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FULL-LENGTH ORIGINAL RESEARCH

Repetitive transcranial magnetic stimulation for the treatment of drug-resistant epilepsy: A systematic review and individual participant data meta-analysis of real-world evidence

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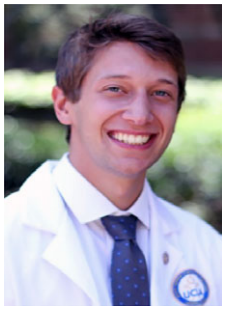

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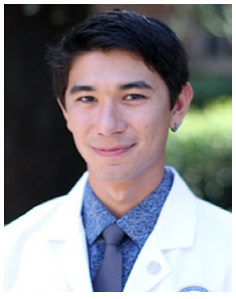

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Summary

Objective: To perform a systematic review and meta-analysis of real-world evidence for the use of low-frequency repetitive transcranial magnetic stimulation (rTMS) in the treatment of drug-resistant epilepsy.

Methods: We systematically searched PubMed, Scopus, Medline, and clinicaltrials.gov for all relevant articles. Relevant patient and stimulation predictors as well as seizure outcomes were assessed. For studies with and without individual participant data (IPD), the primary outcomes were the rate of "favorable response" (reduction in seizure frequency ≥50%) and pooled event rate of mean reduction in seizure frequency, respectively. Outcomes were assessed with comparative statistics and random-effects meta-analysis models.

Results: Of 3,477 identified articles, 12 met eligibility and were included in this review. We were able to obtain IPD for 5 articles constituting 34 participants. Univariate analysis on IPD identified greater favorable response event rates between participants with temporal seizure focus versus extratemporal (50% vs. 14%, p = 0.045) and between participants who were stimulated with a figure-8 coil versus other types (47% vs. 0%, p = 0.01). We also performed study-level meta-analysis on the remaining 7 studies without IPD, which included 212 participants. The pooled mean event rate of 50% seizure reduction using low-frequency rTMS was 30% (95% confidence interval [CI] 12–57%). Sensitivity analysis revealed that studies with a mean age ≤21 years and studies using targeted stimulation had the highest seizure reduction rates compared to studies with a mean age >21 years (69% vs. 18%) and not using a targeted stimulation (47% vs. 14–20%). Moreover, we identified high interstudy heterogeneity, moderate study bias, and high publication bias.

Significance: Real-world evidence suggests that low-frequency rTMS using a figure-8 coil may be an effective therapy for the treatment of drug-resistant epilepsy in pediatric patients. This meta-analysis can inform the design and expedite recruitment of a subsequent randomized clinical trial.

KEY WORDS: Repetitive transcranial magnetic stimulation, Epilepsy, Treatment, Outcome predictors, Meta-analysis.

Transcranial magnetic stimulation (TMS) has become an important noninvasive clinical tool for neuronal perturbation.[1] Single-pulse stimulation has been used in the diagnosis and assessment of corticospinal connectivity following neuronal damage and degeneration.[2] A TMS paradigm known as repetitive transcranial magnetic stimulation

Key Points

- We identified a 30% reduction in seizure frequency following low-frequency rTMS for the treatment of refractory epilepsy
- The most common adverse events reported following rTMS were headaches, fatigue, dizziness, hearing loss/tinnitus, difficulty sleeping, and tremor
- Pediatric patients younger than 21 years of age, use of figure-8 coil, and temporal lobe epileptic focus were each predictors of favorable seizure outcome
- Limitations of the primary studies included high inter-study heterogeneity of treatment variables and patient variables, incomplete/inconsistent reporting, and statistically underpowered studies
- We have presented designed considerations that should be considered for a future randomized clinical trial of rTMS in pediatric epilepsy

(rTMS) can bidirectionally modulate cortical excitability by adjusting stimulation parameters. Generally, cortical excitability is enhanced following rapid stimulation (≥5 Hz) and is reduced by low-frequency stimulation (≤1 Hz).[3,4] In Long-Term Potentiation and Long-Term Depression, high and low stimulation frequencies, respectively, mediate similar bidirectional changes in neuronal excitability. Therefore, rTMS is thought to induce changes in cortical excitability through a related mechanism.[3,5] In 2008, the FDA approved several rTMS devices for the treatment of treatment-resistant depression.

It also holds promising therapeutic potential in the treatment of other neuropsychiatric disorders such as schizophrenia, Parkinson's disease, neuropathic pain, and intractable epilepsy.[6–8]

Epilepsy is a prevalent, etiologically diverse disorder of altered cortical excitability that affects an estimated 1 in 26 individuals over their lifetime.[9] Nearly one-third of patients with epilepsy do not respond to antiepileptic drugs (AEDs). These patients with drug-resistant epilepsy experience significant morbidity.[10,11] For epilepsy phenotypes that are not amenable to resective surgical treatments, low-frequency rTMS has emerged as a means of suppressing cortical excitability. This capability suggests that it might be effective in the noninvasive treatment of intractable epilepsy.[4,12]

Low-frequency rTMS therapy has been reliably demonstrated to be a safe clinical intervention.[6] However, its efficacy in seizure attenuation remains less well established. Several previous reports have indicated that low-frequency rTMS is capable of reducing seizure number and epileptic discharges, often in a robust manner.[13–16] However, other randomized clinical trials have shown no effect above control.[17–19] This discrepancy in results could be attributed to the highly heterogeneous nature of the studies involved. Studies differ in regard to patient populations that are often highly heterogeneous, with nonuniform etiologies for epilepsy.[17,18] Treatment parameters such as stimulation strength, frequency, and duration, as well as coil types are variable.[13,16,20] Outcome measures are heterogeneously reported. Additionally, many of these observational studies are underpowered and lack a comparison arm.[15,21,22]

Although a recent meta-analysis suggests that rTMS reduces seizure frequency in a significant albeit not clinically relevant manner,[14] this analysis is limited by a paucity of data and the heterogeneity of the studies involved. We therefore sought to improve upon the methodological limitations of the existing meta-analysis through an expanded, up-to-date, and transparent literature search strategy unrestricted by publication date or language and perform an individual participant data meta-analysis to address study heterogeneity.

At a recent 2014 Network for Excellence in Health Innovation round table meeting in Washington, D.C., real-world evidence (RWE) was thought to be a potentially transformative force in U.S. health care.[23] RWE is defined as data derived from medical practice among heterogeneous sets of patients in real-life practice settings. Compared to traditional clinical trials, it has several benefits, including expedited generation of research hypotheses that can inform the design of randomized controlled trials (RCTs) and the ability to augment conventional RCTs with data from patients whose diversity reflects real-world practice. Our goal was to provide more conclusive real-world evidence about the efficacy

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and potential role of low-frequency rTMS in the treatment of intractable epilepsy.

Research question

We performed a systematic review and individual participant data (IPD) meta-analysis and reported our findings in concordance with PRISMA[24] and MOOSE guidelines[25] to address the following primary and secondary study questions:

Primary question

How effective is low-frequency rTMS treatment for reduction of seizure frequency in patients with drug-resistant epilepsy?

Secondary question

Are there population characteristics or rTMS stimulation parameters that may predict greater efficacy at reducing seizure burden?

Type of study design used

IPD meta-analysis is recognized as the gold standard methodology for conducting meta-analysis. It allows researchers to: (1) address questions not addressed in the original publications (e.g., determine predictors of outcomes in a study that had an alternative objective); (2) use common definitions, coding, and cut-points; (3) account for the variability in clinical follow-up times; and (4) enhance statistical power in identifying participant characteristics or stimulation parameters that predict seizure outcomes.

However, owing to poor response rate, we were unable to obtain IPD for a significant number of relevant studies. We therefore performed a traditional meta-analysis of study-level statistics in addition to IPD meta-analysis.

Methods

Protocol and registration

We developed a protocol prior to conducting the review but did not register it.

Search strategy

We identified eligible studies in a comprehensive manner as follows. First, an independent information specialist designed an electronic literature search strategy using variations of the following search terms: "epilepsy," "seizures," and "repetitive transcranial magnetic stimulation" (see Appendix S1 for full list of MESH terms). Our search was restricted to human studies but was not restricted by language. These terms were used to search PubMed, Medline, and Scopus databases as well as Clinicaltrials.gov on (02/02/2016). Our research team consists of experts in pediatric epilepsy (G.M.I., A.G.W., and A.F.), rTMS technology (B.S.), and health-research methodology (N.A. and A.F.).

Eligibility criteria

Inclusion criteria for the studies were the following:

[1] Observational cohort studies or randomized clinical trials
[2] Consecutive participants
[3] Participants with a diagnosis of drug-resistant epilepsy (≥2 seizures/month with AED therapy)
[4] Therapeutic intervention with low-frequency (≤1 Hz) rTMS
[5] Seizure frequency reported

Exclusion criteria for the studies were the following:

[1] Single case reports
[2] Participants presented with anomalous features
[3] Reviews and meta-analyses
[4] Participants with status epilepticus
[5] Majority of participants (>50%) that have previously undergone palliative surgical procedures (i.e., corpus callosotomy, multiple subpial transection, or vagal nerve stimulator insertion)
[6] rTMS stimulation protocol inadequately described (i.e., no description of stimulation frequency, coil position, coil type)

Two reviewers (Y.C. and S.P.) initially screened titles and abstracts on the basis of aforementioned criteria independently and in duplicate. The reviewers performed a calibration exercise with 400 article aliquots prior to screening the remaining articles. We calculated Cohen's kappa score to determine the strength of agreement for full-text review manually[26] with the following thresholds for interpretation: <0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and >0.81 as almost perfect agreement. All articles selected by either reviewer were subject to full text review. Two reviewers (Y.C. and S.P.) manually searched bibliographies of all included studies as well as a previously published meta-analyses to identify additional relevant articles.[14] All articles excluded by full-text review were catalogued along with justifications for their exclusion (Appendix S3). Disagreements about article inclusion were resolved by discussion with a third reviewer (A.F.).

Selection and coding of data

We developed a list of all plausible predictors of treatment outcomes for individual participants on the basis of prior literature review and expert consensus. This list is summarized (Table 2) and includes age, generalized seizures (signifying both secondary generalization and primary generalized epilepsy), diagnosis, seizure focus location, single versus multiple focus, stimulating coil type, coil position, stimulation frequency, and stimulation intensity.

Study outcomes

Our primary outcome was the percentage reduction in the frequency of seizures following rTMS. In studies with IPD only, we dichotomized this outcome into "Favorable

response" (equal to or more than 50% reduction in seizure frequency) and "Unfavorable" (<50% reduction in seizure frequency) at the last reported follow-up time. In studies without IPD, we analyzed the pooled event rate of mean seizure reduction at last study follow-up.

Data classification and coding

Data abstraction was performed by one reviewer (Y.C.) and verified by a second reviewer (S.P.). We attempted to obtain IPD from all included studies by contacting the corresponding author. Articles for which IPD could not be obtained were analyzed using reported study-level data.

Assessment of study quality

Two reviewers (Y.C. and S.P.) independently and in duplicate evaluated the risk of bias of each included study. Because no established guide exists to evaluate quality of prognostic studies, judgments were made using an adaptation of a guide we previously developed[27] (Appendix S2). Briefly, five criteria (sample representativeness, prognostic variables being well defined, confidence in outcome assessment, adequacy of follow-up, and standardization of treatment) were used to assess the quality of each study, with response options defined as "definitely yes," "probably yes," "probably no," and "definitely no." "Definitely yes" and "probably yes" responses were assigned a "low risk of bias," and "definitely no" and "probably no" were assigned a "high risk of bias." Reviewers resolved all disagreements through discussion.

Assessment of publication bias and heterogeneity

We assessed publication bias in studies without IPD through visual assessment for symmetry in a funnel plot using the treatment effect as standard error by logit event rate. We also assessed heterogeneity using I^2 statistic (I^2 values more than 40% were defined as moderate-significant heterogeneity).

Statistical methods

Reviewer's agreement

We calculated Cohen's kappa score to determine the strength of agreement for full-text review using computer software[26] with the following thresholds for interpretation: <0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and >0.81 as almost perfect agreement.

Studies with IPD

For continuous data, we reported mean and standard deviation. For dichotomous data, we reported frequencies and percentages. We compared continuous variables using a two-tailed t test and proportions using the Fisher exact test, unless otherwise specified. Data permitting, we planned a multivariable analysis, including adjustment for the study effect. We set the alpha level for accepting statistical significance at 0.05.

Studies without IPD

We calculated pooled event estimates with 95% CIs from all studies using a random-effects model.[28] All statistical analyses were performed using a comprehensive meta-analysis software suite (BioStat, Inc.).

Results

Study selections and characteristics

After searching PubMed, Medline, and Scopus databases as well as Clinicaltrials.gov, we identified 3,477 citations for review (Fig. S1). No additional citations were identified through hand searching. Following title and abstract screening, we identified 25 articles for full-text review and hand-searched the reference list of these articles to identify additional relevant publications, though we identified no further articles (unweighted kappa = 0.89; 95% CI 0.81–0.98; near perfect strength of agreement). We ultimately identified 12 articles for inclusion in this study and were able to obtain IPD from 5 of the 12 articles, comprising 34 participants.[15,18,21,22,29] Appendix S3 contains the excluded articles with reasons for exclusion. No articles were excluded because of inadequate rTMS protocol description.

In the 5 of the 12 included studies (41.7%) with IPD, the median follow-up duration was 4.3 weeks (interquartile ratio [IQR] = 4.0–10.0; range = 2.0–12.0). The remaining 7 articles (59.3%) were pooled using study-level summary data. Here, the median follow-up duration was 8 weeks (range = 2–8) (Table 1).[4,13,16,17,19,20,30] We present summary characteristics of each included study in Table 1. We present summary descriptive statistics for all independent variables analyzed in Table 2. We did not include several variables because they were inconsistently and insufficiently reported. Those included epileptic drug regimen, interictal electroencephalogram (EEG) abnormalities, focal/generalized seizure semiology, stimulation paradigms, and developmental delay.

Assessment of bias

Assessment of risk of bias for all included studies is summarized in Table S1. Overall, we identified moderate to high levels of study bias for patient sample representation and recruitment. Characterization and reporting of prognostic or predictive outcomes were moderately biased. Finally, we identified low risk of bias with regard to outcome assessment and reporting, adequacy of patient follow-up, and treatment standardization within studies.

Analysis of studies with IPD

For the 5 studies with IPD (34 participants), only 9 participants (26.4%) had a favorable response to rTMS

Table 1. Characteristics of included studies

First author (year)	No. of patients	Age (range y.o. or mean ± SD)	Sex (#M, #F)	Study location	Stimulation frequency (Hz)	Stimulation intensity	Coil type	Position (Cz, FCz, PCz, Seizure Focus)	Prior surgery performed	Follow-up duration	Seizure free	Study design
IPD studies												
Brasil-Neto (2004)	5	6–50	4M, 1F	Brazil	0.3	95% rMT	Round	Cz	1/5	3 months	0/5	Co
Daniele (2003)	4	27–33	N/A	Italy	0.5	90% rMT	Figure-8	2Cz, 2SF	N/A	1 month	0/4	Co
Fregni (2005)	8	14–38	3M, 5F	Brazil	0.5	65% MSO	Figure-8	2Cz, 6SF	0/8	1 month	3/8	Co
Kinoshita (2005)	7	16–33	2M, 5F	Japan	0.9	90% rMT or 100% aMT[a]	Round	5FCz, 2PCz	0/7	2 weeks	0/7	Co
Seynaeve (2016)	11	16–75	4M, 7F	Belgium	0.5	90% rMT	Round & Figure-8	11SF	4/11	10 weeks	0/11	R, Db, Cr
Non-IPD studies												
Cantello (2007)	43	36.9 ± 13	26M, 17F	Italy	0.3	100% rMT	Round	Cz	N/A	6 weeks	0/43	R, Db, Sc, Cr
Fregni (2006)	21	21.9 ± 8.1	9M, 12F	Brazil	1.0	70% MSO	Figure-8	Cz, SF	N/A	2,4,8 weeks	3/12 (2 weeks), 0/12 (4 & 8 weeks)	R, Db, Sc
Joo (2007)	35	18–46	18M, 17F	South Korea	0.5	100% rMT	Figure-8	Cz, SF[b]	N/A	8 weeks	0/35	Co
Santiago-Rodriguez (2008)	12	14–54	7M, 5F	Mexico	0.5	110% rMT	Figure-8	SF	N/A	8 weeks	2/8 (8 weeks)	Co
Sun (2012)	60	20.5 ± 7.1	41M, 19F	China	0.5	90% or 20% rMT	Figure-8	SF	20/60	8 weeks	N/A	R, Sb
Tergau (2003)	17	N/A	N/A	Germany	0.3 or 1.0	'Slightly below' rMT	Round	Cz	N/A	4 weeks	0/17	R, Db, Sc,Cr
Theodore (2002)	24	40 ± 14	11M, 13F	U.S.A.	1.0	120% rMT	Figure-8	SF	N/A	8 weeks	N/A	R, Db, Sc

aMT, active motor threshold; Co, cohort; Cr, crossover; Db, double-blind; F, female; M, male; MSO, maximum stimulator output; R, randomized; rMT, resting motor threshold; Sb, single-blind; Sc, sham-controlled; SD, standard deviation.

Cz (central midline), FCz (frontal midline), and PCz (parietal midline) refer to placement coordinates according to the 10-20 EEG placement system.

[a]rMT given except where rMT exceeds maximum stimulator output, in which case aMT given instead.

[b]Coil positioned at seizure focus (SF) for patients with focalized seizures.

(defined as 50% reduction in seizure frequency at last reported follow-up). Table 3 presents the characteristics of all participants with IPD. Table 2 shows the distribution of possible predictors as per treatment response group. Univariate analysis on IPD identified different favorable response event rates between participants with temporal seizure focus versus extratemporal (50% vs. 14%, p = 0.045) and between participants who were stimulated with a figure-8 coil versus with other coil types (47% vs. 0%, p = 0.01) (Table 3). Stimulation frequency did not predict outcome (p = 0.54). Because of stimulation intensity homogeneity between studies, the effect of this parameter could not be meaningfully assessed. Owing to the small number of participants, we could not conduct a robust adjusted multivariate analysis that accounts for confounders effect.

Table 2. Summary table for predictors of seizure outcome for IPD participants

Continuous variables				
Age	Median (27)	IQR 1st–3rd (21–33)	Range (6–75)	Not reported (4)
Discrete variables				
Sex	Male (12)	Female (18)	Not reported (4)	
Generalized seizure	Yes (14)	No (20)		
Diagnosis	Cortical dysplasia (22)	All else (6)	Not reported (6)	
Seizure focus location	Temporal (9)	Extratemporal (21)	Not reported (4)	
Single versus multiple focus	Single (29)	Multiple (4)	Not reported (1)	
Stimulating coil type[a]	Round (14)	Figure-8 (27)	Sham (7)	
Position	Seizure focus (18)	Cz (9)	FCz(5)	PCz (2)
Stimulation frequency	0.3 Hz (5)	0.5 Hz (22)	0.9 Hz (7)	

IQR, interquartile range.
Cz (central midline), FCz (frontal midline), and PCz (parietal midline) refer to placement coordinates according to the 10-20 EEG placement system.
[a]One study (Seynaeve et al. 2016) was designed as a randomized cross-over trial where patients sequentially received stimulation with round, figure-8, and sham coils. Therefore, these patients were 'triple counted' and our reported numbers for this variable add up to greater than the number of total participants, which was 34.

Table 3. Univariate analysis of predictors for studies with IPD

Predictor	Favorable response[a]	Unfavorable response[a]	p value
Age	24.6 ± 9.4	29.5 ± 11.8	0.26
Sex			0.732
Male	3 (27.3)	8 (72.7)	
Female	6 (33.3)	12 (66.7)	
Generalized seizure	6 (42.9)	8 (57.4)	0.095
Cortical dysplasia	7 (33.3)	14 (66.7)	0.441
Seizure focus location			0.045*
Temporal	4 (50)	4 (50)	
Extratemporal	3 (14.3)	18 (85.7)	
Seizure focus number			0.238
Single	6 (21.4)	22 (78.6)	
Multifocal	2 (50)	2 (50)	
Stimulation frequency	0.589 ± 0.17	0.542 ± 0.20	0.545
Coil type			0.010*
Round	0 (0)	7 (100)	
Figure-8	9 (47.4)	10 (52.6)	
Mixed	0 (0)	7 (100)	
Coil position[b]			0.726
Cz	2 (22.2)	7 (77.8)	
Seizure focus	5 (29.4)	12 (70.6)	
FCz	2 (40.0)	3 (60)	
PCz	0 (0)	2 (100)	

Values are presented as no. (%) or mean ± SD.
* refers to p < 0.05.
[a]Individual participants were subcategorized on the basis of defined outcome predictors and then further subclassified into "Favorable Response" (≥50% reduction in seizure frequency) or "Unfavorable Response" (<50% reduction) outcome categories and compared.
[b]Cz (central midline), FCz (frontal midline), and PCz (parietal midline) refer to placement coordinates according to the 10-20 EEG placement system.

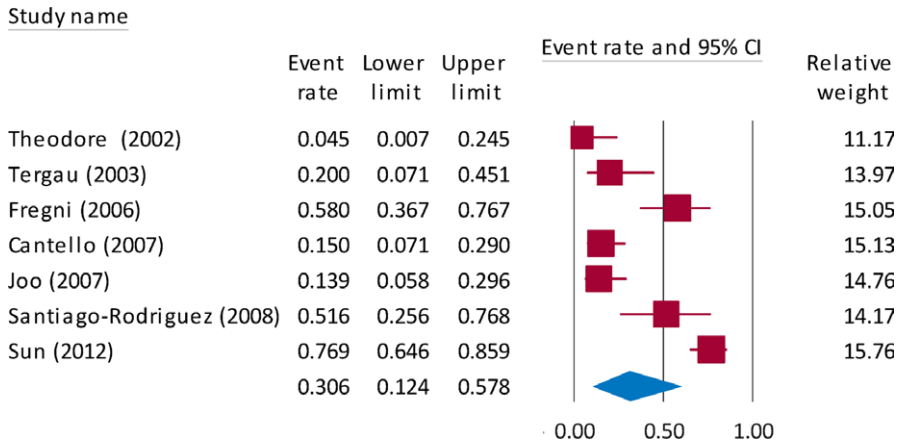

Figure 1.
Forest plot showing pooled event rates of mean reductions in seizures following rTMS and 95% confidence intervals among all included studies without IPD.
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Table 4. Sensitivity analysis of studies without IPD

Factor	Mean reduction rate (95% CI)	I^2	No. of studies
Studies with >20 patients	28% (8–64%)	92%	5
Mean age			
≤21 y.o.	69% (49–84%)	N/A	2
>21 y.o.	18% (9–34%)	14%	5
Focused stimulation[a]			
Focused	47% (20–76%)	84%	4
Diffuse	12% (4–21%)	85%	3
Follow-up time			
≤6 weeks	16% (9–28%)	N/A	2
>6 weeks	37% (13–69%)	89%	5
Stimulation frequency			
0.3 Hz	17% (13–22%)	NA	2
0.5 Hz	47% (12–83%)	90%	3
1.0 Hz	21% (−16 to 57%)	90%	3

For sensitivity analysis, studies were "Factored" on the basis of the variables listed above.
Mean reduction rate refers to the mean seizure reduction.
I^2 refers to the study heterogeneity statistic.
[a]Focused stimulation refers to whether the treatment was focused, whereby a figure-8 coil was used to stimulate the seizure focus (SF), or diffuse, whereby a round coil was used at Cz.

Analysis of study-level meta-data

For the 7 studies without IPD (212 participants), the pooled estimate demonstrated an overall rate of 30% (95% CI = 12–57%, I^2 = 89%) reduction in seizure frequency from low-frequency rTMS intervention at last follow-up (Fig. 1). There was significant heterogeneity between included studies. To answer our secondary question in identifying possible predictors of outcome and to explore sources of heterogeneity, we performed a sensitivity analysis by subclassifying studies according to mean age (older than 21 years compared to younger), stimulation frequency as a discrete variable (0.3, 0.5, and 1.0 Hz), and follow-up duration (>6 weeks of follow-up compared to fewer weeks), as shown in Table 4. Because stimulation coil and coil position were perfectly confounded—figure-8 coil was always used at the seizure focus (SF) and round coil was always used to stimulate central midline (Cz; 10-20 EEG placement system)—we could not independently assess these variables. Therefore, we combined them into a meta-classification of targeted (figure-8 and SF) versus diffuse (round and Cz) stimulation and performed sensitivity analysis on this classification. Studies that included participants with mean age ≤21 years who underwent targeted stimulation using figure-8 coil at the SF had the highest seizure reduction rates compared to studies with participants of mean age >21 years (69% vs. 18%) who did not use targeted stimulation (47% vs. 12%; Table 4). Additionally, we found that stimulation at 0.5 Hz provided the highest seizure reduction compared with 0.3 or 1.0 Hz (47% vs. 17% or 21%). Heterogeneity values were not affected by these factors

except for age. We found no correlation between stimulation intensity and seizure outcomes ($p = 0.34$).

Publication bias

Funnel plot exhibiting effect estimates for studies without IPD shows a considerable and significant publication bias among studies (Fig. S2).

Discussion

We performed a review and meta-analysis of 12 studies investigating the use of low-frequency (≤1 Hz) rTMS for the treatment of drug-resistant epilepsy. Our findings are summarized as follows: (1) we found a significant reduction in overall seizure frequency over an average follow-up period of 6 weeks; (2) in studies without IPD where participants had a mean age of ≤21 years old, rTMS was significantly more effective than in studies with participants of a mean age >21 years old; (3) in studies without IPD, targeted stimulation was associated with the strongest treatment effect. Similarly, in analysis of IPD, univariate analysis of coil type revealed that use of figure-8 coil was associated with greater treatment response; and (4) extratemporal seizure focus predicts worse treatment outcomes.

We identified a 30% reduction in seizure frequency following low-frequency rTMS for the treatment of refractory epilepsy. This effect closely agrees with a previous meta-analysis by Hsu and colleagues that identified a 34% reduction in seizure frequency following rTMS treatment.[14] It should be noted that very few participants achieved full seizure remission; the vast majority of participants experienced a therapeutic reduction in seizure frequency.

Outcome predictors

To facilitate hypothesis generation to design a subsequent clinical trial, we sought to identify optimal treatment parameters and ideal patient characteristics that predict the best seizure outcomes. Analysis of IPD revealed that stimulation with a figure-8 coil resulted in the most robust seizure reduction. Additionally, our analysis of studies without IPD revealed that targeted stimulation achieved the most robust seizure reduction, further suggesting the superiority of figure-8 coils. Figure-8 coils have increased focality compared with round coils, and some authors speculate that more precise focal stimulation is critical for treatment success.[16] Figure-8 coils are currently the standard coil type used in the treatment of depression, although the FDA has recently approved H-coils for this purpose.[31] Among stimulation coils, there is an inverse correlation between focality and penetration depth. Therefore, the figure-8 coils might prove to be less effective than larger diffuse coils (e.g., H-coils) for deeper seizure foci.[32] However, we were unable to assess a relationship between focus depth and outcomes in this review, because the data were not available.

Additionally, treatment of patients <21 years of age was associated with a more favorable response compared with treatment of patients older than 21 years of age. Evidence supporting this phenomenon is generally sparse, because there are few studies that directly compare the effects of age with rTMS response, and interstudy variability has made comparisons difficult.[33] In the refractory depression literature, there is some evidence demonstrating that rTMS might be more effective for adolescent patients possibly because of increased neural plasticity or decreased likelihood for entrenched and maladaptive structural changes.[34] Functional MRI data suggest that adolescence is a period of significant neural development with substantial synaptic pruning and alterations in myelination.[35] Nevertheless, how and why adolescent neural plasticity might translate to increased rTMS responsivity remain poorly understood. Perhaps this difference can also more simply be attributed to decreased skull thickness in pediatric populations enhancing the penetrance of the stimulation dose at the cortex. However, to study this more carefully, a more appropriate cut-point for dichotomization would be 8 years of age, because the head and skull resemble that of an adult by this time. Additionally, comparisons in outcomes between adolescents and adults are confounded by differences in epilepsy etiology. Etiologies in adults significantly favor mesial temporal sclerosis (75% of adult surgical cases), whereas children and adolescents more frequently harbor malformations of cortical development.[11]

Interestingly, we identified conflicting results in regard to the effects of stimulation frequency on seizure reduction. Our analysis of studies with IPD found no effect of stimulation frequency on outcomes, whereas analysis of studies without IPD found that stimulation at 0.5 Hz was optimal when compared with higher (1 Hz) and lower (0.3 Hz) frequencies. This may suggest that there is an optimal frequency setting that may result in the greatest efficacy and that the relationship between stimulation frequency and outcome may not be linear. However, the rTMS frequency effect observed may have been largely driven by the study from Sun et al.[16] Therefore, further studies are needed to establish an optimal rTMS stimulation frequency.

Finally, using IPD, we found that a temporal seizure focus predicted a better treatment response than an extratemporal focus. This finding mimics that of the surgical literature, which has shown significantly improved success of surgical interventions for temporal lobe epilepsy compared with extratemporal epilepsy.[36,37] However, our findings are in direct contrast with the findings of Hsu and colleagues, who found improved TMS efficacy for extratemporal foci.[14] Given this contradiction, poor reporting of seizure origin in the analyzed studies, and low numbers of IPD, this result necessitates further verification. The recent advent of the H-coil stimulator, which has increased depth of penetrance, might further

Table 5. Design considerations for a future randomized controlled trial of rTMS in pediatric epilepsy

Population	The study should be restricted to consecutive children <21 years of age with the following inclusion criteria: Inclusion criteria: (1) drug-resistant epilepsy; (2) focal or multifocal epilepsy localized to the cerebral convexity; and (3) ability to participate in follow-up for at least 1 year. Exclusion criteria: (1) infantile spasms as etiology; (2) previous epilepsy surgery, including a vagal nerve stimulation insertion or corpus callosotomy; (3) hemispheric epilepsy syndrome; (4) other concurrent experimental therapy.
Other design considerations	Random sequence generation; allocations concealed; participants and outcome assessors blinded to therapeutic rTMS stimulation versus sham stimulation. Participants allocated to either treatment arm should continue on best medical management with further nonexperimental antiseizure drug therapy. To improve external validity, the population should comprise a multicenter and international cohort encompassing a large range of socioeconomic backgrounds and diversity in the etiology of epilepsy. Follow-up should be through clinical visits consisting of review of a carefully reported seizure diary.
Intervention	Focal rTMS treatment using the figure-8 coil at 0.5 Hz
Comparison	Sham rTMS therapy
Sample size	Assuming the rate of responders to rTMS (defined by 50% improvement in seizures) is 30% and the rate of responders to sham rTMS therapy is 10%, 70 participants (35 per group) are required to achieve 80% power to detect a statistically significant difference in outcome with alpha set at 0.05.
Outcome measures	Independent neurologist assessing frequency of seizures with the aid of a seizure diary. Outcomes dichotomized to greater than 50% improvement versus <50% improvement in seizure frequency. Follow-up at 1 month, 6 months, and 1 year after the end of treatment.
Blinding	Blinding of outcome assessor (neurologist) with respect to the treatment (medical therapy vs. rTMS).
Follow-up	Loss to follow-up should be minimized to <10% at 1 year. Given the anticipated loss to follow-up, the sample size should be increased accordingly to keep the study well powered.
Statistical analyses	Multivariable logistic regression analysis to determine the efficacy of rTMS treatment over further medical therapy for seizure outcomes after controlling for potential confounding variables (age of the participant at the time of intervention and number of previous treatments).

improve targeting of deep temporal lobe structure and further improve outcomes for patients with temporal lobe epilepsy in particular.[38]

Safety

Low-frequency rTMS is a very well-tolerated therapy.[6,39] In our study, between 17% and 23% of participants reported adverse effects, similar to previous assessments of between 17% and 18%.[6,39] Adverse effects include headache (most common; 60%), fatigue, dizziness, hearing loss/tinnitus, difficulty sleeping, and tremor. More serious adverse events include seizure during stimulation (0.8%) and an increase in seizure frequency following stimulation protocol (1.2%), though it is possible this is an underestimation, because studies without IPD might not have identified individual participants with increased seizure frequency.

Strengths and limitations

This meta-analysis has several strengths: (1) study methodology was designed in advance of performing the review; (2) a comprehensive literature search strategy was designed and performed; (3) IPD was utilized, when available, for quantitative synthesis; and (4) real-world evidence, which closely mimics real-life practice settings, was utilized.

However, there is one limitation of this review in that we were unable to obtain IPD for 7/12 relevant studies, limiting and underpowering our IPD analysis. There were also several limitations in the original studies that prevented us from drawing definitive conclusions: (1) high interstudy heterogeneity for a variety of treatment variables (stimulation strength, frequency, coil type, position); (2) high interstudy heterogeneity of patient characteristics (age, sex, seizure etiology, seizure characteristics, previous surgeries, seizure duration); (3) incomplete/inconsistent reporting of patient characteristics limited IPD predictor analysis; (4) inconsistent or poor trial design—only 5/12 studies were randomized controlled trials; (5) small sample sizes, possibly magnifying effect size and underpowering subsequent analysis; (6) high suspicion of bias for IPD studies, especially in regard to sequential enrollment of participants, generalizability, and treatment uniformity (Table S1); and (7) the presence of publication bias (Fig. S2).

Conclusions

The effect size and outcome predictors we have identified represent RWE and a more accurate assessment of the true efficacy of rTMS treatment in drug-resistant epilepsy and optimal treatment and patient parameters. Younger patient age, temporal localization of the epileptogenic zone, and the use of a fFigure-8 coil each predicted a greater seizure improvement to rTMS. Despite the limitations of the original studies, this review represents the best real-world evidence to date with respect to the efficacy of rTMS in the treatment of medically intractable epilepsy. Given the potential efficacy, cost-effectiveness, and relative safety of rTMS, we recommend it as a therapeutic option, although

we suggest its use be exclusively limited to the context of a clinical trial.

Research implications

Given that the treatment of epilepsy with rTMS is in its infancy, it was not surprising that there was significant study heterogeneity in regard to patient populations, seizure etiologies, and treatment regimens. In this review we have been able to identify parameters that could be used to inform the design of a subsequent RCT. We have presented these design considerations in Table 5.

Author Contributions

Conception and design: B.S., A.G.W., and A. F. Acquisition of data: Y.C. and S. P. Analysis and interpretation of data: Y.C., S.P., N.M.A., and A. F. Statistical analysis: N.M.A. and Y.C. Drafting the article: Y.C., S.P., and N.M.F. Critically revising the article: B.S., A.G.W., G.M.I., A.C.W., and A.F. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: A.F. Study supervision: A.F.

Disclosures

The authors have no personal, financial, or institutional interests in any of the drugs, materials, or devices described in this article. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. PRISMA flow diagram. Flow diagram describing the process for identification and inclusion of relevant studies in accordance with PRISMA standards.

Fig. S2. Funnel plot demonstrating significant asymmetry in effect estimates between studies.

Table S1. Assessment of bias.

Appendix S1. MESH terms and search strategy.

Appendix S2. Criteria for performing assessment of bias.

Appendix S3. Excluded articles and justifications.