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

Supplemental Information

Supplemental Methods

Participants. Exclusion criteria included significant suicidal ideation (SI; PHQ-9 item 9 score >1), severe depression (PHQ-9 total score >23), bipolar disorder, history of psychosis, current or past alcohol or substance dependence, current alcohol abuse, current or past substance abuse, use of illicit drugs (excluding cannabis) within the past year, use of cannabis within the past month, current CBT treatment, history of electroconvulsive therapy, less than ninth grade education, and common MRI contraindications. For detailed information on pre-treatment clinical and demographic characteristics see the original clinical trial publication, in particular Table 2 (1). With regards to comorbidities, 48 (62%) of the 77 participants randomized to the iCBT or MAC group met criteria for one or more current DSM-IV Axis 1 disorder, in addition to their current MDD diagnosis: social phobia (n = 27), generalized anxiety disorder (n = 16), posttraumatic stress disorder (n = 12), specific phobia (n = 3), anxiety disorder NOS (n = 2), obsessive compulsive disorder (n =1), panic disorder without agoraphobia (n = 1), agoraphobia (n = 1), and bulimia nervosa (n= 1).

MRI Acquisition and Processing. The standard preprocessing stream has been described elsewhere; briefly, this includes brain extraction (2), intensity normalization, tessellation of the boundary between gray and white matter, automated topology correction, and deformation of the surface to follow intensity gradients to optimize the placement of gray/white and gray/cerebrospinal fluid borders (3,4). The cerebral cortex was then parcellated using Freesurfer's Destrieux cortical atlas ("aparc.a2009s") (5).

Statistical Analyses: Hierarchical Linear Modeling (HLM). HLM analyses were implemented with mixed-effects repeated-measures models using SAS (version 9.4) PROC MIXED (SAS Institute Inc, Cary, NC). Subject-specific slopes and intercepts were treated as randomly varying across individuals, and unstructured error variance/covariance matrices were estimated (6,7). Models were calculated using full maximum likelihood estimation procedures, and the degrees of freedom for hypothesis tests were estimated with the Kenward–Roger approximation (8).

Supplemental Results

For the PHQ-9 hierarchical linear models (HLM), two participants from the iCBT group and one from the MAC group were excluded due to missing data on one or more baseline variables. In addition, one participant assigned to the MAC group was excluded due to a software issue resulting in this individual completing the same online symptom assessments multiple times. Thus, for the PHQ-9 analyses, the final sample size was 35 for iCBT and 38 for MAC. In addition to the abovementioned 4 participants (2 from each treatment group) who were excluded, 7 iCBT participants and 9 MAC participants dropped out of treatment prior to completing the post-treatment HRSD assessment. Thus, for the HRSD remission analyses the completer sample reported in the main text consisted of 28 subjects for iCBT and 29 for the MAC group.

HRSD Completer Analyses. Within the combined (iCBT and MAC) sample, there were no significant differences in either right ($F[1,42] = 0.70$, $p = 0.406$) or left ($F[1,42] = 0.11$, $p = 0.742$) rACC volume between remitters and non-remitters. Moreover, treatment group did not statistically moderate remitter vs. non-remitter differences in right ($F[1,42] = 1.35$, $p = 0.252$) or

left (F[1,42] = 0.54, p = 0.467) rACC volume. However, within the iCBT group, there were significant differences in 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. Specifically, iCBT participants whose depressive episode remitted had significantly larger pre-treatment right rACC volumes relative to non-remitters (Figure 3). Within the MAC group, there were no significant differences in either right (F(1,16) = 0.11, p = 0.743) or left (F(1,16) = 0.09, p = 0.772) rACC volume as a function of remitter status (Figure 3). All corresponding tests for sgACC volume were nonsignificant (all Fs < 2.88; ps > .109).

HRSD Intent-to-treat Analyses. For the HLMs predicting PHQ-9 symptom improvement, all available data were used (including from dropouts) rendering these HLMs full intent-to-treat analyses. In contrast to the self-report PHQ-9, which was completed 8 times over the course of treatment, the HRSD was administered at pre- and post-treatment. Thus, the HRSD analyses reported in the manuscript excluded participants who dropped out of the iCBT or MAC conditions prior to the post-treatment assessment (i.e., a completer analysis). However, we also conducted intent-to-treat analyses via last observation carried forward (LOCF). Within the combined sample, there were no significant differences in either right (F[1,57] = 0.63, p = 0.432) or left (F[1,57] = 0.02, p = 0.900) rACC volume between remitters and non-remitters, and treatment group did not statistically moderate remitter status differences between right (F[1,57] = 1.92, p = 0.171) or left (F[1,57] = 0.02, p = 0.888) rACC volume. However, similar to the completer analyses, within the intent-to-treat iCBT group there were significant differences in right (F[1,22] = 5.66, p = 0.026), but not left (F[1,22] = 0.00, p = 0.968), rACC volume between treatment remitters and non-remitters. Within the MAC group, there were no significant differences in either right (F[1,25] = 0.24, p = 0.631) or left (F[1,25] = 0.22, p = 0.644) rACC

volume as a function of remitter group. All corresponding tests for sgACC volume were nonsignificant (all *F*s < 1.92; *p*s > .179).

Regional specificity. To assess regional specificity of ACC findings, the primary PHQ-9 (HLM) and HRSD (remission) analyses were re-run with the neighboring dorsal ACC (dACC) volume as the predictor of interest. In the combined sample, neither left nor right baseline dACC volume predicted PHQ-9 symptom improvement (all *F*s < 1.66; *p*s > .204). Similarly, there were no significant differences in right or left dACC volumes between treatment remitters and non-remitters in the combined sample (all *F*s < 0.74; *p*s > .396). When examining each treatment group separately, a larger right ($F[1,32.1] = 4.83$, $p = 0.035$), but not left ($F[1,32.3] = 0.26$, $p = 0.800$), dACC volume did predict greater depressive symptom improvement in the iCBT group (but not the MAC group, *F*s < 0.25; *p*s > .628). However, a likelihood ratio chi-squared test indicated that the addition of a right dACC volume-by-time interaction to the right rACC HLM model predicting PHQ-9 symptom improvement did not significantly improve model fit ($\chi 2[2] = 4.34$, $p = .114$). In contrast, the addition of a right rACC volume-by-time interaction to the right dACC model did significantly improve model fit ($\chi 2[2] = 10.42$, $p = .006$). Moreover, in the latter model (including both right rACC and right dACC predictors), the right rACC volume-by-time term remained significantly associated with symptom change ($p = .011$); whereas the corresponding right dACC volume-by-time term was not significant ($p = .833$). Finally, there were no significant differences in right or left dACC volume between treatment remitters and non-remitters in the iCBT or MAC samples (all *F*s < 3.26; *p*s > .090).

Secondary HRSD Continuous Analyses. To parallel the PHQ-9 continuous analyses, we conducted secondary analyses with the HRSD as a continuous variable (rather than dichotomizing remitters vs. non-remitters). Namely, we tested whether pre-treatment ACC

subregion volume predicted post-treatment HRSD scores, statistically controlling for pre-treatment HRSD scores (as well as including the same clinical and demographics covariates as in the other HRSD and PHQ-9 analyses, and controlling for total intracranial volume). The same pattern of findings emerged as in the HRSD remission analyses. Specifically, 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 predicted lower post-treatment depression scores in the iCBT group, but not the MAC group (For right rACC, F[1,16]= 0.58, t= -0.76, p = 0.457; For left rACC, F[1,16]= 0.22, t= -0.47, p = 0.645). Findings were not significant for all other ACC subregions (all Fs < 3.28; ps > .089). All treatment group x ACC subregion interactions were non-significant (all Fs < 2.77; ps > 103).

Tests of Hemisphere Effects. There is some evidence that left *vs* right ACC morphology may be differentially associated with depressive symptoms (9,10), as well as previous rACC-outcome findings indicating a right lateralized effect (11,12). Accordingly, we examined right vs. left rACC volume separately in relation to treatment outcome. Given the high correlation between the left and right rACC volume (r = .83; p <.0001), and to minimize multicollinearity in our models, left and right rACC volume were included in separate models. Several of the analyses revealed a significant association between right rACC and outcome, but the corresponding test for the left rACC was not significant. To test whether the right and left rACC effects were significantly different, hemisphere x rACC volume interactions were tested. Results indicated that hemisphere did not moderate the association between rACC volume and either PHQ-9 or HRSD symptom improvement (all Fs < 0.64; ps > .431). In light of this null effect, findings were not further interpreted in terms of laterality.

Supplemental References

1. Rosso IM, Killgore WD, Olson EA, Webb CA, Fukunaga R, Auerbach RP, et al. Internet‐based cognitive behavior therapy for major depressive disorder: A randomized controlled trial. Depress Anxiety. 2017;34(3):236–45.

2. Ségonne F, Dale AM, Busa E, Glessner M, Salat D, Hahn HK, et al. A hybrid approach to the skull stripping problem in MRI. NeuroImage. 2004 Jul;22(3):1060–75.

3. Dale AM, Fischl B, Sereno MI. Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction. NeuroImage. 1999 Feb;9(2):179–94.

4. Dale AM, Sereno MI. Improved Localizadon of Cortical Activity by Combining EEG and MEG with MRI Cortical Surface Reconstruction: A Linear Approach. J Cogn Neurosci. 1993 Apr 1;5(2):162–76.

5. Fischl B, Kouwe A van der, Destrieux C, Halgren E, Ségonne F, Salat DH, et al. Automatically Parcellating the Human Cerebral Cortex. Cereb Cortex. 2004 Jan 1;14(1):11–22.

6. Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R. Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. J Consult Clin Psychol. 2009;77(4):775–87.

7. Singer JD, Willett JB. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. 1 edition. Oxford ; New York: Oxford University Press; 2003. 644 p.

8. Kenward MG, Roger JH. Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics. 1997;53(3):983–97.

9. Costafreda SG, Chu C, Ashburner J, Fu CHY. Prognostic and Diagnostic Potential of the Structural Neuroanatomy of Depression. PLOS ONE. 2009 Jul 27;4(7):e6353.

10. Frodl T, Jäger M, Born C, Ritter S, Kraft E, Zetzsche T, et al. Anterior cingulate cortex does not differ between patients with major depression and healthy controls, but relatively large anterior cingulate cortex predicts a good clinical course. Psychiatry Res Neuroimaging. 2008 May 30;163(1):76–83.

11. Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, et al. Cingulate function in depression: a potential predictor of treatment response. [Miscellaneous Article]. Neuroreport. 1997 Mar;8(4):1057–61.

12. Pizzagalli DA, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, et al. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry. 2001 Mar;158(3):405–15.