



# Reduced Hedonic Capacity in Major Depressive Disorder: Evidence from a Probabilistic Reward Task

## Citation

Pizzagalli, Diego A., Dan Iosifescu, Lindsay A. Hallett, Kyle G. Ratner, and Maurizio Fava. 2008. Reduced hedonic capacity in major depressive disorder: Evidence from a probabilistic reward task. *Journal of Psychiatric Research* 43, no. 1: 76-87.

## Published Version

<http://dx.doi.org/10.1016/j.jpsychires.2008.03.001>

## Permanent link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:3708377>

## Terms of Use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Open Access Policy Articles, as set forth at <http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#OAP>

## Share Your Story

The Harvard community has made this article openly available.  
Please share how this access benefits you. [Submit a story](#).

[Accessibility](#)

Word count Abstract: 214  
Number of Tables: 2  
Number of Figures: 4

**Reduced Hedonic Capacity in Major Depressive Disorder:  
Evidence from a Probabilistic Reward Task**

Diego A. Pizzagalli <sup>a,\*</sup>, Dan Iosifescu <sup>b</sup>, Lindsay A. Hallett <sup>b</sup>, Kyle G. Ratner <sup>a</sup>, Maurizio Fava <sup>b</sup>

<sup>a</sup>Department of Psychology, Harvard University, Cambridge, Massachusetts

<sup>b</sup>Depression Clinical and Research Program, Massachusetts General Hospital, Boston, MA  
02114, USA

**\*Please address all correspondence to:**

Diego A. Pizzagalli, Ph.D.

Department of Psychology

Harvard University

1220 William James Hall

33 Kirkland Street

Cambridge, MA 02138, USA

Phone: +1-617-496-8896

Fax: +1-617-495-3728

Email: [dap@wjh.harvard.edu](mailto:dap@wjh.harvard.edu)

## **Abstract**

*Objective:* Anhedonia, the lack of reactivity to pleasurable stimuli, is a cardinal feature of depression that has received renewed interest as a potential endophenotype of this debilitating disease. The goal of the present study was to test the hypothesis that individuals with major depression are characterized by blunted reward responsiveness, particularly when anhedonic symptoms are prominent.

*Methods:* A probabilistic reward task rooted within signal-detection theory was utilized to objectively assess hedonic capacity in 23 unmedicated subjects meeting DSM-IV criteria for major depressive disorder (MDD) and 25 matched control subjects recruited from the community. Hedonic capacity was defined as reward responsiveness — i.e., the participants' propensity to modulate behavior as a function of reward.

*Results:* Compared to controls, MDD subjects showed significantly reduced reward responsiveness. Trial-by-trial probability analyses revealed that MDD subjects, while responsive to delivery of single rewards, were impaired at integrating reinforcement history over time and expressing a response bias toward a more frequently rewarded cue in the absence of immediate reward. This selective impairment correlated with self-reported anhedonic symptoms, even after considering anxiety symptoms and general distress.

*Conclusions:* These findings indicate that MDD is characterized by an impaired tendency to modulate behavior as a function of prior reinforcements, and provides initial clues about which aspects of hedonic processing might be dysfunctional in depression.

Keywords: Anhedonia; Depression; Reward Processing; Endophenotype; Affect



## **1. Introduction**

Anhedonia, the loss of pleasure or lack of reactivity to pleasurable stimuli, is one of the core symptoms of depression (APA, 2000), and has been considered a risk factor increasing vulnerability to depression (Costello, 1972; Meehl, 1975). Over the years, substantial evidence has accumulated suggesting that depression is associated with diminished hedonic capacity and, more generally, dysfunction in an approach-related system subserving positive affect and motivated behavior. First, studies have shown that depression is characterized by low self-reported positive affect and reduced engagement with the environment (e.g., de Beurs et al., 2007; Watson et al., 1995). Moreover, reduced positive affect has been concurrently and prospectively linked to depression in adult samples (Clark et al., 1994). In children, reduced positive affect at age 3 predicted depressotypic cognitive styles at age 7 (Hayden et al., 2006) and was associated with a maternal history of depressive disorders (Durbin et al., 2005).

Second, studies measuring resting brain electrical activity have reported that depression is characterized by relatively reduced activity over left prefrontal regions (e.g., Gotlib et al., 1998; Henriques and Davidson, 1991; Thibodeau et al., 2006) that are assumed to play an important role in approach-related affect (Davidson, 1998). Interestingly, resting activity within left prefrontal regions has been linked to individuals' propensity to respond to reward-related cues (Pizzagalli et al., 2005b), providing convergent evidence that depressed subjects might display reduced hedonic capacity. Finally, studies employing various paradigms have shown that depressed subjects display a blunted emotional response to pleasant cues (e.g., Sloan et al., 2001; Suslow et al., 2001), decreased reward responsiveness (e.g., Henriques and Davidson, 2000), a lack of a positivity bias in attentional tasks (e.g., McCabe and Gotlib, 1995; Wang et al., 2006),

and dysfunctions within the brain reward system (e.g., Keedwell et al., 2005; Tremblay et al., 2002).

Although these studies converge in suggesting diminished hedonic capacity in depression, little is known about which aspects of hedonic processing might be dysfunctional in depressed subjects. Growing evidence indicates, however, that hedonic capacity might not be a unitary construct. For example, studies have shown that reward processing can be decomposed into an anticipatory and consummatory phase (“wanting” vs. “liking”; Berridge and Robinson, 1998). Moreover, preclinical and functional neuroimaging studies indicate that different brain regions are implicated in distinct aspects of reward processing. The medial prefrontal cortex, for example, has been found to be critically involved in response to single reward deliveries (e.g., Dillon et al., 2008; Knutson et al., 2003), while dorsal anterior cingulate regions play an important role in integrating reinforcement history over time (e.g., Ernst et al., 2004; Rogers et al., 2004). In a notable study in non-human primates, Kennerley et al. (2006) recently showed that dorsal anterior cingulate lesions impaired monkeys’ ability to integrate reinforcement history over time, which led to an inability to learn which of two differentially rewarded responses was most advantageous, while sparing the animals’ ability to respond to single feedback trials. These findings suggest that dorsal anterior cingulate regions are critically involved in integrating reinforcement history necessary to guide goal-directed behavior (Rushworth et al., 2007).

This neurobiological evidence is intriguing, particularly when considering that dysfunctions in prefrontal and cingulate regions are amongst the most replicated findings in depression (Davidson et al., 2002; Mayberg, 2003). Decreased activity in dorsal anterior cingulate regions, in particular, has been observed under a variety of conditions, raising the

possibility that hedonic deficits in depression might be due to impairments in integrating reinforcement history over time, leading to difficulties in expressing goal-directed behavior.

Recently, we described a probabilistic reward task based on a differential reinforcement schedule that allowed us to objectively assess participants' propensity to modulate behavior as a function of reward (Pizzagalli et al., 2005a). In this task, participants are confronted with a choice between two responses that are linked to different probabilities of reward. Due to this probabilistic nature, participants cannot infer which stimulus is more advantageous based on the outcome of a single trial but need to integrate reinforcement history over time in order to optimize behavior (cf. Kennerley et al., 2006). In prior studies in non-clinical samples, subjects reporting elevated depressive symptoms showed reduced responsiveness to the more frequently rewarded stimulus (Pizzagalli et al., 2005a); moreover, reward responsiveness negatively correlated with self-reported anhedonic symptoms (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005a), and predicted these symptoms one month later (Pizzagalli et al., 2005a).

Based on these findings, and in light of neurobiological evidence pointing to disruption in frontocingulate regions in depression, we hypothesized that major depression would be characterized by an impaired propensity to modulate behavior as a function of prior reinforcements. The first goal of the present study was to directly test this hypothesis in unmedicated subjects meeting DSM-IV criteria for Major Depressive Disorder (MDD). A second goal was to provide a more fine-grained functional analysis of impaired hedonic capacity in depression. To this end, we computed the probability of specific responses (e.g., selecting the more frequently rewarded response) as a function of the immediately preceding trial (e.g., which stimulus was rewarded in the preceding trial). Unlike prior studies (e.g., Henriques and

Davidson, 2000; Sloan et al., 2001; Suslow et al., 2001), this approach allowed us to evaluate whether blunted hedonic capacity in depression is due to reduced responsiveness to single rewards, or more generally, reduced ability to integrate reinforcement history over time. The third and final goal was to test the hypothesis that reduced hedonic capacity would be most pronounced in MDD subjects reporting elevated anhedonic symptoms in their daily life.

## **2. Methods**

### *2.1. Participants*

Depressed subjects were recruited from treatment studies conducted at the Depression Clinical and Research Program at Massachusetts General Hospital (MGH), whereas control subjects were recruited from the community through advertisements and flyers. Subjects likely to meet study criteria based on a phone screen were invited for a diagnostic interview, which took place at MGH and was conducted by trained psychiatrists. Depressed outpatients were enrolled if the following inclusion criteria were met: (1) DSM-IV diagnosis of MDD (APA, 1994), as determined by the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002); (2) score  $\geq 17$  on the 21-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960); (3) absence of any psychotropic medications for at least 2 weeks (6 months for dopaminergic drugs, 6 weeks for fluoxetine, and 4 weeks for neuroleptics and benzodiazepines); (4) no current or past history of MDD with psychotic features; (5) absence of any other Axis I diagnosis, with the exception of anxiety disorders<sup>1</sup>; and (6) absence of electroconvulsive therapy in the previous 6 months. Dysthymic disorder was allowed only if co-occurring with MDD. Inclusion criteria for controls included absence of medical or neurological illness, absence of current or past psychopathology,

as assessed by the SCID, Non-patient Edition, and absence of any psychotropic medications. All MDD subjects performed the probabilistic reward task (see below) at the SCID session and before starting antidepressant treatment.

After receiving a study description, 23 MDD subjects and 25 control subjects provided written informed consent. Groups did not differ with respect to gender ratio, age, education, ethnicity, and marital status (Table 1), although MDD subjects were slightly older ( $p=0.08$ ). Participants in the MDD sample were moderately to severely depressed, as assessed by their 17-item HRSD<sup>2</sup> (mean $\pm$ SD: 19.40 $\pm$ 3.30) score as well as their Beck Depression Inventory-II (BDI-II; Beck et al., 1996) score (32.13 $\pm$ 8.66). For control subjects, the mean BDI-II score was 3.40 ( $\pm$ 3.59). For the depressed sample, the mean age of MDD onset was 34.8 years (range: 13-53), whereas the mean length of the current MDE was 75.7 months (median: 12 months; range: 2-360 months). The control subjects served as comparison group in a recent study investigating reward learning in bipolar disorder (Pizzagalli et al., in press).

The study was approved by the Committee on the Use of Human Subjects in Research at Harvard University and the Partners Human Research Committee. For their participation, subjects received \$10/hour, as well as their task “earnings” (on average, \$5).

---

INSERT TABLE 1 ABOUT HERE

---

## *2.2. Task and Procedure*

After study eligibility was established, subjects participated in a 25-min task, which was presented on a 17” PC monitor using E-Prime software (version 1.1; Psychology Software Tools, Inc, Pittsburgh, Pennsylvania). The task, which has been previously validated in three

independent samples (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005a, 2008), is rooted within signal-detection theory and allows for the objective assessment of the subject's propensity to modulate behavior as a function of prior reinforcements. Briefly, in signal-detection paradigms, subjects are asked to select whether stimulus A or stimulus B was presented by making an appropriate response A or response B (McCarthy, 1991). Performance can be analyzed with respect to: (1) *discriminability*, which indexes the participants' ability to differentiate between the two stimuli; and (2) *response bias*, which reflects the participant's propensity to select one or the other response irrespective of stimulus presentation. Importantly, a large body research has shown that unequal frequency of reward following correct identification of stimulus A and B produces a systematic preference for the response paired with the more frequent reward (Macmillan and Creelman, 1991; McCarthy, 1991). Accordingly, the degree of response bias toward the more frequently reinforced response can be used to objectively assess reward responsiveness.

In the present study, the subjects' goal was to determine, via button press, whether a short (11.5 mm) or a long (13 mm) mouth was presented on a previously mouthless cartoon face (Fig. 1). The task included three blocks composed of 100 trials. Within each block an equal number of short and long mouths were presented for 100 ms each. Stimulus exposure (100 ms) and the difference between mouth sizes (11.5 vs. 13 mm) were identical to those used in prior studies using this paradigm (Pizzagalli et al., 2005a; Tripp and Alsop, 1999), and were selected after extensive pilot testing to achieve appropriate psychometric properties of the task (e.g., overall hit rates of approximately 75-85%). Importantly, the difference between mouth sizes as well as the duration of stimulus exposure was small, which provided an ideal experimental setting for

allowing the development of a response bias (McCarthy and Davison, 1979) without the risk of inducing performance at chance level.

To elicit a response bias, an asymmetric reinforcer ratio was utilized (McCarthy and Davison, 1979; Tripp and Alsop, 1999). Specifically, correct identification of either the short or long mouth was rewarded (“Correct!! You won 5 Cents”) three times more frequently (“rich stimulus”) than correct identification of the other mouth (“lean stimulus”). The reinforcement allocation and key presses were counterbalanced across subjects. In each block, only 40 correct trials (30 rich, 10 lean) were rewarded so that each subject was exposed to the same reward ratio. To achieve this goal, a controlled reinforcer procedure was implemented according to prior procedures (Johnstone and Alsop, 2000; McCarthy and Davison, 1979). Accordingly, if participants responded incorrectly on a trial that was scheduled to be rewarded based on a pseudorandomized reinforcement sequence, the reward feedback was delayed until the next correct identification of the same stimulus type. Subjects were informed at the beginning of the experiment that the purpose of this task was to win as much money as possible. Moreover, they were instructed that not all correct response would receive a reward feedback but were unaware that one of the stimuli would be disproportionately rewarded.

After the task, subjects completed various questionnaires, including the BDI-II (Beck et al., 1996) and the 62-item version of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995). The BDI-II is a reliable and well-validated self-report instrument that assesses depressive severity (Beck et al., 1996). The MASQ is a self-report questionnaire that assesses anxiety-specific symptoms (Anxious Arousal, AA), depression-specific symptoms (Anhedonic Depression, AD), and general distress (General Distress-Anxious Symptoms, GDA;

General Distress-Depressive Symptoms, GDD). Prior studies have described satisfactory reliability and validity for the MASQ (e.g., de Beurs et al., 2007; Watson et al., 1995).

---

INSERT FIG. 1 ABOUT HERE

---

### 2.3. Data Collection and Reduction

Performance was analyzed with respect to response bias, discriminability, and reaction time (RT), following prior procedures (McCarthy and Davison, 1979; Pizzagalli et al., 2005a; Tripp and Alsop, 1999). Hit rates [(number of hits)/(number of hits + number of misses)] were also computed, although they are imperfect measures of performance, especially in the presence of response biases (Macmillan and Creelman, 1991). Response bias ( $\log b$ ) and discriminability ( $\log d$ ) were computed as:

$$\text{Response Bias:} \quad \log b = \frac{1}{2} \log \left( \frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}} \right) \quad [\text{Equation 1}]$$

$$\text{Discriminability:} \quad \log d = \frac{1}{2} \log \left( \frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}} \right) \quad [\text{Equation 2}]$$

Following prior recommendations (Hautus, 1995), 0.5 was added to every cell of the detection matrix to allow calculations in cases that involve a zero in one cell of the formula. Response bias indexes the systematic preference for the response paired with the more frequent reward (“rich stimulus”), or the extent to which behavior is modulated by reinforcement history. A high response bias emerges when subjects show high rates of correct identification (hits) for the rich stimulus and high miss rates for the lean stimulus (i.e., the stimulus associated with less frequent rewards). To examine general task performance, secondary analyses considered hit rates scores (% correct responses), RT, and discriminability. Discriminability assesses the subjects’

ability to perceptually distinguish between the two stimuli, and thus can be used as a proxy of task difficulty.

#### 2.4. Statistical analyses

Chi-square tests and unpaired t-tests were run to assess whether groups differed in sociodemographic variables. Unpaired t-tests were run to compare BDI-II and MASQ scores between the groups. To test for possible group differences in the reward task, separate mixed ANOVAs with *Group* and *Block* (1,2,3) as factors were performed for response bias and discriminability. For hit rate and RT scores, *Stimulus Type* (Rich, Lean) was included as an additional factor.

To provide a more fine-grained functional analysis of behavioral performance, we computed the probability of specific responses as a function of the immediately preceding trial. To this end, we first identified all trials in which correct identification of the rich or lean stimulus was rewarded. Similarly, we identified all trials in which correct identification of the rich or lean stimulus was *not* rewarded (because a reward was not scheduled). We then computed the probability of selecting “rich” or “lean” in the immediately following trial. Before statistical analyses, the probability values were arcsine-transformed.

Across all ANOVAs, the Greenhouse-Geisser correction was used when applicable. In case of significant findings, post-hoc Newman-Keuls tests were performed. Pearson correlations and hierarchical regression analyses were computed within the MDD sample to investigate relations between response bias and depressive/anxiety symptoms using the four MASQ subscale scores. All statistical tests were two-tailed.

### 3. Results

#### 3.1. Probabilistic reward task

*Response Bias:* As shown in Fig. 2A, relative to control subjects, MDD subjects showed significantly lower overall response bias scores<sup>3</sup> (*Group*:  $F = 5.89$ ,  $df = 1,46$ ,  $p < 0.020$ , partial  $\eta^2 = 0.11$ ). The main effect of *Block* and the *Group* x *Block* interaction were not significant, both  $F_s < 0.72$ ,  $df = 2,92$ , both  $p_s > 0.50$ . The main effect of *Group* was confirmed also when entering age as a covariate<sup>4</sup> ( $F = 6.43$ ,  $df = 1,45$ ,  $p < 0.015$ , partial  $\eta^2 = 0.13$ ).

---

INSERT FIG. 2 ABOUT HERE

---

*Discriminability:* No significant effects emerged, all  $F_s < 0.54$ , all  $p_s > 0.50$ . Accordingly, controls and MDD subjects found the task equally difficult.

*Reaction Time.* In line with prior findings (Pizzagalli et al., 2005a), the main effects of *Block* and *Stimulus Types* were significant,  $F = 12.26$ ,  $df = 2,92$ ,  $p < 0.001$ , partial  $\eta^2 = 0.21$  and  $F = 27.61$ ,  $df = 1,46$ ,  $p < 0.001$ , partial  $\eta^2 = 0.38$ . These effects were due to (1) significantly lower RT in Blocks 2 ( $583.97 \pm 187.68$  ms) and Block 3 ( $577.65 \pm 183.70$  ms) compared to Block 1 ( $634.90 \pm 224.71$  ms) (Newman-Keuls  $p_s < 0.001$ ); and (2) significantly lower RT to the rich than lean stimulus ( $578.89 \pm 194.28$  ms vs.  $618.79 \pm 194.47$  ms). These findings indicate that the reinforcement schedule successfully produced a general preference towards the more frequently rewarded (rich) stimulus. The only other reliable finding was the main effect of *Group*,  $F = 7.31$ ,  $df = 1,46$ ,  $p < 0.01$ , partial  $\eta^2 = 0.14$ , due to significantly higher RT for MDD than control

subjects ( $676.48 \pm 182.16$  ms vs.  $541.55 \pm 179.15$  ms). Importantly, all other effects involving *Group* were not significant (all  $F$ s  $< 2.09$ , all  $p$ s  $> 0.13$ ).<sup>5</sup>

*Hit rates:* Replicating prior studies (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005a), the main effect of *Stimulus Type* was significant,  $F = 42.39$ ,  $df = 1,46$ ,  $p < .001$ , partial  $\eta^2 = 0.48$ , due to significantly higher hit rates for the rich stimulus ( $0.88 \pm 0.06$ ) than lean stimulus ( $0.77 \pm 0.12$ ). Mirroring the RT findings, this hit rate pattern indicates that the differential reinforcement schedule was effective in producing a behavioral preference towards the rich stimulus. Importantly, this effect was qualified by a significant *Group x Stimulus Type* interaction,  $F = 4.70$ ,  $df = 1,46$ ,  $p < 0.035$ , partial  $\eta^2 = 0.09$ . Compared to control subjects, MDD subjects showed *higher* hit rates for the lean but *lower* hit rates for the rich stimulus (Fig. 2B), although only the first effect approached significance (Neuman-Keuls  $p = 0.059$  and  $p > 0.25$ , respectively). Stated differently, although the two groups did not differ in rich miss rates<sup>6</sup>, MDD subjects showed a trend for *lower* lean miss rates (i.e., a lower propensity to select “rich” when a lean stimulus was actually presented) compared to control subjects ( $0.20 \pm 0.14$  vs.  $0.25 \pm 0.10$ ;  $p = 0.059$ ). As a result, relative to control subjects, MDD subjects were characterized by a significantly smaller differentiation between the two stimuli (overall rich – overall lean hit rate:  $0.07 \pm 0.10$  vs.  $0.14 \pm 0.11$ ,  $t = 2.17$ ,  $df = 46$ ,  $p < 0.035$ ).

*Probability analyses.* The analyses summarized above indicate that MDD subjects had lower response bias relative to control subjects. As evident from Equation 1, a low response bias emerges if subjects have (1) low rates of correct identification (hits) for the rich stimulus, and/or (2) low rates of incorrect identification (misses) for the lean stimulus. Analyses of hit rates clarified that the reduced response bias in MDD subjects was associated with the latter effect—

that is, with a low propensity to incorrectly identify the lean stimulus as the rich stimulus. Based on these findings, further analyses focused on the probability of lean misses. Specifically, we calculated the probability of lean misses (i.e., the probability that subjects incorrectly selected “rich” when in actuality the lean stimulus was presented) as a function of whether the preceding correct identification of a rich trial had been rewarded or not, and entered these values into a *Group x Preceding Trial* (rich rewarded vs. rich non-rewarded) ANOVA.

Compared to control subjects, MDD subjects had significantly lower probability of lean misses for trials following a non-rewarded rich stimulus (Neuwman-Keuls  $p < 0.011$ ), whereas the two groups had virtually identical probabilities in trials immediately following a rich reward feedback ( $p > 0.98$ ) (Fig. 3A; *Group x Preceding Trial*:  $F = 3.56$ ,  $df = 1,46$ ,  $p = 0.065$ , partial  $\eta^2 = 0.072$ ). Moreover, for MDD ( $p < 0.002$ ) but not control ( $p > 0.20$ ) subjects, the probability of a lean miss was significantly lower immediately after reward omission compared to reward delivery to a preceding rich stimulus. The main effect of *Group* was not significant,  $F = 1.42$ ,  $df = 1,46$ ,  $p > 0.20$ . Accordingly, MDD subjects showed a reduced bias toward the more frequently rewarded stimulus (as expressed by a diminished tendency to misclassify the lean stimulus), but only in trials following an omission of reward for a correct identification of the rich stimulus (see Fig. 3).

---

INSERT FIG. 3 ABOUT HERE

---

In an additional analysis, we evaluated the probability of rich misses as a function of which stimulus was rewarded in the immediately preceding trial. To this end, we calculated the probability that participants chose “lean” in rich trials (“rich misses”) when the trials were

presented immediately after the preceding rich or lean stimulus had been rewarded, and entered these values into a *Group x Preceding Trial* (rich rewarded vs. lean rewarded) ANOVA. This analysis allowed us to evaluate the strength of response bias as a function of which responses had been reinforced immediately beforehand. Compared to control subjects, MDD subjects had a significantly *higher* probability of rich misses in trials immediately following a rewarded lean (Newman-Keuls  $p < 0.006$ ) but not a rewarded rich ( $p > 0.53$ ) stimulus (Fig. 3B; *Group x Preceding Trial* interaction:  $F = 8.47$ ,  $df = 1,46$ ,  $p < 0.007$ , partial  $\eta^2 = 0.16$ ). The main effects of *Group* and *Preceding Trial* were not significant (both  $F$ s  $< 1.0$ , both  $p$ s  $> 0.30$ ).

### 3.2. Relationships with clinical symptoms

Contrary to our hypothesis, for the MDD sample, response bias at the end of the experiment (Block 3) or response bias learning (Block 3 – Block 1) were not correlated with anhedonic symptoms, as assessed by the AD subscale of the MASQ ( $r = -0.31$  and  $r = -0.05$ , both  $p$ s  $> 0.15$ ). AD scores were, however, positively correlated with probability of rich misses ( $r = 0.519$ ,  $p = 0.011$ ) and negatively correlated with lean miss rates ( $r = 0.356$ ,  $p = 0.095$ ) for trials following non-rewarded correct identification of rich stimuli (Fig. 4). Accordingly, the higher the anhedonic symptoms, the higher the numbers of misses for the more frequently rewarded stimulus, and the lower the numbers of misses for the lean stimulus. Of note, the correlation for trials following *non-rewarded* correct identification of rich stimuli ( $r = 0.519$ ) was significantly higher than the one involving *rewarded* correct identification of rich stimuli ( $r = -0.110$ ), as assessed by the Fisher's z-transformation proposed by Meng et al. (1992) ( $t = 2.21$ ,  $df = 20$ ,  $p = 0.039$ ), and showed a trend for being higher than the correlation involving non-rewarded correct identification of *lean* stimuli ( $r = -0.04$ ;  $t = 1.92$ ,  $df = 20$ ,  $p = 0.069$ ) (Table 2).

---

INSERT FIG. 4 and TABLE 2 ABOUT HERE

---

To investigate whether these correlational findings were specific to anhedonic symptoms, hierarchical regression analyses adjusting for anxiety symptoms and general distress were run within the MDD sample. GDA and AA scores were simultaneously entered in the first step, whereas AD scores were entered in the second step of the model, which predicted rich miss rates for trials following non-rewarded correct identification of rich stimuli.

Neither GDA ( $\beta = 0.20$ ) nor AA ( $\beta = -0.21$ ) scores were significant predictors of rich miss rates (both  $|t|s < 0.97$ , both  $ps > 0.30$ ). AD scores, however, significantly predicted rich miss rates ( $\beta = 0.51$ ,  $t = 2.48$ ,  $p < 0.025$ ), even after adjusting for general distress (GDA) and anxiety symptoms (AA),  $\Delta R^2 = 0.233$ ,  $\Delta F = 6.15$ ,  $df = 1, 19$ ,  $p = 0.023$ . A similar pattern, albeit statistically less strong, emerged when an analogous hierarchical regression was run to evaluate whether AD scores predicted lean miss rates,  $\Delta R^2 = 0.15$ ,  $\Delta F = 3.64$ ,  $df = 1, 19$ ,  $p = 0.072$ .

#### **4. Discussion**

Anhedonia, the loss of interest and lack of reactivity to pleasurable stimuli, has been considered a potential trait marker related to vulnerability to depression (Costello, 1972; Meehl, 1975). In line with this hypothesis, studies have found that anhedonia can precede the onset of depression (Dryman and Eaton, 1991); shows temporal stability (Oquendo et al., 2004); predicts poor outcome 12 months later (Spijker et al., 2001); and is associated with dysfunctions within the brain reward system (Keedwell et al., 2005; Tremblay et al., 2002). Moreover, reward dependence, a putatively heritable trait associated with maintenance of behavior in response to

reward cues, shows trait-like features associated with familiarity of depression (Farmer et al., 2003). Collectively, these findings suggest that anhedonia is among the most promising endophenotypes of depression (Hasler et al., 2004). Still, little is known about which aspects of hedonic processing might be dysfunctional in depression. Using a laboratory-based measure of hedonic capacity, the present findings indicate that major depression is characterized by impairments in the ability to modulate behavior as a function of prior reinforcement history. Since positive reinforcers are stimuli that increase the likelihood of behavior (Rescorla and Wagner, 1972), blunted responsiveness to reinforcers may lead to diminished engagement in pleasurable activities and decreased motivational drive to pursue future rewards. These dysfunctions may in turn foster the generation, maintenance, and/or exacerbation of depressive symptoms, particularly lack of interest in the environment and loss of pleasure. Studies using self-report measures have indeed shown that anhedonia and blunted behavioral activation predicted (1) future depressive symptoms (Hundt et al., 2007; Kimbrel et al., 2007), (2) course of depression and time to recovery (McFarland et al., 2006), and (3) poor treatment outcome 8-12 months later (Kasch et al., 2002; Spijker et al., 2001). Moreover, low positive affect has been identified as a risk factor for the development and maintenance of depressive symptoms in children (Hayden et al., 2006; Joiner and Lonigan, 2000; Lonigan et al., 1999).

In the present unmedicated MDD sample, blunted response bias was mainly due to a reduced tendency to misclassify the lean stimulus as the more frequently rewarded (rich) stimulus. Notably, this dysfunction emerged only in trials following omission of reward for a correctly identified rich stimulus. Moreover, relative to control subjects, MDD subjects showed a higher likelihood of missing the more frequently rewarded stimulus (rich misses) but only in

trials immediately following a rewarded lean stimulus. In addition, the probability of rich misses correlated with anhedonic symptoms experienced by the MDD subjects during the past week. As above, these findings were specific to trials following non-rewarded rich stimuli. Finally, hierarchical regression analyses indicated that anhedonic symptoms uniquely predicted higher rates of rich misses even after controlling for anxiety symptoms and general distress. Taken together, these findings suggest that clinically depressed subjects, while responsive to single rewards, were impaired at integrating reinforcement history over time and expressing a response bias toward a more frequently rewarded cue in the absence of immediate reward. Of note, this blunted hedonic capacity emerged in the absence of any general impairment in task performance (no group differences emerged for discriminability), indicating the reduced hedonic capacity was not due to global cognitive impairments in the MDD sample.

The findings emerging from the present study are consistent with and extend prior reports in depression of reduced reactivity to pleasant cues (e.g., Sloan et al., 2001; Suslow et al., 2001), blunted reward responsiveness (e.g., Henriques and Davidson, 2000), and diminished attentional positivity bias (e.g., McCabe and Gotlib, 1995; Wang et al., 2006). Unlike prior studies, however, the current work provides initial evidence that clinically depressed subjects show a diminished propensity to modulate behavior as a function of reinforcement history, particularly in the absence of immediate reinforcement. Considering that many forms of behavior are acquired through intermittent reinforcement schedules (e.g., Hamburg, 1998), it is reasonable to assume that dysfunctions in integrating reinforcements over time might lead in depression to pervasive difficulty initiating and maintaining goal-directed behavior. This in turn might contribute to the diminished “intrinsic” motivation that is often seen clinically, that is, a difficulty in engaging in

“actions [...] for their own sake that do not require external support or reinforcements to be initiated or sustained” (Barch, 2005, p. 877).

The present report of reduced response bias toward the more frequently rewarded stimulus is intriguing given emerging neurobiological evidence that highlights potential dopaminergic dysfunctions in depression. Although findings derived from experimental animal studies and functional neuroimaging are far from being consistent, recent reviews have raised the possibility that depression might be characterized by decreased sensitivity of dopaminergic receptors and decreased dopaminergic release within ventral striatal regions known to be critically implicated in incentive processing (D’Aquila et al., 2000; Dunlop and Nemeroff, 2007; Gershon et al., 2007). Of relevance to the present findings, in a recent pharmacological challenge study using the same probabilistic reward task, we found that a single dose of a dopamine D2 agonist (pramipexole) – hypothesized to activate presynaptic dopaminergic autoreceptors and thus reduce phasic dopaminergic bursts (e.g., Fuller et al., 1982; Tissari et al., 1983) – impaired the development of response bias and reduced the differentiation between rich and lean hit rates in healthy subjects (Pizzagalli et al., 2008). Future neuroimaging studies in depressed samples are warranted to test the hypothesis that disrupted phasic dopaminergic signaling might underline reduced hedonic capacity in depression.

The present study has several important limitations. First, MDD subjects were recruited from treatment studies conducted at a large academic hospital, and future studies should evaluate the generalizability of our findings. Moreover, among the MDD group, the length of the current depressive episode and the depression severity scores ranged broadly, indicating that this relatively small sample of MDD subjects was quite heterogeneous.

Second, the MASQ and BDI-II were used to assess anhedonic symptoms. Although these scales provide a reliable assessment of depression severity and contain items probing anhedonia, it is important to emphasize that other scales have been developed to specifically assess anhedonia, including the Snaith-Hamilton Pleasure Scale, the Fawcett-Clark Pleasure Capacity Scale, and the Revised Chapman Physical Anhedonia Scale (see Leventhal et al., 2006 for a recent review and psychometric comparison). Accordingly, future studies will be needed to evaluate whether the present findings extend to reports of anhedonic symptoms as assessed by these other scales.

Third, unlike prior studies using the probabilistic reward task in student samples (e.g., Pizzagalli et al., 2005a), the community control subjects investigated in the present study did not show increases of response bias across blocks. Instead, at the end of block 1 these control subjects had a response bias (mean: 0.19) similar to the one achieved by low BDI-II subjects (mean: 0.21) in block 3 of our prior study (Pizzagalli et al., 2005a). Thus, it is possible that the lack of systematic response bias development in the current sample was due to ceiling effects. The observation that the present hit rates were somewhat higher than the ones described in Pizzagalli et al. (2005a) supports this speculation and suggests that the two studies, which were conducted in two different laboratories, were not fully psychometrically matched. These methodological differences might also explain the lack of correlation between response bias and anhedonic symptoms. Although a reliable correlation emerged when considering a secondary variable (probabilities of rich misses) that contributes to reduced response bias (see denominator in Equation 1), the lack of correlation with overall response bias represents an additional limitation of the present study.

Fourth, because only a reward manipulation was used, we cannot determine whether depressed subjects might show dysfunctional responsiveness to other types of feedback (e.g., punishments) or whether findings were due to procedural (implicit) learning deficits (e.g., difficulties in learning the association between a particular stimulus and increased frequency of reward). Moreover, it is possible that blunted response bias in MDD subjects might be partially explained by an impairment in learning that the lean stimulus *is not* associated with frequent reward (cf. Frank, 2005). Although future studies will be required for conclusive tests of these alternative interpretations, a convergence of findings points to blunted reward responsiveness in depression.

First, in the present as well as two prior studies, blunted reward responsiveness specifically correlated with self-reported anhedonic symptoms (e.g., loss of pleasure, energy, interest, and libido; Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005a) and predicted anhedonic symptoms one month later (Pizzagalli et al., 2005a). Second, the current MDD subjects showed lower lean miss rates (i.e., a lower propensity to select “rich” when a lean stimulus was actually presented) and a smaller differentiation between the two stimuli relative to control subjects. When seen within the widely accepted view that positive reinforcers are stimuli that increase the likelihood of subsequent behavior (Rescorla and Wagner, 1972; Schultz, 2007), these findings suggest that task performance in MDD subjects was less influenced by the asymmetrical reinforcement schedule favoring the rich stimulus compared to control subjects. Third, procedural learning (Joel et al., 2005; Vakil et al., 2000; but see Naismith et al., 2006) and punishment responsiveness (Henriques and Davidson, 2000; Henriques et al., 1994) have been found to be unaffected in depression. Finally, and more importantly, the probability analyses

highlighted that MDD subjects were characterized by specific impairments in expressing response bias towards the more frequently rewarded stimulus in trials following omission of rewards, whereas they showed no dysfunctions in responses to single reward. Critically, although this impairment was seen on a group level, patients reporting anhedonic symptoms in the past week showed the lowest hedonic capacity.

In sum, the present findings indicate that unmedicated subjects with major depression are characterized by an impaired tendency to modulate behavior as a function of prior reinforcements, particularly in the absence of immediate rewards, and thus offer initial clues about which aspects of hedonic processing might be dysfunctional in this debilitating disease.

## References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision). Washington, D.C.: American Psychiatric Press, 2000.
- Barch DM. The relationships among cognition, motivation, and emotion in schizophrenia: How much and how little we know. *Schizophrenia Bulletin* 2005; 31:875-881.
- Beck AT, Steer RA, Brown GK. Beck Depression Inventory Manual (2nd ed.). San Antonio: The Psychological Corporation, 1996.
- Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research Review* 1998; 28:309-369.
- Bogdan R, Pizzagalli DA. Acute stress reduces hedonic capacity: Implications for depression. *Biological Psychiatry* 2006; 60:1147-1154.
- Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. *Journal of Abnormal Psychology* 1994; 103:103-116.
- Costello CG. Depression: Loss of reinforcers or loss of reinforcer effectiveness? *Behavior Therapy* 1972; 3 :240-247.
- D'Aquila PS, Collu M, Gessa GL, Serra G. The role of dopamine in the mechanism of action of antidepressant drugs. *European Journal of Pharmacology* 2000; 405:365-373.
- Davidson RJ. Affective style and affective disorders: Perspectives from affective neuroscience. *Cognition and Emotion* 1998; 12:307-320.
- Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annual Review of Psychology* 2002; 53:545-574.

- de Beurs E, den Hollander-Gijsman ME, Helmich S, Zitman FG. The tripartite model for assessing symptoms of anxiety and depression: Psychometrics of the Dutch version of the mood and anxiety symptoms questionnaire. *Behaviour Research and Therapy* 2007; 45: 1609-1617.
- Dillon DG, Holmes AJ, Jahn AL, Bogdan R, Wald LL, Pizzagalli DA. Dissociation of neural regions associated with anticipatory versus consummatory phases of incentive processing. *Psychophysiology* 2008; 45:36-49.
- Dryman A, Eaton WW. Affective symptoms associated with the onset of major depression in the community: Findings from the U. S. National Institute of Mental Health Epidemiologic Catchment Area Program. *Acta Psychiatrica Scandinavica* 1991; 84:1-5.
- Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Archives of General Psychiatry* 2007; 64:327-337.
- Durbin CE, Klein DN, Hayden EP, Buckley ME, Moerk KC. Temperamental emotionality in preschoolers and parental mood disorders. *Journal of Abnormal Psychology* 2005; 114:28-37.
- Ernst M, Nelson EE, McClure EB, Monk CS, Munson S, Eshel N, Zarah E, Leibenluft E, Zametkin A, Towbin K, Blair J, Charney D, Pine DS. Choice selection and reward anticipation: an fMRI study. *Neuropsychologia* 2004; 42:1585-1597.
- Farmer A, Mahmood A, Redman K, Harris T, Sadler S, McGuffin P. A sib-pair study of the Temperament and Character Inventory scales in major depression. *Archives of General Psychiatry* 2003; 60:490-496.

First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute, 2002.

Frank MJ. Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience* 2005; 17:51-72.

Fuller RW, Clemens JA, Hynes MD 3rd. Degree of selectivity of pergolide as an agonist at presynaptic versus postsynaptic dopamine receptors: implications for prevention or treatment of tardive dyskinesia. *Journal of Clinical Psychopharmacology* 1982; 2:371-375.

Gershon AA, Vishne T, Grunhaus L. Dopamine D2-like receptors and the antidepressant response. *Biological Psychiatry* 2007; 61:145-153.

Gotlib IA, Ranganath C, Rosenfeld JP. Frontal EEG alpha asymmetry, depression, and cognitive functioning. *Cognition and Emotion* 1998; 12:449-478.

Hamburg SR. Inherited hypohedonia leads to learned helplessness: A conjecture updated. *Review of General Psychology* 1998; 2:384-403.

Hamilton M. A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 1960; 23:56-62.

Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology* 2004; 29:1765-1781.

Hautus MJ. Corrections for extreme proportions and their biasing effects on estimated values of  $d'$ . *Behavior Research Methods, Instruments, & Computers* 1995; 27:46-51.

- Hayden EP, Klein DN, Durbin CE, Olino TM. Positive emotionality at age 3 predicts cognitive styles in 7-year-old children. *Development & Psychopathology* 2006; 18:409-423.
- Henriques JB, Davidson RJ. Left frontal hypoactivation in depression. *Journal of Abnormal Psychology* 1991; 100:535-545.
- Henriques JB, Davidson RJ. Decreased responsiveness to reward in depression. *Cognition and Emotion* 2000; 14:711-714.
- Henriques JB, Glowacki JM, Davidson RJ. Reward fails to alter response bias in depression. *Journal of Abnormal Psychology* 1994; 103:460-466.
- Hundt NE, Nelson-Gray RO, Kimbrel NA, Mitchell JT, Kwapil TR. The interaction of reinforcement sensitivity and life events in the prediction of anhedonic depression and mixed anxiety-depression symptoms. *Personality and Individual Differences* 2007; 43: 1001-1012.
- Joel D, Zohar O, Afek M, Hermesh H, Lerner L, Kuperman R, Gross-Isseroff R, Weizman A, Inzelberg R. Impaired procedural learning in obsessive-compulsive disorder and Parkinson's disease, but not in major depressive disorder. *Behavioural Brain Research* 2005; 157:253-263.
- Johnstone V, Alsop B. Reinforcer control and human signal-detection performance. *Journal of the Experimental Analysis of Behavior* 2000; 73:275-290.
- Joiner TE, Lonigan CJ. Tripartite model of depression and anxiety in youth psychiatric inpatients: relations with diagnostic status and future symptoms. *Journal of Clinical and Child Psychology* 2000; 29:372-382.

Kasch KL, Rottenberg J, Arnow BA, Gotlib IH. Behavioral activation and inhibition systems and the severity and course of depression. *Journal of Abnormal Psychology* 2002; 111:589-597.

Keedwell PA, Andrew C, Williams SC, Brammer MJ, Phillips ML. The neural correlates of anhedonia in major depressive disorder. *Biological Psychiatry* 2005; 58:843-853.

Kennerley SW, Walton ME, Behrens TEJ, Buckley MJ, Rushworth MFS. Optimal decision making and the anterior cingulate cortex. *Nature Neuroscience* 2006; 9:940-947.

Kimbrel NA, Nelson-Gray RO, Mitchell JT. Reinforcement sensitivity and maternal style as predictors of psychopathology. *Personality and Individual Differences* 2007; 42:1139-1149.

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D. A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. *NeuroImage* 2003; 18:263-272.

Leventhal AM, Chasson GS, Tapia E, Miller EK, Pettit JW. Measuring hedonic capacity in depression: a psychometric analysis of three anhedonia scales. *Journal of Clinical Psychology* 2006; 62:1545-1558.

Lonigan CJ, Hooe ES, David CF, Kistner JA. Positive and negative affectivity in children: confirmatory factor analysis of a two-factor model and its relation to symptoms of anxiety and depression. *Journal of Consulting and Clinical Psychology* 1999; 67:374-386.

Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *British Medical Bulletin* 2003; 65:193-207.

- McCabe SB, Gotlib IH. Selective attention and clinical depression: performance on a deployment-of-attention task. *Journal of Abnormal Psychology* 1995; 104:241-245.
- Macmillan NA, Creelman DC. *Detection Theory: A User's Guide*. New York, NY: Cambridge University Press, 1991.
- McCarthy DC. Behavioral detection theory: Some implications for applied human research. In: Nevin JA, Davison MC, Commons ML, editors. *Signal detection: Mechanisms, models, and applications*. Hillsdale, NJ: Erlbaum, 1991. pp. 239-255.
- McCarthy D, Davison M. Signal probability, reinforcement, and signal detection. *Journal of the Experimental Analysis of Behavior* 1979; 32:373-382.
- McFarland BR, Shankman SA, Tenke CE, Bruder GE, Klein DN. Behavioral activation system deficits predict the six-month course of depression. *Journal of Affective Disorders* 2006; 91:229-234.
- Meehl PE. Hedonic capacity: some conjectures. *Bulletin of the Menninger Clinic* 1975; 39:295-307.
- Meng XL, Rosenthal R, Rubin DB. Comparing correlated correlation coefficients. *Psychological Bulletin* 1992; 111:172-175.
- Naismith SL, Hickie IB, Ward PB, Scott E, Little C. Impaired implicit sequence learning in depression: a probe for frontostriatal dysfunction? *Psychological Medicine* 2006; 36:313-323.
- Oquendo MA, Barrera A, Ellis SP, Li S, Burke AK, Grunebaum M, Endicott J, Mann JJ. Instability of symptoms in recurrent major depression: A prospective study. *American Journal of Psychiatry* 2004; 161:255-261.

- Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: A signal detection approach. *Biological Psychiatry* 2005a; 57:319-327.
- Pizzagalli DA, Sherwood RJ, Henriques JB, Davidson RJ. Frontal brain asymmetry and reward responsiveness: A Source localization study. *Psychological Science* 2005b; 16:805-813.
- Pizzagalli DA, Evins AE, Schetter CE, Frank MJ, Pajtas PE, Santesso DL, Culhane M. Single dose of a dopamine agonist impairs reinforcement learning in humans: Behavioral evidence from a laboratory-based measure of reward responsiveness. *Psychopharmacology* 2008; 196:221-232.
- Pizzagalli DA, Goetz E, Ostacher M, Iosifescu D, Perlis RH. Euthymic patients with Bipolar Disorder show decreased reward learning in a probabilistic reward task. *Biological Psychiatry*, in press, doi:10.1016/j.biopsych.2007.12.001.
- Rescorla RA, Wagner AR. A theory of Pavlovian conditioning and the effectiveness of reinforcement and non-reinforcement. In Black AH, Prokasy WF, editors. *Classical conditioning. 2. Current research and theory*. New York, NY: Appleton-Century-Crofts, 1972. p 64-69.
- Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, Smith SM. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biological Psychiatry* 2004; 55:594-602.
- Rushworth MF, Buckley MJ, Behrens TE, Walton ME, Bannerman DM. Functional organization of the medial frontal cortex. *Current Opinion in Neurobiology* 2007; 17:220-227.
- Schultz W. Behavioral dopamine signals. *Trends in Neuroscience* 2007; 30:203-210.

- Sloan DM, Strauss ME, Wisner KL. Diminished response to pleasant stimuli by depressed women. *Journal of Abnormal Psychology* 2001; 110:488-493.
- Spijker J, Bijl RV, de Graaf R, Nolen WA. 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 Psychiatrica Scandinavica* 2001; 103:122-130.
- Suslow T, Junghanns K, Arolt V. Detection of facial expressions of emotions in depression. *Perceptual & Motor Skills* 2001; 92:857-868.
- Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: a meta-analytic review. *Journal of Abnormal Psychology* 2006; 115:715-729.
- Tissari AH, Rossetti ZL, Meloni M, Frau MI, Gessa GL. Autoreceptors mediate the inhibition of dopamine synthesis by bromocriptine and lisuride in rats. *European Journal of Pharmacology* 1983; 91:463-468.
- Tremblay LK, Naranjo CA, Cardenas L, Herrmann N, Busto UE. Probing brain reward system function in major depressive disorder: Altered response to dextroamphetamine. *Archives of General Psychiatry* 2002; 59:409-416.
- Tripp G, Alsop B. Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. *Journal of Clinical and Child Psychology* 1999; 28:366-375.
- Vakil E, Grunhaus L, Nagar I, Ben-Chaim E, Dolberg OT, Dannon PN, Schreiber S. The effect of electroconvulsive therapy (ECT) on implicit memory: skill learning and perceptual priming in patients with major depression. *Neuropsychologia* 2000; 38:1405-1414.

Wang CE, Brennen T, Holte A. Decreased approach motivation in depression. *Scandinavian Journal of Psychology* 2006; 47;505-511.

Watson D, Weber K, Assenheimer JS, Clark LA, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology* 1995; 104:3-14.

## Footnotes:

<sup>1</sup> Seven MDD subjects met DSM-IV criteria for an anxiety disorder (OCD:  $n = 1$ , PTSD:  $n = 2$ ; GAD:  $n = 1$ ; Social Anxiety Disorder and Panic Disorder:  $n = 1$ ; Social Anxiety Disorder:  $n = 1$ ; Anxiety Disorder NOS:  $n = 1$ ). MDD subjects with and without anxiety comorbidity did not differ in their demographic variables, BDI-II, and HRSD scores (all  $ps > 0.17$ ). Additional ANOVAs revealed no differences in any task performance variable between MDD subjects with vs. without anxiety comorbidity (all  $F$ s  $< 1.38$ , all  $ps > 0.25$ ).

<sup>2</sup> The 17-item HRSD score, which is more commonly used in the literature, was derived from the 21-item version of the scale.

<sup>3</sup> In prior studies using the probabilistic reward task, response bias generally increased across blocks (Bogdan and Pizzagalli, 2006; Pizzagalli et al., 2005a). In the current study, participants (particularly the control subjects) displayed a robust response bias already in Block 1. To further investigate this finding, response bias was calculated for the first and second half of Block 1 (50 trials each). These values were entered in a *Group*  $\times$  *Block* ANOVA, where the factor *Block* had four levels (Block 1-first half, Block 1-second half, Block 2, and Block 3). All effects described in this report were confirmed. In particular, a main effect of *Group* emerged for response bias,  $F = 5.08$ ,  $df = 1,46$ ,  $p < 0.03$ , partial  $\eta^2 = 0.10$ . In addition, a one-way ANOVA using *Block* as repeated measure was conducted for control and MDD subjects separately. For control, but not MDD subjects, the main effect of *Block* was significant,  $F = 3.02$ ,  $df = 3,72$ ,  $p < 0.05$  vs.  $F =$

1.82,  $df = 3,66$ ,  $p > 0.15$ . Post-hoc Newman Keuls revealed that, for control subjects, response bias was significantly higher in the second half of Block 1 ( $p < 0.045$ ), Block 2 ( $p < 0.050$ ), and Block 3 ( $p < 0.035$ ) compared to the first half of Block 1. For MDD subjects, no differences across blocks emerged (all  $ps > 0.11$ ). In sum, control subjects quickly acquired a response bias toward the more frequently rewarded stimulus, whereas MDD subjects failed to show any modulation.

<sup>4</sup> Analogous ANCOVAs were run on discriminability, hit rates, and RT scores using age as a covariate. The findings were identical to the ones reported here.

<sup>5</sup> In light of this overall RT group difference, a *Group x Block* ANCOVA was run on our main variable of interest, response bias, using mean RT scores (averaged across Blocks and Stimulus Type) as covariate. The main effect of *Group* remained significant,  $F = 4.94$ ,  $df = 1,45$ ,  $p < 0.03$ , partial  $\eta^2 = 0.10$ .

<sup>6</sup> Rich miss rate was computed as: (1 - rich hit rate). Analogously, lean miss rate was computed as: (1 - lean hit rate).

**Table 1.** Sociodemographic and mood data in control (n = 25) and MDD (n = 23) subjects

	Control subjects		MDD subjects		Statistics	P value
	(n = 25)		(n = 23)			
	Mean	SD	Mean	SD		
Age	38.36	10.76	43.65	9.55	t = 1.80	.08
Gender ratio (Female/Male)	11/14	N/A	10/13	N/A	$\chi^2 = 0.001$	> .50
Education (% college education)	64.0%	N/A	65.2%	N/A	$\chi^2 = 0.04$	> .20
Ethnicity (% Caucasian)	68.0%	N/A	91.3%	N/A	$\chi^2 = 5.55$	> .10
Marital status (% never married)	64.0%	N/A	69.6%	N/A	$\chi^2 = 0.31$	> .50
BDI-II	3.40	3.59	32.13	8.66	t = 15.23	.0001
HRSD (17-item)	N/A	N/A	19.40	3.30	N/A	N/A
MASQ AD	51.52	12.60	91.00	7.60	t = 13.00	.0001
MASQ GDD	15.64	5.22	40.70	10.71	t = 10.43	.0001
MASQ AA	18.76	5.19	25.30	11.32	t = 2.61	.015
MASQ GDA	14.16	4.34	23.26	8.14	t = 4.89	.0001

BDI-II: Beck Depression Inventory-II (Beck et al., 1996); HRSD: Hamilton Rating Scale for Depression (Hamilton, 1960); MASQ: Mood and Anxiety Symptom Questionnaire (Watson et al., 1995; AD: Anhedonic Depression; GDD: General Distress-Depressive Symptoms; AA: Anxious Arousal; GDA: General Distress-Anxious Symptoms).

**Table 2.** Summary of Pearson’s correlations between MASQ Anhedonic Depression (AD) scores and probabilities of rich misses (i.e., selecting “lean” when a rich stimulus was actually presented) and lean misses (i.e., selecting “rich” when a lean stimulus was actually presented) as a function of the outcome in the preceding correctly executed response.

<i>Preceding trial</i>	<b>MASQ Anhedonic Depression</b>		
		<b>Rich miss</b>	
		<b>rate</b>	<b>Lean miss rate</b>
Rewarded Rich	Pearson's correlation	-0.110 <sup>a</sup>	-0.190
	<i>p</i> -value	.617	.385
Rewarded Lean	Pearson's correlation	0.005	0.290
	<i>p</i> -value	.980	.180
Non-Rewarded Rich	Pearson's correlation	0.519 <sup>a,b</sup>	-0.356
	<i>p</i> -value	.011	.095
Non-Rewarded Lean	Pearson's correlation	-0.041 <sup>b</sup>	-0.267
	<i>p</i> -value	.854	.218

Rich miss rate = (1- rich hit rate), lean miss rate = (1- lean hit rate). MASQ: Mood and Anxiety Symptom Questionnaire (Watson et al., 1995).

<sup>a</sup> Correlations are different at  $p = 0.039$ ,  $t(20) = 2.21$ .

<sup>b</sup> Correlations are different at  $p = 0.069$ ,  $t(20) = 1.92$ .

## Figure legends

**Fig. 1.** Schematic illustration of task design. For each trial, the subjects' task was to decide whether a short (11.5 mm) or a long (13 mm) mouth was presented by pressing either the 'z' or the '/' key of a PC keyboard. The reinforcement allocation and key assignments were counterbalanced across subjects.

**Fig. 2.** (A) Response bias, and (B) mean hit rates (averaged across the three blocks) for the more frequently rewarded (rich) stimulus and the lean stimulus for healthy control subjects ( $n = 25$ ) and MDD subjects ( $n = 23$ ). Error bars represent standard errors.

**Fig. 3.** (A) Probability of misclassifying a lean stimulus (i.e., lean miss rate) as a function of whether the preceding correct identification of a rich trial had been rewarded or not. (B) Probability of misclassifying a rich stimulus (i.e., rich miss rate) as a function of which stimulus was rewarded in the immediately preceding trial. Error bars represent standard errors; arrows and asterisks denote significant findings in post-hoc analyses.

**Fig. 4.** Scatterplot and Pearson correlation between the MASQ Anhedonic Depression (AD) score and probability of rich misses (i.e., selecting "lean" when a rich stimulus was actually presented) for trials following non-rewarded correct identification of rich stimuli ( $r = 0.519$ ,  $p = 0.011$ ) within the MDD subjects ( $n = 23$ ).

MASQ: Mood and Anxiety Symptom Questionnaire (Watson et al., 1995).

Figure 1

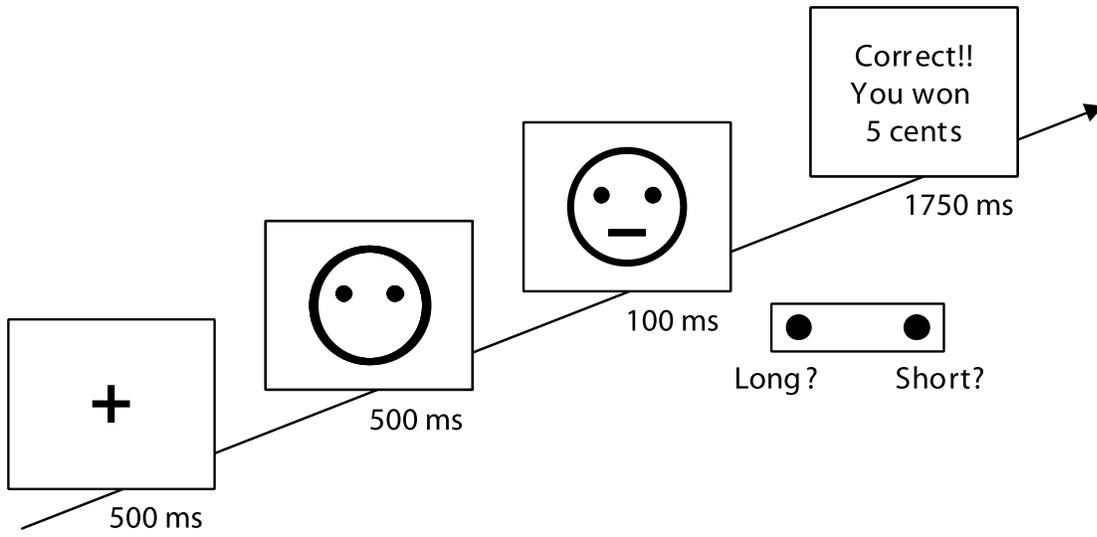


Figure 2

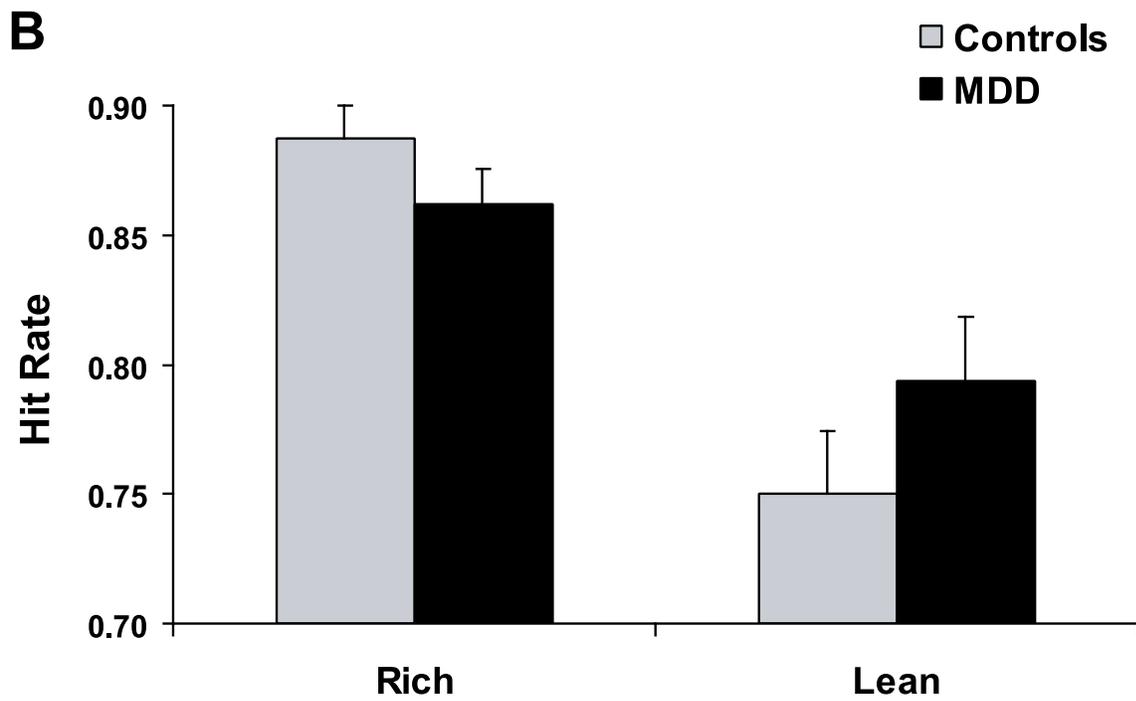
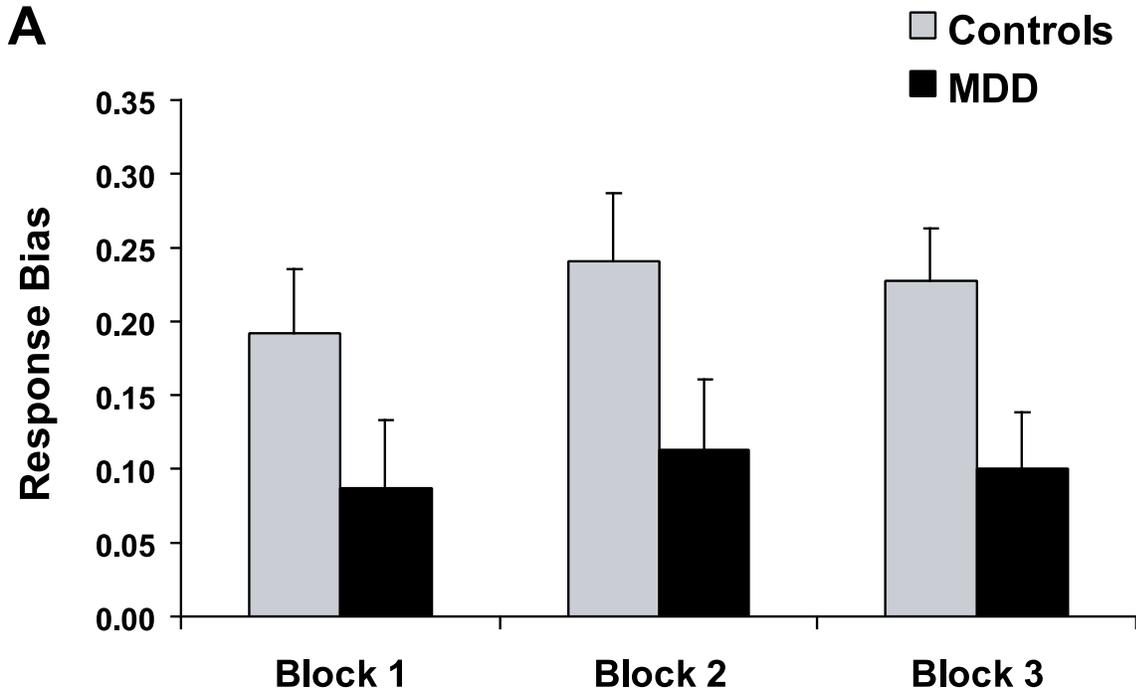




Figure 3

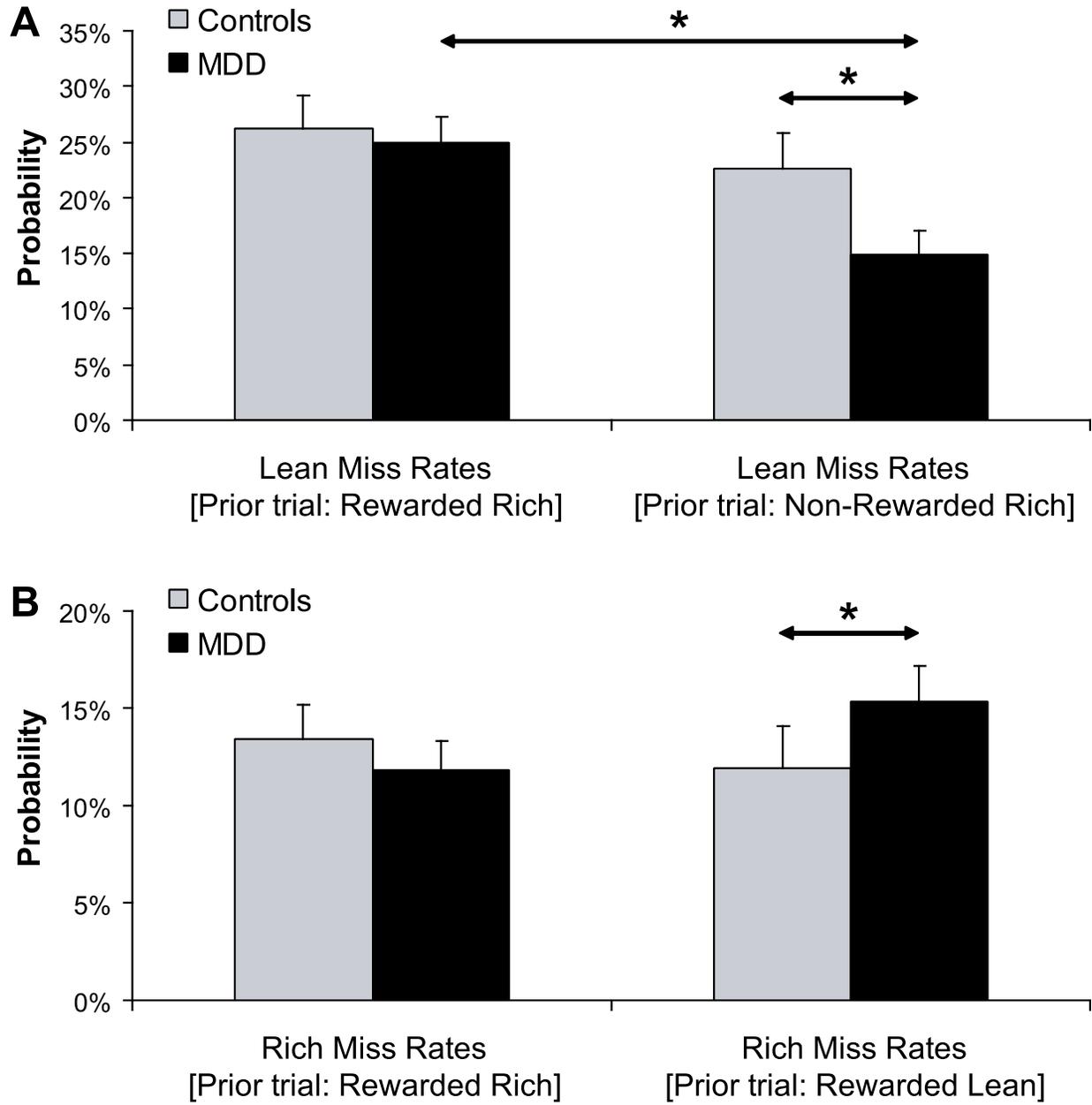


Figure 4

