JAMA Psychiatry | Original Investigation

Pretreatment Rostral Anterior Cingulate Cortex Theta Activity in Relation to Symptom Improvement in Depression
A Randomized Clinical Trial

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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. Increased pretreatment rostral anterior cingulate cortex (rACC) theta 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.

OBJECTIVE To determine whether increased pretreatment rACC theta activity would predict symptom improvement regardless of randomization arm.

DESIGN, SETTING, AND PARTICIPANTS A multicenter randomized clinical trial enrolled outpatients without psychosis and with chronic or recurrent MDD between July 29, 2011, and December 15, 2015 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care [EMBARC]). Patients were consecutively recruited from 4 university hospitals: 634 patients were screened, 296 were randomized to receive sertraline hydrochloride or placebo, 266 had electroencephalographic (EEG) recordings, and 248 had usable EEG data. Resting EEG data were recorded at baseline and 1 week after trial onset, and rACC theta activity was extracted using source localization. Intent-to-treat analysis was conducted. Data analysis was performed from October 7, 2016, to January 19, 2018.

INTERVENTIONS An 8-week course of sertraline or placebo.

MAIN OUTCOMES AND MEASURES The 17-item Hamilton Rating Scale for Depression score (assessed at baseline and weeks 1, 2, 3, 4, 6, and 8).

RESULTS The 248 participants (160 [64.5%] women, 88 [35.5%] men) with usable EEG data had a mean (SD) age of 36.75 (13.15) years. 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. The rACC theta marker, in combination with clinical and demographic variables, accounted for an estimated 39.6% of the variance in symptom change (with 8.5% of the variance uniquely attributable to the rACC theta marker).

CONCLUSIONS AND RELEVANCE Increased pretreatment rACC theta activity represents a nonspecific prognostic marker of treatment outcome. This is the first study to date to demonstrate that rACC theta activity has incremental predictive validity.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01407094

JAMA Psychiatry. 2018;75(6):547-554. doi:10.1001/jamapsychiatry.2018.0252
Published online April 11, 2018.

Supplemental content

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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 multisite STAR*D study, for example, only approximately 50% of individuals with MDD responded (ie, showed ≥50% reduction in depressive symptoms) to the selective-serotonin reuptake inhibitor (SSRI) citalopram, and only 33% achieved remission.[2] In primary care, the rates of nonresponse (70%)[3] and nonremission (75%)[4] to first-line antidepressants are even higher. Compounding these challenges, 4 to 8 weeks of treatment are often needed to evaluate the efficacy of a given antidepressant,[5,6] which can result in protracted symptoms. Modest rates of response and remission are not unique to pharmacology but extend to psychotherapy.[7]

Owing to this limited success, pinpointing variables that predict the likelihood of antidepressant response would be clinically valuable. For example, identification of pretreatment variables that predict remission in a treatment-specific fashion (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, 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. 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 antidepressant therapy, 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 of a race other than white,[2] being unmarried,[13] and lower educational level.[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.

Because of these limitations, there has been increased interest in identifying biological markers that reliably determine clinical outcome. Baseline (ie, pretreatment) level of activity in the rostral (pregenual) anterior cingulate cortex (rACC) (Broadmann area 24/32) has emerged as a particularly promising marker. First reported in 1997,[15] increased pretreatment activity in the rACC has been found to predict a better outcome to a variety of antidepressants, a finding that was replicated using source-localized electroencephalography.[16] A meta-analysis of 23 studies reported that the link between better antidepressant outcome and increased pretreatment rACC activity has been replicated 19 times (effect size, 0.918).[17] This marker has been shown to predict depressive symptom improvement across a range of interventions, including multiple antidepressants (eg, SSRIs, atypical antidepressants, and ketamines), sleep deprivation, transcranial magnetic stimulation, and placebo[18,19]; however, there have been failures to replicate those findings.[20-23] In sum, increased pretreatment rACC theta activity appears to be a general prognostic (treatment-nonspecific) marker of symptom improvement.

Key Points

Question Does increased pretreatment rostral anterior cingulate cortex theta activity have incremental predictive validity with respect to treatment outcome in major depression?

Findings In a randomized clinical trial including 296 patients with major depressive disorder, higher rostral anterior cingulate cortex 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 pretreatment rostral anterior cingulate cortex theta activity represents a nonspecific prognostic marker of treatment outcome that has now been replicated in several studies and thus warrants consideration for implementation in clinical care.

However, prior literature is characterized by 3 important limitations. First, earlier 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 2 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 theta 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 the present study was to address these limitations in the context of the multisite Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study, which recruited more than 300 outpatients with recurrent, nonpsychotic MDD across 4 sites.[26] Electroencephalographic (EEG) data were recorded at baseline and 1 week after the onset of an 8-week clinical trial in which outpatients were randomized to receive sertraline hydrochloride or placebo. The inclusion of 2 EEG assessments allowed us to test (1) the stability of rACC theta activity and (2) the consistency of rACC theta activity–outcome associations over time. Based on prior findings, we hypothesized that increased pretreatment (baseline) and week 1 rACC theta current density would predict depressive symptom improvement regardless of randomization arm, above and beyond clinical and demographic variables previously linked to treatment outcome.

Methods

Participants

Between July 29, 2011, and December 15, 2015, outpatients (age, 18-65 years) meeting criteria for MDD based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders[27] were recruited at 4 sites: Columbia University, New York; Massachusetts General Hospital, Boston; University of Michigan, Ann

Arbor; and University of Texas Southwestern Medical Center, Dallas. The study was approved by the institutional review boards of all sites, and participants provided written consent and received financial compensation (eMethods in Supplement 1). A detailed description of the study design, randomization procedures, and power analyses has been published elsewhere[26] and is available in the protocol (Supplement 2) and in the eMethods in Supplement 1.

Participants had a Quick Inventory of Depressive Symptomatology score[28] of 14 or higher, indicating moderate depression at both the screening and randomization visits. To minimize clinical heterogeneity, only patients reporting early-onset (before age 30 years) MDD that was chronic (episode duration >2 years) or recurrent (≥2 recurrences including the current episode) were enrolled. Additional exclusion criteria are presented in the eMethods in Supplement 1.

Clinical Trial

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

EEG Recordings and Preprocessing

At all sites, resting EEG was recorded during four 2-minute periods, half with eyes closed and half with eyes open in a counterbalanced order (eMethods in Supplement 1). 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 nonoverlapping, artifact-free, 2-second epochs for source localization analyses (eMethods in Supplement 1).

Source Localization Analyses

Source localization analyses were conducted using low-resolution electromagnetic tomography,[16,31] which infers the intracranial generators of scalp-recorded EEG signals, and followed identical procedures as in prior studies[16,24] (eMethods in Supplement 1). To evaluate the robustness of findings, current density for a narrow (6.5-8 Hz) and broader (4.5-7 Hz) theta band was extracted from the rACC cluster (14 voxels) (eFigure 1 and eTable 1 in Supplement 1) previously associated with better antidepressant outcome.[16] This cluster was also used by Korb et al[24] and spatially overlapped with the cluster linked to treatment outcome in 2 additional EEG studies.[32,33]

Statistical Analysis

To test whether rACC theta (4.5-7 Hz) current density predicted greater symptom reduction as measured by the HRSD, we used hierarchical linear modeling, with mixed-effects repeated-measures models implemented in SAS, version 9.4 PROC MIXED (SAS Institute Inc). Slopes and intercepts were treated as randomly varying across participants, and an unstructured covariance structure was used.[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, and chronic depression, as well as pretreatment 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 activity was associated with HRSD improvement over time, we included an rACC theta × time interaction. To evaluate whether treatment group (sertraline vs placebo) moderated this effect, we further included a treatment group × rACC theta × time interaction. Similarly, for each of the above covariates, treatment group × predictor × time interactions were included. A treatment group × site × time interaction was also included in all models to account for different sites.

Given the relatively large number of terms, we used a stepwise procedure to pare down the number of predictors (eMethods in Supplement 1). To the extent that a significant rACC theta activity finding emerged (ie, remained significant in the last step), we also tested whether the inclusion of this rACC theta activity term in our model yielded a significantly improved fit relative to a reduced model (ie, including all predictors from the final model but excluding the rACC theta activity 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 before 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 before the week 8 HRSD assessment (completer, n = 214) (eMethods in Supplement 1). Data analysis was performed from October 7, 2016, to January 19, 2018. Significance was determined at $P < .05$.

Results

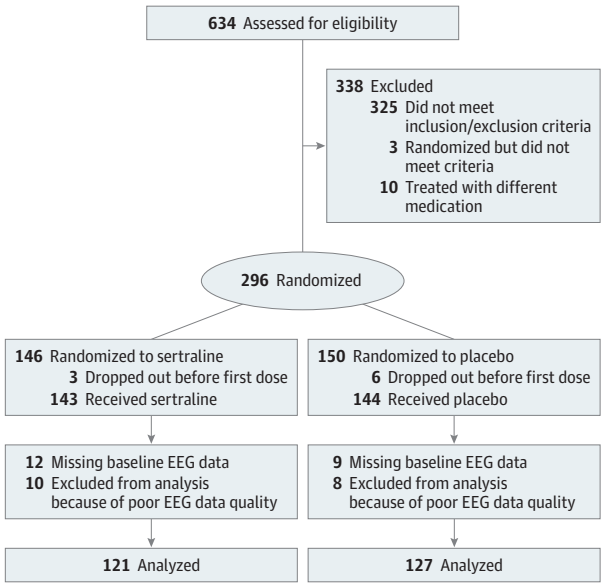
Participant Characteristics

Between July 29, 2011, and December 15, 2015, 634 patients were screened and 296 were randomized (**Figure 1**). Nine randomized patients dropped out before the first medication or placebo dose, leaving 287 participants for analyses. Among the remaining 287 patients, 266 (92.7%) had EEG recordings and 248 (86.4%) had usable EEG data. Clinical and demographic characteristics are reported in **Table 1**.

Test-Retest Reliability

Baseline and week 1 rACC theta activity exhibited acceptable test-retest reliability in both the sertraline ($r = 0.70$; $P < 1 \times 10^{-4}$) and placebo ($r = 0.64$; $P < 1 \times 10^{-4}$) groups (eFigure 2 in Supplement 1).

Figure 1. CONSORT Flow Diagram



Primary hierarchical linear model analyses were intent-to-treat (ie, include dropouts). Thus, the flow diagram summarizes information relevant to intent-to-treat analyses. Information regarding dropout rates between groups and reasons for dropout is available in eTable 2 in Supplement 1.
EEG indicates electroencephalographic.

Table 1. Clinical and Demographic Data for the 248 Participants Included in the Analyses

Characteristic	Participants With MDD
Age, mean (SD), y	36.75 (13.15)
Women, No. (%)	160 (64.5)
Education, mean (SD), y	15.08 (2.41)
White race, No. (%)[a]	171 (69.0)
Marital status, No. (%) married	51 (20.8)
Employment, No. (%) employed	139 (57.0)
Age at MDD onset, mean (SD), y	16.23 (5.70)
Length of current MDE, median, mo	13
No. of prior MDEs, median	4
QIDS score, mean (SD)[b]	18.19 (2.81)
17-Item HRSD score, mean (SD)[c]	18.48 (4.44)

Abbreviations: HRSD, Hamilton Rating Scale for Depression; MDD, major depressive disorder; MDE, major depressive episode; QIDS, Quick Inventory of Depressive Symptomatology score.

[a] Information about race/ethnicity was collected by self-report.

[b] Score indicates, on average, severe depression.[28]

[c] Score indicates, on average, moderate to severe depression.[29]

Prediction of Depressive Symptom Improvement

Table 2 presents the results of the final (step 4) model. There are 2 relevant model terms for each predictor: the effect at the intercept (time centered to represent estimated week 8 HRSD scores) and on the linear slope estimates (captured by the predictor × time interactions). These terms correspond to an effect of the predictor on final HRSD scores and an effect of the predictor on change in HRSD scores over time, respectively. To be conservative, predictors were required to be associated with both outcomes (intercepts and slopes) at $P < .05$ to be considered statistically significant.[13] In the final model, higher rACC theta activity emerged as a significant predictor of lower week 8 HRSD scores (ie, significant effect on the intercept: $t_{219} = -3.11$; $P = .002$; $b = -6.81$; 95% CI, −11.13 to −2.49) and greater depressive symptom improvement (ie, significant effect on slope estimates: $t_{214} = -2.92$; $P = .004$; $b = -1.05$; 95% CI, −1.77 to −0.34) (Table 2 and **Figure 2**A). For every 1-SD increase in rACC theta activity, there was a 1.5-point decrease in week 8 HRSD scores. Similarly, when the latter model was rerun substituting baseline rACC theta activity with week 1 values, rACC theta again emerged as a significant prognostic marker of better HRSD outcome (intercept: $t_{211} = -2.30$; $P < .03$; $b = -5.40$; 95% CI, −10.03 to −0.77; slope: $t_{210} = -2.13$; $P < .04$; $b = -0.83$; 95% CI, −1.60 to −0.06) (Figure 2B). Consistent with our hypothesis, the treatment group × rACC theta activity × time interaction 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 activity, indicating that the association between rACC theta activity and better outcome was not significantly moderated by treatment group.

Table 2. Final Hierarchical Linear Model[a]

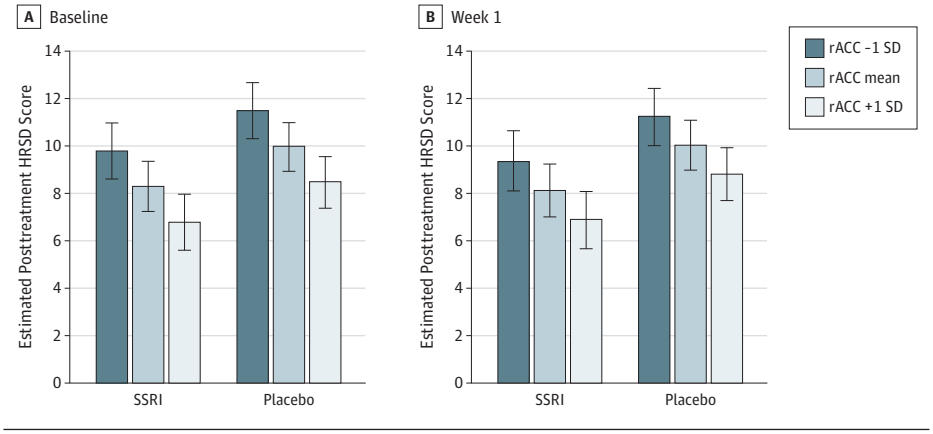
Model Term[b]	*F* Value	*P* Value
Time	101.47_{225}	<.001
Treatment	2.79_{364}	.10
Time × treatment	2.85_{217}	.09
Site	11.91_{223}	<.001
Time × site	8.64_{218}	<.001
Treatment × site	0.22_{225}	.88
Time × treatment × site	0.21_{218}	.89
Depression severity	8.14_{230}	.005
Time × depression severity	23.32_{219}	<.001
Treatment × depression severity	4.33_{251}	.04
Anxiety severity	9.45_{241}	.002
Age	9.05_{238}	.003
Time × age	2.12_{227}	.13
Treatment × age	4.60_{241}	.03
Sex	4.25_{244}	.04
Race/ethnicity	1.55_{229}	.20
Time × race	3.18_{223}	.02
Marital status	2.93_{232}	.01
Employment status	0.14_{255}	.94
Treatment × employment status	3.25_{253}	.02
rACC theta	9.66_{219}	.002
Time × rACC theta	8.52_{214}	.004

Abbreviation: rACC, rostral anterior cingulate cortex.

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

[b] A site effect emerged such that 1 study site (Columbia University) had significantly better outcomes than the other 3 sites. In addition to between-site differences in depression outcome, there were 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.

Figure 2. Estimated Week 8 Hamilton Rating Scale for Depression (HRSD) Scores for the Sertraline and Placebo Groups



Three values of baseline (A) and week 1 (B) rACC theta activity shown: 1 SD below the mean, the mean, and 1 SD above the mean. Error bars represent ±1 SE. rACC indicates rostral anterior cingulate cortex; SSRI, selective-serotonin reuptake inhibitor.

A significant likelihood ratio χ^2 test indicated that the final baseline model (ie, including baseline rACC theta activity and covariates) provided a significantly improved fit relative to a reduced model (ie, including covariates only, $\chi^2_2 = 354.96$, $P < 1 \times 10^{-4}$; when substituting week 1 rACC theta activity, $\chi^2_2 = 802.61$, $P < 1 \times 10^{-4}$). The final baseline model accounted for 39.6% of the between-participant variance in the slope of symptom improvement (38.2% for the week 1 rACC theta activity model). When the rACC theta activity term was removed from this model, the variance accounted for was reduced to 31.1% (eResults in Supplement 1). Thus, baseline rACC theta activity accounted for an estimated 8.5% unique variance in outcome above clinical and demographic covariates. Analyses of participants who completed the 8-week trial are reported in the eResults in Supplement 1.

Discussion

Our goal was to evaluate whether baseline rACC theta activity was a prognostic marker of depressive symptom improvement in the multicenter EMBARC study. Several findings emerged. First, the rACC theta activity marker showed acceptable test-retest stability over 1 week (sertraline: $r = 0.70$; placebo: $r = 0.64$; $P < .001$), 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 activity predicted greater depressive symptom improvement even after accounting for multiple clinical and demographic variables previously associated with better treatment outcomes. The full model, including both rACC theta activity and covariates, accounted for 39.6% of the variance in depressive symptom change and provided a significantly better fit than a reduced model that included all covariates but not the rACC theta activity marker (the latter covariates-only model accounted for 31.1% of the variance in symptom change). Thus, baseline rACC theta activity accounted for an estimated 8.5% of the unique variance in outcome. Third, findings remained significant when considering week 1 rACC theta activity, which, in combination with covariates, accounted for 38.2% of the variance in depressive symptom change. Of all markers examined, only rACC theta activity and baseline severity of depressive symptoms were associated with significant effects on both the intercept (ie, lower week 8 depression scores) and slope of depressive symptom improvement (Table 2). Fourth, the treatment group × rACC theta activity × time interaction was not significant for either baseline or week 1 rACC theta activity, indicating that the association between rACC theta activity and better outcome was not moderated by treatment. Based on the present and prior findings,[17] increased pretreatment rACC theta activity represents a nonspecific prognostic marker of treatment outcome.

Although the link between higher pretreatment rACC theta activity and better antidepressant outcomes has been widely replicated in many studies (but not in some[20-23]), the mechanisms underlying this association remain unclear. When seen in the context of a large number of studies implicating frontocingulate dysfunction in MDD,[17] as well as evidence that the rACC is a hub in the default mode network,[38] we previously speculated that increased resting rACC activity may predict a better clinical outcome, as it may be associated with more adaptive forms of self-referential processing and a better ability to suppress the default mode network in situations requiring recruitment of cognitive control.[17] Collectively, these processes might reduce maladaptive forms of rumination characterized by negatively skewed self-introspection, difficulties dampening negative emotions, and deficits in allocating attention to task demands. Findings highlighting a key role of the rACC in the inhibition of negative information[39] and amygdalar activity in response to emotional conflict,[40] as well as optimistic biases,[41] are consistent with this idea. Studies will be needed to evaluate these hypotheses. Additional research is also required to investigate factors that may moderate rACC–outcome associations and that may help account for inconsistencies (eg, percentage of participants with prior exposure to antidepressants or treatment resistance[20,42]).

In terms of possible neurochemical mechanisms, altered resting rACC activity may reflect glutamatergic[43] or opioidergic[44] abnormalities. A recent study in outpatients with depression reported that increased resting state functional connectivity within the rACC predicted a greater reduction in depressive symptoms in response to both placebo administration with expectations of antidepressant effects and 10-week, open-label treatment with citalopram.[19] Findings linking increased rACC functional connectivity to both placebo and SSRI response in the Sikora et al[19] study fit our results as well as a prior EEG study reporting that resting rACC theta activity predicted treatment outcome in both medicated and placebo MDD groups.[18]

The potential clinical implications of the present findings warrant discussion. First, although the current rACC theta marker has emerged in at least 20 independent studies across laboratories, the need to identify moderators of treatment response and mediators that account for symptom improvement remains a key priority. Whereas moderators could inform treatment selection, mediators could help to pinpoint causal mechanisms implicated in treatment response and could be used to modify treatment strategies early. Promising behavioral (word fluency[45]), electrophysiologic (loudness-dependent, auditory-evoked potential[46]), and imaging (glucose metabolism in the insula[47]) 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 to 7 days after treatment have been found to predict treatment response to SSRIs and serotonin-norepinephrine reuptake inhibitors.[48-50] Although the findings are promising, replications will be needed before any of these behavioral, EEG, or imaging markers can be used to guide clinical care (see also eDiscussion in Supplement 1). Future analyses of the EMBARC data set 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,[46,47] rACC theta activity does not appear to be a moderator of treatment response. Thus, its utility for informing treatment selection appears to be 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 nonresponse will need to be evaluated. Second, future studies might consider clinical trials in which patients with MDD 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. Because prior EEG studies have demonstrated links between pretreatment rACC activity and better antidepressant response using only 28 to 32 electrodes,[16,32,33] this hypothesis could be tested using relatively simple and widely available EEG montages. These and related efforts[51] might allow treatment decisions in the near future to be guided by 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 theta marker was modest (8.5%).

Conclusions

The current multicenter 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.

ARTICLE INFORMATION

Accepted for Publication: January 29, 2018.

Published Online: April 11, 2018. doi:10.1001/jamapsychiatry.2018.0252

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Statistical analysis: Pizzagalli, Webb, Dillon, Trivedi.
Obtained funding: Fava, McGrath, Weissman, Parsey, Oquendo, Trivedi.
Administrative, technical, or material support: Pizzagalli, Dillon, Tenke, Kayser, Goer, Fava, Weissman, Parsey, Adams, Trombello, Cooper, McInnis, Bruder.
Study supervision: Pizzagalli, Tenke, Kayser, Parsey, Trombello, Oquendo, McInnis, Bruder, Trivedi.

Conflict of Interest Disclosures: For activities unrelated to the current research, the authors report the following financial disclosures. In the past 3 years, Dr Pizzagalli received funding from the National Institute of Mental Health (NIMH) and the Dana Foundation and consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Boehringer Ingelheim, Pfizer, and Posit Science. In the past 3 years, Dr Dillon received funding from the NIMH and consulting fees from Pfizer. Dr Fava reports lifetime disclosures of research support from Abbott Laboratories, Acadia Pharmaceuticals,

Alkermes Inc, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir Pharmaceuticals, AXSOME Therapeutics, Biohaven, BioResearch, BrainCells Inc, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Cerecor, Clintara LLC, Covance, Covidien, Eli Lilly and Company, EnVivo Pharmaceuticals Inc, Euthymics Bioscience Inc, Forest Pharmaceuticals Inc, FORUM Pharmaceuticals, Ganeden Biotech Inc, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D LLC, Jed Foundation, Johnson & Johnson Pharmaceutical Research & Development, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Lundbeck Inc, Marinus Pharmaceuticals, MedAvante, Methylation Sciences Inc, National Alliance for Research on Schizophrenia and Depression (NARSAD), National Center for Complementary and Alternative Medicine, National Coordinating Center for Integrated Medicine, National Institute of Drug Abuse, NIMH, Neuralstem Inc, NeuroRx, Novartis AG, Organon Pharmaceuticals, Otsuka Pharmaceutical Development Inc, PamLab LLC, Pfizer Inc, Pharmacia-Upjohn, Pharmaceutical Research Associates Inc, Pharmavite LLC, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche Pharmaceuticals, RCT Logic LLC (formerly Clinical Trials Solutions LLC), Sanofi-Aventis US LLC, Shire, Solvay Pharmaceuticals Inc, Stanley Medical Research Institute, Synthelabo, Taisho Pharmaceuticals, Takeda Pharmaceuticals, Tal Medical, VistaGen, and Wyeth-Ayerst Laboratories; served on an advisory board or as a consultant for Abbott Laboratories, Acadia, Affectis Pharmaceuticals AG, Alkermes Inc, Amarin Pharma Inc, Aspect Medical Systems, AstraZeneca, Auspex Pharmaceuticals, Avanir Pharmaceuticals, AXSOME Therapeutics, Bayer AG, Best Practice Project Management Inc, Biogen, BioMarin Pharmaceuticals Inc, Biovail Corporation, BrainCells Inc, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon Inc, Cerecor, CNS Response Inc, Compellis Pharmaceuticals, Cypress Pharmaceutical Inc, DiagnoSearch Life Sciences (P) Ltd, Dinippon Sumitomo Pharma Co Inc, Dov Pharmaceuticals Inc, Edgemont Pharmaceuticals Inc, Eisai Inc, Eli Lilly and Company, EnVivo Pharmaceuticals Inc, ePharmaSolutions, EPIX Pharmaceuticals Inc, Euthymics Bioscience Inc, Fabre-Kramer Pharmaceuticals Inc, Forest Pharmaceuticals Inc, Forum Pharmaceuticals, GenOmind LLC, GlaxoSmithKline, Grunenthal GmbH, Indivior, i3 Innovus/Ingenis, Intracellular, Janssen Pharmaceutica, Jazz Pharmaceuticals Inc, Johnson & Johnson Pharmaceutical Research & Development LLC, Knoll Pharmaceuticals Corp, Labopharm Inc, Lorex Pharmaceuticals, Lundbeck Inc, Marinus Pharmaceuticals, MedAvante Inc, Merck & Co Inc, MSI Methylation Sciences Inc, Naurex Inc, Navitor Pharmaceuticals Inc, Nestle Health Sciences, Neuralstem Inc, Neuronetics Inc, NextWave Pharmaceuticals, Novartis AG, Nutrition 21, Orexigen Therapeutics Inc, Organon Pharmaceuticals, Osmotica, Otsuka Pharmaceuticals, Pamlab LLC, Pfizer Inc, PharmaStar, Pharmavite LLC, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa Pharmaceuticals Inc, Pharmaceutical Product Development, Purdue Pharma, Puretech Ventures, PsychoGenics, Psylin Neurosciences Inc, RCT Logic LLC (formerly Clinical Trials Solutions LLC), Relmada Therapeutics Inc, Rexahn Pharmaceuticals Inc, Ridge Diagnostics Inc, Roche, Sanofi-Aventis US LLC, Sepracor Inc, Servier Laboratories, Schering-Plough Corporation, Shenox Pharmaceuticals, Solvay Pharmaceuticals Inc, Somaxon Pharmaceuticals Inc, Somerset Pharmaceuticals Inc, Sunovion Pharmaceuticals, Supernus Pharmaceuticals Inc, Synthelabo, Taisho Pharmaceuticals, Takeda Pharmaceutical Company Limited, Tal Medical Inc, Tetragenex, Teva Pharmaceuticals, TransForm Pharmaceuticals Inc, Transcept Pharmaceuticals Inc, Usona Institute Inc, Vanda Pharmaceuticals Inc, Versant Venture Management LLC, and VistaGen; has received compensation for speaking or publishing from Adamed Co, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon Inc, CME Institute/Physicians Postgraduate Press Inc, Eli Lilly and Company, Forest Pharmaceuticals Inc, GlaxoSmithKline, Imedex LLC, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon Pharmaceuticals, Pfizer Inc, PharmaStar, United BioSource Corp, and Wyeth-Ayerst Laboratories; has equity holdings in Compellis and PsyBrain Inc and hold patents for Sequential Parallel Comparison Design, licensed by MGH to Pharmaceutical Product Development LLC (US_7840419, US_7647235, US_7983936, US_8145504, and US_8145505). In the past 3 years, Dr Weissman received funding from the NIMH, NARSAD, the Sackler Foundation, and the Templeton Foundation and royalties from the Oxford University Press, Perseus Press, the American Psychiatric Association Press, and MultiHealth Systems. In the past 3 years, Dr Oquendo received funding from the NIMH and royalties for the commercial use of the Columbia-Suicide Severity Rating Scale. Her family owns stock in Bristol-Myers Squibb. In the past 3 years, Dr McInnis received funding from the NIMH and consulting fees from Janssen and Otsuka Pharmaceuticals. In the past 3 years, Dr Trivedi has served in either a consulting or advisory role for Alkermes Inc, Akili Interactive, Allergan Pharmaceuticals, Arcadia Pharmaceuticals, Avanir Pharmaceuticals, Brintellix Global, Bristol-Myers Squibb, Caudex, Cerecor, Forest Pharmaceuticals, Global Medical Education Inc, Health Research Associates, Insys, Johnson & Johnson Pharmaceutical Research & Development, Lilly Research Laboratories, Lundbeck Research USA, Medscape, Merck & Co Inc, Mitsubishi Pharma, MSI Methylation Sciences–Pamlab Inc, Navitor, Otsuka America Pharmaceutical Inc, One Carbon Therapeutics, Otsuka America Pharmaceutical Inc, Pfizer Inc, and Takeda Global Research; received royalties from Janssen Research and Development LLC; signed author agreements with Janssen Asia Pacific and Oxford University Press; received honoraria from the American Psychiatric Association; and been awarded grants from the Agency for Healthcare Research and Quality, Cancer Prevention and Research Institute of Texas, NIMH, National Institute of Drug Abuse, National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Advancing Translational Sciences, Johnson & Johnson, and Patient-Centered Outcomes Research Institute. No other disclosures are reported.

Funding/Support: The Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care for Depression (EMBARC) study was supported by the NIMH of the National Institutes of Health under award numbers U01MH092221 (Dr Trivedi) and U01MH092250 (Drs McGrath, Weissman, and Parsey). This work was supported by the EMBARC National Coordinating Center at the University of Texas Southwestern Medical Center (Dr Trivedi, coordinating principal investigator) and the Data Center at Columbia and Stony Brook Universities.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Information: Dr Tenke died on December 19, 2017. The coauthors wish to dedicate this publication to him and the central role he played in this project.

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Supplementary Online Content

Pizzagalli DA, Webb CA, Dillon DG, et al. Pretreatment rostral anterior cingulate cortex theta activity in relation to symptom improvement in depression: a randomized clinical trial. *JAMA Psychiatry*. Published online April 11, 2018. doi:10.1001/jamapsychiatry.2018.0252

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Expanded Methodology

Sample size and power analyses for the clinical trial

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[1-3] of the moderators were 0.15 - 0.2.

Methods used to generate the random allocation sequence

The randomization was stratified by site, depression symptom 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.

Participant compensation

Eligible participants received $150 for completing the detailed interview and questionnaires administered at the screening session and $68 for the two EEG sessions. They also received the following compensation for other components not presented here: up to $200 for two MRI sessions, up to $32 in earnings in a behavioral task, $25 to complete blood samples for research purposes (up to $175 total), $50 for genetic blood sampling, and $50 for completing the final clinical rating session of the study. The total possible compensation was $725. Participants were not compensated for the follow-up visits.

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 from the same region.[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 extra smoothing, intermediate over-smoothing, and large smoothing. The key findings were replicated with no extra 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).

eResults. Expanded Results

In the main text, we noted that the final baseline model accounted for 39.6% of the between-subjects variance in the slope of symptom improvement (38.2% 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 activity 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 activity (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* interaction 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).

eDiscussion. Expanded 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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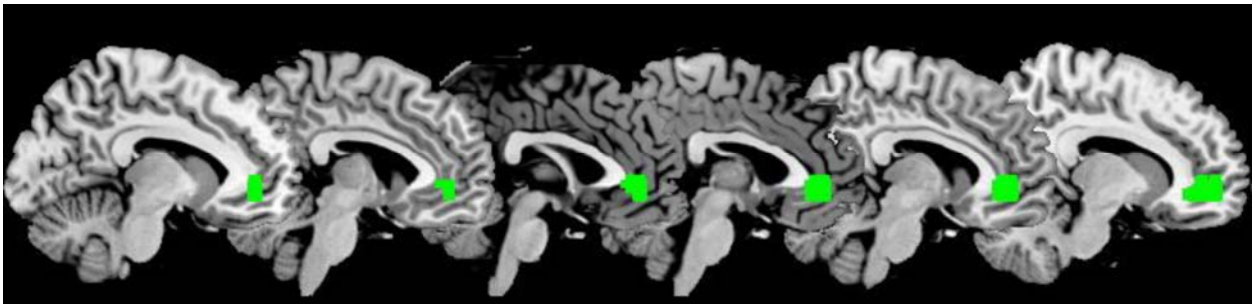
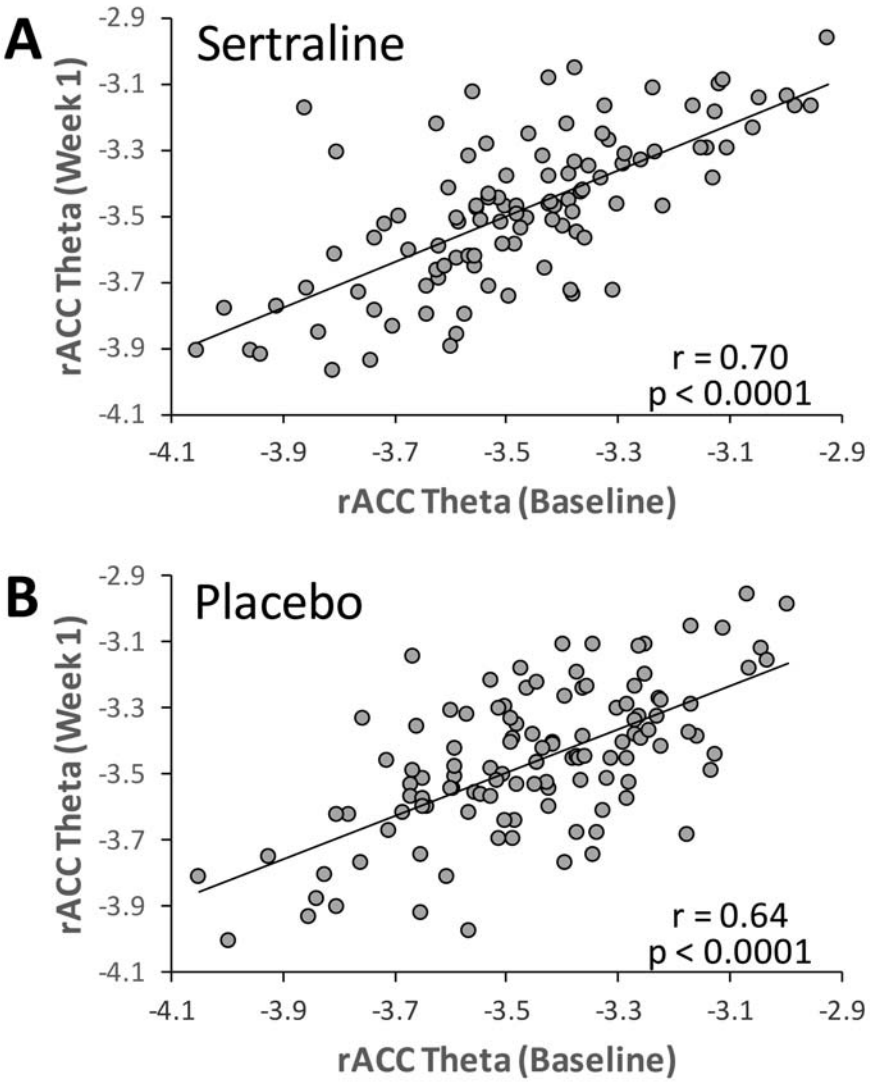
eFigure 1. Location of the *A Priori* Rostral Anterior Cingulate Cortex (rACC) Region of Interest (See Green Cluster) Used for the Analyses.



eFigure 2. Scatterplots Displaying the Significant Association Between Resting rACC Theta Activity at Baseline and One Week Later for the Sertraline and Placebo Groups.



eTable 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

eTable 2. Summary of Dropout Rates for 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 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

eAppendix. Author Contributions

Drs Pizzagalli and Webb served as co-first authors and contributed equally to the work. Each had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

