Noninvasive brain stimulation for Parkinson's disease: a systematic review and meta-analysis of the literature

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Abstract

Objective – To conduct a systematic review and meta-analysis to quantify the efficacy of noninvasive brain stimulation – transcranial magnetic stimulation (TMS) or electroconvulsive therapy (ECT) - for the treatment of motor dysfunction in patients with Parkinson's disease (PD).

Data sources – MEDLINE and other databases. Reference lists and conference abstracts were examined for further relevant articles.

Study selection - We included prospective studies that evaluated the effects of either TMS or ECT on motor function in PD using the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) for TMS studies and any continuous measures of motor function in PD for ECT studies.

Data Synthesis - 12 studies for TMS and 5 studies for ECT met our inclusion criteria. The pooled effect size (standardized mean difference between pre-treatment versus post-treatment means) from the random effects model was 0.62 (95% confidence interval, 0.38, 0.85) for TMS treatment and 1.68 (0.79, 2.56) for ECT treatment; and from the fixed effects model was 0.59 (0.39, 0.78) for TMS treatment and 1.55 (1.07, 2.03) for ECT treatment.

Conclusions - This meta-analysis shows that TMS, across applied stimulation sites and parameters, can exert a significant, albeit modest, effect on the motor function of patients with PD. ECT also may exert a significant effect on the motor function in PD patients. Variability in study methods and other limitations preclude definite conclusions about the clinical utility of these techniques in PD patients, but our findings suggest the importance of well designed clinical trials to address this question.

Keywords: Parkinson's disease, transcranial magnetic stimulation, electroconvulsive therapy, meta-analysis

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease that predominantly affects elderly people, and thus its prevalence tends to increase with the growing age of the population. Although medications are the mainstay for the treatment of the motor symptoms of PD, the clinical utility of these medications tends to become limited over the years, often due to adverse effects such as dyskinesias (see review: Olanow, 2001[1]). Non-pharmacological approaches, such as deep brain stimulation (DBS), are effective in the treatment of PD motor symptoms in selected patients. For instance, in a meta-analysis, Boucai et al (2004) showed that functional neurosurgery for PD is effective to improve the motor function and dyskinesias[2], and may even offer advantages over pharmacologic approaches. Although recent development of invasive brain stimulation for PD, such as improvement of DBS technique and minimally invasive cortical stimulation, has reduced the surgical risks, it still requires a costly and invasive neurosurgical procedure. Therefore, a noninvasive form of brain stimulation would be desirable. Electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are types of noninvasive brain stimulation that have been used in PD patients and been suggested as possible therapeutic tools.

rTMS is a noninvasive, well-tolerated technique of brain stimulation based on electro-magnetic induction. The effects of rTMS spread from the directly targeted brain region along specific neural connections to distant cortical and subcortical regions.[3, 4] Therefore, rTMS provides a mean to modulate activity in specific neural networks, using cortical targets as 'entry ports'. Several studies have investigated the use of rTMS to treat motor symptoms of PD patients. The results of these trials are mixed and no conclusion has been reached so far. ECT induces current in the brain by direct transcranial application of a strong current pulse and is associated with the induction of a seizure. The mechanisms of action of ECT are unclear, but several studies have reported that ECT is effective to treat PD patients. However, most of these studies are case reports, and thus, no conclusions have been reached about the utility of ECT in patients with PD.

Therefore, the question of whether noninvasive brain stimulation (ECT or TMS) is effective to treat PD remains unclear. This information would be important to either support, or provide evidence against, future larger trials of noninvasive brain stimulation for PD. We perform a systematic review of studies that examined the effects of TMS or ECT on motor function of PD. We critically assess the heterogeneity of these study results to better understand the factors that may contribute to a better motor outcome following noninvasive brain stimulation.

Methods

Literature Search

The first step of our meta-analysis was a selective literature search for articles published from 1980 to January 2005. We used the following databases: MEDLINE, EMBASE, Cochrane, SCIELO. In addition, we examined reference lists in systematic reviews and retrieved papers, searched conference abstracts and talked to clinical experts. To check for unpublished trials, we contacted experts on the field, consulted the CRISP database and searched for abstracts. Our key search terms were "*Parkinson's disease*", "*transcranial magnetic stimulation*", "*electroconvulsive therapy*", "*brain stimulation*" and "*noninvasive brain stimulation*". This strategy yielded 127 studies for *transcranial magnetic stimulation and PD* and 143 studies for *electroconvulsive therapy and PD*. Using the terms "*Parkinson's disease*" with either "*brain stimulation*" or "*noninvasive brain stimulation*" did not yield any additional studies.

Selection Criteria

We included prospective studies that evaluated the effects of either TMS or ECT on motor function in PD. We adopted the following inclusion criteria: (1) Manuscript written in English, German, Italian, French, Spanish and Portuguese language; (2) Use of TMS or ECT in PD patients; (3) Motor effects measured with the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) for TMS studies or any other continuous clinical scale that

evaluated the motor symptoms of PD for ECT studies – we decided to use other clinical scales, rather than only UPDRS (e.g., Webster scale was used in Fall's study[5] and Andersen's study[6]) for ECT studies, as most of them were done in the beginning of the 80's and therefore did not report UPDRS scores; (4) The report had to be published in a book, journal, proceeding, or indexed abstraction; (5) The studies had to report the mean and standard deviation of the motor function before and after the treatment or provide other statistical parameters that could be used to deduce these values. For studies that met our criteria but did not report these scores, the authors were contacted to provide these data if available. Four out of five consulted authors replied to our request, and three out of four of these authors could provide these data. For cases where 2 or more published studies reported overlapping data sets, we chose the study with the largest population. Case reports or series of case reports were excluded.

Extraction of the outcome measures

The data were collected using a semi-structured form for each study by one of the authors and checked by another investigator. The discrepancies were resolved by consensus and a third author consulted if needed. All the following variables were extracted: (1) Mean and standard deviation of the motor section (part III) of the UPDRS (or other clinical scale for the ECT studies) for baseline and after the treatment for the active and placebo group (if the study was sham-controlled); (2) Mean and SD for the follow-up period evaluation (if these data were available); (3) Study design; (4) Demographic and clinical characteristics (e.g., number of patients, age, gender, disease duration); (5) Baseline motor UPDRS and Hoehn and Yahr; (6) TMS parameters (frequency, intensity, number of pulses and number of sessions) (7) ECT parameters (uni/bilateral, intensity, number of sessions).

For the studies with more than one active group (i.e., two different doses of TMS), we considered each group as one study in the quantitative analysis. This approach was used for 3 studies: Mally et al. (1999)[7] (four different doses of TMS); Groot et al (2001)[8] (two different

doses of TMS) and Lefaucheur et al (2004)[9] (two different doses of TMS).

Systematic review

Because the literature about ECT and TMS in PD consists mainly of uncontrolled studies, we included both controlled and uncontrolled studies, and compared the results between these two sets of studies.

Qualitative Analysis

We first assessed sources of heterogeneity across studies. Major features that were contributing to between-study heterogeneity were determined a priori and evaluated in our analysis, including study design (controlled and uncontrolled studies); PD clinical characteristics (motor disability – baseline motor UPDRS, baseline Hoehn and Yahr - and duration of disease); demographic characteristics (age, gender) and treatment characteristics (TMS and ECT parameters). Although analyses of subsections of the motor UPDRS, such as tremor, rigidity, gait, and bradykinesia, would have provided useful information, these data were not available in most of the selected studies.

Quantitative analysis

All of our analyses were performed using Stata statistical software, version 8.0 (Statacorp, College Station, Texas). For the continuous measures of motor function, we calculated the standardized mean difference (Cohen d) based either on the pre- and post-test values of one group within each study or comparison of the mean changes in pre-treatment to post-treatment UPDRS of the two independent subject groups (sham and active rTMS) in the controlled trials using the means and SDs, or estimated from the graphs (Ikeguchi's study[10]). For the post-treatment value, we used the evaluation that was carried out immediately after the treatment.

However, for the trials that also reported an additional post-treatment evaluation within 2 months of the end of the treatment (most of them reported a follow-up at 30 days of the end of treatment), we conducted a separate analysis to evaluate the long-term effects of this treatment comparing it to the baseline value (pre-treatment). In the next step, we measured the pooled weighted effect size using the random and fixed effects models. The random effect model gives a relatively more weight to smaller studies and wider confidence intervals than the fixed effect models and its use has been advocated if there is heterogeneity between studies.[11] Although the test for heterogeneity failed to detect heterogeneity in one of our analysis, we decided to report both values (from random and fixed effects model). As all rTMS trials reported the results using the motor UPDRS, we also showed the weighted pooled mean difference to facilitate the interpretation of the results.

Heterogeneity was evaluated with Q statistic. Although some of these tests disclosed a non-significant heterogeneity, this test may have been underpowered due to the small number of studies; therefore, we synthesized the results from individual studies by using the DerSimonian and Laird random-effects model to incorporate both within and between study variability and the fixed effect models to compare the results.

As our meta-analysis included small studies and these studies usually have large effect sizes, we evaluated the influence of individual studies computing the meta-analysis estimates omitting one study at the time.

As we expected heterogeneity in the effect of treatment between studies, we assessed this source of the heterogeneity, in an exploratory manner, performing a meta-regression in which the outcome was the effect size and the covariates were the variables that could have influenced the effect size, such as study design; demographic and clinical characteristics; and TMS parameters. Medication use was not included in this analysis because these data are unavailable for most of these studies. This analysis was not performed for the ECT analysis, as there were only 5 small studies for this analysis.

We assessed publication bias using Begg modified funnel plot,[12] in which the standardized mean difference from each plot was plotted against the standard error.

Results

Studies retrieval

Using the words "*Transcranial magnetic stimulation"* and "*Parkinson's disease*", we could find 127 citations. Five additional citations were found searching the bibliographies of the retrieved papers and reviews. Therefore, 132 publications were identified and carefully reviewed. Initially, we excluded 110 references because of the following reasons: TMS was used to measure other neurophysiologic parameters, reviews, case reports, other topics and other languages. Of the remaining 22 references, 10 were excluded because they used other endpoints, rather than UPDRS, to measure motor improvement, such as reaction time,[13-17] motor evoked potential/silent period[18, 19] and speed of movement[19, 20] and poor data reporting (the mean and SD for the baseline and post-treatment evaluation did not agree with the p-value provided in the study table[21]). Thus 12 studies were selected for the final analysis, eight of them being placebo-controlled studies and four of them being uncontrolled studies.

The same process was performed for ECT. Using the words "*Electroconvulsive therapy"* and "*Parkinson's disease*", we could find 143 citations. Three additional citations were found searching the bibliographies of the retrieved papers and reviews. Of the 146 publications identified, we excluded 135 because of the following reasons: reviews, case reports, other topics and other languages. Of the remaining 11 references 6 were excluded because they were case reports,[22-24] did not give numbers regarding the motor outcome,[25, 26] or were duplicated studies,[27] Therefore 5 studies were selected for the final analysis.

Demographic findings of these studies are summarized in table 1.

Table 1. Demographic findings

	TMS		**ECT**	
Number of patients	224		49	
Age (years, mean ± SD)	63.0	3.8	68.6	3.6
Sex (M:F ratio)	1.3:1		1.1:1	
Disease duration (years, mean ± SD)	6.6	3.1	13.8	2.8
Baseline UPDRS (mean ± SD)	25.7	8.8	*	
Baseline HY (mean ± SD)	2.4	0.8	3.6**	

* Not reported in the ECT trials, ** Just reported in one ECT trial

Meta-analysis results for TMS trials

Characteristics of the TMS trials are summarized in table 2. Initially, we combined data from the controlled, double-blind studies only. Pooling the data of the eight controlled trials, we found a pooled effect size (standardized mean difference between before and after TMS application) from the random effects model of 0.60 (95% C.I., 0.24, 0.96) and from the fixed effects model of 0.56 (95% C.I., 0.30, 0.81) (figure 1). The test for heterogeneity failed to show a significant heterogeneity (Q8, Chi-square=15.4, p=0.052). These results are similar to the pooled effect size when all studies are included (rather than just double-blind studies): the pooled weighted effect size from the random effects model was 0.62 (95% C.I., 0.38, 0.85) and from the fixed effects model was 0.59 (95% C.I., 0.39, 0.78) – no significant heterogeneity was found (Q17, 24.45, p=0.11) (figure 1). This result indicates that the inclusion of uncontrolled studies into our meta-analysis did not alter the outcome of our analysis.

As patients with PD can have a strong placebo effect, we analyzed the effect size on UPDRS change (comparison between before and after treatment) in the sham rTMS group. Although the method of rTMS placebo varied across the different studies – e.g., sham coil,[9, 28-30] active coil angled at either 45°[31, 32] or 90°[33] and active coil stimulation of occipital area,[10] these methods are not expected to cause motor function improvement, other than perhaps through a

placebo effect. For the studies that used active- and sham-control groups, such as Okabe et al. (2003),[29] we used the data from the sham-control group. This analysis disclosed that there was a small, no significant placebo effect. The pooled weighted effect size from the random effects model was 0.1 (95% C.I., -0.16, 0.35). The fixed effects model yielded almost the same value as the random effects model, since the test for heterogeneity showed that these data are strongly homogeneous (Q7, Chi-square=1,14, p=0.992) (figure 2).

In order to check whether the effects shown by the TMS studies were significant when compared to the placebo group, we calculated the effect size using the changes between pre- and post-treatment mean UPDRS scores for the active versus sham TMS groups. This analysis showed a pooled effect size from the random effects model of 1.19 (95% C.I., 0.44, 1.94) and from the fixed effects model of 0.87 (95% C.I., 0.59, 1.15). The test for heterogeneity confirmed that there was a significant heterogeneity in this analysis (Q7, Chi-square=45.61, p<0.0001). This finding demonstrates that the motor improvement observed in the active group cannot be explained by a placebo effect only (Figure 3).

Table 2 – TMS study characteristics

Author	Year	Patients*	Frequency	Pulses	Intensity	Coil	Sessions	Site
Mally [34]	1999	10	1	30[1]	0.2MT	C	10	Vertex
Mally_1 [7]	1999	12	1	30	0.34 T	C	10	Vertex
Mally_2 [7]	1999	12	1	30	0.34 T	C	14	Vertex
Mally_3 [7]	1999	12	1	30	0.57T	C	10	Vertex
Mally_4 [7]	1999	12	1	30	0.80T	C	14	Vertex
Tergau [35]	1999	7	1,5,10,20	1000	90%MT	C	4	N/A
Siebner [32]	2000	10	5	2250	90% MT	F8	1	M1
Boylan [31]	2001	10	10	2000	110%MT	F8	1	SMA
Groot_1 [8]	2001	9	5	2250	90% MT	F8	1	M1
Groot_2 [8]	2001	9	5	2250	90% MT	F8	1	M1
Shimamoto [30]	2001	9	0.2	60	700V	C	8	Frontal
Dragasevic [36]	2002	10	0.5	200	110%MT	C	10	Prefrontal
Ikeguchi [10]	2003	10	0.2	60	70%**	C	6	Prefrontal
Khedr [33]	2003	19	5	2000	120%MT	F8	10	M1
Okabe [29]	2003	85***	0.2	100	110%MT	C	8	Vertex
Fregni [28]	2004	21	15	3000	100%MT	F8	10	Prefrontal
Lefaucheur_1 [9]	2004	12	0.5	600	80%MT	F8	1	M1
Lefaucheur_2 [9]	2004	12	10	2000	80%MT	F8	1	M1

only active rTMS group, ** Maximal output device, *** Total of patients (sham and active)
[1]Twice a day. Coil – C=circular; F8=figure of eight; M1 – primary motor cortex; N/A – not available

In order to provide a more meaningful clinical result, we calculated the pooled weighted mean difference in the motor UPDRS scores (difference of the means between before and after treatment). Performing this analysis, the pooled weighted mean difference was 5.89 (95% C.I., 3.36, 8.43) for the random effects model and 4.14 (95% C.I., 2.78, 5.50) for the fixed effects model (table 3).

Table 3 – Pooled weighted effect size and mean difference

	Random effects model	95% confidence interval		Fixed effects model	95% confidence interval		Q statistic - p-value
Pooled weighted mean difference (All studies)	5.90	3.36	8.44	4.15	2.79	5.50	0.001
Pooled weighted effect size[1] (All studies)	0.62	0.38	0.85	0.59	0.40	0.78	0.11
Pooled weighted effect size[1] (controlled studies)	0.60	0.24	0.96	0.56	0.30	0.81	0.052

[1] effect size – standardized mean difference. The mean difference was calculated using the change from pre- to post treatment UPDRS for the active group

We performed a meta-regression analysis in which we evaluated the following covariates: year of study, study design, age, disease duration, baseline Hoehn and Yahr, frequency of stimulation, number of TMS pulses per session, intensity of TMS, number of sessions. Although we performed multiple testing for this analysis, we considered these to be exploratory analyses and so we did not correct for multiple comparisons. The meta-regression would not support the inclusion of all variables at the same time given the small number of studies and patients. These analyses showed that none of these variables could explain the source of the variability across the different studies (table 4).

Table 4 – Meta-regression results

Covariates*	Coefficient	Std Error	95% confidence interval		P-value
Year	-0.036	0.063	-0.160	0.088	0.567
Design	-0.061	0.248	-0.547	0.425	0.805
Age	-0.039	0.038	-0.115	0.036	0.304
Disease duration	-0.038	0.056	-0.147	0.071	0.493
Hoehn and Yahr	0.287	0.189	-0.083	0.658	0.129
Frequency	-0.048	0.250	-0.538	0.442	0.848
Pulses	-0.00005	0.00011	-0.00027	0.00017	0.671
Intensity	-0.182	0.243	-0.658	0.293	0.452
Number	0.016	0.027	-0.037	0.070	0.550

*Covariates characteristics: year of study (continuous), design of the study (controlled vs. uncontrolled), age (continuous), disease duration (continuous), baseline Hoehn and Yahr (continuous), frequency of stimulation (dichotomized: low- (<= 1Hz) or high-frequency (> 1Hz)), number of TMS pulses per session (continuous), intensity of TMS (dichotomized (above or below the motor threshold)), number of sessions (dichotomized: 1 or multiple sessions).

As some studies evaluated the long-lasting effects of rTMS, we analyzed this effect comparing the motor function scores 30 days after the completion of treatment against the baseline motor function. Six studies performed follow-up evaluation – three of them were controlled and the other three were uncontrolled trials. Follow-up evaluation was done 30 days after the termination of treatment, except for the study of Fregni et al (2004)[28] that evaluated the patients two months after treatment. The pooled weighted effect size (comparing motor function at follow-up vs. baseline) from the random effects model was 0.71 (95% C.I., 0.26, 1.17) and from the fixed effects model was 0.59 (95% C.I., 0.34, 0.84). The test for heterogeneity confirmed that there was a significant heterogeneity in this analysis (Q8, Chi-square=25.21, p=0.001), Interestingly, the studies that showed a significant long-lasting effect were the studies that showed a significant effect of TMS on motor function immediately after the treatment,[7, 33, 34, 36] whereas the other two studies[28, 29] did not show significant motor change either immediately after TMS or 30 days after the end of TMS treatment. This finding suggests that an immediate motor benefit of TMS, when present, is predictive of a long-lasting effect (figure 2).

We evaluated the influence of individual studies computing the meta-analysis estimates omitting one study at the time. Figure 4 shows the results of the random-effects estimates excluding one study at the time. The two studies that had the largest individual influence were the studies of Fregni et al. (2004)[28] and Khedr et al. (2003)[33]. Interestingly, each study had the opposite influence: whereas exclusion of Fregni's study increases the overall estimate (0.66, 95% C.I., 0.43, 0.90), exclusion of Khedr's study decreases the overall estimate (0.51, 95% C.I., 0.31, 0.71). But the overall finding of a positive effect of TMS on motor function in PD remains significant after the exclusion of any single study.

In order to test for publication bias, we performed the funnel plot for the visual assessment. The funnel plot is helpful to identify if smaller studies with no statistically significant effect remain unpublished as this would lead to an asymmetrical appearance of the funnel plot. This plot shows a slight predominance of data points from large studies below the horizontal line (representing the effect size), indicating, thus, an opposite effect of the publication bias, as these studies have negative results (figure 5). Furthermore, the distribution of the funnel plot is fairly symmetric, thus speaking against the publication bias. Finally, the p-value for the Egger test was not significant (p=0.12), therefore supporting that the results of this meta-analysis are not the result of publication bias.

Meta-analysis results for ECT trials

For the meta-analysis of the effects of ECT on motor function in PD patients, only five studies satisfied our inclusion criteria. The characteristics of these studies are described in tables 1 and 5. As only five studies were included into this meta-analysis, we only calculated the pooled effect size using the random and fixed effects model. This analysis showed a pooled effect size from the random effects model of 1.68 (95% C.I., 0.79, 2.57) (figure 2) and from the fixed effects model of 1.55 (95% C.I., 1.07, 2.03). The test for heterogeneity confirmed that there was a significant heterogeneity across the studies (Q4, Chi-square=12.95, p=0.012). Because of the

small number of studies (five studies), further analysis, such as meta-regression and Egger's test, could not be performed. Therefore, we could not systematically assess further heterogeneity and publication bias for this analysis, and thus, the results of ECT trials should be interpreted with caution.

Table 5 – ECT study characteristics

Author	Year	Patients	ECT Parameters	Sessions
Balldin [37]	1981	9	Bilateral	4-8
Andersen [6]	1987	11	Bilateral	N/A
Douyon [38]	1989	7	Bilateral	7
Fall [5]	1995	16	Unilateral	4-9
Fall [39]	2000	6	Unilateral	6-7

N/A – not available

Discussion

The results of this meta-analysis support the hypothesis that noninvasive brain stimulation – TMS and ECT – can be effective in improving the motor symptoms in patients with PD. The analysis of TMS studies showed that this result is consistent across controlled and uncontrolled trials, but the effect is modest. Furthermore, we show evidence against a publication bias or significant heterogeneity, and show that the result remains robust after excluding any single study. Although we showed that the effects of ECT are significant and, indeed, had a larger effect size when compared to TMS, the small number of trials limits our ability to draw any definite conclusion about this technique in PD patients.

Negative and positive effect in rTMS trials

Although this meta-analysis shows a favorable effect of TMS on motor function in PD, a positive effect was not observed in every trial. One of the reasons may be the small sample size of these negative studies. In this scenario, the meta-analysis technique is a valuable method to combine the data from small studies in order to provide a conclusion based on an analysis with better power. However, two studies[28, 29] with relatively large sample sizes showed negative results. One of the reasons to explain this contradiction might be the interface of antiparkinson drugs versus TMS, as these studies assessed the motor UPDRS after the use of levodopa ("on" state). This medication might mask the effects of TMS due to a ceiling effect. Therefore, assessment of patients in the "off" state may provide a more sensitive measure of the benefit of TMS. An alternative explanation is that the variability of the results stems from the wide range of TMS parameters and patient selection criteria used in these studies, i.e., the optimal TMS parameters might vary depending on disease duration and severity. Although the meta-regression results failed to show that TMS parameters could significantly account for the variability across studies in motor improvement, the interaction term (TMS parameters versus patient characteristics) was not analyzed because of lack of power for this type of test.

An important consideration is the low number of pulses and intensity in some of these trials, such as Mally[7] (30 pulses twice a day, intensity of 20% of MT) and Shimamoto's study[30] (60 pulses per day, intensity of 700V). One can argue that these parameters were too low to induce a biological effect. However, the number of sessions may influence the clinical effects of this technique (e.g., depression treatment[40]), and therefore the application of rTMS over several sessions in these studies might explain their reported significant effects.

The site of stimulation appears to be critical for the rTMS induced motor improvement, and a focal coil, such as figure-of-eight coil, should provide the greatest precision in targeted stimulation. However, there was not a significant correlation between motor improvement and coil type. For instance, whereas 5 of the 7 studies that used circular coil showed a significant

motor improvement, 2 of the 5 studies that used figure-of-eight coil did not show any significant motor improvement induced by rTMS. It is likely that the degree of motor improvement depends on interactions between coil type and other parameters, such as frequency, intensity and stimulation site.

Noninvasive brain stimulation for PD

TMS effects are primarily directed at surface cortical regions. Since the dopaminergic deficiency in PD is localized to the subcortical basal ganglia, beneficial effects of rTMS on PD motor symptoms are necessarily somewhat indirect. There are two pathophysiologic categories that can be proposed to explain how cortically directed rTMS may improve PD symptoms: either (1) rTMS induces network changes that connect with and positively affect basal ganglia function or (2) rTMS to cortical sites compensates for systematic abnormal changes in cortical function associated with PD. Indeed, in support of the former category, rTMS might modulate cortical areas, such as prefrontal cortex, primary motor cortex, that are substantially connected to both the striatum and the subthalamic nucleus[41] via glutamatergic projection, and thus modulate indirectly the release of dopamine in the basal ganglia.[42] Several TMS/functional imaging studies have demonstrated this neural network effects of the rTMS[3, 4] (although resolution of most of these studies in the basal ganglia can be limited) and an increase of dopamine in basal ganglia after rTMS of the frontal lobe.[43,44]

In support of the latter category, functional imaging and TMS studies of PD subjects have demonstrated altered cortical physiology in basal ganglia connected areas such as the supplementary motor area, dorsolateral prefrontal cortex and primary motor cortex,[41, 45, 46] characterized by an excessive corticospinal output at rest and a reduced intracortical inhibition. Because a given motor task is associated with a suppression of competing motor networks, these cortical changes in PD patients might avoid this suppression and therefore decrease the performance of the motor system – resulting in symptoms, such as tonic contractions and

rigidity.[41] Therefore, rTMS may serve to compensate for the standard basal ganglia model of underactive pallido-thalamo-cortical drive[8, 17, 19] and to modulate cortical excitability to correct for (pseudonormalize) known or suspected abnormalities in cortical excitability associated with PD.[19, 34] Although these mechanisms of action are based on several studies that have attempted to elucidate the pathophysiology of motor disturbance in PD, they remain unproven, and further investigations are required.

Likewise, the putative mechanism of action of ECT in PD is still not known. One can conjecture that the effects of ECT on the brain are similar as those of rTMS, but the impact might be amplified as the electric current induced by ECT spreads to a larger area when compared to TMS and induces a greater voltage.[47] Although several mechanisms to explain ECT effects on motor function in PD have been proposed (e.g., enhancement of dopaminergic receptors,[48] improvement of depression,[49] disruption of blood-brain barrier[50]), convincing evidence to support these assumptions is lacking. Finally, the role or confound of the seizure which is always associated with ECT, as opposed to rTMS, remains unclear.

Clinical implications

The results of this meta-analysis suggest that rTMS might be an effective treatment for patients with PD, highlighting the need for additional more definitive clinical studies in PD patients. For a treatment to be considered clinical useful in PD patients, it should fulfill the following criteria: (1) the therapy has to have a long-lasting effect (at least hours or days); (2) the motor improvement has to be clinically meaningful; (3) The clinical benefits of a new therapy should outweigh its side effects. Regarding the long-lasting effect, only six studies identified in this meta-analysis investigated the long-lasting effects of TMS on PD patients. The pooled analysis of these six studies suggested that the effect of one or a few sessions of TMS can last at least 30 days after the end of the treatment. Indeed, a long-lasting effect of rTMS has been demonstrated previously in patients with major depression, schizophrenia and stroke and

aphasia.[51, 52] Furthermore recent studies suggest that even longer-term benefits with maintenance TMS treatments are indeed possible and effective for the treatment of depression[53] and PD.[54]

Another important issue is whether the effects of TMS on motor function are clinically relevant, as a statistically significant difference between two treatments (or before and after treatment) does not necessarily equal clinical importance. To analyze this effect, we also report the mean difference (rather than the standardized mean difference) for the TMS studies (as these studies utilized the same scale – motor section of the UPDRS). The pooled mean difference was 5.90 (95% C.I., 3.36, 8.44) points in the UPDRS scale (this represents an improvement of more than 20% in the motor function compared to the baseline UPDRS). The possibility of a placebo effect must be considered as well. Goetz et al (2002) reported a significant placebo effect in 17% of PD patients submitted to a chronic new antiparkinsonian therapy.[55] However, the effect of rTMS on motor UPDRS scores remained significant even for the subset of studies that compared the active rTMS group to a placebo-TMS group (Figure 3). There also may be differences in the impact of the placebo effect between acute treatment (such as rTMS for 1 session) and chronic treatment (such as the use of a new drug for several months). For instance, Fregni et al. (2004) showed no significant motor improvement after a single session of placebo-rTMS compared to a levodopa challenge.[56] Furthermore, studies in which several sessions of rTMS were administered, such as Mally et al. (1999) and Khedr et al. (2003), have the larger clinical effects (substantially larger than 20%).[33, 34] Finally, it is possible that optimization of the TMS treatment protocol and patient selection could result in benefits of greater magnitude. However, it is premature to conclude that a long-term treatment with TMS might be as effective as the one with levodopa. Although a retrospective study[54] raised the possibility that rTMS combined with drugs can slow the development of PD, a proper clinical trial with an adequate sample size, methodology and a long follow-up comparing TMS and the pharmacologic treatment would be desirable.

An important consideration is the side effects of rTMS. In fact, rTMS is a technique associated with few, mild adverse events.[57] Analyzing the side effects of the studies included in

this meta-analyses, four of these studies reported no side-effects.[8-10, 33] Boylan et al. (2001) reported that 1 out of 10 patients could not receive repetitive TMS as single pulse motor studies induced an exaggerated startle response and marked worsening of tremor.[31] In Dragasevic's study,[36] although all the patients tolerated the treatment well, authors reported that 4 patients complained of light burning sensation over the scalp during the stimulation and three patients had mild tension headache. Finally, Fregni et al. (2004) reported mild, benign side-effects such as mild headache, neck pain, mild scalp burning sensation and increase of salivation, that were more prevalent in the placebo group compared to the active group.[28]

The result of this meta-analysis opens an avenue for the exploration of electrical stimulation. For example, studies are needed to assess the efficacy of new methods of brain stimulation in PD patients. Transcranial direct current stimulation is one of these therapies that might be valuable in PD. Recent studies have shown that this therapy can induce modulatory effects in the brain cortex similar to those induced by rTMS.[58] Cortical (epidural) stimulation is another therapy that has been investigated for PD. A case-report[59] and animal study[60] showed that epidural motor cortex stimulation may be a good approach to improve the symptoms of PD and the benefits may be longer lasting than those of rTMS. In any case, even if the effects of noninvasive rTMS were to prove to be short-lived, a rTMS study may be useful to assess the suitability of a given patient for more invasive, cortical stimulation. Extradural cortical stimulation has the advantage (compared to subdural cortical stimulation) of being minimally invasive (needs only local anesthesia to implant the electrodes and is associated with fewer post-operative complications, such as infection and hemorrhage). Future studies are needed to investigate and compare the efficacy of different types of motor cortex stimulation.

Conclusion

This meta-analysis shows that rTMS and ECT can produce statistically significant effects on motor function in PD. Although the results of this TMS meta-analysis are robust and stable

(i.e., not substantially altered by excluding any single study), its effect size was moderate. For ECT, although there was a relatively large and significant effect size, we considered the low number of studies to be a limiting factor, and therefore avoid any definite conclusions about this method of brain stimulation in PD. Furthermore, the results of this meta-analysis do not answer whether or not noninvasive brain stimulation would have a clinically meaningful benefit in PD patients. However, our findings encourage further larger and carefully designed clinical trials to assess the potential clinical value of rTMS for PD patients.

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Legends:

Figure 1 – Effect sizes (standardized mean difference in motor UPDRS scores from baseline to immediately after treatment) from the random effects model for all TMS studies (controlled and uncontrolled) (at the top) and for the sham-controlled studies only (at the bottom). A positive effect indicates an improvement in motor function. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

Figure 2 – Effect sizes representations (squares) and their 95% confidence intervals (lines) of the subanalyses of this meta-analyses. TMS (controlled) indicates the TMS controlled studies only. TMS (ALL) indicates the uncontrolled and controlled studies were pooled together. TMS (act. vs. sham) indicates the sham and active rTMS groups in the controlled trials were compared. Sham only indicates that only the sham group was analyzed. TMS (follow-up) indicates that motor scores at the follow-up (30 days or more) were compared to baseline. ECT is the pooled effect size for the ECT trials (5 studies). A positive effect size indicates that the effect was larger in the post-treatment group, or favored the active group.

Figure 3 - Effect sizes (standardized mean difference of the scores of the change in motor UPDRS from baseline to after treatment between the active and placebo group) from the random effects model. A positive effect indicates an improvement in motor function in the active group compared to placebo group. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

Figure 4 – Assessment of the individual influence of each study. The change in the overall effect size and 95% confidence intervals for the meta-analysis after eliminating the indicated study is

shown. Effect sizes are Cohen d (standardized mean difference), error bars represent the 95% confidence interval.

Figure 5 – Funnel plot (publication bias assessment) of the effect sizes (Cohen d) according to their standard errors. The horizontal solid line is drawn at the pooled effect size, and angled lines represent the expected 95% confidence interval for a given standard error, assuming no between-study heterogeneity.

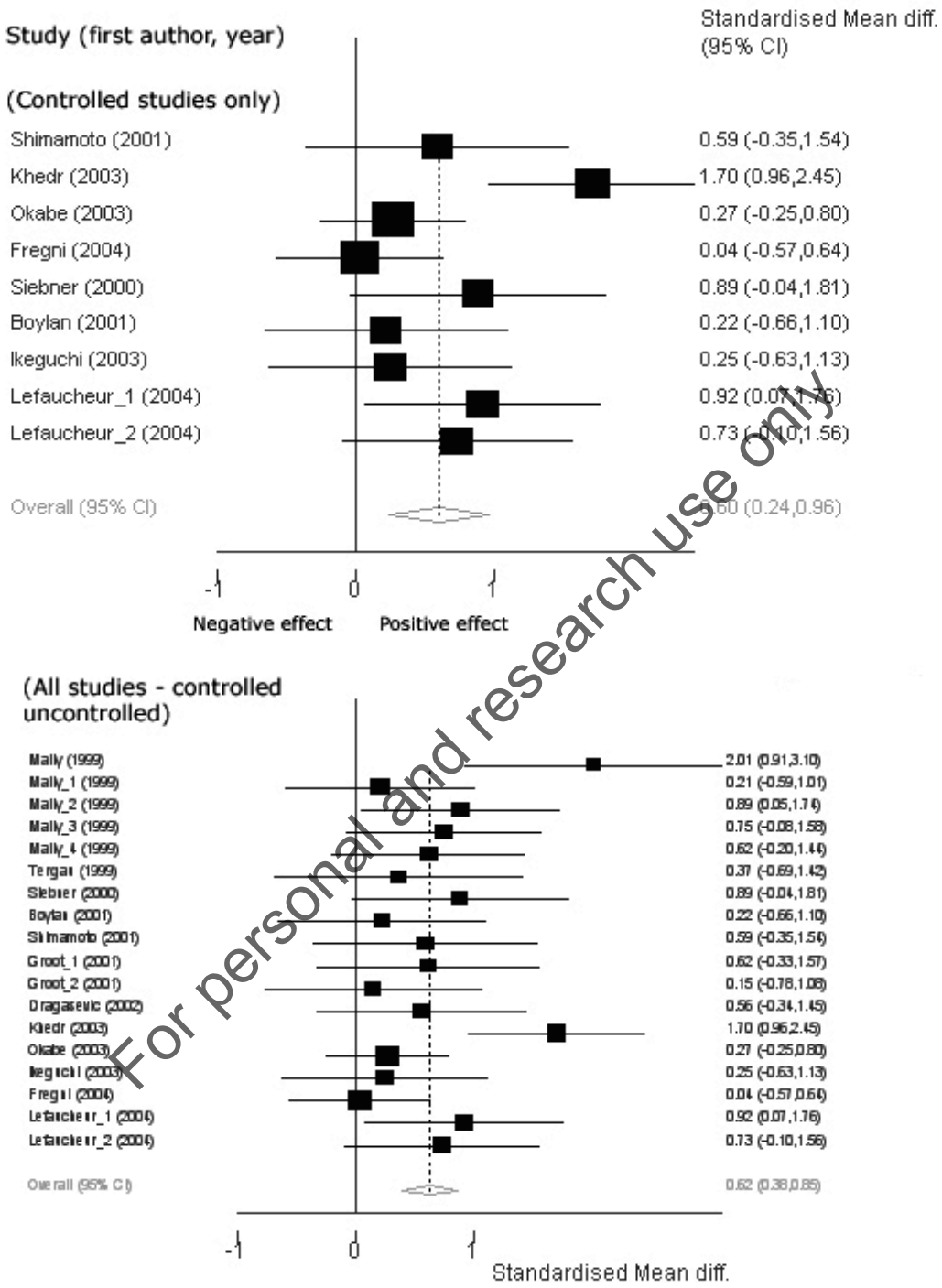
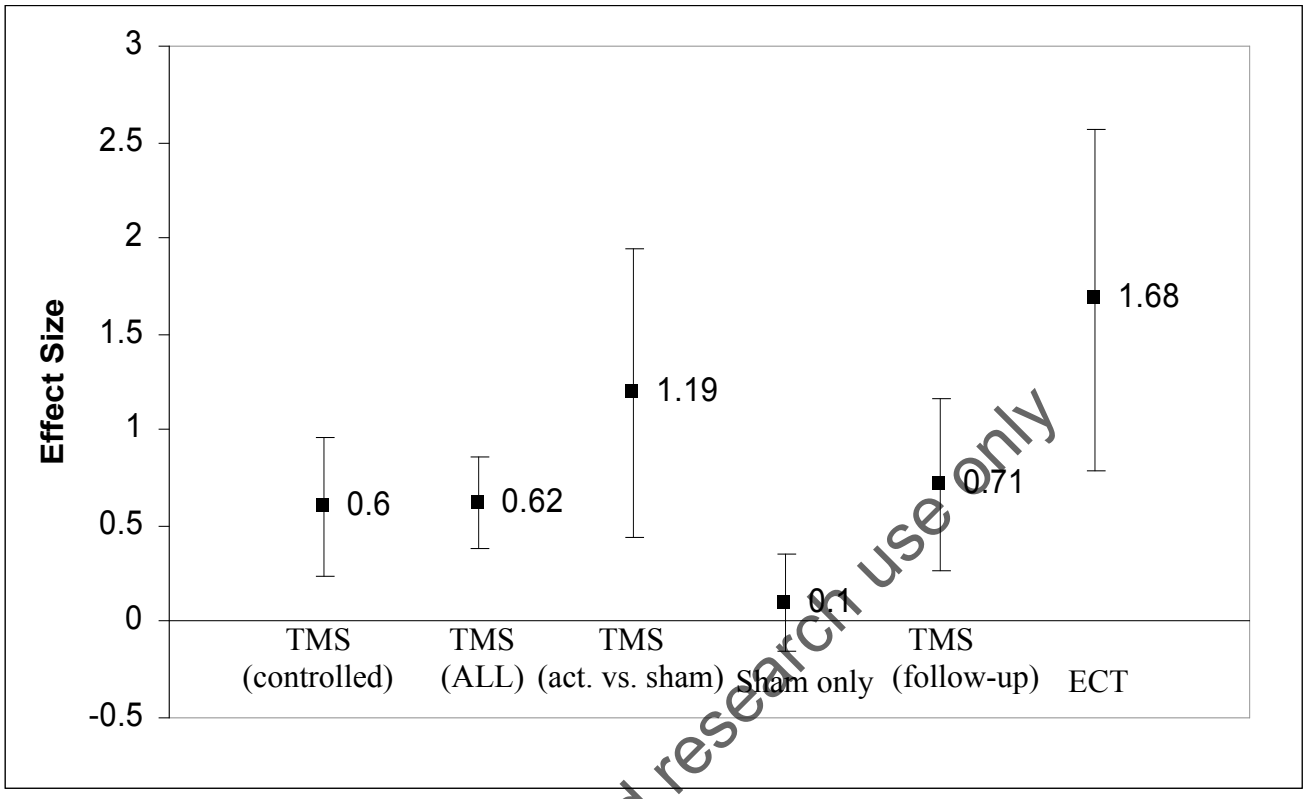


figure 1



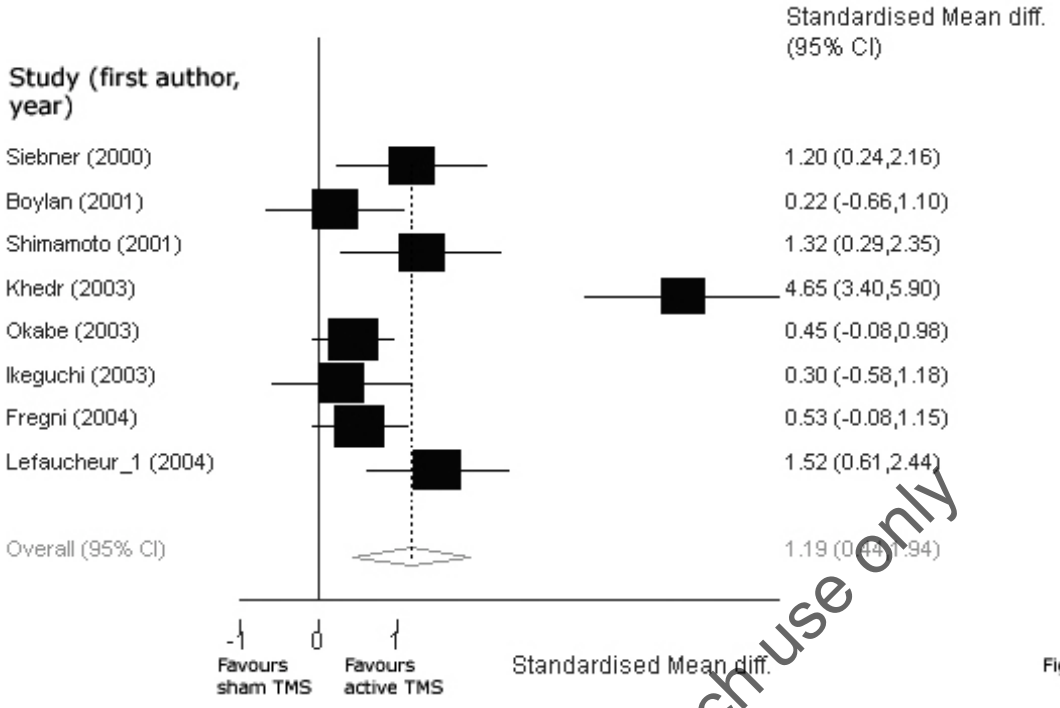


Figure 3

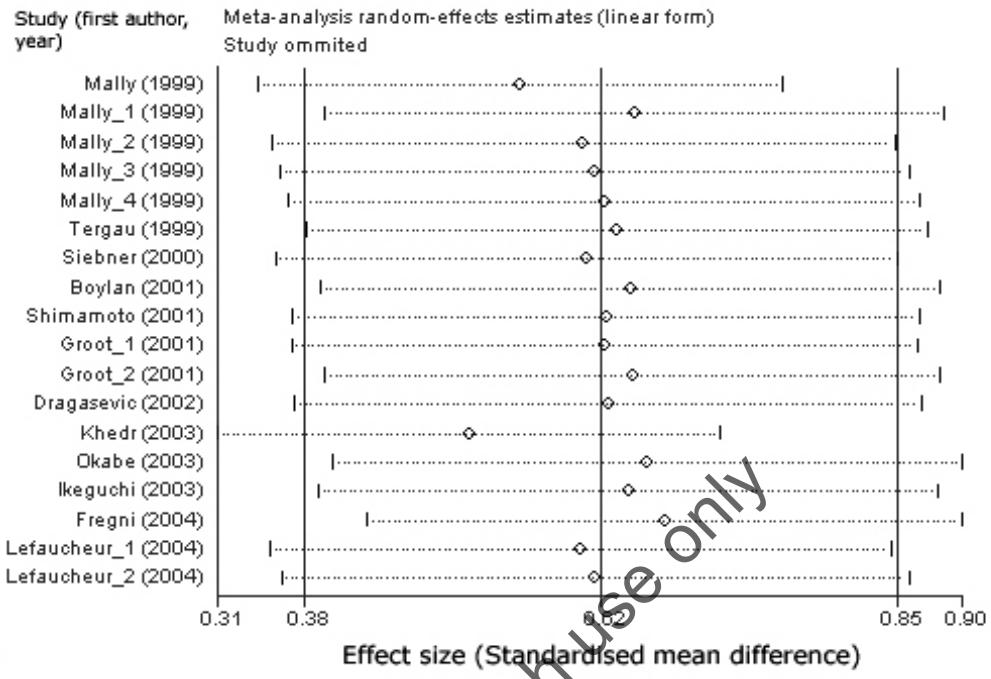


Figure 4

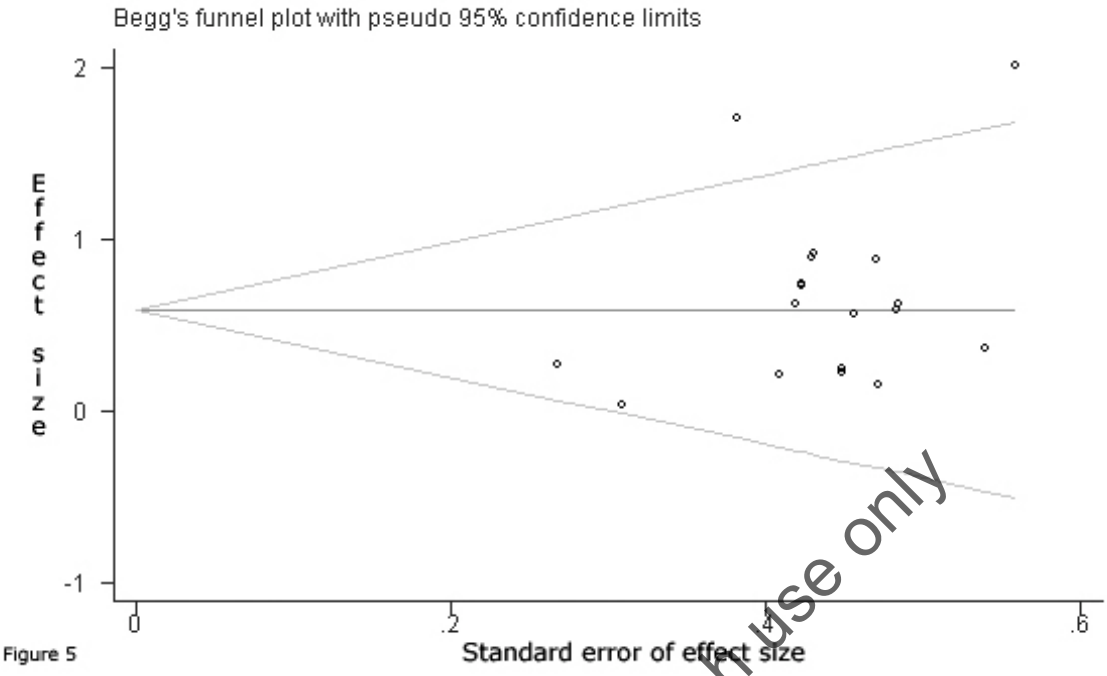


Figure 5