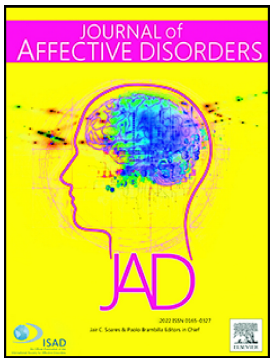

Physiological response to pain in female adolescents with nonsuicidal self-injury as a function of severity

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Physiological Response to Pain in Female Adolescents with Nonsuicidal Self-Injury as a Function of Severity

Running Title: Physiological Pain Response & Self-Injury Severity

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Abstract

Background: Preliminary evidence indicates altered hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) response to experimental pain in individuals with nonsuicidal self-injury (NSSI). This study investigated effects of NSSI severity and severity of psychopathology on the HPA axis and ANS response to pain.

Methods: *N*=164 adolescents with NSSI and *n*=45 healthy controls received heat pain stimulation. Salivary cortisol, α-amylase and blood pressure were repeatedly assessed before and after painful stimulation. Heart rate (HR) and heart rate variability (HRV) were assessed continuously. NSSI severity and comorbid psychopathology were derived from diagnostic assessments. Main and interaction effects of time of measurement and NSSI severity, adjusted for severity of adverse childhood experiences, borderline personality disorder and depression, on HPA axis and ANS response to pain were examined using regression analyses.

Results: Increasing NSSI severity predicted an increasing cortisol response ($\chi^2(3)=12.09$, $p=.007$) to pain. After adjusting for comorbid psychopathology, greater NSSI severity predicted decreased α-amylase levels following pain ($\chi^2(3)=10.47$, $p=.015$), and decreased HR ($\chi^2(2)=8.53$, $p=.014$) and increased HRV($\chi^2(2)=13.43$, $p=.001$) response to pain.

Limitations: Future research should implement several NSSI severity indicators, potentially revealing complex associations with the physiological response to pain. Assessing physiological responses to pain in NSSI in a naturalistic setting presents a promising avenue for future research in NSI.

Conclusions: Findings indicate an increased pain-related HPA axis response and an ANS response characterized by reduced sympathetic and increased parasympathetic activity associated with NSSI severity. Results support claims for dimensional approaches to NSSI and its related psychopathology alongside shared, underlying neurobiological correlates.

Keywords: NSSI severity; Hypothalamic-pituitary-adrenal axis; Cortisol; Heart rate variability; Autonomic nervous system; Stress response systems

1. Introduction

Nonsuicidal self-injury (NSSI), the deliberate and self-inflicted damage to body tissue without suicidal intent (International Society for the Study of Self-injury, 2018), peaks in adolescence (Plener et al., 2015), with lifetime prevalence rates of 13.4–17.2% among non-clinical samples (Swannell et al., 2014) and up to 80% in clinical populations (Plener et al., 2016; Zetterqvist, 2015). NSSI occurs comorbid with a wide range of psychiatric disorders, but also independently (Glenn and Klonsky, 2013; Plener et al., 2018; Zetterqvist, 2015). Consequently, NSSI was introduced in the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a disorder requiring further research (American Psychiatric Association, 2013). Adding to the high prevalence rates, adolescent NSSI has been linked to significantly reduced psychosocial functioning (Ghinea et al., 2021; Washburn et al., 2015) and was shown to predict onset of psychiatric disorders later in life (Wilkinson et al., 2018), as well as future suicide ideation and attempts (Kiekens et al., 2018; Koenig et al., 2017a; Mars et al., 2019). Moreover, an increased risk of NSSI was linked to emotion dysregulation (Wolff et al., 2019; You et al., 2018), increased psychological distress (Baetens et al., 2014) and lower distress tolerance (Nock and Mendes, 2008).

While self-injurious acts are normatively inherently painful, many individuals with NSSI report decreased pain perception or analgesia during self-injurious acts (Nock and Prinstein, 2005), as evidenced by higher pain thresholds and tolerances, lower overall perceived pain intensities (Kirtley et al., 2016; Koenig et al., 2016), and a higher pain endurance (Hooley et al., 2010). Moreover, experimental research revealed that pain is capable of reducing negative affect and aversive tension in individuals engaging in NSSI (Armey et al., 2011; Koenig et al., 2017c; Kranzler et al., 2018; Naoum et al., 2016; Niedtfeld et al., 2010, 2012; Reitz et al., 2012, 2015; Willis et al., 2017) as well as in individuals without NSSI (Navratilova and Porreca, 2014). The growing body of research indicates a complex association between pain and NSSI (severity), influenced by state-dependent psychological and physiological arousal (Selby et al., 2019). Generally, the physiological pain response is marked by a decrease in parasympathetic and an increase in sympathetic nervous activity, derived from changes in vagally mediated heart rate variability (HRV) (Cowen et al., 2015; Koenig et al., 2014), and an

increased cortisol secretion (Goodin et al., 2012). Beyond HRV, pain response has been assessed for other biomarkers of ANS responsivity, and pain is associated with increases in heart rate (HR; Loggia et al., 2011) and blood pressure (BP; Bruehl and Chung, 2004) as well as increases in α-amylase (Wittwer et al., 2016).

Research has only begun to shed light on the neurobiological and -physiological mechanisms of NSSI. The temporal framework model distinguishes between *trait* and *state* markers to advance the understanding of the biology of NSSI (Kaess et al., 2021b). On a trait level, alterations in major biological stress systems – the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Kreibig, 2010; Lupien et al., 2009) – have become apparent in the context of NSSI (Kluetsch et al., 2012; Osuch et al., 2014; Reitz et al., 2015; Schmahl et al., 2006): Studies showing attenuated cortisol secretion and reduced HRV in patients with NSSI support the attenuation hypothesis (Susman, 2006) and the neurovisceral integration model (Thayer and Lane, 2000) respectively. However, few studies have investigated the *state* level, i.e., biological responses of the ANS and HPA axis directly preceding or following NSSI, such as in experimental pain paradigms. In one of the first studies examining adolescents with a history of NSSI and healthy controls (HC), we found significant alterations in both the ANS and HPA axis response to pain in those with NSSI (Koenig et al., 2017c). Individuals with NSSI had a delayed decrease in parasympathetic vagal activity (greater HRV) in anticipation of the painful stimulation and a prolonged recovery (reduced HRV) following painful stimulation compared to HC, which correlated with improved body awareness. Further, individuals with NSSI had a significantly greater cortisol response to painful stimulation compared with HC, which was positively associated with mood-improvement (Koenig et al., 2017c). This hyperresponsiveness of the ANS and HPA axis to painful stimulation was further enhanced by greater childhood adversity (Rinnewitz et al., 2018). While these studies lend first empirical support for alterations of psychophysiological systems in NSSI-related pain experience, further studies replicating and expanding on these findings are needed.

Clinical research and practice have recognized the need for dimensional approaches of psychiatric diagnoses and psychopathology (Michelini et al., 2021). Evidence suggests that categorical diagnoses,

relying on arbitrary thresholds and cutoffs, fail to consider that psychopathology and the underlying mechanisms are naturally continuous, and psychiatric disorders are better defined along the continuum of several overarching dimensions (i.e., internalizing and externalizing) that largely influence the symptomatology of disorders (Kotov et al., 2017; Widiger and Edmundson, 2011). Moreover, categorical classifications seldom consider underlying pathophysiological mechanisms, shared across most traditional diagnoses (Insel et al., 2010). Dimensionally assessing the transdiagnostic symptomatology of NSSI could increase our understanding of how psychological processes and underlying biological mechanisms influence the development and maintenance of NSSI. Phenotypically, NSSI severity has often been conceptualized using the frequency of NSSI acts or days with NSSI (Klonsky, 2009). When NSSID was introduced in the DSM-5, five or more days of self-injurious acts over the past year have been considered as the clinically relevant cutoff (American Psychiatric Association, 2013). However, researchers have criticized the cutoff as too low, reporting significantly higher frequency rates in community (Andover, 2014; Zetterqvist et al., 2013) and clinical samples (Washburn et al., 2015; Zetterqvist et al., 2020). Moreover, significant heterogeneity was found in the severity of comorbid psychopathology and psychosocial impairment with increasing NSSI frequency (Ammerman et al., 2017; Muehlenkamp et al., 2017; Zielinski et al., 2018). If low frequencies of NSSI are linked to overall lower levels of comorbid psychopathology, experienced traumata and impairment, alterations in underlying biological mechanisms ought to be analyzed in light of NSSI severity.

A growing body of literature indicates the presence of neurobiological mechanisms and correlates of NSSI (Kaess et al., 2021a), and the existence of altered pain sensitivity in individuals engaging in NSSI is well evidenced (Koenig et al., 2016). Yet, research on biological correlates of pain processing in NSSI is still scarce (Koenig et al., 2017c), and research on the effect of NSSI severity is virtually missing. Here we aimed to investigate the effect of NSSI severity on physiological responses to pain (focusing on the ANS and HPA axis) in adolescents with NSSI. Based on the existing evidence, we hypothesized that pain sensitivity would decrease as a function of NSSI severity. Further, based on previous findings and existing literature, we hypothesized that the HPA axis response to pain would increase and that the ANS pain response would entail an increased sympathetic and a decreased

parasympathetic activity with increasing NSSI severity. Finally, in additional analyses, we controlled for effects of dimensional psychopathology severity on pain sensitivity, HPA axis and ANS responsivity.

2. Methods

2.1. Participants

Participants were recruited from the specialized outpatient clinic for risk-taking and self-harm behavior "Ambulanz für Risikoverhalten und Selbstschädigung (AtR!Sk)" (Kaess et al., 2017), at the Clinic for Child and Adolescent Psychiatry, University of Heidelberg (Germany). The study consisted of an initial diagnostic interview (AtR!Sk; IRB ethical approval number: S-449/2013) and a neurobiological assessment (AtR!Sk-Bio; IRB ethical approval number: S-514/2015) participants were subsequently invited to.

Recruitment took place between August 2016 and January 2020. Inclusion criteria for patients were a written informed consent by the adolescents and their caregivers, age between 12-17 years, and a completed diagnostic assessment prior to the neurobiological assessment. Exclusion criteria were a lack of speech comprehension (German), signs of acute psychosis, endocrinological or cardiovascular primary diseases likely interfering with the neurobiological assessments. For the present analyses, patients with at least one lifetime incident of NSSI, as defined by the DSM-5 (American Psychiatric Association, 2013), were included, to cover the full dimensional spectrum of NSSI severity. Further, only female participants were considered, due to the relatively small number of male participants and previously reported sex-differences regarding the ANS/HPA activity (Koenig and Thayer, 2016; Kudielka and Kirschbaum, 2005; Melchior et al., 2016). HC were recruited through public advertisement. All HC and their caregivers provided written informed consent. Inclusion and exclusion criteria were mostly identical to the patient group. Additional exclusion criteria were any lifetime NSSI, psychological or psychiatric treatment, or current psychiatric disorder. Due to the nature of the longitudinal AtR!Sk and AtR!Sk-Bio studies, January 2020 was chosen as cut-off for inclusion in the AtR!Sk-Bio study. All participants (patients with NSSI and HC) that had completed the neurobiological assessment until January 2020 were subsequently considered for analyses.

2.2. General Procedures

During the diagnostic assessment, self-injurious and suicidal thoughts and behaviors were assessed using the German version of the *Self-Injurious Thoughts and Behaviors Interview* (SITBI-G) (Fischer

et al., 2014). BPD was assessed with the German version of the *Structured Clinical Interview for DSM-IV Axis II Personality Disorders* (SCID-II) (Wittchen et al., 1997). Axis-I psychiatric disorders were assessed with the *Mini International Neuropsychiatric Interview for Children and Adolescents* (MINI-KID) (Sheehan et al., 2004). The severity of psychiatric symptoms was rated by the trained personal using the *Clinical Global Impression Scale* (CGI-S) (Busner and Targum, 2007), while participants' global functioning was rated using the *Global Assessment of Functioning* (GAF) (Saß et al., 2003). Self-reported depressive symptoms were assessed using the *Depression Inventory for Children and Adolescents* (DIKJ) (Stiensmeier-Pelster et al., 2000). Furthermore, adverse childhood experiences (ACE) were assessed based on self-reports using the German version of the *Childhood Experiences of Care and Abuse* questionnaire (CECA.Q) (Kaes et al., 2011).

HC received an adapted, shortened diagnostic assessment to assess potential current mental disorders as well as psychological or psychiatric treatments. To rule out any history of NSSI, screening questions from the SITBI-G (Fischer et al., 2014) were used. Potential axis-I disorders were assessed using the *Structured Clinical Interview (non-patient edition)* (First et al., 2002). If clinical symptoms became apparent during the interview, the MINI-KID (Sheehan et al., 2004) was used to assess the presence of a psychiatric disorder in detail. If the criteria for any psychiatric disorder were met, participants were excluded from the study.

Recruitment for the second appointment, the assessment of neurobiological markers and variables, occurred within six weeks following the diagnostic interview. Starting at 8 a.m., participants' height and weight were measured. Subsequently, pain sensitivity was assessed using a thermal plate and a standardized procedure (see 2.3.). To assess the HPA axis response to the painful stimulation, saliva cortisol samples were collected repeatedly (see 2.4.). The ANS response was assessed by repeated assessments of blood pressure as well as continuous measurements of HR and HRV (see 2.5.). Participants received 40€ for their participation in the study.

2.3. Pain assessment

Three different aspects of pain sensitivity –pain threshold, pain tolerance and pain intensity– were assessed using a standardized preprogrammed sequence and an AHP-1800CPV Versatile Cold/Hot

Plate (TECA Corp., Chicago, IL, USA). Participants placed their non-dominant hand flat on the plate with a baseline temperature of 32 °C. Following a 3-minute adaptation phase, temperature steadily rose to 50 °C over four minutes. Participants were asked to keep their hand firmly on the plate until the pain became intolerable. Temperatures were noted in °C at first pain sensation (pain threshold) and when pain became intolerable (pain tolerance). Pain intensity was assessed using a visual analogue scale (VAS) ranging from 0 to 100, using the Continuous Measurement System (CMS) software (Messinger et al., 2009). Participants rated pain intensity continuously, using their dominant hand, from the moment pain threshold was reached until the pain became intolerable. To avoid any damage to the skin due to long-term exposure, the sequence ended automatically at 50 °C and participants were asked to remove their hand if pain tolerance was still not reached. Pain intensity scores were calculated based on the rated pain intensity upon reaching pain tolerance. An average score was generated using the VAS ratings within five seconds before and after reaching pain tolerance to account for potential inaccuracies.

2.4. Endocrinological assays

The endocrinological pain response was assessed using salivary samples, collected at five different time-points following a standardized procedure and timeline: A baseline measure following a 5-minute resting period (1), immediately before (2) and after the painful stimulation (3), following a second 5-minute resting period (4) and ten minutes after the fourth salivary sample (5). Participants chewed on a cotton swap (Salivette®; Sarstedt, Numbrecht, Germany) for one minute. Samples were frozen at -20 °C until assay. Salivary α-amylase and cortisol were determined at the Biopsychology Laboratory at the Technical University of Dresden. Before analysis, samples were centrifuged at 3000 rpm to produce a clear supernatant of low viscosity. A-amylase concentration was determined using an enzyme kinetic method. Cortisol concentrations, as proxy of HPA axis responsivity, were determined with a commercially available chemiluminescence immunoassay (CLIA; IBL International, Hamburg, Germany), according to the protocol of the manufacturer. The reference range was 56–200 ng/ml, with inter- and intra-assay coefficients of variation between 2.9–6.0%.

2.5. Cardiovascular activity

HR was continuously recorded at 1024 Hz throughout the neurobiological assessment with an EcgMove 3 sensor (Movisens GmbH; Karlsruhe, Germany), attached to a chest belt with dry electrodes. Recordings lasted from the first resting period until after the second resting period. Raw electrocardiogram (ECG) data were first screened using UnisensViewer (Movisens GmbH; Karlsruhe, Germany). Raw data were processed using the Kubios HRV Premium software (Version 3.0) (Tarvainen et al., 2014). R peaks were manually corrected, accounting for movement artifacts and potential extra systoles. HR in beats per minute and the root mean square of successive differences (rMSSD) of normal-to-normal intervals, as a measure of HRV, in milliseconds were derived. Diastolic (DBP) and systolic blood pressure (SBP) were always assessed following the salivary cortisol samples (see 2.4.), in a sitting position using an OMRON M500 sphygmomanometer (Omron Corporation, Kyoto, Japan).

2.6. Statistical analyses

Prior to analyses, pain sensitivity variables were checked for missing values, with participants being excluded if at least one measure was missing. Missing values were mostly due to miscommunication during pain assessment, indicating incorrect heat pain application or participants' responses. To avoid potential bias on the remaining outcome variables (e.g., physiological pain response), these participants were excluded. Values for pain endurance were generated by subtracting temperature at pain threshold from temperature at pain tolerance (Hooley et al., 2010). Clinical and sociodemographic variables were tested for between-group differences using χ^2-tests for categorical variables and one-way ANOVA analyses for continuous variables. Regarding effects of NSSI severity, associations were investigated using the number of days with NSSI (continuous) in the past six months preceding the assessments, independent of group assignment, to account for recent NSSI (hereafter referred to as "NSSI frequency"). Simple linear regression analyses were calculated to analyze whether NSSI frequency (continuous) in the past six months predicted clinical characteristics and pain sensitivity. Multilevel mixed-effects linear regression analyses were conducted to assess differences in the physiological pain response (separate models for cortisol, α-amylase, SBP, DBP, HR and HRV) with TIME (time of measurement or segment), NSSI FREQUENCY over the past six months

(continuous), and their interaction as fixed effects, and the participants' ID as a random effect. Additionally, contrasts of marginal linear predictions on the main effects of TIME and NSSI FREQUENCY as well as their interaction were derived. Sensitivity analyses were performed for the NSSI group only (excluding those without NSSI) in order confirm the effect of NSSI severity without potential zero-inflation. In additional analyses, the multilevel mixed-effects linear regression analyses were adjusted for ACE, BPD and depression severity (all continuous, separate models were calculated for each covariate), to account for a potential influence of comorbid psychopathology on the physiological pain response. Similarly, additional multiple linear regression analyses were conducted with pain sensitivity measures as dependent variable and NSSI frequency as well as ACE, BPD and depression severity, and their respective interactions with NSSI FREQUENCY as independent variables, to account for a potential influence of psychopathology on pain sensitivity. All analyses were performed using Stata (Version 16; StataCorp LP, College Station, TX, US) with the significance level set to α=0.05. We did not use any corrections for multiple comparisons, as we consider the biological variables tested to be largely independent. As recruitment for the present study was nested in a clinical cohort study with consecutive recruitment of all adolescents presenting at the specialized outpatient clinic AtR!Sk, no a priori power analysis was conducted.

3. Results

3.1. Sample characteristics

N=255 patients provided written informed consent and *n*=242 (94.9%) completed the baseline assessment. Of these, *n*=43 (17.8%) were excluded due to male sex and *n*=5 (2.1%) due to reporting no lifetime incidents of NSSI. *N*=28 (11.6%) patients were excluded due to missing pain data. *N*=58 adolescents provided written informed consent for the HC group, of which *n*=49 (84.5%) completed the baseline assessment. *N*=2 (4.1%) were excluded due to male sex and *n*=4 (8.2%) due to missing pain data. The final sample consisted of *n*=45 HC and *n*=164 female patients with NSSI.

A detailed description of sociodemographic and clinical characteristics is provided in *Table 1*. Groups did not differ on age, height, and BMI. However, patients and HC differed significantly on weight ($F(1,203)=4.28$, $p=.040$) and school-type ($\chi^2(3)=12.45$, $p=.004$). Patients reported significantly more ACE ($F(1,190)=50.61$, $p<.001$), and scored significantly higher on depressive symptoms ($F(1,186)=235.20$, $p<.001$) and BPD symptoms compared to HC ($F(1,206)=105.48$, $p<.001$). Overall, *n*=46 patients (28.1%) fulfilled diagnostic criteria for BPD and *n*=90 (55.0%) fulfilled diagnostic criteria for a depressive episode or disorder. On average, patients reported 60.7 (*SD*=70.32) NSSI episodes within the past 12 months (range: 0–340), and 33.1 (*SD*=37.61) episodes within the past six months (range: 0–160). To assess continuous associations between clinical measures and NSSI frequency (past six months), simple linear regressions were calculated. The number of BPD criteria ($p<.001$), depressive symptoms ($p<.001$), ACE ($p<.001$), and the severity of psychiatric symptoms ($p=.025$) all significantly increased with more frequent NSSI in the past six months, while global functioning ($p<.001$) significantly decreased (see *SM Table 1*).

3.2. Pain sensitivity measures

Simple linear regressions were calculated with pain sensitivity measures as dependent variables and NSSI frequency (six months) as predictor (see *SM Table 1*). Analyses revealed no significant effect of NSSI frequency on pain sensitivity measures. Increasing NSSI frequency led to a non-significant increase in pain threshold ($\beta=0.002$, $p=.753$) and pain tolerance ($\beta=0.002$, $p=.694$) as well as a non-significant decrease in pain endurance ($\beta=-0.000$, $p=.951$) and perceived pain intensity ($\beta=-0.030$,

p=.478) (see *Figure 1*). Analyses were repeated including the patient group only and yielded similar results (for details please refer to *SM Table 2*). Additional regression analyses were conducted to control for a potential additional effect of comorbid psychopathology (e.g., ACE, BPD, depression symptoms). No significant main effects of NSSI frequency or comorbid psychopathology and no interaction effects on pain sensitivity measures were found (see *SM Tables 3-5*).

INSERT TABLE 1 HERE

INSERT FIGURE 1 HERE

3.3. *Endocrinological and autonomic measures*

Results of the multilevel mixed-effects linear regressions with main and interaction effects of time and NSSI frequency (six months) modeled continuously are depicted in *Table 2* (results from the same analyses including the patient group only are detailed in *SM Table 6* and yielded similar results). Results of the additional, adjusted regression models with main and interaction effects of time, NSSI frequency (six months) and psychopathology (e.g., ACE, BPD and depression severity) modeled

continuously are depicted in *SM Tables 7-10*.[1]

3.3.1. *Cortisol*

No significant main effects of TIME ($\chi^2(3)=1.56$, $p=.668$) nor NSSI FREQUENCY ($\chi^2(1)=0.00$, $p=.958$) on cortisol levels were found. However, the TIME*NSSI FREQUENCY interaction on cortisol levels was significant ($\chi^2(3)=12.09$, $p=.007$). Cortisol levels increased significantly stronger following pain induction if individuals self-injured more frequently in the past six months (see *Figure 2a*). Post-hoc analyses revealed that robust significant differences in cortisol response to pain occurred, if participants reported 63 or more incidents of NSSI in the past six months (see *SM Table 10*). Results were robust after adjusting for ACE, BPD, and depression severity, with no moderating effect of psychopathology on the TIME*NSSI FREQUENCY interaction.

3.3.2. *α-amylase*

Analyses indicated a significant main effect of TIME ($\chi^2(3)=26.92$, $p<.001$) on α-amylase, characterized by an increased α-amylase secretion following pain induction (see *Figure 2b*). No significant main effect of NSSI FREQUENCY ($\chi^2(1)=0.87$, $p=.350$) nor TIME*NSSI FREQUENCY interaction ($\chi^2(3)=5.32$, $p=.150$) was observed.

The main effect of TIME was robust after adjusting for potential effects of psychopathology (see *SM Tables 5-7*). However, adjusting for ACE revealed a significant main effect of NSSI FREQUENCY ($\chi^2(1)=4.40$, $p=.036$) not present in the unadjusted model, indicating overall increased α-amylase levels with increasing NSSI frequency when considering the presence of trauma. Adjusting for BPD severity revealed a significant main effect of NSSI FREQUENCY ($\chi^2(1)=17.66$, $p<.001$) and TIME*NSSI FREQUENCY interaction ($\chi^2(3)=10.47$, $p=.015$) not present in the unadjusted model, indicating overall higher α-amylase levels with increasing NSSI frequency and a more pronounced decrease in α-amylase following pain with increasing NSSI frequency. The TIME*NSSI FREQUENCY interaction was not moderated by BPD severity.

[1] Detailed results of these supplemental analyses can be provided upon request.

3.3.3. *Blood pressure*

The main effect of TIME was significant for both SBP ($\chi^2(3)=17.91$, $p<.001$) and DBP ($\chi^2(3)=15.40$, $p=.002$). As illustrated in *Figure 2c-d,* SBP and DBP increased significantly after pain induction compared to baseline (SBP: $\chi^2(1)=4.19$, $p=.041$; DBP: $\chi^2(1)=13.44$, $p<.001$) and decreased significantly after the second resting phase (SBP: $\chi^2(1)=14.89$, $p<.001$; DBP: $\chi^2(1)=6.50$, $p=.011$). Analyses showed no significant main effects of NSSI FREQUENCY nor TIME*NSSI FREQUENCY interaction (see *Table 2*).

Results on SBP were robust when adjusting for psychopathology. Regarding DBP, results of the unadjusted model were overall robust, except when the model was adjusted for depression severity (see *SM Tables 5-7*). Here, the main effect of TIME became non-significant ($\chi^2(3)=7.77$, $p=.051$). No significant main or interaction effects for psychopathology were observed.

3.3.4. *Autonomic reactivity*

Analyses revealed a significant main effect of TIME on HR ($\chi^2(2)=18.20$, $p<.001$), indicating an overall increased HR during painful stimulation ($\chi^2(1)=11.54$, $p<.001$) and the second resting phase ($\chi^2(1)=15.47$, $p<.001$) compared to baseline (see *Figure 2e*). The main effect of NSSI FREQUENCY ($\chi^2(1)=0.00$, $p=.976$) and TIME*NSSI FREQUENCY interaction ($\chi^2(2)=4.58$, $p=.101$) were not significant. The overall model fit for HRV was not significant ($\chi^2(5)=8.71$, $p=.121$).

Results on HR were largely robust when adjusting for effects of psychopathology (see *SM Tables 5-7*). However, controlling for effects of ACE revealed a significant TIME*NSSI FREQUENCY interaction ($\chi^2(2)=8.53$, $p=.014$) not present in the unadjusted model, indicating a progressive decrease in HR with increasing NSSI frequency during pain. No significant moderating effect of ACE was observed.

Regarding HRV, the overall model fit remained nonsignificant after adjusting for effects of ACE and BPD. Adjusting for depression severity revealed a significant model fit ($\chi^2(11)=24.62$, $p=.010$), with no significant main effects of TIME ($\chi^2(2)=1.02$, $p=.601$) nor NSSI FREQUENCY ($\chi^2(1)=0.05$, $p=.820$). However, the TIME*NSSI FREQUENCY interaction was significant ($\chi^2(2)=13.43$, $p=.001$), indicating that HRV increased significantly stronger with greater NSSI frequency following pain

induction. No significant moderating effect of depression severity was observed (see *SM Tables 8-10*).

INSERT TABLE 2 HERE

INSERT FIGURE 2 HERE

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4. Discussion

The present study examined the effect of dimensional NSSI severity on the physiological pain response in adolescents with NSSI. Contrary to our hypothesis, we found no significant association between pain sensitivity and NSSI frequency in general. This supports extant findings that alterations in pain sensitivity may not be a mere effect of habituation to constant or regular pain exposition (Glenn et al., 2014; Koenig et al., 2017b). Between- and within-person variance in pain experiences during NSSI episodes, that is known to be influenced by state-dependent psychological and physiological arousal (Selby et al., 2019), may account for variance in this regard. Future studies should assess affect and tension before and after pain stimulation to clarify the influence of state dependent affect and arousal.

Regarding the physiological response to pain, we found significant increases in cortisol and α-amylase levels, SBP, DBP and HR following pain across the whole sample, indicating successfully increased physiological arousal. In line with our hypotheses, we found increased pain-related cortisol secretion to vary as a function of NSSI severity, independent of comorbid psychopathology. This expands previous findings by our group, further supporting the assumption of a pain-specific HPA axis response (Koenig et al., 2017c), that extends to symptom severity. A blunted HPA axis response to stress has previously been linked to more aversive emotional reactions in a range of psychiatric disorders (Putman and Roelofs, 2011; Zorn et al., 2017). In line with our previous reasoning (Koenig et al., 2017c), stressful situations might not elicit a sufficient HPA axis response in adolescents with NSSI (Kaess et al., 2012; Plener et al., 2017). Engaging in NSSI and the corresponding experience of pain might result in an increased cortisol secretion, which helps to cope with stress and reduce negative affect. Our findings suggest the presence of a compensatory mechanism of NSSI i.e., increased cortisol secretion following pain countering the blunted HPA axis response to stress (Klimes-Dougan et al., 2019). This finding emphasizes the importance of investigating both trait and state markers to understand the biology of NSSI, as suggested by the temporal framework model (Kaess et al., 2021). Important to note, robust significant effects occurred in individuals reporting 63 or more days with NSSI in the past six months. This finding supports previous claims that the DSM-5 threshold for NSSI frequency is rather low (Washburn et al., 2015; Zetterqvist et al., 2020) and that,

especially for research addressing biological mechanisms, meaningful thresholds associated with alterations on the neurobiological level are supposedly significantly higher. Further studies are needed to replicate these findings.

Regarding ANS responsivity, unadjusted analyses revealed no significant effect of NSSI severity. However, further controlling for the influence of comorbid psychopathology yielded several important findings that are partly contrary to our hypotheses that derived from our prior study. As such, we found that HR response decreased with increasing NSSI severity during pain induction, when controlling for ACE. Concerning HRV, adjusting for depression severity revealed increased HRV response following pain induction as a function of greater NSSI frequency. Further, HRV was overall decreased with greater depression severity. Controlling for the potentially opposing effect of depression severity, which was positively correlated with NSSI severity, may have explained additional variance previously masking the TIMExNSSI FREQUENCY effect – potentially explaining that the unadjusted model failed to reach statistical significance. Finally, α-amylase, a sensitive biomarker of ANS responsivity (Nater and Rohleder, 2009), decreased stronger with increasing NSSI frequency following pain induction, when controlling for BPD severity. Similarly, evidence suggests that changes in α-amylase levels indicate greater/reduced sympathetic activity (Nater and Rohleder, 2009; Schumacher et al., 2013), while changes in HR are the product of the interplay of sympathetic and parasympathetic activity, and vagally-mediated HRV is a measure of parasympathetic activity (Thayer et al., 2012, 2010). Consequently, our results potentially suggest that the ANS response to pain is associated with decreased sympathetic and increased parasympathetic activity as a function of greater NSSI severity. Previous data from our group pointed to an increased pain-inflicted autonomic arousal potentially counteracting reduced body awareness and dissociative states (Koenig et al., 2017c). Our current results, however, point to decreased autonomic arousal after pain, which is in line with the affect-regulating and stress-reducing function of NSSI. While further research will need to investigate these conflicting findings, it is important to note that the current findings are based on a larger sample yielding increased statistical power. Overall, like our findings on HPA axis response, ANS related findings indicate more pronounced, stimulus-specific, physiological effects to pain (e.g., decreased α-amylase, HR and increased HRV response) with increasing NSSI frequency.

In line with previous meta-analyses (Kemp et al., 2010; Koenig et al., 2016a, 2016b; Sigrist et al., 2021), our findings indicate an overall increased HR and decreased HRV with greater severity of psychopathology. Lower resting HRV is associated with psychological dysfunctions such as emotion dysregulation (Thayer and Lane, 2009; Williams et al., 2015). NSSI is most often used to regulate emotions and aversive tension (Nock, 2010), and previous research indicates a pain-related decrease in tension, indexed by decreased HR and increased HRV response following pain (Reitz et al., 2015, 2012; Willis et al., 2017). Our findings support the existing evidence, potentially indicating a generally higher tension and more emotional lability associated with the severity of psychopathology – reflecting greater sympathetic dominance (Kaess et al., 2021a) – that are maladaptively regulated by means of engaging in NSSI.

The present study adds to the existing literature employing dimensional approaches to the neurobiological study of phenomena related to psychopathology (Insel et al., 2010; Kotov et al., 2017). First, our findings illustrate that NSSI severity is associated with a progressively altered physiological pain response, indicating that dimensional assessments of NSSI (symptom) severity and its underlying neurobiological mechanisms are warranted. Together with the previously reported heterogeneity in NSSI frequency and associated severity of psychopathology (Brausch, 2019), our findings indicate that relying on diagnostic cutoffs, especially the one currently put forward in DSM-5 criterion A, may not adequately reflect how these psychological and physiological factors contribute to the development and maintenance of NSSI. To expand on our findings, longitudinal research is needed to examine the relationship between NSSI and altered neurobiological functioning, both at rest and in response to acute stressors, across adolescent development, and how changes in NSSI severity relate to changes in underlying neurobiological mechanisms. Second, our findings indicate that altered HPA-axis and ANS activity are shared mechanisms underlying both NSSI and (comorbid) severity of psychopathology, while also revealing different pain-related working mechanisms. Alterations of the HPA-axis and the ANS have previously been linked to the severity of psychopathological symptoms that are central factors in many psychiatric disorders (Williams et al., 2015; Zorn et al., 2017), likely contributing to the high comorbidity rates observed among these disorders. In line with the recently proposed dimensional approaches (Insel et al., 2010; Kotov et al., 2017), our findings indicate that

assessing HPA-axis and ANS functioning at rest and in response to acute stressors/pain dimensionally, across the entire spectrum of their functioning, in heterogeneous samples with varying degrees of NSSI severity and comorbid psychopathologies could further enable researchers to disentangle previously observed effects of comorbidity. While we assessed comorbid severity of psychopathology, future research should include more detailed assessments of underlying symptom severity (e.g., emotional lability, personality traits) (Kotov et al., 2017).

The present study is the first to systematically assess effects of dimensional NSSI severity on the physiological pain response in a large, well-characterized sample of adolescents with and without NSSI. However, several limitations should be addressed. First, we used NSSI frequency as sole indicator of NSSI severity. As previously proposed (Ammerman et al., 2020; Anestis et al., 2015; Whitlock et al., 2008), future research could rely on several indicators (such as NSSI versatility), potentially revealing more complex associations with the physiological response to pain. Second, while heat pain is a reliable method to assess the physiological pain response in individuals with NSSI, it differs considerably from actual NSSI methods. Assessing altered physiological responses to pain in individuals with NSSI during actual NSSI episodes might advance our understanding beyond effects observed in laboratory-based studies. We included participants aged 12-17 years. Given that pain sensitivity in NSSI varies by age (Koenig et al., 2016) our results do not necessarily generalize to younger children or young adults. Longitudinal studies are needed to examine potential developmental effects of pain sensitivity in NSSI. Finally, our sample was limited to female adolescents, limiting the generalizability of findings. Future research should include male subjects to explore potential sex differences.

To conclude, the present study expands existing literature on altered physiological responses to pain in adolescents with NSSI and is the first to indicate a significant effect of NSSI severity. Following pain, increasing NSSI severity was associated with increasing cortisol secretion and an ANS profile characterized by reduced sympathetic (e.g., decreased α-amylase) and increased parasympathetic (e.g., increased HRV) activation – potentially indicating a pain-related decrease in physiological arousal and improved emotion- and stress-regulation capacity in NSSI. These effects remained after controlling for comorbid psychopathology. Our findings highlight the need for a

dimensional assessment of NSSI severity and underlying psychological and neurobiological correlates that may play a role in its development and maintenance. Further research replicating and extending these findings in larger, well-powered and more heterogenous samples are necessary.

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Table 1 Sample Characteristics

Variable	Group; mean ± SD or *N* (%)		*P*[1]
	HC, (n=45)	NSSI, (n=164)	
Age	14.8±1.28	14.8±1.48	0.727
Height	163.5±6.22	165.6±6.87	0.076
Weight	54.6±9.92	58.8±12.25	0.040*
BMI	20.4±3.24	21.4±3.93	0.127
School Type[2]			0.004**
Gymnasium	29 (64.4)	59 (36.0)	
Realschule	13 (28.9)	66 (40.2)	
Hauptschule	2 (4.4)	16 (9.8)	
Other	1 (2.2)	23 (14.0)	
BPD criteria	0.1±0.33	3.2±2.03	<0.001***
DIKJ	6.7±5.25	28.9±9.18	<0.001***
ACE	0.1±0.29	1.3±1.6	<0.001***
GAF	-	51.4±9.22	
CGI	-	4.8±0.83	
NSSI (past 12 months)	-	60.7±70.32	
NSSI (past 6 months)	-	33.1±37.61	
Suicide attempt (past 12 months)	-	72 (44.0)	

BMI = body mass index; BPD = Borderline personality disorder; DIKJ = Depressionsinventar für Kinder und Jugendliche (revised German version of the Children's Depression Inventory); ACE = adverse childhood experiences; GAF= Global Assessment of Functioning, CGI = clinical global impression; NSSI = Nonsuicidal self-injury

[1] Significance: *p*-values refer to differences between groups, with χ^2 tests for categorical variables and one-way ANOVAs for continuous variables.

[2] 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.

* $p < .05$. ** $p < .01$. *** $p < .001$

Table 2 Results of multilevel mixed-effects linear regressions for predictions of cortisol, α-amylase, systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and heart rate variability (HRV) dependent on time and frequency of non-suicidal self-injury (NSSI) in the past 6 months (continuous).

Outcome	Model Fit		Main Effect Time					Main Effect NSSI Frequency				Interaction		
	X^2	*p*	X^2	*p*	Coef.	*SE*	*p*	X^2	*p*	X^2	*p*	Coef.	*SE*	*p*
Cortisol	22.77	.002**	1.56	.668				0.00	.958	12.09	.007**			
Pain/after pain					-0.27	0.24	.262					0.01	0.01	.015*
Postline/after postline					-0.10	0.24	.661					0.02	0.01	.003**
After postline + 10					-0.02	0.24	.930					0.02	0.01	.003**
α-Amylase	38.75	<.001***	26.92	<.001***				0.87	.350	5.32	.150			
Pain/after pain					29.23	8.19	<.001***					-0.13	0.19	.488
Postline/after postline					-8.56	8.20	.297					-0.09	0.19	.645
After postline + 10					19.28	8.19	.019*					-0.40	0.19	.031*
SBP	22.64	.002**	17.91	<.001***				0.08	.773	1.42	.701			
Pain/after pain					1.44	0.70	.041*					-0.01	0.02	.527
Postline/after postline					-1.21	0.71	.069					-0.00	0.02	.915
After postline + 10					1.06	0.71	.135					-0.02	0.02	.295
DBP	19.61	.007**	15.40	.002**				0.63	.427	0.90	.827			
Pain/after pain					2.15	0.59	<.001***					-0.01	0.01	.576
Postline/after postline					0.65	0.59	.268					0.00	0.01	.970
After postline + 10					1.47	0.59	.012*					-0.01	0.01	.472
HR	28.36	<.001***	18.20	<.001***				0.00	.976	4.58	.101			
Pain/after pain					2.06	0.61	.001**					-0.03	0.01	.060
Postline/after postline					2.40	0.61	<.001***					-0.00	0.01	.955
HRV	8.71	.121	4.77	.092				0.01	.916	7.42	.025*			
Pain/after pain					-0.19	1.89	.918					0.03	0.04	.444

Postline/after postline	-3.69	1.90	.052			0.11	0.04	.008**

Cortisol = Cortisol level in nmol/l; α-Amylase = α-Amylase level in U/ml; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; HRV = heart rate variability.

* $p < .05$. ** $p < .01$. *** $p < .001$

Figure Captions

Figure 1 **Pain Sensitivity as a Function of NSSI Frequency:** depicted are mean pain threshold, pain tolerance, pain endurance (all in degrees Celsius), and pain intensity (0-100 visual analogue scale) and their 95% confidence intervals as a function of the frequency of non-suicidal self-injury (NSSI) in the past six months.

Figure 2 **Endocrinological and autonomic response (cortisol, α-amylase, systolic and diastolic blood pressure, heart rate, and heart rate variability) by NSSI frequency (past six months) and time of measurement.** Mean values and 95% confidence intervals of cortisol (a), α-amylase (b), systolic blood pressure (SBP) (c), diastolic blood pressure (DBP) (d), heart rate (HR) (e) and heart rate variability (HRV) (f) independent of group assignment. Times of measurement were during/immediately after a five-minute resting phase (baseline), during/immediately after heat pain stimulation (pain), during/immediately after a second five-minute resting phase (postline) and ten minutes after the postline (recovery).

CRediT Author statement:

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Julian Koenig: Conceptualization, Funding acquisition, Formal analysis, Project administration, Supervision, Writing – review & editing.

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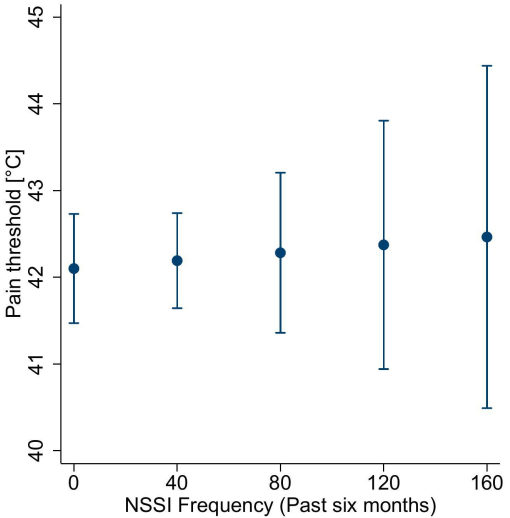
Declaration of interests

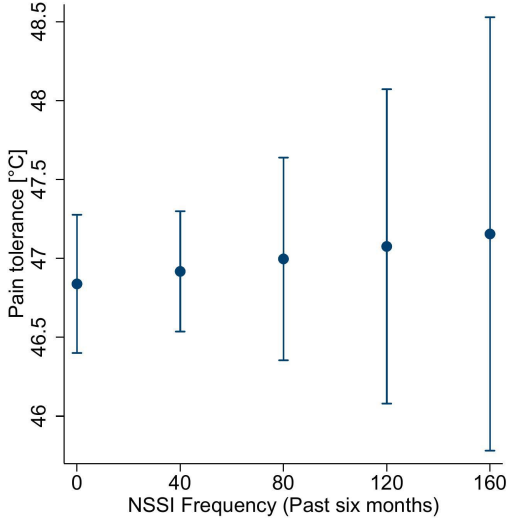
☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

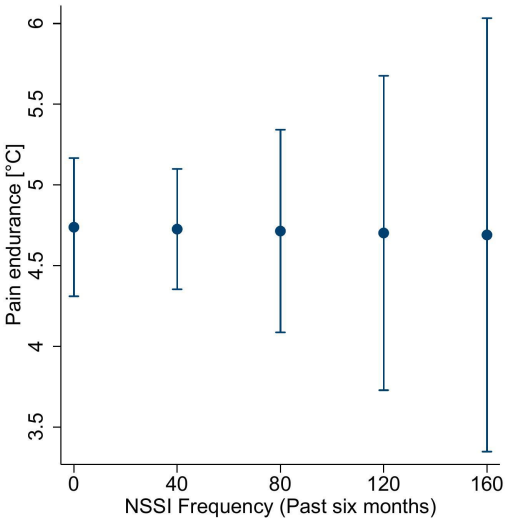
☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Dimensional NSSI severity is associated with altered physiological pain-response
- HPA axis response to pain increases with increasing NSSI severity
- Increased parasympathetic pain-response is likewise linked to NSSI severity
- Pain seems to induce a specific biological stress response in individuals with NSSI


Pain threshold [°C]
40
41
42
43
44
45
0
40
80
120
160
NSSI Frequency (Past six months)


Pain tolerance [°C]
46
46.5
47
47.5
48
48.5
0
40
80
120
160
NSSI Frequency (Past six months)


Pain endurance [°C]
3.5
4
4.5
5
5.5
6
0
40
80
120
160
NSSI Frequency (Past six months)

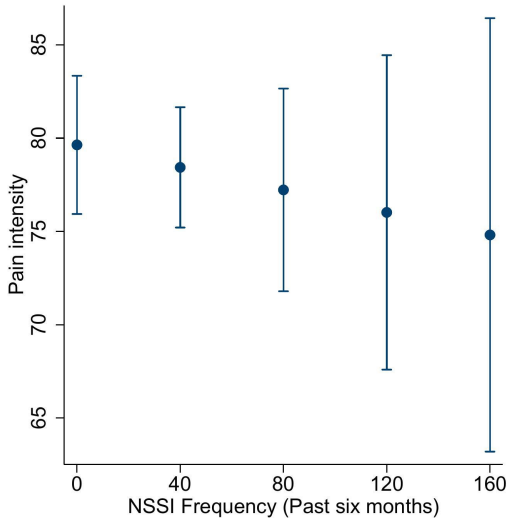
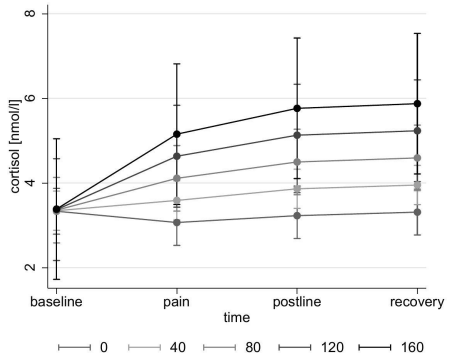
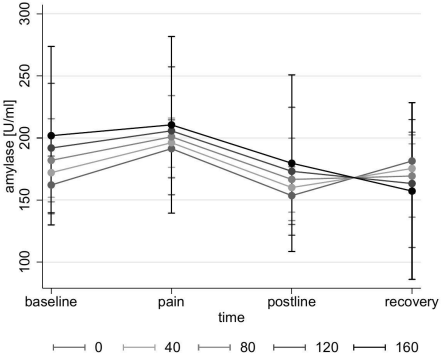
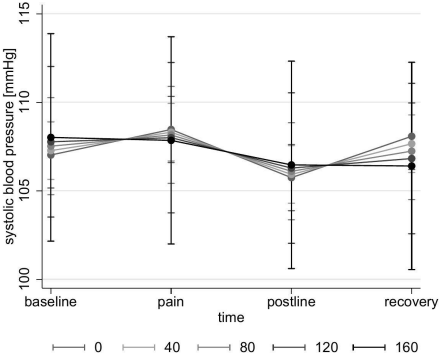
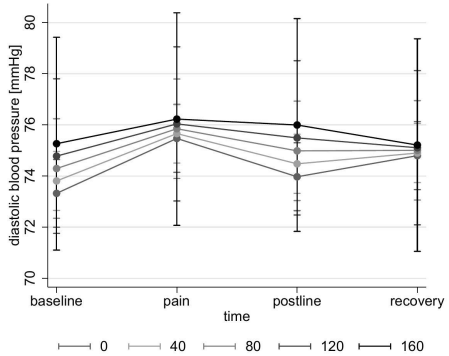

Pain intensity
65
70
75
80
85
0
40
80
120
160
NSSI Frequency (Past six months)

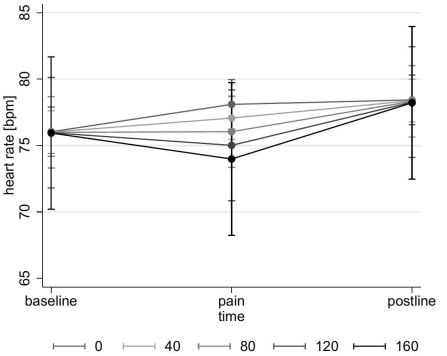
Figure 1


cortisol [nmol/l]
2
4
6
8
baseline
pain
postline
recovery
time
0
40
80
120
160


amylase [U/ml]
100
150
200
250
300
baseline
pain
postline
recovery
time
0
40
80
120
160


systolic blood pressure [mmHg]
100
105
110
115
baseline
pain
postline
recovery
time
0
40
80
120
160


diastolic blood pressure [mmHg]
70
72
74
76
78
80
baseline
pain
postline
recovery
time
0
40
80
120
160


heart rate [bpm]
65
70
75
80
85
baseline
pain
postline
time
0
40
80
120
160

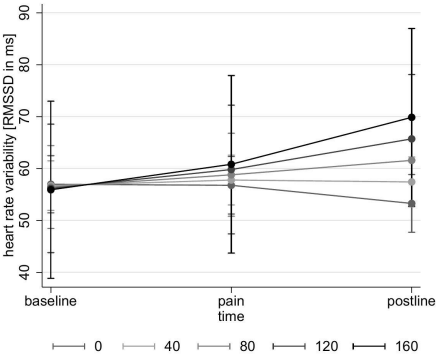

heart rate variability [RMSSD in ms]
40
50
60
70
80
90
baseline
pain
postline
time
0
40
80
120
160

Figure 2