Disconnected self: influence of dissociation on emotional distractibility in Borderline Personality Disorder: a neuroimaging approach

Krause, A.D.

Disconnected Self

Influence of Dissociation on Emotional Distractibility in Borderline Personality Disorder: A Neuroimaging Approach

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Seltsam im Nebel zu wandern!
Einsam ist jeder Busch und Stein,
Kein Baum sieht den anderen,
Jeder ist allein.
Voll von Freunden war mir die Welt,
Als noch mein Leben licht war;
Nun, da der Nebel fällt,
Ist keiner mehr sichtbar.
Wahrlich, keiner ist weise,
Der nicht das Dunkel kennt,
Das unentrinnbar und leise
Von allem ihn trennt.

Vreemd, te wandelen in de mist!
Eenzaam is elke struik en steen,
Geen boom ziet de andere,
Ieder is alleen.
Vol vrienden was mijn wereld,
Toen mijn leven nog licht was;
Maar nu de mist daalt
Is niemand meer te zien.
Waarlijk, niemand is wijs
Die de duisternis niet kent
Die hem onstuitbaar en zacht
Van iedereen scheidt.

Hermann Hesse
Im Nebel
(vertaling: Jan Gielkens & Ton Naaijkens, 1984)

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in Borderline Personality Disorder: A Neuroimaging Approach

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List of most commonly used Abbreviations

ACC	Anterior Cingulate Cortex
BOLD	Blood Oxygen Level-Dependent
BPD	Borderline Personality Disorder
DACC	Dorsal Anterior Cingulate Cortex
D(D)D	Depersonalization(/Derealization) Disorder
DID	Dissociative Identity Disorder
DLPFC	Dorsolateral Prefrontal Cortex
DMPFC	Dorsomedial Prefrontal Cortex
e.g.	for example
EST	Emotional Stroop Task
EWMT	Emotional Working Memory Task
FMRI	Functional Magnetic Resonance Imaging
HC	Healthy controls
IAPS	International Affective Picture System
i.e.	that is
MDD	Major Depressive Disorder
ms.	Milliseconds
OFC	Orbitofrontal Cortex
PD	Personality Disorder
PPI	Psychophysiological Interaction Analysis
PTSD	Posttraumatic Stress Disorder
RT	Reaction times
SSRI	Selective serotonin reuptake inhibitors.
VLPFC	Ventrolateral Prefrontal Cortex
VMPFC	Ventromedial Prefrontal Cortex
WM	Working Memory

Chapter 1

General introduction

CHAPTER 1

1. General Introduction

Stress-related dissociation and emotion dysregulation are central features of Borderline Personality Disorder (BPD), a severe mental disorder associated with high rates of interpersonal trauma (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004; Vermetten & Spiegel, 2014). Emotion dysregulation in BPD involves a heightened sensitivity and reactivity to emotionally salient stimuli, which can have detrimental effects on cognitive functions that are relevant to goal-directed behavior, such as working memory (Winter, Elzinga, & Schmahl, 2014). Dissociation is assumed to disrupt cognitive processing and to dampen emotional reactivity (Spiegel et al., 2011). However, it remains unclear how dissociation influences the behavioral inhibition and neural processing of emotional material (negative pictures or words) presented as distractors during a cognitive task (e.g., a working memory task) in BPD.

The neuroimaging research, described in this thesis, addresses the role of dissociation in altered activity and functional connectivity patterns during an Emotional Working Memory Task, an Emotional Stroop Task, as well as in the absence of experimental stimulation, i.e., during resting-state in female BPD patients with a history of interpersonal trauma compared to healthy controls. The present chapter provides an overview over the relevant background and methods of this thesis. First, a brief introduction into BPD is given. Then, basic principles of task-related and resting-state functional magnetic resonance imaging (fMRI) and brain networks relevant to BPD psychopathology, emotion processing, and dissociation are introduced. Research questions, aims, and hypotheses are derived at the end of this chapter.

1.1. Borderline Personality Disorder

BPD is characterized by a pervasive pattern of instability in affect, cognition, identity, and interpersonal relationships (APA, 2013; Lieb et al., 2004). The following sections provide an overview over epidemiology and course, pathogenesis of BPD, and symptoms that are major focus of this thesis, i.e., emotion dysregulation, cognitive disturbances, and dissociation.

1.1.1. Epidemiology and course

BPD affects about 1.3% of the general population (Coid, Yang, Tyrer, Roberts, & Ullrich, 2006) with a lifetime prevalence of approximately 3% - 5.9% (Grant et al., 2008; Trull, Jahng, Tomko, Wood, & Sher 2010). Prevalences in clinical samples range between 10% and 25% (Lieb et al., 2004). The extreme mental burden of the disorder is reflected by high suicide rates: about 10% of patients with BPD commit suicide and about 70% of individuals show suicide attempts (Black, Blum, Pfohl & Hale, 2004; Brodsky, Groves, Oquendo, Mann, & Stanley, 2006; Holm & Severinsson, 2008; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2005).

There is high comorbidity with other psychiatric disorders, especially depressive disorder and bipolar disorder, Posttraumatic Stress Disorder (PTSD), substance abuse (Grant et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007; Lieb et al., 2004; Zanarini, Frankenburg, Vujanovic, Hennen, Reich, & Silk, 2004), Attention Deficit Hyperactivity Disorder (ADHD) (Philipsen et al., 2008), dissociative disorders, (Brand & Lanius, 2014), and other personality disorders, e.g., avoidant and dependent PD (Grant et al., 2008; Skodol et al., 2005). Comorbid PTSD seems to aggravate BPD psychopathology (Scheiderer, Wood, & Trull, 2015), especially PTSD following childhood sexual abuse (Cackowski, Neubauer, & Kleindienst, 2016).

In most cases, first symptoms, such as affective instability, impulsivity, self-injurious behavior, and low self-esteem occur during adolescence (Bradley, Zittel Conklin, & Westen, 2005), become most severe in young adulthood, and modestly decline over the course of the years (Zanarini et al., 2005; Zanarini, Frankenburg, Reich, Fitzmaurice, Weinberg, & Gunderson, 2008). In the study by Zanarini and colleagues (2005), after 6-year follow-up, about 74% of participants did not fulfill the BPD diagnosis anymore and only about 6% of them showed relapses. In a more recent study of this group, however, only 50% of participants achieved good social integration and about 30% of recovered persons had relapses after 10-year follow-up (Zanarini, Frankenburg, Reich, & Fitzmaurice, 2010). Insufficient psychosocial integration (Zanarini et al., 2010) and the persistence of moderate symptoms, such as low self-esteem and depressive mood after treatment (Jørgensen et al., 2013; Panos et al., 2014) highlight the need of further improving the understanding and treatment of this severe disorder.

1.1.2. Pathogenesis

Current conceptualizations suggest that a complex interplay of genetic, neurobiological predispositions, adverse life events (e.g. interpersonal trauma), maladaptive cognitive schemata (negative beliefs about the self and others), and dysfunctional stress coping contributes to the development and maintenance of BPD (Crowell, Beauchaine, & Linehan, 2009; Leichsenring, Leibing, Kruse, New, & Leweke, 2011; Lieb et al., 2004; Martín-Blanco et al., 2016; Schmahl et al., 2014; Skodol, Gunderson, Pfohl, Widiger, Livesley, & Siever, 2002).

As initially proposed by Marsha Linehan's (1993) biosocial theory, highly sensitive and vulnerable individuals who grow up in an 'invalidating' environment, which does not provide sufficient emotional and social support, may learn to rely on dysfunctional strategies (e.g., substance abuse, gambling, self-injury like skin-cutting or burning, dissociation) to cope with their overwhelming emotions. Such attempts may help to down-regulate negative emotions in the short-term but increase affective vulnerability and interpersonal problems in the long run and thereby contribute to the maintenance of the disorder (Linehan, 1993).

With respect to genetic factors, twin studies suggest a pathway model with a highly heritable component for BPD (Distel et al., 2010; Gunderson, Zanarini, Choi-Kain, Mitchell, Jang, & Hudson, 2011; Reichborn-Kjennerud et al., 2013), while up till now no specific genes have been found to be causative for developing the disorder (Leichsenring et al., 2011). There is growing evidence that alterations in the neuroendocrine system and in brain structure and function may underlie key features of the disorder (Lis et al., 2007; New, Perez-Rodriguez, & Ripoll, 2012; van Zutphen, Siep, Jacob, Goebel, & Arntz, 2015; Wingenfeld & Wolf, 2014). As addressed in more detail in Chapter 2, these alterations include an imbalance of fronto-limbic brain regions (amygdala, anterior cingulate cortex, medial prefrontal cortex, among others), which are critically implicated in stress regulation and cognitive control.

Traumatic stress, especially early and prolonged interpersonal trauma, is assumed to play an important role in the etiology of BPD (Ball & Links, 2009; Battle et al., 2004; Elliott et al., 2016; Ogata, Silk, Goodrich, Lohr, Westen, & Hill, 1990; Soloff, Lynch, & Kelly, 2002; Wolke, Schreier, Zanarini, & Winsper, 2012; Zanarini et al., 2002). Previous research in patients with the disorder found high rates of childhood abuse and neglect with incidents of 92% for emotional maltreatment, 40–76% for sexual abuse, and 25-73% for physical abuse (Golier et al., 2003; Widom, Czaja, & Paris, 2009; Zanarini, 2000). Rates of childhood trauma, most prominently sexual abuse, were substantially higher in BPD than in other personality disorders (Battle et al., 2004; Yen et al. 2002) and more closely related to BPD than to depression or schizophrenia (Pietrek, Elbert, Weierstall, Müller, & Rockstroh, 2013). Considering the high rates of trauma and the phenomenological overlap between BPD and complex PTSD (Herman, Perry, & van der Kolk, 1989), some researcher proposed that BPD should be conceptualized as part of the trauma-related disorder spectrum (Bremner, 2002), while other researcher highlight the fact that a history of psychological trauma is neither sufficient nor specific for developing BPD (see Ford & Courtois, 2014). From a more general perspective, childhood adversities and chronic stress can have devastating consequences on the development of emotion regulation and attachment, thereby contributing to BPD features, such as affective instability and interpersonal disturbances (Agrawal, Gunderson, Holmes, & Lyons-Ruth, 2004; Fossati, Gratz, Somma, Maffei, & Borroni, 2016; Frias, Palma, Farriols, Gonzalez, & Horta, 2016). Disturbed perceptions about safety and trust in close relationships can result in a hypervigilance towards social stimuli signaling potential threat (see section 1.1.3.1).

In summary, previous research has provided evidence for a diathesis-stress model: a complex interaction of vulnerability factors and stressful life events currently provides the best explanation for the pathogenesis of BPD (Crowell et al., 2009; Leichsenring et al., 2011).

1.1.3. Psychopathology

A growing body of research has aimed at investigating mechanisms possibly underlying the complexity and heterogeneity of BPD symptoms (New et al., 2012; Schmahl et al., 2014). Current conceptualizations suggest that at least four core domains underlie the psychopathology of the disorder: 1) emotion dysregulation and disturbed emotion processing (increased affective sensitivity, reactivity, and instability, chronic feelings of emptiness, shame, anger, guilt, etc.), 2) cognitive disturbances (instable self-image and identity disturbances, deficits in executive control), 3) behavioral dysregulation (impulsive and aggressive behavior, self-injury), and 4) interpersonal disturbances (fear of abandonment, rejection sensitivity, difficulties in developing trust in others, social isolation, instable and intense relationships) (Lieb et al., 2004). Emotion dysregulation is assumed to be at the core of BPD (Crowell et al., 2009) and is a major focus of many current treatments (see Stoffers, Vollm, Rucker, Timmer, Huband, & Lieb, 2012). Dissociation is another core symptom of BPD, which affects various aspects of information processing, sensory perception, emotion, cognition, and motor control (Brand & Lanius, 2014, see section 1.1.3.3). As described in the following, emotion dysregulation, dissociation, and cognitive disturbances in BPD appear to be closely linked to each other.

1.1.3.1. Emotion dysregulation

According to current definitions, disturbed emotion regulation in BPD involves 1) a heightened sensitivity to even subtle emotional stimuli, 2) more intense and instable emotional reactions, 3) a slower return of affective arousal to baseline, and 4) a lack of adaptive coping strategies (Carpenter & Trull, 2013; Glenn & Klonsky, 2009; Linehan, Bohus, & Lynch, 2007). In line with this, individuals with BPD reported significantly more intense, instable and long-lasting emotions, more difficulties in identifying, tolerating, and modulating their emotions, and more episodes of emptiness than healthy persons (Ebner-Priemer et al., 2005; Kuo & Linehan, 2009; Rosenthal, Gratz, Kosson, Cheavens, Lejuez, & Lynch, 2008; Stiglmayr, Gratwohl, Linehan, Fahrenberg, & Bohus, 2005; Wolff, Stiglmayr, Bretz, Lammers, & Auckenthaler, 2007). Previous research in BPD further found a slower return of subjective arousal to baseline after an experimental induction of negative mood (Jacob et al., 2008) and psychosocial stress (Reitz, Krause-Utz, Pogatzki-Zahn, Ebner-Priemer, Bohus, & Schmahl, 2012). However, BPD patients did not differ from healthy controls or even demonstrated a hypo-responsiveness to aversive stimuli in studies using psychophysiological measures, such as heart rate, skin conductance, or startle response (Ebner-Priemer et al. 2005, 2009; Ebner-Priemer, Welch, Grossman, Reisch, Linehan, & Bohus, 2007; Herpertz, Kunert, Schwenger, & Sass, 1999; Kuo & Linehan, 2009).

Importantly, psychophysiological reactivity was found to be significantly influenced by dissociation: elevated startle responses to aversive stimuli were observed in patients without peri-experimental dissociation but not in patients with acute dissociation (Barnow et al., 2012; Ebner-Priemer et al., 2005). In BPD, self-reported dissociative experiences are positively correlated to emotional distress (Stiglmayr, Shapiro, Stieglitz, Limberger, & Bohus, 2001; Stiglmayr et al., 2008) and both self-reported dissociation and emotional distress have been linked to elevated pain thresholds (Bohus et al., 2000; Ludäscher, Bohus, Lieb, Philipsen, Jochims, & Schmahl, 2007) as well as altered pain processing (Naoum et al., 2016; Niedtfeld, Schulze, Kirsch, Herpertz, Bohus, & Schmahl, 2010; Reitz et al., 2015). Since attempts to terminate aversive states of dissociation and emotional distress are among the most prevalent motives of non-suicidal self-injury in BPD (Kleindienst et al., 2008; Linehan et al., 2015), understanding the link between emotion dysregulation and dissociation might contribute to a better understanding and treatment of the disorder (Brand & Lanius, 2014).

The most potent triggers of emotional distress in BPD patients are interpersonal stressors, such as perceived social rejection and abandonment (Brodsky et al., 2006; Ebner-Priemer et al., 2007; Stiglmayr et al., 2005). Difficulties in regulating intense feelings of shame, guilt, disappointment, anger, or loneliness may contribute to the intense and instable relationships, which are a clinical hallmark of the disorder (Cackowski et al., 2017; Gratz, Dixon-Gordon, Breetz, & Trull, 2013; Gunderson, 2007; Gunderson & Lyons-Ruth, 2008). Rejection sensitivity, i.e., the tendency to anxiously expect and more readily perceive social exclusion, was found to be significantly more pronounced in individuals with BPD than in patients with social anxiety disorder (Staebler, Helbing, Rosenbach, & Renneberg, 2010). Hypersensitivity towards social stimuli, indicating possible threat or exclusion, may critically interfere with other aspects of social information processing, such as facial emotion recognition and empathy (Andreou et al., 2015; Dinsdale & Crespi, 2013; Roepke, Vater, Preißler, Heekeren, & Dziobek, 2013; Unoka, Fogd, Füzy, & Csukly, 2011; von Ceumern-Lindenstjerna, Brunner, Parzer, Mundt, Fiedler, & Resch, 2010). In previous research, patients with BPD were faster and more accurate in detecting negative emotions in facial expressions or affective eye gaze (Fertuck et al., 2009; Frick et al., 2012; Lynch, Rosenthal, Kosson, Cheavens, Lejuez, & Blair, 2006; Wagner & Linehan, 1999) but also tended to interpret neutral or ambiguous faces as hostile or angry (Barnow et al., 2009; Daros, Zakzanis, & Ruocco, 2012; Domes et al., 2008; Domes, Schulze, & Herpertz, 2009; Dyck et al., 2009). Individuals with BPD further showed an increase in amygdala reactivity and subjective distress, when processing neutral faces (Donegan et al., 2003) or interpersonal scenes (Koenigsberg et al., 2009a; Schulze et al., 2011).

Of importance to the present thesis, hypervigilance towards social cues may also interfere with executive functions, which are crucial to goal-directed behavior, such as working memory (Brück, Derstroff, Jacob, Wolf-Arehult, Wekenmann, & Wildgruber, 2016; von Ceumern-Lindenstjerna et al., 2010). This is discussed in more detail below.

1.1.3.2.Cognitive disturbances and emotional distractibility

Deficits in executive functions, including attention, inhibitory control, memory, learning, and planning have been discussed as a central hallmark of BPD (Bazanis et al., 2002; Dinn, Harris, Aycicegi, Greene, Kirkley, & Reilly, 2004; Gvirts, Harari, Braw, Shefet, Shamay-Tsoory, & Levkovitz, 2012; Judd, 2005; Legris & van Reekum, 2006; Mak & Lam, 2013; Ruocco, 2005). However, not all studies revealed significant deficits in BPD patients compared to healthy controls (Beblo et al., 2006; Hagenhoff et al., 2013; Sprock et al., 2000). More recent research proposed that in BPD deficits in attention, inhibitory control, and memory are mainly related to negative emotional states (see Baer, Peters, Eisenlohr-Moul, Geiger, & Sauer, 2012; Bornovalova, Lejuez, Daughters, Rosenthal, & Lynch, 2005; Fertuck, Lenzenweger, Clarkin, Hoermann, & Stanley, 2006; Sebastian, Jacob, Lieb, & Tüscher, 2013; Winter et al., 2014). For instance, individuals with BPD showed significant deficits in inhibitory control after an experimental stress induction but not under baseline conditions compared to healthy controls (Cackowski, Reitz, Ende, Kleindienst, Bohus, Schmahl, & Krause-Utz, 2014) as well as patients with ADHD (Krause-Utz et al., 2016).

Two major paradigms that were previously used to investigate inhibitory control of emotional stimuli in BPD are the Emotional Working Memory Task (EWMT) and Emotional Stroop Task (EST). These experimental tasks are applied in this thesis and briefly described in the following. Oei, Tollenaar, Spinhoven, and Elzinga (2009) developed a modified version of a Sternberg item-recognition task (Sternberg, 1966), in which participants are instructed to maintain task-relevant information (memoranda, a set of letters) over a short delay interval. Afterwards, a probe (another set of letters) is presented and participants are instructed to indicate whether one of these letters was part of the previous set (memoranda) or not by pressing a ‘yes’ or ‘no’ button. In half of the trials, a target is present, while in the other trials, the target is absent. During the delay interval either no distractors (only a fixation cross) or distracting neutral vs. negative pictures are presented. This EWMT was slightly modified by Krause-Utz, Oei, Niedtfeld, Bohus, Spinhoven, Schmahl, and Elzinga (2012) and applied in a sample of BPD patients with interpersonal trauma history. In this study, interpersonal scenes from the International Picture System (IAPS) (Lang et al., 2005) were selected as distractors, based on norms of arousal and valence ratings, given the important role of interpersonal stressors in BPD.

Negative pictures depicted scenes of interpersonal violence, e.g., a sexual or physical assault, a beaten child or a physically mutilated body. Participants are instructed to ignore these distractors, focusing solely on the WM task, and to respond as fast and accurately as possible to the probes – this means: to voluntarily inhibit emotion processing in favor of cognitive processing. During presentation of neutral and negative interpersonal scenes, BPD patients showed significantly longer reaction times and significantly stronger activity in the amygdala (among other regions), suggesting higher emotional distractibility than healthy controls.

In another study, Krause-Utz, Elzinga, Oei, Spinhoven, Bohus, and Schmahl (2014a) found significantly more errors after distraction by negative interpersonal IAPS pictures as well as fearful faces compared to distractor-free trials in patients with BPD than in healthy controls. In this study, BPD patients further showed significantly more errors after distraction by neutral faces, pointing to a hypervigilance towards social cues that may be perceived as ambiguous.

In line with this, Prehn and colleagues (2013) found significantly more working memory deficits after distraction by salient social scenes in male violent criminal offenders with BPD and comorbid antisocial personality disorder. Compared to healthy controls, these patients showed longer reaction times, independent of working memory load, and increased amygdala activity after distraction by salient social scenes, presented in the background of an n-back task.

Other studies applied adapted version of the EST, in which participants are instructed to name the color of visually presented target words. These words may be neutral, positive, generally negative, or self-relevant. In general, the more time a participant needs to name the color of a word, the more attention is captured by its content (interference effect). Arntz, Appels, and Sieswerda (2000) presented stimuli both on a subliminal and supraliminal level in BPD patients, a comparison group of patients with cluster C personality disorders, and healthy controls. Distractors were neutral words, generally negative words, and BPD-salient words (related to sexual abuse and negative schemata). Compared to healthy controls, BPD patients showed a hypervigilance towards generally negative words and BPD-salient words, while they didn't differ from cluster C patients with regard to supraliminal negative words.

In a study by Sieswerda, Arntz, Mertens, and Vertommen (2007), BPD patients demonstrated a bias towards negative and positive words, which was again more pronounced for negative schemata-related words and significantly related to the severity of childhood sexual trauma. A trend towards increased attention towards supraliminally presented schemata-related words, however, was also found in a clinical comparison group of patients with axis I disorders.

In a more recent study, Wingenfeld and colleagues (2009a) found hypervigilance towards personally relevant words in BPD patients during an individualized version of the EST.

However, this effect was only present in a subgroup of patients with comorbid PTSD, supporting earlier findings of an important impact of trauma severity on EST performance (Sieswerda et al., 2007). Differences in sample characteristics (e.g., trauma history) and material (standardized vs. personalized words, differences in distractor valence etc.) might explain why some EST studies did not observe deficits in BPD compared to healthy groups (Beblo et al., 2006; Domes et al., 2006; Minzenberg, Poole, & Vinogradov, 2008; Sprock et al., 2000; Wingenfeld et al., 2009b). A recent meta-analysis of 11 EST studies, conducted by Kaiser, Jacob, Domes, and Arntz (2016), found evidence for a hypervigilance towards negative words, which was more pronounced for personally relevant than standardized words in patients with BPD compared to healthy controls. Yet, it remains unclear whether this bias is specific for BPD: an attentional bias towards personally relevant words was also present in the other clinical samples. Aside from trauma history, dissociation may affect cognitive control of emotional material during the EWMT and EST, as discussed in more detail in the following section.

1.1.3.3. Dissociation

About 75% of individuals with BPD report transient stress-related dissociative states, which usually last for minutes or hours (APA, 2013; Banich, Mackiewicz, Depue, Whitmer, Miller, & Heller, 2009; Chopra & Beatson, 1986; Korzekwa, Dell, & Pain, 2009a; Korzekwa, Dell, Links, Thabane, & Fougere, 2009b; Simeon, Nelson, Elias, Greenberg, & Hollander, 2003; Zanarini, Frankenburg, Jager-Hyman, Reich, & Fitzmaurice, 2008; Zanarini, Ruser, Frankenburg, Hennen, & Gunderson, 2000). Dissociation is a very complex phenomenon. It has been defined 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). This definition implicates a broad range of psychological and somatoform symptoms, such as depersonalization, derealization, and numbing (subjective detachment from oneself and the environment), memory fragmentations, analgesia, and altered hearing (Nijenhuis, Spinhoven, Van Dyck, Der Hart, & Vanderlinden, 1996; Waller, Putnam, Carlson, & Appelbaum, 1996).

According to Cardena and Spiegel (1993), dissociative symptoms may be classified into the following three categories: (1) a loss of continuity in subjective experience, accompanied by involuntary and unwanted intrusions into awareness or behavior, (2) an inability to access information or control mental functions that are normally amenable to such control or access, and (3) a sense of experiential disconnectedness, including distorted perceptions about the self or the environment. This thesis mainly focuses on disturbances in information processing and symptoms of subjective detachment (e.g., depersonalization, derealization, numbing).

Dissociation has been closely linked to psychological trauma, especially severe childhood abuse and neglect (Dutra, Bureau, Holmes, Lyubchik, & Lyons-Ruth, 2009; Ogawa, Sroufe, Weinfield, Carlson, & Egeland, 1997; Roelofs, Keijsers, Hoogduin, Näring, & Moene, 2002; Shearer, 1994; Van Den Bosch, Verheul, Langeland, & Van Den Brink, 2003; Vermetten & Spiegel, 2014; Watson et al., 2006; Zanarini et al., 2000). It has to be pointed out, however, that this relationship is more complex and the development of dissociative disorders is also influenced by other etiological factors, e.g., genetic and neurobiological dispositions (Lanius et al., 2010; Roelofs, Spinhoven, Sandijck, Moene, & Hoogduin, 2005; Spinhoven et al., 2004).

Dissociation may be understood as a self-protective strategy that helps to cope with extremely stressful experiences when normal coping mechanisms of an individual are exeeded (Janet, 1889; Lanius, Vermetten, Loewenstein, Brand, Schmahl, Bremner, & Spiegel, 2010; Schauer & Elbert, 2010; Van der Kolk, McFarlane, & Weisaeth, 1996; Van der Kolk & van der Hart, 1989). Symptoms of subjective detachment, such as depersonalization and derealization, may create an inner distance to traumatic events by numbing overwhelming emotions and unbearable thoughts. The horrifying situation may be perceived as an unreal film-like scene, observed from a wider distance. Sensory information is often processed in a distorted way, e.g., parts of the own body appear numb or larger than usual and hearing is substantially altered. Somatoform symptoms, such as analgesia and out of body experiences (the sense of floating above one's body) may reduce the awareness of extreme physical pain (Frewen & Lanius, 2006). The cost of this regulatory strategy appears to be a disruption of mental resources that are crucial to goal-directed behavior, including attention and memory (Bremner, Vermetten, Southwick, Krystal, & Charney, 1998; Haaland, & Landrø, 2009; Van der Kolk et al., 1996). However, attention and memory were also found to be enhanced in persons with high trait dissociation (Chiu, Yeh, Huang, Wu, & Chiu, 2009; de Ruiter, Phaf, Elzinga, & van Dyck, 2004; Elzinga, Ardon, Heijnis, De Ruiter, Van Dyck, & Veltman, 2007), which means that effects of dissociation on cognitive processing may be different in different clinical groups.

With respect to BPD, previous findings point to an impaired learning of new emotional information during acute dissociation (Ebner-Priemer et al., 2009) and dissociative symptoms were found to interfere with treatment outcome (Arntz, Stupar-Rutenfrans, Bloo, van Dyck, & Spinhoven, 2015; Kleindienst et al., 2011, 2016; Spitzer, Barnow, Freyberger, & Grabe, 2007). Still, more research is needed to better understand how dissociation influences the neural processing of affective-cognitive tasks in patients with the disorder. Neuroimaging techniques, such as fMRI, might help elucidating this relationship. Some basic principles of task-related and resting-state fMRI are introduced in the next section.

1.2. Functional magnetic resonance imaging

Over the last decades, fMRI has been increasingly used to detect changes in blood-oxygen-level-dependent (BOLD) signal response that might underlie complex psychological processes and psychiatric disorders (Ogawa, Lee, Kay, & Tank, 1990; Ogawa et al., 1992). During symptom provocation, task-dependent changes in brain activity can be estimated by contrasting BOLD signals observed during a specific experimental condition (e.g., working memory trials with negative distractors) to a control condition (e.g., working memory trials with neutral distractors) (Friston, Fletcher, Josephs, Holmes, Rugg, & Turner, 1998; Kim & Ogawa 2012). There is growing consensus that complex mental processes and disorders may be best understood by studying dynamic interactions within large-scale brain networks instead of only focusing on activation patterns in localized brain regions. Thus, more and more studies have applied functional connectivity approaches in the presence or absence of experimental tasks. Functional connectivity refers to the temporal correlation (statistical dependency) of „spatially remote neurophysiological events“ (Friston, 2011, p. 14). These functional connectivity approaches include seed-based correlations and data-driven clustering methods (e.g., Independent Component Analysis, ICA), while techniques are constantly improved and new methods are still emerging (Nichols et al., 2017). In the present thesis, seed-based analyses are applied, which are aimed at detecting brain areas that are functionally connected to a-priori defined seed regions of interest in terms of significant correlations between time courses of activity (Fox & Raichle, 2007; Friston et al., 1997). Stronger correlations of these time courses in activity are thought to reflect increased information exchange between the areas, while no causal conclusions can be drawn, i.e., whether the interaction is causally driven by the seed, the coupled area or a third region (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012).

Resting-state fMRI, i.e., the assessment of synchronized BOLD signal fluctuations in the absence of external stimulation, has become increasingly important for the understanding of dynamic neural processes, which may underlie certain somatic and mental disorders (Cole, Smith, & Beckmann, 2010; Fox & Raichle, 2007). Resting-state functional connectivity (RSFC) was first detected in the motor cortex (Biswal, Yetkin, Haughton, & Hyde, 1995) and in networks involved in language, speech, and visual processing (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002). More recently, it has been shown that relatively robust synchronized BOLD signal fluctuations can also be successfully mapped in large-scale brain networks like the default mode and salience network, widely corresponding to task-related FC patterns (Smith et al., 2009), with high consistency over time, across samples and conditions (Damoiseaux et al., 2006; Zuo, Kelly, Adelstein, Klein, Castellanos, & Milham, 2010).

1.3. Brain networks relevant to the current thesis

According to the triple network model by Menon (2011), the default mode network, salience network, and central executive network are three large-scale networks that are relevant for studying affective and cognitive disturbances in neurological and psychiatric disorders. With respect to BPD, key features of the disorder have also been associated with an imbalanced network of cortico-limbic regions (amygdala, ACC, among others, see below).

1.3.1 Default mode network

Despite different neuroanatomical definitions, the posterior cingulate cortex (PCC), precuneus, mPFC, frontopolar cortex, posterior inferior parietal lobe, angular gyrus, temporoparietal junction, superior temporal gyrus, and hippocampus (parts of the medial temporal lobe network), are seen as important functional nodes of the default mode network (Broyd, Demanuele, Debener, Helps, James, & Sonuga-Barke, 2009; Buckner, Andrews-Hanna & Schacter, 2008; Buckner & Vincent, 2007; Laird et al., 2009; Vincent et al., 2007). Activity in this network has been related to self-referential processes, such as daydreaming, mind-wandering, rumination, and recollection of autobiographical memories (Buckner et al., 2008), as frequently observed during resting-state (Buckner & Vincent, 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001) as well as to social cognition and mentalizing tasks (Laird et al., 2009).

1.3.2. Salience network

The salience network comprises the anterior insula and dorsal ACC (Menon & Uddin, 2010; Seeley et al., 2007), which have been implicated in attention, error monitoring, working memory, encoding of negative emotions, interoceptive awareness, and pain processing (Craig, 2011; Critchley, Mathias, & Dolan, 2001; Lee & Siegel, 2012; Maier et al., 2010). So-called 'task-positive networks' like the salience network and central executive network (a network mainly comprising prefrontal and fronto-parietal regions) appear to be crucial to cognitive performance and goal-directed behavior (Seeley et al., 2007). The salience network also seems to play an important role in switching between networks (i.e., between default mode and executive control) (Goulden et al., 2014; Sridharan, Levitin, & Menon, 2008).

1.3.3. Amygdala and medial temporal lobe network

The amygdala is central to the initiation of fear and stress responses (LeDoux, 1992; Davis & Whalen, 2001; Davidson, 2002). It is assumed that this area modulates the encoding and storage of emotional memories in the hippocampal formation (medial temporal lobe), while the hippocampus modulates amygdala responses to external stimuli (Knight et al., 2004; McGaugh, 2004; Qin, Duan, Supekar, Chen, Chen, & Menon, 2016; Richter-Levin & Akirav 2000).

1.3.4. Networks implicated in emotional distractibility

With respect to the interplay of emotion and cognition, Ochsner and Gross (2007) proposed a model, which might help to understand neural processes underlying difficulties inhibiting emotional information. According to this model, sensory features of emotional stimuli are encoded in thalamic and somatosensory regions and subsequently processed in the basal ganglia, nucleus accumbens, insula, and amygdala (bottom-up appraisal system), facilitating fast autonomic responses in the face of threat. Outputs from amygdala and insula are subsequently processed in brainstem and hypothalamic nuclei. Simultaneously, cognitive emotion regulation strategies, such as cognitive reappraisal or suppression, are thought to activate a top-down system of frontal cortical regions, including the ACC, orbitofrontal cortex (OFC), dlPFC, dorsomedial prefrontal cortex (dmPFC), ventrolateral and ventromedial PFC (vlPFC, vmPFC) which promotes the inhibition of limbic activity (Ochsner & Gross, 2007). The ACC seems to play an important role in the dynamic interplay of bottom-up and top-down processes, being functionally connected to both limbic and cortical regions (Bush, Luu, & Posner, 2000; Etkin et al., 2011; McRae, Hughes, Chopra, Gabrieli, Gross, & Ochsner, 2010). The dorsal ACC and dlPFC are not only implicated in working memory and inhibition of emotional distraction but also in cognitive emotion regulation, which may involve similar processes (Anderson et al., 2004; Banich et al., 2009; Blair et al., 2007; Pessoa, Padmala, Kenzer, & Bauer, 2012; Owen, McMillan, Laird, & Bullmore, 2005; Schweizer et al., 2013). Impaired working memory performance during emotional distraction has been associated with a diminished recruitment of dorsal frontal areas (dACC and dlPFC, among others) and a hyper-reactivity in ventral limbic regions, especially in the amygdala and insula (Anticevic, Repovs, & Barch, 2010; Dolcos & McCarthy, 2006; Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos, Kragel, Wang, & McCarthy, 2006; Dolcos, Miller, Kragel, Jha, & McCarthy, 2007; LaBar, Gitelman, Parrish, & Mesulam, 1999; Mitchell, Luo, Mondillo, Vythilingam, Finger, & Blair, 2008; Perlstein, Elbert, & Stenger, 2002). Increased emotional distractibility during the EWMT was further linked to a stronger coupling of the amygdala with inferior frontal gyrus (Dolcos et al., 2006) and to increased negative amygdala connectivity with dlPFC, dACC, and anterior PFC (Anticevic et al., 2010).

In summary, there is evidence for an important role of the amygdala and ACC in coping with emotional distraction. Yet, complex affective-cognitive processes such as interference inhibition do not only recruit localized brain areas but normally involve dynamic interactions within and between large-scale brain networks (Pessoa et al., 2012; Phan, Wager, Taylor, & Liberzon, 2004).

1.3.4. Networks implicated in Dissociation

Dissociation may substantially alter activity in the cortico-limbic system. Already in 1998, Sierra and Berrios introduced a 'cortico-limbic disconnection model', proposing that changes in the cortico-limbic system underlie symptoms of depersonalization (emotional numbing, emptiness of thoughts, analgesia, and hypervigilance). More specifically, dissociative symptoms are thought to enhance recruitment of the ACC, mPFC, and dlPFC, leading to dampened amygdala activity and a marked attenuation of automatic responses, comparable to a shutting down of the affective system (Sierra & Berrios, 1998).

Based on more recent neuroimaging research in PTSD, Lanius and colleagues (2010) proposed a neurobiological model, differentiating between two types of emotion modulation (p. 640): A "hyper-aroused subtype" of patients suffering from traumatic re-experiencing, such as flashbacks, intense feelings of shame and guilt, and hyperarousal ("emotion under-modulation") and a "dissociative subtype" of patients showing an "over-modulation" of emotions in response to traumatic reminders. According to this model, these two subtypes show distinct neurobiological profiles: the dissociative subtype involves increased recruitment of the dorsal/rostral ACC and mPFC and reduced activity in amygdala and insula, while the reversed pattern (limbic hyperactivity and diminished recruitment of ACC and mPFC) may underlie traumatic re-experiencing (Lanius et al., 2010).

In BPD, neuroimaging research directly aimed at investigating associations between dissociative symptoms and changes in brain activity is still relatively scarce and previous results are mixed (as described and discussed in more detail in Chapter 3). To the author's knowledge, before 2014, only one fMRI study used script-driven imagery to experimentally investigate the effect of a dissociation induction on brain activity in BPD (Ludäscher et al., 2010). Script-driven imagery is a well-established paradigm, aimed at provoking dissociative experiences through a recollection of autobiographical memories: personalized scripts of a situation that involved dissociative experiences ('dissociation script', as compared to an emotionally 'neutral script') are created together with each participant and presented in an experimental setting, e.g., during fMRI. Participants are instructed to recall the specific situation, described in the script, as vividly as possible, which successfully induced dissociation in previous research (Ludäscher et al., 2010). Findings of a pilot study by Ludäscher and colleagues (2010) provided first evidence for increased activity in left inferior frontal gyrus and superior frontal gyrus and diminished temporo-limbic activity in BPD patients during a dissociation script (see Chapter 3). However, no healthy control group was included in this study and the sample size was relatively small.

Moreover, so far, no fMRI study in BPD combined script-driven imagery with neuropsychological tasks to investigate the effect of dissociation on affective-cognitive processing. Another remaining key question is how dissociation may affect the functional coupling of brain regions implicated in affective-cognitive processing, such as the amygdala and ACC. As outlined below, these research questions are addressed in the present thesis.

1.4. Thesis outline: Research questions and hypotheses

The overall aim of this thesis is to examine associations between dissociation and alterations in brain networks relevant to affective-cognitive processing under resting-state and during emotional distraction in unmedicated female BPD patients with a history of interpersonal trauma compared to healthy controls. In the first part of the neuroimaging research, described in this thesis (Chapter 4 and 5), it is investigated whether self-reported levels of trait dissociation and state dissociation predict changes in functional connectivity in large-scale brain networks (medial temporal lobe network, salience network, and default mode network) during resting-state as well as during the EWMT in BPD. The neuroimaging research, described in the second part of this thesis (Chapter 6 and 7), uses a combination of script-driven imagery with the EWMT and EST to study the effect of dissociation on emotional distraction in BPD.

In Chapter 2, previous neuroimaging research in BPD, published before 2014, is reviewed, focusing on structural and functional MRI studies. Chapter 3 provides a more detailed overview of neurobiological models of dissociation and neuroimaging research in dissociative and trauma-related disorders, discussing possible implications for BPD. Chapters 4 to 7 comprise the experimental neuroimaging studies conducted within the scope of this thesis.

The study, described in Chapter 4, is aimed at investigating resting-state functional connectivity (RSFC) of the amygdala (medial temporal lobe network), dorsal ACC (salience network), and ventral ACC (default mode network) in 20 unmedicated women with BPD and 17 healthy controls. Group differences in RSFC of the afore-mentioned seeds with areas mainly located in the vm/dmPFC, insula, and occipital cortex are expected. In addition, it is examined whether dissociative traits (scores on the Dissociative Experience Scale) predict RSFC of these seeds in BPD.

The second fMRI study (Chapter 5) is aimed at investigating changes in functional connectivity of the amygdala (medial temporal lobe network) and dACC (salience network) during the EWMT in 22 women with BPD compared to 22 healthy controls. Patients with BPD are expected to show increased functional connectivity of the amygdala with dorsal frontal brain regions and increased functional connectivity in the salience network compared to controls.

In line with the previous study, it is examined whether acute dissociative symptoms (scores on the Dissociation Stress Scale) predict functional connectivity of these seeds in BPD.

The study, described in Chapter 6, examines the impact of dissociation on interference inhibition during the EST and subsequent memory tasks in BPD. Script-driven imagery is used to induce dissociation in 18 BPD patients, while 19 BPD patients and 19 healthy controls are exposed to neutral scripts. It is hypothesized that dissociation induction is related to (1) inefficient cognitive inhibition of task-irrelevant information (overall slower reaction times and more errors), and altered task-related activity in the ACC, inferior parietal cortex, superior temporal gyrus, and inferior frontal cortex, and to (2) a smaller difference between reaction time latencies and response accuracy and smaller differential task-related activity in the above-mentioned brain regions for negative versus neutral words.

In Chapter 7, script-driven imagery is combined with the EWMT to investigated how dissociation affects amygdala functional connectivity during emotional distraction in the context of a working memory task in BPD. Using script-driven imagery, 12 BPD patients are exposed to a dissociation script, while 17 BPD patients and 18 healthy controls are exposed to a neutral script. A subgroup of these patients also participated in the previous study, described in Chapter 6. Based on previous neuroimaging research, BPD patients in the neutral script condition are expected to show amygdala hyper-reactivity to negative distractors compared to healthy controls, while BPD patients after dissociation induction are expected to demonstrate dampened amygdala reactivity and increased activity in frontal areas (inferior frontal gyrus, medial PFC, ACC).

Chapter 2

Neuroimaging findings in Borderline Personality Disorder

CHAPTER 2

Neuroimaging findings in Borderline Personality Disorder

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[1] For the sake of this thesis, the studies, which are presented in Chapter 4 and 5, are not discussed here: Krause-Utz, Elzinga, Oei, Paret, Niedtfeld, Spinhoven, et al. (2014) and Krause-Utz, Veer, Rombouts, Bohus, Schmahl, & Elzinga (2014). Parts of the original article, in which these studies were described, were therefore excluded (see footnote below)

Abstract

Borderline Personality Disorder (BPD) is a severe mental disorder, characterized by pronounced deficits in emotion regulation, cognitive disturbances including dissociation, impulsivity, and interpersonal disturbances. Over the last decades, neuroimaging has become one of the most important methods to investigate neurobiological alterations possibly underlying core features of BPD. The aim of our article is to provide an overview of the latest neuroimaging research in BPD focusing on functional and structural MRI studies published since 2010. Findings of these studies are depicted and discussed with respect to central domains of BPD psychopathology. On a neurochemical level, altered function in neurotransmitter systems including the serotonin, glutamate, and GABA systems was observed in patients with BPD. On a neural level, individuals with BPD mainly showed structural and functional abnormalities in a fronto-limbic network including regions involved in emotion processing (e.g., amygdala, insula) and frontal brain regions implicated in regulatory control processes (e.g., anterior cingulate cortex, medial frontal cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex). Limbic hyper-reactivity and diminished recruitment of frontal brain regions may yield a link between disturbed emotion processing and other core features of BPD such as impulsivity and interpersonal disturbances. To clarify whether findings are specific to BPD, comparisons with other clinical groups are needed.

Keywords: Borderline personality disorder, dissociation, emotion regulation, functional magnetic resonance imaging, impulsivity, interpersonal disturbances, neuroimaging, pain processing

2.1. Introduction

Borderline Personality Disorder (BPD) is a severe mental disorder affecting 1.3% of the general population (Coid et al., 2006), with a life-time prevalence ranging between 3% and 5.9% (Grant et al., 2008; Trull et al., 2010). There is growing evidence that interplays of disturbed emotion processing, dysfunctional cognitive appraisals, maladaptive behavior patterns, and neurobiological alterations underlie BPD psychopathology (Lis et al., 2007; Leichsenring et al., 2011; O'Neill & Frodl, 2012). Psychopathology of BPD is related to at least four core domains: 1) disturbed emotion processing, 2) cognitive disturbances, 3) behavioral dysregulation and impulsivity, and, 4) interpersonal disturbances (Lieb et al., 2004). Further important clinical features of BPD are dissociation and altered pain perception (Lieb et al., 2004). The understanding of potential neurobiological underpinnings of BPD has grown rapidly over the last decades. Thereby, neuroimaging has become one of the most influential methods to detect abnormalities in individuals with BPD compared to healthy subjects. Functional magnetic resonance imaging (fMRI) can be used to investigate brain activation by means of cerebral blood flow changes (glucose metabolism and hemodynamic response). Structural MRI and Diffusion Tensor Imaging (DTI) are important tools to detect structural and volumetric abnormalities of brain regions. In combination with pharmacologic challenge, positron emission tomography (PET) can be used to investigate neurotransmitter systems in the brain. Using ^{1}H MR spectroscopy (MRS), concentration of neurochemical metabolites such as glutamate, GABA, Nacetylaspartate (NAA), or choline can be measured in specific brain areas. In the last years, more and more neuroimaging studies have applied structural and functional connectivity approaches to investigate dynamic interactions between brain areas during experimental conditions and resting-state in BPD.

Here, we aim to provide an update of an earlier overview of neuroimaging research in BPD (Mauchnik & Schmahl, 2010), thereby focusing on structural and functional MRI studies published since 2010. First, findings of structural studies in BPD are depicted. Afterwards, results of functional neuroimaging studies are described referring to resting-state as well as psychopathology of BPD.

2.2. Structural neuroimaging studies

Numerous studies in BPD investigated neural alterations on a structural level. Reduced volumes in limbic and para-limbic brain regions, most prominently in the amygdala and hippocampus, were reported in patients with BPD compared to healthy controls (for a meta-analysis, see Nunes et al., 2009).

Given the crucial role of the amygdala in emotion processing and in the initiating of stress and fear responses (Ochsner & Gross, 2007), this brain area is of high relevance to BPD psychopathology (Leichsenring et al., 2011). In addition, the hippocampus which is critically implicated in episodic and autobiographical memory may be of great interest for understanding the neurobiology underlying BPD (Lanius et al., 2010).

However, interpretation of early volumetric studies is oftentimes complicated due to methodological aspects such as psychotropic treatment, small sample sizes, and comorbidities such as Posttraumatic Stress Disorder (PTSD). Smaller hippocampus and amygdala volumes were also observed in patients with PTSD compared to healthy and trauma-exposed controls (Karl, Schaefer, Malta, Dorfel, Rohleder, & Werner, 2006). In a meta-analysis by Rodrigues and colleagues (2011), volume reductions in the amygdala and hippocampus were found to be more pronounced in BPD patients with comorbid PTSD than in BPD patients without comorbid PTSD. More recent studies in BPD aimed to overcome some of the limitations of earlier studies by using techniques such as voxel based morphometry (VBM) or Diffusion Tensor Imaging (DTI) and by including clinical control groups or investigating the impact of specific comorbidities (such as PTSD). Niedtfeld, Schulze, Krause-Utz, Demirakca, Bohus, and Schmahl (2013) used VBM to investigate grey matter volume (GMV) in 60 BPD patients compared to 60 healthy controls. They found smaller volumes in BPD than in HC in the amygdala and hippocampus. Importantly, BPD symptom severity predicted volume loss in amygdala regardless of PTSD comorbidity (Kuhlmann, Bertsch, Schmidinger, Thomann, & Herpertz, 2013). Kuhlmann and colleagues (2013) used fully automated DARTEL VBM in 30 BPD patients and 33 healthy controls. This study could also replicate previous findings of reduced hippocampal volumes in BPD patients. As a novel finding, the authors revealed increased GMV in the hypothalamus, which was positively correlated with trauma history in the group of BPD patients. O'Neill and colleagues (2013) used VBM along with manual volumetry to investigate specific subdivisions of the hippocampus in BPD. Patients with the disorder showed reductions of the bilateral hippocampal tail as well as left hippocampal head and body compared to healthy controls (O'Neill, D'Souza, Carballedo, Joseph, Kerskens, & Frodl, 2013). Rossi and colleagues (2012) investigated hippocampal morphology in patients with BPD compared to patients with bipolar disorder (BD) and healthy controls. Smaller hippocampal volumes were found in BPD and BD. In the BPD group, additional alterations were identified in subiculum and in the CA1 regions, whereas in the BD group volumes reductions were observed for the dentate gyrus.

Aside from volume reductions in limbic brain regions, structural abnormalities in various regions of the temporal and parietal lobes were reported in BPD (Soloff, Nutche, Goradia, & Diwadkar, 2008). Subsequent investigations in BPD patients revealed reduced volumes in the orbitofrontal cortex (OFC) (Soloff, Pruitt, Sharma, Radwan, White, & Diwadkar, 2012). In a study by Sala and colleagues (2011), GMV in the dorsolateral prefrontal cortex (dlPFC) was inversely correlated with measures of impulsivity in BPD. The OFC and dlPFC play a critical role in regulatory processes such as the down-regulation of limbic and subcortical activation (Ochsner & Gross, 2007; Pessoa, Padmala, Kenzer, & Bauer, 2012). It is important to note, however, that the dlPFC is a large brain region which has been assigned to different Brodmann areas (BA) in the previous literature, most prominently to BA9 and BA46 (Brodmann, 1909; Mylius et al. 2013).

In another VBM study in BPD, reduced GMV and increased white matter volumes in the anterior cingulate cortex (ACC) were reported (Goodman, Hazlett, Avedon, Siever, Chu, & New, 2011). The ACC is assumed to play an important role in emotion processing, salience detection, inhibitory control, and pain processing (Ochsner & Gross, 2007). In the study by Niedtfeld and colleagues (2013), BPD symptom severity predicted GMV loss in dorsal ACC regardless of PTSD comorbidity. Conversely, increased GMV in the dlPFC and superior temporal gyrus was related to co-occurring PTSD. Another study examined abnormalities in GMV in antisocial offenders who either had psychopathic traits (ASPD+PP) or comorbid BPD (ASPD+BPD) compared to a healthy control group (Bertsch et al., 2013). Both groups of criminal offenders showed reduced GMV in areas of the frontal and occipital cortex compared to healthy controls. In antisocial offenders with comorbid BPD, abnormalities in GMV in OFC and ventromedial PFC were observed, whereas the ASPD+PP group showed reduced GMV in midline cortical areas comprising the dorsomedial PFC and PCC.

Studies using DTI to investigate structural connectivity between brain regions found reduced white matter connections in frontal cortices (Rüsch et al. 2010). Carrasco and colleagues (2012) examined microstructural abnormalities of white matter tracts in the PFC in BPD. In the patient group, a significant damage of white matter in the corpus callosum and bilateral prefrontal white matter fasciculi was observed. Sato, de Araujo Filho, de Araujo, Bressan, de Oliveira, and Jackowski (2012) investigated whether structural abnormalities in regional cortical thickness could discriminate individuals with BPD from individuals without this disorder. A group of 25 BPD patients and 25 healthy subjects were included in this study. Volumes in the OFC, rostral ACC, PCC and middle temporal cortices (among others) were identified as most informative brain regions to discriminate between the groups.

Volumetric alterations were also observed in adolescents with first presentation of BPD. Compared to controls, these adolescents displayed volume reductions of the OFC (Chanen et al., 2008), the ACC (Whittle, Chanen, Fornito, McGorry, Pantelis, & Yucel, 2009), the dlPFC (Brunner et al., 2010), and caudal superior temporal gyrus (Takahashi et al. 2010). In contrast, volumes of the amygdala and hippocampus (Chanen et al., 2008) and corpus callosum size (Walterfang et al., 2010) were found to be unaffected in teenagers with the disorder. In a DTI study by New and colleagues (2013), adolescents with BPD exhibited decreased fractional anisotropy in the inferior longitudinal fasciculus as well as in occipito-frontal and uncinate fasciculi compared to healthy adolescents. Maier-Hein and colleagues (2013) investigated adolescents with BPD, aged between 14-18 years, in comparison to carefully matched healthy and clinical controls. Adolescents with BPD demonstrated decreased tract-specific fractional anisotropy in the fornix. Moreover, these adolescents exhibited white matter abnormalities in interconnections of the heteromodal association cortex as well as alterations in connections between the thalamus and hippocampus. It remains an interesting topic for future studies to examine the predictive value of the afore-mentioned alterations for developing BPD.

To sum up at this point, structural abnormalities in limbic and frontal structures have been discussed as a possible neuronal underpinning of impaired regulatory mechanisms in BPD. As already mentioned, it has to be clarified whether these findings are specific to BPD or rather stem from traumatic events in childhood or are related to comorbid disorders such as PTSD. A recent study found similar reductions in GMV of the hippocampus, OFC, and ACC in healthy subjects with severe childhood maltreatment (Dannlowski et al., 2012). Thus, adverse events in childhood may possibly lead to the discussed alterations which in turn may be one risk factor in the development of psychiatric disorders like BPD, PTSD, or major depression (Gilbert, Widom, Browne, Fergusson, Webb, & Janson, 2009).

2.3. Functional neuroimaging studies

Further evidence for a dysfunctional fronto-limbic network in BPD stems from functional neuroimaging studies. In the following, an overview over these studies is given referring to the three core domains: 1) disturbed emotion and pain processing, 2) cognitive disturbances and dissociation, 3) behavioral dysregulation and impulsivity, and 4) interpersonal disturbances. At first, findings of resting-state studies are discussed. [2]

[2] Sections on the following studies, which are discussed in the original article, are excluded here: Krause-Utz, Elzinga, Oei, Paret, Niedtfeld, Spinhoven, et al. (2014) and Krause-Utz, Veer, Rombouts, Bohus, Schmahl, & Elzinga (2014).

2.3.1. Resting state functional connectivity

Up to 2014, only two fMRI studies reported alterations in resting-state functional-connectivity (RSFC) in BPD. Wolf and colleagues (2011) investigated 17 BPD patients compared to 17 healthy controls using independent component analyses (ICA) and found significant differences in RSFC in the default mode network as well as in a network comprising fronto-parietal regions. More specifically, BPD patients exhibited decreased RSFC in the left cuneus. Furthermore, these patients showed increased RSFC in the left frontopolar cortex and left insula as well as diminished RSFC in the left inferior parietal lobule and right middle temporal cortex. In line with Wolf and colleagues (2011), Doll and colleagues (2013) observed aberrant resting-state functional connectivity in the default mode network and in the Central Executive Network in 14 BPD patients compared to 16 healthy controls. Compared to controls, BPD patients further showed aberrant RSFC patterns within the salience network and demonstrated imbalanced connections between the three networks, which were most prominently reflected in a shift from the central executive network to the salience network. These observations suggest an impaired flexibility in switching between a network primarily activated during rest and a network associated with salience detection in BPD (Doll et al., 2013). Findings of altered resting state functional connectivity within networks associated with emotion processing, encoding of salient events, and self-referential processing may underlie core features of BPD, such as emotion dysregulation and dissociation.

2.3.2. Emotion processing and emotion regulation

Emotion dysregulation, including an increased sensitivity to emotional stimuli, intense emotional reactions, and deficits in emotion regulation, is one of the most prominent and detrimental features of BPD (Carpenter & Trull, 2013). A large number of functional neuroimaging studies investigated reactivity to standardized emotional material (e.g., arousing pictures of naturalistic scenes, negative facial expressions, autobiographical scripts of traumatic events), cognitive tasks, or sensory stimuli in patients with BPD compared to healthy controls (see Mauchnik & Schmahl, 2010). The majority of these studies and some more recent studies observed a hyper-reactivity of limbic brain areas in response to negative emotional stimuli, most prominently in the amygdala (Donegan et al., 2003; Herpertz et al., 2001; Koenigsberg et al. 2009a; Krause-Utz et al., 2012; Niedtfeld et al., 2010; Minzenberg, Fan, New, Tang, & Siever, 2007; Schulze et al, 2011) and in the insula (Beblo et al., 2006; Krause-Utz et al., 2012; Niedtfeld et al., 2010; Ruocco et al., 2013; Schulze et al, 2011) in BPD patients compared to healthy controls. More recent studies in BPD also provided evidence for a slower return of amygdala activation to baseline (Kamphausen et al., 2013).

The amygdala plays a crucial role in the detection and processing of emotionally salient events and in the initiating of stress and fear responses (Ochsner & Gross, 2007). The insula has been further implicated in salience detection, the encoding of unpleasant feelings and interoceptive awareness (Craig, 2011; Critchley, Mathias, & Dolan, 2001; Damasio et al., 2000; Menon & Uddin, 2010; Seeley et al., 2007). Therefore, increased and prolonged limbic activation during emotional challenge may reflect clinically well-observed features of emotional hypersensitivity and intense, long-lasting emotional reactions in individuals with BPD. However, not all studies replicated this finding (e.g., Guitart-Masip et al., 2009) and contradictory findings were also reported: Results of a recent meta-analysis even point to decreased amygdala activity during processing of negative emotions relative to neutral conditions in patients with BPD compared to healthy controls (Ruocco et al., 2013). However, it is important to note that in most studies, picture material from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2005) was used, which was selected according to affective ratings assessed in healthy people. The results of the meta-analysis (Ruocco et al., 2013) are based on brain activations in response to negative stimuli as compared to neutral stimuli. This may be problematic, since BPD patients tend to perceive neutral stimuli (especially neutral faces) as more threatening than healthy controls (Daros, Zakzanis, & Ruocco, 2013). It has been shown that BPD patients exhibit limbic hyper-reactivity already in response to normatively neutral pictures of facial expressions or interpersonal scenes (Donegan et al., 2003; Koenigsberg et al. 2009a; Krause-Utz et al., 2012; Niedtfeld et al., 2010; Schulze et al, 2011), along with higher arousal ratings of these pictures (Donegan et al., 2003; Krause-Utz et al., 2012). Resembling findings of behavioral emotion recognition studies, amygdala hyper-reactivity to neutral social pictures points to a negativity bias, i.e. a tendency to interpret normative neutral stimuli as emotionally arousing in individuals with BPD (Lis & Bohus, 2013). Inconsistencies of emotional challenging studies in BPD may further be attributable to a moderating effect of situational variables such as dissociation, which is discussed in more details below.

In addition to limbic hyper-reactivity, numerous functional neuroimaging studies point to a hypoactivation of frontal brain regions in response to emotionally arousing or trauma-related stimuli in BPD, suggesting an imbalance within a cortico-limbic brain network. In the study by Minzenberg and colleagues (2007), BPD patients not only showed amygdala hyper-reactivity in response to fearful faces, but also exhibited decreased activation in the ACC.

In a positron emission tomography (PET) study, New and colleagues (2007) demonstrated altered metabolic activity in both limbic and prefrontal areas as well as lower correlation between right OFC and ventral amygdala metabolism in BPD patients. In another PET study,

Prossin, Love, Koeppe, Zubieta, and Silk (2010) measured the selective radiotracer [(11)C]carfentanil during induced states of sadness in BPD patients compared to healthy controls. They found that sadness induction was associated with greater reductions in endogenous opioid system activation in the pregenual ACC, left OFC, left ventral pallidum, left amygdala, and left inferior temporal cortex in BPD patients than in the comparison group. Patients also showed deactivation of the endogenous opioid system in the left nucleus accumbens, the hypothalamus, and the right (para)hippocampus relative to control subjects.

Scherpiet, Bruhl, Opialla, Roth, Jancke, and Herwig (2013) investigated whether individuals with BPD show abnormal activation patterns in the anticipation of emotional stimuli. To this end, they presented either visual cues consistently preceding negative pictures or visual cues that ambiguously announced the valence of the upcoming picture. Compared to healthy controls, patients with BPD exhibited diminished activation in the left middle cingulate cortex and dorsal ACC as well as increased activation in the left PCC, perigenual ACC and lingual gyrus during the anticipation of negative pictures. When processing visual cues that ambiguously announced upcoming pictures, BPD patients showed diminished activation in the left middle cingulate cortex and in parts of the dlPFC. Results of this study suggest a hypervigilance to emotionally relevant cues, associated with imbalanced fronto-limbic brain activation already during the anticipation, i.e., expectancy of emotional cues.

Furthermore, there is evidence for increased functional connectivity within a fronto-limbic network, in terms of a stronger coupling between the amygdala and (pre)frontal brain regions during emotional processing in BPD. In a study by Cullen and colleagues (2011), either neutral, overt fear, or masked far faces were presented during fMRI. BPD patients showed increased connectivity of the amygdala (seed region) with rostral ACC during overt fear and with bilateral thalamus as well as right caudate during the masked fear scan. Under neutral conditions, BPD patients demonstrated diminished amygdala functional connectivity with mid-cingulate cortex compared to healthy individuals.

In another fMRI study by Kamphausen and colleagues (2013), participants were instructed that during a later fMRI scan one of two visual stimuli might potentially indicate an aversive event (electrodermal stimulation), whereas the other stimulus would represent safety. Unlike healthy controls, BPD patients did not show a habituation to instructed fear conditions, in terms of a deactivation in the amygdala or an increase of vmPFC activity over time. Furthermore, they exhibited increased amygdala connectivity with vmPFC and a diminished coupling between subgenual and dorsal ACC (Kamphausen et al., 2013).

Further evidence for a failure to effectively engage emotional habituation processes stems from a study by Koenigsberg, Denny, Fan, Liu, Guerreri, Mayson, Rimsky, New, Goodman, and Siever (2014). In this study, BPD patients showed a lack of increase in dorsal ACC activity along with smaller increases in insula-amygdala functional connectivity while being exposed to repeatedly presented (versus novel) negative pictures.

To more directly investigate the neural correlates of voluntary emotion regulation processes, several fMRI studies in BPD patients applied reappraisal paradigms, which have been established in general emotion regulation research (Ochsner, Bunge, Gross, & Gabrieli, 2002). Patients with BPD showed diminished activity in the dlPFC and ventrolateral prefrontal cortices, while they were instructed to cognitively distance themselves from negative pictures (Koenigsberg et al., 2009b). Likewise, Schulze and colleagues (2011) revealed decreased recruitment of the left OFC and increased activation of the insula during cognitive reappraisal in patients with BPD compared to healthy participants. In a study by Lang, Kotchoubey, Frick, Spitzer, Grabe, and Barnow (2012), BPD patients showed diminished recruitment of brain regions associated with up- and down-regulation of negative emotions (e.g. ACC) compared to healthy controls. A similar pattern was also observed in trauma-exposed healthy individuals, raising the question of the specificity of these findings. To sum up at this point, functional neuroimaging studies on emotion processing in BPD point to a dysfunctional network of fronto-limbic brain regions including limbic hyper-reactivity and diminished recruitment of frontal brain regions. A failure to activate prefrontal control regions may underlie deficient emotion regulation capacities in BPD.

2.3.3. Self-Injury and altered pain processing

Another major characteristic of BPD closely linked to emotion dysregulation is non-suicidal self-injurious behavior (NSSI) (Welch, Linehan, Sylvers, Chittams, & Rizvi, 2008). Numerous studies point to substantial alterations in pain perception in individuals with BPD (see Mauchnik & Schmahl, 2010), associated with reduced amygdala activation in response to pain (Schmahl et al., 2006). Kraus and colleagues (2010a) found that deactivation in the right amygdala was less pronounced in BPD patients without comorbid PTSD compared to patients with comorbid PTSD. In another fMRI study by Kraus and colleagues (2010b), brain activation was assessed during a standardized script describing an act of NSSI (i.e., the situation triggering NSSI, emotional and cognitive reactions to the triggering situation, the act of self-injury itself, and consequences of NSSI) in BPD patients compared to healthy controls. When listening to the situation triggering the act of self-injury, BPD patients showed significantly reduced activation in the OFC as well as increased activation in the dlPFC.

When being instructed to imagine the NSSI act itself, BPD patients showed a significant decline in mid-cingulate activation. Niedtfeld and colleagues (2010) investigated the neural correlates of pain processing in the context of emotion regulation: BPD patients were applied thermal stimuli, while they viewed emotionally arousing pictures (compared to neutral pictures). A decrease of limbic activation was observed in both BPD patients and healthy controls, which was not specific to painful stimulation as opposed to non-painful warmth perception. This finding suggests that amygdala deactivation could also be caused by an attentional shift to sensory stimuli per se (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). In a re-analysis of the data set, Niedtfeld, Kirsch, Schulze, Herpertz, Bohus, and Schmahl (2012) focused on patterns of functional connectivity between amygdala, insula, and ACC. They found a stronger negative coupling between (para-)limbic and prefrontal structures, especially in parts of the medial frontal gyrus (BA8) and DLPFC (BA9), in BPD patients who received pain stimuli in addition to emotionally arousing pictures. These results are in line with the assumption that pain has a modulating effect on affective processing in BPD. In healthy participants, this pattern was only observed for negative pictures paired with warm stimuli, which may be a result of automatic emotion regulation processes in response to negative affective states (Ochsner et al., 2004). Further evidence for altered pain processing in BPD stems from another functional connectivity study by Kluetsch and colleagues (2012). In this study, patients showed lower functional connectivity between the PCC and dlPFC, when exposed to painful heat stimulation compared to neutral temperature. Kluetsch and colleagues (2012) further found a reduced integration of the left retrosplenial cortex, right inferior temporal gyrus, and left superior frontal gyrus in the default mode network, possibly indicating altered appraisals of pain (e.g., as being less self-relevant and aversive) in BPD.

To sum up, findings of functional neuroimaging studies on pain processing suggest that NSSI is a dysfunctional mechanism of emotion regulation in BPD, which may be mediated by different mechanisms, such as attentional shift and altered appraisal of pain.

2.3.4. Cognitive disturbances and dissociation

Cognitive disturbances are another major manifestation of BPD (Lieb et al., 2004; Skodol et al., 2002). Individuals with this disorder often show maladaptive cognitive processes and dysfunctional cognitive styles, such as distorted beliefs about the self and the environment, dichotomous thinking, jumping to conclusions, monocausal attributions, and an instable self-image (Moritz et al., 2011). Cognitive functions, such as memory and inhibitory control, appear to be affected by negative affective states in BPD (Winter et al., 2014).

Several fMRI studies investigated cognitive inhibition of task-irrelevant neutral versus emotional stimuli (e.g. words or pictures) in patients with BPD compared to healthy controls. In a study by Wingenfeld and colleagues (2009b), healthy participants – but not patients with BPD - showed increased activation in the ACC and regions of the frontal cortex during emotional interference (as compared to a control condition) in the context of an individual Emotional Stroop Task. On the behavioral level, no significant group differences were found for emotional interference.

Smoski and colleagues (2011) investigated twelve male BPD patients with opiate dependency compared to twelve healthy men. Patients exhibited diminished amygdala activation, when distracted by emotional stimuli in the context of a modified oddball task.

In contrast, distraction by fearful faces (compared to neutral faces) during a modified flanker task was associated with increased amygdala activation along with increased activation in the ACC in BPD (Holtmann, Herbort, Wustenberg, Soch, Richter, & Walter, 2013). However, increased amygdala activation was only observed during the incongruent, i.e. more difficult condition, but not during the congruent condition of the flanker task.

Patients with BPD further showed significantly increased amygdala activation (along with prolonged reaction times) during emotional distraction in the context of a working memory task compared to healthy controls (Krause-Utz et al., 2012).

Likewise, Prehn and colleagues (2013) reported increased susceptibility to emotional distraction during a modified n-back task in male patients with BPD and antisocial personality disorder. When emotional IAPS pictures were presented as distractors in the background, patients showed delayed reaction times in the n-back task as well as increased activation in the left amygdala. The encoding, maintenance, and retrieval of task-relevant information (in working memory) may be disturbed by emotionally arousing pictures in BPD.

During negative affective states, BPD patients further experience transient paranoid states and dissociation (APA, 2000; Korzekwa et al., 2009; Stiglmayr et al., 2001; Stiglmayr et al., 2008). While the neurobiology of dissociation is not yet completely understood, there is growing evidence for an involvement of fronto-limbic brain regions including the amygdala, insula, hippocampus, and ACC, and thalamus (Lanius et al., 2010; Wolf, Lunney, Miller, Resick, Friedman, & Schnurr, 2012). In BPD, there is primary evidence for increased frontal activation and dampened limbic activation during dissociative states (Hazlett et al., 2012; Krause-Utz et al., 2012; Ludäscher et al., 2010). It remains an important topic for future research to gain deeper insight in the neurobiological underpinnings of dissociation in BPD.

2.3.5. Behavioral dysregulation and impulsivity

As another core dimension, individuals with BPD show impulsive features such as high risk behavior, substance abuse, binge eating, aggressive outbursts, or sudden relationship breakups (see Sebastian, Jung, Krause-Utz, Lieb, Schmahl, & Tüscher, 2014). Early FDG-PET studies in BPD patients pointed to blunted baseline metabolism in prefrontal and premotor brain areas as a potential neurobiological underpinning of impulsivity and impulsive aggression (de la Fuente et al., 1997; Juengling et al., 2003; Lange, Kracht, Herholz, Sachsse, & Irle, 2005; Salavert, Gasol, Vieta, Cervantes, Trampal, & Gispert, 2011). In a more recent study, Wolf and colleagues (2012) revealed diminished blood flow in the medial OFC as well as increased metabolism in right and left lateral OFC. As hypothesized, the authors found significant correlations between medial and lateral OFC and self-reported impulsivity. Another study by Schulz and colleagues (2013) reported significant negative correlations between self-reported hostility and metabolism in frontal brain areas in a group of unmedicated BPD patients. Several FDG-PET studies, investigating brain activation in response to serotonergic agents such as fenfluramine or meta-chlorophenylpiperazine (m-CPP), found an altered metabolism in frontal areas during pharmacological challenge (see Mauchnik & Schmahl, 2010). Perez-Rodriguez and colleagues (2010) found a link between aggression in BPD and a haplotype of the serotonergic gene tryptophan-hydroxylase 2. It has been proposed that deficient serotonergic function – associated with impulsive-aggressive behavior and deficient inhibitory control – may serve as an endophenotype of BPD (Goodman, New, Triebwasser, Collins, & Siever, 2010; Mak & Lam, 2013; McCloskey et al., 2009). Studies comparing BPD patients to patients with other psychiatric disorders (e.g., major depression) are needed to clarify whether findings of serotonergic dysfunction are specific to BPD (Goodman et al., 2010). Moreover, aside from serotonin, other neurotransmitters such as glutamate or GABA seem to be critically involved in impulsivity in BPD. For example, a proton MRS study by Hoerst and colleagues (2010) provided initial evidence for a decisive role of glutamate in the ACC in impulsivity. In this study, significantly higher concentrations of glutamate in the ACC were observed in BPD patients compared to healthy controls. Glutamate concentrations in the ACC were positively correlated with self-reported impulsivity [Barratt-Impulsiveness-Scale (BIS) total-score and BIS-subscale Cognitive Impulsiveness] in both the patient and healthy control group. Coccarro, Lee, and Vezina (2013) investigated glutamate levels in cerebrospinal fluid of 38 subjects with personality disorders and ten healthy controls and found correlations between glutamate concentration and measures of aggression and impulsivity in both groups, although they could not detect any group differences in glutamate levels.

To investigate the neural correlates of aggression, New and colleagues (2009) applied the Point Subtraction Aggression Paradigm (PSAP) - a task provoking aggressive behavior – in BPD patients with intermittent explosive disorder. In this FDG-PET study, healthy participants showed decreased relative glucose metabolic rates in the amygdala and OFC, whereas patients showed increased relative glucose metabolic rate in these areas, when performing the PSAP (compared to a control condition without provocation). Moreover, patients showed diminished activation of the dlPFC in response to provocation compared to healthy controls. A re-analysis of this data set focusing on the striatum – a brain region associated with reward processing – revealed a significantly lower relative glucose metabolic rate in male than in female patients and in healthy controls in response to provocation (Perez-Rodrigues et al. 2012).

It is important to point out that impulsivity is a complex construct which comprises different components such as interference control, reward processing, delay discounting, and response inhibition (Bornovalova, Lejuez, Daughters, Rosenthal, & Lynch, 2005; Evenden, 1999; Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001), which may be modulated by motivational and affective states (Sebastian, Jacob, Lieb, & Tüscher, 2013; Stahl et al., 2013).

Silbersweig and colleagues (2007) were the first to investigate interactions between negative emotions and response inhibition on a neural level, applying an emotional version of a Go/No-Go task during fMRI. BPD patients demonstrated significantly more (‘impulsive’) commission errors and more omission errors in the negative No-Go condition associated with decreased activation in the medial OFC and subgenual ACC. These patients further exhibited increased activation in the dorsal ACC, insula, and in lateral orbitofrontal areas. Activation in the ventral striatum and extended amygdala during the negative No-Go-condition was correlated with self-reported emotional states in the patient group. In another fMRI study, participants performed Go/No-Go tasks after induction of a neutral mood, joy, or anger by vocally presented short stories (Jacob et al., 2013). Compared to healthy controls, BPD patients showed decreased activation in the subgenual ACC and stronger activation in the left amygdala during the anger induction. When performing the Go/No-Go task immediately after this anger induction, healthy participants – but not BPD patients - showed increased activation in the left inferior frontal cortex. BPD patients showed increased activation in the subthalamic nucleus – a brain region implicated in inhibitory control. Since no behavioral differences in task performance were observed, increased activation in this area may reflect a compensatory strategy to prevent the occurrence of impulse control deficits on the behavioral level.

Enzi, Doering, Faber, Hinrichs, Bahmer, and Northoff (2013) examined reward processing during the presentation of emotional stimuli in BPD using fMRI. BPD patients showed difficulties in differentiating between reward-related and non-reward-related anticipation, when negative or positive pictures were presented simultaneously, which was associated with a lack of differential activation in the pregenual ACC and less neural activity in the ventral striatum and the bilateral ventral tegmental area. These findings suggest that BPD patients show deficits in reward processing in an emotional context.

To sum up at this point, recent research points to amygdala hyper-reactivity and hypoactivation of frontal areas involved in impulse control (including the OFC, dorsal ACC, dlPFC) and cortico-striatal pathways as well as serotonergic and glutamatergic dysfunction related to impulsivity in BPD. Moreover, there is growing evidence for impaired inhibitory control in the presence of emotional stimuli in BPD patients (Baer et al., 2012; Fertuck, Lenzenweger, Clarkin, Hoermann, & Stanley, 2006; Sebastian et al., 2013; Stahl et al., 2013).

2.3.6. Interpersonal disturbances

Over the last years, more and more experimental studies have focused on social cognition and social interaction processes in BPD, given the pronounced difficulties patients with this disorder encounter in interpersonal situations (Lis & Bohus, 2013). Clinical expressions of interpersonal disturbances in BPD include intense relationships with frequent episodes of breakups and reconciliations, frantic efforts to avoid abandonment, and difficulties in developing trust in others (Gunderson, 2007; Gunderson & Lyons-Ruth, 2008; King-Casas, Sharp, Lomax-Bream, Lohrenz, Fonagy, & Montague, 2008; Lis & Bohus, 2013). Individuals with BPD further showed a hypersensitivity to social rejection (Staebler, Helbing, Rosenbach, & Renneberg, 2010) and felt socially excluded even in normative neutral situations (Renneberg, Herm, Hahn, Staebler, Lammers, & Roepke, 2012). Moreover, they showed a negativity bias, i.e. a tendency to misinterpret neutral facial expressions as angry or hostile (Barnow et al., 2009; Domes, Czieschnek, Weidler, Berger, Fast, & Herpertz, 2008; Domes, Schulze, & Herpertz, 2009; Dyck et al., 2009; Unoka, Fogd, Fuzy, & Csukly, 2011). On the neural level, BPD patients exhibited a hyper-reactivity of the amygdala and other limbic regions in response to social stimuli such as interpersonal scenes or facial expressions (Donegan et al., 2003; Frick et al., 2012; Holtmann et al., 2013; Krause-Utz et al., 2012; Mier et al., 2013; Minzenberg et al., 2007; Prehn et al., 2013). During face processing, patients with BPD further demonstrated increased activation in the ACC and temporal brain areas (Guitart-Masip et al., 2009; Holtmann et al., 2013) as well as decreased activation in the dlPFC (Radaelli, Poletti, Dallaspezia, Colombo, Smeraldi, & Benedetti, 2011).

Studies that assessed brain activation during theory of mind or empathy tasks (e.g. referring the mental states of others from their affective eye gazes) revealed diminished activation in the right superior temporal sulcus and BA 45 in BPD patients compared to controls (Dziobek, Preissler, Grozdanovic, Heuser, Heekeren, & Roepke, 2011; Frick et al., 2012; Hooley, Gruber, Parker, Guillaumot, Rogowska, & Yurgelun-Todd, 2010; Mier et al., 2013). The first study on neural processing of empathy by Dziobek and coworkers (2011) established the Multifaceted Empathy Test (MET) to assess cognitive and emotional components of empathy, which were both found to be altered in BPD. Moreover, BPD patients showed reduced recruitment of left superior temporal sulcus and gyrus during cognitive empathy. During emotional empathy, heightened activation of the right insula was found in BPD patients compared to healthy controls. In the second study by Frick and colleagues (2012), BPD patients were significantly more accurate and faster in detecting affective eye gazes, which was associated with increased activation in the amygdala, left temporal pole, middle temporal gyrus, and medial frontal gyrus. The third study on theory of mind in BPD by Mier and colleagues (2013) implemented three different social cognition tasks involving face processing, recognition of emotions, and attribution of emotional intentions. Depending on the complexity of the task, healthy controls showed increasing activation in superior temporal sulcus and BA 44, while BPD patients showed hypoactivation in these areas. Additionally, BPD patients showed hyper-activation of the amygdala independent of task complexity. The authors conclude that BPD patients exhibit stronger emotional involvement while processing social stimuli which might hinder social-cognitive processing (Mier et al., 2013). Hooley and colleagues (2010) presented auditory scripts in the fourth study, which consisted of neutral or emotionally overinvolved comments characterized by high levels of anxiety and emotional concern. They found BPD patients to show stronger activation in the left superior frontal gyrus regions during statements of over-involvement compared to healthy controls and patients with dysthymia. Ruocco and colleagues (2010) found increased activation in medial prefrontal cortex in BPD patients compared to healthy controls applying near-infrared spectroscopy during a social exclusion paradigm. Medial prefrontal activation was correlated with rejection sensitivity and fear of abandonment in this study. In an fMRI study by Domsalla and colleagues (2014), subjects played a virtual ball-tossing game with three conditions, including inclusion, exclusion, and a control condition with a fixed order of ball-tosses. The authors found that BPD patients and healthy subjects felt similarly excluded during the exclusion condition.

However, during the inclusion and control conditions, subjects with BPD felt more excluded than controls, which is in line with other studies (Renneberg, Herm, Hahn, Staebler, Lammers, & Roepke, 2012; Staebler, Renneberg, Stopsack, Fiedler, Weiler, & Roepke, 2011). Regarding brain activation, BPD patients showed a stronger engagement of the dorsal ACC and medial prefrontal cortex in all experimental conditions. While healthy subjects showed differential brain activation in the insula and the precuneus depending on the experimental condition, BPD subjects` activation in these regions was not modulated by the experimental condition, but was always high (Domsalla et al., 2014).

Investigating cooperative behavior in BPD, King-Casas and colleagues investigated the expectation of unfairness and cooperative behavior in BPD patients both on a behavioral and neuronal level (2008). Cooperation in BPD patients tended to decrease over time, while it was more stable in healthy dyads. Moreover, BPD patients displayed difficulties to repair broken cooperation. On the neuronal level, King-Casas and colleagues found a differential activation in the insula in healthy control subjects - depending on the fairness of the transaction – whereas insula activity in BPD patients was elevated over the course of the whole experiment. Activation in the insula seems to play an important role in the detection of unfairness in the context of social interaction (King-Casas et al., 2008; Meyer-Lindenberg, 2008; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003).

To sum up, patients with BPD show alterations in the processing of social information, which is also characterized by increased limbic activation. Moreover, activation in the posterior and middle insula (among other brain areas) was found to be related to difficulties in empathy in BPD (Dziobek et al., 2011) and was also observed in the course of cooperative games. Thus, the insula seems to be of high relevance to BPD psychopathology, not only related to emotion dysregulation, but also to difficulties in social interactions.

2.4. Conclusion

We aimed to provide an overview of recent neuroimaging research in BPD, which has grown rapidly over the last years. In sum, research in this area points to functional and structural abnormalities in a network of fronto-limbic brain regions including the amygdala, insula, ACC, OFC, and dlPFC. To clarify whether findings summarized above are specific to BPD, future neuroimaging research should include clinical control groups of patients with trauma history and/or with other disorders that are characterized by affective instability and impulsivity (e.g. major depression, PTSD, Attention Deficit Hyperactivity Disorder).

For instance, it remains controversial whether volumetric and functional abnormalities are related to BPD or may rather stem from traumatic events in childhood or comorbid PTSD, since both conditions are highly prevalent in BPD (Krause-Utz & Schmahl, 2010; Lieb et al., 2004). A study in healthy participants demonstrated structural and functional alterations in persons with childhood maltreatment, which were strikingly similar to some findings in BPD research. More specifically, they found amygdala hyper-reactivity during the presentation of threat-related facial expressions as well as reduced grey matter volumes in the hippocampus, OFC, and ACC, all of which were correlated to the severity of traumatic experiences in childhood (Dannlowski et al., 2012). Alterations in limbic brain regions may therefore be interpreted as mediators between adverse events in childhood and the development of psychiatric disorders like BPD, PTSD, or depression (Gilbert et al., 2009). Nonetheless, it has been argued that adverse events in childhood along with reduced abilities to regulate emotions, proneness to dissociative experiences, and impulsivity may be more specific for the development of BPD (Crowell et al., 2009).

It remains an interesting topic for future research to investigate how different core features of BPD are linked to each other. Hyper-reactivity of the amygdala and insula along with diminished recruitment of frontal brain regions seems to reflect clinically well-observed features of disturbed emotion processing and emotion dysregulation in BPD. However, amygdala activation may be modulated by situational variables such as dissociative experiences, which primarily occur during stressful situations in BPD. Moreover, individuals with BPD showed a deactivation of the amygdala, when experiencing pain during the processing of emotionally arousing stimuli – suggesting a soothing effect of pain that may correspond to the dysfunctional mechanism of self-injurious behavior in BPD. Furthermore, amygdala hyper-reactivity was also observed in response to normative neutral - but mostly interpersonal - stimuli suggesting a tendency to interpret (neutral) social stimuli as emotionally salient in patients with BPD. Altered activation in the amygdala – and also in the insula - may therefore also be related to interpersonal disturbances such as a hypersensitivity to social rejection and a negativity bias in social perception in BPD.

Impulsivity, another core feature of BPD, has been associated with hypoactivation in frontal regions, which are critically involved in inhibitory control, such as the OFC and ACC, as well as altered activation in cortico-striatal pathways. On a neurochemical level, dysfunctions in the serotonin, glutamate, and GABA system, were found to be involved in impulsivity in BPD. Yet, cognitive components of impulsivity such as interference inhibition as well as motor inhibition may be aggravated by negative affective states in BPD.

Inhibitory control is not only important for impulse control, but also crucial to cognitive emotion regulation and social interaction abilities (Bjorklund & Harnishfeger, 1995; Rueda, Posner, & Rothbart, 2005). Altogether, emotion dysregulation, interpersonal disturbances, cognitive impairments, dissociation, altered pain processing, and impulsivity may be closely linked to each other sustaining brain alterations, most prominently in fronto-limbic areas, in BPD. Disturbed emotion processing and maladaptive cognitive processes may lead to a negativity bias toward the perception of potentially threatening social stimuli. Likewise, rejection hypersensitivity and altered social perception (e.g. attentional bias towards negative social information) may lead to heightened emotional vulnerability (MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002), reflected in limbic hyper-reactivity. In our view, the complexity of BPD may be best understood by combining multiple measurements of multiple clinical dimensions: Future studies in BPD could investigate core domains of BPD combining neuroimaging methods with subjective, behavioral, and psychophysiological measurements and not only use cross-sectional but also longitudinal designs.

Chapter 3

Dissociation and Alterations in Brain Function and Structure: Implications for Borderline Personality Disorder

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[3] The following studies, which are discussed in the original article, are not mentioned here: Krause-Utz, Elzinga, Oei, Paret, Niedtfeld, Spinhoven, et al. (2014); Krause-Utz, Veer, Rombouts, Bohus, Schmahl, & Elzinga (2014); Krause-Utz, Winter, Schriner, Chiu, Lis, Spinhoven et al., submitted; Winter, Krause-Utz, Lis, Chiu, Lanius, Schriner, et al. 2015). Parts of the original article, in which these studies are mentioned, are excluded.

Abstract

Dissociation involves disruptions of usually integrated functions of consciousness, perception, memory, identity, and affect (e.g., depersonalization, derealization, numbing, amnesia, analgesia). While the precise neurobiological underpinnings of dissociation remain elusive, neuroimaging studies in disorders, characterized by high dissociation (e.g., Depersonalization/Derealization Disorder (DDD), Dissociative Identity Disorder (DID), and the dissociative subtype of Posttraumatic Stress Disorder (D-PTSD)), have provided valuable insight into brain alterations possibly underlying dissociation. Neuroimaging studies in Borderline Personality Disorder (BPD), investigating links between altered brain function or structure and dissociation, are still relatively rare. In this article, we provide an overview of neurobiological models of dissociation, primarily based on research in DDD, DID, and D-PTSD. Based on this background, we review recent neuroimaging studies on associations between dissociation and altered brain function or structure in BPD. These studies are discussed in the context of earlier findings, with respect to methodological limitations, and concerning possible implications for future research and the clinical setting.

Key words: Dissociation, Trauma, Borderline Personality Disorder, Posttraumatic Stress Disorder (PTSD), Depersonalization Disorder, Dissociative Identity Disorder, Neuroimaging, Brain structure and function

3.1. Introduction

Dissociation is a complex heterogeneous phenomenon. It has been defined 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). This definition implicates a wide range of psychological symptoms (e.g., depersonalization, derealization, emotional numbing, memory fragmentations) and somatoform symptoms (e.g., analgesia) (Holmes et al., 2005; Spiegel & Cardena, 1991; Waller et al., 1996). Aside from the inability to access normally amenable information and control motor processes (*negative symptoms*), dissociation includes involuntary intrusions of sensory, affective, and cognitive information into conscious awareness or behavior, e.g., dissociative flashbacks (*positive symptoms*) (Spiegel & Cardena, 1991). Dissociation can be conceptualized both as a general tendency (*trait dissociation*) and transient state (*state dissociation*) and it can be observed in non-clinical populations, albeit at a much lesser extent than in clinical populations (Holmes et al., 2005; Waller et al., 1996).

Pathological dissociation is a trans-diagnostic phenomenon, highly prevalent in dissociative disorders and in trauma-related disorders, including Depersonalization/ Derealization Disorder (DDD), Dissociative Identity Disorder (DID), Posttraumatic Stress Disorder (PTSD), and Borderline Personality Disorder (BPD) (APA, 2013; Spiegel et al., 2011). With respect to PTSD, the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM5) includes a dissociative subtype of PTSD (D-PTSD), characterized by predominately dissociative responses to traumatic reminders and other stressors in the form of depersonalization and/or derealization (APA, 2013; Dalenberg, Glaser, & Alhassoon, 2012). In BPD, dissociation is primarily stress-related and associated with impaired affective-cognitive functioning (Ebner-Priemer et al., 2009; Haaland & Landro, 2009; Loeffler-Staska, Szerencsics & Blueml, 2010; Stiglmayr et al., 2008). The precise neural underpinnings of dissociation are still unclear. Yet, neuroimaging research in clinical samples characterized by high dissociation (e.g., DDD, DID, D-PTSD) have provided valuable insight into structural and functional brain networks possibly involved in dissociation (Lanius et al., 2010; Vermetten & Spiegel, 2014). Compared to this relatively large body of literature, neuroimaging studies on dissociation in BPD are still relatively rare. Our aim is to give an overview of recent neuroimaging studies in BPD examining associations between state and/or trait dissociation and altered brain structure and function.

Disentangling disorder-specific effects is complicated, as disorders characterized by high dissociation (e.g., BPD, D-PTSD, and dissociative disorders) are highly comorbid and may share etiological factors, such as psychological trauma. Therefore, this overview has two objectives: The first aim is to give an introduction into etiological and neurobiological models of dissociation, primarily based on previous findings in DDD, DID, and D-PTSD. A complete review of this literature is beyond the scope of this article, for more extensive reviews see Lanius and colleagues (2010), Lanius, Brand, Vermetten, Frewen, and Spiegel (2012) Spiegel and colleagues (2011), or Vermetten and Spiegel, (2014). The second aim is to discuss previous neuroimaging studies (including measures of state/trait dissociation) in BPD, with respect to key findings related to dissociation, methodological differences and limitations, and possible implications for future research and the clinical setting.

3.1.1. Etiological models: Trauma and dissociation

Psychological trauma, such as severe and chronic childhood abuse / neglect, has been critically implicated in the development of dissociation (Elbert, Rockstroh, Kolassa, Schauer, & Neuner, 2006; Ford & Courtois, 2014; Gershuny & Thayer, 1999; Lanius et al., 2010; Nijenhuis, Spinhoven, van Dyck, van der Hart, & Vanderlinden, 1998; Schauer& Elbert, 2010; Spiegel et al., 2011; Vermetten & Spiegel, 2014; van der Kolk & van der Hart, 1989), suggesting a complex interaction of genetic, neurobiological, and cognitive predispositions / vulnerabilities and stressful life events (Pieper, Out, Bakermans-Kranenburg, & van Ijzendoorn, 2011; Wolf, Rasmusson, Mitchell, Logue, Baldwin, & Miller, 2014).

Dissociation during traumatic events, also referred to as *peritraumatic dissociation* (Marmar, Weiss, & Metzler, 1998), can be an adaptive defense strategy for coping with overwhelming threat that cannot be prevented or escaped (Spiegel & Cardena, 1991; Vermetten & Spiegel, 2014). States of subjective detachment (e.g., depersonalization, derealization, numbing) may help to create an inner distance to the overwhelming experience by dampening unbearable emotions and reducing conscious awareness of the event. The traumatic situation may be perceived as an unreal film-like scene which is not happening to oneself but observed from a wider distance. Somatoform symptoms such as analgesia and out of body experiences (the sense of floating above one's body) may reduce physical injury (Schauer & Elbert, 2010)

While direct translations between animal and human studies are difficult (Hagenaars, Oitzl, & Roelofs, 2014), some models conceptualize peritraumatic dissociation analogous to the freezing response observed in animals (see e.g., Schauer & Elbert, 2010).

The proximity of threat may at first elicit an orienting response, preparing the organism for an active defense mechanism (*fight or flight* reaction, Cannon, 1929), associated with increased sympathetic nervous system activation (e.g. in heart rate, blood pressure, and stress hormones). In situations that cannot be controlled or escaped, the threatened organism may more likely engage in a passive defense mode, accompanied by tonic immobility, increased parasympathic activity and a 'shut-down' of the arousal system (Fanselow & Lester, 1988; Gershuny & Thayer, 1999; Hagenaars et al., 2014; Schauer & Elbert, 2010). Passive reactions (i.e., tonic immobility) in the face of unescapable threat may enhance survival when the chance of escaping or winning a fight is low or impossible, e.g., by reducing the risk of being detected (Fanselow & Lester, 1988; Nesse, 1999). As pointed out before, translations from animal to human research are complicated, however, given the conceptual and methodological differences (for a more detailed overview and discussion see Hagenaars, Oitzl, and Roelofs, 2014).

There is evidence that peritraumatic dissociation increases the risk of subsequent posttraumatic stress symptoms and the development of PTSD (Bovin & Marx, 2011; Candel & Merckelbach, 2004; Lensvelt-Mulders, van der Hart, van Ochten, van Son, Steele, & Breeman, 2008; Marmar et al., 1998; Van der Hart, van Ochten, van Son, Steele, & Lensvelt-Mulders, 2008; Van der Kolk, McFarlane, & Weisaeth, 1996; Van der Velden & Wittmann, 2008). Although the precise underlying mechanisms remain unknown (Marmar et al., 1998; Van der Hart et al., 2008), disturbed information processing, especially memory alterations, may play an important role in this relationship (Bremner, 1999; Bremner, 2006; Elzinga & Bremner, 2002; Krystal, Bennett, Bremner, Southwick, & Charney, 1996). Dissociation is thought to interfere with a coherent encoding of salient events (Conway & Pleydell-Pearce, 2000), leading to a fragmentation (*compartmentalization*) of memory: Sensory, affective, and cognitive aspects of the traumatic event are encoded and stored as separate elements, which later re-occur as implicit intrusive flashback memories, accompanied by strong sensory impressions as if the traumatic event was happing again in the presence (Bremner, Vermetten, Southwick, Krystal, & Charney, 1998; Brewin, 2001; Brewin & Dalgleish, 1996; Ehlers & Clark, 2000; Foa & Riggs, 1995; Van der Kolk et al., 1996). Moreover, individuals who are highly vulnerable to experience peritraumatic dissociation are more likely to respond in a similar way to traumatic reminders later on in life (Bennett, Modrowski, Kerig, & Chaplo, 2015; Frewen & Lanius, 2006; Frewen & Lanius, 2014). Dissociation can also develop in the aftermath of trauma and generalize across situations, i.e. individuals who learned to dissociate in response to traumatic or otherwise stressful situations are more likely to do so in the presence of relatively 'minor' stressors (Lanius et al., 2010).

Such *trauma-related states of consciousness* comprise distortions in time (e.g., flashback memories), thought (e.g., voice hearing in second-person perspective), body (e.g., depersonalization, out of body experiences), and numbing (Frewen & Lanius, 2006, 2014).

3.1.2. Neurobiological models

Up to now, the precise neural/neurobiological underpinnings of dissociation remain elusive. Yet, a growing number of neuroimaging studies in DDD, DID, and D-PTSD have implicated dissociative symptoms in altered brain structure and function. Over the past decades, neuroimaging has become one of the most important tools in clinical neurobiology. Techniques such as magnetic resonance imaging (MRI), MR spectroscopy (MRS), positron emission tomography (PET), and diffusion tensor imaging (DTI) are used to study abnormalities in the brain. Several studies related their neuroimaging findings to higher scores on psychometric scales like the Dissociative Experiences Scale (DES), measuring trait dissociation with the subscales depersonalization/derealization, amnesia, and absorption (Bernstein & Putnam, 1986), or the Dissociation Stress Scale (DSS), a measure of state dissociation, including items on psychological and somatic dissociation and one item on aversive inner tension (Stiglmayr, Braakmann, Haaf, Stieglitz, & Bohus, 2003; Stiglmayr, Schmahl, Bremner, Bohus, & Ebner-Priemer, 2009; Stiglmayr et al., 2010). Some studies used script-driven imagery as an attempt to mimic everyday-life experiences of dissociation (Lanius et al., 2002; 2004; 2005; Ludäscher et al., 2010): A narrative of an autobiographical situation involving dissociative experiences ('dissociation script', as compared to an emotionally neutral script) is created together with each participant and presented in an experimental setting (e.g., during fMRI). Participants are instructed to recall the specific situation as vividly as possible. Other studies used pharmacological challenge (e.g., NMDA antagonists, cannabinoids) to induce dissociative symptoms (Krystal, Bremner, Southwick, & Charney, 1998). In the following, neurobiological models of dissociation, primarily based on research in DDD, DID, and D-PTSD, are discussed.

3.1.2.1. Cortico-limbic-disconnection model: Research in depersonalization disorder

Already in 1998, Sierra and Berrios proposed that symptoms of depersonalization may be associated with a 'disconnection' of a cortico-limbic brain system, involving the amygdala, ACC and prefrontal structures. In this model, depersonalization is more broadly conceptualized as a state of subjective detachment, involving emotional numbing, emptiness of thoughts, analgesia, and hypervigilance (Sierra & Berrios, 1998). It is assumed that these symptoms are associated with increased activity in the medial prefrontal cortex (mPFC), dorsolateral prefrontal cortex (dlPFC), and ACC (Sierra & Berrios, 1998), brain areas implicated in attention, cognitive control, and arousal modulation.

Increased recruitment of the PFC can - both directly and indirectly via the ACC - lead to dampened activity in the amygdala and a marked attenuation of automatic responses, comparable to 'shutting down the affective system' (Phillips, Drevets, Rauch, & Lane, 2003; Sierra & Berrios, 1998; Sierra et al., 2002). The amygdala is fundamentally involved in salience detection and emotion processing such as the initiation of stress and fear responses (Davis & Whalen, 2001; Ochsner & Gross, 2007; Phan et al., 2004; Phillips et al., 2003). States of disconnectedness and numbing may thus be associated with reduced reactivity in this area (Phillips & Sierra, 2003).

Using fMRI, Phillips and colleagues (2001) investigated changes in Blood-Oxygen-Level-Dependent (BOLD) signal (hemodynamic response) during the presentation of aversive versus neutral images in patients with chronic depersonalization disorder, patients with obsessive-compulsive disorder (OCD), and healthy controls (HC). In response to aversive images, depersonalization disorder patients reported less arousal and showed diminished activity in the occipito-temporal cortex, ACC, and insula compared to OCD and HCs (Phillips et al., 2001). The insula plays an important role in attention modulation, encoding of negative emotions, interoceptive awareness, and pain perception (Critchley, Mathias, & Dolan, 2001; Damasio et al., 2000; Dosenbach et al., 2006; Menon, 2011; Menon & Uddin, 2010). Diminished activity in this area may therefore reflect reduced interoceptive/emotional awareness (Phillips et al., 2001; Sedeno et al., 2014) – an assumption that is supported by a more recent study in chronic depersonalization patients: In this study by Lemche and colleagues (2013), altered anterior insula and dorsal ACC reactivity to sad emotional expressions was associated with traits of alexithymia, i.e., difficulties in identifying and describing feelings. In another study of this group (Lemche et al., 2016), a stronger coupling of the dorsomedial PFC (Brodman area (BA) 9) and posterior cingulate cortex (PCC) (BA31) was found in depersonalization disorder patients. The PCC is a critical node of the default mode network (DMN), a brain network that has been implicated in "inward-directed" (self-referential) processes, such as episodic memory encoding and retrieval, self-monitoring, daydreaming, planning, rumination, and pain processing (Greicius, 2008; Greicius et al., 2003; Raichle et al., 2001). Further evidence for altered self-referential processing in depersonalization disorder patients stems from a fMRI study in which DDD patients were exposed to either their own photographs or photographs of a stranger's face (Ketay, Hamilton, Haas, & Simeon, 2014). While viewing own photographs, patients showed stronger activity in areas implicated in self-referential processing, such as the mPFC, which was positively correlated with depersonalization severity.

Brain function in depersonalization disorder may also be altered in the absence of experimental stimulation: In a PET study by Simeon and colleagues (2000), patients with chronic depersonalization disorder demonstrated significantly lower baseline metabolic activity in the right middle/superior temporal gyrus (BA 21/22) and higher glucose metabolism in parietal and occipital areas (BA 7, 39, and 19) - metabolic activity in area 7B was positively correlated with clinical depersonalization scores (Simeon, Guralnik, Hazlett, Spiegel-Cohen, Hollander, & Buchsbaum, 2000). Altered glucose metabolism in tempo-parietal regions may play a role in 'feeling unreal', e.g., altered consciousness, sensory integration, body schema, and memory (Simeon et al., 2000). Further evidence for an important role of temporal regions, including the superior temporal gyrus, stems from observations in patients with temporal lobe epilepsy (Spiegel, 1991) and research on the role of the temporal lobe in memory processing (Bremner, 1999). In sum, there is evidence for altered activity in brain regions associated with emotional and self-referential processing in patients with chronic depersonalization disorder.

3.1.2.2. Models on emotion modulation: Research in the dissociative subtype of PTSD

Based on earlier research in PTSD, Krystal and colleagues (1995) proposed that the thalamus plays an important role in dissociative-like states of altered consciousness. One of the functions of the thalamus is that of a sensory gate or filter, receiving direct and indirect input from sub-cortical areas (e.g. raphe nuclei, locus coeruleus), limbic regions (e.g., amygdala), and frontal areas (e.g., ACC, prefrontal cortices) (Krystal, Bennett, Bremner, Southwick, & Charney, 1995). Within this network, the thalamus may both directly and indirectly modulate responses to environmental stimuli, facilitating or impeding the flow of information (Krystal et al., 1995, 1996, 1998). Furthermore, the hippocampus and para-hippocampal regions may be critical to the understanding of altered memory processing during dissociation (Bremner, 1999; 2006; Elzinga & Bremner, 2002; Krystal et al., 1998).

Based on more recent neuroimaging findings in PTSD, Lanius and colleagues (2010) proposed a neurobiological model that distinguishes between two types of responses to traumatic reminders or other stressors. Patients with a dissociative response type (D-PTSD) who 'over-modulate' their emotions, as opposed to patients who primarily suffer from re-experiencing symptoms, affective hyperarousal, intense feelings of shame, disgust, guilt, and difficulties in emotion down-regulation ('re-experiencing response type') (p. 640). Emotion over-modulation (dissociative response-type) is thought to primarily activate frontal regions implicated in cognitive control and emotion down-regulation (e.g., dorsal/rostral ACC, mPFC), associated with dampened activity in the amygdala and insula.

The reversed pattern - diminished frontal recruitment (ACC, mPFC) and hyperactivity in the amygdala and insula – is assumed to underlie emotion under-modulation (re-experience response type). Central to the development of this model (Lanius et al., 2010) was a script-driven imagery fMRI study (Lanius et al., 2002), in which PTSD patients were exposed to autobiographical narratives of traumatic events. The majority of patients (~70%) reported marked re-experiencing symptoms and showed a substantial increase in heart rate during the script. In a smaller patient group (~30%), however, this heart rate increase was not observed – instead these patients showed stronger activity in medial frontal gyrus, anterior and medial cingulate, middle temporal gyri (BA38), precuneus, occipital areas, and inferior frontal gyrus (IFG), compared to a control group of traumatized persons who had not developed PTSD.

In another fMRI study (Felmingham et al., 2008), patients with D-PTSD showed increased activity in the amygdala, insula, and thalamus while fearful vs. neutral facial expressions were presented non-consciously. Interestingly, these limbic(-related) areas were not significantly activated, when images were presented consciously. In the latter case, dissociative patients showed increased activity in ventral PFC and diminished activity in the dorsomedial PFC, suggesting a conscious over-modulation of emotions and suppression of self-referential processing (Felmingham et al., 2008).

In PTSD patients who showed dissociative responses to autobiographical trauma scripts (compared to patients with a flashback response and healthy controls), furthermore, altered functional connectivity between areas implicated in sensory processing, consciousness, memory, and emotion regulation was found (Lanius et al., 2005). These patients showed stronger FC of left ventrolateral thalamus (VLT) with right insula, middle frontal gyrus, superior temporal gyrus, cuneus, and with left parietal lobe, but reduced VLT-FC with left superior frontal gyrus, right parahippocampal gyrus, and right superior occipital gyrus.
Compared to patients with a flashback response, dissociative patients further demonstrated an increased coupling of right cingulate gyrus with left IFG (Lanius et al., 2005).

In the absence of experimental tasks, altered resting-state functional connectivity (RSFC) in the DMN was found in patients with D-PTSD (Tursich, Ros, Frewen, Kluetsch, Calhoun, & Lanius, 2015), including altered synchrony between the DMN and the Central Executive Network (Menon V, Uddin, 2010; Sridharan, Levitin, & Menon, 2008).
Findings of altered intra-network resting-state connectivity (in DMN) and altered inter-network connectivity were significantly associated with depersonalization and derealization severity (Tursich et al., 2015).

In another RS-fMRI study (Nicholson et al., 2015), patients with D-PTSD (compared to patients without the dissociative subtype and healthy controls) demonstrated increased amygdala FC with prefrontal and parietal regions, including the dorsal PCC and precuneus, which may further point to a distinct 'neurobiological profile' of D-PTSD (Nicholson et al., 2015).

3.1.2.3. Research in dissociative identity disorder (DID)

Evidence suggests that the aforementioned neurobiological alterations may not be specific to a certain disorder but rather represent a trans-diagnostic phenomenon underlying dissociation. Recent findings in DID (Reinders et al., 2006; Reinders, Willemsen, den Boer, Vos, Veltman, & Loewenstein, 2014) resemble findings for D-PTSD, albeit intra-individual (instead of inter-individual) differences were observed: Neurobiological responses significantly differed depending on whether DID patients were in a 'hyper-aroused traumatic identity state' (with voluntary access to traumatic memories) or in their 'normal dissociative identity state' (characterized by dissociative amnesia). In two studies by Reinders and colleagues, DID patients showed elevated cardiovascular responses (heart rate, blood pressure) and stronger amygdala and insula activity, along with lower activity in cingulate gyrus, parietal cortex and para-hippocampus when exposed to a trauma script (versus neutral script) while being in their 'hyper-aroused traumatic identity state' than in their neutral 'hypo-aroused identity state' (Reinders et al., 2006, 2014). In another study, DID patients exhibited increased perfusion in bilateral thalamus while being in their (apparently) 'normal' state of identity compared to an (apparently) 'emotional' identity state (Schlumpf, Reinders, Nijenhuis, Luechinger, van Osch, & Jancke, 2014). More research is needed to clarify whether brain activity patterns may be state-dependent or represent stable inter-individual differences, which may allow for discrimination between diagnostic subgroups (Lanius et al., 2010).

3.1.2.4. Research on structural alterations

Aside from functional alterations, several studies reported structural abnormalities in clinical samples with high trait dissociation, although these structural findings are still quite heterogeneous. In depersonalization disorder, reduced grey matter volumes (GMV) in right thalamus, caudate, and cuneus, and increased GMV in left dorsomedial PFC and right somatosensory regions were observed (Daniels, Gaebler, Lamke, & Walter, 2015).

In DID, reduced volumes in the amygdala and hippocampus (Ehling, Nijenhuis, & Krikke, 2008; Vermetten, Schmahl, Lindner, Loewenstein, & Bremner, 2006) and para-hippocampus (Ehling et al., 2008) were found, although discrepant findings of normal amygdala and hippocampal volumes compared to healthy controls were also reported (Weniger, Lange, Sachsse, & Irle, 2008).

Smaller hippocampal volumes may be related to early life trauma: The hippocampus has a high density of glucocorticoid receptors and is highly sensitive to heightened releases of the stress hormone cortisol - therefore, chronic traumatic stress may lead to cell damage in this area (Bremner, 1999; 2006; Elzinga & Bremner, 2002; Krystal et al., 1996). Smaller hippocampal volumes were also found in healthy individuals with childhood trauma who did not develop a disorder (Dannlowski et al., 2012). Reduced hippocampal volumes in PTSD (Daniels, Frewen, Theberge, & Lanius, 2016; Karl, Schaefer, Malta, Dorfel, Rohleder, & Werner, 2006) may therefore stem from a history of trauma rather than specific to the diagnosis (Woon & Hedges, 2009). In a recent study (Daniels et al., 2016), comparing PTSD patients with versus without the dissociative subtype, no significant group differences in amygdala, hippocampus, and para-hippocampus volumes were observed. Yet, patients with D-PTSD showed increased GMV in right precentral and fusiform gyri and reduced GMV in right inferior temporal gyrus. Severity of depersonalization and derealization was positively correlated with GMV in the right middle frontal gyrus (Daniels et al., 2016). Another study in PTSD (Nardo et al., 2013) found positive associations between trait dissociation and GMVs in medial/lateral PFC, orbitofrontal, temporal polar, para-hippocampal, and inferior parietal cortices – brain regions associated with emotion regulation. Extending findings on GMV alterations, a recent study in dissociative disorders (Basmaci Kandemir et al., 2015) found significantly lower fractional anisotropy in white matter of the right anterior corona radiate (which receives projections from the basal ganglia) compared to healthy controls. More research is needed to understand how these alterations may be related to specific clinical symptoms of dissociation.

As already pointed out in the context of functional neuroimaging studies, interpretation of structural studies may be complicated by the presence of comorbidities. Patients with comorbid PTSD+DID showed significantly larger volumes of the putamen and pallidum than PTSD patients without DID (Chalavi et al., 2015). Volumes of these regions (implicated in motor control (Aron & Robbins, 2014; Goldman-Rakic, Bates, & Chafe, 1992) were negatively correlated with severity of derealization/depersonalization (Chalavi et al., 2015). Patients with PTSD+DID (but not PTSD patients without DID) further showed smaller hippocampal volumes than healthy controls (Chalavi et al., 2015).

Studies with clinical control groups including both functional and structural measures may give additional insight (Krause-Utz & Schmahl, 2016). Of note, structural alterations do not necessarily reflect functional alterations, i.e. more frequent engagement of a specific brain areas does not necessarily have to be reflected in larger volume of this region and vice versa.

3.1.3. Interim summary

In sum, theoretical assumptions and research in depersonalization disorder (DDD), DID, and D-PTSD suggest a link between dissociative symptoms and alterations in brain regions associated with emotion processing and memory (amygdala, hippocampus, parahippocampal gyrus, middle/superior temporal gyrus), attention and interoceptive awareness (insula), filtering of sensory input (thalamus), self-referential processes (PCC, precuneus, mPFC), cognitive control, and arousal modulation (IFG, ACC, lateral prefrontal cortices). Since many studies did not include clinical control groups or groups of traumatized individuals who did not develop a disorder, it remains unclear whether the aforementioned results are related to a specific disorder or a trans-diagnostic feature, possibly underlying dissociation. In general, correlational findings (e.g., linking increased brain activity / structure to higher psychometric scores of dissociation) do not allow causal conclusions, i.e. whether they are a predisposition for or a result of frequent dissociative experiences.

3.2. Dissociation in Borderline Personality Disorder (BPD)

Our second aim is to review neuroimaging studies in BPD that investigated links to dissociative symptoms. We therefore searched databases (PubMed, PsychInfo, Web of Science, Science Direct) for different combinations of 'Borderline Personality Disorder', 'Dissociation', and the following keywords: Brain, Brain Alterations, Functional Magnetic Resonance Imaging, Magnetic Resonance Imaging, Neurobiological, Neuroimaging, Neuro-physiological, Positron Emission Tomography, and Structural Magnetic Resonance Imaging. In the next section, we first describe clinical expressions of dissociation in BPD to provide a background for the subsequent discussion of neuroimaging findings.

3.2.1. Clinical expressions of dissociation in BPD

Transient stress-related dissociative states are a hallmark of BPD (Korzekwa et al., 2009; Stiglmayr et al., 2008; Vermetten & Spiegel, 2014) and have been defined as one of the nine diagnostic criteria for the disorder in DSM-IV (APA, 2000). In DSM5, 'dissociative states under stress' are still listed as an important BPD feature (APA, 2013). Stress-related dissociation occurs in about 75-80% of BPD patients (Chopra & Beatson, 1986; Korzekwa et al., 2009a, 2009b; Skodol et al., 2002; Simeon et al., 2003; Stiglmayr et al., 2008; Zanarini et al., 2000, 2008), typically lasting for minutes and hours or even for days (Banich et al., 2009; Ludäscher et al. 2007). The strength, frequency, and intensity of dissociative experiences are positively correlated to self-reported arousal/stress levels (Stiglmayr et al., 2008).

Research in BPD has found reasonably strong relationships between dissociation and childhood trauma, especially sexual abuse (Dutra et al., 2009; Ross-Gower, Waller, Tyson, & Elliott, 1998; Shearer, 1994; Van Den Bosch et al., 2003; Zanarini et al., 2000), physical abuse, attachment difficulties, and parental neglect (Dalenberg et al., 2012; Ogawa et al., 1997; Zanarini et al., 2000). It has been proposed that stress-related dissociation in BPD may be a form of emotion over-modulation, comparable to observations in D-PTSD, especially in patients with severe childhood trauma (Brand & Lanius, 2014). By interfering with mental resources that are crucial to cognitive functioning, stress-related dissociation may hinder recovery (Arntz et al., 2015). BPD patients with high trait dissociation showed significant impairments across multiple neuropsychological domains, including memory, attention, and interference inhibition (Haaland & Landro, 2009; Winter et al., 2014). More neuroimaging research is needed to understand the effect of experimentally induced dissociation on affective-cognitive functioning on a neural level in BPD.

3.2.2. Neuroimaging research on dissociation in BPD

To our knowledge, only relatively few neuroimaging studies in BPD examined links between trait or state dissociation and brain function during rest (Lange, Kracht, Herholz, Sachsse, & Irle, 2005; Sar, Unal, & Ozturk, 2007; Wolf et al., 2011; Wolf, Thomann, Sambataro, Vasic, Schmid, & Wolf, 2012) or experimental tasks (Hazlett et al., 2012; Kluetsch et al., 2012; Kraus et al., 2009; Krause-Utz et al., 2012, 2015; Wingenfeld et al., 2009b). In the following, we provide an overview of neuroimaging studies. Table 3.1 gives an overview of key results and methodological characteristics of these studies. In all studies, BPD was assessed according to DSM-IV (APA, 2000).

3.2.2.1. Brain function during rest: PET, SPECT, and RS-fMRI studies

Lange and colleagues (2005) used 18fluoro-2-deoxyglucose (FDG-)PET to investigate glucose metabolism in 17 BPD patients with a history of childhood sexual/physical abuse (mixed-gender, partly medicated, see Table 3.1) and 9 healthy controls (HC). BPD patients displayed reduced FDG uptake in the right temporal pole, anterior fusiform gyrus, and left precuneus and PCC. Impaired memory performance among patients was correlated with metabolic activity in ventromedial and lateral temporal cortices (implicated in episodic memory consolidation and retrieval), while no correlations with trait dissociation (DES) were reported. The finding of decreased temporo-parietal metabolism was discussed as a possible neural underpinning of altered memory processes that may play a role in the context of dissociation (Lange et al., 2005). However, sample sizes were relatively small, and due to comorbidities (depersonalization disorder, DID, PTSD) findings may not be specific to BPD.

Table 3.1. *Overview of studies on links between brain function/structure and dissociation in BPD*

Study	**Sample characteristics** Groups (*n*), gender, medication, trauma history, comorbidities	**Neuroimaging technique, Measure of dissociation** Trait/state, time of assessment	**Key findings on dissociation**
Hazlett et al. (2012)	• BPD (*n*= 33), Schizotypal PD (*n*= 28), HC (*n*= 32). Female/male (BPD: 20/13 SPD: 12/16, HC: 20/12) • Medication-free for ≥ 6 weeks and mostly medication-naïve. • High rates of trauma in BPD Exclusion of schizophrenia, psychotic disorder, bipolar I	• Event-related fMRI to assess changes in BOLD response to neutral, pleasant and unpleasant IAPS pictures, each of which presented twice within the respective trial • Self-reported trait dissociation: Dissociation Experience Scale (DES)	• Increased and prolonged amygdala activity during repeated emotional vs. neutral pictures in BPD • Fewer dissociation correlated with greater amygdala activation to repeated negative pictures in both patient groups
Hoerst et al., (2010b)	• BPD (*n*= 30), HC (*n*= 30). Female • Unmedicated for ≥ 3 months • Current/past PTSD in 11/13, MDD in 3/18. No substance abuse, bipolar I, schizophrenia	• Proton magnetic resonance spectroscopy to measure glutamate values in the ACC • Self-reported trait dissociation: DES (among self-reports of impulsivity)	• Significantly higher levels of glutamate in the ACC in BPD than in HC • Positive correlation of glutamate values with dissociation and impulsivity
Irle et al., 2007	• BPD (*n*= 30), HC (*n*= 25). Female • 8 patients received SSRIs, 6 occasionally sedatives • High rates of physical and sexual abuse. Current and past PTSD in 11, DID in 4, DA in 7, DD in 27 patients	• Structural MRI to assess volumes of the superior and inferior parietal cortices. • Assessment of dissociative disorders (SCID-D) and dissociative symptoms (Diagnostic Interview for Borderline Patients)	• Patients with comorbid dissociative disorders had larger left postcentral gyrus volumes than HC and BPD patients without DID/DA • Depersonalization was positively correlated to right precuneus size
Kluetsch et al., (2012)	• BPD with history of self-harm (*n*= 25), HC (*n*= 23). Female • Medication-free for ≥2 weeks • Current/past PTSD in 9/9. No current MDD, schizophrenia, substance abuse, bipolar-I	• FMRI during painful heat vs neutral temperature stimulation • Self-reported trait dissociation (DES) and state dissociation, before and after scan (DSS).	Higher self-reported trait dissociation was associated with an attenuated signal decrease of the default mode network in response to painful stimulation.
Kraus et al., (2009)	• BPD with comorbid PTSD (BPD+PTSD, n=12), BPD without PTSD (n=17). Female • Medication free for ≥2 weeks • Current MDD, substance abuse, schizophrenia and bipolar-I were excluded	• FMRI during painful heat vs neutral temperature stimulation with individually adapted temperature • Self-reported trait dissociation (DES) and state dissociation at the time of scanning (DSS).	• No group differences in pain sensitivity • BPD+PTSD showed more pronounced amygdala deactivation, independent of state dissociation
Krause-Utz et al., 2012	• BPD (*n*= 22), HC (*n*= 22). Female • Medication-free for ≥2 weeks • All patients with interpersonal trauma. Current/past PTSD in 9/11. No crt. MDD, substance abuse, bipolar I, schizophrenia	• Event-related fMRI during an Emotional Working Memory Task (EWMT) with negative vs. neutral IAPS pictures. • Self-reported trait dissociation (DES) and state dissociation before and after scan (DSS4).	In BPD, increase of self-reported dissociation negatively predicted amygdala activity during emotional distraction.

Krause-Utz, et al., 2015	• BPD (*n*= 27), HC (*n*=26). Female • Medication-free for ≥ 4 weeks • Current/lifetime PTSD in 14/18 patients. No lifetime psychotic disorder, bipolar I, and crt. substance abuse.	• FMRI during a differential fear conditioning paradigm with an electric shock as unconditioned stimulus and neutral pictures as CS+, CS-. • Trait dissociation (DES) and state dissociation (DSS).	• Amygdala habituation to $CS+^{paired}$ (in contingency with the aversive event) during acquisition in HC but not in BPD. • No correlations with dissociation.
Lange et al., (2005)	• BPD (*n*=17), HC (*n*=9). Female • 5 patients were treated with antidepressant medication, 3 occasionally with neuroleptics 4 with benzodiazepines. • All patients had suffered from sexual and physical abuse. PTSD in 6, DA in 4, DID in 1, MDD in 16, DD in 14 patients	• (18)fluoro-2-deoxyglucose positron emission tomography (FDG-PET) to assess glucose metabolism in temporo-parietal cortices. • Assessment of comorbid dissociative disorders (SCID-D) and self-reported trait dissociation (DES).	• Reduced FDG uptake in the right temporal pole/anterior fusiform gyrus and in the left precuneus and posterior cingulate cortex in BPD • In BPD, impaired memory performance was correlated with metabolic activity in ventromedial and lateral temporal cortices.
Ludä-scher et al., (2010)	• BPD (*n*=15). Female • Medication-free for ≥ 14 days • Current PTSD in 10 BPD patients (BPD+PTSD) following severe childhood abuse (sexual abuse: 6, physical abuse: 3, neglect: 1). Lifetime psychotic disorder, bipolar I disorder, and current substance abuse excluded.	• FMRI during script-driven imagery: Participants were exposed to personalized dissociative inducing scripts (versus to a neutral script) during the scan. • Self-reported trait dissociation (DES) and state dissociation before and after the script inside the scanner (DSS)	• Increased activity in the left inferior frontal gyrus during the dissociation script • In BPD+PTSD: Stronger activity in the left cingulate gyrus during dissociation, Higher DSS correlated with higher insula activity and lower activity in the right parahippocampal gyrus.
Niedtfeld et al. (2013)	• BPD (*n*=60), HC (*n*= 60). Female • Medication-free for ≥ 14 days • PTSD in 21 patients. No psychotic or bipolar I disorder	• Structural MRI, Voxel Based Morphometry • Trait dissociation (DES) scores were available in 42 BPD patients.	In BPD, trait dissociation (DES scores) were positively correlated to grey matter volumes in middle/ superior temporal gyrus
Paret et al., (2016)	• Group: BPD (*n*=8). Female • All patients were on stable medication.	• Real-time-fMRI based neurofeedback training with feedback from a thermometer on amygdala BOLD signals. • State dissociation (DSS-4) at the end of each run.	• Increased amygdala-vmPFC connectivity during emotion regulation (vs. passive viewing) • State dissociation decreased with training.
Rüsch et al., (2007)	• BPD with comorbid ADHD (*n*= 20), HC (*n*= 20). Female • Medication-free for ≥14 days • Sexual childhood abuse in 10 patients. Current PTSD in 5, past MDD in 4 patients. Exclusion of current MDD and substance abuse, lifetime substance dependence, schizophrenia, and bipolar-I.	• Diffusion tensor imaging (DTI) to measure mean diffusivity and fractional anisotropy in the inferior frontal white matter. • Self-reported trait dissociation (DES).	Patients showed increased mean diffusivity in inferior frontal white matter, which was associated with higher levels of dissociative symptoms, dysfunctional affect regulation, anger-hostility, and general psychopathology but not associated with a history of sexual abuse.

Sar et al., 2007	• DID (*n*= 21, in 15 patients comorbid BPD), HC without trauma history (*n*= 9) • Female/male (BPD: 14/7, HC: 6/3) • Medication-free for ≥ 1 month • All patients reported ≥ one type of severe abuse/ neglect	• Single photon emission computed tomography (SPECT) with Tc99m-hexamethylpropylenamine (HMPAO) as a tracer to measure regional cerebral blood flow. • Trait dissociation (DES).	• Reduced cerebral blood flow in the OFC and occipital regions in DID. • There were no significant correlations between rCBF ratios of the regions of interest and self-reported dissociation
Wingen-feld et al., (2009)	• BPD (*n*=20), HC (*n*=20) • 14 females and 6 males each • 12 patients received psychotropic medication • 17 BPD patients reported at least mild PTSD symptoms. Current PTSD in 5, MDD in 3, bulimia nervosa in 3, social phobia in 1, somatoform disorder in 1 patients. MDD+psychotic symptoms, schizophrenia, schizoaffective disorders and substance dependence were excluded	• FMRI during performance of an individualized Emotional Stroop Task with neutral, general negative words and individual negative words (based on a prior interview with each participant) • Self-reported state dissociation before and after scanning (DSS acute) and in the past 7 days (DSS21).	• BPD patients had slower overall reaction times • HC but not BPD patients - showed significant recruitment of the ACC for negative vs. neutral and individual negative vs. neutral conditions, respectively. • No significant correlations between DSS scores and reaction times or BOLD signal were reported.
Wolf et al., (2011)	• BPD (*n*=17), HC (*n*=17). Female • Stable medication (mood stabilizers, antidepressants, antipsychotics) for ≥14 days. • Current/lifetime MDD in 9/5, past substance abuse in 6 patients. Current PTSD and substance abuse, lifetime schizophrenia, bipolar, and ADHD excluded.	• Resting-state fMRI was acquired to investigate resting state functional connectivity (RSFC) in large-scale brain networks. • Self-reported dissociation (DSS).	Self-reported state dissociation and tension (DSS) positively predicted RS functional connectivity of the insula and precuneus in the BPD group.
Wolf et al., (2012)	• BPD (*n*= 16), HC (*n*= 16). Female • Patients were on stable medication for ≥14 days. • Current/lifetime MDD in 8/5, past substance abuse in n=6. Current PTSD and substance abuse, lifetime schizophrenia, bipolar, and ADHD excluded.	• Continuous arterial spin labeling magnetic resonance imaging. • Self-reported dissociation (DSS).	• Decreased blood flow in medial OFC, increased blood flow in the left and right lateral OFC in BPD • Medial and lateral orbitofrontal blood flow positively correlated with impulsivity, no correlation with DSS.

Note: ACC=Anterior Cingulate Cortex, BOLD=Blood Oxygen Level-Dependent, DA=Dissociative amnesia, DD=Depersonalization Disorder, DID=Dissociative Identity Disorder, fMRI=functional Magnetic Resonance Imaging, HC=Healthy controls, IAPS=International Affective Picture System, MDD=Major Depressive Disorder, *n*=sample size, OFC=Orbitofrontal Cortex, PD=Personality Disorder PTSD= Posttraumatic Stress Disorder, SCID-D=Structural Clinical Interview for DSM-IV Dissociative Disorders, SSRI= Selective serotonin reuptake inhibitors.

Sar, Unal, and Ozturk (2007). used single photon emission computed tomography (SPECT) with Tc99m-hexamethylpropylenamine (HMPAO) as a tracer to investigate regional cerebral blood flow (rCBF) in an unmedicated sample of DID patients (n=21), 15 of whom met criteria for comorbid BPD, and 9 HCs. Compared to HCs, patients showed decreased rCBF ratio in bilateral medial OFC and increased rCBF in medial/superior frontal regions and occipital regions bilaterally. No significant correlation with dissociation was reported.

Wolf and colleagues (2012) used continuous arterial spin labeling MRI to measure alterations in blood flow in 16 female BPD patients without comorbid PTSD (partly medicated but on a stable medication) and 16 HCs. Compared to HCs, patients exhibited decreased blow flow in the medial OFC, while increased blood flow was found in the lateral OFC bilaterally (Wolf et al., 2012). Like in the study by Sar and colleagues (2007), no significant correlation with self-reported dissociation (DSS) was observed. Instead, medial and lateral OFC blood flow was positively correlated with impulsivity, as measured with the Barrett Impulsiveness Scale (BIS) (Patton, Stanford, & Barratt, 1995) – suggesting an association with impulsivity rather than with dissociation. In 17 BPD patients and 17 HCs, Wolf and colleagues (2011) investigated changes in RSFC using RS-fMRI. Within the DMN, patients showed increased RSFC in the left frontopolar cortex and insula and decreased RSFC in the left cuneus. In the fronto-parietal network, patients exhibited decreased RSFC in the left inferior parietal lobule and right middle temporal cortex compared to HCs. No significant group differences were observed in two other networks comprising lateral prefrontal and cingulate regions. In the BPD group, state dissociation (DSS) positively predicted RSFC in the insula and precuneus (Wolf et al., 2011) - as previously mentioned, these regions play a role in self- referential processes. These findings provide primary evidence for a possible role of dissociation in altered RSFC in BPD. As pointed out before, no causal conclusions can be drawn from correlational findings. In order to gain more insight into the impact of dissociation on RSFC of large-scale brain networks in BPD, future studies may acquire resting-state scans before and after experimentally inducing dissociation (e.g. via script-driven imagery) and before and after therapeutic interventions aimed at a reduction of dissociative symptoms. Again, factors such as comorbidities (e.g., with depersonalization disorder (Lange et al., 2005), DID (Lange et al., 2005; Sar et al., 2007)), psychotropic medication (Lange et al., 2005; Wolf et al., 2011; Wolf et al., 2012), and relatively small sample sizes may complicate the interpretation of results.

3.2.2.2. Neurochemical alterations: MRS studies

MRS assesses concentrations of neurochemical metabolites like glutamate, N-acetylaspartate (NAA), lactate, or choline in the brain. To our knowledge, one MRS study in BPD investigated links between trait dissociation (DES) and glutamate levels in the ACC within a sample of un-medicated female BPD patients (n=30) and HCs (n=30) (Hoerst et al., 2010). Significantly higher levels of glutamate in the ACC were found in BPD as compared with HCs. In BPD, glutamate concentrations in the ACC were positively correlated to DES scores, but also to BIS scores. Associations between ACC glutamate levels and impulsivity (BIS scores) could be replicated more recently (Ende et al., 2016; Wang et al., 2016), suggesting a link with impulsivity rather than with dissociation.

3.2.2.3. Task-related fMRI studies

A couple of fMRI studies in BPD examined links between changes in BOLD response during experimental tasks (e.g., viewing aversive images, pain stimulation, cognitive tasks) and self-reported dissociation (e.g., DSS, DES). Kraus and colleagues (2009) investigated amygdala activity in relation to pain processing (heat stimulation) and state dissociation (DSS) in an un-medicated sample of female BPD patients with (n=12) and without comorbid PTSD (n=17) No significant group differences in pain sensitivity were observed. A deactivation of the amygdala during pain processing was found to be more pronounced in BPD patients with co-morbid PTSD than in those without PTSD, while this was not significantly correlated with DSS scores (Kraus et al., 2009).

In a more recent study, pain processing and dissociation (DES, DSS before/after scanning) were investigated in relation to FC changes in an unmedicated female sample of BPD patients (n=25, all with a history of self-harm) and 23 HCs: Kluetsch and colleagues (2012) used Psychophysiological Interaction (PPI) analysis and Independent Component Analysis to analyze changes in FC. Compared to controls, patients showed a reduced integration of the left retrosplenial cortex and left superior frontal gyrus into the DMN. During pain vs. neutral temperature stimulation, patients further exhibited less FC between the PCC (seed region) and left dlPFC. Higher trait dissociation (DES) was associated with an attenuated signal decrease of the DMN in response to painful stimulation (Kluetsch et al., 2012). Since only patients with a history of self-harm and no clinical control group were included, future studies should clarify whether these findings can be replicated in BPD patients without self-injurious behavior, possibly underlying altered pain processing during dissociation.

Wingenfeld et al. (2009b) applied an individualized EST with neutral, general and individual negative words in 20 BPD patients (partly medicated, mixed gender) and 20 HCs.

State dissociation (DSS) was assessed before and after scanning. Patients displayed overall slower reaction times than HCs, while no increase of reaction times after emotional interference was observed. Controls but not BPD patients showed a significant recruitment of the ACC and frontal areas for generally negative vs. neutral and for individual negative vs. neutral words, respectively. No significant correlations between DSS and behavioral measures or neural activity were reported (Wingenfeld et al., 2009b).

Hazlett and colleagues (2012) investigated potentiated amygdala responses to repeatedly presented emotional pictures in an unmedicated sample of BPD patients (n=33), Schizotypal Personality Disorder (SPD) patients (n=28), and 32 HCs (mixed gender, see Table 3.1). Participants underwent event-related fMRI scanning while viewing repeated (versus novel) neutral, pleasant, and unpleasant pictures. BPD patients demonstrated increased amygdala reactivity to repeated emotional but not neutral pictures, and a prolonged return to baseline of amygdala activity across all conditions. Despite amygdala over-activation, BPD patients showed blunted arousal ratings of emotional but not neutral pictures. A significant negative correlation between self-reported dissociation and amygdala activity was found in BPD and also in the SPD group: Higher self-reported dissociation (DES) was associated with lower emotion-challenged amygdala reactivity (Hazlett et al., 2012). This latter finding is in line with the assumption that dissociation may serve as a defensive mechanism for unpleasant stimuli (Lanius et al., 2010). The association between dissociation and brain activity during emotional distraction in the context of a working memory task was investigated in an fMRI study by Krause-Utz and colleagues (2012). 22 unmedicated female BPD patients (all with a history of interpersonal trauma), and 22 HCs performed a modified Sternberg item-recognition-task (EWMT, with neutral versus negative interpersonal pictures versus no distractors). Immediately before and after the EWMT, state dissociation (DSS) was measured. Patients showed significantly increased amygdala activation and impaired task performance during distraction by negative and neutral interpersonal pictures but not in the control condition without distractors, suggesting increased susceptibility to social cues in BPD. Patients who reported a stronger increase of state dissociation (DSS) showed significantly lower amygdala reactivity to negative distractors (Krause-Utz et al., 2012), in line with afore-mentioned findings by Hazlett and colleagues (2012) and theoretical models (Lanius et al., 2010). No significant differences were observed between BPD patients with (n=9) versus without comorbid PTSD.
In another fMRI study, Krause-Utz and colleagues (2015) used a classical fear conditioning paradigm (differential delay conditioning) with an electric shock as unconditioned stimulus and two neutral pictures as CS-/CS+) in 27 unmedicated female BPD patients and 26 HCs.

Controls but not BPD patients showed amygdala habituation during acquisition of CS+^{paired} (CS+ in temporal contingency with the aversive event). No significant effect of trait or state dissociation (DSS) was observed on skin conductance response (SCR) or on brain activity. In contrast to this, an earlier study by Ebner-Priemer and colleagues (2009) found diminished fear conditioning in terms of SCR and subjective ratings in BPD patients with high (compared to those with low) pre-experimental dissociation. These discrepancies may be related to methodological differences (e.g., assessment of skin conductance may have been affected by scanner noise and patients in the study by Krause-Utz et al., 2015) reported relatively low naturally occurring state dissociation).

Ludäscher and colleagues (2007) investigated dissociation and pain sensitivity in BPD patients with (n=10) and without comorbid PTSD (n=5). During fMRI, patients were exposed to a personalized dissociation script versus a neutral script. After the dissociation script, DSS scores were significantly increased, indicating a successful experimental manipulation, and pain sensitivity was decreased. During the dissociation script, patients showed higher activation in the left IFG (BA9). Scores on the DSS positively predicted activation in the left superior frontal gyrus (BA6) and negatively predicted activation in the right middle temporal gyrus (BA21) and inferior temporal gyrus (BA20). In the subgroup of patients with BPD+PTSD (n=10), increased activity in the left cingulate gyrus (BA32) was observed during the dissociation script. Further, DSS scores were positively correlated to bilateral insula activity (BA13) and negatively correlated with right parahippocampal gyrus (BA35) activity. However, the sample size was relatively small and no control group was included.

3.2.2.4. Possible effects of fMRI neurofeedback

Recently, Paret and colleagues (2016) used real time fMRI to investigate the effects of a neurofeedback training task on amygdala activity and amygdala-PFC FC. In four training sessions, female BPD patients (n=8) were instructed to down-regulate emotional responses to aversive images based on feedback from a thermometer display, showing amygdala BOLD signals (Paret et al., 2016). The DSS was applied at the end of each training run. Amygdala-PFC FC was altered across the four sessions, with increased amygdala-vlPFC FC for regulating versus passively viewing aversive pictures. Interestingly, the self-reported 'lack of emotional awareness', as assessed by the Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004) as well as scores on the DSS scores decreased over the four sessions of the neurofeedback training.

3.2.2.5. Structural neuroimaging studies in BPD

A large number of neuroimaging studies in BPD used techniques like structural MRI or DTI to investigate volumetric alterations in comparison to HCs. Some of these studies included psychometric scales to link their findings to dissociation.

Irle, Lange, & Sachsse (2007) used structural MRI to investigate volumes of the superior (precuneus, postcentral gyrus) and inferior parietal cortices in 30 female BPD patients (all with a history of severe sexual and physical abuse, partly medicated, see Table 3.1), and 25 HCs. Comorbid dissociative disorders were determined using the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Steinberg, 1994). BPD patients with comorbid dissociative amnesia or DID had significantly increased left postcentral gyrus volumes compared to HCs (+13%) and BPD patients without these disorders (+11%). In the entire BPD sample, smaller right-sided precuneus volumes (-9%) were observed (compared to HCs) and stronger depersonalization was related to larger right precuneus size, suggesting a possible relationship between dissociative symptoms and volumetric alterations in this region.

Niedtfeld, Schulze, Krause-Utz, Demirakca, Bohus, and Schmahl (2013) used voxel-based morphometry to investigate structural alterations across the entire brain in a female sample of 60 unmedicated BPD patients with (n=21) and without comorbid PTSD (n=31) (mainly following severe childhood trauma such as physical/sexual abuse), and HCs (n=60). In BPD, smaller GMV of right amygdala, hippocampus, ACC, fusiform, and inferior temporal gyrus were found. In patients with comorbid BPD+PTSD, increased GMV in the dlPFC and superior temporal gyrus were observed. For a subsample of 42 BPD patients, scores on the DES could be included, which predicted larger GMV in the middle and superior temporal gyrus. This region has been previously implicated in dissociation (Simeon et al., 2000; Spiegel, 1991).

Extending the above-mentioned findings on GMV alterations, Rüsch and colleagues (2007) used DTI to study white matter alterations in 20 female unmedicated BPD patients and 20 HCs. Mean diffusivity in inferior frontal white matter was associated with higher trait dissociation (DES), but also with measures of general psychopathology. As all BPD patients had comorbid ADHD, it also remains unclear whether these alterations are specific for BPD.

3.2.3. Interim summary

To sum up at this point, structural studies on dissociation in BPD are still relatively rare and heterogeneous. Task-related fMRI studies suggest a role of dissociation in brain regions that play an important role in emotion processing and regulation, pain processing, and impulse control, including the amygdala, medial temporal lobe, insula, fusiform gyrus, precuneus, IFG, ACC, and cortical structures (e.g., dlPFC) (Schulze et al., 2016; van Zutphen et al., 2015).

More research is needed to examine whether effects of dissociation on 'affective brain regions' (e.g., amygdala) may become particularly evident in highly stressful situations and during high state dissociation in BPD. Assuming that dissociative symptoms dampen amygdala reactivity to emotional stimuli, their presence may in part (aside from other factors, e.g., medication (Schulze et al., 2016) explain why some previous studies did not replicate amygdala hyper-reactivity in BPD (see Ruocco et al., 2013).

Apart from the amygdala, the left IFG, which has been implicated in interference inhibition and suppression of impulses (Aron et al., 2014), may be implicated in dissociative states in BPD (Ludäscher et al., 2010). As no clinical control groups were included in these studies and a high percentage of patients or all patients respectively reported a history of trauma (see Table 3.1), it remains unclear whether these findings are specific to BPD. Increased activity in the IFG and stronger IFG FC with right cingulate gyrus was also observed in D-PTSD exposed to autobiographical trauma scripts (Lanius et al., 2002; Lanius et al., 2005). In addition, there is primary evidence for an association between trait dissociation and alterations in regions of the DMN (PCC, precuneus, hippocampus, and dorsal PFC), which has been associated with inward-directed self-referential processes (Greicius, 2008; Greicius et al., 2003; Raichle et al., 2001). Again, it remains unclear whether these alterations in FC are specific to BPD or rather a trans-diagnostic phenomenon, as alterations in DMN (regions) were also found in depersonalization disorder (Lemche et al., 2016) and D-PTSD (Tursich et al., 2015).

3.3. Overall discussion

Our aim was to 1) provide an overview of neurobiological models of dissociation and neuroimaging research in depersonalization disorder, DID, and D-PTSD, and 2) to give an overview of recent neuroimaging studies in BPD that examined links between dissociation and altered brain function/structure.

Pathological dissociation is a complex and heterogeneous phenomenon (Holmes et al., 2005; Spiegel & Cardena, 1991; Waller et al., 1996; Van der Hart, Nijenhuis, Steele, & Brown, 2004), which has been closely linked to traumatic stress (Lanius et al. 2010; Spiegel et al., 2011). Dissociation may be a protective strategy to cope with overwhelming emotions in traumatic/stressful situations (Lanius et al. 2010; Spiegel et al., 2011; Spiegel & Cardena, 1991). The cost of this subjective detachment appears to be a disruption of mental functions that are crucial to the development of identity, self-control, and emotion regulation (Schauer & Elbert, 2010; Simeon et al., 2003; Spiegel et al., 2011).

The precise neurobiological underpinnings of dissociation remain elusive, but there is evidence for a link between dissociative states/traits and altered (co)activity in brain regions involved in emotion processing and memory (e.g., amygdala, hippocampus, para-hippocampal gyrus, middle/superior temporal gyrus), interoception and attention regulation (insula), self-referential processes (e.g., PCC, precuneus), cognitive control, and arousal modulation (e.g., mPFC, IFC, ACC) – functions which may be altered during dissociation (Lanius et al., 2010).

Future studies may address how changes in brain activity during dissociation are related to altered neuropsychological/cognitive functioning, e.g., encoding and subsequent recall of emotional information. It has been proposed that dissociation is associated with diminished recollection of trauma-related emotional information, although heterogeneous findings were reported (Chiu et al., 2009; de Ruiter et al., 2004; Elzinga et al., 2007). The combination of dissociation induction and affective-cognitive neuropsychological tasks in neuroimaging research may contribute to a better understanding of this relationship.

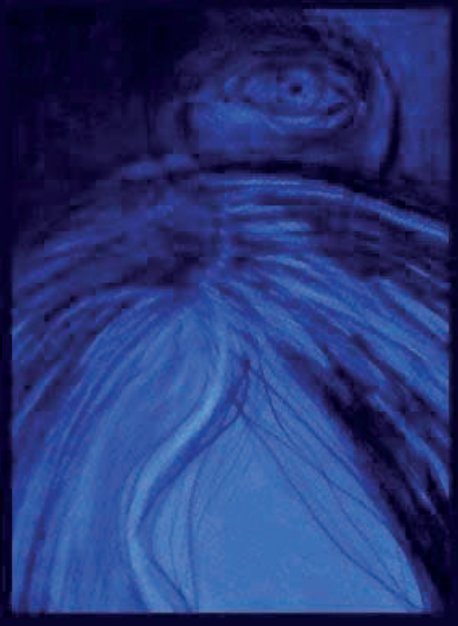
As pointed out before, interpretations of the above-mentioned research are complicated by methodological aspects (e.g., comorbidities, shared etiological factors, psychotropic medication, differences in gender distribution) but also by conceptual differences: Dissociation involves a broad range of psychological and somatoform symptoms (Frewen & Lanius, 2014; Holmes et al., 2005; Spiegel & Cardena, 1991; Van der Hart et al., 2004; Waller et al., 1996).

Most studies used well-established psychometric scales to assess dissociation (e.g., the DES or DSS), which show excellent internal consistency, reliability, and high specificity and sensitivity to change in symptomatology (Stiglmayr et al., 2010). As mentioned above, correlations (e.g., between neuroimaging findings and scores on these scales) give an estimate of the strength of a relationship (between brain structure/function and dissociative symptoms) but do not allow causal conclusions: It remains unclear whether alterations are a predisposition for or the result of frequent dissociation and probably stem from an interplay of multiple factors. Longitudinal studies and/or studies applying approaches like dynamic causal modeling are needed to gain more insight into possible causal relationships. Moreover, other variables that were not assessed in these studies might have moderated (strengthened/ weakened) or mediated (explained) the relationship. To further clarify this, additional longitudinal studies, addressing possible moderating or mediating factors (e.g., trauma) are needed. Further limitations include small sample sizes and sole inclusion of female samples. To gain clearer insight into the role of dissociation in brain structure and function, studies with larger data sets in both female and male patients and meta-analyses are needed to replicate or extend existing findings.

Neuroimaging research on dissociation in BPD may have important clinical implications. Dissociative symptoms were found to hinder treatment outcome, possibly by interfering with habituation processes and new learning: A negative effect of dissociative symptoms on treatment outcome has been shown for several disorders (Kleindienst, et al., 2011; Michelson, Vives, Testa, Marchione, & June, 1998; Rufer et al., 2006; Spitzer, et al., 2007). Tailored interventions can help individuals to reduce/control dissociation at moments when such processes are disruptive and therefore maladaptive (Lanius et al., 2010, 2012). Neuroimaging tools such as real-time fMRI may be used to translate knowledge on neural pathways involved in dissociation into experimental interventions. So far, neuroimaging studies have mainly focused on identifying neural processes possibly underlying dissociation. As a next step, neuroimaging research may help to identify neural changes associated with a dissociative-symptom reduction after tailored interventions (Lanius, 2015) and psychotherapy outcome (Goodman et al., 2014; Schnell & Herpertz, 2007; Winter, Niedtfeld, Schmitt, Bohus, Schmahl, & Herpertz, in press). Real-time fMRI neurofeedback might be a promising add-on tool in combination with pharmaco- and psychotherapeutic treatment (Lanius, 2015). As a first step, more pilot studies are needed to identify which brain regions or functional processes/signals may be suitable targets for such interventions, as so far very little is known about the neural mechanisms of change that are key modulators in this relationship.

Chapter 4 – 7

Neuroimaging studies



CHAPTER 4

Amygdala and Anterior Cingulate Resting-state Functional Connectivity in Borderline Personality Disorder – Associations with Trait Dissociation

Annegret Krause-Utz*, Ilya M. Veer*, Serge A. R. B. Rombouts, Martin Bohus, Christian Schmahl, and Bernet M. Elzinga (2014c). Amygdala and anterior cingulate resting-state functional connectivity in borderline personality disorder patients with a history of interpersonal trauma. *Psychological Medicine, 44*(13), 2889-2901. *contributed equally

Abstract

Background: Studies in Borderline Personality Disorder (BPD) have consistently revealed abnormalities in fronto-limbic brain regions during emotional, somatosensory, and cognitive challenges. Here we investigated changes in resting-state functional connectivity (RSFC) of three fronto-limbic core regions of specific importance to BPD. **Methods:** Functional magnetic resonance imaging data was acquired in 20 unmedicated female BPD patients and 17 healthy controls (HC, matched for age, sex, and education) during rest. The amygdala, dorsal and ventral anterior cingulate cortex (ACC) were defined as seeds to investigate RSFC patterns of a medial temporal lobe network, the salience network, and default mode network. The Dissociation Experience Scale (DES), a measure of trait dissociation, was additionally used as predictor of RSFC with these seed regions. **Results:** Compared to HC, BPD patients showed a trend towards increased RSFC between the amygdala and the insula, orbitofrontal cortex, and putamen. Compared to controls, patients furthermore exhibited diminished negative RSFC between the dorsal ACC and posterior cingulate cortex, a core region of the default mode network, and regions of the dorsomedial prefrontal cortex. Lastly, increased negative RSFC between the ventral ACC and medial occipital regions was observed in BPD patients. DES scores were correlated with amygdala connectivity with the dorsolateral prefrontal cortex and fusiform gyrus. **Conclusions:** Our findings suggest alterations in resting-state networks associated with processing of negative emotions, encoding of salient events, and self-referential processing in individuals with BPD compared to HC. These results shed more light on the role of brain connectivity in the pathophysiology of BPD.

Key words: Borderline Personality Disorder, resting-state fMRI, functional connectivity, amygdala, anterior cingulate cortex, dissociation

4.1. Introduction

Borderline Personality Disorder (BPD) is a severe mental disorder characterized by pronounced difficulties in emotion regulation, interpersonal disturbances (e.g., frantic efforts to avoid abandonment), negative self-concept, and stress-related dissociation (APA, 2000; Skodol et al., 2002; Leichsenring et al., 2011). During emotional and somatosensory challenge, individuals with BPD have shown alterations within a network of fronto-limbic brain regions that might underlie key features of this disorder (see Leichsenring et al., 2011; O'Neill & Frodl, 2012).

Functional magnetic resonance imaging (fMRI) studies of BPD consistently have shown amygdala hyperactivity during exposure to emotionally arousing pictures and fearful faces compared to healthy participants (see Leichsenring et al., 2011; O'Neill & Frodl, 2012). Given the critical role of the amygdala in emotion processing (Davis & Whalen, 2001; Phillips et al., 2003; Phan et al., 2004; Ochsner & Gross, 2007), hyperactivity of this area may underlie clinically well-observed BPD features such as emotional hypersensitivity and intense, long-lasting emotional reactions (Leichsenring et al., 2011). Yet, contradictory results have also been reported (Ruocco et al., 2013), in accordance with findings from behavioral studies in BPD: Whereas some studies revealed enhanced emotion detection, others showed emotion detection to be reduced in BPD (Lis & Bohus, 2013). Specific states may in fact modulate emotion processing and amygdala activation in BPD. For example, it has been proposed that limbic activation is dampened during states of dissociation (Sierra & Berrios, 1998; Lanius et al., 2010), a core feature of BPD (APA, 2000). Moreover, some studies in BPD found amygdala hyperactivity to normative neutral pictures (Donegan et al., 2003; Koenigsberg et al., 2009a; Niedtfeld et al., 2010; Schulze et al., 2011; Krause-Utz et al., 2012), possibly due to a tendency to interpret normative neutral stimuli as emotionally arousing, which may result in increased states of vigilance in BPD (Lis & Bohus, 2013).

Aside from limbic alterations, BPD patients have shown abnormal recruitment of frontal brain regions that are typically involved in top-down emotion regulation (Phillips et al., 2003; Ochsner & Gross, 2007; Etkin et al., 2011; Banks et al., 2007) and impulse control (Pessoa et al., 2012): For example, BPD patients exhibited diminished recruitment of frontal brain regions including the anterior cingulate cortex (ACC), dorsomedial prefrontal cortex (dmPFC), dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex (OFC), while being instructed to inhibit emotional processing (Schulze et al., 2011; Koenigsberg et al., 2009b; Lang et al., 2012) and during cognitive inhibition tasks (Silbersweig et al., 2007). Moreover, BPD patients activated the ACC less than controls during exposure to fearful faces (Minzenberg et al., 2007) and trauma-related scripts (Schmahl et al., 2003, 2004).

Over the last decade, studying how brain regions interact in absence of goal directed behavior (resting-state functional connectivity; RSFC) has become increasingly important in understanding the neurobiology of psychiatric disorders (Greicius, 2008). Yet to date only two studies have investigated this in BPD (Wolf et al., 2011; Doll et al., 2013). Wolf and colleagues revealed altered connectivity within the default mode network, which has been related to pain processing and self-referential processes such as episodic memory and self-monitoring (Raichle et al., 2001; Greicius et al., 2003; Menon, 2011): Compared to healthy participants, BPD patients showed increased RSFC in the left frontal pole and left insula as well as decreased RSFC in the left cuneus. BPD patients further exhibited decreased RSFC in the left inferior parietal lobule and right middle temporal cortex within a network comprising fronto-parietal brain areas (task-positive network) compared to healthy individuals. Interestingly, RSFC of the insula and cuneus was positively correlated with self-reported dissociation (Wolf et al., 2011). Doll and colleagues (2013) reported altered RSFC in the default mode and task-positive networks, in line with the findings of Wolf and colleagues (2011). Moreover, BPD patients showed aberrant RSFC in the salience network, comprising the orbitofrontal insula and dorsal ACC (dACC). This network has been associated with interoceptive awareness, detection of salient events, encoding of unpleasant feelings, and a wide variety of cognitive tasks (Seeley et al., 2007; Menon & Uddin, 2010). Doll and colleagues (2013) further showed imbalanced connections between the three networks, most prominently a shift from RSFC in the task-positive to increased RSFC in the salience network in BPD patients. However, a drawback of both studies was that most patients were on psychotropic medication.

Here, we investigate RSFC patterns in unmedicated individuals with BPD compared to age- and education-matched healthy controls (HC), using three seed regions of interest that are of particular relevance to BPD psychopathology based on current neurobiological models of the disorder and previous neuroimaging research (see Leichsenring et al., 2011). Each of these seed regions has been found to probe a specific intrinsic connectivity network: 1) bilateral amygdala (*medial temporal lobe network*), 2) dACC (*salience network*), and 3) ventral ACC (vACC) (*default mode network*). Based on previous research, we expected altered RSFC between our seeds and brain regions mainly located in the vm/dmPFC, insula, and occipital cortex in BPD patients. In addition, an exploratory analysis was carried out in the BPD group to assess the relation between trait dissociation and RSFC of the three seeds.

4.2. Methods and Materials

4.2.1. Participants

Thirty-nine females between 18 and 45 participated in this study. Two patients were excluded, because they reported to have fallen asleep during scanning. All participants underwent diagnostic assessments including the Structured Interview for DSM-IV Axis-I (SCID-I) (First et al., 1997) and the International Personality Disorder Examination (IPDE) (Loranger et al., 1999) by trained diagnosticians (inter-rater reliability: κ=.77 for all interviews). Clinical assessment included questionnaires on BPD symptom severity (BSL-95, Bohus et al., 2007), Posttraumatic Stress Disorder (PTSD) symptoms and childhood trauma history (PDS, Foa, 1995; CTQ, Bernstein et al., 2003), trait dissociation (DES, Bernstein & Putnam, 1986), dysphoric mood (BDI, Beck et al. 1961), impulsivity (BIS-10, Patton et al. 1995), difficulties in emotion regulation (DERS, Gratz & Roemer, 2004), affect intensity (AIM, Larsen, 1984), and current self-injurious behavior. General MRI exclusion criteria were: metal implants, pregnancy, and left-handedness. BPD patients were free of medication within the last 14 days (in case of fluoxetine 28 days), free of severe somatic illness, and free of substance dependence within the last 6 months. Further exclusion criteria for the patient group were: current major depression, lifetime diagnoses of psychotic disorder, bipolar affective disorder, mental retardation, developmental disorder, and life-threatening suicidal crisis. Exclusion criteria for the HC group were: lifetime diagnoses of psychiatric and somatic disorders. The final patient group comprised 20 unmedicated females meeting criteria for BPD according to DSM-IV (APA, 2000). All patients fulfilled DSM-IV criterion 6 for emotional instability and reported a history of physical, sexual, and/or emotional trauma as assessed by the PDS and CTQ. Clinical characteristics and co-occurring mental conditions in the patient sample are reported in Table 4.1. In our BPD sample, nine patients met criteria for current comorbid PTSD. The final HC group comprised 17 participants without a history of psychiatric disorders and trauma. The groups did not differ regarding age, education level, and body mass index (BMI) (Table 4.1).

4.2.2. Procedure

The experiment was approved by the local medical ethics committee (University of Heidelberg, in accordance to the World Medical Association's Declaration of Helsinki) and conducted at the Central Institute of Mental Health in Mannheim, Germany. All participants were informed about the experiment and scanning procedure. Written informed consent was obtained. Before scanning, participants underwent diagnostic interviews (SCID-I, IPDE) and completed the questionnaires. Acquisition of RS was positioned first in the scanning protocol.

Participants were instructed to lie still with their eyes closed and not to fall asleep during this scan. Compliance to these instructions was verified as part of the exit interview. After the resting-state scan several anatomical and functional scans were acquired (Krause-Utz et al., 2012). After scanning, participants were debriefed, thanked, and paid for participation.

Table 4.1.
Demographic and clinical variables in healthy participants (HC) and patients with Borderline Personality Disorder (BPD)

	BPD (N=20)	**HC (N=17)**	***t*-tests (df=35)**
Age	29.55 ± 7.74	27.53 ± 8.58	t=0.75, p=.456
Weight	70.32 ± 21.23	63.88 ± 13.32	t=1.08, p=.289
BMI	25.24 ± 6.92	23.29 ± 4.17	t=1.00, p=.324
Education level			
9 years secondary school	N=2 (10%)	N=1 (6%)	
10 year secondary school	N=7 (35%)	N=2 (12%)	χ^2=3.25, p=.197
13 year secondary school	N=11 (55%)	N=14 (82%)	
BSL-95 (total score)	188.88 ± 52.40	24.10 ± 12.93	t=13.38, p<.0001
CTQ (total score)	47.38 ± 19.93	20.55 ± 5.41	t=4.49, p<.0001
DES (total score)	32.25 ± 15.78	2.21 ± 1.69	t=8.45, p<.0001
AIM (total score)	50.07 ± 13.68		
BDI (total score)	22.67 ± 10.64		
BIS (total score)	88.82 ± 10.37		
DERS (total score)	87.93 ± 25.76		
Self-injurious behavior	N=9 (45%)		
PTSD current/lifetime	N=9 (45%)		
Past major depression	N=8 (40%)		
Social phobia lifetime	N=2 (10%)		
Panic disorder lifetime	N=2 (10%)		
Specific phobia lifetime	N=1 (5%)		
Past substance abuse	N=4 (20%)		
Eating disorder lifetime	N=7 (35%)		

Note: BSL-95 = Borderline Symptom List 95; CTQ = Childhood Trauma Questionnaire; DES = Dissociation Experience Scale; AIM = Affect Intensity Measure; BDI = Beck Depression Inventory; BIS = Barratt Impulsiveness Scale; DERS = Difficulties in Emotion Regulation Scale; PTSD = Posttraumatic Stress Disorder

4.2.3. *FMRI data acquisition and analysis*

MRI scans were acquired on a Siemens TRIO-3T MRI scanner using an eight-channel head coil (Siemens Medical Solutions, Germany). Whole-brain resting-state scans were acquired using T_2^*-weighted gradient-echo echo-planar imaging (EPI, 150 volumes, 40 sagittal slices scanned in ascending order, repetition time (TR) 2500ms, echo time (TE) 30ms, flip angle 80^0, field of view 220x220mm, 3mm isotropic voxels with no slice gap). A high-resolution 3D T_1-weighted anatomical image (MPRAGE, 1mm isotropic voxels) was acquired for registration purposes. Head movement artifacts and scanning noise were restricted using head cushions and headphones within the scanner coil.

4.2.3.1.FMRI data preprocessing

Prior to analysis, all RS-fMRI data sets underwent a visual quality control check to ensure that no gross artifacts were present in the data. Afterwards, data were analyzed using FSL Version 4.1.7 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). The following preprocessing steps were applied to EPI data sets: motion correction (Jenkinson et al., 2002), removal of non-brain tissue (Smith et al., 2004), spatial smoothing using a Gaussian kernel of 6mm full width at half maximum (FWHM), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, a high-pass temporal filter of 100 seconds (i.e., $\geq$ 0.01Hz). The RS-fMRI dataset was registered to the T_1-weighted image, and the T_1-weighted image to the 2mm isotropic Montreal Neurological Institute (MNI) standard space image (T_1-weighted standard brain averaged over 152 subjects (MNI-152), Montreal, QC, Canada) (Jenkinson et al., 2002; Jenkinson & Smith, 2001). The resulting transformation matrices were combined to obtain a native to MNI space transformation matrix.

4.2.3.2. FMRI time course extraction and statistical analysis

A seed-based correlation analysis (Fox & Raichle, 2007) was employed to reveal brain areas that are functionally connected to a-priori defined seed regions of interest (ROI) during rest. The amygdala (*medial temporal lobe network;* MNI coordinates X=±23, Y=-4, Z=-19; Veer, Oei, Spinhoven, van Buchem, Elzinga, & Rombouts, 2011) was defined as first seed region. The second seed region was the dACC (*salience network*; MNI coordinates X=±5, Y=19, Z=28, seed "I4" in Margulies, Kelly, Uddin, Biswal, Castellanos, & Milham, 2007). The third seed region was the vACC (*default mode network;* MNI coordinates X=±5, Y=47, Z=11, seed "S7" in Margulies et al., 2007). Spherical regions of interest were created around these voxels using a radius of 4mm. Next, all masks were registered to each participant's RS-fMRI preprocessed dataset using the inverse transformation matrix. The mean time courses were subsequently extracted from the voxels falling within each mask in native space.

The time courses of the left and right seeds were entered as a regressor in a general linear model (GLM), for each of the three networks separately, together with nine nuisance regressors comprising the white matter signal, CSF signal, six motion parameters (three translations and three rotations) and the global signal. The latter regressor was included to further reduce the influence of artifacts caused by physiological signal sources (i.e., cardiac and respiratory) on the results (Fox & Raichle, 2007). However, because regression of the global signal can induce either anti-correlations or even group differences (Murphy et al., 2009; Saad et al., 2012), we repeated all analysis without the global signal as regressor in the model. Each individual model was tested using FEAT version 5.98, part of FSL, with contrasts for left and right seeds separately, as well as a contrast to assess FC of the left and right seeds together. The resulting individual parameter estimate maps, together with their corresponding within-subject variance maps, were then resliced into 2 mm isotropic MNI space and fed into a higher level mixed effects regression analysis and compared between groups (independent-samples t-test). Post-hoc correlations were carried out between symptom severity scores (BSL-95) and brain regions showing significant between-group differences. In addition, an exploratory whole-brain analysis was conducted for the BPD group to investigate the relation between trait dissociation scores (DES) and RSFC with each of the three seeds. To this end, a higher-level mixed effects regression analysis was carried out including DES scores as regressor of interest, for each of the three networks separately. All statistical images were whole-brain corrected for multiple comparisons using cluster-based thresholding with an initial cluster-forming threshold of $Z>2.3$ and a corrected cluster significance threshold of $p<0.017$ ($p<.05$, Bonferroni corrected for the 3 networks tested; Worsley, 2001). Based on our a-priori hypothesis on altered amygdala-mPFC connectivity, a small volume correction was applied for mPFC regions, including the pgACC, vm/dmPFC and OFC. A combined mask of these ROIs was created based on the Harvard–Oxford cortical probability atlas, as provided in FSL, which was then used to mask the raw statistical images. Subsequently, correction for multiple comparisons was carried out for those voxels present in the mask (mPFC) using cluster based thresholding with the same parameter settings as for the whole-brain analysis ($Z>2.3$, $p<.017$).

Since nine BPD patients additionally met criteria for PTSD, we ran an additional post-hoc analysis to assess the effects of comorbidity on functional connectivity (details from this analysis can be found in the Supplemental Methods).

4.3. Results

4.3.1. Amygdala connectivity (medial temporal lobe network)

Overall, amygdala RSFC in both groups was highly similar to the patterns previously described in literature (Roy et al., 2009; Veer et al., 2011) (Supplemental Fig. 4.1A). At our stringent threshold of $p<.017$, no differences were observed between the two groups. However, a trend was observed for a cluster comprising the lateral OFC, putamen and dorsal insula ($p<.05$, whole brain corrected; Figure 4.1A): While HC showed no RSFC between the right amygdala and this cluster, this positive functional connection was present in BPD patients (see Table 4.2). Our ROI analysis of amygdala-mPFC RSFC did not yield any differences between the two groups.

Table 4.2.
Resting-state functional connectivity results: Between groups effects

Region	Cluster size 2mm voxels	Peak voxel coordinates (MNI) x	y	z	*Z*-value
Amygdala seed					
BPD>HC					
Insula	331	34	4	8	3.68 *
Orbitofrontal cortex		32	12	-22	3.22 *
Putamen		20	8	-4	2.99 *
Dorsal ACC seed (I4)					
BPD>HC					
Rostral anterior paracingulate cortex	773	8	50	14	3.8
HC>BPD					
Posterior cingulate cortex	521	-2	-56	20	4.17
Ventral ACC seed (S7)					
BPD>HC					
Medial visual cortex	709	-6	-90	10	3.7

Note: all *z*-values are cluster corrected for multiple comparisons ($p<.017$), except for *z*-values with a * ($p<.05$).

4.3.2. Dorsal ACC connectivity (salience network)

In both patients and controls the pattern of brain regions comprising the salience network (see Supplemental Fig. 4.1B) overlapped with connectivity patterns found in previous studies (Seeley et al., 2007; Menon & Uddin, 2010). Figure 4.1B illustrates regions in which group differences in bilateral dACC RSFC were observed between BPD patients and HC (also see Table 4.2): While HC showed strong negative RSFC between bilateral dACC and left PCC, decreased negative RSFC between these regions was found in BPD patients. Additionally, increased dACC RSFC with two clusters in the dorsomedial PFC/paracingulate cortex was found in BPD patients compared to HC. In BPD patients, both clusters were positively correlated with the dACC. In HC, the lower cluster showed negative connectivity and the upper cluster showed diminished connectivity with the dACC (see Table 4.2).

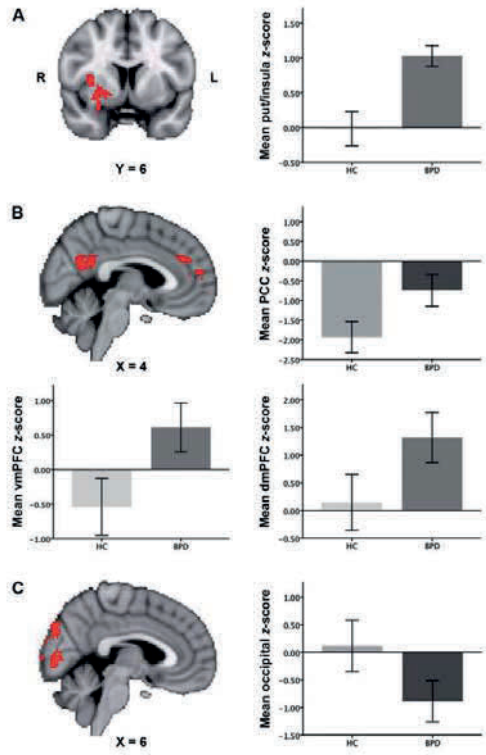


Figure 4.1. Between-group differences in resting-state functional connectivity of each of the three seeds: A) Amygdala (medial temporal lobe network); B) Dorsal ACC (salience network); C) Ventral ACC (default mode network). Connectivity differences are overlaid on the MNI 2mm standard space template. Bar graphs plot the mean *Z*-scores (± 2 standard errors of the mean) in each group for each of the regions where connectivity differences are found ($Z>2.3$, $p<.017$; whole brain cluster corrected, except for Figure 4.1A: $Z>2.3$, $p<.05$).

4.3.3. Ventral ACC connectivity (default mode network)

Both groups demonstrated vACC connectivity with well-described areas of the default mode network including the PCC, precuneus, and lateral parietal cortex (Raichle et al., 2001; Greicius et al., 2003; Menon, 2011) (see Supplemental Fig. 4.1C). Patients showed increased negative RSFC between left vACC and area V1 of the occipital cortex, lingual gyrus, and cuneus compared to HC who exhibited marginal RSFC with these regions (Fig. 4.1C, Table 4.2). In the patient group, there were no significant correlations between BPD symptom severity scores (BSL-95) and the FC strength of any of the brain regions in which between-group differences were found.

4.3.4. Exploratory analysis: Trait dissociation and functional connectivity

In BPD, correlations were found between DES-scores and amygdala RSFC with several brain regions. First, a positive correlation with left amygdala-right dlPFC RSFC was observed (Fig. 4.2A, Table 4.3), illustrating stronger RSFC between these regions in patients with higher self-reported trait dissociation. Secondly, DES scores differentially modulated left amygdala RSFC with a cluster in the occipital lobe including the lingual gyrus, intracalcarine cortex, and fusiform gyrus (Fig 4.2B, Table 4.3), demonstrating increasing negative RSFC between these regions with higher DES scores. Correlations for bilateral amygdala RSFC were similar to those for left amygdala. No associations were found with RSFC of the other seeds.

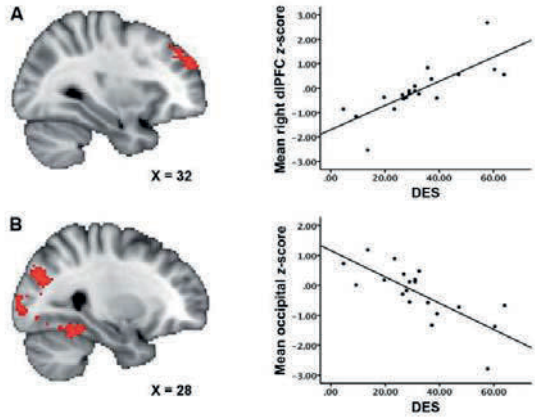


Figure 4.2. Voxel-wise correlations between trait dissociation scores (DES) and amygdala RSFC in BPD (Z>2.3, p<.017; whole brain cluster corrected): A) Left amygdala-dlPFC connectivity is positively associated with trait dissociation; B) Left amygdala-occipital cortex connectivity (including the lingual gyrus, intracalcarine cortex, and fusiform gyrus) is negatively associated with trait dissociation. Results are overlaid on the MNI 2mm standard space template, according to the radiological convention. Scatter plots illustrate the direction of the correlation, with mean Z-scores plotted against the dissociation scores.

Table 4.3.
DES associations with amygdala resting-state functional connectivity in the BPD group

Region	Hemisphere	Cluster size 2mm voxels	Peak voxel coordinates (MNI) X	y	Z	*Z*-value
Positive association						
Dorsolateral prefrontal cortex	R	643	40	38	38	3.76
Negative association						
Lingual gyrus	R	3361	12	-64	-10	4.28
Lateral occipital cortex	R		44	-84	-6	4.05
Fusiform gyrus	R		36	-58	-20	4.00
Intracalcarine cortex	R		4	-86	4	3.93

4.3.5. Effects of global signal regression

Reanalysis without the global signal revealed highly similar results. Although some of the effects did not survive the stringent multiple comparison correction, these could still be observed at a more lenient threshold (see Supplemental Figures S4.2 and S4.3, and Supplemental Tables S4.1 and S4.2).

4.3.6. Subgroup analysis

No differences were found between BPD with or without comorbid PTSD. Full results of this analysis are reported the Supplemental Material.

4.4. Discussion

Here we investigated resting-state functional connectivity in unmedicated Borderline Personality Disorder (BPD) patients compared to healthy controls (HC). Three seeds of high relevance to BPD psychopathology were chosen, each probing a specific brain network: 1) bilateral amygdala (*medial temporal lobe network*), 2) dACC (*salience network*), and 3) vACC (*default mode network*). In both groups, we could replicate connectivity patterns reported in previous studies (Margulies et al., 2007; Veer et al., 2011). Overall, RSFC differences between BPD patients and controls were observed within networks associated with the processing of negative emotions, encoding of salient events, and self-referential processing. The results per seed are discussed in more detail below.

Amygdala connectivity (medial temporal lobe network)

The amygdala plays a key role in emotion processing and the initiation of fear and stress responses (Davis & Whalen, 2001; Phillips et al., 2003; Ochsner & Gross, 2007), and has functional connections with the perigenual ACC, insula, and OFC (Stein et al., 2007).

The insula and OFC have been implicated in identifying the emotional significance of internal and external stimuli and the generation of emotional responses (Phillips et al., 2003; Banks et al., 2007; Kringelbach & Rolls, 2004; Ochsner & Gross, 2007; Etkin et al., 2011). Several studies in BPD patients reported hyperactivity of the amygdala and insula during emotional challenge (Niedtfeld et al., 2010; Schulze et al., 2011; Leichsenring et al., 2011; Krause-Utz et al., 2012; O'Neill & Frodl, 2012). In the present study, we found a stronger coupling between the amygdala and a cluster comprising the dorsal insula, OFC, and putamen in BPD patients than in HC even in the absence of experimental conditions. Since this effect did not pass a more stringent correction for testing multiple seeds, it has to be discusses as a trend effect and therefore treated with caution. Nevertheless, in the context of earlier studies, our trend finding of amygdala hyper-connectivity with other brain regions highly relevant to emotion processing, could reflect the clinically well-observed BPD feature of affective hyperarousal and intense emotional reactions. Indeed, high levels of aversive affective arousal, often accompanied by dissociative experiences, are a major characteristic of BPD (Linehan, 1993; Stiglmayr et al., 2001; Stiglmayr et al., 2008). Affective hyperarousal often leads to self-inflicted harm, suicidal acts and dysfunctional impulsive behavior patterns, therefore having detrimental consequences in patients with BPD (Chapman, Gratz, & Brown, 2006; Kemperman, Russ, & Shearin, 1997; Kleindienst et al., 2008). In addition, we observed a stronger coupling between the amygdala and putamen in BPD patients than in controls. Being part of the basal ganglia, the putamen is involved in movement control (Packard & Knowlton, 2002) and may play an important role in mobilizing an individual to take action in the face of contempt and disgust (Zeki et al., 2008). Furthermore, both the OFC and the putamen play an important role in reward processing, reinforcement learning, and impulsivity (Packard & Knowlton, 2002; Kringelbach & Rolls, 2004; Haber & Knutson, 2010), which is another key feature of BPD.

ACC connectivity (salience network, default mode network)

Being an important constituent of the salience network, the dACC has been related to the detection of salient events and a wide variety of cognitively demanding tasks (Menon & Uddin, 2010; Critchley et al., 2001; Dosenbach et al., 2006; Sridharan et al., 2008). Moreover, recent studies have highlighted the role of the dACC and orbitofrontal insula in switching between different large-scale networks and reallocating cognitive resources in the face of salient events.

Across different samples of healthy participants, Sridharan and colleagues (2008) demonstrated that activation in the dACC temporally precedes activity in nodes of other networks such as the PCC. In other studies, healthy individuals recurrently showed strong anti-correlations between 'task-positive' brain regions (e.g., dACC) and regions commonly activated during rest (e.g., PCC) (Fox et al., 2005; Buckner & Vincent, 2007; Neumann et al., 2010).

Notably, in the present study, healthy controls showed a negative association between the dACC and PCC compared to BPD patients who exhibited diminished anti-correlations between these regions. Moreover, BPD patients showed a stronger RSFC of our seed with the dorsomedial PFC, whereas healthy participants showed diminished connectivity between these regions. The dorsomedial PFC has been critically implicated in self-referential processes such as processing of autobiographical memories and monitoring of internal cognitive and affective states (Buckner & Vincent, 2007).

Our findings of diminished interaction between core regions of the salience and default mode networks could suggest impaired flexibility in switching between the networks. Similarly, a recent RS-fMRI study in BPD patients reported imbalanced inter-network connectivity between the default mode network and the salience network (Doll et al., 2013). Although the nature of these interactions between brain networks is not yet fully understood, our findings might translate into an increased vigilance even to seemingly neutral events in individuals with BPD (Kluetsch et al., 2012; Lis & Bohus, 2013).

BPD patients further showed decreased RSFC between left vACC and area V1 of the occipital cortex, lingual gyrus, and cuneus compared to controls, which showed only marginal RSFC between these regions. In part, these findings are in line with previous fMRI studies in BPD who reported altered RSFC within the default mode network in BPD (Wolf et al., 2011; Doll et al., 2013). More specific, Wolf and colleagues (2011) observed altered RSFC in the left cuneus as well as in the insula and frontopolar cortex in BPD patients compared to HC. Diminished RSFC in occipital areas within the default mode network may be associated with an inflexible integration of sensory stimuli into self-referential processing in individuals with BPD (Wolf et al., 2011). In the previous RS-fMRI study by Wolf and colleagues (2011), altered cuneus RSFC within the default mode network was negatively correlated with self-reported dissociative states in patients with BPD.

Trait dissociation and functional connectivity

Our exploratory analysis revealed negative correlations between self-reported trait dissociation and amygdala RSFC with the cuneus, area V1 of the occipital lobe, and the fusiform gyrus in BPD patients, partly in line with findings by Wolf and colleagues (2011).

Diminished amygdala RSFC in occipital areas may represent an altered gating of sensory input associated with self-reported dissociation (Lanius et al., 2005).

Wolf and colleagues further found positive correlations between self-reported dissociative states and insula RSFC, which were not observed in the present study. Instead, we revealed positive correlations between self-reported dissociation and left amygdala RSFC in the right dlPFC – a brain area involved in working memory, attention deployment, and inhibitory control of emotions (Ochsner & Gross, 2007). It has been proposed that dissociation is associated with increased prefrontal inhibition of limbic brain activation, which reflects an over-modulation of emotional arousal (Lanius et al., 2010). Indeed, states of dissociation negatively predicted amygdala activation during emotional interference in BPD patients with a history of trauma (Krause-Utz et al., 2012). Further neuroimaging studies are needed to gain more insight into the neurobiological underpinnings of this complex phenomenon.

Several limitations need to be addressed: First, since all of our patients reported a history of interpersonal trauma – which is highly prevalent in BPD (APA, 2000; Leichsenring et al., 2011) – our findings could also be related to the history of interpersonal trauma in general, rather than to BPD psychopathology in particular. However, although a recent study in participants with a history of childhood maltreatment demonstrated abnormal amygdala RSFC with the putamen and insula (van der Werff et al., 2012), this connection was decreased rather than increased. Further, the presence of comorbid conditions limits the specificity of our results as well, even though most individuals with BPD have additional axis I disorders (Leichsenring et al., 2011). More specific, nine patients in the present BPD sample additionally met criteria for PTSD. As aberrant amygdala (Sripada et al., 2012; Rabinak et al., 2011) and default mode (Lanius et al., 2010; Daniels et al., 2010) RSFC has been observed in PTSD patients previously, a post-hoc comparison between BPD patients with or without comorbid PTSD was carried out. This revealed no significant differences between subgroups, while BPD patients with and without comorbid PTSD all differed significantly from HC in each cluster found in the main analysis but one. In addition, DES scores predicted amygdala connectivity with the DLPFC and occipital cortex to the same extent in both BPD subgroups. These results suggest that group differences found in our study cannot be explained merely by the presence of comorbid PTSD. Nevertheless, future studies have to compare BPD patients to patients with other disorders (e.g., PTSD) to clarify whether the alterations in RSFC described here are truly specific to BPD. Second, although seed-based connectivity analyses are well suited to address hypothesis driven questions, results are inherently limited to the connections of the a-priori chosen seeds.

This means that differences between BPD patients and controls in neural circuits not associated with one of our seeds might have gone unobserved in the current study.

Data driven methods (including ICA), as used by Wolf et al. (2011) in BPD, do have the potential to look at the data in a more exploratory fashion. Third, BOLD measurements of the amygdala are susceptible to physiological confounds due to its proximity to draining veins. To remove variance associated with these confounding signal sources, we used global signal regression (GSR). Although this method has been proven to be useful in dealing with physiological artifacts and generally increases connection specificity, it is also known to introduce anti-correlations in connectivity analyses (Murphy et al., 2009). Recent research on simulated data demonstrated that GSR could promote connectivity differences between groups due to differences in the underlying noise structure, even when these do not exist (Saad et al., 2012). Therefore, we repeated all analyses without GSR and observed highly similar results, albeit some effects were only found sub-threshold. Importantly, reduced connectivity in the occipital cortex was also observed in a previous RS fMRI study of the DMN in BPD patients that used a different analysis method without GSR (Wolf et al., 2011).

In sum, we observed differences between BPD patients and healthy controls in RSFC of brain regions of high relevance to the disorder. More specific, our findings suggest connectivity changes in brain networks associated with the processing of negative emotions, encoding of salient events and self-referential processing in individuals with BPD compared to healthy individuals. Importantly, our findings corroborate previous resting-state connectivity studies in BPD suggesting an impaired flexibility to switch between large-scale networks during rest. Resting-state fMRI has the potential to map network differences in BPD, and may shed more light on the role of abnormal brain functional connectivity in the pathophysiology of BPD.

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Declaration of Interest: None.

Supplemental Material

Table S4.1.
Resting-state functional connectivity results without global signal regression:

Region	Hemisphere	Cluster size 2mm voxels	Peak voxel coordinates (MNI) X	Y	Z	*Z*-value
Amygdala seed						
BPD>HC						
Insula	R	389	34	4	8	4.00*
Orbitofrontal cortex	R		32	12	-22	3.52 *
Putamen	R		28	8	-4	3.04 *
Dorsal ACC seed (I4)						
BPD>HC						
Rostral anterior	R					
(para)cingulate cortex	R		8	40	26	3.67**
			8	52	14	3.42**
HC>BPD						
Posterior cingulate cortex	L		2	-50	24	2.83**
			-14	-58	22	3.27**
Ventral ACC seed (S7)						
BPD>HC						
Medial visual cortex		709	4	-80	4	3.81*

Note: * *Z*-values are cluster corrected for multiple comparisons ($p<.05$). ** *Z*-values do not survive cluster correction.

Table S4.2.
DES associations with amygdala connectivity in BPD without global signal regression

Region	Hemisphere	Cluster size 2mm voxels	Peak voxel coordinates (MNI) X	y	Z	*Z*-value
Positive association						
Dorsolateral prefrontal cortex	R	918	26	48	32	4.33*
Negative association						
Lingual gyrus	R		12	-64	-10	3.23**
Lateral occipital cortex	R		44	-84	-6	4.38**
Fusiform gyrus	R		36	-58	-20	3.1**
Intracalcarine cortex			4	-86	4	3.55**

Note: * *Z*-values are cluster corrected for multiple comparisons ($p<.05$). ** *Z*-values do not survive cluster correction.

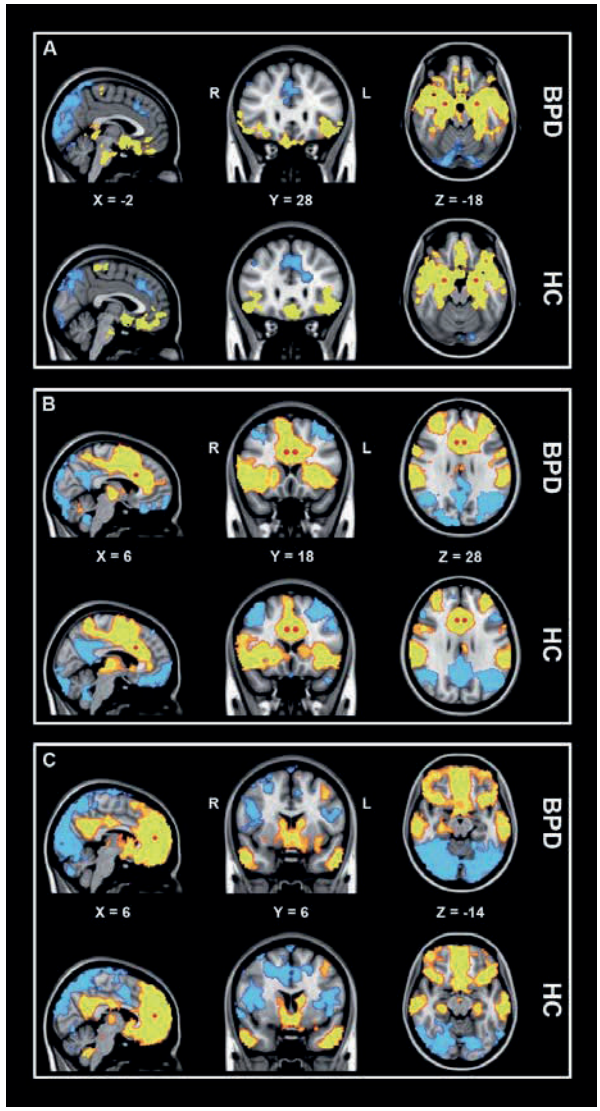

Figure S4. 1. Group main effects demonstrating average RSFC in both groups with each of the three seeds (Z>2.3, p<.05; whole brain cluster corrected): A) Amygdala (medial temporal lobe network); B) Dorsal ACC (salience network); C) Ventral ACC (default mode network). Connectivity differences are overlaid on the MNI 2mm standard space template, according to the radiological convention. Positive connectivity is shown in red to yellow, while blue to light blue illustrates negative connectivity. Red spheres mark the locations of the seeds used in the analysis.

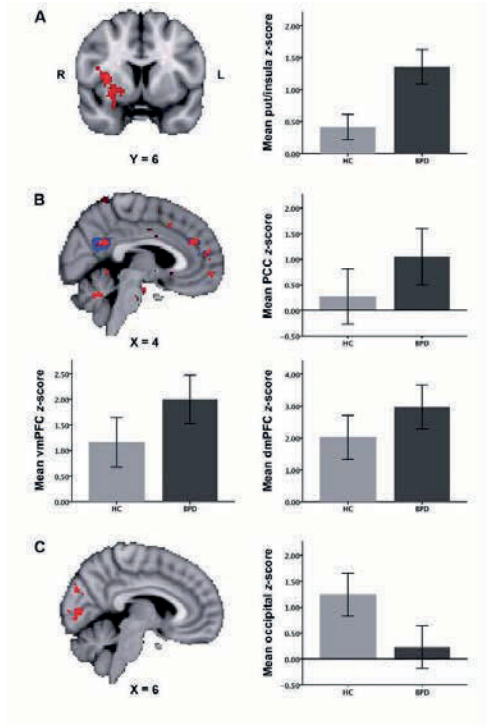

Figure S4.2. Between-group differences in RSFC of each of the three seeds without global signal regression: A) Amygdala (medial temporal lobe network; $p<.05$, cluster corrected); B) Dorsal ACC (salience network; $p<.001$, uncorrected, overlaid on the original result with global signal regression in blue); C) Ventral ACC (default mode network; $p<.05$, cluster corrected). Connectivity differences are overlaid on the MNI 2mm standard space template. Bar graphs plot the mean *Z*-scores (± 2 SEM) in each group for each of the regions where FC differences are found.

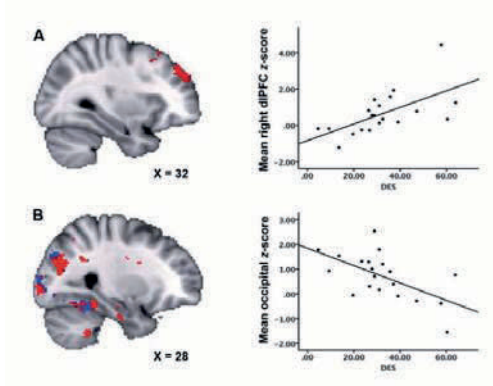

Figure S4.3. Voxel-wise correlations between trait dissociation (DES) and amygdala RSFC without global signal regression in BPD: A) Left amygdala-dlPFC connectivity is positively associated with dissociation ($p<.05$, cluster corrected); B) Left amygdala-occipital cortex FC (including the lingual gyrus, intra-calcarine cortex, and fusiform gyrus) is negatively associated with dissociation ($p<.001$, uncorrected, overlaid on the original result with global signal regression in blue). Results are overlaid on the MNI 2mm standard space template, according to the radiological convention. Scatter plots illustrate the direction of the correlation, with mean *Z*-scores plotted against DES scores.

Additional information on subgroup analysis:

Since nine BPD patients met criteria for PTSD, we ran an additional post-hoc analysis to assess the effects of comorbidity on FC. Given the small group sizes, this analysis was done on the individual *Z*-scores within each of the clusters in which we found an effect. Multivariate analysis of variance (MANOVA) was used with Group as between-subjects factor: HC (n=17), BPD without comorbid PTSD (BPD; n=11), and BPD with current PTSD (BPD+PTSD; n=9). Post-hoc *t*-tests were carried out to compare the three groups to each other. The MANOVA revealed a significant group effect ($p<.001$). Between-subjects effects were found for each of the five clusters of the whole-brain analysis (all p's<.006). Post-hoc tests revealed significant differences between BPD and HC for each cluster (p's<.01) as well as between BPD+PTSD and HC (p's<.05), except for ventral ACC connectivity with the occipital cortex ($p=.10$). No differences were found between the two BPD subgroups (p's>.5). The association between DES scores and left amygdala connectivity with the DLPFC and occipital cortex was observed in both BPD subgroups as well, while DES scores did not differ between the two groups ($p=.33$).

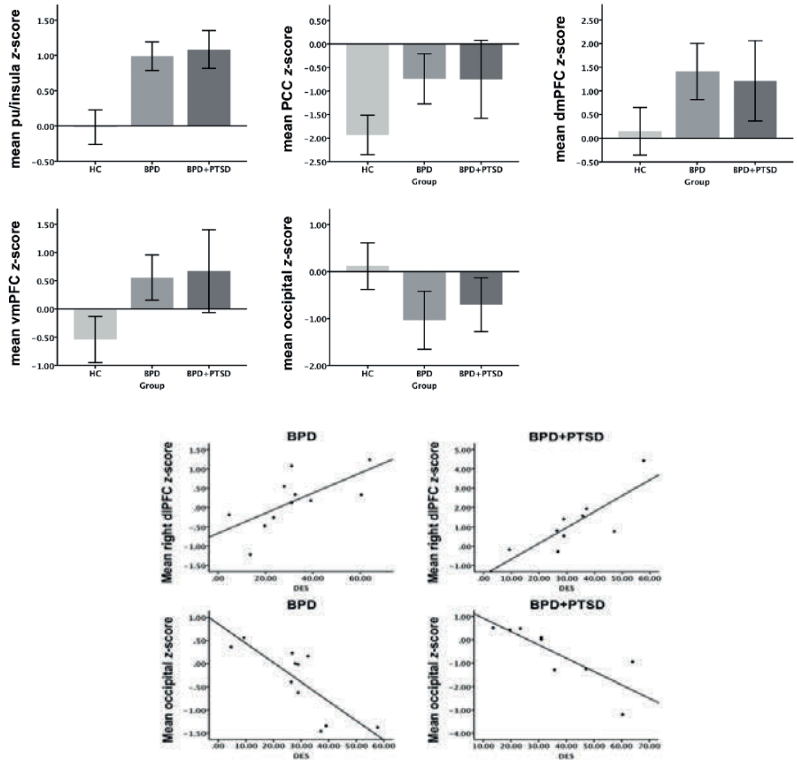

Figure S4.4. Subgroup analysis for HC, BPD patients with comorbid PTSD (BPD+PTSD), and patients without PTSD (BPD). Bar graphs plotting mean *Z*-scores (± 2 SEM) for each cluster found in the main analysis.

CHAPTER 5

Amygdala and dorsal Anterior Cingulate Functional Connectivity during an Emotional Working Memory Task in Borderline Personality Disorder – The Role of State Dissociation

Annegret Krause-Utz, Bernet M Elzinga, Nicole Y.L. Oei, Christian Paret, Inga Niedtfeld, Philip Spinhoven, Martin Bohus, & Christian Schmahl (2014d). Amygdala and dorsal anterior cingulate connectivity during an emotional working memory task in borderline personality disorder patients with interpersonal trauma history. *Frontiers in Human Neuroscience, 8*, 848. doi:10.3389/fnhum.2014.00848.

Abstract

Background: Working memory is critically involved in ignoring emotional distraction while maintaining goal-directed behavior. Antagonistic interactions between brain regions implicated in emotion processing, e.g. amygdala, and brain regions involved in cognitive control, e.g. dorsolateral and dorsomedial prefrontal cortex (dlPFC, dmPFC), may play an important role in coping with emotional distraction. We previously reported prolonged reaction times associated with amygdala hyper-reactivity during emotional distraction in interpersonally traumatized Borderline Personality Disorder (BPD) patients compared to healthy controls (HC): Participants performed a working memory task, while neutral versus negative distractors (interpersonal scenes from the International Affective Picture System) were presented. **Methods:** Here, we re-analyzed data from this study using Psychophysiological Interaction (PPI) analysis. The bilateral amygdala and bilateral dorsal anterior cingulate cortex (dACC) were defined as seed regions of interest. Whole-brain regression analyses with reaction times and self-reported increase of dissociation were performed. **Results:** During emotional distraction, reduced amygdala connectivity with clusters in the left dorsolateral and ventrolateral PFC was observed in the whole group. Compared to HC, BPD patients showed a stronger coupling of both seeds with a cluster in the right dmPFC and stronger positive amygdala connectivity with bilateral (para)hippocampus. Patients further demonstrated stronger positive dACC connectivity with left posterior cingulate, insula, and fronto-parietal regions during emotional distraction. Reaction times positively predicted amygdala connectivity with right dmPFC and (para)hippocampus, while dissociation positively predicted amygdala connectivity with right ACC during emotional distraction in patients. **Conclusion:** Our findings suggest increased attention to task-irrelevant (emotional) social information during a working memory task in interpersonally traumatized patients with BPD.

Keywords: Amygdala, anterior cingulate cortex, borderline personality disorder, emotional distraction, emotional working memory, functional connectivity, interpersonal trauma, psychophysiological interactions

5.1. Introduction

Emotional stimuli tend to capture attention due to their potential relevance to survival (Drevets & Raichle, 1998). Coping with emotional distraction (e.g. irrelevant context information, recollection of unpleasant memories) is crucial to goal-directed behavior across different life domains and has been closely related to self-control and emotion regulation (Ochsner & Gross, 2007; Rueda et al., 2005). Working memory is critically involved in the ability to ignore emotional information while maintaining goal-directed behavior (Banich et al., 2009). A well-established paradigm that has been used to investigate the ability to ignore emotional distraction is the Emotional Working Memory Task (EWMT). In this modified Sternberg working memory task, participants have to remember specific information, such as a set of human faces or a set of letters, across a short time interval. During this delay interval either neutral or emotional distracters (e.g., pictures from the International Affective Picture System, IAPS, Lang et al., 2005) are presented. After the delay interval, participants have to indicate whether a specific stimulus (e.g., a face or a letter) was part of the initial set or not. Participants are instructed to ignore distractors and to respond as fast and accurately as possible to the probes. Prolonged reaction times and impaired accuracy after emotional distraction suggest an increased susceptibility to distraction (Iordan, Dolcos, & Dolcos, 2013).

In previous studies that applied this paradigm in non-clinical samples, working memory impairments during emotional distraction were associated with increased activity in ventral brain areas including the amygdala, insula, and inferior frontal gyrus, and decreased activity in dorsal brain regions including parts of the dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), and dorsal anterior cingulate cortex (dACC) (Anticevic et al., 2010; Chuah et al., 2010; Denkova et al., 2010; Dolcos & McCarthy, 2006; Iordan et al., 2013; Oei, Veer, Wolf, Rombouts, & Elzinga, 2012; Perlstein et al., 2002). Although the neural underpinnings of emotional distraction remain elusive, the above-mentioned studies suggest an antagonistic relationship between brain regions implicated in emotion processing (e.g., amygdala) and areas involved in cognitive control and working memory (e.g., dACC, dlPFC, dmPFC) (Iordan et al., 2013). The amygdala plays a central role in emotion processing and in the initiation of stress responses (Davis and Whalen 2001; Ochsner et al., 2012; Phan et al., 2002; Stein et al. 2007). The dorsal proportion of the ACC (dACC) has been discussed as an important region involved in salience detection, attention regulation, and cognitive control (Bush et al., 2000; Clarke & Johnstone 2013; Dosenbach et al. 2006; Etkin et al., 2011; Niendam et al. 2012; Nee et al., 2007; Petersen & Posner 2012; Seeley et al., 2007; Wager and Smith 2003; Weissman et al. 2006).

There is growing evidence for dynamic interactions between 'hot' ('affective') brain regions and 'cold' ('executive') brain regions during tasks that involve both affective and cognitive processing (Pessoa, 2008). Psychophysiological Interaction (PPI) analysis can be used to investigate changes in the co-activation of a brain region of interest (the 'seed' region) and other regions across the brain, dependent on an experimental condition (Friston et al., 1997; O'Reilly et al. 2012). The principle underlying PPI is that if two brain areas interact in a task-dependent manner, time courses of activity in these areas will be correlated. Stronger correlations, i.e., connectivity between the seed and a 'coupled' brain area is assumed to reflect an increased exchange of information between these brain areas, while no causal conclusions can be made (i.e., whether the interaction is 'driven' by the seed or the other area) (O'Reilly et al. 2012).

Dolcos and colleagues (2006) investigated amygdala connectivity during performance of an EWMT in a non-clinical sample. Stronger positive amygdala connectivity with inferior frontal gyrus was observed during presentation of negative distractors (IAPS pictures).

In a study by Mitchell and colleagues (2008), amygdala activity was positively correlated with activity in cingulate gyrus, posterior cingulate, and middle temporal cortex, while it was negatively correlated with activity in dlPFC and dmPFC (superior frontal gyrus, middle frontal gyrus) as well as parietal regions when emotional distracters (positive and negative IAPS pictures) interfered with a cognitive task (a shape identification task).

Anticevic and colleagues (2010) reported stronger negative correlations between amygdala activity and activity in dlPFC, dACC, anterior PFC, and frontal operculum during presentation of negative distractors (IAPS pictures) compared to neutral distractors and compared to a resting state scan in a non-clinical group (Anticevic et al., 2010). While detrimental effects of emotional stimuli on working memory have been mainly linked to negative correlations between amygdala and dorsal prefrontal regions, an enhancing effect of emotions on memory, such as enhanced encoding or retrieval of self-relevant emotional events has been associated with increased co-activation in the amygdala and regions of the medial temporal lobe, including hippocampus and parahippocampal gyrus (Dolcos et al., 2012). The ability to voluntarily modulate emotional responses through the use of cognitive strategies (e.g. , shifting attention away from irrelevant or unwanted emotional material) is a crucial part of cognitive emotion regulation (Banks et al., 2007; Ochsner & Gross, 2005; Ochsner & Gross, 2007; Schweizer et al., 2013). This ability seems to be impaired in stress-related psychiatric disorders such as Borderline Personality Disorder (BPD) and (complex) Posttraumatic Stress Disorder (PTSD).

Key features of these disorders include difficulties discriminating between harmless and threatening cues, affective hyper-reactivity, pronounced deficits in emotion down-regulation, and traumatic re-experiencing (emotional intrusions) (Banich et al., 2009; Elzinga & Bremner, 2002; Ford & Courtios, 2014; Lieb et al., 2004; Schweizer & Dalgleish, 2011; Schmahl et al. 2014). Intrusive memories of traumatic events can be spontaneously triggered by traumatic reminders and are usually accompanied by strong sensory impressions, as if the event was happening again right now (Ehlers et al., 2004; Ford & Courtois, 2014). Emotional distress caused by traumatic reminders can interfere with goal-directed behavior in everyday life, which can have detrimental effects across multiple life domains, ranging from social interactions to academic success (Ford & Courtois, 2014). In previous studies that used the EWMT, patients with BPD showed prolonged reaction times associated with increased amygdala activity during emotional distraction (presentation of negative IAPS pictures) compared to healthy controls (Krause-Utz et al. 2012, 2014a; Prehn et al. 2013). Studies that applied similar paradigms observed a failure of ACC activation during an Emotional Stroop Task (Wingenfeld et al. 2009b) and an Emotional GoNoGo Task (Silbersweig et al., 2007) as well as increased ACC activation during an Emotional Flanker Task ((Holtmann et al., 2013) in BPD patients compared to healthy participants. Findings of these studies complement results of functional magnetic resonance imaging (fMRI) studies suggesting a hyper-reactivity of limbic brain regions during emotional challenge in BPD patients, although discrepant findings are also observed (for an overview see Krause-Utz et al., 2014b; New et al., 2012; O'Neill & Frodl, 2012; Ruocco et al., 2013; Winter et al., 2014).

Dissociation may modulate emotional distractibility, e.g., activity and functional connectivity of the amygdala in stress-related disorders such as BPD. Importantly, a large proportion of individuals with BPD reports dissociative experiences (Stiglmayr et al., 2008) involving disruptions of usually integrated functions such as depersonalization, derealization, reduced sensory processing, disturbed memory and emotional numbing (APA, 2013). Dissociation was suggested to involve an over-modulaton of otherwise overwhelming emotions in stressful situations, possibly associated with increased recruitment of medial prefrontal regions along with dampened amygdala activation (Lanius et al. 2010). In our above-mentioned study, amygdala activity during presentation of emotional distractors (aversive interpersonal IAPS pictures) was negatively correlated with self-reported increase of state dissociation in the BPD group (Krause-Utz et al., 2012). Moreover, trait dissociation positively predicted the strength of the coupling between amygdala and dlPFC during resting state (Krause-Utz, Veer, et al. 2014c).

Other fMRI studies in BPD observed increased amygdala connectivity with rostral ACC (Cullen et al., 2011) and ventromedial PFC (Kamphausen et al., 2013) during experimentally induced fear or threat. In another previous study, BPD patients showed positive amygdala connectivity with the middle frontal gyrus during an instructed emotion down-regulation task when presentation of negative IAPS pictures was combined with warmth (i.e., not painful) temperature (Niedtfeld et al., 2012). Recently, Koenigsberg and colleagues (2014) reported increased connectivity between insula and ventral ACC during the repeated presentation of negative IAPS pictures in patients with BPD compared to patients with avoidant personality disorder. In sum, previous research suggests amygdala hyper-connectivity in BPD.

To our knowledge, however, no study so far has investigated amygdala and dACC connectivity during performance of the EWMT in BPD. Moreover, little is known about how dissociative states may modulate amygdala connectivity during emotional distraction. Here, we re-analyzed data from our above-mentioned study in 22 unmedicated BPD patients with a history of interpersonal trauma and 22 healthy participants who performed the EWMT during fMRI (Krause-Utz et al. 2012). The bilateral amygdala and bilateral dACC were a-priori defined as seed regions of interest given their important role in neurobiological models of affective-cognitive interactions, delineated above, as well as in BPD psychopathology. We used PPI to analyze task-related changes in connectivity between each of these seed with other areas across the brain. Based on previous research, stronger negative correlations between amygdala and dorsal frontal brain regions involved in cognitive control (dlPFC, dmPFC, dACC) were expected during emotional distraction. We further expected significant group differences during negative distractors. To investigate how WM performance (reaction times) and a self-reported increase in state dissociation may predict amygdala connectivity during negative distractors, whole brain regression analyses were performed.

5.2. Methods:

5.2.1. Sample

A total sample of 53 women (26 patients with BPD according to DSM-IV (APA, 2000) and 27 healthy controls (HC)) aged between 18 and 45 was recruited. Patients with BPD were recruited by advertisement on websites or referred from the inpatient treatment unit of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health (CIMH) in Mannheim, Germany. In parallel, HC who matched to patients regarding age and education were referred from a pool of healthy individuals that had been recruited by newspaper advertisement and had agreed to participate in future studies of our research group.

Two patients with BPD had to be excluded because of alcohol abuse. One patient and two healthy controls canceled study participation at the beginning of the MR scan due to unexpected claustrophobia. One HC was excluded because she reported repeated self-injurious behavior in the past. Data from three HC and one patient had to be excluded from the final analysis due to movement artefacts and/or missing button presses during the EWMT. The final sample comprised 44 women: 22 BPD patients and 22 healthy controls. All participants underwent diagnostic assessments including the Structured Interview for DSM-IV Axis-I (SCID-I, First et al. 1997) and International Personality Disorder Examination (IPDE, Loranger 1999) by trained diagnosticians. Further clinical assessment included questionnaires on BPD symptom severity (Borderline Symptom List 95, BSL-95, Bohus et al. 2001; 2007) and trauma history (Childhood Trauma Questionnaire, CTQ, Bernstein et al. 2003; Posttraumatic Stress (Posttraumatic Stress Diagnostic Scale, PDS, Foa 1995). All participants completed questionnaires on depressive symptoms (Beck Depression Inventory, BDI, Beck et al. 1961), state anxiety (State Anxiety Questionnaire, STAI-X1, Spielberger, Gorsuch, & Lushene 1970) and trait dissociation (Dissociative Experience Scale, DES, Bernstein and Putnam 1986). Immediately before and after the experiment, all participants further completed the Dissociation Stress Scale 4 (DSS-4) (Stiglmayr et al. 2010). The DSS-4 is a self-rating scale consisting of 4 items measuring current dissociative experience (depersonalization, derealization, altered hearing and pain perception) as well as one item on current arousal (all between "0= not at all" and "9= extremely"). General exclusion criteria were severe somatic illness and criteria related to MRI (metal implants, left-handedness, claustrophobia, and pregnancy). All patients were free of medication and did not abuse alcohol or other substances within the last 6 months. Further exclusion criteria were current major depression, lifetime psychotic disorder, bipolar affective disorder, mental retardation, developmental disorder, and a suicidal crisis. Exclusion criteria for the healthy control group were a lifetime history of psychiatric disorders. All patients met criteria for BPD according to DSM-IV (APA, 2000) and fulfilled the DSM-IV criterion for affective instability. Furthermore, all patients reported a history of interpersonal traumatization including emotional maltreatment (e.g., neglect, emotional abuse), physical abuse and/or sexual abuse as assessed by the CTQ and PDS. Nine patients (~41%) currently met diagnosis of posttraumatic stress disorder (PTSD). There were no significant group differences in age, years of education, and body mass index (BMI). Descriptive statistics of demographic variables and questionnaires are reported in Table 5.1.

Table 5.1.
Demographic and clinical variables in healthy controls (HC) and patients with Borderline personality disorder (BPD) and results of the univariate analysis of variance (ANOVA)

	HC (n = 22)	**BPD (n = 22)**	**t-tests (df = 42)**
Age (in years)	27.41 ± 8.49	28.18 ± 7.02	t= 0.33 p= .744
Body mass index	23.24 ± 4.00	25.45 ± 6.69	t= 1.31 p= .197
Years of education	12.14 ± 1.46	11.73 ± 1.49	t= .92 p= .362
DSS-4 before fMRI **DSS-4 after fMRI**	0.10 ± 0.20 0.13 ± 0.26	1.97 ± 1.73 2.97 ± 2.25	t= 4.91 t= 5.75 all p < .001
DES	2.45 ± 1.89	30.85 ± 15.27	t= 8.66 p= <.001
BSL-95 (mean)	0.24 ± 0.11	1.92 ± 0.57	t= 13.48 p= <.001
STAI	34.10 ± 9.04	50.16 ± 8.32	t= 6.14 p= <.001
BDI	1.34 ± 1.74	23.86 ± 9.91	t= 10.50 p= <.001
Comorbidities:			
PTSD current	n=0	n = 9 (~41 %)	
MD lifetime	n=0	n = 8 (~36%)	
Social phobia (current)	n=0	n = 6 (~27 %)	
Specific phobia (current)	n=0	n = 2 (~9 %)	
Panic disorder (current)	n=0	n = 6 (~27 %)	
GAD (current)	n=0	n = 3 (~13 %)	
Bulimia nervosa (current)	n=0	n = 6 (~27 %)	
Anorexia nervosa (current)	n=0	n = 7 (~31 %)	
OCD (current)	n=0	n = 4 (~18 %)	

Note: BDI= Beck Depression Inventory, BPD= Borderline Personality Disorder, BSL= Borderline Symptom List, DES= Dissociative Experiences Scale, DSS= Dissociation Stress Scale, HC= Healthy controls, n= number of participants, PTSD= Posttraumatic Stress Disorder, STAI= State Trait Anxiety Inventory, MD= major depressive disorder, GAD= generalized anxiety disorder, OCD= obsessive-compulsive disorder. Data from questionnaires are presented in mean score ± standard deviation

5.2.2. Emotional Working Memory Task (EWMT)

The EWMT was an adapted Sternberg item recognition task (Sternberg, 1966), modified by Oei and colleagues (Oei et al., 2009, 2010, 2012; Krause-Utz et al. 2012,). The present version consisted of 48 trials, each starting with the presentation of a set with 3 uppercase letters (memoranda, 1000 ms). After a delay interval (1500 ms), again a set of 3 uppercase letters was presented (probe, 2000 ms). Participants had to press the "yes" or "no" button indicating whether they had recognized a target or not. In half of the trials, 1 of the 3 memoranda was present in the probe. During the delay interval either no distractors (only a fixation cross) or neutral distractors versus negative distractors were presented. Distractors were pictures from the IAPS which were selected based on arousal and valance ratings in the general population (Lang et al., 2005). Negatively arousing IAPS depicted interpersonal scenes of interpersonal violence (e.g., a sexual attack, physical assault, a beaten and neglected child or a physically mutilated body). Neutral pictures were matched to negative pictures with regard to number of persons and complexity of the scene in order to avoid confounding differences in visual information processing. This means that neutral distracters were IAPS pictures, which depicted naturalistic interpersonal scenes (e.g., people at a market place or people in a supermarket), which had been rated as neutral (according to valence and arousal ratings) in the general population (Lang et al., 2005). Target-present and target-absent trials were equal in both conditions. The presentation of the conditions within the EWMT was balanced in a pseudo-random manner. In addition to the 3 conditions of the EWMT, 15 trials of the Sternberg item recognition task without distraction (i.e., only a fixation cross) were presented at the beginning of the scan as a measure of baseline working memory. Software Presentation (Neuro-behavioural systems http://www.neurobs.com/) was used to present stimuli and record behavioral data. After scanning, participants rated the pictures together with 30 foils (similar IAPS pictures) regarding arousal and distraction (difficulty of shifting away attention from the picture) as perceived during the task (between "0= not at all" and "9= extremely") and post-hoc recognition of the pictures was tested. As previously reported, we found that this paradigm was capable of inducing emotional distraction in terms of slower reaction times (Krause-Utz et al. 2012, 2014a) and increased activity of the amygdala compared to distraction by neutral pictures. The experimental design of our paradigm is depicted in Figure 5.1.

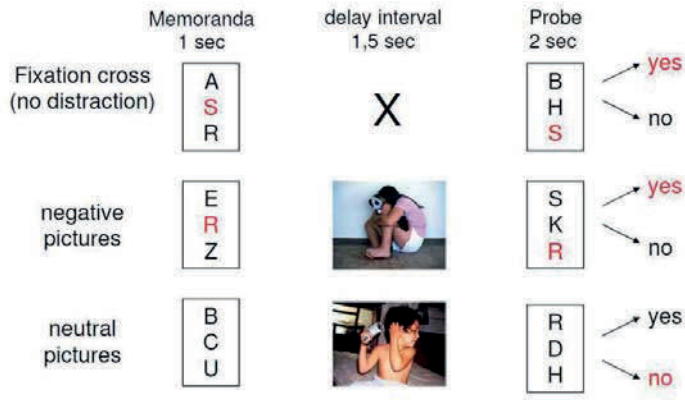

Figure 5.1. Design of the Emotional Working Memory Task (EWMT)

5.2.3. Procedure

The experiment was approved by the local ethics committee (University of Heidelberg, in accordance to the World Medical Association's Declaration of Helsinki) and took place at the Central Institute of Mental Health in Mannheim, Germany. All participants received information about the experiment and scanning procedure and signed written informed consent. At the beginning of the study, participants underwent diagnostics (SCID-I, IPDE) and basic clinical assessment as described above). To ensure that participants understood the instruction correctly, they practiced the EWMT outside the scanner and were given feedback by the experimenter. Immediately before and after scanning, acute dissociation were assessed by the DSS-4. Inside the scanner, participants performed the EWMT, while gradient echo planar imaging (EPI) sequences were acquired. Participants were instructed to focus on the middle of the screen, concentrating only on the task and ignoring distracting pictures. At the end of the experiment, participants were thanked, debriefed, and paid for their participation.

5.2.4. Scanning protocol

Scanning was conducted by a Siemens TRIO-3T MRI (Siemens Medical Solutions, Erlangen, Germany). Using T1-weighted 3-D magnetization prepared rapid acquisition gradient echo (voxel size 1x1x1mm3), a high-resolution anatomical scan was acquired for each participant as an individual template for the functional data. For event-related measurement of BOLD signal, T2-weighted EPI [field of view= 210x210mm, voxel size= 3x3x3mm, echo time=30ms, TR=2500ms] with 40 contiguous 3mm sagittal slices in a 64x64 matrix was used. The first 5 scans were discarded to minimize T1 effects. Head movement artefacts and scanning noise were restricted using head cushions and headphones within the scanner coil.

5.2.5. Data Analysis

Analysis of the behavioral data (working memory performance, picture ratings and post-hoc recognition of the pictures) were previously reported (Krause-Utz et al. 2012). Functional imaging data were analyzed using standard procedures implemented in the Statistical Parametric Mapping package 8 (SPM8; Neurobehavioral systems, Berkeley, CA; http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing of the EPI time series included slice time correction, spatial realignment, and unwarping to correct for head motion, co-registration onto participants' high-resolution T1 scan, normalization to the standard brain of the Montreal Neurological Institute (MNI) space, and smoothing using a Gaussian kernel with a full width at half maximum (FWHM) of 9mm. The statistical analyses of our event-related design relied upon the general linear model to model effects of interest (Friston et al., 1995) as implemented in SPPM8. For each participant, task-related activity was identified by convolving a vector of the onset times of the following two experimental events of interest with a canonical hemodynamic response: 1) 'neutral distracters (IAPS pictures), 2) 'negative distracters' (IAPS pictures). We further defined the following events as regressors of no interest: (i) no distraction during the delay interval of the task, (ii) memoranda (target letters), and (iii) probes. The GLM further included nuisance variables to control for movement artifacts.

5.2.5.1. Psychophysiological interaction (PPI) analysis

We used PPI to analyze changes in connectivity between a seed region of interest and other brain regions dependent on an experimental condition (psychological component). Using PPI, brain regions across the whole brain can be identified whose time courses are significantly correlated to time courses of the seed region given an experimental condition. Thereby, it is possible to analyze whether brain regions are more strongly correlated in one experimental condition than in the other or in one group compared to the other. Increased correlations are assumed to reflect an increased exchange of information between these brain areas, while the causality of this direction remains unknown (Friston et al. 1997; O'Reilly et al. 2012).

In our PPI analysis, two seed regions of interest were a-priori defined based on models of affective-cognitive interactions and previous research in BPD (as delineated above): 1) bilateral amygdala, and 2) bilateral dACC. Since the amygdala is a small structure, an anatomical mask of the bilateral amygdala was created based on the Automatic Anatomical Labeling (AAL) software as provided in SPM8. For the bilateral dACC, a sphere of 9mm was created around a pre-defined voxel (MNI coordinates X=5, Y=19, Z=28) as reported in previous studies (seed "I4" in Margulies et al. 2007, also used in Krause-Utz et al., 2014c).

For each participant, the mean time series of activity in each region of interest were extracted from the voxels falling within each mask. The design matrix (general linear model) of our first level analysis contained three columns: 1) the 'psychological variable' (i.e., experimental condition of interest), 2) the time series of activation in the seed region, and 3) the interaction of both. The regression coefficient modelling the interaction term of the psychological variable and the time course of activation in the seed region ('PPI regressor') provides a measure for connectivity identifying brain regions whose time courses of activity are significantly correlated to activity in the seed dependent on an experimental condition. Separate first-level analyses for 'neutral distracters' and 'negative distracters' were performed for each seed. This means, for each participant separate PPI regressors (i.e., correlations of the seed region and other regions) for 'neutral distracters' and 'negative distracters' were created for the amygdala seed and the dACC seed separately. A contrast of 1 for the PPI regressor and 0 elsewhere was applied to reveal clusters showing a significant positive regression slope with activity in the seed region of interest in a task-dependent manner.

Our second level analysis was based on our two research questions: First, we aimed to analyze task-related changes in connectivity between the seed regions and other areas across the brain as an effect of valence, i.e., negative distracters compared to neutral distracters. Second, we were interested in the effect of group on task-dependent connectivity of the seeds, particularly during presentation of negative distractors. First level contrasts of the PPI regressors for 'neutral distracters' and 'negative distracters' were fed into separate whole-brain 2x2 Full Factorial models for each brain region (i.e., amygdala and dACC). This means, we created two 2x2 Full Factorial Models comprising the factor 'Group' (2 levels: 'BPD', 'HC') and the factor 'Valence' (2 levels: neutral vs. negative distracters) resulting in 4 cells.

One 2x2 Full Factorial Model was created for the amygdala seed and the other 2x2 Full Factorial Model was created for the dACC seed. In each 2x2 Full Factorial Model, F contrasts for the main effect of the two independent variables 'Group' (BPD, HC) and 'Valence' ('neutral distractors', 'negative distractors') and their interaction were defined. To follow-up significant main effects of valence, T contrasts for neutral > negative distractors and vice versa (negative > neutral distractors) were evaluated for the full sample within each 2x2 Full Factorial Model. As this was one of our main contrasts of interest, additional between-group analyses for amygdala connectivity and dACC connectivity during negative distractors were performed using independent t-tests on the whole-brain level (during negative distractors in BPD>HC and in HC>BPD). In all second-level analysis, clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level.

Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. Based on our a-priori hypothesis of amygdala connectivity with dorsal prefrontal regions during presentation of negative distractors, small volume corrections (SVC) were applied for amygdala connectivity with dlPFC and dmPFC regions. Anatomical masks of the dlPFC and dmPFC were created based on the AAL software as provided in SPM8. These masks were then used for SVCs of clusters determined by the main effect of valence of the 2x2 Full Factorial Model of amygdala connectivity as well as for clusters determined by the between-group t-tests for amygdala connectivity during negative distractors. Clusters revealed by SVCs are indicated (by an asterisk) in the result section (see Tables S5.1, S5.2., and S5.3 in Supplemental Material). No SVCs were applied for all other contrasts.

5.2.5.2. Regression analyses

To examine whether reaction times predicted amygdala connectivity during emotional distraction, first level contrasts of interaction terms for amygdala connectivity during 'negative distractors' were entered together with reaction times (in milliseconds) into whole-brain regression analyses for the BPD group and the HC group separately. For the BPD group, another whole-brain regression analysis with self-reported increase of dissociation as regressor of interest was performed. The mean increase of dissociation (DSS-4 scores post-experiment minus DSS-4 scores pre-experiment) was defined as regressor of interest, because we previously reported significant negative correlations between amygdala activity and mean DSS-4 increase during presentation of negative distractors in the BPD group (Krause-Utz et al., 2012). First level contrasts of interaction terms for amygdala connectivity during 'negative distractors' were entered together with mean increase of DSS-4 scores into a whole-brain regression analysis. In all regression analyses, clusters were determined using a significance threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. Clusters meeting a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented.

5.3. Results

Behavioral data and whole brain activation patterns during performance on the EWMT were previously reported (Krause-Utz et al. 2012). In brief, significantly prolonged reaction times during presentation of negative distractors were observed in BPD patients compared to HC. There were no significant group differences in accuracy (i.e., errors). Both BPD patients and healthy controls showed a significant increase in amygdala activation during negative distractors. Amygdala activity during emotional distraction was significantly higher in patients than in HC. Results of our PPI analysis are presented per seed in the following.

5.3.1. Amygdala connectivity

Complete results of the 2x2 Full Factorial Model for amygdala connectivity can be found in Table S5.1 in the Supplemental Material. The analysis revealed a significant *main effect of valence* and a significant *group effect* but no significant *interaction effect* ($p<0.001$, $Z>3.1$).

As shown in Figure 5.2A, a significant main effect of valence was observed for amygdala connectivity with left inferior frontal gyrus. In addition, a significant main effect of valence on amygdala connectivity with left lingual gyrus, bilateral fusiform gyrus, left parahippocampal gyrus (including parahippocampal place area, BA19), left hippocampus, right posterior cingulate, right middle temporal gyrus, and right caudate was observed. The SVC with the dlPFC mask revealed a significant cluster in the left superior frontal gyrus (BA9) (see Figure 5.2B). The SVC with the dmPFC revealed no significant clusters. The coupling of amygdala with the above-mentioned brain regions was significantly weaker during presentation of negative distractors than during presentation of neutral distractors (see Table S5.2). The T contrast negative > neutral distractors revealed no significant clusters (Table S5.2).

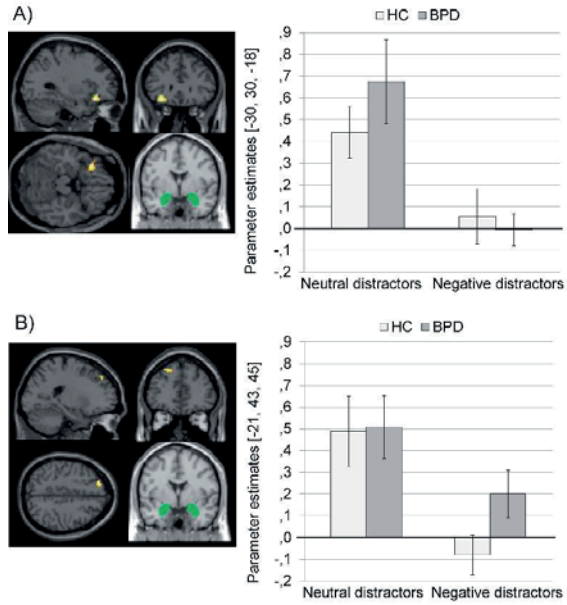

Figure 5.2. Results for the main effect of valence on amygdala connectivity: Figure A) shows means ± standard errors of the mean (SEM) of parameter estimates for connectivity of the bilateral amygdala seed (depicted in green) with left inferior frontal gyrus (MNI: -30, 30, -18) during presentation of neutral distractors and negative distractors in patients with Borderline Personality Disorder (BPD) and healthy controls (HC). Figure B) shows means ± SEM of parameter estimates for amygdala connectivity with left superior frontal gyrus (MNI: -21, 43, 45) during presentation of neutral and negative distractors in BPD patients and HC. For the sake of illustration, activation in the coupled brain regions are depicted by creating a sphere around the peak cluster.

A significant *main effect of group* was found for amygdala connectivity with a cluster in the right lingual gyrus (see Table S5.1 and Figure S5.1. in Supplemental Material). BPD patients showed positive amygdala connectivity with right lingual gyrus during both EWMT conditions, most prominently during presentation of neutral distractors. Healthy controls showed negative amygdala connectivity with right lingual gyrus during presentation of neutral distractors and no or only marginal coupling negative distractors. Results of the independent t-tests for amygdala connectivity during negative distractors are depicted in Figure 5.3.

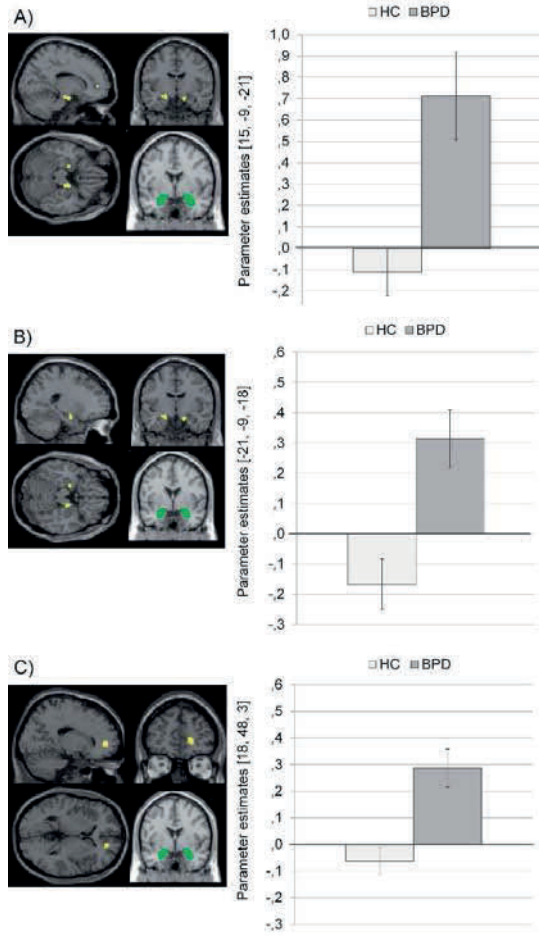

Figure 5.3. Results of the independent t-tests for amygdala connectivity during negative distractors (means ± SEM of parameter estimates for stronger connectivity of bilateral amygdala seed (depicted in green) in BPD than HC during negative distractors). Figure A shows amygdala connectivity with right parahippocampal gyrus (BA34, MNI: 15, -9, -21). Figure B) shows amygdala connectivity with left (para)hippocampus (MNI: -21, -9, -18). Figure C) shows connectivity with right medial frontal gyrus (BA10, MNI: 18, 48, 3). For the sake of illustration, activation in the coupled brain regions are depicted by creating a sphere around the peak cluster.

Patients showed a stronger coupling of the amygdala with clusters in the right parahippocampal gyrus (BA34) (Figure 5.3A) and left hippocampus / parahippocampal gyrus (Figure 5.3B) than HC. In BPD, positive amygdala connectivity with these brain areas was observed, while HC showed negative amygdala connectivity with these regions for negative distractors. SVC with the dmPFC mask revealed a stronger coupling of the amygdala with a cluster in the right medial frontal gyrus (BA10) in BPD than in HC. Figure 5.3C shows that there was positive amygdala connectivity with right medial frontal gyrus in BPD, while HC showed negative amygdala connectivity with this region. SVC for the dlPFC revealed no significant clusters. There were no significant results for HC>BPD (see Table S5.3).

5.3.2. Dorsal anterior cingulate (dACC) connectivity

Results of the 2x2 Full Factorial Model for dACC connectivity can be found in Table S5.4. There was a significant *main effect of valence* for dACC connectivity with bilateral lingual gyrus (BA19), bilateral fusiform gyrus, right posterior cingulate, and bilateral middle/superior temporal gyrus. The coupling with these brain regions was significantly weaker during negative compared to neutral distractors. There was further a significant *main effect of group* on dACC connectivity with a cluster comprising left precuneus and posterior cingulate (BA31) and clusters in the right inferior occipital gyrus and right ACC (BA32) (see Figure S5.2. in Supplemental Material). BPD patients showed positive dACC connectivity with these regions, while HC showed negative dACC connectivity with these areas during both conditions. The 2x2 Full Factorial Model further revealed a significant *interaction effect* of valence by group on amygdala connectivity with right superior temporal gyrus (see Figure S5.3, Supplemental Material). During both EWMT conditions, BPD patients showed positive dACC connectivity with right superior temporal gyrus (most prominently during presentation of negative distractors). Healthy controls showed positive dACC connectivity during presentation of neutral distractors und negative dACC connectivity with this region during negative distractors. Complete results of the independent t-test for dACC connectivity during presentation of negative distractors can be found in Table S5.6 in Supplemental Material. Compared to HC, BPD patients showed a stronger coupling of the dACC with right medial frontal gyrus, left inferior parietal lobule, left precentral gyrus, left insula, left posterior cingulate, left inferior/middle occipital gyrus, left paracentral lobule, left superior temporal gyrus, and left precentral gyrus. Figure 5.4. illustrates that BPD patients demonstrated positive dACC connectivity with right medial frontal gyrus (BA10), left inferior parietal lobule, left insula, and left posterior cingulate, while HC showed negative connectivity between these regions. There were no significant results for the T contrast HC>BPD.

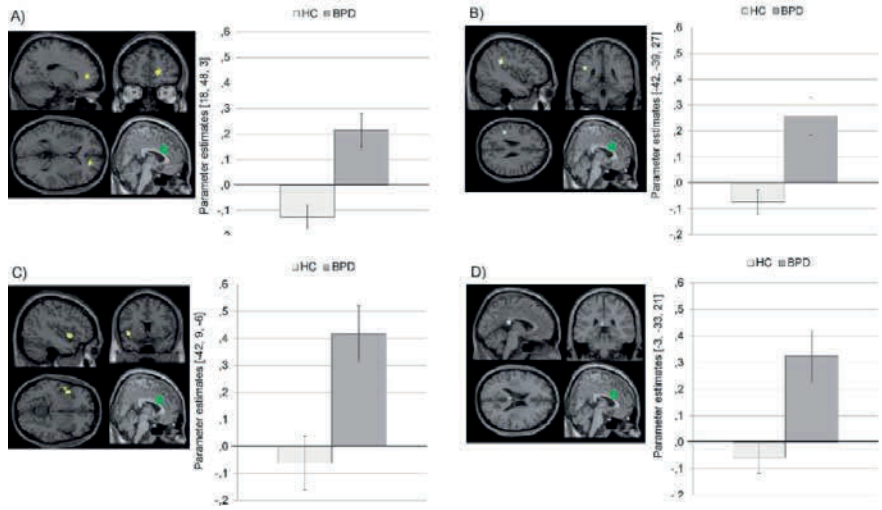

Figure 5.4. Results of the independent t-tests for dACC connectivity during negative distractors (means ± SEM of parameter estimates for connectivity of the dACC seed (depicted in green) during negative distractors in BPD and HC). Figure A) shows connectivity with right medial frontal gyrus (MNI: 18, 48, 3). Figure B) shows connectivity with left inferior parietal lobule (MNI: -42, -39, 27). Figure C) shows connectivity with left insula (MNI: -42, 9, -6). Figure D) shows connectivity with left posterior cingulate (MNI: -3, -33, 21). For the sake of illustration, activation in the coupled brain regions are depicted by creating a sphere around the peak cluster.

5.3.2.5. Regression analyses

Results of the whole-brain regression analysis for reaction times as regressor of interest for amygdala connectivity during presentation of negative distractors are presented in Table S5.7. and Figure S5.4. in the Supplemental Material). In the BPD group, reaction times positively predicted amygdala connectivity with left superior temporal gyrus (BA38), right middle frontal gyrus (BA46), right medial frontal gyrus (BA10), and right parahippocampal gyrus / hippocampus (see Figure S5.4). There were no significant results of the same regression analysis in the HC group (at $p<0.001$, $k\geq10$, $Z>3.1$).

Results of the whole-brain regression analysis with mean increase of DSS-4 scores as predictor for amygdala connectivity during negative distractors in BPD are presented in Table S5.8. in the Supplemental Material. Figure 5.5. illustrates that increases in state dissociation positively predicted amygdala connectivity with left precentral gyrus (BA4), right ACC (BA32), right thalamus, and left insula (BA13).

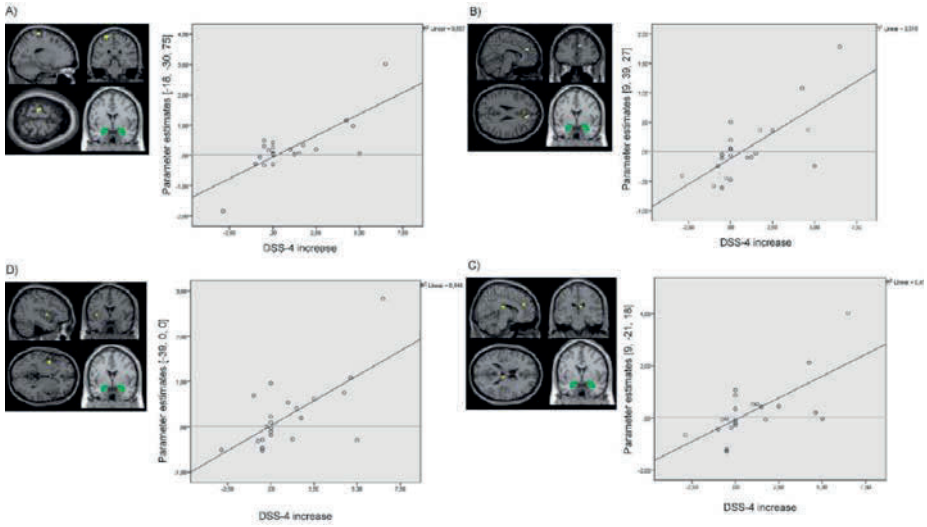

Figure 5.5. Results of the regression analysis with increases in DSS-4 scores as regressor for connectivity of the amygdala seed (depicted in green) during negative distractors in BPD. Figure A) shows connectivity with left precentral gyrus (MNI: -18, -30, 75). Figure B) shows connectivity with right ACC (9, 39, 27). Figure C) shows connectivity with left insula (-39, 0, 0). Figure D) shows connectivity with right thalamus (9, -21, 18).

5.4. Discussion

We used Psychophysiological Interaction (PPI) analysis to investigate functional connectivity during performance of an Emotional Working Memory Task (EWMT) in 22 unmedicated female BPD patients with a history of interpersonal trauma and 22 healthy women (HC). The bilateral amygdala as well as bilateral dorsal anterior cingulate cortex (dACC) were defined as seed regions of interest. Main results were:

- Reduced amygdala connectivity with clusters in the left dlPFC (superior frontal gyrus) and left vlPFC (inferior frontal gyrus) during emotional distraction in the whole group.
- Stronger positive amygdala connectivity with bilateral (para-)hippocampus as well as stronger positive dACC connectivity with left insula, posterior cingulate, superior temporal gyrus, and occipital gyrus in BPD patients during emotional distraction.
- Compared to HC, BPD patients further showed a stronger coupling of both the amygdala and dACC seed with a cluster in the right dmPFC (medial frontal gyrus).
- Reaction times positively predicted amygdala connectivity with right dorsomedial and dorsolateral PFC and right (para)hippocampus during emotional distraction in BPD.
- Self-reported state dissociation positively predicted amygdala connectivity with right ACC, left precentral gyrus, left insula, and right thalamus during emotional distraction in patients.

These results are discussed per seed in the following.

Amygdala connectivity

In the whole group, a reduced coupling of the amygdala with clusters in the left dlPFC (superior frontal gyrus) and left vlPFC (inferior frontal gyrus) as well as right caudate was observed, when negative (compared to neutral) IAPS pictures were presented during the delay interval of the working memory task. The inferior frontal gyrus, superior frontal gyrus, and caudate are parts of a prefrontal-striato-thalamo-cortical loop which has been implicated in interference inhibition and basic working memory processes including the maintenance of information across a delay (Aron et al., 2014; Dolcos et al., 2006; Geier et al., 2009; Goldman-Rakic et al., 1992; Grahn et al., 2009; McGaugh, 2004; Seger et al., 2005). Our finding suggests a reduced information exchange between the amygdala (i.e., a brain region implicated in emotion processing), and regions involved in working memory maintenance, possibly reflecting a disruptive effect of emotional distraction on working memory in the whole group. There were significant group differences in amygdala connectivity during emotional distraction: Compared to HC, BPD patients showed a stronger coupling of the amygdala with right dmPFC (medial frontal gyrus). Reaction times positively predicted amygdala connectivity with right dmPFC (medial frontal gyrus) and right dlPFC (middle frontal gyrus) during emotional interference in the BPD group. This means, a stronger positive coupling of the amygdala with dorsomedial and dorsolateral prefrontal regions was associated with more working memory impairments after emotional distraction in BPD patients. While patients showed positive amygdala with right dmPFC and left dlPFC, healthy controls showed negative amygdala connectivity (suggesting inhibitory interactions) with these regions. In line with the latter finding, negative amygdala connectivity with dorsal prefrontal regions was also observed in previous fMRI studies investigating the neural correlates of emotional distraction in non-clinical samples (Anticevic et al., 2010; Mitchell et al., 2008). Activity in the dmPFC and dlPFC are also observed during working memory tasks (Miller, 2000; Barbey et al., 2013) and have been associated with cognitive emotion regulation. Parts of the dorsomedial and dorsolateral PFC, ventrolateral PFC, and anterior cingulate were found to be more active during emotion down-regulation (e.g., reappraisal) in healthy individuals (Bush et al., 2000; Etkin et al., 2011; Ochsner et al., 2012; Paret et al. 2011; Phan et al. 2002, 2005). In previous research in BPD, diminished activity in the dlPFC, vlPFC (Koenigsberg et al., 2009b), ACC (Lang et al., 2012), and OFC (Schulze et al., 2011) was found during cognitive reappraisal. Moreover, better emotion down-regulation was related to a stronger negative coupling of the amygdala with dorsomedial/dlPFC (Lee et

al., 2011) and vmPFC/vlPFC in healthy persons compared to patients with affective disorders showing positive amygdala-PFC connectivity (Johnstone et al., 2007; Townsend et al., 2012). In healthy individuals, the recruitment of dorsal prefrontal regions during a working memory task may either directly or indirectly via other brain regions suppress amygdala signals during emotional distraction (Anticevic et al., 2010). Since PPI doesn't allow causal conclusions about the direction of interactions (i.e., whether the observed interactions reflect 'bottom-up' or 'top-down' directed mechanisms), future studies should apply other approaches, such as Dynamic Causal Modelling to explicitly test causal models of a predefined network interactions.

In our present study, we further observed a stronger coupling of the amygdala with bilateral (para)hippocampus during emotional distraction in BPD patients than in healthy controls. A stronger coupling of the amygdala with right (para)hippocampus was associated with longer reaction times in the patient group. The hippocampus and parahippocampal gyrus play an important role in memory encoding and retrieval (Squire & Zola-Morgan. 1991). The amygdala appears to modulate encoding and storage of emotional memories in the hippocampal formation, which forms representations of the emotional significance of events, thereby modulating amygdala response to external stimuli (Banich et al., 2009; Dolcos et al., 2012; Knight et al., 2004; McGaugh, 2004; Phelps 2004; Richter-Levin & Akirav 2000). Stronger activation and co-activation in the amygdala, hippocampus, and parahippocampal gyrus has been associated with enhancing effects of emotions on long-term episodic memory (Dolcos et al., 2012; Hahn et al. 2010; Smith et al. 2006) as well as fear conditioning (Tzschoppe et al. 2014). There is evidence that stress leads to enhanced memory retrieval in patients with BPD and patients with PTSD (Wingenfeld et al., 2012; Wingenfeld & Wolf, 2014). In the context of earlier research, our present findings of increased connectivity within the medial temporal lobe network may reflect enhanced processing and encoding of task-irrelevant, but potentially self-relevant emotional social information in BPD, which may interfere with cognitive performance during the working memory task.

Presentation of neutral interpersonal IAPS pictures was associated with increased positive amygdala connectivity with right lingual gyrus in BPD but with negative connectivity between the regions in healthy controls. The lingual gyrus has been implicated in the encoding and retrieval of visual information including complex scenes and faces (Geier et al., 2009; Machielsen et al., 2000; Meng et al. 2012). Increased activity in the lingual gyrus was also found during the anticipation of negative pictures in BPD (Scherpiet et al., 2014). Our finding therefore suggests enhanced processing and enhanced affective evaluation of neutral social stimuli in patients with BPD. Interestingly, a stronger coupling of the amygdala with frontal

regions (right ACC, left precentral gyrus), left insula, and right thalamus during emotional distraction was related to a stronger increase of dissociation during the EWMT in BPD. This finding suggests that dissociative states modulates amygdala connectivity during emotional challenge in BPD. Dissociative states have been discussed as a regulatory strategy to cope with overwhelming emotional arousal in the face of traumatic situations or reminders (Lanius et al. 2010; Wolf et al. 2012). Further neuroimaging studies are needed to gain more insight into the neurobiological mechanisms possibly underlying this complex phenomenon. In particular, it remains an interesting topic for future studies to investigate the impact of dissociation on other memory processes apart from working memory (e.g., episodic memory formation and retrieval) in BPD.

Dorsal anterior cingulate connectivity

During emotional distraction, BPD patients further showed a stronger coupling of the dACC seed with a cluster in the right dmPFC (medial frontal gyrus).

This finding may be related to increased attention to negative interpersonal pictures (Burgess et al., 2007; Koechlin & Hyafil, 2007; Ramnani & Owen, 2004; Reynold et al., 2006;). In addition, BPD patients demonstrated stronger positive dACC connectivity with insula, posterior cingulate, precuneus, and superior temporal gyrus: brain areas involved in salience detection and attention (Bigler et al., 2007; Radua et al., 2010). Connectivity of the dACC with superior temporal gyrus was increased in BPD patients, but decreased (in terms of negative connectivity) in healthy controls during emotional distraction. The superior temporal gyrus is assumed to play an important role in social cognition processes such as the perception of facial stimuli (Bigler et al., 2007; Radua et al., 2010), among other functions.

Group differences in dACC connectivity were not only observed for presentation of negative distractors but also for neutral distractors: BPD patients showed stronger positive dACC connectivity with left posterior cingulate and precuneus during both EWMT conditions, while healthy controls showed negative connectivity between these regions. The posterior cingulate has been implicated in various functions including attention regulation, working memory, episodic memory, and monitoring of arousal states although its precise role remains unknown (Greicius et al. 2003; Leech & Sharp, 2013; Menon and Uddin 2010; Raichle et al. 2001). In particular, activity in the posterior cingulate and precuneus has been associated with self-referential processing (e.g., rumination, self-reflection), being crucial nodes of the default mode network (Raichle et al. 2001; Greicius et al. 2003; Menon 2011). Previous research suggests that healthy individuals commonly show negative correlations between activity in the dACC (being part of task-positive networks) and posterior cingulate cortex (being a central

node of the default mode network, which is mainly activated during rest) (Buckner and Vincent 2007; Fox et al. 2005; Leech & Sharp 2014; Neumann et al. 2010; Sridharan et al., 2008). A flexible modulation of intrinsic connectivity within these large-scale networks is crucial to cognitive efficiency, although the nature of these interactions is not yet completely understood (Berman et al. 2011; Buckner and Vincent 2007; Leech & Sharp 2014; Liddle et al. 2011; van Wingen et al., 2013). Previous studies in BPD provided evidence for imbalanced inter-network connectivity during resting state (Doll et al. 2013; Krause-Utz et al., 2014c; Wolf et al. 2011) and pain processing (Kluetsch et al., 2012).

Interpersonal disturbances, including difficulties developing trust in others, hypersensitivity to social rejection, feelings of being socially excluded in apparently neutral situations, and a tendency to interpret normative neutral stimuli as threatening are important core features of BPD (Donegan et al. 2003; Frick et al., 2012; Koenigsberg et al. 2009a; Krause-Utz et al., 2014a; Lis and Bohus, 2013; Mier et al., 2013; Roepke et al., 2013).
Stronger emotional involvement in the processing of social stimuli may hinder social-cognitive processes (e.g., empathy, facial emotion recognition) in BPD (Domsalla et al., 2014; Mier et al., 2013; Ruocco et al., 2010). In the context of previous research, present findings suggest enhanced attention to both neutral and negative social information, which may involve enhanced self-referential processing (e.g., retrieval of negative memories) in BPD.

To our knowledge, this is the first study investigating amygdala and dACC connectivity during performance of the EWM paradigm in unmedicated BPD patients with a history of interpersonal trauma compared to healthy controls. Some limitations need to be addressed. First, we did not manipulate the cognitive load of our working memory task using sets of 3x3 items, which represents a moderate task difficulty. The strength of the coupling between amygdala and dorsal prefrontal regions may dependent on the cognitive load of the task (Iordan et al., 2013). Moreover, the social dimension of distractors (using neutral interpersonal scenes instead of neutral objects) may influence amygdala connectivity (Britton et al., 2006). Second, we used PPI to investigate our hypothesis-driven research questions. By restricting our analysis to a-priori defined seeds, our results are inherently limited to the connections of these seed with 'coupled' areas. Data driven methods such as ICA have the potential to analyze fMRI data in a more exploratory and comprehensive way. Moreover, as stated above, PPI doesn't allow causal conclusions about the direction of interactions. As PPI analyses tend to lack power for event-related designs (see O'Reilly et al., 2012), to balance the risk of Type I and Type II errors (Lieberman & Cunningham, 2009) an initial clustering threshold of $p<0.001$, uncorrected on the voxel-wise level (for clusters exceeding a size of $k>10$ and a $Z>3.5$) was used in the analysis.

We believe that these findings are worthwhile to report and discuss, as they are related to brain regions, which has been previously identified as being highly relevant to BPD psychopathology. Nevertheless, studies including larger samples with more statistical power, applying stricter clustering threshold are needed to replicate these findings. All patients reported a history of complex and severe interpersonal trauma and some patients met diagnosis for PTSD, which is highly prevalent in BPD (Bremner 2006). Therefore, our findings may also be related to trauma (Dannlowski et al. 2012; Elton et al. 2014; Herringa et al. 2013; Teicher & Samson 2013; van der Werff et al. 2013a, 2013b) or to PTSD (Bluhm et al. 2009; Brown et al. 2014; Daniels et al. 2011; Gilboa et al. 2004; Jin et al. 2013; Lanius et al. 2010b; Nooner et al. 2013; Rabinak et al. 2011; Sripada et al. 2012; Stevens et al. 2013).

All in all, our findings suggest a disrupted information exchange between the amygdala (a brain region critically involved in emotion processing) and brain regions involved in working memory during emotional distraction. Stronger amygdala and dACC connectivity with brain regions involved in salience detection, social cognition, and autobiographical memory retrieval in BPD may underlie difficulties shifting attention away from task-irrelevant, but possibly self-relevant social information and increased self-referential processes in these patients.

Conflict of Interest:

None of the authors declares biomedical financial interests or potential conflicts of interest. Investigator A. Krause-Utz was funded by a Ph.D. doctoral stipend of the SFB636 by the German Research Foundation. Investigator B. M. Elzinga was funded by a VIDI grant by the Netherlands Organization for Scientific Research (grant number 016·085·353).

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Supplemental Material

Table S5.1.
Results of the main effects and interaction effect of the 2x2 Full Factorial Model for task-related bilateral amygdala connectivity

F Contrast	Brain region of coactivation: Label (Brodman area)	Lobe	K	Peak voxel coordinates (X, Y, Z)	F value	Z value	p value
Main effect Valence	Lingual Gyrus			-9, -81, -3	36.29	5.35	
	Fusiform Gyrus (BA19)	Occipital Lobe	398	24, -66, -12	19.58	4.02	p<0.001
	Lingual Gyrus (BA18)	Temporal Lobe		-24, -78, -9	17.56	3.81	
	Parahippocampal Gyrus (BA19)	Limbic Lobe		-24, -48, -9	29.21	4.86	
	Parahippocampal Gyrus (BA36) /	Limbic Lobe	177	-27, -36, -18	19.44	4.01	p<0.001
	Fusiform Gyrus	Anterior Lobe		-36, -51, -24	15.21	3.55	
	Inferior Frontal Gyrus (BA47)	Frontal Lobe	39	-30, 30, -18	23.43	4.38	p<0.001
	Fusiform Gyrus (BA20)	Temporal Lobe	36	33, -39, -21	23.13	4.36	p<0.001
	Posterior Cingulate (BA29)	Limbic Lobe	17	9, -48, 18	22.25	4.28	p<0.001
	Middle Temporal Gyrus (BA21)	Temporal Lobe	16	51, -12, -18	19.21	3.99	p<0.001
	Posterior Cingulate (BA23)	Limbic Lobe	29	3, -36, 27	18.06	3.87	p<0.001
	Caudate	Sub-lobar	11	9, 3, 18	18.02	3.86	p<0.001
	Hippocampus	Limbic Lobe	20	-18, -6, -21	16.42	3.69	p<0.001
	Superior Frontal Gyrus (BA9)*	Frontal Lobe*	11*	-21, 43, 45*	12.88*	3.26*	p<0.01*
Main effect Group	Lingual Gyrus	Occipital Lobe	10	3, -84, -15	12.83	3.25	p<0.001
Interaction effect	No significant clusters at p<0.001 (k≥10, Z<3.1)						

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions (using anatomical masks based on the Automatic Anatomical Labeling software as provided in SPM8).

Table S5.2.
Results of T contrasts for neutral > negative distractors and negative > neutral distractors within the 2x2 Full Factorial Model of task-related amygdala connectivity

T Contrast	Brain region of coactivation: Label (Brodman area)	Lobe	K	Peak voxel coordinates (X, Y, Z)	T value	Z value	p value
Neutral distractors > negative distractors (whole group)	Lingual Gyrus Fusiform Gyrus (BA19) Lingual Gyrus (BA18)	Occipital Lobe Temporal Lobe	550	-9, -81, -3 24, -66, -12 -24, -78, -9	6.02 4.43 4.19	5.48 4.18 3.98	p<0.001
	Parahippocampal Gyrus (BA19) Parahippocampal Gyrus (BA36)/ Fusiform Gyrus	Limbic Lobe Limbic Lobe	227	-24, -48, -9 -27, -36, -18	5.40 4.41	4.99 4.17	p<0.001
	Inferior Frontal Gyrus (BA47)	Frontal Lobe	55	-30, 30, -18	4.84	4.53	p<0.001
	Fusiform Gyrus (BA20)	Temporal Lobe	54	33, -39, -21	4.81	4.51	p<0.001
	Posterior Cingulate (BA29)	Limbic Lobe	21	9, -48, 18	4.72	4.43	p<0.001
	Precuneus / Cingulate Gyrus	Limbic Lobe	16	9, -48, 42	4.22	4.01	p<0.001
	Middle Temporal Gyrus (BA21)	Temporal Lobe	30	51, -12, -18	4.38	4.15	p<0.001
	Cingulate Gyrus	Limbic Lobe	12	18, -54, 27	4.36	4.13	p<0.001
	Hippocampus	Limbic Lobe	59	-18, -6, -21 -24, -12, -18	4.05 4.04	3.86 3.85	p<0.001
	Superior Temporal Gyrus (BA38)	Temporal Lobe	59	-39, 3, -21	3.64	3.50	p<0.001
	Thalamus	Sub-lobar	24	-6, -30, 3	3.28	3.18	p<0.001
	Caudate	Sub-lobar	15	9, 3, 18	4.24	4.03	p<0.001
	Posterior Cingulate (BA23)	Limbic Lobe	38	3, -36, 27	4.25	4.03	p<0.001
	Cingulate Gyrus	Limbic Lobe	23	12, -30, 39	3.57	3.44	p<0.001
	Superior Frontal Gyrus (BA9)*	Frontal Lobe*	15*	-21, 42, 45*	3.37*	3.25*	p<0.01*
Negative > neutral (whole group)	No significant clusters at p<0.001 (k≥10, Z>3.1)						

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions.

Table S5.3.
Results of the between-group differences for bilateral amygdala connectivity during emotional distraction in Borderline Personality Disorder (BPD) patients and healthy controls (HC)

T Contrast	**Brain region of coactivation: Label (Brodman area)**	**Lobe**	**K**	**Peak voxel coordinates (X, Y, Z)**	**T-value**	**Z-value**	**p value**
BPD>HC	Parahippocampal Gyrus (BA34)	Limbic Lobe	20	15, -9, -21	4.02	3.67	p<0.001
	Parahippocampal Gyrus/ Hippocampus	Limbic Lobe	19	-21, -9, -18	3.94	3.61	p<0.001
	Medial Frontal Gyrus (BA10)*	Frontal Lobe*	23*	18, 48, 3*	4.50*	4.04*	p<0.01*
HC>BPD	No significant clusters at p<0.001 (k>10, Z>3.1)						

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions.

Table S5.4.
Results of the main effects and interaction effects of the 2x2 Full Factorial Model for task-related bilateral dorsal anterior cingulate seed connectivity

Contrast	Brain region of coactivation: Label (Brodman area)	Lobe	K	Peak voxel coordinates (X, Y, Z)	F-value	Z-value	P-value
Main effect Valence	Lingual Gyrus (BA19) Fusiform Gyrus Lingual Gyrus	Occipital Lobe	653	-9, -81, -6 33, -39, -18 24, -69, -9	31.66 26.27 24.45	5.04 4.63 4.47	p<0.001
	Parahippocampal Gyrus (BA19) Fusiform Gyrus	Limbic Lobe Temporal Lobe	151	-24, -48, -9 -27, -39, -18	27.00 19.95	4.68 4.06	p<0.001
	Cingulate Gyrus	Limbic Lobe	11	9, 9, 36	19.10	3.97	p<0.001
	Middle Temporal Gyrus (BA39)	Temporal Lobe	22	-45, -78, 18	17.49	3.81	p<0.001
	Superior Temporal Gyrus (BA22)	Temporal Lobe	20	60, -54, 9	16.76	3.73	p<0.001
	Cingulate Gyrus (BA31) Cingulate Gyrus (BA31)	Limbic Lobe	20	9, -30, 39 9, -39, 42	15.68 15.64	3.60 3.60	p<0.001
Main Effect Group	Precuneus (BA31) Posterior Cingulate (BA31)	Parietal Lobe Limbic Lobe	37	-18, -45, 33 -3, -45, 33	22.95 14.62	4.34 3.48	p<0.001
	Anterior Cingulate (BA32)	Limbic Lobe	21	14, 48, 0	19.87	4.05	p<0.001
	Inferior Occipital Gyrus (BA18)	Occipital Lobe	10	36, -87, -15	14.58	3.47	p<0.001
Interaction effect	Middle/Superior Temporal Gyrus	Temporal Lobe	12	51, -48, -15	17.38	3.79	p<0.001

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions (using anatomical masks based on the Automatic Anatomical Labeling software as provided in SPM8).

Table S5.5.
Results of T contrasts for neutral > negative distractors and negative > neutral distractors within the 2x2 Full Factorial Model of task-related bilateral dorsal anterior cingulate cortex connectivity

T Contrast	Brain region of coactivation: Label (Brodman area)	Lobe	K	Peak voxel coordinates (X, Y, Z)	T value	Z value	p value
Neutral distractors > negative distractors (in the whole group)	Lingual Gyrus (BA19) Fusiform Gyrus Lingual Gyrus	Occipital Lobe	855	-9, -81, -6 33, -39, -18 24, -69, -9	5.63 5.13 4.94	5.17 4.77 4.62	p<0.001
	Parahippocampal Gyrus Fusiform Gyrus	Limbic Lobe Temporal Lobe	198	-24, -48, -9 -27, -39, -18	5.20 4.47	4.82 4.22	p<0.001
	Cingulate Gyrus	Limbic Lobe	15	9, 9, 36	4.37	4.14	p<0.001
	Cingulate Gyrus	Limbic Lobe	11	18, -54, 27	4.19	3.98	p<0.001
	Middle Temporal Gyrus	Temporal Lobe	37	-45, -78, 18	4.18	3.97	p<0.001
	Superior Temporal Gyrus	Temporal Lobe	30	60, -54, 9	4.09	3.90	p<0.001
	Cingulate Gyrus Cingulate Gyrus	Limbic Lobe	39	9, -30, 39 9, -39, 42	3.96 3.96	3.78 3.78	p<0.001
	Posterior Cingulate	Limbic Lobe	13	12, -48, 15	3.88	3.71	p<0.001
Negative > neutral (whole group)	No significant clusters at p<0.001 (k≥10, Z>3.1)						

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions (using anatomical masks based on the Automatic Anatomical Labeling software as provided in SPM8).

Table S5.6.
Results of the between-group differences for bilateral dorsal anterior cingulate connectivity during emotional distraction in Borderline Personality Disorder (BPD) patients and healthy controls (HC)

T Contrast	Brain region of coactivation: Label (Brodman area)	Lobe	K	Peak voxel coordinates (X, Y, Z)	T-value	Z-value	P-value
BPD>HC	Medial Frontal Gyrus (BA10)	Frontal Lobe	23	18, 48, 3	5.89	5.00	p<0.001
	Inferior Parietal Lobule	Parietal Lobe	20	-42, -39, 27	4.30	3.89	p<0.001
	Precentral Gyrus Insula	Frontal Lobe Sub-lobar	12	-48, -12, 48 -42, 9, -6	4.15 3.68	3.78 3.40	p<0.001
	Posterior Cingulate (BA23)	Limbic Lobe	10	-3, -33, 21	3.69	3.42	p<0.001
	Medial Frontal Gyrus (BA6)	Frontal Lobe	11	18, -3, 54	4.13	3.77	p<0.001
	Inferior Occipital Gyrus (BA18) Middle Occipital Gyrus (BA19)	Occipital Lobe	14	-36, -90, -15 -42, -84, -15 -48, -84, -3	4.02 3.88 3.63	3.67 3.57 3.36	p<0.001
	Paracentral Lobule (BA5) Cingulate Gyrus (BA31)	Frontal Lobe Limbic Lobe	12	-12, -36, 54 -15, -30, 48	4.01 3.70	3.67 3.42	p<0.001
	Superior Temporal Gyrus (BA22)	Temporal Lobe	14	-54, 0, -6	3.78	3.48	p<0.001
	Precentral Gyrus (BA6)	Frontal Lobe	11	-60, -3, 12	3.69	3.41	p<0.001
HC>BPD	No significant clusters at p<0.01, k>10, Z>3.1						

Note: k=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. (*)=Clusters determined by Small volume corrections (SVC). Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented. SVC were applied for dorsolateral as well as dorsomedial prefrontal regions (using anatomical masks based on the Automatic Anatomical Labeling software as provided in SPM8).

Table S5.7.
Regression analysis: Reaction times as predictor of positive amygdala connectivity during presentation of negative distractors

Group	Brain region of coactivation	Lobe	K	Peak voxel coordinates (X, Y, Z)	T value	Z value	p value	R	R^2
BPD	Superior Temporal Gyrus (BA38)	Temporal Lobe	15	-36, 18, -30 -42, 12, -24	4.45 4.36	3.67 3.61	<0.001	.706	.498
	Middle Frontal Gyrus (BA46)	Frontal Lobe	18	51, 27, 21	4.40	3.63	<0.001	.701	.491
	Medial Frontal Gyrus (BA10)	Frontal Lobe	15	9, 60, 0	4.14	3.48	<0.001	.679	.461
	Parahippocampal Gyrus / Hippocampus	Limbic Lobe	9	24, -3, 24	4.36	3.61	<0.001	.698	.487
HC	No significant clusters at p<0.001 (k>10, Z>3.1)								

Note: BPD= group of Borderline Personality disorder patients; HC= healthy control group, K=Cluster size. Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented.

Table S5.8.
Regression Analysis: Self-reported increase of dissociation (DSS4 score) as predictor of positive amygdala connectivity

Brain region of coactivation	Lobe	K	Peak voxel coordinates (X, Y, Z)	T Value	Z Value	p value	R	R^2
Precentral Gyrus (BA4)	Frontal Lobe	49	-18, -30, 75	5.44	4.21	<0.001	.773	.597
Anterior Cingulate (BA32)	Limbic Lobe	13	9, 39, 27	4.64	3.78	<0.001	.720	.518
Thalamus	Sub-Lobar	15	9, -21, 18	4.21	3.52	<0.001	.686	.470
Insula (BA13)	Sub-lobar	15	-39, 0, 0	4.01	3.40	<0.001	.668	.446

Note: DSS-4: Dissociation Stress Scale 4; K=Cluster size, Clusters were determined using a significant threshold of $p<0.001$ uncorrected at a voxel-wise whole-brain level. Clusters exceeding a Z-value of >3.1 and a cluster size of k≥10 contiguous voxels are presented.

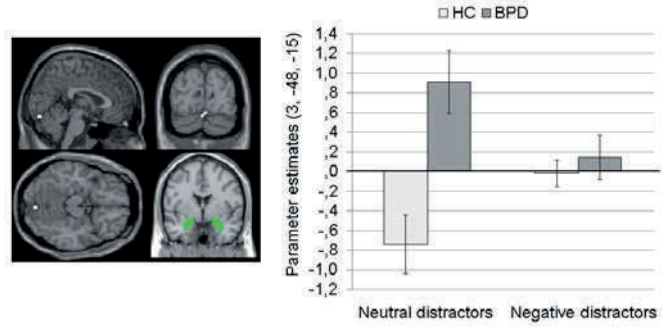

Figure S5.1. Results for the main effect of group on amygdala connectivity (means ± SEM of parameter estimates for connectivity of the amygdala seed (depicted in green) with right lingual gyrus (MNI: 3, -84, -15).

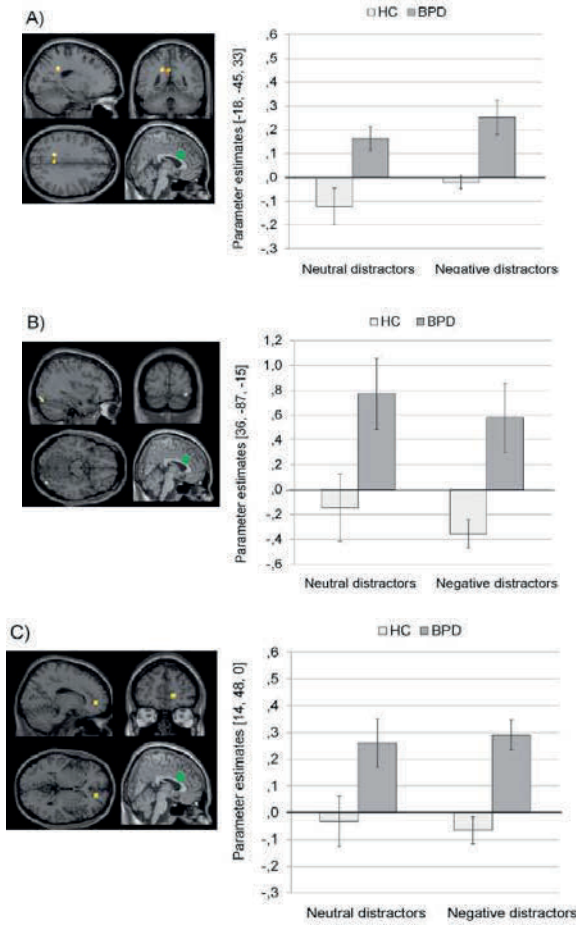

Figure S5.2. Results for the main effect of group on dACC connectivity of the 2x2 Full Factorial Model (means ± SEM of parameter estimates for connectivity of the dACC seed (depicted in green) in patients with BPD and HC). A) shows connectivity with left precuneus (MNI: -18, -45, 33). Figure B) shows connectivity with right inferior occipital gyrus (MNI: 36, -87, -15). Figure C) shows connectivity with right ACC (14, 48, 0).

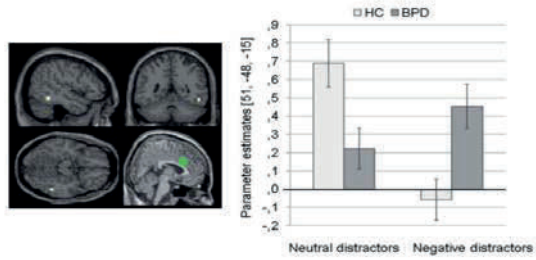

Figure S5.3. Results for the interaction effect on dACC connectivity (means ± SEM of parameter estimates for connectivity of the bilateral dACC) seed (depicted in green) with right superior temporal gyrus (MNI: 51, -48, -15) in patients with Borderline Personality Disorder (BPD) and healthy controls (HC)).

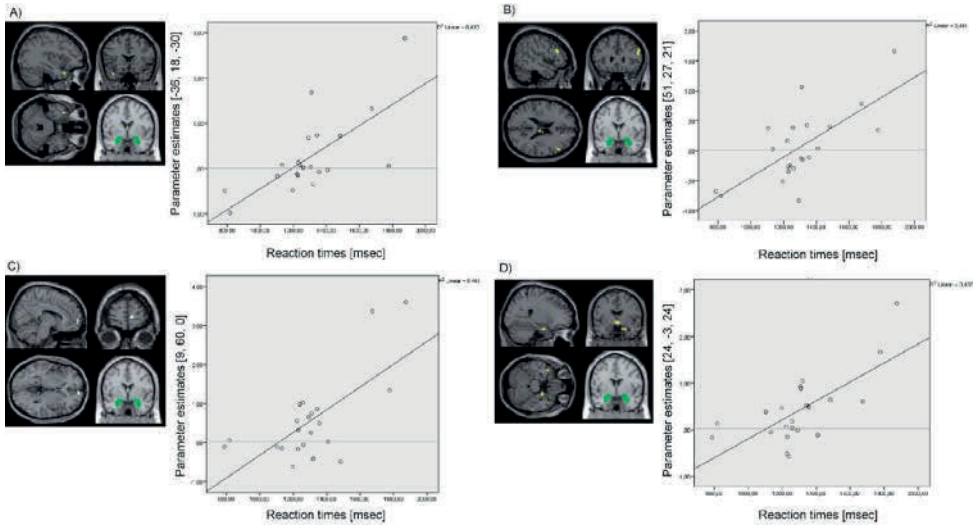

Figure S5.4. Results of the whole brain regression analysis with reaction times as regressor of interest for connectivity of the bilateral amygdala seed: This figure shows results of the whole brain regression analysis with reaction times as regressor of interest for connectivity of the bilateral amygdala seed (depicted in green) during presentation of negative distractors in the group of Borderline Personality Disorder (BPD) patients. Figure A) shows regression for amygdala connectivity with left superior temporal gyrus (MNI: -36, 18, -30). Figure B) shows regression for amygdala connectivity with right middle frontal gyrus (MNI: 51, 27, 21). Figure C) shows regression for amygdala connectivity with right medial frontal gyrus (MNI: 9, 60, 0). Figure D) shows regression for amygdala connectivity with right parahippocampal gyrus / hippocampus (MNI: 24, -3, 24).

CHAPTER 6

Dissociation in Borderline Personality Disorder: Disturbed cognitive and emotional inhibition and its neural correlates

Dorina Winter, Annegret Krause-Utz, Stefanie Lis, Chui-De Chiu, Ruth Lanius, Friederike Schriner, Martin Bohus, Christian Schmahl (2015). Dissociation in borderline personality disorder: Disturbed cognitive and emotional inhibition and its neural correlates. *Psychiatry Research: Neuroimaging*, 233(3), 339-351. doi:10.1016/j.pscychresns.2015.05.018.

Abstract

Background: Evidence is heterogeneous regarding whether patients with Borderline Personality Disorder (BPD) display disturbed emotional inhibition in the Emotional Stroop Task. Previous findings suggest that state dissociation may influence cognitive inhibition of task-irrelevant material, particularly with negative content. **Methods:** Our aim was to examine performance in an Emotional Stroop Task including negative, neutral, and positive words in BPD patients and healthy controls during functional magnetic resonance imaging. In advance, half of the BPD patients underwent a dissociation induction using script-driven imagery. **Results:** BPD patients without dissociation induction showed behavioral performance comparable to that of healthy controls but displayed stronger neural responses, especially to positive stimuli, in the superior temporal gyrus, dorsomedial prefrontal cortex, and anterior cingulate cortex. BPD patients with dissociation induction showed overall slower and less accurate responses as well as increased reaction times for negative versus neutral words compared with BPD patients without dissociation induction. Moreover, they showed comparatively decreased neuronal activity in the fusiform gyrus and parietal cortices independent of valence, but elevated activity in the left inferior frontal gyrus in response to negative versus neutral words. **Conclusion:** In conclusion, experimentally induced dissociation in BPD was associated with inefficient cognitive inhibition, particularly of negative stimuli, in the Emotional Stroop Task.

Keywords: Emotion, Memory, Emotional Stroop, Executive functioning, Cognitive functioning, State dissociation, Script-driven imagery

6. 1. Introduction

Emotion dysregulation is considered to be a core feature of Borderline Personality Disorder (BPD) (Koenigsberg et al., 2002; Zittel Conklin et al., 2006; Glenn and Klonsky, 2009). BPD patients have been found to show intensive and prolonged reactions to aversive stimuli (Herpertz et al., 1997; Wagner and Linehan, 1999; Stiglmayr et al., 2005). Hence, emotional information may capture more attention in BPD patients than in healthy controls, even when this emotional information is irrelevant to the target task (for a review, see Winter et al., 2014). The paradigm most often employed to study this hypothesis of impaired *emotional inhibition* is the Emotional Stroop Task (EST; Mathews and MacLeod, 1985). In the EST, participants are required to name the color of emotional or neutral words. The longer a participant takes to name the color of a word, the more the stimulus' content is thought to capture the participant's attention. Results however are heterogeneous: some studies show that BPD patients have longer reaction times compared to healthy individuals when naming emotional vs. neutral stimuli, especially for negative words (Arntz et al., 2000; Sieswerda et al., 2007; Wingenfeld et al., 2009a), but also for positive words (Sieswerda et al., 2007). In juxtaposition, other studies have not found significant differences between BPD patients and healthy controls for this paradigm (Sprock et al., 2000; Domes et al., 2006; Minzenberg et al., 2008; Wingenfeld et al., 2009b). In addition, inconsistent findings were reported when using functional magnetic resonance imaging (fMRI) to study emotional inhibition. Stronger interference of word content during color naming in the EST is usually associated with increased activity in the anterior cingulate cortex (ACC) and frontal areas including the inferior frontal gyrus (IFG) - areas (among others) active in tasks requiring to divert attention - as well as in areas involved in semantic processing such as the lateral inferior parietal cortex and the superior temporal gyrus (Whalen et al., 1998; Britton et al., 2009; Hart et al., 2010; Mincic, 2010; Ovaysikia et al., 2011). In BPD, one study found that patients lacked differential activation in relevant brain regions including the ACC and prefrontal cortex in response to negative compared to neutral stimuli, suggesting a smaller difference between emotional and neutral stimuli in the EST (Wingenfeld et al., 2009b). Using a modified EST, another study found decreased medial orbitofrontal and subgenual ACC activation as well as increased activity in the insula, dorsal ACC, and lateral orbitofrontal areas in BPD patients in comparison with healthy controls, pointing to increased recruitment of areas associated with diverting attention (Silbersweig et al., 2007). The factors that underlie these inconsistent reports have yet to be established. Some authors suggest that methodological limitations and modifications the original EST study design may explain these inconsistencies (Domes et al., 2006; Minzenberg et al., 2008; Wingenfeld et al., 2009a).

Personal stimulus relevance, anxiety, childhood trauma, Axis I comorbidity and overall prolonged reactions times in BPD may have masked a possible effect of emotional words (Domes et al., 2006; Sieswerda et al., 2007; Wingenfeld et al., 2009a).

So far, no studies have tested whether the current presence of dissociation, hereafter referred to as "state dissociation", may contribute to inconsistencies in EST performance. Dissociation is defined as a "disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behavior" (APA, 2013; p. 291). State dissociation is transiently experienced by two thirds of all BPD patients and has manifold manifestations, including derealization, depersonalization, and amnesia (Zanarini et al., 2000; Zanarini et al., 2008; Korzekwa et al., 2009). Two streams of research suggest that dissociation may influence BPD patients' EST performance. One suggests that inefficient inhibition of task-irrelevant information regardless of valence (further referred to as *cognitive inhibition*) may be a characteristic of BPD patients who exhibit high levels of state dissociation. Only one study to date has investigated the association of this cognitive function and dissociation in BPD, though it observed dissociation solely as a trait but not as a state (Haaland and Landro, 2009). This study found that BPD patients with high levels of trait dissociation performed worse than healthy controls in all tested domains, including executive functioning and, more specifically, performance on a non-emotional Stroop task. This suggests also impairments in cognitive inhibition in BPD patients with high levels of trait dissociation. In this regard, it is interesting to note that BPD patients had overall longer reaction times than healthy controls in most studies using the EST even in response to non-emotional words (Arntz et al., 2000, Domes et al., 2006, but not Wingenfeld et al., 2009b). No study so far has investigated whether this result is associated with high state dissociation in BPD. The second stream of research suggests that dissociation can have an impact on the processing of affect-laden materials. BPD patients with high levels of state dissociation lacked differential reactions to an conditioned stimulus paired with an aversive event (CS+) compared to a neutral stimulus (CS-) in an aversive conditioning paradigm (Ebner-Priemer et al., 2009). Also, state dissociation in BPD was associated with decreased startle responses but increased skin conductance in response to aversive pictures (Barnow et al., 2012). An fMRI study found that state dissociation correlated negatively with activity in the amygdala, hippocampus, ACC and insula during distraction from negative pictures in an emotional working memory task in BPD patients (Krause-Utz et al., 2012). Thus, a valence-specific effect of negative materials on cognitive inhibition may be found in BPD patients with high state dissociation.

To our knowledge, no studies have experimentally manipulated the levels of state dissociation and its effect on task-irrelevant emotional information in BPD yet.

In sum, there is a lack of evidence regarding the association of high state dissociation and (1) inefficient cognitive inhibition over task-irrelevant information and (2) a smaller difference between the inhibition of emotional content compared with neutral content in the EST in BPD. To examine these research gaps, we used personalized script-driven imagery - which has been shown to be capable of inducing high state dissociation (Lanius et al., 2002; Ludäscher et al., 2010) - combined with the EST and related memory tasks (recall and recognition). We hypothesized that dissociation induction in BPD would be associated with (1) inefficient cognitive inhibition over task-irrelevant information as reflected in overall slower reaction times and more errors in the EST and the succeeding memory tasks, as well as altered task-related neural activity e.g. in the ACC, the inferior parietal cortex, the superior temporal gyrus, and the IFG in the EST (Whalen et al., 1998; Britton et al., 2009; Hart et al., 2010; Mincic, 2010; Ovaysikia et al., 2011), and that (2) dissociation induction in BPD would be associated with smaller difference in the inhibition of negative stimuli (compared to neutral stimuli) in the EST, i.e. a smaller difference between reaction time latencies and response accuracy for negative versus neutral words, and smaller differential neuronal task-related activity in these brain regions when comparing negative to neutral words.

6.2. Methods

6.2.1. Sample

The participants comprised 40 women with BPD and 20 healthy controls (HC) between 18 and 45 years of age. Due to movement artefacts during fMRI scanning, four subjects were excluded from the analysis. The final sample included 19 HC, 19 BPD patients who did not undergo dissociation induction (BPDn), and 18 BPD patients who underwent dissociation induction (BPDd). General exclusion criteria were serious somatic illnesses, traumatic brain injuries, current and lifetime psychotic or bipolar-I disorder, psychotropic medication (within 4 weeks prior to the study), developmental disorders, substance dependency during the last year, and substance abuse within two months prior to the study. For MRI, exclusion criteria were metal implants, pregnancy, left-handedness, and claustrophobia. BPD patients had to fulfil the DSM-IV criteria for BPD, including the criterion for stress-related dissociation. Further exclusion criteria for HC were any current or previous mental disorder. BPD patients were randomly assigned to either the BPDn or BPDd group.

Clinical diagnoses were assessed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen et al., 1997) and the BPD section of the International Personality Disorder Examination (IPDE; Loranger, 1999). Self-report measures included questionnaires on BPD symptom severity [Borderline Symptom List short version (BSL-23; Bohus et al., 2009)], childhood trauma [Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003)], trait dissociation [Dissociative Experience Scale (DES; Bernstein and Putnam, 1986)], severity of depressive mood [Beck Depression Inventory (BDI; Beck et al., 1961)], as well as trait and state anxiety [State Trait Anxiety Inventory (STAI; Spielberger et al., 1970)]. Questionnaire data were collected in a 3-day period before or after the experiment. Demographic data and clinical characteristics of the final sample are reported in Table 6.1.

Table 6.1.
Demographic and clinical variables (means ± standard deviation) in healthy controls (HC), Borderline Personality Disorder patients after dissociation induction (BPDd) and Borderline Personality Disorder patients without dissociation induction (BPDn)

	HC (*n*=19)	**BPDn (*n*=19)**	**BPDd (*n*=18)**	**Statistics**
Age – years	28.74 (8.07)	28.05 (7.82)	27.61 (5.95)	HC = BPDn = BPDd
BSL-23 - mean score	0.08 (0.02)	1.65 (0.62)	2.05 (0.80)	HC < BPDn = BPDd
DES - total score	3.20 (2.49)	28.74 (14.30)	32.96 (16.28)	HC < BPDn = BPDd
CTQ - total score	34.47 (11.67)	66.29 (18.97)	59.13 (25.64)	HC < BPDn = BPDd
BDI - total score	1.67 (2.22)	22.19 (11.24)	24.23 (11.78)	HC < BPDn = BPDd
STAI - trait	29.18 (4.83)	58.16 (9.80)	58.75 (7.20)	HC < BPDn = BPDd
- state	29.99 (5.48)	52.32 (9.84)	54.92 (9.59)	HC < BPDn = BPDd
Years of education, *n (%)*				
Less than 9 years	1 (5.3)	2 (10.5)	2 (11.1)	$\chi^2=3.053$
9 years	2 (10.5)	1 (5.3)	0 (0)	df=6
10 years	4 (21.1)	5 (26.3)	3 (16.7)	p= 0.802
13 years	12 (63.2)	11 (57.9)	13 (72.2)	
Co-morbidities, *n (%),*				
major depressive disorder		1 (5.3)	2 (11.1)	
dysthymia		1 (5.3)		
panic disorder		4 (21.1)	3 (16.7)	
social phobia		5 (26.3)	8 (44.4)	
specific phobia		2 (10.5)	3 (16.7)	
obsessive compulsive disorder		3 (15.8)		
posttraumatic stress disorder		7 (36.8)	8 (44.4)	
somatization disorder			1 (5.6)	
pain disorder			2 (11.1)	
unspecific somatoform disorder			1 (5.6)	
anorexia nervosa			2 (11.1)	
bulimia nervosa		1 (5.3)	1 (5.6)	
binge eating disorder			3 (16.7)	

BDI=Beck Depression Inventory; BSL-23=Borderline Symptom List-23; CTQ=Childhood Trauma Questionnaire; DES= Dissociative Experience Scale; STAI=State Trait Anxiety Inventory; RT= reaction time; Post-hoc *t*-test at $p<0.05$ Bonferroni-corrected.

State dissociation and tension were measured using the fMRI-suited DSS-4 (Stiglmayr et al., 2009). The five items in this measure ask for current depersonalization, derealization, analgesia, somatoform dissociation, and tension on a Likert scale ranging from 0 to 9.

Demographic data did not differ between the three groups. As expected, BPD patients had higher scores than HC for clinical variables (BSL-23, DES, CTQ, BDI, and STAI), whereas there were no significant differences in these clinical variables between the BPDn and the BPDd group. All subjects received monetary remuneration for participation in the study. The study was approved by the ethical board of Heidelberg University, Germany, and was conducted according to the declaration of Helsinki at the Central Institute of Mental Health in Mannheim. Written informed consent was obtained from the participants.

6.2.2. Dissociation induction

Dissociation was induced through script-driven imagery (Lanius et al., 2002; Ludäscher et al., 2010). Studies showed that this dissociation induction can lead to disruptions in mental processing, comparable to those reported in naturally occurring dissociation (Ludäscher et al., 2007; Ludäscher et al., 2010). With the help of a clinician (F.S. or D.W.), a 30-s script of a well-remembered recent autobiographical memory was prepared for each participant. For the HC and BPDn groups, an autobiographical memory of a non-emotional everyday episode was collected. For the BPDd group, an autobiographical memory of a non-trauma-related episode in which dissociation was experienced was collected. To examine the validity of the dissociation induction scripts, the finalized scripts were read back to the BPDd group and an increase of at least 1.5 on the DSS was set up as the criterion. A person, unknown to the participants, read the scripts aloud to record them on audio tape. An illustration of the study design can be found in Figure 6.1.

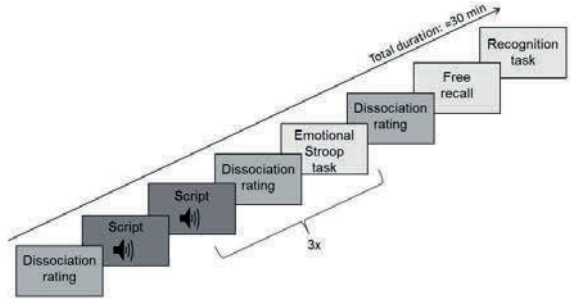

Figure 6.1. Study design–overview. The EST was presented in a block design, with 10 trials of one-word valence (negative, neutral, positive) each, and eight blocks after each script presentation. Valence order was fixed and counterbalanced to control for effects of mood carryover.

During fMRI, the script was presented via headphones, twice before the EST and two further times between the EST blocks. The rationale behind this repeated script presentation was that we aimed to maintain high levels of induced dissociation throughout the whole experiment (compensating for the fact that task performance might lead to a reduction of dissociation).
To measure the level of state dissociation, we used the DSS-4, which also includes a tension rating (0-9 Likert scale), inside the MR scanner immediately before fMRI, after each script presentation, and at the end of the EST.

6.2.3. Emotional Stroop Task

We used an adapted version of the EST (Mathews and MacLeod, 1985; Williams et al., 1996). Negative, positive and neutral words were presented in blue, red, green or yellow. Each color was assigned to a button, which participants were able to press with their right index, middle, ring, or little finger. The participants were given the task of pressing the button that corresponds to the word's printed color. Words were derived from the *Aachener Emotionale Wortliste* (Aachen's emotional word list; Böcker et al., 2014; see Supplementary Table S6.1 for information on stimulus characteristics). Twenty words were included in each category, with comparable ($p < 0.05$) word length for positive, negative, and neutral words and with comparable valence intensity for the positive and negative words. Each word was presented four times (once in each of the four colors) for 1500 ms. Blocks of 10 words of one particular valence (block design) were presented. Block order was fixed, with each valence following each other valence equally often, so that mood carryover effects were equally distributed. Inter-trial intervals between two words were jittered, ranging from 200 to 400 ms, with a mean of 300 ms. The total duration of the EST including dissociation induction was approximately 20 min, depending on the duration of the individual dissociation rating duration. Before the task began, color naming was trained in 20 trials with non-word stimuli.

Immediately after the EST and still lying inside the MR scanner, participants were asked to report all the words they remembered from the color naming task in an incidental free recall task. Subsequently, the 60 old and 60 new words comparable in word length, and valence ratings were presented randomly for a recognition task. Participants were asked to 9 report via button press if a word occurred in the color naming task or not. The software Presentation (http://nbs.neuro-bs.com/) was used for all stimulus presentations.

6.2.4. fMRI scan protocol and data analysis

MRI was conducted using a 3 Tesla Siemens TRIO-Scanner (Siemens, Erlangen). Head cushions and headphones were used to reduce head movement artefacts and scanning noise. Blood oxygen level-dependent (BOLD) signal was measured with 36 3-mm transversal slices

covering the entire brain using gradient-echo echo-planar imaging [EPI, T2-weighted contrast, field of view = 192×192 mm, voxel size 3×3×3 mm³, 64×64 voxel matrix, flip angle= 80°, spin echo time (TE) = 30 ms, inter-scan repetition time (TR) = 2000 ms]. After functional scanning, a high resolution anatomical scan as an individual template for functional data was acquired using three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE, T1-weighted contrast, voxel size 1×1×1 mm³).

6.2.4.1. Statistical analysis of behavioral data

Means of all dissociation and tension ratings after script presentation were calculated. To check if dissociation increased in BPDd, time × group interactions of DSS-4 ratings were calculated using repeated measures analyses of variance (rm-ANOVAs), including the within-subject factor "time" (pre-script presentation, mean postscript presentation) and the between-subject factor "group" (HC, BPDn, BPDd). Post-hoc Bonferroni-corrected *t*-tests were performed in case of a significant interaction effect. To assure that, at any time during the EST, dissociation induction was sufficient, we ran the manipulation check analysis again using all DSS-4 ratings separately in the factor "time" (pre-script measurement and each of the four post-script measurements). Reaction times (RTs) in the EST and the recognition task were examined for outliers ± 2 SD, which were replaced by the mean of the group. To test for group differences and valence × group interactions in RTs and accuracy measures, rm-ANOVAs including the within-subject factor "valence" (negative, neutral, positive) and the between-subject factor "group" (HC, BPDn, BPDd) were conducted. In case of significant effects, post-hoc Bonferroni-corrected *t*-tests were applied to follow up subgroup differences between HC vs. BPDn and BPDn vs. BPDd and to follow up the interaction of valence and group regarding valence differences (negative-neutral, positive-neutral) in each group. All behavioral analyses were performed with IBM SPSS Statistics 20 (IBM, USA) with a statistical significance level of $p < 0.05$, with Greenhouse-Geisser correction when necessary.

6.2.4.2. Statistical analysis of fMRI data.

The first four volumes were discarded to minimize T1 effects. FMRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). EPI time series were preprocessed according to common practice: slice time correction, spatial realignment to the mean image to correct for head motion; coregistration onto participants' segmentated high resolution T1 scan, normalization to the standard brain of the Montreal Neurological Institute (MNI) space; and smoothing with a Gaussian kernel with a full-width at half-maximum of 6 mm. First level analyses were modeled using separate regressors for scripts, ratings, finger responses and the six motion parameters, as well as negative, neutral and positive word blocks (10 words trials per block),

correcting for global signal intensity variation and low-frequency fluctuations with a high-pass filter of 620-s cutoff. For group (second) level analyses, a full factorial model with the factors "group" (HC, BPDn, BPDd) and "valence" (negative, neutral, positive) was calculated. In this model, group differences in the neural activity while performing the EST across all valence conditions (i.e., including the regressors modelling negative, neutral and positive word blocks) were examined: Differences in neural activity between HC vs. BPDn and BPDn vs. BPDd, which were the group comparisons of interest, were analyzed via *t*-tests. In addition, differences in valence processing in each group were calculated by *t*-tests per group within the full factorial model. Also, interactions of group and valence were calculated by planned *t*-test according to the mentioned hypotheses. Whole brain second level analyses were performed with a threshold of $p < 0.001$, $k > 10$ voxel, uncorrected for multiple comparisons at the voxel level following Lieberman and Cunningham (2009) to balance Type I and Type II errors. For the central results, post-hoc correlational analyses were performed by extracting beta values from the respective peak voxel in the respective first level contrasts and correlating them with the corresponding behavioral data in SPSS.

6.2.4.3. Post-hoc analysis controlling for early childhood traumatization, depressive mood, anxiety, and tension.

Several variables have been previously described to influence EST performance (Williams et al., 1996) and thus have been considered in studies on the EST and emotional inhibition in BPD: traumatic experiences (Sieswerda et al., 2007; Wingenfeld et al., 2009a), depression (Gotlib & McCann, 1984; Gotlib & Cane, 1987), anxiety (Domes et al., 2006; Sieswerda et al., 2007) and the current state (Dorahy et al., 2005, 2006) have been associated with slower RTs to negative stimuli. Thus, post-hoc data analyses were run in order to control for the influence of clinical variables (early childhood traumatization, depressive mood, anxiety, and tension to model current emotional state) on main findings in BPD patients. To include tension as a covariate, it was necessary to correct tension ratings for dissociation ratings using partial correlations, as tension and dissociation ratings were highly correlated in the current study, indicating a high level of multicollinearity between these self-report measures (mean correlation $r = 0.727$, $p < 0.001$, when averaged across all measurements after script presentation), which is in line with previous findings and conceptualizations (Stiglmayr et al., 2008; APA, 2013). Behavioral analysis for the EST and the subsequent memory tasks, as well as fMRI data analyses of BPDn vs. BPDd, were repeated with the following covariates: CTQ, BDI, trait STAI, state STAI, and tension ratings (DSS-4 item). More details of these analyses can be found in the Supplementary material.

6.3. Results

6.3.1. Manipulation check: dissociation induction

Means, SDs and statistical analyses of dissociation and tension ratings (DSS-4scores) are summarized in Table 6.2a. There was a time × group interaction, namely that in BPDd, dissociation and tension ratings increased after dissociation induction, but no significant change in dissociation and tension ratings was observed for HC and BPDn. The interaction remained significant when considering each time point of dissociation ratings separately in the factor "time" (F4.2,112.8 = 19.40, $p < 0.001$, $\eta^2 = 0.42$; data not presented in Table 6.2a). All dissociation ratings after script presentation were higher than those before script presentation in BPDd ($p < 0.001$) and there were no such significant differences in BPDn and HC. This suggests successful experimental induction of dissociation in BPDd.

Table 6.2a.
Behavioral data of the measures of dissociation induction, the Emotional Stroop Task and related memory tasks in healthy control participants (HC), patients with Borderline Personality Disorder without dissociation induction (BPDn) or with dissociation induction (BPDd) [Means ± SD]

	HC (*n*=19)	**BPDn (*n*=19)**	**BPDd (*n*=18)**	**Main effect Group**	**Main effect Time**	**Interaction group x time**
DSS-4 dissociation						
before scripts	0.22 (4.78)	1.51 (1.68)	2.08 (1.77)	$F_{2,53}$=33.26, p<0.001, η^2=0.56	$F_{1,53}$=63.19, p<0.001, η^2=0.54	$F_{2,53}$=44.41, p<0.001, η^2=0.63
after scripts	0.20 (.41)	2.06 (2.10)	5.75 (1.81)			
Tension Ratings						
before scripts	1.47 (1.78)	3.32 (2.41)	3.83 (2.31)	$F_{2,53}$=17.72, p<0.001, η^2=0.40	$F_{1,53}$=15.54, p<0.001, η^2=0.23	$F_{2,53}$=18.11, p<0.001, η^2=0.41
after scripts	1.20 (1.85)	3.53 (2.47)	6.57 (1.91)			
Emotional Stroop Task				**Main effect Group**	**Main effect Valence**	**Interaction group x valence**
Reaction times (ms)						
negative words	684.69 (85.45)	679.36 (112.77)	836.51 (170.94)	$F_{2,53}$=6.92, p=0.002, η^2=0.20	$F_{1.7,91.1}$=13.44, p<0.001, η^2=0.20	$F_{3.4,91.1}$=5.91, p=0.001, η^2=0.18
neutral words	680.69 (91.52)	667.44 (99.91)	781.28 (158.58)			
positive words	676.59 (88.92)	673.73 (108.43)	797.41 (153.19)			
accuracy (%)						
negative words	98.88 (1.38)	98.49 (1.59)	95.69 (4.18)	$F_{2,53}$=9.06, p<0.001, η^2=0.24	$F_{1.7,89.5}$=0.47, p=0.597, η^2=0.01	$F_{3.4,89.5}$=0.98, p=0.412, η^2=0.04
neutral words	97.96 (1.51)	98.36 (1.87)	95. 97 (3.70)			
positive words	98.68 (1.21)	98.29 (1.33)	95.28 (4.63)			
Free recall (%)						
negative words	16.32 (8.31)	17.89 (10.04)	12.78 (7.90)	$F_{2,53}$=3.07, p=0.055, η^2=0.10	$F_{2,106}$=38.72, p<0.001, η^2=0.42	$F_{4,106}$=0.27, p=0.899, η^2=0.01
neutral words	5.26 (5.89)	6.58 (7.27)	2.50 (3.93)			
positive words	7.89 (6.52)	11.58 (10.94)	6.94 (7.10)			
Recognition task						
Reaction times (ms)						
negative words	868.37 (101.32)	854.25 (104.90)	954.08 (127.19)	$F_{2,53}$=4.14, p=0.021, η^2=0.14	$F_{2,106}$=5.52, p=0.005, η^2=0.10	$F_{4,106}$=0.66, p=0.620, η^2=0.02
neutral words	837.07 (102.10)	832.19 (138.51)	927.46 (129.69)			
positive words	844.19 (126.92)	861.38 (114.76)	947.14 (117.53)			
accuracy (%)						
negative words	71.32 (10.32)	75.26 (12.27)	66.94 (11.55)	$F_{2,53}$=2.29, p=0.112, η^2=0.08	$F_{2,106}$=7.16, p=0.001, η^2=0.12	$F_{4,106}$=1.31, p=0.271, η^2=0.05
neutral words	67.37 (10.94)	67.50 (44.43)	63.47 (11.79)			
positive words	67.63 (10.78)	74.87 (11.92)	66.94 (10.56)			

Note: significance level p<0.05, reaction times refer to correct responses; %=correct responses, DSS-4=Dissociation Tension Scale Short Version, ms=milliseconds, SD=standard deviation

6.3.2. Emotional Stroop Task

Descriptive statistics and interference statistics (*F*-, *t*-, *p*-values) for behavioral performance (accuracy, RTs) are summarized in Table 6.2a and Table 6.2b. Comparisons between negative-positive words are reported additionally in the Supplementary Table S6.2.

Table 6.2b.
Behavioral data of interference in the emotional Stroop task and related memory tasks in healthy control participants (HC), patients with Borderline Personality Disorder in the neutral (BPDn) or dissociation condition (BPDd) [Means ± standard deviation; reaction times refer to correct responses]

	HC (*n*=19)	**BPDn (*n*=19)**	**BPDd (*n*=18)**	**Significant post-hoc group comparison (Tukey HSD)***
Emotional Stroop task				
Reaction times - ms				
negative - neutral words	4.00 (39.36)	11.70 (29.68)	55.23 (52.08)***	BPDd>HC**,
positive – neutral words	-4.10 (32.76)	6.07 (22.61)	16.13 (29.62)*	BPDd>BPDn**
accuracy - % correct				BPDd>HC$^{(*)}$
negative - neutral words	0.92 (2.31)	0.13 (2.50)	-0.27 (2.93)	
positive – neutral words	0.72 (1.68)$^{(*)}$	-0.07 (2.58)	-0.69 (3.41)	
Free recall – % correct				
negative - neutral words	11.05 (9.51)***	11.32 (9.55)***	10.28 (7.37)***	
positive – neutral words	2.63 (8.72)	5.00 (10.80) $^{(*)}$	4.44 (7.45)*	
Recognition task				
Reaction times– ms				
negative - neutral words	31.30 (58.39)***	22.07 (59.26)	26.62 (62.20) $^{(*)}$	
positive – neutral words	14.41 (62.80)	29.20 (49.20)	19.69 (57.89)	
accuracy - % correct				
negative - neutral words	3.95 (12.73)	7.76 (8.82)**	3.47 (12.22)	
positive – neutral words	0.26 (12.66)	7.37 (7.57)***	3.47 (9.48)	

***p<.001, **p<.01, *p<.05, $^{(*)}$p<.01

The interaction of valence and group as well as the main effect of group regarding RTs in the EST were significant. Only BPDd revealed longer RTs for negative than for neutral words, while there were no significant differences between RTs to positive words and RTs to neutral words in all groups (see Figure 6.2). Figure 6.2C further illustrates that the RT difference of negative compared to neutral words was larger in BPDd than in BPDn and HC and that there was a trend for RT difference of positive compared to neutral words was in BPDd than in HC.

In addition, RTs were longer in BPDd than in BPDn, though RTs for HC and BPDn did not differ significantly (Figure 6.2A). For accuracy measures in the EST there was no significant interaction between group and valence. There was a significant group effect for accuracy. BPDd responded less accurately than BPDn in the EST, but BPDn and HC performed comparably (Figure 6.2B).

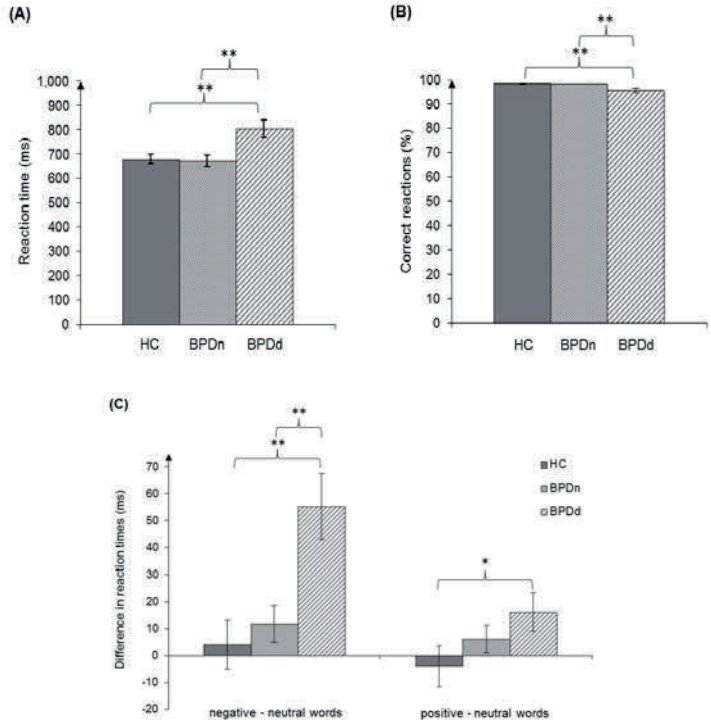

Figure 6.2. Group differences in mean reaction times (A) and accuracy (B) in the emotional Stroop task independent of stimulus valence and (C) in reaction time latencies of emotional versus neutral words in the emotional Stroop task. Note: ***p<0.001, ** p<0.01, * p<0.05, (*) p<0.10. Significance level p<0.05. BPDd= patients with Borderline Personality Disorder with dissociation induction, BPDn = patients with Borderline Personality Disorder without dissociation induction, and HC = healthy controls.

In the recall task, there was no significant interaction between valence and group. BPDd recalled fewer words than BPDn (trend towards a group effect) but word recall among BPDn and HC did not differ significantly. In the recognition task, there was no significant interaction effect between valence and group for RTs. There was a significant group effect for RTs, namely that BPDd responded slower than BPDn, while BPDn and HC performed comparably. There was neither a significant interaction effect of group and valence nor a main effect for group in accuracy in the recognition task.

6.3.4. Functional MRI during the Emotional Stroop Task

With respect to neuronal activity during EST performance, there were significant group differences across all valence conditions (see Table 6.3).

Table 6.3.
Group differences in neural activation in response to words independent of valence in the Emotional Stroop Task. Whole-brain fMRI data at a threshold of p<.001, k>10 voxel-uncorrected.

Anatomical label	BA	Cluster size	MNI x	MNI y	MNI z	*T* value (peak voxel)	*Z* value (peak voxel)
HC – BPDn							
r. cerebellum	-	20	24	-70	-50	3.85	3.76
BPDn – HC							
r. middle occipital gyrus*	18	40	30	-94	1	4.96	4.78
			21	-100	4	3.62	3.54
l. precentral gyrus	4	28	-48	-16	40	4.77	4.60
l. calcarine fissure	18	44	-15	-100	-2	4.61	4.46
l. inferior occipital gyrus	18		-27	-94	-5	4.15	4.04
l. middle occipital gyrus	19		-33	-88	4	3.43	3.37
l. inferior occipital gyrus	37	10	-39	-64	-8	4.23	4.11
l. middle occipital gyrus	39	61	-36	-70	22	4.02	3.92
l. middle occipital gyrus	19		-39	-67	7	3.81	3.72
l. middle temporal gyrus	39		-45	-64	19	3.67	3.59
BPDn – BPDd							
l. fusiform gyrus	19	20	-30	-73	-8	4.79	4.62
l. inferior temporal gyrus	37	12	-42	-64	-8	4.52	4.38
l. superior parietal lobe	7	74	-27	-55	49	4.27	4.15
			-27	-64	52	3.99	3.89
r. superior parietal lobe	7	18	27	-55	49	4.06	3.96
l. inferior parietal lobe	40	49	-45	-43	46	4.05	3.94
l. fusiform gyrus	37	51	-33	-46	-17	3.93	3.84
l. fusiform gyrus	19		-30	-49	-8	3.90	3.80
others: n.s.							

Note: BA= Brodman area; BPDd = borderline personality disorder (BPD) patients after dissociation induction; BPDn = BPD patients without dissociation induction; HC = healthy controls; l.= left; n.s. = not significant; r. = right; *would survive FWE-correction at $p<.05$ peak voxel level

BPDn showed increased activity in occipital areas and the left precentral gyrus, as well as decreased activity in the cerebellum compared with activity in HC. BPDd showed decreased brain activation in the left fusiform gyrus (Figure 6.3A), the bilateral superior parietal cortex, including the intraparietal sulcus (IPS), the inferior parietal gyrus and the temporal gyrus, when compared with BPDn. A positive correlation between neural activation in the left fusiform gyrus and RTs across all valence conditions failed statistical significance (p = 0.180). Complete results for valence differences per group can be found in Table 6.4.

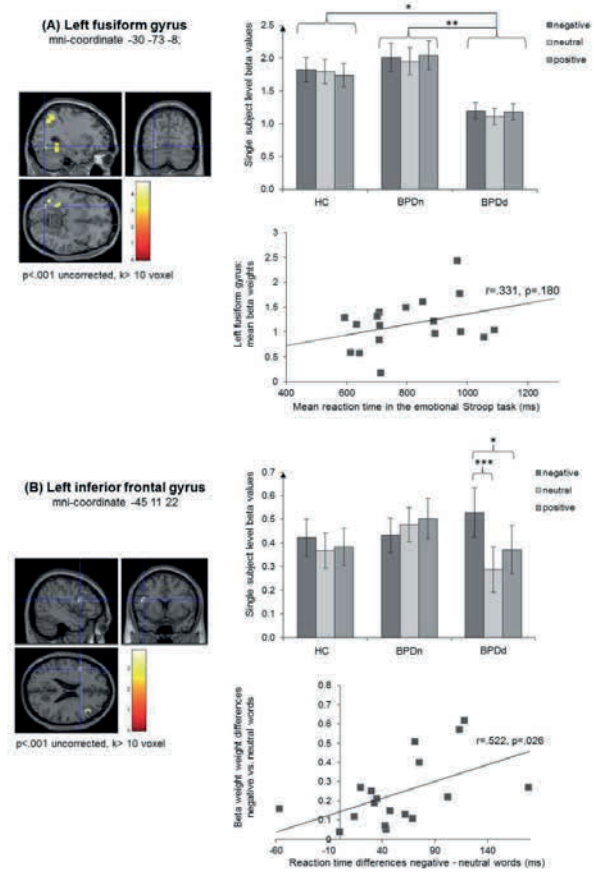

Figure 6.3. Neural activation in response to the emotional Stroop task. (A) Neural activation in response to the Emotional Stroop Task (EST) is higher in patients with borderline personality disorder who did not undergo dissociation induction (BPDn) than in patients who underwent dissociation induction (BPDd) in the left fusiform gyrus (contrast BPDd>BPDn; displayed on the left). After extracting beta values from the respective peak voxel of the single subject fMRI analysis, post-hoc analyses revealed that reduced neural activation in the left fusiform gyrus is specific for BPDd (right top) but not correlated with prolonged reaction times in the EST independent of valence. (B) Neural activation differences in response to negative compared to neutral words in the EST are larger in BPDd than in BPDn in the left inferior frontal gyrus (group level contrast $BPDd_{negative–neutral}$>$BPDn_{negative–neutral}$; displayed on the left). After extracting beta values from the respective peak voxel of the single subject fMRI analysis, post-hoc analyses revealed that this activation difference is specific for BPDd (right top) and correlates in this group with prolonged reaction times in response to negative versus neutral words (right bottom). *p<0.05, **p<0.01, and ***p<0.001, HC=healthy controls

Table 6.4. *Whole-brain data from group level analyses of the EST (p<.001, k>10 voxel uncorrected).*

Anatomical label	BA	Cluster size	MNI x	MNI y	MNI z	*T* value (peak)	*Z* value (peak)
HC: negative – neutral: n.s.							
HC: positive – neutral: n.s.							
BPDn: negative – neutral: n.s.							
BPDn: positive – neutral:							
r. superior temporal gyrus*	22	74	48	-31	4	5.58	5.32
r. superior temporal gyrus*	22	12	51	-10	-11	4.89	4.69
l. superior temporal gyrus	22	34	-54	-7	-11	4.78	4.61
r. supplementary motor area	8	18	9	17	52	4.03	3.93
l. middle temporal gyrus	22	35	-57	-43	1	3.80	3.72
			-51	-37	-2	3.67	3.59
l. orbital inferior frontal gyrus	47	10	-39	23	-14	3.67	3.59
r. superior frontal gyrus	8	11	15	29	46	3.58	3.50
r. medial superior frontal gyrus	9		9	32	40	3.44	3.37
BPDd: negative – neutral:							
l. inferior frontal gyrus	9	508	-42	11	25	5.47	5.23
/ pars triangularis*	47		-39	29	4	4.82	4.65
	46		-51	26	16	4.77	4.60
r. inferior frontal gyrus	45	47	42	23	19	4.72	4.56
l. middle occipital gyrus	19	87	-33	-79	1	4.38	4.25
	18		-30	-88	-5	3.56	3.48
l. inferior temporal gyrus	19	70	-48	-58	-11	4.34	4.22
l. fusiform gyrus	37		-36	-58	-11	3.50	3.43
l. cerebellum			-45	-64	-23	3.39	3.33
l. middle temporal gyrus	39	95	-57	-55	7	4.28	4.16
			-63	-43	7	4.14	4.02
l. superior temporal lobe	40	68	-54	-46	22	3.87	3.78
l. cerebellum			-6	-79	-26	4.20	4.08
r. cerebellum		126	3	-79	-17	3.97	3.87
r. cerebellum			24	-76	-35	4.20	4.08
			30	-79	-26	4.10	3.99
			15	-79	-29	4.02	3.92
l. middle temporal gyrus	39	25	-48	-64	19	4.08	3.97
l. medial superior frontal gyrus	9	45	-6	53	34	3.97	3.87
			-15	56	31	3.62	3.54
l. middle temporal gyrus	21	16	-54	-19	-5	3.89	3.80
r. fusiform gyrus	37	13	33	-49	-17	3.81	3.72
l. thalamus		11	-27	-22	10	3.66	3.58
l. inferior parietal lobe	7	15	-27	-73	43	3.54	3.46
l. thalamus		11	-3	-22	4	3.41	3.34
BPDd: positive – neutral: n.s.							

Note: l=left; r=right; *survive FWE-correction at *p*<.05 peak voxel level

A complete description of supra-threshold clusters for group differences in neuronal activity in response to emotional compared to neutral words is provided Table 6.5.

Table 6.5.
Group differences in neural activation in response to emotional versus neutral words in the emotional Stroop task. Whole-brain fMRI data from group level analyses at a threshold of p<.001, k>10 voxel uncorrected

Anatomical label	**BA**	**Cluster size**	**MNI**			***T* value (peak)**	***Z* value (peak)**
			x	**y**	**z**		
HC-BPDn: negative-neutral: n.s.							
HC-BPDn: positive-neutral: n.s.							
BPDn-HC: negative-neutral							
r. superior temporal gyrus	41	14	48	-7	-11	4.10	4.00
BPDn-HC positive-neutral							
r. superior temporal gyrus*	22	37	48	-31	4	4.89	4.71
			57	-22	-2	3.41	3.35
medial superior frontal gyrus	9	32	0	47	37	4.47	4.33
l. superior frontal gyrus	9	25	-18	50	34	4.31	4.19
r. anterior cingulate	32	21	12	35	16	4.23	4.11
l. medial superior frontal gyrus	10	14	-9	53	13	3.64	3.56
r. medial frontal gyrus	24	10	9	29	37	3.61	3.54
BPDn-BPDd: negative-neutral: n.s.							
BPDn-BPDd: positive-neutral: n.s.							
BPDd-BPDn: negative-neutral							
l. inferior frontal gyrus pars opercularis	9	11	-45	11	22	3.88	3.79
r. middle frontal gyrus	45	10	42	20	19	3.56	3.49
r. middle frontal gyrus	46		45	32	22	3.36	3.30
BPDd-BPDn: positive-neutral: n.s.							

Note: BA= Brodman area; l.= left; n.s. = not significant; r. = right; *would survive FWE-correction at *p*<.05 peak voxel level

For completeness, analyses comparing both emotional valences with each other are reported in the Supplementary Table S6.3. Our analysis revealed that BPDn, compared with HC, exhibited increased neuronal activity to negative vs. neutral as well as positive vs. neutral words in the right superior temporal gyrus.

They also showed increased activation in response to positive vs. neutral words in the dorsolateral (Brodmann area (BA) 9, superior frontal gyrus) and dorsomedial prefrontal cortex (BA 10/24, medial frontal gyrus) and ACCs. BPDd showed increased neuronal response to negative vs. neutral stimuli in the IFG (BA 9) and dorsolateral prefrontal cortex (BA 46, middle frontal gyrus) than did BPDn. Differences in neural activity according to valence in the left IFG per group are presented in Figure 6.3B. In BPDd, higher activation in this brain area in response to negative compared to neutral words was associated with greater RTs to negative words than to neutral words.

6.3.5. Post-hoc analysis controlling for trauma, depression, anxiety, and tension

Post-hoc behavioral analysis controlling for CTQ, BDI, trait STAI, and state STAI scores as well as tension residuals mainly confirmed the described behavioral results. The differences were the following: This analysis revealed a group effect for recall performance ($F2,48 = 3.62$, $p = 0.033$, $\eta^2 = 0.13$), with fewer words recalled in BPDd than in BPDn ($p = 0.037$) but no significant difference between word recall in BPDn and HC. Also, the group effect for RTs in the recognition task remained significant ($F2,48 = 3.92$, $p = 0.026$, $\eta^2 = 0.14$), even though post-hoc tests now only showed a trend ($p = 0.074$) for BPDd to respond more slowly than BPDn. Furthermore, the analysis revealed a trend for a group effect in recognition accuracy ($F2,48 = 2.81$, $p = 0.070$, $\eta^2 = 0.10$), with BPDd recognizing fewer words than BPDn ($p = 0.092$) and no significant difference between BPDn and HC. Comparing BPDd to BPDn in overall neural response during EST performance across all three valence conditions, the results could be replicated at a reduced threshold of $p < 0.005$, $k > 10$ voxel, uncorrected for multiple comparison (Lieberman and Cunningham, 2009), and no replication was possible for the right superior parietal lobe. With respect to the different valences, BPDd still showed enhanced neural processing of negative vs. neutral words in the left IFG and, for a reduced threshold of $p < 0.005$, $k > 10$ voxel, in the right dorsolateral prefrontal cortex (BA46, middle frontal gyrus) when compared to BPDn. No further significant group differences in valence processing were revealed in this post-hoc analysis. In sum, the major behavioral results and, at a more liberal threshold, also the neuroimaging results remained significant after controlling for CTQ, BDI, trait STAI, and state STAI scores as well as tension residuals.

6.4. Discussion

This study investigated BPD patients' performance on the EST after dissociation induction compared to those without dissociation induction and compared with healthy controls.

These were the main results:

(1) Cognitive inhibition was impeded in BPD patients only after dissociation induction. Reactions were slower and less accurate in the EST. These effects were also observed in the subsequent free recall task. Across all valences during the EST, BPD patients who did not undergo dissociation induction showed predominantly stronger occipital activity than healthy control participants. BPD patients who underwent dissociation induction exhibited reduced brain activity in the fusiform gyrus and in the inferior and parietal and temporal cortices compared to patients who did not undergo dissociation induction.

(2) With respect to altered emotional inhibition, BPD patients who did not undergo dissociation induction revealed enhanced neuronal activity in response to positive compared to neutral stimuli in the superior temporal gyrus, the dorsolateral and dorsomedial prefrontal cortex, and the ACC as compared to healthy controls. Furthermore, BPD patients revealed less inhibition of negative stimuli after dissociation induction. They demonstrated prolonged reactions in the EST and exhibited increased neuronal activity particularly in the IFG and dlPFC in response to negative stimuli when compared to BPD patients without dissociation induction.

BPD patients who did not undergo dissociation induction did not differ from healthy controls in terms of behavioral measures. On the neural level, they showed stronger activity in predominantly occipital areas compared to healthy controls. In BPD, previous studies found enhanced occipital activity during the processing (Koenigsberg et al., 2009a) as well as already during anticipation (Scherpiet et al., 2014) of emotional stimuli. These authors interpreted this finding in terms of higher vigilance for emotional stimuli. Previously, enhanced occipital activity was indeed associated with enhanced attentional requirements in visual tasks (Hopfinger et al., 2000; Kelly et al., 2008; Rauss et al., 2009). Thus, our finding may be interpreted in terms of increased recruitment of attentional resources to potentially emotional stimuli in the absence of a behavioral consequence. With respect to BPD patients after dissociation induction, the results are consistent with our first hypothesis that BPD patients show inefficient cognitive inhibition of task-irrelevant information in the EST after dissociation induction independent of stimulus valence. Our findings are in line with studies examining nonclinical participants with dissociation proneness and studies examining clinical participants with dissociative disorders, which suggests that these populations are less efficient in suppressing both emotional and non-emotional distracting material (Freyd et al., 1998; DePrince and Freyd, 1999; Elzinga et al., 2000, 2003; Chiu et al., 2010, 2012). In our study, after dissociation induction patients showed reduced activity in the fusiform gyrus.

This area has been shown to be involved in color processing (Beauchamp et al., 1999; Chao & Martin, 1999; Kellenbach et al., 2001) and word recognition (Nobre et al., 1994; Pammer et al., 2004; Binder et al., 2006), among others. Also, the superior parietal cortex was less activated in BPD patients with dissociation induction than in BPD patients without dissociation induction. The superior parietal cortex is associated with attention (LaBar et al., 1999; Schultz and Lennert, 2009), in particular language processing (Majerus et al., 2006), working memory (LaBar et al., 1999; Todd & Marois, 2004), and sensory-motor coordination (Sakai et al., 2002; Grefkes & Fink, 2005), among others. Being less activated in BPD patients after dissociation induction, the left inferior parietal cortex and the left inferior temporal gyrus have been associated with language processing (Cohen et al., 2000; Simon et al., 2002; Ravizza et al., 2004). Thus, the current findings suggest that inhibition of task-irrelevant information is less efficient in BPD patients during dissociative states, which is likely reflected in reduced activity in the fusiform gyrus as well as the superior and inferior parietal cortex.

For BPD patients without dissociation induction, our findings are consistent with previous studies which found no behavioral differences between BPD patients and healthy controls performing the EST under neutral conditions (Sprock et al., 2000; Domes et al., 2006; Minzenberg et al., 2008; Wingenfeld et al., 2009b). Nevertheless, BPD patients without dissociation induction compared with healthy controls showed enhanced neural activity in the ACC, superior temporal gyrus, dmPFC, and dlPFC, particularly in response to positive versus neutral words. These are areas associated with executive functions including interference inhibition of distracting emotional stimuli and emotion down-regulation (Whalen et al., 1998; Britton et al., 2009; Hart et al., 2010; McRae et al., 2010; Mincic, 2010; Ovaysikia et al., 2011; Kanske et al., 2011; Dorfel et al., 2014). This supports the idea that BPD patients differ from healthy controls in the processing of positive stimuli (Sieswerda et al., 2007). Our findings suggest that BPD patients may exhibit exacerbated neural processing of positive words and may recruit more neural resources to prevent the occurrence of inhibitory deficits (for positive words) on the behavioral level. One possible explanation of this may be that positive stimuli are more ambiguous for BPD patients than for healthy controls (Thome et al., 2016), which could be related to a negative self-image in BPD (Rüsch et al., 2007; Lynum et al., 2008; Kopala-Sibley et al., 2012). This ambiguity may thus lead to more interference and more recruitment of cognitive resources in the EST. We did not replicate attenuated differential activity in response to negative vs. neutral stimuli in the ACC as observed in a previous study in BPD (Wingenfeld et al., 2009b), which may be due to methodological differences in the respective study designs, such as the current study's inclusion of positive words.

After dissociation induction, BPD patients revealed prolonged reactions and heightened IFG activity in response to negative words when compared to neutral words in the EST in comparison to BPD patients without dissociation induction. Since a respective valence effect was not present in the succeeding memory tasks, our finding suggests that alterations associated with high state dissociation in BPD become selectively observable in the process of emotional inhibition. Furthermore, these findings are inconsistent with our second hypothesis that BPD patients after dissociation induction would show a smaller difference in the inhibition of negative compared to neutral information in the EST compared to BPD patients without dissociation induction. Namely, BPD patients after dissociation induction showed behaviorally less emotional inhibition of negative stimuli, which was not the case for BPD patients without dissociation induction. After dissociation induction, BPD patients compared with BPD patients without dissociation induction showed increased activity primarily in the left dorsolateral and inferior frontal gyrus (BA 9/46) in response to negative vs. neutral words. The left IFG is associated with verbal processing and executive functions such as response inhibition, especially with respect to the EST (Britton et al., 2006; Britton et al., 2009; Mincic, 2010; Ovaysikia et al., 2011) and has revealed increased neural activity in BPD patients while they listened to dissociation-inducing scripts (Ludäscher et al., 2010). Due to correlations of stronger activity in the IFG and slower reactions to negative compared to neutral words in BPD patients after dissociation induction, this neural activity may imply that these patients required more neural resources to inhibit negative, task-irrelevant stimuli less successfully. This finding suggests that the left IFG may be a neural substrate for disturbed inhibition of negative stimuli in BPD during induced dissociative states.

In sum our findings are in line with the concept presented by Dorahy (2006) for individuals with clinically relevant dissociation proneness. Dorahy argues that cognitive processes such as directing awareness are dependent on the context which the stimuli are presented in. In a threat-related context, for example, awareness may be directed to threat-related stimuli. Since dissociative states are rather aversive in BPD, it may be possible that during dissociative states the may be more prone to process negative information.

The study's main behavior results and, at a lowered threshold, fMRI results were largely replicated when measures of early childhood traumatization, depressive mood, anxiety, and the specific effect of tension were included as covariates. BPD patient groups also did not differ in demographic data, number of patients with comorbid posttraumatic stress disorder, psychometric measures, or initial dissociation and tension ratings. This suggests that these variables may not have sufficiently accounted for the observable effects.

However, it is still possible that further variables not considered may have been relevant. For example, seven and eight patients in the BPDn and BPDd groups respectively had comorbid posttraumatic stress disorder. However, due to power constraints in a possible subgroup analysis, we suggest that further studies need to address if comorbid posttraumatic stress disorder alters or even determines the influence of induced dissociation on emotional inhibition in BPD. Findings from this study cannot be generalized to all BPD patients as the study sample was composed solely of female BPD patients with high levels of trait dissociation. Thus, this study does not offer conclusions regarding how male BPD patients or those with a low tendency to dissociate perform in the EST. Also, we applied a comparatively liberal threshold for the fMRI data. Thus, a replication of the findings is particularly relevant (Lieberman and Cunningham, 2009). In addition, our stimulus material was counterbalanced for valence and emotional stimuli were comparable in valence intensity, but we did not account for stimulus arousal. Accordingly, we cannot rule out the possibility that stimulus arousal may have contributed to the findings as this was suggested before (Schimmack, 2005; Dresler et al., 2009). Further, dissociation induction may likely have induced stress or negative mood. We considered that dissociation is related to stress in BPD and that dissociation ratings are positively correlated with tension ratings in BPD patients (APA, 2000; Stiglmayr et al., 2008). Even though we attempted to correct for the specific effect of tension, shared mechanisms may account for the observable effects in this study. Since only three patients had a current episode in our study, it remains an interesting topic for future research to assess if the presence of mood disorders has an impact on dissociation induction. It may be discussed whether experimentally induced dissociation is comparable to naturally occurring dissociation. In this study, we examined that a dissociative state occurred via self-report, an approach used previously to infer the role of state dissociation in emotion processing and cognitive functioning in BPD (Ebner-Priemer et al., 2009; Barnow et al., 2012; Krause-Utz et al., 2012). The DSS-4 (Stiglmayr et al., 2009) used in our study was demonstrated to have good - excellent inner consistency and reliability, to discriminate between diagnostic groups and to be sensitive in change in symptomatology. Physiologically, higher scores in this measure were associated with higher pain thresholds (Ludäscher et al., 2010), probably corresponding to a naturally occurring dissociative symptom called analgesia (Ludäscher et al., 2007). We therefore argue that if participants show high DSS-4 scores, they experience dissociation as they would experience it naturally. However, this aspect of the current study's design remains an unaddressed and interesting question for future studies to examine if neuropsychological test performance and neural correlates of induced and naturally occurring dissociation correspond.

As the findings from this study are in line with studies in nonclinical individuals with high dissociation proneness and patients with dissociative disorders, the effects of state dissociation on cognitive and emotional inhibition may not be specific to BPD patients and may be found in other clinical populations with dissociative feature. This is particularly relevant as we did not assess the presence of dissociative disorders apart from transient dissociative states according to the IPDE in our sample. It would be interesting to replicate the finding in other samples in which dissociation can be induced, too, such as in patients with posttraumatic stress disorder or dissociative disorders. Even though we discussed our findings in the framework of inhibition of task-irrelevant material, we cannot infer which specific process is altered by dissociation. It may well be that dissociation is already associated with impaired processing of emotional content or so called "over-modulation" (Lanius et al., 2010) or response execution, which may have led to e.g. longer reaction times in our study. Further studies need to clarify this issue, dismantling the effect of (induced) dissociation on sensory processing, emotion processing, executive functioning, learning and memory as well as motor responding.

In summary, the current study suggests that BPD patients under induced dissociative states show inefficient cognitive inhibition of task-relevant material and impaired inhibition of negative stimuli. These findings offer first experimental evidence for impaired emotional and non-emotional inhibition during high state dissociation in BPD. Thus, we recommend that state dissociation should be measured in studies examining cognitive functioning in BPD. Also, if replicated, the findings of this study may have implications for psychotherapy in BPD patients as these individuals may have difficulty in adequately processing new information and emotional experiences during high state dissociation. This may be a contributing factor regarding the tendency of BPD patients who to show high state dissociation to be predictive of poor psychotherapy outcome (Kleindienst et al., 2011; Kleindienst et al., 2016).

Future studies are therefore needed to clarify which processes are relevant for psychotherapy as well as the maintenance of BPD psychopathology (such as emotion regulation and emotional learning) and whether they are affected by high state dissociation.

Conflict of interest:
None.

Supplementary material

Table S6.1.

Length, valence and frequency of the word stimuli derived from the German Aachener Emotionale Wortliste (Aachen's emotional word list; Böcker, Gruber, Gauggel, in preparation)

	Length		Valence		Frequency	
	letters	*Sd*	*-3 to 3*[a]	*Sd*	*Log*	*Sd*
Negative words						
Emotional Stroop task	5.05	0.80	-1.84	0.30	0.97	0.44
Recognition task	5.05	0.78	-.194	0.38	0.97	0.50
Neutral words						
Emotional Stroop task	5.05	0.80	0.23	0.15	0.97	0.45
Recognition task	5.05	0.78	0.22	0.12	1.07	0.47
Positive words						
Emotional Stroop task	5.05	0.80	1.62	0.21	0.97	0.46
Recognition task	5.05	0.78	1.30	0.27	1.14	0.47

[a]data was collected on a 7-point scale ranging from 1 to 7 and transformed to a scale ranging from -3 to + 3 to assure comparability between valences

Additional information: Post hoc analysis controlling for early childhood traumatization, depressive symptoms, anxiety, and tension.

To control for the influence of early childhood traumatization, depressive symptoms, state and trait anxiety, as well as tension on main findings, the following reanalysis was applied: first, tension ratings were corrected for dissociation ratings, as both measures were highly correlated in the current study (mean correlation r=.727, p<.001, when averaged across all measurements after script presentation). We used a regression analysis with tension ratings as the dependent variable and DSS-4 ratings as independent variable and extracted the unstandardized residuals per participants. Then, the following analyses were performed at the same statistical significance levels as in the respective analyses of behavioral and fMRI data.

Behavioral data. For the dependent measures of the EST and the subsequent memory tasks, rm-ANOVAS were repeated with CTQ, BDI, trait STAI, and state STAI values as well as with tension residuals as covariates.

fMRI data. As it is not possible in SPM8 to include multiple covariates in the ANOVA group level model we used for the fMRI analysis, we needed to calculate the respective contrasts at single subject level (see below for model and test specifications for the group comparison across and considering differential activity between valences in the EST).

Then, at group level, we only repeated the contrast BPDn vs. BPDd and renounced the analysis of HC vs. BPDn as here, group differences in the designated covariates may mask an effect of group in the reanalysis so that the results are not interpretable. In order to include covariates for overall emotional Stroop task performance group comparison (independent of valence), a new single subject level model needed to be calculated as it is not possible in SPM8 to include multiple covariates in the ANOVA group level model we used for the fMRI analysis. This model included one regressor each for scripts, ratings, and responses as well as only one regressor for all task blocks instead of three separate regressors for blocks of each valence. Afterwards, between groups comparison was performed between BPDn and BPDd using a t-test for independent samples with CTQ, BDI, STAI state, and STAI trait values as well as tension residuals per participant as covariates. We did not calculate the contrasts of HC vs. BPDn as group differences in the designated covariates may mask an effect of group in the reanalysis so that the results are not interpretable. To be able to include covariates for group comparisons of valence effects, first contrast between responses to negative vs. neutral and positive vs. neutral words were calculated on single subject level for the original single subject model. Second, for group level comparison between BPDn vs. BPDd, independent sample t-tests with CTQ-, BDI-, STAI state, and STAI trait values as well as tension residuals per participant as covariates were conducted. We again did not calculate the contrasts of HC vs. BPDn as group differences in the designated covariates may mask an effect of group in the reanalysis so that the results are not interpretable.

Table S6.2.

Behavioral data of interference of negative compared to positive stimuli in the EST and related memory tasks in healthy control participants (HC), BPD patients in the neutral (BPDn) or dissociation condition (BPDd) [Means ± SD; reaction times refer to correct responses]

	HC (*n*=19)	**BPDn (*n*=19)**	**BPDd (*n*=18)**	**Significant post-hoc group comparison (Tukey HSD)***
Emotional Stroop task				
Reaction times **-** ms	8.10 (23.96)	5.63 (27.34)	39.10 (50.26)**	BPDd>HC*, BPDd>BPDn*
accuracy **-** % correct	0.20 (1.63)	0.20 (1.92)	0.42 (1.82)	
Free recall – % correct	8.42 (8.17) ***	6.32 (11.65)*	5.83 (9.89)*	
Recognition task				
Reaction times – ms	24.18 (77.57)	-7.13 (54.45)	6.93 (63.83)	
accuracy **-** % correct	3.68 (8.31) (*)	0.40 (10.04)	0.00 (9.96)	

***p<.001, **p<.01, *p<.05, (*)p<.10

Table S6.3.

Neural activation in response to negative versus positive words in the emotional Stroop task per group and in group comparison.

Anatomical label	BA	Cluster size	MNI x	y	z	*T* value (peak voxel)	*Z* value (peak voxel)
HC negative –positive: n.s.							
HC positive – negative: n.s.							
BPDn negative – positive: n.s.							
BPDn positive – negative: n.s.							
BPDd negative – positive:							
r. cerebellum		51	27	-76	-32	4.50	4.36
l. inferior frontal gyrus	9	14	-42	11	25	4.08	3.98
l. inferior frontal gyrus	47	49	-36	26	4	4.02	3.92
			-42	32	1	3.88	3.78
r. anterior cingulate	33	15	6	5	25	3.99	3.89
r. superior frontal gyrus	6	17	9	11	64	3.91	3.81
l. putamen		11	-18	14	10	3.90	3.81
l. cerebellum		13	-39	-58	-26	3.69	3.61
medial cerebellum		41	0	-55	-47	3.63	3.55
			-3	-49	-38	3.62	3.54
			6	-52	-38	3.56	3.49
medial cerebellum		13	6	-76	-17	3.49	3.42
			-3	-76	-11	3.38	3.32
l. inferior parietal lobe	40	12	-54	-46	22	3.47	3.41
BPDd: positive - negative: n.s.							
BPDn-HC: neg. – positive: n.s.							
BPDn-HC: positive – neg.: n.s.							
BPDd-BPDn:negative –positive:							
r. Pons		10	12	-40	-41	3.71	3.63
l. Putamen		11	-18	8	-2	3.51	3.44
BPDd-BPDn: positive -neg.: n.s.							

Note: Whole-brain fMRI data from group level analyses at a threshold of $p<.001$, $k>10$ voxel uncorrected; BA= Brodman area; BPDd = borderline personality disorder after dissociation induction; BPDn = borderline personality disorder without dissociation induction; HC = healthy control participants; l.= left; n.s. = not significant; r. = right

CHAPTER 7

Reduced Amygdala activity and Emotional Distractibility during Dissociative States in Borderline Personality Disorder

Annegret Krause-Utz, Dorina Winter, Friederike Schriner, Chui-De Chiu, Stefanie Lis, Philip Spinhoven, Martin Bohus, Christian Schmahl, and Bernet M. Elzinga (2017). Impact of Dissociation on Amygdala Activity and Functional Connectivity during an Emotional Working Memory Task in Borderline Personality Disorder. *European Archives of Psychiatry and Clinical Neuroscience* (in press).

Abstract

Background: Affective hyperreactivity and impaired cognitive control of emotional material are core features of Borderline Personality Disorder (BPD). A high percentage of individuals with BPD experience stress-related dissociation, including emotional numbing and memory disruptions. So far little is known about how dissociation influences the neural processing of emotional material in the context of a working memory task in BPD. We aimed to investigate whole-brain activity and amygdala functional connectivity (FC) during an Emotional Working Memory Task (EWMT) after dissociation induction in un-medicated BPD patients compared to healthy controls (HC). **Methods**: Using script-driven imagery, dissociation was induced in 17 patients ('BPD_D'), while 12 patients ('BPD_N') and 18 HC were exposed to neutral scripts during fMRI. Afterwards, participants performed the EWMT with neutral vs. negative IAPS pictures vs. no distractors. Main outcome measures were behavioral performance (reaction times, errors) and whole-brain activity during the EWMT. Psychophysiological Interaction analysis was used to examine amygdala connectivity during emotional distraction. **Results**: BPD patients after dissociation induction showed overall WM impairments, a deactivation in bilateral amygdala, and lower activity in left cuneus, lingual gyrus, and posterior cingulate than BPD_N, along with stronger left inferior frontal gyrus activity than HC. Furthermore, reduced amygdala FC with fusiform gyrus and stronger amygdala FC with right middle/superior temporal gyrus and left inferior parietal lobule was observed in BPD_D. **Conclusion**: Findings suggest that dissociation affects reactivity to emotionally salient material and WM. Altered activity in areas associated with emotion processing, memory, and self-referential processes may contribute to dissociative states in BPD.

Key words: Borderline Personality Disorder, Emotional Working Memory, Dissociation, Amygdala, Functional Connectivity, Psychophysiological Interaction Analysis

7.1. Introduction

Borderline Personality Disorder (BPD) is a severe mental disorder, characterized by emotion dysregulation, instable cognitions, impulsivity, interpersonal disturbances, and dissociation (Crowell et al., 2009; Schmahl et al., 2014). Previous neuroimaging studies in BPD suggest that a hyperactivity and altered functional connectivity of the amygdala may underlie disturbed emotion processing in BPD (Schulze et al., 2016; van Zutphen et al., 2015), although discrepant findings were also reported (see Ruocco et al., 2013). The amygdala plays a crucial role in the initiation of fear and stress responses (Davis & Whalen, 2001) and might also been involved in stress-related dissociation (Sierra & Berrios, 1998; Philips & Sierra, 2003).

Dissociation occurs in a high percentage (~75-80) of individuals with BPD (Korzekwa, Dell, & Pain, 2009a; Korzekwa et al., 2009b; Stiglmayr et al., 2008; Vermetten & Spiegel, 2014), involving disruptions in the usually integrated functions of consciousness, perception, identity, memory, and affect (APA, 2013; Spiegel et al., 2011) and has been closely linked to psychological trauma. Dissociative symptoms such as depersonalization, derealization, numbing, and analgesia may provide a state of subjective detachment from extremely stressful experiences, e.g., by dampening overwhelming emotions and reducing awareness of pain (Lanius et al., 2010; Spiegel et al., 2011). In pathological dissociation, the cost of this subjective detachment is a disruption of executive functions that are crucial to goal-directed behavior, such as attention, learning, and memory. More specifically, dissociation may hinder the conscious processing and integration of salient information in autobiographical memory, which can have detrimental effects on the development of identity and emotion regulation capacities. Dissociation may hinder the recall and learning of self-relevant information also during therapy (Lanius et al., 2010) and in BPD, dissociative symptoms predicted poor treatment outcome (Arntz et al., 2015; Kleindienst et al., 2011; Kleindienst et al., 2016; Lanius et al., 2010; Spitzer et al., 2007). However, the precise neuropsychological mechanisms underlying this relationship remain unclear.

Neurobiological models have therefore dissociation to a dampened activity in the amygdala and increased recruitment of 'cognitive control' regions, such as the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and inferior frontal gyrus (Lanius et al., 2010; Sierra & Berrios, 1998) as well as to altered activity in the superior temporal gyrus, precuneus, posterior cingulate, which are implicated in autobiographical memory and self-referential processing (Lanius et al., 2002; Lanius et al., 2005; Ludäscher et al., 2010; Simeon et al., 2000). The amygdala appears to be an important hub within this network, sharing strong functional connections with the ACC, insular and orbitofrontal cortex, mPFC, parahippocampal gyrus,

precuneus, posterior cingulate, among others (Roy et al., 2009; Stein et al., 2007). In summary, it can be assumed that dissociation substantially affects activity within an 'amygdala network' involved in the processing of self-relevant emotional information and the initiation of stress responses. In BPD, however, so far there is little empirical evidence for this. Only few neuroimaging studies in BPD investigated correlations between self-reported dissociation and brain activity during experimental challenge, such as the presentation of aversive images or words (Hazlett et al., 2012; Krause-Utz et al., 2012, 2014b, 2017; Wingenfeld et al., 2009b; Winter et al., 2015).

To the best of our knowledge, only two neuroimaging studies in BPD used script-driven imagery to more directly investigate the effect of experimentally induced dissociation (Ludäscher et al., 2010; Winter et al., 2015). In this well-established paradigm, a narrative of an autobiographical situation involving dissociative experiences ('dissociation script') is created and presented in an experimental setting, e.g. during fMRI (Lanius et al., 2002, 2004). Participants are instructed to listen to this script and to recall their autobiographical experiences as vividly as possible, which successfully induced dissociation in previous research (Ludäscher et al., 2010; Winter et al., 2015). When exposed to a dissociation script (vs. a neutral script), BPD patients showed significantly increased activity in the left inferior frontal gyrus and superior frontal gyrus and diminished temporo-limbic activity, which was even more pronounced in a subgroup of traumatized patients (Ludäscher et al., 2010).

We recently combined script-driven imagery with an Emotional Stroop Task (EST), to investigate the effect of a dissociation induction on interference inhibition, on a behavioral and neural level in BPD (Winter et al., 2015). Patients exposed to a dissociation script showed impaired overall accuracy and slower reaction times for negative words than patients exposed to a neutral script. Patients after dissociation induction further showed increased left inferior frontal gyrus activity in response to negative vs. neutral words (Winter et al., 2015). However, it remains unclear how brain areas, in particular the amygdala, may interact with other brain regions after dissociation induction. To our knowledge, so far no study in BPD investigated how dissociation affects the neural processing of emotional material during a working memory task, which requires the active manipulation of task-irrelevant stressful information.

We previously developed a modified version of the Emotional Working Memory Task (EWMT) (Krause-Utz et al., 2012; Krause-Utz et al., 2014d) in which task-irrelevant neutral vs. negative (trauma-related) interpersonal scenes from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2005) or only a fixation cross (no distractors) are presented during the delay interval of a Sternberg item recognition task. Participants are

instructed to ignore distractors, focusing solely on the working memory (WM) task, thereby voluntarily inhibiting emotion processing in favor of cognitive processing. WM impairments (errors, prolonged RTs) and amygdala reactivity to negative pictures were significantly more pronounced in BPD patients, suggesting stronger emotional distractibility compared to healthy controls (Krause-Utz et al., 2012). During emotional distraction, BPD patients further showed a stronger coupling of the amygdala with the hippocampus and dorsomedial PFC, suggesting enhanced self-referential processing (Krause-Utz et al., 2014d).

Here, we aimed to investigate the impact of experimentally-induced dissociation on brain activity and amygdala functional connectivity during the EWMT. Studying this relationship on a behavioral and neural level might help to shed more light on the effects of stress-related dissociation in BPD. Script-driven imagery was used to induce dissociation. For patients exposed to a neutral script, we hypothesized to replicate previous findings of amygdala hyper-reactivity to emotional pictures, while patients exposed to a dissociation script were expected to show significantly dampened amygdala reactivity and increased activity in frontal areas (ACC, mPFC, inferior frontal gyrus).

7.2. Methods

7.2.1. Sample

Sixty women aged between 18-45 years (40 patients with BPD according to DSM-IV (APA, 2000) and 20 female HC) participated. Patients were recruited via advertisement on websites or referred from the residential treatment unit of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health (CIMH) in Mannheim, Germany. HC were recruited by newspaper advertisement. General exclusion criteria were serious somatic illnesses, traumatic brain injuries, developmental disorders, and MRI-related criteria (metal implants, pregnancy, left-handedness, claustrophobia). Exclusion criteria for HC were lifetime history of axis I/II disorders. Exclusion criteria for patients were psychotropic medication within 4 weeks prior to the study, substance dependence during the last year, substance abuse within two months prior to participation, current/lifetime psychotic or bipolar-I disorder, and life-threatening suicidal crisis. Patients were randomly assigned to two experimental conditions: 20 patients were exposed to a dissociation script (BPDd), while 20 BPD patients (BPDn) and 20 HC were exposed to a neutral script. An increase of $\geq$1.5 scores on the Dissociation Stress Scale 4 (DSS-4, see below) (Stiglmayr et al., 2010) after script compared to baseline was defined as inclusion criterion for the BPDd group (criterion was met by all participants assigned to this group).

To ensure that individuals in the BPDn group were not dissociated, we excluded patients with DSS-4 baseline scores of ≥3 and/or an increase of >1.5 scores after the experiment (three patients had to be excluded for this reason). Furthermore, part of the collected data had to be discarded due to movement artefacts during fMRI (BPDn: n=2, BPDd: n=3, HC: n=2), technical problems during script presentation (BPDn: n=1) or inconsistent button presses (95-100% errors, suggesting that instructions were not understood correctly in BPDn: n=2). The final sample comprised 17 BPDd, 12 BPDn, and18 HC. Diagnoses were assessed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) (First et al., 1997) and International Personality Disorder Examination (IPDE) (Loranger, 1999). Further clinical assessment included questionnaires on symptom severity (Borderline Symptom List 23, BSL-23 (Bohus et al., 2009)), childhood trauma (Childhood Trauma Questionnaire, CTQ (Bernstein et al., 2003)), trait dissociation (Dissociative Experiences Scale, DES (Bernstein & Putnam, 1986)), depression (Beck Depression Inventory II, BDI-II (Beck, Steer, & Brown, 1996)), anxiety (State Trait Anxiety Questionnaire, STAI (Spielberger et al., 1983)), and ADHD (childhood: Wender Utah Rating Scale, WURS (Ward, Wender, & Reimherr, 1993), adulthood: ADHD-Checklist (Roesler et al., 2008)). Groups did not differ in age and years of education. Both BPD groups scored significantly higher than HC on clinical measures but did not differ significantly from each other in this respect. All patients fulfilled DSM-IV criteria for affective instability and stress related dissociation. Moreover, all patients reported at least one type of severe to extreme childhood abuse and/or neglect and didn't differ in the severity of childhood trauma (see Table 7.1). Criteria for comorbid Posttraumatic Stress Disorder (PTSD) was currently met by 7 BPDd patients (41%) and 5 BPDn patients (41%), 8 BPDd (47%) and 5 BPDn (41%) had lifetime PTSD ($\varkappa^2$=0.88, p=.646). Major depressive disorder (MDD) was currently present in 2 BPDd patients, while 15 BPDd (88%) and 8 BPDn (66%) had lifetime MDD ($\varkappa^2$=2.28, p=.131). Other lifetime comorbidities included panic disorder (BPDd: 5 (29%), BPDn: 3 (18%), $\varkappa^2$=0.05, p=.824), social phobia (BPDd: 10 (59%), BPDn: 4 (33%), $\varkappa^2$=1.78, p=.182), specific phobia (BPDd: 3 (18%), BPDn: 1 (8%), $\varkappa^2$=0.48, p=.488), obsessive compulsive disorder (BPDd: 4 (24%), BPDn: 1 (8%), $\varkappa^2$=1.09, p=.296), eating disorders (BPDd: 7 (41%), BPDn: 3 (18%), $\varkappa^2$=0.76, p=.384), and somatization disorder (BPDd: 1 (6%), BPDn: 0 (0%), $\varkappa^2$=0.71, p=.398). 15 BPDd patients (88%) and 10 BPDn patients (83%) reported non-suicidal self-injurious behavior within the last 12 month ($\varkappa^2$=0.14, p=.706). In the BPDd group, 13 patients (76%) were previously medicated, while in the BPDn group, 9 patients (75%) were previously medicated ($\varkappa^2$=0.008, p=.927; for more information see Supplemental Material).

Table 7.1.

Demographic variables, dissociation and arousal ratings, and clinical characteristics

	BPDd (n= 17)	**BPDn (n= 12)**	**HC (n= 18)**	**Group comparisons**
Age [years]	27.41 ± 6.20	25.17 ± 6.21	29.61 ± 8.61	$F_{(2,44)}$=1.38, p=.262
School education [years]	10.59 ± 2.62	10.08 ± 3.03	10.72 ± 1.99	$F_{(2,44)}$=0.25, p=.784
DSS-4 *Dissociation ratings* Baseline	3.44 ± 1.99	2.30 ± 1.14	1.31 ± 0.66	$F_{(2,42)}$=11.27, p<.0001. BPDd - HC: 2.26, p<.0001 BPDn - HC: 1.00, p=.160 BPDd - BPDn: 1.27, p=.062
After script	6.85 ± 2.03	1.85 ± 0.84	1.19 ± 0.51	$F_{(2,42)}$=92.50, p<.0001 BPDd - HC: 5.79, p<.0001 BPDn - HC: 0.60, p=.465 BPDd - BPDn: 5.19, p<.0001
Arousal rating Baseline	4.76 ± 2.36	3.91 ± 1.97	2.72 ± 2.02	$F_{(2,42)}$=3.43, p=.042 BPDd - HC : 1.90, p=.035 BPDn - HC: 1.20, p=.325 BPDd - BPDn: 0.72, p=.672
After script	7.71 ± 2.11	4.50 ± 2.65	2.17 ± 2.28	$F_{(2,42)}$=26.67 p<.0001 BPDd - HC : 5.46, p<.0001 BPDn - HC: 1.83, p=.840 BPDd - BPDn: 3.62, p<.0001
BSL-23 total score (BPD symptom severity)	47.12 ± 19.23	43.33 ± 13.36	1.33 ± 1.81	$F_{(2,44)}$=60.51, p<.0001, f^2=.73 BPDd - HC: 45.78, p<.0001 BPDn - HC: 42.00, p<.0001 BPDd - BPDn: 3.78, p=.737
DES total score (trait dissociation)	31.74 ± 16.52	26.93 ± 13.50	2.68 ± 2.04	$F_{(2,44)}$=28.37, p<.0001, f^2=.56 BPDd - HC: 29.01, p<.0001 BPDn - HC: 24.26, p<.0001 BPDd - BPDn: 4.81, p=.547
BDI-II (depressive symptoms)	24.47 ± 11.89	26.75 ± 10.68	1.67 ± 2.25	$F_{(2,44)}$=38.49, p<.0001, f^2=.64 BPDd - HC: 22.80, p<.0001 BPDn - HC: 25.08, p<.0001 BPDd - BPDn: 2.28, p=.783
STAI state * (state anxiety)	56.19 ± 10.13	52.92 ± 6.36	29.39 ± 5.41	$F_{(2,43)}$=54.90, p<.0001, f^2=.74 BPDd - HC: 26.79, p<.0001 BPDn - HC: 23.53, p<.0001 BPDd - BPDn: 2.55, p=.503
STAI trait * (trait anxiety)	58.13 ± 7.03	60.58 ± 5.83	28.72 ± 4.66	$F_{(2,43)}$=138,83, p<.0001, f^2=.87 BPDd - HC: 29.40, p<.0001 BPDn - HC: 31.86, p<.0001 BPDd - BPDn: 2.05, p=.522
WURS (childhood ADHD symptoms)	98.80 ± 41.16	94.42 ± 27.91	49.53 ± 27.52	$F_{(2,39)}$=9.88, p<.0001, f^2=.39 BPDd - HC: 49.27, p<.0001 BPDn - HC: 44.88, p<.0001 BPDd - BPDn: 4.39, p=.938
ADHD checklist * (adult ADHD symptoms)	14.94 ± 9.80	16.83 ± 8.33	3.94 ± 2.88	$F_{(2,44)}$=14.11, p<.0001, f^2=.39 BPDd - HC: 10.99, p<.0001 BPDn - HC: 12.89, p<.0001 BPDd - BPDn: 1.89, p=.789
CTQ total sum-score (childhood abuse and neglect)	68.23 ± 25.12	70.58 ± 16.46	33.39 ± 11.88	$F_{(2,44)}$=20.34, p<.0001, f^2=.48 BPDd - HC: 34.91, p<.0001 BPDn - HC: 37.19, p<.0001 BPDd - BPDn: 2.29, p=.944

Note: Values are presented in means and standard deviation. DSS-4=Dissociation Stress Scale 4, BSL-23=Borderline Symptom List 23, DES=Dissociative Experience Scale, BDI=Beck Depression Inventory, STAI=State Anxiety Inventory, CTQ=Childhood Trauma Questionnaire, WURS=Wender Utah Rating Scale, PTSD=Posttraumatic Stress Disorder. * STAI scores in one BPD_D patient and WURS scores in 3 HC and 2 BPD_D patients were missing.

Dissociative states were induced using script-driven imagery and assessed by the DSS-4, a self-rating scale with excellent internal consistency and reliability, high specificity, and sensitivity to change in symptomatology (Stiglmayr et al., 2010). The DSS-4 consists of four items on current psychological (derealization, depersonalization) and somatic (pain perception, hearing) dissociation and one item on current tension (10-point Likert scales, 0=not at all, 9=extremely).

7.2.2. Emotional Working Memory Task (EWMT)

The EWMT was a validated modified Sternberg item recognition task (Sternberg, 1966; Oei et al., 2009, 2012). The present version (Krause-Utz et al., 2012) consisting of 48 trials, each starting with a set of 3 uppercase letters (memoranda, 1000 ms.), followed by a delay interval (1500 ms.) and a probe (3 uppercase letters, 2000 ms.). In half of the trials, 1 of the 3 memoranda was present in the probe. Participants had to press a 'yes' or 'no' button indicating whether they had recognized a target or not. During the delay interval either negative or neutral distractors (interpersonal scenes from the IAPS (Lang, Bradley, & Cuthbert, 2005) or only a fixation cross (no distraction) were presented. Distractors were pictures from the IAPS which were selected based on arousal and valance ratings in the general population (Lang et al., 2005). Negative pictures depicted scenes of interpersonal violence (e.g., sexual attack, physical assault, beaten/frightened child, physically mutilated body). Neutral pictures included interpersonal scenes with similar complexity (e.g., people at a market place or supermarket) to avoid confounding differences in visual information processing. Trials without distractors (only a fixation cross) were added, as even neutral interpersonal stimuli were found to be perceived as emotionally arousing in individuals with BPD, increasing amygdala activity (Donegan et al., 2003; Krause-Utz et al., 2012; Lis & Bohus, 2013; Niedtfeld et al., 2010, Schulze et al., 2011). Target-present and target-absent trials were equal in all conditions. Conditions were balanced in a pseudo-random manner. In addition, participants performed 15 trials of the basic Sternberg paradigm without distractors (i.e., only a fixation cross) to assess baseline working memory. Software Presentation (Neurobehavioural systems, http://www.neurobs.com/) was used to present stimuli and record behavioral data.

7.2.3. Procedure

The experiment was approved by the local ethics committee (Heidelberg University) and conducted at the CIMH in Mannheim, Germany. All participants received information about the study and scanning procedure, signed written informed consent, and underwent diagnostic and clinical assessment. Then, participants prepared a personalized script of 30sec length together with one experimenter (F.S. and D.W.). Patients assigned to the BPDd group were instructed to report a non-trauma-related autobiographical situation involving dissociation.

BPDn and HC were instructed to report an emotionally neutral every-day situation. A person unknown to participants read scripts aloud recording it on audio tape. During the experiment, participants first practiced 5 trials of the EWMT outside the scanner. Inside the scanner, scripts were presented via headphones. DSS-4 ratings were assessed before and after scripts.

Then participants performed the EWMT (first the 15 trials of the basic Sternberg paradigm, then the EWMT both with and without distractors). Participants were instructed to focus on the middle of the screen but to concentrate on the task only and to ignore distractors. Event-related fMRI data was acquired during ratings, script, and EWMT.

7.2.4. FMRI scan protocol

MRI was conducted using a 3-Tesla Siemens TRIO-Scanner (Siemens, Erlangen). Head cushions and headphones were used to reduce head movement artefacts and scanning noise. Blood oxygen level-dependent (BOLD) signal was measured with 36 3-mm transversal slices covering the entire brain using gradient echo-planar-imaging (EPI) [T2-weighted contrast, field of view=192x192 mm, voxel size=3x3x3 mm^3, voxel matrix=64x64, flip angle=80°, spin echo time=30ms, inter-scan repetition time (TR)=2000ms]. After fMRI, as individual template for functional data a high resolution anatomical scan was acquired using three-dimensional magnetization-prepared-rapid-acquisition-gradient-echo (MPRAGE) [T1-weighted contrast, voxel size=1x1x1 mm^3].

7.2.5. Statistical analysis

Custom statistical software (*SPSS*, Chicago: *SPSS* Inc) was used for manipulation check, behavioral data analysis, and subgroup comparisons. Normal distribution was checked for all variables using the Kolmogorov-Smirnov test. For repeated measurement analysis of variance (rmANOVA) we checked assumptions of variance equality (Levene's tests) and sphericity (Mauchly's test, in case of violations Greenhouse Geisser corrections were applied). Significant effects were followed-up using between-group or paired *t*-tests ($p<0.05$, two-tailed).

7.2.5.1. Manipulation check

A 3x2 rmANOVA with DSS4-scores before and after script as dependent variables (Time as within-subject factor) and Group as between-subject factor was performed to check whether self-reported dissociation significantly changed after script in BPDd (expecting an increase).

7.2.5.2. Behavioral (WM) data

WM data was checked for outliers. Errors were scored as incorrect, too early responses, and misses separately. Percentage of incorrect responses as well as reaction times for correct trials were analyzed using two separate 3x3 rmANOVAs with Group as between-subjects factor and Condition (no distraction vs. neutral vs. negative distractors) as within-subject factor.

Differences in specific error types (wrong responses, too early responses, misses) were evaluated using a multivariate ANOVA (MANOVA) with Group as fixed-factor.
In addition, basic working memory performance (errors, RTs of correct trials) of trials without distraction (basic WM task) was compered between groups using two separate ANOVAs.

7.2.5.3. Fmri data

Functional imaging data was analyzed using standard procedures implemented in the Statistical-Parametric-Mapping package (SPM8, Neurobehavioral systems, Berkeley, CA; http://www.fil.ion.ucl.ac.uk/spm/). EPI time series were preprocessed according to common standards, including slice time correction, spatial realignment, and unwarping to correct for head motion, co-registration onto participants' high-resolution T1 scan, normalization to the standard brain of the Montreal Neurological Institute (MNI) space, and smoothing using a Gaussian kernel with a full width at half maximum (FWHM) of 9mm. Statistical analyses of our event-related design relied upon the general linear model (GLM) to estimate effects of interest (Friston et al., 1995).

7.2.5.4. Region of interest (ROI) and whole-brain (WB) analysis

Single subject level: For each participant, task-related activity was identified by convolving a vector of the onset times of the following seven experimental events of interest with a canonical hemodynamic response: Memoranda, delay intervals (no, neutral, negative distractors), and probes after no, neutral, and negative distractors respectively. The GLM further included nuisance variables to control for movement artifacts.

Group level: To test our a-priori hypothesis of decreased amygdala activity in BPDd, a ROI analysis was conducted using an anatomical mask of the bilateral amygdala (created by the Automated Anatomical Labeling software, AAL (Tzourio-Mazoyer et al., 2002)), smoothed with a cube of voxels of size (FWHM) of 9mm). Values of percent signal change in this region during delay intervals (no vs. neutral vs. negative distractors) were extracted for each participant using the rfxplot toolbox (Glaescher, 2009) and exported to SPSS. Equivalent to the analysis of behavioral data, a 3x3 rmANOVA (between-subject factor: Group, within-subject factor: Condition) was performed. To ensure that group differences were not confounded by basic differences in arousal or WM, we repeated the analysis with arousal ratings as well as WM errors as covariate, using two separate rmANCOVAs.

WB analysis: Consistent with our previous study (Krause-Utz et al., 2012), a Full Factorial Design was used to model effects of group and experimental task. Within this model, we tested for group differences (F-contrast) during negative distractors relative to no distractors. Gaussianized F/T statistic images were determined using a significance threshold of $p<.05$,

Family-Wise-Error (FWE) corrected for multiple comparisons on the voxel-wise level. Based on our a-priori hypotheses, small volume corrections (SVC) with pre-defined anatomical masks of the IFG, mPFC, and ACC (regions of interest) were applied. To follow-up significant WB group effects in subgroup comparisons, parameter estimates were exported to SPSS, and analyzed using between-group *t*-tests ($p<.05$).

7.2.5.5. Psychophysiological interaction analysis (PPI) analysis

The generalized PPI (gPPI) toolbox by McLaren (McLaren et al., 2012) was applied to analyze changes in the correlation of time-series of the amygdala (seed region) with time-series of regions across the whole brain, dependent on our experimental manipulation (Friston et al., 1997; O'Reilly et al., 2012). For the amygdala seed, the same anatomical mask of bilateral amygdala and contrast (negative vs. no distractors) as in the above-mentioned ROI analyses were used. For each participant, mean time series of activity from voxels falling within this anatomical mask were extracted and first-level contrasts for the EWMT conditions were computed. Since PPI analysis of event-related designs lack power (O'Reilly et al., 2012). increasing the probability of false negative results (Type-II-error), we decided to apply a more lenient initial clustering threshold of $p<0.001$, uncorrected on the voxel-wise level (cluster size $k>10$, $Z>3.5$). Yet, only clusters FWE-corrected for multiple comparisons ($p<0.05$) at the cluster level are discussed. PPI beta estimates of significant clusters for negative vs. no distractors (F contrast) were extracted and exported to SPSS. Overall group differences were evaluated in a MANOVA and followed up by post-hoc *t*-tests. To ensure that group differences were not confounded by basic differences in WM, we repeated the same analysis with WM errors as covariate (MANCOVA).

7.3. Results

7.3.1. Dissociation induction

Means with standard deviation of DSS-4 scores are reported in Table 1. Main effects of Time ($F_{(1,43)}=23.01$, $p<.0001$, $\eta^2=.35$) and Group ($F_{(2,43)}=48.57$, $p<.0001$, $\eta^2=.69$) and the interaction effect ($F_{(2,43)}=43.79$, $p<.0001$, $\eta^2=.67$) were significant with higher scores after script than baseline in BPDd ($t_{(16)}=7.57$, $p<.0001$) but not in the other groups ($p>.05$).

7.3.2. Behavioral data

There were no significant group differences in basic WM (errors or RTs in trials without distractors, $p>.05$, data not shown). Figure 7.1 shows means ± standard errors of the mean (SEM) for percentage of incorrect responses (Fig. 7.1a) and RTs of correct trials (Fig. 7.1b) during the EWMT in BPDd, BPDn, and HC.

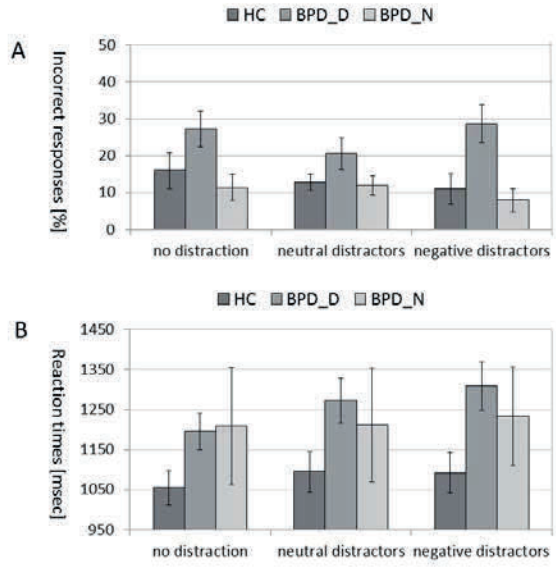

Figure 7.1. Working memory performance during the Emotional Working Memory Task (after no distraction, after neutral distractors, after negative distractors) in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC). Figure A shows means ± standard errors of the mean of percentage of errors. Figure B shows means ± standard errors of the mean of reaction times in correct trials.

7.3.2.1. Errors during the EWMT

The rmANOVA revealed a significant Group effect ($F_{(2,43)}$=4.43, p=.018, η^2=.17) with an overall higher percentage of incorrect responses in BPDd than in BPDn (p=.012) and in HC (p=.019) (see Figure 7.1A).

The MANOVA further indicated that there were significant group differences in the number of misses ($F_{(2,43)}$=6.86, p=.003, η^2=.24), due to more misses in BPDd than in BPDn (p=.001) and in HC (p=.011), as shown in Supplemental Figure S7.1.

7.3.2.2. *Reaction Times during the EWMT*

The rmANOVA revealed a significant Condition effect ($F_{(2,42)}$=4.17, p=.022, η^2=.17) with longer RTs during neutral (p=.019) and negative distractors (p=.003) than during no distractors, but no significant Group effect or interaction effect (both p>.05) (see Figure 7.1B).

7.3.3. *FMRI data*

7.3.3.1. ROI analysis

Figure 7.2 depicts means ± SEM of percent signal change in the bilateral amygdala.

The rmANOVA revealed a significant main effect for Group ($F_{(2,44)}$=5.36, p=.008, f^2=.20) with higher amygdala activity in BPDn than in BPDd (p=.002) and in HC (p=.023). There were no significant differences between BPDd and HC (p>.05). Furthermore, there was a trend for a main effect of Condition ($F_{(2,87)}$=3.21, p=.050, f^2=.13) (interaction effect: p>.05). When including self-reported aversive tension (DSS-4 item) as covariate, group differences remained significant ($F_{(2,44)}$=4.89, p=.012, f^2=.19). Likewise, the rmANCOVA with WM errors as covariate still revealed a significant Group effect ($F_{(2,42)}$=3.43, p=.042, f^2=.14) with higher amygdala activity in BPDn than in BPDd (p=.015) and in HC (p=.043).

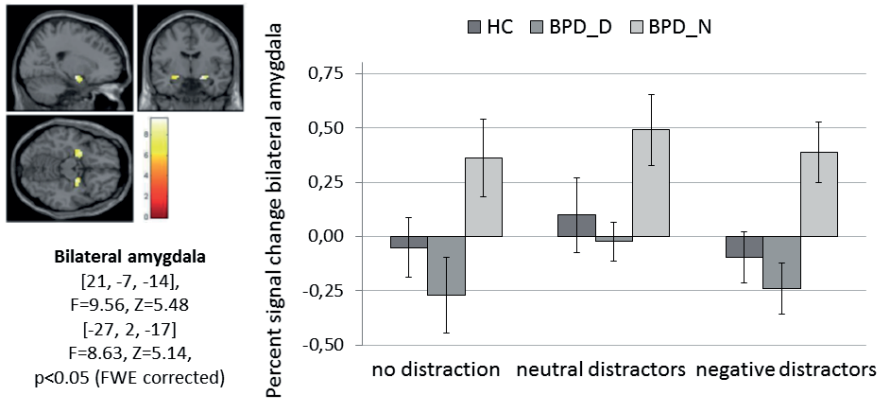

Figure 7.2. Percent signal change in the bilateral amygdala (region of interest analysis) during the Emotional Working Memory Task (no distraction, neutral distractors, negative distractors) in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC). Clusters in the bilateral amygdala, detected by the main effect of task (p<0.05, FWE-corrected on the voxel-wise level) are depicted on the left.

7.3.3.2. Whole-Brain analysis

Results for the main effect of task (F contrast, whole-brain FWE-corrected, p<.05) are presented in Table 7.2. Across all groups, significant activity changes in temporo-limbic regions (amygdala, hippocampus, insula, cingulate gyrus, superior temporal gyrus, fusiform gyrus) and fronto-parietal areas (inferior frontal gyrus, dmPFC, dlPFC, inferior parietal lobule, precuneus, postcentral gyrus) were observed during the EWMT. Significant group differences for brain activity during negative vs. no distractors were found for a cluster comprising left cuneus, lingual gyrus, and posterior cingulate (whole-brain, FWE-corrected, p<.05) and in the left IFG (BA44) and insula (BA13) (after SVC with the IFC mask). Activity in both clusters was significantly stronger in BPDn than in HC.

Furthermore, BPDn showed significantly stronger activity in left cuneus, lingual gyrus, and posterior cingulate than BPDd. In BPDd, there was significantly stronger activity in left IFG than in HC (Table 7.2).

Table 7.2.
Brain activity during the Emotional Working Memory Task (Full Factorial Model)

F Contrast	Brain region (label)	Lobe	Brodman area	k	Peak voxel (X, Y, Z)	F value	Z value	p (FWE)
Main effect of Condition	Fusiform Gyrus	Occipital Lobe	N.A.	6225	30 -58 -14	31.67	Inf	p<0.001
	Fusiform Gyrus	Temporal Lobe	BA 20	6225	36 -43 -20	29.10	Inf	p(<0.001
	Fusiform Gyrus	Temporal Lobe	BA 37	6225	42 -49 -17	28.92	Inf	p<0.001
	Postcentral Gyrus	Parietal Lobe	BA 3	246	-39 -22 52	16.36	7.45	p<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA 6	246	-24 -4 52	12.14	6.31	p<0.001
	Cingulate Gyrus	Limbic Lobe	BA 32	390	-6 11 46	16.11	7.39	p<0.001
	Medial Frontal Gyrus	Frontal Lobe	BA 6	390	-6 -4 55	12.61	6.45	p(<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA 32	390	9 11 49	12.14	6.32	p<0.001
	Insula	Sub-lobar	BA 13	99	-30 23 4	14.92	7.09	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA9	173	-54 8 31	13.44	6.69	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA9	173	-45 5 31	12.51	6.42	p<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA46	173	-48 23 25	7.48	4.68	p=0.029
	Insula	Sub-lobar	BA 13	110	36 20 7	12.22	6.34	p<0.001
	dlPFC	Frontal Lobe	BA 9	104	45 5 31	12.18	6.33	p<0.001
	Putamen	Sub-lobar	Putamen	68	-18 8 -2	12.04	6.29	p<0.001
	Amygdala	Limbic Lobe	Amygdala	68	-27 2 -17	8.63	5.14	p=0.004
	Middle Frontal Gyrus	Frontal Lobe	BA 6	58	30 -4 52	11.06	5.98	p<0.001
	Inferior Parietal Lobule	Parietal Lobe	BA 40	91	-48 -64 40	11.05	5.98	p<0.001
	Putamen	Sub-lobar	Putamen	40	21 8 4	10.83	5.91	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA 47	85	-42 26 -14	10.57	5.82	p<0.001
	Amygdala	Limbic Lobe	Amygdala	65	21 -7 -14	9.56	5.48	p=0.001
	Hippocampus	Sub-lobar	Hippocampus	65	30 -10 -17	9.02	5.28	p=0.002
	Superior Temporal Gyrus	Temporal Lobe	BA 22	8	63 -4 4	8.27	5.00	p=0.007
	Precuneus	Parietal Lobe	BA 7	20	-24 -58 49	8.21	4.98	p=0.008
	Medial Frontal Gyrus	Frontal Lobe	BA 10	9	-3 50 -5	7.89	4.85	p=0.014
	Inferior Frontal Gyrus	Frontal Lobe	BA 46	6	-45 29 16	7.79	4.81	p=0.016
	Superior Temporal Gyrus	Temporal Lobe	BA 38	5	45 20 -23	7.79	4.81	p=0.016
	Hippocampus	Limbic Lobe	Hippocampus	5	-30 -16 -17	7.47	4.68	p=0.029
Main effect of Group (F contrast) negative distractors vs. no distraction	Cuneus	Occipital Lobe	BA18	247	-3 -79 22	13.88	4.63	p=0.031
	Lingual Gyrus	Occipital Lobe	BA19		-15 -61 -5	10.65	3.97	
	Posterior Cingulate	Limbic Lobe	BA30		-15 -64 4	9.34	3.67	
	Inferior Frontal Gyrus	Frontal Lobe	BA9	102	-48 5 28	12.08	4.27	p=.010*
	Inferior Frontal Gyrus	Frontal Lobe	BA44		-54 8 19	11.08	4.07	
	Insula	Sub-Lobar	BA13		-42 11 19	7.92	3.32	

Note: K=cluster size. Z-values were determined by an initial cluster-forming threshold of p<0.05 Family Wise Error (FWE) corrected on a whole-brain voxel-wise level. Clusters detected after small volume correction (p<0.05) are indicated by (*).

7.3.3.3. PPI analysis

Significant group differences were observed for amygdala FC with clusters comprising bilateral fusiform gyrus and culmen, bilateral superior/medial frontal gyrus, bilateral middle frontal gyrus, right superior/middle temporal gyrus (insular cortex), left inferior parietal lobule (insular cortex), left anterior insula, and right cingulate gyrus (p<0.05, FWE-cluster-corrected) as well as right middle occipital gyrus and left claustrum (at p<0.001, uncorrected) (see Table S7.1). HC showed (marginally) negative amygdala FC, while BPD groups showed positive amygdala FC with all of these regions. BPDd differed from HC across all regions (p<0.001), BPDn differed from HC regarding all regions (p<0.05) except for middle occipital gyrus and middle/superior temporal gyrus. Compared to BPDn, BPDd showed reduced FC with left fusiform gyrus (t=2.07, p=.048, Figure 7.3A), while showing a stronger coupling between amygdala and left inferior parietal lobule (t=2.48, p=.020), right superior/middle temporal gyrus (t=2.20, p=.036), and right middle occipital gyrus (t=2.39, p=.024) (see Figure 7.3 B-D).

The MANCOVA with WM errors as covariate revealed similar results, albeit group differences in amygdala FC with left fusiform gyrus were at a trend level ($F_{(1,26)}$=2.25, p=.063) : Compared to BPDn, BPDd still showed a significantly stronger coupling between amygdala and left inferior parietal lobule ($F_{(1,26)}$=5.96, p=.022), right superior/middle temporal gyrus ($F_{(1,26)}$=2.54, p=.046), and right middle occipital gyrus ($F_{(1,26)}$=4.86, p=.034).

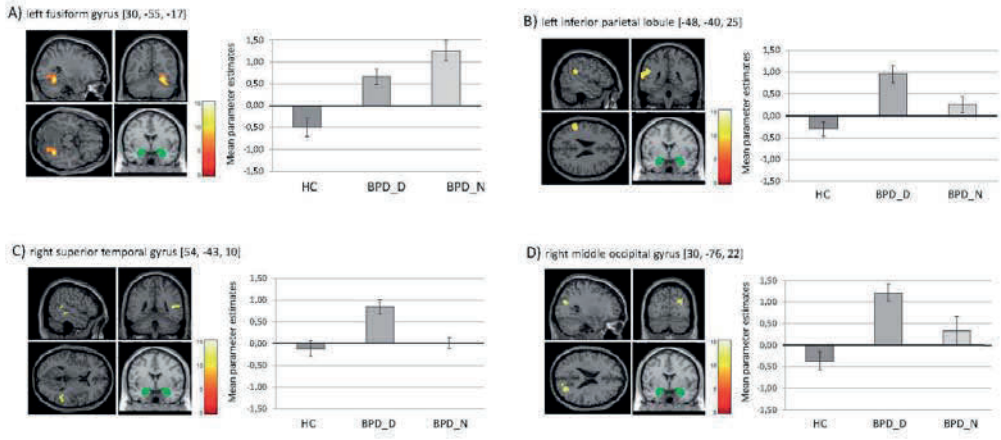

Figure 7.3. Results of the Psychophysiological Interaction analysis for functional connectivity (FC) of the bilateral amygdala seed (depicted in green) during negative distractors versus no distractors in the context of the EWMT in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after neutral script (BPD_N) as well as in healthy controls (HC). The figure shows means ± standard errors of the mean of parameter estimates for amygdala FC with A) left fusiform gyrus, B) left inferior parietal lobule, C) right superior temporal gyrus, and D) right middle occipital gyrus.

7.4. Discussion

This study was aimed at investigating the impact of dissociation on brain activity and amygdala connectivity during emotional distraction in the context of a delay-response WM task in BPD. Using script-driven imagery, dissociation was induced in 17 BPD patients ('BPDd') while 12 patients ('BPDn') and 18 HC were exposed to a neutral script. Afterwards, participants performed an EWMT with negative (trauma-related) vs. neutral interpersonal images vs. no distraction (only a fixation cross). Dampened amygdala reactivity and stronger frontal activity in BPD patients after dissociation induction was expected. Main findings were:

- *Behavioral performance*: Overall WM impairments (more errors, in particular more misses) in BPDd than in the two other groups.
- *Brain activity*: Overall deactivation in the bilateral amygdala and diminished activity in the left cuneus, lingual gyrus, and posterior cingulate during emotional distraction in BPD_D compared to BPD_N; stronger left inferior frontal gyrus activity in BPD_D than in HC.
- *Amygdala FC during negative vs. no distractors:* Compared to the other groups, BPDd showed increased amygdala FC with the left inferior parietal lobule and right superior temporal gyrus, while exhibiting diminished amygdala-fusiform-gyrus connectivity.

The finding of impaired WM in BPD_D is consistent with previous research, pointing to detrimental effects of pathological dissociation on neuropsychological processes, such as learning, memory, attention, and interference inhibition in BPD (Ebner-Priemer et al., 2009; Haaland & Landrø, 2009; Winter et al., 2015).

Consistent with our previous study (Krause-Utz et al., 2012), distractors in the EWMT elicited significant activity changes in brain regions implicated in emotion processing, attention, WM, and interference inhibition. During emotional distraction, significant group differences were observed. BPDn patients exhibited increased activity in amygdala and insula, which is consistent with previous neuroimaging studies (Schulze et al., 2016; van Zutphen et al., 2015). As pointed out before, not all previous studies in BPD replicated the finding of amygdala hyper-reactivity in BPD (see Ruocco et al., 2013). In the current study, increased amygdala activity was only found in BPD patients who did not undergo dissociation induction. Notably, BPD patients after dissociation induction showed dampened amygdala activity compared to BPDn, while they did not differ significantly from HC. As BPD groups were comparable regarding symptom severity, childhood trauma, PTSD comorbidity, anxiety, depressive mood, and basic working memory performance, findings point to a dampening effect of dissociation on amygdala reactivity, as proposed in current models of dissociation (Lanius et al., 2010; Sierra & Berrios, 1998).

During negative vs. no distractors, BPDn further showed significantly stronger activity in the left precuneus and posterior cingulate: brain areas that are important nodes of the default mode network and have been implicated in self-referential processes, such as autobiographical memory and rumination (Buckner et al., 2008; Buckner & Vincent, 2007; Menon, 2011). Decreased activity in these regions may underlie reduced processing of task-irrelevant but probably self-relevant negative social material (reminders of interpersonal violence) in BPD patients after dissociation induction compared to BPDn.

Consistent with previous script-driven imagery studies (Ludäscher et al., 2010; Winter et al., 2015) and largely in line with our hypothesis, BPDd patients showed stronger activity in the left inferior gyrus than HC, although this finding was not specific to BPDd (i.e., increased activity in the inferior frontal gyrus was also found in the BPDn group. As BPDn did not differ significantly in behavioral WM from, stronger recruitment of the inferior frontal gyrus in this group may reflect compensatory efforts to prevent the occurrence of response inhibition deficits (Jacob et al., 2013; van Eijk et al., 2015).

Extending previous research, we used PPI to explore how the amygdala may interact with other brain areas across the brain during negative vs. no distractors. Both BPD groups differed significantly from HC in amygdala connectivity with frontal, temporal, occipital, and parietal areas. HC showed negative amygdala connectivity with these regions, resembling findings of previous fMRI studies using the EWMT or similar cognitive-affective tasks (Anticevic et al., 2010; Krause-Utz et al., 2014d; Mitchell et al., 2008; Oei et al., 2012). In contrast, BPD patients showed positive amygdala connectivity with these areas. Amygdala 'hyper-connectivity' with frontal regions (including ACC and mPFC) during emotional challenges (Cullen et al., 2011; Kamphausen et al., 2013; Koenigsberg et al., 2014; Niedtfeld et al., 2012) and resting-state (Krause-Utz et al., 2014c; Salvador et al., 2016) were previously observed and may reflect disturbed emotion processing in patients with BPD.

Importantly, we observed significant differences in amygdala connectivity between the two BPD groups, dependent on our experimental manipulation: Compared to the other groups, BPD patients exposed to a neutral script showed stronger positive amygdala connectivity with left fusiform gyrus, which points to enhanced encoding/processing of negative social material (Kruschwitz et al., 2015; Molapour et al., 2015). In contrast, BPD patients exposed to the dissociation script showed a stronger coupling of the amygdala with clusters comprising right middle/superior temporal gyrus and left inferior parietal lobule (insular cortex) than the other groups.

The superior temporal gyrus has previously been implicated in depersonalization and derealization (Lanius et al., 2002; Lanius et al., 2005; Simeon et al., 2000) and considered as an important structure in a pathway including the amygdala and PFC, which is implicated in processing of language, social cognition, self-perception (Bigler et al., 2007). In previous studies in BPD, higher self-reported dissociation was correlated to reduced grey matter volume (Niedtfeld et al., 2013) and increased activity in the middle/superior temporal gyrus (Ludäscher et al., 2010). The inferior parietal lobule has been implicated in emotion regulation and working memory (Nicholson et al., 2015). An increased information exchange of the amygdala with these areas may underlie altered emotional and self-referential processing during dissociative states in BPD.

In summary, our neuroimaging findings suggest that a deactivation of the amygdala and altered interactions of this region with areas implicated in self-referential processing, cognitive control, visual perception, and sensory gating may contribute to dissociative states in BPD, while the precise mechanisms underlying the observed neural patterns remain elusive. Dissociative responses may be an adaptive process when 'fight or flight' is impossible (Lanius et al., 2010; Spiegel et al., 2011), possibly stemming from an evolutionary older 'freezing system' (Fanselow & Lester, 1998; Schauer & Elbert, 2010; Zelikowsky et al., 2014, while direct translations from animal to human research are not possible (see Hagenaars et al., 2014)).

The present findings further suggest that dissociation can become maladaptive by hindering a coherent processing of salient sensory, affective, and cognitive information in memory, which is crucial to a flexible adaptation to stressful situations (Lanius et al., 2010; Schauer & Elbert, 2010; Spiegel et al., 2011). Moreover, dissociation might not only dampen negative emotions but also positive emotions, which can have detrimental consequences for the quality of life and the maintenance of close relationships. Given these detrimental effects and previous findings of poor treatment outcome in BPD patients with high dissociative symptoms (Arntz et al., 2015; Kleindienst et al., 2011, 2016; Spitzer et al., 2007), our findings highlight the importance of taking dissociation into account when treating individuals with BPD.

To our knowledge, this is the first study in BPD revealing a significant impact of a dissociation induction on activity and functional connectivity of the amygdala during emotional distraction in the context of the EWMT. Present findings may shed a new light on stress-related dissociation in BPD, as affective-cognitive processing was studied on multiple (subjective, behavioral, neural) levels in an experimental context which requires the conscious manipulation of stressful material in WM. Patient groups were matched regarding psychopathology and basic working memory and it was ensured that BPD_N patients were not dissociated.

However, this led to a relatively small sample size and only female patients with a history of childhood abuse/neglect were included. We did not apply additional drug tests to rule out this possibility of false self-reports of our participants. Furthermore, it is likely that present findings may not be specific to BPD but also observable in other clinical populations with dissociative features, being a trans-diagnostic phenomenon (Lanius et al., 2010, 2012). This means, more research with larger sample sizes, clinical control groups, and extended medical checks is needed to clarify whether the reported neural patterns can be replicated in other samples of BPD patients or are confounded by the afore-mentioned sample characteristics. As we used PPI, findings are restricted to our seed region and causality of interactions remains unknown (Friston et al., 1997; O'Reilly et al., 2012). Tension ratings were significantly higher in BPD_D than BPD_N. Nevertheless, group differences in amygdala reactivity remained significant after including aversive tension as covariate.

All in all, our findings suggest a dampening effect of dissociation on activity in brain areas implicated in the processing of disturbing (trauma-related) information in BPD and an impairing effect on working memory, which plays a crucial role in goal-directed behavior. More research is needed to understand the impact of dissociation on other aspects of emotion regulation, cognition and identity in BPD and to gain more insight into this complex phenomenon.

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Supplemental Material

Table S7.1.
Results of the Psychophysiological Interaction (PPI) Analysis for bilateral amygdala functional connectivity during negative versus no distractors

Label of brain region (aal)	Lobe	Brodman area (BA)	Cluster size	Peak voxel coordinates (X, Y, Z)	F value	Z value	P value
Fusiform Gyrus Fusiform Gyrus Culmen	Occipital Lobe Posterior Lobe Anterior Lobe	N.A. N.A. N.A.	1118	30 -55 -17 -27 -55 -14 39 -52 -29	21.91 18.27 16.99	5.03 4.65 4.50	FWE <0.05
Superior Frontal Gyrus, Medial Frontal Gyrus, Supplemental Motor Area	Frontal Lobe Frontal Lobe Frontal Lobe	BA 6 BA 6 BA 6	457	12 2 70 3 -7 58 -3 5 61	21.36 17.09 16.46	4.97 4.51 4.43	FWE <0.05
Middle Frontal Gyrus Middle Frontal Gyrus	Frontal Lobe Frontal Lobe	BA 6 BA 6	127	42 -4 55 27 -7 64	20.45 9.15	4.88 3.30	FWE <0.05
Inferior Parietal Lobule/ Supramarginal Gyrus Temporal Gyrus (Insular cortex)	Parietal Lobe Parietal Lobe Temporal Lobe	BA 40 BA 13 BA 21	163	-57 -46 22 -48 -40 25 -63 -52 7	14.95 13.45 9.85	4.24 4.03 3.44	FWE <0.05
Precentral Gyrus Middle Frontal Gyrus	Frontal Lobe Frontal Lobe	BA 6 BA 6	76	-42 -4 43 -36 -1 61	14.24 11.05	4.14 3.65	<0.001
Insula Superior Temporal Gyrus	Sub-lobar Temporal Lobe Temporal Lobe	BA 13 BA 38 BA 38	119	39 14 -2 57 5 -8 51 17 -8	13.92 13.89 13.53	4.10 4.10 4.04	(FWE) <0.05
Insula	Sub-lobar	N.A.	16	-33 11 -2	13.12	3.98	(FWE) <0.05*
Claustrum Claustrum	Sub-lobar Sub-lobar	N.A. N.A.	46	-30 11 -5 -27 26 -2	13.72 8.62	4.07 3.20	<0.001
Middle Occipital Gyrus	Occipital Lobe	BA 31	50	30 -76 22	12.26	3.85	<0.001
Superior Temporal Gyrus	Temporal Lobe Temporal Lobe	BA 41 BA 22	34	45 -43 10 54 -43 10	11.91 9.34	3.80 3.34	<0.001
Superior Frontal Gyrus	Frontal Lobe	BA 8	10	-3 32 58	10.83	3.62	FWE) <0.05*
Middle Temporal Gyrus	Temporal Lobe	N.A.	11	51 -34 -5	10.30	3.52	<0.001
Cingulate Gyrus	Limbic Lobe	BA 32	34	6 11 43	13.27	4.01	FWE) <0.05*
Superior Frontal Gyrus	Frontal Lobe	BA 8	10	-3 32 58	10.83	3.62	FWE) <0.05*

Note: Z -values were determined by an initial cluster-forming threshold of $p<0.001$ uncorrected (uncor) on a whole-brain voxel-wise level. FWE = Family Wise Error corrected at a cluster level. Clusters detected after small volume correction (SVC) ($p<0.05$) are indicated by an asterisk (*).

Medication history: *n (%)*	BPD_D (n=17)	BPD_N (n=12)	Chi² tests
Previous medication	13 (76%)	1 (8%)	χ^2=0.37, *p*=.830
Acamprosate	0 (0%)	1 (8%)	
Atypical antipsychotics	1 (6%)	1 (8%)	
BZD	2 (12%)	2 (17%)	χ^2=6.21, *p*=.400
SNRI	3 (18%)	1 (8%)	
SSRI	6 (35%)	3 (18%)	
TCA	1 (6%)		
Time of last medication[1]			
1 month ago	3 (18%)	1 (8%)	
≥ 3 month ago	2 (12%)	1 (8%)	χ^2=4.76, *p*=.190
≥ 6 month ago	2 (12%)	6 (50%)	
≥ 12 month ago	4 (24%)	1 (8%)	

Note: BPD_D= patients with Borderline Personality Disorder exposed to a dissociation script, BPD_N= patients with Borderline Personality Disorder exposed to a neutral script, BZD= Benzodiazepine, SSRI=Selective serotonin re-uptake inhibitor, SNRI=Serotonin–norepinephrine reuptake inhibitor, TCA= Tricyclic antidepressant, [1] information in 2 BPD_D patients was missing

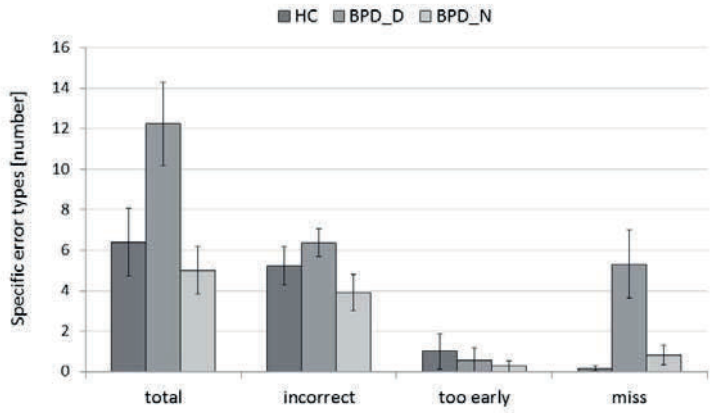

Figure S7.1. Specific types of errors (total number of too early responses (before probe) and misses) during the Emotional Working Memory Task in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC).

Chapter 8

General discussion

CHAPTER 8

General discussion

8. General Discussion

Dissociation, difficulties in emotion regulation, and cognitive disturbances are among the devastating consequences of interpersonal trauma; the combination of these features is highly typical for BPD (Brand & Lanius, 2014; Crowell et al., 2009). In this thesis, associations between dissociation and altered neural patterns in networks relevant to affective-cognitive processing were investigated under resting-state and during emotional distraction in female BPD patients with interpersonal trauma history compared to healthy controls. In the following sections, previous chapters of this thesis are briefly summarized and findings are discussed in the context of earlier research. Afterwards, limitations and strengths of this research are addressed and implications for future research and the clinical setting are discussed.

8.1. Summary

As described in Chapter 1, emotion dysregulation is considered to be at the core of BPD (Schmahl et al., 2014) and typically co-occurs with behavioral disinhibition and dissociative experiences in patients with the disorder (Crowell et al., 2009). Increased and prolonged reactivity to salient emotional stimuli seems to have detrimental effects on goal-directed behavior in BPD (Winter et al., 2014). Previous studies found a hypervigilance towards negative words in the Emotional Stroop Task (EST) (Kaiser et al., 2016) and towards salient social scenes in the Emotional Working Memory Task (EWMT), resulting in impaired performance in patients with BPD compared to healthy controls (Krause-Utz et al., 2012; Prehn et al., 2013). As a remaining key question, the present thesis investigated how dissociation influences the neural processing of emotional distraction during the EST and EWMT in BPD.

8.1.1. Previous neuroimaging research in BPD (Chapter 2)

Previous neuroimaging research in BPD has provided ample evidence for altered structure and function in a network of fronto-limbic brain regions, including the amygdala, hippocampus, insula, ACC, mPFC, OFC, and dlPFC, among others (Krause-Utz et al., 2014b; New et al., 2012; van Zutphen et al., 2015). It has been proposed that a hyper-reactivity of the amygdala may be central to the understanding of disturbed emotion processing in BPD (Herpertz et al., 2001). Imbalanced interactions between a hyperactive ‘bottom-up emotion-generating’ limbic system (including the amygdala) and diminished recruitment of cortical control regions (ACC, mPFC, OFC, dlPFC, among others) may underlie emotion dysregulation, such as increased sensitivity and hyper-reactivity to emotional stimuli in BPD (Mauchnik & Schmahl, 2010).

This assumption has been supported by a recent meta-analysis of neuroimaging studies on affective reactivity in BPD (Schulze et al., 2016), while an earlier meta-analysis had pointed to reduced amygdala reactivity (Ruocco et al., 2013) and some studies found no differences in amygdala activity between BPD patients and healthy controls (Guitart-Masip et al., 2009). Given the complexity and heterogeneity of BPD symptoms and methodological discrepancies in previous research, it is conceivable that amygdala hyper-reactivity is only present in certain subgroups of patients, e.g., in unmedicated samples (see Schulze et al., 2016) or in traumatized groups: volumetric and functional abnormalities in fronto-limbic regions were also found in individuals with traumatic childhood experiences who did not develop a disorder (Dannlowski et al., 2012; Gilbert et al., 2009) and are not specific for BPD, but also observed in other stress-related disorders, such as PTSD and depression (Morey et al., 2009; Wang et al., 2008). Moreover, stress-related dissociation, which is closely linked to emotion dysregulation, may substantially modulate activity in cortico-limbic brain regions in individuals with BPD (Barnow et al., 2012; Ebner-Priemer et al., 2005, 2009), as discussed below.

8.1.2. Neurobiological models of dissociation (Chapter 3)

Dissociation in itself is a very complex phenomenon (Spiegel et al., 2011). In Chapter 3, current conceptualizations of dissociation and neuroimaging research in dissociative disorders were described, discussing possible implications for BPD. The 'cortico-limbic disconnection model' by Sierra and Berrios (1998) suggests that increased prefrontal inhibition of amygdala activity may underlie dissociative symptoms of subjective detachment, comparable to a shutting down of the affective system. In a similar vein, Lanius and colleagues (2010) proposed that increased activity in dorsal/rostral ACC and mPFC and dampened activity in the amygdala and insula underlies the dissociative subtype of PTSD: the opposite pattern of neural activity associated with "emotion under-modulation" (p. 640). As discussed in Chapter 3, fMRI research in BPD aimed at studying the impact of dissociation on limbic and frontal activity during the processing of emotional and cognitive information is still relatively rare and previous findings are mixed.

8.1.3. Present neuroimaging studies (Chapters 4 - 7)

In the first part of the neuroimaging research, described in this thesis, associations between self-reported dissociation and changes in functional connectivity of the amygdala and ACC were examined during resting-state (Chapter 4) and during the EWMT (Chapter 5). The second part of this neuroimaging research combined script-driven imagery with the EST (Chapter 6) and the EWMT (Chapter 7) to experimentally investigate the effect of acute dissociation on emotional distraction in BPD. Table 8.1 summarizes sample characteristics (sample sizes, major comorbidities), methods, and key results of these neuroimaging studies.

Table 8.1. *Methodological characteristics and results of the neuroimaging studies in this thesis*

Neuro-imaging Study (Chapter)	**Sample** Groups (*n*), trauma history, comorbidities	**Methods** Technique, seed regions, tasks and measures	**Summary of key findings**	
			General findings	Findings related to dissociation
Study 1 (Chapter 4)	• BPD (*n*= 20), HC (*n*= 17) • Unmedicated patients • All patients had a history of inter-personal trauma, 9 patients had current PTSD	• Resting-state fMRI • Seed-based correlations for amygdala (medial temporal lobe), dACC (salience network) and vACC (default mode network). • Dissociative Experience Scale	In patients with BPD: • Stronger positive amygdala RSFC with dorsal insula, OFC, putamen. • Diminished anti-correlations of dACC with PCC • Increased negative vACC RSFC with occipital cortex	Trait dissociation (scores on the Dissociative Experience Scale) positively predicted amygdala RSFC with dlPFC and negatively predicted amygdala RSFC with cuneus and fusiform gyrus
Study 2 (Chapter 5)	• BPD (*n*= 22), HC (*n*= 22) • Unmedicated patients • All patients had a history of inter-personal trauma, 9 patients had current PTSD	• Event-related fMRI during an EWMT. • Psychophysio-logical Interaction (PPI) analysis with amygdala (medial temporal lobe) and dACC (salience network) as seeds • Dissociation Stress Scale (DSS)	During emotional distraction, BPD patients showed • stronger positive amygdala FC with hippocampus, associated with longer RTs • stronger dACC FC with left insula, superior temporal gyrus, PCC	In the BPD group, dissociative states positively predicted amygdala FC with left insula, left precentral gyrus, right thalamus, and right ACC during emotional distraction
Study 3 (Chapter 6)	• 18 BPDd: dissociation induction, 19 BPDn; neutral script, 19 HC • Unmedicated • Comorbid PTSD / depression (BPDn: n=7 / n=1, BPDd: n=8 / n=2)	• Task-related fMRI during an EST (with negative, neutral, and positive words). • Script-driven imagery to induce dissociation • DES and DSS at baseline, before EST, within EST and after EST.	• BPD patients after dissociation induction showed overall task impairments and longer reaction times for negative vs. neutral words. • BPDd exhibited less overall activity in the fusiform gyrus and in inferior parietal and temporal cortices, and increased activity in the inferior frontal gyrus and dlPFC to negative words than BPDn • BPDn showed stronger activity in superior temporal gyrus for positive and negative vs. neutral words than HC.	
Study 4 (Chapter 7)	• 17 BPDd: dissociation induction, 12 BPDn: neutral script, 18 HC • Unmedicated patients • Trauma history, 5 BPDn and 7 BPDd with PTSD	• Event-related fMRI during the EWMT • Script-driven imagery to induce dissociation • PPI with amygdala as seed region of interest • DES and DSS at baseline, after script and EWMT	Patients after dissociation induction showed • Overall behavioral impairments • Deactivation in the bilateral amygdala across all conditions, and lower left cuneus, lingual gyrus, and PCC activity during negative distractors than BPDn • Increased inferior frontal gyrus activity than HC • Stronger coupling of bilateral amygdala with right superior/middle temporal gyrus and left inferior parietal lobule • Diminished coupling of amygdala with fusiform gyrus than BPDn.	

8.2. Integration and discussion of present findings

Findings of the studies, summarized in Table 8.1, point to a detrimental effect of dissociation on cognitive performance. Altered interactions of the amygdala with brain regions involved in cognitive control, emotion regulation, visual perception, and self-referential processing might underlie disturbed emotion processing and stress-related dissociation in BPD. In the following, behavioral results and neuroimaging findings are integrated and discussed in the context of previous research.

8.2.1. Behavioral findings in BPD

Both script-driven imagery studies, described in Chapter 6 and Chapter 7, consistently revealed impaired behavioral performance in BPD patients who underwent dissociation induction. In the EST, patients exposed to a dissociation script (BPDd) were less accurate and slower than the other comparison groups. In addition to these overall impairments, significantly longer reaction times for negative words than for neutral words were found in BPD patients after dissociation induction. These results remained significant after controlling for early childhood traumatization, depressive mood, anxiety, and acute tension. While dissociation impeded cognitive performance, no significant behavioral differences were found between BPD patients exposed to a neutral script (BPDn) and healthy controls. While some earlier studies also did not find significant deficits in the EST (Sprock et al., 2000; Domes et al., 2006; Minzenberg et al., 2008; Wingenfeld et al., 2009b), a recent meta-analysis by Kaiser and colleagues (2016) points to a bias for negative words in BPD, which is most pronounced for self-relevant words (BPD-salient words or individualized words) in patients with the disorder compared to healthy controls (see also Arntz et al., 2000; Sieswerda et al., 2007; Wingenfeld et al., 2009a). In the current study, standardized emotional (negative and positive) words were used as distractors. The absence of behavioral deficits in BPD patients without dissociation induction may therefore, in part, be explained by differences in task malterial and sample characteristics (e.g., relatively small sample size).

In the EWMT, BPD patients exposed to a dissociation script were significantly less accurate, regardless of distractor-valence, than the two comparison groups, confirming findings of the previous study (Chapter 6). A follow-up analysis indicated that this impaired accuracy was due to a higher number of omitted responses (misses). A possible explanation for the lack of a valence-specific effect is that neutral distractors (interpersonal pictures) in the EWMT are not entirely neutral for BPD patients (Krause-Utz et al., 2012). Furthermore, negative distractors were highly arousing pictures of interpersonal violence, which might have induced emotional distress, given the high rates of interpersonal trauma in this patient group.

It has been shown that dissociative states linearly increase with the level of subjective arousal in patients with BPD (Stiglmayr et al., 2001, 2008). Therefore, it is conceivable that the EWMT did not only induce distress (arousal) but also dissociative symptoms in BPDd, which might have affected both cognitive control and motor control. Extremely high levels of stress and dissociation can result in a freezing response (Frewen & Lanius, 2006; Lanius et al., 2010; Roelofs, 2017), which might explain the high number of omitted responses in BPDd across all EWMT conditions. When including subjective arousal as statistical covariate in the analysis, group differences remained significant, suggesting that these effects can not solely be explained by higher stress levels in the BPDd group. Nonetheless, further studies should investigate the role of stress hormones in this relationship, as discussed in more detail below (sections 8.3.). Resembling findings of the other script-driven imagery study (Chapter 6), no significant differences in working memory performance after emotional distraction were found in BPD patients who did not undergo dissociation induction compared to healthy controls. Discrepancies to previous research (Krause-Utz et al., 2012., 2014a; Prehn et al., 2012) may be explained by the small sample size, which limited the statistical power to detect significant differences. Several patients in the BPDn group had to be excluded, because they reported a significant increase of dissociative symptoms after the script or after the EWMT and therefore did not match the inclusion criterion for this comparison group. Studies with larger sample sizes are needed to clarify whether working memory impairments after emotional distraction can be found in both dissociative patients and BPD patients without acute dissociation.

All in all, the afore-mentioned findings are largely consistent with previous research, pointing to detrimental effects of pathological dissociation on neuropsychological processes, such as memory and attention (Bremner et al., 1998; Brewin et al., 1996; Ebner-Priemer et al., 2009; Elzinga et al., 2003; Haaland, & Landrø, 2009; Van der Kolk et al., 1996; Winter et al., 2014). Additional evidence for difficulties suppressing neutral and emotional distractors in participants with high proneness to dissociative experiences stems from previous research in non-clinical samples (Freyd et al., 1998; DePrince and Freyd, 1999; Elzinga et al., 2000; Chiu et al., 2010; Chiu et al., 2012). As pointed out before, however, findings of enhanced attention and memory in patients with high trait dissociation were also reported (Chiu et al., 2009; de Ruiter et al., 2004; Elzinga et al., 2007). Therefore, it remains an important topic for future research to identify factors that may moderate or mediate the effects of dissociation on cognitive functioning, and to clarify whether these are disorder-specific or trans-diagnostic effects.

8.2.2. Neuroimaging findings in BPD

Overall, neuroimaging findings, summarized in Table 8.1 may help to extend the knowledge and understanding of possible neural underpinnings of BPD, described in Chapters 2 and 3. Alterations in the amygdala (medial temporal lobe network), salience network, and default mode network may underlie key features of the disorder, such as emotion dysregulation, disturbed self-referential processing (enhanced retrieval of autobiographical memories, instable self-image), deficits in inhibitory control, and dissociation.

Also without external symptom provocation, BPD patients showed altered RSFC in the default mode network (increased negative vACC connectivity with occipital cortex, lingual gyrus, and cuneus) and in the salience network (diminished dACC-PCC connectivity). Present findings of aberrant RSFC of these seeds with brain regions mainly located in the medial PFC, insula, and occipital cortex are largely in line with previous RS-fMRI studies, as discussed in a recent meta-analysis by Visintin, De Panfilis, Amore, Balestrieri, Wolf, and Sambataro (2016). While psychotropic medication may have confounded other resting-state findings in BPD (Wolf et al., 2011; Doll et al., 2013), only medication-free patients were included in the present study. As a novel finding, a stronger coupling of the amygdala with a cluster comprising the dorsal insula, orbitofrontal gyrus, and putamen was found in patients with BPD, possibly underlying altered emotion processing already in the absence of external emotional challenge. Confirming this finding, increased positive amygdala RSFC with frontal areas was recently detected in a larger sample of BPD patients (n=60), based on different assessment and analysis techniques (Salvador et al., 2016, as discussed in Krause-Utz & Schmahl, 2016). Of note, in the present study, self-reported trait dissociation predicted amygdala RSFC in BPD (see section 8.2.3).

Alterations in the amygdala (medial temporal lobe) network, salience network, and default mode regions were also observed during emotional distraction, i.e., for negative vs. neutral interpersonal IAPS in the EWMT (Chapter 5). In both BPD patients and healthy controls, emotional distraction was associated with a disrupted coupling of the amygdala with inferior frontal gyrus and a cluster in the dlPFC, suggesting a reduced information exchange between areas, previously implicated in emotional distraction (Banich et al., 2009; Dolcos et al., 2006, 2007, 2008; Dolcos & McCarthy, 2006; Krause-Utz et al., 2012; Mitchell et al., 2008; Oei et al., 2012; Perlstein et al., 2002). Compared to healthy controls, BPD patients demonstrated hyper-connectivity in the medial temporal lobe (increased amygdala-hippocampus connectivity), salience network (increased dACC-insula connectivity), and a stronger coupling of the dACC with nodes of the default mode network, such as the PCC.

It has been suggested that the salience network plays an important role in switching between large-scale networks (Goulden et al., 2014; Sridharan et al., 2008) and diminished anti-correlations between the dACC (a key node of the salience network) and nodes of the default mode network (PCC) were also observed in the RS-study (Chapter 4) and other previous studies in BPD (Doll et al., 2013; Kluetsch et al., 2012). In this context, the altered coupling between the dACC and PCC may point to impaired flexibility in switching between states of alertness and states of rest in BPD. During the EWMT (Chapter 5), BPD patients further demonstrated a stronger coupling of both the amygdala seed and the ACC seed with a cluster in the right dmPFC, which plays a role in attention and self-referential processing, among others (Ramnani & Owen, 2004; Reynold et al., 2006; Burgess et al., 2007; Koechlin & Hyafil, 2007). Stronger amygdala connectivity with the afore-mentioned areas (dmPFC, dlPFC, and parahippocampal gyrus) was associated with longer reaction times after emotional distraction, a behavioral measure of distractibility. Interestingly, increased positive amygdala with clusters in the dlPFC and dmPFC was also found in the study, described in Chapter 7. In this study, both BPD groups (irrespective of dissociation induction) showed increased positive amygdala with bilateral superior and medial frontal gyrus, bilateral middle frontal gyrus, and right cingulate gyrus during emotional distraction, while healthy participants showed marginally negative amygdala connectivity with these regions. Confirming findings of previous studies (Cullen et al., 2011; Kamphausen et al., 2013; Koenigsberg et al., 2014), amygdala hyper-connectivity with frontal regions (e.g., ACC, mPFC, dlPFC) may underlie disturbed emotion processing, including difficulties ignoring task-irrelevant but possibly self-relevant information in BPD. Importantly, amygdala connectivity with fusiform gyrus, right superior temporal gyrus, and left inferior parietal lobule differed significantly between BPD groups, dependent on the experimental induction of dissociation, as addressed in more detail in the next section.

8.2.3. The role of dissociation in altered brain function in BPD

Both in the absence of experimental stimulation (Chapter 4) and during the EWMT (Chapters 5 and 7), self-reported levels of dissociation were significantly associated with alterations in amygdala connectivity. The reduced coupling of the amygdala with occipital regions, observed during resting-state, might point to an altered processing of sensory input in patients with more frequent dissociative experiences. Patients who reported more dissociative traits further showed stronger positive amygdala RSFC with the dlPFC during resting-state (Chapter 4). In line with this, a stronger coupling of the amygdala with frontal regions (among others) was found in patients who reported an increase of state-dissociation after the EWMT (Chapter 5).

More specifically, patients who experienced a stronger increase of dissociation during the EWMT showed a stronger coupling of the amygdala with the ACC, precentral gyrus, insula, and thalamus. These areas have been implicated in emotion regulation, visual and bodily perception, voluntary control of movements, and sensory gating. For instance, a previous study in BPD suggests a significant link between increases in amygdala-insula connectivity and faster habituation to the repeated presentation of negative IAPS pictures (Koenigsberg et al., 2014). Increases in amygdala-dlPFC connectivity were further linked to better emotion down-regulation during amygdala-targeted neurofeedback training in BPD (Paret et al., 2016). Furthermore, the ACC, insula, and thalamus have been critically implicated in neurobiological models of dissociation (Bremner, 2006; Krystal et al., 1996; Lanius et al. 2010; Sierra & Berrios, 1998, as described in Chapter 3). It is therefore conceivable that altered amygdala functional connectivity with these regions reflects altered emotion processing in patients with acute dissociative symptoms. However, the precise processes underlying the above-mentioned functional connectivity patterns remain unclear.

To more directly investigate the effect of dissociation on amygdala connectivity during emotional distraction, the EWMT was combined with script-driven imagery (Chapter 7). Significant group differences were found for activity in the left inferior frontal gyrus and for a cluster comprising the left cuneus, lingual gyrus, and PCC: while activity in the inferior frontal gyrus was increased in both BPD groups compared to healthy controls, activation in the cuneus, lingual gyrus, and PCC was significantly stronger in BPD patients who did not undergo dissociation induction compared to the other groups. A region of interest analysis of the amygdala revealed stronger activity in BPD patients without dissociation compared to healthy controls, which is in line with findings of the current meta-analysis by Schulze and colleagues (2016). Yet, patients who underwent dissociation induction showed a deactivation in the amygdala during all conditions of the EWMT. Moreover, the coupling of the amygdala with superior temporal gyrus and inferior parietal lobule during emotional distraction was significantly stronger in these patients (BPDd). The superior temporal gyrus and inferior parietal lobule have been implicated in various functions, including attention and working memory (LaBar et al., 1999; Ravizza et al., 2004; Schultz & Lennert, 2009; Todd & Marois, 2004), language processing (Majerus et al., 2006; Simon et al., 2002), sensory-motor coordination (Grefkes & Fink, 2005; Sakai et al., 2002), and the encoding of complex social scenes (Machielsen et al., 2000; Meng et al. 2012). Altered activity in the superior temporal gyrus was also observed patients with high dissociation, such as depersonalization disorder (Simeon et al., 2000) and D-PTSD (Lanius et al., 2005).

Patients exposed to a dissociation script further showed reduced amygdala connectivity with the fusiform gyrus (Chapter 7), resembling findings of the afore-mentioned RSFC study, in which lower amygdala-fusiform-gyrus RSFC was associated with higher trait dissociation (Chapter 4). The fusiform gyrus plays an important role in the processing of complex social information (Kruschwitz et al., 2015; Molapour et al., 2015). Present findings may therefore point to a significant impact of dissociation on the processing of task-irrelevant but possibly self-relevant social material in BPD.

Findings of the study, described in Chapter 6, provide additional insights into altered neural activation patterns during cognitive inhibition of task-irrelevant cues, which might be affected by dissociation. Unlike patients in the neutral script condition, BPD patients exposed to a dissociation script did not show enhanced recruitment of occipital regions during the EST. Increased activity in occipital areas (in the absence of behavioral deficits) may reflect increased recruitment of attentional resources during the anticipation of emotional stimuli in patients exposed to the neutral script (Hopfinger et al., 2000; Kelly et al., 2008; Koenigsberg et al., 2009a; Rauss et al., 2009; Scherpiet et al., 2014). In contrast, patients exposed to a dissociation script showed reduced overall activity in the fusiform gyrus and inferior temporo-parietal cortices as well as increased activity in the inferior frontal gyrus and dlPFC for negative words than the BPDn group. As mentioned above, these areas (dlPFC, fusiform gyrus, inferior frontal gyrus, inferior parietal and temporal cortices) were also associated with altered amygdala functional connectivity in Chapters 4, 5, and 7. Moreover, increased activity in the left inferior frontal gyrus in patients exposed to a dissociation script was also found during the EWMT (Chapter 7) and in the previous script-driven imagery study by Ludäscher and colleagues (2010). The inferior frontal gyrus has been associated with interference inhibition, language processing, emotion recognition, and mentalizing, among others (Aron et al., 2014; Geier et al., 2009; Grahn et al., 2009; McGaugh, 2004; Seger et al., 2005). Moreover, previous research revealed altered activity in this area in samples with high dissociation, such as patients with D-PTSD (Lanius et al., 2005). A discrepancy between the two script-driven imagery studies was that associations between dissociation and amygdala activation were only observed for the EWMT (Chapter 7) but not for the EST (Chapter 6). Likewise, in previous research, negative correlations between dissociative symptoms and amygdala activity were only found for the presentation of negative IAPS pictures (Hazlett et al., 2012; Krause-Utz et al., 2012) but not for emotional words during the EST (Wingenfeld et al., 2009b) or painful stimulation (Kraus et al., 2009; Krause-Utz et al., 2015). It remains unclear whether distractor material (e.g., pictures versus words) plays an important role in this relationship.

Studying the association between dissociation and amygdala reactivity to emotional stimuli in BPD may have important implications for neurobiological conceptualizations of the disorder, as amygdala hyper-reactivity is currently assumed to be a general key feature of the disorder (Herpertz et al., 2001; see Krause-Utz et al., 2014b; Schulze et al., 2016).

All in all, there is primary evidence for reduced activity in limbic (amygdala, posterior cingulate), temporal (inferior and superior temporal gyrus, fusiform gyrus), parietal (inferior and superior parietal lobe), and occipital areas (cuneus, fusiform gyrus, lingual gyrus), and increased activity in frontal areas (inferior frontal gyrus, dlPFC) in BPD patients with high dissociation. Figure 8.1 depicts an overview of these brain regions.

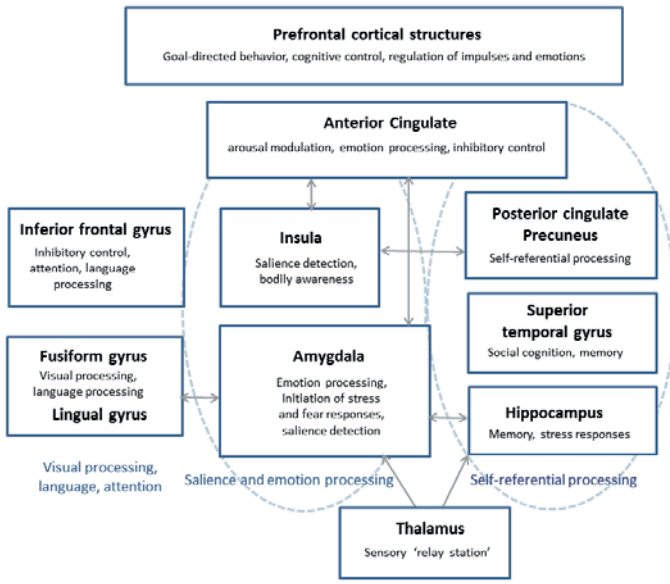

Figure 8.1. This figure depicts a schematic overview of brain regions, which may play a role in dissociation in BPD. While the precise neurobiological underpinnings of dissociation remain elusive, there is evidence for altered activity within brain networks involved in emotion processing and memory (e.g., amygdala, hippocampus, insula), self-referential processes (PCC, precuneus, superior temporal gyrus), and cognitive control (e.g., dlPFC, inferior frontal gyrus, ACC).

BPD patient groups were matched for age, education, basic working memory, trauma history, comorbid PTSD, BPD symptom severity, depression, anxiety, and initial dissociation and tension ratings, which might have confounded the results. All in all, the current findings may deepen the understanding of stress-related dissociation in BPD, while the precise processes underlying the above-mentioned activity and connectivity patterns remain unclear.

For instance, more research is needed to clarify whether these patterns reflect enhanced attempts to modulate states of arousal, as suggested by previous neuroimaging research in the dissociative subtype of PTSD (Lanius et al., 2010). It may very well be that patients who are more prone to experience dissociation already show reduced processing of emotions (alexithymia) or a so-called "over-modulation" of emotions (Lanius et al., 2010), which may account for the current findings. Likewise, way more research is needed to dismantle the effect of induced dissociation on executive functioning, such as learning and memory. General limitations of the present research are discussed below.

8.3. Strength and limitations

To the author's knowledge, neuroimaging research described in this thesis is the first to combine script-driven imagery with affective-cognitive tasks (EST, EWMT) to experimentally investigate the effect of dissociation on the neural processing of emotional distraction in BPD. Studying this relationship on a behavioral and neural level might help to shed more light on the stress-related dissociation in BPD. Patient groups were medication-free and all groups were matched for demographic variables, basic working memory, and other variables that may have accounted for the observed effects (see above). Yet, the present findings need to be interpreted in the light of several limitations, which are addressed in the following.

8.3.1. Sample characteristics

A general limitation of all studies, described in this thesis, is that no clinical control groups were included. Therefore, it remains unclear whether findings are specific to BPD. All patients reported a history of interpersonal trauma and comorbidity with PTSD was relatively high in all studies. In the study, described in Chapter 6, three patients (BPDn: n=1, BPDd: n= 2) had comorbid depressive disorder. Although being representative for clinical groups of BPD patients, the presence of these comorbidities and trauma history might have affected the results (see Krause-Utz & Schmahl, 2010). Moreover, no specific diagnostic instrument other than the DES (e.g., SCID-D), was used to identify the presence of comorbid dissociative disorders. Therefore, it remains unclear whether the present findings are related to comorbid trauma-related or dissociative disorders or to dissociative symptoms as a trans-diagnostic phenomenon rather than to BPD psychopathology. As pointed out before, alterations in cortico-limbic areas and in the default mode network were also reported in PTSD and depression (Daniels et al., 2010; Morey et al., 2009; Rabinak et al., 2011; Shin et al., 2002; Stripada et al., 2012).

Likewise, alterations in the inferior frontal gyrus, cuneus, fusiform gyrus, lingual gyrus, PCC, and superior temporal gyrus were also found in depersonalization disorder (Lemche et al., 2016; Simeon et al., 2000) and in D-PTSD (Lanius et al., 2002, 2005; Tursich et al., 2015). Current findings did not change when differentiating between BPD patients with vs. without comorbid PTSD (Chapter 4) and in post-hoc analyses controlling for childhood trauma (Chapter 6). Nevertheless, future studies investigating similar research questions should include clinical controls, such as trauma-exposed healthy controls and patients with trauma-related and dissociative disorders to clarify whether the afore-mentioned findings are specific for BPD. Furthermore, results cannot be generalized to male patients, as only female patients were included. Strict exclusion criteria (medication, substance abuse, lifetime bipolar and psychotic disorder, etc.) and matching of BPDn and BPDd groups with regard to clinical variables impeded the recruitment and led to relatively small sample sizes, which limited the statistical power to detect effects. Thus, research with larger sample sizes is needed to replicate the results.

8.3.2. Task-characteristics

To investigate interference inhibition, modified versions of the EST and EWMT were used. These tasks may not be directly comparable, as they involve different executive functions. The EST requires a continuous comparison of simultaneously presented information: the color of words has to be compared to their content. In the EWMT, participants are instructed to maintain task-relevant information in working memory for later recognition, which involves a comparison of stimuli sets. The tasks also differ with respect to distractor material. The EWMT includes highly arousing trauma-related images, while the EST involves both generally negative and positive words. Moreover, as pointed out before, neutral distractors in the EWMT were probably not completely neutral for patients with BPD. Future studies should investigate the role of distractor material, i.e., compare pictures vs. words vs. sounds vs. somatosensory stimulation, when investigating the impact of dissociation on emotional interference inhibition.

For the EWMT, a cognitive load of 3x3 letters was used. Since task difficulty may have an impact on measures of emotional distractibility (Holtmann et al., 2013; Oei et al., 2006, 2010), future studies should manipulate the cognitive load to test whether this has a substantial impact on working memory performance after dissociation induction in BPD.

Aside from these task characteristics, it remains unclear whether the current tasks (especially trauma-related scenes in the EWMT) induced traumatic re-experiencing. Likewise, exposure to the dissociation scripts might have induced traumatic memories, even though only trauma-unrelated situations were selected for creating these scripts.

Future script-driven imagery studies should therefore assess the frequency and intensity of intrusions (traumatic re-experiencing) in addition to the levels of state dissociation. Moreover, it remains an important topic for future research to examine whether dissociative states experimentally induced via script-driven imagery and assessed by the DSS-4 (Stiglmayr et al., 2001; 2009) correspond to naturally occurring dissociation in every-day life.

8.3.3 Neuroimaging data analysis techniques

Since complex processes, such as emotion processing and dissociation, probably involve complex interactions within and between large-scale brain networks, seed-based correlation analyses were applied to examine functional connectivity patterns in Chapter 4, 5, and 7. Importantly, this is only one possible way to examine functional connectivity and new methods are still evolving (Nichols et al., 2017). While seed-based analyses are well-suited to address hypothesis-driven questions, results are inherently limited to these a-priori chosen regions of interest and can therefore differ dependent on the selection of these seeds (e.g., whether they are based on pre-defined anatomical masks, previous literature or present functional results). Moreover, network abnormalities that are not associated with one of these seeds might go unobserved and may be better captured by data-driven clustering methods, such as ICA. On the other hand, results of data-driven clustering methods can also differ, dependent on the estimation algorithm, selection and number of dimensions, or decisions about the type of scaling. Given these general concerns about robustness and reproducibility of neuroimaging findings, large-scale meta-analyses, including original data sets and software, are needed to tease apart robust results from false-positive findings (Nichols et al., 2017). While the risk of Type I error should be balanced against the risk of revealing false negative results and missing out relevant findings (Type II error) (Lieberman & Cunningham, 2009; Nichols et al., 2017), uncorrected findings need to be interpreted with caution (Eklund, Nichols, & Knutsson, 2016). In Chapters 4 and 7, corrections for multiple comparisons were applied, while in the other chapters, uncorrected results were reported, indicating which results survive FWE correction. These uncorrected findings concern brain regions that have previously been identified as being highly relevant for BPD and dissociation and therefore appear worthwhile to be reported and discussed here in order to stimulate future research. Nonetheless, these findings need to be interpreted with caution and have to be replicated in studies with larger samples and stricter thresholds. In general, BOLD measurements of the amygdala are susceptible to physiological confounds due to its proximity to draining veins, which may be particularly problematic for the analysis of resting-state data. In the present RS-fMRI study, global signal regression (GSR) was used to remove variance associated with these confounding signal sources.

GSR has been proven successful in dealing with physiological artifacts and increasing specificity. However, GSR may also introduce anti-correlations in functional connectivity analyses and promote the detection of group differences, which are actually not there (Fox & Raichle, 2007; Murphy et al., 2009; Saad et al., 2012). Therefore, general risks of this method should be noted, even though analyses with and without GSR revealed highly similar results in the present RS-fMRI study.

8.4. Implications for future research

As pointed out before, dissociation is a complex and broad phenomenon, involving various psychological and somatoform symptoms (van der Hart et al., 2004). A more precise differentiation between these different symptoms in future fMRI research may help to better understand whether certain brain alterations are specifically related to distinct dissociative features, such as distortion in time, thought, body, and emotion (Frewen & Lanius, 2014). Likewise, an extended and more precise neuropsychological assessment may help to better understand the specific affective-cognitive functions and sub-processes that are disturbed by dissociation. It has been proposed that dissociation especially involves diminished recollection of trauma-related emotional information (Freyd et al., 1998; DePrince and Freyd, 1999), while the existing literature in the field is still heterogeneous. To elucidate this relationship, future neuroimaging studies in BPD may investigate the effect of dissociation on the processing of trauma-related material compared to generally negative information. Studying this relationship might help to identify processes which are relevant for psychotherapy, given the negative effect of dissociation on treatment outcome, as previously observed in BPD (Arntz et al., 2015; Kleindienst et al., 2011, 2016; Spitzer et al., 2007).

In general, acute and chronic stress is known to influence the way emotional material is processed, by enhancing emotional sensitivity and amygdala reactivity to emotional cues (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Veer et al., 2011). It has been shown that acute psychosocial stress influences the retrieval of well-consolidated declarative memory and working memory (Lupien et al., 1999, 2007; Oei et al., 2006; 2009; Tollenaar, Elzinga, Spinhoven, & Everaerd, 2008a, 2008b, 2009a, 2009b). In healthy men, acute stress was found to shift priority towards emotion processing at the cost of cognitive processing during the EWMT (Oei et al., 2012). The reactivity to stimulus material in the EWMT may therefore be moderated by stress hormones, e.g., cortisol. It would be an interesting next step to examine how stress (hormones) affect the behavioral inhibition and neural processing of emotional distraction after dissociation induction in BPD.

A combination of resting-state and task-related fMRI, i.e., the application of resting-state scans before and after experimental tasks (script-driven imagery, stress induction, EWMT, EST etc.) might help to integrate the present findings. Related to this, future fMRI research may use within-subject and longitudinal designs (repeated measurements) to investigate whether alterations, observed in this thesis, are a state-dependent feature (e.g., influenced by stress, critical life events etc.) or a stable characteristic in BPD.

8.5. Clinical implications

Difficulties in emotion regulation may critically contribute to the development of dissociation in vulnerable traumatized individuals (Vermetten & Spiegel, 2014). Dissociation can provide a subjective detachment from the self and / or environment and therefore be a helpful self-protectivce strategy in traumatic or otherwise stressful situations (Spiegel & Cardena, 1991). Present findings suggest that this may have a high cost. Dissociation can hinder the integration of salient information in consciousness and autobiographical memory; such information may then be processed and stored as isolated somatosensory elements, which later re-occur in the form of intrusive flashback memories (Ehlers et al. 2004; Krause-Utz & Elzinga, in press). By hindering the integration of traumatic or otherwise salient events in autobiographical memory, dissociation also interferes with identity, the development of a stable sense of self and understanding of who we are (Schauer & Elbert, 2010; Spiegel et al., 2011; Waters, 2014). Dissociation may not only dampen negative but also positive emotions and thereby lead to chronic feelings of emptiness and inner isolation (Lanius, 2015). Diminished emotional responsiveness may in turn lead to conflicts in close relationships and critically affect parenting (Lanius, 2015). All these maladaptive effects of dissociation can contribute to the development and maintenance of psychiatric disorders, such as PTSD and BPD (Brewin 2001; Brewin, Dalgleish, & Joseph, 1996; Ehlers & Clark 2000; Van der Kolk et al. 1996) and should therefore be taken into account in therapy. It has been shown that individuals who learned to dissociate in traumatic situations, will more likely dissociate in other stressful situations, e.g., during exposure therapy (Frewen & Lanius, 2006). Basic learning mechanisms, such as negative reinforcement (reduction of negative emotions), may explain why the probability is high that dissociative responses reoccur as an automatic response to environmental threat and generalize across situations. These processes may happen unconsciously. Thus, psychoeducation about these mechanisms may help patients to gain more insight into adaptive and maladaptive effects of dissociation.

Interventions that are aimed at helping individuals to reduce dissociative processes at moments when they are disruptive (and therefore maladaptive) are part of many existing psychotherapeutic treatments, such as Dialectical Behavioral Therapy (DBT) (Bohus et al., 2013; Linehan, 1993), Schema Focused Therapy (Sempertegui, Karreman, Arntz, & Bekker, 2013; Young, Klosko, & Weishaar, 2003), Cognitive Processing Therapy (CPT) (Resick & Schnicke, 1993), or Eye-Movement-Desensitization-and-Reprocessing Therapy (EMDR) (Shapiro, 2010; Shapiro & Maxfield, 2002). These techniques include mindfulness training and breathing and grounding techniques, such as motoric balance exercises (Bohus et al., 2013). Patients who tend to over-modulate their emotions may further benefit from trainings in emotional awareness and alternative stress regulation, e.g., how to tolerate painful emotions and how to experience more positive emotions (Lanius, 2015). Computerized interventions, which involve a continuous monitoring of dissociative states and suggestions for anti-dissociative skills, were found to improve the self-application of these skills during self-administered exposure exercises in the context of trauma therapy (Görg et al., 2016). Computerized interventions, aimed at improving executive control, might have a similar effect on the self-application of anti-dissociative skills.

So far, the role of neuroimaging in therapy research on dissociation has been limited. In part, there is still controversy about dissociative disorders and their neurobiological underpinnings (Lanius, 2015). Over the last years, neuroimaging studies have mainly focused on identifying neural processes, altered by dissociation, and already provided more and more insight into its possible neural underpinnings. So far barely anything is known about possible neural mechanisms of change related to dissociation. Yet, over the coming years, neuroimaging techniques might be used to translate the existing clinical and neurobiological knowledge into experimental interventions, such as real-time fMRI (neurofeedback training) (Lanius, 2015). At first, more studies are needed to investigate whether certain brain regions show changes in activity after the reduction of dissociative symptomatology, and whether they may be suitable targets for such add-on interventions. The combination of dissociation induction with symptom provocation may be a helpful step in this relationship.

8.6. Conclusion

The present research suggests that dissociative symptoms can have detrimental effects on cognitive functioning and may influence emotional and self-referential processing in BPD. Therefore, dissociative symptoms should be taken into account in future neuropsychological and neuroimaging studies in BPD, even when it is not the major focus of research.

While the precise mechanisms underlying stress-related dissociation in BPD remain elusive, neuroimaging findings reported here point to reduced activity in limbic (amygdala, posterior cingulate), temporal (inferior and superior temporal gyrus, fusiform gyrus), parietal (inferior and superior parietal lobe), and occipital areas (cuneus, fusiform gyrus, lingual gyrus), and increased activity in frontal areas (inferior frontal gyrus, dlPFC) in BPD patients with elevated dissociative symptoms. The present research further suggests that altered interactions between the amygdala and regions implicated in self-referential processing, cognitive control, visual perception, and sensory gating may play a role in dissociation in BPD. Further research with larger sample sizes and clinical control groups is needed to clarify whether the above-mentioned patterns can be replicated in other samples of BPD patients or are confounded by differences in sample characteristics (e.g., gender, trauma history, comorbidities, and psychotropic medication). In general, the complexity of BPD may be best understood by combining multiple measurements of multiple psychopathological dimensions. Future studies in BPD may combine different neuroimaging techniques (e.g., resting-state and task-related fMRI, seed-based correlations and ICA) with subjective, behavioral, and psychophysiological measurements (e.g., heart rate) to further improve the understanding of this severe and complex disorder.

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Meine Blumen werden die Farbe verlieren.
Meine Spiegel werden zufrieren.
In meinen Büchern werden die Zeilen verwachsen.
Meine Vögel werden in den Gassen
herumflattern und sich an fremden Fenstern verwunden.
Nichts ist mehr mit mir verbunden.
Ich bin von allem verlassen. -
Ich bin eine Insel.

Ich bin eine Insel und allein.

Ich bin reich.
Jetzt geht alles in mir umher,
sicher und sorglos; wie Genesende
gehn die Gefühle, genießend das Gehn,
durch meines Leibes dunkles Haus.
Einige sind Lesende
über Erinnerungen;
aber die jungen
sehn alle hinaus.
Denn wo sie hintreten an meinen Rand,
ist mein Gewand von Glas.

Rainer Maria Rilke
Aus: Die Blinde

Alles Wissen
und alle Vermehrung unseres Wissens
endet nicht mit einem Schlusspunkt,
sondern mit einem Fragezeichen.

Hermann Hesse

Nederlandse samenvatting

Borderline-persoonlijkheidsstoornis (BPS) is een ernstige psychische stoornis, die vaak voorkomt bij mensen met een voorgeschiedenis van interpersoonlijk trauma, zoals kindermishandeling en verwaarlozing (Leichsenring et al., 2011). Belangrijke kenmerken van BPS zijn emotionele disregulatie, stress-gerelateerde cognitieve problemen (verhoogde emotionele afleiding) en dissociatie (Crowell, Beauchaine, & Linehan, 2009; Schmahl et al., 2014; Vermetten & Spiegel, 2014). Emotionele disregulatie betreft zowel een affectieve overgevoeligheid als moeite om emoties en spanning te reguleren. Patiënten met BPS hebben vaak moeite met het uitvoeren van dagelijkse taken in stressvolle situaties, bijvoorbeeld nieuwe informatie te onthouden of oude informatie te herinneren, in het bijzonder als zij dissociatie ervaren.

Dissociatie is een veel voorkomend symptoom bij getraumatiseerde mensen en gaat gepaard met problemen in verschillende cognitieve processen, zoals geheugen en doelgericht gedrag (Cardena & Spiegel., 1993; Spiegel et al., 2011). Dissociatie wordt doorgaans gezien als een strategie om trauma-gerelateerde emoties te moduleren (Lanius, Vermetten, Loewenstein, Brand, Schmahl, Bremner, & Spiegel, 2010; Sierra & Berrios, 1998; Simeon et al, 2000). Tijdens dissociatie (bijvoorbeeld depersonalisatie of derealisatie) kunnen traumatische situaties als een onwerkelijke, filmachtige scène worden ervaren, alsof ze er van een afstand naar kijken. Sensorische elementen van de gebeurtenis kunnen in een vervormde wijze worden waargenomen (bijvoorbeeld geluiden lijken van ver komen, delen van het lichaam kunnen gevoelloos of groter dan normaal lijken). Op deze manier kan dissociatie een innerlijke afstand tot emotionele ervaringen creëren en een demping van het 'affectieve systeem' bevorderen. Dit gaat vaak ten koste van cognitieve processen: geheugenprocessen zijn verstoord, wat kan leiden tot psychogene amnesie. Momenteel is nog onduidelijk wat de invloed is van dissociatie op het functioneren van het brein.

In hoofdstuk 2 worden neuroimaging studies in BPS, gepubliceerd voor 2014, samengevat (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014a). Op het niveau van hersenactiviteit is BPS geassocieerd met een disbalans in cortico-limbische hersengebieden. Stress-gerelateerde cognitieve problemen bij patiënten met BPS hangen samen met processen in netwerken van het brein die betrokken zijn bij de verwerking van interne en externe gebeurtenissen (onder andere amygdala, dorsale anteriore cingulate cortex (ACC), insula) en zelf-referentiële processen, zoals het ophalen van autobiografische herinneringen ('default-mode' gebieden, bijvoorbeeld, ventrale ACC, posteriore cingulate cortex (PCC)).

Hierbij gaat het om hyperreactiviteit van limbische gebieden (onder andere amygdala) en verminderde activatie van frontale corticale 'cognitieve controle' hersengebieden. Zoals beschreven in hoofdstuk 3, is tot nu toe nog weinig bekend over de invloed van dissociatie op de verwerking van emotionele informatie in de context van een cognitieve taak bij BPS, en studies naar de hersenprocessen die hierbij betrokken zijn, zijn nog schaarser.

Het doel van dit proefschrift was om meer inzicht te verkrijgen in de associaties tussen dissociatie en hersenactiviteit, zowel tijdens rust ('resting-state') als gedurende emotionele distractie in patiënten met een BPS. In dit proefschrift is daarom de impact van dissociatie onderzocht op de activiteit en functionele connectiviteit in hersen-netwerken die betrokken zijn bij stressreacties, emotionele verwerking en het geheugen (amygdala, 'medial temporal lobe network'), aandacht (dorsale ACC, 'salience network'), en zelf-referentiële processen (ventrale ACC, posteriore cingulate cortex, 'default mode netwerk').

Aangepaste versies van de emotionele werkgeheugentaak ('Emotional Working Memory Task', EWMT) (zie Krause-Utz, Oei, Niedtfeld, Bohus, Spinhoven, Schmahl, & Elzinga, 2012) en emotionele Stroop Task werden toegepast om cognitieve controle van emotionele stimuli te onderzoeken. Functionele magnetische resonantie imaging (fMRI) werd gebruikt om veranderingen en verschillen in termen van gesynchroniseerde signaal schommelingen van de Blood-Oxygenation Level-Dependent (BOLD) respons te meten tussen patiënten met BPS en gezonde controles. Functionele connectiviteit binnen de eerder genoemde hersen-netwerken werd onderzocht met seed-based correlaties en Psychofysiologische Interaction (PPI) analyse.

In hoofdstuk 4 wordt een resting-state fMRI (RS-fMRI) onderzoek bij 20 patiënten met BPS en interpersoonlijk trauma (ernstige kindermishandeling) en 17 gezonde controles beschreven (Krause-Utz, Veer, Rombouts, Bohus, Schmahl, & Elzinga, 2014c). Alleen medicatie-vrije patiënten werden geïncludeerd, omdat psychotrope medicatie de functionele connectiviteit tijdens resting-states kan beïnvloeden (Wolf et al, 2011;. Doll et al, 2013.). Resting state functionele connectiviteit (RSFC) in het mediale temporale lob netwerk (amygdala seed), Salience netwerk (dACC seed) en default-mode netwerk (ventrale ACC seed) werd onderzocht. Patiënten met BPS vertoonden andere RSFC tussen de eerder genoemde seeds met hersengebieden in de mediale PFC, insula en occipitale cortex. Interessant is dat in de patiëntengroep dissociatie gepaard ging met een sterkere amygdala RSFC met de dorsolaterale prefrontale cortex en een verminderde RSFC van de amygdala met hersengebieden die geassocieerd zijn met visuele verwerking.

In de functionele MRI studie, beschreven in hoofdstuk 5, zijn verschillen in functionele connectiviteit onderzocht tijdens de emotionele werkgeheugentaak (met neutrale vs. negatieve interpersoonlijke foto's vs. geen distractie) in 22 vrouwelijke medicatie-vrije patiënten met BPS en een geschiedenis van interpersoonlijk trauma, vergeleken met 22 gezonde vrouwen. Vergeleken met gezonde vrouwen hadden patiënten met BPS een sterkere functionele connectiviteit tussen de amygdala en hippocampus (medial temporal lobe network), en tussen de dACC en insula (Salience network) en een sterkere koppeling van de dACC met seeds van het default-mode netwerk (posteriore cingulate, superiore temporale gyrus). Hierbij was het opvallend dat bij patiënten met BPS die tijdens emotionele distractie aangaven te dissociëren, de amygdala een sterkere connectiviteit vertoonde met hersengebieden die een rol spelen bij emotieregulatie (ACC), controle van bewegingen en introspectieve bewustzijn (precentrale gyrus, insula), en sensory gating (thalamus).

In het eerste deel van het fMRI-onderzoek, beschreven in dit proefschrift, werd de samenhang onderzocht tussen de mate van spontane dissociatie en functionele connectiviteit tijdens rust en de emotionele werkgeheugentaak. In het tweede deel van dit proefschrift werd script-driven imagery toegepast om dissociatie experimenteel bij patiënten met BPS te induceren. Script-driven imagery is gericht op het induceren van een dissociatieve toestand aan de hand van herinneringen aan dissociatieve ervaringen in het dagelijks leven. Met elke deelnemer werd een autobiografische herinnering aan een situatie waarin dissociatie werd ervaren ('dissociatie script') uitgewerkt en vervolgens tijdens de fMRI aangeboden (Lanius et al, 2002;. Lanius et al., 2004; Ludäscher et al., 2010). De deelnemers kregen de opdracht de specifieke situatie in het script zo levendig mogelijk te herinneren.

In hoofdstuk 6 wordt een studie beschreven naar de invloed deze script-geïnduceerde dissociatie op fouten, reactietijden en hersenactiviteit tijdens de Emotional Stroop Task (met neutrale, positieve of negatieve woorden). De patiënten met BPS bij wie dissociatie werd geïnduceerd, waren langzamer en minder nauwkeurig gedurende de emotionele Stroop Task en een daaropvolgende geheugentaak. Na dissociatie-inductie hadden patiënten langere reactie-tijden voor negatieve vs. neutrale woorden dan patiënten zonder dissociatie inductie en gezonde vrouwen. Vergeleken met patiënten die geen dissociatie inductie hadden gehad, vertoonden patiënten na dissociatie inductie verminderde activiteit in de fusiforme gyrus, inferieure pariëtale en temporale cortex. Na dissociatie-inductie werd een verhoogde activiteit in de inferieure frontale gyrus en dorsolaterale prefrontal cortex gevonden. In combinatie met de langere reactietijden voor negatieve versus neutrale woorden in de emotionele Stroop Task lijkt dit te duiden op een weinig efficiënte cognitieve inhibitie van emotioneel afleidende informatie.

In de fMRI studie, beschreven in hoofdstuk 7, werd de impact van dissociatie op de amygdala-activiteit en functionele connectiviteit onderzocht tijdens de emotionele werkgeheugentaak in (medicatie-vrije) patiënten met BPS en een geschiedenis van mishandeling in de jeugd. Na dissociatie inductie hadden patiënten met BPS significant meer onjuiste antwoorden en missers in de emotionele werkgeheugentaak dan patiënten met BPS zonder dissociatie inductie en gezonde vrouwen (neutrale scripts). Verder vertoonden patiënten met BPS na dissociatie inductie een significant verminderde amygdala activiteit tijdens de emotionele werkgeheugentaak (dit effect was niet valentie-specifiek). Tijdens emotionele distractie, vertoonden patiënten met BPS na dissociatie inductie ook een verminderde activiteit in de cuneus, linguale gyrus en posteriore cingulate cortex in vergelijking met de twee andere groepen. Bovendien werden er afhankelijk van de dissociatie inductie significante groepsverschillen waargenomen wat betreft de functionele connectiviteit in de amygdala. Na dissociatie inductie hadden patiënten met BPS een sterkere koppeling tussen de amygdala en de inferieure pariëtale kwab en superieure temporale gyrus, maar een verminderde functionele connectiviteit tussen de amygdala en fysiforme gyrus dan de twee andere groepen.

Samengevat blijken dissociatieve symptomen bij vrouwelijke patiënten met BPS (en een geschiedenis van kindermishandeling) samen te hangen met andere activiteit en functionele connectiviteit in hersennetwerken die van belang zijn bij het verwerken van emoties en emotieregulatie (amygdala, insula, inferieure frontale gyrus, dlPFC), sensorische gating (thalamus), visuele processen en taalverwerking (cuneus, linguale gyrus, fusiforme gyrus), aandacht en detectie van saillante gebeurtenissen (ACC, insula), en zelf-referentiële processen (posteriore cingulate cortex, superieure temporale gyrus, inferieure pariëtale cortex, mPFC). Deze bevindingen sluiten goed aan bij modellen waarin dissociatie als een zelf-beschermende strategie wordt gezien, (Lanius et al., 2010; Sierra & Berrios, 1998; Simeon et al., 2010). Het blijft onduidelijk of deze bevindingen specifiek zijn voor BPS of een neurobiologische onderbouwing van een algemener, transdiagnostische fenomeen.

De resultaten van dit proefschrift benadrukken de relevantie van het onderzoeken van dissociatieve verschijnselen in neuroimaging onderzoek en in de behandeling van patiënten met een borderline-persoonlijkheidsstoornis. Dissociatieve reacties op (trauma-gerelateerde) stressvolle situaties kunnen helpen om met overweldigende emotionele ervaringen om te gaan, maar kunnen tegelijkertijd cognitieve processen beïnvloeden die van essentieel belang zijn voor het leren, problemen oplossen, en doelgericht gedrag. Het verminderen van dissociatieve symptomen in situaties waarin deze reacties disfunctioneel en onaangepast zijn kan bijdragen tot een beter psychosociaal en cognitief functioneren.

Samengevat levert dit proefschrift duidelijke aanwijzingen op voor een link tussen dissociatieve symptomen en veranderingen in activiteit en functionele connectiviteit tussen hersen-netwerken, die betrokken zijn bij stressreacties, emotionele verwerking en geheugen, aandacht, en zelf-referentiële processen (alle functies die verstoord kunnen zijn tijdens dissociatie). De combinatie van het induceren van dissociatie en het afnemen van affectieve-cognitieve neuropsychologische taken (zoals het emotionele werkgeheugentaak en emotionele Stroop Task) in neuroimaging onderzoek kan bijdragen tot een beter begrip van deze relatie.

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Curriculum vitae

Annegret Dorothea Krause-Utz (nee Krause), born in Mutlangen on September 20th 1980, studied Psychology at the Universities Koblenz-Landau and Mannheim, Germany. In 2007, she received her Diploma in Psychology, graduating on 'the Impact of Aversive Inner Tension on Impulsivity in Patients with Borderline Personality Disorder'. From 2004 to 2014, Annegret worked at the Department of Psychosomatic Medicine and Psychotherapy of the Central Institute of Mental Health (CIMH) in Mannheim, first as a student research assistant and then as a PhD student in Translational Neuroscience. In February 2014, she graduated as Dr. sc. hum. at the Medical Faculty of Heidelberg University on 'Cognitive Processing during Emotional Distraction in Borderline Personality Disorder', supervised by Prof. Ch. Schmahl (summa cum laude). In October 2014, Annegret started her own research group on 'Stress and Cognition' at the CIMH. Between 2009 and 2015, Annegret did a Postgraduate Training in Behavioral Therapy (Zentrum für Psychologische Psychotherapie, ZPP, Heidelberg), with additional focus on Dialectical Behavior Therapy (DBT). From 2011 till 2015, she worked at the inpatient and outpatient treatment unit of the CIMH, primarily treating clients with Borderline Personality Disorder and complex Posttraumatic Stress Disorder. Since December 2014 she has been working at the Faculty of Behavioral and Social Science, currently she works as an Assistant Professor in Clinical Psychology at Leiden University.

List of publications

Original articles:

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