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Transcranial Direct Current Stimulation Based Metaplasticity Protocols in Working Memory

Sandra Carvalho [a,b,c,*], Paulo S. Boggio [d], Óscar F. Gonçalves [a,b,c,e], Ana Rita Vigário [a], Marisa Faria [a], Soraia Silva [a], Gabriel Gaudencio do Rego [d], Felipe Fregni [b,c], Jorge Leite [a,b,c]

[a] Neuropsychophysiology Laboratory, CIPsi, School of Psychology (EPsi), University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[b] Spaulding Neuromodulation Center, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[d] Social and Cognitive Neuroscience Laboratory and Developmental Disorders Program, Center for Health and Biological Sciences, Mackenzie Presbyterian University, 01241-001 Sao Paulo, Brazil
[e] Department of Counseling and Applied Educational Psychology, Bouvé College of Health Sciences, Northeastern University, Boston, USA

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Background: It has been already shown that delivering tDCS that are spaced by an interval alters its impact on motor plasticity. These effects can be explained, based on metaplasticity in which a previous modification of activity in a neuronal network can change the effects of subsequent interventions in the same network. But to date there is limited data assessing metaplasticity effects in cognitive functioning.
Objectives: The aim of this study was to test several tDCS-based metaplasticity protocols in working memory (WM), by studying the impact of various interstimulation intervals in the performance of a 3-back task.
Methods: Fifteen healthy volunteers per experiment participated in this study. Experiments 1 and 2 tested an anodal tDCS-induced metaplasticity protocol (1 mA, 10 + 10′) with 3 interstimulation intervals (10, 30, and 60 min). Experiment 3 determined the effects of a similar protocol—with a 10-min interval between two sessions of cathodal tDCS or anodal plus cathodal tDCS (1 mA, 10 + 10′).
Results: Two consecutive sessions of anodal tDCS delivered with a 10 min interval between them did not improve WM performance ($P = .095$). This effect remained the same if the interval was increased to 30 or 60 min. In contrast, when a 10 min interval was given between two consecutive cathodal tDCS sessions, performance in the 3 back task increased ($P = .042$).
Conclusions: These results suggest that the polarity effects of tDCS on working memory are dependent on the previous level of activity of the recruited neural population.
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Introduction

Electrical stimulation has been used as a tool to modulate human plasticity. Our understanding of how electrical stimulation shapes the organization of the human brain has guided the development of cognitive enhancement protocols. One cognitive domain that is modulated by electrical stimulation is working memory (WM). WM is defined as the ability to maintain and manipulate information online for short periods [1,2]. Several studies have investigated the effects of various transcranial direct current stimulation (tDCS) protocols on working memory [3–7].

In tDCS, a weak constant electric current is used with at least 2 electrodes: anodal (positive pole) and cathodal (negative pole). Anodal tDCS is associated with a depolarizing effect on the neural membrane, whereas cathodal tDCS hyperpolarizes it [8,9]. This initial effect on the properties of the neuronal membrane leads to secondary changes in plasticity by increasing decreasing spontaneous neuronal activity [10]. It is possible to enhance WM using

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* Corresponding author. Neuropsychophysiology Laboratory, CIPsi, School of Psychology (EPsi), University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.

E-mail address: sandrarc@psi.uminho.pt (S. Carvalho).

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anodal tDCS over the dorsolateral prefrontal cortex (DLPFC) [3,6,7,11]. These effects are time-dependent and can persist for at least 30 min after tDCS has ended [5].

Recently, the effects of tDCS on cortical plasticity have been shown to depend on the duration and interstimulation interval. Monte-Silva et al. noted that delivering tDCS in consecutive sessions that are spaced by an interval alters its impact on motor plasticity [12]. These effects can be explained, based on metaplasticity in which a previous modification of the activity in a neuronal network can impact the effects of subsequent interventions to the same network [13]. Thus, tDCS allows us to assess the effects of metaplasticity if a second session of tDCS is delivered during the effects of the previous one. To this end, we were interested in determining these effects using working memory as a surrogate for cognitive plastic changes.

In order for metaplasticity to occur, tDCS stimulation needs to be paused and the second tDCS session (i.e., conditioning tDCS) needs to be delivered during the after effects of the first one (i.e., pre-conditioning tDCS).

Our aim was to examine the effects of metaplasticity on working memory by studying the effects of consecutive sessions of tDCS with various interstimulation intervals. Experiments 1 and 2 tested continuous anodal tDCS and discontinuous anodal tDCS using several interstimulation intervals (i.e. 10, 30 and 60 min). Experiment 3 tested a similar protocol with an interstimulation interval, instead using cathodal tDCS as pre-conditioning and 2 polarities as conditioning stimulation: anodal or cathodal tDCS. We hypothesized that introducing an interval between 2 short sessions of anodal tDCS would enhance its impact on working memory—an effect that could be characterized by potentiation or temporal summation, similar to what is observed with cathodal tDCS in the motor cortex [12].

Methods

Participants

Forty-five healthy volunteers (15 per experiment) were enrolled in this study. In experiment 1, 15 undergraduate students from University of Minho volunteered (12 females; 20.2 ± 2.7 years old). Experiment 2 comprised 15 undergraduate students from Mackenzie University (8 females; 21.5 ± 2.6 years old). In experiment 3, 15 undergraduate students from University of Minho volunteered (14 females; 20.1 ± 1.8 years old).

All participants were right-handed and healthy, with normal or corrected-to-normal visual acuity and no current or past history of neurological or psychiatric disorders. Participants were excluded if any medication or psychotropic drugs had been used in the 4 weeks prior to the study. Participants were advised to avoid alcohol, cigarettes, and caffeinated drinks on the day of the experiment, and none reported fatigue due to insufficient sleep.

All participants gave written informed consent prior to study inclusion. The study was approved by the local ethics committee and was conducted per the Declaration of Helsinki.

Design

Each experiment consisted of 3 sessions, with an intersession interval of at least 1 week. The experimental design of each session comprised 3 blocks: 1) pre-conditioning tDCS; 2) Interval; and 3) Conditioning tDCS, with the experimental task on the last 5 min. The 3 experiments are described below (Fig. 1):

- Experiment 1 (10-min interval): The goal of this experiment was to determine the effects of a 10-min interval (10′i) between the first and second consecutive anodal tDCS sessions compared with 2 control conditions. The 3 conditions were: 1) anodal tDCS-10′i-anodal tDCS (10-min interval with anodal tDCS), 2) rest – anodal tDCS-anodal tDCS (control condition 1, no interval with anodal tDCS), and 3) rest – sham tDCS-sham tDCS (control condition 2, sham tDCS only).
- Experiment 2 (30- and 60-min intervals): The goal of this experiment was to test longer intervals between consecutive anodal tDCS sessions. The design was the same as in experiment 1, except with 30′ and 60′ intervals and the respective sham conditions. Namely, the conditions were: 1) anodal tDCS – 30′i – anodal tDCS (30-min interval with anodal tDCS), 2) sham tDCS – 30′i – sham tDCS (control condition 1, sham tDCS only with a 30′ interval), 3) anodal tDCS – 60′i–anodal tDCS (60-min interval with anodal tDCS), 2) sham tDCS – 60′i – sham tDCS (control condition 2, sham tDCS only with a 60′ interval). Two sham conditions were included in order to increase blinding, due to the different interstimulation interval.
- Experiment 3 (10-min interval with cathodal stimulation): In this experiment, we examined whether cathodal tDCS in the pre-conditioning block alters the effects of metaplasticity, testing 3 conditions: 1) cathodal tDCS-10′i-anodal tDCS (10-min interval with cathodal and anodal), 2) cathodal tDCS-10′i-cathodal tDCS (10-min interval with cathodal and cathodal), and 3) sham tDCS-10′i-sham tDCS (control condition with sham tDCS) (Fig. 1).

Task

The 3-back task was adapted from Fregni et al. [3], in which participants were instructed to respond “Y” (yes) if a letter that appeared on the center of a screen (i.e., target) was the same as the one that flashed 2 letters earlier or “N” (no) if it was not. There were 30 “Y” and 165 “N” responses, totaling 195 trials. Each letter appeared for 30 ms, separated by a 2000-ms intertrial interval (ITI). The order of the letters was randomized, thus reshuffling the actual targets between sessions and preventing memorization effects to be carried over from one tDCS session to the next. This was done in a manner that for each experiment, the 195 trials sequence was randomly generated. Therefore, the 30 “Y” targets were generated for that specific sequence, based on the 3 trials earlier match rule.

Transcranial direct current stimulation (tDCS)

tDCS (1 mA) was applied using 35-cm^2 saline-soaked electrode sponges. For experiments 1 and 3, an Eldith DC Stimulator Plus (Neuroconn, Germany) was used, whereas a locally developed DC stimulator was used for experiment 2 (contact psboggio@gmail.com for technical details).

Each experiment had a within-subject design, in which all participants were subjected to 3 (4 in experiment 2) tDCS conditions. The active electrode (anode or cathode) was placed over the left DLPFC, and the return electrode (cathode or anode) covered the contralateral supraorbital area (F3 and Fp2 electrode sites, respectively) [14]. Anodal or cathodal tDCS (1 mA) were applied in blocks of 10 min (with a 15-s ramp up and down), with the exception of the no interval anodal tDCS condition (experiment 1), which was applied for 20 min consecutively (with 15-s ramp up and down). Sham tDCS was applied with 1 mA intensity during 15 s (with 15-s ramp up and down). Therefore the total duration of active tDCS (1 mA) was 20 min (i.e. pre-conditioning plus conditioning) and 30 s for sham tDCS (i.e. pre-conditioning plus conditioning). The conditioning tDCS in the task block began 5 min before the actual task and continued for the entire duration of the task (5 min).

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