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Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress

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Summary Early life stress can alter hypothalamic pituitary adrenal (HPA) axis function. Differences in cortisol levels have been found in preterm infants exposed to substantial procedural stress during neonatal intensive care, compared to infants born full-term, but only a few studies investigated whether altered programming of the HPA axis persists past toddler age. Further, there is a dearth of knowledge of what may contribute to these changes in cortisol. This prospective cohort study examined the cortisol profiles in response to the stress of cognitive assessment, as well as the diurnal rhythm of cortisol, in children ($n = 129$) born at varying levels of prematurity (24—32 weeks gestation) and at full-term (38—41 weeks gestation), at age 7 years. Further, we investigated the relationships among cortisol levels and neonatal procedural pain-related stress (controlling for multiple medical confounders), concurrent maternal factors (parenting stress, depressive and anxiety symptoms) and children's behavioral problems. For each aim we investigate acute cortisol response profiles to a cognitive challenge as well as diurnal cortisol patterns at home. We hypothesized that children born very preterm will differ in their pattern of cortisol secretion from children born full-term, possibly depended on concurrent child and maternal factors, and that exposure to neonatal pain-related stress would be associated with altered cortisol secretion in children born very preterm, possibly in a sex-dependent way. Saliva samples were collected from 7-year old children three times during a laboratory visit for assessment of cognitive and executive functions (pretest, mid-test, end—study day acute

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stress profile) and at four times over two consecutive non-school days at home (i.e. *morning*, *mid-morning*, *afternoon* and *bedtime*—diurnal rhythm profile). We found that cortisol profiles were similar in preterm and full-term children, albeit preterms had slightly higher cortisol at bedtime compared to full-term children. Importantly, in the preterm group, greater neonatal procedural pain-related stress (adjusted for morphine) was associated with lower cortisol levels on the study day ($p = .044$) and lower diurnal cortisol at home ($p = .023$), with effects found primarily in boys. In addition, child attention problems were negatively, and thought problems were positively, associated with the cortisol response during cognitive assessment on the study day in preterm children. Our findings suggest that neonatal pain/stress contributes to altered HPA axis function up to school-age in children born very preterm, and that sex may be an important factor.

1. Introduction

During their stay in the neonatal intensive care unit (NICU) infants born at very low gestational age undergo many stressful and painful procedures. Early life stress is known to permanently affect neurobiological, hormonal and physiological systems (Heim and Nemeroff, 2002). Preterm infants are particularly at risk for adverse effects of early stress, since their physiological systems are very immature during their time in NICU. Their brains are in period of rapid development (Herlenius and Lagercrantz, 2004; Volpe, 2009) and their stress systems are sensitive to programming (Matthews, 2002) while they are exposed to repeated painful procedures in the NICU. Further, animal studies suggest that early life stress can have sex-dependent effects (e.g. Darnaudery and Maccari, 2008), Although less is known about the impact of early adversity and gender differences in humans, studies are emerging suggesting differential vulnerabilities for males and females in humans (e.g. Sandman et al., 2013; Ruttle et al., 2014). Since pain and stress are difficult to disentangle in very preterm infants, we use the term ''pain-related stress'' to capture stress of invasive procedures (Grunau et al., 2013). Although necessary, frequent invasive procedures during hospitalization of very preterm infants such as blood draws or injections (i.e. 'pain-related stress') may contribute to altered programming of neuroendocrine systems such as the hypothalamic pituitary adrenal (HPA) axis and thus influence stress-related behaviors long-term in children born very preterm (Brummelte et al., 2012; Zouikr et al., 2014). Considering the importance of cortisol in the regulation of behavior and cognition, and the vulnerability of the preterm population to problems in neurodevelopment (e.g. Grunau et al., 2006; Aarnoudse-Moens et al., 2009), it is essential to better understand the mechanisms underlying the differences in HPA axis function, as well as contextual influences that may modulate development of the HPA axis in children born preterm (Brummelte et al., 2011). In a longitudinal cohort, Grunau and colleagues have shown that infants and toddlers born very preterm exhibit altered HPA axis functioning at 3, 8 and 18 months corrected age (CA; age adjusted for prematurity) long after discharge from the NICU (Grunau et al., 2007). Infants born at extremely low gestational age (ELGA; 24—28 weeks gestation) and very low gestational age (VLGA; 29—32 weeks gestation) had significantly lower basal cortisol levels in the NICU (Grunau et al., 2005) and at 3 months CA compared to full-term infants, but at 8 and 18 months CA, ELGA infants had higher cortisol levels than VLGA and full-terms (Grunau et al., 2007). Furthermore, in this cohort, infant and toddler behavior was related to cortisol levels at 3 months (Haley et al., 2008), 8 months (Tu et al., 2007) and 18 months (Brummelte et al., 2011) CA. For instance, at 18 months of age, ELGA children with higher internalizing behaviors (anxiety/depressive symptoms) showed higher basal cortisol levels and more prominent changes in cortisol in response to a cognitive challenge (Brummelte et al., 2011). Although altered patterns of cortisol secretion have been associated with internalizing behavior in children born both preterm (Brummelte et al., 2011) and full-term (Essex et al., 2010), behavioral problems are particularly prevalent and persistent in children born very preterm (for review see: de Jong et al., 2012). Moreover, preterm children appear to be particularly sensitive to environmental influences such as maternal behavior compared to full-term children (Tu et al., 2007; Brummelte et al., 2011). However, little is known of the etiology of these developmental problems and sensitivities in children born very preterm and their association with altered HPA axis function. In other studies, low birth weight has been associated with altered blood pressure and autonomic stress response in children and adults of varying ages; however, studies investigating the cortisol stress response in older children or adults born with low birth weight or low gestational age compared to controls found either non-significant or mixed results (for detailed review see: Kajantie and Raikkonen, 2010). The diurnal cortisol profile (i.e. variations in cortisol levels across the day), has received even less attention; however, one study found that children born preterm (albeit in a small sample) had higher awakening cortisol levels than those born full-term at school-age (Buske-Kirschbaum et al., 2007). As mentioned above, altered cortisol levels may be a result of early stress-induced programming of the HPA axis (Matthews, 2002; Meaney et al., 2007), however it is important to take into account potentially modulating current or prevailing influences such as maternal stress when investigating the impact of early life stress on later HPA axis function (Williams et al., 2013).

We have previously found that children born extremely preterm display behaviors indicative of stress during cognitive assessment at school age significantly more than children born full-term (Whitfield et al., 1997). Moreover we have found that their cortisol response differed during focused attention at 8 months (Grunau et al., 2004) and developmental assessment at 18 months