HI Tiago,

Many thanks for this. I had a chance to give it a quick stab on the data. Running CCA, I find evidence that frontal regions predict cognition, better than MTL (Model 2 in red vs Model1 in blue in bottom panel of figure below), but combination of frontal (PFC) and MTL does not predict cognition than frontal only (Model 3 in green vs Model 2 in red). for completeness I am also showing the comparison for permuted data (top panel with null1, null2, null3).

Chart, histogram

Description automatically generated

This is the case when running the analysis with  PLS instead of CCA.

Chart, histogram

Description automatically generated

I have also confirmed these results using bootstrapping, rather than cross-validations.

Finally, there is no evidence for a second component, i.e. ruling out the possibility that MTL predicted different signals in cognition over and above PFC.

In sum, the quick analysis on this data suggests that frontal regions predict the cognitive measures better than MTL, and there is not much (if anything) in MTL that can tell us about performance on these cognitive tests.

You can possibly confirm this in easier manner. For example, define one cognitive component across all cognitive measures using PCA/EFA/SEM in combinatino with model comparisons. Then perform multiple linear regression with different model complexities:

- model 1: CognitionPCA ~ MTL measures

- model 2: CognitionPCA ~ frontal measures

- model 3: CognitionPCA ~ MTL + frontal measures

I have quickly performed this. For model1 (MTL), x1, x5-x7 predicted uniquely cognition over and above all other predictors (x1-x4)

Text

Description automatically generated

For Model2 (frontal regions), x1,x5 and x6 predicted cognition over and above other predictors.

Table

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For Model 3, predictors x8,x12,x13 (which is x1, x5,x6 in Model2, PFC) remain unique predictors, while only x6 of MTL regions has a tendency to contribute uniquely (which is confirmed through bootstrapping technique and structural equation modeling).

Table

Description automatically generated with medium confidence

In terms of model comparisons - Model3 fits the data better than Model1, i.e. inclusion of PFC to MTL add explanatory value. However, Model3 does not fit the data better than Model2, i.e. MTL does not add significantly to PFC.

I have also run SEM to compare a single factor model (PFC and MTL form a single factor) vs a two factor model (PFC forms a separate factor from MTL) that are predicting a single cognitive factor. The single model was a winner confirming that MTL does not form a separate factor from PFC.

all in all, except for the fact that x6 in MTL explains a tiny portion of variance in cognition over and above PFC, there is convincing evidence that PFC is sufficiently good to explain the variance in these cognitive measures. Having said, you should keep in mind that the result hold for the variables you shared with me. But if you choose another set of MTL regions or cognitive measures, the result may look otherwise.

Happy to share code and talk you through the results if that is helpful.

BW,

Kamen

Hello,

see inline responses.

On Tue, 29 Mar 2022 at 19:23, Karen Campbell <[Karen.Campbell@brocku.ca](mailto:Karen.Campbell@brocku.ca)> wrote:

Yes, thanks for your help, Kamen. Basically, I’d like to stick with the CCA because it shows us the loadings for the item and detail memory scores separately, and these loadings are determined based on the relationship with the brain measures (instead of boiling down the cognitive scores separately in a PCA). But I was happy to see that your PCA followed by regressions approach basically yielded the same answer.

that sounds reasonable. I provide code for these variations in the archive with the main script to adapt 'cca\_model\_comparison.m'.

To move forward with the CCA approach in the paper (and yes, more importantly, Tiago’s PhD thesis!), we are just wondering if there is some kind of statistic to report that corresponds to the figure you attached below showing a lack of overlap between models 1 and 2, and model 3 not fitting much better. Or should we just show this plot?

the model comparisons will come from testing whether the distribution of fit values for one model is statistically higher than the other model (see lines 110-120). In terms of evidence for (or lack of) overlapping/shared information explained by each model can come from comparing the loadings of cognitive measures or subject scores across models (cognition acts as an anchor point across models).

I talked to Dr. Campbell about it, and we decided to keep the CCA analysis we did previously (that code I shared with you), and use your cross-validation / bootstrapping approach to provide evidence on model fit. From there, we thought of thresholding loadings on .5  to define and discuss the significant ones. We decided to take a more direct approach on this to move forward with ease (I need to graduate on time).

sounds good.

Could you, please, share with us the code of the cross-validation / bootstrapping method you used to evaluate model fit and compare the models? Regarding comparing models, what would you suggest for us to include in the paper? We thought of using the bottom panel you shared in the first image (that clearly shows models 2 and 4 have higher correlations with Y), describing its results with numbers, in addition to introducing its reasoning in the methods section. What do you think?

sure, moving forward with CCA, there is a subtle difference in interpretation between cross-validations and bootstrapping in terms of providing estimates of the test error versus providing standard error of the estimates. I have previously done some work on cross-validated CCA for model comparison (Tsvetanov et al 2018), so it may be easier to integrate. As to bootstrapping there are various ways of doing it - I have provided a snippet of code in the main script to get you going (lines 140-170), but it may require some adaptation depending on what parameters you want (e.g. loadings, subjects or model-fit). The toolbox also has the potential for more complex versions of boostrapped-cross-validated CCA (e.g.[Kovacevic et al](https://www.researchgate.net/publication/281402921_Revisiting_PLS_Resampling_Comparing_Significance_Versus_Reliability_Across_Range_of_Simulations) and [Churchil et al](https://personal.utdallas.edu/~herve/abdi2013-csakms-plsnpairs.pdf" \t "_blank)), but I wont go there yet.

In terms of defining and discussing the significant loadings, I noticed that by thresholding it on .5 we would get a few more significant loadings than if we use the PCA approach you used (image attached), but I don't think that would be a problem. In case someone asks us about it we can say we also evaluated the significance of loading with different approaches as well (the PCA analysis you did / Boot4CCA function in R  - which resulted in an even higher number of significant loadings).

you could potentially threshold using an arbitrary threshold, though the script also includes an empirical justification for thresholding based on the permutation-based cross-validated approach (lines 120-138).

For completeness, I am also providing the code for MLR approach.

In case you think a meeting would be helpful, we can certainly arrange that.

see how it goes with the code and let me know if it needs to discuss the approach or results.

In case you run into error messages or dependencies, please do not hesisate to let me know.

see responses below.

I ran the entire script step-by-step and went over its results. The code and comments are very clear, so it was possible to explore the outputs without getting lost in the middle of such a huge amount information there 🙂 (You keep things very organized in multiple structures - and the quality of your work is great!). I think I just need to confirm with you the exact pieces of information we will report from it:

glad to hear that you found the code useful and you were able to set up the analysis. Thanks for the kind words - it is a work of progress and I am still learning how to improve coding practice.

1. For comparing models, we are going to use the cross-validation approach (code lines 110-120) and the plot with the distributions of r values lines 86-96). In this case, for showing the results, I thought of showing the plot and describing the stats with T values and p values available at cfg.tstat amd cfg.p\_orig respectively. (?)

that sounds reasonable.

1. Regarding the significance of loadings, we are going to use your permutation-based cross-validated approach (lines 120-138). For that, I understood I should use the p-values of the loadings for each model available at M{model}.valXLpval and M{model}.valYLpval. (?)

yes, that is correct. I am also happy to implement something like a bootstrap ratio or cross-validated ratio on the Loadings, but I suspect it would be less stringent than what we already have.

I will also have your publication (Tsvetanov et al 2018), as a reference for describing these procedures in the methods section, and I will send it you for you to review once it is ready.

fine.

Then, when it comes to performing the following moderation analysis (to investigate inf the relationship between X and Y is moderate by age / gender), which model would you both recommend using? Model 3 (MTL+PFC) or Model 2 (PFC)? As a refresher, our results indicate that frontal regions predict cognition, better than MTL (Model 2 vs Model1), but combination of PFC and MTL does not predict cognition than PFC only (Model 3 vs Model 2).

I am afraid I don't know  much about the project aims, so Karen is probably in a better position to comment, but happy to discuss in more detail.

BW,

Kamen

Thanks Kamen for your input and help.

Tiago, I think for the follow up regression, you should use the PFC only (model 2) since the evidence suggests that model 3 doesn't offer additional predictive power.

Best,

Karen