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Reward related ventral striatal activity and differential response to sertraline versus placebo in depressed individuals

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Abstract

Medications to treat major depressive disorder (MDD) are not equally effective across patients. Given that neural response to rewards is altered in MDD and given that reward-related circuitry is modulated by dopamine and serotonin, we examined, for the first time, whether reward-related neural activity moderated response to sertraline, an antidepressant medication that targets these neurotransmitters. 222 unmedicated adults with MDD randomized to receive sertraline (n=110) or placebo (n=112) in the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) study completed demographic and clinical assessments, and pre-treatment functional magnetic resonance imaging while performing a reward task. We tested whether an index of reward system function in the ventral striatum (VS), a key reward circuitry

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Supplementary information is available at MP's website.

region, moderated differential response to sertraline versus placebo, assessed with the Hamilton Rating Scale for Depression over 8 weeks. We observed a significant moderation effect of the reward index, reflecting the temporal dynamics of VS activity, on Week-8 depression levels (Fs≥9.67,ps≤0.002). Specifically, VS responses that were abnormal with respect to predictions from reinforcement learning theory were associated with lower Week-8 depression symptoms in the sertraline versus placebo arms. Thus, a more abnormal pattern of pre-treatment VS dynamic response to reward expectancy (expected outcome value) and prediction error (difference between expected and actual outcome), likely reflecting serotonergic and dopaminergic deficits, was associated with better response to sertraline than placebo. Pre-treatment measures of reward-related VS activity may serve as objective neural markers to advance efforts to personalize interventions by guiding individual-level choice of antidepressant treatment.

Trial Registration: NCT01407094; http://clinicaltrials.gov/show/NCT01407094

Introduction

Despite over 50 years of treatment development and dissemination, depression has risen to rank as the number one leading cause of disability worldwide[1]. On average, antidepressant medications, as with evidenced based psychotherapies, outperform placebo in alleviating depressive symptoms, but only approximately 50–60% of patients respond to treatments, and only approximately 35% remit[2]. Currently, choice of antidepressant treatment is not informed by identified neural pathologies, but is often based on trial and error, which can exacerbate patients' distress and raise costs[3]. Although clinical predictors of specific antidepressant treatments have been identified e.g.[4], findings have not been consistently replicated, underscoring the need to identify objective neurobiological predictors to inform understanding of the neural mechanisms underlying response to specific antidepressants, and help lead to more targeted, efficient, and effective treatments for individuals with major depressive disorder (MDD).

Using neuroimaging to examine how functioning in neural circuits underlying reward processing relates to treatment response is an especially promising approach, as this neural circuitry is well-delineated[5]. Key neural regions involved in reward processing are the ventral striatum (VS), responding to reward anticipation and receipt[6,7], medial prefrontal cortex, including ventromedial prefrontal cortex which encodes reward value[8], orbitofrontal cortex which processes specific reward features (e.g., sensory attributes)[9], ventrolateral prefrontal cortex which encodes the value of different decision-making options[10] and links stimulus representations to specific reward outcomes[11,12] and anterior cingulate cortical regions supporting reward-related effort-based decision making[13,14]. It is well established that reward circuitry is modulated not only by dopamine but also by serotonin[15,16], neurotransmitters targeted by antidepressants. Recent animal studies have, for example, underscored the role of serotonin in reward processing via dorsal raphe projections to the ventral tegmental area and VS[17]. Dorsal raphe nuclei serotonergic neurons also contribute to non-social reward behavior[18].

Many neuroimaging studies reported disrupted reward circuitry function in MDD[19,20], including specific functional abnormalities in the VS and medial prefrontal cortex[21,22], and

recent studies employed reinforcement learning models to further elucidate these abnormalities[23,24]. According to these models, the prediction of future reward is updated based on the difference between expected reward and actual reward outcome during learning (i.e., the prediction error; PE)[25]. PE signals are tracked in the VS[26] and, as learning proceeds, VS responding shifts from reward outcome to reward cues, consistent with conditioning. The rate of learning can differ between individuals, such that fast learners show a rapid transition from outcome-locked (i.e., PE) to cue-locked (i.e. reward expectancy; RE) responses, while slow learners show a slower transition. Across all individuals, this would manifest as an inverse relationship between RE and PE. In line with these reinforcement models and earlier work[27], we previously reported an inverse relationship between RE- and PE-related VS activity in healthy individuals, consistent with a shift in VS responding from PE to RE[28]. This relationship was absent in depressed individuals, suggesting a disruption in normative conditioning. We replicated these findings in separate cohorts of 31 healthy individuals and 148 unmedicated individuals with MDD in the EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) study, a multi-site, randomized, placebo-controlled trial of a selective serotonin reuptake inhibitor (SSRI), sertraline[29]. Further, we demonstrated in those healthy individuals the theoretically-predicted shift in VS response from PE to RE (i.e., an increase in RE and a decrease in PE-related activity) across two scans, separated by one week[30]. In both our prior study[28] and EMBARC cohorts[29], the temporal dynamics of RE and PE-related activity differentiated depressed and healthy individuals, but mean VS activity did not. Thus, an abnormal relationship between RE and PE-related VS activity may reflect an underlying pathophysiological process in MDD, which, in turn, may be associated with antidepressant treatment response.

Most treatment studies of neuroimaging markers in MDD have not examined reward paradigms, but rather included resting state or emotion-related paradigms and largely focused on frontolimbic regions involved in cognitive control and emotion processing[31–33]. Only two fMRI studies[34–36] examined the extent to which reward-related neural measures predict treatment response in MDD. Both focused on psychotherapies or psychotherapies combined with medications; neither was a randomized trial with a control condition; and both reported that patterns of VS and medial prefrontal cortical activity were associated with depressive symptom change following treatment.

There are two other limitations of extant neuroimaging studies of antidepressant response in MDD. First, the majority of studies reported on general prediction of treatment response (i.e., associations between pre-treatment measures and subsequent response, irrespective of which treatment was received), rather than on moderators of differential response (i.e., the degree to which scores from a pre-treatment measure are associated with superior response in one treatment condition versus another, typically indicated by a significant pre-treatment-measure-by-treatment-condition interaction effect)[37]. One study[38] did examine moderators of differential treatment response to escitalopram and CBT, using resting Positron Emission Tomography. Here, six regions moderated differential response between treatments, with the strongest pattern in the insula: insula hypermetabolism predicted better response to escitalopram and poorer response to CBT, whereas insula hypometabolism predicted the

opposite pattern. No study has examined whether measures of reward circuitry activity moderate response to antidepressant medications and/or psychotherapies in MDD.

A second limitation concerns the use of placebo. Placebo response in antidepressant trials is substantial, and there is some evidence that it has increased over time[39]. Given the cost and side effects of most prescribed antidepressant medications versus placebo[40], it is essential to identify markers (i.e., moderators) that predict differential response to active treatment versus placebo in order to identify individuals most likely to benefit from active medications. Yet, few previous neuroimaging-based treatment studies included a control condition of any sort, including placebo.

The current study examined whether the temporal dynamics of activity in reward circuitry moderated response to antidepressant medication versus placebo in MDD, using a well-validated monetary reward task used in studies of MDD[28,41]. Participants were individuals with MDD randomized to receive sertraline or placebo in EMBARC, who performed the reward task during functional magnetic resonance imaging (fMRI) prior to randomization.

For each participant, a specific reward index was computed to capture the hypothesized temporal dynamics of RE and PE-related VS activity during the task that are predicted from reinforcement learning models and our previous findings[28,29]. The reward index formula quantifies change in RE and PE-related activity from the 1st to 2nd half of the task with a higher score on this index reflecting a greater increase in neural response to RE and greater decrease in response to PE over the course of the task, associated with conditioning. Our main aim was to determine whether this index of baseline VS activity to reward moderated differential response to sertraline versus placebo, as measured by depressive symptoms at the end of the eight-week treatment course. VS activity is modulated by both serotonin and dopamine[15,16]. Furthermore, sertraline increases VS serotonin and dopamine levels[42]. We thus hypothesized that lower pre-treatment scores on the VS reward index, reflecting more abnormal response with respect to reinforcement learning theory in the serotonin- and dopamine-modulated VS, would be associated with better response to sertraline versus placebo after eight weeks of treatment. We also explored whether a reward index computed in other regions important for reward processing[28,43], and mean levels of activity in the VS and in regions identified in wholebrain analyses to RE and PE across the entire task, predicted or moderated differential response to sertraline versus placebo.

Methods

Participants

296 unmedicated depressed individuals with MDD were randomized to receive sertraline or placebo in the EMBARC study. A complete list of inclusion/exclusion criteria and description of the EMBARC study design and rationale have been previously reported[44].

The flow of participants is displayed in Figure 1 (see Supplementary Figure 1 for the study design). The final sample included 222 (148 females;mean age=36.5,SD=13.1) participants with baseline reward imaging data. The study was approved by the Institutional Review

Boards at each of the four recruitment sites, and all participants gave written informed consent.

Reward task

The task[41, 45] has been described in detail elsewhere[29] and is summarized in Supplementary Information.

Image Acquisition

Neuroimaging data were collected using 3 Tesla magnetic resonance imaging (MRI) scanners at all sites. Imaging parameters and preprocessing procedures are reported in Supplementary Information.

Image Analysis: First-level model

The first-level model included 17 regressors: response (4-second presentations of question mark), anticipation in the 1st half of the task and 2nd half of the task (6-second presentations of arrow), outcome in the 1st half of the task and 2nd half of the task (1 second presentations of the number and feedback arrow), and baseline (3-second presentation of orienting cross). Four additional regressors represented reward expectancy (1st half), reward expectancy (2nd half), prediction error (1st half), and prediction error (2nd half). The reward expectancy regressors, coupled to the anticipation phase, reflected the expected value (EV) of the arrow, set to +0.5 for the up arrow condition (given the 50% chance of winning $1) and to −0.25 for the down arrow condition (given the 50% chance of losing 50 cents). The prediction error regressors, coupled to the outcome, were determined by the difference between the outcome and the EV (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). The reward expectancy and prediction error regressors take into account all 24 trials of the task (12 for each half). To model omission errors, we included another regressor for trials in which a participant failed to respond, which lasted 17 seconds from the onset of the guessing phase of the trial (the question mark). This regressor replaced other trial events during this period. In addition, we included six motion regressors from the realignment phase.

Data Analysis

All analyses were intent-to-treat. The primary outcome measure was the 17-item version of the Hamilton Rating Scale for Depression 17-item (HRSD)[46], which was assessed at weeks 1, 2, 3, 4, 6 and 8. As in previous analyses of the EMBARC data[47], we analyzed HRSD data using multilevel linear models. With these models, growth curves and end-of-treatment (Week-8) depression scores are estimated from a combination of fixed and random effects. To optimally model the pattern of change over time, we examined linear, log-transformed, square-root transformed, and quadratic change trajectories. The best fitting model, determined by the Akaike Information Criteria, was the quadratic representation of time. As such, primary hypotheses focused on model-estimated depression scores at Week-8, and we report differences in the shape of the curvilinear trajectory in Supplementary Information. Intercepts, instantaneous slopes, and quadratic effects were included as random effects, and an unstructured covariance matrix was estimated to model the correlation among these

effects. Full maximum likelihood estimation was used for all models, and degrees of freedom for hypothesis tests were estimated with the Kenward-Roger approximation[48]. Our analytic approach simultaneously examined variables as potential general predictors of symptoms at Week-8 (evidenced by a significant association with estimated Week-8 depression scores, irrespective of treatment assignment) and as potential moderators of differential symptom reduction between sertraline and placebo (evidenced by a significant interaction between the variable and treatment group assignment on estimated Week-8 depression scores)[49]. Analyses were conducted with SAS Version 9.4 PROC MIXED (SAS Institute, Cary, NC).

Predictors and moderators of interest

The main variable of interest was a reward index that measured temporal change in RE and PE-related VS activity during the task. Higher scores on this index reflected a pattern of greater increase in neural response to RE and greater decrease in response to PE over the course of the task - the pattern predicted by reinforcement learning theory. We calculated a separate reward index for the right and left VS using the formula: [RE-related VS activity (2^{nd} half of task) - RE-related VS activity (1^{st} half of task)] + [PE-related VS activity (1^{st} half) - PE-related VS activity (2^{nd} half)]. We examined prediction effects of right and left VS activity related to this index on estimated Week-8 depression scores across sertraline and placebo groups, as well as reward-index-by-group interactions (i.e., moderator effects). We also examined prediction and moderation effects of right and left VS activity related to each separate sub-index (i.e., the RE and PE change components) of the reward index (see Supplementary Figure 2 for distribution histograms for the VS reward index and sub-indices). We used False Discovery Rate corrections[50–52] to control for multiple comparisons for all primary statistical analyses, correcting for a total of 20 tests (10 prediction effects and 10 moderation effects). Variability across sites was evaluated by examining whether the primary statistic of interest, the treatment-by-reward-index interaction, was itself significantly moderated by site and if it (the treatment-by-reward-index interaction) remained significant averaging across any observed site differences.

Secondary analyses examined prediction and moderation effects of the reward index (and RE and PE sub-indices) in additional regions important for reward processing[43,28] and of mean activity (i.e., across the 1^{st} and 2^{nd} half of the task) to RE and PE in the right and left VS, and in regions that emerged in exploratory whole brain (family-wise error correction $p<0.05$) analyses of mean activity to RE and PE (Supplementary Information).

In addition, we conducted exploratory logistic regression analyses of categorical response at Week-8 with reward indices × group interactions, and covariates as above (Supplementary Information).

Baseline demographic/clinical measure covariates

The following baseline measures were used as covariates, as in previous EMBARC studies[47]: 1) Randomization group (sertraline, placebo), 2) Site, 3) Race (Caucasian, non-Caucasian), 4) Sex, 5) Age, 6) Employment status, 7) Education (years), 8) Marital status, 9) Chronicity, 10) Anhedonia (The Snaith–Hamilton Pleasure Scale)[53], 11) Anxiety severity

(The Mood and Anxiety Symptom Questionnaire Anxious Arousal Scale)[54], and 12) Baseline HRSD.

Results

Demographic/Clinical Measures

Table 1 displays demographic and clinical measures for the sertraline (n=110) and placebo (n=112) groups. On average, participants were in their mid-thirties with a college education and moderate levels of depressive symptoms. Approximately two-thirds were Caucasian, two-thirds were female, the majority were single, and nearly 60% were employed. There were no significant group differences for any measures (all ps>0.05); however, we observed a statistically non-significant trend for a greater proportion of males in the placebo group (p=0.06). We observed no significant differences on any measures between the study sample (n=222) and individuals excluded from analysis (n=74;Supplementary Table 2). Sex was included as a covariate, as noted above.

Effects of right and left VS reward indices on Week-8 depression scores

We observed no evidence of a general predictor effect of VS reward index on Week-8 depression scores ($F_{(1,198)}$=0.31,p=0.58,right VS;$F_{(1,193)}$=0.53,p=0.47,left VS;Supplementary Table 3, Supplementary Table 4). We did observe that both the right ($F_{(1,198)}$=9.67,p=0.002) and the left ($F_{(1,193)}$=12.93,p=0.0004) VS reward index moderated treatment effects: lower reward index values were associated with lower estimated Week-8 scores in the sertraline versus placebo groups (Figure 2). The moderation effect of the reward index on the left did not differ significantly across the four sites, and it remained significant on average across any observed site differences (Supplementary Information). The same was not true of the reward index on the right (Supplementary Information) and will not be discussed further. On the left, the difference between sertraline and placebo was estimated to cross the National Institute for Clinical Excellence[55] threshold for a clinically significant difference (raw HRSD difference≥3 points) at an index level of z=−0.21 ($t_{(193)}$=2.38,p=0.02,d=0.32,95% CI:0.06–0.58) on the left (Figure 3a). Thus, patients below this threshold are expected to have a superior response to sertraline than to placebo, or the nonspecific effects of treatment. The lower a particular patient's index score is, the larger the expected advantage of the active medication, sertraline. By contrast, patients above the threshold are not expected to have a clinically meaningfully better response to the active ingredients of sertraline compared to the non-specific effects provided by placebo (Figure 3b).

Effects of the right and left VS reward expectancy (RE) sub-indices on Week-8 depression scores

We observed no evidence of a general predictor effect of VS RE sub-index on Week-8 depression scores ($F_{(1,192)}$≤0.01,p=0.96,right VS;$F_{(1,192)}$=0.44,p=0.51,left VS;Supplementary Table 5, Supplementary Table 6), but we observed a significant moderation effect for left VS RE sub-index ($F_{(1,192)}$=7.68,p=0.006;Figure 4) on estimated Week-8 depression scores and a moderation effect for the right that did not meet false discovery rate-corrected significance ($F_{(1,192)}$=6.16,p=0.014,FDR threshold:p=0.0139).

Focusing on the effect in the left VS, lower values on this sub-index were associated with lower Week-8 depression scores in the sertraline, relative to the placebo, group (Figure 4). As above, the moderation effect of the RE sub-index on the left did not differ significantly across the four sites, and it remained significant on average across any observed site differences (Supplementary Information). The difference between sertraline and placebo was estimated to cross the National Institute for Clinical Excellence[55] threshold for a clinically significant difference (raw HRSD difference≥3 points) at an RE sub-index level of z=−0.38 ($t_{(194)}$=2.31,p=0.02,d=0.31,95% CI:0.05–0.57) on the left (Figure 4).

Effects of the right and left VS prediction error (PE) sub-index on Week-8 depression scores

We observed no evidence of either a general predictor or moderation effect of right or left VS PE sub-index on estimated Week-8 depression scores (all *F*s≤2.76,all ps>0.098).

Effect of covariates

The moderation effects of the left VS reward index and left VS RE sub-index remained significant when excluding all covariates not significantly associated with our primary outcome of interest, estimated week-8 depression scores, for each index (Supplementary Tables 7-8).

Other regions

We observed no evidence of general predictor or moderation effects of reward index and RE and PE sub-indices related activity on Week-8 depression scores in any other regions of interest except for one predictor effect for the reward index in the right orbitofrontal cortex, which only just crossed the FDR-corrected significance threshold ($F_{(1,199)}$=6.28,p=0.013,FDR threshold:139; Supplementary Information).

Discussion

This is the first study to show that reward-related neural measures moderate response to an antidepressant relative to placebo in MDD. Specifically, an index of baseline activity in left VS, reflecting the extent to which changes in response to RE and PE during a monetary reward task followed the pattern predicted by reinforcement learning models, moderated response to sertraline versus placebo. Lower reward index values, reflecting more abnormal VS functioning, were associated with better response, i.e., lower depressive symptoms at Week-8, in the sertraline versus placebo group. Moreover, this effect was robust to different combinations of demographic and clinical covariates in statistical models.

Reward neural circuitry is well-delineated, modulated by dopamine and serotonin[15,16,17,18], as highlighted in the introduction, and associated with functional abnormalities in MDD[19]. Additionally, sertraline increases extracellular dopamine concentrations in the striatum[42]. While SSRIs may diminish dopaminergic activity, at least in the ventral tegmental area, through the inhibitory actions resulting from activation of serotonin receptors[56], sertraline may overcome these inhibitory effects on dopamine signaling, due to its greater affinity for dopamine transporters than other SSRIs[57]. Thus, abnormal patterns of bilateral RE- and PE-

related VS activity in MDD may reflect abnormally low pre-treatment serotonin and dopamine modulation of reward circuitry. Individuals showing greater pre-treatment magnitude of abnormalities in these regions during reward processing, specifically an absence of increases in RE-related and decreases in PE-related activity over time, may show better response to sertraline than placebo because of ameliorating effects of such medication on these neural abnormalities via changes in serotonin and dopamine levels in the VS. Moderator effects of reward index-related activity were specific to the VS and not observed in other regions implicated in reward processing. These findings suggest that abnormalities in pre-treatment serotonin and dopamine modulation may impact the VS in particular, and highlight the VS as a key region in which abnormal reward index-related activity may be a useful clinical moderator of differential treatment response.

Further analyses revealed that the left VS RE sub-index, with the right VS RE sub-index just missing the corrected significance threshold, but not the VS PE sub-indices, was a significant moderator of differential response to sertraline versus placebo. The VS RE sub-index in particular may reflect the extent of reward learning (i.e. conditioning) over the course of the task, as VS activity shifts to the expectancy rather than the outcome phase of the trial. For this reason, the VS RE sub-index may be a better moderator of response than the VS PE sub-index. Thus, abnormal serotonergic and dopaminergic modulation of VS activity may manifest as a failure to show an increase in RE-related VS activity over time, which sertraline may help ameliorate.

The inclusion of a placebo comparison was a critical feature of the study design because it allowed identification of neural marker moderators of differential response to a specific active medication, sertraline, versus placebo. Such markers are important because they point to potential neural mechanisms targeted by the medication, rather than mechanisms associated with nonspecific response to treatment in general. We hypothesized that a critical mechanism of action of sertraline may be to normalize reward circuitry activity for those depressed individuals who show serotonergically and dopaminergically-modulated abnormalities in the functioning of this circuitry at baseline. Future work can test this hypothesis directly, but, if confirmed, such findings would identify targets for guiding and potentially monitoring personalized treatments. Given that active treatments for depression are on average only modestly more efficacious than placebo[58], there is a critical need to identify such targets so that antidepressant treatments can be more effectively and efficiently prescribed to maximize response in individuals with MDD.

We excluded 74 of the 296 participants randomized. Data loss in this range is common in neuroimaging studies of acutely depressed individuals[38]. Importantly, we did not observe any differences between included and excluded groups on demographic or clinical measures. Only pre-treatment neural measures were examined. Although the within-session reward index used in the current study was formed on the basis of theoretical predictions and on observations in healthy individuals across separate scans, more work should validate and refine this measure to capture the precise dynamics of normative reward-related responding over time. Although the direction of the effect of interest was similar in both hemispheres, it was more robust in the left hemisphere. This may reflect the left hemisphere's role in encoding approach-related emotions[59], such as reward, but can be a focus of future studies.

Finally, whereas inclusion of a placebo condition is a strength, there was no active treatment comparator. A different treatment may be even more effective than sertraline for individuals showing abnormal reward-related neural function.

In summary, we observed a moderation effect of reward-related left VS activity on antidepressant response. Specifically, a more abnormal pre-treatment pattern of dynamic VS response to RE and PE, likely reflecting underlying deficits in serotonergic and dopaminergic neurotransmission, was associated with better response to sertraline versus placebo. These findings suggest that pre-treatment measures of individual-level reward-related neural activity, especially within the VS, have potential to serve as objective, neural markers to advance efforts to personalize interventions by guiding individual-level choice of antidepressant treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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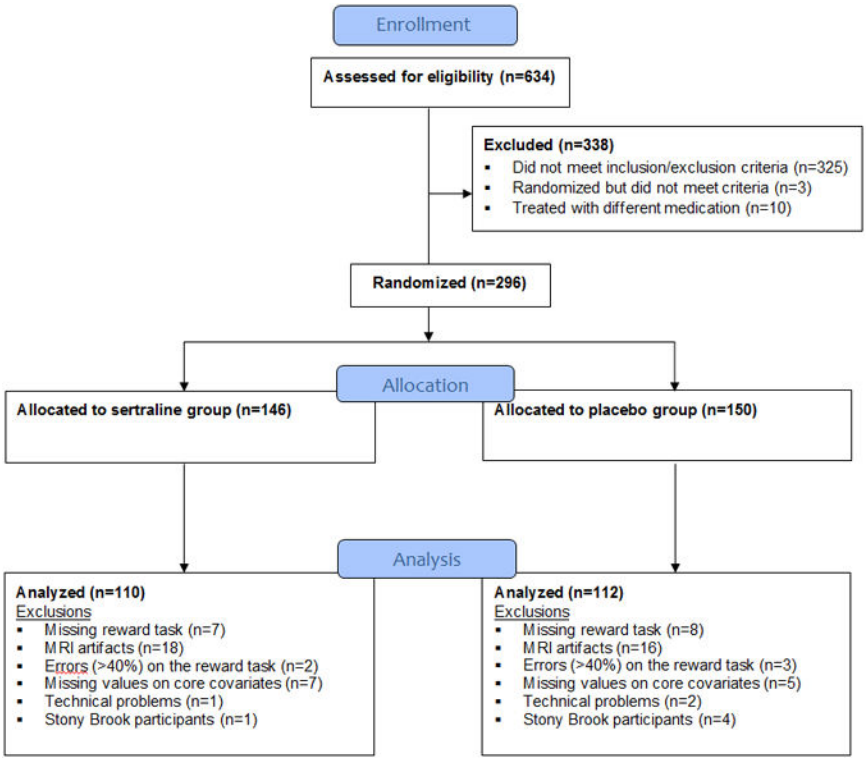

Figure 1. CONSORT Flow Diagram

Of the 296 participants randomized, 15 did not complete the reward task, 34 were excluded for severe artifacts in neuroimaging data acquisition (including motion, inhomogeneity, and ghosting), 12 were excluded due to missing values on core baseline covariates, 5 were excluded for large number of omission errors (> 40%) on the reward task, and 3 were excluded for technical problems. Five (n=5) individuals recruited at a separate clinical site (Stony Brook University) were excluded because the small sample size did not allow adequate control for possible site effects. The final sample included n=222.

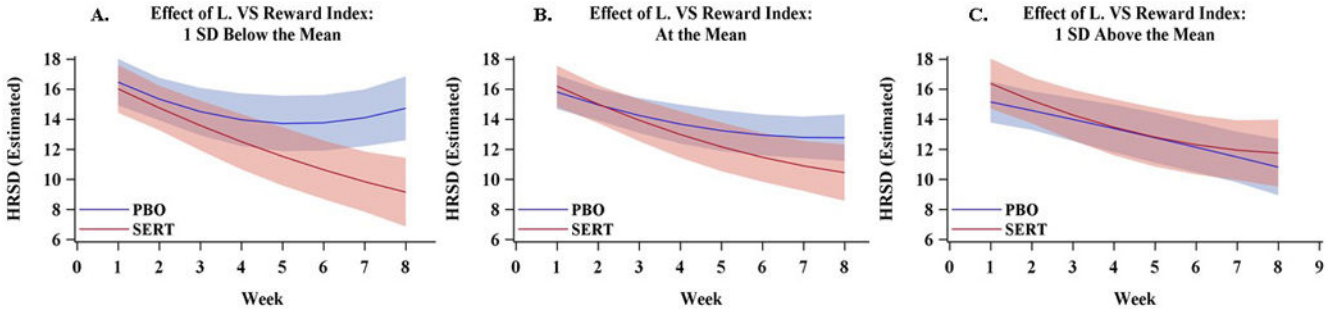

Figure 2. Estimated Depression Scores over Time as a Function of Treatment and the Left Ventral Striatal (VS) Reward Index.

Dark lines represent estimated Hamilton Rating Scale for Depression (HRSD) scores and cones represent 95% confidence intervals. Values were estimated from the primary multilevel statistical model at three levels of the left VS reward index, 1 SD below the mean (Panel A), the mean (Panel B), and 1 SD above the mean (Panel C).

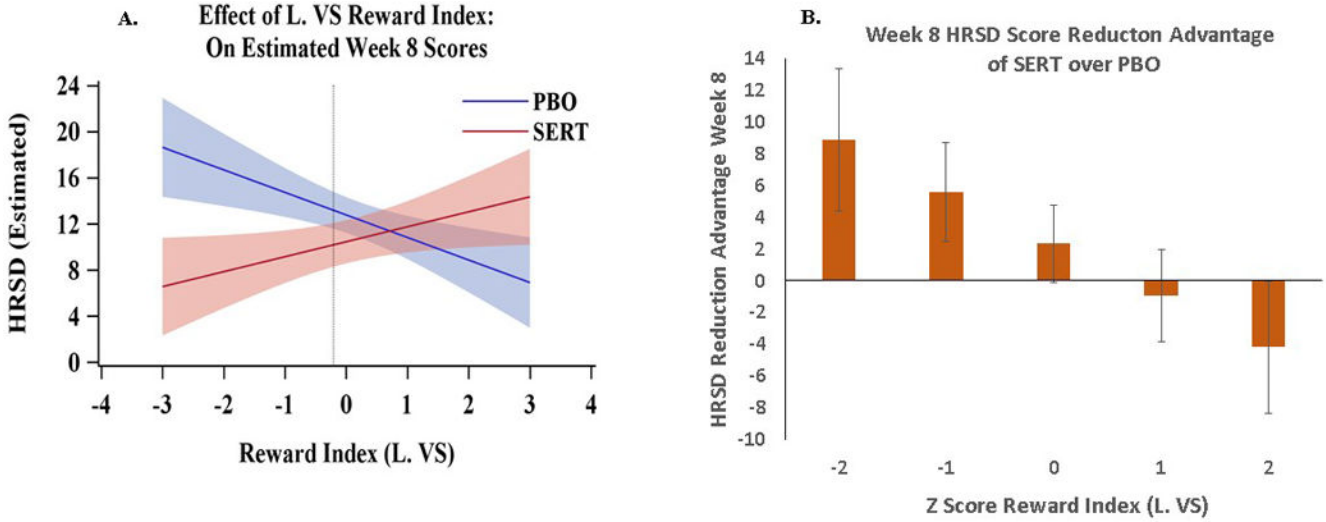

Figure 3. Difference in Estimated Week-8 Depression Scores between the Sertraline and Placebo Groups as a Function of Left Ventral Striatal (VS) Reward Index.

Panel A depicts the estimated Hamilton Rating Scale for Depression (HRSD) scores at Week-8 (y-axis) from across the full range of left VS index scores in the sample (x-axis). The dotted vertical line represents the point below which the sertraline (SERT) and placebo (PBO) difference crosses the NICE threshold for a clinically significant difference (HRSD > 3 points). Individuals below that cutoff are expected to respond better to sertraline than to placebo. Cones represent 95% confidence intervals. Panel B. Represents point estimates for the differences in Week 8 HRSD scores between sertraline and placebo at particular values of the reward index. Error bars represent 95% confidence intervals. This graph indicates, for example, that for a depressed individual with a pre-treatment ventral striatal reward index z score at −2 or below, there will be a likelihood of having an additional 8.8 point reduction in their HRSD score after 8 weeks of taking sertraline relative to those with the same z-score who received placebo.

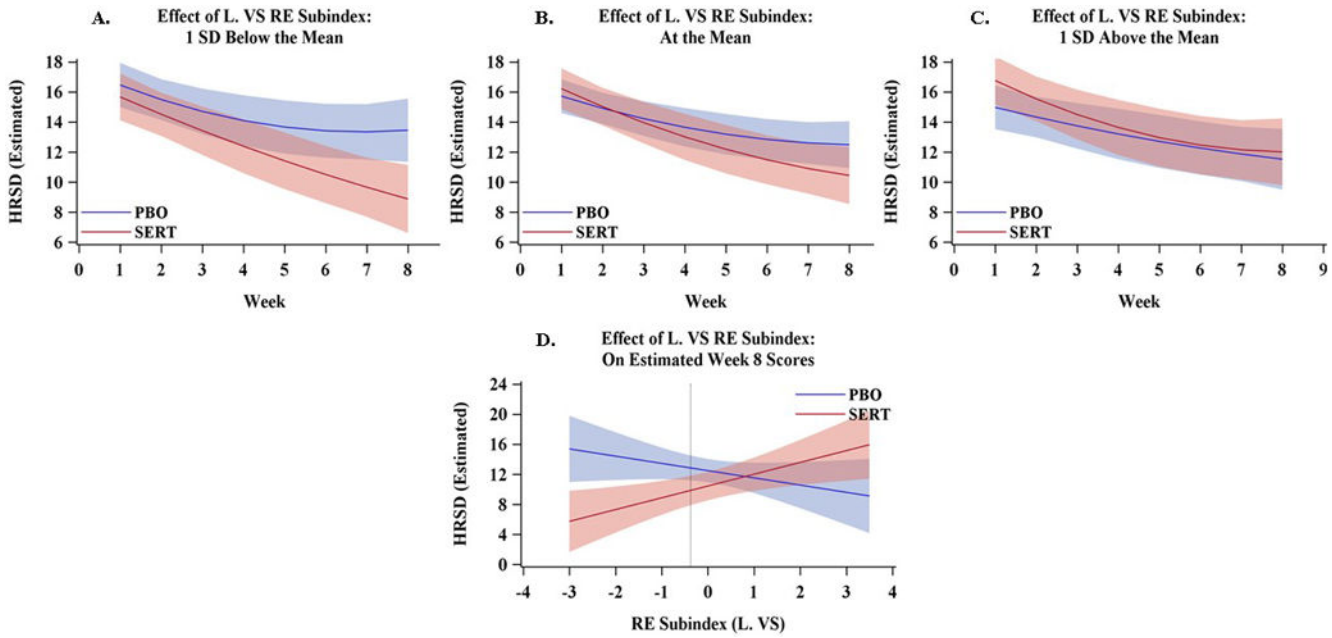

Figure 4. Estimated Depression Scores as a Function of Treatment and the Left Ventral Striatal (VS) Reward Expectancy (RE) Sub-index.

Dark lines represent estimated Hamilton Rating Scale for Depression (HRSD) scores and cones represent 95% confidence intervals. Values were estimated from the primary multilevel statistical model at three levels of the left RE sub-index, 1 SD below the mean (Panel A), the mean (Panel B), and 1 SD above the mean (Panel C). Panel D depicts the estimated HRSD scores at Week-8 (y-axis) from across the full range of left RE sub-index scores in the sample (x-axis). The dotted vertical line represents the point below which the sertraline (SERT) and placebo (PBO) difference crosses the NICE threshold for a clinically significant difference (HRSD ≥ 3 points).

Table 1.

Demographic and clinical measures for the sertraline and placebo groups.

	SERT (n=110)		PBO (n= 112)		Group comparison	
	Frequency	**Percent**	**Frequency**	**Percent**	**Statistic**	**P-value**
Sex (female/male)	80/30	73%/ 27%	68/44	61%/ 39%	$X^2(1)=3.6$	p=0.06
Employment (yes/no)	61/49	55%/ 45%	68/44	61%/ 39%	$X^2(1)=.63$	p=0.43
Marital status (yes/no)	19/91	17%/ 83%	28/84	25%/ 75%	$X^2(1)=1.99$	p=0.16
Race (Caucasian, non-Caucasian)	71/39	65%/ 35%	78/34	70%/ 30%	$X^2(1)=.65$	p=0.42
Chronicity (chronic/non-chronic)	55/55	50%/ 50%	57/55	51%/ 49%	$X^2(1)=.02$	p=0.89
	Mean	**SD**	**Mean**	**SD**		
Age	36.84	13.17	36.94	12.35	t(220)= −.06	p=0.95
Education (years)	14.96	2.68	15.29	2.74	t(220)= −.93	p=0.35
HRSD baseline	18.59	4.36	18.91	4.17	t(220)= −.56	p=0.58
SHAPS	33.65	5.17	32.75	5.64	t(220)= 1.25	p=0.21
MASQ-AA	17.82	5.89	17.01	5.22	t(220)= 1.08	p=0.28

HRSD = Hamilton Rating Scale for Depression; **SHAPS**= Snaith–Hamilton Pleasure Scale (the four response categories were coded as separate scores (ranging from 0 to 3); **MASQ-AA**= Mood and Anxiety Symptom Questionnaire Anxious Arousal Scale