. face-to-face interaction vs free-play).

Notably, in relation to mediation by HCC levels, our results did not support a mediation role for HCC in the association between abuse and maternal withdrawing behavior, even though abuse was robustly related to elevated HCC at 4 months. Instead, number of types of abuse (sexual, physical, or emotional) was associated with increased maternal withdrawing behavior in interaction with the infant at 4 months, regardless of HCC levels. These findings related to abuse contrast with the findings related to severe psychopathology, where cortisol levels beginning in pregnancy were important mediators and were linked to overall disrupted

maternal interaction, characterized particularly by negative-intrusive behavior and disorientation in interaction with the infant (Table 2).

It is important to note that abuse and severe psychopathology are often co-occurring, as was the case here (Table 2). Most of the women experiencing abuse in this sample had also developed severe psychopathology (though not all of the women with psychopathology had been abused), and only one woman from the control group had experienced abuse. Therefore, the effects of abuse found here should be regarded as effects of abuse *in the context of concomitant psychopathology* and may not generalize to abused mothers with less severe, or other types of, psychopathology. However, in this study, the pattern of findings related to abuse and to severe psychopathology differed enough to suggest that the interrelations between abuse and psychopathology will be important to examine in future work. Future work with larger samples during the perinatal period should focus on clinical samples with and without a history of abuse, in order to evaluate how the interaction of abuse and psychopathology might affect maternal HCC and maternal caregiving behavior.

It remains unclear why abuse was significantly related to HCC-4M, with a medium effect size (r_s = .380) (Table 2), but not to HCC-P. It is possible that interacting with the infant in the months after birth may activate the mother's own childhood experiences of abuse and distress, leading to increased HCC at 4 months and to increased withdrawal from the infant. In a study by Martinez-Torteya, Dayton, Beeghly, Seng, McGinnis, Broderick, Rosenblum, & Muzik (2014), childhood maltreatment was not directly associated with maternal parenting at 7 months postpartum, but mothers who experienced childhood maltreatment were more likely to report postnatal psychosocial stress and depressive symptoms which, in turn, were associated with less positive and more hostile maternal parenting behaviors. This is similar to our finding that serious psychopathology, often preceded by childhood abuse, was not directly related to higher levels of disrupted interaction.

Instead, serious psychopathology was associated with higher HCC that, in turn, mediated higher levels of disrupted maternal interaction. Thus, future work should be targeted toward exploring a range of mediators of relations between maternal adverse experiences and maternal patterns of interaction with their infants.

The present study focused on childhood adversity in the form of childhood abuse, but childhood adversity in the form of neglect has also been shown to be an important factor in the development of psychopathology (Varese et al., 2012). Since neglect often occurs in the context of other types of maltreatment (Finkelhor, Ormrod, & Turner, 2007), future studies should also examine the impact of neglect on both maternal HCC and caregiving behavior in larger samples, with abuse controlled.

4.1. Limitations

The small sample size is a limitation of the current study and may limit generalization of our findings. In particular, due to recruitment constraints, the control group was limited to only 14 subjects and is thus much smaller than the clinical group. Small samples increase the risk for both Type I and Type II errors, so results should be regarded as provisional pending replication in additional studies. With additional research, meta-analyses can be conducted to provide more stable estimates of effect sizes linking maternal adversity, HCC, and maternal behavior across studies. Third, assessment of childhood abuse by means of a retrospective self-report measure, combined with a cross-sectional design, does not allow drawing definitive conclusions about any causal relationship between early adversity and caregiving behavior postpartum. Fourth, the abuse measure in the present study was limited to a few questions, and it is possible that a more detailed measure of childhood abuse might reveal a stronger relation between abuse and subsequent cortisol concentrations and parenting. Fifth, this study did not include measures of other stressful life events and did not include frequency of hair washing, both of which could affect HCC (Stalder, Steudte-Schmiedgen, Alexander,

Klucken, Vater, Wichmann, Kirschbaum, & Miller, 2017). In addition, it should be noted that we only asked about hair treatments 3 months prior to hair sampling, although segments of 4 cm hair were analyzed reflecting the prior 4 months. However, meta-analytic estimates (Stalder et al., 2017) concerning the influences of hair washing frequency and hair treatment suggest that under most circumstances their influences would be minimal. We found no correlation between HCC and hair treatment in this study. Finally, although great effort was made to collect hair cortisol in the third trimester, in three cases this was not possible due to scheduling conflicts, and hair was collected in the second trimester. These samples were included in the analyses to maintain maximum statistical power, though this could introduce bias into the examined associations.

The study also has several strengths, including the assessment of three types of maternal adversity among pregnant women with severe psychiatric diagnoses and non-clinical controls. Pregnant women with severe mental illness are rarely included in studies on cortisol and mother-infant interactions. Furthermore, we assessed hair cortisol in contrast to the more unstable measures of serum or salivary cortisol. Finally, the study considered multiple confounders related to HCC often overlooked in the study of cortisol.

4.2. Conclusions

The study found that maternal cumulative cortisol secretion, assessed during the third trimester of pregnancy and in the first 4 months after giving birth, mediated the impact of severe mental illness on disrupted maternal interaction with the infant at 4 months. Maternal childhood abuse was also associated with cortisol levels at 4 months but directly predicted maternal withdrawing behavior towards the infant regardless of cortisol levels. Our findings point to HCC as an important factor linking psychopathology and maternal behavior. Results also indicate that HCC may be a potential early biomarker for future caregiving challenges. Thus, future studies should explore further how HCC, both prenatally and in the early

postnatal period, can best identify women at risk for non-optimal caregiving. The results of the study point to a possible way to reduce disrupted caregiving by focusing on reducing maternal stress during the pre- and early postnatal period for mothers with severe mental illness. Furthermore, the findings indicate a need for reducing postnatal stress and supporting parenting in mothers with a history of childhood abuse.

Notes

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References

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed). Arlington, VA: American Psychiatric Publishing.

Anna-Hernandez, K., Ross, R.G., Natvig, C.L., & Laudenslager, M.L. (2011). Hair cortisol levels as a retrospective marker of hypothalamic–pituitary axis activity throughout pregnancy: Comparison to salivary cortisol. *Physiology & Behavior, 104*, 348–353.

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

Borges, S., Gayer-Anderson, C., & Mondelli, V. (2013). A systematic review of the activity of the hypothalamic-pituitary-adrenal axis in first episode psychosis. *Psychoneuroendocrinology, 38*, 603–611.

Crockett, E.E., Holmes, B.M., Granger, D.A., & Lyons-Ruth, K. (2013). Maternal disrupted communication during face-to-face interaction at 4 months: Relation to maternal and infant cortisol among at-risk families. *Infancy, 18*, 1111–1134.

Danese, A., Moffitt, T.E., Harrington, H., Milne, B.J., Polanczyk, G., Pariante, C.M., … Caspi, A. (2009). Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease. *Archives of Pediatrics & Adolescent Medicine, 163,* 1135-1143.

De Weerth, C. & Buitelaar, J.K. (2005). Physiological stress reactivity in human pregnancy—a review. *Neuroscience and Biobehavioral Reviews, 29*, 295-312.

do Prado, C. H., Grassi-Oliveira, R., Daruy-Filho, L., Wieck, A., & Bauer, M. E. (2017). Evidence for immune activation and resistance to glucocorticoids following childhood maltreatment in adolescents without psychopathology. *Neuropsychopharmacology*, *42,* 2272-2282.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., …

Marks, J.S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine, 14*, 245–58.

Finkelhor, D., Ormrod, R.K., & Turner, H.A. (2007). Poly-victimization: A neglected component in child victimization. *Child Abuse and Neglect, 31*, 7–26.

First, M.B., Williams, J.B.W., Karg, R.S., & Spitzer, R.L. (2016). Structured Clinical Interview for DSM-5 Disorders – Clinical Version (SCID-5-CV). Arlington, VA: American Psychiatric Association.

Fox, J. (2015). Applied regression analysis and generalized linear models. Sage Publications.

Gao, W., Stalder, T., Foley, P., Rauh, M., Deng, H., & Kirschbaum, C. (2013). Quantitative analysis of steroid hormones in human hair using a column-switching LC-APCI-MS/MS assay. *Journal of Chromatography B: Anal Technology Biomedical Life Science, 928*, 1–8.

Ghosh, D., & Vogt, A. (2012). Outliers: an evaluation of methodologies. Joint Statistical Meetings. American Statistical Association San Diego, CA, (3455-3460).

Gonzalez, A., Jenkins, J.M., Steiner, M., & Fleming, A.S. (2009). The relation between early life adversity, cortisol awakening response and diurnal salivary cortisol levels in postpartum women. *Psychoneuroendocrinology, 34,* 76–86.

Gonzalez, A., Jenkins, J.M., Steiner, M., & Fleming, A.S. (2012). Maternal early life experiences and parenting: the mediating role of cortisol and executive function. *Journal of the American Academy of Child and Adolescent Psychiatry, 51,* 673– 682.

Graham, J. W. *(2003).* Adding missing-data-relevant variables to FIML-based structural equation models. *Structural Equation Modeling, 10, 80-100.*

Harder. S., Davidsen, K., Macbeth, A., Lange, T., Minnis, H., Andersen, M.S., …

Gumley, A. (2015). Wellbeing And Resilience: Mechanisms of transmission of health and risk in parents with complex mental health problems and their offspring - The WARM Study. *BMC Psychiatry, 15*, 310-323.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication monographs, 76*, 408-420.

Hayes, A. F. (2013). Mediation, moderation, and conditional process analysis. In Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York: Guilford Publications.

Heim, C., Newport, D.J., Heit, S., Graham, Y.P., Wilcox, M., Bonsall, R., … Nemeroff, C.B. (2000). Pituitary-Adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood. *Journal of the American Medical Association, 284,* 1-6.

Juul, S.H., Hendrix, C., Robinson, B., Stowe, Z.N., Newport, D.J., Brennan, P.A., & Johnson, K.C. (2016). Maternal early-life trauma and affective parenting style: the mediating role of HPA-axis function. *Archives of Women's Mental Health, 19*, 17–23.

Kalmakis, K. A., Meyer, J. S., Chiodo, L., & Leung, K. (2015). Adverse childhood experiences and chronic hypothalamic–pituitary–adrenal activity. *Stress*, *18*, 446-450.

Luo, H., Hu, X., Liu, X., Ma, X., Guo, W., Qiu, C., ... & Hannum, G. (2012). Hair cortisol level as a biomarker for altered hypothalamic-pituitary-adrenal activity in female adolescents with posttraumatic stress disorder after the 2008 Wenchuan earthquake. *Biological psychiatry*, *72*, 65-69.

Lyons-Ruth, K., & Block, D. (1996). The disturbed caregiving system: relations among childhood trauma, maternal caregiving, and infant affect and attachment. *Infant Mental Health Journal, 17,* 257–275.

Lyons-Ruth, K., Bronfman, E., & Parsons, E. (1999). Atypical attachment in infancy and

early childhood among children at developmental risk. Part IV. Maternal frightened, frightening, or atypical behavior and disorganized infant attachment patterns. In J. Vondra & D. Barnett (Eds.), Atypical patterns of infant attachment: Theory, research, and current directions. *Monographs of the Society for Research in Child Development*, 64, 67–96.

Madigan, S., Bakermans-kranenburg, M.J., van IJzendoorn, M.H., Moran, G., Pederson, D.R., & Benoit, D. (2006). Unresolved states of mind, anomalous parental behavior, and disorganized attachment: A review and meta-analysis of a transmission gap. *Attachment & Human Development, 8*, 89–111.

Martinez-Torteya, C., Dayton, C.J., Beeghly, M., Seng, J.S., McGinnis, E., Broderick, A., … Muzik, M. (2014). Maternal parenting predicts infant biobehavioral regulation among women with a history of childhood maltreatment. *Development and Psychopathology, 26,* 379–392.

McCartney, K., Burchinal, M., & Bub, K. (2006). Best practices in quantitative methods for developmentalists. *Monographs of the Society for Research in Child Development, 71*, 1-8.

McEwen, B.S. (2003). Mood disorders and allostatic load. *Biological Psychiatry, 54*, 200–207.

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

Mills-Koonce WR, Propper C, Gariepy JL, Barnett M, Moore GA, Calkins S, Cox MJ. (2009). Psychophysiological correlates of parenting behavior in mothers of young children. *Developmental Psychobiology, 51*, 650-61.

Moehler, E., Biringen, Z., & Poustka, L. (2007). Emotional availability in a sample of

mothers with a history of abuse. American Journal of Orthopsychiatry, 77, 624–628.

Murphy, A., Steele, M., Dube, S.R., Bate, J., Bonuck, K., Meissner, P., … Steele, H. (2013). Adverse Childhood Experiences (ACEs) Questionnaire and Adult Attachment Interview (AAI): Implications for parent child relationships. *Child Abuse & Neglect, 38*, 224–233.

Muzik, M., Morelen, D., Hruschak, J., Rosenblum, K.L., Bocknek, E., & Beeghly, M. (2017). Psychopathology and parenting: An examination of perceived and observed parenting in mothers with depression and PTSD. Journal of Affective Disorders, 207, 242–250.

Perogamvros, I., Keevil, B.G., Ray, D.W., & Trainer, P.J. (2010). Salivary cortisone is a potential biomarker for serum free cortisol. *Journal of Clinical Endocrinology and Metabolism, 95,* 4951-4958.

Perogamvros, I., Owen, L.J., Keevil, B.G., Brabant, G., & Trainer, P.J. (2010). Measurement of salivary cortisol with liquid chromatography-tandem mass spectrometry in patients undergoing dynamic endocrine testing. *Clinical Endocrinologi* (Oxf), 72, 17-21.

Puff, J., & Renk, K. (2014). Relationships among parents' economic stress, parenting, and young children's behavior problems. *Child Psychiatry & Human Development*, *45*(6), 712-727.

Reijman, S., Bakermans-Kranenburg, M. J., Hiraoka, R., Crouch, J. L., Milner, J. S., Alink, L. R., & van IJzendoorn, M. H. (2016). Baseline functioning and stress reactivity in maltreating parents and at-risk adults: Review and meta-analyses of autonomic nervous system studies. *Child maltreatment*, *21*, 327-342.

Rigby, J., Conroy, S., Miele-Norton, M., Pawlby, S., & Happé, F. (2016). Theory of mind as a predictor of maternal sensitivity in women with severe mental illness. *Psychological Medicine, 46*, 1853–1863.

Rippe, R. C., Noppe, G., Windhorst, D. A., Tiemeier, H., van Rossum, E. F., Jaddoe, V. W., ... & van den Akker, E. L. (2016). Splitting hair for cortisol? Associations of socio-economic status, ethnicity, hair color, gender and other child characteristics with hair cortisol and cortisone. *Psychoneuroendocrinology*, *66*, 56-64.

Schechter, D.S., Zeanah, C.H., Myers, M.M., Brunelli, S.A., Liebowitz, M.R., Marshall, R.D., Coates, S.W., Trabka, K.A., Baca, P., & Hofer, M.A (2004). Psychobiological dysregulation in violence-exposed mothers: Salivary cortisol of mothers with very young children pre- and post-separation stress. *Bulletin of the Menninger Clinic, 68*, 319-336.

Schreier, H. M., Enlow, M. B., Ritz, T., Gennings, C., & Wright, R. J. (2015). Childhood abuse is associated with increased hair cortisol levels among urban pregnant women. *Journal of Epidemiological Community Health*, *69*, 1169-1174.

Stalder, T., & Kirschbaum, C. (2012). Analysis of cortisol in hair - State of the art and future directions. *Brain, Behavior, and Immunity, 26*, 1019–1029.

Stalder, T., Steudte-Schmiedgen, S., Alexander, N., Klucken, T., Vater, A., Wichmann, S., … Miller, R. (2017). Stress-related and basic determinants of hair cortisol in humans : A meta-analysis. *Psychoneuroendocrinology,* 77, 261–274.

Staufenbiel, S.M., Penninx, B.W.J.H., Spijker, A.T., Elzinga, B.M., & van Rossum, E.F.C. (2013). Hair cortisol, stress exposure, and mental health in humans: A systematic review. *Psychoneuroendocrinology,* 38, 1220—1235.

Steudte, S., Kolassa, I. T., Stalder, T., Pfeiffer, A., Kirschbaum, C., & Elbert, T. (2011). Increased cortisol concentrations in hair of severely traumatized Ugandan individuals with PTSD. *Psychoneuroendocrinology*, *36*, 1193-1200.

Steudte, S., Kirschbaum, C., Gao, W., Alexander, N., Schönfeld, S., Hoyer, J., & Stalder, T. (2013). Hair cortisol as a biomarker of traumatization in healthy individuals and posttraumatic stress disorder patients. *Biological Psychiatry*, *74*, 639-646.

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R.P. (2012). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin, 38,* 661–671.

Wolthke, W. Longitudinal and multi-group modeling with missing data. (2000). In Little, TD.; Schnabel, K.; Baumert, J., editors. Modeling longitudinal and multiple group data: Practical issues, applied approaches and specific examples. Erlbaum; Mahwah, NJ: p. 269-281.

Yehuda R., Engel, S.M., Brand, S.R., Seckl, J., Marcus, S.M., & Berkowitz, G.S. (2005). Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *The Journal of Clinical Endocrinology & Metabolism, 90,* 4115-4118.

Van IJzendoorn, M. H., Schuengel, C., & Bakermans-Kranenburg, M. J. (1999). Disorganized attachment in early childhood: Meta-analysis of precursors, concomitants, and sequelae. *Development and psychopathology*, *11*, 225-250.

*Table 1. S*ample Characteristics and Distribution of Main Study Variables

Characteristics	***n***	***n (%)***	***M***	***SD***	***Median***	***Percentile***
Demographics						
Education:	44					
≤ Upper secondary education		36 (81.9)				
Race/ethnicity:	44					
White		43 (97.7)				
Asian		1 (2.3)				
Married/living with partner (yes)	44	39 (88.6)				
Primipara (yes)	44	34 (77.3)				
Age (years)	44		30.0	4.47		
Maternal adversity indicators						
Number of abuse types*	44		.59	.84		
More than one type of abuse	44	6 (13.6)				
Symptomatic functioning, P**	44		74.95	14.80		
Symptomatic functioning, 4M**	39		72.95	13.70		
Lifetime diagnosis of severe mental illness (yes)	44	30 (68.2)				
Maternal disrupted interaction						
Overall disrupted interaction	38		4.16	1.67		
Affective communication errors	38		3.79	1.82		
Role confusion	38		2.79	1.45		
Disorientation	38		3.50	1.31		
Negative-intrusiveness	38		3.61	1.72		
Withdrawal	38		2.13	1.04		
Hair Cortisol Variables						
Hair cortisol, P***	38				7.63	4.21, 11.16
Hair cortisol, 4M***	30				7.70	3.84, 12.51
Use of medication, P	39	19 (43.2)				
Use of medication, 4M	38	21 (47.7)				
Cigarette smoking, P	40	6 (15.0)				
Cigarette smoking, 4M	36	7 (19.4)				
Body mass index, P	39		29.62	4.89		
Body mass index, 4M	33		26.85	5.45		
Hair colored, P	37	3 (8.1)				
Hair colored, 4M	32	6 (18.8)				
Gestational age (weeks)	44		34.4	4.2		
Infant age at 4M (weeks)	41		17.68	2.90		
Infant diet	38					
Breastfeeding		16 (36.4)				
Formula		12 (27.3)				
Combination		10 (22.7)				

*Maternal childhood abuse assessed as emotional, physical or sexual abuse. Arithmetic number of abuse types mean and SD. **Assessed from the GAF during 3rd trimester of

pregnancy and postnatally at 4 months infant age. ***Hair cortisol concentration arithmetic median and percentiles, 25^{th} / 75^{th}.

Table 2. Spearman Correlations Among Study Variables of Interest

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. HCC-P	-------											
2. HCC-4 M	.614**	-------										
3. Overall disrupted interaction	.431*	.444*	-------									
4. Subtype: Affective comm. errors	.255	.161	.823**	-------								
5. Subtype: Role confusion	.058	.288	.450**	.254	-------							
6. Subtype: Disoriented behavior	.489**	.323†	.809**	.657**	.279†	-------						
7. Subtype: Negative-intrusion	.387*	.355†	.792**	.757**	.194	.783**	-------					
8. Subtype: Withdrawal	.132	.161	.267	.289†	.110	.247	.282†	-------				
9. Abuse	.083	.380*	.239	.162	.110	.271†	.308†	.232	-------			
10. Severe mental illness	.356*	.419*	.035	-.097	-.196	.101	.030	-.222	.468**	-------		
11. Current symptomatic function (P)	-.377*	-.391*	-.193	-.183	.066	-.169	-.195	-.073	-.526**	-.766**	-------	
12. Current symptomatic function (4M)	-.258	-.240	-.081	-.007	-.003	-.178	-.210	-.079	-.555**	-.636**	.750**	-------

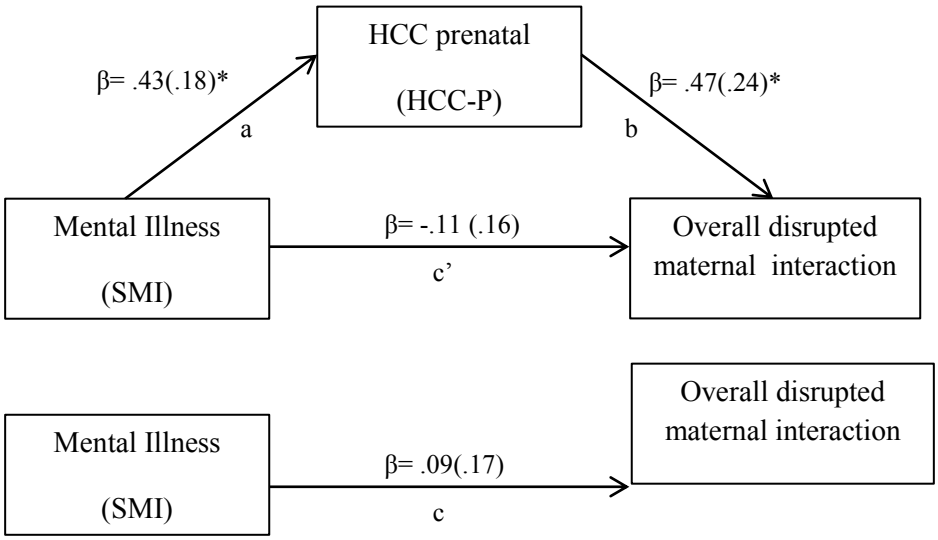
Note: Abuse and hair cortisol variables are log-transformed. †p <.10, *p < .05, ** p < .01; HCC-P = maternal hair cortisol during pregnancy; HCC-4M= maternal hair cortisol at infant age 4 months; N's range from 23 to 44.

Table 3. Mediation Results

	Predictor to Mediator (Path a)			Mediator to outcome (Path b)			Predictor to outcome (direct effect, c')			Total effect (c)			Indirect effect		
	β	**SE**	**CI**	**β**	**SE**	**CI**	**β**	**SE**	**CI**	**β**	**SE**	**CI**	**β**	**SE**	**CI**
Model 1 Predictor = SMI Mediator = HCC-P Outcome = Disrupted interaction	.430*	.181	.052, .670	.467*	.235	.090, .806	-.113	.159	-.369, .125	.088	.17	-.192, .368	.201*	.127	.039, .451
Model 2 Predictor = SMI Mediator = HCC-4M Outcome = Disrupted interaction	.484*	.138	.194, .658	.502*	.191	.167, .776	-.169	.162	-.432, .092	.074	.162	-.193, .330	.243*	.118	.077, .466
Model 3 Predictor = CSF (P) Mediator = HCC-4M Outcome = Disrupted interaction	-.409*	.141	-.612, -.154	.421*	.179	.107, .696	-.016	.121	-.216, .179	-.188	.124	-.370, .040	-.172*	.103	-.368, -.036

Note: SMI = severe mental illness; CSF (P) = current symptomatic functioning in pregnancy; HCC-P = maternal hair cortisol during pregnancy; HCC-4M= maternal hair cortisol at infant age 4 months. Indirect effect is significant if bias corrected CI does not contain zero. *$p < 0.05$.

Figure 1. Mediation Model of Maternal HCC in Pregnancy Mediating the Relationship Between Severity of Mental Illness and Overall Disrupted Maternal Behavior at 4 Months



Note: The values in the figure are coefficients (bootstrap standard error) for each path. Path a, direct effect of mental illness on HCC during pregnancy. Path b, direct effect of HCC during pregnancy on overall disrupted maternal behavior. Path c', direct effect of mental illness on disrupted behavior. Path c, total effect of mental illness on disrupted behavior. Indirect effect β= .201, SE= .12, $p < .05$ [95% CI = .039, .451]. *$p < 0.05$.