Blunted reward responsiveness in remitted depression

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Major depressive disorder has been associated with blunted responsiveness to rewards, but inconsistencies exist whether such abnormalities persist after complete remission. To address this issue, across two independent studies, 47 adults with remitted major depressive disorder (rMDD) and 37 healthy controls completed a Probabilistic Reward Task, which used a differential reinforcement schedule of social or monetary feedback to examine reward responsiveness (i.e., ability to modulate behavior as a function of reinforcement history). Relative to controls, adults with rMDD showed blunted reward responsiveness. Importantly, a history of depression predicted reduced reward learning above and beyond residual depressive (including anhedonic) symptoms and perceived stress. Findings indicate that blunted reward responsiveness endures even when adults are in remission and might be a trait-related abnormality in MDD. More research is warranted to investigate if blunted reward responsiveness may predict future depressive episodes and whether targeting reward-related deficits may prevent the recurrence of the disorder.

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1. Introduction

More than 30 million adults in the United States meet criteria for major depressive disorder (MDD) during their lifetime (Kessler and Wang, 2009). Among individuals with MDD, nearly 40% experience clinically significant anhedonia, defined as the loss of pleasure or lack of reactivity to pleasurable stimuli (Treadway and Zald, 2011). Moreover, residual anhedonic symptoms often persist even when MDD is in remission (Di Nicola et al., 2013). Behavioral research has identified blunted reward responsiveness in participants with acute MDD, including deficits in modulating responses as a function of previous reinforcement history (Henriques et al., 1994; Pizzagalli et al., 2005, 2008b). Consistent with these findings, functional imaging studies have described frontostriatal hypoactivation in rewards in participants with MDD (Epstein et al., 2006; Forbes et al., 2009; Keedwell et al., 2009; Pizzagalli et al., 2009; Schaefer et al., 2006). Similarly, decreased frontostriatal responses to reward have also been found in remitted individuals with a history of MDD (Dichter et al., 2012; McCabe et al., 2009), suggesting that reduced reward-related neural responses might represent a trait characteristic of MDD. Yet other studies have reported a normalization of hedonic capacity in remitted MDD, pointing to possible state-related abnormalities (McFarland and Klein, 2009). As these studies have frequently relied on self-reported ratings of reward experiences that may be affected by reporting biases, it is critical to use laboratory-based, objective measures to determine whether blunted reward responsiveness persists in individuals who are in full remission of MDD.

To address this issue, across two independent studies, we used a well-established objective measure to examine reward responsiveness in a sample of adults with depression in remission and demographically matched healthy controls. Relative to never-depressed controls, we hypothesized that adults with remitted MDD would show blunted reward responsiveness. Moreover, we reasoned that, if blunted reward responsiveness represents a trait-like vulnerability to MDD, differences between remitted depressed and healthy control subjects would remain even when statistically controlling for residual depressive (including anhedonic) symptoms or perceived stress, which have both been linked to deficits in reward processing (Pizzagalli et al., 2007, 2008b).

2. Methods and materials

2.1. Participants

Ninety-two adult participants were recruited through online and printed advertisements for two conceptually-identical studies...
that used equivalent study procedures and inclusion criteria. Eight participants (4 controls, 4 rMDD) were excluded, as they were not task compliant or did not meet criteria for remission from MDD. The final sample (n = 84; Mage = 29.55, SD ± 11.17 years) consisted of: 37 healthy controls (23 females) without current or past psychopathology (controls) and 47 adults (39 females) with remitted major depressive disorder (rMDD). Based on an initial phone interview, participants were excluded if they presented with psychotic symptoms, current mood disorders, somatoform disorders, personality disorders, lifetime substance dependence, substance abuse within the past six months, epileptic seizures, history of electroconvulsive therapy, or use of antidepressant medication within the past two weeks. All participants in the study were administered a Structured Clinical Interview for DSM disorders (SCID; First et al., 2002) by a Master or PhD-level clinical interviewer. Healthy control participants did not meet past or current diagnosis for any Axis I disorders. Participants in the rMDD group met criteria for past but not current MDD as assessed by the SCID, and did not report current anxiety disorder with the exception of current specific phobia (n = 4). In the rMDD group, seven participants reported a remitted anxiety disorder, two participants reported lifetime alcohol abuse. All participants had a Beck Depression Inventory—II (BDI-II; Beck et al., 1996) score lower than 13. Participants in the rMDD group reported a mean number of 2.4 past MDD episodes (SD = 2.2) and, at the time of the study, an average of 3.4 years (SD = 2.7) had elapsed since their last episode. Volunteers took part in lab-wide studies on reward processes in major depressive disorder. Data for Study 1 (which used monetary rewards as feedback) were collected over a period of 24 months between August 2007 and July 2009, whereas data for Study 2 (which used social rewards as feedback) were collected over a period of 10 months between June 2009 and March 2010. Both studies were approved by the Harvard University Institutional Review Board.

2.2. Procedure and measures

After providing informed consent, the SCID was administered. Participants then completed the 21-item BDI-II to assess residual symptoms of depression in the past two weeks and the 14-item Perceived Stress Scale (Cohen et al., 1983) to measure perceived global stress in the past month. Depressive symptoms and increased perceived stress have both been associated with reduced reward responsiveness (Pizzagalli et al., 2007, 2008b), and were thus used as covariates in the analyses. In both studies, anhedonic symptoms were assessed using the 14-item Snath-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995). Following prior recommendations (Franken et al., 1997), a total SHAPS score was computed by summing scores across the four available response categories (higher scores reflect more anhedonic symptoms). One healthy control subject in Study 1 did not complete the SHAPS.

2.2.1. Probabilistic reward task (PRT)

Participants completed a revised version of the probabilistic reward task (PRT) (Pizzagalli et al., 2005; modified after Tripp and Alsop, 1999), which used a differential reinforcement schedule to probe reward responsiveness (i.e., the ability to modulate behavior as a function of reward reinforcement history). We administered two versions of the PRT using either monetary incentives ("Correct! You won 5 cents") (Study 1) or a social praise ("Correct! Well done!") (Study 2) as reward feedback (Pizzagalli et al., 2005, 2008b). To examine potential differences in reward type, Study 2 was entered as a factor in the analysis (21 controls and 15 rMDD completed the monetary reward version; 16 controls and 32 rMDD completed the social reward version). The 15–20 min task was presented on a 17” PC monitor using E-Prime software (Version 1.1.; Psychology Software Tools Inc., Pittsburgh, Pennsylvania). Participants completed either three blocks of 100 trials (monetary reward) or three blocks of 80 trials (social reward) to induce a response bias towards the more frequently rewarded stimulus (RICH) compared to the less frequent rewarded stimulus (LEAN). Reward feedback was provided three times more often for the RICH than the LEAN stimulus. Participants were instructed that the goal of the task was to win as much money (or receive as many praise feedbacks) as possible and were informed that not every correct response would lead to a reward feedback. In each block, a pseudo-random sequence of 50% long and 50% short mouthings was presented. Each trial consisted of a fixation cross (jittered 750–900 ms) followed by a mouth-less line drawing of a face (500 ms), after which either a short (11.5 mm) or a long (13 mm) mouth appeared on the face (100 ms). Participants were instructed to press one of two keyboard keys to indicate whether the mouth was long or short. Reward feedback was displayed on the computer screen (1500 ms). Keys and conditions (long or short mouth as RICH stimulus) were counterbalanced across participants. Participants completed a short series of practice trials to ensure they understood the instructions.

2.3. Analyses

Chi-square tests and independent t-tests evaluated group differences in demographics, BDI-II, PSS and SHAPS scores. For the PRT, following prior procedures (e.g., Pizzagalli et al., 2005, 2008b), trials with reaction times of <150 ms or >1500 ms were removed; next, reaction times falling outside the mean ± 3 SD of the remaining trials (after log transformation) were removed as additional outliers. Signal detection analysis (Macmillan and Creelman, 2005) was used to compute response bias (i.e., the preference for the more frequently rewarded stimulus, which captures reward responsiveness) and discriminability (i.e., the ability to distinguish between stimuli types), which were the main variables of interest. Accuracy (percentage correct responses) and reaction time were used as secondary measures of overall task performance. Response bias and discriminability were calculated as follows:

**Response Bias**: \( \log b = \frac{1}{2} \log \frac{RICHcorrect \cdot LEANincorrect}{RICHincorrect \cdot LEANcorrect} \)

**Discriminability**: \( \log d = \frac{1}{2} \log \frac{RICHcorrect \cdot LEANincorrect}{RICHincorrect \cdot LEANcorrect} \)

In line with prior recommendations (Hautus, 1995), 5 was added to every cell of the detection matrix to permit computations in cases with a zero in one cell of the formula. A high response bias emerges when participants correctly identify the RICH and misclassify the LEAN stimulus as the RICH stimulus. Reward learning was calculated as the change in response bias throughout the task (\( \Delta RB = Response\ Bias\ Block\ 3 - Response\ Bias\ Block\ 1 \)). To examine task performance, a Group (rMDD, controls) \( \times \) Study (monetary, social) \( \times \) Block (1, 2, 3) mixed ANOVA was run separately for response bias and discriminability. For accuracy and reaction time (RT) values, separate Group (rMDD, controls) \( \times \) Study (monetary, social) \( \times \) Block (1, 2, 3) \( \times \) Stimulus (RICH, LEAN) ANOVAs were performed. To account for putative residual depressive symptoms and perceived levels of stress, analyses were repeated using analysis of covariance (ANCOVA) with BDI-II and PSS scores as covariates. Moreover, to test whether groups continued to differ in reward responsiveness when accounting for residual subjective measures of anhedonia and perceived stress, ANCOVAs were repeated entering SHAPS and PSS scores as covariates. For all analyses, the Greenhouse-Geisser correction was used where applicable. Significant findings were followed-up with Bonferroni post-hoc tests.
Finally, a multiple linear regression examined if a history of MDD predicted changes in reward responsiveness beyond the impact of Study, residual depressive symptoms (BDI-II scores), perceived stress (PSS scores) and discriminability. In order to evaluate whether a history of MDD predicted changes in reward responsiveness above and beyond subjective measures of anhedonia, an analogous regression was run by replacing the BDI-II scores with the SHAPS scores.

3. Results

Table 1 summarizes participants’ demographic and clinical data. On average, participants were 30 years old and mainly identified themselves as Caucasian. Groups did not differ in age or ethnicity (Table 1). Although rMDD reported higher level of depressive symptoms than controls \( p < .001 \), only participants with a BDI-II score below clinical threshold were included in the study (BDI-II < 13; range: 0–43). Relative to controls, the rMDD group reported higher levels of global stress (PSS scores) within the past month \( \text{Mean (SD)} = 19.26 (7.76) \) vs. \( 15.68 (8.45) \) \( p = .03 \).

For the PRT task, the overall ratio of rich:lean rewards received did not differ between groups, indicating that rMDD and healthy controls were exposed to the intended 3:1 reward ratio \( (2.97 \pm 0.02) \) vs. \( 3.00 \pm 0.00 \) \( p = .12 \). Follow-up tests revealed significantly greater discriminability in healthy controls compared to rMDD in Block 1 \( (t(82) = 2.22, p = .03) \) and Block 2 \( (t(82) = 2.18, p = .03) \), but not Block 3 (\( p > .05 \)) (Fig. 1B). Moreover, for the rMDD group, discriminability increased from Block 1 to 3 \( (t(46) = -2.48, p = .02) \) and from Block 2 to 3 \( (t(46) = -1.99, p = .053) \), whereas healthy control subjects maintained their discriminability levels over time (all \( p's > .21 \)). Finally, a main effect of Study \( (F(1,80) = 4.06, p = .05) \) indicated greater discriminability in the monetary reward version compared to the social reward version of the task. The Group x Block interaction remained significant when entering (1) BDI-II and PSS scores or (2) SHAPS and PSS scores as covariates. However, the main effect of Study was no longer significant in the ANCOVAs \( (p > .08) \).

3.2. Discriminability

A Group x Block interaction \( (F(2,160) = 3.42, p = .04) \), partial \( \eta^2 = .04 \) emerged from the ANOVA. Follow-up tests showed that rMDD participants displayed significantly greater discriminability in healthy controls compared to rMDD in Block 1 \( (t(82) = 2.22, p = .03) \) and Block 2 \( (t(82) = 2.18, p = .03) \), but not Block 3 (\( p > .05 \)) (Fig. 1B). Moreover, for the rMDD group, discriminability increased from Block 1 to 3 \( (t(46) = -2.48, p = .02) \) and from Block 2 to 3 \( (t(46) = -1.99, p = .053) \), whereas healthy control subjects maintained their discriminability levels over time (all \( p's > .21 \)). Finally, a main effect of Study \( (F(1,80) = 4.06, p = .05) \) indicated greater discriminability in the monetary reward version compared to the social reward version of the task. The Group x Block interaction remained significant when entering (1) BDI-II and PSS scores or (2) SHAPS and PSS scores as covariates. However, the main effect of Study was no longer significant in the ANCOVAs \( (p > .08) \).

3.3. Accuracy

A main effect of Stimulus emerged \( (F(1,80) = 56.10, p < .001) \), partial \( \eta^2 = .41 \), which, as expected, was due to a higher accuracy for the social stimulus than the ANOVA stimulus (Table 1). The 3-way interaction of Group x Block x Stimulus was also significant \( (F(2,160) = 4.05, p = .02) \), partial \( \eta^2 = .05 \). To disentangle the 3-way interaction, follow-up Group x Block ANOVAs were run separately for rich and lean accuracy. For rich accuracy, a main effect of Group emerged, driven by overall lower rich accuracy for the rMDD participants relative to the healthy controls \( (F(1,82) = 4.25, p = .04) \), partial \( \eta^2 = .05 \). For lean accuracy, a main effect Group x Block interaction emerged \( (F(2,164) = 4.08, p = .02) \), partial \( \eta^2 = .05 \). However, follow-up tests did not uncover group differences in lean accuracy for any of the blocks (all \( p's > .07 \)). Finally, a main effect of Study \( (F(1,80) = 6.20, p = .02) \), partial \( \eta^2 = .07 \) indicated overall greater accuracy in monetary reward version than social reward version of the task. All main effects and interactions remained significant when entering (1) BDI-II and PSS scores or (2) SHAPS and PSS scores as covariates.

3.4. Reaction time

As expected, the main effect of Stimulus \( (F(1,80) = 35.97, p < .001) \), partial \( \eta^2 = .31 \) was significant, due to faster reaction times for the rich than lean stimulus (Fig. 1D). Although a Group x Block interaction \( (F(2,160) = 3.50, p = .03) \), partial \( \eta^2 = .04 \) emerged, follow-up tests did not reveal any significant differences. Finally, a main effect of Study \( (F(1,80) = 11.83, p < .001) \), partial \( \eta^2 = .13 \) and a significant Stimulus x Study interaction \( (F(1,160) = 4.27, p = .04) \), partial \( \eta^2 = .05 \) emerged, which were driven by a faster reaction time for the rich than lean stimulus in the monetary reward version than in the social reward version. A Group x Stimulus interaction \( (F(1,80) = 4.28, p = .04) \), partial \( \eta^2 = .05 \) showed faster reaction time for the rMDD group in the monetary reward version than in the social reward version of the task \( (t(45) = 4.21, p < .001) \) while no reaction time differences emerged for controls (\( p > .06 \)). When entering BDI-II and PSS scores as covariates, the main effect of Study and the Stimulus x Study interaction were significant.

Table 1

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<thead>
<tr>
<th>Demographics and clinical data for adults with major depressive disorder in remission (rMDD) and healthy controls (controls).</th>
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<td><strong>Demographics</strong></td>
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<td>Ethnicity, Caucasian, No [%]</td>
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<tr>
<td><strong>Clinical measures</strong></td>
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<td>BDI-II, Means (SD)</td>
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<td>SHAPS, Means (SD)</td>
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<td>No. MDD episodes, Mean (SD)</td>
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<td>Years since MDD episode, Mean (SD)</td>
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P-values marked in bold for \( p \leq .05 \).

* Single data point missing. Note. BDI-II: Beck Depression Inventory-II; PSS: Perceived Stress Scale; SHAPS: Snith Hamilton Pleasure Scale.
4. Discussion

The overarching goal of the present study was to test whether adults with a history of MDD in full remission are able to modulate behavior as a function of reinforcement history. Using an objective measure of reward responsiveness, we uncovered several important findings. First, blunted reward responsiveness was present even when MDD has fully remitted. Specifically, over the course of the task, healthy controls developed a robust response bias towards the more frequently rewarded stimulus. In contrast, individuals with a history of depression did not alter their behavior based on the differential reinforcement schedule. Critically, these results were confirmed when controlling for residual depressive (including anhedonic) symptoms as well as current level of perceived stress, both of which were found to modulate response bias in prior studies using the same probabilistic reward task (Pizzagalli et al., 2005, 2007). Second, throughout the task, healthy controls maintained a high level of discriminability (i.e., ability to distinguish between the two stimuli). Adults with a history of depression displayed lower discriminability at the beginning of the task, but increased their performance to eventually match healthy controls’ discriminability scores. As discriminability captures task difficulty, these findings raise the possibility that group differences in response bias might have been partially due to differences in perceptual discrimination. To exclude this possibility, discriminability scores were entered as covariates in the analyses, and the critical Group × Block interaction for response bias was confirmed. Furthermore, a history of depression predicted changes in discriminability (reward learning) even when controlling for differences in discriminability in the regression analyses. Thus, the reduced reward responsiveness in the remitted sample was not due to difficulty discriminating between the RICH and LEAN stimulus. Third, all participants demonstrated increased accuracy and faster reaction time in response to the more frequently rewarded (RICH) stimulus compared to the less frequently rewarded (LEAN) stimulus, suggesting that the differential reinforcement schedule elicited the intended behavioral effects.

Collectively, these findings suggest that blunted reward responsiveness persists in individuals with a history of MDD years after the last major depressive episode (MDE) (of note, the last MDD episode occurred, on average, 3.0 years in Study 1, and, on average, 3.6 years in Study 2 before administration of the PRT). Moreover, such blunting emerged when using both monetary and social rewards and was confirmed when statistically controlling for residual depressive (including anhedonic) symptoms and recently experienced stress, indicating that reduced reward responsiveness might represent a trait-like abnormality in depression that generalizes across feedback type (and thus context).
In spite of these reliable behavioral findings, we can only speculate about putative neurobiological abnormalities associated with reduced reward responsiveness in the current remitted sample. Of note, response bias, as measured by the current task, has been shown to correlate with striatal activation (Santesso et al., 2008), be modulated by dopamine (Pizzagalli et al., 2008a), and be linked to extrastriatal dopaminergic signaling (Vrieze et al., 2013a), raising the possibility that subtle hypoactivation in dopaminergic striatal and extrastriatal pathways might have contributed to the behavioral abnormalities observed in the current study. Although functional neuroimaging studies will be needed to test this conjecture, it is interesting to note that decreased frontostriatal activation in response to reward has been documented in both adults with remitted depression (Dichter et al., 2012; McCabe et al., 2009) and current MDD (Epstein et al., 2006; Forbes et al., 2009; Keedwell et al., 2009; Pizzagalli et al., 2009; Schaefer et al., 2006).

Interestingly, recent research has shown that reward dysfunctions may precede the onset of MDD (Gotlib et al., 2010; McCabe et al., 2012). McCabe et al. (2012), for example, described differences in neural responses to reward in never-depressed young individuals at increased risk for depression owning a family history of MDD. Specifically, in response to taste and sight of chocolate, the at-risk group showed reduced activation in regions of the reward circuit (rostral and dorsal anterior cingulate, orbitofrontal cortex). In addition, anhedonia and/or reduced reward responsiveness have been found to precede the onset of depression (Dryman and Eaton, 1991), shows temporal stability (Oquendo et al., 2004), and predicts a variety of clinically important variables, including poor outcome in naturalistic studies (Spijker et al., 2001), chronic course of depression over a 10-year period (Moos and Cronkite, 1999), chronicity of an MDD diagnosis (Vrieze et al., 2013b), time to recovery (McFarland et al., 2006), lower remission rates among SSRI-resistant adolescents (McMakin et al., 2012), and future depressive symptoms (Hundt et al., 2007). Collectively, findings support the argument that impaired processing of rewards represents a trait marker that predisposes individuals to depression and persists in-between depressive episodes. From a clinical perspective, these findings highlight the need to focus on blunted reward responsiveness to prevent future relapse.

In spite of the current findings, it should be noted that not all prior studies have shown deficient reward function in the absence of acute symptoms. McFarland and Klein, (2009), for example, reported that currently – but not previously – depressed individuals reported reduced reward responses relative to control participants, suggesting a state effect of reward dysfunctions. However, reward responses in the anticipation of reward delivery were assessed using self-report measures in the study (McFarland and Klein, 2009). It is possible that the objective measure of reward responsiveness used in the present study – which might probe more implicit forms of reinforcement learning (Santesso et al., 2008) – may be more sensitive and thus capture subtle manifestations of a hypofunctional reward system. Consistent with this assumption, group differences in reward responsiveness were confirmed even when accounting for subjective measures of anhedonia (SHAPS scores), highlighting the promise of laboratory-based measures of core symptoms of depression.

Using a laboratory-based measure to assess reward responsiveness, the current study found that adults with past history of MDD are characterized by blunted reward responsiveness, which appears to persist years after the last MDE and beyond current residual symptoms and perceived stress. Deficits in reward responsiveness may thus represent a trait-like marker that endures across depressive episodes. Future studies are warranted to investigate whether deficits in reward responsiveness might predict future depressive episodes and whether BAT intervention might prevent relapse.

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**Contributors**

All authors were involved in the design of the study and conducted data collection. Drs. Pechtel and Pizzagalli managed the statistical analysis and contributed to the writing of the manuscript. All authors have approved of the final manuscript.

**Conflict of interest**

Dr. Pizzagalli has received consulting fees from Advanced Neuro Technology (ANT), AstraZeneca, Ono Pharma USA, Servier, Shire and Johnson and Johnson for projects unrelated to the current research. Pia Pechtel, Sunny Dutra and Elena Goetz report no competing interests.
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