Pituitary volume in adolescents with non-suicidal self-injury: Preliminary evidence for alterations in pituitary maturation

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ABSTRACT

Background: Non-suicidal self-injury (NSSI), typically observed in the context of various mental disorders, represents a highly prevalent and serious problem among adolescents. Based on studies linking NSSI with stress, alterations in hypothalamic-pituitary-adrenal (HPA) axis functioning have been suggested to contribute to the development and maintenance of this behavior. While research has mainly focused on cortisol - the main hormonal output of this system - to our knowledge, no study has examined pituitary gland volume (PGV) - an alternative approach of assessing HPA axis functionality that is less state-dependent - in adolescents engaging in NSSI.

Methods: Magnetic Resonance Imaging (MRI) was performed among n = 35 adolescents (aged 12–17 years) fulfilling the diagnostic criteria for NSSI disorder according to DSM-5 and n = 31 age-matched healthy controls; PGV was obtained by manual tracing. To test for group differences - our primary aim - a hierarchical linear regression model was computed, controlling for several potential confounding variables. Since adolescence reflects a time period for significant brain development - including changes in PGV - we also tested for an age-dependent group effect. In a second step, we aimed to investigate whether differences in PGV are accounted for by the experience of childhood adversity or psychopathology. Finally, following an exploratory approach, the dimensional association between PGV and various clinical characteristics (e.g., frequency of NSSI) were explored.

Results: No evidence was found for overall volumetric differences between healthy control participants and adolescents engaging in NSSI (p > 0.05) - recognizing that small effect size differences could not be detected in the present study - but group membership significantly interacted with age in predicting PGV (p = 0.02). Particularly, while PGV increased linearly with age in healthy controls (B = 61.39, SE = 14.94, p < 0.01), no corresponding association was found in NSSI patients (B = 16.83, SE = 12.20, p = 0.17). PGV was not related to adverse experiences during childhood and none of the clinical characteristics (e.g., frequency of NSSI) significantly correlated with PGV (p > 0.05).

Conclusion: These results provide preliminary evidence for alterations in pituitary maturation in adolescents engaging in NSSI, although replication in longitudinal studies with larger samples is warranted.

1. Introduction

Non-suicidal self-injury (NSSI) is defined as self-inflicted damage to body tissue without suicidal intent (Nock, 2010). NSSI typically first manifests during adolescence (Plener et al., 2015) and is observed in the context of various mental disorders (Ghinea et al., 2020). While a
et al., 2013). NSSI seems particularly relevant in the context of body and the brain (Feelders et al., 2012). Thus, a corresponding pattern of HPA axis dysregulation to chronic stress exposure and maintenance of NSSI behavior (e.g., Kaess et al., 2021). Providing some support for this assumption, studies have found a blunted cortisol response to psycho-social stress in adolescents engaging in NSSI compared to healthy controls or depressed patients without such behavior (Kaess et al., 2012; Klimes-Dougan et al., 2019). In fact, it has been suggested that NSSI may actually help to compensate for the observed inappropriate cortisol response to psychosocial stressors, as painful stimulation itself represents a powerful trigger for HPA axis activity in adolescents with NSSI (Koenig et al., 2017b). There is relatively strong evidence linking a corresponding pattern of HPA axis dysregulation to chronic stress experiences (Miller et al., 2007), particularly those experiences early in life (Bunea et al., 2017), which, as noted before, represent an important risk factor for the development of NSSI. Accordingly, it is currently unclear whether a blunted cortisol stress response, as it has been observed among adolescents engaging in NSSI, actually represents the result of chronic stress experiences and thus precedes the onset of NSSI, or rather reflects a consequence thereof. When secreted in excess - e.g., under prolonged stress exposure - cortisol can have deleterious effects on the body and the brain (Feelders et al., 2012). Thus, a corresponding downregulation may indeed serve an adaptive function that protects the body from these negative effects, an idea subsumed under the so-called "attenuation hypothesis" (e.g., Kaess et al., 2018). Although likely adaptive at first, there is growing evidence linking a blunted cortisol stress response not only to NSSI, but also to several other adverse behavioral and health outcomes (Turner et al., 2020). In summary, regardless of the actual underlying cause (e.g., chronic stress or/and genetic predisposition), changes in the activity of the HPA axis may reflect one pathophysiological pathway that contributes to the occurrence and maintenance of NSSI behavior.

While biochemical characterization remains the gold-standard for assessing HPA axis functionality, assessment of cortisol is heavily influenced by state factors (e.g., menstrual cycle, illness) and thus subject to high inter- and intra-individual variability (Zänkert et al., 2019). Moreover, assessing cortisol in blood or saliva does not reveal information on the origin of the observed function - i.e., at which level along the axis changes may occur that could explain altered HPA axis output. Assessment of pituitary gland volume (PGV) by structural Magnetic Resonance Imaging (MRI) can be considered an alternative approach of assessing HPA axis function that is less state-dependent and reflects more of a proximal trait. Nevertheless, the pituitary gland can undergo volumetric changes in response to functional demands, including for instance the onset of puberty (e.g., Wong et al., 2014). There are now several longitudinal studies that found greater baseline PGV and accelerated PGV growth in adolescent participants with early life adversity, which has been interpreted by the authors as reflecting a state of HPA axis hyperactivity (Farrow et al., 2020; Ganella et al., 2015). Another longitudinal study was able to show that increased PGV in early-adolescence predicted lower cortisol secretion (cortisol awakening response) in mid-adolescence, but only in those participants with relatively high levels of childhood maltreatment, supporting the previously mentioned "attenuation-hypothesis" (Kaess et al., 2018). Finally, structural changes of PGV have been found in various stress-related mental disorders, although a lot of inconsistencies exist between findings (Anastassiadis et al., 2019). To our knowledge, however, no previous study has investigated PGV in an adolescent patient sample fulfilling diagnostic criteria for DSM-5 NSSI disorder.

Therefore, the first aim of the present study was to test for differences in PGV between adolescents engaging in NSSI and healthy controls, while controlling for several potential confounding variables. Based on the literature linking the experience of prolonged stress to NSSI and HPA axis hyperactivity (at least before a corresponding attenuation may follow over time), as well as findings relating stress, particularly chronic stress, to PGV enlargement, we hypothesized that patients engaging in NSSI show larger PGV compared to healthy control participants. In addition, considering the finding that chronic stress has been related not only to greater PGV assessed at a particular point in time but also to accelerated growth of the PGV over time, and considering that the PGV still increases during adolescence before peaking in size in mid-20s to early 30s and declining thereafter (e.g., Anastassiadis et al., 2019), as part of an exploratory approach, we also tested for an age-dependent group effect. Thus, accordingly, adolescents engaging in NSSI may show larger PGVs at younger ages compared to their healthy control participants. Secondly, based on the literature relating adverse childhood experiences - which typically reflect the experience of chronic stress - to greater baseline PGV or accelerated PGV growth, we aimed to investigate whether differences in PGV would be better accounted for by the experience of childhood adversity or psychopathology (i.e., NSSI). Finally, the third aim of this study, following an exploratory approach, was to explore dimensional associations between PGV and clinical characteristics of NSSI frequency, suicidality and the number of BPD criteria fulfilled in patients with NSSI.

2. Methods

2.1. Participants

Adolescents between 12 and 17 years who had engaged in NSSI on at least 5 days during the last 12 months were consecutively recruited from the specialized outpatient clinic for adolescent risk-taking and self-harm behavior (ArisRisk; "Ambulanz für Risikoverhalten & Selbstschädigung") and from inpatient units at the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany. Healthy participants who had never engaged in NSSI and who had neither received a psychiatric diagnosis in their lifetime nor undergone psychiatric treatment were recruited via public advertisement. Adolescents with acute psychotic symptoms, acute suicidality, poor knowledge of the German language, adolescents who were taking glucocorticoid-containing medications, reporting any neurological or endocrinological disorder, or those with a contraindication to MRI (e.g., claustrophobic, pregnant, mental implants, history of brain injury) were not included. The study was approved by the institutional ethics committee of the Medical Faculty, University of Heidelberg and was performed in accordance with the Declaration of Helsinki. All participants and their parents/caregivers gave informed and written consent. For further details on study procedure see Ando et al. (2018) and Reichl et al. (2016; as well as the Supplementary Material).
2.2. Psychological measures

Prior to the MRI scanning session, NSSI and healthy control participants underwent structured clinical assessments by specifically trained clinicians at the University Hospital Heidelberg. During this clinical session, socio-demographic and lifestyle-related information (e.g., age, sex, body mass index (BMI), medication intake, smoking behavior and substance abuse in the past three months and physical activity), data on clinical diagnoses, including BPD symptoms, NSSI history, and information related to the experience of childhood adversity were collected. Psychiatric diagnoses were assessed by means of the Mini-International Neuropsychiatric Interview (M.I.N.I.-KID; Sheehan et al., 2010), a semi-structured interview for the assessment of axis I psychiatric disorders according to DSM-IV and ICD-10. BPD symptomatology was assessed with the corresponding module of the German version of the Structured Clinical Interview for DSM-IV Personality Disorders (SKID II; Fydrich et al., 1997), with BPD being diagnosed if at least five of the nine criteria were met for a duration of at least one year. Depressive symptoms over the past two weeks were assessed with the German version of the Beck Depression Inventory II (BDI-II; Beck et al., 2001) and the occurrence, frequency and characteristics of a variety of suicidal and self-injurious thoughts and behaviors were assessed with the German version of the Self-Injurious Thoughts and Behaviors Interview (SITBI-G; Fischer et al., 2014). Finally, early adverse experiences were assessed with the German version of the Childhood Experiences of Care and Abuse Interview (CECA; Kaess et al., 2011). We focused on the subscales antipathy, neglect, psychological, physical, and sexual abuse which can be rated on a 4-point scale ranging from 0 (no adversity/a-buse) to 3 (severe adversity/abuse). A severity score was calculated by summing up all subscales, with higher scores reflecting more severe adversity. In addition, according to the CECA manual, each subscale can be dichotomized into none/mild versus marked/severe, reflecting the absence or the presence of the corresponding adversity.

2.3. Image acquisition

MRI was conducted on a Siemens Magnetom TrioTim Syno 3T scanner with a 32-channel head coil (Erlangen, Germany). Anatomical scans were acquired in the sagittal plane with the following sequence parameters: repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°, generating 192 T1-weighted contiguous 1.0 mm thick slices (voxel size = 1.0 × 1.0 × 1.0 mm).

2.4. Image processing: pituitary volume

T1-weighted images were visually checked for quality assurance and the pituitary gland was manually traced by two independent researchers (IML, SS) blinded to participant’s diagnosis using the MIRcron software package (https://www.nitrc.org/projects/mrcron) following training by a board-certified neuroradiologist (NS). First, the pituitary gland (lying just beneath the optic chiasm) was identified in the midsagittal view (with the corpus callosum clearly visible). Then, we changed to the coronal plane, where the boundaries of the pituitary gland (diaphragma sellae, superiorly; the sphenoid sinus; inferiorly; cavernous sinuses, bilaterally) are best visualized (Pantaleo et al., 2004). All coronal slices, including the hyper-intense region in the posterior pituitary but excluding the infundibular stalk, were traced using the method described by Pantaleo et al. (2004) and Sassi et al. (2001). Finally, the tracing was checked in sagittal and axial planes and edited if necessary. Pituitary volume estimates (in mm³) were calculated by summing all voxels of all relevant slices. Finally, a mean of the two independent pituitary volume estimates was calculated for each participant and used in statistical analyses. Inter-rater reliability was good (ICC = 0.89). Total brain volume was obtained from automated structural segmentation of the T1-weighted images using FreeSurfer version 6.0 (Reuter et al., 2010).

2.5. Statistical analyses

All analyses were run using R (version 3.6.2; 2019–12–12). Socio-demographic and lifestyle-related data, clinical characteristics and variables related to childhood adversity were tested for between-group differences using two-sided t-tests and χ²-tests (or Mann–Whitney U test and Fisher’s exact test if the respective assumptions were not met). There were no missing data except for total brain volume (n = 4). Outliers with respect to PGV at more than 3 standard deviations (SD) above the group mean were excluded from analyses (n = 1). All continuous variables were centered prior to respective analyses. For our primary objective, a hierarchical linear regression model was computed. Age, use of hormonal contraceptives, medication intake and physical activity were entered into the first block of predictors (step 1), as these factors have been found to affect PGV (e.g., Anastassiadis et al., 2019). Since NSSI and control participants differed with respect to smoking, this variable was also included in the first block. Illicit drug use was highly correlated with smoking and was therefore omitted. NSSI and control participants did not differ with respect to total brain volume, and total brain volume was not correlated with PGV. Furthermore, as total brain volume is not known to be associated with PGV, it has also been omitted. Group membership (NSSI vs. controls) was entered into the second block (step 2; see Supplementary Material for results of power analysis), and the interaction between group membership and age was entered into the final block of predictors (step 3). For aim two, another hierarchical linear regression model was computed, this time entering the dichotomized CECA score into the second block of predictors (step 2) and again the interaction with age into the final block of predictors (step 3). Finally, spearman correlations were calculated to explore dimensional associations between PGV and various clinical characteristics (i.e., NSSI frequency, suicidality, number of BPD criteria fulfilled) in patients with NSSI.

3. Results

3.1. Demographic and clinical characteristics of participants

Overall, N = 67 youths underwent both the clinical appointment and the MRI exam. One patient was excluded from all analyses due to an outlier in PGV (+ 3 SD above the group mean), resulting in a study sample of n = 35 adolescents with NSSI and n = 31 healthy controls. As presented in Table 1, adolescents were comparable on age, sex, and several lifestyle-related measures (including BMI, regular physical activity, regular alcohol intake, use of hormonal contraceptives and medication intake; all p > 0.05) but differed, as expected, with respect to psychopathology. Thirteen (37%) adolescents in the NSSI group fulfilled the diagnostic criteria for BPD, 19 (54%) had attempted suicide at least once, and the mean frequency of NSSI in the past year was 63.31 (SD = 75.59, range = 5–300) respectively 3.26 (SD = 5.32, range = 0–30) in the past month. Participants from the NSSI group were significantly more likely to come from families with separated or divorced parents and to have experienced various types of childhood adversity. See Tables 1 and 2 for further details.

3.2. Primary aim: prediction of PGV by group membership (confirmatory) and the potential moderating role of participant’s age (exploratory)

As mentioned before, NSSI patients and healthy control participants did not differ in terms of total brain volume (NSSI: 1165.82 ± 100.50 cm³; Controls: 1187.58 ± 88.79 cm³, t(60) = 0.90, p = 0.37), and total brain volume was not associated with PGV (r = −0.08, p = 0.53).

Results of the hierarchical linear regression model with PGV as dependent variable are presented in Table 3. The final model (step 3) was significant and explained 30.9% of variance in PGV (F(12,7) = 3.71, p < 0.01). There was no main effect of group membership, meaning that there was no overall difference in PGV between healthy control
Similar results were obtained if analyses were repeated with female sex significantly predicted PGV in adolescents engaging in NSSI (exploratory), and the presence or absence of childhood adversity did not explain significant variance in PGV and childhood adversity did not interact with age in predicting PGV (see Supplementary Material Table 2). Similar results were obtained if using the CECA severity scores instead of the dichotomized score (see Supplementary Material Table 3).

3.3. Second aim: prediction of PGV by childhood adversity (confirmatory) and the potential moderating role of participant’s age (exploratory)

The number of BPD criteria fulfilled significantly correlated with the CECA severity score, the BDI-II total score and the number of lifetime suicide attempts, but, although positively related, did not significantly correlate with the frequency of NSSI during the past year and the frequency of NSSI during the past month. In line with previous findings, the presence or absence of childhood adversity did not explain significant variance in PGV and childhood adversity did not interact with age in predicting PGV (see Supplementary Material Table 2). Similar results were obtained if using the CECA severity scores instead of the dichotomized score (see Supplementary Material Table 3).

3.4. Third aim: dimensional associations between PGV and clinical characteristics of NSSI (exploratory)

The number of BPD criteria fulfilled significantly correlated with the CECA severity score, the BDI-II total score and the number of lifetime suicide attempts, but, although positively related, did not significantly correlate with the frequency of NSSI during the past year and the frequency of NSSI during the past month. In line with previous findings, the presence or absence of childhood adversity did not explain significant variance in PGV and childhood adversity did not interact with age in predicting PGV (see Supplementary Material Table 2). Similar results were obtained if using the CECA severity scores instead of the dichotomized score (see Supplementary Material Table 3).
frequency of NSSI during the past year was significantly related with the number of lifetime suicide attempts, but none of these clinical characteristics were significantly correlated to PGV (see Supplementary Material Fig. 1).

4. Discussion

The main objective of the present study was to test for group differences in PGV between adolescents engaging in NSSI and healthy control participants. Based on the literature linking the experience of prolonged stress to NSSI and HPA axis hyperactivity (at least before a corresponding attenuation may follow over time), as well as findings relating stress, particularly chronic stress, to PGV enlargement, we hypothesized that patients engaging in NSSI would show larger PGVs compared to healthy control participants. However, we did not find evidence for overall volumetric differences between the two groups. Importantly, our study was only powered to detect effects of $f^2 \geq 0.13$ (see also Supplementary Material for corresponding power-analysis); thus, it cannot be ruled out that we have missed smaller effects in the present study. Interestingly, group membership significantly interacted with age in predicting PGV. Specifically, while PGV increased linearly with age in control participants, no corresponding association was found in the patient group. In addition, in healthy controls, age, use of hormonal contraceptives, medication intake and physical activity accounted for a substantial proportion of the variance in PGV, whereas these same variables explained considerably less variance among patients. Neither the frequency of NSSI in the past year or past month, the number of BPD criteria met, the severity of depressive symptoms, nor the number of suicide attempts explained variance in PGV among adolescents engaging in NSSI. In addition, there was no evidence that the experience of childhood adversity could account for variance in PGV better than psychopathology. These results and potential implications are discussed below.

Our findings contrast with studies that observed volumetric changes in various stress-related mental disorders including, for instance, post-traumatic stress disorder, obsessive-compulsive disorder or panic disorder (for an overview see Anastassiadis et al., 2019), as well as studies that observed greater baseline PGV and accelerated PGV growth in adolescents with early life adversity (Farrow et al., 2020; Ganella et al., 2015). However, as mentioned before, although differences in PGV have been described across studies, inconsistencies - particularly in terms of the direction of changes (i.e., PGV enlarged in the patient sample, PGV reduced in the patient sample, or no differences observed) - exist among findings. One potential reason that might explain some of the observed variability relates to the timing at which the association between PGV and psychopathology is examined (Anastassiadis et al., 2019). For instance, while larger PGVs have been found in individuals at risk that later transitioned to psychosis compared to those who did not develop the disorder (Garner et al., 2005; Shah et al., 2015), smaller volumes have been observed among chronically ill schizophrenic patients (Upadhyaya et al., 2007). As suggested by Garner et al. (2005) and Upadhyaya et al. (2007), HPA axis hyperactivity in the early phase of psychotic illness (including the prodromal phase) may contribute to PGV enlargement, which might be then followed - in line with the “attenuation hypothesis” (Kaess et al., 2018) - by a gradual decrease of HPA axis activity (i.e., blunted cortisol stress reactivity; Zorn et al., 2017) as the disorder progresses, resulting eventually in an overall reduction of PGV over time. Accordingly, rather than group differences per se, PG development trajectories might be particularly relevant. At the same time, group differences may actually become invisible - especially in cross-sectional data - if these developmental trajectories differ between patients. Interestingly, similar to the literature on psychosis, patients in the presumably still relatively “early phase” of NSSI disorder - i.e., at ages 12–14.5 years - showed a tendency for larger PGVs compared to their healthy peers. Although we did not find evidence for an overall group effect - keeping in mind the restrictions related to the statistical power to detect small effect size differences - we observed an age-dependent effect. Based on findings from various MRI studies, the volume of the pituitary gland seems to increase gradually in young children, shows a growth spurt during puberty, peaks in the mid-20 s to early 30 s, and starts to decrease thereafter (Anastassiadis et al., 2019; Castillo, 2005; Lurie et al., 1990; Wong et al., 2014). Consistent with these findings (taking into account that our data are cross-sectional) a gradual increase in PGV with age was observed in our healthy control sample. In contrast, no corresponding association was found in patients engaging in NSSI, suggesting that pituitary maturation (i.e., the developmental trajectory of the PG) may be altered in this group. In this context, it’s worth noting that although we did not find evidence that PGV was related to adverse experiences during childhood and/or adolescence, NSSI patients were much more likely to have experienced various types of stressors - such as coming from families with separated or divorced parents and having experienced various forms of child...
This study provides some preliminary evidence for potentially altered pituitary maturation in patients engaging in NSSI compared to healthy controls, although no overall volumetric differences - at least in the range of medium and large effect sizes - were found between the two groups. Several suggestions for future studies emerge from our research. Future studies should (1) replicate our finding incorporating larger samples in longitudinal designs (2) with a diverse population to also examine potential sex differences, (3) try to relate PGV development to stress, including chronic stress experienced early in life (4) aim to link PGV maturation with various HPA axis activity measures (i.e., various cortisol measures), (5) carefully assess and control for other pituitary hormones such as gonadotropin-releasing, growth and thyroid hormones as well as measures of pubertal development, and (6) aim to relate PGV maturation to psychopathological symptoms.

Funding

This research received initial support by the Dres. Majic/Majic-Schelz-Foundation, Germany. The foundation had no involvement in the collection, analysis or interpretation of data, in the writing of the manuscript or the decision to submit the article for publication.

CRediT authorship contribution statement

Selina Schar: Formal analysis, Writing – original draft, Visualization. Ines Mürner-Lavanchy: Methodology, Data curation, Writing – review & editing. Nedelina Slavova: Writing – review & editing. Stefan Lerch: Data curation, Validation. Corinna Reichl: Investigation, Writing – review & editing. Romuald Brunner: Conceptualization, Writing – review & editing. Julian Koenig: Conceptualization, Writing – review & editing. Michael Kaess: Conceptualization, Resources, Writing – review & editing, Supervision, Funding acquisition.

Declarations of interest

None.

Acknowledgments

We thank the Dres. Majic/Majic-Schelz-Foundation, Germany that financially supported this study. We would also like to thank all adolescents and their parents for their participation in the study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105662.

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5. Conclusion

This study provides some preliminary evidence for potentially altered pituitary maturation in patients engaging in NSSI compared to healthy controls, although no overall volumetric differences - at least in the range of medium and large effect sizes - were found between the two groups.
