Reward processing in unipolar and bipolar depression: A functional MRI study

Ronny Redlich, MA [1,§], Katharina Dohm, MSc [1,§], Dominik Grotegerd, MSc [1], Nils Opel[1], Pienie Zwitserlood, MA, PhD [2], Walter Heindel, MD [3], Volker Arolt, MD, PhD [1], Harald Kugel, PhD [3], Udo Dannlowski, MA, MD, PhD [1,4,*]

§ This is to indicate that both authors contributed equally to the present work and should therefore both be regarded as first authors.

[1] Department of Psychiatry, University of Münster, Germany

[2] Department of Psychology, University of Münster, Germany

[3] Department of Clinical Radiology, University of Münster, Germany

[4] Department of Psychiatry, University of Marburg, Germany

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* Corresponding author:

Udo Dannlowski
Department of Psychiatry
University of Muenster
Albert-Schweitzer-Campus 1, A9
48149 Münster, Germany
Phone: +49-251-8357214
Email: mailto:dannlow@uni-muenster.de

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ABSTRACT

Differentiating bipolar disorders (BD) from unipolar depression (UD) remains a major clinical challenge. The identification of neurobiological markers may help to differentiate these disorders, particularly during depressive episodes. This cross-sectional study, including 33 patients with UD, 33 patients with BD and 34 healthy controls, is one of the first to directly compare UD and BD with respect to reward processing. A card-guessing paradigm was employed and brain activity associated with reward processing was investigated by means of fMRI. A 3 (group) × 2 (condition: reward > control, loss > control) ANOVA was conducted using the nucleus accumbens (NAcc) as ROI. Furthermore, a whole-brain approach was applied. A functional connectivity analysis was performed to characterize diagnosis-related alterations in the functional coupling between the NAcc and other brain areas. The ANOVA revealed higher activity for HC than for BD and UD in the NAcc during reward processing. Moreover, UD showed a higher functional connectivity between the NAcc and the VTA than HC. The patients groups could be differentiated in that BD showed a decreased activation, in the reward condition, of the NAcc, caudate nucleus, thalamus, putamen, insula, and prefrontal areas compared to UD. These results may help to refine the understanding of neural correlates of reward processing in both disorders, and to understand the neural underpinnings of anhedonia, a core symptom of depressive episodes.

1. Introduction

Among patients suffering from bipolar disorder, misdiagnosis rates up to 70% have been reported, leading to inappropriate medication treatment and poor prognosis (Hirschfeld *et al*, 2003; Phillips and Kupfer, 2013). The main reason for the failure to accurately identify BD is that diagnostic criteria for a depressive episode are the same in both disorders (Almeida and Phillips, 2013). Therefore, the identification of neurobiological markers may help to differentiate these disorders, particularly during depressive episodes, and may also identify shared neuronal alterations.

Previous neuroimaging studies have already addressed the differentiation of BD and UD employing structural (Redlich *et al*, 2014a; Versace *et al*, 2010) and functional MRI (Almeida and Phillips, 2013; Benson *et al*, 2014; Grotegerd *et al*, 2014). These studies yielded differences in regions that contribute to the dysregulation of emotional and cognitive functions. However, only few studies focused on neural systems associated with reward processing in BD and, to our knowledge, only one study directly compared BD and UD (Chase *et al*, 2013).

A basic function of reward is to induce a subjective feeling of pleasure and positive emotion. Altered responsiveness to reward, and to reinforcing stimuli, could therefore contribute to the generation and maintenance of depressive symptoms (Pizzagalli *et al*, 2009). Diminished responsiveness to commonly rewarding stimuli has already been observed in both disorders, and appears to be mainly driven by the mesolimbic dopamine system including the ventral tegmental area (VTA), a central structure in the reward-processing circuitry (Keller *et al*, 2013).

There are different stages of reward processing, and it is widely discussed whether the NAcc is predominantly involved in reward anticipation (e.g. Knutson *et al*, 2001) or in reward

outcome (e.g. Elliott et al., 2000; Ernst et al., 2005). Given the heterogeneity of previous studies, with different paradigms focussing on different aspects of reward processing, it is difficult to gain a clear picture. In a meta-analysis, Liu et al. (2011) showed that reward outcome often activated the NAcc and medial orbitofrontal cortex, whereas reward anticipation activated the anterior cingulate cortex (ACC), insula and areas within the brainstem.

Several studies examining alterations in the mesolimbic system in UD found reduced activity during reward feedback, relative to healthy controls (HC), in the ventral striatum (VS) including the NAcc (Knutson *et al*, 2008; Pizzagalli *et al*, 2009). Studies in BD reported more heterogeneous results, probably due to a higher variation of mood states. Compared to HC, individuals with BD showed elevated VS activity during hypomania (O'Sullivan *et al*, 2011), no differences or elevated activity in euthymic states (Caseras *et al*, 2013; Nusslock *et al*, 2012), but activity was decreased in euthymic to mildly depressed patients (Trost *et al*, 2014). Chase et al. (2013) is the first study that examined reward feedback in BD during depressive episodes and directly compared BD and UD. With a paradigm that included both anticipation and feedback phases, BD and UD showed less activity in the ACC than HC during reward anticipation, but there were no differences during reward outcome. Given the characteristics of the outcome phase used, it is likely that the activation during reward feedback not only reflects the reaction to the outcome, but is also influenced by the signed prediction error and reward. Therefore, the present study focuses on reward outcome, examining neuronal correlates of reward processing, and directly compares UD and BD suffering from depressive episodes.

Based on the previous research in UD (e.g., Pizzagalli et al., 2009), we hypothesized BD and UD to show reduced activity in the NAcc during reward processing, compared to HC. Due to the lack of studies exclusively focusing on reward feedback, no strong a priori hypothesis regarding group differences were made.

When investigating reward processing, alterations in one structure are likely associated with connectivity abnormalities within a larger system. Thus, it seems important to further investigate the functional interplay between the NAcc and other brain areas. Functional connectivity (Friston, 1994) allows to identify networks of brain regions showing patterns of co-activation throughout the time course of a task. With respect to the functional coupling between the NAcc and other reward-relevant brain areas, we predicted altered functional connectivity to prefrontal and striatal areas in both, BD and UD, based on previous research (Diekhof and Gruber, 2010; Diekhof *et al*, 2008).

2. Methods

2.1 Participants

The present study comprised 33 individuals with BD (mean age: 38.1, SD = 12.6 years), 33 individuals with UD (mean age: 38.5, SD = 12.1 years), and 34 HC (mean age: 38.6, SD = 12.3 years). The groups did not differ in age ($P = 0.88$), sex ($P = 0.72$) and years of education ($P = 0.18$). Further, both patient groups were comparable regarding several clinical variables including number of depressive episodes, time since onset of depression, total duration in depressive state, total duration of acute episode and medication load (all $Ps > 0.17$). However, more time since first inpatient treatment had elapsed for BD patients, and their cumulative life-time duration of inpatient treatment is also longer ($Ps < 0.02$; see **Table 1**). Patients were recruited from the inpatient service of the Department of Psychiatry, University of Muenster. HC were recruited by public notices and newspaper announcements. Diagnoses were verified with the structured clinical interview for DSM-IV (SCID-IV; (Wittchen *et al*, 1997)). All patients suffered from a current major depressive episode and fulfilled the criteria of either MDD or bipolar-I-disorder. For HC, any life-time psychiatric disorder was an exclusion criterion. For patients, additional comorbid life-time diagnoses of

any organic mental disorders, dementia, substance-related disorders, and schizophrenia/ schizoaffective disorders were exclusion criteria. There were no significant differences in comorbidity frequencies between both patient groups (all *Ps* > 0.15, see **Table 2**). All participants were free from any history of neurological abnormalities or brain injury, had normal or corrected-to-normal vision, and had adequate knowledge of German and cognitive abilities (verbal IQ > 80; multiple-choice vocabulary intelligence test MWT-B (Lehrl, 2005)). All participants received a financial compensation. The study was approved by the local IRB, and all participants provided written informed consent before study participation.

To measure total medication load, we used a strategy as described earlier (Redlich *et al*, 2014a). Each psychotropic medication was coded as absent = 0, low = 1 (equal or lower average dose), or high = 2 (greater than average dose), relative to the midpoint of the daily dose range recommended by *Physician's-Desk-Reference.* We calculated a composite measure of total medication load for each individual, reflecting dose and variety of different medications taken, by summing all individual medication.

2.2 Questionnaire Measures and Rating Scales

The Beck Depression Inventory (BDI; Beck and Steer, 1987; Hautzinger et al., 1994) was used to assess the presence of depressive symptoms. Additionally, the Hamilton Rating Scale of Depression (HAMD; Hamilton, 1960) was applied by a clinical interviewer as an objective depression measure. The Young Mania Rating Scale (YMRS, Young et al., 1978) was used to assess manic symptoms.

In order to control for effects of childhood maltreatment and unspecific trait anxiety, the Childhood Trauma Questionnaire (CTQ, Bernstein et al., 1994) and the State-Trait Anxiety Inventory (STAI-trait version; Spielberger et al., 1970) were administered as self-evaluation-questionnaire.

2.3 Materials and Procedure

We employed a card-guessing paradigm (Forbes *et al*, 2009) to detect brain activity associated with reward processing. Participants were told that the final amount of their monetary reward would depend on their performance on the card game, and were unaware that the outcome was actually fixed (10 €).

The pseudo-random blockdesign paradigm comprised 9 blocks: 3 "win" blocks (block 1, 4, 7), 3 "lose" blocks (block 2, 5, 8) and 3 control blocks (block 3, 6, 9), with each block consisting of 5 trials. During each trial, subjects had 3 seconds (s) to guess whether the value of a visually presented card was lower or higher than 5. After the choice was made, the numerical value of the card was shown for 0.5 s, followed by feedback (red downward-oriented arrow for negative feedback, green upward-oriented arrow for positive feedback) for an additional 0.5 s. When positive feedback was given, subjects were asked to confirm the gain via button press. Finally, a crosshair was presented for 1.5 s after odd-numbered stimuli throughout the whole paradigm (e.g. for the first, third, fifth stimulus, etc.), and for 2.5 s after even-numbered stimuli (e.g. for the second, fourth, sixth stimulus, and so on), resulting in a total trial duration of 5.5 s, respectively 6.5 s.

During the three "win" blocks, predominantly positive feedback (four trials, 80% correct) was given whereas during the three "lose" blocks predominantly negative feedback (four trials, 80% false) was given. For each positive feedback, a fictional amount of 1 € was added, while for each negative feedback, a fictional amount of 50 Cents was subtracted. The "win" and "lose" blocks were interleaved with three control blocks. During control blocks, subjects were requested to press the button during the presentation of an 'x' (3 s), followed by an asterisk (0.5 s), a yellow circle (0.5 s) and a crosshair (again 1.5 s for odd-numbered stimuli; 2.5 s for even-numbered stimuli). All blocks were preceded by an instruction (3 s) resulting in a total block length of 32.5 s for odd-numbered blocks and 33.5 s for even-numbered blocks yielding a total task length of 296.5 s.

2.4 fMRI Data Acquisition and Analysis

T2* functional data were acquired with a 3 Tesla scanner (Gyroscan Intera 3T, Philips Medical Systems, Best, NL), using a single-shot echoplanar sequence, with parameters selected to minimize distortion in the region of central interest, while retaining adequate a signal-to-noise ratio (S/N) and T2* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64x64, resolution 3.6 mm × 3.6 mm × 3.6 mm; TR = 2.1 s, TE = 30 ms, FA = 90°). The slices were tilted 25° from the AC/PC line in order to minimize drop out artifacts in the mediotemporal and orbitofrontal region.

All stimuli were projected to the rear end of the scanner (Sharp XG-PC10XE with additional HF shielding). During the experiment, subjects lay supine in the MRI scanner with the response box in their right hand. The head position was stabilized with a vacuum head cushion.

Data were analyzed using statistical parametric mapping software (SPM8, Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Functional data were preprocessed, including realignment, unwarping, and spatial normalization of each participant's functional images to the Montreal Neurological Institute International Consortium (MNI) for Brain Mapping template. Images were smoothed with a Gaussian kernel of 6 mm full-width at half-maximum (FWHM).

The onsets and durations of the experimental conditions (win, loss, control) were modeled using a canonical hemodynamic response function in the context of a GLM, and the model was corrected for serial correlations. A high-pass filter of 128 s was used to remove low-frequency noise.

For each subject, two contrast images were generated in each individual 1st-level analysis (win > control, loss > control). One bipolar depressive patient and two unipolar

depressive patients had to be excluded due to excessive head movement (exclusion criterion 3 mm / 3°).

2nd-level analyses. We calculated a 3 (group: UD vs. BD vs. HC) × 2 (condition: reward > control vs. loss > control) ANOVA, using a full-factorial model, with group as between-subjects factor and reward condition as within-subjects factor. To explore the nature of the interaction, post-hoc analyses were conducted.

To address our hypotheses on differential NAcc responsiveness to reward feedback, ROI-analyses of the bilateral NAcc were performed. A whole-brain analysis was also conducted.

The mask for bilateral NAcc was created with the aid of the WFU PickAtlas (Maldjian *et al*, 2003), dilating the defined mask by 1 mm according to the IBASPM atlas (http://www.fil.ion.ucl.ac.uk/spm/ext/#IBASPM; Aleman-Gomez, Y., Melie-Garcia, & Valdes-Hernandez, 2006). To control for multiple statistical testing, cluster-level false-positive detection rate was kept at $P< 0.05$, using a voxel-level threshold of $P < 0.01$ with a cluster extent (k) empirically determined by Monte Carlo simulations (n = 1000 iterations). This was performed by means of the AlphaSim (Forman *et al*, 1995) procedure, implemented in the REST toolbox (http://restfmri.net/forum/index.php) as reported in previous publications (Dannlowski *et al*, 2014). The empirically determined cluster threshold was $k = 14$ voxel for the bilateral NAcc mask. A more conservative voxel-level threshold of $P < 0.0005$ was used for the whole-brain analysis. The ascertained cluster threshold was $k = 79$ voxel. The anatomical labeling was performed by means of the AAL-Toolbox (Tzourio-Mazoyer *et al*, 2002), and the Brodmann areas (BA) were identified with the Talairach Daemon atlas (http://www.talairach.org).

Functional connectivity analysis. An exploratory functional connectivity analysis was conducted to characterize alterations associated with diagnostic status in the functional coupling between the NAcc and other brain areas. The methods for functional connectivity

analyses have been described previously (Dannlowski *et al*, 2009; Redlich *et al*, 2014b). Briefly, for each subject the signal time course of the entire left NAcc ("seed" region) was extracted and entered into a new 1st level model of the same subject predicting brain activity by the NAcc time series. The experimental conditions were modeled as nuisance regressors to avoid co-activation by the task. Based on the resulting contrast images, we performed a 2nd-level one-way ANOVA with experimental group as factor, using the same statistical threshold as above ($P < .0005$, $k = 79$).

3. *Results*

3.1 ANOVA Analysis

The ROI-analysis with the 3 (group) × 2 (condition) ANOVA revealed a significant condition × group interaction within the bilateral NAcc (right: x = 14, y = 10, z = -6; $F_{(2,188)}$ = 9.05; $P < 0.001$; k = 79 voxels, left: x = -14, y = 14, z = -12; $F_{(2,188)}$ = 7.21; $P = 0.001$; k = 38 voxels). Post-hoc analyses revealed significantly lower activation of the NAcc in BD compared to UD (right: x = 18, y = 6, z = -10; $T_{(61)}$ = 3.64; $P < 0.001$; k = 71 voxels, left: x = -8, y = 6, z = -8; $T_{(61)}$ = 3.02; $P < 0.001$; k = 47 voxels) and to HC (right: x = 18, y = 10, z = -10; $T_{(63)}$ = 4.62; $P < 0.001$; k = 90 voxels, left: x = -16, y = 8, z = -12; $T_{(63)}$ = 3.93; $P < 0.001$; k = 54 voxels). These differences only emerged in the reward > neutral condition, not in the loss > control condition (see **Figure 1** for details). Next, UD also showed a significantly lower activation of the NAcc than HC (right: x = 14, y = 14, z = -8; $T_{(62)}$ = 3.08; $P = 0.001$; k = 40 voxels), again exclusively in the reward > control condition. There also was a significant main effect of condition in the bilateral NAcc (right: x = 10, y = 8, z = -10; $F_{(1,188)}$ = 53.85; $P < 0.001$; k = 88 voxels, left: x = -8, y = 8, z = 10; $F_{(1,188)}$ = 55.45; $P < 0.001$; k = 54 voxels), resulting from overall higher activity for reward > neutral than for loss > neutral. Furthermore, a main effect of group emerged (right: x = 20, y = 10, z = -12; $F_{(2,188)}$ = 7.84; $P = 0.001$; k = 60 voxels, left: x = -14, y = 10, z = -10; $F_{(2,188)}$ = 5.41; $P = 0.005$; k = 30 voxels). Post-hoc T-tests revealed overall higher activity for HC than for BD (right: x = 20, y = 10, z = -12; $T_{(63)}$ = 3.68; $P < 0.001$, 86 voxels; left: x = -14, y = 10, z = -10, $T_{(63)}$ = 3.18; $P = 0.001$, k = 47 voxels) as well as for UD (right: x = 14, y = 14, z = -8, $T_{(62)}$ = 3.08; $P = 0.001$, k = 40 voxels) (see **Figure 1**).

The whole-brain analysis of the 3 (group) × 2 (condition) ANOVA yielded 6 clusters showing an condition × group interaction, comprising the caudate nucleus including the

NAcc, thalamus, putamen, insula, and prefrontal areas including the orbitofrontal cortex. The interaction was due to decreased activation in the reward condition in BD, compared to HC and UD (See **Table 3** for details). There were no significant group differences for the loss > control condition.

The functional connectivity analysis of the NAcc yielded a significant main effect of group, mapping to the VTA (x = -2, y = -24, z = -6; $F_{(94)} = 15.03$; $P < 0.00001$; $k = 81$ voxels). Post-hoc T-tests revealed a higher functional connectivity in UD compared to HC between the NAcc and the VTA (x = -2, y = -24, z = -8; $T_{(62)} = 5.01$; $P < 0.0001$; $k = 158$ voxels). No significant differences were found in BD compared to both UD and HC with this rigorous threshold. A higher connectivity in BD compared to HC emerged as a trend that did not survive the cluster-extent threshold of 79 voxels (x = 0, y = -24, z = -4; $T_{(63)} = 4.25$; $P < 0.0001$; $k = 60$ voxels).

4. Discussion

The present study investigated neural correlates of reward processing and directly compared patients with UD and BD, and also included functional connectivity analyses. Our results revealed an overall lower activity in the NAcc in both BD and UD, compared to HC, as well as differences between the patient groups, with reduced reward responsiveness in BD when compared to UD, in the NAcc, thalamus, putamen, insula, and prefrontal areas. We also found alterations in functional connectivity between the NAcc and the VTA when comparing UD to HC, and a trend for such changes when comparing BD and HC. The changes involved a higher functional coupling between the NAcc and the VTA in the patients.

These results indicate changes in reward processing in UD and BD during depressive mood states. In contrast to Chase et al. (2013), both groups showed reduced activity in the NAcc. Given the differences between our paradigm and Chase's, the findings are not contradictory but rather expected. The NAcc is described as a region that integrates reward-related information and, in case of increased dopaminergic transmission, contributes to positive emotion (Schultz, 1998). More explicitly, patients that suffer from a depressive episode seem to have a reduced hedonic effect of rewarding stimuli than healthy subjects. The inability to experience pleasure from commonly pleasant and rewarding stimuli is one of the two core symptoms in depressive episodes. Reduced reactivity of the NAcc observed in depressed subjects could therefore represent the neurobiological basis of anhedonia, as already suggested in other studies (Keedwell *et al*, 2005; Keller *et al*, 2013). In theory, rewards are needed for the organization of voluntary goal-directed behavior (Schultz, 2000). With a lack of this hedonic effect, it seems more likely that patients could be seeking less frequently for rewards.

Along with the lower activity in the NAcc in BD and UD, compared to HC, we observed a higher functional connectivity between the NAcc and the VTA in UD than in HC, and a threshold trend in the same direction between BD and HC. There were no reliable differences between the patient groups. Reward processing is based on a neuronal circuitry including regions of the mesolimbic dopamine system, consisting of dopamine producing midbrain nuclei (particularly VTA) and their subcortical (e.g., NAcc) and cortical (e.g., OFC and MPFC) target regions (Diekhof *et al*, 2008; Liu *et al*, 2011). The VTA-NAcc-pathway seems to play a crucial role in reward processing, and its manipulation via dopaminergic transmission can regulate depression-like behavior (Keller *et al*, 2013). Thus, it is not surprising that altered connectivity is observed in UD as well as in BD – as a trend that failed statistical criteria. It is interesting that the VTA was the only region showing a significant functional connectivity with the NAcc. Note that connectivity was higher in patients than in controls, which seems counterintuitive. A higher functional coupling between these regions should – regarding their non-inhibitory connection – lead to more innervation of the NAcc by the VTA, but our data demonstrate the opposite. A possible explanation for the higher functional connectivity between NAcc and VTA might be compensatory mechanisms, such as up-regulation of postsynaptic dopamine receptors due to a reduction in dopamine release. Note however that studies of dopamine receptor binding in major depressive disorder have been inconsistent (for an overview see Dunlop and Nemeroff, 2011).

The comparison of the patient groups further revealed a significantly reduced reward responsiveness of the NAcc in BD compared to UD, which might be due to a greater impairment in the structures of the mesolimbic system in BD. The difference between BD and UD may be related to the course of disease: The mesolimbic system of subjects with BD has to deal with manic and hypomanic mood states, phases of elevated mood, during which patients excessively seek for rewarding activities and stimuli (American Psychiatric Association, 2000). Studies with hypomanic patients show elevated VS activity in response to

rewarding stimuli (O'Sullivan *et al*, 2011). A down-regulation of NAcc sensitivity in consequence of these mood states could explain the observed lower reactivity of the NAcc - despite a tendency of higher functional connectivity between NAcc and VTA. The idea of blunted neural responses toward reward has also been proposed for addictive disorders (Martinez *et al*, 2005; Volkow *et al*, 2010). However, this interpretation should be taken with care, because our cross-sectional study design does not allow for more specific conclusions.

Besides differences in the NAcc, the whole-brain analysis revealed reduced activity during reward processing in other reward-related structures, such as the putamen, the caudate nucleus, and the insula, only in BD compared to UD and HC. These specific differences were not found in UD, indicating that the alterations of the mesolimbic system in BD involve the VTA-NAcc-pathway as well as larger parts of the reward circuitry. These results correspond well with findings from meta analyses investigating structural alterations in BD, repeatedly reporting altered insula and basal ganglia structure in BD compared to HC (Bora *et al*, 2012). Similarly, functional MRI studies high-lighted the role of the insula for reward processing in BD (Phillips *et al*, 2008a).

Together, the results indicate a decisive alteration of brain function associated with the dopamine system particularly in BD. The reported neurobiological alterations might reflect a more severe course of disease, and a prevalently poorer outcome in BD than in UD.

Conclusion

Our results may help to refine the neural correlates of reward processing in both affective disorders, and to understand the neural underpinnings of anhedonia as a core symptom of depressive episodes. While the differentiation of BD and UD disorders remains difficult in clinical practice, we showed that they are associated with different patterns of neural activation during reward processing. This seems to concern primarily parts of the VS and the insula. The reward system has an important role in neurobiology and in the treatment

of affective disorders, especially in BD. Future studies should aim to replicate and refine these results.

Limitations

First, all but two patients were medicated and thus differed from healthy controls. Furthermore, the patient groups differed regarding the distribution of medication. However, the total medication load did not differ between patient groups. Furthermore, studies on the effect of psychotropic medication found only a limited impact on fMRI results, revealing normalizing effects, if any (Hafeman *et al*, 2012; Phillips *et al*, 2008b).

Second, the results of the functional connectivity analysis are a correlative approach only and should therefore not be interpreted as proving the presence of structural or causal connections. However, in view of neurochemical studies (e.g. Wickham *et al*, 2013) the assumption that correlations between these areas are primarily based on neuronal connections from VTA to NAcc seems likely.

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Table 1. Sociodemographic and clinical characteristics.

	BD Sample (n = 33)		UD Sample (n = 33)		t-test or χ^2-test	HC Sample (n = 34)	
	Mean	SD	Mean	SD	p-value	Mean	SD
Soziodemographic Characteristics							
Age	38.12	12.55	38.48	12.08	0.91	38.59	12.28
Sex (m / f)	17/ 16		16 / 17		0.81	18 / 16	
Total Education Time	14.76	2.06	14.18	1.83	0.23	14.85	2.20
Verbal IQ	111.58	16.10	111.55	11.76	0.99	118.71	11.53
Questionaires							
BDI	24.85	8.60	27.88	9.29	0.17	1.88	2.51
HAMD	22.88	4.55	24.56	5.92	0.20	1.24	1.37
CTQ	44.88	19.25	41.15	12.05	0.35	34.53	10.05
YMRS	2.45	2.43	1.56	1.66	0.09	0.29	0.68
STAI	57.56	10.75	60.94	9.10	0.18	30.47	6.20
Clinical Characteristics							
Number of depressive episodes	6.73	5.47	4.33	4.02	0.47	n/a	
life-time cumulative duration of depressive states (month)	26.18	21.57	29.68	28.23	0.57	n/a	
Number of manic episodes	3.52	3.73	n/a			n/a	
Life-timecumulative duration of manic states (month)	5.72	6.30	n/a			n/a	
Time since onset of first depressive episode (months)	138.45	123.07	100.15	97.02	0.17	n/a	
Time since first inpatient treatment (months)	83.41	18.54	25.47	9.86	0.01	n/a	
life-time cumulative duration of inpatient treatment (weeks)	26.12	41.40	8.21	10.64	0.02	n/a	
Duration of current episode (weeks)	14.09	13.20	23.76	29.31	0.89	n/a	
Medical Characteristics							
Medication Load Index	3.18	2.13	2.58	1.54	0.19	n/a	
Antidepressants							
SSNRI	8		26		<0.01		
SSRI	5		6		0.74		
SNRI	1		0		0.31		
Tricyclic antidepressants	2		3		0.64		
MAO-Inhibitor	2		0		0.15		
Agomelantine	1		7		0.02		
Mood-Stabilizer	17		3		<0.01		
Antipsychotics	24		14		<0.01		
No Medication	1		1		1		
Monotherapy	8		15		0.07		

Abbreviations: BD, bipolar-I-disorder; UD, unipolar depressive disorder; HAMD, Hamilton Depression Rating Scale; CTQ, Childhood Trauma Questionnaire; YMRS, Young Mania Rating Scale; STAI, State Trait Anxiety Inventory; SSNRI, Selective Serotonin Noradrenaline Reuptake Inhibitor; SSRI, Selective Serotonin Reuptake Inhibitor, SNRI, Selective Noradrenaline Reuptake Inhibitor; MAO, Monoamine Oxidase Inhibitor.

Table 2. Lifetime Comorbidities

	BD Sample (n = 33)	**UD Sample** (n = 33)	**χ^2 p-Value**
Panic Disorder / Agoraphobia	5	8	0.35
Social Phobia	4	3	0.69
Specific Phobia	3	3	1
Obsessive Compulsive Disorder	3	1	0.31
Post-traumatic Stress Disorder	2	1	0.56
Somatoform Disorder	0	2	0.15
Eating Disorder	1	1	1

Abbreviations: BD, Bipolar Depression; UD; Unipolar Depression.

Table 3. Results of the 3 (Group) x 2 (Condition) ANOVA *

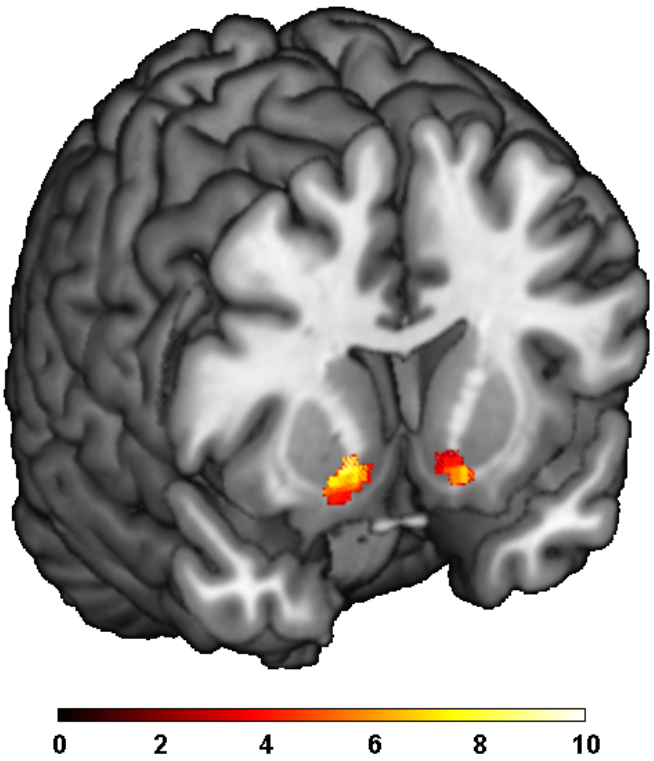
	BA	Cluster Size (k)	MNI (at peak) x	y	z	Side	*F*-value / *T*-value
ANOVA							
Caudate Nucleus incl. NAcc / Thalamus	-	1108	16	10	16	R	18.34
Superior Frontal Gyrus / Middle Frontal Gyrus	10	223	-22	54	12	L	17.87
Inferior Frontal Gyrus, orbital part / Putamen	47 / 13 / 34	663	-30	24	-22	L	14.87
Superior Frontal Gyrus, medial part / / Anterior Cingulate Gyrus	9 / 10	155	12	42	26	R	14.08
Superior Temporal Gyrus / Operculum	42 / 40 / 41	110	64	-24	14	R	12.24
Putamen, Caudate Nucleus incl. NAcc	-	131	6	12	2	R	11.96
HC > BD (Reward > Control)							
Insula / Caudate Nucleus incl. NAcc / Putamen / Thalamus / Hippocampus / Inferior Frontal Gyrus, orbital part / Pallidum / Amygdala	47 / 13 /45 /11 /22 / 44 / 34 / 28	4636	-36	14	6	L	5.44
Inferior Parietal Gyrus / Superior Parietal Gyrus	40 / 7	166	44	-60	46	R	5.06
Fusiform Gyrus / Cerebellum	19	202	32	-60	-14	R	4.94
Inferior Parietal Gyrus / Superior Parietal Gyrus / Angular Gyrus	9 / 10	333	-28	-66	44	L	4.78
Middle Cingulate Gyrus / Anterior Cingulate Gyrus / Superior Frontal Gyrus	24 / 32 / 6	426	2	12	28	R	4.61
Middle Frontal Gyrus / Precentral Gyrus	9 / 8	526	-46	24	40	L	4.59
Cuneus / Calcarine Gyrus / Superior Occipital Gyrus	18 / 31 / 19	119	20	-80	24	R	4.56
Superior Medial Frontal Gyrus	9	186	2	46	30	R	4.5
Precentral Gyrus / Postcentral Gyrus	4 / 6 / 3	173	46	-22	60	R	4.36
UD > BD (Reward > Control)							
Precentral Gyrus / Postcentral Gyrus	3 / 6 / 4	208	44	-24	60	R	4.85
Insula / Operculum / Temporal Pole	13 / 22 / 6	319	50	-4	2	R	4.69
Insula / Superior Temporal Gyrus / Transverse Temporal Gyrus	13 / 22	135	-44	-8	0	L	4.41
Superior Temporal Gyrus	41 / 40 / 42	150	62	-24	16	R	4.36
Putamen / Caudate Nucleus incl. NAcc	-	122	-10	0	6	L	4.06
Insula / Putamen	47 /13	115	26	16	-18	R	3.95

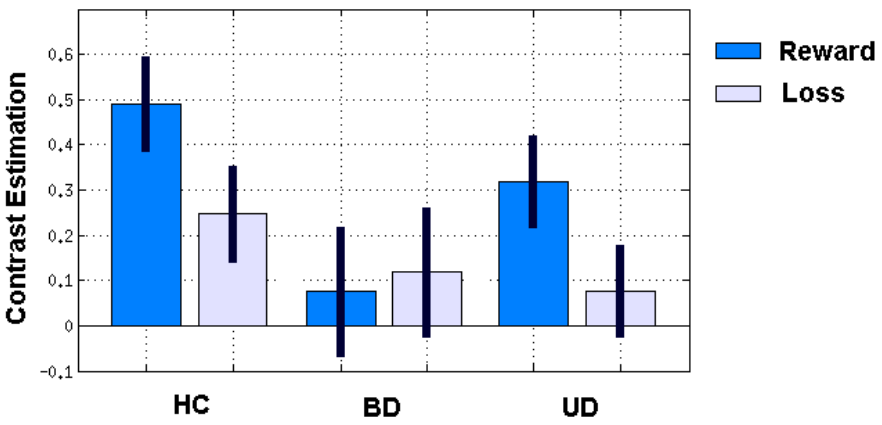
Abbreviations: BA, Brodmann Area; MNI, Montreal Neurologic Institute; HC, Healthy Controls; BD, Bipolar Disorder; UD, Unipolar Depression; NAcc, Nucleus Accumbens.

* Analyses were conducted with a voxel-threshold of $P< 0.0005$ and a minimum cluster volume threshold $k\geq 79$ as determined by AlphaSim. Coordinates based on MNI atlas.

Figure 1.

Left: Coronal slice (MNI coordinates at y = -4) depicting the results of the 2 X 3 ANOVA interaction within the NAcc. Color bar: F-value. Right: The bars depicting the estimated contrast values for HC (Healthy Controls), BD (Bipolar Disorder) and UD (Unipolar Depression) for the reward > control (dark blue) and loss > control (light blue) condition. Abbreviations: MNI, Montreal Neurological Institute.


0
2
4
6
8
10


Contrast Estimation
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
HC
BD
UD
Reward
Loss