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# Sex-specific prediction of hypothalamic-pituitary-adrenal axis activity by pituitary volume during adolescence: A longitudinal study from 12 to 17 years of age

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**Summary**
*Objective:* To investigate the longitudinal relationship between pituitary gland volume (PGV) and parameters of hypothalamic-pituitary-adrenal axis (HPAA) functioning during adolescence.
*Methods:* Participants were 49 adolescents (19 girls and 30 boys) selected from a larger longitudinal, population-based study of adolescent development. Assessments were conducted at three time points (S1, S2 and S3). MRI sessions were at S1 (age: $M = 12.62$, SD = 0.45 years) and S3 ($M = 16.48$, SD = 0.53 years) and multiple assessments of salivary cortisol were undertaken at S2 ($M = 15.51$, SD = 0.35 years). PGV was measured via previously validated manual tracing methods, and the cortisol awakening response (CAR) and diurnal slope (DSL) were used as indices of HPAA functioning.
*Results:* A significant sex-linked interaction was found for PGV at S1 predicting both CAR ($p = 0.025$) and DSL ($p = 0.009$) at S2. Specifically, PGV at S1 significantly predicted CAR ($p = 0.033$) and DSL ($p = 0.010$) in boys only, with no significant results found for girls. Neither CAR nor DSL at S2 predicted growth of PGV from S1 to S3.

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*Conclusions:* PGV in early adolescence predicted HPAA functioning in mid-adolescent boys but not in girls. The results suggest a significant influence of sex-specific development on the relationship between PGV and HPAA activity and reactivity. The findings have potential implications for understanding and interpreting sex-linked and stress related clinical disorders that emerge during mid-to-late adolescence.


## 1. Background

The hypothalamic-pituitary-adrenal axis (HPAA) is the major stress response system of the human body. Developmentally, HPAA functioning is characterized by an initial reactive period after birth, and a so-called stress-hyporesponsive period during childhood, before the HPAA approaches an adult (i.e., stress-hyperresponsive) level during puberty (Gunnar and Quevedo, 2007). Both prenatal and postnatal development of the HPAA appear to be sensitive to early life stress (McCrory et al., 2010) and sex hormones (Bangasser and Valentino, 2012) with both found to induce alterations in structural and functional development of the HPAA. However, it remains to be elucidated how the structural and functional aspects of the development of the HPAA interact with each other through childhood and adolescence.

Both endogenous and exogenous stressors activate the HPAA, causing the release of corticotropin releasing hormone (CRH) from the hypothalamus, which binds to receptors on the anterior pituitary gland and, through a cascade of intracellular events, increases pro-opiomelanocortin (POMC) gene expression and the release of POMC derived peptides such as adrenocorticotropic hormone (ACTH) and β-endorphin. ACTH promotes the synthesis of glucocorticoids (i.e., cortisol in primates), as well as stimulating their release from the adrenal cortex (Gunnar and Quevedo, 2007). The experimental collection of cortisol in human saliva is considered a reliable and valid measure of HPAA functioning (Hellhammer et al., 2009), with measures derived from saliva samples, such as the cortisol awakening response (CAR) and the diurnal slope (DSL), commonly being used as indices of HPAA functioning (Adam and Kumari, 2009). The diurnal cortisol rhythm is typically characterized by high levels upon waking (i.e., a substantial [50—60%] increase in cortisol concentration in the 30—45 min after waking, resulting in the CAR), and a subsequent decline over the remainder of the day, reaching a low point or nadir around midnight (resulting the DSL; Pruessner et al., 1997). Although the exact function and regulation of the profound cortisol increase after awakening is still not fully understood, the CAR is considered a reliable measure of the acute reactivity of the HPAA (Schmidt-Reinwald et al., 1999). By contrast, the DSL is best described as the rate of decline in cortisol levels across the day (Adam and Kumari, 2009), and appears to be strongly influenced by daytime HPAA activity, clearly separating this measure from the CAR, which has been shown to be somewhat independent of cortisol output during the remainder of the day (Schmidt-Reinwald et al., 1999). Therefore, the DSL may represent a measure of more tonic HPAA hyperactivity, rather than reflecting acute reactivity of the HPAA as the CAR does. Importantly, both CAR and DSL dysregulation have been associated with chronic stress and psychopathology in a range of populations (Chida and Steptoe, 2009; Cohen et al., 2006; Steptoe et al., 2005; Wingenfeld and Wolf, 2011).

While both the CAR and the DSL are considered reliable measures of HPAA activity, it is important to note that these measures represent relatively proximal states of the HPAA rather than measures of long-term trait-like aspects of the functioning of this system. Pituitary gland volume (PGV) has previously been investigated as a measure of chronic HPAA functioning, and has also been independently associated with stress and psychopathology (Garner et al., 2005; Jovev et al., 2008; Kessing et al., 2011; MacMaster et al., 2008; Takahashi et al., 2010). PGV is thought to increase with the number or size of corticotropin-releasing cells in the pituitary gland (Lorenzetti et al., 2009), which via ACTH release stimulate the release of cortisol by the adrenal cortex. Therefore, a larger PGV has previously been suggested to either predetermine, or reflect, the effects of chronically elevated HPAA activity (Jovev et al., 2008; MacMaster et al., 2006; Zipursky et al., 2011).

Although salivary cortisol and PGV are each considered indicators of HPAA functioning, only two cross-sectional studies have been performed to date assessing the relationship between the two. Axelson et al. (1992) found a significant correlation between PGV and cortisol levels following dexamethasone suppression in depressed adult patients. In contrast, a recent study investigating PGV and cortisol reactivity to acute, standardized stress in psychotic adults, their siblings and healthy controls did not detect a significant relationship between cortisol and PGV (Habets et al., 2012). It is apparent, therefore, that definitive evidence for a relationship between PGV and cortisol measures of HPAA is lacking (Kessing et al., 2011). In particular, it remains unclear whether PGV predetermines, or is a consequence of, activity of the HPAA (or both). Additionally, no studies have reported on the correlation between PGV and HPAA functioning in children and adolescents, where dramatic changes in brain structure and HPAA function occur (Blakemore et al., 2010).

Sex-differences have been reported with regard to the development of the human brain generally (Giedd et al., 1997; Whittle et al., 2011) and the HPAA in particular (Kajantie and Phillips, 2006; Kudielka and Kirschbaum, 2005). This is not surprising given that adolescence is a period of increased divergence between males and females in physical characteristics, behavior, and risk for psychopathology (Lenroot and Giedd, 2010), not to mention the sexually dimorphic aspects of pubertal development, which profoundly interact with the HPAA (Blakemore et al., 2010). Therefore, sex may be an important factor in the determination of adolescent PGV development.

The primary aim of the current study was to investigate whether PGV prospectively predicts later HPAA functioning during adolescence. Specifically, it was hypothesized that