Cerebral laterality as assessed by functional transcranial Doppler ultrasound in left-and right-handers: A comparison between handwriting and writing using a smartphone.

Notes on the revised manuscript

We would like to thank the reviewers for their continuing evaluation, which has helped us identify areas for improvement in our paper. We have made a concerted effort to address these points.

The manuscript has been updated accordingly, and we have prepared a point-by-point response (see below) where we describe how we implemented the requested changes or provide further clarification on our decisions.

Editor

Your manuscript is close to receiving in-principle acceptance but please be aware that Stage 2 acceptance is contingent on sufficient reliability being observed. While RRs are never rejected based on their main results, but they can be rejected if prospectively defined quality checks or positive controls fail to such an extent that the research question can't be answered. You may formally achieve this by setting the reliability test as a positive control at Stage 1 and passing it a condition at Stage 2.

It could be useful to require a Bayes Factor Design Analysis to establish the probability of observing results in favour of H1 vs H0 (see e.g., https://link.springer.com/article/10.3758/s13423-017-1230-y). BFDAs are very useful for establishing the futility or otherwise of a Bayesian design.

> *Authors' response:*
>
> We thank the editor for their continuing support on this Stage 1 Registered Report. We have already included reliability checks (e.g., odds-even split half reliability for all our tasks). Reliability issues are discussed in more detail below in response to Prof. Bishop's comment. Moreover, throughout this study, and from the first submission of this preregistration, we have adopted the Bayesian Factor Design Analysis for our analysis, specifically the modified Sequential Bayes Factor (SBF) design, as named by Schönbrodt and Wagenmakers (2018), i.e. the paper suggested by the editor.

Reviewer 1

Reviewer's comment 1:

I have to say that I remain unconvinced that this study is of any theoretical interest, but I am also aware that subjective judgements about importance of a research question are not regarded as a valid criterion of evaluation. The more applied point, that smartphone typing could substitute for handwriting in remote studies is reasonable, but it seems a bit of a stretch to then argue one could do studies using remote EEG, when this has not been demonstrated to be valid for assessment of laterality. Laterality assessment with EEG is complicated by choice of reference electrode.

> **Authors' response:**

In response to the reviewer's comment, we have now removed the sentence that refers to remote EEG (page 5, line 8, "Laterality data per se can be collected remotely, for example through remote EEG using EmotivPRO Builder (reference for EmoticPRO Builder) and EmotivLABS (Williams et al., 2023).")

Reviewer's comment 2:

It is good to hear that the authors are already engaged in a study using typewriting. This needs to be referenced in the current paper, I think, as it provides important context. I would like to see a brief account of task analysis for the smartphone typing vs other tasks, including handwriting and typing.

Authors' response:

Following the reviewer' suggestion, we have now referenced the study investigating cerebral laterality during typewriting (page, 6, line 3: "At present, there is no data available on other writing modalities (albeit we are in the process of investigating cerebral laterality for typing on a PC keyboard, Samsouris et al. 2023)."

To convey that the task analysis of typing is comparable to handwriting, we added the following sentence (page 6, line 9): "We believe that, after controlling for the motor component of writing using a smartphone (in this case, using a "random key tapping" task as we describe later in the "Methods" section) the Lateralization Index (LI) for the linguistic component of writing using a smartphone will be directly comparable to the LI for the linguistic component of handwriting".

The description of the different tasks can be found in the Methods section, under the "Assessment of linguistic lateralization" section. Specifically, we describe the tasks in page 10, line 14:

"For the word generation/control period, participants will be instructed to perform one task out of the following four (corresponding to the four conditions of the experiment):

1. "Handwriting": Participants will be instructed to write as many words as possible that start with the cue letter using pen-and-paper.

2. "Handwriting Control": Participants will be instructed to copy the cue letter as many times as possible. This will act as a control condition for the hand motion during handwriting.

3. "Typing": Participants will be instructed to type as many words as possible that start with the cue letter by typing the keyboard of the smartphone using the thumb of their dominant hand.

4. "Typing Control": Participants will be instructed to tap randomly on the smartphone keyboard using the thumb of their dominant hand after the cue letter is presented. This will act as a control condition for the hand motion during writing using a smartphone."

We also describe the way that we will calculate the LIs from the different tasks in page 12, line 11 (see below). We have now enriched our description to make it clearer.

"Six cerebral LIs will be calculated for each participant:

1.   LI_handwriting corresponding to the "Handwriting" condition,

2.   LI_handwriting_control corresponding to the "Handwriting Control" condition,

3.   LI_handwriting_corrected corresponding to the cerebral LI for the linguistic component of handwriting (after hand motion correction, i.e., by subtracting the activation that corresponds to the control task from the activation that corresponds to the handwriting task: LI_handwriting - LI_handwriting_control),

4.   LI_typing corresponding to the "Typing" condition, corresponding to the "Typing Control" condition, and

5.   LI_typing_control corresponding to the "Typing Control" condition,

6.   LI_typing_corrected corresponding to the cerebral LI for the linguistic component of writing on the smartphone (after hand motion correction; i.e., by subtracting the activation the corresponds to the control task from the activation that corresponds to the typing task: LI_typing - LI_typing_control)."

We have further added the following sentence to state the way that we are going to store the data from the "Typing" conditions (page 11, line 11): "In both the "Typing" and "Typing Control" conditions, the participants will be writing in a "notes" file, which will then be saved and archived".

Reviewer's comment 3:

The authors deal with the issue of participant unfamiliarity with single-thumb typing by using a pretest. This is a good solution. They also suggest restricting handedness to those with a clear preference and excluding those in the middle of the handedness distribution – this is in the spirit of what I suggested, though it should be noted that Mazoyer et al argued it was only extreme left-handers (scoring -100) who had high rates of atypical laterality – and these are in the minority. Unfortunately, both of these restrictions of participants will make it more difficult to recruit them.

Authors' response:

We agree that our criteria will make recruitment a demanding task. However, we have succeeded in collecting data from large numbers of left-handers in the past and are confident we will be able to do so now too (e.g., our recently published study Papadopoulou et al, 2023).

Papadopoulou, A.-K., Samsouris, C., Vlachos, F., Badcock, N. A., Phylactou, P., & Papadatou-Pastou, M. (2023). Exploring cerebral laterality of writing and the relationship to handedness: a functional transcranial Doppler ultrasound investigation. *Laterality*, 1–34. https://doi.org/10.1080/1357650X.2023.2284407

Reviewer's comment 4:

If I've understood the method correctly, they will be using split half reliability on a task with 10 trials, so will be correlating LIs from odd and even trial means based on 5 trials. These are very unlikely to be reliable. If you then subtract a control task, the reliability will fall even further.

> **Authors' response:**
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> Each task comprises of 20 (not 10) trials, presented in two blocks of 10 trials. Admittedly, we have set as an inclusion criterion that we need at least 10 trials per task with good signal for a participant to be included in the analysis. The choice of having at least 10 trials (with a maximum of 20) has been made on the basis of previous work in the field of cerebral laterality for writing (Kondyli et al., 2017; Papadatou-Pastou et al., 2022).
>
> Moreover, we found good split-half reliability in a recent study that we conducted in our lab, where 20 trials were used per task (with a minimum of 10 good trials as an inclusion criterion). Specifically, in Papadopoulou et al. (2023) good split-half reliability was found for all tasks (oral word generation: rho = 0.80, BF = 5. x 10^{12}; written word generation: rho = 0.94, BF = 8.50 x 10^{24}; copying letters: rho = 0.92, BF = 2.54 x 10^{23}). Of note, we also calculated the split-half reliability for the LI_difference for this paper, which was also above our reliability threshold (rho =0.63, BF = 6.26 × 105).
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> To test the reliability of our corrected (difference) LIs (i.e., after subtracting the control condition), we added a split-half reliability test for these LIs as well (page 19, line 7):
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> > *LI measurement reliability*: The consistency of the measurement of the lateralization indices across trials will be verified using Spearman correlation of the mean LI of each task type (LI_handwrite, LI_handwrite_control, LI_typing, LI_typing_control) as well as for our corrected LIs (LI_handwrite_corrected, and LI_typing_corrected) between odd and even trials (Bishop et al., 2021).
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> Papadopoulou, A.-K., Samsouris, C., Vlachos, F., Badcock, N. A., Phylactou, P., & Papadatou-Pastou, M. (2023). Exploring cerebral laterality of writing and the relationship to handedness: a functional transcranial Doppler ultrasound investigation. *Laterality*, 1–34. https://doi.org/10.1080/1357650X.2023.2284407
>
> Samsouris, C., Papadopoulou, A.-K., Badcock, N. A., Vlachos, F., & Papadatou-Pastou, M. (2023). Cerebral lateralization during handwritten and typed word generation: A functional transcranial Doppler ultrasound study in left- and right-handers. *Stage 1 Registered Report*. https://orcid.org/0000-0002-2834-4003

Reviewer's comment 5:

I'm not experienced with using Bayesian analyses, though I appreciate that they can be designed to distinguish between results that are inconclusive rather than null or positive. My concern is that, given the weak association between handedness and laterality, and the likely

low reliability of the motor-corrected LIs obtained in the study, the result will be inconclusive, even if the maximum sample size is attained.

Authors' response:

As argued in the previous rounds of review, assuming we might find a high variability in our sample size (between 2 and 3 standard deviations) we can expect to find a BF10 smaller than ⅓ with greater than chance probability with our initially proposed minimum sample size of $n = 16$ (Phylactou & Konstantinou., 2022) (now updated to $n = 40$). Moreover, with these criteria, there is an above 70% chance of detecting evidence in favour of the alternative for our initially proposed maximum sample size of 40 (20 in each group) and a greater than 80% chance for our now updated maximum sample size of 80 (40 in each group; Phylactou & Konstantinou., 2022). We believe this is an acceptable change level for research studies (translating to a power of 0.8 in frequentist statistics).

Reviewer's comment 6:

I think the authors should be allowed to go ahead and do this study if they want, but I see it as very high risk of being inconclusive, and involving a great deal of work, with major issues around recruitment, for an uninterpretable result. I would be very glad to be proved wrong, but would strongly advise the authors to do some simulations of possible datasets before putting a great deal of time into this study.

Authors' response:

We appreciate the reviewer's concerns. However, we wish to go ahead with the study, as it is part of a funded PhD project on writing laterality with technological devices. We believe that the risk of finding inconclusive results (which will be reported as such since we are following the registered report route) is overcome by the skills and knowledge our team and especially the leading author will develop while conducting this study. Moreover, we just collected data for a similar study whereby writing in performed in a PC keyboard, with sufficient results.

Minor points 1

Abstract: I always recommend including sample size in the Abstract, as it is an important detail when evaluating a study.

Authors' response:

We have now added the following sentence in the abstract (page 1, line 13): "Our initial sample will be $n = 40$ participants (20 left-handers and 20 right-handers), with a maximum of $n = 80$ (40 per group) following the Sequential Bayesian Factor (SBF) with Maximal n design."

Minor points 2

P 2 para 2 'laying down' -> 'lying down'

Authors' response:

We thank the reviewer for spotting this typo, which is now corrected.

Minor points 3

P 2 para 2, Altzheimer's disease -> Alzheimer's disease

> **Authors' response:**
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> This typo has also been corrected, thank you.

Minor points 4

P 3, 3rd sentence would benefit from some rewording, e.g. "In FTCD, ultrasound probes are positioned over the temporal windows of the participants on either side of the head to measure the blood flow velocity in the middle cerebral arteries (MCAs). "

> **Authors' response:**
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> We have now adopted the suggested wording (page 3, line 8).

Minor point 5

Also 'temporal window' won't be familiar to many readers, so need to explain it is a thin region in the temporal bone.

> **Authors' response:**
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> We have now incorporated this explanation and the re-worked sentence now reads (page 3, line 8): "In fTCD, ultrasound probes are positioned over the temporal windows (i.e., a thin region in the temporal bone) of the participants on either side of the head to measure the blood flow velocity of the middle cerebral arteries (MCAs)."

Minor point 6

P 6, para 2 : " absence of a motor component in oral language" ; this will seem odd to readers, as there is a speech motor component in oral language. It was unclear whether this referred to the silent nature of the word generation task, or just to the lack of a manual motor component in speech.

> **Authors' response:**
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> We agree with Prof. Bishop that our wording was awkward here. We have added the word "manual, so that the sentence now reads (page 6, line 5): "Oral language tasks, on the other hand, are not directly comparable due to differences like the absence of a manual motor component in oral language."

Minor point 7

P 8, point 2: "total number of written words" (rather than "amount")

> **Authors' response:**
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> "Amount" has been replaced with "number", thank you for this suggestion.

Minor point 8

P 8, exclusion criterion 2: "Consumption of medication with the potential to affect the central nervous system in the last six months" – I wonder if the authors are making life more difficult for themselves than they need. Given the very high rates of consumption of psychotropic drugs, both licit and illicit, this could rule out a lot of people. And some would include caffeine, painkillers and nicotine in such a definition! I'm not sure that such an exclusion is required, and if it is, I'd be more specific, and take a much shorter time scale unless one was talking about a drug that was known to have a long-term effect.

Authors' response:

Following the reviewer's suggestion, we have now removed the phrase (page 8, line 22) "Consumption of medication with the potential to affect the central nervous system in the last six months."

Minor point 9

Immediately below Fig 1: change to "which we will provide"

Authors' response:

The correction had been made.

Minor point 10

P 13. "If the correlation is below 60%". Does this mean r = .6?

Authors' response:

Yes, what we meant is $r = 0.6$ and this is now reflected in our text (page 13, line 21).

Authors' response:

We would like to express our thank to the reviewer for her continuing support in improving our registered report. We trust that these revisions have fine-tuned our manuscript and we hope it will receive an in-principal acceptance.