

Repetitive transcranial magnetic stimulation to SMA worsens complex movements in Parkinson's disease

L.S. Boylan^{a,*}, S.L. Pullman^b, S.H. Lisanby^{c,d}, K.E. Spicknall^d, H.A. Sackeim^{d,e}

^aDepartment of Neurology, New York University School of Medicine, New York, NY, USA

^bDepartment of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

^cDepartment of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, USA

^dDepartment of Biological Psychiatry, New York State Psychiatric Institute, New York, NY, USA

^eDepartment of Radiology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Accepted 1 November 2000

Abstract

Objectives: To evaluate the therapeutic potential of repetitive transcranial magnetic stimulation (rTMS) for Parkinson's disease (PD) by delivering stimulation at higher intensity and frequency over longer time than in previous research. Promising beneficial effects on movement during or after rTMS have been reported.

Methods: Ten patients with idiopathic PD were enrolled in a randomized crossover study comparing active versus sham rTMS to the supplementary motor area (SMA). Assessments included reaction and movement times (RT/MT), quantitative spiral analysis, timed motor performance tests, United Parkinson's Disease Rating Scale (UPDRS), patient self-report and guess as to stimulation condition.

Results: Two of 10 patients could not tolerate the protocol. Thirty to 45 min following stimulation, active rTMS as compared with sham stimulation worsened spiral drawing ($P = 0.001$) and prolonged RT in the most affected limb ($P = 0.030$). No other significant differences were detected.

Conclusions: We sought clinically promising improvement in PD but found subclinical worsening of complex and preparatory movement following rTMS to SMA. These results raise safety concerns regarding the persistence of dysfunction induced by rTMS while supporting the value of rTMS as a research tool. Studies aimed at understanding basic mechanisms and timing of rTMS effects are needed. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Parkinson's disease; Transcranial magnetic stimulation; Supplementary motor area

1. Introduction

Open studies have found substantial clinical improvement in patients with Parkinson's disease (PD) lasting up to 3 months following repetitive transcranial magnetic stimulation (rTMS) (Pascual-Leone et al., 1995; Mally and Stone, 1999). In a controlled study improvement was found *following* rTMS but was of uncertain clinical significance (Siebner et al., 1999a). Improvement in motor performance as tested *during* stimulation was reported with active but not sham stimulation of the primary motor cortex in patients with PD (Pascual-Leone et al., 1994a), but these results were not reproduced in a larger replicative study (Ghabra et al., 1999).

A suggested mechanism to account for these changes is modulation of cortical excitability. Enhancement of cortical excitability by high-frequency rTMS is supported by an increase in amplitude of motor evoked potentials with rTMS (Pascual-Leone et al., 1994b), by persistent focal metabolic activation on PET following rTMS (Siebner et al., 2000), and by facilitation of picture naming following high-frequency rTMS (20 Hz) to Wernicke's area (Mottaghy et al., 1999). Persistent focal activation to the dorsolateral pre-frontal cortex is thought to underlie the promising, if inconsistent, clinical trial data suggesting therapeutic efficacy of rTMS in major depression (George et al., 1999).

Electrophysiological (Cunnington et al., 1997) and some metabolic imaging (Eidelberg et al., 1994) studies suggest that in patients with PD, motor and pre-motor areas of the cortex, including the supplementary motor area (SMA), are both tonically underactivated and inadequately reactive to meet the needs of normal movement. In an attempt to maxi-

* Corresponding author. Department of Neurology, 550 First Avenue, New York, NY 10016, USA. Tel.: +1-212-263-6347; fax: +1-212-263-8228.

E-mail address: laura.boylan@med.nyu.edu (L.S. Boylan).

mize facilitatory effects, we delivered stimuli at a higher intensity and frequency and over longer time than in previous reports. We stimulated the SMA because of its key role in motor planning and processing (Goldberg, 1985; Brust, 1996), and because it is possible to deliver stimuli at intensities above the motor threshold to this area without inducing limb twitches.

2. Methods

Patients had mild to moderate (Hoehn and Yahr stage II–III) degrees of idiopathic PD by standardized criteria (Langston et al., 1992). Patients with signs or symptoms of atypical Parkinsonian syndromes, serious medical problems, implanted devices, brain disease other than PD, or a personal history of seizures were excluded. Patients gave written informed consent for the study, which was approved by the Institutional Review Boards of Columbia-Presbyterian Medical Center and the New York State Psychiatric Institute. Patients took no dopaminergic medication for at least 12 h prior to each session. All patients received active and sham stimulations at least 1 week apart and were randomized as to the order of the stimulation condition.

Testing before and after each of the stimulation sessions included reaction and movement times (RT/MT), spiral analysis, timed motor performance tests, and the United Parkinson's Disease Rating Scale (UPDRS). Spiral analysis and RT/MT were performed 30–45 min before and after rTMS, while timed motor tasks and UPDRS were assessed immediately before and after rTMS. During stimulation patients performed finger and foot tapping tasks. Additionally, patients' judgements as to their own improvement or worsening and their best guess as to the treatment condition were gathered following each intervention and associated testing.

2.1. RT/MT

Subjects were seated comfortably in front of an eye level computer monitor that displayed cues indicating which of two targets on a touch pad they should touch. The touch pads for hands and feet were located at desk and floor levels. Cues and targets were displayed to the left and right of the center (resting) position. Approximately 80 trials were collected for each limb.

RT and MT data were averaged for each testing session. Analyses were conducted off-line and trials were automatically rejected if RT was less than 100 ms (indicating anticipatory movement) or more than 1000 ms (indicating inattention), or if MT was less than 50 ms or greater than 3000 ms. Data were analyzed in terms of both average limb performance and performance of the most affected limb.

2.2. Spiral analysis

The technique of spiral analysis is detailed elsewhere

(Pullman, 1998). To summarize, subjects drew Archimedean spirals with a writing pen held in the normal fashion, without constraints, on a paper overlying a digitizing tablet (Kurta Corporation, Phoenix, AZ, USA). The tablet has a resolution of 100 points/mm with an accuracy of ± 0.127 mm, an output rate of 210 Hz, and 256 levels of measurable pressure. Ten spirals were collected from each hand, and all tracings were monitored on-line for error control. Spiral data for each hand were averaged for each patient.

The degree of severity (DOS) is a rating of spiral drawing impairment and reflects spiral smoothness, symmetry and regularity. The DOS takes into account point by point execution of the spiral as well as measurement of the whole spiral. DOS is extracted from quantified spiral data based on a series of mathematical indices. Severity scoring is based on the results of regression from a large sample of PD patient spiral data ranked by expert movement disorder physicians using a 0–4 modified UPDRS. The DOS has been validated against expert ratings ($r^2 = 0.91$, $P < 0.001$) (Pullman, 1998) based on a sample including patients with PD, dystonia, and age- and sex-matched control subjects.

2.3. Timed tests of walking and hand pronation/supination, UPDRS motor scale

The walking task was the shorter of two times taken to stand from sitting, walk 7 m, turn, and return to sit. In the pronation/supination task, seated subjects tapped their knee with the alternately pronated and supinated hand. The shorter of the two trials in which the patient completed 20 pronation/supinations with each hand was the final time. Average and most affected limb pronation/supination times were both analyzed. These assessments as well as the motor subscale of the UPDRS were performed by an unblinded study neurologist (LSB).

2.4. Subject reports

Subjects rated their clinical change following each of the stimulations as no change or very much/much/minimally better or worse. They also provided their best guess as to the treatment condition received (active or sham).

2.5. Transcranial magnetic stimulation

Repetitive TMS was delivered with a figure-of-8 coil (double 70 mm) using a Magstim Super Rapid (Magstim Co. Ltd., Dyfed, UK) stimulator which has a maximum field strength of 2 T. This device delivers biphasic pulses with a width of approximately 250 μ s.

Patients were seated in a dental chair for the intervention. Protective earplugs were used during stimulation. Stimulus intensity dosing for SMA stimulation was calculated from the hemisphere with the lower motor threshold. Resting motor threshold was determined from the optimal site for first dorsal interosseous (FDI) stimulation and was defined as the minimum intensity that produced 5 motor evoked

potentials of ≥ 50 μV amplitude on 10 consecutive trials of single pulse TMS.

The site for SMA stimulation was determined as follows: stimuli of 150% FDI motor threshold were given over Cz according to the 10–20 system and then moving anteriorly along the sagittal midline in 1 cm increments until a twitch was seen to either leg. Repetitive stimulation was delivered 1 cm anterior to the last site from which a leg twitch could be evoked.

Repetitive TMS was given at up to 110% of patients' motor threshold (or highest tolerated) and at a frequency of 10 Hz. Forty 5 s trains were given over 40 min for a total of 2000 pulses per session. We attempted to maximize stimulation parameters, while not exceeding recommended safety guidelines (Wassermann, 1998). Safety monitoring during stimulation included continuous EEG (C3 or C4) and EMG (biceps and tibialis anterior). Sham stimulation was performed as above, but so as not to induce intracerebral current the coil was angled at 90° perpendicular to the head with one wing of the figure-of-8 in contact with the scalp (Lisanby et al., 1998). The order of sham versus active rTMS sessions was randomized across patients.

2.6. Intra-stimulation testing

During the stimulation session several finger and foot tapping tasks were performed before, during, and after individual trains of pulses according to a standardized protocol. Evaluation was qualitative. The neurologist holding the stimulation coil observed but did not comment on performance. Patient comments were noted but not solicited.

2.7. Data analysis

Analysis of variance (ANOVA) for repeated measures was performed for each dependent variable using StatView 4.5. Time (pre-/post-stimulation) and stimulation condition (active/sham) were the variables examined. The effects of the order of the stimulus condition and having received the full 110% stimulation were examined as between-subject factors. Contingent on ANOVA significance, paired *t* tests for within-subject effects were performed. To evaluate the possibility of carryover effects from active stimulation among the 5 patients who received active stimulation first, we compared baseline scores on the active stimulation day with scores on the sham stimulation day by paired *t* test. The threshold for significance was set at $P < 0.05$. Reliability of RT/MT and DOS measures was assessed by the intraclass correlation coefficient (ICC).

3. Results

Ten patients were enrolled. Three were in Hoehn and Yahr stage II, one was in stage II.5 and the remaining 6 were in stage III. There were 4 women and 6 men, with a mean age of 63.5 years (range 55–77 years), taking an aver-

age of 423 mg (range 100–800 mg) levodopa per day, with 7 patients taking additional agonist therapy. The mean time from diagnosis was 8.6 years (range 2.2–15 years). The mean motor UPDRS motor score was 33.2 (range 24–63).

Two of 10 patients did not tolerate the protocol. One of these patients did not receive any repetitive stimulation, as single pulse motor studies induced an exaggerated startle response and marked worsening of tremor. The other patient who did not finish the study completed a first (sham) but not a second intervention due to intolerance of the 'off' state.

In order to minimize the potential confound of undergoing unpleasant stimulation, we did not encourage patients to accept uncomfortable stimulation intensities. Stimulation was reduced from 110% of motor threshold in 3 patients due to scalp discomfort. These patients were comfortable at lower intensity stimulation at a mean of 72% motor threshold (range 68–78%).

There was a significant interaction between baseline and post-stimulation DOS scores and stimulation condition due to worsening with active as compared to sham stimulation as measured globally ($P = 0.004$) and for the most affected limb ($P = 0.001$) (7 subjects). *T* tests showed that global DOS scores worsened following active stimulation ($P = 0.022$) while there was no change with sham stimulation. In the most affected limb DOS worsened with active stimulation ($P = 0.038$) and improvement following sham stimulation approached significance ($P = 0.053$). There were no between-subject effects on these measures for the order of the stimulation condition or tolerance of 110% motor threshold stimulation. Individual and mean results for DOS are shown in Fig. 1A.

In our evaluation of the 5 patients who received active stimulation first we found a trend towards persistent worsening of DOS comparing baseline DOS prior to any intervention with DOS on the morning of the second session more than a week later. This trend was observed in the global measure ($P = 0.089$) and in the most affected limb ($P = 0.084$). The mean interval between stimulation sessions was 1.6 weeks (range 1–3 weeks). Patients who received active stimulation first are represented by the solid bars in Fig. 1A.

RT data were available for 8 subjects. Among patients who tolerated 110% motor threshold stimulation there was a significant prolongation of RT for the most affected limb with active as compared to sham stimulation ($P = 0.030$) (Fig. 1B).

There were no differences between active and sham rTMS on measures of UPDRS, timed motor tasks, or MT for all limbs or for the most affected limb alone. These findings were not affected by between-subject comparison for the order of the stimulation condition or for receiving 110% motor threshold stimulation. Reliability estimates (ICC) for the global neurophysiological measures were 0.98 for RT, 0.98 for MT, and 0.86 for DOS.

There was no apparent change on intra-stimulation tapping tasks noted by either observers or subjects except in the case of one patient. This patient reported intra-stimu-

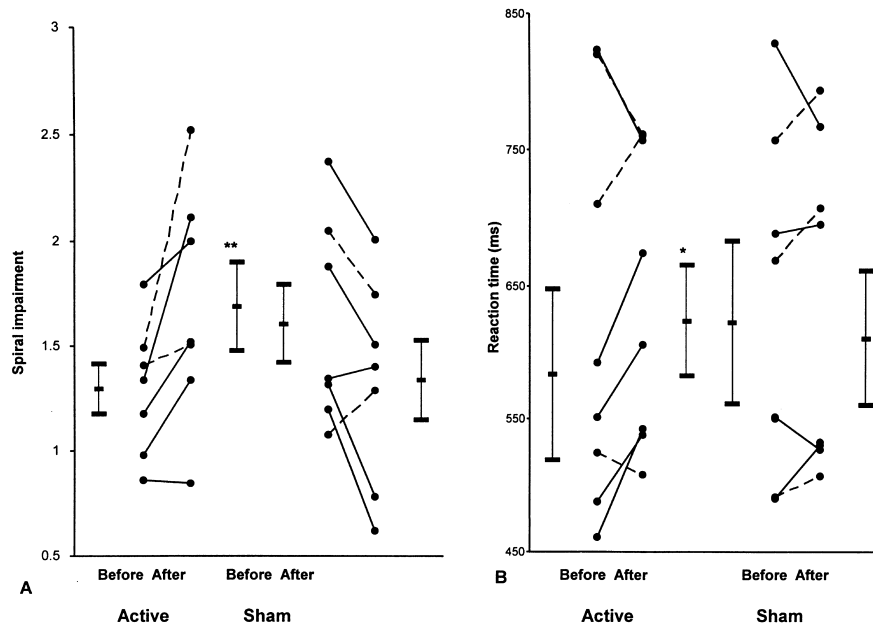


Fig. 1. Spiral drawing impairment and RT in the most affected limb before and after active and sham rTMS to the SMA in patients with PD. (A) DOS scores ($n = 7$). Increasing DOS scores reflect worsening of spiral drawing. Solid lines represent patients who received active stimulation first. Among those who received active stimulation first there was a non-significant trend for persistently worsened DOS measured a week or more following active stimulation. (B) RT scores ($n = 8$). Solid lines represent patients who tolerated stimulation at 110% motor threshold intensity. Patients represented by dotted lines were given lower intensity stimulation (mean 72%, range 68–78%). There was a significant increase in RT among those who received the full 110% intensity stimulation. SMA, supplementary motor area; DOS, degree of severity of spiral impairment by quantitative spiral analysis. The score is 0–4 UPDRS format (normal to most severely impaired). Error bars represent the mean \pm SE. * $P = 0.030$, ** $P = 0.001$ (ANOVA).

lation improvement in hand rigidity with both active and sham stimulation. No patient reported more than minimal clinical change following either active or sham stimulation. Individual patients did not report the same changes with each of their treatments, but overall with each condition 4 patients noted minimal improvement, 3 reported no change, and one reported minimal worsening. After their first treatment, 5 of 9 patients guessed correctly whether the treatment was active or sham. Following the second treatment all 8 patients correctly guessed the treatment condition.

4. Discussion

The major finding of this study was worsening of motor performance on spiral drawing with active rTMS to the SMA of patients with PD. Furthermore, there was an increase in RT among those who received the full 110% intensity stimulation. One patient had noticeable worsening of tremor with single pulse TMS to the motor cortex, a problem also described in a previous study (Ghabra et al., 1999). Disruption of the complex motor task of spiral drawing and the preparatory phase of movement (RT) with preservation of MT is consistent with specific physiologic disturbance of SMA (Cunnington et al., 1996; Gerloff et al., 1997). Cunnington et al. (1996) have previously described disruption of movement with single pulse TMS delivered in the motor preparatory stage in PD. Our results suggest that

such intrastimulation disruptions induced by rTMS can persist.

While our sample was small, the neurophysiological measures were extremely precise and reliable ($r = 0.86$ – 0.98) and thus highly sensitive. We do not believe that the ultimately ineffective blind explains these findings as patients could not guess their treatment condition at the first stimulation session and there was no effect of order on results. Further, the isolated nature and direction of the findings do not suggest that our results are due to the inadequate blind. The trend toward DOS improvement in the most affected limb following sham stimulation most likely represented a practice effect not evident with active stimulation.

While some patients did not tolerate the intended 110% motor threshold stimulation, the actual stimulation intensity required to stimulate SMA or other non-motor areas is unknown. Several studies have demonstrated effects on motor and language performance with stimulation below motor threshold (Mottaghy et al., 1999; Siebner et al., 1999a,b; Rollnik et al., 2000). It might be suggested that our results are based on disruption of cognitive rather than motor processes. However, while cognitive effects of TMS have been shown during stimulation (Pascual-Leone et al., 1991; Mottaghy et al., 2000), several studies have demonstrated no deleterious effects of rTMS on performance of neuropsychological tests before and after rTMS (Pascual-Leone et al., 1993; Wassermann et al., 1996; Little et al., 2000).

To our knowledge, effects of rTMS on cognitive or motor performance as late as 30 min following stimulation have been found in only one other study. In this study performance on a task switching test performed 1 h following stimulation varied depending on the site of stimulation (J. Grafman, pers. commun.). A recent study found decreased cortical excitability as measured by MEP size 30 min following low-frequency rTMS without effects on basic motor behavior (Muellbacher et al., 2000). Non-behavioral late effects have been demonstrated in decreased MEP size as late as 2 days following stimulation (Maeda et al., 2000b). In animal studies an increased amygdalar after-discharge threshold was found 2 weeks following a single 20 Hz train of rTMS (Ebert and Ziemann, 1999). We found a trend towards persistently worsened DOS more than 1 week following stimulation among those for whom we had such data. While concerning, these data should be cautiously interpreted as both the effect and the sample size were small.

We chose high-frequency rTMS in order to facilitate SMA function. It has been suggested that low-frequency rTMS is inhibitory while higher frequencies have facilitatory effects (Pascual-Leone et al., 1994b; Siebner et al., 1999a). We sought facilitation because there is evidence for cortical inhibition in PD due to reduced excitation from thalamocortical projections (DeLong, 1990). However, the relationship of stimulus frequency to physiologic effect remains unclear and, overall, disruption rather than improvement of behavioral processes has been more easily demonstrated.

Disturbance of ongoing cognitive and motor tasks has been demonstrated during high-frequency rTMS (Gerloff et al., 1997; Mottaghy et al., 2000; Pascual-Leone et al., 1991) and facilitation of finger tapping has been demonstrated with 1 Hz rTMS (Wassermann et al., 1996). On the other hand, a study examining the effect of various rTMS frequencies on patients with PD found no change using frequencies from 1 to 20 Hz (Tergau et al., 1999). Effects of TMS at any frequency, even when given to the same brain region, will likely differ between and among healthy subjects and those with different diseases (Cunnington et al., 1996; Pascual-Leone et al., 1991; Siebner et al., 1999b; Maeda et al., 2000a). Also, enhanced function will not necessarily be associated with increased cortical excitability just as dysfunction will not always represent cortical inhibition. For example, improvements in writing among patients with writer's cramp were associated with enhanced intracortical inhibition on TMS paired-pulse studies (Siebner et al., 1999b). Stimulated areas are parts of complex neural networks and rTMS affects both local and distant parts of such networks (Paus et al., 1997).

In the case of this study, the complex effects of rTMS produced subtle and persistent adverse effects. Unfortunately, neither this study nor other controlled studies have demonstrated clinically relevant benefit for rTMS in PD.

Our study demonstrates the research use of rTMS as a

probe of brain function. However, our results also show that subtle regional disruption can persist over 30 min following rTMS and this raises safety concerns. Better definition of the time course of such changes is important. A final caveat is that while sham-controlled, within-subject comparisons with rTMS are an attractive and efficient research tool, the blind may be inadequate.

Acknowledgements

This study was supported in part by the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD) and by RR00645, National Center for Research Resources (NCRR). Drs Sackeim and Lisanby have received research grants from the Magstim Company Ltd.

References

- Brust JC. Lesions of the supplementary motor area. *Adv Neurol* 1996;70:237–248.
- Cunnington R, Inasek R, Thickbroom GW, Laing BA, Mastaglia FL, Bradshaw JL, Phillips JG. Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease. *Brain* 1996;119:815–822.
- Cunnington R, Inasek R, Johnson KA, Bradshaw JL. Movement-related potentials in Parkinson's disease. Motor imagery and movement preparation. *Brain* 1997;120:1339–1353.
- DeLong MR. Primate models of movement disorders of the basal ganglia. *Trends Neurosci* 1990;13:281–285.
- Ebert U, Ziemann U. Altered seizure susceptibility after high-frequency transcranial magnetic stimulation in rats. *Neurosci Lett* 1999;273:155–158.
- Eidelberg D, Moeller JR, Dhawan V, Spetsieris P, Takikawa S, Ishikawa T, Chaly T, Robeson W, Margouloff D, Przedborski S, Fahn S. The metabolic topography of parkinsonism. *J Cereb Blood Flow Metab* 1994;14:783–801.
- George MS, Lisanby SH, Sackeim HA. Transcranial magnetic stimulation: applications in neuropsychiatry. *Arch Gen Psychiatry* 1999;56:300–311.
- Gerloff C, Corwell B, Chen R, Hallett M, Cohen LG. Stimulation over the human supplementary motor area interferes with the organization of future elements in complex motor sequences. *Brain* 1997;120:1587–1602.
- Ghabra MB, Hallett M, Wassermann EM. Simultaneous repetitive transcranial magnetic stimulation does not speed fine movement in PD. *Neurology* 1999;52:768–770.
- Goldberg G. Supplementary motor area structure and function: review and hypotheses. *Behav Brain Sci* 1985;8:567–615.
- Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, Watts R. Core Assessment Program for Intracerebral Transplantations (CAPIT). *Mov Disord* 1992;7:2–13.
- Lisanby SH, Luber BL, Schroeder C, Osman M, Finck D, Amassian VE, Arezzo J, Sackeim HA. rTMS in primates: intracerebral measurement of rTMS and ECS induced voltage in vivo (abstract). *Electroenceph clin Neurophysiol* 1998;107:79P.
- Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, Danielson A, Repella J, Huggins T, George MS, Post RM. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol* 2000;13:119–124.
- Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial

- magnetic stimulation on cortical excitability. *Exp Brain Res* 2000a;133(4):425–430.
- Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clin Neurophysiol* 2000b;111(5):800–805.
- Mally J, Stone TW. Improvement in parkinsonian symptoms after repetitive transcranial magnetic stimulation. *J Neurol Sci* 1999;162:179–184.
- Mottaghy FM, Hungs M, Brugmann M, Sparing R, Boroojerdi B, Foltys H, Huber W, Topper R. Facilitation of picture naming after repetitive transcranial magnetic stimulation. *Neurology* 1999;53:1806–1812.
- Mottaghy FM, Krause BJ, Kemna LJ, Topper R, Tellmann L, Beu M, Pascual-Leone A, Muller-Gartner HW. Modulation of the neuronal circuitry subserving working memory in healthy human subjects by repetitive transcranial magnetic stimulation. *Neurosci Lett* 2000;280:167–170.
- Muellbacher W, Ziemann U, Boroojerdi B, Hallett M. Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. *Clin Neurophysiol* 2000;111(6):1002–1007.
- Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. *Neurology* 1991;41:697–702.
- Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, Valls-Solé J, Brasil-Neto JP, Wassermann EM, Cohen LG, Hallett M. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroenceph clin Neurophysiol* 1993;89:120–130.
- Pascual-Leone A, Valls-Solé J, Brasil-Neto JP, Cammarota A, Grafman J, Hallett M. Akinesia in PD II. Effects of subthreshold rTMS. *Neurology* 1994a;44:892–898.
- Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain* 1994b;117:847–858.
- Pascual-Leone A, Alonso MD, Pascual-Leone Pascual A, Catalá MD. Lasting beneficial effect of rapid-rate transcranial magnetic stimulation on slowness in Parkinson's disease (abstract). *Neurology* 1995;45(Suppl 4):A315.
- Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. *Neuroscience* 1997;17:3178–3184.
- Pullman SL. Spiral analysis: a new technique for measuring tremor with a digitizing tablet. *Mov Disord* 1998;13(Suppl 3):85–89.
- Rollnik JD, Schubert M, Dengler R. Subthreshold prefrontal repetitive transcranial magnetic stimulation reduces motor cortex excitability. *Muscle Nerve* 2000;23:112–114.
- Siebner HR, Mentschel C, Auer C, Conrad B. Repetitive transcranial magnetic stimulation has a beneficial effect on bradykinesia in Parkinson's disease. *NeuroReport* 1999a;10:589–594.
- Siebner HR, Tormos JM, Ceballos-Baumann AO, Auer C, Catalá MD, Conrad B, Pascual-Leone A. Low-frequency repetitive transcranial magnetic stimulation of the motor cortex in writer's cramp. *Neurology* 1999b;52:529–537.
- Siebner HR, Peller M, Willoch F, Minoshima S, Boecker H, Auer C, Drzezga A, Conrad B, Bartenstein P. Lasting cortical activation after repetitive TMS of the motor cortex: a glucose metabolic study. *Neurology* 2000;54:956–963.
- Tergau F, Wassermann EM, Paulus W, Ziemann U. Lack of clinical improvement in patients with Parkinson's disease after low and high frequency repetitive transcranial magnetic stimulation. *Electroenceph clin Neurophysiol Suppl* 1999;51:281–288.
- 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 5-6, 1996. *Electroenceph clin Neurophysiol* 1998;108:1–16.
- Wassermann EM, Grafman J, Berry C, Hollnagel C, Wild K, Clark K, Hallett M. Use and safety of a new repetitive transcranial magnetic stimulator. *Electroenceph clin Neurophysiol* 1996;101:412–417.