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Exploration of baseline and early changes in neurocognitive characteristics as predictors of treatment response to bupropion, sertraline, and placebo in the EMBARC clinical trial

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Abstract

Background. Treatment for major depressive disorder (MDD) is imprecise and often involves trial-and-error to determine the most effective approach. To facilitate optimal treatment selection and inform timely adjustment, the current study investigated whether neurocognitive variables could predict an antidepressant response in a treatment-specific manner.

Methods. In the two-stage Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial, outpatients with non-psychotic recurrent MDD were first randomized to an 8-week course of sertraline selective serotonin reuptake inhibitor or placebo. Behavioral measures of reward responsiveness, cognitive control, verbal fluency, psychomotor, and cognitive processing speeds were collected at baseline and week 1. Treatment responders then continued on another 8-week course of the same medication, whereas non-responders to sertraline or placebo were crossed-over under double-blinded conditions to bupropion noradrenaline/dopamine reuptake inhibitor or sertraline, respectively. Hamilton Rating for Depression scores were also assessed at baseline, weeks 8, and 16.

Results. Greater improvements in psychomotor and cognitive processing speeds within the first week, as well as better pretreatment performance in these domains, were specifically associated with higher likelihood of response to placebo. Moreover, better reward responsiveness, poorer cognitive control and greater verbal fluency were associated with greater likelihood of response to bupropion in patients who previously failed to respond to sertraline.

Conclusion. These exploratory results warrant further scrutiny, but demonstrate that quick and non-invasive behavioral tests may have substantial clinical value in predicting antidepressant treatment response.

Introduction

Major depressive disorder (MDD) is a serious public health problem that affects more than 240 million people worldwide (James et al., 2018). Being prevalent, debilitating and recurrent, it is associated with significant personal, societal and economic costs (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; Kessler et al., 2003). Unfortunately, the treatment of MDD continues to be challenging as clinicians typically rely on trial-and-error to find the most effective approach. In the STAR*D study, which provided every patient with up to four open-label treatment steps each 12 weeks in length, it was found that only ~50% of MDD patients benefited (i.e. responded by showing ⩾50% improvement in symptoms) from the selective serotonin reuptake inhibitor (SSRI) citalopram (Trivedi et al., 2006), and over one-third were resistant to two or more antidepressants (Rush et al., 2006; Souery, Papakostas, & Trivedi, 2006). Within primary care, the response rate to first-line antidepressants is even lower at ~30% (Katon et al., 1996). To worsen these issues, it takes at least 4 weeks to assess whether a particular antidepressant is working. This can result in unnecessarily long trials that can heighten

the risk of suicidal behavior, treatment discontinuation and patient morbidity. Identifying variables that can predict response to different antidepressants would help clinicians to decide, as early as possible, whether a particular treatment might be suitable for the patient.

Emerging research suggests that quick and non-invasive behavioral tests, which index specific neurocognitive impairments in MDD, may be predictors or moderators of antidepressant response. Executive function, psychomotor speed and/or memory tests have been found to predict outcome to treatment by fluoxetine for 4 weeks (Gudayol-Ferré et al., 2010), 8 weeks (Dunkin et al., 2000) and 12 weeks (Taylor et al., 2006); escitalopram for 8 weeks (Etkin et al., 2015) and 12 weeks (Alexopoulos et al., 2015); citalopram for 6 weeks (Kalayam & Alexopoulos, 2003) and 8 weeks (Sneed et al., 2007); bupropion for 8 weeks (Herrera-Guzmán et al., 2008) and 8–12 weeks (Bruder et al. 2014); duloxetine for 6 weeks (Mikoteit et al., 2015); agomelatine for 6–8 weeks (Cléry-Melin & Gorwood, 2017); as well as ketamine after 24 h (Murrough et al., 2014, 2015) and 12 days (Shiroma, Albott, et al., 2014). However, some investigators found no evidence of an association between cognitive performance and response/remission to 8 weeks of sertraline (Etkin et al., 2015), venlafaxine (Etkin et al., 2015), and escitalopram (Alexopoulos et al., 2007), as well as 12 weeks of fluoxetine (Gudayol-Ferré et al., 2012). Although the cause of these discrepancies is unclear, they likely stem partly from differences in specific tasks used (Groves, Douglas, & Porter, 2018). All these studies, however, have focused on predicting response to a single antidepressant. Depressed patients who fail to benefit from an adequate trial of SSRI are often switched to a non-SSRI agent (Fredman et al., 2000). Yet, it remains unknown whether pretreatment cognitive performance could differentiate between responders to a second antidepressant, which is administered immediately after nonresponse to a pharmacologically distinct class of medication, and non-responders resistant to both arms of treatment.

More recently, several reports have suggested that early improvements in cognitive performance may be associated with antidepressant treatment response. However, they mostly focused on 'hot' cognition, which is related to the processing of emotional information. Specifically, greater improvements in early emotional recognition and processing were found to predict treatment outcome with citalopram (Shiroma, Thuras, Johns, & Lim, 2014; Tranter et al., 2009), escitalopram (Godlewska, Browning, Norbury, Cowen, & Harmer, 2016), and reboxetine (Tranter et al., 2009). Surprisingly, previous studies investigating changes in 'cold', non-emotional cognitive variables in MDD have mostly compared performance before and after treatment (Beblo, Baumann, Bogerts, Wallesch, & Herrmann, 1999; Hammar et al., 2009; Herrera-Guzmán et al., 2010; Hinkelmann et al., 2012; Reppermund et al., 2007; Reppermund, Ising, Lucae, & Zihl, 2009). Only one study reported that improvements in cognitive speed, psychomotor function, motivation, and sensory perception from baseline to week 2 were predictive of treatment response to agomelatine after 6 weeks – although these were based on a self-report questionnaire rather than objective behavioral tasks (Gorwood et al., 2015). Thus, the utility of early changes in 'cold' cognition as predictors of antidepressant response is still not well understood.

The current study sought to explore the two aforementioned gaps in the literature by using data from the two-staged Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) trial (Trivedi et al., 2016). Task-based measures of reward processing, cognitive control, verbal fluency, psychomotor, and cognitive processing speed were collected at baseline and 1 week after the onset of an 8-week clinical trial, where outpatients with recurrent and non-psychotic MDD were randomized to receive the SSRI sertraline or placebo (stage 1). Our first goal was to examine whether changes in any behavioral tests within the first week might differentially predict eventual response to antidepressant treatment. Participants who achieved satisfactory response at the end of stage 1 continued on another 8-week course of the same medication, whereas non-responders were crossed-over under double-blinded conditions. Accordingly, sertraline non-responders received bupropion, and placebo non-responders took sertraline in stage 2. This allowed us to pursue our second goal: to identify putative pre-treatment cognitive variables that might distinguish patients who benefit from a non-serotonergic antidepressant (bupropion), after failure to respond to an SSRI (sertraline), from non-responders who are resistant to both classes of medication.

Methods

Participants

Outpatients and healthy volunteers were recruited at four sites in the United States (Columbia University, New York; Massachusetts General Hospital, Boston; University of Texas Southwestern Medical Center, Dallas; and University of Michigan, Ann Arbor) after approval by the institutional review board of each site. All enrolled participants provided written informed consent and were aged between 18 and 65 years. Patients also met the criteria for MDD based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), scored ⩾14 on the Quick Inventory of Depressive Symptomatology Self-Report (Rush et al., 2003) at both screening and randomization visits, and were free of antidepressant medication for >3 weeks prior to completing any study measures. Exclusion criteria included: history of bipolar disorder or psychosis, substance dependence (except for nicotine) in the past 6 months or substance abuse in past 2 months, active suicidality, or unstable medical conditions. In total, 634 patients were assessed for eligibility; 338 were excluded, leaving 296 individuals who were randomized in stage 1. Forty healthy controls were also enrolled. Data from participants who passed quality control criteria for at least one of the cognitive tasks at baseline and completed at least 4 weeks of treatment in stage 1 were included here.

Clinical measure of depression

17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) (Hamilton, 1960)

This is a clinician-administered scale used to assess severity of symptoms of depression experienced over the past week. The $HAMD_{17}$ was administered at each study visit for baseline, stage 1 (weeks 1, 2, 3, 4, 6, and 8), and stage 2 (weeks 9, 10, 12, and 16). Patients were defined as responders if they completed at least 4 weeks of treatment and showed a decrease in $HAMD_{17}$ score of ⩾50% at the last observation compared to when the treatment started.

Neurocognitive measures

Probabilistic reward task (PRT)

This is a signal detection test that differentially rewarded correct responses to two difficult-to-discriminate stimuli in a 3:1 ratio,

in order to assess the extent to which participants modulated their behavior as a function of reward (Pizzagalli, Jahn, & O'Shea, 2005). Performance was analyzed in terms of response bias, which is an objective measure of reward responsiveness (i.e. the tendency to choose the more rewarded stimulus). Details can be found in online Supplementary methods.

Eriksen flanker task (EFT)

On every trial, participants had to indicate, via a button press, whether an arrow in the center of the screen was pointing to the left or right. Crucially, this central arrow was presented with adjacent arrows that either pointed in the same direction (i.e. congruent condition) or opposite direction (i.e. incongruent condition) (Eriksen, 1995). Inhibitory control was indexed by the interference metric ($RT_{\text{incongruent trials}} - RT_{\text{congruent trials}}$). Details can be found in online Supplementary methods.

Choice reaction time task (CRT)

One of four possible stimuli was presented on each trial and participants had to press the button that corresponded to that stimulus as quickly as they could (Thorne, Genser, Sing, & Hegge, 1985). There were 60 trials in total. Psychomotor processing speed was assessed by the median reaction time of correct trials, which is demographically-adjusted and *z*-scored to account for known age, gender, and education effects on scores.

A-not-B reasoning test (ABRT)

Participants were required to determine the accuracy of a statement describing the order of a pair of letters ('AB' and 'BA'). The statements could be: (i) _ comes before _, (ii) _ comes after _, (iii) _ does not come before _, and (iv) _ does not come after _, in all permutations of A and B in the blanks (Baddeley, 1968). There were 32 trials in total. Cognitive processing speed was assessed by the median reaction time of correct trials, which is demographically-adjusted and *z*-scored to account for known age, gender, and education effects on scores.

Verbal fluency test (VFT)

Participants had to produce words beginning with a specific letter within a time limit of 1 min (Benton, Hamsher, & Sivan, 1983). Three different letters ('F', 'A', and 'S') were used and fluency was indexed by the total number of words produced across all three letters, which is demographically-adjusted and *z*-scored to account for known age, gender, and education effects on scores.

Statistical analysis

Aim 1

For each task, we selected subjects who passed pre-determined quality control criteria at baseline and week 1. Separate logistic regressions were used to evaluate whether early changes from baseline in CRT, ABRT, and VFT – whose outcomes were converted to demographically-adjusted *z*-scores and are those used in the EMBARC study and prior studies (Gorlyn et al., 2008; Keilp, Sackeim, & Mann, 2005) – were associated with a difference in likelihood of response to sertraline *v.* placebo. The outcome variable was Responder (yes, no), and covariates were Treatment (sertraline, placebo), baseline score, change in score from baseline to week 1, interaction between Treatment and baseline score, interaction between Treatment and change score, and Site (Columbia, Massachusetts, Texas, Michigan). Because CRT, ABRT, and VFT analyses used demographically-adjusted *z*-scores, we entered age, gender, and education as additional covariates in logistic regressions for the PRT and EFT to harmonize analyses across tasks. For tasks in which early changes in performance differentially predicted response to placebo *v.* sertraline, additional sets of analyses were conducted. First, we broke the full logistic regression into two simpler analyses that included Treatment, either baseline score or change score as well as its interaction with Treatment, and Site. Second, analysis of covariances (ANCOVAs) were used to examine how placebo responders and non-responders compared to healthy controls. The outcome variable was change score from baseline to week 1, factor was Group (responders, non-responders, and controls) and covariates were Site and baseline score.

Aim 2

For each task, we selected subjects who passed the quality control criteria at baseline, were non-responders to sertraline or placebo in stage 1 and completed at least 4 weeks of stage 2 treatment with bupropion (after switching from sertraline) or sertraline (after switching from placebo). Separate logistic regressions were utilized to evaluate whether baseline performance in CRT, ABRT, and VFT was associated with a difference in likelihood of response to bupropion *v.* sertraline. The outcome variable was Responder (yes, no), and covariates were Treatment (bupropion, sertraline), baseline score, interaction between Treatment and baseline score, and Site (Columbia, Massachusetts, Texas, Michigan). To harmonize analyses across tasks, we used similar logistic regressions for PRT and EFT but with additional covariates of age, gender, and education. For tasks in which baseline performance differentially predicted response to bupropion *v.* sertraline, ANCOVAs were conducted to compare bupropion responders and non-responders with healthy controls. The outcome variable was pretreatment task score, factor was Group (responders, non-responders, controls) and covariates were Site, age, gender, and education. Independent samples' *t* test also assessed whether responders and non-responders to bupropion and sertraline differed in baseline HAMD, week 8 HAMD, and change in HAMD from baseline to week 8.

The logistic regression analyses were not corrected for multiple comparisons as the tasks were carefully selected based on prior findings suggesting their potential for predicting response for antidepressants (Gorlyn et al., 2008; Vrieze et al., 2013) and we wanted to examine the value of each test as a predictor.

Results

Early changes in psychomotor and cognitive processing speeds were associated with better response to placebo

For CRT [sertraline: $N = 113$, age = 37.1 (13.8) years; placebo: $N = 125$, age = 38.0 (12.8) years], the full logistic regression revealed that greater improvement in reaction time from baseline to week 1 was associated with increased likelihood of response to placebo [$B = 1.05$, 95% confidence interval (CI) = 0.23–1.86, $p = 0.012$], but lower probability of sertraline response ($B = -0.67$, 95% CI = −1.32 to −0.06, $p = 0.037$). Importantly, these relationships were significantly different ($B = 1.71$, 95% CI = 0.71–2.79, $p = 0.001$), suggesting that early changes in CRT differentially predicted response to placebo and sertraline (Fig. 1*a*). There was also a significant difference in associations between baseline reaction time and likelihood of response to placebo *v.* sertraline ($B = -0.69$, 95% CI = −1.23 to −0.18, $p = 0.010$). Slower

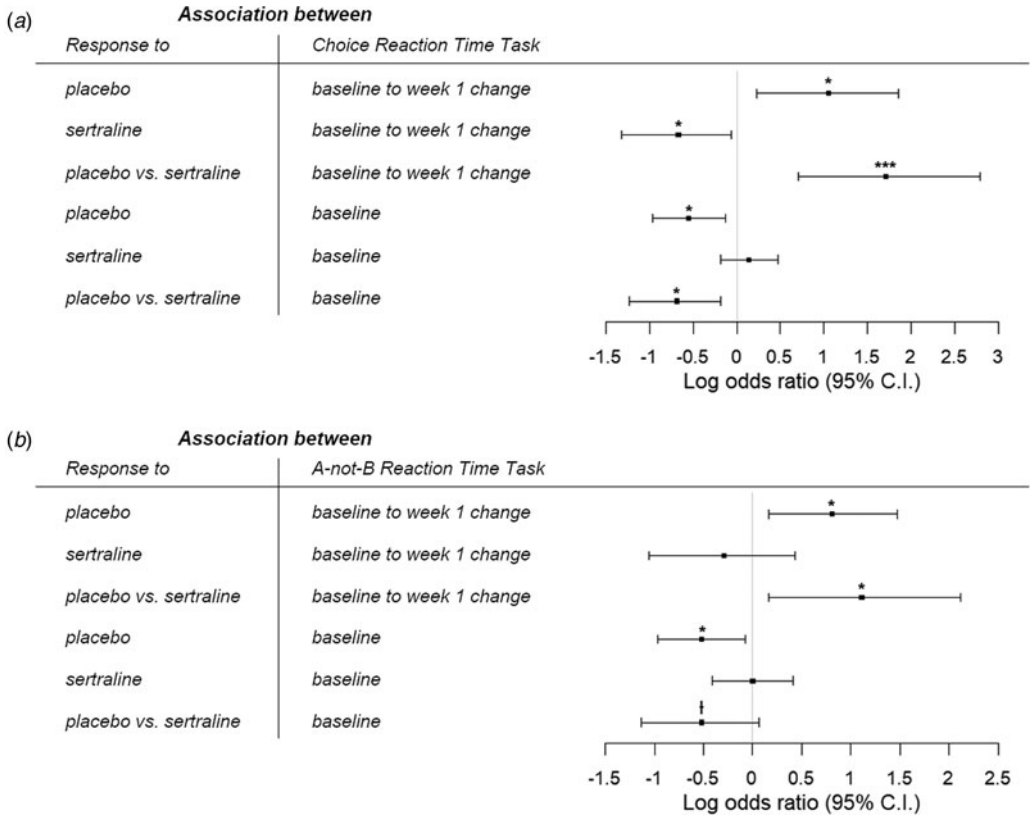

Fig. 1. Log odds ratio for the associations between likelihood of response to placebo and sertraline with (*a*) choice reaction time task and (*b*) A-not-B reaction time task. Greater improvements in psychomotor and cognitive processing speeds within the first week, as well as better pretreatment performance, were specifically associated with higher likelihood of response to placebo. $^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

baseline reaction time was related to reduced odds of placebo response ($B = -0.55$, 95% CI = −0.97 to −0.13, $p = 0.011$), but not associated with probability of response to sertraline ($B = 0.14$, 95% CI = −0.18 to 0.47, $p = 0.392$). See online Supplementary Table S1 for details.

In two simpler logistic regressions that separately examined the effects of baseline and change scores, we found that early changes in CRT within the first week still differentially predicted outcome to placebo and sertraline ($B = 1.03$, 95% CI = 0.19–1.91, $p = 0.018$, online Supplementary Table S2). However, there was no longer a difference in relationships between baseline CRT and response to placebo *v.* sertraline ($B = -0.25$, 95% CI = −0.69 to 0.19, $p = 0.270$, online Supplementary Table S3).

An ANCOVA comparing early change in CRT performance among placebo responders, non-responders, and healthy volunteers revealed a significant effect of group ($F_{(2,157)} = 4.94$, $p = 0.008$, partial $\eta^2 = 0.059$). *Post-hoc* tests found that placebo responders did not differ from controls ($t_{(84)} = 0.272$, $p = 0.79$, Cohen's $d = 0.05$) whereas non-responders had less improvement from baseline to week 1 than healthy individuals ($t_{(117)} = -2.38$, $p = 0.055$, Cohen's $d = 0.46$) and responders ($t_{(124)} = -2.77$, $p = 0.019$, Cohen's $d = 0.51$).

For ABRT [sertraline: $N = 102$, age = 36.8 (13.4) years; placebo: $N = 114$, age = 37.7 (12.7) years], we similarly found in the full logistic regression that greater improvement in reaction time from baseline to week 1 was related to higher likelihood of response to placebo ($B = 0.81$, 95% CI = 0.16–1.47, $p = 0.015$). However, change in ABRT within the first week was not associated with the odds of sertraline response ($B = -0.29$, 95% CI = −1.05 to 0.43, $p = 0.429$); and crucially, these relationships were significantly different ($B = 1.11$, 95% CI = 0.16–2.12, $p = 0.027$), suggesting that early change in ABRT differentially predicted response to placebo and sertraline. We also found a trending difference in associations between baseline reaction time and probability of response to sertraline *v.* placebo ($B = -0.52$, 95% CI = −1.13 to 0.07, $p = 0.088$). Slower baseline ABRT led to reduced likelihood of response to placebo ($B = -0.52$, 95% CI = −0.97 to −0.07, $p = 0.025$), but was not related to sertraline response ($B = -0.002$, 95% CI = −0.41 to 0.41, $p = 0.994$) (Fig. 1*b*). See online Supplementary Table S4 for details.

Simpler logistic regressions investigating the baseline and change scores separately revealed that early changes in ABRT within the first week still differentially predicted outcome to placebo and sertraline, albeit at a trend level ($B = 0.74$, 95% CI = 0.018–1.52, $p = 0.052$, online Supplementary Table S5). In contrast, the difference in relationships between baseline ABRT and response to placebo *v.* sertraline was no longer significant ($B = -0.14$, 95% CI = −0.60 to 0.32, $p = 0.553$, online Supplementary Table S6).

A significant effect of group was found when comparing early change in ABRT performance between placebo responders, non-responders, and healthy individuals ($F_{(2,144)} = 3.32$, $p = 0.039$, partial $\eta^2 = 0.044$). *Post-hoc* tests revealed that placebo responders had greater improvement from baseline to week 1 than non-responders ($t_{(113)} = 2.49$, $p = 0.043$, Cohen's $d = 0.48$), but there

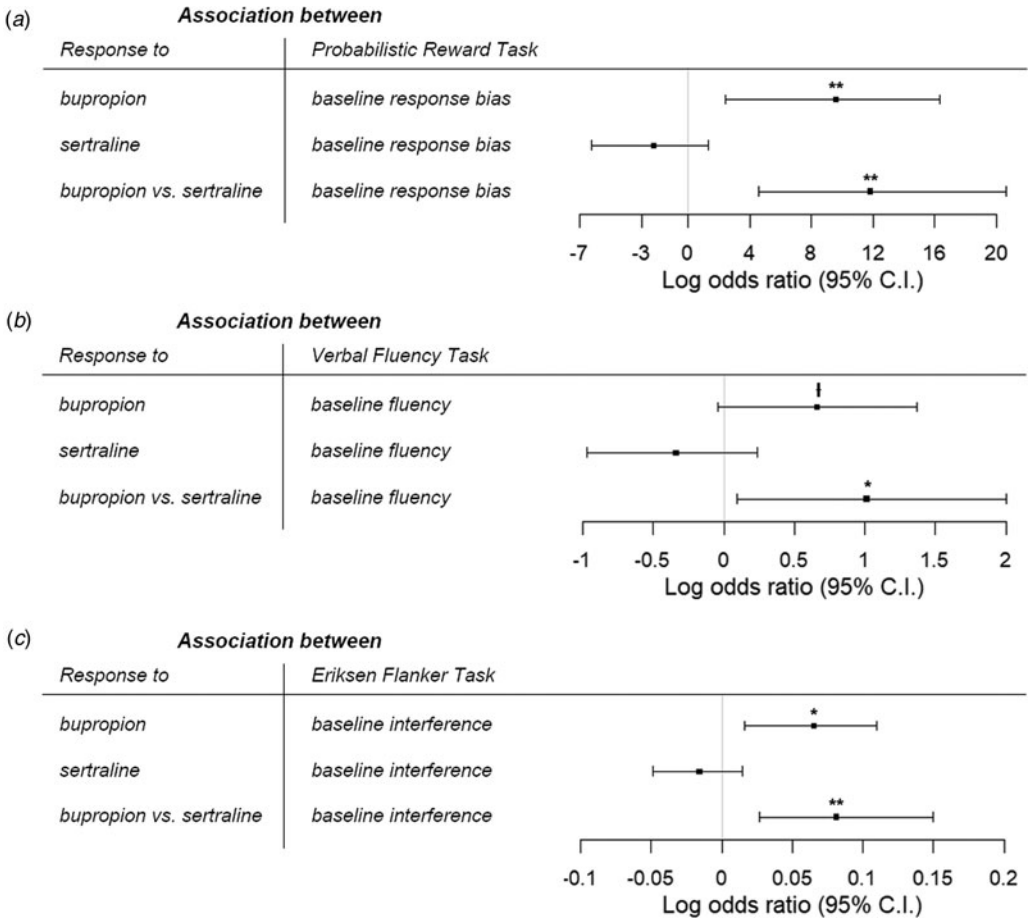

Fig. 2. Log odds ratio for the associations between likelihood of response to bupropion and sertraline with (*a*) probabilistic reward task, (*b*) verbal fluency task, and (*c*) Eriksen flanker task. Better response bias, greater verbal fluency, and higher response interference were specifically associated with greater likelihood of response to bupropion in patients who previously failed to respond to sertraline. $^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

was no difference between controls *v.* responders ($t_{(80)} = 1.93$, $p = 0.168$, Cohen's $d = 0.42$) and controls *v.* non-responders ($t_{(106)} = 0.30$, $p = 0.76$, Cohen's $d = 0.06$).

In contrast, neither baseline nor early change in performance for the VFT, PRT, and EFT differentially predicted response to placebo *v.* sertraline. Details of all these analyses can be found in online Supplementary Tables S7–S9. At the request of an anonymous reviewer, we also repeated all the analyses by adding an additional covariate of smoking status and found that conclusions from all *p* value significance tests remained the same.

Pretreatment reward responsiveness, cognitive control, and verbal fluency are associated with bupropion response

We found that greater pretreatment response bias was associated with higher likelihood of response to bupropion [after switching from sertraline; $N = 38$, age = 38.4 (14.7) years] ($B = 9.59$, 95% CI = 2.46–16.3, $p = 0.008$). However, there was no relationship between response bias and probability of response to sertraline [after previous non-response to placebo; $N = 49$, age = 41.1 (13.1) years] ($B = -2.20$, 95% CI = −6.27 to 1.35, $p = 0.249$). Critically, these associations were significantly different from each other ($B = 11.8$, 95% CI = 4.60–20.6, $p = 0.003$), suggesting that baseline response bias differentially predicted response to bupropion and sertraline (Fig. 2*a*). An ANCOVA comparing baseline response bias among bupropion responders, non-responders, and healthy volunteers revealed a significant effect of group ($F_{(2,67)} = 6.99$, $p = 0.002$, partial $\eta^2 = 0.173$). *Post-hoc* tests found no difference between responders and controls ($t_{(53)} = 0.585$, $p = 0.56$, Cohen's $d = 0.16$), whereas non-responders had significantly lower response bias than healthy people ($t_{(59)} = 3.27$, $p = 0.005$, Cohen's $d = 0.86$) and responders to bupropion ($t_{(37)} = 3.22$, $p = 0.006$, Cohen's $d = 1.00$).

Results for the VFT [bupropion: $N = 42$, age = 38.0 (14.4) years; sertraline: $N = 52$, age = 40.6 (13.4) years] were similar to the PRT. There was a significant difference in associations between baseline verbal fluency and likelihood of response to bupropion *v.* sertraline ($B = 1.01$, 95% CI = 0.097–2.00, $p = 0.035$). Specifically, greater verbal fluency was related to higher probability of bupropion response at a trend level ($B = 0.66$, 95% CI = −0.046 to 1.37, $p = 0.067$), but not associated with odds of response to sertraline ($B = -0.34$, 95% CI = −0.97 to 0.24, $p = 0.259$) (Fig. 2*b*). There was a significant effect of group ($F_{(2,76)} = 6.20$, $p = 0.003$, partial $\eta^2 = 0.140$) when comparing baseline performance among bupropion responders, non-responders, and healthy volunteers. Specifically, bupropion responders and controls did not differ in verbal fluency ($t_{(56)} = 0.505$, $p = 0.62$, Cohen's $d = 0.15$), but non-responders performed worse than healthy individuals ($t_{(64)} = -3.45$, $p = 0.003$, Cohen's $d = 0.88$) and responders ($t_{(41)} = -2.29$, $p = 0.074$, Cohen's $d = 0.71$).

For the EFT [bupropion: $N = 36$, age = 37.4 (13.5) years; sertraline: $N = 50$, age = 40.4 (13.5) years], we also found a significant difference in the relationships between baseline interference and odds of response to bupropion *v.* sertraline ($B = 0.081$, 95% CI = 0.027–0.15, $p = 0.007$). Greater baseline interference (i.e. poorer cognitive control) was surprisingly associated with increased likelihood of bupropion response ($B = 0.065$, 95% CI = 0.016–0.11, $p = 0.010$), whereas there was no relationship between pretreatment interference and probability of response to sertraline ($B = -0.016$, 95% CI = −0.049 to 0.015, $p = 0.321$) (Fig. 2*c*). There was a trending effect of group ($F_{(2,64)} = 2.73$, $p = 0.073$, partial $\eta^2 = 0.079$) when comparing pretreatment performance between bupropion responders, non-responders, and controls. Healthy individuals did not differ from responders ($t_{(50)} = -2.05$, $p = 0.134$, Cohen's $d = 0.65$) or non-responders ($t_{(58)} = 0.38$, $p = 0.71$, Cohen's $d = 0.10$), but responders had greater interference than non-responders at a trend level ($t_{(35)} = 2.22$, $p = 0.089$, Cohen's $d = 0.74$).

Importantly, for each treatment, responders and non-responders did not differ in their $HAMD_{17}$ at baseline, at week 8, and their change in $HAMD_{17}$ from baseline to week 8 (see online Supplementary Tables S15 and S16). This indicates that even though the tasks were administered at baseline, they can be used to distinguish responders from non-responders in stage 2. Together, these findings suggest that reward processing, verbal fluency and cognitive control are capable of distinguishing bupropion responders who did not previously respond to sertraline from non-responders resistant to both classes of medication.

In contrast, pretreatment performance in CRT and ABRT did not differentially predict response to bupropion and sertraline. See online Supplementary Tables S10–S14 for details of these analyses. We also repeated all analyses by adding an additional covariate of smoking status and found that conclusions from all *p* value significance tests remained the same.

Discussion

Treatment for MDD is challenging and often proceeds via trial-and-error with limited success. To facilitate optimal treatment selection and inform timely adjustments, we sought to identify cognitive variables that can predict response in a treatment-specific manner by analyzing data from the EMBARC clinical trial. Several key findings emerged.

First, greater improvements in psychomotor and cognitive processing speeds within the first week, as well as better pretreatment performance, were specifically associated with higher likelihood of response to placebo. Moreover, the improvement of placebo responders in CRT was comparable to healthy individuals, which suggests they might possess a resilience factor. In contrast, non-responders had less CRT improvement than controls, suggesting the presence of a deficient factor. High placebo responses are commonly reported in clinical trials of novel antidepressants (Enck, Bingel, Schedlowski, & Rief, 2013; Schatzberg, 2015) and treatment with placebo has been found to induce distinct changes in brain functioning of depressed individuals (Enck et al., 2013; Leuchter, Cook, Witte, Morgan, & Abrams, 2002; Mayberg et al., 2002). Together, these findings suggest that, rather than having no effect, the administration of placebo is actually an active form of treatment. Accordingly, identifying MDD patients likely to respond to placebo in advance might have real-world clinical implications. Instead of a long-term antidepressant prescription, MDD patients identified as placebo responders could be treated with briefer, lower-cost interventions that are associated with fewer side effects (Enck et al., 2013). Previous studies in this area have largely focused on demographic variables and depressive symptom severity (Entsuah & Vinall, 2007; Fournier et al., 2010; Holmes, Tiwari, & Kennedy, 2016; Kirsch et al., 2008). More recently, Trivedi et al. analyzed 283 baseline variables from the EMBARC study and found that a higher likelihood of placebo response was predicted by baseline theta current density in the rostral anterior cingulate cortex (rACC) and several pretreatment clinical variables, such as anxious arousal, anhedonia, and neuroticism (Trivedi et al., 2018). However, they did not include early changes in cognition. Data from the sertraline arm were also not examined and thus, some of these predictors might not be specific to placebo. For example, Pizzagalli and coworkers demonstrated that increased baseline rACC theta activity represents a nonspecific marker of treatment outcome to both placebo and sertraline (Pizzagalli et al., 2018). Thus, our results extend the findings from these previous studies, suggesting the baseline and early changes in CRT and ABRT might be more specific predictors of placebo response.

Second, greater improvement in CRT within the first week was specifically associated with lower likelihood of response to sertraline. To the best of our knowledge, this is the first time that early changes in objective measures of 'cold' cognition have been reported to predict response to SSRIs. Several prior studies have focused on improvements in 'hot' cognition instead, consistently finding that early increases in emotional processing are associated with subsequent improvement in depressive symptoms during treatment with SSRIs (Godlewska et al., 2016; Shiroma, Thuras, et al., 2014; Tranter et al., 2009). Gorwood et al. also examined early changes in 'cold' cognition and found that improvements in various domains such as psychomotor function, motivation, cognitive speed, and sensory perception within the first 2 weeks all predicted response to the melatonin agonist, agomelatine, after 6 weeks (Gorwood et al., 2015). However, that study utilized a self-report questionnaire of cognition, which is inherently subjective and might be a less accurate measure of cognitive ability than behavioral tasks.

Third, better reward responsiveness, poorer cognitive control, and greater verbal fluency were associated with greater likelihood of response to bupropion in patients who previously failed to respond to sertraline. Furthermore, bupropion responders had comparable response bias and verbal fluency to healthy volunteers, whereas non-responders performed worse than controls. These findings suggest that responders to bupropion possess a resilience factor whereas a deficient factor might be present in non-responders. Prior studies have investigated cognitive predictors of treatment response to various antidepressants, including bupropion (Alexopoulos et al., 2007, 2015; Bruder et al., 2014; Cléry-Melin & Gorwood, 2017; Dunkin et al., 2000; Etkin et al., 2015; Groves et al., 2018; Gudayol-Ferré et al., 2010, 2012; Herrera-Guzmán et al., 2008; Kalayam & Alexopoulos, 2003; Mikoteit et al., 2015; Murrough et al., 2014, 2015; Shiroma, Albott, et al., 2014; Sneed et al., 2007; Taylor et al., 2006). For example, Herrera-Guzmán et al. (2008) showed that bupropion responders had lower pretreatment cognitive processing speed (as indexed by the Stockings of Cambridge test) compared to non-responders. Another study reported that baseline cognitive control (based on the Stroop interference effect) and verbal fluency were not significantly different in eventual responders and non-responders to bupropion (Bruder et al., 2014). In contrast, we found that lower cognitive control and higher verbal fluency

predicted bupropion response, but cognitive processing speed did not. These discrepancies might have occurred due to differences in tasks used and smaller sample sizes in previous studies ($N = \sim 20$ *v.* $N = \sim 40$ here). Also, our findings may be specific to patients receiving secondary treatment with bupropion after failure to respond to sertraline. With regard to reward processing, our finding that bupropion responders have greater response bias on the PRT than non-responders has been reported in a recent publication (Ang et al., 2020), in which greater reward responsiveness and resting state frontostriatal functional connectivity were associated with response to bupropion, and is in line with substantial evidence showing that reward processes are modulated by dopaminergic system in the brain (Berridge, Robinson, & Aldridge, 2009). It is also consistent with a recent study showing depressed individuals with enhanced baseline response bias respond more favorably to pramipexole, a selective dopamine agonist (Whitton et al., 2020). In sum, our study is the first to address cognitive predictors of response to the noradrenaline/dopamine reuptake inhibitor (NDRI) bupropion following a failure to respond to the SSRI sertraline. This might have significant clinical value in identifying patients who are likely to respond to secondary treatment with bupropion and those who are unlikely to benefit from both SSRIs and NDRIs, so that they can be recommended alternative forms of treatment.

Limitations of this study should be acknowledged. First, multiple logistic regressions were conducted, but none of the findings would survive multiple comparisons. Although this might increase the chances of committing a type 1 error, our study is exploratory in nature and we were specifically interested in identifying whether each of the cognitive tasks could be a potential predictor of treatment outcome (Huberty & Morris, 1989). This liberal approach may not be stringent enough and thus, our findings are tentative and require replication. Second, this study adopted relatively strict inclusion criteria in order to minimize clinical heterogeneity. Thus, it is unclear whether findings will generalize to other depressed samples, such as those with psychosis or substance dependence. Third, this study did not exclude participants who had tobacco use disorder. Although chronic cigarette smoking has been associated with poorer cognitive performance across multiple domains (Durazzo, Meyerhoff, & Nixon, 2012; Nooyens, van Gelder, & Verschuren, 2008), all conclusions remained after accounting for an additional covariate of smoking status in our analyses.

Conclusion

Cognitive tasks that are quick, non-invasive, and easy to administer may have important clinical value as predictors of response to antidepressant treatment. The current study showed that psychomotor and cognitive processing speed after 1 week were associated with enhanced clinical response to placebo. Reward sensitivity, cognitive control, and verbal fluency at baseline also differentiated bupropion responders, who did not respond to sertraline previously, from non-responders resistant to both classes of medication. These initial results warrant further scrutiny for possible implementation in clinical care.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Supplemental Material

Supplemental Methods

Probabilistic Reward Task (PRT): This task is rooted in signal detection theory and subjects were asked to determine, via button press, whether one of two stimuli was presented on the screen. The stimulus was either a short (11.5mm) or a long (13mm) mouth superimposed on a previously mouthless cartoon face. In this study, two blocks of 100 trials were presented. An equal number of short and long mouths were presented within each block. Each trial consisted of a fixation cross (jittered 750-900ms) followed by a mouthless face (500ms), after which either the short or a long mouth appeared on the face (100ms). Importantly, to induce a response bias, an asymmetric reinforcer ratio was employed. Thus, correct identification of either the long or short mouth was rewarded ("Correct!! You won 5 Cents") three times more frequently ("rich" stimulus) than the other 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. Keys and conditions (long or short mouth as "rich" stimulus) were counterbalanced across participants. Participants were excluded if any of the following quality control checks were not met: (1) less than 80 valid trials in each block (i.e., less than 20% outlier responses, as defined by RT <150ms or >2500ms and the log-transformed RT exceeding the participant's mean±3SD); (2) less than 20 rich rewards or less than 6 lean rewards in each block; (3) rich-to-lean reward ratio <2.0 in any block. Our main variable of interest, response bias, captured a participant's preference for the more frequently rewarded stimulus and was calculated as:

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

Eriksen Flanker Task (EFT): Participants first completed a practice session consisting of 15 congruent and 15 incongruent trials. The flanking arrows were first presented alone (100ms) and were then joined by the central arrow (50ms), for a total stimulus duration of 150ms. Participants were asked to indicate, via button press, whether the center arrow pointed left or right, as quickly and accurately as possible. Both accuracy and reaction time (RT) were recorded. Following the practice session, participants completed five blocks consisting of 70 trials each (46 congruent, 24 congruent), for a total of 350 trials. To ensure adequate task difficulty, a response deadline was established for each block that corresponded to the 85th percentile of the RT distribution from incongruent trials in the preceding block (in the first block, the practice RT distribution was used). Stimulus presentation was followed by a fixation cross (1400ms). If the participant did not respond by the response deadline, a screen reading “TOO SLOW!” was presented (300ms). Participants were told that if they saw this screen, they should speed up. If a response was made before the deadline, the “TOO SLOW!” screen was omitted and the fixation cross remained onscreen for the 300ms interval. Finally, each trial ended with presentation of the fixation cross for an additional 200-400ms. Thus, total trial time varied between 2050-2250ms. The sequence of congruent and incongruent trials was established with optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq/) and was identical across participants. While data collection was ongoing, block-by-block feedback was added to maintain performance at desired levels. Specifically, if participants made fewer

than three incongruent errors in a block, they were shown a screen reading, “Remember to respond as QUICKLY as possible while still being accurate”. If six or more incongruent errors were committed, the screen read, “Remember to respond as ACCURATELY as possible while still being fast”. Otherwise, the screen read, “Please respond as quickly and accurately as possible”. Pre-defined quality control checks were used to exclude datasets characterized by unusually poor performance. First, for each participant outlier trials were defined as those in which the raw RT was less than 150ms or the log-transformed RT exceeded the participant’s mean±3SD, computed separately for congruent and incongruent stimuli. Second, we excluded datasets with: 35 or more RT outliers (i.e., greater than 10% of trials), fewer than 200 outlier-free congruent trials, fewer than 90 outlier-free incongruent trials, or lower than 50% correct for congruent or incongruent trials. Trials characterized by RT outliers were excluded from all analyses.

Supplementary Results

Table S1. Logistic regression to predict treatment response in Stage 1 using baseline and early changes in choice reaction time (CRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-1.453 [-2.316, -0.649]	0.234 [0.099, 0.523]	-3.430	<.001
Baseline_CRT	0.141 [-0.182, 0.471]	1.152 [0.834, 1.602]	0.856	0.392
Change_CRT	-0.667 [-1.323, -0.059]	0.513 [0.266, 0.942]	-2.090	0.037
Treatment*Baseline_CRT	-0.692 [-1.229, -0.175]	0.501 [0.293, 0.839]	-2.585	0.010
Treatment*Change_CRT	1.713 [0.711, 2.786]	5.546 [2.035, 16.22]	3.249	0.001
Site(CU)	1.157 [0.359, 1.988]	3.180 [1.432, 7.300]	2.794	0.005
Site(MG)	-0.291 [-1.297, 0.689]	0.747 [0.273, 1.993]	-0.579	0.563
Site(TX)	-0.211 [-0.998, 0.584]	0.810 [0.369, 1.793]	-0.525	0.600
Intercept	0.003 [-0.771, 0.769]	1.003 [0.463, 2.157]	0.007	0.995

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_CRT = Baseline_CRT – Week1_CRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S2. Logistic regression to predict treatment response in Stage 1 using early changes in choice reaction time (CRT)

Predictor	**B [95% C.I.]**	**Odds Ratio [95% C.I.]**	***Z***	***p***
Treatment	-1.087 [-1.855, -0.353]	0.337 [0.156, 0.702]	-2.848	0.004
Change_CRT	-0.530 [-1.096, -0.002]	0.589 [0.334, 0.998]	-1.918	0.055
Treatment*Change_CRT	1.032 [0.193, 1.911]	2.806 [1.213, 6.760]	2.367	0.018
Site(CU)	1.051 [0.286, 1.844]	2.861 [1.331, 6.324]	2.654	0.008
Site(MG)	-0.406 [-1.375, 0.535]	0.666 [0.253, 1.707]	-0.838	0.402
Site(TX)	-0.223 [-0.995, 0.558]	0.800 [0.370, 1.746]	-0.565	0.572
Intercept	0.005 [-0.728, 0.730]	1.005 [0.483, 2.075]	0.013	0.989

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_CRT = Baseline_CRT – Week1_CRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S3. Logistic regression to predict treatment response in Stage 1 using baseline choice reaction time (CRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.481 [-1.028, 0.060]	0.618 [0.358, 1.061]	-1.736	0.083
Baseline_CRT	-0.023 [-0.306, 0.256]	0.977 [0.736, 1.292]	-0.163	0.870
Treatment*Baseline_CRT	-0.247 [-0.692, 0.191]	0.781 [0.501, 1.211]	-1.102	0.270
Site(CU)	1.128 [0.350, 1.937]	3.090 [1.419, 6.939]	2.796	0.005
Site(MG)	-0.144 [-1.114, 0.805]	0.866 [0.328, 2.237]	-0.296	0.767
Site(TX)	-0.068 [-0.831, 0.707]	0.934 [0.436, 2.028]	-0.175	0.861
Intercept	-0.384 [-1.067, 0.273]	0.681 [0.344, 1.314]	-1.131	0.258

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_CRT = Baseline_CRT – Week1_CRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S4. Logistic regression to predict treatment response in Stage 1 using baseline and early changes in A-not-B reaction time (ABRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.931 [-1.740, -0.159]	0.394 [0.176, 0.853]	-2.320	0.020
Baseline_ABRT	-0.002 [-0.414. 0.408]	0.998 [0.661, 1.504]	-0.008	0.994
Change_ABRT	-0.295 [-1.050, 0.428]	0.744 [0.350, 1.534]	-0.790	0.429
Treatment*Baseline_ABRT	-0.519 [-1.133, 0.065]	0.595 [0.322, 1.067]	-1.706	0.088
Treatment*Change_ABRT	1.107 [0.158, 2.124]	3.026 [1.171, 8.361]	2.219	0.027
Site(CU)	1.396 [0.532, 2.305]	4.041 [1.702, 10.02]	3.101	0.002
Site(MG)	-0.136 [-1.166, 0.874]	0.873 [0.312, 2.396]	-0.264	0.792
Site(TX)	0.081 [-0.761, 0.942]	1.084 [0.467, 2.565]	0.186	0.852
Intercept	-0.371 [-1.257, 0.489]	0.690 [0.285, 1.631]	-0.840	0.401

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_ABRT = Baseline_ABRT – Week1_ABRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S5. Logistic regression to predict treatment response in Stage 1 using early changes in A-not-B reaction time (ABRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.777 [-1.494, -0.082]	0.460 [0.224, 0.921]	-2.163	0.031
Change_ABRT	-0.283 [-0.838, 0.221]	0.753 [0.432, 1.248]	-1.061	0.289
Treatment*Change_ABRT	0.741 [0.018, 1.520]	2.098 [1.018, 4.573]	1.944	0.052
Site(CU)	1.180 [0.361, 2.036]	3.255 [1.435, 7.658]	2.774	0.006
Site(MG)	-0.247 [-1.266, 0.749]	0.781 [0.282, 2.114]	-0.484	0.628
Site(TX)	-0.059 [-0.877, 0.778]	0.943 [0.416, 2.177]	-0.140	0.889
Intercept	-0.247 [-1.037, 0.520]	0.781 [0.355, 1.682]	-0.627	0.531

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_ABRT = Baseline_ABRT – Week1_ABRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S6. Logistic regression to predict treatment response in Stage 1 using baseline A-not-B reaction time (ABRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.398 [-0.972, 0.169]	0.671 [0.378, 1.184]	-1.371	0.170
Baseline_ABRT	-0.105 [-0.403, 0.179]	0.900 [0.669, 1.196]	-0.716	0.474
Treatment*Baseline_ABRT	-0.138 [-0.600, 0.317]	0.871 [0.549, 1.372]	-0.593	0.553
Site(CU)	1.228 [0.394, 2.101]	3.414 [1.482, 8.171]	2.832	0.005
Site(MG)	-0.260 [-1.277, 0.733]	0.771 [0.279, 2.081]	-0.511	0.609
Site(TX)	-0.012 [-0.836, 0.831]	0.988 [0.434, 2.295]	-0.028	0.977
Intercept	-0.440 [-1.188, 0.276]	0.644 [0.305, 1.318]	-1.186	0.235

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_ABRT = Baseline_ABRT – Week1_ABRT, hence, larger values indicate greater improvement; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S7. Logistic regression to predict treatment response in Stage 1 using baseline and early changes in verbal fluency (VF)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.496 [-1.112, 0.113]	0.609 [0.329, 1.120]	-1.591	0.112
Baseline_VF	0.145 [-0.243, 0.537]	1.156 [0.784, 1.710]	0.733	0.464
Change_VF	-0.233 [-0.882, 0.404]	0.792 [0.414, 1.498]	-0.715	0.474
Treatment*Baseline_VF	0.152 [-0.409, 0.716]	1.164 [0.664, 2.048]	0.530	0.596
Treatment*Change_VF	-0.126 [-1.024, 0.766]	0.882 [0.359, 2.151]	-0.277	0.782
Site(CU)	0.967 [0.200, 1.760]	2.630 [1.222, 5.814]	2.439	0.015
Site(MG)	-0.445 [-1.417, 0.498]	0.641 [0.242, 1.645]	-0.916	0.360
Site(TX)	-0.045 [-0.809, 0.733]	0.956 [0.445, 2.082]	-0.114	0.909
Intercept	-0.250 [-0.968, 0.447]	0.779 [0.380, 1.564]	-0.698	0.485

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_VF = Baseline_VF – Week1_VF, hence, larger values indicate greater decrease; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S8. Logistic regression to predict treatment response in Stage 1 using baseline and early changes in response bias (RB) from the probabilistic reward task

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.649 [-1.486, 0.161]	0.523 [0.226, 1.174]	-1.553	0.121
Baseline_RB	-0.403 [-3.728, 2.851]	0.668 [0.024, 17.31]	-0.243	0.808
Change_RB	0.184 [-3.423, 3.790]	1.202 [0.033, 44.24]	0.101	0.920
Treatment*Baseline_RB	3.876 [-0.741, 8.697]	48.23 [0.477, 5987]	1.618	0.106
Treatment*Change_RB	-1.493 [-6.422, 3.361]	0.225 [0.002, 28.82]	-0.601	0.548
Site(CU)	1.091 [0.259, 1.953]	2.977 [1.295, 7.048]	2.534	0.011
Site(MG)	-0.195 [-1.224, 0.813]	0.823 [0.294, 2.255]	-0.378	0.705
Site(TX)	-0.236 [-1.078, 0.611]	0.790 [0.340, 1.842]	-0.550	0.583
Age	-0.006 [-0.030, 0.018]	0.994 [0.970, 1.019]	-0.469	0.639
Gender	-0.068 [-0.690, 0.556]	0.934 [0.501, 1.744]	-0.214	0.831
Education	0.006 [-0.119, 0.131]	1.006 [0.888, 1.140]	0.098	0.922
Intercept	-0.117 [-2.238, 1.999]	0.889 [0.107, 7.382]	-0.109	0.913

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_RB = Baseline_RB – Week1_RB, hence, larger values indicate greater decrease; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan; Gender is coded as 1 for female and 0 for male. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S9. Logistic regression to predict treatment response in Stage 1 using baseline and early changes in Flanker reaction time interference (FRTI).

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	0.932 [-2.128, 4.024]	2.539 [0.119, 55.93]	0.597	0.551
Baseline_FRTI	0.022 [-0.004, 0.050]	1.022 [0.996, 1.051]	1.617	0.106
Change_FRTI	-0.043 [-0.080, -0.008]	0.958 [0.923, 0.992]	-2.354	0.019
Treatment*Baseline_FRTI	-0.018 [-0.053, 0.017]	0.983 [0.948, 1.017]	-0.983	0.326
Treatment*Change_FRTI	0.025 [-0.022, 0.073]	1.025 [0.978, 1.076]	1.030	0.303
Site(CU)	1.084 [0.226, 1.977]	2.958 [1.253, 7.222]	2.439	0.015
Site(MG)	-0.671 [-1.858, 0.456]	0.511 [0.156, 1.577]	-1.147	0.252
Site(TX)	-0.022 [-0.915, 0.889]	0.979 [0.401, 2.432]	-0.047	0.962
Age	-0.018 [-0.044, 0.008]	0.982 [0.957, 1.008]	-1.351	0.177
Gender	-0.067 [-0.729, 0.598]	0.936 [0.483, 1.818]	-0.198	0.843
Education	0.006 [-0.125, 0.138]	1.006 [0.882, 1.148]	0.093	0.926
Intercept	-1.319 [-4.368, 1.684]	0.267 [0.013, 5.388]	-0.860	0.390

Note: Treatment coded as 1 for placebo and 0 for sertraline; Change_CRT = Baseline_FRTI – Week1_FRTI, hence, larger values indicate improved inhibitory control; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan; Gender is coded as 1 for female and 0 for male. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S10. Logistic regression to predict treatment response in Stage 2 using baseline response bias (RB) from the probabilistic reward task

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-1.430 [-2.825, -0.241]	0.239 [0.059, 0.786]	-2.203	0.028
Baseline_RB	-2.195 [-6.269, 1.348]	0.111 [0.002, 3.851]	-1.154	0.249
Treatment*Baseline_RB	11.78 [4.603, 20.55]	1.30×10^{5} [99.81, 8.44×10^{8}]	2.934	0.003
Site(CU)	-2.037 [-3.883, -0.409]	0.130 [0.021, 0.665]	-2.336	0.019
Site(MG)	-1.209 [-3.321, 0.763]	0.299 [0.036, 2.145]	-1.179	0.239
Site(TX)	-0.565 [-2.176, 0.882]	0.568 [0.114, 2.415]	-0.742	0.458
Age	-0.013 [-0.050, 0.023]	0.987 [0.951, 1.024]	-0.695	0.487
Gender	-0.137 [-1.173, 0.889]	0.872 [0.309, 2.433]	-0.263	0.793
Education	0.067 [-0.123, 0.267]	1.069 [0.884, 1.306]	0.681	0.496
Intercept	0.699 [-3.011, 4.610]	2.012 [0.049, 100.44]	0.366	0.715

Note: Treatment coded as 1 for bupropion and 0 for sertraline; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S11. Logistic regression to predict treatment response in Stage 2 using baseline verbal fluency (VF)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.006 [-0.997, 1.011]	0.994 [0.369, 2.749]	-0.013	0.990
Baseline_VF	-0.343 [-0.965, 0.243]	0.709 [0.381, 1.276]	-1.130	0.259
Treatment*Baseline_VF	1.007 [0.097, 1.995]	2.738 [1.102, 7.351]	2.106	0.035
Site(CU)	-1.011 [-2.509, 0.404]	0.364 [0.081, 1.498]	-1.377	0.168
Site(MG)	-1.498 [-3.300, 0.139]	0.224 [0.037, 1.149]	-1.733	0.083
Site(TX)	-0.543 [-1.916, 0.735]	0.581 [0.147, 2.085]	-0.816	0.415
Intercept	0.656 [-0.605, 2.014]	1.927 [0.546, 7.493]	1.002	0.317

Note: Treatment coded as 1 for bupropion and 0 for sertraline; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S12. Logistic regression to predict treatment response in Stage 2 using baseline Flanker reaction time interference (FRTI)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*P*
Treatment	-8.066 [-14.17, -2.916]	0.0003 [6.99×10^{-7}, 0.054]	-2.850	0.004
Baseline_FRTI	-0.016 [-0.049, 0.015]	0.985 [0.953, 1.015]	-0.992	0.321
Treatment*Baseline_FRTI	0.081 [0.027, 0.146]	1.084 [1.027, 1.157]	2.711	0.007
Site(CU)	-1.490 [-3.263, 0.131]	0.225 [0.038, 1.140]	-1.747	0.081
Site(MG)	-1.298 [-3.363, 0.596]	0.273 [0.035, 1.816]	-1.305	0.192
Site(TX)	-0.375 [-1.937, 1.102]	0.687 [0.144, 3.009]	-0.493	0.622
Age	-0.003 [-0.044. 0.037]	0.997 [0.957, 1.038]	-0.163	0.870
Gender	0.288 [-0.760, 1.360]	1.334 [0.468, 3.898]	0.538	0.591
Education	0.157 [-0.042, 0.374]	1.170 [0.959, 1.454]	1.491	0.136
Intercept	-0.180 [-4.958, 4.728]	0.835 [0.007, 113.02]	-0.074	0.941

Note: Treatment coded as 1 for bupropion and 0 for sertraline; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S13. Logistic regression to predict treatment response in Stage 2 using baseline choice reaction time (CRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.479 [-1.350, 0.377]	0.620 [0.259, 1.457]	-1.092	0.275
Baseline_CRT	0.145 [-0.418, 0.718]	1.156 [0.658, 2.051]	0.509	0.611
Treatment*Baseline_CRT	-0.384 [-1.155, 0.352]	0.681 [0.315, 1.422]	-1.012	0.312
Site(CU)	-1.337 [-2.789, 0.004]	0.263 [0.061, 1.004]	-1.899	0.058
Site(MG)	-1.384 [-3.123, 0.209]	0.251 [0.044, 1.232]	-1.652	0.099
Site(TX)	-0.511 [-1.842, 0.717]	0.600 [0.159, 2.048]	-0.796	0.426
Intercept	0.957 [-0.168, 2.223]	2.603 [0.845, 9.231]	1.600	0.110

Note: Treatment coded as 1 for bupropion and 0 for sertraline; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S14. Logistic regression to predict treatment response in Stage 2 using baseline A-not-B reaction time (ABRT)

Predictor	B [95% C.I.]	Odds Ratio [95% C.I.]	*Z*	*p*
Treatment	-0.245 [-1.141, 0.647]	0.783 [0.319, 1.909]	-0.539	0.590
Baseline_ABRT	-0.223 [-0.810, 0.296]	0.800 [0.445, 1.345]	-0.810	0.418
Treatment*Baseline_ABRT	-0.125 [-0.870, 0.613]	0.882 [0.419, 1.845]	-0.338	0.736
Site(CU)	-0.879 [-2.357, 0.516]	0.415 [0.095, 1.676]	-1.214	0.225
Site(MG)	-1.565 [-3.449, 0.112]	0.209 [0.032, 1.119]	-1.756	0.079
Site(TX)	-0.310 [-1.656, 0.955]	0.733 [0.191, 2.600]	-0.473	0.636
Intercept	0.670 [-0.496, 1.949]	1.955 [0.609, 7.021]	1.097	0.273

Note: Treatment coded as 1 for bupropion and 0 for sertraline; CU=Columbia University, MG = Massachusetts General Hospital, TX = University of Texas, reference level for site is UM = University of Michigan. Significance results remain completely the same even after adding smoker status (yes vs. no).

Table S15. Comparison of $HAMD_{17}$ between Stage 2 bupropion responders and non-responders at different timepoints

	Baseline		Week 8		$\Delta_{\text{baseline-to-week 8}}$	
	t_{df}	*P*	t_{df}	*p*	t_{df}	*p*
PRT	0.508_{36}	.615	-0.266_{36}	.792	0.800_{36}	.429
VFT	0.669_{40}	.508	-0.257_{40}	.799	0.958_{40}	.344
EFT	0.925_{34}	.362	0.138_{34}	.891	0.742_{34}	.463

Table S16. Comparison of $HAMD_{17}$ between Stage 2 sertraline responders and non-responders at different timepoints

	Baseline		Week 8		$\Delta_{\text{baseline-to-week 8}}$	
	t_{df}	*p*	t_{df}	*p*	t_{df}	*p*
PRT	0.340_{47}	.736	-0.519_{47}	.606	0.757_{47}	.453
VFT	0.285_{50}	.777	-0.541_{50}	.591	0.729_{50}	.469
EFT	0.496_{48}	.622	-0.166_{48}	.869	0.537_{48}	.593