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https://escholarship.org/uc/item/7807023v

Journal

Developmental Psychobiology, 62(6)

ISSN

0012-1630

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Publication Date

2020-09-01

DOI

10.1002/dev.21964

Copyright Information

Peer reviewed

Unpredictable maternal behavior is associated with a blunted infant cortisol response

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Abstract

Background: Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with poor physical and mental health. Early-life adversity may dysregulate cortisol response to subsequent stress. This study examines the association between patterns of maternal behavior and infant stress response to a challenge. Specifically, we test whether infant exposure to unpredictable maternal sensory signals is related to the cortisol response to a painful stressor.

Method: Participants were 102 mothers and their children enrolled in a longitudinal study. Patterns of maternal sensory signals were evaluated at 6 and 12 months during a 10-min mother–infant play episode. Entropy rate was calculated as a quantitative measure of the degree of unpredictability of maternal sensory signals (visual, auditory, and tactile) exhibited during the play episode. Infant saliva samples were collected for cortisol analysis before and after inoculation at 12 months.

Results: Unpredictable patterns of maternal sensory signals were associated with a blunted infant cortisol response to a painful stressor. This relation persisted after evaluation of covariates including maternal sensitivity and maternal psychological distress. Conclusions: This study provides evidence that unpredictable patterns of maternal sensory signals are one process through which caregiving affects the function of infant stress response systems.

1 | INTRODUCTION

The hypothalamic–pituitary–adrenal (HPA) axis is a major neuroendocrine system that is key in physiological responses to challenge. The HPA axis response involves a cascade of biochemical events resulting in the release of cortisol from the adrenal cortex (Selye, 1950). Cortisol plays a critical role in prenatal and postnatal brain development (Joëls, Karst, & Sarabdjitsingh, 2018; Kim et al., 2017) and regulates many functions of the central nervous system (e.g., metabolic, endocrine, immune) throughout the lifespan (Adam et al., 2017; Martins et al., 2017; Müller & Quinkler, 2018). Dysregulation of the HPA axis confers risk for a range of physical and mental illnesses (van Bodegom, Homberg, & Henckens, 2017; Moisiadis & Matthews, 2014), and the HPA axis is particularly susceptible to early experiences (for review, see Howland, Sandman, & Glynn, 2017; Noroña, Doom, Davis, & Gunnar, 2020). Parental care is one potent factor that shapes the developing HPA axis, and an extensive literature shows that quality of maternal caregiving as well as the nature of the attachment relationship is associated with infant and child cortisol regulation (Blair et al., 2008; Feldman et al., 2009; Martinez-

Torteya et al., 2014; McLaughlin et al., 2015; Spangler & Zimmermann, 2014). However, the process by which parental signals affect HPA axis development remains poorly understood.

Rodent models have been leveraged to shed light on the role of maternal care in shaping the HPA axis. In the context of caregiving, the dam provides critical sensory signals to the pup (Champagne & Meaney, 2001; Eghbal-Ahmadi, Avishai-Eliner, Hatalski, & Baram, 1999; Levine, 2005). Disruption to essential aspects of the dam's caregiving behaviors and sensory signals, including nursing and licking and grooming, leads to stress in the offspring (Champagne, Francis, Mar, & Meaney, 2003). In addition to the quantity of maternal sensory signals, the patterns of maternal sensory signals profoundly impact the pup (Baram et al., 2012; Chen & Baram, 2016). Manipulations to the dam's environment that create a poverty of bedding and nesting materials alter the care she provides. Specifically, dams exposed to impoverished cage conditions provide unpredictable sensory signals to their pups (Ivy, Brunson, Sandman, & Baram, 2008; Rice, Sandman, Lenjavi, & Baram, 2008). These unpredictable signals provoke stress in the pup, and may also directly influence the maturation of brain circuits (Glynn & Baram, 2019). For example, excitatory synapses onto stress-sensitive hypothalamic neurons that control the response of the HPA axis to subsequent stress are augmented (Gunn et al., 2013). In addition, the maturation of hippocampal circuits, which might influence stress memory, is affected long-term. This includes stunting of dendrites and alterations to synapse number and function in the hippocampus (Ivy et al., 2010; Molet et al., 2016).

Evidence that patterns of sensory signals to the rodent pup impact brain systems involved in regulation of the HPA axis is highly consistent with neurobiological principles governing brain development. It is established that patterns of sensory signals are essential for the maturation of neural circuits involved in processing sensory information. For example, the exposure to light patterns and sound and tone patterns is required for maturation of the visual and auditory systems, respectively (Espinosa & Stryker, 2012; Takesian, Bogart, Lichtman, & Hensch, 2018). Patterns of sensory signals, and particularly their unpredictability, additionally affect the development of systems involved in memory (Molet et al., 2016) and reward (Bolton, Molet, et al., 2018). Recent cross-species (rodents and humans) evidence suggests unpredictable maternal sensory signals affect cognitive function, with replication across continents (North America and Europe) (Davis et al., 2017, 2019).

Because of the importance of patterns of sensory information for neural maturation, and because early-life stressors may lead to dysfunction of the HPA axis, we examine whether aberrant patterns of maternal sensory signals comprise a stressor as indicated by alterations to HPA axis regulation. Specifically, this study tests whether infant exposure to unpredictable maternal sensory signals is related the cortisol response to a painful stressor in human infants.

2 | METHOD

2.1 | Participants

Study participants were 102 mothers and their children (52% male) participating in a longitudinal study evaluating the role of early experiences in development. Inclusion criteria for mothers' enrollment in the study were 18 years of age or older, English ability, and singleton intrauterine pregnancy. Exclusion criteria were tobacco, alcohol, or drug use during pregnancy, and medical conditions involving dysregulated neuroendocrine, cardiovascular, hepatic, or renal functioning. The study participants included in these analyses were the 102 dyads for whom video recordings of maternal–child interactions and child outcomes were available.

Demographic information for the sample appears in Table 1. All study procedures were approved by the Institutional Review Board for Protection of Human Subjects at the University of California Irvine. Each mother provided written, informed consent for herself and her child.

2.2 | Mother–child interaction procedure

The degree of unpredictability of maternal sensory signals as well as maternal global sensitivity were derived from behavioral coding of a play interaction of mother and child as previously described (Davis et al., 2017). Briefly, mothers and infants attended laboratory visits at infant ages 6 and 12 months. These visits included a semi-structured play interaction between the mother and her infant. Mothers were given a standard set of age-appropriate toys and were instructed to play with their infants as they would at home for 10 min (NICHD Early Child Care Research Network, 1999).

TABLE 1 Demographics of the study participants

Factor	M/%	SD
Maternal education (Years)	16.0	2.1
Maternal race = white non-Hispanic	55%	—
Household income (USD)	$66,374	$32,754
Maternal age (Years)	31.1	4.8
Maternal marital status = married	79%	—
Mother cohabitation with partner	91%	—
Mother parity history	0.7	0.8
Child biological sex = male	52%	—

2.3 | Measures

2.3.1 | Unpredictability of maternal sensory signals

Maternal behaviors that provide auditory, visual, or tactile sensory signals to the child were coded on a moment-to-moment basis from digital video recordings of the 6 and 12-month mother–child play interactions using The Observer XT 11 (Noldus). Auditory signals included all maternal vocalizations (e.g., talking, laughing). Visual signals were maternal manipulations of a toy or object while the infant was visually attending. Tactile signals involved all instances of physical contact (e.g., holding, touching) initiated by the mother. Coders were blind to all other information on study participants. Interrater reliability was calculated for 20% of the videos and averaged 89%.

Quantification of the unpredictability of maternal sensory signals was determined by the calculation of the conditional probabilities of transitions between each of the eight possible combinations of maternal visual, auditory and tactile sensory signals (i.e., presence/absence of input of each of the three types of sensory signals). For example, a mother who is speaking to the child while showing her a toy provides both auditory and visual stimulation. If she additionally picks up the child, she now provides tactile stimulation to the child. This is coded as a new state. The transitions among states are modeled as changes in the state of a discrete-state first-order Markov process, and the entropy rate of the process was taken as a measure of unpredictability, as described in Supplementary material of Davis et al. (2017). Alternative Markov chain models (2nd order and 3rd order), as well as a non-parametric approaches confirmed the reliability of the entropy measure (Spearman's rank correlations for the resulting entropy measures ranged from 0.91 to 0.98) (Vegetabile, Stout-Oswald, Davis, Baram, & Stern, 2017). The entropy rate of a sequence of behaviors can be conceptualized as a measure of how random or unpredictable a mother's next behavior would appear to an observer who was making a guess based only on the most recently observed behavior. If one behavior always followed another (e.g., speech was always followed by touch), then this would be highly predictable and there would be little uncertainty for the observer (low entropy rate). In contrast, if the next behavior appeared to be a random choice, then this would be unpredictable (high entropy rate). Entropy rate can vary between a minimum value of zero, when a process is perfectly predictable, to a maximum value of 2.807 (the logarithm [base two] of the number of possible transitions [7] of sensory signals at each step), when all possible transitions in this coding scheme are equally likely and maternal signals are most unpredictable. The entropy rates of maternal sensory signals during the 6 and 12-month mother–infant play interactions were correlated ($r = 0.46$, $p < .01$) and consistent with prior research averaged to create a composite measure of unpredictable maternal sensory signals in infancy (Davis et al., 2019). Additional details regarding the behavioral coding, calculation of entropy, and a description of an R software package for calculating entropy rate are provided in Davis et al. (2017) and available at https://contecenter.uci.edu/shared-resources/.

2.3.2 | Infant salivary cortisol response to the painful stress of an inoculation

Study researchers attended routine 12-month pediatric well-child visits with participating families. Saliva samples were collected from the infants for cortisol analysis at baseline and in

response to an intramuscular injection. The baseline sample was obtained upon arrival to the waiting room and before entering the examination room. The response sample was collected 20 min post-inoculation to capture the peak cortisol response. Saliva was obtained (without any stimulant) by placing a swab in the infant's mouth for up to one minute, and time of day was recorded. After collection, the swab was inserted into a saliva extraction tube (Roche Diagnostics, Indianapolis, IN).

Saliva samples were spun and stored at −20C until assayed. Cortisol levels were determined by a competitive luminescence immunoassay (LIA; IBL-America, Minneapolis, MN) with reported detection limits of 0.015 μg/dl. The cross reactivity of the assay was <2.5% with cortisone, prednisone, and corticosterone and <0.1% with other naturally occurring steroids. The intraand inter-assay coefficients of variance are 5.5% and 7.6%, respectively. Data reduction for the LIA assay was done by an automated four-parameter logistics computer program (software Mikro Win 2000; Berthold Microplate Luminometer, Berthold Detection Systems GmbH; Pforzheim, Germany). Six infants were excluded from analyses for having cortisol concentrations more than four standard deviations above the mean. The change in cortisol concentrations in response to the inoculation was calculated by subtracting baseline levels from response cortisol levels at 20 min after the start of the inoculation.

2.3.3 | Maternal sensitivity

Maternal behaviors during the 6and 12-month mother–child interactions described above were scored from video using a cod ing system developed for the NICHD Study of Early Child Care and Youth Development (NICHD Early Child Care Research Network, 1999). Based on standard procedures, a composite rating of maternal sensitivity was created by summing 4-point ratings of sensitivity to nondistress, positive regard, and intrusiveness (reverse-coded). A composite maternal sensitivity score was calculated by averaging 6and 12-month scores. Sensitivity scores at 6 and 12 months were correlated ($r = 0.47$, $p < .01$) and averaged to create an index of maternal sensitivity over the first postnatal year consistent with prior research (Sulik et al., 2015). All coders were blind to other data gathered on study participants. Twenty percent of sessions were selected at random, without coder knowledge, and coded again by a second independent coder to obtain an index of inter-rater reliability. Reliability for each of the subscales were as follows: sensitivity to nondistress (90%), intrusiveness (90%), and positive regard (93%).

2.3.4 | Maternal distress

Maternal symptoms of anxiety and depression were assessed with the Edinburgh Postnatal Depression Scale (EPDS; Cox & Holden, 2003) and the State-Trait Anxiety Inventory (STAI; Spielberger, 2010) at 6 and 12 months. Each measure was averaged across the two time points to create a composite score for maternal depression (EPDS) and maternal anxiety (STAI) during infancy. The two composites were highly correlated ($r = 0.76$, $p < .01$) and thus were averaged to create an index of maternal distress.

2.3.5 | Data analytic plan

First, covariates were identified. Potential covariates were identified based on the literature and included maternal sensitivity, maternal psychological distress (i.e., anxiety and depression symptoms) and demographic factors (e.g., maternal marital status, household income, maternal age). Any of these variables associated ($p < .1$) with the predictor or the outcome were included as covariates in the analysis. Maternal sensitivity and family income-to-needs ratio met criteria for covariate inclusion and thus were included in the regression model (See Table 2). Although it did not meet covariate criteria, time of day of the cortisol sample was also included due to associations with cortisol values in prior research (e.g., Martin, Kim, Bruce, & Fisher, 2014).

First, we examined whether the inoculation stressor led to an increase in cortisol using a repeated measures ANCOVA adjusting for time of day. Next, to examine the association between unpredictability of maternal sensory signals and infant cortisol response to the inoculation stressor, we employed bivariate correlations followed by linear regression with covariates. We also examined the association between exposure to unpredictable maternal sensory signals and infant baseline (pre-inoculation) cortisol using a bivariate correlation. In addition, we tested sex differences in the relation between exposure to unpredictable maternal sensory signals and cortisol response through inclusion of an interaction term (sex X unpredictability of sensory signals) in the second step of a stepwise regression.

TABLE 2 Descriptive statistics of and intercorrelations among key variables and considered covariates

	M	SD	1	2	3	4	5	6	7	8	9
1. Infant cortisol response (μg/dl)	0.16	0.30	1								
2. Unpredictability of maternal sensory signals	0.79	0.15	−0.22*	1							
3. Infant baseline cortisol (μg/dl)	0.23	0.20	−0.31*	0.13	1						
4. Saliva collection time	11:32	2:32	0.08	0.09	−0.26*	1					
5. Maternal distress (anxiety and depression)	−0.16	0.81	−0.09	0.01	0.00	0.09	1				
6. Maternal sensitivity	9.92	1.17	−0.05	−0.21*	−0.11	−0.14	−0.15	1			
7. Maternal marital status (1 = married)	0.79	0.41	−0.08	−0.11	−0.11	−0.21*	−0.10	0.31*	1		
8. Maternal education (years)	15.83	2.44	−0.12	−0.16	−0.06	−0.29*	−0.05	0.35*	0.43*	1	
9. Family income-to-needs ratio (percent)	434.34	248.22	−0.02	−0.28*	0.04	−0.13	−0.28*	0.33*	0.33*	0.54*	1
10. Maternal age (years)	30.82	5.06	0.11	−0.08	0.01	−0.19	−0.07	0.20*	0.46*	0.34*	0.16

*$p < .05$.

TABLE 3 Linear regression predicting infant cortisol response from unpredictable maternal sensory signals

	B	SE	β	p
Saliva collection time	<0.001	<0.001	0.104	.302
Family income-to-needs ratio	<0.001	< 0.001	−0.049	.654
Maternal sensitivity	−0.020	0.028	−0.074	.486
Unpredictability of maternal sensory signals	−0.538	0.214	−0.261	.014

Note: Significant (p < .05) effects are bolded for emphasis.

3 | RESULTS

On average, cortisol levels of infants exposed to the pain of inoculation increased from 0.26 µg/dl to 0.51µg/dl (F = 14.55, p < .001), illustrating that the manipulation effectively produced a cortisol increase. Infant exposure to unpredictable maternal sensory signals was associated with a blunted cortisol response to inoculation (r = −0.22, p = .026). In contrast, unpredictable maternal sensory signals did not have a significant relation to baseline cortisol concentrations (r = 0.13, p = .206). The association between infant exposure to unpredictable maternal signals and cortisol response to inoculation remained after accounting for covariates: maternal sensitivity, family income-to-needs ratio, and saliva collection time (β = −0.261, B = −0.538); see Table 3. Note that maternal psychological distress was not included in the regression model due to non-significant (p > .1) bivariate correlations with cortisol response and unpredictability of maternal sensory signals. The association between unpredictable maternal signals and child cortisol was not moderated by sex (B = 0.646, p = .293).

4 | DISCUSSION

The principle findings of this study are (a) infants exhibited a significant increase in cortisol following exposure to the painful stimulation of inoculation at 12 months, and (b) unpredictable maternal sensory signals during mother-infant play interactions were associated with a blunted cortisol response to a painful stressor. Importantly, established factors that shape child development broadly including maternal anxiety and depression, maternal sensitivity, and family socioeconomic status did not account for this finding. Unpredictable maternal sensory signals were not related to baseline cortisol levels, only to the change in cortisol following a painful stressor. These findings support the notion that infant exposure to unpredictable maternal sensory signals blunts either the ability of the brain components regulating the stress response to sense the painful stimulation or the magnitude of the hormonal output that is generated. In support of the former possibility, there is evidence that the connectivity of corticotropin releasing

hormone-expressing cells in the hypothalamus, which govern cortisol secretion, is altered by patterns of maternal sensory signals (Gunn et al., 2013; Korosi et al., 2010). Indeed, it is interesting to speculate that as patterns of sensory signals (light and sound) contribute to the normal maturation of visual and auditory circuitries (Espinosa & Stryker, 2012; Takesian et al., 2018; Wiesel & Hubel, 1963), then aberrant patterns of sensory signals from the mother may impact the development of stress-related circuitry (Chen & Baram, 2016; Glynn & Baram, 2019).

Prior human studies have found that the quality of early life experiences, such as caregiver sensitivity, influences HPA axis development. However, variability in both study design and results has made it difficult to draw firm conclusions about how caregiving affects HPA axis function (Blair et al., 2008; Martinez-Torteya et al., 2014). A contribution of the present investigation to this line of inquiry is use of a painful stressor to assess infant cortisol response. Physical pain is an objective, universal stressor that has been established as a precipitant of infant HPA axis response (Davis & Granger, 2009; Gunnar, Porter, Wolf, Rigatuso, & Larson, 1995). In contrast to social stressor tasks (e.g., still-face procedure; Tronick, Als, Adamson, Wise, & Brazelton, 1978) in which an infant's cortisol response may vary as a function of the infant's past interactions with the caregiver, infants are expected to exhibit a cortisol increase in response to a painful event. Thus, this study demonstrates the utility of an objective challenge to examine caregiver influences on HPA axis development and indicates that unpredictable maternal behavior is associated with a blunting of the cortisol response.

Experimental animal work that manipulates patterns of maternal sensory signals affords direct examination of mechanisms underlying the relation between caregiving patterns and offspring HPA axis response (Bolton, Ruiz, et al., 2018; Korosi & Baram, 2010; Plotsky & Meaney, 1993; Singh-Taylor, Korosi, Molet, Gunn, & Baram, 2014). These studies demonstrate that unpredictable patterns of maternal care lead to changes in DNA methylation and aberrant development of neural systems involved in the regulation of the HPA axis. For example, there are observed disruptions in dendritic structure, connectivity, and glucocorticoid receptor gene expression in the hippocampus (Fenoglio, Brunson, & Baram, 2006; Molet et al., 2016; Weaver et al., 2004). In addition, unpredictable maternal sensory signals modulate the number and efficacy of synaptic inputs onto stress-sensitive neurons (Gunn et al., 2013). Thus, it is possible that human infant exposure to unpredictable patterns of maternal sensory signals affects the development of cortisol responsivity through these neurological and epigenetic pathways.

These results should be interpreted in the context of several important study limitations. First, this study employed an observational design, which does not allow for causal inference and makes it challenging to completely rule-out alternative explanations. For example, it is difficult to separate genetic influences from experiences in observational human studies. However, experimental animal models involving cross-fostering, which obviates potential genetic confounding, have demonstrated effects of patterns of maternal sensory information on neurological systems underlying HPA responsivity (Molet et al., 2016). Second, this study included measurement of cortisol, which is only one component of the HPA axis response. The benefit of studying cortisol in young children is that it can be measured noninvasively (e.g.,

saliva collection); however, future studies are encouraged to consider inclusion of additional hormones involved in HPA axis activity, such as ACTH. Last, infants were only followed to 1 year of age. Additional work is needed to determine whether the effect of unpredictable maternal sensory signals in infancy persists across developmental stages.

In summary, findings of this study suggest that unpredictable patterns of maternal sensory signals may presage blunted infant cortisol response. This result builds upon an emerging human literature indicating that unpredictability is a type of early adversity with implications for brain and behavioral development (Baram et al., 2012; Davis et al., 2017, 2019; Glynn & Baram, 2019; Glynn et al., 2018, 2019).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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[Correction added on March 17, 2020 after first online publication: The last author name "Elysia P. Davis" was changed to "Elysia Poggi Davis".]