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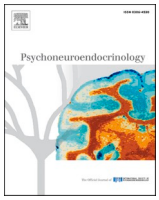

Two-year course of non-suicidal self-injury in an adolescent clinical cohort: The role of childhood adversity in interaction with cortisol secretion

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ABSTRACT

Aim: Non-suicidal self-injury (NSSI) is a highly prevalent phenomenon during adolescence. Nonetheless, research on predictors of the clinical course of NSSI over time is still scarce. The present study aimed at investigating the impact of adverse childhood experiences (ACE) and hypothalamus-pituitary-adrenal (HPA) axis functioning on the longitudinal course of NSSI.

Methods: In a sample of $n = 51$ help-seeking adolescents engaging in NSSI, diurnal cortisol secretion (CAR, cortisol awakening response; DSL, diurnal slope), hair cortisol concentrations and ACE were assessed at baseline. Clinical outcome was defined by change in the frequency of NSSI in the past 6 months measured 12 and 24 months after the baseline assessments. Mixed-effects linear regression models were used to test for effects of ACE and HPA axis functioning on the course of NSSI.

Results: ACE and HPA axis functioning did not show main but interaction effects in the prediction of NSSI frequency over time: Adolescents with a low severity of ACE and either an increased CAR or a flattened DSL showed a steep decline of NSSI frequency in the first year followed by a subsequent increase of NSSI frequency in the second year.

Conclusions: Our findings could be interpreted in the sense of high diurnal cortisol concentrations in the absence of ACE being favorable for clinical improvement on the short-term but bearing a risk of allostatic load and subsequent increase of NSSI frequency. In contrast, adolescents with severe ACE may benefit from elevated cortisol concentrations leading to slower but lasting decreases of NSSI frequency.

1. Introduction

Non-suicidal self-injury (NSSI) refers to the direct, self-inflicted damage to body tissue without suicidal intent and includes behaviors such as cutting, biting, scratching or burning one's skin (Nock, 2010). NSSI typically first manifests during adolescence, with the highest incidence rates seen between the ages 14–16 years (Plener et al., 2015). Repetitive NSSI is particularly common in the clinical context, with prevalence rates of up to 60 % reported in adolescent psychiatric inpatients (e.g., Kaess et al., 2013). While being associated with psychopathology in general (e.g., Ghinea et al., 2020), NSSI represents an important predictor for the development of borderline personality disorder (BPD; Ghinea et al., 2019). Moreover, a history of NSSI constitutes a significant risk factor for suicidal thoughts, suicide attempts and subsequent suicide (Hawton et al., 2015; Koenig et al., 2017a). It could therefore be expected that a successful treatment of NSSI substantially affects the course of future BPD symptomatology and suicidal behavior. With the increasing clinical awareness and importance of studying NSSI, it has been introduced as a diagnostic entity (NSSI disorder) requiring further research in Section 3 of the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5, American Psychiatric Association, 2013).

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Consistent with the postulated emotion-regulation function of NSSI – i.e., reducing negative affective states (Rodríguez-Blanco et al., 2018) – adolescents typically engage in NSSI during periods of heightened stress (Miller et al., 2019). Heightened stress, in turn, is tightly linked to activity of the hypothalamic-pituitary-adrenal (HPA) axis, one of the body's central stress response systems (Nicolaides et al., 2015). Interestingly, cortisol – the main effector hormone of this system – has been suggested to influence mood states, namely, to reduce negative affective states that have evolved in the context of stress (Het et al., 2012), and to be involved in cognitive processes (Law and Clow, 2020). Based on these findings, alterations in the functioning of the HPA axis have been suggested to potentially contribute to the occurrence and maintenance of NSSI (Kaess et al., 2021). As previously summarized by our group (Kaess et al., 2021), there are indeed several studies that have observed changes in the functioning of this important system in patients engaging in NSSI. For example, previous research indicates that adolescents with NSSI show a blunted cortisol response to standardized psychosocial stress procedures (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2017), but an increased cortisol response to pain induction (Koenig et al., 2017b; van der Venne et al., 2023).

A vast body of research has further linked environmental risk factors, particularly adverse childhood experiences (ACE), to the development of NSSI (e.g., Brown and Plener, 2017). Interestingly, as in the case of NSSI, previous studies also suggested a close link between ACE and alterations in HPA functioning. Particularly, previous meta-analyses revealed that ACE are associated with a blunted cortisol secretion in response to psychosocial stress within clinical and non-clinical samples (Hakamata et al., 2022; Schär et al., 2022). This blunted cortisol stress reactivity could be considered as a biological adaptation protecting from consequences of chronic stress experiences (i.e., cortisol excess) during developmental periods with ACE. To date, it is unknown whether alterations in HPA axis functioning among individuals with engagement in NSSI could be explained by the high prevalence of ACE in this population. Moreover, there is a lack of knowledge about the role of HPA functioning in the maintenance of NSSI. In the sense of the differential susceptibility hypothesis (Belsky and Pluess, 2009), it could be assumed that alterations of HPA activity may have an either unfavorable or favorable impact on the course of NSSI depending on the level of early life stress. For example, a blunted cortisol secretion might play a protective role in the course of NSSI for adolescents with ACE while putting adolescents without ACE at risk for the maintenance or aggravation of NSSI.

Moreover, processes associated with HPA axis functioning – particularly emotion regulation and cognitive processes (Het et al., 2012; Law and Clow, 2020) – have been linked to the etiology and maintenance of NSSI. Treatment programs target these elements in different ways, such as cognitive restructuring, the improvement of emotion regulation and stress tolerance (Miller et al., 2007) or the mentalization of inner states (Bateman and Fonagy, 2013). Previous research supports the effectiveness of psychotherapy in the reduction of NSSI among adolescents, particularly highlighting the role of specialized treatment programs: Comparing different interventions, meta-analyses reported the strongest effects in the reduction of self-harm for Dialectic-Behavioral Therapy for Adolescents (DBT-A; Kothgassner et al., 2020; Witt et al., 2021). Another meta-analysis that specifically focused on DBT-A (Kothgassner et al., 2021) reported large (pre-post evaluation studies) or respectively small to medium effects (clinical trials with comparisons to treatment-as-usual) of DBT-A on the reduction of self-harm among adolescents. However, individual changes in NSSI frequency during therapy differ substantially: Previous research revealed that about 25 % of adolescents do not respond to psychotherapy with respect to a reduction of NSSI (Reichl et al., 2023) whereby significantly higher response rates have been reported with regard to DBT-A compared to individual and group supportive therapy (Berk et al., 2022). This leads to the assumption that alterations in HPA axis functioning potentially in interaction with ACE may affect an individual's ability to engage in therapeutic processes and thus contribute to the explanation of interindividual differences in treatment response to psychotherapy.

In this sense, previous studies investigated associations between HPA axis functioning and psychotherapy response. Whereas meta-analytic findings revealed higher pre-treatment cortisol levels to be associated with smaller changes in depressive symptoms (Fischer et al., 2017), no relationship was found between pre-treatment cortisol levels and the reduction of anxiety symptoms (Fischer and Cleare, 2017). Studies predicting the influence of pre-treatment cortisol concentrations on psychotherapy response in the context of post-traumatic stress disorder (PTSD) have reported mostly non-significant or inconsistent findings among adults (Schumacher et al., 2018). In contrast, increased pre-treatment cortisol secretion was associated with better response to trauma-focused therapy among children and adolescents (Zantvoord et al., 2019). To the best of our knowledge, no study has thus far investigated a potential direct effect of cortisol secretion nor an interaction between cortisol secretion and ACE on treatment response among adolescents engaging in NSSI.

Consequently, the aim of the present study was to examine whether (a) the severity of ACE, (b) unstimulated cortisol secretion (CAR, cortisol awakening response; DSL, diurnal slope; hair cortisol), and (c) the interaction of ACE and unstimulated cortisol secretion predict the course of NSSI during a 2-years follow-up period among help-seeking adolescents engaging in NSSI.

2. Materials and methods

2.1. Participants

This study reports results from a subsample of patients enrolled in a clinical cohort study (ethical approval: ID S-449/2013; see Kaess et al., 2017) of youths presenting at the outpatient clinic for risk-taking and self-harming behavior (AtR!Sk; *"Ambulanz für Risikoverhalten & Selbstschädigung"*) at the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany who also participated in a cross-sectional neurobiological study addressing the interaction between childhood adversity and stress-related neurobiology in adolescents engaging in NSSI (ethical approval: ID S-046/2015; see Reichl et al., 2016). The studies were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and approved by the local ethics committee in Heidelberg. All participants and their parents/caregivers (if under 16 years) gave informed and written consent. Patients were between 12 and 17 years old and had engaged in NSSI on at least 5 days during the last 12 months. Exclusion criteria were (1) poor knowledge of the German language, (2) acute psychotic symptoms, (3) acute suicidality, (4) primary neurological or endocrinological disease, (5) intake of glucocorticoid-containing medications, and (6) pregnancy.

2.2. Procedure

As part of the long-term clinical cohort study, each patient underwent a structured clinical baseline assessment (T0) conducted by specifically trained clinicians at the University Hospital Heidelberg. During this clinical assessment, socio-demographic information (e.g., age, sex) and data on clinical diagnoses, including NSSI history, were collected as detailed below. Follow-up assessments were conducted at 12 months (T1) and at 24 months (T2) after the baseline measurement (T0). As mentioned before, eligible patients were invited to participate in a second, cross-sectional neurobiological study shortly after the clinical baseline assessment (T0). As part of this study, information on ACE, saliva and hair cortisol, and various life-style related measures known to influence HPA axis functioning were obtained as detailed below. An overview of the study procedures and assessments is given in Fig. 1.

The majority of patients included in the present analyses received psychotherapeutic treatment at some time between T0 and T2 either at the specialized outpatient clinic AtR!Sk, at inpatient units of the Clinic of

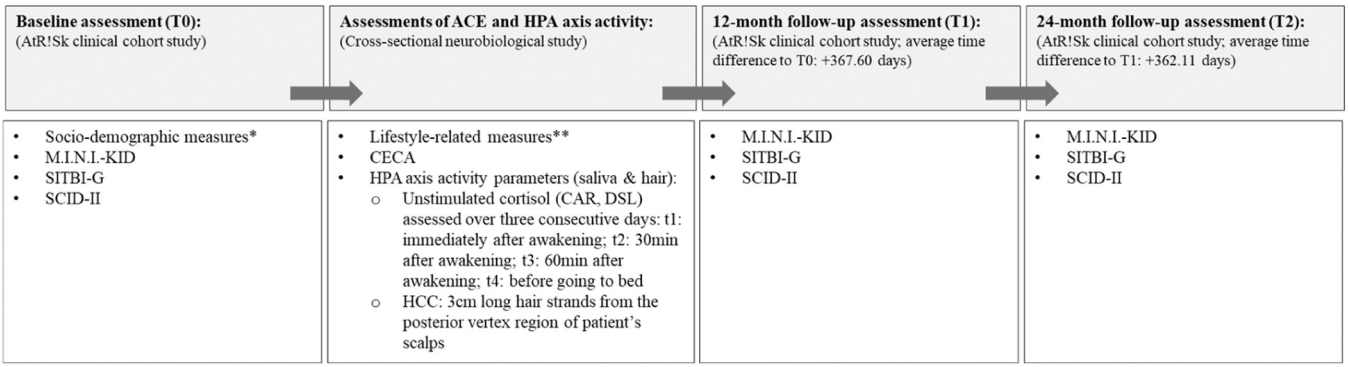

Fig. 1. Study flow chart. *Socio-demographic measures = age, sex, information about school type, family and living situation; M.I.N.I.-KID = Mini-International Neuropsychiatric Interview for Children and Adolescents; SITBI-G = Self-Injurious Thoughts and Behaviors Interview; SCID-II = Structured Clinical Interview for DSM-IV Axis II; ACE = adverse childhood experiences; **Life style related measures = body mass index (BMI), medication intake, days since the last menstrual cycle, smoking behavior and substance abuse in the past three months and physical activity; CECA = Childhood Experiences of Care and Abuse Interview; HPA axis = hypothalamic-pituitary-adrenal axis; CAR = Cortisol awakening response; DSL = Diurnal slope; HCC = Hair cortisol concentration.

Child and Adolescent Psychiatry, University Hospital Heidelberg, or/and at another local outpatient facility.

2.3. Psychological instruments

Current and lifetime axis I disorders according to DSM-IV and ICD-10 were assessed by means of the semi-structured *Mini-International Neuropsychiatric Interview for Children and Adolescents* (M.I.N.I.-KID; Sheehan et al., 2010). BPD symptomatology was measured with 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. NSSI history, including information about the occurrence, frequency and characteristics of NSSI, and information related to suicidality were examined using the German version of *the Self-Injurious Thoughts and Behaviours Interview* (SITBI-G; Fischer et al., 2014). The *M.I.N.I.-KID*, the *SKID II* and the *SITBI-G* were performed at all three study time points (T0, T1, T2). In order to assess ACE, the German version of the *Childhood Experiences of Care and Abuse Interview* (CECA; Kaess et al., 2011) was conducted. This semi-structured interview explores various adverse experiences during childhood and/or adolescence, mostly within the family environment. The subscales psychological, physical, and sexual abuse, antipathy and neglect, experienced by the mother and/or father or a parental figure, were rated on a 4-point scale ranging from 0 (no adversity/abuse) to 3 (severe adversity/abuse). Sexual abuse was also assessed if the offender stems from outside the family environment. A childhood adversity severity score (S-ACE) was calculated by summing up all subscales, with higher scores reflecting more severe adversity (range: 0–15). The CECA interview was performed at T0 as part of the neurobiological study. Finally, as mentioned before, questionnaires on various health-related measures known to influence HPA axis activity (Stalder et al., 2016) were conducted. These questionnaires asked about patient's body mass index (BMI: height/weight^2), regular medication intake (yes or no), smoking behavior (days of smoking per month during the past 3 months: dichotomized into $\leq$ 2 days or $>$ 2 days), substance abuse (drug consumption during the past 3 months: dichotomized into never or at least on 1–2 days), and day since last menstrual cycle.

2.4. Cortisol measures: cortisol awakening response, diurnal slope and hair cortisol

Part of the neurobiological study consisted of patients collecting salivary cortisol samples (Sarstedt collection devices) at home. In order to obtain CAR and DSL measures, patients were instructed to collect saliva samples on three consecutive days at four time points during the day: (t1) immediately after awakening, (t2) 30 min after awakening, (t3) 60 min after awakening, and (t4) before going to bed. Since inaccurate sampling can severely impact the validity of CAR data (Stalder et al., 2016), sampling was strictly monitored by calling patients at agreed fixed times – the first call being a wake-up call – and by using the so-called Medication Event Monitoring System (MEMS®) which records the exact time of opening the saliva box containing the saliva collection devices. Patients were regularly briefed about the sampling procedure and post-awakening behaviors with potentially confounding influences: They received instructions not to eat, have drinks (other than water), smoke, or engage in physical activities one hour before sampling. Saliva samples were stored by participants in their fridge and within three days returned to our laboratory, where they were frozen at −20°C until assayed. In addition to salivary cortisol, hair cortisol samples were obtained at the appointment of the neurobiological study (T0) from a research assistant by cutting two 3 cm long hair strands from the posterior vertex region of patient's scalps. These hair samples were then wrapped in aluminum foil and stored at room temperature. For further details on the exact sampling procedures see Reichl et al. (2016). Salivary and hair cortisol samples were analyzed at the Laboratory of the Department of Biological Psychology at the Technical University of Dresden, Germany (Prof. Clemens Kirschbaum).

2.5. Statistical analyses

The present study followed an exploratory approach. All analyses were performed using Stata/SE (Version 17.0, Stata Corp LLC, College Station, TX, USA) with the alpha-level set to 0.05. First, descriptive statistics were calculated. Since patients were only required to have data available for at least one clinical assessment time point (T0, T1, T2) in order to be included in the present analyses, missing data for the other clinical assessment time points (T0, T1, or T2) were possible.

Secondly, the dependency of S-ACE and cortisol on NSSI was modelled in different sets using mixed-effects linear regression models. As outcome, the frequency of NSSI in the past 6 months was used (assessed by the SITBI-G; Fischer et al., 2014). Four different sets of increasing complexity were specified: Set 1 was the baseline model including only time point as fixed effect. Set 2 included time point, the S-ACE and their interaction as fixed effects. This model was repeated in set 3, but this time including one of the cortisol measures instead of the S-ACE and its interaction with time point as fixed effects. Finally, set 4 included all three predictors: time point, the S-ACE, one of the cortisol measures, and their interactions. All models further controlled for time differences between the first clinical assessment and the assessment of the neurobiological study, which varied to some degree between the participants. By means of stepwise regression analyses (cut-off set to p = 0.15), the influence of the following covariates was tested (in set 4): age,

BMI, smoking, substance abuse, medication intake, and days since last menstrual cycle. Only age remained as a significant predictor in the final stepwise regression model and was therefore included as covariate in all models. In each model subject was used as a grouping variable – allowing for a random intercept – and time point was used as a random slope.

The following indices were used as cortisol measures: the area under the curve with respect to ground (AUC_g), the area under the curve with respect to increase (AUC_i), the diurnal slope (DSL), and hair cortisol concentration (HCC). AUC_g and AUC_i (based on saliva samples t1-t3) were used to quantify the CAR and their calculation was guided by the formula provided by Pruessner et al. (2003). AUC_g and AUC_i are thought to reflect different aspects of HPA axis activity, namely total cortisol production and change in cortisol over time (Khoury et al., 2015). In addition, by subtracting the individually highest cortisol level in the morning from bedtime cortisol (t4) and dividing this value by the total time awake (hours), the DSL was computed. To maximize the accuracy of our cortisol data, saliva samples were not included in the calculation of the respective indices if (1) the signature of the MEMS® was missing, if (2) sampling deviated more than 5 min from the proposed time frame, and if (3) valid samples were only available for one out of the three assessment days. With respect to hair cortisol, the mean of the two hair strands was calculated. Hair samples were not included if samples were shorter than 3 cm. Separate models for each cortisol indices were calculated. All continuous variables (including the S-ACE and all cortisol measures), except our clinical outcome measure (frequency of NSSI) and covariates were centered and outliers, defined as values at more than 3 standard deviations (*SD*) above the group mean, were excluded. In all models, an interaction effect corresponded to a dependency of the change in NSSI on cortisol and/or the S-ACE, respectively. In case of significant interaction effects, these dependencies were further examined by means of post-hoc contrasts. Contrasts were evaluated at +/- 1 *SD* of the continuous variables S-ACE and cortisol, in order to facilitate interpretation. Finally, considering the proven associations between NSSI and suicidality, as a control, the number of suicide attempts within the past 6 months was modeled over time using a negative binomial mixed model with time point as a categorical predictor (T0, T1, T2), while again controlling for the time difference between the first clinical assessment and the assessment of the neurobiological study, as well as for age.

3. Results

3.1. Descriptive statistics

Overall, $N = 51$ female adolescents aged between 13 and 17 years ($M = 14.96$ years; $SD = 1.31$) who had engaged in NSSI on at least 5 days during the year prior to T0 and who participated in both the long-term clinical cohort study and in the neurobiological study formed the basis of the present analyses. Although all $N = 51$ adolescents attended T0, data on NSSI frequency in the past 6 months were available for $n = 50$ adolescents only, which is why descriptive data from T0 are provide for this (sub)sample (see Table 1).

Patients were heterogeneous in terms of clinical diagnoses, with the majority fulfilling the diagnostic criteria for affective disorders (84 %) and/or stress-related disorders (66 %). Half of the patients were diagnosed with BPD and 62 % had attempted suicide at least once during lifetime. The mean age of the onset of NSSI was 12.88 years ($SD = 1.59$; range = 6–16) and adolescents had self-injured on average on 51 days ($SD = 40.01$; range: 4–180) in the past 6 months. The most common forms of NSSI were deliberate cutting (100 %), followed by scratching (64 %), manipulating wounds (50 %), hitting one's body (42 %) and biting oneself (36 %). In total, 68 % of adolescents had experienced at least one form of childhood adversity (according to cut-off scores provided in the CECA manual: none/mild versus marked/severe) with the severity score ranging between 0 and 11.

Table 1
Characteristics of Study Group.

	T0 ($N = 50$)	T1 ($N = 34$)	T2 ($N = 31$)
Demographic and lifestyle-related measures			
Age; mean ± SD (range)	15.00 ± 1.29 (13–17)	16.12 ± 1.32 (14–19)	16.74 ± 1.29 (15–19)
BMI; mean ± SD (range)	21.39 ± 3.53 (15.47–31.07)		
Smoking (past 3 months); *n* (%)	24 (48 %)		
Substance abuse (past 3 months); *n* (%)	13 (26 %)		
Regular medication; *n* (%)	9 (18 %)		
Psychopathology			
Number of mental disorders fulfilled; *n* (%)	4.30 ± 3.68 (0–15)	4.32 ± 3.28 (0–12)	4.06 ± 3.11 (1–12)
Diagnoses, *n* (%)[1]			
F1 - Mental and behavioral disorders due to psychoactive substance abuse	17 (34 %)	13 (38 %)	10 (32 %)
F2 - Schizophrenia, schizotypal and delusional disorders	5 (10 %)	2 (6 %)	2 (6 %)
F3 - Affective disorders	42 (84 %)	30 (88 %)	27 (87 %)
F4 - Neurotic, stress-related and somatoform disorders	33 (66 %)	23 (68 %)	21 (68 %)
F5 - Behavioral syndromes associated with physiological disturbances and physical factors	12 (24 %)	8 (24 %)	7 (23 %)
F9 - Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	14 (28 %)	8 (24 %)	9 (29 %)
Diagnosed BPD; *n* (%)	25 (50 %)	15 (44 %)	9 (29 %)
Number of BPD criteria met; mean ± SD (range)	4.28 ± 2.25 (0–9)	4.24 ± 2.13 (1–9)	3.19 ± 2.51 (0–8)
Suicide attempts last 6 months; mean ± SD (range)	1.22 ± 2.94 (0–20)	0.35 ± 1.01 (0–5)	0.06 ± 0.25 (0–1)
NSSI last 6 months; mean ± SD (range)	51.04 ± 40.01 (4–180)	24.09 ± 33.14 (0–100)	19.16 ± 28.21 (0–110)
In- or outpatient treatment; *n* (%)	-	32 (94 %)	21 (68 %)
Early life adversity (CECA)			
At least one adverse experience[2]; *n* (%)	34 (68 %)		
Severity of adverse experiences; mean ± SD (range)	4.10 ± 3.32 (0–11)		

Note. T0 = baseline assessment; T1 = 12-month follow-up; T2 = 24-month follow-up; SD = standard deviation; BMI = body mass index (height/weight^2); BPD = borderline personality disorder; NSSI = non-suicidal self-injury; CECA = Childhood Experience of Care and Abuse. [1] F0 (organic mental disorders), F6 (Disorders of personality and behavior - see BPD), F7 (mental retardation), F8 (disorders of psychological development) were not fulfilled by any patient and were therefore omitted. [2] 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.

At the 1-year follow-up (average time difference between T0 and T1 = 367.60 days, $SD = 43.10$, range = 315–481), the sample included $n = 34$ adolescents aged between 14 and 19 years ($M = 16.12$ years; $SD = 1.32$) who had engaged in NSSI on average on 24 days ($SD = 33.14$; range = 0–100) in the past 6 months. Of these participants, $n = 32$ (94 %) had received (or were still receiving) a psychotherapeutic intervention at some time between T0 and T1.

Finally, $n = 31$ adolescents aged between 15 and 19 years ($M = 16.74$ years; $SD = 1.29$) participated at the 24-month follow-up (T2; average time difference between T1 and T2 = 362.11 days, $SD = 54.15$; range = 259–506). These participants had engaged in NSSI on average on 19 days ($SD = 28.21$; range = 0–110) in the past 6 months and 68 % had received psychotherapeutic treatment (or were still receiving psychotherapeutic treatment) between T1 and T2.

For further details on clinical and descriptive information for each of the three measurement time points (T0-T2) see Table 1. Of the $N = 51$ patients included in the present analyses, $n = 26$ (50.98 %) provided data on NSSI frequency for all assessment time points (T0-T2), $n = 12$ (23.53 %) for two assessment time points ($n = 8$ T0 and T1; $n = 4$ T0 and T2), and $n = 13$ (25.49 %) for only one assessment time point ($n = 12$ T0, $n = 1$ T2).

3.2. Clinical outcome over time

The baseline mixed-effects linear regression model, including only time point as fixed effect, controlling for age and the time lag between patient's participation in the baseline clinical assessment (T0) and the neurobiological study, yielded a significant overall model ($\chi^2_4 = 36.33$, $p < 0.01$), and a significant time effect ($\chi^2_2 = 29.58$, $p < 0.01$; see also Table 2 set 1) indicating clinical improvement – i.e., an overall decline in the frequency of NSSI over time (T1-T0: $B = -25.29$, $SE = 6.13$, $p < 0.01$; T2-T0: $B = -34.21$, $SE = 6.81$, $p < 0.01$). Similar to this clinical improvement in NSSI – serving as a control – a significant decrease in the number of suicide attempts between consecutive time points was found ($\chi^2_2 = 16.07$, $p < 0.01$).

3.3. Childhood adversity severity score as predictor of clinical outcome over time

Model 2 (i.e., set 2) included the S-ACE in addition to time point as well as their interaction as predictors of NSSI frequency, while still controlling for the two covariates age and the time lag between participation in the two studies. Again, the overall model was significant ($\chi^2_7 = 46.08$, $p < 0.01$) and, comparable to model 1 (set 1), revealed a significant time effect ($\chi^2_2 = 31.54$, $p < 0.01$) showing general a decline in the frequency of NSSI over time. However, no significant interaction between the S-ACE and time point was observed ($\chi^2_2 = 5.80$, $p = 0.06$), suggesting that the S-ACE was not a significant predictor of the frequency of NSSI over time (see also Table 2). In tendency, we observed that higher ACE was associated with more NSSI at baseline and follow-up 1 whereas this association was no longer observed at follow-up 2.

3.4. Cortisol measures as predictor of clinical outcome over time

As expected, overall models were all significant ($p < 0.01$) and yielded a significant time effect ($p < 0.01$), indicating clinical improvement over time. However, similar to model 2 (i.e., set 2), none of the cortisol predictors (i.e., AUC_g, AUC_i, DSL, HCC) explained variance in the frequency of NSSI in interaction with time (all $p > 0.05$; see also Table 2 set 3).

3.5. Childhood adversity severity score and cortisol measures as predictors of clinical outcome over time

The final model (set 4) included all three predictors – time point, the S-ACE, one of the cortisol measures, and their interactions – as fixed effects (while still controlling for the two covariates age and the time lag between the two studies). As expected, overall models were significant ($p < 0.01$), showing significant time effects ($p < 0.01$) that indicated a decline in the frequency of NSSI over time. Consistent with the analyses conducted in set 2 and set 3, neither the S-ACE nor any of the cortisol measures interacted with time point to explain variance in the frequency of NSSI over time (all $p > 0.05$; exception: time point x childhood adversity in the model including HCC: $p < 0.01$). In contrast to these findings, a significant three-way interaction was observed between time point, the S-ACE and AUC_g cortisol (i.e., CAR; $\chi^2_2 = 10.06$, $p < 0.01$, see Fig. 2a) and DSL cortisol ($\chi^2_2 = 6.14$, $p < 0.05$, see Fig. 2b), respectively. According to post-hoc contrasts (see Table 3), those patients with high S-ACE (+ 1 *SD*) and high AUC_g CAR values (+ 1 *SD*) showed a flatter decrease in the frequency of NSSI from T0 to T1 than those patients with low S-ACE (- 1 *SD*) and high AUC_g CAR values (+ 1 *SD*). From T1 to T2, the patients with the high S-ACE scores (+ 1 *SD*) and the high AUC_g CAR values (+ 1 *SD*), who initially (from T0 to T1) showed a flatter decrease in NSSI frequency, showed a further decrease in the frequency of NSSI. Meanwhile, the effects switched for the patients with low S-ACE scores (- 1 *SD*) and the high AUC_g CAR values (+ 1 *SD*), which after an initially (from T0 to T1) more pronounced decrease in NSSI frequency showed an increase in the frequency of NSSI from T1 to T2. In addition, compared to those patients with low S-ACE scores (- 1 *SD*) and high AUC_g CAR values (+ *1 SD*) who showed an increase in the frequency of NSSI from T1 to T2, patients with low S-ACE scores (- 1 *SD*) and low AUC_g CAR values (- *1 SD*) showed a decline in the frequency of NSSI during the respective time interval. With respect to DSL cortisol the following contrasts were significant: (1) Patients with high S-ACE scores (+ *1 SD*) and low DSL cortisol (- 1 *SD*) – i.e., flatter DSL profiles – showed a decrease in the frequency of NSSI from T1 to T2, whereas patients with

Table 2
Results of mixed-effects linear regression models predicting NSSI frequency in past 6 months (T0-T2).

	N	overall model		time point		time point x childhood adversity		time point x cortisol		time point x childhood adversity x cortisol	
		X^2	*p*-value	X^2	*p*-value	X^2	*p*-value	X^2	*p*-value	X^2	*p*-value
Set 1											
	51	36.33	0.01**	29.58	0.01**	-	-	-	-	-	-
Set 2											
	51	46.08	0.01**	31.54	0.01**	5.80	0.06	-	-	-	-
Set 3											
AUC_g (CAR)	47	38.15	0.01**	30.60	0.01**	-	-	1.77	0.41	-	-
AUC_i (CAR)	47	39.77	0.01**	28.91	0.01**	-	-	1.76	0.42	-	-
DSL	49	38.70	0.01**	29.49	0.01**	-	-	1.30	0.52	-	-
HCC	50	45.51	0.01**	34.21	0.01**	-	-	0.85	0.65	-	-
Set 4											
AUC_g (CAR)	47	73.13	0.01**	38.05	0.01**	1.69	0.43	5.94	0.05	10.06	0.01**
AUC_i (CAR)	47	54.67	0.01**	31.00	0.01**	5.29	0.07	1.02	0.60	1.77	0.41
DSL	49	58.45	0.01**	33.94	0.01**	2.95	0.23	2.13	0.34	6.14	0.05*
HCC	50	70.38	0.01**	30.97	0.01**	10.18	0.01**	0.64	0.73	5.93	0.05

Note. NSSI = non-suicidal self-injury, T0 = clinical baseline assessment, T1 = 12-month follow-up, T2 = 24-months follow-up, *N* = Number of participants. X^2 = Chi square, AUC_g = area under the curve with respect to ground, AUC_i = area under the curve with respect to increase, CAR = cortisol awakening response, DSL = diurnal slope, HCC = hair cortisol concentration. All models were adjusted for age and a time difference that resulted from the fact that recruitment for the neurobiological study (and thus the participation in this study) was based on the clinical cohort study (T0 assessment). Subject was used as grouping variable (random intercept) and time point as random slope.

* *p*-value < 0.05,

** *p*-value < 0.01.

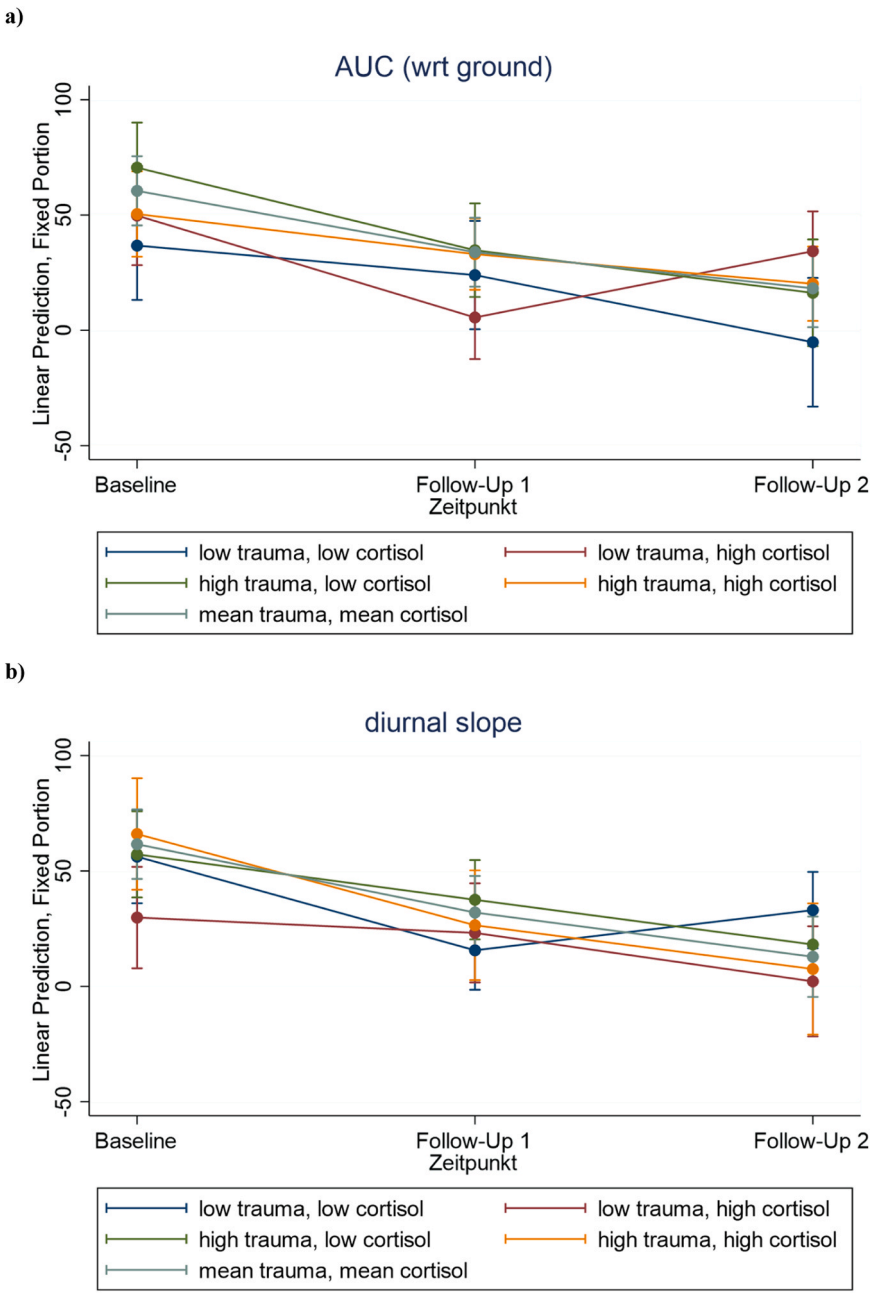

Fig. 2. Interaction of time point, severity of childhood adversity and cortisol (a: area under the curve with respect to ground; b: diurnal slope) in the prediction of NSSI frequency over two years. Note: NSSI = non-suicidal self-injury; AUC (wrt ground) = area under the curve with respect to ground. Low and high values on trauma and cortisol are shown with −1 and +1 standard deviation below and above the mean, respectively, and for mean values.

low S-ACE scores (- 1 *SD*) and flat DSL cortisol profiles (- 1 *SD*) showed an increase in the frequency of NSSI from T1 to T2. (2) In addition, while patients with low S-ACE scores (- 1 *SD*) and high DSL cortisol (steep slopes; + *1 SD*) showed almost no change in NSSI frequency from T0 to T1, those with flat slopes (- 1 *SD*) showed a decrease in NSSI from T0 to T1. (3) However, this effect switched from T1 to T2, where patients with flat slope (- 1 *SD*) now showed an increase in NSSI frequency.

4. Discussion

Results of the present study confirmed a significant mean decrease in the frequency of NSSI over a 2-years follow up period. Neither HPA axis functioning assessed via unstimulated cortisol secretion (CAR, DSL, HCC) nor the severity of ACE showed main effects on the change of NSSI frequency over time. However, our findings suggest that HPA axis functioning and ACE interact in the prediction of the course of NSSI: Solely in the presence of severe ACE, an increased cortisol secretion in the hour after awakening (AUC_g) predicted a slow but steady decrease in NSSI frequency over the 2 years. In contrast, adolescents without ACE but with increased cortisol levels after awakening (AUC_g) showed a more favorable treatment response in the first year but – in contrast to adolescents without ACE and with low cortisol secretion after awakening – an unfavorable increase in NSSI frequency in the second year. In the same vein, only in the presence of severe ACE, a flattened slope of cortisol during the day was associated with continuous clinical improvement throughout the entire 2-years follow-up period. In the absence of ACE, adolescents with a steep DSL showed statistically less improvement in the first year – which however may be a consequence of already lower levels of NSSI frequency at the baseline assessment – followed by continuous clinical improvement in the second year.

Table 3
Results of post-hoc contrasts in case of significant interaction effects.

	Childhood adversity score (high vs. low (± 1 *SD*))	T0 vs. T1				T1 vs. T2			
		delta	*SE*	*p*	95 % CI	delta	*SE*	*p*	95 % CI
AUC_g (CAR)	low	23.99	17.18	0.16	-9.68; 57.67	-8.41	21.23	0.69	-50.02; 33.21
	mean	-1.05	11.30	0.93	-23.20; 21.11	17.09	13.53	0.21	-9.43; 43.61
	high	-26.09	11.53	0.02*	-48.68; −3.49	42.58	12.14	0.01**	18.80; 66.37
	Childhood adversity score (high vs. low (± 1 *SD*))								
DSL	low	-19.27	13.41	0.15	-45.55; 7.00	36.91	13.90	0.01**	9.67; 64.15
	mean	8.18	12.93	0.53	-17.16; 33.52	18.24	15.26	0.23	-11.66; 48.15
	high	35.64	20.47	0.08	-4.49; 75.76	-0.42	24.71	0.99	-48.85; 48.01
	AUC_g (CAR) (high vs. low (± 1 *SD*))	T0 vs. T1				T1 vs. T2			
		delta	*SE*	*p*	95 % CI	delta	*SE*	*p*	95 % CI
Childhood adversity score	low	32.33	17.21	0.06	-1.40; 66.07	-57.40	20.72	0.01**	-98.01; −16.79
	mean	7.29	11.00	0.51	-14.26; 28.85	-31.90	13.10	0.02*	-57.57; −6.23
	high	-17.75	10.87	0.10	-39.06; 3.56	-6.41	12.07	0.60	-30.06; 17.24
	DSL (high vs. low (± 1 *SD*))								
Childhood adversity score	low	-35.28	15.32	0.02*	-65.31; −5.25	36.91	18.22	0.04*	1.19; 72.62
	mean	-7.83	10.56	0.46	-28.52; 12.87	18.24	12.89	0.16	-7.03; 43.51
	high	19.63	15.90	0.22	-11.53; 50.79	-0.42	18.40	0.98	-36.48; 35.64

Note. T0 = clinical baseline assessment, T1 = 12-month follow-up, T2 = 24-month follow-up, *SD* = standard deviation, *SE* = standard error, *p* = *p*-value, 95 % CI = 95 % confidence interval, AUC_g = area under the curve with respect to ground, CAR = cortisol awakening response, DSL = diurnal slope. Post-hoc contrasts were calculated to interpret the dependencies of the change in the frequency of non-suicidal self-injury in past 6 months on cortisol and/or childhood adversity. Contrasts were evaluated by generating (pseudo)groups at ± 1 *SD* of the two continuous variables childhood adversity score (top) and cortisol levels (bottom).
* *p*-value < 0.05,
** *p*-value < 0.01.

Adolescents without ACE and a flattened DSL showed an overall unfavorable course of NSSI with good clinical improvement in the first year but a subsequent increase of NSSI frequency in the second year. No significant interaction effect was found for the AUC_i or HCC and ACE in the prediction of changes in NSSI frequency over time.

The overall reduction of NSSI in our sample is consistent with previous research showing a decline in the frequency of NSSI in community-based and clinical samples during adolescence (Brown and Plener, 2017), and consistent with treatment outcome studies derived from our own group (Kaess et al., 2020; Reichl et al., 2023; Rockstroh et al., 2023). It has to be mentioned, that data of the present study have been collected in our specialized outpatient clinic AtR!Sk, where adolescents receive standardized and evidence-based treatment within a stepped-care approach (step 1: Cutting Down Program, Kaess et al.; 2020; step 2: DBT-A) following the recommendations of the National Institute for Health and Care Excellence guidelines (Natioal Institute for Health and Care Excellence, 2022). Researchers pointed to the need of identifying predictors of non-response to NSSI treatment, as a substantial proportion of adolescents do not show clinical improvement or even demonstrate an increase in NSSI frequency (Berk et al., 2022; Reichl et al., 2023). This may be particularly crucial if non-standardized treatment methods are used, where higher proportions of non-response can be assumed.

Given that ACE have been found to predict the development of NSSI during adolescence (e.g., Poon et al., 2023; Russell et al., 2019), it could be assumed that adolescents with ACE may generally be at elevated risk of showing treatment non-response. Edinger et al. (2020) found adolescents with ACE to show a significantly greater reduction in NSSI frequency during a standardized short-term therapy program compared to adolescents without ACE. In a sample of adolescent inpatients, Poon et al. (2023), found relations between childhood abuse and engagement in NSSI at 12- and 18-months post-hospitalization assessments which were additionally mediated by deficits in emotion regulation strategies. In contrast, results of the present study did not confirm main effects of S-ACE on the course of NSSI. In tendency the ACE dependency of NSSI frequency decreased over time. Unfortunately, we cannot rule out the possibility that we missed main effects of ACE on the course of NSSI due to the small sample size of the present study. These contrasting findings could be attributed to sample-inherent differences: whereas our sample and the sample investigated by Edinger et al. (2020) consisted of adolescents seeking help because of risk-taking or self-harming behavior, youths examined by Poon et al. (2023) where hospitalized due to different mental health issues and about 30 % did not engage in NSSI during lifetime. ACE could potentially increase the risk of NSSI via the impairment of emotion regulation, however psychotherapy programs in general and specifically programs specialized for the treatment of NSSI focus on the improvement of emotion regulation potentially buffering effects of ACE on NSSI. Adolescents from our help-seeking sample were more likely to benefit from specialized treatment programs.

Likewise results of the present study did not confirm main effects of unstimulated cortisol secretion (CAR; DSL; HCC) on the course of NSSI. This finding is in line with previous studies reporting no effects of unstimulated cortisol secretion on psychotherapy response in anxiety disorders among children, adolescents and adults (Fischer and Cleare, 2017) or in PTSD among adults (Schumacher et al., 2018). However, it contradicts findings about elevated pre-treatment cortisol levels to be associated with improved treatment effects in adolescents with PTSD (Zantvoord et al., 2019) and with smaller changes of depressive symptoms in adolescent and adult samples (Fischer et al., 2017). Interestingly, the meta-analysis conducted by Fischer et al. (2017) reported effects for unstimulated cortisol secretion and for the CAR, which the authors considered as post-challenge (= awakening) cortisol secretion. Even though research about the prediction of psychotherapy response by HPA axis functioning is still scarce, it could be hypothesized that effects of cortisol secretion on the course of mental disorders may differ between age groups and further depend on clinical symptomatology. NSSI can be considered as a transdiagnostic risk marker for the development of psychopathology in youths (Ghinea et al., 2020), therefore participants of the present study showed various comorbid mental disorders (see Table 1). Presuming HPA axis functioning plays a distinct role in the treatment of specific symptoms, such as those associated with PTSD or depression, it may be inferred that effects of cortisol secretion

could have been averaged out in the present study.

Most interestingly, effects of HPA axis functioning on changes in NSSI frequency varied as a function of ACE severity. Particularly adolescents without ACE and either increased levels of cortisol secretion after awakening (AUC_g) or a flattened DSL showed better improvement in the treatment of NSSI during the first year followed however by a considerable increase in NSSI frequency during the second year. An increased cortisol secretion – presenting itself by an increased CAR or through a reduced depletion and hence higher concentration of cortisol throughout the day – might be associated to functions that have a positive impact on the psychotherapeutic processes for a certain time. In this context, Dedovic et al. (2009) provided a framework for a complex interplay of HPA axis functioning and activity in brain regions such as the prefrontal cortex (e.g. involved in executive functioning), the amygdala (e.g. involved in processing of threatening stimuli) or the hippocampus (e.g. involved in learning, memory, self-esteem). Cortisol can further support recovery from stressful experiences and the reduction of excitability (de Kloet et al., 2008). However, a prolonged release of cortisol has been shown to increase the risk of health problems (allostatic load theory; McEwen, 1998). In terms of the present study, long-term deteriorating effects of increased cortisol secretion might also present themselves in relapses of NSSI after periods of pronounced clinical improvement. It is worth noting that interactions of HPA axis functioning and ACE on the course of NSSI were not found with regard to the increase of cortisol after awakening (AUC_i) nor for hair cortisol, which captures mean cortisol concentrations over the last three months. Potentially, elevated cortisol levels evolved more closely to the help-seeking behavior of adolescents or did arise temporarily not manifesting themselves in the more stable assessment of hair cortisol.

Findings of the present study suggest that adolescents with severe ACE show a steady decrease of NSSI frequency throughout the entire 2-years follow-up period irrespective of levels of unstimulated cortisol secretion at the time of the baseline assessment. A recently published meta-analysis reported blunted cortisol responses to stress experiences among individuals with ACE (Schär et al., 2022). It could on the one hand be assumed that the elevated cortisol levels (increased AUC_g; flattend DSL) could particularly help adolescents with ACE to compensate for blunted stress responses in the context of daily hassles promoting steady clinical improvements over time. On the other hand, adolescents with ACE still experience more stressful experiences in everyday life. In a recently published review, Li et al. (2020) provided evidence for the association between childhood emotional abuse and later depressive symptoms being partially mediated by early maladaptive schemas, negative cognitive styles, interpersonal conflicts, stressful negative events and emotion dysregulation. Potentially, increased unstimulated cortisol levels provide the basis for coping with these stressors leading to steady clinical improvement in the treatment of NSSI.

Notably, 50 % of our sample fulfilled the criteria for BPD at the time of the baseline assessment. Previous meta-analytic results found adult patients with BPD to show blunted cortisol following psychosocial stress and elevated continuous cortisol secretion (Drews et al., 2019). It would be interesting for future research to test for differences in the course of NSSI in interaction with HPA axis functioning depending on BPD symptomatology. On the one hand, BPD is linked to emotion dysregulation, which may affect the therapeutic process. On the other hand, previous research revealed significantly increased ACE among adolescents with BPD (Temes et al., 2017). Moreover, in light of the proven relationship between NSSI and suicidal behavior (Hawton et al., 2015; Koenig et al., 2017a), it would be important for future research to also test for interactions of ACE and HPA axis activity in the prediction of suicidal behavior. In our study, it was not possible to focus on suicidal behavior as an outcome variable due to a very low number of suicide attempts combined with substantial variance restriction at the time of the follow-up assessments.

4.1. Strengths and limitations

Several strengths of the present study are noteworthy. On the one hand, data provide a solid characterization of the study sample via gold standard clinical assessments of psychiatric symptoms (e.g., NSSI) and ACE as well as on a high-quality measurement of different indices of unstimulated cortisol secretion (CAR; DLS; HCC). The accuracy of salivary cortisol assessments has been improved by instructions via telephone and has further been controlled by the use of a Medication Event Monitoring System (MEMS®). On the other hand, analyses are based on longitudinal data including three measurement points over a time period of two years. Nonetheless, findings of the present study also have to be interpreted with caution due to several limitations: First, analyses are based on a small sample size of $n = 51$ adolescents whereby about half of participants missed at least one clinical assessment for which data had to be imputed. A corresponding power-analysis (see Supplementary Material) showed that we had a 75 % power to detect a medium-sized main effect for the variables of interest (i.e., S-ACE in set 2 and cortisol in set 3). Thus, it cannot be ruled out that we may have missed smaller effects in the present study. Second, even though all adolescents of the present study sought help at the outpatient clinic for risk-taking and self-harming behavior (AtR!Sk), not all received the same standardized outpatient treatment with a small proportion of adolescents not receiving any psychotherapy. Third, due to the retrospective assessment of severity of childhood adversity, biases in the retrieval of ACE cannot be ruled out. Forth, the assessments of unstimulated cortisol secretion have been conducted on two or three days only or at one time point for diurnal patterns (CAR; DSL) and HCC, respectively. Future research would benefit from the assessment of cortisol concentrations at multiple time points throughout the longitudinal study period in order to analyze more closely the relations between HPA axis functioning and the course of NSSI.

4.2. Summary and conclusions

In our study, the frequency of NSSI decreased on a mean level in a sample of help-seeking adolescents over a two-years study period. Interestingly, the course of NSSI was found to be predicted by an interaction of the severity of ACE and HPA axis functioning. Particularly adolescents without ACE and high diurnal cortisol levels showed a steep decline in the frequency of NSSI during the first year but a worsening in the second year. In contrast, adolescents with severe ACE and high cortisol levels (AUC_g; DSL) showed a slower but steady decline in the frequency of NSSI over the full two-years study period that was comparable to the course of NSSI of adolescents with low cortisol levels (AUC_g; DSL) irrespective of ACE. Our findings could point to high cortisol levels being favorable for clinical improvement on the short-term but bearing a risk of allostatic load and subsequent worsening of NSSI for adolescents without ACE. Meanwhile, high cortisol levels might help adolescents with ACE to cope with associated problems such as emotion dysregulation or interpersonal conflicts leading to a favorable decline of NSSI frequency despite high cortisol concentrations. In contrast, nor the increase of cortisol after awakening (AUC_i) nor cortisol measured in hair (HCC) did show main effects or interact with ACE in the prediction of the course of NSSI. Future research should investigate the impact of HPA axis functioning and ACE on the course of NSSI by relying on larger sample sizes and by investigating a broader set of indices of HPA axis functioning (unstimulated cortisol secretion; cortisol response to different stress experiences such as psychosocial stress or pain induction) performing repeated measurements in a longitudinal study design.

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CRediT authorship contribution statement

Corinna Reichl: Writing – original draft, Investigation, Conceptualization. **Selina Schär:** Writing – original draft, Visualization, Formal analysis. **Stefan Lerch:** Visualization, Validation, Formal analysis, Data curation. **Nicole Hedinger:** Writing – review & editing. **Romuald Brunner:** Writing – review & editing, Conceptualization. **Julian Koenig:** Writing – review & editing, Conceptualization. **Michael Kaess:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107093.

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