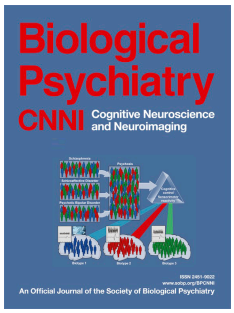

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Canonical Correlation Analysis and Partial Least Squares for identifying brain-behaviour associations: a tutorial and a comparative study

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Abstract

Canonical Correlation Analysis (CCA) and Partial Least Squares (PLS) are powerful multivariate methods for capturing associations across two modalities of data (e.g., brain and behaviour). However, when the sample size is similar or smaller than the number of variables in the data, CCA and PLS models may overfit, i.e., find spurious associations that generalise poorly to new data. Dimensionality reduction and regularized extensions of CCA and PLS have been proposed to address this problem, yet most studies using these approaches have some limitations.

This work gives a theoretical and practical introduction into the most common CCA/PLS models and their regularized variants. We examine the limitations of standard CCA and PLS when the sample size is similar or smaller than the number of variables. We discuss how dimensionality reduction and regularization techniques address this problem and explain their main advantages and disadvantages. We highlight crucial aspects of the CCA/PLS analysis framework, including optimising the hyperparameters of the model and testing the identified associations for statistical significance. We apply the described CCA/PLS models to simulated data and real data from the Human Connectome Project and the Alzheimer's Disease Neuroimaging Initiative (both of n>500). We use both low and high dimensionality versions of each data (i.e., ratios between sample size and variables in the range of ~1-10 and ~0.1-0.01) to demonstrate the impact of data dimensionality on the models. Finally, we summarize the key lessons of the tutorial.

Introduction

Neuroimaging datasets with sample sizes of n>1000 (e.g., UK Biobank, Human Connectome Project, Alzheimer's Disease Neuroimaging Initiative) represent a unique opportunity to advance population neuroscience and mental health (1–3). These datasets comprise multiple data modalities (e.g., structural Magnetic Resonance Imaging (MRI), resting-state functional MRI, mental health, cognition, environmental factors and genetics), several of which can be high-dimensional, meaning there are hundreds or thousands of variables per subject. Understanding the links across these different modalities is fundamental for enabling new discoveries, however, analysing multimodal datasets with more variables than samples poses technical challenges.

The most established methods to find associations across multiple modalities of multivariate data are Canonical Correlation Analysis (CCA) (4) and Partial Least Squares (PLS) (5). CCA and PLS have recently become very popular with numerous applications linking brain imaging to behaviour or genetics (e.g., (6–26)). However, when the variables in at least one modality (e.g., brain) outnumber the sample size, standard CCA and PLS models may overfit, i.e., more likely to find spurious associations that generalize poorly to independent samples (see e.g., (26–28)). Moreover, there is no unique standard CCA solution when the number of variables exceeds the sample size. Two approaches have been proposed to address this problem: i) reducing the dimensionality of the data with Principal Component Analysis (PCA) (9,10,12,22,24,26); ii) using regularized extensions of CCA and PLS (11,20,23,27). Most studies using these approaches have potential limitations, however. For instance: i) they usually do not optimise the hyperparameters (e.g., number of principal components or amount of regularization) (9,10,12,15,22,24,26); ii) many studies do not test the significance of the associations using hold-out data (e.g., out-of-sample correlation) (7,9–11,22); iii) they often do not assess the stability of the CCA/PLS model (7,9,18,21–25). Finally, few studies compare

different CCA/PLS models and analytic frameworks across different datasets with different dimensionalities (see e.g., (25–27)).

Several tutorial papers were recently published on CCA and PLS (29–32). Here, we complement these tutorials by discussing some important conceptual and practical aspects of these methods. These comprise: i) the advantages and disadvantages of the various CCA/PLS models, ii) the impact of PCA and regularization on these models (e.g., on overfitting and stability), and iii) the importance of the analytic framework in optimising the models' hyperparameters and performing statistical inference.

In Part 1, we present the theoretical background of these models and discuss the most common strategies to mitigate the problems caused when the ratio between sample size and number of variables is small (e.g., of around ~0.1-0.01). We also examine the most prevalent analytical frameworks used with CCA/PLS models. In Part 2, we apply the models introduced in Part 1 to simulated data and real data from the Human Connectome Project (HCP) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) (n>500 in all). We illustrate how the different CCA/PLS models perform with data dimensionalities often used in practice (i.e., ratios between sample size and number of variables in the ranges of ~1-10 or ~0.1-0.01). Moreover, we show that regularization can be helpful even when the number of variables in both data modalities is smaller than the sample size. Mathematical details of the CCA/PLS models and their connections are provided in the Supplement.

Part 1: Technical background of CCA and PLS

CCA/PLS optimization and nomenclature

Canonical Correlation Analysis (CCA) (4) and Partial Least Squares (PLS) (5) are multivariate latent variable models that capture associations across two modalities of data (e.g., brain and behaviour). For example (Figure 1), $\boldsymbol{X}$ contains voxel-level brain variables and $\boldsymbol{Y}$ contains behavioural variables from item-level self-report questionnaires (i.e., $\boldsymbol{X}$ and $\boldsymbol{Y}$ are matrices with rows and columns representing subjects and variables, respectively). Standard CCA/PLS find pairs of brain and behavioural weights $\boldsymbol{w}_x$ and $\boldsymbol{w}_y$ (column vectors) such that the linear combination (weighted sum) of the brain and behavioural variables maximises the correlation (CCA) or covariance (PLS) between the resulting latent variables, i.e., between $\boldsymbol{\xi} = \boldsymbol{X}\boldsymbol{w}_x$ and $\boldsymbol{\omega} = \boldsymbol{Y}\boldsymbol{w}_y$, respectively.

In the PLS literature, the weights are often referred to as saliences and the latent variables as scores. In the CCA literature, the weights are often referred to as canonical vectors, the latent variables as canonical variates, and the correlation between the latent variables as canonical correlations. The brain and behaviour weights have the same dimensionality as their respective data modality (e.g., number of brain/behavioural variables) and quantify each brain and behavioural variable's contribution to the identified association. Sometimes the Pearson correlations between the brain and behavioural variables and their respective latent variable are presented instead of the model's weights, and are called structure correlations (CCA) (33) or loadings (PLS) (34) (for details, see the Supplement). The latent variables (one latent variable score per data modality and subject) quantify how the associative effect is expressed across the sample. Table 1 summarizes the different nomenclatures used in the CCA and PLS literature.

While standard CCA refers to a single method, standard PLS refers to a family of methods with different modelling aims (e.g., assuming a symmetric or asymmetric relationship between the

two data modalities; for details, see the Supplement). Standard CCA and PLS can be both solved by iterative (e.g., alternating least squares (35), non-linear iterative partial least squares (36)) and non-iterative (e.g., eigenvalue problem (29,34)) methods. In case of iterative methods, once a pair of weights is obtained, the corresponding associative effect is removed from the data (by a process called 'deflation') and new associations are sought.

Since standard CCA maximises correlation between the latent variables, it is more sensitive to the direction of the relationships across modalities, and it is not driven by within-modality variances. On the other hand, standard PLS – which maximises covariance – is less sensitive to the direction of the across-modality relationships as it is also driven by within-modality variances. Formally, we can see this from the optimization of these models. Standard CCA optimizes correlation across modalities:

$$max_{\boldsymbol{w}_x,\boldsymbol{w}_y} corr(\boldsymbol{X}\boldsymbol{w}_x, \boldsymbol{Y}\boldsymbol{w}_y). \quad \text{(Eq. 1)}$$

Standard PLS optimizes covariance across modalities – the product of correlation and standard deviations (i.e., square root of variance):

$$max_{\boldsymbol{w}_x,\boldsymbol{w}_y}\ cov(\boldsymbol{X}\boldsymbol{w}_x, \boldsymbol{Y}\boldsymbol{w}_y) = corr(\boldsymbol{X}\boldsymbol{w}_x, \boldsymbol{Y}\boldsymbol{w}_y)\sqrt{var(\boldsymbol{X}\boldsymbol{w}_x)}\sqrt{var(\boldsymbol{Y}\boldsymbol{w}_y)}. \quad \text{(Eq. 2)}$$

This also means that standard CCA and PLS are equivalent optimization problems when $var(\boldsymbol{X}\boldsymbol{w}_x) = var(\boldsymbol{Y}\boldsymbol{w}_y) = 1$, which is true when the within-modality variances are identity matrices, i.e., $\boldsymbol{X}^T\boldsymbol{X} = \boldsymbol{Y}^T\boldsymbol{Y} = \boldsymbol{I}$.

Limitations of standard CCA/PLS

When the ratio between the sample size and the number of variables is similar or smaller than 1, standard CCA/PLS models present limitations. These limitations can exist irrespective of sample size if the number of variables is large, or the variables are highly correlated. In case of standard CCA the key limitations are: i) The optimization is ill-posed (i.e., there is no unique solution) when the number of variables in at least one of the modalities exceeds the sample

size; ii) The CCA weights $\boldsymbol{w}_x$ and $\boldsymbol{w}_y$ are unstable when the variables within one or both modalities are highly correlated, known as the multicollinearity problem (37). These limitations might sound familiar, not surprisingly, as standard CCA can be viewed as a multivariate extension of the univariate General Linear Model (38,39). The standard PLS optimization is never ill-posed and copes with multicollinearity (i.e., PLS weights are stable (36)), however, standard PLS and CCA cannot perform feature selection (i.e., setting the weights of some variables to 0) and may therefore have low performance where the effects are sparse.

These limitations can be addressed by dimensionality reduction (i.e., PCA) or regularization. Regularization adds further constraints to the optimization to solve an ill-posed problem or prevent overfitting. For CCA/PLS models, the most common forms of regularization are L1-norm (lasso) (40), L2-norm (ridge) (41) and combinations of L1-norm and L2-norm regularization (elastic-net) (42).

Standard CCA with PCA dimensionality reduction (PCA-CCA)

Principal Component Analysis (PCA) transforms one modality of multivariate data into uncorrelated principal components (PC) (it is also related to whitening, see 'Effects of pre-whitening on CCA/PLS models'). PCA is often used as a naïve dimensionality reduction technique, as PCs explaining little variance are assumed to be 'noise' and discarded, and the remaining PCs entered into standard CCA. However, PCA when applied before CCA can be also seen as a technique similar to regularization: it makes the CCA model well-posed and addresses the multicollinearity problem.

The number of retained PCs can be selected based on their explained variance, e.g., 99% of total variance. In PCA-CCA applications, often the same number of PCs are chosen for both data modalities, based on the lower dimensional data – usually behaviour (e.g., (9,10,22,24)). Sometimes the same proportion of explained variance – rather than numbers of PCs – is used

for both data modalities (e.g., (12,26)). One problem with discarding PCs with low variance is that there is no guarantee that PCs with high variance in either modality are best to link the different data modalities, whilst some discarded PCs might contain useful information. To address this problem, we can use a data-driven approach, by selecting the number of PCs that maximise the correlation across modalities (see 'CCA with dimensionality reduction vs. regularized CCA' in Part 2).

Regularized CCA (RCCA)

L2-norm regularization is a popular form of regularization for ill-posed problems or for mitigating the effects of multicollinearity, originally used in ridge regression (41). In L2-norm regularization, the added constraint corresponds to the sum of squares of all weight values[1], which forces the weights to be small but does not make them zero. L2-norm regularization has been proposed for CCA (43), commonly referred to as regularized CCA (RCCA) (34,44–46). Interestingly, in RCCA, the regularization terms added to the CCA problem leads to a mixture of standard CCA and standard PLS optimization. We can see this from the RCCA optimization problem:

$$max_{\boldsymbol{w}_x,\boldsymbol{w}_y} \frac{corr(\boldsymbol{X}\boldsymbol{w}_x,\boldsymbol{Y}\boldsymbol{w}_y)\sqrt{var(\boldsymbol{X}\boldsymbol{w}_x)}\sqrt{var(\boldsymbol{Y}\boldsymbol{w}_y)}}{\sqrt{(1-c_x)var(\boldsymbol{X}\boldsymbol{w}_x)+c_x}\sqrt{(1-c_y)var(\boldsymbol{Y}\boldsymbol{w}_y)+c_y}}. \quad \text{(Eq. 3)}$$

where the two hyperparameters (c_x, c_y) control the amount of regularization and provide a smooth transition between standard CCA ($c_x = c_y = 0$, not regularized) and standard PLS ($c_x = c_y = 1$, most regularized) (34,44). Importantly, as L2-norm regularization mitigates multicollinearity it increases the stability of the RCCA weights. However, it also means that similar to standard PLS, RCCA can be driven by within-modality variances. For additional

[1] L2-norm: $\|\mathbf{w}\|_2 = \sum_i w_i^2$, where $\mathbf{w} = (w_1, w_2, \ldots, w_n)$ is a vector of size n

connections between standard CCA, RCCA, standard PLS and how they are related to PCA-CCA, see the Supplement.

Sparse PLS (SPLS)

L1-norm regularization was originally proposed in Lasso regression (40). In L1-norm regularization, the added constraint corresponds to the absolute sum of weight values[2], which sets some of the weight values to zero resulting in variable selection and promoting sparsity. Sparse solutions facilitate the interpretability of the model and may improve performance when only a subset of variables is relevant (40). However, sparsity can also introduce instability to the model if different sets of variables provide similar performance. Elastic net regularization is a mixture of L1-norm and L2-norm regularization which combines the properties of both forms of regularization and can mitigate the instability of L1-norm regularization (42). In one popular algorithm (17), which we will refer to as sparse PLS (SPLS), hyperparameters control the amount of L1-norm regularization or sparsity. Since PLS can be seen as CCA with maximal L2-norm regularization (see section before), SPLS can also be viewed as an elastic net regularized CCA (for details, see the Supplement).

Effects of pre-whitening on CCA/PLS models

In machine learning, data are often whitened as a pre-processing step. Whitening transforms the original variables into new, uncorrelated features, which are normalized to have unit length (i.e., L2-norm of each feature equals 1). Whitening is not a unique transformation and the most commonly used forms are PCA-, Mahalanobis- and Cholesky-whitening (55). The critical difference between PCA and PCA-whitening is that PCA retains the variance of the original data, i.e., the principal components are not normalized to have unit length.

[2] L1-norm: $\|\mathbf{w}\|_1 = \sum_i |w_i|$, where $\mathbf{w} = (w_1, w_2, \ldots, w_n)$ is a vector of size n

Whitening as a pre-processing step has a major drawback in CCA/PLS models: the beneficial effects of L1-norm and L2-norm regularization on the original variables cannot be achieved any more as the whitened data are the new inputs of the model. In case of SPLS, L1-norm regularization will result in sparsity on the whitened variables (instead of the original variables) thus the interpretability of the results will not be facilitated. In case of RCCA, L2-norm regularization is not active on whitened data, which means that CCA, RCCA and PLS will yield the same results. For additional details on whitening, see the Supplement.

Analytic frameworks for CCA/PLS models

The statistical significance of the CCA/PLS model (i.e., the number of significant associative effects) can be evaluated using either a descriptive or a predictive (also referred to as a machine learning) framework. The two frameworks have distinct goals: the aim of the descriptive framework is to detect above-chance associations in the current dataset, whereas the aim of the predictive framework is to test whether such associations generalise to new data (56–59).

In the descriptive framework (Figure 2A), CCA/PLS is fitted on the entire sample, thus the statistical inference is based on in-sample correlation. In this framework, there is usually no hyperparameter optimization (i.e., the number of PCs or regularization parameter is fixed *a priori*). In the predictive framework (Figure 2B), CCA/PLS is fitted on a training/optimization set and evaluated on a test/holdout set, thus the statistical inference is based on out-of-sample correlation. This procedure assesses the generalizability of the model, i.e., how well the association found in the training set generalizes to an independent test set. In the predictive framework, the hyperparameters are usually optimized, therefore the training/optimization set is further divided into a training and a validation set and the best hyperparameters are selected based on out-of-sample correlation in the validation set. In both descriptive and predictive frameworks, permutation inference (based on in-sample or out-of-sample correlation) is often used to assess the number of significant associative effects (59,60).

Lastly, an important component of any CCA/PLS framework is testing the stability of the model. Usually a bootstrapping procedure is applied to provide confidence intervals on the model's weights (59). Recently, stability selection (19,20,61–63) has been proposed with the aim of selecting the most stable CCA/PLS model in the first place, rather than evaluating the stability of the model post-hoc. Alternatively, the stability of the CCA/PLS models can be measured as the average similarity of weights across different splits of training data, which avoids the additional computational costs of the previous two approaches (27). For more details on analytic frameworks, see e.g., (22,27,50,59).

Part 2: Demonstrations of CCA and PLS analyses

Description of experiments

In order to demonstrate the properties of different CCA and PLS approaches, we applied the models introduced in Part 1 to real and simulated datasets with different dimensionalities and sample sizes. Table 2 gives an overview of all experiments.

We chose the Human Connectome Project (HCP) and the Alzheimer's Disease Neuroimaging Initiative (ADNI) datasets based on two recent landmark studies (22,50). In the HPC dataset, we used resting-state fMRI connectivity data (19 900 and 300 brain variables in the high- and low-dimensional data, respectively) and 145 non-imaging subject measures (e.g., behavioural, demographic, lifestyle measures) of 1003 healthy subjects. In the ADNI dataset, we used whole-brain grey matter volumes (168 130 and 120 brain variables in the high- and low-dimensional data, respectively) and 31 item-level measures of the Mini-Mental State Examination (MMSE) of 592 elderly subjects. We generated the simulated data with a sparse signal (i.e., 10% of the variables in each modality were relevant to capture the association across modalities) and properties similar to the HCP dataset (in terms of sample size, dimensionality and correlation between latent variables). Table 3 displays the characteristics

of the real and simulated datasets. For further details of the datasets and the simulated data generation, see the Supplement.

The PCA-CCA model was used both with fixed numbers of PCs within a descriptive framework and with optimized number of PCs within a predictive framework. All the other CCA/PLS models were used within a predictive framework. The predictive framework was based on (50), which uses multiple test/holdout sets to assess the generalizability and robustness of the CCA/PLS models (detailed in the Supplement). In both frameworks, permutation testing was used to assess the number of statistically significant associative effects based on in-sample and out-of-sample correlations between the latent variables, respectively. Importantly, the family structure of the HCP dataset was respected during the different data splits (training, validation, test/holdout sets) and permutations (64). We used iterative methods to solve CCA/PLS and applied mode-A deflation for standard PLS and SPLS and generalized deflation for standard CCA, PCA-CCA and RCCA (for details, see the Supplement). For simplicity, we present the results for the first associative effect in most CCA/PLS experiments (for a summary of all associative effects, see Table S1). Throughout the paper, we present the weights (canonical vector for CCA models, salience for PLS models) and latent variables obtained by the model.

We used linear mixed-effects (LME) models to compare the different CCA/PLS models on the following measures across the outer training or test sets: i) in-sample correlation; ii) out-of-sample correlation; iii) similarity of the model weights (measured by Pearson correlation); iv) variance explained by the model. In addition, we compared the number of PCs between PCA-CCA models with fixed vs. data-driven number of PCs. We report significance at $p<0.005$ in all LME models. For further details of the LME analyses, see the Supplement. We also quantified the rank-similarity of the weights (measured by Spearman correlation) across the different CCA/PLS models in the real datasets.

In-sample vs. out-of-sample correlation in high-dimensional data

Figure 3 and Table 4 display the in-sample and out-of-sample correlations for all experiments using all three high-dimensional datasets. On average the out-of-sample correlations are lower than the in-sample correlations ($t(14)=4.51$, $p=0.0005$). In real datasets, CCA/PLS models with dimensionality reduction or regularization provide high out-of-sample correlations in most cases underlining that these models generalize well to unseen data. The only notable exceptions are standard PLS and SPLS, which present significantly lower out-of-sample correlations in the HCP dataset (Figure 3B) ($F(2,56)=289.30$, $p<0.0001$). This can be attributed to the different properties of the HCP dataset (e.g., higher noise level and non-sparse associative effect) and the fact that standard PLS and SPLS are especially dominated by within-modality variance in this dataset (Table 4).

In conclusion, we recommend embedding all models in a predictive framework that splits the data into training and test sets to assess the model's out-of-sample generalizability.

Standard CCA with PCA dimensionality reduction vs. regularized CCA in high-dimensional data

In this section, we present the results of applying PCA-CCA and RCCA to all three high-dimensional datasets. We focus on experiments using the predictive framework and compare PCA-CCA with fixed versus data-driven numbers of PCs, as well as both of these models to RCCA.

Figure 4A-C and Figure 5A-C display the brain and behavioural weights and corresponding latent variables for the three models (note that for the HCP dataset the brain weights were transformed into brain connection strength increases/decreases). Figure 6 compares the brain and behavioural weights using rank-similarity across the models, which indicates that although the weights are similar across the three models, data-driven PCA-CCA and RCCA are more

similar to each other. The model weights and latent variables for the simulated dataset can be found in Figure 7A-C, which suggest that all three models recovered sufficiently the true weights of the generative model. Nevertheless, the non-sparse models attributed non-zero weights for many non-relevant variables (for details, see Table S2).

To further investigate the characteristics of the three models, Table 4 shows the stability of weights and the explained variance by the models. The stability of weights varied significantly across brain and behaviour modalities ($F(1,804)=84.51$, $p<0.0001$) and models ($F(2,804)=91.63$, $p<0.0001$). Notably, the stability of RCCA weights was consistently high. The explained variance varied significantly only across modalities ($F(1,174)=241.55$, $p<0.0001$) but not models ($F(2,174)=0.31$, $p=7303$).

Next, we examined the number of PCs in the two PCA-CCA models. We found a significant interaction between the effect of data modality and model on the number of PCs ($F(1,114)=22.63$, $p<0.0001$). Data-driven PCA-CCA yielded more brain PCs and fewer behavioural PCs than PCA-CCA with the fixed number of PCs (Table S3). These results confirm that lower ranked brain PCs might also carry information that links brain and behaviour and should not necessarily be discarded. Moreover, fixing the same number of PCs for both modalities might not be a good choice.

Based on these results and as the optimal numbers of PCs can vary even across different brain-behaviour associations in the same dataset, we recommend data-driven PCA-CCA over PCA-CCA with fixed numbers of PCs. Furthermore, we found that data-driven PCA-CCA and RCCA gave similar results, both having a similar regularizing effect on the CCA model.

Sparse vs. non-sparse CCA/PLS models in high-dimensional data

In this section, we show how SPLS can find associations between subsets of features in all three high-dimensional datasets, and we compare the SPLS results with standard PLS and RCCA.

Figure 4C-E and Figure 5C-E display the models' weights and latent variables (note that for the HCP dataset the brain weights were transformed into brain connection strength increases/decreases). The first associative effect found by standard PLS and SPLS is similar to the first found by RCCA in both the ADNI and simulated datasets, but in the HCP dataset, the *first* associative effect identified by RCCA is more similar to the *second* effect found by standard PLS and SPLS (Figure 6). This is likely because the within-modality variances in the HCP dataset differ substantially from the identity matrix and therefore the difference between the objectives of CCA and PLS models is more pronounced (see Eqs. 1-2). The brain and behavioural weights were similar across the three models in both real datasets, especially the top-ranked variables (i.e., the variables with the highest weights). Similar to RCCA, standard PLS and SPLS recovered sufficiently the true weights of the generative model, however the SPLS model assigned fewer non-zero weights to non-relevant variables (Figure 7C-E). These results demonstrate that, when the signal is sparse, SPLS can lead to high true positive and high true negative rates of weight recovery (Table S2). Table S4 shows the sparsity of the associative effects identified by SPLS.

The stability of the weights differed significantly between the brain and behavioural modalities ($F(1,804)=75.26$, $p<0.0001$) and the three models ($F(2,804)=61.77$, $p<0.0001$) (Table 4). The stability of the SPLS weights was lowest in the HCP dataset, which is likely due to the model's sparsity and that different sets of variables might provide similar performance. The instability of SPLS could be mitigated by stability selection (20) or a stability criterion during hyperparameter optimization (27). The explained variance varied significantly across modalities ($F(1,174)=80.00$, $p<0.0001$) and the three models ($F(2,174)=28.60$, $p<0.0001$).

In summary, while RCCA is likely to yield similar or higher out-of-sample correlations than standard PLS and SPLS, SPLS can perform variable selection and may improve the

interpretability of the results, however it can also present instabilities. In practice the three models often provide similar weights for the top ranked variables.

Standard vs. regularized CCA/PLS models in low-dimensional data

To investigate the effects of regularization in all three low-dimensional datasets, we compared standard CCA, RCCA, standard PLS, and SPLS. The regularized models (RCCA, SPLS) were more stable ($F(3,1075)=80.54$, $p<0.0001$) (Table S5) and showed a trend towards higher out-of-sample correlations ($F(1,10)=3.35$, $p=0.0972$) (Figure S1) than their non-regularized variants (standard CCA and PLS). The stability of standard PLS and RCCA weights were consistently high, the stability of SPLS varied across datasets, standard CCA was rather unstable (Table S5). SPLS provided sparse results, similar to the high-dimensional datasets (Table S4). As expected, RCCA and standard PLS explained increasingly more within-modality variance than standard CCA. For a detailed description of these results, see the Supplement. Taken together, these results suggest that regularized CCA/PLS models should be preferred even for low-dimensional data.

Conclusion

This tutorial compared standard and regularized CCA and PLS models and highlighted the benefits of regularization. Here, we outline the key lessons.

First, we showed that regularized CCA/PLS models give similar out-of-sample correlations in large datasets (with the exception of standard PLS and SPLS in the high-dimensional HCP dataset) when the sample size is similar or much smaller than the number of variables (i.e., the ratio between examples and variables is ~1-10 or ~0.1-0.01). Importantly, RCCA and SPLS outperformed standard CCA and PLS even when the ratio between examples and variables was ~1-10. Second, we emphasized that it is important to use a predictive framework, since high in-sample correlations do not necessarily imply generalizability to unseen data.

Going beyond model performance, we demonstrated both in theory and practice that standard CCA is prone to instability (Table S3). L2-norm regularization improves stability, which comes at a cost of the models (RCCA, standard PLS, SPLS) being driven by within-modality variances. PCA-CCA with data-driven selection of PCs improves on *a priori* selection. Data-driven PCA-CCA has a comparable regularizing effect to RCCA. Sparsity (i.e., L1-norm regularization) can facilitate the interpretability and the generalizability of the models but it can also introduce instability. Sparsity is most useful when the associative effect itself is sparse (e.g., in the ADNI and simulated datasets). Data-driven PCA-CCA, RCCA and SPLS yielded similar model weights and accounted for similar variances.

We hope that this work together with recent efforts (e.g. (26,27,30,31,60)) and critical exchanges (e.g. (28,67,69–71)) illuminates these complex methods and facilitates their application to the brain and its disorders.

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Code availability

The code used for the different CCA/PLS analyses is implemented in a CCA/PLS toolkit which is available at http://www.mlnl.cs.ucl.ac.uk/resources/cca_pls_toolkit.html together with a demo demonstrating how to use the toolkit for generating the SPLS results for the low-dimensional simulated dataset.

Disclosure

The authors report no biomedical financial interests or potential conflicts of interest.

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Figure Legends

Figure 1. Overview of Canonical Correlation Analysis/Partial Least Squares (CCA/PLS) models for investigating brain-behaviour associations. CCA/PLS models maximize the correlation (CCA) or covariance (PLS) between latent variables extracted as weighted linear combinations of the brain and behavioural variables (see formulae in text). Note that the weights are column vectors but are represented as rows to highlight that they have the same dimensionality as their respective data modality.

Figure 2. Descriptive and predictive (or machine learning) frameworks. **(A)** The descriptive framework fits CCA/PLS with fixed hyperparameters (i.e., the number of principal components or regularization parameter) on the entire sample, thus the statistical inference is based on in-sample correlation. **(B)** The predictive (or machine learning) framework fits CCA/PLS on a training set and evaluates the model on a test set, thus the statistical inference is based on out-of-sample correlation. The hyperparameters are usually optimized: the training set is further divided into a training and a validation set and the best hyperparameters are selected based on out-of-sample correlation in the validation set. We note that although not all models maximize correlation (as described in the previous section), typically all CCA/PLS models are evaluated based on the correlation between the latent variables (see Figure 1).

Figure 3. Dot plot of in-sample and out-of-sample correlations for the first associative effects of all experiments in all three high-dimensional datasets. Each dot represents a model trained on the overall data (descriptive framework) or on 10 random subsets of the data (predictive framework). The horizontal jitter is for visualization purposes. **(A)** High-dimensional ADNI dataset. **(B)** High-dimensional HCP dataset. Note, that we display the *second* associative effect for SPLS as it is the most similar to the *first* associative effects identified by the other

models. **(C)** High-dimensional simulated dataset. fixed PCs, fixed number of principal components; data-driven, data-driven number of principal components; desc, descriptive framework; pred, predictive framework.

Figure 4. Brain weights (left column), behavioural weights (middle column) and latent variables (right column) for the high-dimensional ADNI dataset. For visualization purposes, the model weights are normalized (divided by largest absolute value). Scatter plot between the brain and behavioural latent variables is overlaid by a least-squares regression line separately for the training and test data. **(A)** PCA-CCA with fixed number of principal components. **(B)** PCA-CCA with data-driven number of principal components. **(C)** RCCA. **(D)** Standard PLS. **(E)** SPLS. L, left hemisphere; R, right hemisphere; $corr_{training}$, in-sample correlation in the training data, $corr_{test}$, out-of-sample correlation in the test data.

Figure 5. Brain connection strengths (left column), behavioural weights (middle columns) and latent variables (right column) for the high-dimensional HCP dataset. For visualization purposes, the brain weights were transformed into brain connection strength (i.e., brain weights multiplied by the sign of the population mean connectivity) increases (red) and decreases (blue), summed across the brain nodes (i.e., ICA components where each brain vertex is assigned to an ICA component it is most likely to belong) and normalized (divided by largest absolute value). Only the top 15 positive (red) and top 15 negative (blue) behavioural weights are shown (secondary (e.g., age adjusted) measures that are highly redundant with those shown here are not displayed). The behavioural model weights are normalized (divided by largest absolute value). Scatter plot between the brain and behavioural latent variables is overlaid by a least-squares regression line separately for the training and test data. **(A)** PCA-CCA with fixed number of principal components. **(B)** PCA-CCA with data-driven number of principal

components. **(C)** RCCA. **(D)** Standard PLS. **(E)** SPLS. L, left hemisphere; R, right hemisphere; $corr_{training}$, in-sample correlation in the training data, $corr_{test}$, out-of-sample correlation in the test data.

Figure 6. Comparison of brain weights (left column) and behavioural weights (right column) across CCA/PLS models for the high-dimensional ADNI and HCP datasets obtained by the predictive framework. The similarity between the model weights is measured by Spearman correlation. The similarity between SPLS and the other models is measured only for the subset of variables identified by SPLS (the similarity between the two SPLS models was measured for the subset of variables that were present in both models). **(A)** High-dimensional ADNI dataset. **(B)** High-dimensional HCP dataset. Note, that the *second* associative effect identified by standard PLS (PLS-2) and SPLS (SPLS-2) is similar to the *first* associative effects identified by the other models. Standard PLS-1/2, first/second associative effect identified by PLS; SPLS-1/2, first/second associative effect identified by SPLS; PC, principal component.

Figure 7. Model weights (left column: high-dimensional modality, middle column: low-dimensional modality) and latent variables (right column) for the high-dimensional simulated dataset. For comparison, the true weights (red) of the generative model are overlaid on the model weights (blue). For visualization purposes, the model weights are normalized (divided by largest value) and only a subset of 100 random weights (out of the total 20000) is displayed for the high dimensional modality. Scatter plot between the brain and behavioural latent variables is overlaid by a least-squares regression line separately for the training and test data. **(A)** PCA-CCA with fixed number of principal components. **(B)** PCA-CCA with data-driven number of principal components. **(C)** RCCA. **(D)** Standard PLS. **(E)** SPLS. $corr_{training}$, in-sample correlation in the training data; $corr_{test}$, out-of-sample correlation in the test data.

Tables

Table 1. Different nomenclatures in CCA and PLS literature and summary of the corresponding terms.

Model	Relationship	Model weights	Latent variable	Correlation between original variables and latent variable
CCA	mode/ association	canonical vector/coefficient	canonical variable/variate	structure correlation
PLS	association	salience	score	loading

Table 2. Summary of CCA/PLS models on high and low-dimensional real and simulated data.

Model	Analytical framework	Hyperparameter optimization	Model hyperparameter
High-dimensional data			
PCA-CCA	Descriptive	None (fixed)	Number of PCs
PCA-CCA	Predictive	None (fixed)	Number of PCs
PCA-CCA	Predictive	Data-driven	Number of PCs
RCCA	Predictive	Data-driven	Amount of L2-norm regularization
Standard PLS	Predictive	None	None
SPLS	Predictive	Data-driven	Amount of L1-norm regularization
Low-dimensional data			
Standard CCA	Predictive	None	None
RCCA	Predictive	Data-driven	Amount of L2-norm regularization
Standard PLS	Predictive	None	None
SPLS	Predictive	Data-driven	Amount of L1-norm regularization

PC, principal component

Table 3. Characteristics of real and simulated data.

Data	HCP		ADNI		Simulation	
	Low-dimensional	**High-dimensional**	**Low-dimensional**	**High-dimensional**	**Low-dimensional**	**High-dimensional**
Subjects	Healthy (N=1001)	Healthy (N=1001)	Healthy + clinical (N=592)	Healthy + clinical (N=592)	Not applicable (N=1000)	Not applicable (N=1000)
Brain variables	Connectivity of 25 ICA components (D=300)	Connectivity of 200 ICA components (D=19900)	ROI-wise grey matter volume (D=120)	Voxel-wise grey matter volume (D=168130)	Not applicable (D=100)	Not applicable (D=20000)
Behavioural variables	Behaviour, psychometrics, demographics (D=145)	Behaviour, psychometrics, demographics (D=145)	Items of MMSE questionnaire (D=31)	Items of MMSE questionnaire (D=31)	Not applicable (D=100)	Not applicable (D=100)

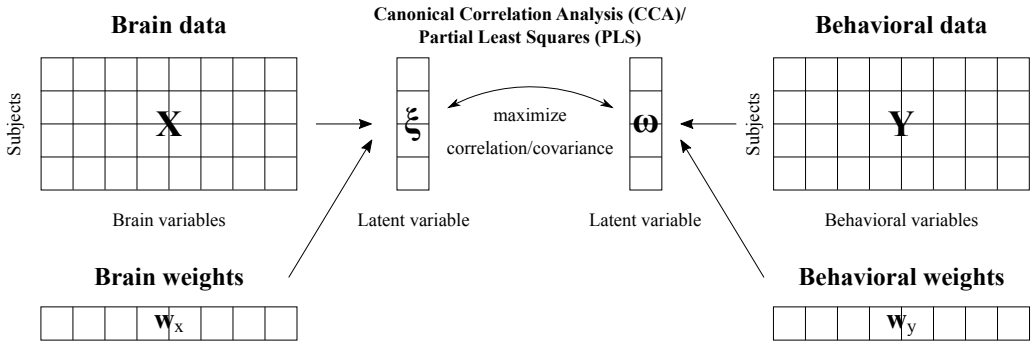
N, number of subjects; D, number of variables; ICA, Independent Component Analysis (i.e., data-driven brain parcellation); ROI, Region of Interest using the Automated Anatomical Labelling 2 atlas (72); MMSE, Mini-Mental State Examination (i.e., cognitive test for dementia) (73).

Table 4. Main characteristics (mean ± SEM for all values) of the first associative effects in the high-dimensional datasets obtained with the different CCA/PLS models using the predictive framework. Note that we display the *second* associative effect for standard PLS (PLS-2) and SPLS (SPLS-2) in the HCP dataset as it is the most similar to the first associative effects identified by the other models.

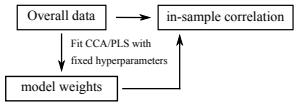
Model	Brain		Behaviour		Across-modality relationship	
	Stability of weights[1]	Explained variance[2]	Stability of weights[1]	Explained variance[2]	In-sample correlation[3]	Out-of-sample correlation[4]
ADNI dataset						
PCA-CCA (fixed PCs)	0.86 (± 0.00)	8.47 (± 0.16)	0.85 (± 0.01)	14.91 (± 0.23)	0.70 (± 0.00)	0.55 (± 0.01)
PCA-CCA (data-driven PCs)	0.70 (± 0.01)	5.26 (± 0.25)	0.93 (± 0.00)	15.73 (± 0.13)	0.83 (± 0.01)	0.65 (± 0.01)
RCCA (L2-reg. opt.)	0.82 (± 0.00)	5.47 (± 0.06)	0.94 (± 0.00)	16.63 (± 0.26)	0.98 (± 0.00)	0.66 (± 0.01)
Standard PLS	0.96 (± 0.00)	21.54 (± 0.16)	0.94 (± 0.00)	18.64 (± 0.21)	0.44 (± 0.00)	0.43 (± 0.01)
SPLS (L1-reg. opt.)	0.83 (± 0.02)	14.05 (± 0.13)	0.96 (± 0.01)	15.86 (± 0.42)	0.60 (± 0.00)	0.61 (± 0.01)
HCP dataset						
PCA-CCA (fixed PCs)	0.72 (± 0.01)	0.42 (± 0.01)	0.78 (± 0.01)	2.67 (± 0.10)	0.76 (± 0.00)	0.47 (± 0.02)
PCA-CCA (data-driven PCs)	0.56 (± 0.02)	0.35 (± 0.03)	0.53 (± 0.04)	3.73 (± 0.39)	0.76 (± 0.01)	0.45 (± 0.03)
RCCA (L2-reg. opt.)	0.78 (± 0.01)	0.29 (± 0.01)	0.88 (± 0.01)	4.39 (± 0.18)	1.00 (± 0.00)	0.52 (± 0.02)
Standard PLS-2	0.52 (± 0.04)	0.50 (± 0.05)	0.62 (± 0.05)	8.07 (± 0.30)	0.79 (± 0.02)	0.21 (± 0.02)
SPLS-2 (L1-reg. opt.)	0.25 (± 0.04)	0.48 (± 0.07)	0.51 (± 0.05)	7.23 (± 0.37)	0.64 (± 0.04)	0.25 (± 0.03)
Simulated dataset						
PCA-CCA (fixed PCs)	0.74 (± 0.01)	0.76 (± 0.01)	0.90 (± 0.00)	1.82 (± 0.01)	0.80 (± 0.00)	0.67 (± 0.01)
PCA-CCA (data-driven PCs)	0.96 (± 0.00)	0.85 (± 0.00)	0.91 (± 0.00)	1.95 (± 0.02)	0.73 (± 0.01)	0.70 (± 0.01)
RCCA (L2-reg. opt.)	0.93 (± 0.00)	0.77 (± 0.00)	0.97 (± 0.00)	1.99 (± 0.01)	0.83 (± 0.01)	0.71 (± 0.01)

Standard PLS	0.94 (± 0.00)	0.84 (± 0.00)	0.97 (± 0.00)	2.07 (± 0.01)	0.81 (± 0.00)	0.71 (± 0.01)
SPLS (L1-reg. opt.)	0.78 (± 0.03)	0.84 (± 0.00)	1.00 (± 0.00)	1.94 (± 0.01)	0.79 (± 0.01)	0.73 (± 0.01)

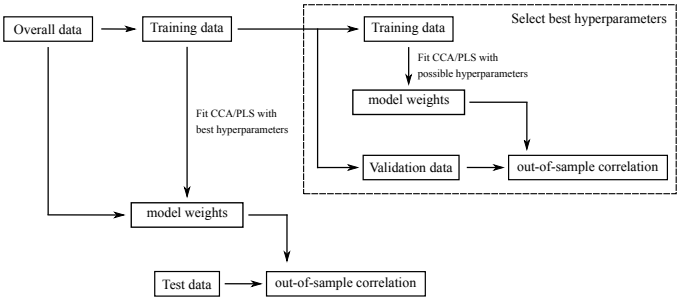
[1]similarity of model weights measured by Pearson correlation between each pair of training sets of the outer data splits; [2]percent variance explained by the model relative to all within-modality variance in the training sets of the outer data splits; [3]correlation between the latent variables in the training sets of the outer data splits; [4]correlation between the latent variables in the test sets of the outer data splits; opt, optimized; PC, principal component; L1-reg., L1-norm regularization; L2-reg., L2-norm regularization.

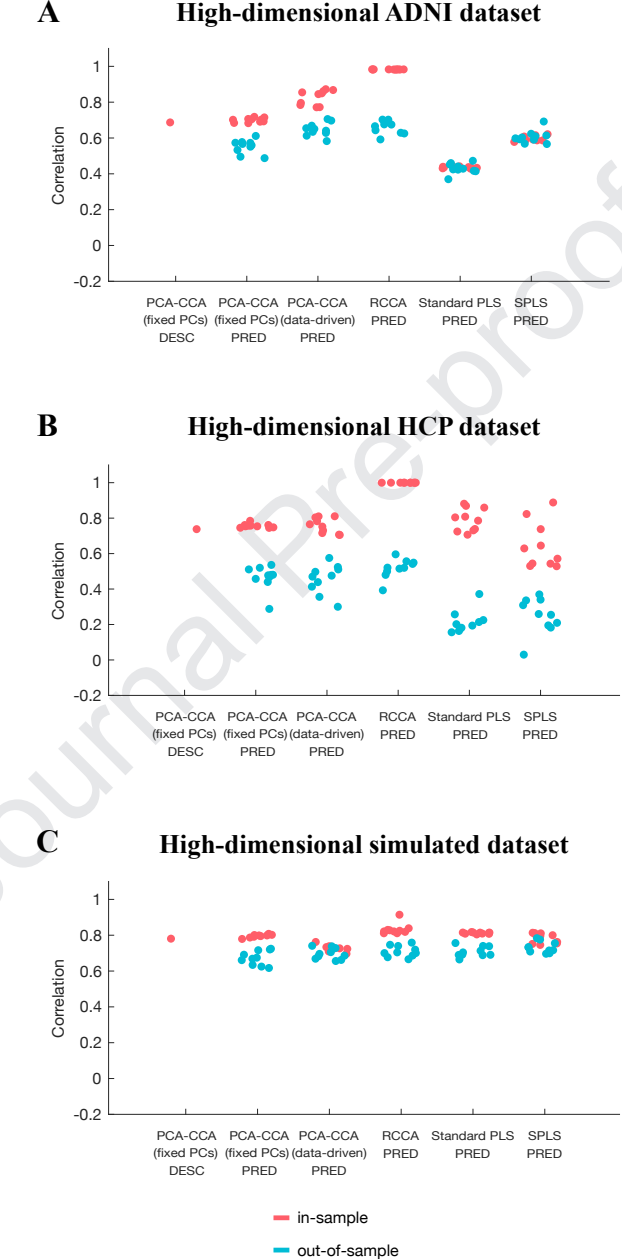


A **Descriptive framework**



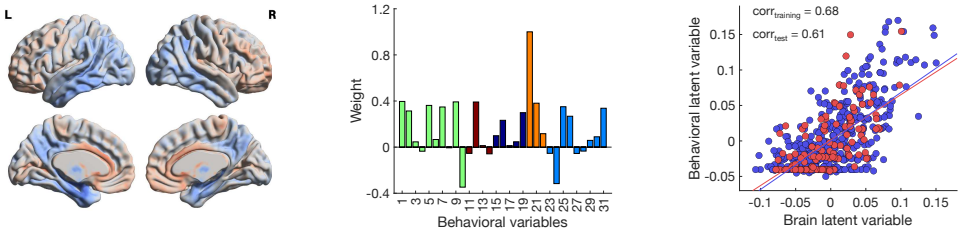
B **Predictive framework**



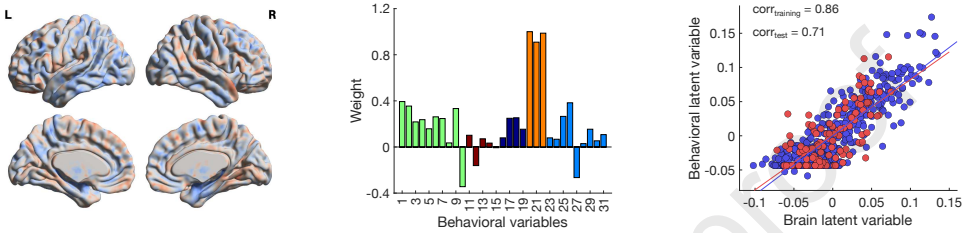


High-dimensional ADNI dataset

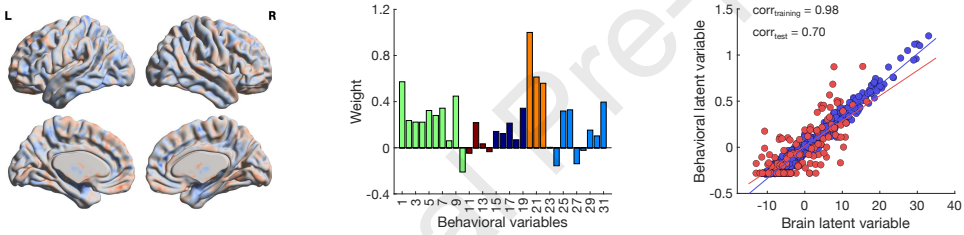
A PCA-CCA (30 PCs)



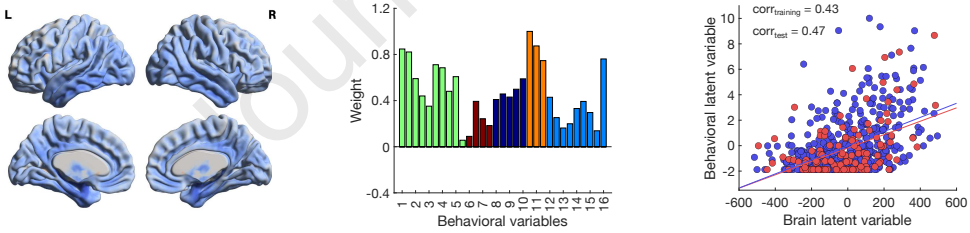
B PCA-CCA (data-driven)



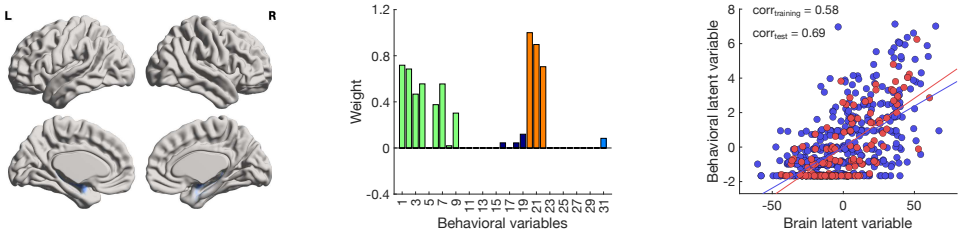
C RCCA

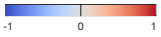


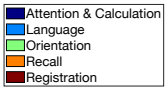
D Standard PLS



E SPLS

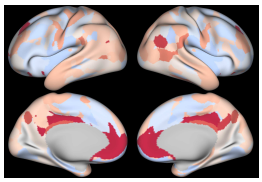






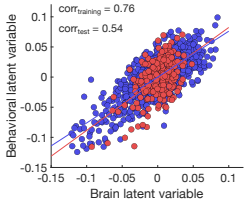
High-dimensional HCP dataset

A PCA-CCA (100 PCs)

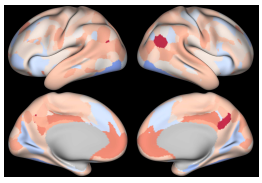


0.83 ↑ DSM **Hyperactivity** Problems
Global feelings and attitudes about one's life
Picture Vocabulary Test
Delay Discounting (AUC for Discounting of $40K)
Fluid intelligence
ASR Other Problems
Smoking history
Intrusive
Avg total weekday **alcoholic** drinks/day in past 7 days
DSM **Avoidant Personality** Problems
Anxious/Depressed
Non-diagnostic screen of **agoraphobia**
Frequency of drinking 5+ **drinks** in past 12 months
Father had **depression**
0.33 Number of symptoms of DSM4 **Alcohol Abuse** over lifetime

-0.39 ↓ Total score of Pittsburgh **Sleep Quality** Index
Attention Problems
Penn Line Orientation (Median Reaction Time)
Total **alcoholic** drinks in past 7 days
Any positive test for THC (**cannabis**)
DSM4 Major **Depressive Episode** over lifetime
Externalizing
Aggressive Behavior
Aggression
Life matters or makes sense
Perception of **stress**
Conscientiousness Scale Score
Perceptions of **loneliness**
Number days smoked/used ANY **TOBACCO** in past 7 days
-1.00 **Thought Problems**

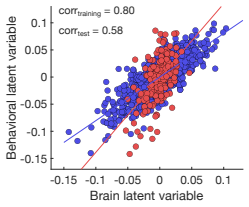


B PCA-CCA (data-driven)

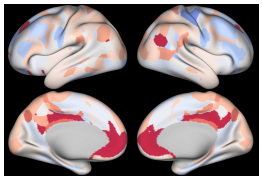


1.00 ↑ **Reading Test**
Picture Vocabulary Test
Fluid intelligence
Penn Line Orientation (Total Number Correct)
List sorting
Openness Scale Score
Picture Sequence **Memory Test**
Delay Discounting (AUC for Discounting of $200)
Delay Discounting (AUC for Discounting of $40K)
Penn Word **Memory** (Total Number of Correct Responses)
Manual **dexterity**
Total **alcoholic** drinks in past 7 days
Number days drank **alcohol** in past 7 days
Global feelings and attitudes about one's life
0.36 **Short Penn CPT** Specificity

-0.20 Perception of **stress**
Hostility and cynicism
Drinks consumed per drinking day in past 12 months
Times used/smoked ANY **TOBACCO** TODAY
Avg weekday **CIGARETTES** per day in past 7 days
Avg weekend **CIGARETTES** per day in past 7 days
Any positive test for THC (**cannabis**)
Total # **CIGARETTES** in past 7 days
Avg total weekday ANY **TOBACCO** per day in past 7 days
Avg total weekend ANY **TOBACCO** per day in past 7 days
Total times used/smoked ANY **TOBACCO** in past 7 days
Perceptions of **rejection** in daily social interactions
Participant still **smoking**
Number days smoked/used ANY **TOBACCO** in past 7 days
-0.68 ↓ **Penn Line Orientation** (Total Positions Off for All Trials)

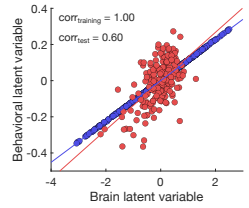


C RCCA

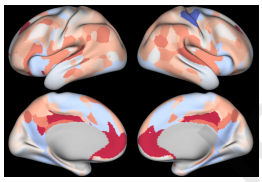


1.00 ↑ **Picture Vocabulary** Test
Global feelings and attitudes about one's life
Delay Discounting (AUC for Discounting of $40K)
Delay Discounting (AUC for Discounting of $200)
Fluid intelligence
DSM **Hyperactivity** Problems
Father had **depression**
Penn **Emotion Recognition** (Correct Anger Identifications)
Intrusive
Mother had **depression**
Pattern Comparison Processing Test
DSM **Avoidant Personality** Problems
Avg total weekday **alcoholic** drinks/day in past 7 days
Penn **Line Orientation** (Total Number Correct)
0.34 **List sorting**

-0.31 **Short Penn CPT** Sensitivity
Conscientiousness Scale Score
Withdrawn
Avg total weekend **alcoholic** drinks/day in past 7 days
Penn Line Orientation (Total Positions Off for All Trials)
Times used **marijuana**
Total **alcoholic** drinks in past 7 days
Number of of Childhood **Conduct problems**
Number days smoked/used ANY **TOBACCO** in past 7 days
Penn **Emotion Recognition** (Correct Neutral Identifications)
Age at **first alcohol** use
Any positive test for THC (**cannabis**)
Thought Problems
Aggression
-0.68 ↓ Total score of Pittsburgh **Sleep Quality** Index

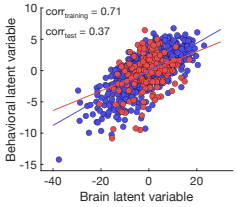


D Standard PLS

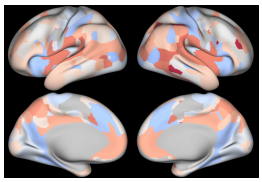


1.00 ↑ **Picture Vocabulary** Test
Reading Test
Fluid intelligence
Penn Line Orientation (Total Number Correct)
Delay Discounting (AUC for Discounting of $40K)
Dimensional Change **Card Sort Test**
Manual **dexterity**
Flanker test
List sorting
Delay Discounting (AUC for Discounting of $200)
Pattern Comparison Processing Test
Picture Sequence **Memory Test**
Total **alcoholic** drinks in past 7 days
Mini Mental Status Exam Total Score
0.42 Penn **Emotion Recognition** (Correct Responses)

-0.38 Frequency of any **alcohol** use in heaviest 12-month drinking period
Aggression
Frequency **drunk** in heaviest 12-month drinking period
Frequency of any **alcohol** use in past 12 months
Participant still **smoking**
Times used/smoked ANY **TOBACCO** TODAY
Any positive test for THC (**cannabis**)
Avg weekend **CIGARETTES** per day in past 7 days
Avg weekday **CIGARETTES** per day in past 7 days
Total # **CIGARETTES** in past 7 days
Avg total weekend ANY **TOBACCO** per day in past 7 days
Avg total weekday ANY **TOBACCO** per day in past 7 days
Penn Line Orientation (Total Positions Off for All Trials)
Total times used/smoked ANY **TOBACCO** in past 7 days
-0.81 ↓ Number days smoked/used ANY **TOBACCO** in past 7 days

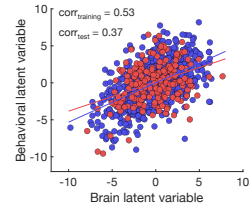


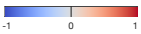
E SPLS

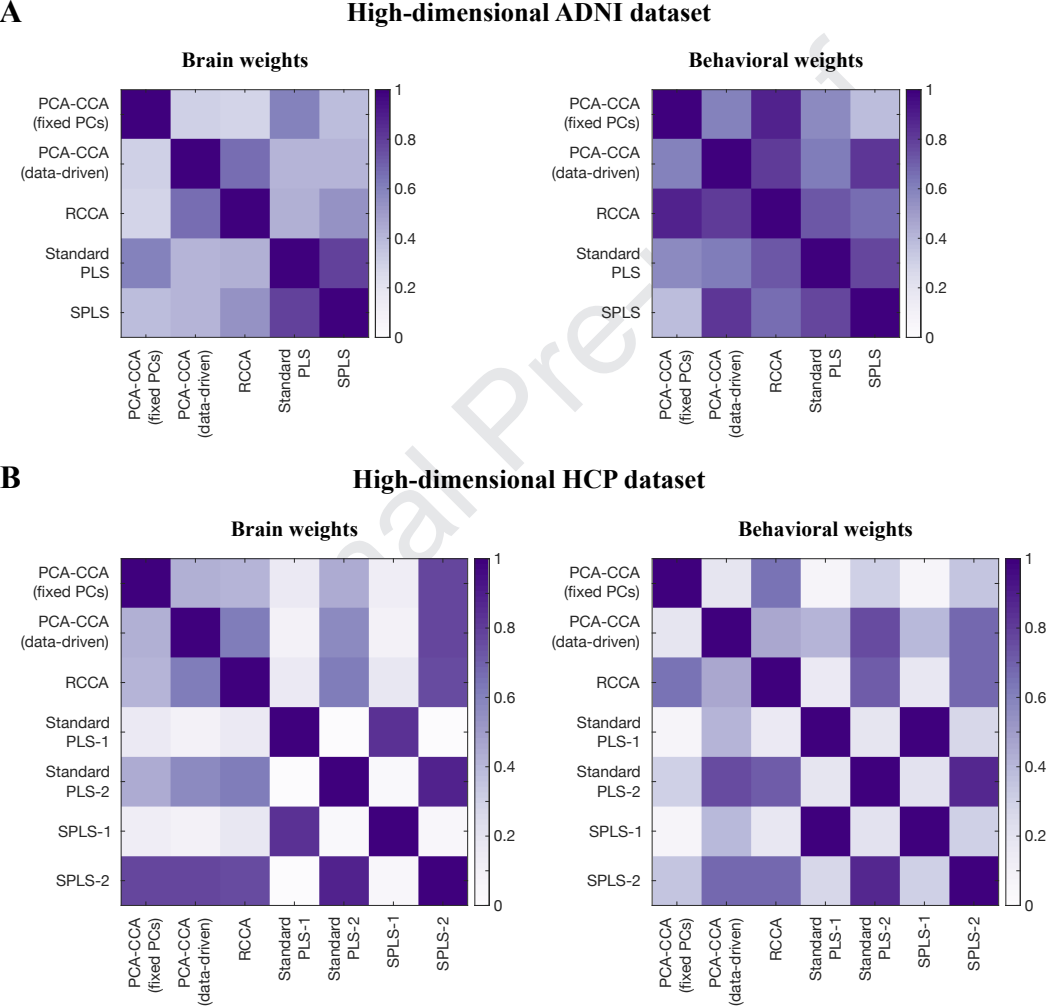


1.00 ↑ **Reading Test**
Picture Vocabulary Test
Dimensional Change **Card Sort Test**
Fluid intelligence
Penn Line Orientation (Total Number Correct)
Delay Discounting (AUC for Discounting of $40K)
List sorting
Number days drank **alcohol** in past 7 days
Flanker test
Mini Mental Status Exam Total Score
Picture Sequence **Memory Test**
Pattern Comparison Processing Test
Total **drinks** in past 7 days
Manual **dexterity**
0.45 **Delay Discounting** (AUC for Discounting of $200)

-0.32 Avg total weekday ANY **TOBACCO** per day in past 7 days
Total times used/smoked ANY **TOBACCO** in past 7 days
Avg total weekend ANY **TOBACCO** per day in past 7 days
Any positive test for THC (**cannabis**)
Aggression
Frequency of drinking 5+ **drinks** in past 12 months
Number days smoked/used ANY **TOBACCO** in past 7 days
Frequency of drinking 5+ **drinks** during heaviest 12-month drinking period
Frequency **drunk** in past 12 months
Electronic **Visual Acuity** Denominator
Age at **first alcohol** use
Frequency of any **alcohol** use in past 12 months
Frequency of any **alcohol** use in heaviest 12-month drinking period
Penn Line Orientation (Total Positions Off for All Trials)
-0.70 ↓ Frequency **drunk** in heaviest 12-month drinking period

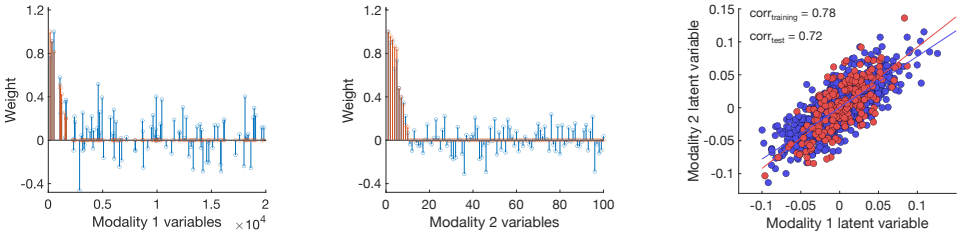




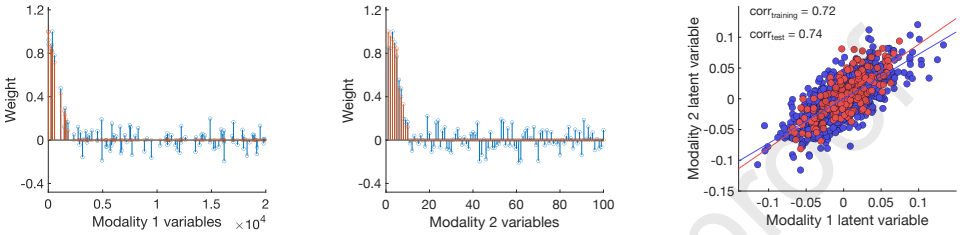

A
High-dimensional ADNI dataset
Brain weights
Behavioral weights
PCA-CCA (fixed PCs)
PCA-CCA (data-driven)
RCCA
Standard PLS
SPLS
1
0.8
0.6
0.4
0.2
0
B
High-dimensional HCP dataset
Brain weights
Behavioral weights
PCA-CCA (fixed PCs)
PCA-CCA (data-driven)
RCCA
Standard PLS-1
Standard PLS-2
SPLS-1
SPLS-2

High-dimensional simulated dataset

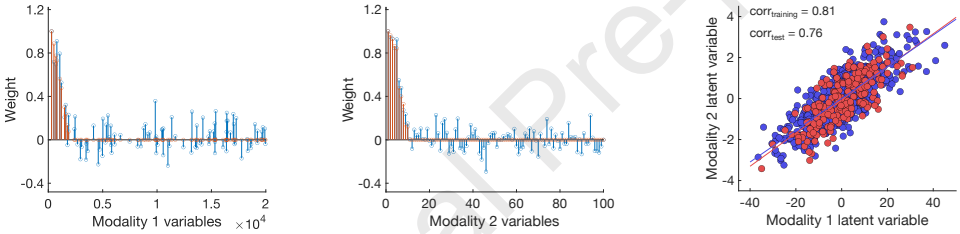
A PCA-CCA (97 PCs)



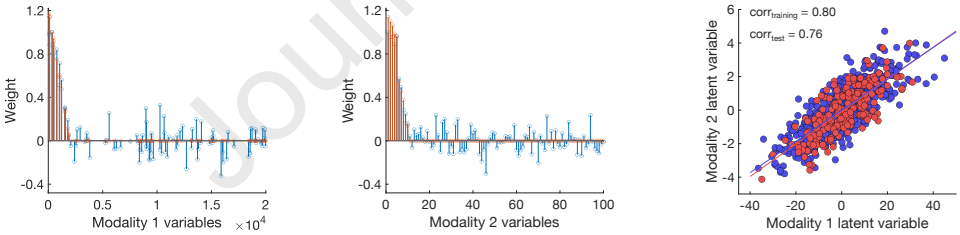
B PCA-CCA (data-driven)



C RCCA



D Standard PLS



E SPLS