Archival Report

Using Multilevel Modeling to Examine Blunted Neural Responses to Reward in Major Depression

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ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is a pernicious disorder characterized by deficits in reward processing. A better understanding of these deficits may help to elucidate the underlying pathophysiology and guide treatment development.

METHODS: This study assessed reward positivity and feedback negativity event-related potentials and their difference scores elicited in response to monetary gains and losses among 100 young adults (52 with MDD). Multilevel modeling was used to assess individual- and trial-level change in neural responses over time.

RESULTS: Trial-level analyses indicated that a diagnosis of MDD and depressive symptom severity significantly moderated the trajectory of reward positivity, with individuals with higher symptoms of depression demonstrating less sensitivity to rewards over time.

CONCLUSIONS: These results provide further support for reward dysfunction in MDD and highlight important individual differences in the trajectory of neural responses to reward. Future studies are warranted to investigate reward sensitivity over time to elucidate important individual- and trial-level differences in reward processing.

Keywords: Depression, ERPs, Feedback negativity, Multilevel modeling, Reward positivity, Reward sensitivity

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Major depressive disorder (MDD) is a pernicious and often chronic affective disorder characterized by sustained negative affect and difficulties experiencing positive affect (1). MDD is a leading cause of global disability and disease (2–4) and is associated with substantial economic burden (5,6). Although surprisingly little is known about the neurobiology underlying depression, one promising area relates to reward dysfunction. Previous research has shown that individuals with MDD evidence decreased brain activation (7) and gray matter volume (8,9) in brain regions associated with reward processing. Diekhof et al. (7) highlighted functional magnetic resonance imaging (fMRI) evidence indicating decreased activation in reward-sensitive regions (ventral striatum, medial prefrontal cortex, amygdala) in response to monetary rewards and positively valenced stimuli in depression. Pizzagalli et al. (8) found decreased striatal gray matter volume and reduced caudate nucleus activation to unpredictable rewarding outcomes in MDD. These impairments in reward processing often persist into remission and are predictive of relapse despite antidepressant treatment (10).

Event-related potentials (ERPs), which reflect voltage fluctuations in the ongoing electroencephalogram (EEG) time-locked to an event, have excellent temporal sensitivity and provide a direct measure of neural activity. ERPs have successfully been used to reveal a number of reward-related and cognitive impairments in MDD (11,12). ERPs elicited by the presentation of feedback indicating rewards and losses are characterized by a relative positivity and negativity, respectively, that are maximal approximately 200 to 300 ms at frontocentral electrode sites (13). Feedback negativity (FN) refers to the relative negativity following losses, whereas relative positivity in the ERP waveform, which is either reduced or absent in response to losses, is referred to as reward positivity (RewP) (14). Previous studies indicated that variability in the difference between the neural response to gains and losses is driven by RewP (15–18); thus, Levinson et al. (19) recently referred to the difference between RewP and FN as $\Delta$RewP. In this study, we adopt this nomenclature to differentiate neural responses to rewards (RewP), losses (FN), and the gain-loss difference ($\Delta$RewP).

RewP and FN demonstrate acceptable-to-excellent psychometric properties (19) and relate to reward-related behavioral (20) and fMRI measures (16,21), making them ideal neural measures to examine reward dysfunction in MDD (22). Indeed, previous studies have shown a smaller RewP and $\Delta$RewP among depressed individuals relative to healthy control individuals (21,23,24). In terms of neural circuitry, RewP may be generated by reward-related striatal activity (16,25–27) [although see (28)], whereas some evidence suggests FN may originate from the dorsal anterior cingulate (29,30). Using a combined ERP and fMRI approach, Carlson et al. (16) found that the ventral striatum,
caudate, amygdala, medial prefrontal cortex, and orbitofrontal cortex were involved in generating RewP; meanwhile, Foti et al. (29) used source localization techniques and observed increased reward-related activity in the basal ganglia. Furthermore, a simultaneous ERP and fMRI study observed that trial-to-trial ERP variation to rewards predicted hemodynamic activity across the reward circuit (26). All of these brain structures are implicated in the mesocorticolimbic dopamine system, an important system in reward circuitry (31), suggesting that reward-related ERPs may be used to detect reward processing deficits in depression.

Typically, ERP studies average data across many trials of the same type to isolate a psychological process of interest and are traditionally analyzed using repeated measures analysis of variance designs. Recently, Volpert-Esmond et al. (32) noted that the underlying assumption of the averaging process is that neural activity does not vary across the course of an experiment. They provided two examples demonstrating how multilevel modeling (MLM) can be used to examine change in neurophysiological processes over the course of an experimental session, while accounting for unique sources of variance (e.g., individual- and trial-level variability).

MLM is particularly relevant for studying the neural response to rewards and losses in gambling paradigms as well as the temporal dynamics of reward processing in depression. For instance, Heller et al. (33) collected fMRI data during an emotion regulation paradigm to test whether depression reflects deficits in the ability to sustain activity in neural structures involved in reward, motivation, and positive affect over a 37-minute scan session. Individuals with MDD were unable to sustain nucleus accumbens activity over time compared with control individuals, which was related to individual differences in self-reported positive affect. In a separate study, antidepressant treatment-induced change in the sustained engagement of prefrontal-striatal circuitry predicted improvements in the experience of positive emotion in daily life (34). In both studies, fMRI data were averaged from the first and second halves of the experimental session to examine engagement over time. Incorporating MLM within ERP experiments allows for the detection of subtle changes in psychological processes that occur across a particular task or experiment. Nonetheless, these findings are provocative and suggest important temporal dynamics in reward processing that can be examined in a laboratory setting.

To date, no study has extended the previous findings of blunted reward processing in depression (14,23,24) using MLM to examine changes in reward processing over the course of an experiment. Understanding neural responses to reward across time may provide insight into mechanisms underlying MDD. Therefore, we examined individual- and trial-level differences in RewP, FN, and ∆RewP using MLM to track the trajectory of responses over successive reward and loss trials. We hypothesized an attenuated ∆RewP for individuals with MDD relative to healthy control individuals. Based on the findings of impaired striatal engagement in depression (33), individuals with MDD were expected to exhibit reduced RewP over time relative to control participants, as indicated by negative linear change across the task. Depression symptom severity was also examined as a moderator of RewP and FN and was expected to be associated with reduced RewP over time. Lastly, we examined the psychometrics of these feedback-related ERPs using internal consistency measures to further establish their utility in psychopathology research (12).

**METHODS AND MATERIALS**

**Participants**

Individuals of all ethnic origins between 18 and 25 years of age (N = 101) were recruited from university counseling and psychiatric clinics and advertisements posted around the surrounding community. All participants were interviewed using the Mini-International Neuropsychiatric Interview and had normal or corrected-to-normal vision. Exclusion criteria included any history or presence of bipolar spectrum disorder, schizophrenia, self-injurious or suicidal ideation, or neurological disorders or injuries resulting in a loss of consciousness. One participant was removed from the analyses owing to poor EEG data quality, resulting in 100 participants (71 female participants; 52 participants with MDD) being included in the analyses. The final sample composition was sufficiently powered to test the primary hypothesis (see the Supplement for the a priori power analysis) and included 38 Asian individuals, 29 white individuals, 13 Hispanic individuals, 12 African-American individuals, and 8 individuals self-identifying as more than one race. Participants provided written informed consent, and the study was approved by the university’s institutional review board.

**MDD Diagnosis**

The Mini-International Neuropsychiatric Interview is a brief, structured interview that is highly reliable (35) and widely used for evaluating diagnoses of psychiatric disorders according to DSM-IV, DSM-5, and ICD-10. The Mini-International Neuropsychiatric Interview was used to screen for Axis I disorders and presence of a current major depressive episode. All interviewers had previous experience in administering structured clinical interviews.

**Depression Symptom Severity**

The Beck Depression Inventory–II (BDI-II) (36), a 21-item self-report inventory, was used to assess depression symptom severity over the past 2 weeks. Each item is scored on a 4-point scale (0–3), with a range of 0 to 63. The BDI-II scores in this sample demonstrated high internal consistency (Cronbach’s α = .92).

**Doors Task**

The doors task (14) was administered using E-Prime Professional 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA) and consisted of five blocks of 20 trials. On each trial, a fixation cross was presented at the center of the screen for 1000 ms followed by the presentation of two doors, which remained on the screen until participants made a left or right button press corresponding to the left or right door using a Logitech F310 response gamepad (Logitech, Newark, CA). Following stimulus offset, another fixation cross was presented for 2000 ms before displaying the feedback stimulus for 2000 ms. Feedback indicated whether the participant won $0.50 (reward trial) or lost $0.25 (loss trial), which was represented by a green upward arrow or a red downward arrow, respectively. After feedback, another fixation cross was
presented for 1500 ms, which was followed by a short break before the next trial. Fifty reward and 50 loss trials were presented on a monitor at a distance of 70 cm centered to the nasion, with vertical and horizontal visual angles of 1.2° and 6.6°, respectively. Participants were compensated their winnings ($12.50) following the task.

**ERP Processing and Measurement**

Continuous EEG was recorded from a 33-electrode actiCAP system (Brain Products, GmbH, Gilching, Germany) arranged according to the 10/20 guidelines. The electro-oculogram activity was recorded from two electrodes placed 2 cm outside the outer canthus of the left eye and 2 cm below the right eye. EEG was amplified using an Electrical Geodesics, Inc. (Eugene, OR) system (20,000 nominal gain, bandpass of 0.10–100 Hz) and sampled at 500 Hz with a 24-bit analog-to-digital converter referenced to the vertex electrode (Cz) at acquisition. Impedances were kept below 20 kΩ throughout recording.

EEG data were exported to EEGLAB toolbox version 14.1.1 (32) in MATLAB version R2016b (The MathWorks, Inc., Natick, MA) for data preprocessing. Data were bandpass filtered using a second-order infinite impulse response Butterworth filter of 0.10 to 30 Hz and adjusted for direct current offset. EEG data were visually inspected for artifacts or extreme offsets and segmented to create feedback-locked epochs for gain and loss trials separately using a −200- to 800-ms time window. Oculomotor artifacts were removed using ICA blink templates provided by ERP PCA toolkit version 2.63 (33) and generated from the current dataset (see the Supplement for additional artifact rejection criteria). Epochs were re-referenced to the mean of the two mastoids (TP9, TP10), averaged separately by rewards and losses, and baseline corrected using the 200-ms prestimulus interval.

Consistent with previous research (14,19,37–39) and the maximal activity at frontocentral sites in the present study, RewP (rewards) and FN (losses) were assessed at FCz. Feedback-locked amplitudes were measured as the mean voltage in a time window 200 to 300 ms post feedback onset and were determined by visual inspection of the grand average waveform collapsed across participants and feedback types to minimize bias (40). The gain-loss difference waveform (ΔRewP), defined as RewP (rewards) minus FN (losses), was derived to isolate reward-related activity (14,38). The regression-based residualized difference (ΔRewP_resid) score was also calculated, as recent research suggests that it may be slightly more reliable than subtraction-based differences scores (19,41). Internal consistency measures were quantified using classical test theory and generalizability theory estimates of dependability (42) (see the Supplement for detailed information about the reliability and dependability estimates).

**Statistical Analyses**

All analyses were performed using IBM SPSS version 24 (IBM Corp., Armonk, NY). To minimize the influence of poor data quality, participants with fewer EEG trials than needed to obtain a dependability point estimate of 0.80 were removed. Removal of 1 participant was due to this criterion. All MDD and control participants had a minimum of 33 (range, 33–100) and 32 (range, 32–100) trials, respectively.

A 2 (feedback type: gain, loss) × 2 (group: MDD, control) repeated measures analysis of variance was used to examine group-level effects in RewP and FN, while an independent-samples t test was conducted to test the primary hypothesis of differences in ΔRewP (and ΔRewP_resid) by depression status. A two-tailed α level of .05 was used, and follow-up tests were adjusted using the Bonferroni correction (p_corrected = .05/2 = .025).

RewP and FN were analyzed using MLM. Owing to the nested structure of the data, two level models were used to examine slopes of RewP and FN across the doors task. MLM accounts for individual differences in baseline responses at the beginning of the experiment (trial 1; random intercept) and changes over time (slopes) in a way that cannot be modeled with traditional approaches. MLM also partitions unique sources of variance, where the predictor variables, such as current diagnosis and depressive severity, are used to predict individual-specific change. MLM was used to model variation in RewP and FN across doors task trials as well as the covariance of nonindependence between repeated measures. These types of models are ideal for ERP data, as MLMs are robust to occasional missing trial-level data (32,43).

For the current models, the dependent variable was within-subject RewP and FN amplitudes. For level 1 (during each trial), predictors were trial (continuous; represents task trial number and linear growth) and task feedback type (dichotomous; 0 = losses, 1 = gains). For level 2 (for each participant), separate models included diagnostic status (dichotomous; 0 = control, 1 = MDD) and depressive symptom severity (continuous; grand-mean centered BDI-II score) as predictors. Model 1 was constructed to determine the prediction of current depression status on RewP and FN. Cross-level interactions between depression status and trial were included to examine the moderating influence of depression status on RewP and FN changes from the beginning to the end of the experiment. Additionally, another cross-level interaction between depression status, feedback type, and trial was included in the model to examine whether depression status served as a moderator of feedback type on RewP and FN over time. Model 2 included the same parameters; however, depression symptom severity was substituted for diagnostic status to examine symptom severity rather than simple presence of a diagnosis. For both models, trial was shifted so that the first trial corresponded with the intercept (t = 0). Thus, the 50 reward and 50 loss trials ranged from 0 to 49 in the MLM analyses. Dichotomous variables, such as depression status, cannot be included as a random effect in mixed models. Whereas trial was retained as a random effect in both models, based on parsimony and the nonsignificant finding for depression severity as a random effect, we retained both diagnostic status and depression severity as fixed effects in the models. Finally, the models used restricted maximum likelihood estimation and an unstructured covariance matrix. See the Supplement for model specifications.

**RESULTS**

Demographic and clinical characteristics are shown in Table 1. Bivariate correlations between depressive symptoms and feedback-related ERP amplitudes are reported in Table 2, and Table 3 displays the internal consistency measures.
**Table 1. Demographic and Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDD</th>
<th>Control</th>
<th>Test Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Male, n (%)</td>
<td>12 (23.6%)</td>
<td>17 (35.4%)</td>
<td>$\chi^2 = 1.8$</td>
<td>.17</td>
</tr>
<tr>
<td>Age, Years</td>
<td>20.0 (1.4)</td>
<td>20.0 (1.5)</td>
<td>t = 0.27</td>
<td>.79</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>23.6 (3.6)</td>
<td>22.9 (3.6)</td>
<td>t = 0.96</td>
<td>.34</td>
</tr>
<tr>
<td>BDI-II Total Score</td>
<td>24.0 (8.8)</td>
<td>7.9 (5.9)</td>
<td>t = 10.83</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BAI Total Score</td>
<td>11.0 (9.1)</td>
<td>8.4 (6.3)</td>
<td>t = 1.65</td>
<td>.10</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>13 (25.5%)</td>
<td>N/A</td>
<td>$\chi^2 = 0.27$</td>
<td>.605</td>
</tr>
<tr>
<td>Medicated, n (%)</td>
<td>5 (10%)</td>
<td>N/A</td>
<td>$\chi^2 = 0.69$</td>
<td>.41</td>
</tr>
</tbody>
</table>

Values are mean (SD), unless otherwise indicated.

**Table 2. Correlations Between Depression Symptom Severity and Feedback-Related ERPs**

<table>
<thead>
<tr>
<th>ERP Measure</th>
<th>BDI-II Total Score (N = 100)</th>
<th>MDD</th>
<th>Control</th>
<th>Test Statistic</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RewP</td>
<td>-0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td>-0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$RewP</td>
<td>-0.25*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$RewP_{residual}</td>
<td>-0.23*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\Delta$RewP, difference between RewP and FN; $\Delta$RewP_{residual}, regression-based residualized difference between RewP and FN.

**Table 3. Psychometric Properties of Feedback-Related ERPs**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Minimum Number of Trials</th>
<th>RewP</th>
<th>FN</th>
<th>$\Delta$RewP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MLM Analyses**

For the unconditional model, the mean intercept (b = 10.29, SE = 0.6, $t_{99} = 16.9, p < .001$) and variance of the intercept across individuals ($b = 36.29, SE = 5.28, Wald = 6.87, p < .001$) were significant. The intraclass correlation coefficient was 0.316, suggesting approximately 31.6% of the variance in feedback-related amplitude was accounted for by between-individual variability, while 68.4% was accounted for within individuals.

Model 1 assessed the moderating influence of diagnostic status on initial reward response and changes in RewP/FN amplitude over time. There was a significant main effect of feedback type (b = 2.59, SE = 0.35, $t_{99} = 7.32, p < .001$), indicating that RewP was 2.59 μV greater than FN amplitude. Although there was no significant main effect of trial, there was significant individual-level variability in RewP/FN amplitude across trials (b = 0.004, SE = 0.001, Wald = 3.65, p < .001).

Additionally, there was a significant cross-level feedback type × trial interaction (b = 0.05, SE = 0.01, $t_{99} = 3.23, p < .001$), indicating positive linear growth for RewP across time (b = 0.03, p < .01, 95% confidence interval [CI] [0.01, 0.05]). Current depression status failed to moderate initial (trial 1) RewP/FN amplitude (b = –1.20, SE = 1.26, $t_{104} = -0.96, p = .34$). Lastly, there was a significant cross-level interaction between diagnostic status × feedback type × trial (b = –0.06, SE = 0.01, $t_{99} = -4.72, p < .001$). Follow-up simple slopes analysis revealed a significant increase in RewP amplitude only for control participants (b = 0.04, p < .05, 95% CI [0.01, 0.07]), whereas all other slopes were nonsignificant (Figure 2).

Model 2 examined the influence of depression severity on initial reward response and slope of change over time. Similar to model 1, model 2 findings indicated a significant feedback type main effect (b = 2.59, SE = 0.36, $t_{99} = 7.30, p < .001$) but no significant feedback type × trial interaction (b = 0.02, SE = 0.01, $t_{99} = 1.22, p = .23$). Although the main effect of trial was nonsignificant, there was significant individual-level variability in RewP/FN amplitude across trials (b = 0.004, SE = 0.001, Wald = 3.64, p < .001). Despite the intercept also varying significantly across individuals, depression severity failed to moderate initial (trial 1) RewP/FN amplitude (b = –0.06, SE = 0.06, $t_{104} = -1.03, p = .30$). Notably, a significant cross-level interaction of depression severity × feedback type × trial emerged (b = –0.002, SE = 0.001, $t_{99} = -3.38, p < .01$). Follow-up simple slopes analyses for RewP indicated a...
positive and significant slope coefficient at low levels of depression severity (1 SD below the BDI-II mean) \( (b = 0.04, p < .05, 95\% \text{ CI } [0.01, 0.07]) \) and average levels of depression (at the BDI-II mean) \( (b = 0.03, p < .01, 95\% \text{ CI } [0.01, 0.05]) \) such that there was a potentiated RewP over time for individuals with lower symptoms of depression (Figure 3). In contrast, all other slopes were nonsignificant. Findings for each model are summarized in Table 4. Findings from models 1 and 2 indicate no differences in initial reward sensitivity (intercept), while results from models 1 and 2 suggest that depression moderates RewP across trials (slope), with a potentiated response over time among individuals with lower symptoms of depression.

**DISCUSSION**

The goal of this study was to examine the neural response to reward and loss feedback in individuals with clinical depression relative to control participants and to extend this line of research by examining individual and trial-level differences in RewP, FN, and \( \Delta \text{RewP} \) over the course of the experiment using MLM. Similar to previous studies (21,24), a blunted \( \Delta \text{RewP} \) was observed among individuals with MDD—an effect that was primarily driven by the neural response to rewards. Additionally, feedback-related ERPs demonstrated acceptable-to-excellent psychometric properties, further supporting their utility in examining individual differences in psychopathology (44). Although current MDD diagnosis and depression severity failed to moderate initial reward processing (i.e., intercept), both MDD diagnosis and depression symptom severity influenced the trajectory of neural responses over the course of the experiment (i.e., slope). Specifically, trial-level analyses indicated that a diagnosis of MDD and depressive symptom severity significantly moderated reward responses over time, with individuals with higher symptoms of depression demonstrating less sensitivity to rewards over time. These findings could not have been identified outside of an MLM framework, highlighting the potential of incorporating MLM in future ERP studies.

The current findings add to previous research indicating aberrant reward-related brain activity among individuals with MDD (21,24). In particular, individuals with current MDD demonstrated a blunted \( \Delta \text{RewP} \) that was primarily driven by an attenuated response to rewards relative to the neural response observed among healthy control participants. Specifically, healthy control participants showed positive linear growth in RewP across time, a finding not found among individuals with MDD. The inclusion of symptom severity as a moderator revealed that individuals with lower symptoms of depression showed a potentiated response to gains as evidenced by a positive linear slope across the doors task. Such a trend was...
not observed among individuals reporting greater depression severity. These findings suggest that greater decreases in neural response to rewards in depressed individuals relative to control participants suggest that a normal RewP response may be characterized by a slight increase over time, which is not characteristic of depressed individuals. This is the first study to examine trial-level differences in reward sensitivity across monetary reward or feedback paradigms, particularly among depressed individuals, and future studies are warranted to replicate these findings.

Individuals with MDD often display poorer modulation of behavior based on prior reward contingencies (45), and the current findings of blunted RewP across time, relative to control participants, may in part reflect this reward system dysfunction. Abnormalities in reward are central to many models of depression—and a blunted neural response to rewards has emerged as a prospective predictor of onset of depression (46). In a sample of 444 adolescents with no history of depression, Nelson et al. (46) found that an attenuated ΔRewP at baseline was a significant predictor of first-onset depressive disorder and greater dysphoria 18 months later. Future prediction studies should include MLM-based analyses in the assessment of risk for depression. In addition, as a blunted ΔRewP represents a composite of reward- and loss-related activity, future research should incorporate time-frequency representations of reward (e.g., reward-related delta) and loss (e.g., loss-related theta) to provide further insight into the underlying nature of reward-related network disruptions in depression (29,47).

The patterns of responding observed are consistent with the notion that depression is characterized by aberrant reward processing, possibly owing to blunted phasic dopaminergic signaling (25). Impaired mesocorticolimbic dopamine pathways (including ventral and dorsal striatal regions) have been hypothesized in MDD and may be related to the decreased motivation and ability to experience reward. To the extent that the RewP indexes individual differences in reward sensitivity, the current data of suppressed reward response over time in individuals with high symptoms of depression is consistent

![Figure 3](image-url)
Reward Processing in Depression

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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