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Associations between early life stress and anterior pituitary gland volume development – A novel index of long-term hypothalamic-pituitary-adrenal axis functioning

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Abstract

Previous research has established associations between early life stress (ELS) and altered pituitary gland volume (PGV) growth during adolescence. The pituitary gland, however, is composed of an anterior and a posterior lobe with distinct histological and neuroendocrinological properties. While the anterior (but not posterior) pituitary gland is directly involved in the hypothalamic-pituitary-adrenal axis (HPAA) stress response, no studies have examined the effects of ELS on anterior PGV (aPGV). The present study investigated whether previously reported associations between ELS and PGV development during adolescence were driven by aPGV versus posterior PGV (pPGV). Ninety-one adolescents (49 males) were included from a longitudinal, community-based adolescent development study investigating risk for psychopathology. ELS (maternal affective behavior, childhood maltreatment, stressful life events) was assessed during early adolescence. Participants underwent two waves of structural magnetic resonance imaging during mid- and late-adolescence, and aPGV and pPGV were manually traced. Regression analyses showed that childhood maltreatment predicted greater aPGV growth in females. This finding was stronger than that previously reported for PGV. No associations were found between ELS and pPGV development. Neither aPGV nor pPGV changes mediated associations between ELS and psychopathology. Results suggest that ELS may accelerate aPGV (but not pPGV) growth throughout adolescence. Investigating the development of aPGV, rather than PGV, represents a novel approach to studying the effects of stress on HPAA functioning.

Keywords: Pituitary Gland, Anterior; Adolescent Development; Neuroimaging; Adverse Childhood Experiences; Maternal Behavior

The hypothalamic-pituitary-adrenal axis (HPAA), the major neuroendocrine regulator of the mammalian stress response, has been widely posited as a potential mechanism underlying the well-established associations between stress and psychopathology. The HPAA continues to mature throughout childhood and adolescence. Disruptions to typical development of the HPAA during these sensitive periods, including as a consequence of early life stress (ELS), have been associated with altered reactivity to stress and increased vulnerability to psychopathology later in life (e.g., Koss & Gunnar, 2018; van Bodegom, Homberg, & Henckens, 2017).

An extensive body of research has therefore focused on the impact of stress on both basal functioning and reactivity of the developing HPAA in childhood and adolescence, as well as with the relationship between HPAA dysfunction and stress-related psychopathology (for reviews, see e.g., Heim & Nemeroff, 2001; McCrory, De Brito, & Viding, 2010). These studies have commonly utilized salivary cortisol levels to measure HPAA functioning (Adam & Kumari, 2009). Despite substantial evidence tying ELS to disruptions in key diurnal cortisol parameters (e.g., cortisol awakening response [CAR] and diurnal slope [DSL]), findings remain inconsistent (Bernard, Frost, Bennett, & Lindhiem, 2017; Tarullo & Gunnar, 2006). This may be due to the fact that acute cortisol levels are heavily influenced by state factors (e.g., circadian rhythm, illness, or sleep) and thus are subject to high intra-individual variability (Hellhammer et al., 2007; Ross, Murphy, Adam, Chen, & Miller, 2014).

Given the integral role of the pituitary gland (PG) in the HPAA cascade, pituitary gland volume (PGV) has been used as an index of HPAA functioning as an alternative to cortisol-based measures. Upon exposure to stress, corticotropin releasing hormone released from the hypothalamus stimulates the secretion of ACTH by the anterior PG, which promotes the synthesis and release of glucocorticoids (cortisol in humans) from the adrenal cortex (Gunnar & Quevedo, 2007). As such, an enlarged PGV has been suggested to indicate HPAA hyperactivity/hyper-reactivity (e.g., Ganella et al., 2015; Zipursky et al., 2011). The relative stability of volumetric measures, even in the context of confounding state factors, represents PGV as an adequate and more stable index to investigate the relatively long-term changes in HPAA function thought to mediate the association between stress and psychopathology. Several lines of research have provided support for the application of PGV as an estimate of HPAA functioning. First, larger PGV has been found to be associated with cortisol-based measures (CAR/DSL) (Kaess et al., 2013), suggesting that PGV may indeed reflect chronic HPAA hyperactivity and reactivity. Second, PGV alterations have been consistently reported in stress-related psychopathology (e.g., Kessing, Willer, & Knorr, 2011; Saunders, Mondelli, & Cullen, 2019). Third, in line with evidence on the impact of ELS on cortisol levels, ELS has been found to significantly influence PGV development from mid- to late-adolescence (Ganella et al., 2015).

Research investigating the associations between stress and PGV has focused on total PGV. The PG, however, is comprised of an anterior and a posterior lobe with markedly distinct histology and neuroendocrinological functions: the anterior lobe contains ACTH-producing corticotrophs, while the posterior lobe is comprised of distal axons of hypothalamic neurons which synthesize and secrete oxytocin and vasopressin (Elster, 1993).

Given that PGV has been postulated to reflect the number and/or size of ACTH-secreting corticotrophs (Gertz et al., 1987; Westlund, Aguilera & Childs, 1985), PGV changes are likely to be largely determined by its anterior region. However, most PGV tracing protocols have failed to consider them as separate volumes, although it is well-established that the anterior (but not posterior) PG is directly involved in the HPAA (Anastassiadis, Jones, & Pruessner, 2019). The posterior lobe makes up less than 20% of the gland, leading some to argue that changes in PGV are likely to reflect variations in the volume of the anterior lobe (Krishnan et al., 1991; Pariante et al., 2004). Others have claimed that it is not possible to accurately delineate these regions (MacMaster & Kusumakar, 2004; Sassi et al., 2001). Early structural magnetic resonance imaging (MRI) studies suggested, however, that the anterior and posterior lobes can be distinguished based on their signal intensity on T1-weighted images. While the anterior lobe appears as isointense, the posterior lobe appears as a hyperintense "bright spot" thought to reflect the functional storage of vasopressin within neurosecretory granules (Bonneville et al., 2006; Kurokawa et al., 1998). This has set the boundary in the few studies that have measured anterior and posterior volumes separately (e.g., Di Iorgi, Morana, Gallizia, & Maghnie, 2012; Soni et al., 2017). No published studies, however, have explored the associations between ELS and anterior (aPGV) vs posterior PGV (pPGV).

The aims of the current study were therefore two-fold: 1) to develop and establish a protocol to manually delineate the boundary between the anterior and posterior lobes of the PG on T1-weighted images; and 2) to examine the utility of aPGV as a novel approach to studying associations between ELS and HPAA function. To do so, we conducted a secondary analysis of a dataset previously reported in a longitudinal study by our group (Ganella et al., 2015), in which ELS (particularly childhood maltreatment and maternal dysphoric behavior) was found to predict accelerated PGV development from mid- to late-adolescence. We investigated 1) whether the associations between ELS and total PGV growth previously reported in Ganella et al. (2015) were driven by aPGV versus pPGV, and 2) whether aPGV versus pPGV growth, was prospectively associated with increased risk of developing psychopathology in late adolescence. We investigated the moderating role of sex given female-specific findings in Ganella et al. (2015), in addition to established sex differences in PGV development (Takano, Utsunomiya, Ono, Ohfu, & Okazaki, 1999; MacMaster et al., 2007), and speculation that stress likely has female-specific effects during and post-puberty (Bale & Epperson, 2015). We hypothesized that ELS would show female-specific significant associations with aPGV but not pPGV development. Moreover, we hypothesized that aPGV

growth would in turn predict depressive and anxiety symptoms in late adolescence (which was not previously found with total PGV, Ganella et al., 2015).

Methods

Participants and Study Procedure

The study sample and procedure have previously been described (Ganella et al., 2015). Briefly, 91 participants (49 males) were selected from a larger longitudinal study of adolescent development (Yap, Allen, & Ladouceur, 2008). Adolescents participated in four waves of data collection (Time 1 to Time 4, T1-T4) from ages 11-19. Maternal behavior was assessed at T1 (ages 11-13) using mother-adolescent interaction tasks, and childhood maltreatment and stressful life events were retrospectively assessed at T2 (ages 13-15) with self-report questionnaires. Participants underwent two waves of MRI at T3 (ages 15-17) and T4 (ages 17-19). Each wave involved the collection of demographic and questionnaire data, and a diagnostic interview of psychopathology (Kiddie - Schedule for Affective Disorder and Schizophrenia for School-Aged Children: Epidemiological Version [KSADS-E]; Orvaschel & Puig-Antich, 1987) to assess for current/past Axis I disorders. Informed consent was obtained from all participants (i.e., adolescents and parents/guardians) in accordance with the guidelines of the Human Research Ethics Committee of the University of Melbourne.

Neuroimaging

See Supplementary Material for image acquisition and pre-processing details.

Image Analysis

Total PGV had been traced manually for the preparation of Ganella et al. (2015), using a previously established technique (Pariante et al., 2004; see Ganella et al., 2015) and the software ANALYZE 11.00 (Mayo Clinic, Rochester, USA). In this study, a method was developed to manually delineate the boundary between the anterior and posterior lobes of the PG based on their level of signal intensity on T1-weighted images. The optimum level of contrast that allowed clear differentiation between the anterior (dark grey) and posterior (bright spot) PGVs within the existing total PGV trace was determined in sagittal view. Then, both coronal and sagittal views were used to guide the tracing of the boundary between the anterior and posterior portions (Figure 1A). aPGV and pPGV estimates were calculated by summing all voxels within the anterior and posterior traced regions on each individual 2D slice. Anterior and posterior PGVs were split by the same investigator (CDA), who was blinded to participant characteristics, after establishing adequate reliability. Intra- and inter-

rater (the latter with a trained graduate researcher) reliability, demonstrated using intraclass correlation coefficients (ICCs; absolute agreement) for ten randomly selected images, were .999 and .996, respectively, for aPGV, and .963 and .883, respectively, for pPGV.

T3 and T4 intracranial volume (ICV) was calculated using FreeSurfer Version 5.3. ICV was not available for one participant.

Measures

Socioeconomic status

Data on participants' parents' occupation (according to the Australian National University Occupational Status (ANU4) Scale; Jones & McMillan, 2001) and education (if occupation data was missing; total years in school, scaled to reflect ANU4 codes) was employed to derive a measure of socioeconomic status (SES).

T1 measures – Maternal behavior

Maternal behavior at T1 was assessed via interaction tasks. Mother-adolescent dyads engaged in event planning (EPI) and problem-solving (PSI) interactions intended to elicit positive and negative behaviors. Video-recorded interactions were coded using the Living in Family Environments (LIFE) coding system (Hops, Biglan, Tolman, Arthur, & Longoria, 1995; see Ganella et al., 2015). Frequency measures of aggressive and dysphoric maternal behaviors during the EPI, and positive maternal behaviors during the PSI, were used in the analyses.

T2 measures – Stressful life experiences and childhood trauma

Adolescents completed the stressful life events questionnaire (SLEQ; adapted from Lewinsohn, Rohde & Gau, 2003) and the Child Trauma Questionnaire (CTQ; Bernstein & Fink, 1998; Bernstein, Ahluvalia, Pogge, & Handelsman, 1997) at T2. The SLEQ is a 30-item self-report checklist measuring the occurrence of normative (e.g., changing schools) and non-normative (e.g., death of a family member) experiences representative of the types of events empirically identified to be stress-provoking for most young people (Holmes & Masuda, 1973; Lewinsohn et al., 2003). The CTQ is a 28-item retrospective scale measuring the frequency and severity of five different dimensions: physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect. Participants rated the frequency with which various events occurred when they were growing up (0 = never true, 5 = very often true). A total maltreatment score was derived and used in analyses.

Psychiatric symptoms

Adolescents completed an assessment of self-reported depressive and anxiety

symptoms at T3 and T4 using the Centre for Epidemiological Studies – Depression Scale (CES-D; Radloff, 1977) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). Lifetime diagnosis of Axis I psychiatric disorders was assessed by trained research assistants using the KSADS-E. Mothers also completed the CES-D and BAI at T1.

Statistical analyses

aPGV and pPGV development from age 16 (T3) to 19 (T4) were the main outcome measures. These were operationalized as residualized change scores calculated by regressing T4 aPGV and pPGV onto T3 aPGV and pPGV, respectively. The analyses replicated those performed in Ganella et al. (2015) for total PGV. First, five hierarchical linear regressions were performed for each of the two outcome variables to assess the association between each early life stressor (childhood maltreatment, stressful life events, maternal aggressive, dysphoric and positive behavior) and aPGV and pPGV growth. In all regressions, covariates (including T3 age, SES, and lifetime Axis I diagnosis, as well as maternal depression/anxiety for regressions involving maternal behaviors) were entered in Block 1, ELS measures and sex in Block 2, and the interaction between ELS and sex in the final block. Lifetime Axis I diagnosis was controlled for to ensure that results were not being driven by psychopathology, and maternal psychopathology to minimize the impact of state mood effects on those analyses involving maternal behaviors. False discovery rate (FDR)-adjusted p-values were used to correct for multiple comparisons (Benjamini & Hochberg, 1995).

Regression analyses were then performed to investigate whether aPGV and pPGV development were associated with depression/anxiety symptoms at T4. For any stress measure found to significantly predict aPGV/pPGV development, mediation analyses were conducted to examine whether these predicted psychiatric symptoms at T4 (controlling for symptoms at T3) via their effects on aPGV/pPGV development.

Supplemental regression analyses were performed to extend upon the analyses in Ganella et al. (2015) by 1) controlling for ICV development from T3 to T4, 2) investigating cross-sectional associations between ELS and aPGV/pPGV at T3 and T4, and 3) examining associations between CTQ subscales and aPGV/pPGV development.

Results

Demographic information for the study sample is shown in Table 1, and bivariate correlations between all variables of interest are included in Supplementary Table S1. Independent samples t-tests revealed that females showed larger aPGV than males at both T3 ($t(89) = 3.93$, $p < .001$) and T4 ($t(89) = 2.89$, $p = .005$), but smaller ICV than males at both

T3 ($t(89) = -5.31$, $p < .001$) and T4 ($t(89) = -5.345$, $p < .001$). CTQ scores were also significantly higher in females than males ($t(86) = 2.08$, $p = .041$). Mixed model ANOVAs were conducted to examine the effect of time on aPGV and pPGV growth by sex, with T3 age as a covariate. Main effects of time ($F(1, 88) = 4.66$, $p = .034$) and sex ($F(1, 88) = 15.03$, $p < .001$) on aPGV were found, whereby aPGV significantly increased across time and was larger in females than males. No similar effects were found for pPGV (p-values > 0.05).

Association between ELS and aPGV/pPGV development

Results of all regression analyses with aPGV and pPGV development are presented in Table 2. Covariates in Block 1 (T3 age, SES, and lifetime Axis I diagnosis, as well as maternal depressive/anxiety symptoms for regressions with maternal behaviors) were not significant and are therefore not shown on the table. While no main effects of ELS on aPGV growth from T3 to T4 were revealed, the interaction between childhood maltreatment and sex was significant ($\beta = -0.530$, $t = -3.305$, $p = .001$). Follow-up regression analyses by sex revealed that higher levels of childhood maltreatment predicted greater aPGV growth in females ($\beta = 0.470$, $t = 3.246$, $p = .003$, Figure 1B), but not males ($\beta = -0.222$, $t = -1.479$, $p = .147$, Figure S1). Findings remained significant following FDR correction. Further analysis showed that, in females, childhood maltreatment predicted larger aPGV at T4 ($\beta = 0.409$, $t = 2.802$, $p = .008$) but not T3 ($\beta = 0.098$, $t = 0.617$, $p = .541$). In contrast to Ganella et al., (2015), the association between maternal dysphoric behavior and aPGV development was not significant. No significant associations were revealed between any of the ELS measures and pPGV growth from T3 to T4.

Association between aPGV/pPGV development and psychopathology

Although certain early life stressors were significantly correlated with depressive/anxiety symptoms at T4 in females (see Table S1), no associations were revealed between aPGV or pPGV development and psychiatric symptoms at T4, either for the whole group or for males and females separately (all p-values > 0.4). Therefore, subsequent mediation analyses were not conducted.

Supplemental analyses

All primary findings were consistent when controlling for change in ICV from T3 to T4, and when testing associations without lifetime Axis I diagnosis and maternal symptomatology as covariates (see Tables S2 and S3).

Cross-sectional regression analyses with aPGV and pPGV at T3 and T4 are shown in Table S4. While effects were more pronounced at T4 relative to T3, these associations did not survive FDR correction.

Additional exploratory regression analyses conducted with the five CTQ subscales revealed no significant associations after FDR correction (see Table S5).

Discussion

In an adolescent sample, we investigated whether ELS was related to the development of aPGV (as opposed to total PGV, as found by our group previously, Ganella et al., 2015), in order to determine whether aPGV may be a more accurate index of chronic HPAA functioning than pPGV or total PGV. In line with our hypothesis, childhood maltreatment significantly predicted greater aPGV growth in females from mid- to late-adolescence. However, no other ELS measures were found to predict aPGV development. As expected, no associations were found between ELS and pPGV development. Contrary to our hypothesis, variations in aPGV development did not mediate the link between ELS and psychopathology in late adolescence.

To the authors' knowledge, this is the first study to investigate associations between ELS and aPGV vs pPGV. This is despite the direct implication of the anterior PG on the HPAA response, which led us to hypothesize that stress-induced HPAA dysfunction may be more accurately reflected by developmental abnormalities in aPGV rather than total PGV. Despite previous neuroimaging studies claiming that the anterior and posterior pituitary lobes cannot be traced as separate volumes (MacMaster & Kusumakar, 2004; Sassi et al., 2001), in this study we demonstrate that PGV can be reliably segmented into aPGV and pPGV based on their intensity signal on T1-weighted images. Although we did not find additional associations between ELS and aPGV as compared to those reported for PGV (Ganella et al., 2015), most of the aPGV analyses in the present study replicated, and were in fact stronger (based on variance explained) than those for total PGV. Specifically, the childhood maltreatment model explained more variance in aPGV (16%) than PGV growth (9%; Ganella et al., 2015). This suggests that aPGV may represent a more robust approach to studying the relationship between stress and HPAA dysfunction. Interestingly, aPGV growth mirrored the well-established normative changes in PGV reported in previous studies (Ganella et al., 2015; Takano et al., 1999), in that, across time, it increased and was consistently larger in females than males. This was not observed for pPGV, suggesting that the sex-specific growth pattern of the PG is driven by aPGV.

Our finding that high levels of childhood maltreatment were associated with increased aPGV growth in females, but not males, is consistent with our previous work on total PGV (Ganella et al., 2015), and is speculated to indicate aberrant stress-induced HPAA hyperactivation and hyper-reactivity in abused/neglected female adolescents. Female-specific effects may be due to the influence of sex-specific gonadal hormones, and their interaction with the HPAA, throughout PGV development (Wong et al., 2014). Maternal dysphoric behavior, on the other hand, emerged as a significant predictor of total PGV (Ganella et al., 2015) but not aPGV growth. Nevertheless, this effect should be interpreted cautiously, given that total PGV findings would not have survived correction for multiple comparisons. No associations between stressful life events or other maternal behaviors and aPGV development were revealed. This is in line with evidence that different types of stressors may have a distinct impact on the HPAA, and could be due, in part, to the distinct nature, timing and associated level of exposure of specific stressors (Miller et al., 2007). Childhood maltreatment is typically chronic and repeated, while stressful life events and observed maternal behaviors may reflect more transient, discrete and context-dependent experiences. Moreover, the maltreatment scale employed in this study comprised severe forms of ELS known to have long-lasting, widespread adverse effects on brain development (Teicher, Samson, Anderson, & Ohashi, 2016; Whittle et al., 2013); whereas the stressful life events questionnaire included both negatively and positively valanced events.

Limitations and Future directions

Findings should be interpreted in light of several limitations, some of which parallel those in Ganella et al. (2015). First, given the previously established link between PGV and hormone-based indicators of HPAA function (CAR and DSL; Kaess et al., 2013), examining whether these associations are present, and perhaps stronger for aPGV, may strengthen the argument for its use as an accurate index of altered HPAA function. Stress-induced increases in cortisol levels are likely to reflect short-term/proximal states of HPAA hyperactivity, however, and may thus not be directly related to changes in more stable, volumetric markers of long-term/chronic HPAA function such as enlarged aPGV (Zipursky et al., 2011). Second, given the developmental stage of the sample (i.e., post-gonadarche), the regulatory effects of gonadal hormones (e.g., estradiol, testosterone) upregulated during adolescent development on HPAA activity (Oyola & Handa, 2017; Wong et al., 2014) should be considered in order to disentangle HPAA-specific changes in aPGV from those mediated by the hypothalamic-pituitary-gonadal axis. Third, focusing on a community-based adolescent sample may have

limited the variance and severity of depressive/anxiety symptoms, which may explain why aPGV development was not found to mediate the association between ELS and psychopathology. Finally, despite the high inter-rater reliabilities obtained in this study, intensity-dependent delineation protocols have been criticized as being susceptible to the observer's biased perception of intensity and to intra-individual variations of the pituitary "bright spot" (Anastassiadis et al., 2019). Replication in other cohorts is therefore required to further establish the validity of the proposed tracing protocol and the use of aPGV as an index to investigate the relationship between ELS and HPAA dysfunction.

Conclusions

Using a newly established tracing protocol to measure aPGV and pPGV separately, we found that ELS, particularly childhood maltreatment, was associated with the development of the anterior PG during adolescence. Whilst previous literature investigating structural correlates of HPAA functioning has focused on whole PGV, we argue that long-term, stress-related changes in HPAA may be more accurately reflected by the developmental trajectory of aPGV, specifically. Further research on the associations between ELS and aPGV across child and adolescent development in healthy and clinical populations is warranted to shed more light on HPAA dysfunction as an underlying mechanism of the associations between stress and psychopathology.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contribution Statement

SW, JGS and CDA conceptualized the project. CDA conducted the analysis of the data. CDA and SW contributed to the interpretation of results and writing of the manuscript. JGS, DEG, OS, JHK, and PF reviewed and provided critical feedback on the manuscript.

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Tables

Table 1. Descriptive statistics of the study sample

	Entire Sample Mean (SD), n	Females Mean (SD), n	Males Mean (SD), n
Age T3	16.46 (0.52), 91	16.46 (0.47), 42	16.45 (0.56), 49
Age T4	18.81 (0.44), 91	18.80 (0.39), 42	18.82 (0.49), 49
ICV (mm^3) T3	1552481.76 (152487.45), 91	1472144.80 (109566.27), 42	1621342.00 (151183.43), 49
ICV (mm^3) T4	1559288.65 (156090.72), 90	1477142.58 (113463.71), 42	1631166.46 (153621.96), 48

aPGV (mm^3) T3*	403.72 (90.09), 91	440.93 (80.92), 42	371.82 (85.88), 49
aPGV (mm^3) T4**	466.25 (85.38), 91	493.15 (89,09), 42	443.20 (75.58),49
pPGV (mm^3) T3	102.77 (26.30), 91	102.58 (24.25),42	102.93 (28.19), 49
pPGV (mm^3) T4	98.86 (25.87), 91	99.33 (28.57), 42	98.46 (23.59), 49
BAI T3	7.90 (7.38), 91	8.11 (5.51), 42	7.72 (8.72), 49
BAI T4	7.09 (7.99), 90	8.02 (8.41), 42	6.27 (7.59), 48
CESD T3	9.77 (7.36), 91	9.71 (6.95), 42	9.82 (7.76), 49
CESDT4	10.53 (9.01), 90	10.91 (9.81), 42	10.19 (8.33), 48
Lifetime Axis I disorder†	0.49 (0.50), 91	0.50 (0.51), 42	0.49 (0.51), 49
Maternal CESD T1	29.34 (9.16), 90	26.98 (6.79), 42	31.42 (10.45), 48
Maternal BAI T1	7.01 (7.52), 90	5.94 (4.74), 42	7.95 (9.26), 48
CTQ T2***	52.80 (4.50), 88	53.85 (4.20), 41	51.89 (4.60), 47
SLEQ T2	8.66 (5.91), 88	9.30 (5.56), 40	8.13 (6.18), 48
SES	61.48 (19.96), 90	62.52 (20.57), 41	60.61 (19.60), 49
Maternal aggressive behavior‡	0.57 (0.41), 68	0.61 (0.43), 34	0.53 (0.38), 34
Maternal positive behavior‡	0.55 (0.34), 68	0.50 (0.31), 34	0.60 (0.37), 34
Maternal dysphoric behavior‡	1.80 (0.67), 68	1.77 (0.71), 34	1.83 (0.64), 34

Note: T2 Time 2, T3 Time 3, T4 Time 4, ICV intracranial volume, aPGV anterior pituitary gland volume, pPGV posterior pituitary gland volume, BAI Beck Anxiety Inventory, CESD Centre for Epidemiological Studies – Depression Scale, CTQ Childhood Trauma Questionnaire, SLEQ Stressful Life Events Questionnaire, SES Socioeconomic Status

* Significant sex difference $p < 0.001$

** Significant sex difference $p < 0.01$

*** Significant sex difference $p < 0.05$

† 0= No lifetime history Axis I disorder, 1= Lifetime history of Axis I disorder

‡ Frequency (rate per minute)

Table 2. Regression analyses with aPGV and pPGV development

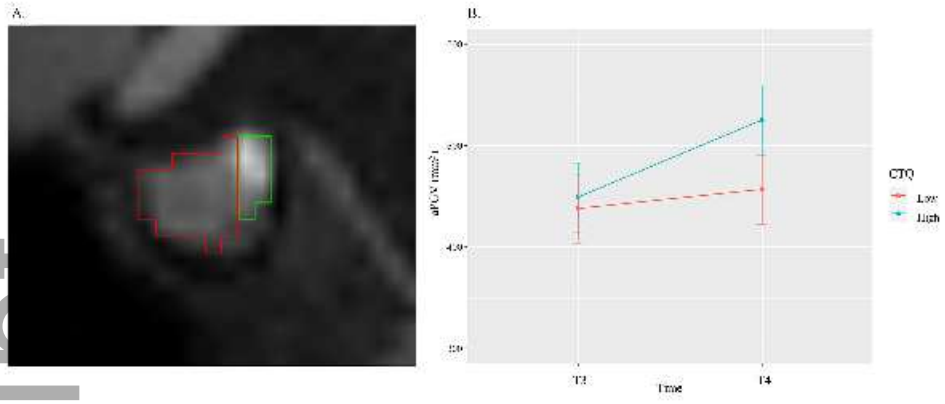
Block	Predictor	β	T	p	Model Fit
Childhood maltreatment					
2	CTQ	0.088	0.790	0.432	$F(5, 82)= 0.717$, $p= 0.613$,
	Sex	-0.027	-0.241	0.810	$R^2= 0.042$
3	CTQxSex	-0.530	-3.305	0.001	$F(6, 81)= 2.490$, $p= 0.029$, $R^2=0.156$
Stressful Life Events					
2	SLEQ	0.054	0.476	0.635	$F(5, 82)= 0.588$, $p= 0.709$,
	Sex	-0.045	-0.414	0.680	$R^2= 0.035$

	3	SLExSex	-0.115	-0.664	0.508	$F(6, 81)= 0.561$, $p= 0.760$, $R^2= 0.040$
	Maternal positive behavior					
Δ aPGV	2	Mpos	0.038	0.279	0.782	$F(7, 59)= 0.707$, $p= 0.666$,
		Sex	0.045	0.335	0.739	$R^2=0.077$
	3	MposxSex	-0.042	-0.239	0.812	$F(8, 58)= 0.616$, $p= 0.761$, $R^2= 0.078$
	Maternal dysphoric behavior					
	2	Mdys	0.249	1.900	0.062	$F(7, 59)= 1.254$, $p= 0.289$,
		Sex	0.022	0.169	0.867	$R^2=0.129$
	3	MdysxSex	0.083	0.430	0.669	$F(8, 58)= 1.105$, $p= 0.373$, $R^2=0.132$
	Maternal aggressive behavior					
	2	Magg	-0.085	-0.629	0.532	$F(7, 59)= 0.757$, $p= 0.626$,
		Sex	0.040	0.300	0.765	$R^2= 0.082$
	3	MaggxSex	0.099	0.568	0.572	$F(8, 58)= 0.695$, $p= 0.695$, $R^2= 0.087$
	Childhood maltreatment					
	2	CTQ	0.121	1.076	0.285	$F(5, 82)= 0.325$, $p= 0.897$,
		Sex	-0.022	-0.194	0.847	$R^2= 0.019$
	3	CTQxSex	-0.099	-0.575	0.567	$F(6, 81)= 0.323$, $p= 0.923$, $R^2= 0.023$
	Stressful Life Events					
	2	SLEQ	-0.070	-0.608	0.545	$F(5, 82)= 0.174$, $p= 0.971$,
		Sex	-0.060	-0.546	0.587	$R^2= 0.011$
	3	SLEQxSex	-0.293	-1.702	0.093	$F(6, 81)= 0.632$, $p= 0.704$, $R^2= 0.045$
Δ pPGV	Maternal positive behavior					
	2	Mpos	0.216	1.598	0.115	$F(7, 59)= 0.647$, $p= 0.716$,
		Sex	-0.128	-0.944	0.349	$R^2= 0.071$
	3	MposxSex	0.070	0.396	0.694	$F(8, 58)= 0.577$, $p= 0.792$, $R^2= 0.074$
	Maternal dysphoric behavior					
	2	Mdys	0.092	0.671	0.505	$F(7, 59)= 0.336$, $p= 0.934$,
		Sex	-0.100	-0.728	0.470	$R^2= 0.038$
	3	MdysxSex	0.019	0.093	0.926	$F(8, 58)= 0.290$, $p= 0.966$, $R^2= 0.039$
	Maternal aggressive behavior					
	2	Magg	0.012	0.083	0.934	$F(7, 59)= 0.271$, $p= 0.963$,
		Sex	-0.087	-0.630	0.531	$R^2= 0.031$
	3	MaggxSex	0.084	0.471	0.640	$F(8, 58)= 0.262$, $p= 0.976$, $R^2= 0.035$

Note: Δ aPGV anterior pituitary gland volume development, Δ pPGV posterior pituitary gland volume development, CTQ Childhood Trauma Questionnaire, SLEQ Stressful Life Events Questionnaire, Mpos maternal positive behavior, Mdys maternal dysphoric behavior, Magg maternal aggressive behavior

Figure Legend

Figure 1. A) Depiction of the delineation protocol. T1-weighted cropped, sagittal slice displaying the traced anterior (red) and posterior (green) lobes of a pituitary gland. B) aPGV development from T3 (*M*age=16.46, *SD*=0.47) to T4 (*M*age=18.80, SD=0.39) in females with high and low levels of childhood maltreatment (defined as +1SD and -1SD, respectively). T3 age, SES, and lifetime history of Axis I disorder are included as covariates. aPGV anterior pituitary gland volume, CTQ childhood trauma questionnaire, T3 time 3, T4 time 4.



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