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Research Paper

Always on guard: emotion regulation in women with borderline personality disorder compared to nonpatient controls and patients with cluster-C personality disorder

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Background: Borderline personality disorder (BPD) is characterized by emotion dysregulation; however, it is unclear whether this is restricted to negative emotional stimuli or to what degree this is specific to BPD. We investigated neural correlates of hypothesized increased emotional sensitivity and impaired emotion regulation in patients with BPD. **Methods:** During functional MRI (fMRI) scanning, patients with BPD, nonpatient controls and patients with cluster-C personality disorder completed an emotion regulation task, including negative, positive and erotic social pictures. **Results:** We included 55 patients with BPD, 42 nonpatient controls and 24 patients with cluster-C personality disorder in our analyses. Passive viewing of negative stimuli resulted in greater activity in the anterior insula, temporoparietal junction and dorsolateral prefrontal cortex in patients with BPD than in nonpatient controls. The increased activity in the anterior insula and temporoparietal junction was also present when patients with BPD viewed positive stimuli. During regulation of negative stimuli compared with passive viewing, nonpatient controls showed greater activity in the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, middle temporal gyrus and bilateral inferior parietal lobule. Patients with BPD did not show this increase in activity. **Limitations:** Findings cannot be generalized to men, and patients represented a heterogeneous group regarding comorbid diagnoses and medication. **Conclusion:** When looking at emotional stimuli, patients with BPD showed a unique pattern of activity, suggesting an increase in brain activity involved in emotion generation. In the case of negative stimuli this is accompanied by increased activity in regulation areas. In contrast, increase of regulation processes seems absent when patients with BPD are explicitly instructed to regulate. Results of diagnosis specificity support a dimensional rather than a dichotomous differentiation between BPD and cluster-C personality disorder regarding emotional sensitivity and emotional regulation of social stimuli.

Introduction

The life of a patient with borderline personality disorder (BPD) can be described as an emotional rollercoaster, as it is characterized by a pervasive pattern of instability in affect regulation and impulse control.[1] The disorder is a life-threatening illness affecting 1%–3% of the general population[2,3] and is associated with high rates of self-injury, suicidal tendencies and reactive aggression.[4] Apart from severe functional impairments, extensive use of health care treatments among patients with BPD results in high societal costs.[4,5]

Leading theories of BPD[6,7] propose that emotional instability can be best explained in terms of an increase in emotional sensitivity and impairments to regulate emotional responses. Supporting these theories, empirical neurobiological studies show that patients with BPD have increased activity in the limbic brain areas, which are involved in emotion generation, and decreased activity in the prefrontal cortex, which is involved in regulatory processes.[8–10] Unfortunately, research findings to date are rather inconclusive and inconsistent,[11] and important issues remain unanswered. First, it remains unclear whether the increased emotional sensitivity is restricted to negative emotions, as nearly all previous studies used negative emotional stimuli only, or whether it also involves other types of emotions. Second, it remains uncertain whether reported findings are specific to BPD or whether they are characteristic of psychopathology in general, as previous studies often lack clinical control groups. Third, most studies were statistically underpowered,[11] which may be an important cause of inconsistency in reported findings. To improve our understanding of BPD, future research should address these issues.

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In the present international, multicentre functional MRI (fMRI) study we investigated emotional sensitivity and emotion regulation abilities in patients with BPD with a focus on stimulus category specificity and diagnosis specificity. We used an emotion sensitivity and regulation paradigm[12–14] with different categories of emotional social stimuli. As a regulation strategy we instructed participants to realize they were safe, inspired by schema therapy theory.[15] We extended previous research by adding positive stimuli, and given the high rates of childhood sexual abuse[16] and relationship problems[1] in patients with BPD, erotic stimuli were also added. We expected erotic stimuli to evoke emotional responses similar to the negative stimuli in patients with BPD. As control groups, we used nonpatients and patients with cluster-C personality disorder. Following the model of cognitive control of emotion,[17] we hypothesized that, compared with both control groups, patients with BPD would show increased activity in brain areas associated with emotion generation (amygdala, ventral striatum, anterior insula, ventromedial prefrontal cortex) when passively viewing negative and erotic pictures. Additionally, we expected that, compared with nonpatients and patients with cluster-C personality disorder, patients with BPD would show decreased activity in brain regions associated with emotion regulation (dorsolateral [dlPFC], posterior, ventrolateral [vlPFC] and dorsomedial prefrontal cortex [dmPFC]; dorsal anterior cingulate cortex [dACC]; inferior parietal cortex) while regulating emotions during the presentation of especially negative and erotic pictures.

Methods

Participants

Participants were recruited from 2 sites in the Netherlands (Maastricht, Heerlen) and 3 sites in Germany (Freiburg, Lübeck, Hamburg). Patients with BPD or cluster-C personality disorder were recruited from mental health clinics at local sites. Nonpatient controls were recruited among the general population at each site via postings and personal contacts. Participants had to be hetero- or bisexual women aged 18–65 years with sufficient understanding of the language at the local sites.

Trained interviewers diagnosed BPD and cluster-C personality disorder according to the DSM-IV criteria using the Structural Clinical Interview (SCID) II[18] and I.[19] We preferred that patients had not started treatment yet before entering the study; however, if they had, measurements had to be finished within 3 months from the start of therapy. Patients with BPD were further screened using the BPD Severity Index;[20–22] to be included their score had to be higher than 20. Patients with narcissistic and antisocial personality disorders, full- or subthreshold, were excluded for reasons related to the clinical trial in which this study sample participated.[23] Patients with cluster-C personality disorder were excluded if they had full- or subthreshold cluster-B personality disorder and if they met more than 2 criteria for BPD. To be included in the study, the nonpatient controls could not meet current diagnostic criteria for Axis I or II disorders assessed using the SCID-I and SCID-II screeners.[18,19] Positive items on screeners were checked with SCID interviews. Additional assessments included the Brief Symptom Inventory,[24] BPD checklist[25] and Interview for Trauma Events in Childhood.[26] Details on participant recruitment and measurements are available in Appendix 1, available at jpn.ca/170008-a1. Both control groups were matched to the BPD group with respect to age, intelligence and handedness in terms of means and variance.

After receiving a complete description of the study, participants provided written informed consent. Participants received a small financial remuneration. The study was approved by the local ethical committees: the Medical Ethics Committee of Maastricht University for the Dutch sites and the Ethics Committee of the Albert-Ludwigs-University Freiburg, the Ethics Committee of the University of Lübeck and the Ethics Committee of the Psychotherapist Association Hamburg for the German sites.

Experimental task

We used an adapted version of a classic emotion regulation paradigm with pictorial stimuli.[12–14] The paradigm we used (Fig. 1) included a traditional "look" condition, requiring participants to attend to the pictures and respond naturally without altering their emotional state. Our adapted regulation condition was the so-called "safe" condition, in which participants were instructed to realize themselves being safe. This regulation strategy was inspired by schema therapy, a highly effective therapy for patients with BPD.[27] Based on the component of schema therapy that "unmet safety needs during childhood" underlie emotional problems, we hypothesized that patients with BPD feel unsafe while experiencing negative emotions,[15] even when realizing they are in a currently safe situation. In other words, while nonpatient controls would be able to use the "safe" instruction to regulate negative emotions, patients with BPD would have problems using this to regulate emotions, as negative emotions are intrinsically threatening for them (a forthcoming study investigates whether the ability of patients with BPD to benefit from realizing the present situation is safe improves with treatment). The 2 conditions were presented in a pseudorandom order (no more than 3 identical conditions in a row) for all participants. Participants were presented with an instruction cue followed by a picture. Just after the picture disappeared, participants assessed their momentary emotional state using a visual analogue scale of –100 to 100 mm. The task consisted of 96 trials divided into 4 runs of 24 trials each. After scanning, participants evaluated arousal and valence for each presented picture using the Self-Assessment Manikin Scale.[28]

We used 4 stimulus categories containing 24 negative, 24 neutral, 24 positive and 24 erotic pictures. We selected pictures from the International Affective Picture System[29] and additional erotic pictures from Jacob and colleagues.[30] Only pictures with social content were selected, as patients with BPD are particularly responsive to interpersonal stimuli.[12] Pictures were randomly presented per participant and balanced across condition types. Presentation of the stimuli and recordings of behavioural responses were controlled by Presentation software (Neurobehavioural Systems Inc.). The

visual stimuli were projected using a personal computer and beamer onto a screen that was viewed through a mirror on the headcoil or via a goggle system.

Statistical analysis

Images were obtained using 3 T scanners. All preprocessing and statistical analyses were performed using BrainVoyager QX version 2.6 (Brain Innovation). The procedure, scanning parameters and preprocessing steps are all described in Appendix 1. To model the hemodynamic response, the applied general linear model included 10 predictors: instruction, negative-look, positive-look, erotic-look, neutral-look, negative-safe, positive-safe, erotic-safe, neutral-safe and ratings. Additionally, we added 6 motion parameters (x, y, z-translation and x, y, z-rotation) as confound predictors.

Differences in brain activity between patients with BPD and nonpatient controls during emotional sensitivity and emotion regulation in response to negative stimuli were first used to define the clusters. In a second step we assessed the effects of positive and erotic stimuli and of patients with cluster-C personality disorder. For each participant we calculated statistical parametric maps from 2 contrasts of interest: negative-look versus neutral-look and negative-safe versus negative-look. These contrast images were entered into group-level analyses, including group (BPD, nonpatient controls) and site (Maastricht, Freiburg, Lubeck) as between-subjects factors. Subsequently, we carried out 2 whole brain random-effects analyses of variance (ANOVA): stimulus (negative-look v. neutral-look) × group (BPD v. nonpatient controls) to examine differences in emotional sensitivity and instruction (negative-safe v. negative-look) × group (BPD v. nonpatient controls) to investigate differences in emotion regulation. The resulting F maps were thresholded at a significance level of $p < 0.005$ and corrected for multiple comparisons with a cluster-size threshold at $p = 0.05$, which seemed an adequate compromise of reducing type-I and II errors.[31] The minimal cluster-size threshold (15 voxels for the emotional sensitivity F map and 20 voxels for the emotion regulation F map) was determined with the cluster-level statistical threshold estimation tool in BrainVoyager that implements a Monte Carlo simulation–based approach of cluster-level correction of multiple comparisons (1000 simulations).[32] Detailed analysis of the resulting clusters was performed with SPSS software version 21 (IBM Corp.) using the extracted mean cluster b of each predictor per participant.

To investigate whether the results were specific to patients with BPD, we extracted mean b values per active cluster of patients with cluster-C personality disorder and used them in post hoc comparisons. We applied the same strategy to examine response uniqueness to negative stimuli in patients with BPD for mean b values per cluster of positive and erotic stimuli. Finally, each cluster was checked post hoc for confounding effects of medication, within the BPD group [stimulus or instruction × medication (medicated v. nonmedicated)].

Results

Participants

In total, 62 patients with BPD, 48 nonpatient controls and 31 patients with cluster-C personality disorder were scanned. After we excluded participants who did not meet scanning or clinical criteria, 55 patients with BPD, 42 nonpatient controls and 24 patients with cluster-C personality disorder were left for the analyses; our study was powered at 80% to detect a large effect size ($d > 0.76$) between groups at $p = 0.005$.

Thirteen participants in the patient groups had been in treatment for an average of 64.62 ± 32.55 days before entering the study. Patients with BPD had a mean score of 31.83 ± 7.32 on the BPD Severity Index. Table 1 shows the demographic and clinical characteristics of all study groups. The groups did not differ significantly in age, handedness or IQ. There was a significant difference in level of education between the

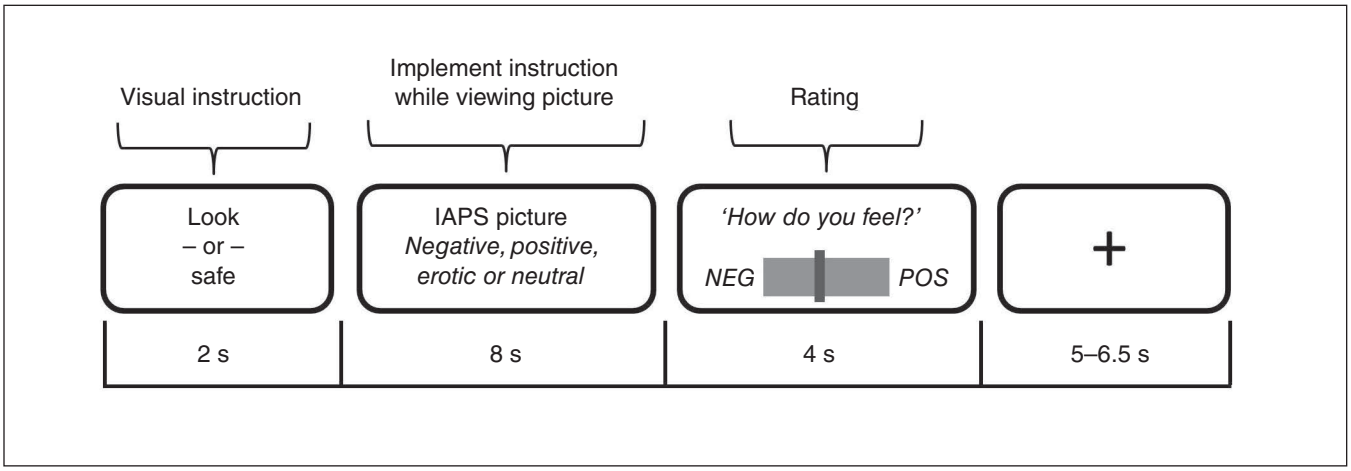

Fig. 1: Overview of a single trial of the task. Each 19- to 20.5-s trial consisted of a 2-s visual instruction to either "look" or "realize being safe," an 8-s presentation of the picture for carrying out the instruction, a 4-s rating period and a 5- to 6.5-s fixation (relax). During the rating period, participants indicated their emotional experience at the moment by moving the pointer on the horizontal scale using a button box between negative (–100) and positive (100). IAPS = International Affective Picture System.

groups; however, education may not reflect the actual intellectual capacities of patients with BPD, as they often have disruptions in their education owing to disorder-related problems.

Manipulation checks

Supporting the assumption that task instructions were implemented successfully, participants' ratings showed a significant task instruction (look v. safe) × stimulus category (negative, positive, erotic, neutral) interaction ($F_{3,116}$ = 4.41, p = 0.006). Neutral and negative, but not positive or erotic stimuli were rated as more pleasant during the safe versus the look condition across groups.

Stimulus ratings after scanning confirmed that negative stimuli, followed by erotic stimuli, were most arousing across groups, whereas positive and neutral stimuli were equally least arousing ($F_{3,85}$ = 67.38, p < 0.001). Valence ratings

Table 1: Descriptive statistics for demographic and clinical variables across the 3 groups (part 1 of 2)

	Group; mean ± SD or no. (%)				
Characteristic	BPD (n = 55)	NPC (n = 42)	CCP (n = 24)	Statistical test	p value
Age, yr	30.80 ± 8.78	28.33 ± 10.50	30.38 ± 11.46	F = 0.77	0.47
Education level*				χ^2 = 8.90	0.012‡
Level 1	13 (23.6)	7 (16.7)	4 (16.7)		
Level 2	8 (14.5)	2 (4.8)	4 (16.7)		
Level 3	15 (27.3)	4 (9.5)	7 (29.2)		
Level 4	3 (5.5)	2 (4.8)	3 (12.5)		
Level 5	13 (23.6)	19 (45.2)	3 (12.5)		
Level 6	3 (5.5)	7 (16.7)	3 (12.5)		
Estimated IQ†	96.66 ± 9.93	100.43 ± 11.03	98.05 ± 9.42	F = 1.59	0.21
Handedness, No. left/right/mixed	5/46/3	2/40/0	0/24/0	χ^2 = 6.72	0.15§
BSI, total score	1.74 ± 0.57	0.13 ± 0.13	1.08 ± 0.45	F = 150.74	< 0.001¶
BPD checklist, total score	120.60 ± 26.92	50.73 ± 5.03	72.96 ± 17.02	F = 147.41	< 0.001**
ITEC				F = 9.90	< 0.001††
Sexual abuse	9.10 ± 8.95	0.13 ± 0.41	1.97 ± 5.01	F = 21.57	< 0.001
Physical abuse	16.93 ± 11.77	1.63 ± 3.51	7.12 ± 10.55	F = 27.41	< 0.001
Emotional abuse	20.36 ± 8.53	2.32 ± 3.27	12.92 ± 8.50	F = 63.46	< 0.001
Emotional neglect	10.89 ± 6.95	0.77 ± 2.02	6.37 ± 6.46	F = 32.19	< 0.001
Physical neglect	9.99 ± 9.08	0.82 ± 2.74	4.76 ± 6.99	F = 17.17	< 0.001
Dissociation				F = 8.97	< 0.001‡‡
Before scanning	20.16 ± 19.44	5.29 ± 6.51	7.04 ± 8.34	F = 14.46	< 0.001
After scanning	31.86 ± 26.11	6.69 ± 8.36	16.60 ± 20.65	F = 17.45	< 0.001
Anxiety				F = 7.68	< 0.001§§
Before scanning	41.90 ± 30.59	10.00 ± 20.03	30.87 ± 30.91	F = 15.37	< 0.001
After scanning	25.60 ± 27.17	5.93 ± 14.75	23.70 ± 32.86	F = 7.66	0.001
Nervousness				F = 10.85	< 0.001¶¶
Before scanning	54.75 ± 32.28	15.68 ± 21.94	36.78 ± 30.67	F = 20.90	< 0.001
After scanning	27.49 ± 27.14	6.05 ± 13.90	30.17 ± 36.52	F = 9.79	< 0.001
Axis I disorders					
Major depressive disorder	49 (89.1)	—	13 (54.2)	χ^2 = 12.07	0.001
Dysthymic	4 (7.3)	—	1 (4.2)	χ^2 = 0.27	0.60
Bipolar type II	1 (1.8)	—	—	χ^2 = 0.44	0.51
Generalized anxiety disorder	2 (3.6)	—	1 (4.2)	χ^2 = 0.01	0.91
Panic disorder with agoraphobia	7 (12.7)	—	2 (8.3)	χ^2 = 0.32	0.57
Panic disorder	7 (12.7)	—	3 (12.5)	χ^2 = 0.001	0.98
Agoraphobia	4 (7.3)	—	—	χ^2 = 1.84	0.18
Specific phobia	10 (18.2)	—	1 (4.2)	χ^2 = 2.74	0.10
Social phobia	19 (34.5)	—	6 (25.0)	χ^2 = 0.70	0.40
Obsessive–compulsive disorder	8 (14.5)	—	2 (8.3)	χ^2 = 0.58	0.45
Posttraumatic stress disorder	20 (36.4)	—	3 (12.5)	χ^2 = 4.61	0.032
Somatoform disorder	5 (9.1)	—	4 (16.7)	χ^2 = 0.95	0.33
Eating disorders	22 (40.0)	—	8 (33.3)	χ^2 = 0.32	0.57
Substance abuse	27 (49.1)	—	1 (4.2)	χ^2 = 14.74	< 0.001
Intermitted explosive disorder	1 (1.8)	—	—	χ^2 = 0.44	0.51

confirmed that negative stimuli were rated as most unpleasant, followed by neutral stimuli, erotic stimuli and positive stimuli ($F_{3,85}$ = 297.39, p < 0.001). Details of self-reported emotional state during scanning and stimulus ratings after scanning are available in Appendix 1.

Emotional sensitivity

The whole brain random-effects ANOVA F map of the stimulus (negative-look v. neutral-look) × group (BPD v. nonpatient controls) analysis resulted in 4 significant clusters identified at the right anterior insula (AIC), left dlPFC, left temporoparietal junction (TPJ) and left cerebellum (Table 2 and Fig. 2). In line with our hypothesis of increased emotional sensitivity in patients with BPD, simple effects showed increased activity in the AIC in patients with BPD compared with nonpatient controls for negative stimuli. Interestingly, patients with BPD also showed increased activity in the dlPFC and TPJ compared with nonpatient controls for negative stimuli.

We tested the resulting clusters for stimulus category specificity. Results showed that, compared with nonpatient controls, patients with BPD showed increased activity for positive versus neutral stimuli in the TPJ ($F_{1,95}$ = 6.68, p = 0.011) and a trend toward increased activity in the AIC ($F_{1,95}$ = 3.83, p = 0.053).

When testing the resulting clusters for diagnosis specificity, we found a significant difference between patients with BPD and those with cluster-C personality disorder in the TPJ ($F_{1,77}$ = 4.44, p = 0.038), suggesting specificity for BPD. No significant differences were found in the AIC and dlPFC for the comparison of patients with BPD versus those with cluster-C personality disorder, indicating that activity in these clusters generalizes over personality disorders. Results remained similar when we added medication as a covariate. We tested linear and quadratic trends of brain responses post hoc in association with severity of personality psychopathology from nonpatient controls to patients with cluster-C personality disorder to patients with BPD. We examined only the trends within the clusters that showed a stimulus category or

Table 1: Descriptive statistics for demographic and clinical variables across the 3 groups (part 2 of 2)

	Group; mean ± SD or no. (%)				
Characteristic	BPD (n = 55)	NPC (n = 42)	CCP (n = 24)	Statistical test	p value
Axis II disorders					
Avoidant PD	27 (49.1)	—	17 (70.8)	χ^2 = 3.20	0.07
Dependent PD	10 (18.2)	—	2 (8.3)	χ^2 = 1.26	0.26
Obsessive compulsive PD	11 (20.0)	—	8 (33.3)	χ^2 = 1.63	0.20
Passive–aggressive PD	4 (7.3)	—	—	χ^2 = 1.84	0.18
Depressive PD	15 (27.3)	—	2 (8.3)	χ^2 = 3.85	0.06
Paranoid PD	15 (27.3)	—	—	χ^2 = 8.08	0.004
Schizotypal PD	1 (1.8)	—	—	χ^2 = 0.44	0.51
Schizoid PD	1 (1.8)	—	—	χ^2 = 0.44	0.51***
Medication					
Antidepressants	37 (67.3)	—	9 (37.5)	χ^2 = 6.09	0.014
Antipsychotics	8 (14.3)	—	—	χ^2 = 3.88	0.049
Hypnotics	3 (5.5)	—	—	χ^2 = 1.36	0.24
Mood stabilizers	1 (1.8)	—	—	χ^2 = 0.44	0.51

ANOVA; analysis of variance; BSI = Brief Symptom Inventory; BPD = borderline personality disorder; df = degrees of freedom; ITEC = Interview Traumatic Events Childhood; MANOVA = multivariate analysis of variance; PD = personality disorder.
*Based on International Standard Classification of Education (ISCED); levels range from lower secondary school to master's degree.
†Assessed using 4 subtasks of the Wechsler Adult Intelligence Scale. Data unavailable for 1 nonpatient control; df = 2, 117
‡Kruskal–Wallis test. Data unavailable for 1 nonpatient control; df = 2.
§Data unavailable for 1 patient with BPD; df = 4.
¶Data unavailable for 2 nonpatient controls; df = 2, 116.
**Data unavailable for 2 nonpatient controls and 1 patient with cluster-C personality disorder; df = 2, 115.
††The MANOVA (df = 10, 212) and ANOVAs (df = 2, 109) showed significant group effects over traumas. Patients with BPD experienced significantly more trauma than both control groups regarding sexual abuse (both p < 0.001), physical abuse (both p < 0.001) and physical neglect (p < 0.001 v. nonpatient controls; p = 0.014 v. patients with cluster-C personality disorder). The 3 groups significantly differed on emotional abuse (p < 0.001) and emotional neglect (BPD v. nonpatient controls p < 0.001; BPD v. cluster-C personality disorder p = 0.0006; nonpatient controls v. cluster-C personality disorder p = 0.002), with patients with BPD experiencing the most trauma, followed by those with cluster-C personality disorder. Data unavailable for 8 nonpatient controls and 1 patient with cluster-C personality disorder.
‡‡Data available for 51 patients with BPD, 40 nonpatient controls and 23 patients with cluster-C personality disorder. The MANOVA (df = 4, 222) and ANOVAs (df = 2, 111) showed significant group effects over dissociation. Patients with BPD dissociated significantly more before and after scanning than with both control groups (before scanning: BPD v. nonpatient controls p < 0.001, BPD v. cluster-C personality disorder p = 0.001; after scanning: BPD v. nonpatient controls p < 0.001, BPD v. cluster-C personality disorder p = 0.011). Repeated-measures ANOVA showed a significant group × dissociation interaction ($F_{2,11}$ = 5.27; p = 0.007). Patients with BPD dissociated significantly more after than before scanning compared with nonpatient controls (p = 0.006).
§§Data available for 52 patients with BPD patients, 40 nonpatient controls and 23 patients with cluster-C personality disorder. The MANOVA (df = 4, 224) and ANOVAs (df = 2, 112) showed significant group effects over anxiety. Nonpatient controls were significantly less anxious before and after scanning than both other groups (before scanning: BPD v. nonpatient controls p < 0.001, nonpatient controls v. patients with cluster-C personality disorder p = 0.013; after scanning: patients with BPD v. nonpatient controls p = 0.001, nonpatient controls v. patients with cluster-C personality disorder p = 0.023). Repeated-measures ANOVA showed no significant group × anxiety interaction ($F_{2,112}$ = 2.12; p = 0.125).
¶¶Data available for 51 patients with BPD, 40 nonpatient controls and 23 patients with cluster-C personality disorder. The MANOVA (df = 4, 222) and ANOVAs (df = 2, 111) showed significant group effects over nervousness. All 3 groups significantly differed in their nervousness before scanning, with patients with BPD being most nervous, followed by those with cluster-C personality disorder (BPD v. nonpatient controls p < 0.001, BPD v. patients with cluster-C personality disorder p = 0.042 and nonpatient controls v. patients with cluster-C personality disorder p = 0.017). Nonpatient controls were significantly less nervous after scanning compared with both other groups (BPD v. nonpatient controls p < 0.001, nonpatient controls v. patients with cluster-C personality disorder p = 0.002). Repeated-measures ANOVA showed a significant group × nervousness interaction ($F_{2,111}$ = 5.57, p = 0.005). Patients with BPD were significantly more nervous after than before scanning compared with nonpatient controls (p = 0.016).

instruction × group interaction. Significant linear trends support the hypothesis that strength of response is a linear function of degree of personality pathology, with patients who have cluster-C personality disorder falling between nonpatient controls and patients with BPD, whereas significant quadratic trends support the hypothesis that patients with cluster-C personality disorder are either similar to nonpatient controls or to patients with BPD. Our results support the linear severity hypothesis, with the patients with cluster-C personality disorder scoring between patients with BPD and nonpatient controls; we found no evidence for quadratic trends (Table 3).

Because the whole brain random-effects ANOVA did not result in the hypothesized and previously reported[6,10,33] significant differential amygdala activity, we performed an additional, less stringent amygdala region of interest analysis. We found a main effect of stimulus category in which both patients with BPD and nonpatient controls showed increased

Table 2: Resulting clusters for whole brain random-effects analysis of variance testing differences in emotional sensitivity and emotion regulation between patients with borderline personality disorder and nonpatient controls regarding negative stimuli*

Analysis; brain region	L/R	BA	Cluster size, mm³	Talairach peak voxel			*F*	*p* value
				x	*y*	*z*		
Emotional sensitivity								
Negative look v. neutral look								
Anterior insula	R	13	1065	33	17	16	9.74	0.002
Middle frontal gyrus, dorsolateral prefrontal cortex	L	8	650	–30	35	43	12.55	0.001
Supramarginal gyrus, temporoparietal junction	L	40	413	–45	–43	37	9.38	0.003
Cerebellum	L		1022	–21	–34	–38	12.59	0.001
Emotion regulation								
Negative safe v. negative look								
Middle frontal gyrus, dorsolateral prefrontal cortex	R	8	831	36	26	37	13.96	< 0.001
Dorsal anterior cingulate cortex	R	32	1791	12	17	34	17.80	< 0.001
Middle temporal gyrus	R	21	1596	57	–25	–11	20.47	< 0.001
Supramarginal gyrus, inferior parietal lobule	R	40	1228	51	–52	31	12.59	0.001
Supramarginal gyrus, inferior parietal lobule	L	40	2496	–45	–43	34	17.54	< 0.001
Cerebellum	R		569	27	–37	–42	8.35	0.005
Cerebellum	L		1166	–6	–73	–41	3.03	0.085

BA = Brodmann area; L = Left; R = Right.
*Thresholded at $p < 0.005$ and cluster size.

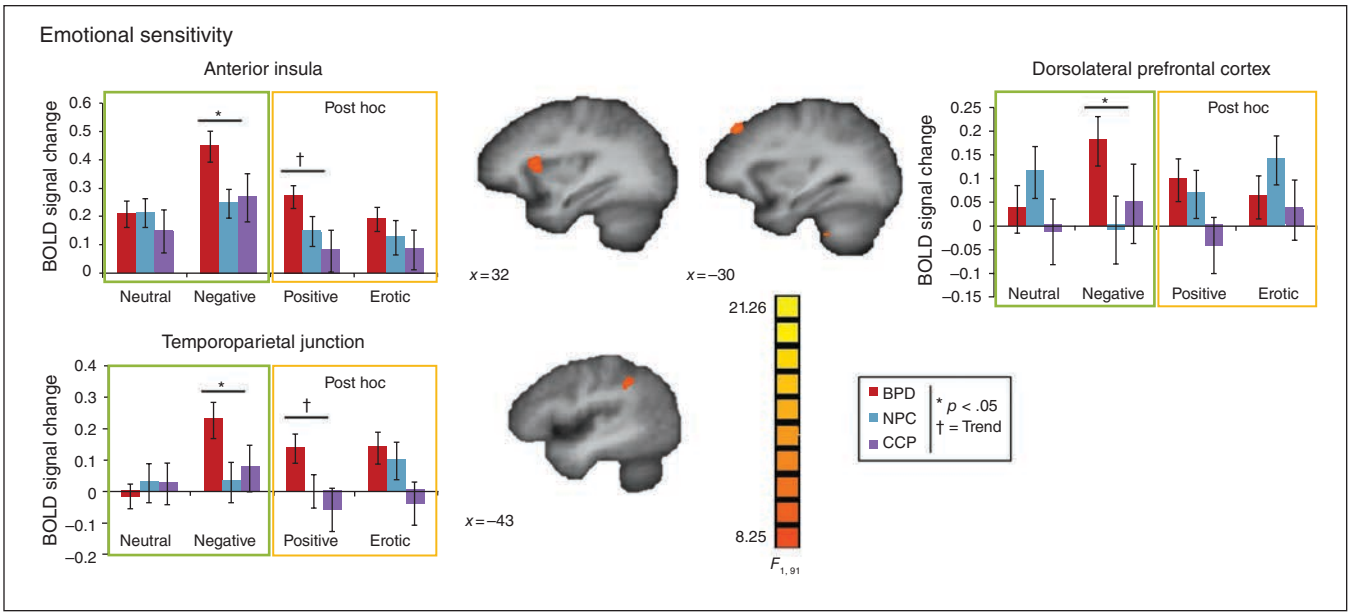

Fig. 2: Locations and bar plots of b values of clusters resulting from whole brain random-effects analyses of variance testing differences in emotional sensitivity. Bar plots represent blood oxygen level–dependent (BOLD) signal change in *z*-scores, and error bars indicate standard errors of the mean. Cluster coordinates are reported in Talairach space. BPD = borderline personality disorder; CCP = cluster-C personality disorder; NPC = nonpatient controls.

amygdala activity in response to negative versus neutral stimuli (Table 4 and Fig. 3). However, no significant interaction effects could be detected, even at uncorrected $p = 0.05$. It seems unlikely that ambiguity of the neutral social stimuli accounts for the failure to detect group differences in amygdala responses,[33] as we found no evidence for increased amygdala responses to the neutral stimuli in patients with BPD (Fig. 3). Additional timing analysis, taking the fast habituation of amygdala responses into account,[34,35] could not explain this null finding. The right amygdala showed a significant stimulus × group interaction during the first run; however, the simple effect revealed no group differences, but rather increased activity during negative versus neutral stimuli in both groups. Other potential confounding factors, including medication, dissociation, trauma, posttraumatic stress disorder, depression (Brief Symptom Inventory subscale) and lateralization, also did not explain this null finding (Table 4).

Emotion regulation

The whole brain random-effects ANOVA *F* map of the instruction (negative-look v. negative-safe) × group (BPD v. nonpatient controls) analysis resulted in 7 significant clusters identified at the right dACC, right dlPFC, right middle temporal gyrus (MTG), bilateral inferior parietal lobule (IPL) and bilateral cerebellum (Table 2 and Fig. 4). In line with our hypothesis of impaired emotional regulation abilities in patients with BPD, simple effects showed no significant difference between the safe and the look condition in the dlPFC and decreased activity during the safe versus the look condition in the dACC in patients with BPD in response to negative stimuli. Additionally, patients with BPD showed less activity during the safe than the look condition in the MTG. In contrast, nonpatient controls showed significantly more activity in the dACC, dlPFC, MTG and bilateral IPL during the safe than the look condition.

Resulting clusters were tested for stimulus category specificity. We found no differences between patients with BPD and nonpatient controls for positive and erotic stimuli in the safe compared with the look condition. This indicates that activity in these clusters is specific to negative stimuli. Results remained the same when corrected for activity during neutral stimuli.

When testing the resulting clusters for diagnosis specificity, we found a significant interaction for the comparison with patients with cluster-C personality disorder in the MTG ($F_{1,77} = 6.66$, $p = 0.012$) in which the patients with cluster-C personality disorder showed a significant difference between the safe and the look condition, suggesting BPD diagnosis specificity. Other clusters did not reveal a significant difference between BPD and cluster-C personality disorder groups, indicating that activity in these clusters is not specific to BPD. Except for the dACC, the results remained the same when medication was added as a covariate, so there may be an effect of medication in the dACC for the comparison BPD versus cluster-C personality disorder. Again, testing post hoc linear and quadratic trends of brain responses in association with severity of personality psychopathology showed a linear

Table 3: Significance levels of linear and quadratic trends of brain responses in relation to severity of personality psychopathology

	p value	
Analysis; brain region	Linear	Quadratic
Look negative – look neutral		
Anterior insula	0.002	0.82
Dorsolateral prefrontal cortex	0.001	0.56
Temporoparietal junction	0.002	0.39
Look positive – look neutral		
Anterior insula	0.043	0.33
Temporoparietal junction	0.008	0.05
Safe negative – look negative		
Dorsolateral prefrontal cortex	0.001	0.88
Dorsal anterior cingulate cortex	< 0.001	0.81
Middle temporal gyrus	< 0.001	0.45
Inferior parietal lobule, right	0.001	0.31
Inferior parietal lobule, left	< 0.001	0.49

Table 4: Amygdala region of interest analyses and potential confounding factors

	Left amygdala		Right amygdala	
Analysis; confounding factor	Statistical test	*p* value	Statistical test	*p* value
Main effect stimulus	$F_{1,95} = 26.97$	< 0.001	$F_{1,95} = 31.71$	< 0.001
Stimulus × group interaction	$F_{1,95} = 0.76$	0.39	$F_{1,95} = 0.07$	0.79
Time single run 1	$F_{1,92} = 0.001$	0.98	$F_{1,92} = 4.94$	0.029
Time run 1–4	$F_{1,85} = 0.52$	0.47	$F_{1,85} = 0.05$	0.82
Dissociation*	$F_{1,88} = 0.59$	0.44	$F_{1,88} = 0.08$	0.77
Childhood trauma severity†	$F_{1,86} = 0.06$	0.81	$F_{1,86} = 0.05$	0.82
Posttraumatic stress disorder	$F_{1,94} = 0.58$	0.45	$F_{1,94} = 0.22$	0.64
Depression (BSI subscale)	$F_{1,92} = 0.53$	0.47	$F_{1,92} = 0.03$	0.86
Medication	$F_{1,94} = 0.01$	0.93	$F_{1,94} = 0.06$	0.80
Lateralization	$F_{1,95} = 0.11$	0.74	see left amygdala	

BSI = Brief Symptom Inventory.
*Dissociation is mean score of dissociation before and after scanning.
†Childhood trauma severity is the total score of the 5 subscales: sexual, physical and emotional abuse, and emotional and physical neglect.

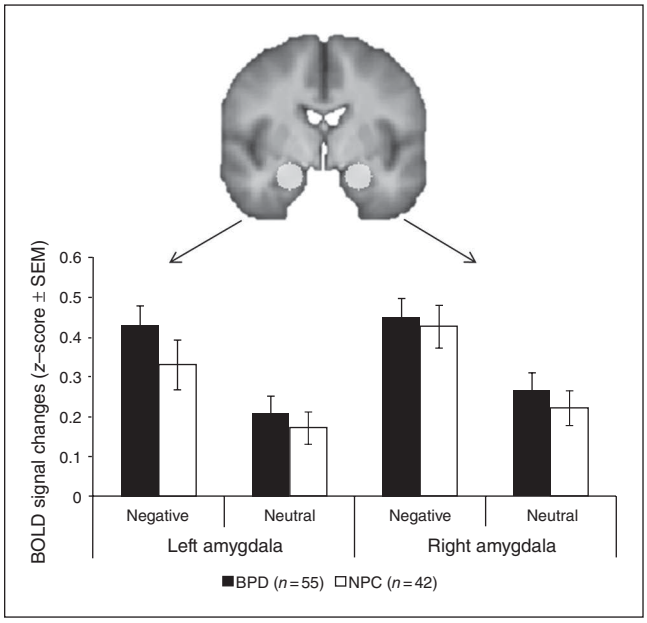

Fig. 3: Location of the left and right amygdala regions of interest (Talairach coordinates: *x*, *y*, *z* = ± 21, –5, –15) and bar plots of b values of both amygdala seeds showing a main effect of stimulus category comparing negative versus neutral stimuli. BOLD = blood oxygen level–dependent; BPD = borderline personality disorder; NPC = nonpatient controls; SEM = standard error of the mean.

association across the 3 groups, with the patients with cluster-C personality disorder scoring between patients with BPD and nonpatient controls (Table 3).

Discussion

The aim of the present study was to investigate stimulus category specificity and diagnosis specificity of neural correlates associated with the hypothesized increased emotional sensitivity and impaired emotion regulation underlying emotional instability in patients with BPD. Extending previous research, we added positive and erotic stimuli to the traditional negative and neutral stimuli and included nonpatient control and cluster-C personality disorder comparison groups. In line with our hypothesis, passive viewing of negative stimuli resulted in increased activity in the AIC of patients with BPD compared with nonpatient controls. Interestingly, passive viewing of negative stimuli also led to increased activity in the TPJ and dlPFC in patients with BPD. The effect in the AIC and TPJ was not specific to negative stimuli, as passive viewing of positive stimuli also resulted in increased activity in patients with BPD compared with nonpatient controls. The results of the regulation compared with the look condition showed increased activity in the dACC, dlPFC, MTG and bilateral IPL when the nonpatient controls were instructed to realize being safe for negative stimuli only; patients with BPD did not show a similar significant increase in activity. As

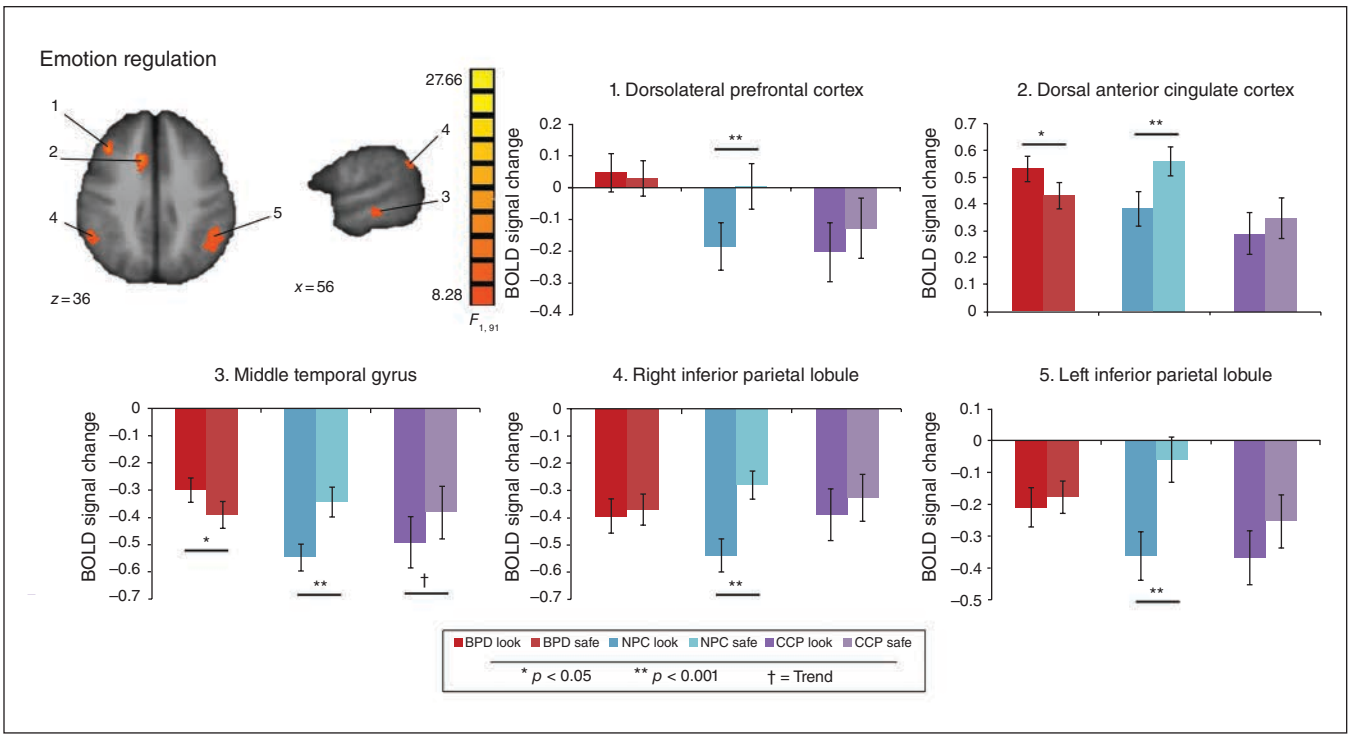

Fig. 4: Locations and bar plots of b values of clusters resulting from whole brain random-effects analyses of variance testing differences in emotion regulation concerning negative stimuli. Bar plots represent blood oxygen level–dependent (BOLD) signal change in *z*-scores, and error bars indicate standard errors of the mean. The *F* map was overlaid on an average brain of all participants shown in the radiological convention. Cluster coordinates are reported in Talairach space. BPD = borderline personality disorder; CCP = cluster-C personality disorder; NPC = nonpatient controls.

the dACC and dlPFC are important areas for emotion regulation,[17,36] this finding supports the hypothesis of impaired emotion regulation in patients with BPD.

Surprisingly, previous findings of increased amygdala activity in patients with BPD during the presentation of emotional stimuli[6,10,33] were not replicated in the present study. We therefore ran additional analyses taking dissociation, trauma, posttraumatic stress disorder, depression (Brief Symptom Inventory subscale), medication, lateralization or fast habituation into account, but could not explain this null finding. Supporting the notion that the amygdala is involved in processing emotional stimuli, we did find a main effect of stimulus category, as both patients with BPD and nonpatient controls showed increased amygdala activity for negative versus neutral stimuli. Although T_2-weighted slices were optimized with a negative 30° tilt, the lack of a significant group × stimulus category interaction could be explained by the vulnerability for susceptible artifacts of the amygdala. Additionally, a smaller voxel size than $3 \times 3 \times 3$ mm^3 might improve to distinguish the amygdala from other nearby structures.[37] However, when differentiating patients with BPD from nonpatient controls, our findings rather hint at a key role of the AIC and TPJ in patients with BPD regarding emotional sensitivity. Previous research suggests that the AIC is involved in processing emotional state and affective experience[38] and that the TPJ is proposed to be involved in mentalizing.[39,40] Maybe patients with BPD mainly engage in mentalizing processes when confronted with negative or positive social stimuli, which affect their emotional state and affective experience.

Also striking, in contrast to previous studies[10,12,14] our study showed enhanced activity in the dlPFC when patients with BPD passively viewed negative stimuli. The dlPFC is commonly associated with effortful control and inhibition processes.[17,36] Potentially this enhanced activity is an implicit reaction to the increase in bodily state (e.g., arousal) and emotional affect, as indicated by the increased activity in the AIC and TPJ. This constant and at least partially failing effort for regulation might exhaust patients with BPD and thus contribute to their emotional instability. Additionally, the IPL within the attentional network is involved in preventing reorientation to unimportant stimuli.[41] Therefore, the inability of patients with BPD to activate the IPL during emotion regulation might interfere with cognitive control, resulting in difficulty disengaging attention from negative stimuli. It should be noted that our reported findings might differ from those previous studies[12,14] because we applied a new regulation condition.

The specific failure of patients with BPD to activate emotion regulation areas when instructed to realize they are safe is in line with the view that BPD is characterized by a perceived lack of safety when experiencing negative emotions, even when reminded.[15] An important goal of treatment might therefore be to help patients experience negative emotions while feeling safe, so that negative emotions no longer need to be avoided and can be processed.

Results regarding stimulus category specificity during emotional sensitivity showed that the AIC and TPJ activity was increased for both negative and positive stimuli, pointing to a general increase in emotional sensitivity in patients with BPD. The emotion regulation results were unique for negative stimuli. This, however, makes sense considering that regulation of positive emotions is in most cases undesirable. Finally, we did not find the hypothesized effect for the erotic stimuli. Ratings showed that the valence of the erotic stimuli were more positive as expected, especially in patients with BPD. Our erotic stimuli were associated with romance and intimacy and may not have triggered the expected negative emotional responses associated with sexual abuse.

Regarding diagnosis specificity we found a linear association in many areas with activity in patients with cluster-C personality disorder falling between that of nonpatient controls and patients with BPD. This supports the idea that patients with cluster-C personality disorder show a number of features in common with, yet weaker than, those of patients with BPD and that the observed effects are more a matter of degree than dichotomous. Considering that social stimuli were used, it makes sense that patients with cluster-C personality disorder showed similar response patterns to those of patients with BPD, as both disorders show interpersonal difficulties.[1] Consequently, it may be useful to manipulate social versus nonsocial stimuli to examine whether this dimensionality holds.

Limitations

Compared with previous studies, the main strengths of the present study are its wider range of stimuli, inclusion of the clinical control group and higher statistical power.[11] However some limitations also need to be acknowledged. First, we recruited only women, which limits the generalizability of our results to men. Second, the patients with BPD represented a rather heterogeneous group given the presence of co-occurring disorders. Comorbid psychiatric disorders are typical in individuals with BPD; such a sample is more representative, as "pure" BPD clinical samples (i.e., patients with BPD without co-occurring disorders) are uncommon. As a consequence, we cannot exclude the possibility that our results may have been affected by these comorbidities. Third, many patients with BPD (69.1%) were taking psychotropic medication, which may have altered individuals' brain responses and was therefore a potentially confounding factor.[42,43] However, we decided not to exclude patients on medication in order to recruit a representative and severe clinical sample. Within any of the resulting clusters no significant interactions of medication within the BPD group were found, indicating the results were robust to medication effects. It should also be acknowledged that it is not clear whether patients being free of medication for several weeks before scanning[6,12,14] results in a normal brain state at the moment of scanning. Moreover, requiring patients to stop their medication can contribute to a sampling bias. Furthermore, for some medications the washout effect can be several months, and long-lasting effects in the brain cannot be ruled out.[44] Fourth, because we did not monitor eye movement, we cannot rule out interference of looking away or closing eyes during the task, even though participants were explicitly instructed not to do so. Fifth, scanner

parameters across sites could not be perfectly equalized. Unfortunately, no interscanner reliability measurements are available. Yet, the reported clusters did not show overlap with the significant clusters of group × stimulus × site interaction at a lenient significance level of $p < 0.05$ (Appendix 1). Additionally, more detailed analyses within SPSS did not show a significant group × stimulus × site interaction, and the group × stimulus interaction remained significant after adding site and its interactions to the model. Therefore, we are convinced that site had a minimal effect on our findings. Sixth, a voxel size of $3 \times 3 \times 3$ mm^3 might be large for measuring structures like the amygdala. Finally, we did not consider the menstrual cycle of the participants, which might have affected results, especially with regard to erotic stimuli.[45,46] On the other hand, these effects should be random given the large sample size.

Conclusion

Patients with BPD showed an elevated response in brain areas important for generation and regulation of emotions when passively viewing negative stimuli compared with nonpatient controls. Additionally, patients with BPD did not show an increased activity in emotion regulation areas during the safe versus look condition when presented with negative stimuli, whereas nonpatient controls did. In patients with BPD, the enhanced responses in brain areas important for emotion generation were also present during passive viewing of positive stimuli. Linearity analyses showed evidence of intermediate responses in patients with cluster-C personality disorder falling between those of patients with BPD and nonpatient controls, implying a dimensional rather than a dichotomous differentiation.

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