Dear Recommender and Reviewers,

Thank you for the prompt and thoughtful feedback. Our responses to the comments below are in green text and any new text since the previous submission is in blue.

Sincerely,

Gavin Hsu and Lucas Parra

Dear Gavin Hsu,

Thank you for resubmitting a revision of your registered report. The reviewers had a close look at the revision and were mostly satisfied. Thus, I would like to invite a revision of your registered report by taking into account the last remaining points of the reviewer and, additionally, one more formal point: Please write in the analysis section or pilot data section whether or not the pilot data will be included in final data set for analyses of the current study or not.

> We have added the following to our Analysis Plan section:
>
> > Power analyses are based on our previous behavioral data and described in more detail in the Pilot Data section. These previous data and pilot data will not be included in the current study's data set for analysis.

Thank you for submitting your registered report to PCI-RR. We are looking forward to receive your minor revisions.

Best regards, Christina Artemenko

by Christina Artemenko, 15 May 2024 15:07
Manuscript: https://osf.io/cwb6p
version: 1.2

Review by anonymous reviewer 1, 18 Apr 2024 12:50
The authors have addressed my concerns.

Review by Charlotte Wiltshire, 15 May 2024 07:18
Comments have been addressed comprehensively. I still have a few comments, but I view these as minor and serve as suggestions, only. I look forward to seeing the results when they appear.

There is now added discussion of the null-effects reported in studies with similar designs. I appreciate the desire to not stoke more controversy! However, I do think it's an important issue to tackle. There are reports of null findings at low intensities as well as intermediate intensities. I'm unaware of any at higher intensities as used here. One prediction would be that higher intensities may facilitate the likelihood of finding an effect over and above low- and intermediate-intensities (as we suggest in Wiltshire et al., 2020). This would, in my mind, provide further justification for this work.

This is just a suggestion, feel free to leave it as is. I provide our reference as it helps me to expand on the point that I'm trying to make, but it does not need to be included in the text, of course!

"Some null results of tDCS on MEP may be explained as reversal of effects at higher intensities 28 leading to a "no man's land" at intermediate intensities[29]"

> Thank you for the suggestion. We have added these examples of null effects at lower intensities and clarified our expectation of stronger effects at higher intensities.
>
> > Studies on the effects of tDCS on motor skill learning have given mixed results[23–25], and there is skepticism around reproducibility of MEP effects of tDCS[26,27]. Some null results of tDCS on MEP may be explained as reversal of effects at increasing intensities in the range of 1 to 2 mA[28,29] leading to a "no man's land" at intermediate intensities[30]. Especially at lower intensities (1 mA), null results on learning behavior and excitability[31] have been found along with conflicting findings at 2 mA[32,33]. We hypothesize a monotonic effect of tDCS where higher intensities produce more prominent effects, but remain open to the possibility of a reversal of the effects on MEP or motor skill learning.

I'm still not completely convinced by the typing task. I still think that this represents touch-typing proficiency rather than any measure of general dexterity within the hands. Justification has been included to show a relationship between typing speed and motor learning outcomes, but I don't think this justifies conceptualising the task as a measure of baseline motor dexterity. Perhaps consider rephrasing or adding this caveat – this is a suggestion only.

> Thank you for the suggestion and we concede that it would be better not to over-generalize here. We have removed the claim that it measures baseline levels of dexterity, and now simply state:
>
> > Here we will use a baseline typing task to measure typing speed. This will be used to balance group assignments and as a covariate to control for variance across subjects.
>
> Likewise, we now removed the claim that we are controlling for dexterity:

> At the beginning of the experiment, each subject will complete a typing test to assess baseline typing speed that will serve to control for intersubject variability.

Rossi et al., (2020) will help to justify that combining tDCS with TMS is within safety limits (to an extent). This is an update from the 2009 paper already cited. See ref below, section 3.3 of paper.

> Thank you for the recommendation! We have added this reference to our discussion of TMS safety concerns:
>
> > The total number of TMS trials falls within historical safety guidelines[77] and the amount used for motor mapping[78]. The combination of TMS and tDCS is expected to be safe[79], although we are currently not aware of any prior reports on TMS with tDCS intensities used in this study.
>
> We have also added the following to the Caveats:
>
> > We are not aware of reports on lasting effects of 0.2 Hz single-pulse TMS, despite decades of research using this modality. We therefore do not not expect any interactions with the sequence learning task nor tDCS. At the same time, we cannot in theory rule out such interaction effects, as the literature has not yet seen TMS combined with the intensity levels of tDCS used here.

The analysis of the right hemisphere is listed as exploratory, but I still think there seems like a prediction here – that you will use it as a within-subject control. Therefore, an analysis plan could be added and specified in advance.

> We are not yet sure what outcomes to expect due to possible effects of intermanual transfer and diffuse electric fields, but we now propose the following possible parameters for fitting a model:
>
> > Although they may serve as a within-subject control, there may be behavioral carryover effects due to intermanual transfer[89], and the high tDCS intensities may cause parts of the left hemisphere to be stimulated. We will implement mixed-effects models that will consider tDCS intensity, left/right hemisphere, pre/post tDCS as main factors and potential interactions between these, as well as a random effect of subjects. We currently have no specific hypothesis, but we will at least observe whether there are any changes in MEP and TEP amplitude on the right hand.

I'd like to see the description of how MEPs were included/excluded included in the text (as supplementary materials, perhaps). The following text is not enough to enable replication, however the text included in the response, would be sufficient. "The average will only include trials with a detectable biphasic MEP."

We agree that transparency for replicability is important. The processing and analysis code will be made available, along with the deidentified data. We have added our text from our previous response:

> The average will only include trials with a biphasic MEP detected using the MATLAB findpeaks() function. Inclusion criteria consist of a positive peak with a minimum Peak Prominence and maximum Peak Width, followed by a negative valley with a minimum Peak Prominence and minimum Peak Width. The peak has to occur within a time window after the TMS trigger (approximately 20-50ms). There may be outliers that require refining these specific criteria, but any changes will be finalized before unblinding for the final statistical analysis.

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L. L., Cincotta, M., Chen, R., Daskalakis, J. D., Di Lazzaro, V., Fox, M. D., George, M. S., Gilbert, D., Kimiskidis, V. K., Koch, G., Ilmoniemi, R. J., Pascal Lefaucheur, J., Leocani, L., … Hallett, M. (2020). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology. https://doi.org/10.1016/j.clinph.2020.10.003

Wiltshire, C. E. E., & Watkins, K. E. (2020). Failure of tDCS to modulate motor excitability and speech motor learning. Neuropsychologia, 107568. https://doi.org/10.1016/j.neuropsychologia.2020.107568