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

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Chapter 1

General introduction

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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).