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Pretreatment reward sensitivity and frontostriatal resting-state functional connectivity are associated with response to bupropion after sertraline non-response

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Abstract

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Background—Standard guidelines recommend selective serotonin reuptake inhibitors (SSRIs) as first-line antidepressants for adults with Major Depressive Disorder (MDD), but success is limited and patients who fail to benefit are often switched to non-SSRI 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 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care), 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 non-responders crossed-over to bupropion and sertraline, respectively. Data from 241 participants were analyzed. The Stage 2 sample comprised 87 MDD patients who switched medication and 38 healthy controls. 116 MDD participants 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, as well as 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.

Conclusion—Pretreatment reward sensitivity and frontostriatal connectivity may identify patients likely to benefit from bupropion following SSRI failures. Results call for a prospective replication based on these biomarkers to advance clinical care.

Trial registration—clinicaltrials.gov Identifier: NCT01407094

Keywords

Biomarkers; antidepressant response; sertraline; bupropion; reward sensitivity; frontostriatal connectivity

Introduction

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 over 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 four weeks to evaluate the efficacy of an antidepressant. This can lead to lengthy treatment trials that are insufficient and unnecessary, thereby increasing patient morbidity, drop-outs 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 depressed individuals 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.

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 non-emotional stimuli in frontocingulate (11–13) and parietal regions (14), were 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). Additionally, 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 plus 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 SSRI. Current guidelines recommend SSRIs as first-line antidepressant treatments (38), but response rates are modest and depressed patients 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 non-responders 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 (mPFC) – 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 (CBT) or CBT plus SSRI (56). The placebo-controlled Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial in unmedicated MDD individuals 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 beg the question of whether, and if so, which reward markers might be associated with response to dopaminergic (but not serotonergic-based) antidepressants.

The present 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 non-psychotic 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 non-responders were crossed over under double-blinded conditions. Thus, sertraline non-responders received bupropion, and placebo non-responders received sertraline in Stage 2. For comparison, baseline PRT and resting-state fMRI data were also collected from healthy controls.

Our goal was to examine whether neural and behavioral markers of reward processing were associated with response to secondary treatment by bupropion (after non-response to sertraline) and sertraline (after non-response 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 within the reward circuit would disproportionally benefit from a dopaminergic antidepressant (bupropion), after failure to respond to an SSRI (sertraline), and distinguish them from non-responders who were resistant to both classes of medication. Also, we did not expect these reward markers to differentiate response to sertraline.

Methods and Materials

Participants

The EMBARC trial recruited MDD outpatients 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 aged between 18–65 years old. Details of the study design and list of inclusion/exclusion criteria can be found in (61)

Probabilistic Reward Task

The probabilistic reward task (PRT) assessed the ability to modulate behavior based on rewards received (55). On every trial, participants viewed one of two briefly presented (100ms) and perceptually similar stimuli (11.5mm vs. 13.0mm lines). Participants had 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 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 modelling

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, four different models were fitted to participants' trial-by-trial data (64). Following previously established procedures, we used expectation-maximization to derive group priors and 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 resting-state functional connectivity (RSFC) of a seed region of bilateral nucleus accumbens (NACC), defined using the AAL 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 ventral striatum (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 the administration of 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 ROI in the RSFC analyses.

Magnetic Resonance Imaging 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 timecourse 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. non-responders) in voxelwise NACC. The contrast was sertraline responder (−1), sertraline non-responder (+1), bupropion responder (+1), bupropion non-responder (−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 $p<0.001$ (two-sided), cluster corrected to false discovery rate (FDR) of $p<0.05$.

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 vs. non-responders, and

between bupropion responders vs. non-responders, using independent t-tests and effect sizes comparison. Additionally, post-hoc voxelwise analyses were performed comparing bilateral NACC RSFC of responders vs. non-responders within each medication group.

Clinical Measure

***17-item Hamilton Rating Scale for Depression (HAMD)* (77):** The HAMD 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 to when treatment started.

Statistical Analysis

We included participants who passed the PRT quality control criteria, were non-responders 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 non-responders to bupropion or sertraline differed in baseline HAMD, week 8 HAMD and change in HAMD from baseline to week 8. Next, separate two-way *Treatment* (sertraline vs. bupropion) × *Response* (responder vs. non-responder) ANOVAs were run to evaluate pretreatment differences in response bias, discriminability, reward sensitivity and learning rate. Significant *Treatment* × *Response* interactions were followed up with simple effects analyses comparing responders and non-responders to each treatment. $P<0.05$ 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 (H_1) and generally (79): $1<BF_{10}<3$ indicates anecdotal evidence, $3<BF_{10}<10$ indicates substantial evidence, $10< BF_{10}<30$ indicates strong evidence, $30<BF_{10}<100$ indicates very strong evidence and $BF_{10}>100$ indicates extreme evidence for H1.

Results

Participant characteristics

Data from 241 participants were analyzed. 87 patients had valid PRT data (of which 84 had valid MR data) and completed ≥4 weeks of Stage 2 medication (Supplemental Fig. 1). Thirty-eight were non-responders to sertraline in Stage 1 and took bupropion in Stage 2, while 49 were placebo non-responders who switched to sertraline. Thirty-eight healthy controls were also analyzed. The clinical and demographic characteristics are reported in Table 1. In addition, we included a replication sample of 116 MDD patients who had valid PRT data (of which 112 had valid MR data) and completed ≥4 weeks of sertraline treatment in Stage 1 (Supplemental Table S2). These participants served as an independent group to verify our Stage 2 sertraline findings.

Pretreatment response bias differentiated responders to bupropion after failing sertraline from non-responders resistant to both classes of medication

To investigate whether PRT response bias could differentiate between response to bupropion (after switching from sertraline) and sertraline (after previous non-response to placebo) in Stage 2, we conducted a *Treatment* (sertraline vs. bupropion) × *Response* (responders vs. non-responders) ANOVA. Notably, the only significant effect to emerge was the *Treatment* × *Response* interaction ($F(1,83)=7.21$, $p<0.01$, $\eta_p^2=0.080$, $BF_{10}=5.27$) (Fig. 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 non-responders ($p<0.01$, $d=0.90$, $BF_{10}=15.57$). Conversely, there was no difference between sertraline responders and non-responders ($p>0.05$, $d=0.26$, $BF_{10}=0.38$). 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 (Supplemental Results). Moreover, bupropion responders exhibited comparable response bias scores as healthy controls, ($t(52)=1.17$, $p>0.05$, $d=0.35$, $BF_{10}=0.51$) but non-responders had significantly lower response bias than healthy counterparts ($t(58)=-2.77$, $p<0.01$, $d=0.74$, $BF_{10}=5.90$). This suggests that individuals who eventually responded favorably to bupropion had normal reward responsiveness, whereas non-responders did not.

Importantly, for each treatment, responders and non-responders to bupropion or sertraline did not differ in HAMD at baseline (BUP: $t(36)=0.51$, $p>0.05$, $d=0.17$, $BF_{10}=0.35$; SER: $t(47)=0.34$, $p>0.05$, $d=0.10$, $BF_{10}=0.30$) and Week 8 (BUP: $t(36)=-0.27$, $p>0.05$, $d=0.09$, $BF_{10}=0.33$; SER: $t(47)=-0.52$, $p>0.05$, $d=0.15$, $BF_{10}=0.32$), and change in HAMD from baseline to Week 8 (BUP: $t(36)=-0.41$, $p>0.05$, $d=0.13$, $BF_{10}=0.34$; SER: $t(47)=-0.63$, $p>0.05$, $d=0.18$, $BF_{10}=0.34$, Table 1). Thus, PRT findings were not influenced by differences in symptom severity at baseline or during Stage 1, and baseline response bias distinguished Stage 2 responders and non-responders 1216 weeks later.

Computational modelling revealed that bupropion responders had greater reward sensitivity, but not learning rate, than non-responders

An ANOVA revealed a significant *Treatment* × *Response* interaction for reward sensitivity ($F(1,83)=7.12$, $p<0.05$, $\eta_p^2=0.079$, $BF_{10}=5.15$, Fig. 1B). Follow-up tests showed that eventual bupropion responders were more sensitive to rewards at the pretreatment session than non-responders ($p<0.05$, $d=0.87$, $BF_{10}=7.48$), whereas Stage 2 sertraline responders and non-responders did not differ ($p>0.05$, $d=0.29$, $BF_{10}=0.36$). We also found that reward sensitivity for bupropion responders was similar to healthy volunteers ($t(52)=0.82$, $p>0.05$, $d=0.26$, $BF_{10}=0.39$), but that for non-responders was significantly lower than controls ($t(58)=-2.14$, $p<0.05$, $d=0.59$, $BF_{10}=1.75$). This suggests that patients who responded better to bupropion showed normative reward sensitivity. When considering learning rate, the *Treatment* × *Response* effect was not significant ($F(1,83)=0.55$, $p>0.05$, $\eta_p^2=0.007$, $BF_{10}=0.38$, Fig. 1C). Results remained significant when including site as a covariate (Supplemental Results). Thus, the difference in response bias between bupropion responders and non-responders was likely driven by variations in reward sensitivity, rather than learning rate.

Higher resting-state functional connectivity between nucleus accumbens and rostral anterior cingulate cortex was associated with better response to bupropion

Whole-brain analyses showed a significant interaction between medication type and medication response in RSFC between bilateral NACC and a region of rostral anterior cingulate cortex (rACC; cluster peak at MNI coordinates −6, 30, 12, maximum t=5.76, k=170 voxels, clustering threshold p<0.001 FDR p<0.05, Fig. 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<0.01, d=1.21, BF_{10}>100). There was also a significant positive correlation between reward sensitivity and NACC-rACC RSFC (r=0.22, p<0.05), indicating that individuals with greater frontostriatal connectivity were more sensitive to rewards.

Compared to healthy controls, bupropion responders had significantly larger NACC-rACC RSFC (t(51)=3.64, p<0.001, d=1.05, BF_{10}=44.25) while that for non-responders were lower than controls at a trend level (t(55)=−1.84, p=0.07, 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<0.01, d=0.93, BF_{10}=37.47). Sertraline responders also had lower NACC-rACC RSFC than healthy controls (t(60)=−3.70, p<0.001, d=0.97, BF_{10}=58.92), but there was no difference between non-responders and controls (t(58)=0.83, p>0.05, 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 (Fig. 3).

Findings for sertraline were replicated in an independent sample

Unique individuals were treated with sertraline in Stages 1 vs. 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 non-responders to sertraline in Stage 1 did not differ in PRT response bias (t(114)=0.24, p>0.05, d=0.04, BF_{10}=0.23), reward sensitivity (t(114)= −0.15, p>0.05, d=0.03, BF_{10}=0.20) or learning rate (t(114)=−0.58, p>0.05, d=0.11, BF10=0.27). There was also no statistical difference in NACC-rACC RSFC between Stage 1 responders and non-responders to sertraline (t(110)=1.53, p>0.05, d=0.29, BF10=0.57).

No difference in dosage of sertraline received in Stage 1 by eventual bupropion responders and non-responders

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 200mg 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 200mg (mean=118.3mg, SD=26.7, range=57.1–155.2). Hence, it is 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 depressed patients who do not benefit from an adequate trial of SSRI 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 non-responders 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 controls. In contrast, both reward sensitivity and NACC-rACC connectivity in bupropion non-responders were lower than healthy volunteers. Our results cannot provide a mechanistic explanation, but we speculate that these might reflect compensatory mechanisms in depression, in which elevated frontostriatal network functional connectivity is needed to respond normatively to reward. 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 non-response 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 MDD patients with more normative reward-related brain responses benefitted 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 non-dopaminergic 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 serotonin reuptake inhibitor 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 includes switching to a different medication, augmenting with a non-antidepressant drug, dose escalation or combination with a different antidepressant (38). However, there is no clear evidence for a particular strategy 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 NDRIs could be prescribed if first-line SSRIs are not beneficial. Individuals likely to be resistant to NDRIs could be recommended alternative strategies, including augmentation, psychotherapy, or 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 (16 responders vs. 22 non-responders) and N=49 sertraline (25 responders vs. 24 non-responders) patients. 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, rather than impaired, reward processing systems respond more favorably to bupropion. Future, more mechanistic studies should investigate this.

Fourth, we have shown that reward sensitivity and frontostriatal connectivity distinguished between responders to bupropion, after failing to benefit from sertraline, and non-responders 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, since non-responders to sertraline in Stage 1 of the *EMBARC* trial were all given bupropion, rather than being randomized to bupropion or placebo. In other words, due to the lack of placebo controls 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 since 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 non-responders 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 post-treatment. Hence, it is unknown whether reward sensitivity and frontostriatal connectivity will change with treatment to bupropion as a function of response.

Conclusion

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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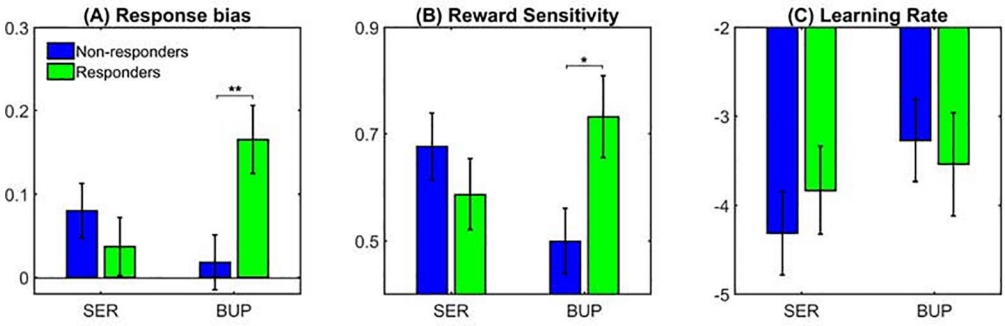

Figure 1. Comparison of (A) response bias, (B) reward sensitivity and (C) learning rate for the probabilistic reward task at baseline.

Bupropion responders in Phase 2 have significantly greater baseline (pretreatment) response bias and reward sensitivity, but not learning rate, compared to non-responders (*p<0.05, **p<0.01). On the other hand, there was no difference on these metrics between responders and non-responders to sertraline. Note that the reward sensitivity and learning rate parameters have been transformed to prevent issues with non-Gaussianity.

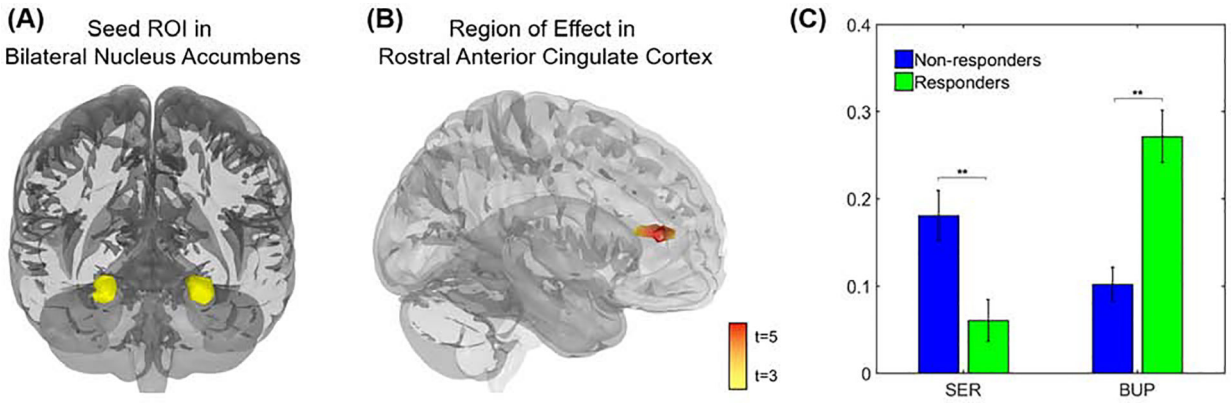

Figure 2. Baseline resting-state functional connectivity (RSFC) of bilateral nucleus accumbens (NACC) is associated with differential response to bupropion (BUP) compared with sertraline (SER).

(A) Shown is the seed region of interest (ROI) in bilateral nucleus accumbens, anatomically defined using the AAL 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 nucleus accumbens 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 (Fig. 3). Patients randomized to sertraline who responded to treatment showed lower NACC-rACC RSFC than sertraline non-responders, but this effect failed to emerge in separate voxelwise analyses within the sertraline group (Fig. 3). Note: Voxelwise analyses thresholded at peak $p<0.001$, two-sided, FDR corrected $p<0.05$.

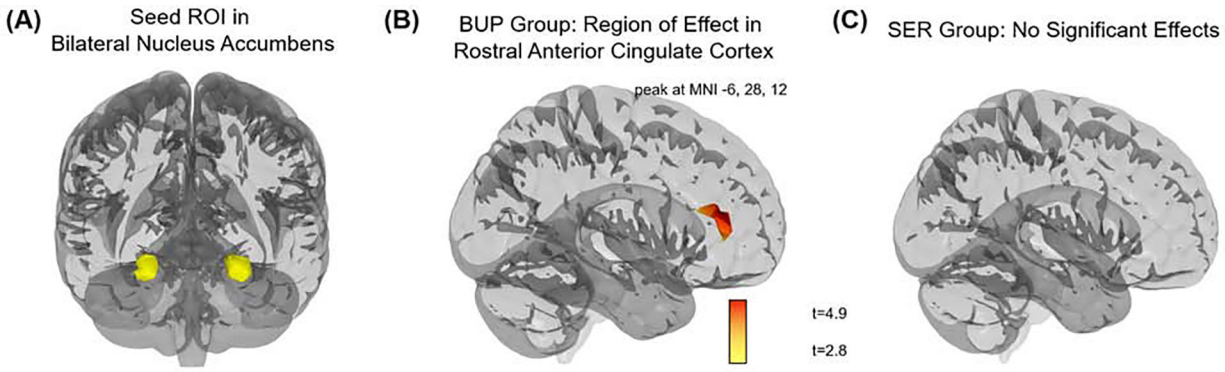

Figure 3. Voxelwise resting-state functional connectivity (RSFC) of bilateral nucleus accumbens (NACC) of responders versus non-responders, within treatment groups.

(A) Shown is the seed region of interest (ROI) in bilateral nucleus accumbens, anatomically defined using the AAL atlas. **(B)** Patients randomized to bupropion who responded to treatment showed higher NACC-rACC RSFC than patients who failed to respond to bupropion. **(C)** Among patients randomized to sertraline (SER), there was no difference in NACC RSFC between those who responded, or failed to respond, to treatment. Note: Voxelwise static analyses thresholded at peak $p<0.005$, two-sided, FDR corrected $p<0.05$.

Table 1.

Clinical and demographic characteristics of Stage 2 sample

Variable	Healthy controls	MDD patients	BUP			SER		
			Resp	Non-resp	*p*	Resp	Non-resp	*p*
N	38	87	16	22		25	24	
Age, mean (SD), years	37.4 (14.9)	39.9 (13.8)	37.0 (14.6)	39.4 (15.1)	0.63[a]	42.1 (11.9)	40.0 (14.5)	0.57[a]
Women, No. (%)	23 (60.5)	56 (64.4)	10 (62.5)	17 (77.3)	0.32[b]	16 (64.0)	13 (54.2)	0.48[b]
Education, mean (SD), years	15.6 (4.5)	15.2 (2.6)	15.6 (2.0)	14.6 (3.0)	0.28[a]	15.4 (2.6)	15.4 (2.5)	0.93[a]
Age at MDD onset, mean (SD), years	-	16.1 (5.5)	14.1 (3.6)	16.3 (6.8)	0.26[a]	16.4 (5.5)	17.0 (5.2)	0.70[a]
Length of current MDE, median, months	-	24	27	36	-	18	27	-
No. of prior MDEs, median	-	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)	0.62[a]	18.3 (4.6)	18.7 (3.2)	0.74[a]
†Week 4–8 HAMD score, mean (SD)	-	16.7 (4.9)	17.1 (5.1)	16.7 (5.0)	0.79[a]	16.9 (5.3)	16.2 (4.2)	0.61[a]
†Week 12–16 HAMD score, 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)	0.22[a]	17.7 (2.5)	18.1 (3.0)	0.61[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.

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KEY RESOURCES TABLE

Resource Type	Specific Reagent or Resource	Source or Reference	Identifiers	Additional Information
Add additional rows as needed for each resource type	Include species and sex when applicable.	Include name of manufacturer, company, repository, individual, or research lab. Include PMID or DOI for references; use “this paper” if new.	Include catalog numbers, stock numbers, database IDs or accession numbers, and/or RRIDs. RRIDs are highly encouraged; search for RRIDs at https://scicrunch.org/resources.	Include any additional information or notes if necessary.
Biological Sample	EMBARC Dataset (MDD Datients and controls)	NIMH Data Archive	Collection ID: 2199	URL: https://nda.nih.gov/edit_collection.html?id=2199
Software; Algorithm	MATLAB R2017a	MathWorks	RRID: SCR_001622	
Software; Algorithm	JASP v0.11.1	JASP Team	RRID:SCR_015823	
Software; Algorithm	SPSS v22.0	IBM	RRID:SCR_002865	