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

Evan Fletcher[1]

1 University of California, Davis

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There is a need for simple indices of brain health using brain imaging as input. Since imaging is multidimensional and often difficult to interpret, developing robust, understandable phenotypes associated with outcomes of interest (aging, health, cognition, for example) could be extremely valuable, and it is a topic of great interest in current research.

This paper shows promise because the brain index it bases its work on (the GM-BHQ) and the new one it develops (FC-BHQ, derived from functional MRI) could satisfy the need to be relatively easy to compute and potentially useful for predicting health related conditions and trajectories.

I have a few suggestions that I hope would be helpful in improving the clarity of the work and the usefulness of the results.

1. The BM-GHQ method. Although the present authors cannot retroactively change a previous approach (Nemoto), I suggest that a more useful index for the current paper could be feasibly constructed using more detailed input data. Thus, the original GM-BHQ was based on the difference: (individual IGMV - mean(GMV))/ std(GMV). This is fine, but to my eye it omits valuable details that could be easily obtained, such as regional values for GM that might be more associated to aging and cognition. By the way, it is an interesting innovation to design the formula as an analog of intelligence quotient (IQ) by making the mean = 100 and the standard deviation = 15.
2. Thus, I suggest that the current paper could start with a potentially more powerful GM index by incorporating other key brain measures (for example, hippocampal volume, temporal lobe or entorhinal cortex, posterior cingulate, or even looking at the literature on "brain signatures" of aging or cognition, e.g. [1][2][3][4]).
3. A key element of the current paper is to develop a functional connectivity index (FC-BHQ) analogous to GM-BHQ. This is a good idea, given that other aspects of brain structure and functioning beyond gray matter are important contributors to outcomes of interest. However, the FC-BHQ is based on the BrainGNN (neural net regression learning) prediction of the GM-BHQ. It therefore risks being a bit redundant with the former GM index. In other words, it is not a given that this new index will contribute substantially new information about the variation of outcomes beyond that predicted by GM-BHQ. At least to me, the more correlated the FC index is to the GM index, the less potential it may have for giving useful additional information.
4. The three stated goals of this paper are to "learn a relationship" between rs-fMRI and GM-BHQ, "verify the

applicability" of BrainGNN to regression rather than categorization, and "identify brain regions" of structure and function associated with aging. Maybe it's my limitation, but I found these goals a little diffuse. For example: (a) why focus only on associations with aging? (b) why not put the methodological goal (verifying the BrainGNN methodology for regression) into a supplement, so that we can focus on the power and utility of the brain indices for outcomes of interest?
5. In sum, I had trouble understanding a clear, focused result from this paper. Since the discussion seems to focus primarily on aging, it might be helpful to revise the abstract and introduction to make it clear that this is the main goal.

I also found some of the methods hard to follow. Thus, I could not follow the points in section 2.3.2. Could you elaborate there or elsewhere on several points:

1. What exactly is the "brain graph"? Please define it in full detail prior to getting into the methodology.
2. What is a node in the graph, and to which ROI is it associated? I couldn't find a description of the ROIs used, how they were selected, etc. Maybe this information is conveyed in section 2.3.4, but it would make for easier reading if introduced sooner.
3. The formula for the Pearson correlation (equation (1)) may not be necessary to show here, since it is so familiar. But what do you mean by "node features" being the CC coefficients (between what x and y?) and "partial correlation coefficients for the edges"?
4. You say that "y-hat" is the prediction of BrainGNN for the GM-BHQ variable. Thus, y-hat is really a GM-BHQ estimate. If so, then please explain in more detail how this yields an index for functional connectivity.
5. It may be useful to provide a figure showing the diagram of the neural net being used. The textual description in section 2.3.4 overview is hard to visualize.
6. The "soft-clustering" or "hard clustering" methodology in 2.3.6 could better explained in more detail. This is crucial because apparently the clustering is used to identify brain regions that predict GM-BHQ (section 2.3.7)

Some points about the Results:

1. In section 3.1, you show the relationship between GM-BHQ and age. Is the purpose here to validate GM-BHQ? Otherwise, I am not sure how this fits into the goal of developing the new FC-BHQ measure.
2. Also, the strength of the correlations seems to be somewhat weaker than other "brain age" results, e.g.,[5][6], perhaps underlining my earlier point that indices of brain age other than GM-BHQ may be more powerful indicators of aging.
3. You state that "it is necessary to emphasize that FC-BHQ refers to the GM-BHQ predicted using rs-fMRI". Maybe I am missing something, but to me this again raises the question of how useful the new measure is, i.e, how much new information is obtained from this formulation of FC-BHQ. In other words, I could envision an alternative derivation of FC-BHQ from functional data alone (i.e., distinct from GM data), thereby making it easier to see that this is a new index that could be useful in models that incorporate both FC-BHQ and GM-BHQ.
4. I had difficulty interpreting Figure 5. The purpose seems to be showing that there is a "clear separation" "confirming the significance of the ROI-based learning". More explanatory text or summary here would be very helpful.
5. Table 2 and Figure 7. These are potentially very interesting. It would be useful to understand in more detail how these

partial regression associations are derived using the methodology in sections 2.3. There, the statistical techniques are quite sophisticated, and non-experts (of which I am one) could benefit by more explanation.

Some points about the discussion:

1. In section 4.1, you say “there is room for improvement in our model” because the correlation between FC-BHQ and GM-BHQ is moderate. As I said earlier, this might not necessarily be bad, since we could hope that these two indices might explain complementary portions of outcome variance in age, brain health, etc. In other words, if you could achieve, for example, r > 0.95, then essentially the two indices would be almost synonymous measures of the same underlying factor. Please explain.
2. In much of the discussion, the focus seems to be on the relevance of the ROIs for aging. This is interesting. However, a couple of observations are relevant here.

- First, other recent efforts have focused on developing “brain age” measures (see the references I gave earlier), so it might be appropriate to discuss the current results in that context, in order to get a better idea of the novel contributions of the current article.
- Next, the abstract and introduction talk about the need for new brain indices associated to brain health, which sounds like a broader category than just aging. It might be appropriate to clarify the purpose of the current article, or else add some discussion on how the two indices might be useful for other factors than aging alone.

References

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