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Bilateral sequential motor cortex stimulation and skilled task performance with non-dominant hand

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H I G H L I G H T S

- Both, contralateral M1 iTBS and ipsilateral M1 cTBS improved non-dominant skilled-task performance.
- Bilateral sequential M1 TBS (contralateral cTBS followed by ipsilateral iTBS) improved skilled-task performance more than unilateral or sham TBS.
- Bilateral sequential M1 TBS may be particularly effective in improving motor learning, also in the neurorehabilitation setting.

A B S T R A C T

Objective: To check whether bilateral sequential stimulation (BSS) of M1 with theta burst stimulation (TBS), using facilitatory protocol over non-dominant M1 followed by inhibitory one over dominant M1, can improve skilled task performance with non-dominant hand more than either of the unilateral stimulations do. Both, direct motor cortex (M1) facilitatory non-invasive brain stimulation (NIBS) and contralateral M1 inhibitory NIBS were shown to improve motor learning.
Methods: Forty right-handed healthy subjects were divided into 4 matched groups which received either ipsilateral facilitatory (intermittent TBS [iTBS] over non-dominant M1), contralateral inhibitory (continuous TBS [cTBS] over dominant M1), bilateral sequential (contralateral cTBS followed by ipsilateral iTBS), or placebo stimulation. Performance was evaluated by Purdue peg-board test (PPT), before (T0), immediately after (T1), and 30 min after (T2) an intervention.
Results: In all groups and for both hands, the PPT scores increased at T1 and T2 in comparison to T0, showing clear learning effect. However, for the target non-dominant hand only, immediately after BSS (at T1) the PPT scores improved significantly more than after either of unilateral interventions or placebo.
Conclusion: M1 BSS TBS is an effective intervention for improving motor performance.
Significance: M1 BSS TBS seems as a promising tool for motor learning improvement with potential uses in neurorehabilitation.

1. Introduction

Fluctuations in excitability of the primary motor cortex (M1) are associated with various aspects of motor behavior including motor learning. Number of animal (e.g. Rioult-Pedotti et al., 2000, 1998) and human (e.g. Iezzi et al., 2008; Jung and Ziemann, 2009; Ziemann et al., 2004) studies have demonstrated substantial role of M1 long-term potentiation (LTP) and long-term depression (LTD) synaptic plasticity in processes of motor learning. Neuromodulatory non-invasive brain stimulation (NIBS) methods, based either on transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (TDCS), applied directly over M1 can effectively increase or reduce M1 excitability and induce LTP-like or LTD-like effects (Nitsche et al., 2012), which subsequently may have substantial impact on motor performance

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and learning (Muellbacher et al., 2002; Reis et al., 2008; Teo et al., 2011).

Besides their direct action at the site of application and changes in excitability and activation of the stimulated M1 area, the NIBS methods can indirectly, via the corpus callosum, modulate the excitability and activation of M1 area of the contralateral hemisphere too (Kobayashi et al., 2004; Schambra et al., 2003; Stefan et al., 2008; Suppa et al., 2008). This induced change of the contralateral hemisphere excitability and activation can as a result bring about changes in motor learning with the ipsilateral arm (Kobayashi, 2010; Kobayashi et al., 2009). Although the reciprocal functional connections between the M1s might vary according to the specific motor task tested, ranging from mutual inhibition to mutual facilitation, the NIBS induced effects on the contralateral hemisphere have typically opposite direction to the effects on the ipsilateral hemisphere; i.e. NIBS induced direct inhibition of the ipsilateral M1 is associated with facilitation of the contralateral M1 and vice versa, particularly if tested at rest. It was shown that indirectly induced increased activity and facilitation of the M1 may be equally effective in improving acquisition or consolidation of early motor learning (Kobayashi, 2010; Kobayashi et al., 2009), as is the case with the direct stimulation of M1 (Kim et al., 2004; Teo et al., 2011).

Given the aforementioned, it is tempting to assume that if the facilitation of one hemisphere is combined with inhibition of the opposite hemisphere there is a possibility that even greater effects can be achieved. In other words, two neuromodulatory methods with complementary physiological effect on the target hemisphere may be able to achieve a higher level of performance improvement than the application of each of them separately. However, it is equally possible that instead of promoting motor learning, successive application of two neuromodulatory methods with complementary physiological effect may lead to activation of homeostatic mechanisms which would eventually impede learning (Siebner, 2010; Ziemann and Siebner, 2008).

There is relatively little experimental evidence which could provide a definite answer to the later query. In particular, bilateral application of NIBS has been explored in only a handful of studies of motor functions. Most often, bilateral simultaneous TDCS setup with inhibitory cathodal TDCS on one hemisphere and facilitatory anodal TDCS over another has been used (Kidgell et al., 2013; Lindenberg et al., 2010; Vines et al., 2008; Waters-Metenier et al., 2014; Williams et al., 2010). However, although relatively easy for application and without any major known side effects, TDCS suffers from serious lack of anatomical precision. Relatively large electrodes used in standard TDCS deliver their modulatory effect over wide cortical areas thus affecting not only the intended target area, but also a number of other neighboring areas, some with potentially conflicting physiological effect. In contrast, the TMS based NIBS methods can deliver their modulatory effects over much more focused space allowing thus for far better anatomical precision. However, combinations of TMS methods, applied bilaterally but in succession, have been tried only rarely (Park et al., 2014; Takeuchi et al., 2009). Moreover, in all of these studies for facilitation of the non-dominant M1 a high-frequency (HF; i.e. 10 Hz) repetitive TMS (rTMS) was used, which was preceded either by inhibitory low-frequency (LF; i.e. 1 Hz) rTMS (Takeuchi et al., 2009) or by cathodal TDCS (Park et al., 2014) over the dominant M1. A significant drawback of these approaches is that they require quite long interventional protocols, lasting for almost an hour, with potential to provoke discomfort in tested subjects. This is of particular importance for population of patients with neurological disorders since they may be even less able to tolerate and sustain long treatment protocols.

Given its short duration, a few minutes only, and yet rather robust after-effects (Suppa et al., 2016; Wischnewski and Schutter, 2015), theta burst stimulation (TBS) may be perfectly suited to overcome the mentioned limitations of other TMS based approaches. Beneficial effects on hand motor function recovery in a group of post-stroke patients was reported after 10 daily sessions of 1 Hz rTMS over unaffected M1 followed by 10 daily sessions of the facilitatory intermittent TBS (Sung et al., 2013). However, to the best of our knowledge, there has been no report of possible effects of bilateral application of TBS over M1 on motor learning. Therefore, in this study, we tried to explore whether application of an inhibitory TBS protocol (i.e. continuous TBS – cTBS) (Huang et al., 2005) to the dominant M1 area, followed immediately after by an excitatory TBS protocol (intermittent TBS – iTBS) (Huang et al., 2005) applied to the target non-dominant M1 area, would bring improvement in performance of a complex motor task with non-dominant hand, which would be above the effects seen by unilateral applications of either of the TBS types in isolation. The order of stimulation was chosen with intention to first inhibit the negative impact of the dominant hemisphere in learning with non-dominant hand (Kobayashi et al., 2004; Netz et al., 1995) and, then to further excite non-dominant hemisphere. This is the situation comparable with the one often seen in post-stroke patients, where undamaged hemisphere actively inhibits damaged hemisphere preventing it from acquiring new motor skills (Murase et al., 2004; Talelli and Rothwell, 2006).

2. Materials and methods

2.1. Subjects

Forty healthy people (24 males) between 19 and 33 years of age (mean ± SD: 25 ± 3 years) participated in this study. All participants were right handed as determined by the Laterality Quotient from the Edinburgh Handedness Inventory (Oldfield, 1971). The participants did not take any medication and were free from any relevant medical condition in their history. They were randomly assigned into one of the four groups named after the side on which an intervention was applied: contralateral (CL), ipsilateral (IL), bilateral (BL), and placebo (PL) (Table 1, Fig. 1). Participants in the CL group had facilitatory iTBS over the non-dominant target M1 (i.e. contralateral to the target hand). Participants in IL group had inhibitory cTBS over the dominant M1 (i.e. ipsilateral to the target hand). Participants in BL group had TBS applied sequentially over both M1, first cTBS over dominant M1 (i.e. ipsilateral inhibition) followed by iTBS over the non-dominant M1 (i.e. contralateral facilitation). Participants in the PL group had placebo stimulation applied over the non-dominant M1. All participants gave written informed consent, in accordance with the Declaration of Helsinki; the study protocol was approved by the local Ethics Committee.

This study is in fact a part of larger ongoing project focused on the effects of various NIBS on motor learning. The participants for the main experimental group, the BL group, and for the one of the comparison/reference groups, the IL group, were recruited specifically for this study. Other two comparison/reference groups, the CL and the PL groups, were taken from a previously published companion article (Jelić et al., 2015).

2.2. Motor task

Same as in our previous article (Jelić et al., 2015), motor performance was assessed by two motor tasks of different complexity. For the simple task, the so called simple reaction time task (RTT), participants were asked to respond quickly to a buzzer tone presented randomly every 6–10 s. The response was a rapid squeeze, with thumb and index finger, of a hand-held rubber oval object. The time between the sound onset and the start of the contraction