Prolonged Corticomotor Homeostatic Plasticity - Effects Of Different Protocols And Their Reliability

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Homeostatic plasticity complements synaptic plasticity by stabilizing neural activity within a physiological range. Human homeostatic plasticity has been investigated using two blocks of non-invasive brain stimulation (NIBS) with an interval of no stimulation in-between blocks, and the homeostatic response captured by changes in M1 excitability by quantifying the amplitude of motor-evoked potentials (MEPs) [1]. A homeostatic response of reduced MEPs amplitude when a block of excitatory stimulation is primed by another block of excitatory stimulation has been demonstrated in humans [2–4]. Conversely, a homeostatic response of increased MEPs amplitude has been observed when a block of inhibitory stimulation is primed by another inhibitory block [4,5]. An impaired homeostatic response has been detected in subjects with migraine, and chronic low back pain [2,6]. It is possible that homeostatic plasticity mechanisms are affected over time, throughout the development of the disease [2,3]. To date, studies investigating homeostatic plasticity have been conducted using cross-sectional designs [1,7]. In order to investigate long-term homeostatic plasticity changes, it is important to verify the reliability of homeostatic plasticity induction protocols. No studies have investigated the reliability of protocols using two blocks of inhibitory transcranial direct current stimulation (tDCS), and little is known about the reliability of the duration of corticomotor excitability changes post-homeostatic plasticity induction. Here we present the duration of homeostatic response and the test-retest reliability of corticomotor excitability changes, provoked by two homeostatic plasticity induction protocols (cathodal tDCS and anodal tDCS).

A sample size calculation was conducted ($\alpha = 0.05$, $\beta = 0.80$, effect size = 0.48 based on MEPs comparisons reported in previous studies [2,3]) resulting in a needed sample size of 13 participants. To account for differences in study designs and possible dropouts, recruitment of 15 participants for each experiment was targeted. Participants were recruited continuously for both experiments and data was collected from fifteen participants for cathodal tDCS experiment (6 males, 25.3 ± 3.8 years) and fifteen participants for anodal tDCS experiment (4 males, 24.6 ± 4.24 years). Each participant took part in two experimental sessions on the same time on two consecutive days. The corticomotor excitability in response to the homeostatic plasticity protocol (cathodal-tDCS or anodal-tDCS) was measured before and immediately post homeostatic plasticity induction (time point 0-min), and then every 10 minutes for 70 minutes (ethical approval VN-20190069).

Homeostatic plasticity was induced in the left M1 using tDCS applied for 7 minutes followed by 3 minutes of no stimulation and another block of 5 minutes of tDCS [2–4]. A constant current of 1 mA was transmitted through the tDCS system (Starstim 32, Neuroelectrics, Barcelona, Spain), using two 3.14 cm^2 Ag/AgCl gelled electrodes placed into a neoprene cap corresponding to the international 10/10 EEG system (NE056 Headcap R, Neuroelectrics, Barcelona, Spain). For cathodal-tDCS, the cathode was placed at C3 and the anode placed at Fp2. In the anodal-tDCS experiment, the anode was placed at C3 and the cathode was placed at Fp2.

A magnetic stimulator (Magstim 200^2, Magstim Company, Whitland, UK) was used to deliver monophasic pulses, using a focal figure-of-8 coil. A stimulation intensity of 120% of the resting motor threshold was used for MEP assessment of the right first dorsal interosseous muscle. Peak-to-peak amplitude was extracted for each MEP and averaged across 15 sequential MEPs recorded at each time point (5–7 s inter-stimulus intervals). The averaged MEPs were used for analysis. All TMS methods were conducted according to the TMS guidelines [8].

MEPs at all-time points were log-transformed and used for subsequent analyses. Two-way repeated measures analysis of variance (ANOVA) was conducted on MEPs with factors *Day* (Day1 and Day2) and *Time* (pre-tDCS, 0-min, 10-min, 20-min, 30-min, 40-min, 50-min, 60-min, and 70-min post-tDCS). Bonferroni corrections were used and level of statistical significance considered $p \leq 0.05$. Intra-class correlation coefficient (ICC; 3,k) and Bland–Altman methods were used for the analysis of test-retest and absolute reliability (Appendix).

Increased MEPs were observed from 10 to 30 minutes post-cathodal tDCS compared with pre-cathodal tDCS (main effect of Time $F_{3.8,\ 54.5} = 6.51$; $p < 0.001$, Fig. 1A). Main effect of Day and Day × Time interaction were not significant ($F_{1,14} = 1.22$; $p = 0.287$ and $F_{8,112} = 0.343$; $p = 0.947$, respectively). Reduced MEPs were observed from 10 to 40 minutes post-anodal tDCS compared with pre-anodal tDCS (main effect of Time $F_{3.6,51.2} = 8.9$; $p < 0.001$, Fig. 1B). Main effect of Day and Day × Time interaction were not significant ($F_{1,14} = 0.67$; $p = 0.428$ and $F_{8,112} = 1.83$; $p = 0.078$, respectively).

Excellent test-retest reliability was observed for resting motor threshold and MEP amplitudes measured pre-tDCS. Moderate-to-excellent reliability was observed for post-tDCS MEPs at each

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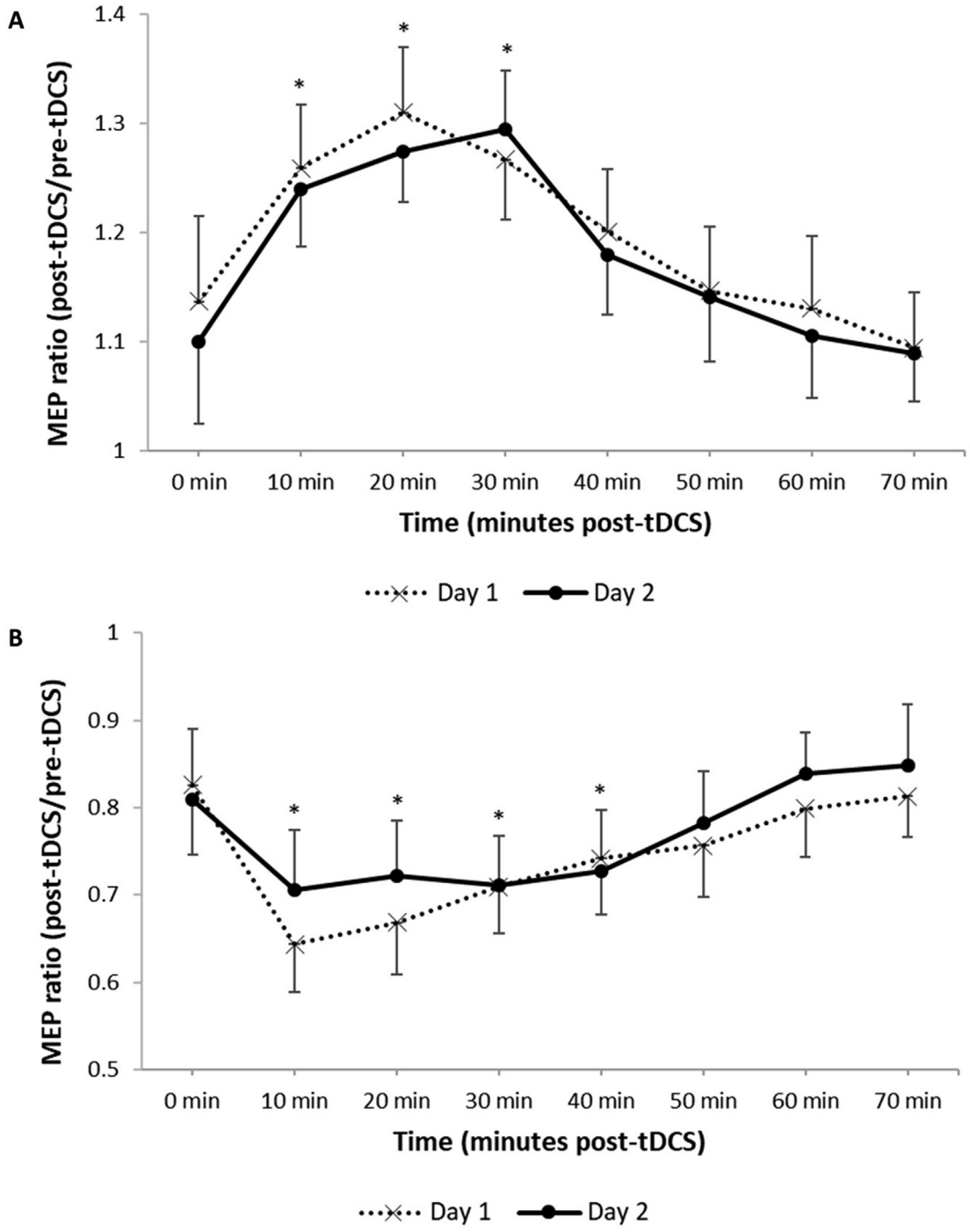

Fig. 1. Mean (+/− standard error of the mean, N = 15) of motor evoked potential (MEP) ratios for each time point at Day1 and Day2 following cathodal-tDCS (A) and anodal-tDCS (B). Significantly different MEPs compared with pre-tDCS (*, $p \leq 0.05$).

time point normalised by pre-tDCS (Table A1, Appendix). Bland-Altman analysis indicates no systematic bias when assessing RMT, pre-tDCS MEPs, and post-tDCS MEPs normalised to pre-tDCS MEP at any time point (Table A1; Fig A2 and A3, Appendix).

Results indicate that reliable homeostatic response that lasts up to 40 minutes, can be induced using two blocks of cathodal or anodal M1 tDCS with an interval of no stimulation in between blocks. Similar homeostatic responses have been identified in human M1 with a variety of homeostatic plasticity induction protocols [1,3,5]. Nonetheless, non-homeostatic responses have been observed when using similar protocols in healthy participants [9,10]. It is possible that differences between studies are due to homeostatic and non-homeostatic mechanisms that may interact when using NIBS [1]. Furthermore, differences in findings may be related to variability in responses to protocols of NIBS. Further studies are needed to investigate the relationship between homeostatic and non-homeostatic mechanisms when using NIBS to investigate homeostatic mechanism in humans.

Lasting effects of homeostatic plasticity up to 40 minutes post-tDCS can be reliably induced and assessed using tDCS over an interval of 24 hours without carry over effects. This finding is in agreement with a study investigating reliability of a homeostatic plasticity induction protocol at intervals of 2, 7, and 14 days, when using the same anodal tDCS protocol as in the present study [3]. Taken together, these findings indicate that the present protocols may be used in studies investigating homeostatic plasticity over time.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.01.017.

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