Neuroscience Letters 567 (2014) 24–29

Contents lists available at ScienceDirect

Neuroscience Letters

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

Effects of dual-mode non-invasive brain stimulation on motor function

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HIGHLIGHTS

- tDCS on the contralateral side modulated the effects of subsequent rTMS on M1.
- Preconditioning with cathodal tDCS enhanced the 10 Hz rTMS effect.
- Preconditioning with anodal tDCS eliminated the 10 Hz rTMS effect.

ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form 30 January 2014
Accepted 16 March 2014

Keywords:
Non-invasive brain stimulation
Transcranial magnetic stimulation
Transcranial direct current stimulation
Interhemispheric interaction

ABSTRACT

The purpose of this study was to investigate the effects of dual-mode non-invasive brain stimulation (NBS) on motor function and cortical excitability using both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) over the bilateral primary motor cortices (M1s) of healthy individuals. Fifteen healthy right-handed volunteers (8 women; mean age 23.2 years) participated in this sham-controlled random-ordered crossover study. All of the participants received four randomly arranged dual-mode stimulations with a 24-h washout period: condition 1, preconditioning with cathodal tDCS over the left M1 followed by 10 Hz rTMS over the right M1; condition 2, preconditioning Lt. anodal tDCS followed by Rt. 10 Hz rTMS; condition 3, Lt. sham tDCS followed by Rt. 10 Hz rTMS; and condition 4, Lt. sham tDCS followed by Rt. sham rTMS. Corticomotor excitability and motor function were assessed in the left hand before and after stimulation. The motor evoked potential (MEP) amplitudes significantly increased after dual-mode stimulation in conditions 1 and 3, and significantly decreased in condition 2. The MEP latency became significantly shorter in condition 1. The motor function tests revealed a significant improvement in the Purdue pegboard test in condition 1, and in the box and block tests in conditions 1 and 3. The preconditioning tDCS over the contralateral M1 modulated the effects of subsequent rTMS on cortical excitability and motor function.

1. Introduction

Two types of non-invasive brain stimulation (NBS), repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), are widely used to modulate neural excitability [1,5,7,33]. In stroke patients, the level of corticomotor excitability changes in both the affected and unaffected hemispheres, and there is excessive interhemispheric inhibition from the contralesional primary motor cortex (M1) to the ipsilesional M1 [33]. Studies have attempted to modulate corticomotor excitability using NBS methods such as rTMS and tDCS with the ultimate goal of modulating the motor function of the affected extremities [1,21,30,33]. The selected strategies have included using either the inhibiting mode of rTMS or tDCS over the unaffected M1 to disinhibit the transcallosal inhibition, or using the facilitating mode to enhance the excitability of the affected M1 [11,14].

Among the various modes of application, high frequency rTMS over the M1 has been shown to increase corticomotor excitability during or after stimulation in healthy subjects and patients who

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http://dx.doi.org/10.1016/j.neulet.2014.03.022
0304-3940/

have suffered from motor disorder after stroke [2,10,13,22]. Similarly, anodal tDCS applied over the M1 improved corticomotor excitability and performance of the hand contralateral to the stimulated hemisphere in healthy subjects as well as stroke patients [3,9,18,19]. Alternatively, the application of low frequency rTMS and cathodal tDCS over the M1 has been shown to improve ipsilateral hand function [13,29,31]. These outcomes are considered to be the result of interhemispheric interactions modulating the inhibitory transcallosal connections between the two motor cortices [8,17]. In this context, the simultaneous application of tDCS over the bilateral M1s (anodal electrode in one hemisphere and cathodal electrode in the other) has been reported to have more of an effect on motor function than unilateral tDCS [15,16,31]. However, to the best of our knowledge, there has been no attempt to use dual NBS methods over the bilateral M1s to improve the effects of single applications.

In this study, we investigated the interactive effects of dual-mode NBS applied over the bilateral M1s on cortical excitability and motor function in healthy individuals as a preliminary study of developing a therapeutic intervention for post-stroke patients with motor disorders. We hypothesized that preconditioning the stimulation of the contralateral M1 using cathodal tDCS would disinhibit the transcallosal inhibitory function to the target M1, and that this would then augment the modulating effect of the high frequency rTMS over the target M1.

2. Materials and methods

2.1. Participants

Fifteen healthy volunteers (7 men and 8 women, with a mean age of 23.2 ± 2.24 years in the range of 20–28) who reported no history of psychiatric, neurological or orthopedic problems participated in this study. The experiments were conducted with the full understanding and written consent of each participant, and the study was approved by the Institutional Review Board of the Samsung Medical Center. All of the participants were right-handed, as determined by the Edinburgh Handedness Inventory, with laterality quotients ranging from 80 to 100. All the participants completed the experimental procedure with no reported adverse side effects.

2.2. Experimental design

A random-ordered, double-blinded, parallel and sham-controlled design was adopted in the study. The participants underwent four randomly arranged, dual-mode stimulation sessions under the following conditions; preconditioning with cathodal tDCS over the left M1 followed by 10 Hz of rTMS over the right M1 (condition 1), preconditioning with anodal tDCS over the left M1 followed by 10 Hz of rTMS over the right M1 (condition 2), sham tDCS over the left M1 followed by 10 Hz of rTMS over the right M1 (condition 3) and sham tDCS over the left M1 followed by sham rTMS over the right M1 (condition 4). Each stimulation session was conducted on a different day, such that consecutive stimulation sessions were separated by a washout period of at least 24 h (Fig. 1). The magnitude of the change in corticomotor excitability in the right M1 was measured by the amplitude and latency of the motor-evoked potentials (MEPs) before and immediately after each stimulation session. For the motor function assessment, the participants performed the box and block test (BBT), the Purdue pegboard test (PPT) and the grip strength test with their left hand before and immediately after each session.

2.3. Determination of the motor cortex and resting motor threshold

To determine the optimal scalp location of the bilateral M1s and the intensity of the rTMS and to evaluate the cortical excitability, a single-pulse TMS was performed on each subject before each session. Each subject was seated comfortably in a reclining armchair with both hands pronated on a pillow. Electromyography (EMG) data were collected from the contralateral first dorsal interosseus muscle via surface electrodes placed over the muscle in a belly tendon montage. The EMG activity was amplified using the EMG/EP system (Synergy®, Medelec, UK) and the data were band-pass filtered at 10–2000 kHz. The optimal scalp location ('hot spot') was determined using a TMS system (Magstim Rapid2® stimulator: Magstim Ltd, UK) and a 70 mm figure-eight coil. The handle of the coil was oriented at 45° posterior to the midline such that the electromagnetic current flowed perpendicular to the central sulcus, and the stimulator was moved over the scalp in 1 cm increments [18,20]. Once a hot spot was identified, a single-pulse TMS was delivered to the location to determine the resting motor threshold (RMT), which was defined as the lowest stimulus intensity necessary to produce an MEP ≥ 50 μV peak-to-peak amplitude in 5 of 10 subsequent trials. The muscle activity was carefully monitored by real-time EMG to confirm a relaxed state before stimulation [26].

2.4. Repetitive transcranial magnetic stimulation

In each session, rTMS was applied to the M1 of the right target motor cortex area corresponding to the left hand using a Magstim Rapid2® (Magstim, UK) stimulator with two booster modules. Real rTMS was delivered at 10 Hz and 90% RMT for 5 s with a 55 s inter-train interval. One thousand pulses were delivered over a period of 20 min. Stimulation was applied to the motor cortex by holding the figure-eight coil tangential to the skull. In this study, the rTMS protocols adhered to the safety guidelines for rTMS applications [25]. As with the real rTMS, the sham rTMS was performed with the coil held at 90° to the scalp using the same stimulation parameters (duration, time, and frequency) [10].

2.5. Transcranial direct current stimulation

Transcranial DCS was applied using a battery-driven DC stimulator (NeuroConn, Ilmenau, Germany) over the left M1. A constant current flow of 1 mA was applied for 20 min through wet sponge electrodes (size: 7 cm × 5 cm) positioned over the M1 and the contralateral supraorbital area. The M1 electrode was placed on the target site for cortical stimulation (the left M1). The supraorbital electrode was placed over the eyebrow contralateral to the stimulating M1. The electrode placed over the M1 measured the tDCS polarity. For the cathodal tDCS, the cathode was placed over the left M1 and for the anodal tDCS, the anode was positioned over the left M1. For the sham tDCS, the DC stimulator was preprogrammed to activate at the beginning of the stimulation and then fade off after 5 s of stimulation [23].

2.6. Assessment of hand motor function

To evaluate hand motor function performance, each participant performed the PPT [32], the BBT [4], and the grip strength test [4] using his or her left hand before and immediately after each experimental session.

2.7. Data analysis

SPSS/PC software version 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A paired *t*-test was used to assess