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

Supplemental Information

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Supplemental Methods

Probabilistic reward task

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

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

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

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

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

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

Computational modelling

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Magnetic Resonance Imaging Acquisition and Analyses

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

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

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

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

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

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

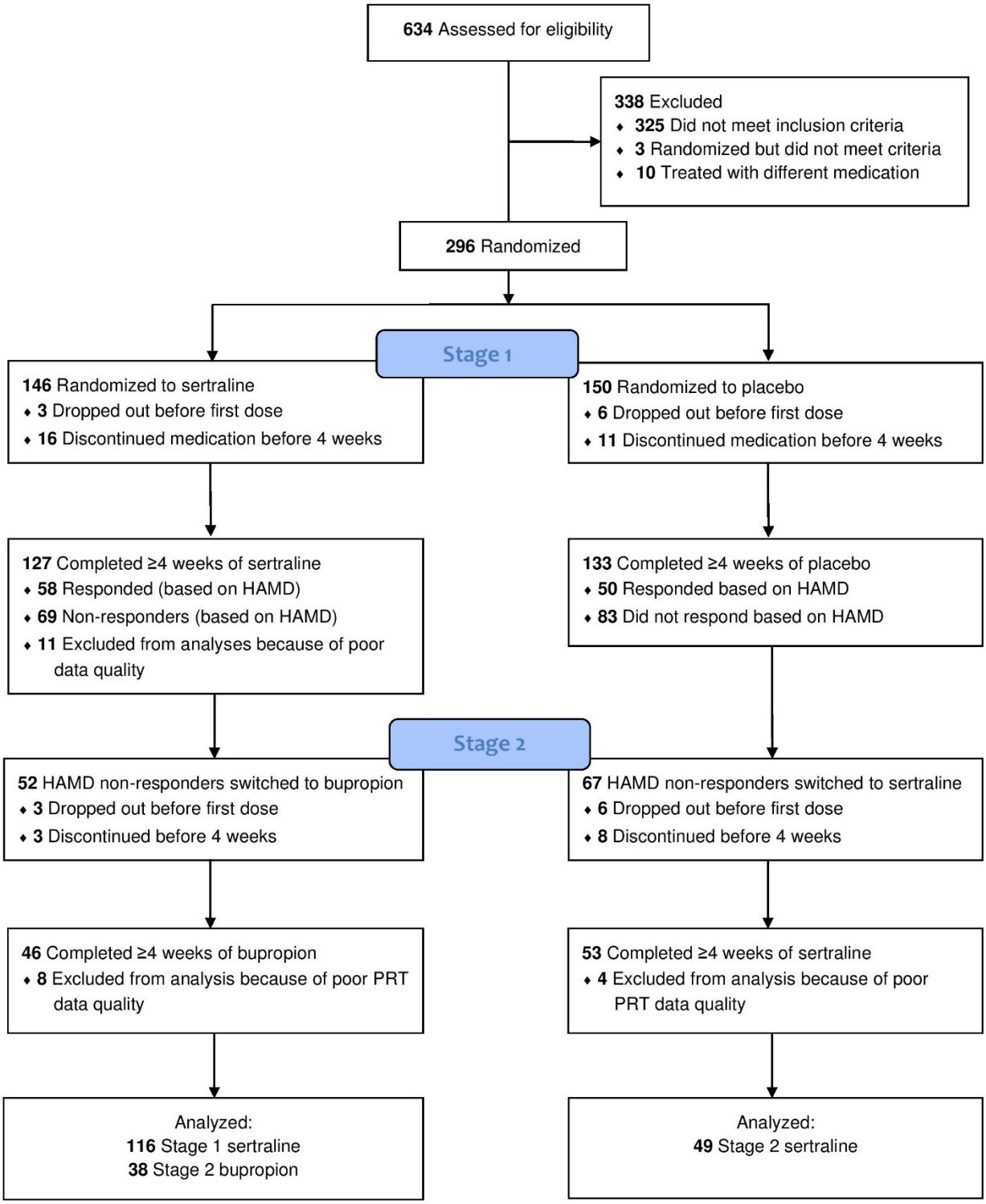

Table S1. Imaging acquisition parameters

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

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

Supplemental Results

Table S2. Clinical and demographic characteristics of replication sample

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

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

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

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

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

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

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

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

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

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

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

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

Effect of Treatment x Response on discriminability after covarying for site

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

Supplemental References

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