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Updates on Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

Sarah L. Garnaat, PhD^{1,2}, Shiwen Yuan, MD¹, Haizhi Wang, MD, PhD¹, Noah S. Philip, MD^{1,2,3}, Linda L. Carpenter, MD^{1,2}

¹Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

²Butler Hospital, Providence, RI, USA

³Providence VA Medical Center, Providence, RI, USA

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Introduction

Major depression is a leading cause of disability; however, a subset of patients do not experience sufficient relief from existing first-line treatments¹ or have trouble tolerating side-effects of antidepressant medications. Thus, identifying alternative treatments has been an area of significant interest. Transcranial magnetic stimulation (TMS) has emerged over the last few decades as one such potential option for treatment-resistant depression.

TMS involves application of a strong, pulsed magnetic field to a targeted brain region. A coil generating an electromagnetic field is placed on the scalp, such that strong magnetic pulses are delivered to a relatively focal area of cerebral cortex, resulting in regional neuronal depolarization and generation of action potentials. In treatment protocols, TMS is typically delivered in bundles or “trains” of pulses, separated by periods of rest; this is called repetitive TMS (rTMS, hereafter referred to as “TMS”). In 2008, the United States Food and Drug Administration (FDA) cleared the first TMS device to treat major depressive disorder (MDD); now multiple devices have regulatory approval in the US and internationally.

*Corresponding Author: **Linda L. Carpenter**, c/o Butler Hospital Mood Disorders Research, 345 Blackstone Blvd., Providence, RI 02906; linda_carpenter_md@brown.edu.

Authors' contact information:

Sarah L. Garnaat, c/o Butler Hospital OCD Research, 345 Blackstone Blvd., Providence, RI 02906;

Shiwen Yuan, c/o Residency Training Program, Brown University, Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906;

Haizhi Wang, c/o Residency Training Program, Brown University, Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906;

Noah S. Philip, c/o Center for Neurorestoration and Neurotechnology, Providence VA Medical Center, 830 Chalkstone Ave Providence RI 02908; Butler Hospital Mood Disorders Research, 345 Blackstone Blvd., Providence, RI 02906;

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The most common target for TMS for depression is the dorsolateral prefrontal cortex (DLPFC). Both high-frequency (e.g., pulses delivered at 10 Hz)^{2,3} TMS to left DLPFC and low-frequency (1 Hz) TMS to right DLPFC⁴ have shown efficacy for pharmacoresistant depression, as well as bilateral TMS (a combination of these approaches).⁵ Antidepressant efficacy has also been suggested for high-frequency TMS targeting broader prefrontal cortex.⁶ In addition, open trial results show preliminary support for TMS to dorsomedial prefrontal cortex (DMPFC)⁷ for depression. Recent research has examined efficacy of TMS delivered using a pulse pattern called theta-burst,⁸ a form of stimulation that has shown ability to promote synaptic plasticity in motor cortex; preliminary evidence suggests theta-burst TMS is as effective as standard stimulation for MDD, but sessions are much shorter. Additionally, a small number of studies have investigated accelerated TMS protocols, delivering 2 or more TMS sessions per day, potentially shortening the number of weeks that comprise a course of TMS therapy. Preliminary findings suggest accelerated approaches may be efficacious,^{e.g.,9,10} though definitive trials have yet to be conducted.

The TMS for depression field depression is growing quickly, with new studies seeking to optimize parameters for delivery and to identify biomarkers of treatment response. Hereafter, we review efficacy data from controlled TMS trials for depression and discuss ongoing areas of research aimed at further improving this treatment, including research identifying neuroimaging and neurophysiological biomarkers.

Evidence for Efficacy of TMS for Depression

Over the past 20–30 years, studies of TMS for depression have shifted from small trials focused on safety, tolerability, and preliminary efficacy to larger multicenter trials and refinement treatment parameters. Thus, many randomized, controlled trials (RCTs) of TMS for depression in the literature are underpowered. Additionally, studies have varied in target population (i.e., unipolar vs. bipolar depression), patient medication status, quality of sham procedures, and total sessions in a course of treatment (with studies generally increasing the number of sessions over time, from 5–10 in early studies, to 20–30 sessions in more recent trials, now comprising the standard of care). Accordingly, meta-analyses have been conducted to clarify findings across studies.

Meta-analytic Findings.—Meta-analyses of TMS for depression have largely supported statistically significant differences favoring active TMS over sham in terms of symptom improvement,^{e.g.,11–14} as well as clinical response.^{e.g.,12,15} While most meta-analyses have focused on high-frequency TMS, meta-analyses examining antidepressant efficacy of low-frequency TMS also found it superior to sham in terms of effect size¹⁶ and rates of response and remission.¹⁵ One meta-analysis found better outcomes with bilateral TMS versus sham.¹⁷ A recent meta-analysis by Brunoni et al.¹⁴ utilized a network-based approach to compare multiple TMS approaches and sham. This analysis, including 81 studies, found low-frequency, high-frequency, and bilateral TMS all to be more effective than sham.

Findings from large multi-site, sham-controlled RCTs.—To date, three large multisite, sham-controlled trials have been conducted to more definitively evaluate efficacy of TMS as a monotherapy for depression.^{2,3,6} The first study³ randomized 325 medication-

free patients with treatment-resistant depression to undergo 5 sessions per week of high-frequency TMS to left DLPFC or sham over 4–6 weeks.¹⁸ In this pivotal trial, TMS was delivered at 120% resting motor threshold (MT) in a series of 4-sec trains of 10-Hz, separated by 26 sec intervals of no stimulation, totaling 3,000 pulses per session. After four weeks, change in the primary outcome (Montgomery Asberg Depression Rating Scale [MADRS] score) fell short of the threshold for statistical significance ($p = 0.057$). However, change in secondary measures of depression severity (Hamilton Depression Rating Scale [HRSD]-17 and -24) showed significant improvement for active TMS vs. sham, and post-hoc analyses aiming to correct for baseline differences between conditions in MADRS scores also suggested significant differences in outcomes between conditions. Additionally, response rates on all three depression measures were significantly higher following 4 weeks of active TMS (18.1–20.6%), relative to sham (11.0–11.6%). Data from this trial supported FDA clearance of the first TMS device for depression.

A second large multisite RCT for TMS for depression was reported by George and colleagues.² TMS was delivered using the same devices and parameters described above, but with 5 sessions per week for 3 weeks. After 3 weeks, participants showing improvement continued for up to 3 additional weeks. Those not showing improvement were crossed over to open treatment. In total, 199 patients were randomized, with 190 comprising the intent-to-treat (ITT) sample used for primary analyses. Primary findings indicated a significant difference in remission rates for active TMS (14.1%) vs. sham (5.1%) in the blinded phase. Response rates also differed between conditions, favoring active stimulation (15% vs. 5%). Secondary analyses showed significant differences between conditions at the end of the blinded phase in MADRS score, global severity ratings, and self-reported depressive symptoms.

A third multicenter trial sought to evaluate efficacy of TMS using an H-coil.⁶ Patients with treatment-resistant depression received 4 weeks of high-frequency TMS delivered to a broad prefrontal cortex area (left>right). During the acute treatment phase (4 weeks), participants received 5 daily sessions per week at 18-Hz before transitioning to a twice/week treatment schedule in weeks 5–12. Stimulation was delivered at 120% MT, with 2-sec stimulation trains separated by 20-sec rest intervals, totaling 1980 pulses per session. ITT analyses failed to reach statistical significance for the primary outcome (change in HRSD after 22 sessions; $p = 0.0578$), though secondary analyses investigating response and remission rates showed significant group differences at week 5, favoring active TMS. Analyses using a per-protocol (PP) sample, excluding participants who did not receive stimulation at the specified intensity (120% MT), showed significant group differences in HDRS change from baseline to week 5, as well as significant differences between conditions in both response and remission rates at week 5.

A recent multi-site, RCT investigated a two-coil TMS array for treatment-resistant or -intolerant depression¹⁹ in patients ($N=92$) allowed to remain on stable (ineffective) pharmacotherapy regimens. The two-coil array was designed to stimulate deeper into the cortex through placement of center-folded double coils over DMPFC and DLPFC. Participants were randomized to 20 sessions of active or sham 10-Hz TMS over 4 weeks, with pulse trains delivered from both coils, (3000 pulses/session, 120% MT). The PP

sample, but not the ITT sample, showed significantly greater change in HRDS for active vs. sham. No significant differences were found in response or remission rates. A future, fully-powered trial may be warranted to more definitely determine efficacy of this approach.

Naturalistic Findings.—After FDA-approval and launch of the first US TMS device, a study was published describing real-life outcomes from TMS delivered by non-research psychiatrists at 42 real-world clinics.²⁰ MDD patients (n=307) paid for TMS therapy out-of-pocket or through insurance. Parameters and course were determined by treating physicians. Results confirmed that positive TMS outcomes were achievable in a variety of psychiatry clinical practice settings, with naturalistic data showing significant improvement in depression severity from baseline to end of treatment, and response (58.0%) and remission (37.1%) rates consistent with those in research populations. A subset of this naturalistically-treated sample (n=257) completed long-term follow-up assessments over a year to examine durability outcomes.²¹ These data revealed that acute TMS benefits were generally sustained throughout the follow-up period, with the majority (62.5%) of acute TMS responders maintaining their status over a year; approximately a third of patients received some “reintroduction” TMS sessions during the year-long follow-up period. Statistically significant improvement was also found in functional status on a broad range of mental health and physical health domains after acute TMS.²²

Optimizing TMS Therapy for MDD

Pressing clinical questions surrounding TMS therapy today concern selection of optimal stimulation parameters, treatment schedules, and other variables in protocols used for treating depression, with increasing interest in individually customizing stimulation. Data from RCTs have underscored safety and potential efficacy of TMS, even with protocols expanding well beyond those used in predecessor trials, with regard to magnetic stimuli exposure.²³ Outcomes from both blinded²⁴ and open-label²⁵ continuation phase studies suggest there is not a “one size fits all” dosing strategy, and that some patients will require more treatments than others to experience maximal symptom relief.²⁶ A meta-analysis of RCTs using high-frequency stimulation confirmed greater number of daily sessions (within a single TMS course) was associated more favorable outcomes.¹³ Positive effects of TMS may only last a few weeks in some patients,²⁷ and while open label data²⁸ support a plan for offering “booster” treatments,^{21,29} the best approach for achieving durable positive effect with TMS remains unknown. It is, however, fairly clear that, after positive response is achieved with TMS therapy, about a third of patients will need re-introduction of stimulation within a year to avoid relapse or to recapture prior level of benefits in the face of depressive symptom re-emergence;^{21,30} The ideal schedule or protocol for maintenance of effect has yet to be identified and confirmed in a prospective trial.³¹

The questions of ideal treatment target site³² and laterality for TMS stimulation also remain critical, with some studies yielding preliminary suggestions that TMS sequential delivery to both hemispheres is better than one-sided stimulation,¹⁴ and others suggesting that right-sided stimulation is better for cognition,³³ and that benefits may still be derived from left-sided stimulation after a patient has failed a TMS course over right DLPFC.³⁴ Stimulation protocols for MDD using the theta-burst pulse pattern appear effective when compared to

sham treatments⁸ but have not yet demonstrated superiority over standard TMS parameters with regard to symptom improvement or response rates in RCTs. Retrospective analyses of a large open-label Canadian database recently suggested that TMS sessions delivered twice daily, rather than once, may bring about earlier clinical response,³⁵ but again, prospective controlled trials are needed to properly test this notion.

Imaging Biomarkers

Development of biomarkers for guiding TMS application for depression is in its infancy, in part due to great voids in our understanding of neurobiological underpinnings of MDD and only nascent insights about how stimulation impacts the brain. Nevertheless, findings emerging from metabolic imaging and functional connectivity studies have begun to identify specific regional and network abnormalities, and their alterations following TMS.

Resting state SPECT/PET (metabolic imaging)

Regional cerebral blood flow (rCBF) and metabolic activity of brain areas can be evaluated with either single photon emission computed tomography (SPECT) or positron emission tomography (PET) by evaluating the regional uptake of a tagged metabolic substrate, (e.g., 18-fluorodeoxyglucose; FDG).³⁶ Findings of hypofrontality in left DLPFC observed in MDD^{37,38} provided some rationale for application of high-frequency TMS to that region in early treatment studies. This approach was reinforced by PET studies observing that high-frequency (20Hz) stimulation increased prefrontal rCBF (including amygdala, hippocampus, insula, parahippocampus, thalamus and cerebellum) while low frequency (1Hz) stimulation was associated with distal rCBF reductions in right prefrontal cortex, left medial temporal cortex and amygdala.^{38–40}

However, the directionality of rCBF changes under different stimulation frequencies correlate modestly with clinical improvement. For instance, high-frequency stimulation studies (20Hz)⁴¹ found that higher baseline subgenual anterior cingulate cortex (sgACC) activity predicted superior clinical outcomes, and clinical response corresponded to reduced sgACC activity. Clinical efficacy is correlated with changes in numerous regions related to mood regulation, including DLPFC; basal ganglia, orbitofrontal cortex (OFC), and ventromedial prefrontal cortex (VMPFC; which have direct anatomical connections with DLPFC); and sgACC and posterior cingulate cortex^{41–43} (which have polysynaptic relationships to DLPFC). Contrarily, Kito et al.^{44–46} found that increased rCBF in VMPFC predicted treatment response to 1Hz TMS. Treatment efficacy was also associated with reduced rCBF in prefrontal cortex, OFC, putamen, anterior insula and sgACC. Reduced sgACC activity following stimulation has been consistently shown in SPECT/PET studies to associate with positive treatment effect.^{41,45} However, these studies have been limited by lower stimulation intensity, fewer sessions, and modest sample sizes.

Resting State Functional Connectivity and Neural Networks

The three principle networks in mood regulation are the default model network (DMN), frontoparietal executive control network (ECN), and the attention/limbic or salience network (SN).⁴⁷ These are often measured via fluctuations in resting-state blood oxygenation levels with functional MRI (i.e., functional connectivity). In MDD, sgACC/DMN activity is

considered a core component of pathological network dysfunction, which compromises the ability for dynamic network change of an otherwise healthy brain in response to changing demands.⁴⁸ Fox and colleagues^{32,49} conducted several studies linking MDD treatment response and reduced sgACC connectivity, and suggesting that suppression of sgACC connectivity leads to clinical improvement.

TMS to DLPFC—Connectivity changes associated with TMS can also be interpreted in the context of the primary stimulation site. An ACC-centered network was shown to be the only mediator of TMS effects in an experiment with healthy individuals, and only with TMS delivered to DLPFC.⁵⁰ After TMS treatment targeting DLPFC, sgACC-to-DMN connectivity was attenuated, and reduced connectivity was observed between DLPFC and MPFC/VMPFC.⁵¹ Reducing sgACC-to-DMN connectivity and inducing negative connectivity between DLPFC and DMN have been considered possible putative mechanisms of TMS therapy.

Considering clinical response, patients who experience significant symptom reduction with TMS have demonstrated, at baseline, greater negative connectivity between sgACC and superior medial prefrontal cortex, including portions of DMPFC,⁵² greater connectivity between sgACC and OFC,⁵³ stronger DMN-to-SN connectivity,⁵⁴ and higher left DLPFC-to-striatum connectivity.⁵⁵ Greater pre-treatment sgACC connectivity generally predicts superior clinical outcomes.⁵¹ In contrast, higher baseline connectivity between posterior cingulate and insula has predicted TMS non-response.⁵⁶ Following a course of TMS, sgACC connectivity was reduced in all responders, whereas no sgACC changes were observed in non-responders.⁵² TMS responders have also shown reduced negative connectivity between sgACC and medial prefrontal cortex (MPFC), reduced sgACC connectivity with the middle frontal gyrus and motor cortex, increased sgACC connectivity with VMPFC,⁵⁷ and reduced DLPFC-to-caudate connectivity.⁵⁸

TMS to DMPFC—Clinical responders to TMS targeting DMPFC have been found to have intact reward circuit function^{7,59} while non-responders displayed lower connectivity in reward pathways comprised of VMPFC, ventral tegmental area, and striatum. Examination of clinical response predictors revealed that superior antidepressant outcomes were associated with positive midcingulate-to-sgACC/MPFC connectivity, negative midcingulate-to-thalamus, -hippocampus and -amygdala connectivity, higher sgACC-to-DLPFC connectivity, and lower sgACC-to-insula, -putamen and -parahippocampus/amygdala connectivity.⁶⁰ Coinciding with DLPFC-based studies, better clinical responses were associated with more negative DMPFC-sgACC connectivity.

Seeking to characterize global neurobiological changes in depression, a multisite study⁶¹ provided evidence of four discrete biotypes within depression, according to frontostriatal and limbic connectivity. For a subset of MDD patients (n=124) who received TMS to DMPFC, one specific imaging biotype, characterized by reduced connectivity in fronto-amygdala networks and in anterior cingulate and orbitofrontal areas, showed the best treatment response.

Findings arising from TMS imaging studies should be interpreted with the caveat of the considerable heterogeneity of variables in these neuroimaging studies, including treatment parameters, imaging modalities and analytic approaches. While these preliminary findings do not yet lend themselves to clinical application, a convergence of evidence to date underscores the sgACC as a critically important target for TMS to treat depression. With further investigation and refinement, imaging biomarkers might someday be useful for clinical decision-making in delivering TMS for depression.

EEG Biomarkers

Electroencephalography (EEG) is a non-invasive method for measuring brain activity using superficial recording electrodes on the scalp to detect rhythmic electrical events generated by large populations of neurons. EEG recordings reflect regional oscillatory brain activity defined by key anatomical landmarks according to a standardized topographical method, capturing signals in discrete frequency “bands” based on periodicity of the waveform, e.g., delta (0.5–3 Hz), theta (3–7 Hz), alpha (7–13 Hz), beta (13–30 Hz) and gamma (>30 Hz). Quantitative EEG (qEEG) analyses can locate source, strength, and orientation of brain activity; provide its spatial representation; compare temporal relationships of signals from different recording sites (coherence analysis); and capture event-related potentials (ERPs; small voltage changes in EEG in response to certain events in real time). Since spatially discrete neuronal groups can interact effectively only when they are oscillating at a coherent (synchronized) rhythm, analysis of phase synchronization or coherence of change in EEG data can reveal functional connectivity among multiple cortical and deeper brain regions, representing functional circuits or hubs in a coordinated network. For example, a combined EEG-fMRI experiment found that frontal theta activity correlated significantly with activation of the DMN.⁶² Due to relative ease of application in clinical settings, EEG holds significant promise for elucidating biomarkers to guide customization of TMS treatments, or for predicting negative outcomes before investing substantial time and resources in a course of TMS.

Studies comparing EEG pre- and post-TMS treatment have identified changes induced by stimulation and/or by resolution of depressive symptoms and provide preliminary insights regarding possible therapeutic mechanisms of TMS for depression. Llinas and colleagues proposed that perturbation in thalamocortical neural oscillations may be central to MDD pathogenesis, with abnormal increases in theta activity and coherence of low-frequency oscillations.⁶³ In a study of 44 healthy subjects, resting EEG showed that TMS induces short-term effects in the thalamocortical interplay of low-frequency brain oscillatory activities: 10-Hz stimulation induced transient synchronization of delta and theta rhythms, while low-frequency (1-Hz, 5-Hz) stimulation induced desynchronization of these slow waves.⁶⁴ The transient de-synchronizing effects of TMS at thalamocortical neural circuits in healthy subjects (inferred by decreased power of delta and theta rhythms) resembles the opposite of patterns observed in depression,⁶⁵ raising the possibility that TMS effects on oscillatory neural rhythms are related to its therapeutic mechanism of action. Furthermore, TMS transiently induces oscillations that synchronize with the stimulating frequency (i.e., entrainment), e.g.,^{66–68} followed by re-emergence of intrinsic natural local cortical oscillations.⁶⁹ Transient entrainment of brain oscillations by TMS has thus been

hypothesized to promote normal intrinsic rhythm and plasticity to bring about therapeutic effects in MDD.^{70,71}

Activity in the gamma frequency band has produced several potential EEG biomarkers relevant to TMS for depression. In an open label study comparing pre- and post-treatment EEG in 31 depressed patients, TMS targeting left DLPFC induced significant increases in resting gamma power at the F3 electrode, corresponding to symptom improvement.⁷² TMS treatment has also been shown to alter functional connectivity within gamma band in resting EEG, with increased gamma activity in left DLPFC and decreased gamma activity in precuneus following TMS.⁷³

Cordance is an EEG measure using various algorithms to yield indicators corresponding to cerebral perfusion/metabolism. In a retrospective study of MDD or dysthymia patients (n=90) treated with TMS, several pretreatment EEG variables were shown to distinguish non-responders from responders. Before treatment, TMS nonresponders had slower anterior individual alpha peak frequency, increased fronto-central theta power, and decreased prefrontal delta and theta cordance.⁷⁴ Another study of 25 MDD patients treated with TMS showed that decreases in prefrontal theta cordance at week 1, compared to pretreatment baseline, successfully predicted week 4 response.⁷⁵ A study analyzing non-linear metrics in baseline EEG identified a measure of alpha signal complexity that significantly predicted TMS response.⁷⁶ Here, slower anterior alpha peak frequency was also found in non-responders. Another study with 18 clinically-stable depressed outpatients receiving open-label TMS found change in theta cordance in left DLPFC at week 1 was a significant predictor of outcome at week 6.⁷⁷ Finally, using machine learning, an artificial neural network was developed using pre-treatment frontal EEG cordance to identify TMS responder status in MDD subjects (n=55); responders were identified with sensitivity of 93% and overall accuracy of 89%.⁷⁸

Some EEG researchers have posited that optimal clinical outcomes may be achieved with individually customized stimulation protocols matching pulse frequency to the patient's individual alpha frequency. Pilot studies^{79,80} have begun investigating this approach using a low-field TMS device with promising preliminary results that require further testing with standard-intensity TMS protocols. With continued research, refinement of EEG biomarkers may someday enhance TMS treatment outcomes. However, at present, data are insufficient to suggest individual EEG could be used to guide treatment decisions in standard TMS care settings.

Conclusion

Overall, findings continue to support efficacy of TMS for treatment-resistant depression. Work continues on development of alternative treatment regimens and optimization of protocols, including stimulation parameters, treatment targets, and TMS delivery schedules. Ongoing research using neuroimaging and EEG is laying the foundation for a deeper understanding of treatment-resistant depression and therapeutic mechanisms of TMS. While these findings are still in their infancy, these efforts may someday provide valuable insights for optimizing TMS for treatment-resistant depression.

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Key points:

- Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation therapy developed for use in treatment-resistant depression.
- Meta-analyses and large, randomized controlled trials largely support efficacy of TMS targeting dorsolateral prefrontal cortex for major depressive disorder.
- TMS for depression continues to advance, with studies focusing on refining parameters for treatment optimization, and identification of biomarkers related to treatment response.

Synopsis:

Transcranial magnetic stimulation (TMS) has emerged as a treatment option for treatment-resistant depression. While existing data largely support efficacy of TMS for major depressive disorder (MDD), ongoing research aims to optimize treatment parameters and identify biomarkers of treatment response. Below, we describe data from controlled trials and on-going efforts to enhance TMS outcomes for MDD. Findings from preliminary research aimed at identifying neuroimaging and neurophysiological biomarkers of TMS effects are discussed.