Neurobiology of Aging 51 (2017) 31–42

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Preconditioning tDCS facilitates subsequent tDCS effect on skill acquisition in older adults

Hakuei Fujiyama [a,b,*], Mark R. Hinder [c], Azadeh Barzideh [b], Charis Van de Vijver [b], Andreea C. Badache [b], Maria Nathalya Manrique-C [b], Paola Reissig [c], Xue Zhang [d], Oron Levin [b], Jeffery J. Summers [c,e], Stephan P. Swinnen [b,f]

[a] *Action and Cognition Laboratory, School of Psychology and Exercise Science, Murdoch University, Perth, Australia*
[b] *Motor Control Laboratory, KU Leuven, Research Center of Movement Control and Neuroplasticity, Group Biomedical Sciences, Leuven, Belgium*
[c] *Human Motor Control Laboratory, School of Medicine, University of Tasmania, Hobart, Australia*
[d] *Neural Control of Movement Laboratory, ETH, Zurich, Switzerland*
[e] *Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK*
[f] *KU Leuven, Leuven Research Institute for Neuroscience & Disease (LIND), Leuven, Belgium*

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 8 November 2016
Accepted 19 November 2016
Available online 1 December 2016

Keywords:
Healthy aging
Skill acquisition
Homeostatic metaplasticity
Transcranial direct current stimulation
Primary motor cortex

ABSTRACT

Functional motor declines that often occur with advancing age—including reduced efficacy to learn new skills—can have a substantial impact on the quality of life. Recent studies using noninvasive brain stimulation indicate that priming the corticospinal system by lowering the threshold for the induction of long-term potentiation–like plasticity before skill training may facilitate subsequent skill learning. Here, we used "priming" protocol, in which we used transcranial direct current stimulation (tDCS) applying the cathode over the primary motor cortex (M1) before the anode placed over M1 during unimanual isometric force control training ($FORCE_{training}$). Older individuals who received tDCS with the cathode placed over M1 before tDCS with the anode placed over M1 concurrent with $FORCE_{training}$ showed greater skill improvement and corticospinal excitability increases following the tDCS/$FORCE_{training}$ protocol compared with both young and older individuals who did not receive the preceding tDCS with the cathode placed over M1. The results suggested that priming tDCS protocols may be used in clinical settings to improve motor function and thus maintain the functional independence of older adults.

1. Introduction

Aging is often accompanied by a decline in many domains of motor function including slowing of movements (e.g., Ketcham and Stelmach, 2001), declined movement accuracy and stability (e.g., Fujiyama et al., 2013; Heuninckx et al., 2004), and reduced ability to learn new skills (e.g., Swinnen et al., 1998; Wishart and Lee, 1997). It has been suggested that neurophysiological changes that occur with advancing age underpin these motor declines (Levin et al., 2014). Moreover, reduced capacity for neuroplasticity with advancing age has been observed in older adults which can contribute to behavioral impairments in the absence of significant pathology (Burke and Barnes, 2006). Interestingly, despite mounting evidence indicating that older adults undergo neurophysiological changes and show a decline in motor function, the ability to acquire new skills in later life is, at least, to some extent, preserved (Voelcker-Rehage, 2008).

Previous studies have shown that the functional organization of the primary motor cortex (M1) in adult mammals is constantly reshaped by behavioral demands to learn new motor skills (e.g., Nudo et al., 1997). This reorganization, or neuroplasticity, is mediated, at least in part, by activity or use-dependent processes that involve synaptic modification inducing either long-term potentiation (LTP) or long-term depression (LTD) of synapses (Sanes and Donoghue, 2000). As well as the brain reorganization that occurs in response to activity or use (use-dependent neuroplasticity), there is good evidence to suggest that noninvasive brain stimulation (NIBS) also induces similar neuroplastic changes in the central nervous system, at least for a short period of time (<1 hr; Nitsche et al., 2008). Transcranial direct current stimulation (tDCS) is one such form of NIBS which involves the application of a weak electrical current to the scalp, and that has been extensively used to mimic LTP- and LTD-like processes in humans (e.g., Nitsche and Paulus, 2001). tDCS is thought to induce shifts in transmembrane neuronal potentials and, thus, influence corticospinal excitability

* Corresponding author at: Action and Cognition Laboratory, School of Psychology and Exercise Science, Murdoch University, 90 South Street, Murdoch, Western Australia 6500, Australia. Tel.: +61 08 9360 2879; fax: +61 08 9360 6491.
E-mail address: H.Fujiyama@murdoch.edu.au (H. Fujiyama).

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2016.11.012

(Nitsche et al., 2008). It is assumed that the neuronal changes associated with the persisting effects of tDCS are analogous to activity-dependent synaptic plasticity (i.e., LTP and LTD; Di Lazzaro et al., 2012) which is N-methyl-D-aspartate (NMDA) receptor dependent (Di Lazzaro et al., 2012). The application of tDCS over the M1 elicits changes in corticospinal excitability in a polarity specific manner: motor-evoked potentials (MEPs) evoked by transcranial magnetic stimulation (TMS) are potentiated by tDCS with the anodal electrode placed over M1 and suppressed by tDCS with the cathodal electrode placed over M1 (Nitsche and Paulus, 2000), suggesting the facilitatory and inhibitory nature of anodal and cathodal under the stimulation site, respectively.

Despite the abundance of research reporting tDCS effects on plasticity, in recent years large inter-individual variability in response to tDCS has been recognized (Datta et al., 2012; Fujiyama et al., 2014; Puri et al., 2015; Wiethoff et al., 2014). For example, Fujiyama et al. observed that approximately 20% of the participants (8 out of 39) did not show the expected corticospinal excitability increase following tDCS with anode placed over M1. Of particular relevance is a recent paper that considered responses to tDCS in 54 healthy older (mean age = 66.9 years; Puri et al., 2015), in which participants underwent 2 sessions receiving tDCS with the anode placed over M1 with different stimulation durations (i.e., 10 minutes and 20 minutes). Less than half (46%) of older adults exhibited the expected potentiation in corticospinal excitability in both sessions.

One plausible explanation for the large interindividual variability in response to NIBS is the history of synaptic activity before the stimulation (Ridding and Ziemann, 2010). It appears that the human motor system is regulated by homeostatic metaplasticity mechanisms (Muller et al., 2007; Murakami et al., 2012; Siebner et al., 2004). According to the Bienenstock-Cooper-Munro theory of homeostatic metaplasticity (Bienenstock et al., 1982), plasticity at a synapse is bidirectional, resulting in either LTP or LTD. The threshold for the induction of LTP versus LTD at synapses varies according to the history of postsynaptic activity. In the presence of low previous activity of the postsynaptic neuron, the synaptic modification threshold decreases, favoring the induction of LTP over LTD. In contrast, if the previous postsynaptic activity was high, the synaptic modification threshold increases which leads to the increased probability of the occurrence of LTD over LTP (Bienenstock et al., 1982). It is apparent, therefore, that the history of postsynaptic activity can affect the response to NIBS techniques.

Based on the aforementioned theory, an interesting strategy to facilitate motor skill acquisition is to decrease the threshold for induction of LTP-like synaptic plasticity by lowering neuronal activity in the M1 before commencing a motor training regime (Ziemann et al., 2004). Using this idea, a recent study by Christova et al. (2015) revealed that the application of tDCS with the cathode placed over M1 before tDCS with the anode placed over M1 resulted in greater improvement in motor performance (conducted simultaneously with the tDCS with the anode placed over M1) relative to the improvement in motor function observed when tDCS with the anode placed over M1 and motor training were proceeded by sham stimulation. tDCS with placing anode over M1 during skill acquisition is thought to facilitate the neuronal firing rates in task-specific networks imposing additional strengthening of specific synaptic connections (Fritsch et al., 2010) and additional application of tDCS with the cathode placed over M1 before the tDCS with the anode placed over M1 during task acquisition is beneficial for skill acquisition by lowering the synaptic modification threshold favoring the induction of LTP. Thus, the combination of 2 functionally opposite tDCS protocols appeared to promote larger gains in motor performance, possibly due to homeostatic metaplasticity. However, the utilization of 2 mechanistically opposing tDCS protocols has never been investigated in the context of aging. There is good evidence to suggest that the responsiveness to tDCS (in terms of improving motor behavior) is greater in older adults compared with younger adults (Hummel et al., 2010; Zimerman et al., 2013), and corticospinal excitability increases following tDCS with the anode placed over M1 are comparable between young and older adults (Fujiyama et al., 2014). As such, tDCS may have substantial potential as a clinical intervention tool to facilitate motor learning in older adults thereby potentially maintaining functional independence. In this study, we investigated the effect of tDCS with the anode placed over M1 primed with tDCS with the cathode placed over M1 on motor learning and neurophysiological changes in older adults. Based on the homeostatic metaplasticity hypothesis, we expected that tDCS with the cathode placed over M1 followed by tDCS with the anode placed over M1 would result in a greater skill gain and larger neurophysiological changes (e.g., greater increases in corticospinal excitability) relative to tDCS with the anode placed over M1 in the absence of preconditioning by tDCS with the cathode placed over M1 in both young and older adults. However, we expected that the benefit of the priming protocol (downregulation of corticospinal excitability) on subsequent skill acquisition and neurophysiological change would be limited in older adults since the ability to flexibly modulate synaptic activity declines with advancing age (Eisen et al., 1996).

2. Methods

2.1. Participants

Thirty healthy young (16 females, $M = 24.8$, standard deviation [SD] = 3.0 years) and 30 healthy older volunteers (15 females, $M = 68.0$, $SD = 4.6$ years) were recruited for the study. All participants were right-handed, as assessed by the Edinburgh handedness questionnaire Oldfield 1971 (scores 85.8% ± 13.3%). Participants were screened for cognitive impairments using the Montreal Cognitive Assessment (Nasreddine et al., 2005), with all participants scoring within the normal range (≥26). Screening for contraindications of tDCS and TMS (metal or electronic implants, chronic medical conditions, neurological conditions, substance abuse, skin irritations, and pregnancy) was conducted before participation. A pre-experiment questionnaire revealed that no participants had any known sensorimotor or neurological deficits. The protocol was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the local ethical committee of KU Leuven, Belgium. Written informed consent was obtained from all participants before participation. Participants were financially compensated after the study.

2.2. Experimental design

The study consisted of 2 sessions conducted on 2 consecutive days at the same time of the day. Fig. 1 outlines the experimental procedure. The first session involved 8 blocks of motor training (see Section 2.5) with neurophysiological and behavioral assessments conducted before and after the training. The second session served as a retention test to examine behavioral performance and neurophysiological measures. In the first session, participants were randomly allocated to either a tDCS with the cathode placed over M1 followed by tDCS with the anode placed over M1 (C-A) group (15 young, 9 females, $M = 25.3$, $SD = 2.7$ years; 15 older, 8 females, $M = 68.0$, $SD = 3.2$ years) or a sham followed by tDCS with the anode placed over M1 (S-A) group (15 young, 7 females, $M = 25.5$, $SD = 3.3$ years; 15 older, 7 females, $M = 68.0$, $SD = 5.7$ years). The C-A group received tDCS with the cathode placed over M1 for 10 minutes at 1.5-mA intensity before the 26 minutes