Archival Report

Rostral Anterior Cingulate Cortex Morphology Predicts Treatment Response to Internet-Based Cognitive Behavioral Therapy for Depression

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ABSTRACT

BACKGROUND: Rostral and subgenual anterior cingulate cortex (rACC and sgACC) activity and, to a lesser extent, volume have been shown to predict depressive symptom improvement across different antidepressant treatments. This study extends prior work by examining whether rACC and/or sgACC morphology predicts treatment response to Internet-based cognitive behavioral therapy (iCBT) for major depressive disorder. This is the first study to examine neural predictors of response to iCBT.

METHODS: Hierarchical linear modeling tested whether pretreatment rACC and sgACC volumes predicted depressive symptom improvement during a six-session (10-week) randomized clinical trial of iCBT (*n* = 35) versus a monitored attention control condition (*n* = 38). Analyses also tested whether pretreatment rACC and sgACC volumes differed between patients who achieved depression remission versus patients who did not remit.

RESULTS: Larger pretreatment right rACC volume was a significant predictor of greater depressive symptom improvement in iCBT even when controlling for demographic (age, gender, race) and clinical (baseline depression, anhedonia, and anxiety) variables previously linked to treatment response. In addition, pretreatment right rACC volume was larger among patients receiving iCBT whose depression eventually remitted relative to patients who did not remit. Corresponding analyses in the monitored attention control group and for the sgACC were not significant.

CONCLUSIONS: rACC volume before iCBT demonstrated incremental predictive validity beyond clinical and demographic variables previously found to predict symptom improvement. Such findings may help inform our understanding of the mediating anatomy of iCBT and, if replicated, may suggest neural targets to augment treatment response (e.g., via modulation of rACC function).

Keywords: Anterior cingulate, Cognitive behavioral therapy, Depression, Internet, Magnetic resonance imaging, Treatment prediction

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Over the past 2 decades, there has been a rapid proliferation in the development of Internet-based cognitive behavioral therapy (iCBT) programs targeting depression. These Internet-based interventions have the potential to substantially increase access to clinical care by reducing barriers associated with traditional face-to-face psychotherapy or pharmacotherapy, including costs, long wait lists, limited access to psychiatric care, and perceived stigma of seeking psychiatric treatment. Internet-based interventions for depression—the majority of which are cognitive behavioral in nature—are currently offered at reduced cost and can be accessed from the convenience and privacy of home. Growing evidence supports the efficacy of iCBT programs for reducing depressive symptoms (1,2). However, similar to face-to-face CBT and pharmacotherapy for depression, rates of treatment nonresponse to iCBT are high, with approximately 40% to 60% of depressed individuals failing to respond (3–5). Accordingly, research is needed to determine for whom iCBT is most

effective and who might be better suited to an alternative intervention.

To date, studies on predictors of treatment response to iCBT have investigated a range of clinical and demographic variables (2). To our knowledge, no study has examined neurobiological predictors of treatment response to iCBT for depression. To be clinically useful, neural variables must demonstrate incremental predictive validity above and beyond much more inexpensive and easily administered clinical and demographic measures previously found to predict treatment response, including age (6), gender (7–10), and race (11) as well as pretreatment severity of depressive symptoms (10,12–15), anxiety (16–18), and anhedonia (19–21).

Given the low-cost and low-risk nature of brief, web-based cognitive behavioral interventions, it is unlikely that costly neuroimaging assessments will be integrated into clinical care to inform treatment assignment to iCBT. However, beyond guiding treatment selection, the identification of pretreatment

moderators of symptom improvement can directly inform research on mediators of change (22). Specifically, a particular pretreatment patient characteristic that significantly moderates treatment response may inspire hypotheses regarding the mechanisms through which this moderator exerts its therapeutic effects (i.e., mediation). Moreover, research on neural moderators of treatment response can suggest targets for augmenting treatment outcome (23).

Anterior cingulate cortex (ACC) function—especially activity within the rostral (rACC) and subgenual (sgACC) subdivisions—has been found to predict depressive symptom improvement across several treatment modalities. Among the most replicated neural predictors of treatment response in the depression literature is increased rACC activity during either resting state or simple cognitive/emotional tasks and, to a lesser extent, greater rACC volume (24). These findings have been replicated across different imaging modalities and treatment approaches (e.g., pharmacotherapy, repetitive transcranial magnetic stimulation [rTMS], sleep deprivation). Moreover, other studies have found that larger rACC volume predicts greater depressive symptom improvement to pharmacotherapy (25–27) [also see Bryant et al. (28)]. As a key hub within the default mode network (DMN) (29), rACC abnormalities—manifested as blunted resting activity or reduced volume—may contribute to maladaptive forms of self-referential processing (24), which could interfere with successful engagement in depression treatment.

With regard to traditional, face-to-face CBT, several studies have found that lower resting (30,31) and task-related (32,33) sgACC activity predicts greater depressive symptom improvement. Specifically, two resting-state positron emission tomography studies found CBT responders to have decreased metabolism in the sgACC at pretreatment relative to nonresponders (30,31); moreover, lower pretreatment sgACC reactivity in response to negative words has been found to predict greater depressive symptom improvement in CBT (32,33). Given that the sgACC has been implicated in the downregulation of limbic hyperreactivity (34–36), patients with relatively blunted levels of sgACC activity may be well suited to CBT, which focuses on the development of top-down emotion regulation skills (32,33).

The present study represents the first investigation of neural predictors of treatment response to iCBT for depression and focuses on pretreatment morphological rather than functional predictors. In contrast to functional magnetic resonance imaging (fMRI), which may be affected by either the task performed or by the specific pattern of off-task cognition (i.e., for resting-state fMRI), morphometric results derived from structural MRI studies are likely to be relatively temporally stable and may thus provide greater insight into traitlike predictors of treatment response (37,38). This study extends prior research by testing whether rACC and sgACC volumes predict depressive symptom improvement within iCBT versus a monitored attention control (MAC) condition. Owing to prior findings, we hypothesized that larger rACC volumes would emerge as a general prognostic (nonspecific) predictor of greater depressive symptom improvement (i.e., across both the iCBT and the MAC groups), whereas sgACC volume was expected to predict outcome in the iCBT condition only. To evaluate regional specificity, we also conducted analyses with dorsal ACC (dACC) volume and hypothesized that it would not

be associated with symptom improvement in either treatment group. To provide a more stringent test of our hypotheses and to evaluate incremental predictive validity, we examined whether the volumes of each ACC subregion predicted treatment response, while controlling for pretreatment clinical and demographic variables that have been previously linked with depressive symptom improvement. The majority of prior studies examining neural predictors of depressive symptom improvement (across any treatment modality) did not test for incremental predictive validity but instead included limited or no covariates (e.g., controlling only for pretreatment depressive symptoms) (30,39). In addition, most prior studies examining predictors of depressive symptom improvement relied on single-arm designs. Thus, the inclusion of both an iCBT and a control group allows us to test the specificity of ACC volume-treatment outcome associations. Finally, and paralleling the treatment outcome analyses from the clinical trial publication (5), to assess the robustness of predictive effects, we tested whether pretreatment ACC subregion volumes were associated with both self-reported depressive symptom improvement and clinician-rated remission status.

METHODS AND MATERIALS

Participants

Data were derived from a recently published randomized clinical trial of iCBT ($n = 37$) versus a MAC ($n = 40$) condition for adults (18–45 years of age) with a diagnosis of major depressive disorder (5). The study was approved by the Institutional Review Board of Partners Healthcare (ClinicalTrials.gov Identifier: NCT01598922), and all participants provided written informed consent. Participants were recruited through flyers posted in the greater Boston area and Internet advertisements. Participants met criteria for a primary diagnosis of current major depressive disorder according to DSM-IV-TR (40) and had Patient Health Questionnaire-9 (PHQ-9) (41) scores between 10 and 23 (inclusive). Additional inclusion criteria were the ability to read English, regular access to a phone and computer with Internet access, absence of psychotropic medications for at least 2 weeks (6 weeks for fluoxetine, 6 months for neuroleptics), and right-handedness. For additional details on exclusion criteria and baseline patient characteristics, see Supplemental Methods and the original clinical trial report (5).

Procedure

Study procedures have been described in detail in a previous publication (5) and thus are explained only briefly here. After completing a telephone screen, participants were invited for an initial visit to determine eligibility based on the PHQ-9, the Structured Clinical Interview for DSM-IV Axis I Disorders (42), and MRI safety screening. Participants who met inclusion criteria were invited for a second study visit consisting of self-report questionnaires and clinical interviews, including the PHQ-9 and 17-item version of the Hamilton Depression Rating Scale (HDRS), administered by doctoral-level clinicians who were blinded to treatment group assignment. Participants subsequently underwent an MRI scan. At the end of the

second study visit, participants were notified of their treatment group assignment (iCBT or MAC). Following the 10-week treatment (or control group) period, participants returned for a third study visit, which included a repeat MRI scan and questionnaires and interviews including the PHQ-9 and HDRS (administered by doctoral-level clinicians blinded to treatment assignment). Participants were remunerated up to $500 based on the time invested in completing the study, including two MRI scans, prorated for early termination.

iCBT Treatment Program and Control Group. Participants randomly assigned to the iCBT condition accessed a modified version of the technician-assisted Sadness Program (43,44) hosted on a secure server. The program consists of six web-based "lessons," which guide participants through cognitive behavioral content, including psychoeducation about depressive symptoms, the cognitive behavioral model of depression, monitoring thoughts and activities and their relation to symptoms, behavioral activation, reducing depressive rumination, sleep hygiene, identifying and modifying depressogenic cognitions, structured problem solving, developing a graded hierarchy to face fears, assertiveness training, effective communication and active listening, and relapse prevention strategies. Participants completed each lesson in sequential order and within 10 weeks. Immediately on logging in to the iCBT server and before each lesson, participants completed the PHQ-9. Each lesson concluded with homework that participants downloaded, and iCBT participants also had access to optional supplemental resources. Participants randomly assigned to the MAC group also logged into the online system six times during the 10-week period. However, their "lessons" consisted only of completing the PHQ-9. Participants in both the iCBT and the MAC groups received brief (3–5 minutes) weekly supportive check-in telephone calls from trained bachelor's-level research assistants.

The iCBT group exhibited significantly greater self-reported (PHQ-9) (41) and clinician-rated (17-item HDRS) (45) improvement in depressive symptoms relative to the MAC condition. Moreover, 57% ($n = 21/37$) of the participants randomly assigned to iCBT met depression remission criteria (posttreatment HDRS score ≤ 7) compared with only 14% ($n = 5/40$) of MAC participants. For additional details, see original clinical trial report (5).

MRI Acquisition and Processing
Structural T1-weighted three-dimensional magnetization prepared rapid acquisition gradient-echo images were collected over 176 sagittal slices (repetition time = 2.1 seconds, echo time = 2.25 ms, flip angle = 12°, 256 × 256 matrix) with voxel size = 1 × 1 × 1 mm³. Volumetric segmentation to obtain ACC volumes used the standard FreeSurfer processing pipeline (http://surfer.nmr.mgh.harvard.edu) (46,47). Bilateral volumes of the subcallosal gyrus (sgACC), anterior cingulate gyrus and sulcus (rACC), and middle-anterior cingulate gyrus and sulcus (dACC) were extracted. This parcellation uses y = +30 to divide the anterior from middle-anterior parts of the cingulate gyrus and sulcus (Figure 1 provides depiction of ACC subregions). Estimated total intracranial volume was obtained from the segmentation and used as a covariate.
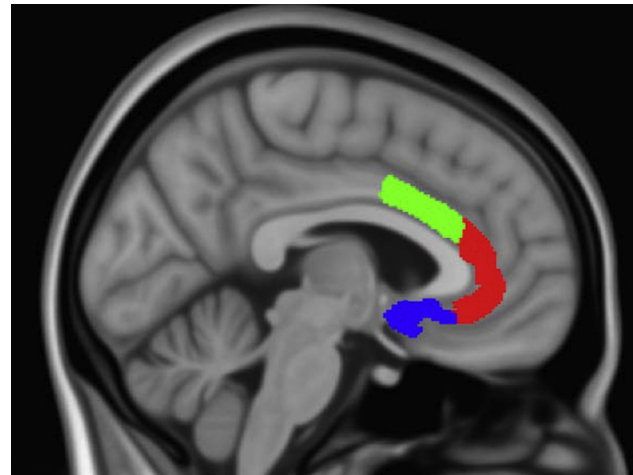

Figure 1. Anterior cingulate cortex (ACC) subregions superimposed on Montreal Neurological Institute 152 brain for display purposes (0.5-mm isotropic). Dorsal ACC is in green, rostral ACC is in red, and subgenual ACC is in blue.

Measures
Depressive symptoms were assessed via self-report (PHQ-9) (41) and clinician rating (HDRS) (45). The PHQ-9 was completed at eight time points: pretreatment, immediately before each of the six weekly lessons, and posttreatment. The HDRS, which is frequently used to define "remission" (posttreatment HDRS score ≤ 7), was administered at pretreatment and posttreatment.

Statistical Analyses
Predicting Depressive Symptom (PHQ-9) Improvement From Pretreatment ACC Subregion Volume. To test whether ACC subregion volumes predicted depressive (PHQ-9) symptom improvement, we utilized hierarchical linear models (HLMs), implemented with mixed-effects repeated-measures models using SAS Version 9.4 PROC MIXED (SAS Institute Inc., Cary, NC) (see Supplemental Methods). To test the incremental predictive validity of rACC, sgACC, and dACC volume, each HLM covaried for baseline clinical and demographic variables previously found to predict depressive symptom improvement, including age, gender, and race as well as pretreatment severity of depressive symptoms (PHQ-9), anxiety (General Distress Anxiety subscale of the Mood and Anxiety Symptom Questionnaire short form) (29), and anhedonia (Anhedonic Depression subscale of the Mood and Anxiety Symptom Questionnaire short form). To examine whether each ACC subregion volume was associated with PHQ-9 improvement, we included in each model a subregion-by-time interaction (adjusting for a total intracranial volume-by-time interaction). To test whether treatment group (iCBT vs. MAC) moderated these associations, we further included treatment group-by-subregion-by-time interactions. Given evidence that left versus right ACC morphology may be differentially associated with depressive symptoms (25,48) and to minimize multicollinearity in our HLMs ($r = .83$; $p < .0001$ for left and right rACC volume), left and right hemisphere ACC

subregion volumes were included in separate models. All available data were used (including from dropouts), rendering these HLMs full intent-to-treat analyses. When a significant ACC subregion volume predictor finding emerged, we also tested whether the inclusion of this ACC volume term in our model (i.e., a "full" model) yielded significantly improved fit relative to a "reduced" model (i.e., including all covariates but excluding the ACC term). The fit of the full model was compared with the fit of the reduced model by means of likelihood ratio tests between the models' deviance statistics (49).

Differences in Pretreatment ACC Subregion Volume Between Remitters and Nonremitters. We examined whether treatment remitters (HDRS score $\leq$ 7) versus nonremitters differed in pretreatment ACC subregion volumes using a series of general linear models implemented with SAS PROC GLM. These HDRS general linear models entered remission status (remitted vs. nonremitted) as an independent variable and covaried for age, gender, and race as well as pretreatment HDRS score, anxiety, anhedonia, and total intracranial volume. To test whether treatment group statistically moderated remitter versus nonremitter differences in ACC subregion volume, treatment group-by-remitter status interactions were modeled.

RESULTS

HLM Analyses Predicting Depressive Symptom (PHQ-9) Improvement

Combined (iCBT and MAC) Sample. Larger right ($F_{1,63.2} = 6.89$, $t = -2.62$, $p = .011$), but not left ($F_{1,63.1} = 0.40$, $t = -0.63$, $p = .529$), rACC volume predicted greater decline in PHQ-9 scores. A significant likelihood ratio χ^2 test indicated that the "full" right rACC model (i.e., including right rACC volume and covariates) provided significantly improved fit relative to a "reduced" model (i.e., covariates but excluding the right rACC term): $\chi^2_6 = 24.74$, $p < .001$. In contrast, neither right ($F_{1,62.8} = 0.07$, $t = -0.27$, $p = .791$) nor left ($F_{1,66.5} = 1.23$, $t = 1.11$, $p = .272$) sgACC volume predicted PHQ-9 scores. In a follow-up analysis entering both right rACC and right sgACC volumes as significant predictors of PHQ-9 scores, only right rACC volume was significant ($F_{1,62.6} = 7.88$, $t = -2.81$, $p = .007$). The latter model, which also included baseline clinical and demographic covariates, accounted for an estimated 40.5% of the between-subjects variance in linear slope estimates of depressive symptom improvement.

Only right sgACC volume interacted with treatment group in predicting symptom improvement ($F_{1,62.8} = 5.56$, $b = -0.002$, SE = 0.0008, $p = .021$; for left sgACC, $F_{1,66.6} = 0.62$, $b = 0.0005$, SE = 0.0007, $p = .433$; left rACC, $F_{1,63.1} = 0.10$, $b = -0.0001$, SE = 0.0004, $p = .751$; right rACC, $F_{1,63.2} = 0.53$, $b = -0.0002$, SE = 0.0003, $p = .469$). To decompose this significant interaction—and given our iCBT-specific hypothesis and the significant differences in depressive symptom improvement between the iCBT and MAC samples (5)—the above analyses were run separately for each treatment group.

iCBT Sample. Similar to the analyses in the combined sample, right ($F_{1,32.2} = 8.47$, $t = -2.91$, $p = .007$), but not left

($F_{1,32.9} = 0.56$, $t = -0.75$, $p = .460$), rACC volume predicted greater depressive symptom improvement in the iCBT group (Table 1 and Figure 2). A significant likelihood ratio χ^2 test indicated that the full right rACC model provided significantly improved fit relative to a reduced model: $\chi^2_2 = 17.47$, $p < .001$. In contrast, neither right ($F_{1,32.5} = 2.92$, $t = -1.71$, $p = .097$) nor left ($F_{1,33.5} = 1.43$, $t = 1.20$, $p = .240$) sgACC volume predicted symptom improvement. Similar to the analyses in the combined sample, right rACC volume remained significantly associated with symptom improvement even when right sgACC volume was added as an additional covariate ($F_{1,32.6} = 7.56$, $t = -2.75$, $p = .010$). The latter model accounted for an estimated 44.5% of the between-subjects variance in linear slope estimates of PHQ-9 improvement.

MAC Sample. Neither rACC (right: $F_{1,31} = 1.39$, $t = -1.18$, $p = .248$; left: $F_{1,30.3} = 0.04$, $t = -0.19$, $p = .849$) nor sgACC (right: $F_{1,30.4} = 2.61$, $t = 1.62$, $p = .117$; left: $F_{1,33.5} = 0.04$, $t = 0.20$, $p = .841$) volumes predicted depressive symptom change (Table 1 and Figure 2).

Differences in Pretreatment ACC Subregion Volume Between Remitters and Nonremitters

Paralleling the above HLM analyses, there were significant differences in pretreatment right ($F_{1,16} = 6.01$, $p = .026$), but not left

Table 1. HLM Results by Treatment Group

Predictor	F	df	p
iCBT			
Total intracranial volume	7.58	33.9	.009[a]
Age	0.00	36.5	.953
Gender	0.05	34.9	.817
Race	0.86	34.6	.496
Depression	26.63	34.1	< .001[a]
Anxiety	1.21	38.7	.279
Anhedonia	2.61	35.8	.115
Right rACC volume	8.47	32.2	.007[a]
MAC			
Total intracranial volume	0.88	31.1	.355
Age	7.31	37.6	.010[a]
Gender	0.19	36.7	.664
Race	1.03	36.0	.413
Depression	46.01	37.6	< .001[a]
Anxiety	0.10	35.1	.755
Anhedonia	0.27	35.2	.606
Right rACC volume	1.39	31.0	.248

Predicting depressive (PHQ-9) symptom improvement in iCBT (n = 35) and MAC (n = 38) condition. Symptom measures were the pretreatment PHQ-9 for depression, the pretreatment MASQ-GDA for anxiety, and the pretreatment MASQ-AD for anhedonia.

HLM, hierarchical linear model; iCBT, Internet-based cognitive behavioral therapy; MAC, monitored attention control; MASQ-AD, Mood and Anxiety Symptom Questionnaire short form Anhedonic Depression subscale; MASQ-GDA, Mood and Anxiety Symptom Questionnaire short form General Distress Anxiety subscale; PHQ-9, Patient Health Questionnaire-9; rACC, rostral anterior cingulate cortex.
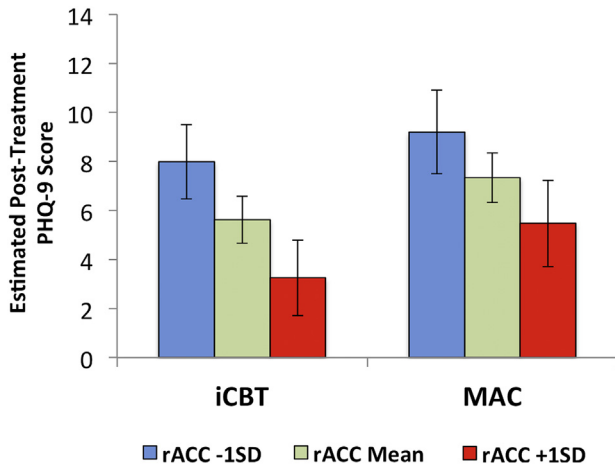
[a]Significant effects.

Figure 2. Estimated posttreatment Patient Health Questionnaire-9 (PHQ-9) scores for the Internet-based cognitive behavioral therapy (iCBT) (n = 35) and monitored attention control (MAC) (n = 38) groups at three values of pretreatment right rostral anterior cingulate cortex (rACC) volume: 1 SD below the mean, the mean, and 1 SD above the mean. Error bars represent ± 1 SE.

($F_{1,16}$ = 0.31, p = .586), rACC volume between treatment remitters and nonremitters in the iCBT group (Figure 3). No such differences were observed in the MAC group. Continuous analyses of posttreatment HDRS scores (adjusting for pretreatment values) yielded similar findings with larger pretreatment right ($F_{1,16}$ = 4.69, t = −2.17, p = .046), but not left ($F_{1,16}$ = 0.28, t = 0.53, p = .602), rACC volume predicting lower posttreatment depression scores in the iCBT group only (see Supplemental Results for details and for regional specificity analyses).

DISCUSSION

The present study is the first to examine neural predictors of treatment response in iCBT and demonstrates the incremental predictive validity of rACC volume in predicting depressive symptom change. Analyses of both self-reported (PHQ-9 scores) and clinician-rated (HDRS scores and remission status) depressive symptoms indicated that larger right rACC volumes were associated with better treatment outcomes. Specifically, HLM indicated that larger right rACC volume at pretreatment predicted greater self-reported depressive symptom improvement in iCBT. The latter model—based solely on pretreatment patient characteristics (i.e., rACC volume and covariates)—accounted for an estimated 44.5% of the between-subjects variance in linear slope estimates of PHQ-9 improvement. Similarly, analyses involving the clinician-rated HDRS indicated that pretreatment right rACC volume was significantly larger among patients receiving iCBT whose depression had remitted at the posttreatment visit relative to patients who did not remit. Continuous analyses of HDRS scores yielded a similar pattern of findings. Importantly, these findings were significant after controlling for a number of clinical and demographic variables previously linked with depressive symptom improvement—specifically, age (6), gender (7,10), and race (11)—as well as pretreatment severity of depressive symptoms (10), anxiety (16), and anhedonia (19) (and when statistically adjusting for total intracranial volume in

all models). Thus, in contrast to most prior studies that include no or few such control variables, our findings indicate that right rACC volume provides predictive information above and beyond previously established clinical and demographic predictors. It is unclear why right, but not left, rACC volume was associated with symptom improvement, although the lack of a significant rACC volume-by-hemisphere interaction in the current study precludes laterality claims. Nevertheless, there is some evidence that left versus right ACC morphology may be differentially associated with depressive symptoms (25,53) as well as previous rACC-outcome findings indicating a right lateralized effect (50,51).

In contrast to our rACC volume findings and hypotheses, sgACC volume was not associated with either self-reported (PHQ-9) or clinician-rated (HDRS) symptom improvement in either group. Considering the relatively larger body of literature supporting the role of resting rACC activity (and to a lesser extent larger rACC volume) in depressive symptom improvement, it may not be surprising that findings were specific to the rACC. Regional specificity analyses did reveal a significant association between a larger right dACC volume
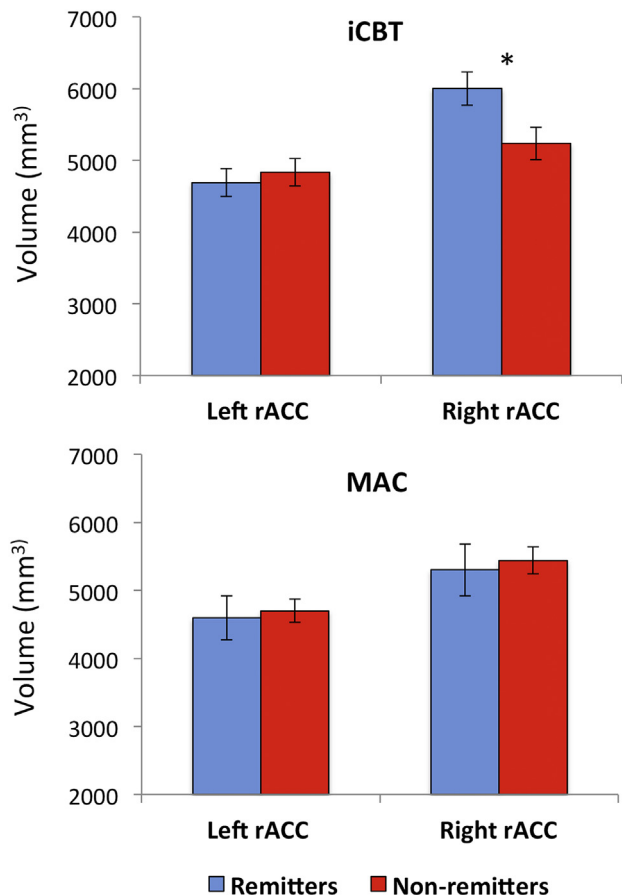

Figure 3. Estimated pretreatment right and left rostral anterior cingulate cortex (rACC) volume for the Internet-based cognitive behavioral therapy (iCBT) (n = 28) and monitored attention control (MAC) (n = 29) groups for treatment remitters (posttreatment Hamilton Depression Rating Scale [HDRS] ≤ 7) vs. nonremitters. Error bars represent ± 1 SE. *p < .05.

and PHQ-9 (but not HDRS) symptom improvement. However, the latter dACC-outcome association was no longer significant when controlling for right rACC volume (see Supplemental Results).

Smaller rACC volumes have been repeatedly linked with elevated depressive symptoms in cross-sectional studies (52,53). Indeed, within our data, smaller rACC volumes were correlated with higher depression severity at baseline (for HDRS, right rACC $r = -.29$, $p = .01$; left rACC $r = -.32$; $p < .01$; for PHQ-9, both $p > .79$). Given that our analyses controlled for baseline depression severity, the present findings suggest that right rACC volume also accounts for significant variance in subsequent depressive symptom improvement, over and above its association with concurrent depressive symptoms. This raises the question of what mediates the association between rACC volume and treatment outcome in depression. The rACC has been implicated in a range of cognitive and affective functions that may help account for its link with depressive symptom improvement, including 1) optimistic biases (54), 2) coping style (55), 3) self-referential processing (56), 4) error processing (57), 5) inhibitory processes (58), and 6) dampening of amygdala hyperactivity and regulation of emotional conflict (59). Moreover, as a key hub within the DMN (29), rACC abnormalities—such as manifested in reduced volume—may contribute to maladaptive forms of self-referential processing (24), which could interfere with successful engagement in depression treatment. Of relevance—although not specifically focused on the rACC—a recent study found that greater deactivation of the DMN while engaging with an emotional task predicted enhanced antidepressant response (60).

Although right rACC volume predicted depressive symptom improvement in the iCBT, but not the MAC, group, a nonsignificant treatment group-by-rACC volume interaction indicated that rACC-outcome associations were not significantly different between groups. Indeed, although rACC volume did not emerge as a statistically significant predictor of treatment response within our MAC condition, the effect was in the same direction as the iCBT group (at least for the PHQ-9) (Figure 2). Moreover, larger rACC volume has been shown to predict greater depressive symptom improvement to antidepressant medication, and elevated rACC activity has been found to predict treatment response across a range of interventions, including pharmacotherapy, rTMS, and sleep deprivation (24). Furthermore, the finding that larger rACC volume predicts enhanced treatment response to CBT for posttraumatic stress disorder suggests that the therapeutic benefits of larger volume in this region may extend beyond depression (28). Taken together, enhanced resting rACC activity—and larger rACC volume—may represent a general or nonspecific "prognostic" predictor (6) of the likelihood of symptom improvement. To determine whether resting rACC activity and/or volume indeed represent markers of the likelihood of spontaneous remission, studies testing rACC-outcome associations within the context of assessment-only conditions are needed.

Given the growing body of research supporting the role of rACC function (and, to a lesser extent, volume) in predicting symptom improvement, there may be important implications for augmenting treatment response via modulation of rACC

function. Certain tasks, including cognitive paradigms with high demands on sustained attention and working memory (23), and mindfulness practices focused on cultivating attentional control (61), have been shown to enhance rACC activity. Of particular relevance, a recent study found that increasing rACC activity via a cognitive task enhanced the antidepressant effects of rTMS (23). Additional research is needed to replicate this finding and to examine the extent to which increased rACC activation is sustained over time. Moreover, research is needed to investigate whether increasing rACC activity augments treatment response to interventions beyond rTMS (e.g., CBT, selective serotonin reuptake inhibitors). Of course, the fact that a pretreatment patient characteristic (e.g., age) is found to predict symptom improvement does not necessarily imply that it can be manipulated in service of enhancing treatment outcomes.

Limitations

Some limitations of the present study should be noted. First, although our MAC comparison condition did control for some "common factors" that may contribute to depressive symptom improvement (i.e., weekly symptom monitoring, staff contact and support), a placebo control group (or an alternative active treatment) would have been more stringent. Patients in the MAC condition completed symptom assessments each time they logged in to the site (and received weekly supportive check-in calls from staff), but they did not have access to the CBT lessons. Thus, their total time commitment on the site was lower than the iCBT group. Nevertheless, in contrast to most prior treatment prediction studies that have typically relied on single-arm designs (i.e., one treatment group with no comparison condition), the present study makes an important contribution by testing predictors of treatment response in an iCBT group and a control group. Second, our participants were self-selected based on responses to study advertisements, were willing to engage in lengthy diagnostic and neuroimaging assessments, and were remunerated. Moreover, patients with severe levels of depression or elevated suicidal ideation were excluded. Thus, it is unclear to what extent our findings will generalize to more severe, treatment-seeking depressed individuals.

Conclusions

Limitations notwithstanding, the current findings extend prior research in showing that rACC volume provides incremental predictive validity in its relation to iCBT treatment response. Given the growing body of research implicating rACC function and morphology in symptom improvement across a range of treatment modalities, studies are needed to clarify the mechanisms through which rACC function/volume exerts its therapeutic effects. The present study focused on pretreatment ACC volume and not function. Pretreatment and posttreatment resting-state fMRI data were collected in this trial. We plan to examine the predictive role of resting rACC activity—and functional connectivity of this region [e.g., with other DMN nodes (11) and limbic regions (12)]—in relation to treatment response. Additional research is also needed to investigate the potential therapeutic benefits of experimentally manipulating

rACC function for depressed individuals at elevated risk of nonresponse.

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ARTICLE INFORMATION

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