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Research paper

Pain sensitivity and plasma beta-endorphin in adolescent non-suicidal self-injury

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ABSTRACT

Background: Beta-endorphin (BE) has been suggested to play a central role as to why people engage in NSSI. To our knowledge, no study has systematically assessed this potential relationship in adolescents with NSSI.
Methods: 94 adolescents with NSSI (according to DSM-5 criteria) and 35 healthy controls (HC) were enrolled. All participants received heat pain stimulation, with pain threshold and tolerance measured in °C. Plasma BE levels were assessed. Sociodemographic and clinical characteristics were obtained via semi-structured interviews and self-report questionnaires.
Results: Adolescents with NSSI showed increased pain thresholds ($t_{(127)} = 2.071$, $p = .040$), lower pain intensity ($t_{(114)} = = 2.122$, $p = .036$) and lower plasma BE levels ($t_{127} = = 3.182$, $p = .002$) compared to HC. Groups did not differ on pain tolerance ($t_{(127)} = 0.911$, $p = .364$). Greater pain threshold correlated positively with borderline personality disorder (BPD) symptoms ($r = 0.182$, $p = .039$), while pain intensity ($r = -0.206$, $p = .033$) and BE levels ($r = -0.246$, $p = .007$) correlated negatively with depression severity. No significant relationship was found between pain threshold and plasma BE ($r = -0.013$, $p = .882$).
Limitations: Future studies should implement repeated plasma BE measures to assess BE release in association with pain in NSSI. Validity of plasma BE measures compared to central measures should be considered. Assessing the association between pain sensitivity (PS) and BE in a naturalistic setting presents a promising avenue for future research in NSSI.
Conclusions: Findings support both reduced PS and basal opioid deficiency as independent biological correlates and potential risk-factors for NSSI. Further longitudinal and experimental studies are needed to investigate the role of BE levels and PS as well as their potential association.

1. Introduction

Non-suicidal self-injury (NSSI) is defined as the deliberate and self-inflicted hurting or destruction of one's own body tissue without suicidal intent (International Society for the Study of Self-injury, 2018; Nock, 2010). Commonly, NSSI has its onset in adolescence; with lifetime prevalence rates of 17.2% for adolescents (Swannell et al., 2014), it presents a serious threat to psychosocial development during adolescence. Despite being a key symptom of borderline personality disorder (BPD), NSSI frequently accompanies other psychiatric disorders, e.g. major depressive disorder (MDD), thereby affecting a heterogeneous clinical population (Glenn and Klonsky, 2013; Nock, 2009). Reasons for engaging in NSSI have been linked to negative affect, dissociation and emotion dysregulation, with NSSI serving as a dysfunctional coping mechanism (Klonsky, 2007). These phenotypes underlying NSSI are commonly found in both BPD and MDD. In addition to diverse types of psychopathology, the experience of adverse childhood experiences (ACE) has been defined as a central risk factor for the

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occurrence of NSSI (Cipriano et al., 2017; Glenn and Klonsky, 2013), with up to 80% of individuals with a history of NSSI reporting ACE (Gratz et al., 2002). However, NSSI also occurs independently (Zetterqvist, 2015) without comorbid psychiatric disorders (Wilkinson, 2013), supporting the notion of NSSI as an independent disorder (American Psychiatric Association, 2013). So far, research has focused on psychological functions and risk factors related to the occurrence of NSSI, yet its underlying biological mechanisms are still poorly understood.

Based on reports that individuals with a history of NSSI feel little to no pain (hypo-/analgesia) during or following self-injury (Nock and Prinstein, 2005), researchers proposed alterations in pain processing as a potential risk factor for NSSI (Nock, 2010). Pain perception and processing are complex, comprising sensory, affective and cognitive dimensions (Navratilova and Porreca, 2014), including the involvement of a number of brain areas (e.g. anterior cingulate cortex (ACC), amygdala, insula, prefrontal cortex) that are largely interconnected, serving somatosensory and affective/cognitive aspects of the holistic pain sensation (Garland, 2012; Price, 2000). While noxious stimuli are normally perceived as aversive, resulting in avoidance as a self-preserving measure, Nock hypothesized that individuals with lower pain sensitivity (PS), and subsequently no aversion to anticipated pain, are at greater risk to engage in NSSI (Nock, 2010). These assumptions were confirmed in two research reviews that reported significantly higher pain threshold and tolerance in individuals with a history of NSSI across all age groups (Kirtley et al., 2016; Koenig et al., 2016). Further support stems from recent neuroimaging studies showing that reduced PS seems to be related to altered pain perception, with altered activation patterns following painful stimuli in brain areas commonly associated with affective and cognitive processes of pain perception (Schmahl et al., 2006, 2004). Initial theories hypothesized processes of habituation as an explanation for lowered PS in individuals with NSSI (Joiner, 2007). However, with recent studies yielding no support for these assumptions (Koenig et al., 2017b), a potential role of comorbid psychopathology has been discussed. Consistently, PS was found to be negatively correlated with the severity of BPD symptomatology (Ludäscher et al., 2009), as well as with MDD (McCoy et al., 2010; Thompson et al., 2016). Moreover, emotion dysregulation, self-criticism and neuroticism – central characteristics in BPD and depression alike (American Psychiatric Association, 2013; Bradley et al., 2011) – were found to be associated with lowered PS (Bunderla and Kumperščak, 2015; Franklin et al., 2012), with emotion dysregulation accounting for significant variance in the association between NSSI and pain tolerance (Franklin et al., 2012). Further, ACE have been related to lower PS (Fillingim and Edwards, 2005) and are central risk factors for BPD (Lieb et al., 2004), MDD (Bradley et al., 2011), dissociation (Korzekwa et al., 2009) and emotion dysregulation (Lieb et al., 2004). These findings support the assumption of a complex relationship between PS and comorbid psychopathology in NSSI. Nevertheless, more research is warranted to assess the nature of these associations.

A well-established relationship exists between analgesia, pain perception and the endogenous opioid system, one of the innate pain-relieving systems (Akil et al., 1984). Especially the activity of μ- and δ-receptors is linked to the reduction of pain perception (Benarroch, 2012; Bresin and Gordon, 2013), emphasizing foremost the role of beta-endorphin (BE) as a μ- and δ-receptor agonist. μ- and δ-receptors, and BE are present in both the central and peripheral nervous system (Benarroch, 2012; Rachinger-Adam et al., 2011), and modulation of pain perception and analgesia are exerted through central and peripheral nervous BE release alike (Benarroch, 2012; Stein et al., 2009). Consistently, Zubieta and colleagues showed that increased μ-opioid receptor activity in the ACC is linked to lower self-reported levels of pain unpleasantness and that increased μ-opioid receptor activity in the amygdala is linked to lower perceived pain intensity (Zubieta et al., 2001). Further, Bruehl and colleagues showed that resting plasma BE levels predicted analgesic response to morphine in chronic pain patients (Bruehl et al., 2017). Based on the existing literature, the potential role of BE in NSSI has come to increasing attention. In line with the small number of existing studies, opioid deficiency theories suggest that people engaging in NSSI have lower resting levels of BE and, driven by an innate desire to restore a homeostasis, engage in actions, such as NSSI, that are likely to result in releases of BE (Bresin and Gordon, 2013; Hooley and Franklin, 2018). First support for these models was drawn from animal studies illustrating that rhesus monkeys with a history of self-biting behavior showed lower basal plasma levels of BE than a matched group of monkeys without such behavior (Tiefenbacher et al., 2005). Stanley and colleagues reported lower BE levels in cerebral spinal fluid (CSF) in participants with personality disorders, a history of suicide attempts and a history of NSSI (Stanley et al., 2010). Prossin and colleagues, using positron emission tomography (PET), found lower μ-opioid receptor activity in the orbitofrontal cortex and the left amygdala in individuals with BPD (Prossin et al., 2010). Despite some empirical support of these theoretical models, studies are limited mostly to animal models or assessed the role of changes in BE in different psychiatric disorders without assessing NSSI (Prossin et al., 2010). Additionally, most human studies solely included adults.

NSSI is most common in adolescents (Nock, 2010) and marks a serious risk factor for future suicide attempts, risk-taking behaviours, and potential long-term mental health problems, even beyond cessation into adulthood (Brown and Plener, 2017). While some evidence suggests altered biological mechanisms are already present in adolescence (Kirtley et al., 2016; Koenig et al., 2016), more research in adolescent populations is needed in order to increase the understanding of this phenomenon. A focus on younger samples further allows to rule out effects of long-term illness and secondary effects of chronification, as well as age-dependent differences in the endogenous opioid systems (Gibson and Farrell, 2004). Thus, in this study, we aimed to systematically investigate PS and basal BE levels in adolescents with NSSI compared with a group of healthy matched controls. We hypothesized that adolescents with NSSI show altered PS (indexed by higher pain threshold and tolerance, and lower pain intensity). In addition, we hypothesized that adolescents engaging in NSSI show lower resting plasma BE levels. Given the high comorbidity of NSSI, we further explored potential associations between PS and BE with BPD symptoms, depressive symptoms, trauma severity and general psychiatric symptom severity, respectively. Finally, our study is the first to assess the potential association between altered plasma BE levels and PS in adolescent NSSI.

2. Methods

2.1. Participants

Patients with NSSI were recruited from the outpatient clinic for risk-taking and self-harm behavior “Ambulanz für Risikoverhalten und Selbstschädigung (AtR!Sk)” (Kaess et al., 2017) at the Department of Child and Adolescent Psychiatry, University of Heidelberg. Following an initial diagnostic assessment, patients are invited to participate in the nested AtR!Sk-Bio cohort, which is an ongoing study aiming at identifying biological correlates of risk-taking and self-harming behavior in adolescence. The Ethics Committee of the Faculty of Medicine, University of Heidelberg, approved the scientific evaluation of AtR!Sk (IRB approval number S-449/2013) and the add-on neurobiological assessments (IRB approval number S-514/2015).

Recruitment for AtR!Sk-Bio takes places within six weeks after the diagnostic assessment in AtR!Sk. Inclusion criteria comprise: age 12–17 years; completed diagnostic assessment; informed and written consent of adolescents and their caregivers. Patients showing acute psychotic symptoms or lacking speech comprehension are excluded. For the present analyses, only patients fulfilling the criteria for NSSI, defined as five or more incidents of NSSI in the last 12 months according to the

DSM-5 (American Psychiatric Association, 2013), were included. Further, based on known sex-differences regarding the prevalence of NSSI and PS, only data from female patients were considered. Healthy controls (HC) were recruited via public advertisements and underwent an adapted form of the diagnostic assessment used in AtR!Sk. Eligibility criteria for HC comprised: age 12–17 years; no history of NSSI; no endorsement of any psychiatric disorder and no treatment for any psychiatric disorder prior to participation in the study. All HC and their caregivers provided informed and written consent to participate in the study. Due to the ongoing nature of the AtR!Sk and AtR!Sk-Bio studies, August 2018 was chosen as cut-off for inclusion in the present study. All participants (patients with NSSI and HC) that had completed the neurobiological assessment until August 2018 were subsequently considered for analyses.

2.2. General procedures

The study comprised two separate appointments. The first appointment consisted of the diagnostic assessment for the patient group and the HC respectively, with relevant instruments described below (see *2.3.*). The biological assessment, marking the second appointment, started at 8 a.m. with measures of height and weight, as well as questions regarding participants' smoking habits; physical illness within the past three months; and regular medication intake. To account for potential interferences with the blood draw, participants were asked whether they were fasting as instructed, as well as to their cigarette consumption at the day of the assessment. Next, the fasting blood draw described in detail below (see *2.4.*) followed. After a resting period, PS was assessed as described below (see *2.5.*). All participants received 40€ upon completion of the neurobiological assessment.

2.3. Measures

NSSI and suicide attempts were measured using single items of the German version of *the Self-Injurious Thoughts and Behaviors Interview* (SITBI-G) (Fischer et al., 2014), a semi-structured interview for the detailed assessment of self-injurious thoughts and behaviours that was slightly modified to meet DSM-5 criteria for NSSI. The SITBI-G was carried out in its entirety and shows good psychometric properties (Fischer et al., 2014). BPD symptoms were assessed using the respective part of the German version of the *Structured Clinical Interview for DSM-IV Axis II Personality Disorders* (SCID-II) (Wittchen et al., 1997), with items showing good internal consistency (Cronbach's $\alpha = 0.83$). In addition, patients underwent the *Mini International Neuropsychiatric Interview for Children and Adolescents* (MINI-KID) (Sheehan et al., 2004), a short semi-structured interview designed to assess common axis I psychiatric disorders in children and adolescents aged 6–19 years. Self-reported depressive symptoms were measured using the *Depression Inventory for Children and Adolescents* (DIKJ) (Stiensmeier-Pelster et al., 2000). The 26 items of the DIKJ were constructed based on DSM-IV criteria for depression, showing excellent psychometric properties (Stiensmeier-Pelster et al., 2000). Similarly, we found excellent internal consistency in the present study (Cronbach's $\alpha = 0.95$). Severity of psychiatric symptoms was rated based on the *Clinical Global Impressions-Severity* (CGI-S) (Busner and Targum, 2007) scale; This seven-point scale requires the clinician to rate how mentally ill a patient is, based upon observed and reported symptoms, behavior and function over the past seven days. To account for ACE, all participants completed the German translation of the *Childhood Experiences of Care and Abuse* questionnaire (CECA.Q) (Kaess et al., 2011), showing good psychometric properties. The CECA.Q items were taken directly from the interview version and adapted, covering modules for parental care (antipathy and neglect), physical abuse and sexual abuse. To assess trauma severity, we created a dimensional trauma score using four modules of the CECA.Q, showing moderate to excellent internal consistency (Cronbach's α: *antipathy* (maternal $\alpha = 0.91$; paternal $\alpha = 0.92$), *neglect* (maternal $\alpha = 0.83$; paternal $\alpha = 0.92$), *physical abuse* (maternal $\alpha = 0.60$; paternal $\alpha = 0.70$), *sexual abuse* ($\alpha = 0.85$)). Following dichotomization of each variable, a mean score ranging from 0 (no trauma) to 1 (multiple trauma) was generated for each participant. Smoking behavior and tobacco use were assessed during the first appointment using a short questionnaire, as well as during the second appointment using screening questions to account for potential influences on BE. While inconclusive, current literature indicates that acute nicotine administration could increase BE levels, while chronic exposure could eventually inhibit the biosynthesis of beta-endorphin, leading to a chronic decrease in beta-endorphin levels (del Arbol et al., 2000; Tziomalos and Charsoulis, 2004).

2.4. Blood draws

Fasting blood samples were collected between 8:30 a.m. and 9:00 a.m. by trained medical personal via venepuncture from the crook of the arm, under sterile conditions. Blood samples were subsequently sent to the central laboratories of the Heidelberg University Hospital for further analyses. BE levels were determined using an enzyme-linked immunosorbent assay (ELISA) by Cloud Clone (Houston, TX, US), according to the protocol of the manufacturer. Blood samples were left to rest at room temperature for two hours, before being centrifuged for 20 min at 1000xg and stored at -18 °C within the central laboratories until assay. To determine BE levels, samples were thawed to room temperature and 50μL were added to each well of pre-coated 96-well strip plates. 50μL/well of detection reagent A were added and the plates were set to incubate for 1 hour at 37 °C. After incubation, the wells were washed and 100μL of detection reagent B were added to each well. Following incubation for 30 min at 37 °C, the wells were washed again and 90μL of substrate solution was added. The wells were incubated, protected from light, for 10 – 20 min at 37 °C. Subsequently, 50μL of Stop solution were added to each well. After the liquids mixed uniformly, absorbance was measured immediately at 450 nm. Samples were tested in duplicate. Central and peripheral BE play a role in the modulation of pain perception and analgesia (Benarroch, 2012; Stein et al., 2009), however plasma BE levels have been found to be sensitive to effects of stress (De Riu et al., 1997). Despite this sensitivity, studies assessing resting plasma BE levels across repeated sessions were able to show that resting plasma BE levels remained relatively stable (Bruehl et al., 2017; Leppäluoto et al., 2008), supporting the assumption that resting plasma BE levels are a reliable and relatively stable marker.

2.5. Pain sensitivity

PS was assessed using an AHP-1800CPV Versatile Cold/Hot Plate (TECA Corp., Chicago, IL, USA) and a predefined programmed sequence for the temperature. Baseline adaptation temperature was set at 32 °C. Temperature was sealed off at 50 °C to avoid tissue damage. Participants were instructed to place their non-dominant hand flat on the plate as soon as baseline temperature was reached. After a 3-minute adaptation phase, temperature raised up to 50 °C within 4 min, increasing linear by 1 °C over 13.3 s. Participants were asked to keep their hand firmly on the plate until the pain became intolerable. Temperature at the first pain sensation (pain threshold) and temperature at intolerable pain sensation (pain tolerance) was measured in °C. Pain intensity was assessed via visual analogue scale (VAS) using the Continuous Measurement System (CMS) software (Messinger et al., 2009). When pain threshold was reached, participants were instructed to continuously rate pain intensity on a scale from 0 to 100 using their dominant hand until pain tolerance was reached. If pain tolerance was not reached at 50 °C, the sequence ended automatically and participants were asked to remove their hand. For the present study, pain intensity scores were calculated for each participant based on the rated pain intensity upon reaching pain tolerance. To account for potential

inaccuracies, an average score was generated, using all VAS ratings within five seconds prior to- and following attained pain tolerance.

2.6. Statistical analysis

Prior to analyses, the main variables (NSSI, BE, pain threshold, and tolerance) were checked for missing values. BE data were additionally checked and corrected using sensitivity analyses. Sociodemographic and clinical variables were tested for between-group differences using two-sided *t*-tests and χ^2-tests respectively. Between-group differences regarding pain threshold and tolerance, as well as between-group differences regarding pain intensity and plasma BE levels were analysed using two-sided *t*-tests. To account for the potential influence of smoking behavior on BE, we calculated a regression model with BE as dependent variable and group, smoking prior to the neurobiological assessment and smoking during the last 12 months as independent variables. In additional regression models the potential influence of medication intake and body-mass-index (BMI) on BE and PS was assessed. Next, Pearson product-moment correlations were used to assess associations between pain threshold, intensity and tolerance, and BE. Finally, we conducted exploratory analyses, using Pearson product-moment correlations, to assess potential associations between clinical characteristics and pain threshold, intensity, tolerance, and BE respectively. Analyses regarding the number of NSSI episodes and severity of psychiatric symptoms were solely conducted for the patient group. All analyses were performed using Stata (Version 16; StataCorp LP, College Station, TX, USA) with the significance level set to $\alpha = 0.05$. Adjustments for simultaneously testing two directed hypotheses were not performed, as tests were two-sided. No a priori power analysis was conducted, as the studies, from which the data stem, are still ongoing and do not aim at recruiting up to an a priori fixed number of participants.

3. Results

3.1. Sample characteristics

For the present analyses, only data from participants up to August 2018 were included. Since recruitment for the AtR!Sk-Bio cohort started in August 2016, $n = 203$ patients passed the diagnostic assessment in AtR!Sk, making them eligible for the additional neurobiological assessments of AtR!Sk-Bio. $N = 148$ patients had completed the neurobiological assessments until August 2018 (participation rate: 72.9%). Of these, $n = 31$ (20.9%) patients were excluded due to not meeting DSM-5 criteria for NSSI. $N = 10$ patients (6.8%) were excluded due to male sex. Of the remaining $n = 107$ patients, $n = 17$ (11.5%) were excluded due to missing BE ($n = 16$; 10.8%) or pain data ($n = 1$; 0.7%). Data from one patient was excluded because this patient had, with 224.1 μg/ml, an extremely high BE value (the next highest value was 97.7 μg/ml). Sensitivity analyses showed that this patient had an undue influence on results. $N = 40$ healthy female adolescents were recruited as control group, with $n = 5$ (12.5%) being excluded from analyses for missing BE data due to an insufficient quantity of blood for assay. The final study sample consisted of $n = 94$ female patients with NSSI and $n = 35$ HC.

Sociodemographic and clinical characteristics of the study sample are presented in *Table 1*. No significant difference could be found regarding mean age, height, weight, or body-mass-index (BMI). Participants differed significantly regarding school type, ($\chi^2(3) = 16.07$, $p = .001$). $N = 20$ (15.5%) participants were taking at least one form of medication (NSSI: $n = 19$, 14.7%; HC $n = 1$, 0.8%). Patients were significantly more likely to have smoked in the past 12 months compared to HC ($\chi^2(6) = 16.62$, $p = .011$). Similarly, significantly more patients had smoked prior to the neurobiological assessment compared to HC ($\chi^2(1) = 4.48$, $p = .034$).

Patients reported on average 70.66 ($SD = 70.01$) episodes of NSSI within the past 12 months. Mean age of onset for NSSI was 12.85 years ($SD = 1.36$) and on average, patients reported engagement in NSSI for 1.9 years ($SD = 1.66$). $N = 42$ patients (44.7%) reported at least one previous suicide attempt, with an average of 3.41 ($SD = 6.42$) lifetime attempts. $N = 89$ patients fulfilled diagnostic criteria for at least one psychiatric disorder (MINI-KID). On average, patients endorsed 3.37 ($SD = 0.22$) BPD criteria, with $n = 30$ (31.9%) patients fulfilling the diagnostic threshold for BPD diagnosis. Further, $n = 52$ (58.4%) patients fulfilled the diagnostic threshold for either a depressive episode ($n = 35$) or recurrent depressive disorder ($n = 17$). Patients scored significantly higher on depressive symptoms (DIKJ) compared to HC ($t(116) = 14.993$, $p < .001$). Patients reported significantly higher ACE compared to HC ($\chi^2(1) = 32.38$, $p < .001$).

3.2. Pain ratings

The NSSI group showed a significantly higher pain threshold compared to HC (NSSI: $M = 43.27$, SD = 3.77, HC: $M = 41.77$, SD = 3.36; $t(127) = 2.071$, $p = .040$, 95% CI[-0.80, -0.02], Cohen's $d = 0.41$; Fig. 1). No significant differences between groups were found on measures of pain tolerance (NSSI: $M = 47.16$, SD = 2.47, HC: $M = 46.73$, SD = 2.17; $t(127) = 0.911$, $p = .364$, 95% CI[-0.57, -0.021], Cohen's $d = 0.18$; Fig. 1). The NSSI group reported a significantly lower pain intensity compared to HC ($t(114) = -2.122$, $p = .036$, 95% CI[0.03, 0.84], Cohen's $d = 0.44$).

For exploratory analyses, we further assessed potential associations between clinical characteristics and PS (pain threshold, pain tolerance, and pain sensitivity respectively). Pain threshold showed a significant positive correlation with BPD symptoms ($r = 0.182$, $p = .039$; Fig. 2). No significant relationship was found between pain threshold and the number of NSSI episodes in the past 12 months ($r = -0.064$, $p = .543$), depression scores (DIKJ; $r = 0.091$, $p = .325$), severity of psychiatric symptoms (CGI; $r = -0.037$, $p = .729$) or severity of ACE ($r = 0.101$, $p = .270$). No significant relationship was found between pain tolerance and BPD symptoms ($r = 0.104$, $p = .239$), number of NSSI episodes in the past 12 months ($r = -0.098$, $p = .347$), depression scores (DIKJ; $r = 0.003$, $p = .976$), severity of psychiatric symptoms (CGI; $r = -0.032$, $p = .763$) or severity of ACE ($r = 0.037$, $p = .687$). Pain intensity showed a significant negative correlation with depression scores ($r = -0.206$, $p = .033$). No significant relationship was found between pain intensity and BPD symptoms ($r = -0.108$, $p = .250$), number of NSSI episodes in the past 12 months ($r = 0.080$, $p = .474$), severity of psychiatric symptoms (CGI; $r = 0.037$, $p = .743$) or severity of ACE ($r = 0.049$, $p = .607$). Additional exploratory analyses were conducted to determine what factors explain unique variance in PS. Sub-group analyses within the NSSI group revealed no significant differences for patients with BPD compared to patients without BPD (pain threshold: $t(92) = -0.549$, $p = .585$; pain tolerance: $t(92) = 0.437$, $p = .663$; pain intensity: $t(81) = -0.642$, $p = .523$), patients with MDD compared to patients without MDD (pain threshold: $t(92) = 1.042$, $p = .300$; pain tolerance: $t(92) = -0.235$, $p = .815$; pain intensity: $t(81) = 1.214$, $p = .228$) and patients with previous suicide attempts compared to patients without previous suicide attempts (pain threshold: $t(92) = -0.391$, $p = .696$; pain tolerance: $t(92) = -0.595$, $p = .553$; pain intensity: $t(81) = -0.497$, $p = .621$). Subsequently, multiple regressions, using group, BPD symptoms and depression scores as independent variables, revealed a significant multiple regression model for pain threshold ($F_{(3, 114)} = 3.68$, $p = .014$), with an adjusted R^2 of 0.06. However, no significant predictors could be found: group ($\beta = 0.29$, $p = .074$), BPD symptoms ($\beta = 0.23$, $p = .053$), depression scores ($\beta = -0.29$, $p = .070$). Finally, stepwise regressions were performed to assess best model fit for individual factors. BPD symptoms significantly predicted pain threshold, $b = 0.39$, $t(118) = 2.65$, $p = .009$, with the model explaining a significant proportion of variance in pain threshold, $R^2 = 0.06$, $F_{(1, 116)} = 7.02$, $p = .009$. Group significantly predicted pain intensity, $b = -9.66$, $t(118) = -2.20$, $p = .030$, with the model explaining a significant proportion of variance in pain threshold, $R^2 = 0.04$, $F(1105) = 4.85$, $p = .030$.

Table 1
Sociodemographic characteristics of the study sample.

Variable	Group; mean ± SD or *N* (%)		Effect Size[b]	*P*[a]
	HC, (*n* = 35)	NSSI, (*n* = 94)		
Age (yr)	14.9 ± 1.29	14.9 ± 1.44	0.03	0.877
Height (cm)	164.5 ± 5.39	165.9 ± 6.26	0.25	0.211
Weight (kg)	57.6 ± 10.91	61.7 ± 14.06	0.31	0.116
BMI	21.2 ± 3.29	22.37 ± 4.79	0.27	0.183
School Type[c]			0.35	<0.001
Gymnasium	26 (74.3)	35 (37.2)		
Realschule	8 (22.9)	34 (36.2)		
Hauptschule	0 (0.0)	11 (11.7)		
Other	1 (2.8)	14 (14.9)		
Smoked past 12 months	9 (25.7)	50 (53.2)	0.36	0.011
Smoked prior bio. Assess.	0 (0)	11 (11.7)	0.19	0.034
ICD-10 Diagnoses				
Organic, including symptomatic, mental disorders	–	0 (0)		–
Mental and behavioural disorders due to psychoactive substance use	–	20 (21.3)		–
Schizophrenia, schizotypal and delusional disorders	–	0 (0)		–
Mood [affective] disorders	–	60 (63.8)		–
Neurotic, stress-related and somatoform disorders	–	42 (44.7)		–
Behavioural syndromes associated with physiological disturbances and physical factors	–	12 (12.8)		–
Disorders of adult personality and behavior	–	35 (37.2)		–
Mental retardation	–	0 (0)		–
Disorders of psychological development	–	1 (1.1)		–
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence/Unspecified mental disorder	–	21 (22.3)		–
DIKJ[d]	5.4 ± 3.62	29.6 ± 9.12	3.05	<0.001
CGI[d]	-	5.04 ± 0.69		
CECA.Q[d]				
Experienced ACE	3 (8.6)	57 (65.5)	0.52	<0.001

BMI = body mass index; DIKJ = *Depressionsinventar für Kinder und Jugendliche*; CGI = clinical global impression; CECA.*Q* = *Childhood Experiences of Care and Abuse* questionnaire.

[a] Significance: Values refer to differences between groups, with t-tests for continuous variables and χ^2 tests for categorical variables.

[b] Effect Size; Effect sizes were calculated using Cohen's d for t-tests and Cramer's V for χ^2 tests.

[c] Hauptschule: secondary school terminating with a lower secondary-school level II certificate: Realschule: secondary school terminating with a secondary-school level I certificate; Gymnasium: secondary school terminating with the general qualification for university entry.

[d] Due to missing data, analyses were carried out with varying N for HC and NSSI-group: DIKJ (*N* = 34 HC & *N* = 84 NSSI); CGI (*N* = 92 NSSI); CECA.Q (*N* = 35 HC & *N* = 87 NSSI).

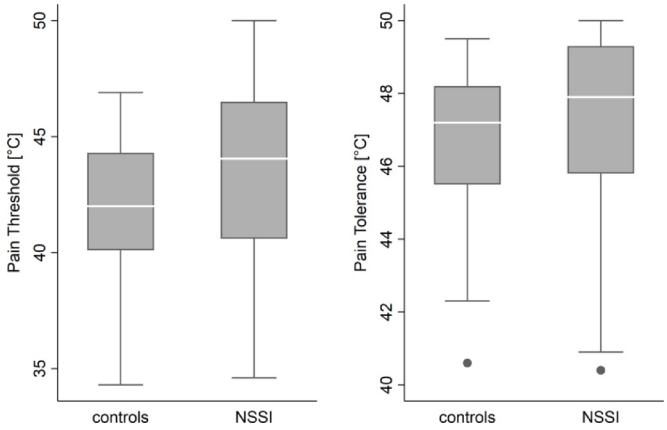

Fig. 1. Group differences in pain ratings. NSSI = Non-suicidal self-injury.

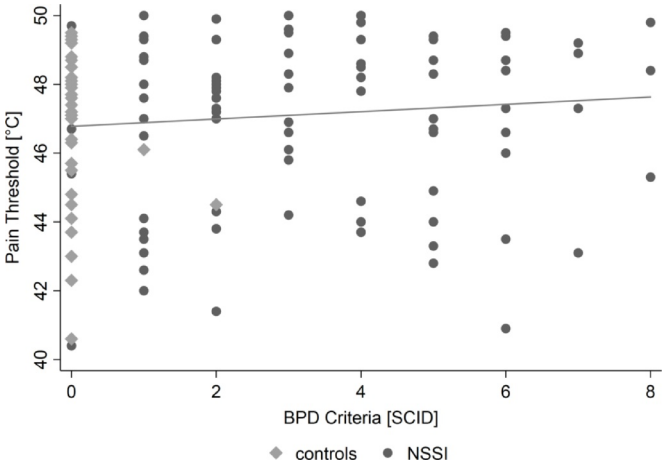

Fig. 2. Correlation scores between BPD symptoms and pain threshold. BPD = Borderline personality disorder.

3.3. Beta-Endorphin

The groups differed significantly on plasma BE levels ($t(127) = -3.182$, $p = .002$, 95% CI[0.23, 1.03], Cohen's $d = 0.63$): As depicted in Fig. 3, patients had significantly lower BE levels ($M = 26.21$ pg/ml, $SD = 20.64$) compared to the HC ($M = 39.02$ pg/ml, $SD = 19.45$). Regarding a potential influence of smoking habits, a significant regression equation was found for the multiple regression model ($F_{(3, 125)} = 4.25$, $p = .007$), with an R^2 of 0.093. Group significantly predicted BE levels ($\beta = -12.55$, $p = .004$), while smoking prior to the neurobiological assessment ($\beta = -11.57$, $p = .110$) and smoking over the last 12 months ($\beta = 3.53$, $p = .460$) had no significant influence.

Further, in several exploratory analyses, we assessed potential associations between clinical characteristics and plasma BE levels. A significant negative correlation was found between BE levels and depression scores (DIKJ: $r = -0.246$, $p = .007$, Fig. 4). No significant relationship was found between BE levels and the number of NSSI episodes in the past 12 months ($r = 0.086$, $p = .412$), BPD symptoms ($r = -0.100$, $p = .258$), severity of psychiatric symptoms (CGI: $r = 0.052$,

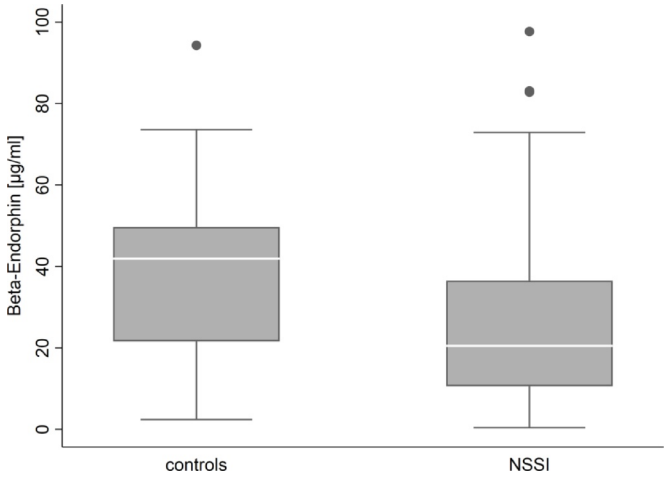

Fig. 3. Group differences in plasma beta-endorphin levels. NSSI = Non-suicidal self-injury; pg/ml = picogram per milliliter.

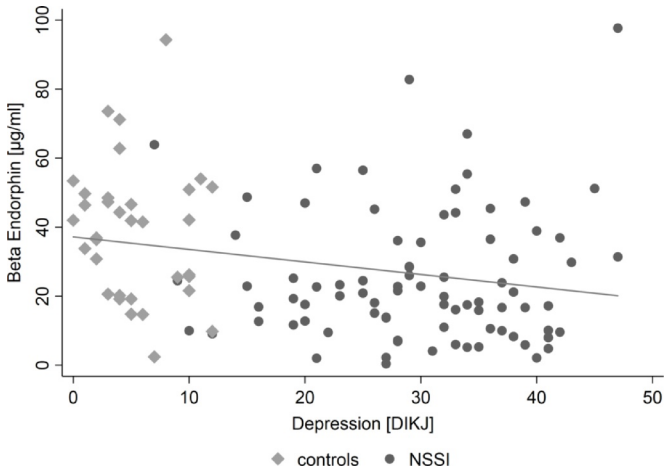

Fig. 4. Relationship between plasma beta-endorphin levels and depression scores.

$p = .621$) or severity of ACE ($r = -0.126$, $p = .168$). Similarly, no significant relationship was found between BE levels and pain threshold ($r = -0.013$, $p = .882$), pain tolerance ($r = 0.053$, $p = .553$) and pain intensity ($r = 0.012$, $p = .898$). Again, additional exploratory analyses were conducted to determine what factors explain unique variance in BE levels. Sub-group analyses within the NSSI group revealed no significant differences for patients with BPD compared to patients without BPD ($t(92) = -0.517$, $p = .607$), patients with MDD compared to patients without MDD ($t(92) = -0.411$, $p = .682$) and patients with previous suicide attempts compared to patients without previous suicide attempts ($t(92) = -0.507$, $p = .613$). Subsequently, using group, BPD symptoms and depression scores as independent variables, we found a significant multiple regression model for BE levels ($F_{(3, 114)} = 4.76$, $p = .004$), with an adjusted R^2 of 0.09. Group significantly predicted BE levels ($\beta = -0.40$, $p = .014$), while BPD symptoms ($\beta = 0.15$, $p = .211$) and depression scores ($\beta = 0.15$, $p = .915$) had no significant influence. Finally, a stepwise regression was performed to assess best model fit for individual factors. Group significantly predicted BE levels, $b = -13.84$, $t(118) = -3.56$, $p < .001$, with the model explaining a significant proportion of variance in BE levels, $R^2 = 0.10$, $F_{(1, 116)} = 12.70$, $p < .001$.

4. Discussion

Adolescents with NSSI had significantly higher pain thresholds and reported lower pain intensities compared to HC, indicating lower overall PS. This finding is in line with previous research in adolescents (Koenig et al., 2017b) and findings on self-harm across all ages (Koenig et al., 2016). In accordance with more recent findings (Glenn et al., 2014; Koenig et al., 2017a), we found no association between a lower PS and NSSI frequency, yielding further support against previous theories on the effect of habituation (Joiner, 2007). In line with our second hypothesis, individuals with NSSI had significantly lower basal BE levels compared to HC. The endogenous opioid system is a key factor in the experience and processing of pain (Bresin and Gordon, 2013; Bruehl et al., 2012). In particular, BE release is linked to a reduction in pain unpleasantness and perceived PS (Zubieta et al., 2001). Previous research found that adults with a history of NSSI had altered basal BE levels (Sher and Stanley, 2008). Based on these findings a homeostasis model of NSSI was suggested (Stanley et al., 2010) – the opioid deficiency model. In line with this model, we demonstrate robust alterations of basal BE levels in adolescents with NSSI. However, we found no direct link between plasma BE levels and PS. Important to note, the opioid deficiency model postulated that BE release, rather than the baseline BE level, modulates pain experience, with lower baseline BE levels potentially increasing the sensitivity for the analgesic effects of BE release (Bresin and Gordon, 2013), subsequently leading to a lower PS following NSSI. This assumption is supported by studies showing that increases in μ-opioid receptor availability lead to a heightened sensitivity for μ-opioid receptor agonists (Bresin and Gordon, 2013), with other studies showing that BE levels were elevated following intense physical sensations (Ribeiro et al., 2005; Sandman and Hetrick, 1995). Further, some evidence exists that BE levels are elevated following NSSI compared to baseline levels (Sandman et al., 2003; Sandman and Hetrick, 1995), but these studies did not assess related pain experience. Unfortunately, we did not assess BE release in this study. Therefore, while we provide evidence on the first assumptions of the opioid deficiency model in adolescent NSSI (lower basal BE level), we were not able to test for effects of BE release. Overall, the exact role of plasma BE for PS in adolescent NSSI has not yet been extensively researched. More studies combining assessment of basal BE and BE release in response to painful stimulation are warranted.

In additional exploratory analyses we assessed potential links between common comorbid psychopathologies in NSSI, and PS and plasma BE levels respectively. We found PS to be positively associated with BPD severity, further supporting assumptions that psychopathology underlying NSSI has a greater effect on PS compared to the behavior itself. Central functions of NSSI have repeatedly been associated with emotion regulation as well as ending dissociative states (Klonsky, 2007), with the latter seemingly representing a more specific function of NSSI in the context of BPD (Bracken-Minor and McDevitt-Murphy, 2014). Stress-related dissociative states as part of the diagnostic entity have been reported in up to 80% of individuals with BPD (Krause-Utz et al., 2017) and were found to be linked to lower PS (Ludäscher et al., 2010). More precisely, lower PS has been shown to be related to both state and trait dissociation (Ludäscher et al., 2007; Russ et al., 1992), with more pronounced effects during times of distress (Bohus et al., 2000; Stiglmayr et al., 2008). While these findings could explain our finding of a significant association between PS and BPD severity, we did not assess measures of dissociation in our study. Thus, we are unable to verify this assumption.

Further support for the effect of psychopathology underlying NSSI on PS derives from the significant association between PS and depression scores. Our finding partly supports current literature of altered pain processing in depression (McCoy et al., 2010; Thompson et al., 2016). However, relatively strong heterogeneity has been noted, with our findings being in line with experimental study designs using exteroceptive painful stimuli (Thompson et al., 2016). The association could be explained by referring to models of attentional pain processing, which state that pain might be perceived to a lesser extent if an individuals' attention is turned towards other stimuli (e.g. internal

thoughts/emotions) (Eccleston and Crombez, 1999). Mood disorders are characterized by depressed moods, anhedonia and emotion dysregulation (American Psychiatric Association, 2013; Bradley et al., 2011). As such it seems plausible that, while engaging in NSSI subsequently helps to regulate emotions and resolve negative affect (Klonsky, 2007), the initial focus on depressed moods could decrease the subjectively perceived pain intensity. However, this assumption and the overall association between PS and depression warrant further research.

An alternative explanation for altered PS could be related to ACE, either through a direct association between ACE and altered PS or through an indirect pathway via the role of ACE in the BPD specific pathology. ACE are a central risk factor for the occurrence of NSSI (Cipriano et al., 2017; Glenn and Klonsky, 2013) and BPD alike (Battle et al., 2004; Lieb et al., 2004) with high prevalence rates in both pathologies (Gratz et al., 2002; Lieb et al., 2004). Regarding the assumption of a direct association between ACE and PS, previous studies using experimentally induced pain showed that experiencing traumatic events during childhood was related to an overall lower PS (Fillingim and Edwards, 2005; Russ et al., 1993). In line with these findings, we found significantly higher ACE in our NSSI patients compared to our HC. However, we found no direct association between ACE and altered PS, thus again supporting the potential role of BPD specific pathology. Apart from its central role in the etiology of BPD, previous studies further reported ACE as an important risk factor for the occurrence of emotion dysregulation and dissociation (Korzekwa et al., 2009; Lieb et al., 2004). Studies also indicate that the severity of ACE is associated with the severity of BPD symptoms (Hébert et al., 2018; Silk et al., 1995; Zanarini et al., 2002). As such, it could be assumed that higher scores in ACE in our patient group are indicative of increased BPD severity. This could subsequently indicate more severe emotion dysregulation and more frequent and severe dissociative states, which modulate the PS (Bekrater-Bodmann et al., 2015).

BE release has previously been associated with analgesic effects, modulation of reward, emotion regulation, mood-enhancing and anxiolytic effects (Bresin and Gordon, 2013; Hegadoren et al., 2009). In line with these findings, Bandelow and colleagues proposed an intriguing theoretical model in which they discuss a potential role of alterations in BE in the pathophysiology of BPD (Bandelow et al., 2010). They propose that the frequently observed risk and attention-seeking behaviors could be explained by efforts to trigger the rewarding effects of human attachment, and that NSSI and sensation seeking behaviors might be direct attempts to artificially increase BE levels. Further, they assume that the regularly reported feelings of emptiness and anhedonia might be a result of the reduced availability of BE (Bandelow et al., 2010). Support for this model comes from experimental studies that reported lower BE levels in the CSF in individuals with a Cluster B personality disorder diagnosis with a history of NSSI and at least one suicide attempt (Stanley et al., 2010), as well as higher BE specific receptor availability in a number of brain regions in individuals with BPD (Prossin et al., 2010). However, we found no significant association between BE levels and BPD severity. As already mentioned by Bandelow and colleagues, “it may be argued that it is too simple to attribute so many behavioral dimensions to just one neurobiological system.” (Bandelow et al., 2010)(p.631). Thus, assessing BE alone in the context of BPD might not be enough to elicit significant associations.

Interestingly, we found a significant negative correlation between BE and depression scores, indicating a link between lower basal BE levels and greater depression severity. Studies suggested BE as a key factor for the development and chronification of MDD, due to its role in emotion regulation (Daley, 2008; Hegadoren et al., 2009). Similar as for BPD (Bandelow et al., 2010), reduced BE availability has been linked to the occurrence of anhedonia (Der-Avakian and Markou, 2012) which could explain our association of greater depression severity with lower basal BE levels. Further, the association between BE and depression scores may be linked to our previously reported association between depression scores and PS. As such, we could assume that lower basal BE levels lead to more severe depression symptoms, prompting individuals to engage in NSSI. The increased depression severity could result in a stronger attentional focus on the internal emotions and states, resulting in a decreased PS while these individuals engage in NSSI (Bradley et al., 2011). Based on our present findings, one may speculate on a joint mechanism, linking affective symptomatology and basal BE in adolescent NSSI. While the mechanisms responsible for alterations in BE are still largely unknown, the experience of severe and continuous traumatic events has previously been associated with decreased levels of BE (Bremner and Pearce, 2016). However, we found no significant association between ACE and BE. This could be due to the fact that we assessed ACE as global score. As such, we did not account for severity or duration of experienced ACE. Future studies including more detailed assessments of ACE might be able to show an association with BE.

Overall, multiple regression analyses, stepwise regression analyses and sub-group analyses in the patient sample confirmed that group status explained most variance in measures of pain intensity and BE. However, BPD severity was the strongest predictor for pain threshold as further reflected by the reported correlation. While our exploratory analyses hint at potential associations between psychopathology, PS and BE levels respectively, further evidence is needed. As such, future research is needed to further investigate these associations in well-powered studies, using a confirmatory approach.

Finally, while the present paper mainly focusses on biological mechanisms of NSSI, it is important to consider psychological factors and their impact on pain perception and BE. Individuals engaging in NSSI often report an improvement in mood (e.g. decreased negative affect and increased positive affect) following self-injury, which subsequently could reinforce future NSSI (Nock and Prinstein, 2004). This phenomenon has been suggested to relate to brain circuits involved in emotion and pain processing (Navratilova and Porreca, 2014). Further, there is an extensive overlap between neural circuits that process physical pain and emotional pain (e.g. negative affect and emotional distress), with evidence indicating that the offset of physical pain results in an offset of emotional pain (Eisenberger, 2012). In line with this, several studies were able to show that the offset of pain was indeed associated with a subsequent reduction in negative affect (Franklin et al., 2010) and an increase in positive affect (Franklin et al., 2013b, 2013a). As such, it can be assumed that individuals engaging in NSSI learn to associate an improvement of mood with NSSI and more precisely the offset of experienced pain, subsequently reinforcing NSSI due to its rewarding effects. This is supported by findings where pain relief correlated with the blood oxygen level-dependent response in brain areas commonly involved in processing pain and reward (Osuch et al., 2014). Further, studies also showed that the expectation of pain relief leads to alterations in μ-opioid receptor activity in brain regions again associated with emotion, pain and reward processing (Bushnell et al., 2013; Wager et al., 2007), potentially indicating that anticipated pain relief could potentiate pain-related BE release or elicit BE release itself (Wager et al., 2007). In line with the opioid deficiency model of NSSI and evidence for increased μ-opioid receptor sensitivity for BE release (Bresin and Gordon, 2013), it could be assumed that BE release following NSSI also has increased effects on reward circuitry. As such, it could be assumed that the anticipation of reward (e.g. improvement in mood) potentiates analgesic effects often observed in individuals with NSSI, subsequently reinforcing NSSI as behavior.

Further support for a potential impact of psychological factors stems from findings that individuals with a history of NSSI and high levels of self-criticism endured pain significantly longer and reported improvement of mood during the experience of pain, which was not found in individuals with low self-criticism (Fox et al., 2017). This led researchers to assume that mood is improved, because highly self-critical individuals believe they deserve to be punished and subsequently view NSSI and pain as self-affirming, thus they are willingly enduring pain for longer (Hooley and Fox, 2019). In line with the above-mentioned mechanisms, it can be assumed that high levels of self-criticism are

distressing, creating emotional pain. The experience of physical pain might elicit BE release, which subsequently improves mood and reinforces NSSI through the effect of BE on reward circuitry. This assumption is further supported by a study that used a brief cognitive intervention to enhance self-worth in order to reduce self-critical beliefs, in individuals with NSSI (Hooley and St. Germain, 2014). Results showed that an increase in self-worth significantly reduced pain endurance, as well as willingness to endure pain in individuals with NSSI (Hooley and St. Germain, 2014). Again, in line with the above-mentioned mechanisms, increasing self-worth with a brief cognitive intervention could be an alternate pathway to reduce the emotional distress, induced by self-critical beliefs, which reduces the beneficial effect of pain on mood and subsequently reduces willingness to endure pain. Following this line of thought, it could be assumed that increasing self-worth, by reducing self-critical beliefs, is rewarding, potentially indicating a subsequent release of BE. As such, BE levels could already be increased, reducing the necessity to engage in NSSI to achieve the same effect. It seems evident that psychological factors impact biological mechanisms of NSSI (and vice versa), however these interactions are complex and often hypothetical, as more research is needed.

Our study is not without limitations. First, BE levels were solely assessed at rest. While findings in two studies indicate that resting BE levels are a relatively stable measure (Bruehl et al., 2017; Leppäluoto et al., 2008), future studies should implement multiple measures, especially before and after the pain stimulation, to enable a more precise investigation of the adaptive plasma BE response to painful stimuli and its potential link to PS. Besides, BE measures were assessed from plasma. Studies have shown that plasma levels of BE are not correlated with central measures from CSF (De Riu et al., 1997; Kirtley et al., 2015). Yet, the exact role of plasma BE levels in pain processing remains unknown, and it has been argued that plasma BE levels, which are easily affected by stress factors (De Riu et al., 1997), could prove especially useful for studies interested in dynamic measures of BE release following painful stimuli (Kirtley et al., 2015). It is evident that further research is necessary to clarify the exact role of BE levels, central and peripheral alike, in NSSI. While our pain stimulation paradigm enabled us to systematically assess pain threshold and tolerance in an experimental setting, the paradigm itself is very different from self-inflicted pain associated with actual NSSI. Future studies should consider using pain stimuli more akin to methods used by individuals engaging in NSSI (Shabes et al., 2016). It might be worthwhile to investigate the use of blunted blade stimuli (Ammerman et al., 2018) as they elicit similar affective and sensory evaluations of pain compared to real incisions (Shabes et al., 2016). Further, the cross-sectional nature of the data marks an important limitation. Annual follow-up measurements could prove valuable to assess temporal changes, to investigate potential interconnections with other physiological- and psychological variables and the respective predictive value of altered PS and lowered BE levels for events of NSSI. Finally, although subjects were instructed to fast on the morning of testing, we cannot rule out the possibility that subjects took analgesics before participating in the laboratory session.

The large sample of well-characterized adolescents engaging in NSSI marks a clear strength of the present study. Furthermore, the present study is, to our knowledge, the first to systematically assess BE and PS in an adolescent sample.

4.1. Conclusion

The present study found significantly lowered PS (i.e.: increased pain threshold, lower reported pain intensity) and lower basal BE levels in adolescents with NSSI, that, in line with previous findings of alterations of the endogenous stress system (Koenig et al., 2017b), suggest that significantly altered biological processes are linked to the onset and maintenance of NSSI. No significant relationship could be found between increased pain thresholds and lower basal BE levels, potentially indicating that reduced PS and basal opioid deficiency might be independent biological correlates for NSSI. There is additional support of a modulating role of psychopathologies underlying NSSI for PS and basal opioid deficiency, respectively.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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