Published in final edited form as:

Psychol Sci. 2011 May ; 22(5): 650–658. doi:10.1177/0956797611404084.

Hypothalamic-Pituitary-Adrenal Axis Reactivity in the Preschool-Aged Offspring of Depressed Parents: Moderation by Early Parenting

Lea R. Dougherty,
University of Maryland, College Park

Daniel N. Klein,
Stony Brook University

Suzanne Rose, and
Stony Brook University

Rebecca S. Lupton
Stony Brook University

Abstract

The hypothalamic-pituitary-adrenal (HPA) axis is posited to play a role in the pathogenesis of depression. We tested the hypothesis that parenting behavior would moderate the relation between parental lifetime depression history and offspring's cortisol reactivity to a psychosocial stressor. A sample of 160 preschool-aged children was exposed to stress-inducing laboratory tasks, and four salivary cortisol samples were obtained. Parents completed clinical interviews and an observational parent-child interaction task. Parental hostility moderated the relation between parental depression and offspring cortisol reactivity. Only offspring whose parents had a history of depression and demonstrated hostility toward their child evidenced high and increasing cortisol levels. The moderating effect was specific to offspring who were exposed to maternal depression during the first few years of life. Similar to findings in animals, this study underscores the importance of the early rearing environment in the intergenerational transmission of stress sensitivity.

Keywords

Depression; HPA-axis reactivity; cortisol; risk for depression; offspring; parenting

Major depressive disorder (MDD) is a chronic mental illness that affects a significant portion of the population and is a leading cause of disability worldwide (Michaud, Murray, & Bloom, 2001). One of the most consistent and robust findings in depression research is the relation between life stress and the onset and course of depression (Monroe, Savich, & Georgiades, 2009). The hypothalamic-pituitary-adrenal (HPA) axis, one of the body's major stress-response systems, is frequently posited to mediate associations between stress and depression (Holsboer, 2000). Thus, it has been hypothesized that individual differences in biological reactivity to stressors may predispose some individuals to depression (Gotlib, Joormann, Minor, & Hallmayer, 2008).

Abnormalities in HPA-axis reactivity to psychosocial stress have been observed in both depressed adults and youths (for reviews see Burke, Davis, Otte, & Mohr, 2005; Lopez-Duran, Kovacs, & George, 2009). In addition, a few studies have found increased cortisol reactivity in the infants of depressed mothers (Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007; Brennan et al., 2008; Feldman et al., 2009), suggesting that increased HPA-reactivity is present in at-risk offspring and may precede and possibly contribute to the development of depression. Nevertheless, little is known about the developmental origins of HPA-axis reactivity in the offspring of depressed parents, and no studies, to our knowledge, have examined whether these effects are evident beyond infancy.

Currently, it is unclear whether abnormalities in cortisol function in the offspring of depressed mothers are direct reflections of a familial vulnerability for depression, result from exposure to maternal depression and its effects on parenting, or result from their joint, interactive effects, as these factors are often confounded. There is evidence that children's cortisol reactivity is moderately heritable (Steptoe, van Jaarsveld, Semmler, Plomin, & Wardle, 2009). Moreover, there are compelling data from both animal and human studies that the early rearing environment and the parent-child relationship contribute to individual differences in cortisol reactivity (Francis et al., 1999; Gunnar & Vazquez, 2006).

There is a significant gap in our knowledge of the influence of the early parenting context on the relation between parental depression and offspring's stress physiology (Murray, Halligan, Goodyer, & Herbert, 2010). Maternal depression has been associated with problematic parenting, specifically, negative, hostile child-rearing behaviors (Lovejoy, Graczyk, O'Hare, Neuman, 2000). Furthermore, parental hostility is the parenting dimension most strongly linked to depression in older youth (McLeod, Weisz, & Wood, 2007) and disturbances in offspring's neuroendocrine functioning (Gunnar & Vazquez, 2006).

Consistent with diathesis-stress models that propose individual differences in susceptibility to environmental experiences (Monroe & Simons, 1991), and particularly heightened risk in the offspring of depressed parents (Goodman & Gotlib, 1999), we aim to determine whether a maladaptive parenting context moderates the relation between parental depression history and offspring's cortisol reactivity. Because early parenting appears to impact the development of offspring's regulatory capacities to respond to stress, the parenting context may serve as a moderating factor that perturbs HPA-axis reactivity in high-risk offspring. Furthermore, it is well-documented that there is significant neuroplasticity during the first several years of life (Nelson, de Haan, & Thomas, 2006), which may make the brain more vulnerable to contextual risks, including parental depression and maladaptive parenting.

This study examined whether parental hostility moderates the relation between parental depression history and offspring's cortisol reactivity to a psychosocial stressor. We used an observational measure of parenting to assess hostility directed at the child. We hypothesized that offspring of parents with a history of depression and who also evidence current hostile parenting behaviors would exhibit the highest cortisol responses. We also explored the role of the timing of parents' depression, as there is emerging evidence suggesting that maternal depression occurring early in the offspring's development may particularly impact the child's stress system (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Essex, Klein, Cho, & Kalin, 2002; Halligan, Herbert, Goodyer, & Murray, 2004). We focused on preschool-aged children because depression is rare before middle-late childhood, and we wanted to ensure that cortisol dysfunction was not a concomitant or consequence of depression.

Method

Participants

The sample was obtained from a consecutive series of 166 children who were recruited from a larger community sample participating in a study on risk for depression ($N = 559$) (Olino, Klein, Dyson, Rose, & Durbin, in press). One hundred sixty children (80 females) completed the cortisol assessment. There were no significant differences between families who did and did not participate in the cortisol assessment on any key variable.

Participants were identified using a commercial mailing list. Children between the ages of 3 and 4 years, with no significant medical/developmental disabilities, who lived with at least one English-speaking biological parent were eligible. Children's mean age was 43.5 months ($SD = 2.8$). Most children were Caucasian (87.5%) and came from two-parent (98.1%), middle-class families, as measured by Hollingshead's Four Factor Index of Social Status ($M = 46.1$; $SD = 10.3$) (Hollingshead, 1975). Children were of average cognitive ability as indexed by the Peabody Picture Vocabulary Test ($M = 105.0$, $SD = 14.1$) (Dunn & Dunn, 1997). No children met criteria for a mood disorder as assessed in a parent interview using the Preschool-Age Psychiatric Assessment (PAPA; Egger, Ascher, & Angold, 1999).

Measures

Parental Psychopathology—Biological mothers and fathers of the children were interviewed using the Structured Clinical Interview for DSM-IV, non-patient version (SCID-NP; First, Spitzer, Gibbon, & Williams, 1996). If a parent could not be interviewed, we obtained information from the co-parent using the family history method. Based on audiotapes of 30 assessments, interrater reliability (kappa) for lifetime mood disorder was .93. We had diagnostic information on 152 mothers and 148 fathers. Direct SCID interviews were obtained from all mothers and 118 (79.7%) fathers. MDD and dysthymic disorder (DD) were collapsed into a single category reflecting depressive disorder. Of the parents, 45 (29.6%) mothers and 22 (14.9%) fathers had a history of MDD or DD. Children were considered to have a family history of depression if either parent had a diagnosis ($n = 58$; 38.2%). If a parent had lifetime MDD or DD based on the SCID, the onset and offset dates of all episodes were recorded to determine whether the parent was depressed during the child's life. Of the parents, 26 (17.1%; 19 mothers, 8 fathers) had MDD or DD during the child's life. Only 5 parents (3.3%) had a current depressive disorder. No parent had a history of bipolar disorder, and no mothers reported taking psychotropic medication during pregnancy.

Parental Hostility—Of the 160 children, 149 (93.1%) participated with a parent (96.0% mothers) in a second laboratory session that included a modified version of the Teaching Tasks battery (Egeland et al., 1995). The battery included six standardized tasks (e.g., book-reading, block-building) designed to elicit different parent and child behaviors. Parental hostility, which captures a parent's expression of anger, frustration, and/or criticism toward the child, was rated on a five-point scale for each task and ratings were averaged across tasks ($M = 1.17$, $SD = .27$, Range: 1–3). Coders were unaware of the data on parental psychopathology and the cortisol assessment. The internal consistency ($\alpha = .76$) and the interrater reliability ($ICC = .83$, $n = 55$) of the hostility scale were acceptable.

Cortisol Collection and Stress Task

During the initial laboratory visit, which took place at either 1000h (68.8%) or 1400h, children participated with a female experimenter in 12 standardized tasks selected from the Laboratory Temperament Assessment Battery (Lab-TAB; Goldsmith et al., 1995). Tasks were designed to elicit a range of emotions and behaviors from the child. Parents were asked

to refrain from feeding their child for one-hour prior to coming to the laboratory, and from giving their child caffeinated products for two hours prior to the session, as these factors are known to alter cortisol values (Gunnar & Talge, 2008).

Similar to other studies employing stress assessments in preschool-aged children, we used sequential measures of salivary cortisol to capture the continuous activity of the HPA-axis in response to the challenges (Luby et al., 2003; Talge, Donzella, & Gunnar, 2008). The timing of samplings was based on findings that salivary cortisol levels reflect the degree of stress experienced in the prior 20–40 minutes (Dickerson & Kenemy, 2004). The first sample was collected 20 minutes following adaptation to the laboratory. The second sample was collected 30 minutes following the Stranger Approach task, which has been used to evoke individual differences in cortisol reactivity in preschoolers (Luby et al., 2003). During this episode, the child was separated from his/her parent and a stranger entered the room and slowly approached the child. The third salivary cortisol sample was taken 60 minutes after Stranger Approach, which was 30 minutes after a frustration-inducing stressor. In this episode, the experimenter locked a toy in a transparent box. The child was then left alone with a set of keys, none of which fit the lock, to try to open the box. The final sample was collected 20 minutes after the final task, which was another frustration-inducing stressor. During this task, the child was left alone with a wrapped empty box to open, under the pretense that an appealing toy was inside. In sum, samples were taken at baseline (0 min), 30 minutes after Stranger Approach (+60 min after the initial sample), 60 minutes after Stranger Approach (+90 min), and 20 minutes after the final task (+130 min).

Saliva for cortisol determination was obtained by having children dip a 2-inch cotton dental roll into .025 g of cherry Kool-Aid® mix. Children then placed the cotton in their mouths until saturated. The wet cotton was then expressed into vials for storage at -20°C until assayed. Samples were shipped to the Biochemistry Laboratory at the University of Trier. Samples were assayed in duplicate, using a time-resolved fluorescence immunoassay with fluorometric end-point detection (DELFI). The use of the oral stimulant was carefully monitored across all samples. The procedures employed here have been shown to yield little-to-no effect on cortisol concentrations (Talge et al., 2005). Inter- and intra-assay coefficients of variation were 7.1%–9.0% and 4.0%–6.7%, respectively.

Potential confounds—Several factors were assessed as potential confounds on children's cortisol levels: child age, gender, time of visit, parental lifetime anxiety ($n = 66$; 41.3%) and substance-use ($n = 76$; 50.0%) disorders, observer-rated child activity level during the visit, and parent-reported child internalizing and externalizing problems as assessed using the Child Behavior Checklist/1½–5 (Achenbach & Rescorla, 2000). Child activity ($\alpha = .73$; ICC = .85) was coded on a single scale for each episode of the Lab-TAB and averaged across episodes.

Results

Table 1 shows the means, standard deviations, and N 's for the covariates and cortisol levels in nanomoles per liter (nmol/L) by parental depression history. Offspring of parents with a history of depression were significantly more likely to also have a parent with a lifetime anxiety disorder ($p < .001$), had significantly more internalizing problems ($p = .008$), were younger three-year olds ($p = .048$), attended more afternoon visits ($p = .006$), and had a trend for more externalizing problems ($p = .084$). Parental depression history was not significantly associated with current parental hostility ($p = .176$).

Stress reactivity, parental depression, and parenting

Because the cortisol samples were nested within individuals, we estimated the effects of parental depression, parental hostility and their interaction with multilevel modeling (Singer & Willett, 2003). Multilevel modeling allows an assessment of individual-level cortisol change (level-1) and correlates of individual-level differences in change (level-2). A log10 transformation of cortisol values yielded an unskewed response variable and was treated as the dependent variable.

Two levels of equations were estimated. On level-1, we estimated each individual's cortisol levels at baseline (i.e., intercept) and their change in cortisol in response to the stressors (i.e., slope and curvature). As seen in Table 2, the level-1 model demonstrated that mean cortisol levels evidenced a significant linear decrease in slope from sample 1 to 2 followed by a rise for samples 3 and 4, as evidenced by a significant positive quadratic effect. The random error terms associated with the intercept, slope and curvature were significant, demonstrating variability among children's cortisol activity, supporting the examination of between-person predictors of these components. The observed cortisol responses are similar to those reported in other studies of young children using analogous stress-inducing tasks (Gunnar, Talge, & Herrera, 2009).

On level-2, we initially examined potential confounds on children's cortisol. Afternoon visits were significantly associated with a lower intercept ($p = .013$), marginally associated with less of a decline in linear slope ($p = .064$), and significantly associated with a slower, flatter rate in curvature ($p = .043$). This reflects the expected diurnal rhythm in cortisol levels across the day. Older three-year olds had lower baseline cortisol levels ($p = .035$). Child sex, parental lifetime anxiety and substance-use, socioeconomic status, child activity and internalizing and externalizing symptoms were not associated any component of the growth curve. In all remaining analyses, time of visit and child age were included as covariates at level-2.

Next, we examined associations between offspring's cortisol responses and parental depression history and parental hostility. Parental lifetime depression was not significantly associated with the intercept ($\beta = -.05$, $SE = .05$, $t(148) = -.96$, $p = .341$), slope ($\beta = .00$, $SE = .04$, $t(148) = .04$, $p = .967$), or curvature ($\beta = .00$, $SE = .01$, $t(148) = .12$, $p = .906$) of offspring's cortisol activity. Parental hostility was significantly associated with a higher intercept ($\beta = .19$, $SE = .08$, $t(145) = 2.35$, $p = .020$), marginally significantly associated with a positive linear slope ($\beta = .16$, $SE = .09$, $t(145) = 1.86$, $p = .064$), and significantly associated with a concave downward curvature ($\beta = -.04$, $SE = .02$, $t(145) = -2.40$, $p = .016$).

The interaction between parental depression and parental hostility was significantly associated with the slope and curvature of offspring's cortisol activity (see Table 2). As seen in Figure 1, for offspring of parents with lifetime depression, parental hostility was significantly associated with a higher intercept ($\beta = .06$, $SE = .03$, $t(143) = 2.33$, $p = .021$), an increasing slope ($\beta = .08$, $SE = .02$, $t(143) = 3.25$, $p = .001$), and a flatter curvature ($\beta = -.02$, $SE = .01$, $t(143) = -3.95$, $p = .001$), whereas for offspring of parents with no lifetime depression, parental hostility was not significantly associated with the intercept ($\beta = .11$, $SE = .07$, $t(143) = 1.60$, $p = .112$), slope ($\beta = -.05$, $SE = .05$, $t(143) = -1.00$, $p = .317$), or curvature ($\beta = .01$, $SE = .01$, $t(143) = .50$, $p = .616$). Thus, the combination of parental depression and high parental hostility was associated with high and increasing offspring cortisol levels. Results were similar when controlling for parental anxiety and substance-use disorders, and no interactions between these disorders and parental hostility were observed.

Child exposure to parental depression

We explored whether the findings varied as a function of the timing of parents' depression. Using multilevel modeling with dummy-coded variables indicating the timing of parents' depression, parental depression occurring during the child's life ($n = 26$) and parental depression occurring only prior to the child's life ($n = 32$) were not significantly associated with children's cortisol responses.

We next examined whether the interaction between parental depression history and parental hostility varied as a function of the timing of parents' depression. Only the interaction between parental depression during the child's life and parental hostility was significant. For children who were exposed to parental depression during their first few years of life, parental hostility was significantly associated with higher intercept ($\beta = .29$, $SE = .13$, $t(139) = 2.17$, $p = .031$), increasing slope ($\beta = .37$, $SE = .05$, $t(139) = 7.53$, $p < .001$) and a flatter curvature ($\beta = -.09$, $SE = .01$, $t(139) = -7.76$, $p < .001$). This interaction was not observed for children whose parents had depression only prior to the child's birth or whose parents had no lifetime depression.

Parallel analyses were conducted examining the effects of maternal ($n = 45$) and paternal ($n = 22$) depression separately. Results were similar for the main effects; however, only the interaction between maternal depression and parental hostility was significantly associated with the intercept, slope, and curvature of offspring's cortisol responses.

Area under the curve (AUC)

In addition to multilevel modeling, we calculated the area under the curve (AUC) with respect to ground (AUC_g) and the increase (AUC_i) in cortisol following Pruessner and colleagues (2003). The AUC_g is an estimate of total cortisol secretion, and the AUC_i is an estimate of the total change in cortisol, which captures overall reactivity. The majority of children (63.8%, $N = 102$) exhibited a positive AUC_i (see Table 1). Parental lifetime depression was not significantly associated with AUC_g ($pr = -.03$, $p = .679$) but showed a trend-level association with AUC_i ($pr = .14$, $p = .095$). Parental hostility was significantly associated with both AUC_g ($pr = .31$, $p < .001$) and AUC_i ($pr = .19$, $p = .020$). Next, after entering parental depression history, hostility and the covariates in Step 1, we examined whether the interaction term entered at Step 2 was associated with AUC_g and/or AUC_i using multiple regression. The interaction between parental depression and parental hostility was significantly associated with AUC_i ($pr = .21$, $p = .014$) but not with AUC_g ($pr = .12$, $p = .166$). Results were similar to those reported using multilevel modeling and are presented in Figures 2a and 2b.

Children exposed to parental depression showed a trend ($p = .087$) for greater change in AUC_i ($M = 3.97$, $SD = 11.77$) than children of parents with no lifetime depression ($M = -2.32$, $SD = 15.00$), but did not differ from children whose parents had a depressive episode prior to the child's life ($M = -.00$, $SD = 3.85$). There was a significant linear trend in AUC_i, $F(1,149) = 4.94$, $p = .028$, demonstrating that AUC_i increased with respect to timing of parental depression. This effect was specific to maternal depression.

Discussion

We examined whether the non-depressed, preschool-aged offspring of parents with lifetime depression demonstrated increased cortisol reactivity to a psychosocial stressor and whether parenting behavior moderated this relation. Offspring of parents with lifetime depression and who displayed hostile parenting behaviors during an observational task evidenced high and increasing cortisol levels in response to the laboratory stressors. In contrast, offspring of parents with lifetime depression and whose parents demonstrated low hostility did not

evidence increasing cortisol responses and were similar to the offspring of parents with no lifetime depression. We further noted that the moderating effect of parental hostility was specific to children whose *mothers* had been depressed during the child's lifetime, highlighting the integral role of mother-child relationships on children's developing neuroendocrine system.

Our work extends the literature documenting increased stress reactivity in depressed individuals and those at risk for depression and underscores the significance of contextual factors on the early regulatory capacities of the stress system. Our results are consistent with another study observing higher basal cortisol levels in the infants of mothers with a psychiatric diagnosis and who displayed insensitive parenting behaviors (Kaplan, Evans, & Monk, 2008). These findings are consistent with longitudinal research suggesting that the origins of stress sensitivity in depressed adults are rooted in childhood experiences (e.g., Dougherty, Klein, Davila, 2004; Hammen, Henry, & Daley, 2000), and indicate that early hostile parenting may exacerbate, rather than mediate, the effects of parental psychopathology. Nevertheless, a large body of research has shown that having a depressed parent is associated with numerous biological and environmental risks, including genetic and neurobiological susceptibility, and maladaptive parenting and familial contexts (Goodman & Gotlib, 1999). Therefore, the processes involved in these relations are likely multifaceted, and further investigation into the transmission of risk is needed.

The moderating effect observed in this study appears to be specific to maternal depression occurring during the child's life, which is consistent with an early programming hypothesis and evidence from animal research documenting the intergenerational transmission of stress reactivity via parental care (Francis et al., 1999). Moreover, there is emerging evidence suggesting that maternal depression during the child's first few years has a particularly strong impact on offspring's stress systems. For instance, maternal depression during the child's first few years has predicted elevated basal cortisol levels later in childhood (Ashman et al., 2002; Essex et al., 2002; Halligan et al., 2004), and now our study is the first to show a similar effect on cortisol reactivity. Overall, these findings suggest that the first few years of life may capture a sensitive neurodevelopmental period, and environmental exposures during this period may lead to lasting perturbations on offspring's stress physiology.

Unlike findings in infants of depressed mothers, we did not observe that preschool-aged offspring of parents with depression, as a group, evidenced increased cortisol reactivity. Differences in findings may be due to the timing of exposure to maternal depression during the post-partum period, which may be a particularly sensitive period in the development of the stress system. Additionally, as previous samples were selected for risk, the depressed mothers may have had more severe forms of depression or greater hostility and many more mothers may have been currently depressed, which may have created a main effect and masked an interaction.

The study had a number of strengths. This is the first study that has examined stress reactivity in the offspring of parents, including mothers and fathers, with a history of depression beyond infancy. Even though our findings appear to be specific to maternal depression, this should be interpreted with caution, given the limited number of fathers with depression. This study also had a number of methodological strengths, including four cortisol samplings in response to laboratory challenges; an observational assessment of parenting; and attention to whether or not the child was exposed to parental depression. Lastly, we examined stress reactivity during early childhood, which may be an important time in investigating the stress system and the rearing context, perhaps because of developmental processes that increase neurobiological plasticity in response to environmental influences.

This study also had limitations. First, the study was cross-sectional, and causal effects cannot be tested. Second, the sample was largely Caucasian and from two-parent families. Future studies should examine these associations in more diverse samples. Third, similar to other studies in young children, the laboratory paradigm did not evoke increases in cortisol in all children, which poses difficulty in interpreting the results in terms of *cortisol reactivity* (Gunnar et al., 2009); nevertheless, significant variability in children's responses was observed, which afforded the examination of individual differences in cortisol responses. Additionally, since we did not assess children's cortisol levels under a no stress condition at matched times to the laboratory samplings, we cannot be certain that the observed increases in cortisol were due to the stress manipulation or rather a more general disturbance in offspring's diurnal rhythm. Fifth, we are unable to take account of possible genetic or child characteristics that could underlie these relations (Gotlib et al., 2008). Lastly, the study relied on retrospective parent-reports of the timing of depression, and we assessed current parenting behaviors in one parent (typically the mother), which may have influenced why the interactive effect was specific to mothers. It is important to replicate our findings using a longitudinal design that assesses the course of parental depression along with concurrent maternal and paternal parenting.

In sum, our finding that early exposure to maternal depression and hostile parenting behaviors is associated with young offspring's increased stress sensitivity has the potential to shed light on the mechanisms involved in the transmission of risk and the origins of stress sensitivity observed in depression. Furthermore, this work may have significance beyond depression as HPA-axis abnormalities have been linked to numerous physical and mental health problems. Lastly, these results suggest the potential importance of parenting interventions for parents with depressive disorders, particularly during periods of significant neurodevelopmental plasticity.

Acknowledgments

This work was supported by the following grants: NIMH RO1 MH069942 (DNK), F31 MH075484-01A2 (LRD), the Society for a Science of Clinical Psychology Dissertation Grant Award (LRD), the Emeritus Faculty Dissertation Award (LRD), a GCRC Grant no. M01-RR10710 to Stony Brook University from the National Center for Research Resources.

References

- Achenbach, TM.; Rescorla, LA. Manual for the ASEBA Preschool Form & Profiles. Burlington, VT: University of Vermont Department of Psychiatry; 2000.
- Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkinson CW. Stress hormone levels of children of depressed mothers. *Development and Psychopathology*. 2002; 14:333–349. [PubMed: 12030695]
- Azar R, Paquette D, Zoccolillo M, Baltzer F, Tremblay RE. The association of major depression, conduct disorder, maternal overcontrol with a failure to show a cortisol buffered response in 4-month-old infants of teenage mothers. *Biological Psychiatry*. 2007; 62:573–579. [PubMed: 17336943]
- Brennan PA, Pargas R, Walker EF, Green P, Newport DJ, Stowe Z. Maternal depression and infant cortisol: Influences of timing, comorbidity and treatment. *Journal of Child Psychology and Psychiatry*. 2008; 49:1099–1107. [PubMed: 18492036]
- Burke HM, Davis MC, Otte C, Mohr DC. Depression and cortisol responses to psychological stress: A meta-analysis. *Psychoneuroendocrinology*. 2005; 30:846–856. [PubMed: 15961250]
- Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*. 2004; 130:355–391. [PubMed: 15122924]

- Dougherty LR, Klein DN, Davila J. A growth curve analysis of the course of dysthymic disorder: The effects of chronic stress and moderation by adverse parent-child relationships and family history. *Journal of Consulting and Clinical Psychology*. 2004; 72:1012–1021. [PubMed: 15612848]
- Dunn, LM.; Dunn, LM. Peabody Picture Vocabulary Test. 3rd edition. Circle Pines, Minnesota: American Guidance Service; 1997.
- Egeland, B.; Weinfield, N.; Hiester, M.; Lawrence, C.; Pierce, S.; Chippendale, K. Teaching tasks administration and scoring manual. University of Minnesota; 1995.
- Egger, HL.; Ascher, BH.; Angold, A. The Preschool Age Psychiatric Assessment: Version 1.1. Durham, NC: Center for Developmental Epidemiology, Department of Psychiatry and Behavioral Sciences, Duke University Medical Center; 1999.
- Essex MJ, Klein MH, Cho E, Kalin ND. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biological Psychiatry*. 2002; 52:776–784. [PubMed: 12372649]
- Feldman R, Granat A, Pariente C, Kanety H, Kuint J, Gilboa-Schechtman E. Maternal depression and anxiety across the postpartum year and infant social engagement, fear regulation, and stress reactivity. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009; 48:919–927. [PubMed: 19625979]
- First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW. Structured clinical interview for DSM-IV Axis I disorders: Non-patient edition (SCID-I, Version 2.0). New York: Biometrics Research, New York State Psychiatric Institute; 1996.
- Francis D, Diorio J, Liu D, Meaney MJ. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*. 1999; 286:1155–1158. [PubMed: 10550053]
- Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review*. 1999; 106:458–490. [PubMed: 10467895]
- Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA axis reactivity: A mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry*. 2008; 63:847–851. [PubMed: 18005940]
- Gunnar, MR.; Talge, NM. Neuroendocrine measures in developmental research. In: Schmidt, LA.; Segalowitz, SJ., editors. *Developmental psychophysiology: Theory, systems, and methods*. New York: Cambridge University Press; 2008. p. 343–366.
- Gunnar, MR.; Vazquez, DM. Stress neurobiology and developmental psychopathology. In: Cicchetti, D.; Cohen, D., editors. *Developmental psychopathology: Developmental neuroscience*. 2nd ed.. Vol. Vol. 2. New York: Wiley; 2006. p. 533–577.
- Halligan SL, Herbert J, Goodyer IM, Murray L. Exposure to postnatal depression predicts cortisol in adolescent offspring. *Biological Psychiatry*. 2004; 55:376–381. [PubMed: 14960290]
- Hammen C, Henry R, Daley SE. Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology*. 2000; 68:782–787. [PubMed: 11068964]
- Hollingshead, AB. Four factor index of social status. 1975. Unpublished manuscript.
- Holsboer F. The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*. 2000; 23:477–501. [PubMed: 11027914]
- Kaplan LA, Evans L, Monk C. Effects of mothers' prenatal psychiatric status and postnatal caregiving on infant biobehavioral regulation: Can prenatal programming be modified? *Early Human Development*. 2008; 84:249–256. [PubMed: 17761394]
- Lopez-Duran NL, Kovacs M, George CJ. Hypothalamic–pituitary–adrenal axis dysregulation in depressed children and adolescents: A meta-analysis. *Psychoneuroendocrinology*. 2009; 34:1272–1283. [PubMed: 19406581]
- Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: A meta-analytic review. *Clinical Psychology Review*. 2000; 20:561–592. [PubMed: 10860167]
- Luby JL, Heffelfinger A, Mrakotsky C, Brown K, Hessler M, Spitznagel E. Alterations in stress cortisol reactivity in depressed preschoolers relative to psychiatric and no-disorder comparison groups. *Archives of General Psychiatry*. 2003; 60:1248–1255. [PubMed: 14662557]

- McLeod BD, Weisz JR, Wood JJ. Examining the association between parenting and childhood depression: A meta-analysis. *Clinical Psychology Review*. 2007; 27:986–1003. [PubMed: 17449154]
- Michaud CM, Murray CJL, Bloom BR. Burden of disease—Implications for future research. *Journal of American Medical Association*. 2001; 285:535–539.
- Monroe SM, Simons AD. Diathesis-stress theories in the context of life-stress research: Implications for the depressive disorders. *Psychological Bulletin*. 1991; 110:406–425. [PubMed: 1758917]
- Monroe, SM.; Slavich, MS.; Georgiades, K. The social environment and life stress in depression. In: Gotlib, IH.; Hammen, CL., editors. *Handbook of depression*. New York, NY: Guilford Press; 2009. p. 340-360.
- Murray L, Halligan SL, Goodyer I, Herbert J. Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: A preliminary study. *Journal of Affective Disorders*. 2010; 122:218–223. [PubMed: 19632727]
- Nelson, CA.; de Haan, M.; Thomas, KM. *Neuroscience of cognitive development*. Hoboken, NJ: John Wiley & Sons; 2006. *Neural Plasticity: Background*; p. 30-43.
- Olino TM, Klein DN, Dyson MW, Rose SA, Durbin CE. Temperamental emotionality in preschool-aged children and depressive disorders in parents: Associations in a large community sample. *Journal of Abnormal Psychology*. (in press).
- Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*. 2003; 28:916–931. [PubMed: 12892658]
- Singer, JD.; Willett, JB. *Applied longitudinal data analysis: Modeling change and event occurrence*. New York, NY: Oxford University Press; 2003.
- Steptoe A, van Jaarsveld CHM, Semmler C, Plomin R, Wardle J. Heritability of daytime cortisol levels and cortisol reactivity in children. *Psychoneuroendocrinology*. 2009; 34:273–280. [PubMed: 18938040]
- Talge NM, Donzella B, Gunnar MR. Fearful temperament and stress reactivity among preschool-aged children. *Infant and Child Development*. 2008; 17:427–445. [PubMed: 19122850]
- Talge NM, Donzella B, Kryzer EM, Gierens A, Gunnar MR. It's not that bad: Error introduced by oral stimulants in salivary cortisol research. *Developmental Psychobiology*. 2005; 47:369–376. [PubMed: 16284967]

Figure 1. Multilevel regression coefficients indicating children's log₁₀ transformed cortisol levels in nanomoles/Liter (nmol/L) as a function of parental depression history and parental hostility. Regression coefficients were adjusted to account for time of cortisol data collection.

Figure 2.

a. Offspring's total change (AUCi) in cortisol in nmol/L as a function of parental depression history and parental hostility. Within-group analyses testing the significance of the slopes for the offspring groups found that among offspring with a parent with a lifetime history of depression, parental hostility was associated with greater AUCi ($b = 4.31$, $SE = 1.42$, $pr = .25$, $p < .01$). In contrast, among offspring with parents with no lifetime depression, parental hostility was not associated with AUCi ($b = -2.93$, $SE = 2.71$, $pr = -.09$, $p = .28$).

b. Offspring's total change in cortisol (AUCi) in nmol/L as a function of offspring's exposure to parental depression and parental hostility. Within-group analyses testing the significance of the slopes for the offspring groups found that among offspring who were exposed to parental depression, there was a significant and positive relation between parental hostility and AUCi ($b = 7.97$, $SE = 2.10$, $pr = .32$, $p < .01$). In contrast, there was not a significant association between parental hostility and children's AUCi for offspring whose parents were depressed before their life only ($b = .89$, $SE = 2.51$, $pr = .03$, $p = .72$) or were never depressed ($b = -2.14$, $SE = 2.41$, $pr = -.07$, $p = .38$).

Table 1

Subject characteristics and cortisol indicators for offspring of parents with and without a lifetime history of depression

	Offspring of parents with no lifetime depression (<i>n</i> = 94)	Offspring of parents with lifetime depression (<i>n</i> = 58)
Characteristic		
Sex, male (%)	56.4	41.4
Age, mean (SD), months	43.82 (2.71)	42.88 (3.00)
≥ 1 parent college graduate (%)	28.0	23.6
Time of lab visit (% 10 AM)	76.6	55.2
Activity level, mean (SD)	1.60 (.33)	1.58 (.34)
CBCL Internalizing, mean (SD)	7.83 (4.63)	10.56 (7.88)
CBCL Externalizing, mean (SD)	11.99 (6.77)	14.04 (7.44)
Parental lifetime anxiety disorder (%)	28 (29.8)	38 (65.5)
Parental lifetime substance use disorder (%)	43 (45.7)	33 (56.9)
Parenting behavior		
Parental hostility, mean (SD)	1.15 (.19)	1.21 (.36)
Salivary cortisol indicator, mean (SD)	43 (45.7)	33 (56.9%)
Cortisol level at time 1, nmol/L	5.37 (8.52)	3.50 (4.41)
Cortisol level at time 2, nmol/L	3.91 (5.46)	4.19 (7.09)
Cortisol level at time 3, nmol/L	4.26 (4.63)	3.49 (3.77)
Cortisol level at time 4, nmol/L	5.92 (5.48)	5.69 (5.96)
AUC _g , mean (SD), nmol/L	13.82 (15.01)	12.28 (14.81)
AUC _i , mean (SD), nmol/L	-2.32 (15.00)	1.77 (8.53)
AUC _i positive, N (%)	56 (59.6)	34 (58.6)

Note. AUC_g and AUC_i = area under the curve with respect to ground and increase.

Table 2

Multilevel model of associations between parental psychopathology, parenting, and children's cortisol reactivity (N = 148)

Fixed effect	β	<i>SE</i>	<i>t</i>	<i>P</i>
<i>Cortisol intercept</i>	.48	.02	20.01	.001
Time of visit (1400h)	-.11	.05	-2.05	.042
Age	-.01	.01	-1.89	.060
Parental depressive disorder	.12	.21	.58	.564
Parental hostility	.31	.17	1.77	.078
Parental depressive disorder $\times$ parental hostility	-.16	.19	-.83	.406
<i>Cortisol linear slope</i>	-.09	.02	-5.31	.001
Time of visit (1400h)	.04	.04	1.14	.256
Age	.01	.01	1.01	.316
Parental depressive disorder	-.45	.17	-2.66	.009
Parental hostility	-.11	.13	-.84	.403
Parental depressive disorder $\times$ parental hostility	.38	.15	2.63	.010
<i>Cortisol quadratic curvature</i>	.03	.00	8.27	.001
Time of visit (1400h)	-.01	.01	-1.25	.215
Age	-.00	.00	-.56	.576
Parental depressive disorder	.09	.04	2.31	.023
Parental hostility	.01	.03	.31	.754
Parental depressive disorder $\times$ parental hostility	-.07	.03	-2.23	.027
Random effect of unconditional growth curve	Variance Component	<i>SD</i>	χ^2	<i>P</i>
Level 1 intercept	.08	.28	1164.51	.001
Linear slope	.03	.17	523.71	.001
Quadratic curvature	.00	.04	500.76	.001