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A negative relationship between ventral striatal loss anticipation response and impulsivity in borderline personality disorder

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ABSTRACT

Patients with borderline personality disorder (BPD) frequently exhibit impulsive behavior, and self-reported impulsivity is typically higher in BPD patients when compared to healthy controls. Previous functional neuroimaging studies have suggested a link between impulsivity, the ventral striatal response to reward anticipation, and prediction errors. Here we investigated the striatal neural response to monetary gain and loss anticipation and their relationship with impulsivity in 21 female BPD patients and 23 age-matched female healthy controls using functional magnetic resonance imaging (fMRI). Participants performed a delayed monetary incentive task in which three categories of objects predicted a potential gain, loss, or neutral outcome. Impulsivity was assessed using the Barratt Impulsiveness Scale (BIS-11). Compared to healthy controls, BPD patients exhibited significantly reduced fMRI responses of the ventral striatum/nucleus accumbens (VS/NAcc) to both reward-predicting and loss-predicting cues. BIS-11 scores showed a significant positive correlation with the VS/NAcc reward anticipation responses in healthy controls, and this correlation, while also nominally positive, failed to reach significance in BPD patients. BPD patients, on the other hand, exhibited a significantly negative correlation between ventral striatal loss anticipation responses and BIS-11 scores, whereas this correlation was significantly positive in healthy controls. Our results suggest that patients with BPD show attenuated anticipation responses in the VS/NAcc and, furthermore, that higher impulsivity in BPD patients might be related to impaired prediction of aversive outcomes.

1. Introduction

Borderline personality disorder (BPD) causes considerable and prolonged distress to the affected individuals and, at the same time, often poses a diagnostic and therapeutic challenge to clinicians (Jordanova and Rossin, 2010). One reason for the difficulties in diagnosing BPD is the clinical heterogeneity of the disorder. Both the International Classification of Diseases (ICD-10; World Health Organization, 1992) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000; see also DSM-5; American Psychiatric Association, 2013), require the fulfillment of five out of nine diagnostic criteria, resulting in –at least theoretically– 126 different combinations and clinical representations. According to both DSM-IV and ICD-10, BPD is characterized by behavioral impulsivity, instability in interpersonal relationships, chronic feeling of emptiness, and aggression, most notably autoaggressive behavior, including suicide attempts or gestures (Lieb et al., 2004; Mauchnik and Schmahl, 2010).

Impulsivity is considered a key symptom of BPD and has been implicated in neurobehavioral models of the disorder (Lieb et al., 2004). According to DSM-IV, impulsivity in at least two potentially self-damaging areas such as excessive spending, promiscuity, substance abuse, binge eating, reckless driving, or physically self-damaging acts is required to fulfill the diagnostic criteria for BPD. Impulsivity has been defined as a failure to resist an impulse, despite potentially

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harmful consequences to oneself or others (Chamberlain and Sahakian, 2007; Moeller et al., 2001). Furthermore, criteria suggested to define impulsivity include (i) deficient tolerance for delay of gratification and (ii) the inability to inhibit or delay voluntary behavior (Ho et al., 1998).

In clinical settings, the Barratt Impulsiveness Scale (BIS-11) (Barratt, 1993; Patton et al., 1995) is a commonly applied self-report tool to assess impulsivity-related cognitive and behavioral traits. Impulsivity as assessed with the BIS-11 can be further subdivided into attentional, motor, and non-planning impulsivity, but most clinical studies employ the sum score. Compatible with the clinical observation of frequent impulsive behavior in BPD, higher BIS-11 scores have frequently been observed in BPD patients compared to healthy controls (Henry et al., 2001; Berlin et al., 2005; McCloskey et al., 2009; Jacob et al., 2010; Lynam et al., 2011; Sebastian et al., 2013) and also to other patient groups like patients with bipolar II disorder (Henry et al., 2001; Wilson et al., 2007; Boen et al., 2015) or even patients with orbitofrontal cortex lesions (Berlin et al., 2005). Several studies of impulsivity in BPD using laboratory tasks have provided direct evidence for behavioral manifestations of impulsivity, such as impaired response inhibition (Leyton et al., 2001; Hochhausen et al., 2002; Rentrop et al., 2008), difficulties in feedback-guided decision making (Haaland and Landro, 2007; Maurex et al., 2009; Svaldi et al., 2012; Mak and Lam, 2013), and higher levels of impulsive aggression (Dougherty et al., 1999; New et al., 2009) in BPD patients compared to clinical and nonclinical controls. Most prominently, BPD patients are more likely to make disadvantageous, risky choices in gambling tasks (Legris et al., 2012; Haaland and Landro, 2007; Maurex et al., 2009; Schuermann et al., 2011), even in the presence of explicit rules and constantly provided feedback (Svaldi et al., 2012). Svaldi and colleagues linked their observations to the clinical phenomenon that BPD patients make risky or self-harming decisions despite explicitly knowing their adverse outcomes. On the other hand, in the absence of choice or risk-taking behavior there is considerably less evidence for heightened impulsivity in BPD patients compared to healthy controls (Hochhausen et al., 2002; Kunert et al., 2003; Volker et al., 2009; McCloskey et al., 2009; Jacob et al., 2010, 2013; Beblo et al., 2011; Legris et al., 2012). These discrepancies may be explained by comorbidities, particularly attention deficit hyperactivity disorder (ADHD), medication, but also by negative emotional states at the time of testing (Sebastian et al., 2013). Like patients with major depressive disorder (MDD), BPD patients typically exhibit severe negative affective states, but, compared to MDD, negative affect in BPD is often characterized by more pronounced feelings of anger, hostility, and self-devaluation, which may give rise to impulsive behavior (Bellodi et al., 1992; Sullivan et al., 1994).

Pathological manifestations of impulsivity-like phenotypes have been described not only in BPD, but in several psychiatric disorders, including alcohol dependence (Beck et al., 2009) and ADHD (Plichta and Scheres, 2014). Human neuroimaging studies in both healthy participants and psychiatric patient populations have provided a functional neuroanatomical link between impulsive phenotypes and the processing of appetitive and aversive stimuli in the mesolimbic reward system and its core structure, the ventral striatum/nucleus accumbens (VS/NAcc). Activations of the VS/NAcc have primarily been observed during dopamine-dependent rewarded tasks, with a dual role of the VS/NAcc in signaling both reward prediction and prediction errors (Knutson et al., 2001; Pessiglione et al., 2006; Schott et al., 2007, 2008). Importantly, converging evidence suggests that impulsivity modulates VS/NAcc reward responses differentially in healthy individuals as compared to psychiatric populations. In healthy individuals, most studies linking striatal reward processing to impulsivity suggest that VS response to reward shows a positive correlation with self-reported impulsivity (Abler et al., 2006; Hariri et al., 2006; Forbes et al., 2009; Plichta and Scheres, 2014). On the other hand, higher impulsivity in addiction (Beck et al., 2009) and ADHD (Plichta and Scheres, 2014) is apparently accompanied by reduced VS/NAcc activation during reward anticipation and feedback processing.

It must be kept in mind that, given the rather broad definition of the term *impulsivity* (Barratt, 1993), the clinical forms of impulsivity in BPD and the experimentally used definitions might reflect, at least partly, distinct (neuro)-psychological phenomena (Sebastian et al., 2013; Stahl et al., 2014). Nevertheless, the replicated observations linking pathological impulsivity to functional alterations in the mesolimbic reward system highlight the possibility that dysfunctional ventral striatal processing of gains and losses might contribute to the psychopathology of BPD. Thus far, only few studies have investigated the neural correlates of striatal reward processing in BPD patients. A study employing event-related potentials (ERPs) revealed that the propensity to perform risky decisions might result from dysfunctional processing of positive and negative feedback in BPD patients (Schuermann et al., 2011). Völlm and colleagues conducted a functional magnetic resonance imaging (fMRI) study on reward processing in male patients with a Cluster B personality disorder (Borderline and/or antisocial personality disorder). Group comparisons revealed hypoactivation of the striatum and midbrain in the patients during a rewarded compared to a control task. Patients additionally showed reduced activation of the left medial orbitofrontal cortex (OFC), the left dorsolateral prefrontal cortex (DLPFC), the right frontal pole, as well as the anterior cingulate cortex (ACC) (Völlm et al., 2007). While that study provided initial evidence for dysfunctional striatal reward processing in Cluster B personality disorders, several questions remain open. The relatively small study sample of eight male participants included not only patients with BPD, but also antisocial personality disorder, and the results may thus not be specific to BPD. Second, the study employed a blocked design and did therefore not allow the authors to separate effects of reward (or loss) anticipation from feedback effects. In the study by Völlm and colleagues, impulsivity was related to reduced prefrontal activation in the Cluster B patient group, but the authors provided no information regarding a potential relationship between impulsivity and gain or anticipation responses in the striatum. There is to date only one other study investigating striatal reward processing in BPD (Enzi et al., 2013). In that study, the sample was more homogenous and included 17 female BPD patients and age-matched healthy female controls. Compared to controls, patients exhibited a reduced differentiation between anticipated rewards versus neutral outcomes in the VS/NAcc and, when cues were presented together with emotional pictures, a blunted reward anticipation response in the rostral ACC.

Given the sensitivity of BPD patients to aversive events and their difficulties in regulating negative emotions (Schmahl et al., 2014), it seems to be of particular importance to investigate not only gain, but also loss anticipation in relation to a potential association with impulsivity. At this point little is known about a potential relationship between loss processing and impulsivity-related phenotypes in psychiatric populations. One study in individuals with pathological levels of psychopathy (assessed with the Psychopathy Check List – Revised, PCL-R; Hare, 2003) demonstrated differential relationship between individual psychopathy scores and ventral striatal responses to gains and losses, respectively (Pujara et al., 2014). The clinical construct of psychopathy as defined in the PCL-R shows considerable overlap with antisocial personality disorder, and consists of two factors (Factor 1: “fearless dominance”: blunted affect, stress immunity, narcissism; and Factor 2: impulsivity, boredom susceptibility, aggressiveness), with BPD patients typically scoring high on Factor 2 (Hunt et al., 2015; Harpur et al., 1989).

In the present study, we aimed to investigate the relationship between altered striatal anticipation of gains and losses in BPD and self-reported impulsivity. Based on previous research (Völlm et al., 2007; Enzi et al., 2013), we hypothesized that BPD patients would exhibit reduced reward anticipation responses in the VS/NAcc. At the psychometric level, we expected significantly higher levels of self-reported impulsivity in BPD patients compared to an age-matched group of healthy female control participants with comparable intelligence and educational background. Additionally, we hypothesized that ventral striatal reward or loss anticipation would correlate with self-reported

impulsivity in BPD patients, but, given the ambiguous results of previous studies investigating the relationship between impulsivity and mesolimbic reward system function in other psychiatric populations (Beck et al., 2009; Forbes et al., 2009; Pujara et al., 2014; Sebastian et al., 2014), we did not make a directional prediction with respect to such a correlation.

2. Methods

2.1. Participants

Because in clinical settings BPD is more common in women (Schmahl and Bremner, 2006; Skodol and Bender, 2003) and because the clinical presentation varies to some extent between sexes (Mancke et al., 2015), only female patients were included. The final study sample consisted of 21 female patients with BPD (age range 18 to 43 years) and 23 healthy controls (age range 20 to 46 years). Table 1 displays the demographic characteristics of both groups. BPD patients were recruited at the Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin or referred by privately practicing psychiatrists and psychotherapists. All patients met the DSM-IV criteria for BPD. Comorbid Axis I and Axis II diagnoses were assessed according to DSM-IV criteria. To assess Axis-I disorders, we employed the German version of the Mini International Neuropsychiatric Interview (MINI, Ackenheil et al., 1999) in the patients recruited from the inpatient ward of the Department of Psychiatry, Charité Campus Benjamin Franklin, and the Structural Clinical Interview for DSM-IV, Part I (SCID-I; First et al., 1997; German version Wittchen et al., 1997), in the patients referred from external practitioners. Axis-II comorbidities were assessed using SCID-II in all patients. BPD-related psychopathology was quantified by self-report questionnaires, specifically the Borderline Symptom List (BSL; Bohus et al., 2001), the Barratt Impulsiveness Scale (BIS-11, Patton et al., 1995), and the Beck Depression Inventory (BDI, Hautzinger et al., 1994). Diagnosis of BPD was confirmed by a consultant psychiatrist with extensive experience in the diagnosis and treatment of BPD. Co-morbid DSM-IV Axis I or Axis II disorders in the patients are shown in Table 2.

Exclusion criteria were history of major psychoses (schizophrenia, bipolar disorder, schizoaffective disorder), lifetime diagnosis of adult ADHD, illicit substance use disorder within six months prior to participation or alcohol abuse at the time of study. Criteria for adult ADHD was guided by the diagnostic indicators outlined in the adult ADHD criterion range, German Society for Psychiatry, Psychotherapy, and Neurology (Ebert et al., 2003). This process includes an adult ADHD-Checklist for DSM-IV (ADHD-CL; Hesslinger et al., 2002) and a semi-structured clinical interview based on DSM-IV-TR adult ADHD criteria (American Psychiatric Association, 2000). Patients further had to be free of psychotropic medication for at least two weeks before participation (six weeks in case of fluoxetine; six months in case of depot neuroleptics).

Exclusion criteria for control subjects were any current or past DSM-IV Axis I or Axis II psychiatric disorders (as screened with the SCID I and II; Wittchen et al., 1997), neurological disorders or medical conditions influencing cerebral metabolism (e.g., diabetes, systemic corticosteroid medication) and the diagnosis of borderline personality disorder in a first degree relative. MRI contraindications and pregnancy were exclusion criteria for both patients and controls.

Table 2
Comorbidities of the BPD-patients (N = 21).

	Diagnosis	N	%
AXIS I	Major depressive disorder (F32.x, F33.x)	12	57
	Eating disorder (F50.x)	9	43
	Alcohol abuse (F10.1)	4	19
	Drug abuse (F19.1)	4	19
	Posttraumatic stress disorder (F43.1)	2	10
	Social anxiety disorder (F40.1)	2	10
AXIS II	Avoidant personality disorder (F60.6)	1	5
	Histrionic personality disorder (F60.4)	1	5
Without comorbidities		4	19

Diagnosis based on DSM-IV-criteria; Axis I: substance-related disorders, affective disorders, eating disorders, schizophrenia, phobic disorders, posttraumatic stress disorder, eating disorders, attention deficit hyperactivity disorder; Axis II: personality disorders.

The BPD and control group were highly comparable with respect to age, crystalline intelligence (assessed with the Multiple-Choice Vocabulary Intelligence Test/"Mehrfachwahl-Wortschatz-Intelligenztest," MWT-B; Lehrl, 2005), and fluid intelligence (assessed with subtests 3 and 4 of the Performance Testing System/"Leistungsprüfsystem", L-P-S; Horn, 1983). Intelligence measures were considered to be a more appropriate measure than years of education, as patients often had disruptions of their educational and professional careers resulting from disorder-related periods of prolonged illness and/or hospitalization. There was a significant difference in smoking habits (see Table 1) that was taken into account in our data analyses (see below).

All subjects gave written informed consent prior to study participation. The study was carried out in accordance with the Declaration of Helsinki and approved by the ethics committee of the Charité - Universitätsmedizin Berlin.

2.2. Experimental paradigm

We used a categorical version of the monetary incentive delay (MID) task (Knutson et al., 2001; Wittmann et al., 2005) to invoke anticipation of reward (*gain* trials), of avoidable punishment (*loss* trials), or of a neutral outcome (*neutral* trials) in BPD patients and healthy controls. Stimulus presentation was carried out using the experimental control software Presentation (Neurobehavioral Systems Inc., Albany, CA).

Before entering the scanner, participants were informed that they could actually win or lose money and that their monetary outcome would depend on their performance in a simple reaction time task, with the condition (gain, loss, or neutral) being signaled by a picture of a simple object at the beginning of the task. Task details are given in Fig. 1. After entering the scanner, participants performed a short practice version of the MID task in order to reduce learning effects during the actual task and to estimate the start value of the automatically adapted

Table 1
Demographic and clinical characteristics.

	HC ($N = 23$)	BPD ($N = 21$)	Statistics
Age	25.78 (5.75)	25.67 (5.98)	$t_{42} = 0.07$, n. s.
Smoking	7 never	2 never	$\chi^2 = 9.23$, $p = 0.010$
	9 former or occasional	3 former or occasional	
	7 current	16 current	
LPS (PR subtest 3 + 4)	86.01 (13.59)	77.41 (20.02)	$t_{42} = 1.68$, n. s.
MWT-B (IQ)	108.83 (12.58)	101.95 (13.91)	$t_{42} = 1.72$, n. s.
BIS-11-sum	61.43 (8.55)	80.14 (12.72)	$t_{42} = -5.77$, $p < 0.001$
BDI-sum	3.52 (3.41)	30.38 (10.93)	$t_{23.54} = -10.79$ (unequal variance assumed), $p < 0.001$
BSL-sum	30.57 (16.07)	208.05 (75.91)	$T_{21.64} = -10.50$ (unequal variance assumed), $p < 0.001$

Mean scores of psychometric measures for the BPD and HC group. Standard deviations are given in parentheses. LPS: "Leistungsprüfsystem" (subtests 3 + 4: reasoning); MWT-B: "Mehrfachwahlwortschatztest" form B; BIS-11: Barratt Impulsiveness Scale-11; BDI: Beck Depression Inventory; BSL: Borderline Symptom List.

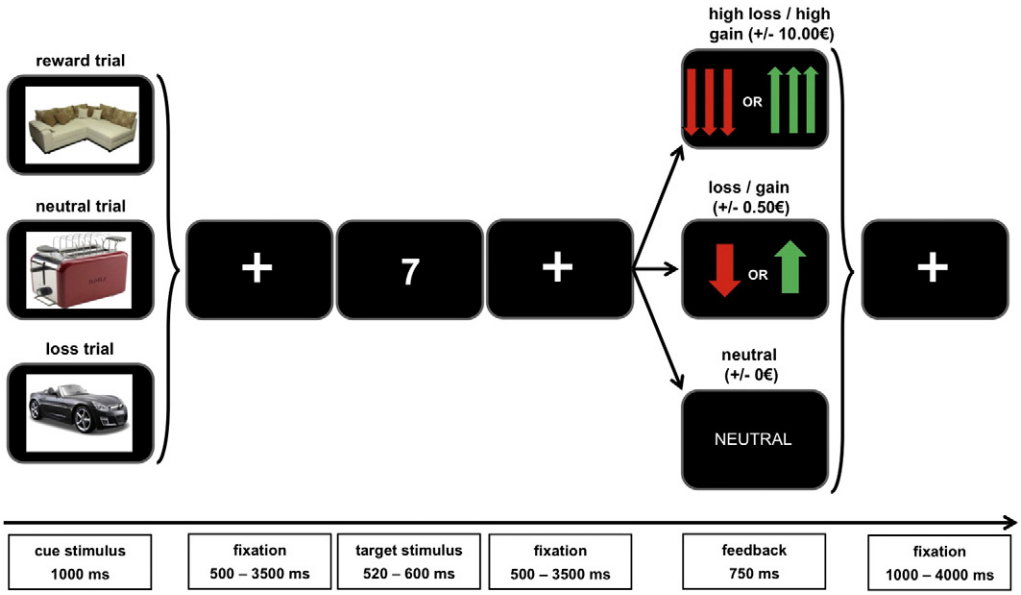

Fig. 1. Example study trial sequence. Each trial started with a cue picture (three categories, indicating gain, loss, or neutral outcome, respectively). After a variable delay, participants had to respond to a target number and indicate via button press whether the number was larger or smaller than 5. After a further variable delay, positive, negative, or neutral feedback was given, depending upon subjects' response accuracy and speed. In 10 reward and loss trials, respectively, a high gain or loss feedback was given.

reaction time (RT) threshold (see below). Once in the scanner, anatomical and functional scans were collected.

The actual MID task consisted of two runs comprising 102 trials each, yielding a total of 204 trials. Three out of six different picture categories (vehicles, kitchen devices, clothes, furniture, bags, or musical instruments; example pictures are displayed in Fig. 1) served as cues signaling (potential) reward, (avoidable) loss, and neutral outcome. The categories were chosen based on the availability of a large number of distinct images in each category. Each participant was assigned three categories randomly (counterbalanced across participants, to exclude category-specific brain responses as a confound), with one picture category indicating one condition, respectively. During each trial, participants first saw a picture from one of the three categories (cue; 1000 ms) showing that they could either win or avoid losing different amounts of money (gain condition with +0.50€: $n = 30$ per run; loss condition with −0.50€: n = 30 per run; high gain condition +10.00€: $n = 6$ per run; high loss condition −10.00€: n = 6 per run) or that they should respond despite no monetary outcome (±0.00€, irrespective of the response: n = 30 per run). After a variable fixation delay of 500–3500 ms, participants were prompted to perform a simple arithmetic task correctly and to respond within a time window of 2 s, answering if the presented one-digit number (1, 2, 3, 4, 6, 7, 8, 9) was larger or smaller than 5 via button press (target; 520–600 ms). Feedback followed after a further variable fixation delay of 500–3500 ms. Incorrect, too slow, or omitted responses all resulted in neutral feedback in the gain condition and in negative feedback in the loss condition. Exceptions were the rare high gain and high loss trials, in which feedback was given independently of subjects' responses. The next trial started after a delay of 1000–4000 ms.

In the rewarded trials, feedback consisted of either a green arrow pointing up indicating a gain or a grey double-arrow pointing sideways indicating no gain. In the loss trials, a grey double-arrow pointing sideways indicated successful avoidance of losing money, and a red arrow pointing down indicated a loss. In neutral conditions, feedback always consisted of the grey double-arrow pointing sideways. To obtain approximately equal winning rates across the cohort, task difficulty was adapted throughout the experiment. Initially, a response deadline was set based on the reaction times collected during the practice session prior to scanning, and this deadline was continuously and automatically adapted for each condition throughout the experiment, such that each participant would succeed on approximately 66% of their target responses.

High gain and high loss trials were introduced to investigate the potential presence of abnormal prediction errors to unexpected events in BPD as compared to healthy controls and were intermixed randomly. In these trials, either three green arrows pointing up (in gain trials) or three red arrows pointing down were presented in the feedback phase indicating a high gain or loss (±10.00€), independent of participants' actual performance. Participants were previously informed about the possibility of such feedback, but were unaware about the exact number of presentations and that it was unrelated to their performance. The inter-stimulus interval (ISI) was jittered using a near-exponential jitter (ISI range: 3950–12,950 ms), to improve estimation of the trial-specific blood oxygen level-dependent (BOLD) responses (Hinrichs et al., 2000).

2.3. fMRI data acquisition

MRI data were acquired on a 3 Tesla Siemens Tim Trio MR tomograph located at the Dahlem Institute for Neuroimaging of Emotion (D.I.N.E.; Research Center *Languages of Emotion*, Free University of Berlin) equipped with a 12-channel phased-array head coil with whole brain coverage. Functional MRI data were acquired using a gradient, T2*-weighted echo-planar imaging (EPI) sequence. Thirty-seven adjacent axial slices were acquired along the anterior commissure/posterior commissure (AC-PC) plane in ascending order, with a 64×64 matrix and 192 mm field of view (voxel size $3 \times 3 \times 3$ mm, TR = 2000, TE = 30, flip angle = 70). Prior to fMRI data collection, a 3D T1-weighted MPRAGE image (voxel size = $1 \times 1 \times 1$ mm; TR = 1900 ms; TE = 2.52 ms) and a co-planar proton density (PD)-weighted MR image (voxel size = $0.7 \times 0.7 \times 2$ mm; TR = 2740 ms; TE = 8.2 ms) were acquired. The MPRAGE image was used for orientation of the EPIs along the AC-PC line, and the PD-weighted image was employed to improve spatial normalization of subcortical structures (see below).

2.4. Data processing and analysis

2.4.1. Behavioral data analyses

Behavioral data were analyzed using SPSS (IBM, Armonk, NY, USA) and Matlab (Mathworks Inc., Natick, MA) and consisted of mean reaction times (mean value of all correct but not RT thresholded trials)

which were corrected for task difficulty as covariate (task difficulty = abs(digit-5)) and accuracy rates (proportion of correct responses over all trials per condition) for each subject.

2.4.2. fMRI data processing and analyses

Functional MRI data processing and analysis were performed using Matlab and the Matlab-based Statistical Parametric Mapping software package (SPM8, Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). EPIs were first corrected for acquisition delay (*slice timing*) and head motion (*realignment*) using the algorithms implemented in SPM. To optimize spatial normalization, the co-planar PD image was then co-registered to the mean EPI obtained from motion correction. We used PD images as they provide a good grey/white matter contrast in subcortical regions like the VS/NAcc (D'Ardenne et al., 2008; Schott et al., 2008). The PD image was then segmented into grey matter, white matter, and cerebrospinal fluid using the segmentation algorithm provided by SPM, and EPIs were warped into a standard stereotactic reference space (Montreal Neurological Institute, MNI) using the normalization parameters obtained from segmentation (final voxel size = 3 × 3 × 3 mm). Normalized EPIs were smoothed with a Gaussian kernel of 8 mm^3 FWHM. Finally, a 1/128 Hz temporal high-pass filter was applied to the data to remove low-frequency noise.

For statistical analysis a two-stage mixed effects model was applied. In the first stage, individual general linear models (GLMs) were set up for each subject. GLMs contained separate regressors for the conditions of interest [cues: *gain, (avoidable) loss, neutral;* feedback: *gain, loss, high gain, high loss, no gain, avoided loss, predicted neutral feedback; target numbers;* all convolved with the canonical hemodynamic response function implemented in SPM] and further covariates of no interest for the six rigid-body transformations obtained from motion correction, plus a single constant (the mean over scans).

After confirming sufficient variance explanation by the model employed at the first level (Supplementary Fig. S1), second-level random effects analyses were then computed over the single subjects' contrasts. To this end, single subjects' contrasts of interest [*gain anticipation*: gain cues – neutral cues; *loss anticipation*: loss cues – neutral cues] were submitted to a random effects ANOVA model including age as covariate of no interest. Planned comparisons were carried out by means of T contrasts on the regressors of the second level GLMs. The significance level was set to $p < 0.05$, whole-brain corrected for family-wise error rate (FWE) in all within-group analyses (see Supplementary Tables S1–S6).

Because of our *a priori* anatomical hypothesis regarding the role of the striatum in human reward processing and its relationship to impulsivity, we performed a between-group region of interest (ROI)-based analyses in the striatum, with an anatomical ROI obtained from the WFU Pickatlas (Wake Forest University; http://fmri.wfubmc.edu/software/pickatlas) and a significance level of $p < 0.05$ FWE corrected for the ROI volume. SPM betas at the local maximum within the VS/NAcc were also submitted to bootstrap-based confidence interval estimation. For exploratory whole-brain between-group analyses, the significance level was set to $p < 0.001$, uncorrected, and activations surviving cluster-level FWE correction are marked as such.

Correspondence between brain structures and activation foci were determined using the Automated Anatomical Labeling (Tzourio-Mazoyer et al., 2002) as implemented in the WFU Pickatlas.

2.4.3. Brain-behavior correlations

To investigate the relationship between striatal responses to motivational cues (gain, loss) and self-reported impulsivity as assessed with the Barratt Impulsiveness Scale (BIS-11), we computed a contrast of the additive effect of diagnostic group and motivation (i.e., main effect of group [(gain-neutral$_{HC}$ AND loss-neutral$_{HC}$) vs. (gain-neutral$_{BPD}$ AND loss-neutral$_{BPD}$)], inclusively masked with the positive effect of motivation [(anticipate gain > anticipate neutral)$_{HC}$ AND (anticipate gain > anticipate neutral)$_{HC}$] AND (anticipate loss > anticipate neutral)$_{HC}$ AND (anticipate loss > anticipate neutral)$_{HC}$)]) and extracted participants' contrasts of parameter estimates of each condition at the peak voxel within the VS/NAcc. These values were correlated with individual BIS-11 scores using Sheperd's *Pi* correlations. Shepherd's *Pi* correlations have recently been proposed to improve robustness of brain-behavior correlations. They are based on Spearman's non-parametric correlation, but additionally include a bootstrap-based estimation of the Mahalanobis distance, thereby allowing for an unbiased removal of outliers (Schwarzkopf et al., 2012). Because, in addition to higher BIS-11 scores, patients had substantially higher BDI scores reflecting depressive symptoms (Table 1), Shepherd's *Pi* correlations were also computed between striatal anticipation responses and BDI scores, and multiple regression analyses were conducted in order to control for depressive symptoms.

3. Results

3.1. Behavioral results

3.1.1. Psychometric results

Mean scores of the BIS-11, BDI, and BSL are displayed in Table 1, separated by diagnostic group. In line with our predictions, BPD patients exhibited higher BIS-11 scores compared to healthy controls. Additionally, patients showed significantly higher BDI scores, reflecting depressive symptoms, and BSL scores, reflecting BPD-related psychopathology. On the other hand, the groups were highly comparable with respect to tests of fluid (LPS) and crystalline (MWT) intelligence.

3.1.2. Accuracy

Mean reaction times and accuracy rates for both groups are presented in Table 3. Because Kolmogorov-Smirnov (KS) tests with Lilliefors significance correction (Lilliefors, 1967) applied to accuracy rates indicated a significant deviation from the normal distribution, non-parametric testing procedures were adopted for accuracy rates (Friedman's tests for within-subject comparisons and Mann-Whitney *U* tests for between-subject comparisons). The non-parametric tests revealed a trend for a between-group difference in accuracy during neutral trials only ($p = 0.100$; Mann-Whitney *U* test) and a further trend for an unequal distribution of accuracies in the patient group ($p = 0.096$; Friedman test), most likely reflecting lower accuracy in the patient group during neutral trials. No further trends for within-group or between-group differences in accuracy rates were observed (all $p > 0.162$).

3.1.3. Reaction times

The distribution of RTs did not depart significantly from the predicted normal distribution in any of the conditions (KS tests with Lilliefors significance correction), neither in the control nor in the BPD group (all $p > 0.127$). We thus compared the average RTs (corrected for task difficulty (= abs(digit-5))) using an ANCOVA for repeated measures (within-subject factor *condition* – reward, (avoidance of) loss, and neutral; between-subject factor *group*; age as covariate). Degrees of freedom were corrected using Greenhouse-Geisser correction to account

Table 3
Behavioral results of the fMRI study.

	RT (ms)		Accuracy	
	HC	BPD	HC	BPD
Condition				
Neutral	599.03 (85.66)	557.14 (67.14)	0.966 (0.03)	0.942 (0.05)
Gain	569.29 (90.07)	548.94 (69.94)	0.964 (0.03)	0.950 (0.05)
Loss	575.42 (102.89)	555.23 (66.54)	0.955 (0.03)	0.935 (0.05)

Mean response times (RT) and accuracy in the three conditions of interest in the BPD patients (BPD) and the control group (HC). Standard deviations are given in parentheses.

for non-sphericity. There was a significant main effect of condition ($F_{1.71,70.11} = 4.57$, $p = 0.018$), reflecting the shorter RTs in motivated, particularly rewarded, trials (Table 3). Moreover, a significant condition by age interaction ($F_{1.71,70.11} = 4{,}49$, $p = 0.019$) and a trend for a condition by group interaction ($F_{1.71,70.11} = 3.08$, $p = 0.060$) were observed, with the latter most likely reflecting the fact that patients had nominally shorter RTs, but lower RT differences between motivated and neutral trials (Table 3).

3.2. Functional MRI results

3.2.1. Effects of motivational salience

A comparison of brain responses to cue pictures signaling a reward or avoidable loss [positive effect of gain anticipation; (anticipate gain > anticipate neutral)$_{HC}$ AND (anticipate gain > anticipate neutral)$_{BPD}$] elicited widespread activations within the mesolimbic reward system, including the ventral and dorsal striatum, the dorsal anterior cingulate cortex, extending into the supplementary motor area (dACC/SMA) and the thalamus ($p < 0.05$, whole-brain FWE-corrected; see Supplementary Table S1), replicating previous results (Wittmann et al., 2005; Schott et al., 2007). Similarly, anticipation of avoidable losses [positive effect of loss anticipation; (anticipate loss > anticipate neutral)$_{HC}$ AND (anticipate loss > anticipate neutral)$_{BPD}$] also engaged the striatum and prefrontal neocortical structures in both groups, including the dACC/SMA ($p < 0.05$, whole-brain FWE-corrected; Supplementary Table S2).

Reward feedback (gain - neutral) was associated with an increased activation of the VS/NAcc whereas loss feedback (loss - neutral) elicited a deactivation of the VS/NAcc (F-contrast testing reward feedback against loss feedback across groups; Supplementary Fig. S2). An exploratory ANCOVA model testing for potential effects of the high gains or losses revealed no reliable activation differences between high gains or losses and standard gain or loss feedback, respectively.

3.2.2. Reduced striatal anticipation responses in BPD patients

While computing the gain and loss anticipation contrasts separately for healthy controls and BPD patients, we observed reliable mesolimbic (i.e., ventral striatal and midbrain) activations during gain, but not loss anticipation in the patients (at $p < 0.05$, whole-brain FWE-corrected; Fig. 2). In an exploratory analysis at a more liberal significance level ($p < 0.001$, uncorrected), BPD patients exhibited activation of the striatum, the midbrain, and the dACC during both gain and loss anticipation (details available upon request), suggesting that the activation difference observed was a quantitative rather than qualitative one.

A direct comparison of the anticipation responses to rewards and losses in healthy controls and BPD patients [(gain-neutral$_{HC}$ AND loss-neutral$_{HC}$) vs. (gain-neutral$_{BPD}$ AND loss-neutral$_{BPD}$)] showed a significantly reduced activation of the VS/NAcc in the patient group (left: [x y z] = [−15 17–5], $T = 4.01$, $p = 0.044$, FWE-corrected for ROI of the bilateral striatum; right: [x y z] = [9 8 1], $T = 4.15$, $p = 0.028$, small-volume FWE-corrected; see Fig. 3). Including smoking status (coded as 0 = never-smoker, 1 = former or occasional smoker, 2 = current smoker) as a covariate in the GLM did not qualitatively affect the group difference in the striatum. Bootstrap-based estimation of the 90% confidence intervals further showed that, in BPD patients, the median ventral striatal activation during gain anticipation was below the 5th percentile of the healthy controls' median, and that the 90% confidence intervals of the median parameter estimates during loss anticipation did not overlap between healthy controls and BPD patients (Fig. 3, left panel) [*Note:* Despite the bootstrap-based confidence interval estimation suggesting a more pronounced between-group difference for loss anticipation versus gain anticipation, the formal group-by-motivation interaction contrast revealed no significant activation clusters in the striatum, even at $p < 0.005$, uncorrected].

An exploratory analysis of between-group differences at $p < 0.001$, uncorrected, additionally revealed reduced prefrontal and occipital cortical activations during gain and loss anticipation in BPD patients (Table 4). Notably, in this exploratory analysis, only the activation difference in the right striatum remained significant after whole-brain FWE correction at cluster level, and a trend towards significance after cluster-level FWE correction was observed in the left striatum.

During feedback, both groups exhibited positive ventral striatal prediction errors to gains and negative striatal prediction errors to losses, but there was no significant between-group difference with respect to striatal prediction errors (Supplementary Fig. S2). An exploratory analysis revealed an increased activation of the hippocampus in patients, but not in controls, during positive feedback (main effect of group: $F_{1,81} = 37.27$; $p = 0.002$, whole-brain FWE-corrected).

3.2.3. Correlation of striatal anticipation responses and impulsivity

To test how altered anticipation of gains and/or losses in BPD patients might be related to self-reported individual impulsivity, we

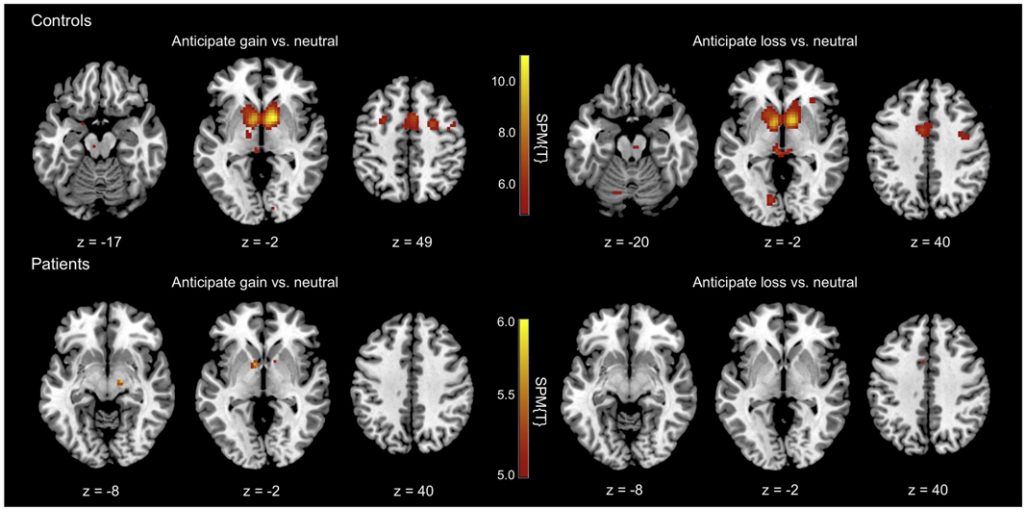

Fig. 2. Functional MRI correlates of gain and loss anticipation in healthy controls and BPD patients. Top: In healthy controls, anticipation of both gains and losses was associated with activation of the midbrain (substantia nigra / ventral tegmental area, slice 1, 4), the VS/NAcc (slice 2, 5), and the dACC (slice 3, 6). Bottom: In BPD patients, midbrain and ventral striatal activation was observed during gain anticipation (slice 1, 2), but did not survive whole-brain FWE correction in the dACC (slice 3), while the reverse activation was observed during anticipation of losses (slices 4–6). All activation maps are thresholded at $p < 0.05$, whole-brain FWE corrected.

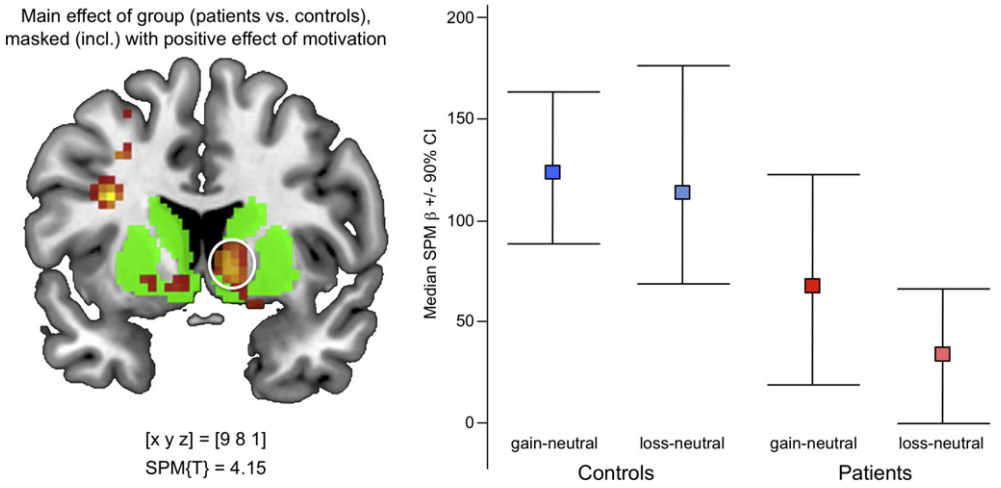

Fig. 3. Reduced ventral striatal anticipation of gains and losses in BPD patients. Left: Maximum of the ventral striatal between-group difference during the anticipation of gains and losses ($p = 0.028$, small-volume FWE-corrected for the bilateral striatum), inclusively masked with the positive effect of motivational salience (anticipate gain-neutral and anticipate loss-neutral) is displayed, thresholded at $p < 0.001$, uncorrected, for illustrative purposes. Plots depict median contrasts of parameter estimates (SPM betas) of the conditions of interest (anticipate gain-neutral and anticipate loss-neutral, separated by group) at the peak voxel of the group difference ([x y z] = [9 8 1]); error bars display 90% confidence intervals of the medians as estimated via bootstrap resampling.

computed Shepherd's *Pi* correlations, a non-parametric correlation statistic robust to outliers (Schwarzkopf et al., 2012). As displayed in Fig. 4, controls exhibited a positive correlation between BIS-11 total scores and the ventral striatal anticipation responses to both gains and losses (gains: $\pi = 0.55$, $p = 0.031$; losses: $\pi = 0.55$, $p = 0.018$). In the patients, the correlation between striatal gain anticipation and impulsivity was not significant, albeit also positive in sign ($\pi = 0.23$; $p = 0.657$). When correlation coefficients between patients' and controls' responses to gains and impulsivity were directly compared, however, no significant difference between groups was found (Fisher's $Z = 1.09$; $p = 0.276$, two-tailed).

Most notably, the correlation between striatal loss anticipation responses and impulsivity scores was significantly negative in the patients ($\pi = -0.59$; $p = 0.012$). Fisher's Z test confirmed a significant between-group difference between the correlation coefficients of ventral striatal loss anticipation and impulsivity ($Z = 3.99$; $p = 0.0001$). [*Note:* when computing Spearman's correlations without outlier removal, the signs and significance levels of all correlations did not change substantially]. The correlations did not change qualitatively in direction or significance when the parameter estimates in the VS/NAcc were adjusted for smoking status.

Unlike impulsivity, depressive symptoms as assessed with the BDI did not correlate with striatal anticipation of gains or losses in either BPD patients or healthy controls (all $p > 0.407$). When, separately for controls and BPD patients, both BDI and BIS-11 scores were entered into linear regression analyses with striatal anticipation responses as the dependent variable, BIS-11 was negatively associated with striatal loss anticipation responses in BPD patients ($\beta_{BIS\text{-}11} = -0.514$, $p = 0.017$), whereas BDI scores did not explain a significant proportion of the variance in either group or condition (all abs(β_{BDI}) < 0.147, all $p > 0.490$). Furthermore, correlating depressiveness and striatal anticipation responses across the entire cohort yielded no effect of BDI scores when covarying for diagnostic group.

Table 4
fMRI between-group activation differences during gain and loss anticipation.

	x	y	z	*t*	k	$p_{FWE,cluster}$
Left inferior frontal gyrus	−33	8	25	5.03	23	0.366
Left middle frontal gyrus	−27	5	52	3.88	12	0.720
	−30	8	40	3.80		
Right striatum	12	5	−2	4.44	105	0.003**
Right superior occipital gyrus/cuneus	18	−85	19	4.25	20	0.446
	18	−88	7	3.22		
Left striatum	−15	17	−5	4.01	45	0.084*
	−9	5	−5	3.45		

Peak activations at the local maxima are displayed at $p < 0.001$, uncorrected; k = cluster size; $p_{FWE,cluster}$ = significance level corrected for family-wise error rate at cluster level.
** $p < 0.01$, FWE-corrected at cluster level.
* $p < 0.10$, FWE-corrected at cluster level.

4. Discussion

The goal of our present study was to uncover potential neural mechanisms underlying dysfunctional anticipation of rewards and losses in borderline personality disorder and their potential relationship to impulsivity. In line with previous studies (Völlm et al., 2007; Enzi et al., 2013), we observed reduced activation of the VS/NAcc during the anticipation of gain and loss in a homogenous sample of unmedicated female BPD patients in comparison to an age-matched healthy control group with comparable cognitive ability. In line with our hypotheses, BPD patients compared to healthy controls exhibited higher self-reported impulsivity scores as measured with the Barratt Impulsiveness Scale (BIS-11). Brain-behavior correlation analyses revealed positive correlations between the ventral striatal anticipation responses to both gains and losses and BIS-11 total scores in the control group, while patients, on the other hand, showed no significant correlation of striatal gain anticipation and impulsivity, but exhibited a significantly negative correlation between striatal loss anticipation responses and BIS-11 scores.

4.1. Reduced ventral striatal anticipation responses in BPD and other psychiatric disorders

The finding of unmedicated female BPD patients exhibiting a relatively reduced activation of the VS/NAcc during anticipation of reward – and also losses – is consistent with previously observed reduced VS/NAcc reward responses in male Cluster B patients (Völlm et al., 2007) and in a sample of BPD patients comparable to that of the present study (Enzi et al., 2013). Reduced ventral striatal activations during rewarded tasks, most prominently monetary incentive delay (MID) task adaptions (Knutson et al., 2001), have previously been described in a number of patient populations with other psychopathologies, including alcohol-dependent patients (Wrase et al., 2007; Beck et al., 2009), unmedicated patients with schizophrenia (Juckel et al., 2006), patients with schizophrenia receiving typical neuroleptics (Schlagenhauf et al., 2008), and patients with ADHD (Ströhle et al.,

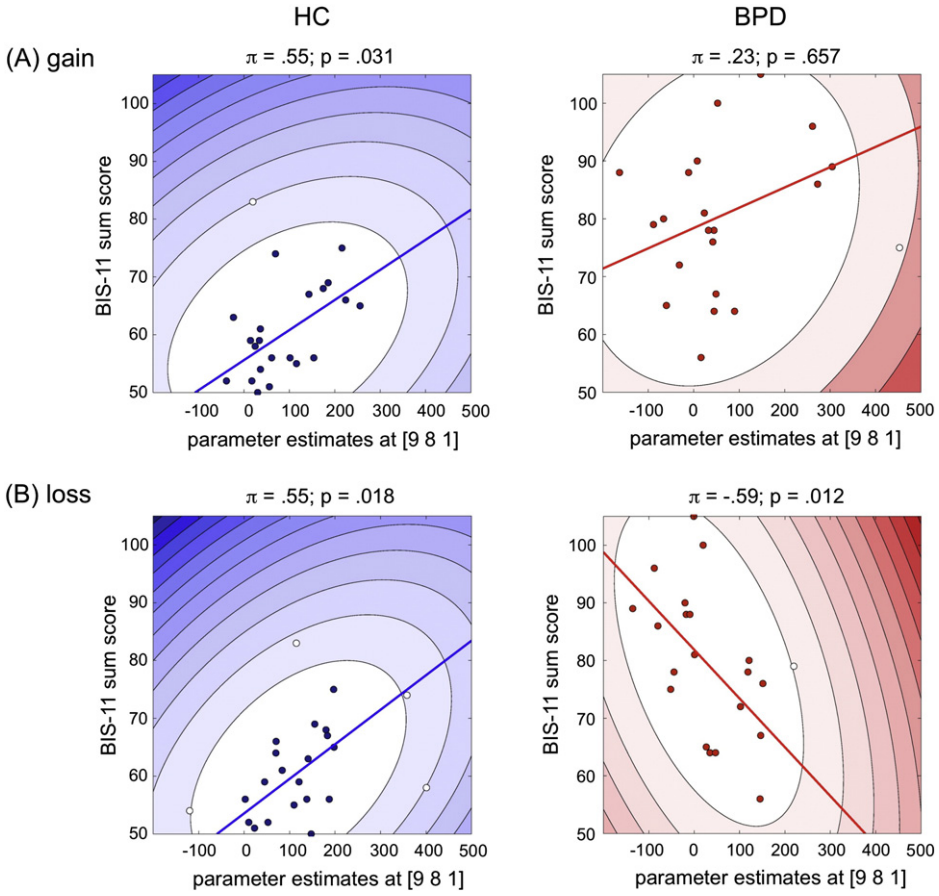

Fig. 4. Correlation of striatal anticipation responses with impulsivity. A: Left panel: Controls exhibited a positive correlation between the ventral striatal ([x y z] = [9 8 1]) gain anticipation response and impulsivity (as reflected by the BIS-11 sum score; $\pi = 0.55$, $p = 0.031$). Right panel: In the patients, this correlation was also positive, but failed to reach statistical significance ($\pi = 0.23$; $p = 0.671$). B: While controls showed a significant positive correlation between the striatal loss anticipation response and the BIS-11 sum score (left panel; $\pi = 0.55$, $p = 0.018$), the correlation was significantly negative in patients (right panel; $\pi = -0.59$; $p = 0.012$). *Note:* One control subject had a beta value of >500, resulting in an outlier that is not displayed in the figure.

2008; Schuermann et al., 2011; for a review see Plichta and Scheres, 2014). This is in apparent contrast to the observation that patients with addictions, ADHD, or Cluster B personality disorders like BPD commonly show a high propensity to actively seek rewards, and particularly short-term rewarding experiences at the expense of long-term goals (Sonuga-Barke, 2005; Svaldi et al., 2012). One rather parsimonious explanation for this phenomenon would be that reduced neural responsiveness to reward-associated stimuli might provoke increased reward-seeking behavior as a means of compensation, as described in patients with pathological gambling (Reuter et al., 2005).

Such an explanation would be based on the assumption that reduced VS responses might constitute a neural signature of pathological impulsivity or related phenotypes. There is, however, a considerable body of literature reporting alterations of ventral striatal reward processing in a number of psychiatric disorders in which impulsivity is not considered a prominent feature (Hägele et al., 2015), and also in normal aging. In the healthy elderly, reduced striatal anticipation responses to losses (Samanez-Larkin et al., 2007), but also gains (Schott et al., 2007; Mell et al., 2009; Eppinger et al., 2013) have been commonly reported, whereas BIS-11 normative data suggest that –at least self-reported– impulsivity decreases with age (Spinella, 2007). Considering this discrepancy, one should keep in mind the possibility that blunted ventral striatal anticipation responses in aging and in psychiatric disorders may constitute a common outcome of a number of distinct neurocognitive mechanisms. At a neural level, this phenomenon may be mediated by differential structural and functional alterations of the mesolimbic dopamine system in the elderly and in different psychiatric patient populations. Mesolimbic reward prediction and reward-based learning are intimately linked to dopaminergic neurotransmission (Pessiglione et al., 2006; Schott et al., 2008), and older adults show relatively symmetric reductions of presynaptic dopamine synthesis and release capacity, and of postsynaptic dopamine D2 receptor expression, which have been linked to age-related cognitive decline (Bäckman et al., 2006) and also altered reward processing (Dreher et al., 2008). In psychiatric patient populations, functional neuroanatomical alterations of the dopamine system are commonly asymmetric with, for example, alcohol-dependent patients showing reduced postsynaptic D2 receptor binding capacity (Heinz et al., 2004), but presynaptic dopamine transporter binding comparable to healthy controls (Heinz et al., 2005). Patients with schizophrenia, on the other hand, have been shown to exhibit increased presynaptic dopamine release capacity when compared to healthy controls (Breier et al., 1997; Goto and Grace, 2007). The aforementioned studies collectively suggest that the mesolimbic reward system is sensitive to a variety of dysregulations in the mesolimbic dopaminergic system, with profound impact on motivated behavior, including reinforcement learning, novelty processing, or decision-making (Camara et al., 2009). Conversely, switching patients with schizophrenia from typical to atypical neuroleptics has been associated with a partial restoration of the VS/NAcc reward anticipation (Schlagenhauf et al., 2008, 2010) and, similarly, a relative normalization of the striatal gain anticipation response in ADHD under methylphenidate treatment has been reported (Aarts et al., 2015).

With respect to BPD, a possible contribution of dysfunctional reward processing to the pathogenesis of the disorder has received considerable theoretical interest in recent years. Disturbances of the endogenous opioid system – a key transmitter system in motivated behavior – have been suggested to constitute an important pathophysiological mechanism in BPD (Stanley and Siever, 2010), with the dysfunctional behaviors of the affected patients being driven by unconscious attempts to stimulate their endogenous opioid system – and thereby also indirectly the dopaminergic reward system. Evidence of dysregulation of regional endogenous opioid function in BPD supports this hypothesis (Prossin et al., 2010). Dopaminergic system dysfunction was suggested to play a role in BPD as early as 2004 (Friedel, 2004) and has been implicated in three dimensions of the disorder: emotional dysregulation, impulsivity, and cognitive-perceptual impairment like dissociative states. However, thus far little empirical evidence exists for dysfunctions in the mesolimbic dopamine system in BPD. Ventral striatal BOLD signals during reward processing have been associated with individual dopamine release capacity in healthy humans (Scott et al., 2007; Schott et al., 2008; Buckholtz et al., 2010), although this relationship may be disrupted in patients with certain psychiatric disorders like schizophrenia (see Breier et al., 1997 vs. Juckel et al., 2006) or pathological gambling (see Boileau et al., 2013 vs. Reuter et al., 2005). In BPD patients, a recent event-related brain potential (ERP) study (Schuermann et al., 2011) has shown a reduced amplitude of the feedback-related negativity (FRN) during performance of the Iowa Gambling Task. The dynamics of the FRN have been suggested to indirectly reflect a temporary reduction of midbrain dopaminergic activity in response to unexpected aversive outcomes (Schultz, 1998). Together with the previous observations by Völlm et al. (2007) as well as Enzi et al. (2013), our results provide further evidence for dysfunction of the dopaminergic system in BPD.

While reduced anticipation responses to gains have been extensively documented in several different psychiatric patient populations, alterations of the striatal loss anticipation have been investigated less frequently. Increased ventral striatal loss anticipation responses have been reported in pathological gamblers, but not in alcohol-dependent patients and might therefore constitute a relatively disorder-specific mechanism in pathological gambling (Romanczuk-Seiferth et al., 2015). Reduced anticipation responses to (avoidable) losses have been reported in patients with MDD or bipolar II disorder (Ubl et al., 2015; Yip et al., 2015). Indeed, patients with BPD, including our sample, commonly exhibit depressive symptoms, and the potential contribution of depression-related psychopathology will be discussed below. Furthermore, as anticipation responses to both gains and losses are subject menstrual cycle-dependent hormonal changes in women (Bayer et al., 2013), the previously reported hormonal dysregulations in female BPD patients (Roepke et al., 2010; Eisenlohr-Moul et al., 2015) may also have contributed to the reduced ventral striatal anticipation response in our patient sample.

One limitation of the present study is that, while the separate analyses of gain and loss anticipation in healthy controls and BPD patients suggest that the patients also exhibited reduced anticipation responses in cortical regions like the dACC (Fig. 2), a direct between-group comparison revealed a robust between-group difference only in the striatum (Fig. 3, Table 4). We cannot exclude that this may result from insufficient statistical power in brain regions outside the striatum, and it is indeed plausible to assume that reduced VS/NAcc activation during reward anticipation would likely be accompanied by decreased activation of other nodes within the reward-responsive network, including cortical regions like the dACC and the insula.

From a pharmacological perspective, little is thus far known about the clinical potential of addressing the suspected dopaminergic system dysfunction in BPD patients. A few studies, however, suggest that certain atypical antipsychotic agents may exert a beneficial effect on symptom control in BPD patients. For example, aripiprazole, a partial agonist on D2 type dopamine receptors that has been shown to enhance the VS reward anticipation response in patients with schizophrenia (Schlagenhauf et al., 2010), can improve symptoms of depression, anxiety, and anger in BPD patients (Nickel et al., 2006). Given the clinical heterogeneity of BPD, future research should be directed at the identification of a potential subpopulation of BPD patients who might show the most pronounced clinical benefit from such an intervention.

4.2. The relationship between ventral striatal loss prediction and impulsivity in BPD

As predicted, self-reported impulsivity, indexed by the BIS-11 scores, were significantly higher in the BPD patients when compared to healthy controls. When correlating the activation during anticipation of gains and losses with BIS-11 scores, different patterns were observed in BPD patients and healthy controls. Healthy control participants showed a positive correlation between BIS-11 scores and VS/NAcc gain anticipation responses, which is in line previous studies (Plichta and Scheres, 2014). Unmedicated female BPD patients, on the other hand, showed a non-significant positive correlation between BIS-11 scores and gain anticipation, and, more importantly, exhibited a negative correlation between impulsivity and the VS/NAcc responses to loss anticipation. This pattern differs markedly from previous studies in other psychiatric patient populations with increased trait impulsivity like alcohol-dependent patients (Beck et al., 2009) or patients with ADHD (Scheres et al., 2007), which have reported negative correlations between VS/NAcc *gain* responses and self-reported impulsivity. While impulsivity has been previously suggested to constitute a neurocognitive phenomenon common to BPD and substance use disorders (Bornovalova et al., 2005), the discrepancy across diagnostic groups with respect to correlation with VS/NAcc responsivity suggests that self-report measures of impulsivity in these different clinical populations might reflect, at least partly, dissociable entities. Like patients with ADHD or substance use disorders, BPD patients tend to make unfavorable choices despite possessing declarative knowledge about the long-term aversive consequences (Svaldi et al., 2012). At the same time, BPD patients, somewhat paradoxically, also show high levels of self-reported harm avoidance (Fassino et al., 2009).

In our study, BPD patients who exhibited higher VS/NAcc responses to loss cues reported lower impulsivity as assessed with the BIS-11. One might thus argue that among BPD patients, who generally have a propensity to make risky choices without considering potential harmful outcomes (Svaldi et al., 2012), those who describe themselves as less impulsive could be more receptive to negative reinforcement and therefore process avoidable losses in a similar way as potential gains. On the other hand, the simultaneous presence of high harm avoidance and elevated impulsivity in BPD patients might compromise these patients' capacity to cope with aversive outcomes of their actions, possibly causing higher emotional distress, which may then give rise to self-destructive behaviors in BPD patients. In this context, it must be kept in mind that the term “impulsivity” is somewhat poorly defined and, in BPD patients, might potentially refer to (at least) two distinct phenomena: On the one hand, BPD patients are highly sensitive to emotionally aversive events, and negative emotional experience commonly trigger impulsive behavior (Brown et al., 2002; Crowell et al., 2009; Trull et al., 2008). This type of “impulsivity” might be relatively specific to BPD, further research is necessary to establish clinical tools that would be better-suited to quantify this phenomenon. On the other hand, “impulsivity” as assessed with the BIS might reflect a trait that is common to several psychiatric disorders, including addiction or ADHD.

There is limited previous evidence with respect to altered loss processing in BPD patients and a potential relationship with impulsivity. One study in male Cluster B patients reported a negative relationship between the processing of monetary gain and impulsivity in the prefrontal cortex, but no correlation was reported in the striatum (Völlm et al., 2007). One reason for the lack of a negative correlation between impulsivity and ventral striatal reward signals in the study by Völlm and colleagues might be that their patient sample was substantially

smaller ($n = 8$). Also, the demographic characteristics differed considerably, as Völlm and colleagues investigated only male participants, some of whom had been diagnosed with an antisocial rather than borderline personality disorder, and manifestations of impulsivity can differ between these two disorders (DeShong and Kurtz, 2013). On the other hand, in a sample clearly distinct from our study sample, but more comparable to the sample investigated by Völlm and colleagues, a similar pattern as observed here has previously been reported: In a cohort of prison inmates with high psychopathy scores measured via the Psychopathy Check List – Revised (PCL-R; Hare, 2003) who were compared to prisoners with low psychopathic traits (Pujara et al., 2014), a positive correlation of the striatal response difference between gain and loss feedback and the overall psychopathy score was observed selectively in the individuals with high PCL-R scores. Notably, this relationship resulted largely from a negative correlation of PCL-R scores and striatal loss responses, compatible with previously reported deficits in the anticipation of aversive outcomes in individuals with psychopathic traits (Prehn et al., 2013). Regarding the widely used two-factor model of psychopathy implemented in the PCL-R, BPD patients typically show low scores on Factor 1 (blunted affect, stress immunity, narcissism), while they score high on Factor 2 (impulsivity, boredom susceptibility, aggressiveness) (Hunt et al., 2015). In the study by Pujara et al. (2014), overall PCL-R scores showed a more robust correlation with the ventral striatal BOLD response during loss processing than either factor alone, and the analogy in the results of the two studies must be interpreted with caution [*Note:* In the course of the preparation of this article, we re-analyzed the data from Pujara et al., 2014, using Shepherd's *Pi* correlations, which did not affect the previously reported results (details available upon request).]. With respect to the clinic, the observed similarity of the results would nevertheless be in line with the dysfunctional behavioral patterns observed in both populations, namely a problematic preference for risky choices, risk taking without fear of consequences, and frequently experienced frustration due to negative consequences of one's own behavior, all of which are in turn commonly associated with emotional dysregulation.

Given the previously suggested common genetic basis for impulsivity across personality disorders (Kendler et al., 2008), it is tempting to conclude that impulsivity might largely result from a reduced ability to predict aversive outcomes [*Note:* While psychopathy is not a personality disorder *per se*, the construct as implemented in the PCL-R shows a well-known diagnostic overlap with antisocial personality disorder, and also other Cluster B personality disorders, most prominently narcissistic and histrionic personality disorder (Hare and Neumann, 2005; Blackburn, 2007)]. However, additional factors must not be neglected. Importantly, studies in healthy participants suggest that individual levels of impulsivity (Plichta and Scheres, 2014) or psychopathic traits (Buckholtz et al., 2010) are positively correlated with the anticipatory response to gains, a relationship also observed in inmates with pathological psychopathy scores (Pujara et al., 2014). These findings suggest that –rather than impaired loss processing alone– a dysfunctional bias of the responsivity of the mesolimbic dopaminergic system towards the processing of rewards in comparison to losses might constitute a more accurate description of a motivation-related neural mechanism underlying clinically relevant levels of impulsivity.

Despite apparently similar mechanisms with respect to impaired loss processing, it must be kept in mind that BPD and psychopathy are clinically distinct entities. One fundamental difference between BPD patients and individuals with high trait psychopathy concerns the role of depressive symptomatology, with psychopathic traits –particularly those defined by Factor 1– being negatively related to depressive symptoms (Berg et al., 2015), whereas BPD patients almost invariably show severe depressive symptoms. A potential contribution of depressive symptomatology to altered gain and loss processing in BPD will be discussed in the following paragraph.

4.3. Ventral striatal reward processing and depressive symptoms in BPD

An additional, or alternative, explanation for the reduced anticipation responses to gains and losses in the patient group may be related to the presence of considerable depressive symptomatology in BPD patients. In fact, almost all BPD patients show considerable depressive symptomatology, and comorbidity with MDD is estimated to be as high as 50 to 90% (Stanley and Wilson, 2006; Wilson, 2007; Silk, 2010; Zanarini et al., 1998; Gunderson et al., 2000), a phenomenon also observed in the sample investigated here (Tables 1, 2).

Previous studies have demonstrated reduced striatal reward anticipation responses in MDD patients compared to healthy controls (Stoy et al., 2012; Arrondo et al., 2015; for a meta-analysis see Zhang et al., 2013), and, using a dimensional approach, Hägele and colleagues demonstrated a correlation between self-reported depressive symptoms and VS/NAcc reward anticipation responses in patients from several diagnostic groups, including MDD, schizophrenia, ADHD, and alcohol dependence (Hägele et al., 2015). Moreover, not only gain, but also loss anticipation responses have been shown to be reduced in patients with unipolar depression and bipolar II disorder (Ubl et al., 2015; Yip et al., 2015). It is thus conceivable that the between-group differences in striatal gain and loss anticipation might in part be related to depressive symptoms.

On the other hand, unlike MDD patients (Zhang et al., 2013) the BPD patients investigated in the present study did not differ significantly from healthy controls in their striatal *feedback* responses. This raises the possibility that the neurobiological mechanisms underlying depressive symptoms in BPD and their relationship between gain and loss processing might, at least in part, differ from those in MDD. In line with this notion, BDI scores did, despite the between-group difference mirroring the fMRI results, not correlate significantly with either gain or loss anticipation responses in the VS/NAcc in *within* the groups, and did also not influence the negative correlation between BIS-11 scores and VS/NAcc loss anticipation responses in BPD patients. We tentatively suggest that this might be related to the clinical observation that depressive symptoms in BPD are partly distinct from those in MDD at the clinical level, with more pronounced cognitive symptoms like feelings of guilt and self-devaluation, and self-reported depressiveness in BPD is typically higher than clinician-assessed depressive symptoms (Stanley and Wilson, 2006; Wilson et al., 2007; Silk, 2010).

One potential explanation for this apparent discrepancy might be that BPD patients are highly sensitive to social rejection (Lis and Bohus, 2013; Domsalla et al., 2014), and aversive social interactions are typically one of the most common causes for dysfunctional behavior in these patients (Wagner and Linehan, 1999). An important direction for future research would therefore be the use of social rather than monetary reward and punishment conditions (Richey et al., 2014; Barman et al., 2015), which might constitute more disorder-relevant stimuli in BPD patients.

5. Conclusion

Our results show that BPD patients exhibit reduced, but yet significantly positive, anticipation responses to anticipated rewards and losses in the VS/NAcc. Impulsivity shows a specific negative correlation with ventral striatal loss, but not gain, anticipation in BPD patients, whereas depressive symptoms did not significantly modulate striatal anticipation of gains or losses in BPD. Our results suggest that impaired mesolimbic processing of losses may constitute a neural mechanism that promotes the emergence of dysfunctional impulsivity and related behaviors. In light of previous studies showing correlations between gain anticipation and impulsivity in other psychiatric populations, our results highlight the need for future research directed at the systematic comparative investigation of commonly used psychopathological entities like “impulsivity” across diagnostic groups.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.08.011.

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