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# Direct Demonstration That Repetitive Transcranial Magnetic Stimulation Can Enhance Corticospinal Excitability in Stroke

Vincenzo Di Lazzaro, MD; Michele Dileone, MD; Paolo Profice, MD; Fabio Pilato, MD; Beatrice Cioni, MD; Mario Meglio, MD; Fioravante Capone, MD; Pietro A. Tonali, MD; John C. Rothwell, PhD

**Background and Purpose**—Preliminary studies suggest that electrical stimulation of the damaged cortex may be able to enhance motor recovery after stroke. The hypothesis has been that this increases cortical excitability, making it easier for the system to respond to and learn from conventional physiotherapy. However, there is no direct evidence that the cortex of patients with stroke can respond in this fashion; hence, the basis of these new approaches has been questioned.

**Methods**—We had the opportunity to evaluate directly the effects of noninvasive cortical stimulation on the excitability of corticospinal output from the damaged hemisphere of a chronic stroke patient who had epidural electrodes implanted in the upper dorsal cord for treatment of pain.

**Results**—We found that it was possible to enhance corticospinal activity evoked by single test stimuli.

**Conclusions**—This study confirms directly that it is possible to noninvasively manipulate cortical excitability in stroke. (*Stroke*. 2006;37:2850-2853.)

**Key Words:** motor cortex ■ stroke ■ transcranial brain stimulation

Central nervous system reorganization, a process that is often termed plasticity, is an important contributor to recovery of motor function after stroke.<sup>1</sup> There is thus considerable interest in developing methods that can speed or even enhance such plasticity to improve recovery. One approach is related to the fact that an increase in cortical excitability, often coupled with a decrease in  $\gamma$ -aminobutyric acid-ergic activity, seems to facilitate cortical plasticity.<sup>2,3</sup> However, under natural conditions, hyperexcitability is observed only in the early phase of stroke, up to 4 months after the lesion.<sup>3</sup> There have therefore been several attempts to promote hyperexcitability in chronic stroke to encourage plasticity months or years after the lesion.<sup>1</sup>

A number of investigators have used continuous, low-intensity stimulation through implanted epidural electrodes over the damaged cortex to enhance the response to subsequent behavioral training sessions. This produced a sustained improvement of motor function in rats,<sup>4,5</sup> in primates,<sup>6</sup> and in humans.<sup>7,8</sup> Because transcranial brain stimulation techniques can induce long-lasting changes in cortical excitability, it has been proposed that these might also be a useful noninvasive means to achieve the same effects.<sup>9</sup> Hummel and coworkers<sup>10</sup> evaluated the effects of noninvasive, transcranial, direct-current stimulation of the affected motor cortex in stroke

patients by using a protocol of stimulation that increased motor cortex excitability.<sup>11,12</sup> They observed a substantial improvement of function of the hand contralateral to the affected motor cortex after a single treatment session<sup>10</sup> but did not make any physiological measures to test for cortical hyperexcitability. Thus, the cause of the improved function was unknown. Kim and coworkers<sup>13</sup> recently showed that high-frequency repetitive transcranial magnetic stimulation (rTMS) of the lesioned motor cortex increased motor evoked potential (MEP) amplitude and improved motor performance in patients with chronic stroke. Khedr and coworkers<sup>14</sup> used rTMS of the motor cortex in a large number of patients within the first 2 weeks of their stroke. They found that compared with sham TMS, 10 daily sessions improved patients' hand function for at least 10 days after the end of treatment, but the relation to changes in corticospinal excitability was unclear.

We had the almost-unique opportunity to evaluate directly the effects of transcranial stimulation on the excitability of corticospinal output from the damaged hemisphere of a chronic stroke patient who had an epidural stimulator implanted in the upper dorsal cord for treatment of intractable dorsolumbar pain. We found that a novel rTMS paradigm, termed intermittent theta-burst stimulation (iTBS),<sup>15</sup> produced a long-lasting increase in cortical excitability. This confirms directly that it is possible to

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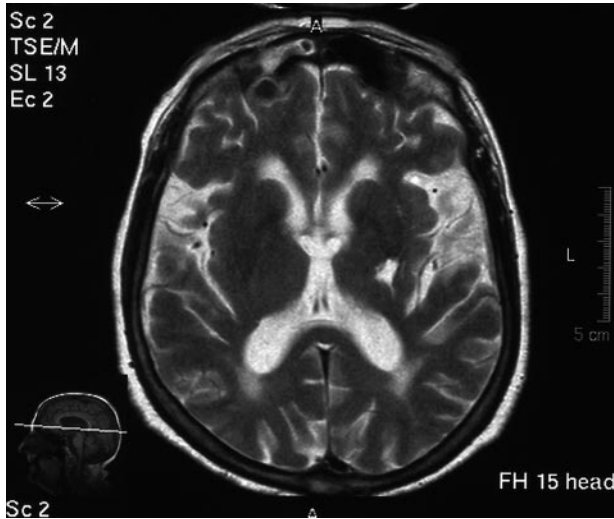
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**Figure 1.** Magnetic resonance imaging of the brain of the patient. Axial T2-weighted image at the thalamic level. There are several supratentorial subcortical vascular lesions involving the white matter around the occipital horn of the lateral ventricle. On the left side, there is a definite lacunar lesion (hyperintense on T2) located in the posterior limb of the internal capsula.

increase cortical excitability in the damaged hemisphere of patients after stroke. It may provide a physiological basis for improving functional recovery in the chronic stage.

### Patient and Methods

#### Patient

We studied a 75-year-old woman with a history of hypertension who had experienced sudden-onset right hemiplegia 6 years previously. Neurological examination on admission showed a complete motor deficit of the right upper limb, a severe right lower-limb motor deficit with hyperactive tendon reflexes, and right Babinski sign and

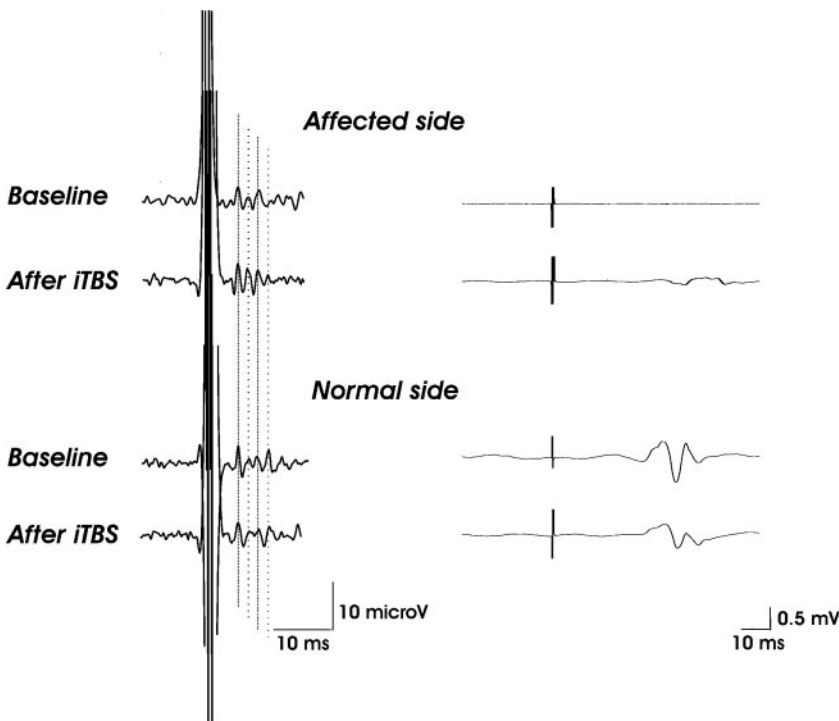
severe spasticity on the right side. Magnetic resonance imaging of the brain showed a definite lacunar lesion located in the posterior limb of the internal capsula (Figure 1).

#### Methods

As described in previous publications,<sup>16,17</sup> we recorded, with ethics committee approval, descending corticospinal activity evoked by TMS of the lower-limb motor cortex directly from the high dorsal epidural space. Recordings were made simultaneously from the epidural electrode and from the tibialis anterior muscle (TA) of both sides. Epidural potentials were recorded between the most proximal and most distal of the 4 electrode contacts. These had a surface area of 2.54 mm<sup>2</sup> and were 30 mm apart. The distal contact was connected to the reference input of the amplifier. Surface electromyograms (EMGs) were obtained via two 9-mm-diameter Ag:AgCl electrodes with the active electrode over the motor point of the muscle and the reference electrode on the ligamentum patellae. EMGs and corticospinal volleys were amplified and filtered (bandwidth, 3 Hz to 3 kHz) by D150 amplifiers (Digitimer). Data were collected on a computer with a sampling rate of 10 kHz per channel and stored for later analysis with a CED 1401 A-D converter (Cambridge Electronic Design).

MS was performed with a high-power Magstim 200 (Magstim Co). A figure-of-eight coil, with external loop diameters of 9 cm and a maximum magnetic field strength of 2.2 T, was held over the motor cortex at the optimum scalp position to elicit motor responses in the contralateral TA muscle (motor cortical “hot spot”). The induced current in the brain flowed in a posterior-to-anterior direction because we have previously shown that in subjects with no abnormality of the central nervous system, multiple descending volleys are readily evoked with this direction of induced current.<sup>16,17</sup> Intensities were expressed as a percentage of the maximum output of the stimulator. Active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a consistent motor evoked response ( $\approx 200 \mu\text{V}$  in 50% of 10 trials) during isometric contraction of the tested muscle at  $\approx 20\%$  of maximum voluntary contraction.

rTMS was delivered over the motor cortical hot spot for EMG responses in the right TA muscle with a MagPro (Medtronic A/S Denmark) stimulator connected to a figure-of-eight coil (MCF B65, Medtronic A/S Denmark). The initial direction of the current induced in the brain was anterior to posterior. To stimulate at high frequen-



**Figure 2.** Corticospinal volleys (left) and MEPs recorded from the TA muscle at rest (right) evoked by single-pulse MS of the lower-limb right (normal side) and left (affected side) motor cortex in baseline conditions and after intermittent iTBS in a patient with chronic stroke. Left, Single-pulse MS evoked a series of descending waves, 4 waves after right motor cortex stimulation and 3 waves after left motor cortex stimulation in baseline conditions. After iTBS, the size and number of corticospinal volleys evoked by stimulation of the affected hemisphere were increased; 4 descending waves are clearly recognizable. There is slight reduction of the amplitude of corticospinal volleys evoked after stimulation of the normal side. The vertical lines are aligned to the peak latency of the volleys. Each trace is the average of 15 sweeps. Right, There is no MEP after left motor cortex stimulation in baseline conditions. After iTBS, a small MEP was recorded after left motor cortex stimulation. There is reduction of the amplitude of MEP evoked after stimulation of the normal side. Each trace is the average of 15 sweeps.

cies, the magnetic stimulus had a biphasic waveform with a pulse width of  $\approx 280 \mu\text{s}$  and a maximum magnetic field strength of 1.5 T. The stimulation intensity was defined in relation to AMT evaluated with the MagPro stimulator. An intensity of 80% AMT was used.<sup>14</sup> rTMS was performed with the iTBS protocol, in which 10 bursts of high-frequency stimulation (3 pulses at 50 Hz) were applied at 5 Hz every 10 seconds for a total of 190.04 seconds (600 pulses).<sup>15</sup>

We compared the corticospinal volleys, evoked by a standard TMS pulse before and after iTBS. Recordings were performed in baseline conditions and 7 minutes after the end of iTBS, because at this interval, there is the maximum of facilitation.<sup>15</sup> The responses to 15 stimuli were averaged at rest with use of a stimulus intensity of 120% AMT for the right motor cortex and a stimulus intensity corresponding to the maximum stimulator output for the left, lesioned hemisphere. These intensities evoked volleys of approximately the same magnitude.

### Statistics

The effect of iTBS on corticospinal volley amplitude was assessed by the 2-tailed Student unpaired *t* test ( $P < 0.05$ ). Because only 1 subject was studied, we compared the individual trials before and after iTBS.

### Results

AMT was higher for the left motor cortex. It was 88% of the maximum stimulator output for the left motor cortex and 62% of the maximum stimulator output for the right motor cortex.

### Surface EMG Recordings

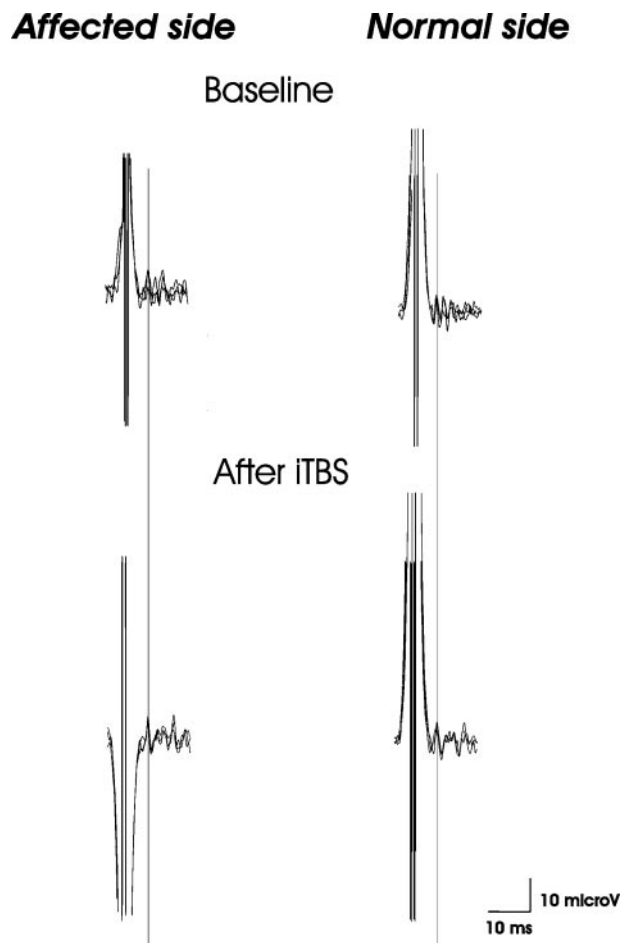
Before iTBS, stimulation of the left motor cortex (at 100% stimulator output, because the high threshold made it impossible to stimulate at 120% AMT) did not evoke any MEP from the TA muscle at rest (Figure 2). Stimulation of the right motor cortex at 120% AMT evoked an MEP from the TA muscle at rest with an amplitude of 0.9 mV and a latency of 30 ms (Figure 2).

After left motor cortex iTBS, a small MEP with an amplitude of 0.2 mV and a latency of 38 ms (Figure 2) was recorded from the TA muscle at rest. In contrast, the amplitude of the MEP recorded from the relaxed TA muscle after right motor cortex stimulation decreased by  $\approx 45\%$  (0.5 mV).

### Epidural Recordings

Before iTBS, stimulation of the left motor cortex (at 100% stimulator output, because the high threshold made it impossible to stimulate at 120% AMT) evoked 3 descending waves: The earliest wave had a latency of 5.6 ms; the second, a latency of 7.4 ms; and the third, a latency of 9.1 ms (Figure 2). These epidural volleys are very similar to those that we have described previously in nonstroke patients, that presumably originate from transsynaptic activation of corticospinal cells.<sup>16,17</sup> Stimulation of the right motor cortex at 120% AMT evoked 4 descending waves: The earliest wave had a latency of 5.4 ms; the second, a latency of 7.4 ms; the third, a latency of 8.6 ms; and the last, a latency of 10.4 ms (Figure 2). The difference in numbers of volleys probably is because of the fact that stimulation was more effective in recruiting corticospinal activity in the nonstroke than the stroke hemisphere. Figure 3 shows superimposed subaverages of epidural recordings to illustrate the reproducibility of the main volleys.

The mean amplitude of the total corticospinal volley (the sum of the amplitudes of individual waves) was  $10.2 \pm 1.2 \mu\text{V}$  after left motor cortex stimulation and  $12.9 \pm 3 \mu\text{V}$  after right



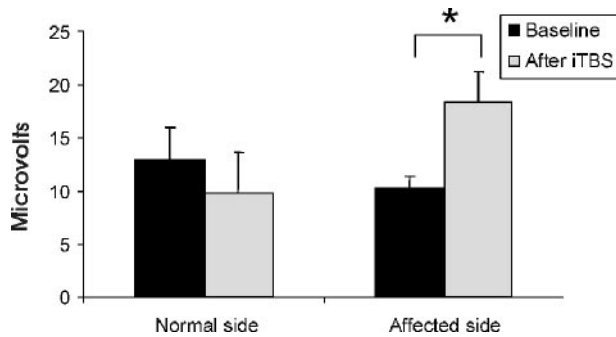
**Figure 3.** Superimposed subaverages (of 5 trials each) of corticospinal volleys evoked by single-pulse MS of the lower-limb right (normal side) and left (affected side) motor cortex in baseline conditions and after iTBS in a patient with chronic stroke, illustrating the repeatability of the recordings. The vertical line is aligned to the peak latency of the earliest volley.

motor cortex stimulation (Figure 4). The mean amplitude of the total corticospinal volley evoked by left motor cortex stimulation increased  $>80\%$  ( $18.3 \pm 3 \mu\text{V}$ ) after left motor cortex iTBS ( $P < 0.05$  when compared with baseline values), with the appearance of a further descending wave. In contrast, the total corticospinal volley evoked by right motor cortex stimulation decreased by  $\approx 40\%$  ( $9.9 \pm 3.7 \mu\text{V}$ ) after left motor cortex iTBS. However, this change was not significant ( $P > 0.05$  when compared with baseline values).

Despite these changes in corticospinal excitability, iTBS did not lead to any obvious clinical change in spasticity or muscle strength. In healthy subjects, behavioral effects of TBS are only apparent in more complex tasks,<sup>15</sup> which were not studied here.

### Discussion

This study provides the first direct demonstration that noninvasive transcranial stimulation over the stroke hemisphere of a conscious human patient can increase excitability of the corticospinal output from the leg motor cortex. The effect of iTBS was substantial and increased corticospinal activity evoked by single-pulse TMS by  $\approx 80\%$ . Because descending



**Figure 4.** Histograms showing the mean amplitude of the epidural volleys evoked by MS of the affected and normal motor cortex before and after iTBS of the affected motor cortex. The mean amplitude of the total corticospinal volley evoked by left (affected) motor cortex stimulation is increased >80% after left motor cortex iTBS ( $*P < 0.05$  when compared with baseline values). In contrast, the total corticospinal volley evoked by right motor cortex (normal) stimulation is decreased by  $\approx 40\%$  after left motor cortex iTBS. However, this change is not significant ( $P > 0.05$  when compared with baseline values). Bars represent standard deviations.

volleys to single-pulse TMS are thought to originate from synaptic activity within the motor cortex,<sup>16,17</sup> an increase in amplitude of corticospinal volleys suggests that there is an increment in the efficacy of synaptic connections within the cortex. Finally, the EMG recordings from leg muscles showed that this increase in corticospinal excitability was accompanied by larger evoked motor responses, suggesting that it might have a functional benefit during voluntary activation of paretic muscle.

iTBS has been applied previously to healthy subjects, in whom it increased the amplitude of MEPs for 30 minutes or so. Therefore, in this respect, it is not unexpected that there might also be an increase in the number and size of descending corticospinal activity. Indeed, we have shown a similar correlation between reduced MEPs and decreased corticospinal volleys for its sister (inhibitory) technique of continuous TBS.<sup>15–18</sup> However, the important point in the present study is that the effect occurred in the damaged hemisphere of a patient who had had a subcortical stroke some 6 years previously and whose lower limb was still severely paretic. It implies that the motor cortex of this female patient was still capable of responding to iTBS. Given the previous observations in animals<sup>4–6</sup> and in human patients implanted with chronic stimulating electrodes,<sup>7–8</sup> it suggests that iTBS might be a suitable method to combine with physiotherapy to improve recovery of useful limb function in patients even years after a stroke.

Interestingly, the increase in corticospinal activity evoked by stimulation of the lesioned cortex was associated with a decrease in the excitability of the corticospinal output of the opposite hemisphere. This suggests that the increase in excitability of the lesioned hemisphere is associated with a change in functional connectivity involving both lesional and nonlesional hemispheres. One possibility is that iTBS, in addition to increasing corticospinal output from the lesioned cortex, also increases interhemispheric inhibition onto the nonlesioned cortex. Indeed, previous neurophysiological studies have shown that there may be an imbalance between the 2 hemispheres after stroke, with disinhibition in the nonlesioned motor cortex<sup>19</sup> and an inability to remove interhemispheric inhibitory drive from the intact

motor cortex to the lesioned motor cortex before movement of the paretic hand.<sup>20</sup> The present enhancement of excitability of the lesioned motor cortex may help counteract this imbalance by increasing interhemispheric inhibition onto the nonlesioned cortex.

## Disclosures

None.

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