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Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment

G Koch[1,2], S Rossi[1,2], C Prosperetti[1,2], C Codecà[1,2], F Monteleone[1,2], L Petrosini[2,3], G Bernardi[1,2] and D Centonze[1,2]

We tested the effects of 5-Hz repetitive transcranial magnetic stimulation (rTMS) over the motor cortex in multiple sclerosis (MS) subjects with cerebellar symptoms. rTMS improved hand dexterity in cerebellar patients ($n = 8$) but not in healthy subjects ($n = 7$), as detected by a significant transient reduction of the time required to complete the nine-hole pegboard task. rTMS of the motor cortex may be a useful approach to treat cerebellar impairment in MS patients. *Multiple Sclerosis* 2008; **14:** 995–998. http://msj.sagepub.com

Key words: cerebellum; motor functions; multiple sclerosis; rTMS; transcranial magnetic stimulation

Introduction

Patients with multiple sclerosis (MS) frequently develop symptoms owing to cerebellar lesions, such as dysmetria leading to hand dexterity impairment [1]. The cerebellum takes part in several motor functions through its influence on the motor cortex and corticospinal outputs and the cerebral cortex and the cerebellum are tightly interconnected by a large descending fiber system, the cerebro–ponto–cerebellar projections [2,3]. Recent studies in patients with cerebellar ataxia and cerebellar stroke revealed the existence of abnormalities in intracortical circuits of the motor cortex, supporting the idea that the cerebellum physiologically exerts a facilitatory influence on the motor cortex which is decreased following cerebellar damage [4]. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that induces changes in cortical excitability at the site of stimulation and at distant sites, leading to either facilitation or inhibition depending on the frequency of the pulses. High-frequency (>5 Hz) excitatory motor cortex rTMS enhances motor cortex excitability both in healthy subjects and MS patients [5,6]. On the basis of this background, in the current study we applied facilitatory rTMS of the motor cortex at the aim to verify whether this could result in improvement of hand dexterity in MS patients presenting with cerebellar deficits.

Methods

The experiments were approved by Ethical Committee of the University of Tor Vergata, Rome. Eight clinically stable patients with MS and dysmetria affecting predominantly the dominant right upper limb were included in this part of the study (five female, three male; aged 18-49 years). Seven right-handed healthy volunteers (HV) were included as controls subjects (four female, three male; aged 23–46 years). All of them were naive about the procedure and gave written informed consent to the study. The diagnosis of relapsing–remitting (RR) MS was established by clinical, laboratory and magnetic resonance imaging (MRI) criteria and matched the criteria of McDonald, *et al.* [7]. Inclusion criteria were a clinically definite diagnosis of RRMS with dysmetria of the dominant upper

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limb and no evidence of visual, pyramidal or sensory dysfunction. Other symptoms of cerebellar dysfunction co-existed in these subjects, and included dysarthria (1 pz), intentional tremor (6 pz), gait and balance disturbances (4 pz), adiadochokinesia (4 pz) [1]. All of these patients had MRI evidence of lesions in the cerebellum or in the cerebellar pedunculi, and were clinically stabile for at least 4 months. The integrity of the cortico-spinal tract was assessed with motor evoked potentials (MEPs).

A MagStim Rapid magnetic stimulator (Magstim Company, Whitland, Wales, UK), connected with a figure-of-eight coil with a diameter of 90 mm was used to deliver rTMS over the scalp site corresponding to the arm area of primary motor cortex contralateral to the dominant limb. According to international standards [8], the resting motor threshold (RMT) was defined as the lowest stimulus intensity required to evoke MEPs of 50 μV in peak-to-peak amplitude in at least three of five consecutive trials in the first dorsal intersseous (FDI) muscle. The figure-of-eight coil was applied tangentially to the subject's head surface with the handle pointing posteriorly and positioned at 45° with respect to mid-sagittal axis of the head.

Eighteen rTMS trains of 50 stimuli at 5 Hz and at 100% RMT (train duration: 10 s) separated by a 40 s pause were delivered for a total of 900 pulses (total duration: 15 min). For sham rTMS, 18 trains of 50 stimuli at a frequency of 5 Hz separated by a 40 s pause were delivered (100% RMT). The coil was held close to the target site, but angled away so that no current was induced in the brain [6]. All of the MS patients underwent both real and sham stimulation, applied over two consecutive days. The order of presentation of the two rTMS protocols was pseudo-randomized across subjects. HV subject underwent real rTMS.

Clinical evaluation of dysmetria

The nine-hole pegboard task was used to measure hand dexterity. This task is typically altered in patients with cerebellar lesions, as well as in normal subjects following rTMS of the cerebellum [9,10].

Subjects were first trained in performing the nine-hole pegboard task for five consecutive trials using the left and right hand in alternate trials. The inter-trial interval was 60 s. For each trial, the subject began with the hand resting beside the pegboard, which was held steady on the table with the other hand. The experimenter started the trial with a verbal ready–steady–go command, and timed the trial with a digital stopwatch. After five training trials, we recorded the baseline performance for each subject in another five trials. The sum of each of the five trials was then calculated. The evaluation was repeated immediately after (t1) the rTMS procedure, and 10 (t2) and 20 min (t3) later.

Statistical analysis

A within-subjects repeated analysis of variance (ANOVA) was performed on mean subjects' performance at the nine-hole pegboard task, taking factors of CONDITION (sham or real stimulation), HAND (left or right) and TIME (pre, t1, t2, t3). A further ANOVA was performed on normalized values (percentage of change before and after real rTMS) with GROUP (MS versus HS) as between subjects and TIME as within-subject main factors. The significance level was established at $p < 0.05$.

Results

We found that 5 Hz rTMS significantly improved hand dexterity in cerebellar patients, as detected by a significant reduction of the time required to complete the nine-hole pegboard task with the affected limb. This borne out from repeated measure ANOVA performed on the mean subjects' performance, showing a significant main effect of the HAND (F = 4, 16; $p < 0.05$), TIME (F = 32, 64; $p < 0.05$) and CONDITION (F = 17, 64; $p < 0.05$) main factors, with a significant CONDITION × HAND × TIME triple interaction (F = 3, 98; $p < 0.05$). *Post hoc* analysis showed that in comparison with sham stimulation, MS patients performed faster with the right hand immediately after real rTMS ($p < 0.01$ at *post hoc* analysis) and 10 min later ($p < 0.01$), but not 20 min after the stimulation ($p > 0.1$); see Figures 1(a) and (b)). It is worth noting that real stimulation failed to affect the time required for the completion of the task in healthy subjects. In healthy subjects ANOVA showed only a significant main effect of HAND (F = 3, 96; $p < 0.05$), because subjects performed faster with their preferred right hand (Figure 1(c)).

Further ANOVA analyses with diagnosis (MS or HV) as between factors performed on the percentage of change in comparison with baseline following real rTMS for the right hand, showed a significant main effect of GROUP factor (F = 3, 66; $p < 0.05$) as well a significant GROUP × TIME interaction (F = 2, 97; $p < 0.05$), confirming that the rTMS-induced effect were observed transiently only in the MS group (Figure 1(d)).

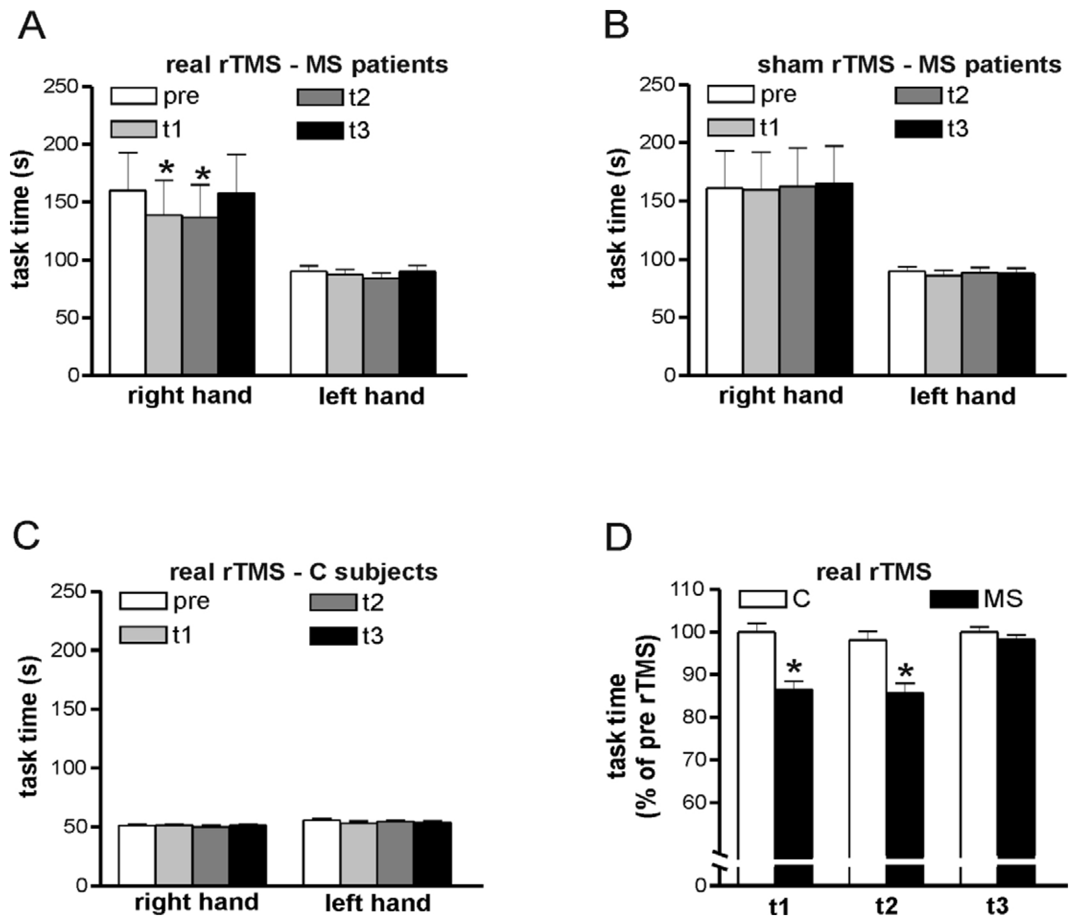

Figure 1 Facilitation of motor cortex by rTMS ameliorates cerebellar symptoms in MS patients. (A), (B) The graph shows the mean times calculated for MS patients to complete the pegboard task with the right (contralateral to stimulated hemisphere) and left hand (ipsilateral to the stimulated hemisphere) after (A) real and (B) sham rTMS. (C) The graph shows the mean times calculated for healthy subjects to complete the pegboard task with right (contralateral to stimulated hemisphere) and left hand (ipsilateral to the stimulated hemisphere) after real rTMS. (D) The graph shows that the mean percentage time for the task was decreased after rTMS only in patients with dysmetria (MS group). $^*p < 0.05$.

Discussion

A pattern of excitatory rTMS that has been shown to facilitate motor cortex excitability was able to transiently improve dysmetria in MS patients. Since these patients did not present pyramidal tract dysfunction, it is possible that recovery of symptoms secondary to cerebellar dysfunction was due to modulation of cerebro–pontine–cerebellar projections [2,3]. In alternative it is possible that 5 Hz rTMS counteracted the reduced drive from the cerebellum, secondary to demyelinization of such structure, which contributed to the development of hand dexterity impairment. As the benefits were only transient, further investigations with repeated sessions of stimulation could verify whether it is possible to induce persistent clinical improvement of cerebellar dysfunction in MS patients.

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