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Pain-mediated affect regulation is reduced after dialectical behavior therapy in borderline personality disorder: a longitudinal fMRI study

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Abstract

Borderline Personality Disorder (BPD) is characterized by affective instability, but self-injurious behavior appears to have an emotion-regulating effect. We investigated whether pain-mediated affect regulation can be altered at the neural level by residential Dialectical Behavior Therapy (DBT), providing adaptive emotion regulation techniques. Likewise, we investigated whether pain thresholds or the appraisal of pain change after psychotherapy. We investigated 28 patients with BPD undergoing DBT (self-referral), 15 patients with treatment as usual and 23 healthy control subjects at two time points 12 weeks apart. We conducted an fMRI experiment eliciting negative emotions with picture stimuli and induced heat pain to investigate the role of pain in emotion regulation. Additionally, we assessed heat and cold pain thresholds.
At first measurement, patients with BPD showed amygdala deactivation in response to painful stimulation, as well as altered connectivity between left amygdala and dorsal anterior cingulate cortex. These effects were reduced after DBT, as compared with patients with treatment as usual. Pain thresholds did not differ between the patient groups. We replicated the role of pain as a means of affect regulation in BPD, indicated by increased amygdala coupling. For the first time, we could demonstrate that pain-mediated affect regulation can be changed by DBT.

Key words: borderline personality disorder; emotion regulation; dialectical behavior therapy; pain, self-injury; fMRI

Introduction

Borderline Personality Disorder (BPD) is a highly prevalent personality disorder (Coid *et al.*, 2006; Trull *et al.*, 2010), characterized by instability in affective states, self-image, interpersonal relationships, and dysfunctional behavior such as non-suicidal self-injury (NSSI). According to the biosocial theory (Linehan, 1993; Crowell *et al.*, 2009), those with BPD show heightened emotional sensitivity and an inability to regulate intense emotional responses. Congruent with this theoretical concept, a recently published meta-analysis of neuroimaging studies on emotion processing in BPD showed left amygdala hyperactivity and reduced dorsolateral prefrontal control (Schulze *et al.*, 2016). Furthermore, heightened emotional sensitivity and

dysfunctional emotion regulation were found to lead to dysfunctional behavior, such as non-suicidal self-injury (NSSI) (Stiglmayr *et al.*, 2005; Kleindienst *et al.*, 2008). NSSI was suggested to have an affect-regulating effect (Klonsky, 2007; Kleindienst *et al.*, 2008), and is used by patients to reduce aversive tension (Chapman *et al.*, 2006).

A high percentage of BPD patients (70%) engage in NSSI (Zanarini *et al.*, 2008), and report that injuring themselves leads to immediate relief from aversive tension (Herpertz, 1995), an instant decrease of dissociative symptoms, and elevated mood (Kemperman *et al.*, 1997). Additionally, many patients (50–60%) report analgesic phenomena during NSSI (Leibenluft *et al.*, 1987). Examining pain perception in BPD, pain was induced experimentally via temperature, electric shocks, or laser stimuli. It was repeatedly observed that patients with BPD and current NSSI reveal significantly reduced sensitivity to pain compared with healthy control (HC) subjects (for an overview, see Ducasse *et al.* 2014). Cross-sectional data suggest an underlying learning mechanism, since patients show normalizing pain perception after termination of NSSI (Ludascher *et al.*, 2009).

At the neural level, harmful stimuli result in the activation of the so-called pain matrix, comprising primary and secondary somatosensory cortex, anterior and posterior insula, and anterior cingulate cortex (ACC) (Iannetti and Mouraux, 2010). More specifically, (Treede *et al.* 1999) proposed a model with respect to pain perception, distinguishing a sensory-discriminative component and an affective-motivational component. The former, which is necessary for stimulus localization, intensity, and quality discrimination, proceeds in a 'lateral' pathway projecting from the lateral thalamic nuclei to the primary and secondary somatosensory cortices. In contrast, the latter component, which is responsible for the evaluation of pain and emotional or behavioral reactions, is anatomically conceptualized as a 'medial' pathway projecting from the medial thalamic nuclei to the insula and the ACC.

Previous neuroimaging studies on the processing of painful thermal stimuli in BPD found reduced amygdala and perigenual ACC activity together with enhanced activation of dorsolateral prefrontal cortex (dlPFC) in response to pain (Schmahl *et al.*, 2006), which was interpreted as an altered affective appraisal of pain. During processing of thermal pain, patients with BPD also exhibited less connectivity between the posterior cingulate cortex and dlPFC (Kluetsch *et al.*, 2012), suggesting that appraisal of pain in patients with BPD is less self-relevant and aversive. Examining the neural mechanisms underlying the role of self-inflicted pain as a dysfunctional attempt to regulate negative emotions in BPD, the effect of heat pain on the processing of aversive visual stimuli was investigated (Niedtfeld *et al.*, 2010). In a functional connectivity analysis, negative pictures combined with painful sensory stimuli, as opposed to non-painful warm sensations, resulted in negative coupling between limbic (i.e. amygdala, perigenual ACC) and prefrontal structures (i.e. BA8 and BA9) in BPD, reflecting inhibition of limbic arousal (Niedtfeld *et al.*, 2012). Simulating NSSI with an experimental pain model, two recent studies showed a soothing effect of tissue damage after stress induction in BPD at the subjective, physiologic, and neural level (Reitz *et al.*, 2012; Reitz *et al.*, 2015). In response to tissue damage, those with BPD also showed enhanced connectivity between amygdala and BA8 (Reitz *et al.*, 2015). It was concluded that NSSI in BPD has a soothing effect and constitutes an attempt to attenuate aversive arousal, thereby compensating the failure of other functional emotion regulation strategies.

Dialectical Behavior Therapy (DBT, (Linehan, 1993)) aims to establish functional emotion regulation strategies to reduce NSSI and suicidality. Although DBT has repeatedly proven to be an effective treatment with regard to borderline symptomatology (Kliem *et al.*, 2010; Stoffers *et al.*, 2012), only two studies examined the effects of DBT on neural processing. The first study investigated emotion processing in six BPD patients before and after a 12-week inpatient DBT program and found reduced ACC and anterior insula activity during the passive viewing of negative pictures after DBT (Schnell and Herpertz, 2007). The second study investigated habituation using repetitive emotional pictures before and after 12 months outpatient DBT treatment and showed reduced amygdala activity after DBT (Goodman *et al.*, 2014). However, these studies did not use a BPD control group without DBT to differentiate between effects attributable to DBT itself from unspecific time effects. Pain perception and pain processing before and after DBT has not been studied so far.

Consequently, the goal of this study was to examine whether the affect-regulating function of pain in BPD can be normalized by DBT treatment. To this end, we compared female BPD patients participating in a 12-week inpatient DBT treatment (BPD-DBT) with BPD patients without DBT (BPD-TAU) and a HC group. At two time points 12 weeks apart, participants took part in an fMRI study combining the presentation of emotional pictures in order to elicit emotional arousal with thermal stimuli to induce heat pain. We hypothesized that in response to painful stimuli combined with negative emotional stimuli, we would replicate previous findings of (i) attenuated limbic (i.e. amygdala, ventral ACC) arousal and (ii) negative connectivity of limbic and prefrontal (i.e. dlPFC, BA8, dorsal ACC) structures in BPD. We further hypothesized that this effect of pain-mediated affect regulation in BPD is normalized after 12 weeks of DBT. More specifically, at the second measurement point we assumed to find (iii) no deactivation of limbic regions when negative stimuli are paired with painful stimulation in BPD, pointing to lower effectiveness of pain with regard to emotion regulation. We also expected (iv) a negative connectivity between limbic and prefrontal structures in conditions without painful stimulation in BPD, speaking for improved emotion regulation. Accordingly, (v) pain sensitivity was expected to be reduced in BPD before therapy and increased after DBT treatment.

Methods and materials

Sample and diagnostic assessment

34 BPD patients receiving DBT treatment (BPD-DBT) were recruited at specialized inpatient treatment units at the Central Institute of Mental Health Mannheim and at Heidelberg University Hospital. Both treatment units administer a standard DBT program (Bohus *et al.*, 2004), including individual therapy, and skills training group (2.5 h per week). The two control groups of patients without DBT but treatment as usual (BPD-TAU, $n = 18$) and HC subjects (HC, $n = 29$) were recruited through advertisement. Patients with BPD selected the treatment according to their preferences independently. See Table 1 for demographic and clinical characteristics. BPD + TAU patients continued the non-DBT treatment they had at study entrance: various forms of outpatient individual psychotherapy (43.8%), residential crisis intervention (6.3%), pharmacotherapy (37.5%), self-help group (6.3%), and non-specific community-based treatment (43.75%). No patient in this group was waiting for DBT treatment. We had to exclude 15 subjects from the fMRI analyses due to technical difficulties with the pain application (2 BPD + TAU), or excessive head movement (6 BPD + DBT,

Table 1. Demographic and clinical characteristics

	BPD + DBT (n = 34)			BPD + TAU (n = 18)			HC (n = 29)			Statistics	
	AM	s.d.	n	AM	s.d.	n	AM	s.d.	n		P
Age (years)	27.71	7.24		25.06	5.81		28.14	8.35		$F_{(2)} = 1.068$	0.349
professional qualification										$\chi^2_{(6)} = 9.57$	0.615
none		0 (0%)			1 (5.6%)			0 (0%)			
vocational training		14 (41.1%)			17 (94.4%)			6 (20.7%)			
college		10 (29.4%)			14 (77.8%)			11 (37.9%)			
university degree		3 (8.8%)			2 (11.1%)			1 (3.4%)			
Number of Axis I-co-morbidities	1.76	1.16		1.67	1.09					$t_{(50)} = 0.297$	0.768
ZAN-BPD	16.88	5.91		15.89	5.94					$t_{(50)} = 0.576$	0.568
BSL	2.11	0.65		2.08	0.87					$t_{(50)} = 0.157$	0.876
DERS	132.7	24.69		131.6	25.08					$t_{(50)} = 0.145$	0.886
psychotropic medication											
number of drugs	1.06	1.09		1.06	1.47					$t_{(50)} = 0.009$	0.993
unmedicated		13 (38.2%)			9 (50.0%)					$\chi^2_{(1)} = 0.617$	0.414
SSRI		13 (38.2%)			6 (33.3%)						
SNRI		7 (20.6%)			2 (11.1%)						
other antidepressants		7 (20.6%)			3 (16.7%)						
neuroleptics		2 (5.9%)			3 (16.7%)						
mood stabilizers/anticonvulsants		2 (5.9%)			3 (16.7%)						
other (e.g. Naltrexon)		5 (14.7%)			2 (11.1%)						

Table 2. Frequency and Type of NSSI in BPD + DBT and BPD + TAU

	BPD + DBT (n = 34)		BPD + TAU (n = 18)		Statistics	
	AM	s.d.	AM	s.d.		P
Frequency NSSI (last month)	2.29	1.45	2.44	1.67	$t_{(48)} = 0.311$	0.757
Period of time since last NSSI (days)	28.06	52.74	18.71	26.34	$t_{(49)} = 0.687$	0.495
Types of NSSI during the last month	n		n			
cutting	25 (73.5%)		8 (44.4%)			
burning	1 (2.9%)		1 (5.6%)			
scalding	5 (14.7%)		3 (16.7%)			
bang head against wall	11 (32.4%)		4 (22.2%)			
hemorrhage	0 (0%)		1 (5.6%)			
pricking	2 (5.9%)		4 (22.2%)			
hitting	7 (20.6%)		5 (27.8%)			
scratching	14 (41.2%)		6 (33.3%)			
skinning	9 (26.5%)		2 (11.1%)			
pulling hair	2 (5.9%)		3 (16.7%)			
drug use	5 (14.7%)		4 (22.2%)			

3 BPD + TAU, 6 HC). Therefore, the final sample for the fMRI analyses consisted of 28 BPD + DBT, 15 BPD + TAU, and 23 HC.

All BPD patients met DSM-IV diagnosis for BPD, including affective instability and NSSI during the last month prior to the first assessment. They all engaged in NSSI frequently during the last 6 months (see Table 2 for more detailed information on NSSI). Additionally, patients had no significant prior experience with DBT skills training, and were either unmedicated or had a constant medication at both time points (61.8% in the BPD + DBT group, 50% in the BPD + TAU group; for more information on medication and comorbid diagnoses, see Table 1). HC did not meet any lifetime psychiatric disorder and received no psychotropic medication. We excluded participants with left-handedness, traumatic brain injury, lifetime schizophrenia or bipolar I disorder, mental or developmental disorders, substance dependence during the last year, drug consumption in the last two months, current severe depressive episode, and benzodiazepine use.

Diagnoses were assessed by trained clinical psychologists carrying out the German Versions of the Structured Clinical Interview for DSM-IV (Wittchen *et al.*, 1997), and the International Personality Disorder Examination (Loranger *et al.*, 1998). Symptom severity was assessed via the Zanarini Rating Scale for BPD (ZAN-BPD (Zanarini *et al.*, 2003)), and the Borderline Symptom List (BSL; Bohus *et al.*, 2009)]. Emotion regulation difficulties were assessed using the Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004). Treatment response was assessed via dimensional ZAN-BPD scores, using reliable change index (Jacobson and Truax, 1991), resulting in 13 DBT treatment responders and 15 non-responders. Treatment responders and non-responders did not differ significantly in age, education, frequency of NSSI during

the last month, number of Axis I-co-morbidities, number of Psychotropic Drugs, or emotion regulation difficulties, but treatment responders had higher symptom levels (ZAN-BPD and BSL) before therapy (Supplementary Table S1).

The study was part of a larger project on alterations in neural correlates of emotion regulation in BPD after DBT, which was registered as a clinical trial (German clinical trials registration (DRKS), registration ID DRKS00000778). It was approved by the Ethics Board II of the Medical Faculty Mannheim, University of Heidelberg. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Each subject provided written informed consent after the procedures had been fully explained.

Stimulus material and procedure

All subjects participated in two fMRI sessions (t_1 and t_2) 12 weeks apart. Every session consisted of assessment of self-report measures reported above, assessment of pain thresholds, and an fMRI session with three different emotion regulation paradigms presented in randomized order (we report on the sensory shift paradigm in the following; cognitive distraction and reappraisal are reported elsewhere). In contrast to classical emotion regulation paradigms (reappraisal, distraction), the sensory shift paradigm paradigm was not designed to investigate intentional emotion regulation but rather to test whether psychotherapy modulates BPD patients' maladaptive emotion regulation strategy to attenuate aversive arousal through pain. Therefore, the participants did not have an emotion regulation task to perform. Their task was to watch the pictures, which were combined with temperature stimuli.

Pain thresholds

After arrival and completion of questionnaires, heat and cold pain thresholds were determined using the method of limits. Subjects were presented three ascending and three descending temperature stimuli (with a rising/falling rate of 2°C per second, starting from a non-painful temperature of 38°C), and had to indicate via button press as soon as they experienced pain. Additionally, we determined an individualized painful stimulus equalling 60% of the subjective pain scale, which served as painful stimulus within the fMRI session. To this end, we used three runs of ascending and descending heat stimuli with 6 s duration, each rated on a subjective pain scale ranging from 0% (no pain) to 100% (worst imaginable pain). Subjects were instructed that 60% equals to a painful yet still tolerable sensation, which they should be able to tolerate 36 times (i.e. the number of painful stimuli during fMRI session). Temperature stimuli were delivered using a Thermal Sensory Analyzer II (Medoc Advanced Medical Systems Ltd, Ramat Yishay, Israel), a device to induce thermal stimuli at with a 3×3 cm surface area at the left volar forearm.

fMRI measurement

Then, subjects were positioned in the scanner and were instructed to watch the presented pictures. The task was designed to incorporate two within-subject factors ('picture valence' with the factor levels negative and neutral, and 'temperature stimulus' with the factor levels painful *vs.* baseline). The 72 experimental trials consisted of negative or neutral picture stimuli (presented for 6 s), which were selected from standardized

picture sets (International Affective Picture System, Lang *et al.*, 2005), and the Emotional Picture Set (Wessa *et al.*, 2010). We formed six picture sets that were parallelized regarding valence and arousal ratings. These were presented in randomized order for each participant within the temperature condition (painful/baseline) and sessions (t_1/t_2), thereby controlling for condition and time effects. Valence and arousal ratings of the picture sets within the same condition did not differ significantly. Negative pictures showed human or animal threat, accidents, interpersonal violence, and mutilation. Neutral pictures did not show humans or interpersonal scenes.[1]

Simultaneously, participants received either the baseline temperature (32°C), or the individual painful temperature stimulus. As the baseline temperature was present during the whole experiment, subjects did only notice the occurrence of the painful temperature stimulus. This setup results in 18 trials of every experimental condition (i.e. negative painful, negative baseline, neutral painful, neutral baseline). Between trials, participants saw a white fixation cross on a black screen, presented for a jittered time interval of 3–8 s. To monitor vigilance of the participants, 24 catch trials (i.e. the letter 'O') were included between experimental trials that required an immediate button press response.

Psychometric and behavioral data analyses

With regard to symptom severity and pain thresholds, we were interested in alterations over time dependent on the group. Therefore, we computed 3×2-rmANOVAs with the between-subjects factor Group (BPD + DBT, BPD + TAU, HC) and the within-subjects factor Time (t_1 *vs* t_2) for each of the dependent variables (ZAN-BPD, heat pain threshold, cold pain threshold, and individualized painful temperature). All analyses were performed at a threshold of $p < 0.05$ with SPSS Statistics 22 (IBM, USA).

Brain imaging and data analyses

Brain images were acquired using a 3 Tesla MRI scanner (TRIO, Siemens Medical Systems, Erlangen, Germany) with a 32-channel head coil and a T2*-weighted gradient echo-planar imaging sequence (repetition time = 2000 ms, echo time = 30 ms, voxel size = $3 \times 3 \times 3$ mm, matrix = 64×64, number of slices = 36). A high-resolution T1-weighted structural scan was acquired for co-registration of functional images. Functional data were analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom), and functional connectivity was investigated using the generalized psychophysiological interaction (gPPI) toolbox (McLaren *et al.*, 2012).

The echo-planar imaging time series were pre-processed according to custom practice. Procedures comprised slice time correction, spatial realignment, segmentation of T1 scan, coregistration onto T1 scan, normalization to the standard brain of the Montreal Neurological Institute space, resampling to 3 mm^3 voxels, smoothing with a Gaussian kernel with a full-width at half maximum of 6 mm. As mentioned above, we had to exclude 6 BPD + DBT, 3 BPD + TAU, and 6 HC due to excessive head movement. The first-level analyses were modeled using an event-related design with a high-frequency cutoff filter of 128 Hz. We modeled four regressors of interest, resulting from the combinations of the 2×2 factor levels of the task (negative painful, negative baseline, neutral painful, neutral baseline), and seven regressors of no interest (button presses, six movement parameters). The individual maps of the respective

Table 3. Psychometrics in BPD + DBT and BPD + TAU

	BPD + DBT (n = 34)					BPD + TAU (n = 18)					Group differences at t1		Group by time interaction	
	t_1		t2		t_1–t_2	t1		t2		t_1–t_2				
	AM	s.d.	AM	s.d.	P	AM	s.d.	AM	s.d.	P	t	P	F	P
ZAN-BPD	16.88	5.91	9.97	6.20	0.001	15.89	5.94	12.39	6.29	0.01	0.576	0.568	3.433	0.70
BSL	2.11	0.65	1.76	0.80	0.01	2.08	0.87	2.03	0.88	0.625	0.157	0.876	2.488	0.12
DERS	132.71	24.69	108.76	23.50	0.001	131.6	25.08	130.99	26.49	0.848	0.145	0.886	11.68	0.001

BSL, borderline symptom list; DERS, difficulties in emotion regulation scale; ZAN-BPD, Zanarini rating scale for borderline personality disorder.

Table 4. Pain thresholds in BPD + DBT and BPD + TAU

	BPD + DBT (n = 28)					BPD + TAU (n = 15)					Group differences at t1		Group by time interaction	
	t_1		t_2		t_1–t_2	t_1		t_2		t_1–t_2				
	AM	s.d.	AM	s.d.	P	AM	s.d.	AM	s.d.	P	t	P	F	P
Heat pain	46.40	2.73	46.14	2.73	.423	46.21	2.75	45.61	3.28	.028	0.794	.431	0.122	.73
Cold pain	7.99	8.00	7.97	8.53	.607	13.00	10.76	11.55	10.25	.696	2.207	.032	0.212	.65
Ind. Temp.	46.81	2.13	46.36	2.35	.262	45.97	2.53	46.67	2.23	.569	1.726	.091	4.868	.03

Ind. Temp. = individualized temperature stimulus equalling 60% of the subjective pain scale.

contrasts of interest ('negative painful, negative baseline, neutral painful, neutral baseline') were entered into the second level analyses. The differential contrast images for each participant and time point were entered into a second-level full factorial design with the factors Group (BPD + DBT, BPD + TAU, HC), Valence (negative vs neutral), Temperature (painful vs baseline), and Time (t_1 vs t_2). We chose a voxelwise family-wise error correction procedure with a threshold of $P_{(FWE)} < 0.05$ at the whole brain level. In case of a significant result, we extracted beta values of the respective peak voxel, calculated Cohens f (Cohen, 1988) for interaction effects and Cohens d for post-hoc t-tests, and reported it in the results section. According to Cohen (Cohen, 1988), an effect size of $d = 0.2$ or $f = 0.1$ reflects a small effect, $d = 0.5$ or $f = 0.25$ a medium effect, and $d = 0.8$ or $f = 0.4$ a large effect size.

Additionally, we conducted region-of-interest analyses by applying small volume correction (SVC) with a threshold of $P_{(FWE)} < 0.05$. In line with our hypotheses, we wanted to investigate the effect of pain on limbic (i.e. amygdala, ACC) and prefrontal (i.e. dlPFC, BA8) brain areas processing negative affect. Therefore, we used two masks, located within the left amygdala and the left DLPFC, which were both derived from a recent meta-analysis on emotion processing in BPD (Schulze et al., 2016). To this end, the meta-analytic statistical map of the contrast negative > neutral in BPD > HC were downloaded (http://neurovault.org/collections/TDPEZUJL/), and the significant clusters within the left amygdala and the left dlPFC were saved as a binary mask image. The ACC and BA8 masks were derived from a previous article on the effect of pain on emotion regulation in BPD, using a very similar experimental paradigm (Niedtfeld et al., 2012). All masks were smoothed with a Gaussian kernel with a full-width at half maximum of 6 mm.

Finally, a gPPI (McLaren et al., 2012) analysis of functional connectivity used the amygdala cluster described above for the definition of the seed region. In contrast to standard PPI, the gPPI analysis is configured to automatically include more than two task conditions in the same PPI model, thereby spanning the full space of the experimental design. Activation time series

from the amygdala seed region was extracted and entered into a first level analysis together with the psychological predictors (i.e. task vectors convolved with HRF) and the interaction of both. Contrast maps for connectivity of the left amygdala in response to negative pictures combined with painful temperature ('negative painful'), and combined with baseline temperature ('negative baseline') were computed and entered into a second level full factorial design with the factors group, temperature, and time. The valence factor (i.e. neutral pictures) was omitted within the second-level analysis to ensure that our findings are still interpretable with regard to positive versus negative connectivity (which is not the case when subtracting negative-neutral at the first level), and at the same time avoiding a four-factorial design in the second level analysis due to reduced statistical power. We chose a voxel-wise family-wise error correction procedure with a threshold of $P_{(FWE)} < 0.05$ at the whole brain level, and tested the region of interests described earlier using SVC.

Results

Demographic and clinical characteristics

We found no significant differences at t_1 between BPD + DBT and BPD + TAU in age, professional qualification, measures of borderline symptom severity (ZAN-BPD, BSL), or time since the last NSSI (Tables 1 and 2). Data and statistics for Group by Time interactions of clinical characteristics are summarized in Table 3. Comparing alterations over time between the patient groups, BPD + DBT displayed large and significant decreases in all psychometric measures (Cohens d within group t_2 - t_1 in BPD + DBT: ZAN-BPD = 1.14, BSL = 0.48, DERS = 0.99). These decreases were larger in the BPD + DBT group than in the BPD + TAU group (Cohens d between groups: ZAN-BPD = 0.54, BSL = 0.47, DERS = 1.13), although the corresponding interaction effects (group by time) reached statistical significance only for the DERS.
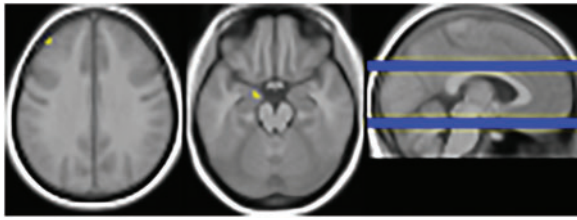
Fig. 1. Significant clusters in the amygdala and dlPFC, four-way interaction effect (group by valence by temperature by time), small volume corrected.

Pain thresholds and subjective rating of pain

As expected, pain thresholds at t_1 (heat and cold) were lower, and the temperature with a subjective painfulness of 60%**** was higher in patients with BPD compared with HC [$t_{(77)}$ = 5.37, $P < 0.001$, $d = 1.26$; $t_{(77)}$ = 4.83, $P < 0.001$, $d = 1.13$; $t_{(77)}$ = 1.76, $P < 0.05$, $d = 0.41$; respectively]. With regard to treatment effects, we compared BPD + DBT and BPD + TAU and did not observe significant group by time interactions with regard to heat or cold pain thresholds (Table 4), why we could only partly support our fifth hypothesis regarding pain sensitivity. However, we found a significant group by time interaction for the individualized pain stimulus [$F_{(1,41)}$ = 4.868, $P < 0.05$, $f = 0.36$], which showed a slight decrease in the BPD + DBT group and an increase in DBT + TAU. *Post-hoc* pairwise *t*-tests revealed that changes over time were not significant for BPD + DBT, but significant for DBT + TAU [$t_{(15)}$ = 2.43, $P < 0.05$, $d = 0.26$].

fMRI data

The four-way interaction effect Group (BPD + DBT *vs* BPD + TAU *vs* HC) by Valence (negative *vs* neutral) by Temperature (painful *vs* baseline temperature) by Time (t_1 *vs* t_2) resulted in significant clusters in the amygdala (SVC) and dlPFC (SVC) (Figure 1 and Table 5). At the whole brain level, we did not observe any clusters that survived FWE-correction.

In the ROI analysis of the amygdala, we observed a neural deactivation in response to negative pictures combined with painful temperature ('negative painful') in BPD + DBT at t_1, which was not present anymore at t_2 (Figure 2a), also indicated by the respective *post-hoc* t-test for dependent samples [$t_{(27)}$ = 2.055, $P = 0.05$, $d = 0.44$]. Similar *post-hoc* t-tests of amygdala activation in response to every experimental condition, comparing t_1 *vs* t_2 within each group did not reach significance. This supports our hypothesis 1 regarding the dampening effect of pain on amygdala reactivity before therapy, as well as hypothesis 3 on treatment effects.

Regarding activation of the dlPFC (BA9, Figure 2b), *post-hoc* t-tests revealed significant changes from t_1 to t_2 in the BPD-DBT group only with regard to negative pictures combined with baseline temperature: Negative pictures (without pain) resulted in marked activation at t_1, and reduced activation of the dlPFC at t_2 [$t_{(27)}$ = 4.273, $P < 0.001$, $d = 0.69$]. Similar *post-hoc* t-tests of dlPFC activation comparing t_1 *vs* t_2 within the BPD-TAU group did not reach significance. In the HC group, negative pictures combined with baseline temperature resulted in reduced activation at t_1, while we found increased activation at t_2 [$t_{(22)}$ = 2.917, $P < 0.05$, $d = 0.66$]. The data did not support our hypothesis 1 with regard to increased dlPFC activation in response to pain.

PPI analysis of functional connectivity

The interaction effect group (BPD + DBT *vs* BPD + TAU *vs* HC) by temperature (painful vs. baseline temperature) by time (t_1 *vs* t_2) resulted in no significant clusters at the whole brain level [$P_{(FWE)} < 0.05$], but a trend for significance in the BA32/dorsal ACC [SVC $P_{(FWE)} = 0.08$, $f = 0.62$]. *Post-hoc* t-tests (Figure 3), comparing t_1 and t_2 in BPD + DBT, point to an alteration of connectivity after therapy for both experimental conditions [$t_{(27)}$ = 2.722, $P < 0.05$, $d = 0.45$ for 'negative hot'; $t_{(27)}$ = 3.542, $P < 0.01$, $d = 0.74$ for 'negative baseline'], thereby supporting our hypothesis 4 on altered amygdala connectivity. At t_1, the dorsal ACC showed only marginal connectivity with the amygdala when negative pictures were combined with painful stimuli, and a positive connectivity in response to negative pictures with baseline temperature. This pattern was altered at t_2, showing positive connectivity when negative pictures were combined with painful stimuli and a negative connectivity in response to negative pictures with baseline temperature. We did not find any significant changes from t_1 to t_2 in the other groups.

Discussion

The central goal of this study was to replicate earlier results that painful stimuli serve as dysfunctional attempt to regulate limbic arousal in BPD and to investigate how the neural correlates of this effect may change after DBT treatment. As hypothesized, patients in the DBT treatment group as compared with BPD patients with treatment as usual and HC subjects show differences in brain activation in dlPFC (BA9) and left amygdala. More specifically, before treatment, we could replicate previous findings of neural deactivation of the amygdala in response to painful stimuli (Schmahl *et al.*, 2006; Reitz *et al.*, 2015). More importantly, this amygdala deactivation was not present any longer in BPD + DBT patients after treatment. Since the left amygdala was consistently found to be hyperactive in BPD (Schulze *et al.*, 2016), the soothing effect of pain in BPD appears to be present at the first measurement and is reduced after DBT treatment.

Complementing the results of brain activation, in the BPD + DBT group we found uncoupling between left amygdala and dACC in response to painful stimuli before treatment, as well as positive connectivity in response to baseline temperature, and a negative connectivity in response to baseline temperature after treatment. More specifically, after DBT we observed inhibitory coupling in response to negative pictures combined with baseline temperature, which might be interpreted as a neural correlate of functional emotion regulation processes (Comte *et al.*, 2016). The dorsal ACC has been described as the cognitive part of the ACC (Bush *et al.*, 2000). Therefore, this suggests an increased inhibition of limbic activity at t_2, possibly due to increased emotion regulation capacity after DBT treatment. More specifically, intentional emotion regulation skills taught within the DBT skills group might have enabled patients to regulate amygdala activity more efficiently.

With regard to pain thresholds, we could replicate previous results of reduced sensitivity to pain in BPD before therapy (Ducasse *et al.*, 2014), but found no evidence for a treatment effect. Specifically, there were no significant treatment effects in heat and cold pain thresholds operationalized by the method of limits. However, with regard to the individualized temperature stimuli, we found a slight but nonsignificant reduction after therapy for the BPD + DBT group, and a significant increase in BPD + TAU. Although descriptively we observed a

Table 5. Statistic results of region of interest analyses, four-way interaction effect (group by valence by temperature by time)

Location		Statistics				Coordinate (MNI)		
Brodmann Area	aal	cluster	Z	p(uncorr)	Cohens f from peak voxel	x {mm}	y {mm}	z {mm}
BA 9	Superior Frontal Gyrus	48	3.90	0.01 (SVC)	0.52	−36	41	37
Amygdala	Amygdala	7	2.84	0.03 (SVC)	0.63	−18	−4	−23
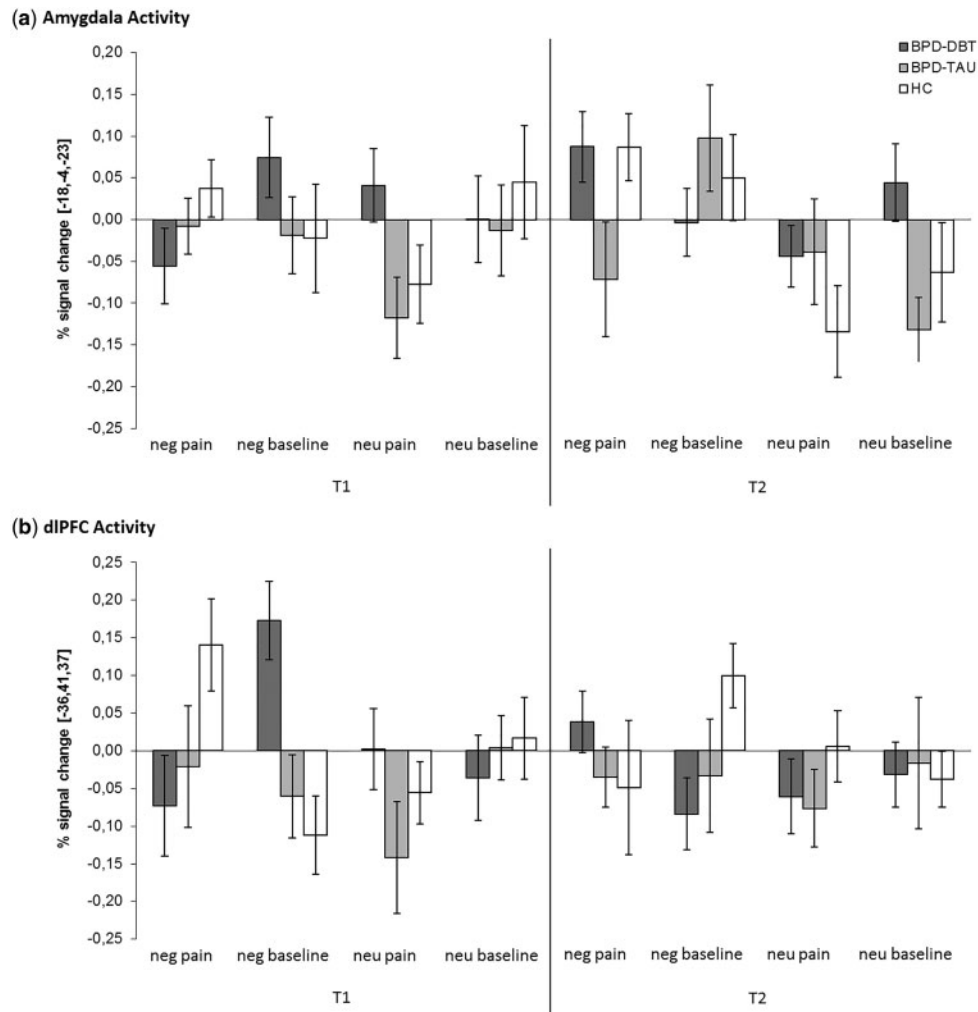
Fig. 2. Percent signal change of brain activity, four-way interaction effect (group by valence by temperature by time), error bars indicate standard error.

reduction in BPD + DBT, and it was found previously that pain thresholds tend to normalize in BPD patients who stopped self-injurious behavior (Ludascher *et al.*, 2009), it is possible that our second measurement was too early to observe any significant effects.

Although our results provide first longitudinal insights into effects of psychotherapy on pain perception and on neural processing of pain in BPD, there are several limitations that need to be considered. First, to attribute the reported alterations specifically on DBT treatment, a randomized controlled trial (DBT *vs* TAU) with blinded raters would have been mandatory. Although the inclusion of a TAU group is advantageous to control for time effects, we cannot exclude self-selection processes or other effects due to our study design. Although BPD + DBT

and TAU patients were comparable regarding age, professional qualification, number of Axis I-co-morbidities, psychotropic medication,as well as frequency and recency of SIB, we did not assess IQ level to control for possible confounds. Second, our analyses suffer from low statistical power due to the small sample size in the BPD + TAU group (*n* = 15), and the PPI method. Although the inclusion of a TAU group is an advantage of our study in other respects, it was not possible to recruit more BPD patients without any experiences with the DBT program. The same issue of statistical power must also be considered when interpreting the results regarding treatment effects for the psychometric measures, which were non-significant although we found medium effect sizes between BPD + DBT and BPD + TAU in self- and observer-ratings of borderline symptom severity.
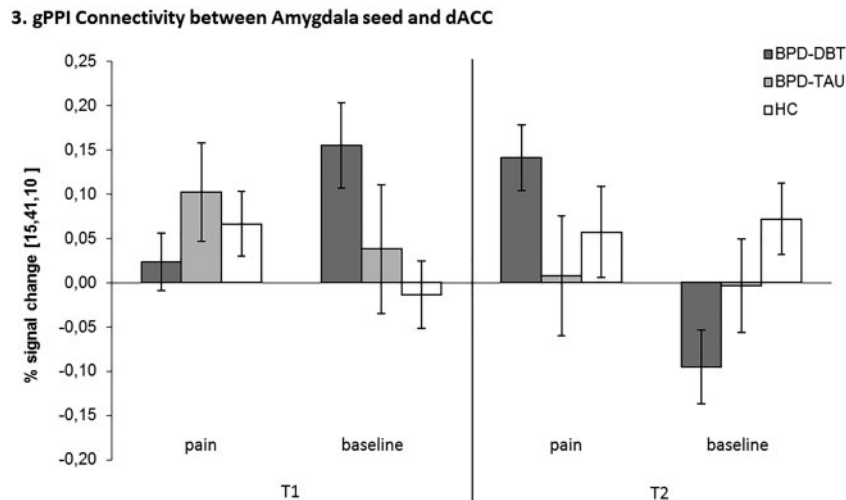
3. gPPI Connectivity between Amygdala seed and dACC

Fig. 3. Brain connectivity with the left amygdala, three-way interaction effect (group by temperature by time) error bars indicate standard error.

Finally, we did not ask for painfulness ratings during scanning, which would have assured that the pain stimuli were perceived equally throughout the experiment. However, we applied pain stimuli in previous studies using very similar pain application methods (Niedtfeld *et al.*, 2010; Bungert *et al.*, 2015), and found that subjective pain ratings were higher after stress, but did not differ between BPD patients and HCs. Likewise, we decided against ratings of picture valence and arousal, in order to reduce patient burden. In previous studies using similar picture sets, it was found that BPD patients rated IAPS pictures as more arousing than HCs (Schulze *et al.*, 2011) and tended to show less habituation over the course of the experiment (Koenigsberg *et al.*, 2014). Consequently, from this study we cannot draw conclusions with regard to the soothing effect of pain on subjective arousal ratings. This is an important question for further research, especially with regard to discrepancies between subjective arousal levels and physiological measures (e.g. Hazlett *et al.*, 2012).

Summing up our results, this study provides further evidence for a soothing effect of pain in BPD patients at the neural level. After 12 weeks of DBT treatment, but not after treatment as usual, neural pain processing in BPD tended to normalize. We conclude that this may be due to increased functional emotion regulation after DBT treatment.

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