

Review of: "Prediction and Analysis of Structural Brain Health Indicators Using Deep Learning Models with Functional Brain Images as Input"

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Potential competing interests: No potential competing interests to declare.

The authors present an interesting approach to derive an index of brain health and aging from standard resting-state (rs) functional magnetic resonance imaging (fMRI) data, referred to as 'functional connectivity brain healthcare quotient' (FC-BHQ). It is mainly motivated as an addition (or alternative index) to the existing 'gray matter brain healthcare quotient' (GM-BHQ) introduced by Nemoto et al. (2017; <https://doi.org/10.1371/journal.pone.0187137>). In general, a combination of such indices obtained from non-invasive neuroimaging data could provide valuable information on structure and function and their relation in studies of healthy or pathologic aging. The manuscript is well written and the methods and results are presented at sufficient detail. In the following, I am adding a few specific comments for potential consideration or discussion:

1. The general idea of looking into correlations of FC-BHQ with GM-BHQ is a good starting point for establishing an index based on rs-fMRI data and interesting in itself. However, one would also like to see how to move on from here. If the findings are restricted to brain areas showing high correlations, it may also suggest redundancy as one parameter would already be sufficient if there is no indication of complementarity.
I do agree though that the use of correlations is useful to demonstrate consistency of the results obtained with both indices. Is there any suggestion how to verify that FC-BHQ yields meaningful information beyond such correlations or whether one index might perform better or worse in certain brain regions?
2. Related to the previous point: The expression of artifacts (e.g., distortions, sensitivity to motion, contribution from non-neural sources to fluctuations in rs-fMRI time series) is rather different on the MRI input data. Would this impact the regional performance of the two indices?
3. Introduction: From a physicist's point of view, it seems possible that a spread of neuronal dendrites or increase in synapses might impact the contrast on T1-weighted structural MRI scans (e.g., through slightly enhanced interactions of membranes and water molecules). However, in my opinion there are no convincing data available demonstrating a particular sensitivity of voxel-based morphometry (VBM) to such alterations or even a specificity compared to other potential sources of subtle contrast alterations. I agree though that this is of only little relevance in the context of the current work.

