ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation

journal homepage: www.archives-pmr.org

Archives of Physical Medicine and Rehabilitation 2014;95:1141-7

ORIGINAL ARTICLE

Deep Repetitive Transcranial Magnetic Stimulation With H-coil on Lower Limb Motor Function in Chronic Stroke: A Pilot Study

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Abstract

Objectives: To assess the efficacy of high-frequency (20Hz) brain stimulation on lower limb motor function in subjects with chronic (>6mo) subcortical stroke.

Design: Double-blind, placebo-controlled crossover study.

Setting: University hospital.

Participants: Right-handed subjects (N = 10) affected by a first-ever subcortical stroke in the territory of the middle cerebral artery were included in this study.

Interventions: Repetitive transcranial magnetic stimulation (rTMS) was delivered with the H-coil, specifically designed to target deeper and larger brains regions. Each subject received both real and sham rTMS in a random sequence. The 2 rTMS cycles (real or sham) were composed of 11 sessions each, administered over 3 weeks and separated by a 4-week washout period.

Main Outcome Measures: Lower limb functions were assessed by the lower limb Fugl-Meyer scale, the 10-m walk test, and the 6-minute walk test before and 1 day after the end of each treatment period, as well as at a 4-week follow-up.

Results: Real rTMS treatment was associated with a significant improvement in lower limb motor function. This effect persisted over time (follow-up) and was significantly greater than that observed with sham stimulation. A significant increase in walking speed was also found after real rTMS, but this effect did not reach statistical significance in comparison with the sham stimulation.

Conclusions: These data demonstrated that 3 weeks of high-frequency deep rTMS could induce long-term improvements in lower limb functions in the chronic poststroke period, lasting at least 1 month after the end of the treatment.

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Stroke is a leading cause of long-term disability, and noninvasive brain stimulation techniques have been recognized as a promising intervention for the treatment of poststroke motor deficits.[1-3] Although the ability to walk is impaired in more than 80% of poststroke subjects,[4] the pathophysiological reorganization of lower limb motor areas after stroke is still unclear, as relatively fewer data are available for the lower limb than for the upper limb.

Supported through the joint Italian-Israeli laboratory on brain modulation in neuroimmune, neurodegenerative, and mental disorders (Italian Ministry of Foreign Affairs).

No commercial party having a direct financial interest in the results of the research supporting this article has conferred or will confer a benefit on the authors or on any organization with which the authors are associated (Chieffo, De Prezzo, Houdayer, Nuara, Di Maggio, Coppi, Ferrari, Straffi, Spagnolo, Velikova, Sessa, Comola, Comi, Leocani).

A commercial party having a direct financial interest in the results of the research supporting this article has conferred or will confer a financial benefit on the author or one or more of the authors. Zangen is a key inventor of deep TMS H-coils and has financial interest in Brainsway Ltd.

0003-9993/14/$36 - see front matter © 2014 by the American Congress of Rehabilitation Medicine
http://dx.doi.org/10.1016/j.apmr.2014.02.019

A study[5] performed with a near-infrared spectroscopic imaging system in stroke subjects during walking showed that the cortical activation patterns of the motor, premotor, and supplementary lower limb motor cortex were greater for the unaffected hemisphere than for the affected hemisphere. The latter data suggest that the concept of interhemispheric competition, proposed for the upper limb motor areas,[6] might be applied even in the case of lower extremity poststroke recovery. Consistently, improvements of gait parameters of the paretic lower limb have been found to be associated with a reduction of the interhemispheric asymmetry of the primary sensorimotor cortical activations.[7] Wang et al[8] first evaluated, in a placebo-controlled study, the therapeutic effect of task-oriented training associated with 1-Hz repetitive transcranial magnetic stimulation (rTMS) (with the figure-of-8 coil) that was performed to inhibit the unaffected lower limb motor cortex in chronic stroke subjects. The authors found that inhibitory rTMS enhanced the effect of task-oriented training on walking performance and motor control ability, leading to a more symmetrical gait pattern. Recovery of motor deficits was associated with a reduction of the interhemispheric asymmetry of the leg motor excitability.

In the chronic phase after stroke, however, the interhemispheric competition, at least in the upper limb, has been found to be less pronounced than in the subacute period, and it is commonly observed that the transcallosal asymmetry slows down with time.[9] Moreover, since foot movements in healthy subjects have been proposed to be under bihemispheric control,[10] one could hypothesize a positive, rather than detrimental, role of the unaffected lower extremity motor system in recovery mechanisms occurring after stroke. In a more recent placebo-controlled crossover study,[11] a single session of high-frequency rTMS over the leg motor area bilaterally, using a double-cone coil, was reported to significantly improve walking performance for 20 minutes after stimulation in comparison with sham stimulation in a group of chronic poststroke subjects.

The purpose of our study was to assess the safety and efficacy of bilateral, excitatory, high-frequency rTMS over the lower limb cortical motor representation in persons with chronic subcortical stroke. To reach the lower limb cortical motor areas, deeply located in the mesial cortical surface of the hemispheres, we delivered rTMS using the H-coil, which is designed to effectively stimulate at about a depth of 3 to 5cm below the skull.[12,13] Compared with the standard figure-of-8 coil, the H-coil has been reported to require lower intensities to obtain lower limb motor responses[14] and larger volumes of the induced electric field.[14,15] The H-coil rTMS has been reported to be effective in the treatment of psychiatric disorders such as major depressive disorder or bipolar depression.[13,16,17] Recently, analgesic effects in subjects with painful diabetic neuropathy were obtained using deep rTMS with H-coil targeting the leg motor cortex.[15]

We hypothesized that high-frequency rTMS delivered with the same H-coil type over the lower limb motor cortical areas could improve the paretic lower limb function in chronic poststroke subjects.

List of abbreviations:

ANOVA	**analysis of variance**
FM	**Fugl-Meyer**
rTMS	**repetitive transcranial magnetic stimulation**
6MWT	**6-minute walk test**
10MWT	**10-m walk test**

Methods

Participants

Ten right-handed subjects affected by a first-ever stroke in the territory of the middle cerebral artery were included in this study. The inclusion criteria for participants were as follows: (1) evidence of an acute brain lesion on computed tomography or magnetic resonance scans at symptoms onset; (2) time between the stroke event and the enrollment in the protocol ranging from 6 months to 3 years (chronic phase); (3) age at admission between 25 and 80 years; and (4) ability to walk independently for at least 10m, even with assistive devices (cane, ankle-foot orthoses, etc). Exclusion criteria were as follows: (1) history of other neurologic disorders; (2) lesions involving the cortical lower limb motor representation; (3) use of drugs acting on the central nervous system; and (4) presence of contraindications to undergo rTMS such as pregnancy, the presence of cochlear implants, a neurostimulator, metal in the brain or skull, or a cardiac pacemaker, history of epilepsy, or history of head trauma diagnosed as a concussion.[18]

Subjects' age at admission ranged between 49 and 74 years (mean, 62.2y). All subjects had sustained a subcortical stroke; the affected hemisphere was the right in 6 subjects, while the other 4 subjects had a lesion in the left hemisphere. Subjects' data and lesion localization are reported in table 1.

All subjects gave their signed written informed consent to participate in the study, which was approved by our local ethics committee (protocol no. 111/11).

Procedures

We performed a double-blind, placebo-controlled crossover study. Each subject received both real and sham rTMS treatment cycles separated by a 4-week washout period in a random sequence (sham-real or real-sham). After full randomization, performed through administrative personnel not involved in the protocol, each participant was assigned 2 blank-coded magnetic cards (A and B), to be used respectively in the first and second cycle. Each card pair contained opposite types of treatments (sham and real). Consecutive subjects were randomly assigned with a global 1:1 ratio, so that 5 participants performed the real-sham and 5 the sham-real treatment sequence. Active or sham modes were determined by a switch controlled through the assigned magnetic card. This procedure ensured blindness of subjects, examiners, and treating personnel. Each treatment cycle lasted 3 weeks for a total of 11 high-frequency rTMS sessions (5 in the first week and 3 in the second and third weeks) (fig 1). No specific motor task involving the lower limb was associated with the rTMS treatment.

Deep rTMS

A Magstim Rapid^2 stimulator[a] was coupled with an H-coil[b] to deliver rTMS. The H-coil, designed for effective activation of the hand or leg motor cortex, contained 14 windings. Three medial groups conduct current along a posteroanterior axis, and 2 other groups return currents in the opposite (anterior-posterior) direction.[15] Resting motor threshold was measured after positioning the H-coil over the vertex on the optimal location for obtaining lower limb motor responses. Resting motor threshold was defined as the minimal intensity evoking visible movements on either lower limb or electromyographic motor-evoked potentials on the tibialis anterior muscles that were monitored bilaterally, with an