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Hyporeactivity of ventral striatum towards incentive stimuli in unmedicated depressed patients normalizes after treatment with escitalopram

Meline Stoy¹, Florian Schlagenhauf¹, Philipp Sterzer¹, Felix Bermohi¹, Claudia Hägele¹, Kristina Suchotzki³, Katharina Schmack¹, Jana Wrase¹, Roland Ricken¹, Brian Knutson², Mazda Adli¹, Michael Bauer³, Andreas Heinz¹ and Andreas Ströhle¹

Abstract
Major Depressive Disorder (MDD) involves deficits in the reward system. While neuroimaging studies have focused on affective stimulus processing, few investigations have directly addressed deficits in the anticipation of incentives. We examined neural responses during gain and loss anticipation in patients with MDD before and after treatment with a selective serotonin reuptake inhibitor (SSRI). Fifteen adults with MDD and 15 healthy participants, matched for age, verbal IQ and smoking habits, were investigated in a functional magnetic resonance imaging (fMRI) study using a monetary incentive delay task. Patients were scanned drug-free and after 6 weeks of open-label treatment with escitalopram; controls were scanned twice at corresponding time points. We compared the blood oxygenation level dependent (BOLD) response during the anticipation of gain and loss with a neutral condition. A repeated measures ANOVA was calculated to identify effects of group (MDD vs. controls), time (first vs. second scan) and group-by-time interaction. Severity of depression was measured with the Hamilton Rating Scale of Depression and the Beck Depression Inventory. MDD patients showed significantly less ventral striatal activation during anticipation of gain and loss compared with controls before, but not after, treatment. There was a significant group-by-time interaction during anticipation of loss in the left ventral striatum due to a signal increase in patients after treatment. Ventral striatal hyporesponsiveness was associated with the severity of depression and in particular anhedonic symptoms. These findings suggest that MDD patients show ventral striatal hyporesponsiveness during incentive cue processing, which normalizes after successful treatment.

Keywords
Anticipation, fMRI, loss, reward, SSRI, unipolar depression, ventral striatum

Introduction
Key symptoms of Major Depressive Disorder (MDD) such as anhedonia and avolition may be associated with dysfunctions in reward processing (Pizzagalli et al., 2009; Tremblay et al., 2005). Depressed patients show a decreased motivation to seek rewards (Pizzagalli et al., 2005) and are less responsive towards monetary reward cues (Henriques and Davidson, 2000). This could lead to difficulties in avoiding negative events and making new positive experiences to overcome depressive mood during an acute depressive episode (American Psychiatric Association, 1994). Consistent with this account, a growing body of literature postulates dysfunctions in the responsiveness of dopaminergic mesolimbic regions implicated in reward processing (Dunlop and Nemeroff, 2007), including alterations in the ventral striatum (Drevets, 2001) and reward dysfunctions, as a promising biological marker in MDD (Hasler et al., 2004). However, the specific neural reward dysfunctions and modifications of these during the course of treatment and during the natural history of the disease are poorly understood.

Neural evidence for a hypofunction in the reward system comes from animal models of depression indicating an increased postsynaptic sensitivity in the ventral striatum (indicative of decreased synaptic dopamine (Dunlop and Nemeroff, 2007)) and a correlation between decreased dopamine concentrations and reduced effort to work for rewards (Neill et al., 2002). Pharmacological studies of depressive patients have demonstrated hypersensitive responses in reward-related brain areas (including the ventral striatum) during treatment with escitalopram.

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to low doses of psychostimulants like dextroamphetamine, again consistent with decreased synaptic dopamine and hypersensitive postsynaptic receptors (Tremblay et al., 2005).

Several functional neuroimaging studies have postulated that individuals with depressive symptoms show dysfunctions in reward-related brain areas and exhibit a diminished hedonic response to reward. Decreased ventral striatal activation to pleasant stimuli in unmedicated acutely depressed (Epstein et al., 2006; Lawrence et al., 2004), recovered (McCabe et al., 2009) and medicated patients during positive feedback (Steele et al., 2007) have been reported. Furthermore, hyporesponsiveness of the ventral striatum has been associated with symptom severity in antidepressant-unresponsive patients during a Pavlovian learning task (Kumar et al., 2008). In particular, anhedonic symptoms seem to correlate with reduced ventral striatal activity in MDD patients during processing of positive stimuli (Epstein et al., 2006; Keedwell et al., 2005) and negative feedback (Steele et al., 2007).

However, several researchers have proposed that the mesolimbic dopaminergic system is related, rather, to incentive motivation, that is, the ‘wanting’ of hedonic rewards (Berridge, 2007; Salamone et al., 2009). Studies in primates (Schultz et al., 1997) as well as in healthy humans have shown the ventral striatum to be preferentially activated during anticipation of incentive cues (Elliott et al., 2004; Knutson et al., 2003; O’Doherty et al., 2001). In line with this, ventral striatal dopamine depletion reduces the willingness to expend effort for rewards in animals (Salamone et al., 2007), but not the hedonic response to reward (Berridge, 2007). In humans, anhedonia is behaviorally associated with a decreased effort to work for rewards (Treadway et al., 2009) and hyporesponsiveness of the mesolimbic dopaminergic system has been linked to symptoms of anhedonia in depression (Forbes et al., 2009; Tremblay et al., 2009) as well as in schizophrenia during the anticipation of incentive cues (Juckel et al., 2006a, 2006b).

The monetary incentive delay task (MID) allows us to measure functional activation in reward circuits separately for the anticipation and consumption of rewards (Knutson et al., 2001a, 2001b). Contrary to their expectation, recent studies using a MID task in unmedicated patients with MDD did not find differences in the recruitment of the ventral striatum during anticipation of gains and losses. Instead, decreased activity of the posterior putamen (Pizzagalli et al., 2009) and increased activity of the dorsal anterior cingulate cortex (ACC) (Knutson et al., 2008) has been shown during gain anticipation. While the activity of the dorsal ACC was increased during gain, it was decreased during loss anticipation (Knutson et al., 2008). It is still unclear whether the negative finding in the ventral striatum results from a preserved recruitment of the ventral striatum during anticipation compared with consumption, symptom patterns, or severity (Knutson et al., 2008; Kumar et al., 2008; Wacker et al., 2009).

Even less is known about how antidepressant drug treatment might influence ventral striatal responses during incentive cue processing. In MDD patients, treatment with fluoxetine and sertraline can normalize altered neural activation during processing of emotional stimuli (Fu et al., 2004; Sheline et al., 2001), whereas ventral striatal responses remained blunted in antidepressant-unresponsive patients (Kumar et al., 2008). Numerous studies implicate a strong anatomical interconnection between the dopaminergic and serotonergic systems and a modulating, either increasing or even decreasing, effect of serotonin on reward processes (for review see Kranz et al., 2010). Different modulating effects have been postulated for reward and punishment. For example, Daw et al. (2002) postulated that phasic dopaminergic firing plays a role in the prediction of future reward, whereas serotonin release would represent a prediction error for future punishment. In healthy subjects, serotonin depletion enhanced the ability to predict punishment in a reversal-learning task, possibly abolishing a protective bias in healthy subjects (Cools et al., 2008). Selective serotonin reuptake inhibitors (SSRIs) elevate the serotonergic tone and are capable of indirectly regulating dopaminergic activity (for review see Alex and Pehhek, 2007). However, SSRIs often fail to improve amotivational symptoms and show a rather dampening effect on reward functions (for review see Kranz et al., 2010; Nutt et al., 2007). A low effectivity of SSRIs in reducing reward-related symptoms of depression, such as loss of interest and motivation, has been suggested (Price et al., 2009). Other researchers postulate that amotivational symptoms respond with latency (Boyer et al., 2000). Taken together, the importance of serotonin in reward processes is well documented, but results are rather conflicting and underlying mechanisms are still not quite elucidated.

In summary, functional magnetic resonance imaging (fMRI) studies have found evidence of hyporesponsiveness of the ventral striatum in MDD (Epstein et al., 2006; Lawrence et al., 2004; McCabe et al., 2009; Steele et al., 2007), while studies on the anticipation phase of reward failed to find differences (Knutson et al., 2008; Pizzagalli et al., 2009). If these differences in findings are related to differences in the severity of illness or specific symptoms (e.g. anhedonia), more affected patients should show the least ventral striatal activation during the anticipation of positive incentives. Furthermore, ventral striatal activity should be modified after successful treatment (Fu et al., 2004). Given that ventral striatal function during anticipation of incentives can be related to valence and behavioral salience (Cooper and Knutson, 2008), there are two possible hypotheses with regard to negative incentives: during an acute episode processing of these stimuli could be enhanced, considering the mood-congruent attentional bias (Fu et al., 2004; Sheline et al., 2001; Surguladze et al., 2005), or blunted, following the postulate of reduced approach and avoidance behavior in anhedonia (Chase et al., 2009) and valence-independent processing of incentive cues in the mesolimbic dopaminergic system (Heinz, 2002; Seymour et al., 2007).

The aim of the present study was to examine whether antidepressant treatment with the SSRI escitalopram could modify ventral striatal activity during anticipation of gain and loss in MDD patients. Furthermore, we would like to assess whether dysfunctions in the ventral striatum are associated with symptom severity in general and anhedonic symptoms in particular. Therefore, we used event-related fMRI to examine neural responsiveness during anticipation of incentive monetary cues in unmedicated patients and never-depressed healthy participants, and tracked changes in ventral striatal responsiveness before and after therapeutic treatment with escitalopram. On the basis of recent findings (Knutson et al., 2008; Pizzagalli et al., 2009), secondary analyses of the
anticipation and feedback phases are reported in the supplementary material that can be found online. We predicted 1) that unmedicated patients would show reduced ventral striatal activation during the anticipation of gain as well as alterations in the response to anticipation of loss, and 2) that successful treatment with escitalopram would diminish ventral striatal alterations in MDD patients.

**Methods and materials**

**Participants**

Fifteen right-handed (Edinburgh Handedness Inventory (Oldfield, 1971)) unmedicated adults diagnosed with MDD (10 male) and 15 healthy control participants (10 male), matched for age, verbal IQ using a verbal knowledge test (Schmidt and Metzler, 1992) and cigarette smoking, participated after providing written informed consent (Table 1). Patients had no personal or family history of other psychiatric disorders. Controls had no personal or family history of any psychiatric disorder (Structured Clinical Interview for DSM-IV Disorders [SCID I/II]; see First et al., 1997; First et al., 2001) and an IQ >80. Patients were recruited from the inpatient and outpatient center of the Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Campus Charité Mitte. Control participants were recruited from the local community by advertisement. The study was approved by the local ethics committee. Clinical experts diagnosed current MDD according to DSM-IV criteria. Patients were included in the study if their score in the Hamilton Rating Scale for Depression (HRSD) was 16 or higher (mean 19.70; standard deviation [SD] 3.06). In addition, patients and controls rated subjective symptoms of depression with the Beck Depression Inventory (BDI; \( n = 13 \)). Patients and controls were under no psychotropic medication at T1 (first assessment) and had no severe medical disorder.

**Table 1. Demographical, Behavioral and Clinical Characteristics.**

<table>
<thead>
<tr>
<th>Group Characteristics</th>
<th>MDD ( N = 15 )</th>
<th>CON ( N = 15 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, F/M (N)</strong></td>
<td>(5/10)</td>
<td>(5/10)</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td>41.9 12.2</td>
<td>39.5 11.9</td>
</tr>
<tr>
<td><strong>Verbal IQ (WST)</strong></td>
<td>112.1 10.2</td>
<td>110.2 6.3</td>
</tr>
<tr>
<td><strong>Years of education</strong></td>
<td>12.3 0.4</td>
<td>11.7 0.4</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
<td>7.2 0.6</td>
<td>6.7 2.3</td>
</tr>
<tr>
<td><strong>Marital Status (partnership), N</strong></td>
<td>6 (9/6)</td>
<td>7 (9/6)</td>
</tr>
<tr>
<td><strong>Scan interval (days)</strong></td>
<td>60 12.3</td>
<td>48 20.7</td>
</tr>
<tr>
<td><strong>Behavioral Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time total (ms) (T1)</td>
<td>251.6 58.6</td>
<td>274.2 87.8</td>
</tr>
<tr>
<td>Reaction time total (ms) (T2)</td>
<td>231.3 34.2</td>
<td>270.1 107.2</td>
</tr>
<tr>
<td>VAS effort total (T1)</td>
<td>6.3 1.6</td>
<td>7.8 1.2</td>
</tr>
<tr>
<td>VAS effort total (T2)</td>
<td>7.2* 1.3</td>
<td>7.7 1.5</td>
</tr>
<tr>
<td><strong>Symptom Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRSD Total Score (T1)</td>
<td>18.7 2.9</td>
<td>-</td>
</tr>
<tr>
<td>HRSD Total Score (T2)</td>
<td>-</td>
<td>4.0</td>
</tr>
<tr>
<td>BDI Total Score (T1), ( n = 13 )</td>
<td>23.6 8.7</td>
<td>8.7 2.5</td>
</tr>
<tr>
<td>BDI Total Score (T2), ( n = 13 )</td>
<td>13.4* 6.9</td>
<td>2.8 1.7</td>
</tr>
<tr>
<td>BDI Anhedonia Score (T1), ( n = 13 )</td>
<td>4.5 2.1</td>
<td>-</td>
</tr>
<tr>
<td>BDI Anhedonia Score (T2), ( n = 13 )</td>
<td>3.6 1.5</td>
<td>-</td>
</tr>
<tr>
<td><strong>Past Medical History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, mean (SD), years</td>
<td>32.6 (12.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Previous major depressive episodes, mean (SD), ( N )</td>
<td>3.6 (3.7)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of the current episode at T1, d</td>
<td>50.8 (27.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Family history (positive), ( N )</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td><strong>Treatment History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication status before the first scanning (drug-naive), ( N )</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>Dose of Escitalopram at T2, mg, mean (SD)</td>
<td>17.7 (7.53)</td>
<td>NA</td>
</tr>
<tr>
<td>Responder / Remission / Nonresponder, ( N )</td>
<td>4 / 7 / 4</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Hollingshead, 1975. Means (M), standard deviations (SD) and frequencies (N) of group characteristics. \( p \)-values: two-tailed significance-value for \( t \)- and \( \chi^2 \)-tests MDD vs CON; *significant difference between T1 and T2, paired \( t \)-test \( (p < 0.05) \). BDI: Beck Depression Inventory, CON: healthy control subjects, F: female, HRSD: Hamilton Rating Scale for Depression, M: male, MDD: Major Depressive Disorder, NA: not applicable, NS: non-smoker, S: smoker, T1: first scanning session, T2: second scanning session, VAS: Visual Analogue Scale, WST: Wortschatztest.
All participants were scanned for a second time (T2) after 6 ± 2 weeks (interval: MDD: mean 60 days; SD 12.3; controls: mean 48 days, SD 20.7). The escitalopram monotherapy began the day after the first scanning (first 3 days 5 mg in the morning, an additional 5 mg every 3 days until a therapeutically effective dose was reached [mean 17.7 mg; SD 7.53; range: 10–30 mg]). Further treatment characteristics are reported in the supplementary material online (Supplementary Table 1). Remission was defined as HRSD score < 7. Control participants underwent the same study procedures, including neuropsychological testing and structured diagnostic interviews, but underwent no treatment. None of the controls reported current or lifetime clinically relevant symptoms of MDD.

Monetary incentive delay task

We used a ‘monetary incentive delay’ task as described by Knutson et al. to study neural responses to incentive stimuli (Knutson et al., 2001a, 2001b). Further information on the task is given in the supplementary material online and in previous publications (Juckel et al., 2006a, 2006b; Schmack et al., 2008; Ströhle et al., 2008; Wrase et al., 2007). For the different cues presented during the anticipation phase and their monetary values, see Figure 1A. MID task trial structure is depicted in Figure 1B. A functional MID task session consisted of two runs including 72 trials each. To minimize learning effects during scanning, each subject completed a practice version of the task beforehand during acquisition of the anatomical scan, for which they did not receive monetary payment. Directly after scanning, participants undertook a retrospective rating of their own effort in response to each of the seven cues on a visual analogue scale (VAS effort).

fMRI

Event-related fMRI was performed on a 1.5 Tesla scanner (Magnetom VISION Siemens®) using gradient-echo-planar imaging (GE-EPI, TR = 1.9 s, TE = 40 ms, flip angle = 90°, matrix = 64 × 64). To optimize signal-to-noise and minimize signal drop-out in our main target region, the ventral striatum, we used a voxel size of 4 × 4 × 3.3 mm (Schmack et al., 2008; Ströhle et al., 2008; Wrase et al., 2007) (similar sequence [3.75 × 3.75 × 4 mm3]; TR = 40 ms (Knutson et al., 2001a)). Eighteen slices approximately parallel to the bicommissural plane (ac-pc-plane) were collected. The slices covered the mesolimbic and prefrontal regions of interest, as delineated by prior research (Knutson et al., 2001a). For anatomical reference, a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo, TR = 9.7 ms; TE = 4 ms; flip angle 12 degrees; matrix = 256 × 256, voxel size 1 × 1 × 1 mm) image data set was acquired.

Data analysis

FMRI data were analyzed with SPM5 (Statistical parametric mapping; http://www.fil.ion.ucl.ac.uk/spm). After discharging the first three volumes, slice time correction, realignment, spatial normalization into the MNI standard space and smoothing with an 8 mm full width at half maximum (FWHM) kernel were performed. Patients and controls did not differ in their maximum, mean and cumulative head motion (repeated measures ANOVA with time as intrasubject factor and group as between subject factor: all main effects and interaction p > 0.1).

At the first level analysis, changes in the BOLD response for each subject were assessed by linear combinations of the estimated GLM parameters (beta values), which are displayed by the individual contrast images (effect size equivalent to percent signal change). This analysis was performed by modeling the seven cue conditions, the target and the five feedback conditions separately as explanatory variables convolved with the canonical hemodynamic response function as provided in SPM5. Realignment parameters were included as additional regressors in the statistical model. To maximize

![Figure 1. A: Different cues presented during the anticipation phase and their monetary values. B: Trial structure for a representative successful gain (3€) trial. Each trial lasted 6.4 s and the mean inter-trial interval was 5 s.](http://jop.sagepub.com/com/jup)
sensitivity, we analyzed the anticipation phase by contrasting the anticipation of maximum gain (+36) vs. the anticipation of neutral (‘anticipation of gain vs. neutral’) and the anticipation of maximum loss (−36) vs. the anticipation of neutral (‘anticipation of loss vs. neutral’). A mixed ANOVA using time (T1 vs. T2) as repeated measure, group as a between-subject factor (controls vs. MDD) and subject as a random factor was calculated for the contrast images for gain and loss anticipation described above. We chose this method although our design – without a treated control group – was not fully factorial, in order to reveal neural changes between T1 and T2 in the MDD group, which are absent in the control group using an a priori defined interaction ([(MDD patients T2 > T1) – (Controls T1 > T2)]). Furthermore, we report the results (t-values) of within group activation at each time point; comparisons between both groups before and after treatment and changes within each group over time were calculated within the ANOVA design.

Given our a priori hypothesis of ventral striatal activation during the anticipation phase of the MID task (Knutson et al., 2001a, 2001b; Schmack et al., 2008), we used SPM’s small volume correction to correct for multiple testing. The ventral striatal region of interest (ROI) was specified from a publication-based probabilistic Montreal neurological institute (MNI) atlas used as a binary mask at the threshold of 0.75 probability (please refer to http://hendrix.imm.dtu.dk/services/jerne/voi/index-alphabetic.html; right: 1431 mm³, 53 voxels and left: 1485 mm³, 55 voxels). The significance level was p < 0.05 family-wise error (FWE)-corrected for the ventral striatal ROI. Exploratory t-tests at p < 0.05 FWE whole brain corrected and further results of other regions of interest (ACC, putamen) are reported in the supplementary material online (Supplementary 2.2). Transformation of MNI to Talairach coordinates was performed with the script ‘mni2tal’ provided by Matthew Brett (http://imaging.mrc-cbu.cam.ac.uk/ imaging/MniTalairach).

Behavioral and clinical data

Group differences (controls vs. MDD) in reaction times and self-reported motivation were analyzed within a repeated measures ANOVA with time (T1 vs. T2) and cue (anticipation of gain/loss vs. neutral) as intrasubject factors and reported at p < 0.05. Additionally, we tested whether ventral striatal activation during gain and loss anticipation correlated with symptom severity of depression or anhedonia in MDD patients. Therefore, we calculated a BDI anhedonia subscale consisting of the items: loss of pleasure (Item 4), loss of interest (Item 12) and loss of interest in sex (Item 21) (Leventhal et al., 2006; Pizzagalli et al., 2005). The individuals’ (i.e. beta values) ventral striatal maxima from the interaction effect of our ANOVA for the contrast ‘anticipation gain vs. neutral’ (Tal: x = −9, y = 14, z = −8) and ‘anticipation of loss vs. neutral’ (Tal: x = −18, y = 6, z = −3) were correlated with HRSD and BDI global scores and the BDI anhedonia subscale at baseline using Pearson’s linear correlation coefficients. To analyze the association between treatment response and the normalization of activity in the ventral striatum, we correlated the differences between ventral striatal activation at T2 versus T1 with the difference of symptom severity between T1 and T2.

Results

Symptom characteristics and behavioral data

Depression severity in patients significantly decreased after treatment with escitalopram (paired t-test, HRSD t = 11.14 and BDI (n = 13); t = 3.50; all p < 0.005), but this symptom improvement did not reach significance in the subjective BDI anhedonia scale. Eleven patients showed a clinically significant response (30% reduction of the HRSD score) and four were classified as non-responders.

Both groups displayed significantly faster responses on incentive trials compared with neutral trials (main effect of cue: F(2,27) = 39.537, p < 0.001), but no significant group difference, time effect or interaction (F-values: 0.136–1.76; all p < 0.1; Table 1). Analysis of self-reported effort to gain or loss revealed a significant effect of cue (F(2,27) = 67.104, p < 0.001), indicating greater self-reported effort during incentive trials compared with neutral trials and a trendwise group-by-time interaction (F(2,27) = 3.483, p = 0.074), indicating a tendency towards greater effort in the MDD patients after treatment (T2 > T1: t = −2.4, p < 0.03), while controls did not differ (t = 0.2, p = 0.84). No other significant main effects or interactions were observed (F-values: 0.142–1.809, all p > 0.1). Further details on reaction times and subjective effort during the MID task are reported in the supplementary material online (Supplementary Table 2, Supplementary Figures 1 and 2).

Brain activation during anticipation

Repeated measures ANOVA revealed a significant main effect of group during anticipation of loss in the ventral striatum (right side: F(1,28) = 15.19, p < 0.01, x = 12, y = 6, z = −5; left side: F(1,28) = 13.29, p < 0.05, x = −12, y = 6, z = −5) and a group-by-time interaction in the left ventral striatum (F(1,28) = 8.60, p = 0.05; x = −18, y = 6, z = −3; t = 2.93, p < 0.05; Figure 2A, B and Figure 3B top). The equivalent ANOVA for gain anticipation revealed no significant main effect of group or time but did reveal a trendwise group-by-time interaction in the left ventral striatum (t = 2.4; x = −9, y = 14, z = −8; p < 0.07, Figure 3B bottom).

Group comparisons between MDD patients and controls at baseline revealed blunted bilateral ventral striatal activation in MDD patients during loss anticipation (left side: t = 3.63, x = −12, y = 6, z = −5, p = 0.006 and right side: t = 3.59, x = 12, y = 6, z = −5, p = 0.007; Table 2 and Figure 3A top) and blunted right ventral striatal activation during gain anticipation (t = 2.9; x = 9, y = 11, z = −6, p = 0.025; Table 2 and Figure 3A bottom) After 6 weeks of treatment with escitalopram, patients and controls did not differ significantly in their ventral striatal activation, and both groups displayed strong activation during anticipation of both gain and loss (Table 2).

Paired t-tests comparing neural responses at baseline with responses after treatment revealed a significant increase of ventral striatal activity during anticipation of loss in the MDD group (t = 3.55; x = −18, y = 6, z = −3, p = 0.007; Figure 2B), Supplementary Table 2).
but not in controls (contrast ‘anticipation of loss > neutral’: uncorrected \( p > 0.05 \)). During anticipation of gain neural responses trendwise decreased in the control group (\( t = 2.45; x = 9, y = 12, z = -6; p = 0.063 \)), while no differences were found in the MDD group comparing both scanning sessions (contrast ‘anticipation of gain > neutral’: uncorrected \( p > 0.05 \)). Other significant regions (FWE-corrected for the whole brain) for both groups and sessions are listed in Supplementary Tables 3 and 4 online.

To further analyze the effect for the anticipation compared with the feedback phase we conducted additional analyses (see Supplementary 2.3–2.4 online).

**Associations between brain activation and symptom characteristics**

At baseline ventral striatal activation during anticipation of potential loss was inversely associated with the BDI total score (\( n = 13; r = -0.57, p = 0.04 \), Figure 2C left) and BDI anhedonia subscore (\( n = 13; r = -0.70, p = 0.007 \), Figure 2C middle), indicating a higher subjective rating of depressive symptoms in patients with reduced ventral striatal activation. We did not find a significant association between the ventral striatal activity during anticipation of gains with the three symptom measures and losses with the HRSD global score. The increase of activation elicited by loss anticipation over the course of treatment was positively associated with the subjective treatment response, that is, patients with the greatest decrease of depressive symptoms in the subjective BDI total score (T2–T1) had the highest increase in neural activity in the ventral striatum (T1–T2; \( n = 13; r = 0.58, p = 0.04 \), Figure 2C right). We found a comparable trendwise association between the neural activity increase in the ventral striatum during gain anticipation (T2–T1) and the BDI total score decrease over the course of treatment (T1–T2; \( n = 13; r = 0.54, p = 0.058 \)). It is important to note that only the correlation of the baseline activity in the ventral striatum and the BDI anhedonia subscore reached significance after correction for multiple testing, with regard to the number of conducted correlations performed (tests: 0.05/3 behavioral measures = 0.017).

**Controls for gender, subjective motivation and valence**

Consistent gender differences have been reported for depression (Nolen-Hoeksema and Hilt, 2009). Even if the number of male and female participants were equal in our groups, we calculated a repeated measures ANOVA for anticipation of gain and loss including gender as a covariate. Gender as a covariate did not change our result during anticipation of loss and revealed identical \( F-, t- \) and \( p- \)values.
Figure 2. A: Group-by-time interaction effect for the contrast ‘anticipation of loss vs. neutral’ (displayed at MNI y = 6; F > 4.1). B: Parameter estimates for the contrast ‘anticipation of loss vs. neutral’ in the peak voxel $x = -18$, $y = 6$, $z = -3$. C: Significant correlations between ventral striatal activity during anticipation of loss at the peak voxel and symptom severity scores ($N = 13$). Left: baseline activity correlated with BDI total score at T1. Middle: baseline activity correlated with BDI anhedonia subscale at T1. Right: effect of time (i.e. difference T2−T1) on BOLD responses correlated with improvement in BDI total score (T1–T2). Pearson’s coefficient; significant $p$, two-tailed.

Figure 3. A: Baseline group differences: Top: during anticipation of maximum loss compared with neutral, MDD patients show significantly less bilateral ventral striatal activation (Talairach coordinates: $x = -12/12$, $y = 6$, $z = -5$, $t > 3.58$, $p < 0.01$ corrected for small volume) compared with controls. Bottom: during anticipation of maximum gain compared with neutral, MDD patients show significantly less right ventral striatal (VS) activation ($x = 9$, $y = 11$, $z = -6$, $t = 2.9$, $p = 0.025$ corrected for small volume) compared with controls (for illustrative purposes, $p < 0.01$ uncorrected). B: Effect sizes ($\beta$-values) for the interaction effect of group-by-time in the ventral striatum during anticipation of maximum loss (top, $x = -18$, $y = 6$, $z = -3$; $p < 0.05$ FWE-corrected) and the trendwise interaction effect of group-by-time during the anticipation of maximum gain (bottom; $x = -9$, $y = 14$, $z = -8$; $p < 0.07$ FWE-corrected) vs. neutral.
During anticipation of gain, this ANOVA did not reveal a significant main effect of time, group and group-by-time effect in the ventral striatum, but differential effects were still significant. During baseline, MDD patients showed a slightly more strongly decreased response of the ventral striatum compared with controls \((t = 2.94, x = 9, y = 12, z = -6, \text{FWE-corrected} \ p = 0.025; \text{without covariate:} \ t = 2.90, p = 0.025)\). After treatment, groups did not differ. Therefore, we conclude that gender does not have a strong effect on our results. While the result was stable during loss anticipation, it was slightly stronger during gain.

As groups differed in subjective effort to gain at baseline and after treatment, we calculated a repeated measures ANOVA for the contrast anticipation of gain vs. neutral including the subjective effort to gain money as a covariate (visual analog scale). There was no significant main effect for group, time and no group-by-time effect in the ventral striatum during anticipation of gain. It is plausible to suggest that we controlled for the influence of subjective motivation by including the scale ‘subjective effort to gain money’ as a covariate. If we control for the variance in the neuronal data explained by subjective motivation, we weaken our results of a group-by-time interaction. This result underpins the association between the decrease of ventral striatal activity during anticipation of gain and subjectively reduced motivation independent of psychopathology and speaks against a direct neurovascular effect of the pharmacological agent.

As participants generally assign a greater weight to a loss than a gain of equal magnitude (e.g. see Kahneman and Tversky, 1979), we calculated a repeated measures ANOVA for the contrast ‘middle loss magnitude \((-0.606)\) vs. the maximal reward magnitude \((+3\varepsilon)\) cues’. There was no main effect for group, time and no group-by-time effect in the ventral striatum. Additionally, patients and controls did not differ at baseline or after treatment in group comparison.

**Discussion**

To the best of our knowledge, this study is the first to report hyporeactivity of the ventral striatum – a core region of the brain reward system – during the anticipation of positive and negative monetary incentives in unmedicated MDD patients relative to controls before, but not after, 6 weeks of successful treatment with escitalopram. We found a significant group-by-time interaction during processing of negative incentives due to increased ventral striatal activity in patients after treatment. In addition, ventral striatal hyporesponsiveness was associated with the severity of depression, in particular anhedonic symptoms.

**Brain activation before treatment**

The finding of diminished recruitment of the ventral striatum during the anticipation of loss and gain cues in acutely depressed patients adds to the literature that ventral striatal activity is not only reduced in response to pleasant stimuli (Epstein et al., 2006; Keedwell et al., 2005; Lawrence et al., 2004) and during reinforcement learning (Kumar et al., 2008; Steele et al., 2007), but also in response to incentive cues. This result stands in contrast to studies using a comparable reward task, which did not find alterations in the ventral striatum in MDD patients during anticipation (Knutson et al., 2008; Pizzagalli et al., 2009). Furthermore, a large body of fMRI research documented decreased responses to positive stimuli, but increased subcortical responses to negative emotional stimuli (Fu et al., 2004; Keedwell et al., 2005, 2009; Surguladze et al., 2005). Using a specific reward paradigm, we revealed decreased ventral striatal activity during cues of negative and positive valence and did not detect differences related to loss compared with gain anticipation (Supplementary 2.5 online).

Our results indicate that patients who show minimal ventral striatal activation during anticipation of loss cues reported more depressive symptoms, particularly related to anhedonia. Prior studies showed a relationship between a ventral striatal hypofunction and anhedonic symptoms in non-clinical subjects (Wacker et al., 2009), depression (Epstein et al., 2006; Keedwell et al., 2005; Kumar et al., 2008; Steele et al., 2007) and schizophrenia (Juckel et al., 2006a, 2006b). Keedwell et al. (2005) and other researchers found neuronal hyporeactivity during acute depression towards negative incentives to be more strongly associated with anhedonia than neuronal hyporeactivity towards positive incentives. However, they used a paradigm to induce negative mood rather than anticipation of loss.

The present finding of dysfunctions during the anticipation but not the feedback phase could, for example, be due to experimental differences from the study of Pizzagalli et al. (2009). The probability of winning in their study was balanced out by chance (i.e. 50%, versus 66% in the present study) for each trial type. Hypothetically, phasic dopaminergic bursts (Schultz et al., 1997) never fully transitioned to anticipatory from outcome stimuli in the study of Pizzagalli et al. (2009), but they did in our study. Our secondary analysis on the specificity of ventral striatal hypofunction during the anticipation phase did not reveal a group-by-time-phase interaction (see Supplementary 2.3–2.4 online). Therefore the debate on a specific deficit during the anticipation or consumption of incentives remains open. Another reason for the discrepancy from other studies using similar tasks (Knutson et al., 2008; Pizzagalli et al., 2009) might be that the current sample also included inpatients. It is, however, acknowledged that suggestions about a higher severity of illness with stronger anhedonic symptoms than in the present sample remain speculative. Moreover, since whole brain images were not acquired, we could not verify altered activation in the dorsal ACC (Knutson et al., 2008). Further studies may examine the relationship between anhedonia as well as anergia in MDD patients and ventral striatal activation in greater detail using more specific instruments to assess these symptoms.

Clinically, our results are in line with the assumption of a global belief of lacking personal influence in depression, as postulated in the learned helplessness theory (Seligman, 1978). This would also predict less effort in approach and withdrawal behavior (Chase et al., 2009). These results further support the notion that ventral striatal activation is elicited by incentive salience (‘wanting’) (Berridge, 2007; Heinz, 2002; Seymour et al., 2007) rather than by valence (Cooper and Knutson, 2008) in humans. Reduced ventral striatal responses to loss and gain cues could lead to less effort to work for positive experiences and to avoid negative ones.
Brain activations after treatment

The main aim of this study was to examine whether ventral striatal activity varies before and after treatment. Our results confirm the hypothesis that successful treatment diminishes ventral striatal alterations in MDD patients. Group comparisons revealed decreased activity during processing of potential loss and gain indicating cues before, but not after, pharmacotherapy. However, the group-by-time effect was only significant for loss cues.

Increased ventral striatal activation during anticipation of potential loss after pharmacotherapy in MDD patients was associated with a reduction in subjectively experienced depressive symptoms over the course of treatment. In line with this, other treatment strategies, like deep brain stimulation in the ventral striatum, increase glucose metabolism and reduce anhedonic symptoms (Bewernick et al., 2010; Schlaepfer et al., 2008). Increased activity in the dorsal striatum during anticipation of reward has also been found after ‘Behavioral Activation Therapy for Depression’, a psychotherapy modality designed to increase engagement with rewarding stimuli and to reduce avoidance behaviors (Dichter et al., 2009). In addition, measures of subjective effort to gain money increased over the course of treatment in our patient sample. Our finding of increased ventral striatal activity over the course of treatment to loss indicating cues stands in contrast to the hypothesis of reduced reactivity of the ventral striatum during reward processing (and potentially related anhedonic symptoms) as a stable endophenotype of depression (Hasler et al., 2004). Based on the present findings, ventral striatal responsivity may instead index an motivational state during a depressive episode. Together these results are consistent with findings indicating an indirect delayed improvement of depressive symptoms via enhanced emotional information processing after antidepressant treatment (Harmer et al., 2003, 2008).

While a non-significant decrease of ventral striatal response in the healthy control group may indicate a habituation effect, in depressed patients no such habituation effect was detected. It is plausible to suggest that patients with MDD were getting less familiar with the task and felt a greater challenge (in a phase of the illness when they are motivated to escape their deficits) than healthy participants. However, we found no significant differences between MDD patients and healthy participants in behavioral task performance, even if within both groups the reaction time varied according to the value of presented cues (see Supplementary Figure 1 online). The MID task is aimed at minimizing unspecific behavioral changes of performance, cooperation or attention. The task includes a training session before scanning and seems to be too simple to detect differences in this behavioral measure between groups. The lack of differences between healthy participants and patients has already been reported in other studies (Juckel et al., 2006a, 2006b; Kumar et al., 2008; Ströhle et al., 2008) and indicates that MDD patients and controls followed the instructions well but might have performed at ceiling.

The more pronounced abnormal response during the anticipation of potential loss pretreatment and the higher activity changes after treatment are contrary to the notion that ventral striatal dysfunctions are more related to the presentation of positive rewarding stimuli (Wacker et al., 2009). It may be possible that the mood-congruent bias during depression causes a negative bias in the reward expectancy, that is, depressive patients overestimate the failure to avoid losing, and therefore the loss condition could have a lower motivational salience during the depressive state. Another explanation would be that the shift of ventral striatal activation from feedback to anticipation (Schultz et al., 1997) is weaker for loss in MDD, which would account for the greater differences in the loss condition. Accordingly, Pizzagalli et al. (2009) may have found decreased activity during feedback of loss because ventral striatal signals evoked in healthy subjects during anticipation of loss were still evoked during feedback in MDD patients, thus increasing ventral striatal activity during feedback of loss in depressed subjects. Furthermore, while anhedonic symptoms have been shown to be more strongly related to neural hyporeactivity in acutely depressed patients, neural changes over the course of treatment were most strongly related to symptom improvement during sad emotional face processing (Keedwell et al., 2009). From a pharmacological perspective, SSRI treatment could have a slightly more pronounced or faster impact on the anticipation of potential loss than on gain anticipation, as serotonin has been suggested to be strongly involved in processing aversive stimuli and anxiety-induced avoidance (Cools et al., 2008; Daw et al., 2002; Graeff et al., 1996).

Limitations

One limitation of the present study involves the open-label design, since no MDD patient group treated with placebo (or, respectively, a healthy control group receiving escitalopram) could be included for ethical reasons. Thus, the present design was not fully factorial and we cannot rule out that the observed increase of ventral striatal activity during anticipation of loss cues may be due to an unspecific amelioration of depressive symptoms or a specific effect of escitalopram on reward functions. The former interpretation is supported by studies suggesting a rather dampening effect of SSRIs on reward functions (for review see Kranz et al., 2010 and Nutt et al., 2007) and a low effectivity of SSRIs in reducing reward-related symptoms of depression, like loss of interest and motivation (Price et al., 2009). Furthermore, associations of symptom reductions and subjective effort with changes in neural activity support an illness-related account rather than a direct medication effect. However, delayed reduction of anhedonic symptoms after SSRI treatment has been shown in patients with MDD (Boyer et al., 2000) and some animal studies suggest that serotonin facilitates dopamine release in reward-related areas such as the nucleus accumbens, for example, after chronic antidepressant treatment (Zangen et al., 2001). Previous studies showed an inverse effect of acute medication on reward learning signals, since acute administration of an SSRI (citalopram) significantly reduced rather than increased signal in reward-related areas in healthy subjects, a finding that was also observed in a group of treatment-resistant, medicated patients (Kumar et al., 2008). The authors suggested that differences in activation between patients and unmedicated controls should be diminished in
patients responsive to medication, which fits well with the presently observed ‘normalization effect’ after successful treatment.

**Summary**

In summary, our findings indicate diminished neural response in the ventral striatum during anticipation of monetary incentives in unmedicated MDD patients, which were related to depressive and particularly anhedonic symptoms. We also observed a normalization of the diminished responsiveness to negative incentives after 6 weeks of successful treatment with serotonergic medication, which was negatively correlated with symptom severity. Further investigations will have to assess effects of different pharmacological agents as well as analyze subgroups of treatment responders and non-responders (see Supplementary 2.6 online) over the time of treatment to specify state and trait characteristics of ventral striatal hyporesponsiveness.

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**Conflicts of interest**

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