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Early life stress alters pituitary growth during adolescence—A longitudinal study

Despina E. Ganella[a,b], Nicholas B. Allen[d,e], Julian G. Simmons[d,g], Orli Schwartz[d], Jee Hyun Kim[a,b], Lisa Sheeber[f], Sarah Whittle[c,d,*]

[a] *Behavioural Neuroscience Division, The Florey Institute of Neuroscience and Mental Health, Parkville 3052, VIC, Australia*
[b] *Florey Department of Neuroscience and Mental Health, The University of Melbourne, Parkville 3052, VIC, Australia*
[c] *Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne, and Melbourne Health, Parkville 3052, VIC, Australia*
[d] *Melbourne School of Psychological Sciences, The University of Melbourne, Parkville 3052, VIC, Australia*
[e] *Department of Psychology, University of Oregon, Eugene OR 97403, USA*
[f] *Oregon Research Institute, Eugene, OR 97403 USA*
[g] *Orygen Youth Health Research Centre, The Centre for Youth Mental Health, The University of Melbourne, Parkville 3052, VIC, Australia*

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Abstract The pituitary gland is integral in mediating the stress-response via its role in hypothalamic—pituitary—adrenal (HPA) axis function. Pituitary gland volume (PGV) is altered in stress-related psychopathology, and one study to date has shown stress to be associated with age-related PGV change during adolescence. The current study investigated the effects of a number of different types of early life (i.e., childhood and adolescent) stress (including childhood maltreatment, stressful life events, and maternal affective behavior) on PGV development from mid- to late adolescence using a longitudinal design. The influence of PGV development on depressive and anxiety symptoms was also investigated. Ninety one (49 male) adolescents took part in mother-child dyadic interaction tasks when they were approximately 12 years old, reported on childhood maltreatment and stressful life events when they were approximately 15 years old, and underwent two waves of structural magnetic resonance imaging (MRI) scans, when they were approximately 16 and 19 years old. Results revealed that childhood maltreatment predicted accelerated PGV development in females, and maternal dysphoric behavior predicted accelerated PGV development in the whole sample. PGV development was not associated with depressive or anxiety symptoms. These results suggest an effect of early life stress

* Corresponding author at: Melbourne Neuropsychiatry Centre Alan Gilbert Building, Level 3 161 Barry St, Carlton 3053, VIC Australia. Tel.: +61 3 8344 1958; fax: +61 3 9342 3743.
E-mail address: swhittle@unimelb.edu.au (S. Whittle).

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on altered HPA axis function across mid- to late adolescence. Further research is required to assess functional implications and whether these changes might be associated with risk for subsequent psychopathology.

1. Introduction

The pituitary gland is integral in mediating the stress-response via its role in hypothalamic—pituitary—adrenal (HPA) axis function. The pituitary is under the influence of hypothalamic corticotropin releasing factor (CRF) and secretes adrenocorticotropin hormone (ACTH), which works in a feedback loop to propagate the stress response, and therefore may be a region that is critically affected by stress dysregulation. The HPA system is not fully mature at birth and there are significant changes that occur throughout childhood and adolescence in both basal HPA activity and cortisol reactivity (Gunnar and Donzella, 2002). During this extended period of development, experience plays a role in shaping the basal rhythms and reactivity of the HPA system (Gunnar and Quevedo, 2007). Consequently, the developing HPA axis is likely to be particularly sensitive to early life (i.e., childhood and adolescent) experience.

It is well established that early life stress is associated with changes in basal functioning and reactivity of the HPA axis (see Heim and Nemeroff, 2001, for a review). This is supported by animal work, where prolonged early life stress in rats caused by chronic maternal separation is associated with protracted increases in CRF, ACTH and corticosterone in response to restraint stress in adulthood (Plotsky and Meaney, 1993). Complementary findings in rats reveal that increased maternal caregiving behavior is highly correlated with reduced ACTH and CORT and CRF mRNA in response to stress (Caldji et al., 1998). In humans, there is evidence that stressors such as childhood maltreatment and other adverse early life experiences may have long-term influences on HPA function, in terms of HPA axis basal activity and reactivity (Tarullo and Gunnar, 2006). However, there is some evidence that (a) different types of stressors can have differential effects, and (b) effects may change over time. Recent and chronic stress is generally associated with increases in HPA output, while distant traumas is often associated with blunted HPA axis basal activity and reactivity (Miller et al., 2007). Further, it has been suggested that early life stress may result in initial hypercortisolism in childhood and adolescence, and subsequent low basal cortisol levels and reduced stress reactivity in adulthood, and that this transition may me modulated by a normative developmental change in basal cortisol levels (i.e., increase from childhood to adolescence) (Tarullo and Gunnar, 2006). Taken together, these studies suggest that early life stress can induce long-lived changes in HPA axis function, but that different types of stressors may have effects that unfold differently over time.

Despite the central role of the pituitary gland in the HPA axis stress response, few studies have investigated the relationship between stressors and pituitary gland morphology. There is general consensus that the size of the pituitary gland may be used as an index of long-term HPA function. Pituitary gland volume (PGV) has been hypothesized to represent an increased number and/or size of CRF cells in the area (Gertz et al., 1987). Such assertions are supported by evidence that enlarged PGV reflects an increase in the size and number of the corticotrophic cells that produce and secrete ACTH, and it is hypothesized to be a consequence of either HPA axis hyperactivity or of a specific dysfunction of a subgroup of CRF neurons that provokes HPA axis hyperactivity (Pariante et al., 2004). While PGV may best be used as an index of long-term and total systemic HPA axis activity, larger PGV has been found to be associated with both cortisol awakening response and diurnal slope in humans, suggestive of a link between PVG and both HPA axis hyper tonic activity and acute reactivity (Kaess et al., 2013). Although it is important to note that current functioning of the stress system cannot be solely implied by PGV, use of PGV as an index of HPA axis function is an attractive alternative to hormone markers such as cortisol or CRF, given the relative stability of volumetric measures and relative lack of sensitivity to confounding state effects or temporal changes (Kunugi et al., 2005).

Findings that variations in PGV are commonly associated with psychiatric illnesses, where stress is thought to be a common precipitating factor, support a possible link between stress and PGV (e.g., MacMaster and Kusumakar, 2004; MacMaster et al., 2006a,b; Pariante et al., 2005; Thomas and De Bellis, 2004). Of interest, Thomas and De Bellis (2004) assessed the effect of pediatric maltreatment-related PTSD on PGV and found a significant age-by-group effect, whereby PTSD subjects had a larger PGV during the pubertal/post-pubertal, but not during the prepubertal period. This study highlights that the developmental period must be taken into account when assessing PGV in relation to adverse early life experience, particularly during adolescence when there is a well-established pituitary hypertrophy seen in both sexes (Elster et al., 1990).

There are a number of outstanding issues regarding the effects of early stress on PGV. First, in the studies of psychopathology mentioned above, it is unclear to what extent PGV changes are related to precipitating stress versus the disorder itself. That is, it is unknown whether PGV abnormalities might represent a risk factor for subsequent development of psychopathology. Second, different types of stressors (e.g., early life, chronic, acute) appear to have different effects on HPA axis function. It is unknown whether different types of stressor or adverse experience have a different effect on PGV. Finally, the effects of early stressors on PGV *development* are currently unknown. Understanding the dynamic effects of stress is important given that they may interact with the normative changes in HPA axis function and PGV across adolescence.

The current longitudinal study aimed to assess the effect of different types of adverse early life experiences on