Neuroscience Letters 553 (2013) 148–152

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Inhibitory theta burst stimulation of affected hemisphere in chronic stroke: A proof of principle, sham-controlled study

Vincenzo Di Lazzaro[a,b,*], John C. Rothwell[c], Penelope Talelli[c], Fioravante Capone[a,b], Federico Ranieri[a,b], Amanda C. Wallace[c], Gabriella Musumeci[a,b], Michele Dileone[a,d]

[a] Institute of Neurology, Campus Biomedico University, Rome, Italy
[b] Fondazione Alberto Sordi – Research Institute for Ageing, Rome, Italy
[c] Sobell Department, UCL Institute of Neurology, London, UK
[d] Neuroscience Department, San Bortolo Hospital, Vicenza, Italy

HIGHLIGHTS

- We evaluated if inhibitory modulation of stroke hemisphere can enhance recovery.
- We found no deleterious effects of inhibitory stimulation on recovery.
- All patients showed some improvement from a retraining protocol for the upper limb.
- Inhibition of stroke hemisphere is safe and has the potential to enhance recovery.

ARTICLE INFO

Article history:
Received 19 April 2013
Received in revised form 22 June 2013
Accepted 8 August 2013

Keywords:
Transcranial magnetic stimulation
Stroke
LTP
LTD
Rehabilitation

ABSTRACT

Non-invasive brain stimulation is presently being tested as a potential therapeutic intervention for stroke rehabilitation. Following a model of competitive interactions between the hemispheres, these interventions aim to increase the plasticity of stroke hemisphere by applying either excitatory protocols to the damaged hemisphere or inhibitory protocols to the non-stroke hemisphere. Here we test the safety and feasibility of using an inhibitory protocol on the stroke hemisphere to improve the response to conventional therapy via a homeostatic increase in learning capacity. Twelve chronic stroke patients received TBS to stroke hemisphere (6 patients inhibitory TBS and 6 sham TBS) followed by physical therapy daily for 10 working days. Patients and therapists were blinded to the type of TBS. Action Research Arm Test (ARAT), Nine-Hole Pegboard Test (NHPT) and Jebsen–Taylor Test (JTT) were the primary outcome measures, grip and pinch-grip dynamometry were the secondary outcome measures. All patients improved ARAT and JTT scores for up to 3 months post-treatment. ARAT scores improved significantly in both real and sham groups, but only patients receiving real TBS significantly improved on the JTT: 3 months post-treatment mean execution time was reduced compared to baseline by 141 s for real group and by 65 s for the sham group. This small exploratory study suggests that ipsilesional inhibitory TBS is safe and that it has the potential to be used in a larger trial to enhance the gain from a late rehabilitation program in chronic stroke patients.

1. Introduction

Non-invasive human brain stimulation in the form of repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) can induce long-lasting changes in the excitability of central motor circuits via long-term potentiation/depression (LTP/LTD)-like phenomena that share major properties of LTP/LTD described at cellular level [18]. Several recent studies tested whether induction of LTP-like effects in the stroke hemisphere can enhance the effects of motor rehabilitation after stroke [10,16]. The hypothesis is that stimulation facilitates the stroke hemisphere and initiates changes in synaptic plasticity that improve therapy by enhancing learning-related changes in synaptic connections that are required for reacquisition of skills [17]. Conversely, inhibitory stimulation of the non-stroke hemisphere might reduce its excitability and reduce transcallosal inhibition of stroke hemisphere, with the same consequences for learning. Several clinical studies reported some positive effects from repeated sessions of brain stimulation [1], however, the effects were limited and variable.

* Corresponding author at: Institute of Neurology, Campus Biomedico University, Via Alvaro del Portillo 200, 00128 Rome, Italy. Tel.: +39 06225411320; fax: +39 06225411936.
E-mail address: v.dilazzaro@unicampus.it (V. Di Lazzaro).

0304-3940/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neulet.2013.08.013

Recent work has, however, suggested that rTMS could improve learning via a different mechanism that involves the phenomenon of "homeostatic" plasticity. This postulates that the ease of producing synaptic LTP/LTD depends on the prior history of neural activity. The greater the activity the more difficult it is to induce LTP; whereas LTD is more difficult to induce with a history of low activity. Homeostatic-like interactions have been reported in the human brain using a variety of brain stimulation protocols [12]. For example, a protocol capable of inducing LTD-like effects strongly facilitates motor learning while protocols inducing LTP-like effects have a less pronounced and short-lived facilitatory effect on learning [12]. In the context of stroke this would predict that, contrary to present practice which uses excitatory protocols, an inhibitory rTMS protocol that induces LTD-like effects on the stroke hemisphere would lead to better relearning in stroke patients through mechanisms of homeostatic metaplasticity [12].

We designed a proof-of-principle double blinded semi-randomised sham-controlled trial to assess the safety and potential efficacy of this approach by measuring whether clinically important long-lasting differences can be achieved by adding continuous theta burst stimulation (cTBS) of the lesioned hemisphere to a standardized physiotherapy protocol for the upper limb in chronic stroke. CTBS is a robust form of inhibitory rTMS; its after-effects, thought to be due to LTD-like changes [8], can last up to 1 h, an excellent time window for a therapy session. We hypothesized that immediate and long-term outcomes of the active treatment would be significantly better than sham treatment.

2. Subjects and methods

2.1. Subjects

12 chronic stroke patients gave their written informed consent for the study which was performed according to the Declaration of Helsinki and approved by the local ethics committee. Inclusion criteria were: (a) first-ever ischemic stroke at least 1 year earlier; (b) moderate residual hand function, defined as grasp strength $\geq$1% of the unaffected hand, preserved extension at the wrist ($\geq$20°), and baseline score in Nine Hole Pegboard Test (NHPT) $\leq$70% of the unaffected hand; (c) ability to give informed consent and comprehend instructions. Exclusion criteria were: (a) significant spasticity (Ashworth score >2); (b) patients not able to perform dynamometry; (c) concomitant neurological conditions, including any history of epilepsy and significant comorbidities; (d) cognitive impairment or any substantial decrease in alertness, language reception, or attention that might interfere with understanding instructions for motor testing; (e) apraxia; (f) excessive pain in any joint of the paretic extremity; (g) contraindications to TMS such as metal head implants; (h) advanced liver, kidney, cardiac or pulmonary disease; (i) history of significant alcohol or drug abuse; (l) depression or use of neuropsychotropic drugs such as antidepressants or benzodiazepines. The National Institute of Health Stroke Scale (NIHSS) and the Barthel Index (BI) were used to evaluate neurological impairment and disability at the enrolment.

2.2. Primary outcome measures

Since this was an exploratory trial in which we aimed to evaluate changes in global hand function, we chose 3 primary outcome measures that evaluate different aspects of that. These were Action Research Arm Test (ARAT; score 0–57), Jebsen-Taylor Test (JTT) and Nine Hole Pegboard Test (NHPT).

(1) ARAT is a broad measure of upper extremity function in patients with focal disability [7].

(2) Jebsen–Taylor Test (JTT) has been shown to be valid and reliable in the normal population [11] and in chronic stroke patients [5,9]. The modified version used here has 6 subsets. Items were tested 5 times at each assessment. The time in seconds to complete each subset was recorded: the maximal amount of time allotted for each item was 120 s so that 120 s were assigned to the tasks that could not be concluded [4]. The hands were tested alternately. Since performance stabilizes after 2–3 trials, only the last two trials were averaged and used for analysis. However, to better characterize performance in patients who were not able to perform any of the JTT tasks at baseline, we used the method of calculation performed in one of our previous studies about hand function in chronic stroke patients [14]. Thus, scores were normalized to the performance of unaffected hand and computed as follows: cannot do or <0.05 = 1, 0.05–0.09 = 2, 0.1–0.14 = 3, and so on; thus, the range was 1–20, each point reflecting an improvement of 5% of the maximum score that is, the score of the unaffected hand. The items were then summed to produce a JTT total score (range 6–120, 11.4 points reflecting 10% improvement) [14].

(3) NHPT is a test sensitive to changes in finger dexterity [6]. Each hand was tested alternately for 3 times, starting from the paretic one. Sixty seconds were allowed for each single attempt: if not completed, the number of pegs placed in 60 s was recorded. Final scores were computed as the ratio pegs/s placed by the paretic hand, averaged over 3 trials and normalized to the average score of the unaffected hand (range 0–1; 0, cannot do).

2.3. Secondary outcome measures

Grasp and pinch grip dynamometry were performed using a digital dynamometer (Biometrics Ltd, Newport, UK). Each patient was instructed to perform 3 attempts at grip and pinch, alternating the hands. Maximal grip strength, when normalized to the unaffected hand, is highly reproducible in chronic stroke patients [2].

2.4. Motor cortex excitability

We evaluated changes in motor cortex excitability in a subgroup of patients [4 in the real group (mean age: 59.5 $\pm$ 11.7 (SD) years) and 4 in the sham group (age: 56.7 $\pm$ 16.1; $p = 0.5$)] of both affected (AH) and unaffected (UH) hemisphere at baseline, T1 and T2.

AMT was evaluated for all the patients of the real group at each time point to set the intensity for cTBS.

Magnetic stimulation was performed with a high-power Magstim 200 (MagstimCo., Whitland, Dyfed). A figure-of-eight coil with external loop diameters of 9 cm was held over the motor cortex at the optimum scalp position to elicit MEPs in the contralateral first dorsal interosseous muscle (FDI). The induced current flowed in a postero-anterior direction.

For both AH and UH, we evaluated active (AMT) and resting (RMT) motor threshold and amplitude of motor evoked potentials (MEPs). MEPs were band pass filtered (bandwidth 3 Hz–3 kHz) (Digitimer D360 amplifiers) and each single trial was recorded on computer for later analysis using a CED 1401 A/D converter (Cambridge Electronic Design, Cambridge, UK) and associated software. The responses to 20 stimuli obtained at rest at an intensity of 120% RMT were averaged.

2.5. Interventions

Real or sham brain stimulation, followed by physical therapy targeting the arm, was delivered daily for 10 consecutive working days.