

Pretreatment Rostral Anterior Cingulate Cortex Theta Activity in Relation to Symptom Improvement in Depression

A Randomized Clinical Trial

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[+ Supplemental content](#)

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.

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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 $\geq 50\%$ 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) (Brodmann 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

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.

rACC theta activity appears to be a general prognostic (treatment-nonspecific) marker of symptom improvement.

However, prior literature is characterized by 3 important limitations. First, earlier work had limited statistical power, with the largest sample in the aforementioned meta-analysis¹⁷ 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 Disorders²⁷ 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 elsewhere²⁶ and is available in the protocol (Supplement 2) and in the eMethods in Supplement 1.

Participants had a Quick Inventory of Depressive Symptomatology score²⁸ 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 pipeline³⁰ 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 al²⁴ 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 covari-

ance 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 (Snaitth Hamilton Pleasure Scale).³⁷

To test whether rACC theta activity was associated with HRSD improvement over time, we included an rACC theta \times time interaction. To evaluate whether treatment group (sertraline vs placebo) moderated this effect, we further included a treatment group \times rACC theta \times time interaction. Similarly, for each of the above covariates, treatment group \times predictor \times time interactions were included. A treatment group \times site \times 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

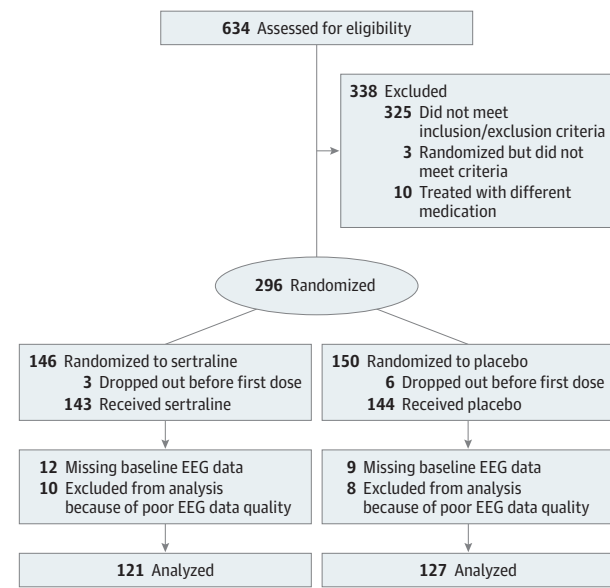
Participant Characteristics

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.

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 2A). 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 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

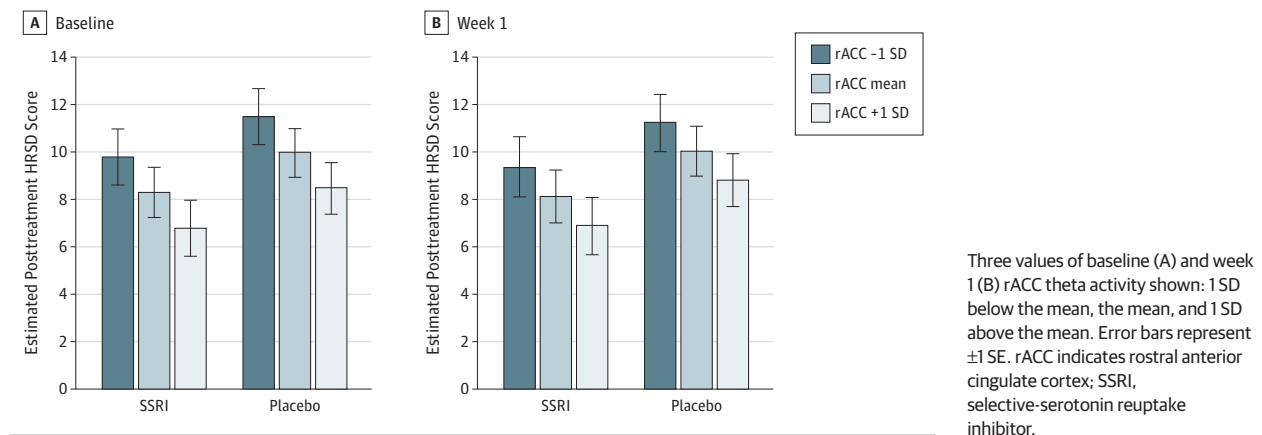
Table 2. Final Hierarchical Linear Model^a

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 studies¹⁶ 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

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 \times rACC theta activity \times 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 some²⁰⁻²³), 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 information³⁹ 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 glutamatergic⁴³ or opioidergic⁴⁴ 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 al¹⁹ 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 fluency⁴⁵), electrophysiologic (loudness-dependent, auditory-evoked potential⁴⁶), and imaging (glucose metabolism in the insula⁴⁷) 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 impli-

cations. 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 efforts⁵¹ 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.

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Author Contributions: Drs Pizzagalli and Webb served as co-first authors and contributed equally to the work (eAppendix in Supplement 1). 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.

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