HIGH LIGHT

A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients

Abstract—The authors investigated the use of slow-frequency repetitive transcranial magnetic stimulation (rTMS) to the unaffected hemisphere to decrease interhemispheric inhibition of the lesioned hemisphere and improve motor function in patients within 12 months of a stroke. Patients showed a significant decrease in simple and choice reaction time and improved performance of the Purdue Pegboard test with their affected hand after rTMS of the motor cortex in the intact hemisphere as compared with sham rTMS.

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Recent studies suggest that invasive cortical brain stimulation is a useful therapy for stroke recovery.[1,2] Transcranial magnetic stimulation (TMS) offers a noninvasive, painless alternative to stimulate the human cerebral cortex in conscious subjects. Therefore, repetitive TMS (rTMS) may be useful to modulate brain activity after stroke and enhance stroke recovery noninvasively. Due to interhemispheric interaction, we hypothesize that a possible target for rTMS is the contralateral undamaged motor cortex, the suppression of which by slow rTMS may release inhibition of the damaged hemisphere and promote recovery.[3] After stroke, the nonlesioned hemisphere is disinhibited, perhaps due to the reduction in the transcallosal inhibition from the stroke-damaged hemisphere.[4] This in turn may increase inhibition of the lesioned hemisphere by the disinhibited, unaffected hemisphere and could impair functional recovery.[5] We report the results of a crossover, sham stimulation-controlled, double-blind study assessing the effects of modulation of the unaffected motor cortex by slow rTMS in patients within 12 months of a stroke.

Methods. We studied 10 stroke patients (three men and seven women) aged 37 to 73 years (mean 53.3) within 12 months of a stroke and six healthy controls (three men and three women) aged 28 to 52 years (mean 43.6). Written informed consent was obtained from all participants before inclusion in the study, which was approved by the local ethics committee.

Participants received three sessions of rTMS (1 Hz, 100% of motor threshold, 600 pulses) to the unaffected hemisphere over the primary motor (real or sham rTMS) and over the premotor cortex (real rTMS). The order of these different rTMS sessions was randomized and counterbalanced across participants. The different rTMS sessions were separated by 1 hour to minimize carryover effects. Stimulation was delivered using a Magstim Super Rapid Stimulator equipped with a commercially available 8-shaped coil. For the sham stimulation, we implemented the same stimulation parameters used for the motor cortex stimulation (location and rTMS pulse train properties) but used a sham coil (Magstim Inc.).

All participants underwent the following battery of tests to evaluate the motor function of the affected hand: 1) simple reaction time (sRT), 2) four-choice reaction time (cRT), 3) Purdue Pegboard Test, and 4) finger tapping. Each patient was tested at baseline and after sham, motor, and premotor rTMS. At baseline testing, participants were carefully evaluated regarding their ability to perform the required tasks, and they were allowed to practice until performance was stable. At this stage, two patients were excluded because they showed very prominent cocontractions and proximal movements. The healthy controls were also tested at three time points each separated by 1 hour, but they did not receive TMS. The effects of rTMS to motor or premotor cortex on ipsilateral motor function have been previously investigated at our facility[6] and were not the focus of this study.

Our analysis was primarily focused on changes in sRT, cRT, Purdue Pegboard Test, and finger tapping performance. We used repeated measures of analysis of variance to test whether there was an overall effect of rTMS type (condition). When appropriate, post hoc comparisons were carried out using Fisher least significant difference correction for multiple comparisons. Significance was set at a p value <0.05.

Results. The table summarizes patient demographics and stroke characteristics.

Repeated-measures analysis of variance (ANOVA) showed that there was a main effect of condition on sRT ($p = 0.043$) and cRT ($p = 0.045$). Post hoc comparisons demonstrated a decrease in sRT ($p = 0.014$) and cRT ($p = 0.013$) after real motor rTMS when compared with sham rTMS. Subjects also tended to be faster after real premotor compared with sham rTMS; however, this result did not reach significance (figure 1A).

The Purdue Pegboard Test results were similar to those of the reaction time tests, although three patients could not perform this task due to proximal arm weakness. Repeated-measures ANOVA demonstrated a main effect of rTMS condition ($p = 0.006$). Post hoc comparisons revealed an increase in the number of correctly placed pegs after real motor rTMS (6.2 ± 2.9) as compared with sham stimulation (4.2 ± 2.4; $p = 0.002$). The effects of rTMS on premotor cortex did not reach significance (see figure 1B).

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Table *Patient demographics and stroke characteristics*

Patient	Age (y)	Medical history	Classification of ischemic stroke (Toast criteria)*	Localization of stroke	Neurologic deficits
1	51	HTN, NIDDM	Cardioembolic	Right frontal	Mild left hemiparesis
2	61	HTN, NIDDM	Small vessel	Right internal capsule	Mild left hemiparesis
3	35	HTN	Small vessel	Left corona radiata	Mild right hemiparesis
4	63	HTN, NIDDM	Small vessel	Left internal capsule	Moderate right hemiparesis
5	55	HTN, Tob	Small vessel	Right corona radiata	Mild left hemiparesis
6	57	NIDDM, HLP, Tob	Small vessel	Right internal capsule	Moderate left hemiparesis
7	43	HTN, Tob	Small vessel	Left internal capsule	Subtle right hemiparesis
8	58	HTN, NIDDM, HLP	Large art/atherosclerosis	Left frontal	Moderate right hemiparesis
9†	37	HTN, HLP, Tob	Cardioembolic	Right frontal	Left hemiparesis and spasticity
10†	73	HTN, NIDDM	Small vessel	Right internal capsule	Severe left hemiparesis

* Classification of the subtypes of strokes was based on the TOAST criteria.
† Patients 9 and 10 were excluded from this study because they could not perform the motor tasks adequately.

HTN = hypertension; NIDDM = non–insulin-dependent diabetes mellitus; Tob = tobacco use; HLP = hyperlipoproteinemia.

Because of the small number of patients (five patients), a nonparametric approach was used to validate our results. Wilcoxon signed rank demonstrated an increase in the number of correctly placed pegs after real motor rTMS as compared with sham stimulation ($p = 0.043$).

However, for the finger tapping test, repeated-measures ANOVA showed that there was no main effect of the rTMS condition on the finger-tapping test ($F = 0.27$; $df = 7,2$; $p = 0.76$). Although performance tended to be better after real motor rTMS when compared with sham stimulation, this effect was small (<5%) and variable across patients (see figure 1B).

In the control experiment, healthy participants did not show changes in any of the four tests across repeated testing (figure 2). Repeated-measures ANOVA showed that there was no main effect of the testing condition for any of our tests.

Discussion. Our results are consistent with those of similar studies in healthy subjects and patients with nonmotor strokes. rTMS (1 Hz, 90% motor threshold) applied for 10 minutes to the motor cortex of 16 healthy subjects resulted in a shortening of execution time of an overlearned motor task with the ipsilateral hand.[6] Furthermore, improvement of behavior by disruption of activity in the undamaged hemisphere with 1-Hz rTMS has also been demonstrated in patients with nonmotor strokes, such as patients with neglect after parietal lesions[7] and patients with nonfluent aphasia after a left hemispheric frontal stroke.[8]

However, a similar study of five stroke patients showed no improvement in the motor function of the paretic hand after 1-Hz rTMS of the undamaged hemisphere.[9] The different results may be due to patient selection: patients with chronic stroke (more than 1 year after stroke) and task evaluation (only finger tapping). In our study, our patients were studied within the first year after their stroke, and we also failed to find significant changes in the finger tapping test. Indeed, a lack of significant effects observed after ipsilateral stimulation on the finger tapping test has been previously described[10] and might be the result of task-specific variables, small sample size, or a ceiling effect.

Some methodologic concerns should be addressed. First, the sample size of this study is small and the results have to be confirmed in a larger study. Second, our study design, despite counterbalancing rTMS conditions across patients, cannot rule out learning effects that might confound our results. Our findings in control subjects showed that repeated testing in our tasks in this short period of time does not cause performance enhancement due to learning or practice. However, it is possible that practice effects might be greater in stroke patients. Third, one could argue that our results may be due to the nonmotor effects of the stimulation, for example, a general attention-enhancing effect. However, the nonsignificant effects of premotor cortex rTMS and the selective impact on some tasks (pegboard and reaction time) but not others (finger tapping) establishes a task- and brain location–specific effect of rTMS and suggest a motor system mechanism. Finally, despite our hypothesis that beneficial effects of rTMS would be due to interhemispheric effects, we elected not to experimentally assess transcallosal in-

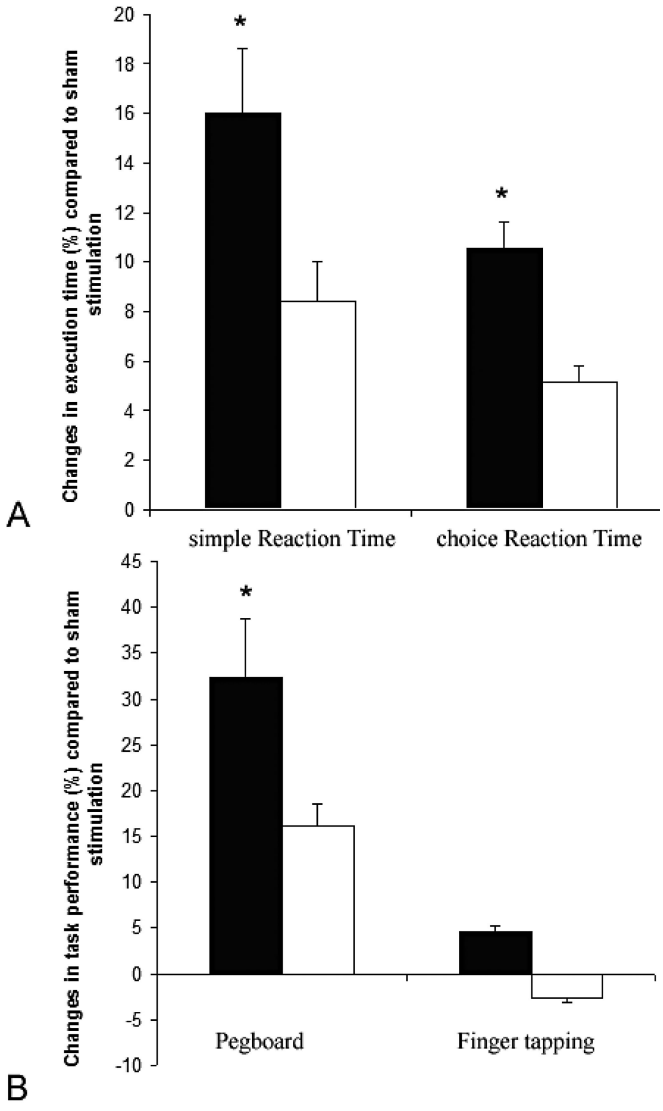

*Figure 1. The effects of repetitive transcranial magnetic stimulation (rTMS) of the ipsilateral motor primary cortex and premotor cortex on motor task performance (simple reaction time, choice reaction time, pegboard, and finger tapping) compared with sham stimulation. (A) Execution time after rTMS. Change (%) in simple reaction time and choice reaction time after rTMS of motor (solid column) and premotor cortex (open column) compared with sham stimulation. The execution times (simple reaction time and choice reaction time) were significantly shorter only after rTMS of the primary motor area. (B) Pegboard and finger tapping performance after rTMS. Change (%) in pegboard and finger tapping performance after rTMS of motor (solid column) and premotor cortex (open column) compared with sham stimulation. There was a significant increase in the number of correctly placed pegs after real motor rTMS compared with sham stimulation. There was no significant effect of TMS in finger tapping performance after stimulation of either motor or premotor cortex. Each column represents mean performance on the task ± SEM. *Significant when compared with sham stimulation.*

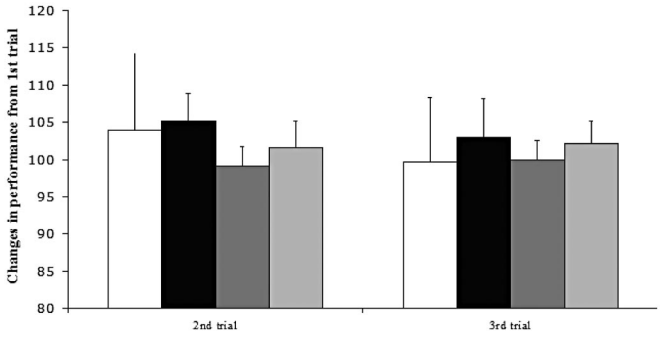

Figure 2. In the control experiment, healthy participants did not show significant changes in any of the four tests (simple reaction time [open column], choice reaction time [solid column], Pegboard [darkly shaded column], finger tapping [shaded column]) across repeated testing. Each column represents mean performance on the task ± SEM.

hibition, which, although feasible, would have increased the duration of the neurophysiologic measures, thus delaying and possibly compromising the functional motor evaluation. In the present preliminary study, we elected to focus on assessing a possible clinical benefit of our intervention. Future studies are needed to confirm the findings and explore mechanisms of action.

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