The incremental predictive validity of rostral anterior cingulate cortex activity in relation to symptom improvement in depression: A randomized clinical trial

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Key Points

Question: Does increased pretreatment rostral anterior cingulate activity (rACC) have incremental predictive validity with respect to treatment outcome in major depression?

Findings: Higher rACC theta activity at both baseline and Week 1 predicted greater improvement in depressive symptoms, even when controlling for clinical and demographic variables previously linked to treatment response.

Meaning: Increased pre-treatment rACC theta activity represents a non-specific, prognostic marker of treatment outcome that has now been replicated in several studies, and thus warrants consideration for implementation in clinical care.

Abstract

Importance: Major depressive disorder (MDD) remains challenging to treat. Although several clinical and demographic variables have been found to predict poor antidepressant response, these markers have not been robustly replicated to warrant implementation in clinical care.

Objective: Increased pretreatment rostral anterior cingulate (rACC) activity has been linked to better antidepressant outcomes. However, no prior study has evaluated whether this marker has incremental predictive validity over clinical and demographic measures. We hypothesized that increased pre-treatment rACC theta activity would predict symptom improvement regardless of randomization arm.

Design: Randomized clinical trial enrolling MDD outpatients between August 2011 and December 2015 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression; EMBARC). Resting electroencephalographic (EEG) data were recorded at baseline and one week after trial onset, and rACC theta activity was extracted using source localization.

Setting: Multi-center study at four university hospitals.

Participants: Non-psychotic outpatients with chronic or recurrent MDD (18-65 years) consecutively recruited from four university hospitals. 634 patients were screened, 296 were randomized, 266 had EEG recordings, and 248 had usable EEG data.

Intervention: Randomized clinical trial involving an 8-week course of sertraline or placebo.

Main Outcome: Hamilton Rating Scale for Depression score (assessed at baseline, weeks 1, 2, 3, 4, 6 and 8).

Results: The 248 participants (160 women, 88 men) with usable EEG data had a mean age of 36.75 (SD=13.15) and were mostly female (64.52%). Higher rACC theta activity at both

baseline (*b*=-1.05, 95% CI, -1.77 to -0.34, p=.004) and Week 1 (*b*=-0.83, 95% CI, -1.60 to -0.06, p<.04) predicted greater depressive symptom improvement, even when controlling for clinical and demographic variables previously linked with treatment outcome. These effects were not moderated by treatment arm.

Conclusions and Relevance: Increased pre-treatment rACC theta activity represents a non-specific, "prognostic" marker of treatment outcome. This is the first study to demonstrate that rACC theta activity has incremental predictive validity. The rACC marker–in combination with clinical and demographic variables–accounted for an estimated 39.6% of the variance in symptom change (with 8.6% of the variance uniquely attributable to the rACC marker).

Trial Registration: NCT01407094; http://clinicaltrials.gov/show/NCT01407094

Key Words: Biosignatures, antidepressant response, EMBARC, sertraline, rostral ACC, personalized treatment, LORETA, EEG, theta activity

Introduction

Major Depressive Disorder (MDD) is a prevalent and recurrent condition associated with substantial disability, economic costs, and suicide rate[1]. Despite significant effort, MDD remains challenging to treat. In the multi-site STAR*D study, for example, only about 50% of individuals with MDD responded (i.e., showed ≥50% reduction in depressive symptoms) to the selective-serotonin reuptake inhibitor citalopram, and only 33% achieved remission.[2] In primary care, the rates of non-response (70%)[3] and non-remission (75%)[4] to first-line antidepressants are even higher. Compounding these challenges, 4-8 weeks of treatment are often needed to evaluate the efficacy of a given antidepressant[5,6], which can result in protracted symptoms. Importantly, modest rates of response and remission are not unique to pharmacology but extend to psychotherapy.[7]

Owing to this limited success, identifying variables that predict the likelihood of antidepressant response would be clinically valuable. For example, identification of pre-treatment variables that predict remission in a treatment-specific fashion (so-called *moderators*) could facilitate optimal treatment selection. Identification of variables that change early in treatment and predict subsequent symptom improvement (*mediators*) could inform timely adjustments. Finally, identification of nonspecific markers of depressive symptom improvement (*prognostic markers*) could be used to allocate individuals at risk of poor outcome to a more intensive intervention from the outset and suggest more careful monitoring. Equally important, identification of such variables could inform our understanding of treatment mechanisms, and hasten the development of novel interventions.[8]

Several clinical and demographic variables have been found to predict poor outcome to antidepressants, including comorbid psychiatric disorders[9], general medical conditions[2], greater

depressive severity[2], depression chronicity[10], anxious depression[11], anhedonia[12], being male[2], older age[13], lower socioeconomic status[14], being non-Caucasian[2], being unmarried[13], and lower education[2]. However, many of these markers have not been robustly replicated to warrant implementation in clinical care, and are not particularly informative with respect to mechanisms implicated in treatment response.

Due to these limitations, there has been increased interest in identifying biological markers that reliably predict clinical outcome. Baseline (i.e., pre-treatment) level of activity in the rostral (pregenual) anterior cingulate cortex (rACC; Broadmann area 24/32) has emerged as a particularly promising predictor. First reported in 1997[15], increased pre-treatment activity in the rACC has been found to predict better outcome to a variety of antidepressants, a finding we replicated using source-localized electroencephalography.[16] A meta-analysis of 23 studies reported that the link between better antidepressant outcome and increased pre-treatment rACC activity has been replicated 19 times (effect size: 0.918).[17] Critically, this marker has been shown to predict depressive symptom improvement across a range of interventions, including multiple antidepressants (e.g. SSRIs, atypical antidepressants, ketamine), sleep deprivation, transcranial magnetic stimulation, and placebo[18,19] (but see failures to replicate[20–23]). In sum, increased pre-treatment rACC activity appears to be a general prognostic (treatment non-specific) marker of symptom improvement.

However, prior literature is characterized by three important limitations. First, prior work had limited statistical power, with the largest sample in the aforementioned meta-analysis[17] including only 44 MDD outpatients. Second, a placebo arm was missing in all but two reports[24,25], with most studies using open-label or single-arm designs. Third, and most importantly, no study has evaluated the incremental validity of the rACC marker—that is, its

ability to predict symptom improvement while controlling for clinical and demographic variables previously linked to treatment outcome. Given the relative ease associated with collecting clinical and demographic variables, imaging measures must show incremental predictive validity to justify the costs and technical complexities associated with their use in the context of treatment outcome prediction.

The goal of this study was to address these limitations in the context of the multi-site EMBARC study, which recruited over three hundred outpatients with recurrent, non-psychotic MDD across four sites.[26] EEG data were recorded at baseline and one week after onset of an 8-week clinical trial, in which outpatients were randomized to sertraline or placebo. The inclusion of two EEG assessments allowed us to test (1) the stability of rACC theta activity, and (2) the consistency of rACC–outcome associations over time. Based on prior findings, we hypothesized that increased pre-treatment (baseline) and Week 1 rACC current density would predict depressive symptom improvement regardless of randomization arm, above and beyond clinical and demographic variables previously linked to treatment outcome.

Methods

A detailed description of the study design, randomization procedures, and power analyses can be found in [26] and the *Supplement*.

Participants

Outpatients (18-65 years) meeting criteria for MDD based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[27] were recruited at four sites: Columbia University, Massachusetts General Hospital, University of Michigan, and University of Texas

Southwestern Medical Center. The study was approved by the Institutional Review Boards of all sites, and participants provided informed written consent. Participants had a Quick Inventory of Depressive Symptomatology score (QIDS-SR)[28] of ≥14 at both the screening and randomization visits. To minimize clinical heterogeneity, only patients reporting early onset (before age 30) MDD that was chronic (episode duration >2 years) or recurrent (≥2 recurrences including the current episode) were enrolled. For additional exclusion criteria, see *Supplement*.

Clinical Trial

Using a double-blind design, participants were randomized to an 8-week course of sertraline (up to 200 mg daily) or placebo. Dose adjustments were allowed at weeks 1, 2, 3, 4, and 6. The Hamilton Rating Scale for Depression 17-item (HRSD)[29] was the primary outcome variable, and was administered at baseline (week 0), weeks 1, 2, 3, 4, 6 and 8.

EEG Recordings and Pre-processing

At all sites, resting EEG was recorded during four 2-minute periods, half with eyes-closed (C) and half eyes-open (O) in a counterbalanced order (*Supplement*). Because different EEG acquisition systems were used across sites, a manual was developed to standardize recordings and instructions provided to participants. To minimize cross-site differences, EEG data were interpolated to a common montage (72 channels) and sample rate (256 Hz), and a single, standardized analysis pipeline[30] was implemented to extract non-overlapping, artifact-free, 2-s epochs for source localization analyses (see *Supplement*).

Source Localization Analyses

Source localization analyses were conducted using Low Resolution Electromagnetic Tomography (LORETA)[16,31], which infers the intracranial generators of scalp-recorded EEG signals, and followed identical procedures as in prior studies[16,24] (*Supplement*). To evaluate the robustness of findings, current density for a narrow (6.5-8.0 Hz) and broader (4.5-7 Hz) theta band was extracted from the rACC cluster (14 voxels; see *Supplement Figure 1* and *Supplement Table 1*) previously associated with better antidepressant outcome.[16] This cluster was also used by [24] and spatially overlapped with the one linked to treatment outcome in two additional EEG studies.[32,33]

Statistical Analyses

To test whether rACC theta (4.5-7 Hz) current density predicted greater symptom reduction, as measured by the HRSD, we utilized hierarchical linear modeling (HLM), with mixed-effects repeated-measures models implemented in SAS (version 9.4) PROC MIXED (SAS Institute Inc, Cary, NC). Slopes and intercepts were treated as randomly varying across participants, and unstructured error variance/covariance matrices were estimated.[13,34] Models were implemented with full maximum likelihood estimation procedures and degrees of freedom for hypothesis tests were estimated with the Kenward–Roger approximation.[35] To test the incremental predictive validity of rACC theta current density ("rACC theta"), models covaried for baseline clinical and demographic variables previously found to predict depressive symptom change, including age, sex, race, employment status, marital status, number of years of education, chronic depression, as well as pre-treatment severity of depressive symptoms (HRSD), anxiety (Anxious Arousal subscale of the Mood and Anxiety Symptom Questionnaire)[36] and anhedonia (Snaith Hamilton Pleasure Scale).[37]

To test whether rACC theta was associated with HRSD improvement over time, we included a *rACC theta* X *Time* interaction. To evaluate whether treatment group (sertraline vs. placebo) moderated this effect, we further included a *Treatment Group* X *rACC theta* X *Time* interaction. Similarly, for each of the above covariates, *Treatment Group* X *Predictor* X *Time* interactions were included. A *Treatment Group* X *Site* X *Time* interaction was also included in all models to account for different sites.

Given the relatively large number of terms, we used a step-wise procedure to pare down the number of predictors (*Supplement*; see ref. [12]). To the extent that a significant rACC theta finding emerged (i.e., remained significant in the last step), we also tested whether the inclusion of this rACC theta term in our model yielded significantly improved fit relative to a "reduced" model (i.e., including all predictors from the final model, but excluding the rACC theta term). Model fits were compared by computing a likelihood ratio test on deviance statistics.[34] All available data were used (including from dropouts), rendering these full intent-to-treat analyses (n=248). Patients missing baseline EEG data or who dropped out prior to receiving at least 1 dose of sertraline (or placebo) were excluded. Follow-up completer analyses were also conducted by excluding patients who dropped out of treatment prior to the Week 8 HRSD assessment (completer N=214; see *Supplement*).

Results

Participant Characteristics

Between August 2011 and December 2015, 634 patients were screened and 296 were randomized (Figure 1). Nine randomized patients dropped out prior to the first

231 medication/placebo dose, leaving 287 participants for analyses. Among the remaining 287
232 patients, 266 (92.3%) had EEG recordings, and 248 had usable EEG data (Table 1).
233 *Test-Retest Reliability*
234 Baseline and Week 1 rACC theta exhibited acceptable test-retest reliability in both the
235 sertraline ($r=0.70$; $p<1\times10^{-4}$) and placebo ($r=0.64$; $p<1\times10^{-4}$) groups (*Supplement Figure 2)*.
236 *Prediction of Depressive Symptom Improvement*
237 Table 2 presents the results of the final (Step 4) model. It is important to note that there
238 are two relevant model terms for each predictor: the effect at the intercept (*Time* centered to
239 represent estimated Week 8 HRSD scores) and on the linear slope estimates (captured by the
240 *Predictor* X *Time* interactions). These correspond to an effect of the predictor on final HRSD
241 scores, and an effect of the predictor on change in HRSD scores over time, respectively. To be
242 conservative, predictors were required to be associated with both outcomes (intercepts and
243 slopes) at $p<.05$ in order to be considered statistically significant.[13] In the final model, higher
244 rACC theta emerged as a significant predictor of lower week 8 HRSD scores (i.e., significant
245 effect on the intercept: $t(219)=-3.11$, $p=0.002$, $b=-6.81$, 95% CI: -11.13 to -2.49) and greater
246 depressive symptom improvement (i.e., significant effect on slope estimates: $t(214)=-2.92$,
247 $p=.004$, $b=-1.05$, 95% CI: -1.77 to -0.34; Table 2 & Figure 2A). For every 1 SD increase in
248 rACC theta, there was a 1.5-point decrease in week 8 HDRS scores. Similarly, when the latter
249 model was re-run substituting baseline rACC theta with Week 1 values, rACC theta again
250 emerged as a significant predictor of better HRSD outcome (intercept: $t(211)=-2.30$, $p<.03$,
251 $b=-5.40$, 95% CI: -10.03 to -0.77; slope: $t(210)=-2.13$, $p<.04$; $b=-0.83$, 95% CI:-1.60 to -0.06;
252 Figure 2B). Consistent with our hypothesis, the *Treatment Group* X *rACC theta* X *Time* was not
253 significant for either baseline ($t(217)=0.45$, $p=.65$, $b=0.32$, 95% CI: -1.08 to 1.72) or Week 1

(t(210)=1.76, p=.08, b=1.36, 95% CI: -0.16 to 2.88) rACC theta, indicating that the association between rACC theta and better outcome was not significantly moderated by treatment group. [1]

Critically, a significant likelihood ratio chi-squared test indicated that the final baseline model (i.e., including baseline rACC theta and covariates) provided significantly improved fit relative to a "reduced" model (i.e., including clinical and demographic covariates only): $\chi 2(2)=354.96$, $p<1\times10^{-4}$ (when substituting Week 1 rACC theta, $\chi 2(2)=802.61$, $p<1\times10^{-4}$). The final baseline model accounted for 39.63% of the between-subjects variance in the slope of symptom improvement (38.24% for the Week 1 rACC model). When the rACC term was removed from this model the variance accounted for was reduced to 31.06% (see *Supplemental Results*). Thus, baseline rACC theta activity accounted for an estimated 8.57% unique variance in outcome above clinical and demographic covariates. For completer analyses, see *Supplement*.

Discussion

Our goal was to evaluate whether baseline rACC theta activity predicted depressive symptom improvement in the multi-site EMBARC study. Several findings emerged. First, the rACC theta marker showed acceptable test-retest stability over one week (sertraline: r=0.70; placebo: r=0.64; ps<0.0001), replicating prior findings in controls.[30] These findings are notable considering that the second EEG assessment took place after trial onset, and they suggest that resting rACC theta activity may be a relatively stable individual characteristic related to subsequent symptom improvement. Second, higher pretreatment rACC theta predicted greater

[1] Analyses described here were based on theta activity defined as 4.5-7 Hz, and while applying an intermediate smoothing parameter to LORETA data. Some LORETA studies have defined theta activity in a relatively narrow frequency band (6.5-8 Hz) and have applied no extra smoothing (e.g., [16]). Accordingly, we re-ran our final models with the narrower theta range (6.5-7 Hz) and with no extra smoothing. A similar pattern of findings emerged (see *Supplemental Results*).

depressive symptom improvement even after accounting for multiple clinical/demographic variables previously associated with better treatment outcomes. The full model, including both rACC theta and covariates, accounted for 39.63% of variance in depressive symptom change, and provided a significantly better fit than a "reduced" model that included all covariates but not the rACC marker (the latter covariates-only model accounted 31.06% of the variance in symptom change). Thus, baseline rACC theta activity accounted for an estimated 8.57% unique variance in outcome. Third, findings remained when considering Week 1 rACC theta activity, which–in combination with covariates–accounted for 38.24% of the variance in depressive symptom change. It is important to note that of all predictors examined, only rACC theta activity and baseline severity of depressive symptoms were associated with significant effects on *both* the intercept (i.e., lower week 8 depression scores) and slope of depressive symptom improvement (Table 2). Fourth, the *Treatment Group* X *rACC theta* X *Time* interaction was not significant for either baseline or Week 1 rACC theta, indicating that the association between rACC theta and better outcome was not moderated by treatment. Based on current and prior findings[17], increased pre-treatment rACC theta activity represents a non-specific "prognostic" marker of treatment outcome.

Although the link between higher pre-treatment rACC activity and better antidepressant outcomes has been widely replicated (but see [20–22,38]), the mechanisms underlying this association remain unclear. When seen in the context of a large literature implicating frontocingulate dysfunction in MDD[17], as well as evidence that the rACC is a hub in the default mode network (DMN)[39], we previously speculated that increased resting rACC activity may predict better clinical outcome as it may be associated with more adaptive forms of self-referential processing and a better ability to suppress the DMN in situations requiring

297 recruitment of cognitive control.[17] Collectively, these processes might reduce maladaptive forms
298 of rumination characterized by negatively skewed self-introspection, difficulties dampening
299 negative emotions, and deficits in allocating attention to task demands. Findings highlighting a
300 key role of the rACC in the inhibition of negative information[40] and amygdalar activity in
301 response to emotional conflict[41], as well as optimistic biases[42], are consistent with this idea.
302 Future studies will be needed to evaluate these hypotheses. Additional research is also required
303 to investigate factors that may moderate rACC-outcome associations and help account for
304 inconsistencies (e.g., percentage of participants with prior exposure to antidepressants or
305 treatment resistance[20,43]).

306 In terms of possible neurochemical mechanisms, altered resting rACC activity may
307 reflect glutamatergic[44] or opioidergic[45] abnormalities. Critically, a recent study in depressed
308 outpatients reported that increased resting state functional connectivity within the rACC
309 predicted greater reduction in depressive symptoms in response to both placebo administration
310 with expectations of antidepressant effects and a 10-week open label treatment with citalopram.[19]
311 Findings linking increased rACC functional connectivity to both placebo and SSRI response in
312 the Sikora et al. study fit our results as well as a prior EEG study reporting that resting rACC
313 theta activity predicted treatment outcome in both medicated and placebo MDD groups.[18]

314 The potential clinical implications of the current findings warrant discussion. First,
315 although the current rACC theta marker has emerged in at least 20 independent studies across
316 labs, the need to identify *moderators* of treatment response and *mediators* that account for
317 symptom improvement remains a key priority. Whereas moderators could inform treatment
318 selection, mediators could help pinpoint causal mechanisms implicated in treatment response and
319 could be used to modify treatment strategies early. Promising behavioral (word fluency[46]),

electrophysiological (loudness dependent auditory evoked potential[47]) and imaging (glucose metabolism in the insula[48]) moderators have been described. Similarly, decreases in frontal theta cordance (a measure that combines both absolute and relative scalp EEG theta power) from baseline to 2-7 days post-treatment have been found to predict treatment response to SSRIs and serotonin-norepinephrine reuptake inhibitors.[49–51] Although promising, replications will be needed before any of these behavioral, EEG or imaging markers can be used to guide clinical care. Future analyses of the EMBARC dataset will test whether a combination of variables yields moderators and mediators that could be prospectively evaluated for guiding treatment selection.

In contrast to other neural markers,[47,48] rACC theta activity does not appear to be a moderator of treatment response. Thus, its utility for informing treatment selection appear limited. However, there may be important clinical implications. First, it may be possible to develop cognitive training interventions that target rACC function to potentiate or accelerate response to antidepressants. The recent demonstration of an augmentation of the antidepressant effect of transcranial magnetic stimulation in a treatment-resistant MDD sample via such a strategy is encouraging[8]. Whether similar effects will extend to patients without a history of treatment non-response will need to be evaluated. Second, future studies might consider clinical trials in which MDD patients at elevated risk of poor outcome–by virtue of low resting rACC theta activity in combination with other baseline markers of poor prognosis–are randomly assigned to a first-line antidepressant vs. a more intensive intervention or combined treatment. Of note, because prior EEG studies have demonstrated links between pre-treatment rACC activity and better antidepressant response using only 28-32 electrodes[16,32,33], this hypothesis could be tested using relatively simple and widely available EEG montages. These and related efforts[52] might allow in the near future to guide treatment decisions based on individual patient

characteristics, rather than a trial-and-error approach that still dominates clinical depression care.

Limitations

Some limitations should be acknowledged. First, source localization requires specialized expertise, which could limit applications in clinical settings. Second, this study used relatively strict inclusion criteria, and it is unclear whether findings will generalize to treatment-resistant samples. Third, the unique variance explained by the rACC marker was modest (8.57%).

Conclusions

The current multi-site study shows that higher baseline rACC theta activity predicted greater improvement in depressive symptoms, even when controlling for clinical and demographic variables previously linked to treatment response. This prognostic marker of treatment outcome warrants further scrutiny for possible implementation in clinical care.

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Figure Captions

Figure 1. CONSORT flow diagram. Primary hierarchical linear model (HLM) analyses were intent-to-treat (i.e., include dropouts). Thus, the flow diagram summarizes information relevant to intent-to-treat analyses. For information regarding follow-up, dropout rates between groups, and reasons for dropout, see *Supplement.*

Figure 2. Estimated week 8 Hamilton Depression Rating Scale (HRSD) scores for the sertraline and placebo groups at three values of baseline rACC theta activity: one standard deviation below the mean, the mean, and one standard deviation above the mean. Error bars represent ±1 standard error.

Table 1: Clinical and demographics data for the sample included in the analyses (n=248)

	MDD subjects	
	Mean	SD
Age	36.75	13.15
% Female	64.52	-
Years of Education	15.08	2.41
Ethnicity (% Caucasian)	68.95	-
Marital status (% married)	20.82	-
Employment (% employed)	56.97	-
Age of MDD onset (years)	16.23	5.70
Length of current MDE (months)	13 (median)	
Number of prior MDEs	4 (median)	
QIDS	18.19	2.81
HRSD (17-item)	18.48	4.44

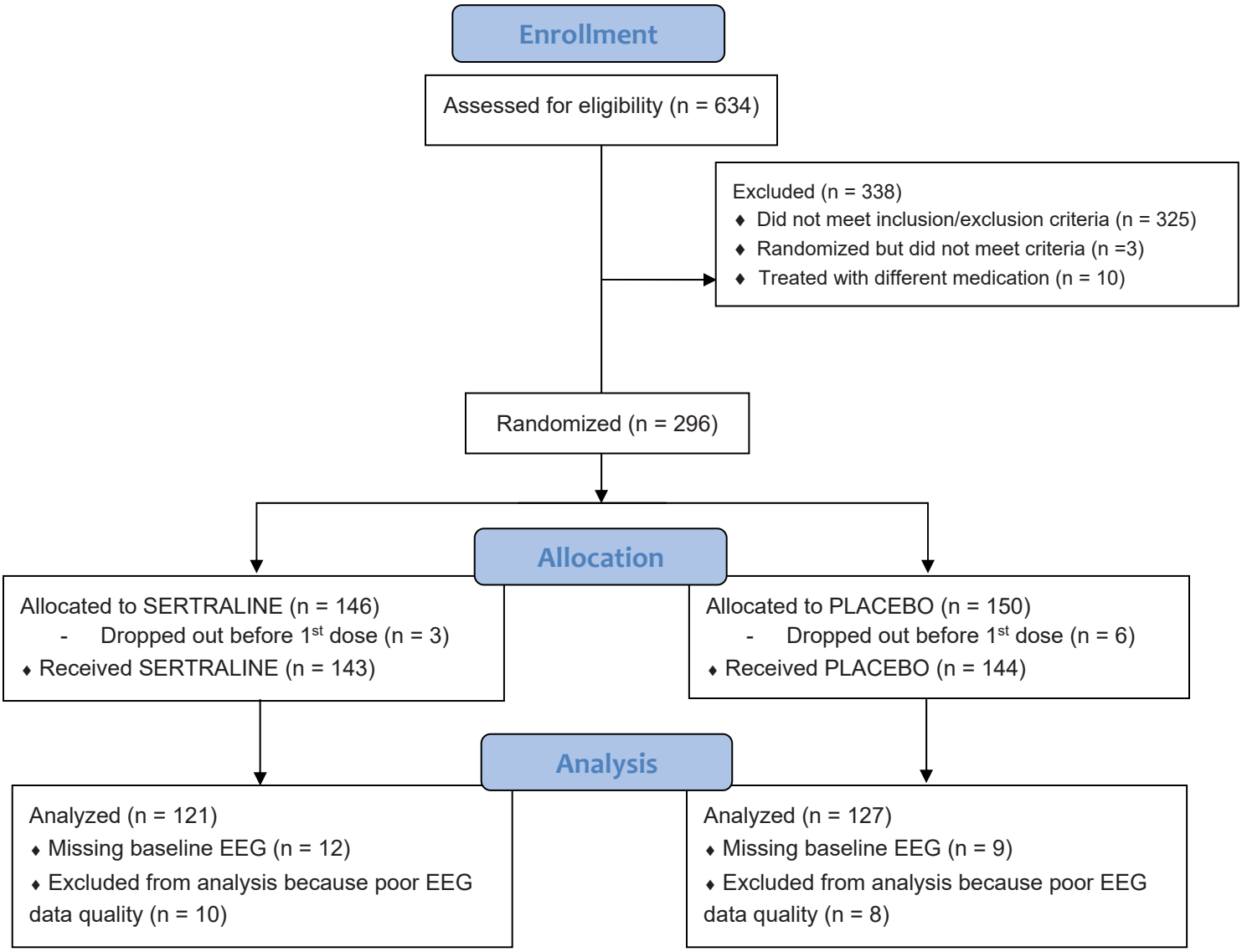
Notes: Information about ethnicity was collected by self-report. MDE: Major Depressive Episode. QIDS: Quick Inventory of Depressive Symptomatology score[28], HRSD: Hamilton Rating Scale for Depression[29]

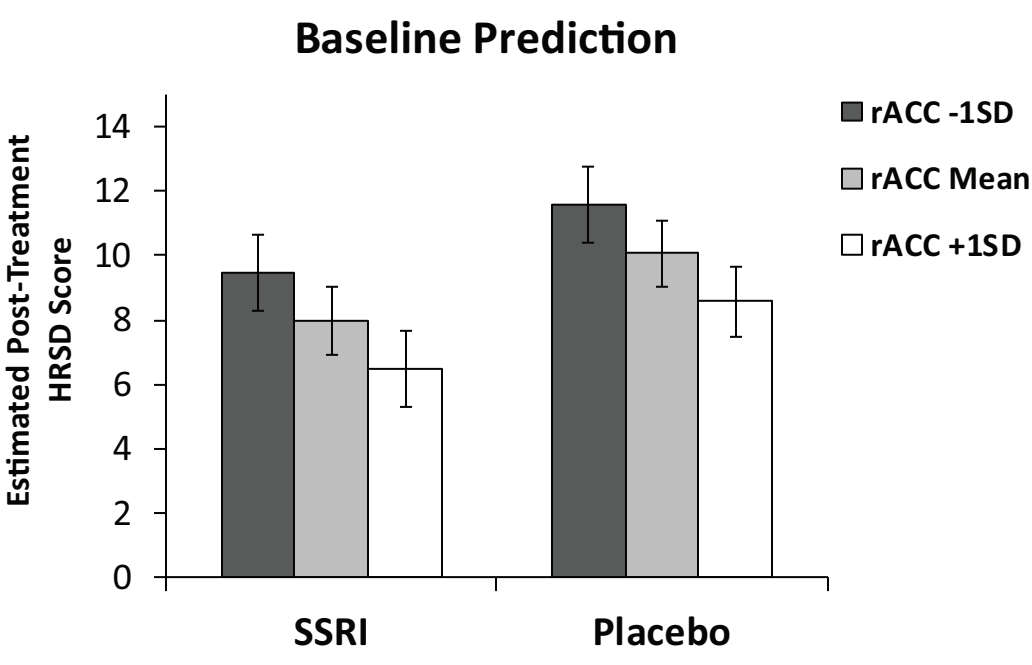
Table 2. Final Hierarchical Linear Model

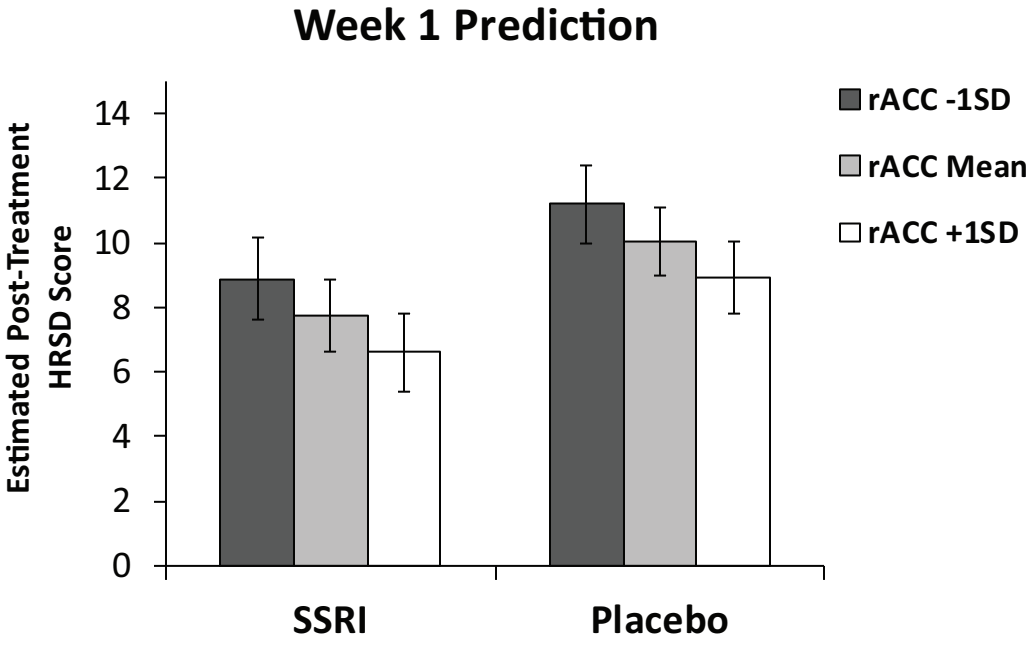
Model Term	*F*	*df*	*p*
Time	101.47	225	<.0001
Treatment	2.79	364	.10
Time x Treatment	2.85	217	.09
Site	11.91	223	<.0001
Time x Site	8.64	218	<.0001
Treatment x Site	0.22	225	.88
Time x Treatment x Site	0.21	218	.89
Depression Severity	8.14	230	.005
Time x Depression Severity	23.32	219	<.0001
Treatment x Depression Severity	4.33	251	.04
Anxiety Severity	9.45	241	.002
Age	9.05	238	.003
Time x Age	2.12	227	.13
Treatment x Age	4.60	241	.03
Gender	4.25	244	.04
Race	1.55	229	.20
Time x Race	3.18	223	.02
Marital Status	2.93	232	.01
Employment Status	0.14	255	.94
Treatment x Employment Status	3.25	253	.02
rACC theta	9.66	219	.002
Time x rACC Theta	8.52	214	.004

Notes: A site effect emerged such that one site (CU) had significantly better outcomes than the other three sites. In addition to between-site differences in depression outcome, there were also significant between-site differences in resting rACC theta levels, $F(3,244)=35.99$, $p<.001$. To address this, Site was entered as a factor in all analyses.

Figure1. CONSORT Flow Diagram




Baseline Prediction
Estimated Post-Treatment HRSD Score
14
12
10
8
6
4
2
0
SSRI
Placebo
rACC -1SD
rACC Mean
rACC +1SD


Week 1 Prediction
Estimated Post-Treatment HRSD Score
14
12
10
8
6
4
2
0
SSRI
Placebo
rACC -1SD
rACC Mean
rACC +1SD

Supplemental Material

The incremental predictive validity of rostral anterior cingulate cortex activity in relation to symptom improvement in depression: A randomized clinical trial

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Supplemental Material

The original trial protocol and statistical analysis plan are available at the JAMA Psychiatry website as a separate online supplemental file (see also refs. [1,2]).

Sample size and power analyses

The sample size of n=300 was determined to allow sufficient power (at least 80%) of a significance test with alpha=.05 two-sided, to detect interaction effects of multiple (about 40) potential moderators of the treatment effect on the primary outcome, after adjusting for multiple testing. The postulated effect sizes[3] of the moderators were 0.15 - 0.2.

Methods used to generate the random allocation sequence

The randomization was stratified by site, depression symptoms severity, and chronicity. Within each stratum, block randomization with random block size of 2 or 4 was implemented through a commercial clinical trial data managing software StudyTrax. When a site coordinator provided information about all study inclusion/exclusion criteria for a patient, the software checked for eligibility and if the patient was eligible the software provided a randomization assignment, which was directly communicated to the site pharmacist.

Exclusion criteria

In addition to the exclusion criteria mentioned in the main text, participants were excluded when any of the following criteria were met: 1) current pregnancy, breastfeeding, no use of contraception; 2) lifetime history of psychosis or bipolar disorder; 3) substance dependence in the past six months or substance abuse in the past two months; 4) unstable psychiatric or general medical conditions requiring hospitalization; 5) study medication contraindication; 6) clinically significant laboratory abnormalities; 7) history of epilepsy or condition requiring an anticonvulsant; 8) electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS) or other somatic treatments in the current episode; 9) medications (including but not limited to antipsychotics and mood stabilizers); 10) current psychotherapy; 11) significant suicide risk; or (12) failure to respond to any antidepressant at adequate dose and duration in the current episode.

Participants lost to follow-up

Of the 143 participants who received sertraline, 117 completed the 8-week intervention and 26 discontinued (7 lost to follow-up). Of the 144 participants who received placebo, 125 completed the 8-week intervention and 19 discontinued (5 lost to follow-up). For a detailed summary of reasons for discontinuing the study for each group, see Supplementary Table 2.

EEG acquisition setup

Resting EEG was recorded during four 2-minute periods (4 min: eyes-closed (C); 4 min: eyes open (O)) in a counterbalanced order (COOC or OCCO). Participants were instructed to

remain still and minimize blinks or eye movements, and to fixate on a centrally presented cross during the eyes-open condition.

For participants recruited through Massachusetts General Hospital, EEG data were collected at McLean Hospital. At Columbia University College of Physicians & Surgeons, 72-channel EEG were collected using a 24-bit BioSemi system (sampling rate: 256 Hz, bandpass: DC-251.3 Hz), a Lycra stretch electrode cap (Electro-Cap International Inc., Ohio), and an active reference (ActiveTwo EEG system) at electrode locations PPO1 (common mode sense) and PPO2 (driven right leg). At McLean Hospital, 129-channel EEG data were collected using a Geodesic Net system (sampling rate: 250 Hz, bandpass: 0.01-100 Hz), with Cz as reference (Electrical Geodesics Inc., Oregon). At the University of Michigan, 60-channel EEG data were collected using the 32-bit NeuroScan Synamp (Compumedics, TX) system (sampling rate: 250 Hz, bandpass: 0.5-100 Hz), a Lycra stretch electrode cap, and a nose reference. Finally, at the University of Texas, 62-channel EEG data were recorded (sampling rate: 250 Hz, bandpass: DC-100 Hz) using a 32-bit NeuroScan Synamp system, a Lycra stretch electrode cap, and a nose reference. At all sites, amplifier calibrations were performed.

Experimenters were certified by the Columbia EEG team (Drs. Tenke, Kayser, Bruder) after demonstrating accurate EEG cap placement and delivery of task instructions via video conference, and then submitting satisfactory EEG data from a pilot subject.

EEG preprocessing

To minimize cross-site differences, a standardized analysis pipeline was developed and executed by the Columbia site (see [4] for details). Briefly, a common montage was created to allow integration of data across all sites, and electrodes with poor signal were interpolated using

spherical splines.[5] Recordings with more than 20% unusable data were dropped. Next, a spatial principal component analysis approach[6] was used to correct for blink artifacts. Blink-free EEG data were then segmented into non-overlapping 2-s epochs and band-passed at 1-60 Hz (24 dB/octave). Residual artifacts (e.g., amplifier drift, movement-related artifacts) were identified on a channel-by-channel and trial-by-trial (epoch-by-epoch) basis[7], and flagged epochs were interpolated using spherical spline from data of all valid channels for a given epoch. No differences emerged with respect to the number of artifact-free, 2-sec EEG epochs available for source localization analyses (mean ± SD: Columbia: 92.6 ± 3.1; McLean: 87.9 ± 3.3; University of Texas: 86.5 ± 5.9; University of Michigan: 84.2 ± 12.1). Of the 266 subjects with EEG recordings, 248 (93%) had usable EEG data for analyses. The 18 subjects with unusable EEG recordings were primarily attributable to too many bad EEG channels.

Low Resolution Electromagnetic Tomography (LORETA): Processing steps, assumptions and cross-modal validation

LORETA steps: LORETA analyses were conducted at the McLean Hospital site, blind to randomization arm and clinical outcome. First, a discrete Fourier transform was applied to the scalp EEG data for a narrow (6.5-8.0 Hz) and broader (4.5-7 Hz) theta band. Second, LORETA was used to compute current density (i.e., the amount of electrical current flowing through a solid; unit: amperes per square meter, Å/m^2) as the linear, weighted sum of the scalp electrical potentials, which was squared to obtain power of current density for each voxel. Third, LORETA data were normalized so that, for each frequency band separately, the total current density across all voxels equaled 1, and were then log-transformed to normalize their distribution. Finally, theta current density was extracted from the rACC cluster (14 voxels; Supplement Figure 1 and

Supplement Table 1) previously associated with better antidepressant outcome.[8] This cluster was also used by ref. [9] and spatially overlapped with the one linked to treatment outcome in two additional EEG studies.[10,11] For comparability with all prior EEG studies in this area (e.g., [8–11]), the original LORETA algorithm was used (number of voxels: 2394; voxel dimension: 7 mm^3).

Assumptions: LORETA[12] is a form of Laplacian-weighted minimal norm solution that solves the inverse problem without postulating a specified number of sources by making two assumptions: (i) neighboring neurons are synchronously activated; and (ii) scalp-recorded EEG originates mostly from cortical gray matter. The first assumption is implemented by computing the "smoothest" of all possible activity distributions (i.e., the solution with the smoothest spatial distribution) by minimizing the Laplacian (i.e., the second spatial derivatives) of the current sources. The second assumption is implemented by constraining the solution space to cortical gray matter (and hippocampi), as defined by a brain template from the Montreal Neurological Institute (MNI). For the current study, we used the LORETA version that implements a three-shell spherical head model registered to the Talairach brain atlas (available as digitized MRI from the Brain Imaging Centre, Montreal Neurological Institute[13]) and EEG electrode coordinates derived from cross-registrations between spherical and realistic head geometry.[14] The solution space (2,394 voxels: voxel dimensions: 7x7x7 mm) is limited to cortical gray matter and hippocampi, as defined by a digitized probability atlas provided by the MNI.

Cross-modal validation of LORETA: Validation for the LORETA algorithm comes from various sources. First, physiologically meaningful findings that mirror data from functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) studies have emerged for basic visual, auditory, motor and cognitive tasks (e.g., [15–18]) and epileptic discharges (e.g., [19,20]). Second, validation emerged from studies directly combining LORETA with

functional fMRI[21,22], structural MRI[23,24], PET[25, but see 26], and intracranial recordings[27,28], with localization deviations from fMRI loci of 16 mm[21] and 14.5 mm[22], which is in the range of the spatial resolution of LORETA (~1-2 cm). Finally, and directly relevant to the current analyses, a prior concurrent EEG-PET study provided evidence that rACC theta activity (extracted from the identical cluster as used in the current study) was positively correlated with glucose metabolism.[29] These cross-modal findings indicate that EEG and PET findings linking rACC function and outcome in MDD might reflect similar processes.

Spatial smoothing. To minimize potential site differences, LORETA data were computed using three degrees of spatial smoothing: no over-smoothing, intermediate over-smoothing, and large smoothing. The key findings were replicated with no smoothing and use of a narrower theta frequency range (see *Supplemental Results*).

Theta band definition: To evaluate the robustness of the findings, analyses were performed using both a narrow (6.5-8.0 Hz) and broader (4.5-7 Hz) theta band. This choice was also motivated by the fact that prior studies on this topic have used different definitions of the theta band, including 6.5-8 Hz,[8,10] 4-7 Hz,[9] and 4.5-7.5 Hz.[11]

Predictor selection

Given the relatively large number of terms, we used a step-wise procedure to pare down the number of predictors in our model.[30] In Step 1, all predictors were included. In Step 2, we retained those predictors from Step 1 significant at $p<.20$. In Step 3, we retained those predictors from Step 2 with $ps<.10$. Finally, in Step 4, we retained those predictors from Step 3 with $ps<.05$. To the extent that a significant rACC theta finding emerged (i.e., remained significant in Step 4), we also tested whether the inclusion of this rACC theta term in our model yielded

significantly improved fit relative to a "reduced" model (i.e., including all predictors from the final model, but excluding the rACC theta term).

Supplemental Results

In the main text, we noted that the final baseline model accounted for 39.63% of the between-subjects variance in the slope of symptom improvement (38.24% for Week 1 rACC theta model). Similar to ref. [30], these values were estimated by comparing the covariance parameter estimates (from the HLM output) representing the total variance in the slope of change across subjects from an *unconditional growth model* (i.e., where *Time* is the only predictor in the model) relative to the residual variance in the slope of change from the final (Step 4) model. (For additional details, see ref. [31], in particular equation 4.14).

Test-Retest Reliability

In the main text we note that baseline and Week 1 rACC theta exhibited acceptable test-retest reliability in both the sertraline ($r=0.70$; $p<1\times10^{-4}$; Supplemental Figure 2A) and placebo ($r=0.64$; $p<1\times10^{-4}$; Supplemental Figure 2B) groups. However, in response to a reviewer's suggestion, we also tested a *Group* (SSRI vs. Placebo) x *Time* (Baseline, Week 1) interaction, which was non-significant ($F(1,233)=0.00$, $p=.95$), indicating no group differences in rACC theta levels over time.

Completer Analyses

The final model was re-run excluding those patients who dropped out of treatment prior to the Week 8 HRSD assessment (n=34). Higher baseline rACC theta (4.5-7Hz) remained

significantly associated with depressive symptom improvement (intercept: t(202)=-2.95, p=.004, b=-6.61, 95% CI, -11.03 to -2.20); slope: t(207)=-2.88, p=.004, b=-1.04, 95% CI, -1.76 to -0.33). The corresponding analyses with Week 1 data yielded significant findings for the intercept (t(194)=-2.04, p=.043, b=-4.92, 95% CI, -9.68 to -0.15) but a nonsignificant trend for the slope (t(198)=-1.85, p=0.07, b=-0.73, 95% CI, -1.51 to 0.50).

Analyses Using Different Theta Frequency Definition and Spatial Smoothing

Analyses described in the main text were based on theta activity defined as 4.5-7 Hz, and while applying an intermediate smoothing parameter to LORETA data. Other LORETA studies have defined theta activity as 6.5-8 Hz and applied no extra smoothing (e.g., [8]). Accordingly, we re-ran our final models from our intent-to-treat and completer analyses with the narrower theta range (6.5-7 Hz) and with no extra smoothing. A similar pattern of findings emerged for our intent-to-treat sample for both baseline and the Week 1 EEG assessments (all |ts|>1.99 and ps<.05), although findings were less consistent with the completer sample [baseline rACC theta effect at intercept: t(204)=-2.26, p=.03, b=-5.41, 95% CI, -10.13 to -0.70; slope: t(209)=-1.96, p=.05, b=-0.76, 95% CI, -1.53 to 0.003; Week 1 rACC theta effect at intercept: t(197)=-1.63, p=.10, b=-3.98, 95% CI, -8.78 to 0.83; slope: t(199)=-1.49, p=.14, b=-0.59, 95% CI, -1.38 to 0.19].

Exploratory Analyses of Trending *Group* x *rACC theta* x *Time* interaction for Week 1

As reported in the main text, the *Treatment Group* x *rACC theta* x *Time* was not significant for either baseline [t(217)=0.45, p=.65, b=0.32, 95% CI: -1.08 to 1.72] or Week 1 [t(210)=1.76, p=.08, b=1.36, 95% CI: -0.16 to 2.88] rACC theta (intent-to-treat analyses). At the request of an anonymous reviewer, we explored the trending *Treatment Group* x *rACC theta* x

Time interaction for the Week 1 data, which revealed that at relatively lower levels of (Week 1) rACC theta there was greater improvement in SSRI than placebo, in comparison to those with higher levels of rACC theta where the between-group difference in symptom improvement was smaller. It is important to note that there are two relevant interaction terms that test whether treatment group moderates rACC-outcome associations: the *Treatment Group* x *rACC theta* effect at the intercept (time centered to represent estimated post-treatment HRSD scores) and on the linear slope estimates (captured by the *Treatment Group* x *rACC theta* x *Time* interaction). Moreover, these two interactions can be tested for both baseline rACC theta and Week 1 rACC theta, resulting in 4 interaction tests in total. In the end, all 4 of these effects are nonsignificant (for baseline rACC theta: effect on the intercept [t(222)=-0.02, p=.99, b=-0.07, 95% CI: -8.56 to 8.41] and on the linear slope estimates [t(217)=0.45, p=.65, b=0.32, 95% CI: -1.08 to 1.72]; for Week 1 rACC theta: effect on the intercept [t(212)=1.58, p=.12, b=7.31, 95% CI: -1.82 to 16.44] and on the linear slope estimates [t(210)=1.76, p=.08, b=1.36, 95% CI: -0.16 to 2.88]. For these reasons, although we describe these effects in the Supplement, we chose not to interpret or discuss in the main text the 1 out of 4 tests which was a nonsignificant trend.

Association with baseline characteristics

At the request of an anonymous reviewer, we tested the association between rACC theta activity and a range of relevant baseline patient characteristics. A significant inverse association emerged between age and rACC theta at both baseline (r=-.23; p<.01) and Week 1 (r=-.25; p<.01). Associations were not significant when testing other baseline characteristics, including depressive symptom severity, anxiety severity, anhedonia severity, and years of education (all ps>.18). In response to an additional request from an anonymous reviewer, we also tested

whether the estimated number of previous major depressive episodes (MDEs) or receiving medication treatment since the onset of the current episode was related to rACC levels. Neither the number of previous MDEs (p=.09) or medication treatment (p=.11) correlated with rACC theta levels, nor moderated rACC theta-outcome associations (all ps>.19).

Prediction model removing clinical and demographic covariates

At the request of an anonymous reviewer, an additional control analysis was performed by removing all clinical and demographic characteristics. Accordingly, we re-ran our baseline and Week 1 rACC final models removing these model terms. The same pattern of findings emerged with rACC theta activity significantly predicting depressive symptom improvement. Specifically, higher baseline rACC theta emerged as a significant predictor of lower Week 8 HRSD scores [i.e., significant effect on the intercept: t(229)=-3.04, p=.003, b=-7.12, 95% CI: -11.73 to -2.50] and greater depressive symptom improvement [i.e., significant effect on slope estimates: t(225)=-3.47, p<.001, b=-1.31, 95% CI: -2.05 to -0.56]. For Week 1 rACC theta, these corresponding effects were also both significant [t(218)=-2.78, p=.006, b=-6.97, 95% CI: -11.93 to -2.03 and t(217)=-2.08, p=.040, b=-0.86, 95% CI: -1.67 to -0.04, respectively].

Prediction model examining rACC alpha power

In prior EEG studies on this topic, theta activity in the rACC emerged as the most replicated finding.[8,10,11,32] Critically, in the first study to test the relation between rACC theta activity and outcome, Pizzagalli et al.[8] tested seven frequency bands (from the delta to high beta band) and the rACC-outcome findings were specific to theta. This specificity had been expected in light of independent literature (1) linking rACC activity and treatment response[33] and (2)

highlighting the rACC as a generator of theta activity in both rodents and humans.[34–36] These independent lines of evidence justified our *a priori* hypotheses focused on the theta band, which also limited the number of statistical tests.

Given alpha-related abnormalities in MDD reported in the literature, an anonymous reviewer requested analyses testing whether alpha power localized to the rACC would predict treatment outcome. For lower alpha (8.5-10 Hz), higher baseline rACC alpha activity emerged as a significant predictor of lower Week 8 HRSD scores [i.e., significant effect on the intercept: t(226)=-2.26, p=.025, b=-4.41, 95% CI: -8.26 to -0.56] but not greater depressive symptom improvement [i.e., non-significant effect on slope estimates: t(221)=-1.91, p=.06, b=-0.62, 95% CI: -1.26 to 0.02]. The latter two effects were both non-significant (both ps>.81) when controlling for corresponding rACC theta activity (whereas both theta effects remained significant [both ps<.04] when controlling for rACC (lower) alpha activity). For higher alpha (10.5-12 Hz) activity, neither effect was significant (both ps>.20).

Supplemental Discussion

As discussed in the main text, links between increased pretreatment theta activity in the rACC have been replicated in several studies using LORETA.[8–11; but see 37] These replications contrast with inconsistent findings emerging from studies evaluating scalp frontal theta power (for review, see [38,39]). For example, *decreased* pretreatment theta band activity predicted response to tricyclic antidepressants, imipramine and SSRIs.[40,41] In contract, *increased* pre-treatment theta power was found to differentiate paroxetine responders from non-responders.[42] Similarly, increased pre-treatment theta power predicted better treatment response to a variety of antidepressants.[43] The reasons for these opposite patterns are unclear. Collectively, these findings

indicate that source-localized rACC theta current density might represent a more reliable prognostic predictor of treatment outcome.

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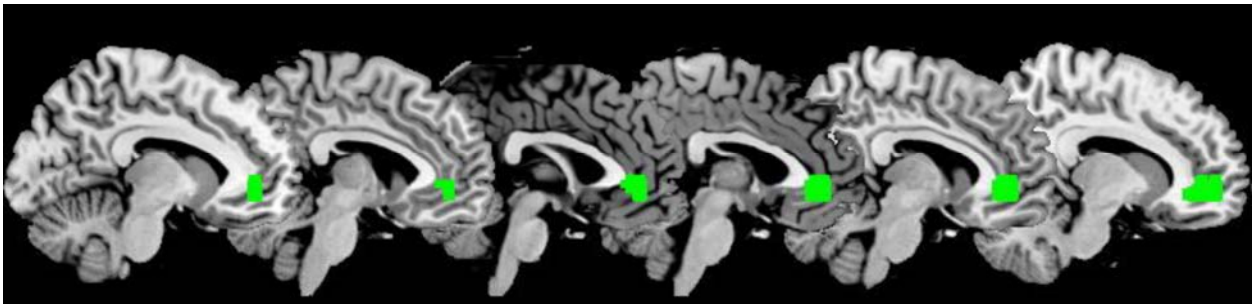
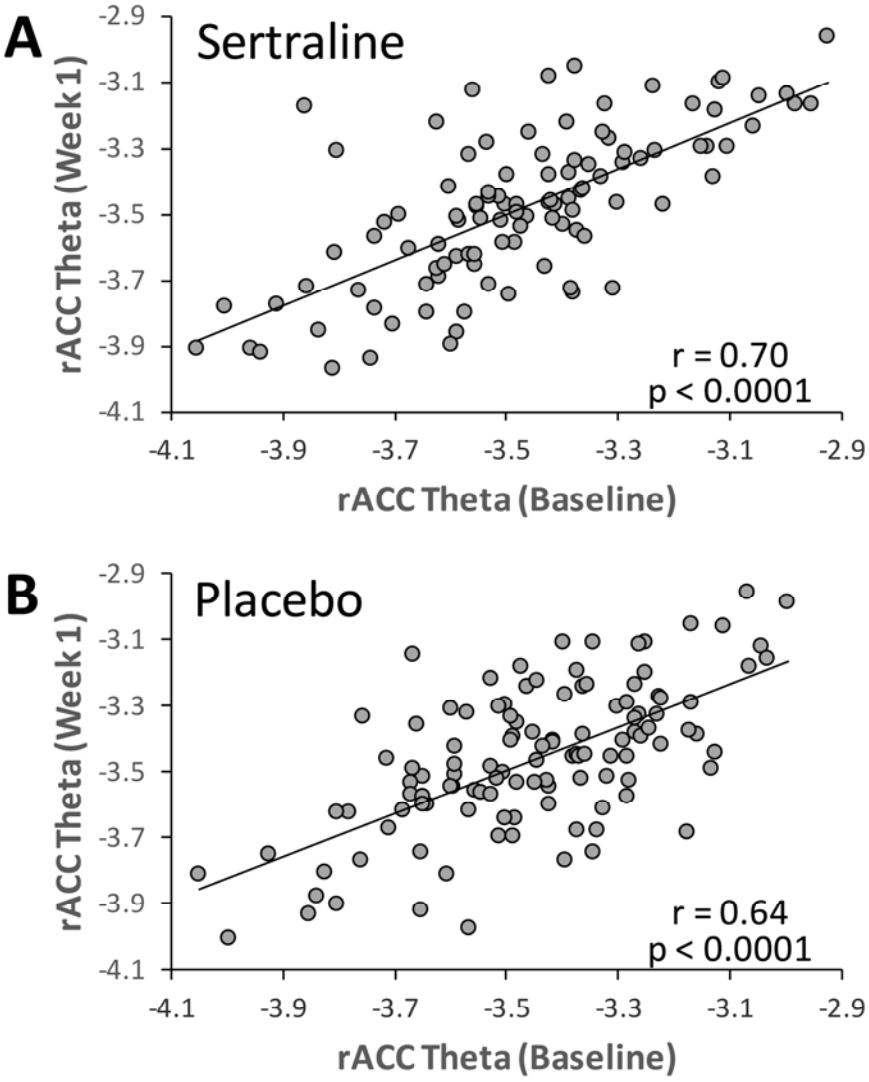
Supplement Figure 1: Location of the *a priori* rostral anterior cingulate cortex (rACC) region of interest (see green cluster) used for the analyses.



Supplement Figure 2: Scatterplots displaying the significant association between resting rACC theta activity at baseline and one week later for the sertraline (A) and placebo (B) groups.



Supplement Table 1: Coordinates (in mm, origin at anterior commissure) and Brodmann areas of the voxels included in the rACC regions-of-interest used for the current analyses. This identical ROI has been used by ref. [8] and [9], and spatially overlapped with rACC clusters emerging from additional studies in this area.[10,11]

X=left(-) to right(+); Y=posterior(-) to anterior(+); Z=inferior(-) to superior(+).

X	Y	Z	Brodmann area	Region	Side
11	45	-6	BA32	Anterior Cingulate Cortex	Right
11	38	-6	BA10	Medial Frontal Gyrus	Right
4	45	-6	BA32	Anterior Cingulate Cortex	Right
11	52	-6	BA32	Anterior Cingulate Cortex	Right
4	38	1	BA24	Anterior Cingulate Cortex	Right
-3	38	1	BA24	Anterior Cingulate Cortex	Left
4	45	1	BA32	Anterior Cingulate Cortex	Right
11	45	1	BA10	Anterior Cingulate Cortex	Right
-3	45	-6	BA32	Anterior Cingulate Cortex	Left
4	38	-6	BA32	Anterior Cingulate Cortex	Right
-3	45	1	BA32	Anterior Cingulate Cortex	Left
11	52	1	BA10	Medial Frontal Gyrus	Right
-10	45	-6	BA32	Anterior Cingulate Cortex	Left
-10	45	1	BA10	Anterior Cingulate Cortex	Left

Supplement Table 2: Summary of dropout rates for the sertraline and placebo group.

Discontinued Sertraline (n = 26)	Discontinued Placebo (n = 16)
- 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 discontinued Medication (n=4)
- Believed treatment not working (n=1)	- Believed treatment 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