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Sensory alterations and affective-sensory interactions: Implications for the psychopathology of Borderline Personality Disorder

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ABBREVIATIONS

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
AVH	Auditory verbal hallucination
BA	Brodmann area
BOLD	Blood-oxygen-level dependent
BPD	Borderline personality disorder
BSC	BOLD signal changes
cBPD	Current borderline personality disorder
DACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS-4	Dissociation Stress Scale, 4 item version
e.g.	Example gratia, for example
EPI	Echo-planar imaging
etc.	Et cetera, and so forth
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWE	Family-wise error
HC	Healthy controls
HPA	Hypothalamic-pituitary-adrenal
HPT	Heat pain thresholds
IADS	International Affective Digitized Sounds
i.e.	Id est, that is
IPDE	International Personality Disorder Examination
L	left
M	Mean
MMN	Mismatch negativity
MPFC	Medial prefrontal cortex
NSSI	Non-suicidal self-injury
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex

PTSD	Posttraumatic stress disorder
R	right
rBPD	Remitted borderline personality disorder
ROI	Region of interest
SCID	Structured Clinical Interview for DSM
SD	Standard deviation
SE	Standard error
SSRI	Selective serotonin reuptake inhibitor
VAS	Visual analogue scale
VLPFC	Ventrolateral prefrontal cortex
WPT	Warm perception thresholds

1 THEORETICAL BACKGROUND

Sensory processing patterns seem to be modulated by the individual's affect. In the light of an evolutionary aspect to emotions, one of the functions of fear, as a negative emotion, is to enhance sensory perception, including extending one's visual field, accelerating eye movements, and enlarging nasal volume as well as increasing air velocity during inspiration (Susskind et al., 2008). Moreover, negative affect, including that induced by acute or chronic stress, has shown effects on tactile (Kelley & Schmeichel, 2014) and pain sensitivity (Geva & Defrin, 2018). It seems that the modulation of sensory perception promotes responding to negative affect or stress-evoking stimuli as a natural reaction. This relationship becomes rather more complex, when pathological alterations of sensory-affective interaction are examined, which represent an essence of some psychological disorders.

Disturbed emotion processing and alterations of somatosensory perception are core features in borderline personality disorder (BPD). Particularly, a large part of the studies on sensory processing patterns and affect have shown reduced pain sensitivity, which may be associated with dissociation and self-injurious behavior (Schmahl & Baumgartner, 2015). However, the interaction between different sensory modalities and affectivity has not yet been investigated, and it is still unclear whether these alterations, which occur primarily in aversive affective situations, are a core variable or a type of coping behavior associated with the disorder. Prior large-scale studies on the course of BPD demonstrated that individuals with BPD generally have high rates of symptomatic remission and few relapses (Gunderson et al., 2011; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2012; Zanarini, Frankenburg, Reich, & Fitzmaurice, 2016; Zanarini et al., 2014). It is still open which of the psychopathological and neurobiological characteristics of BPD after symptomatic remission, for example, in sensory perception, are related to the affective states. Thus, it is important to gain insight into the processes in the current and remitted phase of BPD in order to contribute to developing adequate therapeutic interventions that improve persevering features of BPD psychopathology. The aim of this thesis is to provide an understanding of the processing of the sensory-affective interaction at the behavioral and neural level in patients with BPD in the acute phase and after remission.

In Chapter 1, the theoretical background on the characteristics of the pathological symptomatology of BPD, the mechanisms of alteration in sensory processing and the

psychobiology for emotional influences on perception as well as the current state of research on BPD after symptom remission are presented. At the end of Chapter 1, the hypotheses of the present thesis are derived from the preceding theoretical background. In Chapter 2, two empirical studies are presented. In Chapter 3, findings from Chapter 2.1 empirical study 1 and Chapter 2.2. empirical study 2 are discussed in detail with a focus on the integration into previous research and future research and therapeutic perspectives, considering limitations and concluding with practical implications.

1.1 Borderline Personality Disorder

1.1.1 Diagnostic Criteria

Borderline personality disorder is a serious and complex mental disorder. Due to its heterogeneous phenotype, diagnosing BPD remains challenging, there are, moreover, similarities to other mental disorders, particularly mood disorders (Biskin & Paris, 2012; Garland & Miller, 2020). According to the current classification system of mental disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), hallmarks of BPD are characterized by a widespread pattern of instability in affect regulation, self-identity, and social interaction, along with impulsivity and self-harming behavior. These diagnostic criteria comprise four crucial symptom domains of BPD (Garland & Miller, 2020; Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2007) and DSM-5 requires five out of nine criteria to be met to make a diagnosis (American Psychiatric Association, 2013):

- Emotional domain:
    - **Affective instability**
        - Heightened emotional sensitivity
        - Impaired emotional regulation
        - Slow return to baseline from emotionally heightened state
    - **Chronic feelings of emptiness**
    - **Difficulty controlling angry feelings**
- Interpersonal domain:
    - **Abandonment fears**
    - **Relational instability**
- Behavioral domain:
    - **Impulsive behaviors** (e.g. binge eating, substance misuse, reckless spending)
    - **Suicidal behavior and/or self-harming**
- Cognitive domain:

- **Identity disturbance**
- **Dissociative experiences or transient stress-related paranoid ideation/psychotic symptoms**

Patients with BPD often experience aversive tension states associated with intense emotional arousal due to perceived stress (Stiglmayr et al., 2008; Stiglmayr et al., 2005). The intense emotional arousal often induces dissociation (Ebner-Priemer et al., 2009; Krause-Utz, Frost, Winter, & Elzinga, 2017; Stiglmayr et al., 2008). According to DSM-5, dissociation is described as a 'disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior' and manifests clinically as depersonalization, derealization or amnesia (American Psychiatric Association, 2013). Stress-related dissociation occurs in up to 80% of BPD patients (see review: Krause-Utz, Frost, et al., 2017).

1.1.2 Epidemiology of BPD

According to an epidemiological study in the USA, the lifetime prevalence of BPD was 5.9% and there were no significant differences in the proportions of BPD among males and females (Grant et al., 2008). In another study in the UK that evaluated the prevalence and correlates of personality disorder in a representative community sample, the community prevalence of BPD was 0.7% (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006). It appears likely that the prevalence of BPD in the general population is not much higher than the average prevalence of personality disorders, but the prevalence of BPD is considerably higher among patients in samples with mental disorders. In fact, BPD patients show high prevalence rates in all treatment settings (Bender et al., 2001; Zanarini, Frankenburg, Hennen, & Silk, 2004). Individuals with BPD generally require high levels of healthcare resources. The cost of clinical treatments for BPD is estimated to be around €3.3 billion per year, accounting for approximately up to 25% of total expenditure on psychiatric inpatient treatment in Germany (Bohus, 2007). In addition, BPD patients seem to be affected by comorbid axis-I mental disorders including mood disorders (e.g. major depressive disorder or bipolar disorders), anxiety, stressor-related (e.g. posttraumatic stress disorder or acute stress disorder), substance use, somatoform, dissociative, neurodevelopmental (e.g. attention deficit hyperactivity disorder), eating disorders, and also other axis-II personality disorders (McGlashan et al., 2000; Shah & Zanarini, 2018; Torgersen, 2014; Zanarini, Frankenburg, Dubo, et al.,

1998; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2004). In a study of the 10-year course of BPD, it was shown that BPD has high remission (i.e. 85%) and low relapse rates (i.e. 12%) (Gunderson et al., 2011). It has been suggested that BPD patients with acute symptoms such as self-injurious or (para-) suicidal behaviors may achieve a better symptomatic remission over a 2-year period and over a 4-year period compared to BPD patients with temperamental symptoms such as chronic anger or intolerance of loneliness (Zanarini et al., 2016). Notwithstanding this, large-scale, long-term follow-up studies of the 10-year course of BPD have shown that BPD patients still suffered from severe and persistent deficits in social functioning (Gunderson et al., 2011) and only a minority (i.e. 40%) of BPD patients, who lost their level of psychosocial functioning, were able to regain it over ten years of follow-up (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010).

1.2 Psychopathological features of BPD

1.2.1 Emotional information processing and emotion regulation

Emotions occur in response to something relevant to us and orchestrate a rapid information-processing system that facilitates us to perform minimal thinking (Tooby & Cosmides, 2008). However, emotional responses can also misguide us, when physical and social circumstances differ extremely from those that have shaped our emotions over the millennia (Gross, 1999). When our emotions are perceived to be inappropriate for a situation we are facing, we attempt to regulate emotional responses so that they better serve our goals (Gross, 2002). Emotion regulation refers to various ways individuals use to influence the experience and expression of their emotions, and deficits are thought to underlie several mental disorders (Gross, 1998, 2002). According to a prominent model of the emotion regulation process, Gross (2002) postulates antecedent-focused emotion regulation strategies, such as situation selection and modification, attentional deployment, or cognitive change and response-focused strategies, such as behavioral, experiential, or physiological response modulation. A key question is whether the way an emotion is generated has an impact on the effort to regulate subsequent emotions (McRae, Misra, Prasad, Pereira, & Gross, 2012). Emotion research has focused particularly on “bottom-up” and “top-down” processes: bottom-up processes arise from perceptual stimuli in everyday life and are crucial for detecting salience, i.e. bottom-up generation of emotion is a stimulus-focused view of emotional processing, and individual changes in emotional responses are seen as a

consequence of differences in perceptual sensibility, or in the biologically based susceptibility and intensity of the emotional response system (McRae et al., 2012). The amygdala, hippocampus, insula and rostral Anterior Cingulate Cortex (ACC) play a role in bottom-up emotion processing (Ochsner et al., 2009; Ochsner, Silvers, & Buhle, 2012). On the other hand, top-down processes involve cognitive control areas related to the following goals and strategic decision-making, i.e. top-down emotion generation is a cognition-focused view of emotion processing, and variation in emotional response is considered to account for differences in each individual's goal states or appraisal biases (McRae et al., 2012). Important prefrontal brain areas (e.g. the dorsal ACC and the orbitofrontal, ventrolateral and dorsolateral Prefrontal Cortices (OFC, VLPFC and DLPFC) are involved in top-down emotion processing (Ochsner et al., 2009; Ochsner et al., 2012).

1.2.2 Disturbed emotional processing and emotion dysregulation in BPD

It is of particular importance to study mechanisms of dysfunctional emotion processing, as maladaptive emotion processing triggers emotion dysregulation. As mentioned above, core domains of psychopathology in BPD are disturbed emotion processing and emotion dysregulation based on affective instability, impairment of (inter)personality functioning and behavioral dysregulation and impulsivity (Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Lieb et al., 2007). A recently published study examined the diagnostic efficiency of BPD criteria in a large adult inpatient population (inpatients with BPD-diagnosis n=352 vs. inpatients with mental disorders but without personality disorders n=1,271), and it was found that affective instability has a role as a gate criterion in the BPD inpatients in the study (Fowler et al., 2021). Emotion dysregulation in BPD is composed of emotion sensitivity, heightened and labile negative affect, a deficit of appropriate regulation strategies and a surplus of maladaptive regulation strategies, including behavioral dysregulation such as physical self-injury, alcohol and substance abuse or uncontrollable eating patterns (Carpenter & Trull, 2013; Selby, Anestis, Bender, & Joiner, 2009).

From a sociobiological perspective, most of the social-interpersonal dysfunctions of BPD patients (e.g. rejection sensitivity, mistrust in interpersonal relationships or antagonistic behavior) could be explained by biological vulnerability and dysfunctional emotional-interpersonal experiences in childhood, such as invalid attachment/primary care, early loss or sexual/emotional maltreatment (Linehan, 1993). These negative

experiences are likely to lead to (i) a so-called “negativity bias”, i.e. negative effects on emotional and cognitive information processing (e.g. attention, perception, memory, physiology, affect, behavior, motivation and decision-making), and (ii) deficits in processing and recognizing emotional states of self and others (Crowell, Beauchaine, & Linehan, 2009; Linehan, 1993). In particular, the ability to accurately recognize emotional facial expressions is a crucial cue to guide a person’s behavior and emotional state in the social context. Therefore, the functioning of social interaction is anchored in the recognition of facial emotions. The essential key to social functioning is considered as a person being capable of recognition of internal from external cues, and this capability facilitates empathy, interpersonal trust and prosocial behavior (Marsh & Ambady, 2007). Misunderstanding and misinterpretation due to deficits in facial emotion recognition may lead to impaired emotion processing and inadequate social interaction in people with mental illness (Domes, Schulze, & Herpertz, 2009). Meta-analyses of emotion processing in BPD show that individuals with BPD have no general impairment in emotion recognition compared to healthy controls, but they appraise neutral or ambiguous facial expressions more negatively (“threat hypersensitivity”) and show increased arousal and difficulty recognizing negatively valenced emotions such as anger and disgust (Daros, Zakzanis, & Ruocco, 2013; Mitchell, Dickens, & Picchioni, 2014).

1.2.3 Altered sensory perception in BPD

Emotions and sensory perceptions are closely interlinked in humans. For example, the visual sensory system responds more rapidly to fear-inducing stimuli (e.g. snakes, spiders) than to fear-irrelevant stimuli in an array of distracter images (Öhman, Flykt, & Esteves, 2001). Furthermore, fear-inducing stimuli are found to elicit greater event-related potentials in primary visual cortex only 90 ms after stimulus presentation compared to neutral stimuli. The escalation in visual processing of threatening stimuli appears to reflect affective information or motivational relevance (Stolarova, Keil, & Moratti, 2005). Emotionally modulated sensory perception has also been found in the tactile domain in healthy controls (HC). Previous studies examining the effect of fear on tactile perception revealed that experimental inductions of fear states reduce tactile sensitivity (Kelley & Schmeichel, 2014).

In the past years, several studies have indicated sensory processing deficits in individuals with BPD. For example, BPD patients compared to HC and depressed patients

showed lower pleasantness and higher disgust ratings after ingestion of gustatory stimuli (e.g. 10 mL orange juice, quinine dihydrochloride at 0.006 mol/L, water). Interestingly, juice disgust ratings were associated with self-disgust in BPD, suggesting close relationships between sensory processing and self-identity in BPD. It appears likely that the hedonic experience of both positive and negative gustatory stimuli is negatively biased in BPD (Arrondo et al., 2015). A recent study using magnetic resonance imaging examined the morphology changes of the olfactory sulcus as found in BPD. In particular, the adolescent BPD group with a traumatic experience had a significantly shallower right olfactory sulcus compared to HC, but no significant group difference in its anterior-posterior length has been reported (Takahashi et al., 2019). This finding of an abnormally shallow olfactory sulcus in BPD and its relation to BPD symptom severity might suggest that there is a functional overlap between olfactory and emotion processing (Takahashi et al., 2019). According to a study on the processing of auditory stimuli that used event-related potentials, BPD patients compared to HC show increased P50 sensory gating (P50 difference), resulting from a higher amplitude triggered by the first stimulus (Grootens et al., 2008). This would suggest that individuals with BPD might have an increased physiological preattentive stage to respond to new stimuli compared to HC (Grootens et al., 2008). Niemantsverdriet et al. (2019) investigated two possible mechanisms of auditory verbal hallucination (AVH) in BPD patients using sensory gating (P50 ratio and P50 difference) and change detection (mismatch negativity, MMN). P50 sensory gating deficits seemed to underlie psychotic vulnerability in BPD patients with AVH, but there was no significant P50 difference between BPD patients without AVH and HC. Moreover, there was no significant difference between BPD patients with AVH, BPD patients without AVH and HC in P50 amplitudes, P50 ratio, and MMN. The authors suggest that individuals with BPD with or without AVH had no problems with auditory change detection (Niemantsverdriet et al., 2019). These inconsistent findings may be due to the BPD symptom severity and comorbidities such as mood disorders (Grootens et al., 2008; Niemantsverdriet et al., 2019). Thus, there is no clear evidence for general impairment in auditory sensory processing in BPD.

Since problems with emotional functioning play a central role in BPD, studies are needed to better understand whether BPD is related to differential reactivity to sensory perception in general or to specific sensory domains in particular. In a preliminary study, Rosenthal et al (2011) investigated reactivity to single domains of sensations, i.e.

auditory, gustatory, olfactory, tactile, and visual between participants with BPD and HC, after controlling for trait emotional reactivity (Rosenthal, Ahn, & Geiger, 2011). Patients with BPD showed significantly greater reactivity than HC across all types of sensory input, and BPD patients in particular showed stronger reactivity than HC to auditory stimuli compared to other types of sensory stimuli. Moreover, the difference between BPD and HC participants in reactivity to auditory input was more pronounced than the difference between these two groups in reactivity to gustatory, tactile and visual stimuli (Rosenthal et al., 2011).

An important mechanism of sensory processing in BPD is pain processing. Various studies have demonstrated alterations of the somatosensory response in BPD (e.g., pain perception) in recent decades (for reviews, see: Jochims, Ludäscher, Bohus, Treede, & Schmahl, 2006; Schmahl & Baumgartner, 2015). In particular, reduced pain sensitivity appears to be a specific feature of BPD, as other mental disorders with an analogous etiology show no such impairment in this sensory modality (Jochims et al., 2006; Schmahl et al., 2010; Tesarz, Baumeister, Andersen, & Vaegter, 2020), although no generalized deficits in somatosensory domains have been found in BPD patients compared to HC or individuals with currently remitted mental disorder, for example, major depressive disorder (Pavony & Lenzenweger, 2013). Using multi-method assessments, including self-report measures, fMRI and other established psychophysiological measures (e.g., startle or skin conductance responses, heart rate), the impaired interaction of affective-sensory processing in individuals with BPD can be better understood at the psychobiological level. This is the focus of the following Chapter 1.3.

1.3 Interaction of affective-sensory processing in BPD

1.3.1 Stress-related dissociation and pain processing in BPD

Several studies showed heightened aversive tension (Stiglmayr et al., 2005; Stiglmayr, Shapiro, Stieglitz, Limberger, & Bohus, 2001), distress (Ebner-Priemer et al., 2008; Ebner-Priemer et al., 2007), and dysphoric states in BPD (Biskin, Frankenburg, Fitzmaurice, & Zanarini, 2014; Zanarini, Frankenburg, DeLuca, et al., 1998), suggesting that individuals with BPD are exposed to increased stress levels. The increased stress-level influences the increased dissociative experience in BPD (Ebner-Priemer et al., 2005; Philipsen et al., 2004; Stiglmayr et al., 2001; Zanarini, Ruser, Frankenburg, & Hennen, 2000). Stress-induced dissociation is therefore considered as a common

symptom of BPD , manifesting in approximately 75%-80% of individuals with BPD. It is closely related to other relevant features of this disorder such as emotion dysregulation, identity disturbances, and interpersonal instability (Korzekwa, Dell, & Pain, 2009; Skodol et al., 2002; Stiglmayr et al., 2008).

Dissociation

Dissociation is a multifarious phenomenon, which has been described as a *"disruption of and/or discontinuity in the normal, subjective integration of one or more aspects of psychological functioning, including – but not limited to – memory, identity, consciousness, perception, and motor control"* (Spiegel et al., 2011; p.826).

Dissociative symptoms can be explained by a continuous phenomenon as general characteristic (trait dissociation) and temporary state (state dissociation) from normal dissociative experiences to dissociative disorders. Disturbances of dissociative disorders include a broad spectrum of psychological and somatoform functions and may have an impact on functioning in everyday life. States of subjective detachment including depersonalization and derealization, memory fragmentations such as amnesia, and identity disturbances come under psychological aspects of dissociation. Somatoform dissociation is considered as a dysfunction of motor control or/and body representation, and altered pain perception (Spiegel et al., 2011). Dissociative symptoms can be found in several mental disorders, particularly in stress-related disorders (Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; van der Hart, Nijenhuis, & Steele, 2005) and personality disorders (Krause-Utz et al., 2021; Scalabrini, Cavicchioli, Fossati, & Maffei, 2017). Patients with other mental disorders such as schizophrenia, affective disorders, obsessive-compulsive disorders and somatoform disorders may also show dissociative symptoms (Lyssenko et al., 2018).

A common maladaptive behavior associated with emotion dysregulation in BPD is non-suicidal self-injury (NSSI) (Welch, Linehan, Sylvers, Chittams, & Rizvi, 2008), which is performed to regulate negative affective states and dissociation (Chapman, Gratz, & Brown, 2006; Kleindienst et al., 2008; Zanarini, Laudate, Frankenburg, Wedig, & Fitzmaurice, 2013). Interestingly, analgesic phenomena such as reduced pain sensitivity have been observed in BPD during self-injury (Kemperman et al., 1997; Shearer, 1994). From a pathophysiological aspect, injury would induce stress and pain in HC (Schmahl & Baumgartner, 2015). In the animal model, however, increased stress

would trigger reduced pain perception and pain-related behavior, so-called stress-induced analgesia. Most patients with BPD show an altered interaction between negative affective state (e.g. stress) and pain perception, in which NSSI is used as a dysfunctional strategy to reduce aversive inner tension with 'side effect' of pain, which helps to relieve the elevated aversive inner tension levels (Schmahl & Baumgartner, 2015). In previous work by Niedtfelt et al. (2010) that investigated the aspect of emotion regulation by self-injury pain as sensory stimulation, BPD patients compared with HC generally showed stronger activation of the amygdala, insula, and ACC. Positive correlations were observed between amygdala activation and self-reported measures of emotion regulation. Interestingly, during the experimentally induced thermal pain stimulation, decreased amygdala and ACC activation were found in patients with BPD, which was not associated with painfulness (Niedtfeld et al., 2010). Functional connectivity analyses indicated normal inhibitory connectivity between the left amygdala and medial prefrontal cortex (MPFC) and between the right anterior insula and DLPFC when negative visual stimuli were coupled with painful heat pain stimuli but not with non-painful warm stimuli (Niedtfeld et al., 2012). Presumably, there is a specific mechanism of pain processing in the emotion regulation process in BPD. However, the basic psychobiological mechanism of stress-related pain processing and NSSI is still open: It is supposed to be attributed to a direct contradictory feedback mechanism between self-injury and stress, with stress decreasing after self-injury via autonomic-limbic pathways (Schmahl & Baumgartner, 2015). The other conjecture is that pain experience with injury is associated with a contradictory feedback, i.e. pain leads to a reduction of stress or aversive inner tension and a downregulation of nociceptive and limbic-behavioral networks (Schmahl & Baumgartner, 2015). Individuals with BPD who have been engaging in NSSI generally show a diminished pain sensitivity (Hooley, Ho, Slater, & Lockshin, 2010; Koenig, Thayer, & Kaess, 2016; Ludascher et al., 2009). This relationship could result from adaptive processes in areas of the central nervous system that process nociception (so-called central habituation). This tonic influence may be maintained as a trait by prolonged self-harm behavior and is unlikely derived from phasic prefrontal cortex overactivity with top-down inhibitory modulation of insular activity and blocking of incoming nociceptive signals from the spinal cord dorsal horn (Schmahl & Baumgartner, 2015). Future studies need to elucidate a clear underlying mechanism.

So far, only a few studies have been conducted on the behavioral and neurobiological correlates of stress-related dissociation and pain sensitivity in BPD patients. In a study assessing self-report state dissociation, pain sensitivity, and changes in BOLD responses in 15 BPD patients presented with either a dissociation script or a neutral script, it was found that patients showed increased activation in the left inferior frontal gyrus while listening to the dissociation script (Ludascher et al., 2010). Higher dissociative symptoms based on a self-rating questionnaire predicted increased activation in the left superior frontal gyrus and decreased activation in the middle and inferior temporal gyrus. The results suggested increased frontal activity and decreased temporolimbic activity during acute dissociation in BPD (Ludascher et al., 2010). In another study using fMRI to examine default mode network (DMN) activity during painful heat versus neutral temperature stimulation in BPD patients with current self-mutilating behavior, higher BPD symptom severity and trait dissociation were associated with attenuated signal reduction in the DMN in response to painful stimulation, and BPD patients exhibited reduced posterior cingulate cortex (PCC) connectivity to the left DLPFC during painful stimulation (Kluetsch et al., 2012), while in a more recent study (Defrin et al., 2019), no significant association was observed between increased heat pain thresholds and trait dissociation scores in BPD patients. This suggests that dissociative experiences may be related to neural alterations that reflect a different cognitive and affective appraisal of pain as less self-relevant and aversive (Kluetsch et al., 2012; Ludascher et al., 2010).

Taken together, the past two decades of research on stress-related dissociation, pain processing, and a link between them have considerably expanded our understanding of BPD. Nonetheless, there are many challenges and questions that are still remain to be addressed.

1.3.2 Psychobiology of affective-sensory processing in BPD

In the past years, numerous research groups have provided evidence on the presumed disturbances in the processing and regulation of emotions by using various behavioral, psychophysiological and neurobiological approaches (for reviews, see: Domes et al., 2009; Rosenthal et al., 2008; van Zutphen, Siep, Jacob, Goebel, & Arntz, 2015). Interestingly, studies have shown inhomogeneous results of psychophysiological measures. Some studies reported that BPD patients compared to HC show an enhanced psychophysiological response to emotional stimuli, as evidenced by accelerated heart rate

(Ebner-Priemer et al., 2007; Lobbestael & Arntz, 2010), higher skin conductance responses (Eddie et al., 2018; Lobbestael & Arntz, 2010), heightened startle responses (Hazlett et al., 2007; Hazlett et al., 2012), while other studies showed that individuals with BPD had lower skin conductance responses (Herpertz, Kunert, Schwenger, & Sass, 1999; Pfaltz et al., 2015) in response to emotional stimuli compared to HC, suggesting reduced emotional reactivity in BPD. Furthermore, this decreased effect of emotional reactivity might be mediated by dissociative experiences. For example, Barnow et al (2012) demonstrated that increased dissociative experiences were linked to a decreased startle response (Barnow et al., 2012). However, there have also been studies that found no significant differences in startle amplitude or affect modulation of the startle-response in BPD patients compared to HC (Herpertz & Koetting, 2005; Herpertz et al., 1999; Herpertz, Werth, et al., 2001). In previous studies using BPD-specific words or scripts to examine reactions to unpleasant stimuli, BPD patients showed heightened startle responses (Hazlett et al., 2007), especially those with current comorbidity of posttraumatic stress disorder (PTSD) (Limberg, Barnow, Freyberger, & Hamm, 2011). Compared to PTSD patients, BPD patients only showed a tendency to alteration of skin conductance responses to BPD-salient scripts such as abandonment scripts. It could be considered that BPD and PTSD differ in their psychophysiological reactivity, although both disorders are associated with childhood trauma (Schmahl, Elzinga, et al., 2004). In summary, the current evidence from psychophysiological research in BPD points to the complexity in psychophysiological activity and reactivity. Alterations in psychophysiological function may be associated with adverse childhood experiences (e.g. early traumatic experiences) and display close relations to characteristics of cues (e.g. BPD-specific/salient words/scripts) and dissociation as well as general BPD symptom severity.

In the past decade, a number of studies on the biological basis of BPD have shifted the focus to direct visualization of brain structure and function using neuroimaging. The majority of findings shows that brain regions involved in emotional processing involve not only the amygdala but also insula, PCC, hippocampus, ACC and prefrontal regulatory regions, including the OFC, DLPFC and VLPFC. In BPD, several studies have revealed structural and functional alterations in these regulatory regions. Functional neuroimaging is the main approach to investigate emotional processing in BPD. A meta-analysis of fMRI findings in BPD patients showed increased activation during processing of negative emotional stimuli in the left amygdala, left hippocampus and

PCC, and decreased activation in prefrontal regions (including the DLPFC) (Schulze, Schmahl, & Niedtfeld, 2016). Ruocco et al. (2013) reported increased activity in the insula and diminished activation in the subgenual ACC in BPD patients, but no hyperactivity in amygdala under conditions of negative emotionality (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013). Contrasting amygdala results may be considered to be influenced by the medication status of BPD patients, as psychotropic drugs dampen limbic activity. Pharmacological studies have also shown reduced metabolic activity in the ACC and OFC in response to serotonergic challenge in individuals with BPD who exhibit impulsive-aggressive behavior and affective instability, and reduced coupling or quiescent metabolism between the OFC and the ventral ACC has been observed (New et al., 2007). In summary, a characteristic response in the frontolimbic brain network was found for BPD patients compared to HC, consisting of increased limbic activity and reduced prefrontal activity in response to emotional stimuli (Koenigsberg et al., 2009; Minzenberg, Fan, New, Tang, & Siever, 2007; Schulze et al., 2011; Silbersweig et al., 2007). It is known that limbic brain areas are linked to emotion detection and generation processes and prefrontal areas are related to cognitive control processes (Davidson & Irwin, 1999; Phillips, Drevets, Rauch, & Lane, 2003).

There is evidence from structural MRI studies that individuals with BPD have diminished volume in brain regions related to emotion processing and regulation, compared with HC. In a meta-analysis of brain volume based on a combined sample of 205 individuals with BPD and 222 HC from 11 imaging studies, significant volume reductions were reported in individuals with BPD bilaterally in amygdala and hippocampus (Ruocco, Amirthavasagam, & Zakzanis, 2012). There are also volume studies in adolescent-onset BPD populations, but no significant volume differences were found as in studies with adult-BPD samples. This might be due to small sample size, discrepant imaging techniques and highly comorbid disorders (Goodman, Perez-Rodriguez, & Siever, 2014).

Other imaging methodologies used in BPD include diffusion tensor imaging, which allows visualization of white matter integrity. Previous data suggest that impairments in frontolimbic connections are associated with symptom severity (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014). Functional connectivity analyses provide information about which brain regions are co-activated and can be investigated using seed-based correlations and independent component analysis. In BPD, there are abnormalities in

the connections between the 3 networks (a) DMN, which is involved in self-referential thinking and is connected to the MPFC and PCC, (b) salience network, together with the OFC and the dorsal ACC (dACC), and (c) medial temporal lobe network, which plays a key role in processing negative emotions. These are associated with particularly altered connectivity between salience detection and self-referential encoding. This leads to misinterpretation of neutral stimuli and further to a disturbance in the integration of salience information with internal representations. Krause-Utz et al. (2014) revealed an attenuation of the negative correlations between the dACC and the PCC as well as increased connectivity of the amygdala and the rostral ACC by means of psychophysiological interaction analyses (Krause-Utz, Elzinga, et al., 2014). In a study investigating neural correlates of emotional distraction, positive connectivity between the amygdala and prefrontal regions (right default mode PFC and left DLPFC) was found in BPD patients (Krause-Utz et al., 2012).

Taken together, the last two decades of research on the psychobiological correlates of affective-sensory processing have noticeably expanded our understanding of BPD. Neuroimaging studies indicate that BPD patients have structural and functional alterations in a frontolimbic network, notably decreased amygdala volume and increased amygdala response to negatively valenced stimuli. There is also evidence of structural changes in the prefrontal cortex and functional alterations related to pain perception, memory recall and processing of emotional stimuli. Nonetheless, there are innumerable challenges that are yet to be resolved.

1.4 Remission and recovery from BPD: normalization of psychopathological alterations?

Hitherto, the pathogenesis of BPD is still controversial, a prevailing idea being an interaction between genetic predisposition and psychosocial stress in childhood and adolescence. Some researchers suggest that sexual, physical and emotional trauma, manifested in severe interpersonal exclusion sensitivity, is closely associated with the development of BPD (Ball & Links, 2009; Battle et al., 2004). These psychopathological and neurobiological features of BPD could be considered trait parameters (Schmahl et al., 2014). However, it is unclear whether the BPD-specific alterations are reversible after remission of current BPD symptoms. Therefore, the questions about clinical image after symptomatic remission could help us understand a mechanism of disturbed emotional processing of BPD. Common notions of recovery have been clinically based

and focus on the remission of symptoms (or no longer meeting diagnostic criteria) and the recuperation and/or improvement to an earlier stage of functioning (Le Boutillier et al., 2015). The primarily underlying definition as remission was no longer meeting the criteria for BPD and for recurrence was meeting diagnostic criteria following a period of achieving remission (Ng, Bourke, & Grenyer, 2016). As briefly noted in chapter 1.1.2, epidemiological studies on the course of BPD have taken a positive view of the long-term prognosis of BPD (Gunderson et al., 2011; Zanarini et al., 2012). Although longitudinal studies observed a rapid decrease in the number of BPD criteria met within a few years, with remission rates of up to 99% at 16-year follow-up, there have still been problems with psychosocial impairment and crucial BPD features such as dependency or/and anger (Zanarini et al., 2012). This necessitates further research into the underlying pathophysiology in BPD beyond remission, which I suggest below may be related to the processing of affective and sensory stimuli, and the translation of these findings into a new generation of psychotherapeutic interventions.

The aim of this thesis is to identify the characteristics of maladaptive sensory processing and possible explanations for these dysfunctions, considering BPD-specific symptomatology such as dissociation, and to investigate the neural correlates of affective-sensory interaction in individuals with not only current BPD also after remission.

1.5 Hypotheses

The first empirical study of this dissertation investigated the effects of negative emotions on sensory perceptions in a sample of individuals with current (cBPD) and remitted BPD (rBPD) as well as HC. Thus far, existing BPD research has demonstrated alterations in pain perception, particularly pain hyposensitivity, which seems to be a prominent BPD-specific feature. Patients with BPD are vulnerable to emotional stress, which often induces the aversive inner tension related to dissociation. A number of findings also show a close relationship between dissociative states and altered pain perception. However, there is a lack of research on pain perception and dissociative states in individuals with BPD after remission from symptoms. Therefore, it is necessary to investigate the behavioral mechanisms during the processing of negative emotions during aversive arousal and emotional stress in patients with cBPD and rBPD. In other words, there is a need to investigate whether rBPD patients show stress-related dissociative states compared to cBPD and HC and whether these dissociative states

lead to an altered response to the thermal pain stimuli during the sensory processing of rBPD. Using a script-driven imagery approach (Ludascher et al., 2010; Shalev, Orr, & Pitman, 1992), a relationship between sensory insensitivity with thermal pain stimuli during experimental stress-induced dissociation was investigated in cBPD patients, individuals with BPD after symptom remission and HC. The hypotheses of the first empirical study were thus:

1) In a neutral condition, patients with cBPD compared to HC group show a significantly higher level of dissociation and lower pain sensitivity, but no difference between rBPD and HC groups.
2) Individuals with rBPD respond similarly to the cBPD group with increased dissociation and increased pain thresholds in a stress condition, while the HC group shows no changes in these measures.
3) There is a significant positive relationship between dissociation and pain hyposensitivity in current and remitted BPD groups.

The second empirical study in this thesis employed a functional imaging approach and aimed to investigate the effects of emotion processing on brain activation during listening to emotionally valenced sounds in patients with cBPD and rBPD as compared to HC. Earlier neuroimaging studies have reported alterations in a frontolimbic network during the processing of emotional stimuli in BPD, and visual stimuli (e.g. affective pictures or facial stimuli) have mostly been used to examine emotion processing in BPD (Krause-Utz, Winter, et al., 2014; van Zutphen et al., 2015). There are very few published studies using auditory stimuli, although it is likely that individuals with BPD show significant emotional reactivity to auditory stimuli over other sensory domains (Pfaltz et al., 2015; Rosenthal et al., 2011). To date, no studies are known to examine the neural correlates of affective auditory processing of emotionally valenced sounds in individuals with BPD after symptom remission. The hypotheses for the second empirical study were:

1) Both current and remitted BPD patients show increased brain activation during listening to emotionally valenced sounds compared to HC. Expected patterns include enhanced activation in response to positive and negative sounds in

amygdala in cBPD patients compared to HC, while there are no differences in response to neutral sounds among three groups.

2) Patients with rBPD show a normalization of brain activation in response to positive and negative sounds in amygdala along with clinical improvement. Patients with rBPD do not differ from HC.
3) Self-reported intensity of valence and arousal to both negative and positive emotion-evoking auditory stimuli are more emphasized in both current and remitted BPD patients than in HC.

2 EMPIRICAL STUDIES

2.1 Dissociation proneness and pain hyposensitivity in current and remitted borderline personality disorder[1]

[1] Publikation:
Chung, B. Y., Hensel, S., Schmidinger, I., Bekrater-Bodmann, R.*, & Flor, H.* (2020). Dissociation proneness and pain hyposensitivity in current and remitted borderline personality disorder. *European Journal of Pain, 24*(7), 1257-1268. doi:10.1002/ejp.1567
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Abstract

Background: Stress-related dissociation has been shown to negatively co-vary with pain perception in current borderline personality disorder (cBPD). While remission of the disorder (rBPD) is associated with normalized pain perception, it remains unclear whether dissociation proneness is still enhanced in this group and how this feature interacts with pain sensitivity.

Methods: Twenty-five cBPD patients, 20 rBPD patients, and 24 healthy controls (HC) participated in an experiment using the script-driven imagery approach. We presented a personalized stressful and neutral narrative. After listening to the scripts, dissociation and heat pain thresholds (HPT) were assessed.

Results: Compared to HC, cBPD patients showed enhanced dissociation and exhibited significantly enhanced HPT in the neutral condition, whereas rBPD participants were in between. After listening to the stress script, both clinical groups exhibited enhanced dissociation scores. Current BPD participants responded with significantly higher HPT, whereas rBPD only showed a trend in the same direction. However, both BPD groups showed significantly increased HPT compared to the HC in the stress condition, but did not differ from each other. Dissociation proneness correlated significantly positively with pain hyposensitivity only in cBPD.

Conclusion: Dissociation proneness is enhanced in both BPD groups. This feature is clearly positively related to pain hyposensitivity in cBPD, but not in rBPD. However, the data indicate that stress causes the pain perception in rBPD to drift away from that obtained in HC. These results highlight the volatile state of BPD remission and might have important implications for the care of BPD patients in the remitted stage.

Significance: Both current (cBPD) and remitted borderline personality disorder (rBPD) patients show enhanced proneness to dissociation. This feature is significantly linked with pain hyposensitivity in cBPD in a paradigm that induces stress using a script-driven imagery approach, whereas this connection cannot be observed in rBPD. However, in the stress compared to the neutral condition, rBPD participants also show pain hyposensitivity compared to healthy controls. This study provides new insights into the pain processing mechanisms of BPD and its remission.

Key words: Borderline personality disorder; pain perception; dissociation proneness; stress

1 Introduction

Borderline personality disorder (BPD) is characterized by a prolonged pattern of maladaptive behaviour, including impairments in self-image, interpersonal functioning, affectivity, and inhibition (American Psychiatric Association, 2013). Another prominent BPD feature is pain hyposensitivity, which has been demonstrated using various types of stimulation procedures (e.g. Bekrater-Bodmann et al., 2015; Ludäscher et al., 2007; Ludascher et al., 2010; Schmahl et al., 2010; Schmahl, Elzinga, et al., 2004), and which appears to be specific for BPD compared to other stress-related mental disorders (Schmahl et al., 2010). Pain hyposensitivity is positively related to dissociation (Bohus et al., 2000; Ludäscher et al., 2007), describing perceived detachment from reality in a dysfunctional attempt to cope with emotional stress. Self-injurious behaviour, involving the infliction of pain on oneself (e.g., Bohus et al., 2000; Ludäscher et al., 2007; Magerl, Burkart, Fernandez, Schmidt, & Treede, 2012) is often performed to release the aversive tension associated with dissociation (Kleindienst et al., 2008; Schmahl & Baumgartner, 2015) and is not perceived as painful. Since BPD is often associated with early traumatic stress, pain hyposensitivity has been viewed as an acquired coping response (Bohus et al., 2000).

Only a few studies investigated the course of BPD, which is often characterized by symptomatic remission defined as a state in which patients no longer fulfilled diagnostic BPD criteria for at least two years. About 99% of BPD patients fulfilled at least temporarily the remission criteria over the course of 16 years. However, recurrence of the disorder can be observed in up to 36% of the cases (Zanarini et al., 2012). Thus, the state of BPD remission seems rather elusive in terms of stable clinical improvement. Pain perception, at least to a certain degree, returns to normal when BPD is remitted (Bekrater-Bodmann et al., 2015), with heat pain thresholds (HPT) no longer being statistically different from those of healthy controls (HC). However, recent findings revealed enhanced stress responsivity in remitted BPD compared to HC, as remitted BPD patients react with an increased urge for self-injurious behaviour to the induction of stress (Willis et al., 2018). Thus, despite symptomatic remission, stress regulation deficits may still exist in remitted BPD. However, while previous studies investigated the stress-relieving effect of pain (Willis et al., 2018) in current (cBPD) and remitted BPD (rBPD) patients, it remains open whether pain perception in both groups is differentially influenced by dissociation proneness. The responses in rBPD are of particular

importance in this context, because these might give insight into the nature of still existing stress regulation deficits in symptomatic BPD remission.

In this present study, we investigated HPT in both cBPD and rBPD patients and its relationship to the response to the experimental induction of dissociation by script-driven imagery (Ludäscher et al., 2010; Shalev, Orr, & Pitman, 1992). In order to evaluate specificity of the expected findings for the pain domain, we also assessed warm perception thresholds. We hypothesized that HC would show significant differences in dissociation and pain sensitivity compared to cBPD patients in a neutral condition, whereas rBPD would not differ from HC. However, for the stress condition, we hypothesized that rBPD patients should respond similarly to the cBPD patients with enhanced dissociation and elevated pain thresholds, whereas HC should not show changes in these measures. We further expected a significant positive relationship between dissociation proneness and pain hyposensitivity in both BPD groups.

2 Methods

2.1 Participants

Participants with current BPD were recruited from online announcements, flyers, and the pool of in- and out-patients of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health and of the Department of General Psychiatry at the University of Heidelberg. Remitted BPD patients from the pool of patients formerly treated at the Central Institute of Mental Health were asked to participate in the study, whereas HC were recruited through the local resident's registration office. Recruitment of all participants in our study was undertaken by the central office of the KFO 256, a Clinical Research Unit funded by the German Research Foundation (DFG) for investigating the mechanism of disturbed emotion processing in BPD (Schmahl et al., 2014). Hence, all projects linked to the KFO 256 included participants from a joint database.

We performed an a priori sample size calculation based on large effects for script-driven imagery on pain in cBPD (Ludäscher et al., 2010; Cohen's d = 1.46). For rBPD, we only can estimate this effect and assume a smaller one of d = 1. HC and rBPD previously showed a medium effect size for differences in pain perception (Bekrater-Bodmann et al., 2015; d = 0.48). The linear relationship between dissociation and pain perception in cBPD has been shown to be medium to large (r between .54 and .83, mean r = .69; Bekrater-Bodmann, 2015; Ludäscher et al., 2007); given the low levels

and low variance of dissociation in rBPD, the previously reported non-significant relationships with pain (Bekrater-Bodmann et al., 2015) have to be evaluated with care so that we assume in our dissociation induction experiment a mean correlation of at least r = .55. Assuming an α of .05 and a power of 80%, at least 19 participants per group had to be included to detect the smallest of expected effects (G*Power v3.1.9.4, Faul, Erdfelder, Buchner, & Lang, 2009).

In total, we included 69 participants, 25 with cBPD (mean (M) age = 27.44 years, standard deviation (SD) = 6.87), 20 with rBPD (M age = 30.10 years; SD = 4.83), and 24 HC (M age = 27.67 years; SD = 5.75). All participants were female and there was no significant group difference in age, $F_{2,66} = 1.31$, $p = .28$. Except for two left-handed and three ambidextrous rBPD subjects as well as three subjects with missing data (two cBPD, one HC), all participants were right-handers by self-report. Eighteen (72%) patients with cBPD, 15 (75%) participants with rBPD and seven (29%) HC had already participated in another study on pain perception (Bekrater-Bodmann et al., 2015). All participants were fluent in the German language.

The diagnosis of BPD according to DSM-5 (American Psychiatric Association, 2000) was assessed with the International Personality Disorder Examination (IPDE; Loranger, 1999). Trained psychologists with at least a master's degree conducted the assessments. Participants had to fulfil five or more IPDE criteria for at least the last 5 years for inclusion in the cBPD group, whereas participants who had fulfilled full BPD diagnostic criteria (i.e., IPDE ≥ 5 criteria) once in their life and who fulfilled three or less criteria throughout 2 years prior to participation were considered rBPD. Particularly, self-harming behaviour must not have been shown more than twice within the last 2 years (in the present rBPD sample, only one patient reported such behaviour in the last 12 months, whereas all cBPD patients answered this question in the affirmative, according to a custom-made self-rating questionnaire for the assessment of NSSI behaviour (Kleindienst et al., 2008; Reitz et al., 2015; Willis et al., 2018). The validity of the criteria for symptomatic remission was confirmed by a previous longitudinal BPD study (Zanarini et al., 2014). However, symptomatic remission of BPD cannot be regarded as the recovery of the disorder (Zanarini et al., 2014). We did not include participants with scars at the palmar side of the hands due to the potential interference with painful stimulation. Further exclusion criteria were a lifetime diagnosis of schizophrenia or bipolar-I disorder, substance dependence within two years prior to study participation, current substance abuse, pregnancy, history of epilepsy, brain trauma or tumor, or other significant neurological or medical conditions. Highly potent

psychotropic medication (such as neuroleptics) had to be discontinued at least two weeks and pro re nata medication (such as sedative-hypnotics or benzodiazepines) at least 2 days before and throughout study participation. Selective serotonin reuptake inhibitors (SSRIs) were allowed to be taken during study participation (in this study, three cBPD and one rBPD subjects reported current intake of SSRIs), as SSRIs are often used to treat anxiety disorders and depression commonly co-occurring with BPD (Ripoll, 2013; Stoffers & Lieb, 2015), and thus, discontinuation is not recommended. Current and lifetime comorbid mental disorders and medication of the participants are given in Table 1. The study was approved by the ethics review board of the Medical Faculty Mannheim, Heidelberg University, and adhered to the Declaration of Helsinki in its current form. All participants gave written informed consent before study participation.

Table 1. Comorbid mental disorders and medication of the samples.

Comorbidities, n (%)	**cBPD N = 25**	**rBPD N = 19[a]**	**HC N = 24**
comorbid major depression (current)	4 (16%)	0 (0)	0 (0)
major depression (lifetime)	22 (88%)	14 (73.7%)	0 (0)
comorbid anxiety disorders and phobias (current)	16 (64%)	6 (31.6%)	0 (0)
comorbid posttraumatic stress disorder (current)	9 (36%)	0 (0)	0 (0)
posttraumatic stress disorder (lifetime)	10 (40%)	5 (26.3%)	0 (0)
other comorbid disorders	11 (44%)	1 (5.3%)	0 (0)
Medication, n (%)			
None	13 (52%)	15 (78.9%)	23 (95.8%)
Selective serotonin reuptake inhibitor	3 (12%)	1 (5.3%)	0 (0)
Neuroleptic	6 (24%)	1 (5.3%)	0 (0)
Benzodiazepines	3 (12%)	2 (10.5%)	0 (0)
Proton pump inhibitor	0 (0)	0 (0)	1 (4.2%)
Oral contraceptives	3 (12%)	1 (5.3%)	0 (0)
Thyroid hormones	4 (16%)	2 (10.5%)	0 (0)
Asthma medication	1 (4%)	1 (5.3%)	0 (0)

[a] One participant in the rBPD group was not included due to insufficient data collection. cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control.

2.2 Script-driven imagery

Script-driven imagery has been previously used to experimentally induce dissociation in cBPD patients (Barnow et al., 2012; Bichescu-Burian, Steyer, Steinert, Grieb, & Tschoke, 2017; Krause-Utz et al., 2018; e.g., Ludascher et al., 2010; Winter et al., 2015). This approach has been shown to activate memories, which can be evaluated using affective self-report measures and psychophysiological assessments (Bichescu-Burian et al., 2017). Since mentally imagined interaction with a stimulus can induce similar emotional reactions as a real interaction with the same stimulus (Lang, 1979), our subjects were instructed to vividly imagine autobiographical events. For this purpose, the participants were asked to describe autobiographical situations in which they experienced low or high tension due to emotional stress. The order of script preparation (neutral first) was fixed. After giving the instruction for preparing a script, the subjects completed the short version of the Dissociation Tension Scale (DSS-4; Stiglmayr, Schmahl, Bremner, Bohus, & Ebner-Priemer, 2009) to assess the baseline level of dissociation. The DSS-4 is the short form of the Dissociation-Tension Scale acute (DSS-acute; Stiglmayr, Braakmann, Haaf, Stieglitz, & Bohus, 2003), and represents an instrument for repeated assessment of dissociation during experimental and real-life settings. The DSS-4 contains four items that assess somatoform dissociation (reduced auditive sensory perception), analgesia, depersonalization, and derealization. Dissociation scores are calculated as means of the four items of the DSS-4. Then, the investigator started to ask for some examples of emotionally neutral situations in the participant's daily life, along with additional questions about experiences in a specific situation in the recent past. The participant was asked to detail the situation and it was assessed how a) stressful, b) relevant for her personal life, and c) emotionally upsetting the situation was using a visual analogue scale (VAS, 100mm, with the endpoints 'not at all' and 'very strong'). Neutral scripts had to have a value of 20/100 or below on the VAS targeting stress. For three cBPD participants, who were not able to report a situation below this value, even when several events had been evaluated, a value of < 35/100 on the VAS was accepted. Valence and arousal of the situation were rated using the non-verbal Self-Assessment Manikin scales (Bradley & Lang, 1994). The scales were later converted to ratings ranging from 1 (pleasantness/high arousal) to 9

(unpleasantness/low arousal). The participants were then asked to tell the story in detail in first-person perspective and in the present tense with a focus on sensations, thoughts, and emotions (Lanius et al., 2001; Ludascher et al., 2010; Pitman & Orr, 1993), not exceeding about 60s. The story was written down and then read to the participant who was allowed to change the content, if desired. The finalized script was read again by the experimenter, whereas the participant was instructed to relive the situation as vividly as possible. Then, the DSS-4 was again used to assess state dissociation.

Subsequently, an emotionally stressful script, which was selected to not contain traumatic elements, was constructed and transcribed in the same way. The participants were instructed to remember aversive emotionally upsetting situations, which caused stress ratings of > 80/100. Due to inability to report an everyday stressful situation fulfilling this criterion in six participants (two subjects from each group), a story with a stress rating value of > 70/100 was accepted. Trauma-related situations were explicitly excluded in order to ensure at least partly comparable emotionally stressful scripts between BPD participants and HC. For this purpose, we used the Posttraumatic Stress Diagnostic Scale (German version by Ehlers, Steil, Winter, & Foa, 1996) to check the stressful narrative and excluded it and assessed another situation in case of positive ratings.

In all groups, the participants predominantly chose narratives about routines of daily life for the neutral script and interpersonal conflicts for the stressful script (a detailed content analysis is given in Supplementary Table S1). The specific values characterizing neutral and stressful scripts (provided in Supplementary Table S2) indicate that the stress script was rated as significantly higher in all assessed variables (DSS-4 score, inner tension rating, perceived stress, personal relevance, emotional upsetting, perceived valence, and perceived arousal) compared to the neutral script across all groups. Except for reported dissociation and tension, the groups did not significantly differ in their ratings of the stories, suggesting comparable stimulus material for the experimental sessions.

2.3 Warm perception and heat pain threshold assessment

For the assessment of the participants' warm perception (WPT) and heat pain thresholds (HPT) we used a contact thermode (30x30 mm, Thermal Sensory Analyzer, Medoc Advanced Medical Systems Ltd, Ramat Yishai, Israel). The order of threshold assessment was fixed, starting with the assessment of WPT. The thermode was

attached to the left thenar eminence of each participant's hand and the temperature was increased continuously by 1.2 °C/s for warm perception and 3.0 °C/s for heat pain (Leung, Wallace, Schulteis, & Yaksh, 2005). All participants were instructed to immediately respond to the onset of warm or heat pain perception with a mouse-click, which recoded the temperature before returning to the baseline point (32 °C) for the next trial. For WPT and HPT, five trials were performed, and the mean of the last four trials served as threshold value.

2.4 Experimental procedure

Each participant came for three assessments on separate days (Fig. 1). At least 1 day before the first of two experimental sessions, an emotionally neutral and an emotionally stressful script were assessed by a trained experimenter (RBB), based on the procedure described by Ludäscher et al. (2010). The transcription of the collected narratives, read by a female German native speaker, was recorded and digitally stored. The experimental sessions were performed on two consecutive days. Before presentation of the personalized scripts in randomized order, we assessed state dissociation using the DSS-4. Each script was played twice in order to enhance the intensity of the induced state (Ludascher et al., 2010). The participants were instructed to carefully listen to the script and to imagine themselves as vividly as possible in the situation so that they relived it. Immediately after presentation of the scripts, dissociative responses were again assessed with the DSS-4. Due to a later implementation of vividness ratings, only a subsample of participants (15 cBPD, 15 rBPD, 11 HC) was specifically asked for the vividness of the imagery (using a numeric rating scale ranging from 0 = 'not at all' to 9 = 'as if it were real') (Ludascher et al., 2010). Immediately after the ratings, we assessed WPT and HPT as described earlier.

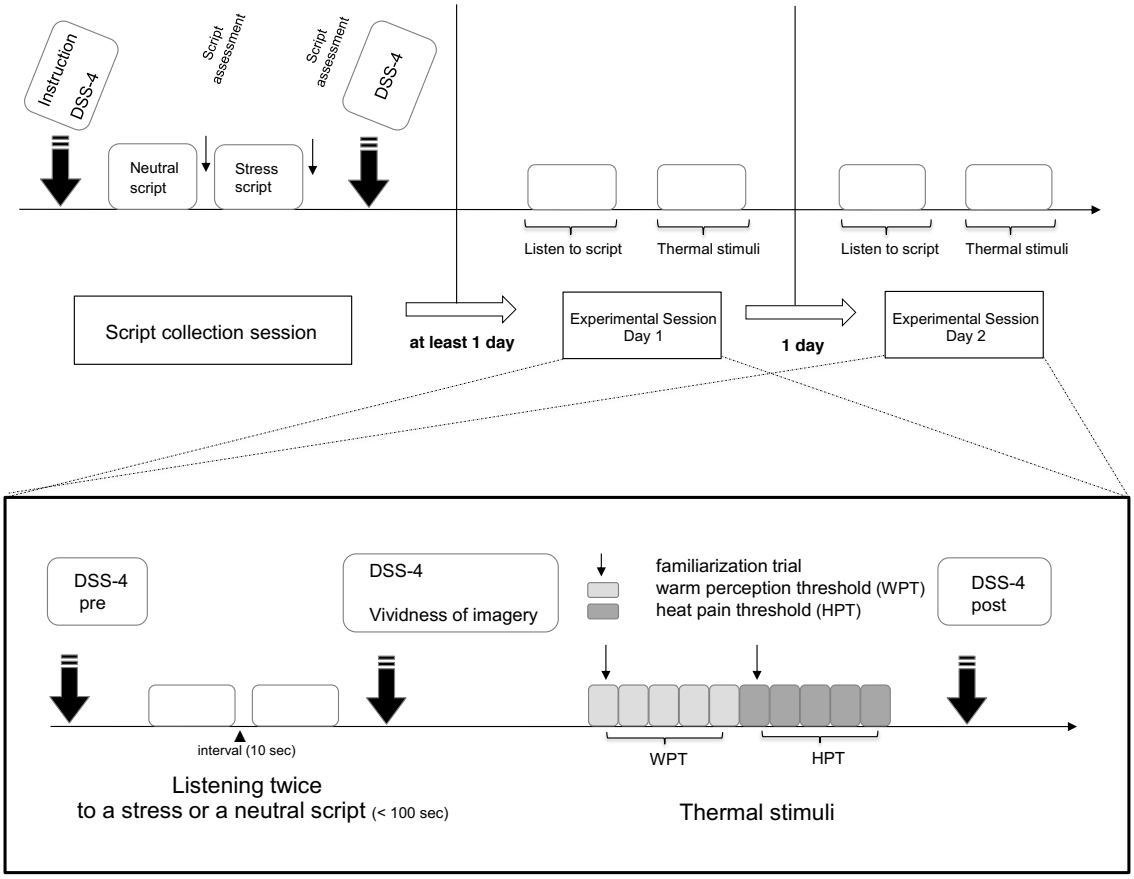

Figure 1: Study design. This present study took place on 3 days. First, at least 1 day before the first of two experimental sessions, two autobiographical scripts with neutral and stress content were obtained (Script collection session). The experimental sessions were implemented on two subsequent consecutive days. State dissociation (assessed by the Dissociation Tension Scale, DSS-4) before and after listening to the personalized scripts and vividness of imagery were assessed. After the psychometric assessments, warm perception threshold (WPT) and heat pain threshold (HPT) were assessed. The duration of each script was less than 100 s. Each of the two scripts was played twice.

2.5 Statistical analyses

We entered DSS-4 dissociation data in a 2 (factor point in time; pre and post script) x 2 (factor condition; neutral and stress) x 3 (factor group; cBPD, rBPD, and HC) mixed-model ANOVA. We report on test statistics and effect sizes (η^2), and used Bonferroni correction (p_{Bonf}; α of .05) whenever post hoc tests were performed. Significant interactions were further analysed by simple effects analyses. In order to analyse whether or not substantial dissociation was induced, we used a composite dissociation score: in an attempt to account for group-specific differences in the extent of dissociation, we

subtracted the mean of the DSS-4 score after script presentation from the reported mean of the dissociation score before listening to the script in each group, separately for the stress and the neutral condition (i.e., induced dissociation (ID) = mean of DSS-$4_{post\_stress/neutral}$ minus mean of DSS-$4_{pre\_stress/neutral}$). Then we subtracted the value obtained in the neutral condition from the value obtained in the stress condition (i.e. the composite dissociation score $ID_{composite} = ID_{stress}$ minus $ID_{neutral}$). $ID_{composite}$ has a possible range from -18 to +18, with positive values representing stronger induced dissociation in the stress condition compared to the neutral condition, controlled for individual differences, and thus, the score reflects dissociation proneness. We used one-sample t-tests with the test value 0 for each group in order to test for significant dissociation proneness. We report on test statistics, p_{Bonf}, and Cohen's d (based on n, M and SD) as a measure of effect size. The vividness scores were similarly analysed using a mixed-model ANOVA, excluding the factor point in time.

Previous results indicated that thermal pain threshold assessment might underestimate the extent of pain hyposensitivity especially in cBPD (Bekrater-Bodmann et al., 2015b), since the increase in temperature stops for safety reasons when a temperature of 52 °C is reached although the subjects may not yet have reached the pain threshold. Twenty-two participants (2 HC, 6 rBPD, and 14 cBPD) had at least one trial where the thermode stopped heating. In an attempt to compensate for the underestimation of HPT, we rounded these trials to 54 °C (i.e., adjusted HPT), which is still in the range of C nociceptor responsiveness (e.g., Van Hees & Gybels, 1981). Non-significant Kolmogorov-Smirnov tests (group-wise; $H_{20\text{-}24} \leq .16$; all $p \geq .12$) indicated that the normal distribution assumption was not violated by this procedure. Furthermore, missing data in single trials (due to technical reasons) were replaced by the individual's mean per condition (which was the case in 2.5% of all trials). Again, we used a mixed-model ANOVA by entering the factors group and condition. The mean effect for condition was decomposed for each group by applying dependent sample t-tests (one-tailed, uncorrected p value). For WPT, we performed an identical analysis. In order to further separately analyse the pattern of HPT data in the neutral and the stress condition, we used independent t-tests. Note that the results for these analyses are also reported for the non-adjusted HPT data (see Supplementary Table S4).

Finally, we performed two-tailed Pearson correlation analyses in order to examine the relationship between the composite dissociation score ($ID_{composite}$; see above for calculation procedure) and changes in HPT (HPT in the stress condition minus HPT in the neutral condition; positive values in the resulting score thus represent higher HPT in

the stress compared to the neutral condition). We provide the correlation coefficient r and the two-sided p value for each group separately (uncorrected). All statistical analyses were carried out with IBM SPSS Statistics (v22.0).

3 Results

3.1 Induction of dissociation

M and SD of induced dissociation data are provided in Table 2. The ANOVA revealed a significant main effect for the factor condition ($F_{1,66} = 9.52$, $p = .003$, $\eta^2 = .13$), with higher dissociation ratings in the stress compared to the neutral condition. Furthermore, there was a significant main effect for the factor group ($F_{2,66} = 15.07$, $p < .001$, $\eta^2 = .31$). Post hoc comparisons revealed that cBPD reported significantly higher dissociation compared to HC ($p_{Bonf} < .001$) and rBPD ($p_{Bonf} = .001$), whereas HC and rBPD did not significantly differ ($p_{Bonf} = .83$). Moreover, there was a significant main effect for the factor point in time ($F_{1,66} = 21.19$, $p < .001$, $\eta^2 = .24$), which was driven by significantly higher dissociation ratings after compared to before listening to the script. However, there also was a significant point in time * condition interaction ($F_{1,66} = 23.86$, $p < .001$, $\eta^2 = .27$). The subsequent simple effects analysis revealed that the main effect for point in time solely relied on the increase of dissociation in the stress condition ($p_{Bonf} < .001$), whereas there was no significant change in the neutral condition ($p_{Bonf} = .45$). There also was a significant point in time * group interaction ($F_{2,66} = 5.53$, $p = .006$, $\eta^2 = .14$). A simple effects analysis revealed that cBPD reported stronger dissociation compared to rBPD and HC (all $p_{Bonf} \leq .001$ before and after listening to the scripts), whereas HC and rBPD did not significantly differ (all $p_{Bonf} \geq .37$). The simple effects analysis for the significant point in time * condition * group interaction ($F_{2,66} = 8.20$, $p = .001$, $\eta^2 = .20$) further showed that cBPD reported significantly higher dissociation compared to rBPD and HC (all $p_{Bonf} \leq .009$), whereas there was no significant difference between rBPD and HC (all $p_{Bonf} \geq .14$), regardless of point in time and condition. However, as depicted in Figure 2a, the slope from pre to post script in rBPD under neutral conditions resembles the slope obtained in HC, whereas in the stressful condition, the slope obtained in the rBPD resembles that from the cBPD. This suggests that BPD-specific responses (regardless of whether the state of the disorder is current or remitted) cause the significance in the two- and three-way interactions involving the factor group.

In an attempt to further examine this interpretation, we separately tested $ID_{composite}$ against 0 in the three groups. Both cBPD (M = 1.45, SD = 1.73; t_{24} = 4.19, d = 0.84, p_{Bonf} < .001) and rBPD (M = 0.80, SD = 1.32; t_{19} = 2.71, d = 0.61, p_{Bonf} = .042), but not HC (M = -0.01, SD = 0.14; t_{23} = -0.37, d = -0.08, p_{Bonf} = 1.00), showed significant positive scores, indicating substantial dissociation proneness only in the clinical groups, albeit different in extent. This indicates that both BPD groups respond with dissociation when stress is induced. These data are visualized in Figure 2b. Note that vividness of imagery during the experimental sessions was comparable between groups and conditions, as revealed by non-significant main and interaction effects for this measure (see Supplementary Table S3).

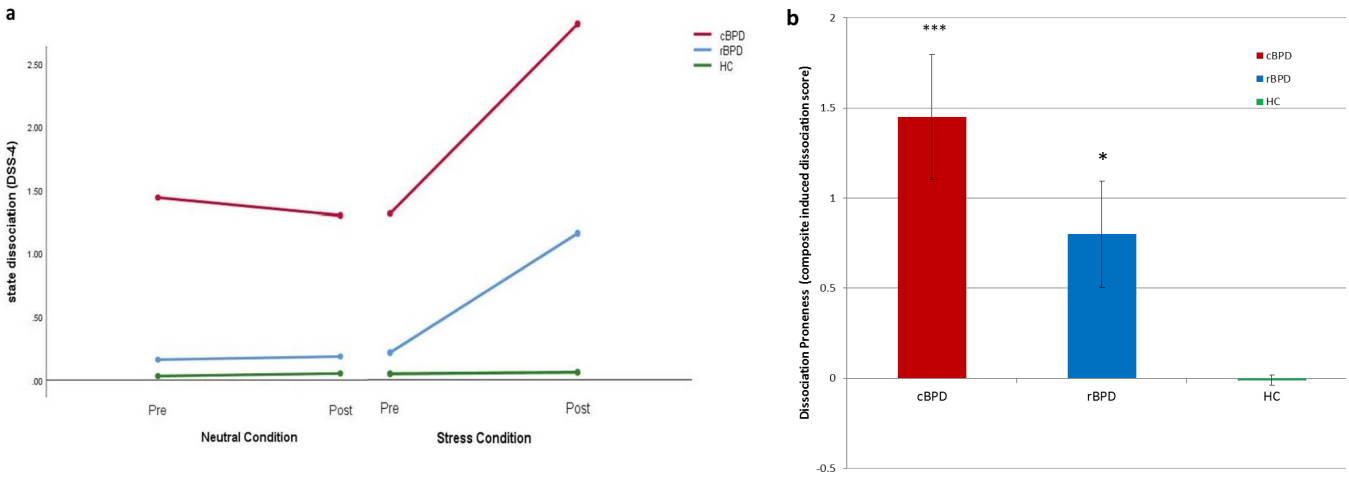

Figure 2: State Dissociation slopes and dissociation proneness in current borderline personality disorder (cBPD), remitted borderline personality disorder (rBPD), and healthy controls (HC). a) State dissociation slopes (mean values). b) Dissociation proneness (mean values); error bars indicate the standard error of the mean. ***p < .001; *p < .05 (2-tailed one-sample *t*-test with test value 0)

3.2 Heat pain and warm perception thresholds

For HPT, there was a significant main effect for condition ($F_{1,66}$ = 4.12, p = .046, η^2 = .06) which was driven by elevated HPT in the stress compared to the neutral condition. However, this effect was mainly associated with the cBPD participants, as revealed by a significant increase of HPT in the stress compared to the neutral condition only in this group (t_{24} = 1.81, p = .041, d = 0.34). For rBPD, there only was a trend in the same direction (t_{19} = 1.60, p = .064, d = 0.38), and in HC, no significant changes were

observed (t_{23} = -0.81, p = .21, d = -0.17). We further found a significant effect of group ($F_{2,65}$ = 10.32, p < .001, η^2 = .24) with cBPD having significantly higher thresholds compared to HC (p_{Bonf} < .001). Remitted BPD did not significantly differ from cBPD (p_{Bonf} = .14) or HC (p_{Bonf} = .08). The interaction condition * group missed significance ($F_{2,66}$ = 2.08, p = .13, η^2 = .06). M and SD of HPT data for each group are given in Table 2. Note that the main effects of the factors condition and group were specific for the nociceptive domain, since an analysis using WPT did not reveal significant main effects (both p ≥ .06, η^2 ≤ .08; M and SD are given in Table 2). The pattern of results is similar for the non-adjusted HPT data (see supplement).

In order to further analyse the pattern of results for HPT, we performed t-tests in the groups separately comparing the HPT in the neutral and stress condition. For the neutral condition, we found HPT to be significantly higher for cBPD versus HC (t_{47} = 3.34, d = 0.96, p_{Bonf} = .005), whereas there was no significant difference between cBPD and rBPD (t_{43} = 1.64, d = 0.50, p_{Bonf} = .32) or between rBPD and HC (t_{42} = 1.33, d = 0.40, p_{Bonf} = .58). For the stress condition, however, we found significantly higher HPT for both cBPD compared to HC (t_{47} = 5.43, d = 1.55, p_{Bonf} < .001) and rBPD compared to HC (t_{42} = 2.68, d = 0.80, p_{Bonf} = .031) but not between cBPD and rBPD (t_{43} = 1.72, d = 0.51, p_{Bonf} = .28, see Figure 3). The pattern of significances remains valid also for the non-adjusted HPT data (see supplement).

Table 2: Mean and standard deviation of state dissociation, heat pain thresholds (HPT) and warm perception (WPT) after listening to the stress script and neutral script (experimental sessions).

	cBPD (N = 25)		**rBPD (N = 20)**		**HC (N = 24)**	
	Neutral script M (SD)	**Stress script M (SD)**	**Neutral script M (SD)**	**Stress script M (SD)**	**Neutral script M (SD)**	**Stress script M (SD)**
DSS-4 Score pre	1.44 (1.73)	1.15 (1.46)	.16 (.33)	.19 (.52)	.03 (.15)	.04 (.16)
DSS-4 Score post	1.30 (1.75)	2.46 (2.16)	.19 (.49)	1.01 (1.60)	.05 (.15)	.05 (.16)
HPT	48.39 (4.08)	49.90 (3.63)	46.36 (4.17)	47.77 (4.68)	44.89 (3.19)	44.55 (3.25)
WPT	34.20 (1.43)	34.96 (1.75)	34.48 (1.98)	34.51 (1.57)	33.78 (.81)	33.73 (.45)

cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control subjects; M = mean; SD = standard deviation; N = sample size; DSS-4 = Dissociation Tension Scale-4 (0 = not at all – 9 = very strong); WPT = warm perception thresholds; HPT = heat pain thresholds.

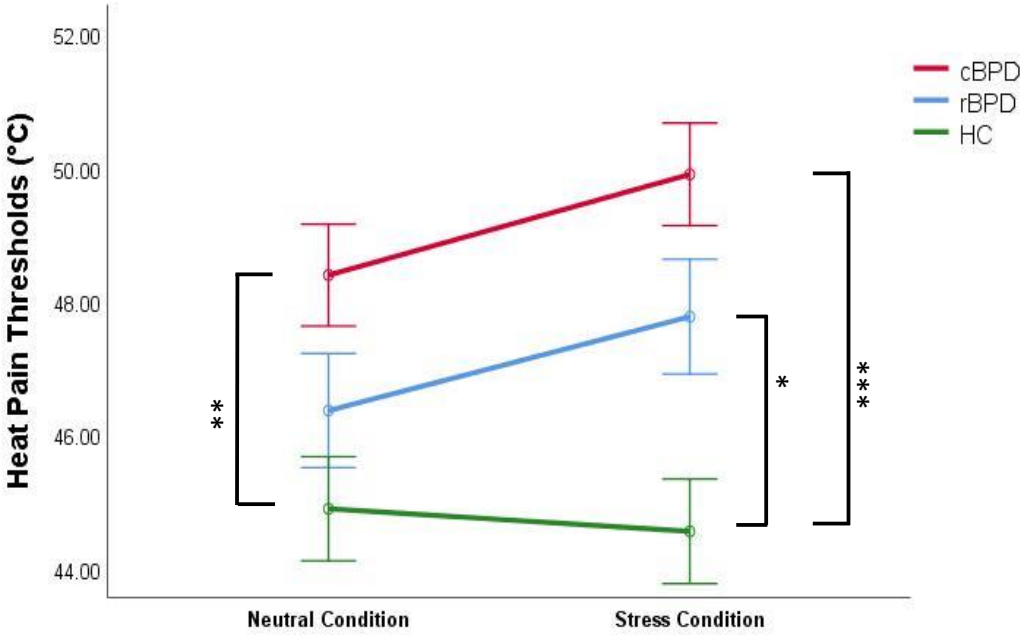

Figure 3: Heat pain thresholds in the neutral and the stress condition. cBPD, current borderline personality disorder; rBPD, remitted borderline personality disorder; HC, healthy controls. Error bars indicated the standard error of the mean. ***p < .001; **p < .01; *p < .05.

3.3 Relationship between dissociation proneness and heat pain thresholds

Pearson correlation analyses revealed that dissociation proneness correlated significantly positively with induced changes in HPT in participants with cBPD (r_{23} = .40, p = .047), whereas there were no significant relationships in rBPD (r_{18} = .22, p = .36) and HC (r_{22} = -.37, p = .08). The scatter plot for cBPD is given in Figure 4.

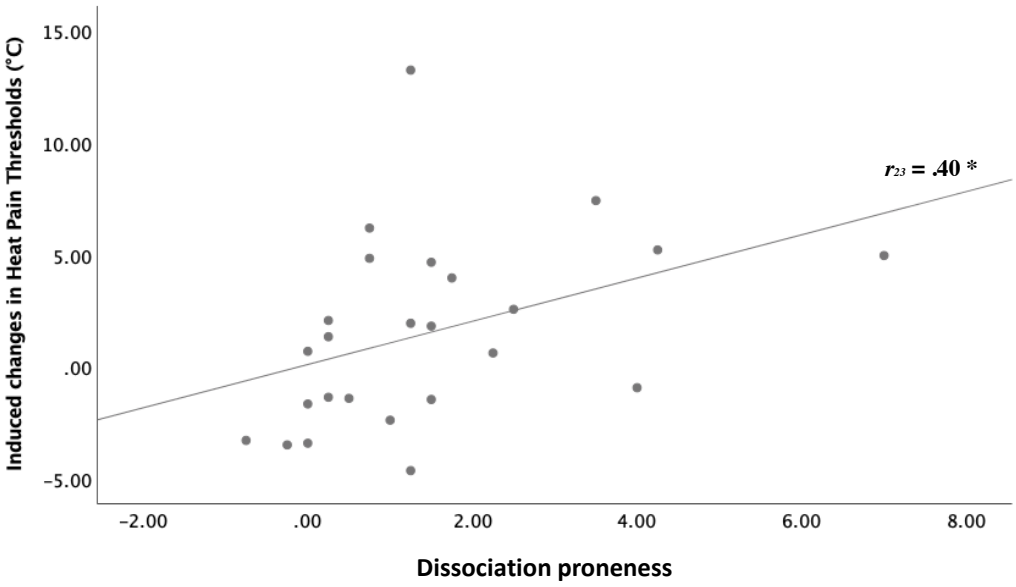

Figure 4: Relationship between dissociation proneness and heat pain threshold changes in the stress versus neutral condition in participants with current borderline personality disorder. *p < .05.

4 Discussion

In this study, we investigated the relationship between dissociation proneness and pain hyposensitivity in patients with current and remitted BPD as well as HC as a non-clinical control group. Recordings of autobiographical stressful narratives, compared to neutral narratives in the control condition, were used to induce dissociation on two consecutive days. This procedure reliably induced dissociation in both clinical groups. We found that cBPD participants displayed reduced heat pain perception compared to HC, replicating previous results (Bohus et al., 2000; Ludascher et al., 2010; Niedtfeld et al., 2010; Russ et al., 1992; Schmahl et al., 2010; Schmahl, Vermetten, Elzinga, & Bremner, 2004). Remitted BPD participants were in between, and did not differ significantly from either cBPD or the HC in the neutral condition. However, after listening to the stressful script, rBPD participants showed significantly reduced pain sensitivity compared to HC, perceptually resembling cBPD participants, even though the overall level of pain hyposensitivity was lower. In cPBD, but not in rBPD, dissociation proneness was significantly positively related to pain hyposensitivity. These results suggest that BPD-specific altered pain sensitivity is associated with trait dissociation proneness in the current stage of the disorder;

in rBPD patients, however, pain hyposensitivity is present under stressful, but not neutral, conditions (although weaker in extent compared to cBPD), independent of dissociation proneness. These results are indicative of differential mechanisms of pain perception in the clinical groups, and highlight the elusive state of BPD remission in terms of stable clinical improvement.

4.1 Dissociation proneness

The results might help to resolve some of the inconsistencies about the relationship between stress, dissociation, and pain in BPD reported before. Stress-related pain hyposensitivity has been reliably associated with cBPD (e.g., Bohus et al., 2000; Russ et al., 1992; Schmahl, Greffrath, et al., 2004; Schmahl et al., 2010). For dissociation, however, the empirical evidence is rather inconsistent: while state dissociation has been found to be more reliably correlated with pain hyposensitivity (Bekrater-Bodmann et al., 2015; Ludäscher et al., 2007), for trait dissociation, there are mixed results (Bekrater-Bodmann et al., 2015; Defrin et al., 2019; Ludäscher et al., 2007, 2015), highlighting the dissociable nature between trait and state stress responses in cBPD. By introducing the measure of dissociation proneness, we offer a new variable for experimental investigations, reflecting the level of state dissociative responses corrected by individual trait differences. Although prospective studies have to further evaluate the validity of this measure, the differences between cBPD and rBPD in the present study indicate that stress and dissociation independently contribute to BPD-specific pain hyposensitivity. It would be particularly interesting to test for relationships between this measure and recently identified central (Kraus et al., 2009; Schmahl et al., 2006) and peripheral physiological (Defrin et al., 2019) correlates of cBPD-associated pain hyposensitivity and the potential underlying mechanisms.

4.2 Altered pain sensitivity and its potential importance for NSSI behavior

Non-suicidal self-injurious behavior (NSSI) is often performed in cBPD in a dysfunctional attempt to cope with stress (Reitz et al., 2012, 2015). It has been shown that individuals who have higher pain thresholds are more likely to engage in NSSI, and repeated NSSI might in turn lead to elevated pain thresholds over time (Hooley, Ho, Slater, & Lockshin, 2010). This bi-directional link of nociception and behaviour might be the basis for operant learning mechanisms underlying dysfunctional coping strategies such as self-harm. Dissociation has been identified to be an important mediator for the relationship between

pain perception and NSSI in cBPD (Ludäscher et al., 2010). The present data, however, indicate that stress-responses other than dissociation might play a role for this relationship: when the disorder is in its remitted stage, we found stress-associated hyposensitivity in rBPD which cannot completely be explained by still enhanced dissociation proneness. Enhanced stress reactivity in rBPD and associated increase in the urge for NSSI (Willis et al., 2018) might reflect the stability of learned dysfunctional coping behaviour beyond the disorder's current stage. This interpretation, together with the present's studies results regarding altered stress-related pain sensitivity in rBPD, might be of importance for therapeutic considerations for individuals in the remitted stage. Longitudinally, NSSI has been found to be associated not only with dissociative symptoms but also with female gender, severity of dysphoric cognitions, major depression and a history of childhood and adult sexual abuse (Zanarini, Laudate, Frankenberg, Reich, & Fitzmaurice, 2011). Although Zanarini et al. (2011) did not differentiate between BPD in the current and the remitted stage, other reports of the same cohort suggest very high rates of – at least temporarily stable – symptomatic remission (Zanarini et al., 2012), indicating that the identified predictors of NSSI might also be crucial for rBPD. While this study's results suggest that dissociation might play a minor role in rBPD, enhanced stress levels due to dysfunctional cognitions, mood disorders and a history of adverse experiences might still affect pain perception which in turn might reduce the inhibition threshold to engage in NSSI (see Hooley et al., 2010). However, it is remarkable that only one out of 20 rBPD patients in this study reported self-harming behaviour in the last 12 months (compared to 100% of the cBPD patients), suggesting rather high competence of rBPD patients to deal with adverse effects of everyday life stressors. The identification of successful coping strategies might be of interest for future studies on therapeutic aftercare for BPD patients in the remitted stage of the disorder.

4.3 Limitations and perspective

Several limitations of our study must be noted. Firstly, although we implemented a randomized order of scripts, the participants could predict the content to a certain degree. After the experiment, some participants with current and remitted BPD spontaneously reported that they prepared themselves for the second experimental session, be it settling in anticipation of a stressful script or keeping relaxed in anticipation of a neutral script. This might have interfered with the induction of dissociation, as the scores we assessed were relatively low (about 1.2 averaged sum score points in the DSS-4) compared to

other studies (Bichescu-Burian et al., 2017; Krause-Utz et al., 2018; Ludascher et al., 2010, with converted values of 1.5 and higher). The purposeful exclusion of traumatic events might account for the rather low scores in the present study, while increasing the ecological validity of findings. However, the slightly lower dissociation level cannot really explain the small effect sizes. While Ludäscher et al. (2010) reported effect sizes larger than 1 for pain modulation by the script-driven imagery approach, we found rather small effect sizes for both BPD groups between d = 0.3 and 0.4. The reasons for these lower effects need to be further investigated. Secondly, our approach to round HPT for participants who reached the safety limit of the thermode might have induced a bias in our data. Although we used a stimulation procedure described before (Leung et al., 2005), the heating rate of 1.2°C/s might not have been optimal in the present context. Slower heating rates induce temporal summation resulting in increased pain perception and accordingly reduced pain thresholds (Arendt-Nielsen and Petersen-Felix 1995; Eide 2000; Vierck, Cannon, Fry, Maixner, & Whitsel, 1997), which might be beneficial for the investigation of pathologically enhanced HPT. It might be useful to carefully adapt the pain stimulation procedure for populations with mental disorders in general and BPD in particular in prospective studies. Alternatively, ceiling effects could be avoided in the future using other types of painful stimulation such as mechanical, chemical, or electrical stimulation (Ludäscher et al., 2007; Magerl et al., 2012), where the thermal-specific stimulation restrictions are not given. However, the similarity of result patterns for adjusted (results section) and non-adjusted data (supplement) suggests robustness of effects, which in fact might remain underestimated in this study. Finally, future studies should validate our results with physiological measures of stress, since we can only indirectly conclude that dissociation proneness as defined in this study is a consequence of stress reactivity. Moreover, prospective studies should implement longitudinal designs in which dissociation proneness and pain perception can be evaluated over an extended period of time, from the disorder's current stage into remission. Without longitudinal data, we do not know whether rBPD patients had similarly severe BPD symptoms, compared to the cBPD group, when they were in their current stage, or had simply been milder cases, with less pronounced dissociation symptomatology (Löffler, Kleindienst, Cackowski, Schmidinger, & Bekrater-Bodmann, 2019).

4.4 Conclusion

Taken together, our results suggest enhanced dissociation proneness not only in cBPD, but also in rBPD. However, the interaction with pain perception might be rather complex. Compared to HC, remitted BPD react with pain hyposensitivity under stressful compared to neutral conditions, although smaller in extent compared to cBPD. While this feature is clearly positively related to dissociation proneness in cBPD, this association cannot be observed in rBPD. However, the data indicate that stress causes the pain perception rBPD to drift away from that of the HC. The clinical value of these findings as well as its importance for therapeutic considerations in the aftercare of BPD needs to be further evaluated in the future.

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Supplementary Table S1: Content analysis of the scripts.

	Category and content script	cBPD N = 25	rBPD N = 20	HC N = 24	Total N = 69
Neutral script N (%)	**daily routine** 'feed cats', 'morning routine', 'prepare breakfast', 'take a shower'	5 (20.0)	10 (50.0)	7 (29.2)	22 (31.9)
	housekeeping 'go shopping', 'clean the house', 'make a salad', 'do the cooking'	7 (28.0)	2 (10.0)	6 (25.0)	15 (21.7)
	public transport rides 'drive a car', 'take the bus/train/car', 'waiting area at airport'	7 (28.0)	1 (5.0)	5 (20.8)	13 (18.8)
	go for a walk 'go for a walk with friend/dogs/in the park'	4 (16.0)	6 (30.0)	-	10 (14.5)
	social contact 'meet up with friends', 'go for coffee', 'prepare for a peer tutoring/group study appointment'	1 (4.0)	1 (5.0)	5 (20.8)	7 (10.1)
	work 'work life', 'small talk'	1 (4.0)	-	1 (4.2)	2 (2.8)
Stress script N (%)	**interpersonal conflicts** 'conflicts with partners/friends/family', 'abandonment', 'rejection'	9 (36.0)	11 (55)	9 (37.5)	29 (42.1)
	inferiority feeling/ pressure of achievements and failures 'exam/performance/job interview anxiety', 'inferiority feeling during a job interview/exam'	1 (4.0)	4 (20)	10 (41.6)	15 (21.7)
	grief and loss	2 (8.0)	3 (15)	3 (12.5)	8 (11.6)

	Category and content script	cBPD N = 25	rBPD N = 20	HC N = 24	Total N = 69
	'death of a parent/pet', 'funeral', 'visiting a graveyard'				
	feelings of anger/rage/helplessness 'unpleasant/tense psychotherapy session', 'disappointment with a stay in a psychiatric hospital' 'notification of mother's breast cancer diagnosis'	8 (32.0)	-	1 (4.2)	9 (13.1)
	daily hectic 'train/flight delays, missing a connecting train/flight', 'late arrival because of traffic jam/accident'	2 (8.0)	2 (10)	1 (4.2)	5 (7.2)

Supplementary Table S2: Statistical characteristics of scripts (script collection session)

			cBPD (N=25)			rBPD (N=20)			HC (N=24)		
	Neutral script	**Stress script**	**Neutral script**	**Stress script**	t value	**Neutral script**	**Stress script**	t value	**Neutral script**	**Stress script**	t value
	***F*-Test**	***F*-Test**	**M (SD)**	**M (SD)**		**M (SD)**	**M (SD)**		**M (SD)**	**M (SD)**	
	Group effect	***Group effect***									
	Post-Hoc-Test	**Post-Hoc-Test**									
	***p* < .05**	***p* < .05**									
DSS-4 Score [b]	$F_{2,66}$ = 10.14***	$F_{2,66}$ = 17.91***									
	cBPD -. rBPD	cBPD – rBPD	1.16	3.02	t_{24} = -4.90***	.11	1.31	t_{19} = -3.67**	.03	.18	t_{23} = -1.77
	1.047**	1.707**	(1.59)	(2.35)		(.24)	(1.58)		(.11)	(.46)	
	cBPD – HC	cBPD – HC									
	1.128***	2.842***									

	rBPD – HC, *ns* $F_{2,66}$ = 6.09* cBPD - rBPD, *ns* cBPD – HC, 1.456** rBPD – HC, *ns*	rBPD- HC, *ns* $F_{2,66}$ = 2.33, *ns*									
Tension Rating [b]			2.04 (1.95)	5.48 (1.66)	t_{24} = -7.96***	.95 (1.47)	5.30 (2.25)	t_{19} = -9.12***	.58 (.93)	4.33 (2.04)	t_{23} = -8.46***
Assessment of script: Please rate the story you told us concerning the following variables.											
perceived stress[d]	$F_{2,66}$ = 1.83, *ns*	$F_{2,66}$ = .05, *ns*	8.09 (7.95)	90.78 (6.72)	t_{24} = -44.83***	6.38 (5.91)	91.50 (8.60)	t_{19} = -33.07***	4.52 (5.27)	91.17 (7.79)	t_{23} = -39.56***
personal relevance[d]	$F_{2,66}$ = 1.36, *ns*	$F_{2,66}$ = .83, *ns*	5.10 (5.81)	66.42 (28.93)	t_{24} = -9.80***	11.04 (15.79)	74.60 (26.22)	[a]t_{18} = -9.27***	9.17 (14.19)	75.38 (24.59)	t_{23} = -10.30***
emotionally upsetting[d]	$F_{2,66}$ = 2.06, *ns*	$F_{2,66}$ = 1.50, *ns*	2.83 (2.48)	89.43 (14.26)	t_{24} = -30.89***	5.65 (6.67)	95.45 (6.87)	t_{19} = -40.82***	3.33 (4.94)	89.46 (15.43)	t_{23} = -25.00***

perceived valence[c]	$F_{2,66}$ = .36, *ns*	$F_{2,66}$ = 1.10, *ns*	4.12 (1.13)	8.52 (.71)	t_{24} = -15.89***	4.35 (.81)	8.60 (.99)	t_{19} = -13.14***	4.13 (1.03)	8.21 (1.10)	t_{23} = -11.82***
perceived arousal[c]	$F_{2,66}$ = 1.47, *ns*	$F_{2,66}$ = 1.30, *ns*	7.24 (1.42)	2.40 (1.73)	t_{24}= 10.85***	7.90 (1.07)	1.80 (1.06)	t_{19}= 16.85***	7.67 (1.37)	1.86 (1.23)	t_{23} = 16.27***
Duration of script (sec)											
	$F_{2,66}$ = 1.82, *ns*	$F_{2,66}$ = .88, *ns*	41.84 (11.03)	46.04 (11.19)	t_{24}= -2.77*	45.15 (12.63)	44.65 (13.69)	t_{19}= .31	38.54 (10.88)	41.63 (10.89)	t_{23} = -2.30*
					Question specifically asks for when it happened [e]						
	[f]H (2) = 4.74, *ns*	[f]H (2) = 2.04, *ns*	Mdn .00	Mdn 1.00	[g]Z = -3.44**	Mdn .00	Mdn 2.50	[g]Z = -3.04**	Mdn .00	Mdn 3.00	[g]Z = -3.50***

[a] n = 1 missing data.

Neutral scripts had to have a value of 20/100 or below on the VAS targeting stress, and stress script had to be rated as > 80/100. cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control; DSS-4 = Dissociation Tension Scale-4; M=mean; SD=standard deviation; N=Sample size. DSS-4[b] and tension[b] (0=not at all to 9=very strong); stress rating[d] and emotional arousal[d] by Visual Analogue Scale (100 mm-line with endpoints 'not at all' and 'very strong'); valence rating[c] and arousal rating[c] using the Self-Assessment Manikin (converted to valence/arousal: 1=completely pleasantness/high arousal to 9=completely unpleasantness/low arousal); Question specifically asks for when it happened[e] (0= less than a month ago, 1= from one to three months ago, 2= from three to six months ago, 3= from six to three years ago, 4= from three to five years ago, 5=longer than five years ag0), Mdn = median, Kruskal-Wallis-Test (H-Test)[f]. Wilcoxon signed-ranks test[g] ; uncorrected, 2-tailed, *ns* = not significant, **p* <.05; ***p* <.01; ****p* <.001.

Supplementary Table S3: vividness of imagery after listening to the stress script and neutral script (experimental sessions).

	cBPD (N=15)		rBPD (N=15)		HC (N=11)	
	Neutral script M (SD)	Stress script M (SD)	Neutral script M (SD)	Stress script M (SD)	Neutral script M (SD)	Stress script M (SD)
Vividness rating†	5.13 (2.20)	5.33 (1.76)	6.67 (1.50)	6.13 (1.36)	5.18 (2.27)	5.45 (1.51)

cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control; M = mean; SD = standard deviation; N = sample size. Vividness rating (0 = not at all -to 9 = as if it were real).

Supplement: Additional analyses with non-adjusted HPT data

For HPT, there was a non-significant main effect for condition ($F_{1,66}$ = 3.78, p = .056, η^2 = .05). This tendency was mainly associated with the cBPD participants, as revealed by a significant increase of HPT in the stress compared to the neutral condition only in this group (t_{24} = 1.95, p = .031, d = 0.37). For rBPD, there only was a trend in the same direction (t_{19} = 1.47, p = .079, d = 0.35), and in HC, no significant changes were observed (t_{23} = -0.97, p = .17, d = -0.20). We further found a significant effect of *group* ($F_{2,65}$ = 10.07, p < .001, η^2 = .23) with cBPD having significantly higher thresholds compared to HC (p_{Bonf} < .001). Remitted BPD did not significantly differ from cBPD (p_{Bonf} = .14) or HC (p_{Bonf} = .09). The interaction *condition * group* missed significance ($F_{2,66}$ = 2.30, p = .11, η^2 = .07). *M* and *SD* of HPT data for each group are given in Supplementary Table 4.

In order to further analyze the pattern of results for HPT, we performed *t*-tests in the groups separately comparing the HPT in the neutral and stress condition. For the neutral condition, we found HPT to be significantly higher for cBPD versus HC (t_{47} = 3.21, d = 0.92, p_{Bonf} = .007), while there was no significant difference between cBPD and rBPD (t_{43} = 1.60, d = 0.48, p_{Bonf} = .35) or between rBPD and HC (t_{42} = 1.26, d = 0.38, p_{Bonf} = .64). For the stress condition, however, we found significantly higher HPT for both cBPD compared to HC (t_{47} = 5.56, d = 1.59, p_{Bonf} < .001) and rBPD compared to HC (t_{42} = 2.66, d = 0.79, p_{Bonf} = .033) but not between cBPD and rBPD (t_{43} = 1.81, d = 0.54, p_{Bonf} = .23).

Supplementary Table S4: Mean and standard deviation of non-adjusted heat pain thresholds (HPT) data after listening to the stress script and neutral script (experimental sessions).

	cBPD (N = 25)		rBPD (N = 20)		HC (N = 24)	
	Neutral script M (SD)	**Stress script M (SD)**	**Neutral script M (SD)**	**Stress script M (SD)**	**Neutral script M (SD)**	**Stress script M (SD)**
non-adjusted HPT (°C)	48.02 (3.78)	49.41 (3.14)	46.19 (3.90)	47.41 (4.24)	44.86 (3.12)	44.47 (3.08)

cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control subjects; M = mean; SD = standard deviation; N = sample size; HPT = heat pain thresholds.

2.2 Neural correlates of affective auditory processing in current and remitted borderline personality disorder[2]

[2] Chung, B. Y., Bekrater-Bodmann, R., Andoh, J., Diesch, E., & Flor, H. (2021). Neural correlates of affective auditory processing in current and remitted borderline personality disorder. Submitted for publication.

Abstract

Background: Emotional hyperreactivity to negative affective stimuli (i.e., negativity bias) is a core feature of borderline personality disorder (BPD). However, there is still a lack of evidence related to behavioral and neural correlates of affective auditory processing in BPD. It also remains open whether this negativity bias exists after remission of the disorder.

Methods: Functional magnetic resonance imaging (fMRI) with sparse sampling was employed in twenty-one current BPD (cBPD) patients, 15 participants with remitted BPD (rBPD), and 22 healthy controls (HC). During fMRI scanning, an intermixed series of 36 positive, neutral, and negative sounds were randomly presented twice. After the fMRI scans, the sound series was rated on four dimensions: perceived valence, perceived arousal, how important the sound is for participant's life, and effect of perceived interpersonal interaction, which often are dominated by human vocalization elicit recognition of an emotional response.

Results: Both, cBPD and rBPD, compared to HC, showed a dampened response to emotionally positive but not negative sounds based on self-report measures. Negative auditory stimuli but not emotionally positive sounds showed a pronounced frontolimbic activation in cBPD. The rBPD group showed significantly enhanced amygdala activity during the processing of negative sounds compared to that of positive and neutral sounds, while HC showed no differences in amygdala activity during processing of emotionally valenced sounds.

Conclusion: A damping of the response to emotionally positive sounds was observed in both BPD groups. However, our results demonstrated mixed findings with regard to brain activations during processing of emotionally negative sounds in both BPD groups. The data on increased amygdala activity to negative sounds in rBPD underline the unstable state of BPD remission to the negative emotional stimuli in everyday life. Further research is needed to address these complex mechanisms.

Key words: Borderline personality disorder; Emotional reactivity; functional MRI; Amygdala; Negative bias

1 Introduction

Borderline personality disorder (BPD) is associated with a persistent pattern of instability, most remarkably in the areas of interpersonal functioning, behavior, emotion and self-concept. Among other symptoms, BPD is characterized by dysfunctional and volatile patterns of affective processing in response to social situations (American Psychiatric Association, 2013). Problems in affective processing may also relate to impulse disinhibition and related to self-destructive behavior (Carpenter & Trull, 2013; Linehan, 1993). According to the biosocial theory of BPD (Linehan, 1993), the etiology of BPD relies on the individual's biological vulnerabilities and their specific environmental influences such as maltreating caregivers or adverse childhood experiences. These negative experiences may lead to a negatively biased perception and deficits in processing of socio-emotional cues in everyday life (Daros et al., 2013; Mitchell et al., 2014). A number of studies have shown that persons with BPD in fact show increased sensitivity to emotional social stimuli such as facial stimuli. The results did not reveal a general deficit in emotion recognition, however, individuals with BPD evaluated neutral or ambiguous facial expressions more negatively and they showed difficulties in the detection of anger and disgust compared with healthy controls (HC) (Daros et al., 2013; Mitchell et al., 2014). Several studies also demonstrated heightened emotional reactivity to emotional stimuli in BPD patients compared with HC (Ebner-Priemer et al., 2007; Hazlett et al., 2007; Limberg et al., 2011; Lobbestael & Arntz, 2010). Earlier laboratory-based studies investigating emotional reactivity have mainly been performed by using the visual stimuli. In a study examining the relationship between BPD and responsivity and types of sensory input, the response to emotionally aversive stimuli across several sensory domains (e.g., auditory, gustatory, olfactory, tactile, and visual sensations) in individuals with BPD and HC was evaluated using self-report and interviews (Rosenthal et al., 2011). Participants with BPD compared to HC were most significantly differentially reactive in response to auditory stimuli (Rosenthal et al., 2011). Pfaltz et al. (2015) investigated emotional reactivity in the acoustic modality in BPD on the behavioral and psychophysiological level. Compared to HC patients with BPD showed reduced skin conductance responses to negative sounds and a lack of responding in the zygomaticus muscle as well as more negative valence ratings in response to positive acoustic stimuli than observed in HC. Functional magnetic resonance imaging (fMRI) has revealed the neurobiological mechanisms underlying the disturbed processing of emotional stimuli in BPD (see for reviews: Krause-Utz, Winter, et al., 2014; van Zutphen et al., 2015). These studies reported structural and functional

alteration in a frontolimbic network, characterized by increased activations of amygdala (e.g., Donegan et al., 2003; Herpertz, Dietrich, et al., 2001; Krause-Utz et al., 2012; Minzenberg et al., 2007; Niedtfeld et al., 2010; Schulze et al., 2011) and insula (e.g., Beblo et al., 2006; Krause-Utz et al., 2012; Niedtfeld et al., 2010; Ruocco et al., 2013; Schulze et al., 2011) in response to emotional visual stimuli (e.g., pictures, facial expressions) and decreased brain activation in anterior cingulate cortex (ACC), medial frontal cortex, orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (dlPFC) involved in inhibitory control processes (e.g., Kamphausen et al., 2013; Koenigsberg et al., 2009; Lang et al., 2012; Minzenberg et al., 2007; Schulze et al., 2011).

Studies on the longitudinal course of BPD showed that the majority of BPD patients develop symptomatic remission and the rate of remission increases by evidence-based psychosocial treatment (Gunderson, Herpertz, Skodol, Torgersen, & Zanarini, 2018; Gunderson et al., 2011; Zanarini et al., 2012). Moreover, a 16-year-prospective follow-up study by Zanarini et al. (2012) reported that the recurrence rates can be up to 36 % after a symptom remission of BPD (Zanarini et al., 2012). However, empirical evidence on the emotional processing in remitted BPD (rBPD) is still sparse. A study of event-related potentials based on electroencephalographic recordings used an emotion classification paradigm comprising blends of angry and happy faces. Here, rBPD patients did not differ significantly from HC in P100 amplitudes associated with early general visual information processing, while alterations were still present in later processing stages (P300) associated with attention and memory processing, as found in cBPD, indicating higher uncertainty during processing of social cues, although the negativity bias was reduced (Schneider et al., 2017). Individuals with rBPD did not show significant differences in the confidence in facial emotion recognition compared to HC, however, confidence in judging happiness in predominantly happy faces was negatively correlated with BPD symptom severity (Kleindienst et al., 2019). It is still unclear how psychobiological indicators of emotional reactivity to auditory stimuli is altered in rBPD.

In the present study, we used ratings and performed fMRI to assess neural correlates of affective auditory processing by including three emotionally valenced sound categories (positive, negative, and neutral). We hypothesized that current BPD patients but not HCs show increased activation in response to positive and negative sounds in amygdala, while we expected no significant differences in response to neutral sounds among three groups. In participants with rBPD, we assumed a normalization of brain activation in response to positive and negative sounds in the amygdala along with clinical improvement.

Further, we expected that valence ratings of positive emotional auditory stimuli are dampened and negative ratings of emotional auditory stimuli are more emphasized in both current and remitted BPD patients compared to HC.

2 Methods

2.1 Participants

We included 21 participants with cBPD (mean (*M)* age = 27.81 years; standard deviation (*SD*) = 7.58; range = 19 to 46 years), 15 participants with rBPD (*M* age = 29.47 years; *SD* = 5.08; range = 22 to 42 years), and 22 HC (*M* age = 26.77 years; *SD* = 6.56; range = 19 to 48 years). Four rBPD patients and 8 HC already participated in a previous study on pain perception (Chung, Hensel, Schmidinger, Bekrater-Bodmann, & Flor, 2020), however, all participants were naïve to the aims of the present study. All participants were female and there was no significant group difference in age ($F_{2,55}$ = 0.74, p = .48). Assessment of BPD was according to DSM-5 (American Psychiatric Association, 2013). Diagnoses were made by trained psychologists using the Structured Clinical Interview (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) and the International Personality Disorder Examination (IPDE; Loranger, 1999). Participants had to fulfil five or more IPDE criteria for inclusion in the cBPD group, whereas participants who had fulfilled full BPD diagnostic criteria once in their life and who fulfilled three or less criteria in the last five years prior to participation were considered rBPD (Gunderson et al., 2011; Zanarini et al., 2014). General exclusion criteria were a lifetime diagnosis of schizophrenia or bipolar-I-disorder, substance dependence within two years prior to study participation, current substance abuse, pregnancy, history of epilepsy, brain trauma or tumor, or other significant neurological or medical conditions, metal implants in the body, left-handedness, and claustrophobia. Psychotropic medication (except for selective serotonin reuptake inhibitors) had to be discontinued at least two weeks and pro re nata medication at least two days before and throughout study participation. Current and lifetime comorbid mental disorders are given in Table 1. The study was approved by the ethics review board of the Medical Faculty Mannheim, Heidelberg University, and adhered to the Declaration of Helsinki of 1975, as revised in 2008. All participants gave written informed consent before study participation.

Table 1 Comorbid mental disorders of the samples.

Comorbidities, n (%)	**cBPD n = 21**	**rBPD n = 15**	**HC n = 22**
Major depression (current)	5 (23.8 %)	0 (0)	0 (0)
Major depression (lifetime)	18 (85.7 %)	12 (80 %)	0 (0)
Anxiety disorders and phobias (current)	9 (42.9 %)	2 (13.3 %)	0 (0)
Anxiety disorders and phobias (lifetime)	11 (52.4%)	10 (66.67%)	0 (0)
Posttraumatic stress disorder (current)	6 (28.6 %)	0 (0)	0 (0)
Posttraumatic stress disorder (lifetime)	7 (33.3 %)	5 (33.3 %)	0 (0)
Other disorders* (current)	8 (38.10 %)	0 (0)	0 (0)
Other disorders* (lifetime)	12 (57.14%)	11 (73.3%)	0 (0)

cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control; n = number.

2.2 Stimuli

Thirty-six stimuli were selected from the *International Affective Digitized Sounds 2nd Edition* (IADS-2: Bradley & Lang, 2007). Twelve sounds were negative (e.g., vomit, attack, fight and car wreck[3]), 12 were neutral (e.g., rain, rooster, train and walking[4]) and 12 were positive (e.g., baby, laughing, applause and harp[5]). Their duration was 6 s, and they contained an emotional variety, based on the female norm sample valence ratings. Negative

* Eating Disorders (Anorexia Nervosa, Bulimia Nervosa, Binge eating disorder), adjustment disorder
[3] Negative stimuli: No 255, 275, 277, 278, 279, 284, 285, 286, 290, 292, 424, 600.
[4] Neutral stimuli: No 114, 120, 170, 204, 322, 368, 373, 425, 698, 701, 722, 720.
[5] Positive stimuli: No 110, 220, 226, 230, 311, 351, 353, 809, 810, 811, 815, 817.

sounds had to be below 3 in the mean normative valence rating by females, *M (SD)* = *1.87* (*.073*), range 1.36 - 1.76, those selected for the neutral sounds had to be between 4 and 6, *M (SD)* = *4.97* (*.046*), range 4.83 - 5.18 , those for the positive sounds had to be above 7, *M (SD)* = *7.49* (*.065*), range 7.46 - 8.13. Eleven German healthy volunteers participated in a pilot experiment planned for stimulus selection. To control for level of ambivalence and credibility as significant confounders (e.g., Viinikainen, Katsyri, & Sams, 2012), the selected stimuli were rated by German healthy female volunteers on a 9-point scale ranging from 1 (very uncertain) to 9 (very certain) on how certain the identifications were. The subjects showed no significant difference in certainty ratings for the three stimulus categories ($F_{2,35}$ = 3.10, p = .058), but the positive and negative sounds induced significantly more arousal compared to neutral sounds ($F_{2,35}$ = 9.70, p < .001), whereas positive and negative sounds did not significantly differ arousal (p = .094). In order to examine the extent of interpersonal involvement, such as interpersonal conflicts that might cause intense anger, distress or fears of rejection or abandonment in persons with BPD (Butler, Brown, Beck, & Grisham, 2002), we additionally asked about the intensity of social interaction on a 9-point scale ranging from 1 (very low) to 9 (very high). The intensity of social interactions was rated to be significantly different across the sound groups ($F_{2,35}$ = 7.11, p < .001). Across affective sound categories, positive sounds (M = 6.53, SD = 1.98, *standard errors (SE)* = .57) were given the highest intensity of social interaction ratings, followed by negative (M = 5.30, SD = 2.23, SE = .64), and neutral sounds (M = 3.27, SD = 2.23, SE = .64). The intensity of social interactions for the positive and negative sounds was rated significantly higher compared to neutral sounds (negative vs. neutral: t_{22} = 2.24, p = .04, d = .91; positive vs. neutral: t_{22} = -3.81, p = .001, d = 1.55), whereas positive and negative sounds did not significantly differ in the ratings of the intensity of social interactions (negative vs. positive: t_{22} = -1.44, p = .16).

2.3 MRI data acquisition

MR imaging was performed by a 3 T whole-body MR scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany). Due to the elevated baseline activation level produced by continuous scanner noise, there is a reduced dynamic range of auditory cortex BOLD responses to transient acoustic stimulation (Peelle, Eason, Schmitter, Schwarzbauer, & Davis, 2010; Schmitter et al., 2008). During the acquisition process of functional neuroimaging, acoustic noise is inevitably produced by the scanner whenever

the magnetic resonance signal is read out (Hall et al., 1999). In order to improve the processing of the auditory stimulation, we used a “sparse” sampling with a gradient-echo T2*-weighted echo-planar imaging (EPI: TR = 14900 ms, TE = 22 ms, flip angle = 90°, field of view (FOV) = 220 x 220 mm^2, matrix size = 64 x 64, slice thickness = 2.8 mm, number of slices 28 and number of functional volumes 101). The sparse imaging approach employs a clustered-volume acquisition sequence to reduce intravolume noise interference Hall et al. (1999) by decreasing the rate of bursts of scanner acoustic noise by an increased duration of the interscan interval (see Figure 1).

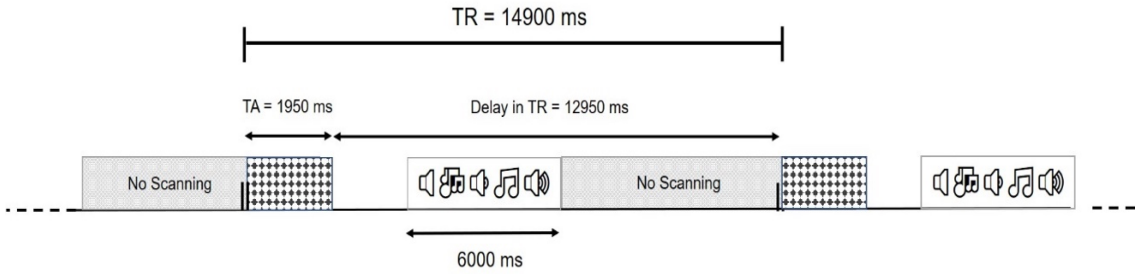

Figure 1. Design of the sparse sampling paradigm. The timeline is given in milliseconds (ms), TR (repetition time) = 14900 ms, TA (acquisition time) = 1950 ms, sound presentation = 6000 ms. Trial onsets were jittered over 2000 ms. Total 36 sound trials and 12 silence baseline trials were randomly presented twice and measured.

2.4 Experimental procedure

Before MR scanning, the state of dissociation was assessed by using the short version of the dissociation tension scale (DSS-4: C. Stiglmayr et al., 2009). Each participant was instructed to attend to various sounds that may induce emotions and to avoid moving as much as possible while in the scanner. During the fMRI measurement, each sound piece was presented stereophonically over headphones in a randomized counterbalanced order and separated by a fixed stimulus onset asynchrony of 14875 ms. The experimenter checked on the loudness of standardized sound volume before the start of the fMRI measurement. Participants were instructed not to move during the scan and to simply focus on the sound in an eyes-open state. In addition to 36 sounds (see “2.2. Stimuli” section), the

presentation sequence included 12 baseline periods during which the stimuli were replaced by 6 s of non-sound stimuli. All stimuli were presented twice in the scanner.

2.5 Post-scan rating of the auditory stimuli

Immediately after the fMRI-measurement, the participants completed the DSS-4 outside the scanner. Afterwards, participants were instructed to rate the thirty-six auditory stimuli for valence, arousal, and intensity of social interaction (see "2.2 Stimuli" section). All participants identified what they had listened to and the certainty of the identification for each sound was evaluated. To assess the level of emotional intensity that might manifest in contexts in which the stimulus triggers the problems or concerns of a person with BPD and might have a strong influence on emotional processing (Beck, Freeman, & Associates, 1990), we additionally evaluated the intensity of self-reference („How important is this sound for your life? ") on scale from 1 (not important) to 9 (very important). The rating of the stimuli was programmed in Presentation® (Neurobehavioral Systems, Berkeley, CA, USA). Each sound was presented only once in randomized order, and the ratings were obtained by pressing a spacebar. Then the participants completed the DSS-4 again.

2.6 Data analysis

fMRI data

Functional imaging data were analyzed using the FSL (version 6.0.0, **F**MRIB's (Analysis Group at the Oxford Centre for Functional MRI of the Brain) **S**oftware **L**ibrary) software package (Smith et al., 2004). The DICOM raw images from every participant were transferred to be converted to NIFTI format, and then processed with the FEAT 6.00 tool provided with the FSL package 6.0.0. Preprocessing of fMRI data included motion correction, high-pass temporal filtering (with a cut-off of 100s). Additional preprocessing steps included removal of non-brain structures from the echo planar imaging volumes using the Brain Extraction Tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET). The images were subsequently smoothed with a Gaussian kernel of full-width at half-maximum of 5 mm and motion-corrected. fMRI volumes were registered to the individual's structural scan and to the Montreal Neurological Institute (MNI-152) standard space images using FMRIB's Linear Image Registration Tool (MCFLIRT) (http://fsl.fmri.ox.ac.uk/fsl/fslwiki/FLIRT). The

activation analysis for each series was carried out using an optimized implementation of the general lineal model (GLM) in the fMRI Expert Analysis Tool (FEAT) version 6.0. To analyze activation patterns during listening to each of the sound categories, we defined four regressors (positive, neutral, negative sound valence and baseline (no sound)) for each subject and 12 contrasts were matched for each person: 1. Positive minus baseline (POS+), 2. baseline minus positive (POS-), 3. negative minus baseline (NEG+), 4. baseline minus negative (NEG-), 5. neutral minus baseline (NEU+), 6. baseline minus neutral (NEU-), 7. positive minus negative (POS-NEG), 8. positive minus neutral (POS-NEU), 9. negative minus neutral (NEG-NEU), 10. negative minus positive (NEG-POS), 11. neutral minus positive (NEU-POS), 12. neutral minus negative (NEU-NEG). The higher-level group analysis among three groups (cBPD, rBPD and HC) for each affective auditory stimulus category was performed using the FLAME method (FMRI's local analysis of mixed effects). Areas of significant activation were identified using a threshold of z=2.3 per voxel and a corrected family-wise error (FWE) cluster significance threshold at p = 0.05 (Worsley, 2001).

Based on our a priori hypotheses, we conducted a small volume correction in the following regions of interest (ROI: left amygdala and right amygdala). Both amygdala ROIs were defined in each hemisphere according to centromedial and laterobasal landmarks and modified volumes of the Juelich atlas in FSL. The Juelich coordinates of the amygdala ROIs were centered on x = +/- 22, y = -6, and z = -10. Mean BOLD activation within the ROI was calculated and extracted for each subject using FEAT and FSL's Feat-Query tool. The units of measurement for BOLD signal changes (BSC) were % activation (z-scores).

Further statistical analysis

Self-report data (valence, arousal, intensity of social interaction, and the magnitude of self-reference) were separately analyzed using separate 3 (factor *affective sound: positive, negative, neutral*) x 3 (factor *group: cBPD, rBPD, HC*) mixed-model ANOVAs. If the ANOVAs were significant, Bonferroni-corrected post hoc tests were computed for main effects and additional t-tests for dependent or independent measures were conducted for interactions. Greenhouse-Geisser corrections were applied whenever the assumption of homogeneity of variances was violated and corrected degrees of freedom are reported. For the amygdala ROI, we again used a mixed-model ANOVA by entering the factors *affective sound* and *group.* In addition, the main effect for affective sound was

decomposed for each group by performing paired sample *t*-tests. We report on test statistics and effect sizes for the ANOVAs separately. To test whether changes in amygdala activity during listening to affective sounds were related to changes in participants' behavioral ratings (i.e., valence, arousal, intensity of social interaction and self-reference), we performed Pearson correlations between BSC and rating responses for each sound valence category in separate groups. To estimate group-specific differences in net state dissociation scores, we subtracted the DSS-4 score after the fMRI-session from the DSS-4 score before the experiment (DSS-$4_{post\text{-}pre}$). All statistical analyses were performed using IBM SPSS v25 (IBM Corp., Armonk, NY).

3 Results

3.1 Behavioral data

Valence ratings

Means (*M*), standard errors (*SE*), and pairwise comparisons for group effects in valence (A) and arousal (B) ratings are visualized in Figure 2. For valence ratings (Figure 2(A)), we found a significant main effect for the factor *affective sound* ($F_{1.50,\ 82.61} = 349.84$, $p < 0.001$, $\eta^2 = .86$) and for the factor *group* ($F_{2,\ 55} = 11.22$, $p < 0.001$, $\eta^2 = .29$) as well as a significant interaction for *affective sound x group* ($F_{3.00,\ 82.61} = 3.47$, $p = 0.02$, $\eta^2 = .11$). All groups assigned the lowest rating to positive sounds (*M* = 3.52, *SD* = 1.21, *SE* = .16) followed by neutral (*M* = 4.46, *SD* = .92, *SE* = .12) and negative sounds (*M* = 7.13, *SD* = .89, *SE* = .12; negative vs. neutral: $t_{57} = 20.33$, $p < .001$, d = 2.67; positive vs. neutral: $t_{57} = -8.10$, $p < .001$, d = 1.61; negative vs. positive: $t_{57} = 20.15$, $p < .001$, d = 2.65). The least pleasant ratings for the positive sounds were found in cBPD, followed by rBPD, and HC. In post hoc Bonferroni-corrected tests, there was a significant difference between cBPD and HC ($t_{41} = 4.48$, $p < .001$, d = 1.37) and between rBPD and HC ($t_{35} = 3.20$, $p = .003$, d = 1.08), but not between cBPD and rBPD ($t_{34} = 1.15$, $p = .26$). In addition, the cBPD evaluated the neutral sounds as more unpleasant compared to rBPD and HC. In post hoc Bonferroni-corrected tests, there was a significant difference between cBPD and HC ($t_{41} = 3.60$, $p = .001$, d = 1.10) and cBPD and rBPD ($t_{34} = 3.50$, $p = .001$, d = 1.22), but not between rBPD and HC ($p = .88$). For the ratings of negative sounds, there were no significant group differences ($p = .14$).

Arousal ratings

For arousal ratings, we found a significant main effect of *affective sound* ($F_{2, 110}$ = 29.55, p < 0.001, η^2 = .35), but no significant effects for *group x affective sound* ($F_{4, 110}$ = 1.49, p = 0.12) or *Group* ($F_{2,55}$ = 2.10, p = 0.13). Across the affective sound categories, the negative sounds (M = 5.03, SD = 1.43, SE = .19) were given the highest arousal ratings, followed by positive (M = 4.66, SD = 1.76, SE = .23), and neutral sounds (M = 3.86, SD = 1.35, SE = .18; negative vs. neutral: t_{57} = 8.55, p < .001, d = 1.84; positive vs. neutral: t_{57} = -5.24, p < .001, d = 1.07.; negative vs. positive: t_{57} = 2.13, p = .04, d = .49). Figure 2(B) illustrates the differences in arousal ratings for the categories.

Ratings of the intensity of social interaction and self-reference

For the rating of the intensity of social interaction (Figure 2C)), there was a main effect of *affective sound* ($F_{2, 110}$ = 261.67, p < 0.001, η^2 = .83). Across affective sound categories, positive sounds (M = 4.85, SD = 1.37, SE = .18) were given the highest intensity of social interaction ratings, followed by negative (M = 4.00, SD = 1.23, SE = .16), and neutral sounds (M = 2.56, SD = .88, SE = .12; negative vs. neutral: t_{57} = 12.10, p < .001, d = 1.59; positive vs. neutral: t_{57} = 23.00, p < .001, d = 3.02; negative vs. positive: t_{57} = -11.81, p < .001, d =-1.55). However, there were no significant effects of group *x affective sound* ($F_{4, 110}$ = 1.26, p = 0.29) or *group* ($F_{2,55}$ = .21, p = 0.82).

For the ratings of the intensity of self-reference (Figure 2(D)), we found a significant effect for *group x affective sound* ($F_{3.31, 90.92}$ = 3.82, p = 0.01, η^2 = .12), but no significant main effects of *affective sound* ($F_{1.65, 90.92}$ = 1.08, p = .33) or *group* ($F_{2,55}$ = .13, p = .88). HC evaluated positive sounds as more important to them than negative and neutral sounds (positive vs. neutral: t_{21} = 3.20, p = .004, d = .68; negative vs. positive: t_{21} = -2.94, p = .008, d =-1.55; negative vs. neutral: t_{21} = -1.08, p = .29), whereas both current and remitted BPD groups did not differ in the intensity of self-reference ratings for positive (p = .17), neutral (p = .98) and negative sounds (p = .27). Post hoc tests did not become significant.

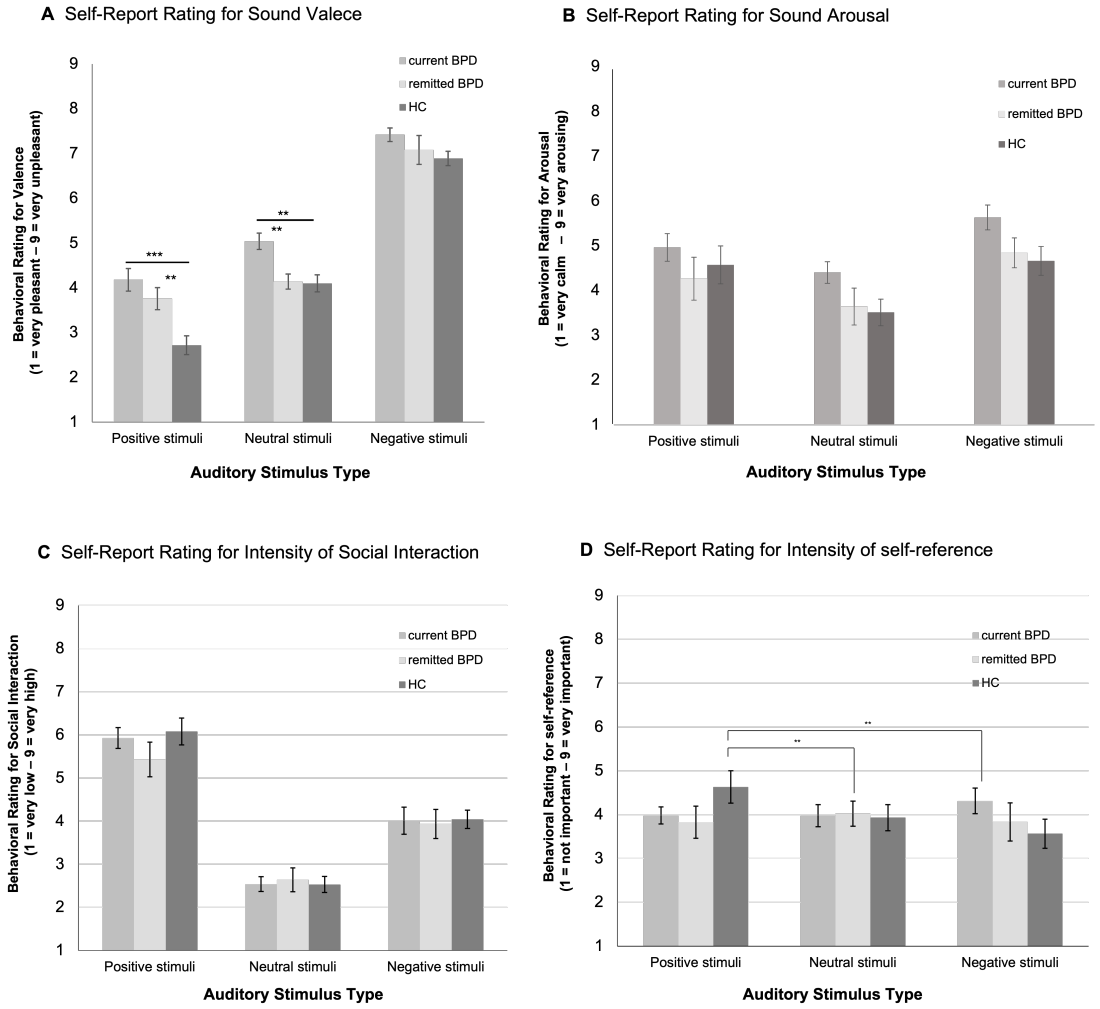

Figure 2. Self-report data (mean and standard errors of the means) for **(A)** emotional sound valence, **(B)** arousal, (**C)** intensity for social interaction, and **(D)** intensity for self-reference to the positive, neutral, and negative auditory stimuli. **p* < .05, ***p* < .01, ****p* < .001

3.2 Functional magnetic resonance imaging

Whole-Brain Activation during emotional sound processing

For sound valence, we found enhanced BOLD signals in the left and right superior temporal gyrus (BA 41, BA 22), the left cingulate gyrus (BA 24), the right cuneus (BA 23), the right middle occipital gyrus, the right lingual gyrus, transverse temporal gyrus (BA 41) across all three groups. With respect to between-group differences in the contrast NEG+, we found a significantly enhanced activation of the right inferior frontal gyrus (BA 45) and insular cortex (BA 13) in cBPD compared to HC. Furthermore, in rBPD compared to HC, there was significantly greater activity in the left amygdala and the right putamen (whole-brain, $p_{FWE} < 0.05$). For the NEG - NEU contrast, there was a significant group effect (Figure 3), showing a significant activation of amygdala (right amygdala: k = 575, Z = 3.52, $p_{FWE} < 0.01$) and frontal medial gyrus (BA 47: k = 419, Z = 3.42, $p_{FWE} < 0.05$) in rBPD compared to HC. We reported the highest Z-score and the corresponding MNI152 coordinates for that voxel within the region (see Table 3).

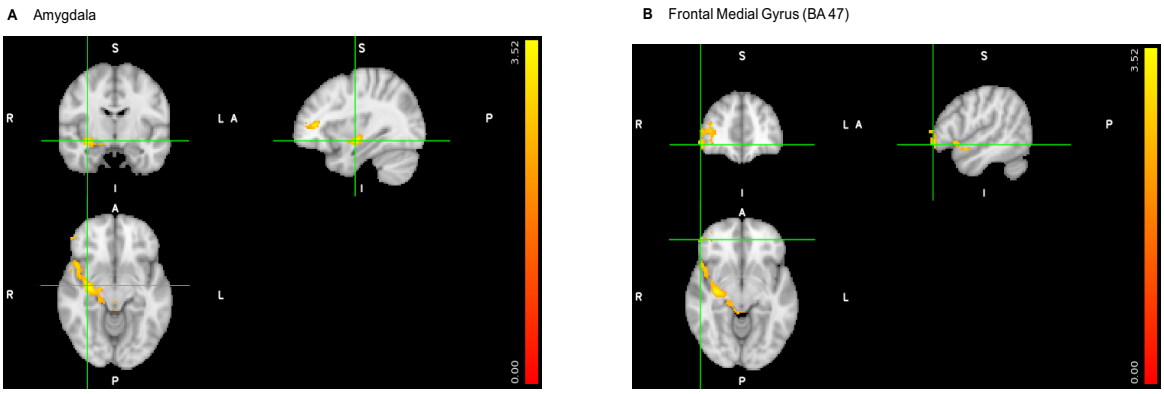

Figure 3. significant brain activation in response to subtracting the NEG - NEU contrast of **(A)** the right amygdala (k = 575, Z = 3.52, $p_{FWE} < 0.01$) and **(B)** the right frontal medial gyrus (BA 47: k = 419, Z = 3.42, $p_{FWE} < 0.05$) in rBPD versus HC.

Table 2 Significant clusters of neural activation during processing of emotional auditory stimuli

	Brain region: label Brodmann Area (BA)	Cluster size (k)	Peak voxel coordinates MNI152 (mm)			*Z* score	p_{FWE}
			X	*Y*	*Z*		
Single group comparisons							
POS+	cBPD						
	Superior Temporal Gyrus (BA 41), L	35629	-38	-32	14	8.32	< 0.001
	Transverse Temporal Gyrus, R		46	-24	10	7.72	
	Middle Occipital Gyrus, R	1228	24	-98	20	3.9	< 0.001
	Lingual Gyrus, R		4	-90	-4	3.84	
	rBPD						
	Superior Temporal Gyrus (BA 41), L	34864	-40	-32	14	7.1	< 0.001
	Superior Temporal Gyrus (BA 42), R		66	-20	8	6.93	
	HC						
	Superior Temporal Gyrus (BA 22), L	32308	-48	-18	4	8.05	< 0.001
	Superior Temporal Gyrus, R		46	-20	8	7.64	
	Lingual Gyrus, R	1031	2	-80	4	3.63	< 0.001
	Lingual Gyrus, R		14	-100	-2	3.46	
NEG+	cBPD						
	Superior Temporal Gyrus (BA 41), L	36065	-38	-32	14	8.29	< 0.001

	Superior Temporal Gyrus, R		60	-4	0	8.14	
	Cuneus (BA 23), R	2515	16	-72	14	4.51	< 0.001
	Lingual Gyrus, L		0	-82	-10	4.15	
	Cingulate Gyrus (BA 24), L	1379	-2	-10	42	4.7	< 0.001
	Cingulate Gyrus (BA 24), R		6	0	30	3.77	
	rBPC						
	Transverse Temporal Gyrus (BA 41), L	45020	-42	-30	12	7.53	< 0.001
	Superior Temporal Gyrus (BA 42), R		66	-20	8	7.20	
	HC						
	Superior Temporal Gyrus (BA 22), L	31765	-48	-16	4	8.08	< 0.001
	Superior Temporal Gyrus, L		-38	-32	14	7.58	
	Lingual Gyrus, R	556	2	-84	4	3.37	< 0.01
	Lingual Gyrus, L		-14	-86	8	3.22	
NEU+	cBPD						
	Transverse Temporal Gyrus, R	38819	46	-24	10	8.08	< 0.001
	Transverse Temporal Gyrus, L		-42	-30	12	8.02	
	Superior Temporal Gyrus, L		-38	-32	14	8.03	
	Cingulate Gyrus (BA 24), L	1190	-2	-10	42	4.41	< 0.001
	Cingulate Gyrus (BA24), L		-4	-4	36	3.84	
	rBPD						
	Transverse Temporal Gyrus (BA 41), L	30861	-44	-30	12	7.41	< 0.001

	Middle Temporal Gyrus, R		64	-30	4	7.04	
	HC						
	Superior Temporal Gyrus (BA 22), L	26936	-48	-16	4	8.05	< 0.001
	Superior Temporal Gyrus, R		46	-20	8	7.53	
	Cuneus (BA 17), L	744	-18	-78	14	3.33	< 0.01
	Cuneus, R		18	-72	8	3.27	
POS-NEG	cBPD						
	Middle Frontal Gyrus, L	936	-28	60	6	3.67	< 0.001
	Middle Frontal Gyrus, L		-30	52	-2	3.65	
	Posterior Cingulate, R	701	10	-54	14	4.12	< 0.01
	Posterior Cingulate, L		-8	-52	10	3.45	
	Superior Frontal Gyrus, R	493	20	52	20	3.75	< 0.05
	Superior Frontal Gyrus, R		30	58	20	3.73	
	HC						
	Middle Frontal Gyrus, R	653	40	48	18	3.78	< 0.01
	Middle Frontal Gyrus, R		38	50	10	3.43	
	Superior Frontal Gyrus, L	496	-36	56	12	3.78	< 0.05
	Superior Frontal Gyrus, L		-26	54	8	3.74	
NEG-POS	cBPD						
	Superior Temporal Gyrus, R	3723	60	-22	2	6.23	< 0.001
	Superior Temporal Gyrus, R		60	-36	8	5.92	

	Superior Temporal Gyrus, L	3397	-62	-18	-2	6.17	< 0.001
	Superior Temporal Gyrus, L		-60	-18	-2	5.82	
	rBPD						
	Superior Temporal Gyrus, L	4585	-64	-22	0	5.76	< 0.001
	Superior Temporal Gyrus, L		-58	-34	12	5.53	
	Superior Temporal Gyrus, R	3935	64	-28	4	5.37	< 0.001
	Superior Temporal Gyrus, R		60	-20	-4	5.16	
	HC						
	Superior Temporal Gyrus, L	4450	-62	-18	-2	5.59	< 0.001
	Superior Temporal Gyrus, L		-64	-20	6	5.57	
	Superior Temporal Gyrus, R	3085	64	-18	0	5.88	< 0.001
	Superior Temporal Gyrus, R		62	-26	6	5.37	
POS-NEU	cBPD						
	Medial Frontal Gyrus, R	507	8	56	10	3.71	< 0.05
	Superior Temporal Gyrus, R		20	54	18	3.70	
	Medial Frontal Gyrus, L	483	-14	46	20	3.25	< 0.05
	Superior Temporal Gyrus, L		-18	50	18	3.10	
NEG-NEU	cBPD						
	Superior Temporal Gyrus, R	3535	62	-18	6	6.52	< 0.001
	Superior Temporal Gyrus, R		60	-4	0	6.43	
	Superior Temporal Gyrus, L	3508	-62	-18	-2	6.16	< 0.001

	Superior Temporal Gyrus, L		-64	-12	4	6.11	
	rBPD						
	Superior Temporal Gyrus, L	13640	-64	-22	0	5.4	< 0.001
	Superior Temporal Gyrus, L		-64	-18	4	5.28	
	Cingulate Gyrus, L	1450	0	-16	42	3.86	< 0.001
	Precuneus, L		-4	-68	40	3.85	
	HC						
	Superior Temporal Gyrus, L	4264	-62	-20	0	6.48	< 0.001
	Superior Temporal Gyrus, L		-66	-12	4	6.45	
	Superior Temporal Gyrus, R	3176	68	-22	4	6.09	< 0.001
	Superior Temporal Gyrus, R		64	-22	6	6.05	
NEU-NEG	HC						
	Middle Frontal Gyrus, R	634	36	52	6	3.7	< 0.01
	Middel Frontal Gyrus, R		34	58	14	3.46	
Constrast analysis							
NEG+	cBPD < rBPD						
	Middle Frontal Gyrus, L	495	-38	62	2	4.22	< 0.05
	Middle Frontal Gyrus, L		-36	62	-2	3.92	
	cBPD > HC						
	Inferior Frontal Gyrus (BA 45), R	556	42	26	2	3.41	< 0.01
	Insular Cortex (BA13), R		36	22	-4	3.23	<0.05

	rBPD > HC						
	Left Amygdala	1784	-16	-2	-10	4.04	< 0.001
	Left Amygdala		-12	-4	-14	3.96	
	Right Putamen	1428	26	20	4	3.97	< 0.001
	Right Amygdala		28	6	-16	3.50	
NEU+	rBPD > HC						
	Anterior Cingulate, L	394	-10	32	22	4.50	0.049
	Cingulate Gyrus, L		-8	22	30	4.20	
NEG-NEU	rBPD > HC						
	Right Amygdala	575	34	-10	-10	3.52	< 0.01
	Right Amygdala		30	-14	-8	3.51	
	Frontal Medial Gyrus (BA 47), R	419	52	46	-8	3.42	< 0.05
	Middle Frontal Gyrus, R		38	42	8	3.08	

Brain regions in the whole-brain analysis showing significant within-subject differences and significant between-group differences in activation during processing emotional auditory stimuli. We reported the highest z-score and the corresponding MNI 152 coordinates for that voxel within the region. For the amygdala clusters, we report the cluster size within the amygdala. For all other clusters, we report the contiguous cluster size. cBPD = current borderline personality disorder; rBPD = remitted borderline personality disorder; HC = healthy control; L = left; R = right

ROI analysis

Figure 4 illustrates *M* and *SE* of the percent BSC (% BSC) in the left and right amygdala. In the left amygdala, ROI analysis revealed a significant main effect of *% BSC* for *sound valence* ($F_{2, 110} = 4.25$, $p = 0.017$, $\eta^2 = .072$; Figure 4 (A) and (C)). We performed dependent *t*-test analyses between % BSC during listening to valenced auditory stimuli separately for each group. Only patients with BPD in remission showed significantly increased activation in the left amygdala (POS+ vs. NEU+: $t(14) = 2.58$, $p = 0.02$, d = 0.67; NEG+ vs. NEU+: $t(14) = 4.02$, $p = 0.001$, d = 1.04). No significant main effect for *Group* ($p = .56$) or interaction effect for *Group x sound valence* were found for the left amygdala ($p = .20$). The % BSC data of the right amygdala also showed a significant main effect of % *BSC valence* ($F_{2, 110} = 9.42$, $p < 0.01$, $\eta^2 = .15$; Figure 4 (B) and (D)), but there was neither a significant main effect for *Group* ($p = .39$) nor interaction effect *Group x sound valence* for the right amygdala ($p = .5$). Likewise, rBPD patients, but not cBPD patients and HC, showed during listening to positively and negatively valenced auditory stimuli compared to neutral auditory stimuli significantly increased activations in the right amygdala (POS+ vs. NEU+: $t(14) = 2.21$, $p = 0.04$, d = 0.57; NEG+ vs. NEU+: $t(14) = 3.28$, $p = 0.005$, d = 0.85). We did not detect any significant correlations between % BSC in both amygdalae and behavioral ratings for any of the sound valence categories (all $p > .10$).

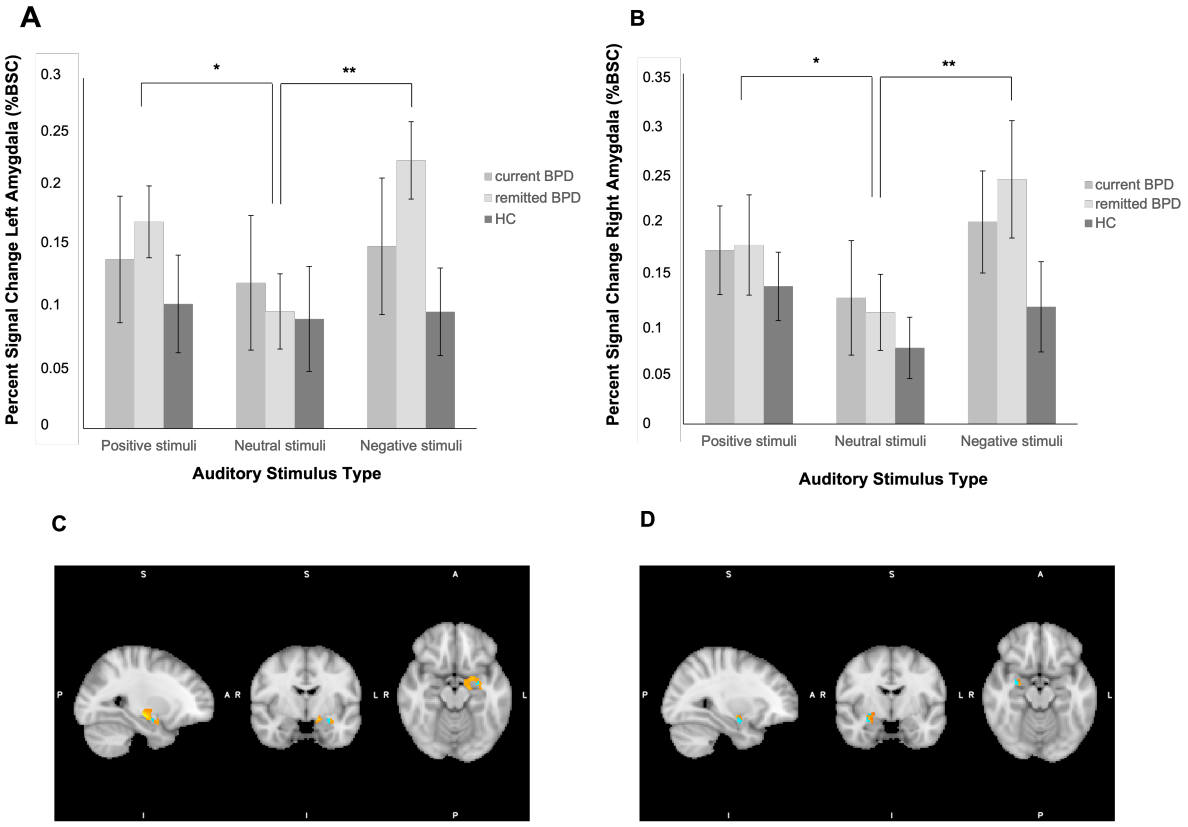

Figure 4. Percent BOLD signal change (% BSC) in **(A)** the left amygdala, and **(B)** the right amygdala (region of interest analysis) during listening to emotionally positive, neutral, and negative sounds in participants with current (cBPD) and remitted borderline personality disorder (rBPD), as well as healthy controls (mean and standard errors of the means).

(C) significant brain activation in response to subtracting the POS-NEU contrast (z = 2.89, depicted in blue), the NEG-NEU contrast (z = 3.02, depicted in orange) of the left amygdala in rBPD (x = -22, y = -6, z = -10), p_{FWE} <.05. **(D)** significant brain activation in response to subtracting the POS-NEU (z = 2.81, depicted in blue), the NEG-NEU (z = 3.13, depicted in orange) of the right amygdala in rBPD (x = 22, y = -6, z = -10), p_{FWE} <.05. *p < .05, **p < .01

4 Discussion

In this study we investigated the impact of the emotionally valenced auditory stimuli on self-report and brain activation in female patients with current and remitted BPD compared to female HC subjects. We examined how current and remitted BPD patients evaluate the positive, neutral, and negative sounds in valence, arousal, and intensity of social interaction, as well as the intensity of self-reference. Our data revealed that cBPD, compared to HC, assessed positive sounds as significantly less pleasant. This is in line with previous studies that found a more negative evaluation of positive emotional visual stimuli cBPD (Hazlett et al., 2012; Pfaltz et al., 2015; Thome et al., 2015). Furthermore, participants with rBPD were in between, and did not significantly differ from cBPD patients in valence ratings of positive sounds, but there was a significant difference between rBPD and HC in evaluating positive sounds. Our findings support the notion that people with rBPD are still prone to altered recognition of positive social stimuli (Kleindienst et al., 2019; Schneider et al., 2017). Current BPD also rated neutral sounds as significantly less pleasant/more unpleasant than rBPD and HC, whereas rBPD and HC did not significantly differ from each other. This is in line with a previous finding (Schneider et al., 2017), indicating that rBPD patients rate maximally ambiguous emotional face expressions more positively and recognize happy faces faster compared to cBPD. These results suggest a partial normalization in the evaluation of neutral stimuli in rBPD patients similar to those of the HC.

Our results also indicated significant BOLD activations across the groups in the left superior temporal gyrus (BA 41 in both BPD and BA 22 in HC), which is mainly implicated in auditory processing and social-emotional processing as well as in the function of language (Bigler et al., 2007; Mellem, Jasmin, Peng, & Martin, 2016). Similar brain activations in the primary and associative auditory cortices in the superior temporal gyrus have been shown in healthy volunteers for erotic versus neutral prosody (Ethofer et al., 2007) and to happy and sad music stimuli compared to neutral music stimuli (Mitterschiffthaler, Fu, Dalton, Andrew, & Williams, 2007). In addition to the activations in auditory cortex, individuals with cBPD, but neither rBPD nor HC, showed enhanced activation in the right cuneus (BA 23) and in the left cingulate gyrus (BA 24) during the processing of emotionally negative sounds. As a major part of the “anatomical limbic system”, the cingulate gyrus plays a role in the processing of emotion, sensory, motor, and cognitive information (Vogt, Finch, & Olson, 1992). Anterior cingulate cortex (ACC) consists of BA 24/25, and it is likely to be linked with the amygdala, while posterior

cingulate cortex (PCC) is comprised of BA 29/30/23/31, which might be involved in spatial orientation and memory processes (Vogt et al., 1992). In agreement with an activation-likelihood-estimation meta-analysis (Ruocco et al., 2013), demonstrating broad areas of activation in ACC and PCC, our findings of activation in the contrast NEG+ in BA 23/24 suggest that there might be an alteration in a diffuse network of neural structures related to negative emotion processing in individuals with cBPD. Interestingly, the right insula (BA 13) also showed significantly increased activity in the contrast NEG+ in cBPD patients compared to HC. The insula is regarded as a key region for the integration of external and internal emotional information to form a "global emotional moment" (Craig, 2009) and is involved in representing the degree of experienced negative emotion (Diekhof, Geier, Falkai, & Gruber, 2011). The insula has afferent and efferent connections to many regions including the medial and orbitofrontal cortices, anterior cingulate, and amygdala (Augustine, 1996) all of which showed significantly enhanced activations in BPD patients (Ruocco et al., 2013; Schulze et al., 2016). The insula has an efferent connection to the inferior frontal gyrus, which showed greater activation in cBPD patients in accordance with our findings (Augustine, 1996). In view of the large interconnections of the insula with neural regions involved in emotion representation and emotion regulation, this study results support the notion that the insula contributes to the modulation of negative emotions in patients with cBPD (Ruocco et al., 2013), and greater insula activation may suggest a heightened processing of negative sound in this disorder.

However, our results did not confirm the hypothesis of increased amygdala activity in cBPD compared to HC during processing of positive and negative sounds. A possible explanation for the lack of amygdala activation might be individual differences in dissociation, which is closely linked to neuropsychological functioning in BPD (for a review see: Krause-Utz & Elzinga, 2018). Based on the frontolimbic disconnection model of dissociation, it was postulated that the medial PFC inhibits the amygdala and diminishes emotional reactivity and the autonomic response (Sierra & Berrios, 1998; Sierra et al., 2002). Some studies indicated that BPD patients with low dissociation, compared to BPD patients with high dissociation and HC, display a heightened startle reaction (Ebner-Priemer et al., 2005) and higher activation in bilateral amygdala activity (Krause-Utz et al., 2018). In this study, the cBPD group compared to rBPD showed higher dissociation scores in the DSS-4, albeit not statistically significant (cBPD: M = .082, SD = .61, rBPD: M = .032, SD = .22*)*. The dampening effect of dissociation in

BPD should be taken into consideration. Interestingly, participants with rBPD, compared with the HC group, showed enhanced activity in the right amygdala during listening to negative sounds. For the comparison between rBPD and HC, the present study indicated that the amygdala was more strongly activated during the processing of negative emotional sounds. Patients with rBPD, compared with HC, showed greater activations of the left amygdala and the right putamen in the contrast NEG+, stronger activations of the right amygdala and the frontal medial gyrus (BA 47) in the contrast NEG-NEU. This pattern is consistent with the findings from previous studies, which reported an increased response in the amygdala during the processing of negative emotional facial stimuli (Donegan et al., 2003; Minzenberg et al., 2007) or negative emotional pictures (Hazlett et al., 2012; Herpertz, Dietrich, et al., 2001; Koenigsberg et al., 2009; Schulze et al., 2011) in BPD patients compared with HC. It appears likely that emotion processing might be still impaired in BPD after symptomatic remission. More research is needed to explain and understand the processing of emotional stimuli in this disorder beyond the acute stage.

Several limitations of this study should be taken into account. First, we investigated only female subjects in a relatively small sample with comorbidity in some patients. Some longitudinal studies estimated a life-time frequency of comorbidity between mood disorders and BPD at 96 % (Shah & Zanarini, 2018; Zanarini, Frankenburg, Dubo, et al., 1998) with rates of major depressive disorder up to 85% (Gunderson et al., 2018; Gunderson et al., 2008; McGlashan et al., 2000; Zanarini, Frankenburg, Dubo, et al., 1998). There is a link between major depressive disorder and abnormal emotional reactivity similar to altered emotional reactivity in BPD including potentiated reactivity to negatively valenced stimuli, attenuated reactivity to positively valenced stimuli, and emotion-context insensitivity (Hill, South, Egan, & Foti, 2019). In our sample, 23.8 % of the patients with cBPD had diagnoses with comorbid major depression (see Table 1). The results, therefore, should be interpreted carefully. Second, we failed to find a significant correlation between the BOLD activation of amygdala and valence ratings in BPD. In this study, behavioral ratings were carried out after fMRI scanning. This non-simultaneous comparison between brain activation and sound ratings could be related to the low correlations between self-report and neural measurements. Furthermore, the current study employed stimuli with social and non-social interaction contexts and found a significant difference among three categories of sound valence. However, it is unclear whether similar group differences would be obtained by means

of non-social interaction-related sounds. Future investigations should compare social and non-social interaction contexts simultaneously during fMRI scanning. Finally, our findings were based on a cross-sectional study. Prospective studies using a longitudinal study design are needed to provide more insights into the alterations in emotion processing over the course of BPD and after symptomatic remission.

5 Conclusion

Not only cBPD, but also rBPD patients showed a dampened response to positive affective sound by self-report measures. However, neural responses to emotional auditory stimuli in BPD seem to be rather complex. BPD patients displayed a pattern of frontolimbic activation during processing of emotionally negative sounds, but no significantly different activations during the processing of emotionally positive sounds were present. In addition, this study suggests that there still might be altered amygdala activation during processing of emotionally negative auditory stimuli in BPD after symptomatic remission. We believe that our results could be an important first step to clarify mechanisms of auditory emotional processing in rBPD. More research is necessary to clarify these complex mechanisms.

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3 GENERAL DISCUSSION

3.1 Main findings

The aim of this dissertation was to provide new insights into the characteristics of the neural and behavioral responses during affective and sensory processing in BPD and after remission from this disorder. The first study examined the relationship between stress-induced dissociation and altered pain sensitivity in patients with current and remitted BPD and HC. The second study investigated both BPD patient groups and HC to determine whether BPD show impaired evaluation and patterns of brain activation during listening to emotionally valenced sounds is impaired in BPD and whether altered patterns of activation in the amygdala in response to emotionally valenced sounds are normalized in participants with rBPD.

In the first study, we used audio recordings of autobiographical stressful scripts compared to neutral scripts as a control condition to manipulate affective states and to induce dissociation in both BPD groups. In line with previous literature (e.g. Bohus et al., 2000; Ludascher et al., 2010; Niedtfeld et al., 2010; Russ et al., 1992; C. Schmahl et al., 2010), our findings indicated that cBPD patients demonstrated decreased heat pain perception compared to HC. Participants with rBPD were in between, showing no significant differences from cBPD or HC in the neutral condition. However, in the stress condition, rBPD participants displayed significant pain hyposensitivity compared to HC, being perceptually similar to the cBPD group. This reaction was specific for the nociceptive domain, since there was no such pattern for warm perception thresholds. Our findings suggest that BPD patients appear to be still vulnerable even when the disorder is in remission. Interestingly, the stressful scripts of more than one-third of participants in each group included situations of interpersonal conflicts such as social rejection or abandonment, which are considered BPD-specific interpersonal dysfunctions. Consistent with this, remitted patients spontaneously reported interpersonal conflicts in particular (55% of all) as topic for the stressful scripts, suggesting that the social field is experienced as particularly problematic for these participants. A study examining the extent of rejection sensitivity in cBPD and rBPD patients showed that rejection sensitivity is a relevant characteristic not only in cBPD but also in rBPD patients, who clearly differ from HC in this respect (Bungert et al., 2015). This fits well with the finding that impairments in social functioning are still important after successful completion of BPD

treatments (Gunderson et al., 2011), and that vulnerability to social stressors in rBPD might be still associated with dysfunctional behavior.

In addition only the cBPD showed a significantly positive association between dissociation proneness and pain hyposensitivity. The results of several studies point to inconsistent findings about state and trait dissociation. For example, state dissociation has been shown to be closely associated with pain hyposensitivity (Bekrater-Bodmann et al., 2015; Ludäscher et al., 2007), but there is heterogenous evidence for trait dissociation (Bekrater-Bodmann et al., 2015; Defrin et al., 2019; Ludäscher et al., 2007; Ludascher et al., 2015). In our study, we suggest that the level of state dissociative responses adjusted for individual trait differences might better characterize this state. Previous findings and our own results highlighting the differences between cBPD and rBPD suggest that stress and dissociation contribute independently to BPD-specific pain hyposensitivity. Dissociation plays an important mediating role in the relationship between pain perception and non-suicidal self-injurious behavioral (NSSI) in cBPD (Ludascher et al., 2010). However, we found a different function of stress-responses compared to dissociation. In the remitted stage of the disorder, we found stress-associated hyposensitivity in rBPD, which cannot be completely explained by increased dissociation proneness. Individuals with BPD in the remitted stage report self-destructive impulses, albeit to a weaker extent than in cBPD, as a dysfunctional stress regulation strategy to cope with social stress (Willis et al., 2018). This interpretation and our own results regarding altered stress-related pain sensitivity in rBPD suggest that personal relationships might be a particular target for therapeutic aftercare in rBPD in order to prevent a backslide into BPD-associated behavior. While results of the first study indicate that dissociation may play a less important part in rBPD, increased stress levels due to dysfunctional cognitions, mood disorders and a history of adverse experiences may still contribute to altered pain perception, which in turn may reduce the inhibition threshold to engage in NSSI (Hooley et al., 2010; Levine, Aljabari, Dalrymple, & Zimmerman, 2020). However, only one out of 20 rBPD patients in the first study reported self-harming behavior in the last 12 months (compared to 100% of the cBPD patients), suggesting a noteworthy achievement of individuals with rBPD to manage adverse effects of the daily occurrence stressors. The identification of successful coping strategies could be of interest for future studies on therapeutic aftercare for BPD patients in the remitted stage of the disorder.

Evidence of BPD-associated abnormalities in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates between behavioral and physiological stress responses (Zimmerman & Choi-Kain, 2009), suggest that BPD patients show significant alterations in their physiological stress reactivity in terms of cortisol level, heart rate, and skin conductance level, which is notably distinct from patients with cluster C personality disorders (Aleknaviciute et al., 2016). It is unclear whether remission of BPD is associated with normalization of HPA axis activity, and indeed preliminary data suggest the opposite, as assessed by stress-modulated heart rate changes (Willis et al., 2018). These findings, together with the results of the present study, suggest that participants with rBPD might still show altered responses to stress, although we did not directly test HPA axis function. The results indicate comparable stress reactivity and stress-related pain hyposensitivity in rBPD as in cBPD (although weaker), highlighting the importance of a BPD diagnosis for the extended periods of time. The non-significant relationship between pain hyposensitivity and dissociation proneness in rBPD reported here, while showing a clear pain hyposensitization effect in stress, indicates that alterations in pain perception in rBPD might be based on different mechanisms than in cBPD, where we showed a medium-sized positive relationship. Future studies should validate the findings with physiological measurements.

The results of the first study provide new insight inti BPD for several reasons. First, the current study demonstrated that not only cBPD but also and rBPD patients show enhanced proneness to dissociation. Second, while this feature of dissociation proneness is significantly associated with pain hyposensitivity in cBPD under induced stress using a script-driven imagery approach, rBPD patients do not exhibit this association between dissociation proneness and hyposensitivity. This indicates that BPD-specific altered pain sensitivity is associated with trait dissociation proneness in the current stage of the disorder. Third, in rBPD patients, pain hyposensitivity is observed under stressful, but not neutral, conditions (although weaker in extent compared to cBPD), independent of dissociation proneness. These findings suggest differential mechanisms of pain perception in the clinical groups.

The second study focused on the evaluation as well as brain activation patterns of emotional auditory stimuli in individuals with current and remitted BPD compared to HC. Although BPD patients reported greater aversive reactivity to unpleasant auditory sensory stimuli compared to HC (Rosenthal et al., 2011), few studies have investigated emotional reactivity using auditory stimuli in patients with BPD (e.g. Pfaltz et al., 2015;

Rosenthal et al., 2016), and no imaging study has examined emotion processing with auditory stimuli in sample with BPD. We hypothesized that BPD patients would evaluate the sounds as more arousing and more negatively valenced and would perceive a higher intensity of social interaction and higher intensity of self-reference in the sounds than HC. We found that cBPD patients tended to rate emotionally neutral sounds as significantly less pleasant/more unpleasant than rBPD and HC, while rBPD and HC did not significantly differ from each other. This is consistent with previous results indicating that rBPD patients still show impaired recognition patterns for emotionally positive social stimuli such as happy facial expressions, but not for neutral emotional stimuli (Kleindienst et al., 2019; Schneider et al., 2017). However, we found no significant differences in other behavioral ratings. There was only a tendency for patients with cBPD compared to rBPD and HC to rate negative sounds as more important to their lives than other sounds compared to rBPD and HC, while HC compared to both BPD groups viewed positive sounds as more important for their lives than negative and neutral sounds.

At the neural level, we expected that cBPD patients would show increased activation in response to positively and negatively valenced sounds in amygdala compared to HC, while there would be no differences in response to emotionally neutral valenced sounds between current and remitted BPD and the HC groups. In individuals with rBPD, we expected a normalization of the amygdala activation in response to positive and negative emotional auditory stimuli compared to HC. We observed that individuals with cBPD, but neither rBPD nor HC, showed increased activations in the right cuneus (BA 23) and the left cingulate gyrus (BA 24) during processing of negative emotional sounds (NEG+). In addition, the right insula (BA 13) was more activated in cBPD patients compared to HC. These results seem to be consistent with the theory that BPD patients show hyperarousal in response to negatively valenced emotional stimuli, which could be at least partly due to increased activity in the insular cortex (Ruocco et al., 2013). This hyperarousal may affect attentional uncoupling from emotionally salient stimuli via efferent projections from the insula to anterior brain regions (such as ACC, DLPFC), which show significantly reduced functional activation in BPD (Ruocco et al., 2013). Patients with BPD may have a reduced ability to modulate the intensity of perceived negative emotions, possibly due to aberrant reciprocal connections between the insula and the PFC (Ruocco et al., 2013). However, we did not find heightened amygdala activation in cBPD compared to HC while they listened to positively or

negatively valenced auditory stimuli. Interestingly, participants with rBPD compared to the HC group showed increased activity in the right amygdala during listening to negatively valenced sounds. When comparing rBPD and HC, the ROIs in the right and left amygdala and whole-brain analysis showed that the amygdala in the rBPD group was more strongly activated when they listened to negatively valenced auditory stimuli (e.g. increased activity in the left amygdala and right putamen during processing of emotionally negative sounds (NEG+) and heightened activity in the right amygdala and frontal medial gyrus (BA47) in contrast to NEG-NEU). The increased amygdala response could be related to disturbed emotion processing in rBPD, which has been frequently reported in BPD (for reviews, see: Bertsch, Hillmann, & Herpertz, 2018; Domes et al., 2009; Schulze et al., 2016), even after symptomatic remission. Further studies are required to clarify the processing of emotional stimuli in this disorder beyond the acute stage.

The lack of a significantly increased amygdala response in cBPD compared to HC while they listened to positively and negatively valenced auditory stimuli might be related to individual differences in dissociation that have often been characterized in BPD (Krause-Utz & Elzinga, 2018). Dissociation has been related to reduced medial PFC activity together with abnormally increased amygdala activity (Sierra et al., 2002). The group of cBPD patients generally tends to have higher self-reported dissociative states (DSS4 scores) compared to rBPD patients and HC. Consequently, the attenuating effect of dissociation in BPD should be taken into consideration. Interestingly, participants with rBPD in this study showed increased activity in the right amygdala while listening to negatively valenced sounds compared with the HC group. In previous studies, BPD patients with low dissociation have been shown to have increased startle response (Ebner-Priemer et al., 2005) and higher bilateral amygdala activity compared to BPD patients with high dissociation and HC (Krause-Utz et al., 2018). This suggests that BPD patients may achieve symptom remission such as decreased dissociation, but may still display altered patterns of emotional processing.

Overall, the main findings from studies 1 and 2 suggest that altered affective-sensory interaction plays a key role in the maintenance (and perhaps also etiology) of BPD. Patients with cBPD showed pain hyposensitivity in a stress situation (study 1) and a negativity bias of emotionally valenced auditory stimuli (study 2). Impaired sensory processing in cBPD seems to be related to a trait dissociation proneness in the current stage of the disorder. However, in rBPD patients, pain hyposensitivity is present

independent of dissociation proneness in a stressful but not in a neutral condition (study 1). Similar to cBPD patients, individuals with rBPD rated positively valenced auditory stimuli as less pleasant (study 2). Only patients with cBPD exhibited altered patterns of emotional reactivity to negatively valenced auditory stimuli in frontolimbic regions such as the left cingulate gyrus and the right insula. Furthermore, we observed increased amygdala activation during the processing of negatively valenced auditory stimuli in BPD after symptomatic remission.

3.2 Limitations

Several limitations associated with both studies should be noted. In the first study, participants were able to predict the content to some extent, as only two scripts (stressful versus neutral) served to induce dissociation in a randomized order. This might have had an influence on the induction of dissociation, resulting in DSS-4 scores being rather low (about 1.2 points below the mean of sum score) compared to other studies (Bichescu-Burian et al., 2017; Krause-Utz et al., 2018; Ludäscher et al., 2010, with converted values of 1.5 and higher). The deliberate exclusion of traumatic events also could also have contributed to the relatively low scores in the first study, while the ecological validity of findings was increased by the use of non-traumatic scripts, which indicate stress responses of daily life rather than responses in life-threatening situations. We used a ceiling value of heat pain thresholds (HPT) for participants who reached the safety limit of the thermode (i.e. 52 °C) and this manner might have resulted in a bias in our data. The heating rate of 1.2°C/s might also not have been optimal in this context. Slower heating rates induce temporal summation resulting in increased pain perception and correspondingly lower pain thresholds (e.g., Eide, 2000), which could have been advantageous in this of pathologically enhanced HPT. Further, we did not assess peripheral physiological measures of responding to stress such as skin conductance, heart rate or startle responses. Therefore, we can only indirectly conclude that dissociation proneness, as defined in the study may be a consequence of stress reactivity.

In the second study, we could not provide a sex-specific analysis of the data because we only included female subjects in a relatively small sample size. Further, it should be noted that 23.8 % of cBPD patients have been diagnosed with comorbid major depression, which could have an impact on abnormal emotional reactivity in cBPD.

There were some aspects that could be improved in the experimental approach. We performed a not-simultaneous comparison between brain activation and sound rating; the behavioral assessment was carried out outside the fMRI scanner after the scan. Furthermore, we used stimuli with social and non-social interaction content. However, it is unclear whether group differences would be obtained by means of non-social interaction contained sounds. The findings therefore should be considered with some caution.

3.3 Outlook

The results of these studies point to several important mechanisms of dysfunctional sensory-affective processing that function as putative risk factors for emotion dysregulation. First, we found that persons with BPD show increased proneness to dissociation in the current and remitted stage of this disorder. Second, this characteristic is significantly associated with pain processing such as pain hyposensitivity in cBPD in the induced stress situation, whereas this link cannot be confirmed in individuals with rBPD. Comparing pain sensitivity in the stress condition with that in the neutral condition, rBPD patients still show decreased pain sensitivity compared to HC. Third, we could demonstrate impaired emotional reactivity to positively valenced auditory stimuli in current and remitted BPD. We found that activity in frontolimbic areas (e.g. left cingulate gyrus, right insula) was increased during processing of negatively valenced sounds in cBPD compared to HC. Furthermore, we observed increased amygdala activation during listening to negatively valenced sounds only in rBPD, but not in cBPD, compared to HC, which might be related to a dissociative state in cBPD and contribute to the understanding of emotional reactivity during the course of BPD.

The current findings also indicate that further research is required to elucidate the mechanisms of sensory-affective interaction involved in remission of BPD and its relevance to therapeutic rationales after symptom remission. Although pain insensitivity is a prominent feature of BPD, the disorder is further characterized by a complex pattern of maladaptive behaviors, including impairments in the sense of self, interpersonal functioning, negative affectivity, and disinhibition (American Psychiatric Association, 2013) and it is not clear how they aggravate or re-emerge under everyday social stress. It should be noted that due to the cross-sectional design, it is almost impossible to

account for variables that might be associated with cBPD or rBPD. Present data on mental disorders over the life course suggest that this number is higher for current BPD than for remitted BPD. This suggests that participants who remitted from the disorder might have been less psychologically burdened in general. In addition, long-term studies reported therapeutic optimism in terms of recovery and symptomatic remission. A recent systematic review of studies from 1990 to 2017, which included naturalistic and post-treatment methods, found a remission rate of 50-70 % in 873 participants from nine countries who were followed for between 5 and 15 years (Álvarez-Tomás, Ruiz, Guilera, & Bados, 2019). However, despite the therapeutically optimistic prognosis, it has been long known that impaired recovery from BPD is associated with negative psychosocial function such as vocational impairment and/or physical health problems related to unhealthy lifestyle patterns (e.g. heavy smoking, lack of regular exercise), whereas acute symptoms (e.g. self-mutilation) decline more rapidly and recur less frequently than temperamental symptoms (e.g. chronic depressed affect) (Soloff & Chiappetta, 2020; Temes & Zanarini, 2018). Prospective studies should implement longitudinal designs in which stress reactivity and emotional processing of aversive events and associated BPD-symptoms can be evaluated over an extended period of time into the remission states.

The results of study 1 showed enhanced dissociation proneness not only in cBPD but also rBPD, and the differences between cBPD and rBPD suggest that stress and dissociation may independently lead to BPD-specific pain hyposensitivity. In addition, low dissociation could potentially be associated with increased amygdala activation to negatively valenced auditory stimuli in rBPD, whereas cBPD patients with high dissociation do not show increased amygdala activation (study 2). This neural reactivity to negative emotion in cBPD might lead to subsequent alterations in other sensory perceptions (like in pain perception of study 1) and/or altered body ownership sensation (Bekrater-Bodmann et al., 2016; Löffler, Kleindienst, Cackowski, Schmidinger, & Bekrater-Bodmann, 2020), which in turn could result in dysfunctional behaviors such as self-injurious behaviors. Interestingly, we did not find any significant group differences in brain activations during the processing of positively valenced sounds, however, cBPD and rBPD patients rated them as significantly less pleasant compared to HC. All in all, these results shed light on the volatile state of BPD remission, although rBPD patients may have achieved symptom improvement. Future research should further investigate these complex processes which point to inconsistencies in the processing of emotional

stimuli. In addition, the central and peripheral physiological correlates of BPD-specific sensory reactivity like pain hyposensitivity and negativity bias to social cues and the potential underlying mechanisms of this disorder in the current stage and after remission need to be investigated.

In conclusion, gaining insights into mechanisms centrally involved in BPD also has implications for how the disorder is treated. Disturbances of emotion processing and alterations in sensory processing characterize BPD and these will continue to serve as putative mechanisms that further our understanding of the disorder. Deeper understanding of underlying processes is needed to draw explicit conclusions and designing effective therapeutic interventions. Despite that, this thesis provides several important starting points for advanced development of psychotherapeutic interventions, while pointing to future directions for extended research that will hopefully help explain BPD patients' struggles with stress and emotion reactivity in their everyday lives. This in turn could help to sustainably improve patients' psychosocial functioning in the future.

4 SUMMARY

Borderline personality disorder (BPD) is a persistent, severe and complex mental disorder characterized by an interplay between disturbed emotional processing and an altered perception of the body that include sensory deficits, such as reduced pain perception, which are related to dissociation and self-injurious behavior. However, it is still unclear if these alterations, which occur primarily in aversive affective situations, are a core variable or some type of coping behavior related to the disorder. Emotional processing may play an important role in the social-cognitive functions of BPD for example, in evaluating emotional stimuli, which could lead to impairment in their interpersonal relationships. The investigation of the psychopathological and neurobiological features of BPD after symptomatic remission, for example, in sensory perception related to the affective states might help to gain insight into the processes in the current and remitted phase of BPD.

The present thesis focuses on the characterization of the altered affective-sensory processing and potential explanations of these dysfunctions, considering BPD-specific symptomatic aspects such as dissociation and investigating of the neural correlates of affective-sensory interaction in individuals with current and remitted BPD compared to healthy subjects.

In the first study, we examined the relationship between stress-induced dissociation and altered heat pain sensitivity using personalized stressful and neutral scripts in patients with current and remitted BPD as well as healthy controls. In the second study, we investigated both BPD patient groups and healthy controls to determine whether a pattern of brain activation during listening to affective auditory stimuli is altered in both BPD groups compared to healthy controls, and whether altered activation patterns in the amygdala in response to emotionally valenced sounds are normalized in participants with remitted BPD. The results of the first study demonstrate that current BPD patients compared to healthy controls display significantly increased dissociation and heat pain thresholds in the neutral situation, while individuals with remitted BPD were in-between. After listening to the stress script, both clinical samples showed enhanced dissociation scores. Participants with current BPD exhibited pain hyposensitivity with significantly higher heat pain thresholds, while remitted BPD only displayed a trend in the same direction. Both BPD groups showed significant heat pain hyposensitivity in the stress condition compared to the healthy controls, but did not significantly differ

from each other. However, in the stress compared to the neutral condition, remitted BPD participants showed pain hyposensitivity compared to healthy controls. These findings suggest different mechanisms involved in pain hyposensitivity and current and remitted BPD.

In the second study, both current and remitted BPD patients compared to healthy controls rated positively valenced auditory stimuli as significantly less pleasant. We found increased activation patterns of frontolimbic activation during processing of negatively valenced but not positively valenced auditory stimuli in current BPD: current BPD patients showed increased activations in the right cuneus (BA23) and left cingulate gyrus (BA24). Compared to healthy controls, current BPD patients showed greater activations in the right insula (BA13). Regarding amygdala activations, only remitted BPD patients exhibited significantly different amygdala activity during processing of negatively and positively valenced sounds compared to neutrally valenced sounds.

The two studies comprising this thesis provide evidence for processing of sensory-affective interaction in various sensory modalities, more specifically dissociation proneness and pain hyposensitivity as well as disturbed emotional reactivity during the processing of auditory stimuli (such as negativity bias). This altered processing of sensory-affective interaction could be characterized in BPD and these will continue to serve as putative mechanisms that further our understanding of the disorder. Furthermore, altered neural activity with increased amygdalar activation during the processing of negatively valenced sounds in BPD patients after remission could explain the unstable state of BPD remission. Prospective studies are required to clarify this mechanism. The clinical value of these findings, as well as their relevance for therapeutic considerations in the aftercare of BPD, needs to be further evaluated in the future.

5 ZUSAMMENFASSUNG

Die Borderline-Persönlichkeitsstörung (BPS) ist eine anhaltende gravierende psychische Störung, die durch ein Zusammenspiel zwischen einer gestörten emotionalen Verarbeitung und einer veränderten Körperwahrnehmung gekennzeichnet ist, zu der auch sensorische Defizite wie eine verminderte Schmerzwahrnehmung gehören, welche wieder mit Dissoziation und selbstverletzendem Verhalten in Zusammenhang stehen. Es ist jedoch noch unklar, ob diese sensorischen Veränderungen, die insbesondere in aversiven affektiven Situationen auftreten, eine Kernvariable oder eine Art von Bewältigungsverhalten im Zusammenhang mit der Störung sind. Die emotionale Verarbeitung könnte eine wichtige Rolle bei den sozial-kognitiven Funktionen der BPS spielen, z. B. könnte die bestimmte Bewertung emotionaler Reize zu einer Beeinträchtigung von zwischenmenschlichen Beziehungen führen. Die Untersuchung der psychopathologischen und neurobiologischen Merkmale der BPS nach der symptomatischen Remission, z. B. der sensorischen Wahrnehmung im Zusammenhang mit den affektiven Zuständen, könnte dazu beitragen, Erkenntnisse über die Prozesse in der aktuellen und remittierten Phase der BPS zu gewinnen.

Diese Dissertationsarbeit konzentriert sich auf die Charakterisierung der veränderten affektiv-sensorischen Verarbeitung und die potenzielle Erklärung dieser Störungen, wobei BPS-spezifische Symptome wie Dissoziation berücksichtigt und die neuronalen Korrelate der affektiv-sensorischen Interaktion bei Patientinnen mit akuter und remittierter BPS im Vergleich zu gesunden Probandinnen untersucht werden. In der ersten Studie untersuchten wir den Zusammenhang zwischen stressinduzierter Dissoziation und veränderter Hitzeschmerzempfindlichkeit unter Verwendung von personalisierten Stress- und Neutralskripten bei Patientinnen mit akuter und remittierter BPS sowie bei gesunden Probandinnen. In der zweiten Studie untersuchten wir beide BPS-Patientengruppen und gesunde Probandinnen, um festzustellen, ob die Bewertung und ein Muster der Hirnaktivierung beim Hören affektiver Geräusche in beiden BPS-Gruppen im Vergleich zu gesunden Probandinnen verändert sind und ob veränderte Aktivierungsmuster in der Amygdala als Reaktion auf Geräusche mit emotionaler Valenz bei remittierten BPS-Patientinnen in ähnlicher Weise wie bei gesunden Probandinnen normalisiert sind. Die Ergebnisse der ersten Studie zeigten, dass akute BPS-Patientinnen im Vergleich zu gesunden Probandinnen signifikant erhöhte Dissoziations- und Hitzeschmerzschwellen in der neutralen Situation aufwiesen, während remittierte BPS-

Patientinnen dazwischen lagen. Nach Hören des Stress-Skripts wiesen beide (akute und remittierte) BPS-Gruppen erhöhte Dissoziationswerte auf. Patientinnen mit akuter BPS zeigten eine Schmerzhyposensitivität mit signifikant höheren Hitzeschmerzschwellen, während die remittierte BPS-Gruppe nur einen Trend in dieselbe Richtung aufwies. Beide BPS-Gruppen hatten eine signifikante Hitzeschmerz-Hyposensitivität in der Stressbedingung im Vergleich zu gesunden Probandinnen, unterschieden sich aber nicht voneinander. Im Vergleich zu gesunden Probandinnen zeigten remittierte BPS-Patientinnen jedoch eine Schmerzhyposensitivität in der Stressbedingung im Vergleich zur neutralen Bedingung, wenn auch in geringerem Ausmaß als bei akuten BPS-Patientinnen. Diese Befunde deuten auf gestörte Mechanismen der Schmerzverarbeitung bei BPS und deren Remission hin. In der zweiten Studie bewerteten sowohl akute als auch remittierte BPS-Patientinnen im Vergleich zu gesunden Probandinnen Geräusche mit positiver Valenz anhand von Selbsteinschätzungen als deutlich weniger angenehm. Wir fanden veränderte Muster der frontolimbischen Aktivierung während der Verarbeitung von Geräuschen mit negativer Valenz aber nicht positiver Valenz bei akuter BPS: akute BPD-Patientinnen zeigten erhöhte Aktivierungen im rechten Cuneus (BA23) und linken Gyrus cinguli (BA24). Im Vergleich zu gesunden Probandinnen zeigten akute BPS-Patientinnen größere Aktivierungen in der rechten Insula (BA13). Was die Amygdala-Aktivierungen betrifft, so zeigten nur remittierte BPS-Patientinnen eine signifikant erhöhte Amygdala-Aktivität während der Verarbeitung von Geräuschen mit negativer Valenz im Vergleich zu Geräuschen mit positiver und neutraler Valenz, während bei akuter BPS-Gruppe keine signifikante Amygdala-Aktivierung beobachtet wurde. Die beiden Studien, die diese Dissertationsarbeit umfassen, liefern Hinweise für die gestörte Verarbeitung sensorisch-affektiver Interaktionen in verschiedenen sensorischen Modalitäten, insbesondere Dissoziationsneigung und Schmerzhyposensibilität sowie gestörte emotionale Reaktivität bei der Verarbeitung auditiver Reize (wie Negativitätsbias). Diese Veränderung in der Verarbeitung sensorisch-affektiver Interaktionen könnte bei der BPS charakterisiert werden und weiterhin als ein möglicher Wirkmechanismus dienen, der unser Verständnis der Störung fördert. Darüber hinaus könnte eine veränderte neuronale Aktivität mit erhöhter amygdalarer Aktivierung während der Verarbeitung negativ bewerteter Geräusche bei remittierten BPS-Patientinnen den instabilen Zustand der BPS-Remission mit bedingen. Es sind prospektive Studien erforderlich, um diesen Mechanismus weiter zu klären. Der

klinische Wert dieser Ergebnisse sowie ihre Relevanz für therapeutische Überlegungen in der Nachsorge von BPS müssen in Zukunft weiter untersucht werden.

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7 PUBLICATIONS

Chung, B. Y., Hensel, S., Schmidinger, I., Bekrater-Bodmann, R.*, & Flor, H.* (2020). Dissociation proneness and pain hyposensitivity in current and remitted borderline personality disorder. *Eur J Pain,* 24(7), 1257–1268. https://doi.org/10.1002/ejp.1567

Bekrater-Bodmann R, **Chung BY**, Foell J, Gescher D, Bohus M, Flor H (2016). Body plasticity in borderline personality disorder: A link to dissociation. *Comprehensive Psychiatry,* Volume 69, 36-44. https://doi.org/10.1016/j.comppsych.2016.05.002

Bekrater-Bodmann R, **Chung BY**, Richter I, Wicking M, Foell J, Mancke F, Schmahl C, Flor H (2015). Deficits in pain perception in borderline personality disorder: results from the thermal grill illusion. *Pain,* 156(10), 2084-2092. https://doi.org/10.1097/j.pain.0000000000000275

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