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

Krause, A.D.

CHAPTER 7

Reduced Amygdala activity and Emotional Distractibility during Dissociative States in Borderline Personality Disorder

Annegret Krause-Utz, Dorina Winter, Friederike Schriner, Chui-De Chiu, Stefanie Lis, Philip Spinhoven, Martin Bohus, Christian Schmahl, and Bernet M. Elzinga (2017). Impact of Dissociation on Amygdala Activity and Functional Connectivity during an Emotional Working Memory Task in Borderline Personality Disorder. *European Archives of Psychiatry and Clinical Neuroscience* (in press).

Abstract

Background: Affective hyperreactivity and impaired cognitive control of emotional material are core features of Borderline Personality Disorder (BPD). A high percentage of individuals with BPD experience stress-related dissociation, including emotional numbing and memory disruptions. So far little is known about how dissociation influences the neural processing of emotional material in the context of a working memory task in BPD. We aimed to investigate whole-brain activity and amygdala functional connectivity (FC) during an Emotional Working Memory Task (EWMT) after dissociation induction in un-medicated BPD patients compared to healthy controls (HC). **Methods**: Using script-driven imagery, dissociation was induced in 17 patients ('BPD_D'), while 12 patients ('BPD_N') and 18 HC were exposed to neutral scripts during fMRI. Afterwards, participants performed the EWMT with neutral vs. negative IAPS pictures vs. no distractors. Main outcome measures were behavioral performance (reaction times, errors) and whole-brain activity during the EWMT. Psychophysiological Interaction analysis was used to examine amygdala connectivity during emotional distraction. **Results**: BPD patients after dissociation induction showed overall WM impairments, a deactivation in bilateral amygdala, and lower activity in left cuneus, lingual gyrus, and posterior cingulate than BPD_N, along with stronger left inferior frontal gyrus activity than HC. Furthermore, reduced amygdala FC with fusiform gyrus and stronger amygdala FC with right middle/superior temporal gyrus and left inferior parietal lobule was observed in BPD_D. **Conclusion**: Findings suggest that dissociation affects reactivity to emotionally salient material and WM. Altered activity in areas associated with emotion processing, memory, and self-referential processes may contribute to dissociative states in BPD.

Key words: Borderline Personality Disorder, Emotional Working Memory, Dissociation, Amygdala, Functional Connectivity, Psychophysiological Interaction Analysis

7.1. Introduction

Borderline Personality Disorder (BPD) is a severe mental disorder, characterized by emotion dysregulation, instable cognitions, impulsivity, interpersonal disturbances, and dissociation (Crowell et al., 2009; Schmahl et al., 2014). Previous neuroimaging studies in BPD suggest that a hyperactivity and altered functional connectivity of the amygdala may underlie disturbed emotion processing in BPD (Schulze et al., 2016; van Zutphen et al., 2015), although discrepant findings were also reported (see Ruocco et al., 2013). The amygdala plays a crucial role in the initiation of fear and stress responses (Davis & Whalen, 2001) and might also been involved in stress-related dissociation (Sierra & Berrios, 1998; Philips & Sierra, 2003).

Dissociation occurs in a high percentage (~75-80) of individuals with BPD (Korzekwa, Dell, & Pain, 2009a; Korzekwa et al., 2009b; Stiglmayr et al., 2008; Vermetten & Spiegel, 2014), involving disruptions in the usually integrated functions of consciousness, perception, identity, memory, and affect (APA, 2013; Spiegel et al., 2011) and has been closely linked to psychological trauma. Dissociative symptoms such as depersonalization, derealization, numbing, and analgesia may provide a state of subjective detachment from extremely stressful experiences, e.g., by dampening overwhelming emotions and reducing awareness of pain (Lanius et al., 2010; Spiegel et al., 2011). In pathological dissociation, the cost of this subjective detachment is a disruption of executive functions that are crucial to goal-directed behavior, such as attention, learning, and memory. More specifically, dissociation may hinder the conscious processing and integration of salient information in autobiographical memory, which can have detrimental effects on the development of identity and emotion regulation capacities. Dissociation may hinder the recall and learning of self-relevant information also during therapy (Lanius et al., 2010) and in BPD, dissociative symptoms predicted poor treatment outcome (Arntz et al., 2015; Kleindienst et al., 2011; Kleindienst et al., 2016; Lanius et al., 2010; Spitzer et al., 2007). However, the precise neuropsychological mechanisms underlying this relationship remain unclear.

Neurobiological models have therefore dissociation to a dampened activity in the amygdala and increased recruitment of 'cognitive control' regions, such as the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and inferior frontal gyrus (Lanius et al., 2010; Sierra & Berrios, 1998) as well as to altered activity in the superior temporal gyrus, precuneus, posterior cingulate, which are implicated in autobiographical memory and self-referential processing (Lanius et al., 2002; Lanius et al., 2005; Ludäscher et al., 2010; Simeon et al., 2000). The amygdala appears to be an important hub within this network, sharing strong functional connections with the ACC, insular and orbitofrontal cortex, mPFC, parahippocampal gyrus,

precuneus, posterior cingulate, among others (Roy et al., 2009; Stein et al., 2007). In summary, it can be assumed that dissociation substantially affects activity within an 'amygdala network' involved in the processing of self-relevant emotional information and the initiation of stress responses. In BPD, however, so far there is little empirical evidence for this. Only few neuroimaging studies in BPD investigated correlations between self-reported dissociation and brain activity during experimental challenge, such as the presentation of aversive images or words (Hazlett et al., 2012; Krause-Utz et al., 2012, 2014b, 2017; Wingenfeld et al., 2009b; Winter et al., 2015).

To the best of our knowledge, only two neuroimaging studies in BPD used script-driven imagery to more directly investigate the effect of experimentally induced dissociation (Ludäscher et al., 2010; Winter et al., 2015). In this well-established paradigm, a narrative of an autobiographical situation involving dissociative experiences ('dissociation script') is created and presented in an experimental setting, e.g. during fMRI (Lanius et al., 2002, 2004). Participants are instructed to listen to this script and to recall their autobiographical experiences as vividly as possible, which successfully induced dissociation in previous research (Ludäscher et al., 2010; Winter et al., 2015). When exposed to a dissociation script (vs. a neutral script), BPD patients showed significantly increased activity in the left inferior frontal gyrus and superior frontal gyrus and diminished temporo-limbic activity, which was even more pronounced in a subgroup of traumatized patients (Ludäscher et al., 2010).

We recently combined script-driven imagery with an Emotional Stroop Task (EST), to investigate the effect of a dissociation induction on interference inhibition, on a behavioral and neural level in BPD (Winter et al., 2015). Patients exposed to a dissociation script showed impaired overall accuracy and slower reaction times for negative words than patients exposed to a neutral script. Patients after dissociation induction further showed increased left inferior frontal gyrus activity in response to negative vs. neutral words (Winter et al., 2015). However, it remains unclear how brain areas, in particular the amygdala, may interact with other brain regions after dissociation induction. To our knowledge, so far no study in BPD investigated how dissociation affects the neural processing of emotional material during a working memory task, which requires the active manipulation of task-irrelevant stressful information.

We previously developed a modified version of the Emotional Working Memory Task (EWMT) (Krause-Utz et al., 2012; Krause-Utz et al., 2014d) in which task-irrelevant neutral vs. negative (trauma-related) interpersonal scenes from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2005) or only a fixation cross (no distractors) are presented during the delay interval of a Sternberg item recognition task. Participants are

instructed to ignore distractors, focusing solely on the working memory (WM) task, thereby voluntarily inhibiting emotion processing in favor of cognitive processing. WM impairments (errors, prolonged RTs) and amygdala reactivity to negative pictures were significantly more pronounced in BPD patients, suggesting stronger emotional distractibility compared to healthy controls (Krause-Utz et al., 2012). During emotional distraction, BPD patients further showed a stronger coupling of the amygdala with the hippocampus and dorsomedial PFC, suggesting enhanced self-referential processing (Krause-Utz et al., 2014d).

Here, we aimed to investigate the impact of experimentally-induced dissociation on brain activity and amygdala functional connectivity during the EWMT. Studying this relationship on a behavioral and neural level might help to shed more light on the effects of stress-related dissociation in BPD. Script-driven imagery was used to induce dissociation. For patients exposed to a neutral script, we hypothesized to replicate previous findings of amygdala hyper-reactivity to emotional pictures, while patients exposed to a dissociation script were expected to show significantly dampened amygdala reactivity and increased activity in frontal areas (ACC, mPFC, inferior frontal gyrus).

7.2. Methods

7.2.1. Sample

Sixty women aged between 18-45 years (40 patients with BPD according to DSM-IV (APA, 2000) and 20 female HC) participated. Patients were recruited via advertisement on websites or referred from the residential treatment unit of the Department of Psychosomatic Medicine and Psychotherapy at the Central Institute of Mental Health (CIMH) in Mannheim, Germany. HC were recruited by newspaper advertisement. General exclusion criteria were serious somatic illnesses, traumatic brain injuries, developmental disorders, and MRI-related criteria (metal implants, pregnancy, left-handedness, claustrophobia). Exclusion criteria for HC were lifetime history of axis I/II disorders. Exclusion criteria for patients were psychotropic medication within 4 weeks prior to the study, substance dependence during the last year, substance abuse within two months prior to participation, current/lifetime psychotic or bipolar-I disorder, and life-threatening suicidal crisis. Patients were randomly assigned to two experimental conditions: 20 patients were exposed to a dissociation script (BPDd), while 20 BPD patients (BPDn) and 20 HC were exposed to a neutral script. An increase of $\geq$1.5 scores on the Dissociation Stress Scale 4 (DSS-4, see below) (Stiglmayr et al., 2010) after script compared to baseline was defined as inclusion criterion for the BPDd group (criterion was met by all participants assigned to this group).

To ensure that individuals in the BPDn group were not dissociated, we excluded patients with DSS-4 baseline scores of ≥3 and/or an increase of >1.5 scores after the experiment (three patients had to be excluded for this reason). Furthermore, part of the collected data had to be discarded due to movement artefacts during fMRI (BPDn: n=2, BPDd: n=3, HC: n=2), technical problems during script presentation (BPDn: n=1) or inconsistent button presses (95-100% errors, suggesting that instructions were not understood correctly in BPDn: n=2). The final sample comprised 17 BPDd, 12 BPDn, and18 HC. Diagnoses were assessed by trained diagnosticians using the Structured Clinical Interview for DSM-IV Axis-I Disorders (SCID-I) (First et al., 1997) and International Personality Disorder Examination (IPDE) (Loranger, 1999). Further clinical assessment included questionnaires on symptom severity (Borderline Symptom List 23, BSL-23 (Bohus et al., 2009)), childhood trauma (Childhood Trauma Questionnaire, CTQ (Bernstein et al., 2003)), trait dissociation (Dissociative Experiences Scale, DES (Bernstein & Putnam, 1986)), depression (Beck Depression Inventory II, BDI-II (Beck, Steer, & Brown, 1996)), anxiety (State Trait Anxiety Questionnaire, STAI (Spielberger et al., 1983)), and ADHD (childhood: Wender Utah Rating Scale, WURS (Ward, Wender, & Reimherr, 1993), adulthood: ADHD-Checklist (Roesler et al., 2008)). Groups did not differ in age and years of education. Both BPD groups scored significantly higher than HC on clinical measures but did not differ significantly from each other in this respect. All patients fulfilled DSM-IV criteria for affective instability and stress related dissociation. Moreover, all patients reported at least one type of severe to extreme childhood abuse and/or neglect and didn't differ in the severity of childhood trauma (see Table 7.1). Criteria for comorbid Posttraumatic Stress Disorder (PTSD) was currently met by 7 BPDd patients (41%) and 5 BPDn patients (41%), 8 BPDd (47%) and 5 BPDn (41%) had lifetime PTSD ($\varkappa^2$=0.88, p=.646). Major depressive disorder (MDD) was currently present in 2 BPDd patients, while 15 BPDd (88%) and 8 BPDn (66%) had lifetime MDD ($\varkappa^2$=2.28, p=.131). Other lifetime comorbidities included panic disorder (BPDd: 5 (29%), BPDn: 3 (18%), $\varkappa^2$=0.05, p=.824), social phobia (BPDd: 10 (59%), BPDn: 4 (33%), $\varkappa^2$=1.78, p=.182), specific phobia (BPDd: 3 (18%), BPDn: 1 (8%), $\varkappa^2$=0.48, p=.488), obsessive compulsive disorder (BPDd: 4 (24%), BPDn: 1 (8%), $\varkappa^2$=1.09, p=.296), eating disorders (BPDd: 7 (41%), BPDn: 3 (18%), $\varkappa^2$=0.76, p=.384), and somatization disorder (BPDd: 1 (6%), BPDn: 0 (0%), $\varkappa^2$=0.71, p=.398). 15 BPDd patients (88%) and 10 BPDn patients (83%) reported non-suicidal self-injurious behavior within the last 12 month ($\varkappa^2$=0.14, p=.706). In the BPDd group, 13 patients (76%) were previously medicated, while in the BPDn group, 9 patients (75%) were previously medicated ($\varkappa^2$=0.008, p=.927; for more information see Supplemental Material).

Table 7.1.

Demographic variables, dissociation and arousal ratings, and clinical characteristics

	BPDd (n= 17)	**BPDn (n= 12)**	**HC (n= 18)**	**Group comparisons**
Age [years]	27.41 ± 6.20	25.17 ± 6.21	29.61 ± 8.61	$F_{(2,44)}$=1.38, p=.262
School education [years]	10.59 ± 2.62	10.08 ± 3.03	10.72 ± 1.99	$F_{(2,44)}$=0.25, p=.784
DSS-4 *Dissociation ratings* Baseline	3.44 ± 1.99	2.30 ± 1.14	1.31 ± 0.66	$F_{(2,42)}$=11.27, p<.0001. BPDd - HC: 2.26, p<.0001 BPDn - HC: 1.00, p=.160 BPDd - BPDn: 1.27, p=.062
After script	6.85 ± 2.03	1.85 ± 0.84	1.19 ± 0.51	$F_{(2,42)}$=92.50, p<.0001 BPDd - HC: 5.79, p<.0001 BPDn - HC: 0.60, p=.465 BPDd - BPDn: 5.19, p<.0001
Arousal rating Baseline	4.76 ± 2.36	3.91 ± 1.97	2.72 ± 2.02	$F_{(2,42)}$=3.43, p=.042 BPDd - HC : 1.90, p=.035 BPDn - HC: 1.20, p=.325 BPDd - BPDn: 0.72, p=.672
After script	7.71 ± 2.11	4.50 ± 2.65	2.17 ± 2.28	$F_{(2,42)}$=26.67 p<.0001 BPDd - HC : 5.46, p<.0001 BPDn - HC: 1.83, p=.840 BPDd - BPDn: 3.62, p<.0001
BSL-23 total score (BPD symptom severity)	47.12 ± 19.23	43.33 ± 13.36	1.33 ± 1.81	$F_{(2,44)}$=60.51, p<.0001, f^2=.73 BPDd - HC: 45.78, p<.0001 BPDn - HC: 42.00, p<.0001 BPDd - BPDn: 3.78, p=.737
DES total score (trait dissociation)	31.74 ± 16.52	26.93 ± 13.50	2.68 ± 2.04	$F_{(2,44)}$=28.37, p<.0001, f^2=.56 BPDd - HC: 29.01, p<.0001 BPDn - HC: 24.26, p<.0001 BPDd - BPDn: 4.81, p=.547
BDI-II (depressive symptoms)	24.47 ± 11.89	26.75 ± 10.68	1.67 ± 2.25	$F_{(2,44)}$=38.49, p<.0001, f^2=.64 BPDd - HC: 22.80, p<.0001 BPDn - HC: 25.08, p<.0001 BPDd - BPDn: 2.28, p=.783
STAI state * (state anxiety)	56.19 ± 10.13	52.92 ± 6.36	29.39 ± 5.41	$F_{(2,43)}$=54.90, p<.0001, f^2=.74 BPDd - HC: 26.79, p<.0001 BPDn - HC: 23.53, p<.0001 BPDd - BPDn: 2.55, p=.503
STAI trait * (trait anxiety)	58.13 ± 7.03	60.58 ± 5.83	28.72 ± 4.66	$F_{(2,43)}$=138,83, p<.0001, f^2=.87 BPDd - HC: 29.40, p<.0001 BPDn - HC: 31.86, p<.0001 BPDd - BPDn: 2.05, p=.522
WURS (childhood ADHD symptoms)	98.80 ± 41.16	94.42 ± 27.91	49.53 ± 27.52	$F_{(2,39)}$=9.88, p<.0001, f^2=.39 BPDd - HC: 49.27, p<.0001 BPDn - HC: 44.88, p<.0001 BPDd - BPDn: 4.39, p=.938
ADHD checklist * (adult ADHD symptoms)	14.94 ± 9.80	16.83 ± 8.33	3.94 ± 2.88	$F_{(2,44)}$=14.11, p<.0001, f^2=.39 BPDd - HC: 10.99, p<.0001 BPDn - HC: 12.89, p<.0001 BPDd - BPDn: 1.89, p=.789
CTQ total sum-score (childhood abuse and neglect)	68.23 ± 25.12	70.58 ± 16.46	33.39 ± 11.88	$F_{(2,44)}$=20.34, p<.0001, f^2=.48 BPDd - HC: 34.91, p<.0001 BPDn - HC: 37.19, p<.0001 BPDd - BPDn: 2.29, p=.944

Note: Values are presented in means and standard deviation. DSS-4=Dissociation Stress Scale 4, BSL-23=Borderline Symptom List 23, DES=Dissociative Experience Scale, BDI=Beck Depression Inventory, STAI=State Anxiety Inventory, CTQ=Childhood Trauma Questionnaire, WURS=Wender Utah Rating Scale, PTSD=Posttraumatic Stress Disorder. * STAI scores in one BPD_D patient and WURS scores in 3 HC and 2 BPD_D patients were missing.

Dissociative states were induced using script-driven imagery and assessed by the DSS-4, a self-rating scale with excellent internal consistency and reliability, high specificity, and sensitivity to change in symptomatology (Stiglmayr et al., 2010). The DSS-4 consists of four items on current psychological (derealization, depersonalization) and somatic (pain perception, hearing) dissociation and one item on current tension (10-point Likert scales, 0=not at all, 9=extremely).

7.2.2. Emotional Working Memory Task (EWMT)

The EWMT was a validated modified Sternberg item recognition task (Sternberg, 1966; Oei et al., 2009, 2012). The present version (Krause-Utz et al., 2012) consisting of 48 trials, each starting with a set of 3 uppercase letters (memoranda, 1000 ms.), followed by a delay interval (1500 ms.) and a probe (3 uppercase letters, 2000 ms.). In half of the trials, 1 of the 3 memoranda was present in the probe. Participants had to press a 'yes' or 'no' button indicating whether they had recognized a target or not. During the delay interval either negative or neutral distractors (interpersonal scenes from the IAPS (Lang, Bradley, & Cuthbert, 2005) or only a fixation cross (no distraction) 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). Negative pictures depicted scenes of interpersonal violence (e.g., sexual attack, physical assault, beaten/frightened child, physically mutilated body). Neutral pictures included interpersonal scenes with similar complexity (e.g., people at a market place or supermarket) to avoid confounding differences in visual information processing. Trials without distractors (only a fixation cross) were added, as even neutral interpersonal stimuli were found to be perceived as emotionally arousing in individuals with BPD, increasing amygdala activity (Donegan et al., 2003; Krause-Utz et al., 2012; Lis & Bohus, 2013; Niedtfeld et al., 2010, Schulze et al., 2011). Target-present and target-absent trials were equal in all conditions. Conditions were balanced in a pseudo-random manner. In addition, participants performed 15 trials of the basic Sternberg paradigm without distractors (i.e., only a fixation cross) to assess baseline working memory. Software Presentation (Neurobehavioural systems, http://www.neurobs.com/) was used to present stimuli and record behavioral data.

7.2.3. Procedure

The experiment was approved by the local ethics committee (Heidelberg University) and conducted at the CIMH in Mannheim, Germany. All participants received information about the study and scanning procedure, signed written informed consent, and underwent diagnostic and clinical assessment. Then, participants prepared a personalized script of 30sec length together with one experimenter (F.S. and D.W.). Patients assigned to the BPDd group were instructed to report a non-trauma-related autobiographical situation involving dissociation.

BPDn and HC were instructed to report an emotionally neutral every-day situation. A person unknown to participants read scripts aloud recording it on audio tape. During the experiment, participants first practiced 5 trials of the EWMT outside the scanner. Inside the scanner, scripts were presented via headphones. DSS-4 ratings were assessed before and after scripts.

Then participants performed the EWMT (first the 15 trials of the basic Sternberg paradigm, then the EWMT both with and without distractors). Participants were instructed to focus on the middle of the screen but to concentrate on the task only and to ignore distractors. Event-related fMRI data was acquired during ratings, script, and EWMT.

7.2.4. FMRI scan protocol

MRI was conducted using a 3-Tesla Siemens TRIO-Scanner (Siemens, Erlangen). Head cushions and headphones were used to reduce head movement artefacts and scanning noise. Blood oxygen level-dependent (BOLD) signal was measured with 36 3-mm transversal slices covering the entire brain using gradient echo-planar-imaging (EPI) [T2-weighted contrast, field of view=192x192 mm, voxel size=3x3x3 mm^3, voxel matrix=64x64, flip angle=80°, spin echo time=30ms, inter-scan repetition time (TR)=2000ms]. After fMRI, as individual template for functional data a high resolution anatomical scan was acquired using three-dimensional magnetization-prepared-rapid-acquisition-gradient-echo (MPRAGE) [T1-weighted contrast, voxel size=1x1x1 mm^3].

7.2.5. Statistical analysis

Custom statistical software (*SPSS*, Chicago: *SPSS* Inc) was used for manipulation check, behavioral data analysis, and subgroup comparisons. Normal distribution was checked for all variables using the Kolmogorov-Smirnov test. For repeated measurement analysis of variance (rmANOVA) we checked assumptions of variance equality (Levene's tests) and sphericity (Mauchly's test, in case of violations Greenhouse Geisser corrections were applied). Significant effects were followed-up using between-group or paired *t*-tests ($p<0.05$, two-tailed).

7.2.5.1. Manipulation check

A 3x2 rmANOVA with DSS4-scores before and after script as dependent variables (Time as within-subject factor) and Group as between-subject factor was performed to check whether self-reported dissociation significantly changed after script in BPDd (expecting an increase).

7.2.5.2. Behavioral (WM) data

WM data was checked for outliers. Errors were scored as incorrect, too early responses, and misses separately. Percentage of incorrect responses as well as reaction times for correct trials were analyzed using two separate 3x3 rmANOVAs with Group as between-subjects factor and Condition (no distraction vs. neutral vs. negative distractors) as within-subject factor.

Differences in specific error types (wrong responses, too early responses, misses) were evaluated using a multivariate ANOVA (MANOVA) with Group as fixed-factor.
In addition, basic working memory performance (errors, RTs of correct trials) of trials without distraction (basic WM task) was compered between groups using two separate ANOVAs.

7.2.5.3. Fmri data

Functional imaging data was analyzed using standard procedures implemented in the Statistical-Parametric-Mapping package (SPM8, Neurobehavioral systems, Berkeley, CA; http://www.fil.ion.ucl.ac.uk/spm/). EPI time series were preprocessed according to common standards, including 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. Statistical analyses of our event-related design relied upon the general linear model (GLM) to estimate effects of interest (Friston et al., 1995).

7.2.5.4. Region of interest (ROI) and whole-brain (WB) analysis

Single subject level: For each participant, task-related activity was identified by convolving a vector of the onset times of the following seven experimental events of interest with a canonical hemodynamic response: Memoranda, delay intervals (no, neutral, negative distractors), and probes after no, neutral, and negative distractors respectively. The GLM further included nuisance variables to control for movement artifacts.

Group level: To test our a-priori hypothesis of decreased amygdala activity in BPDd, a ROI analysis was conducted using an anatomical mask of the bilateral amygdala (created by the Automated Anatomical Labeling software, AAL (Tzourio-Mazoyer et al., 2002)), smoothed with a cube of voxels of size (FWHM) of 9mm). Values of percent signal change in this region during delay intervals (no vs. neutral vs. negative distractors) were extracted for each participant using the rfxplot toolbox (Glaescher, 2009) and exported to SPSS. Equivalent to the analysis of behavioral data, a 3x3 rmANOVA (between-subject factor: Group, within-subject factor: Condition) was performed. To ensure that group differences were not confounded by basic differences in arousal or WM, we repeated the analysis with arousal ratings as well as WM errors as covariate, using two separate rmANCOVAs.

WB analysis: Consistent with our previous study (Krause-Utz et al., 2012), a Full Factorial Design was used to model effects of group and experimental task. Within this model, we tested for group differences (F-contrast) during negative distractors relative to no distractors. Gaussianized F/T statistic images were determined using a significance threshold of $p<.05$,

Family-Wise-Error (FWE) corrected for multiple comparisons on the voxel-wise level. Based on our a-priori hypotheses, small volume corrections (SVC) with pre-defined anatomical masks of the IFG, mPFC, and ACC (regions of interest) were applied. To follow-up significant WB group effects in subgroup comparisons, parameter estimates were exported to SPSS, and analyzed using between-group *t*-tests ($p<.05$).

7.2.5.5. Psychophysiological interaction analysis (PPI) analysis

The generalized PPI (gPPI) toolbox by McLaren (McLaren et al., 2012) was applied to analyze changes in the correlation of time-series of the amygdala (seed region) with time-series of regions across the whole brain, dependent on our experimental manipulation (Friston et al., 1997; O'Reilly et al., 2012). For the amygdala seed, the same anatomical mask of bilateral amygdala and contrast (negative vs. no distractors) as in the above-mentioned ROI analyses were used. For each participant, mean time series of activity from voxels falling within this anatomical mask were extracted and first-level contrasts for the EWMT conditions were computed. Since PPI analysis of event-related designs lack power (O'Reilly et al., 2012). increasing the probability of false negative results (Type-II-error), we decided to apply a more lenient initial clustering threshold of $p<0.001$, uncorrected on the voxel-wise level (cluster size $k>10$, $Z>3.5$). Yet, only clusters FWE-corrected for multiple comparisons ($p<0.05$) at the cluster level are discussed. PPI beta estimates of significant clusters for negative vs. no distractors (F contrast) were extracted and exported to SPSS. Overall group differences were evaluated in a MANOVA and followed up by post-hoc *t*-tests. To ensure that group differences were not confounded by basic differences in WM, we repeated the same analysis with WM errors as covariate (MANCOVA).

7.3. Results

7.3.1. Dissociation induction

Means with standard deviation of DSS-4 scores are reported in Table 1. Main effects of Time ($F_{(1,43)}=23.01$, $p<.0001$, $\eta^2=.35$) and Group ($F_{(2,43)}=48.57$, $p<.0001$, $\eta^2=.69$) and the interaction effect ($F_{(2,43)}=43.79$, $p<.0001$, $\eta^2=.67$) were significant with higher scores after script than baseline in BPDd ($t_{(16)}=7.57$, $p<.0001$) but not in the other groups ($p>.05$).

7.3.2. Behavioral data

There were no significant group differences in basic WM (errors or RTs in trials without distractors, $p>.05$, data not shown). Figure 7.1 shows means ± standard errors of the mean (SEM) for percentage of incorrect responses (Fig. 7.1a) and RTs of correct trials (Fig. 7.1b) during the EWMT in BPDd, BPDn, and HC.

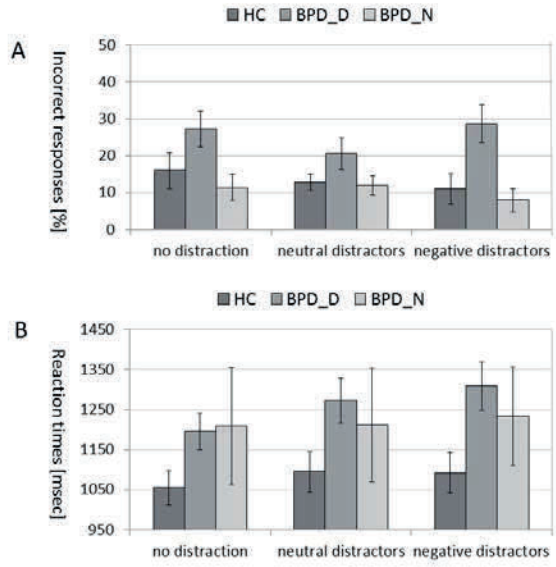

Figure 7.1. Working memory performance during the Emotional Working Memory Task (after no distraction, after neutral distractors, after negative distractors) in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC). Figure A shows means ± standard errors of the mean of percentage of errors. Figure B shows means ± standard errors of the mean of reaction times in correct trials.

7.3.2.1. Errors during the EWMT

The rmANOVA revealed a significant Group effect ($F_{(2,43)}$=4.43, p=.018, η^2=.17) with an overall higher percentage of incorrect responses in BPDd than in BPDn (p=.012) and in HC (p=.019) (see Figure 7.1A).

The MANOVA further indicated that there were significant group differences in the number of misses ($F_{(2,43)}$=6.86, p=.003, η^2=.24), due to more misses in BPDd than in BPDn (p=.001) and in HC (p=.011), as shown in Supplemental Figure S7.1.

7.3.2.2. *Reaction Times during the EWMT*

The rmANOVA revealed a significant Condition effect ($F_{(2,42)}$=4.17, p=.022, η^2=.17) with longer RTs during neutral (p=.019) and negative distractors (p=.003) than during no distractors, but no significant Group effect or interaction effect (both p>.05) (see Figure 7.1B).

7.3.3. *FMRI data*

7.3.3.1. ROI analysis

Figure 7.2 depicts means ± SEM of percent signal change in the bilateral amygdala.

The rmANOVA revealed a significant main effect for Group ($F_{(2,44)}$=5.36, p=.008, f^2=.20) with higher amygdala activity in BPDn than in BPDd (p=.002) and in HC (p=.023). There were no significant differences between BPDd and HC (p>.05). Furthermore, there was a trend for a main effect of Condition ($F_{(2,87)}$=3.21, p=.050, f^2=.13) (interaction effect: p>.05). When including self-reported aversive tension (DSS-4 item) as covariate, group differences remained significant ($F_{(2,44)}$=4.89, p=.012, f^2=.19). Likewise, the rmANCOVA with WM errors as covariate still revealed a significant Group effect ($F_{(2,42)}$=3.43, p=.042, f^2=.14) with higher amygdala activity in BPDn than in BPDd (p=.015) and in HC (p=.043).

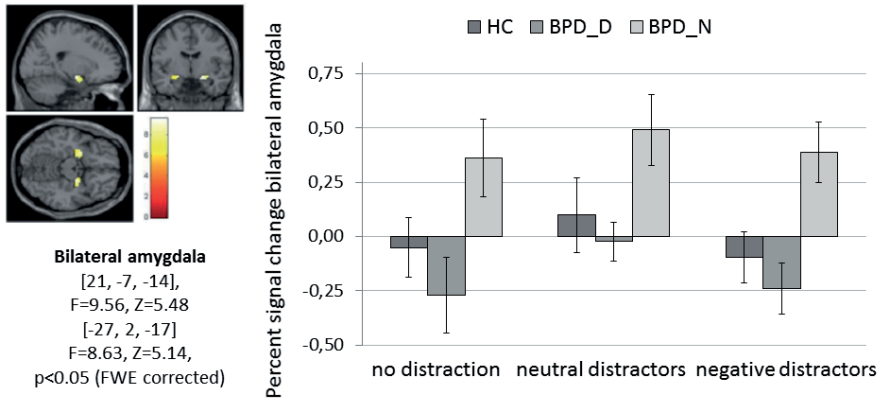

Figure 7.2. Percent signal change in the bilateral amygdala (region of interest analysis) during the Emotional Working Memory Task (no distraction, neutral distractors, negative distractors) in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC). Clusters in the bilateral amygdala, detected by the main effect of task (p<0.05, FWE-corrected on the voxel-wise level) are depicted on the left.

7.3.3.2. Whole-Brain analysis

Results for the main effect of task (F contrast, whole-brain FWE-corrected, p<.05) are presented in Table 7.2. Across all groups, significant activity changes in temporo-limbic regions (amygdala, hippocampus, insula, cingulate gyrus, superior temporal gyrus, fusiform gyrus) and fronto-parietal areas (inferior frontal gyrus, dmPFC, dlPFC, inferior parietal lobule, precuneus, postcentral gyrus) were observed during the EWMT. Significant group differences for brain activity during negative vs. no distractors were found for a cluster comprising left cuneus, lingual gyrus, and posterior cingulate (whole-brain, FWE-corrected, p<.05) and in the left IFG (BA44) and insula (BA13) (after SVC with the IFC mask). Activity in both clusters was significantly stronger in BPDn than in HC.

Furthermore, BPDn showed significantly stronger activity in left cuneus, lingual gyrus, and posterior cingulate than BPDd. In BPDd, there was significantly stronger activity in left IFG than in HC (Table 7.2).

Table 7.2.
Brain activity during the Emotional Working Memory Task (Full Factorial Model)

F Contrast	Brain region (label)	Lobe	Brodman area	k	Peak voxel (X, Y, Z)	F value	Z value	p (FWE)
Main effect of Condition	Fusiform Gyrus	Occipital Lobe	N.A.	6225	30 -58 -14	31.67	Inf	p<0.001
	Fusiform Gyrus	Temporal Lobe	BA 20	6225	36 -43 -20	29.10	Inf	p(<0.001
	Fusiform Gyrus	Temporal Lobe	BA 37	6225	42 -49 -17	28.92	Inf	p<0.001
	Postcentral Gyrus	Parietal Lobe	BA 3	246	-39 -22 52	16.36	7.45	p<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA 6	246	-24 -4 52	12.14	6.31	p<0.001
	Cingulate Gyrus	Limbic Lobe	BA 32	390	-6 11 46	16.11	7.39	p<0.001
	Medial Frontal Gyrus	Frontal Lobe	BA 6	390	-6 -4 55	12.61	6.45	p(<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA 32	390	9 11 49	12.14	6.32	p<0.001
	Insula	Sub-lobar	BA 13	99	-30 23 4	14.92	7.09	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA9	173	-54 8 31	13.44	6.69	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA9	173	-45 5 31	12.51	6.42	p<0.001
	Middle Frontal Gyrus	Frontal Lobe	BA46	173	-48 23 25	7.48	4.68	p=0.029
	Insula	Sub-lobar	BA 13	110	36 20 7	12.22	6.34	p<0.001
	dlPFC	Frontal Lobe	BA 9	104	45 5 31	12.18	6.33	p<0.001
	Putamen	Sub-lobar	Putamen	68	-18 8 -2	12.04	6.29	p<0.001
	Amygdala	Limbic Lobe	Amygdala	68	-27 2 -17	8.63	5.14	p=0.004
	Middle Frontal Gyrus	Frontal Lobe	BA 6	58	30 -4 52	11.06	5.98	p<0.001
	Inferior Parietal Lobule	Parietal Lobe	BA 40	91	-48 -64 40	11.05	5.98	p<0.001
	Putamen	Sub-lobar	Putamen	40	21 8 4	10.83	5.91	p<0.001
	Inferior Frontal Gyrus	Frontal Lobe	BA 47	85	-42 26 -14	10.57	5.82	p<0.001
	Amygdala	Limbic Lobe	Amygdala	65	21 -7 -14	9.56	5.48	p=0.001
	Hippocampus	Sub-lobar	Hippocampus	65	30 -10 -17	9.02	5.28	p=0.002
	Superior Temporal Gyrus	Temporal Lobe	BA 22	8	63 -4 4	8.27	5.00	p=0.007
	Precuneus	Parietal Lobe	BA 7	20	-24 -58 49	8.21	4.98	p=0.008
	Medial Frontal Gyrus	Frontal Lobe	BA 10	9	-3 50 -5	7.89	4.85	p=0.014
	Inferior Frontal Gyrus	Frontal Lobe	BA 46	6	-45 29 16	7.79	4.81	p=0.016
	Superior Temporal Gyrus	Temporal Lobe	BA 38	5	45 20 -23	7.79	4.81	p=0.016
	Hippocampus	Limbic Lobe	Hippocampus	5	-30 -16 -17	7.47	4.68	p=0.029
Main effect of Group (F contrast) negative distractors vs. no distraction	Cuneus	Occipital Lobe	BA18	247	-3 -79 22	13.88	4.63	p=0.031
	Lingual Gyrus	Occipital Lobe	BA19		-15 -61 -5	10.65	3.97	
	Posterior Cingulate	Limbic Lobe	BA30		-15 -64 4	9.34	3.67	
	Inferior Frontal Gyrus	Frontal Lobe	BA9	102	-48 5 28	12.08	4.27	p=.010*
	Inferior Frontal Gyrus	Frontal Lobe	BA44		-54 8 19	11.08	4.07	
	Insula	Sub-Lobar	BA13		-42 11 19	7.92	3.32	

Note: K=cluster size. Z-values were determined by an initial cluster-forming threshold of p<0.05 Family Wise Error (FWE) corrected on a whole-brain voxel-wise level. Clusters detected after small volume correction (p<0.05) are indicated by (*).

7.3.3.3. PPI analysis

Significant group differences were observed for amygdala FC with clusters comprising bilateral fusiform gyrus and culmen, bilateral superior/medial frontal gyrus, bilateral middle frontal gyrus, right superior/middle temporal gyrus (insular cortex), left inferior parietal lobule (insular cortex), left anterior insula, and right cingulate gyrus (p<0.05, FWE-cluster-corrected) as well as right middle occipital gyrus and left claustrum (at p<0.001, uncorrected) (see Table S7.1). HC showed (marginally) negative amygdala FC, while BPD groups showed positive amygdala FC with all of these regions. BPDd differed from HC across all regions (p<0.001), BPDn differed from HC regarding all regions (p<0.05) except for middle occipital gyrus and middle/superior temporal gyrus. Compared to BPDn, BPDd showed reduced FC with left fusiform gyrus (t=2.07, p=.048, Figure 7.3A), while showing a stronger coupling between amygdala and left inferior parietal lobule (t=2.48, p=.020), right superior/middle temporal gyrus (t=2.20, p=.036), and right middle occipital gyrus (t=2.39, p=.024) (see Figure 7.3 B-D).

The MANCOVA with WM errors as covariate revealed similar results, albeit group differences in amygdala FC with left fusiform gyrus were at a trend level ($F_{(1,26)}$=2.25, p=.063) : Compared to BPDn, BPDd still showed a significantly stronger coupling between amygdala and left inferior parietal lobule ($F_{(1,26)}$=5.96, p=.022), right superior/middle temporal gyrus ($F_{(1,26)}$=2.54, p=.046), and right middle occipital gyrus ($F_{(1,26)}$=4.86, p=.034).

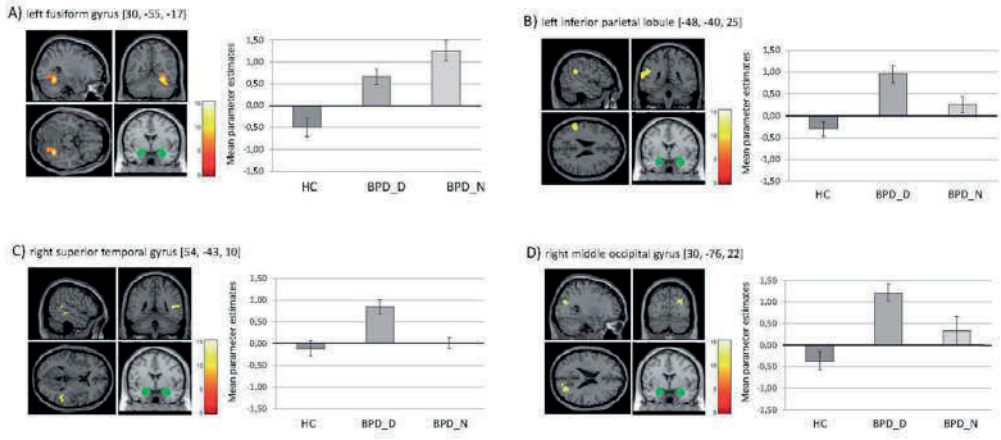

Figure 7.3. Results of the Psychophysiological Interaction analysis for functional connectivity (FC) of the bilateral amygdala seed (depicted in green) during negative distractors versus no distractors in the context of the EWMT in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after neutral script (BPD_N) as well as in healthy controls (HC). The figure shows means ± standard errors of the mean of parameter estimates for amygdala FC with A) left fusiform gyrus, B) left inferior parietal lobule, C) right superior temporal gyrus, and D) right middle occipital gyrus.

7.4. Discussion

This study was aimed at investigating the impact of dissociation on brain activity and amygdala connectivity during emotional distraction in the context of a delay-response WM task in BPD. Using script-driven imagery, dissociation was induced in 17 BPD patients ('BPDd') while 12 patients ('BPDn') and 18 HC were exposed to a neutral script. Afterwards, participants performed an EWMT with negative (trauma-related) vs. neutral interpersonal images vs. no distraction (only a fixation cross). Dampened amygdala reactivity and stronger frontal activity in BPD patients after dissociation induction was expected. Main findings were:

- *Behavioral performance*: Overall WM impairments (more errors, in particular more misses) in BPDd than in the two other groups.
- *Brain activity*: Overall deactivation in the bilateral amygdala and diminished activity in the left cuneus, lingual gyrus, and posterior cingulate during emotional distraction in BPD_D compared to BPD_N; stronger left inferior frontal gyrus activity in BPD_D than in HC.
- *Amygdala FC during negative vs. no distractors:* Compared to the other groups, BPDd showed increased amygdala FC with the left inferior parietal lobule and right superior temporal gyrus, while exhibiting diminished amygdala-fusiform-gyrus connectivity.

The finding of impaired WM in BPD_D is consistent with previous research, pointing to detrimental effects of pathological dissociation on neuropsychological processes, such as learning, memory, attention, and interference inhibition in BPD (Ebner-Priemer et al., 2009; Haaland & Landrø, 2009; Winter et al., 2015).

Consistent with our previous study (Krause-Utz et al., 2012), distractors in the EWMT elicited significant activity changes in brain regions implicated in emotion processing, attention, WM, and interference inhibition. During emotional distraction, significant group differences were observed. BPDn patients exhibited increased activity in amygdala and insula, which is consistent with previous neuroimaging studies (Schulze et al., 2016; van Zutphen et al., 2015). As pointed out before, not all previous studies in BPD replicated the finding of amygdala hyper-reactivity in BPD (see Ruocco et al., 2013). In the current study, increased amygdala activity was only found in BPD patients who did not undergo dissociation induction. Notably, BPD patients after dissociation induction showed dampened amygdala activity compared to BPDn, while they did not differ significantly from HC. As BPD groups were comparable regarding symptom severity, childhood trauma, PTSD comorbidity, anxiety, depressive mood, and basic working memory performance, findings point to a dampening effect of dissociation on amygdala reactivity, as proposed in current models of dissociation (Lanius et al., 2010; Sierra & Berrios, 1998).

During negative vs. no distractors, BPDn further showed significantly stronger activity in the left precuneus and posterior cingulate: brain areas that are important nodes of the default mode network and have been implicated in self-referential processes, such as autobiographical memory and rumination (Buckner et al., 2008; Buckner & Vincent, 2007; Menon, 2011). Decreased activity in these regions may underlie reduced processing of task-irrelevant but probably self-relevant negative social material (reminders of interpersonal violence) in BPD patients after dissociation induction compared to BPDn.

Consistent with previous script-driven imagery studies (Ludäscher et al., 2010; Winter et al., 2015) and largely in line with our hypothesis, BPDd patients showed stronger activity in the left inferior gyrus than HC, although this finding was not specific to BPDd (i.e., increased activity in the inferior frontal gyrus was also found in the BPDn group. As BPDn did not differ significantly in behavioral WM from, stronger recruitment of the inferior frontal gyrus in this group may reflect compensatory efforts to prevent the occurrence of response inhibition deficits (Jacob et al., 2013; van Eijk et al., 2015).

Extending previous research, we used PPI to explore how the amygdala may interact with other brain areas across the brain during negative vs. no distractors. Both BPD groups differed significantly from HC in amygdala connectivity with frontal, temporal, occipital, and parietal areas. HC showed negative amygdala connectivity with these regions, resembling findings of previous fMRI studies using the EWMT or similar cognitive-affective tasks (Anticevic et al., 2010; Krause-Utz et al., 2014d; Mitchell et al., 2008; Oei et al., 2012). In contrast, BPD patients showed positive amygdala connectivity with these areas. Amygdala 'hyper-connectivity' with frontal regions (including ACC and mPFC) during emotional challenges (Cullen et al., 2011; Kamphausen et al., 2013; Koenigsberg et al., 2014; Niedtfeld et al., 2012) and resting-state (Krause-Utz et al., 2014c; Salvador et al., 2016) were previously observed and may reflect disturbed emotion processing in patients with BPD.

Importantly, we observed significant differences in amygdala connectivity between the two BPD groups, dependent on our experimental manipulation: Compared to the other groups, BPD patients exposed to a neutral script showed stronger positive amygdala connectivity with left fusiform gyrus, which points to enhanced encoding/processing of negative social material (Kruschwitz et al., 2015; Molapour et al., 2015). In contrast, BPD patients exposed to the dissociation script showed a stronger coupling of the amygdala with clusters comprising right middle/superior temporal gyrus and left inferior parietal lobule (insular cortex) than the other groups.

The superior temporal gyrus has previously been implicated in depersonalization and derealization (Lanius et al., 2002; Lanius et al., 2005; Simeon et al., 2000) and considered as an important structure in a pathway including the amygdala and PFC, which is implicated in processing of language, social cognition, self-perception (Bigler et al., 2007). In previous studies in BPD, higher self-reported dissociation was correlated to reduced grey matter volume (Niedtfeld et al., 2013) and increased activity in the middle/superior temporal gyrus (Ludäscher et al., 2010). The inferior parietal lobule has been implicated in emotion regulation and working memory (Nicholson et al., 2015). An increased information exchange of the amygdala with these areas may underlie altered emotional and self-referential processing during dissociative states in BPD.

In summary, our neuroimaging findings suggest that a deactivation of the amygdala and altered interactions of this region with areas implicated in self-referential processing, cognitive control, visual perception, and sensory gating may contribute to dissociative states in BPD, while the precise mechanisms underlying the observed neural patterns remain elusive. Dissociative responses may be an adaptive process when 'fight or flight' is impossible (Lanius et al., 2010; Spiegel et al., 2011), possibly stemming from an evolutionary older 'freezing system' (Fanselow & Lester, 1998; Schauer & Elbert, 2010; Zelikowsky et al., 2014, while direct translations from animal to human research are not possible (see Hagenaars et al., 2014)).

The present findings further suggest that dissociation can become maladaptive by hindering a coherent processing of salient sensory, affective, and cognitive information in memory, which is crucial to a flexible adaptation to stressful situations (Lanius et al., 2010; Schauer & Elbert, 2010; Spiegel et al., 2011). Moreover, dissociation might not only dampen negative emotions but also positive emotions, which can have detrimental consequences for the quality of life and the maintenance of close relationships. Given these detrimental effects and previous findings of poor treatment outcome in BPD patients with high dissociative symptoms (Arntz et al., 2015; Kleindienst et al., 2011, 2016; Spitzer et al., 2007), our findings highlight the importance of taking dissociation into account when treating individuals with BPD.

To our knowledge, this is the first study in BPD revealing a significant impact of a dissociation induction on activity and functional connectivity of the amygdala during emotional distraction in the context of the EWMT. Present findings may shed a new light on stress-related dissociation in BPD, as affective-cognitive processing was studied on multiple (subjective, behavioral, neural) levels in an experimental context which requires the conscious manipulation of stressful material in WM. Patient groups were matched regarding psychopathology and basic working memory and it was ensured that BPD_N patients were not dissociated.

However, this led to a relatively small sample size and only female patients with a history of childhood abuse/neglect were included. We did not apply additional drug tests to rule out this possibility of false self-reports of our participants. Furthermore, it is likely that present findings may not be specific to BPD but also observable in other clinical populations with dissociative features, being a trans-diagnostic phenomenon (Lanius et al., 2010, 2012). This means, more research with larger sample sizes, clinical control groups, and extended medical checks is needed to clarify whether the reported neural patterns can be replicated in other samples of BPD patients or are confounded by the afore-mentioned sample characteristics. As we used PPI, findings are restricted to our seed region and causality of interactions remains unknown (Friston et al., 1997; O'Reilly et al., 2012). Tension ratings were significantly higher in BPD_D than BPD_N. Nevertheless, group differences in amygdala reactivity remained significant after including aversive tension as covariate.

All in all, our findings suggest a dampening effect of dissociation on activity in brain areas implicated in the processing of disturbing (trauma-related) information in BPD and an impairing effect on working memory, which plays a crucial role in goal-directed behavior. More research is needed to understand the impact of dissociation on other aspects of emotion regulation, cognition and identity in BPD and to gain more insight into this complex phenomenon.

Disclosure: None of the authors declares biomedical financial interests or potential conflicts of interest. Investigator B. M. Elzinga was funded by a VIDI grant by the Netherlands Organization for Scientific Research (grant number 016·085·353).

Acknowledgements: We thank all participants of this study for their collaboration.

Supplemental Material

Table S7.1.
Results of the Psychophysiological Interaction (PPI) Analysis for bilateral amygdala functional connectivity during negative versus no distractors

Label of brain region (aal)	Lobe	Brodman area (BA)	Cluster size	Peak voxel coordinates (X, Y, Z)	F value	Z value	P value
Fusiform Gyrus Fusiform Gyrus Culmen	Occipital Lobe Posterior Lobe Anterior Lobe	N.A. N.A. N.A.	1118	30 -55 -17 -27 -55 -14 39 -52 -29	21.91 18.27 16.99	5.03 4.65 4.50	FWE <0.05
Superior Frontal Gyrus, Medial Frontal Gyrus, Supplemental Motor Area	Frontal Lobe Frontal Lobe Frontal Lobe	BA 6 BA 6 BA 6	457	12 2 70 3 -7 58 -3 5 61	21.36 17.09 16.46	4.97 4.51 4.43	FWE <0.05
Middle Frontal Gyrus Middle Frontal Gyrus	Frontal Lobe Frontal Lobe	BA 6 BA 6	127	42 -4 55 27 -7 64	20.45 9.15	4.88 3.30	FWE <0.05
Inferior Parietal Lobule/ Supramarginal Gyrus Temporal Gyrus (Insular cortex)	Parietal Lobe Parietal Lobe Temporal Lobe	BA 40 BA 13 BA 21	163	-57 -46 22 -48 -40 25 -63 -52 7	14.95 13.45 9.85	4.24 4.03 3.44	FWE <0.05
Precentral Gyrus Middle Frontal Gyrus	Frontal Lobe Frontal Lobe	BA 6 BA 6	76	-42 -4 43 -36 -1 61	14.24 11.05	4.14 3.65	<0.001
Insula Superior Temporal Gyrus	Sub-lobar Temporal Lobe Temporal Lobe	BA 13 BA 38 BA 38	119	39 14 -2 57 5 -8 51 17 -8	13.92 13.89 13.53	4.10 4.10 4.04	(FWE) <0.05
Insula	Sub-lobar	N.A.	16	-33 11 -2	13.12	3.98	(FWE) <0.05*
Claustrum Claustrum	Sub-lobar Sub-lobar	N.A. N.A.	46	-30 11 -5 -27 26 -2	13.72 8.62	4.07 3.20	<0.001
Middle Occipital Gyrus	Occipital Lobe	BA 31	50	30 -76 22	12.26	3.85	<0.001
Superior Temporal Gyrus	Temporal Lobe Temporal Lobe	BA 41 BA 22	34	45 -43 10 54 -43 10	11.91 9.34	3.80 3.34	<0.001
Superior Frontal Gyrus	Frontal Lobe	BA 8	10	-3 32 58	10.83	3.62	FWE) <0.05*
Middle Temporal Gyrus	Temporal Lobe	N.A.	11	51 -34 -5	10.30	3.52	<0.001
Cingulate Gyrus	Limbic Lobe	BA 32	34	6 11 43	13.27	4.01	FWE) <0.05*
Superior Frontal Gyrus	Frontal Lobe	BA 8	10	-3 32 58	10.83	3.62	FWE) <0.05*

Note: Z -values were determined by an initial cluster-forming threshold of $p<0.001$ uncorrected (uncor) on a whole-brain voxel-wise level. FWE = Family Wise Error corrected at a cluster level. Clusters detected after small volume correction (SVC) ($p<0.05$) are indicated by an asterisk (*).

Medication history: *n (%)*	BPD_D (n=17)	BPD_N (n=12)	Chi² tests
Previous medication	13 (76%)	1 (8%)	χ^2=0.37, *p*=.830
Acamprosate	0 (0%)	1 (8%)	
Atypical antipsychotics	1 (6%)	1 (8%)	
BZD	2 (12%)	2 (17%)	χ^2=6.21, *p*=.400
SNRI	3 (18%)	1 (8%)	
SSRI	6 (35%)	3 (18%)	
TCA	1 (6%)		
Time of last medication[1]			
1 month ago	3 (18%)	1 (8%)	
≥ 3 month ago	2 (12%)	1 (8%)	χ^2=4.76, *p*=.190
≥ 6 month ago	2 (12%)	6 (50%)	
≥ 12 month ago	4 (24%)	1 (8%)	

Note: BPD_D= patients with Borderline Personality Disorder exposed to a dissociation script, BPD_N= patients with Borderline Personality Disorder exposed to a neutral script, BZD= Benzodiazepine, SSRI=Selective serotonin re-uptake inhibitor, SNRI=Serotonin–norepinephrine reuptake inhibitor, TCA= Tricyclic antidepressant, [1] information in 2 BPD_D patients was missing

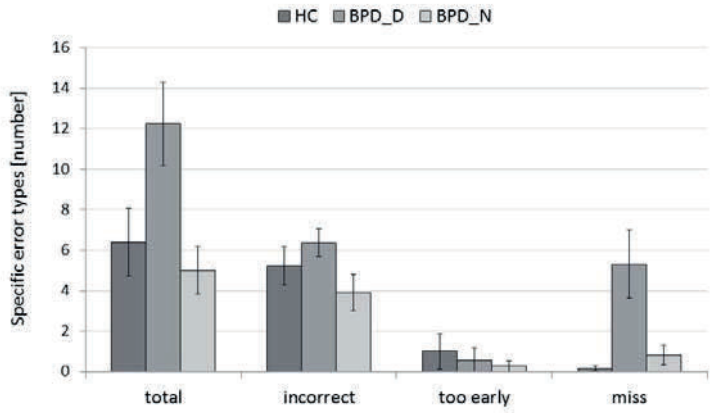

Figure S7.1. Specific types of errors (total number of too early responses (before probe) and misses) during the Emotional Working Memory Task in patients with Borderline Personality Disorder (BPD) after dissociation induction (BPD_D) and after the neutral script (BPD_N) as well as in healthy controls (HC).