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

PCI RR, Stage 2, Revision 01

Comments by the Recommender

First, you have removed from the Stage 1 manuscript your previous pilot analysis, and also moved the timeline section (describing Stage 1 state of knowledge of the data) to the end of the manuscript. The timeline section should be reinstated within the Methods for correspondence with the approved Stage 1 plan. If you wish to remove the pilot analysis from the Stage 2 manuscript, you should explain your reasoning in your response, so that it can be evaluated, and you should at least add a footnote to the Stage 2 Methods to inform the reader that a pilot analysis included at Stage 1 has been omitted for brevity but can be found in the archived Stage 1 manuscript, providing a link to that document.

> We appreciate this advice. We moved the timeline subsection to the Methods section, noting, however, that in the Stage 1 manuscript, the timeline was included at the very end of the document (just before Acknowledgements). We decided to remove the results of the pilot data analysis from the Stage 2 manuscript because they do not provide substantial new insight beyond our 2022 paper, and only served to illustrate the proposed and pre-registered analysis pipeline. We added a comment that the pilot data can be found in the archived Stage 1 report, as follows:
> **[ll. 261--267] Summary data from the first 1000 imaging data points of the HCHS have been published with (Schlemm, 2022) and formed the basis for the hypotheses tested in this replication study. Before pre-registration, we had implemented our prespecified analysis pipeline described above in R and Matlab, and applied it to this previous sample. Data, code and results from this pilot analysis have been stored with the archived Stage 1 report on GitHub (https://github.com/csi-hamburg/HCHS_brain_states_RR, v1.5) and preserved on Zenodo (https://zenodo.org/records/8083554).**

In passing, I note two very minor typographical/stylistic points: (1) please regularise 'subjects' to 'participants'; (2) there seems to be a word or two missing from the following: "network activation profiles were computed for brain states estimated Schaefer parcellations..."

> Thanks, both issues have been changed in the revised manuscript.

Reviews

Reviewed by anonymous reviewer, 15 Nov 2024 23:34

The authors present a phase 2 pre-registered replication study to examine associations between dynamic resting-state fMRI, small vessel disease (WMH), and cognition. The research question is scientifically valid, but the theoretical rationale requires some additional clarification and justification. The sample and methods are mostly appropriate, but I offer some suggestions for improved rigor. Results are presented clearly, but I offer some suggestions for additional transparency. My strongest critique is that the authors' characterization of "robustness" in the behavioral association does not appear to be supported by the data.

> We thank the reviewer for their time and insights, and respond to their questions, comments and suggestions below.

1. Figure 1 should be updated to report the achieved sample rather than expected.

> We are happy to include the achieved sample size (n=1651) in Figure 1. For transparency, we prefer to also keep the expected sample size, as estimated prior to commencing the study.
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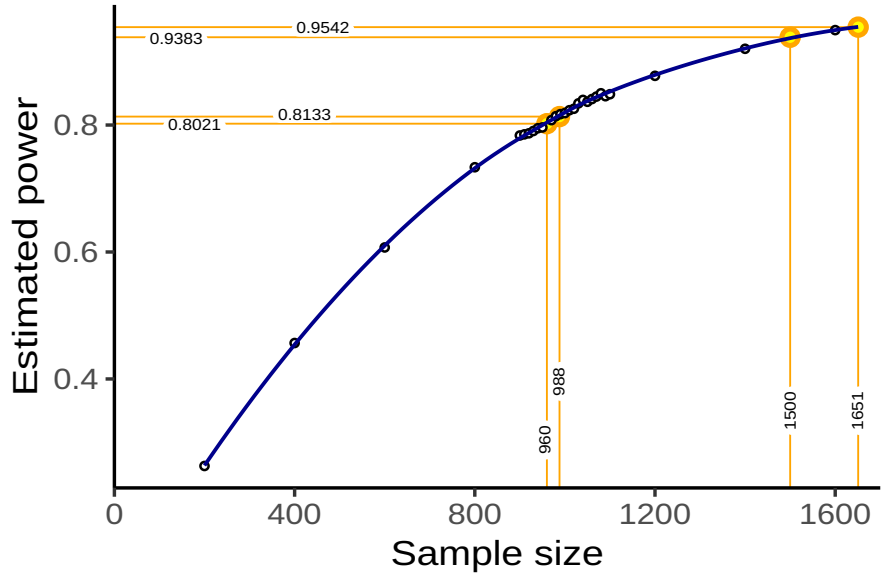
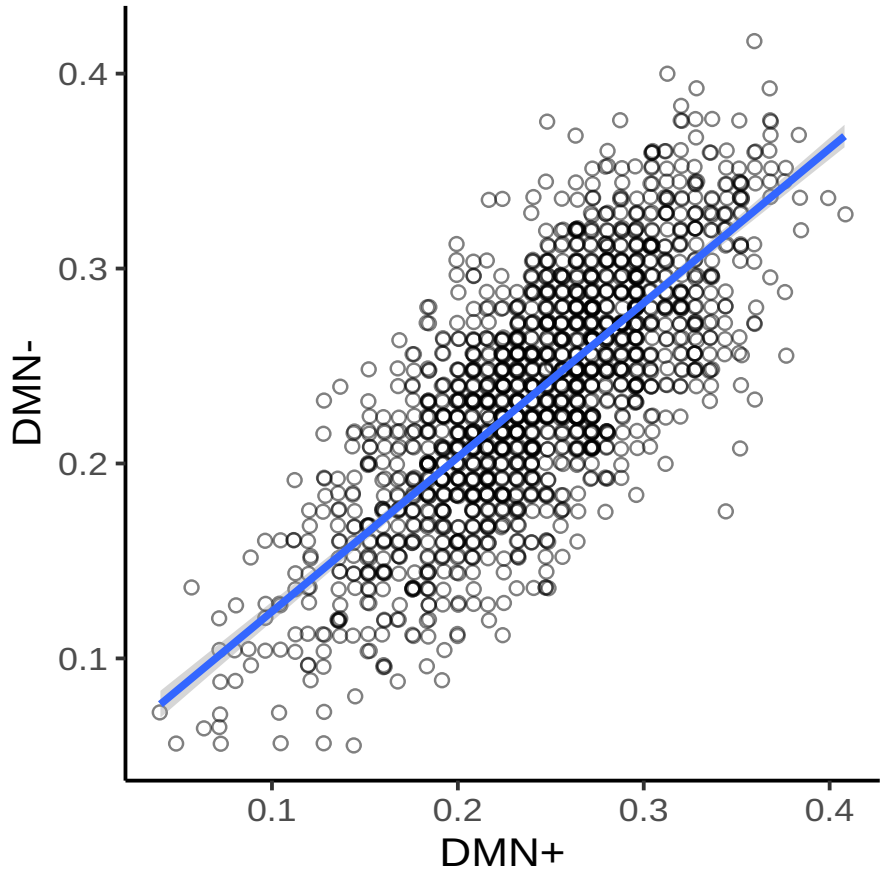
> 
>
>
> The caption has been updated to read:
> **[Caption Fig 1] Highlighted in orange are the smallest sample size ensuring a power of at least 80% (n=960), the sample size of the pilot data (n=988, post-hoc power 81.3%), the expected sample sample size for this replication study (n=1500, a-priori power 93.9%), and the achieved sample size (n=1651, a-priori power 95.4%).**

2. What is the justification for focusing on average fractional occupancy in either DMN+ or DMN- clusters? How is occupancy in these two clusters related across individuals? Are similar associations with WMH or cognition observed for DMN+ or DMN- occupancy individually?

Fractional occupancies in DMN+ and DMN- are highly correlated (Pearson correlation 76%). This was expected from our previous work and we therefore did not plan to analyze occupancies in DMN+ and DMN- separately.



It follows from the high correlation that associations with WMH or cognition would be expected to be similar as for the average.

3. “49/81 (39/81) negative and 8/81 (0/81) associations of nominal statistical significance” I assume this sentence is missing the word “positive” after (0/81)?

Thanks, corrected.

4. The authors acknowledge that the TMT-B results are “somewhat less robust” than the WMH results, but this wording seems too generous given that the effect nominally replicates in less than 20% of the analyses. At the very least, they should remove the word “somewhat” as this effect is clearly less robust than the WMH effect. It is also misleading to state that both effects are robust in line 301 and line 344 without qualification. Overall robustness should be assessed in a meta-analysis-like approach by calculating the average effect size and CI across the multiverse analyses. Is the average effect significantly different from 1? How does it compare to the observed effect size in the 2022 paper?

We appreciate this constructive criticism. We agree that robustness of the associations between WMH and FO on the one hand, and FO and TMT-B on the other, was not assessed in a quantitative fashion, and the qualifier "somewhat" should, therefore, be omitted. Indeed, with the multiverse analysis not being the main focus of the paper, no explicit rules were prespecified to infer "robustness" from its result. We do not agree, however, that our statements in the Summary and Discussion section are misleading, given that adjusted odds ratios for the association between FO and TMT-B are less than 1 for 64/81 specifications, even if only 8/81 reach nominal statistical significance. It is not clear how to conduct a meta-analytical pooling of the individual estimates and CIs of the multiverse analysis. Given that the sampling distributions of effect size estimates corresponding to different parcellations and regression models are not independent, usual meta-analytical methods cannot be used. It is also unclear what the epistemological value of such a pooled estimate would be. We have removed the word "somewhat" from the manuscript and moderated our language in the Results and Summary sections, which now read:
[ll. 316--318] In a multiverse analysis, the main findings of associations between WMH load and FO and, to a lesser extent, between FO and TMT-B were robust with respect to the processing choices of brain parcellation and confound regression strategy.
[ll. 360--362] In a pre-planned multiverse analysis, findings relating to our primary and, to a lesser extent, secondary hypotheses were robust with respect to variations in brain parcellations and confound regression strategies.

5. Forest plots of the multiverse analyses for periventricular and deep WMH volumes should be provided as supplementary material.

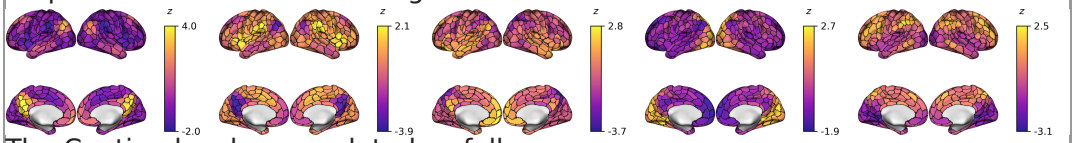
We are grateful for this suggestion and include the mentioned plots in a Supplementary Appendix. They are referenced in the caption to Figure 5 follows:
[Caption Fig. 5] Corresponding data based on periventricular and deep WMH volumes are presented in the Supplementary Appendix.

6. Figure 6. Do these spider plots align with network patterns identified in the 2022 paper?

Yes. Qualitatively, the spider plots in Figure 6 align well with the network patterns reported earlier. In particular, the two high-occupancy states are almost inverses of each other and characterized by a sharp peak of activation / suppression of DMN and a less sharp peak of suppression / activation of SAL. Two of the remaining three states can be identified with VIS+ and VIS-; the fifth state is less well defined. as before.

7. The spider plots do not characterize regional patterns of high vs. low activation in the clusters. Please provide brain images as well.

We thank the reviewer for this suggestion and have included brain surface maps of cluster centroids to Figure 6.



The Caption has been updated as follows:
[Caption Fig. 6] Centroids of each identified brain state visualized in brain space. Note the individual color scales.

8. It does not appear that the tests of additional cognitive relationships were corrected for multiple comparisons.

That is correct. For these exploratory analyses we only report nominal, uncorrected P values. Indeed, we considered not reporting P values for these associations at all and relegated them to the insets in Figure 7. Upon further reflection, we have no removed them from there as well, and only report adjusted and unadjusted effect size estimates.

9. “all reported associations were robust to additional, unplanned adjustments for DVARS, RMSD or mean framewise displacement.” - please provide the details of these analyses as supplementary material.

We appreciate this suggestion and include regression tables of the main hypotheses, adjusted for motion parameters, as supplementary material. We note that for our secondary hypothesis, the effect size estimate becomes greater (OR 0.71 rather than 0.98), while he nominal P value increases (0.0718 vs. 0.0116). They are referenced in the main text as follows:
[ll. 377--380] We further explored, and report in the Supplementary appendix, the effect of motion; results relating to our primary and, to a lesser extent, secondary, hypotheses were robust to additional, unplanned adjustments for DVARS, RMSD and mean framewise displacement.
We do not think that it would be helpful to present the results of another multiverse analysis, adjusted for motion.