Journal of Psychiatric Research 47 (2013) 1864–1869

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Blunted reward responsiveness in remitted depression

Pia Pechtel [a, *], Sunny J. Dutra [b], Elena L. Goetz [c], Diego A. Pizzagalli [a, *]

[a] McLean Hospital & Harvard Medical School, USA
[b] Yale University, USA
[c] Duke University, USA

ARTICLE INFO

Article history:
Received 21 March 2013
Received in revised form
10 August 2013
Accepted 15 August 2013

Keywords:
Reward
Positive reinforcement
Major depressive disorder

ABSTRACT

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 re-occurrence of the disorder.

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 to 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

* Corresponding authors. McLean Hospital, Harvard Medical School, Center for Depression, Anxiety and Stress Research, Laboratory for Affective and Translational Neuroscience, De Marneffe Building, Room 233B, 115 Mill Street, Belmont, MA 02478-9106, USA. Tel.: +1 617 855 4234 (PP), +1 617 855 4230 (DAP); fax: +1 617 855 4231.
E-mail addresses: ppechtel@mclean.harvard.edu (P. Pechtel), dap@mclean.harvard.edu (D.A. Pizzagalli).

0022-3956/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jpsychires.2013.08.011

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 ($n = 84$; $M_{age} = 29.55$, 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 a remitted eating disorder and 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 Snaith-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* 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 mouths 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:

$$\textbf{\textit{Response Bias}} : Log\ b = \frac{1}{2}\log\frac{\text{RICHcorrect}*\text{LEANincorrect}}{\text{RICHincorrect}*\text{LEANcorrect}}$$

$$\textbf{\textit{Discriminability}} : Log\ d = \frac{1}{2}\log\frac{\text{RICHcorrect}*\text{LEANcorrect}}{\text{RICHincorrect}*\text{LEANincorrect}}$$

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 (ΔRB = Response Bias Block 3 – Response Bias Block 1).

To examine task performance, a *Group* (rMDD, controls) × *Study* (monetary, social) × *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) × *Study* (monetary, social) × *Block* (1, 2, 3) × *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.

Table 1
Demographics and clinical data for adults with major depressive disorder in remission (*rMDD*) and healthy controls (*controls*).

	rMDD ($n = 47$)	Controls ($n = 37$)	χ^2/*t*-Value	*P*-Value
Demographics				
Age, Means (SD)	27.87 (9.87)	31.75 (12.47)[a]	1.58	.12
Ethnicity: Caucasian, No (%)	33 (68.80%)	27 (77.10%)[a]	.73	.95
Clinical measures				
BDI-II, Means (SD)	4.28 (3.84)	1.30 (1.77)	−4.71	**<.001**
PSS, Means (SD)	19.26 (7.76)[a]	15.68 (8.45)	−2.01	**.05**
SHAPS, Means (SD)	20.74 (4.44)	21.06 (4.92)[a]	.30	.76
No. MDD episodes, Mean (SD)	2.39 (2.15)[a]	0	N/A	N/A
Years since MDD episode, Mean (SD)	3.38 (2.68)	N/A	N/A	N/A

P-values marked in bold for $p \leq .05$.
[a] Single data point missing. *Note.* BDI-II: Beck Depression Inventory-II; PSS: Perceived Stress Scale; SHAPS: Snaith Hamilton Pleasure Scale.

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: 0–12). Relative to controls, the rMDD group reported higher levels of global stress (PSS scores) within the past month ($p = .05$). Groups did not differ in their SHAPS scores.

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 ± .12 vs. 3.00 ± .08; $t(82) = 1.37$, $p > .17$).

3.1. Response bias

The only significant effect emerging from the *Group* × *Study* × *Block* ANOVA was the *Group* × *Block* interaction [$F(2,160) = 4.01$, $p = .02$; partial eta$^2 = .05$], highlighting significant group differences in reward learning. Follow-up tests revealed significantly lower response bias in the rMDD compared to controls in Block 2 ($t(82) = 2.63$, $p = .01$), but not in Block 1 ($t(82) = -.13$, $p > .90$) or Block 3 ($t(82) = 1.49$, $p = .14$) (Fig. 1A). Moreover, controls increased their response bias from Block 1 to 2 ($t(36) = -2.22$, $p = .03$) and marginally from Block 1 to 3 ($t(36) = -1.95$, $p = .06$), whereas rMDD did not show any changes in response bias across the blocks (all *p's* > .40). To control for putative residual symptoms, a control analysis entered BDI-II and PSS scores as covariates (ANCOVA). The *Group* × *Block* interaction was confirmed [$F(2,154) = 3.60$, $p = .03$, partial eta$^2 = .05$] and a main effect of *Study* ($F(1,77) = 4.17$, $p = .05$, partial eta$^2 = .05$) emerged.[1] A significant *Group* × *Block* interaction was confirmed also when entering SHAPS and PSS scores as covariates [$F(2,152) = 4.40$, $p = .02$, partial eta$^2 = .06$]. Finally, in light of the fact that groups differed in their discriminability in Blocks 1 and 2 (see below), an additional *Group* x *Block* ANCOVA was run by entering overall discriminability as a covariate. The critical *Group* × *Block* interaction was confirmed again [$F(2,158) = 4.13$, $p = .02$, partial eta$^2 = .05$].

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 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 ($p > .65$) (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* × *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 RICH than the LEAN stimulus (Fig. 1C). The 3-way interaction of *Group* × *Block* × *Stimulus* was also significant ($F(2, 160) = 4.05$, $p = .02$, partial eta$^2 = .05$). To disentangle the 3-way interaction, follow-up *Group* × *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 significant *Group* × *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* × *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* × *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* × *Study* 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* × *Study*

[1] In ensuing analyses, ANCOVA results are only reported when different from the ANOVAs.

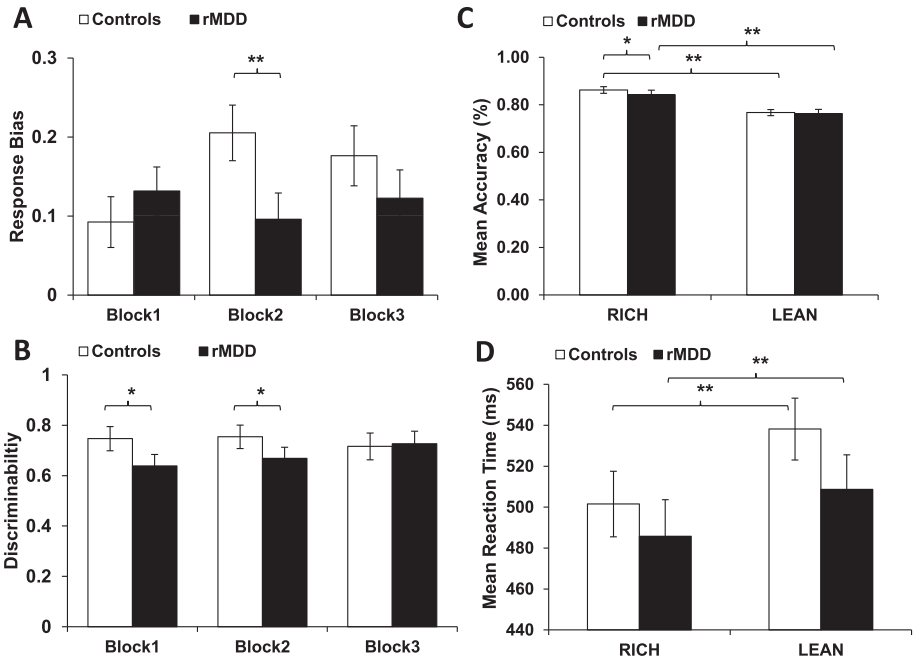

Fig. 1. Group differences in the probabilistic reward task ($n = 84$). (A) Response bias; (B) discriminability; (C) accuracy; (D) reaction time. All data based on healthy controls ($n = 37$) and adults with remitted major depressive disorder (rMDD; $n = 47$). Error bars represent standard errors. $^{**}p < .01$, $^{*}p < .05$.

interaction remained significant, whereas these effects were not confirmed when entering SHAPS and PSS scores as covariates.

3.5. Regression analysis

A hierarchical linear regression examined the impact of a diagnosis of rMDD (entered in the second step) on reward learning (ΔRB = Response Bias Block 3 − Response Bias Block 1) when controlling for the effects of study, discriminability, residual depressive symptoms (BDI-II scores), and recent stress (PSS scores), which were all entered in the first step of the regression. The model showed a statistical trend ($\Delta R^2 = .043$, $\Delta F(1,77) = 3.59$, $p = .062$). In light of the fact that group differences in response bias emerged in Block 2, the regression was re-ran by considering reward learning between Block 1 and 2 (Response Bias Block 2 − Response Bias Block 1). A history of depression predicted changes in reward learning (beta = −.33, $t(78) = -2.60$, $p < .01$) above and beyond the effects of study, discriminability, BDI-II scores, and PSS scores ($\Delta R^2 = .079$, $\Delta F(1,77) = 6.74$, $p = .011$). In the second set of regression analyses, history of depression was found to predict changes in reward learning between Block 1 and Block 2 ($\Delta R^2 = .093$, $\Delta F(1,76) = 7.97$, $p = .006$) as well as between Block 1 and Block 3 ($\Delta R^2 = .055$, $\Delta F(1,76) = 4.47$, $p = .038$) above and beyond the effects of study, discriminability, SHAPS scores, and PSS scores.

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 response bias (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 generalize 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 owing 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.

Studying mechanisms underlying depression from a dimensional perspective is in line with the NIMH strategic plan embodied in the Research Domain Criteria (RDoC) initiative (Insel and Cuthbert, 2010; Sanislow et al., 2010). MDD is a heterogeneous disorder that would greatly benefit from new conceptualizations that emphasize fundamental dimensions of observable behavior (e.g., reward learning) and underlying neurobiological underpinings, an approach which might ultimately lead to personalized treatments. In this context, it is interesting to note that Behavioral Activation Treatment (BAT), a psychotherapeutic intervention designed to increase engagement with rewarding behaviors, has shown particular promise in the treatment of depression. Specifically, a large randomized-control trial found that, in severely depressed patients, BAT was as effective as antidepressant medication and initially more effective than cognitive therapy (Dimidjian et al., 2006). Critically, a brief intervention of BAT in adults with MDD was found to normalize function in brain regions implicated in processing reward feedback (i.e., paracingulate gyrus, orbital frontal gyrus; Dichter et al., 2009). Future research should examine whether (1) MDD subjects with blunted reward responsiveness might preferentially benefit from BAT intervention and (2) BAT intervention might prevent relapse in remitted individuals with persistent deficits in reward responsiveness.

4.1. Limitations

Several limitations should be acknowledged. First, this study utilized a cross-sectional design. Accordingly, no causal conclusions can be drawn on whether deficits in reward responsiveness represent a “scar” or vulnerability factor for depression. Second, the current study used a behavioral paradigm of reward processing without assessing the neural correlates of these processes. Explicit aspects of reward processing (anticipation vs. consummation of reward) will need to be targeted by carefully-designed behavioral and neuroimaging studies. Finally, different reward tasks were used in the study. Although monetary rewards formed a more salient cue associated with greater discriminability and accuracy, group differences emerged across studies, highlighting the robustness of the findings.

5. Conclusion

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 warrented to investigate whether deficits in reward responsiveness might predict future depressive episodes and whether BAT intervention might prevent relapse.

Funding sources

Funding for this study was provided by a research fellowship by the German Research Foundation (Deutsche Forschungsgemeinschaft) to Pia Pechtel and grants from NIMH (R01 MH68376, R21 MH078979) to Diego A. Pizzagalli.

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.

Acknowledgments

The authors are grateful to Nancy Hall Brooks, M.Ed., LMHC for her skilled assistance with participants' subjective recruitment and clinical assessments.

References

Beck A, Steer R, Brown G. Beck depression inventory manual. 2nd ed. San Antonio: Psychological Corporation; 1996.
Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health and Social Behavior 1983;24:385–96.
Dichter GS, Felder JN, Petty C, Bizzell J, Ernst M, Smoski MJ. The effects of psychotherapy on neural responses to rewards in major depression. Biological Psychiatry 2009;66:886–97.
Dichter GS, Kozink RV, McClernon FJ, Smoski MJ. Remitted major depression is characterized by reward network hyperactivation during reward anticipation and hypoactivation during reward outcomes. Journal of Affective Disorders 2012;136:1126–34.
Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. Journal of Consulting and Clinical Psychology 2006;74:658–70.
Di Nicola M, De Risio L, Battaglia C, Camardese G, Tedeschi D, Mazza M, et al. Reduced hedonic capacity in euthymic bipolar subjects: a trait-like feature? Journal of Affective Disorders 2013;147:446–50.
Dryman A, Eaton WW. Affective symptoms associated with the onset of major depression in the community: findings from the US National Institute of Mental Health Epidemiologic Catchment Area Program. Acta Psychiatrica Scandinavica 1991;84:1–5.
Epstein J, Pan H, Kocsis JH, Yang Y, Butler T, Chusid J, et al. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. American Journal of Psychiatry 2006;163:1784–90.
First M, Spitzer R, Gibbon M, Williams J. Structured clinical interview for DSM-IV-TR Axis I disorders research version non-patient edition (SCID-I/NP). New York: Biometrics Research New York State Psychiatric Institute; 2002.
Forbes EE, Hariri AR, Martin SL, Silk JS, Moyles DL, Fisher PM, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. American Journal of Psychiatry 2009;166:64–73.
Franken IHA, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). Journal of Affective Disorders 2007;99:83–9.
Gotlib IH, Hamilton J, Cooney RE, Singh MK, Henry ML, Joorman J. Neural processing of reward and loss in girls at risk for major depression. Archives of General Psychiatry 2010;67:380–7.
Hautus MJ. Corrections for extreme proportions and their biasing effects on estimated values of d'. Behavior Research Methods. Instruments and Computers 1995;27:46–51.
Henriques JB, Glowacki JM, Davidson RJ. Reward fails to alter response bias in depression. Journal of Abnormal Psychology 1994;103:460–6.
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;43:1001–12.
Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. American Journal of Psychiatry 2010;167:748–51.
Keedwell P, Drapier D, Surguladze S, Giampietro V, Brammer M, Phillips M. Neural markers of symptomatic improvement during antidepressant therapy in severe depression: subgenual cingulate and visual cortical responses to sad, but not happy, facial stimuli are correlated with changes in symptom score. Journal of Psychopharmacology 2009;23:775–88.
Kessler RC, Wang PS. Epidemiology of depression. In: Gotlib IH, Hammen CL, editors. Handbook of depression. 2nd ed. New York: Guilford Press; 2009. p. 5–22.
Macmillan NA, Creelman CD. Detection theory: a user's guide. 2nded. Mahwah: Lawrence Erlbaum Associates; 2005.
McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. Psychopharmacology 2009;205:667–77.
McCabe C, Woffindale C, Harmer CJ, Cowen PJ. Neural processing of reward and punishment in young people at increased familial risk of depression. Biological Psychiatry 2012;72:588–94.
McFarland BR, Klein DN. Emotional reactivity in depression: diminished responsiveness to anticipated reward but not to anticipated punishment or to non-reward or avoidance. Depression and Anxiety 2009;26:117–22.
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;91:229–34.
McMakin DL, Olino TM, Porta G, Dietz LJ, Emslie G, Clarke G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment–resistant depression. Journal of the American Academy of Child & Adolescent Psychiatry 2012;51:404–11.
Moos R, Cronkite R. Symptom-based predictors of a 10-year chronic course of treated depression. The Journal of Nervous and Mental Disease 1999;187:360–8.
Oquendo MA, Barrera A, Ellis SP, Li S, Burke AK, Grunebaum M, et al. Instability of symptoms in recurrent major depression: a prospective study. Amercian Journal of Psychiatry 2004;161:255–61.
Pizzagalli DA, Bogdan R, Ratner KG, Jahn AL. Increased perceived stress is associated with blunted hedonic capacity: potential implications for depression research. Behaviour Research and Therapy 2007;45:2742–53.
Pizzagalli DA, Evins A, Schetter E, Frank M, Pajtas P, Santesso D, et al. Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology 2008a;196:221–32.
Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. American Journal of Psychiatry 2009;166:702–10.
Pizzagalli DA, Iosifescu D, Hallett LA, Ratner KG, Fava M. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. Journal of Psychiatric Research 2008b;43:76–87.
Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biological Psychiatry 2005;57:319–27.
Sanislow CA, Pine DS, Quinn KJ, Kozak MJ, Garvey MA, Heinssen RK, et al. Developing constructs for psychopathology research: research domain criteria. Journal of Abnormal Psychology 2010;119:631–9.
Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, et al. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. NeuroImage 2008;42:807–16.
Schaefer HS, Putnam KM, Benca RM, Davidson RJ. Event-related functional magnetic resonance imaging measures of neural activity to positive social stimuli in pre- and post-treatment depression. Biological Psychiatry 2006;60:974–86.
Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. British Journal of Psychiatry 1995;167:99–103.
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). Psychiatrica Scandinavica 2001;103:122–30.
Treadway MT, Zald DH. Reconsidering anhedonia in depression: Lessons from translational neuroscience. Neuroscience and Biobehavioral Reviews 2011;35:537–55.
Tripp G, Alsop B. Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder. Journal of Clinical Child Psychology 1999;28:366–75.
Vrieze E, Ceccarini J, Pizzagalli DA, Bormans G, Vandenbulcke M, Demyttenaere K, et al. Measuring extrastriatal dopamine release during a reward learning task. Human Brain Mapping 2013a;34:575–86.
Vrieze E, Pizzagalli DA, Demyttenaere K, Hompes T, Sienaert P, de Boer P, et al. Reduced reward learning predicts outcome in major depressive disorder. Biological Psychiatry 2013b;73:639–45.