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Moderation of the Relationship Between Reward Expectancy and Prediction Error-Related Ventral Striatal Reactivity by Anhedonia in Unmedicated Major Depressive Disorder: Findings From the EMBARC Study

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Abstract

Objective—Anhedonia, disrupted reward processing, is a core symptom of major depressive disorder. Recent findings demonstrate altered reward-related ventral striatal reactivity in depressed individuals, but the extent to which this is specific to anhedonia remains poorly understood. The authors examined the effect of anhedonia on reward expectancy (expected outcome value) and prediction error-(discrepancy between expected and actual outcome) related ventral striatal reactivity, as well as the relationship between these measures.

Method—A total of 148 unmedicated individuals with major depressive disorder and 31 healthy comparison individuals recruited for the multisite EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) study underwent functional MRI during a well-validated reward task. Region of interest and whole-brain data were examined in the first- (N=78) and second- (N=70) recruited cohorts, as well as the total sample, of depressed individuals, and in healthy individuals.

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Results—Healthy, but not depressed, individuals showed a significant inverse relationship between reward expectancy and prediction error-related right ventral striatal reactivity. Across all participants, and in depressed individuals only, greater anhedonia severity was associated with a reduced reward expectancy-prediction error inverse relationship, even after controlling for other symptoms.

Conclusions—The normal reward expectancy and prediction error-related ventral striatal reactivity inverse relationship concords with conditioning models, predicting a shift in ventral striatal responding from reward outcomes to reward cues. This study shows, for the first time, an absence of this relationship in two cohorts of unmedicated depressed individuals and a moderation of this relationship by anhedonia, suggesting reduced reward-contingency learning with greater anhedonia. These findings help elucidate neural mechanisms of anhedonia, as a step toward identifying potential biosignatures of treatment response.

Anhedonia, the disruption of reward processing, is a core symptom of depressive illness (1, 2). Numerous demonstrations of the influence of anhedonia on reward-guided behavior are reported (3, 4), for example, absence of a reward-related response bias in a signal detection task (5). However, examination of the neural underpinnings of this effect has yielded inconsistent findings. While several studies report reduced reward-related reactivity in striatal and medial frontal regions in individuals with major depressive disorder (6) or with high levels of anhedonia (7), other studies show robust anticipatory striatal activation in depressed individuals (8), as well as different affected loci within the striatum (9).

Some of these findings may be reconciled using reinforcement learning models to capture the variation of neural reactivity and to conceptualize abnormalities observed in individuals with major depressive disorder (10). One such model is the temporal difference model, which proposes that during learning, the prediction of future reward is updated based on the difference between the expected reward magnitude (from previous experience) and the actual reward outcome (11, 12). Prediction error signals are tracked in the ventral striatum (13, 14) and, as learning progresses, ventral striatal responding shifts from reward outcome (i.e., prediction error) to reward cues (i.e., reward expectancy), reflecting the process of conditioning (11). Preliminary evidence implicates reduced prediction error encoding in major depressive disorder, which is associated with severity of anhedonia symptoms (15).

We recently reported an inverse relationship between reward expectancy and prediction error ventral striatal reactivity in healthy individuals, consistent with a transfer of ventral striatal responding from prediction error to reward expectancy predicted by the temporal difference model (16). Importantly, this association was absent in medicated depressed individuals with bipolar disorder or major depressive disorder, which provides further evidence of disrupted temporal difference encoding in depressed individuals (16). Given that this finding was reported in medicated individuals with major depressive disorder and that psychotropic medications, including antidepressants, can modulate prefrontalstriatal dopamine function (17), it is important to determine whether a similar pattern of altered ventral striatal functioning is present in unmedicated depressed individuals with major depressive disorder. Furthermore, the extent to which this pattern of altered reward expectancy and prediction

error-related ventral striatal reactivity is specifically associated with anhedonia, rather than with other symptom dimensions in major depressive disorder, remains unknown.

We first sought to adopt a conventional diagnostic categorical approach and compare reward expectancy and prediction error-related ventral striatal reactivity in a large group of unmedicated depressed individuals with major depressive disorder and a group of healthy individuals using a well-validated reward task. In a novel step forward, we then adopted a dimensional approach, paralleling the approach advocated by the National Institute of Mental Health Research Domain Criteria (18), and determined, across both groups, the extent to which alteration in the expected inverse relationship between reward expectancy and prediction error-related ventral striatal reactivity was moderated specifically by the severity of anhedonia rather than other symptoms. Participants were recruited for the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care) study, a large multisite randomized controlled trial aiming to identify biomarkers of treatment response in major depressive disorder (data available upon request from MH Trivedi, PJ McGrath, M Weissman, R Parsey, and M Fava, principal investigators; ClinicalTrials.gov identifier: NCT01407094 [also see reference 19]). The design of EMBARC allowed us to test the following hypotheses separately in the first and second recruited cohorts of 100 depressed individuals and in the total sample of 200 depressed individuals.

In accordance with the temporal difference model and a previous report (16), we hypothesized that healthy individuals would demonstrate an inverse relationship between reward expectancy and prediction error-related ventral striatal reactivity and that this association would be absent in depressed individuals with major depressive disorder. Based on the disruptive effect of anhedonia on reward-related reactivity (7, 20, 21) and functional connectivity (20), as well as specifically on prediction error encoding in the ventral striatum (15), we further hypothesized that the relationship between reward expectancy and prediction error-related ventral striatal reactivity in depressed individuals with lower, compared with higher, anhedonia severity would more closely follow the pattern observed in healthy individuals.

METHOD

Participants

Participants were 200 unmedicated depressed individuals with major depressive disorder and 40 healthy individuals recruited for EMBARC. The study was conducted at four clinical sites: Columbia University, Massachusetts General Hospital, the University of Michigan, and the University of Texas Southwestern Medical Center. All individuals were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P [22]) to confirm diagnoses of major depressive disorder in patients and absence of diagnoses of lifetime axis I mood, anxiety, and psychotic disorders and current substance abuse in healthy individuals. To be eligible for the study, individuals had to be 18–65 years old, had to report an age at onset of depression occurring before 30 years old, and had to be fluent in English. Additional inclusion/exclusion criteria are presented in the data supplement accompanying the online edition of this article.

Fifty depressed patients and nine healthy individuals were excluded because of excessive motion (>4 mm), low slice signal-to-noise ratio (<80), and severe artifacts in MRI data. This exclusion rate is in line with other neuroimaging data sets (23). Two depressed patients were excluded because of a large number of omission errors (≥11) for the reward task. This yielded a final sample of 148 depressed patients (97 women; mean age=37.11 years [SD=12.93]) and 31 healthy individuals (19 women; mean age=38.42 years [SD=15.74]). A total of 158 participants were right-handed, 20 were left-handed, and one was ambidextrous. The two groups did not differ in age, sex ratio, handedness, and education level. The study was approved by the institutional review boards at each of the four clinical sites. All participants provided written, informed consent.

Clinical Measures

All participants were rated on the Hamilton Depression Rating Scale (HAM-D [24]) for severity of depression. Participants also completed the anhedonic depression subscale from the Mood and Anxiety Symptom Questionnaire (25), as well as the Snaith-Hamilton Pleasure Scale (26), to assess anhedonia severity, the anxious arousal subscale from the Mood and Anxiety Symptom Questionnaire (25) to assess somatic arousal severity, the Spielberger State-Trait Anxiety Inventory (27) to assess state anxiety, and the Altman Self-Rating Mania Scale (28) to determine hypomania severity. All self-report questionnaires were completed on the scanning day except the Altman Self-Rating Mania Scale, which was completed during an initial evaluation visit.

Reward Task

A well-validated monetary reward task comprised 24 trials presented in pseudorandom order with predetermined outcomes (29–31). There were four possible trial types (N=6 each): the expectation of a possible win, followed by a win or no change outcome, and the expectation of a possible loss, followed by a loss or no change outcome (Figure 1). During each trial, individuals guessed using button press whether the value of an upcoming card would be higher or lower than the number 5 (presentation of a question mark; 4 seconds). An upward or downward arrow was then presented for 6 seconds, representing a possible win or possible loss, respectively, while the participant anticipated the outcome. The outcome then appeared for 1 second (a number for 500 ms and then an upward or downward arrow for win and loss outcomes, respectively, or a yellow circle for no change outcomes, for 500 ms), followed by a 9-second intertrial interval. Participants were informed that their performance would determine a monetary reward after the scan, with $1.00 for each win and 50 cents deducted for each loss. The total possible earnings were, in fact, fixed at $3.00 to equalize rewards between participants. Previous data indicate that participants are unaware of the latter and believe that outcome is determined by chance (29). Participants completed a practice run of the task prior to the scan.

Image Acquisition

Neuroimaging data were collected using 3-T MRI scanners at all sites (for imaging parameters at each site, see the online data supplement).

Image Analysis

Preprocessing procedures were performed with Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Functional images for each participant were realigned to the first volume in the time series, coregistered with the corresponding anatomical image and smoothed with an 8-mm Gaussian kernel. The first-level model included the following four regressors: response (4-second presentations of a question mark), anticipation (6-second presentations of an arrow), outcome (1-second presentations of the number and feedback arrow), and baseline (3-second presentation of an orienting cross). In addition, we included two regressors representing reward expectancy and prediction error. The reward expectancy regressor, coupled with the anticipation phase, reflected the expected value of the arrow, set to +0.5 for the up arrow condition (given the 50% chance of winning $1.00) and to −0.25 for the down arrow condition (given the 50% chance of losing 50 cents). The prediction error regressor, coupled with the outcome, was determined by the difference between the outcome and the expected value (i.e., +0.5 for a win following an up arrow, −0.5 for no win following an up arrow, +0.25 for a no loss following a down arrow, −0.25 for a loss following a down arrow).

To model omission errors, we included another regressor, which lasted 17 seconds from the onset of the question mark and replaced other trial events during this period. Finally, we included the six motion parameters from the realignment phase as covariates of no interest. Serial autocorrelations were modeled using a first-order autoregressive process.

The main conditions of interest were reward expectancy and prediction error. We conducted a region of interest analysis focused on the ventral striatum. Mean parameter estimates reflecting reward expectancy and prediction error reactivity were extracted using two separate functional masks for the right and left ventral striatum, based on our previous findings (16). We conducted bivariate and partial correlational analyses (covarying for age, sex, site, and slice signal-to-noise ratio) to examine the relationship between reward expectancy and prediction error-related ventral striatal reactivity in the two groups (major depressive disorder group and healthy group).

We conducted hierarchical regression analyses to examine the effect of anhedonia, anxiety, and depression severity on the relationship between reward expectancy and prediction error-related ventral striatal reactivity, as well as on reward expectancy and prediction error-related ventral striatal reactivity per se, using the covariates described above.

We also conducted whole-brain analyses that paralleled the region-of-interest analyses using a family-wise error cluster threshold of $p<0.05$ (see the online data supplement).

The above analyses were conducted in the first-recruited cohort of 100 depressed patients (referred to as cohort MDD_{100a}; N=78 with usable data) and healthy individuals (N=31 with usable data), in the second-recruited cohort of 100 depressed patients (referred to as cohort MDD_{100b}; N=70 with usable data) and healthy individuals, and in all 200 depressed patients (referred to as cohort MDD_{200}; N=148) and healthy individuals.

RESULTS

Demographic Variables

There were no group differences in age, sex ratio, and level of education for the MDD_{100a} cohort (all p values >0.28), the MDD_{100b} cohort (all p values >0.1), or the MDD_{200} cohort (all p values >0.11) and healthy individuals (Table 1).

Clinical Measures

Depressed individuals had higher scores on the HAM-D, Mood and Anxiety Symptom Questionnaire anhedonic depression subscale, Snaith-Hamilton Pleasure Scale, Mood and Anxiety Symptom Questionnaire anxious arousal subscale, and Spielberger State-Trait Anxiety Inventory than healthy individuals (all p values <0.001 for cohorts MDD_{100a}, MDD_{100b}, and MDD_{200} [see Table 1]). There were no group differences in Altman Self-Rating Mania Scale scores between cohorts MDD_{100a} (p=0.3), MDD_{100b} (p=0.75), or MDD_{200} (p=0.6) and healthy individuals. For one depressed participant, scores on the Mood and Anxiety Symptom Questionnaire anhedonic depression and anxious arousal subscales were not available, and for six depressed participants, scores on the Altman Self-Rating Mania Scale were not available. For two healthy participants, HAM-D scores were not available.

Reward Task

Behavioral measures—There were no group differences in reaction time and number of omission errors between cohorts MDD_{100a} (p=0.19 and p=0.69, respectively), MDD_{100b} (p=0.79 and p=0.41, respectively), or MDD_{200} (p=0.4 and p=0.51, respectively) and healthy individuals (Table 1).

Neural reactivity

Region-of-interest analysis: reward expectancy and prediction error: There were no differences in reward expectancy and prediction error-related reactivity in the right or left ventral striatum between cohorts MDD_{100a} (all p values >0.38), MDD_{100b} (all p values >0.31), or MDD_{200} (all p values >0.47) and healthy individuals.

Relationship between reward expectancy and prediction error-related ventral striatal reactivity: There was a significant inverse correlation between reward expectancy and prediction error-related right ventral striatal reactivity in healthy individuals (r=−0.39, df=29, p=0.03) but not in depressed individuals (cohort MDD_{100a}: r=0.12, df=76, p=0.31; cohort MDD_{100b}: r=−0.07, df=68, p=0.58; cohort MDD_{200}: r=0.03, df=146, p=0.72 [Figure 2]).These correlation coefficients differed significantly between the healthy group and cohort MDD_{100a} (z=−2.4, p=0.02) and cohort MDD_{200} (z=−2.15, p=0.03) but not cohort MDD_{100b} (z=−1.55, p=0.12). The latter comparison was nearly significant for a one-tailed t test (p=0.06).

There was a similar pattern of relationships between the left ventral striatal reward expectancy and prediction error-related reactivity in healthy and depressed individuals (healthy participants: r=−0.22, df=29, p=0.25; cohort MDD_{100a}: r=0.12, df=76, p=0.31;

cohort MDD_{100b}; r=−0.06, df=68, p=0.62; cohort MDD_{200}: r=0.04, df=146, p=0.67), but the major depressive disorder group compared with healthy comparison group differences in correlation coefficients were not significant (z=−1.63, p=0.1, z=−0.7, p=0.48 and z=−1.23, p=0.22, respectively). Similar between-group differences in correlational patterns between the right ventral striatal reward expectancy and prediction error-related reactivity were observed when controlling for age, sex, and site (healthy participants: r=−0.41, df=24, p=0.04; cohort MDD_{100a}: r=0.07, df=71, p=0.59; cohort MDD_{100b}: r=−0.144, df=62, p=0.26; cohort MDD_{200}: r=−0.03, df=140, p=0.74).

Effects of anhedonia, anxiety, and depression severity on the relationship between reward expectancy and prediction error-related ventral striatal reactivity

MDD_{100a} and healthy individuals: We conducted a hierarchical multiple regression with right ventral striatal prediction error-related reactivity as the dependent variable. To control for age, sex, site, and slice signal-to-noise ratio, we included these covariates in the first step of the model. We then entered the two independent variables of interest: right ventral striatal reward expectancy-related reactivity and scores on the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale. Finally, we added the interaction term for the two independent variables. The interaction term accounted for significant variance in right ventral striatal prediction error-related reactivity (R^2_{change}=0.12, F_{change}=14.6, df=1, 98, p<0.001). To examine this finding further, we subdivided individuals with major depressive disorder into three subgroups defined by tertile split of scores on the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale: major depressive disorder-low anhedonia, major depressive disorder-moderate anhedonia, and major depressive disorder-high anhedonia. We then examined the interaction between anhedonia and right ventral striatal reward expectancy-related reactivity using these three subgroups and healthy individuals. This analysis revealed that a reduced inverse regression slope was associated with higher anhedonia severity (F=3.75, df=3, 94, p=0.01 [Figure 3A]).

Similar analyses were conducted to examine the effect of somatic arousal (Mood and Anxiety Symptom Questionnaire anxious arousal subscale), depression severity (HAM-D), and state anxiety (Spielberger State-Trait Anxiety Inventory) on the relationship between reward expectancy and prediction error-related right ventral striatal reactivity. There was a significant moderation effect for the Mood and Anxiety Symptom Questionnaire anxious arousal subscale (R^2_{change}=0.05, F_{change}=5.4, df=1, 98, p=0.02), an effect that fell short of statistical significance for HAM-D (p=0.07), and no effect for the Spielberger State-Trait Anxiety Inventory (p=0.37).

To determine to what extent the moderation effects observed were specific to anhedonia, we conducted a moderation analysis with scores from all symptom measures (Mood and Anxiety Symptom Questionnaire anhedonic depression and anxious arousal subscales, HAM-D, and Spielberger State-Trait Anxiety Inventory) included in one regression model. First, we entered the covariates to the model, next we entered all the independent variables of interest, and then we entered the three interaction terms for the Mood and Anxiety Symptom Questionnaire anxious arousal subscale, HAM-D, and Spielberger State-Trait

Anxiety Inventory and right ventral striatal reward expectancy-related reactivity. In the last step, we added the interaction term for the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale and right ventral striatal reward expectancy-related reactivity. The Mood and Anxiety Symptom Questionnaire anhedonic depression subscale remained a significant moderator of the relationship between right ventral striatal reward expectancy and prediction error-related reactivity, with all other symptom measures included (R^2_{change}=0.1, F_{change}=12.19, df=1, 90, p=0.001). Furthermore, t tests examining the effect of each predictor (beta) in the model showed that the interaction term for the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale and right ventral striatal reward expectancy-related reactivity was the only significant predictor of right ventral striatal prediction error-related reactivity (t=3.49, p=0.001).

Moderation effect of anhedonia within each depressed cohort and all depressed individuals only: The moderation effects of anhedonia with and without other symptom measures were significant for cohort MDD_{100a} (R^2_{change}=0.16, F_{change}=14.33, df=1, 67, p<0.001; R^2_{change}=0.17, F_{change}=15.82, df=1, 61, p<0.001, respectively) and MDD_{200} (R^2_{change}=0.04, F_{change}=5.91, df=1, 135, p=0.02 and R^2_{change}=0.06, F_{change}=9.721, df=1, 129, p=0.002, respectively) but not for MDD_{100b} (both p values >0.1). However, the correlation coefficients for reward expectancy and prediction error-related ventral striatal reactivity did not differ between the two MDD cohorts (p=0.28). A possible factor for the absence of an anhedonia moderation effect on the ventral striatal region of interest in cohort MDD_{100b} was the restricted range of Mood and Anxiety Symptom Questionnaire anhedonic depression subscale scores in this cohort (21 compared with 34 in cohort MDD_{100a}), particularly at the low end of the scale.

Moderation effect of anhedonia within all depressed and healthy individuals: The moderation effect of the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale on the relationship between right ventral striatal reward expectancy and prediction error-related reactivity was significant (R^2_{change}=0.03, F_{change}=6.53, df=1, 166, p=0.01 [Figure 3B]). This effect of anhedonia remained significant with all other symptom measures added to the model (R^2_{change}=0.04, F_{change}=8.54, df=1, 158, p=0.004).

Effects of anhedonia, anxiety symptoms, and depression levels on reward expectancy and prediction error-related ventral striatal reactivity: To test whether scores on the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale, Snaith-Hamilton Pleasure Scale, Mood and Anxiety Symptom Questionnaire anxious arousal subscale, HAM-D, or Spielberger State-Trait Anxiety Inventory were significantly associated with reward expectancy or prediction error-related right ventral striatal reactivity in depressed and healthy individuals, we conducted simple regressions with each symptom measure as an independent variable and either reward expectancy or prediction error-related right ventral striatal reactivity as the dependent variable; all covariates were included for these analyses. There was no effect for any of the symptom measures on either reward expectancy or prediction error-related right ventral striatal reactivity in cohort MDD_{100a} (all p values >0.1), cohort MDD_{200} (all p values >0.12), or healthy individuals (all p values >0.1), except for the Mood and Anxiety Symptom Questionnaire anxious arousal subscale

on prediction error-related right ventral striatal reactivity in cohort MDD_{100b} (p=0.02; all other p values >0.12).

Whole-brain moderation analysis (accounting for covariates): Two separate whole-brain analyses showed, in the first (MDD_{100a}) cohort and healthy individuals and in the second (MDD_{100b}) cohort and healthy individuals, moderation effects of the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale on the relationship between reward expectancy and prediction error-related reactivity in the anterior caudate, just anterior to the ventral striatal region of interest above (see the online data supplement). Across all participants, there was a significant moderation effect of the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale on this relationship in four striatal loci (Figure 4). Furthermore, correlation coefficients between reward expectancy and prediction error-related reactivity, based on parameter estimates extracted from the right anterior caudate, from the latter whole-brain analysis, showed comparable patterns in each of the two MDD cohorts for anhedonia range-equivalent subgroups (Figure 4).

DISCUSSION

The goal of the present study was to determine the extent to which anhedonia disrupts normal patterns of functioning in a key region of reward circuitry, the ventral striatum, during uncertain reward and loss expectancy and outcome. Our findings indicate that while depressed and healthy individuals exhibited similar reward expectancy and prediction error-related ventral striatal reactivity, there were marked group differences in the relationship between the two measures. Healthy, but not depressed, individuals showed an inverse correlation between right ventral striatal reward expectancy and prediction error-related reactivity. Across participants, increased anhedonia severity was associated with a reduced inverse correlation between reward expectancy and prediction error-related right ventral striatal reactivity. These findings were present in the first-recruited cohort of depressed and healthy individuals and the larger sample of all recruited participants. Whole-brain analyses showed a similar moderation effect of anhedonia on the reward expectancy prediction error relationship in the anterior caudate (just anterior to the ventral striatal region of interest), a region key to disrupted reward processing in major depressive disorder (6), in both the first and second cohorts of depressed individuals and healthy individuals and across all participants.

A core feature of conditioning is the transfer in the control of behavior from reinforcement itself to antecedent stimuli that predict reinforcement (32). The temporal difference model provides a unifying account of this transfer, with a single signal that becomes coupled to the earliest reliable predictor of reward (11). Our finding in healthy individuals of an inverse relationship across individuals between reward expectancy and prediction error-related right ventral striatal reactivity is consistent with this model, since right ventral striatal reactivity transferred from the outcome (prediction error) to its antecedent cue (reward expectancy). Here, individuals who show greater reward expectancy than prediction error-related ventral striatal reactivity may show a faster reward cue-outcome contingency learning rate. The absence of this relationship in depressed individuals and the moderating effect of anhedonia upon this relationship suggest that more severely anhedonic individuals may show deficient

temporal difference encoding and/or reward cue-outcome contingency learning in rewarding or potentially rewarding contexts. Our findings also highlight the specificity of this deficit to anhedonia, rather than this being a feature of major depressive disorder in general.

Previous findings indicate reduced prediction error-related ventral striatal reactivity in depressed individuals during reward learning (10, 15) and an association between decreased prediction error-related ventral striatal reactivity and greater anhedonia severity (15). Our study is the first, to our knowledge, to examine the relationship among reward expectancy and prediction error-related ventral striatal and whole-brain reactivity and the moderating effect of anhedonia on this relationship in a large sample of unmedicated depressed individuals. Furthermore, while these previous studies reported attenuated prediction error-related ventral striatal reactivity in depressed individuals when using temporal difference (10), or similar (15, 33) modeling approaches, cue-outcome contingency learning was captured by a fixed (10, 15) or individually determined (15, 33) learning rate. The fit of neural reactivity was therefore obtained by matching the observed pattern of dynamically changing ventral striatal reactivity with the parametric model of this reactivity. Thus, a poor fit in depressed individuals could be obtained for two reasons: 1) a general failure to activate the ventral striatum or 2) a failure of the model to reflect the abnormal pattern of fluctuation in ventral striatal reactivity in these individuals. Our findings support the latter, rather than the former account, given that depressed individuals showed normal levels of reward expectancy and prediction error-related ventral striatal reactivity but an aberrant relationship between these measures, especially in more severely anhedonic individuals.

The neurobiological basis of temporal difference learning is thought to involve modulation of ventral striatal activity by the midbrain (ventral tegmental area) dopamine system. The ventral tegmental area, which projects to the ventral striatum, is calibrated to optimize its signal-to-noise ratio by adapting to contextual rates of reinforcement (34). The dysregulation of this contextual adaptation in depressed individuals with greater anhedonia may thus be associated with variability of ventral tegmental area firing and lead to a ventral striatal reactivity pattern that does not tightly correspond to the temporal difference signal. Nevertheless, the ventral striatum may still show robust prediction error-related reactivity, as we show in depressed individuals in the present study, as well as in our previous findings (16).

Our findings are the first to show an absence of the expected inverse relationship between reward expectancy and prediction error-related ventral striatal reactivity in a large group of unmedicated individuals with major depressive disorder and suggest a neural mechanism for deficits in temporal difference learning in the illness. Furthermore, this aberrant pattern of striatal reactivity was associated with greater severity of anhedonia, even after controlling for other symptoms, in both cohorts of depressed individuals and all participants. The identification of a neural measure that may reflect a pathophysiological process underlying a core symptom of major depressive disorder is an important step forward in elucidating biomarkers of different affective symptom dimensions that, in turn, can help identify biomarkers and biosignatures that predict differential treatment response in the illness. These findings may also point to focused target of treatment in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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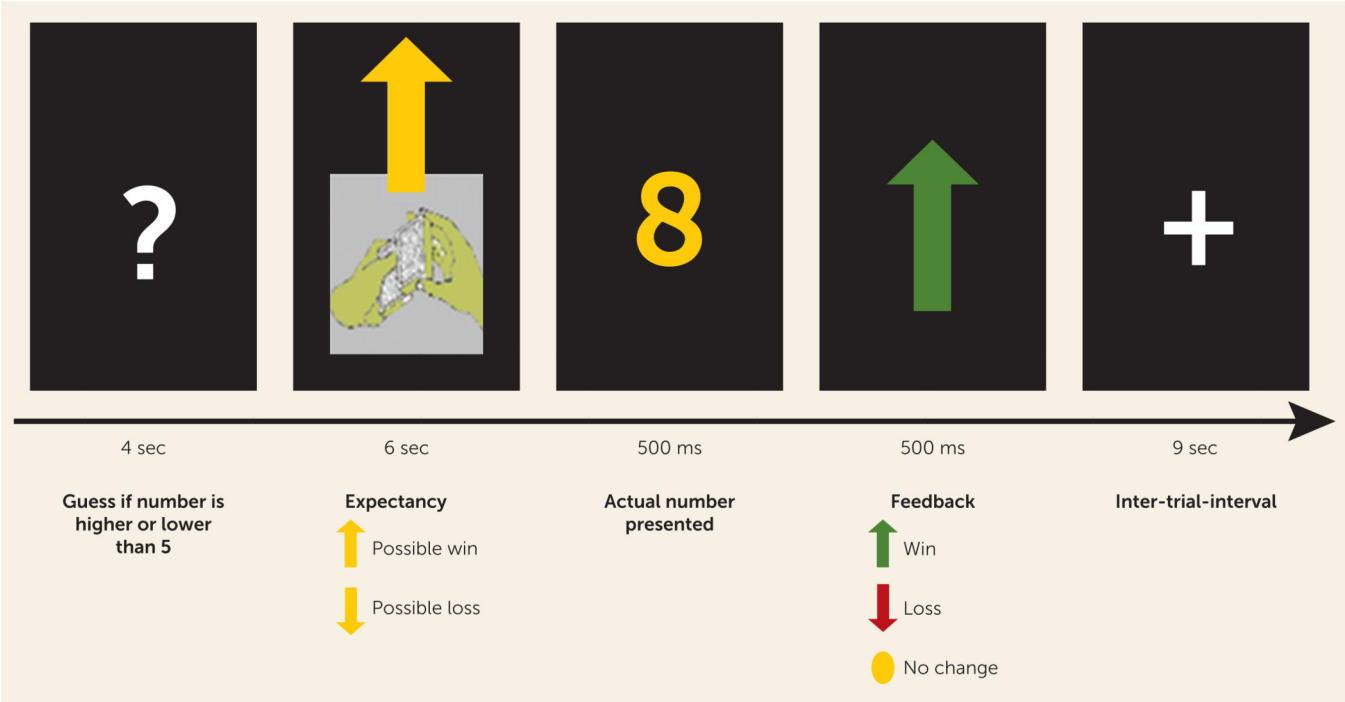

FIGURE 1.

Diagram of Given Trial From the Reward Task[a]

[a] The paradigm consists of 24 trials: 12 are reward-expectation trials, in which an arrow points upward and the possible outcomes are a win (six trials) or no change (six trials), and 12 are loss-expectation trials, in which the arrow points downward and the possible outcomes are a loss (six trials) or no change (six trials).

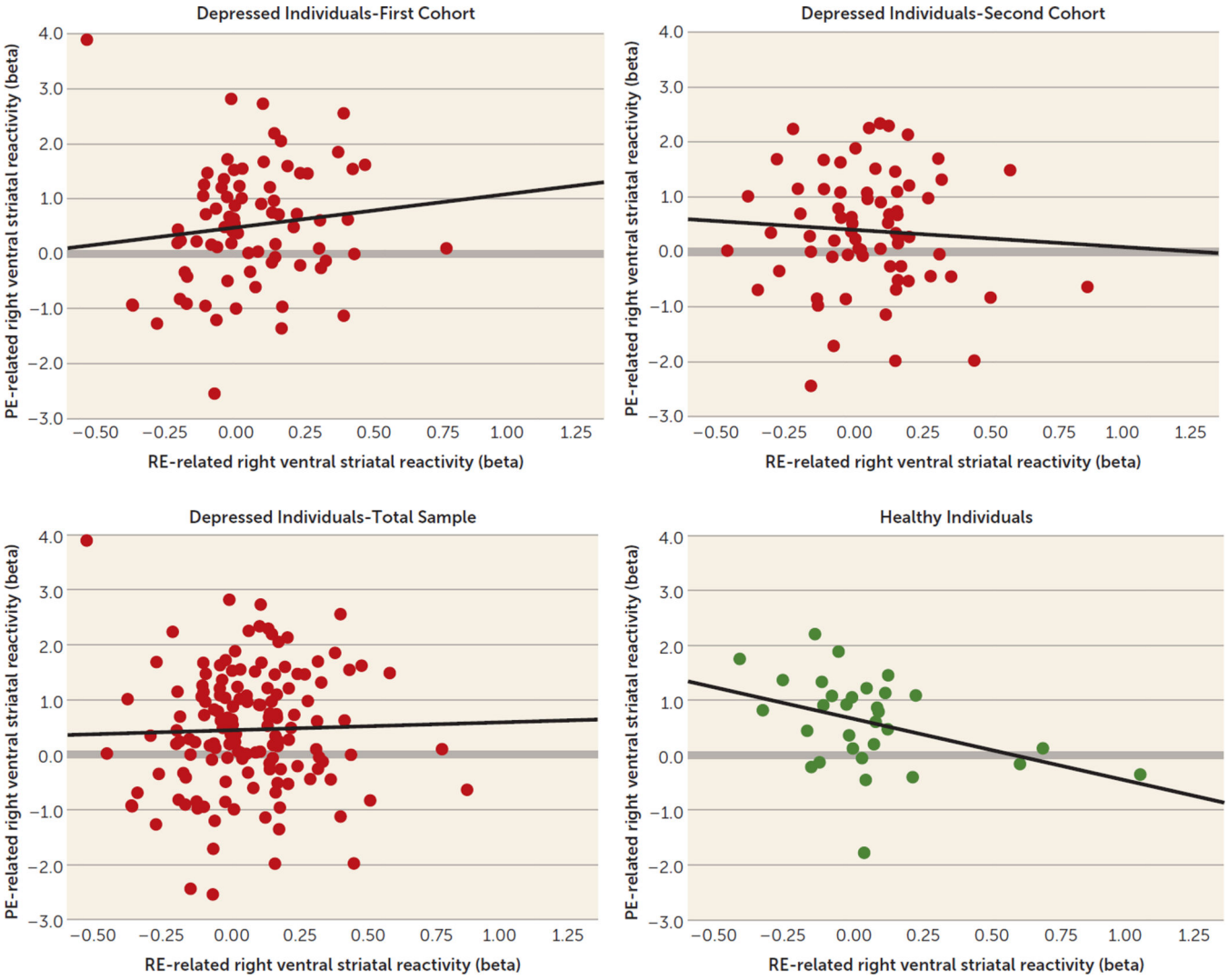

FIGURE 2.

Association Between Reward Expectancy and Prediction Error-Related Reactivity in the Right Ventral Striatum in the First-Recruited Cohort (N=78), Second-Recruited Cohort (N=70), and the Total Sample (N=148) of Depressed Individuals and Healthy Comparison Subjects (N=31)a

[a] RE=reward expectancy; PE=prediction error.

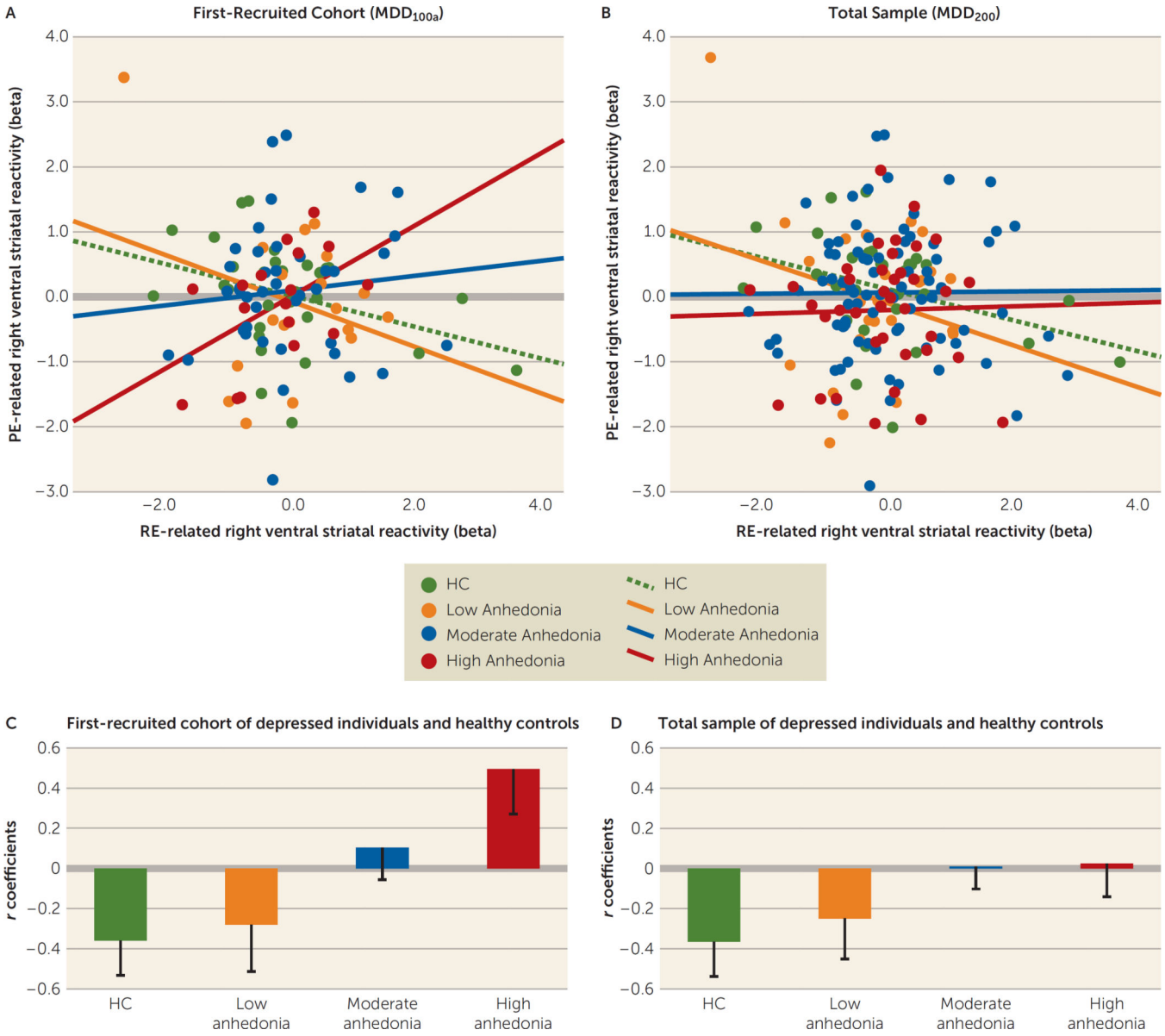

FIGURE 3.

The Relationship Between Reward Expectancy and Prediction Error-Related Right Ventral Striatal Reactivity in Healthy Comparison (HC) Subjects and in Individuals With Low, Moderate, and High Symptoms of Anhedonia in the First-Recruited Cohort (MDD_{100a}) and Total Sample (MDD_{200}) of Individuals With Major Depressive Disorder[a]

[a] The scatter plots (A, B) show the relationship between reward expectancy and prediction error-related right ventral striatal reactivity. The bar graphs (C, D) show correlation coefficients and standard errors for HC subjects and anhedonia subgroups (defined by tertile split of anhedonia scores) within the MDD_{100a} cohort and for HC subjects and anhedonia subgroups within the MDD_{200} cohort. RE=reward expectancy; PE=prediction error.

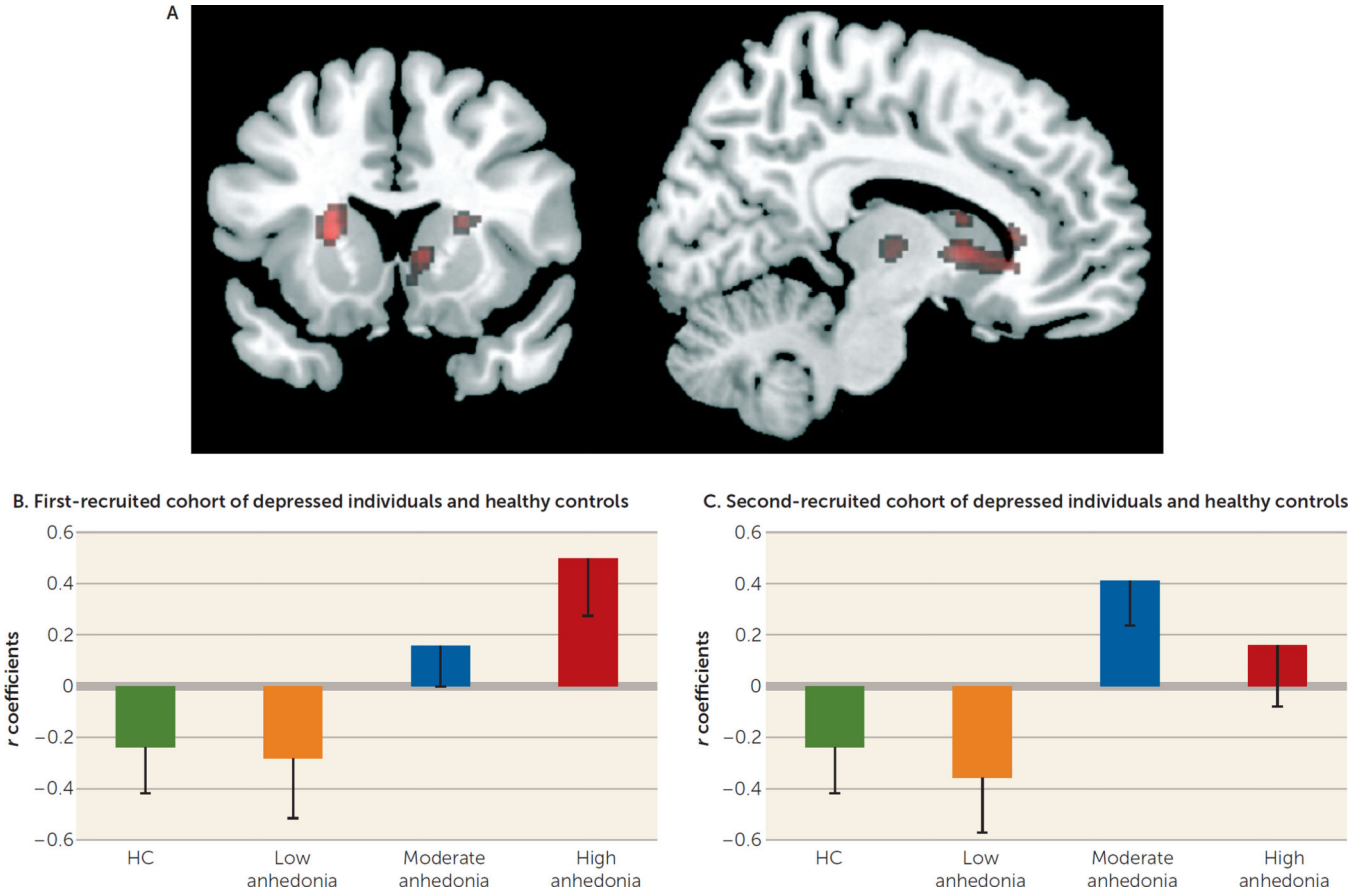

FIGURE 4.

Whole-Brain Moderation Analysis Across All Participantsa

[a] Whole-brain analysis across all participants was conducted to investigate the significant moderation effect of anhedonia at a voxel-wise level. A regression model was constructed in which prediction error was predicted on the basis of reward expectancy, Mood and Anxiety Symptom Questionnaire anhedonic depression subscale scores, and Mood and Anxiety Symptom Questionnaire anhedonic depression subscale-by-reward expectancy interaction, as well as the other covariates used for the region-of-interest analysis. This regression model (A) was fitted to each voxel. The resulting map was thresholded at a t statistic of 4.6 and a cluster size of 5, corresponding approximately to the peak/cluster family-wise-error corrected threshold (the map was thresholded at t>3.4 for display purposes). For the Mood and Anxiety Symptom Questionnaire anhedonic depression subscale-by-reward expectancy interaction effect, four clusters reflecting an increasingly positive/decreasingly negative correlation between reward expectancy and prediction error with increasing anhedonia were obtained. Two clusters were centered slightly more anteriorly with respect to the ventral striatum regions of interest, in the anterior caudate (left: peak voxel: t=5.36, df=167, p<0.05 [family-wise error] [coordinates: −16, 28, 2; 46 voxels]; right: peak voxel: t=5.60, df=167, p<0.05 [family-wise error] [coordinates: 16, 26, 0; 26 voxels]), while a small cluster was slightly more posterior, on the right (peak voxel: t=4.75, df=167, p<0.05 [family-wise error] [coordinates: 8, 12, 2; 5 voxels]). The fourth cluster was centered on the left dorsal striatum (peak voxel: t=5.63, df=167, p<0.05 [family-wise error] [coordinates: −22, 16, 8; 41 voxels;

all reported coordinates are in Montreal Neurological Institute space]). There were no significant voxels for the opposite direction of the interaction. The bar graphs show correlation coefficients (and standard errors) between reward expectancy and prediction error-related reactivity (extracted from a 6-mm sphere centered at coordinates 16, 26, 0) for healthy comparison subjects and anhedonia range equivalent subgroups (defined by tertile split of anhedonia scores) in the (B) first-recruited cohort (MDD_{100a}) and (C) second-recruited cohort (MDD_{100b}) of depressed individuals.

TABLE 1

Demographic, Clinical, and Behavioral Data for the First-Recruited Cohort of Individuals With Major Depressive Disorder (MDD_{100a}), the Second-Recruited Cohort (MDD_{100b}), the Total Sample of Depressed Participants (MDD_{200}), and Healthy Comparison Subjects[a]

	MDD_{100a} Cohort (N=78)		MDD_{100b} Cohort (N=70)		MDD_{200} Cohort (N=148)		Healthy Comparison Subjects (N = 31)	
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	38.47	13.21	35.60	12.54	37.11	12.9	38.42	15.74
Education (years)	15.13	2.46	14.60	2.90	14.88	2.68	15.88	4.77
Clinical measures								
Hamilton Depression Rating Scale (24-item) score[b–d]	25.91	5.70	27.20	5.49	26.52	5.62	0.79	1.08
Mood and Anxiety Symptom Questionnaire anhedonic depression subscale score[b–d]	43.12	6.62	44.14	4.68	43.61	5.78	25.35	6.91
Snaith-Hamilton Pleasure Scale (ordinal) score[b–d]	33.04	5.50	33.93	5.44	33.46	5.48	20.52	5.45
Mood and Anxiety Symptom Questionnaire anxious arousal subscale score[b–d]	17.56	5.48	18.49	6.43	18.00	5.95	10.81	0.98
Spielberger State-Trait Anxiety Inventory score[b–d]	46.90	10.80	48.56	10.61	47.68	10.7	23.84	4.43
Altman Self-Rating Mania Scale score	1.84	2.15	1.28	1.48	1.58	1.89	1.39	1.8
Reward task (reaction time) (ms)	732.00	203.73	686.14	246.45	710.3	225	672.2	241.7
Reward task (omission errors)	0.410	0.653	0.500	0.897	0.45	0.78	0.355	0.608

[a]The female/male ratio for the MDD_{100a} cohort, MDD_{100b} cohort, MDD_{200} cohort, and healthy comparison subjects is as follows: 52/26, 45/25, 98/50, and 19/12, respectively.

[b]Significant difference between cohort MDD_{100a} and comparison groups ($p<0.001$, t test).

[c] Significant difference between cohort MDD100b and comparison groups ($p<0.001$, t test).

[d] Significant difference between MDD200 and comparison groups ($p<0.001$, t test).