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ALTERED PERCEPTION OF APPETITIVE AND AVERSIVE SOMATOSENSORY STIMULI IN BORDERLINE PERSONALITY DISORDER

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ABBREVATIONS

BPD	borderline personality disorder
CT	C-tactile afferents
DSM	Diagnostic and Statistical Manual of Mental Disorders
HC	healthy controls
ICD	International Classification of Diseases
IPDE	International Personality Disorder Examination
NMDA	*N*-methyl-*D*-aspartate
NSSI	non-suicidal self-injury
RIII-reflex	nociceptive flexion reflex
SCID	Structured Clinical Interview for DSM
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
TPT	touch perception task

CHAPTER 1

Introduction

"People with BPD [borderline personality disorder] are like people with third degree burns over 90% of their bodies. Lacking emotional skin, they feel agony at the slightest touch or movement"

Marsha Linehan (n.d.)

The skin is the largest organ of the human body and fulfills a number of different functions. It separates the inside from the outside of the body, has an important protective function and plays a crucial role in thermoregulation. In addition, the skin is part of the somatosensory system and signals, for instance, touch, temperature or pressure. Thereby, it also receives and transmits numerous affective signals from our environment, for example, a tender caress or the cozy warmth of a fireplace, but also the pinch of a tight shoe or the burning pain of a slap in the face.

When Marsha Linehan, one of the most prominent researchers in the field of borderline personality disorder (BPD), spoke of people with BPD lacking emotional skin, she did not mean it literally, but was referring to the inability to regulate affective states. However, there is indeed evidence for altered affective somatosensation in BPD - at least for negative stimuli in terms of pain perception. Patients with BPD report no or only little pain during non-suicidal self-injury (NSSI) (Leibenluft et al., 1987) and a recent meta-analysis confirmed reduced pain perception in BPD (Fales et al., 2021). However, even though there are consistent findings of reduced pain perception in BPD, the mechanism behind it remains largely unknown (Bekrater-Bodmann, 2021). To elucidate this mechanism and its contribution to psychopathological aspects of BPD, it is important to investigate whether the alterations in BPD are specific to pain or also related to other affective somatosensory modalities including positive ones. A comprehensive and deeper understanding of altered positive and negative somatosensation in BPD and its relation to BPD symptomatology might help to understand the psychopathology of the disease and would also provide novel insights into the mechanisms of somatosensation.

The aim of this thesis was therefore to investigate positive and negative affective somatosensation in BPD, and relate it to BPD symptomatology, mainly dissociation and NSSI, which are common features of the disorder. This thesis starts with a brief

introduction into BPD, emphasizing affective disturbances as well as dissociation, and NSSI, which have been shown to be associated with altered pain perception in BPD. Thereafter, the somatosensory system is described with a focus on pain and pleasant touch and previous findings on somatosensory processing in BPD are summarized. Based on this, the research questions and hypotheses of this thesis are presented. The original contributions consist of one study on pleasant touch perception in BPD and one study on the processing of single and repetitive painful stimuli in BPD. The thesis closes with an overall discussion including limitations and an outlook for future research as well as clinical implications.

1.1 Borderline personality disorder

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5, American Psychiatric Association, 2013) defines borderline personality disorder as a pervasive pattern of instability of interpersonal relationships, self-image, and affect, as well as marked impulsivity based on nine criteria. Among these three criteria are related to affective dysfunctions, all emphasizing disturbances in negative affect: *affective instability* (especially with regard to dysphoria, irritability, and anxiety), *feelings of emptiness*, and *inappropriate intense anger or difficulty in controlling anger*. Two criteria highlight impulsive self-harming behavior, one of the most prominent features of BPD: *recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior* and *impulsivity in potentially self-damaging areas* (e.g. substance abuse, binge eating, sexual behavior). Two criteria refer to disturbed self-image: *identity disturbances* and *transient, stress related paranoid ideation or severe dissociation*. Problems in interpersonal functioning are described in two criteria: *frantic efforts to avoid real or imagined abandonment* and *a pattern of unstable and intense interpersonal relationships*.

Historically, the term borderline personality was used to describe patients on the border between neurotic and psychotic behavior, who were poorly responsive to psychotherapy (Stern, 1938). Today, it is the most widely researched personality disorder for which numerous evidence-based treatments have been developed. Therefore, the borderline personality classifier, which essentially relies on the DSM-5 definition of BPD, remained the exclusive one in the *International Classification of Diseases, 11th Revision* (ICD-11, World Health Organization, 2021), which otherwise

does not further distinguish among different personality disorders but takes a dimensional view (Reed, 2018). Despite great scientific progress, patients with borderline personality disorder still account for 10-12% of the outpatients with mental disorders and 20-22% of the inpatients with mental disorders (Ellison et al., 2018; Trull et al., 2010) and is associated with high health care costs, exceeding those of other mental disorders, for example major depressive disorder (Bode et al., 2017). BPD is not only an enormous burden on the health care system, but also on each individual patient, culminating in a suicide rate of 10% of patients diagnosed with BPD (Paris & Zweig-Frank, 2001).

According to one of the most influential models of BPD, the biosocial model put forward by Marsha Linehan (1993), BPD arises from a biological/genetic disposition and an invalidating developmental environment, characterized by intolerance towards the expression of emotions. This results in emotional dysregulation, which in turn is the basis for other BPD features such as dysfunctional self-related cognitions or psychosocial problems. Empirical studies support the important role of environmental risk factors such as harsh or insensitive parenting, emotional neglect, physical or sexual abuse and victimization as well as a role of genetic factors for the development of BPD. ,The central role of emotional dysregulation in the psychopythology of BPD has also been supported by neurobiological findings, which identified disturbances in a cortico-limbic network as main neural alteration in BPD (Bohus et al., 2021). This network includes areas known to be involved in emotion processing (mainly amygdala and insula) as well as areas associated with in regulatory processes (e.g. anterior cingulate cortex, medial frontal cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex (Krause-Utz et al., 2014b). Given the central role of emotional dysregulation in the context of BPD, it is a main focus of BPD research (Bertsch et al., 2018)

1.1.1 *Affective disturbances*

In a review of the recent literature on affective processing in BPD, Bertsch et al. (2018) reported empirical evidence for a negativity bias in BPD, i.e. a negatively biased perception of what compared to healthy controls (HC), which was assumed to be related to threat-hypersensitivity. These results were mainly derived from studies that assessed the perception of neutral or ambiguous faces and similar results have already been found in meta-analyses before (Daros et al., 2013; Mitchell et al., 2014). Increased amygdala-activation that has been shown in response to (negative)

emotional stimuli might underlie threat-hypersensitivity in BPD (L. Schulze et al., 2016). This is further supported by a study using combined functional magnetic resonance imaging and eyetracking, which revealed the strongest amygdala activation for those participants with BPD who exhibited more and faster initial fixation to the threatening part of the depicted angry faces (Bertsch et al., 2013). Compared to the investigation of neutral or negative emotional stimuli, there are only a few studies that assessed the perception and processing of positive affective stimuli. These studies observed a pronounced negative evaluation tendency even for positive emotional faces in BPD compared to HC (e.g. Fenske et al., 2015; Thome et al., 2016). A study that used positive, negative, and neutral words as stimuli and additionally manipulated referential processing by adding a preceding self-referential pronoun, an other-referential pronoun, or no reference, revealed that more negative evaluation of positive cues might be especially pronounced for self-referential information (Winter et al., 2015). This deficient perception and detection of positively valenced stimuli may hinder patients to detect safety signals or make positive interpersonal experiences (Bertsch et al., 2018).

1.1.2 *Dissociation and non-suicidal self-injury*

Dissociation is a complex phenomenon characterized by a ‘disruption of perception, consciousness, identity, and memory (American Psychiatric Association, 2013), which is highly prevalent in BPD (Lyssenko et al., 2018) and has been linked to other core features of the disorder (Krause-Utz, 2022). Trauma models of dissociation suggest that it is a defensive mechanism aimed at coping with overwhelming negative experiences (e.g. Vermetten & Spiegel, 2014). This assumption is supported by neuroimaging studies indicating that higher functional coupling between amygdala and prefrontal regions might be involved in emotion regulation in dissociative states (Nicholson et al., 2015). While dissociation might be an adaptive mechanism during potentially traumatic situations, it may become maladaptive when it also occurs under normal stressful situations. Psychological symptoms of dissociation range from detachment from one’s self or environment (depersonalization and derealization) and memory impairments to somatoform symptoms, including reduced pain perception and loss of voluntary movement. Milder forms of dissociative symptoms like absorption may occur also in healthy persons, for example due to stress, but should be distinguished from their pathological form (Spiegel & Cardeña, 1991). Studies on healthy people

revealed that intravenous administration of ketamine, an *N*-methyl-*D*-aspartate (NMDA) antagonist, induced pathological dissociative symptoms (Krystal et al., 1994) as assessed with the Clinician-Administered Dissociative States Scale (J. D. Bremner et al., 1998). This indicates that NMDA-dysfunction might play a role in pathological dissociation.

Reduction of dissociative states and related aversive inner tension are the most frequently reported motives for NSSI in BPD (Kleindienst et al., 2008; Perez et al., 2020). NSSI is defined as a repeated infliction of injuries to the surface of the skin without any suicidal intent (American Psychiatric Association, 2013) and can manifest in different forms whereby cutting is by far the most frequently type of self-inflicted injury reported among female persons with BPD (Kleindienst et al., 2008). While studies using ecological momentary assessment confirmed patterns of increasing negative affect prior to NSSI (Andrewes et al., 2017; Houben et al., 2017; Koenig et al., 2021), the results on the effects of NSSI revealed mixed results. Some studies did provide evidence for a decrease in negative affective state (Andrewes et al., 2017) or affective variability (Vansteelandt et al., 2017) after NSSI. Other studies did not provide such evidence or even reported an increase in negative affective states following NNSI (Houben et al., 2017; Koenig et al., 2021). In an experimental setting, Reitz et al. (2012, 2015) tested the effect of incision after stress induction in BPD and HC. They found a more pronounced decrease of aversive inner tension in BPD and, moreover, a decrease of amygdala activity and a selective normalization of functional connectivity of amygdala with the superior frontal gyrus in the BPD group, supporting the assumption of an influence of NSSI on emotion regulation.

1.2 Somatosensation

The somatosensory system is part of the sensory nervous system and composed of different ascending pathways carrying signals of different modalities starting from receptors in the skin, muscles, tendons and joints via the spinal cord to the brain. Somatosensory modalities include information on touch, temperature, pain, and position of the body (proprioception). Thus, the somatosensory system plays an important role in informing us about our body and our environment. Beyond the pure discriminative information, somatosensory signals play also an important role in affective experiences and communication. Thereby, mainly pain – signaling threat –

and touch that is perceived as pleasant – signaling safety and affiliation – are involved (de Haan & Dijkerman, 2020).

1.2.1 *Pain*

The *International Association for the Study of Pain* defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020, p.2). This definition emphasizes that pain has both a sensory and an affective component and that its main function is protective.

Nociceptive pain results from the stimulation of nociceptors, free nerve endings that respond to stimuli approaching or exceeding a harmful intensity and can be distinguished according to their fiber type. Aδ-fibers are myelinated, evoke a sharp first pain, while C-fibers are unmyelinated, and evoke a dull second pain. Afferent fibers transport nociceptive signals to the spinal cord, where several excitatory and inhibitory interactions occur. The further ascending pathway to the brain can be separated into two parts: (1) the lateral tract, mainly projecting to the lateral thalamus and the primary and secondary somatosensory cortices (SI and SII), is primarily involved in the sensory-discriminative component of pain, in terms of intensity, spatial and temporal aspects and (2) the medial tract, mainly projecting to the medial thalamus, the anterior- and mid-cingulate cortex and other limbic structures like the amygdala and prefrontal cortex, is primarily involved in the affective component of pain. This distinction was already described more than 50 years ago by Melzack and Casey (1968) and today the perception of both components is typically assessed via ratings of perceived pain intensity and unpleasantness.

Despite the anatomical-functional distinction of both components, the possibility to distinguish both components on a perceptual level was questioned and has been attributed to demand characteristics (Fernandez & Turk, 1994, 1992). Furthermore, it has been shown that ratings of both components are highly correlated (Chapman et al., 2001). However, pain intensity and pain unpleasantness are differentially related to specific facial expressions (Kunz et al., 2012). The independence of sensory and affective components has also been demonstrated in a case study of a stroke patient with lesion in SI and SII. In response to a laser stimulus, scaled up to around three times the pain threshold of the non-affected side, the patient reported a clearly unpleasant sensation but was not able to describe the sensory quality, location or

intensity of the stimulus (Ploner et al., 1999). Furthermore, studies using hypnotic suggestions report alterations of the affective pain component without changes in perceived pain intensity (Rainville et al., 1999), indicating selective top-down modulation capability of both pain components. This is further supported by a study using positron emission tomography (Hofbauer et al., 2001). Hypnotic suggestions for decreased-pain intensity led to significant changes in pain-evoked SI activity.

Wind-up, a pain-facilitating process, describes a C-fiber mediated reversible activation-dependent neural plasticity in spinal dorsal horn neurons following repetitive noxious stimulation (Mendell & Wall, 1965). It results in a prolongation and accumulation of excitatory post-synaptic potentials and is further intensified by NMDA sensitive receptors (Mendell & Wall, 1965). The latter view is supported by animal studies indicating that NMDA receptor antagonists inhibit wind-up (Davies & Lodge, 1987) and that the excitability of spinal flexion withdrawal reflexes is related to wind-up (Woolf & Thompson, 1991). The perceptual correlate of wind-up is temporal summation of pain, which refers to an increase in perceived second pain when noxious stimuli with constant physical intensity are delivered repeatedly with frequencies above 0.3 Hz (Kleinböhl et al., 2006; Price, 1972) or during tonic painful stimulation (Granot et al., 2006; Kleinböhl et al., 1999). Temporal summation of pain can be used to investigate wind-up in humans. It is reduced after NMDA-antagonist intake, for example ketamine, in humans (Eide, 2000). Moreover, in humans the temporal summation of the nociceptive flexion reflex (RIII-reflex) in response to repeated nociceptive stimulation is decreased after ketamine intake (Arendt-Nielsen et al., 1995), supporting the validity to use the RIII-reflex as a marker of spinal nociceptive processing in studies on temporal summation of pain. The RIII-reflex is a polysynaptic and multisegmental spinal reflex that induces a withdrawal movement of the limb against potential damage. The reflex threshold is associated with the pain threshold and its amplitude correlates with perceived pain intensity. In pain research, it can be used as a measure of spinal nociceptive processing. However, it is also modulated by supraspinal processes like attention, stress, or affect (Sandrini et al., 2005).

1.2.2 *Pleasant touch*

It is well known that large fast-conducting myelinated Aβ-fibers mainly propagate sensory discriminative aspects of tactile stimulation. Although it was reported some time ago that a distinct subgroup of slowly conducting unmyelinated tactile fibers in

mammalian (e.g. Kumazawa & Perl, 1977) and human (e.g. Vallbo et al., 1999) hairy skin respond to light touch, the function of these C-tactile afferents (CT) has long been unknown. A case study in a patient with a specific loss of large myelinated fibers revealed that a stroking stimulation with a soft brush in the affected body area evoked a pleasant percept in the patient that was comparable to that of healthy controls, while perceived intensity of the stimulation was significantly reduced. Additionally, in the same study neuroimaging was used to explore brain responses to the stimulation. Interestingly the patient did not show significant activation in somatosensory areas (SI and SII) as was the case for HC, but significant activation in the insula similar to that of HC. From their results the authors conclude that stroking stimulation activated CT, which signal the affective component of touch (Olausson et al., 2002). This was confirmed by a larger study on healthy persons using microneurography. This study revealed a strong correlation between the firing rate of CT and pleasantness ratings while this association was not present for other tactile afferents, suggesting a specificity of CT for transmitting the affective component of touch. Furthermore, results of the same study revealed that CT afferents mainly respond to stroking applied with velocities between 1 and 10 cm/s with decreased firing rates for lower and higher speeds (Löken et al., 2009). However, also other types of afferents might contribute to a pleasant touch percept, as a touch can perceived as pleasant even if it is applied to the glabrous skin, which is lacking CT (McGlone et al., 2012).

On a central level, pleasant touch perception is associated not only with activation in the insula (Gordon et al., 2013; Morrison et al., 2011; Olausson et al., 2002), but also with brain activity in the orbitofrontal-cortex and the anterior cingulate cortex (Gordon et al., 2013; Rolls et al., 2003) as well as the medial prefrontal cortex and the amygdala (Gordon et al., 2013). Interestingly, these brain regions are also involved in the processing of the affective component of pain, indicating a common neurobiology of the two affective somatosensory modalities of pain and pleasure (Leknes & Tracey, 2008).

1.2.3 *Similarities between pain and pleasant touch*

In addition to the similarity on the brain level mentioned above, there are other shared characteristics between pain and pleasant touch. Both, both pain and pleasant touch can be signaled via thin slow-conducting C-fibers, indicating a similarity of both affective somatosensory modalities even on peripheral level. Research on the

ascending pathway of pleasant touch at the spinal cord level has just begun, and the pathway through the spinal cord is not yet fully understood. However, animal studies suggest that there might be some parallel spinal pathways for pain and pleasant touch (Choi et al., 2021), but spinal transmission of pleasant touch in humans involves also non-spinothalamic pathways (Marshall, 2022), indicating that it is at least partly distinct from the transmission of pain.

The interaction between pain and pleasant touch is supported by studies demonstrating that touching stimulation applied with velocities within the CT-optimal range but not outside this range, reduce the perception of an experimentally induced painful stimulus (Liljencrantz et al., 2017; Mohr et al., 2018) as well as temporal summation of pain (Fidanza et al., 2021). Even if the mechanism remains elusive, it has been proposed that this pain modulating effect could occur due to a downregulation within the cerebral system that processes both pain and pleasant touch stimuli (Meijer et al., 2022). Moreover, pleasant touch perception and processing have been shown to be altered in chronic pain patients. Participants with chronic pain perceive pleasant touch as less pleasant and processing in orbitofrontal-cortex, insula, ventral striatum and anterior cingulate cortex is altered compared to HC (Nees et al., 2019), indicating that alterations in the processing of pain and pleasant touch might be interrelated.

1.3 Somatosensation in BPD

Starting with reports that the majority of patients with BPD feel little or no pain while self-injuring (Leibenluft et al., 1987), previous studies on somatosensation in BPD have focused mainly on the perception and processing of painful stimuli. These results are summarized in this chapter. In the following chapter, the few studies that have investigated the perception of other somatosensory stimuli in BPD are presented.

1.3.1 *Pain*

Russ et al. (1992) validated the clinical experience of reduced pain perception in BPD under experimental conditions by using the cold pressor task. Since then, numerous studies have confirmed pain insensitivity in BPD using different pain modalities like thermal (e.g. Schmahl et al., 2006), electrical (e.g. Ludäscher et al., 2007), mechanical and chemical (Magerl et al., 2012) painful stimuli. Furthermore, a recent systematic

review and meta-analysis confirmed lower pain ratings in response to experimentally applied pain stimuli as well as higher pain thresholds in BPD compared to HC (Fales et al., 2021).

It has been shown that reduced pain sensitivity in BPD involves both, Aδ-mediated first pain, induced by mechanical pin prick stimulation as well as chemically induced pain using capsaicin-injection eliciting a burning second pain, mainly conducted via C-fibers, indicating that altered pain perception is independent of nociceptive modality (Magerl et al., 2012). In a study using laser radiant heat stimuli, Schmahl et al. (2004) found unaltered spatial discrimination ability of nociceptive stimuli as well as unaltered laser evoked potentials in BPD compared to HC, suggesting normal processing of sensory-discriminative aspects of pain in BPD. Imaging studies revealed that reduced pain sensitivity in BPD might be related to increased prefrontal activation along with decreased activation in posterior parietal cortex, perigenual anterior cingulate gyrus and amygdala (Kraus et al., 2009; Schmahl et al., 2006). It has been proposed that this might be the antinociceptive mechanism behind reduced pain sensitivity in BPD and modulate pain perception mainly by an increased top-down regulation of the affective pain component (Schmahl et al., 2006; Schmahl & Baumgärtner, 2015).

Pain hyposensitivity in BPD has been shown to be associated with dissociative states (Bohus et al., 2000; Ludäscher et al., 2007) and might thus be part of the dysfunctional attempt to cope with stressful situations. A recent study assessed both, dissociative states and pain perception in BPD and HC under a neutral condition as well as after stress induction using a script-driven imagery approach (Chung et al., 2020). A positive correlation between heat pain threshold and dissociation proneness was observed, indicating that pain hyposensitivity in BPD is associated with the level of state dissociation, corrected for individual trait differences. Pain induced by the thermal grill illusion, i.e. non-nociceptive pain, was reduced and negatively correlated with state dissociation in BPD (Bekrater-Bodmann et al., 2015). Based on this result, the authors proposed that NMDA-dysfunction might play an important role in altered pain perception in BPD as NMDA-receptors are involved in both, dissociation (see above) and perception of the thermal grill illusion.

As outlined above NMDA-receptors play an important role in temporal summation of pain and a few recent studies started to assess temporal summation of pain in BPD. A study in a non-clinical sample with healthy subjects reported an association between

greater borderline features and greater temporal summation of heat pain (You & Meagher, 2017). A study in participants with BPD using repetitive mechanical stimuli in terms of von Frey filaments (Ginzburg et al., 2018) did not provide any evidence for altered temporal summation in BPD compared to HC. Another recent study in participants with BPD using tonic heat pain stimulation reported a non-significant trend for a lesser amount of temporal summation in BPD compared to HC. Moreover, there was a negative correlation between heat pain threshold and temporal summation in BPD but not HC, indicating that altered pain perception in BPD might be related to reduced temporal summation of pain (Defrin et al., 2020).

1.3.2 *Other somatosensory modalities*

Most of the findings on non-painful somatosensation in BPD derive from studies that focused on pain perception, but additionally investigated the perception of non-painful stimuli. For example, Bekrater-Bodmann et al. (2015) found unaltered warm perception and thermal discrimination thresholds, but heightened cold perception thresholds in BPD compared to HC. Unaltered warm perception thresholds were replicated by the same group (Chung et al., 2020) and this was also supported by a similar thermal perception as measured by a combined score of warmth and cold perception in BPD and HC (Schmahl et al., 2004; but see Defrin et al., 2020). Beside thermal perception, Schmahl et al. (2004) also assessed dorsal column function by testing vibration sense, proprioception, and tactile sensibility. A composite score of the results of all these tests did not significantly differ between BPD and HC. And also for electrical detection threshold, there was no evidence for alterations in BPD compared to HC (Ludäscher et al., 2009).

A study focusing on non-painful somatosensation in BPD assessed exteroception in terms of two-point discrimination and proprioception in terms of weight discrimination in a nonclinical sample with high BPD features compared to subjects with low BPD features (Pavony & Lenzenweger, 2014). There was no evidence for differences in exteroception or proprioception between both groups. In an fMRI study. Malejko et al. (2018) applied unpleasant but non-painful stimulation with four different levels of intensity to a clinical sample of participants with BPD and a HC sample. Behaviorally, accuracy of discrimination of stimulus intensity was not different between BPD and HC. This was supported by similar intensity-encoding neural activation in SI and SII, the posterior insula, the posterior midcingulate cortex, and the supplementary motor area.

The authors conclude from their results that observed alterations in affective appraisal of painful stimuli might be initiated by the higher salience of unpleasant painful stimuli compared to unpleasant non-painful stimuli.

1.4 Aims and hypotheses

As outline above, both, pain and pleasant touch are C-fiber mediated processes and there is a common neurobiology of pain and pleasure on the brain-level with involvement of amygdala, insula, prefrontal cortex and orbitofrontal cortex (Leknes & Tracey, 2008). These brain regions have also been shown to be involved in main psychopathological features of BPD (Krause-Utz et al., 2014b). Furthermore, there is growing evidence that the negativity bias observed in BPD also affects the perception of positive stimuli (Bertsch et al., 2018). All this raises the question, whether the perception of pleasant touch is altered in BPD. Therefore, in study 1, pleasant touch perception was assessed and affect-modulated acoustic startle responses served as physiological correlates of affective modulation. The magnitude of the startle response to a startling acoustic probe has been shown to be increased when unpleasant stimuli are processed and decreased during pleasant stimulation (Lang et al., 1990).

The first hypothesis addressed the question of altered positive somatosensation BPD:

1.1 Participants with BPD perceive pleasant touch stimuli as less positive compared to HC.

1.2 Inhibition of affect-modulated startle responses during pleasant touch stimulation is diminished in participants with BPD compared to HC.

In this study, pain perception was also assessed in terms of heat pain thresholds.

The second hypothesis addressed the association of deficient positive and negative somatosensation in BPD:

2 Less pleasant perception of pleasant touch is associated with higher heat pain thresholds in participants with BPD.

This study further explored the association between pleasant touch perception and dissociative state.

Study 2 aimed to investigate temporal summation of pain, a C-fiber mediated NMDA-dependent pain process and its relation to dissociation. Nociceptive processing on the spinal cord level was assessed by using the RIII-reflex. The hypothesis stated:

3 Temporal summation of pain perception is reduced in participants with BPD compared to HC.

4 A higher level of dissociation is associated with a lower temporal summation of pain in participants with BPD.

This study further aimed to explore nociceptive processing on a spinal cord level, as assessed with the RIII-reflex as well as the association between nociceptive processing on spinal cord level and pain perception as well as dissociation in BPD.

CHAPTER 2

Study I: Pleasant touch perception in borderline personality disorder and its relationship with disturbed body representation

An adapted version of this chapter has been published as ‘Löffler, A., Kleindienst, N., Neukel, C., Bekrater-Bodmann, R., & Flor, H. (2022). Pleasant touch perception in borderline personality disorder and its relationship with disturbed body representation. *Borderline Personality Disorder and Emotion Dysregulation, 9*(1), 1-16**.’**

2.1 Theoretical background study I

Borderline personality disorder (BPD) is a severe mental disorder characterized by dysfunctional affect regulation, impulsivity, problematic social interaction, and an unstable self-image (Lieb et al., 2004). All of these features are related to altered processing of affective stimuli, with evidence supporting the assumption of a negativity bias (Carpenter & Trull, 2013). Altered affective processing has mainly been shown for the responses to negatively valenced stimuli (L. Schulze et al., 2016). But there is growing evidence that positive affective processing is altered as well (Bertsch et al., 2018). In comparison to healthy controls (HC), negative evaluation tendencies have been reported for positive facial expressions (e.g. Fenske et al., 2015; Thome et al., 2016), positive taste stimuli (Arrondo et al., 2015), and positive social cues in terms of self-relevant appreciating sentences (Reichenberger et al., 2017).

Whereas previous studies repeatedly demonstrated significant reductions in pain sensitivity (Bekrater-Bodmann et al., 2015; Chung et al., 2020; Ludäscher et al., 2007, 2009; Russ et al., 1992; Schmahl et al., 2004, 2010), with the affective component of pain, compared to its sensory-discriminative component, being particularly affected (e.g. Schmahl et al., 2006), they found no evidence for altered proprioception, exteroception, and two-point discrimination (Pavony & Lenzenweger, 2014) or warmth perception thresholds (Bekrater-Bodmann et al., 2015; Chung et al., 2020; c.f. Defrin et al., 2020), suggesting that somatosensory dysfunction is limited to affective stimuli. However, it remains unclear whether altered somatosensory processing in BPD is specific for pain perception or also affects positive affective somatosensation.

A recent systematic review and meta-analysis proposes light stroking at a velocity of approximately 3 cm/s for the assessment of somatosensory pleasantness, i.e. pleasant touch, parallel to the assessment of pain (Taneja et al., 2021). Thereby, C-tactile (CT) afferents, which are activated by touches applied with velocities between 1 and 10 cm/s, seem to mainly code pleasant sensation (Löken et al., 2009; Olausson et al., 2002). In addition, other types of afferents might contribute, as stroking touch can be pleasant when applied to glabrous skin, a site lacking CT afferents (McGlone et al., 2012). Interestingly, on a central level there is a common neurobiology of pain and pleasure (Leknes & Tracey, 2008) with common involvement of brain regions such as insula, amygdala, prefrontal cortex and orbitofrontal cortex. Due to the neurobiological similarities between pain and pleasure, it can be hypothesized that the processing of both positive and negative affective somatosensory information might be altered in BPD. The assumption of altered pleasant touch processing in BPD is also supported by a previous study by Croy, Geide, et al. (2016), who assessed pleasant touch perception in a heterogeneous sample of psychotherapy outpatients suffering from different disorders (mood and affective disorders, post-traumatic stress disorder, anxiety disorder, personality disorders). In this study, patients, particularly those with personality disorders, rated pleasant touch as less pleasant compared to HC. However, Croy, Geide, et al. (2016) did not report results for different types of personality disorders, so that BPD-associated alterations remain unknown.

To assess positive and negative affective processing on a physiological level, the affect-modulated acoustic startle response is a common peripheral physiological measure. The magnitude of the blink response to a startling acoustic probe is increased when unpleasant stimuli are processed and decreased during pleasant stimulation (Lang et al., 1990). A recent study confirmed that the response strength is modulated primarily by the centromedial region of the amygdala (Kuhn et al., 2020), while the prefrontal cortex has shown to play an important role specifically in pleasure-induced inhibition of the startle response (Hurlemann et al., 2015). Amygdala and prefrontal dysfunctions have been identified as important neural deficits in BPD (Krause-Utz et al., 2014a) and have been further related to processing of affective stimuli in the disorder (L. Schulze et al., 2016). In line with this, previous studies assessing affect-modulated startle responses in BPD found exaggerated affective startle in response to negative and borderline-salient stimuli compared to HCs (Hazlett et al., 2007; Limberg et al., 2011; but see Herpertz et al., 1999). Therefore, dampened

affect-modulated acoustic startle responses might serve as a physiological correlate for less pleasant processing of pleasant touch in BPD.

Experimental studies in healthy subjects suggest that pleasant touch might play a role in the experience of body ownership, i.e. the sensation that the body and all its parts belong to oneself. Compared to neutral touch, pleasant touch has shown to produce higher levels of ownership for an artificial limb in the rubber hand illusion paradigm (Crucianelli et al., 2013) and can reduce the feeling of deafference (Panagiotopoulou et al., 2017), i.e., unpleasant and numbness sensation about the body induced by a temporal mismatch between seen and felt tactile stimulation (Longo et al., 2008). Moreover, a recent study on neurological patients with reduced body ownership indicates that the application of pleasant touch could increase body ownership experiences (Jenkinson et al., 2020). Interestingly, dissociation, a common symptom and diagnostic feature of BPD (American Psychiatric Association, 2013), includes the feeling of foreignness related to the own body, and body ownership experiences have been shown to be reduced in BPD (Löffler et al., 2020). Thereby, from a psychopathological perspective, it might be interesting to assess whether pleasant touch stimulation might modulate (dissociative) body experiences in BPD.

The main aim of the present study was to investigate whether perception of positive somatosensory stimulation is less positive in BPD compared to HC. Therefore, we applied standardized pleasant touch to the back of the hand of participants with BPD and a sample of HC. We specifically expected a less positive perception of pleasant touch assessed by self-report in BPD compared to HC. On a physiological level, we expected a diminished inhibition of the acoustic startle response in the BPD versus control group. In order to investigate the specificity of somatosensory alterations for affective stimuli, we assessed mechanical and warm perception as well as heat pain thresholds of the skin. Thereby, we expected to replicate heightened pain thresholds in BPD compared to HC, and further expected an association between deficient processing of pleasant touch and deficient pain processing. Specifically a more negative evaluation of pleasant touch was assumed to be associated with higher levels of heat pain thresholds. We further explored whether there is a pleasant touch-associated modulation of dissociation and dissociative body experiences in terms of reduced body ownership in BPD.

2.2 Methods study I

Sample

We examined 27 female participants with BPD and 26 female healthy controls (HC) who were centrally recruited by Clinical Research Unit 256 (Schmahl et al., 2014). The measurement had to be prematurely terminated due to intolerable tension evoked by the experimental paradigm in two subjects with BPD and circulatory problems in one HC subject. Accordingly, the final sample consisted of 25 subjects with a current diagnosis of BPD (mean (*M*) age = 31.28 years, standard deviation (*SD*) = 7.57) and 25 HC (*M* age = 26.72 years, *SD* = 8.57). The groups did not significantly differ in age, $t(48) = 2.00$, $p > .05$. All subjects were fluent in German and all but three participants were right-handed (two ambidextrous participants in the BPD and one ambidextrous participant in the HC group) as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Regular psychotropic and pain medication had to be discontinued for at least two weeks prior to study participation (with the exception of selective serotonin reuptake inhibitors (SSRIs), of which discontinuation is not recommended given the evidence for adverse physical and psychological symptoms that may occur with its discontinuation (Fava et al., 2015)). None of the subjects had been on on-demand medication (such as sedative-hypnotics or benzodiazepines) for two days prior to participation. The study was approved by the Ethics Commission of the Medical Faculty Mannheim of Heidelberg University and complied with the Declaration of Helsinki. All participants provided written informed consent and received a reimbursement of 26€ for participation.

Clinical diagnoses according to the Diagnostic and Statistical Manual for Mental Disorder IV (DSM-IV) (American Psychiatric Association, 2000) were obtained by a trained clinical psychologist using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (Wittchen et al., 1997) and the International Personality Disorder Examination (IPDE) (Loranger et al., 1997). Participants with BPD had to meet five or more of the BPD IPDE criteria within the last two years prior to study participation, and at least one of these criteria had to be present during childhood or adolescence.

We excluded subjects with scars on the back of the left hand (due to self-injurious behavior or other reasons) to avoid a potential bias due to reduced sensitivity in the stimulated body part. Further exclusion criteria were life-time diagnosis of bipolar I disorder or schizophrenia, insufficient speech comprehension, mental retardation,

body mass index < 16.5, substance use disorder within the last year (in case of current substance abuse, abstinence of at least two months was required), fibromyalgia, serious physical illness, severe brain disorder or concussion, and pregnancy. The prevalence of comorbid life-time and current mental disorders as well as psychopathological characteristics of the BPD sample are given in Table 1. No current or life-time mental disorders were present in the HC group, as assessed with the SCID (Wittchen et al., 1997).

Psychological assessment

To assess general symptom severity, we used the mean score of the *Borderline Symptom List* (BSL-23) (Bohus et al., 2009). Values are ranging from 0 to 4 with higher values indicating a higher symptom severity. To assess depressiveness, we used the *Beck-Depression-Scale* (BDI) (Hautzinger et al., 1995). The overall sum score ranges from 0 to 63 with higher values indicating higher depressiveness. The *State-Trait-Anxiety Inventory* (STAI) (Laux et al., 1981) was used to assess anxiety. The sum score for the state and trait subscale, ranges from 40 to 160 each, with higher values indicating higher anxiety. Data of BSL-23, and STAI (trait) were missing for one BPD subject, BDI and STAI (state) data were missing for two BPD subjects.

Table 1: *Prevalence of comorbid axis I disorders and psychopathological characteristics of the borderline personality disorder sample (n = 25)*[1].

	Prevalence		Psychopathological characteristics	
	Current *n* (%)	**Life-time *n* (%)**		***M (SD)***
Major depressive disorder	7 (28)	18 (72)	**Symptom severity (BSL-23) (*n* = 24)**	1.59 (0.70)
Post-traumatic stress disorder	8 (32)	15 (60)	**Depressiveness (BDI) *(n* = 23*)***	18.26 (8.00)
Anorexia nervosa	0 (0)	6 (24)	**Trait anxiety (STAI) *(n* = 24*)***	63.29 (6.31)
Other Eating disorders	7 (28)	7 (28)	**State anxiety (STAI) (*n* = 23)**	54.87 (9.30)
Other mental disorders (only current)	20 (80)	-		
More than one mental disorder (only current)	11 (44)	-		

BPD = borderline personality disorder; n = number; M = mean; SD = standard deviation; BSL-23 = Borderline Symptom List (Bohus et al., 2009), BDI = Beck-Depression Scale (Hautzinger et al., 1995), STAI = State-Trait-Anxiety Inventory (Laux et al., 1981). Lifetime diagnosis Includes current diagnosis.

[1] Data presented in this table were collected by trained clinical psychologists of the Clinical Research Unit 256 (Schmahl et al., 2014).

Experimental paradigm

The experimental setup is depicted in Figure 1a. We applied pleasant touch stimulation on the subjects' back of the left hand (i.e., hairy skin) using a soft brush and a custom apparatus (see Figure 1b), which applied touch without social interaction and with a standardized velocity of 3cm/s. Using a similar device and setup in HCs, has been shown to validly evoke a pleasant touch percept as well as touch-related activation in brain areas typically involved in the processing of pleasant touch (Nees et al., 2019). The left hand of the subjects was placed on a vacuum cushion underneath the brush to rest it comfortably and stably during the experiment. In order to apply gentle touches with comparable forces, the brush was adjusted for each subject dependent on the size of the individual's hand in a way that just the tip of the brush touched the skin. Using a privacy screen, the pleasant touch device and the stimulated hand were positioned out of the subjects' view. The subjects were instructed to fixate a cross presented on a screen in front of them and attend to their stimulated left hand throughout the experiment. The touch stimulation was applied in 12 blocks, lasting 60s each, with a stroke length of 8cm, going back and forth between the metacarpal bones of the participants' left third and fourth digit.

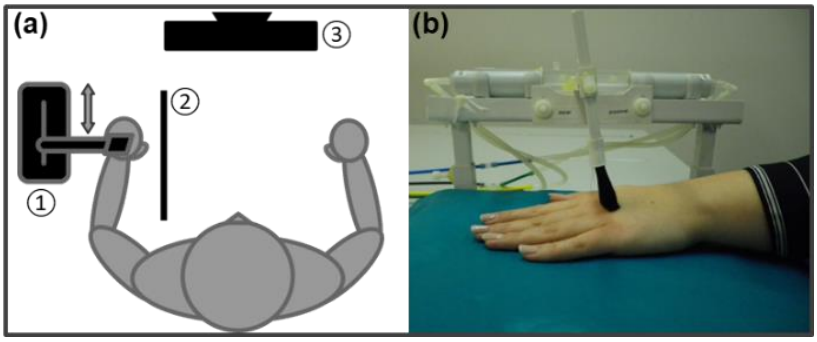

Figure 1: ***(a)*** Schema of the experimental setting consisting of a brushing machine (1), a privacy screen (2), and a computer screen (3); ***(b)*** Stimulation of the back of the left hand (i.e., hairy skin) using a soft brush

After each block, the subjects were asked to rate the perceived intensity and valence of touch. Intensity of touch was assessed using a visual analogue scale (VAS) using the verbal anchors "no perception" and "very intense perception". Perceived pleasantness of touch was assessed with a VAS with the anchors "not pleasant" and

“very pleasant”, and perceived unpleasantness of touch was assessed with a separate VAS using the anchors “not unpleasant” and “very unpleasant”. For all VAS scales the answers were converted in values ranging from 0 (“no perception”, “not pleasant”, not unpleasant”) to 100 (“very intense perception”, “very pleasant”, “very unpleasant”). We assessed valence of touch in a two-dimensional manner in accordance with previous recommendations (Cacioppo & Berntson, 1994; Norris et al., 2010; Watson & Tellegen, 1985), and combined the ratings of pleasantness and unpleasantness for the main analyses by subtracting the unpleasantness rating from the pleasantness rating, resulting in a bipolar valence score ranging from -100 (indicating maximum net negative valence) to +100 (indicating maximum net positive valence) with values of 0 indicating neutral valence. Furthermore, subjects rated qualitative aspects of touch perception by using a German adaptation of the touch perception task (TPT, Guest et al., 2011) (see the supplement for translation, cultural adaptation, and details of the assessment of the TPT items. The TPT assesses touch perception by four empirically identified sensory factors (slip, pile, roughness and firmness) with 26 descriptors and two affective factors (comfort and arousal) with 14 descriptors (see Table S1 in the supplement).

To assess state dissociation before and after touch application, we used the mean score of the short version of the Dissociation-Tension Scale acute (DSS-4) (Stiglmayr et al., 2009), immediately before the experiment started and after the last block of stimulation. Before and after pleasant touch application we further asked participants for perceived body ownership disturbances employing the shortened version of a previously used body ownership interview (Löffler et al., 2020), assessing ownership for the right and left arm. Participants were asked to verbally rate the perceived degree of current ownership for their shoulders, upper and lower arms as well as hands (left and right each) by indicating a percentage from 0% (“body part does not belong to me”) up to 100% (“body part belongs to me”) in 10% increments. To assess disturbances of body ownership in BPD of both the stimulated and non-stimulated arm, we separately computed the mean score of the left (internal consistency in the present study $\alpha = .96$ before and $\alpha = .94$ after stimulation) and right (internal consistency in the present study $\alpha = .94$ before and $\alpha = .95$ after stimulation) body sites. All items were presented on the computer screen in front of the participants, and were answered using a keyboard. The experiment was programmed in Presentation (v17.0; Neurobehavioral Systems, Inc., Albany, CA, USA).

Startle data collection and scoring of affect-modulated acoustic startle response

Recording and analysis of startle data followed the recommendations by (Blumenthal et al. (2005). A 50ms white noise burst set to a volume of 95db was used as acoustic startle probe, and eight startle probes were presented for habituation purposes before the experiment started. Experimental probes then occurred randomly once or twice at least 15s after the onset of touch in half of the stimulation-blocks, with an inter-probe interval of at least 18s (Lissek et al., 2008). Stimuli were presented randomly once or twice in half of the fixation-blocks (a fixation-block with a random duration between 60 and 69s without stimulation preceded each block of touch application and served as baseline interval). The startle probe occurred 9 times with and 9 times without tactile stimulation. The probes were delivered using the amplifier Phone Amp G100 (Lake People, Konstanz, Germany) and insert earphones EarTone® 3A 10-Ohm (Aearo Company Auditory Systems Production, Indianapolis, USA) with 10mm earplugs (ER3-14B, Etymotic Research Inc., Elk Grove Village, USA). The acoustic startle response was measured by recording electromyographic (EMG) activity of the musculus orbicularis oculi of the left eye using Ag-AgCl electrodes with a diameter of 40mm filled with high-conductivity electrode gel (Electro Cap International Inc., Eaton, USA). The ground electrode was attached to the right forehead. The electrodes were applied between the threshold assessments and the experiment. The skin was cleaned with alcohol and abraded using V17 Abralyt 2000 (Easycap GmbH, Herrsching, Germany) to lower the impedances. Physiological data were amplified and recorded using a BrainAmp ExG amplifier (Brain Vision, Morrisville, USA) and the Brain Vision Recorder software v1.10 (Brain Vision, Morrisville, USA). The sampling rate was set to 5000Hz. Frequencies below 28 Hz and above 400 Hz were filtered out, and a notch filter of 50Hz was applied.

Brain Vision Analyzer v2.0 was used for offline analysis of the EMG signal. Startle amplitude was defined as the difference between the peak startle activity within a time window of 20ms to 120ms after stimulus onset and the mean EMG activity 50ms before stimulus onset. Prior to analysis, EMG recordings were visually examined and screened for artefacts. Segments with noise, movement artefacts or spontaneous or voluntary blink before the minimal onset latency value within a time frame of 50ms before to 200ms after stimulus onset, or segments without a startle reaction (defined as peaks below 10μV) were excluded from analysis. Remaining segments were rectified and smoothed by a moving average with a 10ms window. Finally, segments

of the fixation-block and the stimulation-block were averaged separately. The affect-modulated acoustic startle response (ASR) was calculated in percent by the following formula:

$$\frac{(startle\ during\ stimulation)-(startle\ without\ stimulation)}{(startle\ without\ stimulation)} \times 100.$$

Thus, positive scores indicate an increase in startle amplitude during stimulation relative to baseline and negative scores indicate a decrease. Reporting relative scores for affect-modulated ASR is recommended to remove any dependence on baseline eye blink amplitude (Blumenthal et al., 2005). Due to technical problems during data recording, we could not sample physiological data of three BPD and two HC participants. To ensure that a sufficient number of trials per block were included, the required number of valid segments per subject and block (on/off) was set to four. Using this criterion, we had to exclude additional three BPD and three HC participants. Thus, we analyzed physiological data of 19 BPD and 20 HC subjects.

Assessment of thresholds for mechanical detection, warm perception, and heat pain

Touch sensitivity was assessed at the beginning of the experiment by mechanical detection thresholds using the standard examination protocol for Quantitative Sensory Testing (QST) of the German Research Network on Neuropathic Pain (Rolke et al., 2006). Thresholds were recorded on the skin between the metacarpal bones of the third and fourth finger of the participants' left back of the hand. We used a standardized set of von-Frey filaments with forces between 0.25mN and 512mN (Opti-hair2, MARSTOCK-Nervtest, Schriesheim, Germany), implementing a staircase procedure to ascertain the mechanical threshold, defined as the geometric mean of five below- and five above-threshold intensities.

We then assessed warm perception and heat pain thresholds using a Thermal Sensory Analyzer device (Medoc Ltd, Ramat Yishai, Israel) with a 30x30mm thermode attached to the subjects' left thenar. Starting at a baseline temperature of 32°C, the temperature rose with a rate of 1.2°C/s for the assessment of the warm perception threshold, and with a rate of 3°C/s for the assessment of heat pain threshold (Leung et al., 2005). The subjects signaled the onset of warm perception or heat pain perception by pressing a button resulting in a fall of temperature back to baseline temperature in five trials each. The first trial served as familiarization trial while the average of the remaining four trials was used for further analyses. For safety reasons, the thermode was shut down when

a temperature of 52°C was reached. This safety limit was reached in 3 trials of one participant with BPD and in one trial of two HC each. For these trials, the temperature was rounded to 53°C (Bekrater-Bodmann et al., 2015). Due to technical problems with the thermal stimulator during the main period of data assessment, we could not assess thresholds in eleven BPD subjects and one HC, and thus, subsequent analyses on perception thresholds were performed only for subsamples.

Statistical analyses

Data were tested for normal distribution using a Kolmogorov-Smirnov test. If the assumption of normality was violated, non-parametric statistics were used. To test our main hypothesis, we compared data of BPD and HC participants for perceived valence, intensity, and qualitative aspects of pleasant touch using t-tests for independent samples or, in the case of non-normal distribution, Mann-Whitney-U-Tests. Because there was an unexpected difference in perceived intensity of touch between BPD and HC, a robust rank based ANCOVA (Conover & Iman, 1982) was performed to control for perceived intensity of touch on the effects of perceived valance of touch. We further correlated perceived valence and intensity of touch with symptom severity as assessed by the BSL in the BPD group using Pearson or Spearman correlations. Additionally, we compared both groups regarding affect-modulated ASR, and correlated affect-modulated ASR with perceived valence and intensity of touch using Pearson or Spearman correlation in both groups separately.

To explore the effect of pleasant touch stimulation on dissociation in BPD, we compared state dissociation and arm ownership before and after pleasant touch stimulation using paired t-tests or, in the case of non-normal distribution, Wilcoxon signed-rank tests. Further, we calculated difference scores in state dissociation and arm ownership from before to after pleasant touch stimulation. We correlated perceived valence and intensity of touch with the change in dissociation and arm ownership of the stimulated and non-stimulated arm using Spearman rank correlations. In order to test whether there was a specific effect for the correlation between perceived valence of touch and change of ownership in the stimulated arm, we compared this correlation with the correlation between perceived valence of touch and change in ownership of the non-stimulated arm as well as with the correlation between perceived valence of touch and change in dissociation using a procedure based on Fisher’s r-to-z transformation. This has been shown to be robust with respect to Type

I error, also when applied for non-parametric Spearman correlation (Myers & Sirois, 2006). We further used non-parametric partial correlations for testing the relationship between perceived valence of touch and change in arm ownership while controlling for change in state dissociation as assessed by the DSS-4. Since HC experienced constantly high body ownership and constantly low dissociation, both measures lacking substantial variance (see Table S3 in the supplement), we performed these analyses only for the BPD group. As comorbid PTSD has previously been found to influence dissociative experiences (Vermetten & Spiegel, 2014), we further compared change in dissociation and arm ownership from pre to post stimulation between BPD participants with and without PTSD using Wilcoxon signed-rank tests.

In order to investigate the specificity of alterations in affective somatosensory processing, we compared data of participants with BPD and HC for mechanical detection thresholds (MDT), warm perception thresholds (WPT), and heat pain thresholds (HPT) using t-tests for independent samples or Mann-Whitney-U tests. To assess whether there was an association between positive and negative somatosensation, we further correlated perceived valence and intensity of touch with HPT in both groups separately. Due to the small sample sizes for these analyses, the results are reported in the supplement.

Initially, perception of touch in trials with and without startle stimuli was compared in both groups separately using paired t-tests or Wilcoxon signed-rank test. This was done to test for potential effects of the acoustic startle probe on touch perception. Since there were no significant differences in ratings between trials with and without startle probes in either group (see Table S2 in the supplement), we used the mean ratings of touch with and without startle probes for all analyses.

We report test statistics, *p*-values (in case of multiple testing we report Bonferroni-corrected *p*-values, i.e., p_{Bonf}), and absolute values of effect sizes using Cohen's *d* (based on pooled *SD*), *r* (applying the equation $\frac{z}{\sqrt{n}}$), or partial η^2. All statistical analyses were performed using IBM SPSS v25.

2.3 Results study I

Perception of pleasant touch and affect modulated ASR in BPD and HC participants

Perceived valence of touch was significantly lower in participants with BPD (M = -4.50, SD = 41.56) compared to HC (M = 56.85, SD = 39.78), t(48) = -5.33, p < .001, d = 1.51 (see Figure. 2a). Both groups further differed significantly in the sensory aspect of pleasant touch perception: the intensity ratings were significantly lower in participants with BPD (Mdn = 55.67, IQR = 20.87) compared to HC (Mdn = 74.67, IQR = 30.21), U = 126.00, z = -3.62, p < .001, r = .72 (see Figure. 2b). The result of the rank based ANCOVA suggests that, after controlling for the effect of perceived intensity, there was a significant difference in perceived touch valence between both groups, $F(1,47)$ = 19.52, p < .001, η^2 = .29.

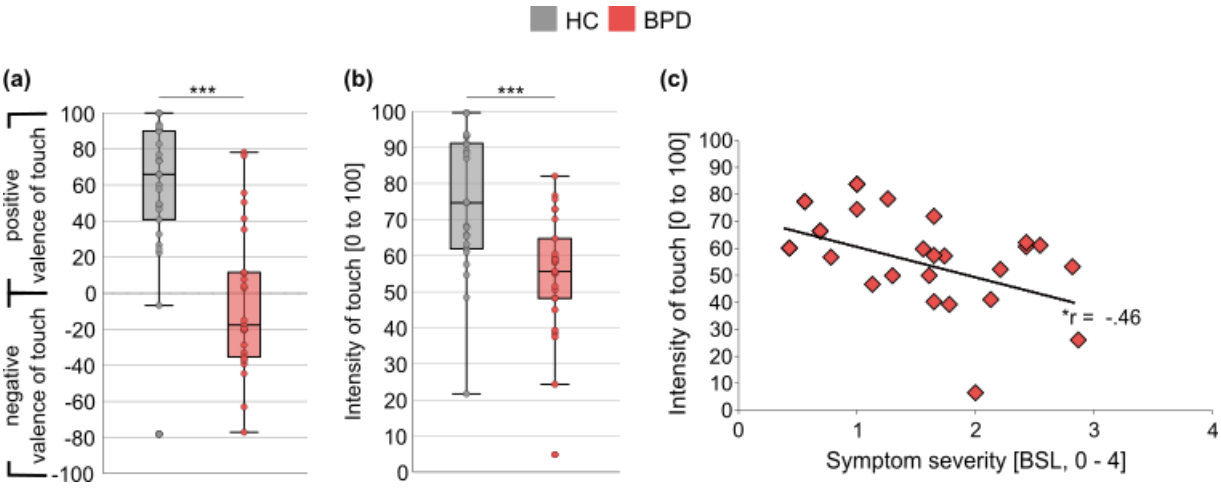

***Figure 2**: **(a)** Perceived valence of touch in healthy controls (HC) and participants with borderline personality disorder (BPD) **(b)** Perceived intensity of touch in HC and BPD. **(c)** Association between perceived intensity of touch and symptom severity as assessed with the Borderline symptom list (BSL) in BPD. Boxplots: Medians and quartiles are marked by the lines of the boxes. Whiskers indicate 1.5 inter-quartile range or minimum/maximum value. Values of single subjects are marked by a dot. *p < .05, ***p< .001.*

In BPD there was a significant negative correlation of symptom severity with perceived intensity of touch ($r(22)$ = -.46; p = .025) (see Figure. 2c) but not with perceived valence of touch ($r(22)$ = .08, p = .720).

Descriptive data for the qualitative aspects of touch for both groups as well as test statistics for the group comparisons can be found in Table 2 and are further visualized in Figure 3. BPD participants rated the touch as being significantly rougher and firmer compared to the HC group. For the affective component, BPD participants indicated significantly less comfort than the HC group.

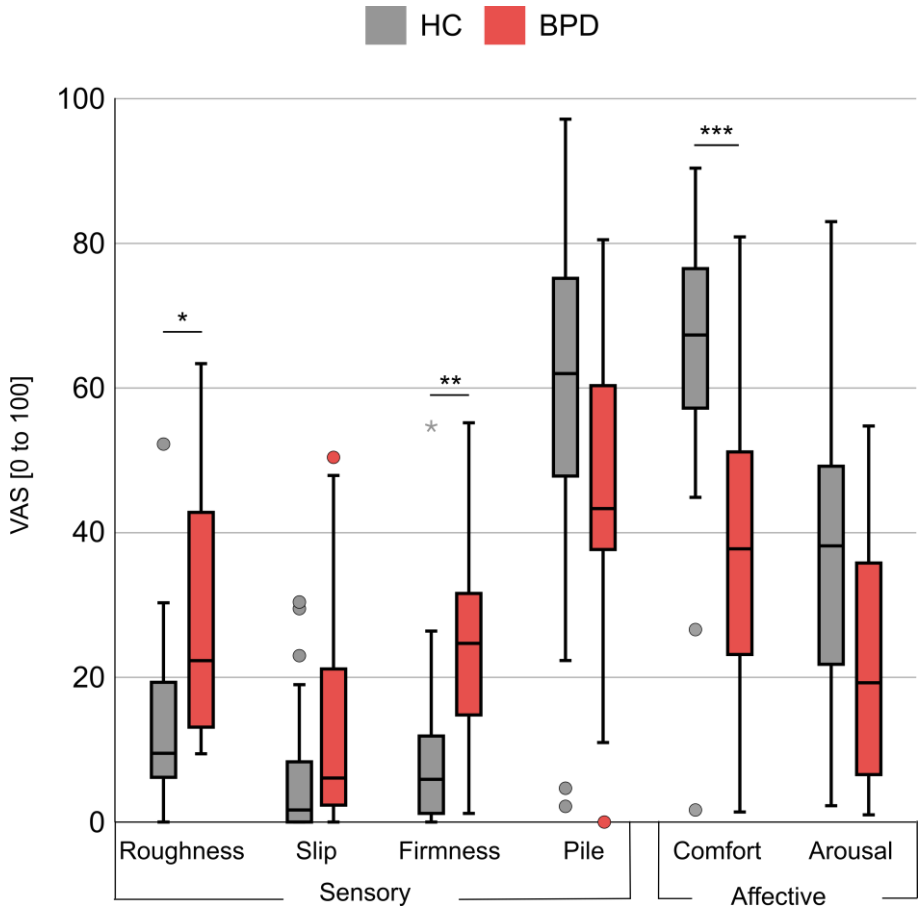

Figure 3: Boxplots for ratings of qualitative aspects of touch perception in healthy controls (HC) and participants with borderline personality disorder (BPD). Medians and quartiles are marked by the lines of the boxes. Whiskers indicate 1.5 IQR or minimum/maximum value. Outliers are marked by a dot; extreme values are marked by a colored asterisk. * $p < .05$, ** $p < .01$, *** $p < .001$.

Table 2: *Pleasant touch perception in participants with borderline personality disorder (BPD) and healthy controls (HC).*

	BPD (*n* = 25)	**HC (*n* = 25)**	**Statistics**
	M(*SD*) *Mdn (IQR)*	*M*(*SD*) *Mdn(IQR)*	
Valence	-4.50 (41.56) -17.58 (59.29)	56.85 (39.78) 65.83 (53.54)	$t(48) = -5.33$, $p < .001$
Intensity	54.58 (17.30) 55.67 (20.87)	74.64 (19.15) 74.67 (30.21)	$U = 126.00$, $z = -3.62$, $p < .001$
Sensory components			
Roughness	27.80 (16.53) 22.31 (31.72)	13.49 (11.33) 9.50 (13.63)	$U = 128.00$, $z = -3.58$, $p_{Bonf} = .002$
Slip	14.08 (16.03) 6.08 (21.83)	7.22 (9.83) 1.67 (13.00)	$U = 216.00$, $z = -1.89$, $p_{Bonf} = .349$
Firmness	23.44 (14.57) 24.70 (22.00)	9.15 (11.93) 5.90 (11.30)	$U = 121.50$, $z = -3.71$, $p_{Bonf} = .001$
Pile	47.13 (19.83) 43.33 (24.33)	57.37 (25.79) 62.00 (38.42)	$U = 215.00$, $z = -1.89$, $p_{Bonf} = .354$
Affective components			
Comfort	36.81 (19.88) 37.78 (30.89)	64.22 (19.88) 67.33 (22.69)	$t(48) = -4.87$, $p_{Bonf} < .001$
Arousal	22.72 (16.99) 19.25 (31.25)	35.45 (20.19) 38.19 (27.56)	$t(48) = -2.41$, $p_{Bonf} = .119$

BPD = borderline personality disorder; HC = healthy control; n = number; *M* = mean; *SD* = standard deviation; *Mdn* = median; *IQR* = interquartile range; p_{Bonf} = Bonferroni corrected *p*-value

There was no significant difference in affect-modulated ASR between BPD (M = -6.22µV, SD = 23.04) and HC (M = -2.55µV, SD = 25.17), $t(37) = -0.47$, $p = .638$, $d = 0.15$. Affect-modulated ASR was not significantly related to perceived valence of touch in BPD ($r(17) = -.13$, $p = .589$) or HC ($r(18) = .15$, $p = .538$). There was also no significant correlation between affect-modulated ASR and perceived intensity of touch (BPD: $r(17) = .33$, $p = .162$; HC: $r_s(18) = .31$, $p = .182$).

Pleasant touch and dissociative states in BPD

Descriptives for state dissociation and body ownership distortions before and after stimulation as well as the respective change scores can be found in Table 3. The changes from pre to post stimulation are further visualized in Figure 4a and 4b. In BPD, state dissociation prior to the experiment was negatively correlated with perceived intensity of touch ($r(23) = -.480$, $p_{Bonf} = .045$) but not with perceived valence of touch ($r(23) = -.079$, $p_{Bonf} > .999$). There was no significant association between body ownership experiences prior to the experiment and perceived valence or intensity of touch (all $r_s \leq |.232|$, all $p_{Bonf} \geq .558$.)

In BPD, there was a significant increase in state dissociation from pre to post pleasant touch stimulation, $t(24) = -2.87$, $p_{Bonf} = .024$, $d = 0.88$ (see Table 3). However, there was no significant pre-post difference for body ownership, neither for the stimulated left arm, $z = -1.80$, $p_{Bonf} = .219$, $r = .25$, nor the non-stimulated right arm, $z = -1.19$, $p_{Bonf} = .738$, $r = .17$ (see Table 3).

Perceived valence of touch was significantly positively correlated with changes in ownership of the stimulated left arm in BPD ($r_s(23) = .624$, $p_{Bonf} = .003$, see Figure. 4c). Results of a bootstrapping procedure (10,000 samples) revealed a BCa (Bias corrected and accelerated) *95% CI* [.306, .821], indicating that it is a robust correlation. There was no significant correlation between perceived valence of touch and change in ownership of the non-stimulated right arm ($r_s(23) = .221$, $p_{Bonf} = .867$) and change in state dissociation ($r_s(23) = -.262$ $p_{Bonf} = .618$) in BPD. The correlation between perceived valence of touch and change of ownership in the stimulated arm significantly differed from the correlation between perceived valence and change of ownership in the non-stimulated arm ($z = 2.43$, $p_{Bonf} = .030$) as well as from the correlation between perceived valence and change of dissociation ($z = 2.68$, $p_{Bonf} = .014$), indicating that the association between perceived valence of touch and change in ownership was specific for the stimulated arm. However, change in state dissociation was significantly related to both change in ownership of the stimulated left arm ($r_s(23) = -.588$, $p_{Bonf} = .004$) and the non-stimulated arm ($r_s(23) = -.556$, $p_{Bonf} = .004$). After controlling for the change in state dissociation, perceived valence of touch was still significantly related to the change in ownership of the stimulated left ($r_s(22) = .603$, $p_{Bonf} = .004$), but not the right non-stimulated arm ($r_s(22) = .094$, $p_{Bonf} > .999$). There was no significant

correlation between the perceived intensity of touch and change in dissociative levels (all $r_s \leq |.288|$. all $p_{Bonf} \geq .489$).

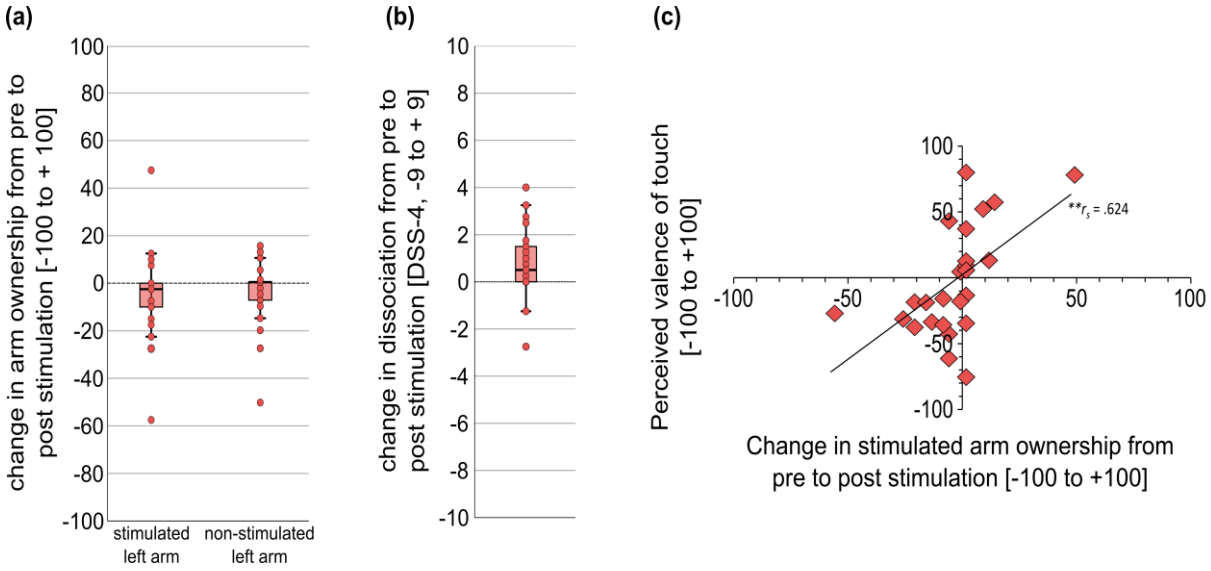

Figure 4: (a) Change in body ownership experiences from pre to post stimulation in participants with borderline personality disorder (BPD); ***(b)*** Change in dissociation as assessed with the Dissociation-Tension scale acute (Dss-4) from pre to post stimulation in BPD; ***(c)*** Association between perceived valence of touch and change in stimulated arm ownership from pre to post pleasant touch perception in BPD. ** $p < .01$

There was no significant difference in the change in ownership from pre to post stimulation between BPD with and without PTSD for the stimulated arm (U = 29.50, z = -1.42, p = .156) or the non-stimulated arm (U= 50.00, z = 0.00, p > .999). There was also no significant difference for changes in general dissociation as assessed with the DSS-4 when comparing these subgroups of participants with BPD (U= 27.50, z = -1.56, p = .120).

Table 3: *Body ownership and state dissociation before and after stimulation with pleasant touch in participants with borderline personality disorder*

	Pre *M* (*SD*) *Mdn (IQR)*	**Post** *M* (*SD*) *Mdn (IQR)*	**Change** *M* (*SD*) *Mdn (IQR)*
Body ownership stimulated left arm [%]	74.50 (28.80) 87.50 (46.25)	69.20 (29.56) 67.50 (52.50)	-5.30 (18.09) -2.50 (12.50)
Body ownership non stimulated right arm [%]	78.50 (24.58) 87.50 (37.50)	74.44 (26.69) 82.50 (45.00)	-4.06 (13.57) 0.00 (9.25)
State dissociation (DSS-4)	1.85 (1.42) 1.50 (2.38)	2.68 (2.24) 2.00 (4.25)	0.83 (1.44) 0.50 (1.63)

Pre = before pleasant touch application; Post = after pleasant touch application, Change = Post-Pre; *M* = mean; *SD* = standard deviation; *Mdn* = median; *IQR* = interquartile range; DSS-4 = Short version of the Dissociation tension scale acute (Stiglmayr et al., 2009).

2.4 Discussion study I

The aim of the present study was to investigate whether pleasant touch perception is disturbed in BPD. We applied standardized pleasant touch stimuli to the back of the left hand of female participants with BPD and HC. We assessed the perception of touch as well as its affective processing in terms of affect-modulated acoustic startle responses. In order to explore a potential modulating effect of pleasant touch on state psychopathology, we assessed changes in state dissociation and dissociative body experiences in terms of reduced body ownership, before and after touch application. We further investigated the specificity of somatosensory alterations and aimed to test whether the perception of somatosensory stimuli with positive and negative valence is interrelated.

As expected, the perceived valence of pleasant touch was less positive in BPD compared to HC. After controlling for the potentially confounding effect of perceived intensity of touch, perceived valence of touch still remained less positive in individuals with BPD compared to HC with an effect of η^2 = .29. We further found alterations in qualitative aspects of touch perception in BPD compared to HC, which (a) confirmed our main results regarding reduced positive perception of pleasant touch in terms of reduced comfort ratings in BPD compared to HC and (b) revealed differences in certain sensory aspects of touch. Thus, participants with BPD rated the perceived touch rougher and firmer compared to HC. Finally, our results suggest that perceived valence of touch was related to changes in dissociative body perception in terms of disturbed body ownership, especially of the stimulated body site, but not to the dissociative state in general. The positive correlation between perceived valence of touch and the change in arm ownership of the stimulated site suggests that a more unpleasant perception of touch is associated with a decrease in body ownership experiences from pre to post stimulation, while a more positive perception of touch was related with an increase in reported arm ownership.

Our main result of pleasant touch disturbances in BPD is in line with previous results indicating that perception of positively valenced stimuli is altered in the disorder (Arrondo et al., 2015; Fenske et al., 2015; Reichenberger et al., 2017; Thome et al., 2016). It extends previous findings on somatosensory alterations in BPD by suggesting

that not only pain perception, but also the perception of its positive counterpart is altered in BPD. Together, this supports the assumption of altered affective somatosensory processing in BPD. Interestingly, similar to our results on altered qualitative touch experiences, a recent study found alterations in qualitative pain ratings in BPD, in terms of a specific loss of the pain component sharpness (Schloss et al., 2019). Qualitatively changed somatosensory perception might be due to altered evaluation of negative (Schloss et al., 2019) and positive somatosensory stimuli and related cognitive processes. There is a common neurobiology of pain and pleasure (Leknes & Tracey, 2008) and evidence for cognitive top-down modulation of both. It has been shown that top-down cognitive factors can influence the affective representation of touch in healthy subjects (McCabe et al., 2008). For the pain domain, cognitive down-regulation of the affective pain component has been proposed as an antinociceptive mechanism in BPD, represented by an interaction between prefrontal and limbic areas (Schmahl et al., 2006). Taken together, it can be assumed that a dysregulation of cortico-limbic pathways might be an underlying neural mechanism for altered affective somatosensation in BPD.

Unexpectedly, we found not only alterations in the affective component of pleasant touch but also a reduced touch sensitivity, in terms of heightened mechanical detection threshold and reduced perceived intensity of pleasant touch. This suggests that for the touch domain both, perception of the affective and sensory component might be altered. Interestingly, only perceived intensity of touch but not perceived valence of touch, was associated with symptom severity and state dissociation in BPD. Similarly, (Bekrater-Bodmann et al. (2015) reported an association between state dissociation and the magnitude of the pain percept but not with affective pain perception in terms of perceived unpleasantness. Altered gating and reduced processing of sensory input in acute dissociation (Krause-Utz & Elzinga, 2018) might mainly affect perceived intensity of a somatosensory stimulus. In consequence, higher levels of dissociation in BPD might decrease the salience of somatosensory stimuli, making it more difficult for them to be perceived, as has been proposed before (Defrin et al., 2020). This might be true especially for the sensory aspects of pain and (pleasant) touch, stimuli with a relatively high salience. For exteroception as assessed by two point discrimination or proprioception as assessed by weight-discrimination there is no evidence of altered perception in BPD (Pavony & Lenzenweger, 2014). However, the alteration of the affective component of pleasant touch was independent of reduced touch sensitivity,

indicating that at least partly distinct processes might underlie alterations in the sensory and affective components of touch processing.

The missing association between perceived valence of touch and symptom severity in BPD raises the question whether alterations in affective touch perception are disorder-specific or reflect unspecific alterations in psychopathological states. Studies on other mental disorders are sparse, but there is first evidence of altered pleasant touch processing in current (Crucianelli et al., 2016; Davidovic et al., 2018) and remitted (Crucianelli et al., 2020) anorexia nervosa, as well as posttraumatic stress disorder (Strauss et al., 2019), all of which are common comorbidities in BPD (Zimmerman & Mattia, 1999). The assumption of an unspecific alteration might further be supported by the results of Croy, Geide, et al. (2016) who reported reduced pleasant perception of touch in a heterogeneous sample of psychiatric outpatients suffering from different mental disorders. Interestingly, a recent study found that pleasant touch perception is affected by disorganized attachment (Spitoni et al., 2020), an attachment style characterized by inconsistent attachment behavior, which is overrepresented in personality disorders such as BPD (Westen et al., 2006) as well as patients suffering from anorexia nervosa (Delvecchio et al., 2014), and which has been linked to psychological traumatization (Liotti, 2004). According to attachment research, disorganized attachment is often a second-generation effect characterized by frightening and/or frightened parental interaction by caregivers suffering themselves from attachment-related trauma or losses (Hesse & Main, 1999; Main & Solomon, 1990). Touch perception is the earliest sensory modality to develop (A. J. Bremner & Spence, 2017) and might thus be particularly prone to adapting to adverse developmental circumstances (Crucianelli & Filippetti, 2020). Thus, from an etiological perspective, it can be speculated that growing up in a frightening environment, where caregivers do not represent a secure base, might result in disturbed interpretation of safety signals like pleasant touch, which, depending on other contributing factors (e.g. certain genotypes or other environmental factors), could manifest in various psychopathological states.

From a psychopathologial perspective, the results of our study have some important implications. Mainly, our data suggest that more negative perception of touch is

associated with a further decrease in body ownership experiences in BPD, while on the other hand touch stimulation, which is perceived as pleasant, might have beneficial effects on disturbed body ownership experiences of the stimulated limb in BPD. Thus our results point out that the effect of stimulation on body ownership experiences in BPD depends not only on the properties of the touching stimulus but its perceived valence might also play an important role. This differs from the results of Jenkinson et al. (2020), who found an increase in body ownership experiences after pleasant touch stimulation of the affected limb of stroke patients, which was not associated with perceived valence. The authors propose that increased body ownership experiences might be the result of integrating new sensation from the affected part with one's multimodal self-representation. However, they only report positive touch perception, which might foster an embodied self. A negative perception of touch, as present in some of the BPD subjects of this study, might hinder or even reverse this integrative process. Results of a recent study suggest that uncertainty and affective incongruences can disrupt the multisensory integration process that leads to the experience of body ownership (Filippetti et al., 2019), highlighting the importance of top-down processes, for example, information processing guided by higher-level knowledge and expectations, for the experience of body ownership. Expectations or anticipation of the affective input were not assessed in the current study. However, based on a spontaneous statement of one BPD subject after the present experiment who stated that the applied touch "felt like the touch of someone who wants to comfort you but doesn't mean it", it is conceivable that there might be a high level of perceived inconsistency for some participants with BPD during touch experiences. Thereby, negative self-evaluations, which are common in BPD (Kleindienst et al., 2020; Winter et al., 2017), might play an important role, as they have been suggested to result in a devaluation of self-referential positive experiences (Winter et al., 2015). To further assess hypothesized top-down influences on the effect of pleasant touch stimulation on body ownership experiences, future studies might combine pleasant touch stimulation with other affective stimuli, for example, affective pictures or other self-relevant stimuli.

Moreover, reduction of body ownership experiences from pre to post stimulation might also be the result of a coping process. As proposed by trauma models of dissociation, dissociative responses, including the experience of being detached from one's own body, may be a mechanism to cope with overwhelming experiences especially in

threatening situations without chance to escape (e.g. Hesse & Main, 1999). Further, it has been proposed that trauma-related memories and re-experiencing symptoms might be specifically triggered by perceptual stimuli associated with the traumatic event (Ehlers & Clark, 2000). Even though there was no evidence for differences in BPD with and without PTSD in the current study, it is possible that for some BPD participants with specific traumatic experiences the pleasant touch stimulation during the experiment might have reactivated traumatic experiences when touch was associated with negative experiences (Maier et al., 2020), which in turn might result in unpleasant touch perception and related reduction in body ownership experience. To probe this hypothesis, further studies with larger sample sizes comparing BPD individuals with and without traumatic experiences might take into account the type of trauma and its association with perception of pleasant touch stimuli as well as body-related psychopathology. From a more clinical perspective, our results suggest that touch stimulation, which is perceived as pleasant, might be a promising candidate to target reduced body ownership experiences in BPD, which have been shown to normalize in the remitted state of the disorder (Löffler et al., 2020). Therefore, it might be important to create a situation where the patient feels safe and anticipates a positive incoming signal. Individualized positive cues or being touched with materials that are positively connotated might help to re-evaluate incoming pleasant touch-signals.

Several limitations of our study must be noted. First, sample sizes, especially for the assessment of thermal perception and pain thresholds, were relatively small. Even though our supplemental results indicate an association between perception of positive and negative somatosensation in HC, there was no significant correlation between altered heat pain threshold and pleasant touch perception in BPD. However, interpretation of this result is limited not only due to the small sample size but also because pain thresholds reflect only one facet of altered pain perception in BPD. In future studies, beyond thresholds, the assessment of sensory, affective, and qualitative aspects of positive and negative somatosensory stimuli might be necessary to elucidate somatosensory alteration in BPD. Another limitation is that the intake of SSRIs was not interrupted in this study. SSRIs have been successfully used to treat chronic pain (Patetsos & Horjales-Araujo, 2016) and sensory alterations as possible side effects cannot be ruled out. All subjects in the present study were female, limiting the generalizability of our results. Previous results on a gender effect of pleasant touch

perception are mixed, with some studies indicating that female subjects perceive touch as more pleasant (Croy et al., 2014; Jönsson et al., 2017), but there is also a study indicating that there is no significant gender effect (Sehlstedt et al., 2016). Furthermore, there was no control condition where touch was applied with a velocity outside the range of CT optimal velocities (e.g. Crucianelli et al., 2020) and we did not test if differences in perceived valence and intensity of touch between BPD and HC might be extended to touch applied with non-CT velocities. Therefore, future studies are necessary to investigate whether alterations in touch perception in BPD relate specifically to the CT system. We further did not include a clinical control sample to investigate disorder-specific effects. Future studies on pleasant touch perception in BPD might further include samples suffering from eating disorder and PTSD, as both are common comorbidities in BPD and have been shown to be related to disturbances in pleasant touch perception (Crucianelli et al., 2016, 2020; Davidovic et al., 2018; Strauss et al., 2019). Moreover, expanding the investigation of patients by incorporating dimensional approaches might be helpful to disentangle the mechanisms behind disturbances in pleasant touch processing in BPD and its relationship with dissociative experiences. Finally, even if the difference in perceived valence of touch was obvious on a perceptual level, we could not provide evidence for differences between both groups in its physiological correlate, in terms of affect-modulated ASR. Affect-modulated ASR was not previously tested in pleasant touch studies in HCs before and the missing association between affect-modulated ASR and perceived valence of touch in HC raises the question whether ASR is an appropriate peripheral physiological correlate for the specific case of pleasant touch perception at all. EMG of the of the zygomaticus major (smile) muscle might be a more suitable physiological correlate of pleasant touch perception (Pawling et al., 2017).

Future studies also need to investigate the association between altered touch perception and deficits in social interaction. Pleasant touch plays an important role for initiating affiliative interaction, the maintenance of social bonds, contributes to the nonverbal communication of emotions (Björnsdotter et al., 2010) and reduces feelings of social exclusion (Von Mohr et al., 2017), all social functions that are impaired in BPD (Lis & Bohus, 2013).

Conclusion

The results of the current study provide novel empirical findings that pleasant touch perception is altered in BPD. A complex and partly distinct mechanism might underlie alterations in sensory and affective aspects of somatosensation, and accordingly, disturbances in sensory and affective processing might be differentially related to BPD psychopathology. Altered evaluation of pleasant touch might be related to negative self-evaluation and traumatic experiences and could play an important role in impairments in social interaction, as pleasant touch is a basic affiliative social signal. A deeper understanding of the mechanisms behind altered processing of pleasant touch and the effects of pleasant touch stimulation might help in the development of innovative treatment approaches, as our results indicate that there might be beneficial effect of pleasant touch stimulation on state psychopathologies in case of positive touch perception. If future studies reveal antecedents of positive touch perception in BPD, a positively valenced somatosensory stimulation might serve as a substitute action for self-infliction of pain in terms of nonsuicidal self-injury behavior which is common in BPD (Zanarini et al., 2008) and primarily motivated by a reduction of aversive inner tension and related dissociative states (Kleindienst et al., 2008).

CHAPTER 3

Study II: Temporal summation of pain intensity, unpleasantness, and nociceptive reflexes in borderline personality disorder

An adapted version of this chapter has been prepared for publication: Löffler, A., Kleinböhl, D., Steinmann, S., Herpertz, S. C., Bekrater-Bodmann, R., & Flor, H. Temporal summation of pain intensity, unpleasantness, and nociceptive reflexes in borderline personality disorder. (in prep)

3.1 Theoretical background study II

Borderline personality disorder (BPD) is a frequent mental disorder with a lifetime prevalence of 6% (Grant et al., 2008). It is characterized by affective instability, interpersonal difficulties, and identity disturbances (American Psychiatric Association, 2013). Reduced pain sensitivity is a prominent feature of BPD and the majority of patients with BPD report no or only little pain during acts of non-suicidal self-injury (NSSI, Leibenluft et al., 1987). BPD can therefore serve as a model to study the mechanisms underlying hypoalgesia. Reduced sensitivity to experimental pain has been demonstrated in various studies and for different pain modalities (e.g. Bekrater-Bodmann et al., 2015; Ludäscher et al., 2007; Magerl et al., 2012; Schmahl et al., 2006). Furthermore, a recent systematic review and meta-analysis confirmed lower pain ratings in response to experimentally applied pain stimuli as well as higher pain thresholds in BPD compared to HC (Fales et al., 2021).

Despite the numerous findings on reduced pain sensitivity in BPD, the underlying mechanisms are still largely unknown (Bekrater-Bodmann, 2021). The results of imaging studies suggest the involvement of prefrontal-limbic connections in reduced pain perception in BPD (Schmahl & Baumgärtner, 2015). A pain modulating mechanism, which might be involved in reduced pain perception in patients with BPD is temporal summation of pain: It is an N-methyl-D-aspartate (NMDA) related process (Eide, 2000) and NMDA is also involved in dissociation (Krystal et al., 1994; Newcomer et al., 1999), a common and diagnostic feature in BPD (American Psychiatric

Association, 2013). Dissociation has been related to reduced pain sensitivity in BPD (e.g. Ludäscher et al., 2007), suggesting that NMDA receptor dysfunction, might play a role in altered pain perception in BPD (Bekrater-Bodmann et al., 2015; Grosjean & Tsai, 2007). Temporal summation of pain refers to an increase in perceived pain when noxious stimuli with constant physical intensity are delivered repeatedly with frequencies above 0.3 Hz and has been viewed as representing the perceptual correlate of wind-up, an excitatory nociceptive spinal process (Kleinböhl et al., 2006; Price, 1972).

Using thermal and mechanical stimuli, previous studies did not find altered temporal summation of pain in BPD (Defrin et al., 2020; Ginzburg et al., 2018). However, heat pain threshold and temporal summation were found to be negatively correlated in BPD, but not in HC, suggesting that reduced temporal summation of pain might be related to altered pain perception in BPD (Defrin et al., 2020). Temporal summation can also be assessed with electrical stimuli and in addition, summation can be assessed via spinal reflexes to differentiate spinal and supraspinal mechanisms. The assessment of the nociceptive lower limb flexion reflex (RIII-reflex) is a widely used neurophysiological approach to investigate spinal nociceptive processing (Sandrini et al., 2005).

In the present study, we used painful electrical stimulation to assess pain thresholds and temporal summation of pain in participants with BPD compared to HC and further recorded the RIII-reflex as a marker of spinal nociceptive processing. We expected reduced temporal summation of pain and the RIII-reflex in BPD compared to HC and an association between altered pain perception and clinical markers of BPD, especially dissociation and NSSI.

3.2 Methods study II

Sample

We recruited 29 female participants with BPD and 28 female healthy controls (HC) through a central recruitment unit of a Clinical Research Unit on BPD (Schmahl et al., 2014). In seven subjects (5 BPD and 2 HC), the measurement had to be terminated due to anxiety about pain stimuli after non painful electrical stimulation (*n* = 1 HC), intolerable pain in an early phase of the experiment (*n* = 1 HC), severe dissociation during threshold assessment (*n* = 1 BPD), or because electrical stimulation was not tolerated (*n* = 4 BPD). We decided to exclude two HC who were statistical outliers (M at least 2 SD higher than group mean) for pain threshold and additionally reported former injury in the stimulation area, as this might indicate abnormal nociceptive processing. None of the other participants (HC or BPD) who reported former injuries in the stimulation area was a statistical outlier. The final sample consisted of 24 participants with a current diagnosis of BPD and 24 HC. Results of an independent samples t-test revealed no significant differences between both groups in age (BPD: *M* = 29.25 years, *SD* = 7.70; HC: *M* = 30.42 years, *SD* = 8.46), $t(46) = 0.50$, $p = .62$.

All participants were fluent in German and all but three participants (two ambidextrous in BPD, one in HC) were right-handed as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). The BPD discontinued their regular medication (psychotropic and pain medication) for at least two weeks prior to study participation, with the exception of selective serotonin reuptake inhibitors, SSRI), and for two days prior to participation for pro re nata medication. Information about medication is missing from one participant with BPD. Three participants with BPD reported to take SRRI during study participation. The study was approved by the ethics commission of the Medical Faculty Mannheim of the University of Heidelberg, and complied with the Declaration of Helsinki. All participants provided written informed consent and were compensated for participation with 26€.

Clinical diagnosis according to the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV; American Psychiatric Association, 2000) was performed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis I Disorders (Wittchen et al., 1997) and the International Personality Disorder Examination (IPDE; Loranger et al., 1997). Participants with BPD had to meet five or

more of the BPD IPDE criteria within the last two years prior to study participation, and at least one of these criteria had to begin during childhood or adolescence.

A priori, we excluded subjects with scars in the area of the ankle or back of the thigh of the right leg (due to self-injurious behavior or other reasons) to avoid reduced sensitivity in the stimulated body part or problems with electromyography (EMG) recording. Further exclusion criteria were life-time diagnosis of bipolar I disorder or schizophrenia, insufficient speech comprehension, intellectual disability, body mass index < 16.5, substance abuse disorder within the last year (in case of current substance abuse, abstinence of two month was required), fibromyalgia, serious physical illness, severe brain diseases or concussion, and pregnancy. Prevalence of comorbid life-time and current mental disorders as well as a clinical characterization of the BPD sample are given in Table 4. A history of mental disorders was an exclusion criterion for the HC group. Eight participants (5 BPD and 3 HC) reported former pain episodes or injuries (e.g. torn ligament or ankle sprain) in the stimulation area and two participants (1 BPD and 1 HC) reported regular pain in terms of back pain or migraine. Due to the central recruitment, we have decided to not exclude participant who (a) reported former injury in the stimulation area, or (b) reported regular pain, or (c) reported intake of SSRI a priori, but screened for statistical outliers at the beginning of the data analysis (see above). We further repeated all main analysis excluding the participants who reported one of the issues mentioned above and report results in the supplement.

Table 4: *Prevalence of comorbid axis I disorders in participants with borderline personality disorder and clinical characteristic of the samples*[2]

Prevalence of comorbid axis I disorders in BPD [*n* = 23]		**Current** ***n* (%)**	**Lifetime** ***n* (%)**
Major depressive disorder		7 (30)	18 (78)
Post-traumatic stress disorder		4 (17)	6 (26)
Eating disorders		2 (9)	13 (57)
Other mental disorders (only current)		10 (43)	-
More than one mental disorder (only current)		9 (39)	-
Clinical characteristics	**HC** [*n* = 24] ***M (SD)*** ***Mdn (IQR)***	**BPD** [*n* = 22] ***M (SD)*** ***Mdn(IQR)***	**test statistic**
Symptom severity (BSL-23)	0.09 (0.09) 0.07 (0.17)	1.34 (0.84) 1.24 (1.51)	*z* = -5.74, *p* < .001, *r* = 0.85
Frequency NSSI last month[a)]	-	6.64 (5.88) 4.00 (7.00)	-
Trait dissociation (FDS)	2.96 (2.20) 2.27 (2.67)	20.57 (12.56) 20.45 (16.14)	*z* = -5.36, *p* < .001, *r* = 0.78
Depressiveness (BDI)	1.96 (2.51) 1.00 (3.25)	18.86 (10.65) 22.00 (13.00)	*z* = -5.15, *p* < .001, *r* = 0.76
Trait anxiety (STAI)	31.88 (6.26) 29.50 (9.50)	65.00 (7.43)[b)] 67.00 (9.50)	*t*(45) = -16.52, *p* < .001, *d* = 4.82
State anxiety (STAI)	29.33 (4.05) 29.50 (5.00)	52.86 (12.70) 53.00 (20.50)	*t*(44) = -8.62, *p* < .001, *d* = 2.50

HC = healthy controls; BPD = borderline personality disorder; n = number, M = mean, SD = standard deviation, BSL-23 = Borderline Symptom List (Bohus et al., 2009), NSSI = non-suicidal self-injury, FDS = Fragebogen zu Dissoziativen Symptomen [Questionnaire of dissociative symptoms] (Freyberger et al., 1999), BDI = Beck Depression Inventory (Hautzinger et al., 1995), STAI = State-Trait-Anxiety Inventory (Laux et al., 1981); [a)]reported only from those subjects who performed NSSI at all. None of the HCs reported NSSI, BPD: *n* = 21; [b)]*n* = 23

[2] Data presented in this table were collected by trained clinical psychologists of the Clinical Research Unit 256 (Schmahl et al., 2014)

Psychological assessment

We used the mean score of the German Borderline Symptom List (BSL-23; Bohus et al., 2009) to assess general symptom severity. The values of the BSL-23 range from 0 (“not at all”) to 4 (“very strong”) with higher values indicating higher symptom severity. For the assessment of depressiveness, we used the overall sum score of the German version of the Beck Depression Inventory (BDI; Hautzinger et al., 1995), with values ranging from 0 to 63 and higher scores indicating higher depressiveness. The German version of the State-Trait-Anxiety Inventory (STAI; Laux et al., 1981) was used assess anxiety. For both, the state and trait subscale, the sum scores range from 40 to 160 with higher values indicating higher anxiety. For the assessment of trait dissociation we used the total score of the Fragebogen zu Dissoziativen Symptomen [Dissociative Symptoms Questionnaire] (FDS; Freyberger et al., 1999), which is the German adaptation of the Dissociative Experience Scale (Bernstein & Putnam, 1986). FDS total scores range from 0 to 100, with higher values indicating higher trait dissociation. Frequency of NSSI was assessed by the self-reported number of self-injurious behaviors within the last month prior to study participation for those subjects who had reported NSSI in the last year prior to study participation. These data were assessed on a separate day and were missing for 1 participant with BPD for FDS, NSSI, and trait anxiety, as well as for 2 participants with BPD for BSL and state anxiety.

During the experiment, we assessed state dissociation using the German short version of the Dissociation-Tension Scale acute (DSS-4; Stiglmayr et al., 2009) immediately before and after painful stimulation. The mean score ranges from 0 to 9 with higher values indicating higher dissociation. Data were missing for 1 participant with BPD after painful stimulation.

Electric stimulation and EMG recording

Before attaching the electrodes, electrode sites were cleaned with surgical spirit and abraded with V17 Abralyt 2000 (Easycap GmbH, Herrsching, Germany) to achieve impedances of less than 10 kΩ. The external retro-malleolar pathway of the sural nerve of the right leg was stimulated percutaneously using a Nicolet surface bar electrode (bipolar stimulating electrode of 8mm diameter with 30mm interelectrode distance) that was applied with anode inferior (e.g. Rhudy & France, 2007). To ensure that the sural nerve was stimulated, a position on the ankle was chosen where electrical stimulation was felt on the outer edge of the foot by the participant. After attaching the electrode,

the ankle was fixed at 90° (Sandrini et al., 2005) using a SAM splint (SAM Medical, Tualtin, Oregon, USA) and a bandage. Electric stimuli were generated by an electrical stimulator (Digitimer, DS7A; Digitimer Ltd, Welwyn Garden City, UK) controlled by Presentation (v17.0; Neurobehavioral Systems, Inc., Albany, CA, USA) and consisted of standard pulse trains of five rectangular pulses (each of 1ms duration) delivered at 250Hz (Terry et al., 2011). These pulse trains are typical for RIII studies and have been shown to be most efficacious to evoke an EMG response (Sandrini et al., 2005). Since it is extremely brief, one pulse train is perceived like a single stimulus by the participant. To record biceps femoris activity of the right leg, two surface electrodes (Neonatal ECG electrode, Philips HP Agilent, Palo Alto, California, USA) were attached over the muscle belly. Further, a ground electrode was attached above the tibia, midway between the knee and ankle. To achieve muscle relaxation during the experiment, participants were sitting comfortably on an examination table, the knee supported with a knee roll (120° - 130° between the upper and lower leg) and the upper body reclined (angle of approx. 100° between the upper body and the upper leg). To prevent the legs from cooling down, they were covered with a blanket. EMG activity was amplified using a bioamplifier V75-04 of a LabLinc V System (Coulbourn Instruments, Allentown, PA, USA) with a signal bandwith of DC - 1kHz. The signal was processed using a CED 1401 Power analog-to-digital converter and Spike2 version 2.13 software with a sampling rate of 5 kHz (both: Cambridge Electronic Design Lfg, Cambridge, England). In one BPD subject the left instead of the right leg was stimulated because the subject reported reduced sensibility in the innervation area of N. suralis after a herniated disk.

Threshold assessment

Before the main experiment started, electrical detection threshold (EDT), electrical pain threshold (EPT) and RIII-reflex threshold (RT) were assessed by stimulating the external retro-malleolar pathway of the sural nerve of the right leg using single pulse trains and three ascending-descending staircases of electric stimuli. The interval between two pulse trains varied randomly between 8 and 12 s to reduce predictability and habituation (Terry et al., 2011). We always started with the assessment of EDT, followed by EPT and RT assessment. For the RT procedure, the EMG signal was analyzed online and stimulus intensity was adjusted accordingly. However, post-hoc offline analysis revealed that due to slow drifts in the EMG signal, results of the online analysis might have been misleading, and thus RT is not reported. Since stimulation

intensity was adjusted depending on the result of EPT and a DC-correction was applied to the data for all offline-analyses of the EMG data (see below), the described issue did not influence the reported results.

Participants were instructed to say 'yes' as soon as they perceived the electrical stimulation (EDT) and as soon as the stimulus was perceived as just painful (EPT). For the assessment of EDT, electric stimulation started with 0mA and increased in 2mA steps until perception was reported. The current was then decreased in 1mA steps until it was no longer perceived by the participants. The next two ascending-descending staircases continued with 1mA steps. EDT was defined as the average stimulation intensity (mA) of the 2 peaks and 2 troughs of the last two ascending-descending staircases. For EPT assessment, starting from calculated EDT, electrical stimulation was increased in 2mA steps until it was perceived as just painful. The current was then decreased in 1mA steps until it was no longer perceived painful, followed by two ascending-descending staircases in 1 mA steps. EPT was defined as the average stimulation intensity (mA) of the last 2 peaks and 2 troughs of the last two ascending-descending staircases.

Experimental paradigm

Stimulus intensity was set to 1.5xEPT to ensure a painful stimulation intensity likely to evoke RIII-reflexes during the experiment. The experiment consisted of five blocks with three series of stimuli each. Within a series, a single pulse train was followed by a series of five pulse trains with one of three frequencies, 0.2Hz, 1Hz and 2Hz, with the latter two being within the range of frequencies that are known to evoke wind-up (Eide, 2000). Each frequency was presented only once per block and the order of frequencies within each block was randomized, so that each subject received a different order. Participant rated perceived pain intensity and unpleasantness of the single pulse trains and the 5^{th} stimulus of the series, each immediately after its occurrence. We have decided to rate a single stimulus and the 5^{th} stimulus of a series directly after the respective stimulus presentation to avoid a rating bias (might occur if e.g. after the end of a series the first and the last stimulus of the series are rated). Pain ratings were assessed by a visual analog scale (VAS), presented on a screen, with the anchors "not painful" or "not unpleasant" and "strongest pain imaginable" or "very unpleasant", using a keyboard. The answers of the VAS scales were converted in values ranging from 0 ("not painful", "not unpleasant") to 100 ("strongest pain imaginable", "very unpleasant").

Each rating phase was preceded by a short sound delivered via headphones indicating to open the eyes. After each rating phase subjects were instructed to close their eyes and focus on the ankle of the right leg for the stimulation phase. Within one series, the period between ratings of the single pulse train and the start of the series of pulse trains varied randomly between 1.5 and 3 s. The resting period varied randomly between 8 and 12 s within and consisted of 1-2 min between blocks. The experimental protocol is depicted in Figure 5. Each subject received 90 pulse trains (15 single pulse trains and 15 series of 5 pulse trains) in the course of the experiment. Two BPD terminated the experiment at a very late phase (both during the penultimate of 5 blocks) due to strong dissociation or intolerable pain, respectively. However, as most of the data of these subjects were available, their data were included in the final analysis, with missing data for the last blocks.

The entire experiment was controlled by Presentation (v17.0; Neurobehavioral Systems, Inc., Albany, CA, USA).

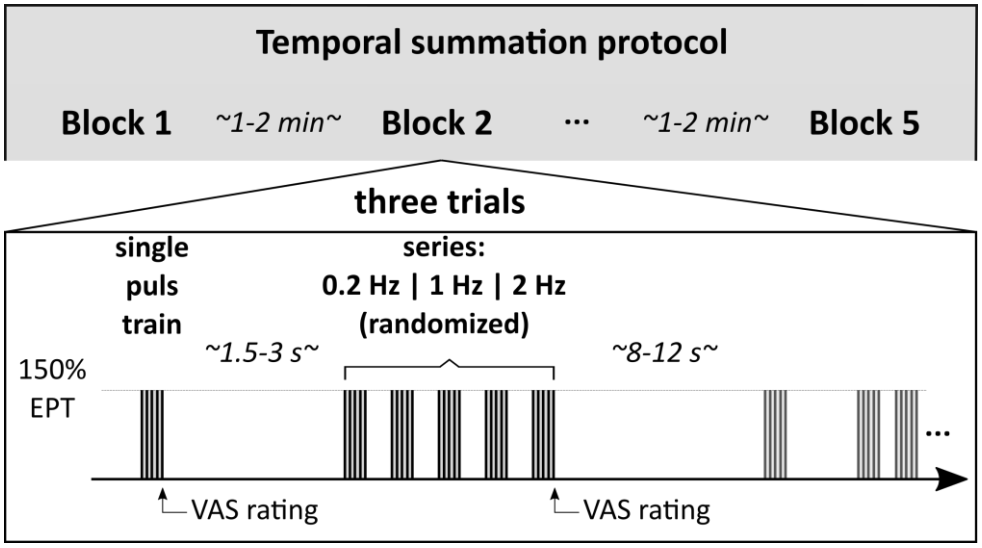

Figure 5: Temporal summation protocol. The experiment consisted of 5 blocks with 3 trials each. One trial consisted of a single pulse train and a series of 5 pulse trains, each with 5 single pulses of 1ms duration. The series of 5 pulse trains was delivered with 0.2Hz, 1Hz, and 2Hz with a base rate of 250Hz. The single puls train and the 5th puls train were immediately followed by assessment of perceived pain intensity and unpleasantness rating on a visual analogue scales (VAS), presented on a PC display. Stimulus intensities were preset to 150% of electrical pain threshold (EPT). Temporal summation is measured as the difference between the single puls train and the 5th puls train of a series VAS rating

EMG data preprocessing

Due to technical problems during recording, EMG data of three HC subjects were not available. Further, there were missing data for two BPD subjects who terminated the experiment late in the experimental procedure (see above), and some missing data for 4 BPD and 2 HC (e.g., due to system failure of the recording computer). In total, we analyzed EMG responses to 2,039 (*M* = 87.21, *SD* = 7.43) pulse trains from *n* = 24 BPD participants and 1,847 (*M* = 87.95, *SD* = 10.61) stimuli from n = 21 HC. For offline analysis of the EMG data, we used Spike2 software (Cambridge Electronic Design Lfg, Cambridge, England, version 5.21). The EMG signal was rectified and the Spike2 built-in DC correction (time constant 0.02s) was applied to remove low-frequency electric drift. A visual inspection of the data of all subjects revealed no artifacts. We calculated the RIII-reflex interval *z* score by applying the formula $\frac{reflex\ interval\ mean - baseline\ mean}{baseline\ standard\ deviation}$, resulting in a standardized EMG response score measured in standard deviation units relative to baseline. The reflex window was defined as 90-150ms after stimulus onset, while the 60ms pre-stimulus interval served as baseline interval (Rhudy & France, 2007). Due to inevitable baseline contamination in the course of a temporal summation series, for all pulse trains within a temporal summation series, the baseline of the first pulse train of the respective series was used for baseline correction (Terry et al., 2011). A valid RIII-reflex response was defined as a mean EMG response in the reflex interval that exceeded the mean EMG activity during the baseline interval by at least 1 SD (Rhudy et al., 2005). However, if not explicitly described otherwise, we decided to include all EMG responses into the analyses to capture the full picture of modulation including low modulation between two responses below the reflex threshold as well as high modulation if only one of two reflexes was above the reflex threshold.

Statistical analyses

All statistical analysis were conducted in the R environment (R Core Team, 2021). Beside test-statistics and p-values, we report absolute values of effect sizes computed as Cohen's *d* or *r*, when applicable.

Data of thresholds and stimulation intensities were tested for normal distribution using the Shapiro-Wilk test. If the assumption of normality was violated, non-parametric statistics were used. To test for differences in thresholds and stimulation intensity, we

compared data of BPD and HC participants using t-tests for independent samples or, in the case of non-normal distribution, Mann-Whitney-U tests.

Experimental data were analyzed with linear mixed effects models (LMM) using the *lmerTest* package (Kuznetsova et al., 2017) and the *lmer* function. Significance of the fixed effects was tested using the *anova* function, applying Satterthwaite's method to estimate degrees of freedom. Significant main effects and interactions were followed by pairwise post-hoc comparisons of the estimated marginal means using *emmeans* (Lenth, 2022). Where appropriate, correction for multiple testing was applied using Bonferroni-correction to avoid alpha inflation. In all our LMMs, the random effect (1| subject) allows for variable intercepts for each subject. Because of the way variance is partitioned in LMMs (e.g. Rights & Sterba, 2019), there is no agreed-on method to calculate standard effect sizes for individual model terms such as main effects or interactions. Therefore, we do not report effect sizes for main or interaction effects of LMMs. Nevertheless, we used LMMs because mixed models are superior to alternative approaches in controlling for Type 1 errors and results from mixed models are more likely to generalize to new observations (e.g. Barr et al., 2013).

By using LMMs, we first analyzed the effect of group (HC vs. BPD), frequency (0.2Hz vs. 1Hz vs. 2Hz) and the group by frequency interaction on perceived pain intensity and unpleasantness as well as the EMG-response related to the single pulse trains. We further correlated EMG-responses on single pulse trains with perceived pain intensity and unpleasantness using Spearman rank correlations (r_s). To test for differences in temporal summation, we further analyzed the effect of group (HC vs. BPD), frequency (0.2Hz vs. 1Hz vs. 2Hz), stimulus (single stimulus vs. last stimulus of a series), and their interactions on perceived pain intensity and unpleasantness as well as the EMG response. For the EMG-response, this was repeated taken only trials with valid reflexes into account. Further, to control for the effect of (different) stimulation intensites, an additional LMM on EMG response was performed with stimulation intensity as fixed factor in addition to group, frequency, and stimulus. Both additional analysis are reported in the supplement.

Descriptively, we report arithmetic means and standard deviations of perceived pain intensity, pain unpleasantness, and EMG responses of the single puls train and the 5th puls train of a temporal summation series for both groups and each frequency separately. In the supplement we further report descriptively arithmetic means and

standard deviations of the respective difference score (difference between the respective values of the 5th pulse train of a series and the value of the preceding single pulse train (Marouf et al., 2015), with positive values indicating an increase), i.e. temporal summation. To assess the association between temporal summation of pain perception and the EMG response, we restricted the analysis to the results of the 2Hz trials, because only these (but not 1 Hz trials) differed significantly from the EMG responses at the baseline condition of 0.2 Hz, which is in line with previous studies (Terry et al., 2011). We correlated temporal summation of the EMG response at 2 Hz with temporal summation of perceived pain intensity and unpleasantness for each group separately using Spearman rank correlations (r_s). We further used non-parametric partial correlation for testing the relationship between temporal summation of the EMG response at 2 Hz with temporal summation of perceived pain intensity and unpleasantness while controlling for applied stimulus intensity.

Finally, we correlated the temporal summation of the EMG response, perceived pain intensity, and unpleasantness at 2 Hz with clinical markers of symptom severity, state and trait dissociation, change in state dissociation (from pre to post stimulation with positive values indicating an increase in dissociation) as well as pain threshold only in the BPD group.

In the supplement, we further report the results of the main analysis, which revealed significant effects (comparison pain threshold between groups, LMMs on pain intensity, pain unpleasantness, and EMG response as well as correlation between temporal summation of pain perception and reflex response) after excluding subjects who (a) reported former injury in the stimulation area, or (b) reported regular pain, or (c) reported intake of SSRIs.

3.3 Results study II

Thresholds and stimulation intensity in BPD and HC

Descriptive statistics for perception and pain thresholds can be found in Table 5. There was no significant difference in perception threshold between BPD and HC, $z = -1.25$, $p = .21$, $r = 0.18$. Pain threshold was significantly higher in BPD compared to HC $t(46) = -3.74$, $p < .001$, $d = -1.08$.

As a result of the significant differences in pain threshold between the samples, stimulation intensity was also significantly higher in BPD (M = 10.46mA, SD = 3.67) compared to HC (M = 6.79mA, SD = 3.1), $t(46) = -3.74$, $p < .001$, $d = -1.08$.

***Table 5**: Perception and pain thresholds as well as stimulation intensities in participants with borderline personality disorder and healthy controls.*

	Perception threshold [mA]		**Pain threshold** [mA]		**Stimulation intensity** [mA]	
	BPD (n = 24)	**HC** (n = 24)	**BPD** (n = 24)	**HC** (n = 24)	**BPD** (n = 24)	**HC** (n = 24)
Mean (SD)	0.81 (0.46)	0.62 (0.29)	6.97 (2.45)	4.53 (2.06)	10.46 (3.67)	6.79 (3.10)
Median (IQR)	0.50 (1.00)	0.50 (0.00)	6.38 (3.06)	3.88 (3.51)	9.6 (4.60)	5.81 (5.27)

BPD = borderline personality disorder; HC = healthy control; n = number; SD = standard deviation; IQR = interquartile range.

Pain Perception and EMG responses to single stimuli in BPD and HC

We observed no significant effect of group, frequency, or the group*frequency interaction on perceived pain intensity (all $F < 0.23$, all $p > .63$), unpleasantness (all $F < 0.66$, all $p > .52$), or EMG responses (all $F < 1.86$, all $p > .16$) of the single stimuli. By taking only the EMG responses of valid RIII-reflexes into account, the resulting pattern of the LMM on EMG responses of the single stimuli remained unaltered (all $F < 0.58$, all $p > .56$).

There was no significant correlation between EMG-response and perceived pain intensity or unpleasantness, neither in BPD (all $r_s < .05$, all $p > .82$) nor in HC (all $r_s < 0.29$, all $p > .20$). This was also true if only valid reflexes and the respective ratings were analyzed (all $r_s < .26$, all $p > .32$).

Temporal summation in BPD and HC

Descriptive data for temporal summation of pain intensity and unpleasantness as well as EMG–responses are visualized in Figure 6 and are further reported in Table S4 in the supplement.

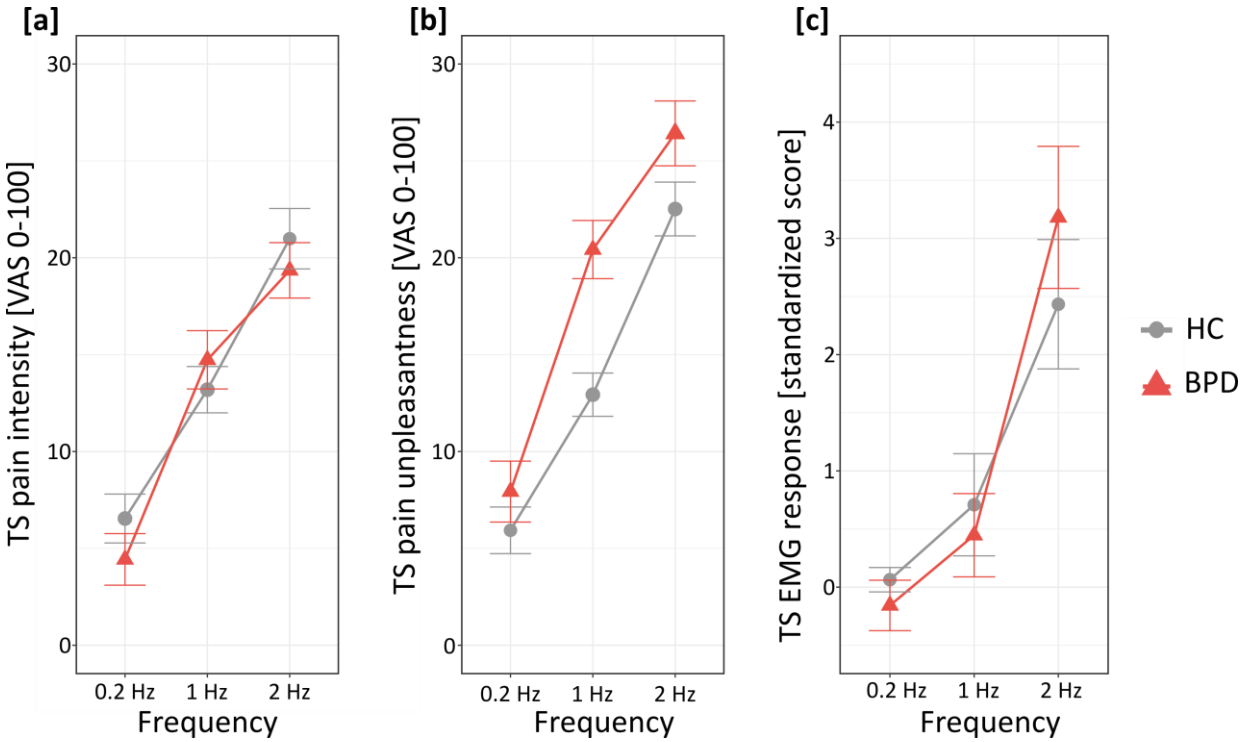

Figure 6: Parameters of temporal summation at three stimulation frequencies and for both groups, participants with borderline personality disorder (BPD) and healthy controls (HC). **[a]** shows results of temporal summation (TS) of pain intensity ratings, **[b]** shows temporal summation of unpleasantness ratings, **[c]** shows temporal summation of reflex responses. Each of the three parameters is calculated as the difference between the responses to the single puls train and the 5th stimulus in the sequence of one trial; VAS = visual analog scale, EMG = electromyography

Descriptive data for pain intensity and unpleasantness as well as EMG responses for the single and the 5th puls train of a temporal summation series in different stimulation frequencies can be found in Table 6 and are further visualized in Figure S1 in the supplement.

***Table 6**: Pain intensity, pain unpleasantness, and reflex response for the single puls train and 5th puls train of a temporal summation series in participants with borderline personality disorder and healthy controls*

	BPD [*n* = 24]						**HC** [*n* = 24]					
Frequency	**0.2 Hz**		**1 Hz**		**2 Hz**		**0.2 Hz**		**1 Hz**		**2 Hz**	
	single	**5th**	**single**	**5th**	**single**	**5th**	**single**	**5th**	**single**	**5th**	**single**	**5th**
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
Intensity [VAS 0 – 100]	36.69 (23.51)	41.13 (23.96)	36.63 (23.98)	51.36 (23.21)	36.49 (24.00)	55.84 (23.60)	33.57 (24.99)	40.11 (26.25)	34.23 (24.43)	47.42 (26.43)	33.38 (23.83)	54.36 (26.30)
Unpleasantness [VAS 0 – 100]	40.47 (24.17)	48.41 (23.31)	40.59 (24.08)	61.01 (20.51)	40.63 (24.22)	67.05 (21.93)	33.35 (25.04)	45.28 (25.98)	41.35 (24.50)	54.28 (26.40)	39.38 (22.93)	61.89 (27.42)
Reflex response [standardized score]	1.69 (3.23)	1.53 (2.72)	1.97 (4.23)	2.41 (3.25)	1.81 (2.92)	4.99 (6.86)	0.63[1] (1.67)	0.69[1] (2.07)	1.03[1] (2.65)	1.74[1] (4.90)	0.95[1] (2.54)	3.38[1] (5.47)

BPD = borderline personality disorder; HC = healthy control; n = number; *M* = mean; *SD* = standard deviation; VAS = visual analogue scale; [1] *n* = 21

For perceived pain intensity, there was a significant main effect of stimulus (i.e. temporal summation), $F(1,1364.02) = 393.51$, $p < .001$, and frequency, $F(2,1364.03) = 39.59$, $p < .001$, as well as a significant stimulus*frequency interaction, $F(2,1364.02) = 40.94$, $p < .001$. All post hoc tests were significant with positive estimates (see Table 7), indicating that the effect of stimulus on perceived pain intensity was significantly stronger for 2Hz compared to 1Hz and 0.2Hz stimulation, and also for 1Hz compared to 0.2Hz. However, neither the main effect of group nor any of the interactions with group were significant (all $F < 0.74$, all $p > .48$), i.e. there were no significant differences (in temporal summation) between groups.

For perceived pain unpleasantness, there was a significant group*stimulus interaction $F(1,1364.01) = 11.71$, $p < .001$. A post hoc test of this interaction was significant with a positive estimate, indicating that the effect of stimulus (i.e. temporal summation) in BPD compared to HC was significantly stronger. Similar to the effect on perceived pain intensity, there were significant main effects of stimulus (i.e. temporal summation), $F(1,1364.01) = 604.13$, $p < .001$, and frequency, $F(2,1364.03) = 64.78$, $p < .001$, as well as a significant stimulus*frequency interaction $F(2,1364.01) = 60.66$, $p < .001$. All post hoc tests were significant with positive estimates (see Table 7), indicating that the effect of the stimulus on perceived pain unpleasantness was significantly stronger for 2Hz compared to 1Hz and 0.2Hz, and also for 1Hz compared to 0.2 Hz. There was no significant main effect of group, group*frequency or three-way interaction group*frequency*stimulus (all $F < 1.52$, all $p > .22$).

For the EMG response, there was a significant main effect of stimulus (i.e. temporal summation) $F(1, 1253.07) = 41.94$, $p < .001$ and frequency $F(2, 1253.18) = 31.57$, $p < .001$ as well as significant stimulus*frequency interaction $F(2, 1253.07) = 25.37$, $p < .001$. Post hoc pairwise comparisons revealed that that the effect of stimulus was stronger at 2 Hz compared to 1 Hz and 0.2 Hz, but no significant difference between 0.2Hz and 1Hz emerged (see Table 7 and Figure 6c). The main effect of group or the interactions with group were not significant (all $F < 2.23$, all $p > .14$), i.e. there were no sig. difference (in temporal summation) between groups.

The results for EMG-response did not significantly change when only those trials with at least one valid reflex were taken into account (see Table S5 in the supplement). In

addition, results for EMG did not significantly change after controlling for the absolute level of stimulation (see Table S6 in the supplement).

Table 7: *Results of post hoc pairwise comparisons of linear mixed models for perceived pain intensity and unpleasantness as well as EMG responses*

		estimate	*SE*	*df*	*t*	p_{Bonf}
pairwise comparisons of the stimulus by frequency interaction for perceived pain intensity						
single stimulus vs. 5th stimulus of series	**0.2 Hz vs. 1 Hz**	8.84	1.63	1,364	5.20	< .001
	0.2 Hz vs. 2 Hz	14.68	1.63	1,364	9.01	< .001
	1 Hz vs. 2 Hz	6.20	1.63	1,364	3.80	< .001
pairwise comparisons of the stimulus by group interaction for perceived pain unpleasantness						
single stimulus vs. 5th stimulus of series	**HC vs. BPD**	4.46	1.30	1,364	3.42	< .001
pairwise comparisons of the stimulus by frequency interaction for perceived pain unpleasantness						
Single stimulus vs. 5th stimulus of series	**0.2 Hz vs. 1 Hz**	9.75	1.60	1,364	6.10	< .001
	0.2 Hz vs. 2 Hz	17.53	1.60	1,364	10.99	< .001
	1 Hz vs. 2 Hz	7.79	1.60	1,364	4.87	< .001
pairwise comparisons of stimulus by frequency interaction for EMG response						
single stimulus vs. 5th stimulus of series	**0.2 Hz vs. 1 Hz**	0.62	0.42	1,253	1.49	.41
	0.2 Hz vs. 2 Hz	2.85	0.42	1,253	6.78	< .001
	1 Hz vs. 2 Hz	2.23	0.42	1,253	5.29	< .001

Hz = Hertz, SE = standard error, df = degrees of freedom, HC = healthy controls, BPD = borderline personality disorder

Correlation between temporal summation of pain and EMG responses

For HC, there was a significant positive correlation between temporal summation of the EMG response and temporal summation of perceived pain intensity (r_s = 0.51, p = .02) and unpleasantness (r_s = 0.45, p = .04). In BPD, however, temporal summation of the EMG response was not significantly associated with temporal summation of pain perception (all r_s < 0.16, all p > .46) (see Figure 7 and Table 8)

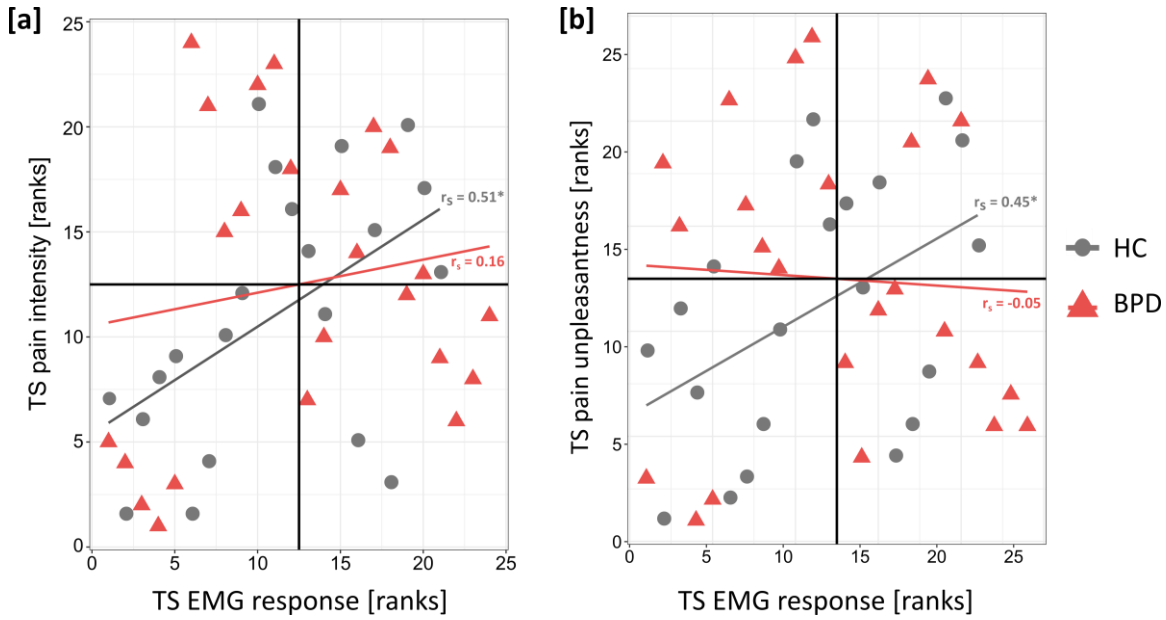

Figure 7: Association between temporal summation of reflex response and perceived pain intensity **[a]** and unpleasantness **[b]** in the sample of participants with borderline personality disorder (BPD) and healthy controls (HC); TS = temporal summation; EMG = electromyogram

After controlling for applied stimulus intensity, there was a trend towards significance for a positive relationship between temporal summation of the EMG response and perceived pain intensity (r_s = 0.39, p = .09) and unpleasantness (r_s = 0.41, p = .07). In BPD, the relationship between temporal summation of the EMG response and pain perception remained not significant (all r_s < 0.16, all p > .46).

When analyzing the data, we observed a small cluster of participants with BPD with very low temporal summation of the EMG response and low temporal summation of perceived pain intensity or unpleasantness seemed to be separated from the main cluster (see the bottom left quadrant of in Figure 7a and Figure 7b). An exploratory of the association between temporal summation of pain perception and EMG responses

in the main cluster of participants with BPD only revealed a significant negative correlation between temporal summation of the EMG response and temporal summation of perceived pain intensity (r_s = - 0.67, p < .01) and unpleasantness (r_s = - 0.53, p < .01). Even if the interpretability of this result is limited due to the exploratory character of the analysis, we decided to report this result, as it might also stimulate future research.

Association between temporal summation of pain, pain thresholds, and clinical markers in BPD

There was a trend toward significance for a negative association between change in state dissociation from pre to post stimulation and temporal summation of perceived pain intensity (r_s = -.41, p = .054) and unpleasantness (r_s = -.37, p = .08). None of the correlations between temporal summation of the EMG response, perceived pain intensity, or unpleasantness with the assessed clinical markers was significant. There was also no significant correlation between temporal summation of pain or EMG response with pain threshold in BPD (see Table 8).

Result patterns of the main analysis after excluding subjects who (a) reported former injury in the stimulation area, or (b) reported regular pain, or (c) reported intake of SSRI, did not significantly differ from the results of the entire sample (see Tables S7-S9 in the supplement).

Table 8: *Association between temporal summation of pain, pain thresholds, and clinical markers in participants with borderline personality disorder*

	Trait Dissociation (FDS)	**Symptom severity (BSL-23)**	**Frequency NSSI last month**	**State Dissociation pre (DSS-4)**	**Change in state Dissociation (post – pre)**	**TS pain intensity**	**TS pain unpleasantness**	**Pain threshold**
TS EMG response	r_s = 0.29 p = .18	r_s = 0.32 p = .15	r_s = 0.18 p = .42	r_s = -0.02 p = .95	r_s = -0.29 p = .18	r_s = 0.16 p = .46	r_s = -0.05 p = .80	r_s = 0.09 p = .69
TS pain intensity	r = -0.23 p = .29	r = -0.11 p = .64	r_s = -0.01 p = .98	r_s = 0.12 p = .57	r_s = -0.41 p = .05		r = 0.82 p < .001	r = 0.24 p = .27
TS pain unpleasantness	r = -0.08 p = .73	r = -0.20 p = .37	r_s = -0.18 p = .42	r_s = 0.22 p = .30	r_s = -0.37 p = .08			r = 0.32 p = .12
Pain threshold	r < -0.01 p = .98	r = 0.23 p = .30	r_s = 0.10 p = .66	r_s = 0.05 p = .83	r_s = -0.23 p = .28			

FDS = Fragebogen zu Dissoziativen Symptomen [Questionnaire of dissociative symptoms] (Freyberger et al., 1999); BSL-23 = Borderline Symptom List (Bohus et al., 2009); NSSI = non-suicidal self-injury; DSS-4 = Dissociation-Tension Scale acute (short version) (Stiglmayr et al., 2009); pre = before the stimulation started; post = after the stimulation; Change in state dissociation was assessed as difference score with positive values indicating an increase in dissociation from pre to post stimulation; TS = temporal summation

3.4 Discussion study II

In this study, we investigated pain processing in participants with BPD compared to HC. Using electrical stimulation, pain thresholds were acquired as well as temporal summation of perceived intensity, unpleasantness and reflex level of pain for three different frequencies of stimulation. We further related temporal summation of pain perception and spinal responses to each other, and examined the relationship of the pain measures and clinical markers of BPD.

Concerning BPD, we replicated the findings of reduced pain thresholds commonly found in that group. Moreover, participants with BPD were not any different from HC concerning perceived pain intensity or unpleasantness rating of single stimuli, when the stimulation was adapted to the different pain thresholds (resulting in significantly higher stimulation intensities for BPD compared to HC). These findings are in line with previous reports on reduced pain sensitivity in BPD (Fales et al., 2021).

There was also no significant difference between BPD and HC in EMG reflex response to single stimuli. The intensity of the single pulses being adjusted to the individual pain threshold, we interpret this as a comparable spinal activity given different nociceptive input (different stimulus intensities).

Temporal summation was found in pain intensity, unpleasantness and EMG reflex measures. Contrary to our expectation, temporal summation of pain unpleasantness was significantly higher in BPD compared to HC, independent of stimulation frequency. The previously observed significant positive correlation between temporal summation of reflex responses and perceived pain was replicated for HC (Marouf et al., 2015) but was not present in BPD. Exploratory results revealed that the association between temporal summation of reflex responses and perceived pain might be even reversed for most of the participants with BPD. Among the assessed clinical markers there was a trend for a negative association between temporal summation of pain intensity and unpleasantness with change in dissociative state from pre to post stimulation, indicating that a lower temporal summation of perceived pain might be associated with a higher increase in dissociative state. In contrast to previous results (Defrin et al., 2020), temporal summation of pain intensity and unpleasantness was not significantly correlated with pain threshold.

Independent of the group, the effect of stimulus, i.e. temporal summation of perceived pain intensity and unpleasantness, was significantly higher at 2Hz vs 1Hz vs 0.2Hz. This is in line with previous results indicating stronger temporal summation of pain at higher stimulation frequencies (e.g. Kleinböhl et al., 2006). Temporal summation of the reflex response did not significantly differ between 1Hz and 0.2 Hz, but both differed from 2 Hz, supporting previous results that temporal summation of RIII-reflex is best elicited at 2Hz (Terry et al., 2011). In general, this supports the validity of our experimental protocol.

Our results indicate that temporal summation of pain unpleasantness in BPD is enhanced and thus extend results of previous studies which did not found altered temporal summation of pain in BPD (Defrin et al., 2020; Ginzburg et al., 2018). However, in these studies only sensory but not affective aspects aspects of temporal summation of pain were assessed. The effect of temporal summation in BPD might also differ between different stimulation modalities. Defrin et al. (2020) used tonic heat pain stimulation to evoke temporal summation of pain (Granot et al., 2006; Kleinböhl et al., 1999), and found a negative association between temporal summation of pain intensity and pain threshold in BPD. In contrast, in our current study temporal summation of pain was not associated with pain thresholds using repetitive electrical stimuli. However, this divergence is in line with a study comparing temporal summation of pain evoked by tonic and repetitive stimuli, which revealed that although both types of summation are correlated, only tonic temporal summation of pain, but not repetitive temporal summation of pain, was associated with pain thresholds (Granot et al., 2006). While pain thresholds have been associated with nociceptive activity (Tillman et al., 1995), repetitive temporal summation of pain is caused by wind-up, i.e. a frequency-dependent neuronal plasticity in spinal dorsal horn neurons resulting in an increased action potential discharge, which can additionally be intensified by NMDA receptor activation (Eide, 2000; Mendell & Wall, 1965). Especially for the latter, top down-modulation might play an important role since heightened repetitive temporal summation of pain has been related to anxiety (Granot et al., 2006), which is a common feature in BPD (Bohus et al., 2021).

In contrast to HC, in BPD temporal summation of the reflex response and pain intensity or unpleasantness were not positively correlated, indicating a dissociation of temporal summation of pain from spinal activity. Moreover, our exploratory analysis revealed that the association between spinal pain processes and pain perception was in a

negative direction for most of the participants with BPD. This might indicate that enhanced temporal summation could be pronounced at low levels of spinal activity, and is less marked at higher levels of spinal activity. Our exploratory result might therefore indicate, that in BPD with increased spinal activity there could be a shift towards higher descending modulation, which indeed is enhanced in BPD (Defrin et al., 2020). We therefore suggest that the interaction of two antagonistic mechanisms (ascending pathways and descending-modulation) is altered as a function of spinal nociceptive activity in BPD, resulting in altered temporal summation of the affective component of pain.

Interestingly, temporal summation of pain was not associated with state dissociation before the experiment started but there was a trend that lower temporal summation was associated with a higher increase in dissociation from pre to post stimulation, indicating that (top-down modulated) temporal summation of pain might contribute to establishing or maintaining a dissociative state. According to the trauma-models of dissociation, dissociation is a defensive mechanism to cope with overwhelming negative experiences, including physical threat without chance to escape (Hesse & Main, 1999). A mechanism to reduce perception of a protective signal, i.e. lower temporal summation of pain, and at the same time feeling detached from one's self and environment, i.e. being dissociated, might enable the person to better tolerate the aversive experience. Thereby NMDA-receptor deactivation might be involved, as NMDA-antagonists like Ketamin reduce temporal summation of pain (Eide, 2000) and induce dissociation (Krystal et al., 1994; Newcomer et al., 1999). However, at the same time, the negative correlation between temporal summation of pain and change in dissociation suggest that a high amount of (top-down modulated) temporal summation of pain, potentially reflecting amplified ascending sensory information, might be associated with a lower increase or even decrease in dissociative state and would thus give the individual the possibility to better respond to threat. In BPD, dissociation occurs in everyday stressful situations and frequently attempts are made to relieve the associated aversive inner tension through self-infliction of pain, i.e. NSSI (Kleindienst et al., 2008). It has been proposed that thereby pain processing might play an important role (Willis et al., 2017). Our results extend this by suggesting that it might be specifically processing of c-fiber mediated temporal summation of pain that is related to tension relief following NSSI.

Limitations and outlook

In the temporal summation procedure, one individually calibrated stimulation intensity was used. This might have resulted in stimulation-intensities not high enough to reliably evoke RIII-reflexes and thus limiting the interpretability of the results. This might be true, especially for HC, as the mean stimulation intensity in this group (6.79 mA) was below the reported reflex threshold for HC (8.6-10.8 mA) (Skljarevski & Ramadan, 2002). However, the main result patterns were the same if only EMG-responses of valid reflexes were taken into account or after controlling for the effect of stimulus intensity. Nevertheless, future studies are necessary to disentangle altered pain processing on spinal und supraspinal levels in BPD by applying different stimulation intensities, based on both pain- and reflex thresholds. Furthermore, assessing temporal summation of pain – on a perceptual and reflex level – evoked by different stimulation intensities would allow to investigate the proposed relation between descending modulation of pain and nociceptive spinal activity in BPD.

Our sample size was relatively small and the sample consisted solely of female subjects. Further studies in larger samples, including male subjects, are necessary to replicate and generalize our findings. There is a gender effect on temporal summation, with women showing enhanced temporal summation of pain compared to men, indicating gender-specific differences in central processing of nociceptive stimuli (Sarlani et al., 2004). Whether or not our results on altered temporal summation of pain unpleasantness in female participants with BPD can be generalized to men needs to be investigated in future studies including male participants. Replication of our results in larger studies is necessary to strengthen our findings. This might be interesting especially for the association between temporal summation of pain and changes in dissociation from pre to post stimulation, which showed a trend with a medium effect in the present study.

Furthermore, our exploratory analysis of the main cluster of BPD was based on excluding a minority of clustered subjects with extremely low levels of temporal summation that just visually differed from the majority of participants with BPD. Future larger studies are necessary to investigate whether such subgroups can be replicated also based on objective criteria.

Another limitation is that intake of SSRIs was not interrupted for study participation. SSRIs have been successfully used to treat chronic pain (Patetsos & Horjales-Araujo,

2016) and might thus have influenced our results. Also including subject who reported regular pain or former injury in the area of stimulation might be limiting. However, main results pattern remained the same after excluding all these subjects from the analysis.

Future studies on pain in BPD should not only assess pain thresholds or ratings of painful stimuli but also include measures of pain modulation such as conditioning and pharmacological mediators of pain modulation. Drug studies with NMDA antagonists would be needed to assess their effect on the association between temporal summation of pain and dissociation. If this could be replicated and strengthened by similar results with higher ecological validity, this might aid in the development of mechanism-based treatment approaches.

Conclusion

The results indicate an enhanced temporal summation of perceived pain unpleasantness in BPD compared to HC. Different mechanisms might underlie reduced pain sensitivity in terms of heightened pain threshold and the observed enhanced temporal summation of pain. Temporal summation of pain in BPD might be the net effect of an altered interaction of ascending and descending pain mechanisms. There might be an association between temporal summation of pain and change in dissociation from pre to post painful stimulation. Thereby, reduced temporal summation might contribute to a further increase in dissociative state, while a stronger temporal summation of pain might even be related to a decrease in dissociation.

CHAPTER 4

General Discussion

This thesis aimed to investigate positive and negative somatosenation in terms of pleasant touch and temporal summation of pain in BPD. Therefore, two studies were conducted in a clinical sample of participants with BPD as well as a HC sample. In study 1, standardized pleasant touch was applied with a CT-optimal velocity (3cm/s) to the back of the hands of the subjects using a custom apparatus. Perception of touch was assessed by self-report. Additionally, the affect-modulated acoustic startle response served as physiological indicator of affective modulation. In study 2, temporal summation of pain was assessed using electrical painful stimulation and pain perception was assessed by self-report. To assess nociceptive processing on a spinal cord level, the RIII-reflex was employed.

In the following chapters, the main findings are first summarized in light of the hypotheses that were formulated. The findings are then integrated into the current literature, with a focus on potential mechanisms that might underlie altered positive and negative somatosensation. In addition, the relevance of altered somatosensation for the psychopathology of BPD in terms of self- and interpersonal functioning is described. Limitations and implications for future research as well as conclusions are discussed.

4.1 Summary of findings

The main result of study 1 confirmed hypothesis 1.1: participants with BPD perceived pleasant touch stimuli as less pleasant than HC. Additionally, the results of study 1 indicate that qualitative aspects of pleasant touch perception were altered in BPD compared to HC. However, there was no evidence that inhibition of affect-modulated startle response during pleasant touch perception was diminished in participants with BPD compared to HC. Furthermore, there was no significant correlation between touch perception and the magnitude of the affect-modulated startle response, neither in BPD nor in HC. Therefore, hypothesis 1.2 was not supported. Study 1 further aimed to investigate whether there is an association between altered positive and negative somatosensation in BPD. There was no significant correlation between perceived

valence of touch and assessed heat pain thresholds in BPD. This would not support hypothesis 2. Exploratory analysis further revealed a positive correlation between perceived valence of touch and changes in dissociative experiences in terms of body ownership of the stimulated body part from pre to post stimulation. A more negative perception of pleasant touch was associated with an increase in body-related dissociative state, while a more positive pleasant touch perception of touch was related with a reduction of dissociative experience.

The results of study 2 replicated the finding of a higher pain threshold in BPD compared to HC (Fales et al., 2021). However, there was no support for hypothesis 3, which assumed reduced temporal summation of pain in participants with BPD compared to HC. While there was no significant effect of group for temporal summation of perceived pain intensity, temporal summation of perceived pain unpleasantness was – unexpectedly – higher in BPD compared to HC. Hypothesis 4 was also not supported: Results on the RIII-reflex-amplitude revealed no significant difference in temporal summation of the reflex response between BPD and HC. Temporal summation of pain was not associated with state or trait dissociation in BPD, which contradicts hypotheses 4. However, there was a trend for significance for a negative correlation between temporal summation of pain and change in state dissociation from pre to post stimulation, indicating that higher temporal summation of pain was associated with a lower increase or even decrease in temporal summation of pain.

4.2 Integration of findings

Previous studies on affective somatosensation in BPD focused on pain perception and provided meta-analytical evidence of reduced pain sensitivity in terms of heightened pain threshold or reduced pain ratings for experimentally applied stimuli in BPD (Fales et al., 2021). The results of this thesis extend these findings by providing evidence that not only negative but also positive somatosensation in terms of pleasant touch is altered in BPD. The results of study 2 indicate that several mechanisms might underlie altered pain perception in BPD.

4.2.1 Threat-hypersensitivity

Unexpectedly – but in line with a report of a positive relationship between borderline features and temporal summation of pain in an non-clinical sample (You & Meagher, 2017) – temporal summation of pain unpleasantness was higher in BPD compared to HC. However, there was no significant difference in RIII-reflex amplitude between BPD and HC, suggesting a modulation of temporal summation of pain unpleasantness on the supraspinal level in BPD. The critical frequency to evoke repetitive temporal summation of pain corresponds to the natural frequency of C-nociceptors that discharge every 2-3s when stimulus intensities are low (Torebjörk & Hallin, 1974) and might thus be part of normal pain processing to allow optimal responses to noxious stimuli. Thereby facilitatory pain processes might specifically contribute to the protective function of pain as it signals increasing need of protection of the body and enhanced threat (Bingel & Tracey, 2008) . Specifically, enhanced temporal summation of pain unpleasantness in BPD but not reduced pain sensitivity in terms of heightened pain thresholds might therefore be related to threat hypersensitivity - a common feature of BPD (Bertsch et al., 2018). This is supported by findings that anxiety, which is related to threat-hypersensitivity (Goodwin et al., 2017), has been found to be associated specifically with repetitive temporal summation of pain but not pain threshold (Granot et al., 2006). In BPD, threat hypersensitivity in terms of a negatively biased perception of social signals has been shown in numerous experiments on emotional face recognition (Bertsch et al., 2018), including positive faces (Fenske et al., 2015; Kleindienst et al., 2019; Thome et al., 2016) and this might also underlie altered pleasant touch perception. Using electroencephalographic recordings, a study on the processing of emotional faces revealed that participants with BPD showed higher occipital P100 amplitudes, reflecting an early hyperresponsiveness in parts of striatal and extrastriatal cortices (Izurieta Hidalgo et al., 2016) along with an increased negativity bias. This early bias for threat might be driven by enhanced amygdala activation that has been identified in brain imaging studies on emotional face processing in BPD (Bertsch et al., 2018). Thus, it is possible that threat hypersensitivity, an early bias for threat, might underlie altered affective somatosensory processing in terms of more unpleasant perception of pleasant touch and enhanced temporal summation of pain unpleasantness. However, temporal summation of pain unpleasantness was not related to heightened pain threshold in

BPD, indicating that different mechanisms might underlie altered pain perception in BPD.

4.2.2 Altered evaluation of affective somatosensory signals

Reduced pain sensitivity in BPD has been related to (a) a deactivation in the amygdala and enhanced negative coupling between the medial prefrontal cortex and limbic areas, which might reflect a top-down regulation mechanism, and (b) an enhanced coupling between dorsolateral prefrontal cortex and posterior insula, potentially reflecting an altered evaluation of pain (Schmahl & Baumgärtner, 2015). On the behavioral level, altered evaluation of pain has been shown by altered qualitative sensory aspects of pain perception, as assessed with the Schmerzempfindungsskala, a pain perception scale that differentiated affective and sensory pain dimensions (Geissner, 1995). Participants with BPD perceived incision-like pain as less sharp compared to HC (Schloss et al., 2019). Sharp was exactly the sensory component that was rated as being the most applicable in HC in line with the applied stimuli, which were a surrogate for sharp incisional pain and mainly evoked by Aδ-fibers. Similarly, using a touch perception task (TPT; Guest et al., 2011), study 1 revealed altered sensory qualitative aspects of pleasant touch perception in BPD compared to HC. Specifically, BPD perceived the pleasant touch as rougher and firmer compared to HC. These qualities were rated by the HC as having very little applicability to the applied stimulus, suggesting that perceived roughness and firmness played only a minor role in the HC's overall perception of the stimulus. Even though roughness and firmness represent sensory aspects of touch, they may still have contributed to the reduced perceived pleasantness of touch perception in participants with BPD. This might be true especially for the heightened roughness, because roughness and comfort correlate negatively (Guest et al., 2011). By assessing pleasantness and unpleasantness of touch separately, study 1 revealed that a touch stimulus that is perceived as pleasant by HC was on average perceived as unpleasant by participants with BPD. In pain research, however, the affective component of pain is usually assessed on a scale ranging from "not unpleasant" to "very unpleasant”. This could impede the detection of a similar reversal of valence of pain, which might also reflect a qualitative difference in perception. Schloss et al. (2019) reported that participants with BPD explicitly asked for positive labels such as “pleasant” for the painful stimulus in the course of their experiment, confirming the assumption that there might be

patients with a more positive perception of pain. Together these findings suggest that a different weighting of qualitative aspects of a stimulus might result in an altered evaluation and perception of affective somatosensory stimuli in BPD, i.e., altered cognitive evaluation processes might underlie altered perception of affective somatosensation.

4.2.3 Altered affective somatosensation and disturbed self-functioning

Since somatosensory stimuli are received directly through one's own skin, they obviously have a strong self-referential value, potentially higher than other sensory signals. This is supported by a shared neural network of self-referential processing and affective somatosensation. There is growing evidence that self-referential processing involves the cortical midline structures (CMS), including the orbitofrontal cortex, medial prefrontal cortex, anterior and posterior cingulate cortex, and precuneus (Feng et al., 2018; Northoff et al., 2006; Northoff & Bermpohl, 2004), brain regions that are also involved in the processing of pain and pleasant touch (Gordon et al., 2013; Leknes & Tracey, 2008). By experimentally manipulating self-reference, Winter et al. (2015) found a negative evaluation bias particularly for positive and neutral self-referential information. Evidence that altered processing in self-referential networks might be involved in altered pain perception in BPD, arises from a neuroimaging study, which found an enhanced connectivity between the insula and precuneus as well as posterior cingulate cortex in BPD (Niedtfeld et al., 2012). This was interpreted by the authors as a higher self-referential experience of pain in BPD compared to HC. A study on people who engage in NSSI (not exclusively patients with BPD) revealed that self-worth mediated the association between NSSI and pain hyposensitivity (Glenn et al., 2014), indicating an association between self-image and pain perception. This assumption was further supported by an experimental study, which compared a brief cognitive intervention to improve positive self-worth with a positive mood-induction (hearing positive music) and an attention task (Hooley & St. Germain, 2014). The time participants tolerated a painful stimulation was reduced compared to before the experimental condition specifically after the cognitive self-worth intervention. However, it must be noted that in these studies pain sensitivity was operationalized by a measure of pain endurance, which reflects how long a pain stimulus is tolerated, and is not only related to pain sensitivity. Self-image in BPD is characterized by an unstable sense of self, lower self-esteem and derogatory self-evaluation (Bohus et al., 2021). From a

theoretical perspective, the effect of negative self-image on perception could explain both, less positive touch perception but also reduced pain sensitivity. If one perceives oneself as not valuable or lovable, pleasant touch stimuli do not fit into the negative self-concept. To resolve this contradiction, modulated perception might occur. Based on Bayesian brain theories and the related concept of predictive coding (e.g. Friston, 2003; Knill & Pouget, 2004), which understand perception as an active process of top-down predictions and bottom-up signals, an adjusted perception might occur in order to minimize prediction error (mismatch between expectation and sensation). In the context of psychopathology, it has been proposed that updating of predictions might be impaired resulting in frequent prediction errors or perceived discrepancies (Paulus et al., 2019). In relation to reduced pain sensitivity, a reduced perception of pain could be associated with a reduced perception of the own body as worthy of protection. Altered perception might also have a reverse effect and thereby contribute to the maintenance of a negative self-image. Taken together, it can be assumed that a negative self-image might be related to altered somatosensory perception, and conversely, altered somatosensory perception might contribute to the maintenance of a negative self-image.

Dissociation reflects an extreme distortion of self-processing characterized by a disruption of perception, consciousness, identity and memory (American Psychiatric Association, 2013). In both studies, the perceived valence of the stimulus was associated with a change in dissociative experience. A less positive touch perception was related to an increase in dissociative state in terms of a further decrease in perceived body ownership from pre to post stimulation. For temporal summation of pain, there was a trend towards significance indicating that a higher temporal summation of pain was associated with a further increase in dissociative state from pre to post stimulation. These findings suggest it is not the mere perception of valence (in the sense of pleasantness or unpleasantness) that is related to the change in dissociation but an interaction of stimulus type and perceived valence. A recent study investigated the influence of perceived affective congruence using the rubber hand illusion paradigm (Filippetti et al., 2019). Study participants were stimulated with either a soft or a rough material on their unseen hand. At the same time, they looked at a rubber hand that was synchronously touched with either the same (affective congruency) or the other material (affective incongruency). Results revealed that,

irrespective of any valence effect, the affective congruent stimulation was related with higher body ownership perception of the artificial limb compared to the affective incongruent stimulation, suggesting that congruency in affective top-down aspects are important for the perception of body ownership. In Study 1, the decrease in body ownership could therefore have been - in the sense of a prediction error - a result of a perceived divergence between the expectation of how the touch would feel and the actual perceived sensation of the touch. For the pain domain, the result of an modulating effect of painful stimulation on dissociative state is in line with reports of patients that they engage in NSSI to reduce aversive inner tension and dissociation (Kleindienst et al., 2008) and previous experimental results indicating that the processing of painful stimuli might play an important role for stress reduction in BPD (e.g. Willis et al., 2017). It further extends these findings by indicating that the perception of pain rather than the pure nociceptive processing might be important. Indeed, after initial reports that the majority of patients with BPD perceive no pain during NSSI (Leibenluft et al., 1987), studies on larger samples reported that about half of the subjects do experience at least some pain during NSSI (Nock et al., 2006; Shearer, 1994). Using ecological momentary assessment, Selby et al. (2019) found that most of their subjects reported pain during NSSI. Further, they observed that those patients who were characterized by high emotional instability and reported higher pain levels during NSSI, experienced more NSSI episodes. Interestingly, in the same study those who reported less pain during an NSSI episode, recorded more self-injurious behavior during the respective episode. This might suggest that subjects even adjust their self-harm behavior to induce more pain, for example, by deeper cuts or more pain-inducing behavior like burning of the skin (Carpenter & Hepp, 2021), in order to get the painful sensation they expect . These results suggest that affective congruency might play an important role for the effects of stimulation with salient affective somatosensory stimuli on dissociative state in BPD. Thus, affective incongruency might be related to the induction or increase of dissociative state, while affective congruency might be related with a reduction of dissociative state.

4.2.4 Altered pleasant touch perception and interpersonal functioning

Pleasant touch is as an important affiliative social signal (Björnsdotter et al., 2010), with a strong biological foundation: it has been shown that CT-afferents discharge preferentially to CT-optimal stimulation when the stimulator has typical skin

temperature, i.e. 32°C (Ackerley et al., 2014) and there are experimental results indicating that CT-optimal touch frequency is intuitively used to touch another human but not an object (Croy, Luong, et al., 2016). It therefore seems possible that altered pleasant touch perception might be related to problems in interpersonal functioning in BPD, which is characterized by a pattern of unstable and intense interpersonal relationships, pervasive loneliness, and proneness to rejection sensitivity/perceived social exclusion (Bohus et al., 2021). In an experimental study in HC using a common social exclusion paradigm, i.e. the cyberball task, it has been shown that application of CT-optimal but not CT-non-optimal touch after the social exclusion condition of the cyberball task reduced feelings of ostracism beyond a general effect on mood (Von Mohr et al., 2017). Since pleasant touch is for obvious reasons associated with physical proximity, altered pleasant touch perception could in particular affect close social relationships. Patients with BPD prefer larger interpersonal distances (Abdevali et al., 2021; Fineberg et al., 2018; Schienle et al., 2015), which has been related to altered touch perception (but not specifically CT-optimal touch) in individuals with a history of childhood maltreatment (Maier et al., 2020). Empirical evidence for the association between altered touch perception in BPD and social aspects arises from a recent study, which assessed social touch in participants with BPD (A. Schulze et al., 2022). Three facets of social touch were assessed: (1) general attitude toward interpersonal touch was assessed via self-report questionnaire, (2) liking of touch was assessed in an online experiment using video clips presenting positive versus negative touch in a social versus non-social context, and (3) importance of touch toward members of an individual's social network was assessed via self-report. Compared to HC, participants with BPD reported disturbances in all three facets, in terms of a lower need for touch, a lower liking of in particular positive interpersonal touch, and a lower importance of touch in relationships. Although this study did not assess altered perception of applied touch stimuli, these results are relevant for the interpretation of altered pleasant touch perception in BPD. Altered pleasant touch perception in BPD might be associated with problems in interpersonal functioning.

4.3 Limitations and implication for future research

Besides the limitations that have already been discussed in the context of the individual studies, additional limitations for the studies included in this thesis must be noted.

The first limitation relates to the question of an association between altered positive and negative somatosensation in BPD. Due to technical problems, data on both pleasant touch perception and pain perception could only be collected from a small sample of participants with BPD. Thus, a valid test of the hypothesized association between altered pain and pleasant touch perception was not possible. However, based on the results of this thesis and the existing literature, it has been proposed that different mechanisms might underlie altered perception of affective somatosensory stimuli, implying differential associations between different aspects of positive and negative somatosensation. To test this empirically, future studies are necessary to assess the broad range of different aspects of positive and negative somatonsensation and investigate associations between alterations of the different aspects. Thereby, sensory, affective, and qualitative characteristics of positive and negative somatosensory stimuli should be assessed and extended by measurements of pain-modulating processes like temporal summation of pain or conditioned pain modulation. Further, perception of the different aspects needs to be correlated with the assumed psychopathological characteristics, mainly in terms of anxiety/threat-hypersensitivity and negative self-image. Studies using neuroimaging or electroencephalographic recordings are needed to examine the relationship of the underlying neurobiological correlates of the different mechanisms with the respective presumed changes on the perceptual level. For the pain domain, it would be important to assess perceived pleasantness in addition to perceived unpleasantness.

Another limitation is to be seen in the diagnosis of participants with BPD. This was done based on the International Personality Disorder Examination (IPDE) criteria for BPD. In the meantime, the diagnostic system of personality disorders has changed, especially with the introduction of ICD-11 (World Health Organization, 2021), and is now carried out on a dimensional level in terms of severity of impairments in self- and interpersonal functioning. By investigating patients diagnosed according to ICD-11, it can be tested whether, as proposed in the discussion, altered pleasant touch perception is associated with impaired self- and interpersonal functioning and altered pain perception is associated primarily with impaired self-functioning. In both studies altered perception of positive and negative affective somatosensation was not related to symptom severity as assessed with the Borderline Symptom List (Bohus et al., 2009), raising the question of the specificity of the findings for patients with a BPD diagnosis according to IPDE criteria. In a previous study, altered perception of pleasant

touch was demonstrated for a sample of participants with various personality disorders, without reporting results for individual personality disorders (Croy, Geide, et al., 2016), whereas pain perception has so far been primarily investigated in BPD. Comparing patients with personality disorders with and without borderline classifier according to ICD-11 could shed light on whether altered perception of pleasant touch or pain or a combination of both is unique to BPD.

Furthermore, the ecological validity of the results is limited. The work aimed to investigate the mechanisms behind altered affective somatosensation in BPD. Therefore, the studies were carried out in an experimental setting. Pleasant touch stimuli were applied by using a custom apparatus in order to standardize the stimulus and to minimize the influence of the experimenter. In everyday life, pleasant touch naturally takes place in a complex setting and touch can be influenced by various contextual factors, like characteristics of the toucher (e.g. Ellingsen et al., 2016). In study 2, for the assessment of the RIII-reflex, a special setting was necessary. The stimulation must be applied to the ankle and the foot must be fixed at 90°. It can be assumed that this greatly limited the perceived controllability of the stimulus, which is known to influence pain processing (Salomons et al., 2004). Therefore, future studies should extend laboratory studies by adding methods with high ecological validity, like ecological momentary assessment, to relate experimental results with impairments assessed in daily life. For the context of this study, it might be especially interesting to relate altered pain perception of experimental pain to NSSI (Carpenter & Hepp, 2021), and pleasant touch perception as assessed in a standardized fashion in the laboratory with reported frequency and quality of close interpersonal contacts.

The results on the valence-specific effect of affective somatosensory stimulation on dissociative states might inspire future experiments. For example, to test the presumed association of expectation, perception, and change in dissociative state, expectation for an incoming stimulus and its fulfillment can be experimentally manipulated by instruction or by using a priming signal and the administration of a congruent vs. non-congruent stimulus. The effect of stimulation on induced stress or dissociation can be assessed by using, for example, the script-driven imagery approach that has been shown to successfully induce dissociation in patients with BPD (Bichescu-Burian et al., 2017).

4.4 Conclusion

The studies of this thesis contributed relevant findings on altered perception of affective somatosensory stimuli in patients with BPD, but also raised further questions.

Study 1 provided evidence that participants with BPD perceive pleasant touch stimuli as less pleasant, on average even slightly unpleasant, compared to HC. Study 2 extended previous findings on reduced pain sensitivity in BPD by indicating that facilitatory pain processes related to pain unpleasantness might be enhanced. The results of both studies suggest that affective incongruency of somatosensory stimulation might increase dissociative state, while affectively congruent stimulation could decrease dissociative state.

Three different mechanisms might underlie altered perception of affective somatosensory stimuli: (1) threat hypersensitivity (2) altered cognitive evaluation (3) negative self-image. It would be important to empirically assess these putative mechanisms in future studies to improve the understanding and, above all, mechanism-based therapy of patients with (borderline) personality disorder. While altered perception of pain might be mainly related to disturbed self-functioning, altered pleasant touch perception is assumed to have far-reaching negative consequences also for interpersonal functioning.

SUMMARY

Borderline personality disorder (BPD) is characterized by altered perception of affective stimuli, including pain. Little is known about positive somatosensation and the mechanisms behind altered pain perception. This thesis aimed to investigate altered affective somatosensation and the underlying mechanisms in BPD. Two studies each on participants with BPD and healthy controls (HC) were conducted.

In study 1, standardized pleasant touch was applied to the hands of 25 participants with BPD and 25 HC. Perception of touch was assessed via self-report and the affect-modulated startle response served as physiological correlate of the valence of touch perception. Body-related dissociative state, in terms of body ownership, was assessed before and after touch stimulation. We observed a significantly reduced perceived pleasantness of touch in BPD compared to HC. In BPD, a more negative touch perception was associated with a decrease in body ownership from pre to post stimulation. The results suggest that altered somatosensation in BPD is not limited to pain perception and a perception-specific effect of pleasant touch stimulation on dissociative state.

In study 2, temporal summation of pain was assessed in 24 BPD and 24 HC. Pain perception was assessed via self-report and the RIII-reflex served as measure of nociceptive processing on the spinal level. Dissociative state was assessed before and after pain stimulation. Heightened pain thresholds in BPD compared to HC were replicated. Unexpectedly temporal summation of pain unpleasantness was higher in BPD compared to HC, whereas temporal summation of pain intensity and the RIII-reflex was not significantly different. Pain threshold and temporal summation of pain were not interrelated. There was a trend towards significance for a perception-specific effect of pain stimulation on dissociative state with higher temporal summation of pain being associated with decreased dissociative state. Different neural mechanisms might underlie reduced pain sensitivity in terms of heightened pain threshold and enhanced temporal summation of pain unpleasantness. Temporal summation of pain might be related to reduction in dissociation in response to painful stimulation.

Three different mechanisms are discussed to underlie altered affective somatosensation in BPD: (1) threat hypersensitivity (2) altered cognitive evaluation (3) negative self-image. It is suggested that altered affective somatosensory perception in BPD is related to self-functioning, and specifically altered pleasant touch perception might play an important role in disturbed interpersonal functioning.

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SUPPLEMENT

Supplemental material study 1

Development of a German set of qualitative descriptors for pleasant touch perception

To develop a set of qualitative sensory and affective descriptors of pleasant touch, we were guided by the touch perception task (TPT) from Guest et al. (2011). In a back translation design, all 96 adjectives that were identified to provide a candidate lexicon for sensory and emotional aspects of touch by Guest et al. (2011) were translated from English into German. Afterwards they were re-translated into English by a second translator. The original and the back translated version were compared to obtain the final German version. Finally, each adjective was evaluated by both translators to ensure semantic correspondence. Both translators are a bilingual person with German as first language.

In a pilot study we applied pleasant touch to 14 healthy control subjects (6 male) using the same custom apparatus as in the main study. In this study, the touch was applied to the left forearm for one minute in 10 blocks. After each block up to 10 adjectives were presented and the subjects rated to which extend the respective aspect of touch was appropriate on a 5-point Likert scale (“not appropriate” – “completely appropriate”). From all 96 adjectives, we selected for the present study, those adjectives that were (1) included in the final version of the TPT, or (2) defined as low loading in the preliminary version of the TPT by Guest et al. (2011). Additionally we selected those that were (3) of relevance for pleasant touch (defined as rating “not appropriate” from less than 67%) in our pilot study. This procedure results in a final set of 59 adjectives, that were used in the main study (37 sensory, 22 affective) (see Table S1).

Table S1: *Sensory and affective attributes of pleasant touch*

English original	German translation	English original	German translation	English original	German translation	English original	German translation
rough[1a]	rau	firm[1c]	fest	pleasurable[1e,f]	vergnüglich	textured[3]	strukturiert/ texturiert
smooth[1a]	glatt	sharp[1c]	scharf	exciting[1f]	aufregend	velvety[3]	samtig
bumpy[1a]	uneben	hot[1c]	heiß	arousing[1f]	erregend	wooly[3]	wollig
prickly[1a]	stachlig	burning[1c]	brennend	thrilling[1f]	spannend	cool[3]	kühl
soft[1a]	weich	fuzzy[1d]	flaumig	sensual[1f]	sinnlich	blissful[3]	herrlich
lumppy[1a]	klumpig	fluffy[1d]	flauschig	sexy[1f]	sexy	heavenly[3]	himmlisch
gritty[1a]	kieselig	dry[1d]	trocken	hairy[2]	haarig	intense[3]	intensiv
jagged[1a]	zerklüftet	irritating[1e]	irritierend	sticky[2]	klebrig	meaningful[3]	bedeutungsvoll
wet[1b]	nass	comfortable[1e]	bequem	vibrating[2]	vibrierend	nice[3]	nett
damp[1b]	feucht	discomfort[1e]	unbehaglich	warm[2]	warm	weird[3]	merkwürdig
greasy[1b]	fettig	relaxing[1e]	entspannend	feathery[3]	federig	gentle[3]	behutsam
cold[1b]	kalt	calming[1e]	beruhigend	furry[3]	pelzig	tender[3]	zärtlich
slippery[1b]	rutschig	soothing[1e]	wohltuend	satiny[3]	seidig	gummy[4a]	gummihaft
rubbery[1b]	gummiartig	enjoyable[1e,f]	angenehm	silky[3]	seidenweich	spongy[4b]	schwammartig
hard[1c]	hart	desirable[1e,f]	begehrenswert	squishy[3]	schwammig		

[1]Attributes of the factors of the original version of the touch perception task (TPT, Guest et al., 2011) [1a] sensory factor roughness [1b] sensory factor slip [1c] sensory factor firmness [1d] sensory factor pile [1e] affective factor comfort [1f] affective factor arousal [2] low loading attributes in the original version of the TPT [3]adjectives of relevance for pleasant touch [4] >67% rejection in pilot study but used due to it semantic similarity to the German word for rubbery[a] or squishy[b]

Assessment and analysis of qualitative aspects of touch perception

In the main study, after each block of touch stimulation up to 10 of the 59 selected adjectives were presented on the computer screen. For each adjective, subjects indicated to what extend it was applicable, on a visual analog scale ranging from 0 (“not appropriate”) to 100 (“exactly appropriate”). Each adjective was presented twice, once after a trial with startle and once after a trial without startle.

We calculated the sensory and affective factors of the TPT (Guest et al., 2011) by the mean of the rating of the respective attributes. For these factors, ratings for trials with and without startle were compared using paired sample t-tests for both groups separately. For group comparisons, t-tests for independent samples were conducted using the TPT factors as dependent variables. We descriptively analyzed the remaining adjectives separately, and we report *M* and *SD* (see Table S2).

Results on other sensory modalities

Mechanical detection threshold (MDT) was significantly higher in BPD (*Mdn* = 2.645) compared to HC (*Mdn* = 1.28), *U* = 155.5; *z* = -3.05, *p* = .002, *r* = .43, indicating a reduced touch sensitivity in BPD compared to HC.

There was no significant difference in warm perception thresholds between the BPD (*Mdn* = 34.29) and HC groups (*Mdn* = 34.04), *U* = 134.00, *z* = -1.20, *p* = .230, *r* = .19. Descriptively heat pain threshold in BPD (*M* = 46.75°C, *SD* = 3.21) was higher than in HC (*M* = 44.40°C, *SD* = 3.93). But the difference did not reach significance level, *t*(36) = 1.896, *p* = .066, *d* =.54.

In the HC group, there was a significant positive correlation between HPT and perceived valence of touch (*r*(22) = .456, *p* = .025), indicating that a more positive perception of touch was associated with a higher pain threshold. There was no significant correlation between HPT and perceived intensity of touch in HC (r_s(22) = -.188, *p* = .379) or between HPT and perceived valence (*r*(12) = -.183, *p* = .531) or intensity of touch (r_s(12) = .007, *p* = .982) in BPD

Table S2: *Perception of touch in trials with and without startle in participants with borderline personality disorder and healthy controls*

	BPD (n = 25)			**HC** (n = 25)		
	Without startle *M* (*SD*) Mdn (IQR)	**With startle** *M* (*SD*) Mdn (IQR)	**statistics**	**Without startle** *M* (*SD*) Mdn (IQR)	**With startle** *M* (*SD*) Mdn (IQR)	**statistics**
Intensity	53.08 (18.13) 54.17 (28.08)	56.09 (18.31) 58.00 (26.25)	*z*= -1.06, *p*= .290	74.91 (19.19) 74.83 (29.50)	74.36 (19.28) 72.67 (30.50)	*z*=-1.18, *p*= .247
Valence	-4.91 (41.14) -17.67 (57.00)	-4.09 (43.99) -6.00 (64.00)	*t*(24)= -0.22, *p*= .828	57.49 (39.79) 64.67 (51.33)	56.21 (40.51) 66.67 (53.00)	*t*(24)= 0.59, *p*= .562
Roughness (TPT)	27.05 (15.16) 24.50 (24.75)	28.55 (18.80) 23.88 (30.88)	*z*= -0.03, *p*=.976	13.68 (10.86) 11.63 (14.19)	13.29 (12.18) 9.38 (15.06)	*z*=-0.67, *p*=.501
Slip (TPT)	13.58 (15.46) 8.67 (22.25)	14.58 (18.87) 5.17 (27.08)	*z*= -1.11, *p*= .268	7.77 (9.77) 2.17 (15.33)	6.67 (10.38) 2.17 (11.08)	*z*= -0.09, *p*= .931
Firmness (TPT)	24.3 (16.37) 26.00 (27.60)	22.58 (16.29) 21.00 (27.30)	*t*(24)= 0.58, *p*= .565	9.61 (12.73) 5.60 (12.60)	8.69 (11.45) 6.20 (10.80)	*z*= -0.11, *p*= .914
Pile (TPT)	46.2 (19.70) 46.00 (29.33)	48.05 (22.75) 52.67 (32.67)	*t*(24)= -0.60, *p*= .554	55.84 (27.18) 61.67 (42.00)	58.89 (26.64) 66.00 (34.83)	*z*= -0.61, *p*= .539
Comfort (TPT)	36.75 (19.00) 40.89 (33.39)	36.87 (22.20) 32.22 (30.44)	*t*(24)= -0.05, *p*= .958	66.06 (20.39) 72.56 (21.11)	62.38 (20.03) 64.11 (23.56)	*t*(24)= 2.54, *p*= .018
Arousal (TPT)	20.9 (17.73) 16.50 (28.81)	24.55 (17.74) 22.25 (32.69)	*t*(24)= -1.80, *p*= .084	36.09 (21.94) 35.63 (31.00)	34.8 (19.15) 35.88 (27.69)	*t*(24)= 0.79, *p*= .436

BPD = Borderline personality disorder; HC = healthy control; n = number; *M* = mean; *SD* = standard deviation; TPT = Touch perception task

Table S3: *Body ownership and state dissociation before and after stimulation with pleasant touch in HC*

	Pre *M* (*SD*) *Mdn (IQR)*	**Post** *M* (*SD*) *Mdn (IQR)*	**Change** *M* (*SD*) *Mdn (IQR)*
Body ownership stimulated left arm [%]	99.66 (1.17) 100.00 (0.00)	99.32 (2.34) 100.00 (0.00)	-0.34 (1.60) 0.00 (0.00)
Body ownership non stimulated right arm [%]	99.89 (0.53) 100.00 (0.00)	99.77 (1.07) 100.00 (0.00)	-0.11 (1.21) 0.00 (0.00)
State dissociation (DSS-4)	0.16 (0.40) 0.00 (0.00)	0.11 (0.25) 0.00 (0.00)	-0.05 (0.22) 0.00 (0.00)

Pre = before pleasant touch application; Post = after pleasant touch application, Change = Post-Pre; *M* = mean; *SD* = standard deviation; *Mdn* = median; *IQR* = interquartile range; DSS-4 = Short version of the Dissociation tension scale acute (Stiglmayr et al., 2009)

Supplemental material study 2

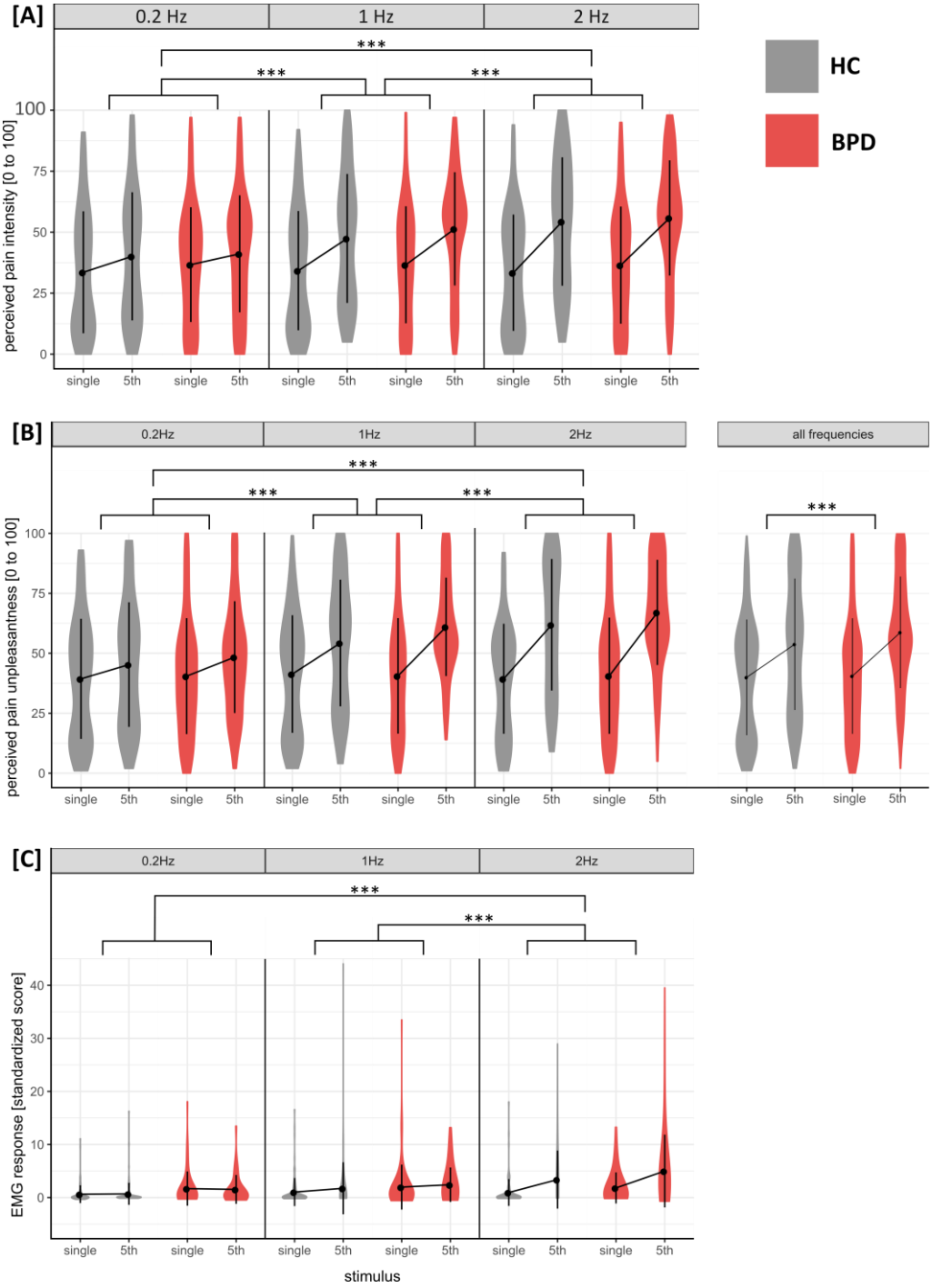

Figure S1: Violin plots of **[A]** perceived pain intensity, **[B]** perceived pain unpleasantness, and **[C]** electromyographic (EMG) responses in participants with borderline personality disorder (BPD) and healthy controls (HC). Depicted are mean, standard deviation, and distribution for the single stimulus and the 5th stimulus of a series, applied at 0.2Hz, 1Hz, and 2Hz. *** $p < .001$

Table S4: *Temporal summation of pain intensity, pain unpleasantness, and reflex response in participants with borderline personality disorder and healthy controls*.

	BPD [*n* = 24]			**HC** [*n* = 24]		
Frequency	**0.2 Hz**	**1 Hz**	**2 Hz**	**0.2 Hz**	**1 Hz**	**2 Hz**
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
TS intensity [VAS 0 – 100]	4.54 (9.11)	15.10 (13.00)	19.30 (9.82)	6.54 (8.34)	13.20 (8.91)	21.00 (13.80)
TS unpleasantness [VAS 0 – 100]	8.00 (9.53)	20.53 (13.74)	26.52 (13.25)	5.93 (7.51)	12.93 (5.51)	22.52 (11.51)
TS reflex responses [standardized score]	-0.12 (1.35)	0.51 (2.89)	3.53 (5.29)	0.06[1] (0.18)	0.70[1] (3.05)	2.51[1] (4.95)

BPD = borderline personality disorder; HC = healthy control; n = number; M = mean; SD = standard deviation; TS = temporal summation; VAS = visual analogue scale; [1] *n* = 21

Additional Analysis: Linear mixed effect models (LMM) on reflex response

I. Effect of group (HC vs. BPD), stimulus (single stimulus vs. 5th stimulus of a series), frequency (0.2Hz vs. 1Hz vs. 2Hz), and their interaction on reflex responses. Only trials with at least one valid reflex are taken into account.

Table S5: *ANOVAS of linear mixed effect models for reflex response (only valid reflexes).*

Predictor	*df num*	*df den*	*F*	*p*
group	1	16.82	0.01	0.90
stimulus	1	289.82	4.21	**0.04**
frequency	2	298.15	3.83	**0.02**
group*stimulus	1	289.82	0.10	0.75
group*frequency	2	298.15	1.23	0.29
stimulus*frequency	2	289.82	2.54	0.08
group*stimulus*frequency	2	289.82	1.57	0.21

Statterwaite's method was used to estimate degree of freedoms (df), *F* and *p* values, as implemented in the *R* package *lmerTest*; ANOVA = analysis of variance

II. Effect of group (HC vs. BPD), frequency (0.2Hz vs. 1Hz vs. 2Hz), stimulus (single stimulus vs. 5th stimulus of a series), and their interaction on reflex responses. Absolute level of stimulation intensity was taken into account as additional fixed factor to control for the effect of stimulation intensity

Table S6: *ANOVAS of linear mixed effect models for reflex response*

Predictor	*df num*	*df den*	*F*	*p*
group	1	42.06	0.38	0.53
stimulus	1	1253.08	41.94	**<.001**
frequency	2	1253.19	31.57	**<.001**
stimulation intensity	1	41.88	1.84	0.18
group*stimulus	1	1253.08	0.07	0.80
group*frequency	2	1253.19	0.62	0.54
stimulus*frequency	2	1253.08	25.37	**<.001**
group*stimulus*frequency	2	1253.19	0.92	0.40

Statterwaite's method was used to estimate degree of freedoms (df), *F* and *p* values, as implemented in the *R* package *lmerTest* (Kuznetsova et al., 2017); ANOVA = analysis of variance

Additional Analysis: Main analysis for subsample

We excluded subjects who (a) reported regular pain (1 BPD and 1 HC; back pain or migraine), (b) reported intake of SSRI (3 BPD), or (c) reported former pain episodes or injuries (e.g., torn ligament or ankle sprain) in the stimulation area (5 BPD and 3 HC) and report results of the main analysis, which revealed significant results for the entire sample. One HC reported regular pain and former injury. One participant with BPD reported intake of SSRI and former injury. In total n = 11 subjects were excluded (8 BPD and 3 HC), resulting in a sample size of n = 16 BPD and n = 21 HC (n = 16 BPD and n = 18 HC for data on reflex responses)

I. Pain threshold

Table S7: *Pain thresholds in participants with borderline personality disorder and healthy controls.*

	Pain threshold [mA]		
	BPD (*n* = 16)	**HC** (*n* = 11)	**Test statistic**
Mean (SD)	7.09 (2.61)	4.79 (2.06)	t_{35} = -3.00, p < 0.01, d = 0.98
Median (IQR)	6.75 (2.50)	4.50 (3.55)	

BPD = borderline personality disorder; HC = healthy control; n = number; SD = standard deviation; IQR = interquartile range.

II. Linear mixed effect models on pain intensity, pain unpleasantness and reflex response

Table S8: *ANOVAS of linear mixed effect models for pain intensity, pain unpleasantness and reflex responses*

Outcome	Predictor	*df num*	*df den*	*F*	*p*
Pain intensity	group	1	35.02	0.08	0.78
	stimulus	1	1045.01	293.81	**< 0.001**
	frequency	2	1045.03	27.21	**< 0.001**
	group*stimulus	1	1045.01	0.75	0.39
	group*frequency	2	1045.03	0.08	0.92
	stimulus*frequency	2	1045.01	23.46	**< 0.001**
	group*stimulus*frequency	2	1045.01	1.43	0.24
Pain unpleasantness	group	1	35.02	<0.01	0.95
	stimulus	1	1045.01	455.20	**< 0.001**
	frequency	2	1045.03	42.29	**< 0.001**
	group*stimulus	1	1045.01	9.31	**< 0.01**
	group*frequency	2	1045.03	0.19	0.83
	stimulus*frequency	2	1045.01	36.43	**< 0.001**
	group*stimulus*frequency	2	1045.01	2.06	0.13
Reflex responses	group	1	31.08	2.51	0.12
	stimulus	1	936.12	38.64	**< 0.001**
	frequency	2	936.22	28.20	**< 0.001**
	stimulation intensity	1	30.90	2.27	0.14
	group*stimulus	1	936.12	0.16	0.69
	group*frequency	2	936.22	0.45	0.64
	stimulus*frequency	2	936.12	27.02	**< 0.001**
	group*stimulus*frequency	2	936.12	0.91	0.40

Statterwaite's method was used to estimate degree of freedoms (df), *F* and *p* values, as implemented in the *R* package *lmerTest* ; ANOVA = analysis of variance

III. Correlation between temporal summation of pain perception and reflex responses in participants with BPD and HC

Table S9: *Correlation between temporal summation of pain perception and reflex responses in participants with borderline personality disorder and healthy controls*

		Temporal summation pain intensity	**Temporal summation pain unpleasantness**
Temporal summation	**HC**	r_s = 0.58, ***p* < 0.05**	r_s = 0.47, ***p* < 0.05**
reflex response	**BPD**	r_s = 0.27, p = 0.30	r_s = -0.15, p = 0.57

BPD = borderline personality disorder; HC = healthy control

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