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Differential role of anterior and posterior pituitary lobes in healthy aging and perceived stress

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The volume of the pituitary gland (PG) is impacted by both age and sex. However, their respective impact on the anterior and posterior lobes of the PG (APG and PPG) remains unclear, despite known distinctions in their neuroendocrinal roles. In this context, we investigated the impact of age and sex on the volume of each PG lobe across healthy adulthood. Lastly, we also tested whether perceived stress was influenced by the volumes of the APG and/or PPG and if the effects varied by age or sex. Results showed that older adults had a smaller APG but a larger PPG, compared to the younger adults. Women had a larger APG than men. Lastly, a main negative effect of PPG and an interaction between age-group and APG were reported on stress level, with the younger adults showing a negative association while the older adults had a positive association. Overall, we demonstrated that each PG lobe shows a different sex effect and age-related trajectory, with each having a different modulation on stress. This work underscores the need to examine the distinct roles of APG and PPG in the context of healthy and pathological aging.

Keywords Healthy aging, Pituitary gland, Stress, Structural volumes, Sex

The pituitary gland (PG) is the largest gland in the brain and is known to fluctuate in size over the lifespan[1,2] and between males and females[3–5]. It consists of two separable lobes (anterior and posterior, referred to as APG and PPG) that have dissociable structural, functional and neuroendocrinal features[6]. However, to date, the majority of magnetic resonance imaging (MRI) studies investigating the PG have largely focused on either the whole PG or the APG only due to its large role in stress response[7], mental health[8–11] and the fact that the APG produces most of the pituitary hormones[6,12]. In contrast, the PPG has received much less attention despite histological evidence that the structural integrity of the PPG is impacted by aging and could lead to altered blood pressure in late adulthood[13]. Indeed, the PPG's role remains essential as it is largely responsible for the storage and release of vasopressin, an antidiuretic hormone which helps regulate the amount of water in the body[14], and oxytocin, a hormone linked to lower anxiety and social stress[15]. Oxytocin has also been found to increase with older age[16]. Given that healthy older adults typically report an overall lower level of perceived stress and anxiety than younger adults[17], it begs the question on whether this positivity effect could be linked with distinct age-related changes in the APG versus PPG. However, to our knowledge, no study has yet traced the APG and PPG separately in older adults to fill up this gap.

Current literature conducted on the normal physiological development and maturation of the PG suggests that aging is associated with smaller whole PG[1,3,5]. The whole PG seems to reach its peak volume during the 2nd or 3rd decade of life, and later declines[2,4,18,19]. However, some conflicting results appear in studies focused on older individuals, such that some did not report any change in volume in the APG in adults aged 50 and above[20]. In contrast, studies have relatively consistently reported a sex effect with females having bigger whole PG[1,5] or APG[10,20] than men, in both adolescents and adults. There is currently no consistent investigation of the impacts of healthy aging and sex on both anterior and posterior lobes of the PG, as prior work has overwhelmingly focused on the whole PG volume, which prevents a clear understanding of the specific trajectories of change of both PG lobes, their respective hormones, as well as their respective link with stress and anxiety as these factors evolve throughout the lifespan. Such investigations could also provide some insight into the inconsistencies reported across past studies, particularly those focused on whole PG volume.

Evidence from patient populations and animal studies demonstrate the negative consequences of alteration of the PG by specific medical conditions and disorders on cognitive ability and mental health. For instance, a recent

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study conducted by Wei and Huang[21] reported that patients with hypopituitarism had a significantly higher risk of incident depression and anxiety disorders than those without hypopituitarism. Further, interventions to remove PG tumors have been linked with significant cognitive impairments across many domains but especially in the memory domain[22,23]. While most of these observations are unable to determine the specific role of APG vs. PPG, other evidence further points to differential impacts of each lobe in cognitive ability with links to measurements of PG-related hormone concentrations. In fact, epidemiological studies have shown a strong correlation between high follicle-stimulating hormone (FSH) levels, secreted by the APG, and cognitive decline, particularly in older women[24,25]. Furthermore, high serum levels of FSH have been associated with the onset of Alzheimer's Disease (AD)[26,27]. Consistently, in mice displaying features of AD, FSH was shown to directly act on hippocampal and cortical neurons to accelerate amyloid-β and Tau deposition, both hallmarks of AD, and impair cognition[28]. Together, understanding the role of each PG lobe and their respective hormonal output in the context of healthy or pathological aging will be essential to bring new avenues of research in understanding their respective involvement in mental health and cognitive states throughout the lifespan.

Our study aimed to specifically investigate the volumes of both APG and PPG in the context of healthy aging and sex in young and older adults. We further tested whether perceived stress was driven by the volumes of the APG and/or PPG and if the effects varied by age group or sex. Our hypotheses were: (1) older age would be associated with smaller APG[20], (2) female participants would show bigger APG than male participants based on our previous work[10] and others[20]. Lastly, given how hormones such as oxytocin or growth hormone (GH), from the PPG and APG respectively, have been reported as playing key roles in regulation of stress responses and emotional regulation[10,29–31], we also expected that higher levels of perceived stress would be differently associated with the APG and PPG lobes. This work aims to pave the way in defining the role of APG and PPG in healthy aging and how each PG lobe may modulate perceived stress levels, before investigating pathological aging, especially when stress has been implicated among the potential mechanisms behind neurodegenerative pathology.

Results

Effect of age and sex on PG volumes

The repeated-measures ANOVA revealed a significant interaction between PG volumes and age group ($F = 49.8$, $p < .001$; Fig. 1A). In detail, older adults showed a smaller APG ($t = 5.6$, $p < .001$, Cohen $d = 0.94$) and bigger PPG ($t = -3.8$, $p < .001$, $d = -0.64$) than the younger adults. In addition, a significant interaction between PG volumes and sex was also present ($F = 4.7$, $p = .033$; Fig. 1B). Female participants had a bigger APG than male participants ($t = -2.5$, $p = .006$, $d = -0.43$), which was not the case for the PPG ($p = .79$). There was no sex-by-age interaction ($p = .37$).

Relationship between PG volumes and stress

At the behavioral level, the older adults reported lower perceived stress level than the younger adults ($t = 6.4$, $p < .001$).

The ANCOVA revealed a significant main effect of PPG volume ($F = 10.88$, $p = .001$; Fig. 2A), showing that smaller PPG was associated with higher stress. We also revealed a significant age group-by-APG volume interaction ($F = 6.24$, $p = .014$, Fig. 2B). In detail, younger participants showed a negative association ($\beta = -2.01$) while the older adults showed a positive association ($\beta = 1.87$) between stress level and the APG volume.

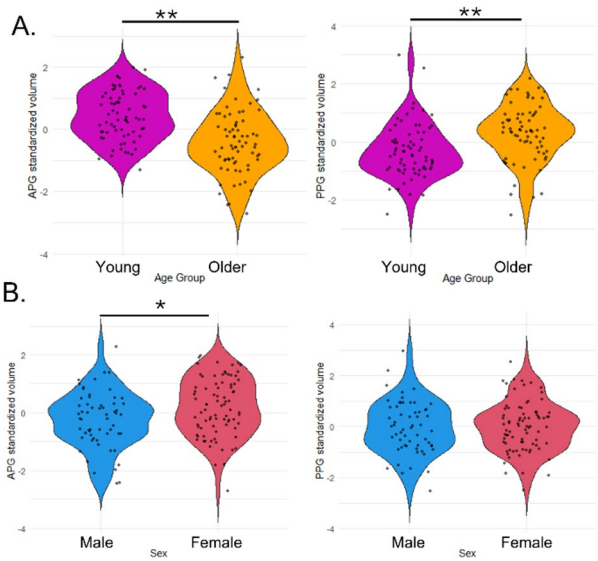

Fig. 1. Effect of age and sex on the anterior and posterior lobes of the pituitary gland (APG/PPG). (**A**) effect of age group. (**B**) effect of sex. *: $p < .05$; **: $p < .001$. Each PG volume is corrected for scanner and ICV.

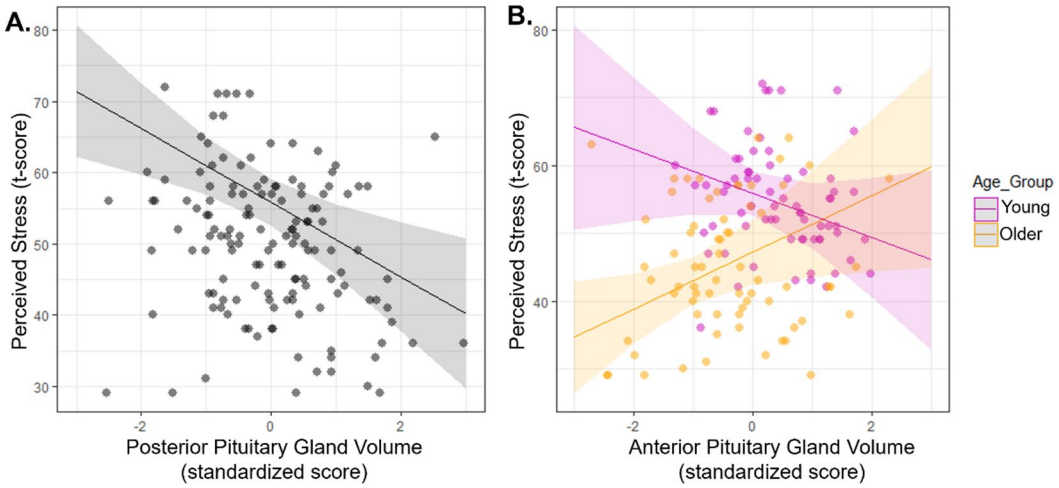

Fig. 2. Relationship between stress level and PG volumes. (**A**) Negative association between stress and the volume of the posterior PG. (**B**) Anterior PG by age group interaction significantly explaining emotional support.

Discussion

This study demonstrates the differential impact of healthy aging and sex on the volumes of the anterior and posterior lobes of the PG in adulthood. In detail, older adults showed smaller APG and bigger PPG than young adults; while women had larger APG than men, regardless of their age. Furthermore, we showed that the volumes of the APG and PPG differentially moderated perceived stress levels in young and older adults. Lower stress level was associated with larger PPG across all adults, and was also associated with larger APG in the younger adults but smaller APG in the older adults.

Our first main findings relate to the differential effect of age on the volumes of APG and PPG, with older adults showing smaller APG but bigger PPG than younger adults. Previous MRI studies conducted on the normal physiological development of adolescent and adult (whole) PG have suggested that the pituitary size reaches its peak during the 2nd or 3rd decade of life, and later declines[2,4,18,19]. However, some conflicting results appear in studies focused on individuals above 50 years old. The current study may therefore shed light on the causes of these discrepancies, by providing evidence that the impact of aging is different between the anterior and posterior lobes of the PG. In this context, we think that these previous studies may have had some level of bias in their (whole) PG tracing toward either the anterior or posterior lobe, likely due to differential quality of the MRI sequence used[20]. These differences and bias could further be due to the relative disappearance of the PPG bright signal on T1-weighted MRI in older adults, suggested to be caused by a reduced storage of the neurophysin-peptide complex[32].

While the current work is among the first studies tracing both anterior and posterior lobes of the PG in an adult population, this result is largely in line with studies investigating levels of hormones secreted by APG and PPG, respectively. In fact, the levels of adrenocorticotrophic hormone (ACTH) and growth hormones (GH), secreted by the APG, have been reported to decrease with older age[16,33]. Consistently, a positive association between the volume of the PG and ACTH concentration has been reported in healthy adults[34], suggesting that as adults become older, their APG becomes smaller, possibly leading to lower concentration of ACTH. In contrast, oxytocin, which is secreted by the PPG, has been found to increase with older age[16]. Interestingly, oxytocin is known to attenuate stress responses in social situations, by decreasing both levels of cortisol and anxiety[15,16]. Our findings are consistent with this as we also report lower stress levels in the older adults, who have bigger PPG than the younger adults. While we do not have hormonal levels for the participants, our findings support that the volumes of APG and PPG may reflect individual differences in hormonal levels secreted by each PG lobe, which should be systematically investigated in future work. Alternatively, the increased volume of the PPG with older age could also be linked with the increasing presence of tau protein in this structure with older age[13]. Indeed, a prior histological study found higher frequency of occurrence for deposition of tau protein in the neurites of the PPG in older individuals with and without tauopathy[13]. Thus, there are still open questions regarding both the healthy and pathological aging patterns of the PPG that should be examined in subsequent studies.

Our previous study examining pituitary development in adolescents, aged 9 to 17 years, reported age-related increases in volumes of both APG and PPG[11]. Together, our findings expand these results and suggest that the impact of age on each PG lobe fluctuates dynamically throughout the lifespan. In detail, it might indicate that the APG size increases from early life to early adulthood, and then decreases toward late adulthood, suggesting a potential non-linear trajectory of the APG throughout the lifespan. Interestingly, it seems that the size of the APG may come to a plateau in the fifties as Berntsen, et al[20]. reported no effect of age on the APG size in older adults aged 50 to 66 years-old; which is similar to our data when testing a correlation between the APG volume and age within our older adults (r=-.11, p =.33). Overall, it may indicate that the major age-related changes on the APG happen before the approximate age of 50 years old in healthy individuals, and then continue to gradually decline from there at a milder pace. In contrast, the PPG seems to follow a more linear trajectory as it

increases from childhood to late adulthood. Such different trajectories underscore the need to investigate each PG lobe separately throughout the lifespan and to determine whether these trajectories remain similar with longitudinal projects, and how they impact age-related neuroendocrinal, behavioral and health changes.

The second main finding from the present work indicates that female participants had a larger APG than male participants, while the PPG was similar in size between the two sexes. This result is in line with previous reports conducted in large adult[1,3,5,20] and adolescent[11] populations which reported that either the whole PG or the APG specifically was larger in females than in males, underscoring an overall reproducible sex effect on the APG from adolescence to late adulthood. Note that this effect is irrespective of overall intracranial volume, which tends to vary between sexes. Taken together, these findings may suggest that sex steroid hormones shape emergent sex differences in the APG specifically during the adolescent period, suggesting a potential sensitive period of brain development in line with the organizational-activational hypothesis[35–37]. Briefly, this hypothesis claims that sexual hormones, such as testosterone and estradiol, have two main impacts on neural development. In particular, prior work has shown that adolescence is one of the sensitive periods for pituitary development, but the current study demonstrates that sex differences likely extend into adulthood, and may likely co-occur with other dynamic sexually-dimorphic hormonal fluctuations (e.g., menopause). However, further studies are needed to assess if similar patterns are seen in children prior to pubertal onset.

The APG is known to produce most of the pituitary hormones including gonadotropic hormones which are the main regulators of the reproductive system in both males and females. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the main regulating hormones of gonads and the reproductive cycle in females while FSH stimulates the growth and maturation of sperm cells in males. Based on blood levels, the concentration of FSH and LH varies by age and sex as well as ovarian cycle in females. Because we did not find a sex-by-age interaction, similar to other studies[1,5], it is unclear how much the sex differences reported in the current work are related to the concentration of gonadotropic hormones and their changes over the lifespan, especially in women who go through major hormonal changes (e.g., during the menopause associated with sharp increased secretion of FSH[38]). However, several studies have reported that the PG undergoes a near doubling in size during healthy pregnancy[39,40]; and while these studies did not distinguish between the anterior and posterior lobes, we anticipate that this effect may likely be driven by the APG. In our study, no women were pregnant or post-partum so a larger APG may be a baseline (outside of pregnancy), that may be more dynamically modulated by hormonal changes caused by pregnancy. Alternatively, these sex differences in APG volume could reflect differences in the other hormones secreted by the APG such as prolactin (PRL) known to have different impacts between males and females[6]. Future studies in other age ranges and pituitary-related disorders could help understand this sex difference and identify how changes in PG volumes are linked to hormonal fluctuations at varying timescales (e.g., day-to-day, monthly, and across different development and aging windows), or other factors such as stress level.

Lastly, we reported differential effects of APG and PPG volumes on the level of perceived stress in adults. Across all adults, smaller PPG was associated with higher stress reported. In addition, we found an age-by-APG interaction, where in younger adults, smaller APG was related with more stress, while it was the inverse in older adults. Importantly, the older adults reported an overall lower level of perceived stress than the younger adults, which aligned with the positivity effect reported in late adulthood[17]. We believe that the impact of PPG on stress level is linked to its role in the production of oxytocin, a hormone linked to lower anxiety and social stress[15]. Our report that older adults have bigger PPG and less perceived stress could have major implications on understanding the brain mechanism behind the positivity effect and generally what brain regions modulate levels of stress and anxiety among healthy adults. In fact, most neuroimaging studies investigating stress are typically largely focused on cortical and/or other subcortical regions (e.g[41].), ignoring the role of the PG; however, our study highlights the need to further include the PG activity in these investigations as it seems to play a significant role in stress level.

In regard to the APG, we found a differential effect between the younger and older adults, with a smaller APG being linked to higher stress level in younger adults. The ACTH, secreted by the APG, regulates the level of cortisol, a hormone typically used to reflect stress level[42], leading to them being highly correlated[43–45]. However, while ACTH has been found to be positively correlated with the whole PG volume in healthy adults[34], no association between whole PG volume and serum cortisol concentrations was reported in a different study[1]. In this context, two main interpretations can be raised: based on the findings from the current study, we suggest that the lack of significant correlation between the PG volume and cortisol concentration could be due to not specifically distinguishing the APG from the PPG in the analyses. Second, as suggested by the authors, the way to measure cortisol and ACTH (e.g., one measure at one time point versus at multiple time points) may have a significant impact on the results, especially when considering the circadian rhythm impacting their secretion[1]. In the context of our study, we propose two potential explanations for the opposite association between stress and APG volume between older and younger adults: first, given that older adults were found with a smaller APG, more stress in younger adults (associated with smaller APG as well) may possibly reflect early signs of accelerating aging in the APG, even in the case of a healthy population with no diagnosis of anxiety disorders. This would be consistent with current knowledge about the various negative impacts of stress on the brain and body[46–48]. Second, smaller APG volume in stressed young adults could reflect hypothalamic-pituitary-adrenal (HPA) axis exhaustion or dysregulation. Future investigations will be required to disentangle these options.

ACTH has also other physiological functions such as increasing blood flow in addition to its involvement in the production and secretion of glucocorticoids, mineralocorticoids, and sex steroid hormones. Its release is also influenced by many stress factors such as low blood sugar, exposure to cold, pain, surgery and depression[49]. It is therefore possible that the alteration of the APG volume by other stress factors is different between younger and older adults, which leads to a differential impact on the secretion of ACTH, with further consequences on stress responses but also on health functions such as blood pressure known to change with older age. Under stress, the

HPA axis is typically activated which leads to an increase in ACTH release, stimulating an increase in cortisol release. Because the younger adults show smaller APG with higher stress levels (while the opposite association is reported in the older adults), it will be essential to test the direct association between ACTH, cortisol and APG/PPG volumes to understand these complex interactions throughout the lifespan.

While this study is among the first to explore the anterior and posterior lobes of the PG in a sample of healthy adults, we should acknowledge some limitations. First, our analyses were based on cross-sectional samples and we cannot make causal interpretations. Investigating the rate of within-subject change will be essential to understand and identify changes in APG and PPG integrity across the lifespan. Our sample also did not include a group of middle-aged adults which would have allowed us to consider age as a continuous rather than categorical variable, and define a better trajectory of age-related differences and identify whether the age-related changes follow a linear or non-linear trajectory. Second, we did not collect blood, saliva, or hair samples that could have provided concentrations of hormones secreted by each PG lobe and link them to the respective PG volume. Third, participants in this study did not have clinical levels of psychopathology, which have been linked to changes in PG volume in prior studies (Picci et al., 2025). Thus, future work should seek to replicate and extend these effects in samples with diagnosed psychiatric disorders. However, there is first a need to characterize the link between each PG lobe and healthy levels of symptomology and stress across the lifespan, before investigating the whole spectrum, where subclinical or preclinical symptoms could set the stage for diagnostic levels of psychopathology in the long term. Fourth, we only had a measure of perceived stress rather than chronic stress, which could have been more relevant. It will be essential to test the association between each PG lobe and other stress-related metrics to confirm the robustness of our findings. Fifth, the data were collected on two different scanners and used different MRI acquisition parameters which led us to have to apply a harmonization approach. While applying a site harmonization approach is common among multi-site neuroimaging studies, there is always a small risk that meaningful variance is removed in the process. Lastly, this study was not pre-registered[50].

Taken together, the present study provides a novel contribution to a body of literature documenting the impact of aging, sex and stress on each PG lobe in a healthy adult sample. We reported differential effects of age and sex on each PG lobe and a significant moderation of APG and PPG volumes on perceived stress level. This adds important nuance to the existing aging literature, which has largely focused on cortical and subcortical regions only when investigating the mechanisms behind stress or the whole PG. This work underscores the benefit of examining the distinct roles of APG and PPG in the context of healthy aging. Lastly, it also opens up a new avenue of research begging the investigation of the role of both APG and PPG in neurodegenerative disorders since stress has been implicated among the potential mechanisms behind neurodegenerative pathology.

Methods

Participants

A total of 141 healthy adults were recruited, including 70 young adults aged 19 to 34 years (mean age (SD) = 25.93 (3.43), 39 females) and 71 older adults aged 51 to 82 (mean age = 62.60 (6.13), 43 females). Exclusion criteria included any chronic medical illness affecting central nervous and endocrine system function, any neurological or psychiatric disorder, acute intercurrent illness, pregnancy, history of head trauma, current substance use disorder, and presence of any ferrous metal implant which may interfere with the MRI data acquisition. No included participant had a pituitary tumor or related anatomical abnormalities, based on their MRI scan (reviewed by a neuroradiologist). The study was approved by the Institutional Review Board for Research with Human Subjects at Boys Town National Research Hospital (IRB# 20-05-XP). This research was performed in accordance with the regulations provided by the Declaration of Helsinki. Each participant provided written informed consent, and all participants completed the same protocol.

Stress assessment

All participants completed the emotion battery from the NIH Toolbox[51]. Due to the role of PG in generated and regulating hormones responsible for stress responsivity[6,7], we selected the perceived stress t-score variable for further analyses.

MRI data acquisition

Brain structural MRI data were collected on two different scanners, although both were a 3 T Siemens Prisma scanner. Out of the 141 participants, 58 were scanned on "Scanner 1" and 83 were scanned on "Scanner 2". Within each scanner, each sample had a similar number of younger and older adults (48% and 51% were younger adults in Scanner 1 and 2, respectively). For Scanner 1, the structural images were acquired using a T1-weighted, 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: Repetition Time (TR) = 2400 ms, Echo Time (TE) = 2.22 ms, Field of View (FOV): 256 × 256 mm, 0.8 mm isotropic resolution, Inversion Time (TI) = 1000 ms, 8 degree-flip angle, bandwidth = 220 Hz/Pixel, echo spacing = 7.5 ms, in-plane acceleration GRAPPA (GeneRalized Autocalibrating Partial Parallel Acquisition) factor 2. For Scanner 2, the structural images were acquired using a T1-weighted, 3D MPRAGE sequence with the following parameters: TR = 2400 ms, TE = 2.05 ms, FOV = 256 × 256 mm, 1 mm isotropic resolution, TI = 1000 ms, 8 degree-flip angle, bandwidth = 240 Hz/Pixel, echo spacing = 7.0 ms, in-plane acceleration GRAPPA factor 2.

Pituitary tracing

The anterior and posterior PG (APG and PPG) were manually segmented for each individual, using 3D Slicer software (https://www.slicer.org/), as described in the protocol reported previously[10,11]. Briefly, the pituitary was defined based upon previously published tracing techniques[9]. Several surrounding structures were visually identified by the tracers to determine the boundaries of the PG, including the diaphragm sellae and lateral

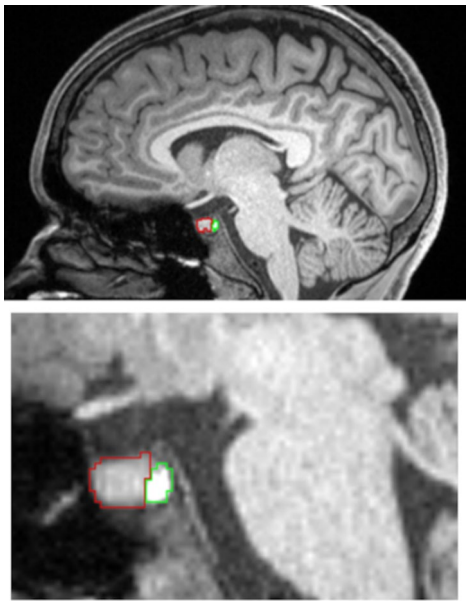

Fig. 3. Segmentation of the anterior and posterior pituitary gland in a representative participant in the sagittal view. The red border delineates the anterior section, while the green border delineates the posterior section. The bottom picture shows a close-up of the top picture, focused on the PG.

ventricles located superiorly, the sphenoid sinus located inferiorly and bilaterally, and the internal carotid arteries located bilaterally[10,11]. Contrast differences in the sagittal view were used to determine the boundary between the anterior and posterior lobes of the PG, which appear darker and lighter, respectively. Estimates for the anterior and posterior lobe volumes were computed by summing all the voxels selected by tracers across all slices. The full sample was segmented by a trained tracer (MD) and results were validated with an expert tracer (GP) using 10% of the overall samples with excellent interrater reliability calculated with intraclass correlations (ICC) for each lobe separately (ICC: APG = 0.96; PPG = 0.92). Figure 3 displays the APG and PPG segmentation for a representative participant.

To account for any variation in volumes across scanners, PG volumes and total intra-cranial volume (ICV, calculated through CAT12) were run through ComBat Harmonization v1.0.1 for MATLAB[52,53]. In detail, ComBat harmonization is an empirical Bayes method that was created to correct for site effects, while being robust to outliers. The process starts by standardizing the input data and proceeds to estimate hyperparameters using the method of moments. It then uses parametric empirical priors to find estimates for site effect parameters. The data is then adjusted for site effects in a similar manner to Location and Scale (L/S) adjustments, except that the empirical bayes estimated site effects are used, instead of site means and variances[54].

Lastly, ICV was regressed out for APG and PPG and standardized residuals were used for further statistical analyses.

Statistical analyses

First, we aimed to test the effect of age group (young vs. older) and sex (female vs. male) on APG and PPG volumes. For this, we conducted a two-way repeated-measures analysis of variance (ANOVA) with APG and PPG ICV-adjusted volumes as the dependent variables, and age group and sex as the independent variables.

Second, we further investigated whether the variability in perceived stress level was driven by the volumes of the APG and/or PPG and if the effects varied by age group or sex. For this, we conducted an ANCOVA with the perceived stress being the dependent variable, while the age group and sex were set up as fixed factors and the APG and PPG volumes were entered as continuous covariates. We included all 2-way, 3-way and 4-way interactions in the model.

Data availability

All data are available upon request to corresponding author G.E. Doucet (gaelle.doucet@boystown.org).

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Author contributions

G.E.D. and G.P. designed research; M.D., A.T.M. and G.P. analyzed data; G.E.D. conducted the statistical analyses; G.E.D. supervised the project; G.E.D. wrote the original draft; M.D., A.T.M., G.P. reviewed and edited the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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