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Maternal distress and child neuroendocrine and immune regulation

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ABSTRACT

Rationale: Neuroendocrine-immune regulation is essential for maintaining health. Early-life adversity may cause dysregulation in the neuroendocrine-immune network through repeated activation of the stress response, thereby increasing disease risk.
Objective: This paper examined the extent to which maternal psychological well-being moderates neuroendocrine-immune relations in children.
Methods: We used data from a laboratory-based study of mothers and their five-year old children (n = 125 mother–child pairs) conducted from 2011 to 2013 in Baltimore, Maryland. Child saliva was assayed for markers of immune function (i.e., cytokines: interleukin [IL]-1β, IL-6, IL-8, tumor necrosis factor alpha [TNF-α]) and hypothalamic-pituitary-adrenal activity (i.e., cortisol). A composite score for depressive symptoms, anxiety, and parenting stress characterized maternal psychological distress. Multilevel mixed models examined the relationship between maternal psychological well-being and child neuroendocrine-immune relations.
Results: Significant cytokine × maternal distress interactions indicated that as maternal distress increased, expected inverse cytokine–cortisol relations within children became weaker for IL-1β, IL-6, and TNF-α. Sex-stratified models revealed that these interactions were only significant among girls. Among boys, there were inverse cytokine–cortisol relations for all cytokines, and, while in the same direction as observed among girls, the cytokine × maternal distress interactions were non-significant.
Conclusion: The findings suggest that maternal distress is associated with child neuroendocrine-immune relations in saliva and may alter the sensitivity of inflammatory immune processes to cortisol's inhibitory effects. This desensitization may place the child at risk for inflammatory diseases. The findings support efforts for the early detection and treatment of at-risk mothers to protect maternal and child health and well-being.

1. Introduction

Early-life adversity contributes to poorer mental and physical health throughout life (Danese and McEwen, 2012; J. Shonkoff et al., 2012). Preventing and identifying early-life adversity are increasingly important aspects of social, education, public health and clinical policies and programs aiming to promote healthy development and lifelong well-being (Brent and Silverstein, 2013; Garner et al., 2012). Developing effective interventions, however, requires advanced understanding of the mechanisms linking adversity and disease.

Early-life adversity activates a developing child's stress response. While acute activation of the stress response protects the child in the short-term and helps the child cope with immediate dangers or threats (McEwen, 2005), repeated activation of the stress response, as a consequence of chronic or frequent childhood adversities, may result in physiologic damage or dysfunction in the system of nervous, endocrine and immune processes involved in the body's response to stress (Danese and McEwen, 2012; Hertzman and Boyce, 2009; McEwen, 2005). Coordination within

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the neuroendocrine-immune (NEI) network is essential for maintaining homeostasis (Johnson, Riley, Granger, & Riis, 2013). Adversity-related NEI disruptions early in life may render the body vulnerable to imbalanced NEI activity and increase disease risk later in life. For example, adversity may make inflammatory immune processes less sensitive to inhibitory signals from the central nervous system (i.e., cortisol), thereby increasing risk for chronic inflammation (Miller et al., 2009).

Previous research suggests, however, that the negative effects of adversity on health may be buffered by a supportive caregiver (Chen, Miller, Kobor, & Cole, 2011; Miller et al., 2011; J. P. Shonkoff, 2012). A sensitive and attentive adult caregiver is one of the most important protective factors supporting child health (Chen et al., 2011; Miller et al., 2011; J. P. Shonkoff, 2012). Animal studies have shown a potential link between the quality of early-life maternal care and later-life immune functioning with dysfunctional maternal behavior associated with an inflammation-prone immune response in offspring (Coe and Lubach, 2003). While the study of these biologic effects in humans is limited, there is evidence that high levels of social support and maternal care are associated with lower and more regulated inflammatory processes in adults otherwise at risk for stress-related increases in inflammatory processes (Chen et al., 2011; Miller, Cohen, & Ritchey, 2002). These findings demonstrate the importance of social-emotional supports in NEI network regulation, particularly under high stress conditions.

Infancy and early childhood, when the hypothalamic-pituitary-adrenal (HPA) axis and immune system are undergoing developmental change, represent sensitive periods during which stress, and a supportive caregiver, may have profound, and possibly lasting, impacts on NEI network functioning (Coe and Lubach, 2003; Miller, Chen, & Zhou, 2007). Studying NEI relations in children, however, has traditionally been limited by the need for blood-based biomeasures. Blood collection can be especially difficult for studies involving children (Djuric et al., 2008). In contrast, saliva collection is minimally-invasive, low-cost and generally more socially acceptable (Djuric et al., 2008; Marques, Silverman, & Sternberg, 2010). Research focused on salivary immune markers in healthy young children is limited; however, there is a growing body of literature, especially examining interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) (El-Sheikh, Buckhalt, Granger, Erath, & Acebo, 2007; Keller, El-Sheikh, Vaughn, & Granger, 2010; Riis, Granger, DiPietro, Bandeen-Roche, & Johnson, 2015). These salivary inflammatory biomarkers open up new opportunities to gain a better understanding of NEI functioning in children and the role caregivers play in moderating stress-related damage within the NEI network. This emerging line of inquiry may help illuminate a link between early-life adversity and health, which, in turn, may contribute to more effective screening tools and interventions.

This study uses salivary biomeasures to examine whether coordination between HPA axis and inflammatory immune system functioning varies by level of maternal distress in five-year old children from diverse socioeconomic backgrounds. This paper addresses two gaps in current knowledge. First, unlike prior studies that do not adequately parse financial and psychosocial aspects of adversity (Slopen, Koenen, & Kubzansky, 2012), we used several markers of maternal psychological well-being and socioeconomic status (SES) to separate the effects of caregivers from SES. Second, rather than examining a single biologic system, we assessed relations between the HPA and immune systems to gain a nuanced understanding of the biologic consequences of early-life adversity. We hypothesized that maternal psychological well-being would moderate HPA-immune system relations regardless of SES.

2. Methods

This study used data from the Fetus to Five study, supplemented with data collected from a community sample (DiPietro et al., 2010; Riis et al., 2015).

2.1. Participants

Mother-child pairs were recruited in 2011–2013 as detailed previously (DiPietro et al., 2010; Riis et al., 2015). Approximately a third of the sample (58 pairs) was recruited from mothers who participated in a fetal development study in 2006–2007. Enrollment in the fetal development study was limited to low-risk, healthy women (DiPietro et al., 2010). To increase the diversity of the sample, an additional 93 participant pairs were enrolled from Baltimore, Maryland via community postings. English fluency was required, and child participants had to be five-years old. Mother-child pairs were excluded if mothers reported that the child had health or developmental conditions impairing cognitive, motor, or regulatory functioning.

2.2. Procedures

The Johns Hopkins Bloomberg School of Public Health Institutional Review Board approved the study protocol. Mothers provided written consent. During a 90-minute study visit, five-year old children (Mean [*M*] = 5.45 years, standard deviation [*SD*] = 0.29) completed neuropsychological and behavioral assessments and participated in emotional stressor tasks. Four saliva samples were collected from children; two before and two after the stressor tasks (*M* [*SD*] minutes from sample 1–2 = 12.15 [2.87]; 2–3 = 14.58 [2.94]; 3–4 = 23.36 [6.06]). Mothers provided sociodemographic and child health information, and completed a battery of psychological assessments.

2.2.1. Emotional stressor tasks

Children participated in three age-appropriate emotional stressor tasks including: the Disappointing Gift Game, the Not Sharing Game, and Mischel's Delay of Gratification Task (Mischel and Mischel, 1983). These tasks elicit negative emotions and challenge behavioral and emotional regulation (Cole, Zahn-Waxler, & Smith, 1994; Gagne, Hulle, Aksan, Essex, & Goldsmith, 2011; Jahromi and Stifter, 2008; Kieras, Tobin, Graziano, & Rothbart, 2005; Mischel and Mischel, 1983; Spinrad et al., 2009). The Not Sharing Game also elicits an increase in salivary cortisol in young children (Spinrad et al., 2009). Detailed descriptions of the tasks were previously published (Riis et al., 2015).

2.2.2. Family sociodemographic data

Sociodemographic data included: family income, maternal education, marital status, and the number of moves during the child's life. Financial stress was measured using a six-item instrument adapted from Essex and colleagues (Essex, Klein, Cho, & Kalin, 2002) assessing the frequency of financial stressors in the last three months (e.g., difficulty paying bills, fears of losing home/job).

2.2.3. Maternal psychological measures

Maternal psychological well-being was measured using three commonly-used, validated instruments. Maternal depressive symptoms in the last week were measured using the Center for Epidemiologic Studies Depression Scale (CESD-20; Radloff, 1977). Trait-anxiety was assessed using the Speilberger State-Trait Anxiety Inventory-Form Y2 (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Maternal parenting and life stress were measured using the Parenting Stress Index-Short Form (PSI; Aibidin, 1995).