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Network Mechanisms of Clinical Response to Transcranial Magnetic Stimulation in Posttraumatic Stress Disorder and Major Depressive Disorder

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Abstract

Background: Repetitive transcranial magnetic stimulation (TMS) therapy can modulate pathological neural network functional connectivity in major depressive disorder (MDD). Posttraumatic stress disorder (PTSD) is often comorbid with MDD, and symptoms of both disorders can be alleviated with TMS therapy. This is the first study to evaluate TMS-associated changes in connectivity in patients with comorbid PTSD and MDD.

Methods: Resting state functional connectivity magnetic resonance imaging was acquired before and after TMS therapy in 33 adult outpatients in a prospective open trial. 5Hz TMS was delivered, in up to 40 daily sessions, to left dorsolateral prefrontal cortex (DLPFC). Analyses used *a priori* seeds relevant to TMS, PTSD or MDD (subgenual anterior cingulate cortex (sgACC), DLPFC, hippocampus, and basolateral amygdala) to identify imaging predictors of response and to evaluate clinically relevant changes in connectivity after TMS, followed by leave-one-out cross validation. Imaging results were explored using data-driven multivoxel pattern activation (MVPA).

Results: More negative pretreatment connectivity between sgACC and default mode network (DMN) predicted clinical improvement, as did more positive amygdala-to-ventromedial prefrontal cortex connectivity. After TMS, symptom reduction was associated with reduced connectivity between sgACC and DMN, DLPFC, and insula, and reduced connectivity between hippocampus and salience network (SN). MVPA confirmed seed-based predictors and correlates of treatment outcomes.

Conclusions: These results highlight the central role of the sgACC, DMN and SN as predictors of TMS response, and suggest their involvement in mechanisms of action. Furthermore, this work

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indicates there may be network-based biomarkers of clinical response relevant to these commonly comorbid disorders.

(5Hz Repetitive Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder Comorbid With Major Depressive Disorder; ClinicalTrials.gov;)

Keywords

resting state functional connectivity; major depressive disorder; posttraumatic stress disorder; transcranial magnetic stimulation; default mode network; subgenual anterior cingulate

INTRODUCTION

PTSD and MDD: A Common Comorbidity

Posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) are common psychiatric disorders associated with significant clinical symptoms and psychosocial dysfunction (1–5). These disorders are often comorbid, as up to 50% of patients with PTSD are also diagnosed with MDD (6, 7). In both disorders, a substantial number of patients remain symptomatic despite standard treatment (8–11), and those with comorbid depressive and anxiety symptoms have poorer treatment outcomes (12–14). One promising way to address both conditions utilizes the emerging understanding of neural network abnormalities in PTSD and MDD.

Network Abnormalities in PTSD and MDD

The brain is organized into discrete neural networks (15–17). Of these, three have been the focus of recent study in psychiatry: the default mode network (DMN), executive control network (ECN) and salience network (SN). The DMN is implicated in self-referential processing and episodic memory retrieval. Core DMN regions include medial prefrontal cortex (MPFC), medial parietal regions, midline precuneus/posterior cingulate cortex and posterior hippocampus (18). The ECN is involved in executive function and emotion regulation; core regions include dorsolateral prefrontal cortex (DLPFC) and lateral posterior parietal regions (19). The SN is involved in detection of, and direction of attention to, salient environmental stimuli (20), with core regions comprised of dorsal anterior cingulate (dACC), anterior insula, amygdala and anterior hippocampus (21). Each of these three networks demonstrates some degree of pathological function in both PTSD and MDD. For example, a recent meta-analysis demonstrated increased SN connectivity in PTSD, reflecting a pathological threat-detection system (22), alongside some degree of DMN disruption. Imaging meta-analyses of MDD indicate that DMN connectivity is increased, perhaps reflecting pathological rumination (23) associated with highly correlated activity between the DMN and subgenual anterior cingulate cortex (sgACC) (24, 25), alongside SN involvement. In PTSD and MDD, the ECN, and particularly DLPFC, is hypoactive (26) and hypo-connected (27–29) with other ECN regions and nodes of the DMN and SN (reviewed in (22)), suggesting failure of top-down regulation of rumination or salience signaling. This shared pathology suggests that interventions that target the DLPFC might improve symptoms of both disorders.

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (TMS or rTMS, hereafter simply TMS) is an FDA-cleared treatment for pharmacoresistant MDD. TMS therapy uses pulsed magnetic fields, typically delivered to the DLPFC, to improve symptoms of depression (30). While the mechanism of TMS remains under study, prior research in patients with MDD has consistently shown that TMS to DLPFC can induce physiologic changes distal to the stimulation site, particularly in sgACC. Kito et al. (31) reported that a 3-week course (12 sessions) of 1Hz TMS to right DLPFC reduced cerebral blood flow to sgACC, and this reduction correlated with improved clinical symptoms. A subsequent study showed that increased sgACC blood flow at baseline predicted subsequent response to TMS (32). Baeken et al. (33) found that higher baseline sgACC metabolic activity predicted response to a 2-week course (10 sessions) of 20Hz TMS to the DLPFC, and clinical response was associated with reduced sgACC metabolism. Liston et al. (34) acquired resting state functional connectivity (RSFC) magnetic resonance imaging (MRI) data prior to and following 5-weeks (25 sessions) of daily 10Hz TMS, and reported that TMS reduced depression-related connectivity between sgACC and DMN. While TMS produced minimal connectivity change within the ECN, they observed increased anticorrelations between DLPFC and DMN after treatment, perhaps reflecting normalization of network relationships.

Other studies, again in MDD patients, also implicated the sgACC in clinical response to TMS. In a cross-sectional RSFC study of TMS coil placement, Fox et al. (35) found that the strongest clinical effects of TMS were associated with stimulation of DLPFC regions with the strongest connectivity with the sgACC. Salomons et al. (36) measured RSFC before and after a 4-week course (20 sessions) of 10Hz TMS targeting the dorsomedial prefrontal cortex, and also found TMS was associated with attenuation of sgACC-to-DMN connectivity. Importantly, all of these studies focused on patients with MDD, and generally excluded patients with comorbid PTSD, so the relevance of these findings to understanding the therapeutic mechanism of action of TMS in patients with comorbid PTSD and MDD is yet unknown.

In this study, we recruited patients with comorbid PTSD and MDD, and acquired RSFC MRI before and after a course of TMS. This approach was undertaken to provide data on a patient population that is commonly represented in clinical practice, may uniquely benefit from TMS due to overlapping network pathology, and yet is often excluded from studies that select participants based on diagnostic criteria for a single disorder. This study addressed two specific goals: 1) identifying imaging predictors of response to TMS and 2) characterizing network mechanisms of TMS therapy. We hypothesized that predictors of treatment response and treatment-associated changes would be relevant to symptoms of both disorders under study, and specifically that uncoupling of the SN and DMN would correspond with clinically meaningful reductions in PTSD and MDD symptoms, respectively.

METHODS AND MATERIALS

Participants

Following informed consent, baseline RSFC MRI was acquired on 33 participants. These were patients receiving care at neuromodulation clinics (Butler Hospital, Providence VA) at Brown University-affiliated hospitals. Of the current sample, 31 of 33 participants were enrolled in a prospective, unblinded trial of 5Hz TMS for comorbid PTSD and MDD (NCT02273063).Detailed clinical efficacy outcomes will be reported separately. Twenty-six individuals completed baseline and post-TMS MRI scans; one participant did not have usable data. Imaged participants (N=33) were 51.3±11.1 years old, 39.3% (n=13) female. Participants were eligible if they met DSM-IV-TR (37) criteria for both PTSD and MDD, with symptoms of at least moderate severity for both disorders as defined by the Clinical Global Impressions (CGI) scale (38). These entry criteria were used ensure recruitment of a sufficiently comorbid sample representative of patients seeking care in our clinics. We did not seek to establish which diagnosis was “primary,” as this is often unclear or impossible to accurately determine in clinical samples. PTSD symptoms were measured using the PTSD checklist for DSM-5 (PCL-5) (39). MDD symptoms were measured using the Inventory of Depressive Symptomatology, Self-Report (IDSSR) (40). All rating scale data were analyzed in an intent-to-treat, last-observation-carried forward fashion for participants who completed baseline procedures and at least one TMS session. Detailed inclusion/exclusion criteria and concurrent medications during TMS are presented in Supplement Information. The Providence VA Medical Center and Butler Hospital Institutional Review Boards approved this study, with identical procedures at both sites.

Transcranial Magnetic Stimulation and Clinical Response

Parameters for TMS therapy were informed by our prior work evaluating the use of 5Hz stimulation as an alternative high frequency setting for patients with MDD and common psychiatric comorbidities (41), including PTSD (42). We administered 5Hz rTMS over left DLPFC using NeuroStar TMS Therapy System devices (Neuronetics, Inc., Malvern, Pennsylvania), delivering a total of 3000–4000 pulses per session. Participants received 33±9 TMS sessions, which could be inclusive of a treatment taper phase delivered over a 3-week period. Stimulation to the DLPFC was targeted with the Beam method (43). To facilitate imaging analyses of comparable magnitudes across two disparate symptom rating scales, categorical TMS response was operationally defined for each participant for each disorder, with “meaningful clinical improvement” considered present when post-treatment score was >2 standard deviations lower than pre-treatment baseline score (44, 45). This corresponded to a post-TMS participants’ PCL score of 23 or less, and an IDSSR score of 15 or less. These values approximated MDD remission criteria in prior TMS studies (e.g., 46) and were modestly lower than what is considered “threshold” PTSD (39). Sensitivity analyses, using published IDSSR remission and PCL threshold scores produced very similar results (see Supplemental Information for further details).

MRI Data Acquisition and Analysis

Neuroimaging data were acquired at the Brown University MRI Research Facility using a Siemens 3T MRI (Siemens, Erlangen, Germany) equipped with a 32-channel head coil.

Imaging acquisition included high-resolution (1 mm^3) anatomical images and eight minutes of standard resting state echoplanar imaging. Neuroimaging acquisition, preprocessing, quality control, and motion (used in first- and second-level analyses) are described in Supplemental Information. MRI data processing used the CONN Functional Toolbox (47) unless otherwise indicated.

Subject-level seed-to-voxel analyses

Whole brain statistical maps, consisting of bivariate Pearson's correlations between residual BOLD time courses extracted from seed regions and all other brain voxels, were created during first-level analyses. Subject-level seed maps were converted to Fisher transformed Z-scores to conform to the assumptions of generalized linear models (GLMs).

Seed-based Functional Connectivity

A priori seeds were based on prior TMS, MDD or PTSD studies. We used the MarsBar Toolbox (http://marsbar.sourceforge.net/) to create seeds by drawing spheres around reported coordinates in MNI space. Seeds related to prior MDD and TMS studies included sgACC (left: MNI −4 26 −8, right: MNI 5 26 −8)(48) and left DLPFC (MNI −44 40 29)(35). PTSD-related seeds used anterior and posterior hippocampus, following Chen and Etkin (21) using maximum probability maps (49). Anatomically defined seeds in basolateral amygdala (BLA)(50) were evaluated because of the amygdala's role in threat detection and consolidation of fear learning (51), prior imaging work implicating altered functional BLA connectivity in PTSD (e.g., (52, 53)), and reduced amygdala-to-MPFC connectivity in MDD (23).

Group-level Seed-to-voxel Analyses and Hypothesis Testing

Two overarching analytic approaches were used for hypothesis testing: 1) determining whether specific baseline patterns of connectivity predicted categorical positive clinical response to TMS (i.e., utilizing dichotomous variables), and 2) evaluating whether changes in connectivity were associated with the degree in symptom improvement (i.e., continuous outcomes utilizing percent change in baseline-to-endpoint symptom severity).

To identify baseline clusters predictive of clinical improvement for each symptom domain (i.e., PCL or IDSSR), subject-level seed maps of pre-treatment seed-to-voxel connectivity were entered into an ANCOVA (using mean-centered age and baseline symptom severity as covariates), with the between-subjects factor of meaningful clinical improvement (present or absent) using the whole (N=33) dataset. This was followed by seed-based analysis (n=25) to compare pre- vs. post-treatment connectivity associated with clinical changes (using age, baseline symptom severity, and scanner as covariates). Sex effects were evaluated with a sensitivity analysis. Connectivity changes associated with changes in PTSD and MDD (using the PCL and IDSSR) were computed with corresponding scatterplots displaying percentage change for readability and clinical interpretation.

Data were corrected and validated in two steps. First, whole brain results were thresholded using cluster-based false discovery rate (FDR) correction at $p<.05$ (54) (hereafter simply corrected $p<.05$). This step used a voxel height of $p<.005$ to permit more inclusive

identification of clusters for validation. We then used leave-one-out cross-validation (LOOCV) to test cluster validity. In brief, LOOCV group-level GLMs were iteratively re-estimated using the same thresholding procedures and N-1 participants. We excluded clusters if they were present in less than 80% of cross-validation masks. When testing the validity of clusters extracted from a between-group comparison, the 80% threshold was applied at the group level. Only those results that survived LOOCV are presented in this report. Thus, though a less conservative cluster-forming threshold was initially used, resultant clusters underwent stringent correction and validation. In keeping with the neural network focus of this paper, supplemental results (Tables S4–S10) are presented using the peak activation voxel and, when applicable, corresponding network in a sample of 1,000 healthy adults, implemented in Neurosynth (Neurosynth.org; (55)).

Subject-level MVPA

MVPA was used to conduct model-free exploratory analyses of voxel-wise RSFC (47, 56) to evaluate predictors of response and identify mechanisms of clinical change. This approach was designed to provide data-driven replication (or refutation) of seed-based results, and to potentially uncover results outside of canonical network locations. For each subject and session, the BOLD time course was extracted from each voxel and pair-wise correlations were calculated for all within-brain voxels. Principal components analysis (PCA) was used to reduce data dimensionality, where five spatial principal components were retained to approximate a 5:1 ratio between observations and independent variables (56–57), and adjusted for age, baseline symptom severity, and scanner. Second-level MVPA statistical models were constructed similarly to seed-to-voxel models, with the addition of the between-measures contrast of the PCA component, corrected for multiple comparisons and submitted to LOOCV.

RESULTS

Clinical outcomes

Most trauma exposure was related to physical assault, unwanted sexual encounters, sexual assault, and motor vehicle accidents (Table S1). Participants completed 36±9 TMS sessions (median=36, mode=40, range 5–40); those with pre- and post-TMS imaging data completed 36±6 sessions (median=37, mode=40, range 13–40). Twelve of 33 (36.4%) participants demonstrated meaningful clinical improvement on the PCL, and 11 (33.3%) demonstrated improvement on the IDSSR. Of the subset (n=25) with usable pre- and post-treatment imaging data, the same 12 (46.2%) and 11 (42.3%) participants met threshold response criterion for PTSD and MDD, respectively. Symptom changes on PTSD and MDD scales were highly correlated ($r = .91$, $p < .001$).

Baseline Predictors of Improvement: sgACC Seed

Several baseline predictors of improvement emerged when examining the right sgACC; left sgACC did not yield results and is not included hereafter. More negative connectivity between sgACC and midline precuneus/PCC at baseline predicted subsequent clinical improvement in PTSD, as did more negative connectivity between sgACC and left visual regions and medial/superior bilateral frontal regions of the DMN and SN (all corrected p<.

001, validated in 90–100% of tests). There was a significant (corrected p=.014) and nominally valid (80% of tests) cluster indicating that greater connectivity between sgACC and left inferior frontal gyrus at baseline was associated with clinical improvement in PTSD symptoms following TMS therapy (Figure 1A; Table S4). There were no effects of sex on this seed or any other predictors of improvement.

Baseline Predictors of Improvement: BLA Seed

Increased pretreatment connectivity between the bilateral BLA and bilateral MPFC was associated with subsequent improvement in both PTSD and MDD symptom domains (corrected p<.001 for left MPFC for both PTSD and MDD, p=.002 for right MPFC for MDD, >90% validated). Increased connectivity between BLA and left ventromedial prefrontal cortex (VMPFC) at baseline predicted subsequent improvement in PTSD (corrected p<.002, 100% validated)(Figures 1B–C; Tables S5–6). There were no valid baseline imaging predictors of response observed with DLPFC or hippocampal seeds.

Baseline Predictors of Improvement: MVPA

Exploratory MVPA indicated that changes in connectivity of the right inferior parietal lobule (IPL), right amygdala, left parahippocampal gyrus, right DLPFC, and bilateral VMPFC predicted improvement in PTSD, whereas changes in the right IPL, right dACC, and left insula predicted MDD improvement (all corrected p<.001; 100% validated)(Figure 1D, Table S7).

Correlates of Clinical Improvement: sgACC Seed

Reduction in PTSD symptoms was associated with baseline-to-endpoint decreases in connectivity between right sgACC and left precuneus/PCC, dACC, left DLPFC, left insula and visual regions (all corrected p<.001; 100% validated) and right insula (corrected p=.003; 100% validated). Changes associated with reduced MDD symptoms included decreased connectivity of sgACC with midline precuneus/PCC, midline dACC (corrected p<.001) and bilateral somatosensory/motor regions (corrected p=.003, 85% validated). There was also decreased connectivity between the sgACC and the posterior lateral temporal cortex (a part of the auditory network) (corrected p=.004, 100% validated). Sensitivity analysis revealed an effect of sex (p=.038) such that male participants were more likely to exhibit this result (Figure 2A; Table S8). Scatterplot depiction of the correlation between sgACC-to-left DLPFC connectivity change and clinical symptoms is displayed in Figure 2C.

Correlates of Clinical Improvement: Anterior Hippocampus Seed

Changes in anterior hippocampal connectivity with midline dACC, right insula, and left putamen were associated with reduced PTSD symptoms (corrected p<.001; 90–100% validated) (Figure 1B& 2B; Table S9). Scatterplot depiction of the correlation between hippocampus-to-dACC connectivity change and clinical symptoms is displayed in Figure 2C.

Connectivity between the anterior hippocampus and multiple SN regions (right insula (corrected p<.001; 100% validated), left IPL (corrected p<.024; 90% validated), and left

putamen (corrected p<.024; 80% validated)) was associated with reduced MDD symptoms. There were no valid results from other seeds.

Correlates of Clinical Improvement: MVPA

MVPA revealed several significant clusters associated with PTSD symptom changes that corresponded with regions found in seed-based analyses (Figure 2D; Table S10). These included left hippocampus, right caudate, left putamen, left inferior frontal gyrus and right amygdala (corrected p<.001; 100% validated). MVPA also revealed changes in several regions related to change in MDD symptoms, including the right insula, midline dACC, left ACC, right caudate, bilateral motor cortex, and right fusiform gyrus (all p<.005; 100% validated).

DISCUSSION

Predictors of Response to TMS in Patients with PTSD and MDD

This is the first study to evaluate predictors and potential mechanisms of response to TMS in patients with comorbid PTSD and MDD. This study addresses an important issue by focusing on a common clinical comorbidity while examining brain regions implicated in prior studies of TMS, MDD and PTSD using a network-based approach. Our results are consistent with prior observations of abnormal sgACC function in a broad range of psychiatric conditions, including MDD (58–60), fear extinction and PTSD (61–63), and others (e.g., (56, 64, 65)), and further support the suggestion that sgACC is broadly associated with psychiatric pathology. In our results, baseline sgACC connectivity was a predictor of TMS response, and change in sgACC connectivity during the course of TMS therapy was associated with clinical improvement.

These results underscore the crucial role of sgACC connectivity in brain stimulation, described in the deep brain stimulation (66) and TMS depression research (34, 35). What is unique here appears to be the direction of effect. Liston et al. (34) reported that baseline hyperconnectivity between subgenual and DMN predicted subsequent clinical response to TMS in depressed patients, whereas in our sample, reduced subgenual-to-DMN connectivity predicted subsequent improvements. There might be several reasons for this finding, including different MRI data processing pipelines, varied participant samples (e.g., PTSD/MDD in this study vs. major depressive episodes in Liston et al. (34)), different stimulation frequencies (5Hz vs. 10Hz, respectively), and varied average stimulation intensity (120% of motor threshold in our participants vs. 85% (range 50–109) in the Liston et al. (34)).

Increased connectivity between amygdala and prefrontal cortex was also an important predictor of TMS response. For example, increased connectivity between VMPFC and BLA predicted subsequent TMS response, and aberrant connections between these two regions are thought to represent a core component of PTSD. Heightened amygdala response is a hallmark of PTSD imaging studies (e.g., (52, 67–69)), and most RSFC studies of PTSD demonstrate reduced connectivity between amygdala and VMPFC (52, 70, 71), although some have not (72). A recent meta-analysis of MDD imaging studies found reduced

amygdala-to-MPFC coupling (23), confirming the important role of this circuit in depression. Therefore, our data indicate that some degree of RSFC between amygdala and VMPFC is important for subsequent response to TMS for PTSD symptoms, whereas connectivity between amygdala and MPFC is important for a subsequent response for MDD. Both seed-based and data-driven results identified similar brain regions, which underscore the importance of these areas as potential predictors of response. Our findings suggest that patients with more severe underlying neural pathology (i.e., reduced BLA-VMPFC connectivity) may be less responsive to TMS therapy, at least when using our target and parameters. Future studies will need to evaluate whether structural deficits in these connections, observed in both MDD and PTSD (67, 73, 74), contribute to these functional findings.

Taken together, the present findings suggest a relationship between the degree of network pathology and treatment outcome, such that a “healthier” signature of network connectivity (characterized by a less hyperconnected DMN and greater prefrontal-to-amygdala connectivity) predicted TMS response. While the symptom phenotypes of patients in our sample were heterogeneous, some degree of preserved network function may be essential for TMS to exert its therapeutic effects. This interpretation suggests that targeting these connections, perhaps using transcranial direct current stimulation (e.g., 75, 76), might be a promising approach to engage or augment these circuits prior to treatment and therefore facilitate a greater subsequent TMS response. Additional data are needed to determine whether the network changes we observed in relation to symptom improvement are durable or fluctuate with different stages of illness.

Potential Mechanisms of Clinical Response to TMS

Positive response to TMS was associated with two principal findings: reduced sgACC-to-DMN connectivity and reduced connectivity between hippocampus and SN. These results support prior hypotheses (25) that reducing sgACC-to-DMN connectivity would improve symptoms of depression. They are also consistent with reduced sgACC-to-MPFC connectivity following TMS (34), and reduced MPFC blood flow in patients who responded to deep brain stimulation of the sgACC (77). A potential mechanism of action of TMS suggested by other studies (33, 34) has been uncoupling of the connectivity between sgACC and DLPFC. We did not observe this using our DLPFC seed, but did when seeding sgACC, and only in association with reduced PTSD symptoms. While the lack of change associated with MDD might represent type II error, an alternative interpretation is that changes in subgenual-to-DLPFC connectivity indicate a biological marker of broader network-based realignment associated with clinical improvement brought about by TMS therapy.

Our other key observations was that reduced connectivity between hippocampus and SN, in particular dACC, was related to reduced PTSD symptoms, and reduced hippocampus-to insula connectivity was associated with reduced PTSD and MDD symptoms. These findings are aligned with the extensive body of work implicating abnormal dACC function ((23, 24, 78, 79), reviewed in Patel et al. (80)) and altered insula function and connectivity in both PTSD and MDD (22, 23). These findings indicate the importance of reductions in connectivity between memory and salience circuitry as a critical component to clinical

improvement in both disorders. These results also suggest that TMS might improve the salience network's role in shifting internal resources between internal and external needs (20).

MVPA results largely supported seed-based findings, and underscore the importance of changes in DMN, salience and somatomotor connectivity with TMS-related clinical improvements. Furthermore, insula connectivity changes, regardless of seed location, were consistently associated with clinical improvement. This suggests that direct insula stimulation, via TMS or other modalities, might be a promising direction for future research. Although not the primary focus of our *a priori* hypotheses, we also observed instances of reduced connectivity of sgACC with numerous somatomotor and visual regions related to reductions in depressive symptoms. The lingual gyrus, with its putative role in visual processing and integration, has been implicated in imaging studies of MDD, conflict resolution, and impaired reward response (81–83), whereas the postcentral gyrus has been associated with depression and pain (84).

Our study has several limitations. Consistent with prior imaging studies of TMS (34, 36), there was no sham condition, and our results should be interpreted within that context. Several lines of evidence suggest that brain regions implicated here and in prior work (e.g., subgenual, insula, dACC, etc.) are involved in the neural response to placebo (85–88). This underscores the need for sham-controlled TMS imaging studies, but also raises the possibility that the therapeutic action of TMS might occur through enhancement of the brain's ability to generate a placebo response. This idea, while speculative, would have significant implications. Other limitations included a modest sample size, although comparable to prior TMS imaging studies, and we implemented cross-validation to mitigate this issue. Another limitation was our use of global illness severity as an entry criterion rather than a minimum score on standardized scales. It is possible that requiring higher baseline scores would have provided more variance in change in outcome measures. We did not adjust for treatment resistance because there is no operational definition of resistance in this comorbid patient sample. We also did not include a healthy control group, as our hypotheses focused on developing neuroimaging predictors in patients, and a fully controlled design would have required repeated neuroimaging of healthy controls, patients with comorbid MDD and PTSD, patients with only MDD, and patients with only PTSD. Future imaging studies of TMS in PTSD should evaluate whether our findings are unique to comorbid status.

In summary, this study demonstrated a central role of sgACC and SN as predictors of TMS response and their involvement in potential mechanisms of action. This work underscores the progress of the field towards individualized approaches to treatment that might ultimately be able to use our understanding of neural networks to improve patient outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Hoge CW, Castro CA, Messer SC, MuGurk D, Cotting DI, Koffman RL. (2004): Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N Engl J Med 35: 13–22.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. (2005): Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62(6): 617–627. [PubMed: 15939839]
3. Thomas JL, Wilk JE, Riviere LA, McGurk D, Castro CA, Hoge CW. (2010): Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch Gen Psychiatry 67(6): 614–623. [PubMed: 20530011]
4. Godard J, Baruch P, Grondin S, Lafleur MF. (2012): Psychosocial and neurocognitive functioning in unipolar and bipolar depression: a 12-month prospective study. Psychiatry Res 196(1): 145–153. [PubMed: 22370154]
5. Shimizu Y, Kitagawa N, Mitsui N, Fujii Y, Toyomaki A, Hashimoto N, et al. (2013): Neurocognitive impairments and quality of life in unemployed patients with remitted major depressive disorder. Psychiatry Res 210(3): 913–918. [PubMed: 24041752]
6. Rytwinski NK, Scur MD, Feeny NC, Youngstrom EA. (2013): The co-occurrence of major depressive disorder among individuals with posttraumatic stress disorder: a meta-analysis. J Trauma Stress 26(3): 299–309. [PubMed: 23696449]
7. Flory JD, Yehuda R. (2015): Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment consideration. Dialogues Clin Neurosci 17(2): 141–150. [PubMed: 26246789]
8. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. (2006): Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. Am J Psychiatry 163(1): 28–40. [PubMed: 16390886]
9. Nelson JC. (2006): The STAR*D study: A four-course meal that leaves us wanting more. Am J Psychiatry 163(11): 1864–1866. [PubMed: 17074931]
10. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. (2006): Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 163(11): 1905–1917. [PubMed: 17074942]
11. Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. (2013): Meta-analyses of the efficacy of treatments for posttraumatic stress disorder. J Clin Psychiatry 74(6): e541–e550. [PubMed: 23842024]
12. Holtzheimer PE, Russo J, Zatzick D, Bundy C, Roy-Byrne PP. (2005): The impact of comorbid posttraumatic stress disorder on short-term clinical outcome in hospitalized patients with depression. Am J Psychiatry 162(5): 970–976. [PubMed: 15863800]

13. Campbell DG, Felker BL, Liu CF, Yano EM, Kirchner JE, Chan D, et al. (2007): Prevalence of depression-PTSD comorbidity: implications for clinical practice guidelines and primary care-based interventions. J Gen Intern Med 22(6): 711–718. [PubMed: 17503104]
14. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. (2014): A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry 75(12): 1394–1401. [PubMed: 25271871]
15. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 102(27): 9673–9678. [PubMed: 15976020]
16. Fox MD, Raichle ME. (2007): Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8(9): 700–711. [PubMed: 17704812]
17. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. (2012): Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex 22(1): 158–165. [PubMed: 21616982]
18. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. (2001): A default mode of brain function. Proc Natl Acad Sci U S A 98(2): 676–682. [PubMed: 11209064]
19. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. (2001): Annu Rev Neurosci 24: 167–202. [PubMed: 11283309]
20. Uddin LQ. (2015): Salience processing and insular cortical function and dysfunction. Nat Rev Neurosci 16(1): 55–61. [PubMed: 25406711]
21. Chen AC, Etkin A. (2013): Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. Neuropsychopharmacology 38(10): 1889–1898. [PubMed: 23673864]
22. Koch SB, van Zuiden M, Nawijn L, Frijling JL, Veltman DJ, Olff M. (2016): Aberrant resting-state brain activity in posttraumatic stress disorder: A meta-analysis and systematic review. Depress Anxiety 33(7): 592–605. [PubMed: 26918313]
23. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. (2015): Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry 72(6): 603–611. [PubMed: 25785575]
24. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. (2012): Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response. Am J Psychiatry 169(7): 693–703. [PubMed: 22535198]
25. Hamilton JP, Farmer M, Fogelman P, Gotlib IH. (2015): Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. Biol Psychiatry 78(4): 224–230. [PubMed: 25861700]
26. New AS, Fan J, Murrough JW, Lui X, Liebman RE, Guise KG, et al. (2009): A functional magnetic resonance imaging study of deliberate emotion regulation in resilience and posttraumatic stress disorder. Biol Psychiatry 66(7): 656–664. [PubMed: 19589502]
27. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. (2007): Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. J Neurosci 27(9): 2349–2356. [PubMed: 17329432]
28. Cisler JM, Scott-Steele J, Smitherman S, Lenow JK, Kilts CD. (2013): Neural processing correlates of assaultive violence exposure and PTSD symptoms during implicit threat processing: a network-level analysis among adolescent girls. Psychiatry Res 214(3): 238–246. [PubMed: 23969000]
29. Shang J, Lui S, Meng Y, Zhu H, Qui C, Gong Q, et al. (2014): Alterations in Low-Level Perceptual Networks Related to Clinical Severity in PTSD after an Earthquake: A Resting-State fMRI Study. PLoS One 9(5): e96834.
30. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. (1996): Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348(9022): 233–237. [PubMed: 8684201]

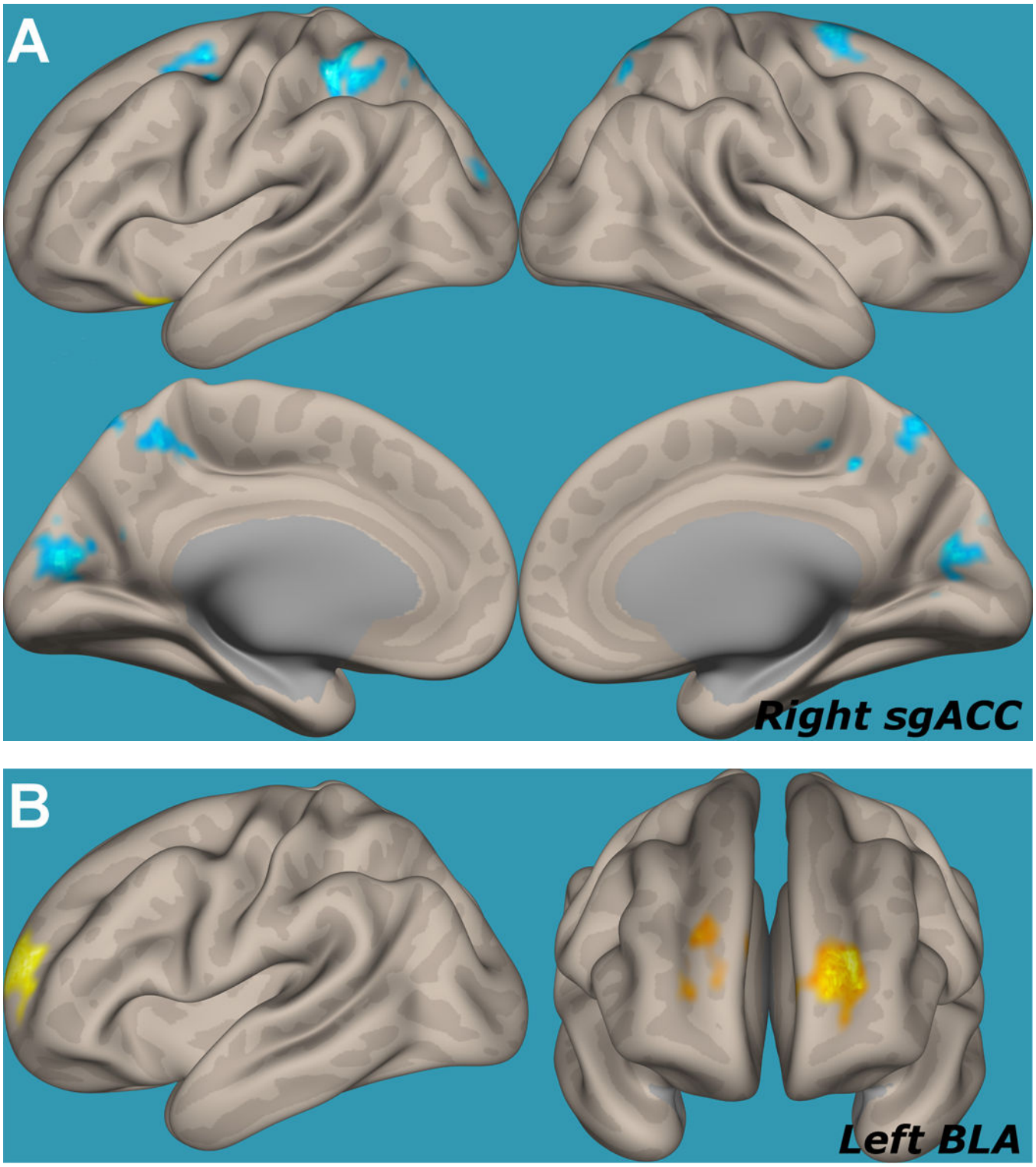
31. Kito S, Hasegawa T, Koga Y. (2011): Neuroanatomical correlates of therapeutic efficacy of low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. Psychiatry Clin Neurosci 65(2): 175–182. [PubMed: 21414091]
32. Kito S, Hasegawa T, Koga Y. (2012): Cerebral blood flow in the ventromedial prefrontal cortex correlates with treatment response to low-frequency right prefrontal repetitive transcranial magnetic stimulation in the treatment of depression. Psychiatry Clin Neurosci 66(2): 136–145.
33. Baeken C, Marinazzo D, Everaert H, Wu GR, Van Hove C, Audenaert K, et al. (2015): The Impact of Accelerated HF-rTMS on the Subgenual Anterior Cingulate Cortex in Refractory Unipolar Major Depression: Insights From 18FDG PET Brain Imaging. Brain Stimul 8(4): 808–815. [PubMed: 25744500]
34. Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, Leuchter B, et al. (2014): Default mode network mechanisms of transcranial magnetic stimulation in depression. Biol Psychiatry 76(7): 514–526.
35. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. (2012): Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry 72(7): 595–603. [PubMed: 22658708]
36. Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe I, et al. (2014): Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder. Neuropsychopharmacology 39(2): 488–498. [PubMed: 24150516]
37. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Press.
38. National Institute of Mental Health (1976): 028-CGI. Clinical Global Impressions In: Guy E, editor. ECDEU Assessment Manual for Psychopharmacology, rev ed. Rockville, Maryland: US Department of Health, Education, and Welfare, pp 217–222.
39. Weathers FW, Litz BB, Keane TM, Palmieri PA, Marx BP, Schnurr PP. (2013): The PTSD Checklist for DSM-5 (PCL-5). Available from the National Center for PTSD at www.ptsd.va.gov.
40. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. (1996): The inventory of depressive symptomatology (IDS): psychometric properties. Psychol Med 26(3): 477–486. [PubMed: 8733206]
41. Philip NS, Carpenter SL, Ridout SJ, Sanchez G, Albright SE, Tyrka AR, et al. (2015): 5Hz Repetitive transcranial magnetic stimulation to left prefrontal cortex for major depression. J Affect Disord 186: 13–17. [PubMed: 26210705]
42. Philip NS, Ridout SJ, Albright SE, Sanchez G, Carpenter LL. (2016): 5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression. J Trauma Stress 29(1): 93–96. [PubMed: 26748883]
43. Beam W, Borckardt JJ, Reeves ST, George MS. (2009): An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul 2(1): 50–54. [PubMed: 20539835]
44. Jacobson NS, Truax P. (1991): Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 59(1): 12–19. [PubMed: 2002127]
45. Bauer S, Lambert MJ, Nielsen SL. (2004): Clinical Significance Methods: A Comparison of Statistical Techniques. J Pers Assess 82(1): 60–70. [PubMed: 14979835]
46. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. (2012): Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 29(7): 587–596. [PubMed: 22689344]
47. Whitfield-Gabrieli S, Nieto-Castanon A. (2012): Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2(3): 125–141. [PubMed: 22642651]
48. Fox MD, Buckner RL, Liu H, Chakravarty MM, Lozano AM, Pascual-Leone A. (2014): Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological disease. Proc Natl Acad Sci U S A 111(41): E4367–E4375. [PubMed: 25267639]
49. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. (2005): A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. NeuroImage 25(4): 1325–1335. [PubMed: 15850749]

50. Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah NJ, et al. (2005): Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. Anat Embryol (Berl) 201(5): 343–352.
51. LeDoux J (2007): The amygdala. Curr Biol 17(20): R868–R874. [PubMed: 17956742]
52. Brown VM, LaBar KS, Haswell CC, Gold AL, Mid-Atlantic MIRECC Workgroup, McCarthy G, et al. (2014): Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. Neuropsychopharmacology 39(2): 351–359. [PubMed: 23929546]
53. Rabellino D, Densmore M, Frewen PA, Théberge J, McKinnon MC, Lanius RA. (2016): Aberrant Functional Connectivity of the Amygdala Complexes in PTSD during Conscious and Subconscious Processing of Trauma-Related Stimuli. PLoS One 11(9): e0163097.
54. Chumbley J, Worsley K, Flandin G, Friston K. (2010): Topological FDR for neuroimaging. Neuroimage 49(4): 3057–3064. [PubMed: 19944173]
55. Yarkoni T, Poldrack RA, Nichols TE, Van Essen DC, Wager TD. (2011): Large-scale automated synthesis of human functional neuroimaging data. Nat Methods 8(8): 665–670. [PubMed: 21706013]
56. Whitfield-Gabrieli S, Ghosh SS, Nieto-Castanon A, Saygin Z, Doehrmann O, Chai XJ, et al. (2016): Brain connectomics predicts response to treatment in social anxiety disorder. Mol Psychiatry 21(5): 680–685. [PubMed: 26260493]
57. Hair J, Anderson R, Tatham R, Black W. (1998): Multivariate data analysis, 5th ed. Englewood Cliffs, NJ: Prentice-Hall.
58. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. (1997): Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386(6627): 824–827. [PubMed: 9126739]
59. Drevets WC, Savitz J, Trimble M. (2008): The subgenual anterior cingulate cortex in mood disorders. CNS Spectr 13(8):663–681. [PubMed: 18704022]
60. Rodríguez-Cano E, Sarró S, Monté GC, Maristany T, Salvador R, McKenna PJ, et al. (2014): Evidence for structural and functional abnormality in the subgenual anterior cingulate cortex in major depressive disorder. Psychol Med 44(15): 3263–3273. [PubMed: 25066663]
61. Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A. (2006): A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 30(7): 1004–1031. [PubMed: 16730374]
62. O'Doherty DC, Chitty KM, Saddigui S, Bennett MR, Lagopoulos J. (2015): A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. Psychiatry Res 232(1): 1–33. [PubMed: 25735885]
63. Helpman L, Marin MF, Papini S, Zhu X, Sullivan GM, Schneier F, et al. (2016): Neural changes in extinction recall following prolonged exposure treatment for PTSD: A longitudinal fMRI study. NeuroImage Clin 12: 715–723. [PubMed: 27761402]
64. Arnold-Anteraper S, Triantafyllou C, Sawyer AT, Hofmann SG, Gabrieli JD, Whitfield-Gabrieli S. (2004): Hyper-connectivity of subcortical resting-state networks in social anxiety disorder. Brain Connect 4(2): 81–90.
65. Klumpp H, Keutmann MK, Fitzgerald DA, Shankman SA, Phan KL. (2014): Resting state amygdala-prefrontal connectivity predicts change after cognitive behavioral therapy in generalized social anxiety disorder. Biol Mood Anxiety Disord 4: 14. [PubMed: 25540682]
66. Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, et al. (2008): Anatomical Connectivity of the Subgenual Cingulate Region Targeted with Deep Brain Stimulation for Treatment-Resistant Depression. Cereb Cortex 18(6): 1374–1383. [PubMed: 17928332]
67. Shin LM, Rauch SL, Pitman RK. (2006): Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 1071: 67–79. [PubMed: 16891563]
68. Hughes KC, Shin LM. (2011): Functional neuroimaging studies of post-traumatic stress disorder. Expert Rev Neurother 11(2): 275–285. [PubMed: 21306214]
69. Huang MX, Yurgil KA, Robb A, Angeles A, Diwakar M, Risbrough VB, et al. (2014): Voxel-wise resting-state MEG source magnitude imaging study reveals neurocircuitry abnormality in active-

duty service members and veterans with PTSD. NeuroImage Clin 5: 408–419. [PubMed: 25180160]

70. Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, et al. (2012): Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci 37(4): 241–249. [PubMed: 22313617]
71. Jin C, Qi R, Yin Y, Hu X, Duan L, Xu Q, et al. (2014): Abnormalities in whole-brain functional connectivity observed in treatment-naïve post-traumatic stress disorder patients following an earthquake. Psychol Med 44(9): 1927–1936. [PubMed: 24168716]
72. Rabinak CA, Angstadt M, Welsch RC, Kenndy AE, Lyubkin M, Martis B, et al. (2011): Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. Front Psychiatry 2: 62. [PubMed: 22102841]
73. Hamilton JP, Siemer M, Gotlib IH. (2008): Amygdala volume in Major Depressive Disorder: A meta-analysis of magnetic resonance imaging studies. Mol Psychiatry 13(11): 993–1000. [PubMed: 18504424]
74. Morey RA, Gold AL, LaBar KS, Beall SK, Brown VM, Haswell CC, et al. (2012): Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. Arch Gen Psychiatry 69(11): 1169–1178. [PubMed: 23117638]
75. Philip NS, Nelson BG, Frohlich F, Lim KO, Widge AS, Carpenter LL. (2017): Low-Intensity Transcranial Current Stimulation in Psychiatry. Am J Psychiatry (Epub ahead of print). doi: 10.1176/appi.ajp.2017.16090996
76. van ‘t Wout M, Longo SM, Reddy MK, Philip NS, Bowker MT, Greenberg BD. (2017): Transcranial direct current stimulation may modulate extinction memory in posttraumatic stress disorder. Brain Behav 7(5): e00681.
77. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. (2008): Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. Biol Psychiatry 64(6): 461–467. [PubMed: 18639234]
78. van Rooij SJ, Rademaker AR, Kennis M, Vink M, Kahn RS, Geuze E. (2015): Neural correlates of trauma-unrelated emotional processing in war veterans with PTSD. Psychol Med 45(3): 575–587. [PubMed: 25036523]
79. Lei D, Li K, Li L, Chen F, Huang X, Lui S, et al. (2015): Disrupted Functional Brain Connectome in Patients with Posttraumatic Stress Disorder. Radiology 276(3): 818–827. [PubMed: 25848901]
80. Patel R, Spreng RN, Shin LM, Girard TA. (2012): Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav Rev 36(9): 2130–2142. [PubMed: 22766141]
81. Dichter GS, Felder JN, Petty C, Bizzell J, Ernst M, Smoski MJ. (2009): The effects of psychotherapy on neural responses to rewards in major depression. Biol Psychiatry 66(9): 886–897. [PubMed: 19726030]
82. Kessler H, Taubner S, Buchheim A, Münte TF, Stasch M, Kächele H, et al. (2011): Individualized and clinically derived stimuli activate limbic structures in depression: an fMRI study. PLoS One 6(1): e15712.
83. Chechko N, Augustin M, Zvyagintsev M, Schneider F, Habel U, Kellermann T. (2013): Brain circuitries involved in emotional interference task in major depression disorder. J Affect Disord 149(1–3): 136–145. [PubMed: 23394712]
84. Bär KJ, Wagner G, Koschke M, Boettger S, Boettger MK, Schlösser R, et al. (2007): Increased prefrontal activation during pain perception in major depression. Biol Psychiatry 62(11): 1281–1287. [PubMed: 17570347]
85. Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. (2002): Changes in brain function of depressed subjects during treatment with placebo. Am J Psychiatry 159(1): 122–129. [PubMed: 11772700]
86. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al. (2002): The functional neuroanatomy of the placebo effect. Am J Psychiatry 159(5): 728–737. [PubMed: 11986125]
87. Wager TD, Atlas LY. (2015): The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci 16(7): 403–418. [PubMed: 26087681]

88. Peciña M, Bohnert AS, Sikora M, Avery ET, Langenecker SA, Mickey BJ, et al. (2015): Association Between Placebo-Activated Neural Systems and Antidepressant Responses: Neurochemistry of Placebo Effects in Major Depression. JAMA Psychiatry 72(11): 1087–1094. [PubMed: 26421634]



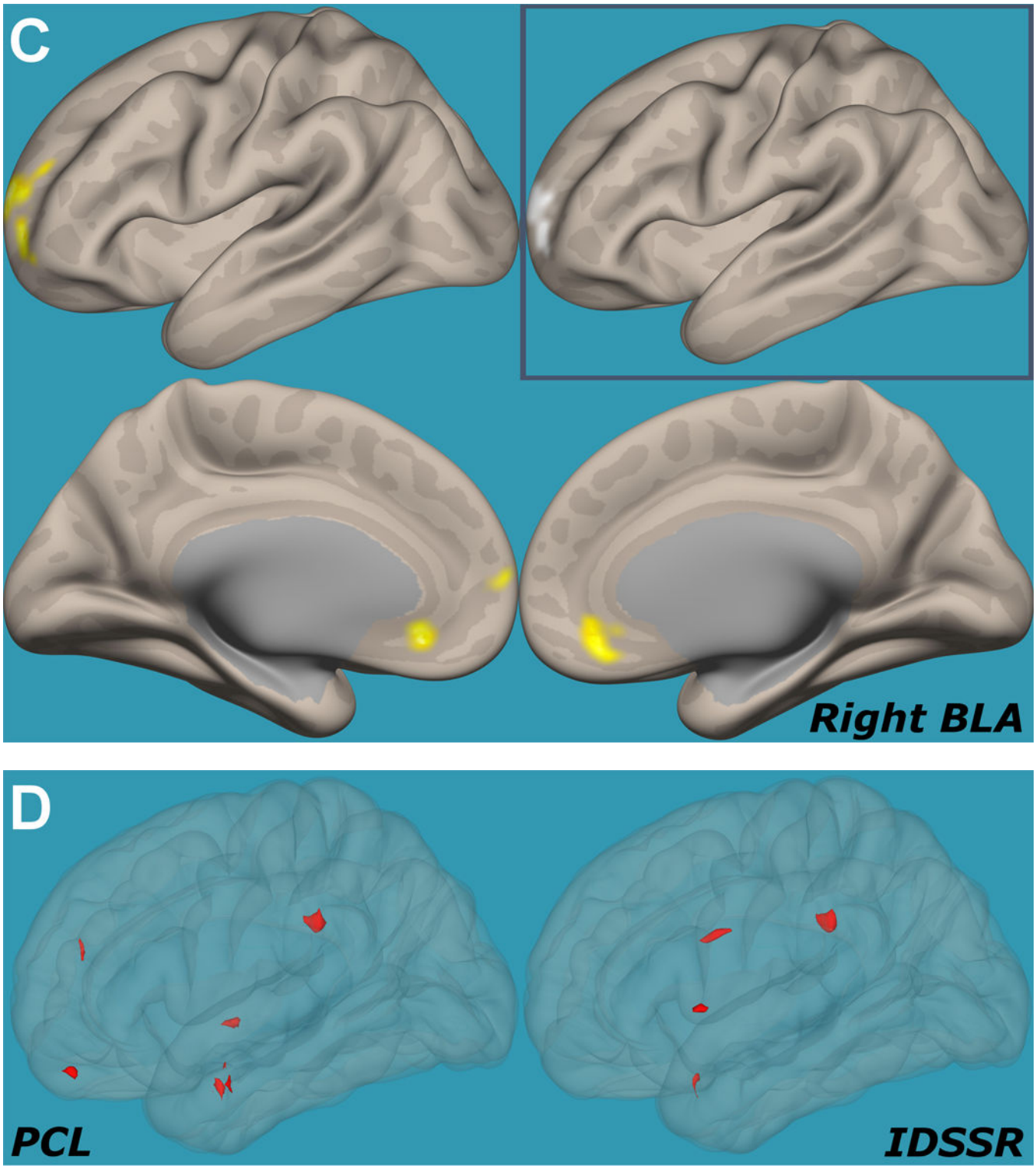
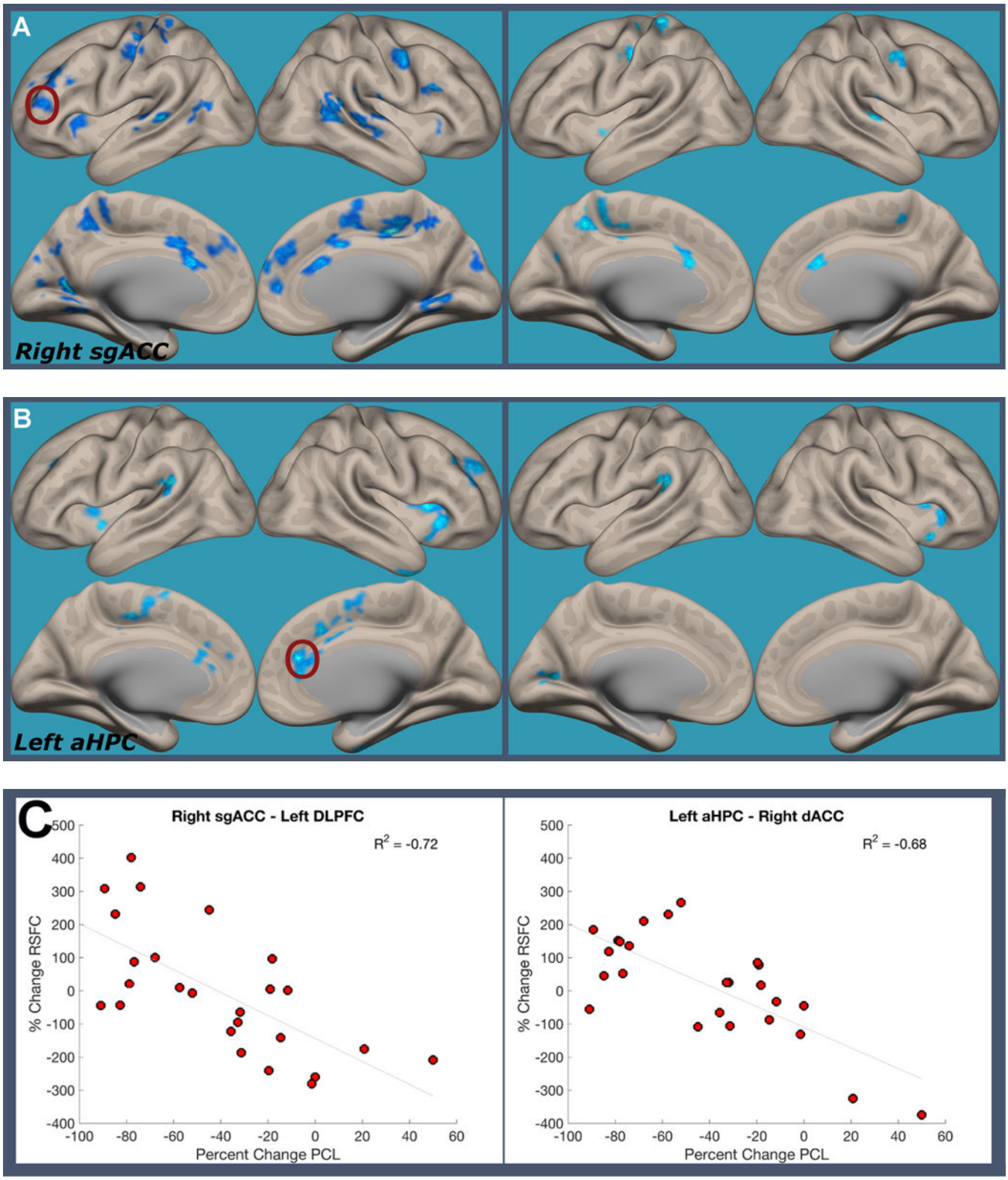


Figure 1. Predictors of Therapeutic Response.

A) Anticorrelations between sgACC and the precuneus/PCC (DMN), medial and superior frontal cortex (DMN & SN), inferior frontal gyrus, and visual cortex predicted post-treatment improvement in PCL scores. B) Positive connectivity between left BLA and

medial prefrontal cortex predict PCL (left) and IDSSR (right) improvement. C) Positive connectivity between right BLA and MPFC predicts IDSSR (inset) and PCL improvement, greater BLA and ventromedial prefrontal cortex (VMPFC) connectivity is also associated with subsequent PCL reduction. D) MVPA indicated that changes in IPL, amygdala, parahippocampal gyrus, DLPFC, and VMPFC connectivity are predictive of later PTSD symptom reduction (right), whereas changes in IPL, dACC and insula connectivity predict MDD symptom reduction (left). Images are shown using neurologic convention, and only include regions that survived cluster-based FDR $p<.05$ and LOOCV.



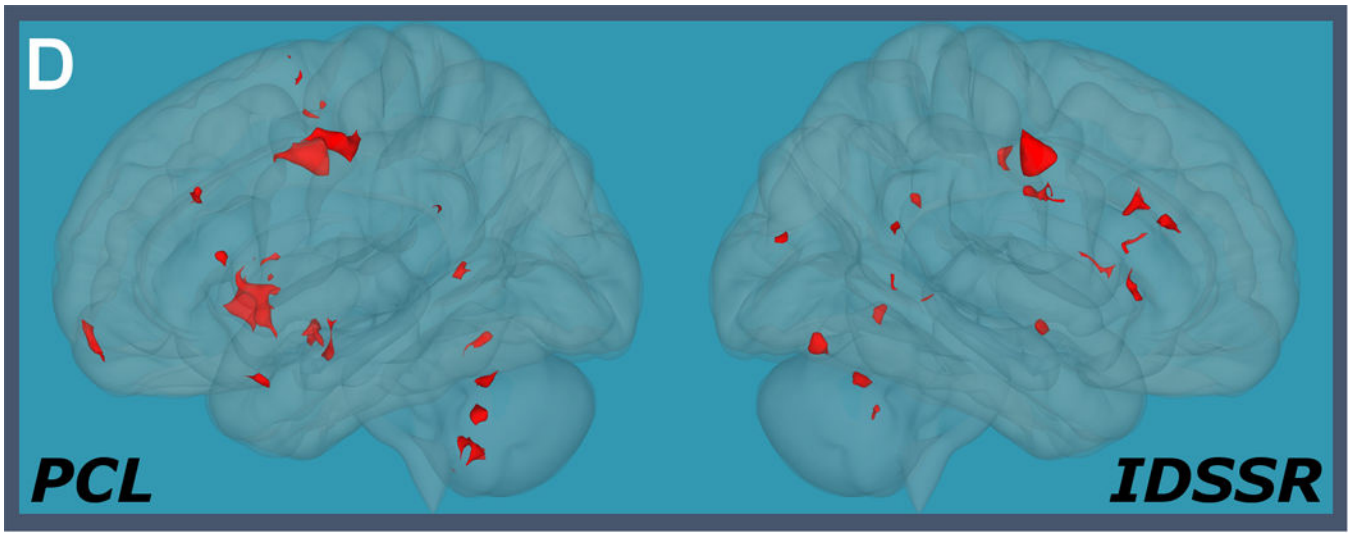


Figure 2. Potential Mechanisms of Therapeutic Response.

A) Post-TMS changes in connectivity between the right sgACC and the precuneus/PCC, dorsomedial prefrontal cortex, DACC, left DLPFC, bilateral insula, and visual processing regions were associated with PTSD improvement (left); precuneus/PCC, dACC, and somatosensory/motor anticorrelations were inversely associated with reduced MDD symptoms (right). B) Post-TMS changes in connectivity between left aHPC and SN network regions are inversely associated with PCL (left) and IDSSR (right) improvement. Images only include regions that survived cluster-based FDR $p<.05$ and LOOCV. C) Functional connectivity values are represented as percent signal change on the y-axis; post-treatment scale scores on the x-axis are in percent change relative to baseline. Statistics refer to partial Spearman's correlations, adjusted for age, scanner, and baseline symptom severity. Post hoc scattergram results are displayed for the relationship between connectivity and clinical changes (i.e., scan 2 minus scan 1) in sgACC-to-DLPFC, and hippocampus-to-dACC connectivity, with corresponding circles in Figures 2A and B, respectively. D) MVPA results indicated components related to the PCL improvement (left) included the somatomotor network (pre/post central gyrus), hippocampus and dACC, whereas components related to IDSSR improvement (right) included somatomotor regions, insula and medial frontal gyrus.