Abstract word count: 183
Article word count: 3,070
Document word count: 4,955
2 tables, 3 figures

**Cingulate prediction of response to antidepressant and cognitive behavioral therapies for
depression: Theory, meta-analysis, and empirical application**

Marlene V. Strege, M.S.^{1,2}, Greg J. Siegle, Ph.D.³, Kymberly Young, Ph.D.³

¹ Virginia Polytechnic Institute and State University

² University of Pittsburgh Medical Center

³ University of Pittsburgh School of Medicine

Corresponding author:

Greg J. Siegle, Ph.D.

3811 O'Hara St, Pittsburgh, PA 15213-2593

e-mail: gsiegle@pitt.edu | ph: 412-864-3501

MVS reports no financial relationships with commercial interests. GJS reports no financial relationships with commercial interests. KY reports no financial relationships with commercial interests. Supported by the National Institute of Mental Health MH082998, MH074807, MH58356, MH69618, MH115927, and the Pittsburgh Foundation, Emmerling Fund M2007-0114.

Abstract

Objective: In the interest of precision medicine, we sought to derive preclinical markers of neural mechanisms associated with treatment response in unipolar depression, separated by treatment type. **Methods:** We conducted separate neuroimaging meta-analyses of neural predictors for response to Cognitive Behavioral Therapy (CBT) and Selective Serotonin Reuptake Inhibitors (SSRIs). We assessed whether reactivity of derived regions predicted clinical change in a preference trial of patients with major depressive disorder (MDD) who received CBT (n = 61) or SSRIs (n = 19). **Results:** The meta-analyses yielded regions within the perigenual (pgACC) and subgenual anterior cingulate cortex (sgACC) associated with SSRI and CBT response, respectively. In our sample, reactivity of the sgACC region was prognostic for response to CBT, but neither cingulate region was prognostic for response to SSRIs using a linguistic task; most prognostic SSRI studies used images. An exploratory analysis revealed a pgACC region for which reactivity to images was prognostic for response to SSRIs. **Conclusions:** Results suggest that neural reactivity of the sgACC and pgACC are associated with CBT and SSRI response for unipolar depression. Further research incorporating methodological considerations is necessary for translation.

Introduction

Precision medicine is increasingly central to healthcare, though is far from the standard of care in psychiatry where pre-treatment biological assessments are rarely used. Neuroimaging has the potential to identify mechanisms that could guide development of clinical measures and targeted interventions. This use is hindered by variable results, data collection, and analytic methods. Meta-analyses (1,2) could address these issues. To obtain possibly predictive indicators, we subjected published neuroprediction studies to separate meta-analyses for two common interventions for depression - Cognitive Behavioral Therapy (CBT) and Selective Serotonin Reuptake Inhibitors (SSRIs). We further examined whether obtained results applied to a preference neuroimaging CBT/SSRI trial for major depressive disorder (MDD) (“confirmatory sample”). We focus on the perigenual and subgenual regions of the anterior cingulate cortex (pgACC and sgACC), which have been implicated in treatment outcome in depression (for meta-analyses see (1) and (2)).

Our first question (Q1), examined via our meta-analysis, is whether these regions are differentially predictive in the literature. We have, based on the state of the literature a decade ago, hypothesized (3) that lower pre-treatment sgACC reactivity to negative information is associated with greater symptom improvement (4,5) and that greater pre-treatment pgACC and sgACC reactivity to negative emotional stimuli are implicated in better antidepressant medication outcomes (6–9). Our second question (Q2) regards the generalizability of these results, which we considered by examining the predictive utility of the derived regions in the confirmatory sample. If robust regions are detected meta-analytically which strongly predict in the confirmatory sample (Q2a) we could suggest the literature has identified preclinical indicators that are useful at the single subject level. If regions are detected that require more

work to replicate in the confirmatory sample (Q2b), we can suggest the literature has identified mechanistic targets for understanding vulnerability to treatment failure and potentially for pre-treatment remediation but is not yet ready for these regions to be used as clinical predictors in new studies.

Method

Meta-Analytic Methodology

To obtain studies for the meta-analyses, we reviewed all articles included in recent reviews of the neuroimaging depression treatment outcome prediction literature through March 2019 (1,2,10,11). We also conducted supplemental literature searches via PubMed and Google Scholar using relevant terms such as “depression,” “neural predictors,” “treatment,” and “cognitive behavioral therapy.” Articles were included if they reported pre-treatment neural activation (fMRI or PET) as prognostic or predictive of treatment outcome in depression. We limited the meta-analyses to studies that assessed treatment response to SSRIs or CBT (including variants such as behavioral activation), provided coordinates for their region results, and were published before March of 2019. We also limited the meta-analyses to studies with emotional stimuli that reported on activation (not exclusively connectivity) consistent with our theoretical framework. Table 1 lists included articles; Supplement Table 1 lists obtained articles that were excluded and reasons for exclusion.

From included articles we subjected all coordinates reported as predictive of treatment response in depression to GingerALE (version 3.0.2), a software package that conducts activation likelihood estimation (ALE) meta-analyses using coordinate-based data. We conducted separate meta-analyses for CBT and SSRI studies. If a study reported a region that was predictive of response to both treatments, coordinates were included in both meta-analyses.

For both meta-analyses, we set cluster-level familywise error to 0.05, voxelwise p-value threshold to 0.005. This is consistent with prior work (12) suggesting that a more conservative threshold (e.g., voxel threshold of $p < .001$) may be too conservative for neuroimaging studies in clinical samples. Threshold permutations were set to 1,000, with GingerALE's dilated 2mm mask size parameter.

Confirmatory sample

Our confirmatory sample consisted of 98 individuals with MDD recruited in an expanded sample from our prior fMRI CBT-outcome-prediction study (5) and a parallel preference-based SSRI-outcome-prediction study (not yet published) (Consort Diagram in Supplement 2). The sample for the CBT study was largely that used in one of the studies in the meta-analysis (5) but was slightly enlarged as additional data were collected after the initial article submission and missing clinical response variables were imputed. Participants with MDD were thus recruited from two clinical trials (ClinicalTrials.gov: NCT00183664; NCT00787501) and were treated with either SSRIs prescribed by a psychiatrist or CBT by 6 community clinicians (Ph.D.'s, M.D.'s, M. Ed.'s, LCSW's) who ranged widely in CBT experience (described fully in (5)). Participants described no health problems, eye problems, or psychoactive drug abuse in the past six months and no history of psychosis, manic, or hypomanic episodes. Participants had not used antidepressants within two weeks of initial testing (six weeks for fluoxetine) due to either medication naivety or supervised withdrawal from unsuccessful medications. Participants reported no excessive use of alcohol in the two weeks prior to testing and scored in the normal range on a cognitive screen (13), VIQ-equivalent > 85 . Of the initial 98 patients, 80 individuals completed treatment and are reported on in this paper.

Protocol and Treatment Procedures

Full details on treatment procedures are provided in Supplement 3. Briefly, after obtaining written informed consent, participants completed a diagnostic interview (Structured Clinical Interview for DSM-IV, SCID) (14), and fMRI assessment as in (5). The first N=17 depressed participants were part of a CBT trial (15). Subsequent participants selected CBT (N=57) or medication (N=24) trial by preference. Of the combined sample, CBT (N=61) and SSRI (N=19) completed treatment. We conducted analyses both in a sample restricted to completers as well as a sample including non-completers (Supplements 7, 8), consistent with previous work (5). CBT and medication were given at the same frequency; 2 sessions/week for the first four weeks followed by 8 weekly sessions for “early-responders” (HRSD reduction <40% at session 9; 16 total sessions) or 2 sessions/week for the first 8 weeks followed by 4 weekly sessions for non-early-responders (20 total sessions). CBT followed Beck’s (16) guidelines (5). Pharmacotherapy sessions involved only general mood check, Hamilton Rating Scale for Depression (HDRS) (17) assessment, psychoeducation on drug effects, side effects assessments, and treatment regime change discussion. The default prescribed medication was escitalopram (N=15; 10-30mg/day), or if that had previously been failed, then a comparable dose of sertraline (N=4), fluoxetine (N=4), or, in N=1 case, another SSRI/SNRI. Participants were scanned again within 2 weeks of completion.

Clinical response

Our primary outcome measure was the Beck Depression Inventory (BDI-II) (18), a widely-employed 21-item self-report measure of depression, assessing symptom severity on a 0 (not present) to 3 (severe) scale with strong psychometric properties (19,20). Consistent with prior work (5), we considered improvement as both BDI-II change (post-pre) as well as residual severity, calculated as final severity controlling for initial severity. Six participants were missing

pre-treatment BDI scores, and 13 participants were missing post-treatment BDI scores.

Imputation procedures are described in Supplement 4.

fMRI task

Apparatus. Twenty-nine 3.2mm slices were acquired parallel to the AC-PC line (3T Siemens Trio, T2*-weighted images depicting BOLD contrast; posterior-to-anterior, TR=1500ms, TE=27ms, FOV=24cm, flip=80), yielding 8 whole-brain images per 12 second trial. Stimuli were displayed in black on a white background via a back-projection screen (.88° visual angle). Responses were recorded using a Psychology Software Tools™ glove.

Personal relevance rating task (PRRT). As described fully in our previous publication on this sample (5), in 60 slow-event related trials, participants viewed a fixation cue (1 s; row of X's with prongs around the center X) followed by a positive, negative, or neutral word (200 ms; only negative words analyzed here), followed by a mask (row of X's; 10.8 s). Participants pushed a button for whether the word was relevant, somewhat relevant, or not relevant to them or their lives (button orders balanced across participants), as quickly and accurately as they could. Participant-generated and normed words were used as in our previous studies of depression (4). For fMRI data preparation see Supplement 4.

Analyses

Analyses involved examination of whether Q2a) activity averaged over the meta-analytically derived regions were predictive in the directions suggested by the meta-analysis in the new dataset (i.e., whether the meta-analytic regions could serve as pre-clinical markers), Q2b) whether subregions or regions close to the meta-analytic regions were predictive (i.e., whether meta-analytic regions could guide mechanistic investigations useful for treatment refinement in new studies).

Results

Q1. Meta-analytic identification of brain regions prognostic for treatment outcome in depression

The ALE meta-analysis for CBT and related treatments included 10 studies and resulted in 2 significant clusters (Figure 1a). One cluster in the right sgACC (size = 4158.65 mm³, (MNI centroid coordinates are used throughout this manuscript) $x = 7, y = 23, z = -12$), which involved activation shared by 3 studies. After applying a gray matter mask, this became a 2488.96 mm³ cluster with the same centroid coordinates, see Figure 1b. The other cluster was in the right amygdala (3548.97 mm³, $x = 22, y = -1, z = -22$) and corresponded to shared activation of 4 studies. The meta-analysis for SSRI treatment studies included 8 articles and resulted in 2 significant clusters (Figure 2a) including the right pgACC (8745.13 mm³, $x = 19, y = 36, z = 0$) and right caudate (3670.22 mm³, $x = 20, y = 12, z = 19$). After applying a gray matter mask to the pgACC-centered cluster, we applied a minimum cluster threshold of 20 voxels (this is in addition to the aforementioned cluster corrections and was set to limit reporting on small clusters created from applying the gray matter mask). This yielded 5 clusters spanning the right pgACC, (746.51 mm³, $x = 15, y = 41, z = 0$, see Figure 2b) along with activations in the right caudate and other medial frontal regions (non-ACC clusters in Supplement 5).

Q2. Prospective application of meta-analytically derived regions to a new clinical dataset

Demographics of the clinical sample. Treatment groups did not differ on gender, age, ethnicity, number of depressive episodes, or depressive symptoms (BDI-II). The CBT patient sample reported more years of education than the SSRI sample, $t(76) = 3.03, p = .003$, Hedges' $g = 0.79$ (Table 2). Similar demographics for the entire sample (not limited to those who completed treatment) are reported in Supplement 6.

Q2a. Prediction based on activity averaged over meta-analytically derived ROIs.

sgACC ROI from CBT studies. For patients who received CBT, sgACC ROI responses to linguistic stimuli were weakly but significantly prognostic for BDI change scores $R^2 = .07$, $F(1,59) = 4.33$, $p = 0.042$ (Figure 3). Less sgACC reactivity to negative stimuli was associated with stronger response to CBT. Although comparable in effect size, this relationship failed to meet statistical significance for BDI residuals ($p = .057$). This ROI was not prognostic for BDI change scores $R^2 < .01$, $F(1,18) = <.01$, $p = 0.989$ or residuals $R^2 < .01$, $F(1,18) = <.01$, $p = 0.989$ in the SSRI sample.

pgACC ROI from SSRI studies. pgACC ROI responses to linguistic stimuli were not significantly prognostic for BDI change scores $R^2 = 0.08$, $F(1,18) = 1.52$, $p = 0.234$ or residuals $R^2 = 0.15$, $F(1,18) = 2.87$, $p = 0.108$, though effect sizes were comparable to or larger than the sgACC effect for CBT responders. In contrast to the meta-analytic association, higher reactivity was associated with higher residual symptomatology. The ROI also was not associated with greater treatment response for CBT patients (change scores: $R^2 < .01$, $F(1,60) = 0.15$, $p = 0.705$, residuals: $R^2 < .01$, $F(1,60) = 0.04$, $p = 0.842$). Similar effects (Supplements 7, 8) were found when examining the entire clinical dataset (not limited to those who completed treatment).

Q2b. Prediction based on indices derived from the meta-analytic regions

Subregions. Our first consideration involved whether subregions of the meta-analytic region were more strongly predictive than the overall region. As shown in Figure 3B,C, subregions of each of the meta-analytically derived regions were more strongly predictive (R^2 's up to 0.36) than the average over the regions, with some parts of these regions being negatively and other parts being positively associated with response to each treatment modality. The largest part of the sgACC was associated with outcome for CBT in the meta-analytically predicted

direction (less activity was associated with better response). Part of the sgACC was associated, in the opposite direction, with outcome for SSRIs, but unlike the meta-analysis, the only significant associations within the pgACC were the same as for CBT.

Potential moderation of SSRI prediction by stimulus modality. The lack of correspondence of the current sample SSRI prediction with the meta-analysis prompted us to consider what was different between this sample and the literature. Of the SSRI studies that contributed to the perigenual cluster (6–9,21), all except (21) found that greater reactivity of the pgACC was prognostic of better treatment outcome, and all except (21) used picture stimuli. In contrast, (21) used linguistic stimuli similar to our study and found that less reactivity to negative words predicted better treatment response. As our SSRI sample also completed Hariri's emotional faces task (22), we were able to test whether stimuli modality moderated prediction. In that task, increased pgACC reactivity to fearful and angry faces was prognostic for decreased depressive severity as in the meta-analysis in the region as a whole (Supplement 9).

Public dissemination of results. So that other researchers can examine our meta-analytically derived regions on their own data, we have made them publicly available at: https://www.pitt.edu/~gsiegle/strege_metaanalysis_rois.tar.gz.

Discussion

Our primary question was whether meta-analytically derived cingulate regions were differentially predictive of response to SSRIs and CBT. Indeed, our meta-analysis revealed that anterior cingulate subregions were broadly prognostic for stronger response to treatment for depression, which is largely consistent with other meta-analyses (1,2). CBT outcome for major depressive disorder was associated with decreased right sgACC reactivity, whereas SSRI outcome was associated with increased right pgACC as well as caudate reactivity. Our second

question (Q2) regarded the robustness of these regions when applied to a single study which used a linguistic task. Regarding the meta-analytic regions considered as a whole, in the simplest analyses (Q2a), the CBT-study derived sgACC ROI reactivity to negative words was moderately associated with clinical response to CBT in the single study - not strongly enough to be considered a robust indicator for use in clinics (R^2 's < .3). The SSRI-study derived pgACC ROI reactivity to negative words was not associated with clinical response to SSRIs in that sample. That said, we also considered whether slightly more nuanced analyses would reveal interesting mechanistic generalizability (Q2b). This analysis revealed 1) that subregions of the meta-analytically derived regions were differentially predictive for the new sample and 2) that the apparent differentiation examined in the meta-analysis may be due to the primary use of linguistic stimuli in CBT studies and images in SSRI studies. Indeed, pgACC reactivity to negative images was associated with clinical response (Supplement 9). We also found the right caudate was associated with response to SSRIs. The caudate's roles in reward reactivity (23) and depression (24) could help to explain this finding.

That the meta-analytic finding for pgACC prediction of SSRI response was supported by pictures, and not word stimuli in our local sample could suggest that differential meta-analytic results for treatment modality are actually due to systematic differences in stimulus type employed by the literature. Indeed, all but one (21) of the SSRI studies contributing to the meta-analytic pgACC cluster used picture stimuli (6–9). The study that used linguistic stimuli (21) found the opposite effect direction, consistent with our study. Results in our sample were consistent with this explanation though our SSRI sample was atypical in other potentially important ways, e.g., having weekly provider meetings. Further work examining neuroprediction

associations with stimulus modality and treatment session frequency would help clarify the influence of study methodology on prognostic findings.

Results suggest that the meta-analytically derived regions need refinement before being translated to the clinic. Extension to robust predictors that work in novel datasets, and understanding of methodological moderation effects, pre-treatment scans or associated physiological, EEG (25), or self-report measures could help to determine the intervention patients should be encouraged to receive, particularly if they are amenable to both therapy and medications.

An avenue for future research more strongly supported by the current investigation involves the potential to target the proposed regions to optimize likely treatment response based on an individual's treatment preference. For example, (26) found that healthy individuals could successfully downregulate reactivity to negative pictures within sgACC with neurofeedback training and the strategy of increasing positive mood. Other studies have trained both healthy participants and patients with schizophrenia to increase the activity in the sgACC with neurofeedback while recalling positive memories and imagining playing sports and listening to music (27,28). Thus, perhaps, treatment-seeking individuals could benefit from fMRI-guided pre-treatment neurofeedback of anterior cingulate subregion reactivity (to increase or decrease reactivity with respect to the level found in healthy individuals). While emerging evidence suggests fMRI neurofeedback may be an effective intervention for depression (29), one common critique is that it is too expensive to ever be widely clinically implemented (30); however for patients who are not predicted to respond to any intervention, fMRI neurofeedback may be a particularly viable approach.

Results should be interpreted with consideration of multiple limitations. The meta-analysis had few studies of CBT including two from our lab, one of which was on a subset of participants in our confirmatory sample, making it a non-independent replication. Nearly all of the included studies had small sample sizes. Our confirmatory sample had non-random treatment assignment; it was a convenience sample of some participants coming from a preference trial and others from a CBT-only trial. As we did not assess other depression interventions, if patients were predicted to not respond to either CBT or SSRIs, our results do not indicate whether they would respond to other interventions, such as electroconvulsive therapy or whether there are pre-treatment remediations that could be employed, such as neurofeedback, to change their predictive status.

These limitations notwithstanding, the current data suggest that neuroimaging provides promising neural correlates (sgACC and pgACC) of treatment response to two of the most common and well-validated interventions for unipolar depression, CBT and SSRIs. They are not yet robust as predictors for new studies without attending to subregions and stimulus type, but can serve to guide intervention development and pre-treatments. Attending to stimulus type and treatment session frequency could make it more likely our meta-analytically derived regions generalize in future studies.

References

1. Fu CHY, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiol Dis.* 2013 Apr;52:75–83.
2. Pizzagalli DA. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology.* 2011 Jan;36(1):183–206.
3. DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci.* 2008 Oct;9(10):788–96.
4. Siegle GJ, Carter CS, Thase ME. Use of fMRI to predict recovery from unipolar depression with cognitive behavior therapy. *Am J Psychiatry.* 2006 Apr;163(4):735–8.
5. Siegle GJ, Thompson WK, Collier A, Berman SR, Feldmiller J, Thase ME, et al. Toward clinically useful neuroimaging in depression treatment: prognostic utility of subgenual cingulate activity for determining depression outcome in cognitive therapy across studies, scanners, and patient characteristics. *Arch Gen Psychiatry.* 2012;69(9):913–24.
6. Chen C-H, Ridler K, Suckling J, Williams S, Fu CHY, Merlo-Pich E, et al. Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry.* 2007 Sep 1;62(5):407–14.
7. Godlewska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ. Predicting Treatment Response in Depression: The Role of Anterior Cingulate Cortex. *Int J Neuropsychopharmacol.* 2018 Nov 1;21(11):988–96.
8. Victor TA, Furey ML, Fromm SJ, Öhman A, Drevets WC. Changes in the neural correlates of implicit emotional face processing during antidepressant treatment in major depressive disorder. *Int J Neuropsychopharmacol.* 2013 Nov;16(10):2195–208.
9. Roy M, Harvey P-O, Berlim MT, Mamdani F, Beaulieu M-M, Turecki G, et al. Medial prefrontal cortex activity during memory encoding of pictures and its relation to symptomatic improvement after citalopram treatment in patients with major depression. *J Psychiatry Neurosci.* 2010 May;35(3):152–62.
10. Fonseka TM, MacQueen GM, Kennedy SH. Neuroimaging biomarkers as predictors of treatment outcome in Major Depressive Disorder. *J Affect Disord.* 2018 Jun;233:21–35.
11. Langenecker SA, Crane NA, Jenkins LM, Phan KL, Klumpp H. Pathways to Neuroprediction: Opportunities and challenges to prediction of treatment response in depression. *Curr Behav Neurosci Rep.* 2018 Mar;5(1):48–60.
12. Carter CS, Lesh TA, Barch DM. Thresholds, Power, and Sample Sizes in Clinical Neuroimaging. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2016 Mar;1(2):99–100.

13. Owen AM. National adult reading test, 2nd Edition. Hazel E. Nelson with Jonathan Willison. 1991, NFER-Nelson. Price: £45 VAT. No. of pages: 23 [Internet]. Vol. 7, International Journal of Geriatric Psychiatry. 1992. p. 533–533. Available from: <http://dx.doi.org/10.1002/gps.930070713>
14. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). New York, New York State Psychiatric Institute. Biometrics Research. 1995;
15. Jarrett RB, Minhajuddin A, Gershenfeld H, Friedman ES, Thase ME. Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. JAMA Psychiatry. 2013 Nov;70(11):1152–60.
16. Beck AT, John Rush A, Shaw BF, Emery G. Cognitive Therapy of Depression. Guilford Press; 1979. 425 p.
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960 Feb;23:56–62.
18. Beck A, Steer R, Brown G. Manual for the Beck depression inventory-II (BDI-II). 1996; Available from: <https://www.scienceopen.com/document?vid=9feb932d-1f91-4ff9-9d27-da3bda716129>
19. Dozois DJA, Dobson KS, Ahnberg JL. A psychometric evaluation of the Beck Depression Inventory--II. Psychol Assess. 1998;10(2):83.
20. Wang Y-P, Gorenstein C. Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. Braz J Psychiatry. 2013 Oct;35(4):416–31.
21. Miller JM, Schneck N, Siegle GJ, Chen Y, Ogden RT, Kikuchi T, et al. fMRI response to negative words and SSRI treatment outcome in major depressive disorder: a preliminary study. Psychiatry Res. 2013 Dec 30;214(3):296–305.
22. Hariri AR. Serotonin Transporter Genetic Variation and the Response of the Human Amygdala [Internet]. Vol. 297, Science. 2002. p. 400–3. Available from: <http://dx.doi.org/10.1126/science.1071829>
23. Delgado MR, Miller MM, Inati S, Phelps EA. An fMRI study of reward-related probability learning. Neuroimage. 2005 Feb 1;24(3):862–73.
24. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009 Jun;166(6):702–10.
25. Kremer H, Lutz FPC, McIntosh RC, Dévieux JG, Ironson G. Interhemispheric Asymmetries and Theta Activity in the Rostral Anterior Cingulate Cortex as EEG Signature of HIV-Related Depression [Internet]. Vol. 47, Clinical EEG and Neuroscience. 2016. p. 96–104.

Available from: <http://dx.doi.org/10.1177/1550059414563306>

26. Hamilton JP, Paul Hamilton J, Glover GH, Hsu J-J, Johnson RF, Gotlib IH. Modulation of subgenual anterior cingulate cortex activity with real-time neurofeedback. *Hum Brain Mapp*. 2010;32(1):22–31.
27. Cordes JS, Mathiak KA, Dyck M, Alawi EM, Gaber TJ, Zepf FD, et al. Cognitive and neural strategies during control of the anterior cingulate cortex by fMRI neurofeedback in patients with schizophrenia. *Front Behav Neurosci*. 2015 Jun 25;9:169.
28. Gröne M, Dyck M, Koush Y, Bergert S, Mathiak KA, Alawi EM, et al. Upregulation of the rostral anterior cingulate cortex can alter the perception of emotions: fMRI-based neurofeedback at 3 and 7 T. *Brain Topogr*. 2015 Mar;28(2):197–207.
29. Young KD, Siegle GJ, Zotev V, Phillips R, Misaki M, Yuan H, et al. Randomized Clinical Trial of Real-Time fMRI Amygdala Neurofeedback for Major Depressive Disorder: Effects on Symptoms and Autobiographical Memory Recall. *Am J Psychiatry*. 2017 Aug 1;174(8):748–55.
30. Stoeckel LE, Garrison KA, Ghosh S, Wighton P, Hanlon CA, Gilman JM, et al. Optimizing real time fMRI neurofeedback for therapeutic discovery and development. *Neuroimage Clin*. 2014 Jul 10;5:245–55.
31. Costafreda SG, Khanna A, Mourao-Miranda J, Fu CHY. Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. *Neuroreport*. 2009 May 6;20(7):637–41.
32. Dichter GS, Felder JN, Smoski MJ. The effects of Brief Behavioral Activation Therapy for Depression on cognitive control in affective contexts: An fMRI investigation. *J Affect Disord*. 2010 Oct;126(1-2):236–44.
33. Doerig N, Krieger T, Altenstein D, Schlumpf Y, Spinelli S, Späti J, et al. Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression. *Br J Psychiatry*. 2016 Feb;208(2):175–81.
34. Fu CHY, Williams SCR, Cleare AJ, Scott J, Mitterschiffthaler MT, Walsh ND, et al. Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biol Psychiatry*. 2008 Sep 15;64(6):505–12.
35. Ritchey M, Dolcos F, Eddington KM, Strauman TJ, Cabeza R. Neural correlates of emotional processing in depression: changes with cognitive behavioral therapy and predictors of treatment response. *J Psychiatr Res*. 2011 May;45(5):577–87.
36. Straub J, Plener PL, Sproeber N, Sprenger L, Koelch MG, Groen G, et al. Neural correlates of successful psychotherapy of depression in adolescents. *J Affect Disord*. 2015 Sep 1;183:239–46.
37. Yoshimura S, Okamoto Y, Onoda K, Matsunaga M, Okada G, Kunisato Y, et al. Cognitive

- behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Soc Cogn Affect Neurosci*. 2014 Apr;9(4):487–93.
38. Ruhé HG, Booij J, Veltman DJ, Michel MC, Schene AH. Successful pharmacologic treatment of major depressive disorder attenuates amygdala activation to negative facial expressions: a functional magnetic resonance imaging study. *J Clin Psychiatry*. 2012;73(4):451.
 39. Spies M, Kraus C, Geissberger N, Auer B, Klöbl M, Tik M, et al. Default mode network deactivation during emotion processing predicts early antidepressant response. *Transl Psychiatry*. 2017 Jan 24;7(1):e1008.
 40. Forbes EE, Olinos TM, Ryan ND, Birmaher B, Axelson D, Moyles DL, et al. Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cogn Affect Behav Neurosci*. 2010 Mar;10(1):107–18.

Table 1. List of papers included in meta-analyses

Treatment Type	Study	Sample (N)
CBT and Related		
	Costafreda et al., 2009 (31)	MDD adults (16)
	Dichter et al., 2010 (32)	MDD adults (12) Controls (15)
	Doerig et al., 2016 (33)	MDD adults (21)
	Fu et al., 2008 (34)	MDD adults (16)
	Ritchey et al., 2011 (35)	MDD adults (22) Controls (14)
	Siegle et al., 2006 (4)	MDD adults (14)
	Siegle et al., 2012 (5)	MDD adults (49)
	Straub et al., 2015 (36)	MDD adolescents (22)
	Yoshimura et al., 2014 (37)	MDD adults (23)
SSRI		
	Chen et al., 2007 (6)	MDD adults (17)
	Godlewska et al., 2018 (7)	MDD adults (32)
	Miller et al., 2013 (21)	MDD adults (15)
	Roy et al., 2010 (9)	MDD adults (20)
	Ruhe et al., 2012 (38)	MDD adults (20)
	Spies et al., 2017 (39)	MDD adults (22)
	Victor et al., 2013 (8)	MDD adults (10)
CBT & SSRI		
	Forbes et al., 2010 (40)	MDD adolescents (6)

Table 2. Demographics of unipolar depression patients, limited to patients who completed the protocol

	Whole Patient Sample (N = 80)	CT Patient Sample (N = 61)	SSRI Patient Sample (N = 19)
Gender	Female (N = 56, 70.00%)	Female (N = 43, 70.49%)	Female (N = 13, 68.42%)
Age	36.66 (10.69) years	36.23 (10.23) years	38.05 (12.24) years
Ethnicity	Caucasian (N = 64, 80.00%) Non-Caucasian (N = 16, 20.00%)	Caucasian (N = 49, 80.33%) Non-Caucasian (N = 12, 19.67%)	Caucasian (N = 15, 78.95%) Non-Caucasian (N = 4, 21.05%)
Education	15.38 (2.32) years	15.81 (2.30) years*	14.05 (1.87) years*
Depressive episodes	3.64 (2.69)	3.70 (2.74)	3.44 (2.62)
Beck Depression Inventory - II (BDI-II)	Pre Treatment: 29.69 (8.58) Post Treatment: 11.68 (9.52)	Pre Treatment: 30.15 (8.29) Post Treatment: 11.80 (9.37)	Pre Treatment: 28.20 (9.55) Post Treatment: 11.32 (10.24)

Note. Means for age, education, number of depressive episodes, and Hamilton Depression Rating Scale are followed by standard deviations in parentheses. * Denotes that the CT and SSRI patient samples statistically differ on this variable. CT sample education (N=59), number of depressive episodes (N=56). SSRI sample number of depressive episodes (N=18).

Figure 1. ALE meta-analysis results from CBT studies in depression

Notes: a. Significant clusters from the ALE meta-analysis of CBT studies in depression b.

Resulting subgenual cingulate region after graymatter mask of ALE meta-analysis significant clusters

Figure 2. ALE meta-analysis a) results of SSRI studies in depression and b) perigenual cingulate region surviving gray matter mask

Notes: a. Significant clusters from the ALE meta-analysis of SSRI studies in depression b. Resulting perigenual cingulate region after graymatter mask of ALE meta-analysis significant clusters

Figure 3. A) Therapy ROI (subgenual cingulate) and BDI-II change scores for those who completed treatment. B,C) Associations (R^2) of residual BDI with voxelwise reactivity (scans 2-7) in response to negative words (as in (5)) within pgACC and sgACC regions with residual symptomatology. Thus red values indicate associations of higher activity with less negative residual symptomatology (poorer recovery); lower activity is associated with better recovery. Significant ($p < .05$) associations are circled. In the CBT group, lower sgACC activity to words was associated with improved recovery. In the SSRI group, higher sgACC activity and lower pgACC activity to words was associated with improved recovery. For both groups R^2 s as high as 0.36 were observed in some voxels.