# Reduced Reward Learning Predicts Outcome in Major Depressive Disorder

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**Background:** Reduced reward learning might contribute to the onset and maintenance of major depressive disorder (MDD). In particular, the inability to utilize rewards to guide behavior is hypothesized to be associated with anhedonia, a core feature and potential trait marker of MDD. Few studies have investigated whether reduced reward learning normalizes with treatment and/or reward learning predicts clinical outcome. Our goal was to test whether MDD is characterized by reduced reward learning, especially in the presence of anhedonic symptoms, and to investigate the relationship between reward learning and MDD diagnosis after 8 weeks of treatment.

**Methods:** Seventy-nine inpatients and 63 healthy control subjects performed a probabilistic reward task yielding an objective measure of participants' ability to modulate behavior as a function of reward. We compared reward responsiveness between depressed patients and control subjects, as well as high- versus low-anhedonic MDD patients. We also evaluated whether reward-learning deficits predicted persistence of MDD after 8 weeks of treatment.

**Results:** Relative to control subjects, MDD patients showed reduced reward learning. Moreover, patients with high anhedonia showed diminished reward learning compared with patients with low anhedonia. Reduced reward learning at study entry increased the odds of a persisting diagnosis of MDD after 8 weeks of treatment (odds ratio 7.84).

**Conclusions:** Our findings indicate that depressed patients, especially those with anhedonic features, are characterized by an impaired ability to modulate behavior as a function of reward. Moreover, reduced reward learning increased the odds for the diagnosis of MDD to persist after 8 weeks of treatment.

**Key Words:** Anhedonia, major depression, psychopathology, outcome, reward learning task, reward responsiveness

Anhedonia is a core feature and potential trait marker of major depressive disorder (MDD) (1,2). The presence of anhedonic symptoms has been found to predict poor treatment outcome in MDD (3). However, the precise mechanisms underlying anhedonia in MDD remains poorly understood. Clinical and neurobiological studies over the past 10 years suggest that anhedonia is not a monolithic phenomenon but can be parsed in 1) a reduction in experienced pleasure (liking reward), 2) a dysfunction in the approach-related system subserving motivated behavior (wanting reward), and/or 3) disrupted reward learning (4,5). In particular, evidence suggests that anhedonia in MDD is associated with an inability to respond to positive reinforcers, leading to abnormal reward-based decision making and impairment in goal-directed behaviour (6,7). For instance, depressed patients have shown a reduced ability to integrate previous reinforcements and modulate behavior accordingly (8,9), and several studies have described altered patterns of reinforcement-related decision making in depressed patients compared with control subjects (10,11). These behavioral abnormalities have been complemented by reports of dysfunctional activation in MDD within mesocorticolimbic regions critically implicated in reward processing (12–16).

Despite compelling evidence indicating that MDD is characterized by reduced reward responsiveness, several important questions remain largely unanswered. First, it is unclear whether such dysfunctions are generally present in MDD or might be characteristic of patients reporting anhedonic symptoms in their daily life. Second, few studies have investigated whether blunted reward learning persists after treatment of MDD. Finally, little is known about whether blunted reward learning predicts a persisting MDD diagnosis despite treatments.

The goal of the current study was to address these gaps in the literature. Accordingly, we aimed to assess reward learning in a relatively large sample of treatment-seeking patients with MDD and investigate the association between anhedonia and reward learning within an depressed inpatient sample. In addition, we investigated the relationship between reward learning and clinical outcome after 8 weeks of treatment. To pursue these goals, we used a laboratory-based probabilistic reward task that objectively measures participants' ability to modulate behavior as a function of reward (17). We hypothesize that, relative to control subjects, MDD inpatients would show reduced reward learning toward a more frequently rewarded stimulus, and patients with high anhedonic symptoms would show such dysfunction compared with less anhedonically depressed subjects. In addition, we expected that reduced reward learning would predict a persisting diagnosis of MDD after 8 weeks of treatment.

## Methods and Materials

### Participants

Eighty-three patients meeting DSM-IV criteria for MDD were included. All patients were hospitalized at the University

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Psychiatric Center of the University of Leuven and were evaluated within their first week of admission. Participants with bipolar disorder, substance-related disorders, or any other unstable medical condition were excluded. Almost all patients had already started antidepressant treatment before admission. During follow-up, treatment was not standardized, and patients were treated with psychopharmacology and/or psychotherapy, as clinically appropriate. Sixty-eight healthy volunteers were included. Controls were matched by age and gender. Exclusion criteria for controls were as follows: any current or past psychiatric disorder, past mood disorder, or any other current unstable medical condition including thyroid problems. After 8 weeks, a follow-up session with clinical assessments and read-ministration of the reward task took place for the depressed group (control subjects were tested only at baseline). Participants signed an informed consent, and the study was approved by the local ethics committee.

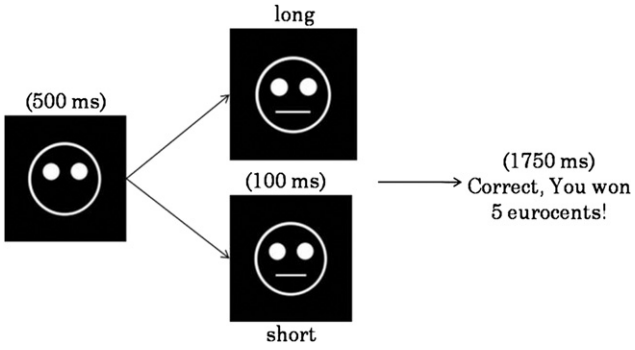


**Figure 1.** Schematic representation of the probabilistic reward task. In each trial, participants identified (via key press) whether a short or long mouth stimulus had been presented in the mouthless face on the screen. In approximately 40% of the trials, a positive reinforcement (monetary reward) was presented.

## Task and Procedures

**Clinical Assessment.** The Structured Clinical Interview for DSM-IV-TR (18) was used to ascertain whether patients met DSM-IV criteria for MDD. The 17-item Hamilton Rating Scale for Depression (HDRS) (19) was used to assess depression severity. In addition, all participants completed the Snaith Hamilton Pleasure Scale (SHAPS) (20). The SHAPS is a 14-item questionnaire designed to measure hedonic tone or its absence, anhedonia. Higher scores indicate higher anhedonic symptoms (21).

**Reward Task.** We used a computerized reward-learning task rooted in signal detection theory that yields an objective measurement of participant's ability to modulate behavior as a function of rewards (6). The task was previously shown to have adequate test–retest reliability (17), as well as convergent and predictive validity. Specifically, among nonclinical samples, reward learning in this task correlated negatively with self-reported anhedonic symptoms and predicted these symptoms 30 to 40 days later (17,22). In addition, the task was found to measure reward responsiveness objectively in healthy volunteers (6,17) as well as in MDD (6,23) and bipolar disorder patients (24). The task is described extensively in Pizzagalli *et al.* (17).

Briefly, the task was presented on a 17-inch flat screen using E-prime software (version 1.2; Psychology Software Tools Inc., Pittsburgh, Pennsylvania). The task lasted approximately 25 minutes and included 300 trials, divided in 3 blocks of 100 trials, separated by two short breaks (30 sec). Each trial started with a fixation point, shown for 500 msec in the middle of the screen, which was replaced with a mouthless cartoon face. After 500 msec, a short (11.5 mm) or long (13 mm) mouth appeared for 100 msec (Figure 1). Participants were instructed to make a key response to identify which type of mouth had been presented.

In each block, both stimuli were shown an equal number of times, and a monetary reward feedback was given to approximately 40 correct answers. To induce a response bias, an asymmetrical reinforcer schedule was used, such as correct responses for 1 mouth (referred to as the "rich stimulus") were rewarded three times more frequently (30 vs. 10) than correct responses of the other mouth (referred to as the "lean stimulus"). The reinforcement allocation and key presses were randomized across subjects. Coupled with the small difference between mouth sizes and the brief stimulus exposure time (100 msec), the asymmetric reinforcement schedule reliably induces a response bias among healthy participants (25). Before the task, participants received verbal and written instructions. It was emphasized that the main goal of the task was to win as much money as possible and the total amount of accumulated money (approximately 5 euros) would be handed out in cash at the end of the experiment. Participants were informed that not all correct responses would result in a monetary reward. However, it was emphasized that more correct identifications would result in more earnings. Because of the unequal frequency of reward feedback, participants with high reward responsiveness were expected to develop a response bias in favor of the rich stimulus. Subjects with low reward responsiveness were expected to develop a smaller or no bias. Participants were informed about the task contingencies and fully debriefed only at the end of the study.

## Data Collection and Reduction

Before analyses, outlier responses were identified using a two-step procedure (17): first trials with reaction time (RT) shorter than 150 msec or longer than 1500 msec were excluded; second, for each participant, trials with mean $\pm$ 3 SD were excluded (after applying a log transformation to normalize RT distribution). Moreover, participants with more than 30 outlier trials were excluded from the analyses.

Task performance was assessed by analyzing two main variables: 1) discriminability (DIS), which is an index of participants' ability to perceptually distinguish between the two stimuli and is used as a proxy of task difficulty and 2) response bias (RB), which reflects participants' preference for the stimulus paired with more frequent rewards. RB toward the rich stimulus was used as a measure for reward learning (see formulas) and was our main behavioral variable of interest. To enable RB and DIS calculation in cases with zero in one cell of the formula, .5 was added to each cell in the matrix (6).

Response Bias:

$$\log b = \frac{1}{2}\log\left(\frac{(\text{Rich}_{\text{correct}}+.5)*(\text{Lean}_{\text{incorrect}}+.5)}{(\text{Rich}_{\text{incorrect}}+.5)*(\text{Lean}_{\text{correct}}+.5)}\right)$$

Discriminability:

$$\log d = \frac{1}{2}\log\left(\frac{(\text{Rich}_{\text{correct}}+.5)*(\text{Lean}_{\text{correct}}+.5)}{(\text{Rich}_{\text{incorrect}}+.5)*(\text{Lean}_{\text{incorrect}}+.5)}\right)$$

## Statistical Analysis

Analyses were performed with SAS version 9.2 (SAS institute, Cary, North Carolina). $\chi^2$ tests and unpaired *t* tests were run to

**Table 1.** Demographic and Clinical Features of Control Group ($n = 63$) and Depressed Group at Baseline ($n = 79$)

| | Control | | MDD | | Statistics | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | *p* |
| Age | 44.5 | 11.6 | 45.0 | 11.9 | $t = .3$ | >.5 |
| Female/Male | 38/25 | — | 48/31 | — | $\chi^2 < .01$ | >.5 |
| Anxiety Disorder (%)[a] | — | — | 49.4 | — | — | — |
| Age of Onset | — | — | 36.0 | 13.0 | — | — |
| Number of Episodes[b] | — | — | 2.5 | 1.9 | — | — |
| Medication (Yes/No)[c] | — | — | 76/3 | — | — | — |
| HDRS | — | — | 16.9 | 4.9 | — | — |
| SHAPS | .4 | .9 | 7.3 | 3.6 | $t = 14.8$ | <.01 |

HDRS, Hamilton Depression Rating Scale; SHAPS, Snaith Hamilton Pleasure Scale.

[a]Anxiety disorder = Structured Clinical Interview for DSM-IV-TR diagnosis of panic disorder and/or agoraphobia ($n = 33$), social phobia ($n = 5$), and/or obsessive-compulsive disorder ($n = 1$).

[b]Number of episodes = average (34.5% first episode; 32.2% second episode; 33.3% third or higher episode).

[c]Medication: number of patients taking psychopharmacology yes/no (40.5% selective serotonin reuptake inhibitor; 34.2% serotonin and norepinephrine reuptake inhibitor; 5.3% others [e.g., tricyclic, mirtazepine, bupropion]).

examine group differences in sociodemographic and clinical variables. Several sets of analyses were performed to test the study hypotheses. First, to assess overall group differences in the reward task, separate mixed analyses of variance (ANOVAs) with Group (MDD, control) and Block (1, 2, or 3) as factors were performed for RB and DIS. Second, to test the hypothesis that high anhedonic MDD patients would specifically show blunted reward learning, mixed ANOVAs with MDD Subgroup (low- vs. high-anhedonic MDD) and Block as factors were run on RB and DIS. MDD subgroups were defined by using a median split of SHAPS score; patients with SHAPS scores above 7 were defined as "high anhedonic" and those with SHAPS ≤7 as "low anhedonic." This categorical approach was supplemented by complementary analyses in which anhedonic symptoms were considered as a continuum. Thus, Pearson correlations and hierarchical regression analyses were computed to evaluate the relation between SHAPS scores and RB. To directly assess overall reward-learning ability, a difference score (Δresponse bias) between RB over time was calculated ($\Delta RB_{3-1} = RB_{Block3} - RB_{Block1}$). Third, to evaluate whether treatment normalized reward-learning dysfunction, mixed ANOVAs on RB and DIS were performed comparing controls' baseline data and patients' follow-up data (after 8 weeks of treatment). Finally, a logistic regression analysis was performed to test whether baseline reward learning ($\Delta RB_{3-1}$) predicted a persisting diagnosis of MDD after 8 weeks of treatment while controlling for depression severity at baseline. Throughout the ANOVAs, significant effects were followed up with one-way ANOVA entering Block (1, 2, or 3) as repeated measure for each group separately as well as post hoc Tukey-Kramer tests. The Greenhouse-Geisser correction was used when appropriate.

## Results

### Demographic and Clinical Data

Eighty-three MDD patients and 68 control subjects were included. We excluded four MDD and 5 control subjects due to task noncompliance, leaving 79 patients and 63 control subjects for the analyses. Forty-four patients had high anhedonic symptoms (SHAPS >7), and 35 patients had low anhedonic symptoms (SHAPS ≤7). None of the control subjects had high anhedonic symptoms. Nineteen patients dropped out before the assessment at 8 weeks, so 60 patients completed the follow-up screening after 8 weeks. Sociodemographic and clinical information of the final sample are listed in Tables 1 through 3.

**Table 2.** Demographic and Clinical Features of the Depressed Group at Follow-up (After 8 Weeks; $n = 60$)

| | Mean | SD |
|---|---|---|
| MDD Diagnosis[a] | 32/28 | — |
| Anxiety Disorder (%)[b] | 28.7 | — |
| Medication (Yes/No)[c] | 60/0 | — |
| HDRS | 10.8 | 6.6 |
| SHAPS | 4.5 | 4.1 |

HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; SHAPS, Snaith Hamilton Pleasure Scale; SCID-I, Structured Clinical Interview for DSM-IV-TR.

[a]MDD diagnosis at follow up with SCID-I: number of patients yes/no.

[b]Anxiety disorder = SCID diagnosis of panic disorder and/or agoraphobia ($n = 11$), social phobia ($n = 5$), and/or obsessive-compulsive disorder ($n = 1$).

[c]Medication: number of patients taking psychopharmacology yes/no (35.0% selective serotonin reuptake inhibitor; 40.0% serotonin and norepinephrine reuptake inhibitor; 25.0% others [e.g., tricyclic, mirtazepine, bupropion]).

As assessed by the Structured Clinical Interview for DSM, 49.37% suffered from a comorbid anxiety disorder (33 patients with panic disorder and/or agoraphobia, 8 with social phobia, and 1 with obsessive-compulsive disorder). Patients with comorbid anxiety did not differ from those without anxiety with regards to age, gender ratio, HDRS scores, and SHAPS scores (all $ps > .07$). Furthermore, ANOVA analyses revealed no significant differences in RB and DIS

**Table 3.** Demographic and Clinical Features of MDD Subgroups at Baseline: Low Anhedonic Patients ($n = 34$) and High-Anhedonic Patients ($n = 44$)

| | Low Anhedonia[a] | | High Anhedonia[b] | | Statistics | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | *p* |
| Age | 47.6 | 11.9 | 43.0 | 11.6 | $t = 1.7$ | .1 |
| Female/Male | 17/17 | — | 30/14 | — | $\chi^2 = 2.3$ | .1 |
| Anxiety Disorder (%)[c] | 48.6 | — | 50.0 | — | $\chi^2 = .02$ | >.5 |
| Age of Onset | 36.8 | 14.0 | 35.0 | 12.2 | $t = .61$ | >.5 |
| Number of Episodes[d] | 2.3 | 1.9 | 2.6 | 2.0 | $t = .64$ | >.5 |
| Medication (Yes/No)[e] | 33/1 | — | 42/2 | — | $\chi^2 = .01$ | >.5 |
| HDRS | 14.7 | 4.5 | 18.6 | 4.5 | $t = 3.8$ | .01 |
| SHAPS | 4.0 | 2.4 | 9.8 | 1.9 | $t = 12.0$ | <.01 |

HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; SHAPS, Snaith Hamilton Pleasure Scale; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Low anhedonia = SHAPS score ≤7.

[b]High anhedonia = SHAPS >7.

[c]Anxiety disorder = Structured Clinical Interview for DSM-IV-TR diagnosis of panic disorder and/or agoraphobia, social phobia and/or obsessive-compulsive disorder.

[d]Number of episodes = average (Low anhedonia = 35.9% first; 38.5% second; 25.6% third or more. High anhedonia = 33.3% first; 26.7% second; 40.0% third or more).

[e]Medication: number of patients taking psychopharmacology yes/no (Low anhedonia = 35.0% SSRI; 40.0% SNRI; 25.0% others. High anhedonia = 37.8% SSRI; 35.6% SNRI; 22.2% others).

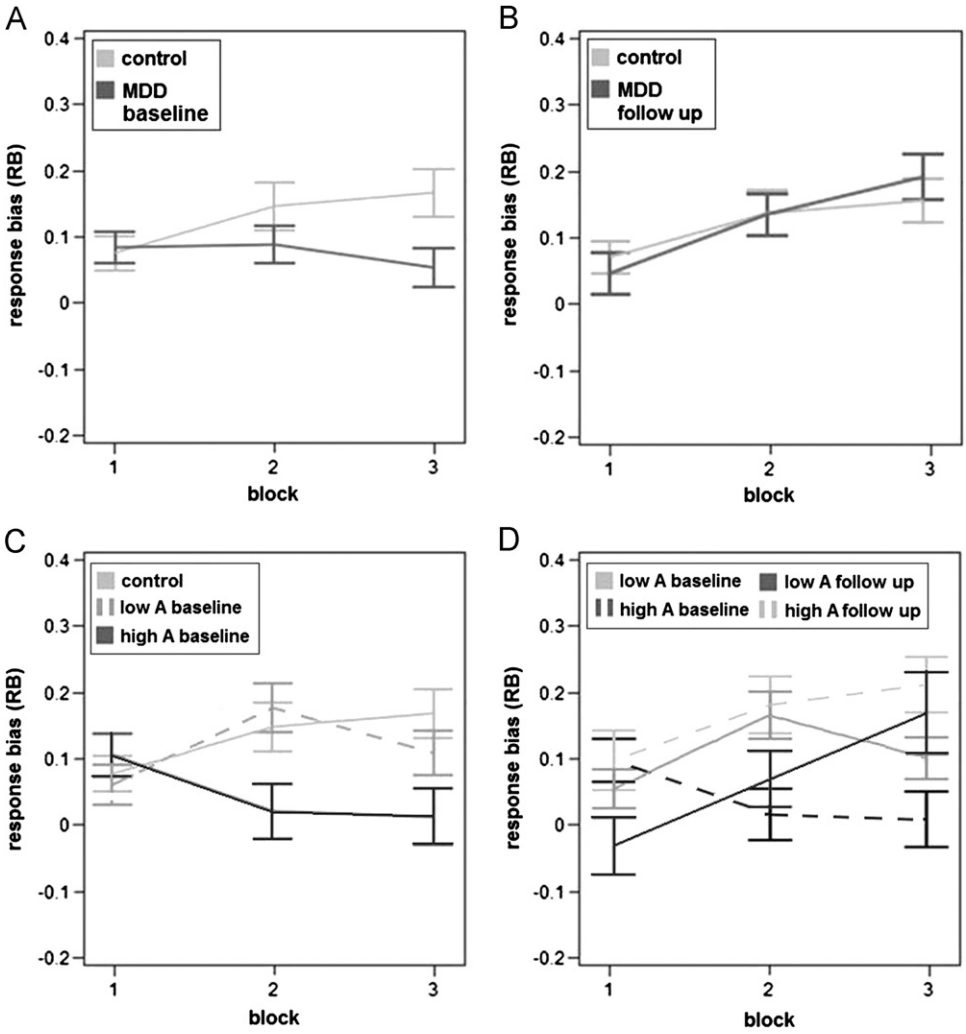


**Figure 2.** Response bias (RB) as a function of blocks for **(A)** control and major depressive disorder (MDD) groups at baseline; **(B)** control and MDD groups at follow-up (after 8 weeks); **(C)** control, low-anhedonic (low A) and high-anhedonia (high A) groups at baseline; and **(D)** low-A and high-A groups at baseline as well as at follow-up (after 8 weeks). Error bars denote SEM.

between MDD patients with versus without anxiety comorbidity (all $Fs < .36$, all $ps > .35$). Age of onset and number of previous MDD episodes were not significant predictors of the overall response bias at baseline or after 8 weeks of treatment. Similarly, HDRS scores did not correlate with overall response bias at baseline. Moreover, ANOVA analysis showed no significant differences in task performance (both in RB and DIS) between MDD patients on selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), or another psychopharmacologic treatment at baseline. Among the MDD sample, baseline HDRS and SHAPS scores were significantly correlated (Pearson $r = .49$, $p < .0001$).

## Task Performance

**Between Group (MDD, Control) Comparisons**. The ANOVA on RB scores revealed a significant Group × Block interaction [$F(2,280) = 3.53$, $p = .03$, $\varepsilon = .95$], due to a reduced reward-learning ability in MDD patients compared with controls (Figure 2A). Unpaired $t$ tests showed that, relative to control subjects, MDD patients had significantly lower RB in Block 3 ($t = 2.45$, $p = .01$). Moreover, follow-up one-way ANOVAs showed that the control group had a significant increase of RB over time [Block effect: $F(2,124) = 4.83$, $p = .01$, $\varepsilon = .91$] due to significantly higher RB in Block 2 ($t = 2.63$, Tukey–Kramer adjusted [Adj]$p = .03$) and Block 3 ($t = 2.60$, Adj$p = .03$) relative to Block 1. An analogous one-way ANOVA in the MDD group revealed no Block effect ($p = .55$), indicating that patients failed to develop a response bias toward the rich stimulus.

When considering DIS, no significant effect emerged, suggesting that controls and MDD subjects performed equally well in discriminating the short from the long mouth (all $Fs < .56$, all $ps > .55$). Moreover, one-way ANOVA on DIS scores revealed no significant effect of Block for either groups (all $Fs < .37$, all $ps > .67$).

**Within Depressed Group (Low Anhedonia, High Anhedonia) Comparisons at Baseline**. With regard to RB, high-anhedonic patients showed a significantly reduced reward learning over time compared with low-anhedonic patients [MDD Group × Block interaction: $F(2,152) = 5.15$, $p = .009$, $\varepsilon = .94$; Figure 2C]. Follow-up one-way ANOVA in the low-anhedonic patients revealed significant learning over time [Block effect: $F(2,68) = 3.34$, $p = .046$, $\varepsilon = .93$) due to higher RB in Block 2 relative to Block 1 ($t = 2.85$, Adj$p = .02$). In contrast, the main effect of Block was not significant in high-anhedonic patients, indicating blunted reward learning. Additionally, unpaired $t$ tests in each Block showed a significant difference between high anhedonic group compared with control subjects in Block 2 ($t = 2.31$, $p = .02$) and Block 3 ($t = 2.76$, $p = .007$). Low-anhedonic patients did not differ from controls when comparing RB in each block.

With regard to DIS, no significant effects emerged (all $Fs < 1.63$, $ps > .2$), indicating that the two MDD subgroups found the task equally difficult. Similarly, one-way ANOVA on DIS scores revealed no significant effect over time for both depressed subgroups (all $Fs < 1.86$, $ps > .17$). We also found no group differences, for DIS scores between control subjects and low- as well as high-anhedonic patients (all $Fs < 2.20$, $ps > .11$).

As shown in Table 3, low- and high-anhedonic patients were matched in their demographic variables, but the high-anhedonic group had more severe depression. To evaluate whether the reward-learning difference between the MDD subgroups was specifically related to anhedonia and not simply due to depression severity, we conducted a regression analysis (stepwise selection) of RB in Blocks 1, 2, and 3, as well as reward learning across the 300 trials ($= RB_{Block3} - RB_{Block1}$) and 200 trial ($= RB_{Block2} - RB_{Block1}$), with HDRS scores and MDD subgroup (high anhedonia and low anhedonia) as independent variables. Findings revealed that MDD subgroup was the unique predictor of RB in Block 2 ($R^2 = .09$, $p = .008$), ΔRB over 200 trials ($R^2 = .13$, $p = .001$) and ΔRB over 300 trials ($R^2 = .04$, $p = .07$). HDRS scores were not related to the performances on the reward task.

**Relationship Between Reward Learning and Anhedonic Symptoms Within MDD Group at Baseline.** For the depressed group, overall reward learning ($= RB_{Block3} - RB_{Block1}$) did not correlate with anhedonic symptoms, as measured by the SHAPS scale. When considering RB learning after 200 trials ($= RB_{Block2} - RB_{Block1}$) in a post hoc analysis, SHAPS scores in the MDD group were significantly related to reward learning in the expected direction ($r = -.33$, $p = .003$).

To better understand the nature of the relationship between anhedonic symptoms and reward learning, we conducted a linear stepwise regression analysis with $\Delta RB_{2-1}$ as dependent variable to test whether anhedonic symptoms (considered as continuum) predicted reward learning when accounting for depression severity and anxiety comorbidity. To this end, SHAPS and HDRS scores and the presence of an anxiety disorder (dummy coded) were entered in the model. SHAPS scores were the unique predictor of $\Delta RB_{2-1}$ ($\beta = .33$, $t = 3.08$, $p = .003$), revealing a significant overall effect [$R^2 = .11$, $F(1,76) = 9.47$, $p = .003$].

**Between Group (MDD [Follow-up], Control [baseline]) Comparisons**. With regard to RB, when comparing the control group (baseline) with the depressed patients after 8 weeks of treatment, we found no significant group differences [Group × Block interaction: $F(2,242) = .94$, $p = .40$, $\varepsilon = .97$], indicating a performance normalization in the MDD group at follow-up (Figure 2B). After treatment, depressed patients showed a significant reward-learning effect [Block effect: $F(2,118) = 9.33$, $p = .0002$, $\varepsilon = .97$] due to a significant increase in RB from Block 1 to Block 2 and 3 (all Adj $ps < .03$). Similarly, no significant Group or Group × Block effects emerged when comparing RB for the control group (assessed at baseline) with the high- and low-anhedonic groups at follow-up (all $Fs < 1.82$, all $ps > .17$).

For the low-anhedonic group, a Time (baseline, follow-up) × Block ANOVA on RB revealed no significant Time effect. However, for the high-anhedonic group, the Time [$F(2,76) = 6.25$, $p = .015$, $\varepsilon = .99$] and Time * Block [$F(2,152) = 5.27$, $p = .0061$, $\varepsilon = .99$] effects were significant, due to increased RB after 8 weeks of treatment (Figure 2D).

Regarding DIS, Group × Block ANOVAs on DIS scores at follow-up revealed no significant effect (all $ps > .42$).

**Relationship Between Reward Learning and MDD Diagnosis After 8 weeks of Treatment.** At the follow-up assessment after 8 weeks, 52.5% of patients were still diagnosed with MDD.

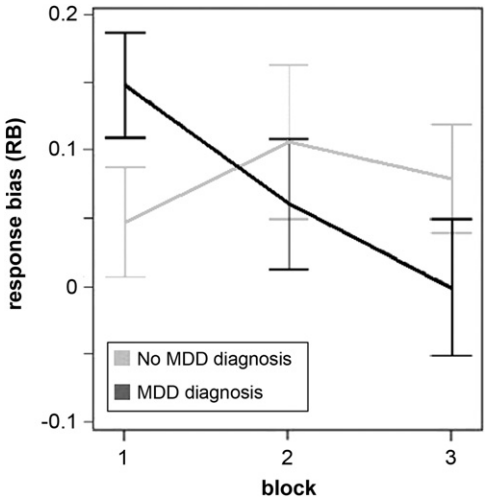


**Figure 3.** Response bias (RB) as a function of blocks for patients with (major depressive disorder [MDD] diagnosis) vs. without (No MDD diagnosis) MDD diagnosis at follow-up. Error bars denote SEM.

A logistic regression model was run to predict the persisting diagnosis of MDD after 8 weeks of treatment (yes or no). The overall reward learning at baseline (calculated as $RB_{Block3} - RB_{Block1}$) was entered as the independent variable in the model. Baseline HDRS scores, anxiety comorbidity, age, and gender were entered as covariates. Results indicated that reduced reward learning at baseline was a unique predictor of MDD diagnosis at 8 weeks (odds ratio = 7.84, 95% confidence interval 1.17–52.42, $p = .03$). These findings remained when correcting for the type of psychopharmacological treatment at week 8. The relationship between reward learning and MDD status after 8 weeks is summarized in Figure 3.

## Discussion

The overarching goal of this study was to test the hypotheses that patients with MDD—particularly those with high anhedonic symptoms—are characterized by an inability to adapt behavior as a function of rewards and reduced reward learning before treatment predicted a persisting diagnosis of MDD. Both hypotheses were confirmed. Specifically, using a probabilistic reward task that allowed us to assess reward learning objectively, we found that depressed patients showed a reduced ability to integrate reinforcement history over time compared with control subjects. Moreover, this difference was driven by patients with high-anhedonic symptoms. Depressed patients reporting high-anhedonic symptoms showed more blunted reward learning compared with patients with less anhedonic symptoms. After 8 weeks of treatment, the reward-learning ability of the MDD group normalized to healthy control subjects' levels. Critically, and highlighting the specificity of the current findings, reward-learning ability before treatment onset predicted a persisting diagnosis of MDD after 8 weeks, even after controlling for anxiety comorbidity and HDRS scores at time of inclusion.

Of note, our findings were not due to general impairment in task performance or difficulty, because we found no group differences in discriminability, indicating that reduced reward learning in the MDD sample was not associated with global cognitive deficits. Also, among the MDD group, discriminability

scores at follow-up did not significantly change compared to baseline, suggesting there was no learning effect of the task.

Overall, our findings are in line with previous reports highlighting reduced reactivity (26) and attention (27) to positive stimuli, blunted reward-related decision making, as well as a failure to develop a reward bias in MDD (7,28). A blunted response to positive reinforcement probably represents a deficit in the approach-related system and may result in low motivational drive, reduced goal-directed behavior, and diminished engagement in pleasurable behavior and/or anhedonia, which are presumed to be important risk factors for MDD (29,30). Importantly, by showing that treatment normalizes blunted reward learning and a decreased ability to modulate behavior as a function of reward before treatment predicts the persistence of an MDD diagnosis, our findings extend these previous data in two critical ways.

Our findings that reward learning was most disrupted in MDD patients reporting elevated anhedonic symptoms is consistent with previous findings in clinical (6) and nonclinical (17,31) studies reporting significant correlations between anhedonic symptoms and blunted reward learning in the same task and supports conceptualizations highlighting the need to identify more homogenous subgroups of patients that might be characterized by a distinct pathophysiology (32). Of note, in our study, a relationship between anhedonic symptoms and reward learning emerged only over the first 200 trials, rather than the entire 300 trials. The reason for this difference between studies is not clear and warrants additional study.

In addition, our findings provide, we believe for the first time, direct evidence that reduced reward learning is predictive of a persisting diagnosis of MDD 8 weeks later, even when accounting for baseline depression severity and anxiety comorbidity. These data extend previous studies highlighting the predictive ability of positive affect for treatment outcome (4,33), residual symptoms (34,35), and course of illness (36) in depression. The fact that reward-learning deficits predicted treatment outcome is intriguing given that anhedonia is a particularly difficult symptom to treat with current pharmacotherapy (e.g., SSRIs) (37,38). There is some recent evidence on the influence of different antidepressant medication (e.g., SSRI, SNRI) on reward processing in the brain (39–41). However, it has also been hypothesized that motivational and reward-related deficits are not adequately addressed in current treatment (42), and neurobiological evidence is emerging on the involvement of a dopamine (DA) dysfunction in MDD (43,44). Notably, in a recent dynamic positron emission tomography study, we found that the development of a response bias in the task used in the current study was associated with dopamine release in extrastriatal dopaminergic regions in healthy volunteers (45). Furthermore, a single dose of a DA agonist, hypothesized to activate DA autoreceptors and thus reduce DA release, blunted reward responsiveness (29) and altered reward-related dorsal anterior cingulate cortex activation (46) in healthy volunteers. Collectively, these findings raise the possibility that persistent MDD diagnosis is associated with reduced DA transmission.

This study had several limitations. First, MDD patients were recruited from different psychiatric wards in an academic hospital, and all depressed patients were medicated at the time of inclusion. Psycho(pharmaco)logic treatment was not standardized, and patients received treatment as clinically appropriate during follow-up. The fact that antidepressants potentially influence reward learning in a negative way and compliance is known to decrease during recovery of MDD, may have affected the results. Second, depression severity scores ranged broadly but, on average, HDRS scores at time of inclusion were moderate. This indicates that reduced reward sensitivity is not restricted to severe depression but is also relevant in mild to moderate MDD, replicating previous findings in unmedicated, nontreatment seeking MDD participants recruited from the community (6). Future studies should evaluate the generalizability of our findings to more severe inpatient samples. Third, even though we attempted to take into account most relevant clinical differences between the high- and low-anhedonic subgroups, we realize that these control analyses are probably incomplete because of limitations of the rating scales and/or lack of sampling of other clinical features. Fourth, control subjects were not followed longitudinally. Although this was not essential to test our main hypothesis, the lack of a second assessment for control subjects prevented us from investigating potential learning effects. Fifth, only one type of incentive manipulation was used. Future studies should evaluate whether depressed patients also show deficits to other types of incentive learning (e.g., punishment feedback).

In sum, our results indicate that depressed inpatients, particularly those with high-anhedonic symptoms, have an impaired ability to modulate behavior as a function of rewards. Critically, reward-learning deficits predicted treatment outcome above and beyond baseline depression severity and anxiety comorbidity. These findings suggest that blunted reward learning might contribute to the persistence of MDD or treatment resistance. Moreover, they underscore the relevance of developing specific assessment methods in MDD, based on the knowledge of more homogeneous subdimensions of the disease. More adequate assessments in MDD will not only benefit clinical research in the identification of risk factors and development of new treatments but also assist clinical practice in refining the diagnosis, predicting response and outcome, and selecting complementary treatment options.

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1. Clark DA, Beck AT, Beck JS (1994): Symptom differences in major depression, dysthymia, panic disorder, and generalized anxiety disorder. *Am J Psychiatry* 151:205–209.
2. American Psychiatric Association JS (2000): *Diagnosic and Statistical Manual of Mental Disorders, 4th ed., text revision.* Washington, DC: American Psychiatric Press.
3. Spijker J, Bijl RV, de Graaf R, Nolen WA (2001): Determinants of poor 1-year outcome of DSM-III-R major depression in the general

population: Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand* 103:122–130.
4. Davidson RJ (2003): Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology* 40:655–665.
5. Treadway MT, Zald DH (2011): Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neurosci Biobehav Rev* 35:537–555.
6. Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M (2008): Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *J Psychiatr Res* 43:76–87.
7. Eshel N, Roiser JP (2010): Reward and punishment processing in depression. *Biol Psychiatry* 68:118–124.
8. Forbes EE, Shaw DS, Dahl RE (2007): Alterations in reward-related decision making in boys with recent and future depression. *Biol Psychiatry* 61:633–639.
9. Takahashi T, Oono H, Inoue T, Boku S, Kako Y, Kitaichi Y, *et al.* (2008): Depressive patients are more impulsive and inconsistent in intertemporal choice behavior for monetary gain and loss than healthy subjects—an analysis based on Tsallis' statistics. *Neuro Endocrinol Lett* 29:351–358.
10. Must A, Szabó Z, Bódi N, Szász A, Janka Z, Kéri S (2006): Sensitivity to reward and punishment and the prefrontal cortex in major depression. *J Affect Disord* 90:209–215.
11. Smoski MJ, Lynch TR, Rosenthal MZ, Cheavens JS, Chapman AL, Krishnan RR (2008): Decision-making and risk aversion among depressive adults. *J Behav Ther Exp Psychiatry* 39:567–576.
12. 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.
13. Forbes EE, May JC, Siegle GJ, Ladouceur CD, Ryan ND, Carter CS, *et al.* (2006): Reward-related decision-making in pediatric major depressive disorder: An fMRI study. *J Child Psychol Psychiatry* 47:1031–1040.
14. Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008): Neural responses to monetary incentives in major depression. *Biol Psychiatry* 63:686–692.
15. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al.* (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166:702–710.
16. Smoski MJ, Felder J, Bizzell J, Green SR, Ernst M, Lynch TR, Dichter GS (2009): fMRI of alterations in reward selection, anticipation, and feedback in major depressive disorder. *J Affect Disord* 118:69–78.
17. Pizzagalli DA, Jahn AL, O'Shea JP (2005): Toward an objective characterization of an anhedonic phenotype: A signal-detection approach. *Biol Psychiatry* 57:319–327.
18. Spitzer RL, Williams JB, Gibbon M, First MB (1992): The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry* 49:624–629.
19. Hamilton M (1960): A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.
20. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P (1995): A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry* 167:99–103.
21. Franken IH, Rassin E, Muris P (2007): The assessment of anhedonia in clinical and non-clinical populations: Further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). *J Affect Disord* 99:83–89.
22. Bogdan R, Pizzagalli DA (2006): Acute stress reduces reward responsiveness: Implications for depression. *Biol Psychiatry* 60:1147–1154.
23. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, *et al.* (2009): Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry* 166:702–710.
24. Pizzagalli DA, Goetz E, Ostacher M, Iosifescu DV, Perlis RH (2008): Euthymic patients with bipolar disorder show decreased reward learning in a probabilistic reward task. *Biol Psychiatry* 64:162–168.
25. McCarthy D, Davison M (1979): Signal probability, reinforcement and signal detection. *J Exp Anal Behav* 32:373–386.
26. Sloan DM, Strauss ME, Wisner KL (2001): Diminished response to pleasant stimuli by depressed women. *J Abnorm Psychol* 110:488–493.
27. Wang CE, Brennen T, Holte A (2006): Decreased approach motivation in depression. *Scand J Psychol* 47:505–511.
28. Henriques JB, Glowacki JM, Davidson RJ (1994): Reward fails to alter response bias in depression. *J Abnorm Psychol 1994;103*:460–466.
29. Rescorla RA, Wagner AR (1972): A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black AH, Prokasy WF, editors. *Classical Conditioning II: Current Research and Theory*. New York: Appleton Century Crofts, 64–99.
30. Bylsma LM, Morris BH, Rottenberg J (2008): A meta-analysis of emotional reactivity in major depressive disorder. *Clin Psychol Rev* 28: 676–691.
31. Pizzagalli DA, Bogdan R, Ratner KG, Jahn AL (2007): Increased perceived stress is associated with blunted hedonic capacity: Potential implications for depression research. *Behav Res Ther* 45:2742–2753.
32. Hasler G, Drevets WC, Manji HK, Charney DS (2004): Discovering endophenotypes for major depression. *Neuropsychopharmacology* 29: 1765–1781.
33. Kasch KL, Rottenberg J, Arnow BA, Gotlib IH (2002): Behavioral activation and inhibition systems and the severity and course of depression. *J Abnorm Psychol* 111:589–597.
34. Hundt NE, Nelson-Gray RO, Kimbrel NA, Mitchell JT, Kwapil TR (2007): The interaction of reinforcement sensitivity and life events in the prediction of anhedonic depression and mixed anxiety-depression symptoms. *Pers Indiv Diff* 43:1001–1012.
35. Kimbrel NA, Nelson-Gray RO, Mitchell JT (2007): Reinforcement sensitivity and maternal style as predictors of psychopathology. *Pers Indiv Diff* 42:1139–1149.
36. McFarland BR, Shankman SA, Tenke CE, Bruder GE, Klein DN (2006): Behavioral activation system deficits predict the six-month course of depression. *J Affect Disord* 91:229–234.
37. Shelton RC, Tomarken AJ (2001): Can recovery from depression be achieved? *Psychiatr Serv* 52:1469–1478.
38. Price J, Cole V, Goodwin GM (2009): Emotional side-effects of selective serotonin reuptake inhibitors: Qualitative study. *Br J Psychiatry* 195: 211–217.
39. McCabe C, Mishor Z (2011): Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. *Neuroimage* 57:1317–1323.
40. Seymour B, Daw ND, Roiser JP, Dayan P, Dolan R (2012): Serotonin selectively modulates reward value in human decision-making. *J Neurosci* 32:5833–5842.
41. Rogers RD (2011): The roles of dopamine and serotonin in decision making: Evidence from pharmacological experiments in humans. *Neuropsychopharmacology* 36:114–132.
42. Nutt D, Demyttenaere K, Janka Z, Aarre T, Bourin M, Canonico PL, *et al.* (2007): The other face of depression, reduced positive affect: The role of catecholamines in causation and cure. *J Psychopharmacol* 21: 461–471.
43. Nestler EJ, Carlezon WA Jr (2006): The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 59:1151–1159.
44. Dunlop BW, Nemeroff CB (2007): The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry* 64:327–337.
45. Vrieze E, Ceccarini J, Pizzagalli DA, Bormans G, Vandenbulcke M, Demyttenaere K, *et al.* (2011): Measuring extrastriatal dopamine release during a reward learning task [published online ahead of print November 23]. *Hum Brain Mapp*.
46. Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA (2009): Single dose of a dopamine agonist impairs reinforcement learning in humans: Evidence from event-related potentials and computational modeling of striatal-cortical function. *Hum Brain Mapp* 30:1963–1976.