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

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Chapter 3

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

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Annegret Krause-Utz, Rachel Frost, Dorina Winter, & Bernet M. Elzinga (2017). Dissociation and Alterations in Brain Function and Structure: Implications for Borderline Personality Disorder. *Current Psychiatry Reports*, 19(1), 1-22. doi:10.1007/s11920-017-0757-y. [3]

[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.