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## Safety and Behavioral Effects of High-Frequency Repetitive Transcranial Magnetic Stimulation in Stroke

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### Abstract

**Background and Purpose**—Electromagnetic brain stimulation might have value to reduce motor deficits after stroke. Safety and behavioral effects of higher frequencies of repetitive transcranial magnetic stimulation (rTMS) require detailed assessment.

**Methods**—Using an active treatment-only, unblinded, 2-center study design, patients with chronic stroke received 20 minutes of 20 Hz rTMS to the ipsilesional primary motor cortex hand area. Patients were assessed before, during the hour after, and 1 week after rTMS.

**Results**—The 12 patients were  $4.7 \pm 4.9$  years poststroke (mean  $\pm$  SD) with moderate–severe arm motor deficits. In terms of safety, rTMS was well tolerated and did not cause new symptoms; systolic blood pressure increased from pre- to immediately post-rTMS by 7 mm Hg ( $P=0.043$ ); and none of the behavioral measures showed a decrement. In terms of behavioral effects, modest improvements were seen, for example, in grip strength, range of motion, and pegboard performance, up to 1 week after rTMS. The strongest predictor of these motor gains was lower patient age.

**Conclusions**—A single session of high-frequency rTMS to the motor cortex was safe. These results require verification with addition of a placebo group and thus blinded assessments across a wide spectrum of poststroke deficits and with larger doses of 20 Hz rTMS.

### Keywords

plasticity; recovery; stroke; transcranial magnetic stimulation; treatment

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Motor deficits are a major contributor to disability after stroke. A number of forms of brain stimulation are under study for improving these deficits. Detailed assessment of these interventions, particularly safety, remains incomplete. The current study examined high-frequency repetitive transcranial magnetic stimulation (rTMS) with an emphasis on safety assessments. Prior studies of high-frequency rTMS to date suggest good safety in healthy subjects<sup>1,2</sup> and in patients with stroke.<sup>3–5</sup> A secondary aim was to characterize behavioral changes, including “offline” effects, ie, those that endure after the end of stimulation.

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### Disclosures

None.

Favorable neurological effects have been reported after high-frequency rTMS in patients with stroke.<sup>3,4</sup> However, a detailed description of the safety and neurological effects of a single 20-Hz rTMS session has not been previously described.

The current study used an active treatment-only, unblinded, 2-center study design to address the hypothesis that in patients with chronic stroke, a single session of 20 Hz rTMS applied to the ipsilesional hand motor area is safe and has favorable “offline” behavioral effects. As an additional secondary aim, predictors of rTMS behavioral effects were evaluated.

## Methods

### Subjects

Consenting patients were aged 18 to 85 years; stroke that is supratentorial, unilateral, ischemic, or hemorrhagic but not subarachnoid and does not come within 15 mm of the rTMS target; arm motor Fugl-Meyer score = 15 to 55 out of 66; and stroke >11 weeks prior. Exclusion criteria were prestroke Rankin score >1; history of seizure; other focal cortical pathology; Zung Depression score  $\geq$  50; decreased alertness, language reception, or attention; pregnant/lactating; advanced systemic disease; terminal illness; coexistent neurological/psychiatric disease; prior TMS; and TMS/MRI contraindication. Local human subjects committees and the US Food and Drug Administration approved the study.

### Study Structure

A standard approach was achieved through a detailed manual of operating procedures and regular videoconferences. At Visit 1, history/physical was followed by scoring on 7 behavioral outcome measures and then anatomic/functional MRI scanning. Visit 2, 1 day later, repeated Fugl-Meyer, grip strength, 9-hole peg test, and 2 active ranges of motion; vital signs were taken; rTMS was applied; and a rigidly timed schedule of testing was performed during the post-rTMS hour. Patients returned for Visit 3 at 7 days after rTMS.

### Safety Outcome Measures

Patients were asked about any new symptoms at Visit 3 and the end of Visit 2; change in vital signs; and decrements in any of the 7 behavioral outcome measures.

### Behavioral Outcome Measures

Behavioral outcome measures consisted of the Barthel Index, Fugl-Meyer, Action Research Arm Test, hand grip strength, 9-hole peg test, and active ranges of motion at the affected side wrist and index finger metacarpophalangeal joint.

### MRI Acquisition and Analysis

Using a Philips 3-T scanner, a T1-weighted whole-brain anatomic image was followed by 2 functional MRI (fMRI) runs, each 96 seconds long contrasting 24 seconds rest with 24 seconds squeezing (25 axial slices with 4-mm thickness/1-mm gap, TR=2000 ms, TE=30 ms). Squeezing was isometric with the affected hand closing on a smooth, inflexible wooden object whose dimensions approximate those of a Jamar dynamometer. An investigator observed patient movements during scanning.

Using SPM2, fMRI images were realigned, normalized to MNI space, and then spatially smoothed (full width at half maximum =8 mm). Images at rest were contrasted with images during task performance with the 2 fMRI series for each task combined when neither was contaminated by excess head motion. Analysis of the primary sensorimotor cortex (“hand

area” from <http://hendrix.IMdtu.dk/services/jerne/ninf/voi.html>) yielded activation volume ( $P<0.001$ , uncorrected) and task-related fMRI signal change and a laterality index.<sup>6</sup>

### Application of Repetitive Transcranial Magnetic Stimulation

Each patient’s head was coregistered with his or her MRI using a frameless stereotaxic system. The rTMS target was the posterior precentral gyrus at the hand knob.<sup>7,8</sup> Single-pulse TMS (figure-of-8 coil; Magstim 200) of the ipsilesional hemisphere identified resting motor threshold that produced a motor-evoked potential  $50 \mu\text{V}$  in the stroke-affected first dorsal interosseus in 3/5 stimuli. The patient sat relaxed while 40 rTMS trains of 40 pulses at 20 Hz, separated by an intertrain interval of 28 seconds, were delivered for a total of 1600 pulses using the Magstim Rapid. Stimulation intensity was 90% motor threshold; for the 7 patients with no elicitable motor-evoked potential, default stimulation intensity was 60% device output.

### Predicting Behavioral Effects

The ability of 14 variables recorded before rTMS to predict behavioral effect was examined. These measures were demographic (age and time poststroke), behavioral (Zung Depression score, National Institutes of Health Stroke Scale score, Barthel Index, Fugl-Meyer, and grip strength), neurophysiological (motor-evoked potential threshold, using 100% for patients with no elicitable motor-evoked potential), and fMRI (activation volume in contra- and ipsilesional hand sensorimotor area and their laterality index plus task-related fMRI signal change in the same 2 areas and their laterality index).

### Data Analysis

Two-tailed parametric statistics were used (JMP; SAS, Cary, NC). Changes over time were evaluated by paired *t* tests. This was an exploratory study with no corrections made for multiple comparisons.

### Results

Patient characteristics are described in Table 1. All had received a course of standard rehabilitation therapy during the subacute stroke period. A motor-evoked potential could be evoked in 5 of 12 patients, among whom motor threshold was  $76\pm 13\%$  of maximum device output. Stroke topography is presented in Figure 1.

### Safety Outcome Measures

There were no witnessed adverse events during rTMS, and patients reported no new symptoms through Visit 3. Systolic blood pressure, assessed in the first minute after rTMS, increased 7 mm Hg as compared with immediately prerTMS ( $P<0.05$ , Table 2), a change accounted for by 9 of 12 patients, but no such change was apparent for diastolic blood pressure or pulse. None of the behavioral measures showed a decrement.

### Behavioral Outcome Measures

None of the 5 measures changed across the 2 baseline examinations. A significant within-subject change after rTMS was found for 5 of 7 measures (Table 2; Figure 2). Fugl-Meyer increased 30 minutes after rTMS ( $P=0.071$ ), which reached significance ( $P<0.02$ ) 1 week later, the latter accounted for by an increase in 8 of 12 patients. Affected hand pegboard testing (Figure 2A) increased from pre-rTMS to 60 minutes post-rTMS ( $P<0.05$ ), accounted for by 5 of 12 patients; a trend ( $P=0.057$ ) at Day 7 suggested retention. Grip strength (Figure 2B) at 40 and 60 minutes post-rTMS increased ( $P<0.03$  each) versus pre-rTMS, accounted for by 8 to 9 patients. The active ranges of motion, assessed 7 minutes after rTMS, increased

7° ( $P=0.051$ ) in the affected wrist extensor and 5° ( $P<0.02$ ) in the affected index finger metacarpophalangeal joint, each accounted for by 7 of 12 patients. Barthel Index and Action Research Arm Test did not change over time.

Of the 10 patients with usable fMRI data, 2 showed mirror movements in the unaffected hand and 5 showed adventitious foot movements. Mean activation volumes were  $1916\pm 972$  mm<sup>3</sup> and  $982\pm 836$  mm<sup>3</sup> within the ipsi- and contralesional hand sensorimotor cortex, respectively, with laterality index averaging  $0.33\pm 0.51$ . Respective values for task-related fMRI signal change were  $0.84\pm 0.57\%$  and  $0.66\pm 0.51\%$ , laterality index averaging  $0.13\pm 0.54$ . These values were fed into the predictive models.

### Predicting Behavioral Effects

The dependent measure was an increase in grip strength 1 hour after rTMS, present in 9 patients. Of the 14 variables examined, one had significant ( $P<0.05$ ) predictive value: age ( $r=-0.77$ ,  $P<0.004$ ).

### Discussion

In patients with chronic stroke, a single 20-minute session of 20 Hz rTMS applied to the ipsilesional hand motor area was safe, although with a mild systolic blood pressure increase.

Results are overall consistent with prior studies of rTMS at 3 to 20 Hz in patients with stroke.<sup>3-5</sup> Khedr et al found that 10 sessions of 3 Hz rTMS to the motor cortex improved disability and overall neurological status to a greater extent than sham rTMS did in patients with subacute stroke.<sup>3</sup> Kim et al found that a single session of 10 Hz rTMS to the motor cortex improved motor learning more than sham rTMS did in patients with chronic stroke.<sup>4</sup>

The current focus was 20 Hz because some evidence suggests that motor cortex facilitation increases in parallel with the hertz at which rTMS is applied, possibly on the basis of increases in cortical excitability and metabolism,<sup>1,9,10</sup> the latter linked with potential for providing greater behavioral gains. However, higher rTMS frequencies might also carry greater risk for adverse events such as seizure,<sup>1</sup> although no serious adverse events were found here.

Although the focus of this study was safety, motor assessments found favorable changes in arm motor function that persisted at least 1 hour, and in some cases 1 week, after rTMS completion. These motor gains showed a significant and negative relationship with age. This is consistent with the negative association that increased age has in studies of the natural history of stroke recovery.<sup>11,12</sup>

A strength of the current study was effective implementation of a protocol that required multiparameter MRI, single-pulse TMS, rTMS, and behavioral assessments in patients with stroke at 2 sites that span a continent. Weaknesses of the current study include absence of a control intervention and thus blinded outcomes assessment and the possibility of Type I error. Brief electromyographic bursts, a potential harbinger of seizure induction,<sup>13</sup> were not measured in the current study. Anatomic (current study) versus physiological<sup>3-5,13</sup> methods of defining the rTMS target might be compared in a future study. Finally, the interaction between rTMS and concomitant secondary therapies such as occupational therapy or pharmacological intervention also warrants further study, especially in a maximally diverse stroke population. The current results suggest safety and support further studies of 20 Hz rTMS in patients with stroke.

## Acknowledgments

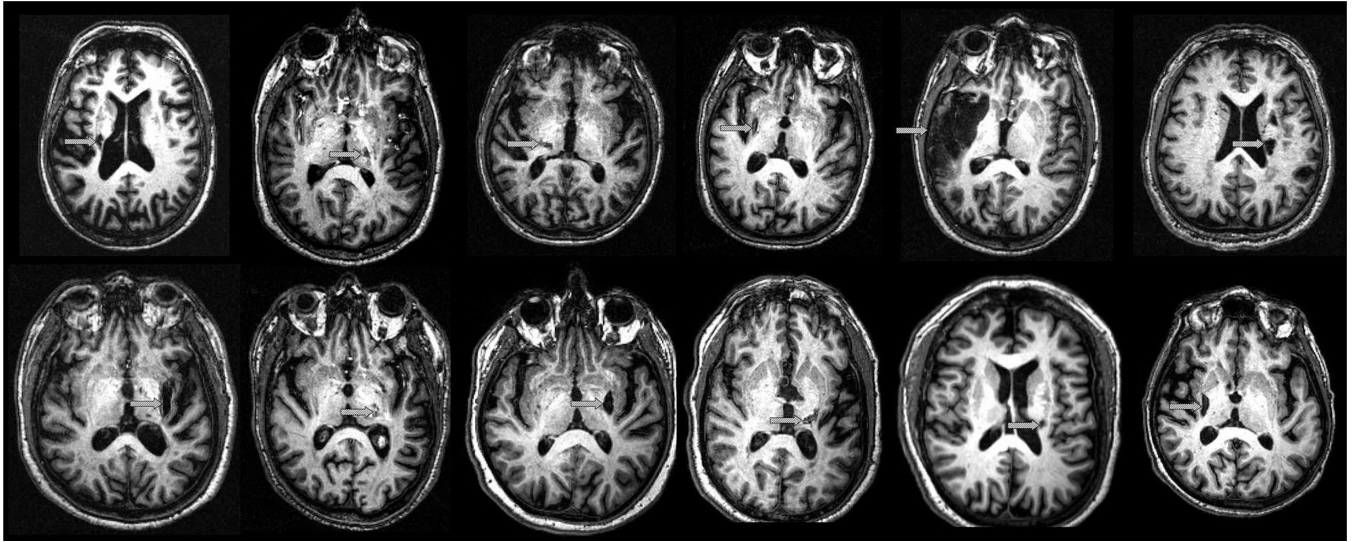
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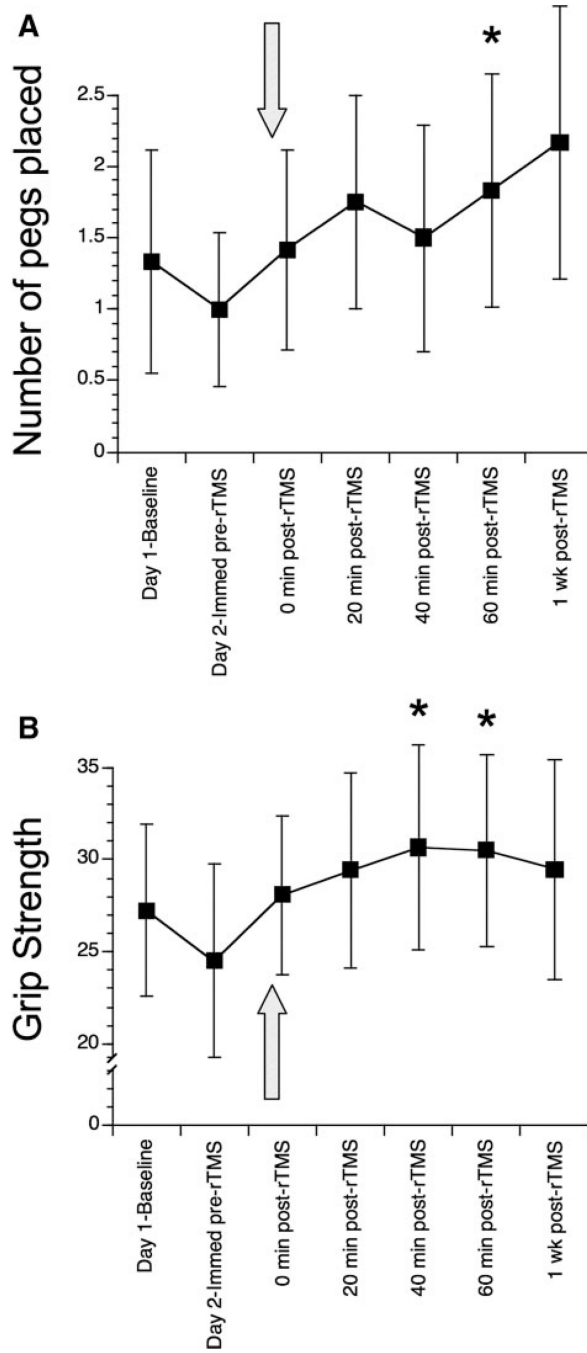
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**Figure 1.**

On a representative slice from the T1-weighted anatomic image from each of the 12 study patients, an arrow indicates stroke location. Stroke was subcortical in 11 (although directly abutting the cortex in 5 of 11) and cortical in one.



**Figure 2.** A, Number of pegs placed in the 9-hole pegboard over 60 seconds by the affected hand. B, Grip strength is the maximum force of squeezing by the affected hand on a Jamar dynamometer in pounds. For both A and B, the pre-rTMS baseline was stable, showing no significant change over time. The arrow indicates timing of rTMS application. Values are mean±SEM \**P*<0.05 versus immediately pre-rTMS, paired testing.



**Table 1**

## Patient Characteristics

n	12
Age, years	67 ± 12
Time poststroke, years	4.7 ± 4.5
Gender	10 M/2 F
Brain side affected by stroke	7 L/5 R
Baseline National Institutes of Health Stroke Scale score	4 ± 2
Zung depression score (lower is better, depression present with score > 50)	35 ± 10
Modified Nottingham sensory score (normal=12, higher is better)	11 ± 2
Handedness	11 R/1 L
Site of patient enrollment	8 at Irvine/4 at Boston
Hypertension present	10
Hyperlipidemia present	10
Diabetes mellitus present	4

Results are mean±SD.

M indicates male; F, female; L, left; R, right.

**Table 2**

## Within-Subject Changes Before versus After rTMS

Measure Evaluated	Pre-rTMS	Immediately Post-rTMS	1-Week Follow-Up
Barthel Index	85 ± 14		85 ± 14
Active range of motion, affected wrist extensor, degrees	63 ± 45	71 ± 45 <sup>†</sup>	69 ± 46
Active range of motion, affected index finger metacarpophalangeal joint, degrees	38 ± 41	43 ± 43 <sup>*</sup>	39 ± 38
Arm Fugl-Meyer motor score	34.5 ± 15	35.6 ± 15	36.0 ± 15 <sup>*</sup>
Pegs placed by affected hand	1 ± 1.9	1.8 ± 2.8 <sup>*</sup>	2.2 ± 3.3 <sup>†</sup>
Grip strength, affected hand	25 ± 18	31 ± 18 <sup>*</sup>	29 ± 21
ARAT score	19 ± 18	21 ± 18	21 ± 18
Systolic blood pressure	128 ± 11	135 ± 12 <sup>*</sup>	
Diastolic blood pressure	77 ± 10	80 ± 10	
Pulse	66 ± 9	66 ± 8	

Values are mean±SD. *P* values reflect paired testing (\**P*<0.05, †*P*<0.06, comparison with pre-rTMS values). For data in the immediately post-rTMS column, the time that measurement started after rTMS was rigidly controlled and was 7 minutes for active range of motion, 30 minutes for Fugl-Meyer score, 60 minutes for no. of pegs placed by the affected hand, 60 minutes for grip strength (pounds) by the affected hand, 10 minutes for ARAT score, and 1 minute for the 3 vital signs. All pre-rTMS measures were recorded on the day of rTMS, immediately before brain stimulation, except for the Barthel Index, which was assessed at the baseline examination.

ARAT indicates Action Research Arm Test.