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What Dyadic Reparation Is Meant to Do: An Association with Infant Cortisol Reactivity

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Key Words
Maternal anxiety disorder · Still-Face paradigm · Interactive repair · Infant cortisol reactivity · Self-comforting behaviors · Distress during pregnancy

Abstract
Background: The latency to reparation of interactive mismatches (interactive repair) is argued to regulate infant distress on a psychobiological level, and maternal anxiety disorders might impair infant regulation. ***Sampling and Methods:*** A total of 46 dyads (19 mothers with an anxiety disorder, 27 controls) were analyzed for associations between interactive repair and infant cortisol reactivity during the Face-to-Face-Still-Face paradigm 3–4 months postpartum. Missing cortisol values (n = 16) were imputed. Analyses were conducted on both the original and the pooled imputed data. ***Results:*** Interactive repair during the reunion episode was associated with infant cortisol reactivity (original data: $p < 0.01$; pooled data: $p < 0.01$) but not maternal anxiety disorder ($p > 0.23$). Additional stepwise regression analyses found that latency to repair during play ($p < 0.01$), an interaction between distress during the first trimester of pregnancy and latency to repair during reunion ($p < 0.01$) and infant self-comforting behaviors during the reunion episode ($p = 0.04$) made independent contributions to cortisol reactivity in the final regression model. ***Conclusions:*** This is the first study demonstrating that interactive repair is related to infant psychobiological stress reactivity. The lack of a relation to maternal anxiety disorder may be due to the small sample size. However, this result emphasizes that infants respond to what they experience and not to the maternal diagnostic category.

Introduction

Exposure to high levels of stress during the early postnatal period is related to alterations in brain functioning [1]. A critical question is why some infants react to stressful experiences and others do not [2]. During the first months of life, HPA axis functioning is associated with the quality of the caregiver-infant interaction [3], which is argued to provide an external source of regulation [4]. Higher ratings of maternal sensitivity and dyadic coordination in infancy are associated with increased behavioral and physiological regulation [5, 6] and emotional resilience at older ages [7]. For example, the more sensitively the mother interacts with her 3-month-old infant, the better is the infant's cortisol recovery from an everyday stressor [8]. For the most part, existing studies utilize

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global ratings of maternal sensitivity. While sensitivity has proven to be critical for understanding attachment, it is recognized that sensitivity ratings are both multidimensional and global and do not specify what aspects of sensitivity are at work [9]. One putative mechanism underlying sensitivity might be interactive reparation [10, 11], which refers to the quality and form of the mutual regulation between infants and mothers. It is the capacity of both members of the dyad, infant and caregiver, to repair affective and behavioral uncoordinated (mismatching) states and consequently, stressful states change back to more positive and coordinated (matching) states [12]. The successful transformation of mismatching into positive matching states might account for an early form of implicit relational knowing that social interactions can be positive and repairable [13]. The establishment of this implicit knowledge of relationship might be of vital importance for infant emotional development. Recently, matching states were demonstrated to be associated with infant affective regulation [14]. Nevertheless, to our knowledge, there are no studies using microanalytical and psychobiological measurements which evaluate the hypothesis that short latencies to the reparation of microtemporal affective mismatching states scaffold infant regulation, whereas long latencies increase dysregulation and distress [15].

Infants have a repertoire of early self-regulatory behaviors (hand-to-mouth movements, nonnutritive sucking) that are thought to regulate infants' stressful experiences [16]. However, these self-directed regulatory behaviors (self-comforting behaviors) are limited in downregulating heightened affective states [17]. Furthermore, these self-comforting behaviors decrease with age as infants engage in more complex regulatory strategies by shifting attention, using objects and engaging with the caregivers [18]. Certainly, by 3 months of age, if not earlier, infants signal the caregiver to resume interaction if the dyad is in mismatching states (e.g. the caretaker is unresponsive) [9]. If these attempts fail to reestablish dyadic coordination, the infants experience negative affect and distress [19]. Chronic failure is likely to have negative effects on the infant's emotional, social and cognitive development [10, 19].

The developmental risk for infants of parents with affective disorders is well established [20] and might in part be mediated by an impaired mother-infant interaction. For example, dyads where mothers suffer from major depression show fewer positive matched states and longer latencies to reparation of mismatching states [21] during the Face-to-Face-Still-Face paradigm (FFSF) [22], an experimental paradigm in which infants experience a socio-emotional stressful event. Furthermore, infants of clinically depressed mothers use more self-comforting behaviors as a regulatory strategy compared to control infants, who engage in social monitoring to signal interactive re-engagement [23].

Dyads with anxious mothers, though less well studied than dyads with depressed mothers, also show interactive difficulties. In a study on depressed mothers and their 3-month-old infants [24], the authors found that mothers with high scores in the State-Trait-Anxiety Inventory (STAI) [25] interacted less positively and more intrusively than controls. In another study [26] in which participants with comorbid depression were excluded, mothers who were more anxious showed less sensitivity and emotional vocalizations in their interactions with their 10- to 14-month-old infants. A study on mothers with a generalized anxiety disorder according to DSM-IV criteria [27] suggested that mothers with this diagnosis were less responsive in the interaction with their 10-month-old infant, especially when a ruminating style of thinking was induced [28]. At older ages (7–12 years), it was found that anxious mothers interacted more intrusively and less warmly with their children, effects that were moderated by the child's expression of anxiety and mediated by the mother's experience of negative emotions [29]. Thus, the authors suggested that maternal anxiety is associated with reduced tolerance of children's negative emotions. It is also a frequent finding that anxious mothers demonstrate more insensitive behaviors compared to healthy controls [30], and as a consequence infants of anxious mothers might frequently lack sufficient regulatory scaffolding. Recently, excessive crying in infants was predicted by the mothers' anxiety disorder prior to pregnancy [31]. This dysregulation might in part underlie the increased risk for the development of mental disorders in infants of anxious caregivers [20].

It has been argued that an early and chronic dysregulation of the HPA axis may account for developmental risks [32] observed in infants of mothers with anxiety disorders. However, there are only few studies on the influence of maternal anxiety on infant psychobiology. In a study on 6-month-old infants of mothers with comorbid depression and anxiety, the infants were found to express significantly increased cortisol reactivity in comparison to control subjects [33]. Another study demonstrated that a prepartum maternal anxiety disorder and global measures of maternal sensitivity at 7 months postpartum independently predicted infant cortisol reactivity in the FFSF [34]. Furthermore, this research group demonstrated that the association between maternal sensitivity and infant distress was especially marked for infants of women who ex-

perienced a prepartum anxiety disorder [35]. However, anxiety disorders meeting DSM criteria have not been investigated sufficiently with regard to their influence on early dyadic regulation on a microtemporal level in combination with psychobiological measurements.

The FFSF is the prevailing method to investigate mother-infant interaction and the effects of distress on infants [36]. The experimental interruption of maternal engagement (still-face episode) is a socioemotional stressor to the infant [9, 36]. Affective and behavioral responses to the still-face are striking and include a decrease in positive affect, an increase in negative affect and infant behaviors that are aimed at changing the mothers' behavior and reducing stress such as gaze and self-comforting behaviors [9, 36]. Infants also show signs of physiological reactions of vagal tone [37, 38] and skin conductance [38, 39]. During the reunion episode, mother and infant are challenged to reestablish interactive coordination and mutual regulation following the stress of the still-face. This reunion episode is particularly informative regarding the regulatory quality of the interaction [40]; infants gaze more towards the mother and express more positive affect. Negative affect also decreases, though it may still be at higher levels than in the first play episode [40]. Although cardiac measures recover [41], it has been found that skin conductance remained high during the reunion episode [38]. In addition to these physiological markers of distress [37, 39], salivary cortisol concentrations were successfully used to quantify an increase in reactivity of the HPA axis in response to the still-face [42, 43].

The primary purpose of this study was to examine the influence of microtemporal interactive reparation and maternal anxiety disorders on infant cortisol reactivity. For this analysis, we concentrated on the challenging reunion episode of the FFSF. We expected that shorter intervals to interactive reparation would be associated with lower infant cortisol reactivity. Furthermore, we expected that infants of mothers with a diagnosed anxiety disorder would have increased cortisol reactivity in comparison to the control group and that the association between latency to repair and cortisol reactivity would be greater for dyads in the clinical group. Additionally, the associations of positive dyadic matching states, infant self-comforting behaviors and maternal distress during pregnancy with cortisol reactivity were examined. We assumed coordinated states to be negatively related and infant self-comforting as well as distress during pregnancy to be positively related to infant cortisol reactivity. Finally, using regression analyses we evaluated the independent contributions of these variables to infant cortisol reactivity.

Methods

Sample

This sample was part of a larger longitudinal study [44, 45]. The study protocol was approved by the ethics committee of the medical faculty, Ruprecht-Karls University, Heidelberg. Recruitment took place using flyers, newspaper advertisements and public birth announcements as well as by pregnancy screenings at the Heidelberg University Women's Hospital between July 2006 and October 2010. In total, 122 women were recruited for the larger study. Mental health disorders were diagnosed according to DSM-IV criteria. For the clinical group, comorbid acute axis I disorders and acute suicidal tendencies were exclusion criteria. The controls needed to have no current or antecedent mental health problems. For the present analyses, the following were excluded from the total sample: 14 dyads who met the diagnostic exclusion criteria, 37 dyads as recruited too late (entering the study later than age 4.5 months) and 2 dyads for whom the video recording failed. In the remaining subsample, 47 mothers agreed to salivary cortisol sampling of their infants. Infant medication (e.g. cortisone) was an exclusion criterion (n = 1). Furthermore, prematurity (defined as a gestational age at birth below the completion of the 37th week) and small for gestational age (as evaluated by obstetricians/gynecologists and/or pediatricians) were infant exclusion criteria. However, there were no such cases in the final sample (n = 46). It consisted of 19 dyads with mothers who had an anxiety disorder (clinical group) and 27 dyads with mothers who had no clinical diagnosis (control group). In the clinical group, 15 women suffered from more than one anxiety disorder, 12 women were diagnosed with a panic disorder with or without agoraphobia (or agoraphobia without history of panic disorder), 9 women had a generalized anxiety disorder, 8 women had an obsessive-compulsive disorder, 6 women were diagnosed with a social phobia, and 6 mothers had a specific phobia; 1 woman suffered from a posttraumatic stress disorder and 1 woman was diagnosed with an anxiety disorder not otherwise specified. All mothers had a prepartum onset of anxiety disorder and did not suffer from any somatic disease. The infants were born full term and had no congenital abnormalities. All APGAR scores were equal to or higher than 7. Maternal and infant demographic statistics are presented in table 1.

Procedure and Instruments

After arrival at the laboratory, the mothers were informed about the study aims and procedures and completed a questionnaire assessing their sociodemographic status. Written informed consent was obtained. The mother-infant interaction was assessed between the third and fourth month postpartum in a video laboratory of the Heidelberg University Hospital using the FFSF. The infant was secured in a booster seat in front of the mother who was briefed using a standard text. One camera focused on the infant while another was focused on the mother. A single screen, simultaneously displaying the two different frontal views, was created by transmitting both recordings through a split-screen generator.

The FFSF paradigm consists of three episodes. First, there is an initial face-to-face interaction in which the mothers are instructed to play with their infant as usual but without the aid of toys and pacifiers. Next, the still-face episode takes place, in which the mother turns her head aside while silently counting to 10 and then looks back at the infant but does not make any gestures, facial expressions or vocalizations, creating a prolonged state of interac-

Table 1. Maternal and infant demographics and tests on comparability of subgroups

	General	Control	Anxiety	t	Female	Male	t
Maternal age, years	32.4±5.1	33.2±4.8	31.3±5.5	1.27 (0.21)	31.5±4.9	34.1±5.3	1.64 (0.11)
Gestational age, weeks	39.6±1.3	39.7±1.4	39.3±1.3	0.96 (0.35)	39.7±1.3	39.2±1.4	1.15 (0.26)
APGAR (average)	9.4±0.7	9.4±0.7	9.4±0.7	0.44 (0.66)	9.4±0.8	9.4±0.5	0.18 (0.86)
Infant age, months	3.3±0.4	3.3±0.3	3.4±0.4	1.42 (0.16)	3.7±0.4	3.3±0.3	0.99 (0.33)
	General	Control	Anxiety	U	Female	Male	U
Maternal education							
University degree	25	15	10		17	8	
University entrance qualification	7	5	2	231.5 (0.54)	4	3	232.0 (0.99)
High secondary qualification	12	7	5		9	3	
Low secondary qualification	2	0	2		1	1	
Number of children							
1 infant	28	14	14		22	6	
2 infants	13	9	4	197.0 (0.13)	6	7	165.0 (0.07)
3 infants	5	4	1		3	2	
	General	Control	Anxiety	χ^2	Female	Male	χ^2
Marital status							
Married	32	22	10	2.67[a] (0.10)	21	11	0.74[b] (0.39)
Not married	10	4	6		8	2	
Infant gender							
Female	31	19	12	0.26[c] (0.61)	–	–	–
Male	15	8	7		–	–	–

Values are means ± SD or frequencies, as appropriate; p values are given in parentheses. Maternal age: min = 22.0, max = 43.0. Gestational age: min = 37.0, max = 41.9. APGAR: min = 7.0, max = 10.0. Infant age: min = 2.5, max = 4.3.

[a] 1 cell has expected count <5, minimum expected count is 3.81. [b] 1 cell has expected count <5, minimum expected count is 3.10. [c] 0 cells have expected count <5, minimum expected count is 6.20.

tional mismatch. Finally, the procedure ends with the reunion episode in which the mother resumes the face-to-face play with her infant. Each of the three FFSF episodes lasted 2 min and was ended by a tap from a research assistant from the adjoining room, which likewise served as the initiation of subsequent episodes.

Salivary cortisol is a valid marker for infant stress reactivity in early infancy [8, 44], despite the weak circadian organization of the HPA axis in early months [3, 46]. It was collected immediately prior to (C_1), immediately after (C_2) and 20 min after the FFSF paradigm (C_3). Infants sucked on a cotton pad until it was saturated. The saliva was then expressed and stored at –20°C until analysis. To account for possible effects of circadian rhythm on cortisol reactivity, we attempted to have the visits to the laboratory between 10.00 and 11.00 a.m. (mean = 10.9 a.m., SD = 1.7 h), though this was not feasible for every mother; 10 infants (21.7% of study sample) were assessed after 11 a.m. (mean = 13.4 a.m., SD = 1.58 h). Consequently, time of day was considered as a potential confounder. Moreover, since cortisol reactivity is strongly associated with daytime napping or feeding, the mothers were instructed to keep their infants well rested and well fed on their usual routine in order not to confound the cortisol assessment. Additionally, the time to and length of prior feeding and napping were considered as potential confounders.

Diagnosis of Maternal Anxiety Disorder

Following the FFSF, the German version of the Structured Clinical Interview for DSM-IV-disorders (SKID) [47] was administered to the mothers. According to the DSM-IV, anxiety disorders include generalized anxiety disorder, panic disorder with and without agoraphobia, agoraphobia without history of panic disorder, specific phobias, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and anxiety disorder not otherwise specified.

Coding of Mother-Infant Interactions

The behavior of the infants and mothers during the FFSF was coded by two trained and reliable coders using the German translation and revision of the microanalytical Infant and Caregiver Engagement Phases (ICEP-R) [48]. The coders were blinded to the hypotheses of the study and the maternal psychiatric status. The

ICEP-R phases combine information from the face, direction of gaze and vocalizations of the infants and caregivers. The ICEP-R engagement phases for the infant are negative engagement (further divided into withdrawn and protest), object/environment engagement, social monitor, and social positive engagement. The ICEP-R codes for the caregiver are negative engagement (further divided into withdrawn, hostile and intrusive), noninfant focused engagement, social monitor/no vocalizations or neutral vocalizations, social monitor/positive vocalizations, and social positive engagement. Additionally, for infants and cooccurring with the engagement codes, oral and manual self-comforting behaviors, distancing and autonomic stress indicators were coded. Oral self-comforting included the following: (1) the infants' initiated skin contact between their own body parts and their mouth, (2) the infants' initiated mouth contact to objects or (3) sucking on the caregiver's hand or fingers (self-initiated or not). Manual self-comforting behaviors are coded if the infants touch one hand with the other. Distancing and autonomic stress indicators occurred too rarely to be included in the analyses (distancing: mean = 0.06%; autonomic stress indicators: mean = 0.15% over the whole FFSF).

We coded the video tapes using the Noldus Observer VideoPro® coding system with 1-second time intervals; 20% (n = 9 dyads) were randomly selected and coded by the two independent study coders. The coders were not aware of coding reliability videos. Interrater reliability was determined for the categorical engagement phase codes on a second-by-second basis. It was computed using mean Cohen's κ [49] (κ = 0.82 for the infant codes; κ = 0.73 for the maternal codes). This interrater reliability is similar to those reported in previous studies [21, 50].

Matching states are defined as the mother and infant simultaneously exhibiting the same affective-behavioral state [15]. We concentrated on one type of match – positive social match. We assumed this coordinated state to be a sign of positive interaction [51]. A positive social match was defined as follows: the mother is in positive engagement or social monitor/positive vocalizations and the infant is in positive engagement or social monitor.

The primary independent measure, the latency to interactive repair, was calculated as the average time interval from positive social match offset to positive social match onset, that is, the average mismatch duration in seconds (play episode: mean = 10.46 s, SD = 8.57, min = 1.45, max = 36.56; reunion episode: mean = 9.45 s, SD = 5.31, min = 1.08, max = 20.79). Additional measures were relative time durations (for descriptive results multiplied by 100%) of positive social matching states and infant self-comforting behaviors, that is, the sum of seconds the dyads were in the positive social matching states divided by the time of the FFSF episode (play episode: mean = 17.38%, SD = 18.29, min = 0.00, max = 68.60; reunion episode: mean = 15.86%, SD = 13.63, min = 0.00, max = 55.00) and the sum of seconds in which infants engaged in either oral or manual self-comforting behaviors divided by the time of the FFSF episode (play episode: mean = 12.99%, SD = 21.43, min = 0.00, max = 94.00; still-face episode: mean = 15.30%, SD = 24.89, min = 0.00, max = 85.90; reunion episode: mean = 10.97%, SD = 17.27, min = 0.00, max = 76.70).

Assessment of Infant Cortisol Reactivity

Sampling, storage, transport and analysis of cortisol samples took place according to standard protocols [52]. The limit of detection of the used assay was 0.1–15.0 ng/ml. Intra-assay variances were 5.95% volume for 2.6 μg/100 ml, 1.59% for 17 μg/100 ml and 4.62% for 26.6 μg/100 ml. The C_1 value was missing for 2 infants of the sample, the C_2 for 1 infant and the C_3 for 13 infants. The reasons for these missing values were too small amounts of saliva and interruption of assessment by breastfeeding or by infants falling asleep. Average salivary cortisol values in the C_1 (mean = 1.29 ng/ml, SD = 1.41, min = 0.10, max = 7.10), the C_2 (mean = 1.30 ng/ml, SD = 1.34, min = 0.10, max = 6.50) and the C_3 measurement (mean = 1.05 ng/ml, SD = 1.00, min = 0.10, max = 3.90) were comparable to normative values [53]. Following analytical procedures [54], the area under the curve with respect to increase (AUC_I) was calculated as an index for infant cortisol reactivity. This measure is the integral of the curve resulting out of the three cortisol measures (C_1, C_2, C_3) and denotes the time distance between measurements in contrast to statistical tests for repeated measures. AUC_I is calculated with reference to the first value (C_1) and therefore measures the change over time. The AUC_I mean (mean = –5.06 ng/ml × min, SD = 19.31, min = –46.00 ng/ml × min, max = 39.20 ng/ml × min) was negative in our sample. This indicates that cortisol levels decreased from the baseline (C_1) to the C_2 and C_3 assessments. Given this finding, we separated infants whose AUC_I lay 1 SE (3.53 ng/ml × min) above zero to estimate the rate of responders. The procedure revealed 9 responders (30%) in the sample of infants who had cortisol values for all three points of measurement (n = 30). For the analyses, all infants were considered whether they were responders or not. The AUC_I was screened for outlying values defined as any value deviating more than 3 interquartile ranges from the median. No outlying values were identified. AUC_I was checked for associations with potential confounding variables (infant and maternal age, marital status, financial concerns, gestational age, PDA, breastfeeding, number of infants, Apgar values, daytime of assessment, time distance to and length of prior feeding and napping, count and length of daytime naps and nighttime awakes, sleeping arrangement, and childcare). No significant associations with confounders were found (all $p > 0.19$). Consequently, we excluded these variables as potential confounders.

Prenatal Emotional Stress Index

The Prenatal Emotional Stress Index (PESI) is a self-report instrument which assesses emotional distress during pregnancy separately for each trimester [55]. It consists of 33 items – 11 items per pregnancy trimester. The items assess anxiety, sadness, joy, distress, and tension of the mother via a visual analog scale ranging from 0 to 100%. The scale value is computed by summing the 11 items (2 items with reversed polarity) for each trimester and averaging the sum by the number of items, resulting in a PESI for each trimester ranging from 0 to 100. Cronbach's α revealed excellent reliability for our data (α = 0.91 for the first, 0.92 for the second and 0.93 for the third trimester). The correlations between the first and second trimester ($r = 0.87$, $p < 0.01$), between the second and third trimester ($r = 0.86$, $p < 0.01$) and between the first and third trimester ($r = 0.68$, $p < 0.01$) revealed a medium-to-high interscale consistency. Mean scores were 32.85 (SD = 26.61, min = 0.00, max = 92.27) for the first, 29.17 (SD = 22.24, min = 0.00, max = 83.18) for the second and 30.63 (SD = 22.88, min = 0.00, max = 85.45) for the third trimester. Compared to the descriptive results of Möhler et al. [55], the PESI was slightly increased. Their general mean in the nonclinical sample was 26.52 (SD = 14.29) compared to the general mean in our sample, which was 30.88 (SD = 22.23, min = 2.42, max = 86.97).

Statistical Analyses

We used the Statistical Package for Social Sciences (IBM® SPSS® v. 22.0.0.0) for all the analyses conducted in this study. Power estimations for the confirmative analysis were computed using G-Power v. 3.1.9.2 [56, 57]. Before carrying out the main analyses, we evaluated whether the list-wise case exclusions as described in Methods were valid for our data set. This was done using Little's MCAR (missing-completely-at-random) condition test [58]. The MCAR test evaluates whether the MCAR condition is fulfilled. If nonsignificant, differences between excluded cases and the remaining sample are unlikely. In addition, missing values are unlikely to depend on third variables. Consequently, the MCAR test was repeated for the study sample prior to the multiple imputation procedure. Furthermore, differences related to maternal age, gestational age, Apgar values, infant age, maternal education, number of children, and marital status between controls and their clinical counterparts and between males and females were explored (via t tests, U tests and χ^2 tests) to ensure comparability between the groups. Generalized linear modelling with robust maximum likelihood estimation was used, since the distributions of interactive variables were significantly skewed ($p < 0.01$ in Kolmogorov-Smirnov and Shapiro-Wilk test). Especially in small samples and between unequally sized groups, the general linear model may lack sufficient robustness against the violation of mathematical assumptions (e.g. normal distribution) and thus may lead to progressive statistical decisions [59]. Primary hypotheses were all tested in one model, avoiding the cumulation of α-errors. Variables were not centered. Thus, B-weights were not standardized. However, as an estimator for effect sizes, w^2 (χ^2/N) was computed for significant results. According to Cohen's conventions [60], $w^2 = 0.01$ are small, $w^2 = 0.09$ are medium-sized and $w^2 = 0.25$ are large effects. The critical α-error for the analyses was $\alpha = 0.05$. Empirical p values were one-tailed for the directional hypotheses. The α-errors of the additional analyses were not adjusted. To evaluate the independent contribution of additional variables of interest (e.g. positive social matching states, self-comforting behaviors and distress during pregnancy) to infant cortisol reactivity, a stepwise backward regression was chosen since a forward regression bears the risk of not selecting independent variables with small but meaningful effects. In backward regression, variables are stepwise eliminated if they do not prove to be a significant parameter for the criterion among the remaining variables.

Results

Preliminary Data Analyses

For the MCAR test, we considered the following variables: sociodemographic data (e.g. age, infant gender), distress during pregnancy (PESI), interaction variables and matching data (ICEP-R), cortisol data (including its potential confounders), data assessed at birth (e.g. gestational age), and breastfeeding. The test was nonsignificant ($\chi^2 = 1{,}056.24$, d.f. = 1,089, $p = 0.76$); the list-wise case exclusions were valid for our sample and the subpopulation was representative of the larger sample. In order to ensure comparability between the clinical and the control group and between males and females, the distribution of demographic and birth-related variables (e.g. gestational age) were compared using t tests, U tests and χ^2 tests. As demonstrated in table 1, no differences were found between the groups.

We only had complete cortisol data for 30 infants (65.2% of study sample), but the remaining infants had at least one valid measure. We estimated the missing values for these infants (n = 16, 34.8% of study sample) using multiple imputations [61] with all variables analyzed in this study as predictors according to standard practice [62]. Multiple imputations are a valid method of estimating missing data if the MCAR condition is fulfilled, as it was in the final sample ($\chi^2 = 706.24$, d.f. = 779, $p = 0.97$). We exceeded the recommendations [61] and estimated the missing values (n = 16) in 25 data sets (fully conditional, linear, two-way interaction between categorical variables, max 50 iterations). Estimated cortisol values were restricted to the limit of detection of the cortisol assay (0.1–15.0 ng/ml). The analyses were done on the original data set and in each of the 25 completed data sets. The results of the latter were then pooled. Consequently, two results are reported: one for the original data set and one pooled result for the imputed data sets. Means and SD of pooled imputed values and the pooled sample after the imputation procedure (averaged over the 25 data sets) can be found in table 2. A visual analysis of the iteration process revealed no systematic variations of estimated values. Variation occurred within the scope of random variations.

Primary Analyses

We used generalized linear modelling with robust maximum likelihood estimations to evaluate the primary hypotheses. The dependent variable was infant cortisol reactivity (AUC_I). We included maternal anxiety disorder (dummy coded) and latency to repair as main effects in the model. Additionally, we included an anxiety disorder × latency to repair interaction term to evaluate whether a potential effect of latency to repair differed between the groups. The analysis was adjusted for a potential effect of infant gender (dummy coded).

As demonstrated in table 3, there was no effect of anxiety disorder or infant gender. Additionally, the anxiety disorder × latency to repair interaction term was nonsignificant. The only significant main effect was for latency to repair (original data: $p < 0.01$; pooled data: $p < 0.01$) – the longer the latency to repair, the higher the infant's cortisol reactivity or the slower its decline. This ef-

Table 2. Pooled imputation results (averaged over 25 data sets) of infant salivary cortisol (ng/ml)

Assessment	Imputed values				Data after imputation (n = 46)			
	mean	SD	min	max	mean	SD	min	max
C_1 (2 imputed values)	1.59	0.67	1.11	2.06	1.31	1.40	0.15	7.10
C_2 (1 imputed value)	0.97	–	–	–	1.29	1.33	0.15	6.50
C_3 (13 imputed values)	1.14	0.82	0.23	3.02	1.07	0.96	0.15	3.95

Table 3. Generalized linear regression model on infant cortisol reactivity (AUC_I)

Parameter	B	SE	Lower 95% CI	Upper 95% CI	Wald χ^2	p
Original data (n = 30)						
Anxiety disorder	11.02	14.85	−18.08	40.13	0.55	0.23
Latency to repair	3.12	0.97	1.21	5.02	10.28	<0.01
Anxiety disorder × latency to repair	−1.55	1.16	−3.81	0.72	1.79	0.09
Female gender	−4.29	6.34	−16.71	8.14	0.46	0.25
Intercept	−29.19	12.13	−52.96	−5.41	5.79	<0.01
Scale	253.67[a]	71.75	145.72	441.60	–	–
Pooled data (n = 46)						
Anxiety disorder	7.34	13.71	−19.54	34.23	0.37	0.30
Latency to repair	2.01	0.85	0.34	3.68	5.92	<0.01
Anxiety disorder × latency to repair	−1.20	1.05	−3.25	0.85	1.46	0.13
Female gender	−6.82	5.64	−17.87	4.24	1.56	0.11
Intercept	−14.13	9.34	−32.43	4.17	2.62	0.07
Scale	316.42[a]	83.38	152.55	480.28	–	–

Wald χ^2: for pooled analyses, averaged over original and imputed data sets. Original data: likelihood ratio omnibus test compares the fitted model against the intercept-only model ($\chi^2 = 12.33$, $p = 0.02$). Pooled data: average likelihood ratio $\chi^2 = 7.76$, average $p = 0.12$.

[a] Maximum likelihood estimate.

fect was large for the original data ($w^2 = 0.34$) and medium-sized for the pooled data ($w^2 = 0.14$).

The power for this analysis was approximated for linear multiple regressions. The chance of finding a large effect ($f^2 = 0.35$) of single coefficients in our sample was $1 - \beta = 0.99$ ($1 - \beta = 0.93$ for original data). Medium-sized effects ($f^2 = 0.15$) could be detected with a power of $1 - \beta = 0.83$ ($1 - \beta = 0.66$ for original data). Only small effects ($f^2 = 0.02$) could not be sufficiently detected in our sample ($1 - \beta = 0.24$ for pooled data; $1 - \beta = 0.19$ for original data).

Additional Analyses

Pearson correlations were carried out to evaluate the associations of additional interactive variables in different episodes of the FFSF (positive social matching states and infant self-comforting behaviors) as well as the association of distress during pregnancy with infant cortisol reactivity (AUC_I) in the original and pooled data sets (table 4). Here, we exclusively present the pooled results, since they were more conservative. The correlation between cortisol reactivity and latency to repair was positive and significant during the play episode – the longer the latency to repair, the higher the infant's subsequent cortisol secretion or the slower its decline. Additionally, the relative time durations of positive social matches and infant self-comforting during the reunion episode were significantly associated with cortisol reactivity. The longer the duration of the matches and the less the infants engage in self-comforting behaviors, the lower their cortisol reactivity or the stronger its decline. Furthermore, maternal distress during the first trimester of pregnancy was significantly associated with infant cortisol reactivity be-

Table 4. Pearson correlations to infant cortisol reactivity (AUC_I)

		Latency to repair (play)	Positive social matches (play)	Positive social matches (reunion)	Self-comforting (play)	Self-comforting (still-face)	Self-comforting (reunion)	PESI 1st trimester	PESI 2nd trimester	PESI 3rd trimester
Original data (n = 30)	r	0.325	–0.270	–0.399	0.197	0.058	0.332	0.450	0.426	0.402
	p	<0.05	0.07	0.01	0.15	0.38	0.04	0.01	0.02	0.02
Pooled data (n = 46)	r	0.309	–0.214	–0.298	0.249	0.200	0.380	0.315	0.275	0.272
	p	0.03	0.08	0.03	0.08	0.11	0.03	0.04	0.05	0.05

Table 5. Final generalized linear regression model (Step 7 of backward procedure) on infant cortisol reactivity (AUC_I)

Parameter	B	SE	Lower 95% CI	Upper 95% CI	Wald χ^2	p
Step 7						
Self-comforting (reunion)	29.10	15.87	–2.76	60.97	11.64	0.04
Latency to repair (play)	0.65	0.28	0.11	1.20	5.98	<0.01
PESI 1st trimester × repair (reunion)	0.00	0.00	0.00	0.00	11.90	<0.01
Intercept	–18.03	5.85	–29.50	–6.57	9.61	<0.01
Scale	206.24[a]	57.44	93.59	318.89	–	–

Wald χ^2: averaged over original and imputed data sets. Step 7: likelihood ratio omnibus test compares the fitted model against the intercept-only model (average $\chi^2 = 15.72$, average $p = 0.002$).

[a] Maximum likelihood estimate.

tween the third and fourth month of infant age – the more maternal distress, the higher the cortisol reactivity or the weaker its decline.

To evaluate the unique and independent relation of latency to repair during the reunion episode with infant cortisol reactivity, we carried out a stepwise backward regression (generalized linear models) with latency to repair and all other significant associations from the correlation analyses in the pooled data as independent variables and infant cortisol reactivity (AUC_I) as the criterion. Furthermore, we were interested to see whether the effect of prepartum emotional distress during the first trimester of pregnancy was moderated by postpartum dyadic interaction or self-comforting behaviors. Consequently, we integrated interaction terms between the 'PESI 1st trimester' and self-comforting behaviors, positive matches and latency to repair. Table 5 presents only the pooled analyses of the final regression step (step 7). Steps 1–6 are reported in online supplementary appendix A (see www.karger.com/doi/10.1159/000439225 for all online suppl. material). The final model consisted of self-comforting behaviors during the reunion episode ($w^2 = 0.25$), latency to repair during play ($w^2 = 0.13$) and the interaction term between maternal perceived prepartum distress during the first trimester of pregnancy and latency to repair during the reunion episode ($w^2 = 0.27$). The effects of self-comforting behaviors and the interaction term were large [61]. Relative time duration of positive social matches during the reunion episode and latency to repair were significantly intercorrelated (play: $p = 0.02$; reunion: $p < 0.01$). Since all other independent variables in these analyses were not intercorrelated (all $p > 0.28$), multicollinearity can be excluded in the final model. Additionally, these analyses suggest that latency to repair during the reunion episode moderates the effect of distress during the first trimester of pregnancy.

Discussion

To our knowledge, this is the first study that supports the hypothesis that quicker reparation of dyadic mismatching states in early mother-infant interactions provides better psychobiological stress regulation in infants. Microanalytical data reveal that latency to positive social

matches is significantly associated with infant cortisol reactivity. Due to missing values in cortisol data, especially at the second post-FFSF assessment, we decided to impute missing data. The association between latency to repair and infant cortisol reactivity was significant in both the original and the pooled data. Multiple imputations are a valid method if missing values do not depend on any other variable in the data set and if all variables used in the analyses are used as predictors. Both conditions were fulfilled. Nevertheless, for the main analyses, results of both the original and the pooled data were presented, leading to the same inferences, that is, the shorter the duration of mismatch, the lower the infant's salivary cortisol output throughout the experimental paradigm. These results are in line with the predictions of the mutual regulation model of Tronick [15], which emphasizes the critical regulatory function of reparation. In addition, and as suggested in another study [39], these results support the idea that affective-behavioral regulation between caregiver and infant promotes better infant regulation at other somatic regulatory levels such as the HPA axis.

For the confirmatory analysis, maternal anxiety disorder was not found to be significantly associated with infant cortisol reactivity nor was the association between latency to repair and infant cortisol reactivity different between the groups. This lack of findings contradicts recent research [33–35], but at least one other study found that prepartum maternal anxiety disorder was not associated with infant physiological regulation [63]. Though somewhat unexpected, our finding for mothers with anxiety disorders is in line with research suggesting that some women with affective disorders, such as major depression, interact with their infants in relatively sensitive ways compared to other women with similar levels of depression [64]. In addition, in a critical study [65], it was observed that parenting difficulties in mothers with an anxiety disorder were only evident to a disorder-specific challenge. Of course, we might have failed to discover small effects, or for the original data set medium-sized effects, since the power was low. Furthermore, our clinical group was heterogeneous since we did not focus on specific anxiety disorders, which might have added to this null finding. This lack of consistency requires further research in larger and homogeneous samples. Nevertheless, the results reported in this study indicate that the actual quality of the reparatory process plays a central role in infant stress reactivity and that simply using diagnostic status as a marker of problematic infant regulation might not be adequate. Infants react to what they are experiencing and not to the diagnostic status of their mothers, and maternal diagnoses are hardly related in a one-to-one fashion to what the mothers actually do.

It must be noted that interactive reparations can be initiated mutually within a dyad [66]. Since we did not assess who initiated the interactive repair, we cannot infer that the mothers initiated the reparations. In another study of our group, however, it was demonstrated that latency to positive social matches is significantly associated with macroanalytical measures of maternal sensitivity [11], suggesting that it is maternal behavior that underlies reparations. Nevertheless, future studies might use time series analyses to determine the extent to which the caregiver or the infant is initiating reparations and compare those findings to more macroanalytical measures of maternal sensitivity.

Furthermore, the mean durations of interactive reparation were unexpectedly extended by approximately 10 s for both the play and the reunion episode. Weinberg et al. [67] reported marked lower mismatch durations of 2–6 s, while Reck et al. [21] found comparable latencies of interactive reparation. This might be explained by cultural differences between American and German samples or it may be due to differences in used methods and instruments. Additionally, it may be possible that we failed to observe some interactive matches due to the 1-second time interval used for the observation. If matches occurred below this time unit, we would have overestimated the mean mismatch duration. Future analyses could try to determine cultural influences on interactive reparation and use a higher time resolution in the observation of interactive matches.

We cannot draw causal conclusions between interactive reparation and infant cortisol reactivity. It is possible that high cortisol reactivity makes reparation to a positive dyadic state more difficult. Infants who respond to the FFSF with a higher release of cortisol might be less able to make appropriate adjustments to maternal signals because their arousal level narrows their perception or disrupts their behavior [68]. Thus, the finding raises the question of whether behavior is driving the cortisol response or the cortisol response is driving the behavior. More than likely, the two processes dynamically interact, but this question is beyond the aims of this study. To clarify this issue, future studies require longitudinal data regarding behavior and cortisol as well as a causal analytical approach.

There were marked individual differences in cortisol reactivity for the infants in this study. For the whole sample there was no mean increase in cortisol following the FFSF. This might be due to the fact that infant salivary

cortisol samples were only taken prior to, immediately after and 20 min after the FFSF. Consequently, we may not have had a full coverage of the possible cortisol peak times, though many studies have used similar intervals, as demonstrated in the review of Gunnar et al. [69]. This review also indicates that, on average, psychological stimuli (such as separation) do not provoke cortisol reactivity in young infants. Haley and Stansbury [70] were able to find an increase in cortisol reactivity following the double FFSF and an observation interval of 30 min after the stressor. As Haley [71] was able to replicate the finding, the double FFSF and this sampling interval might be appropriate for future studies on infant cortisol reactivity.

Additionally, it might be conceivable that the missing values accounted for the lack of cortisol increase. Nevertheless, this is unlikely since the missing values were random. However, a finding of a nonresponse in the mean value may be surprising given the established stressful nature of the FFSF. Nevertheless, some infants respond with an increase in cortisol to blood draws, whereas others respond to undressing, weighing and length measurement prior to the draw [72]. A low-to-medium rate of infant cortisol responders (30% for our original data) and thus a decrease in cortisol means is often found in infant and child stress research [2, 69]. It must be noted that the lack of reactivity does not imply that the measurement of cortisol reactivity in response to psychological stressors is not meaningful. Rather, it has been argued that the individual differences might bring to light factors that account for the individual differences as well as potential risk factors that may adversely affect infant development [2, 69]. Accordingly, the authors of the AUC_I procedure recommend proceeding with analyses even in the case of negative values, since it may be important even to explain a decrease. Respective indices must then be interpreted as an index of decrease over time [54]. Moreover, a dampening of cortisol responses to stressors in rodents and humans during early development [3] might play a role in our results. Although the reasons and duration of this dampening period is still unknown, there are many factors affecting stress reactivity. These include genetic influences [73], temperament differences [74], age-related changes [2], individual differences in sensitivity to the nature of the stimuli and contexts [69], and a sculpting of stress reactivity by interactive history [75].

Our findings lend some support to the sculpting hypothesis [75], in particular, that interactive reparation may play a role in maintaining low cortisol activity during this period. While we recognize that the observations of the interactions in this study were brief, it seems reasonable to assume that the quality of reparation is related to the dyad's typical patterns of interaction, as has been found for measures of sensitivity [51]. Thus, the differences in cortisol reactivity seen in this study may be chronically experienced and affect the functioning of the HPA axis. An early and chronic dysregulation of the HPA axis might account for the risk of developing mental or affective disorders later in life [32]. Such an interpretation is not exclusive of the role of other factors but fits with the hypothesis that quotidian stressors, especially microstressors such as mismatches, sculpt the regulating systems and lead to resilience or vulnerability depending on the quality of their resolution [10]. Nevertheless, the answer to this question was beyond the scope of this study. Future research might integrate repeated measures of caregiver-infant interaction over the course of development in different contexts to support this hypothesis.

The results of the additional analyses further revealed that the relative time durations of the positive social matches and infant self-comforting during the reunion episode, as well as perceived maternal distress during the first trimester of pregnancy, were associated with infant stress reactivity. However, in the backward regression procedure, the relative time duration of the positive social matches was no longer found to make an independent contribution in the used variable set, that is, only being in positive dyadic states for longer durations seems insufficient for affecting infant cortisol reactivity. Cortisol reactivity rather appears to need the flexible interplay between mismatching and positive matching states as indexed by latency to repair.

An effect of prepartum distress on infant cortisol reactivity is well established [76]. These observations refer to the phenomena of fetal programming [77–79]. Prepartum influences on the fetal HPA axis are said to occur via maternal cortisol overcoming the placental barrier [80]. Processes such as methylation of the CpG regions in the promotor region of the glucocorticoid receptor gene [78, 79] are suggested to be involved in these phenomena. Additionally, these influences might be especially marked during the first two trimesters of pregnancy, as the cortisol-degrading 11-β-HSD enzyme is not expressed in the fetus that early [81, 82]. According to this assumption, it was the distress during the first trimester of pregnancy which was associated with infant cortisol reactivity, underpinning the validity of our results. Of course, it would have been preferable to use maternal cortisol data as a predictor for infant cortisol reactivity. However, according to studies that suggest epigenetic programming to be modified by postpartum caregiving [63, 79], we found

that the association between distress during the first trimester of pregnancy and cortisol reactivity was moderated by postpartum interactive quality. In line with this research, the result suggests that prepartum alterations of the fetal HPA axis by maternal distress during pregnancy might be overcome by a well-adapted postpartum caregiver-infant interaction. Future research should involve longitudinal data including prepartum assessments of maternal cortisol as well as epigenetic data. Such studies could improve our understanding of the interplay between fetal programming and postpartum interactive history for infant stress reactivity.

In the final regression model, latency to repair during play was a significant medium-sized parameter for infant cortisol reactivity besides the interaction term between maternal prepartum distress during the first trimester of pregnancy and latency to repair during the reunion episode. Surprisingly, latency to repair between play and reunion were not intercorrelated, and both latency to repair during the play episode and the interaction term independently explained the variance of infant cortisol reactivity. Apart from low power, this might underline the macrotemporal divergence of contexts between the play and the reunion episode of the FFSF [67]. Perhaps the function of latency to repair might be different depending on the FFSF episode. In the play episode, interactive reparation might reflect the regulation of typical microtemporal stressors (mismatches), while in the reunion episode it might have the function of regulating the distress caused by macrotemporal disengagement of the still-face. This idea could explain why maternal prepartum distress during the first trimester of pregnancy only interacted with latency to repair during the reunion episode. It might be that the experience of regulatory success alone after a stressful event (such as the still-face) can counteract potential negative influences of maternal prepartum distress on the infant's stress regulatory system – the HPA axis. Future studies could examine this idea by characterizing dyads depending on their level of interactive reparation in both the play and the reunion episode as well as by varying the experimental paradigm (FFSF vs. free play).

Additionally, only self-comforting behaviors during the reunion episode after the socioemotional stressor of maternal disengagement in the still-face episode remained as a negative parameter along with latency to repair and the interaction between prepartum distress during the first trimester of pregnancy and latency to repair during the reunion episode. Though causal conclusions cannot be drawn, this finding might underline that self-comforting behaviors are not fully effective in regulating distress [17]. Rather, they may be a sign that the infant's self-regulating strategies are overtaxed [19]. Future analyses should investigate infant self-comforting behaviors more fully regarding their change during the FFSF and their associations with markers of infant distress. It would be interesting to know whether self-comforting behaviors significantly increase during the still-face and whether this increase is associated with cortisol reactivity or whether cortisol values taken prior to the experiment predict the increase of self-comforting behaviors. Furthermore, the role of maternal anxiety disorder regarding infant self-comforting behaviors remains unclear and should be analyzed in future studies.

It was also surprising that latency to repair and self-comforting behaviors were not negatively intercorrelated given the reported developmental shift from self-comforting behaviors to dyadic regulation [18]. Of course, given the small sample size an interpretation of null findings is limited. Nevertheless, it might be that self-comforting behaviors decrease after 4 months of age if dyadic regulation is well established, and both regulation strategies might exist in parallel. Future studies could address this issue by repeated observations throughout the first year of life.

Summary of Limitations

The validity of null findings (especially for small and medium-sized effects) cannot be fully evaluated given the small sample size. The clinical group was heterogeneous, since we did not concentrate on specific anxiety disorders. The data assessment for the main finding was cross-sectional. Consequently, we cannot draw causal conclusions. Additionally, we cannot draw conclusions on who initiated the reparation, since we did not apply lagged time series analyses. Infant salivary cortisol samples were only taken prior to, immediately after and 20 min after the FFSF. Consequently, we may not have had full coverage of possible peak cortisol reactivity times, which may in part account for the negative mean cortisol reactivity. As we had no maternal cortisol data from the prepartum period, it was not possible to validate the subjective and retrospective reports of perceived distress during pregnancy. Missing values in the cortisol assessment were imputed, which potentially can decrease the external validity for the pooled data. Our sample contains a greater proportion of controls, academic mothers and female infants, which also might decrease external validity and the discriminatory power within these variables. For the additional analyses, the findings must be interpreted cautiously because of α-error cumulation. However, for those

analyses, we exclusively used the results of the imputed data sets and generalized linear modelling with robust estimators, which were more conservative. Moreover, the results might add important aspects to future research.

Conclusions

The results of this study suggest that latency to repair is associated with stress reactivity in infants as assessed with salivary cortisol. This association supports the hypothesis that the reparation of dyadic mismatching states is associated with infant psychophysiological regulation [10, 15]. According to the literature [32, 83, 84], individual differences in psychobiological responsiveness to stress are associated with increased susceptibility to behavioral problems and disorders in children and adolescents. Hence, preventive mother-infant interventions targeted at changing maladaptive forms of dyadic interaction to ones that more effectively reduce infant distress might be useful. As interactive reparation occurs in a clearly detectable time range (seconds), video interventions [85, 86] may be useful for increasing the flexibility in the dyadic interplay between mismatching and positive matching states. In particular, our results suggest that central elements of an intervention, rather than focusing on maternal disorder or just positive matching states, might better focus on reparation of mismatching states and the recognition of infant signs of distress (e.g. self-comforting behaviors).

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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