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The role of non-suicidal self-injurious behavior on stress regulation in patients with current and remitted Borderline personality disorder

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
BPD	Borderline Personality Disorder
BPD-C	Patients with current Borderline Personality Disorder
BPD-R	Patients with remitted Borderline Personality Disorder
BSL	Borderline Symptom List
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DSM	Diagnostic and Statistical Manual of Mental Disorders
HC	Healthy control
HRV	Heart rate variability
IAPS	International Affective Picture System
ICD	International Classification of Diseases
IPDE	International Personality Disorder Examination
MIST	Montreal Imaging Stress Task
NSSI	Non-suicidal self-injury
PFC	Prefrontal cortex
PTSD	Posttraumatic stress disorder
SCID II	Structured Clinical Interview for Axis-II disorders
SSRI	Selective serotonin reuptake inhibitors

1 INTRODUCTION

1.1 Preface

With a lifetime prevalence of about 6 %, Borderline Personality Disorder (BPD) is a frequent psychiatric disorder and accounts for about 30 % of total cost for psychiatric inpatient care in Germany (Bohus & Schmahl 2007; Grant et al. 2008). BPD is a complex and serious mental disorder and patients show emotion dysregulation, impulsive aggression, repeated self-injury and chronic suicidal tendencies (Lieb et al. 2004). Dysfunctional behavior such as non-suicidal self-injury (NSSI) is a challenge for the social environment and therapy of BPD patients. NSSI is used by approximately 60-90% of patients with current BPD (DiClemente et al. 1991; Briere & Gil 1998; Zanarini et al. 2008). It has emotion and stress regulating functions (Niedtfeld & Schmahl 2009) and one of its most important motives is the reduction of aversive inner tension (Kleindienst et al. 2008). For NSSI, BPD patients mostly use tissue-damaging methods (Manca et al. 2014; Andover 2014).
One of the aims of the Clinical Research Unit “Mechanisms of Disturbed Emotion Processing in Borderline Personality Disorder” is to illuminate mechanisms and maintaining factors of non-suicidal self-injurious behavior. The first research paper investigates the role of tissue injury and nociception on stress regulation in patients with current BPD. The focus of the second research paper is on remitted BPD patients. Remission is a common phenomenon in the course of BPD (Gunderson et al. 2011; Zanarini et al. 2012; Zanarini et al. 2007; Zanarini et al. 2006; Zanarini et al. 2003). There is evidence that emotion dysregulation is still relevant for remitted BPD patients, whereas the mechanisms of NSSI in stress regulation seem to be of less importance (Zanarini et al. 2016; Gunderson et al. 2011). Still, it remains unclear whether the association of stress regulation with NSSI still exists in remitted BPD patients. The second research paper elaborates on this open question

1.2 Borderline Personality Disorder

1.2.1 Symptomatology

BPD is characterized by a pervasive pattern of instability in affect and emotion regulation, disturbed impulse control, disturbed cognition, instable interpersonal relationships as well as a disturbed self-image (Skodol et al. 2002; Lieb et al. 2004).

High levels of aversive inner tension are one of the cardinal symptoms of BPD (Bohus & Schmahl 2007). Compared to healthy controls, the experienced states of aversive inner tension are considerably longer and more intense among BPD patients. Moreover, BPD patients are unable to associate these states of arousal with a distinct emotion, e.g. anxiety, guilt or anger. Nevertheless, during such episodes BPD patients desire to terminate these states of aversive inner tension immediately (Stiglmayr et al. 2001). Further, BPD patients also tend to experience frequent and rapid mood changes within one day. Episodes of intense dysphoria, anxiety or irritability can rapidly turn into euthymia and vice versa (Lieb et al. 2004). In contrast to these episodes of high emotional reactivity, BPD patients also experience feelings of chronic emptiness and emotional numbness. Another aspect of affective disturbance among BPD patients is the occurrence of extreme and inappropriate anger and difficulties to control this anger, which often leads to fights (Lieb et al. 2004).

65 % of BPD patients suffer from severe dissociative symptoms such as depersonalization and derealization. These symptoms significantly correlate to states of high aversive inner tension (Stiglmayr et al. 2001). Further aspects of disturbed cognition also include psychotic-like symptoms, for instance delusions and hallucinations, as well as non-psychotic overvalued ideation, such as being a bad person (Lieb et al. 2004). In general, BPD patients have a predominantly negative self-concept and an inconsistent and unstable image or sense of themselves.

In terms of impulsivity, there are two types: deliberately physically self-harming and more general forms of impulsivity (Lieb et al. 2004). Forms of more general impulsivity include reckless driving, substance abuse, spending sprees, verbal outbursts and disordered eating. Suicide threats, gestures and behavior belong to the self-destructive type. Non-suicidal self-injurious behavior (NSSI) is classified as a type of deliberately physically self-harming impulsivity (Lieb et al. 2004), but it is also regarded to belong to affect dysregulation (Paris 2005).

Interpersonal relationships of BPD patients are characterized by the constant fear of abandonment on the one hand – on the other hand, close and intimate relationships can trigger feelings of fear, guilt and shame (Kernberg 1993). Therefore, BPD patients show ambiguous behavioral patterns including tremendous efforts to avoid real or imagined abandonment with clingy behavior and idealization of other persons, which can suddenly turn into degradation. Relationships are often instable, intense and include frequent arguments, breakups and rapprochements.

The characteristic symptoms of BPD are well described by the nine BPD criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013), see **Tab. 2** in section 1.2.2.

1.2.2 Diagnostic assessment

For the diagnosis of BPD, several criteria according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA 2013) or the International Classification of Diseases (ICD-10, WHO 2016) have to be fulfilled. Before a specific BPD diagnostic is made, all general criteria for a personality disorder have to be fulfilled. To diagnose a general personality disorder, an enduring pattern of inner experience and behavior that deviates from the expectations of the individual’s culture has to be manifested in at least two of the following areas: cognition, affectivity, interpersonal functioning and impulse control. Moreover, this pattern needs to be stable across several situations, is of long duration (onset can be traced back to adolescence or early adulthood), leads to suffering and impairment of the individual, and cannot be explained by any other mental disorder, substance abuse or any other medical condition (DSM-5, APA 2013).

For the diagnosis of BPD according to DSM-5, at least five out of nine diagnostic criteria have to be fulfilled (see **Tab. 2**). The International Personality Disorder Examination (IPDE; (Loranger 1999) is a semi-structured clinical interview which is often used to diagnose BPD. Alternatively, the Diagnostic Interview for DSM-IV Personality Disorders (DIPD-IV, Zanarini, M. C., Frankenburg et al. 1996), as well as the Structured Clinical Interview for Axis-II disorders (SCID II, Fydrich 1997) exist to diagnose BPD.

To assess Borderline severity, the ZAN-Scale (Zanarini 2003), the Borderline Personality Disorder Severity Index (BPDSI-IV, Giesen-Bloo et al. 2010), and the Borderline Symptom List (BSL, Bohus et al. 2001) are available.

Table 2: DSM-5 criteria for Borderline personality disorder (301.83, (F60.3); DSM-5, APA 2013)

Affective criteria
1. Affective instability due to a marked reactivity of mood.
2. Innappropriate, intense anger or difficulty controling anger.
3. Chronic feelings of emptiness.

Cognitive criteria
4. Transient, stress-related paranoid ideation or severe dissociative symptoms.
5. Identity disturabance: markedly and persistently unstable self-image or sense of self.

Behavioral criteria/ Impulsivity
6. Recurrent suicidal behavior, gestures, or threats, or self-injurious behavior.
7. Impulsivity in at least two areas that are potentially self-damaging (do not include suicidal or self-mutilating behavior).

Interpersonal criteria
8. Frantic efforts to avoid real or imagined abandoment (do not include suicidal or self-mutilating behavior).
9. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.

1.2.3 Epidemiology and course of BPD

The point prevalence of BPD is estimated to be about 2% in the general population (Torgersen et al. 2001; Stone 2000). The lifetime prevalence is higher with about 5-6% (Grant et al. 2008), since the prevalence is higher in young patients and decreases with increasing age. Among inpatients, BPD is significantly more frequent in women than in men (70% vs. 30%), however in the general population, the distribution between the sexes is equal (Grant et al. 2008). Female BPD patients rather tend to display self-destructive behavior, whereas male BPD patients often show aggressive behavior against others (Bohus & Schmahl 2007). Therefore, male BPD patients are more likely to come in contact with forensic or judiciary departments rather than psychiatric institutions (Bohus & Schmahl 2007). Since BPD is predominantly diagnosed in women, most studies, including the following two, only include female BPD patients.

The clinic and therefore the course of BPD are highly heterogeneous. Since only five out of nine criteria have to be met for the BPD diagnosis, this leads to 151 possible

combinations for the diagnosis (Skodol et al. 2002). There is variance in the onset of the disorder as well. In a group of patients, first symptoms such as suicidal behavior, affective instability, and NSSI can already be apparent during childhood or early adolescence, whereas other patients present first symptoms in their mid-twenties (Jerschke et al. 1998).
Further, a high number of comorbidities is characteristic for BPD. Patients with BPD often fulfill criteria for other personality disorders (Zanarini et al. 1998b). Moreover, anxiety disorders, mood disorders, and Posttraumatic Stress disorder (PTSD) are common among BPD patients (Zanarini et al. 1998a).
Suicidal behavior is the main risk factor for the course of the disorder. 60-70% of BPD patients commit suicide attempts (Gunderson 2009), leading to increased mortality. Up to 10 % of BPD patients commit suicide (Lieb et al. 2004; Oldham 2006). Consequently, in BPD the suicide rate is elevated, and about 50 times higher than in the general population (Lieb et al. 2004; Oldham 2006). The risk of suicide as well as the general impairment caused by BPD is higher at a younger age and decreases with increasing age (Gunderson et al. 2011).

1.2.4 Remission in BPD

Several studies suggest that remission and improvement of symptoms are common and stable in patients with BPD (Gunderson et al. 2011; Zanarini et al. 2012; Zanarini et al. 2007; Zanarini et al. 2006; Zanarini et al. 2003). A 16-year follow-up study reports that 99% of included BPD patients had two-year remissions and 78% had eight-year remissions. The same study showed that the longer a patient is remitted, the lower are the recurrence rates. After two-year remissions, recurrence rates were at 36% and after eight-year remission they were at 10% (Zanarini et al. 2012).
However, there is no standard definition of remission in BPD. Zanarini et al. define remission as no longer meeting five diagnostic criteria for BPD (Zanarini et al. 2008; Zanarini et al. 2012; Zanarini et al. 2003). Whereas for Gunderson et al. remission is defined as no longer meeting two or more BPD criteria for at least 12 months (Gunderson et al. 2011).

Additionally, it has been suggested that BPD symptoms are more fluid than remission and recurrence rates (Zanarini et al. 2016). There is some evidence that the most common 24 symptoms can be divided into two groups: into 12 more state-like or acute and 12 more trait-like or temperamental symptoms (Zanarini et al. 2007; Zanarini et al. 2016). State-like symptoms include areas of impulsivity (e.g. NSSI and suicide efforts) and active attempts to manage interpersonal difficulties (e.g. problems with demandingness/entitlement and serious treatment regressions). They resolve the most quickly. Trait-like symptoms contain affective symptoms such as areas of chronic dysphoria (e.g. anger and loneliness/emptiness), and interpersonal symptoms reflecting abandonment and dependency issues (e.g. intolerance of aloneness and counter-dependency problems). These symptoms seem to be rather chronic (Zanarini et al. 2007; Zanarini et al. 2016). In a different sample, these findings were not supported. Over a course of 10 years, a decline of all 9 BPD criteria was found, however, rates of decline of the 9 criteria were similar; the criteria, which were most prevalent at baseline, remained the most prevalent. Still, after 10 years, the most common criterion was affective instability, and the least common was NSSI and suicide attempts (Gunderson et al. 2011).
It appears that affective instability and dysregulated affect could still be relevant for remitted BPD patients, whereas the use of NSSI seems to be rather rare. After four

years, self-injurious behavior remitted in 91% of BPD patients, whereas affective instability only remitted in 73% of BPD patients (Zanarini et al. 2016).

1.3 Emotion regulation, non-suicidal self-injurious behavior, and pain

1.3.1 Emotion dysregulation in BPD

Emotion dysregulation is a key symptom of BPD (Skodol et al. 2002; Lieb et al. 2004; Linehan 1993). M. Linehan describes three central features of dysregulated emotion in BPD patients: high baseline negative emotional intensity, high emotional reactivity and slow return to baseline (Linehan 1993). Several studies were able to show high baseline negative intensity, such as high baseline levels of aversive inner tension, and slow return to baseline in BPD patients, but found no evidence for increased emotional reactivity (Kuo & Linehan 2009; Reitz et al. 2012; Rosenthal et al. 2008).

Emotion regulation in general is interpreted as a combination of processes that allow individuals to influence how and when they experience emotion, and how the emotion is then expressed (Gross 1998; Niedtfeld & Schmahl 2012). A working model for emotion regulation has been introduced by Ochsner & Gross (Ochsner & Gross 2007). They identified two main systems for the processing of emotion: A bottom-up and a top-down system. The bottom-up system is understood to create emotion as a response to stimuli with intrinsic or learned reinforcing properties, which encode either for pleasant or unpleasant outcomes or consequences. Neural correlates for the bottom-up system are located in subcortical areas. Furthermore, the amygdala encodes the affective component of stimuli (Ochsner & Gross 2007). Correlates for the top-down system are located in the prefrontal cortex (PFX) and the anterior cingulate cortex (ACC). Emotions created by bottom-up processes can be controlled and changed by top-down mechanisms relying on higher cognitive processes. Top-down beliefs can lead to reappraisal of the perceived stimulus and alter the way it is experienced (Ochsner & Gross 2007).

Relating findings in the field of neurobiology of BPD to the emotion regulation model of Ochsner and Gross, Niedtfeld and Schmahl presented evidence for a hypersensitive bottom-up system in combination with disturbed top-down control mechanisms (Niedtfeld & Schmahl, 2009). On a neural level, limbic hyperactivity (bottom-up-system) and a disturbed metabolism in the PFC (top-down-system) can be observed in BPD (Minzenberg et al. 2007; Herpertz et al. 2001; Niedtfeld, I., Schulze, L., Kirsch, P., Herpertz, S. C., Bohus, M., & Schmahl 2010; Schmahl et al. 2003; C. G. Schmahl et al. 2004). Limbic hyperactivity may be responsible for BPD patients being more sensitive to emotional stimuli – especially negative, whereas the disturbance of top-down control mechanisms may lead to a diminished function of appraisal systems (Niedtfeld & Schmahl, 2009). The authors conclude that these mechanisms contribute to the frequently observed affective instability in BPD, resulting in states of high levels of aversive inner tension (Niedtfeld & Schmahl 2009).

1.3.2 Non-suicidal self-injurious behavior

Non-suicidal self-injurious behavior (NSSI) is defined as the deliberate self-inflicted destruction of body tissue without suicidal intent (Nock 2010; Manca et al. 2014). It is a prominent issue in psychiatry of adolescents and young adults, but also notable in the general population (Resch et al. 2008; Brunner et al. 2007; Muehlenkamp et al. 2012; Manca et al. 2014). It is particularly frequent among patients with Borderline personality disorder (BPD). In BPD, 60-90% of patients inflict NSSI on themselves (DiClemente et al. 1991; Briere & Gil 1998; Zanarini et al. 2008).

For NSSI, BPD patients mostly use tissue-damaging methods. Among those, cutting is most frequent, followed by other methods such as excoriation, skin picking, and burning. Moreover cutting is the primarily used method in 80% of the cases if individuals practice more than one (Manca et al. 2014; Andover 2014).

The most important motive for NSSI in BPD patients is the reduction of stress and aversive inner tension. Other reasons include the reduction of unpleasant feelings, self-punishment, regaining of control, and regaining awareness of physical sensations (Briere & Gil 1998; Schoenleber et al. 2014; Chapman et al. 2006; Kleindienst et al. 2008; Paris et al. 1987; Andover 2014; Klonsky 2007). Prior to the act of NSSI, most patients experience a state of extreme aversive inner tension and afterwards feelings of relief and relaxation (Kleindienst et al. 2008; Chapman et al. 2006).
Corroborating these findings, the use of proxies for NSSI led to a reduction of arousal and negative affect. Self-injurers were asked to imagine a situation before NSSI and then they had to either imagine the act of self-injury or a control task (e.g. accidently cutting oneself with a kitchen knife). Before the imagined self-injury arousal levels were high and afterwards participants felt more relaxed and calm. After the imagination of the control task arousal did not decrease (Klonsky 2007; Haines et al. 1995; Brain et al. 1998).
In a laboratory setting, S. Reitz et al. used an incision (Kawamata et al. 2002; Pogatzki-Zahn et al. 2010) to capture something similar to the tissue injury, which is often implicated by NSSI (Reitz et al. 2012). In 14 BPD patients and 18 healthy controls, stress was induced via the Montreal Imaging Stress Task, (MIST; Dedovic et al. 2005) in combination with the presentation of pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). After successful stress induction either an incision stimulus or a control stimulus (sham) was applied on the right volar forearm. Each participant received both stimuli on consecutive days. For the incision stimulus a 4 mm long and 5-7 mm deep incision through skin, fascia and muscle was performed. For sham, the forearm was slightly touched with the blunt back of a scalpel. In the group of BPD patients arousal levels were significantly lower after the incision compared to the sham stimulus 15, 20 and 30 minutes after stimulus application. Directly after the application of the incision stimulus, there was a significantly stronger decrease of heart rate in BPD patients compared to healthy controls (Reitz et al. 2012). The stress-reducing effects of incision could be replicated in a fMRI-study with a similar setup (Reitz et al. 2015). After the incision stimulus BPD patients showed a greater decrease of arousal compared to healthy controls, whereas after the sham condition there was a stronger decrease of arousal in the group of healthy controls. (For neural findings of this study, see 1.3.4)

1.3.3 Pain sensitivity in BPD

The general process of pain processing can be divided into three components: A sensory-discriminative, an affective-motivational and a cognitive-evaluative component (Melzack & Casey 1968). The sensory-discriminative component is fundamental for localization, intensity, and quality of the stimulus (nociception). The affective-motivational component is important for the emotional evaluation of pain. These two components are influenced by the cognitive-evaluative component, which compares a current pain stimulus with experiences from the long-term memory and thereby creates a general evaluation of the pain stimulus. Neural correlates for the sensory-discriminative component are the lateral thalamic nuclei projecting to the primary and secondary somatosensory cortices. Medial thalamic nuclei projecting to the insula and anterior cingulate cortex (ACC) correlate to the affective-motivational component (Treede et al. 1999).

Among BPD patients, reduced pain sensitivity is a robust finding. Previous studies have used the cold-pressor test (Bohus et al. 2000), laser-evoked pain potentials (C. Schmahl et al. 2004), electric pain stimulation (Ludaescher et al. 2007), and punctate probes (Magerl et al. 2012). Furthermore, 50-70 % of BPD patients report that they feel no or only reduced pain during acts of non-suicidal self-injurious behavior (NSSI) (Bohus et al. 2000). Neither for laser-evoked potentials nor for thermal stimuli an impairment of the sensory-discriminative component was found (C. Schmahl et al. 2004; Bekrater-Bodmann et al. 2015). However, there is evidence that in BPD patients the aspect of unpleasantness of pain is reduced and it has been suggested that in BPD patients the affective and sensory-discriminative dimensions of pain are uncoupled (Magerl et al. 2012).
Moreover, it has been suggested that pain insensitivity in BPD patients is closely linked to NSSI. In patients with current BPD who had ceased using NSSI for at least six months, pain perception normalized (Ludäscher et al. 2009).
Furthermore, there is evidence that pain sensitivity is negatively correlated with severity of BPD (Ludäscher et al. 2009). In line with these findings, partially normalized pain thresholds for remitted BPD patients were found (Bekrater-Bodmann et al. 2015). The study showed reduced pain sensitivity in patients with current BPD for cold and heat pain, whereas for remitted patients still elevated cold pain thresholds, but normalized heat pain thresholds were found.

1.3.4 Non-suicidal self-injurious behavior and pain to regulate emotion

Affective regulation, in form of escape from unwanted emotions, thoughts, or other experiences, is believed to be the strongest maintaining factor of NSSI (Klonsky 2007; Chapman et al. 2006).
Three different hypotheses to explain the mechanisms of tension relief after NSSI have been introduced: the opioid hypothesis, the self-punishment hypothesis, and the distraction hypothesis (Chapman et al. 2006): The opioid hypothesis proposes that NSSI leads to an increase of endogenous opioids thereby creating analgesia, which relieves emotional distress. The self-punishment hypothesis states that NSSI is used as self-punishment to confirm negative-self-concepts, which may lead to a reduction of aversive inner tension. However, evidence for these theories is sparse, since only few empirical studies exist (Chapman et al. 2006). The distraction hypothesis suggests that NSSI is a physical stimulation that distracts from emotional arousal, causing an attentional shift from emotional pain towards physical pain (Chapman et al. 2006).
Besides being a distraction, the application of painful stimuli in BPD patients leads to a deactivation of the amygdala and the perigenual ACC, giving another possible explanation for the relaxing effect of pain (Schmahl et al. 2006). Moreover, painful

stimuli were followed by a greater activation of prefrontal regions in BPD patients compared to healthy controls, which might be related to a disturbed evaluation of painful stimuli (Niedtfeld & Schmahl 2009; Schmahl et al. 2006).
Niedtfeld et al. suggested that the attentional shift could also be of a more general nature and might not be specific for BPD or pain. In both BPD patients and healthy controls, they found reduced limbic activation not only after painful stimuli (heat pain), but also after non-nociceptive sensory stimulation (warm temperature) (Niedtfeld, I., Schulze, L., Kirsch, P., Herpertz, S. C., Bohus, M., & Schmahl 2010). Since the deactivation of the hyperactivated amygdala was not only found after painful stimuli among BPD patients, it could not be explained why BPD patients use NSSI to reduce states of aversive inner tension. The authors speculated that due to the higher stress levels experienced before acts of NSSI, only painful stimuli are sufficient to create an attentional shift (Niedtfeld, I., Schulze, L., Kirsch, P., Herpertz, S. C., Bohus, M., & Schmahl 2010). Corroborating this hypothesis, further analyses showed that in BPD patients, pain only led to increased connectivity between limbic regions and prefrontal control areas during states of increased emotional reactivity. In healthy controls this pattern was only observed after the application of non-nociceptive stimuli. The authors conclude that pain in BPD leads to enhanced inhibition of limbic regions by prefrontal control areas. Therefore painful stimuli seem to improve emotion regulatory processes in BPD patients, which may be caused by a combination of an attentional distraction by pain and by a different appraisal of painful stimuli (Niedtfeld et al. 2012).
In line with these findings, on a neurobiological level the tissue-injuring incision stimulus was followed by reduced amygdala activity in BPD patients. The opposite pattern was observed in the control group (Reitz et al. 2015). Further, enhanced coupling between the amygdala and prefrontal regions was found after incision compared to a tactile, non-nociceptive stimulus in current BPD patients. For healthy controls modulatory coupling was only detected after the tactile stimulus (Reitz et al. 2015). Increased connectivity between limbic and prefrontal areas has been suggested to correlate to the downregulation of emotional states and the recovery from stress (Veer et al. 2011). Reitz et al. speculated that these regulating processes are disturbed by the incision stimulus in HCs, whereas in current BPD patient they are promoted by incision (Reitz et al. 2015). Furthermore, the authors found a reduced heart rate variability (HRV) in BPD patients (Reitz et al. 2015). It has been suggested that reduced HRV indexes are associated with dysregulated affective styles (Beauchaine 2001). Reitz et al. proposed that reduced HRV in BPD patients reveals a high sympathetic tone and reduced resources for stress adaption (Reitz et al. 2015).

In short, NSSI can be understood as dysfunctional construct to cope with dysregulated affect. The function of NSSI may be to compensate for deficient cognitive control mechanisms in emotion regulation. The tension relief and relaxation caused by NSSI negatively reinforce and thereby maintain this dysfunctional behavior. Furthermore, NSSI may lead to an altered appraisal of pain. Taken together, the combination of disturbed emotion regulation and dysfunctional NSSI creates a vicious circle.

1.4 Research Questions

Emotion dysregulation is one of the key symptoms of BPD (Skodol et al. 2002; Lieb et al. 2004; Linehan 1993). BPD patients show affective instability and often suffer from states of elevated aversive inner tension (Stiglmayr et al. 2001). In this context, the use of NSSI plays a very important role as it is primarily used to create a tension relief (Kleindienst et al. 2008). Previous laboratory studies have found a tension-reducing effect of tissue injury after the application of an incision in current BPD patients (Reitz et al. 2012; Reitz et al. 2015). However, it is still unclear whether stress reduction induced by incision is based on the effect of tissue injury, or the effect of nociception or pain. The first research paper elaborates on this open question.

The role of NSSI in context with affect regulation in patients with remitted BPD has not been investigated so far. Even though remission is a common phenomenon, we do not know much about remitted BPD patients. After remission of BPD, affective instability and dysregulated affect still seem to be apparent. The use of NSSI, however, is rather rare (Gunderson et al. 2011; Zanarini et al. 2016). It remains unclear whether the association of stress regulation with pain perception still exists in remitted BPD patients. It appears likely that affective instability and dysregulated affect are still relevant for remitted BPD patients, whereas the mechanisms of NSSI in stress regulation seem to be of less importance. Therefore, in the second research paper we focus on remitted BPD patients.

In the first research paper "*The role of nociceptive input and tissue injury on stress regulation in Borderline Personality Disorder*", we investigated whether painful tissue injury leads to a stronger stress reduction than a sole non-invasive nociceptive stimulus.

In this study, 57 patients with current BPD and 60 healthy controls (HCs) received either an incision, or a non-tissue-injuring mechanical nociceptive stimulus ("blade") typically perceived as painful, or a non-nociceptive tactile sham stimulus (blunt end of scalpel). Before the application of the stimulus, stress was induced through repetitive mental arithmetics of increasing difficulty including negative feedbacks. For stress assessment, subjective and objective parameters were measured.

We hypothesized that patients with BPD (Ia) will show a greater reduction of subjective (arousal and urge for NSSI) and objective (heart rate) stress parameters directly after incision compared to blade application. Furthermore, we assumed that as an immediate effect, (Ib) the application of the blade stimulus will lead to a stronger stress reduction than the application of a sham stimulus. In addition, we sought to replicate the findings that (Ic) the incision stimulus, in comparison to a sham stimulus, leads to a greater decrease of stress directly after the stimulus application (Reitz et al. 2012; Reitz et al. 2015). In addition, we tested whether the application of incision and blade is associated with a stress reduction 30 minutes after stimulus application (intermediate effects) (II). We further investigated whether the magnitude of the effects of incision and blade depend on the diagnosis (III).

The second research paper "*Stress reactivity and pain-mediated stress regulation in remitted patients with Borderline Personality Disorder*" aimed at investigating to what extent remitted BPD patients experience states of high aversive inner tension compared to patients with current BPD and healthy controls. Furthermore, we investigated the open question whether remitted patients are still able to regulate emotions with nociceptive experiences.

For this, subjective and objective stress parameters were assessed in 30 remitted BPD patients, 30 patients with current BPD, and 30 healthy controls. After a stress induction, a tissue-injuring incision, a non-invasive pain stimulus or a non-nociceptive tactile sham stimulus was applied on the right volar forearm.
We hypothesized that remitted BPD patients show lower stress levels than patients with current BPD, but still higher stress levels than healthy controls (I). In remitted BPD patients, we suspected a smaller increase of stress parameters compared to current BPD patients, but a smaller increase compared to healthy controls (II). Furthermore, we hypothesized that nociceptive stimuli will lead to a greater stress reduction in current BPD patients compared to remitted BPD patients and we tested if remitted BPD patients show a different response to nociceptive stimuli than healthy controls (III).

2 THE ROLE OF NOCICEPTIVE INPUT AND TISSUE INJURY ON STRESS REGULATION IN BORDERLINE PERSONALITY DISORDER

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2.2 Abstract

Approximately 60-90% of patients with Borderline Personality Disorder (BPD) show non- suicidal self-injurious behavior (NSSI) with cutting being the most frequently applied method. One of NSSI's functions is to reduce aversive tension. Previous studies have found a tension-reducing effect of painful tissue injury by an incision. It is still unclear whether this effect is based on the effect of tissue injury or the effect of pain experience, or both. The aim of this study was to determine whether tissue injury leads to a stronger stress reduction than a sole pain stimulus in patients with BPD. After stress induction, 57 BPD patients and 60 healthy controls (HCs) received either an incision or a non-tissue-injuring mechanical nociceptive stimulus ("blade") typically perceived as painful, or a non-nociceptive tactile sham stimulus (blunt end of scalpel). Participants were unaware of which procedure was applied. For stress assessment, subjective and objective parameters were measured. As immediate response to the stimulus application, we found greater stress reduction after both painful stimuli (incision and blade) in BPD patients, but no difference in stress decrease between the tissue-injuring incision and the non-tissue-injuring pain stimulus ("blade"). Compared to HCs, incision and blade were followed by greater immediate decrease of arousal in BPD patients. Our findings confirm, that among BPD patients the nociceptive input leads to stress reduction. In contrast, the impact of tissue damage on stress reduction was relatively small. In addition, the results suggest that painful stimuli lead to a greater stress reduction in BPD patients compared to HCs.

2.2.1 Short summary

The tension relieving effects of non-suicidal self-injurious behavior in BPD patients resulted from nociceptive processes.

2.3 Introduction

Non-suicidal self-injurious behavior (NSSI) is defined as the deliberate self-inflicted destruction of body tissue without suicidal intent (Nock 2010; Manca et al. 2014). It is a prominent issue in psychiatry of adolescents and young adults, but also notable in the general population (Resch et al. 2008; Brunner et al. 2007; Muehlenkamp et al. 2012; Manca et al. 2014). It is particularly frequent among patients with Borderline Personality Disorder (BPD). In BPD, 60-90% of patients use NSSI (DiClemente et al. 1991; Briere & Gil 1998; Zanarini et al. 2008).

For NSSI, BPD patients mostly use tissue-damaging methods. Among those, cutting is most frequent, followed by other methods such as excoriation, skin picking, and burning. Moreover, cutting is the primarily used method in 80% of the cases if individuals practice more than one (Manca et al. 2014; Andover 2014). The most important motive for NSSI is the reduction of stress and aversive inner tension. Other reasons include the reduction of unpleasant feelings, self-punishment, regaining of control, and regaining awareness of physical sensations (Briere & Gil 1998; Schoenleber et al. 2014; Chapman et al. 2006; Kleindienst et al. 2008; Paris et al. 1987; Andover 2014; Klonsky 2007).

Prior to the act of NSSI, most patients experience a state of extreme aversive inner tension and afterwards feelings of relief and relaxation (Kleindienst et al. 2008; Chapman et al. 2006). Two of our previous studies (Reitz et al. 2012; Reitz et al. 2015) were able to show this phenomenon in a laboratory setting where an incision was performed on the volar forearm after a stress induction (Kawamata et al. 2002; Pogatzki-Zahn et al. 2010). The incision led to an immediate decrease of subjective and objective stress parameters (rating of aversive tension and heart rate) in patients with BPD (Reitz et al. 2015; Reitz et al. 2012). On a neurobiological level, incision was followed by reduced amygdala activity and improved amygdala-prefrontal connectivity in BPD patients. This was interpreted as NSSI being a dysfunctional attempt to cope with dysregulated affect (Reitz et al. 2015).

However, it is still unclear whether stress reduction induced by incision is based on the effect of tissue injury or the effect of nociception or pain. The current study was conducted to elaborate on this open question by investigating whether painful tissue injury (incision) leads to a stronger stress reduction than a sole non-invasive nociceptive stimulus ("blade"). Accordingly, we hypothesized that patients with BPD (Ia) will show a greater reduction of subjective (arousal and urge for NSSI) and objective (heart rate) stress parameters directly after incision compared to blade application. Furthermore, we assumed that as an immediate effect, (Ib) the application of the blade stimulus will lead to a stronger stress reduction than the application of a sham stimulus. In addition, we sought to replicate the findings that (Ic) the incision stimulus, in comparison to a sham stimulus, leads to a greater decrease of stress directly after the stimulus application (Reitz et al. 2012; Reitz et al. 2015). Besides, we tested whether the application of incision and blade is associated with a stress reduction 30 minutes after stimulus application (intermediate effects) (II). We further investigated whether the magnitude of the effects of incision and blade depends on the diagnosis (III).

2.4 Method and Materials

2.4.1 Participants

57 BPD patients and 60 healthy controls (HC) participated in this study. All participants were female and between 18 and 45 years old. There was no significant difference in age between both groups (BPD: 27.98 ± 7.86, HC: 27.53 ± 7.06, p = 0.80).
Patients with BPD had to fulfill at least five criteria for BPD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013), which were determined via the International Personality Disorder Examination (IPDE) (Loranger 1999). Psychiatric comorbidities were assessed using the Structured Clinical Interview for Axis-I disorders (SCID-I) (First et al. 1995). We only included patients who had shown NSSI with skin lesions at least once in the six months prior to study. We used a custom-made questionnaire including 13 different forms of NSSI to assess NSSI behavior. The frequency and form of NSSI during the last month and the frequency of NSSI during the last year were also evaluated. For socio-demographic data and NSSI behavior see Tab. 1.
For BPD patients, exclusion criteria comprised of a lifetime diagnosis of bipolar I disorder or schizophrenia, mental retardation, a history of severe neurological dysfunction, the presence of severe psychopathology that required immediate treatment, and a current (past month) diagnosis of substance use disorder. The intake of psychotropic medication with the exception of selective serotonin or norepinephrine reuptake inhibitors (SSRI/SNRI) was another exclusion criterion. In behalf of the high prevalence of psychotropic medication among BPD patients, especially SSRI/SNRI, the complete exclusion would have led to a biased sample. For current medication see Tab. 1. Healthy controls were screened using the IPDE and SCID-I as well. They were excluded if they met the diagnosis for any past or present psychiatric disorder or for substance abuse. Due to the pain assessments in this study, BPD patients and HCs with moderate to severe chronic pain and use of pain medication in the two weeks prior to participation were also excluded. Psychologists with experience in psychometric assessments performed all interviews and diagnostic procedures.
All participants gave their written consent after having received a verbal and written explanation of the task and no further questions remained. The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty Mannheim/University of Heidelberg (application no. 2008-234N-MA).

Table 1: Demographic Data and Psychiatric Comorbidities

	BPD	HC	*p*
Number	57	60	
Age (years)			*p*= 0.80[1]
Mean (standard deviation)	27.98 (7.86)	27.53 (7.06)	
Educational background			*p*< 0.01[2]
University-entrance diploma	32 (56%)	49 (82%)	
Secondary school certificate	25 (44%)	11 (18%)	

[1]Mann-Whitney-U-Test, [2]Fisher's exact test

Table 1: Demographic Data and Psychiatric Comorbidities (continued)

	BPD	HC	*p*
Psychiatric comorbidities			
Mood disorder, current	14 (25%)	/	
Mood disorder, lifetime	50 (88%)	/	
Substance abuse, lifetime	21 (37%)	/	
Substance dependence, lifetime	15 (26%)	/	
Anxiety disorder, current	25 (44%)	/	
Anxiety disorder, lifetime	30 (57%)	/	
Posttraumatic stress disorder, current	25 (44%)	/	
Posttraumatic stress disorder, lifetime	28 (49%)	/	
Eating disorder, current	18 (32%)	/	
Eating disorder, lifetime	29 (51%)	/	
Frequency of NSSI in the month of study participation			
Average frequency	14.44 (17.66)	/	
No NSSI in the month of study	14 (25%)	60 (100%)	
1-5 times	10 (18%)	/	
6-10 times	6 (11%)	/	
11-20 times	9 (16%)	/	
21-30 times	7 (12%)	/	
More than 30 times	11 (19%)	/	
Unknown	2 (4%)	/	
Used methods of NSSI in the last year			
Cutting	43 (75%)	/	
Scratching to the point of bleeding	34 (60%)	/	
Skin-picking	12 (21%)	/	
Self hitting	25 (44%)	/	
Burning/Scalding	16 (28%)	/	
Sticking needles or nails into skin	11 (19%)	/	
Hair tearing	8 (14%)	/	
Banging head against wall	17 (30%)	/	
Unknown	/	/	

Table 1: Demographic Data and Psychiatric Comorbidities (continued)

	BPD	HC	*p-value*
Medication			
SSRI	10 (18%)	/	
Thyroid hormones	9 (16%)	6 (10%)	
Oral contraceptives	7 (12%)	17 (28%)	
Blood pressure lowering agents	3 (7%)	2 (3%)	
Lipid lowering agents	/	1 (2%)	
Proton pump inhibitors	2 (4%)	/	
Anti-diabetic medication	1 (2%)	/	
Asthma medication	2 (4%)	1 (2%)	
Antihistamine	1 (2%)	/	

2.4.2 Procedure

Stress induction

For stress induction, a version of the Montreal Imaging Stress Task (MIST) (Dedovic et al. 2005) was used, which was modified for Microsoft Windows. In this program, participants have to solve arithmetic problems. Apart from the challenge of the arithmetics itself, it creates disappointment by using an algorithm that contributes to a high percentage of incorrect answers. The software combines three different modes (rest, control, and experimental). During two of these modes, participants have to calculate - during “control” without, and during “experimental” with a time limit. During rest, no calculations have to be performed. If the participants answer too many problems correctly, the software reduces the time limit and increases the level of difficulty. Additionally, the program shows that the performance of the participant is constantly below a fictitious average. We used the control mode to let the participants practice the program for 3 minutes before starting the actual program.

After a 3.5 minute baseline, participants had to complete six MIST runs (MIST1-MIST6). Each run lasted 3.5 minutes and contained all three modes (rest, control, experimental). To add a social stress component, the investigator reminded the participants between the second and the third run that the study depended on a good performance and that at least an average level should be reached.

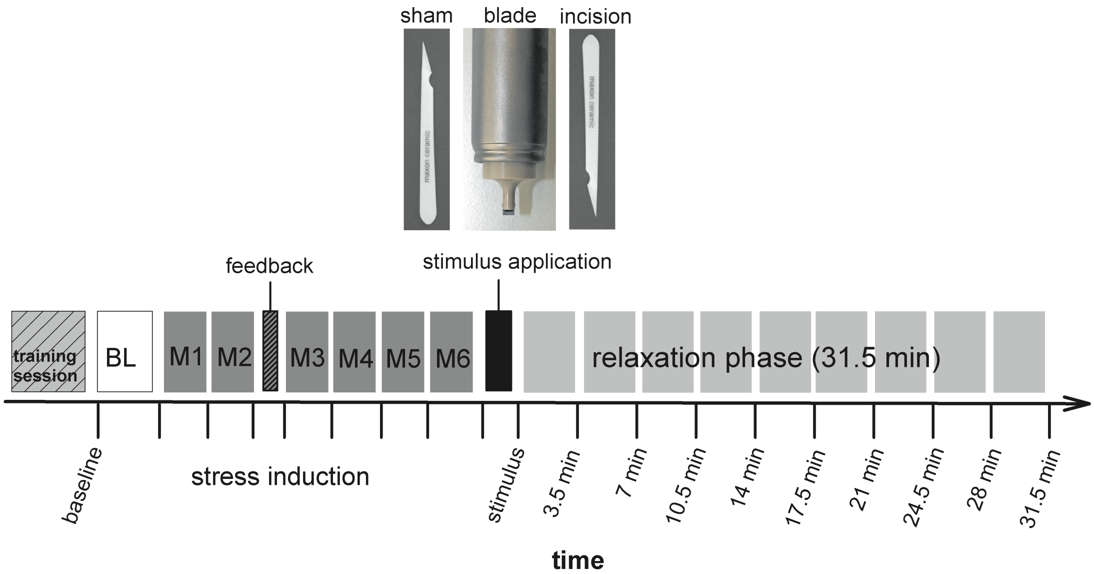
Nociceptive and control stimuli

After stress induction, the participants were asked to put their right forearm behind a shield screen. After disinfection with alcohol (70%), balanced across groups either (1) a small incision was made (nociceptive with tissue injury), or (2) a blade stimulus not penetrating the skin (nociceptive without injury), or (3) a sham stimulus (non-nociceptive; tactile) was applied. The incision stimulus was conducted according to the standardized incision protocol (Kawamata et al. 2002). With a sterile scalpel, a 4 mm long and 5-7 mm deep incision through skin, fascia and muscle was performed. The small incision was well tolerated by all participants and if there was bleeding, it stopped in less than one minute. The blade stimulator consisted of a blunt blade (tip dimensions 4.0 x 0.1 mm) attached to a plastic cylinder mounted with a weight that

moves freely within a steel tube. With repeated application, exertion of the same force is ensured (4096 mN; MRC Systems GmbH, Heidelberg, Germany). This stimulus has recently been introduced as a surrogate model for sharp mechanical pain and yielded subjective pain ratings similar to an incision in healthy volunteers (Shabes et al. 2016). The blade stimulus was applied for seven seconds. For the sham stimulus, the forearm was touched with the blunt back of the scalpel, which evoked a slight sensation of touch.
Participants were informed that they would receive one of the three stimuli behind a shield screen so that they would not know which stimulus to expect until the application itself. They were clearly informed about each stimulus and possible consequences (e.g. bleeding in case the incision was applied).
The stimulus application was followed by a 31.5 minute relaxation phase.

Dependent variables
As a subjective parameter of stress, participants rated their current level of arousal using a modified version of the Self-Assessment Manikins (SAM) (Bradley & Lang 1994). The original SAM is a picture-oriented instrument to assess pleasure, arousal and dominance. For this study we only used the arousal dimension, which ranges from a relaxed, sleepy figure to an excited, wide-eyed figure (Bradley & Lang 1994). Participants rated arousal on this visual analogue scale from 1 (relaxed) to 9 (under extreme tension) at 19 time points: before and after baseline, seven times during stress induction, and ten times after stimulus application (directly after the application (T0), 3.5 min (T1), 7 min (T2), 10.5 min (T3), 14 min (T4), 17.5 min (T5), 21 min (T6), 24.5 min (T7), 28 min (T8) and 31.5 min (T9) after stimulus application). In addition, participants rated the urge for NSSI and pain intensity on a visual scale from 0 (none) to 10 (extreme) at the same time points.
In addition to subjective stress parameters, we assed heart rate as an objective stress parameter. For the continuous recording of heart rate, we used ECG recording amplified with a Biosemi Active Two AD-Box (Honsbeek, Kuiper & Van Rijn, Biosemi B.V., Amsterdam, The Netherlands) and reusable flat active Ag-AgCl electrodes, digitized at 2 kHz. Heart rate was analyzed at 28 time points: during baseline, 18 times during stress induction (for each run: rest, control and experimental), and at the corresponding time points during the relaxation period T1-T9 after stimulus application aggregating across the time between each two points. Dissociative symptoms were assessed using the Dissociation-Tension-Scale (Dissoziations-Spannungs-Skala, DSS-acute) before and after the experiment (Stiglmayr, C. E. Braakmann et al. 2003). For study procedure see Fig. 1.

Figure 1: Study design



After stress induction with the MIST program (M1-M6), the sham, blade or incision condition was applied to the right volar forearm. The stimulus was followed by a 31.5 min relaxation phase. Arousal, urge for NSSI, pain intensity and heart rate were assessed throughout the experiment.

2.4.3 Data analysis

For statistical analysis, SPSS (Version 22.0.0.0) was used. The level of significance was set to $p \leq 0.05$ (two-tailed). As effect sizes, Cohen's d was reported for t-test analyses, Cohen's f2 for analyses of variance (ANOVAs) and r for hierarchical linear models (HLM)(Rosenthal 1994).
We considered the following variables: 1) subjective level of arousal (SAM ratings), 2) urge for NSSI (ratings), 3) heart rate and 4) pain (ratings). Because of technical problems, heart rate data of only 55 patients with BPD (19 in the sham, 18 in the blade and 18 in the incision group) and 58 HCs (20 in the sham, 20 in the blade and 18 in the incision group) could be analyzed.

Manipulation Check
To test whether stress induction using the MIST was successful, a 2*2 repeated measure analysis of variance (rm-ANOVA) with Group (HC & BPD) as between-factor and Time (1. (mean-)baseline and 2. MIST6) as within-factor was calculated, for both arousal ratings and heart rate. Since the repeated measure factor Time included only two levels, the sphericity assumption was always met and no correction for the degrees of freedom had to be implemented. For urge for NSSI, a paired t-test for mean-baseline and MIST6 was conducted for the BPD group.

Pain intensity of the stimulus
To analyze group differences in pain ratings, a univariate ANOVA, with Group (BPD and HC) and Condition (sham, blade and incision) as fixed factors, was computed for the time point directly after stimulus application (T0). In addition, post hoc t-tests for stimulus comparison within one group and between groups were calculated at the same time point. If the assumption of homogeneous variances was violated,

Satterthwaite's correction of the degrees of freedom was carried out (Satterthwaite 1946).

Dissociative symptoms
Differences in DSS-ratings between the two time points (before and after the experiment) and between BPD patients and HCs were calculated with Mann-Whitney-U tests. In the BPD group, Spearman correlations for the pain ratings of the nociceptive stimuli (blade and incision) with the mean DSS score were computed for both time points.

Hypotheses testing
To test our hypotheses, we used hierarchical linear models (HLM) to analyze repeatedly assessed continuous outcome data of arousal, urge for NSSI, and heart rate. The decline over time started with the expected peak levels at the end of stress induction (MIST6), which was modeled by random slope and intercept models. For immediate effects (Hypothesis I), only the first time point directly after stimulus application was considered (T0 for arousal and urge for NSSI, and T1 for heart rate respectively). Depending on the hypothesis, the following conditions among the group of BPD patients were used: Ia) incision vs. blade, Ib) blade vs. sham, and Ic) incision vs. sham. In addition, we tested whether an overall effect of the stimulus can be found. For intermediate effects (Hypothesis II), the same calculations as for hypothesis I, including all time points were conducted (T0 – T9 for arousal and urge for NSSI, and T1 – T9 for heart rate).
To test whether the effects depend on the diagnosis (Hypothesis III), the same tests were carried out for the HC group. Additionally, both the effects of Condition and Group (HC vs. BPD) were taken into account. The modeling of differential effects of Condition and Group was realized by introducing both two-way and three-way interaction terms. The estimations in the linear hierarchical models were computed as maximum likelihood estimators using the MIXED procedure in SPSS.

2.5 Results

2.5.1 Manipulation Check

For arousal (SAM), the 2*2 rm-ANOVA revealed a significant increase over time in both groups ($F_{1,115}$=107.48, p< 0.001, f^2= 0.93). Patients with BPD showed significantly higher levels of arousal than healthy controls ($F_{1,115}$= 47.09, p< 0.001, f^2= 0.41). However, the stress test did not affect the two groups in a different manner, since there was no Time*Group interaction ($F_{1,115}$= 1.55, p= 0.22, f^2= 0.01).
Heart rate increased during stress induction in both groups. The 2*2 rm-ANOVA revealed a significant main effect for Time ($F_{1,111}$= 52.15, p< 0.001, f^2= 0.48).
For the evaluation of urge for NSSI, only the group of BPD patients was considered since the group of healthy controls did not present an urge for NSSI at any time. The paired t-test revealed a significant increase of urge for NSSI during stress induction (urge at baseline: 1.67 (2.05), urge after stress induction: 3.23 (2.80), t= -5.57, df= 56, p< 0.001, d= -1.48).

2.5.2 Pain ratings of the stimulus

The univariate ANOVA conducted to evaluate the pain ratings revealed a significant difference in the intensity of pain between the three stimuli incision, blade, and sham

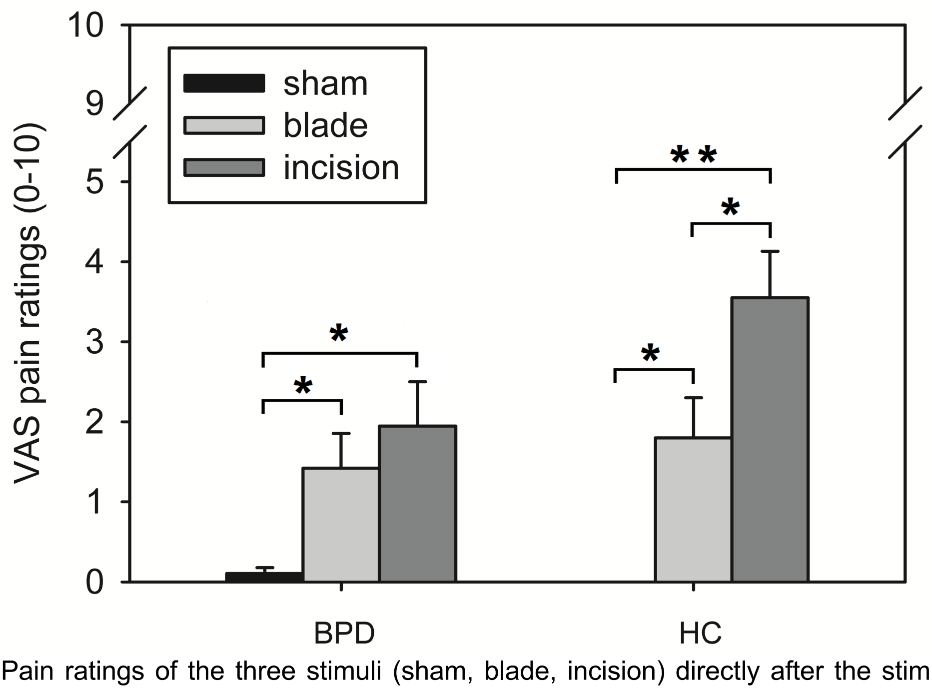
($F_{2,111}$= 20.04, p< 0.001, f^2= 0.36). The difference in pain ratings between BPD patients and healthy controls was not statistically significant ($F_{1,111}$= 3.21, p= 0.08, f^2= 0.03). The Group*Stimulus interaction was not significant ($F_{4,111}$= 1.01, p= 0.41, f^2= 0.03), indicating BPD patients and HCs did not respond to the three stimuli in a different way.

As depicted in Fig. 2, post hoc t-test showed that BPD patients experienced no significant difference in pain intensity between the incision and blade stimulus (t= 0.75, df= 36 p= 0.46, d= 0.25). Both incision and blade were rated significantly more painful than the sham stimulus (incision vs. sham: t= 3.28, df= 36, p< 0.01, d= 1.10; blade vs. sham: t= 2.99, df=36, p< 0.01, d= 1.00).

In HCs, post hoc t-tests showed a significant difference between incision and sham and blade and sham as well (incision vs. sham: t= 6.09, df= 19, p< 0.001, d= 2.80; blade vs. sham: t= 3.60, df= 19, p< 0.01, d= 1.65). Also, incision was rated to be more painful than blade (t= 2.75, df= 38, p< 0.05, d= 0.74).

Comparing the two groups, there was no significant difference in pain intensity ratings for the conditions (sham: t= -1.46 p= 0.16, df= 18, d= -0.69; blade: t= 0.57, df= 37, p= 0.57, d= 0.19; incision: t= 1.99, df= 37, p= 0.05, d= 0.65).

Figure 2: Pain ratings



Pain ratings of the three stimuli (sham, blade, incision) directly after the stimulus application among BPD patients and HCs with standard error of the mean. Post-hoc t-tests: * p < 0.05, ** p < 0.001

2.5.3 Dissociative Symptoms

DSS-scores were significantly higher in the BPD group both before (BPD: 1.75 (0.96), HC: 1.02 (0.01), p< 0.001) and after the experiment (BPD: 1.98 (1.12), HC: 1.01 (0.03), p< 0.001). BPD patients had higher DSS-scores after than before the experiment (p< 0.01); in the HC group, there was no difference. No correlation between pain ratings for the nociceptive stimuli and DSS-scores was found (before: r_s = -0.01, p= 0.99; after: r_s = 0.04, p= 0.81).

2.5.4 Hypotheses testing

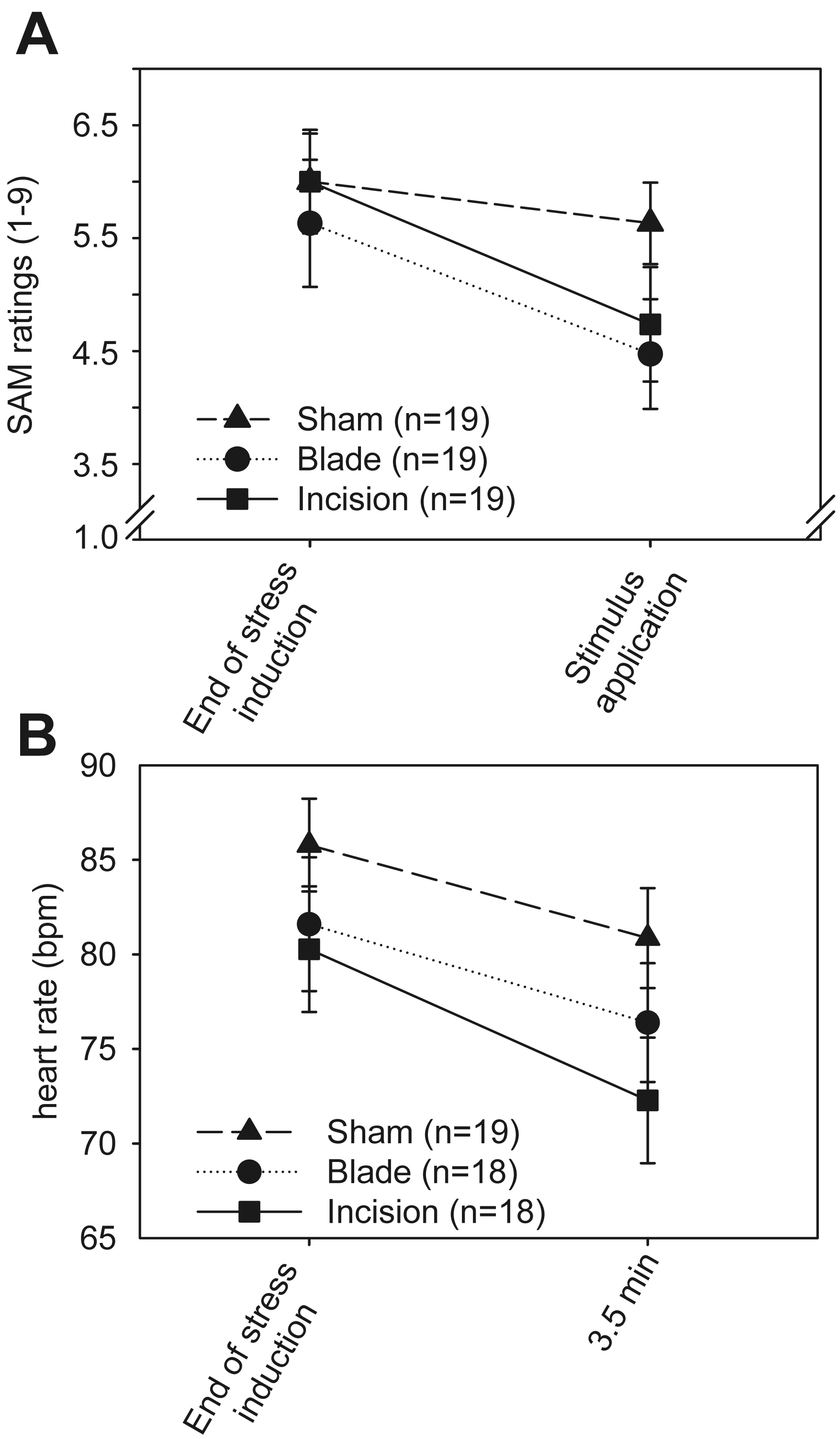
I) Immediate effects

Hierarchical linear regression analysis for the comparison of incision and blade (Ia) showed a significant decrease of arousal directly after the application of both stimuli (β= -1.16 (0.38), t= -3.05, df= 38, p< 0.01, r= 0.44). In contrast to our hypothesis, we did not detect a more pronounced decrease after incision than after blade (β= -0.11 (0.54), t= -0.20, df= 38, p= 0.85, r= 0.03). A similar pattern of findings was obtained regarding heart rate. Considering incision and blade, a significant decrease of heart rate over time (β= -5.20 (2.04), t= -2.55, df= 36, p< 0.05, r= 0.39), but no interaction effect of Time*Condition was found (β= -2.79 (2.88), t= -0.97, df= 36, p= 0.34, r= 0.16). The numerical decrease of urge for NSSI after both painful conditions was not statistically significant in our sample (β= -0.84 (0.46), t= -1.82, df= 38, p= 0.08, r= 0.28). Again, there was no difference in decrease between incision and blade (β= 0.16 (0.65), t= 0.24, df= 38, p= 0.81, r= 0.04). The hierarchical linear model for the comparison of arousal after blade and sham application (Ib) showed no significantly larger decrease of arousal after having received the blade stimulus (β= -0.79 (0.42), t= -1.82, df= 38, p= 0.07, r= 0.28). Concerning the urge for NSSI, neither an effect for Time (β= 0.26 (0.39), t= 0.67, df= 38, p= 0.51, r= 0.11), nor an interaction effect Time*Condition (β= -0.58 (0.56), t= -1.08, df= 38, p= 0.31, r= 0.17) was detected. The linear regression analysis indicated that after both stimuli the patients' heart rate decreased over time (β= -4.92 (1.89), t= -2.61, df= 37, p< 0.05, r= 0.39). There was no significant interaction effect for Time*Condition (β= -0.28 (2.71), t= -0.12, df= 37, p= 0.92, r= 0.02).

For SAM ratings considering incision and sham (Ic), there was a significant interaction effect for Time*Condition (β= -0.89 (0.44), t= -2.03, df= 38, p< 0.05, r= 0.31), indicating as hypothesized a larger decrease of arousal after incision compared to sham. This effect was not found for the ratings of urge for NSSI (β= -0.42 (0.56), t= -0.74, df= 38, p= 0.49, r= 0.12). Regarding heart rate, there was no significantly greater decrease after incision compared to sham in our sample (β= -3.07 (1.57), t= -1.96, df= 37, p= 0.06, r= 0.31).

For immediate effects in SAM ratings and heart rate among patients with BPD see Fig. 3.

Figure 3: Immediate effects in BPD patients



(A) Decrease of arousal shown for all three stimuli (sham, blade, incision). Arousal ratings for two time points (end of stress induction and directly after stimulus application) with standard error of the mean.

(B) Decrease of heart rate shown for all three stimuli (sham, blade, incision). Heart rate for two time points (end of stress induction and the first 3.5 minutes after stimulus application) with standard error of the mean.

II) Intermediate effects

The stress-reducing effects of incision and blade could not be demonstrated to last until 30 minutes after the stimulus application among patients with BPD. For arousal, there was no significant interaction effect for Time*Condition (β= 0.08 (0.07), t= 1.14, df= 38, p= 0.26, r= 0.18) when only incision and sham were considered.

A significant interaction effect for Time*Condition was also not found for ratings of urge for NSSI or heart rate (NSSI: β= 0.02 (0.07), t= -0.27, df= 38, p= 0.78, r= 0.04; heart rate: β= -0.17 (1.14), t= -1.23, df= 37, p= 0.23, r= 0.20).

However, dependent post hoc t-tests performed with delta values (MIST6 – T1, MIST6 – T2, etc.) indicating the relative decrease, revealed significantly greater reductions of heart rate after incision compared to sham 10.5 minutes (t= 2.18, df= 35, p< 0.05, d= 0.74), 14 minutes (t=2.29, df= 35, p< 0.05, d= 0.77), and 31.5 minutes (t= 2.06, df= 35, p< 0.05, d= 0.70) after stimulus application.

Comparing blade and sham, hierarchical linear regression analysis showed no greater decrease of arousal after blade over time (β= -0.07 (0.08), t= -0.89, df= 38, p= 0.38, r= 0.14). Similarly, the two-way interaction effect for Time*Condition was not significant for the urge for NSSI (β= -0.08 (0.08), t= 1.00, df= 38, p= 0.34, r= 0.16) or heart rate (β= -0.09 (0.19), t= -0.45, df= 37, p= 0.65, r= 0.07).

Comparing the incision and blade stimulus, no differences in decrease of stress parameters were found until 30 minutes after stimulus application (arousal: β= 0.01 (0.08), t= 0.17, df= 38, p= 0.86, r= 0.03; heart rate: β= -0.09 (0.18), t= -0.48, df= 36 p= 0.63, r= 0.08; urge for NSSI: β= -0.07 (0.08), t= -0.72, df= 38, p= 0.48, r= 0.12).

III) Group comparison

In the HC group, hierarchical linear regression analysis indicated that independent of the stimulus there was no immediate decrease of arousal (Time: β= -0.07 (0.52), t= -1.35, df= 60, p= 0.18, r= 0.17; Time*Condition: β= -0.13 (0.24), t= -0.52, df= 60, p= 0.60, r= 0.07). For heart rate, the HLM showed an immediate decrease of heart rate levels independent of the applied stimulus (Time: β= -6.30 (2.66), t= -2.37, df= 58, p< 0.01, r=0.30; Time*Condition: β= -1.09 (1.25), t= -0.87, df= 58, p= 0.39, r=0.11). For complete results regarding the HC group, see Tab. 2.

A hierarchical linear regression analysis comparing both groups and all three conditions combined, revealed a decrease of the stress parameters (arousal and heart rate) directly after stimulus application (SAM ratings: β= -1.17 (0.32), t= -3.71, df= 117, p< 0.001, r= 0.32; heart rate: β= - 4.81 (1.61), t= -2.98, df= 111, p< 0.01, r= 0.27). We found significantly higher levels of arousal among BPD patients compared to HCs (β= - 1.87 (0.27), t= -4.41, df= 116, p< 0.001, r= 0.38), but there was no difference in heart rate levels between the two groups (β= -0.35 (1.76), t= -0.96, df= 112, p= 0.83, r= 0.09). The HLM comparing the incision and blade stimulus within the two groups showed a Time*Group interaction for arousal ratings (β= 0.46 (0.19), t= 2.40, df= 82, p< 0.05, r=0.26), indicating that immediately after both incision and blade application, a greater decrease of arousal was found among patients with BPD, see Fig. 4. Further, two-way interactions (Time*Group) or three-way interactions (Time*Group*Stimulus) were neither significant for arousal nor for heart rate.

Since we did not detect longer-lasting differences between the three stimuli among the group of BPD patients, for intermediate effects we only searched for overall differences between the two groups. In the HC group, we found a decrease of arousal levels independent of stimulus type (Time: β= -0.25 (0.59), t= -4.31, df= 60, p< 0.001, r= 0.49; Time*Condition: β= 0.01 (0.03), t= 0.31, df= 60, p= 0.76, r= 0.04). Heart rate levels did not significantly decrease during the 30 minutes after stimulus application and were independent of the applied stimulus (Time: β= -0.44 (2.66), t= -

1.65, *df*= 521, *p*= 0.10, *r*= 0.07; Time*Condition: *β*= -0.06 (0.13), *t*= -0.51, *df*= 521, *p*= 0.61, *r*= 0.02).
The HLM considering both groups and the three conditions together, revealed significantly higher arousal ratings in BPD patients compared to HCs (SAM ratings: *β*= -0.84 (0.19), *t*= -4.35, *df*= 117, *p*< 0.001, *r*= 0.37). Arousal ratings decreased in both groups (*β*= -0.12 (0.04), *t*= -2.76, *df*= 117, *p*< 0.01, *r*= 0.25). For heart rate, no overall Time, Time*Group or Time*Group*Stimulus effect was found.
For complete results of the comparison of stress decrease between the group of BPD patients and HCs see Tab. 3 and 4 in the Supplement.

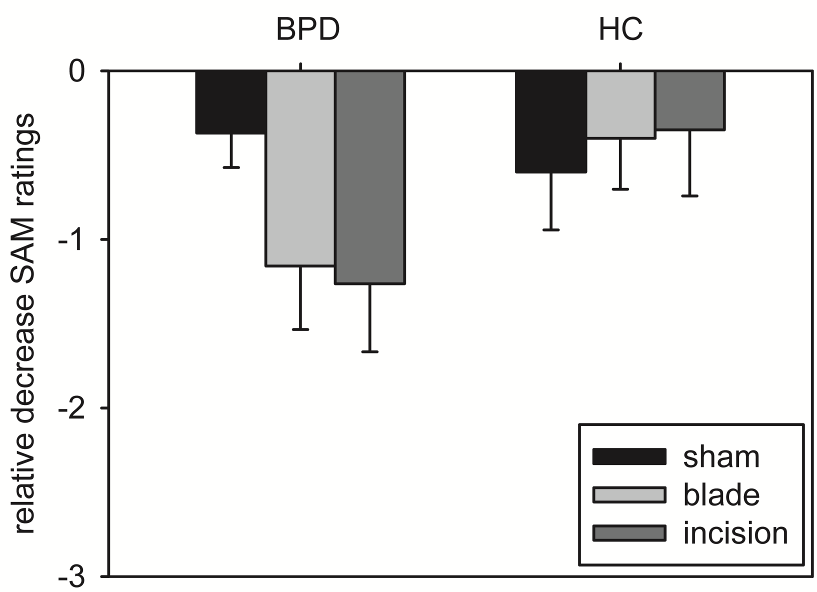
Table 2: HLM for immediate effects in HCs

SAM ratings						
		Parameter estimate (mean ± standard error)	*df*	*t*-value	*p*-value	*r*-value
Time		-0.70 (0.52)	60	-1.35	p = 0.18	0.16
Time*Condition		-0.13 (0.24)	60	-0.52	p = 0.60	0.07
Condition: incision & blade	β_1: Time	-0.40 (0.34)	40	-1.17	p = 0.25	0.18
	β_2: Time*Condition	0.05 (0.48)	40	0.10	p = 0.92	0.02
Condition: blade & sham	β_1: Time	-0.60 (0.32)	40	-1.90	p = 0.06	0.29
	β_2: Time*Condition	0.20 (0.45)	40	0.45	p = 0.66	0.07
Condition: incision & sham	β_1: Time	-0,60 (0.36)	40	-1.67	p = 0.10	0.26
	β_2: Time*Condition	0.25 (0.51)	40	0.49	p = 0.63	0.08

Table 2: HLM for immediate effects in HCs (continued)

Heart rate						
		Parameter estimate (mean ± standard error)	*df*	*t*-value	*p*-value	*r*-value
Time		-6.30 (2.66)	58	-2.37	p = 0.02	0.30
Time*Stimulus		-1.09 (1.25)	58	-0.87	p = 0.39	0.11
Condition: incision & blade	$β_1$: Time	-9.39 (1.92)	38	-4.88	p < 0.001	0.62
	$β_2$: Time*Condition	0.35 (2.80)	38	1.12	p = 0.90	0.18
Condition: blade & sham	$β_1$: Time	-6.86 (1.84)	40	-3.72	p = 0.001	0.51
	$β_2$: Time*Condition	-2.52 (2.59)	40	-0.98	p = 0.34	0.15
Condition: incision & sham	$β_1$: Time	-6.95 (1.29)	38	-5.39	p < 0.001	0.66
	$β_2$: Time*Condition	-2.09 (1.85)	38	-1.13	p = 0.27	0.18

Figure 4: Relative decrease of arousal in BPD patients and HCs



Relative values (stimulus application – MIST 6) for arousal ratings directly after stimulus application (sham, blade, incision) in BPD patients and HCs with standard error of the mean (SEM). Negative values reflect a decrease of arousal. Directly after the application of nociceptive stimuli (blade and incision) BPD patients show a significantly stronger decrease of arousal compared to HCs.

2.6 Discussion

To our knowledge, this is the first study which investigated the effect of tissue injury uncoupled from pain perception on stress regulation in BPD patients. We found that among BPD patients both tissue-injuring nociceptive stimuli (incision) and non-invasive nociceptive stimuli (blade) induce tension relief. Since both nociceptive stimuli - with and without tissue injury – led to a reduction of stress levels, it is likely that nociceptive processing is a major mechanism for the tension-relieving effects of NSSI. The impact of tissue damage during NSSI still has to be established, as it was small and not significant in our sample.
Immediately after the stimulus application, we found a significantly stronger decrease of arousal after the incision compared to the sham condition in BPD patients. Our results tend towards a stronger decrease of arousal after blade compared to sham application, but missed statistical significance. With no significant difference in pain intensity perceived during either incision or blade application, we observed a significant decrease of arousal levels after both conditions. A decrease of heart rate was found when only the blade and incision condition were considered. Additionally, our results indicate a greater decrease of heart rate after incision compared to sham, but missed statistical significance. The application of the blade and incision stimulus appears to lead to a reduction of urge for NSSI, albeit not statistically significant. We were thus able to replicate the stress-reducing effects of incision (Reitz et al. 2012; Reitz et al. 2015). Contrary to our hypothesis, we found no evidence for greater stress reduction after tissue injury compared to a non-invasive nociceptive stimulus.
Since 50-80% of BPD patients do not feel pain during NSSI (Bohus et al. 2000), it cannot be deduced that the stress-reducing effects of NSSI are due to the perception of pain. There seems to be no impairment of the sensory discriminative pain component in BPD patients (C. Schmahl et al. 2004), and it has been suggested that in BPD patients the affective and sensory-discriminative dimensions of pain are uncoupled (Magerl et al. 2012). These findings indicate that pain stimuli are processed by the nociceptive system, but are not experienced as painful on the cerebral level. Therefore, we conclude that the stress-reducing effects of painful stimuli in BPD patients are rather due to nociceptive processes than to the experience of pain.

We were not able to show any longer-lasting differential effects of pain application. A possible reason is that stress levels induced by the MIST program were in a medium range, whereas BPD patients tend to experience considerably higher tension levels (Stiglmayr et al. 2005). Therefore, the return to baseline stress levels may have occurred within a shorter time period. Moreover, the states of elevated inner tension in BPD patients are closely related to negative evaluation, social rejection (Chapman et al. 2014) and the experience of shame (Schoenleber et al. 2014). A stress test considering these components might have been more powerful to create higher stress levels in BPD. However, since we also included HCs we aimed for a paradigm which can be equally used in both groups. For further studies, it might be considered to use paradigms which reach higher stress levels in BPD patients.

In previous studies, a significantly stronger decrease of arousal after sham compared to incision (Reitz et al. 2015), or even an increase of arousal after incision was found in HCs (Reitz et al. 2012). However, this effect was not statistically significant in the present study. We could replicate that painful stimuli lead to a greater decrease of arousal in BPD patients than in HCs (Reitz et al. 2012; Reitz et al. 2015). These findings suggest a different response to pain stimuli concerning stress regulation between HCs and BPD patients. On a neurobiological level, incision was associated with reduced amygdala activity and improved amygdala-prefrontal connectivity in BPD patients. The opposite pattern was described for incision in HCs (Reitz et al. 2015). A point of interest for future studies could be to investigate the neurobiological mechanisms of the blade stimulus in BPD patients and HCs.

The question remains why the majority of BPD patients engage in tissue-injuring forms of NSSI (Kleindienst et al. 2008; Andover 2014; Manca et al. 2014). A possible explanation could be, that a certain nociceptive input or pain level is necessary to create a stress-reducing effect. Taking into account that BPD patients tend to experience even higher stress levels before using NSSI (Chapman et al. 2006), stress-induced analgesia may also play a role. Therefore, significantly higher pain levels than reached by the incision or blade stimulus may be needed. It is possible that these intense pain levels are reached more easily by using tissue-injuring forms of NSSI. Another explanation could be that other factors implicated by tissue injury, such as seeing blood or the ritual of performing the damage, are required for the full tension reducing effect (Glenn & Klonsky 2010; Naoum et al. 2016)

Regarding general differences between the two groups, we found statistically significant differences in baseline stress levels but not in pain perception. Our data supports previous findings (Kuo & Linehan 2009; Reitz et al. 2012), where higher baseline stress levels but no elevated stress reactivity in BPD patients compared to HCs were found.
Reduced pain sensitivity is a robust finding in BPD (Bohus et al. 2000; C. Schmahl et al. 2004; Ludaescher et al. 2007; Magerl et al. 2012). In our sample, pain ratings tended to be lower in the BPD group; however, the difference was not statistically significant. Especially the incision condition was perceived more painful among HCs. The difference in pain perception between BPD and HC concerning the blade and sham stimulus was less pronounced. We can think of two possible explanations for the variance in pain perception. First, we did not assess whether the participating BPD patients generally do or do not feel pain during NSSI. The experience of analgesia during NSSI might explain the variation within BPD patients. Second, elevated pain thresholds correlate with dissociation (Ludaescher et al. 2007). In our sample, DSS scores, reflecting dissociative symptoms, were relatively low and did not correlate to pain ratings.
In our study, HCs perceived the incision stimulus to be significantly more painful than the blade stimulus. Our results do not confirm the findings of the study introducing the blade stimulus (Shabes et al. 2016). A possible explanation could be that in the first study pain was assessed as an online rating during blade application until 30 seconds after, whereas in this report pain was assessed immediately, but still retrospectively, after the stimulus application. There is evidence, that even though continuous ratings and post hoc ratings correlate well, differences regarding maximum pain ratings can be found (Koyama et al. 2004), possibly due to variability in memory consolidation in the early phase of memorizing pain (Jantsch et al. 2009).

We would like to address certain limitations. The first limitation relates to the small sample size. When comparing only two conditions in one group, our study was underpowered ($1-\beta < 0.80$) to detect correlations smaller than 0.59 and standardized mean differences smaller than 0.66. Accordingly, the lack of a significant difference between incision and blade with respect to stress regulation is compatible with quite substantial differences and requires further investigation. Moreover, 18 % of BPD patients were on SSRI medication, which may have influenced the relation between dysregulated affect and pain perception. It would therefore have been desirable to exclude all patients with psychotropic medication. However as already mentioned above, due to the high prevalence of psychotropic medication in BPD complete exclusion of medication would have led to a biased sample. Furthermore, we excluded patients with bipolar I and current substance abuse disorder, since the associated affective fluctuations could have biased our findings. Given the frequent co-occurrence in BPD this is a limitation in respect to generalizability. We only investigated the role of tissue injury on stress regulation and did not consider any other motives for NSSI. Tension relief is the most important motive, however it is not the only one (Klonsky 2007; Kleindienst et al. 2008). Hence, our findings may not be valid for all BPD patients. Moreover, the incision condition differs from a real NSSI event. After stimulus application, participants were not able to see the injury. They could feel the pain, but other possibly stress-reducing factors implicated by tissue injury were not considered. Furthermore, the stimulus application was not self-inflicted but applied by the investigator. The effect of self- and extrinsic infliction should be investigated in further studies. As objective parameters we only assessed heart rate levels. There is evidence that NSSI events are preceded by high levels of cortisol, which drop down after acts of NSSI (Sachsse et al. 2002). For future studies it would be interesting to include the assessment of salivary cortisol.

In sum, we believe that this study is an important step in the understanding of the role of nociceptive input and tissue injury in NSSI. We replicated the stress-reducing effect of incision in BPD patients. Furthermore, we found differences between BPD patients and HCs concerning the response to painful stimuli. These findings indicate that pain plays a different role in stress regulation in BPD patients compared to HCs. Most importantly, we systematically investigated whether the stress-reducing effect of incision in BPD patients is based on the effect of tissue injury. Our data do not support a stress-reducing effect of tissue injury itself. Because we observed similar stress reductions with both tissue-injuring and non-tissue-injuring stimuli, it is possible that the stress reduction effect is due to nociceptive signal processing. This first study was not able to address this question. Independent replication of these findings is needed, and extensions to further study the underlying mechanism of potential stress reduction without tissue injury.

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2.8 Conflict of interest

F. W., S. K., N. K., J. N., S. B., M. B., R.-D. T., U. B. and C. S. have no conflict of interest to declare.

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2.10 Supplement

Table 3: HLM results for the Group comparison BPD & HC – Immediate Effects

SAM ratings						
		Parameter estimate mean (standard error)	*df*	*t*-value	*p*-value	*r*-value
Time		-1.17 (0.32)	117	-3.71	p < 0.001	0.32
Group		-1.19 (0.27)	116	-4.41	p < 0.001	0.38
Time*Group		0.24 (0.19)	143	1.26	p = 0.21	0.10
Time*Group*Stimulus		-0.001 (0.07)	164	-0.02	p = 0.99	< 0.01
Condition: incision & blade	β_1: Time*Group	0.46 (0.19)	83	2.40	p< 0.05	0.25
	β_2: Time*Condition*Group	-0.13 (0.13)	111	-0.67	p = 0.50	0.10
Condition: incision & sham	β_1: Time*Group	0.17 (0.19)	83	0.93	p = 0.36	0.10
	β_2: Time*Condition*Group	-0.003 (0.13)	109	-0.02	p = 0.98	< 0.01
Condition: blade & sham	β_1: Time*Group	0.09 (0.17)	82	0.55	p = 0.58	0.06
	β_2: Time*Condition*Group	0.08 (0.12)	108	0.63	p = 0.53	0.06

Table 3: HLM results for the Group comparison BPD & HC – Immediate Effects (continued)

Heart rate						
	Parameter estimate (mean ± standard error)		*df*	*t*-value	*p*-value	*r*-value
Time	-4.82 (1.61)		111	-2.98	p < 0.001	0.27
Group	-0.37 (1.76)		112	-0.21	p = 0.83	0.02
Time*Group	-0.96 (0.99)		135	-0.96	p = 0.34	0.08
Time*Group*Stimulus	-0.13 (0.35)		154	-0.37	p = 0.71	0.03
Condition: incision & blade	β_1: Time*Group	-1.34 (1.07)	78	-1.25	p = 0.22	0.14
	β_2: Time*Condition*Group	0.05 (0.77)	106	0.07	p = 0.95	0.01
Condition: incision & sham	β_1: Time*Group	-0.52 (0.67)	80	-0.78	p = 0.44	0.09
	β_2: Time*Condition*Group	-0.52 (0.51)	92	-0.10	p = 0.32	0.01
Condition: blade & sham	β_1: Time*Group	-1.48 (1.01)	81	-1.47	p = 0.15	0.16
	β_2: Time*Condition*Group	-0.12 (0.72)	110	-0.17	p = 0.86	0.02

Table 4: HLM results for the Group comparison BPD & HC – Intermediate Effects

SAM ratings					
	Parameter estimate (mean ± standard error)	*df*	*t*-value	*p*-value	*r*-value
Time	-0.12 ± 0.04	117	-2.76	p < 0.01	0.25
Group	-0.84 ± 0.19	117	-4.35	p < 0.001	0.37
Time*Group	-0.05 ± 0.03	141	-1.91	p = 0.06	0.16
Time*Group*Stimulus	0.01 ± 0.01	161	0.65	p = 0.52	0.05
Heart rate					
	Parameter estimate (mean ± standard error)	*df*	*t*-value	*p*-value	*r*-value
Time	-0.08 ± 0.13	1013	-0.61	p = 0.54	0.02
Group	-1.88 ± 1.12	113	-1.68	p = 0.095	0.16
Time*Group	-0.12 ± 0.09	1014	-1.38	p = 0.17	0.04
Time*Group*Stimulus	-0.02 ± 0.03	985	-0.70	p = 0.48	0.02

3 STRESS REACTIVITY AND PAIN-MEDIATED STRESS REGULATION IN REMITTED PATIENTS WITH BORDERLINE PERSONALITY DISORDER

3.1 Authors

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3.2 Abstract

Objective: Patients with Borderline Personality Disorder (BPD) use non-suicidal self-injury (NSSI) to cope with states of elevated inner tension. It is unclear to what extent remitted BPD patients experience these states and whether the experience of pain still regulates emotion. The purpose of this study was the investigation of baseline stress levels, stress reactivity and pain-mediated stress regulation in remitted BPD patients.
Method: Subjective and objective stress parameters were assessed in 30 remitted, 30 current BPD patients and 30 healthy controls. After stress induction, a non-nociceptive tactile stimulus, a tissue-injuring or a non-invasive pain stimulus was applied to the right volar forearm.
Results: Baseline stress levels of remitted BPD patients lie in between the stress levels of current BPD patients and healthy controls. Urge for NSSI increased significantly more in current than remitted BPD patients. The experience of pain led to a greater decrease of arousal in current compared to remitted BPD patients and healthy controls.
Conclusions: States of increased tension still seem to appear in remitted BPD patients. The role of pain-mediated stress regulation appears to be reduced in remitted patients.

3.2.1 Significant Outcomes

- Baseline stress levels of remitted BPD patients lie in between the stress levels of current BPD patients and healthy controls.
- Stress induction did not lead to a differential increase of arousal ratings or heart rate between current and remitted BPD patients and healthy controls, however, the increase of urge for NSSI was significantly larger in patients with current BPD.
- Immediately after the stimulus application the experience of pain was associated with a larger decrease of arousal ratings in current than in remitted BPD patients.
- Higher pain experience was associated with lower arousal ratings in current BPD patients, whereas in remitted BPD patients and healthy controls higher pain experience was associated with higher arousal ratings.

3.2.2 Limitations

- Our study had a relatively small sample size and accordingly our results cannot be considered final and require replication.
- We compared the urge for NSSI between current and remitted BPD patients, even though inclusion criteria regarding the use of NSSI differed between the two groups. To create a more comparable situation between the two groups, these were matched according to urge for NSSI at baseline.
- To avoid a biased sample, we did not exclude patients with SSRI medication. SSRI have emotion regulating effects and therefore may have influenced our results.

3.3 Introduction

In Borderline Personality Disorder (BPD), emotion dysregulation is characterized by high baseline negative emotional intensity, high reactivity and slow return to baseline (Linehan 1993). Reflecting this dysregulated affect, BPD patients experience states of high aversive inner tension (Stiglmayr et al. 2001). The termination of these states of arousal is the most prevalent motive for the use of non-suicidal self-injury (NSSI) and has been reported for 60-90% of BPD patients (Briere & Gil 1998; Schoenleber et al. 2014; Chapman et al. 2006; Kleindienst et al. 2008; Paris et al. 1987; Andover 2014; Klonsky 2007; DiClemente et al. 1991; Zanarini et al. 2008). Most BPD patients describe states of extreme aversive inner tension prior to acts of NSSI, and afterwards feelings of relief and relaxation (Kleindienst et al. 2008; Chapman et al. 2006). Therefore it has been suggested that NSSI reflects a dysfunctional attempt to cope with dysregulated affect (Niedtfeld & Schmahl 2009; Reitz et al. 2015). In patients with current BPD (BPD-C) it was demonstrated that a tissue-injuring pain stimulus (incision) leads to a reduction of stress indicated by both subjective (arousal ratings) and objective (heart rate) parameters (Reitz et al. 2015; Reitz et al. 2012; Willis et al. 2016). Comparing current BPD patients with healthy controls (HC), there was a significantly greater decrease of stress after the incision stimulus in BPD patients (Reitz et al. 2015; Reitz et al. 2012). Further, a recent study revealed that stress reduction was achieved after both the application of an incision and a non-invasive pain stimulus suggesting that no tissue damage is necessary to reduce stress (Willis et al. 2016). On the neural level, the incision was followed by reduced amygdala activity and enhanced amygdala-prefrontal connectivity in BPD patients, suggesting that there is a link between pain perception and emotion regulation in BPD.

Remission and improvement of symptoms is a common phenomenon in BPD. (Gunderson et al. 2011; Zanarini et al. 2012; Zanarini et al. 2007; Zanarini et al. 2006; Zanarini et al. 2003; Zanarini et al. 2016). A 16-year follow-up study reports that 99% of included BPD patients had two-year remissions and 78% had eight-year remissions (Zanarini et al. 2012). The recurrence rates were 36 % after a remission period of two years and 10% after a remission period of eight years (Zanarini et al. 2012). Concerning NSSI 97% of BPD patients had two-year remissions and 91% of BPD patients had four-year remissions (Zanarini et al. 2016). Here, after two-year remissions of NSSI, the recurrence rate was 43% and after four-year remission it was 33% (Zanarini et al. 2016). However, remitted BPD patients (BPD-R) still show persistent impairment in social functioning (Gunderson et al. 2011). We do not know to what extent remitted BPD patients still experience states of elevated aversive inner tension. It is also unclear whether the association of pain perception with stress regulation still exists in remitted BPD patients.

We hypothesized that remitted BPD patients show lower stress levels than patients with current BPD, but still higher stress levels than healthy controls (I). In remitted BPD patients, we suspected a smaller increase of stress parameters compared to current BPD patients, but a smaller increase compared to healthy controls (II). Furthermore, we hypothesized that nociceptive stimuli will lead to a greater stress reduction in current BPD patients compared to remitted BPD patients and we tested if remitted BPD patients show a different response to nociceptive stimuli than healthy controls (III).

3.3.1 Aims of the study

To investigate whether states of high aversive inner tension still exist in patients with remitted BPD, whether stress reactivity differs between remitted and current BPD patients and healthy controls, and whether remitted patients are still able to regulate emotions with nociceptive experiences.

3.4 Method and Materials

3.4.1 Participants

From a larger, previously described sample (Willis et al. 2016) 30 female patients with current BPD and 30 female healthy controls (HC) were matched with a new group of 30 female remitted BPD patients according to age and educational background. Current and remitted BPD patients were additionally matched according to subjective ratings of urge for NSSI at the beginning of the experiment. Thus, participants did not significantly differ in age (BPD-R: 28.97 (4.54), BPD-C: 28.03 (6.07), HC: 28.73 (5.46) Chi^2= 1.18 *df* = 2, *p*= 0.56), education (Chi^2= 3.21 *df* = 2, *p*= 0.20) or urge for NSSI (BPD-R: 0.12 (0.41), BPD-C: 0.23 (0.39), $t_{(58)}$= 1.13, *p*= 0.26, *d*=0.28).

For the group of current BPD patients, we only included patients who had shown NSSI with skin lesions at least once during the six months prior to study participation. Patients who met the criteria for remission, were excluded if they had engaged in more than two acts of NSSI in the last two years; but all of them had used NSSI

before. NSSI was assessed by a custom-made questionnaire assessing the frequencies and forms of NSSI. The frequency and form of NSSI during the last month and the frequency of NSSI during the last year were evaluated (see Tab. 1).
Current BPD patients fulfilled at least 5 criteria for BPD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013). Remission was defined as no longer meeting a DSM-5 diagnosis for BPD (Zanarini et al. 2010; Zanarini et al. 2012; Zanarini et al. 2016; Gunderson et al. 2011). In our study, remitted BPD patients met no more than 3 criteria for BPD within the last two years, but had met the criteria for BPD at an earlier point in time (for details see Tab. 1). BPD criteria were assessed via the International Personality Disorder Examination (IPDE) (Loranger 1999).
Exclusion criteria for remitted and current BPD patients contained a lifetime diagnosis of bipolar I disorder or schizophrenia, mental retardation, a history of severe neurological dysfunction, the presence of severe psychopathology that required immediate treatment, and a current (past month) diagnosis of substance use disorder (including substance abuse and dependence). Patients with psychotropic medication were also excluded, except for those taking selective serotonin reuptake inhibitors (SSRI) which were allowed (for current medication see suppl. Tab. 1). Co-occurring psychiatric disorders were determined using the Structured Clinical Interview for Axis-I disorders (SCID-I) (First et al. 1995). Healthy controls were screened using the IPDE and SCID-I as well. They were excluded if they met the diagnosis for any past or present psychiatric disorder or for substance abuse. All participants with a history of moderate to severe chronic pain, as well as participants with pain medication use in the two weeks prior to study participation were excluded. For socio-demographic data and psychopathology, see suppl. Tab. 1.
Recruitment was done by the central project of the KFO 256, a Clinical Research Unit funded by the German Research Foundation (DFG; KFO 256) dedicated to investigating mechanisms of disturbed emotion processing in BPD (Schmahl et al., 2014). Thus, all projects which originate from the KFO 256 include subjects from a joint database.
After having received a verbal and written explanation of the study procedure, all participants gave their written consent. The study was conducted according to the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty Mannheim/University of Heidelberg (application no. 2008-234N-MA).

Table 1: **Socio-demographic data and pathology**

	BPD remitted	BPD current	HC	*p*
Number	30	30	30	
Age (years)				
Mean (standard deviation)	29.0 (4.5)	28.0 (6.1)	28.73 (5.46)	*p*= 0.56[1]
Educational background				
University-entrance diploma	22 (73%)	17 (57%)	23 (77%)	*p*= 0.20[2]
Secondary school certificate	8 (27%)	13 (43%)	7 (23%)	
Number of BPD criteria (current)				
Average number of criteria	0.8 (1.1)	6.8 (1.2)	/	
0	16 (53%)	/	/	
1	6 (20%)	/	/	
2	5 (17%)	/	/	
3	3 (10%)	/	/	
4	/	/	/	
5	/	6 (20%)	/	
6	/	6 (20%)	/	
7	/	9 (30%)	/	
8	/	7 (23%)	/	
9	/	2 (7%)	/	

[1]Kruskal-Wallis-Test, [2]Chi-squared test

Table 1: **Socio-demographic data and pathology (continued)**

	BPD remitted	BPD current	HC	*p*
BPD criteria, current				
Frantic efforts to avoid abandonment	2 (7%)	15 (50%)	/	
Unstable, intense interpersonal relationships	2 (7%)	24 (80%)	/	
Identity disturbance	3 (10%)	20 (67%)	/	
Impulsivity in at least two potentially damaging areas	3 (10%)	16 (53%)	/	
Recurrent suicidal behaviour, threats, gestures	1 (3%)	28 (93%)	/	
Affective instability	5 (17%)	29 (97%)	/	
Chronic feelings of emptiness	1 (3%)	26 (87%)	/	
Inappropriate, intense anger	3 (10%)	20 (67%)	/	
Paranoid ideation or dissociative symptoms	5 (17%)	25 (83%)	/	

Table 1: **Socio-demographic data and pathology (continued)**

	BPD remitted	BPD current	HC	*p*
Frequency of NSSI in the month before study participation				
Average frequency	0.3 (0.7)	16.1 (20.3)	/	
No NSSI in the month of study	28 (93%)	8 (27%)	/	
1-5 times	2 (7%)	6 (20%)	/	
6-10 times	/	2 (7%)	/	
11-20 times	/	1 (3%)	/	
21-30 times	/	6 (20%)	/	
More than 30 times	/	5 (17%)	/	
Unknown	/	2 (7%)		
Used methods of NSSI in the last year				
Cutting	1 (3%)	24 (80%)	/	
Scratching to the point of bleeding	/	19 (63%)	/	
Skin-picking	1 (3%)	8 (27%)	/	
Self-hitting	/	14 (47%)	/	
Burning/Scalding	/	10 (33%)	/	
Sticking needles or nails into skin	/	6 (20%)	/	
Hair tearing	/	8 (27%)	/	
Banging head against wall	/	9 (30%)	/	
Unknown	2 (7%)	/	/	

3.4.2 Experimental paradigm

Stress induction
After a 3.5 minute baseline, stress was induced using a modified version of the Montreal Imaging Stress Task (MIST) (Dedovic et al. 2005), a generic stress task which induces stress in most subjects. Participants have to solve arithmetic tasks under time pressure. The program creates stress by manipulating both difficulty and time limit in order to simulate a poor performance. To add a social stress component, the participant's performance is displayed in relation to a fictitious average and the investigator reminds the participants that the study depends on an above-average performance.

Nociceptive and tactile control stimuli
After the 30-minutes stress induction, the participants were asked to put their right forearm behind a shield screen. After disinfection with alcohol (70%), balanced and randomized across groups either (1) a small incision was made (nociceptive with tissue injury), or (2) a blade stimulus not penetrating the skin (nociceptive without injury), or (3) a sham stimulus (non-nociceptive; tactile) was applied. The incision

stimulus was conducted according to the standardized incision protocol (Kawamata et al. 2002). With a sterile scalpel, a 4 mm long and 5-7 mm deep incision through skin, fascia and muscle was performed. The small incision was well tolerated by all participants. The blade stimulator consisted of a blunt blade (tip dimensions 4.0 x 0.1 mm) attached to a plastic cylinder mounted with a weight that moves freely within a steel tube. With repeated application, exertion of the same force is ensured (4096 mN; MRC Systems GmbH, Heidelberg, Germany). The blade stimulus was applied for seven seconds. For the sham stimulus, the forearm was touched with the scalpel grip, which evoked a slight sensation of touch. Until the stimulus was applied, participants were unaware of which stimulus to expect. The stimulus application was followed by a 31.5-minutes relaxation phase.

Dependent variables

As a subjective measure of stress, participants rated their current level of arousal on a visual analogue scale using Self-Assessment Manikins (SAM) (Bradley & Lang 1994). Participants rated arousal from 1 (relaxed) to 9 (under extreme tension) at 19 time points: before and after baseline (average score: mean-baseline), seven times during stress induction, and ten times after stimulus application. Additionally, participants rated the urge for NSSI on a visual scale from 0 (none) to 10 (extreme) at the same time points. Directly after stimulus application, participants rated the pain intensity of the stimulus on a visual analogue scale from 0 (no pain) to 10 (worst imaginable pain)

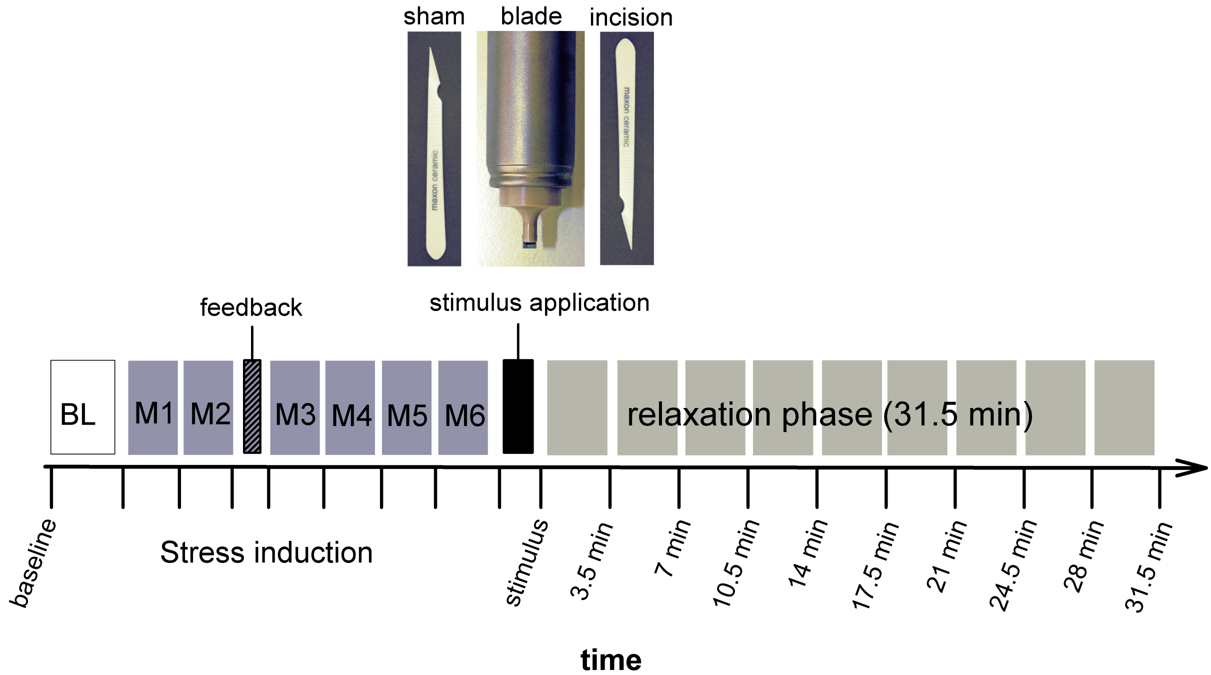
In addition to subjective stress parameters, we continuously recorded heart rate as an objective measure of stress. We used ECG recording amplified with a Biosemi Active Two AD-Box (Honsbeek, Kuiper & Van Rijn, Biosemi B.V., Amsterdam, The Netherlands) and reusable flat active Ag-AgCl electrodes, digitized at 2 kHz. For the analysis, the experiment was split into 28 time points analogue to the subjective ratings: baseline (3.5 mins.), 18 time points during stress induction (1.2 min.-intervals) and nine time points during the relaxation period (3.5 min.-intervals). For study procedure see Fig. 1. See also (Willis et al. 2016) for a more detailed description of the study procedure.

At the beginning of the experiment, participants were informed that they would receive one of the three stimuli behind a shield screen so that they would not know which stimulus to expect until the application itself. Further, they were told that after the stimulus application, they will only have to rate their current arousal as well as their current urge for NSSI every 3.5 minutes for a total time of 30 minutes.

As reported in the above-mentioned study (Willis et al. 2016) it appears likely that the stress reducing effect of the stimuli is caused by pain experience. Due to the smaller sample size and wider distribution of pain ratings for each stimulus in this sample (see suppl. Fig. 1), in this study not the stimulus type but the pain rating directly after stimulus application was treated as independent variable.

As dependent variables, we used 1) subjective levels of arousal (SAM ratings), 2) heart rate (as objective, neurophysiological measure of stress) and 3) urge for NSSI (ratings).

Figure 1: Study design



After a 3.5 minutes' baseline stress was induced with the MIST program (M1-M6). Then either the incision, blade or sham stimulus was applied on the right volar forearm. The pain intensity of the stimulus was rated directly after the stimulus application. The stimulus application was followed by a relaxation phase. Current level of arousal, urge for NSSI and heart rate were assessed throughout the experiment. This figure was modified from Willis et al. 2017.

3.4.3 Data analysis

For the statistical analysis SPSS (Version 22.0.0.0) was used. The level of statistical significance was set to $p \leq 0.05$ (two-tailed). For effect sizes, Cohen's *d* was reported for t-test analyses, Cohen's f^2 for analyses of variance (ANOVAs) and *r* for hierarchical linear models (Rosenthal 1994).

Baseline stress levels and stress increase
To test whether the groups differ in baseline subjective arousal levels a 3*2 repeated measure analysis of variance (rm-ANOVA) with Group (BPD-R vs. BPD-C vs. HC) as between-factor and Time (pre-baseline vs. post-baseline) was calculated. For baseline heart rate levels an Oneway-ANOVA was used.
To test stress reactivity (II), a 3*2 repeated measure analysis of variance (rm-ANOVA) with Group (BPD-R vs. BPD-C vs. HC) as between-factor and Time ((mean-)baseline vs. post-stress) as within-factor was calculated for SAM-ratings, urge for NSSI and heart rate. Since none of the HCs showed an urge for NSSI, the tests were only performed for BPD-R and BPD-C.

Stress decreases and group comparisons
In line with our previous study comparing patients with current BPD and healthy controls (Willis et al. 2016) we used hierarchical linear models (HLM) to analyse the decrease of arousal, heart rate, and urge for NSSI directly (immediate effects) and 30 minutes (intermediate effects) after stimulus application.

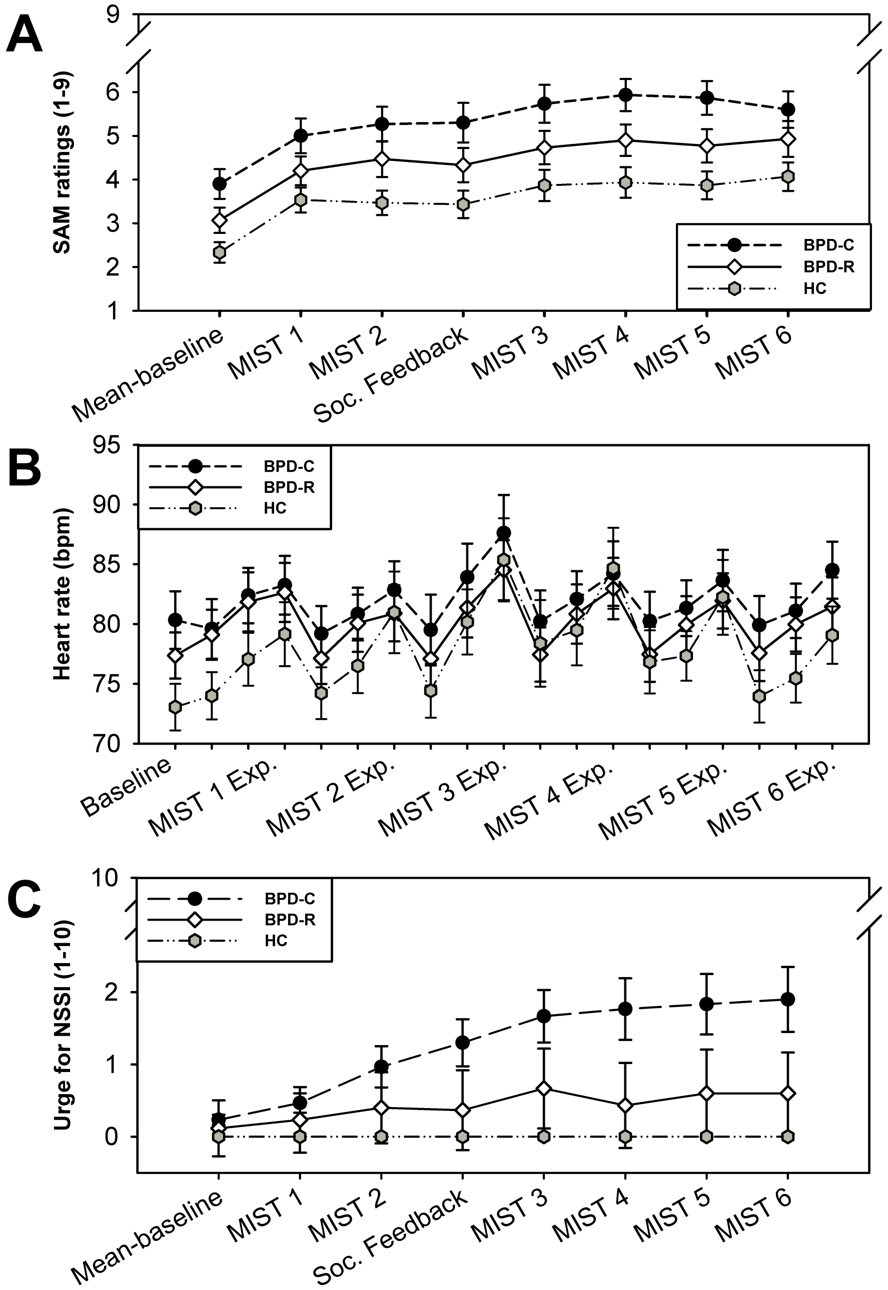
For immediate effects, only the first time point directly after stimulus application and for intermediate effects all time points after stress induction were analysed.
To test to what extent pain experience leads to a reduction of stress parameters in patients with remitted BPD compared to current BPD-patients and HC (III), both the effects of Pain intensity (pain rating) and Group (BPD-R vs. BPD-C vs. HC) were considered introducing both two-way and three-way interaction terms (Time*Group, Time*Pain Intensity, Group*Pain Intensity, Time*Group*Pain Intensity). As post-hoc analyses HLMs with only two groups (BPD-R vs. BPD-C, BPD-R vs. HC, and BPD-C vs. HC) were performed. Again, analyses concerning urge for NSSI only included BPD-C and BPD-R. To prevent confounding by different levels of SAM, heart rate and NSSI, baseline levels were used as an independent covariable.
The estimations in the linear hierarchical models were computed as maximum likelihood estimators using the MIXED procedure in SPSS.

3.5 Results

3.5.1 Baseline levels and stress induction

Concerning arousal, we found a significant difference for baseline levels between the three groups ($F_{2,87}$=7.17, p= 0.001, f^2= 0.16). The highest baseline arousal levels were found in BPD-C, followed by BPD-R, and HCs had the lowest baseline arousal levels (see Fig. 2). In post-hoc Bonferroni tests, there was a significant difference between BPD-C and HC, but not between BPD-R and BPD-C, as well as between BPD-R and HCs (BPD-C vs. BPD-R: p= 0.14; BPD-R vs. HC: p= 0.24, BPD-C vs. HC: p= 0.001). The same results were found for heart rate at baseline ($F_{2,87}$= 3.06, p= 0.05, Bonferroni: BPD-C vs. BPD-R: p= 0.94; BPD-R vs. HC: p= 0.15, BPD-C vs. HC: p= 0.02).
During stress induction arousal levels significantly increased in all three groups, with BPD-C showing the highest and HCs showing the lowest arousal levels (main effect *Time*: $F_{1,87}$=91.14, p< 0.001, f^2= 1.05; main effect *Group*: $F_{2,87}$= 6.58, p< 0.01, f^2= 0.15; Bonferroni: BPD-C vs. BPD-R: p= 0.25; BPD-R vs. HC: p= 0.10, BPD-C vs. HC: p= 0.001). Heart rate increased in all three groups as well, but there was no significant difference between them (main effect *Time*: $F_{1,87}$=28.68, p< 0.001, f^2= 0.33; main effect *Group*: $F_{2,87}$= 2.38, p= 0.10, f^2= 0.05).
We found no significant *Time*Group* interaction for arousal and heart rate during stress induction (all p> 0.05), indicating no difference in arousal and heart rate reactivity between the groups.
In contrast, regarding the urge for NSSI there were differences between BPD-R and BPD-C. Since the groups were matched for urge for NSSI at baseline, there was no significant difference in the beginning of the experiment ($F_{1,87}$=1.29, p= 0.26, f^2= 0.02). During stress induction, however, the urge for NSSI increased significantly stronger in BPD-C (*Time*Group*: $F_{1,58}$=5.80, p= 0.02, f^2= 0.10). For baseline levels and stress increase of all three parameters see Fig. 2.

Figure 2: Stress induction



(A) Ratings of current level of arousal (SAM ratings) at baseline and during stress induction (MIST 1 - MIST 6) among BPD-C, BPD-R and HC. Arousal levels increased significantly in all groups. SAM ratings of BPD-R lie in between the ratings of BPD-C and HC. Error bars stand for the standard error of the mean (SEM).

(B) Heart rate at baseline and during stress induction. The MIST software combines three different modes (rest, control, and experimental). During rest, no calculations have to be performed. During control and experimental participants have to calculate - during control without, and during experimental with a time limit. Heart rate levels of BPD-R lie in between the heart rate levels of BPD-C and HC. Heart rate increased significantly during stress induction in all groups. Error bars stand for the standard error of the mean (SEM).

(C) Ratings of urge for NSSI at baseline and during stress induction (MIST 1 - MIST 6). During stress induction urge for NSSI increased significantly more in BPD-C compared to BPD-R. Error bars stand for the standard error of the mean (SEM).

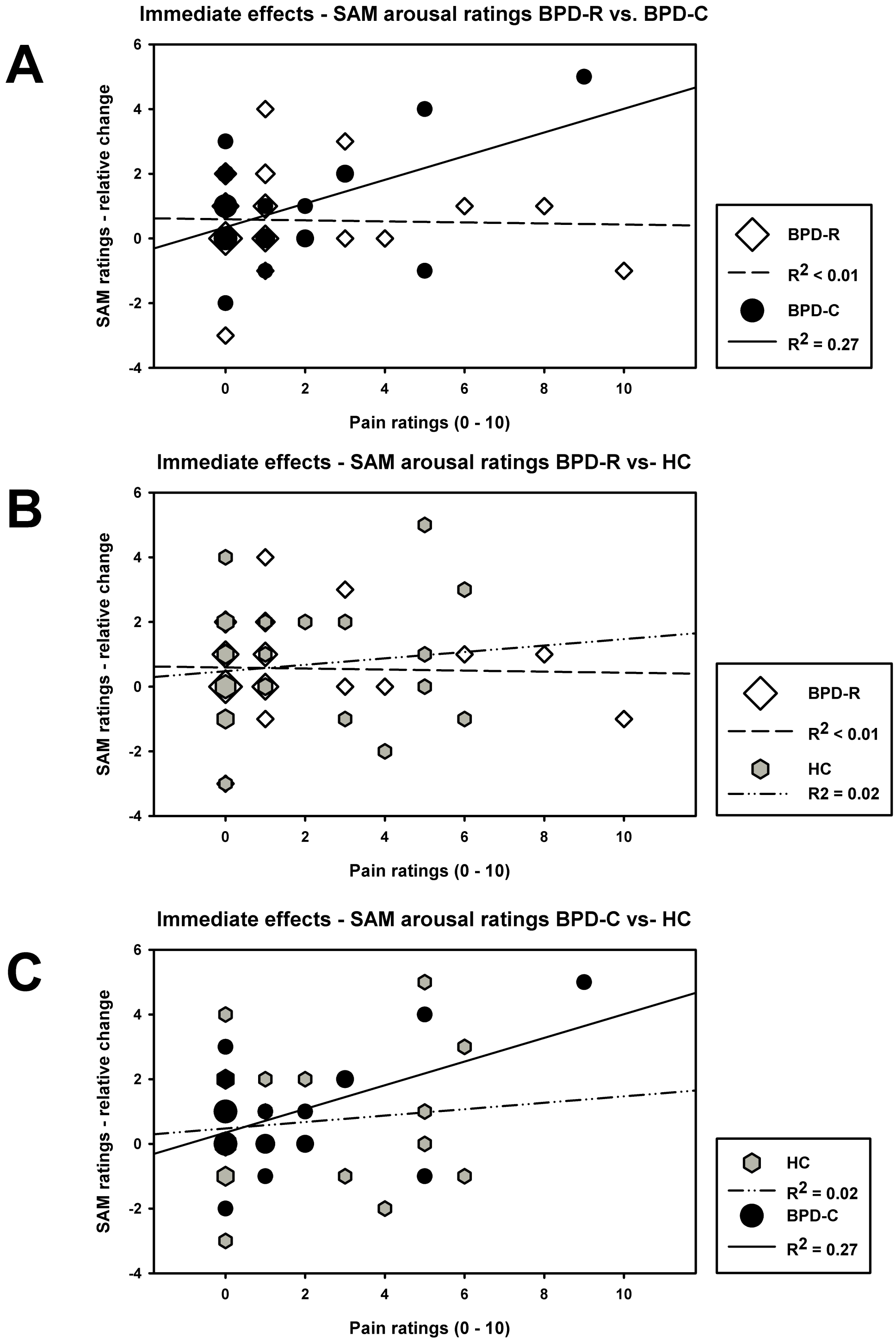
3.5.2 Stress levels after pain stimulation

SAM

The HLM analysing the behaviour of SAM ratings dependent on the pain intensity of the stimulus directly after its application within all three groups showed a significant *Time*Pain intensity* interaction (β= -0.42 (0.21), *t*= 5.01, *df*= 82, *p*= 0.05, *r*= 0.48), indicating that there is an association between pain experience and the course of arousal. A significant *Time*Pain intensity* interaction was also found comparing BPD-R with BPD-C (β= -0.81 (0.27), *t*= -3.06, *df*= 53, *p*= 0.003, *r*= 0.39), as well as BPD-C with HC (β= -0.55 (0.22), *t*= -2.51, *df*= 56, *p*= 0.02, *r*= 0.32). Regarding all groups, there was no significant *Time*Group*Pain intensity* interaction (β= 0.13 (0.10), *t*= 1.38, *df*= 81, *p*= 0.17, *r*= 0.15). This effect was found, comparing BPD-R to BPD-C (*Time*Pain Intensity*Group*: β= 0.41 (0.16), *t*= 2.55, *df*= 53, *p*= 0.01, *r*= 0.33), indicating that only in BPD-C a higher pain experience led to a greater decrease of arousal (see Fig 3A). The same pattern was found analysing BPD-C and HC (see Fig. 3C), but missed statistical significance (β= 1.14 (0.10), *t*= 1.47, *df*= 56, *p*= 0.15, *r*= 0.19). Concerning BPD-R and HC no significant two- or three-way interactions were found (all p > 0.05) (see Fig. 3B).

Considering the entire relaxation period, BPD-C patients had significantly higher SAM ratings compared to BPD-R patients (*Group*: β= -1.50 (0.61), *t*= -2.47, *df*= 60, *p*= 0.01, *r*= 0.30) and compared to HC (β= -1.09 (0.31), *t*= -3.51, *df*= 60, *p*= 0.001, *r*= 0.41). There was no main effect of *Group* comparing BPD-R to HC (β= -0.68 (0.57), *t*= -1.21, *df*= 60, *p*= 0.23, *r*= 0.15). The HLM showed a significant *Pain Intensity*Group* interaction comparing BPD-R and BPD-C (β= 0.53 (0.24), *t*= 2.23, *df*= 60, *p*= 0.01, *r*= 0.28), indicating that greater pain experience was associated with higher SAM levels in the BPD-R group, whereas in BPD-C patients greater pain experience was related to lower SAM ratings (see Fig. 4A). This effect was also found regarding BPD-C and HCs, but it did not reach statistical significance (β= 0.20 (0.12), *t*= 1.66, *df*= 60, *p*= 0.10, *r*= 0.21) (see Fig. 4C). In both, BPD-R and HC higher pain intensities were associated with higher arousal ratings (see Fig. 4B).

Figure 3: Immediate effects of stimulus application on arousal in BPD-C, BPD-R and HC.



Positive relative values for arousal change (arousal at stimulus application – MIST 6) reflect a decrease and negative values reflect an increase of arousal. Symbol size reflects the number of patients.

(A) Arousal change in BPD-R vs. BPD-C directly after stimulus application with corresponding pain ratings reflecting the significant Time*Pain intensity*Group interaction (*p*= 0.01, *r*= 0.33).

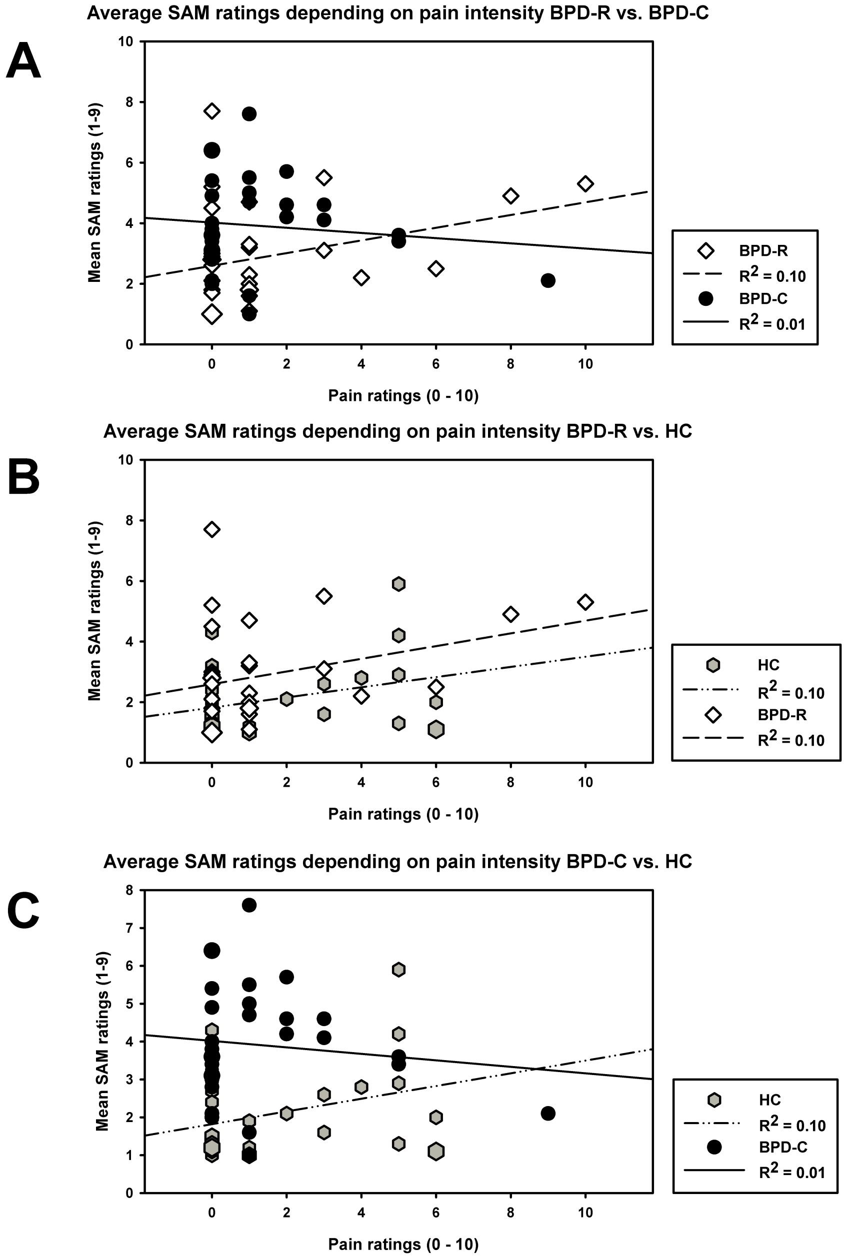
(B) BPD-R and HC do not show a change in arousal depending on the pain intensity of the stimulus

(C) Comparing BPD-C to HC shows the same pattern as in Fig. 3A comparing BPD-C to BPD-R, but missed statistical significance.

Heart rate
Directly after stimulus application, heart rate levels decreased in all three groups (*Time*: *β*= -43.83 (3.52), *t*= -12.46, *df*= 109, p< 0.001, *r*= 0.77). Heart rate decrease did not differ significantly between the groups and was not significantly related to pain perception (*Time*Pain Intensity*Group*: *β*= -0.09 (0.50), *t*= -0.19, *df*= 118, *p*= 0.85, *r*= 0.02).The same results were found regarding the entire relaxation period (*Time*: *β*= -4.86 (0.50), *t*= -9.75, *df*= 113, p< 0.001, r= 0.68; *Time*Pain Intensity*Group*: *β*= 0.09 (0.06), *t*= 1.49, *df*= 48, *p*= 0.14, *r*= 0.21).
Urge for NSSI
Immediately after the stimulus application, there were no significant two- or three-way interactions regarding the urge for NSSI. Ratings of urge for NSSI tended to be higher in the BPD-C group but this difference did not reach statistical significance (*Group*: *β*= -1.36 (0.74), *t*= -1.85, *df*= 60, *p*= 0.07, *r*= 0.23). Regarding the entire relaxation period, BPD-C patients showed significantly higher ratings of urge for NSSI than BPD-R patients (*Group*: *β*= -1.33 (0.55), *t*= -2.44, *df*= 60, *p*= 0.02, *r*= 0.30). The urge for NSSI significantly decreased in both groups, but the decrease was stronger in BPD-C than BPD-R (*Time*: *β*= -2.00 (0.06), *t*= -3.06, *df*= 56, *p*= 0.003, *r*= 0.38; *Time*Group*: *β*= 0.08 (0.04), *t*= 2.07, *df*= 54, *p*= 0.04, *r*= 0.27). The pain intensity of the stimulus was largely unrelated to the decrease of urge for NSSI (*Time*Pain Intensity*: *β*= -0.01 (0.03), *t*= -0.26, *df*= 54, *p*= 0.80, *r*= 0.04; *Time*Pain Intensity*Group*: *β*= 0.01 (0.02), *t*= 0.42, *df*= 54, *p*= 0.68, *r*= 0.06).

For all two- and three-way interactions see Tab. 2 - 4 in the supplement.

Figure 4: Mean levels of SAM ratings during the relaxation period in BPD-C, BPD-R and HC



(A) Mean of SAM ratings during the relaxation period depending on pain ratings in BPD-C and BPD-R. In BPD-C higher pain ratings are associated with lower SAM ratings reflecting the significant Pain intensity*Group interaction (p= 0.01, r= 0.28).
(B) In both, BPD-R and HC, higher pain ratings are associated with higher SAM ratings and lower pain ratings are associated with lower SAM ratings.
(C) Comparing BPD-C to HC shows the same pattern as in Fig. 4A comparing BPD-C to BPD-R, but did not reach statistical significance.

3.6 Discussion

To our knowledge, this is the first study to investigate pain-mediated stress regulation in remitted BPD patients. Our results suggest that tension levels of remitted BPD patients seem to lie in between the levels of current BPD patients and healthy controls. The role of pain-mediated stress regulation, however, appears to have evanesced in remitted BPD patients.

In our sample, remitted BPD patients seem to experience lower stress levels than current BPD patients, but still higher stress levels than healthy controls. There were no signs of increased stress reactivity between current and remitted BPD patients as well as healthy controls, as in response to the MIST stress paradigm, we found no difference in increase of stress parameters. However, remitted BPD patients still reacted with an increase of urge for NSSI during stress induction, even though acts of NSSI in this group were rare. Still, in current BPD patients stress induction led to a significantly greater increase of urge for NSSI.

Before acts of NSSI, patients with BPD tend to experience high levels of aversive inner tension (Stiglmayr et al. 2005). Affect regulation is believed to be the strongest maintaining factor of NSSI and that the urge for NSSI is conditioned on aversive inner tension (Klonsky 2007; Chapman et al. 2006). Our findings support these theories in current BPD patients, who develop an urge for NSSI during stress induction. However, the remitted BPD patients in our sample, who still seem to experience increased tension levels did not react with a similar increase of urge for NSSI. Our sample of current BPD patients regularly used NSSI, whereas the group of remitted patients barely did. We therefore propose that urge for NSSI is not only conditioned to the presence of aversive inner tension, but also that the regular use of NSSI reinforces itself and leads to an increased urge for NSSI during states of high aversive inner tension. Considering the concept of benign masochism (enjoying initially negative experiences after realization that the event is not threatening (Rozin et al. 2013)), it could be possible that the more often NSSI is used the less threatening it is perceived. Whereas after a period of NSSI-abstinence the threshold to use NSSI is higher. It appears likely that states with increased levels of aversive inner tension still exist in remitted BPD patients, but we do not know how they were able to cease the dysfunctional behaviour of NSSI. It might be speculated that remitted BPD patients found other methods than NSSI to cope with elevated inner tension. These methods and the association of stress levels with completed treatments should be investigated in future studies.

Regarding self-reported arousal, we could confirm our hypothesis that the experience of pain leads to a greater stress reduction in current compared to remitted BPD patients. As an immediate effect, the painfulness of the stimulus was correlated with arousal: the stronger the experience of pain, the more marked was the decrease of arousal ratings in current BPD patients. Comparing remitted BPD patients to healthy controls, in both groups there were no signs of pain-mediated stress regulation.

However, we these results were not corroborated by the analysis of heart rate. Interestingly, several studies find discrepancies between subjective and objective measures of emotions in BPD (Lampe et al. 2007; Krause-Utz, A et al. 2013; Willis et al. 2016; McCloskey et al. 2009). There might also be some more basic discrepancies between the assessment of emotions by questionnaires and by behavioural measures. BPD patients might tend to overrate emotional reactions or impulsivity on a psychometric level, which then cannot be completely verified in the laboratory. Also, the strong fluctuations of stress levels might lead to an over-estimation of emotions or impulsivity. For future studies, here it might be helpful to

additionally analyse heart rate variability and skin conductance to bridge this gap and add knowledge on the interaction of stress and emotions.
In line with our previous study (Willis et al. 2016), we did not find any longer lasting effects of the stimuli on stress decrease in any of the groups. Two recent studies suggest (Vansteelandt et al. 2017; Houben et al. 2017) that in BPD patients NSSI seems to help stabilizing negative affect rather than decreasing it. However, the above-mentioned studies did not capture the immediate effects (seconds until minutes) directly following acts of NSSI. Therefore, it might be possible that NSSI has different short and long term effects on stress regulation.
Still, there were differences concerning the reaction to pain experience concerning the 30-minute time interval succeeding the stimulus application. While among remitted BPD patients and healthy controls high pain intensity was associated with higher arousal ratings, the opposite pattern was observed for current BPD patients, where higher pain experience was associated with lower SAM ratings. This shows a difference in pain evaluation with remitted patients demonstrating a more normal correlation between pain experience and stress. These findings could, however, not be supported by the analysis of heart rate or urge for NSSI.
On a neurobiological level, incision is associated with reduced amygdala activity and improved amygdala-prefrontal connectivity in current BPD patients (Schmahl et al. 2006; Niedtfeld et al. 2012). In HCs, the opposite pattern was observed. This was interpreted as NSSI being a dysfunctional attempt to cope with dysregulated affect (Reitz et al. 2015). In the present study, we found that states of increased inner tension might still occur in remitted BPD patients, since they show stress levels between current BPD patients and healthy controls. However, the effects of nociceptive stimuli on stress regulation seem to have ceased, and the appraisal of pain appears to have normalized in remitted BPD patients. Whether on a neural level, the link between emotion regulation and pain perception is still present in remitted BPD patients or whether they show similar neural activation patterns to HCs should be investigated in future studies.

As a limitation, we would like to stress that our study had a relatively small sample size. For the main hypotheses, our study was adequately powered to detect medium to large effects (1-beta >= 0.80; alpha = 0.05), however, due to the sample size, we may have missed smaller effects. Accordingly, our results cannot be final and conclusive and require further investigation. In this study, we compare the urge of NSSI between current and remitted BPD patients, even though inclusion criteria regarding the use of NSSI differed between the two groups. Frequent use of NSSI reflects the presence of severe dysfunctional behaviour and is not consistent with our understanding of remission in BPD. However, we would like to stress that acts of NSSI and the urge for NSSI are not the same. To create a more comparable situation between the two groups, they were matched according to urge for NSSI at baseline. Furthermore, we did not exclude patients with SSRI medication. SSRIs have emotion regulating effects, which may have influenced the relation between dysregulated affect and pain perception. However, due to the high prevalence of psychotropic medication in BPD, the complete exclusion of psychotropic medication would have led to a biased sample. Furthermore, as already discussed elsewhere (Willis et al. 2016), after stress induction stress levels were only in a medium range, whereas before acts of NSSI BPD patients tend to experience higher tension levels (Stiglmayr et al. 2005).This might be related to the chosen stress induction, which limitedly considers components such as social rejection and the experience of shame, which are closely related to states of elevated inner tension in BPD patients (Chapman et

al. 2014; Schoenleber et al. 2014). However, the strength of the MIST paradigm as generic stress induction is that it causes stress in most subjects.
Another difficulty discussing remission in BPD is the absence of a standard definition. Zanarini et al. define remission as no longer meeting five diagnostic criteria for BPD for two years (Zanarini et al. 2008; Zanarini et al. 2012; Zanarini et al. 2003). Whereas for Gunderson et al. remission is defined as no longer meeting two or more BPD criteria for at least 12 months (Gunderson et al. 2011). As stated above, in our sample remitted BPD patients did not meet more than three BPD criteria for at least two years. Further, fulfilling the remission criteria does not assess the functioning of the patients. Attaining good functioning is called recovery of BPD, which Zanarini et al. defined as a Global Assessment of Functioning (GAF) score higher than 60 (Zanarini et al. 2012).
In our study, we only investigated two BPD symptoms, namely NSSI and tension/stress levels reflecting a dysregulated affect. But we did not assess the functioning of the patients on an everyday basis. Therefore, we cannot evaluate recovery of BPD in our sample of remitted BPD patients.
We found evidence for a fading association between nociception and tension relief, as well as for a reduced presence of urge for NSSI, and for a normalization of pain evaluation. For us it is likely that these are important changes which might be necessary to recover from BPD.
In sum, we believe that our findings are an important step in the understanding of remitted BPD patients. But since our study was a pioneering study it awaits replication from an independent sample to confirm the present findings.

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3.8 Declaration of interest

F. W., S. K., N. K., S. L., J. N., M. J., C. N., M. B., R.-D. T., U. B. and C. S. have no conflict of interest to declare.

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3.10 Supplement

Figure 1: Distribution of pain ratings for all three stimuli among BPD-R, BPD-C and HC.

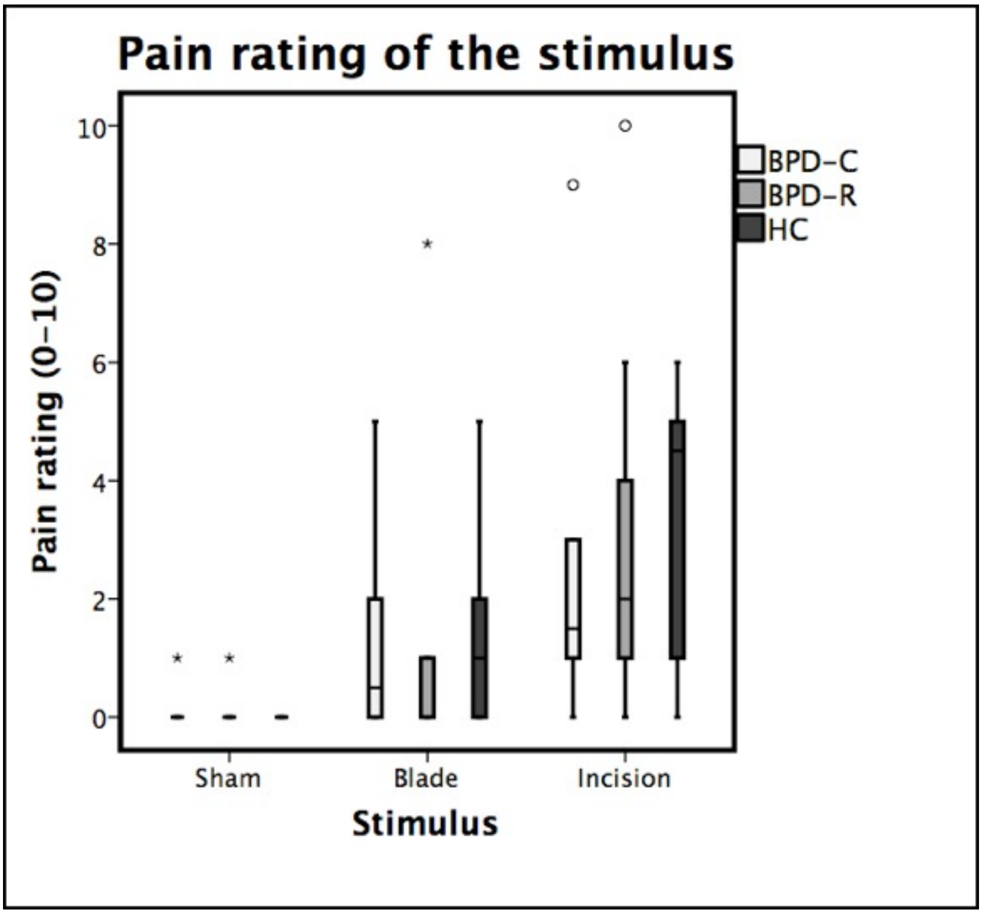

Table 1: Psychiatric comorbidities and medication

	BPD remitted	BPD current	HC
Psychiatric comorbidities			
Mood disorder, current Mood disorder, lifetime	2 (7%) 24 (80%)	6 (20%) 25 (83%)	/ /
Substance abuse, lifetime	11 (37%)	12 (40%)	/
Substance dependence, lifetime	7 (23%)	9 (30%)	/
Anxiety disorder, current Anxiety disorder, lifetime	5 (17%) 14 (47%)	12 (40%) 14 (47%)	/ /
Posttraumatic stress disorder, current Posttraumatic stress disorder, lifetime	/ 12 (40%)	14 (47%) 16 (53%)	/ /
Obsessive-compulsive disorder, current Obsessive-compulsive disorder, lifetime	1 (3%) 2 (7%)	3 (10%) 4 (13%)	/ /
Eating disorder, current Eating disorder, lifetime	2 (7%) 17 (57%)	8 (27%) 14 (47%)	/ /
Number of current diagnoses			
0	19 (63%)	4 (13%)	/
1	8 (27%)	12 (40%)	/
2	1 (3%)	9 (30%)	/
3	/	2 (7%)	/
4	/	3 (10%)	/
Medication			
SSRI	3 (10%)	4 (13%)	
Thyroid hormones	4 (13%)	4 (13%)	4 (13%)
Oral contraceptives	4 (13%)	2 (7%)	6 (20%)
Blood pressure lowering agents	/	1 (3%)	/
Proton pump inhibitors	1 (3%)	1 (3%)	/
Antihistamine	/	1 (3%)	/

Supplementary Table 2: HLM for immediate effects

SAM ratings – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.13 (0.24)	85	0.55	p = 0.59	0.06
Time*Pain Intensity	-0.42 (0.21)	82	-2.03	**p = 0.05**	0.22
Group*Pain Intensity	-0.10 (0.18)	90	-0.54	p = 0.59	0.06
Time*Group*Pain Intensity	0.13 (0.10)	81	1.38	p = 0.17	0.15
Heart rate – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.87 (1.27)	118	0.68	p = 0.50	0.06
Time*Pain Intensity	0.37 (1.10)	118	0.34	p = 0.73	0.03
Group*Pain Intensity	0.02 (0.95)	169	0.03	p = 0.98	<0.01
Time*Group*Pain Intensity	-0.09 (0.50)	118	-0.19	p = 0.85	0.02
SAM ratings BPD-R vs BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.06 (0.41)	53	-0.16	p = 0.88	0.02
Time*Pain Intensity	-0.81 (0.27)	53	-3.06	**p < 0.01**	0.39
Group*Pain Intensity	-0.20 (0.35)	60	-0.58	p = 0.56	0.16
Time*Group*Pain Intensity	0.41 (0.16)	53	2.54	**p = 0.01**	0.33
Heart rate BPD-R vs BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.06 (2.34)	76	0.25	p = 0.80	0.03
Time*Pain Intensity	-0.82 (1.52)	76	-0.54	p = 0.60	0.06
Group*Pain Intensity	-1.07 (1.73)	114	-0.62	p = 0.54	0.06
Time*Group*Pain Intensity	0.73 (0.91)	76	0.81	p = 0.42	0.09

Supplementary Table 2: HLM for immediate effects (continued)

Urge for NSSI BPD-R vs. BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.24 (0.28)	60	0.88	p = 0.38	0.11
Time*Pain Intensity	-0.03 (0.18)	60	-0.19	p = 0.85	0.02
Group*Pain Intensity	-0.05 (0.29)	60	-0.20	p = 0.85	0.03
Time*Group*Pain Intensity	0.01 (0.11)	60	0.10	p = 0.92	0.01
SAM ratings – BPD-R vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.38 (0.52)	53	0.73	p = 0.47	0.10
Time*Pain Intensity	-0.25 (0.47)	52	0.53	p = 0.60	0.07
Group*Pain Intensity	0.001 (0.32)	60	0.003	p = 1.00	<0.01
Time*Group*Pain Intensity	-0.13 (0.19)	52	-0.68	p = 0.50	0.09
Heart rate – BPD-R vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	1.19 (2.44)	66	0.49	p = 0.63	0.06
Time*Pain Intensity	2.35 (2.19)	66	1,07	p = 0.29	0.13
Group*Pain Intensity	1.02 (1.70)	111	0.60	p = 0.55	0.07
Time*Group*Pain Intensity	-0.85 (0.89)	66	-0.96	p = 0.34	0.12
Sam ratings – BPD-C vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.15 (0.25)	59	0.59	p = 0.56	0.08
Time*Pain Intensity	-0.55 (0.22)	56	-2.50	**p = 0.02**	0.32
Group*Pain Intensity	-0.10 (0.19)	60	-0.55	p = 0.58	0.07
Time*Group*Pain Intensity	0.14 (0.10)	56	1.47	p = 0.15	0.19
Heart rate – BPD-C vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.87 (1.35)	85	0.65	0.53	0.07
Time*Pain Intensity	0.02 (1.22)	85	0,02	p = 0.99	<0.01
Group*Pain Intensity	-0.02 (0.98)	114	-0.02	p = 0.98	<0.01
Time*Group*Pain Intensity	-0.09 (0.54)	85	-0.16	p = 0.87	0.02

Table 3: HLM for intermediate effects (continued)

SAM ratings – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.03 (0.03)	73	0.83	p = 0.41	0.10
Time*Pain Intensity	0.01 (0.03)	70	0.47	p = 0.64	0.06
Group*Pain Intensity	0.19 (0.12)	90	1.58	p = 0.12	0.16
Time*Group*Pain Intensity	-0.01 (0.01)	69	-0.92	p = 0.36	0.11
Heart rate – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.10 (0.16)	48	-0.64	p = 0.53	0.08
Time*Pain Intensity	-0.19 (0.14)	48	-1.40	p = 0.17	0.20
Group*Pain Intensity	-0.91 (0.72)	90	-1.26	p = 0.21	0.13
Time*Group*Pain Intensity	0.09 (0.06)	48	1.49	p = 0.14	0.21
SAM ratings BPD-R vs BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.05 (0.07)	45	0.69	p = 0.50	0.10
Time*Pain Intensity	0.05 (0.05)	45	1.03	p = 0.31	0.15
Group*Pain Intensity	0.53 (0.24)	60	2.23	**p = 0.03**	0.28
Time*Group*Pain Intensity	-0.04 (0.03)	44	-1.33	p = 0.19	0.20
Heart rate BPD-R vs BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.08 (0.30)	23	-0.26	p = 0.80	0.05
Time*Pain Intensity	-0.28 (0.19)	23	-1.42	p = 0.17	0.28
Group*Pain Intensity	-0.37 (1.39)	60	-0.27	p = 0.79	0.03
Time*Group*Pain Intensity	0.15 (0.12)	23	1.31	p = 0.20	0.26
Urge for NSSI BPD-R vs. BPD-C					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.08 (0.04)	54	2.07	p = 0.04	0.27
Time*Pain Intensity	-0.01 (0.03)	54	-0.26	p = 0.80	0.04
Group*Pain Intensity	0.004 (0.21)	60	0.18	p = 0.97	0.02
Time*Group*Pain Intensity	0.01 (0.02)	54	0.42	p = 0.68	0.06

Table 3: HLM for intermediate effects (continued)

SAM ratings – BPD-R vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.01 (0.06)	45	0.20	p = 0.84	0.03
Time*Pain Intensity	-0.05 (0.06)	44	-0.83	p = 0.41	0.12
Group*Pain Intensity	-0.12 (0.21)	60	-0.59	p = 0.56	0.08
Time*Group*Pain Intensity	0.01 (0.02)	44	0.48	p = 0.63	0.07
Heart rate – BPD-R vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.09 (0.16)	36	-0.59	p = 0.56	0.12
Time*Pain Intensity	-0.22 (0.15)	36	-1.55	p = 0.13	0.25
Group*Pain Intensity	-0.90 (0.72)	60	-1.26	p = 0.21	0.16
Time*Group*Pain Intensity	0.10 (0.06)	36	1.55	p = 0.13	0.25
Sam ratings – BPD-C vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.02 (0.03)	51	0.69	p = 0.49	0.10
Time*Pain Intensity	0.03 (0.03)	48	0.95	p = 0.35	0.14
Group*Pain Intensity	0.20 (0.12)	60	1.66	p = 0.10	0.21
Time*Group*Pain Intensity	- 0.01 (0.01)	47	-1.08	p = 0.28	0.16
Heart rate – BPD-C vs. HC					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.08 (0.30)	23	-0.26	p = 0.80	0.05
Time*Pain Intensity	-0.28 (0.19)	23	-1.42	p = 0.17	0.28
Group*Pain Intensity	-0.37 (1.39)	60	-0.27	p = 0.79	0.03
Time*Group*Pain Intensity	0.15 (0.12)	23	1.31	p = 0.20	0.26

Supplementary Table 4: HLM for immediate effects and immediate effects depending on the stimulus type

SAM ratings – immediate effects – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	-0.12 (0.54)	80	-0.22	p = 0.83	0.02
Time*Stimulus	-0.62 (0.54)	70	-1.16	p = 0.25	0.14
Group*Stimulus	-0.22 (0.48)	90	-0.47	p = 0.64	0.05
Time*Group*Stimulus	0.20 (0.25)	79	0.82	p = 0.42	0.09
Heart rate – immediate effects – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	1.27 (2.77)	120	0.46	p = 0.65	0.04
Time*Stimulus	1.36 (2.75)	120	0.49	p = 0.62	0.04
Group*Stimulus	-0.01 (2.39)	171	-0.002	p = 1.00	<0.01
Time*Group*Stimulus	-0.25 (1.28)	120	-0.20	p = 0.85	0.02
Urge for NSSI ratings – immediate effects – BPD-C and BPD-R					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.85 (0.61)	60	1.39	p = 0.17	0.18
Time*Stimulus	0.32 (0.45)	60	0.72	p = 0.48	0.09
Group*Stimulus	0.90 (0.76)	60	1.18	p = 0.24	0.15
Time*Group*Stimulus	-0.30 (0.28)	60	-1.06	p = 0.29	0.14
SAM ratings – immediate effects – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.004 (0.07)	70	0.06	p = 0.95	0.01
Time*Stimulus	0.004 (0.07)	69	0.07	p = 0.95	0.01
Group*Stimulus	0.22 (0.32)	90	0.69	p = 0.49	0.07
Time*Group*Stimulus	0.002 (0.03)	69	0.07	p = 0.94	0.01
Heart rate – immediate effects – all groups					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.23 (0.34)	49	0.67	p = 0.51	0.10
Time*Stimulus	0.40 (0.34)	48	1.17	p = 0.25	0.17
Group*Stimulus	-0.19 (1.80)	90	-0.11	p = 0.92	0.01
Time*Group*Stimulus	-0.10 (0.16)	48	-0.61	p = 0.55	0.09
Urge for NSSI ratings – immediate effects – BPD-C and BPD-R					
	Parameter estimate (mean ± standard error)	*df*	*t*	*p*	*r*
Time*Group	0.13 (0.09)	54	1.44	p = 0.16	0.19
Time*Stimulus	0.06 (0.07)	55	0.93	p = 0.36	0.12
Group*Stimulus	0.47 (0.56)	60	0.83	p = 0.41	0.11
Time*Group*Stimulus	-0.02 (0.04)	54	-0.43	p = 0.67	0.06

4 DISCUSSION

Both research papers “The role of nociceptive input and tissue injury on stress regulation in Borderline Personality Disorder” (Willis et al. 2016) and “Stress reactivity and pain-mediated stress regulation in remitted patients with Borderline Personality Disorder” (Willis et al. 2018) elaborate on NSSI and dysregulated affect in BPD. Since the reduction of aversive inner tension is one of the most important motives of NSSI (Kleindienst et al. 2008), those two aspects are barely separable. In this context both papers investigate the influence of pain respectively nociceptive input on stress regulation.
The findings of each paper contribute to the understanding pain-mediated stress regulation among current and remitted BPD patients.

The first research paper (Willis et al. 2016) elaborates on patients with current BPD. We investigated the influence of an invasive and non-invasive pain stimulus on subjective and objective stress parameters in 57 current BPD patients and 60 healthy controls (HC). During the entire experiment, we assessed arousal ratings as subjective and heart rate as objective stress parameters as well as the subjective urge for NSSI. After a 30-minute period of stress induction either a tissue-injuring stimulus (incision), a non-invasive stimulus (blade) - in previous examinations perceived as equally painful (Shabes et al. 2016) - or a tactile control stimulus (sham) was applied. This was followed by a 30-minute relaxation period and regular assessment of the above-mentioned parameters.
We showed that among current BPD patients subjective arousal levels were higher compared to HC during the entire experiment - at baseline as well as after stress induction and during the relaxation period. Regarding heart rate as an objective stress parameter there was no difference between BPD patients and HCs. During stress induction objective and subjective stress increased in both groups, but there was no increased stress reactivity in BPD patients.
After stress induction one of the three stimuli incision, blade or sham was applied on the right volar forearm behind a shield screen. Regarding all three stimuli, there was no statistically significant difference in the perceived pain intensity between the two groups; nonetheless pain ratings tended to be higher among HCs. Among current BPD patients, incision and blade were rated to be significantly more painful than the sham condition. BPD patients did not rate the incision stimulus as significantly more painful than the blade stimulus. HCs however, perceived the incision stimulus to be more painful than the blade stimulus and both, the incision as well as the blade stimulus were rated to be more painful than the sham stimulus.
Immediately after the stimulus application arousal ratings of current BPD patients significantly decreased after the application of the two nociceptive stimuli. Compared to the sham condition, we found a significantly greater decreased of arousal ratings after incision. Comparing blade and incision, there was no difference in reduction of arousal ratings immediately after the application. There was a tendency for a greater decrease of arousal ratings after blade compared to sham, but it missed statistical significance. These findings were partially supported by the analysis of heart rate. Again, a significant decrease of heart rate was found after the application of the two painful stimuli, but there was no difference in heart rate decrease between the two stimuli. Moreover, the decrease of heart rate tended to be more pronounced after incision compared to sham, but also slightly missed statistical significance.

Concerning the urge for NSSI no differential decrease depending on the stimulus application was observed.
Considering the entire relaxation period, no intermediate effects of the stimulus on arousal ratings, heart rate and urge for NSSI were observed.
In addition, we assessed the DSS score to measure dissociation. As a reflection of the disorder, DSS scores were higher among current BPD patients compared to healthy controls. Among current BPD patients DSS scores were higher after study participation than before, whereas they stayed the same in the group of HCs. In both groups, we found no correlation between the DSS scores and pain perception.

The second research paper (Willis et al. 2018) focusses on remitted BPD patients. We used the same study design as in the first research paper. To a new group of 30 remitted BPD patients we matched 30 healthy controls according to age and education and 30 current BPD patients according to age, education and the urge of NSSI at the beginning of the experiment from the previous described sample (Willis et al. 2016). Due to the smaller sample size and consequently smaller power, we did not treat the stimulus type but the pain rating directly after stimulus application as independent variable, since in the previous study it appeared likely that the stress-reducing effect of the stimuli is caused by pain experience (Willis et al. 2016).
We confirmed the findings of the previous study with current BPD patients showing significantly higher baseline arousal levels than HCs. Remitted BPD patients showed higher arousal ratings than HCs, but lower ratings than current BPD patients. The same pattern was observed for heart rate levels. During stress induction, arousal ratings increased in all three groups without any difference regarding stress reactivity; so that at the end of stress induction, current BPD patients still had the highest and HCs the lowest arousal ratings and the ratings of remitted BPD patients lay in between the two other groups. Heart rate also increased in all three groups without showing a differential stress reactivity.
We found that directly after the stimulus application only in current BPD patients a higher pain experience led to a greater decrease of arousal. In HCs as well as remitted BPD patients, we did not find any evidence of greater reduction of arousal depending on the painfulness of the stimulus. Regarding heart rate, there was a decrease after stimulus application in all three groups but independent of the pain intensity of the stimulus. Current BPD patients showed a more pronounced decrease of urge for NSSI compared to remitted BPD patients, but it was not correlated to the painfulness of the stimulus.
As in the first research paper, we did not find any longer lasting effects of the stimulus concerning heart rate levels and the urge for NSSI. For arousal ratings, however, we found that among current BPD patients, overall arousal ratings in the entire relaxation period were higher after low pain intensity and arousal ratings were lower with increased pain intensity. The opposite reaction was observed for remitted BPD patients, where higher pain ratings were associated with higher arousal ratings and lower pain ratings were associated with lower arousal ratings. HCs showed a corresponding pattern to remitted BPD patients.

The results of both papers, considering current and remitted BPD patients compared to each other and to HCs, enable us to get a better insight of the mechanisms of NSSI and the influence of pain-mediated stress regulation in the course of BPD. As already stated in the introduction, NSSI can be understood as dysfunctional construct to cope with dysregulated affect (Reitz et al. 2015). The function of NSSI may be to compensate for deficient cognitive control mechanisms in emotion regulation

(Niedtfeld et al. 2012). The tension relief and relaxation caused by NSSI negatively reinforce and thereby maintain this dysfunctional behavior. Furthermore, NSSI may lead to an altered appraisal of pain (Niedtfeld et al. 2012). Taken together, the combination of disturbed emotion regulation and dysfunctional NSSI creates a "vicious circle".

Since NSSI is mainly used in states of high aversive tension, we induced stress via the Montreal Imaging Stress Task (MIST) (Dedovic et al. 2005) and investigated tension levels throughout the entire experiment. Reflecting the dysregulated affect typical for BPD, in both papers overall tension levels were significantly higher in current BPD patients compared to HCs (Willis et al. 2016; Willis et al. 2018). Remitted BPD patients still seem to experience elevated levels of inner tension to some extent, as they experienced higher stress levels than HCs but lower stress levels than current BPD patients (Willis et al. 2018). Confirming previous findings (Kuo & Linehan 2009; Reitz et al. 2012), we found elevated baseline stress levels but no elevated stress reactivity in current BPD patients compared to remitted BPD patients and HCs.

Regarding pain-mediated stress reduction, in the first research paper our findings showed that among BPD patients both tissue-injuring nociceptive stimuli (incision) and non-invasive nociceptive stimuli (blade) induce tension relief. Since both nociceptive stimuli - with and without tissue injury – led to a reduction of stress levels, it appears likely that pain perception or nociceptive processing is a major mechanism for the tension-relieving effects of NSSI. We critically discussed this aspect, whether the tension relieving effects are rather due to pain perception or nociceptive processes (Willis et al. 2016). 50-80% of BPD patients do not feel pain during NSSI (Bohus et al. 2000), which we did not assess in our study. As we do not know if the current BPD patients in our sample do or do not feel pain during NSSI, it cannot be deduced that the stress-reducing effects of NSSI are due to the perception of pain. Moreover, it has been suggested that in BPD patients the affective and sensory-discriminative dimensions of pain are uncoupled (Magerl et al. 2012), but there seems to be no impairment of the sensory discriminative pain component in BPD patients (C. Schmahl et al. 2004). These findings indicate that painful stimuli are processed by the nociceptive system, but are not experienced as painful on the cerebral level. Therefore, we conclude that the stress-reducing effects of painful stimuli in BPD patients might as well be due to nociceptive processes and not necessarily to the experience of pain.
We did not find any evidence for tissue injury leading to a greater stress reduction. The impact of tissue injury on stress regulation during acts of NSSI, however, cannot be answered with our paper. This question has to be further established, due to the fact that based on a limited sample size our findings cannot be considered as conclusive (Willis et al. 2016). If the stress reducing effects are not mainly caused by tissue injury, the question remains why most BPD patients use tissue-injuring methods as primary methods for NSSI (Kleindienst et al. 2008; Andover 2014; Manca et al. 2014). We hypothesized that maybe a certain nociceptive input or stress level is necessary to create stress reduction (Willis et al. 2016). Considering that in our study induced stress levels lay only in a medium range and that preceding a real NSSI event current BPD patients tend to experience higher stress levels (Chapman et al. 2006), stress-induced analgesia may be of importance. Therefore, significantly higher pain levels than reached by the incision or blade stimulus might be needed. Here we speculated that these higher pain levels might be reached more easily using tissue-

injuring forms of NSSI (Willis et al. 2016). Moreover, we argued that, other factors associated with tissue-injury, like the effect of seeing blood or the ritual of performing NSSI itself (Glenn & Klonsky 2010; Naoum et al. 2016) might be necessary to achieve the full tension-relieving effect (Willis et al. 2016).
In our second study (Willis et al. 2018), we could confirm our previous findings that the experience of pain leads to a reduction of self-rated arousal in current BPD patients. The stronger the experience of pain, the more marked was the decrease of arousal ratings in current BPD patients. In comparison to remitted BPD patients the decrease of arousal was significantly stronger in current than in remitted BPD patients. In contrast to current BPD patients, in both remitted BPD patients and HCs, we found no evidence for pain-mediated stress regulation.
As already stated above, we cannot be sure whether the tension relieving effects of blade and incision are due to pain perception or nociceptive processes. Therefore, the decision to investigate the decrease of stress parameters depending on pain intensity of the stimulus for analytical reasons in the second research paper should be discussed critically. We did not assess whether the participants generally experience analgesia or states of elevated inner tension during NSSI. Hence, choosing the painfulness of the stimulus might have biased our results as in the second paper we were able to show the effect of pain perception but did not investigate the effect of nociception on stress parameters. However, due to the small number of available remitted BPD patients, other analyses were not possible since the statistical power would have been insufficient.
Taking the results of the two papers into consideration, our findings suggest that the experience of nociceptive stimuli respectively pain to regulate stress plays an important role in patients with current BPD. Regarding remitted BPD patients, they still seem to experience increased levels of aversive inner tension; the role of pain-mediated stress regulation, however, appears to have faded.

In both research papers, we could show effects of the stimulus application on arousal. The effect on heart rate levels, however, was less pronounced (Willis et al. 2016) or not observed at all (Willis et al. 2018). Also in other studies discrepancies between objective and subjective measures of emotions in BPD have been described (Lampe et al. 2007; Krause-Utz, A et al. 2013; McCloskey et al. 2009). We speculated that the difference might also depend on the assessment of emotion in current BPD patients, e.g. whether a questionnaire or behavioral measures are used (Willis et al. 2018): Current BPD patients might tend to overrate emotional reactions or impulsivity on a psychometric level, which then cannot be completely verified in the laboratory. Also, the strong fluctuations of stress levels might lead to an over-estimation of emotions or impulsivity. Therefore, we suggested in both papers that for further studies it might be helpful to additionally analyze other objective stress parameters such as heart rate variability, skin conductance or salivary cortisol to bridge this gap and add knowledge on the interaction of stress and emotions (Willis et al. 2016; Willis et al. 2018).

In current BPD patients, affect regulation is believed to be the strongest maintaining factor of NSSI and that the urge for NSSI is conditioned on aversive inner tension (Klonsky 2007; Chapman et al. 2006). However, regarding remitted BPD patients our results do not support these theories. In both studies, we assessed the urge for NSSI. During stress induction, current BPD patients reacted with a significant increase of urge for NSSI (Willis et al. 2016; Willis et al. 2018). Remitted BPD patients still reacted with an increase of urge for NSSI during stress induction, even

though acts of NSSI in this group of patients was rare (Willis et al. 2018). Here, it must be stressed that urge for NSSI and acts of NSSI are not the same. The presence or absence of acts of NSSI with skin lesions were including criteria for the group of current and remitted BPD patients respectively, which may confound the analysis of urge for NSSI between the two groups. However, regular use of NSSI is a correlate of severe dysfunctional behavior and is not consistent with our understanding of remission in BPD. In the second research paper where we compared the urge of NSSI between current and remitted BPD patients, the two groups were matched according to the urge for NSSI at baseline to create a more comparable situation.
We showed that urge for NSSI is more present and pronounced in current compared to remitted BPD patients, even though remitted BPD patients in our sample still seem to experience increased levels of aversive inner tension (Willis et al. 2018). We therefore proposed that urge for NSSI is not only conditioned to the presence of aversive inner tension, but also that the regular use of NSSI reinforces itself and leads to an increased urge for NSSI during states of high aversive inner tension (Willis et al. 2018).
In this context, we speculated that to remit from NSSI other methods to cope with increased tension levels were developed (Willis et al. 2018). Meanwhile, a recent fMRI study demonstrated for the first time, that pain-mediated affect regulation can be changed by Dialectical Behavior Therapy (DBT) and that after 12 weeks of DBT treatment pain processing in BPD tended to normalize (Niedtfeld et al. 2017).

In both studies (Willis et al. 2016; Willis et al. 2018), we did not show any longer lasting effects of the stimuli on stress reduction. A possible explanation might be that the stress levels induced via the MIST test were only within a medium range, whereas before acts of NSSI BPD patients experience higher levels of aversive inner tension (Stiglmayr et al. 2005). Therefore, the return to baseline might have occurred within a shorter period. Other authors suggest that NSSI rather has stabilizing than decreasing effects on negative affect (Vansteelandt et al. 2017; Houben et al. 2017). However, in these two reports the immediate effects of NSSI were not investigated. Therefore, the existence of different short and long term effects of NSSI on stress regulation seems possible.

Pain-mediated stress regulation in BPD is closely linked to the topic of pain perception in general in patients with BPD. Among current BPD patients, reduced pain sensitivity is a robust finding (Bohus et al. 2000; C. Schmahl et al. 2004; Ludaescher et al. 2007; Magerl et al. 2012). In line with these findings, pain ratings tended to be lower in current BPD patients compared to HCs in the first study, however the difference did not reach statistical significance (Willis et al. 2016). The incision stimulus was perceived to be more painful in the group of HCs, whereas the difference concerning the blade stimulus was less pronounced. We discussed two possible explanations for the variance in pain perception: First, the experience of analgesia might explain the variation within BPD patients, which was not assessed in our sample. Second, elevated pain thresholds are associated with dissociation (Ludaescher et al. 2007). In our sample, however, DSS scores reflecting dissociation were rather low and did not correlate to pain ratings (Willis et al. 2016).
The blade stimulus was calibrated to be perceived as equally painful compared to the incision stimulus (Shabes et al. 2016). Interestingly, in our sample this only applied to current BPD patients, whereas HCs rated incision to be more painful than blade (Willis et al. 2016). As a possible explanation, we discussed the nature of pain

assessment in both studies (Willis et al. 2016): In Shabes et al. 2016 pain was assessed as an online rating during blade application until 30 seconds after, whereas in Willis et al. 2016 pain was assessed immediately, but still retrospectively, after the stimulus application. There is evidence that even though continuous ratings and post hoc ratings correlate well, differences regarding maximum pain ratings can be found (Koyama et al. 2004), possibly due to variability in memory consolidation in the early phase of memorizing pain (Jantsch et al. 2009).
In the second study, we found differences regarding the response to pain perception. In current BPD patients, higher pain ratings of the stimulus were associated with lower arousal ratings. Whereas the opposite pattern was found for remitted BPD patients and HCs as higher pain ratings were associated with higher arousal ratings. This shows a different evaluation of pain experience between current BPD patients and remitted BPD patients as well as HCs, who show similar responses as remitted BPD patients. These findings suggest a more normal correlation between stress and pain experience among remitted BPD patients (Willis et al. 2018). This is in line with previous findings, that the evaluation of nociceptive stimuli and pain sensitivity is linked to the regular performance of NSSI and BPD severity (Ludäscher et al. 2009; Bekrater-Bodmann et al. 2015; Niedtfeld et al. 2012).

The two studies do not answer any questions regarding the underlying neurobiological mechanisms of NSSI and pain-mediated stress regulation. On a neurobiological level, incision was associated with reduced amygdala activity and improved amygdala-prefrontal connectivity in BPD patients. The opposite pattern was described for incision in HCs, which was interpreted as NSSI being a dysfunctional attempt to cope with dysregulated affect (Reitz et al. 2015).
A recent fMRI study investigating the effect of DBT treatment on pain-mediated stress regulation showed that after 12 weeks of treatment amygdala deactivation in response to painful stimuli was no longer verifiable, suggesting a normalization of pain evaluation and emotion control (Niedtfeld et al. 2017).
For further studies, it would be interesting to investigate the neurobiological mechanisms of the blade stimulus in BPD patients compared to HCs and remitted BPD patients. Moreover, it would be interesting to investigate whether the link between emotion regulation and pain perception is still present in remitted BPD patients or whether the above-mentioned changes after DBT can be replicated for all remitted BPD patients and whether they show similar neural activation patterns to HCs.

Limitations of both studies have already been discussed at length elsewhere (Willis et al. 2016; Willis et al. 2018). Most importantly, both studies have a relatively small sample size and therefore await replication from a larger sample. Since we excluded patients under psychotropic medication except SRRI there might be a selection bias. We excluded most psychotropic medications since they have emotion regulating effects and would have influenced the analysis of dysregulated affect and pain perception. This also applies for SRRI; still we did not exclude SRRI due to the high prevalence among BPD patients which would also have led to a biased sample.
Furthermore, we only investigated the effect of NSSI on stress regulation to reduce states of aversive inner tension and did not consider any other motives for NSSI (Klonsky 2007; Kleindienst et al. 2008). Eventhough tension relief is the primary motive for most BPD patients it is not the only one and our findings might not apply for all BPD patients.

In addition, the setting in our study differed from a real NSSI event. First of all, the chosen stress task only induced stress levels in a medium range, whereas patients tend to experience higher levels of aversive inner tension before acts of NSSI (Stiglmayr et al. 2005). The MIST was chosen as a generic stress task since it induces stress in most subjects - in BPD patients as well as HCs. Nonetheless, in BPD other components namely social rejection and the experience of shame which are related to the experience of increased tension levels were not considered (Chapman et al. 2014; Schoenleber et al. 2014).
Second, the application of the incision and even more of the blade stimulus itself differed from an act of NSSI. Participants could feel the pain, but were not able to see the arm where the stimulus was applied, so that other possible stress-reducing factors – such as seeing blood – were not considered (Naoum et al. 2016). Moreover, the application of the stimulus was not self-inflicted and the participant had no control over the stimulus application. In this context, the effect of self- and extrinsic infliction would be interesting to investigate in further studies.
Regarding the second research paper, it should be noted, that there is no standard definition of remission. Zanarini et al. define remission as no longer meeting five diagnostic criteria for BPD for two years (Zanarini et al. 2008; Zanarini et al. 2012; Zanarini et al. 2003). Whereas for Gunderson et al. remission is defined as no longer meeting two or more BPD criteria for at least 12 months (Gunderson et al. 2011). In our sample, remitted BPD patients did not meet more than three criteria in at least two years prior to study participation (Willis et al. 2018). In addition, it should be considered, that fulfilling the remission criteria does not assess the functioning of the patients. Attaining good functioning is called recovery of BPD, which Zanarini et al. defined as a Global Assessment of Functioning (GAF) score higher than 60 (Zanarini et al. 2012). In our study, we only investigated the BPD symptoms NSSI and dysregulated affect reflected by tension levels (Willis et al. 2018). Therefore, we cannot address the topic of recovery in our sample of patients.

Taken together, our studies contribute to the understanding of the mechanisms of NSSI. On the one hand, we received more insight into the role of tissue injury in NSSI and on the other hand, we proposed further maintaining factors for NSSI underlying the complexity of this dysfunctional behavior. Moreover, the studies are an important step regarding the understanding of NSSI, pain perception and pain-mediated stress regulation in the course of BPD. Our results suggest that among current BPD patients pain perception respectively nociception plays an important role regarding stress regulation, especially compared to HCs and remitted BPD patients. In remitted BPD patients, we showed a fading association between nociception and tension relief, a reduced presence of urge for NSSI, and a normalization of pain evaluation. Considering these results, it appears likely that remitted BPD patients found methods to escape the “vicious circle” of NSSI and disturbed emotion regulation, which might be an important step to recover from BPD.

5 ABSTRACT

Borderline personality disorder (BPD) is characterized by a pervasive pattern of instability in affect and emotion regulation, disturbed impulse control, disturbed cognition, instable interpersonal relationships as well as a disturbed self-image. High levels of aversive inner tension are one of the cardinal symptoms of BPD. Approximately 60-90% of patients with Borderline Personality Disorder (BPD) show non- suicidal self-injurious behavior (NSSI) with cutting being the most frequently applied method. One of NSSI's functions is to reduce aversive tension. Previous studies have found a tension-reducing effect of painful tissue injury by an incision. It is still unclear whether this effect is based on the effect of tissue injury or the effect of pain experience, or both. Further, it remains unclear to what extent remitted BPD patients experience states of aversive inner tension and whether the experience of pain still regulates emotion.
The aim of this dissertation is to elaborate on these open questions.

To determine whether tissue injury leads to a stronger stress reduction than a sole pain stimulus in patients with BPD, we investigated pain-mediated stress regulation in 57 female patients with current BPD and 60 female healthy controls (HC). After a successful stress induction, the participants received either a tissue-injuring incision or a non-tissue-injuring mechanical nociceptive stimulus ("blade") typically perceived as painful, or a non-nociceptive tactile sham stimulus (blunt end of scalpel). For stress assessment, subjective and objective parameters were measured.
As an immediate response to the stimulus application, there was a greater stress reduction after both painful stimuli (incision and blade) in BPD patients, but no difference in stress decrease between the tissue-injuring incision and the non-tissue-injuring pain stimulus ("blade"). Compared to HCs, incision and blade were followed by greater immediate decrease of arousal in BPD patients.

To investigate baseline stress levels, stress reactivity and pain-mediated stress regulation in remitted BPD patients, the above described study procedure was performed with 30 female remitted BPD patients. This new group was matched according to age and educational background to 30 female patients with current BPD and 30 female healthy controls from the larger, above-mentioned sample.
The results show that baseline stress levels of remitted BPD patients lie in between the stress levels of current BPD patients and healthy controls. Urge for NSSI increased significantly more in current than remitted BPD patients. Moreover, the experience of pain led to a greater decrease of arousal in current compared to remitted BPD patients and healthy controls.

These findings confirm, that among BPD patients the nociceptive input leads to stress reduction. In contrast, the impact of tissue damage on stress reduction was relatively small. In addition, the results suggest that painful stimuli lead to a greater stress reduction in BPD patients compared to healthy controls.
Regarding remitted BPD patients, states of increased tension still seem to exist. The role of pain-mediated stress regulation, however, appears to be reduced in remitted patients compared to current BPD patients.

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