JAMA Psychiatry | Original Investigation | META-ANALYSIS

Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes
A Systematic Review With Network Meta-analysis

Andre R. Brunoni, MD, PhD; Anna Chaimani, PhD; Adriano H. Moffa, PsyD, MPhil; Lais B. Razza, PsyD; Wagner F. Gattaz, MD, PhD; Zafiris J. Daskalakis, MD, PhD; Andre F. Carvalho, MD, PhD

IMPORTANCE Although several strategies of repetitive transcranial magnetic stimulation (rTMS) have been investigated as treatment of major depressive disorder (MDD), their comparative efficacy and acceptability is unknown.

OBJECTIVE To establish the relative efficacy and acceptability of the different modalities of rTMS used for MDD by performing a network meta-analysis, obtaining a clinically meaningful treatment hierarchy.

DATA SOURCES PubMed/MEDLINE, EMBASE, PsycInfo, and Web of Science were searched up until October 1, 2016.

STUDY SELECTION Randomized clinical trials that compared any rTMS intervention with sham or another rTMS intervention. Trials performing less than 10 sessions were excluded.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers used standard forms for data extraction and quality assessment. Random-effects, standard pairwise, and network meta-analyses were performed to synthesize data.

MAIN OUTCOMES AND MEASURES Response rates and acceptability (dropout rate). Remission was the secondary outcome. Effect sizes were reported as odds ratios (ORs) with 95% CIs.

RESULTS Eighty-one studies (4233 patients, 59.1% women, mean age of 46 years) were included. The interventions more effective than sham were priming low-frequency (OR, 4.66; 95% CI, 1.70-12.77), bilateral (OR, 3.96; 95% CI, 2.37-6.60), high-frequency (OR, 3.07; 95% CI, 2.24-4.21), θ-burst stimulation (OR, 2.54; 95% CI, 1.07-6.05), and low-frequency (OR, 2.37; 95% CI, 1.52-3.68) rTMS. Novel rTMS interventions (accelerated, synchronized, and deep rTMS) were not more effective than sham. Except for θ-burst stimulation vs sham, similar results were obtained for remission. All interventions were at least as acceptable as sham. The estimated relative ranking of treatments suggested that priming low-frequency and bilateral rTMS might be the most efficacious and acceptable interventions among all rTMS strategies. However, results were imprecise and relatively few trials were available for interventions other than low-frequency, high-frequency, and bilateral rTMS.

CONCLUSIONS AND RELEVANCE Few differences were found in clinical efficacy and acceptability between the different rTMS modalities, favoring to some extent bilateral rTMS and priming low-frequency rTMS. These findings warrant the design of larger RCTs investigating the potential of these approaches in the short-term treatment of MDD. Current evidence cannot support novel rTMS interventions as a treatment for MDD.

TRIAL REGISTRATION clinicaltrials.gov Identifier: PROSPERO CRD42015019855.

JAMA Psychiatry. 2017;74(2):143-153. doi:10.1001/jamapsychiatry.2016.3644
Published online December 28, 2016. Corrected on February 22, 2017.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Andre R. Brunoni, MD, PhD; Interdisciplinary Center for Applied Neuromodulation; Av. Professor Lineu Prestes, 2565, 3o andar, CEP 05508-000, São Paulo (SP), Brazil (brunoni@usp.br).

In 2010 depressive disorders were the second leading cause of disability among all diseases worldwide.[1] The treatment options available are suboptimal, with most patients being refractory.[2] Therefore, there is an urgent need to develop and optimize novel treatments for depression, such as repetitive transcranial magnetic stimulation (rTMS).

Repetitive TMS induces changes in brain activity according to the applied frequency; high-frequency (HF) rTMS (usually ≥10 Hz) induces an increase whereas low-frequency (LF) rTMS (usually ≤1 Hz) has the opposite effect.[3] According to the major depressive disorder (MDD) prefrontal asymmetry theory—ie, hypoactivity of the left and hyperactivity of the right dorsolateral prefrontal cortex (DLPFC)[4]—HF-rTMS and LF-rTMS are respectively applied over the left and right DLPFC. If both procedures are performed in the same session, the intervention is described as "bilateral." These interventions are more effective than sham in improving depressive symptoms,[3] although the effect size is modest.

Recently, novel forms of rTMS therapy have been investigated. These include: (1) deep (H-coil) TMS over the left DLPFC, which uses a different coil format that can allegedly stimulate deeper cortical and subcortical structures[5]; (2) θ-burst stimulation (TBS), either inhibiting (continuous) the right or stimulating (intermittent) the left DLPFC—TBS is potentially advantageous owing to its short session duration and neuroplasticity induction[6]; and (3) low-field synchronized TMS (sTMS), which can theoretically perform a stimulation synchronized to an individual's α frequency.[7] Finally, HF-rTMS and LF-rTMS variations, such as accelerated HF-rTMS (aTMS) and priming LF-rTMS (pTMS), have also been tested. The former intervention applies 4 or more HF-rTMS stimulation sessions per day to intensify antidepressant response, whereas pTMS consists of "priming" the strategy by delivering high-frequency rTMS before LF-rTMS, theoretically boosting LF-rTMS efficacy.[8]

This systematic review and network meta-analysis (NMA) aims to establish a clinically meaningful hierarchy of efficacy and acceptability of different rTMS modalities for MDD treatment through the integration and synthesis of available evidence. In contrast to standard pairwise meta-analyses, NMAs allow the comparison of different rTMS interventions, even if they have not been directly compared in head-to-head trials.[9]

Key Points

Question What is the most effective and tolerable repetitive transcranial magnetic stimulation (rTMS) intervention for acute depressive disorder?

Findings In this systematic review and network meta-analysis collecting data from 81 randomized clinical trials (4233 patients), priming low-frequency, bilateral, high-frequency, low-frequency, and θ-burst rTMS—but not novel (accelerated, synchronized, and deep rTMS) strategies—were more effective than sham regarding response rates. All interventions were at least as acceptable as sham.

Meaning Only few differences were found in clinical efficacy and acceptability between the different rTMS; current evidence cannot support novel rTMS interventions for treating acute depression.

Methods

A study protocol was registered with PROSPERO and published a priori (Supplement 1).[10] This report also adheres to the PRISMA statement[11] and its extension for NMA.[12]

Literature Review

We searched the PubMed/MEDLINE, EMBASE, PsycInfo, and Web of Science from inception up until October 1, 2016. The full search strategy is described in eAppendix 1 in Supplement 2. Two authors (A.R.B. and A.F.C.) independently performed the search. Disagreements were discussed with a third author (Z.J.D.) and resolved by consensus.

Eligibility Criteria

Only randomized clinical trials (RCTs) enrolling patients with a primary diagnosis of an acute unipolar or bipolar depressive episode, including those that did not preclude comorbidities, such as anxiety or personality disorders, were included. We excluded studies that enrolled participants with secondary mood disorders (eg, poststroke depression).

We included trials that compared at least 2 of the following interventions: LF-rTMS over the right DLPFC, HF-rTMS over the left DLPFC, bilateral rTMS (LF over the right and HF over the left DLPFC), TBS (including intermittent TBS over the left DLPFC, continuous over the right DLPFC or bilateral), pTMS over the right DLPFC, aTMS over the left DLPFC, sTMS, dTMS over the left DLPFC, and sham. Also, 1 Hz or less and 5 Hz or more defined low-frequency and high-frequency, respectively.

Exclusion criteria were other study designs, trials performing less than 10 rTMS sessions, using frequencies between 2 to 4 Hz, or comparing only 1 modality of rTMS intervention.

Data Extraction and Outcome Measures

The first and last authors independently performed the search and extracted the data according to an a priori elaborated data extraction checklist. For crossover (within-participants) trials, we considered only data from the first period (before crossover).

The primary outcome measures were response rates and acceptability (dropout rate). Remission rates were a secondary outcome.

Response and remission rates were obtained from each study based on the study primary outcome scale. If the study did not specify the primary outcome scale, response and remission rates would be obtained based on the Hamilton Depression Rating Scale, 17-items (HDRS-17). Response was defined as 50% or greater improvement from baseline according to the study primary depression scale. Remission was defined as 7 or less, 8 or less, or 10 or less on the HDRS-17, HDRS-21, or Montgomery-Åsberg Depression Rating Scale (MADRS), respectively. Responders and remitters to treatment were calculated on an intention-to-treat basis, ie, analyses were based on the total number of participants at baseline. Therefore, we

used the most conservative scenario considering the participants that did not provide outcome data as failures.

For acceptability, we assessed the number of patients that initially enrolled, dropped out, and completed the study to estimate the dropout rate.

We also extracted data on the following characteristics that may act as effect modifiers: sex, age, recruitment of only treatment-resistant depression samples, bipolar depression, baseline depression severity, parameters of stimulation (frequency in hertz, motor threshold, number of sessions, number of pulses per session, and coil positioning method), and sham procedure. Also, studies were classified as "add-on," when rTMS was delivered to patients in a stable pharmacological regimen; "monotherapy," when rTMS was delivered in antidepressant-free patients; and "augmentation," when rTMS and the pharmacological intervention started simultaneously, rTMS being used to enhance ("accelerate") the efficacy of the pharmacotherapy.

Finally, we contacted the trial authors to request missing outcome data or other missing characteristics when these could not be obtained from the available report.

Risk of Bias Assessment

Two independent authors (A.R.B. and A.H.M.) evaluated the risk of bias (interrater reliability, 0.84) for each domain described in the Cochrane risk of bias tool.[13] Studies were then further classified in an overall risk of bias category (eAppendix 2 in Supplement 2).

Evaluation of Clinical Assumptions

We examined whether the identified studies were sufficiently homogenous by comparing qualitatively study and population characteristics across eligible trials. Transitivity (ie, the assumption that one can validly compare indirectly treatments A and B via 1 or more anchor treatments)[14] is the fundamental premise underlying NMA and needs careful evaluation. We evaluated the plausibility of transitivity in our data by initially assessing the similarity of the competing interventions when they were evaluated in studies with different designs (eg, if they were administered in the same way in active- and sham-controlled trials) and then comparing the distribution of the potential effect modifiers with enough data across the different direct comparisons.[15]

Data Synthesis and Assessment of Statistical Assumptions

We initially performed standard pairwise meta-analyses to estimate the available direct relative effects of the competing interventions using a random-effects model in Stata statistical software (metan package, version 3.03; StataCorp).[16] In these analyses we estimated a different heterogeneity parameter for each pairwise comparison and we assessed statistical heterogeneity using the statistic and its 95% CIs.[17,18]

Subsequently, we performed NMA for each outcome using the approach of multivariate meta-analysis in Stata statistical software (network package, version 1.2.0; StataCorp)[19] and assuming a common heterogeneity parameter across all comparisons within an outcome.[20] Results are presented as summary relative odds ratios (ORs) for every possible pairwise comparison. In the text, ORs greater than 1 favor the first mentioned intervention. Treatment hierarchy was estimated using the surface under the cumulative ranking curve (SUCRA), which expresses the effectiveness and acceptability of each treatment compared with a hypothetical treatment that would be ranked always first without uncertainty.[21] To evaluate the magnitude of statistical heterogeneity (ie, the differences in relative effects among trials beyond to what would be expected by chance) in each network we compared the heterogeneity parameter (τ) with the empirical distributions suggested by Turner et al.[22] We also estimated the predictive intervals of the network estimates to assess the level of additional uncertainty anticipated in future studies owing to the heterogeneity[23] using the network graphs package in Stata statistical software (version 1.2.1; StataCorp).[24,25]

We assessed the assumption of consistency (ie, that the relative effects from obtained direct and indirect evidence from the same treatment comparison are in agreement) locally using the loop-specific approach (assuming a common heterogeneity across all loops in each outcome) and the node-splitting (or side-splitting) method.[24,26,27] We also used the design-by-treatment interaction model that accounts for all possible sources of inconsistency in the network and provides a global test for assessing inconsistency in the entire network.[28]

Small-Study Effects and Additional Analyses

We evaluated the presence of small-study effects for each outcome by drawing a comparison-adjusted funnel plot[25] that accounts for the fact that different studies compare different sets of interventions. Funnel plots included all comparisons of an active intervention against sham.

Whenever important heterogeneity or inconsistency was found we considered the predefined clinical-demographic characteristics that may act as effect modifiers as possible sources. Specifically, we ran network meta-regression using as covariates the following variables for which sufficient data were available: age of participants, baseline severity, method (monotherapy, add-on, augmentation), inclusion of treatment-resistant depression (TRD, which was analyzed according to the number of failed trials and in a binary fashion, owing to imprecisions in the definition of TRD[29]), inclusion of bipolar patients, percentage of females, and follow-up period.

We finally performed 3 sensitivity analyses for the 2 primary outcomes in which: (1) we excluded studies at high risk of overall bias; (2) we included only studies on primary use of rTMS, hence on treatment-resistant patients and as an add-on intervention; and (3) we synthesized only studies with at least 15 sessions.

Results

Characteristics and Risk of Bias of the Included Studies

Of 1121 references, 1040 were excluded for several reasons, and 81 RCTs were included[5,7,30-107] (70 two-arm and 11 three-arm studies), which provide information on 101 comparisons between 9 different rTMS groups (including sham) (**Figure 1**). Note that in Stern et al[100] a study group that performed low-frequency rTMS over the left DLPFC was not included. HF-rTMS vs sham was the most prevalent comparison

Figure 1. Flowchart of the Study Selection Process

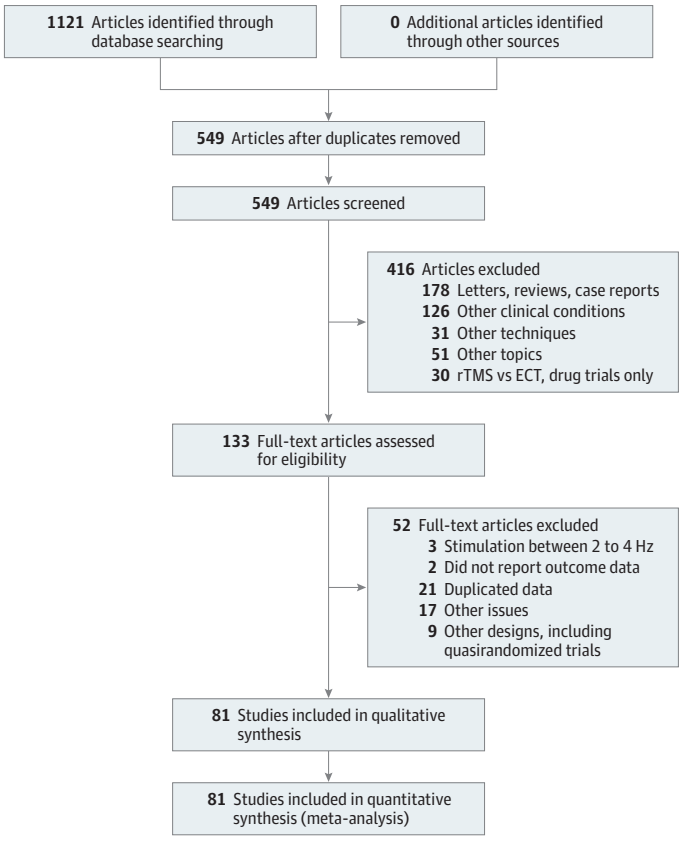
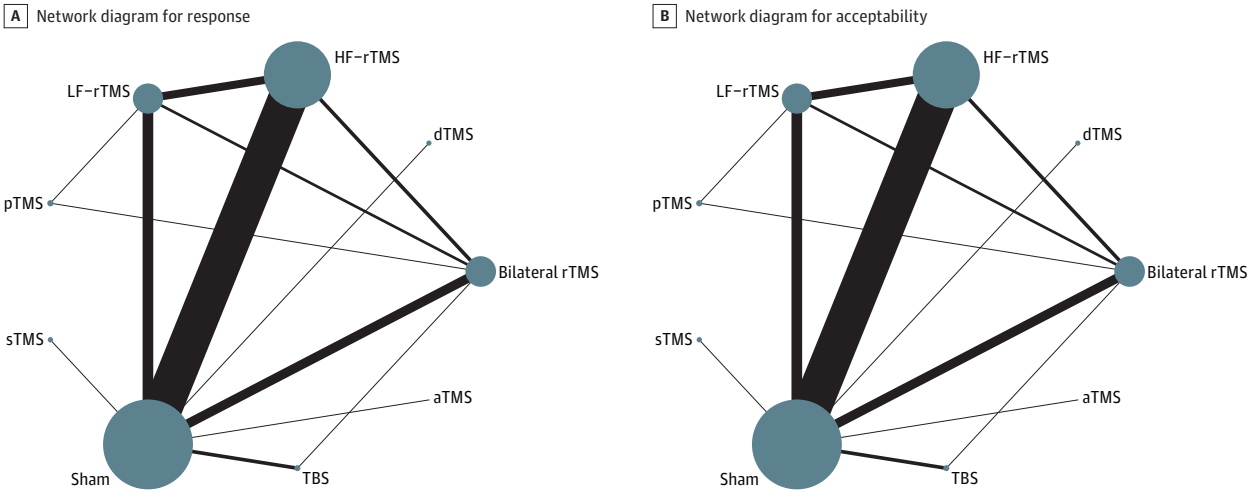


Figure 2. Network Diagrams



aTMS indicates accelerated TMS; dTMS, "deep" (H-coil) TMS; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation. A, Response; and B, acceptability. The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines proportional to the number of studies evaluating each direct comparison.

(**Figure 2**), with the largest contribution in the estimation to the entire network for both response (eFigure 1 in Supplement 2) and remission (eFigure 2 in Supplement 2).

We found that 21.0%, 67.9%, and 11.1% of studies had an overall low, unclear, and high bias risk, respectively. Mostly, unclear risk of bias occurred owing to imprecisions in report-

Table. Relative Odds Ratios Estimated From the Network Meta-analysis Comparing Every Pair of the 9 Interventions With Respect to Response (Lower Triangle) and Acceptability (Upper Triangle)[a]

	pTMS	Bilateral rTMS	HF-rTMS	TBS	aTMS	LF-rTMS	dTMS	sTMS	Sham
pTMS	...	0.43 (0.16-1.14)	0.29 (0.10-0.87)	0.23 (0.05-1.06)	0.27 (0.00-17.43)	0.27 (0.09-0.80)	0.42 (0.11-1.58)	0.23 (0.07-0.77)	0.27 (0.09-0.80)
Bilateral rTMS	1.18 (0.47-2.98)	...	0.68 (0.41-1.14)	0.54 (0.17-1.75)	0.64 (0.01-36.25)	0.62 (0.36-1.07)	0.98 (0.39-2.44)	0.53 (0.25-1.12)	0.64 (0.39-1.03)
HF-rTMS	1.52 (0.55-4.16)	1.29 (0.76-2.20)	...	0.79 (0.26-2.43)	0.94 (0.02-52.26)	0.92 (0.55-1.54)	1.43 (0.62-3.29)	0.78 (0.42-1.47)	0.94 (0.70-1.25)
TBS	1.83 (0.50-6.70)	1.55 (0.60-4.03)	1.21 (0.48-3.00)	...	1.18 (0.02-75.27)	1.15 (0.36-3.75)	1.81 (0.48-6.86)	0.99 (0.29-3.34)	1.18 (0.40-3.49)
aTMS	2.07 (0.11-38.55)	1.76 (0.11-28.69)	1.36 (0.09-21.61)	1.13 (0.06-20.11)	...	0.98 (0.02-55.58)	1.53 (0.03-91.24)	0.84 (0.01-48.01)	1.00 (0.02-55.27)
LF-rTMS	1.97 (0.74-5.24)	1.67 (0.97-2.87)	1.30 (0.83-2.02)	1.07 (0.41-2.79)	0.95 (0.06-15.32)	...	1.57 (0.63-3.90)	0.85 (0.41-1.78)	1.02 (0.64-1.64)
dTMS	3.12 (0.70-13.85)	2.65 (0.79-8.89)	2.06 (0.66-6.43)	1.71 (0.42-6.90)	1.51 (0.08-28.99)	1.59 (0.49-5.17)	...	0.55 (0.21-1.43)	0.65 (0.30-1.42)
sTMS	4.29 (0.92-20.11)	3.65 (1.02-13.06)	2.83 (0.84-9.49)	2.35 (0.55-10.05)	2.08 (0.11-41.00)	2.18 (0.63-7.62)	1.38 (0.28-6.83)	...	1.20 (0.68-2.10)
Sham	4.66 (1.70-12.77)	3.96 (2.37-6.60)	3.07 (2.24-4.21)	2.54 (1.07-6.05)	2.25 (0.14-35.03)	2.37 (1.52-3.68)	1.49 (0.50-4.47)	1.08 (0.34-3.49)	...

Abbreviations: aTMS, accelerated TMS; dTMS, "deep" (H-coil) TMS; elipses, not applicable; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation.

[a] τ = 0.47 for response and τ = 0 for acceptability. Values larger than 1 favor the intervention in the lower triangle for response and the intervention in the upper triangle for acceptability. The interventions in the diagonal have been ordered according to their estimated relative ranking for response. Data presented as odds ratios (95% CIs) and τ is the heterogeneity standard deviation for each outcome.

ing randomization or allocation procedures and/or imperfect blinding (eAppendix 2 in Supplement 2).

Evaluation of Clinical Assumptions

Of 4233 patients, with a mean age of 46 years, 2501 were women (59.1%). Most trials (74.1%) recruited only treatment-resistant depressed patients, performed 10 to 15 rTMS sessions (69.1%), used the "5cm" or "6cm" method for coil positioning (79%), and used rTMS as an add-on therapy (69.1%) (eTable 1 in Supplement 2). No important discrepancies were present regarding age, baseline severity, sex distribution, and number of sessions across the available direct comparisons (eFigure 3 in Supplement 2). Therefore, the assumption of transitivity is likely to hold in our data.

Relative Effects and Relative Ranking of Interventions

Response

According to direct evidence, bilateral, HF-rTMS and LF-rTMS and TBS were statistically significantly more effective than sham with respect to response (OR, 3.39 [95% CI, 1.91-6.02]; OR, 3.28 [95% CI, 2.33-4.61]; OR, 2.48 [95% CI, 1.22-5.05]; OR, 2.57 [95% CI, 1.17-5.62], respectively) (eTable 2 in Supplement 2). pTMS has not been directly compared with sham (Figure 2). None of the active interventions appeared to perform better when contrasted to another active comparator.

According to the NMA results, bilateral (OR, 3.96; 95% CI, 2.37-6.60), HF-rTMS (OR, 3.07; 95% CI, 2.24-4.21), and LF-rTMS (OR, 2.37; 95% CI, 1.52-3.68) as well as pTMS (OR, 4.66; 95% CI, 1.70-12.77) and TBS (OR, 2.54; 95% CI, 1.07-6.05) appeared to be more effective than sham (**Table**). Also, bilateral rTMS was more effective than sTMS (OR, 3.65; 95% CI, 1.02-13.06) but no other important difference was found between the 8 active rTMS interventions.

According to the SUCRAs, pTMS (84.5%) and bilateral rTMS (82.0%) were ranked in the 2 first positions for response (eFigure 4 in Supplement 2).

Acceptability

Direct evidence suggested that bilateral rTMS is more acceptable than LF-rTMS (OR, 2.43; 95% CI, 1.11-5.30) (eTable 3 in Supplement 2). However, this finding is primarily based on Fitzgerald et al[54] with 92% weight in the estimation, whereas in Pallanti et al[92] these interventions did not differ in terms of acceptability. No important differences were found between the dropout rates of the other interventions.

The NMA model suggested that pTMS is significantly more acceptable than HF-rTMS (OR, 3.45; 95% CI, 1.15-10.0) and LF-rTMS (OR, 3.70; 95% CI, 1.25-11.1), as well as sTMS (OR, 4.35; 95% CI, 1.3-14.29) and sham (OR, 3.70; 95% CI, 1.25-11.11) (Table).

The estimated relative ranking for acceptability was generally compatible with the response ranking, hence pTMS and bilateral rTMS were placed in the 2 first ranks (eFigure 5 in Supplement 2).

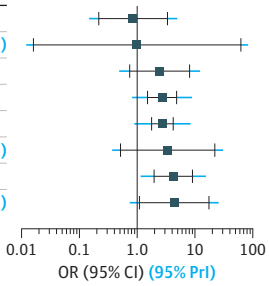
Remission

Results were similar to response, although more uncertain. Direct evidence implied that bilateral rTMS is more effective than HF-rTMS (OR, 4.02; 95% CI, 1.3-12.35) and both interventions

Figure 3. Forest Plot Showing the Network Relative Odds Ratios (ORs) With Their 95% CIs and Predictive Intervals (PrI)

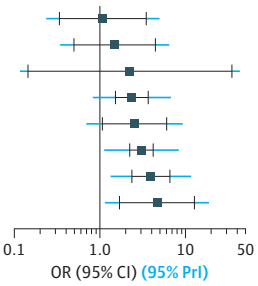
A Remission

Active Device	OR (95% CI) (95% PrI)
sTMS	0.85 (0.22-3.35) (0.15-4.94)
aTMS	1.00 (0.02-62.31) (0.01-83.19)
dTMS	2.45 (0.74-8.07) (0.49-12.28)
LF-rTMS	2.70 (1.51-4.82) (0.82-8.89)
HF-rTMS	2.73 (1.78-4.20) (0.89-8.40)
TBS	3.37 (0.52-22.05) (0.37-30.69)
Bilateral rTMS	4.22 (1.96-9.05) (1.15-15.47)
pTMS	4.37 (1.10-17.47) (0.74-25.69)



B Response

Active Device	OR (95% CI) (95% PrI)
sTMS	1.08 (0.34-3.49) (0.24-4.98)
dTMS	1.49 (0.50-4.47) (0.34-6.48)
aTMS	2.25 (0.14-35.03) (0.12-43.39)
LF-rTMS	2.37 (1.52-3.68) (0.83-6.78)
TBS	2.54 (1.07-6.05) (0.70-9.32)
HF-rTMS	3.07 (2.24-4.21) (1.12-8.37)
Bilateral rTMS	3.96 (2.37-6.60) (1.34-11.70)
pTMS	4.66 (1.70-12.77) (1.15-18.91)



aTMS indicates accelerated TMS; dTMS, "deep" (H-coil) TMS; HF, high frequency; LF, low frequency; pTMS, priming TMS; sTMS, synchronized TMS; TBS, θ-burst stimulation.

perform better than sham (OR, 5.75; 95% CI, 1.93-17.24 and OR, 2.72; 95% CI, 1.92-3.86, respectively) (eTable 4 in Supplement 2).

Results from NMA implied that bilateral rTMS performs better than sTMS in terms of remission (OR, 4.95; 95% CI, 1.03-23.71) while bilateral (OR, 4.22; 95% CI, 1.96-9.05), LF-rTMS (OR, 2.70; 95% CI, 1.51-4.82), HF-rTMS (OR, 2.73; 95% CI, 1.78-4.20), and pTMS (OR, 4.37; 95% CI, 1.10-17.47) are more effective than sham (eTable 5 in Supplement 2).

Finally, bilateral rTMS and pTMS were ranked again in the 2 first places with respect to the relative ranking of the interventions (eFigure 6 in Supplement 2).

Evaluation of Statistical Heterogeneity and Inconsistency

Network heterogeneity was moderate to large for response (τ = 0.47) considering the predictive distributions for a subjective outcome.[108] The prediction intervals suggest that increased uncertainty is anticipated in a future study for the comparisons LF-rTMS vs sham and TBS vs sham (**Figure 3**). The network heterogeneity for acceptability was estimated being zero. However, important heterogeneity was present for HF-rTMS vs bilateral (τ = 0.58; I^2, 42% [95% CI, 0%-80%]). Compared with response, heterogeneity for remission was larger and also the confidence and/or prediction intervals for some comparisons were wider (Figure 3).

The design-by-treatment interaction model did not suggest the presence of statistical inconsistency for any outcomes (response, P = .92; acceptability, P = .89; remission, P = .35).

The loop-specific approach identified 1 loop (formed by bilateral, HF-rTMSand LF-rTMS) presenting statistical inconsistency for remission (inconsistency factor, 1.74; 95% CI, 0.19-3.30) and none for response and acceptability (eFigure 7 in Supplement 2). Similar conclusions were derived by the side-splitting method, which found that direct and indirect evidence are not in statistical agreement for the comparison of bilateral vs LH-rTMS and bilateral vs HF-rTMS for remission (eTable 6 in Supplement 2).

Small-Study Effects and Additional Analyses

The comparison-adjusted funnel plots appeared symmetrical for both efficacy outcomes, but rather asymmetrical for acceptability, suggesting that small studies tended to favor the active interventions more than large studies regarding dropouts (eFigure 8 in Supplement 2).

No explanatory variables used in meta-regression reduced the estimated heterogeneity for response, the regression coefficients were nonsignificant and close to zero; however, this finding might be partly explained by low power to detect important associations.

The sensitivity analysis in which we excluded studies assessed at high risk of overall bias gave similar but less precise results compared with our primary analysis (eTable 7 in Supplement 2). Also, the results did not change materially when we synthesized only studies that used rTMS as an add-on therapy on treatment resistant patients; nevertheless the heterogeneity of this restricted analysis was much smaller (almost zero) for response compared with the primary analysis (eTable 8 in Supplement 2). When we restricted the analysis to studies with at least 15 sessions results were even more uncertain and only bilateral, LF-rTMS and HF-rTMS appeared to be more effective than sham (eTable 9 in Supplement 2).

Discussion

We compared the effects of 8 rTMS interventions (accelerated, bilateral, deep, high-frequency, low-frequency, priming low-frequency, synchronized, and θ-burst rTMS) and sham in MDD using data from 81 RCTs (4233 patients with depression) using standard pairwise and network meta-analyses. Only pTMS, bilateral, HF, TBS, and LF were superior to sham for response and, excluding TBS, for remission. Moreover, bilateral rTMS appeared to be superior to sTMS. The estimated relative ranking of treatments implied that pTMS and bilateral rTMS perform better among all rTMS interventions in terms of efficacy. Nonetheless, findings were imprecise for most comparisons between active interventions and therefore no definite evidence of superiority could be supported for any particular intervention. Finally, acceptability of all active interventions were similar to sham, confirming that they were well tolerated.

pTMS was found to be more acceptable (ie, with smaller dropout rate) than HF-rTMS, LF-rTMS, sTMS, and sham. This intervention consists of inducing greater excitability suppression by priming a low-frequency protocol with a short period of higher-frequency stimulation—a mechanism described as homeostatic plasticity, and based on the Bienenstocke-Coopere-Munro (BCM) theory that predicts that LTP/LTD synaptic activity is homeostatically adjusted to the previous level of postsynaptic activity.[109] Notwithstanding, the body of evidence is small, as only 2 RCTs, both conducted by the same group and not sham-controlled, were conducted for MDD.[8,53]

Previous standard meta-analyses[110] have also demonstrated the superiority of bilateral rTMS vs sham. Its efficacy relies on the assumption of combining high-frequency (excitability increasing) stimulation over the hypoactive left DLPFC and low-frequency (excitability decreasing) rTMS over the hyperactive right DLPFC.[111] Bilateral rTMS could be more effective than HF-rTMS and LF-rTMS. In fact, direct evidence showed that bilateral rTMS was superior to HF for remission and network evidence showed that it was also superior to synchronized TMS for response and remission. Our findings suggest that larger RCTs should be performed to further explore the efficacy of this intervention.

Also, TBS was more effective than sham for treating MDD. This finding merits further clinical investigation, because the TBS session lasts only approximately 5 minutes compared with 30 minutes or longer for other strategies.

Finally, deep, synchronized, and accelerated TMS were not more effective than sham based on the ITT data and our statistical approach. Nonetheless, these interventions were insufficiently investigated and warrant more controlled studies to determine their efficacy.

Credibility of Evidence and Limitations of the Present Review

We combined the contributions of the direct comparisons for the 2 primary outcomes with the risk of bias assessments to obtain the percentage of information coming from low, unclear, and high risk of bias studies.[112] The data presented in eFigure 9 in Supplement 2 imply that the bulk of evidence for both primary outcomes comes from studies at unclear risk of bias. Nonetheless, in our sensitivity analysis results were not affected by risk of bias.

Most studies presented an unclear risk of bias, mainly owing to blinding inadequacy, which is a well-known methodological shortcoming in rTMS RCTs.[113] Blinding is particularly vulnerable in studies using an angled coil as sham and also in studies comparing 2 or more active stimulations. Owing to such issues, most trials presented an unclear blinding bias risk.

We could not formally examine the impact of every potential effect modifier on transitivity plausibility owing to lack of data. However, we did not find important discrepancies across the direct comparisons in the distribution of study characteristics for which enough data were available.

We found moderate inconsistency in 1 particular loop of the network for both efficacy outcomes as well as moderate to large heterogeneity. This finding could be explained by the study by Blumberger et al[37] that, despite being similar to previous bilateral rTMS trials, used an optimized strategy (more treatment sessions, magnetic resonance imaging–based localization of DLPFC, and higher intensity) not observed previously.

Some nodes were not well linked (Figure 2), which could have caused the imprecise relative effect estimates particularly when comparing different active interventions. Also, some of the active-sham treatment comparisons (eg, dTMS, sTMS) are based on 1 study, warranting further RCTs. Moreover, owing to the low number of TBS studies, "TBS" as shown in Figure 2 represents results from left iTBS, right cTBS, and bilateral TBS, which were examined together.

The comparison-adjusted funnel plots suggested that small-study effects may operate for the outcome of acceptability but not for the efficacy outcomes. Moreover, we believe publication bias is unlikely considering our comprehensive search strategy that also encompassed unpublished data as well as studies presented in conferences and reference lists from previous meta-analyses.

Finally, most trials handled missing data using the last observation carried forward (LOCF) approach, which, although broadly used, can introduce bias.[114] However, this is a typical approach followed in psychiatric trials and there is no way thus far to reduce this bias at the meta-analysis level because the systematic reviewers only have access to LOCF imputed data.

Conclusions

Differences in clinical efficacy and acceptability between rTMS modalities might exist but could not be confirmed from the available data. Our data suggest that bilateral rTMS is probably more effective than LF-rTMS because their relative OR was only marginally not statistically significant and similarly acceptable as both LF-rTMS and HF-rTMS; this finding implies that bilateral rTMS could be considered also prior to these techniques. The positive results for TBS and pTMS compared with sham warrant further investigation. Novel interventions (accelerated, deep, and synchronized rTMS) were not found to be more effective than sham. Nonetheless, available evidence on interventions other than bilateral, LF-rTMS and HF-rTMS is scarce. Thus, new high-quality RCTs are necessary to establish their efficacy with a higher degree of credibility.

ARTICLE INFORMATION

Accepted for Publication: October 26, 2016.

Correction: This article was corrected for errors on February 22, 2017.

Published Online: December 28, 2016. doi:10.1001/jamapsychiatry.2016.3644

Author Affiliations: Service of Interdisciplinary Neuromodulation, Department and Institute of Psychiatry, Laboratory of Neurosciences (LIM-27), University of São Paulo, São Paulo, Brazil (Brunoni, Moffa, Gattaz); Interdisciplinary Center for Applied Neuromodulation University Hospital, University of São Paulo, São Paulo, Brazil (Brunoni, Moffa, Razza, Gattaz); Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece (Chaimani); Temerty Centre for Therapeutic

Brain Intervention, Ontario, Canada (Daskalakis); Campbell Family Research Institute, Ontario, Canada (Daskalakis); Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto, Ontario, Canada (Daskalakis); Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil (Carvalho).

Author Contributions: Dr Brunoni had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Brunoni, Gattaz, Carvalho.
Acquisition, analysis, or interpretation of data: Brunoni, Chaimani, Moffa, Razza, Daskalakis, Carvalho.
Drafting of the manuscript: Brunoni, Chaimani, Razza.
Critical revision of the manuscript for important intellectual content: Brunoni, Chaimani, Moffa, Gattaz, Daskalakis, Carvalho.
Statistical analysis: Brunoni, Chaimani, Daskalakis.
Administrative, technical, or material support: Brunoni, Gattaz.
Supervision: Brunoni, Carvalho.
Other: Moffa.

Conflict of Interest Disclosures: In the past 3 years, Dr Daskalakis received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. Dr Daskalakis has also served on the advisory board for Sunovion, Hoffmann-La Roche Limited, and Merck, and received speaker support from Eli Lilly. The Brain Intervention unit from CAMH is supported by the Ontario Mental Health Foundation (OMHF), the Canadian Institutes of Health Research (CIHR), the Brain and Behaviour Research Foundation, the Temerty Family, and Grant Family, and through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Institute. Dr Brunoni is supported by the following grants: 2013 NARSAD Young Investigator from the Brain & Behavior Research Foundation (Grant Number 20493), 2013 FAPESP Young Researcher from the São Paulo State Foundation (Grant Number 20911-5), and National Council for Scientific and Technological Development (CNPq, Grant Number 470904). Dr Brunoni is a recipient of a research fellowship award from CNPq (303197). The Laboratory of Neuroscience (LIM27) receives financial support from the Associação Beneficente Alzira Denise Hertzog da Silva (ABADHS). Drs Carvalho and Brunoni are supported by a research fellowship award from CNPq (Level 2). The authors have no other conflicts of interest to disclose.

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