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

Krause, A.D.

Citation

Krause, A. D. (2017, November 16). *Disconnected self: influence of dissociation on emotional distractibility in Borderline Personality Disorder: a neuroimaging approach*. Retrieved from https://hdl.handle.net/1887/60261

Author: Krause, A.D.
Title: Disconnected self: influence of dissociation on emotional distractibility in Borderline Personality Disorder: a neuroimaging approach
Issue Date: 2017-11-16

Chapter 8

General discussion

CHAPTER 8

General discussion

8. General Discussion

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

8.1. Summary

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

8.1.1. Previous neuroimaging research in BPD (Chapter 2)

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

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

8.1.2. Neurobiological models of dissociation (Chapter 3)

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

8.1.3. Present neuroimaging studies (Chapters 4 - 7)

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

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

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

8.2. Integration and discussion of present findings

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

8.2.1. Behavioral findings in BPD

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

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

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

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

8.2.2. Neuroimaging findings in BPD

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

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

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

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

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

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

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

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

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

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

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

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

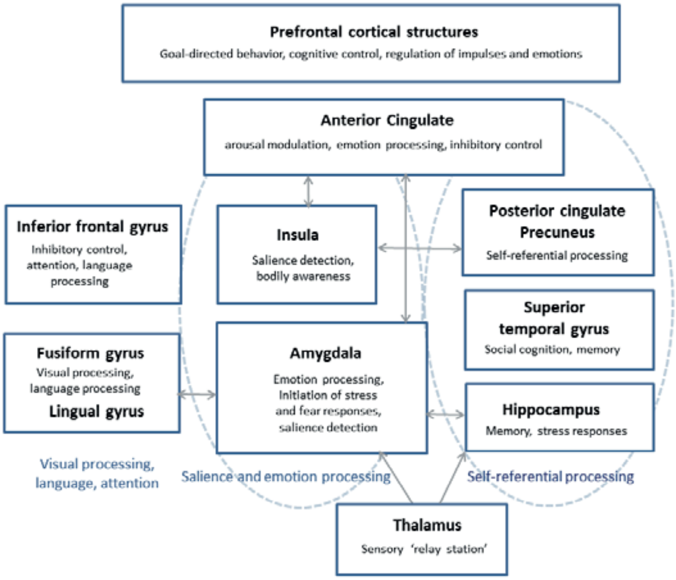

Figure 8.1. This figure depicts a schematic overview of brain regions, which may play a role in dissociation in BPD. While the precise neurobiological underpinnings of dissociation remain elusive, there is evidence for altered activity within brain networks involved in emotion processing and memory (e.g.,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

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

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

8.3. Strength and limitations

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

8.3.1. Sample characteristics

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

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

8.3.2. Task-characteristics

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

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

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

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

8.3.3 Neuroimaging data analysis techniques

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

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

8.4. Implications for future research

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

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

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

8.5. Clinical implications

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

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

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

8.6. Conclusion

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

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