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Childhood maltreatment, pituitary volume and adolescent hypothalamic-pituitary-adrenal axis – Evidence for a maltreatment-related attenuation

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ABSTRACT

Background: Alterations of the development of the hypothalamic-pituitary-adrenal axis (HPAA) have been suggested to be related to experiences of early maltreatment. It has been postulated that early stress (i.e., maltreatment) leads to initial hyperactivation of the HPAA, which subsequently may progress to hypoactivation during the course of adolescence, however empirical studies on this hypothesis are rare. In the current study, we aimed to examine the longitudinal relationships between childhood maltreatment, early adolescent pituitary gland volume (PGV) and mid-adolescent cortisol output in an existing data set to explore the utility of PGV as a measure of HPAA function, and as an indirect test of the attenuation hypothesis.

Methods: The sample comprised 69 adolescents (30 females), subsampled from a larger longitudinal, community-based study on adolescent development. PGV, as an estimate of chronic childhood HPAA activity, was measured by magnetic resonance imaging during early adolescence (mean age 12.62 ± 0.45 years). Cortisol output was assessed via multiple salivary cortisol measures in mid-adolescence (mean age 15.52 ± 0.39 years). The cortisol awakening response (CAR) was calculated as a measure of HPAA functioning. Retrospective assessment of childhood maltreatment was performed using the Childhood Trauma Questionnaire (CTQ). Regression analyses were conducted to examine whether childhood maltreatment, PGV, and their interaction, predicted mid-adolescent CAR.

Results: No main effect of PGV or maltreatment was found on adolescent CAR. PGV did however significantly interact with childhood maltreatment in predicting the CAR ($t = -2.26$; $p = 0.024$). Larger PGV positively predicted lower CAR in the context of relatively high childhood maltreatment ($t = 2.032$; $p = 0.046$), but showed no relationship in the context of relatively low maltreatment ($t = 0.723$; $p = 0.472$). Maltreatment also interacted with sex, such that (only) in females, higher levels of maltreatment predicted a lower CAR ($t = -2.04$, $p = 0.042$).

Conclusions: In the presence of childhood maltreatment, larger PGV was associated with lower CAR in adolescence, providing support for the application of PGV in studies of HPA axis function. Our finding is consistent with a maltreatment-related attenuation of HPAA functioning that may derive from a stress induced chronic hyperactivation during childhood. Prospective longitudinal studies are now required to further explicate these findings and relationships with psychopathology.

1. Background

Child maltreatment is a widespread phenomenon affecting the lives of millions of children all over the world (Stoltenborgh et al., 2015). Preclinical and clinical studies suggest that experiences of childhood maltreatment lead to enduring changes in both the activity, and particularly the reactivity, of the hypothalamic-pituitary-adrenal axis (HPAA); however, data on the exact developmental pathways of these

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alterations are rare (McCrory et al., 2010; Tarullo and Gunnar, 2006). The HPAA is one of the major stress response systems of the human body (Gunnar and Quevedo, 2007); HPAA activation causes the release of corticotropin releasing hormone (CRH) from the hypothalamus, which binds to receptors on the anterior pituitary gland. Through a cascade of intracellular events, adrenocorticotropic hormone (ACTH) is released, which promotes the synthesis of glucocorticoids (i.e., cortisol in primates), as well as stimulating their release from the adrenal cortex (Gunnar and Quevedo, 2007).

Human diurnal cortisol rhythms are typically characterized by high levels upon waking (i.e., a substantial [50–60%] increase in cortisol concentration in the 30–45 min after waking), described as the cortisol awakening response (CAR) (Pruessner et al., 1997). The CAR is considered a reliable and distinct measure of HPAA functioning (Stalder et al., 2016). While the CAR seems to be influenced by trait-like (e.g., genetic) factors (Hellhammer et al., 2007), it may also index relatively proximal states of the HPAA (Law et al., 2013).

In contrast, pituitary gland volume (PGV) has previously been investigated as a measure of chronic HPAA functioning. The PGV is thought to increase with the number and/or size of corticotropin-releasing cells in the anterior pituitary gland (Axelson et al., 1992; Dinç et al., 1998; Garner et al., 2005; Krishnan et al., 1991), which via ACTH release stimulates the release of cortisol by the adrenal cortex. Recent data from our group has shown that early adolescent PGV is associated with measures of mid-adolescent HPAA functioning (including the CAR; Kaess et al., 2013). Importantly, PGV is considered an index of long-term and total systemic HPAA activity. Although there are normative changes in PGV during the course of adolescence (i.e., growth), and factors such as puberty and stress significantly influence this growth trajectory (Ganella et al., 2015), given the relative stability of volumetric measures and their minimal sensitivity to confounding state effects, PGV is unlikely to solely reflect current functioning of the HPAA (Ganella et al., 2015). Rather, a larger PGV has been suggested to either predetermine, or reflect, the effects of *chronically* elevated HPAA activity (Ganella et al., 2015; Jovev et al., 2008; MacMaster et al., 2006; Zipursky et al., 2011).

Developmentally, HPAA functioning is characterized by an initial reactive period after birth, followed by a period of context-dependent hypo-responsivity to stressors (Gunnar et al., 1996), which is suggested to be related to social regulation or parental buffering of the HPAA (Gunnar and Donzella, 2002). When entering adolescence, the HPAA approaches an adult level that is characterized by higher cortisol levels and increased HPAA reactivity (Gunnar and Quevedo, 2007, 2008). In addition, HPAA development seems to be strongly influenced by sex, which in turn may be related to the sex-specific timing of neurodevelopment and the functional cross-talk between the HPAA and the hypothalamic-pituitary-gonadal axis (HPGA) (Marceau et al., 2015). Indeed, previous results from our group suggest a significant influence of sex on the longitudinal relationship between PGV and HPAA functioning, whereby a large PGV predicted increased adolescent CAR in males only, while this effect was reversed (although non-signficant) in females (Kaess et al., 2013).

Experience (i.e., environmental factors) plays a prominent role in shaping the basal rhythms and reactivity of the HPAA during development (Gunnar and Quevedo, 2007). Consequently, development of the HPAA appears to be sensitive to early maltreatment (McCrory et al., 2010), and such experiences are commonly associated with changes in both basal functioning and reactivity of the HPAA (Heim and Nemeroff, 2001). Several studies on the impact of childhood maltreatment and trauma on HPAA functioning have shown increased HPAA activity during childhood (Danese and McEwen, 2012; Simmons et al., 2016; Trickett et al., 2010). It has been hypothesized that this initial HPAA hyperactivity may commonly be accompanied by a subsequent attenuation of HPAA functioning (Miller et al., 2007), which may be biologically adaptive given the adverse consequences of chronic exposure to glucocorticoids (Susman, 2006), or reflect an overwhelmed and hypoactive system, consistent with homeostatic failure in the reactive scope model (Romero et al., 2009). Indeed, in earlier work with the cohort examined here we found the CAR was attenuated where childhood maltreatment was reported (this effect was moderated by borderline personality disorder symptoms in girls, but not boys; Kaess et al., 2017).

Only three studies, to our knowledge, have investigated the direct link between trauma-related chonic hyperactivation of the HPAA and a consequent attenuation of HPAA functioning. Trickett et al. (2010) reported that single basal cortisol measures were elevated in sexually abused children at six time points from childhood to adulthood, but levels decreased during adolescent development into early adulthood. Doom et al. (2014) modelled cortisol activity in children over 20 weeks, and found that maltreated children with higher cortisol at the first assessment showed cortisol suppression over time. Lastly, Alink et al. (2012) examined cortisol over five days in children for two consecutive years. They reported indirect effects of maltreatment on morning cortisol at follow-up, such that higher levels of maltreatment were associated with lower morning cortisol levels, via lower prosocial and higher disruptive/aggressive behaviour. Each of these studies suggest potential HPAA blunting after chronic high cortisol levels.

Testing the attenuation hypothesis for childhood maltreatment directly requires a prospective longitudinal design that presents a number of challenges: 1) the measurement of HPAA activity via cortisol presents both methodological (e.g., protocol collection compliance, many confounds) and participant burden issues (e.g., large number of samples required from young children); and, 2) the measurement of childhood maltreatment is also problematic, in that the only way to examine samples prior to onset is on a large population scale, which presents feasibility issues, and particularly for collecting salivary cortisol data. Taking another methodological approach by using early-adolescent PGV as a retrospective proxy of chonic childhood HPAA activity (Dinç et al., 1998) presents another means, albeit an indirect one, of exploring childhood maltreatment and the attenuation hypothesis. We have previously reported a relationship between childhood maltreatment and adolescent PGV change in this cohort (Ganella et al., 2015) and contend that this novel measure of HPAA function requires further study. We postulate that - within a longitudinal, community-based cohort - a trauma-dependent attenuation of HPAA functioning will be evidenced by a reversed association between PGV and CAR, namely a large early-adolescent PGV and low mid-adolescent CAR in traumatized individuals. To be clear, while not directly testing the attenuation hypothesis, this approach will provide convergent validity for the application of these measures for future larger scale studies.

Accordingly, the primary aim of the current study was to investigate the role of childhood maltreatment in influencing the longitudinal relationship between early-adolescent PGV and mid-adolescent HPAA functioning. Analyses were conducted on an existing data set to explore this aim. Specifically, it was hypothesized that PGV and HPAA activity would show a positive relationship where a history of low childhood maltreatment was reported, and that a history of high childhood maltreatment would reverse this positive relationship; thus, lead to a negative relationship where a high PGV predicts low HPAA activity. Secondly, given that we previously found sex-specific associations between PGV and HPAA (Kaess et al., 2013), we investigated whether sex was a potential moderator of these relationships.

2. Methods and materials

2.1. Study procedure

The study comprised data from adolescents recruited from schools across metropolitan Melbourne, Australia as part of the Orygen Adolescent Development Study (OADS; see Yap et al. (2008b) for further details). The OADS involved an in-school screening of grade 6 students (aged 10–12 years), such that those with high and low

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