Research Paper

Psychobiological response to pain in female adolescents with nonsuicidal self-injury

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Background: Nonsuicidal self-injury (NSSI) is associated with reduced pain sensitivity and alterations in top–down processing of nociceptive information. The experience of acute pain is characterized by reactivity of the autonomic nervous system (ANS) and hypothalamic–pituitary–adrenal (HPA) axis, which to our knowledge has not been systematically investigated in the context of NSSI. **Methods:** Adolescents fulfilling DSM-5 diagnostic criteria for NSSI and matched healthy controls received cold pain stimulation. We obtained self-reports on psychological distress and measured blood pressure, heart rate variability (HRV) and saliva cortisol. Regression analyses were used to investigate group differences on observed difference scores, adjusting for confounding variables. **Results:** We included 30 adolescents engaging in NSSI and 30 controls in our study. Adolescents in the NSSI group showed a greater pain threshold. Groups significantly differed in their psychological response to pain. In patients with NSSI, mood and body awareness increased after painful stimulation; in controls it decreased. Tension increased in controls only. The HPA axis response to painful stimulation was increased in the NSSI compared with the control group. Analysis of ultra-short-term recordings of HRV revealed significant group differences during the anticipation of pain and recovery. **Limitations:** Future studies should incorporate multiple measures of saliva cortisol and replicate the present findings in a naturalistic setting. **Conclusion:** Compared with controls, individuals engaging in NSSI show psychological benefits in response to pain. Biological findings highlight decreased physiologic arousal before and prolonged arousal (ANS and HPA axis response) after painful stimulation in adolescents engaging in NSSI. Greater pain-inflicted autonomic arousal and cortisol secretion may counteract dissociative states, reduce negative affect and increase body awareness in adolescents engaging in NSSI, lending support for a neurobiological pathomechanism underlying the intraindividual and antisuicide functions of NSSI.

Introduction

Nonsuicidal self-injury (NSSI) — the intentional, self-directed act of injuring one's own body tissue — is a common phenomenon among adolescents in various cultures.[1,2] According to a recent meta-analysis, the prevalence for NSSI in nonclinical samples is 17.2% among adolescents.[2] It is an important risk factor for suicidal behaviour[3] and strongly associated with other risk behaviours and comorbid psychopathology.[4] Individuals engaging in self-injurious behaviour (SIB; here referred to as self-injury independent of the suicidal intent) often report altered pain perception and analgesia during acts of self-injury.[5] Self-injurers consistently report decreased pain sensitivity compared with controls in studies using experimentally induced pain, as indexed by a greater pain threshold and tolerance, and they report lower pain intensity.[6]

Early research on pain sensitivity in SIB conducted in patients with borderline personality disorder (BPD) focused on psychological phenomena (i.e., dissociation, body awareness) potentially underlying altered nociceptive processing.[7–9] While biological and neurological mechanisms underlying altered pain sensitivity in self-injury were discussed early on, they were not empirically addressed until 1997.[7] The first neuroimaging study on the topic found increased response in the dorsolateral prefrontal cortex and deactivation in the anterior cingulate and the amygdala following painful stimulation in patients with BPD engaging in SIB.[10] Others found that patients with BPD showed significant alterations in default mode network connectivity and proposed that these alterations may reflect a different cognitive and affective appraisal of pain, framed as less self-relevant and aversive.[11]

Human pain response is characterized by the involvement and reactivity of various peripheral and central processes of the organism.[12] The reactivity of the autonomic nervous system (ANS) to experimentally induced pain is best described by an increase in sympathetic nervous system activity and a

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decrease in parasympathetic, vagal activity.[13] Nociception is further associated with a response of the hypothalamic–pituitary–adrenal (HPA) axis, as painful stimulation typically leads to an increase in cortisol secretion.[14] Previous research has linked the subjective experience of pain to changes in the aforementioned physiologic systems,[15] highlighting the possible utility of biomarkers to objectively assess and characterize acute pain experience. On the other hand state-dependent or chronic alterations of the physiologic functions (i.e., hypertension-related hypoalgesia) endogenously modulate the experience of acute pain.[16]

Previous research on HPA axis activity in adolescents engaging in NSSI found a hyporesponsiveness following experimentally induced psychosocial stress.[17] Also, lower cortisol following a dexamethasone suppression test has been shown to be associated with greater retrospective reports of SIB in depressed adolescents.[18] Studies on ANS activity in NSSI and related disorders have shown reduced resting state parasympathetic activity in patients with BPD[19] and in parasuicidal adolescents.[20] The latter study also found greater ANS reactivity during negative mood induction.[20]

To our knowledge, ANS and HPA axis reactivity to experimentally induced pain and their contribution to altered pain sensitivity in individuals engaging in SIB have not been systematically investigated. Bohus and colleagues[9] measured heart rate and skin conductance in a small sample of 12 patients with BPD and 19 controls before, during and after painful stimulation with the cold pressor task (CPT). The authors found no group differences in autonomic response. However, the interpretation of the findings was limited by the small sample sizes.[9] Similarly, Russ and colleagues[8] found no significant differences investigating pulse amplitude and pulse rate in a small sample of 14 patients with BPD and 6 healthy controls. A recent doctoral thesis assessed blood pressure (BP; beat-to-beat), skin conductance levels, end tidal CO_2, and T-wave amplitudes from electrocardiography (ECG) recordings in 17 self-injurers, 22 controls and 22 individuals meeting diagnostic criteria for blood injection–injury phobia who received painful stimulation with the CPT.[21] While the group × time of measurement interaction showed only trends toward statistical significance, the authors concluded that sympathetic activity over the procedure may have been elevated in self-injurers compared with controls.[21]

Given the phenomenon of altered pain sensitivity in individuals engaging in NSSI and evidence that ANS and HPA axis reactivity to pain is closely linked to pain experience, we aimed to investigate the psychological and neurobiological concomitants of altered pain sensitivity in adolescents with NSSI, focusing on the ANS and HPA axis. We hypothesized that ANS and HPA axis response to experimentally induced pain in adolescents engaging in NSSI would differ from that in controls. More specifically, given the large body of evidence showing decreased pain sensitivity in indivduals engaging in NSSI,[6] the intercorrelation of the subjective pain experience and ANS/HPA reactivity to pain[15] and a hyporesponsiveness of endogenous stress systems to other types of stressors in NSSI,[17] we hypothesized that ANS and HPA axis response to acute pain would be blunted, in line with self-reports and behavioural measures indicating lower pain sensitivity and less aversive pain experience. To test this hypothesis we aimed to explore differences in the psychological, autonomic and endocrine responses to a standardized painful stimulus in adolescents engaging in NSSI and in matched healthy controls.

Methods

The study was an experimental laboratory trial using a case–control design, comparing adolescents who met DSM-5 diagnostic criteria for NSSI, as assessed by a structured clinical interview, with matched healthy controls. The Ethical Committee of the Medical Faculty, Heidelberg University, Heidelberg, Germany approved our study protocol (Study: ID S-471/2013), which was carried out in accordance with the declaration of Helsinki.[22] The trial was registered at the German Clinical Trials Register (Study ID: DRKS00007807), and the study protocol was published in advance.[23]

Participants

We used a priori power analysis based on findings from a meta-analysis on pain sensitivity in individuals with SIB[6] to determine the sample size required per group to reveal significant differences in pain sensitivity.[23] Adolescents (12–17 yr) with NSSI and healthy controls matched for age, sex and school type were enrolled in the study. Recruitment was restricted to female adolescents, given the known sex differences in the prevalence of NSSI,[2,4] HPA axis response to stress[24] and pain sensitivity.[25–27] Participants in the NSSI group were recruited consecutively from the specialized outpatient clinic for risk-taking and self-harm behaviour (AtRiSk) at the Clinic for Child and Adolescent Psychiatry, Centre of Psychosocial Medicine, University of Heidelberg. Healthy controls were recruited via public advertisements. All participants and their legal guardians provided written informed consent before inclusion in the study. Participants received an allowance of 30€ for participation.

Adolescents with NSSI reporting at least 5 incidents of NSSI during the past 12 months according to DSM-5 section 3 diagnostic criteria[28] were recruited. Individuals reporting any cardiovascular disease, hypertension, past cramp attacks or blackouts, chilblains, Raynaud disease, open wounds, or fractures of the hands were excluded owing to possible interference with the type of painful stimuli used. Weight and height were recorded. Individuals were excluded if they had an IQ below 70 or a body mass index (BMI) below 17.5 or above 30. Participants were asked to indicate their dominant hand and to confirm whether they previously took part in a study involving experimental painful stimulation, specifically cold pain.

Procedures and assessments

Study procedures comprised 2 appointments after recruitment. During the first appointment participants underwent an initial baseline diagnostic assessment. The second

appointment included all experimental procedures. The delay between the first and second appointments was 0–43 (mean 7.56 ± 9.11) days. Appointments for the experiment were all scheduled in the afternoon (between 2 and 5 pm) to control for circadian variation in HPA axis and ANS activity.

Sociodemographic variables

Aside from the assessment of basic sociodemographic variables, weight and height measurements were taken to calculate BMI. The type of school visited and the housing situation (e.g., living with mother) was assessed. We assessed alcohol intake during the 30 days preceding the study categorically, with participants reporting alcohol consumption as follows: none, 1–2 days, 3–5 days, 6–9 days, 10–19 days, 20–29 days, or all 30 days. Based on the distribution of data, we coded alcohol consumption as a dichotomous variable (yes/no). In a similar fashion, we assessed drug use, the type of drugs used, and cigarette smoking. In contrast to the assessment of alcohol, smoking was assessed categorically based on the number of cigarettes smoked per day (none, < 1, 2, 3, 4, > 5) during the 30 days preceding the study to better capture variance in the actual number of cigarettes smoked by smokers versus nonsmokers.

Diagnostic procedures

We used the German version of the Self-Injurious Thoughts and Behaviour Interview (SITBI-G) for the detailed assessment of NSSI.[29] The SITBI-G is a semistructured interview for the assessment self-injurious thoughts and behaviours and shows excellent psychometric properties. To meet DSM-5 criteria for NSSI, the SITBI was slightly modified to assess the days of engagement in NSSI. Psychiatric diagnoses were obtained using the German version of the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I-KID 6.0).[30,31] The M.I.N.I.-KID is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders for children and adolescents aged 6–19 years. In addition, the respective part of the German version of the Structured Clinical Interview for DSM-IV Axis II Disorders (SKID-II) was used to assess BPD.[32] Finally, the clinical assessment included the Children's Global Assessment Scale (C-GAS), which is a widely used numeric rating scale (1–100) to measure the general functioning of children younger than 18 years.[33]

Participants recruited for the control group also completed screening questions of the SITBI-G and were rated on the C-GAS. In addition, they completed the structured clinical interview for DSM-IV-TR, non-patient edition (SCID-N/P).[34]

Painful stimulation

We assessed sensitivity to cold pain twice using a previously evaluated CPT procedure[35] that is most frequently used in studies on pain sensitivity in self-injury populations.[6] The immersion of the dominant or nondominant hand was cross-randomized across trials. Here, only findings from the first pain induction are reported, to avoid introducing effects of habituation. In short, participants were asked to immerse their hand up to the wrist in an acrylic glass tank with circulating water. Participants were instructed to keep their hands open in the water until cold pain became intolerable, with a maximum cutoff time of 4 min. Participants were not informed about the ceiling time. The latencies to the first pain sensation (pain threshold) and to intolerable pain sensation (pain tolerance) were measured in seconds. Details on the test set-up have been published elsewhere.[23,35]

Self-report assessment before and after pain stimulation

Pain intensity on hand removal was assessed on a 100 mm visual analogue scale (VAS), as part of the German version[36] of the Short Form McGill Pain Questionnaire (SF-MPQ)[37] derived from the McGill Pain Questionnaire (MPQ).[38] In addition, participants were asked to rate 3 self-developed scales before and after painful stimulation, addressing state-dependent mood and distress. Participants rated their momentary mood (How do you feel right now [very bad to very good]?), their felt tension (How high is your current tension/stress right now [no stress to massive stress]?) and their body awareness (How well do you sense/feel yourself right now [not at all to very well]?), each on a 100 mm VAS.

Cardiovascular activity

Heart rate was continuously recorded throughout the experimental procedures using a Polar RS800CX with electrodes attached to an elastic belt affixed to the chest. The device is capable of recording interbeat intervals (IBI) between adjacent heart beats at a sampling frequency of 1000 Hz, providing a temporal resolution of 1 ms for each RR interval. We used device-specific software (Polar ProTrainer 5) to transfer IBI recordings to a personal computer. We exported IBI data and analyzed heart rate variability (HRV). The IBIs were corrected for artifacts, excluding IBIs above or below the tenth interquartile range. The square root of the mean squared difference of successive RR intervals (RMSSD) reflecting parasympathetic vagal activity as well as the mean RR (IBI), as equivalent to mean heart rate, were derived for analysis.

We derived indices of HRV for different time segments during the course of the procedures. First, we determined HRV for a 5-min resting baseline segment before painful stimulation and for the individuals' time during the CPT to reflect immediate, fast-lived autonomic reactivity to painful stimulation, in line with previous research.[13] Data on mean RR ($\chi^2 = 8.13$, $p = 0.017$) and RMSSD ($\chi^2 = 34.81$, $p < 0.001$) were not normally distributed, and were successfully log-transformed before analysis (mean RR_{log}: $\chi^2 = 1.03$, $p = 0.60$; $RMSSD_{log}$: $\chi^2 = 0.05$, $p = 0.98$). Second, for exploratory analyses we derived ultra-short-term samples of 30 s duration[39] for 2 segments of the minute preceding painful stimulation (to explore effects of pain anticipation) and for 2 segments of the minute following painful stimulation (to explore effects of ANS recovery). Data for each segment were log-transformed.

In addition to the assessment of HRV, we measured BP as an index of autonomic response before painful stimulation and immediately after hand removal from the CPT using an automated digital device (Braun ExactFit™ 3 BP6000). Systolic (SBP) and diastolic (DBP) BP values were derived for further analysis. Data on SBP ($\chi^2 = 12.21$, $p = 0.002$) and DBP ($\chi^2 = 7.39$, $p = 0.025$) were not normally distributed, and were successfully log-transformed before analysis (SBP_{log}: $\chi^2 = 2.57$, $p = 0.28$; DBP_{log}: ($\chi^2 = 0.49$, $p = 0.78$).

Cortisol assays

We assessed HPA axis response using salivary cortisol samples as reliable and valid proxies of free plasma cortisol levels[40,41] sensitive to changes in HPA axis activation due to stressors,[40] such as experimentally induced pain.[42] The method has been used previously in numerous studies involving children and adolescents.[43–45] We collected salivary samples before and 15 min after painful stimulation by having participants chew on a cotton role (Salivettes; Sarstedt) for 2 min. Details on the storage and analysis of saliva cortisol have been published elsewhere.[23] One participant from the control group reporting cortisol intake was excluded from all analyses. Data on cortisol were not normally distributed ($\chi^2 = 28.10$, $p < 0.001$), and were successfully log-transformed before analysis ($\chi^2 = 0.06$, $p = 0.97$).

Statistical analysis

Differences between groups on sociodemographic, diagnostic and all baseline variables were tested using 2-sided independent-samples *t* tests for continuous variables and χ^2 tests for categorical variables. We tested all dependent physiological variables for normal distribution using skewness and kurtosis testing for normality[46] and the ladder of powers,[47] and variables were log-transformed before analysis, as needed. Figures illustrate non–log-transformed values of dependent measures for the sake of clarity and ease of interpretation. We analysed between-group differences in pain threshold and pain tolerance in seconds using independent-samples *t* tests after testing for normality and log-transformation according to recent suggestions for handling dependent measures derived from CPT protocols.[48] Three confirmatory hypotheses (psychological, autonomic and endocrine pain response) were tested. With respect to joint hypothesis testing, *p* values of tests with multiple outcomes (psychological and autonomic pain response) were Bonferroni-corrected. Observed difference scores were calculated to quantify pain response,[49,50] subtracting values obtained before from those taken after (psychological and endocrine) or during (autonomic) painful stimulation. Multiple linear regression models were calculated to analyze predictors of pain response (Δ variables). First, we calculated unadjusted models using the factor group as a single predictor. Second, we adjusted models for BMI (continuous), use of medication (yes/no), use of contraceptive pill (yes/no), number of cigarettes smoked per day (categorical), alcohol consumption (yes/no) and drugs taken during the 30 days preceding the study (yes/no). We calculated η^2 as a measure of effect size for all regression analyses. With respect to the exploratory analysis of ultra-short-term HRV, we explored anticipatory effects in contrast to baseline recordings, and we compared effects of recovery with recordings taken during painful stimulation using *t* tests. All analyses were performed using Stata/SE software version 14.0 (StataCorp LP), with α set to 0.05. Graphs were prepared using GraphPad Prism version 6.0 (GraphPad Software Inc.).

Results

Participants

We initially contacted 95 adolescents, of whom 61 were interested in participating in the study and fulfilled the inclusion criteria. Of the 34 participants who were excluded, 15 (44.1%) were initially considered for the control group and 19 (55.9%) were considered for the NSSI group. Of the excluded patients, 3 (15.8%) reported fewer than 5 days of NSSI during the previous year, 4 (21.1%) had a BMI below 17.5, 1 (5.3%) had an BMI above 30, 1 (5.3%) had an IQ below 70, 1 (5.3%) had high BP, 4 (36.8%) declined to participate, the parents of 1 (5.3%) did not provide written informed consent, and 4 (36.8%) did not show up for their appointment and no further contact was possible. Of those excluded from the control group, 2 (13.3%) reported suicidal ideation, 2 (13.3%) had a BMI below 17.5, 1 reported a single event of self-injury (6.7%), 1 (6.7%) had attention-deficit/hyperactivity disorder, 2 (13.3%) had completed psychotherapeutic treatment before recruitment, 1 (6.7%) had Raynaud disease, 3 (23.1%) declined to participate, the parents of 2 (13.3%) refused participation or did not provide written informed consent, and 1 (6.7%) did not show up for her appointment and no further contact was possible. Of the 61 participants enrolled in the study, 1 participant in the control group disclosed having engaged in self-injury during a follow-up visit and was excluded from analyses. The final sample comprised 60 adolescents: 30 with NSSI and 30 controls.

Sample characteristics

Sociodemographic and clinical characteristics of the study sample are provided in Table 1. Participants with NSSI had a significantly greater BMI than controls ($t_{58} = 3.367$, $p < 0.001$), reflecting significant group differences in weight ($t_{58} = 2.818$, $p = 0.007$). Patients with NSSI were more likely than controls to report drug use ($\chi^2 = 6.667$, $p = 0.010$) and smoked more cigarettes on average per day ($\chi^2 = 30.000$, $p < 0.001$) during the 30 days preceding the study. Patients with NSSI scored worse than controls on current general functioning ($t_{58} = –17.242$, $p < 0.001$).

Five (16.7%) participants in the NSSI group were taking psychotropic medication: fluoxetine ($n = 1$) or agomelatine ($n = 4$). One (3.3%) participant in the control group was taking L-thyroxine, and 1 (3.3%) was using antihistamines and cortisone. The participant taking cortisone was excluded from all analyses on endocrine reactivity, and all analyses were adjusted for medication intake. No participant reported use of analgesics that might interfere with experimental pain induction. Eleven

(36.7%) participants in the NSSI group and 6 (19.4%) controls were taking the contraceptive pill during the 30 days preceding the experiment. There were no significant differences in medication intake ($\chi^2 = 7.000$, $p = 0.07$) or use of the contraceptive pill ($\chi^2 = 2.273$, $p = 0.13$) between the groups.

Eighteen (60.0%) patients with NSSI fulfilled diagnostic criteria for BPD. On average, patients with NSSI reported 96.1 ± 77.5 acts of NSSI within the past 12 months, and the mean age of NSSI onset was 12.4 ± 1.7 years. Methods of NSSI differed widely, with all patients reporting cutting (100%) and engagement in multiple methods, including skin scratching (80%) and wound manipulation (56.7%). The most frequent reasons for NSSI were to elevate negative affect or to increase body awareness (both 90%).

Pain ratings and self-reports of momentary distress

Results of the *t* tests showed significantly greater pain threshold$_{log}$ in the NSSI group than the control group ($t_{58} = 2.365$, $p = 0.021$), but no significant differences between groups on pain tolerance$_{log}$ ($t_{58} = 0.790$, $p = 0.43$) or pain intensity ($t_{58} = –0.540$, $p = 0.59$; Fig. 1).

At baseline, groups differed on self-reports of momentary mood ($t_{58} = –7.554$, $p < 0.001$), felt tension ($t_{58} = 3.302$, $p = 0.002$) and body awareness ($t_{58} = –7.269$, $p < 0.001$). Patients with NSSI reported decreased momentary mood, greater felt tension and less body awareness than controls. We found significant group differences in changes in Δ momentary mood ($t_{58} = 3.881$, $p < 0.001$, $p_{corrected} = 0.001$), Δ felt tension ($t_{58} = –2.751$, $p = 0.008$, $p_{corrected} = 0.024$) and Δ body awareness ($t_{58} = 2.926$, $p = 0.005$, $p_{corrected} = 0.015$; Fig. 2). In patients with NSSI, mood and body awareness increased after painful stimulation; in controls it decreased. Felt tension increased in controls only.

Cardiovascular and endocrine reactivity

Groups did not differ on any physiologic measure obtained at baseline (cortisol$_{log}$: $t_{57} = –0.384$, $p = 0.70$; SPB$_{log}$: $t_{58} = –1.122$, $p = 0.27$; DBP$_{log}$: $t_{58} = –1.010$, $p = 0.32$; mean RR$_{log}$: $t_{58} = –1.253$, $p = 0.22$; RMSSD$_{log}$: $t_{58} = –0.663$, $p = 0.51$). Adjusted regression analysis revealed significant group differences on Δ cortisol ($\beta = –0.281$, $t_{57} = –2.07$, $p = 0.044$), indicating a greater cortisol release after nociceptive stimulation in the NSSI group than in the control group (Fig. 3 and Fig. 4). Results from regression analyses on predictors of physiological response are reported in Table 2.

Ultra-short-term changes in ANS activity

Our exploratory analysis of ultra-short-term HRV before painful stimulation revealed significant group differences in RMSSD$_{log}$ ($t_{58} = 2.760$, $p = 0.008$; Fig. 5) 60 s before CPT onset. As illustrated in Figure 4, these differences vanished 30 s before CPT onset, indicating a later decrease in parasympathetic vagal activity in light of anticipating painful stimulation in patients with NSSI. With respect to ANS recovery after painful stimulation, analysis showed significant group differences

Table 1: Sociodemographic and clinical characteristics of the study sample by group

Characteristic	Group; mean ± SD or no. (%)		*p* value*
	NSSI, *n* = 30	Control, *n* = 30	
Age, yr	15.27 ± 1.36	15.27 ± 1.31	> 0.99
Height, cm	166.20 ± 5.86	165.27 ± 7.84	0.60
Weight, kg	62.54 ± 8.70	8.70 ± 8.02	0.007
BMI	22.59 ± 2.56	20.60 ± 1.98	0.001
German nationality	29 (96.7)	30 (100)	0.31
Type of school†			0.35
Realschule	12 (40.0)	12 (40.0)	
Gymnasium	16 (53.3)	18 (60.0)	
Other	2 (6.7)	0 (0)	
Housing			
Living with mother			0.07
Mother	24 (80.0)	29 (96.7)	
Stepmother	1 (3.3)	1 (3.3)	
No mother	5 (16.7)	0 (0)	
Living with father			0.09
Father	16 (53.3)	24 (80.0)	
Stepfather	2 (6.7)	1 (3.3)	
No father	12 (40.0)	5 (16.7)	
Other living situation			0.23
Hospitalized	1 (3.3)	0 (0)	
Emergency accommodation	1 (3.3)	0 (0)	
Hostel	2 (6.7)	0 (0)	
Non-other	26 (86.7)	30 (100)	
Right-handed	27 (90.0)	28 (93.3)	0.64
Alcohol past 30 d	21 (70.0)	18 (60.0)	0.42
Drugs past 30 d	10 (33.3)	2 (6.7)	0.010
Cigarettes/d			< 0.001
None	9 (30.0)	27 (90.0)	
< 1	0 (0)	2 (6.7)	
2	3 (10.0)	0 (0)	
3	5 (16.7)	0 (0)	
4	3 (10.0)	1 (3.3)	
≥ 5	10 (33.3)	0 (0)	
Acts of NSSI			
Past year	96.1 ± 77.47	—	< 0.001
Past 30 d	2.87 ± 3.64	—	< 0.001
BPD	18 (60.0)	—	< 0.001
Primary diagnosis other than NSSI and BPD			< 0.001
None	1 (3.3)	—	
Current MDD	13 (43.3)	—	
Past MDD	10 (33.3)	—	
Recurrent MDD	5 (16.7)	—	
Nongeneralized SAD	1 (3.3)	—	
C-GAS score	52.57 ± 14.49	98.33 ± 1.15	< 0.001

BMI = body mass index; BPD = borderline personality disorder; C-GAS = Children's Global Assessment Scale; MDD = major depressive disorder; NSSI = nonsuicidal self-injury; SAD = social anxiety disorder; SD = standard deviation.
*Group differences based on χ^2 tests (categorical variables) or *t* tests (continuous variables).
†Realschule = 6 yr and concludes with a general certificate of secondary education; Gymnasium = 8 yr and provides a general university entrance qualification.

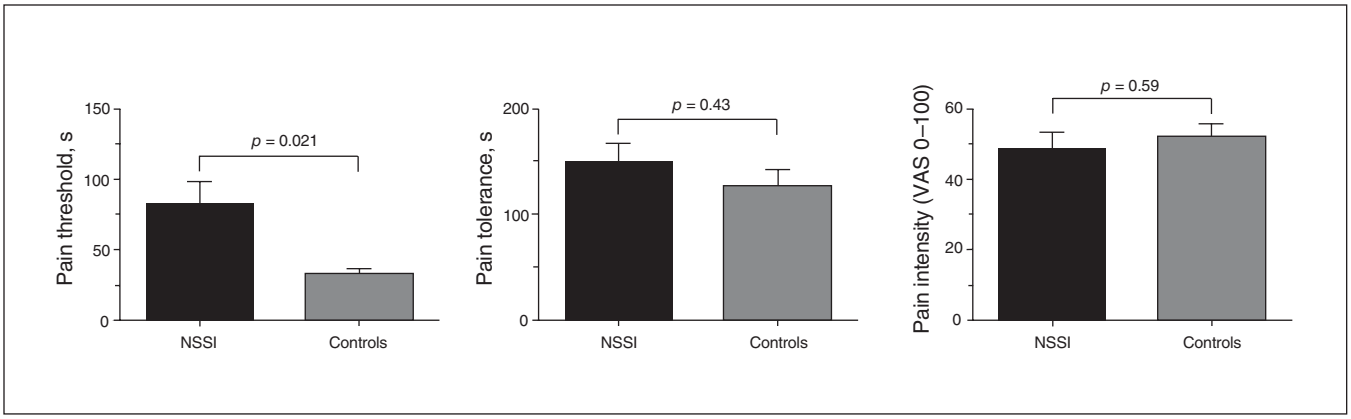

Fig. 1: Pain-related outcome by group. The *p* values for group differences were derived using *t* tests. Pain threshold and pain tolerance were log-transformed before analysis. Absolute values are displayed as means and standard errors of the mean. NSSI = nonsuicidal self-injury; VAS = visual analogue scale.

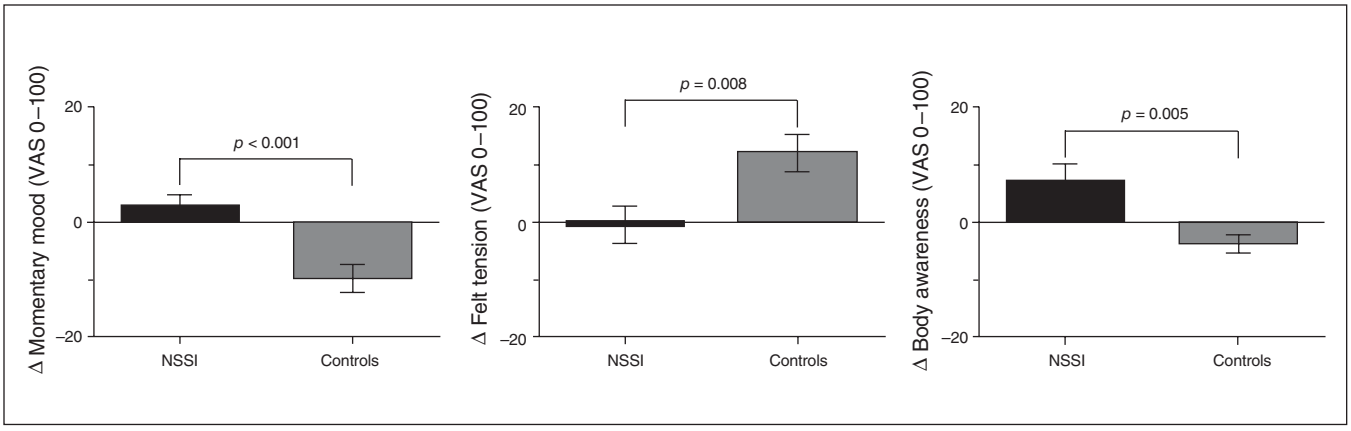

Fig. 2: Change in self reports of momentary distress by group after painful stimulation. The *p* values for group differences were derived using *t* tests. All Δ are relative to self-reports before painful stimulation. All values are displayed as means and standard errors of the mean. The Bonferroni-corrected *p* values are as follows: momentary mood $p_{corrected}$ = 0.001; felt tension $p_{corrected}$ = 0.024; body awareness $p_{corrected}$ = 0.015. NSSI = nonsuicidal self-injury; VAS = visual analogue scale.

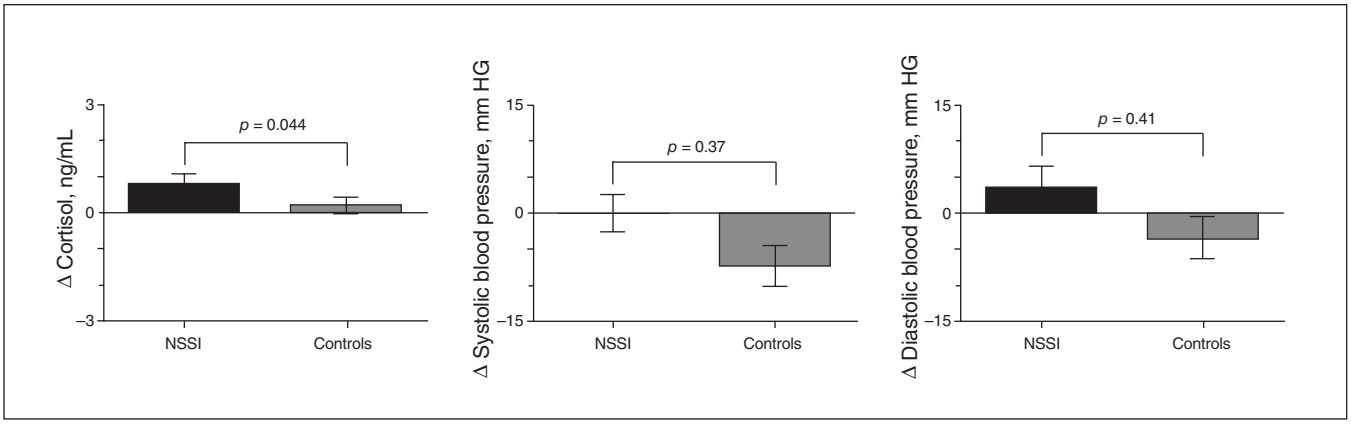

Fig. 3: Change in blood pressure and cortisol by group after painful stimulation. The *p* values for group differences were derived from adjusted linear regression analysis. Systolic (SBP) and diastolic blood pressure (DBP) and cortisol were log-transformed before analysis. Absolute values are displayed as means and standard errors of the mean. All Δ are relative to measures taken before painful stimulation. One participant was excluded from the analysis on cortisol because she was taking cortisol. The Bonferroni-corrected *p* values are as follows: SBP $p_{corrected}$ > 0.99; DBP $p_{corrected}$ > 0.99. NSSI = nonsuicidal self-injury.

30 s after hand removal from cold water, indicating lower $RMSSD_{log}$ in the NSSI group than in the control group (t_{58} = –2.045, p = 0.045; Fig. 6). Group differences were no longer present on ANS activity 60 s after painful stimulation.

Discussion

The present study sought to explore differences in psychobiological pain response between adolescents with NSSI and matched controls. In line with a large body of research,[6] we found lower pain sensitivity in patients with NSSI than controls, indexed by greater pain threshold. Unlike in controls, painful stimulation led to marked improvements of momentary mood and body awareness in self-injurers, supporting evidence on the intrapersonal functions of self-injury, such as reducing negative affect or dissociative states.[51] Although one might expect felt tension to decrease after pain induction in adolescents engaging in NSSI, we found no significant change in patients with NSSI. Significant increases in felt tension in controls indicate that the procedure itself induced considerable stress, but only in controls. The release of felt tension in patients might have been prohibited by the nature of the procedure or the fact that pain was not self-induced.

In both groups cortisol increased after painful stimulation. Mean RR and RMSSD decreased, indicating increased physiological arousal during painful stimulation, as expected. Although the physiological pain response in the NSSI group was largely comparable to that in the control group, the present findings point to some important differences. After adjusting for health-related behaviour (i.e., smoking) that showed marked differences between groups, we found the cortisol response to experimentally induced pain to be significantly greater in the NSSI group than the control group. This finding is contrary to our hypothesis and to the findings of previous studies showing blunted HPA stress reactivity in individuals engaging in NSSI. Previous research on HPA axis stress response in NSSI using standardized stressors (e.g., Trier social stress test or the dexamethasone suppression test) found the HPA axis to be hyporesponsive in adolescents with NSSI,[17,18] consistent with findings from adults with BPD[52] and animal studies.[53] This blunted cortisol response has commonly been linked to more aversive emotional reactions to stress.[54] Given that we found the HPA axis to be hyper-responsive toward painful stimuli in adolescents with NSSI, HPA reactivity seems to be stimulus-specific. We suggest that cortisol secretion after self-injury might help to cope with environmental stressors that do not induce the appropriate HPA axis response in individuals with NSSI, such as interpersonal stress,[17] which in turn may be needed to cope with stressful experiences.[54] Interestingly, in an exploratory analysis we found a positive correlation between cortisol increase and an increase in momentary mood following painful stimulation in the NSSI group only that missed the set level of significance (r = 0.360, p = 0.08). This is in line with previous experimental research in healthy humans that revealed a positive effect of cortisol on affect in stressful situations.[54] Furthermore, others have shown that decreased pain sensitivity after a cognitive laboratory stressor was associated with a strong cortisol response.[55] Thus, greater cortisol secretion in individuals engaging in NSSI might directly influence pain sensitivity.

Finally, our analysis of ultra-short-term measures of HRV yielded interesting findings. It has been shown previously that the anticipation of pain increases heat pain thresholds and leads to larger amygdala deactivation in patients with BPD compared with controls.[56] From a theoretical standpoint, it is hypothesized that individuals without an aversion toward the anticipated pain are more likely to actually engage in SIB.[57] First, we found that anticipation of pain led to delayed withdrawal of parasympathetic vagal activity (RMSSD), indicating decreased physiological arousal facing painful stimulation in adolescents engaging in NSSI compared with controls. Second, we found altered recovery following painful stimulation, indexed by a subsequent reincrease of parasympathetic vagal activity after painful stimulation, in line with our findings of an increased cortisol response. Controls showed faster recovery after painful stimulation than adolescents engaging in NSSI. Group differences on short-term ANS activity were not found for mean RR, highlighting the importance of altered parasympathetic vagal activity in psychiatric patients,[19,58] as mean RR does not adequately capture the influence of the sympathetic and parasympathetic branches of the ANS in regulating the

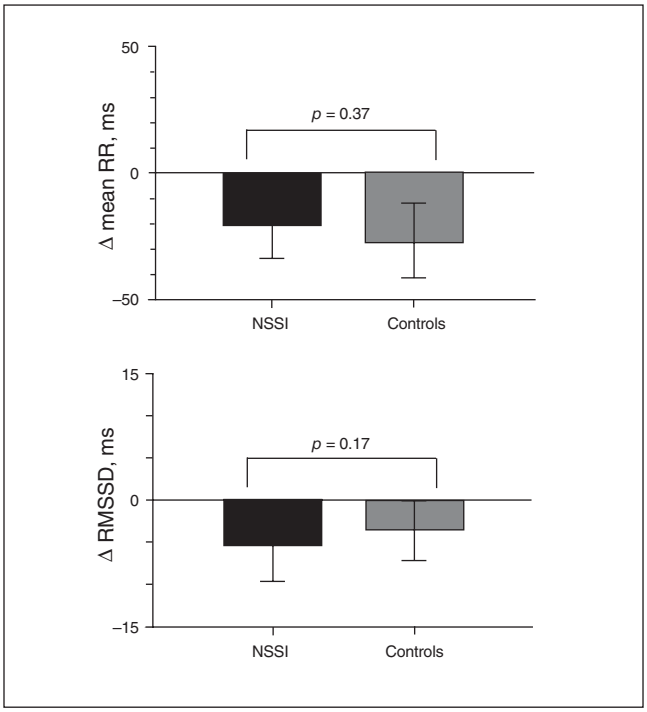

Fig. 4: Changes in heart rate variability by group during painful stimulation. The p values for group differences were derived from adjusted linear regression analysis. Mean interbeat intervals (RR) and root mean square of successive differences (RMSSD) were log-transformed before analysis. Absolute values are displayed as means and standard errors of the mean. All Δ are relative to measures taken during painful stimulation (individual segments based on exposure time). The Bonferroni-corrected p values are as follows: mean RR $p_{corrected}$ > 0.99; RMSSD $p_{corrected}$ = 0.66. NSSI = nonsuicidal self-injury.

human heart rate. Our findings suggest altered autonomic cardiac control in patients with NSSI. These differences in the time-course of ANS short-term reactivity when facing and recovering from pain indicate less arousal toward but greater or preserved arousal following painful experiences in individuals engaging in NSSI. Further, in an exploratory analysis greater decrease of vagal activity during painful stimulation was associated with greater improvements in body awareness following painful stimulation only in patients with NSSI ($r = –0.423$, $p = 0.040$). This finding underlines the importance of pain-induced physiological arousal to counteract dissociative states in individuals engaging in NSSI and with related psychopathology, such as BPD. Findings on prolonged autonomic arousal following inflicted pain are in line with the present findings of greater pain-specific cortisol responsiveness. Lower arousal while anticipating pain points to less aversion toward the painful experiences.

To summarize, the present findings show that greater pain-inflicted autonomic arousal (i.e., prolonged reductions in parasympathetic vagal activity following pain) and cortisol secretion may facilitate improving mood and restoring body awareness in adolescents engaging in NSSI. These findings lend support to a neurobiological mechanism underlying the intraindividual psychological and antisuicide function of NSSI[51,59] by promoting stress relief and decreasing emotional distress. Although we can only speculate on the developmental trajectories promoting this pathomechanism, we suggest the following pathway: chronic exposure to a stressful environment (or the experience of such) could lead to long-term alterations of the endogenous stress systems (ANS and HPA axis) that are less responsive to acute environmental demands. Inappropriate support from these endogenous systems to cope with acute stressors may lead to difficulties in emotion regulation and increased psychological distress. The experience of acute physical pain is capable of activating endogenous stress response systems, leading to increased cortisol secretion and prolonged autonomic arousal. In return, both promote stress relief and counteract dissociative states, thereby supporting intraindividual functions of NSSI. Further studies are necessary to test these assumptions in a naturalistic setting outside of the laboratory.

Limitations

The present study has some limitations, and we see potential for improvements. Given our finding on cortisol, studies would do well to take multiple cortisol samples over time to trace the time course of changes in cortisol following painful stimulation. With respect to the measurement of BP, future studies should integrate beat-to-beat measures to continuously record BP in order to investigate the involvement of baroreflex activity. Our measurement of BP before and after the CPT may have taken too long to adequately capture short-lived BP pain response, particularly in younger participants with fast BP recovery. Further, we assessed drug use based on self-reports only. Future studies should administer drug tests

Table 2: Regression coefficients (95% confidence intervals) and effect sizes from multiple linear regression models predicting physiologic response

Variable*	Δ SBP	η^2	Δ DBP	η^2	Δ mean RR	η^2	Δ RMSSD	η^2	Δ Cortisol	η^2
Group, unadjusted	–0.062 (–0.128 to 0.004)	0.058	–0.082 (–0.190 to 0.027)	0.038	–0.011 (–0.065 to 0.043)	0.003	–0.076 (–0.291 to 0.139)	0.009	–0.153 (–0.354 to 0.048)	0.039
Group, adjusted	–0.045 (–0.146 to 0.056)	0.015	–0.068 (–0.231 to 0.095)	0.013	0.036 (–0.044 to 0.117)	0.016	0.199 (–0.084 to 0.482)	0.037	–0.281 (–0.554 to –0.008)†	0.077
Smoking	0.003 (–0.019 to 0.025)	0.002	–0.008 (–0.044 to 0.027)	0.004	0.006 (–0.012 to 0.023)	0.008	0.011 (–0.050 to 0.073)	0.003	–0.077 (–0.137 to –0.017)†	0.115
BMI	0.005 (–0.011 to 0.021)	0.008	0.016 (–0.010 to 0.042)	0.029	0.010 (–0.003 to 0.023)	0.045	0.087 (0.041 to 0.132)†	0.221	0.050 (0.007 to 0.093)†	0.095
Alcohol	0.020 (–0.062 to 0.103)	0.005	0.045 (–0.089 to 0.178)	0.009	–0.035 (–0.100 to 0.031)	0.021	–0.021 (–0.253 to 0.210)	0.001	0.068 (–0.154 to 0.291)	0.007
Drugs	–0.038 (–0.150 to 0.075)	0.009	–0.007 (–0.189 to 0.174)	0.000	0.021 (–0.068 to 0.110)	0.004	0.172 (–0.143 to 0.487)	0.023	0.115 (–0.195 to 0.426)	0.011
Medication	0.017 (–0.104 to 0.139)	0.002	–0.046 (–0.242 to 0.151)	0.004	0.030 (–0.066 to 0.127)	0.007	–0.138 (–0.478 to 0.203)	0.013	–0.189 (–0.528 to 0.151)	0.024
Contraceptive pill	–0.012 (–0.091 to 0.067)	0.002	–0.062 (–0.189 to 0.065)	0.018	–0.026 (–0.088 to 0.036)	0.013	–0.214 (–0.434 to 0.006)	0.068	–0.010 (–0.221 to 0.202)	0.000

BMI = body mass index; DBP = diastolic blood pressure; NSSI = nonsuicidal self-injury; RMSSD = root mean square of successive differences; RR = interbeat interval; SBP = systolic blood pressure.
*Group coded as NSSI (1), controls (2). Adjusted for BMI (continuous), use of medication (yes/no), contraceptive pill (yes/no), number of cigarettes smoked (categorical), alcohol use in the past 30 d (yes/no) and drugs used in the past 30 d (yes/no). One participant was excluded from the analysis on cortisol because she was taking cortisol. The variables SBP, DBP, Cortisol, mean RR and RMSSD were log-transformed before analysis.
†$p < 0.05$.

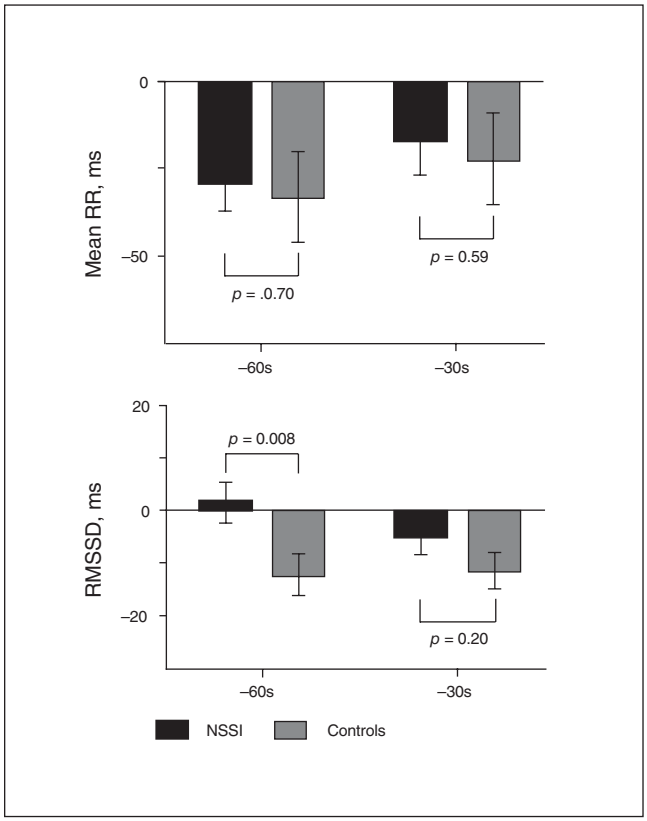

Fig. 5: Anticipatory effects on ultra-short-term heart rate variability (HRV) by time and group. All Δ are relative to HRV at baseline. Values are reported as means and standard errors of the mean. NSSI = nonsuicidal self-injury; RMSSD = root mean square of successive differences; RR = interbeat intervals.

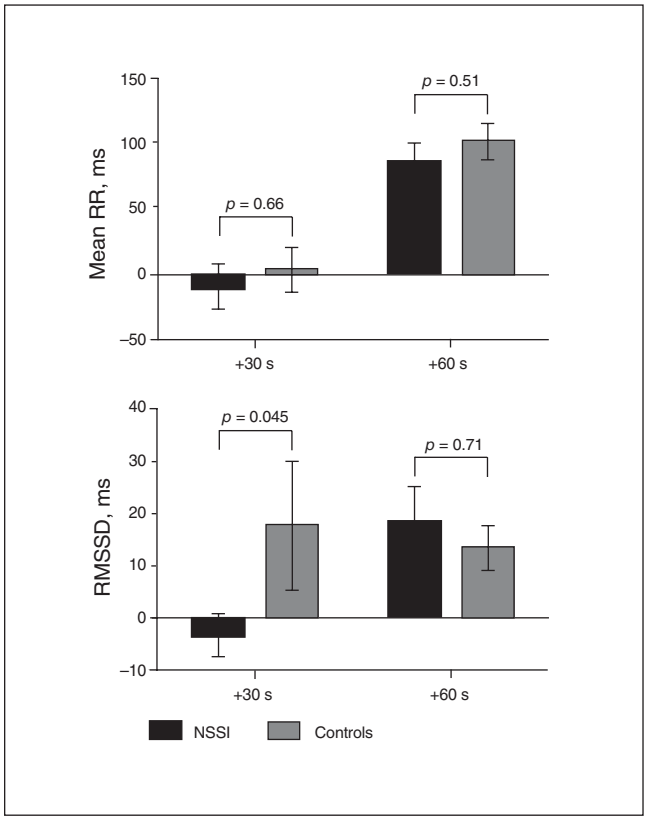

Fig. 6: Recovery of ultra-short-term heart rate variability (HRV) by time and group after painful stimulation. All Δ were relative to HRV during painful stimulation. Values are reported as means and standard errors of the mean. NSSI = nonsuicidal self-injury; RMSSD = root mean square of successive differences; RR = interbeat intervals.

to objectively assess drug intake — especially of drugs affecting ANS and HPA-axis function. Finally, in addition to NSSI, some patients in our sample fulfilled diagnostic criteria for BPD. While our sample was too small to address potential differences in the physiologic pain response comparing adolescents with NSSI and those with NSSI and comorbid BPD, such analyses represent an interesting avenue for future research.

The strengths of our study include the large sample size of well-characterized adolescent self-injurers and the simultaneous measurement of a variety of physiologic processes in addition to self-reports on psychological outcomes.

Conclusion

The psychobiological pain response in individuals engaging in NSSI differs to that of healthy controls. Pain response in those with NSSI is characterized by greater cortisol secretion and prolonged autonomic arousal. These alterations might underlie decreased pain sensitivity owing to the endogenous modulation of the pain experience and promote body awareness and relief of inner tension. Focusing on alterations of endogenous stress systems (ANS and HPA axis), to our knowledge this study is the first to provide a potential pathomechanism underlying the psychological function of self-injury. Further studies extending on these findings and the theoretical framework outlined are necessary.

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