**Changes in memory function in adults following SARS-CoV-2 infection: findings from the Covid and Cognition online study**

*Josefina Weinerova, Sabine Yeung, Panyuan Guo, Alice Yau, Connor Horne, Molly Ghinn, Lyn Curtis, Francess Adlard, Vidita Bhagat, Seraphina Zhang, Muzaffer Kaser, Mirjana Bozic, Denis Schluppeck, Andrew Reid, Roni Tibon, Lucy Cheke*

Stage 2 Review for PCI-RR - ArticleID #945

*Reviewed by Phivos Phylactou*

**After previously reviewing the Stage-1 report by Weinerova and colleagues, I have now carefully read the Stage-2 report. In this report, the authors present an investigation of the effects of Long COVID on different long-term memory modalities (associative vs item) and different types of stimuli (verbal vs visual). In addition, differences in memory performance between fully vaccinated and not fully vaccinated individuals are tested. In their report, Weinerova et al. also include numerous exploratory analyses, exploring the effects of COVID on other cognitive tasks, the potential mediating role of anxiety and depression on long-term memory, the role of time since infection on memory, and the relationship between their measured memory effects with self-reported memory issues. Even though some evidence was shown for the effects of COVID on the accuracy of some long-term memory tasks, the data did not replicate earlier findings showing similar effects for reaction times. No interactions were noted between memory modalities or stimulus type. Bayesian evidence for vaccination status effects in memory performance was deemed inconclusive.**

**I congratulate the authors on following their registration and completing the study. Their findings are insightful and the addition of numerous exploratory analyses provide a thorough view into the potential effects of COVID on memory.**

**Below, I provide some feedback and some suggestions, which I think will help strengthen the current report. I begin with feedback based on the suggested PCI-RR guidelines, followed by some additional minor comments/suggestions.**

**2A. Whether the data are able to test the authors’ proposed hypotheses (or answer the proposed research question) by passing the approved outcome-neutral criteria, such as absence of floor and ceiling effects or success of positive controls or other quality checks.**

The authors here aimed to replicate earlier findings from their group as well as extend their earlier work with additional investigation (e.g., looking into memory type and stimulus type). To this extent, the data were adequate to test the proposed hypotheses. Some considerations relating to ceiling effects are evident, though the authors identify and discuss this accordingly in their report.

Additionally, there is some difficulty in the interpretation of the replication results. The frequentist ANCOVA replicated previous effects only on accuracy (not on RT), but Bayesian analyses failed to reach the specified decision threshold. The authors do a great job in transparently presenting all their findings in regards to this replication, though I feel like the authors’ interpretation of what to make of this is missing. What do these results mean in terms of the replication? Did the replication hold up or not? Is the current data adequate or inconclusive for the replication results? The authors do comment that “*We have replicated a previously found effect […]*” (abstract), and “*As far as we are aware this is a first study on the cognitive impairment following Covid-19 infection which included a replication of previously found effects. In this case, we have replicated the effect of Covid-19 on accuracy in two long term memory tasks*.” (conclusions), however, I feel like this might be an issue of analytic flexibility (mentioned in Stage-1, too). For the said effects, can we talk about a successful replication? On one hand, the frequentist effect size is similar to the original one, but on the other hand, the Bayesian threshold wasn’t reached. I am unsure on what suggestion can be made to this stage to address this, but maybe the two things that I would like to see are (i) the authors interpretation in the discussion section (paragraph 1 where they discuss the replication) about whether the replication was successful/failed/inconclusive (guided by the study design table), and (ii) maybe point out that the replication of effects was only evident in the frequentist ANCOVA (when mentioning in abstract and conclusions or wherever relevant).

**2B. Whether the introduction, rationale and stated hypotheses (where applicable) are the same as the approved Stage 1 submission.**

The authors did not make any changes to the introduction, rationale, or hypotheses outside what is expected (changes in tense, corrections, etc.).

**2C. Whether the authors adhered precisely to the registered study procedures.**

The authors adhered to their registered procedures. Even though some adjustments were needed retrospectively (e.g., for normality assumptions), the authors still remained within their registration procedure and provided the adjustments as additional (exploratory) analyses. To this point, I would like to request two additional clarification to the methods.

1. Even though methods should be identical to the IPA Stage-1 protocol, I think it is important to clarify whether the Reaction Time data included all responses to the task, or only RTs from correct responses (the authors do mention ‘overall’ RT, but it is unclear whether that means ‘including everything’ or ‘average correct response RT’).
2. The behavioral tasks provided the option of ‘I don’t know’ to participants. It is unclear how this was treated in the calculation of accuracy or RT. Were ‘I don’t know’ responses included in the data? If so, how did they contribute? Were they treated as correct or incorrect responses? Where they included in the RT calculations?

**2D. Where applicable, whether any unregistered exploratory analyses are justified, methodologically sound, and informative.** This criterion addresses the quality and value of any additional data analyses that are reported at Stage 2 but were not included in the registered Stage 1 submission. Such analyses are often highly valuable. For instance, a new analytic approach might become available between IPA and Stage 2 review, or a particularly interesting and unexpected finding may emerge. Alternatively, some unexpected characteristic of the data might suggest that the preregistered analyses, while bias-free, are not as sensitive as planned, and therefore a more sensitive post hoc analysis could be informative. Such analyses are admissible but must be clearly identified (e.g. through a separate heading in the Results for “Exploratory Analyses” or “Unregistered analyses”), justified, and appropriately caveated. Authors should also be careful not to base their conclusions entirely on the outcome of unregistered analyses.

The authors present numerous exploratory analyses. These analyses are justified, sound, and informative. Even though some analyses were inconclusive or did not provide any additional information (in regards to the registered analyses), these exploratory analyses provide completeness to the study and illustrate how the authors took into consideration potential alternatives.

For these analyses, some additional information is required, for clarity. Specifically, the authors mention that *z*-scores were estimated for some analyses. Details on *z* estimation is important (e.g., do *z* scores include variance across all groups/levels or were they calculated separately?).

**2E. Whether the authors’ conclusions are justified given the evidence.**

**With the exemption of my earlier comment regarding the replication results, the authors did a great job in keeping their claims based on the provided evidence. Moreover, even though the authors presented multiple exploratory analyses, they were transparent about the exploratory nature of these results and drew the appropriate cautions were necessary.**

**Additional minor Comments/Suggestions:**

1. **In p6: “*The Covid group included 209 participants (18-75 years old, average=42.72, SD = 13.51; 47 males [22.5%], 161 females 77%] and 1 transgender [0.5%])*” the underlined text is missing a square bracket.**
2. **Table 1:**
   1. **Table 1 is presented in p12 but is not referred to until p15. I am assuming that some reference to the table was meant by the authors earlier but was likely omitted.**
   2. **‘Original’ and ‘Scaled’ should be replaced with ‘Raw’ and ‘*z*-score’ respectively.**
3. **In p13 the authors state: “*However, given the results of the frequentist analysis described above, we were now expecting an effect of Covid status on accuracy but not on RTs.*” Predictions should not change in Stage-2 but remain coherent with Stage-1. The statement is understandable, but should be removed from this Stage-2 report.**
4. **Figure 3: the graphical representation of the model is a great idea! Kudos!**
5. **In p17 (and onwards were applicable) “*[the model] had its odds increased*” is not appropriate Bayesian terminology. Maybe ‘had higher posterior probability’ or ‘had a higher BF’.**
6. **In pp18-19 the authors state “*We analysed the effect of vaccination prior to infection on all the dependent variables separately using a subgroup of participants who have had Covid only once. These were further divided into two groups: those who have been fully vaccinated at least 2 weeks prior to infection (N=69), and those who had not been vaccinated at all at the point of infection (N=59).*” However, in pp6-7 the authors say “*For analyses that included vaccination status, participants who had received at least 2 doses of vaccine (or one dose if vaccinated by a one dose vaccine type) at least 3 weeks prior to infection onset were considered to be fully vaccinated (N=69, 18-75 years old, average = 43.45 , SD = 13.11). This was to ensure the 14 days delay for the vaccine immunity to take full effect as recommended by the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2024).*” It is unclear if the criterion is 3 weeks or 2 weeks, which is likely a typo, but should be corrected.**
7. **In p21 there seems to be a typo: “We evaluated whether Covid-19 has differential effects of various aspects of long-term memory, or whether the effect on long-term memory in more global.”**
8. **In p22, the authors discuss the addition of ‘binary variables’. This binary nature is not explained until later in the manuscript (p31). I would suggest moving the explanation in the parenthesis from p31 to p22.**
9. **In p22 the abbreviation DVs should be explained or omitted.**
10. **In p29 the authors report a median statistic. Though I don’t have strong feelings about this issue, for completeness, it might be a good idea to include the medians in the results, especially if the authors plan to refer to them in the discussion (maybe in Table 1?).**
11. **In p30 the authors make some claims, which require some backing. I suggest that some references are added in the following: “*Notably, the verbal mnemonic task in our study only requires semantic understanding, whereas the Word/Syntax task also depends on syntactic understanding. It is therefore plausible that the verbal difficulties post Covid-19 represent reduction in specific linguistic processes (e.g. syntactic awareness) rather than a general verbal impairment. However, it should be noted that Word/Syntax task also relies on working memory. We did not see impairment on other working memory reliant tasks in this study (such as the digit span task), but it is possible that there are differences between the tasks in difficulty level and that is why we detected an effect only in the Word/Syntax task.*”**
12. **Throughout the results section: I advise the authors to accommodate the BFs with the posterior probabilities of the model given the data for a more complete picture of the results.**

Overall, the authors did a great job in adhering to their Stage-1 IPA protocol. There results are informative and comprehensive, providing a thorough The current design is sufficient to answer the proposed research questions. The authors can decide if replicating the previous findings can serve as a positive control for their study, based on my suggestions mentioned in the previous sections.

I hope that the authors find my suggestions insightful.

Respectfully,

Phivos Phylactou