REVIEW

# A Systematic Review Assessing Patient-Related Predictors of Response to Transcranial Magnetic Stimulation in Major Depressive Disorder

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**Objective:** The safety and efficacy of transcranial magnetic stimulation (TMS) in the acute treatment of major depressive disorder (MDD) is well established. However, it is not well understood which patient-related factors are associated with a more robust antidepressant response. Identifying predictive factors for therapeutic response to TMS treatment in depression will guide clinicians in patient selection.

**Methods:** By systematic review of clinical trial data, the current study aims to identify and analyze reported patient-specific predictors of response to an acute course of TMS treatment for MDD. PubMed was searched for randomized controlled trials of TMS for patients with depression. Studies were appraised for risk of bias using components recommended by the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Results:** TMS data were available from 375 studies, 18 of which were included in this review. Treatment response is inversely associated with treatment refractoriness and age.

**Conclusion:** Inadequate sample size and large heterogeneity in study parameters among clinical trials limit any strong conclusions from being drawn; nonetheless, despite these limitations, there is mounting evidence, which points to age and treatment refractoriness as candidate variables for predicting clinical outcome. Implications of these findings for treatment of MDD are discussed.

**Keywords:** depression, neurostimulation, TMS

## Introduction

The principle of electromagnetism demonstrated by Michael Faraday during the 1830s is the basis of transcranial magnetic stimulation (TMS). Dr. Anthony T. Barker introduced the first stable TMS device in 1985. Originally, it was developed as a neurodiagnostic tool to noninvasively examine the connection between the central nervous system and skeletal muscle.[1] Using a pulsed magnetic field, responses are elicited in those muscles that receive corticomotor input from the stimulated motor area.[2]

Not long after TMS was introduced, reports of a therapeutic effect began to emerge.[3] Antidepressant effects, according to Grunhaus et al,[4] were observed as early as 1993, and after several landmark clinical trials repetitive transcranial magnetic stimulation (rTMS) was shown to have a clinically significant benefit for depression.[5–7] In October of 2008, the United States Food and Drug Administration approved the rTMS protocol employed in a multisite trial[8] for use for major depressive disorder (MDD), specifically to alleviate symptoms in patients with treatment-resistant depression who have not found relief from prior antidepressant medication for the current depressive episode.

Patients who exhibit depressive symptomatology that follows a medication resistant course may find clinical benefit from TMS. Evidence suggests that for every 10 patients undergoing TMS, three[9,10] to five[11–13] will respond but will not necessarily achieve remission. This certainly begs the question, what patient-related factors influence outcome? However, a proper analysis of patient-related predictors must necessarily include an analysis of the procedural aspects

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of TMS, for variations in outcome are highly dependent upon treatment parameters. As a corollary, it should be borne in mind that the optimal treatment parameters for the management of depression have yet to be established at the writing of this review.

## TMS Procedure

TMS treatment involves placing an insulated coil over the scalp surface. The coil is connected to a stimulator, which generates an electric current, resulting in a magnetic field around the coil. Magnetic pulses pass through hair, scalp, and skull unimpeded, stimulating the underlying cortex.

Regarding treatment location, magnetic pulses are delivered to a region of the brain implicated in the pathophysiology of depression, namely the dorsolateral prefrontal cortex (DLPFC). Due to its proximity to the scalp surface and its connections with remote areas that are also involved in mood (eg, the subgenual anterior cingulate cortex), the DLPFC is an ideal treatment target. With functional neuroimaging showing a reduction in glucose metabolism of depressed patients in the left DLPFC, TMS has generally been directed to this region.[14] Historically, the DLPFC was located using the "5-centimeter method" in accordance with which the coil is placed 5 centimeters (cm) anterior along a parasagittal line from the motor spot that elicited motor-evoked potentials in the abductor pollicis brevis. While practical and simple, this method fails to account for anatomical differences such as skull size and cortical morphology. Eventually, it was determined to be more effective to move the treatment location slightly more anterior and lateral. For this reason, many researchers and clinicians – if they do not have access to more reliable targeting methods – move 5.5 or 6 cm forward from the motor threshold location.[15,16]

Meta-analyses support superior efficacy of high-frequency TMS administered to the left DLPFC.[17] There is also evidence from a small number of studies that suggests low-frequency TMS administered to the right DLPFC may produce a similar antidepressant effect.[18,19] On the basis thereof, conventional clinical approaches generally follow one of these two treatment paradigms. However, as more research is conducted and more advanced technology is produced, more techniques arise. A combination of the two protocols just described has been investigated for example. Commonly referred to as bilateral rTMS, this protocol consists of high-frequency TMS administered to the left DLPFC followed by low-frequency TMS administered to the right DLPFC, applied sequentially during the same session. Questions surrounding its efficacy led researchers to test whether bilateral rTMS is superior or inferior to unilateral stimulation of the left or right DLPFC. The consensus is that bilateral rTMS is comparable to unilateral rTMS in treating major depression.[15,20–23]

Frequency, as it relates to TMS treatment, modulates cortical excitability. Protocols using 5 hertz (Hz) or higher are considered high-frequency TMS and low-frequency TMS corresponds to approximately 1 Hz.[24] An increase or decrease in neuronal activity is achieved by using a higher or lower frequency, respectively. As aforementioned, imaging studies correlate left-right DLPFC imbalance with depression, specifically, left DLPFC hypoactivity and right DLPFC hyperactivity.[14,25] Thus, it is hypothesized that to bring neuronal activity in the left DLPFC to a normalized state high-frequency TMS would be administered, given that it induces an excitatory effect, and whereas high-frequency TMS has an excitatory effect, low-frequency TMS has an inhibitory effect on the receiving neurons. Right DLPFC hyperactivity would thus be moderated by low-frequency TMS. In consideration of the foregoing, stimulation parameters alone do not determine cortical excitability. That the modulation of cortical excitability depends, in part, on the baseline neural activity prior to stimulation, is of paramount importance, given that the direction and amplitude of stimulation is partly determined by the activity of neural tissue preceding stimulation.[26]

Changes in cortical excitability, as studies have demonstrated, are sustained beyond the stimulation period.[27] A meta-analysis reporting on the durability of the antidepressant effect of rTMS among patients who responded to an initial acute course of treatment stated that 67% of patients sustained response after 3 months and 46% of responders maintained response 1 year after treatment.[28]

## Patient-Related Predictors of Response

Of the patient-related factors hypothesized as influential determinants of clinical response age is frequently reported. Several studies have found that age is inversely correlated with antidepressant response, that is, younger adults with

depression tend to benefit more from TMS treatment compared to their older adult counterparts.[13,29–35] On the other hand, a few studies have failed to replicate these findings.[36–38] In a review by Sabesan et al,[39] the authors note a similar treatment effect among younger and older adults.

These inconsistent findings can be explained in part by aging-related changes. Researchers report that smaller frontal gray matter volumes were associated with a poorer response to TMS.[34,40] Magnetic pulses are attenuated by distance so the distance between the scalp (where the coil is placed) and the cortex is a key variable for providing effective treatment. Atrophy affects the brain such that it increases the distance between the scalp and the cortex, thus reducing the treatment effect of the magnetic pulses. This is of special importance seeing as many studies use a figure-of-eight coil, which produces relatively focal stimulation only penetrating to a depth of about 2 cm. Therefore, older adults in some of the earlier studies may have failed to find benefit from rTMS because the DLPFC was never stimulated in the first place or perhaps only partially.

Moreover, many of these earlier studies did not use the standard dose of 120% of the resting motor threshold.[40] Under these conditions, the right treatment location may have been stimulated, but the dose was insufficient to produce any meaningful response. Advances in brain mapping techniques, such as MRI-guided TMS, will increase treatment target identification and improvements in coil design will help to ensure that the treatment location is stimulated, and that the stimulation delivered is of a sufficient dose.

The brain's plasticity during younger age has been linked to higher rates of response among younger adults. Younger adults, that is to say, the younger brain, may be more responsive to TMS than the older brain. The obverse of this is that there might be a delayed effect in older adults. Older adults might require more time to respond to stimulation than what has generally been allocated in clinical trials. Along these lines, it has been proposed that initially non-responsive patients could benefit from a larger number of pulses than responders.[34,41] More pulses per session was associated with positive TMS outcomes according to Sackeim et al,[38] with patients who averaged 4000 or more pulses per session seeing greater benefit.

Research has also identified a link between clinical response and treatment refractoriness, noting less treatment-refractory patients as being more likely to respond to rTMS.[33,37,42,43] Otherwise stated, a lower degree of medication resistance in the current or recent episode predicts superior antidepressant response to rTMS. This is in line with copious research demonstrating a strong negative correlation between treatment refractoriness and response to antidepressant medication.[37,44]

A greater antidepressant effect has been observed among women.[38,41,45,46] The superior response seen in women has been attributed to a combination of factors – the type of depressive symptoms women typically manifest relative to men,[47] gender differences in cranio-facial anatomy,[48] and estrogen levels.[45,48] Upon closer examination, the variation in treatment response between genders might not be due to gender alone but moderated by age.[38,41,45] Female hormonal fluctuations across the lifecycle could partly explain age as a moderator. Evidence suggests, for example, that the pre-menopausal stage, as compared with post-menopause, is associated with improved response to rTMS.[45,46]

In terms of neurobiological predictors, brain derived neurotrophic factor[49–52] and pre-treatment regional cerebral blood flow[51,53–56] have been suggested, but further investigation with high-quality studies is required.

The most effective intervention for treatment refractory depression is electroconvulsive therapy (ECT) but for several reasons – be it tolerability, side effects, or nonresponse – patients with previous exposure to ECT might seek out rTMS as a treatment strategy. Taking that into account, determining whether history of ECT is an independent predictor of TMS response is clinically important. According to one retrospective analysis, the data revealed no significant difference between patients with previous ECT exposure versus those with no history of ECT and TMS outcomes[57] (see also Fitzgerald et al).[21]

A group of researchers conducted an open-label study with high refractory MDD patients (at least three failed adequate trials of different antidepressants) and found 10 Hz modulation of corticomotor excitability to be a positive predictor of antidepressant response to DLPFC rTMS.[58] They then followed up with another study, further substantiating this hypothesis.[59] However, given the open-label nature of these studies and the fact that plasticity was assessed in the motor cortex as opposed to the DLPFC where treatment was applied, further evidence is needed.

Findings relating to depressive symptoms associated with the antidepressant properties of TMS are mixed.[60] Researchers have found symptoms such as psychomotor retardation[36,61] and sleep disturbance[36] among responders, but the data is scarce. Cognitiveaffective symptoms of depression, especially loss of interest, were identified as potential predictor variables by Rostami et al.[13] A possible explanation for this depressive symptom subtype, as opposed to a somatic subtype, has to do with the DLPFC as the treatment target. Owing to the fact that the prefrontal cortex plays a critical role in emotion regulation, the likelihood that a patient will benefit from rTMS over the DLPFC might be higher for a patient with cognitive-affective symptoms than one with a more somatic symptom profile.

## Methods

The present systematic review was performed in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Search terms used were "predictors transcranial magnetic stimulation." Based on a literature search conducted using the PubMed database in December of 2022, a total of 375 records on TMS involving humans published in English from 1986 until December 5, 2022, were retrieved. Additional relevant articles (n=18) were obtained by scanning the reference lists of articles identified in the initial search. A PRISMA study selection flow diagram has been included (Figure 1).

Inclusion criteria were randomized sham-controlled studies in which at least five sessions of TMS were administered over a limited number of days with stimulus parameters comparable to those of conventional TMS and studies with well-described outcome measures (ie, valid rating scales), clearly defined stimulus parameters, response and remission rates, as well as
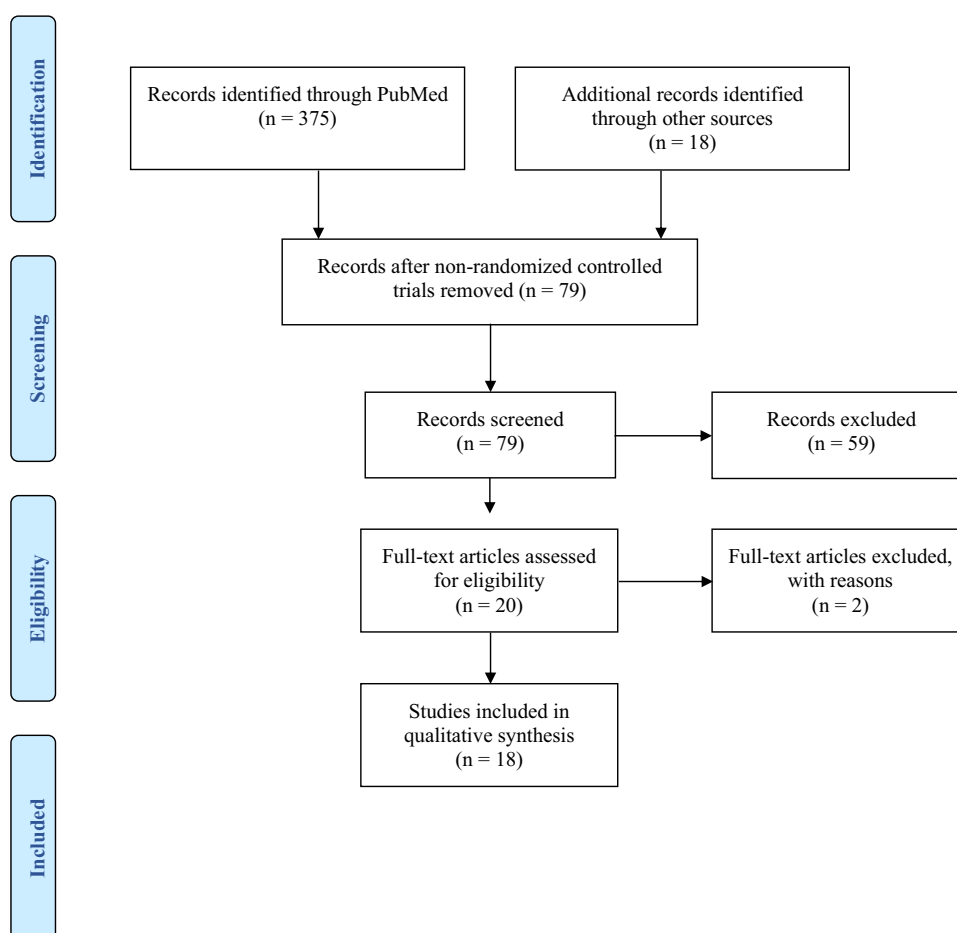


**Figure 1** PRISMA flow diagram.
**Notes**: PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of clinical epidemiology. 2009;62(10). Creative Commons.[62]

statistical analyses. The author included studies with male or female patients 18 years of age and older for indications of MDD. Studies which investigated forms of depression caused by injury or disease were not included. Studies did not meet inclusion criteria if they evaluated forms of depression with organic factors as the origin (eg, studies investigating post-stroke depression were excluded). Only studies that stimulated over the prefrontal cortex were included. Open-label and naturalistic studies were excluded.

## Selection and Quality Assessment

One reviewer evaluated articles identified as a result of the search. Studies were initially screened for relevance in the title and abstract. The remaining full-text articles were reviewed. Studies were assessed for eligibility and risk of bias using the recommendations of the Cochrane Collaboration: sequence generation, allocation concealment, blinding of subjects, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. The final papers chosen for inclusion were also searched to ensure other eligible trials were not missed.

## Outcome Measures and Data Collected

The main outcome measure was response, generally defined as a 50% or greater reduction in scores from pretreatment to post-treatment as assessed by an appropriate psychometric scale, such as the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), or the Beck Depression Inventory (BDI). Remission of symptoms, as determined by the change in scores according to a predetermined threshold set by each study, was also a meaningful outcome here. Study data were collected on data collection forms, which recorded reference data, randomization, treatment arms, inclusion and exclusion criteria, TMS treatment parameters, demographic information, as well as numbers of participants in the active and control groups.

# Results

The search strategy identified 375 published articles. Once the "clinical trial" filter was applied in PubMed, 314 articles were removed. The author reviewed titles and abstracts of the remaining 61 articles and excluded papers that were not clinical trials, implemented treatment methods vastly dissimilar to conventional TMS or which reported Supplementary Data (see Supplementary Material) from trials published elsewhere. The full text of the remaining 20 articles was assessed for eligibility. After studies were excluded on the basis of study design, randomization, indication, and study blinding, the search strategy yielded 18 randomized sham-controlled trials[8,9,16,31,35,63–75] that enrolled 1316 patients (see Table 1).

Of the 18 studies identified, two studies reported age as associated with outcome.[35,69] Using a $p < 0.05$ level of significance, Aguirre et al[35] showed that age correlated with improvement of depressive symptoms at the end of 4 weeks of treatment (r=−0.683, p=0.002). In the study conducted by Loo et al,[69] the mean age for responders and non-responders who received active TMS was 43.2 ± 13 and 53.3 ± 13 (p=0.032), respectively.

One study reported that treatment refractoriness is implicated in treatment response,[8] whereby patients with a moderate level of treatment resistance to medication benefitted from TMS. In that study, patients had an average of 1.6 failed medication trials for the current episode[8] and the primary endpoint – change in MADRS scores – established significance for the active treatment group (p=0.057).

The linear regression model performed by Baeken et al[72] revealed that duration of the current depressive episode was significant in the model (p=0.03). Yesavage et al[16] reported that, in their study of United States veterans, treatment effect was moderated by comorbid posttraumatic stress disorder (PTSD), that is, veterans with comorbid PTSD displayed the least improvement. With a p value of 0.03, PTSD comorbidity was significantly correlated with rates of remission.[16]

Eijndhoven et al[74] performed analysis and found an inverse association between change in HDRS score and the Dutch measure for quantification of treatment resistance in depression, however this was not statistically significant relative to sham (p>0.1).

Both active treatments in Fitzgerald et al[63] were significantly different from sham (p<0.005 for both). A higher baseline agitation score on the Clinical Outcomes in Routine Evaluation scale was associated with an increased response (p=0.004) but only predicted the response for the low-frequency TMS group (p=0.01, $r^2$=0.29).

**Table 1** Characteristics of the 18 Randomized Controlled Trials Identified by the Search Strategy

| Study | Design | TMS Parameters | Total Pulses per Session | Number of Sessions | n | Diagnosis | Mean Age for Active Group (Sham) | Males in Active Group (Sham) | Females in Active Group (Sham) | Conclusions/Candidate Predictor Variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Aguirre et al 2011[35] | Randomized sham-controlled | 110% MT, 1 Hz, 20 trains, 60s on, 45s off, RDLPFC | 1200 | 20 | 34 | Unipolar Major Depression (DSM-IV) | Data not available | 8 | 11 | Analysis showed that age is correlated with reduction in Hamilton Scale scores, however, the study did not establish efficacy of LF-TMS. |
| Akpinar et al 2022[75] | Randomized sham-controlled cross over study | 110% MT, 10 Hz, 25 trains, 2.5s on, 20s off, LDLPFC | 1000 | 20 | 38 | Major Depressive Disorder (DSM-V) | 43.7 (45.6) | 3 (3) | 17 (15) | TMS provides clinically significant improvement as an adjunct to pharmacotherapy in patients with treatment-resistant depression, and is beneficial for comorbid anxiety symptoms. |
| Anderson et al 2007[67] | Randomized sham-controlled study | 110% MT, 10 Hz, 20 trains, 5s on, 30s off, LDLPFC | 1000 | 12 (+6 for responders) | 29 | Major Depressive Disorder (DSM-IV) | 48 (46) | 6 (7) | 7 (9) | TMS therapy administered three times a week for 4 to 6 weeks is a useful addition to medication in treatment resistant depression. |
| Avery et al 2006[9] | Randomized sham-controlled | 110% PT, 10 Hz, 32 trains, 5s on, 25–30s off, LDLPFC | 1600 | 15 | 68 | Major Depressive Disorder (DSM-IV) | 44.3 (44.2) | 14 (17) | 21 (16) | Active rTMS is superior to sham. Response and remission rates for the active group were 30.6% and 20%, respectively. |
| Baeken et al 2013[72] | Within subjects placebo-controlled | 110% MT, 20 Hz, 40 trains, 1.9s on, 12s off, LDLPFC | 1560 | 20 | 21 | Unipolar treatment resistant depression (Thase & Rush) | 49.25 | 8 | 13 | Duration of the current depressive episode was significant as a clinical predictor. Compared to non-responders, responders had a significantly shorter episode duration. |
| Dai et al 2020[73] | Randomized double-blind sham-controlled parallel group | 100% MT, 10 Hz, 20 trains, 4s on, 56s off, LDLPFC | 800 | 20 | 124 | Depression (ICD-10) | 69.33 (67.15) | 23 (25) | 39 (37) | TMS in conjunction with medication exhibited a fast acting antidepressant effect in elderly inpatients after 2 weeks of treatment with further improvement after 4 weeks of treatment. |
| Eijndhoven et al 2020[74] | Randomized sham-controlled trial | 110% MT, 10 Hz, 60 trains, 5s on, 25s off, LDLPFC | 3000 | 20 | 31 | Major Depressive Disorder (DSM-IV) | 47.3 (49.7) | 6 (3) | 9 (13) | Between active and sham conditions no differences in antidepressant response. Analysis revealed however, a correlation between treatment resistance and lower degree of response in the active group, but this was not statistically significant. |
| Fitzgerald et al 2003[63] | Double-blind randomized placebo-controlled | 100% MT, 1 Hz, 5 trains, 60s on, 60s off, RDLPFC | 300 | 10 (up to 20 for crossover phase) | 60 | Major Depressive Disorder (DSM-IV) | 45.55 (49.15) | 13 (9) | 7 (11) | Greater degree of baseline psychomotor agitation is predictive of response to LF-TMS. |
| | | 100% MT, 10 Hz, 20 trains, 5s on, 25s off, LDLPFC | 1000 | | | | 42.2 | 12 | 8 | |

| Study | Design | Stimulation parameters | | | | Diagnosis | | | | Findings |
|---|---|---|---|---|---|---|---|---|---|---|
| Hausmann et al 2004[64] | Double-blind sham controlled "add on" trial | 100% MT, 10 Hz, 10 trains, 10s on, 90s off, LDLPFC | 2000 | 10 | 38 | Major Depressive Disorder (DSM-IV) | 47.33 (47) | 6 (4) | 6 (9) | TMS as adjuvant to medication provides no benefit. |
| | | 100% MT, 10 Hz, 10 trains, 10s on, 90s off, LDLPFC augmented with 120% MT, 1 Hz, 10 min on, RDLPFC | 2600 | | | | 45.23 | 5 | 8 | |
| Herwig et al 2007[68] | Multicenter randomized, double-blind sham-controlled | 110% MT, 10 Hz, 100 trains, 2s on, 8s off, LDLPFC | 2000 | 15 | 127 | Major Depressive Disorder (DSM-IV) | 50 (49) | 18 (33) | 44 (32) | Analyses did not show any meaningful interaction of age, gender, device type, or concomitant medication with outcome. |
| Pallanti et al 2010[71] | Three group double-blind randomized controlled trial | 110% MT, 1 Hz, 3 trains, 140s on, 30s off, RDLPFC | 420 | 15 | 60 | Major Depressive Disorder (DSM-IV) | 51.20 (47.85) | 8 (8) | 12 (12) | Only unilateral right sided rTMS and not bilateral rTMS was more effective than sham. Age, duration of illness, duration of current episode, the number of medication failures, and the number of previous episodes were not found to be predictors. |
| | | 110% MT, 1 Hz, 3 trains, 140s on, 30s off, RDLPFC augmented with 100% MT, 10 Hz, 20 trains, 5s on, 25s off, LDLPFC | 1420 | | | | 47.6 | 9 | 11 | |
| Loo et al 2007[69] | Randomized sham-controlled | 110% MT, 10 Hz, 30 trains, 5s on, 25s off, LDLPFC | 1500 | 20 | 38 | Major Depressive Disorder (DSM-IV) | 49.8 (45.7) | 9 (11) | 10 (8) | Responders and non-responders differed significantly in age (43±13 and 53±13, respectively). |
| Mogg et al 2008[70] | Randomized sham-controlled | 110% MT, 10 Hz, 20 trains, 5s on, 55s off, LDLPFC | 1000 | 10 | 59 | Major Depressive Disorder (DSM-IV) | 55 (52) | 13 (9) | 16 (21) | No relationship found between recorded variables and treatment response. No benefit derived from TMS. |
| Mosimann et al 2004[31] | Randomized sham-controlled | 100% MT, 20 Hz, 40 trains, 2s on, 28s off, LDLPFC | 1600 | 10 | 24 | Treatment-resistant Major Depression (DSM-IV, ICD-10) | 60 (64.4) | 10 (4) | 5 (5) | Study did not find a correlation between age and depression rating. However, the study notes a reduced effect of TMS in elderly patients. |
| O'Reardon et al 2007[8] | Multi-site randomized double-blind sham-controlled | 120% MT, 10 Hz, 75 trains, 4s on, 26s off, LDLPFC | 3000 | 30 | 301 | Major Depressive Disorder (DSM-IV) | 47.9 (48.7) | 69 (72) | 86 (74) | Antidepressant effect of TMS is superior to sham in medication-free patients, with a higher degree of treatment refractory depression decreasing likelihood of response. |
| Rossini et al 2005[65] | Randomized double-blind placebo-controlled | 80% MT, 15 Hz, 20 trains, 2s on, 28s off, LDLPFC | 600 | 10 | 54 | Major Depressive Disorder (DSM-IV) | 54 (56.3) | 4 (6) | 15 (11) | Patient characteristics did not affect outcome. More benefit derived from stimulation at 100% of MT than 80% MT. |
| | | 100% MT, 15 Hz, 20 trains, 2s on, 28s off, LDLPFC | | | | | 57.4 | 6 | 12 | |

(Continued)

**Table 1** (Continued).

| Study | Design | TMS Parameters | Total Pulses per Session | Number of Sessions | n | Diagnosis | Mean Age for Active Group (Sham) | Males in Active Group (Sham) | Females in Active Group (Sham) | Conclusions/Candidate Predictor Variables |
|---|---|---|---|---|---|---|---|---|---|---|
| Rumi et al 2005[66] | Randomized double-blind placebo-controlled | 120% MT, 5 Hz, 25 trains, 10s on, 20s off, LDLPFC | 1250 | 20 | 46 | Major Depressive Disorder (DSM-IV) | 39.3 (38.9) | 3 (4) | 19 (20) | TMS is effective in accelerating the onset and augmenting the therapeutic response to amitriptyline. |
| Yesavage et al 2018[16] | Double-blind randomized sham-controlled trial | 120% MT, 10 Hz, LDLPFC | 4000 | 20 to 30 (Remitters received 20 to 30 + 6 for taper) | 164 | Major Depressive Disorder (DSM-IV) | 55.6 (54.8) | 67 (65) | 14 (18) | Active rTMS was slightly better than sham. PTSD comorbidity found to be a potential moderator for veterans with MDD. |

For several studies, treatment response appeared to be unrelated to the demographic and clinical characteristics recorded.[9,31,65,68,71]

Though no predictors of response were identified by Avery et al,[9] active TMS was superior to sham. In the active group, higher response (Fisher's p = 0.008) and remission rates (Fisher's p = 0.033) were observed, compared with sham.[9]

Based on the results in the study by Mosimann et al,[31] there was no correlation between age and depression rating or episode duration, nor did active stimulation differ from sham.

With 9 out of 28 subjects in the active group classified as responders and 3 out of 29 in the sham group classified as responders (p=0.06), the data from Hausmann et al[64] suggest that TMS is not effective as an adjuvant to medication.

Data from 14 studies in this review demonstrated the efficacy of TMS,[7,9,16,31,63,65–69,71–73,75] while the remaining four studies reported null findings – that no benefit is derived from rTMS.[35,64,70,74]

## Discussion

Based on the results provided by these studies, age emerges as one of the strongest candidate predictor variables associated with rTMS response. For the Aguirre et al study,[35] no other variable besides age correlated with change in HDRS scores. Similarly, the two-tailed *t*-tests run by Loo et al[69] only found age to be significant. Thus, in both cases it was a bivariate correlation. That notwithstanding, the study conducted by Dai et al[73] was able to establish the effectiveness of TMS in an elderly sample in which the mean age was 68.2. Indeed, this was a sample of inpatients so the results might not translate to other populations.

Treatment refractoriness is another possible predictor variable that holds promise.[8,74] The most compelling evidence came from a multi-site trial with a large sample size (n=301).[8] According to the data, a lower degree of medication resistance predicts a response.[8] Patients who had one medication failure exhibited greater improvement in depression rating scale scores, compared to patients who had two or more medication failures. Of note, in their analyses no other predictor variables interacted with treatment resistance.[8]

Treatment refractoriness, as it was defined by most studies included in this review, is taken to mean a failure to respond to two adequate trials of antidepressant medication. This is consistent with previous research that has attempted to formalize an operational definition for treatment-resistant depression.[76] Treatment refractoriness as a predictor of TMS response hangs together with the literature on antidepressant medication, in that the more stubborn the depression, the less likely one is to find relief.[37,44] As a rule, "treatment resistance portends treatment resistance."[76] It is important to keep in mind, however, that a patient refractory to medication may not necessarily display the same degree of resistance to TMS. Indeed, as we learn more about the mechanisms of action of rTMS from those of antidepressants, we will be better suited to explain the variability in response between these interventions.

As researchers hone-in on effective treatment parameters, patients will receive better treatment, potentially leading to patients responding who may not have responded previously using older, less precise methods. A reduction in the number of partial and non-responders is therefore to be expected.

Once a patient has responded to an initial acute course of rTMS, the treatment plan that follows may involve long-term maintenance therapy with TMS. TMS maintenance therapy spanning several years has been shown to be safe and effective.[77] For older adults in this situation, it may do well to incorporate the occasional brain mapping session to control for atrophy, though it is hard to say how frequently such sessions should occur. Including more brain mapping sessions would greatly increase the overall costs associated with TMS treatment but, on the other hand, the economic burden associated with MDD[78] may far outweigh the addition of a few brain mapping sessions. If it means a life where one's depression is in partial or full remission so that one can go about his or her daily life, the added costs may be well worth it.[79]

A common criticism brought against TMS clinical trials is the perceived lack of a suitable sham method. Despite researcher's best efforts to make sham stimulation indistinguishable from active stimulation – largely by orienting the magnetic field away from the treatment location (usually at a 45- or 90-degree angle) – it has been shown that these forms of sham can be active.[80] Based on that, one might argue that the integrity of TMS clinical trials is compromised.

Through meta-analyses, however, it turns out that this is not the case. Overall, studies had acceptable levels of blinding integrity and the use of angulation versus sham coil in trials produced similar results.[81]

All the studies included in this review had serious limitations. First, small and homogeneous samples limit generalizability. Many early studies did not include patients over 65 years of age,[40] which greatly restricts drawing conclusions from the data. Take for instance the study conducted by Rumi et al.[66] It was determined that TMS accelerated the onset and augmented the therapeutic response to Amitriptyline,[66] yet, they had a relatively young sample. The mean age of the active and sham arm was 39.3 and 38.9, respectively.[66] Therefore, the results must be interpreted in that particular context.

In addition to inadequate samples, generalizing study findings are restricted by study design and methodological differences. Stimulation protocols differ markedly between studies with respect to total number of pulses, treatment duration, stimulation at different motor thresholds, site of stimulation, intervals, and duration of trains. Often enough, parameters are not held constant within the same study. Unless a study is designed to incorporate flexible dosing rather than a fixed dose, attention must be given to controlling for treatment parameters because improvements in mood could be due to more stimulation as opposed to different frequencies, motor thresholds, or sites of stimulation.

Conventional rTMS is based on the paradigmatic clinical trial that was carried out by O'Reardon et al,[8] and yet, very few studies after 2008 use these evidence-based treatment parameters. Instead, most studies in this review implemented a lower number of pulses per session and treatment sessions. These reasons alone could account for much of the futility observed in many studies. The main weakness of this review is the use of a single reviewer, which may have introduced bias in the initial search of studies. The current study also did not include treatment methods such as intermittent theta burst stimulation or deep transcranial magnetic stimulation, as they were deemed too dissimilar from conventional rTMS.

The current systematic review was concerned with determining and analyzing patient-related predictive factors for therapeutic response to TMS in major depressive disorder. At present, there are very few randomized sham-controlled studies that address this question. Of those studies that do, drawing comparisons between them is problematic because of the differences in study design. Having said that, there is accumulating evidence pointing to age[35,69] and treatment refractoriness[8] as potential predictor variables. The data in support of these variables, however, are not robust enough to warrant excluding a patient from TMS treatment.

Given the heterogeneity in the presentation of depression combined with the limited understanding of the mechanisms of action of TMS, it is not surprising that the identification of reliable patient-specific predictors of response to TMS has been challenging. Even so, this endeavor is an important one because not only will it aid clinicians in identifying suitable candidates for treatment but also it will elucidate the place of TMS in the stock of interventions for depressive disorders. For these reasons, further research is warranted.

## Disclosure

## Reference

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