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Differing dose details and controlling confounding covariates in modulating motor cortex excitability by transcranial direct current stimulation

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Dear Editor

We appreciate the recent letter [1] that commented on our study of modulating motor cortex excitability by transcranial direct current stimulation (tDCS) [2]. The main point of the letter was that our reported modulation of motor evoked potentials (MEPs) by tDCS was more consistent and thus had a larger effect size than previously reported results in the literature. We agree with the author that our results are much clearer than the ones from previous studies in the field and that the standard mean difference calculated for pairwise comparisons substantially exceeds what has been previously reported. Yet, there are several underappreciated aspects that can easily explain this difference in findings.

First and foremost, one fallacy that the field has yet to fully grapple with is the idea that tDCS is a monolithic entity, leading sometimes to absurd questions such as 'Does tDCS work?" Even tDCS applied to the motor cortex can take many different forms and numerous experimental details, often neither controlled for nor reported in published analyses, that do likely matter. One aspect that has gotten lost in the debate is that we on purpose used a higher current density than the vast majority of tDCS summarized in a recent meta-analysis [3]: we used 2 mA stimulation current with 25cm^2 electrode surface area (for example only 15% employed 2mA stimulation, 12% used same or smaller electrode size, and 0% of studies used 2mA and same or smaller electrodes). This discrepancy questions whether the comparison of our results to the meta-analysis results is appropriate and illustrates the principle that stronger perturbations can reduce heterogeneity but not necessarily raw magnitude of an effect. Furthermore, the resulting electric field and thus the perturbation to neural activity is sufficiently weak for tDCS that the "stimulation dose" concept makes only limited sense since the effect of stimulation is likely mostly determined by endogenous brain activity patterns that are often neither measured nor analyzed. Yet, the field has become enamored with electric field simulations that can be helpful but are often misunderstood. Knowing the strength of the electric field (or at least having a reasonably accurate estimate from a physics simulation) may have little to do with which neurons (where in the brain) change their activity in response to stimulation. Likely more important, given the small change in membrane voltage caused by tDCS, is the state of neuron in terms of how close to firing threshold it is. While indeed our publication did not show significant correlations between the effect of tDCS and the simulated electric fields, we found significant correlations between oscillatory dynamics (pre-stimulus mu rhythms) and the response to tDCS both in terms of MEPs and transcranial magnetic stimulation (TMS) evoked potentials (TEPs). In addition, anodal tDCS increased and cathodal tDCS decreased the pre-stimulus mu rhythm oscillatory power, respectively. In other words, our report directly supports the model in which endog enous state trumps simulated electric field strength as a predictor of the response to TMS.

Second, we appreciate the statistical considerations provided by Bland [1] but would offer for consideration that a comparison across studies only makes sense if they are reasonably similar (in addition to the point above that we used a higher current density than most studies in the field). We have yet to see another study that shared the design choice we made for our study in terms of strategies to reduce heterogeneity. In that sense, we fully agree with the call for a replication, ideally across multiple sites, to provide a more final answer to the question of how tDCS modulates motor cortex excitability. We take this opportunity to summarize the unique measures we took to reduce variability. Just to offer few obvious experimental design choices that likely enhanced our chance to find a clear effect (but also reduced external validity): we severely restricted participant age, we only recruited males, we used individual 3T MR scans for neuronagivation, we kept the time of the day of the session constant, we maintained and verified the motor hotspot across sessions, we maintained and verified the TMS intensity across sessions, we asked participants to focus on the muscle twitches during stimulation, we asked participants not to close their eyes during stimulation, we applied the tDCS electrodes centered on the motor hotspot, we maintained correct coil positioning in case of head movement during stimulation, and maintained coil orientation and angle during stimulation and across sessions. We do not know which of these measures were key to obtaining the result we report, but we believe that these efforts to control confounding variables would result in cleaner results.

Third, we offer that our study included numerous neurophysiological measurements of the response to the TMS pulses that elicit the MEPs. Importantly, the change in TEP amplitude both in sensor and source space correlated with the change in MEP by tDCS. By our

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detailed investigation of successful target engagement of the cortical networks that drive the motor output, we added plausibility and independent confirmation for the presence and magnitude of the effect found in our study sample.

Finally, we would like to thank Bland [1] for taking the time to respond to our paper and to meaningfully contribute to the scientific conversation.

Declaration of competing interest

FF is the lead inventor of IP filed by UNC. FF is founder, shareholder, and chief science officer of Pulvinar Neuro, which did not play any role in the writing of this article. FF has received honoraria from the following entities in the last twelve months: Sage Therapeutics, Academic Press, Insel Spital, and Strategic Innovation. SA has nothing to declare.

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References

[1] Bland NS. Is two decades of tDCS work wrong? Commentary on Ahn and Frohlich. Brain Stimul: Basic, Transl, Clin Resear Neuromodul 2021;14(2):438–9.

[2] Ahn S, Fröhlich F. Pinging the brain with transcranial magnetic stimulation reveals cortical reactivity in time and space. Brain Stimul 2021;14(2):304–15.

[3] Dissanayaka T, et al. Does transcranial electrical stimulation enhance corticospinal excitability of the motor cortex in healthy individuals? A systematic review and meta-analysis. Eur J Neurosci 2017;46(4):1968–90.

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