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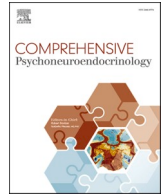
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Salivary cortisol reactivity in 6-month-old infants of mothers with severe psychiatric disorders: findings from the face-to-Face Still-Face paradigm

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ABSTRACT

Background.

Maternal psychopathology is associated with altered HPA axis functioning in offspring. Most studies have focused on mildly affected populations, but less is known about the effect of severe maternal psychopathology. In our explorative study we investigated in a heterogenic sample of mothers with severe and long-lasting psychiatric disorders, if a diagnosis of depression and severity of general maternal psychiatric symptomatology were associated with infant salivary cortisol reactivity to the Face-to-Face Still-Face (FFSF) paradigm at 6 months of age.

Methods.

A clinical sample of 36 mother-infant dyads was explored. All mothers fulfilled criteria for a severe psychiatric disorder and had psychiatric complaints for the last two consecutive years. Maternal diagnosis was established during pregnancy using a diagnostic interview and general maternal psychiatric symptom severity was established by self-report at the time of the FFSF procedure. The FFSF paradigm was used to assess infants' response to social stress at the age of 6 months. Infant saliva samples were collected at three time points: 5 min before and 15 and 30 min after the social stressor. Cortisol reactivity was operationalized as incremental Area Under the Curve (AUCi). Potential confounders were identified and adjusted for.

Results.

In regression analyses, a negative relationship was found between infant cortisol reactivity (AUCi) during the FFSF paradigm at 6 months and general maternal symptom severity at time of the FFSF paradigm (unadjusted $n = 36$, $\beta = -0.331$, $B = -9.758$, $SE = 4.8$, $p = .048$; adjusted $n = 36$, $\beta = -0.335$, $B = -9.868$, $SE = 4.5$, $p = .039$) and for diagnosis of perinatal depression at trend level (unadjusted $n = 36$, $\beta = -0.293$, $B = -8.640$, $SE = 4.8$, $p = .083$; adjusted $n = 36$, $\beta = -0.317$, $B = -9.347$, $SE = 4.6$, $p = .052$). Analyses were adjusted for gestational age.

Conclusions.

Preliminary results on cortisol reactivity in 6-month-old infants of mothers with severe and long-lasting psychiatric disorders show a significant reduction in the group of mothers who experienced a high level of psychiatric symptoms in the post-partum period, compared to mothers with lower levels of psychiatric symptomatology. The same trend was found for mothers with and without a diagnosis of perinatal depression. Since these infants are considered to be at increased risk for later psychopathology, our study suggests that future longitudinal studies should investigate whether reduced cortisol reactivity in babies could be a marker for any adverse outcomes, besides other possible risk factors (e.g. (epi)genetic phenomena).

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1. Introduction

Severe maternal psychopathology may deeply impact child outcomes. Previous studies have shown that infants affected by maternal depression have reduced resilience and higher risks for psychiatric disorders and other health issues [1]. More specifically, previous literature suggests that maternal psychopathology can cause early disturbance of infant HPA-axis functioning. This disturbance might be a mechanism that explains the higher vulnerability to both mental and physical disease [2]. Most research on HPA-axis functioning in infants of mothers with mild psychopathology has reported mixed results, with both hyper- and hypo-activation of the infant stress system [3]. However studies found that under extremely stressful conditions children showed reduced rather than increased cortisol responses to stressors [4,5]. A recent study showed this might be transmitted by genetic factors as well, as a history of maternal childhood maltreatment was associated with downregulation of cortisol in newborns [6]. Thus, both over- and under-activation should be considered as a form of dysregulation and as potential outcomes of the impact of maternal psychopathology on child mental and physical development.

Assessment of salivary cortisol response to the Face-to-Face Still-Face (FFSF) paradigm is a widely adopted experimental procedure to assess infants' response to social stress during the first months of life [7]. The FFSF paradigm consists of a three-step interaction of infant and adult, in which there is [1] a normal interaction episode [2], the episode of the 'still-face' in which the adult becomes unresponsive maintaining a neutral facial expression, and [3] a reunion episode with normal interaction. Most studies on the FFSF paradigm have demonstrated that infants respond by showing an increase of distress from baseline to still-face and a decrease of distress during the reunion phase [8].

Research in clinical populations on infant response to the FFSF paradigm has mainly focused on the impact of maternal depression, because maternal depression has frequently been associated with diminished emotional sensitivity and responsivity in both mother and child [9,10]. Previous studies on cortisol reactivity following the FFSF paradigm in clinical samples have shown inconsistent results. Two studies showed an increased infant cortisol response in infants of mothers experiencing depression and anxiety [11,12]. Another study did not find a relationship between maternal psychopathology and infant cortisol response [13].

To our knowledge, no studies to date have examined cortisol reactivity in response to the FFSF paradigm in infants of mothers with severe and long-lasting psychiatric disorders. Parental emotional sensitivity and behavioral responsivity are assumed to be crucial in the development of adequate stress regulation in infants [14]. A pattern of inadequate caregiving and/or emotional unavailability in the post-partum period is an important source of stress also for infants of mothers with broader psychopathology. Especially in the case of severe and long-lasting psychiatric disorders, mothers might be unable to adequately adjust focus to their infants' needs [15]. Considering this, the FFSF paradigm might not evoke a similar marked reaction – both emotionally, behavioral and biologically - in these infants as it would in infants of a less or unaffected mother, because of habituation of the infant to generally diminished responsivity of the mother. We hypothesized both persistence of higher symptom severity postpartum as well as depression might be associated with diminished cortisol reactivity in 6-month old infants. To explore these hypotheses, we assessed the influence of psychiatric symptom severity and an established diagnosis of depression in a high-risk psychiatric population of new mothers.

2. Methods

2.1. Study design and sample

The current study was embedded in an observational study on parenting capacity of mothers with severe psychiatric disorders and

their infant's development during the first year of life (INCAS study NL42662.078.12). For this purpose, multiple measurements were conducted in the patient group; the control group only participated at 6 weeks post-partum. It was approved by the Erasmus MC medical research ethics committee. Mothers were recruited in the third trimester of pregnancy from specialized Psychiatry-Obstetrics-Pediatric (POP) secondary and tertiary outpatient clinics and other specialized mental health care institutions where pregnant women who suffer from psychiatric disorders are treated. All fulfilled criteria for a current severe psychiatric disorder established with a validated instrument (SCID I [16], with at least two previous years of treatment, together with dysfunction, as indicated by lower scores (<65) on the Global Assessment of Functioning (GAF) scale [17]. The GAF scale rates impairment of social, occupational and psychological functioning, ranging from 100 (extremely high functioning) to 1 (severely impaired). Infant salivary cortisol was available for 43 mother-infant pairs during the FFSF paradigm when the infant was 6 months old. Mother-infant pairs ($n = 7$) were excluded from analysis based on the following predefined criteria [1]: use of locally administered or systemic corticosteroids by infant ($n = 0$) [2], insufficient amount of saliva for cortisol assay ($n = 1$) [3], perinatal complications including prematurity (<37 weeks) ($n = 3$) and [4] missing information on maternal symptom severity ($n = 3$). The final sample for analyses consisted of 36 mother-infant pairs with salivary cortisol measurements during the FFSF paradigm and information on maternal symptom severity.

2.2. Measures

2.2.1. Dependent variable

Salivary cortisol was obtained in a standardized amount of 100 μ l from infants 5 min before the FFSF paradigm and 15 and 30 min thereafter, using Salimetric Child Swabs (Salimetrics, State College PA) [18]. The duration of sampling was at least 60 s, but if the swab was not visibly saturated sampling was prolonged until (visible) saturation, or as long as the infant would allow the researcher. Samples were centrifuged for 10 min at 3000 rpm to extract the saliva and frozen at -80°C . Cortisol concentrations were quantified by solid phase extraction (SPE) liquid chromatography – tandem mass spectrometry (LC-MS/MS) (Waters XEVO-TQ-S system, Waters Corporation, Milford, MA, USA). Labeled glucocorticoids were present as internal standard. The Limit of Quantification (LOQ) in LC-MS/MS for salivary cortisol was 1.0 nmol/L. LLOQ were set where the precision was <20 % and the signal to noise ratio >10. Day-to-day precision was determined on two levels (low–high, resp. 0.98 and 17.0 nmol/L). The coefficient of variation (CV) was 6 % for both levels. For details on the LC-MS/MS procedure in our laboratory we refer to Noppe et al. [19].

Cortisol values at all three time points (C1 = baseline, C2 = 15 min after and C3 = 30 min after) were checked for outlying values (>3 SD above or below the mean). Outlying values (C1 $n = 4$, C2 $n = 0$, C3 $n = 2$) were winsorized using a conservative approach, by replacing the outlying value with the next highest (but not outlying) value in the dataset [7]. Measurements were log-transformed (10log) to approach normality. Missing data (C1 $n = 6$, C2 $n = 9$, C3 $n = 12$; 25 % (27/108) of data points; mainly caused by an insufficient volume of salivary for cortisol measurement) were imputed by multiple imputation (using 5 imputed data sets), using all suitable variables in our dataset. Both unimputed and imputed data were described. Repeated analyses including all outlying values resulted in similar results (results not shown). Uncertainty regarding the selection of the most suitable cortisol indices to measure reactivity has long been subject to debate. Pruessner and colleagues [20] recommend to use the area under the curve for analyses on datasets containing repeated measures of cortisol. The area under the curve with respect to increase (AUCi) best captures cortisol change over time [21] and was used as the dependent variable in our analyses.

2.2.2. Primary independent variable

Maternal psychiatric diagnosis was assessed in the third trimester of pregnancy with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID-IV) for all axis I psychiatric disorders (SCID I) [16]. Interviews were administered by a trained interviewer. Maternal diagnosis established with the SCID (depressive disorder y/n) was used as an independent variable.

Maternal symptom severity was evaluated with the Brief Symptom Inventory (BSI), which consists of 53 items on nine symptom dimensions (Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, and Psychoticism) [22]. The General Severity Index (GSI) represents the mean BSI score. BSI data were collected 6 weeks and 6 months postpartum; the GSI on both time points was highly correlated ($\beta = 0.857$, $SE = 0.09$, $p < .001$) suggesting stability of symptom severity over time. Normative data are available for clinical and non-clinical samples. Regarding maternal current symptom severity, mothers were classified as either higher or lower in symptom severity based on split of the GSI at the group median ($=0.83$), which is just below the cut-off score for Dutch outpatient clinical females ($=0.93$) closely resembling the healthy population [23].

2.2.3. Potential confounders

Potential confounders were explored based on theoretical and empirical grounds. The primary measure for reactivity of infant cortisol during the FFSF paradigm (AUCi) was checked for associations with all potential confounding variables available in our data (infant and maternal age, marital status, parity, maternal education level, maternal ethnicity (European or Non-European origin), maternal psychotropic medication use, smoking during pregnancy (yes or no), gestational age, birthweight, infant gender and feeding type (breastfeeding or formula feeding). Only gestational age was associated with infant cortisol reactivity at trend level ($p = .06$). Consequently, we included gestational age as a potential confounder in the analyses.

2.3. Analytic strategy

We used the Statistical Package for Social Sciences version 24 for all analyses conducted in this study (IBM, New York, USA). A sensitivity power analysis showed that within a sample size of 36 women we would be able to detect a medium to large effect size of psychiatric symptomatology including gestational age as a confounder ($f^2 = 0.23$) with 80 % power and a significance level of 5 % in a two-sided test (G*Power v3 [10,11]). In our study we found a medium effect size; f^2 was 0.12. Therefore we underline the fact this is an exploratory study and results have to be interpreted with caution. Multiple linear regression analyses were conducted using the imputed dataset. Assumptions of multiple linear regression (linearity, multivariate normality, absence of multicollinearity and homoscedasticity) were checked visually (scatterplots, histograms, Q-Q plots, P-P plots) and statistically (Mardia's test, tolerance, $>.2$ VIF <10 , Durbin-Watson between -2 and 2). The area under the curve with respect to increase (or change) (AUCi) was calculated based on imputed infant cortisol data, using the following formula: $\{[(15 \text{ min value} + \text{baseline value})/2] \times \text{time in minutes}\} + \{[(30 \text{ min value} + 15 \text{ min value})/2] \times \text{time in minutes}\} - [\text{baseline value} \times (\text{time} + \text{time})]$. Missing at random (MAR) assumption was tested. No significant differences were found when cases with and without missing data points were compared with regard to demographic, psychiatric and cortisol indices. Maternal symptom severity (lower/higher) and maternal depression (y/n) were regressed on infant AUCi, and adjusted for gestational age at birth. Imputed results are reported. We reported standardized beta (β) and unstandardized B (B) with accompanying standard error (SE). Analysis was repeated using the unimputed dataset, by means of a sensitivity analysis.

Table 1

Descriptive characteristics of mothers and infants ($n = 36$).

Mothers		
Demographic characteristics		range
Age, years ^a	32.6 (5.51)	19–44
Ethnicity		
• European origin	77%	
• Non-European origin	19%	
Married/partnered (yes)	81%	
Education level (higher professional or university education)	50%	
Parity (multiparous)	61%	
Smoking during pregnancy (yes) ^b	22%	
Psychotropic medication use during pregnancy (yes) ^b	53%	
Clinical characteristics		
Psychiatric disorder during pregnancy		
• SCID diagnosis of depression or dysthymia	47%	
• SCID diagnosis of anxiety	56%	
• SCID diagnosis (other) ^c	36%	
• General Severity Index (BSI) ^d 6 months pp	1.01 (.71)	
Infants		
Demographic characteristics		range
Age (months) ^e	5.7 (.53)	4–6
Gender (boy)	58%	
Gestational age (weeks) ^f	39.3 (1.70)	37–46
Birthweight (grams) ^f	3336 (465)	2040–4225

Note: with regards to psychiatric characteristics there is some overlap because of psychiatric comorbidity (i.e. depressive AND anxiety disorder).

Abbrev: The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (SCID); Brief Symptom Inventory (BSI).

^a Age at the moment of the Face-to-Face-Still-Face paradigm.

^b Psychotropic medication includes antidepressants (SSRI/nSRI/TCA), anti-psychotics, and anxiolytics.

^c Including bipolar and psychotic disorder ($n = 8$) and eating disorders ($n = 5$); diagnoses of addiction and PTSD were evaluated, but not present in this sample.

^d Mean reference range for Dutch outpatient clinical females: 0.93–1.32 and for healthy females: 0.29–0.45.

^e Values are mean (SD).

3. Results

Table 1 presents the descriptive characteristics of the sample. Depressive and anxiety disorders were most common (resp. 47 and 56 %) and psychiatric comorbidity was substantial (41 %). Approximately half of the patient group used psychotropic medication during pregnancy, mostly antidepressants. Median General Severity Index (GSI) of the BSI was 0.83 (0.4–2.75).

The analysis based on imputed data revealed a negative association between general maternal psychiatric symptom severity and infant AUCi (unadjusted $n = 36$, $\beta = -0.331$, $B = -9.758$, $SE = 4.8$, $p = .048$; adjusted for gestational age $n = 36$, $\beta = -0.335$, $B = -9.868$, $SE = 4.5$, $p = .039$). Unimputed data showed a similar result at trend level (unadjusted $n = 24$, $\beta = -0.421$, $B = -11.142$, $SE = 5.4$, $p = .051$; adjusted for gestational age $n = 24$, $\beta = -0.397$, $B = -10.487$, $SE = 5.4$, $p = .068$). Diagnosis of depression showed a negative association at trend level in imputed data (unadjusted $n = 36$, $\beta = -0.293$, $B = -8.640$, $SE = 4.8$, $p = .083$; adjusted $n = 36$, $\beta = -0.317$, $B = -9.347$, $SE = 4.6$, $p = .052$). Unimputed data in 24 infants with availability of three subsequent cortisol measurements, showed a negative trend although not significant (unadjusted $n = 24$, $\beta = -0.155$, $B = -4.038$, $SE = 5.5$, p -value = .470; adjusted $n = 24$, $\beta = -0.174$, $B = -4.521$, $SE = 5.4$, p -value = .415). A regression table of all analyses is available as supplementary material. No significant differences were found between subgroups of mothers (lower vs. higher symptom severity and depression y/n) with regard to baseline characteristics (e.g. maternal age, ethnicity, education level,

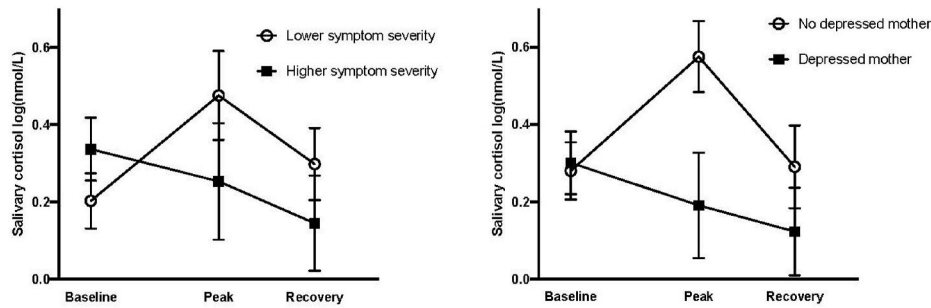


Fig. 1. Salivary cortisol log (nmol/L) 5 min before ('baseline') and 15 min ('peak') and 30 min ('recovery') after Face-to-Face Still-Face (FFSF) paradigm in 6 month old infants in infants from mothers a) with ($n = 17$) and without ($n = 19$) a depressive disorder and b) with high ($n = 18$) and low ($n = 18$) general maternal psychiatric symptom severity based on the Brief Symptom Inventory (BSI). Note: standard errors are reported.

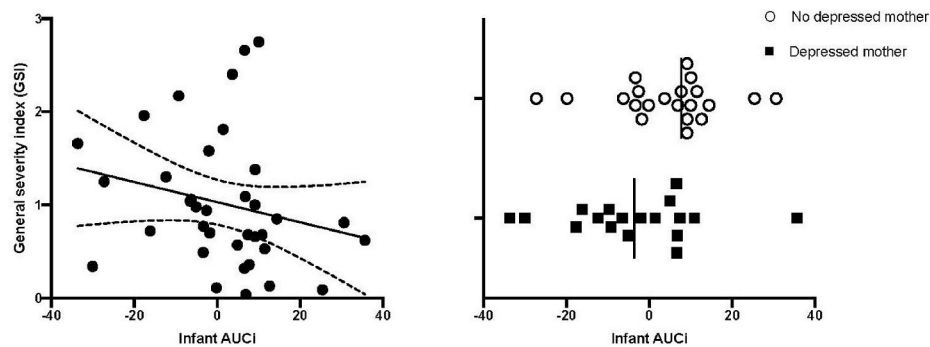


Fig. 2. Scatterplot of the maternal General Severity Index (GSI) (left) and presence of a depressive disorder (right) and the incremental area under the curve (AUCi) of three salivary cortisol measurements before and after Face-to-Face Still-Face (FFSF) paradigm in 6 month old infants in infants.

smoking or psychotropic medication use). Fig. 1 depicts infant salivary cortisol reactivity before and during the FFSF paradigm within groups of mothers with lower vs. higher symptom severity and mothers with depressive disorders (y/n). Fig. 2 shows scatterplots of the correlation between the infant cortisol AUCi during the FFSF paradigm and the maternal GSI (left) and presence of a depressive disorder (y/n) (right).

4. Discussion

This explorative study is among the first to examine the association between severe maternal depression and general psychiatric symptom severity and infant cortisol reactivity. We hypothesized both persistence of depression and higher symptom severity postpartum in a group of mothers with severe and long-lasting psychiatric disorders would be associated with diminished infant cortisol reactivity. Our preliminary results show diminished cortisol reactivity during the FFSF paradigm in 6-month-old infants of mothers with a high concurrent level of general psychiatric symptoms. Generally, our findings are in line with previous studies in children living in high-risk environments, showing reduced rather than elevated cortisol responses to new stressors when conditions are chronically stressful [4,5]. Low cortisol levels and diminished reactivity to stressors have been found in adults with prolonged or recurrent depression or PTSD [24,25] as well as in infants of traumatized mothers [26]. We hypothesize this pattern might already be present in (very) early stages of life, as a subtype and early marker of HPA-axis dysregulation.

With regards to HPA-axis functioning, it is known that both too high and too low cortisol levels contribute to disease states; balance is critical, particularly quick recovery following a perturbation [27]. Diminished cortisol responses possibly reflect lower responsivity to social stressors associated with chronic maternal emotional unavailability. Different studies, mostly in mothers with depression, have demonstrated that these mothers behave less adequate toward their infants [8]. However,

this effect is not consistently reflected in infants' behavioral responses during FFSF paradigm; some infants show less distressed behavior than control infants [9], whereas other studies find higher arousal and more negative infant behavior (e.g. gaze aversion) [28,29]. Possibly, the same pattern applies to infant cortisol reactivity during the FFSF paradigm, with the addition that the most chronically deprived infants might show diminished reactivity as opposed to a more clearly marked reaction in their less or non-deprived counterparts. A possible explanation might be a dose-response relationship between maternal "stress" (coming from different sources, i.e. the severity of their psychiatric complaints, their psychiatric and possible maltreatment history as well as from difficult life circumstances) and more pronounced alterations (both higher and lower) in the infants' (cortisol) reactivity to maternal non-responsiveness. This might be the reason other studies found enhanced [11,12] or no [13] cortisol reactivity in relation to the FFSF paradigm, as these samples consisted of low-risk or mildly affected populations.

It is often hypothesized deviations of cortisol measures (high or low) directly point to impairment or 'disease states'. But as the HPA axis is an adaptive biological system, it might be more accurate to view changes in activity and reactivity of cortisol markers as an adaptation to 'non average' circumstances. In our population of infants, it could be hypothesized the infant (and consequently the infant HPA axis) is not so easily 'impressed' by a relatively minor trauma like the still-face procedure. This adaptation of the HPA axis could also be seen as a change intended to promote resilience under these specific circumstances [30].

Our study has several strengths and limitations. Limitations include the absence of a control group. As a result, we only assessed variations within infants with a psychiatrically affected mother. Additionally, our sample size was limited. Following our power calculation, we had an 80 % chance that a medium to large effect size would result in a significant result. We cannot rule out that our results, although significant and robust across analysis, might reflect a spurious effect instead of a true

effect. Furthermore, information on feeding and napping time was not available, two factors that might affect cortisol reactivity in infants.

The foremost strength is our diverse sample, that brings into focus a more severely affected clinical population. The fact we found between-group differences in this sample might point to the potentially great impact of symptom severity, with the caution of spurious effects. Further strengths are the availability of detailed and reliable diagnostic information in mothers. To date, most studies have focused on enhanced stress reactivity in at-risk infants; our preliminary results show reduced cortisol responses in infants from the most affected mothers (both in relation to depression and general psychiatric symptom severity). This finding highlights the need to elucidate the mechanisms of early HPA-axis development (and the complex interplay of gene x environment phenomena) in the subgroup of infants from mothers with severe and long-lasting psychiatric disorders to better understand the trans-generational transmission.

Conflict of interest

None.

CRediT authorship contribution statement

Carlinde W. Broeks: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Rianne Kok:** Conceptualization, Data curation, Funding acquisition, Methodology, Writing – review & editing. **Vandhana Choenni:** Conceptualization, Data curation, Funding acquisition, Methodology, Writing – review & editing. **Rien Van:** Writing – review & editing. **Witte Hoogendijk:** Writing – review & editing. **Manon Hillengers:** Writing – review & editing. **Astrid Kamperman:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Mijke P. Lambregtse-Van den Berg:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cpnec.2021.100078>.

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