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ORIGINAL PAPER

Altered emotion processing circuits during the anticipation of emotional stimuli in women with borderline personality disorder

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Abstract Borderline personality disorder (BPD) is associated with disturbed emotion processing, typically encompassing intense and fast emotional reactions toward affective stimuli. In this study, we were interested in whether emotional dysregulation in BPD occurs not only during the perception of emotional stimuli, but also during the anticipation of upcoming emotional pictures in the absence of concrete stimuli. Eighteen female patients with a diagnosis of BPD and 18 healthy control subjects anticipated cued visual stimuli with prior known emotional valence or prior unknown emotional content during functional magnetic resonance imaging. Brain activity during the anticipation of emotional stimuli was compared between both groups. When anticipating negative pictures, BPD patients demonstrated less signal change in the left dorsal anterior cingulate cortex (dACC) and left middle cingulate cortex (MCC), and enhanced activations in the left pregenual ACC, left posterior cingulate cortex (PCC) as well as in left visual cortical areas including the lingual gyrus. During the anticipation of ambiguously announced stimuli, brain activity in BPD was also reduced in the left MCC extending into the medial and bilateral dorsolateral prefrontal cortex. Results point out that deficient recruitment of brain areas related to cognitive–emotional interaction already during the anticipation phase may add to emotional dysregulation in BPD. Stronger activation of the PCC could correspond to an increased autobiographical reference in BPD. Moreover, increased preparatory visual activity during negative anticipation may contribute to hypersensitivity toward emotional cues in this disorder.

Keywords Borderline personality disorder · Anticipation · Emotion · Neurobiology · fMRI

Introduction

Borderline personality disorder (BPD) is a serious and debilitating psychiatric disorder with a lifetime prevalence of about 3 % [1]. It is characterized by a broad constellation of symptoms including affective dysregulation, impaired impulse control, unstable self-image, and problems with cognitive control functions [2, 3]. Regardless of the variety in BPD psychopathology, increased emotional sensitivity in combination with an impairment to modulate emotional responses is highly linked to disturbed emotion processing in this illness [4] (reviews [5, 6]). Most functional magnetic resonance imaging (fMRI) studies addressing the neurobiology of dysfunctional emotion regulation in BPD patients have focused on emotion processing brain regions, such as the amygdala (review [7]). Nearly all of these studies investigated neural differences during the confrontation with unpleasant stimuli. Irrespective of the stimulus type used, i.e., aversive pictures

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[8–11], faces [12, 13], or scripts [14], a hyperreactivity of the amygdala and a hypoactivity in prefrontal regions are the most consistent findings in BPD. There is substantial evidence for a disturbed connection between bottom-up emotional reactivity and cognitive top-down control in BPD [15, 16] supporting the model of a reduced medial prefrontal modulation of limbic structures (reviews [6, 17, 18]). Lately, findings on alterations in the anterior cingulate cortex (ACC), particularly the more dorsal subregions [6], have become more prominent in the BPD literature. This involves abnormalities in structure [19, 20] and in function, where patients predominantly exhibited reduced activations relative to healthy individuals [12, 13, 21, 22]. Hence, this diminished ACC activity in BPD could possibly represent a correlate of disturbed emotion–cognition interaction [23, 24], which is a relevant clinical feature of the disorder.

Up to now, imaging studies on BPD have mainly concentrated on altered perception of emotional stimuli. However, already the anticipation period prior to actual stimulus exposure is associated with intense emotional processes and is sensitive to distortions and biases on the behavioral level as well as on the neural level (healthy subjects [25, 26]; major depression [27–29]; anxiety [30–33]; rodent model [34]). Typically, this anticipation phase is characterized by emotional reactions comparable to the actual perception or confrontation [35] and is linked to distinct brain areas as the ACC, medial and dorsolateral prefrontal regions (MPFC, DLPFC), amygdala, and others (e.g., [36–38]). Overall, anticipatory processes are eminent cognitive functions. During anticipation, behavioral strategies are developed and decisions for certain actions are made in order to adapt in a changing and potentially arousing environment [39, 40]. Biased and dysfunctional anticipatory cognitive–emotional processes may play an important role in the psychopathology of BPD. In particular, BPD patients characteristically have an increased emotional arousal in general. Usually, they show a range of dysphoric affects that go in hand with more rapid and stronger mood reactions combined with poor impulse control [2]. These maladaptive cognitions and emotions already during anticipation may affect the perception of the emotional stimulus itself. Enhanced affective responses and emotional dysregulation during the anticipation period in BPD might add to the stronger emotional reactions.

Understanding the neural correlates of these anticipatory processes may add valuable insights into the neurobiological mechanisms of emotional dysregulation in this disorder. To date, neurobiological facets of anticipation in BPD have only been addressed to limited extent. Enzi et al. [41] have recently investigated anticipation in the frame of reward which, however, represents a different construct compared to the anticipation of negative and positive emotional stimuli [42]. On the other hand, Kamphausen et al. [43] have used an instructed fear task in BPD. Although this is one way to induce anticipatory anxiety [44], the authors focused on the specific mechanisms underlying social fear learning rather than emotional anticipation in general. Therefore, this fMRI study addressed the neural correlates involved in the anticipation of nonspecific, general emotional stimuli of prior known valence (positive, negative, neutral) and prior ambiguous valence (positive or negative) to extend prior fMRI findings in BPD research. Preparatory mechanism during emotional anticipation was analyzed separately in patients with BPD and then compared with healthy participants. Based on the clinical symptoms in BPD patients, we hypothesized that the biased and typically maladaptive cognitive processes would have an effect on anticipation processes prior to stimulus exposure already. Hence, we expected to find group differences in brain regions underlying the interaction between cognitive and emotional processes during the anticipation of emotional stimuli, particularly of negative and unknown valence. The main neural correlates assumed to be involved in the emotional-cognitive interplay include cognitive and monitoring regions such as the anterior and middle cingulate cortex (ACC, MCC), MPFC, and DLPFC [45–48]. Due to the known general intensified emotion processing and dysfunctional emotion regulation circuits in BPD, we expected patients to exhibit a rather lower engagement in brain regions involved in cognitive and emotional control. Also, we expected an increased emotional involvement in BPD reflected in a hyperreactivity of the amygdala during the anticipation phase.

Methods

Subjects

A total of 22 female BPD patients were recruited from in- and out-patient clinics at the University Hospital of Psychiatry Zurich, Switzerland, and via mailing lists. Four of these patients had to be excluded. One patient aborted the experiment during scan acquisition; another patient had to be excluded due to severe movement artifacts in fMRI images; and two further data sets could not be used due to data loss associated with technical problems of the MRI scanner. The remaining 18 patients were matched by age with a control group of 18 healthy female volunteers. All healthy subjects (HC) were free from psychiatric medication. The two groups did not differ in age (ages 19–50, BPD $M_{age} = 28.44$, SD = 8.50;

HC $M_{age} = 28.89$, SD = 7.11; t (34) = −0.17, $p = .87$). All subjects were righthanded according to the handedness questionnaire [49]. BPD diagnosis was made by the referring physicians of the individual patients using an extensive assessment, which also comprised background and previous psychiatric records. A trained psychiatrist (ABB) and a psychologist (SO) then confirmed the diagnosis of borderline personality disorder according to ICD-10 and DSM-IV criteria [50]. To determine the current degree of clinical symptoms, BPD patients completed a short version of the Borderline Symptom List (BSL-23 [51]; German version [52]), a self-rating questionnaire assessing state borderline-typical symptomatology. Comorbid Axis-I diagnoses were evaluated using the German version [53] of the Mini-International Neuropsychiatric Interview for DSM-IV [54]. Patients were excluded if they met DSM-IV criteria for present or previous bipolar I disorder, schizophrenia, or schizoaffective disorder. Due to the known high rate of comorbid psychiatric disorders in BPD [2, 55], we did not exclude current depressive episodes [56]. We allowed occasional use of cannabinoids and alcohol [57], but excluded abuse of opioids and benzodiazepines and other psychotropic drugs. Sporadic low-dose use of prescribed tranquilizers was allowed (<3 mg lorazepam or equivalents per week), though patients were asked to abstain from intake at least 24-h prior scanning. Among the BPD group, eleven subjects took psychotropic medication regularly (ten patients took antidepressants, five patients took mood stabilizers, seven patients took tranquilizers (intermittently), and one patient took low-dose antipsychotic medication). In all patients, the dose of drugs had been qualitatively and quantitatively stable for more than one month according to documentation at the time of participation. No active substance or alcohol consummation at the time of study was reported. Table 1 lists psychotropic medication as well as comorbid lifetime diagnoses of psychiatric disorders for the patient group. A positive family history of psychiatric disorders was present in 55.6 % of the patients (mostly depression and alcohol dependence). To assess the level of depression in the patient sample, we obtained ratings on the Hamilton Depression Rating Scale (HAMD) [58], Montgomery-Asberg Depression Rating Scale (MADRS) [59], and on the Beck's Depression Inventory (BDI) [60].

For all participants, general exclusion criteria, such as previous or current neurological disorders, head trauma, pregnancy, excessive consumption of alcohol (regular intake of >7 units/week), and MRI contraindications, were assessed during a semi-structured interview prior to scanning. All subjects provided written informed consent after receiving a complete description of the study and were compensated for their participation. The study was approved by the local ethics committee.

Table 1 Comorbid psychiatric disorders and psychotropic medication of the included BPD sample

BPD[a] subjects	Current diagnoses	Lifetime diagnoses	Psychotropic medication
1	–	–	Lamotrigine, escitalopram, quetiapine
2	Substance abuse[b]	MDD[c], ADHD[d]	–
3	Substance abuse	–	Amisulpride, lorazepam[f]
4	Substance abuse, eating disorder	–	–
5	Substance abuse, eating disorder	–	Quetiapine, lamotrigine, venlafaxine
6	Substance abuse	–	Trimipramin, fluoxetine, gabapentin, venlafaxine
7	Substance abuse	–	–
8	–	–	Fluoxetine, quetiapine
9	–	–	–
10	MDD	PTSD[e]	Escitalopram, quetiapine
11	Substance abuse	MDD	Duloxetine, lamotrigin, doxepine
12	–	MDD	–
13	–	PTSD	–
14	–		–
15	ADHD, anxiety disorder	–	Methylphenidate, lamotrigine, mirtazapine, zolpidem
16	MDD	Eating disorder	Escitalopram
17	–	MDD	Citalopram
18	–	–	Sertraline, quetiapine

[a] *BPD* borderline personality disorder

[b] Substance abuse includes alcohol, sedatives, and cannabinoids

[c] *MDD*:major depressive disorder

[d] *ADHD* attention deficit hyperactivity disorder

[e] *PTSD* posttraumatic stress disorder

[f] Given only on a provisional basis, no intake >48 h before scanning

Self-report measurements

Both groups completed German versions of questionnaires to examine the degree of depression (Self-Rating Depression Scale, SDS [61]) and anxiety (State-Trait Anxiety-Inventory, STAI [62]). Borderline patients additionally completed a retrospective self-report on traumatic childhood experiences (Childhood Trauma Questionnaire, CTQ [63]). Due to the known tendency to experience dissociative symptoms, BPD patients were given the DSS-4 acute questionnaire directly after the fMRI experiment to measure their current dissociative state (short version of Dissociation Tension Scale acute, DSS-4 [64, 65]).

Stimuli

Pictures serving as visual stimuli in this study were taken from the International Affective Picture System (IAPS; Peter Lang, Miami, USA [66]). A series of 56 digital color photographs were matched for valence difference (neutral, negative, and positive) according to the IAPS picture ratings as well as for complexity, contents, and, as far as possible, for arousal (for discussion of arousal matching refer to [26]). Pictures were presented in a pseudo-randomized order once per experiment. All participants viewed the same stimulus sequence. After scanning, participants were given printouts to rate the emotional valence of the shown pictures on a nine-point Likert scale (1—very negative, 9—very positive).

Experimental paradigm

During fMRI scanning, subjects performed an emotional anticipation task, which allows investigating the anticipation phase and perception phase separately (for reference, see [26], Fig. 1). The participants anticipated and perceived cued emotional pictures of known or unknown valence. In known trials, a cue indicated either a positive "∪," a negative "∩," or a neutral "−" picture after an anticipation period (cue 1,000 ms, anticipation period 6,920 ms). In unknown or ambiguous trials, the symbol "I" indicated an emotional picture of either pleasant or unpleasant content (50 % probability each). Following the symbol, a blank black screen with a small white fixation point appeared for 6,920 ms (cue + anticipation: four times of MR volume repetition time (TR) 1,980 ms = 7,920 ms). Subsequently, the respective emotional picture was presented for 7,920 ms (4 TR). A baseline period of 15,840 ms (8 TR) allowed the BOLD signal to wear off before the next trial. The experimental task consisted of one run including 56 randomized trials, 14 for each condition: known positive (ps), known negative (ng), known neutral (nt), and unknown (uk), with a total duration of 30 min. To

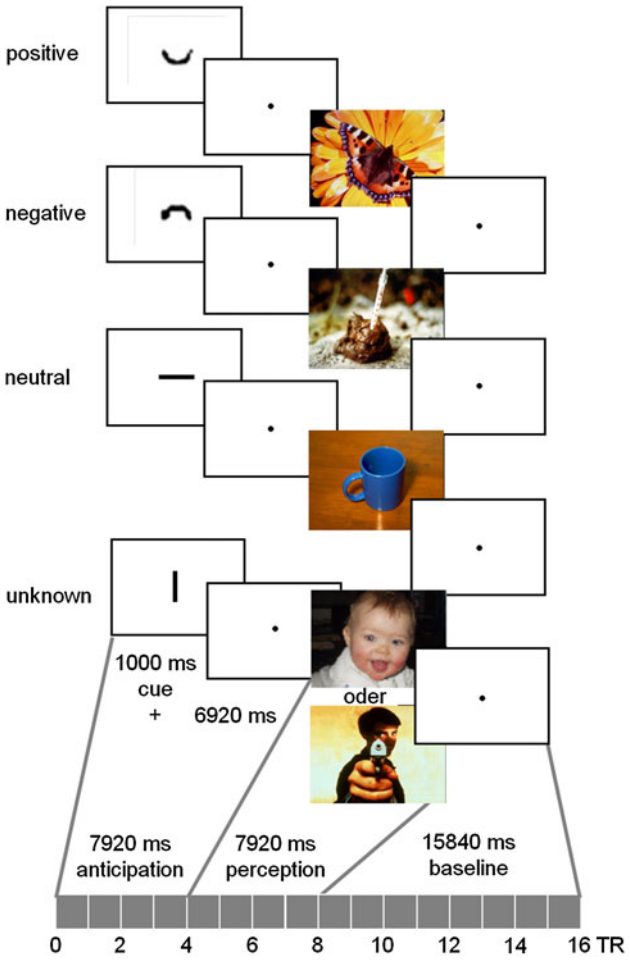

Fig. 1 Illustration of experimental task. Cues are enlarged for presentation reasons. Their actual height in the experiment was about 1/40 screen size

familiarize the participants with the task, a practice session was performed outside the scanner prior to the fMRI experiment, showing pictures that were not used in the experiment itself. The paradigm was programmed with Presentation™ (Neurobehavioral Systems, USA) and presented via digital video goggles (Resonance Technologies, Northridge, CA, USA). The cues were intuitive and did not require intensive cognitive resources to understand their meaning. All subjects confirmed that they were able to perform the general task.

fMRI data acquisition

The experiment was performed using a 3.0 T GE Signa™ HD Scanner (GE Medical Systems, Milwaukee, USA) equipped with an eight-channel head coil. Echo-planar imaging was performed for fMRI (TR/TE 1,980/32 ms, 22 sequential axial slices, whole-brain, patient group and 14 subjects of the control group: slice thickness 3.5 mm, 1 mm gap, resulting voxel size 3.125 × 3.125 × 4.5 mm,

matrix 64 × 64, FOV 200 mm, flip angle 70°; due to technical reasons changed parameters in 5 subjects of the control group: slice thickness 5 mm, 0.5 mm gap, voxel size 3.4 × 3.4 × 5 mm, FOV 220 mm, flip angle 70°). A total of 908 volumes were obtained per subject. High-resolution 3D T1-weighted anatomic volumes were acquired (TR/TE 9.9/2.9 ms; matrix size 256 × 256; 1 × 1 × 1 mm^3 resolution, axial orientation) for co-registration with the functional data. Furthermore, T2-weighted images in parallel to the EPI sequence were acquired to exclude possible T2-sensitive brain abnormalities.

Psychometric analysis

To test differences in depression (SDS) and anxiety (STAI) between both samples, independent t tests were performed by using the Statistical Package for the Social Sciences (SPSS) version 20. Also, correlations between borderline symptomatology (BSL-23), self-reported dissociation (DSS-4), and depression scales (HAMD, MADRS, BDI) were calculated. A p value of <.05, 2-tailed, was considered as significant.

fMRI data analysis

Data were analyzed using BrainVoyager™ QX 2.4.0 (Brain Innovation, Maastricht, The Netherlands [67]). The first four images of each functional scan were discarded to allow for T1* equilibration effects. Preprocessing of the functional scans included motion correction, slice scan time correction, high-frequency temporal filtering, and removal of linear trends. Functional images were superimposed on the 2D anatomic images and incorporated into 3D data sets. The individual 3D data sets were then transformed into Talairach and Tournoux space [68] resulting in a voxel size of 3 × 3 × 3 mm and then spatially smoothed with an 8-mm Gaussian kernel for following group analyses. Single trials with fMRI signal artifacts of more than threefold mean signal change amplitude with resulting outliers of beta weights (e.g., due to head movements) were eliminated manually. Anticipation conditions (ng, ps, nt, uk) and the respective perception conditions were implemented in the design matrix resulting in eight predictors and the factor group. Anticipation period and picture presentation were modeled as epochs with the standard two-gamma hemodynamic response function (HRF) adapted to the applied period duration provided by BrainVoyager. The fMRI data analysis based on the general linear model (GLM) involved the following steps: Fixed-effects analyses were calculated separately for each subject for the anticipation phase (a), with the contrasts anticipation negative versus anticipation neutral (ang > ant), anticipation unknown versus anticipation neutral (auk > ant), and anticipation positive versus anticipation neutral (aps > ant) as well as for the perception phase (p) contrasts negative versus neutral (png > pnt) and positive versus neutral (pps > pnt) resulting in summary images. The respective neutral condition was subtracted in order to focus on emotion processing without general effects of the anticipation and perception of stimuli. The summary images were then subjected to second-level analyses, separately for both, BPD patients and healthy subjects. In the next step, a random-effects whole-brain group comparison (rfx) for the specified contrasts (ang > ant, auk > ant, aps > ant) was performed. We also investigated group effects during the perception period with the defined contrasts (png > pnt, and pps > pnt). Results on differential neural correlates during the perception of emotional stimuli between the two groups are reported in the supplementary material and are not focused in this present work (Online Resource 1). To correct for multiple comparisons, maps with a voxel-wise threshold of $p < .005$ were submitted to a Monte Carlo simulation [67] for estimating cluster-level false-positive rates, yielding a corrected cluster-level of $p < .05$.

A hypothesis-driven region-of-interest analysis (ROI) within a predefined cubic ROI in the amygdala (edge length 9 mm, 729 mm^3, center $x, y, z = 19/-19, -5, -17$) according to the Talairach Client [69] was carried out for each contrast during anticipation. Further, the activity in the primary visual cortex (edge length 9 mm, 729 mm^3, center $x, y, z = 5/-5, -86, -3$) and in the lateral geniculate nucleus (LGN) bilaterally (edge length 6 mm, 216 mm^3, LGN left: center $x, y, z = -21, -23, -4$, LGN right: center $x, y, z = 22, -22, -4$; for details on LGN coordinates refer to [70]) during the anticipation and perception period was examined to control for general perceptual and attentional differences between groups; for instance, closed eyes or markedly diverted gaze would have resulted in decreased activity in LGN and V1.

Results

Psychometric data results

Details on demographic and psychometric data are summarized in Table 2. The evaluation of psychometric data revealed significant differences between both samples in clinically relevant degrees of depression and anxiety. In general, a relevant number of patients showed symptoms of major depressive disorder (MDD) according to the clinical depression scales (HAMD-21 score >20 in ten patients, BDI score >20 in ten patients, MADRS score >20 in nine patients). CTQ scores suggested increased traumatic

Table 2 Demographic and psychometric characteristics of included subjects

	BPD[a]		HC[b]		*T*	*p*
Sample, *n*	18		18			
Mean age, years (SD)[c]	28.44 (8.50)		28.89 (7.11)		−0.17	<.870
Mean scale scores (SD)						
SDS[d]	68.40 (8.43)	n = 16	37.35 (9.21)	$n = 17$	10.08	<.001*
STAI[e]-X1	51.41 (11.18)	$n = 17$	34.53 (8.64)	$n = 17$	4.93	<.001*
STAI-X2	57.41 (9.26)	$n = 17$	35.82 (10.48)	$n = 17$	6.36	<.001*
BSL-23[f]	1.83 (1.08)	$n = 17$	–			
BDI[g]	26.93 (9.98)	$n = 16$	–			
HAMD-21[h]	22.20 (8.18)	$n = 15$	–			
MADRS[i]	22.53 (8.99)	$n = 15$	–			
DSS-4[j]	2.32 (1.91)	$n = 15$	–			
CTQ[k]—emotional abuse	15.38 (7.26)	$n = 16$	–			
CTQ—physical abuse	11.75 (5.45)	$n = 16$	–			
CTQ—sexual abuse	4.81 (2.48)	$n = 16$	–			
CTQ—emotional neglect	19.13 (9.42)	$n = 16$	–			

[a] *BPD* patients with borderline personality disorder

[b] *HC* healthy subjects

[c] *SD* standard deviation

[d] *SDS* Self-Rating Depression Scale (score <50: not depressed)

[e] *STAI* Spielberger State-Trait Anxiety Inventory, X1: state section; X2: trait section

[f] *BSL-23* Borderline Symptom List 23 [scores between 0 (= none) and 4 (= very much) represent current borderline symptomatology]

[g] *BDI* Beck Depression Scale (score <15: not depressed)

[h] *HAMD-21* Hamilton Depression Scale (score <15: not depressed)

[i] *MADRS* Montgomery–Asberg Depression Rating Scale (score <20: not depressed)

[j] *DSS-4* short version of Dissociation Tension Scale acute

[k] *CTQ* Childhood Trauma Questionnaire (subscale score <5–8: minimal-to-none traumatic experience, subscale score ≥16: severe-to-extreme traumatic experience)

experiences during childhood, in particular on the emotional level. Nine patients scored higher than "16" on emotional neglect, and eight patients rated higher than "16" on the emotional abuse scale indicating severe-to-extreme traumatic experiences during childhood. According to the BSL-23 questionnaire, the patient sample showed moderate borderline symptomatology at the time of the experiment. DSS-4 ratings after the fMRI scan propose some degree of dissociative states in the patient sample, whereby eight patients scored above "2" suggesting relevant elevated dissociative experience during scanning. Our sample of control subjects was healthy according to the standard values for questionnaires regarding depression and anxiety [71].

Measurements of depression (HAMD, MADRS, BDI) in the patient sample were highly intercorrelated. Scores of the borderline symptom list and of the dissociation tension scale significantly correlated with all the three depression questionnaires. Additionally, we observed a significant positive correlation between BPD symptomatology and self-reported dissociation (Online Resource 2).

Behavioral data results

The mean ratings of emotional valence for positive ($M_{HC} = 7.05$, $SD_{HC} = 1.29$; $M_{BPD} = 7.09$, $SD_{HC} = .87$), negative ($M_{HC} = 2.83$, $SD_{HC} = .59$; $M_{BPD} = 2.97$, $SD_{HC} = .87$), and neutral pictures ($M_{HC} = 5.09$, $SD_{HC} = .83$; $M_{BPD} = 5.02$, $SD_{HC} = .64$) did not differ significantly between the two groups (t_{ps} (33) = .091, $p = .928$; t_{ng} (33) = .579, $p = .567$; t_{nt} (33) = −.266, $p = .792$). Internal consistencies for positive (Cronbach's $\alpha = .839$, $N = 33$), negative ($\alpha = .799$, $N = 34$), and neutral ($\alpha = .809$, $N = 34$) valence revealed good internal reliability.

fMRI data results

Whole-brain analysis in the BPD group during emotional anticipation

When anticipating negative compared to neutral pictures, patients showed increased brain activity in the right ventral

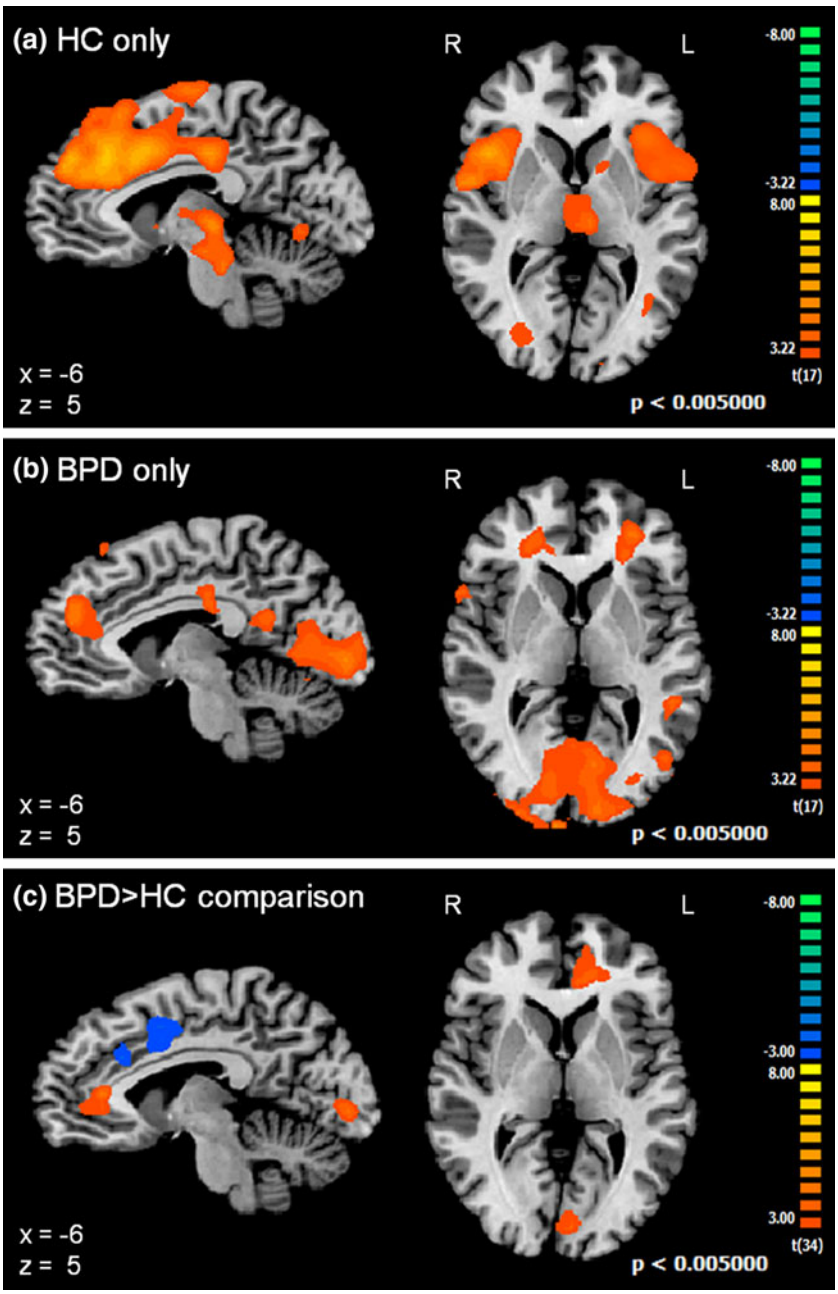

Fig. 2 Contrast anticipation of negative versus anticipation of neutral stimuli (ang > ant) **a** in healthy controls only, **b** in patients with borderline personality disorder only, and **c** in a group comparison BPD > HC. The *t* values of the contrasts are given in the *color bar*. *L* left, *R* right, *HC* healthy controls, *BPD* patients with borderline personality disorder

anterior cingulate cortex (ACC) including a large cluster of the medial frontal gyrus as part of the medial prefrontal cortex (MPFC), in the right lingual gyrus and cuneus, and in the left posterior cingulate cortex (Fig. 2). The anticipation of pictures with ambiguous emotional content versus neutral pictures activated the right inferior frontal gyrus within the ventrolateral prefrontal cortex (VLPFC) and the insula in patients with BPD. The contrast anticipation of positive versus neutral stimuli revealed activations in the right lingual gyrus, left superior occipital gyrus extending into the angular gyrus, and also in the left medial frontal gyrus. Details are given in Table 3.

Whole-brain analysis in the HC group during emotional anticipation

Healthy subjects showed large activation clusters of increased brain activity in the right anterior cingulate cortex (ACC) extending into the midcingulate cortex (MCC) and parts of the medial prefrontal cortex (MPFC) during the anticipation of negative compared to neutral pictures. Enhanced brain activity was also found in the insula bilaterally, in the right middle occipital gyrus, right culmen, and in the left thalamus and midbrain during the respective contrast (Fig. 2). Anticipating pictures of unknown valence in comparison with the

Table 3 Whole-brain activations in the BPD sample during emotional anticipation

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
Lingual gyrus/cuneus	R	18/17	24,853	−11	−102	6	5.0	.000102
Medial frontal gyrus/ACC	R	9/32	14,146	2	43	30	5.7	.000025
Posterior cingulate/caudate tail	L	31	15,945	−16	−35	24	8.0	.000000
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
Inferior frontal gyrus/insula	R	47/13	1,287	32	22	−3	4.4	.000419
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Lingual gyrus	R	18	4,913	8	−83	0	4.6	.000280
Superior occipital gyrus/angular gyrus	L	39	2,366	−55	−65	21	4.9	.000148
Medial frontal gyrus	L	10	1,664	−13	52	6	4.1	.000740

Activated areas in a random-effects analysis (rfx) in the BPD sample with a voxel-wise threshold of $p < .005$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: (a) anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster threshold: 1,383 mm^3 (52 functional voxels), (b) anticipation of unknown stimuli > anticipation of neutral stimuli, cluster-threshold: 840 mm^3 (32 functional voxels), and (c) anticipation of positive stimuli > anticipation of neutral stimuli, cluster-threshold: 1,106 mm^3 (43 functional voxels)

ACC anterior cingulate cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

anticipation of neutral pictures revealed increased brain activity covering the bilateral insula, left inferior frontal gyrus, left precentral-, middle-, and superior frontal gyrus within the DLPFC, the left MCC, and ACC extending into the medial frontal gyrus, and the inferior parietal lobe (IPL) bilaterally. The right lingual gyrus, however, was less activated during the anticipation of unknown stimuli relative to neutral. When anticipating positive compared to neutral pictures, control subjects showed enhanced brain activity in the right precentral gyrus, right medial frontal gyrus, right lingual gyrus and cuneus, and in the left middle temporal gyrus. For details refer to Table 4.

Group comparison (BPD > HC) during emotional anticipation

Whole-brain analyses during the anticipation of negative compared to neutral stimuli revealed reduced brain activity in the left dorsal ACC as well as in the left MCC in patients relative to controls (Fig. 4). As opposed to healthy participants, the BPD sample additionally showed increased brain activity in the left pregenual ACC, left lingual gyrus, and in the left posterior cingulate cortex (PCC) during the same contrast (Fig. 3). When anticipating stimuli with unknown valence versus neutral, patients showed reduced brain activations in the left MCC extending into the medial frontal gyrus within the MPFC region (Fig. 4), in the left precentral gyrus and in the right middle frontal gyrus belonging to the DLPFC. Further, reduced brain response in the left intraparietal sulcus (IPS), right precentral gyrus, and right inferior temporal gyrus during the same contrast was found in BPD patients compared to healthy participants. Differential activations between the two groups during the anticipation of positive versus neutral pictures did not survive the Monte Carlo correction for multiple comparisons (for details refer to Table 5).

There were no significant correlations between clinical symptoms, including scores of the borderline symptom list (BSL) and scores of the Dissociation Tension Scale (DSS4-acute) and the beta weights of the above-mentioned significant differential activations in the BPD sample (Online Resource 4).

ROI analyses

ROI analyses in the predefined amygdala region showed no significant group differences, irrespective of contrast. ROI analyses investigating hemodynamic differences in V1 and LGN revealed that BPD patients compared to healthy controls showed increased brain activity in the left primary visual cortex when anticipating negative versus neutral stimuli (t (34) = 2.31, $p < .03$, Cohen's $d = .62$, medium effect). The lateral geniculate nucleus (LGN) was bilaterally not differentially activated in any contrast during emotional anticipation between both samples (for details refer to Online Resource 3).

Discussion

We investigated the neural correlates of the anticipation of nonspecific, general emotional stimuli (negative, positive,

Table 4 Whole-brain activations in the HC sample during emotional anticipation

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
Dorsal ACC/MCC/MPFC	R	8/9/32	61,388	5	25	27	7.6	.000001
Middle occipital gyrus	R	18	5,004	29	−83	−9	4.9	.000124
Culmen	R		2,276	8	−62	−6	4.4	.000424
Insula	R	13	17,852	41	13	0	6.5	.000005
Insula/superior temporal gyrus	L	13/22	12,608	−52	7	0	6.5	.000005
Thalamus/midbrain	L		6,443	−7	−23	0	5.4	.000044
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
Insula/Inferior frontal gyrus	R	13/47	7,088	32	16	0	5.7	.000028
Insula	L	13	5,571	−31	22	3	6.7	.000004
Middle frontal gyrus/DLPFC	L	9	3,254	−40	16	45	5.2	.000064
Precentral/middle/superior frontal gyrus/DLPFC	L	4/6/8/9/44	3,603	−43	−2	54	5.1	.000090
ACC/MCC/medial frontal gyrus	L	6/24/32	48,909	−10	16	36	7.4	.000001
Inferior parietal lobe/supramarginal gyrus	L	40	3,711	−58	−56	33	5.6	.000032
Inferior parietal lobe	R	40	2,719	50	−50	33	4.7	.000216
Lingual gyrus	R		1,533	8	−53	9	−5.8	.000020
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Precentral gyrus	R	4	3,365	41	−17	36	5.0	.000119
Medial frontal gyrus	R	6	1,402	8	−8	54	5.0	.000100
Lingual gyrus/cuneus	R	17	7,423	20	−80	9	5.6	.000035
Middle temporal gyrus	L	19	1,092	−31	−56	9	4.8	.000173

Activated areas in a random-effects analysis (rfx) in the HC sample with a voxel-wise threshold of $p < .005$. Activated minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: (a) Anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster threshold: 1,616 mm^3 (59functional voxels), (b) Anticipation of unknown stimuli > anticipation of neutral stimuli, cluster-threshold: 1,502 mm^3 (56 functional voxels), and (c) Anticipation of positive stimuli > anticipation of neutral stimuli, cluster-threshold: 1,032 mm^3 (40 functional voxels)

HC healthy controls, *ACC* anterior cingulate cortex, *MCC* midcingulate cortex, *MPFC* medial prefrontal cortex, *DLPFC* dorsolateral prefrontal cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

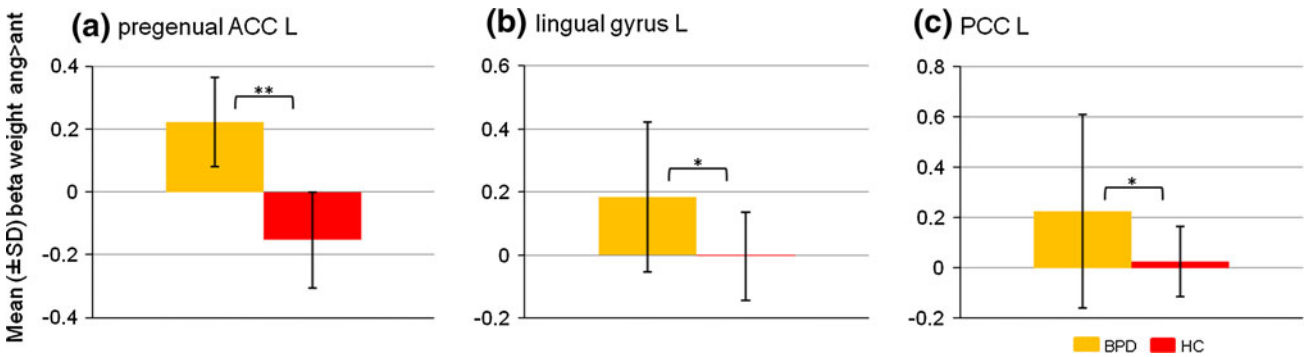

Fig. 3 Enhanced brain activity in BPD patients compared to healthy controls during the anticipation of negative versus neutral pictures (contrast ang > ant). Given are the mean beta weights within **a** left pregenual ACC ($x = -16$, $y = 37$, $z = 24$), [t (34) = 3.63, $p < .001$], **b** left lingual gyrus ($x = -4$, $y = -86$, $z = 0$), [t (34) = 2.78, $p < .01$], and **c** left PCC ($x = -19$, $y = -38$, $z = 24$), [t (34) = 3.29, $p < .002$], as derived from the contrast analyses. Error bars indicate standard deviations. *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex, *BPD* borderline personality disorder

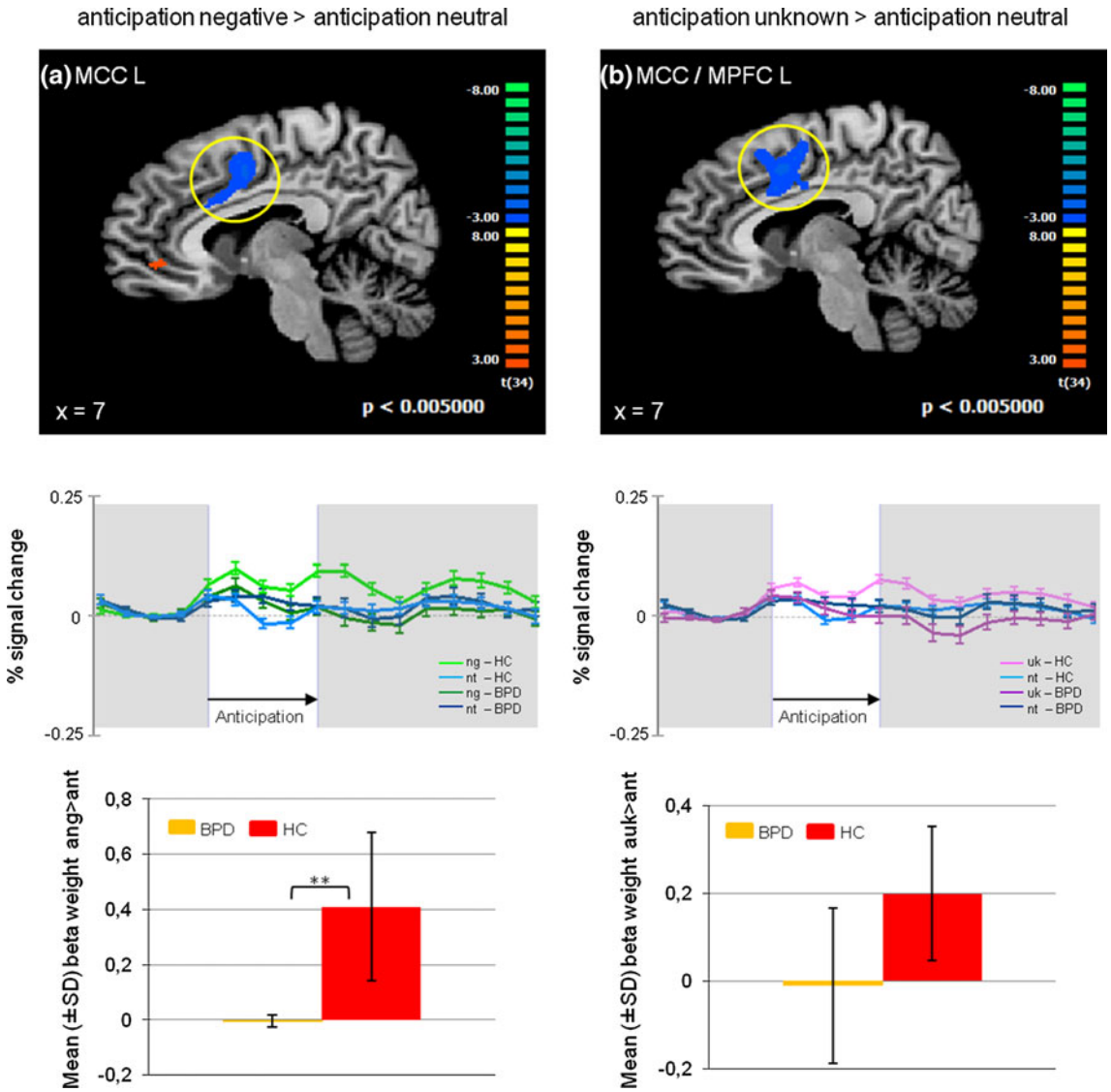

Fig. 4 Reduced activity in the group comparison BPD > HC within **a** the left MCC ($x = -10$, $y = 4$, $z = 42$) during the anticipation of negative versus neutral stimuli (ang > ant) and within **b** left MCC adjacent to the MPFC ($x = -13$, $y = 13$, $z = 36$) during the anticipation of unknown cued versus neutral pictures (auk > ant). The t values of the contrasts are given in the *color bar*. Below each contrast, given are the respective time courses (also consider the delay of the hemodynamic response function) and the mean beta weights including standard deviations within the corresponding regions. **a** [t (34) = 3.62, $p < .001$], **b** [t (34) = 1.93, $p < .06$]. *ACC* anterior cingulate cortex, *MCC* midcingulate cortex, *MPFC* medial prefrontal cortex, *L* left, *HC* healthy controls, *BPD* borderline personality disorder

and unknown) in relation to neutral pictures in patients with BPD compared to healthy participants. BPD patients showed neural differences in anticipating cued emotional pictures, in particular those of known negative and potentially negative valence, but not of positive stimuli. Differential activations were primarily detected in functional alterations of the cingulate cortex and adjacent prefrontal regions as well as in the visual cortex. Our study provides evidence that disturbed emotion processing in BPD also occurs during the anticipation of emotional stimuli, in addition to disturbances during the actual perception phase (e.g., [8, 9, 12, 13]). Reduced brain activity in cognition-related areas and increased activations in the pregenual ACC and in the visual cortex during the emotional anticipation in BPD patients indicate a disturbance in cognition–emotion interaction and a heightened visual sensitivity to negative cues. Moreover, enhanced activation in the PCC area suggests an increased autobiographical reference in BPD, even though no specific stimuli were anticipated.

The cognitive domain of emotion regulation comprises particularly the anterior cingulate as well as the medial and dorsolateral prefrontal cortical brain regions [72]. In our

Table 5 Whole-brain group comparison (BPD > HC) during the anticipation of emotional stimuli

Anatomic region	Lat	BA	Cluster size (mm^3)	Peak Talairach coordinates			*t*-max	*p*-max
				x	*y*	*z*		
(a) Anticipation of negative stimuli > anticipation of neutral stimuli								
MCC	L	24	4,450	−10	4	42	−3.9	.000481
Dorsal ACC	L	32	1,222	−10	22	24	−4.5	.000068
Pregenual ACC	L	32	3,282	−16	37	24	5.2	.000008
Lingual gyrus	L	18	1,131	−4	−86	0	4.5	.000074
Posterior cingulate	L	31	866	−19	−38	24	4.6	.000062
(b) Anticipation of unknown stimuli > anticipation of neutral stimuli								
MCC/medial frontal gyrus	L	24/32/6	5,603	−13	13	36	−5.1	.000015
Precentral gyrus	L	6	920	−61	−5	27	−3.9	.000433
Intraparietal sulcus	L	7	739	−25	−68	36	−3.8	.000666
Middle frontal gyrus/DLPFC	R	9	800	26	28	24	−3.6	.000880
Precentral gyrus	R	4	798	41	−17	48	−3.5	.001182
Inferior temporal gyrus	R	20	837	47	−32	−15	−3.8	.000555
(c) Anticipation of positive stimuli > anticipation of neutral stimuli								
Exploratory results for cluster-threshold: 135 mm^3								
Ventral ACC	R	24	315	8	28	9	3.4	.001921
Ventral ACC	L	24	393	−13	34	9	3.6	.000911
Thalamus	L		235	−4	−5	0	3.7	.000871
Medial frontal gyrus	L	10	289	−13	52	6	3.5	.001341

FMRI analysis of emotion anticipation in the BPD group versus the control group. Activated areas in a random-effects analysis (rfx) with a voxel-wise threshold of $p < .005$ mean that the contrast difference (anticipation of emotional stimuli > anticipation of neutral stimuli) were greater in the BPD group compared to the control group. (a) Anticipation of negative stimuli > anticipation of neutral stimuli. Minimum cluster size for global error probability of $p < .05$: 729 mm^3 (28 functional voxel). (b) Anticipation of unknown stimuli > anticipation of neutral stimuli. Minimum cluster size for global error probability of $p < .05$: 760 mm^3 (29 functional voxel). (c) Minimum cluster size for global error probability (Monte Carlo correction) of $p < .05$: 593 mm^3 (23 functional voxels) showed no differences between the groups during the anticipation of positive stimuli > anticipation of neutral stimuli, but clusters exceed a threshold of 135 mm^3 (5 functional voxels)

ACC anterior cingulate cortex, *MCC* midcingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *BA* Brodmann area, *Lat* lateralization, *R* right, *L* left

study, left dorsal ACC and MCC were less active in patients compared to healthy controls during the anticipation of negative stimuli. During the anticipation of ambiguously cued pictures, patients exhibited additionally reduced activations in the MPFC (adjacent to the MCC) and DLPFC. With regard to the interaction of cognitive and emotional processes, dorsal subregions of the cingulate cortex have been associated with cognitive processes such as attention for action, anticipation, and action selection [46, 73–78]. Moreover, functions related to integration and control of emotional stimuli [23, 24, 79] as well as the anticipation of unpleasant stimuli [25] have been linked to the cingulate cortex. In parallel, prefrontal regions including the MPFC and DLPFC play a central role in selecting, implementing, and monitoring cognitive control and executive strategies [23] and in emotion regulation [80–83].

Functional alterations of the cingulate cortex could represent neural correlates of clinical features in BPD, mainly including affective dysregulation and poor impulse control. Prior reports on BPD have shown an impaired modulation of emotion processing brain circuits by ACC activity (review [6]). Further, the role of prefrontal brain regions in BPD has received great attention. A number of studies have consistently demonstrated a failure of "top-down" frontal modulation of limbic brain areas. In particular, during emotional provocation, there seems to be a decreased inhibitory effect of control processes mediated by the PFC on hyperreactive bottom-up emotion generating brain areas ([84, 85]; review [18]; meta-analysis [86]). In the current study, BPD patients showed reduced activity in the DLPFC and MPFC and in the cingulate cortex already during emotional anticipation. This pattern was in particular eminent when patients anticipated negative or potentially negative pictures. Foremost, this demonstrates a specific bias and vulnerability with respect to negative valence, which is in line with the BPD psychopathology [87]. Further, the extended reductions in brain activity in

areas as the MCC, MPFC, and DLPFC in patients during the anticipation of ambiguously cued stimuli could indicate that this condition may be even more prone to dysregulation. Reduced brain activity in cognition-related brain areas in BPD could account for a diminished automatic emotion regulation during anticipation. Compared to healthy subjects, BPD patients may have difficulties to intuitively engage in emotion regulation when being cued to anticipate emotional pictures. Our results suggest that reduced activations in brain regions related to cognition and emotion regulation during emotional anticipation may contribute to the general deficient regulatory processing in BPD patients. Consequently, this dysregulation may add to the symptomatic heightened emotional reactivity during stimulus perception.

In contrast to reductions in cognitive-regulating brain regions, BPD patients exhibited more pronounced brain activity differences in the pregenual ACC during the anticipation of negative stimuli. The pregenual ACC is the most ventral part of the cingulate cortex and is particularly involved in affective processing [74]. Further, it has strong connections to the amygdala [46, 88] and has been associated with dysfunctions in depression (meta-analysis [89]) typically showing elevated physiological activity during depressed phases [90]. In our study, a relevant number of patients showed depressive symptoms. However, this is not surprising given that cooccurrence of depression is very common in this illness [56]. Stronger activations in the pregenual ACC during emotional anticipation could therefore be a correlate of heightened emotional involvement in BPD patients. Our findings fit in well with previous work documenting a deficit in connectivity within fronto-limbic networks in BPD. For instance, Kamphausen and colleagues [43], who investigated fear-inducing anticipation, showed that BPD patients compared to healthy participants exhibited increased connectivity of limbic brain structures with ventromedial prefrontal regions, but decreased connectivity of ventral ACC subregions with the dorsally located parts of the ACC. The authors suggested that the functional disconnection between ventral and dorsal prefrontal areas may be part of the neural mechanisms underlying emotional dysregulation in BPD patients. Cullen et al. [16] examined overtly and covertly processing of fearful faces and also found interesting connectivity alterations in the cingulate cortex in BPD. Their findings revealed a lower connectivity between limbic structures and mid-cingulate cortical regions and higher connectivity between limbic areas and the ventral ACC in BPD patients. Moreover, Koenigsberg and colleagues [45] have examined distancing to negative social cues as a form of emotion regulation and observed less signal change in dorsal subareas of the ACC, further indirectly underpinning a failure of fronto-limbic emotion regulation in BPD. In the current study, increased activations in the pregenual ACC and reduced brain activity in dorsally located areas of the ACC and MCC during negative anticipation point to a disrupted interplay between emotional and cognitive processes before actual stimulus exposure in BPD.

During negative emotional anticipation, BPD patients additionally showed enhanced activations in the visual cortex, mainly in the lingual gyrus, and also in the PCC. Heightened brain activity in the visual cortex points to enhanced basic sensory processing of cues [91, 92], which could be due to modulatory effects of attentional circuits [93, 94]. Increased activity of visual cortical brain regions in BPD patients was also observed at baseline in a positron emission tomography (PET) study [84]. Similarly, Koenigsberg and colleagues [9] found heightened visual activity in BPD when processing negative emotional stimuli. The authors interpreted their finding as an imbalance between reflexive automatically responding networks and higher-level conscious cortical processes, which could correspond to a general "hyperawareness" in BPD in the context of emotional situations. Our data revealed comparable enhanced activations in visual areas as early as during the anticipation period. This raises the possibility that during anticipation, the emotional response for the upcoming perception is primed [35]. Brain activity in the PCC was also more pronounced in BPD patients compared to controls when anticipating negative pictures. The PCC is associated with autobiographical memory [95], and it is also implicated in evaluating self-relevant sensations [79] and self-reference in general (meta-analysis [96]). In the case of BPD, heightened PCC activation already during the anticipation of unspecific, not self-related emotional stimuli could fit in well with the prominent self-reference in everyday life situations. This aspect may explain a stronger emotional engagement in BPD patients compared to healthy participants. In addition, increased self-reference via the PCC could further involve a visual-orienting network that is connected with the parietal lobe [97]. This may play a role in the visual preparation for upcoming negative stimuli [98], as shown here. In a general sense, current findings are in line with the cognitive approach by Beck & Freeman [99] suggesting that individuals with BPD are hyperattentive to negative emotional signals. More generally, BPD patients may have difficulty in controlling their attention and may be focused on the past, the future, or current self-related processing rather than the task itself, as has been proposed by Linehan [100] (review [87]).

Many studies have found an increased activation of the amygdala in BPD in tasks using either the perception of emotional stimuli or self-referential paradigms (e.g., [8, 13, 14, 101]). The amygdala plays a central role in the processing of emotional stimuli (meta-analysis [102]), which is consistent with the observed emotional hyperactivity in

BPD. However, in the current study, the amygdala was not differentially active in patients compared to healthy subjects when anticipating negative and potentially negative, ambiguous emotional stimuli. This is in parallel with a PET resting state study [84]. One reason for the lack of differential activation in the amygdala in our study could be that the anticipation of emotional stimuli represents a stimulation, which BPD patients are able to cope with. This is also given by the nonsocial and nonthreatening setting of a MR scanner. Another possible explanation for the lack of differences in the amygdala activation across both groups could be the nonspecificity of used stimuli. Subjects were not exposed to emotional challenges or to stressful memories, and only a limited number of social and interpersonal stimuli were shown.

One limitation of this study, but from a certain point of view also strength, is that no behavioral control was used. With this approach, we aimed to avoid interference due to preparatory and executive processes during task performance, as has been done reliably in several prior studies with this task (e.g., [25, 29, 103]). As another limitation of the current work, it could be discussed that the patient sample was rather heterogeneous with regard to comorbid diagnoses and medication, although age and gender were perfectly matched with control subjects. Patients taking medication and patients with cooccurring disorders, especially current depression and substance abuse, were included for reasons of representing a typical group of patients with BPD symptoms. Other cooccurring psychiatric symptoms and disorders, such as lifetime MDD [56] as well as substance use disorders [57], are very frequent and even typical in BPD. While studying an unmedicated sample could have avoided possible confounds due to medication [104], it would have meant to investigate a less severely ill and less representative sample of BPD patients. This could have resulted in examining only a subgroup of individuals with BPD leading to less generalizable results.

Our data provide clinical relevance for psychotherapy training. For BPD patients, learning to regulate one's emotions before actual emotional confrontation could be of advantage in dealing with daily affective situations. For this purpose, different regulation strategies during emotional anticipation could be tested [105]. In the course of psychotherapy, patients could train to become more aware of affective cues already prior to an emotional situation. In this way, they could learn to better cope with their own tensions and consequently to be able to anticipate following emotional reactions more appropriately. Future studies could investigate whether heightened activity in visual cortical regions in patients with BPD is mainly related to cue sensitivity per se or whether it demonstrates a more perceptive identification of negative cues within a particular context. The question arises whether patients actually are consciously more attentive to negative cues in terms of hyperawareness [9] or whether heightened visual activity is limited to the basic perception level. Investigating interconnections between the visual cortex and emotion processing regions, such as the amygdala [106], in the context of emotional anticipation could provide more insights into the basic emotion processing in BPD. Future studies should also look into the mechanisms of top-down regulation in the prefrontal cortex and cingulate regions but also regarding the heightened activity in the visual cortex by means of connectivity analysis during the anticipation period. Further, it would be interesting to vary the length of the anticipation period or subdivide it to disentangle preparatory processes during emotional anticipation into early versus late anticipation.

In conclusion, neural differences between patients and healthy participants were prominent during the cued anticipation of negative and ambiguous pictures. Our data indicate a negative emotional bias, which fits well with the BPD symptomatology. On the behavioral level, emotional dysfunction in BPD typically is observed in negative emotional states and dysphoric affects [2]. Present data suggest that failure to recruit brain areas related to cognitive monitoring is associated with dysfunctional preparatory processes for affective situations. Moreover, we observed a clear bias toward negative cues on the neural level suggesting enhanced visual sensitivity in this regard in patients with BPD. Further, autobiographical self-reference in patients with BPD appears to play a role, although no self-related stimuli are presented. Our results point out that emotional dysregulation already during the anticipation of an emotional stimulus may constitute a contributing factor in BPD pathology.

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Conflict of interest The authors declare that they have no conflict of interest.

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