Integration of model information into model-free multivariate analyses of structural and diffusion MRI data

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INTRODUCTION Two common distinctions in analysis methods for imaging data are A) *univariate* (all voxels' timeseries/"subjectseries" processed separately from each other) vs. *multivariate* (the entire dataset analysed simultaneously), and B) *model-based* (we use a model comprising one or more timeseries/subjectseries, or even spatial maps, as predictors to fit against the data) vs. *model-free* (we do not impose a known model but look for patterns of interest within the data). Such patterns almost always involve comparing time series across different localities in the brain, i.e., operating within a multivariate framework. We therefore have three common analysis methodologies: univariate model-based (e.g., "GLM"), multivariate model-based (e.g., PLS, CVA, SVD-CVA, MLM), and multivariate model-free (e.g., PCA, ICA). Model-based methods can have an increased reliability in identifying expected responses, aiding interpretability of results. Conversely, model-free methods are able to find "surprising" effects in the data (which may or may not be fully interpretable), or at least separate out structured confound processes from signals of interest, improving sensitivity. Very little work has to date been carried out on attempting to combine the best aspects of the different possible approaches. Here we present some initial results from attempting to insert model information into a multivariate model-free approach (ICA) and compare this approach to a GLM analysis as well as to PLS and CVA. We find that results from approaches containing both model-based and data-driven aspects are almost always more interpretable than rigidly enforcing model structure (as in GLM/PLS/CVA), and in some cases the optimal approach appears to be not to use the model at all.

DATA & PREPROCESSING From the EAGLE study of mild cognitive impairment (MCI) and AD, we used MRI data from 47 controls, 50 AD and 57 MCI patients. In order to prepare data for multivariate analyses, we applied FSLVBM (Voxel-Based Morphometry using FSL tools, to test for differences across groups in grey matter density, as imaged by structural MRI) and TBSS (Tract-Based Spatial Statistics, part of FSL, to test for differences in white matter microstructure across groups, as imaged by diffusion MRI). Our model included age, disease duration and clinical dementia rating, as well as a separate group membership covariate for each of the 14 diagnosis X gender X APOE subgroup combinations.

MULTIVARIATE METHODOLOGY ICA (independent component analysis) is typically preceded by dimensionality reduction and data whitening through the used of an initial PCA (principal component analysis). Hence the first possible use of a model can be to *inform the PCA dimensionality reduction*, in order, for example, to ensure that the reduced data space fully includes the space of the model. In our case, we first projected the data onto the model and applied PCA to the residuals of this model fit (in order to find covariance structure in the data that is not explained by the model), and then projected the original data onto the combined space of the model and the residual-based strongest PCA eigenvectors. The resulting reduced data is then passed through to the ICA unmixing, which attempts to separate out spatio"temporal" components on the basis of their (in this case) spatial independence. At this stage, the second possible use of the model can be to project the model into the reduced data space, and use the resulting projected model weights to *initialise the ICA unmixing matrix* (which is then optimised according to the ICA cost function). Alternatively, one could attempt to *force* the ICA unmixing to keep some components fixed according to covariates in the model; however, this is likely to lead to instabilities in the ICA optimisation, and furthermore is unlikely to give satisfactory results when the model is imperfect. We here compare the first vs. second option and also evaluate the performance of the proposed approach against fully model-based multivariate methods, including PLS and CVA, applied to the same datasets.

RESULTS & DISCUSSION With fully data-driven ICA, several interpretable group-discriminating components were found in both structural and diffusion data. When inserting the model into the initial PCA-based dimensionality reduction, the final components were in some cases less spatially interpretable, and less discriminative between the subjects groups. When using "standard" PCA, but initialising the ICA using the model, the results were quite similar to the fully model-free analyses (this is not very surprising as the ICA unmixing is known to be generally robust against the exact choice of initialisation), but with a slight improvement in spatial interpretability and group discrimination. From this analysis, the figure shows the 3 ICA components which most strongly discriminate control, AD and MCI groups (all thresholded at Z>5). Relative to mean grey matter density in controls, and considering the losses seen in AD, the MCI group sees relatively more grey matter loss in the medial temporal lobe (red) and less in the inferior precuneus (green). It would appear that at the stage of dimensionality reduction, moving the balance of power from purely data-driven towards model-based can be detrimental to the final results. In the case of an FMRI timeseries analysis, this could arise because of imperfections in the temporal modelling (HRF convolution, activation nonstationarity over time, etc.). In the case of multisubject structural or diffusion analysis, this could arise because the aspects of the model of interest (such as genotype) influence the phenotype (as seen through the MR imaging) via a complex route, for example including interactions with unmodelled factors such as environmental influences; hence, although the resulting effect of [modelled factor combined with unmodelled factor] in the data may still be strongly subject-specific (and hence potentially valuable within a covariance-based multivariate analysis), it does not perfectly correlate with the model. By splitting such effects in the data into model-based and non-model-based parts, we may reduce the variance in the non-modelled part of this effect to such an extent that this aspect of the data is ignored in the dimensionality reduction stage, and hence lose power in our final multivariate component identification. Fully model-based multivariate approaches (such as PLS and CVA) can be expected to suffer even more strongly from this problem, and indeed our results were even less interpretable and discriminative when using these methods. Such complications will be further exacerbated as we also extend multivariate approaches to simultaneous analyses of multiple modalities (for example, feeding the structural and diffusion data into a single simultaneous analysis using ICA).