A Sham-Controlled Trial of a 5-Day Course of Repetitive Transcranial Magnetic Stimulation of the Unaffected Hemisphere in Stroke Patients

Felipe Fregni, MD, PhD; Paulo S. Boggio, MSc; Angela C. Valle, PhD; Renata R. Rocha; Julia Duarte; Merari J.L. Ferreira; Tim Wagner, MSc; Shirley Fecteau, PhD; Sergio P. Rigonatti, MD, PhD; Marcelo Riberto, MD; Steven D. Freedman, MD, PhD; Alvaro Pascual-Leone, MD, PhD

Background and Purpose—It has been recently shown that a single session of repetitive transcranial magnetic stimulation (rTMS) of the unaffected hemisphere can improve motor function in stroke patients; however, this improvement is short-lasting. We therefore conducted a randomized, sham-controlled, phase II trial to evaluate whether five sessions of low-frequency rTMS can increase the magnitude and duration of these effects and whether this approach is safe.

Methods—Fifteen patients with chronic stroke were randomized to receive active or sham rTMS of the unaffected hemisphere. A blinded rater assessed motor function and corticospinal excitability at baseline, during and after 2 weeks of treatment. Safety was assessed using a neuropsychologic battery and electroencephalogram.

Results—Active rTMS resulted in a significant improvement of the motor function performance in the affected hand that lasted for 2 weeks. These effects were not observed in the sham rTMS group (affected and unaffected hand) and in the unaffected hand in the active rTMS group. Corticospinal excitability decreased in the stimulated, unaffected hemisphere and increased in the affected hemisphere. There was a significant correlation between motor function improvement and corticospinal excitability change in the affected hemisphere. Cognitive performance and electroencephalogram were not changed significantly throughout the trial in both groups of treatment.

Conclusions—These results support and extend the findings of previous studies on rTMS in stroke patients because five consecutive sessions of rTMS increased the magnitude and duration of the motor effects. Furthermore, this increased dose of rTMS is not associated with cognitive adverse effects and/or epileptogenic activity. **(*Stroke*. 2006;37:2115-2122.)**

Key Words: cerebrovascular accident ■ electrical stimulation of the brain ■ recovery of function ■ stroke

After stroke, the brain undergoes plastic changes involving areas beyond the site of lesion in an attempt to recover function.[1] Recent evidence suggests that the results of some of these changes, however, may not be beneficial, but rather maladaptive. After stroke, the interhemispheric inhibitory drive from the unaffected to the affected hemisphere is increased and might be an important causal factor for the motor function impairment.[1]

The recent development of the techniques of noninvasive brain stimulation has provided a new alternative to modulate this imbalanced activity between motor cortices. Two techniques of noninvasive brain stimulation, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been used to improve motor function. For instance, motor cortex stimulation with either excitability-diminishing low-frequency rTMS[2,3] or cathodal tDCS[4] of the unaffected hemisphere and with either excitability-enhancing high-frequency rTMS[5] or anodal tDCS[4,6] of the affected hemisphere are associated with motor function improvement.

Although these studies represent an important contribution to the development of novel, neurorehabilitative strategies for stroke recovery; they, with the exception of one study, applied rTMS for only one session and showed short-lasting effects. It has been shown that the magnitude and duration of the clinical effects of rTMS depend on the number of rTMS sessions.[7] Although in Khedr's study,[5] the effects of several rTMS sessions were investigated, these authors used high-frequency rTMS over the lesioned cortex that raises safety concerns—increased risk of seizures and methodological difficulties—the electrical field can be modified in magnitude, location, and orientation by the anatomic changes after a stroke.[8]

Therefore, we aimed to study the efficacy and safety of repeated, consecutive sessions of low-frequency rTMS of the unaffected hemisphere on motor function in chronic stroke patients.

Received January 21, 2006; final revision received February 15, 2006; accepted March 8, 2006.

From the Harvard Center for Non-Invasive Brain Stimulation, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass (F.F., T.W., S.F., S.D.F., A.P.-L.); the Departments of Experimental Psychology (P.S.B.), Psychiatry (S.P.R.), and Pathology (A.C.V.), University of Sao Paulo, Sao Paulo, Brazil; Mackenzie University, Sao Paulo, Brazil (P.S.B., J.D., R.R.R., M.J.L.F.); the Division of Physical Medicine and Rehabilitation, University of Sao Paulo, Sao Paulo, Brazil (M.R.); and the Institut Guttmann (A.P.-L.), Universidad Autonoma de Barcelona, Spain.

Correspondence to Felipe Fregni, MD, PhD; Harvard Center for Non-invasive Brain Stimulation, 330 Brookline Ave, KS 452, Boston, MA 02215. E-mail ffregni@bidmc.harvard.edu

Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000231390.58967.6b**

Methods

Subjects

We studied 15 patients (11 men and 4 women) aged 38 to 75 years (mean, 56±11.5 years) at least 1 year after stroke. The diagnosis was made by clinical features and confirmed by neuroimaging studies. Patients were regarded as suitable to participate if they fulfilled the following criteria: (1) single ischemic stroke with more than 1 year of duration; and (2) mild to moderate motor deficit. Although not planned, most of our patients had left-sided (12 of 15) and subcortical (13 of 15) strokes. We excluded patients with any clinically significant or unstable medical disorder, with a history of substance abuse, any neuropsychiatric comorbidity other than stroke, and contraindications to rTMS. Written informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee.

Experimental Design

This study was a longitudinal, randomized, parallel-design, sham-controlled, phase II trial that had four phases: (1) randomization, (2) training and baseline evaluation, (3) treatment, and (4) follow-up evaluation after 2 weeks of study completion.

Initially, patients were randomized in a 1:2 ratio to receive sham or active rTMS, respectively. This randomization strategy (1:2) reflects conventional strategy in randomized phase II trials (which are often quite small) because it can offer additional information regarding the active treatment.[9] Although this strategy decreases the power of the study (because less information from the sham group is provided), we accounted for this decrease of power in our sample size calculation.

Measurement of Corticospinal Excitability: Motor Threshold Assessment

The resting motor threshold (MT) of the first dorsal interosseous (FDI) in the affected and unaffected hemisphere was measured using the published guidelines.[10] As we have pointed out in prior work,[8] in stroke patients, a comparison of MT between hemispheres is not valid; however, here we analyzed each hemisphere's MT levels individually pre- and posttreatment. Measurements were performed on day 1 (baseline), 2, 3, 4, and 5 for the unaffected hemisphere and on day 1 (baseline), and 5 (last day of treatment) for the affected hemisphere. The measurement schedule was different in the affected and unaffected hemisphere because the measurements of day 1 and 5 (in both hemispheres) were to investigate changes in the corticospinal excitability and the daily measurements in the unaffected hemisphere were to adjust the stimulation intensity.

Repetitive Transcranial Magnetic Stimulation

Participants received five sessions of rTMS to the unaffected hemisphere over the primary motor cortex—corresponding to the "hot spot" for the stimulation of the FDI cortical area representation as defined during the MT determination—with the following parameters: intensity of 100% MT, frequency of 1 Hz, 1200 stimuli as a single, continuous train lasting 20 minutes. For the repetitive and also single-pulse TMS, we used a figure-of-eight coil and the magnetic stimulus had a biphasic waveform. All the treatments were administered by only one investigator who was not involved in the motor function, cognitive, and corticospinal excitability assessment. For the sham stimulation, we placed the coil at the same place that was used for the motor cortex stimulation and used the same stimulation parameters; however, a sham coil was used.

Evaluations

For the motor function evaluation, we used the Jebsen-Taylor Hand Function Test (JTT), simple reaction time (sRT), choice reaction time (cRT), and Purdue Pegboard test (PTT). These tests have been shown to be a reliable instrument of motor function evaluation in our previous investigations.[2,4] All evaluations were performed by a blinded rater at baseline daily during the treatment period (before and after rTMS sessions) and in the follow up, except for the JTT that was performed at the baseline, day 5, and follow up. Subjects were instructed to practice until they reach a stable plateau as defined by less then 10% change in the last two trials for the cRT, sRT, and PTT. For JTT, subjects performed this test five times and this indeed showed to be sufficient to reach a stable performance plateau as shown in the "Results" section. After the training session, there was a rest period of 2 hours before the baseline measurement.

Cognitive Function and Safety

We performed a neuropsychologic battery of tests to detect changes in cognition after this treatment that consisted of the following tests: Mini-Mental State Examination (general cognitive test), Stroop test (colors, words, and interference)—to test selective attention and interference susceptibility, digit span forward and backward—to test attention, information storage, working memory, and reversing operations.

Furthermore, although we used low-frequency rTMS, we monitored brain activity with an online electroencephalogram (EEG) system (Eldith GmbH) to detect subclinical seizure activity. We used a standard 12-channel EEG. EEG signals were filtered at a sampling frequency of 2048 Hz and monitored online by specially developed software (NeuroPrax; Eldith). The reference electrode was placed at the right mastoid and the ground at the left mastoid and the active electrodes were placed at: Cz-C3-C4-P3-P4-F3-F4-T3-T4. Furthermore, patients were observed by a trained neurologist during the stimulation and for 2 hours after treatment.

Statistical Analysis

Analyses were done with SAS statistical software (version 9.1). We used a mixed linear model to analyze motor function changes. The advantage of linear models rather than analysis of variance is that time can be analyzed as a continuous (rather than categorical) variable. We modeled motor performance change (as indexed by JTT, sRT, cRT, PPT) using the covariates of time, group, and interaction between treatment and time. Because in a longitudinal data, the variability of within-individual differences is always smaller than the variability of the between-individual differences, the covariance of the repeated measures within each patient was also modeled. Using the test of the difference in the −2 log likelihood to compare models with different covariance matrices, we chose the compound symmetry matrix.

For the cognitive and corticospinal excitability assessment, we used a repeated-measures analysis of variance in which the dependent variable was the performance in the cognitive tests (Mini-Mental Status Examination [MMSE], DSF, DSB, and Stroop test) or MT and the independent variables were: group (sham and active rTMS), time of treatment (baseline, day 5, and follow up) and interaction treatment * time. When appropriate, post hoc comparisons were performed using Bonferroni correction.

Using Pearson correlation test, we tested whether there was a correlation between motor improvement after active rTMS with poststroke duration, degree of motor impairment (as indexed by the MRC), and cortical excitability changes (as indexed by motor threshold change).

There were no dropouts and the few missing data were considered missing at random. Statistical significance refers to a two-tailed probability value <0.05.

Results

Patients tolerated the treatment well. The Table shows the demographic and clinical characteristics of these patients at baseline. There were no significant differences between these two groups of treatment.

Motor Improvement: Comparison of Unaffected Versus Affected Hand and Sham Versus Active Repetitive Transcranial Magnetic Stimulation

We initially compared whether the slopes (motor function performance versus time) were different across the four groups (affected hand in the active rTMS group [affected active],

Demographic and Stroke Characteristics

Patient No.	Age	Gender	Time Poststroke*	MS	ASS	Stroke Location
Active rTMS group						
1	60	Female	3.23	4.50	0.50	Left basal ganglia
2	63	Male	3.75	3.00	1.00	Left internal capsule
3	49	Male	5.96	4.80	0.50	Left putamen
4	75	Male	2.12	4.00	1.00	Left internal capsule
5	67	Male	2.15	4.75	0.50	Left corona radiata
6	70	Male	3.75	4.00	0.50	Left internal capsule (posterior limb)
7	43	Male	10.67	3.50	1.50	Left internal capsule
8	42	Male	1.05	4.00	1.00	Right lentiform nucleus
9	52	Female	1.40	4.50	1.50	Right internal capsule
10	56	Male	1.13	3.00	1.00	Left somatosensory cortex
Mean	57.70		3.52	4.01	0.90	
SD	11.27		2.93	0.66	0.40	
Sham rTMS group						
11	52	Male	6.54	3.00	1.50	Right frontal lobe
12	62	Male	2.49	3.00	2.00	Left temporofrontal
13	38	Female	7.10	3.50	1.00	Left putamen and caudate
14	43	Male	1.45	4.50	0.50	Left corona radiata
15	68	Female	2.27	4.50	0.50	Left putamen
Mean	52.60		3.97	3.70	1.10	
SD	12.56		2.64	0.76	0.65	
P†	0.44	0.56	0.78	0.44	0.43	

*In years; MS indicates motor strength; ASS, Ashworth Spasticity Score (note that 0.5 corresponds to 1− and 1.5 to 1+). For MS and ASS, we examined the fingers flexors.

†Student *t* test for the comparison of continuous variables and Fisher exact test for the comparison of categorical variables.

affected hand in the sham rTMS group [affected sham], unaffected hand in the active rTMS group [unaffected active], unaffected hand in the sham rTMS group [unaffected sham]). In the sRT model, the slopes unaffected sham, affected sham, and unaffected active were not significantly different between themselves (Figure 1A); however, the slope affected active was different from the other three slopes (comparison with affected sham [$P=0.004$], unaffected active [$P=0.007$], and unaffected sham [$P=0.0003$]). The slope for the affected active was highly significant ($P<0.0001$) and showed a coefficient of −70.98 ms, suggesting that there was a mean decrease in reaction time of 70.94 ms after each session of rTMS. This model also revealed a significant interaction term − time * treatment ($F_{[3,26]}=7.31$; $P=0.001$).

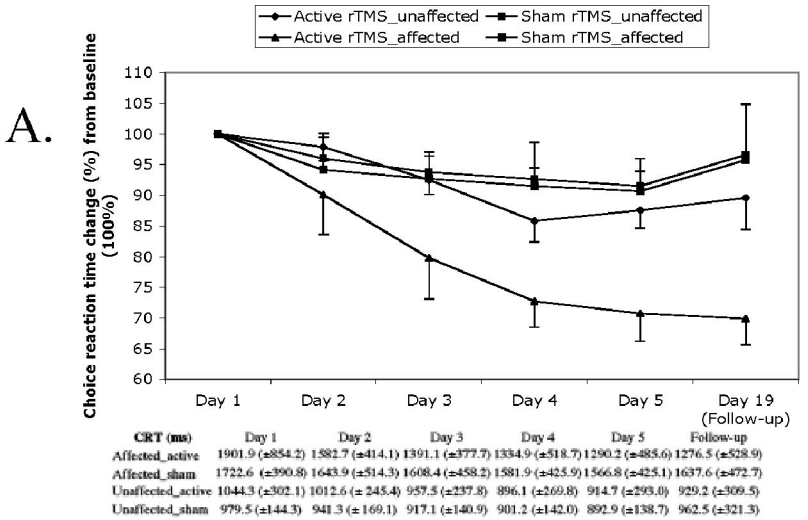
We repeated the same analysis including the cRT as the dependent variable and we obtained similar results (Figure 1B, details in supplemental Table I, available online at http://stroke.ahajournals.org). Although the Figure 1C suggests a similar pattern for the PTT performance, similar analysis failed to show that the slope of the affected active was different from the other slopes. The relatively small magnitude of the improvement in this test (ceiling effect) in comparison with reaction time tasks might have contributed for this lack of significance. We then explored the results from the affected hand only, comparing sham versus active stimulation.

Motor Improvement—Analysis of Affected Hand Only: Comparison Sham Versus Active Repetitive Transcranial Magnetic Stimulation

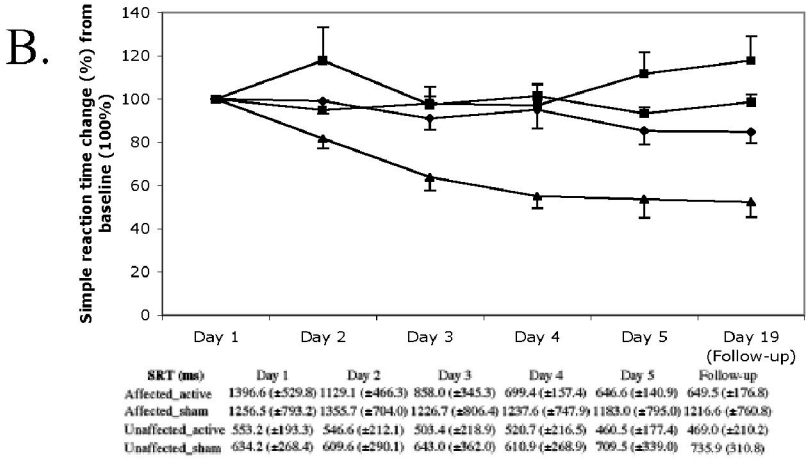
We performed a linear, repeated-measures model in which the dependent variable was motor function change (as indexed by sRT, cRT, and PTT) and the covariates were group (affected sham and affected active), time, and interaction term (time*treatment). Using profile analysis (treating time as categorical), the main effect of group (sRT model) was not significant ($F_{1,13}=1.13$, $P=0.31$), but there was a significant effect of time ($F_{5,65}=8.86$, $P<0.0001$) and the interaction time*group ($F_{5,65}=5.71$, $P=0.0002$). Motor performance change (comparison between baseline and poststimulation), for the affected active, was significant for all the time points (day 2 versus baseline, $P=0.031$; day 3 versus baseline, $P=0.026$; day 4 versus baseline, $P<0.0001$; day 5 versus baseline, $P<0.0001$; follow up versus baseline, $P<0.0001$).

We compared the parametric model—using time as a linear trend—with the nonparametric model—using time as a categorical variable. Using the difference in the −2 log likelihood, we showed that these models were not significantly different, and therefore the nested model (using time as a continuous variable − linear trend) is adequate to explain our data.

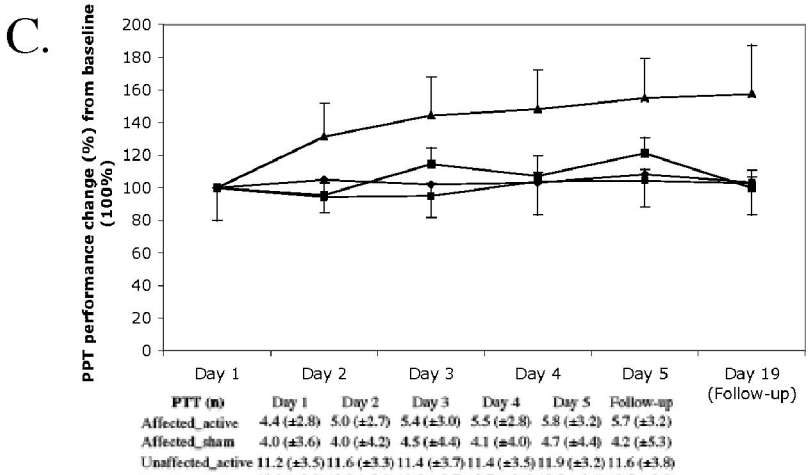
We performed the same analysis for the cRT and PPT models and obtained similar results: a significant effect of time and interaction time*group. In addition, both of these models were



CRT (ms)	Day 1	Day 2	Day 3	Day 4	Day 5	Follow-up
Affected_active	1901.9 (±854.2)	1582.7 (±414.1)	1391.1 (±377.7)	1334.9 (±518.7)	1290.2 (±485.6)	1276.5 (±528.9)
Affected_sham	1722.6 (±390.8)	1643.9 (±514.3)	1608.4 (±458.2)	1581.9 (±425.9)	1566.8 (±425.1)	1637.6 (±472.7)
Unaffected_active	1044.3 (±302.1)	1012.6 (± 245.4)	957.5 (±237.8)	896.1 (±269.8)	914.7 (±293.0)	929.2 (±309.5)
Unaffected_sham	979.5 (±144.3)	941.3 (± 169.1)	917.1 (±140.9)	901.2 (±142.0)	892.9 (±138.7)	962.5 (±321.3)



SRT (ms)	Day 1	Day 2	Day 3	Day 4	Day 5	Follow-up
Affected_active	1396.6 (±529.8)	1129.1 (±466.3)	858.0 (±345.3)	699.4 (±157.4)	646.6 (±140.9)	649.5 (±176.8)
Affected_sham	1256.5 (±793.2)	1355.7 (±704.0)	1226.7 (±806.4)	1237.6 (±747.9)	1183.0 (±795.0)	1216.6 (±760.8)
Unaffected_active	553.2 (±193.3)	546.6 (±212.1)	503.4 (±218.9)	520.7 (±216.5)	460.5 (±177.4)	469.0 (±210.2)
Unaffected_sham	634.2 (±268.4)	609.6 (±290.1)	643.0 (±362.0)	610.9 (±268.9)	709.5 (±339.0)	735.9 (310.8)



PTT (n)	Day 1	Day 2	Day 3	Day 4	Day 5	Follow-up
Affected_active	4.4 (±2.8)	5.0 (±2.7)	5.4 (±3.0)	5.5 (±2.8)	5.8 (±3.2)	5.7 (±3.2)
Affected_sham	4.0 (±3.6)	4.0 (±4.2)	4.5 (±4.4)	4.1 (±4.0)	4.7 (±4.4)	4.2 (±5.3)
Unaffected_active	11.2 (±3.5)	11.6 (±3.3)	11.4 (±3.7)	11.4 (±3.5)	11.9 (±3.2)	11.6 (±3.8)
Unaffected_sham	13.3 (±3.9)	12.3 (±3.2)	12.5 (±3.7)	13.7 (±3.4)	13.5 (±2.0)	13.5 (±3.0)

Figure 1. Motor function performance change over time as indexed by choice (A) RT, (B) sRT, and (C) PTT. Motor function was assessed at baseline (day 1), day 2, day 3, day 4, day 5, and follow up (after 2 weeks of the treatment). Data are normalized for baseline values (100%). Each point represents mean and error bars represent standard error of mean. The table below each figure shows the absolute mean value and standard deviation for each group in each time point.

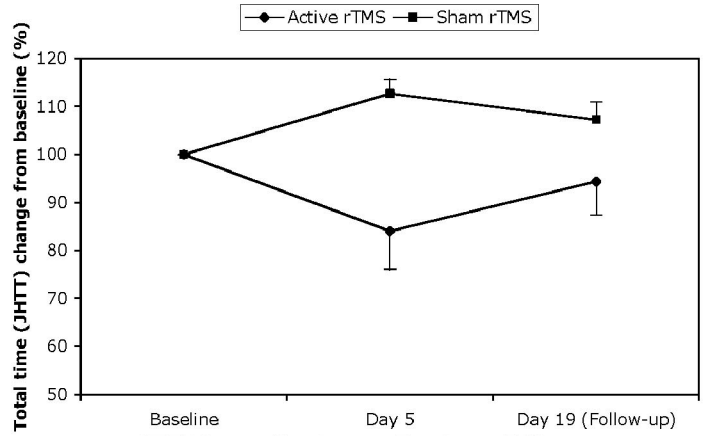
satisfactorily explained by linear, parametric models (see supplemental Table I for details).

Motor Improvement: Jebsen-Taylor Hand Function Test

Given three time points (baseline, day 5, and follow up) for the JTT, the repeated-measures mixed model showed a significant interaction term time*group ($F_{5,65}=5.83$, $P=0.0081$). The comparison of the motor function for the active group between baseline and day 5 (beta coefficient=−34.1 seconds) was significant ($P=0.0024$) and there was a trend toward a significant difference between baseline and follow up (beta coefficient=−14.6 seconds, $P=0.09$) (Figure 2A). Furthermore, the comparison of the area under the curve between the two groups (normalizing baseline values) revealed a significant mean difference between groups of 14.9% ($P=0.007$).

Figure 2B showed that patients reached a plateau after the second session of training. The comparison of the third, fourth,

A.



JTT (s)	Day 1	Day 5	Follow-up
Active rTMS	117.1 (±81.3)	94.6 (±60.4)	107.6 (±69.5)
Sham rTMS	113.6 (±65.1)	126.3 (±67.3)	119.1 (±64.1)

B.

Mean time (s)		Task 1 (cards)	Task 2 (small objects)	Task 3 (feeding)	Task 4 (checkers)	Task 5 (light cans)	Task 6 (heavy cans)	Total (s)
Active rTMS	Baseline	14.1	29.2	24.6	15.5	13.7	19.9	117.1
	Day 5	11.5	20.9	22.4	12.7	12.1	15.0	94.6
	Day 19 (Follow-up)	11.5	25.4	26.2	14.1	13.2	17.3	107.6
Sham rTMS	Baseline	14.3	24.9	21.9	17.8	21.1	17.1	117.1
	Day 5	17.3	27.3	23.3	16.1	23.1	19.2	126.3
	Day 19 (Follow-up)	14.2	28.1	21.7	13.6	23.5	18.1	119.1

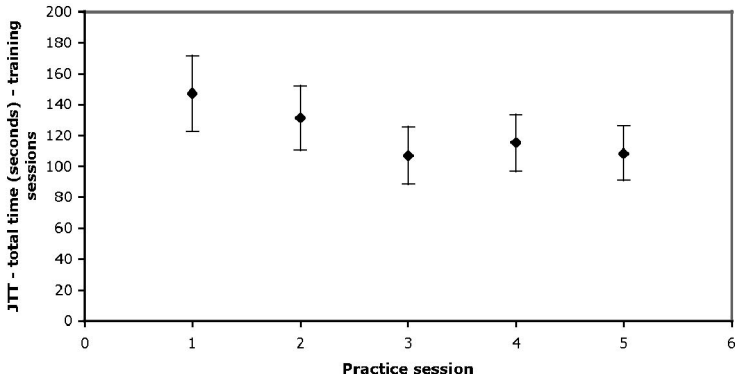


Figure 2. Motor function performance change over time as indexed by (A) JTT. Motor function was assessed at baseline (day 1), day 5, and follow up (after 2 weeks of the treatment). The table below A shows the absolute mean value and standard deviation for each group in each time point. (B) The motor performance improvement and plateau in the training sessions; note that after the second session of practice, the motor performance in this test stabilized. Data are normalized for baseline values (100%). Each point represents mean and error bars represent standard error of mean.

and fifth practice sessions showed no significant difference in the motor performance.

Corticospinal Excitability: Motor Threshold Assessment

A repeated-measures analysis of variance in which the motor threshold in the unaffected hemisphere was the dependent variable showed a significant effect of group (active versus sham rTMS; $F_{1,65}=22.7$, $P<0.0001$), time (day 1, 2, 3, 4, and 5; $F_{4,65}=238.9$, $P<0.0001$), and interaction term time*group ($F_{4,65}=2.7$, $P=0.037$). In the active rTMS group, compared with baseline, there was a trend toward a significant increase in the MT (indicating a decrease in the corticospinal excitability) on days 2 and 3 ($P=0.07$ and $P=0.08$, respectively), and this increase was significant on days 4 and 5 ($P=0.005$ and $P=0.03$, respectively). For the sham rTMS group, these comparisons were not significant (Figure 3A).

In the affected hemisphere, there was a significant difference in the MT change (baseline versus day 5) between the two treatment groups ($F_{4,65}=2.7$, $P=0.037$). For the active rTMS group, there was a significant decrease in the motor threshold by 13.5% (95% confidence interval [CI], 6.3 to 20.4%), indicating a significant increase in the corticospinal excitability. For the sham rTMS group, the change in the motor threshold (increase by 1.6%) was not significant (95% CI, −8.9 to 12.1%) (Figure 3B).

Safety Assessment: Cognitive Function and Electroencephalogram Analysis

For the MMSE, a repeated-measures analysis of variance showed no significant main effect of time, group of treatment, and interaction term time*group ($F<1$ for the three analyses). Performing a similar analysis, we obtained analogous results for Stroop (colors, words, and interference) and Digit Span (forward and backward): no significant effect of time, group, or interaction time*group. Therefore, the results of MMSE and neuropsychologic tests performance suggest that both treatments (active and sham rTMS) were not associated with cognitive changes (see supplemental Table II for details, available online at http://stroke.ahajournals.org).

There were few adverse events. In the active group, one patient reported a mild headache (contralateral to the side of

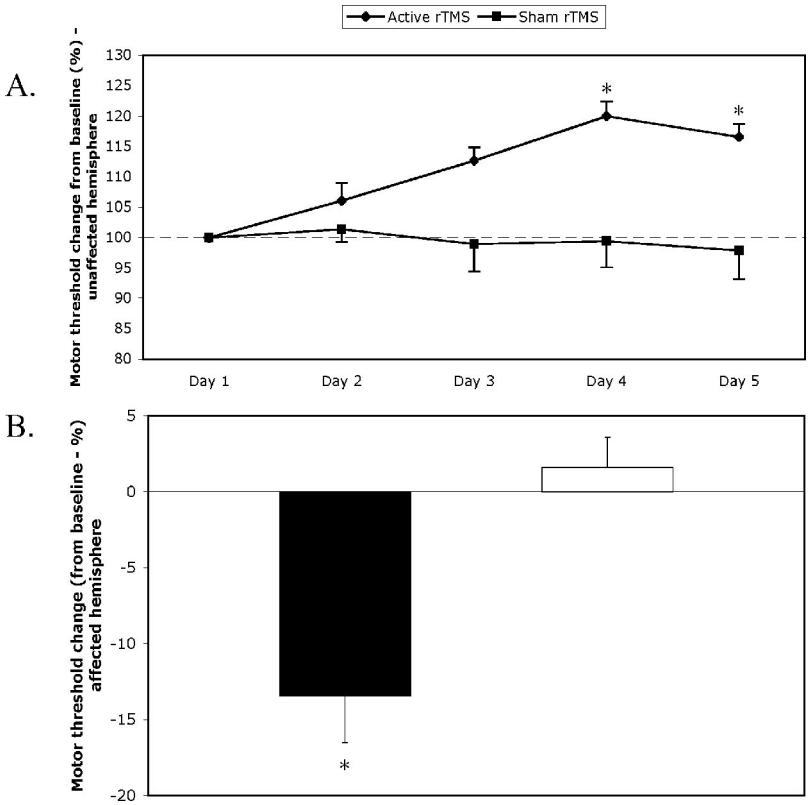


Figure 3. Motor threshold changes after active and sham rTMS in the (A) unaffected hemisphere (data are normalized for baseline values; 100%) and (B) affected hemisphere. *Statistically significant when compared with baseline. Each point represents mean and error bars represent standard error of mean.

TMS application) and one patient reported an increase in anxiety. In the sham rTMS group, one patient reported an increase in the tiredness and one patient reported a mild headache.

Finally, there was no abnormal behavior during or after the stimulation that could have suggested a complex partial or secondarily generalized seizures as observed by a licensed neurologist. The EEG analysis disclosed no ictal activity, epileptiform discharges, or changes when comparing the pre- to the post-EEG.

Correlations

The correlation analysis showed a significant correlation between motor function improvement (as indexed by JTT test) and corticospinal excitability change in the affected hemisphere ($r=-0.69$, $P=0.027$) (Figure 4A), and motor function improvement and baseline motor strength ($r=0.74$, $P=0.015$) (Figure 4B), suggesting that patients with milder motor deficits and with greater corticospinal excitability increase in the affected hemisphere had the larger motor improvement. There was a trend for a significant correlation between motor function improvement and scores in the Ashworth scale for spasticity ($r=-0.56$, $P=0.087$). Finally, there was no correlation between motor function improvement versus stroke duration and versus age.

Discussion

Our results show that motor function improvement after rTMS treatment is specific to the treatment (active versus sham rTMS) and hand (affected versus unaffected), increases over time during the treatment period, and is long-lasting (lasted for 2 weeks after the completion of the treatment). This study was based on the hypothesis that the inhibition of the activity of the unaffected hemisphere would result in a decrease in the transcallosal inhibition to the affected hemisphere and an increase in the excitability of this hemisphere that ultimately would translate into a motor function improvement. For such mechanism be valid, some facts must support it such as (1) the activity in the unaffected hemisphere is increased and associated with poor recovery in stroke[11]; (2) such increased activity results in an increased transcallosal inhibition from the unaffected to the affected hemisphere[1]; (3) 1 Hz rTMS decreases transcallosal inhibition to the contralateral hemisphere[12]; and (4) a decrease in transcallosal inhibition improves the motor function in the hand ipsilateral to the stimulation site in healthy subjects.[13] If the improvement observed in our study is consequence of the decrease in the transcallosal inhibition to the affected hemisphere, one can conceptualize that direct stimulation of the affected hemisphere would yield a similar effect. In fact, either excitability-enhancing anodal tDCS[4,6] or high-frequency rTMS[5] of the affected hemisphere result in motor function improvement. In addition, we showed that inhibitory low-frequency rTMS decreased corticospinal excitability in the stimulated (unaffected) hemisphere and increased it in the contralateral (affected) hemisphere. Finally, the increase in the activity in the affected hemisphere can improve motor function not only by enhancing the activity of the remaining neurons in M1, but also by unmasking local and distant latent neural networks as suggested by Takeuchi et al.[3] However, we believe that motor function improvement was associated predominantly with primary motor cortex activity modulation because the simple motor tasks such as the simple and choice reaction time showed more stable results compared with the Jebsen-Taylor task.

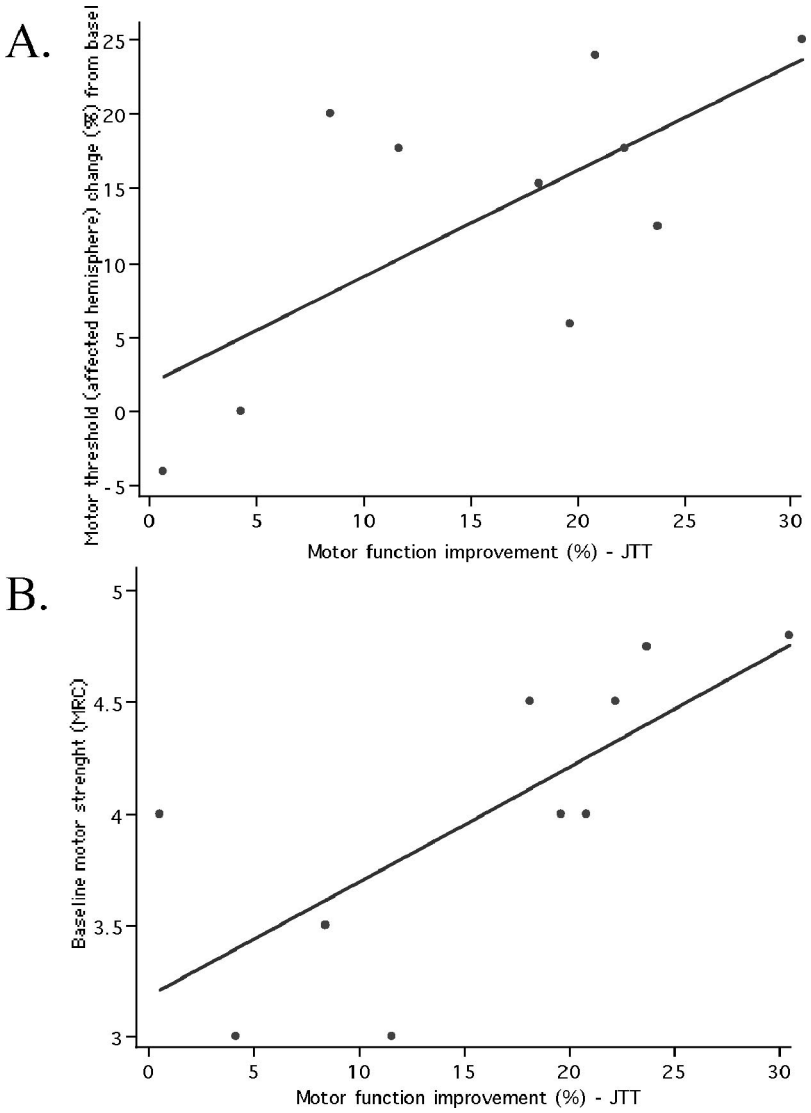


Figure 4. Correlation between motor function changes (as indexed by sRT changes) versus (A) motor threshold changes and versus (B) baseline motor strength. Note that there was a positive significant correlation between these variables such as that patients with less motor deficits and more changes in the motor threshold had a better outcome (improvement in the motor function).

One important result from the present investigation is that the effects of rTMS are cumulative and lasted for at least 2 weeks. It has been shown that the behavioral effects of rTMS treatment depend on the number of rTMS sessions,[7] and we speculate that one potential mechanism to explain this cumulative and long-lasting effect would involve a combination of direct and also behavioral-driving plastic changes similarly to the effects of constraint-induced therapy (CIT). Given that rTMS decreases the neural activity of the unaffected hemisphere, this treatment might be considered a form of "central" CIT. It has been shown that if a restriction of the intact limb through CIT is maintained for 1 to 2 weeks, it can lead to a permanent change in the ability to the use of the paretic forelimb. Therefore, daily inhibition of the affected hemisphere for 5 consecutive days might mimic the effects of a prolonged course of CIT and induce similar plastic changes. Indeed, repeated consecutive rTMS sessions over M1 leads to cumulative changes in cortical excitability.[14] We speculate that the motor function benefit during the stimulation period might have increased the use of the paretic limb overcoming the "learned nonuse" of the limb. This behavioral effect, similarly to CIT (that can last up to 2 years), can be longlasting. Indeed, the increase in the motor threshold in the affected hemisphere can be a result of the increase in the use of the paretic limb and might be similar to the effects of CIT on the cortical excitability of the affected hemisphere.[15] This increase in the local excitability might represent an increase in the synaptic efficacy and also be associated with the "resurgence" of some areas that are down-regulated as a result of the stroke. This putative mechanism leads us to hypothesize that the combination of this therapy with motor training might further enhance motor recovery.

This study has some limitations that should be entertained. First, for the corticospinal excitability measurement, we only measured the motor threshold, and, thus, other parameters of corticospinal excitability such as motor evoked potentials and silent period were not assessed. In addition, although we decided not to measure the motor threshold daily in the affected hemisphere (as explained in the "Methods" section), we acknowledge that further studies should explore in details cortical excitability changes in both hemispheres during several time points and using other methods of assessment such as paired-pulse technique. Second, a methodological

problem of rTMS studies is the sham method. For instance, an ideal sham coil should produce the same scalp sensation (stimulation of the superficial nerves and muscles). Because sham stimulation does not result in muscle twitch, a patient might feel the difference between the active and sham coil. Given that all our patients were naive to rTMS, it is unlikely that this might have unblinded the rTMS treatment. Third, this study might have a decreased external validity because most of our patients had subcortical and left-sided strokes. This fact encourages future studies to investigate other stroke populations with different demographic and clinical characteristics.

Acknowledgments

F.F. conceived the initial idea, designed the study, and analyzed the data. Furthermore, he supervised all the steps of the study and drafted and revised the manuscript. P.S.B. was involved in patients' recruitment, data acquisition and interpretation, and revision of the manuscript., A.C.V., R.R.R., J.D., M.J.L.F., and M.R. were involved in data acquisition and revision of the manuscript. T.W. and S.F. contributed to the interpretation of the data and revision of the manuscript. S.P.R., S.D.F., and A.P.-L. were involved in study design, revision of the manuscript, and administrative support. We thank Barbara Bonnetti for the help on the coordination of this study.

Sources of Funding

This work was supported by a grant from the Harvard Medical School Scholars in Clinical Science Program (NIH K30 HL04095) to F.F. A.P.-L. is supported by K24 RR018875, RO1-EY12091, RO1-DC05672, RO1-NS 47754, RO1-NS 20068, and R01-EB 005047.

Disclosures

None.

References

1. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 2004;55:400–409.
2. Mansur CG, Fregni F, Boggio PS, Riberto M, Gallucci-Neto J, Santos CM, Wagner T, Rigonatti SP, Marcolin MA, Pascual-Leone A. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology*. 2005;64:1802–1804.
3. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*. 2005;36:2681–2686.
4. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJ, Lima MC, Rigonatti SP, Marcolin MA, Freedman SD, Nitsche MA, Pascual-Leone A. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport*. 2005;16:1551–1555.
5. Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology*. 2005;65:466–468.
6. Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*. 2005;128:490–499.
7. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry*. 2003;160:835–845.
8. Wagner T, Fregni F, Eden U, Ramos-Estebanez C, Grodzinsky A, Zahn M, Pascual AP. Transcranial magnetic stimulation and stroke: a computer based human model study. *Neuroimage.* In press.
9. Peto R. Clinical trial methodology. *Biomedicine.* 1978;28:24–36.
10. Rossini PM, Barker AT, Berardelli A. Non-invasive electrical and magnetic stimulation of the brain spinal cord and roots: basic principles and procedures for routine clinical application: report of an ICFN committee. *Electroencephalogr Clin Neurophysiol*. 1994;91:79–91.
11. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*. 2003; 126:2476–2496.
12. Pal PK, Hanajima R, Gunraj CA, Li JY, Wagle-Shukla A, Morgante F, Chen R. Effect of low-frequency repetitive transcranial magnetic stimulation on interhemispheric inhibition. *J Neurophysiol*. 2005;94:1668–1675.
13. Kobayashi M, Hutchinson S, Theoret H, Schlaug G, Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology*. 2004;62:91–98.
14. Baumer T, Lange R, Liepert J, Weiller C, Siebner HR, Rothwell JC, Munchau A. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. *Neuroimage.* 2003;20: 550–560.
15. Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. Treatment-induced cortical reorganization after stroke in humans. *Stroke*. 2000;31:1210–1216.