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No association between hair cortisol or cortisone and brain morphology in children

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ABSTRACT

Little is known about the relationship between the long-term hypothalamic-pituitary-adrenal (HPA) axis functioning and brain structure in children. Glucocorticoid in hair has emerged as an important biomarker of HPA activity. In this study, we investigated the associations of hair cortisol and cortisone concentrations with brain morphology in young children. We included 219 children aged 6–10 years from the Generation R Study in Rotterdam, the Netherlands. We examined cortisol and cortisone concentrations by hair analysis using liquid chromatography–tandem mass spectrometry, and assessed brain morphometric measures with structural magnetic resonance imaging. The relationships of hair cortisol and cortisone concentrations with brain volumetrics, cortical thickness, cortical surface area and gyrification were analyzed separately after adjustment for several potential confounding factors. We observed a positive association between cortisol concentrations and cortical surface area in the parietal lobe, positive associations of cortisone concentrations with thalamus volume, occipital lobe volume and cortical surface area in the parietal lobe, and a negative association between cortisone concentrations and cortical surface area in the temporal lobe in the regions of interest analyses. A negative association between cortisol or cortisone concentrations and hippocampal volume was observed in children with behavioral problems. The whole brain vertex-wise analyses did however not show any association between cortisol or cortisone concentration and brain morphometric measures after correction for multiple testing. Although some associations are noted in region of interest analyses, we do not observe clear association of hair cortisol or cortisone with brain morphometric measures in typically developing young children.

1. Introduction

The biological mechanisms underlying the association between stress and various health outcomes in humans are not fully established. One extensively studied pathway is the hypothalamic-pituitary-adrenal (HPA) axis. Upon experience of stress, the hypothalamus releases corticotropin-releasing hormone, which stimulates the production of adrenocorticotropic hormone from the pituitary gland, leading to the secretion of glucocorticoids (mainly cortisol in humans) by the adrenal cortex (Lupien et al., 2009).

There is substantial evidence for a relation between hyper- or hypo-secretion of cortisol and stress from fetal life to adulthood (Gunnar and Donzella, 2002; Lupien et al., 2009). A growing body of research shows a relationship of the HPA axis regulation with cognitive development and psychopathology in children (Guerry and Hastings, 2011; Saridjan et al., 2014a). For example, cortisol

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reactivity and variation of the cortisol circadian rhythm have been associated with memory, language comprehension, posttraumatic stress disorder, and emotional and behavioral problems in children (Carrion et al., 2002; Haley et al., 2006; Saridjan et al., 2014a,b). These findings indicate that different patterns of cortisol secretion may have consequences for the structure and function of the developing brain.

Cortisone is a metabolite originating from local conversion of cortisol by the 11β-hydroxysteroid dehydrogenase type 2 enzyme. It has been considered an inactive metabolite of cortisol which can be activated by the 11β-hydroxysteroid dehydrogenase type 1 enzyme, and has represented another useful stress biomarker (Vanaelst et al., 2013). Thus, the assessment of cortisone in parallel with cortisol can provide a more systematic evaluation of the effect of active and inactive glucocorticoids. Moreover, cortisone concentrations have been shown to be higher than those of cortisol in the hair of children, thus cortisone might be more reliably measured than cortisol (Raul et al., 2004). Cortisol and cortisone concentrations in saliva, blood, or urine are regulated by the circadian rhythm and other daily fluctuations, and mainly reflect short-term glucocorticoids levels (Wosu et al., 2013). Hair has a stable growth rate and can be readily accessed and stored (Noppe et al., 2014). Although hair cortisol concentration has been only weakly correlated with single plasma or serum cortisol concentration, a recent in-depth validation study shows that hair cortisol concentration is strongly associated with the integrated salivary cortisol secretion measured over a corresponding one-month period, suggesting that the assessment of hair cortisol or cortisone allows reliable retrospective evaluation of cortisol or cortisone secretion over a time period during which the hair segment has grown (Sauve et al., 2007; Vanaelst et al., 2012; Wosu et al., 2013; Short et al., 2016).

Glucocorticoids are important for normal brain maturation and function (Pruessner et al., 2010). Their liposoluble characteristics allow them to easily cross the blood–brain barrier and access the brain. Animal studies showed that direct excessive glucocorticoid exposure can lead to decreased dendritic branching, alterations in synaptic terminal structure, disruption of cellular metabolism and increased vulnerability of neurons to insults (Bremner, 1999). Most of the current knowledge about the association between glucocorticoids and the human brain originates from studies of aging population or clinical patient samples (Lupien et al., 1998; Huang et al., 2009). These studies specifically hypothesized that exposure to toxic concentrations of glucocorticoids may contribute to brain degeneration. During childhood, the brain undergoes significant development and it might be particularly vulnerable to stress and stress hormones (Lupien et al., 2009). Existing literature suggested that higher cortisol levels in children might be associated with smaller hippocampus, amygdala, and prefrontal lobe volumes (Carrion et al., 2010; Pagliaccio et al., 2014). There has been little work exploring prolonged cortisol exposure and whole- and regional-brain morphometrics. To unravel the mechanisms determining the structural heterogeneity of the developing brain in relation to stress, it is necessary to understand the potential association between cumulative effect of HPA axis activity and brain morphology in children.

The aim of this study was therefore to enrich the understanding on the impact of prolonged HPA axis functioning on the structural brain development by examining the associations of hair cortisol and cortisone concentrations with brain morphology separately in children aged 6–10 years. Hair samples were collected and assessed to indicate the cortisol and cortisone levels over a three month period. Magnetic resonance imaging (MRI) scans were conducted to assess different aspects of brain morphology including volumetrics, cortical thickness, cortical surface area and gyrification.

2. Materials and methods

2.1. Study participants

This study was embedded in the Generation R Study, an ongoing population-based cohort investigating growth, development and health from fetal life onward in Rotterdam, the Netherlands. This cohort has been described in detail elsewhere (Jaddoe et al., 2012) and was approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam. Parents of all participants provided written informed consent.

From September 2009 to July 2013, a total of 1070 children between the ages of 6–10 years participated in the first neuroimaging study within the Generation R Study (White et al., 2013). Exclusion criteria for participation in the neuroimaging study included contraindications for the MRI procedure (e.g., pacemaker, ferrous metal implants) and various disorders including severe motor or sensory disorders (e.g., deafness or blindness), severe neurological conditions (e.g., seizure disorder, neuromotor disorder or a history of brain tumors), moderate to severe head injuries with loss of consciousness, and claustrophobia (White et al., 2013). To improve the ethnic homogeneity of the participants, only the 726 children of Dutch national origin were eligible for the present study. Of these, 280 children were invited to participate in hair sample collection as this procedure was added to an ongoing data collection nearly 2 years after the start of the study (Kruithof et al., 2014). Twenty children did not provide hair samples due to too short hair, no consent or other reasons. The final sample for analysis consisted of 219 children after the exclusion of 41 children: 1) whose hair cortisol or cortisone concentrations were unmeasurable or determined as statistical outliers (N = 13), 2) who had unusable or poor T_1-weighted structural images (N = 8), 3) who had unusable FreeSurfer-processed MR-images (N = 18), or 4) whose MR-images were unusable due to incidental findings (N = 2) (see below and Supplementary Fig. 1 in Appendix A).

2.2. Hair cortisol and cortisone measurement

All participating children visited the Generation R research center in the Erasmus University Medical Center-Sophia Children's Hospital regularly for various somatic and behavioral assessments (Jaddoe et al., 2012). Around the child's age of 6 years, a sample of approximately 100 hairs was collected from the posterior vertex of the head. The hairs were cut as close to the scalp as possible, with the scalp end marked, stored in an envelope at room temperature, and transported to the Laboratory of Neuro-endocrinology, Department of Internal Medicine, Erasmus University Medical Center for processing and storage. The proximal 3 cm of the hair samples were used. With a growth rate of around 1 cm/month, these segments of hairs were assumed to reflect the previous 3 months' cumulative cortisol and cortisone production (Myers and Hamilton, 1951). Hair washing, and steroid extraction and cleaning have been described elsewhere (Noppe et al., 2015; Rippe et al., 2015). Cortisol and cortisone concentrations were determined on a Waters Xevo TQ-S liquid chromatography–tandem mass spectrometry (Noppe et al., 2015).

Six children, whose hair cortisol and cortisone concentrations could not be measured due to technical reasons, were excluded. To normalize data, all cortisol and cortisone measures were log10 transformed prior to statistical analysis. Seven children whose hair cortisol or cortisone concentrations (log10 transformed) fell below or above the 3 times standard deviation from the mean were considered outliers and excluded [e.g. (Pulopulos et al., 2014)]. This left 247 of the 260 children who had undergone an MRI assessment (see Supplementary Fig. 1 in Appendix A).