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ORIGINAL INVESTIGATION

Reduced deactivation in reward circuitry and midline structures during emotion processing in borderline personality disorder

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Abstract

Objectives. Borderline personality disorder (BPD) is characterized by a pervasive affective dysregulation. While recent imaging studies demonstrated the neural correlates of abnormal emotion processing in BPD and recently one study reported alterations of the reward circuit in this patient group, the exact neural mechanisms underlying the impact of abnormal emotion on reward behavior remain unclear. *Methods.* We therefore conducted an fMRI study in healthy controls and BPD patients to investigate the modulation of the anticipation of reward by simultaneously presented emotional pictures. *Results.* BPD patients revealed a disturbed differentiation between reward and non-reward anticipation in the bilateral pregenual anterior cingulate cortex if a positive or negative emotional picture is presented simultaneously. In the ventral striatum and the bilateral ventral tegmental area, BPD patients and healthy controls are able to differentiate between reward and non-reward even under emotional stimulation, but BPD patients show a reduced deactivation in the above mentioned regions compared to healthy controls. *Conclusions.* Altered emotion processing in BPD patients is likely to affect the reward system. More basic deficits in reward circuitry and other midline regions' level of resting state activity may contribute to this effect.

Key words: *Borderline personality disorder, reward, emotion, functional imaging, functional magnetic resonance imaging*

Introduction

Borderline personality disorder (BPD) is a complex clinical condition that is characterized by an instability in affect regulation, impulse control, interpersonal relationships, and self-image (Lieb et al. 2004). The clinical relevance of the pervasive emotional dysregulation led to several imaging studies investigating neuronal mechanisms during emotional processing. One of the most consistent findings in these studies is a hyperactivity in the amygdala and a hypoactivity in prefrontal regions, especially in reaction to aversive emotional stimuli, that was interpreted as a disturbed fronto-limbic inhibition (Herpertz et al. 2001; Mauchnik and Schmahl 2010). Other regions showing abnormalities during emotional processing in BPD patients include the anterior cingulate cortex (ACC), the adjacent ventromedial prefrontal cortex (VMPFC) as well as other subcortical regions like the midbrain and the ventral striatum (VS) (Minzenberg et al. 2007; Silbersweig et al. 2007; Mauchnik and Schmahl 2010). A recent functional imaging study investigated the discrimination of social and non-social emotional stimuli (Koenigsberg et al. 2009). Compared to healthy subjects, BPD patients showed a hypoactivation of the ACC and the intraparietal sulcus (IPS), less deactivation of the amygdala, and greater activation in the superior temporal sulcus and superior frontal gyrus after negative social emotional stimuli. Koenigsberg and colleagues (2009) concluded that BPD patients engage less cognitive

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control regions when employing a distancing strategy to regulate emotional reactions, which might contribute to their affective instability.

A specific situation that is associated with particular emotional activation is reward. The so-called reward system in the brain represents a complex network including various subcortical and cortical brain regions, like, e.g., midbrain dopaminergic neurons, VS, ventral putamen, ACC and the orbital frontal cortex. Regulating structures of the reward system are dorsal prefrontal cortex, amygdala, hippocampus, thalamus, lateral habenular nucleus, and specific brainstem structures (Haber and Knutson 2010). In this context, it is important to distinguish the anticipation of reward from processing a rewarding outcome. Knutson and colleagues developed the so-called monetary incentive delay task, which allows to investigate the anticipation phase and the feedback phase separately. They reported activations in typical reward regions like, e.g., the nucleus accumbens, the caudate nucleus and the putamen, as well as in mesial forebrain structures (including insula and mesial prefrontal cortex) during reward anticipation, while a rewarding outcome activated mainly the ventromedial frontal cortex (Knutson et al. 2000, 2001, 2003).

Several psychiatric disorders have been demonstrated to be associated with alterations of the reward system. Adults with ADHD (Ströhle et al. 2008), detoxified alcoholics (Beck et al. 2009), and schizophrenics (Juckel et al. 2005) showed a reduced ventral striatal activation during reward anticipation, whereas major depression is associated with an increased ACC activation during anticipation of reward. So far, only one neuroimaging study investigated the reward system in cluster B personality disorders (Völlm et al. 2007). Völlm and collegues (2007) reported an absence of neuronal responses in the PACC, the caudate bordering to the VS, and the midbrain including the ventral tegmental area (VTA) to rewarding outcomes in eight patients with borderline and/or antisocial personality disorder. The exact origin of altered neural activity in the reward system in borderline patients remains unclear though. Either it may stem from reward itself or, at least in part, from abnormal emotion processing that recruits overlapping regions, e.g., amygdala, VS, ACC, and midbrain areas. This could be tested by investigating the interaction between reward and emotion processing which has not yet been done in BPD subjects, whereas a recent study in healthy subjects investigated the interaction between reward and emotion and its impact on memory formation (Wittmann et al. 2008).

Based on the results reported above it was assumed that borderline patients – due to their affective dysregulation – show an alteration of reward anticipation particularly in combination with negative emotional stimuli. To investigate this interaction, we used a modified version of the well-established Monetary Incentive Delay Task (Knutson et al. 2000) in combination with the presentation of emotional pictures (negative, positive, neutral) during the anticipation of reward. Concerning our control subjects, we hypothesized that there is no influence of emotion on the above described differentiation between reward and no outcome in so-called reward regions (putamen, ventral striatum, ventral tegmental area) and in closely linked regions relevant for emotion processing (pregenual anterior cingulate cortex). For borderline patients, we hypothesized that emotion processing influences the reward/non-reward differentiation in the above-mentioned regions. According to the current literature (Donegan et al. 2003), we expected to observe a hyperreactivity to emotional stimulation in borderline patients for the bilateral amygdala and a disturbed reward/non-reward differentiation under emotional stimulation in the very same region.

Material and methods

Ethics statement

The presented study was approved by the ethics committees of the Universities of Münster and Magdeburg, Germany. After a detailed explanation of the study, all subjects gave their written informed consent.

Subjects

We investigated 17 healthy, female subjects with no psychiatric, neurological or medical illnesses (average age 26.41 ± 6.97 years, range 19–49 years, 15 right-handed, two left handed), and 17 carefully matched patients suffering from borderline personality disorder (all female, average age 28.88 ± 9.34 years, range 20–48 years, 15 right-handed, two left-handed).

Borderline patients suffered from 4.53 ± 1.84 DSM-IV Axis I diagnoses and 3.47 ± 1.51 DSM-IV Axis II diagnoses according to SCID-I and -II (Fydrich et al. 1997; Wittchen et al. 1997) (for details see Supplementary material available online). In the control group, two subjects were diagnosed with specific phobia (insects).

All healthy subjects were free from psychiatric medication. Among the borderline group, 11 patients took regularly psychiatric medication (only antidepressants: five patients; only neuroleptics: one patient; antidepressants and neuroleptics: four patients; antidepressants, neuroleptics, and sedatives: one patient)

(for details see Supplementary material available online).

All subjects completed four well-established neuropsychological tests: the LPS-3 (German: Leistungsprüfsystem-3; Horn, 1983) and MWT-A (German: Mehrfachwortschatzintelligenztest A; Lehrl et al. 1991) as measurements of general intelligence, Beck Depression Inventory (BDI; Hautzinger et al. 1994), and the Toronto Alexythymia Scale (TAS; Bach et al. 1996).

Experimental paradigm

Before scanning, all subjects completed a short practice version of the task to familiarise with the experiment. We used the behavioural data, i.e. the reaction times, obtained in this practice session, as an estimate of each individual's reaction time.

The fMRI scanning session was divided into three scanning runs. In the first scanning run, subjects had to perform a modified version of the well-established monetary incentive delay task (Knutson et al. 2001), requiring that the subject press a button with the index finger of their right hand within a certain time of a target image (a black square in the centre of the screen; see Supplementary Figure 1) being displayed. The length of this time period was determined in accordance with the average reaction time obtained in the pre-scan trial run, allowing the difficulty of the task to be modulated according to the individual's ability, and varied between 0.2 and 0.35 s. Furthermore, we wanted to ensure that in approximately 60% of all trials the required response was successful. Prior to this target image being displayed, a symbol indicating what the possible outcomes of the task would be – either reward, punishment, or no-outcome – was shown for 2 s, followed by a 2.25–2.75-s anticipation period. The trial type indicator took the form of a black circle with a small white circle within it at one of the cardinal points. Each position represented a different trial type (e.g., a circle in the "North" position would represent a reward trial). During the anticipation period a light-coloured cross was displayed in the centre of the screen.

In reward trials, completing the task successfully resulted in the subject winning €1, whilst failure meant that they would neither win nor lose anything. During punishment trials, a response within the required time period resulted in the subject neither winning nor losing money, whilst an unsuccessful response resulted in €1 being deducted from their total. Finally, in no-outcome trials no money was either won or lost, regardless of whether the subject responded within the required time period or not. Subjects were, however, instructed to still respond to the cue as quickly as possible. In total, 40 reward and punishment trials and 30 no outcome trials were displayed in a pseudo-random order. Each trial was followed by a feedback stage during which the subject was informed of the outcome. The amount of money won or lost in the preceding trial was displayed, along with the running total for their winnings, for a period of 1.65 s. Trials were separated by a 2.5–3.5-s inter-trial interval, during which the same light-coloured cross as that shown during the anticipation period was displayed. The anticipatory period for reward (ant rew), punishment (ant pun) and no-outcome (ant noc) trials were included in our design matrix along with their respective feedback periods.

In the second and third run a modified version of the above described monetary incentive delay task was presented (Figure 1). Simultaneously with the presentation of the outcome indicating symbol, i.e. reward, punishment or no outcome, an emotional picture was presented, resulting in a 3×3 factorial design. The pictures were taken from the International Affective Picture System (Lang et al. 1999) and were categorized according to their affective norms (positive, negative or neutral emotion). The total number of conditions was balanced to ensure the calculation of valid contrasts in SPM5 (e.g., 30 reward trials with positive emotion, 30 reward trials with negative emotion and 20 reward trials with neutral emotion). All different time periods (cue, anticipation, target, feedback and ITI) were

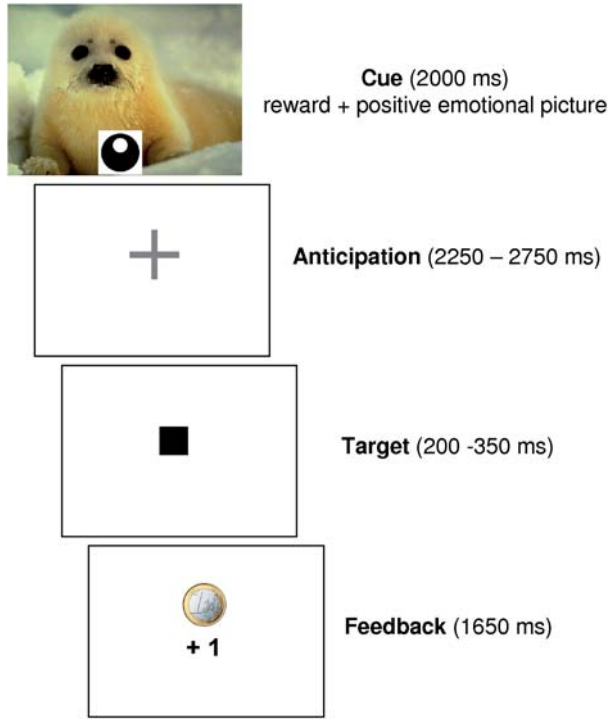

Figure 1. Structure of a single trial, representing the interaction between reward and a positive emotional picture.

equal to the above mentioned monetary incentive delay task without emotional modulation.

In all functional runs, a separate baseline condition (duration 4.5–5.5 s), was presented pseudo-randomized after approximately 10 trials. All participants received the amount of money they had earned during the whole experiment.

fMRI data acquisition and analysis

Functional data was collected using a 3-Tesla whole body MRI system (Philips Achieva) equipped with a Philips transmit and receive head coil. Using a midsagittal scout image, a stack of 32 $T2^*$-weighted single-shot echo-planar images (sshEPI) was aligned parallel to the bicommissural plane. During each functional run 540 whole brain volumes were acquired (matrix 64×64, field-of-view 230×230 mm, spatial resolution: $3.59 \times 3.59 \times 3.60$ mm, TE = 30 ms, TR = 2000 ms, flip angle 90°). Prior to the functional scanning session, a high-resolution, T1-weighted anatomical 3D gradient echo scan was acquired for each subject (matrix $256 \times 153 \times 80$, FOV $256 \times 204 \times 160$ mm, spatial resolution $1 \times 1.33 \times 2$ mm reconstructed to $0.5 \times 0.5 \times 1$ mm, TE = 3.4 ms, TR = 6.9 ms, flip angle 9°, two averages).

The functional data were preprocessed and statistically analysed using the SPM5 software package (Wellcome Department of Cognitive Neuroscience, University College London, UK; http://www.fil.ion.ucl.ac.uk) and MATLAB 6.5.1 (The Mathworks Inc, Natick, MA, USA). The first five volumes were discarded due to saturation effects. After temporal correction and correction for between-scan motion artifacts by realignment to the first volume, the anatomical scan was coregistered to a mean functional image. The normalization was generated by warping the subject's anatomical T1-weighted scan on the T1-template provided by SPM5 (MNI stereotactic space) and applying these parameters to all functional images. The images were resampled to a voxel size of $3 \times 3 \times 3$ mm^3 and smoothed with an isotropic 8-mm full-width half-maximum Gaussian kernel. The time-series fMRI data were filtered using a high pass filter and cut-off of 100 s.

For the monetary incentive delay task without emotional modulation presented in the first run, all relevant conditions, i.e. anticipation of reward, anticipation of punishment, anticipation of no outcome, their feedback phase according to task performance (success vs. no success) and the baseline condition were modeled, resulting in 10 conditions. Additionally, the six realignment parameters were entered as regressors of no interest. With regard to the interaction runs, we were mainly interested in the emotional modulation of the anticipation phase. Therefore, we modelled all combinations of the conditions "task" (anticipation of reward, punishment and no outcome) and "emotion" (positive, negative and neutral), as well as our baseline condition as regressors. Including the realignment parameters, this resulted in 16 conditions. A statistical model for each subject was computed by convolving a canonical haemodynamic response function with the above-mentioned design (Friston et al. 1994, 1998).

Regionally specific condition effects were tested by employing linear contrasts for each subject and each condition of interest. In a first step, we were mainly interested in the differentiation between "reward" and "no outcome" in healthy subjects and borderline patients, so we calculated the contrast ["anticipation of reward" > "anticipation of no outcome"] for each subject. The resulting contrast images were submitted to a second-level random-effects analysis by calculating an one-sample *t*-test to the images acquired for all subjects in the above mentioned condition.

For the emotion-reward interaction task, we defined all possible combinations between "task" (reward, punishment and no outcome) and "emotion" (positive, negative and neutral) separately on the first level. Using the "full factorial"-option implemented in SPM5, we calculated an ANOVA with the factors "group" (healthy vs. borderline patients), "task" (reward, punishment and no outcome) and "emotion" (positive, negative and neutral). As contrast of interest we concentrated on the *f*-contrast [interaction "group" × "task"], collapsed over all emotions. Furthermore, we calculated the *t*-contrast [positive interaction "group" × "task: anticipation of reward > anticipation of no outcome"] only for negative emotions. Following the "functional localizer approach" (de Greck et al. 2008) and using the two above-mentioned contrasts, we also extracted independent raw data from the monetary incentive delay task without emotional modulation, i.e. the conditions "anticipation of reward" and "anticipation of no outcome". To control for the multiple testing problem we performed a voxel-wise false discovery rate correction (Genovese et al. 2002). The anatomical localization of significant activations was assessed with reference to the standard stereotactic atlas by superimposition of the SPM maps on an averaged brain of all subjects.

Using sphere shaped regions of interest (ROI; radius 5 mm) centered upon the peak voxel within each area of interest, beta-values for each condition were extracted and transformed into percent signal change using the Marseille Region of Interest Toolbox (MarsBaR; http://marsbar.sourceforge.net/) software package (Brett et al. 2002).

All further statistical analysis (repeated measurement ANOVA, *t*-tests for dependent and independent samples) are calculated using the software package SPSS 11 (SPSS Inc., Chicago, IL).

Results

Neuropsychological data

Healthy subjects and borderline patients did not differ significantly with regard to age ($t(32) = -0.874$, $P = 0.389$) and intelligence (LPS-3: $t(32) = 1.906$, $P = 0.066$; MWT-A: $t(32) = 1.979$, $P = 0.056$), whereas the BDI score indicated that borderline patients were more depressed than healthy subjects. In total, 15 out of 17 borderline patients showed a BDI > 18 (mean $BDI_{healthy}$: 1.7 ± 2.9; mean $BDI_{patients}$: 32.7 ± 9.2; $t(32) = 13.267$, $P < 0.001$).

According to the TAS, eight out of 17 borderline patients scored higher than 60. Borderline patients scored significantly higher than healthy subjects on the subscale "difficulties indentifying feelings" (DIF) (mean $DIF_{healthy}$: 9.88 ± 1.97, mean $DIF_{patients}$: 24.65 ± 3.39; $t(32) = -15.54$, $P < 0.001$). The subscale "difficulties describing feelings" (DDF) revealed also a deficit in borderline personality disorder (mean $DDF_{healthy}$: 9.0 ± 2.6, mean $DDF_{patients}$: 17.18 ± 3.26; $t(32) = -8.081$, $P < 0.001$), whereas the subscale "externally-oriented thinking" (EOT) showed no difference between healthy and borderline patients (mean $EOT_{healthy}$: 16.76 ± 5.26, mean $EOT_{patients}$: 18.82 ± 4.57; $t(32) = -1.218$, $P = 0.232$).

Behavioural data

We compared the total number of successful trials using a repeated measurement ANOVA (within-subject factor "task" – reward, punishment, and no outcome – and between-subject factor "group"). For the monetary incentive delay task, the interaction group × task ($F(2,31) = 0.454$, $P = 0.639$) failed significance, as well as for the interaction task ($F(2, 31) = 0.323$, $P = 0.726$).

For comparison of the reaction times, we calculated a repeated measurement ANOVA with the within subject factor "task" (no outcome, punishment, reward) and the between subject factor "group" (healthy, borderline patients). For the monetary incentive delay task ($F(2,31) = 0.287$, $P = 0.683$) and the interaction task ($F(2,31) = 1.014$, $P = 0.374$), the interaction task × group failed significance.

Functional imaging data

Activation in reward circuitry. We first investigated whether our paradigm reliably activates the reward system in healthy subjects and borderline patients. For that purpose we calculated one-sample *t*-tests for the contrast [anticipation of reward >anticipation of no outcome] for each group separately. We were able to detect a consistent set of regions typically associated with reward processing, including the bilateral ventral striatum (VS), the putamen, the bilateral ventral tegmental area (VTA), and the dorsomedial thalamus in healthy subjects (P[FWE] < 0.05, $k > 10$), as well as in borderline patients (P[FDR] < 0.02, $k > 20$) (Figure 2).

Comparison between healthy subjects and borderline patients. In order to compare significant differences in signal changes between healthy subjects and borderline patients, we calculated the *f*-contrast "interaction [group × task]" collapsed over all emotions, P[FDR] < 0.03, $k > 10$ voxel. This contrast yielded significant differences in main regions of the reward system including bilateral PACC, bilateral caudate, bilateral VTA, and left putamen, as well as closely related regions like the bilateral dorsomedial thalamus, the cuneus/precuneus, and the ventromedial prefrontal cortex (VMPFC) (Figure 3, Supplementary Figure 2 and Table 1).

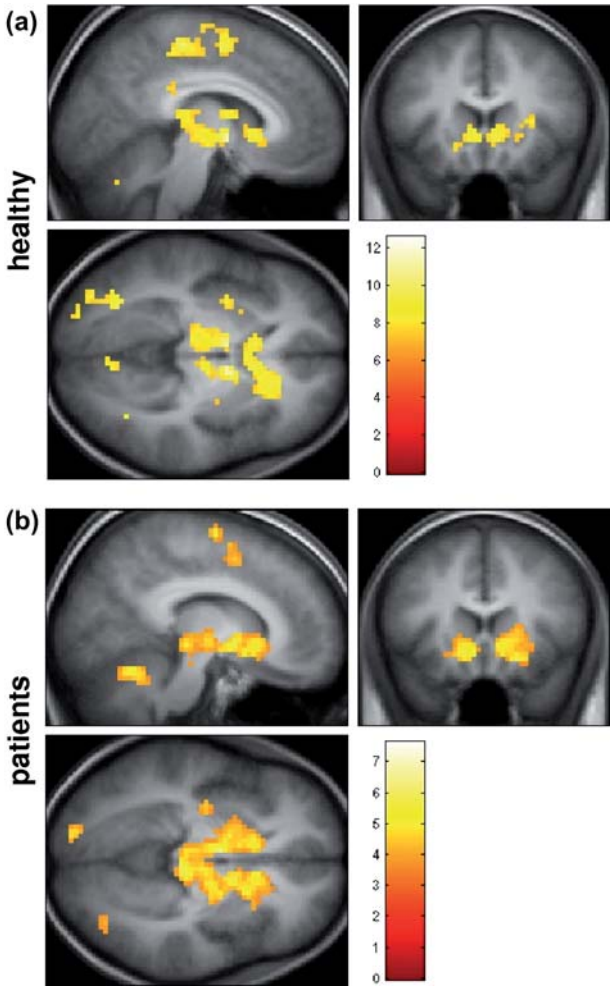

Figure 2. Contrast [anticipation of reward] > [anticipation of no outcome] in healthy controls and patients suffering from borderline personality disorder. Statistical parametric maps were thresholded at P [FWE] < 0.05, $k > 10$ for healthy subjects ($n = 17$), and P [FDR] < 0.02, $k > 10$ for borderline patients ($n = 17$).

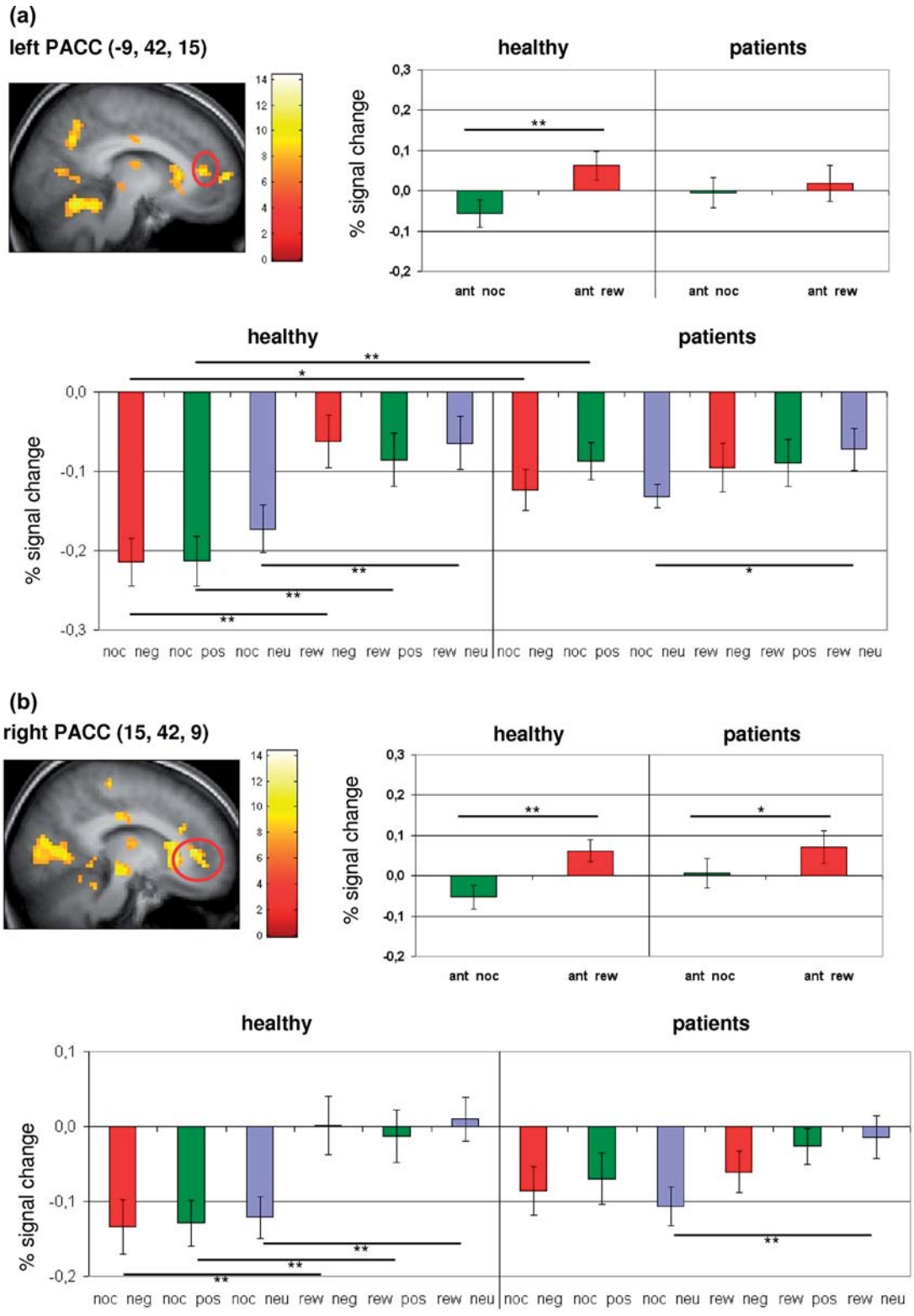

Figure 3. *F*-contrast "interaction [group × task]" collapsed over all emotions thresholded at P [FDR] < 0.03, $k > 10$ voxel, showing the neuronal response and the percent signal change in the left PACC (a), the right PACC (b) and the left putamen/VS (c).

In the left PACC (MNI co-ordinates at [–9, 42, 15]), healthy subjects are able to differentiate significantly between reward and no outcome ($t(16) = –5.516$, $P < 0.001$), whereas borderline patients show no significant differentiation between the above mentioned conditions ($t(16) = –0.872$, $P = 0.396$). In the very same region, healthy subjects are able to differentiate significantly between reward

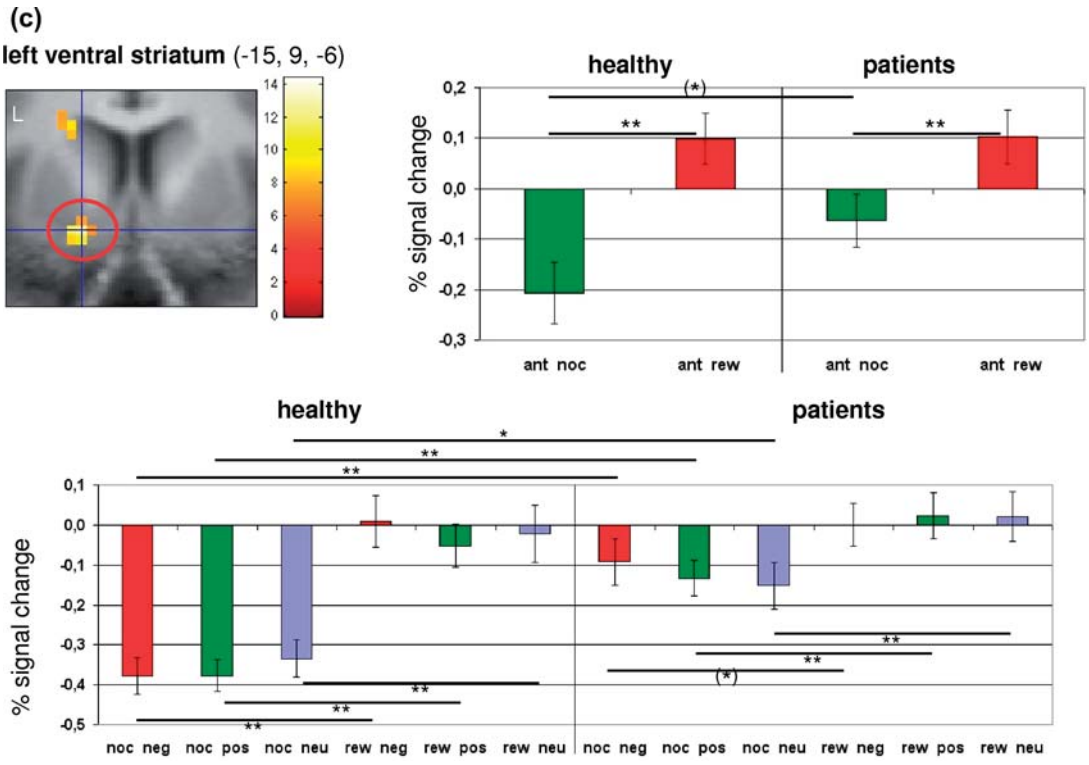

Figure 3. *(Continued)*.

and no outcome, even if an emotional picture is presented, whereas borderline patients are only able to differentiate between reward and no outcome if a neutral emotion is presented ($t(16) = -2.3, P = 0.035$). Moreover, borderline patients show a significantly reduced deactivation in the left PACC compared to healthy subjects for the conditions "no outcome + negative emotion" ($t(32) = -2.294$, $P = 0.028$) and "no outcome + positive emotion" ($t(32) = -3.215$, $P = 0.003$) (Figure 3a).

In the right PACC (MNI: 15, 42, 9), both groups are able to differentiate between the conditions "reward" and "no outcome" (healthy: $t(16) = -6.198$, $p < 0.001$; borderline patients: $t(16) = -2.6$, $P = 0.019$). Concerning the emotional modulation, healthy subjects are able to differentiate significantly between reward and no outcome, even if an emotional picture is presented), whereas borderline patients are only able to differentiate between reward and no outcome if an neutral emotion is presented ($t(16) = -4.706$, $P < 0.001$) (Figure 3b).

As typical, so-called reward regions, we investigated the left putamen/ventral striatum (VS) and the bilateral midbrain/ ventral tegmental area (VTA).

Table I. MNI coordinates of activations: interaction [group × task].

ROI name	Coordinates [MNI]	*P* [FDR]	*f* value	*z* value
Left PACC	–9, 42, 15	0.024	9.26	3.66
Right PACC	15, 42, 9	0.024	11.29	4.12
Left VMPFC	–9, 60, 9	0.024	10.56	3.96
Right dorsal cingulate cortex	9, 30, 30	0.024	9.22	3.65
Left dorsomedial thalamus	–3, –12, 21	0.024	10.03	3.84
Right dorsomedial thalamus	6, –12, 18	0.024	10.05	3.85
Left precuneus/BA7	–3, –66, 45	0.024	8.69	3.52
Left cuneus/BA 18	–6, 72, 15	0.024	8.31	3.42
Right cuneus/BA 18	9, 81, 21	0.024	10.03	3.84
Left putamen	–15, 9, –6	0.024	12.25	4.32
Left VTA	–3, –15, –6	0.024	10.94	4.04
Right VTA	9, –15, –6	0.024	10.35	3.91
Left caudate	–6, 18, 6	0.024	8.85	3.56
Right caudate	9, 24, 6	0.024	14.33	4.72

Interaction [group × task], collapsed over all emotions, *F*-test, *P*[FDR] < 0.03, $k > 10$.
VMPFC, ventromedial prefrontal cortex; PACC, pregenual anterior cingulate cortex; VTA, ventral tegmental area; BA, Brodmann area.

In the left VS (MNI: –15, 9, –6), healthy subjects ($t(16) = -6.678$, $P < 0.001$) and borderline patients ($t(16) = -5.332$, $P < 0.001$) are both able to differentiate significantly between reward and no outcome. Although both groups can differentiate between reward and no outcome, healthy subjects show an increased deactivation for the condition "no outcome" compared to borderline patients ($t(32) = -1.792$, $P = 0.083$). Concerning the interaction task, healthy subjects as well as borderline patients are able to differentiate significantly between reward and no outcome if an emotional picture is presented. Moreover, we were able to detect a significant difference between healthy subjects and borderline patients for the conditions "no outcome + negative emotion" $t(32) = -3.878$, $P = 0.001$), "no outcome + positive emotion" ($t(32) = -4.119$, $P < 0.001$) and "no outcome + neutral emotion" ($t(32) = -2.456$, $P = 0.02$) (Figure 3c).

Furthermore, borderline patients showed significantly reduced deactivation during the anticipation of no outcome in the bilateral VTA, especially if a simultaneous emotional picture, i.e., positive or negative as distinguished from neutral, is presented (Figure 4).

In the left VTA (MNI: –3, –15, –6; healthy: $t(16) = -8.144$, $P < 0.001$; borderline patients: $t(16) = -3.998$, $P = 0.001$) and the right VTA (MNI: 9, –15, –6; healthy: $t(16) = -6.652$, $P < 0.001$; borderline patients: $t(16) = -4.468$, $P < 0.001$), both groups are able to differentiate between reward and no outcome.

In addition, in the left VTA, healthy subjects as well as borderline patients are able to differentiate significantly between reward and no outcome if an emotional picture is presented. Moreover, we were able to detect a significant difference between healthy subjects and borderline patients for the condition "no outcome + negative emotion" ($t(32) = -2.803$, $P = 0.009$).

In the right VTA, we were able to detect a similar pattern for the modulation of reward processing by emotions in both groups, i.e. healthy controls and borderline patients. Both groups are able to differentiate between reward and no outcome regardless of the shown emotion. Furthermore, the emotional modulation of the condition "no outcome" showed a significant group difference between healthy subjects and borderline patients ("no outcome + negative emotion": $t(32) = -3.192$, $P = 0.003$; "no outcome + positive emotion": $t(32) = -2.503$, $P = 0.018$; "no outcome + neutral emotion": $t(32) = -1.924$, $P = 0.063$) (Figure 4b).

Based on previous studies examinating the impact of negative emotion processing on amygdala activity in borderline personality disorder, we calculated the *t*-contrast "positive interaction [group] × [task]" only for negative emotions, P[FDR] < 0.03, $k > 10$ voxels, in SPM5. This yielded significant signal changes in the left extended amygdala and related regions like the right parahippocampal gyrus. Interestingly, Borderline patients were unable to properly differentiate between anticipation of reward and no outcome in the amygdala only in the presence of negative emotions.

Moreover, in the left extended amygdala borderline patients show less deactivation during the condition "no outcome plus negative emotion" compared to healthy subjects. In the right parahippocampal gyrus, significant group differences for the conditions "no outcome plus negative emotion", "no outcome plus positive emotion" and "no outcome plus neutral emotion" were detected, reflecting a stronger activation, and thus hyperreactivity, in borderline patients (see Supplementary Material and Supplementary Figure 2 for details).

Medication effect. Since some of our patients were on medication, we also calculated the interaction of medication with signal changes. We henceforth calculated a repeated measurement ANOVA with the factors "task" (reward, punishment, no outcome) and "emotion" (positive, negative, neutral) and the between subject factor "medication" for the Borderline patients in order to exclude possible medication effects. This yielded non-significant results for the interaction medication × task × emotion and medication × emotion in all of the above-mentioned regions (only the interaction medication × task turned out to be significant for the left PACC and the bilateral VTA; see Supplementary Material for statistical details concerning all regions). Nevertheless, we cannot completely exclude possible medication effects for the bilateral VTA and the left PACC, since our study was not designed to deal with medication effects in borderline disorder.

Discussion

We here investigated the neural interaction between reward anticipation and emotion processing in BPD. Borderline patients were not able to differentiate between reward and no outcome if a positive or negative emotional picture is presented simultaneously. This pattern of abnormal differentiation was observed in the bilateral PACC and the right parahippocampal gyrus. In the bilateral VTA and the left ventral striatum, healthy subjects and borderline patients were both able to differentiate between reward and no outcome, but borderline patients showed a reduced deactivation concerning the condition "no outcome" with (positive, negative and/or neutral) emotional modulation. This finding demonstrates for the first time the impact of emotion

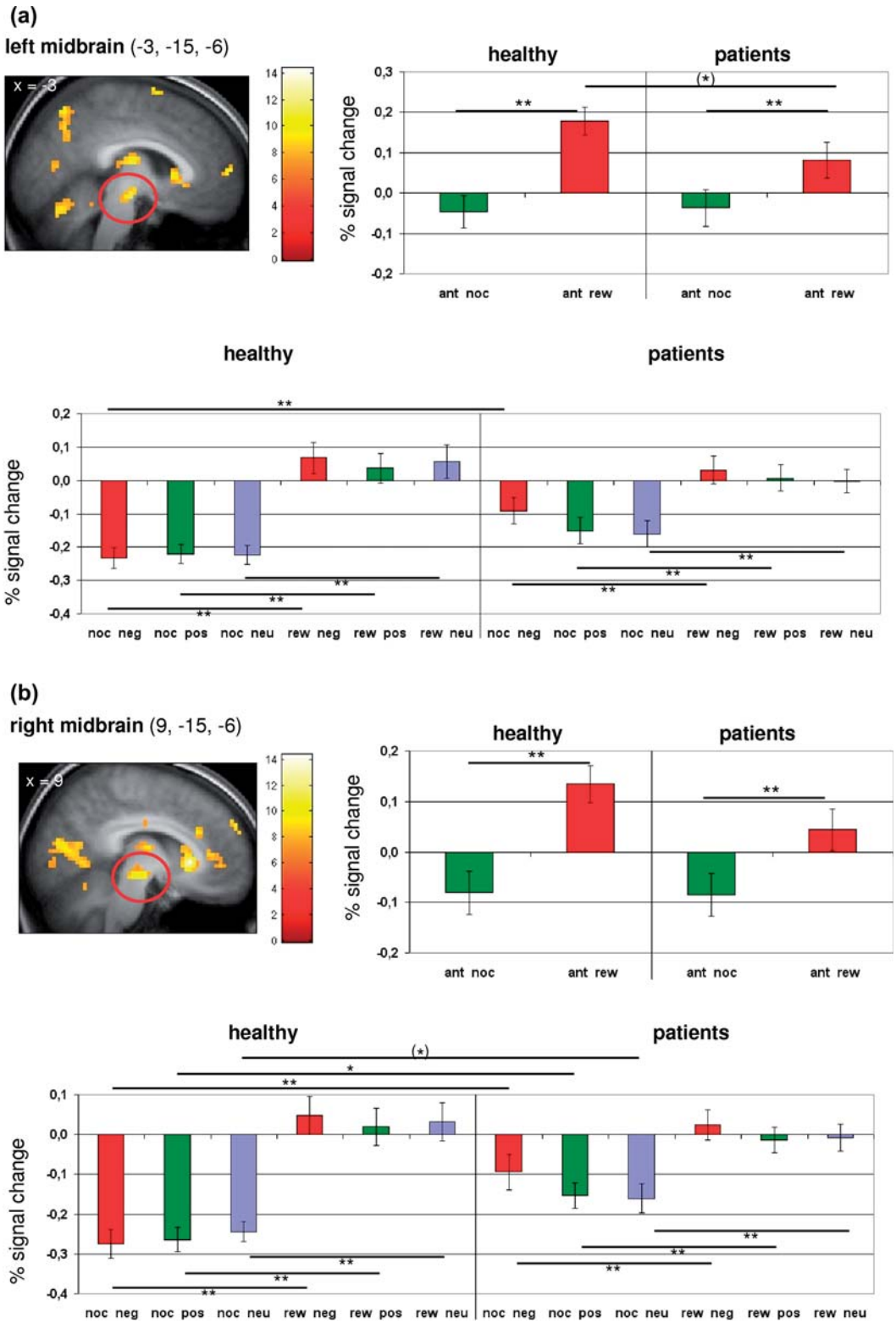

Figure 4. *F*-contrast "interaction [group × task]" collapsed over all emotions thresholded at P [FDR] < 0.03, $k > 10$ voxel, showing the neuronal response and the percent signal change in the left (a) and right midbrain (b).

processing on the reward circuitry in borderline patients.

The relative hyperactivity of the amygdala as a consequence of negative emotional stimuli is in line with previous imaging studies in BDP patients (Herpertz et al. 2001; Donegan et al. 2003; Minzenberg et al. 2007; Silbersweig et al. 2007; Mauchnik and Schmahl, 2010). In addition to the abnormal amygdala activity,

these studies demonstrated altered signal changes in ACC, VMPFC, midbrain areas, and VS.

Our results shed new light on the interaction of the partly overlapping brain areas of the reward system and those active during emotion processing. In borderline patients the reward sytem is altered during (negative or positive) emotional states. More precisely, brain regions typically involved in reward processing, like, e.g., VTA, AS, and PACC, show disturbed differentiation between reward and no outcome after an emotional stimulus. A crucial role in this mutual interaction might play the amygdala, which is know to moderate the reward system (Haber and Knutson 2010). It can be hypothesized that the hyperactivity of the amygdala elicited by, e.g., a negative emotional stimulus triggers the ongoing activity in the reward system. As a consequence, it can be assumed that the reward system in BPD patients is not impaired per se, but is disturbed by altered processing of affective states.

One main finding of the present study consists the abnormal differentiation between reward and no outcome in BPD patients in the left and right PACC. In this brain region, borderline patients are only able to differentiate neuronally between reward and non-reward if a neutral or no emotional stimulation occurs. This so-called "affective subdivision of the ACC" (Bush et al. 2000) is closely connected to the amygdala and the ventral striatum and functionally involved in "assessing the salience of emotional and motivational information and the regulation of emotional responses" (Bush et al. 2000). In subcortical regions like the ventral striatum and the ventral tegmental area, borderline patients are able to differentiate significantly between reward and no outcome regardless of the emotion presented simultaneously. But compared to healthy controls, BPD patients show a significantly reduced deactivation in the above mentioned regions concerning the condition "no outcome" with negative, positive, and neutral emotional stimulation. Because of the close anatomical connections between these regions and the amygdala (Postuma and Dagher 2006), our results indicate a basic disturbance in reward differentiation caused by an emotional dysregulation in BPD patients.

An additional mechanism may have contributed to our findings: The basically disturbed sense of self in BPD patients.

Reduced deactivation in emotional states observed in subcortical–cortical midline structures like, e.g., the PACC or the VS indicates an altered neural activity in BDP patients. Psychologically, the subcortical-cortical midline structures have been associated with self-relatedness, i.e., the attribution of the personal relevance to external stimuli (Northoff and Bermpohl 2004; Northoff et al. 2006; Northoff and Panksepp 2008; Enzi et al. 2010). Based on our findings, one would thus assume alterations in self-relatedness which is indeed well in accordance with clinical observations of an unstable and incoherent self in borderline patients (Doering et al. 2010; Hörz et al. 2010).

It should be noted, that patients suffering from major depressive disorder showed a similar disturbed neuronal response during emotional stimulation in the pregenual anterior cingulate cortex (Grimm et al. 2009), probably due to co-occurrence between borderline personality disorder and major depressive disorder (Grant et al. 2008).

There are three noteworthy limitations of our study. (1) We did not control for emotional perception independent of reward as we did for reward independent of emotions. Hence, our paradigm cannot be considered a full-fledged interaction design which would be necessary to make the assumption of a specific alteration in reward × emotion interaction as distinguished from deficits in emotion or reward themselves. (2) We focused on reward and its interaction with emotion while we neglected punishment or aversion. This is in part due to the fact that the punishment condition in the MID must rather be considered as "mild reward", i.e. subjects succeed in 2/3 in avoiding punishment, than true punishment or aversion. Hence, future studies may be necessary to investigate the interaction between punishment/aversion and emotion in BDP (Völlm et al. 2007). (3) The BPD patients were not free of medication. We tried to rule out a medication effect by comparing medicated with non-medicated BPD patients, which revealed almost no significant group differences. (4) Another inherent problem of all sudies caried out in patients suffering from borderline pesonality disorder is psychiatric comorbidity, like, e.g., major depressive disorder (Donegan et al. 2003; Grant et al. 2008).

In conclusion, we here demonstrate for the first time the impact of emotion processing on neuronal activity in the reward system in borderline personality disorder. This indicates that the emotional disturbances in BPD have wide ranging impact beyond the emotional domain which converges with clinical symptoms of altered reward behavior in these patients (Dougherty et al. 1999) and probably even the interpersonal attachment problems of BPD patients (Fonagy and Bateman 2006). Manualized psychological treatments of borderline patients like dialectic-behavior therapy (DBT; Linehan 1993) or transference-focused psychotherapy (TFP; Clarkin et al. 2006) focus on emotional dysregulation in interpersonal relationships. Our results confirm the clinically derived view that potentially rewarding interpersonal situations can result in an increased emotional reaction during the treatment of borderline patients.

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Statement of Interest

None to declare.

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Supplementary material available online

Comorbidity and psychotropic medication in the patient sample

Supplementary Table 1. Comorbidity among the borderline patients

Supplementary Table 2. Psychotropic medication in the borderline patients

Statistical details

Medication effect in borderline patients for all regions

Supplementary Table 3. MNI coordinates of activations: Positive Interaction [group × "ant rew >ant noc"] for negative emotions