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

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# CHAPTER 5

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

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**Abstract**

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

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

## 5.1. Introduction

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

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

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

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

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

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

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

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

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

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

## 5.2. Methods:

### *5.2.1. Sample*

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

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

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

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

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

### *5.2.2. Emotional Working Memory Task (EWMT)*

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

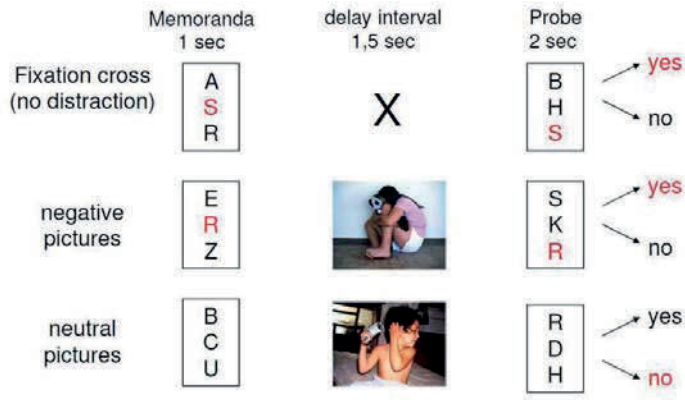


Figure 5.1. Design of the Emotional Working Memory Task (EWMT)

### *5.2.3. Procedure*

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

### *5.2.4. Scanning protocol*

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

### *5.2.5. Data Analysis*

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

#### *5.2.5.1. Psychophysiological interaction (PPI) analysis*

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

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

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

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

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

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

*5.2.5.2. Regression analyses*

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

## 5.3. Results

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

### *5.3.1. Amygdala connectivity*

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

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

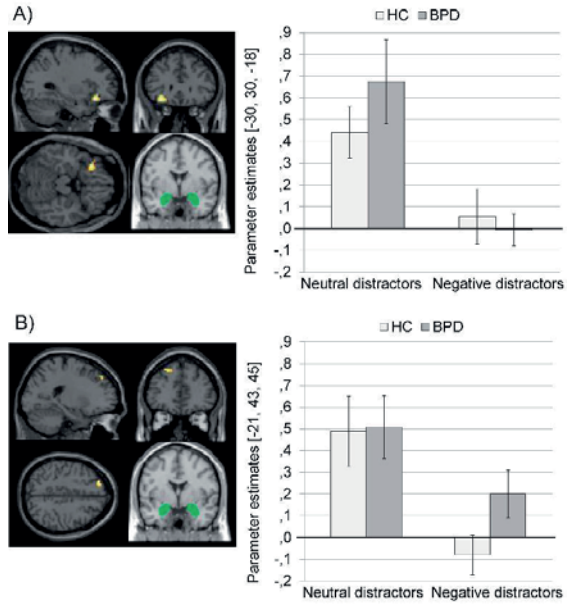


Figure 5.2. Results for the main effect of valence on amygdala connectivity: Figure A) shows means ± standard errors of the mean (SEM) of parameter estimates for connectivity of the bilateral amygdala seed (depicted in green) with left inferior frontal gyrus (MNI: -30, 30, -18) during presentation of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

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

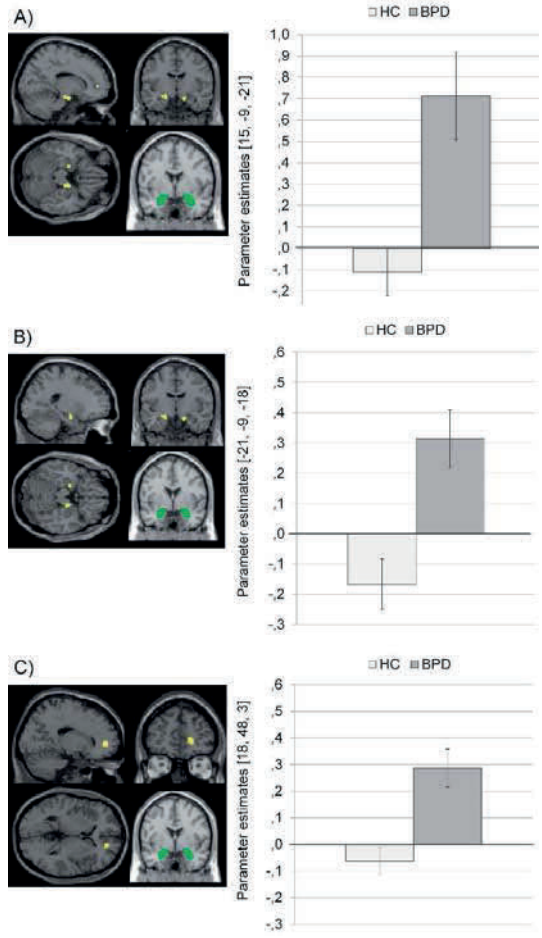


Figure 5.3. Results of the independent t-tests for amygdala connectivity during negative distractors (means ± SEM of parameter estimates for stronger connectivity of bilateral amygdala seed (depicted in green) in BPD than HC during negative distractors). Figure A shows amygdala connectivity with right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

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

### *5.3.2. Dorsal anterior cingulate (dACC) connectivity*

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

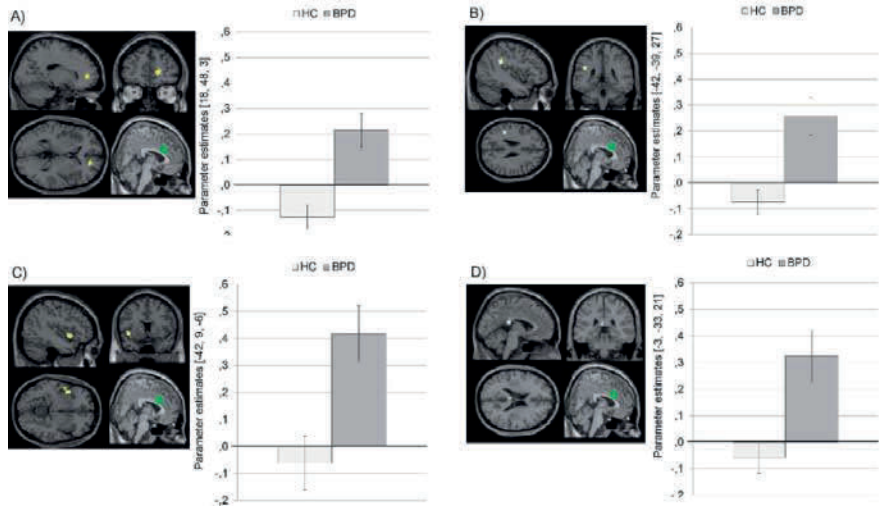


Figure 5.4. Results of the independent t-tests for dACC connectivity during negative distractors (means ± SEM of parameter estimates for connectivity of the dACC seed (depicted in green) during negative distractors in BPD and HC). Figure A) shows connectivity with right medial frontal gyrus (MNI: 18,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

### *5.3.2.5.* Regression analyses

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

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

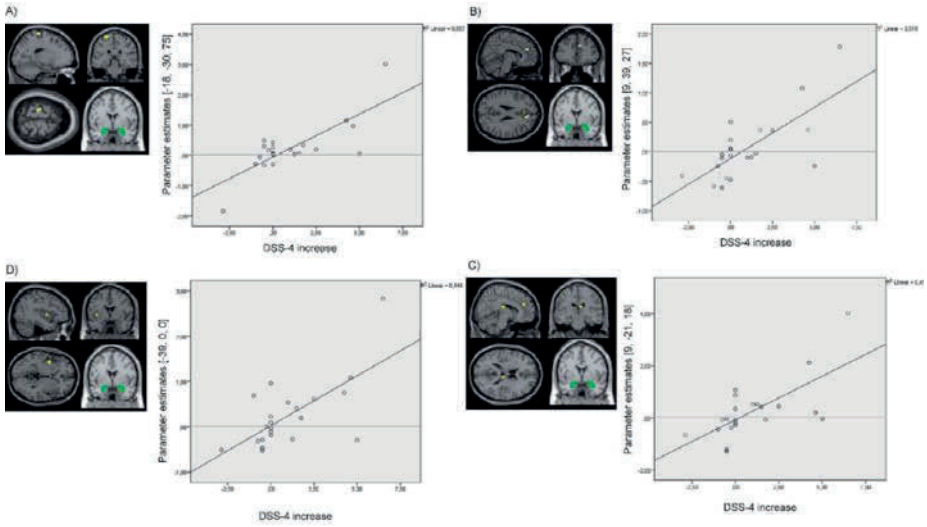


Figure 5.5. Results of the regression analysis with increases in DSS-4 scores as regressor for connectivity of the amygdala seed (depicted in green) during negative distractors in BPD. Figure A) shows connectivity with left precentral gyrus (MNI: -18, -30, 75). Figure B) shows connectivity with right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

## 5.4. Discussion

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

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

These results are discussed per seed in the following.

*Amygdala connectivity*

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

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

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

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

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

*Dorsal anterior cingulate connectivity*

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

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

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

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

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

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

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

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

**Conflict of Interest:**

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

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## Supplemental Material

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

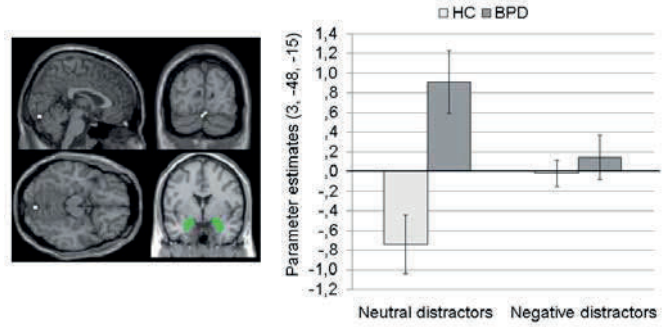


Figure S5.1. Results for the main effect of group on amygdala connectivity (means ± SEM of parameter estimates for connectivity of the amygdala seed (depicted in green) with right lingual gyrus (MNI: 3, -84, -15).

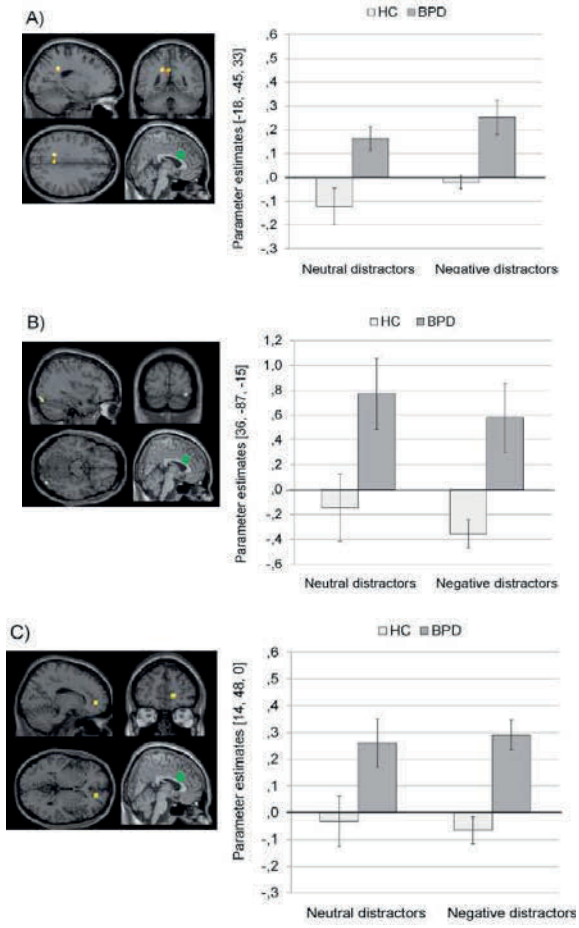


Figure S5.2. Results for the main effect of group on dACC connectivity of the 2x2 Full Factorial Model (means ± SEM of parameter estimates for connectivity of the dACC seed (depicted in green) in patients with BPD and HC). A) shows connectivity with left precuneus (MNI: -18, -45, 33). Figure B) shows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

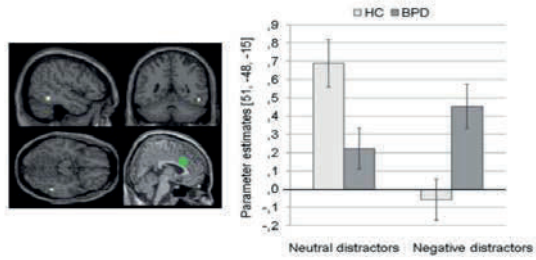


Figure S5.3. Results for the interaction effect on dACC connectivity (means ± SEM of parameter estimates for connectivity of the bilateral dACC) seed (depicted in green) with right superior temporal gyrus (MNI: 51, -48, -15) in patients with Borderline Personality Disorder (BPD) and healthy controls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

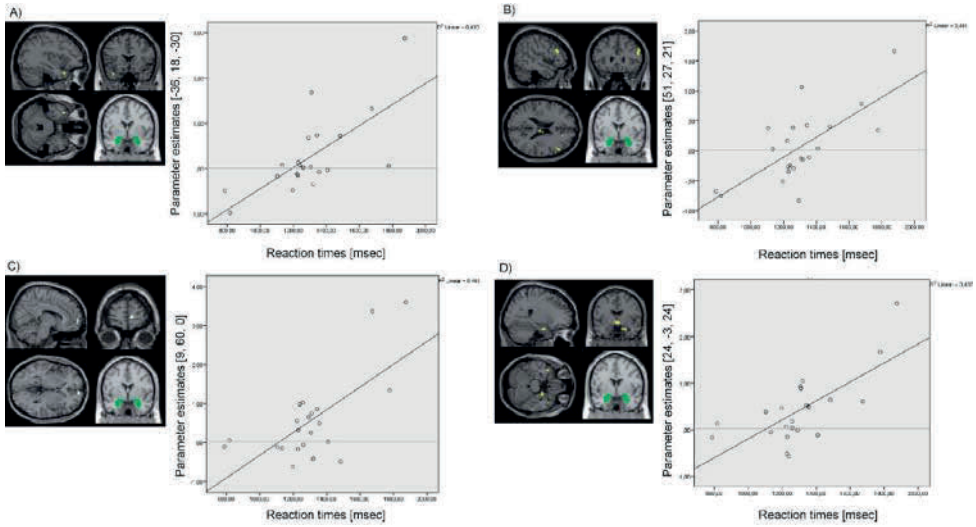


Figure S5.4. Results of the whole brain regression analysis with reaction times as regressor of interest for connectivity of the bilateral amygdala seed: This figure shows results of the whole brain regression analysis with reaction times as regressor of interest for connectivity of the bilateral amygdala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