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Biol Psychiatry Cogn Neurosci Neuroimaging. Author manuscript; available in PMC 2018 June 18.

Published in final edited form as:

Biol Psychiatry Cogn Neurosci Neuroimaging. 2018 March ; 3(3): 255–262. doi:10.1016/j.bpsc.2017.08.005.

Rostral anterior cingulate cortex morphology predicts treatment response to internet-based CBT for depression

Christian A. Webb, Ph.D.[1,2], **Elizabeth A. Olson, Ph.D.**[1,2], **William D.S. Killgore, Ph.D.**[3], **Diego A. Pizzagalli, Ph.D.**[1,2], **Scott L. Rauch, M.D.**[1,2,*], and **Isabelle M. Rosso, Ph.D.**[1,2,*]

[1]Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA

[2]Department of Psychiatry, Harvard Medical School, Boston, MA

[3]Department of Psychiatry, University of Arizona, Tucson, AZ

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 (MDD). This is the first study to examine neural predictors of response to iCBT.

Methods—Hierarchical linear modeling tested whether pre-treatment rACC and sgACC volumes predicted depressive symptom improvement during a 6-session (10-week) randomized clinical trial of iCBT ($n = 35$) *vs.* a monitored attention control (MAC; $n = 38$). Analyses also tested whether pre-treatment rACC and sgACC volumes differed between patients who achieved depression remission versus those who did not remit.

Results—Larger pre-treatment 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, pre-treatment right rACC volume was larger among iCBT patients whose depression eventually remitted relative to those who did not remit. Corresponding analyses in the MAC group and for the sgACC were not significant.

Conclusions—rACC volume prior to 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).

ClinicalTrials.gov Identifier—NCT01598922

Corresponding author: Isabelle M. Rosso, Ph.D., Center for Depression, Anxiety, and Stress Research, McLean Hospital, 115 Mill Street, Belmont, MA 02478, Tel: 617-855-2607, Fax: 617-855-4231, (irosso@hms.harvard.edu).

*Authors who contributed equally to the work.

Financial Disclosures

Over the past 3 years, DAP has received consulting fees from Akili Interactive Labs, BlackThorn Therapeutics, Pfizer and Posit Science, for activities unrelated to the current research. All other authors declare no biomedical financial interests or potential conflicts of interest.

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Keywords

anterior cingulate; treatment prediction; depression; cognitive behavioral therapy; Internet; magnetic resonance imaging

Introduction

Over the past two 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 40–60% 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. In order 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 pre-treatment 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 pre-treatment moderators of symptom improvement can directly inform research on mediators of change (22). Namely, a particular pre-treatment patient characteristic that significantly moderates treatment response may inspire hypotheses regarding the mechanism(s) 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

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and treatment approaches (e.g., pharmacotherapy, rTMS, sleep deprivation). There have also been studies that 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 regards 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 PET studies found CBT responders to have decreased metabolism in the sgACC at pretreatment relative to non-responders (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

The present study represents the first investigation of neural predictors of treatment response to iCBT for depression, and focuses on pre-treatment 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 MRIs are likely to be relatively temporally stable and may thus provide greater insight into trait-like 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 (non-specific) predictor of greater depressive symptom improvement (i.e., across both the iCBT and 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 pre-treatment 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., only controlling for pre-treatment 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 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 pre-treatment ACC

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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 (ages 18–45) diagnosed with MDD (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 MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (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 are thus only explained briefly here. After completing a telephone screen participants were invited for an initial visit to determine eligibility based on an the PHQ-9, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)(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 HRSD, administered by doctoral-level clinicians blind 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, including a repeat MRI scan and questionnaires/interviews including the PHQ-9 and HRSD (administered by doctoral-level clinicians blind 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 randomized 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 6 web-based “lessons,” which guides 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 ending with relapse prevention strategies.

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Participants completed each lesson in sequential order and within 10 weeks. Immediately upon logging into the iCBT server, and prior to 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 randomized 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 MAC groups received brief (3–5 minute) weekly supportive check-in telephone calls from trained bachelor's level research assistants.

The iCBT group exhibited significantly greater self-reported (Patient Health Questionnaire-9; PHQ-9) (41) and clinician-rated (17-item Hamilton Rating Scale for Depression; HRSD) (45) improvement in depressive symptoms relative to the MAC condition. Moreover, 57% (n = 21/37) of the participants randomized to iCBT met depression remission criteria (post-treatment HRSD ≤ 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 3D magnetization-prepared rapid gradient-echo (MPRAGE) images were collected over 176 sagittal slices (TR/TE/flip angle = 2.1s/2.25ms/12°, 256×256 matrix) with voxel size = 1×1×1 mm^3. 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 (see Figure 1 for depiction of ACC subregions). Estimated total intracranial volume (eTIV) was obtained from the segmentation and used as a covariate.

Measures

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

Statistical Analyses

Predicting depressive symptom (PHQ-9) improvement from pre-treatment ACC subregion volume—To test whether ACC subregion volumes predicted depressive (PHQ-9) symptom improvement, we utilized hierarchical linear models (HLM), 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/dACC volume, each HLM covaried for baseline clinical and demographic variables previously found to predict depressive symptom improvement, including age, gender, race, as well as pre-treatment severity of depressive symptoms (PHQ-9), anxiety (anxiety-related general distress subscale of the Mood and Anxiety Symptom Questionnaire-Short Form (MASQ-GDA)) (29) and anhedonia (anhedonic

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depression subscale of the MASQ (MASQ-AD)). 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 *vs* right ACC morphology may be differentially associated with depressive symptoms (25, 53), 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 to that of the reduced model by means of likelihood ratio tests between the models' deviance statistics (54).

Differences in pre-treatment ACC subregion volume between remitters and non-remitters—We examined whether treatment remitters (HRSD score ≤ 7) *vs.* non-remitters differed in pre-treatment ACC subregion volumes, using a series of general linear models (GLMs) implemented with SAS PROC GLM. These HRSD GLMs entered remission status (remitted *vs* nonremitted) as an independent variable, and covaried for age, gender, race, as well as pre-treatment HRSD score, anxiety, anhedonia and total intracranial volume. To test whether treatment group statistically moderated remitter *vs* non-remitter 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 ($F[1,63.2] = 6.89$, $t = -2.62$, $p = 0.011$), but not left ($F[1,63.1] = 0.40$, $t = -0.63$, $p = 0.529$), rACC volume predicted greater decline in PHQ-9 scores. A significant likelihood ratio chi-squared 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): $\chi^2(6) = 24.74$, $p < 0.001$. In contrast, neither right ($F[1,62.8] = 0.07$, $t = -0.27$, $p = 0.791$) nor left ($F[1,66.5] = 1.23$, $t = 1.11$, $p = 0.272$), 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 ($F[1,62.6] = 7.88$, $t = -2.81$, $p = 0.007$). 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, $p = 0.021$; for left sgACC, $F[1,66.6] = 0.62$, $b = 0.0005$, SE= 0.0007, $p = 0.433$; left rACC, $F(1, 63.1) = 0.10$, $b =$

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−0.0001, SE= 0.0004, p = 0.751; right rACC, F(1, 63.2)= 0.53, b= −0.0002, SE= 0.0003, p = 0.469). 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 = 0.007), but not left (F[1,32.9]= 0.56, t= −0.75, p = 0.460), rACC volume predicted greater depressive symptom improvement in the iCBT group (see Table 1 and Figure 2). A significant likelihood ratio chi-squared test indicated that the full right rACC model provided significantly improved fit relative to a reduced model: $\chi 2$ (2)= 17.47, p < 0.001. In contrast, neither right (F[1,32.5]= 2.92, t= −1.71, p = 0.097) nor left (F[1,33.5]= 1.43, t= 1.20, p = 0.240), 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 = 0.010). 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 = 0.248; left, F[1,30.3]= 0.04, t= −0.19, p = 0.849) or sgACC volumes (right, F[1,30.4]= 2.61, t= 1.62, p = 0.117; left, F[1,33.5]= 0.04, t= 0.20, p = 0.841) predicted depressive symptom change (see Table 1 and Figure 2).

Differences in pre-treatment ACC subregion volume between remitters and non-remitters

Paralleling the above HLM analyses, there were significant differences in pre-treatment right (F[1,16]= 6.01, p= 0.026) but not left (F[1,16]= 0.31, p= 0.586) rACC volume between treatment remitters and non-remitters in the iCBT group (see Figure 3). No such differences were observed in the MAC group. Continuous analyses of post-treatment HRSD scores (adjusting for pre-treatment values) yielded similar findings with larger pretreatment right (F[1,16]= 4.69, t= −2.17, p = 0.046) but not left (F[1,16]= 0.28, t= 0.53, p = 0.602) rACC volume predicting lower post-treatment 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 (HRSD scores and remission status) depressive symptoms indicated that larger right rACC volumes were associated with better treatment outcomes. Specifically, hierarchical linear modeling indicated that larger right rACC volume at pre-treatment predicted greater self-reported depressive symptom improvement in iCBT. The latter model – based solely on pre-treatment 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 HRSD indicated that pre-treatment right rACC volume was significantly larger among iCBT patients whose

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depression had remitted at the post-treatment visit, relative to those who did not remit. Continuous analyses of HRSD 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), and pre-treatment severity of depressive symptoms (10), anxiety (16), and anhedonia (19) (as well as 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 X hemisphere interaction in the current study precludes laterality claims. Nevertheless, there is some evidence that left *vs* right ACC morphology may be differentially associated with depressive symptoms (25, 53), as well as previous rACC-outcome findings indicating a right lateralized effect (55, 56).

In contrast to our rACC volume findings and hypotheses, sgACC volume was not associated with either self-reported (PHQ-9) or clinician-rated (HRSD) 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 and PHQ-9 (but not HRSD) 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 (57, 58). Indeed, within our data, smaller rACC volumes were correlated with higher depression severity at baseline (for HRSD, right rACC $r = -.29$; $p = .01$, left rACC $r = -.32$; $p < .01$; for PHQ-9, both *ps* >.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 which may help account for its link with depressive symptom improvement, including: 1) optimistic biases (59), 2) coping style (60), 3) self-referential processing (61), 4) error processing (62), 5) inhibitory processes (63), and 6) dampening of amygdala hyperactivity and regulation of emotional conflict (64). Moreover, as a key hub within the default mode network (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 (65).

Although right rACC volume predicted depressive symptom improvement in the iCBT but not the MAC group, a non-significant treatment group-by-rACC volume interaction

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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, see 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, repetitive rTMS and sleep deprivation (24). Furthermore, the finding that larger rACC volume predicts enhanced treatment response to CBT for PTSD 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 non-specific “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 (66), 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, SSRIs). Of course, the fact that a pre-treatment patient characteristic is found to predict symptom improvement does not necessarily imply that it can be manipulated in service of enhancing treatment outcomes (e.g., age).

Limitations

Some limitations of the present study should be noted. First, although our MAC comparison condition did control for some “common factors” that 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 did not have access to the CBT lessons. Thus, their total time commitment on the site was lower than the iCBT group. Nevertheless, unlike 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 sample was self-selected based on responses to study advertisements, was willing to engage in lengthy diagnostic and neuroimaging assessments, and was 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.

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Conclusions

These 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 mechanism(s) through which rACC function/volume exerts its therapeutic effects. The present study focused on pre-treatment ACC volume and not function. Pre- and post-treatment 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 non-response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research activities were funded by the US Army Military Operational Medicine Research Program (Award # W81XWH-12-1-0109; PI: Rauch). In addition, CAW was partially supported by NIMH K23 MH108752, a NARSAD Young Investigator Award, as well as the Klingenstein Third Generation Foundation. IMR was partially supported by NIMH R01 MH096987. DAP was partially supported by R37 MH068376. The funding sources 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.

The findings within this manuscript were previously presented by Dr. Rauch in poster format at the annual meeting of the American College of Neuropsychopharmacology in Hollywood, FL (December 4–8, 2016) and by CAW in an oral presentation at the annual meeting of the Society of Biological Psychiatry in San Diego, CA (May 18–20, 2017).

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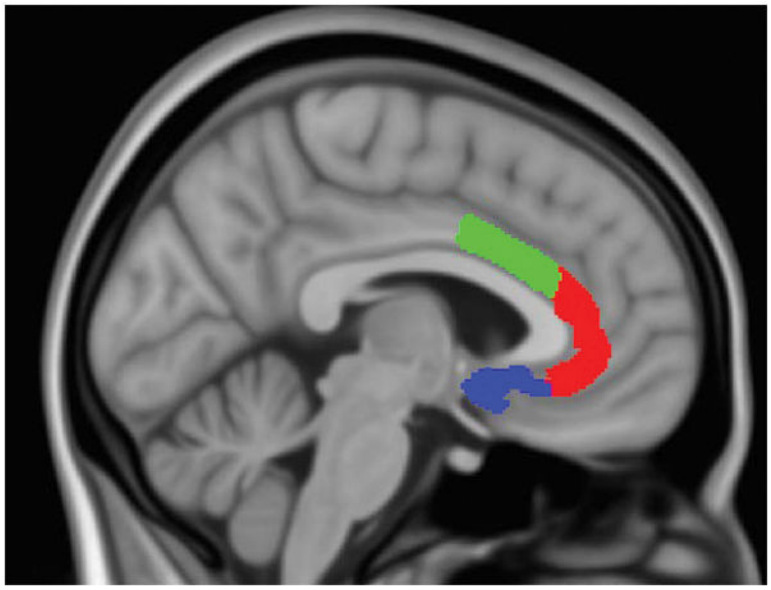

Figure 1.
ACC subregions superimposed on MNI152 brain for display purposes (0.5 mm isotropic). Dorsal anterior cingulate cortex (dACC) is in green; Rostral anterior cingulate cortex (rACC) is in red; Subgenual anterior cingulate cortex (sgACC) is in blue.

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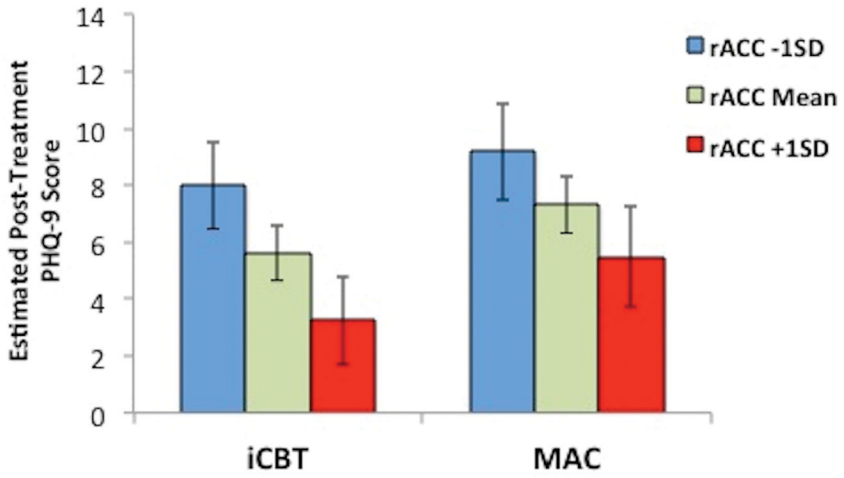

Figure 2.

Estimated post-treatment Patient Health Questionnaire – 9 (PHQ-9) scores for the iCBT (n = 35) and MAC (n = 38) groups at three values of pre-treatment right rACC volume: one standard deviation below the mean, the mean, and one standard deviation above the mean. Error bars represent ±1 standard error.

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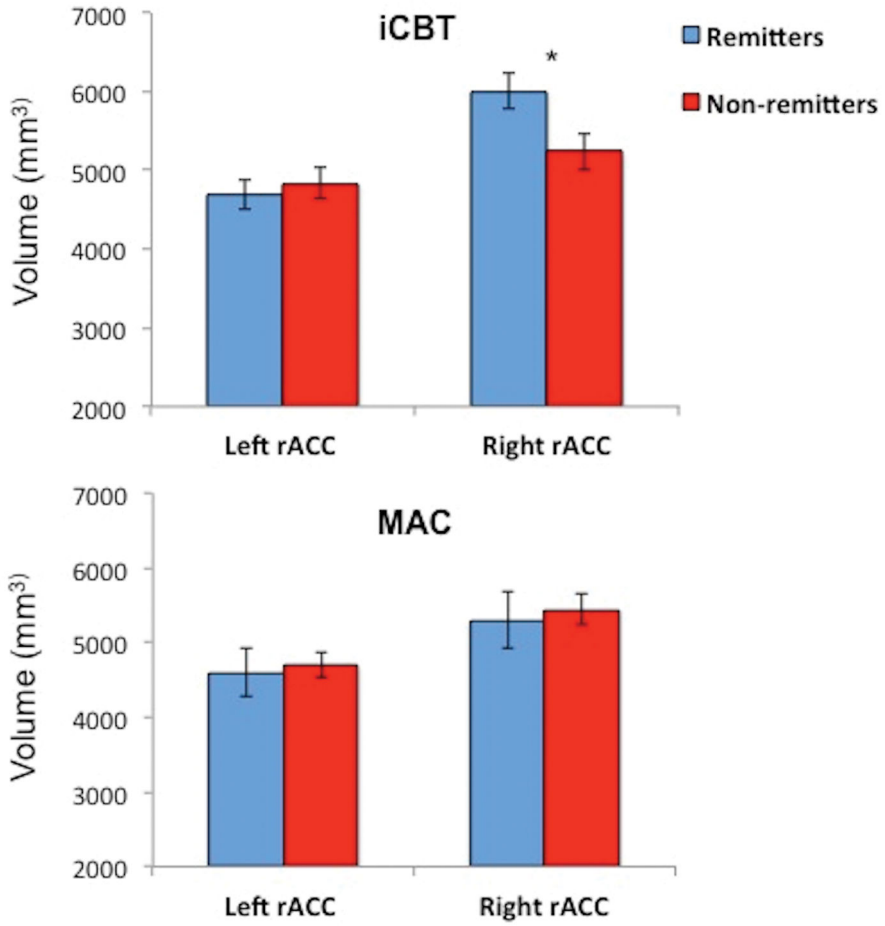

Figure 3.

Estimated pre-treatment right and left rACC volume for the iCBT (n = 28) and MAC (n = 29) groups for treatment remitters (post-treatment HRSD ≤ 7) *vs* non-remitters. Error bars represent ±1 standard error.

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Table 1

HLM Results by Treatment Group: Predicting Depressive (PHQ-9) Symptom Improvement in internet-based cognitive behavior therapy (iCBT; $n = 35$) and a monitored attention control (MAC; $n = 38$) condition.

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

Note: Depression = Pre-treatment PHQ-9; Anxiety = Pre-treatment MASQ-GDA; Anhedonia = Pre-treatment MASQ-AD. Significant effects are bolded.