**Complexity of cathodal tDCS: Relevance of stimulation repetition, interval, and intensity**

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Since the formal introduction of transcranial direct current stimulation (tDCS), it has been exponentially used for studying and modulating brain physiology. The ability to non-invasively modulate brain physiology made opportunities for studying healthy brain functions in the hope to translate the findings into clinical populations. Yet, our knowledge about the underlying mechanisms of tDCS-induced neurophysiological modulation and cognitive effects is limited. Moreover, with the daily-increasing number of studies reporting significant effects of tDCS, there are reports of tDCS null-effects as well. One potential source of tDCS null-effects is the inter-individual variability as observed also in other neuromodulatory interventions. Furthermore, suboptimal stimulation parameters also contribute to the variability of tDCS results which are not systematically covered by the literature.

TDCS-induced neuroplasticity in the motor cortex is polarity-specific. Here, we focus on the cathodal polarity. Cathodal tDCS with standard protocols reduces cortical excitability and can induce LTD-like plasticity with sufficiently long stimulation duration. With an increasing number of studies, it is more clearly emerging that the neuroplastic effects induced by conventional protocols are not necessarily obtained by protocols with different stimulation parameters, including altered stimulation duration, intensity, and repetition rate. These parameters, which were not systematically explored until recently, add complexity to the field. Lately, however, cathodal tDCS parameters, especially stimulation intensity and duration, were systematically explored. Stimulation repetition is another important parameter of cathodal tDCS efficacy. The rationale behind this parameter is that repeated stimulation is expected to extend tDCS neuroplastic aftereffects from early-phase LTD (lasting for up to 3 h after intervention) to late-phase LTD (longer-lasting aftereffects). Repeated brain stimulation with relatively short intervals has been shown to induce late-phase LTD in animal models. In human tDCS studies, the ability of repeated stimulation protocols to induce late-phase LTD was first explored in a study that contrasted a classic cathodal tDCS protocol with doubling stimulation duration and repetition intervals shorter than 30 min (time window for inducing late-phase plasticity in animal models) or between 3 and 24 h (Monte-Silva et al. 2010). In brief, they found that none of the extended protocols induced late-phase plasticity.

The effect of repeated cathodal tDCS was further explored in the recent study by Mosayebi-Samani et al. (2020) published in the Journal of Physiology providing further insight into this parameter. The authors specifically explored the capability of repeated cathodal tDCS over the primary motor area to induce late-phase LTD. To this end, they first applied the conventional (1 mA, 15 min) and intensified/optimized (3 mA, 20 min) protocols and then repeated each protocol with short (20 min) and long (24 h) intervals in 16 healthy, right-handed volunteers. They then measured motor evoked potentials (MEPs), induced by transcranial magnetic stimulation (TMS), up to the next day evening to measure late-phase LTD.

Their major and novel findings include two main aspects: first, they found that single-repetition of both conventional and intensified protocols did not induce late-phase plasticity (after-effects lasting for longer than 3 h). The longest after-effects were observed in the single intervention of the optimized protocol and the repetition of the same protocol with 20 min interval between sessions which did not last longer than 120 min. Secondly, they found that the effects of the repeated intensified protocol were reduced with the 24 h interval. Indeed, repeated cathodal stimulation with the intensified but not conventional protocol, diminished after-effects immediately after repeated intervention with the 24 h interval in the early epoch (up to 30 min). Specifically, Mosayebi-Samani et al. (2020) found that of all the active cathodal conditions (1 and 3 mA, 1 and 3 mA with 20 min interval, 1 and 3 mA with 24 h interval), only the intensified protocol with the 24 h interval failed to significantly reduce motor cortical excitability already in the early epoch (first 30-min after-effects). Interestingly, the neuroplastic after-effects obtained from the single intervention of the intensified protocol were significantly stronger than those obtained from the repeated intensified protocol with 24 h interval at early (up to 30 min) and late (60–120 min) epochs (Mosayebi Samani et al. 2020). These results indicate that the intensified protocol with single-session repetition indeed reduced the efficacy of tDCS after-effects. This interaction of intensity and repetition in cathodal tDCS after-effects indicates complexity of cathodal stimulation and the importance of stimulation parameters for prolongation of after-effects. In what follows, we discuss these parameters in the light of Mosayebi-Samani et al. (2020) findings and also discuss the clinical significance of their findings.

**Cathodal tDCS parameters: Relevance of stimulation repetition interval**

Cathodal tDCS parameters that are investigated in recent years include stimulation intensity, duration, and repetition, with the latter parameter recently explored by Mosayebi-Samani et al. (2020). The first systematic investigation of cathodal tDCS intensity was reported a few years ago. In that study, non-linear dosage-dependent effects on motor cortical excitability were found. Specifically, 2 mA cathodal tDCS resulted in an
excitability-enhancing effect and increased MEP amplitudes, whereas 1 mA cathodal tDCS decreased corticocortical and corticospinal excitability (Batsikadze et al. 2013). Results of this study were replicated and extended by Mosayebi-Samani and colleagues in their earlier work that explored cathodal tDCS after-effects under different intensities and durations. They found that while cathodal tDCS with 1 and 3 mA induced LTD-like plasticity (decreased MEP amplitude), 2 mA-20 min stimulation induced LTP-like plasticity (enhanced MEP amplitude) (Mosayebi-Samani et al. 2019). Moreover, 3 mA-20 min cathodal tDCS showed a trend-wise larger excitability-diminishing effect compared to 1 mA stimulation introduced as the optimized/intensified protocol for inducing LTD-like plasticity. Based on these findings, they then investigated the effect of a single repetition of cathodal tDCS (induced by conventional and optimized protocols) in prolonging after-effects (Mosayebi-Samani et al. 2020), which was described in the previous section.

Mosayebi-Samani et al. (2020) also replicated and extended the results of Monte-Silva et al. (2010). In this earlier study, the authors examined different durations and repetition intervals (no break, 3 or 20 min, 3 or 24 h interval) on cathodal tDCS-induced plasticity (1 mA, 9 min) and found that repeated stimulation with short intervals (3 or 20 min) increased after-effects for up to 120 min, whereas repeating stimulation 3 or 24 h after the first intervention abolished after-effects. Mosayebi-Samani et al. (2020) extended this by testing 3 mA cathodal stimulation (optimized protocol) and showed that repetition with a 24 h interval reduced the efficacy of the protocol, as after-effects were abolished in this specific intervention. Taken together, these results suggest that stimulation interval might be a more relevant contributing factor in prolongation of cathodal tDCS after-effects, than stimulation intensity. This finding, although delivers crucial information about cathodal tDCS repetition effects, is limited to single-repetition effects of cathodal stimulation. Multiple repetitions with different intervals need to be explored in order to provide a more comprehensive picture about the relevance of the repetition parameter in cathodal tDCS. It is likely that multiple repetitions of cathodal stimulation differentially affect prolongation of after-effects, as shown by animal studies (Huang et al. 2004), which is an important open question for future studies.

The importance of intervention interval has been recently documented in other plasticity-inducing interventions such as physical exercise. Recently, it was shown that different protocols of physical exercise, which is tightly related to hippocampal plasticity, differentially affect memory consolidation. Interestingly, short intervals of uninterrupted rest after learning increased the likelihood of remembering at a later date and moderate exercises improved memory performance the most (Pyke et al. 2020). This indicates that the underlying physiology of brain neuroplasticity, whether induced by tDCS or other interventions, might not follow a linear relationship between intervention intensity, duration and repetition rate.

Clinical significance

From a clinical standpoint, stimulation protocols are required to produce after-effects lasting for days or weeks. This is usually assumed to be achieved by either prolonging stimulation duration or repetition of stimulation. Mosayebi-Samani et al. (2020) explained the reduced efficacy of the intensified protocol with the long interval, with homeostatic effects. In other words, the plasticity induced by the first intervention might make it more difficult for the second intervention to induce identically directed effects because of the altered brain state due to the first intervention. Inducing late-phase plasticity thus requires specific protocols that do not induce counter-regulatory effects, and has yet to be identified. Candidate protocols first need to consider multiple repeated cathodal tDCS, which was not investigated in Mosayebi-Samani et al. (2020), while in clinical studies multiple tDCS sessions are routinely conducted and shown to induce cumulative effects, in accordance with animal models, which involved more than one repetition. Secondly, for these protocols it will be important to take into account that the physiology of abnormal vs healthy brains differs. Due to the state-dependency effects of neuromodulatory tDCS, the stimulation itself could have different effects in clinical populations in whom baseline brain activity, and excitability might differ from healthy humans. This could be especially important with respect to non-linear effects of cathodal tDCS. Homeostatic plasticity, which is assumed to be relevant in this behalf, is pathologically altered in specific diseases. In dystonia, patients show reduced homeostatic effects (Quartarone et al. 2005). Cathodal tDCS effects, depending on the stimulation intensity and interval, could be affected by respective altered brain physiology. Accordingly, longer-lasting LTD (in the case of cathodal tDCS) might require optimized protocols that take stimulation parameters (e.g. required intensity, repetition, stimulation interval) and patient-specific corticospinal excitability response patterns into account.

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Additional information

Competing interests

The authors conduct their PhD research projects at the Dept. Psychology & Neurosciences, Leibniz-Institut für Arbeitsforschung und Ruhr-University Bochum.
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