Neural Responsiveness to Reward as an Index of Depressive Symptom Change Following Cognitive-Behavioral Therapy and SSRI Treatment

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ABSTRACT

Objective: Reward positivity (RewP), a neurophysiologic index of reward responsivity, is consistently reduced in participants with depression and, to a lesser extent, anxiety. It remains unknown, however, whether RewP can be altered as psychiatric symptoms change with treatment. The current study addressed this question by examining differences in RewP within patients before and after 12 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI) or cognitive-behavioral therapy (CBT). We also examined the utility of RewP as a predictor of symptom change during CBT and SSRI treatment.

Methods: Participants were recruited between 2014 and 2017 and included adults with a primary *DSM-5* anxiety or depressive disorder (n = 63) and healthy controls (n = 25). At baseline and 12 weeks, participants completed a monetary award task while electroencephalogram (EEG) was recorded. Between EEG sessions, patients completed CBT or SSRI treatment.

Results: At baseline, higher levels of depressive symptoms were associated with a more attenuated RewP. We found no significant differences between patients and healthy controls in the degree of RewP change across the 12 weeks; however, among patients, the extent of increase in RewP robustly correlated with the extent of decline in depressive ($t = -2.21$, $P = .03$) and anxiety ($t = -2.57$, $P = .02$) symptoms following CBT and SSRI treatment. Additionally, a more attenuated RewP at baseline predicted a greater reduction in depressive symptoms following treatment with SSRIs ($t = -2.04$, $P < .05$), but not after CBT.

Conclusions: These findings highlight neural responsiveness to reward as both a mechanism and a predictor of depressive symptom change that may be used serve as an objective index of symptom improvement.

Trial Registration: ClinicalTrials.gov identifier: NCT01903447

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Internalizing psychopathologies, encompassing anxiety and depressive disorders, are characterized by deficits in several aspects of reward processing, including effort valuation, reward outcome, and decision-making processes in the context of reward.[1,2] The Research Domain Criteria (RDoC) Initiative of the National Institute of Mental Health (NIMH) has identified a number of reward-related biologically based constructs within the positive valence system to promote better ways of classifying psychiatric disorders and identifying treatment targets. Initial responsiveness to reward attainment is one construct within the positive valence system that is consistently linked to depressive disorders,[3] and, to a lesser extent anxiety,[2] and refers to the mechanisms associated with hedonic responses (eg, behavioral, physiologic, and neurologic responses to pleasurable or positive stimuli) and culmination of reward seeking.

There is substantial evidence at self-report and behavioral levels that depressive disorders, particularly when accompanied by anhedonia, are characterized by diminished hedonic responses and an inability to modulate behavior as a function of rewards.[4] There is some evidence that deficits in reward responsiveness also extend to anxiety disorders. For instance, even when depression history is controlled for, social anxiety is characterized by diminished positive experiences, infrequent positive events, and fear responses to overtly positive experiences.[5] Diminished hedonic responses have also been documented among individuals with posttraumatic stress disorder[6] and generalized anxiety disorder,[7] albeit with mixed evidence. Specifically, there is also evidence for intact reward responses among individuals with anxiety disorders at self-report and behavioral levels.[8] It has been suggested that the relationship between anxiety and reward responsiveness might vary as a function of self-regulatory abilities[5] or the presence of anhedonia[1] among individuals.

To capture individual differences in reward responsiveness at the psychophysiologic level, researchers have utilized reward positivity (RewP), an event-related potential (ERP) component. RewP, also referred to as *feedback negativity* or *feedback-related negativity*, appears as a frontocentral ERP component occurring approximately 250–350 milliseconds after the receipt of

Clinical Points

- Reward positivity (RewP), a neurophysiologic index of reward responsivity, is consistently reduced among individuals with depression. It is unknown, however, whether RewP can be altered as depressive symptoms change with treatment or serve as a marker of treatment success.
- Findings suggest that initial responsiveness to reward at the neural level may serve as a novel, objective psychophysiologic indicator of depressive symptom improvement following cognitive-behavioral therapy and selective serotonin reuptake inhibitor (SSRI) treatment. Findings from the current study also highlight neural responsiveness to reward as a predictor of SSRI treatment response.
- This study is the first to suggest that event-related potentials, which are cost-effective and have potential to be utilized in clinical settings, can track treatment effects for depressive symptom reduction.

a reward, and is thought to reflect the processing of positive feedback for reward relative to feedback for nonreward or losing.[9] Studies have consistently documented a negative relationship between RewP and depressive symptoms and diagnoses across development.[10–14] A decreased RewP has been also observed to prospectively predict future depressive symptoms[15] and diagnoses[16] in youth. Fewer studies have examined the association between RewP and anxiety, and findings have been less consistent relative to studies with depression. For instance, whereas some studies have found a relationship between an attenuated RewP and anxiety symptoms in youth[17] and adults,[18] others have failed to find a significant relationship.[10,11]

Taken together, extant data indicate an attenuated RewP response in depressive disorders across development, with some mixed evidence in individuals with anxiety. In one study,[15] the significant negative relationship between RewP and depressive symptoms was maintained at a separate testing point 2 years later among a sample of adolescents, suggesting that RewP indexes a trait-like vulnerability factor for depression. Providing additional support for this notion, studies[19,20] have found evidence for a blunted RewP among adults in remission from depression. No studies to date, however, have examined the malleability, or lack thereof, of RewP in these populations as it pertains to treatment. Specifically, it remains unknown whether RewP can be altered as psychiatric symptoms change over time and is therefore a candidate treatment target.

Functional magnetic resonance imaging (fMRI) studies[21,22] provide some evidence that neural responsiveness to reward is improved following behavioral activation and selective serotonin reuptake inhibitor (SSRI) treatment. For instance, Stoy et al[22] found that depressed patients exhibited hypoactivation of the ventral striatum, an area linked to RewP,[23] during reward processing at baseline and that this deficit was normalized after SSRI use. This finding suggests that RewP may dynamically change along with symptom improvement and thus serve as an objective marker of treatment progress. Addressing whether RewP is disrupted in internalizing disorders and is malleable with treatment is critical in advancing the NIMH RDoC Initiative, which seeks to develop objective dimensional assays that align with brain circuits and, in turn, enable quantification of treatment response.[24]

The current study examined the malleability of RewP to standard treatments in a heterogeneous treatment-seeking sample with anxiety and depressive disorders. We first sought to replicate previous findings demonstrating a negative relationship between RewP and depressive symptomatology among patients and healthy controls at baseline. We examined whether RewP is amenable to change after 12 weeks of either cognitive-behavioral therapy (CBT) or SSRI treatment. Consistent with the fMRI literature,[21,22] we predicted that RewP would be enhanced after 12 weeks of treatment. We also evaluated whether pretreatment-to-posttreatment change in RewP would correlate with change in depressive symptoms in patients. For healthy controls, we suspected that RewP would remain relatively stable over the same time period given the previously documented stability of RewP among healthy adults.[25]

In addition to examining whether RewP increases after treatment, we explored whether individual differences in pretreatment RewP predicted symptom change following treatment. Specifically, response rates to CBT and SSRIs vary, with a range of 38%–87% across anxiety and depressive disorders.[26,27] Identifying predictors of symptom reduction following CBT and/or treatment with SSRIs has the potential to inform clinical decision making and precision medicine. Indeed, recent evidence highlights the advantage of utilizing ERPs, versus self-report and behavioral measures, to identify which individuals respond to prevention[28] and intervention[29] programs. We recently showed, in a separate cohort of patients with comorbid anxiety and depression,[30] that an attenuated RewP response at baseline predicted a greater reduction in depressive symptoms after 12 weeks of CBT. Findings from this previous study suggest that individuals who exhibit preexisting deficits in reward processing may respond better with this form of treatment. In the current study, we sought to extend this previous finding to examine whether a similar prediction pattern would be observed for both CBT and SSRI treatment response.

We explored whether treatment type moderated the predictive power and malleability of RewP; however, we did not have specific hypotheses, as both forms of treatment have been shown to be effective at reducing internalizing symptoms of psychopathology.[26,27] We also investigated whether RewP served as a mechanism or predictor of anxiety symptom change following treatment.

METHODS

Participants and Procedure

The current study was designed to be consistent with, and funded by, the NIMH RDoC Initiative (RFA-MH-13-080) and therefore enrolled a treatment-seeking community

sample of adults with a wide range of internalizing symptoms. Potential participants were recruited from the community through a variety of means (eg, mass e-mails, referrals, flyers at local businesses and outpatient clinics) between 2014 and 2017. To be included as a patient, participants were required to have all of the following: a current full-threshold or subthreshold *DSM-5* depressive or anxiety disorder, a Global Assessment of Functioning (GAF)[31] score of ≤ 60, and a total score of ≥ 23 on the 21-item Depression Anxiety Stress Scale (DASS-21).[32] Healthy controls were required to have no lifetime diagnosis of a psychiatric disorder as determined by the Structured Clinical Interview for *DSM-5* Disorders (SCID-5).[33] Exclusionary criteria for both groups included an inability to provide consent and read and write in English; a major active medical or neurologic problem; a history of mania, psychosis, an intellectual disability, or pervasive developmental disorder; current substance dependence; any contraindication to receiving SSRIs; being currently enrolled in psychiatric treatment; a history of traumatic brain injury; and being pregnant. This study was approved by the University of Illinois-Chicago Institutional Review Board, and informed consent was obtained from all participants. The study was registered on ClinicalTrials.gov (Identifier: NCT01903447).

A total of 50 healthy controls and 168 patients initially enrolled in the study. Among the healthy controls, 4 were deemed ineligible and withdrawn from the study, 4 dropped out prior to the baseline assessment, 2 were lost to follow-up, 11 discontinued, and 4 had poor-quality EEG data at either baseline or follow-up (ie, having fewer than 15 artifact-free trials per condition), resulting in a final sample of 25 controls. For the patients, 39 were deemed ineligible, 35 dropped out prior to baseline, 13 were lost to follow-up, and 18 had poor-quality EEG data at either baseline or follow-up, resulting in a final sample of 63 patients.

Assessment of Psychopathology

Psychiatric diagnoses were assessed via the SCID-5[33] by a trained masters-level assessor, PhD-level psychologist, or psychiatrist. The breakdown of current diagnoses was 73.0% (n = 46) generalized anxiety disorder, 57.1% (n = 36) social anxiety disorder, 54.0% (n = 34) major depressive disorder, 27.0% (n = 17) panic disorder, 19.0% (n = 12) persistent depressive disorder, 19.0% (n = 12) specific phobia, and 14.3% (n = 9) posttraumatic stress disorder. The breakdown of primary diagnoses was 41.3% (n = 26) generalized anxiety disorder, 27.0% (n = 17) social anxiety disorder, 20.6% (n = 13) major depressive disorder, 6.3% (n = 4) panic disorder, 3.2% (n = 2) posttraumatic stress disorder, and 1.6% (n = 1) persistent depressive disorder. The patients had a high rate of comorbid diagnoses, which is reflected by 59.1% of the adults having co-occurring anxiety and depressive disorders and participants having a mean ± SD of 3.6 ± 1.19 internalizing psychopathology diagnoses.

At pretreatment, trained clinical research assessors blinded to treatment randomization administered healthy controls and patients the Hamilton Anxiety Rating Scale (HARS),[34] a 14-item interview-based measure of broad anxiety and somatic symptoms, and the Hamilton Depression Rating Scale (HDRS),[35] a 17-item interview-based measure of broad depressive and somatic symptoms. Participants also completed the Beck Depression Inventory[36] and Beck Anxiety Inventory[37] self-report measures, each of which includes 21 items to capture common symptoms of depression (eg, sadness, anhedonia, worthlessness, suicidal ideation, psychomotor complaints) and anxiety (eg, physical/panic sensations, nervousness, fear of bad things happening), respectively. Patients also completed these measures at posttreatment.

Treatment Procedures

Participants were randomized to 12 weeks of either CBT (n = 34) or SSRI treatment (n = 29). For participants randomized to SSRIs (sertraline, fluoxetine, paroxetine, escitalopram, or citalopram), the dosing schedule was flexible depending on tolerability and aimed to reach target dose by week 8. Patients receiving SSRIs attended medication management sessions that lasted approximately 20–30 minutes with their study psychiatrist at 0, 2, 4, 8, and 12 weeks. For participants randomized to CBT, treatment was delivered through 12 once-weekly 60-minute sessions led by a PhD-level clinical psychologist under the supervision of a licensed clinical psychologist with expertise in clinical trials with CBT. Evidence-based manuals were used based on the patient's principal diagnosis and predominant symptoms.[38–40] As per the manualized protocol, sessions began with psychoeducation and cognitive restructuring and then expanded to include strategies such as behavioral change (eg, exposures, behavioral activation) and relapse prevention.

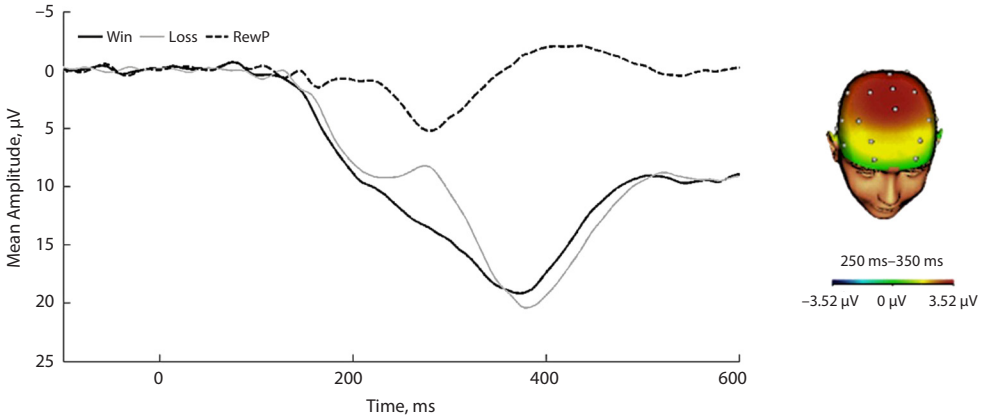
Reward Task

Participants completed a well-validated computerized guessing task[10,11,16] that consisted of 40 trials. On each trial, participants were asked to choose 1 of 2 doors shown side by side on a computer monitor; the graphic remained visible until a choice was made. A fixation mark then appeared for 1,000 milliseconds, followed by feedback screen for 2,000 milliseconds. Feedback consisted of either a green "↑", indicating a gain of $0.50, or a red "↓", indicating a loss of $0.25; these amounts were chosen to give gains and losses equivalent subjective values. After receiving feedback, a fixation mark was presented for 1,500 milliseconds, followed by a screen reading "Click for the next round," which remained onscreen until participants responded. Participants received 20 trials each of gain and loss feedback, presented in a random order.

EEG Data Acquisition and Processing

Continuous EEG was recorded during the task using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, the Netherlands). Thirty-four standard electrode sites were used. The data were digitized at 24-bit resolution with a least significant bit (LSB) value of 31.25nV

Figure 1. Response-Locked ERP Waveforms (Pooling of FCz and Fz Electrodes) Following Gain, Loss, and the Gain-Minus-Loss Difference Wave (RewP) Across the Entire Sample (n = 82) at Time 1 (Pretreatment) and Topographic Scalp Map of Neural Activity Depicting the Gain-Minus-Loss Difference 250–350 ms After the Response



Abbreviations: ERP = event-related potential, RewP = reward positivity.

Table 1. Demographics and Clinical Characteristics of the Sample[a]

Variable	Patients, Mean (SD)	HCs, Mean (SD)	*t* Value	CBT, Mean (SD)	SSRI, Mean (SD)	*t* Value
Age	28.70 (9.55)	23.56 (8.20)	2.36*	28.68 (8.90)	28.72 (10.43)	−0.02
BDI symptoms						
T1	25.21 (8.42)	1.12 (1.81)	14.14***	24.85 (8.09)	25.62 (8.90)	−0.36
T2	8.16 (6.75)	…	…	8.85 (7.25)	7.34 (6.14)	0.88
BAI symptoms						
T1	20.71 (10.18)	0.96 (1.54)	9.63***	22.15 (10.70)	19.03 (9.47)	1.22
T2	7.39 (8.08)	…	…	7.45 (6.99)	7.32 (9.27)	0.61
HDRS symptoms						
T1	11.97 (3.96)	0.48 (0.65)	14.38***	10.94 (2.81)	12.17 (4.76)	−1.44
T2	5.11 (3.66)	…	…	5.12 (3.83)	5.10 (3.52)	0.02
HARS symptoms						
T1	17.67 (6.82)	1.24 (1.76)	11.85***	16.50 (5.48)	19.03 (8.00)	−1.48
T2	6.70 (5.26)	…	…	6.09 (4.35)	7.41 (6.16)	−0.99
	Patients, n (%)	HCs, n (%)	χ^2	CBT, n (%)	SSRI, n (%)	χ^2
Female	47 (74.6)	11 (44.0)	7.46**	25 (73.5)	22 (75.9)	0.05
White	43 (68.3)	12 (48.0)	3.13	23 (67.6)	20 (69.0)	0.01
Hispanic/Latino	9 (14.3)	2 (8.0)	0.65	5 (14.7)	4 (13.8)	0.01

[a]The sample included 63 patients and 25 healthy controls; 34 patients received CBT, and 29 patients received SSRIs.
*P < .05. **P < .01. ***P < .001.
Abbreviations: BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, HARS = Hamilton Anxiety Rating Scale, HC = healthy control, HDRS = Hamilton Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor (n = 29), T1 = pretreatment, T2 = posttreatment.

and a sampling rate of 1,024 Hz, using a low-pass fifth order sinc filter with a −3 dB cutoff point at 204.8 Hz. Off-line analyses were performed using Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). Data were re-referenced to the average of the 2 mastoids and high-pass (0.1 Hz) and low-pass (30 Hz) filtered. Standard eyeblink and ocular corrections were performed utilizing the Gratton and Coles algorithm, which corrects ocular artifacts by using a regression-based approach.[41] Semi-automated artifact rejection procedures removed artifacts with the following criteria: voltage step of more than 50 μV between sample points, a voltage difference of 300 μV within a trial, and a maximum voltage difference of less than 0.5 μV within 100-millisecond intervals. Additional artifacts were removed using visual inspection. Data were baseline corrected using the 200-millisecond interval prior to feedback. ERPs were averaged across gain and loss trials, and RewP was scored as the mean amplitude 250–350 milliseconds following feedback at a pooling of FCz and Fz electrodes, for which the gain-minus-loss difference was maximal (see Figure 1). Consistent with previous research,[9] analyses focused on the gain-minus-loss difference score (RewP); more positive values for the difference score indicate greater reactivity to reward.

Table 2. Examination of Whether Change in RewP Predicts Change in Depressive and Anxiety Symptoms From Pretreatment to Posttreatment[a]

	Change in Depression (Composite *z* Score)			Change in Anxiety (Composite *z* Score)		
Variable	β	*t*	*P* Value	β	*t*	*P* Value
Step 1						
Baseline symptoms[b]	0.19	1.45	.15	0.31	2.47	**.02**
Arm[c]	0.16	1.28	.21	0.02	0.16	.87
Change in RewP[d]	−0.29	−2.21	**.03**	−0.30	−2.57	**.02**
Step 2						
RewP change × arm	−0.59	−1.54	.13	−0.29	0.73	.47

[a]Boldface indicates statistical significance.
[b]Baseline symptoms = depression composite *z* score for change in depression model or anxiety composite *z* score for change in anxiety model.
[c]Arm = medication or cognitive-behavioral therapy.
[d]Change in RewP from pretreatment to posttreatment.
Abbreviation: RewP = reward positivity.

Statistical Analyses

To reduce the number of statistical analyses conducted, composite depression (HDRS and BDI) and anxiety (HARS and BAI) scores were created by summing standardized *z* scores. A series of planned within-subjects and between-subjects analysis of variance (ANOVA) tests were conducted to verify that SSRIs and CBT were successful in reducing depressive and anxiety symptoms. We also conducted a series of bivariate correlations to examine relations between depressive and anxiety symptoms and RewP at baseline.

Next, to assess mean level RewP changes from pretreatment (T1) to posttreatment (T2), we conducted a 2 × 3 time (T1 and T2) × group (controls, SSRI, CBT) omnibus ANOVA. To examine whether change in RewP corresponded to changes in symptoms among patients only, a series of hierarchical linear regression analyses were conducted with change (pretreatment minus posttreatment) in anxiety and depressive symptoms serving as the dependent variables. For all models, baseline symptoms, RewP change (centered), and treatment arm (CBT, SSRI) were entered in step 1, and the 2-way interaction between RewP change and treatment arm was entered in step 2.

Finally, to examine whether RewP at T1 predicted change in symptoms during treatment with CBT or SSRIs within patients, hierarchical linear regression analyses were conducted. For all models, baseline symptoms, RewP at T1 (centered), and treatment arm (CBT, SSRI) were entered in step 1 and the 2-way interaction between T1 RewP and treatment arm was entered in step 2.

RESULTS

Descriptive and Clinical Characteristics

Table 1 provides demographic and clinical characteristics of the sample separated by group. Within patients, depressive ($t_{63} = 4.27$, $P < .001$) and anxiety ($t_{63} = 3.86$, $P < .001$) symptoms decreased from pretreatment to posttreatment. Neither baseline measures nor the extent of reduction in internalizing symptoms differed based on treatment modality (SSRI vs CBT; *P* values > .18).

Bivariate correlations revealed that participants with higher depressive symptoms exhibited a more attenuated RewP at baseline ($r = -0.27$, $P = .01$). However, the relationship between baseline anxiety symptoms and RewP was nonsignificant ($r = -0.13$, lowest $P = .20$).

RewP Before and After Treatment

An omnibus ANOVA, controlling for age and sex, was conducted to examine whether group (controls, SSRI, CBT) influenced the extent to which RewP changed from T1 to T2. These analyses revealed no significant main effects of group or time and no significant time × group interaction (lowest $P = .09$).*

Association Between Change in RewP and Change in Symptoms Among Patients

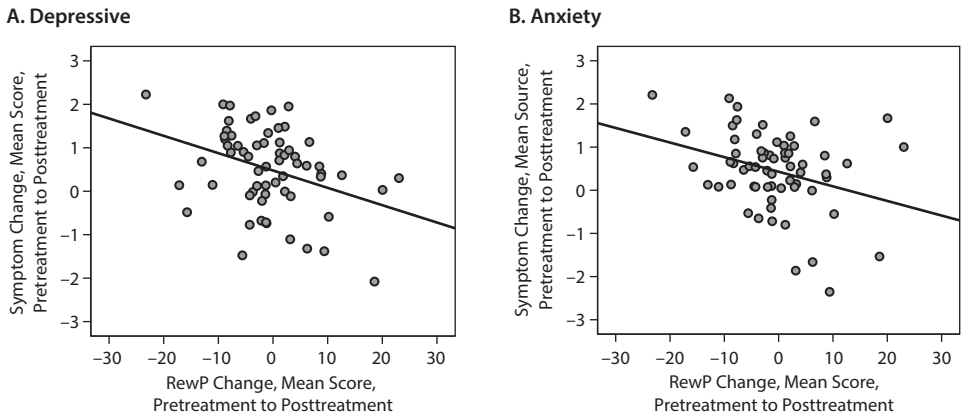
As shown in Table 2, changes in RewP correlated with changes in symptoms of depression (Figure 2A) and anxiety (Figure 2B) from pretreatment to posttreatment. Specifically, decreases in symptoms were associated with an increase in RewP from pretreatment to posttreatment. The association between RewP change and depressive and anxiety symptom change was not moderated by treatment arm (Table 2).†

Pretreatment RewP as a Predictor of Symptom Reduction Among Patients

Finally, we examined whether RewP at baseline predicted symptom change following treatment (Table 3). For change in anxiety symptoms, findings revealed no main effects of T1 RewP or 2-way interactions. However, results revealed a significant T1 RewP × arm interaction for change in depressive symptoms (Figure 3). Follow-up analyses indicated that within patients who received SSRIs, a more attenuated T1 RewP was associated with greater reduction in depressive symptoms ($\beta = -0.39$, $t = -2.04$, $P < .05$). Meanwhile, within patients who received CBT, T1 RewP was not associated with change in depressive symptoms ($\beta = 0.14$, $t = 0.75$, $P = .46$). We also probed this interaction utilizing the Johnson-Neyman technique,[42] which gives a value of the moderator at which the significance of the predictor on outcome changes. The result of this procedure suggested a RewP cutoff of −4.71 μV ($P < .05$) and thus confirmed that patients assigned to SSRIs were more likely to exhibit depressive

*Pearson correlation coefficients revealed moderate to high stability of the ERP gain and ERP loss variables from T1 to T2 among both patients (ERP gain: $r = 0.59$, $P < .001$; ERP loss: $r = 0.63$, $P < .001$) and healthy controls (ERP gain: $r = 0.61$, $P < .01$; ERP loss: $r = 0.72$, $P < .001$). The stability of RewP was low among both groups (lowest $P = .50$).
†Post hoc analyses were conducted to determine whether changes in the ERP gain and/or ERP loss variables correlated with changes in symptoms of depression and/or anxiety from pretreatment to posttreatment. None of these analyses reached significance (lowest $P = .09$).

Figure 2. Scatter Plots Reflecting the Association Between RewP Change (Non-Centered) and Change in (A) Depressive (Composite HDRS and BDI *z* Scores) and (B) Anxiety (Composite HARS and BAI *z* Scores) Symptoms Following Cognitive-Behavioral Therapy and Selective Serotonin Reuptake Inhibitor Treatment[a]



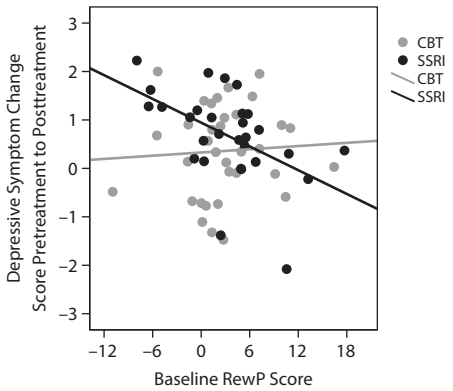
[a]The diagonal line is the linear fit line.

Table 3. Examination of Whether Baseline RewP Predicts Change in Depressive and Anxiety Symptoms From Pretreatment to Posttreatment[a]

	Change in Depression (Composite *z* Score)			Change in Anxiety (Composite *z* Score)		
Variable	β	*t*	*P* Value	β	*t*	*P* Value
Step 1						
Baseline symptoms[b]	0.28	2.03	**<.05**	0.29	2.35	**.02**
Arm[c]	0.12	0.94	.35	0.00	−0.02	.98
Baseline RewP	−0.10	−0.71	.48	−0.11	−0.89	.38
Step 2						
Baseline RewP × arm	−0.76	−1.98	**<.05**	−0.68	−1.76	.09

[a]Boldface indicates statistical significance.
[b]Baseline symptoms = depression composite *z* score for change in depression model or anxiety composite *z* score for change in anxiety model.
[c]Arm = medication or cognitive-behavioral therapy.
Abbreviation: RewP = reward positivity.

Figure 3. Scatter Plot Reflecting the Association Between RewP Change (Non-Centered) and Change in Depressive Symptoms (Composite HDRS and BDI *z* Scores) Following CBT and SSRI Treatment[a]



[a]The diagonal line is the linear fit line.
Abbreviations: BDI = Beck Depression Inventory, CBT = cognitive-behavioral therapy, HDRS = Hamilton Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

symptom reduction if they exhibited a blunted RewP at baseline.‡

DISCUSSION

The current study examined whether RewP, an objective neurophysiologic marker of reward responsiveness, served as a biological target of depressive and anxiety symptom change following CBT and SSRI treatment. Replicating previous studies,[10–16,19,20] greater depressive symptoms were associated with a more attenuated RewP at baseline. Contrary to our initial hypothesis, patients and controls did not differ in the degree of RewP change over the course of 12 weeks. Although some studies[21,22] highlight changes in neural structures implicated in reward as a result of treatment for depression, our finding is somewhat consistent with other studies[19,20,43,44] showing that reward responsiveness at the behavioral and neural levels continues to be reduced among individuals in remission from depression. Importantly, the current study did demonstrate that RewP may be a novel, objective psychophysiologic indicator of depressive symptom change following CBT and SSRI treatment. Specifically, within patients, the more that RewP increased, the more that depressive symptoms improved following both treatments. These initial findings provide initial support for RewP serving as an objective marker of treatment success for depressive symptom reduction.

In a distinct set of results, the current study also found that a more attenuated RewP at baseline predicted

‡Post hoc analyses were conducted to determine whether the ERP gain and/or ERP loss variables predicted changes in symptoms of depression and/or anxiety from pretreatment to posttreatment. None of these analyses reached significance (lowest $P = .18$).

greater reduction in depressive symptoms following SSRI treatment, but not following CBT. Notably, this is in slight contrast to our previous study[30] using a separate clinical sample in which we found that a more blunted pretreatment RewP is associated with greater depressive symptom change following CBT among adults with comorbid anxiety and depression. Although the precise reason for this discrepant finding is unclear, differences in study population and design may account for the different pattern of findings across studies. For instance, the current study included a more severely ill patient population with a greater number of comorbid diagnoses relative to the previously reported study.[30] Alternatively, the monetary award tasks used to elicit RewP may be influencing the different results across studies. In our previous study,[30] the reward task included an anticipation phase in which participants received feedback regarding whether the condition was a gain (versus breaking even) or loss (versus breaking even) condition. As a result, the consumption phase, in which RewP was measured, tended to reflect sustained reward responsiveness, whereas the current task is more representative of initial reward reactivity. Although speculative, this finding may mean that individuals who exhibit attenuated sustained reward responses may perform better with CBT, whereas SSRIs may more directly target initial reward responsiveness. Future, larger studies are needed to test this hypothesis. If the finding is replicated, RewP may have an important role in the application of precision medicine and the mission of RDoC, especially considering it is a more time- and cost-effective option than other brain measures, such as neuroimaging, and has the potential to be utilized in psychiatric clinics.

The current set of findings appears to be specific to depressive, versus anxiety, symptoms. That is, consistent with previous research,[18] we found no evidence for a relationship between RewP and anxiety symptoms at baseline and no evidence that RewP acts as a predictor of anxiety symptom change following treatment. However, change in RewP did correlate with change in anxiety symptoms following CBT and SSRI treatment, providing some evidence that RewP exhibits transdiagnostic features. Given the high content overlap of the scales utilized to assess anxiety and depressive symptoms, it is possible that the correlation with anxiety is more of a reflection of the association of RewP with depression. Alternatively, the current findings may have been driven by high levels of anhedonia, which is common to both anxiety and depressive disorders.[1] It will be important for future studies to examine how diagnostic subgroups (eg, anhedonia or low positive affect, mixed anxiety/depression) influence the current pattern of findings.

There were several limitations to the current study. First, due to the RDoC strategy of enrolling patients with comorbid internalizing psychopathologies, we were unable to examine whether specific psychiatric diagnoses (ie, major depressive disorder) moderated any of these findings because of the high comorbidity rates. Although studying the moderating role of individual diagnoses was never the intention of the RDoC approach, future studies may benefit from examining whether these effects are specific for certain diagnostic groups. Similarly, future studies with larger sample sizes are needed to determine if other factors (eg, sex, age) influence the pattern of findings. In addition, the current study included only 2 assessments of RewP and was unable to statistically demonstrate that changes in RewP lead to subsequent change in depression. An alternative explanation may be that changes in depressive symptoms lead to subsequent changes in reward responding at the neural level. To rule out this possibility and to accurately model state and trait influences, additional assessment points of these measures are needed. Next, the healthy control participants were not administered symptom measures at the follow-up assessment. Future studies are needed to determine if the relation between change in symptoms and change in RewP is specific to patients or is also observed for healthy individuals not receiving treatment. It will be also important for future studies to include positive valence measures (eg, anhedonia, well-being) as clinical outcome measures to determine if the current findings are specific to changes in positive affect or depression more broadly. Similarly, the inclusion of other measures of reward responsiveness (eg, behavioral responses from the probabilistic reward task[4]) in future studies will be important to determine the incremental validity of RewP as a predictor of symptom improvement following treatment. Finally, although change in RewP correlated with change in depressive symptoms, the lack of a waitlist "treatment control" group makes it difficult to rule out whether the primary findings may have been influenced by general effects related to symptom change over time.

In summary, these findings highlight neural responsiveness to reward as both a mechanism and a predictor of depressive symptom change that may be used to not only serve as an objective index of symptom improvement but also help guide treatment selection. Although previous fMRI studies have provided evidence for changes in neural structures implicated in reward following treatment,[26,27] this study is the first to examine this question using ERPs. Future mechanistically based interventions aimed at directly enhancing reward positivity may prove to be most useful in reducing depression symptoms for patients who demonstrate preexisting deficits in this area.

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