



ORIGINAL INVESTIGATION

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

BJOERN ENZI^{1*}, STEPHAN DOERING^{2*}, CORNELIUS FABER⁴, JENS HINRICHS³, JUDITH BAHMER³ & GEORG NORTHOFF⁵

¹Department of Psychiatry & Psychotherapy, University of Bochum, Bochum, Germany, ²Department of Psychoanalysis & Psychotherapy, Medical University Vienna, Vienna, Austria, ³Department of Psychosomatics & Psychotherapy, University of Muenster, Muenster, Germany, ⁴Department of Clinical Radiology, University of Muenster, Muenster, Germany, and ⁵Mind, Brain Imaging and Neuroethics, University of Ottawa Institute of Mental Health Research, Ottawa, Canada

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

*These authors contributed equally to this work.

Correspondence: Georg Northoff, MD, PhD, Research Unit Director, Mind, Brain Imaging and Neuroethics, Royal Ottawa Healthcare Group, University of Ottawa Institute of Mental Health Research, 1145 Carling Avenue, Room 6959, Ottawa, ON, Canada K1Z 7K4. Tel: +1 613 7226521, ext. 6801. E-mail: georg.northoff@rohcg.on.ca

(Received 11 August 2010; accepted 5 April 2011)

ISSN 1562-2975 print/ISSN 1814-1412 online © 2011 Informa Healthcare
DOI: 10.3109/15622975.2011.579162

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 colleagues (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)

1 (for details see Supplementary material available
2 online).

3 All subjects completed four well-established neu-
4ropsychological tests: the LPS-3 (German: Leistung-
5sprüfsystem-3; Horn, 1983) and MWT-A (German:
6Mehrfachwortschatzintelligenztest A; Lehl et al.
71991) as measurements of general intelligence, Beck
8Depression Inventory (BDI; Hautzinger et al. 1994),
9and the Toronto Alexythymia Scale (TAS; Bach
10et al. 1996).

11
12 *Experimental paradigm*
13

14 Before scanning, all subjects completed a short prac-
15tice version of the task to familiarise with the exper-
16iment. We used the behavioural data, i.e. the reaction
17times, obtained in this practice session, as an
18estimate of each individual’s reaction time.

19 The fMRI scanning session was divided into three
20scanning runs. In the first scanning run, subjects had
21to perform a modified version of the well-established
22monetary incentive delay task (Knutson et al. 2001),
23requiring that the subject press a button with the
24index finger of their right hand within a certain time
25of a target image (a black square in the centre of the
26screen; see Supplementary Figure 1) being displayed.
27The length of this time period was determined in
28accordance with the average reaction time obtained
29in the pre-scan trial run, allowing the difficulty of the
30task to be modulated according to the individual’s
31ability, and varied between 0.2 and 0.35 s. Further-
32more, we wanted to ensure that in approximately
3360% of all trials the required response was successful.
34Prior to this target image being displayed, a symbol
35indicating what the possible outcomes of the task
36would be – either reward, punishment, or no-outcome
37– was shown for 2 s, followed by a 2.25–2.75-s antic-
38ipation period. The trial type indicator took the form
39of a black circle with a small white circle within it at
40one of the cardinal points. Each position represented
41a different trial type (e.g., a circle in the “North”
42position would represent a reward trial). During the
43anticipation period a light-coloured cross was
44displayed in the centre of the screen.

45 In reward trials, completing the task successfully
46resulted in the subject winning €1, whilst failure
47meant that they would neither win nor lose anything.
48During punishment trials, a response within the
49required time period resulted in the subject neither
50winning nor losing money, whilst an unsuccessful
51response resulted in €1 being deducted from their
52total. Finally, in no-outcome trials no money was
53either won or lost, regardless of whether the subject
54responded within the required time period or not.
55Subjects were, however, instructed to still respond to
56the cue as quickly as possible. In total, 40 reward

and punishment trials and 30 no outcome trials were
57displayed in a pseudo-random order. Each trial was
58followed by a feedback stage during which the sub-
59ject was informed of the outcome. The amount of
60money won or lost in the preceding trial was dis-
61played, along with the running total for their win-
62nings, for a period of 1.65 s. Trials were separated
63by a 2.5–3.5-s inter-trial interval, during which the
64same light-coloured cross as that shown during the
65anticipation period was displayed. The anticipatory
66period for reward (ant rew), punishment (ant pun)
67and no-outcome (ant noc) trials were included in our
68design matrix along with their respective feedback
69periods.
70

71 In the second and third run a modified version of
72the above described monetary incentive delay task
73was presented (Figure 1). Simultaneously with the
74presentation of the outcome indicating symbol, i.e.
75reward, punishment or no outcome, an emotional
76picture was presented, resulting in a 3 × 3 factorial
77design. The pictures were taken from the Interna-
78tional Affective Picture System (Lang et al. 1999)
79and were categorized according to their affective
80norms (positive, negative or neutral emotion). The
81total number of conditions was balanced to ensure
82the calculation of valid contrasts in SPM5 (e.g.,
8330 reward trials with positive emotion, 30 reward
84trials with negative emotion and 20 reward trials
85with neutral emotion). All different time periods
86(cue, anticipation, target, feedback and ITI) were
87

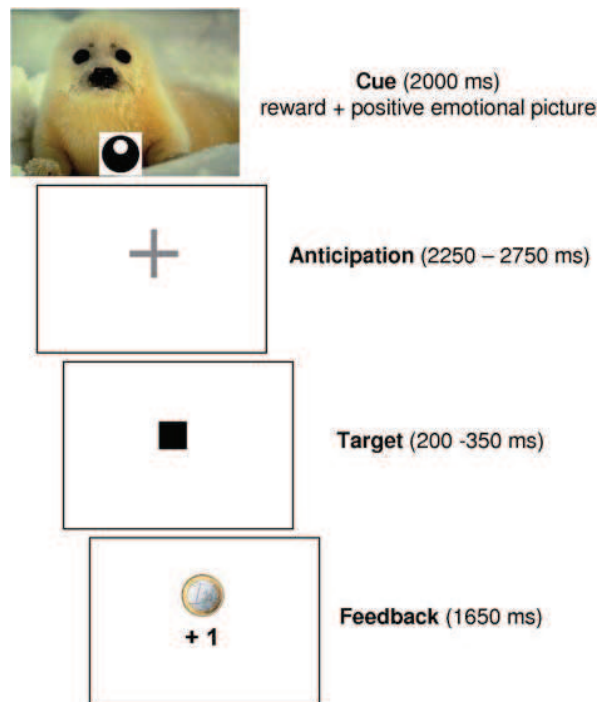


Figure 1. Structure of a single trial, representing the interaction between reward and a positive emotional picture.

mono for print colour online

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 $3 \times 3 \times 3$ mm³ 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 128 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. 1995, 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” \times “task”], collapsed over all emotions. Furthermore, we calculated the *t*-contrast [positive interaction “group” \times “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 \times 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 \times 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 \times 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).

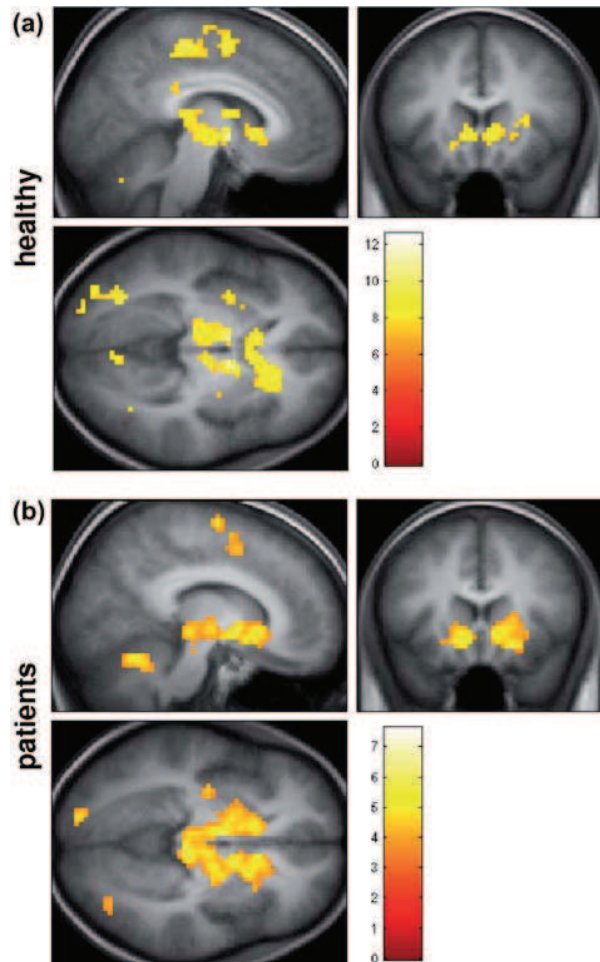


Figure 2. Contrast [anticipation of reward] > [anticipation of no outcome] in healthy controls and patients suffering from borderline personality disorder. Statistical parametric maps were thresholded at $P[FWE] < 0.05$, $k > 10$ for healthy subjects ($n = 17$), and $P[FDR] < 0.02$, $k > 10$ for borderline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

mono for print colour online

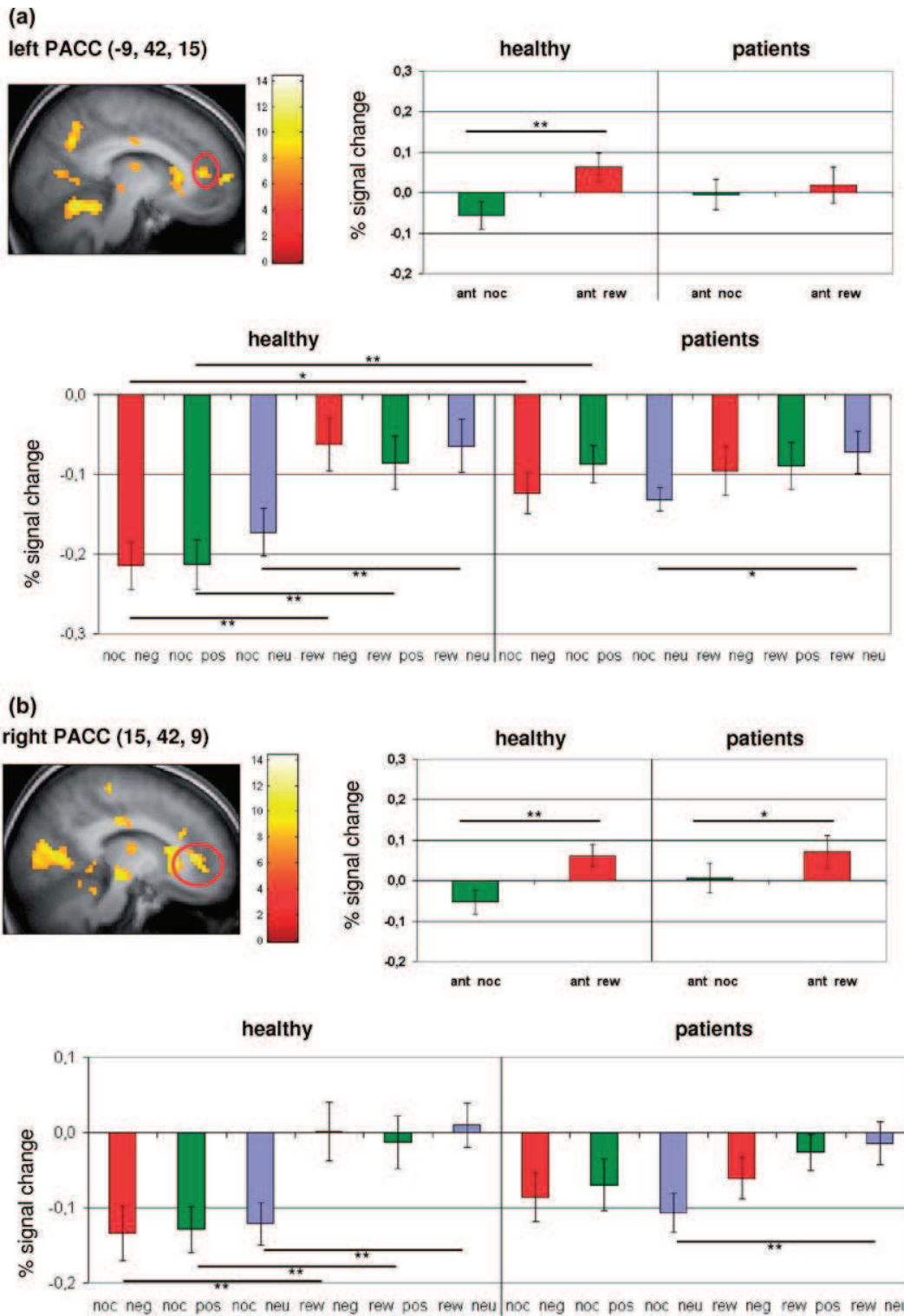


Figure 3. *F*-contrast “interaction [group × task]” collapsed over all emotions thresholded at P [FDR] < 0.03, $k > 10$ voxel, showing the neuronal response and the percent signal change in the left PACC (a), the right PACC (b) and the left putamen/Vs (c).

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

57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112

mono for print colour online

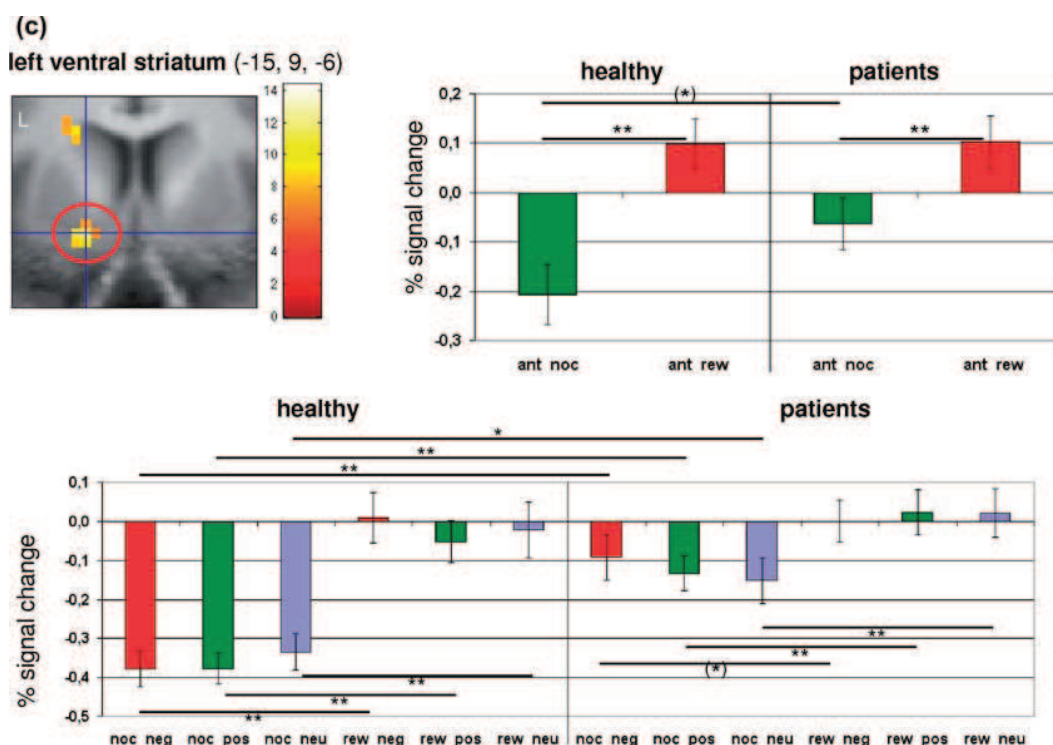


Figure 3. (Continued).

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 \times 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 \times 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.

57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112

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 ($t(32) = -1.792, P = 0.83$). 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 examining the impact of negative emotion processing on amygdala activity in borderline personality disorder, we calculated the t -contrast “positive interaction [group] \times [task]” only for negative emotions, $P[\text{FDR}] < 0.03, k > 10$

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 \times task \times emotion and medication \times emotion in all of the above-mentioned regions (only the interaction medication \times 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

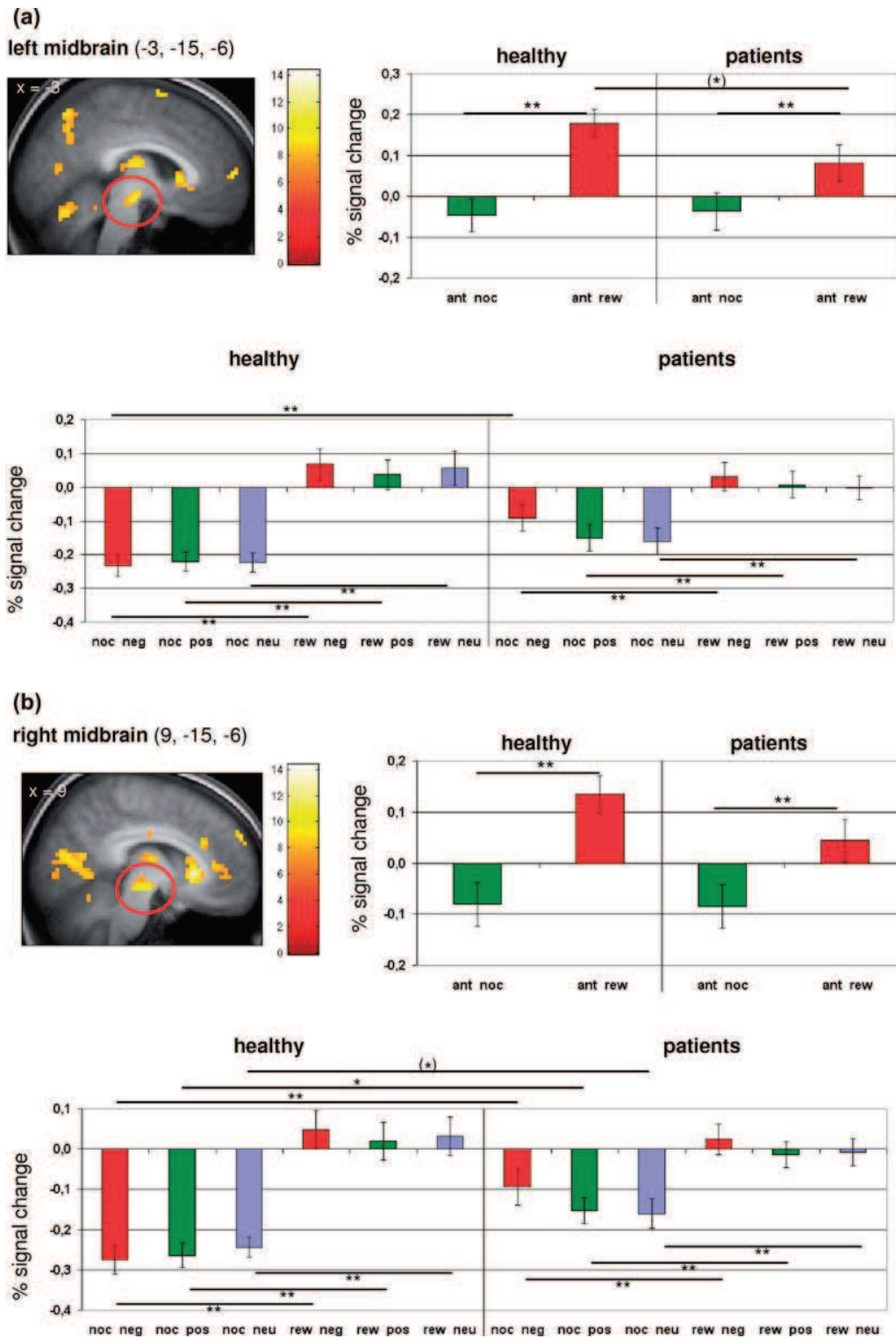


Figure 4. *F*-contrast “interaction [group × task]” collapsed over all emotions thresholded at P [FDR] < 0.03, $k > 10$ voxel, showing the neuronal response and the percent signal change in the left (a) and right midbrain (b).

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,

mono for print colour online

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

3 Our results shed new light on the interaction of
4 the partly overlapping brain areas of the reward sys-
5 tem and those active during emotion processing. In
6 borderline patients the reward system is altered dur-
7 ing (negative or positive) emotional states. More pre-
8 cisely, brain regions typically involved in reward
9 processing, like, e.g., VTA, AS, and PACC, show dis-
10 turbed differentiation between reward and no out-
11 come after an emotional stimulus. A crucial role in
12 this mutual interaction might play the amygdala,
13 which is known to moderate the reward system (Haber
14 and Knutson 2010). It can be hypothesized that the
15 hyperactivity of the amygdala elicited by, e.g., a neg-
16 ative emotional stimulus triggers the ongoing activity
17 in the reward system. As a consequence, it can be
18 assumed that the reward system in BPD patients is
19 not impaired per se, but is disturbed by altered
20 processing of affective states.

21 One main finding of the present study consists of
22 the abnormal differentiation between reward and no
23 outcome in BPD patients in the left and right PACC.
24 In this brain region, borderline patients are only able
25 to differentiate neuronally between reward and non-
26 reward if a neutral or no emotional stimulation
27 occurs. This so-called “affective subdivision of the
28 ACC” (Bush et al. 2000) is closely connected to the
29 amygdala and the ventral striatum and functionally
30 involved in “assessing the salience of emotional and
31 motivational information and the regulation of emo-
32 tional responses” (Bush et al. 2000). In subcortical
33 regions like the ventral striatum and the ventral teg-
34 mental area, borderline patients are able to differen-
35 tiate significantly between reward and no outcome
36 regardless of the emotion presented simultaneously.
37 But compared to healthy controls, BPD patients
38 show a significantly reduced deactivation in the above
39 mentioned regions concerning the condition “no out-
40 come” with negative, positive, and neutral emotional
41 stimulation. Because of the close anatomical connec-
42 tions between these regions and the amygdala (Pos-
43 tuma and Dagher 2006), our results indicate a basic
44 disturbance in reward differentiation caused by an
45 emotional dysregulation in BPD patients.

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

49 Reduced deactivation in emotional states observed
50 in subcortical–cortical midline structures like, e.g., the
51 PACC or the VS indicates an altered neural activity
52 in BPD patients. Psychologically, the subcortical-
53 cortical midline structures have been associated with
54 self-relatedness, i.e., the attribution of the personal
55 relevance to external stimuli (Northoff and Bermpohl
56 2004; Northoff et al. 2006; Northoff and Panksepp

2008; Enzi et al. 2010). Based on our findings, one
57 would thus assume alterations in self-relatedness
58 which is indeed well in accordance with clinical obser-
59 vations of an unstable and incoherent self in border-
60 line patients (Doering et al. 2010; Hörz et al. 2010).
61

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

69 There are three noteworthy limitations of our
70 study. (1) We did not control for emotional percep-
71 tion independent of reward as we did for reward
72 independent of emotions. Hence, our paradigm can-
73 not be considered a full-fledged interaction design
74 which would be necessary to make the assumption
75 of a specific alteration in reward \times emotion interac-
76 tion as distinguished from deficits in emotion or
77 reward themselves. (2) We focused on reward and its
78 interaction with emotion while we neglected punish-
79 ment or aversion. This is in part due to the fact that
80 the punishment condition in the MID must rather
81 be considered as “mild reward”, i.e. subjects succeed
82 in 2/3 in avoiding punishment, than true punishment
83 or aversion. Hence, future studies may be necessary
84 to investigate the interaction between punishment/
85 aversion and emotion in BPD (Völlm et al. 2007).
86 (3) The BPD patients were not free of medication.
87 We tried to rule out a medication effect by comparing
88 medicated with non-medicated BPD patients, which
89 revealed almost no significant group differences. (4)
90 Another inherent problem of all studies carried out in
91 patients suffering from borderline personality disorder
92 is psychiatric comorbidity, like, e.g., major depressive
93 disorder (Donegan et al. 2003; Grant et al. 2008).

94 In conclusion, we here demonstrate for the first
95 time the impact of emotion processing on neuronal
96 activity in the reward system in borderline personal-
97 ity disorder. This indicates that the emotional distur-
98 bances in BPD have wide ranging impact beyond the
99 emotional domain which converges with clinical
100 symptoms of altered reward behavior in these patients
101 (Dougherty et al. 1999) and probably even the inter-
102 personal attachment problems of BPD patients
103 (Fonagy and Bateman 2006). Manualized psycho-
104 logical treatments of borderline patients like dialectic-
105 behavior therapy (DBT; Linehan 1993) or
106 transference-focused psychotherapy (TFP; Clarkin
107 et al. 2006) focus on emotional dysregulation in
108 interpersonal relationships. Our results confirm the
109 clinically derived view that potentially rewarding
110 interpersonal situations can result in an increased
111 emotional reaction during the treatment of borderline
112 patients.

Acknowledgments

We are grateful for the excellent technical and clinical support from the Institute of Clinical Radiology, University of Muenster, Germany (Nina Nagelmann), the Alexianer Hospital Muenster, Germany (Dr Klaus Telger, Dr Michael Platte), and the LWL-Hospital Lengerich (Dr Elisabeth Ehmann-Hänsch, Dr Christoph Theiling), Germany. We are indebted to the German Research Foundation (SFB 779/A6), the Canada Research Chair Program, the CIHR, the Hope of Depression Research Foundation (HDRF), and the EJLB-Michael Smith Foundation for financial support to GN.

Statement of Interest

None to declare.

References

- Bach M, Bach D, deZwaan M, Serim M, Böhmer F. 1996. Validation of the German version of the 20-item Toronto Alexithymia Scale in normal persons and psychiatric patients. *Psychother Psychosom Med Psychol* 46:23–28.
- Beck A, Schlagenhauf F, Wüstenberg T, Hein J, Kienast T, Kahnt T, et al. 2009. Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry* 66:734–742.
- Brett M, Anton J, Valabrgue R, Poline J. 2002. Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. *Neuroimage* 13:210–217.
- Bush G, Luu P, Posner MI. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.
- Clarkin JF, Yeomans FE, Kernberg OF. 2006. *Psychotherapy for borderline personality. Focusing on object relations*. Washington, DC: American Psychiatric Publishing.
- De Greck M, Rotte M, Paus R, Moritz D, Thiemann R, Proesch U, et al. 2008. Is our self based on reward? Self-relatedness recruits neural activity in the reward system. *Neuroimage* 39:2066–2075.
- Doering S, Hörz S, Rentrop M, Fischer-Kern M, Schuster P, Benecke C, et al. 2010. Transference-focused psychotherapy v. treatment by community psychotherapists for borderline personality disorder: randomised controlled trial. *Br J Psychiatry* 196:389–395.
- Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. 2003. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry* 54:1284–1293.
- Dougherty DM, Bjork JM, Huckabee HCG, Moeller FG, Swann AC. 1999. Laboratory measures of aggression and impulsivity in woman with borderline personality disorder. *Psychiatry Res* 85:315–326.
- Enzi B, de Greck M, Prösch U, Tempelmann C, Northoff G. 2009. Is our self nothing but reward? Neuronal overlap and distinction between reward and personal relevance and its relation to human personality. *PlosOne* 4:e8429.
- Fonagy P, Bateman AW. 2006. Mechanisms of change in mentalization-based treatment of BPD. *J Clin Psychol* 62:411–430.
- Friston KJ, Holmes A, Worsley K, Poline JB, Frith C, Frackowiak RSJ. 1995. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Map* 2:189–210.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. 1998. Event-related fMRI: characterizing differential responses. *Neuroimage* 7:30–40.
- Fydrich T, Renneberg B, Schmitz B, Wittchen HU. 1997. *Strukturiertes Klinisches Interview für DSM-IV, Achse II: Persönlichkeitsstörungen*. Göttingen: Hogrefe.
- Genovese C, Lazar N, Nichols T. 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15:870–878.
- Grant BF, Chou P, Goldstein RB, Huang B, Stinson FS, Saha TD, et al. 2008. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry* 69:533–545.
- Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, et al. 2009. Altered negative BOLD response in the default mode network during emotion processing in depressed subjects. *Neuropsychopharmacology* 34:932–943.
- Haber SN, Knutson B. 2010. The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26.
- Hautzinger M, Bailer M, Worall H, Keller F. 1994. *Beck-Depressions-Inventar (BDI)*. Bern: Huber.
- Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, et al. 2001. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry* 50:292–298.
- Horn W. 1983. *L-P-S Leistungsprüfsystem*. Göttingen: Hogrefe.
- Hörz S, Rentrop M, Fischer-Kern M, Schuster P, Kapusta N, Buchheim P, et al. 2010. Strukturniveau und klinischer Schweregrad der Borderline-Persönlichkeitsstörung. *Z Psychosom Med Psychother* 56:136–149.
- Juckel G, Schlagenhauf F, Koslowski M, Wüstenberg T, Villringer A, Knutson B, et al. 2005. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 29:409–416.
- Knutson B, Westdorp A, Kaiser E, Hommer D. 2000. Fmri visualization of brain activity during a monetary incentive delay task. *Neuroimage* 12:20–27.
- Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. 2001. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12:3683–3687.
- Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. 2003. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *Neuroimage* 18:263–272.
- Koenigsberg HW, Fan J, Ochsner KN, Liu X, Guise KG, Pizzarello S, et al. 2009. Neural correlates of the use of psychological distancing to regulate responses to negative social cues: a study of patients with borderline personality disorder. *Biol Psychiatry* 66:854–863.
- Lang PJ, Bradley MM, Cuthbert BN. 1999. *International affective picture system (IAPS)*. University of Florida: The Center for Research in Psychophysiology.
- Lehrl S, Merz J, Burkhard G, Fischer B. 1991. *Mehrfachwortschatz-Intelligenztest (MWT)*. Erlangen: Perimed.
- Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. 2004. Borderline personality disorder. *Lancet* 364:453–461.
- Linehan MM. 1993. *Cognitive-behavioral treatment of borderline personality disorder*. New York: The Guilford Press.
- Mauchnik J, Schmahl C. 2010. The latest neuroimaging findings in borderline personality disorder. *Curr Psychiatry Rep* 12:46–55.
- Minzenberg MJ, Han J, New AS, Tang CY, Siever LJ. 2007. Fronto-limbic dysfunction in response to facial emotion

1	in borderline personality disorder: An event-related fMRI study. <i>Psychiatry Res</i> 155:231–243.	57
2		58
3	Northoff G, Bermpohl F. 2004. Cortical midline structures and the self. <i>Trends Cogn Sci</i> 8:102–107.	59
4		60
5	Northoff G, Panksepp J. 2008. The trans-species concept of self and the subcortical-cortical midline system. <i>Trends Cogn Sci</i> 12:259–264.	61
6		62
7	Northoff G, Heinzel A, deGreck M, Bermpohl F, Dobrowolny H, Panksepp J. 2006. Self-referential processing in our brain – a meta-analysis of imaging studies on the self. <i>Neuroimage</i> 31:440–457.	63
8		64
9	Postuma RB, Dagher A. 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. <i>Cereb Cortex</i> 16:1508–1521.	65
10		66
11	Silbersweig D, Clarkin JF, Goldstein M, Kernberg O, Tuescher O, Levy K, et al. 2007. Failure of frontolimbic inhibitory function in the context of negative emotion in borderline personality disorder. <i>Am J Psychiatry</i> 164:1832–1841.	67
12		68
13		69
14		70
15		71
16	Supplementary material available online	72
17	Comorbidity and psychotropic medication in the patient sample	73
18		74
19	Supplementary Table 1. Comorbidity among the borderline patients	75
20		76
21	Supplementary Table 2. Psychotropic medication in the borderline patients	77
22		78
23	Statistical details	79
24	Medication effect in borderline patients for all regions	80
25		81
26	Supplementary Table 3. MNI coordinates of activations: Positive Interaction [group × “ant rew >ant noc”] for negative emotions	82
27		83
28		84
29		85
30		86
31		87
32		88
33		89
34		90
35		91
36		92
37		93
38		94
39		95
40		96
41		97
42		98
43		99
44		100
45		101
46		102
47		103
48		104
49		105
50		106
51		107
52		108
53		109
54		110
55		111
56		112

1 *Supplementary Material for Enzi B, Doering S, Faber C, Hinrichs J, Bahmer J & Northoff G. Reduced* 57
 2 *deactivation in reward circuitry and midline structures during emotion processing in borderline personality* 58
 3 *disorder. World J Biol Psychiatry, 2011, doi 10.3109/15622975.2011.579162* 59
 4 60

5 **Comorbidity and psychotropic medication in** 61 6 **the patient sample** 62

7 *Comorbidity in the patient sample* 63

8 One patient (5.9%) had one comorbid axis I diag- 64
 9 nosis, two (11.8%) had two, three (17.6%) had 65
 10 three, five (29.4%) had five, four (23.5%) had six, 66
 11 and two (11.8%) had seven axis I diagnoses. 67
 12 Including BPS, one patient (5.9%) had one axis II 68
 13 diagnosis, three (17.6%) had two, seven (41.2%) 69
 14 had three, two (11.8%) had four, one (5.9%) had 70
 15 five, and three (17.6%) had six axis II diagnoses. 71
 16 72
 17 73
 18 74

19 *Psychotropic medication* 75

20 Eleven (75.7%) out of 17 borderline patients received 76
 21 psychotropic medication. Supplementary Table 2 77
 22 gives detailed information on the medication of the 78
 23 eleven medicated patients. 79
 24 80
 25 81
 26 82
 27 83

28 **Statistical details** 84

29 *Left PACC* 85

30 In the left PACC (MNI co-ordinates at [-9, 42, 15]), 86
 31 healthy subjects are able to differentiate significantly 87
 32 between reward and no outcome ($t(16) = -5.516$, 88
 33 $p < 0.001$), whereas borderline patients show no sig- 89
 34 nificant differentiation between the above mentioned 90
 35 conditions ($t(16) = -0.872$, $p = 0.396$). In the very 91
 36 same region, healthy subjects are able to differentiate 92
 37 significantly between reward and no outcome, even if 93
 38 an emotional picture is presented (reward + negative 94
 39 emotion vs no outcome + negative emotion: $t(16)$ 95
 40 $= -4.217$, $p = 0.001$; reward + positive emotion vs no 96
 41 outcome + positive emotion: $t(16) = -5.263$, $p < 0.001$; 97
 42 reward + neutral emotion vs no outcome + neutral 98
 43 emotion: $t(16) = -6.203$, $p < 0.001$), whereas border- 99
 44 line patients are only able to differentiate between 100
 45 reward and no outcome if a neutral emotion is pre- 101
 46 sented ($t(16) = -2.3$, $p = 0.035$). Moreover, border- 102
 47 line patients show a significantly reduced deactivation 103
 48 in the left PACC compared to healthy subjects for the 104
 49 conditions 'no outcome + negative emotion' ($t(32)$ 105
 50 $= -2.294$, $p = 0.028$) and 'no outcome + positive 106
 51 emotion' ($t(32) = -3.215$, $p = 0.003$) (Figure 3a). 107
 52 108
 53 109
 54 110
 55 111
 56 112

53 *Right PACC* 113

55 In the right PACC (MNI: 15, 42, 9), both groups are 114
 56 able to differentiate between the conditions 'reward' 115

and 'no outcome' (healthy: $t(16) = -6.198$, 61
 $p < 0.001$; borderline patients: $t(16) = -2.6$, 62
 $p = 0.019$). Concerning the emotional modulation, 63
 healthy subjects are able to differentiate significantly 64
 between reward and no outcome, even if an emo- 65
 tional picture is presented (reward + negative emo- 66
 tion vs no outcome + negative emotion: 67
 $t(16) = -3.649$, $p = 0.002$; reward + positive emo- 68
 tion vs no outcome + positive emotion: $t(16) = -6.9$, 69
 $p < 0.001$; reward + neutral emotion vs no out- 70
 come + neutral emotion: $t(16) = -5.057$, $p < 0.001$), 71
 whereas borderline patients are only able to differen- 72
 tiate between reward and no outcome if an neutral 73
 emotion is presented ($t(16) = -4.706$, $p < 0.001$) 74
 (Figure 3b). 75
 76
 77
 78
 79
 80
 81
 82
 83
 84
 85
 86
 87
 88
 89
 90
 91
 92
 93
 94
 95
 96
 97
 98
 99
 100
 101
 102
 103
 104
 105
 106
 107
 108
 109
 110
 111
 112

84 *Left putamen/ left ventral striatum* 85

86 In the left VS, healthy subjects ($t(16) = -6.678$, 87
 88 $p < 0.001$) and borderline patients ($t(16) = -5.332$, 89
 90 $p < 0.001$) are both able to differentiate significantly 91
 92 between reward and no outcome. Although both 93
 94 95
 96
 97
 98
 99
 100
 101
 102
 103
 104
 105
 106
 107
 108
 109
 110
 111
 112

Supplementary Table 1. Comorbidity among the borderline 85
 patients. 86

DSM-IV diagnosis	n
axis I	
substance-related disorders (without current dependence or intoxication)	4
bipolar II disorder	2
major depressive disorder	12
agoraphobia	2
panic disorder without agoraphobia	1
panic disorder with agoraphobia	7
specific phobia	7
social phobia	11
generalized anxiety disorder	2
obsessive compulsive disorder	9
somatization disorder	1
posttraumatic stress disorder	5
anorexia nervosa	5
bulimia nervosa	5
eating disorder not otherwise specified	4
axis II	
paranoid personality disorder	8
schizoid personality disorder	1
antisocial personality disorder	3
borderline personality disorder	17
narcissistic personality disorder	2
avoidant personality disorder	9
dependent personality disorder	4
obsessive-compulsive personality disorder	7
depressive personality disorder	5
passive-aggressive personality disorder	3

Supplementary Table 2. Psychotropic medication in the borderline patients.

Patient code	antidepressant (mg per day)	neuroleptics (mg per day)	sedatives (mg per day)
P1	escitalopram (20), mirtazapin (30)	quetiapin (200)	
P2	escitalopram (15)	promethazin (50)	lorazepam (0,5), zolpidem (5)
P3	venlafaxin (225)		
P4	trimipramin (25), fluoxetine (20)		
P7	venlafaxin (225)	melperon (50)	
P8	venlafaxin (300)	amisulprid (100), promethazin (75)	
P9		pipamperon (40)	
P10	paroxetin (40)		
P11	duloxetine (30)	pipamperon (40)	
P12	venlafaxin (150)		
P14	venlafaxin (225)		

groups can differentiate between reward and no outcome, healthy subjects show an increased deactivation for the condition 'no outcome' compared to borderline patients ($t(32) = -1.792$, $p = 0.83$). Concerning the interaction task, healthy subjects (reward + negative emotion vs no outcome + negative emotion: $t(16) = -5.904$, $p < 0.001$; reward + positive emotion vs no outcome + positive emotion: $t(16) = -5.731$, $p < 0.001$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -6.556$, $p < 0.001$) as well as borderline patients (reward + negative emotion vs no outcome + negative emotion: $t(16) = -2.085$, $p = 0.053$; reward + positive emotion vs no outcome + positive emotion: $t(16) = -3.331$, $p = 0.004$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -4.822$, $p < 0.001$) 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).

Left ventral tegmental area

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 (reward + negative emotion vs no outcome + negative emotion: $t(16) = -7.236$, $p < 0.001$; reward + positive emotion vs no outcome + positive emotion:

$t(16) = -8.290$, $p < 0.001$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -8.367$, $p < 0.001$) as well as borderline patients (reward + negative emotion vs no outcome + negative emotion: $t(16) = -3.776$, $p = 0.002$; reward + positive emotion vs no outcome + positive emotion: $t(16) = -5.788$, $p < 0.001$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -6.207$, $p < 0.001$) 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' ($t(32) = -2.803$, $p = 0.009$).

Right ventral tegmental area

In the right VTA, we were able to detect a similar pattern for the modulation of reward processing by emotions (healthy: reward + negative emotion vs no outcome + negative emotion: $t(16) = -5.238$, $p < 0.001$; reward + positive emotion vs no outcome + positive emotion: $t(16) = -5.145$, $p < 0.001$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -6.317$, $p < 0.001$; borderline patients: reward + negative emotion vs no outcome + negative emotion: $t(16) = -3.822$, $p = 0.002$; reward + positive emotion vs no outcome + positive emotion: $t(16) = -5.475$, $p < 0.001$; reward + neutral emotion vs no outcome + neutral emotion: $t(16) = -6.906$, $p < 0.001$). 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': $t(32) = -1.924$, $p = 0.063$).

1 *Left extended amygdala*

2 Left (extended) amygdala (MNI co-ordinates at
3 [-24, -18, -3]) derived from the SPM contrast
4 'Interaction [group] × [task]' only for negative emo-
5 tions, $p[\text{FDR}] < 0.03$, $k > 10$ voxel.

6 In the left amygdala, healthy subjects are able to dif-
7 ferentiate significantly between reward and no out-
8 come, even if an emotional picture is presented
9 (reward + negative emotion vs no outcome + negative
10 emotions: $t(16) = -3.664$, $p = 0.002$; reward + posi-
11 tive emotion vs no outcome + positive emotions:
12 $t(16) = -5.587$, $p < 0.001$; reward + neutral emotion
13 vs no outcome + neutral emotions: $t(16) = -3.702$,
14 $p = 0.002$), whereas borderline patients are only able
15 to differentiate between reward and no outcome if
16 positive and neutral emotions are presented
17 (reward + positive emotion vs no outcome + positive
18 emotions: $t(16) = -2.844$, $p = 0.012$; reward + neu-
19 tral emotion vs no outcome + neutral emotions:
20 $t(16) = -2.841$, $p = 0.012$) and not if a negative emo-
21 tional stimuli is displayed (reward + negative emotion
22 vs no outcome + negative emotions: $t(16) = -0.086$,
23 $p = 0.933$). Moreover, borderline patients show an
24 increased response for the condition 'no outcome + neg-
25 ative emotion' compared to 'no outcome + neutral
26 emotion' ($t(16) = 3.542$, $p = 0.016$).

27 In the left amygdala, healthy subjects
28 ($t(16) = -4.964$, $p < 0.001$) and borderline patients
29 ($t(16) = -3.291$, $p = 0.005$) are both able to differen-
30 tiate significantly between reward and no outcome.

31 Moreover, the emotional modulation of the condi-
32 tion 'no outcome' by negative emotions showed a
33 significant group difference between healthy subjects
34 and borderline patients ('no outcome + negative
35 emotion': $t(32) = -2.110$, $p = 0.043$), i.e. border-
36 line patients show less deactivation in the left
37 extended amygdala.

38 *Right parahippocampal gyrus*

39 Right parahippocampal gyrus (MNI co-ordinates at
40 [39, -15, -18]) derived from the SPM contrast
41 'Interaction [group] × [task]' only for negative emo-
42 tions, $p[\text{FDR}] < 0.03$, $k > 10$ voxel.

43 Healthy subjects are able to differentiate signifi-
44 cantly between reward and no outcome, even if an
45 emotional picture is presented (reward + negative
46 emotion vs no outcome + negative emotions:
47 $t(16) = -5.899$, $p < 0.001$; reward + positive emo-
48 tion vs no outcome + positive emotions:
49 $t(16) = -2.359$, $p = 0.031$; reward + neutral emotion
50 vs no outcome + neutral emotions: $t(16) = -2.5$,
51 $p = 0.024$), whereas borderline patients are not able
52 to differentiate between reward and no outcome if
53 an emotional picture is presented simultaneously
54 with the reward indicating symbol. Borderline
55
56

57 patients show an increased response during presen- 57
58 tation of the condition 'no outcome + negative emo- 58
59 tion' compared to 'no outcome + neutral emotion' 59
60 ($t(16) = 2.762$, $p = 0.014$). 60

61 In the very same region, healthy subjects are able 61
62 to differentiate between reward and no outcome 62
63 ($t(16) = -5.476$, $p < 0.001$), whereas borderline 63
64 patients cannot differentiate between the above men- 64
65 tioned conditions ($t(16) = -1.639$, $p = 0.121$). 65

66 Furthermore, concerning the emotional modula- 66
67 tion of the condition 'no outcome' we were able to 67
68 detect significant group differences between healthy 68
69 subjects and borderline patients ('no outcome + 69
70 negative emotion': $t(32) = -3.911$, $p < 0.001$;
71 'no outcome + positive emotion': $t(32) = -2.517$,
72 $p = 0.017$; 'no outcome + neutral emotion':
73 $t(32) = -2.162$, $p = 0.038$) reflection an emotional
74 hyperreactivity of the right parahippocampal gyrus.
75

76 **Medication effect in borderline** 77 **patients for all regions**

78 *Left PACC*

79 (*MNI co-ordinates at [-9, 42, 15]*). For the borderline
80 patients, a repeated measurement ANOVA with the
81 factors 'task' (reward, punishment, no outcome) and
82 'emotion' (positive, negative, neutral) and the
83 between subject factor 'medication' was calculated
84 in SPSS to exclude possible medication effects. The
85 interaction ['task' × 'emotion' × 'medication'] failed
86 significance ($F(4,12) = 1.490$, $p = 0.266$), as well as
87 the interaction ['emotion' × 'medication'] ($F(2,$
88 $14) = 0.031$, $p = 0.970$). The interaction ['task'
89 × 'medication'] showed a significant result ($F(2,$
90 $14) = 5.521$, $p = 0.017$), so that we cannot com-
91 pletely exclude a medication effect for this region.
92
93

94 *Right PACC*

95 (*MNI co-ordinates at [15, 42, 9]*). For the borderline
96 patients, a repeated measurement ANOVA with the
97 factors 'task' (reward, punishment, no outcome) and
98 'emotion' (positive, negative, neutral) and the
99 between subject factor 'medication' was calculated
100 in SPSS to exclude possible medication effects. The
101 interaction ['task' × 'emotion' × 'medication'] failed
102 significance ($F(4,12) = 0.439$, $p = 0.778$), as well as
103 the interactions ['emotion' × 'medication'] ($F(2,$
104 $14) = 1.258$, $p = 0.314$) and ['task' × 'medication']
105 ($F(2, 14) = 2.029$, $p = 0.168$).
106
107

108 *Left putamen/VS*

109 (*MNI co-ordinates at [-15, 9, -6]*). For the borderline
110 patients, a repeated measurement ANOVA with the
111 factors 'task' (reward, punishment, no outcome) and
112

'emotion' (positive, negative, neutral) and the between subject factor 'medication' was calculated in SPSS to exclude possible medication effects. The interaction ['task' × 'emotion' × 'medication'] failed significance ($F(4,12) = 2.459, p = 0.102$), as well as the interactions ['emotion' × 'medication'] ($F(2, 14) = 0.283, p = 0.757$) and ['task' × 'medication'] ($F(2, 14) = 0.589, p = 0.570$).

Left midbrain/VTA

(MNI co-ordinates at [-3, -15, -6]). For the borderline patients, a repeated measurement ANOVA with the factors 'task' (reward, punishment, no outcome) and 'emotion' (positive, negative, neutral) and the between subject factor 'medication' was calculated in SPSS to exclude possible medication effects. The interaction ['task' × 'emotion' × 'medication'] failed significance ($F(4,12) = 0.934, p = 0.477$), as well as the interaction ['emotion' × 'medication'] ($F(2, 14) = 0.563, p = 0.582$). The interaction ['task' × 'medication'] showed a significant result ($F(2, 14) = 7.055, p = 0.008$), so that we cannot completely exclude a medication effect for this region.

Right midbrain/VTA

(MNI co-ordinates at [9, -15, -6]). For the borderline patients, a repeated measurement ANOVA with the factors 'task' (reward, punishment, no outcome) and 'emotion' (positive, negative, neutral) and the between subject factor 'medication' was calculated in SPSS to exclude possible medication effects. The

interaction ['task' × 'emotion' × 'medication'] failed significance ($F(4,12) = 2.102, p = 0.143$), as well as the interaction ['emotion' × 'medication'] ($F(2, 14) = 1.523, p = 0.252$). The interaction ['task' × 'medication'] showed a significant result ($F(2, 14) = 6.988, p = 0.008$), so that we cannot completely exclude a medication effect for this region.

Left extended amygdala

For the borderline patients, a repeated measurement ANOVA with the factors 'task' (reward, punishment, no outcome) and 'emotion' (positive, negative, neutral) and the between subject factor 'medication' was calculated in SPSS to exclude possible effects due to psychiatric medication. The interaction ['task' × 'emotion' × 'medication'] failed significance ($F(4,12) = 1.158, p = 0.377$), as well as the interactions ['emotion' × 'medication'] ($F(2, 14) = 2.131, p = 0.156$) and ['task' × 'medication'] ($F(2, 14) = 0.394, p = 0.681$).

Right parahippocampal gyrus

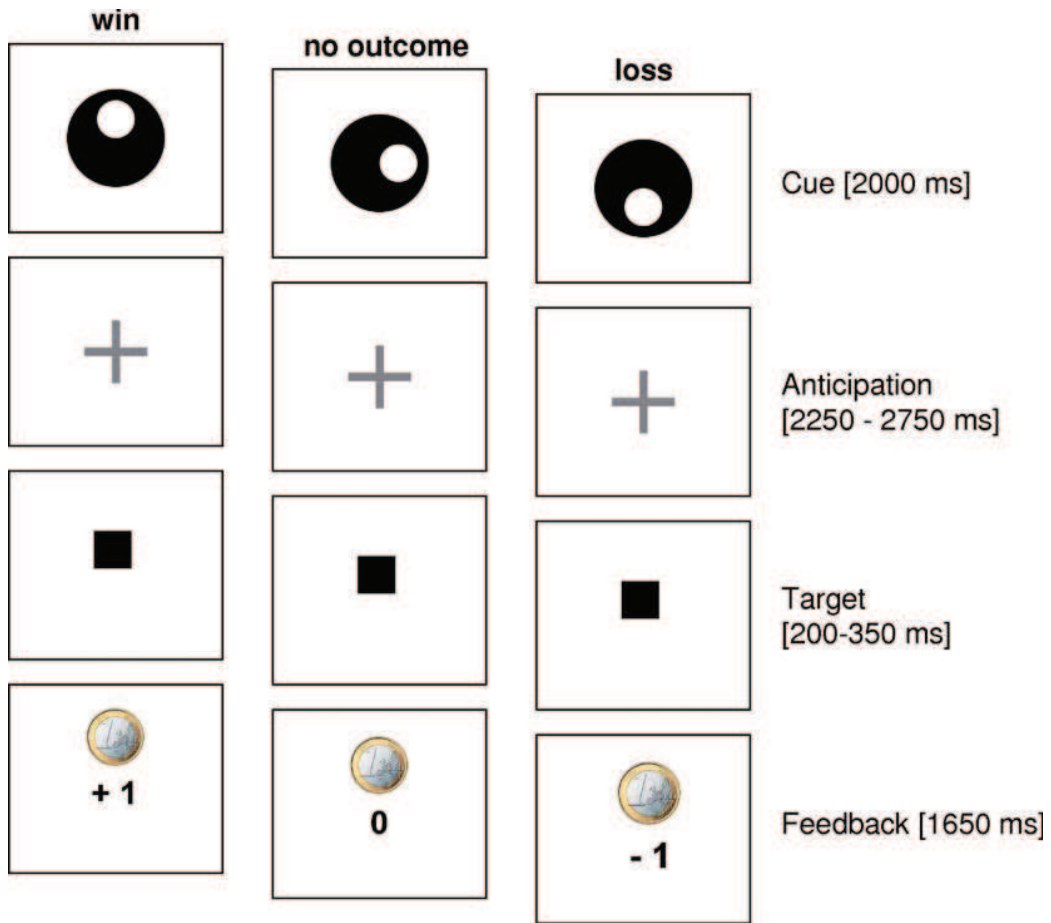
For the borderline patients, a repeated measurement ANOVA with the factors 'task' (reward, punishment, no outcome) and 'emotion' (positive, negative, neutral) and the between subject factor 'medication' was calculated in SPSS to exclude possible medication effects. The interaction ['task' × 'emotion' × 'medication'] failed significance ($F(4,12) = 0.570, p = 0.690$), as well as the interactions ['emotion' × 'medication'] ($F(2, 14) = 0.183, p = 0.834$) and ['task' × 'medication'] ($F(2, 14) = 0.037, p = 0.964$).

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

ROI name	coordinates [MNI]	p [FDR]	t-value	z-value
left PACC	-9, 42, 3	0.023	3.27	3.24
right PACC	9, 45, 3	0.025	3.17	3.14
left VLPFC	-33, 39, 3	0.023	3.28	3.25
right VLPFC	36, 42, 3	0.02	3.73	3.68
left gyrus temp. sup.	-51, 6, -15	0.023	3.31	3.27
left precuneus	-18, -63, 6	0.02	4.18	4.11
right precuneus	12, -60, 6	0.02	3.7	3.65
left putamen/ VS	-15, 9, -6	0.02	4.5	4.42
right putamen/ VS	21, 6, -6	0.024	3.24	3.2
right caudate	21, 24, 9	0.022	3.57	3.53
left amygdala	-24, -18, -3	0.02	3.73	3.68
right gyrus parahippocamp.	39, -15, -18	0.022	3.56	3.52
left dorsomed. thalamus	-3, -12, 21	0.02	4.12	4.06
right VTA/ midbrain	9, -15, -6	0.02	4.47	4.39

Positive Interaction [group × 'ant rew > ant noc'] for negative emotions, t test, $p[\text{FDR}] < 0.03, k > 10$.

PACC: pregenual anterior cingulate cortex, VLPFC: ventrolateral prefrontal cortex, VMPFC: ventromedial prefrontal cortex, VS: ventral striatum, VTA: ventral tegmental area.



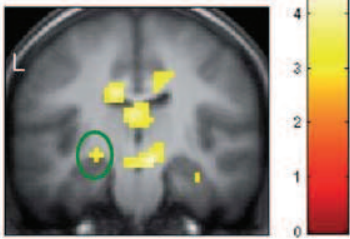
Supplementary Figure 1.

[AQ3]

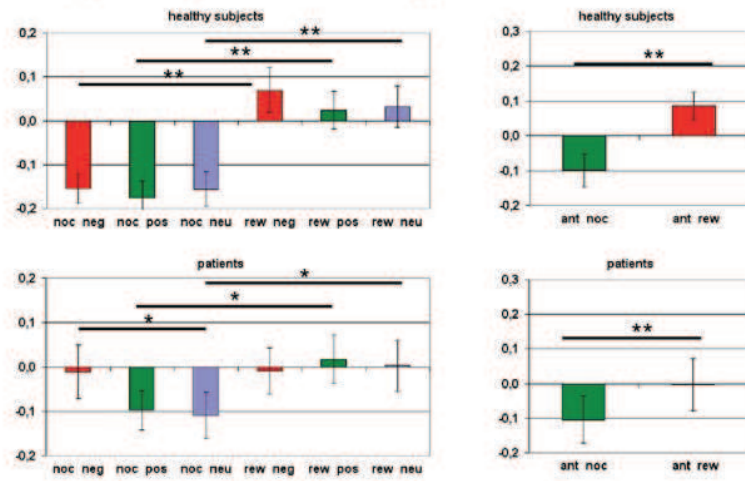
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112

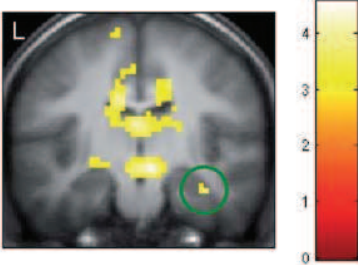
a. left extended amygdala (-24, -18, -3)



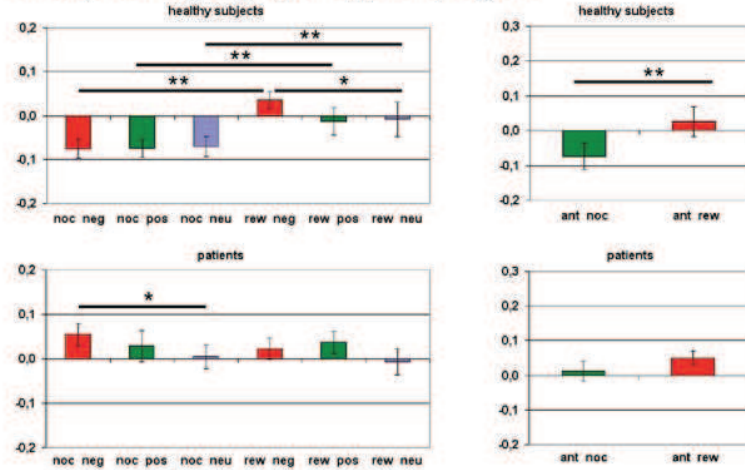
b. % signal change: left extended amygdala



c. right parahippocampal gyrus (39, -15, -18)



d. % signal change: right parahippocampal gyrus



Supplementary Figure 2.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56

57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112