

Enhanced negative feedback responses in remitted depression

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Major depressive disorder (MDD) is characterized by hypersensitivity to negative feedback that might involve frontocingulate dysfunction. MDD patients exhibit enhanced electrophysiological responses to negative internal (errors) and external (feedback) cues. Whether this dysfunction extends to remitted depressed (RD) individuals with a history of MDD is currently unknown. To address this issue, we examined the feedback-related negativity in RD and control participants using a probabilistic punishment learning task. Despite equivalent behavioral performance, RD

participants showed larger feedback-related negativities to negative feedback relative to controls; group differences remained after accounting for residual anxiety and depressive symptoms. The present findings suggest that abnormal responses to negative feedback extend to samples at increased risk for depressive episodes in the absence of current symptoms. *NeuroReport* 19:1045–1048 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Major depressive disorder (MDD) is a common disorder with a chronic course characterized by the recurrence of depressive episodes. Emerging evidence indicates MDD is associated with widespread impairments in cognitive function including excessive sensitivity to negative reinforcement, negative processing biases, and deficits in adjusting behavior after errors or negative feedback [1]. Although some studies report recovery of executive functions after remission [2], others note persistent deficits in planning, monitoring, and attention [3].

Dysfunctions within brain areas implicated in reinforcement learning, such as the basal ganglia and the anterior cingulate cortex, might play a role in abnormal responses to negative feedback in MDD [4,5]. The feedback-related negativity (FRN) may be used as an electrophysiological index of responses to feedback [6,7] and has been localized to the anterior cingulate cortex, among other regions [7,8]. Using a speeded task, Tucker *et al.* [9] demonstrated that, compared with controls, moderately depressed patients showed larger FRNs, particularly after negative feedback (but see ref. [10]).

Although these findings suggest that MDD patients are characterized by abnormal responses to negative feedback, it is unclear whether this abnormality is a result of current depressed mood. The goal of this study was to examine FRN responses to negative feedback in remitted depressed (RD) individuals, who are not currently experiencing depressive symptoms, and can thus provide critical information about vulnerabilities associated with MDD [11].

Using a probabilistic punishment learning task, we hypothesized that, relative to controls, RD patients would show increased sensitivity to negative feedback as indexed by (i) stronger response bias against the more frequently punished stimulus; and (ii) larger FRNs.

Methods

Participants

Twenty-seven participants (12 RD, 15 controls) were recruited from the community through advertisements. All participants completed the Structured Clinical Interview for DSM-IV (SCID) [12]. RD patients were enrolled if they had (i) at least one major depressive episode within the past 10 years; (ii) less than two threshold or subthreshold major depressive episode symptoms in the last 8 weeks, neither of which included anhedonia or depressed mood; and (iii) a Beck Depression Inventory (BDI-II) [13] score < 14. Three RD patients reported past substance abuse occurring more than 1 year before the study; no participants met criteria for lifetime substance dependence. Controls reported no current or past Axis I disorder. At the time of testing, no participants were taking psychotropic medications or receiving psychotherapy. The RD and control groups did not differ on age ($M \pm SD$: 24.83 ± 4.15 vs. 25.20 ± 6.42 years), male/female ratio (1/11 vs. 2/13), and education (16.13 ± 1.51 vs. 16.47 ± 1.36 years) ($P > 0.35$). For the RD sample, the mean number of earlier major depressive episodes (MDE) was 2.6 (range: 1–10), the mean age of MDD onset was 18.4 years (range: 11–30), and the mean

time since recovery was 41.7 months (range: 4–96). Participants received \$15/h for completing the SCID, \$10/h for the electroencephalogram (EEG) session, and an additional \$10 in 'winnings'. Participants provided written informed consent to a protocol approved by the Committee on the Use of Human Subjects at Harvard University.

Data collection and reduction

Probabilistic punishment task

This task consisted of 240 trials, divided into three blocks of 80 trials, and was adapted from Tripp and Alsup [14]. Each trial started with a fixation point presented for 1000 ms that was replaced by the target stimulus presented for 350 ms (Fig. 1). Target stimuli consisted of 10 different patterns of circles and squares containing 17 shapes (either seven squares and 10 circles or 10 squares and seven circles). For each trial, participants pressed a button with either their left or right hand (counterbalanced) to indicate whether the target contained more circles or squares. Within each block, stimuli were presented an equal number of times ($n=40$) in a pseudorandomized sequence. A blank screen followed target stimuli for 1500 ms. For each block, 20 correct responses were followed by negative feedback ('You lose 10 cents!') for 1500 ms. To induce a response bias, an asymmetrical reinforcement ratio was used: correct responses for one stimulus were punished three times more frequently ($n=15$) than correct responses for the other stimulus ($n=5$). Participants were given \$10 to start the task.

Participants were administered a second version of the task, in which correct responses of one stimulus were disproportionately rewarded. Unlike earlier studies [15], this reward version failed to elicit a response bias toward the more frequently rewarded stimulus in controls. In light of these unsatisfactory psychometric properties, data in the reward condition were not further analyzed (data are available upon request).

Behavioral analyses

Performance was decomposed into response bias and discriminability. Unlike our earlier work using a reward task [15], here response bias assesses the systematic preference for the response paired with less frequent punishment, and was calculated as:

$$0.5 \times \log_{10} \frac{[(S1_{\text{correct}} + 0.5)] \times [(S2_{\text{incorrect}} + 0.5)]}{[(S1_{\text{incorrect}} + 0.5)] \times [(S2_{\text{correct}} + 0.5)]}$$

where S1 and S2 is the stimulus associated with less versus more frequent punishment, respectively.

Discriminability assesses the participant's ability to distinguish between the two stimuli and was used as an indicator of general task performance (see ref. [15] for formula, which was modified by adding 0.5 to the matrix

cells). After the task, participants completed the BDI-II and Mood and Anxiety Symptom Questionnaire (MASQ) [16] to assess current level of depressive symptoms, general distress, anhedonia, and anxious arousal. In addition, the BIS subscale of the Behavioral Activation and Inhibition Scale (BIS/BAS) [17] was used to assess sensitivity to punishment, negative affect, and inhibition associated with negative outcomes.

Scalp event-related potentials

EEG was recorded using a 128-channel Electrical Geodesics system (EGI Inc., Eugene, Oregon, USA) at 250 Hz with 0.1–100 Hz analog filtering referenced to the vertex. Data were processed using Brain Vision Analyzer (Brain Products GmbH, Germany). Offline data were segmented and re-referenced to an average reference. Each trial was visually inspected for movement artifacts and automatically removed with a $\pm 75 \mu\text{V}$ criterion. Eye-movement artifacts were corrected by independent component analysis. Artifact-free EEG epochs were extracted beginning 200 ms before and ending 600 ms after feedback presentation. Event-related potentials (ERPs) were averaged for blocks 2 and 3 to allow adequate exposure to the differential reinforcement schedule. ERPs were filtered at 1–30 Hz and a 200 ms prestimulus baseline correction was used. The FRN was scored as the most negative peak 250–450 ms after feedback presentation relative to the immediately preceding positivity at midline sites (Fz, FCz, Cz).

Source localization analyses

LORETA [18] was used to estimate intracerebral current density underlying the FRN following published procedures [19]. Using all 128 channels, current density was computed within a 280–400 ms post-feedback time window, which captured the mean peak latency of the FRN (327 ms) across the midline sites.

Statistical analyses

For response bias and discriminability, separate analysis of variance tests (ANOVAs) with 'group' (RD, control) and 'block' (1, 2, 3) were performed. Mixed ANOVAs were used to analyze the FRN with 'group' and 'site' (Fz, FCz, Cz) as factors. Follow-up independent *t*-tests were performed to decompose significant effects. The Greenhouse–Geisser correction was used when appropriate. For the LORETA data, the groups were contrasted at each voxel ($N=2394$) using unpaired *t*-tests; a combination of *P* value (0.01) and cluster extent (5 voxels) threshold was used to identify significant findings. Two-tailed Pearson's correlations were performed over all participants between the FRN and self-report measures. Hierarchical regressions were performed to examine whether group differences remained after partialing out the variance associated with self-report

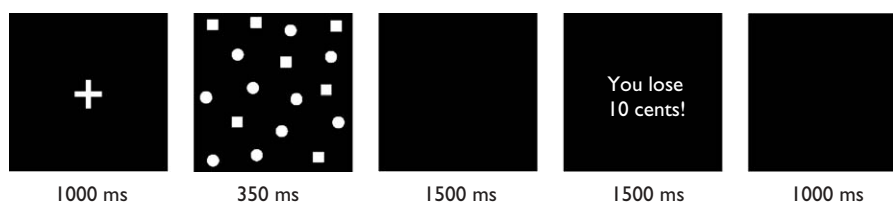


Fig. 1 Schematic representation of the probabilistic punishment learning task.

measures (performed separately for the MASQ, BIS, and BDI-II). Group was entered in the second step, whereas the self-report measure was entered in the first step.

Results

Self-report and behavioral data

Compared with controls, RD patients reported higher BDI-II [2.33 ± 2.10 vs. 0.53 ± 1.06 ; $t(25)=2.89$, $P < 0.017$], MASQ general distress/depression [18.17 ± 5.17 vs. 14.80 ± 2.36 ; $t(25)=2.25$, $P=0.055$], and anhedonic depression [52.83 ± 9.14 vs. 44.80 ± 10.33 ; $t(25)=2.11$, $P < 0.045$] scores. No groups differences were found for the BIS [21.08 ± 3.31 vs. 19.93 ± 2.89 ; $t(25)=0.96$, $P > 0.30$] or the other MASQ subscales ($P > 0.18$).

A significant main effect for 'block' emerged for response bias, $F(2,50)=4.24$, $P < 0.035$, $\epsilon=0.74$. Post-hoc tests indicated that response bias toward the less frequently punished stimulus was significantly higher in block 3 (0.23 ± 0.44) than block 1 (0.05 ± 0.19) and block 2 (0.13 ± 0.35), $t(26) > 2.27$, $P < 0.035$. Contrary to our hypotheses, no effects involving 'group' emerged ($P_s > 0.71$). An analysis for discriminability revealed no differences across blocks or between groups ($P_s > 0.12$), indicating that groups did not differ with respect to task difficulty.

Feedback-related negativity data

A significant effect for 'site' emerged, $F(2,50)=20.42$, $P < 0.001$, $\epsilon=0.55$, due to larger FRN at Fz relative to FCz and Cz, $t_s(26) > -4.49$, $P_s < 0.0002$. A main effect of 'group' was also significant [$F(1,25)=7.50$, $P < 0.015$], due to an overall larger (i.e., more negative) FRN for RD than control participants (0.54 ± 1.89 vs. $2.69 \pm 2.14 \mu\text{V}$) (Fig. 2). [The main effect of 'group' was confirmed also when the factor 'condition order' (punishment vs. reward condition run first) was added to the ANOVA on FRN values, $F(1,23)=6.76$, $P < 0.017$.] Thus, further analyses focused on the FRN averaged across the three sites. Pearson's correlations indicated that higher BDI-II total scores were related to larger FRN, $r=-0.38$, $P < 0.05$. A similar relation was found for BIS scores ($r=-0.40$, $P < 0.04$) and MASQ general distress/depression subscale ($r=-0.37$, $P=0.057$), whereas scores on the MASQ anhedonic depression subscale were not related to the FRN ($P > 0.39$).

Hierarchical regressions revealed that 'group' was a significant predictor of FRN amplitude after accounting

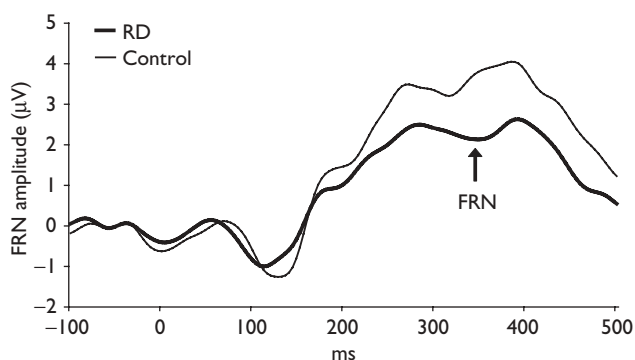


Fig. 2 Averaged event-related potential waveforms from 200 ms before to 500 ms after the presentation of negative feedback during the probabilistic punishment task for individuals with remitted depression (RD; heavy line) and controls (light line) averaged across Fz and FCz and Cz.

for the MASQ general distress/depression and anhedonic depression scores [$R^2=0.26$; $\Delta R^2=0.17$; $\Delta F(1,23)=5.39$, $P < 0.030$] or BIS scores [$R^2=0.33$; $\Delta R^2=0.27$; $\Delta F(1,23)=6.09$, $P < 0.025$]. A similar (albeit less robust) pattern was observed for BDI-II scores [$R^2=0.26$; $\Delta R^2=0.11$, $\Delta F(1,24)=3.58$, $P=0.07$]. LORETA analyses revealed no differences between RD participants and controls.

Discussion

The goal of this study was to examine electrophysiological correlates of negative feedback processing in unmedicated individuals with a history of MDD but no current depressive symptoms using a probabilistic punishment learning task. As predicted, individuals with RD showed larger (i.e., more negative) FRNs than controls. The magnitude of the FRN increased with depressive symptoms consistent with Tucker *et al.* [9], as well as with self-reported sensitivity to punishment (BIS). Unlike Tucker *et al.*, however, the depression scores were well below the clinical threshold (BDI-II < 6); thus, correlational findings involving the BDI should be interpreted with caution. Notably, group differences remained after accounting for self-report measures of anxiety/punishment sensitivity (BIS), general distress and anhedonic symptoms (MASQ subscales), suggesting that the enhanced FRN in RD participants was not due to the presence of residual clinical symptoms (we note, however, that group differences in FRN were slightly reduced when considering BDI scores). Collectively, these findings indicate that dysfunctional neural responses to negative feedback are not only observed in currently depressed patients [9], but extend to patients at increased vulnerability to MDD in the absence of clinical symptoms, and support prior reports that RD patients are characterized by negative cognitive styles [20]. Whether abnormal ERP responses to negative feedback reflects a consequence ('scar') of a prior MDE or a trait-like risk factor for MDD cannot be evaluated in this study. Future studies in at-risk samples before the first MDE are required to test this critical differentiation.

The ability to learn response–outcome associations (i.e. develop a response bias toward a less frequently punished stimulus) was similar for RD patients and controls. This result suggests that negative feedback did not have a detrimental effect on behavioral performance in a remitted state [4]. Thus, negative reinforcement learning, at least as probed by the current task, was not exacerbated in the current RD sample. This finding is not necessarily at odds with Pizzagalli *et al.* [15], who reported that individuals with elevated depressive symptoms, who might also be at risk for future major depressive episodes, were impaired at developing a response bias toward a more frequently rewarded stimulus. Unfortunately, in this study, we were unable to test whether RD patients are similarly impaired in positive reinforcement learning. In light of emerging evidence indicating that positive and negative reinforcement learning might rely on different mechanisms [5,21], studies using psychometrically matched reward and punishment learning tasks will be needed to identify putative markers that might be associated with increased vulnerability to depression.

The FRN has been compared with the response-locked error-related negativity (ERN), which occurs after error commission. The ERN may reflect error and conflict detection [22], and unlike the FRN, is internally generated.

Interestingly, enhanced ERN amplitude has been reported in MDD patients (e.g. ref. [23]), suggesting that depression is characterized by both a hypersensitivity to internal (errors) and external (feedback) cues of performance monitoring. Findings of potentiated responses to negative outcomes are intriguing, particularly when considering the role of cognitive diatheses in the etiology of depression. According to Beck's cognitive theory of depression, for example, increased vulnerability to depression results from the activation of negative schemas about worthlessness, loss, and expected failure when facing stressors [24]. Abnormal responses to negative outcomes might thus be a manifestation of such depressogenic cognitive schemata.

The limitations of this study should be noted. First, although our task successfully elicited a response bias away from the more frequently punished stimulus, groups did not differ in their behavioral indices of punishment sensitivity. It is unclear whether this null finding is a peculiarity of the present task, or whether the FRN provided a more sensitive probe of punishment sensitivity as abnormal brain activation may emerge in MDD despite spared behavioral performance (see e.g. ref. [25]). Second, no group differences emerged in the LORETA analyses. We note that in two earlier studies using a similar reinforcement learning task, differences underlying the neural sources of the FRN were, in part, driven by group differences in the ability to develop a response bias for the more frequently 'rewarded' stimulus (Santesso *et al.*, [26]). Thus, task differences and the lack of group differences in behavioral performance might explain the LORETA null findings.

Conclusion

Participants with a history of MDD were characterized by increased electrophysiological responses to negative feedback, indicating that hypersensitivity to negative reinforcement persists during remission in the absence of current symptoms. On the basis of these findings, we suggest that the FRN provides a sensitive tool for examining subtle impairments in negative reinforcement learning in RD and might be useful to predict future depressive episodes.

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References

- Pizzagalli DA, Dillon DG, Bogdan R, Holmes AJ. Reward and punishment processing in the human brain: Clues from affective neuroscience and implications for depression research. In: Vartanian O, Mandel D, editors. *Neuroscience of decision making*. New York, NY: Psychology Press (in press).
- Biringer E, Lundervold A, Stordal K, Mykletun A, Egeland J, Bottlender R, *et al.* Executive function improvement upon remission of recurrent unipolar depression. *Eur Arch Psychiatry Clin Neurosci* 2005; **255**:373–380.
- Paelecke-Habermann Y, Pohl J, Leplow B. Attention and executive functions in remitted major depression patients. *J Affect Disord* 2005; **89**:125–135.
- Elliot R, Sahakian BJ, Michael A, Paykel ES, Dolan RJ. Abnormal responses to feedback on planning and guessing tasks in patients with unipolar depression. *Psychol Med* 1998; **28**:559–571.
- Steele JD, Kumar P, Ebmeier KP. Blunted response to feedback information in depressive illness. *Brain* 2007; **130**:2367–2374.
- Gehring WJ, Willoughby AR. The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 2002; **295**:2279–2282.
- Miltner WHR, Braun CH, Coles MGH. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a "generic" neural system for error detection. *J Cogn Neurosci* 1997; **9**:788–798.
- Van Veen V, Holroyd CB, Cohen JD, Stenger VA, Carter CS. Errors without conflict: implications for performance monitoring theories of anterior cingulate cortex. *Brain Cogn* 2004; **56**:267–276.
- Tucker DM, Luu P, Frishkoff G, Quiring J, Poulsen C. Frontolimbic response to negative feedback in clinical depression. *J Abnorm Psychol* 2003; **112**:667–678.
- Ruchow M, Hernberger B, Beschoner P, Gron G, Spitzer M, Kiefer M. Error processing in major depressive disorder: evidence from event-related potentials. *J Psychiatric Res* 2006; **40**:37–46.
- Scher CD, Ingram RE, Segal ZE. Cognitive reactivity and vulnerability: empirical evidence of construct activation and cognitive diatheses in unipolar depression. *Clin Psychol Rev* 2005; **25**:487–510.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured clinical interview for DSM-IV Axis I Disorders – Clinician Version (SCID-CV)*. Washington, D.C.: American Psychiatric Press, Inc; 1997.
- Beck AT, Steer RA, Brown GK. *Beck Depression Inventory manual*, 2nd ed. San Antonio, Texas: The Psychological Corporation; 1996.
- Tripp G, Alsup B. Age-related changes in sensitivity to relative reward frequency. *NZ J Psychol* 1999; **28**:30–36.
- Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. *Biol Psychiatry* 2005; **57**:319–327.
- Watson D, Clark LA, Weber K, Assenheimer JS, Strauss ME, McCormick RA. Testing a tripartite model: I. Evaluating the convergent and divergent validity of anxiety and depression symptom scales. *J Abnorm Psychol* 1995; **104**:3–14.
- Carver CL, White TL. Behavioral inhibition, behavioral activation, and affective responses to impeding reward and punishment: the BIS/BAS scales. *J Pers Soc Psychol* 1994; **67**:319–333.
- Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MC, Hell D, *et al.* Low resolution brain electromagnetic tomography LORETA functional imaging in acute, neuroleptic-naive, first-episode, productive schizophrenia. *Psychiatry Res: Neuroimaging* 1999; **90**:169–179.
- Pizzagalli DA, Lehmann D, Hendrick AM, Regard M, Pascual-Marqui RD, Davidson RJ. Affective judgments of faces modulate early activity (~160 ms) within the fusiform gyri. *Neuroimage* 2002; **16**:663–677.
- Haefel GJ, Abramson LY, Voelz ZR, Metalsky GI, Halberstadt L, Dykman BM, *et al.* Negative cognitive styles, dysfunctional attitudes, and the remitted depression paradigm: a search for the elusive cognitive vulnerability to depression factor among remitted depressives. *Emotion* 2005; **5**:343–348.
- Frank MJ, Seeberger L, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in Parkinsonism. *Science* 2004; **306**:1940–1943.
- Nieuwenhuis S, Holroyd CB, Mol N, Coles MG. Reinforcement-related brain potentials from medial frontal cortex: origins and functional significance. *Neurosci Biobehav Rev* 2004; **28**:441–448.
- Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch Gen Psychiatry* 2008; **65**:179–188.
- Beck AT, Rush AJ, Shaw BF, Emery G. *Cognitive therapy of depression*. New York: Guilford Press; 1979.
- Rose EJ, Simonotto E, Ebmeier KP. Limbic over-activity in depression during preserved performance on the n-back task. *Neuroimage* 2006; **29**:203–215.
- Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, Pizzagalli DA. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. *Neuroimage* (in press).