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Salivary alpha-amylase and cortisol in infancy and toddlerhood: Direct and indirect relations with executive functioning and academic ability in childhood

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Summary Using data from a predominantly low-income, population-based prospective longitudinal sample of 1292 children followed from birth, indicators of children's autonomic (salivary alpha-amylase; sAA) and hypothalamic—pituitary—adrenal (HPA) axis (salivary cortisol) activity at 7, 15, and 24 months of age were found to predict executive functioning at 36-months and academic achievement in pre-kindergarten. The findings suggested that the respective cortisol and sAA effects on executive functioning and academic achievement were interactive. Optimal developmental outcomes were associated with asymmetrical cortisol/sAA profiles. Higher cortisol levels were predictive of lower executive functioning and academic abilities, but only for those with concurrently moderate to high levels of sAA. In contrast, higher sAA concentrations were predictive of better executive functioning and academic abilities, but only for those with concurrently moderate

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to low levels of cortisol. These relations were statistically identical across infancy and toddlerhood. The conditional effects of cortisol and sAA on pre-kindergarten academic achievement were mediated fully by links between these early physiological indicators and executive functioning.

1. Introduction

A converging literature indicates that the physiological response to stress can impact diverse aspects of cognition, such as declarative memory and executive functioning (de Kloet et al., 1999; Joëls et al., 2006). Although the exact cellular mechanisms remain somewhat unclear, the effects of stress physiology on cognition occur, in part, through the action of neuroendocrine hormones on synaptic activity in specific brain regions (de Kloet et al., 2008; Groeneweg et al., 2011). Activation of autonomic nervous system (ANS) and hypothalamic—pituitary—adrenal (HPA) axis responses to stimulation results in increases in levels of hormones (catecholamines and glucocorticoids, respectively) that act as neuromodulators, increasing and decreasing long-term synaptic potentiation (Diamond et al., 2007; Robbins and Arnsten, 2009). At moderate levels, neuroendocrine hormones are associated with greater synaptic activity in areas of prefrontal cortex (PFC) that underlie executive functions and working memory ability. At very high or low levels, however, neuroendocrine hormones are associated with reduced activity in these brain regions (Ramos and Arnsten, 2007).

1.1. Stress physiology and cognition in children

The relation of neuroendocrine hormones to cognition has been well documented using animal models and in pharmacological studies with adults; however, far less is known about relations between stress hormones and cognition in children. Technical advances that enable the minimally invasive measurement of surrogate markers of stress-related physiology in saliva allow for the examination of these questions, even with very young children. Salivary cortisol, a glucocorticoid hormone activated by cascading processes within the HPA axis, is a well-validated marker of HPA activity in children (Schwartz et al., 1998). Normatively, baseline or 'resting' levels of cortisol tend to show a diurnal pattern across the span of the day, typically peaking shortly after waking, declining over the course of the day, and reaching nadir shortly after the onset of continuous sleep (Sapolsky et al., 2000). Cortisol production is also markedly increased during times of acute experiential stress (Kirschbaum and Hellhammer, 1989).

The limited available evidence suggests that salivary cortisol measured in early childhood may be meaningfully related to aspects of cognitive development. Higher resting cortisol levels in infancy have been linked with less effective executive functioning (Blair et al., 2011a) and short-term memory in early childhood (Bugental et al., 2010). Similarly, when confronted with a moderate stressor, cortisol profiles marked by a brief increase followed by a decrease (presumably, reflecting stress regulation) have been associated with more effective executive functioning with preschool-aged children (Blair et al., 2005).

Beyond HPA axis functioning alone, numerous investigators have underscored the importance of examining multiple physiological indicators simultaneously, as a way to potentially address cross-system coordination between the HPA axis and the autonomic nervous system (ANS) (Bauer et al., 2002; Granger et al., 2007a). The main ANS neurotransmitter, norepinephrine (NE) is also associated with executive cognitive ability (see Robbins and Arnsten, 2009), and there is a growing indication that ANS activity may be reflected in a surrogate marker found in saliva, alpha-amylase (sAA).

Salivary alpha-amylase is an enzyme released from salivary glands that helps to break down carbohydrates (Granger et al., 2007a; Rohleder and Nater, 2009). Salivary alpha-amylase levels also increase during times of acute psychological stress (Chatterton et al., 1996; Engert et al., 2011; Gordis et al., 2006; Granger et al., 2007a) and are correlated with multiple indicators of ANS activity, including plasma NE (Rohleder et al., 2004), pre-ejection period (Bosch et al., 2003), skin conductance (El-Sheikh et al., 2008), and respiratory sinus arrhythmia (Granger et al., 2006). Indeed, spurred by the demonstration that sAA may serve as a reliable and valid surrogate marker of autonomic nervous system activity (see Granger et al., 2007a; Rohleder and Nater, 2009), sAA is increasingly studied in combination with salivary cortisol in studies of development (e.g., El-Sheikh et al., 2008; Gordis et al., 2006; Rudolph et al., 2010, 2011).

The ANS and HPA axis systems are known to function in a coordinated manner to regulate stress physiology (see Sapolsky et al., 2000; Granger et al., 2007a). In particular, a growing number of studies suggest potentially asymmetric and reciprocal relations between the HPA and ANS systems, noting: (1) opposite patterns of diurnal change in which cortisol decreases and sAA increases throughout the day (Nater et al., 2007); (2) patterns of response to stress in which increase and decrease in sAA precede those in cortisol, leading to higher cortisol but lower sAA 10+ minutes post stressor (Gordis et al., 2006; Engert et al., 2011); (3) opposite long-term developmental trends in resting levels across infancy and early childhood, such that normative sAA increases are evident between 2 and 24 months of age (Davis and Granger, 2009), whereas normative decreases in children's resting cortisol levels have been shown across infancy and early childhood (Blair et al., 2011b), and (4) opposite associations of sAA and cortisol with emotionality in children, with higher levels of sAA related to approach and positive emotion and higher levels of cortisol related to withdrawal and negative emotion (Fortunato et al., 2008).

With respect to executive functioning in early childhood, no studies of which we are aware have examined the combined associations of cortisol and sAA with objective measures of executive functioning. However, in keeping with a multi-system approach (Bauer et al., 2002), recent empirical work with related phenotypes suggest that sAA and cortisol effects may be (statistically) interactive, such that the effect of one system on children's development may be conditional