Letter to the editor: Is two decades of tDCS work wrong?

Dear editor,

I read with great interest the article recently published by Ahn and Fröhlich [1] reporting that 10 minutes of 2 mA transcranial direct current stimulation (tDCS) over human primary motor cortex (M1) can induce extraordinary modulations to corticospinal excitability, as indicated by changes in the amplitude of motor-evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS). The observed effects on excitability (MEP ratio; mean MEP amplitude post-/pre-tDCS) were predictive of a range of EEG measures, including mu power and cortical reactivity to TMS (TMS-evoked potentials; TEPs). The effects reported in the article are worthy of attention, not just for their magnitude, but for their place in a field so often plagued by subtle effects with large variability both between and within participants [2-4].

The experiment by Ahn and Fröhlich is well-considered for a number of reasons: a fully-repeated measures design probing the effect of tDCS across 3 double-blinded sessions (all 18 participants received anodal, sham, and cathodal tDCS; counterbalanced order), and great care was taken to reduce variability both between and within participants (e.g., 100 MEPs were elicited before and after tDCS, structural scans were acquired for electric field modelling, M1 hotspots were targeted with neuronavigation, and only male participants aged 18-35 years were recruited). The sample size—resulting in 54 analysable datasets—is highly respectable (especially considering concurrent EEG was recorded), and their study protocol was registered a priori. To further minimise MEP variability across stimuli, neuronavigation was used to track TMS pulse locations in real-time and used to verify hotspot targeting. However, all MEPs with amplitudes below 50 µV were removed (4.4 ± 7.2 of 100 MEPs), irrespective of hotspot validity.

Their effort to control multiple sources of variability was seemingly rewarded by a strong effect of tDCS on MEP ratio [$F_{2,28} = 255$, $\eta^2 = 0.906$]. Indeed, the authors themselves seem surprised by the size of this effect, stating that it is “higher than [the average] effect size (0.67) from a recent meta-analysis.” However, this statement does a disservice to the truly remarkable size of their observed effects: the value (0.67) pulled from [5] was not $\eta^2$ but rather the standardised mean difference (SMD), akin to Cohen’s $d$. Converted to SMD, Ahn and Fröhlich actually show an effect size of 3.55 for anodal tDCS (a-tDCS; relative to sham) and −4.32 for cathodal tDCS (c-tDCS; relative to sham).

To put these effects into perspective, they exist far outside the 95% confidence intervals for the SMD of a-tDCS [0.49, 0.86] and c-tDCS [−0.78, −0.39] established across studies spanning the past two decades [5]—and they were fortunate enough to observe two similarly strong effects in the one study. While the majority of research that generated these estimates likely did not control for the many factors that contribute to the large variability inherent to TMS−tDCS studies—at least to the same extent as Ahn and Fröhlich—it is surprising just how large their effects are. For example, I simulated studies with anodal and cathodal effect sizes twice their most extreme boundary value (1.72 for a-tDCS; $-1.56$ for c-tDCS), and not a single experiment from 1 million (all equivalent in sample size to Ahn and Fröhlich) generated data with within-condition variability as low as they observed.

Because their reported tDCS-induced effects on MEP ratio were so compelling, I was surprised to read that the estimated cortical field strengths (based on participants’ structural scans) failed to predict the MEP response to either a-tDCS [$r_{16} = 0.16$, $p = .53$] or c-tDCS [$r_{16} = 0.12$, $p = .62$]. This relationship has been demonstrated in datasets with much subtler group-level effects [6,7]. Similarly, I found that participants’ MEP ratios for a-tDCS did not negatively correlate with their MEP ratios for c-tDCS [$r_{16} = −1.11$, $p = .68$], which is surprising given such effects of tDCS depend so heavily on anatomical factors.

The study by Ahn and Fröhlich [1] highlights the unbelievable benefits of controlling just a few common sources of variability in TMS−tDCS studies, and challenges the view that low-intensity transcranial electric stimulation effects are weak at best [8]. For this reason, a replication of the protocol within a similarly controlled sample would be highly beneficial for the field, specifically with consideration of the impact of excluding all MEPs under 50 µV. Because this study largely challenges two decades of tDCS work (including many failed attempts to find any effect of tDCS on MEP amplitude; see [9] for a recent example using 2 mA tDCS), I hope that it receives the attention it deserves from the brain stimulation community.

Method

MEP ratios were supplied by [1]. The SMD was computed separately for the anodal and cathodal effects of tDCS on MEP ratio using the data supplied, and following the procedure in [5]. A one-way repeated measures ANOVA was performed on the MEP ratios across the three tDCS conditions (anode, sham, cathode; $F_{2,34} = 259.72$), supporting the linear mixed-effects model reported by Ahn and Fröhlich. For consistency, their F-ratio was also reported here. Pearson’s correlations for the cortical field strengths and MEP ratio for a-tDCS and c-tDCS were taken from their supplementary materials. The correlation between the MEP ratios for the two active tDCS conditions was computed using the data supplied. The simulations were performed in MATLAB, with data generated using effect sizes determined by doubling the more extreme boundary of the 95% confidence interval for a-tDCS and c-tDCS SMDs reported in [5]. The condition means and sample sizes matched those reported.
by Ahn and Fröhlich, with the outcome variable being the observed sum of the standard deviations across the three conditions (anode, sham, cathode) given the desired effect magnitudes (code supplied below). The sum of standard deviations was used to capture the experiment-specific variability across all three conditions simultaneously.

% Pop. Params: mean and sd supplied
anodeMu = 1.3217;
anodeSD = 0.0990;
shamMu = 1.0341;
shamSD = 0.0528;
cathodeMu = 0.7303;
cathodeSD = 0.0817;

% Exp. Params: doubled SMD extremes
numExp = 1000000;
numData = 18;
SD_anode = 0.5*(anodeMu - shamMu)/0.86;
SD_cathode = 0.5*(shamMu - cathodeMu)/0.78;
SD_sham = mean([SD_anode SD_cathode]);

summarySDs = zeros(numExp,3);
for exp = 1:numExp
    data = [SD_anode*randn(numData,1) + anodeMu, ...
            SD_sham*randn(numData,1) + shamMu, ...
            SD_cathode*randn(numData,1) + cathodeMu];
    summarySDs(exp,:) = std(data,1);
end

Histogram(sum(summarySDs,2))
y = ylim;
hold on
plot(ones(1,2)*sum([anodeSD shamSD cathodeSD]), [y(1) y(2)],’r-‘)

Declaration of competing interest

The author declares no conflict of interest.

Acknowledgements

My employment is funded by the Office of Naval Research (N62909-17-1-2139). For feedback on an earlier draft of this letter, I thank Dr Brendan Keane and Dr Martin Sale.

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10 February 2021
Available online 26 February 2021