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Effect of Transcranial Magnetic Stimulation on Parkinson Motor Function—Systematic Review of Controlled Clinical Trials

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Abstract: The objective of this study was to evaluate the effects of repetitive Transcranial Magnetic Stimulation (rTMS) on motor signs in Parkinson's disease (PD). Medline, Embase, CINAHL, Web of Science, Scopus bibliographic, and Google Scholar databases were searched. Relevant controlled clinical trials published between January 1985 and October 2007 were extracted, reviewed, and validated according to the study protocol. The outcome of interest was the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS). We calculated the effect size for the included studies. Sensitivity analysis was performed to further assess factors that may change the results. Ten randomized, controlled clinical trials were included in the meta-analysis. Pooling of the results from these trials yielded an effect size of −0.58 in UPDRS for high-frequency rTMS studies and no significant effects for low-frequency rTMS studies. The benefit of high-frequency rTMS on motor signs in PD was confirmed by the meta-analysis. Lower frequency rTMS had little effect on motor signs in PD. © 2008 Movement Disorder Society

Key words: Parkinson's disease; meta-analysis; motor function; tremor

Since transcranial magnetic stimulation (TMS) was introduced by Barker et al. in 1985,[1] it has become a safe, noninvasive, and painless way to study the central nervous system. Repetitive pulses of TMS (rTMS) can modulate the excitability of the targeted brain area. rTMS at frequencies of 5 Hz and higher can enhance motor cortex excitability,[2,3] whereas lower frequencies rTMS (1 Hz and lower) can transiently depress cortical excitability.[4]

rTMS has been studied as a potential treatment in many neurological and psychiatric disorders. TMS and imaging studies suggested that there is decreased cortical excitability in Parkinson's disease (PD).[5] Several randomized controlled trials used rTMS to treat the PD motor symptoms. However, the sample size was small in these studies and certain effects may not be detected because of insufficient power. We therefore conducted a meta-analysis to evaluate the effect of TMS on motor signs in PD.

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MATERIALS AND METHODS

Search Strategy

The Medline, Embase, CINAHL, Web of Science, Scopus bibliographic, and Google Scholar databases were searched for studies investigating the effect of TMS in PD. Articles published between January 1985 and October 2007 were retrieved. The search terms were "TMS," "noninvasive brain stimulation," "UPDRS," and "PD." The reference lists from retrieved articles were also hand searched for any additional applicable studies. Conference abstracts and unpublished data were not included.

Selection Criteria

The search strategy outlined above yield 164 relevant articles. Inclusion criteria for this study were as

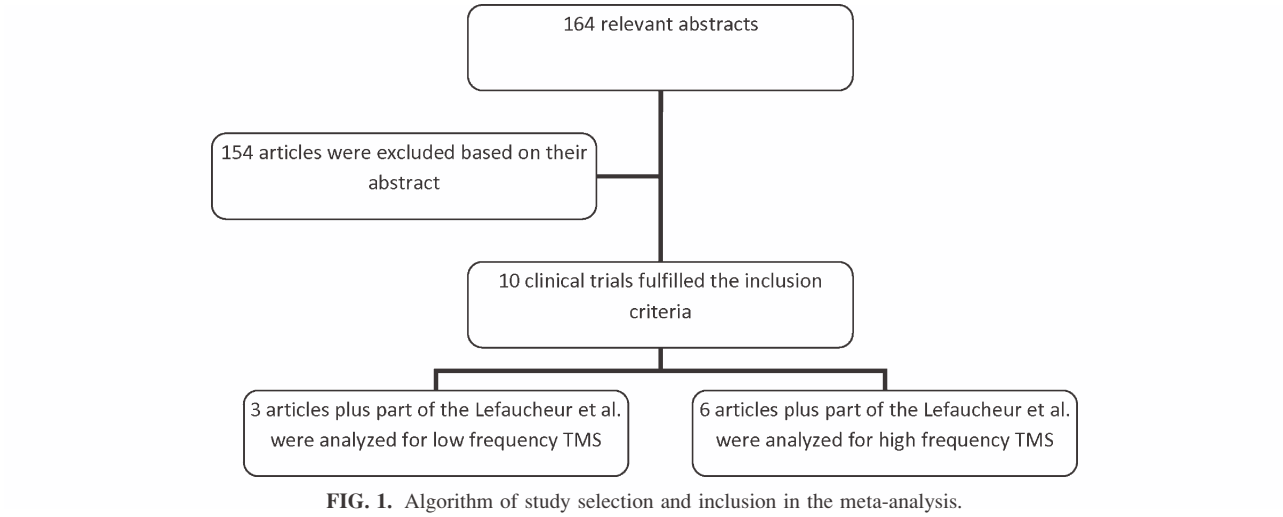

FIG. 1. Algorithm of study selection and inclusion in the meta-analysis.

follows: (1) prospective clinical studies, (2) must have a control group (3) the motor function was measured with the Motor (Part III) section of the Unified Parkinson's Disease Rating Scale (UPDRS), and (4) the results were reported in the form of mean and standard deviation. A few studies did not report the mean or standard deviation and we contacted the authors for these values. No language limitation was imposed.

Two authors independently reviewed the articles for the quality and validity of the trials. Data on the therapeutic regimen, sample size, and trial duration were extracted, and results were summarized in a standard summary data sheet. The selection process is shown in Figure 1. Disagreements were resolved by discussion and consensus between reviewers. Data from the selected studies are shown in Table 1.

Analysis

All the included studies were pooled and weighted. The data were analyzed using Statsdirect (2.6.1). Effect size and confidence intervals (95% CI) were calculated using the DerSimonian–Laird method. Effect size is the magnitude of a treatment effect and was calculated as the difference in scores between treatment and control groups divided by the standard deviation of the scores. The absolute effect size (d) of more than 0.5 was traditionally considered as medium to high effect[6] and is likely to be clinically relevant. The Cochran Q and I square inconsistency tests were used to examine heterogeneity. Funnel-plot analysis was used as bias indicator. Sensitivity analysis was performed to examine the effects of certain methodological variations among studies. Both random and fixed effect model were used to arrive at a conclusion.

RESULTS

The included trials represented 275 patients from 10 studies.[7–16] Sham treatment was given to 125 patients in the control groups, and 135 patients were in the rTMS groups. The treatment regimen, pulse intensity, and concomitant drug intake varied among studies and are summarized in Table 1. All the included studies were randomized controlled clinical trials. In most of the studies, the patients and UPDRS raters were blinded to the treatment assignment.[7,12–15,17] In one study, the patients and raters were not blinded.[16] In two studies, it was not stated whether the raters were blinded.[9,11]

We separated studies into two groups, those that used rTMS at frequencies higher than 1 Hz and studies that used 1 Hz or lower frequencies. The reason for this classification is the opposite effect of these frequencies on cortical excitability. Low-frequency rTMS (1 Hz or less) over the primary motor cortex produce inhibitory effects,[4] whereas high-frequency rTMS generally increases cortical excitability.[18,19] There were 152 patients in high-frequency group and 123 patients in low-frequency group. Patients in sham group of Lefaucheur et al.[13] were included in both the low- and high-frequency groups because this study compared both low- and high-frequencies rTMS to sham stimulation.

Sensitivity Analysis

For higher frequency rTMS studies, early (same day) versus late UPDRS evaluation did not change the final result. There is also no significant difference between the fixed and random effect models. Cochran

TABLE 1. *Summary of included studies*

Study	Blinding	Mean age (yr)	PD duration (yr)	Men/ women	H & Y stage	Evaluation time after rTMS	PD drug status	rTMS parameters						Part of UPDRS used	UPDRS after sham rTMS	UPDRS after real TMS
								Intensity	Pulses per day	Days	Frequency (Hz)	Coil	Site			
Siebner et al., 2000[16]	Nonblinded	57		7/3	1–2.5	1 hr	Off	90% MT	2,250	1	5	F8	M1	Part III	24.7 ± 7.4	18.0 ± 6.3
Okabe et al., 2003[15]	Blinded rater	67.2	8.8 ± 5.1	48/37		16 wk	Off	110% MT	100	1	0.2	C	M1	Part III	20.7 ± 12.1	24.8 ± 14.1
Shimamoto et al., 2001[7]	Blinded rater	65.1	7.0 ± 4.2	7/2	1.5–4	2 mo	On	0.31 T	60	1	0.2	C	Frontal	Total	45.0 ± 21.1	22.6 ± 12.2
del Olmo et al., 2007[9]	?	61.7		6/7	1–3	10 days	On	90% MT	450	10	10	F8	DLPFC	Part III	26.5 ± 12.2	25.9 ± 16.4
Khedr et al., 2003[12]	Blinded rater	57.7	3.26 ± 2.8	23/13	2–3	1 mo	Off	120% MT	2,000	10	5	F8	M1	Part III	23.7 ± 7.6	15.6 ± 6.5
Fregni et al., 2004[10]	Blinded rater	65.6	7.5	26/16	1–4	8 wk	Off	110% MT	200	10	15	F8	Left DLPC	Part III	40.1 ± 17.6	34.5 ± 15.6
Lomarev et al., 2006[14]	Blinded rater	64.5	13.8 ± 6.8	15/3	2–4	1 mo	On	100% MT	1,200	1	25	F8	Bilateral DLPFC	Part III	25.4 ± 11.1	22.0 ± 8.7
Boggio et al., 2005[8]	Blinded rater	65.2		15/10		8 wk	On	110% MT	200	10	15	F8	Left DLPFC	Part III	37.3 ± 16.9	27.7 ± 11.7
Ikeguchi et al., 2003[11]	?	68.8	7.8 ± 4.5	12 subjects	1–4	Immediate	Off	70% output	30	6	0.2	C	Prefrontal	Part III	~25 ± 12[a]	~24 ± 10[a]
Lefauheur et al., 2004[13]_1	Blinded rater	64		7/5	2.5–4	Immediate	Off	80% MT	600	1	0.5	F8	Left M1	Part III	~32 ± 10[a]	~28 ± 10[a]
Lefaucheur et al., 2004[13]_2	Blinded rater	64		7/5	2.5–4	Immediate	Off	80% MT	2,000	1	10	F8	Left M1	Part III	~32 ± 10[a]	~28 ± 10[a]

PD duration and UDPRS scores are expressed as mean ± standard deviation.

[a]Extracted from the figures.

PD, Parkinson's disease; H&Y, Hoehn and Yahr scale; rTMS, repetitive transcranial magnetic stimulation; MT, motor threshold; T, tesla; F8, figure of eight; C, circular; M1, motor cortex; DLPFC, dorsolateral prefrontal cortex; UPDRS, Unified Parkinson's Disease Rating Scale.

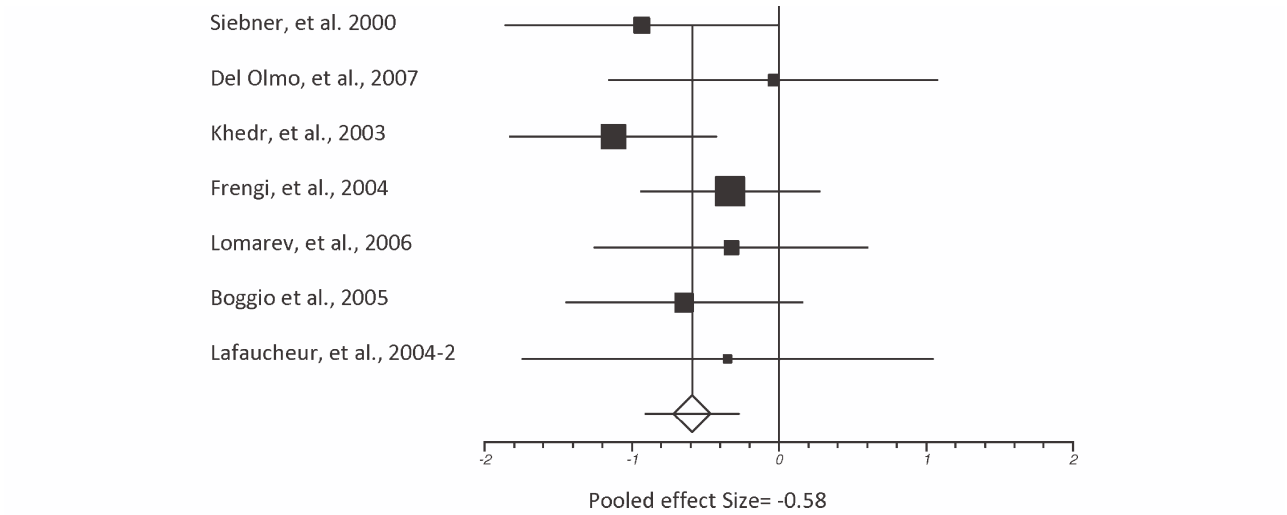

FIG. 2. Individual and pooled effect size for motor UPDRS in PD patients treated with high-frequency rTMS. The size of the squares increases with increasing sample size.

Q test for heterogeneity (Cochran Q = 4.83; P = 0.56) and I square inconsistency (I^2 = 0%) tests indicate that the included studies for high-frequency rTMS are sufficiently homogenous for the result to be combined in a fixed effect model (Fig. 2).

For lower frequency TMS studies, the results were heterogeneous (Cochran Q = 11.49; $P < 0.01$). I^2, a measure of the inconsistency of the results and is less dependent on the number studies than the Cochran Q, also showed high inconsistency between studies. Sensitivity analysis of the evaluation time (immediately after vs. days to months after) resulted in significant difference in effect sizes when Okabe et al. study was included. The results from remaining studies showed acceptable consistency (I^2 = 24.4%; Cochran Q = 2.64; P = 0.266). However, the Okabe et al. study was the largest and had more patients than the other low-frequency studies combined.

High-Frequency rTMS Studies

The pooled mean effect size estimate (d+) is calculated using direct weights defined as the inverse of the variance of d for each study/stratum, which was −0.58 (95% CI = −0.90 to −0.27; P = 0.0003) for the fixed effect model and −0.58 (95% CI = −0.90 to −0.27) for the random effect model. Therefore, with the random effects model, the true effect size was at least 0.58 lower in the treatment groups compared with the control groups (Fig. 2). This is equivalent to a 6.68 (95% CI = −9.66 to −3.69) point decrease in motor UPDRS score in the random and fixed effect models.

Regression of normalized effect versus precision for high-frequency studies is shown in Figure 3. Although we found no significant asymmetry (Egger: bias = 0.82 (95% CI = −2.98 to 4.6) P = 0.6), because of the small number of studies and different methodologies used, the results should be interpreted with caution and the power of this analysis is low (Fig. 3).

Low-Frequency rTMS Studies

Studies in this category are different both in their design and in the reported outcomes. The largest study by Okabe et al.[15] on 85 patients showed decrease in motor UPDRS from 26.1 ± 16.3 (mean ± SD) to 24.8 ± 14.1 rTMS group but the reduction in motor UPDRS was even greater in the sham rTMS group (from 22.3 ± 1 2.6 to 20.7 ± 12.1).

Shimamoto et al.[7] reported total UPDRS but not motor UPDRS, which is our outcome of interest. Therefore, we analyzed the two remaining studies with the total of 16 patients in each group and showed no significant reduction in motor UPDRS between control and treatment group. The effect size calculated using the random effect model (DerSimonian–Laird method for weighted mean difference) was −1.86 (P = 0.62) (Fig. 4).

DISCUSSION

This study confirms that high-frequency rTMS can significantly reduce motor signs in PD patients and all included trials showed this reduction. On the other hand, our low-frequency rTMS studies showed variable

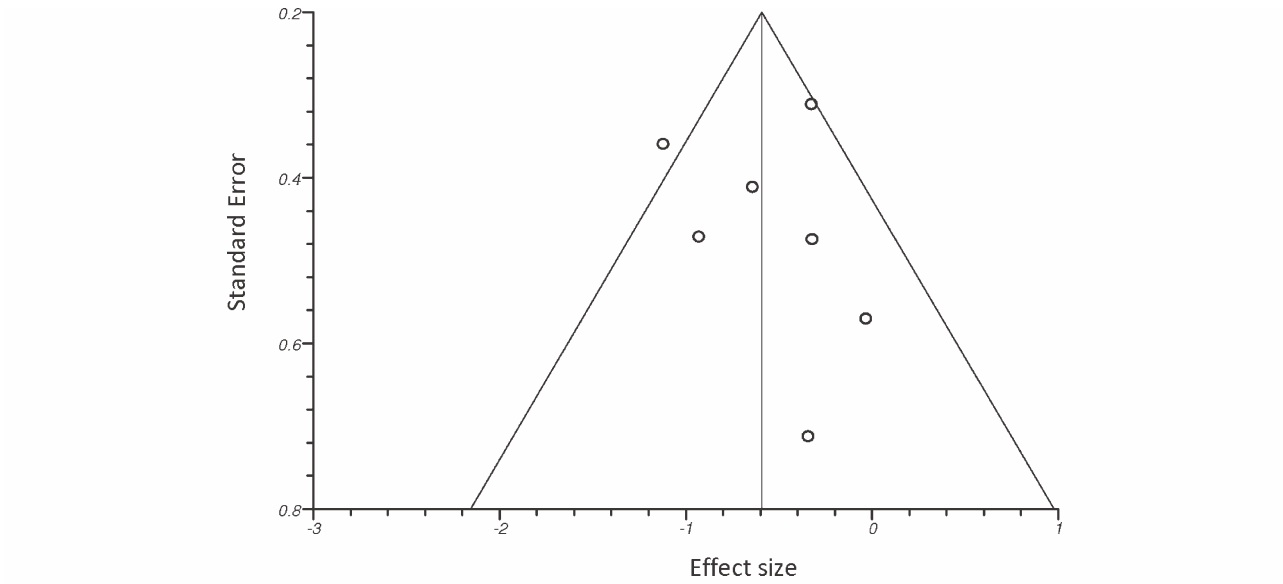

FIG. 3. Bias indicator for high-frequency rTMS controlled studies. Each dot represents one study. The horizontal axis shows the effect size. The vertical axis shows the standard error of the effect size, which is an indicator of the sample size. Larger studies have smaller standard errors and they are located in higher part of the graph and smaller studies are in lower part of the graph. The vertical line represents the pooled effect size. The diagonal lines show linear extrapolation of the 95% confidence limit of the effect size.

results with no significant overall improvement in UPDRS scores.

There are several limitations of our study. First, the study outcomes were not uniformly reported. Second, there are considerable differences in the rTMS protocol. Moreover, the analyzed studies also varied in patient selection criteria, demographics, and duration of follow-up and stages of PD. We used sensitivity

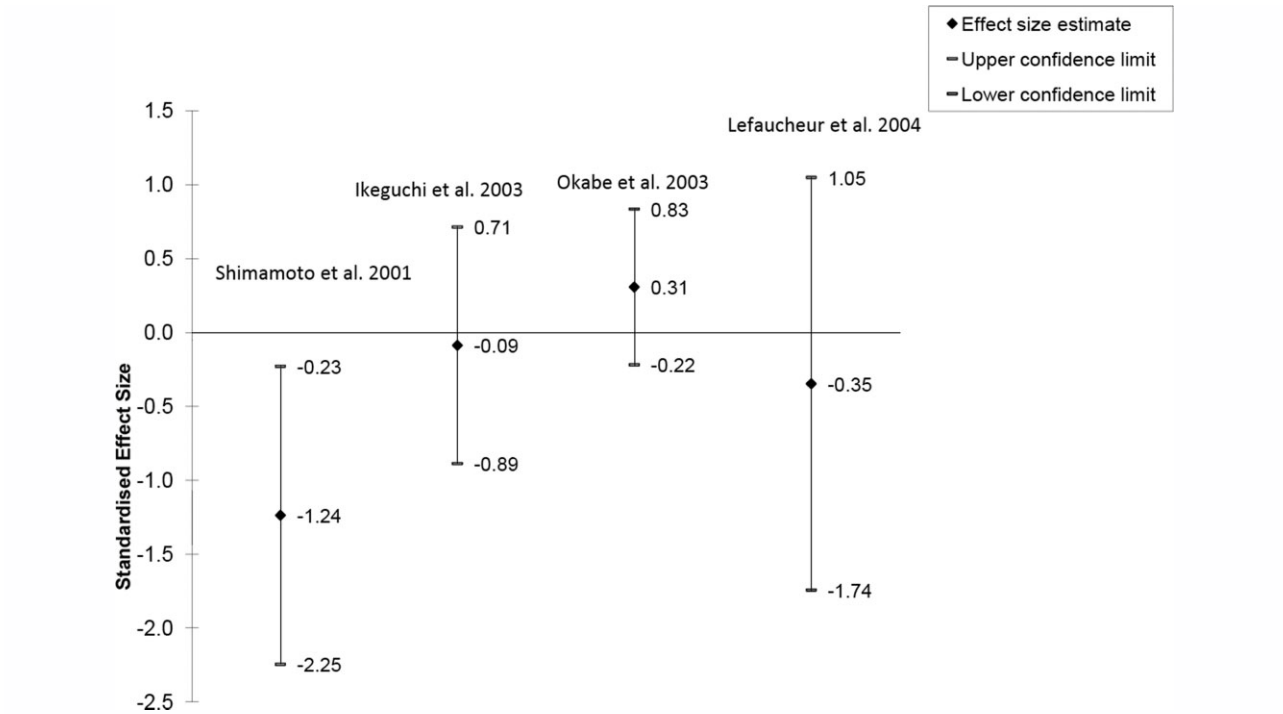

FIG. 4. Standardized effect sizes for with low-frequency rTMS studies. The mean and 95% confidence limits for each study are shown.

analysis to examine some of these sources of the heterogeneity such as time to evaluate motor function after intervention. We also used I^2 as an index of inconsistency; if there was little variation between trials, I^2 would be low and a fixed effects model might be appropriate. An alternative approach, "random effects," allows the study outcomes to vary in a normal distribution between studies. Many investigators consider the random effects approach to be a more natural choice than fixed effects model, for example, in the context of medical decision making.[20] We therefore used both random effect and fixed effect models of analysis.

The different blinding techniques in rTMS studies may also have influenced our results. Several different methods of sham (placebo) stimulation were used. Five trials used a sham coil,[7,8,10,13,15] three studies used changes in coil angle,[9,12,16] one study stimulated the occipital area,[11] and one study flipped the side of the coil applied to the scalp.[14] However, the findings from high-frequency rTMS studies are consistent and the effects of this variability are likely to be small.

Motor UPDRS, our outcome of interest, is a widely accepted scale. It had been shown to be a reliable and valid, with high internal consistency.[21] Our study supports the hypothesis that high-frequency rTMS can modulate underactive brain regions in PD patients[22,23] and produce clinically significant motor improvement. On the other hand, the lower frequency rTMS, although potentially safer, do not have such effect. However, low-frequency rTMS is a potential treatment for levodopa-induced dyskinesia, which was not analyzed in this study.[24,25]

Fregni et al.[26] reviewed the efficacy of rTMS and electroconvulsive therapy (ECT) for the treatment of motor dysfunction in PD. They calculated a pooled effect size of 0.62 in a random effects model for TMS treatment and 1.68 for ECT treatment, and from a fixed effects model the effect size was 0.59 for TMS and 1.55 for ECT treatment. Our study included more recently TMS literature,[9,14] and we separated high- and low-frequencies rTMS studies.

Although high-frequency rTMS has potential adverse effects, including induction of seizures, it is generally safe when used within safety guidelines.[27,28] It is well tolerated, easy to apply, and can be used as an adjunct to other treatment modalities in PD patients. Some of the factors that limit wide spread clinical use of therapeutic rTMS are the cost and limited availability of the devices to specialized centers, less knowledge of potential long-term side effects compared with drug therapies, and the requirement for skilled personnel. However, our results showed that high-frequency rTMS is a promising treatment of motor symptoms in PD. A large, randomized controlled trial with appropriate follow-up will be useful to further define its role in the treatment of PD. Future studies are also needed to clarify the optimal stimulation parameters, how the different stages of PD affect the response to rTMS, and the effects of rTMS on other aspects of the disease such as gait, cognition, and memory.

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REFERENCES

1. Barker AT, Jalinous R, Freeston IL. Noninvasive magnetic stimulation of human motor cortex. Lancet 1985;2:1106–1107.
2. Pascual-Leone A, alls-Sole' J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–858.
3. Pascual-Leone A, Valls-Sole J, Brasil-Neto JP, Cohen LG, Hallett M. Akinesia in Parkinson's disease. I. Shortening of simple reaction time with focal, single-pulse transcranial magnetic stimulation. Neurology 1994;44:884–891.
4. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–1403.
5. Ellaway PH, Davey NJ, Maskill DW, Dick JP. The relation between bradykinesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects. Electroencephalogr Clin Neurophysiol 1995;97:169–178.
6. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, New Jersey: Lawrence Erlbaum Associates; 1988.
7. Shimamoto H, Takasaki K, Shigemori M, Imaizumi T, Ayabe M, Shoji H. Therapeutic effect and mechanism of repetitive transcranial magnetic stimulation in Parkinson's disease. J Neurol 2001; 248 (Suppl 3):III48–III52.
8. Boggio PS, Fregni F, Bermpohl F, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord 2005; 20:1178–1184.
9. del Olmo MF, Bello O, Cudeiro J. Transcranial magnetic stimulation over dorsolateral prefrontal cortex in Parkinson's disease. Clin Neurophysiol 2007;118:131–139.
10. Fregni F, Santos CM, Myczkowski ML, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:1171–1174.
11. Ikeguchi M, Touge T, Nishiyama Y, Takeuchi H, Kuriyama S, Ohkawa M. Effects of successive repetitive transcranial magnetic stimulation on motor performances and brain perfusion in idiopathic Parkinson's disease. J Neurol Sci 2003;209:41–46.
12. Khedr EM, Farweez HM, Islam H. Therapeutic effect of repetitive transcranial magnetic stimulation on motor function in Parkinson's disease patients. Eur J Neurol 2003;10:567–572.
13. Lefaucheur JP, Drouot X, Von Raison F, Menard-Lefaucheur I, Cesaro P, Nguyen JP. Improvement of motor performance and modulation of cortical excitability by repetitive transcranial magnetic stimulation of the motor cortex in Parkinson's disease. Clin Neurophysiol 2004;115:2530–2541.
14. Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermann EM, Hallett M. Placebo-controlled study of rTMS for the treatment of Parkinson's disease. Mov Disord 2006;21:325–331.

15. Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in Parkinson's disease. Mov Disord 2003;18:382–388.
16. Siebner HR, Rossmeier C, Mentschel C, Peinemann A, Conrad B. Short-term motor improvement after sub-threshold 5-Hz repetitive transcranial magnetic stimulation of the primary motor hand area in Parkinson's disease. J Neurol Sci 2000;178:91–94.
17. Fregni F, Boggio PS, Bermpohl F, et al. Immediate placebo effect in Parkinson's disease—is the subjective relief accompanied by objective improvement? Eur Neurol 2006;56:222–229.
18. Fujiki M, Steward O. High frequency transcranial magnetic stimulation mimics the effects of ECS in upregulating astroglial gene expression in the murine CNS. Brain Res Mol Brain Res 1997; 44:301–308.
19. Speer AM, Kimbrell TA, Wassermann EM, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000;48:1133–1141.
20. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making 2005;25: 646–654.
21. Martinez-Martin P, Gil-Nagel A, Gracia LM, Gomez JB, Martinez-Sarries J, Bermejo F. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord 1994;9:76–83.
22. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995;118:913–933.
23. Tada Y. Motor association cortex activity in Parkinson's disease—a functional MRI study. Rinsho Shinkeigaku 1998;38:729–735.
24. Wagle-Shukla A, Angel MJ, Zadikoff C, et al. Low-frequency repetitive transcranial magnetic stimulation for treatment of levodopa-induced dyskinesias. Neurology 2007;68:704–705.
25. Koch G, Brusa L, Caltagirone C, et al. rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. Neurology 2005;65:623–625.
26. Fregni F, Simon DK, Wu A, Pascual-Leone A. Non-invasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature. J Neurol Neurosurg Psychiatry 2005;76:1614–1623.
27. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998;108:1–16.
28. Chen R, Gerloff C, Classen J, Wassermann EM, Hallett M, Cohen LG. Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. Electroencephalogr Clin Neurophysiol 1997;105:415–421.