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The dual nature of hypothalamic-pituitary-adrenal axis regulation in dyads of very preterm infants and their mothers

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A R T I C L E I N F O

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A B S T R A C T

The co-regulation of the hypothalamic-pituitary-adrenal (HPA) axis in mother-infant dyads is thought to be key for infant and child development. Nonetheless, previous literature presents some inconsistencies that might at least partially be due to the presence of risk conditions and the use of different statistical approaches to measure HPA axis co-regulation. Very preterm (VPT) birth represents one of these risk conditions as the early foundation of mother-infant interaction is disrupted. Both VPT infants and their mothers present evidence of altered HPA axis regulation. Nonetheless, the comparison of mother-infant HPA axis co-regulation in VPT infants compared to full-term (FT) ones has not been previously investigated. In this study, 3-month-old (corrected age) VPT infants and FT counterparts with their mothers took part in a well-validated stress-inducing laboratory task (i.e., double Face-to-Face Still-Face, FFSF paradigm). Salivary cortisol samples were obtained before (Baseline) and after (Early reactivity, Late reactivity and Recovery) the FFSF procedure. Dyadic HPA axis co-regulation was assessed at each sample time-point (i.e., *in-moment* coupling) as well as across samples (i.e., *in-time synchrony*). Significant *in-moment* coupling emerged at Baseline, Late reactivity and Recovery for FT infants' dyads only. An overlying pattern of salivary cortisol trajectories emerged between mothers and infants in the VPT group, whereas a more complex pattern of reciprocal and complementary co-regulation was found for FT infants' dyads. Although both groups gave evidence of HPA axis co-regulation, dyads of VPT infants appear to be less able to adapt reciprocally and dynamically to stressful conditions. These findings suggest that multiple approaches to account for dyadic HPA axis co-regulation should be used in order to depict the complex pattern of biological rhythms coordination in mother-infant dyads.

1. Introduction

The mother-infant dyad is meant to be an open, non-linear dynamic system in which mothers and infants reciprocally regulate their states in order to adjust to challenging and stressful conditions (Provenzi et al., 2015a,b; Tronick and Beeghly, 2011). The emergence of patterns of behavioral and biological rhythms co-regulation is key to this dyadic self-regulating system (Feldman, 2006; Welch, 2016; Provenzi et al., 2016d). At the behavioral level, mother-infant coordination has been widely investigated (see Provenzi et al., 2018) and conceptualized as a coupling of behavioral and affective states in a given moment (e.g., dyadic matching; Weinberg et al., 2006) and as the ongoing mutual regulation of individual trajectories in time (e.g., dyadic synchrony; Feldman et al., 2011). The hypothalamic-pituitary-adrenal (HPA) axis is the major biological system for stress regulation, but the emergence of patterns of mother-infant co-regulation of salivary cortisol secretion has received less attention in previous research. Moreover, differently from research on mother-infant behavioral coordination, the dyadic co-regulation of HPA axis has been previously investigated as present or absent (Davis et al., 2018; Tarullo et al., 2017), with very few attempts to jointly provide different conceptualizations of biological rhythms coordination in terms of *in-moment* coupling or *in-time synchrony* (Bernard et al., 2017).

Very preterm (VPT) infants need long-lasting hospitalization in the Neonatal Intensive Care Unit (NICU) during which they are exposed to stressful experiences, such as frequent invasive and painful practices

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(e.g., skin-breaking procedures, mechanical ventilation, sensory inputs) as well as maternal separation (Montirosso and Provenzi, 2015). Not surprisingly, VPT infants have been found to present an altered pattern of HPA axis regulation (i.e., dampened reactivity to physical and socio-emotional stress) later in life (Grunau, 2013; Provenzi et al., 2016b). Unfortunately, very little is known about HPA axis regulation in VPT infants' mothers and the pattern of dyadic HPA axis co-regulation in dyads of VPT infants and their mothers. In the present study, the individual trajectories of HPA axis regulation as well as the dyadic HPA axis co-regulation pattern are compared between dyads of VPT *vs.* full-term (FT) infants and their mothers.

2. Background

2.1. Why does dyadic HPA axis co-regulation matter?

The early emergence of attuned biological co-regulation of stress in mother-infant dyads is meant to be a positive factor for the development of higher-order behavioral development and socio-emotional attunement (Feldman, 2006; van Bakel and Riksen-Walraven, 2008). Feldman (2006) proposed that the emergence of social rhythms and interactive attunement in mother-infant dyads emerges from precocious forms of biological attunement and co-regulation of autonomic and neuroendocrine systems. The HPA axis is the main neuroendocrine system for stress regulation and by far the most studied neuroendocrine stress regulation system in human infants (Gunnar et al., 2009). Bernard and colleagues (Bernard et al., 2017) have recently proposed that the attuned dyadic HPA axis co-regulation might be considered as an ongoing process and a reflection of how the dyad typically responds to stressful events, which in turn is key to support infants' socio-emotional development (Müller et al., 2015).

A recent review of studies investigating dyadic HPA axis co-regulation highlighted the importance of considering the context of early chronic stress exposures as a critical factor affecting the emergence of coordinated patterns of neuroendocrine regulation between mothers and infants (Davis et al., 2018). Nonetheless, findings to date are inconsistent. While some authors reported evidence of attuned HPA axis co-regulation (Hibel et al., 2015; Laurent et al., 2012), others did not find any significant attunement between infants and mothers' salivary cortisol trajectories (Crockett et al., 2013; Thompson and Trevathan, 2009). A major source of inconsistencies may be related to the presence of different risk conditions. First, when authors compared the dyadic HPA axis co-regulation between groups of high- and low-risk dyads, they found increased attuned co-regulation of individual salivary cortisol trajectories in dyads that had previous adverse experiences. For example, attuned HPA axis co-regulation was documented during a laboratory stress-inducing procedure (i.e., Strange Situation) in dyads of 18-month-old infants and mothers with a history of pre-post-natal depression, but was not found in their control counterparts (Laurent et al., 2011). Similarly, in younger infants, a pattern of attuned dyadic HPA axis co-regulation emerged during a stress-inducing set of laboratory tasks (i.e., selected from the Lab-TAB procedure) at 7 months in dyads that reported exposure to households with violence or restrictive/punitive parenting behaviors (Hibel et al., 2009). As such, it seems plausible to hypothesize that attuned dyadic HPA axis co-regulation might be particularly evident in mother-infant dyads that experienced repeated and/or chronic adverse conditions (Bernard et al., 2017) or in dyads in which mothers exhibit higher level of chronic physiological stress (Tarullo et al., 2017).

An additional source of inconsistency might be due to the fact that previous research accounted for the presence or absence of mother-infant HPA axis co-regulation using different approaches and statistical methods (Bernard et al., 2017). Consistently, a recent review of literature (Davis et al., 2018) suggested that different approaches in the study of dyadic HPA axis co-regulation might reflect different kinds of biological rhythms coordination, finally yielding different and potentially inconsistent findings (Butler, 2011). For instance, the use of bivariate correlations applies to one single data point and appears to reflect the coupling of salivary cortisol secretion between mother and infant in a specific moment (e.g., pre- or post-stress exposure; Ostfeld-Etzion et al., 2015). Nonetheless, this approach does not account for a different kind of HPA axis co-regulation, which is the dynamic *in-time* changes in synchrony that is better accounted for by using linear modelling (Davis et al., 2018).

2.2. Acute vs. Repeated stress exposures: A rationale to study dyadic HPA axis co-regulation in dyads of VPT infants and their mothers

A potential explanation for the emergence of attuned dyadic HPA axis co-regulation in dyads with a history of adversity might at least partially depend on the functioning of the HPA axis under acute and repeated exposures to stress. When individuals are exposed to acute stressors, HPA axis regulation occurs in a two-step process: reactivity (i.e., usually increased secretion of salivary cortisol at 10-to-20 min post-stress; Tsigos and Chrousos, 2002) and subsequent recovery (i.e., at least partial return to baseline values about 30-to-40 min after stress exposure; Haley et al., 2006; Koss and Gunnar, 2018). Nonetheless, the repeated activation of the HPA axis in response to chronic and reiterated stressors might result in a down-regulation of the salivary cortisol secretion (i.e., allostatic load; McEwen, 2003), which might be detected as a pattern of dampened reactivity (Gunnar and Vazquez, 2001; Montirosso et al., 2016). As such, it might be hypothesized that when mothers and infants are exposed to a chronic stressful environment, both their HPA axis might be affected, resulting in an altered profile of salivary cortisol regulation due to allostatic regulation.

VPT birth and the subsequent hospitalization in the NICU is an adverse condition during which both the infant and the mother experience daily sources of stress. VPT infants are exposed to frequent pain-related stress including skin-breaking procedures and invasive ventilation (Grunau, 2013). This early exposure to a life-saving yet adverse environment is able to affect the HPA axis regulation of VPT infants. A pattern of dampened salivary cortisol reactivity has been observed in VPT infants during the first months of life in response to physical (Grunau et al., 2005) as well as socio-emotional stress in comparison to age-paired FT infants (Provenzi et al., 2017). It should be highlighted that the NICU environment is highly stressful for mothers of VPT infants as well. The most common sources of distress include the physical environment of the NICU, the sight of their own infants connected to tubes and exposed to invasive procedures and especially the precocious maternal separation and postponed transition to parenting (Franck et al., 2005). Mothers of FT infants exposed to stress-inducing laboratory conditions (e.g., frustration tasks; Hibel et al., 2009) regulate their HPA axis with a negative slope (i.e., salivary cortisol decreased from baseline to post-stress samples at 20 and 40 min after the end of the stressful procedure). Unfortunately, to the best of our knowledge, the study of HPA axis regulation in VPT infants' mothers has received limited attention. Additionally, the evidence on dyadic HPA axis co-regulation in dyads of VPT infants is scarce. Neu and colleagues (Neu et al., 2009) demonstrated that early maternal holding contact is associated with a more attuned pattern of HPA axis co-regulation in dyads of VPT infants. Additionally, Mörelius and colleagues (Mörelius et al., 2012) have documented that an early NICU intervention focused on parental involvement and mother-infant interaction may increase the matching between preterm infants and their mothers' salivary cortisol levels. Nonetheless, to the best of our knowledge there are no studies comparing dyadic HPA axis co-regulation between VPT and FT infant dyads.

2.3. The present study

In the present study, 3-month-old (corrected age, CA) VPT and FT infants have been exposed to an age-appropriate stress-inducing laboratory procedure involving mother-infant interaction, namely the double Face-to-Face Still-Face paradigm (FFSF; DiCorcia et al., 2015). Dyadic HPA axis co-regulation was assessed as the *in-moment* coupling of magnitude of salivary cortisol secretion using bivariate correlations for each sample time-point, and as the *in-time* synchrony of individual trajectories using a linear modelling approach. Based on previous literature, we hypothesized that a pattern of attuned HPA axis co-regulation would have emerged in dyads of VPT infants, but not in dyads of their FT counterparts. Prior to the assessment of dyadic HPA axis co-regulation we investigated the potential differences in the individual trajectories of salivary cortisol secretion between VPT and FT infants as well as between their mothers. Based on previous research on VPT infants' HPA axis reactivity, we hypothesized a down-regulation pattern of salivary cortisol regulation in VPT infants and an opposite pattern of increased salivary cortisol reactivity in FT counterparts. Though tentative due to the lack of previous studies on maternal HPA axis regulation in VPT infants' mothers, we expected a trend for a decreasing salivary cortisol response to the FFSF procedure based on previous findings on mothers of FT infants (Hibel et al., 2009).

3. Methods

3.1. Participants

One-hundred-nine 3-month-old infants (45 VPTs, 64 FTs) and their mothers participated in the study. VPT infants (gestational age ≤ 32 weeks) were enrolled at the NICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan (Italy). Exclusion criteria for VPT infants were: major brain lesions as documented by cerebral ultrasound, neuro-sensorial deficits, genetic syndromes, and/or major malformations. FT infants were recruited at Pediatric Unit, Sacra Famiglia Hospital Fatebenefratelli, Erba (Italy). All FT infants were healthy and had no neonatal morbidities or prenatal/perinatal-risk factors. Maternal exclusion criteria for both groups were: age below 18 years, psychotropic medication during pregnancy, and prenatal depression or anxiety assessed by the NICU psychologist. All mothers signed a written informed consent, and the study was approved by the Ethics Committees of the Scientific Institute IRCCS E. Medea, Bosisio Parini (Italy) and participating hospitals.

3.2. Procedures

All lab sessions occurred in the morning, between 9:00 and 12:00 at the home of the participating families. After giving the mother a brief description of the procedures, salivary cortisol was collected using oral swabs from both the mother and the infant (i.e., Baseline). Soon after the first salivary cortisol sample, the mother and the infant participated in a double FFSF paradigm, specifically developed to assess HPA axis reactivity to socio-emotional stress in young infants (Provenzi et al., 2016c). The episodes are described in detail in Fig. 1. Post-stress samples were obtained at +10 (i.e., Early reactivity), +20 (i.e., Late reactivity), and +30 (i.e., Recovery) minutes after the FFSF ended. Oral stimulants were avoided for both mothers and infants. Saliva samples were stored at −80 °C until assayed in the biology laboratory of the Scientific Institute IRCCS E. Medea, Bosisio Parini (Italy) according to producer guidelines (Salimetrics LLC, State College, PA). Intra- and inter-assay coefficients of variation (i.e., 51% and 7.3%, respectively) were controlled for. Infants' feeding was not allowed for the hour preceding the lab session. At the end of the lab session, socio-demographic information was obtained through maternal reports and mothers completed questionnaires on depressive and anxious symptoms (see below).

3.3. Measures

3.3.1. Perinatal variables

Infants' variables (i.e., gestational age, birth weight, and Apgar at minute 5) were obtained from medical records. Socio-economic status (SES) was obtained from maternal report of income and educational level and SES coding was based on Hollingshead's (1975) classification.

3.3.2. Maternal emotional states

As VPT birth is associated with an increased risk of post-natal maternal depression and/or anxiety symptoms (Pace et al., 2016), mothers from the two groups (i.e., VPT and FT) completed the 21-item Beck Depression Inventory (BDI; Beck et al., 1961) and the 40-item State-Trait Anxiety Inventory (STAI-Y; Spielberger et al., 1983). The BDI items are rated on a 4-point scale, indicating the absence/presence and severity of self-reported depressed feelings, behaviors, and symptoms. The STAI-Y includes a measure of transient anxiety symptoms (state anxiety: items 1–20) as well as a measure of anxiety traits (trait anxiety: items 21–40). Each STAI-Y item is rated on a 4-point intensity scale.

3.3.3. Salivary cortisol data reduction

Salivary cortisol was expressed in μmol/l. Twenty-seven dyads (12 VPT and 15 FT) had at least one missing value for maternal and/or infants' salivary cortisol assay. According to a conservative approach, we excluded dyads with incomplete set of salivary cortisol data from the analyses. These infants and mothers presented no significant differences compared to the included sample for what pertains perinatal and maternal variables. The final sample included 33 VPT infants' dyads and 49 FT infants' dyads. As the raw values of salivary cortisol were not normally distributed for both infants (Kolmogorov-Smirnov (K–S) Z range: 1.212 to 1.626, $0.010 < p < .143$) and mothers (K–S Z range: 1.371 to 1.767, $0.004 < p < .047$), they were log10-transformed. The log10 cortisol values were normally distributed (infants' K–S Z range: 0.625 to 1.359, $.050 < p < .829$; mothers K–S Z range: 0.543 to 1.095, $.182 < p < .930$).

3.4. Plan of analysis

3.4.1. Preliminary analyses

The statistical analyses were carried using SPSS 21 for Windows and setting a significance threshold $p < .05$. The two groups (i.e., VPT and FT) were compared for infants and maternal variables by means of mean comparisons (t-test for independent samples) and frequency analysis (chi-squared tests).

3.4.2. Salivary cortisol individual trajectories

Two separate 4 × 2 general linear models (GLMs) with salivary cortisol time-points (i.e., Baseline, Early reactivity, Late reactivity, Recovery) as within-subject variable and group (i.e., VPT *vs.* FT) as between-subject factor was used to assess the trajectories of salivary cortisol across the FFSF procedure for infants and mothers. Main effects as well as 2-way interactions were investigated. Planned repeated pairwise contrasts were used to assess significant 2-way interaction effects.

3.4.3. Dyadic HPA axis co-regulation

The *in-moment coupling* is meant to reflect the presence of the coordination of the magnitude of salivary cortisol concentration in a specific time point (e.g., Baseline) between two interactive partners. This measure has been applied in each time point (i.e., Baseline, Early reactivity, Late reactivity and Recovery), separately for the two groups (VPT and FT). The *in-moment* coupling of mother and infant magnitude of salivary cortisol secretion was assessed with separate Pearson's bivariate correlations at each sample time-point (i.e., Baseline, Early reactivity, Late reactivity, Recovery).

The *in-time synchrony* has been defined has a pattern of significant coupling of individual trajectories across time. The *in-time synchrony* of

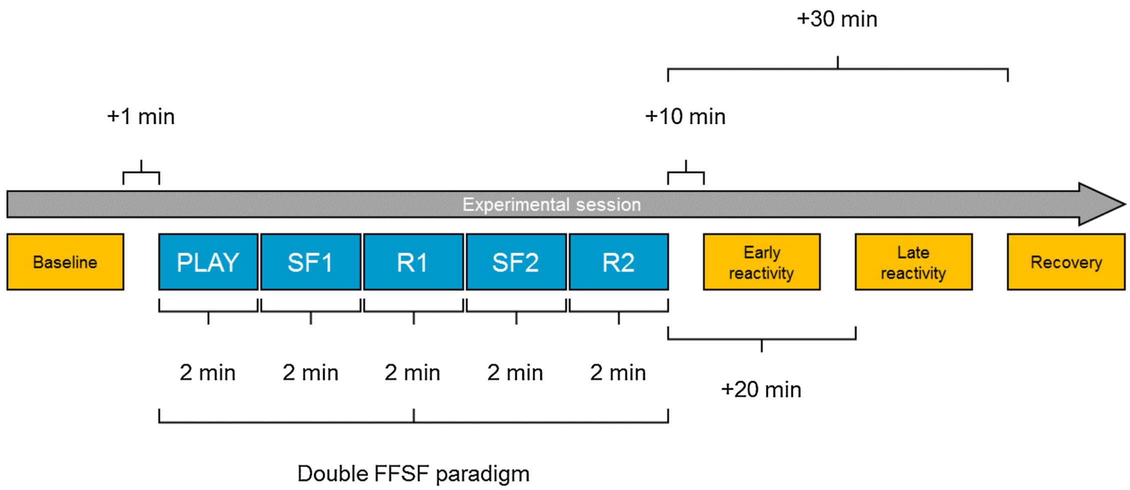

Fig. 1. Graphical representation and description of the double Face-to-Face Still-Face (FFSF) procedure together with time points of salivary cortisol samples. Note. Yellow boxes (black text in print) refer to salivary cortisol sample. Blue boxes (white text in print) refer to the episodes of the FFSF procedure. Legend: FFSF, Face-to-Face Still-Face; PLAY, mother and infant face-to-face interaction; SF1 (Still-Face 1), mother instructed to maintain a still, poker face looking at the infant and avoiding any communication; R1 (Reunion 1), mother and infant face-to-face interaction; SF2 (Still-Face 2), mother instructed to maintain a still, poker face looking at the infant and avoiding any communication; R2 (Reunion 2), mother and infant face-to-face interaction.

individual salivary cortisol trajectories was assessed with a 4 × 2x2 GLM with salivary cortisol time-points and dyadic membership (i.e., infants *vs.* mothers) as within-subject variables and group as between-subject factor. Main effects as well as 2- and 3-way interactions were investigated. Significant 3-way interaction was assessed with two separate 4 × 2 GLMs for VPT and FT dyads including salivary cortisol time-points and dyadic membership. Planned repeated pair-wise contrasts were used to assess significant 2-way interaction effect.

4. Results

4.1. Descriptive statistics and preliminary data

Table 1 includes descriptive statistics and mean comparisons for infants and mothers' characteristics. There was no significant difference in infants' gender distribution between the VPT and FT groups, $\chi^2 = .002$, $p = .969$. Raw values for salivary cortisol of infants and mothers are reported in Table 2, whereas log10-transformed salivary cortisol trajectories are reported in Fig. 2. No differences emerged in the day time of FFSF session between VPT and FT groups.

Table 2
Descriptive statistics for infants and mothers salivary cortisol (μmol/l), split by group and for the whole sample.

	Groups					
	VPT infants' dyads		FT infants' dyads		Whole sample dyads	
	Mean	SD	Mean	SD	Mean	SD
Infant						
Baseline	.24	.14	.21	.15	.22	.15
Early reactivity	.20	.12	.25	.17	.23	.16
Late reactivity	.20	.13	.24	.13	.22	.13
Recovery	.23	.14	.22	.11	.22	.12
Mother						
Baseline	.23	.14	.26	.14	.25	.14
Early reactivity	.19	.11	.20	.11	.19	.11
Late reactivity	.19	.09	.17	.10	.18	.09
Recovery	.19	.09	.17	.10	.18	.10

Note. VPT, very preterm infants; FT, full-term infants; Salivary cortisol expressed in μmol/l.

Table 1
Descriptive statistics for infants and mothers split by group.

	Groups					
	VPT infants' dyads (N = 34; 19 females)		FT infants' dyads (N = 49; 28 females)		Mean comparison	
	Mean	SD	Mean	SD	*t*	*p*
Gestational age (weeks)	30.33	2.29	39.25	1.22	−19.53	< .001
Birth weight (grams)	1423.94	401.91	3338.16	409.28	−20.92	< .001
Apgar (minute 1)	6.58	1.37	9.81	0.59	−13.94	< .001
Apgar (minute 5)	8.27	0.84	9.98	0.15	−11.52	< .001
Length of NICU stay (days)	48.64	26.57	N/A	N/A	N/A	N/A
Number of skin-breaking procedures	32.88	24.54	N/A	N/A	N/A	N/A
Maternal age (years)	36.73	4.45	33.05	4.61	3.56	0.001
Maternal education (years of study)	15.58	2.66	14.80	3.61	1.06	0.291
Maternal Socio-Economic Status (SES)	48.79	22.88	51.63	25.77	−0.51	0.610
BDI score	7.90	4.45	6.27	5.40	1.13	0.264
STAI-Y (state score)	31.50	7.03	29.58	5.88	1.07	0.288
STAI-Y (trait score)	36.94	6.21	36.50	6.10	0.25	0.800

Note. VPT, very preterm infants; FT, full-term infants; NICU, Neonatal Intensive Care Unit; BDI, Beck Depression Inventory; STAI-Y, State-Trait Anxiety Inventory – Form Y; N/A, Not applicable.

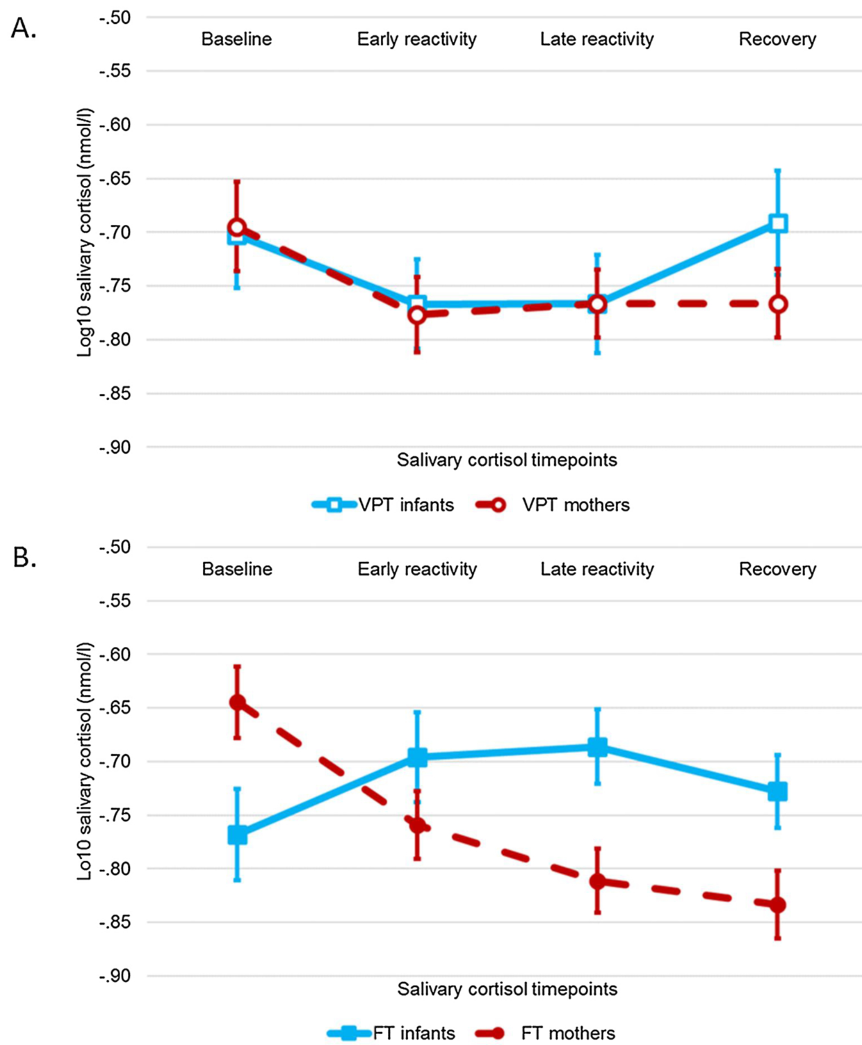

Fig. 2. Salivary cortisol trajectories of infants and mothers in the two groups (A, VPT dyads; B, FT dyads).

4.2. Salivary cortisol individual trajectories

There was no significant main effect of time-points for infants' salivary cortisol trajectories, $F(3,240) = .25$, $p = .859$, $\eta_p^2 = .003$, and of group, $F(1,80) = .05$, $p = .823$, $\eta_p^2 = .001$. A significant 2-way interaction emerged, $F(3,240) = 3.00$, $p = .031$, $\eta_p^2 = .037$. From Baseline to Early reactivity VPT infants showed a decrease in salivary cortisol, whereas FT infants showed an increase, $F(1,80) = 4.06$, $p = .047$, $\eta_p^2 = .049$. Moreover from Late reactivity to Recovery VPT infants exhibited an increase in salivary cortisol, whereas FT infants showed a decrease, $F(1,80) = 6.70$, $p = .011$, $\eta_p^2 = .078$.

A significant effect emerged for time-points, $F(3,240) = 20.40$, $p < .001$, $\eta_p^2 = .203$. No significant group effect was detected, $F(1,80) = .06$, $p = .794$, $\eta_p^2 = .001$. The main effect of time-points was further specified by the significant 2-way interaction between group and time-points, $F(3,240) = 4.26$, $p = .006$, $\eta_p^2 = .051$. From Early to Late reactivity the mothers of VPT infants showed a stable level of salivary cortisol, whereas the counterparts of FT infants exhibited a significant decrease, $F(1,80) = 7.96$, $p = .006$, $\eta_p^2 = .090$.

4.3. Dyadic HPA axis co-regulation

Pearson's bivariate correlations between infant and mother salivary cortisol concentrations are reported in Table 3 separately for VPT and FT groups. No significant correlations emerged for the *in-moment* couplings in the VPT group, whereas infants' salivary cortisol concentration was positively and significantly correlated to maternal one at Baseline, Late reactivity and Recovery time-points in the FT group.

Table 3
Pearson's bivariate correlations between infants and mothers' salivary cortisol concentrations at each sample time-point, separately for VPT and FT groups.

Mothers / Infants	1.	2.	3.	4.
VPT group				
1.	**.32 (.074)**	*.47 (.006)*	*.39 (.025)*	*.42 (.014)*
2.	.11 (.553)	**.03 (.87)**	−.03 (.869)	−.01 (.981)
3.	.32 (.066)	.15 (.401)	**.07 (.682)**	.06 (.748)
4.	*.47 (.005)*	.19 (.286)	.16 (.371)	**.12 (.524)**
FT group				
1.	***.31 (.031)***	.24 (.092)	*.28 (.048)*	*.34 (.018)*
2.	.14 (.341)	**.23 (.111)**	*.34 (.017)*	*.38 (.008)*
3.	.06 (.685)	*.31 (.031)*	***.42 (.004)***	*.42 (.002)*
4.	−.01 (.963)	.24 (.098)	.26 (.070)	***.31 (.029)***

Note. VPT, very preterm infants; FT, full-term infants. Significant correlation indexes are reported in italics. *In-moment* couplings are reported in bold.

A significant effect emerged for time-points, $F(3,240) = 4.19$, $p = .007$, $\eta_p^2 = .050$. Moreover, a 2-way significant interaction emerged between time-points and dyadic membership, $F(3,240) = 7.34$, $p < .001$, $\eta_p^2 = .085$. The main effect of time-points and the 2-way interaction were further specified by the 3-way interaction among time-points, dyadic membership and group, $F(3,240) = 4.12$, $p = .007$, $\eta_p^2 = .050$. In the VPT group, there was no significant difference between the salivary cortisol trajectory of mothers and infants at any time-point, $F(3,96) = .83$, $p = .478$, $\eta_p^2 = .026$. In the FT group, the salivary cortisol trajectories of mothers and infants significantly differed, $F(3,144) = 13.76$, $p < .001$, $\eta_p^2 = .223$. Contrasts revealed that significant differences in salivary cortisol trajectories between FT infants' and their mothers emerged from Baseline to Early reactivity, $F(1,48) = 14.66$, $p < .001$, $\eta_p^2 = .234$, and from Early to Late reactivity, $F(1,48) = 4.49$, $p = .039$, $\eta_p^2 = .085$.

5. Discussion

The main goal of the present study was to assess the dyadic HPA axis co-regulation in dyads of VPT infants and their mothers compared to the FT counterparts accounting for two different kinds of biological rhythm co-regulation: (a) *in-moment* coupling of salivary cortisol concentrations and (b) *in-time* synchrony of individual trajectories. Preliminary to this objective, we assessed differences in individual HPA axis regulation between VPT and FT infants as well as between their mothers.

5.1. Salivary cortisol individual trajectories

VPT infants showed a different salivary cortisol regulation pattern in response to the FFSF paradigm when compared to FT counterparts. Specifically, from Baseline to Early reactivity (i.e., 10 min after the FFSF procedure ended) VPT infants showed a decrease in cortisol level whereas FT infants presented an increase. Furthermore, from Late reactivity to Recovery (i.e., between 20 and 30 min after the FFSF procedure ended) VPT infants showed an increase in salivary cortisol whereas FT infants exhibited a decrease. This finding is consistent with previous literature (Grunau, 2013) and further expands the knowledge on VPT infants' regulation of stressful conditions during the first months of life. On the one hand, previous research has documented that VPT infants exhibit reduced HPA axis reactivity to physical stress at 32 weeks post-conception (Holsti et al., 2005) as well as to contingency learning conditions (Haley et al., 2010) and socio-emotional stress (Provenzi et al., 2016a) at 3 months CA, compared to FT counterparts. Nonetheless, previous studies mainly reported on salivary cortisol reactivity (i.e., change in salivary cortisol concentrations between one pre- and one post-stress sample) to different stressors, rather than on reactivity and recovery together. As such, the present study adds to previous literature suggesting that at 3 months CA VPT infants might present a different pattern of HPA axis down-regulation (i.e., reactivity and recovery), and not only dampened reactivity.

VPT infants' mothers showed a different salivary cortisol trajectory in response to the FFSF paradigm compared to mothers of FT infants. Specifically, whereas mothers of both groups showed a decreasing trajectory of salivary cortisol, VPT infants' mothers exhibited a less pronounced decrease from early to late reactivity samples (i.e., between 10 and 20 min after the FFSF procedure ended). The down-regulation of maternal HPA axis in response to an infant laboratory stressful procedure was previously documented. For example, mothers of FT infants exposed to stress-inducing laboratory conditions (e.g., frustration tasks; Hibel et al., 2009) regulate their HPA axis with a negative slope (i.e., salivary cortisol decreased from baseline to post-stress samples at 20 and 40 min after the end of the stressful procedure). The present study further extends this evidence to mothers of VPT infants. Additionally, VPT infants' mothers decreased salivary cortisol secretion only from baseline to early reactivity (i.e., +10 min after FFSF procedure ended), whereas a flat trajectory was detected from early to late reactivity and to recovery.

5.2. Dyadic HPA axis co-regulation

The investigation of two different kinds of biological rhythms of co-regulation revealed specific and intriguing insights on the dual nature of HPA axis co-regulation in healthy FT and VPT infant dyads. First, when we looked at the *in-moment* coupling between infants and their mothers' magnitude of salivary cortisol concentration, we found two very different patterns of bivariate correlations. In VPT infant dyads no significant correlations emerged, suggesting that in none of the investigated time-points (Baseline, Early reactivity, Late reactivity and Recovery) a biological coupling between the HPA axis of the infants and their mothers was present. In FT dyads, significant correlations emerged at Baseline, as well as at Late reactivity and Recovery time-points, whereas no significant correlation was found at Early reactivity. In other words, during a quiet state (i.e., before the onset of the stressful FFSF paradigm) the two partners presented coupled salivary cortisol concentration. Soon after the experimental manipulation of maternal behavior and the occurrence of a socio-emotional stress condition (Early reactivity), non-significant coupling was found between mothers and infants suggesting that the dyad, like a system, was facing a perturbation and facing a challenge in their previous observed biological coordination. On the other side, a significant coupling was reached again during Late reactivity and Recovery. This finding can indicate that the dyadic system managed to cope with the stressful condition and to recover an homeostatic equilibrium. This pattern of dyadic HPA axis coupling is reminiscent of flexibility typically observed in an open dynamic system functioning, which faces an environmental perturbation and stressful condition (Tronick and Beeghly, 2011). In contrast, in dyads of VPT infants and their mothers we did not detect any HPA axis coupling, suggesting that, like a system, these dyads might have difficulties in the co-regulation of biological rhythms especially when facing interactive ruptures and stressful exposures.

As for the *in-time* synchrony, while a significant difference emerged between infants and mothers' individual trajectories in the FT group, no difference was found for VPT dyads, which documented a globally overlying pattern (see Fig. 2). From this perspective it might be hypothesized that point-by-point adrenocortical coordination was present in dyads of VPT infants, but not in the FT counterparts. Nonetheless, when taking into account the two kinds of dyadic HPA axis co-regulation, it's possible to speculate that different ways of dyadic HPA axis co-regulation were at work in the two groups. On the one hand, in the healthy FT dyads, the mother and the infant are actively and jointly contributing to the emergence of a dynamically coordinated system of biological stress regulation. The way they regulate their HPA axes is in some way reciprocal and complementary (see Fig. 2), as suggested by the switch in salivary cortisol concentration and the temporary loss of coupling observed soon after the end of the FFSF procedure and the subsequent return to significant coupling during late reactivity and recovery. On the other hand, although the individual trajectories might be very similar in the VPT group as a whole (see Fig. 2), VPT infants and their mothers never show a coupled secretion of salivary cortisol at the pre- and post-stress time-points. In other words, although they might be apparently synchronous, they are not jointly regulating their HPA axes and they are only limitedly contributing to the reciprocal adjustment to the external challenging condition provoked by the FFSF procedure.

Although the early emergence of biological rhythm coordination plays a fundamental role in socio-emotional development (Kalomiris and Kiel, 2018), previous research provided inconsistent findings for what pertains the presence or absence of dyadic HPA axis co-regulation in healthy and at-risk samples. Nonetheless, the present study suggests that when multiple approaches are jointly taken into account, the focus can change from the assessment of the presence *vs.* absence of biological rhythms coordination to the investigation of different way of dyadic co-regulation. From this perspective it is not possible to claim that dyadic HPA axis co-regulation is present in healthy conditions (i.e., FT group) or absent in at-risk dyads (i.e., VPT infants and their mothers). Rather, it should be considered that different ways of coordinating biological rhythms between mothers and infants might occur, similarly to what happens at the behavioral level (Provenzi et al., 2018). Notably, based on the present findings we cannot clarify whether differences in the pattern of *in-moment* coupling and *in-time* synchrony of HPA axis co-regulation reflect an adaptive adjustment to the early exposure of VPT infants and their mothers to the stressful nature of the NICU hospitalization or a specific risk factor for further infant and child development later in life. Future studies are needed to explore how different patterns of dyadic HPA axis co-regulation are affected by early adverse exposures and associate with developmental outcomes in healthy as well as in low and high risk samples.

The present study has limitations. First, the sample size is relatively small and the investigation of individual differences (e.g., gender-related differences) within the two groups (i.e., FT and VPT) was not feasible. Moreover, the presence of different individual and dyadic trajectories of salivary cortisol secretion in response to the FFSF procedure might be associated with different NICU-related stress exposures (e.g., length of hospitalization, pain-related stress, mechanical ventilation, sensory inputs, maternal separation), which were not assessed in the present study. Additionally, the potential buffering role of maternal behavior (e.g., maternal holding, maternal sensitivity) during stressful mother-infant interaction was previously documented (Neu et al., 2009), but was not controlled for in the present study. As such, the present findings should be considered preliminary and more complex models including the mediation/moderation effect of both NICU-related risk factors and maternal-related protective factors are warranted to be tested in future studies.

6. Conclusions

This study provides initial evidence on the importance of considering different kinds of HPA axis co-regulation indexes (i.e., *in-moment* coupling and *in-time* synchrony) in dyads of VPT and FT infants and their mothers. Indeed, the *in-moment* coupling and the *in-time* synchrony measures independently contributed to show a complex pattern of coordination of HPA activity between healthy FT infants and their mothers while facing a socio-emotional stress exposure. This evidence highlights the need to include both measures to fully characterize co-regulatory dimensions of stress physiology. Furthermore, the overlying and less dynamic pattern of HPA axis coordination observed in VPT infants might suggest either an adjustment to the early NICU hospitalization and/or a risk factor for further infant and child socio-emotional development later in life (Welch et al., 2015).

Although indirectly, our findings have implications for promoting early caregiving quality in the at-risk mother-infant dyads. Appropriate parenting requires coordination of multiple systems, including both behavioral and physiological components, to read infant signals and respond sensitively (Abraham et al., 2018; Barrett and Fleming, 2011; Welch, 2016). As mothers of preterm infants experience high levels of stress themselves due to emotional trauma for the prematurity of their infants (Provenzi et al., 2016a), these systems may be negatively affected resulting in altered profiles of mother-infant HPA axis co-regulation. On the other hand, maternal behavior moderates infant salivary cortisol reactivity (Grant et al., 2009; Provenzi et al., 2015a,b; Thompson and Trevathan, 2009) and previous research suggests that early parental intervention during the NICU stay (Mörelius et al., 2012) improves coupling between mothers and their VPT infants salivary cortisol concentration. As such, it appears crucial that early intervention during NICU stay and at the immediate post-discharge period should focus on the dyads as a system in order to promote adequate and adaptive patterns of co-regulation and to sustain infants' behavioral and emotional development (Hane et al., 2003). These interventions may not only have an effect on infants' neurobehavioral stability, but could also contribute to better psychobiological co-regulation.

Conflicts of interest

None.

Authors contributions

Livio Provenzi contributed to study design, conceptualization, project administration, data curation, data analysis, methodology, original drafting.

Lorenzo Giusti contributed to methodology and data analysis, review and editing.

Monica Fumagalli contributed to data acquisition, resources, data curation, review and editing.

Susanna Frigerio contributed to data analysis and original drafting.

Francesco Morandi contributed to data acquisition, resources, data curation.

Renato Borgatti contributed to funding acquisition, supervision, review and editing.

Fabio Mosca contributed to supervision and methodology, review and editing.

Rosario Montirosso contributed to funding acquisition and supervision, review and editing.

All authors agreed to submit the final version to Psychoneuroendocrinology and validated the final draft.

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