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Pretreatment Reward Sensitivity and Frontostriatal Resting-State Functional Connectivity Are Associated With Response to Bupropion After Sertraline Nonresponse

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ABSTRACT

BACKGROUND: Standard guidelines recommend selective serotonin reuptake inhibitors as first-line antidepressants for adults with major depressive disorder, but success is limited and patients who fail to benefit are often switched to non–selective serotonin reuptake inhibitor agents. This study investigated whether brain- and behavior-based markers of reward processing might be associated with response to bupropion after sertraline nonresponse.

METHODS: In a two-stage, double-blinded clinical trial, 296 participants were randomized to receive 8 weeks of sertraline or placebo in stage 1. Individuals who responded continued on another 8-week course of the same intervention in stage 2, while sertraline and placebo nonresponders crossed over to bupropion and sertraline, respectively. Data from 241 participants were analyzed. The stage 2 sample comprised 87 patients with major depressive disorder who switched medication and 38 healthy control subjects. A total of 116 participants with major depressive disorder treated with sertraline in stage 1 served as an independent replication sample. The probabilistic reward task and resting-state functional magnetic resonance imaging were administered at baseline.

RESULTS: Greater pretreatment reward sensitivity and higher resting-state functional connectivity between bilateral nucleus accumbens and rostral anterior cingulate cortex were associated with positive response to bupropion but not sertraline. Null findings for sertraline were replicated in the stage 1 sample.

CONCLUSIONS: Pretreatment reward sensitivity and frontostriatal connectivity may identify patients likely to benefit from bupropion following selective serotonin reuptake inhibitor failures. Results call for a prospective replication based on these biomarkers to advance clinical care.

Keywords: Antidepressant response, Biomarkers, Bupropion, Frontostriatal connectivity, Reward sensitivity, Sertraline

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Major depressive disorder (MDD) is a debilitating and recurrent condition associated with substantial personal socioeconomic costs (1,2). Despite significant efforts, treatment of MDD remains imprecise and involves trial and error to determine the most effective approach. Findings from the STAR*D trial revealed that only about half of individuals with MDD responded (i.e., exhibited ≥50% reduction in depressive symptoms) to the selective serotonin reuptake inhibitor (SSRI) citalopram (3), and more than one third failed to respond to two or more antidepressants (4,5). The situation is even worse in primary care, where only ~30% respond to first-line antidepressants (6). To exacerbate these issues, it takes at least 4 weeks to evaluate the efficacy of an antidepressant. This can lead to lengthy treatment trials that are insufficient and unnecessary, thereby increasing patient morbidity, dropouts, and suicide risk.

This limited success partially stems from the fact that treatment selection is not based on identification of the underlying biomarker abnormality that reflects pathophysiology (7,8). Hence, some individuals with depression may benefit from SSRIs, while others might be better suited to other classes of medication. Identifying objective markers that reliably predict responses to different classes of antidepressants would critically help clinicians decide whether a particular medication might be suitable for the patient.

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Functional magnetic resonance imaging (fMRI) studies have reported that pretreatment activation to emotional stimuli in the anterior cingulate cortex (9) and amygdala (10), as well as to nonemotional stimuli in the frontocingulate (11–13) and parietal (14) regions, was associated with greater improvements in depressive symptoms on SSRIs (15). Moreover, a recent study found that connectivity within the cognitive control network during a response inhibition task differentially predicts response to sertraline and venlafaxine (16). Converging evidence from resting-state studies also suggests that increased pretreatment activity in the rostral anterior cingulate cortex (rACC) predicts treatment response across a variety of interventions, including multiple antidepressants (17,18). In addition, executive dysfunction, psychomotor slowing, and impaired memory at baseline have been linked to poor clinical outcome on various medications (19–31), although lack of replications exists (32–34). Finally, higher pretreatment levels of C-reactive protein (35), interleukin-17 (36), and platelet-derived growth factor (37) were associated with better improvement in depressive severity when treated with a combination of bupropion and escitalopram.

Despite these promising findings, two important gaps exist in prior literature. First, to the best of our knowledge, no study has examined brain–behavior factors associated with response to second-line antidepressants, especially after failing a full course of an SSRI. Current guidelines recommend SSRIs as first-line antidepressant treatments (38), but response rates are modest, and patients with depression who fail to benefit are often switched to non-SSRI agents (38–41). Previous studies have never explored whether pretreatment biological and behavioral markers can differentiate between responders to a second antidepressant, after failure on a pharmacologically distinct class of medication, and nonresponders resistant to both arms of treatment.

Second, alterations in the reward processing circuitry—modulated by dopamine and centered on the ventral striatum (VS) and medial prefrontal cortex—have been implicated in MDD (15,17,42–53). Emerging research also suggests that an impaired ability to respond to rewards is associated with anhedonia, a core feature of MDD (45,54,55). However, few studies have examined the degree to which markers of reward processing predict antidepressant response. A small open-label study in adolescents showed that pretreatment VS activity during reward anticipation was not linked to the severity of depressive symptoms after cognitive behavioral therapy or cognitive behavior therapy plus SSRI (56). The placebo-controlled Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial in unmedicated individuals with MDD also reported that pretreatment reward responsiveness did not associate with treatment outcome to the SSRI sertraline (57); however, better response to sertraline was linked to more abnormal VS temporal dynamics during a reward task (58). Given the key role of dopamine in reward processing (59,60), these previous findings raise the question of whether reward markers might be associated with response to dopaminergic (but not serotonergic-based) antidepressants, and if they are, which ones.

The current study sought to address the two aforementioned gaps in the context of the two-stage, double-blinded EMBARC study (61). A probabilistic reward task (PRT) was a priori selected to investigate response to bupropion, a noradrenaline/dopamine reuptake inhibitor. PRT reward responsiveness and resting-state fMRI data were collected at baseline of an 8-week clinical trial, where outpatients with recurrent and nonpsychotic MDD were randomized to receive sertraline or placebo (stage 1). Participants who achieved satisfactory response at the end of stage 1 continued on another 8-week course of the same intervention, while nonresponders were crossed over under double-blinded conditions. Thus, sertraline nonresponders received bupropion and placebo nonresponders received sertraline in stage 2. For comparison, baseline PRT and resting-state fMRI data were also collected from healthy control subjects.

Our goal was to examine whether neural and behavioral markers of reward processing were associated with response to secondary treatment by bupropion (after nonresponse to sertraline) and sertraline (after nonresponse to placebo). Based on the premise that dopaminergic blunting plays an important role in anhedonic phenotypes (62,63), we hypothesized that patients with more impaired reward responsiveness and resting-state functional connectivity (RSFC) within the reward circuit would disproportionally benefit from a dopaminergic antidepressant (bupropion) after failure to respond to an SSRI (sertraline), distinguishing them from nonresponders who were resistant to both classes of medication. In addition, we did not expect these reward markers to differentiate response to sertraline.

METHODS AND MATERIALS

Participants

The EMBARC trial recruited outpatients with MDD and healthy volunteers from Columbia University (New York), Massachusetts General Hospital (Boston), University of Texas Southwestern Medical Center (Dallas), and University of Michigan (Ann Arbor) between July 29, 2011, and December 15, 2015, after approval by the institutional review board of each site. All enrolled participants provided written informed consent and were 18 to 65 years old. Details of the study design and a list of inclusion/exclusion criteria can be found in Trivedi *et al.* (61).

Probabilistic Reward Task

The PRT assessed the ability to modulate behavior based on rewards received (55). On every trial, participants viewed one of two briefly presented (100 ms) and perceptually similar (11.5- vs. 13.0-mm lines) stimuli. Participants needed to indicate which stimulus was shown via a button press. Importantly, and unbeknownst to participants, a 3:1 reinforcement ratio was adopted such that correct responses to one stimulus were rewarded three times more frequently than to the other—a manipulation that induces a response bias (i.e., preference for the more frequently rewarded stimulus). Performance was analyzed in terms of response bias (objective measure of reward responsiveness) and discriminability (ability to distinguish between the stimuli). See Supplemental Methods for details.

Computational Modeling

To dissociate the influence of reward sensitivity (i.e., immediate behavioral impact of rewards) and learning rate (i.e., ability

to accumulate and learn from rewards over time) on PRT performance, 4 different models were fitted to participants' trial-by-trial data (64). Following previously established procedures, we used expectation maximization to derive group priors and used individual Laplace approximation of posterior distributions for parameter estimations for each participant. Models were compared using integrated group-level Bayesian information criterion factors. See Supplemental Methods for details.

Region of Interest

Analyses focused on voxelwise RSFC of a seed region of the bilateral nucleus accumbens (NACC), defined using the Automated Anatomical Labeling atlas (65). The NACC was selected because significant evidence has implicated this region as a key area in different aspects of reward processing (60), including reinforcement learning and reward anticipation (66–71), as well as acquisition and development of reward-based behavior (72–74). Moreover, the VS (which includes the NACC) contains widespread afferent connections to cortical regions that mediate reward processes such as the ventromedial prefrontal, orbitofrontal, and anterior cingulate cortices (60,75). Pharmacological challenge studies provide further support, showing that administering drugs that enhance ventrostriatal signaling improves reward learning, while disrupting phasic dopamine release causes an impairment (50,52). Collectively, these findings motivated us to focus on the NACC region of interest in the RSFC analyses.

MRI Acquisition and Analyses

Acquisition, Preprocessing, Head Motion and Artifact Detection, and Denoising. See Supplemental Methods.

First-Level Analysis. Fisher's *z*-transformed Pearson's correlation coefficient was computed between time course of the NACC seed and that of all other voxels. For each participant, this yielded a beta map containing, at each voxel, an estimate of the correlation in activity between the NACC seed and that voxel over the scan duration.

Group-Level Analyses. Group-level analyses were performed by entering first-level maps into a whole-brain analysis to test for an interaction between medication type (sertraline vs. bupropion) and response status (responders vs. nonresponders) in voxelwise NACC. The contrast was sertraline responder (−1), sertraline nonresponder (+1), bupropion responder (+1), bupropion nonresponder (−1). Scanner site and motion variables were included as covariates, but the inclusion of these covariates did not affect the significance of RSFC effects. Group-level effects were considered significant if they exceeded a peak amplitude of $p < .001$ (two-sided), cluster corrected to false discovery rate of $p < .05$.

Post Hoc RSFC Analyses. To interrogate the nature of group differences underlying significant interaction effects, RSFC estimates were extracted from clusters identified by voxelwise analysis using REX (https://www.nitrc.org/projects/rex/) (76). Then, RSFC in clusters of effect was compared between sertraline responders and nonresponders and between bupropion responders and nonresponders using independent *t* tests and effect size comparison. In addition, post hoc voxelwise analyses were performed comparing bilateral NACC RSFC of responders vs. nonresponders within each medication group.

Clinical Measure

The 17-item Hamilton Rating Scale for Depression (HAMD) (77) was administered at baseline, stage 1 (weeks 1, 2, 3, 4, 6, and 8), and stage 2 (weeks 9, 10, 12, and 16). Here, patients were defined as responders for each stage if they completed at least 4 weeks of treatment and showed a decrease in HAMD score of ≥50% at the last observation compared with when treatment started.

Statistical Analysis

We included participants who passed the PRT quality control criteria, were nonresponders to sertraline or placebo in stage 1, and completed ≥4 weeks of stage 2 treatment on bupropion (after switching from sertraline) or sertraline (after switching from placebo). Independent-samples *t* tests assessed whether responders and nonresponders to bupropion or sertraline differed in baseline HAMD, week 8 HAMD, and change in HAMD from baseline to week 8. Next, separate 2-way treatment (sertraline vs. bupropion) × response (responder vs. nonresponder) analyses of variance were run to evaluate pretreatment differences in response bias, discriminability, reward sensitivity and learning rate. Significant treatment × response interactions were followed by simple-effects analyses comparing responders and nonresponders to each treatment. $p < .05$ was taken to be statistically significant unless otherwise stated. Bayesian statistical analyses were also conducted using JASP (78) to complement classical statistics. The Bayes factor (BF_{10}) quantifies the amount of evidence in favor of the alternative hypothesis and generally (79), with $1 < BF_{10} < 3$ indicating anecdotal evidence, $3 < BF_{10} < 10$ indicating substantial evidence, $10 < BF_{10} < 30$ indicating strong evidence, $30 < BF_{10} < 100$ indicating very strong evidence, and $BF_{10} > 100$ indicating extreme evidence for the alternative hypothesis.

RESULTS

Participant Characteristics

Data from 241 participants were analyzed. A total of 87 patients had valid PRT data (84 of whom had valid MR data) and completed ≥4 weeks of stage 2 medication (Figure S1). Of these patients, 38 were nonresponders to sertraline in stage 1 and took bupropion in stage 2, while 49 were placebo nonresponders who switched to sertraline. In addition, 38 healthy control subjects were also analyzed. The clinical and demographic characteristics are reported in Table 1. In addition, we included a replication sample of 116 patients with MDD who had valid PRT data (112 of whom had valid MR data) and completed ≥4 weeks of sertraline treatment in stage 1 (Table S2). These participants served as an independent group to verify our stage 2 sertraline findings.

Table 1. Clinical and Demographic Characteristics of Stage 2 Sample

Variable	Healthy Control Subjects (n = 38)	MDD Patients (n = 87)	Bupropion			Sertraline		
			Responders (n = 16)	Nonresponders (n = 22)	p	Responders (n = 25)	Nonresponders (n = 24)	p
Age, Years, Mean (SD)	37.4 (14.9)	39.9 (13.8)	37.0 (14.6)	39.4 (15.1)	.63[a]	42.1 (11.9)	40.0 (14.5)	.57[a]
Women, n (%)	23 (60.5%)	56 (64.4%)	10 (62.5%)	17 (77.3%)	.32[b]	16 (64.0%)	13 (54.2%)	.48[b]
Education, Years, Mean (SD)	15.6 (4.5)	15.2 (2.6)	15.6 (2.0)	14.6 (3.0)	.28[a]	15.4 (2.6)	15.4 (2.5)	.93[a]
Age at MDD Onset, Years, Mean (SD)	–	16.1 (5.5)	14.1 (3.6)	16.3 (6.8)	.26[a]	16.4 (5.5)	17.0 (5.2)	.70[a]
Length of Current MDE, Median, Months	–	24	27	36	–	18	27	–
Prior MDEs, Median No.	–	5	5	6.5	–	6	3.5	–
Baseline HAMD Score, Mean (SD)	0.7 (0.8)	18.7 (4.1)	18.5 (4.0)	19.2 (4.6)	.62[a]	18.3 (4.6)	18.7 (3.2)	.74[a]
Week 4–8 HAMD Score,[c] Mean (SD)	–	16.7 (4.9)	17.1 (5.1)	16.7 (5.0)	.79[a]	16.9 (5.3)	16.2 (4.2)	.61[a]
Week 12–16 HAMD Score,[c] Mean (SD)	–	10.1 (6.2)	5.9 (3.3)	13.9 (4.5)	<.001[a]	5.8 (3.6)	13.9 (6.6)	<.001[a]
Baseline QIDS Score, Mean (SD)	1.4 (1.3)	18.3 (2.9)	19.6 (3.2)	18.3 (3.1)	.22[a]	17.7 (2.5)	18.1 (3.0)	.61[a]

p Values are comparisons between responders and nonresponders.

HAMD, 17-item Hamilton Rating Scale for Depression; MDD, major depressive disorder; MDE, major depressive episode; QIDS, Quick Inventory of Depressive Symptomatology.

[a] t test.

[b] χ^2 test.

[c] If patients completed at least 4 weeks of treatment but not the full 8-week course, we considered their last HAMD observation as the outcome of the treatment.

Pretreatment Response Bias Differentiated Responders to Bupropion After Failing Sertraline From Nonresponders Resistant to Both Classes of Medication

To investigate whether PRT response bias could differentiate between response to bupropion (after switching from sertraline) and response to sertraline (after previous nonresponse to placebo) in stage 2, we conducted a treatment (sertraline vs. bupropion) × response (responders vs. nonresponders) analysis of variance. Notably, the only significant effect to emerge was the treatment × response interaction ($F_{1,83}$ = 7.21, p < .01, η_p^2 = .080, BF_{10} = 5.27) (Figure 1A). Follow-up simple-effects tests revealed that eventual stage 2 bupropion responders had larger (rather than lower, as originally hypothesized) pretreatment response bias than nonresponders (p < .01, d = 0.90, BF_{10} = 15.57). Conversely, there was no difference between sertraline responders and nonresponders (p > .05, d = 0.26, BF_{10} = 0.38). We conducted a separate analysis including site as a covariate and obtained similar results. Control analyses using discriminability also showed no significant interaction or main effects, suggesting that findings were specific to response bias (see Supplemental Results). Moreover, bupropion responders exhibited comparable response bias scores as healthy control subjects (t_{52} = 1.17, p > .05, d = 0.35, BF_{10} = 0.51), but nonresponders had significantly lower response bias than healthy counterparts (t_{58} = −2.77, p < .01, d = 0.74, BF_{10} = 5.90). This suggests that individuals who eventually responded favorably to bupropion had normal reward responsiveness, whereas nonresponders did not.

Importantly, for each treatment, responders and nonresponders to bupropion or sertraline did not differ in HAMD at baseline (bupropion: t_{36} = 0.51, p > .05, d = 0.17, BF_{10} = 0.35; sertraline: t_{47} = 0.34, p > .05, d = 0.10, BF_{10} = 0.30) or week 8 (bupropion: t_{36} = −0.27, p > .05, d = 0.09, BF_{10} = 0.33; sertraline: t_{47} = −0.52, p > .05, d = 0.15, BF_{10} = 0.32) or in change in HAMD from baseline to week 8 (bupropion: t_{36} = −0.41, p > .05, d = 0.13, BF_{10} = 0.34; sertraline: t_{47} = −0.63, p > .05, d = 0.18, BF_{10} = 0.34) (Table 1). Thus, PRT findings were not influenced by differences in symptom severity at baseline or in stage 1, and baseline response bias distinguished stage 2 responders and nonresponders 12 to 16 weeks later.

Computational Modeling Revealed That Bupropion Responders Had Greater Reward Sensitivity, but Not Greater Learning Rate, Than Nonresponders

An analysis of variance revealed a significant treatment × response interaction for reward sensitivity ($F_{1,83}$ = 7.12, p < .05, η_p^2 = .079, BF_{10} = 5.15) (Figure 1B). Follow-up tests showed that eventual bupropion responders were more sensitive to rewards at the pretreatment session than nonresponders (p < .05, d = 0.87, BF_{10} = 7.48), whereas stage 2 sertraline responders and nonresponders did not differ (p > .05, d = 0.29, BF_{10} = 0.36). We also found that reward sensitivity for bupropion responders was similar to that for healthy volunteers (t_{52} = 0.82, p > .05, d = 0.26, BF_{10} = 0.39), but reward sensitivity for nonresponders was significantly lower than that for control subjects (t_{58} = −2.14, p < .05, d = 0.59, BF_{10} = 1.75). This suggests that patients who responded better to bupropion showed normative reward sensitivity. When

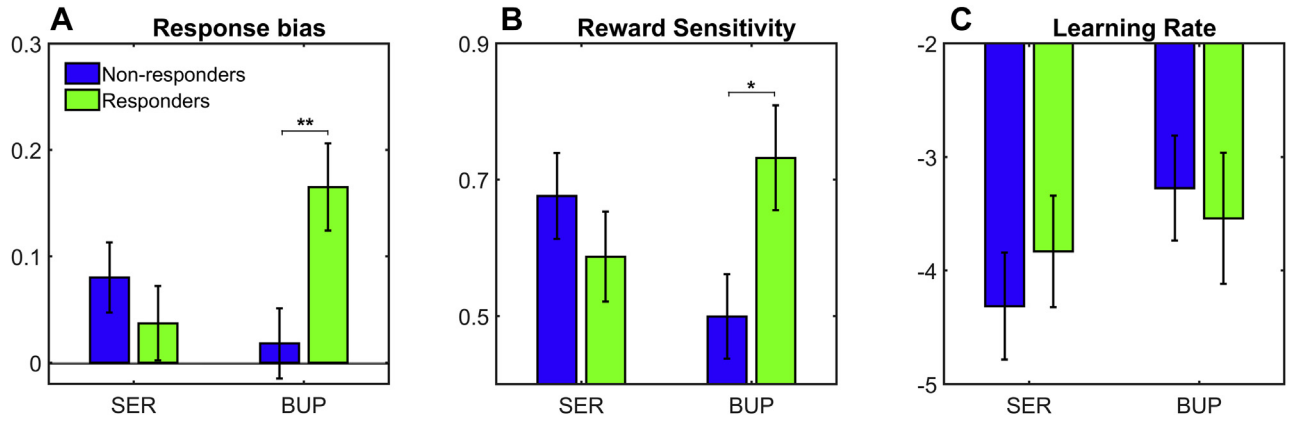

Figure 1. Comparison of response bias **(A)**, reward sensitivity **(B)**, and learning rate **(C)** for the probabilistic reward task at baseline. Bupropion (BUP) responders in phase 2 have significantly greater baseline (pretreatment) response bias and reward sensitivity, but not learning rate, compared with nonresponders. On the other hand, there was no difference on these metrics between responders and nonresponders to sertraline (SER). Note that the reward sensitivity and learning rate parameters have been transformed to prevent issues with non-Gaussianity. $^{*}p < .05$, $^{**}p < .01$.

considering learning rate, the treatment × response effect was not significant ($F_{1,83} = 0.55$, $p > .05$, $\eta_p^2 = .007$, $BF_{10} = 0.38$) (Figure 1C). Results remained significant when including site as a covariate (see Supplemental Results). Thus, the difference in response bias between bupropion responders and nonresponders was likely driven by variations in reward sensitivity rather than learning rate.

Higher RSFC Between NACC and rACC Was Associated With Better Response to Bupropion

Whole-brain analyses showed a significant interaction between medication type and medication response in RSFC between the bilateral NACC and a region of the rACC (cluster peak at Montreal Neurological Institute coordinates x = −6, y = 30, z = 12, maximum $t = 5.76$, $k = 170$ voxels, clustering threshold $p < .001$, false discovery rate $p < .05$) (Figure 2). Post hoc analyses indicated that among those assigned to bupropion, patients with higher NACC–rACC RSFC showed better treatment response than those with lower NACC–rACC RSFC ($t_{34} = 4.48$, $p < .01$, $d = 1.21$, $BF_{10} > 100$). There was also a significant positive correlation between reward sensitivity and NACC–rACC RSFC ($r = .22$, $p < .05$), indicating that individuals with greater frontostriatal connectivity were more sensitive to rewards.

Compared with healthy control subjects, bupropion responders had significantly larger NACC–rACC RSFC ($t_{51} = 3.64$, $p < .001$, $d = 1.05$, $BF_{10} = 44.25$), while that for nonresponders was lower at a trend level ($t_{55} = -1.84$, $p = .07$, $d = 0.51$, $BF_{10} = 1.10$). This suggests that patients who responded better to bupropion exhibited elevated NACC–rACC RSFC. Conversely, among individuals randomized to sertraline, patients with higher NACC–rACC RSFC showed poorer treatment response than those with lower NACC–rACC RSFC ($t_{46} = 4.48$, $p < .01$, $d = 0.93$, $BF_{10} = 37.47$). Sertraline responders also had lower NACC–rACC RSFC than healthy control subjects ($t_{60} = -3.70$, $p < .001$, $d = 0.97$, $BF_{10} = 58.92$), but there was no difference between nonresponders and control subjects ($t_{58} = 0.83$, $p > .05$, $d = 0.21$, $BF_{10} = 0.36$).

Of note, separate voxelwise analyses performed within each medication group converged with the full-group results and suggested that NACC–rACC RSFC was especially related to treatment response in the bupropion group. Within the bupropion group, those who responded to treatment showed higher NACC–rACC RSFC, and no other significant effects were observed across the brain; however, within the sertraline group, there were no significant differences in NACC RSFC across the brain (Figure 3).

Findings for Sertraline Were Replicated in an Independent Sample

Unique individuals were treated with sertraline in stage 1 versus stage 2. Hence, patients randomized to sertraline in stage 1 could serve as an independent sample to replicate results. Consistent with stage 2 findings, responders and nonresponders to sertraline in stage 1 did not differ in PRT response bias ($t_{114} = 0.24$, $p > .05$, $d = 0.04$, $BF_{10} = 0.23$), reward sensitivity ($t_{114} = -0.15$, $p > .05$, $d = 0.03$, $BF_{10} = 0.20$), or learning rate ($t_{114} = -0.58$, $p > .05$, $d = 0.11$, $BF_{10} = 0.27$). There was also no statistical difference in NACC–rACC RSFC between stage 1 responders and nonresponders to sertraline ($t_{110} = 1.53$, $p > .05$, $d = 0.29$, $BF_{10} = 0.57$).

No Difference in Dosage of Sertraline Received in Stage 1 by Eventual Bupropion Responders and Nonresponders

The mechanism of action of bupropion is postulated to be primarily related to the inhibition of the reuptake of both dopamine and norepinephrine (80). Conversely, sertraline typically inhibits the neuronal reuptake of serotonin—although it also shows relatively high affinity for the dopamine transporter. As such, it has been suggested that sertraline might inhibit the reuptake of dopamine, particularly at high doses of 200 mg and above (63). When evaluating sertraline doses in Stage 1 by patients who went on to receive bupropion in stage 2, we found that the average dose was well below 200 mg (mean = 118.3 mg, SD = 26.7, range = 57.1–155.2). Hence, it is

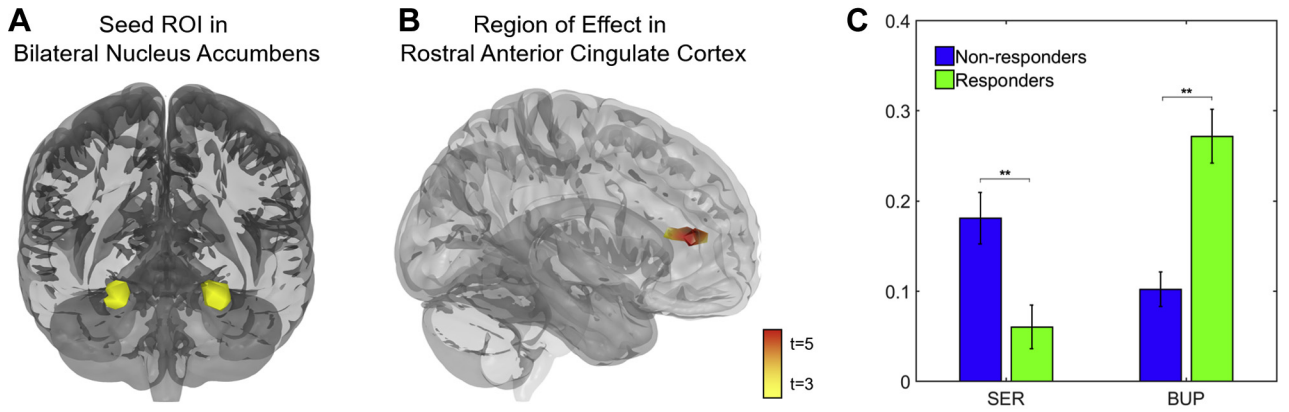

Figure 2. Baseline resting-state functional connectivity (RSFC) of bilateral nucleus accumbens (NACC) is associated with differential response to bupropion (BUP) compared with sertraline (SER). **(A)** Shown is the seed region of interest (ROI) in bilateral NACC, anatomically defined using the Automated Anatomical Labeling atlas. **(B)** The interaction between antidepressant type and response to treatment was associated with RSFC (Fisher's *z*-transformed Pearson's correlations across the full duration of the resting scan) between bilateral NACC and a region of rostral anterior cingulate cortex (rACC). **(C)** Patients randomized to bupropion for stage 2 who responded to treatment showed higher NACC–rACC RSFC before the onset of stage 1 than patients who failed to respond to bupropion, and this pattern also emerged in separate voxelwise analysis within the bupropion group (Figure 3). Patients randomized to sertraline who responded to treatment showed lower NACC–rACC RSFC than sertraline nonresponders, but this effect failed to emerge in separate voxelwise analyses within the sertraline group (Figure 3). Voxelwise analyses thresholded at peak $p < .001$ (two-sided), false discovery rate–corrected $p < .05$. $^{**}p < .01$.

difficult to disentangle the contributions of dopamine and norepinephrine to the efficacy of bupropion.

DISCUSSION

Treatment for MDD is challenging and often proceeds with SSRIs as first-line antidepressants (38). Unfortunately, treatment selection is not informed by biomarkers, response rates are modest, and patients with depression who do not benefit from an adequate trial of SSRIs are typically switched to non-SSRI agents (38–41). To the best of our knowledge, this is the first study to investigate behavioral and neural factors associated with response to the atypical antidepressant bupropion (which is assumed to increase dopaminergic and noradrenergic transmission) following a failure to respond to the serotonergic-based antidepressant sertraline.

Notably, we found that greater reward sensitivity and higher RSFC between the NACC and rACC distinguished bupropion responders, who previously failed to respond to sertraline, from nonresponders resistant to both classes of medication. Moreover, patients who responded better to bupropion had comparable reward sensitivity and potentiated NACC–rACC RSFC relative to healthy control subjects. In contrast, both reward sensitivity and NACC–rACC connectivity in bupropion nonresponders were lower than those in healthy volunteers. Our results cannot provide a mechanistic explanation, but we speculate that these might reflect compensatory mechanisms in depression, where elevated frontostriatal network functional connectivity is needed to respond normatively to reward.

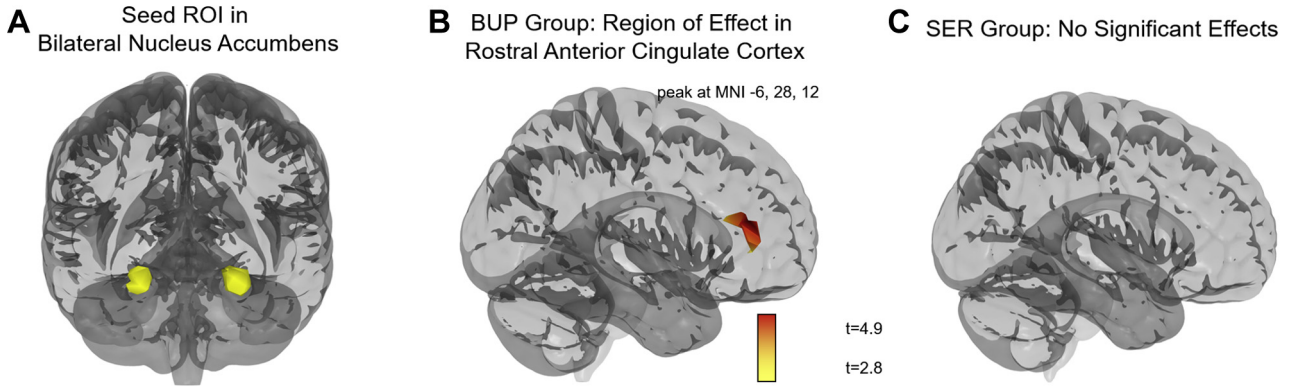

Figure 3. Voxelwise resting-state functional connectivity (RSFC) of bilateral nucleus accumbens (NACC) of responders vs. nonresponders within treatment groups. **(A)** Shown is the seed region of interest (ROI) in bilateral NACC, anatomically defined using the Automated Anatomical Labeling atlas. **(B)** Patients randomized to bupropion (BUP) who responded to treatment showed higher NACC–rACC RSFC than patients who failed to respond to BUP. **(C)** Among patients randomized to sertraline (SER), there was no difference in NACC RSFC between those who responded to treatment and those who failed to respond to treatment. Voxelwise static analyses thresholded at peak $p < .005$ (two-sided), false discovery rate–corrected $p < .05$. MNI, Montreal Neurological Institute; rACC, rostral anterior cingulate cortex.

Future studies are needed to test this hypothesis. Our findings also suggest that depressed individuals with more normative reward behavior and potentiated brain reward system responded better to bupropion after failing an 8-week treatment with sertraline. In contrast, we found that these reward markers were not associated with response to sertraline in stage 2 (after previous nonresponse to placebo) and replicated this null finding in an independent sample of patients randomized to sertraline in stage 1. These findings contrast with our original hypotheses, which were originally derived from the assumptions that 1) SSRIs poorly address anhedonic phenotypes (81) and 2) patients with behavioral and neural markers indexing blunted reward processing would disproportionally benefit from pharmacological treatment assumed to increase dopaminergic (and noradrenergic) transmission (62,63,82).

Although unexpected, our results are in line with earlier suggestions that patients with a subtype of depression characterized by preserved reward sensitivity may preferentially improve with dopaminergic pharmacotherapy (83) and recent reports that patients with MDD with more normative reward-related brain responses benefited the most from behavioral activation treatment (84,85). Moreover, a recent study found that depressed individuals with higher baseline response bias responded more favorably to treatment by pramipexole, a selective dopamine agonist (86,87). However, this latter study did not include placebo or nondopaminergic control. The current study demonstrated that better reward sensitivity and more positive RSFC among regions putatively involved in reward processing were associated with superior response to treatment by bupropion, one of the few antidepressants that prevent the reuptake of dopamine. In contrast, these effects were not found for the common SSRI sertraline.

Current results might have significant clinical implications. Although extant guidelines recommend SSRIs when starting treatment for MDD (38)—with sertraline being the most widely prescribed antidepressant in the United States (88) and Japan (89)—only 50% of patients benefit from them. A failure to respond to first-line antidepressants requires consideration of various second-line treatments, which include switching to a different medication, augmenting with a nonantidepressant drug, dose escalation, and a combination with a different antidepressant (38). However, there is no clear evidence for a particular strategy's being superior (40,41,90–101), and secondary treatment guidelines are needed (102). Although further scrutiny is required, our results suggest that laboratory-based paradigms such as the PRT and/or imaging might be useful in informing whether norepinephrine and dopamine reuptake inhibitors could be prescribed if first-line SSRIs are not beneficial. Individuals likely to be resistant to norepinephrine and dopamine reuptake inhibitors could be recommended alternative strategies, including augmentation, psychotherapy, and neurostimulation. Hence, a prospective replication based on these biomarkers could advance clinical care.

Limitations of this work should be acknowledged. First, although the sample size for stage 1 was large (N = 296), that for stage 2 was more modest with n = 38 bupropion patients (16 responders vs. 22 nonresponders) and n = 49 sertraline patients (25 responders vs. 24 nonresponders). Nevertheless, this is the first study to examine reward biomarkers of second-line antidepressant response and thus will be valuable in guiding future studies. Second, the EMBARC trial adopted relatively strict inclusion criteria to minimize clinical heterogeneity. Hence, it is unclear whether findings will generalize to other depressed samples such as those with psychotic features or comorbid substance abuse. Third, our results are not sufficient to provide any mechanistic explanation for why patients with intact reward processing systems respond more favorably to bupropion than those with impaired reward processing systems. Future, more mechanistic studies should investigate this.

Fourth, we have shown that reward sensitivity and frontostriatal connectivity distinguished between subjects who responded to bupropion but had failed to benefit from sertraline, and nonresponders resistant to both classes of medication. However, it remains to be investigated whether these reward markers might also differentiate responders to secondary treatment by placebo, given that nonresponders to sertraline in stage 1 of the EMBARC trial all were given bupropion rather than being randomized to bupropion or placebo. In other words, owing to the lack of placebo control subjects for the active treatments in stage 2, the specific secondary treatment effect of bupropion cannot be determined. This should be noted when interpreting our findings because of the considerable placebo response rate observed in stage 1. Nevertheless, the results of our study might still be useful in informing choice of second-line antidepressant when primary SSRI treatments fail, given that placebos are not prescribed in practice. Fifth, patients who received bupropion in stage 2 took sertraline in stage 1, while those in the sertraline group had previously been given placebo. While we confirmed that responders and nonresponders to secondary treatment with bupropion or sertraline did not differ in depressive symptomatology at baseline, as well as during and after stage 1, it is still possible that the baseline states prior to stages 1 and 2 may have been different. Sixth, unlike previous investigations such as the International Study to Predict Optimized Treatment in Depression (iSPOT-D) (103), measures in EMBARC were not collected posttreatment. Hence, it is unknown whether reward sensitivity and frontostriatal connectivity will change with treatment to bupropion as a function of response.

Conclusions

Using a multimodal approach, the current study showed that behavioral and neural markers of reward processing—specifically, computationally derived reward sensitivity and NACC–rACC connectivity—distinguished depressed individuals likely to benefit from a dopaminergic medication, following failure on SSRIs, and patients expected to be resistant to both classes of antidepressants. With further scrutiny, these findings could have important implications for clinical care.

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Pretreatment Reward Sensitivity and Frontostriatal Resting-State Functional Connectivity Are Associated With Response to Bupropion After Sertraline Non-Response

Supplemental Information

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Supplemental Methods

Probabilistic reward task

The probabilistic reward task (PRT) is a signal detection test that differentially rewarded correct responses in a 3:1 ratio, in order to assess the extent to which participants modulated their behavior as a function of reward (1,2). There were two blocks of 100 trials. On every trial, a fixation cross was first presented for 750–900ms. Participants then saw a mouthless face for 500ms, after which either a short (11.5mm) or long (13.0mm) mouth briefly appeared for 100ms. The mouthless face stayed on the screen until they identified which stimulus was presented by pressing either the 'c' or 'm' key on the keyboard. For every block, an equal number of short and long mouths was presented in a pseudo-randomized manner, with the constraint that the same stimulus was presented no more than three times consecutively.

To induce a response bias, an asymmetric 3:1 reinforcement ratio was employed. Correct identification of the short mouth was rewarded ("Correct!! You won 20 Cents") three times more frequently ("rich" stimulus) than correct identification of the long mouth ("lean" stimulus). Participants were informed at the beginning of the task that the purpose of the game was to win as much money as possible, but that not every correct response would yield reward feedback. Our main variable of interest, response bias, captured a participant's preference for the more frequently rewarded stimulus and was calculated as:

$$logb = \frac{1}{2} log \left[\frac{(\mathrm{Rich}_{\mathrm{correct}} + 0.5)(\mathrm{Lean}_{\mathrm{incorrect}} + 0.5)}{(\mathrm{Rich}_{\mathrm{incorrect}} + 0.5)(\mathrm{Lean}_{\mathrm{correct}} + 0.5)} \right]$$

where $\mathrm{Rich}_{\mathrm{correct}}$ and $\mathrm{Rich}_{\mathrm{incorrect}}$ refers to the number of correct and incorrect responses to the rich stimulus and, correspondingly, $\mathrm{Lean}_{\mathrm{correct}}$ and $\mathrm{Lean}_{\mathrm{incorrect}}$ to the lean stimulus. Discriminability between the two stimuli was computed as:

$$logd = \frac{1}{2} log \left[\frac{(\text{Rich}_{\text{correct}} + 0.5)(\text{Lean}_{\text{correct}} + 0.5)}{(\text{Rich}_{\text{incorrect}} + 0.5)(\text{Lean}_{\text{incorrect}} + 0.5)} \right]$$

Participants were excluded if any of the following quality control checks were not met: (1) <80 valid trials in each block (i.e., more than 20% outlier responses, as defined by RT <150ms or >2500ms and the log-transformed RT exceeding the participant's mean±3SD); (2) <20 rich rewards or <7 lean rewards in each block; (3) rich-to-lean reward ratio <2.0 in any block.

Computational modelling

Building on prior work (3), four reinforcement learning models that explicitly probe different hypotheses of how participants performed the PRT were considered.

The 'Belief' model proposed that participants associated rewards with a mixture of two stimulus-action associations weighted by an uncertainty factor. We write the probability of making a particular action with the softmax equation:

$$p(a_t|s_t) = \frac{1}{1 + e^{-(W_t(a_t,s_t) - W_t(\bar{a}_t,s_t))}}$$

where a_t and s_t refer, respectively, to the executed action and stimulus presented, and $\bar{a}_t$ and $\bar{s}_t$ to the alternative action and stimulus on trial *t*. Weights for the choices are given by W_t:

$$W_t(a_t, s_t) = \gamma I(a_t, s_t) + \varphi Q_t(a_t, s_t) + (1 - \varphi) Q_t(a_t, \bar{s}_t)$$

γ captures the participant's ability to follow instructions; I is a binary variable with value 1 if a_t is the instructed action for s_t and 0 otherwise; φ determines how certain the participant is about the identity of the presented stimulus; Q_t refers to the expected reward on trial *t* with initial value Q_0 and is updated on every trial as follows:

$$Q_{t+1}(a_t, s_t) = Q_t(a_t, s_t) + \varepsilon\big(\rho r_t - Q_t(a_t, s_t)\big)$$

r_t refers to the reward obtained on trial *t*, ε is learning rate and ρ indexes reward sensitivity.

Two other models are simpler variants of the 'Belief' model. In the 'Stimulus-Action' model, participants were assumed to treat both stimuli as entirely separate and associated rewards with stimulus-action pairs. In other words,

$$W_t(a_t, s_t) = \gamma I(a_t, s_t) + \varphi Q_t(a_t, s_t)$$

On the other hand, the 'Action' model assumed that participants neglected the stimuli and learned only the values of actions when forming expectations. Hence,

$$W_t(a_t, s_t) = \gamma I(a_t, s_t) + \frac{1}{2} Q_t(a_t, s_t) + \frac{1}{2} Q_t(a_t, \bar{s}_t)$$

Finally, the 'Punishment' model is a more complex variant of the 'Belief' model and tested whether participants treated zero reward as aversive losses by including an additional parameter ρ^- that indexes sensitivity to losses. This impacts the updating step:

$$Q_{t+1}(a_t, s_t) = Q_t(a_t, s_t) + \varepsilon\big(\rho r_t + \rho^-(1 - r_t) - Q_t(a_t, s_t)\big)$$

We fitted models by using expectation-maximization to derive group priors and individual Laplace approximation of posterior distributions for parameter estimations for each participant. Model comparison was then conducted using integrated group-level Bayesian Information Criterion factors (iBIC), which captures a trade-off between model fit and model complexity. Difference between any two models' iBIC values approximate the models' relative log Bayes factor and differences above 10 are considered to be strong evidence for one model over the other.

The 'Action' model gave the most parsimonious account of the data (group-level log Bayes factor compared to the second-best model = 51, which represents very strong evidence in favor of the better fitting model). This model has four parameters that were computed in the transformed space in order to prevent issues with non-Gaussianity: *reward sensitivity*, $\log \rho$, mean=0.62, SD=0.31; *learning rate*, $\log\left(\frac{\varepsilon}{1-\varepsilon}\right)$, mean=-3.77, SD=2.30; *instruction sensitivity*, $\log \gamma$, mean=0.15, SD=0.44; *initial bias*, Q_0, mean=-0.09, SD=0.12. The present study focused on the reward sensitivity and learning rate parameters.

Magnetic Resonance Imaging Acquisition and Analyses

MR Acquisition. Baseline MRI data, including a high-resolution T1-weighted anatomical scan and a six-minute eyes-open resting functional scan, were collected using 3T scanners from GE (Columbia University), Phillips (The University of Texas Southwestern Medical Center, University of Michigan), and Siemens (Massachusetts General Hospital) (see *Supplemental Table S1* for acquisition parameters). Resting-state functional data were collected with the same acquisition parameters across sites, immediately following the anatomical scan and prior to other functional scans. There were no auditory or visual stimuli presented during resting-state scanning.

***General image preprocessing*.** General preprocessing was performed using SPM12 and included slice-time correction, realignment, normalization in Montreal Neurological Institute (MNI) space, and smoothing with a 6-mm kernel.

Head motion and artifact detection. Motion correction and denoising procedures were performed as established in previous studies (4,5) and consistent with

recommendations in Power et al. (6). First, SPM12 was used to assess head motion by translation and rotation in *x, y, z* directions. Second, Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect/) were used to calculate time points of significant head motion or spikes in the magnetic field (>0.5 mm motion from previous frame, global mean intensity >3 SD from mean intensity across functional scans) for each participant. Any participant with >15% outlier volumes out of the resting-state scan series was excluded from group-level analyses. Third, the output from ART was included in each participant's first-level general linear model (see denoising, below) to censor outlier volumes. Finally, correlations were performed to compare composite estimates of motion outliers or framewise displacement against experimental variables in group-level analyses. Proportion of motion outliers was not significantly related to RSFC effects at the group level (r=-0.003, p=0.97).

***Denoising*.** Timeseries denoising was performed with the CONN toolbox (https://www.nitrc.org/projects/conn/) (7) and CompCor (8) to calculate physiological noise from cerebrospinal fluid and white matter for each participant using principal component analysis. The first five components were regressed out of each participant's functional data on the first level of analysis (along with motion and outlier regressors). Next, a band-pass filter of 0.009–0.10 Hz was applied to the time series with a range selected to remove high-frequency activity related to cardiac and respiratory activity and low-frequency activity related to scanner drift (<0.009 Hz) (9). These corrections yielded, at each voxel, a residual BOLD time course that was used for subsequent analyses.

Supplemental Figure S1. CONSORT Flow Diagram. Reasons for discontinuation at both stages are available in *Supplementary Tables S3* and *S4*.

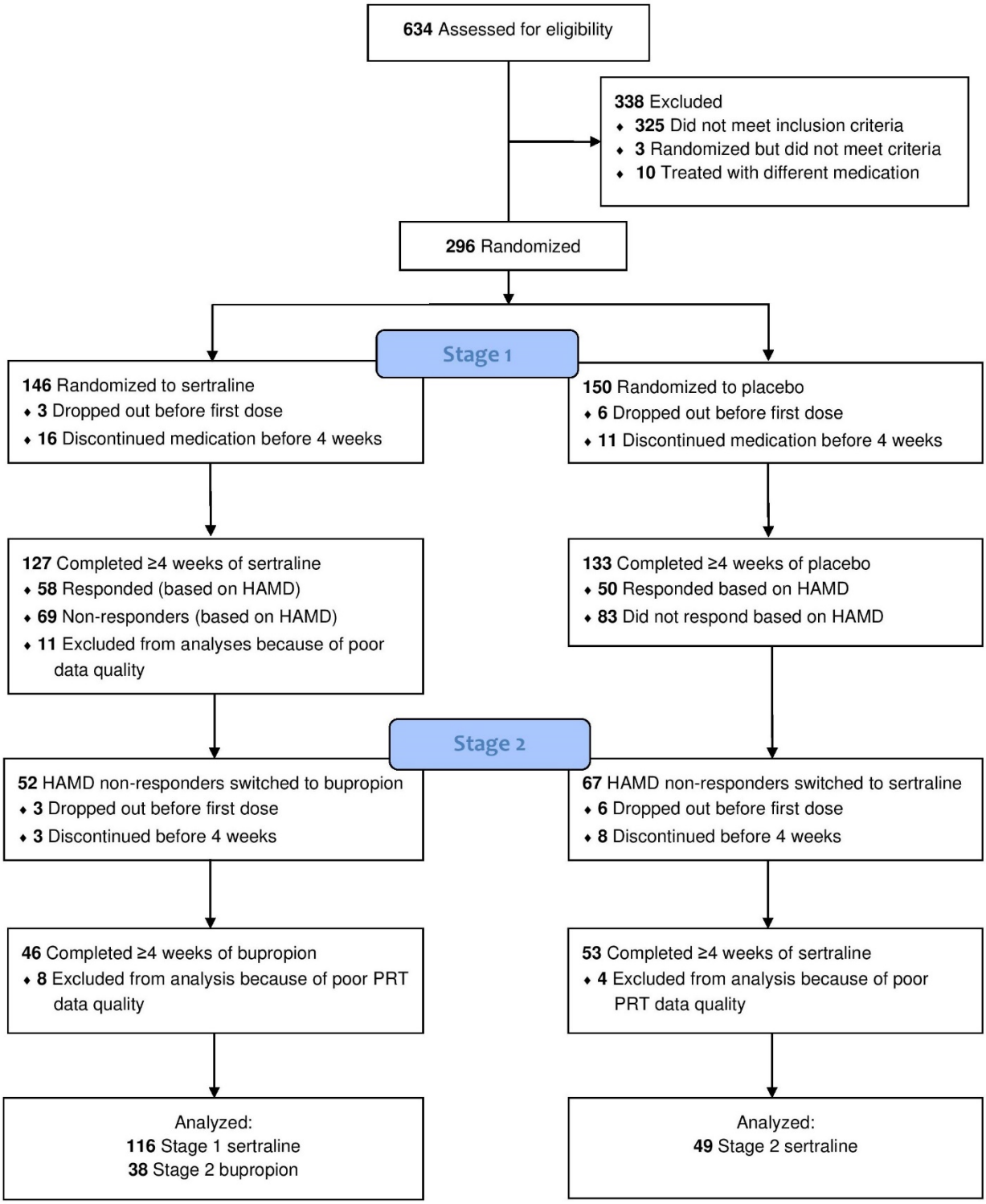

Table S1. Imaging acquisition parameters

	Columbia University	University of Texas	University of Michigan	Massachusetts General Hospital	Stony Brook University
Scanner	GE 3T	Philips 3T	Philips 3T	Siemens 3T	Siemens 3T
Anatomical (T1) Scan Parameters					
Sequence	IR FSPGR	MPRAGE	3D TFE	MPRAGE	MPRAGE
TR (ms)	6000	8000	8150	2300	2300
TE (ms)	2.4	3.7	3.74	2.49	2.54
Flip angle	9	12	12	9	9
# slices	178	178	178	176	176
FOV (mm)	256	256	256	256	256
Matrix	256 × 256	256 × 256	256 × 256	256 × 256	256 × 256
Voxel Size (mm^3)	1 × 1 × 1	1 × 1 × 1	1 × 1 × 1	1 × 1 × 1	1 × 1 × 1
Functional (BOLD) Scan Parameters					
Sequence	GE EPI	GE EPI	GE EPI	GE EPI	GE EPI
TR (ms)	2000	2000	2000	2000	2000
TE (ms)	28	28	28	28	28
Flip angle	90	90	90	90	90
# slices	39	39	39	39	39
FOV (mm)	205	205	205	205	205
Matrix	64 × 64	64 × 64	64 × 64	64 × 64	64 × 64
Voxel Size (mm^3)	3.2 × 3.2 × 3.2	3.2 × 3.2 × 3.2	3.2 × 3.2 × 3.2	3.2 × 3.2 × 3.2	3.2 × 3.2 × 3.2

	Columbia University	University of Texas	University of Michigan	Massachusetts General Hospital	Stony Brook University
Duration (s)	306	314	314	306	306
# volumes	180	180	180	180	183

Supplemental Results

Table S2. Clinical and demographic characteristics of replication sample

Variable	MDD patients	SER		
		Resp	Non-resp	*p*
N	116	54	62	-
Age, mean (SD), years	37.1 (13.8)	38.2 (13.6)	36.1 (14.1)	0.41[a]
Women, No. (%)	81 (69.8)	37 (68.5)	44 (71.0)	0.77[b]
Education, mean (SD), years	15.1 (2.5)	15.2 (2.2)	15.0 (2.7)	0.69[a]
Age at MDD onset, mean (SD), years	15.8 (5.8)	15.5 (6.0)	16.0 (5.7)	0.61[a]
Length of current MDE, median, months	21.5	11	25	-
No. of prior MDEs, median	5	4	5	-
Baseline HAMD score, mean (SD)	18.6 (4.4)	19.1 (4.1)	18.2 (4.6)	0.23[a]
[†]Week 4–8 HAMD score, mean (SD)	10.9 (6.9)	5.0 (3.0)	16.0 (5.1)	<.001[a]
Baseline QIDS score, mean (SD)	18.5 (3.0)	18.5 (3.0)	18.6 (2.9)	0.84[a]

Note: *p*-values are comparisons between responders and non -responders via [a]*t*-tests or [b]chi-square tests. [†]If patients completed at least 4 weeks of treatment but not the full 8-week course, we considered their last HAMD observation as the outcome of the treatment. Resp: Responders, Non-resp: Non-responders.

Table S3. Reasons for discontinuation before 4 weeks in Stage 1

Discontinued sertraline (*N*=16)	Discontinued placebo (*N*=11)
▪ Lost to follow-up (*N*=2)	▪ Moved from area (*N*=1)
▪ Non-adherent (*N*=4)	▪ Lost to follow-up (*N*=3)
▪ Found study too burdensome (*N*=3)	▪ Non-adherent (*N*=4)
▪ Wanted to discontinue medication (*N*=2)	▪ Wanted to discontinue medication (*N*=1)
▪ Believe treatment not working (*N*=1)	▪ Believe treatment not working (*N*=2)
▪ Side effects unacceptable (*N*=8)	▪ Side effects unacceptable (*N*=1)
▪ Developed medical condition (*N*=1)	▪ Other reasons (*N*=3)
▪ Other reasons (*N*=3)	

Note: Numbers add up to more than total because some patients discontinued for more than one reason.

Table S4. Reasons for discontinuation before 4 weeks in Stage 2

Discontinued bupropion (*N*=6)	Discontinued sertraline (*N*=14)
▪ Lost to follow-up (*N*=2)	▪ Moved from area (*N*=1)
▪ Non-adherent (*N*=2)	▪ Lost to follow-up (*N*=4)
▪ Other reasons (*N*=3)	▪ Non-adherent (*N*=2)
	▪ Found study too burdensome (*N*=1)
	▪ Wanted to discontinue medication (*N*=2)
	▪ Believe treatment not working (*N*=1)
	▪ Side effects unacceptable (*N*=2)
	▪ Hospitalized for suicidal ideation (*N*=1)
	▪ Other reasons (*N*=2)

Note: Numbers add up to more than total because some patients discontinued for more than one reason.

Effect of Treatment x Response on response bias after covarying for site

Given the multisite nature of this study, we conducted an ANCOVA to examine whether PRT response bias still differentially predicted response to bupropion (after switching from sertraline) or sertraline (after previous non-response to placebo) when including site as a covariate. Similar to the findings reported in the main text, there was a significant *Treatment* x *Response* interaction ($F(1,80)=6.23$, $p<0.05$, $\eta_p^2=0.072$, $BF_{10}=4.20$). Post-hoc comparison tests revealed that bupropion responders had larger pretreatment response bias than non-responders ($p<0.05$, Cohen's $d=0.75$, $BF_{10}=7.30$), but there was no difference between sertraline responders and non-responders ($p>0.05$, Cohen's $d=0.32$, $BF_{10}=0.42$).

Effect of Treatment x Response on reward sensitivity and learning rate after covarying for site

Similar to what reported in the main text, we found a significant *Treatment* x *Response* interaction for reward sensitivity when including site as a covariate ($F(1,80)=6.01$, $p<0.05$, $\eta_p^2=0.070$, $BF_{10}=3.33$). Follow-up tests revealed that bupropion responders exhibited greater sensitivity to reward than non-responders ($p<0.05$, Cohen's $d=0.92$, $BF_{10}=12.22$), but that between sertraline responders and non-responders did not differ ($p>0.05$, Cohen's $d=0.15$, $BF_{10}=0.29$). In contrast, ANCOVA on learning rate found no statistical significance for the interaction effect of Treatment*Response ($F(1,80)=0.76$, $p>0.05$, $\eta_p^2=0.009$, $BF_{10}=0.41$).

Effect of Treatment x Response on discriminability after covarying for site

As reported in the main text, an ANOVA revealed that there was no significant *Treatment* x *Response* interaction for discriminability ($F(1,83)=0.86$, $p>0.05$, $\eta_p^2=0.010$, $BF_{10}=0.42$). This was the same when including site as a covariate ($F(1,80)=0.49$, $p>0.05$, $\eta_p^2=0.006$, $BF_{10}=0.41$), suggesting that the findings were specific to response bias.

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