Brain Stimulation 10 (2017) 298–304

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults

George M. Opie [a], Eleni Vosnakis [a], Michael C. Ridding [b], Ulf Ziemann [c], John G. Semmler [a, *]

[a] Discipline of Physiology, School of Medicine, The University of Adelaide, Adelaide, Australia
[b] Robinson Research Institute, School of Medicine, The University of Adelaide, Adelaide, Australia
[c] Department of Neurology & Stroke, Hertie-Institute for Clinical Brain Research, Eberhard Karls University of Tübingen, Tübingen, Germany

ARTICLE INFO

Article history:
Received 17 December 2016
Accepted 3 January 2017
Available online 4 January 2017

Keywords:
Ageing
Transcranial magnetic stimulation
Theta burst stimulation
Metaplasticity
Priming

ABSTRACT

Background: Primary motor cortex neuroplasticity is reduced in old adults, which may contribute to the motor deficits commonly observed in the elderly. Previous research in young subjects suggests that the neuroplastic response can be enhanced using non-invasive brain stimulation (NIBS), with a larger plastic response observed following priming with both long-term potentiation (LTP) and depression (LTD)-like protocols. However, it is not known if priming stimulation can also modulate plasticity in older adults.
Objective: To investigate if priming NIBS can be used to modulate motor cortical plasticity in old subjects.
Methods: In 16 young (22.3 ± 1.0 years) and 16 old (70.2 ± 1.7 years) subjects, we investigated the response to intermittent theta burst stimulation (iTBS; LTP-like) when applied 10 min after sham stimulation, continuous TBS (cTBS; LTD-like) or an identical block of iTBS. Corticospinal plasticity was assessed by recording changes in motor evoked potential (MEP) amplitude.
Results: In young subjects, priming with cTBS (cTBS + iTBS) resulted in larger MEPs than priming with either iTBS (iTBS + iTBS; $P = 0.001$) or sham (sham + iTBS; $P < 0.0001$), while larger MEPs were seen following iTBS + iTBS than sham + iTBS ($P < 0.0001$). In old subjects, the response to iTBS + iTBS was not different to sham + iTBS ($P > 0.9$), whereas the response to cTBS + iTBS was reduced relative to iTBS + iTBS ($P = 0.02$) and sham + iTBS ($P = 0.04$).
Conclusions: Priming TBS is ineffective for modifying M1 plasticity in older adults, which may limit the therapeutic use of priming stimulation in neurological conditions common in the elderly.

1. Introduction

It is now well recognised that the neural architecture of the human brain is not static, but instead demonstrates extensive and remarkable flexibility. This flexibility, referred to as neuroplasticity, has been shown to represent a fundamental component of learning and memory [1,2], in addition to being important for recovery from brain injury or damage [3]. While the mechanisms contributing to neuroplasticity are not fully understood, an extensive body of literature has identified several contributing factors, including alterations to inhibitory neurotransmission [4] and unmasking of latent neuronal pathways [5]. However, animal research has shown that long-term potentiation (LTP) or depression (LTD) of synaptic strength is particularly important (see [6]). These findings have been supported in humans by studies using non-invasive brain stimulation (NIBS), a technique able to induce and measure LTP- and LTD-like changes within the human brain [7].

Some of the best evidence for the functional importance of neuroplasticity is seen in situations where plasticity is altered. While such changes are often associated with central nervous system damage or pathology [8–10], they may also be observed in otherwise healthy individuals. For example, several lines of

Abbreviations: cTBS, continuous TBS; EMG, electromyography; FDI, first dorsal interosseous; iTBS, intermittent TBS; LTD, long-term depression; LTP, long-term potentiation; MEP, motor evoked potential; mGluR, metabotropic glutamate receptor; M_{max}, maximum M-wave; MMSE, mini-mental state examination; MSO, maximum stimulator output; NIBS, non-invasive brain stimulation; NMDA, N-methyl-D-aspartate; RMT, resting motor threshold; rTMS, repetitive TMS; TBS, theta burst stimulation; TMS, transcranial magnetic stimulation; PAS, paired associative stimulation.

* Corresponding author. School of Medicine, The University of Adelaide, Adelaide, South Australia, 5005, Australia.
E-mail address: john.semmler@adelaide.edu.au (J.G. Semmler).

http://dx.doi.org/10.1016/j.brs.2017.01.003
1935-861X/

evidence suggest that neuroplastic capacity is reduced by healthy ageing. This includes reports that older adults demonstrate a reduced potentiation of corticospinal excitability following the application of plasticity-inducing NIBS paradigms [11–14], as well as following a period of motor training [15,16]. The functional importance of neuroplasticity suggests that this reduced response in older adults may contribute to the motor deficits commonly associated with the ageing process. An improved understanding of age-related reductions in plasticity, as well as the development of interventions able to ameliorate this deficiency, therefore represents an important area of neuroscience research.

The response to a plasticity-inducing paradigm is known to be affected by a number of factors, including time of day, attentional focus and genetics (see [17]). However, one major influence on plasticity induction is the level of previous activity within the area targeted by the intervention [18]. A history of increased synaptic activity within the target area can reduce or even reverse the expected response to a plasticity inducing NIBS paradigm. This type of interaction is referred to as metaplasticity and has been suggested to represent a means of homeostatically moderating changes in synaptic excitability in order to avoid the potentially destabilising influence of run-away potentiation/depression that LTP and LTD are inherently capable of producing (see [19]). However, this mechanism has also formed the basis for interventions aiming to manipulate the plasticity response by first 'priming' synapses of the target area. This approach has been studied in young subjects using a number of different NIBS techniques, with the findings suggesting that the resulting neuroplastic modifications are stronger, longer lasting and more stable [20]. However, it is currently unknown if priming stimulation can be used to compensate for age-related reductions in the plasticity response to NIBS interventions.

Therefore, the aim of the current study was to investigate the efficacy of priming stimulation in healthy elderly adults. This was accomplished by comparing the response to paired blocks of a NIBS protocol (theta burst stimulation, TBS [21]), separated by a 10 min rest period, between young and old adults. In keeping with homeostatic metaplasticity mechanisms, we hypothesised an increase in LTP-like plasticity when the induction protocol was primed by a prior LTD-like plasticity protocol. However, based on previous observations of age-related declines in the response to TBS [13], we also expected that this effect would be reduced in elderly adults.

2. Methods

16 young (mean ± SD, 22.3 ± 1.0 years; 11 females) and 16 old (mean ± SD, 70.2 ± 1.7 years; 9 females) subjects were recruited from the university and wider community to participate in the current study. Exclusion criteria included a history of neurological or psychiatric disease, or current use of psychoactive medication (sedatives, antipsychotics, antidepressants etc.). Hand preference and laterality were assessed using the Edinburgh Handedness Inventory [22], while cognitive impairment was assessed using the mini-mental state examination (MMSE [23]). All experimentation was approved by the University of Adelaide Human Research Ethics Committee and conducted in accordance with the declaration of Helsinki. Each subject provided written, informed consent prior to participation.

2.1. Experimental arrangement

Subjects were required to attend the laboratory on 3 occasions separated by at least 1 week. To avoid the confounding influence of diurnal variations in cortisol on the induction of cortical plasticity [24], all experiments were conducted between 11 a.m. and 4 p.m., with repeat sessions within each subject always occurring at the same time of day. During each experimental session, subjects sat in a chair with their right arm abducted approximately 45° at the shoulder, and right forearm and hand resting on a cushion placed next to them. Surface electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscle of the right hand using two Ag–AgCl electrodes placed approximately 2 cm apart in a belly-tendon montage and a strap placed around the wrist to ground the electrodes. EMG signals were amplified (x 1000) and band-pass filtered (20 Hz–1 kHz) using a CED 1902 signal conditioner (Cambridge Electronic Design Co. Ltd, Cambridge, UK), before being digitized at 2 kHz using a CED 1401 analogue-to-digital converter (Cambridge Electronic Design Co. Ltd, Cambridge, UK) and stored on a computer for later off-line analysis.

2.2. Experimental procedures

The experimental protocol is shown in Fig. 1. Within each session, all baseline and post-test TBS measures were the same. However, the type of intervention differed between sessions.

2.2.1. Maximal compound muscle action potential (M_{max})

In a subset of subjects (13 young, 13 old), electrical stimulation applied at the wrist was used to stimulate the ulnar nerve, generating maximal compound muscle action potentials within FDI. Stimuli were applied using a constant-current stimulator (DS7AH, Digitimer, UK) and bipolar surface electrodes with the cathode positioned distally. Each stimulus was a square wave pulse of 100 μs duration and intensity set at 120% of that required to produce a maximal response in FDI (i.e. 120% M_{max}). M_{max} was obtained by averaging the responses to 5 stimuli delivered at the beginning of each experimental session.

2.2.2. Transcranial magnetic stimulation (TMS)

TMS was applied to the hand area of the left primary motor cortex using a figure-of-eight coil connected to a Magstim 200[2] magnetic stimulator (Magstim, Dyfed, UK). The coil was held tangentially to the scalp at an angle of 45° to the sagittal plane, with the handle pointed backwards and laterally, producing an anteriorly directed current flow in the brain. The coil was positioned on the scalp over the location producing an optimum response in the relaxed FDI muscle. This location was marked on the scalp for reference and continually checked throughout the experiment. TMS was delivered at 0.2 Hz for all measurements.

Resting motor threshold (RMT) was defined as the minimum stimulus intensity producing an MEP amplitude $\geq$ 50 μV in at least 3 out of 5 trials while the right FDI was completely relaxed. RMT was assessed at the beginning of each experimental session and expressed as a percentage of maximum stimulator output (MSO). Corticospinal excitability was assessed by investigating changes in the amplitude of the motor evoked potential (MEP) recorded during complete relaxation of FDI. At baseline, the stimulus intensity was set at the level producing an MEP with peak-to-peak amplitude of ~1 mV when averaged over 20 trials. This intensity was then used to record all subsequent blocks of MEPs. Following baseline measurements, 10 MEPs were recorded between the first (priming TBS) and second (test TBS) blocks of TBS (referred to as post-priming TBS MEPs), and then every 10 min for the 60 min following test TBS (referred to as post-test TBS MEPs).

2.2.3. Theta burst stimulation (TBS)

Theta burst stimulation was applied to the hand area of the left primary motor cortex using a Super Rapid magnetic stimulator (Magstim, Dyfed, UK) connected to an air-cooled figure-of-eight coil. The stimulation protocol was the same as that originally described by Huang et al. [21], consisting of TMS triplets applied at