Timeline of manuscript

25th March 2021 – Manuscript submitted as a ‘Letter to the Editor’ to the *Journal of Neurophysiology* (Line 12 – 132 below).

15th April 2021 – Reviewer comments received with an editorial ‘Reject’ decision (Appendix A).

19th April 2021 – Editor e-mailed to reconsider decision with a response to reviewer’s comment document (Line 133 – 251 below).

14th June 2021 – In light of a lack of response by the Editor, the manuscript, the reviewer comments, and the response to the reviewer’s comments uploaded to *PsyArXiv* preprint server.

Statistical reminders involving indirect comparisons and non-significant results: a case study

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Dear Editor: I read with interest the paper by MacDonald and colleagues titled “The role of interhemispheric communication during complete and partial cancellation of bimanual responses” (1) in which it was concluded that a) the anticipated bimanual response involves a release of interhemispheric inhibition (IHI) from both primary motor cortices (M1s), b) the complete cancellation of the bimanual response involved a re-engagement of IHI onto both M1s, and c) the partial cancellation of the bimanual response involved the ‘bifurcation of IHI’ – re-engagement of IHI onto the cancelled digit along with a facilitation of the responding digit – 175 or 250 milliseconds after the stop cue when the dominant or non-dominant hand was responding, respectively.

However, an important statistical issue – *indirect* comparisons between separate statistical tests – undermines some of the conclusions, with the opportunity also taken to highlight another statistical issue – inferring *absence* of an effect from non-significant tests conducted within the null-hypothesis significant testing (NHST) framework.

Indirect comparisons

Based on a significant *t* test at one of three time-points ($p = 0.037$ at the later time-point of 250 ms after the stop cue and $p > 0.731$ at earlier time-points of 200 and 225 ms after the stop cue), it was inferred that the bifurcation of IHI occurred at that later time-point in partial cancellation trials involving a response of the non-dominant hand. Besides the heightened false positive Type I error rate (~14.3% vs. 5%), it is erroneous to indirectly compare the significant result at the later time-point with the non-significant results at the other two earlier time-points to infer temporal specificity of this later time-point (2) as the “the difference between significant and not significant is not itself necessarily significant” (3). Indeed, the interaction effect – which is the appropriate statistical result for this inference – is non-significant. Furthermore, following on from this inference, another indirect comparison is made between the significant time-point in partial cancellation trials involving a response of the non-dominant (250 ms) and dominant (175 ms) hand to state that “...the non-dominant hand took on average 75 ms longer than the dominant hand to uncouple on partial cancellation trials”. All these aspects make conclusion c) tenuous and an experimental design that allows a 2 (hand/muscle: dominant vs. non-dominant) x 2 (time after stop cue: 175 ms vs. 250 ms) x 2 (stop/response type: left vs. right) analysis may be better suited.

Similarly, indirect comparisons support conclusion b) and the statement that “compared to the disinhibition across Go bimanual trials, IHI had to be increased again onto both FDI representations following a non-selective cue” as no direct statistical test was conducted comparing inhibition in Go trials to inhibition in non-selective Stop trials.

Non-significant null-hypothesis results

In the NHST framework, the null hypothesis (often, that the true effect is 0) is either rejected (i.e., $p < \alpha$ level) or not rejected (i.e., $p > \alpha$ level) with the former indicating a statistically significant result and the latter, a statistically non-

significant result. Of particular inferential importance is that non-significant results do not necessarily imply the *absence* of an effect, as is often incorrectly concluded (4). However, in the article, there are numerous instances of non-significant results between conditions being inferred as “comparable”, “similar”, and there being “no effect”. Using statistical tools, either in the frequentist (equivalence tests) or Bayesian (Bayes factors) framework (5), researchers can better understand non-significant results, increasing the overall informativeness of their data.

Finally, and most importantly, it would be remiss to perceive the aforementioned statistical issues to be specific to the paper highlighted as these are prevalent in the wider literature as well (2,6). Given this prevalence, though no systematic search has been conducted, it is not unlikely that these statistical issues exist, more specifically, in physiology as well as non-invasive brain stimulation literature. I hope the insights shared here encourages academic dialog and leads to not only enhanced author and reviewer knowledge of robust statistical methodologies but also the update of existing statistical guidelines for American Physiology journals (7) as well as the creation of formal statistical guidelines by non-invasive brain stimulation journals such as *Brain Stimulation*.

101 **Acknowledgements**

102 I would like to acknowledge support through an Australian Government Research
103 Training Program stipend.

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Response to reviewer (reviewer's comments in italics)

- *The author's point about the interpretation of statistically non-significant results seems better suited to a general review of multiple papers or a larger opinion piece. It seems strangely fastidious to argue that one cannot interpret the lack of a main effect in an ANOVA as 'no effect' for that factor, or argue that using 'similar' to put the numerical value into words is incorrect. By its very nature, the test is saying that to a set level of confidence, you can accept the null hypothesis and conclude no effect of that factor. I agree that it is a worthwhile endeavour to encourage the scientific community to move towards statistical tests beyond simple p values, for example using the Bayesian framework, or as has been done throughout the MacDonald et al. paper, including effect sizes. However, for the author to make this point, it doesn't seem appropriate to single out one paper and assume it generalises to the wider literature. As the author acknowledges, to make such claims would require a systematic search of the literature.*

- The reviewer's statement "*By its very nature, the test is saying that to a set level of confidence, you can accept the null hypothesis and conclude no effect of that factor*" confirms the utility of the manuscript as this is one of the most common statistical fallacies (i.e., failing to reject the null hypothesis does not equate to *accepting* the null hypothesis). This point is highlighted explicitly by statistical guidelines of numerous journals ("Do not accept the null hypothesis. In a court case, defendants are declared guilty or not guilty; there is no verdict of 'innocent'" section in Assel et al., 2019, *Guidelines for reporting of statistics for clinical research in urology*, and " p Value Greater Than 0.05 Does Not Mean Equivalence" section in Ou et al., 2020, *Guidelines for Statistical Reporting in Medical Journals*).

Furthermore, the manuscript is not necessarily encouraging the scientific community to move towards statistical tests beyond simple p values. With this issue, the manuscript is purely highlighting the statistical issue (as noted in the previous paragraph) and providing solutions, both within the frequentist and Bayesian frameworks. In fact, one of the solutions (i.e., equivalence tests by way of two one-sided t -tests) *uses* p values to test statistical equivalence.

Indeed, it is agreed that a larger opinion piece would be suitable but the issue of accepting the null hypothesis has been prevalent for over 7 decades in the wider literature (stable average of ~ 38% in the *Journal of Applied Psychology* as per reference 6 in the manuscript). It would be extremely improbable that the field of physiology and non-invasive brain stimulation is immune to these relatively common statistical issues (the highlighted study by MacDonald and colleagues is a case in point).

- *I do not agree with the author's first point. Ironically, if the ANOVA interaction effect had reached the somewhat arbitrary 0.05 significance threshold, it appears the author would have had no problem with the interpretation. However, conclusion c) (as they have labelled it) is built on evidence beyond*

181 *that single statistical test. I would argue interpretation of any statistical test*
182 *needs to be based on a clear hypothesis and considered in light of a wider*
183 *body of data. Indeed, there is a clearly stated data-driven hypothesis for this*
184 *experiment and comparison in the analysis, directly built on behavioural and*
185 *neurophysiological results from experiment 1. Importantly, the significant t test*
186 *is therefore interpreted in light of not just the ANOVA but both experiments as*
187 *a whole and all neurophysiological and behavioural evidence combined.*
188 *Furthermore, as experiment 2 was specifically designed to test this*
189 *hypothesis, the author's contention that a different statistical design would be*
190 *more suited is not appropriate, as this comparison is not possible with the*
191 *current data. I acknowledge this is a worthwhile comparison for future*
192 *research, but the idea to investigate this in future does not detract from the*
193 *current results. On this point the author further contends that the ANOVA*
194 *cannot be used to infer temporal specificity. Although a repeated measures*
195 *ANOVA in isolation may not speak to the temporal relationship between*
196 *events, the behavioural results do and all timepoints in the neurophysiological*
197 *analysis are pegged to the same relative trial start time. Therefore, it seems*
198 *unnecessarily fastidious to criticise this wording in the article.*
199

- 200 - Though I agree with the reviewer's comment about the general nature of
201 the arbitrariness of the 0.05 alpha level, the use of this argument appears
202 to be an example of a 'red herring' (i.e., redirecting the argument to
203 another issue – arbitrariness of the alpha level – and abandoning the
204 original argument – the correct statistical tool to support the stated
205 conclusions). Ironically, if the arbitrariness of the interaction effect alpha
206 level is an issue, then it suggests that the reviewer agrees that the
207 interaction effect is indeed the correct statistical effect.
208

209 Indeed, statistical tests need to be based on a clear hypothesis and
210 considered in light of a wider body of data. However, the data collected
211 and analyses conducted in Experiment 2 lack a clear data-driven
212 temporally-specific hypothesis. MacDonald and colleagues state that the
213 "...dissociation in interhemispheric communication would occur on GS
214 trials at a later time point given the longer SSRTs in GS compared to SG
215 trials". Given that rationale and given that SSRTs on GS trials were ~ 50
216 ms greater than SG trials in Experiment 1, if Experiment 2 was "*directly*
217 *built on behavioural and neurophysiological results from experiment 1*",
218 shouldn't data be collected at only 225 ms post-stop cue in Experiment 2,
219 as opposed to three time-points? Moreover, in light of a lack of
220 hypothesized temporal specificity, could one test 10 'later' time-points in
221 Experiment 2 and utilise one of the significant time-points to make
222 conclusions regardless of the ~ 40% Type I error rate? Furthermore,
223 regardless of the presence of significant 'data-driven' hypothesis tests with
224 heightened Type I error rates, these tests cannot be compared to non-
225 significant hypothesis tests indirectly to infer temporal specificity. Figure 1
226 from the aptly titled paper "Erroneous analyses of interactions in
227 neuroscience: a problem of significance" (reference 2 in the current
228 manuscript) highlights the aforementioned issues elegantly.
229

230 Lastly, the reviewer's comment that "...the author further contends that the
231 ANOVA cannot be used to infer temporal specificity" is exactly opposite of
232 what the manuscript is stating. Line 65-66 of the manuscript clearly state
233 that "Indeed, the interaction effect – which is the appropriate statistical
234 result for this inference – is non-significant". With the interaction effect
235 coming from the ANOVA, the author is stating that the interaction effect
236 from the ANOVA *can*, and should, be used to infer temporal specificity.

- 237
- 238 • *Finally, it is not clear why the author mentions non-invasive brain stimulation*
239 *and the Brain Stimulation journal. The points raised relate to statistics, without*
240 *any specific relation to non-invasive brain stimulation.*

- 241
- 242 - The mention of 'non-invasive brain stimulation' is because MacDonald et
243 al., use the aforementioned procedure to make inferences about the role
244 of interhemispheric communication during complete and partial
245 cancellation of bimanual responses.

246

247 Most top journals in their fields such as the *New England Journal of*
248 *Medicine* have explicit statistical reporting guidelines. However, Brain
249 Stimulation, being the premier journal for brain stimulation, currently has
250 no explicit statistical reporting guidelines, and hence it is hoped that this
251 manuscript would lead to the creation of them.

Appendix A**Decision on JN-00129-2021 submitted to JNP**

jn@msubmit.net <jn@msubmit.net>

Fri 16/04/2021 12:11 AM

To: Rohan Puri <rohan.puri@utas.edu.au>

Dear Dr. Puri,

You will find with this letter the comments of the referees of your manuscript, Rigorous statistical reminders involving indirect comparisons and non-significant results. Unfortunately, the reviewers have serious reservations about the suitability of the manuscript for publication in JNP. On the basis of their concerns and my assessment of the manuscript, I am sorry to say that JNP will not be able to publish the manuscript.

We assure you that the negative outcome of the review of this manuscript in no way precludes a more positive outcome of a different future study, and strongly encourage you to continue to submit your work to JNP. We hope you'll take a few minutes to complete our author satisfaction survey: <https://www.surveymonkey.com/r/APSAuthors>.

Please note, if you wish, we will provide these reviews to another journal that participates in the Neuroscience Peer Review Consortium, without the reviewers' names, if they wish to remain unidentified.

Please send requests for transfer of reviews to the JNP Editorial Assistant: jnpoffice@the-aps.org.

Sincerely,

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Reviewer #2 (Comments to the Author (Required)):

The author's point about the interpretation of statistically non-significant results seems better suited to a general review of multiple papers or a larger opinion piece. It seems strangely fastidious to argue that one cannot interpret the lack of a main effect in an ANOVA as 'no effect' for that factor, or argue that using 'similar' to put the numerical value into words is incorrect. By its very nature, the test is saying that to a set level of confidence, you can accept the null hypothesis and conclude no effect of that factor. I agree that it is a worthwhile endeavour to encourage the scientific community to move towards statistical tests beyond simple p values, for example using the Bayesian framework, or as has been done throughout the MacDonald et al. paper, including effect sizes. However, for the author to make this point, it doesn't seem appropriate to single out one paper and assume it generalises to the wider literature. As the author acknowledges, to make such claims would require a systematic search of the literature.

I do not agree with the author's first point. Ironically, if the ANOVA interaction effect had reached the somewhat arbitrary 0.05 significance threshold, it appears the author would have

had no problem with the interpretation. However, conclusion c) (as they have labelled it) is built on evidence beyond that single statistical test. I would argue interpretation of any statistical test needs to be based on a clear hypothesis and considered in light of a wider body of data. Indeed, there is a clearly stated data-driven hypothesis for this experiment and comparison in the analysis, directly built on behavioural and neurophysiological results from experiment 1. Importantly, the significant t test is therefore interpreted in light of not just the ANOVA but both experiments as a whole and all neurophysiological and behavioural evidence combined. Furthermore, as experiment 2 was specifically designed to test this hypothesis, the author's contention that a different statistical design would be more suited is not appropriate, as this comparison is not possible with the current data. I acknowledge this is a worthwhile comparison for future research, but the idea to investigate this in future does not detract from the current results. On this point the author further contends that the ANOVA cannot be used to infer temporal specificity. Although a repeated measures ANOVA in isolation may not speak to the temporal relationship between events, the behavioural results do and all timepoints in the neurophysiological analysis are pegged to the same relative trial start time. Therefore, it seems unnecessarily fastidious to criticise this wording in the article.

Finally, it is not clear why the author mentions non-invasive brain stimulation and the Brain Stimulation journal. The points raised relate to statistics, without any specific relation to non-invasive brain stimulation.

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