A Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation in Patients with Refractory Epilepsy

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Objective: To study the antiepileptic effects of rTMS in patients with refractory epilepsy and malformations of cortical development in a randomized, double-blind, sham-controlled trial.

Methods: Twenty-one patients with malformations of cortical development and refractory epilepsy underwent five consecutive sessions of low-frequency rTMS, either sham or active (1Hz, 1,200 pulses), focally targeting the malformations of cortical development. The number of epileptiform discharges in the electroencephalogram and the number of clinical seizures were measured before (baseline), immediately after, as well as 30 and 60 days after rTMS treatment.

Results: rTMS significantly decreased the number of seizures in the active compared with sham rTMS group ($p < 0.0001$), and this effect lasted for at least 2 months. Furthermore, there was a significant decrease in the number of epileptiform discharges immediately after ($p = 0.01$) and at week 4 ($p = 0.03$) in the active rTMS group only. There were few mild adverse effects equally distributed in both groups. The preliminary cognitive evaluation suggests improvement in some aspects of cognition in the active rTMS group only.

Interpretation: Noninvasive brain stimulation for epilepsy may be an alternative treatment for pharmaco-resistant patients with clearly identifiable seizure foci in the cortical convexity and who are not eligible for surgical treatment.

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A growing body of evidence suggests that electrical stimulation of the brain may be a powerful therapy to reduce seizure frequency (see Goodman's review[1]). Therefore, the investigation of noninvasive forms of brain stimulation for epilepsy is appealing. Indeed, several open-label studies have suggested that repetitive transcranial magnetic stimulation (rTMS) has a significant antiepileptic effect.[2–6] However, a randomized, double-blind, sham-controlled study showed only a trend toward a short-term decrease in seizures in the group of patients who received active rTMS, though the effect was more marked in patients with neocortical foci.[7] It appears clear that the available evidence is insufficient to reach firm conclusions on the antiepileptic potential of rTMS, and that more studies are needed.

rTMS in patients with malformations of cortical development (MCD) may be particularly effective because: (1) the epileptic focus can be more accurately localized due to the anatomically identifiable malformation; (2) the focus is in the cortical convexity; thus, it can be reliably reached by rTMS; and (3) epileptogenesis in these patients might be the result of an imbalance between excitatory and inhibitory neurons[8] or associated with the mechanism of long-term potentiation.[9] Because of its hypothesized mechanism of action with enhancement of GABAergic activity[10] and a decrease in the synaptic transmission (long-term depression–like mechanism),[11] low-frequency rTMS might be ideally suited to the underlying pathophysiology. Therefore, in this study, we sought to evaluate whether the findings of our preliminary open-label study[2] that suggested antiepileptic efficacy could be replicated in a proper randomized, double-blind, sham-controlled study.

Patients and Methods

Patients

Twenty-one patients (mean age, 21.9 ± 8.1 years; 12 female patients) participated in this study. Patients were prospectively and sequentially selected from a specialized epilepsy clinic (Clinics Hospital, University of Sao Paulo, Sao Paulo,

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Table 1. Demographic and Clinical Characteristics at Baseline

		ACTIVE RTMS	SHAM RTMS	
		Mean (SD)/n	Mean (SD)/n	*p*-value*
Number		12	9	
Age – mean (SD)		21.3 (6.4)	22.7 (10.3)	ns
Seizure frequency/28 days (baseline) – mean (SD)		13.6 (10.1)	11.4 (14.8)	ns
Concomitant AEDs (number of patients)	0	0	0	ns
	1	2	0	
	2	6	7	
	3	4	2	
Lesions (cortical dysplasias)	Polymicrogyria	6	5	ns
	Heterotopia	2	2	
	Other dysplasias	4	2	

*student t-test for the continuous variables and Fisher exact's test for the categorical variables (ns – not significant).
rTMS – repetitive transcranial magnetic stimulation; SD – standard deviation.

Brazil) if they fulfilled the following criteria: (1) diagnosis of MCD based on magnetic resonance imaging (MRI) of the brain; (2) refractory epilepsy as defined by the occurrence of an average of at least one seizure per month during the preceding year, despite the use of two or more antiepileptic drugs (AEDs) in adequate doses; (3) nonsurgical candidacy defined by surgical contraindications (ie, more than one MCD lesion) or patient's decision not to pursue surgical treatment; and (4) compliance with AED treatment for the preceding year (defined as repeatedly documented adequate AED plasma levels). All these patients were observed by a senior clinical epileptologist (K.D.V) for several years, and each patient's epilepsy was extensively investigated and characterized.

All patients continued their antiepileptic medications as prescribed by their treating physician and medication changes were not allowed, unless there was a strong clinical reason. This was necessary in only one patient; however, this did not confound our results because this patient was in the sham rTMS group and there was no change in his seizure frequency or epileptiform discharges (EDs) despite the medication change. The general clinical characteristics of the patients are summarized in Table 1.

The study was performed in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee of the University of Sao Paulo.

Experimental Design

This study was a randomized, double-blind, sham-controlled, parallel-design clinical trial that consisted of three main phases: (1) baseline evaluation that consisted in a 4-week period of seizure observation to establish a baseline for seizure frequency; (2) 5-day double-blind treatment that consisted in daily treatment sessions with sham or active rTMS for 5 consecutive days; and (3) a follow-up period of 2 months. Patients and the investigators, except the investigator who applied rTMS, were blinded to the treatment arm.

During the baseline period, patients were randomized in a 3:4 ratio to receive sham (3 in each 7 patients) or active (4 in each 7 patients) rTMS. We chose this randomization strategy (3:4) to increase the sample size of the active treatment. This strategy of randomization is advocated in small sample size phase II trials that do not have adequate information on the efficacy of a new treatment (see Peto's article[12]). The disadvantage of this strategy is that it decreases the power of the study (because less information from the sham group is provided). However, we accounted for this decrease of power (that is minimal with the 3:4 ratio) in our sample size calculation.

Randomization was performed using the order of entrance in the study and a randomization table previously generated by a computer using randomization blocks of seven (for each seven patients, three were randomized to sham and four to active rTMS) to minimize the risk for unbalanced group sizes.

To determine the sample size, we assumed a mean reduction in seizures of at least 50% in the active group. We chose this effect size from our preliminary data[2] and because our aim was to assess whether rTMS may have a truly clinically meaningful impact. In the sham rTMS group, we assumed mean reduction of seizure frequency of 15%. This was based on the placebo effect reported in Theodore's study.[7] Considering a power of 95% (this represents a power of 92.5% considering an unequal randomization; see Pocock's article[13]) and a critical $\alpha = 0.05\%$ (double-sided), 16 patients (8 in each group) are needed to detect group differences. To account for dropouts and an increased variability of our sample, we increased the sample size to 21 patients.

Transcranial Magnetic Stimulation

The stimulation site was determined according to the 10-20 International electroencephalogram (EEG) electrode system and the site of the lesion. The epileptogenic focus was targeted in patients with focal ED and Cz (vertex) in patients with multifocal or diffuse abnormalities in the EEG or multiple lesions in the MRI. Only 4 patients had diffuse abnormalities, as documented by the EEG, and received rTMS over Cz (3 in the active and 1 in the sham rTMS group); the remainder of the patients (17 patients) had a focal epileptogenic focus as defined by EEG results. The epileptogenic focus was defined by a clinical epileptologist (K.D.V.) based on the EEG and MRI findings.

rTMS (1Hz, 70% of maximum stimulator output intensity, 20 minutes) was performed using a commercially avail-

able figure-of-eight coil (outside diameter of each wing, 7cm) and a Dantec stimulator (Medtronic, Minneapolis, MN). We chose a fixed TMS intensity because the threshold for stimulation in nonmotor areas may vary and may not be correlated to the motor threshold.[14] Therefore, using this stimulation intensity, the likelihood of delivering suprathreshold stimulation is greater than the stimulation based on the motor threshold. In addition, in our previous study,[2] we used fixed stimulation intensity and obtained positive results. We decided to use stimulation frequency of 1Hz because low-frequency rTMS (≤1 Hz) can decrease the excitability of the targeted cortical regions.[11,15,16] Patients received five consecutive sessions of rTMS from Monday to Friday applied in the morning (8 to 10 AM). For the sham stimulation, we used the same stimulation parameters; however, a specially designed sham coil (Medtronic), which produces the same sound artifact and has a similar appearance, was used.

Clinical Outcome (Seizure Frequency)

Patients and their relatives were asked to maintain a diary of seizures, and thus record all the seizures. They were instructed to write detailed descriptions of each event, and in addition, we reinforced the necessity of an accurate recording in each patient visit and also by phone calls performed by a research assistant (P.O.). This calendar was started in the month before the treatment to have a reliable count of seizures in the baseline period, and it was maintained during the follow-up period (2 months after the rTMS treatment).

Using these calendars, an epileptologist blinded to the study group assignment reviewed each event with the patients and classified the event as a seizure or nonepileptic spell. This is particularly important because relatives tend to overestimate the number of seizures. If there was an uncertainty regarding a given event, this epileptologist could consult another clinician from the same clinical team. Indeed, in one of the patients, it was determined that most of her clinical seizures were nonepileptic spells.

Using this information, we counted the number of seizures for two different periods (baseline is the month before rTMS treatment; posttreatment is weeks 2, 4, and 8). Patients were asked to report any abnormal sensation, such as those typically experienced during auras or complex partial seizures during and immediately after the stimulation. Patients were observed by a trained neurologist during the stimulation and for 3 hours after treatment. Any abnormal behavior suggesting epilepsy was recorded.

Patients were told that rTMS could potentially improve their epilepsy based on preliminary reports in the literature. However, in the informed consent process, they were also warned about the possibility that the seizures could actually increase after rTMS application.

Electroencephalogram Analysis: Epileptiform Discharges (Secondary Outcome)

All patients underwent 18-channel EEG recordings before, immediately after the end of the 5-day rTMS treatment, as well as 30 and 60 days after rTMS treatment. Patients were kept awake during this procedure to control for the effects of sleep on ED frequency. The total duration of each EEG was 20 minutes. Initially, each EEG recording was inspected visually and all segments containing eye movements or muscle activity were rejected. Thereafter, we counted the number of EDs for the total duration of the artifact-free EEG. The EEG analysis was performed by a clinical epileptologist (K.D.V.) who was blinded about the timing of the EEG relative to rTMS and to treatment arm (active or placebo).

The EEG was also used to measure the safety of this treatment. Therefore, EEG recordings were also analyzed regarding the occurrence of after-discharges immediately after the stimulation, ictal activity, and changes in the pattern of interictal discharges compared with the baseline period.

Cognitive Assessment (Secondary Outcome)

As the other secondary outcome measure, we assessed the cognitive effects of this therapy for two reasons: (1) to obtain preliminary data on one safety aspect of this treatment in patients with MCD, and (2) to follow up the findings of our pilot study,[2] where several relatives spontaneously reported a cognitive improvement after rTMS treatment. However, it needs to be underscored that the cognitive assessment was not a primary aim of this study, and thus was assessed in a preliminary way. We evaluated cognitive changes using a subjective scale and objective tests.

In the subjective scale, we asked the following questions to the patient or their parents: (1) How would you rate the change in ability to interact socially with relatives after the treatment? (2) How would you rate the change in overall energy after the treatment? The answers could be markedly worse (−3), moderately worse (−2), slightly worse (−1), no change (0), slightly better (1), moderately better (2), and markedly better (3). This evaluation was performed after the treatment and at weeks 4 and 8.

For the objective cognitive assessment (performed before, after, and at week 8), the following tests were used:

Digit span forward and backward: These two tests are relatively simple to apply and provide valuable information about attention, information storage, working memory, mental double-tracking, and reversing operations.

Simple reaction time: We used a simple reaction time task in which patients were seated in front of a computer screen placed at eye level. A circle of 4cm in diameter was presented in the center of the screen after a warning sign (a small cross in the center of the screen) after a randomly variable interval of 2 to 5 seconds. The patients were asked to push a response key as soon as they saw the circle on the screen using the right index finger (and then repeated with the left finger), which was rested on the response key. The time between the appearance of the circle and the key press was defined as simple reaction time. The experiment consisted of blocks of 30 trials. Patients were allowed to practice for 60 trials before the test to familiarize themselves with the procedure. The stimuli were generated and response times recorded using Superlab pro v2.0 software (Cedrus Corporation, San Pedro, CA).

Stroop test: This test allows evaluation of selective attention and interference susceptibility. It measures cognitive domains that involve focused attention, response inhibition, and decision-making, and thus provides a measure of executive (frontal) function.

Table 2. Characteristics of Antiepileptic Drug Use

	ACTIVE RTMS		SHAM RTMS		
	N	Mean Dosage mg -(SD)	N	Mean Dosage mg -(SD)	*p*-value††
Lamotrigine	3	233 (243)	3	167 (57.7)	ns
Carbamazepine	9	1156 (517)	5	980 (593)	ns
Benzodiazepine†	9	1.83 (1.03)	5	1.2 (0.57)	ns
Phenobarbital	1	200	2	125 (35.4)	ns
Topamax	2	300 (141)	0	—	ns
Phenitoin	0	—	1	300	ns
Valproate	5	1425 (391)	4	1188 (688)	ns

†-benzodiazepine equivalents (Ashton, H. Benzodiazepine Abuse, Drugs and Dependence, Harwood Academic Publishers (2002), 197-212, Routledge, London & New York)
†† - Fisher's test (ns – not significant)

N – number of patients; rTMS – repetitive transcranial magnetic stimulation; SD – standard deviation

Data Analysis

Analyses were done with STATA statistical software (version 8.0; STATA, Cary, NC). Data input was performed by a blinded researcher (K.D.V.). The primary outcome of this study was seizure frequency. We initially performed a 2×4 analysis of variance (ANOVA) with the factors Group (active vs sham rTMS) and Time (baseline vs posttreatment vs week 4 vs week 8) with repeated measures on time. If appropriate, post hoc comparisons, corrected for multiple comparisons using Bonferroni correction, were performed. For each of the secondary outcomes (EDs and cognitive performance), a similar statistical analysis was performed.

We also evaluated whether any clinical or demographic variable was related to clinical outcome. For this analysis, we tested the variable seizure frequency against the clinical and demographic variables baseline seizure frequency, baseline number of EDs, social interaction, age, type of lesion, and stimulation site. This analysis was performed in an exploratory way (without correction for multiple comparisons) using Pearson's correlation coefficient for the continuous variables (eg, age) and one-way ANOVA for categorical variables (eg, type of lesion).

Finally, to analyze whether AED confounded our results, we performed correlation tests (using Person's correlation coefficient) between seizure frequency reduction (%) and AED dosage, and *t* tests between patients using and patients not using certain AEDs such as lamotrigine and topiramate. Data are reported as mean and standard deviation. Statistical significance refers to a two-tailed p value less than 0.05.

Results

Patients were randomized (in the proportion 3:4; see Patients and Methods) to receive either sham (n = 9) or active rTMS (n = 12). There were no significant baseline differences (demographic and clinical characteristics) between these two groups (see Table 1).

All patients completed the entire protocol, and only one patient (in the active group) missed one rTMS session due to a sinus infection that prevented him from coming to the hospital. No patients were lost to follow-up. Patients tolerated the rTMS treatment well. There were few adverse effects. Three patients (25%) in the active and two patients (22%) in the sham rTMS group complained of mild headache after rTMS treatment. In addition, one patient (11%) in the sham rTMS group complained of difficulty sleeping after the rTMS treatment. Importantly, there was no seizure induction related to the 5-day treatment of low-frequency rTMS.

AED use remained unchanged during the study (except for one patient in the sham group who needed a medication adjustment after 4 weeks at the end of the rTMS treatment due to a significant worsening of her seizure frequency) and is listed in Table 2. There were no differences in AED use between the active and sham rTMS groups.

Clinical Outcome: Seizure Reduction

The mean number of seizures was not different between the active (13.6 ± 10.1) and sham rTMS (11.4 ± 14.8) groups at baseline ($p = 0.69$), but was affected differently by rTMS across groups (Fig 1). The corresponding repeated-measures ANOVA with the factors Group (active vs sham) and Time (baseline vs week 2 vs week 4 vs week 8) showed a significant interaction effect ($F_{(3,57)} = 8.9$; $p < 0.0001$). There was no significant group effect ($F_{(1,19)} = 0.91$; $p = 0.35$); however, there was a significant effect of time ($F_{(3,57)} = 9.6$; $p < 0.0001$). In the active group, there was a significant reduction in the frequency of seizures after 2 weeks of treatment there was a significant reduction in the frequency of seizures at week 2 when compared with baseline (reduction of 72%; $p = 0.003$, post hoc tests corrected for multiple comparisons). This effect continued at weeks 4 (reduction of 53%; $p = 0.002$) and 8 of follow-up (reduction of 58%; $p = 0.001$). Although the absolute values of seizure frequency reduction suggest a possible decrease of the therapeutic effects after week 2, there was no significant difference between weeks 2 and 4 ($p = 0.39$), weeks 2 and 8 ($p = 0.75$), and weeks 4 and 8 ($p = 0.39$) in the active group. Finally, the post hoc analysis in the sham group showed no significant change in seizure frequency

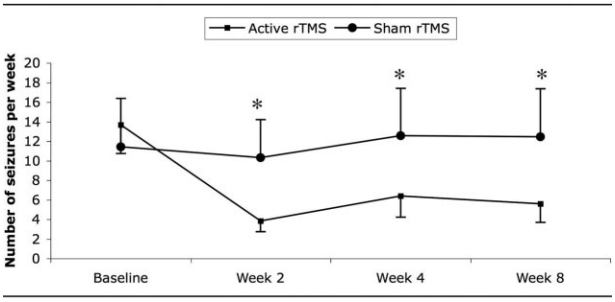

Fig 1. Mean number of seizures per week for each treatment group (active [squares] *and sham* [circles] *stimulation) throughout the trial.* Asterisks *denote statistically significant when compared with baseline.* Error bars *represent the standard error of the mean. rTMS = repetitive transcranial magnetic stimulation.*

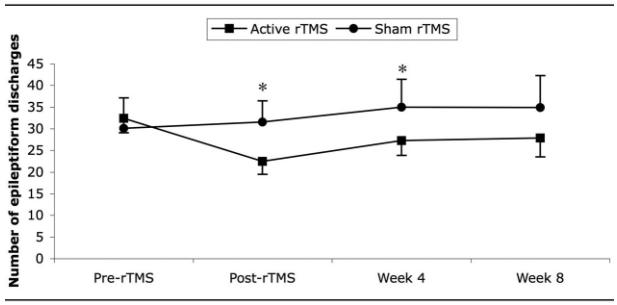

Fig 2. Mean number of epileptiform discharges in the electroencephalogram for each group of treatment (active [squares] *and sham* [circles] *stimulation) throughout the trial.* Asterisks *denote statistically significant when compared with baseline.* Error bars *represent the standard error of the mean. rTMS = repetitive transcranial magnetic stimulation. Post rTMS represents the period immediately after the 5-day rTMS treatment.*

when compared with baseline and after 2 ($p = 0.99$), 4 ($p = 0.54$), and 8 ($p = 0.99$) weeks of treatment.

Because three patients in the active group had diffuse or multifocal EDs in the EEG, and therefore received stimulation over Cz, we decided to perform a subanalysis excluding these patients. This analysis demonstrated similar results: a significant interaction term group × treatment ($F_{(3,45)} = 6.6$; $p = 0.0009$) and significant differences between posttreatment and baseline in the active group (T2 vs T0: $p = 0.006$; T4 vs T0: $p = 0.009$; T8 vs T0: $p = 0.004$; mean number of seizures per week for each period: baseline, 14.1 ± 11.1; T2, 3.6 ± 4.3; T4, 7.4 ± 6.6; and T8, 6.3 ± 7.7).

Three patients (25%) in the active rTMS group and none in the sham rTMS group were seizure-free in the initial 2 weeks of evaluation. However, no patient in either treatment group was free of seizures in the evaluations at weeks 4 and 8. There were 10 responders (reduction of 50% or more in seizure frequency) in the active group and zero in the sham rTMS group ($p = 0.001$, χ^2 test).

Electroencephalogram Analysis: Epileptiform Discharges (Secondary Outcome)

In analogy to the frequency of seizures, there was no significant difference in the baseline number of EDs between the active and sham rTMS groups ($p = 0.68$), but there was a differential effect of rTMS treatment (Fig 2). The corresponding ANOVA showed no significant group effect ($F_{(1,19)} = 0.37$; $p = 0.55$); however, it did show a significant effect of time ($F_{(3,57)} = 3.51$; $p = 0.021$) and a significant two-way interaction ($F_{(3,57)} = 4.52$; $p = 0.0065$). Post hoc tests showed that there was a significant reduction in the number of EDs in the active group, when compared with baseline, immediately after 5-day rTMS treatment (reduction of 31%; $p = 0.0012$) that was still present at week 4 (reduction of 16%; $p = 0.027$), but tended to wash out at week 8 of follow-up (reduction of 14%; $p = 0.09$). In the sham rTMS group, the number of EDs, compared with baseline, did not change immediately after treatment ($p = 0.63$) or at weeks 4 ($p = 0.48$) or 8 ($p = 0.69$).

Cognitive Evaluation (Secondary Outcome)

The cognitive evaluation was the other secondary outcome of this study. The subjective evaluation assessed social interaction and energy level (Table 3). For social interactions, ANOVA showed a significant group effect ($F_{(1,19)} = 6.65$; $p = 0.018$), time effect ($F_{(3,38)} = 16.64$; $p < 0.0001$), and interaction effect ($F_{(3,38)} = 9.21$; $p = 0.0005$). Post hoc tests showed that the comparison between active and sham groups yielded a significant difference in their evaluation after treatment ($p = 0.0001$), a trend toward a significant difference after week 4 ($p = 0.13$), and no difference after week 8 ($p = 0.74$) (see Table 3). The results for energy level were similar. The ANOVA showed that the two main effects and the interaction were significant (group: $F_{(1,19)} = 6.48$; $p = 0.020$; time: $F_{(3,38)} = 10.36$; $p = 0.0003$; and group × time: $F_{(3,38)} = 4.90$; $p = 0.013$). Post hoc tests showed a difference for energy levels after treatment in the active rTMS group only ($p = 0.009$). This effect was not significant after weeks 4 ($p = 0.59$) or 8 ($p = 0.87$).

Two patients (one in the active group and one in the sham rTMS group) could not perform the simple reaction time task. A repeated-measures ANOVA including all the time points (baseline, after treatment, and follow-up) did not show any significant effect for group, time, and interaction group × time—although there was a trend toward a significant decrease in reaction time in the right hand after active rTMS treatment only (see Table 4 for details). Only 14 patients were able to complete the Stroop test due to the severity of cognitive deficits in some patients. The ANOVA showed that the main effect of group was not significant ($F_{(1,17)} = 0.002$; $p = 0.96$); however, there was a

Table 3. Subjective Cognitive Evaluation

		ACTIVE RTMS	SHAM RTMS	
		Mean (SD)	Mean (SD)	*p*-value*
Social Interaction**	After treatment	2.33 (0.98)	0.44 (0.73)	0.0005
	Week 4	0.83 (1.11)	0.11 (0.93)	
	Week 8	0.08 (0.90)	0.22 (0.97)	
Energy Level**	After treatment	1.83 (0.72)	0.44 (0.73)	0.013
	Week 4	0.42 (0.90)	0.22 (0.67)	
	Week 8	0.17 (0.72)	0.11 (0.93)	

rTMS – repetitive transcranial magnetic stimulation; SD – standard deviation.

**Subjective scale in which subjects had to answer from -3 to +3 ((-3) markedly worse; (-2) moderately worse; (-1) slightly worse; (0) no change; (1) slightly better; (2) moderately better; (3) markedly better) in respect to whether they had any changes in these two domains after treatment with rTMS. *interaction term (time vs. group) from a 2-way ANOVA.

significant time effect ($F_{(2,24)} = 6.49$; $p = 0.0056$) and a significant interaction group × time ($F_{(2,24)} = 10.34$; $p = 0.0006$). Post hoc tests showed that, in the active group, there was a significant performance improvement, compared with baseline, after treatment ($p = 0.033$) and in the follow-up evaluation (week 8; $p = 0.028$) (Table 4).

The digit span forward and backward were tested in the same 14 patients. The results showed that performance in both of these tasks (digit span forward and digit span backward) did not change significantly in any of the two groups (active and sham rTMS) throughout the trial ($p > 0.25$ for the two main effects [time and group] and the interaction time × group effect for both tasks; see Table 4 for details).

Correlations

In an exploratory way, we performed correlations to assess whether clinical and demographic characteristics were associated with a good outcome. The results showed that seizure frequency reduction was not significantly correlated with baseline seizure frequency ($r = -0.0075$; $p = 0.98$), baseline EDs ($r = 0.15$; $p = 0.64$), social interaction change ($r = 0.30$; $p = 0.35$), site of epileptogenic foci/stimulation ($p = 0.86$), or type of lesion ($p = 0.85$). There was a trend toward a significant correlation between seizure frequency reduction and age ($r = 0.57$; $p = 0.06$), indicating that older patients had a better clinical response to rTMS.

To rule out that AEDs could have affected our results, we analyzed whether there was a correlation between drug use and seizure improvement. The correlation between AED dosage and seizure frequency change was not significant for any of the tested AEDs, that is, carbamazepine ($r = 0.23$; $p = 0.55$), benzodiazepine ($r = 0.12$; $p = 0.76$), and valproate ($r = -0.29$; $p = 0.63$). Note that we performed this test only for drugs that six or more patients were using. Similarly, there was no difference in seizure reduction among patients who were and were not taking lamotrigine ($p = 0.61$) and topiramate ($p = 0.13$).

Discussion

This randomized, sham-controlled study showed that active, but not sham, 5-day low-frequency rTMS significantly reduces seizures in patients with MCD and pharmaco-resistant epilepsy. The beneficial effect of rTMS as applied appears to last for approximately 2 months. In addition, active rTMS decreases the number of EDs observed in the EEG. Adverse effects were mild and similar for both active and sham treatments. The preliminary cognitive evaluation showed that active rTMS does not worsen cognitive function and, paradoxically, significantly improves Stroop performance, the subjective report of social interaction, and may be associated with reaction time test improvement in the right hand, possibly due to the cognitive benefit of reduced seizure activity.

Our study provides meaningful follow-up to Theodore and colleagues' study,[7] which concluded that "TMS may have a weaker effect than reported previously on seizure frequency," because the authors found only a trend toward a beneficial, antiepileptic effect of rTMS in their recent, carefully designed study. However, as Theodore and colleagues pointed out, the effects they observed were stronger in patients with epilepsy of neocortical origin than in those with mesial temporal foci. Our previous open study[2] and findings by others using similarly small study samples[2–4] support the notion that rTMS effects on epileptic foci are largely limited to instances where the epileptic discharges arise from the cortical convexity, and thus can be reached directly and reliably by rTMS. Our results further confirm this notion and promote several conclusions on the antiepileptic effects of rTMS and provisional suggestions for successful treatment parameters.

First, low-frequency rTMS can lead to a suppression of epileptic activity[17] and a resulting reduction in seizure frequency. This is consistent with the notion of rTMS leading to a suppression of cortical excitability in the directly targeted cortical region that outlasts the duration of the rTMS train itself.[16,18] Such effects ap-

Table 4. Cognitive Performance Changes (%) from Baseline

		ACTIVE RTMS	SHAM RTMS	
		Mean (SD)	Mean (SD)	*p*-value*
SRT (right hand)‡	After rTMS treatment	16.2% (24.6)	−4.3% (20.4)	0.19
	Follow-up	10.8% (26.1)	1.1% (18.8)	
SRT (left hand)‡	After rTMS treatment	9.2% (32.4)	−6.1% (24.4)	0.46
	Follow-up	9.1% (26.5)	−7.8% (30.5)	
Stroop†	After rTMS treatment	18.4% (11.2)	−1.5% (13.3)	0.006
	Follow-up	17.1% (10.1)	−2.7% (15.2)	
Digit span - forward††	After rTMS treatment	2.2% (17.2)	0.7% (13.0)	0.85
	Follow-up	5.5% (13.6)	7.8% (25.4)	
Digit span - backward††	After rTMS treatment	9.7% (15.2)	4.8% (47.8)	0.3
	Follow-up	8.3% (29.3)	2.4% (69.7)	

The results are shown as performance change (in percentage) from baseline – note that a positive percentage value indicates performance improvement. Only 14 patients could complete this assessment.

rTMS – repetitive transcranial magnetic stimulation; SD – standard deviation.

*p-value according to a two-way ANOVA (interaction term group*time).

pear mediated by a reduction of cortical excitability, presumably through an increase in GABAergic activity[10] or, alternatively, a decrease in synaptic strengthening (long-term depression).[11]

Second, rTMS is suitable for patient with epileptogenic foci located on the cortical convexity, whereas patients with mesial temporal foci are much less likely to show a clinical response.[7] The impact of TMS decays with the square of the distance; thus, direct impact to structures beyond the cortical convexity are unlikely.[19] However, beyond its local effects on the neurons directly underlying the stimulation coil, TMS also has been shown to have a distant impact along specific neural networks through connections with the local target area.[20–22] For instance, suprathreshold stimulation of the primary sensory-motor cortex is associated with an activity change in the supplementary motor area, dorsal premotor cortex, cingulate motor area, putamen, and thalamus.[20] Such a network rTMS effect could have been partially responsible for the effects observed in the few patients with diffuse or multifocal epileptogenic activity.

Third, precise targeting of the epileptic focus is essential. In our study, all patients had structural abnormalities (ie, MCD) that could be identified on MRIs and were used to guide the placement of the TMS coil. In contrast, such patients were excluded in Theodore and colleagues' study.[7]

Fourth, patients with MCD may be particularly well suited for the antiepileptic effects of rTMS. These patients have dysmorphic neurons, balloon cells, giant neurons, and immature neurons[23] that show intrinsic epileptogenesis due to an imbalance between excitatory and inhibitory circuits.[8] Therefore, the epileptogenic mechanisms in these patients may be different from those in patients with no structural abnormality, and they may respond better to rTMS because the fundamental dysfunction is localized to a restricted and easily identifiable cortical region with suppressed or absent inhibitory activity. In such a scenario, focal modulation of the dysfunctional area by slow rTMS may reduce its activity and reestablish the normal activity of the surrounding healthy cortex. Indeed, these pathophysiological characteristics make these patients also good candidates for surgical approaches, as shown in a series of patients with MCD in whom surgery resulted in 84% of patients becoming seizure-free.[24] rTMS treatment therefore may be investigated as a therapeutic option when the eloquent cortex is involved and surgical approaches are not an option.

Fifth, high-intensity rTMS may be needed to achieve a reliable and sustained antiepileptic effect. It has been shown that the effects of 1Hz rTMS on cortical excitability are dependent on the stimulus intensity.[25] We used a fixed, relatively high rTMS intensity (70% of the maximal output stimulator). Theodore and colleagues[7] applied stimulation at a lower intensity based on the subject's motor threshold. Because the stimulation threshold of nonmotor areas may differ from the motor areas (see Robertson and colleagues[14] for review), the stimulation intensity used in Theodore and colleagues' study[7] may not have been sufficient to induce significant therapeutic effects.

Sixth, in studies on the therapeutic effects of rTMS, in epilepsy or otherwise, a suitable sham condition is critical. This is not an easy challenge, and at this point, a perfect sham is not available. However, patients naive to rTMS who are randomized to real or sham rTMS applied using a sham coil, as was the case in our study, appear to be reliably blinded. In Theodore and colleagues' study,[7] the motor threshold of all patients was measured using a real TMS coil properly placed for stimulation on the patients' scalp, and for sham treatment, this coil was angled 90 degrees away from the

scalp. This practice has been applied in many rTMS studies in the past,[26] but could partially unblind some of the patients, thus effectively breaking the double-blind design. In our study, patients were naive to rTMS, and the motor threshold was not assessed because we used a fixed rTMS intensity. This may explain the positive placebo effect observed in our study in contrast with the negative placebo effect in Theodore and colleagues' study.[7]

One important question is whether the effectiveness of rTMS to reduce seizure frequency translates to other epileptic syndromes. A prediction based on our results would be largely speculative. There is certainly behavioral and neurophysiological data supporting that low-frequency rTMS decreases brain activity.[11,27–30] However, as Theodore and colleagues[7] demonstrated, patients with deep, mesial temporal foci respond less to cortical stimulation with rTMS. In this respect, one dimension that could be investigated is whether proper targeting of areas that are connected to the seizure focus, that is, that are part of the same anatomical or functional network, can lead to seizure reduction even in patients with deep epileptic foci through antiepileptic effects downstream to stimulation.

Since our previous open study, we showed that rTMS has a long-lasting effect. One reason for the long-lasting effect observed in this trial is the number of rTMS sessions. It has been shown extensively that consecutive sessions induce long-lasting behavioral effects. For instance, cumulative long-lasting plastic changes have been observed when two rTMS sessions are administered within 24 hours of each other, but not when they are at least 1 week apart.[31] The mechanisms that induce this cortical plasticity are not yet fully elucidated. One possible explanation is that rTMS modulates synaptic transmission through the modulation of the *N*-methyl-D-aspartate receptors, similar to rTMS-induced long-term depression– and long-term potentiation–like mechanisms observed in the auditory cortex of rodents.[32] Furthermore, studies with centrally acting drugs also suggest that *N*-methyl-D-aspartate modulation is involved with rTMS effects.[33] Another putative mechanism that has been proposed is the change of immediate early gene expression.[34,35]

The number of rTMS sessions might not be the only factor associated with the long-lasting effects observed in our study. We believe that the intrinsic epileptogenic characteristics of the zone with cortical dysplasia also may have played an important role in determining the duration of rTMS effects. The dysfunctional innervations from dysplastic cells—which show an imbalance between GABAergic inhibition and glutamate-mediated excitation[36,37] and can generate ictal-like epileptiform events,[38]—to the normal surrounding cortex generates hyperexcitability in a large area as shown in experimental models[39,40]; thus, in turn, it can inhibit the inhibitory drive from the normal cortex to the irritative zone. In fact, it has been shown that prolonged after-discharges occur more frequently in patients with neuronal migration disorders than in patients with other epileptic disorders.[41] Therefore, a decrease in the local excitability in the area with cortical dysplasia may result in a decrease of the abnormal excitatory input to the normal, healthy surrounding cortex that ultimately results in an increase of the inhibitory drive to the dysplastic cells. Because rTMS may disrupt this pathological excitatory network, the reestablishment of the normal activity is possible. If this hypothesis is valid, then rTMS modulation in MCD lesions requires precise spatial targeting and direct reaching of the malformation, and that the rTMS effects, if induced, might be long-lasting.

One limitation of this study is that, although we focused on patients with epilepsy due to MCD, the population of patients in this study might be considered somewhat heterogeneous because it included patients with focal and diffuse abnormalities. However, there were only four patients with diffuse or multifocal abnormalities in the EEG, and when analyzing the data without these patients, we obtained similar results. Another potential limitation that should be discussed is the difference between sham and active rTMS. We used a specially designed sham stimulation coil (commercially available from Medtronic, Minneapolis, MN) that has the same appearance as the real rTMS coil. This sham rTMS contains a small copper wire loop inside a plastic casing and produces a similar sound artifact and a mechanical tapping sensation on the subject's scalp. Subjects and patients naive to TMS are truly blinded by this sham coil, despite that it does not induce scalp muscle contractions as may be induced by real rTMS (Center for Noninvasive Brain Stimulation, unpublished data). This limits the utility of this sham coil for patients who have experienced rTMS before, but does not affect blinding in our population that was naive to rTMS.

In summary, based on our results and previous studies, we conclude that rTMS has a potential clinical use in pharmaco-resistant epilepsy patients with MCD or other patients with epilepsy of neocortical origin in whom anatomical information can be used to guide rTMS coil placement, if low-frequency rTMS is applied at relatively high intensities over repeated sessions. Further studies evaluating individual-based rTMS parameters may be necessary to optimize the clinical impact of this method of brain stimulation. In this context, the use of ictal and interictal EEG, MRI, and ictal positron emission tomography to guide and ultimately control the site, timing, and intensity of rTMS may be beneficial.

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References

1. Goodman JH. Brain stimulation as a therapy for epilepsy. Adv Exp Med Biol 2004;548:239–247.
2. Fregni F, Thome-Souza S, Bermpohl F, et al. Antiepileptic effects of repetitive transcranial magnetic stimulation in patients with cortical malformations: an EEG and clinical study. Stereotact Funct Neurosurg 2005;83:57–62.
3. Menkes DL, Gruenthal M. Slow-frequency repetitive transcranial magnetic stimulation in a patient with focal cortical dysplasia. Epilepsia 2000;41:240–242.
4. Daniele O, Brighina F, Piazza A, et al. Low-frequency transcranial magnetic stimulation in patients with cortical dysplasia: a preliminary study. J Neurol 2003;250:761–762.
5. Brasil-Neto JP, de Araujo DP, Teixeira WA, et al. Experimental therapy of epilepsy with transcranial magnetic stimulation: lack of additional benefit with prolonged treatment. Arq Neuropsiquiatr 2004;62:21–25.
6. Misawa S, Kuwabara S, Shibuya K, et al. Low-frequency transcranial magnetic stimulation for epilepsia partialis continua due to cortical dysplasia. J Neurol Sci 2005;234:37–39.
7. Theodore WH, Hunter K, Chen R, et al. Transcranial magnetic stimulation for the treatment of seizures: a controlled study. Neurology 2002;59:560–562.
8. Sullivan LR, Kull LL, Sweeney DB, Davis CP. Cortical dysplasia: zones of epileptogenesis. Am J Electroneurodiagnostic Technol 2005;45:49–60.
9. Morgan SL, Teyler TJ. Epileptic-like activity induces multiple forms of plasticity in hippocampal area CA1. Brain Res 2001; 917:90–96.
10. Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847–858.
11. Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology 1997;48:1398–1403.
12. Peto R. Clinical trial methodology. Biomedicine 1978;28(Spec No):24–36.
13. Pocock SJ. Allocation of patients to treatment in clinical trials. Biometrics 1979;35:183–197.
14. Robertson EM, Theoret H, Pascual-Leone A. Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J Cogn Neurosci 2003;15:948–960.
15. Maeda F, Keenan JP, Tormos JM, et al. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000;111:800–805.
16. Gangitano M, Valero-Cabre A, Tormos JM, et al. Modulation of input-output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. Clin Neurophysiol 2002;113:1249–1257.
17. Anschel DJ, Pascual-Leone A, Holmes GL. Anti-kindling effect of slow repetitive transcranial magnetic stimulation in rats. Neurosci Lett 2003;351:9–12.
18. Gugino LD, Romero JR, Aglio L, et al. Transcranial magnetic stimulation coregistered with MRI: a comparison of a guided versus blind stimulation technique and its effect on evoked compound muscle action potentials. Clin Neurophysiol 2001;112:1781–1792.
19. Wagner TA, Zahn M, Grodzinsky AJ, Pascual-Leone A. Three-dimensional head model simulation of transcranial magnetic stimulation. IEEE Trans Biomed Eng 2004;51:1586–1598.
20. Bestmann S, Baudewig J, Siebner HR, et al. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci 2004;19: 1950–1962.
21. Chouinard PA, Van Der Werf YD, Leonard G, Paus T. Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. J Neurophysiol 2003;90:1071–1083.
22. Valero-Cabre A, Payne BR, Rushmore J, et al. Impact of repetitive transcranial magnetic stimulation of the parietal cortex on metabolic brain activity: a 14C–2DG tracing study in the cat. Exp Brain Res 2005;163:1–12.
23. Palmini A, Najm I, Avanzini G, et al. Terminology and classification of the cortical dysplasias. Neurology 2004;62:S2–S8.
24. Kral T, Clusmann H, Blumcke I, et al. Outcome of epilepsy surgery in focal cortical dysplasia. J Neurol Neurosurg Psychiatry 2003;74:183–188.
25. Fitzgerald PB, Brown TL, Daskalakis ZJ, et al. Intensity-dependent effects of 1 Hz rTMS on human corticospinal excitability. Clin Neurophysiol 2002;113:1136–1141.
26. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 1996;348:233–237.
27. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–156.
28. Mansur CG, Fregni F, Boggio PS, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. Neurology 2005;64:1802–1804.
29. Fregni F, Monte-Silva KK, Oliveira MB, et al. Lasting accelerative effects of 1 Hz and 20 Hz electrical stimulation on cortical spreading depression: relevance for clinical applications of brain stimulation. Eur J Neurosci 2005;21:2278–2284.
30. Romero JR, Anschel D, Sparing R, et al. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 2002;113:101–107.
31. Gorsler A, Baumer T, Weiller C, et al. Interhemispheric effects of high and low frequency rTMS in healthy humans. Clin Neurophysiol 2003;114:1800–1807.
32. Wang H, Wang X, Scheich H. LTD and LTP induced by transcranial magnetic stimulation in auditory cortex. Neuroreport 1996;7:521–525.
33. Siebner HR, Rothwell J. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Exp Brain Res 2003;148:1–16.
34. Hausmann A, Weis C, Marksteiner J, et al. Chronic repetitive transcranial magnetic stimulation enhances c-fos in the parietal cortex and hippocampus. Brain Res Mol Brain Res 2000;76:355–362.
35. Ji RR, Schlaepfer TE, Aizenman CD, et al. Repetitive transcranial magnetic stimulation activates specific regions in rat brain. Proc Natl Acad Sci U S A 1998;95:15635–15640.
36. Hagemann G, Kluska MM, Redecker C, et al. Distribution of glutamate receptor subunits in experimentally induced cortical malformations. Neuroscience 2003;117:991–1002.
37. Luhmann HJ, Raabe K, Qu M, Zilles K. Characterization of neuronal migration disorders in neocortical structures: extracellular in vitro recordings. Eur J Neurosci 1998;10:3085–3094.
38. Avoli M, Bernasconi A, Mattia D, et al. Epileptiform discharges in the human dysplastic neocortex: in vitro physiology and pharmacology. Ann Neurol 1999;46:816–826.
39. Jacobs KM, Gutnick MJ, Prince DA. Hyperexcitability in a model of cortical maldevelopment. Cereb Cortex 1996;6:514–523.
40. Holmes GL, Sarkisian M, Ben-Ari Y, et al. Consequences of cortical dysplasia during development in rats. Epilepsia 1999; 40:537–544.
41. Chitoku S, Otsubo H, Harada Y, et al. Characteristics of prolonged afterdischarges in children with malformations of cortical development. J Child Neurol 2003;18:247–253.