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

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# Chapter 2

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

**Abstract**

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

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

## 2.1. Introduction

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

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

## 2.2. Structural neuroimaging studies

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

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

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

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

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

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

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

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

### 2.3. Functional neuroimaging studies

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

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

### *2.3.1. Resting state functional connectivity*

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

### *2.3.2. Emotion processing and emotion regulation*

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

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

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

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

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

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

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

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

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

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

#### *2.3.3. Self-Injury and altered pain processing*

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

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

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

#### *2.3.4. Cognitive disturbances and dissociation*

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

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

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

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

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

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

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

### *2.3.5. Behavioral dysregulation and impulsivity*

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

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

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

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

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

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

#### *2.3.6. Interpersonal disturbances*

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

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

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

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

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

### 2.4. Conclusion

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

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

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

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

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