Functional MRI brain state occupancy in the presence of cerebral small vessel disease -- pre-registration for a replication analysis of the Hamburg City Health Study

PCI RR, Revision 02

Comments by the Editor

Thank you for the revisions made to this Stage 1 Registered Report. As you will see, the reviewers are now generally happy with the plan, although Reviewer#1 (Olivia Hamilton) has a couple more suggestions for aspects of the protocol that should be made explicit. It is probably best to include these details in the Stage 1 plan, rather than adding them at Stage 2, and you have the opportunity to do so, because there is one other small matter that needs to be attended to before IPA can be issued.

> Thanks for this assessment and thanks also to the reviewers for agreeing to evaluate the revised manuscript.

Specifically, you have two main hypotheses, as stated in your Introduction, the second of which concerns the relation of fractional occupancy to the time to complete TMT-B. A summary specification of this hypothesis should be included in the study design table (Table 1). You should also make it clear in the text (paragraph beginning line 63, page 3) whether this finding was reported by the previous analysis of Schlemm et al (2021). It would also be helpful if this paragraph could be expanded beyond simply stating that this previous study 'found associations', to providing some quantitative clarification of the associations that were found.

> Thank you for these suggestions. We have now included the second hypothesis in the Study Design Template Table 1. We have expanded the introduction by including the sentence:

> [l. 68--72] *Specifically, [in (2022, Schlemm),] every 4.7-fold increase in WMH volume was associated with a 0.95-fold reduction of the odds of occupying a DMN-related brain state; every 2.5 seconds (i.e., one repetition time) not spent in one of those states was associated with a 1.06-fold increase of TMT-B completion times.*

Once these comments have been addressed, I anticipate being able to issue IPA.

Reviews

Reviewed by Olivia Hamilton, 13 Jun 2023 10:56

I read the authors responses with interest and just have a couple of additional thoughts, which do not necessarily require a response.

> Thanks for this continued engagement with our manuscript and the additional suggestions for improvement, which are much appreciated.

In response to the second point about how missing data will be handled, the authors state that they will be carrying out a complete-case analysis. In the final report from this work, it would be good to see a justification of this choice. I would suggest that the authors eventually report how many participants were excluded from the sample due to incomplete data and consider any biases that this might introduce (if any).

> Thanks for allowing us to clarify this point. The justification for planning to do a complete-case analysis is -- quite pragmatically -- that we expect only a small number of missing values for the imaging and demographic variables that are needed for the primary hypothesis (<1% in (2022, Schlemm)). We therefore do no expect more sophisticated methods to deal with missingness, such as multiple imputation, to provide substantial additional value. If there is, indeed, a substantial number of missing values, we will need to discuss this as a limitation of our results and might include a multiple imputation sensitivity analysis in the exploratory part of the stage 2 manuscript. As stated in [ll. 152--153], the number of missing values will be reported for each variable.

In response to the third point regarding additional exclusion criteria, the authors state that they will not exclude participants with dementia. It would be beneficial to explicitly state this in the final report, and state the proportion of the sample with a dementia diagnosis (if available, if not, this is a limitation), in order to better characterise the sample and contextualise the findings.

> We appreciate this suggestion and agree that reporting the prevalence of dementia will be a useful addition. We have added the following sentence to Methods->Demographic and clinical characterization

> [ll. 102--104]*For descriptive purposes, we will also extract data on past medical history and report the proportion of participants with a previous diagnosis of any dementia.*

Best of luck to the authors with the submission of their work!

Reviewed by anonymous reviewer, 17 Jun 2023 21:45

The authors have addressed my previous comments. The pre-registration has been improved as a result of these and the other modifications.

Thanks.