Pretreatment Rostral Anterior Cingulate Cortex Connectivity With Salience Network Predicts Depression Recovery: Findings from the EMBARC Randomized Clinical Trial

Supplementary Information

Contents:

Supplementary Methods and Materials

Sample size and power analyses for the clinical trial

The sample size of 300 was chosen to allow at least 80% power (α=0.05, two-tailed) to detect interaction effects of multiple (~40) potential moderators of the treatment on depressive symptom improvement, after adjusting for multiple comparisons. Based on prior work, the effect sizes of the moderators were hypothesized to be between 0.15 and 0.2.

Methods used to generate the random allocation sequence

Randomization was conducted according to site, depression severity and depression chronicity. Within each of these levels, block randomization with a random block size of 2 or 4 was applied using the commercial clinical trial data management software StudyTrax. For each potential participant, a site coordinator would input information regarding all inclusion/exclusion criteria, after which the software crosschecked this information for eligibility. If the participant was deemed to be eligible, the software provided a random assignment, which was communicated directly to the site pharmacist.

Participant inclusion/exclusion criteria

All patients reported MDD onset before 30, and had either a chronic (episode duration > 2 years) or recurrent (≥ 2 recurrences including the current episode) illness course. Participants were excluded from the study if they were currently pregnant, breastfeeding or were planning to become pregnant in the near future; had a lifetime history of bipolar disorder or psychotic disorder; met criteria for substance dependence in the past six months or substance abuse in the past two months; displayed evidence of unstable medical or psychiatric symptoms that required hospitalization; had any study medication contraindications; had clinically significant laboratory abnormalities; had a history of epilepsy or any condition requiring anticonvulsant medication; had received transcranial

magnetic stimulation, vagal nerve stimulation or electroconvulsive therapy during the current depressive episode; were currently taking psychotropic medications; were currently receiving psychotherapy; displayed evidence of significant suicide risk; failed to respond to any antidepressant at adequate dose and duration in the current episode.

Participant compensation

Compensation for the study components relevant to the current analyses was as follows:

- Completion of the detailed interview and questionnaires administered at screening – $150
- Completion of the two EEG recordings – $68

Compensation for other study components that are not presented in this study, was as follows:

- Completion of two MRI scans – up to $200
- Completion of a behavioral task – up to $32
- Completion of blood samples for research purposes – $25 per sample, up to $175 total
- Completion of genetic blood sampling – $50
- Completion of the final clinical rating session of the study – $50

The total possible compensation for the study was $725.

Participants lost to follow-up

Of the 143 participants who received sertraline, 117 completed all 8 weeks of the intervention, whereas 26 discontinued (7 of whom were lost to follow-up). Of the 144 participants who received placebo, 125 completed all 8 weeks of the intervention, whereas 19 discontinued (5 of whom were lost to follow-up). A summary of the reasons why participants dropped out is provided in Table S1.

EEG systems used across the four recording sites

Columbia University. 72-channel EEG was recorded using a 24-bit BioSemi system with a Lycra stretch electrode cap (Electro-Cap International Inc., Ohio), sampled at 256 Hz (bandpass:

DC-251.3 Hz). An active reference (ActiveTwo EEG system) at electrode locations PPO1 (common mode sense) and PPO2 (driven right leg) were used.

McLean Hospital. 129-channel EEG was recorded using a Geodesic Sensor Net system (Electrical Geodesics, Inc., Eugene, Oregon), sampled at 250 Hz (bandpass: 0.01-100 Hz). Data were referenced to the vertex (Cz) at acquisition.

University of Michigan. 60-channel EEG was recorded using a 32-bit NeuroScan Synamp system (Compumedics, TX) using a Lycra stretch electrode cap (Electro-Cap International Inc., Ohio), sampled at 250 Hz (bandpass: 0.5-100 Hz). A nose reference was used during acquisition.

University of Texas. 62-channel EEG was recorded using a 32-bit Neuroscan Synamp system (Compumedics, TX) using a Lycra stretch electrode cap (Electro-Cap International Inc., Ohio), sampled at 250 Hz (bandpass: DC-100 Hz). A nose reference was used during acquisition.

EEG preprocessing

A standardized analysis pipeline was developed and implemented by researchers at the Columbia site to minimize cross-site differences (1). First, data were interpolated to a common, 72-channel montage using spherical spline (2) and resampled at 256 Hz. Second, electrodes with poor signal were interpolated using a spherical spline interpolation (recordings with less than 80% of usable data were discarded). Third, a spatial principal component analysis was used to correct for blink artifacts (3). Fourth, artifact-free data were segmented into 2 second, non-overlapping epochs, and bandpass filtered at 1-60 Hz (24-dB/octave). Fifth, residual artifacts were identified on an individual channel basis within each epoch using a semiautomated reference-free approach (4). Finally, flagged channels were interpolated using spherical spline from data of all valid channels for a given epoch if less than 25% of channels were flagged for this epoch.

Evidence for the validity of the LORETA algorithm

The eLORETA solution space consists of 6239 cortical gray matter voxels in a realistic head model using the Montreal Neurological Institute 152 template. Validation for the LORETA algorithm comes from studies using simultaneous EEG and fMRI (5) as well as in an EEG localization study for epilepsy (6). The algorithm has also received validation from studies examining LORETA and fMRI data (7-9), or LORETA and PET data (10-12) in the same samples. In a review of independent source localization techniques, sLORETA – the algorithm upon which the eLORETA algorithm used in the current study was based – was found to perform best in terms of localization error (13). In the context of functional connectivity, eLORETA has been found to minimize the detection of false positive connections significantly more so compared to other EEG source localization methods (14).

Additional information about computation of lagged phase synchronization

Lagged phase synchronization is a metric that refers to the nonlinear dependence between the phases of pairs of intracortical EEG source estimates. It is a measure of phase synchrony between intracortical signals in the frequency domain (calculated using normalized Fourier transforms). The strength of this method is its ability to minimize the impact of volume conduction on EEG source-based connectivity estimates. Specifically, volume conduction refers to the tendency for intracortical signals to spread laterally upon contact with the skull, and this causes spurious correlations in activity detected at neighboring scalp-level electrodes. To minimize the effects of volume conduction, the instantaneous "zero-lag" contribution is excluded from the total phase synchronization, leaving only non-instantaneous synchronization.

Total phase synchronization (which is susceptible to volume conduction effects) is typically computed using the following formula:

$$\varphi^2{}_{x,y}(\omega) = \left|f_{x,y}(\omega)\right|^2 = \left\{\mathrm{Re}\left[f_{x,y}(\omega)\right]\right\}^2 + \left\{\mathrm{Im}\left[f_{x,y}(\omega)\right]\right\}^2 \qquad (1)$$

where: $$f_{x,y}(\omega) = \frac{1}{N_R}\sum_{k=1}^{N_R}\left|\frac{x_k(\omega)}{|x_k(\omega)|}\right|\left|\frac{y_k^*(\omega)}{|y_k(\omega)|}\right| \qquad (2)$$

In this algorithm, "ω" refers to the frequency band, and "x" and "y" are the intracortical sources (i.e., two ROIs in each connectivity pair). "Re" and "Im" indicate the real and the imaginary parts of a complex element *C*, respectively; x (ω) and y (ω) denote the Fourier transforms of the two signals x and y, respectively, at frequency "ω".

The second part of the formula (2) explains the cycle of *C* and "*" denotes a complex conjugate (this is where the sign of the imaginary part of a complex number is flipped but the real part is left unchanged). The instantaneous connectivity component is closely related to the real ("Re") part of the phase synchronization.

Lagged phase synchronization partials out the instantaneous component of total connectivity, and is defined as:

$$\varphi^2_{x,y}(\omega) = \frac{\left\{\mathrm{Im}\left[f_{x,y}(\omega)\right]\right\}^2}{1-\left\{\mathrm{Re}\left[f_{x,y}(\omega)\right]\right\}^2} \qquad (3)$$

This measures the similarity of two time series according to the phases of the signal, after the instantaneous similarity has been removed. A value of 0 indicates no synchronization and 1 indicates perfect synchronization. This measure is thought to capture only physiological connectivity. Additional details on the eLORETA connectivity algorithm can be found in Pascual-Marqui et al (15). In the current study, lagged phase synchronization was computed in the theta (4.5-7 Hz) and beta (12.5-21 Hz) frequency bands using a normalized Fourier transform.

Supplementary Results

Models showing significant connectivity effects at only the intercept or the slope, but not both

Two of the connectivity variables under consideration were found to have significant effects at either the intercept or the slope, but not both, specifically:

In the beta band, there was a significant *Connectivity* x *Time* interaction (effect on the slope) for rACC-PCC (the DMN hub) connectivity (B=-0.54, 95% CI=-1.00, -0.09, p=0.02) but the main effect of *Connectivity* (effect at intercept) was at trend (B=-2.12, 95% CI=-4.59, 0.36, p=0.09). Exploratory analyses confirmed that adding beta-band rACC-PCC connectivity terms did not provide a significantly better model fit compared to the reduced model that contained the covariates and rACC theta activity (LR=5.62, p=0.06).

Also in the beta band, there was a main effect of *Connectivity* (effect at intercept) for rACC-rAI (the SN hub) connectivity (B=2.75, 95% CI=0.15, 5.35, p=0.04) however the *Connectivity* x *Time* interaction term was not significant (B=0.10, 95% CI=-0.38, 0.58, p=0.68). The addition of beta-band rACC-rAI connectivity terms did not provide a better model fit than the reduced model containing covariates and rACC theta activity model (LR=5.20, p=0.07).

Results of mediation models

For illustration purposes, the results of the two mediation models tested are shown in Figure S2. The indirect effect of baseline rACC theta activity on HRSD improvement through baseline theta-band rACC-rAI connectivity was -0.17 (SE=0.30; 95% CI=-0.88, 0.34). In the second mediation model, where change in theta-band rACC-rAI connectivity from baseline to week 1 was evaluated as the potential mediator, the indirect effect was 0.02 (SE=0.03; 95% CI= -0.49, 0.49). The inclusion of zero within the CIs for both models indicated that neither baseline theta-band rACC-rAI connectivity nor early change (baseline to week 1) in this connectivity was a mediator.

Control analyses examining potential confounds in the link between theta-band rACC-rAI connectivity and remission status

The between-subjects variability in theta-band rACC-rAI connectivity at baseline and week 1, between the placebo and sertraline groups is shown in Fig. S3. As is evident, there were no differences in connectivity between the groups at either time point.

Theta-band rACC-rAI connectivity changes from baseline to week 1 predicted remission status after controlling for baseline HRSD scores (odds ratio=2.90, 95% CI=1.11, 7.58, p=0.03). Aligning with the absence of moderation or mediation effects, we confirmed that theta-band rACC-rAI connectivity changes predicted remission status even when rACC theta activity change was entered into the model (odds ratio=2.94, 95% CI=1.12, 7.71, p=0.03) indicating that the relationship between early theta-band rACC-rAI connectivity changes and symptom remission was not related to early rACC theta activity changes. Theta-band rACC-rAI connectivity also remained a significant predictor when recruitment site was entered into the model as a covariate (p=0.04).

Link between rACC connectivity and depression chronicity

Relative to those with non-chronic MDD at baseline (n=122), those with chronic (episode duration longer than 2 years) MDD (n=116) – defined as having had lower baseline theta-band rACC-rAI connectivity, $t(236)=2.83$, p=0.005, Cohen's d=0.37 [chronic M=-1.12, SD=0.22; non-chronic M=-1.04, SD=0.21]. This was not driven by differences in symptom severity, as chronic and non-chronic MDD patients did not differ in baseline HRSD scores, $t(236)=-0.62$, p=0.53, and connectivity differences remained significant when controlling for baseline HRSD scores, $F(1, 235)=7.93$, p=0.005, η_p^2=0.03.

Tests of whether early changes in theta-band rACC-rAI connectivity reflect a marker of depression remission that is already in progress during the first week of treatment

As requested by an anonymous Reviewer, we examined whether remitters who were predicted by early changes in theta-band rACC-rAI connectivity were those who showed a decline in HRSD scores from baseline to week 1. If this were the case, then this may indicate that early changes in theta-band rACC-rAI connectivity represents a potential marker of depression remission that is already in progress during the first week of treatment.

To do this, we generated the predicted group membership (remitter vs. non-remitter) from the binary logistic regression model examining the degree to which early changes in theta-band rACC-rAI connectivity from baseline to week 1 predict depression remission status at week 8. The model accurately classified 109 of the 122 individuals who did not remit (89.3% accuracy) but only 12 of the 73 individuals who did remit (16.4% accuracy). Next, we ran a *Remitter* (predicted remitter, predicted non-remitter) x *Week* (baseline, week 1) repeated measures ANOVA to determine whether predicted remitters showed greater depressive symptom reductions from baseline to week1 relative to predicted non-remitters. Of the 195 individuals with remission status data available, 186 had HRSD data at both baseline and week 1. The *Remitter* x *Week* interaction was not significant, $F(1,184)=0.09$, $p=0.73$, $\eta_p^2<0.001$, indicating that the predicted remitters and predicted non-remitters did not differ in their overall change in HRSD scores from baseline to week 1. There was a main effect of *Week*, $F(1,184)=25.06$, $p<0.001$, $\eta_p^2=0.12$, where across both groups, HRSD scores decreased significantly from baseline to week 1. Furthermore, there was a main effect of *Remitter*, $F(1,184)=23.75$, $p<0.001$, $\eta_p^2=0.11$, where averaged across baseline and week 1, the HRSD scores of the predicted remitters was significantly lower than the predicted non-remitters (predicted remitters: $M=13.60$, $SE=0.76$; predicted non-remitters: $M=17.58$, $SE=0.29$).

These results suggest that remitters, as predicted by early changes in theta-band rACC-rAI connectivity, were more likely to have lower HRSD scores at the beginning of treatment. This is consistent with the widely-replicated link between lower baseline depression severity and greater responses to treatment.

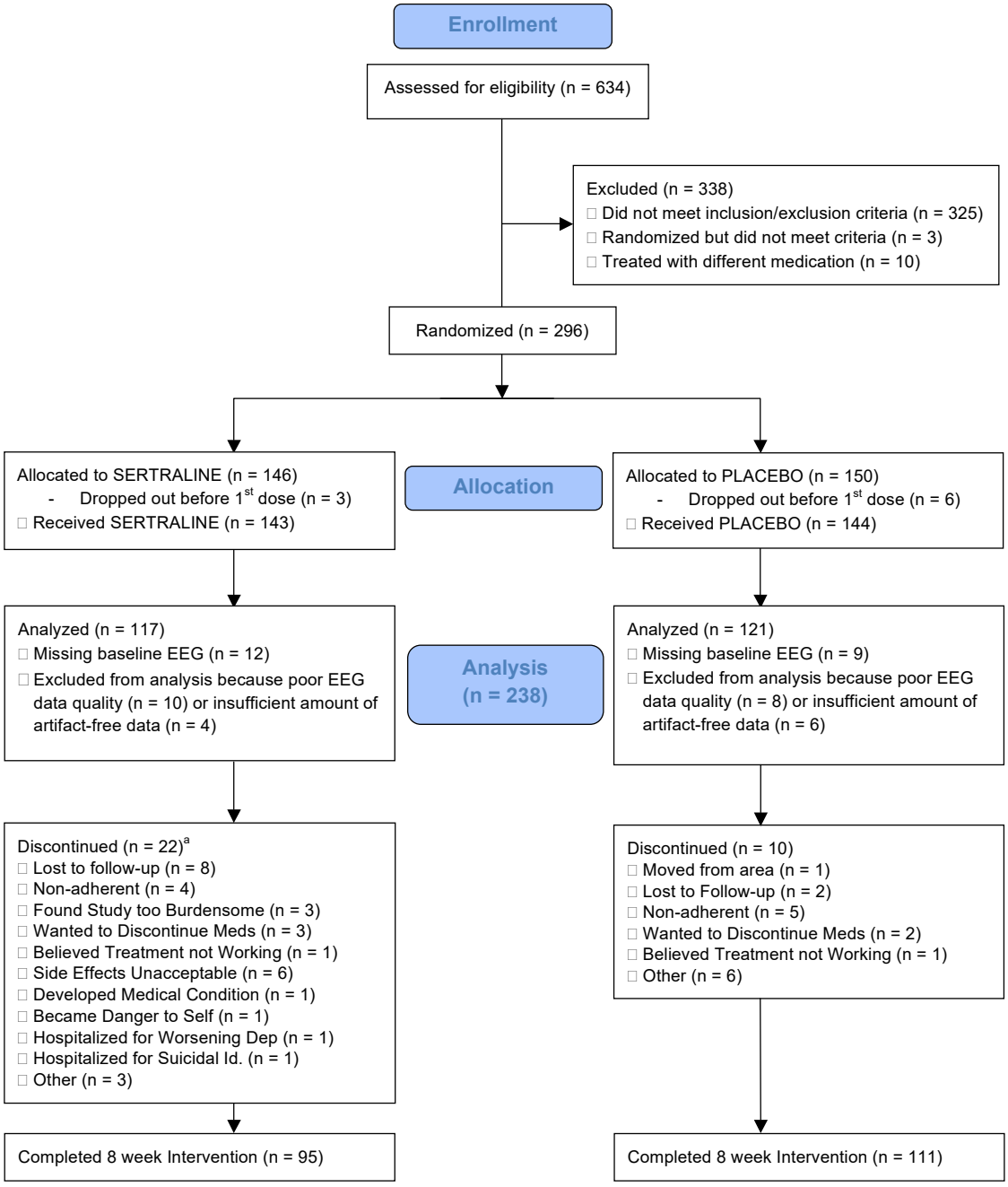
Symptom trajectories in first and second-stage treatment remitters

At the suggestion of an anonymous Reviewer, we also conducted an exploratory analysis that sought to compare the symptom trajectories of individuals who remitted at the first stage of treatment (i.e., at week 8 and who were predicted by early changes in theta-band rACC-rAI connectivity) to individuals who remitted after a second stage of treatment (i.e., at week 16 and who were not predicted by early changes in theta-band rACC-rAI connectivity) to individuals who never remitted.

The second stage of treatment was conducted from weeks 9 to 16, where some individuals who were randomized to placebo at the first stage of treatment received either placebo or sertraline at the second stage, and some individuals who received sertraline at the first stage were randomized to sertraline again, or to bupropion or placebo at the second stage. To inspect the rate of symptom improvement, we first divided the sample into those who remitted at the first stage of treatment (i.e., those who had a HDRS score ≤7 at week 8), those who remitted at the second stage of treatment (i.e., those who had a HDRS score ≤7 at week 16), and those who never remitted (i.e., those who had a HDRS score >7 at week 16) and plotted the raw mean HDRS (±SEM) scores over time (Fig. S4). Pairwise comparisons focused on differences in HDRS scores at week 8, since early changes in theta-band rACC-rAI connectivity predicted remission status at week 8.

Results showed that week 8 HDRS scores in second stage remitters (M=12.87, SD=3.42) were significantly higher than first stage remitters (M=3.96, SD=2.25), $t(119)=17.27$, $p<0.001$, but

were significantly lower than non-remitters (M=16.65, SD=5.25), $t(129)=18.84$, $p<0.001$. These findings suggest that second stage remitters fall intermediate between remitters who were predicted by early changes in theta-band rACC-rAI connectivity (i.e., first-stage remitters) and non-remitters in terms of symptom severity. It is possible that second stage remitters may be captured by changes in theta-band rACC-rAI connectivity over a longer time course (e.g., from baseline to week 8). Although EEG data were only obtained at baseline and week 1 in the current study, future studies examining changes in theta-band rACC-rAI connectivity over a longer time course would assist in determining whether this connectivity marker reflects remission that is "in progress" or whether it is a marker that indicates a person's likelihood of achieving remission/early response.



[a]Note that there are more reasons for exclusion than there are total discontinued participants as some participants discontinued for more than one reason.

Figure S1. CONSORT flow diagram showing numbers of participants who were randomized to treatment, who received treatment, who had valid EEG data available for the current analyses, and who completed 8 weeks of treatment.

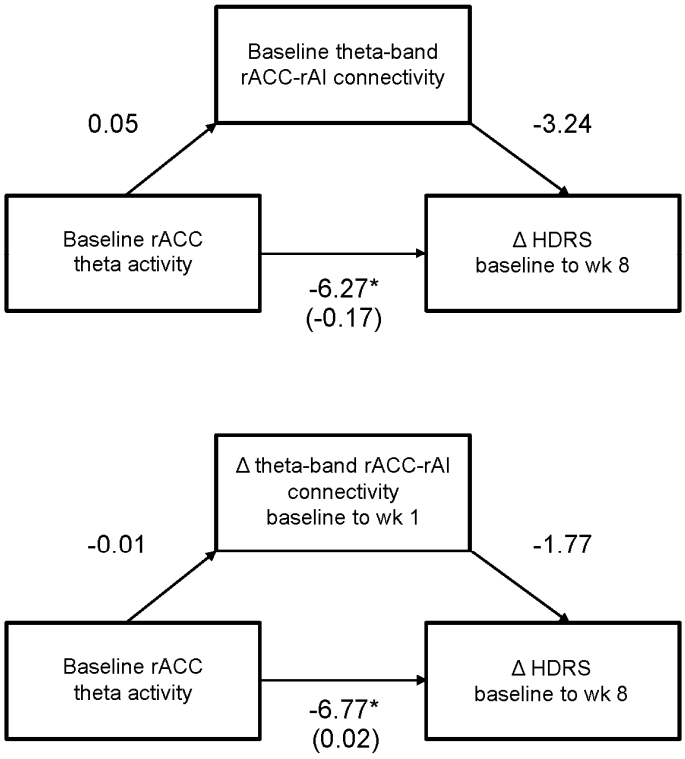


Figure S2. Figure shows mediation models examining the indirect (mediating) effect of baseline theta-band rACC-rAI connectivity (top model) and changes in theta-band rACC-rAI connectivity from baseline to week 1 (bottom model) as potential mediators of the link between elevated baseline rACC theta activity and greater reduction in HRSD scores from baseline to week 8. Neither model shows evidence of theta-band rACC-rAI connectivity acting as a mediator. rACC=rostral anterior cingulate cortex; rAI=right anterior insula, ΔHRSD=change in Hamilton Rating Scale for Depression scores from baseline to week 8; *=significant at $p<0.05$.

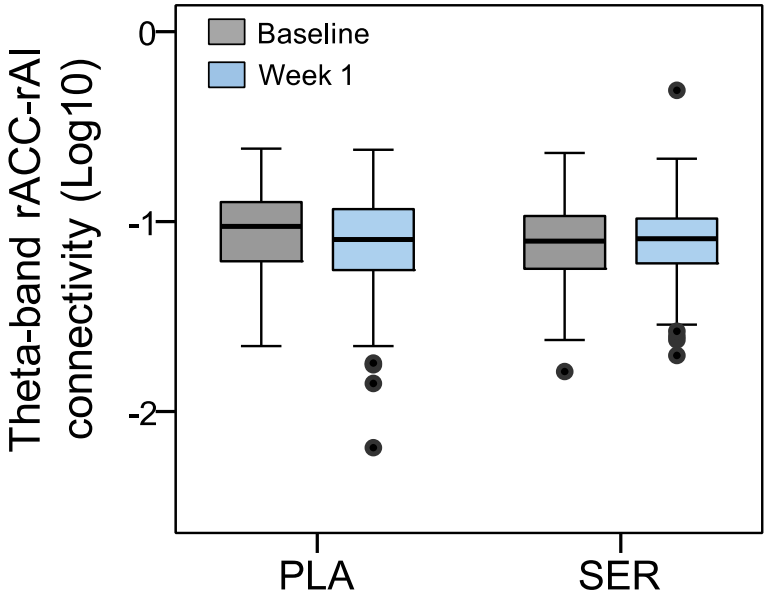


Figure S3. Box plots showing the between-subject variability in theta-band rACC-rAI connectivity between the placebo (PLA) and sertraline (SER) groups at baseline (grey bars) and week 1 (blue bars). Cases represented by black dots are greater than ±2SD from the mean but less than ±3SD, and are not considered outliers. The figure shows that there were no differences in theta-band rACC-rAI connectivity between the two treatment arms either at baseline or at week 1. This suggests that early changes in theta-band rACC-rAI connectivity and their relationship with depression remission at week 8 cannot be solely attributable to the acute effects of sertraline (since the same effects were observed for the placebo group). This further highlights theta-band rACC-rAI connectivity as a prognostic, yet treatment non-specific indicator of depression improvement.

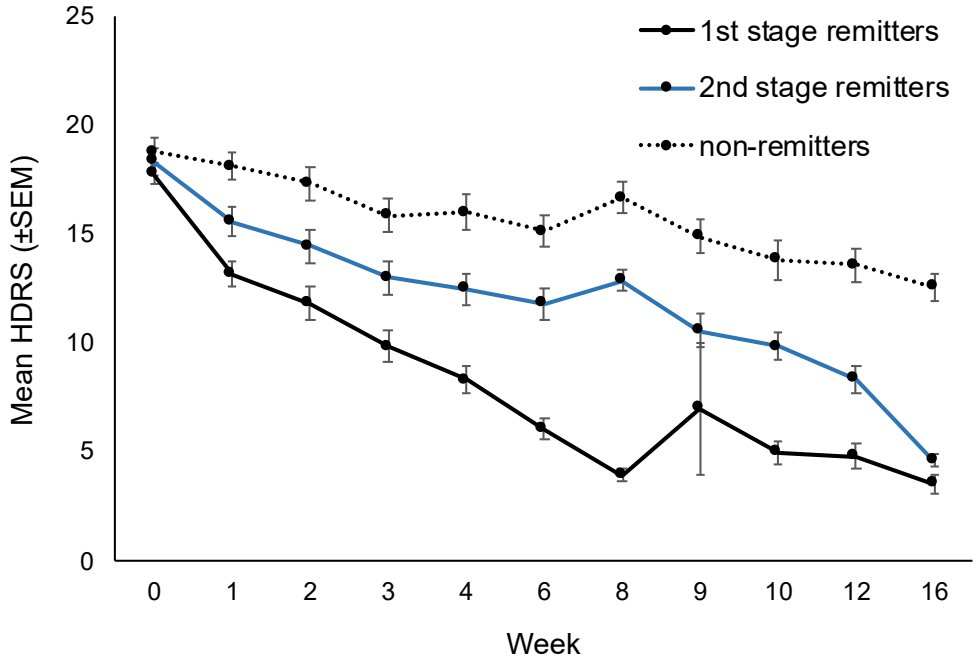


Figure S4. Mean (±SEM) HDRS scores across the first stage (weeks 0-8) and second stage (weeks 9-16) of treatment in individuals who were classified as: 1st stage remitters (HDRS ≤7 by week 8); 2nd stage remitters (HDRS ≤7 by week 16); non-remitters (HDRS >7 at weeks 8 and 16).

Table S1. Reasons for participant dropout across the sertraline and placebo groups

Discontinued Sertraline (n=26)	**Discontinued Placebo (n=19)**
Lost to follow-up (n=7)	Lost to follow-up (n=5)
Non-adherent (n=6)	Non-adherent (n=6)
Wanted to discontinue medication (n=3)	Wanted to discontinue medication (n=4)
Believed treatment was not working (n=1)	Believed treatment was not working (n=2)
Side effects unacceptable (n=9)	Side effects unacceptable (n=1)
Found study too burdensome (n=3)	Moved from area (n=1)
Developed medical condition (n=1)	Became pregnant (n=1)
Became danger to self (n=1)	Other (n=6)
Hospitalized for worsening depression (n=1)	
Hospitalized for suicidal ideation (n=1)	
Other (n=4)	

Note. Numbers add up to more than the totals because participants discontinued for more than one reason.

Table S2. Seed regions used for connectivity analyses

Region	X	Y	Z	Reference
Rostral anterior cingulate cortex	11	45	-6	Pizzagalli et al. (2001), Fig. 1
Posterior cingulate cortex	0	-52	26	Yeo et al. (2011), Table 5
Left dorsolateral prefrontal cortex	-43	22	34	Dosenbach et al. (2007), Table 1
Right anterior insula	42	10	-12	Seeley et al. (2007) Supp. Table 2

Note. X=left(-) to right(+); Y=posterior(-) to anterior(+); Z=inferior(-) to superior(+). Note that regions-of-interest were not registered to subject space from the MNI template, but rather, were retained in MNI space.

Table S3. Demographic and clinical factors that have been identified as predictors of poor outcome in prior studies of depression. Variables capturing each of these factors were used as covariates in our final model and the model reported in Table 2 of Pizzagalli, Webb, et al. (2018)

Covariate	**Reference**
Greater baseline depression severity (QIDS-SR, HAM-D)	Trivedi *et al*. (2006)
Anxious depression (anxiety factor score on the HAM-D)	Fava *et al*. (2008)
Anhedonia (CIDI)	Spijker *et al*. (2001)
Male gender	Trivedi *et al*. (2006)
Older age	Fournier *et al*. (2009)
Lower socioeconomic status	Jakubovski *et al*. (2014)
Being non-Caucasian	Trivedi *et al*. (2006)
Being unmarried	Fournier *et al*. (2009)

Note. QIDS-SR=Quick Inventory of Depressive Symptoms, Self-Report; HAM-D=Hamilton Rating Scale for Depression; CIDI=Composite International Diagnostic Interview.

Table S4. Demographic and clinical characteristics of the sertraline and placebo groups for the subsample included in the current analysis (n=238)

	Whole sample (n=238)	**Sertraline (n=117)**	**Placebo (*n*=121)**	***P* Value**
Age in years, M (SD)	36.9 (13.2)	36.6 (13.5)	37.3 (13.0)	0.68
Female, No. (%)	151 (63.4)	79 (67.5)	72 (59.5)	0.20
Years of education, M (SD)	15.1 (2.4)	14.9 (2.4)	15.3 (2.4)	0.21
Caucasian, No. (%)	163 (68.5)	78 (66.7)	85 (70.2)	0.55
Hispanic, No. (%)	42 (17.6)	20 (17.1)	21 (17.4)	0.90
Married, No. (%)	49 (20.6)	22 (26.5)	29 (24.0)	0.19
Employed, No. (%)	135 (56.7)	64 (54.7)	71 (58.7)	0.54
Age of MDD onset, M (SD)	16.3 (5.7)	16.5 (5.8)	16.1 (5.6)	0.63
Current MDE length (months), median	15.5	13.0	18.0	0.49
Number of prior MDEs, median	4	4	5	0.42
QIDS, M (SD)	18.2 (2.8)	18.6 (2.8)	17.7 (2.8)	0.02
HRSD 17-item, M (SD)	18.5 (4.5)	18.4 (4.5)	18.5 (4.4)	0.89

Note. MDD=Major Depressive Disorder; MDE=Major Depressive Episode; QIDS=Quick Inventory of Depressive Symptoms; HRSD=Hamilton Rating Scale for Depression; *P* Values indicate the significance value for tests of differences between the sertraline and placebo group.

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