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Altered Representation of Expected Value in the Orbitofrontal Cortex in Mania

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Abstract: Objective: Increased responsiveness to appetitive and reduced responsiveness to aversive anticipatory cues may be associated with dysfunction of the brain reward system in mania. Here we studied neural correlates of gain and loss expectation in mania using functional magnetic resonance imaging (fMRI). **Method:** Fifteen manic patients and 26 matched healthy control individuals performed a monetary incentive delay task, during which subjects anticipated to win or lose a varying amount of money. Varying both magnitude and valence (win, loss) of anticipatory cues allowed us to isolate the effects of magnitude, valence and expected value (magnitude-by-valence interaction). **Results:** Response times and total gain amount did not differ significantly between groups. FMRI data indicated that the ventral striatum responded according to cued incentive magnitude in both groups, and this effect did not significantly differ between groups. However, a significant group difference was observed for expected value representation in the left lateral orbitofrontal cortex (OFC; BA 11 and 47). In this region, patients showed increasing BOLD responses during expectation of increasing gain and decreasing responses during expectation of increasing loss, while healthy subjects tended to show the inverse effect. In seven patients retested after remission OFC responses adapted to the response pattern of healthy controls. **Conclusions:** The observed alterations are consistent with a state-related affective processing bias during the expectation of gains and losses which may contribute to clinical features of mania, such as the enhanced motivation for seeking rewards and the underestimation of risks and potential punishments. *Hum Brain Mapp 31:958–969, 2010.* © 2009 Wiley-Liss, Inc.

Key words: dysfunction; bipolar disorder; mood-congruent processing bias; functional magnetic resonance imaging; monetary incentive delay task; gain and loss anticipation; reward system

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INTRODUCTION

A fundamental role of neural circuits that support motivation is to regulate approach and avoidance behavior in response to anticipatory cues [Berridge and Robinson, 1998; Panksepp, 1998]. Expectations about gains and losses constitute an important basis for decision making [Knutson et al., 2005]. Clinical observation suggests altered anticipatory cue processing in mania, leading to changes in assigning motivational value to anticipated appetitive and aversive outcomes: patients with mania show exaggerated responsiveness to anticipatory cues signaling future rewards, evidenced by an enhanced motivation for seeking pleasure, increased sociability and hypersexual behavior [Association, 2000; Gray 1994,; Kaplan and Sadock, 1997]. At the same time, mania is characterized by reduced responsiveness to aversive anticipatory cues: manic patients show decreased motivation to withdraw from possible negative outcomes and tend to underestimate risks and potential punishments, which can result in loss of normal social inhibitions, unrestrained buying sprees, reckless driving, or impulsive business decisions. Consistent with these clinical observations, self-reported sensitivity to appetitive anticipatory cues correlates with manic symptoms in individuals at risk for bipolar disorder [Meyer et al., 1999] and with manic symptom intensification over time in patients diagnosed with bipolar disorder [Meyer et al., 2001]. Altered reactivity to anticipatory cues may emerge from overly optimistic success expectations [reported for a coin-toss task by Johnson, 2005; Stern and Berrenberg, 1979] and results in impaired decision-making strategies [as observed in the Cambridge Decision Making Task by Murphy and Sahakian, 2001].

Functional magnetic resonance imaging (fMRI) studies in healthy subjects have identified brain regions involved in processing appetitive and aversive anticipatory cues [Breiter et al., 2001; Jensen et al., 2003; Knutson et al., 2001; O'Doherty et al., 2002]. These brain regions include the ventral striatum (including the nucleus accumbens), the amygdala, the medial prefrontal and the orbitofrontal cortex, i.e., brain regions that are part of the mesolimbic dopaminergic system. Clinical and neuropsychological observations of abnormal gain and loss anticipation in mania may indicate a dysfunction of this circuitry. This hypothesis is supported by the effectiveness of antidopaminergic medications in the treatment of mania and by functional neuroimaging studies showing alterations in these brain regions in mania. Specifically, morphometric studies report reduced prefrontal volumes [Lopez-Larson et al., 2002; Sax et al., 1999] and increased striatal size in bipolar disorder [Strakowski et al., 2002]. FMRI and Positron Emission Tomography (PET) studies in mania revealed alterations in prefrontal (including orbitofrontal) and ventral striatal brain function using different cognitive and emotional tasks, including resting state [Al-Mousawi et al., 1996], emotional face-matching [Altshuler et al., 2005a], probability-based decision-making [Rubinsztein et al., 2001], motor inhibition [Leibenluft et al., 2007], word generation [Blumberg et al., 1999], affective go/no-go [Elliott et al., 2004], and letter-based go/no-go [Altshuler et al., 2005b]. However, although several studies have examined the perception of pleasant and unpleasant stimuli in mania [Abler et al., 2008; Altshuler et al., 2005a; Bermpohl et al., 2009], investigations directly addressing the anticipation of gain and loss outcomes have only recently begun [Abler et al., 2008].

Here we examine gain and loss anticipation in mania, using a previously established monetary incentive delay (MID) task [Knutson et al., 2001]. Thus focusing on monetary aspects of reward anticipation, the present task may particularly relate to clinical symptoms like unrestrained buying sprees and impulsive business decisions. During the MID task, participants see anticipatory cues indicating that they may win a certain amount of money (gain expectation), wait for a variable anticipatory delay period, and then respond to a target with a rapid button press to win the money (gain receipt). The gain expectation period of this task reliably increases blood oxygen level-dependent signal (hereafter, "activation") in the mesolimbic system (including the ventral striatum and the orbitofrontal cortex) in healthy individuals [Juckel et al., 2006b; Kirsch et al., 2003; Knutson et al., 2001; Wrase et al., 2007].

Studying gain anticipation and receipt in manic patients compared to healthy controls, Abler et al. [Abler et al., 2008] found significant group differences during gain receipt (with blunted ventral striatal responses in the manic group), but not during gain anticipation. Here we again address the anticipation of incentives in mania. The present study differs from the study by Abler et al. [Abler et al., 2008] in that it includes both gain and loss conditions and does not involve a decision component. In addition, we use a parametric modulation approach to analyze BOLD responses to anticipatory cues which allows modeling all anticipatory conditions at once and, importantly, disentangling the effects of expected magnitude, expected valence, and, in particular, expected value (magnitude-by-valence interaction, here with fixed probabilities).

Overall, we predict altered anticipatory cue processing in mania: based on prior neuroimaging studies of gain and loss anticipation in healthy subjects [Juckel et al., 2006b; Kirsch et al., 2003; Knutson et al., 2001; Wrase et al., 2007] and on prior neuroimaging studies in mania (mostly unrelated to grain and loss anticipation) [Abler et al., 2008; Al-Mousawi et al., 1996; Altshuler et al., 2005a,b; Blumberg et al., 1999; Elliott et al., 2004; Leibenluft et al., 2007; Rubinsztein et al., 2001], our hypotheses focus on the ventral striatum, the medial prefrontal and the orbitofrontal cortex. Given the clinical and neuropsychological observations of increased responsiveness to appetitive and decreased responsiveness to aversive anticipatory cues in mania, we expect stronger responses to increasing gain anticipation and weaker responses to increasing loss anticipation in these brain areas. In our parametric MID task, this would correspond to a group difference between

TABLE I. Demographic and clinical characteristics of study groups

Characteristic	Manic ($n = 15$)	Remitted ($n = 7$)	Controls ($n = 26$)
Sex, F/M, No.	7/8	4/3	11/15
Age, mean ± SD, y	38.6 ± 13.7	36.1 ± 11.1	38.7 ± 13.7
Smoker, No.	8	5	12
Verbal IQ (WST), mean ± SD	113.7 ± 9.8	113.0 ± 11.1	108.0 ± 8.3
Response time, mean ± SD, ms	284.8 ± 110.5	250.9 ± 48.6	268.5 ± 96.0
Total gain, mean ± SD	28.4 ± 19.4	38.0 ± 21.3	31.9 ± 15.1
Duration of illness, mean ± SD, y	16.2 ± 9.1	17.3 ± 10.9	—
Manic episodes, mean ± SD, No.	4.4 ± 3.7	3.7 ± 2.1	—
Depressive episodes, mean ± SD, No.	3.7 ± 4.1	3.3 ± 2.1	—
Psychiatric hospitalizations, mean ± SD, No.	2.4 ± 1.8	2.0 ± 1.4	—
Psychotropic medication naïve, No.	0	2	—
Psychotropic medication, No.			
Lithium	8 (37 mmol)	4 (35 mmol)	—
Valproic acid	5 (1480 mg)	3 (1250 mg)	—
Carbamazepine	1 (1200 mg)	0	—
L-Thyroxine	3 (67 μg)	1 (100 μg)	—
Quetiapine	8 (407 mg)	1 (200 mg)	—
Olanzapine	2 (12.5 mg)	0	—
Risperidon	1 (1 mg)	0	—
Zuclopenthixoldecanoat	1 (100 mg)	0	—
YMRS score, mean ± SD	18.9 ± 6.2	3.2 ± 2.7	—

Abbreviations: F, female; m, male; No, number; SD, standard deviation; y, years; YMRS, Young Mania Rating Scale; IQ, intelligence quotient; WST, Wortschatztest (Vocabulary Test). The family history refers to first degree relatives. Mean dosages are listed for medications.

manic patients and healthy controls in the representation of expected value (i.e., a group-by-magnitude-by-valence interaction). On the basis of neuroimaging studies showing that treatment can reverse alterations in bipolar disorder [Blumberg et al., 2005; Haldane et al., 2008; Phillips et al., 2008], we also predict normalization with remission, reflected in group differences between acutely manic and remitted patients, but not between remitted patients and healthy controls.

METHODS

Subjects

Sixteen patients with bipolar I disorder admitted to the Department of Psychiatry at the Charité and 26 healthy controls were included in the study (Table I). During the main fMRI investigation all patients met DSM-IV criteria for an acute manic episode (Structured Clinical Interview for DSM-IV Axis I Disorders, First et al., 2001] and showed Young Mania Rating Scale (YMRS) scores $\geq$13 (maximum score reachable: 56, Young et al., 1978]. Data of one manic patient could not be analyzed due to technical problems. Seven patients were scanned for a second time (T2) in the remitted state (DSM-IV; YMRS $\leq$8). The average time interval between T1 and T2 was 38 weeks (range, 9–100 weeks).

Healthy controls had no psychiatric Axis I or II disorder (SCID-interview, First et al., 1997,2001]. The three study groups (manic, remitted, controls) did not differ significantly with regard to age ($F = 0.06$; $P = 0.94$), gender (Chi-Square = 0.49, $P = 0.79$), smoking behavior (Chi-Square = 1.68, $P = 0.43$), and verbal IQ ($F = 1.97$; $P = 0.15$). All study participants were right-handed [Oldfield, 1971]. Exclusion criteria were comorbid axis I disorder, current neurological or severe medical disorder, history of head injury resulting in loss of consciousness, and age below 18 or above 65 years. The study was approved by the local ethics committee and was compliant with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Monetary Incentive Delay Task

A monetary incentive delay (MID) task as previously described [Knutson et al., 2001] was used to induce anticipation of potential monetary gain, loss or no consequences. The subjects' monetary gain depended on their performance in a simple reaction time task (Fig. 1a).

In each trial, subjects saw one of seven geometric figures (anticipatory cues), which indicated that they could either gain or prevent losing different amounts of money via a fast button press in response to a target cue (white square). Number of horizontal lines (one, two, or three)

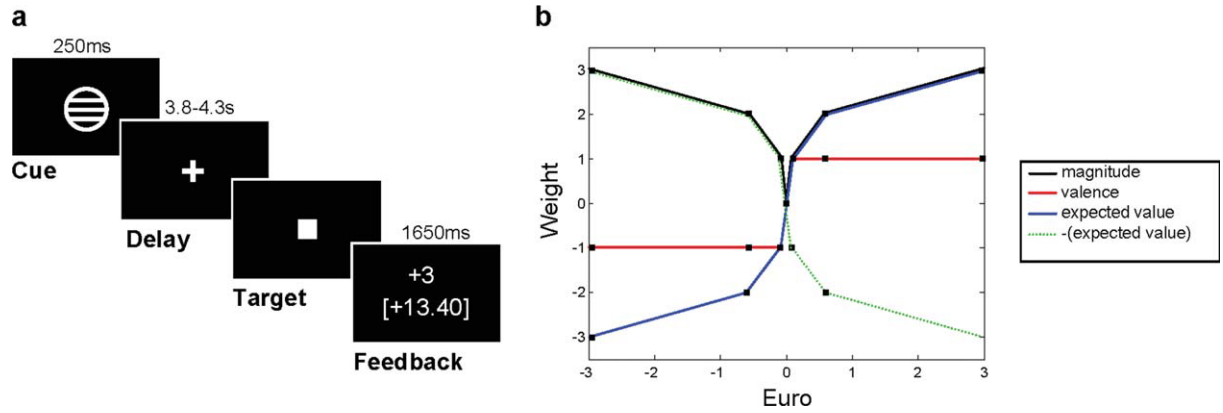

Figure 1.

Experimental Design. (**a**) Monetary incentive delay task (example trial). In each trial an incentive cue indicates the amount of money that can be gained or lost. Subjects had to react to the white target square in order to gain or avoid losing money. Subsequently, feedback was given. (**b**) FMRI data were modeled using magnitude, valence, and expected value (magnitude-by-valence interaction) as parametric regressors of interest. Illustrated are the weights that were used to model magnitude (black line), valence (red line) and expected value (blue line). Parametric analysis of cued incentive magnitude identifies brain regions that respond according to the following model: expectation of 3.00 [euro] gain or loss weighted with +3, 0.60 [euro] gain or loss with +2, 0.10 [euro] gain or loss with +1, and neutral outcome with 0 (analogously for valence and expected value). The dotted green line illustrates the negative magnitude-by-valence interaction. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

indicated incentive magnitude (0.10 [euro], 0.60 [euro], or 3.00 [euro], respectively), shape (circle or square) indicated incentive valence (potential gain or loss, respectively). No monetary outcome (0.00 [euro]) was denoted by a triangle. Before the target was presented, a variable interval (delay: 3,800, 4,050, or 4,300 ms) was implemented. Participants were instructed to respond to the target with a single button press as quickly as possible, independent of the preceding cue. After the button press, feedback appeared (1,650 ms). Subjects performed two scanning sessions, each consisting of 72 trials (27 potential gain, 27 potential loss and 18 neutral trials) in random order. Subjects were informed that they would receive the money from the scanning session in which they performed best. An adaptive algorithm for target duration (dependent on the individual response times) ensured in an online manner that subjects succeeded on an average of 67% of trials. Accordingly, the total monetary gain did not differ between the three groups ($F = 0.73$, $P = 0.49$).

Behavioral Data Analysis

Response time data was analyzed using a mixed ANOVA (SPSS) with the between-subjects factor group (healthy, manic, remitted) and the within-subjects factor value (−3.00, −0.60, −0.10, 0.00, 0.10, 0.60, 3.00 [euro]). The significance level was set to $P < 0.05$.

FMRI Data Acquisition

Functional magnetic resonance imaging (fMRI) was performed on a 1.5-T scanner (Magnetom VISION Siemens®) equipped with a standard circularly polarized 4-channel head coil using gradient echo-echo planar imaging. We used the following parameters: GE-EPI, TE 40 ms, flip angle 90°, matrix 64 × 64. To optimize signal-to-noise and minimize signal drop-out in our main target regions, the ventral striatum, the medial prefrontal and the orbitofrontal cortex, we used a voxel size of 4 × 4 × 3.3 mm. Eighteen slices were collected every 1.87 s approximately parallel to the bicommissural plane, covering the inferior part of the frontal lobe, the whole temporal lobe and large parts of the occipital region. The paradigm consisted of two sessions, resulting in a total of 144 trials (54 gain trials, 54 loss trials, 36 trials with neutral outcome). Totally, 450 volumes were acquired per session.

FMRI Data Analysis

Analyses focused on changes in activation during the expectation periods for both hit and miss trials. FMRI data were analyzed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). Preprocessing included slice time correction, realignment to the first volume, normalization to the standard EPI template of the Montreal Neurological Institute and smoothing using a 8 mm full width at half maximum Gaussian kernel. Movement did not differ significantly between the three groups (healthy, manic, remitted) for all translation (X: $F = 0.04$, n.s.; Y: $F = 2.86$, n.s.; Z: $F = 2.80$, n.s.) and rotation (pitch: $F = 0.13$, n.s.; roll: $F = 0.14$, n.s.; yaw: $F = 1.62$, n.s.) parameters (sum of absolute scan-to-scan movement).

The pre-processed fMRI data was then analyzed in the context of the general linear model (GLM), using a

parametric modulation approach as implemented in SPM [Buchel et al., 1998]. Parametric designs provide information about the relationship between one or more stimulus parameters and the BOLD response elicited by the stimulus. In this study, the onsets of the anticipatory cues were parametrically modulated by trialwise changes in the stimulus parameters (1) magnitude, (2) valence, and (3) their interaction (expected value). For this purpose, we defined one cue onset regressor with three parametric regressors (magnitude, valence, and expected value). The three resulting parameter estimates of the parametric regressors indicate the correlation between the observed BOLD signal and (1) magnitude, (2) valence, and (3) expected value, respectively, independent of cue processing per se. Although SPM standard analyses compare experimental conditions (categorical comparison), the parametric approach characterizes brain regions using their response profile in relation to specific stimulus parameters. In contrast to categorical analyses (e.g., analyses comparing gain and loss expectation conditions separately with neutral outcome anticipation), this parametric approach allows (1) including all cue conditions in one (onset) regressor and (2) studying the effects of valence, magnitude and expected value independent of each other. Figure 1b illustrates the weights that were used to model the parametric regressors, i.e., magnitude (expectation of 3.00 [euro] gain or loss weighted with +3, 0.60 [euro] gain or loss with +2, 0.10 [euro] gain or loss with +1, and neutral outcome with 0), valence (expectation of gain weighted with +1, loss with −1, and neutral outcome with 0), and their interaction (expected value; expectation of 3.00 [euro] loss weighted with −3, 0.60 [euro] loss with −2, 0.10 [euro] loss with −1, neutral outcome with 0, 0.10 [euro] gain with +1, 0.60 [euro] gain with +2, and 3.00 [euro] gain with +3). The weighting of the incentive magnitude attempts to reflect the psychological (subjective) rather than the monetary value of the incentive cue. This is in accordance with Kahnemann and Tversky [Kahneman and Tversky, 1979] who suggested that the value function is normally concave for gains and convex for losses. In contrast to some earlier studies on expected value in healthy subjects (e.g., Knutson et al., 2005], we did not include a probability variable in order to ensure sufficient power in the present study comparing patients with healthy controls. Though not involved in the main parametric analysis of this study, the feedback period was modeled as a regressor of no interest to avoid possible confounds in the cue period by subsequent feedback-related BOLD responses. The realignment parameters were included as additional regressors of no interest into the statistical model. The parametric regressors as well as the cue onset and feedback regressors were convolved with a hemodynamic response function (hrf) provided by SPM5. The parametric regressors were orthogonalized with respect to the cue onset regressor and then simultaneously regressed against the BOLD signal in each voxel.

In a first level analysis, parameter estimates of the parametric regressors were used to compute individual SPM maps for the factors magnitude, valence and expected value (i.e., magnitude-by-valence interaction). Individual SPM maps of healthy and manic subjects were included in a second level random effects analysis, identifying between-group differences with a *t*-test for independent groups. Our a priori interest lay in the ventral striatum, the medial prefrontal and the orbitofrontal cortex, based on theoretical considerations, findings in healthy subjects in this task and alterations reported in mania in different tasks. For this reason, an acceptable level of Type 1 error control for these regions only was $P < 0.001$, uncorrected, voxel level with an extent threshold $k = 5$ voxels [Hayasaka and Nichols, 2004]. Although we report all regions passing this threshold, we will focus our discussion on the regions that were hypothesized to be of interest.

The parametric modulation analysis revealed effects in the ventral striatum bilaterally and in the left lateral orbitofrontal cortex (cf. Figs. 2a and 3a). These clusters were used as regions of interest for further analyses.

To assess effects in the remitted group, parameter estimates of the magnitude effect were extracted from the left and right ventral striatal region of interest for all three study groups. Analogously, parameter estimates of the expected value effect were extracted from the left lateral orbitofrontal region of interest. Effects were then compared between remitted patients and the healthy control group (*t*-test for independent groups, two-tailed) as well as between remitted patients and the subgroup of manic patients that was scanned for a second time in the remitted state (paired *t*-test, two-tailed).

To further explore the pattern of activation in the regions of interest, an additional GLM was performed (standard SPM analysis), modeling the different anticipatory cues separately as explanatory variables convolved with a hrf. Again, movement parameters and the feedback period were included as regressors of no interest. Parameter estimates were extracted from the regions of interest for all groups and averaged across voxels.

To assess the acute impact of antipsychotic medication (exhibiting antidopaminergic effects) on effects observed in regions of interest in the parametric modulation analysis, we employed two strategies suggested by Phillips [Phillips et al., 2008]: First, we compared effects in patients taking ($n = 10$) versus those not taking ($n = 5$) antipsychotic medication. Second, we converted doses of antipsychotic medications into chlorpromazine dose equivalents [Woods, 2003], followed by correlational analyses to examine associations between medication doses and parameter estimates.

To study BOLD effects during the outcome period, another GLM was performed (standard SPM whole-brain analysis), modeling the following regressors: gain anticipation, neutral outcome anticipation, loss anticipation, win outcome (following gain anticipation), no-win outcome (following gain anticipation), neutral outcome (following

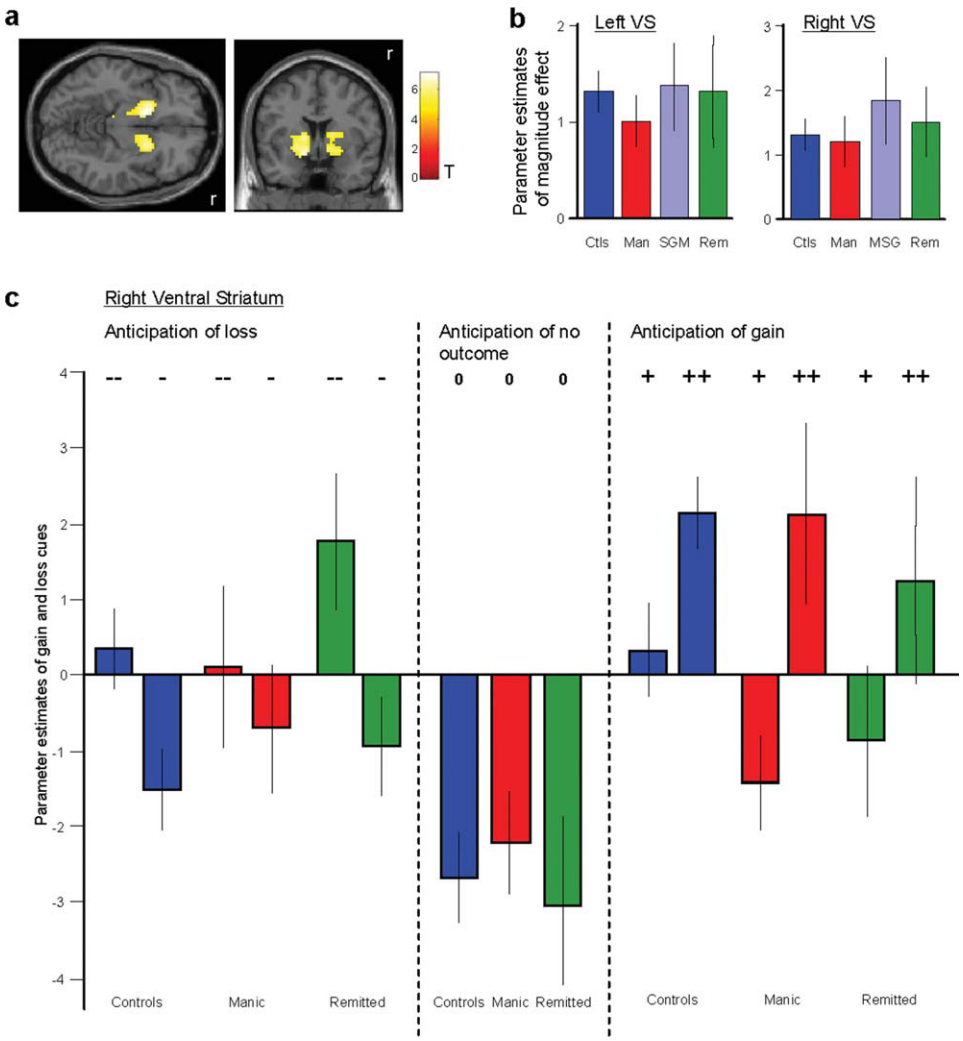

Figure 2.

Effect of magnitude. (**a**) Effects of cued incentive magnitude (SPM parametric modulation analysis). One-sample *t*-test; healthy control subjects and manic patients pooled to one group. SPM map presented in section views through the left ventral striatal peak voxel, $T = 7.14$; $x = -15$, $y = 3$, $z = -9$ (MNI space). Peak voxel in the right ventral striatum ($T = 6.18$) at $x = 21$, $y = 9$, $z = -9$ (MNI space). For illustration purposes the significance level was set at $P < 0.05$, FWE-corrected. R, right. (**b**) Parameter estimates for cued incentive magnitude in the left and right ventral striatum (SPM parametric modulation analysis). Effects are shown for healthy control subjects (Ctls), manic patients (Man), remitted patients (Rem), and the subgroup of manic patients that was re-tested after remission (SGM). Values refer to the functional regions of interest identified in Figure 2a (mean of ROI). Error bars show the standard error of the mean. VS, ventral striatum. (**c**) Parameter estimates for anticipatory cues in the right ventral striatum (standard SPM analysis, modeling the anticipatory cues separately as explanatory variables). Expectation of 3.0 [euro] gain (++), expectation of 0.1 [euro] gain (+), expectation of neutral outcome (0), expectation of 3.0 [euro] loss (–), expectation of 0.1 [euro] loss (−). Values refer to the functional region of interest identified in Figure 2a (mean of ROI). Error bars show the standard error of the mean. Very similar activations were found in the left ventral striatum. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

neutral outcome anticipation), loss outcome (following loss anticipation), and no-loss outcome (following loss anticipation). The contrasts "win > no-win" and "loss > no-loss" were compared between healthy and manic subjects (SPM *t*-test for independent groups; $P < 0.001$, uncorrected; $k = 5$ voxels).

RESULTS

Behavioral Performance

Reaction times for the button response given during fMRI were 268.5 ms (±96.0, mean ± SD) in healthy

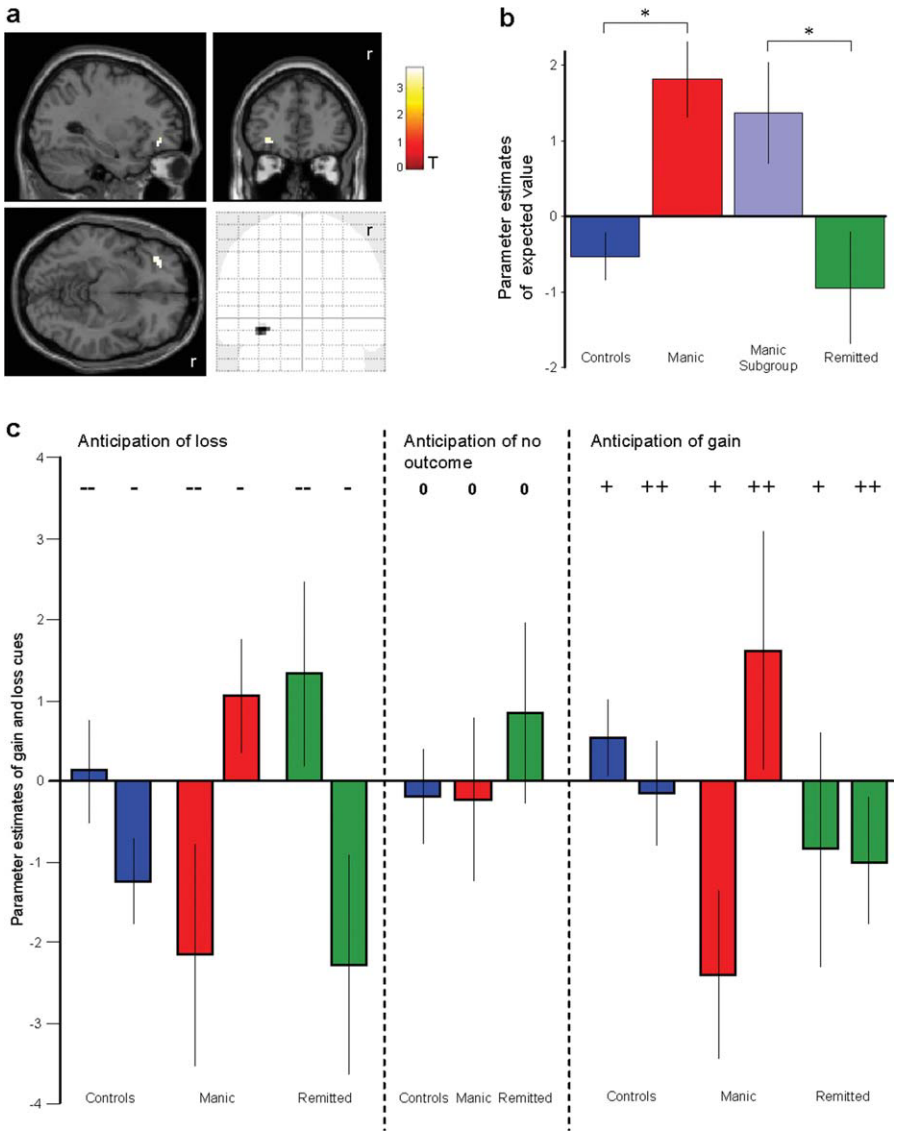

Figure 3.

Effect of expected value. (**a**) Effect of expected value representation in manic patients compared to healthy controls (SPM parametric modulation analysis). Two-sample *t*-test: manic patients > healthy controls. SPM map presented in section views through the peak voxel ($T = 3.77$) at $x = -30$, $y = 42$, $z = -9$ (MNI space). $P < 0.001$, uncorrected. R, right. (**b**) Parameter estimates for expected value in the left lateral OFC (SPM parametric modulation analysis). Effects are shown for healthy control subjects, manic patients, remitted patients, and the subgroup of manic patients that was retested after remission. Values refer to the functional region of interest identified in Figure 3a (mean of ROI). Error bars show the standard error of the mean. Manic patients activate according to expected value, while healthy controls and remitted patients tend to show an inverse effect. (**c**) Parameter estimates for incentive cues in the left lateral OFC (standard SPM analysis, modelling the anticipatory cues separately as explanatory variables). Expectation of 3.0 [euro] gain (++), expectation of 0.1 [euro] gain (+), expectation of neutral outcome (0), expectation of 3.0 [euro] loss (–), expectation of 0.1 [euro] loss (−). Values refer to the functional region of interest identified in Figure 3a (mean of ROI). Error bars show the standard error of the mean. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

subjects, 284.8 ms (±110.5) in manic, and 250.9 (±48.6) in remitted patients. A mixed ANOVA revealed no significant effect for the factors expected value ($F = 1.4$, n.s.) and group ($F = 0.3$, n.s.), nor for their interaction ($F = 1.6$, n.s.), indicating that the attentional load was comparable across groups and conditions.

FMRI Data

In a first step, BOLD responses associated with cued incentive magnitude (SPM parametric modulation analysis) were compared between groups. Responses did not differ between healthy subjects and manic patients, as revealed by SPM two-sample t-tests ("manic > healthy" and "healthy > manic"). This null-finding was not due to a general lack of activation in our experiment, as both groups showed robust BOLD responses to incentive magnitude bilaterally in the ventral striatum including the nucleus accumbens and extending to the dorsal striatum, globus pallidus, thalamus and midbrain (Fig. 2a and 2b; overall analysis of both groups). Similar effects were observed in the group of remitted patients (Fig. 2b), whose magnitude-related responses in the ventral striatum (functional ROIs as identified in Fig. 2a) differed neither from the healthy group (*t*-test for independent groups; right ventral striatum: $T = 0.37$, n.s.; left ventral striatum: $T = 0.01$, n.s.) nor from the subgroup of manic patients that were scanned for a second time after remission (paired *t*-test; right ventral striatum: $T = 0.55$, n.s.; left ventral striatum: $T = 0.11$, n.s.). In all three groups, BOLD responses in the ventral striatum increased as incentive magnitude increased, regardless whether gains or losses were expected (Fig. 2c).

Second, BOLD responses associated with cued incentive valence (SPM parametric modulation analysis) were compared between healthy and manic subjects. The comparison "manic patients > controls" showed no significant effect. The reverse contrast ("controls > manic patients") revealed differential effects in the right posterior cingulate adjacent to the cuneus (BA 30, peaking at [$x = 21$, $y = -66$, $z = 3$]; $T = 3.83$). In this region, healthy controls showed stronger effects of incentive valence than manic patients. Although our predictions did not focus on this area, this finding is in accordance with earlier studies implicating the posterior cingulate and cuneus in reward expectation [Kirsch et al., 2003; Wittmann et al., 2005] and reporting alterations in this area in patients with bipolar disorder [Malhi et al., 2004; Malhi et al., 2007].

Third, BOLD responses associated with expected value (i.e., magnitude-by-valence interaction in SPM parametric modulation analysis) were compared between groups. The comparison "controls > manic patients" showed no significant effect. The reverse contrast ("manic patients > controls") revealed a differential effect in the left lateral orbitofrontal cortex (OFC, BA 11, 47; Fig. 3a). As illustrated in Figure 3b, BOLD responses according to expected value were found in manic patients, while healthy subjects tended to show the inverse effect (i.e., a negative magnitude-by-valence interaction) in this brain region. Figure 3c illustrates the patterns of activation present during the expectation of gains and losses: manic patients showed increasing OFC responses with increasing cued gain magnitude and decreasing OFC responses with increasing cued loss magnitude, while no such effect, but rather the inverse pattern was found in healthy individuals.

Effects of expected value in the left OFC (functional ROI as identified in Fig. 3a) did not differ between remitted patients and healthy individuals (Fig. 3b; *t*-test for independent groups, $T = 0.60$, n.s.), but between remitted patients and the subgroup of manic patients that was scanned for a second time after remission (Fig. 3b; paired *t*-test, $T = 2.45$, $P < 0.05$). As illustrated in Figure 3c, the remitted patients showed effects of expected value similar to the healthy group.

Fourth, to examine the potential effects of antipsychotic medication (exhibiting antidopaminergic effects) on findings obtained in the parametric modulation analysis, we employed two strategies: First, comparing manic patients taking ($n = 10$) versus those not taking ($n = 5$) antipsychotic medication (for medication see Table I), we found no significant difference for the parametric magnitude effect in the left and right ventral striatum (functional ROI as identified in Fig. 2a; left: $T = 1.25$, $P = 0.24$; right: $T = 1.44$, $P = 0.18$) nor for the parametric effect of expected value in the left OFC (functional ROI as identified in Fig. 3a; $T = 0.95$, $P = 0.36$). Second, correlational analyses revealed no significant association between chlorpromazine dose equivalents and the parametric effects observed in the left and right ventral striatum (magnitude effect; left: Pearson $r = 0.08$, $P = 0.79$; right: Pearson $r = -0.03$, $P = 0.91$) and the left OFC (effect of expected value; Pearson $r = 0.18$, $P = 0.53$).

Finally, BOLD responses during the outcome period were compared between healthy and manic patients (SPM *t*-test for independent groups). The contrasts "win > no-win" and "loss > no-loss" revealed no significant group differences in the whole-brain analyses ($P < 0.001$, uncorrected). When the threshold was tentatively lowered to $P < 0.005$ (uncorrected), we still observed no differential effects in the ventral striatum.

DISCUSSION

The main finding of this study is a significant group difference for the representation of expected value in the left lateral OFC. In this region, manic patients show stronger responses to increasing gain cues and weaker responses to increasing loss cues compared to healthy controls. These alterations occur in spite of similar task performance and comparably strong ventral striatal responses to cued incentive magnitude, and tend to normalize with remission of symptoms. Our findings suggest that although manic patients have the capacity to perform the MID task according to instruction and to activate the ventral striatum according to incentive magnitude, they show state-related alterations in processing the expected value in the left OFC.

To the best of our knowledge, this is the first study using a MID task to investigate the expectation of both gain and loss in mania. Our finding of altered OFC responses in mania is consistent with earlier fMRI studies

in mania, reporting attenuated OFC responses during different cognitive tasks [Altshuler et al., 2005a,b; Blumberg et al., 1999; Rubinsztein et al., 2001]. Our finding is also in line with clinical and neuropsychological observations, suggesting altered gain and loss anticipation [Kaplan and Sadock, 1997; Meyer et al., 1999,2001], unrealistic outcome expectations [Johnson, 2005; Stern and Berrenberg, 1979] and impaired decision-making [Murphy and Sahakian, 2001]. Extending these earlier findings, our present data directly link OFC dysfunction to alterations in incentive cue processing.

A recent fMRI study in mania also reports alterations in the dopaminergic mesolimbic circuit [Abler et al., 2008]. This study provided striking evidence for attenuated activation in dopaminergic brain areas (including the ventral striatum) during gain receipt, but found no significant group difference between manic and healthy subjects during gain expectation. While this study contrasted high versus low gain expectation and high versus no gain expectation, our present paradigm also includes loss conditions. Varying both magnitude and valence of anticipatory cues allows us to disentangle the effects of magnitude, valence and expected value. Our main finding of altered processing of expected value in the OFC also relies on differences during loss anticipation, which may explain the discrepancy between studies with regard to the anticipation period. Discrepant findings with respect to gain receipt (contrast "gain versus no-gain" during outcome period) may be related to differences in task demands [which can influence ventral striatal activation in reward processing, cf. Zink et al. 2004]: whereas no judgement was required in our task, the study by Abler et al. [Abler et al., 2008] involved a decision component.

Healthy individuals tend to show increasing responses in the lateral OFC with increasing cued loss magnitude. This finding is consistent with earlier reports implicating the lateral OFC in the expectation of loss [Juckel et al., 2006b; Liu et al., 2007], punishment processing [O'Doherty et al., 2001], risk aversion and processing of uncertainty [Critchley et al., 2001; Tobler et al., 2007]. A recent meta-analysis [Kringelbach and Rolls, 2004] suggests that the lateral OFC is involved in the evaluation of punishers which can lead to a change in ongoing behavior. Our present finding of altered lateral OFC function in mania may reflect a positive affective bias in anticipatory cue processing: During loss expectation, manic patients show decreasing lateral OFC responses with increasing loss magnitude, i.e., an activation pattern opposite to that found in healthy individuals. During gain expectation, manic patients show increasing OFC responses with increasing gain magnitude, i.e., an activation pattern analogous to that observed in healthy individuals during loss expectation. Such altered anticipatory cue processing could lead to alterations in assigning motivational value to expected positive and negative outcomes, potentially helping to explain clinical features of mania, such as decreased motivation to withdraw from impending negative outcomes and increased drive to engage in pleasurable activities.

On the basis of our orbitofrontal finding, one could expect shorter response times with increasing expected value in mania and shorter response times with decreasing expected value in healthy control subjects. The absence of such interaction between group and expected value is related to the MID task that was used to isolate brain activity specifically associated with gain and loss expectation. This task is designed to dissociate expectation of incentives and task performance [Knutson et al., 2001] as well as to control choice behavior [Knutson et al., 2005]. Thus, our present study did not intend to provide a behavioral measure to investigate whether or how altered incentive cue processing in the OFC influences response times or decision-making. However, our behavioral data allow the exclusion of some confounding factors that often constrain interpretation of neuroimaging data in patients [Weinberger and Berman, 1996]. Specifically, the lack of significant impairment in MID task performance (response times and total gain) indicates that unspecific effects, such as attention, cooperation, motor preparation and arousal, do not account for our findings.

Although the sample size is small ($n = 7$) and practice effects cannot be excluded totally, our findings in remitted patients indicate that incentive cue processing in the OFC may recover with remission of symptoms, representing a state characteristic of mania. This assumption is in line with a PET study showing OFC dysfunction during decision-making in mania, but not in depression [Rubinsztein et al., 2001]. It is also in accordance with fMRI studies showing that treatment with mood-stabilizers may reverse abnormalities in bipolar disorder [Blumberg et al., 2005; Haldane et al., 2008; Phillips et al., 2008]. However, other studies observed abnormal OFC responses also in euthymic bipolar patients [Kronhaus et al., 2006; Malhi et al., 2005; Pavuluri et al., 2007; Wessa et al., 2007] which may indicate a trait-like alteration. It seems that the clinical state's impact on OFC function depends on which task is employed and which subregion within the OFC is under consideration.

In the ventral striatum, both the manic and healthy control group show increasing activation as they expected increasing incentive magnitude, independent of gain or loss conditions. Our finding in healthy individuals is in accordance with earlier reports, demonstrating that the ventral striatum responds to both appetitive and aversive incentive cues [Heinz, 2002; Jensen et al., 2003; Knutson et al., 2005; Wrase et al., 2007; Zink et al., 2004]. The absence of a group difference in the ventral striatum is in accordance with the study by Abler et al. [Abler et al., 2008] in manic patients. However, it somehow contrasts with earlier studies employing the MID paradigm in other psychiatric disorders. Compared to healthy individuals, patients with schizophrenia [Juckel et al., 2006b], alcohol dependence [Wrase et al., 2007], ADHD [Strohle et al., 2008] and unipolar depression [Stoy et al., submitted, see

however Knutson et al., 2008; Pizzagalli et al., 2009] show reduced ventral striatal activation during the expectation of gain, indicating that ventral striatal activation might vary with motivational symptom profiles [Keedwell et al., 2005]. It could be concluded that in mania, altered expectation of incentives does not mainly concern cued magnitude processing in the ventral striatum. In mania, it may rather concern the integration of expected magnitude and valence (i.e., representation of expected value) in the lateral OFC.

The present investigation relies on monetary gain and loss to study reward and punishment anticipation in mania. While monetary tasks are frequently used in fMRI experiments, it is acknowledged that different tasks could have been chosen to address our research question. These tasks could have focused on other aspects of reward anticipation, concerning, for instance, sociability or sexual behavior. It is well possible that these aspects involve distinct neuronal correlates and that some manic patients show alterations in one aspect of reward anticipation but not another.

Limitations of our study are the relatively small sample size and the relatively liberal threshold of $P < 0.001$ (uncorreced) used in a priori regions of interest. Thus, the current results are preliminary and await replication in further studies. A further limitation is that all manic patients received psychotropic medication. However, after remission of symptoms, OFC function tended to normalize in a subgroup of seven patients, when they were still taking psychotropic medication. In addition, our main finding in the OFC concerns qualitative group differences (i.e., increased responses as cued gains increased and decreased responses as cued losses increased), whereas several neuroimaging studies suggest that mood stabilizers and antipsychotics generally attenuate BOLD responses [Blumberg et al., 2005; Caligiuri et al., 2003; Lawrence et al., 2004; Takahashi et al., 2005]. Furthermore, a recent review indicates either no or ameliorative effects of psychotropic medications on abnormal functional neuroimaging measures in bipolar disorder [Phillips et al., 2008]. Finally, we find no significant effect of antipsychotic medication on our main findings in the OFC and ventral striatum, which may be explained by the use of atypical rather than typical neuroleptics; the former appear to have lower impact on motivational processes and, specifically, ventral striatal function [Juckel et al., 2006a; Schlagenhauf et al., 2008]. Nonetheless, we cannot fully exclude confounding effects of current medication. In addition, one has to consider confounding effects of previous medications, given that the duration of illness was more than 15 years. To isolate effects of acute manic episodes from (short and long term) medication effects and plastic changes of brain circuits after several manic episodes, it would be desirable to study the present paradigm in drug naïve patients with a first manic episode.

In conclusion, manic patients show state-related alterations in processing the expected value of incentives in the left lateral OFC, although they have the capacity to perform the MID task according to instruction and to activate the ventral striatum according to cued incentive magnitude. This OFC alteration may reflect a positive affective processing bias, with an increased responsiveness to high gain cues and reduced responsiveness to high loss cues compared to healthy individuals. Such biased incentive cue processing could have implications for goal-directed behavior, resulting in enhanced motivation for seeking rewards and in an underestimation of risks and potential punishments. While the present study specifically addresses gain and loss expectation, independent of choice behavior, future research may focus on the impact of the identified OFC alterations on decision making.

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REFERENCES

Abler B, Greenhouse I, Ongur D, Walter H, Heckers S (2008): Abnormal reward system activation in mania. Neuropsychopharmacology 33:2217–2227.

Al-Mousawi AH, Evans N, Ebmeier KP, Roeda D, Chaloner F, Ashcroft GW (1996): Limbic dysfunction in schizophrenia and mania. A study using 18F-labelled fluorodeoxyglucose and positron emission tomography. Br J Psychiatry 169:509–516.

Altshuler L, Bookheimer S, Proenza MA, Townsend J, Sabb F, Firestine A, Bartzokis G, Mintz J, Mazziotta J, Cohen MS (2005a) Increased amygdala activation during mania: A functional magnetic resonance imaging study. Am J Psychiatry 162:1211–1213.

Altshuler LL, Bookheimer SY, Townsend J, Proenza MA, Eisenberger N, Sabb F, Mintz J, Cohen MS (2005b) Blunted activation in orbitofrontal cortex during mania: A functional magnetic resonance imaging study. Biol Psychiatry 58:763–769.

Association AP (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.

Bermpohl F, Dalanay U, Kahnt T, Sajonz B, Heimann H, Ricken R, Stoy M, Hägele C, Schlagenhauf F, Adli M, Wrase J, Ströhle A, Heinz A, Bauer M (2009): A preliminary study of increased amygdala activation to positive affective stimuli in mania. Bipolar Disord 11:70–75.

Berridge KC, Robinson TE (1998): What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 28:309–369.

Blumberg HP, Stern E, Ricketts S, Martinez D, de Asis J, White T, Epstein J, Isenberg N, McBride PA, Kemperman I, Emmerich S, Dhawan V, Eidelberg D, Kocsis JH, Silbersweig DA (1999): Rostral and orbital prefrontal cortex dysfunction in the manic state of bipolar disorder. Am J Psychiatry 156:1986–1988.

Blumberg HP, Donegan NH, Sanislow CA, Collins S, Lacadie C, Skudlarski P, Gueorguieva R, Fulbright RK, McGlashan TH, Gore JC, Krystal JH (2005): Preliminary evidence for medication effects on functional abnormalities in the amygdala and anterior cingulate in bipolar disorder. Psychopharmacology (Berl) 183:308–313.

Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P (2001): Functional imaging of neural responses to expectancy and experience of monetary gains and losses. Neuron 30:619–639.

Buchel C, Holmes AP, Rees G, Friston KJ (1998): Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. Neuroimage 8:140–148.

Caligiuri MP, Brown GG, Meloy MJ, Eberson SC, Kindermann SS, Frank LR, Zorrilla LE, Lohr JB (2003): An fMRI study of affective state and medication on cortical and subcortical brain regions during motor performance in bipolar disorder. Psychiatry Res 123:171–182.

Critchley HD, Mathias CJ, Dolan RJ (2001): Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron 29:537–545.

Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ (2004): Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. Biol Psychiatry 55:1163–1170.

First MB, Spitzer RL, Gibbon M, Williams J (1997): Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II). Washington, D.C.: American Psychiatric Press.

First MB, Spitzer RL, Gibbon M, Williams J (2001): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition With Psychotic Screen (SCID-I/P W/ PSY SCREEN). New York, NY: Biometrics Research Department, New York State Psychiatric Institute.

Gray JA (1994): Framework for a taxonomy of psychiatric disorder. In: Van Goozen HM, Van De Poll NE, Sergeant JA, editors. Emotions: Essays on emotion theory. Hillsdale, NJ: Lawrence Erlbaum Associates. pp 29–59.

Haldane M, Jogia J, Cobb A, Kozuch E, Kumari V, Frangou S (2008): Changes in brain activation during working memory and facial recognition tasks in patients with bipolar disorder with Lamotrigine monotherapy. Eur Neuropsychopharmacol 18:48–54.

Hayasaka S, Nichols TE (2004): Combining voxel intensity and cluster extent with permutation test framework. Neuroimage 23:54–63.

Heinz A (2002): Dopaminergic dysfunction in alcoholism and schizophrenia–psychopathological and behavioral correlates. Eur Psychiatry 17:9–16.

Jensen J, McIntosh AR, Crawley AP, Mikulis DJ, Remington G, Kapur S (2003): Direct activation of the ventral striatum in anticipation of aversive stimuli. Neuron 40:1251–1257.

Johnson SL (2005): Mania and dysregulation in goal pursuit: A review. Clin Psychol Rev 25:241–262.

Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wustenberg T, Villringer A, Knutson B, Kienast T, Gallinat J, Wrase J, Heinz A (2006a): Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl) 187:222–228.

Juckel G, Schlagenhauf F, Koslowski M, Wustenberg T, Villringer A, Knutson B, Wrase J, Heinz A (2006b): Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 29:409–416.

Kahneman D, Tversky A (1979): Prospect theory: An analysis of decision under risk. Econometrica 47:263–292.

Kaplan HI, Sadock BJ (1997): Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences, clinical psychiatry. Baltimore: Lippincott Williams and Wilkins.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML (2005): The neural correlates of anhedonia in major depressive disorder. Biol Psychiatry 58:843–853.

Kirsch P, Schienle A, Stark R, Sammer G, Blecker C, Walter B, Ott U, Burkart J, Vaitl D (2003): Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: An event-related fMRI study. Neuroimage 20:1086–1095.

Knutson B, Adams CM, Fong GW, Hommer D (2001): Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 21:RC159.

Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008): Neural responses to monetary incentives in major depression. Biol Psychiatry 63:686–692.

Knutson B, Taylor J, Kaufman M, Peterson R, Glover G (2005): Distributed neural representation of expected value. J Neurosci 25:4806–4812.

Kringelbach ML, Rolls ET (2004): The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 72:341–372.

Kronhaus DM, Lawrence NS, Williams AM, Frangou S, Brammer MJ, Williams SC, Andrew CM, Phillips ML (2006): Stroop performance in bipolar disorder: Further evidence for abnormalities in the ventral prefrontal cortex. Bipolar Disord 8:28–39.

Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML (2004): Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. Biol Psychiatry 55:578–587.

Leibenluft E, Rich BA, Vinton DT, Nelson EE, Fromm SJ, Berghorst LH, Joshi P, Robb A, Schachar RJ, Dickstein DP, McClure EB, Pine DS (2007): Neural circuitry engaged during unsuccessful motor inhibition in pediatric bipolar disorder. Am J Psychiatry 164:52–60.

Liu X, Powell DK, Wang H, Gold BT, Corbly CR, Joseph JE (2007): Functional dissociation in frontal and striatal areas for processing of positive and negative reward information. J Neurosci 27:4587–4597.

Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM (2002): Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biol Psychiatry 52:93–100.

Malhi GS, Lagopoulos J, Sachdev P, Mitchell PB, Ivanovski B, Parker GB (2004): Cognitive generation of affect in hypomania: an fMRI study. Bipolar Disord 6:271–285.

Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R (2005): An emotional Stroop functional MRI study of euthymic bipolar disorder. Bipolar Disord 7 (Suppl 5):58–69.

Malhi GS, Lagopoulos J, Sachdev PS, Ivanovski B, Shnier R, Ketter T (2007): Is a lack of disgust something to fear? A functional magnetic resonance imaging facial emotion recognition study in euthymic bipolar disorder patients. Bipolar Disord 9:345–357.

Meyer B, Johnson SL, Carver CS (1999): Exploring behavioral activation and inhibition sensitivities among college students at risk for bipolar spectrum symptomatology. J Psychopathol Behav Assess 21:275–292.

Meyer B, Johnson SL, Winters R (2001): Responsiveness to threat and incentive in bipolar disorder: Relations of the BIS/BAS scales with symptoms. J Psychopathol Behav Assess 23:133–143.

Murphy FC, Sahakian BJ (2001): Neuropsychology of bipolar disorder. Br J Psychiatry 178 (Suppl 41):S120–S127.

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001): Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4:95–102.

O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ (2002): Neural responses during anticipation of a primary taste reward. Neuron 33:815–826.

Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.

Panksepp J (1998): Affective Neuroscience. The Foundations Of Human and Animal Emotions. New York: Oxford University Press.

Pavuluri MN, O'Connor MM, Harral E, Sweeney JA (2007): Affective neural circuitry during facial emotion processing in pediatric bipolar disorder. Biol Psychiatry 62:158–167.

Phillips ML, Travis MJ, Fagiolini A, Kupfer DJ (2008): Medication effects in neuroimaging studies of bipolar disorder. Am J Psychiatry 165:313–320.

Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, Dougherty DD, Iosifescu DV, Rauch SL, Fava M (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry 166:702–710.

Rubinsztein JS, Fletcher PC, Rogers RD, Ho LW, Aigbirhio FI, Paykel ES, Robbins TW, Sahakian BJ (2001): Decision-making in mania: A PET study. Brain 124(Part 12):2550–2563.

Sax KW, Strakowski SM, Zimmerman ME, DelBello MP, Keck PE, Jr., Hawkins JM (1999): Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry 156:139–141.

Schlagenhauf F, Juckel G, Koslowski M, Kahnt T, Knutson B, Dembler T, Kienast T, Gallinat J, Wrase J, Heinz A (2008): Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. Psychopharmacology (Berl) 196:673–684.

Stern GS, Berrenberg JL (1979): Skill-set, success outcome, and mania as determinants of the illusion of control. J Res Personal 13:206–220.

Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, Shear P, Adler CM (2002): Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am J Psychiatry 159:1841–1847.

Strohle A, Stoy M, Wrase J, Schwarzer S, Schlagenhauf F, Huss M, Hein J, Nedderhut A, Neumann B, Gregor A, Juckel G, Knutson B, Lehmkuhl U, Bauer M, Heinz A (2008): Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. Neuroimage 39:966–972.

Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y (2005): Effects of dopaminergic and serotonergic manipulation on emotional processing: A pharmacological fMRI study. Neuroimage 27:991–1001.

Tobler PN, O'Doherty JP, Dolan RJ, Schultz W (2007): Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. J Neurophysiol 97:1621–1632.

Weinberger DR, Berman KF (1996): Prefrontal function in schizophrenia: Confounds and controversies. Philos Trans R Soc Lond B Biol Sci 351:1495–1503.

Wessa M, Houenou J, Paillere-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL (2007): Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. Am J Psychiatry 164:638–646.

Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Duzel E (2005): Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron 45:459–467.

Woods SW (2003): Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 64:663–667.

Wrase J, Schlagenhauf F, Kienast T, Wustenberg T, Bermpohl F, Kahnt T, Beck A, Strohle A, Juckel G, Knutson B, Heinz A (2007): Dysfunction of reward processing correlates with alcohol craving in detoxified alcoholics. Neuroimage 35:787–794.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978): A rating scale for mania: Reliability, validity and sensitivity. Br J Psychiatry 133:429–435.

Zink CF, Pagnoni G, Martin-Skurski ME, Chappelow JC, Berns GS (2004): Human striatal responses to monetary reward depend on saliency. Neuron 42:509–517.