


Original Investigation

Effects of Repetitive Transcranial Magnetic Stimulation on Motor Symptoms in Parkinson Disease

A Systematic Review and Meta-analysis

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IMPORTANCE Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been closely examined as a possible treatment for Parkinson disease (PD). However, results evaluating the effectiveness of rTMS in PD are mixed, mostly owing to low statistical power or variety in individual rTMS protocols.

OBJECTIVES To determine the rTMS effects on motor dysfunction in patients with PD and to examine potential factors that modulate the rTMS effects.

DATA SOURCES Databases searched included PubMed, EMBASE, Web of Knowledge, Scopus, and the Cochrane Library from inception to June 30, 2014.

STUDY SELECTION Eligible studies included sham-controlled, randomized clinical trials of rTMS intervention for motor dysfunction in patients with PD.

DATA EXTRACTION AND SYNTHESIS Relevant measures were extracted independently by 2 investigators. Standardized mean differences (SMDs) were calculated with random-effects models.

MAIN OUTCOMES AND MEASURES Motor examination of the Unified Parkinson's Disease Rating Scale.

RESULTS Twenty studies with a total of 470 patients were included. Random-effects analysis revealed a pooled SMD of 0.46 (95% CI, 0.29-0.64), indicating an overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms ($P < .001$). Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46-1.08; $P < .001$) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13-0.87; $P = .008$) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (ie, high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, -0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, -0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, we characterized the quality of evidence presented in this meta-analysis as moderate quality.

CONCLUSIONS AND RELEVANCE The pooled evidence suggests that rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of rTMS effects. The findings of our meta-analysis may guide treatment decisions and inform future research.

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Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by resting tremor, bradykinesia, rigidity, gait disorder, and postural instability. It is estimated that 6 to 10 million people worldwide have PD, affecting all races and ethnicities. The incidence of PD rises rapidly with age, affecting approximately 1% of the population older than 60 years and approximately 4% of those older than 80 years.¹ As the average age of the population increases, the prevalence of PD worldwide is expected to more than double by 2030.²

Medical therapy substantially improves quality of life and functional capacity in PD; however, most patients develop complications after 5 years of treatment, including dyskinesia and motor fluctuations.³ Surgical techniques, including deep brain stimulation, improve advanced symptoms above the best medical therapy, although less than 5% of the PD population may be eligible for the procedure.⁴ During the past 2 decades, repetitive transcranial magnetic stimulation (rTMS) has been closely examined as a possible treatment for PD.⁵⁻⁷ As a non-invasive procedure, rTMS does not require surgery or anesthesia. It delivers repeated magnetic pulses to a specific brain area within a short time through a stimulation coil placed over the scalp. The repeated magnetic pulses not only alter excitability at the site of stimulation but also influence brain regions anatomically connected to the stimulation site.⁸ Because rTMS can produce changes in neural activity and behavior that last well after stimulation, this technique has generated much interest as a potential therapeutic intervention for patients with PD.

Accumulating studies investigating the effectiveness of rTMS have yielded mixed results, possibly owing to low statistical power and wide variation in treatment protocols. Thus, it is critical to integrate and arrange these findings based on rTMS-related factors to more accurately estimate the effects of rTMS on PD. The objectives of this meta-analysis were to (1) systematically evaluate the efficacy of rTMS intervention compared with sham controls for motor dysfunction in PD from randomized clinical trials (RCTs) and (2) identify factors of rTMS protocols that may moderate the rTMS effects. The objectives were defined in terms of population, interventions, comparators, outcomes, and study designs.

Methods

Study Design and Registration

Our meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement⁹ and is registered with PROSPERO (registration number CRD42014013372).

Search Strategy

To identify studies for inclusion in this meta-analysis, we searched PubMed, EMBASE, Web of Knowledge, Scopus, and the Cochrane Library from inception through June 30, 2014. Databases were searched using combinations of the following terms: *Parkinson disease* and *repetitive transcranial magnetic stimulation* or *rTMS* or *repetitive TMS*. The complete docu-

mentation of the search procedure is included in the eAppendix in the Supplement. We also searched the reference lists of general reviews on rTMS for PD¹⁰⁻¹² and of meta-analyses^{6,7} to identify additional relevant articles.

Inclusion Criteria for Study Selection

Studies identified through database searches were first screened on the basis of their title and abstract. Studies were excluded if it was clear from the article title or abstract that the trial was not relevant or did not meet the inclusion criteria. If relevance was unclear, we assessed the article in its entirety. We included trials that met the following criteria: population (patients with a diagnosis of idiopathic PD), intervention (rTMS), comparators (sham-controlled group or condition), outcome measure (motor examination of the Unified Parkinson's Disease Rating Scale [UPDRS-III]), study design (parallel or crossover RCTs that used a sham-controlled group or condition), and language (articles written in English). Studies were excluded if they did not have data available for effect size estimation or were a conference abstract or presentation.

Data Extraction

Two authors (Y.-h.C. and M.S.) independently performed data extraction, with disagreement resolved by discussion. Extracted data included sample size, sample characteristics, study design, rTMS protocol, statistical data on the UPDRS-III score for effect size estimation, medication state during assessment ("on" or "off"), and timing of outcome measurements (short-term, <1 week; or long-term, ≥1 week). When reported data were insufficient for data analysis, we contacted the study author to request access to additional data.

Statistical Analysis

Effect Size Calculation

We used standardized mean difference (SMD [Cohen *d*]) to express the size of the rTMS effect on motor symptoms measured with the UPDRS-III. A random-effects model was used to calculate pooled effect sizes and test whether the mean effect size was significantly different from zero ($P \leq .05$, 2-tailed). The mean effect was expressed as SMD with 95% CIs. If a study had multiple effect sizes from the same patient group (eg, short-term and long-term rTMS effects), we obtained one mean effect size across multiple effect sizes within this study. For total effect size estimation, the unit of analysis was *study*.

Heterogeneity Analysis

Multiple types of heterogeneity were present in the included studies: (1) variability in the participants, intervention characteristics, and the timing of outcome measurements (clinical heterogeneity); (2) variability in study design and risk of bias (methodologic heterogeneity); and (3) variability in treatment effects (statistical heterogeneity).¹³ Methodologic and clinical sources of heterogeneity contribute to the magnitude and presence of statistical heterogeneity¹³; we used the *Q* statistic and the *I*² index to assess the statistical heterogeneity. A probability value of $P \leq .05$ and an *I*² value of greater than 40% are indicative of heterogeneity between included studies as the values exceed what is expected by chance.¹⁴

Publication or Selection Bias

Publication or selection bias was evaluated with the Egger test of asymmetry¹⁵ and the Orwin fail-safe N approach.¹⁶ In the absence of publication or selection bias, effect sizes are symmetrically distributed around the overall mean effect size, since the sampling error is random. The Egger test evaluated whether the amount of asymmetry was significant. In addition, studies that demonstrated a lack of benefit might not have been published or submitted for publication. Therefore, we used the Orwin fail-safe N test to estimate the number of missing studies that we would need to retrieve and incorporate in our meta-analysis to make the summary effect become trivial.

Subgroup Analysis

For subgroup analysis, the unit of analysis was *trial* (ie, effect size that was reported or could be estimated from a study). Our prespecified comparisons included rTMS site (primary motor cortex [M1] vs other frontal regions), rTMS frequency (low [≤ 1 Hz] vs high [≥ 5 Hz]), interaction between rTMS site and rTMS frequency, timing of outcome measurement (short-term [< 1 week] vs long-term [≥ 1 week]), medication state during assessment (on-state vs off-state), and type of sham-rTMS approach.

Meta-regression

We used meta-regression to identify the major sources of between-study variation in the results by using the SMD from each study or trial as a dependent variable and rTMS variables as predictors. All values from predictor variables were z transformed for meta-regression.

Sensitivity Analysis

The process of undertaking a meta-analysis involves making decisions about inclusion criteria. We performed a sensitivity analysis to examine whether our results would have differed if we had included non-RCTs into the meta-analysis.

Risk of Bias Assessment in Individual Studies

We assessed the risk of bias using the Cochrane risk of bias assessment tool outlined in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0*.¹³ The Cochrane tool classifies studies as having low, high, or unclear risk of bias in the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and carryover effect. In addition, we used the Physiotherapy Evidence Database (PEDro) scale^{17,18} to quantify the quality of included studies. The PEDro scale scored 11 items (eTable 1 in the Supplement) as either present or absent. The final score is the number of positive answers on all questions. We considered a PEDro score of 11 to represent an excellent-quality study, scores of 8 to 10 a good-quality study, scores of 6 and 7 a fair-quality study, and scores of 5 or lower a low-quality study.¹⁹

Risk of Bias Assessment Across Studies

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess

the quality of evidence.²⁰ Four levels of quality of evidence are specified: high, moderate, low, and very low. An initially assumed high level of evidence would be downgraded for meeting any of the following criteria²¹: (1) risk of bias (downgrade once if less than 75% of the included studies are at low risk of bias across all risk of bias domains), (2) heterogeneity (downgrade once if heterogeneity between the included studies is significant and the I^2 value is greater than 40%), (3) indirectness (downgrade once if more than 50% of the participants were outside the target group), (4) imprecision (downgrade once if fewer than 400 participants),²² and (5) publication/selection bias (downgrade once if the publication/selection bias is significant).

Results

Search Results

Our initial search of all databases retrieved 2203 studies (eAppendix in the Supplement), yet many of these were identified as duplicates. After screening for title and abstract, the full texts of 60 articles were obtained for examination. Of these, 40 studies were excluded and 20 studies²³⁻⁴² that met the inclusion criteria were evaluated in this meta-analysis (eFigure 1 in the Supplement). Two studies presented different phenomena (eg, on or off state) from the same group of patients in 2 articles^{37,38}; therefore, the SMDs from these 2 studies were averaged for total effect size estimation.

Study Characteristics

The 20 eligible studies included 470 participants (mean [SD] age, 63.59 [8.24] years; 57% men). The total effect size of rTMS on UPDRS-III score was 0.46 (95% CI, 0.29 to 0.64), indicating a medium effect size favoring active rTMS over sham rTMS ($z = 5.18$; $P < .001$). The mean score change in the UPDRS-III following active rTMS intervention was -6.42 (5.79), corresponding to a moderate clinically important difference.⁴³ The main characteristics of the included studies are described in Tables 1, 2, and 3, and the distribution of effect sizes is illustrated in Figure 1.

Heterogeneity between the included studies did not exceed that expected by chance ($Q_{18} = 16.22$; $P = .58$; $I^2 = 0.00$), implying that the results across the included studies were statistically homogeneous. Publication bias was evaluated using the Egger test of asymmetry and Orwin fail-safe N approach. The Egger test did not reveal significant asymmetry across included studies (intercept₁₇ = 0.77; $t = 1.12$; 2-tailed $P = .28$) (eFigure 2 in the Supplement). The Orwin fail-safe N analysis showed that 157 studies with a mean effect size of 0 would be needed to change our conclusion (ie, from determining that active rTMS is more effective than the sham rTMS in reducing motor symptoms to determining that active rTMS is not more effective than the sham rTMS in reducing motor symptoms). The results demonstrate that our findings are robust without significant concerns regarding publication bias.

Table 1. Characteristics of Included Studies: Participants

Source	Sample Size, No.	Age, Mean (SD), y	Sex (M/F)	DD, Mean (SD), y	H and Y Stage
Siebner et al, ⁴² 2000	10	57 (11)	7/3	6 (3)	1-2
Boylan et al, ³⁵ 2001	8	63.5 ^a	6/4 ^a	8.6 ^a	2-3
Shimamoto et al, ²⁸ 2001	18	65 (7)	12/6	7 (5)	1.5-4
Khedr et al, ²⁴ 2003	36 ^b	58 (9)	24/12	3 (2)	2-3
Lefaucheur et al, ³⁹ 2004	12	64 (9)	7/5	11 (5)	2.5-4
Khedr et al, ³³ 2006	20	60 (10)	NA	4 (2)	3-5
Lomarev et al, ²⁵ 2006	16	65 (10)	14/2	12 (5)	2-4
Brusa et al, ³⁶ 2006	10	61 (8)	6/4	16 (5)	NA
del Olmo et al, ³¹ 2007	13	62 (5)	6/7	8 (5)	1-3
Hamada et al, ³⁴ 2008	98	66 (9)	54/44	8 (5)	2-4
Sedláčková et al, ⁴¹ 2009	9	64 (7) ^a	9/1 ^a	8 (7) ^a	NA
Filipović et al, ^{37,38} 2010, 2009	10	65 (10)	5/5	16 (6)	2-4
Pal et al, ²⁷ 2010	22	69 (8)	11/11	6 ^c	NA
Arias et al, ²³ 2010	18	66 (9)	9/9	7 (3)	2-4
González-García et al, ²⁹ 2011	17	65 (5)	11/6	NA	2-3
Benninger et al, ³² 2012	26	64 (9)	20/6	9 (5)	2-4
Maruo et al, ²⁶ 2013	21	63 (11)	11/10	12 (6)	2-4
Shirota et al, ³⁰ 2013	102 ^d	67 (8) ^d	43/59 ^d	5 (6) ^d	2-4 ^d
Nardone et al, ⁴⁰ 2014	4	66 (4)	3/1	10 (5)	2-4

Abbreviations: DD, disease duration; H and A, Hoehn and Yahr; NA, not available.

^a Data from enrolled participants.

^b Participants who completed the repetitive transcranial magnetic stimulation sessions and the evaluation 1 hour after the session.

^c Median disease duration.

^d Data analyzed.

Table 2. Characteristics of Included Studies: rTMS Variables

Source	rTMS Site	rTMS Frequency	Intensity, %	No. of Pulses ^a	Treatment Duration	Sham rTMS
Siebner et al, ⁴² 2000	M1	5 Hz	90 RMT	2250 (2250 × 1)	1 d	Tilted coil
Boylan et al, ³⁵ 2001	SMA	10 Hz	Approximately 96 MT	2000 (2000 × 1)	1 d	Tilted coil
Shimamoto et al, ²⁸ 2001	Frontal	0.2 Hz	700 V	480 (60 × 8)	2 mo	Inactive coil and sound
Khedr et al, ²⁴ 2003	M1	5 Hz	120 RMT	20 000 (2000 × 10)	10 d	Tilted coil
Lefaucheur et al, ³⁹ 2004	M1	0.5 and 10 Hz	80 RMT	600 (600 × 1); 2000 (2000 × 1)	1 d	Sham coil
Khedr et al, ³³ 2006	M1	10 Hz	100 MT	18 000 (3000 × 6)	6 d	Occipital stimulation
Lomarev et al, ²⁵ 2006	M1/DLPFC	25 Hz	100 MT	9600 (1200 × 8)	4 wk	Coil back surface
Brusa et al, ³⁶ 2006	SMA	1 Hz	90 RMT	4500 (900 × 5)	5 d	Tilted coil
del Olmo et al, ³¹ 2007	DLPFC	10 Hz	90 RMT	4500 (450 × 10)	10 d	Tilted coil
Hamada et al, ³⁴ 2008	SMA	5 Hz	110 AMT	8000 (1000 × 8)	8 wk	Realistic sham
Sedláčková et al, ⁴¹ 2009	PMD/DLPFC	10 Hz	100 RMT	1350 (1350 × 1)	1 d ^b	Occipital stimulation
Filipović et al, ^{37,38} 2009, 2010	M1	1 Hz	Approximately 90 RMT	7200 (1800 × 4)	4 d	Sham coil
Pal et al, ²⁷ 2010	DLPFC	5 Hz	90 RMT	6000 (600 × 10)	10 d	Tilted coil
Arias et al, ²³ 2010	Vertex	1 Hz	90 RMT	1000 (100 × 10)	10 d	Inactive and active coils
González-García et al, ²⁹ 2011	M1	25 Hz	80 RMT	30 000 (2000 × 15)	12 wk	Occipital stimulation
Benninger et al, ³² 2012	M1	50 Hz	80 AMT	4800 (600 × 8)	2 wk	Inactive and active coils
Maruo et al, ²⁶ 2013	M1	10 Hz	100 RMT	3000 (1000 × 3)	3 d	Realistic sham
Shirota et al, ³⁰ 2013	SMA	1 and 10 Hz	110 RMT	8000 (1000 × 8)	8 wk	Realistic sham
Nardone et al, ⁴⁰ 2014	DLPFC	1 Hz	Below AMT	1800 (1800 × 1)	1 d	Sham coil

Abbreviations: AMT, active motor threshold (MT); DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMd, dorsal premotor cortex; RMT, resting MT; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area.

^a Total number of pulses (number of pulses per session times number of sessions).

^b Treatment was 1 day for each region; these treatment days were separated by at least 1 day.

Subgroup Analysis

rTMS Site and rTMS Frequency

Our subgroup analysis revealed that there were no significant differences in effect size between rTMS sites (M1 vs

other frontal regions) and between high-frequency and low-frequency rTMS. However, there was a significant difference in effect size among different combinations of rTMS frequency and rTMS site ($Q_3 = 7.82$; $P = .05$). The effect sizes

Table 3. Characteristics of Included Studies: Outcome Measurements

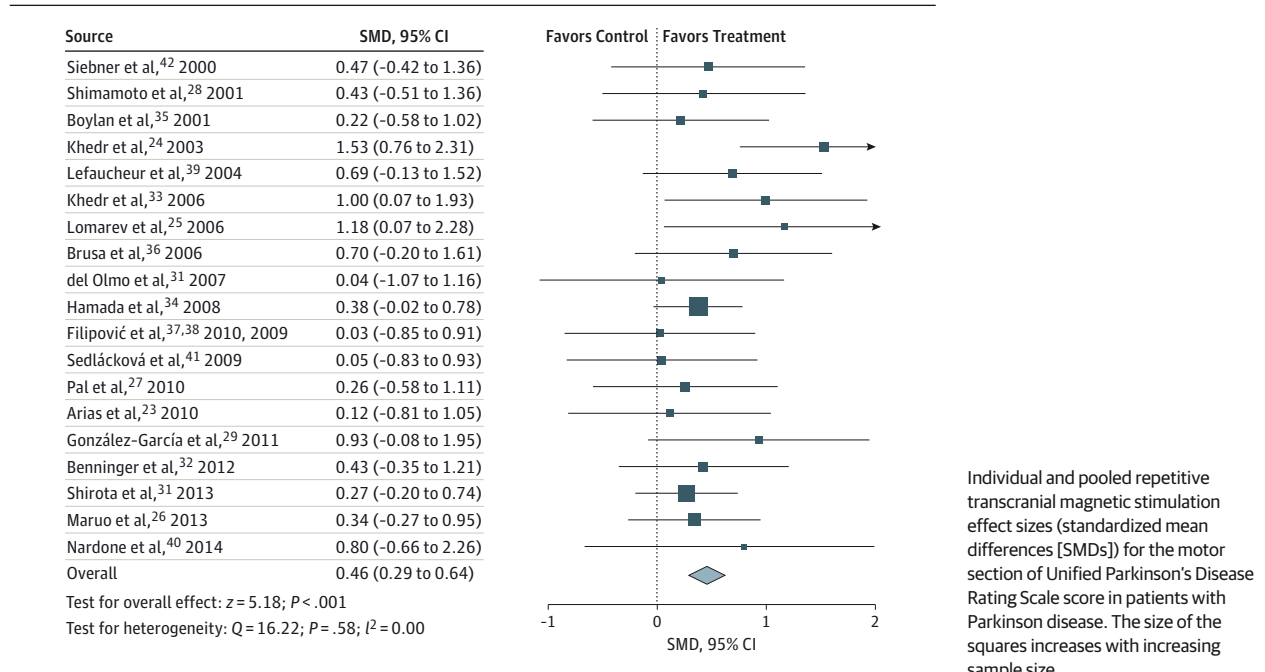
Source	On/Off ^a	Post-rTMS Evaluation	rTMS Change ^b	
			Active	Sham
Siebner et al, ⁴² 2000	Off	1 h	-7.40	-2.90
Boylan et al, ³⁵ 2001	Off	Immediately	NA	NA
Shimamoto et al, ²⁸ 2001	On and off	Immediately	-8.35	-0.80
Khedr et al, ²⁴ 2003	Off	1 h and 1 mo	-14.3	-0.62
Lefaucheur et al, ³⁹ 2004	Off	20 min	-6.50	-2.00
Khedr et al, ³³ 2006	Off	Immediately	NA	NA
Lomarev et al, ²⁵ 2006	On and off	1 d and 1 mo	-3.50	1.08
Brusa et al, ³⁶ 2006	On	1 h	-23.90	-20.80
del Olmo et al, ³¹ 2007	On	1 d	NA	NA
Hamada et al, ³⁴ 2008	On	4 wk	-4.78	0.01
Sedláčková et al, ⁴¹ 2009	Off	Immediately	0.05	0.80
Filipović et al, ^{37,38} 2009, 2010	On and off	1 d	-1.75	-1.40
Pal et al, ²⁷ 2010	On	1 d and 1 mo	-5.00	-1.50
Arias et al, ²³ 2010	On and off	Immediately and 1 wk	-6.78	-3.83
González-García et al, ²⁹ 2011	On	15 min	-7.50	-0.80
Benninger et al, ³² 2012	On and off	1 d and 1 mo	-2.10	-0.88
Maruo et al, ²⁶ 2013	Off	1 h	-5.90	-0.40
Shirota et al, ³⁰ 2013	On	1 and 12 wk	-3.91	-3.20
Nardone et al, ⁴⁰ 2014	On	1, 12, and 24 h	-1.17	-0.75

Abbreviations: NA, not available; rTMS, repetitive transcranial magnetic stimulation.

^a Medication state during assessment.

^b Changes in the motor section of the Unified Parkinson's Disease Rating Scale-III score (post-rTMS score minus pre-rTMS score). More negative values (ie, greater decrements in the score) represent greater improvement in motor symptoms following rTMS sessions.

Figure 1. Overall Forest Plot

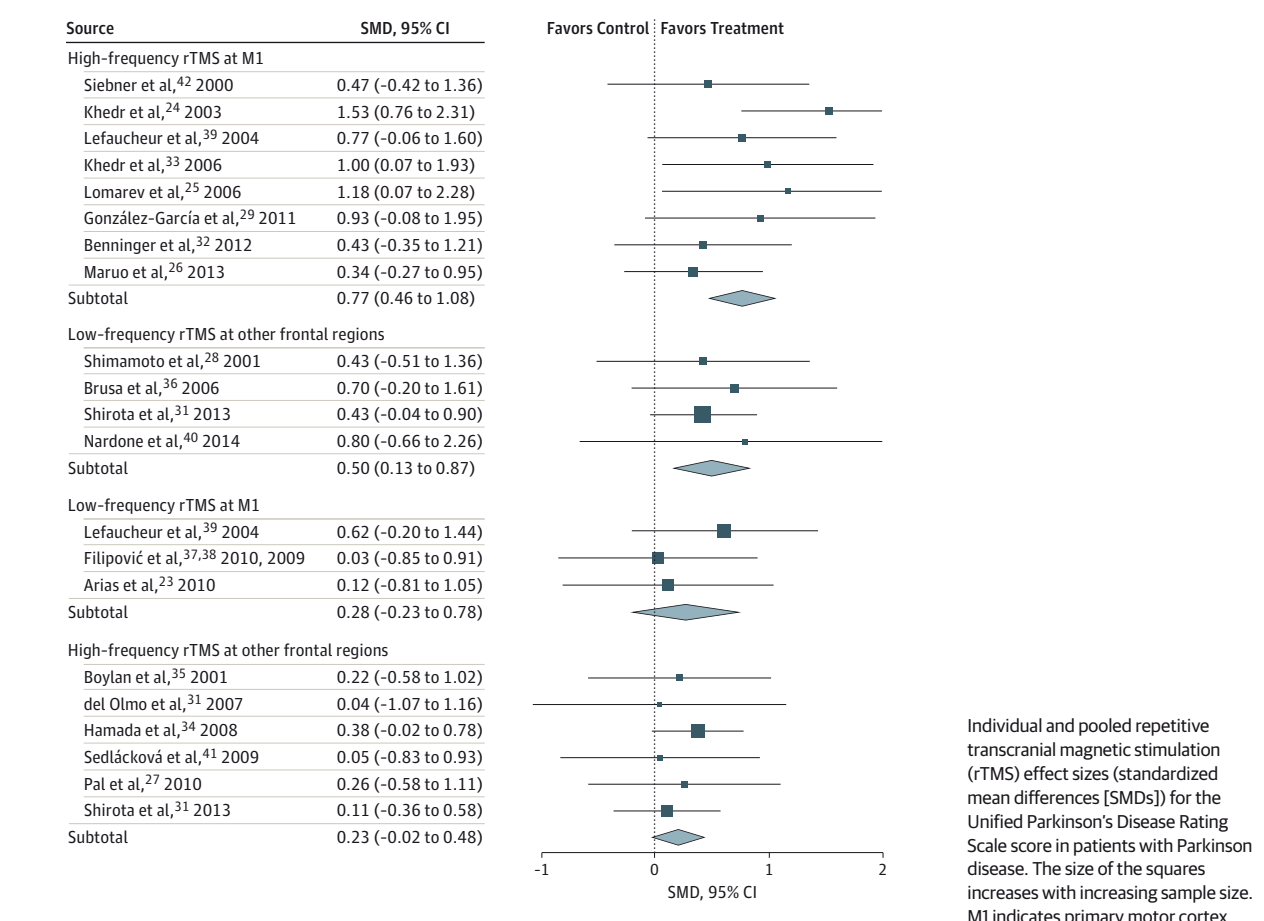


estimated from high-frequency rTMS targeting M1 (SMD, 0.77; $P < .001$) and from low-frequency rTMS applied over other frontal regions (SMD, 0.50; $P = .008$) were significant (Figure 2). The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (ie, high-others: SMD, 0.23, and low-M1: SMD, 0.28) were not significant.

Timing of Outcome Measurements

Seventeen trials^{23-29,31-33,35-42} assessed UPDRS-III at the short-term stage (<1 week), and 7 trials^{23-25,27,30,32,34} reported collecting long-term outcome (≥ 1 week). The short-term assessment was administered immediately after, 15 or 20 minutes after, 1 hour after, 12 hours after, or 1 day after rTMS sessions; the long-term assessment occurred 1 week, 1 month, or 12 weeks after rTMS sessions

Figure 2. Forest Plot for Subgroups



(Table 3). There was no significant difference between short-term rTMS effect (SMD, 0.50; 95% CI, 0.29-0.71) and long-term rTMS effect (SMD, 0.59; 95% CI, 0.19-1.00).

Medication State During Assessment

The UPDRS-III was assessed in 12 trials* during the off state and in 12 trials^{23,25,27-32,34,36-38,40} during the on state (Table 3). The estimated effect sizes were not significantly different between the off-state (SMD, 0.53; 95% CI, 0.27-0.79) and on-state (SMD, 0.39; 95% CI, 0.17-0.60) evaluations.

Sham-rTMS Conditions/Group

Different sham rTMS approaches were used in the included studies (Table 2). The rTMS effects for different sham rTMS approaches are summarized in eTable 2 in the Supplement. The subgroup analysis did not reveal a significant difference in effect sizes between different sham rTMS conditions/groups ($P = .73$).

Meta-regression

We performed meta-regression to examine whether effect sizes varied with rTMS variables. The mean (SD) number of rTMS treatment sessions was 5.95 (4.16) (range, 1-15), the mean number of rTMS pulses per session was 1285.50 (790.10) (range, 60-

*References 23-26, 28, 32, 33, 35, 37, 39, 41, 42

3000), and the mean number of rTMS pulses across treatment sessions (ie, number of pulses per session times the number of sessions) was 6754.00 (7649.99) (range, 480-30 000). The mean intensity was 95% (11%) of the active/resting motor threshold (range, 96%-120%), and the mean adjusted total number of rTMS pulses by intensity (ie, total number of pulses across sessions times intensity) was 7110.00 (7486.60) (range, 480-30 000).

The meta-regression analysis across trials showed that the number of pulses per session ($r = 0.20$; $P = .05$), the total number of pulses across sessions ($r = 0.25$; $P = .02$), and the adjusted total number of pulses across sessions by intensity ($r = 0.27$; $P = .01$) were significant predictors of the rTMS effect, suggesting that an increased number of pulses per session or across sessions yields enhanced the effects of rTMS. The number of sessions and intensity were not significant predictors.

Adverse Events

Thirteen studies^{24-27,30,32,33,36-40,42} evaluated the incidence of adverse events. Of these, 9 studies^{24,26,32,36-40,42} did not observe any adverse events. Shirota et al³⁰ and Pal et al²⁷ reported that 2 patients in the active-rTMS group in each one of the studies experienced mild headache that did not require medical treatment. Khedr et al³³ reported an occasional mild,

transient headache in some patients. Lomarev et al²⁵ reported that 1 patient in the active-rTMS group could not tolerate the pain under the coil and so withdrew from the study.

Sensitivity Analysis

We included 14 non-RCTs (18 trials in total; eReferences in the Supplement) into our meta-analysis to examine whether the results would change if we used a different inclusion criterion for study design. Inclusion of non-RCTs did not significantly alter findings. The pooled rTMS effect from both RCTs and non-RCTs remained moderate and significant (SMD, 0.50; 95% CI, 0.35-0.65; $z = 6.64$; $P < .001$), as did the pooled effect from RCTs.

Risk-of-Bias Assessment in Individual Studies

Ten studies† had incomplete data for risk-of-bias assessment. We were unable to locate one group of authors. Of the remaining 9 groups of authors, 5 individuals (56%) responded to information requests. The assessment of risk of bias for all included studies is summarized in eTable 3 in the Supplement. Overall, 11 of 19 included studies were at low risk of bias across all 6 domains. Similar to the risk-of-bias assessment, our quantitative analysis showed that 8 studies were of excellent methodologic quality (PEDro scale, 11 of 11), 10 studies were of good methodological quality (8-10), and 1 study was of fair methodologic quality (7). Additional analyses regarding whether the quality of studies would influence the overall rTMS effect size are described in the eResults and eTable 3 in the Supplement.

Risk-of-Bias Assessment Across Studies

Using the GRADE criteria, we characterized the quality of evidence presented in this meta-analysis as moderate. An initially assumed high level of evidence was downgraded once because less than 75% of the included studies were at low risk of bias across all domains. Despite the risk of bias, our meta-analysis exhibited homogeneity, directedness (ie, all participants were patients with PD), and precision (ie, >400 participants), and it is free from publication/selection bias across included studies.

Discussion

There are several relevant general conclusions one can draw based on the findings of this meta-analysis. First, the random effects across 20 RCTs revealed a significant medium effect size (SMD, 0.46) favoring active rTMS over sham rTMS in the reduction of motor symptoms for patients with PD. Second, the rTMS effects were significant when high-frequency (≥ 5 Hz) rTMS was targeted at M1 (SMD, 0.77; $P < .001$) or when low-frequency (≤ 1 Hz) rTMS was applied over other frontal regions (SMD, 0.50; $P = .008$). The effect sizes estimated from the other 2 combinations of rTMS frequency and site (high-others: SMD, 0.23; low-M1: SMD, 0.28) were not significant. Third, the meta-regression analysis showed that the number of pulses per session

($r = 0.20$; $P = .05$), the total number of pulses across sessions ($r = 0.25$; $P = .02$), and the adjusted total number of pulses across sessions by intensity ($r = 0.27$; $P = .01$) were significant predictors of rTMS effect, suggesting that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Fourth, no significant differences in rTMS effects were found between short-term (≤ 1 week: SMD, 0.50) and long-term (> 1 week: SMD, 0.59) outcome or between off-state (SMD, 0.53) and on-state (SMD, 0.39) during assessment. In addition, 13 studies evaluated the incidence of adverse events and, of these, no severe adverse events were reported. Finally, using the GRADE criteria, we characterized the quality of evidence of our meta-analysis as moderate.

One of the most important findings emerging from our meta-analysis is that the rTMS effects were stronger and significant when high-frequency rTMS was targeted at M1 or when low-frequency rTMS was applied over other frontal regions. We speculate that the results could be attributed to the state of brain activity (eg, degree of brain activation or interregional connectivity) at the time of stimulation. The state-dependent effects have been explained in terms of homeostatic plasticity, in which the form of synaptic plasticity—long-term potentiation or long-term depression—can be flexibly adjusted to stabilize corticospinal excitability depending on the state of brain activity.^{44,45} According to Siebner et al,⁴⁶ a brain region with a prolonged reduction in postsynaptic activity (thereby decreasing levels of activity) would reduce a “modification threshold,” favoring the induction of long-term potentiation. Conversely, a brain region with a prolonged increase in postsynaptic activity (thereby increasing levels of activity) would raise the modification threshold, favoring the induction of long-term depression. Increased levels of activity in the supplementary motor area (SMA) and prefrontal cortex have been found in patients with PD and animal models of PD relative to healthy controls.^{47,48} The increased levels of activity in these frontal regions may result in the inhibition of action via a hyperdirect pathway that connects several frontal regions (including the SMA, dorsolateral prefrontal cortex, and inferior frontal gyrus) and the subthalamic nucleus.⁴⁹ Successful therapies, such as deep brain stimulation or medication, are associated with reductions in activity of the SMA and prefrontal cortex.⁵⁰ A direct comparison between high-frequency (10 Hz) and low-frequency (1 Hz) rTMS over the SMA was conducted recently by Shirota et al³⁰ in patients with PD. Their results demonstrated a long-lasting beneficial effect of low-frequency rTMS targeted at the SMA, whereas this effect was not significant for high-frequency rTMS targeting the same brain region. Coupled with previous findings, the results of our meta-analysis suggest that the stimulation site or, more precisely, the state of brain activity of the stimulated brain region, will be critical for choosing an optimal rTMS frequency.

This article updates preceding meta-analyses with the inclusion of new RCTs, and our estimated medium rTMS effect size is in agreement with the effect sizes previously reported by Fregni et al⁷ and Elahi et al.⁶ In addition, our findings highlight the importance of considering the interplay between rTMS frequency and the state of brain activity of the rTMS site, as well as the number of pulses per session

†References 24, 26, 28, 31, 33, 36-39, 41, 42

and across sessions when developing a treatment protocol. Regarding the limitations of the present meta-analysis, our results could be constrained by the unclear risk of bias on certain domains owing to incomplete data in a few studies. In addition, several uncontrolled variables, such as medication use, disease stage, side of onset, side of rTMS stimulation, age, and sex, exist that could confound the results and must be acknowledged.

Conclusions

To date, evidence-based alterations in rTMS protocols for patients with PD have been only partially explored, and better rTMS protocols created from these findings have the potential to be more effective and more potent than current op-

tions. Future multimodal rTMS studies that combine the use of rTMS with different neuroimaging techniques are needed to better understand how brain activities are modulated by rTMS intervention, to more accurately and consistently target stimulation site, and to guide future rTMS treatment protocols.⁸ In addition, future research should attempt to establish a more precise relationship between rTMS effect and patients' clinical and demographic characteristics, such as medication use, stage of disease, side of onset, dominant motor symptoms (eg, bradykinesia, resting tremor, rigidity, postural instability, or levodopa-induced dyskinesia), nonmotor symptoms (eg, depression or cognitive dysfunction), age, or sex. Establishing specificity in rTMS intervention and elucidating the role these potential factors could play in moderating rTMS effects will be necessary to guide the optimization of rTMS intervention in the near future.

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