DONDERS INSTITUTE

Machine Learning 2: advanced

Andre F. Marquand
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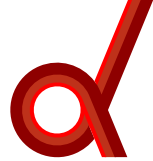
Outline



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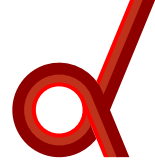
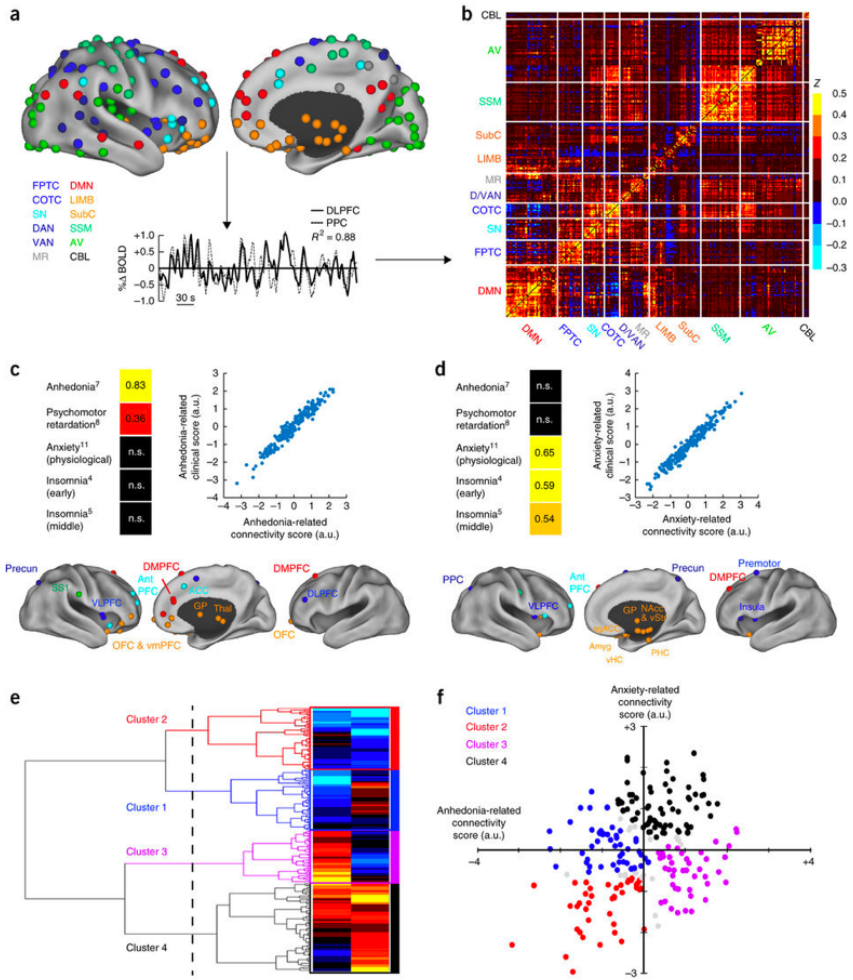
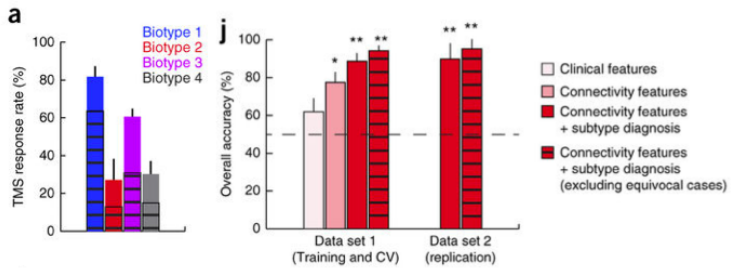


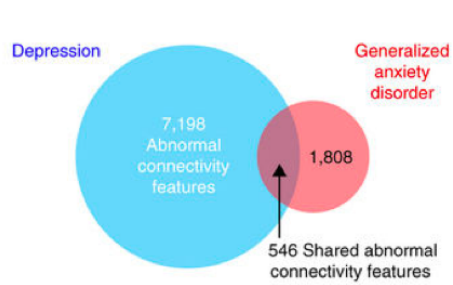
Stratification of major depression



- Extensive validation
- Predict treatment response (TMS)

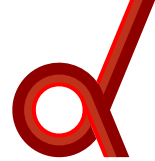


- Cut across diagnoses



Drysdale et al. (2017)

Finding mappings between brain and behaviour



- **Canonical Correlation Analysis** is a standard statistical tool for finding multivariate relationships between datasets
- Generalises Pearson correlation to multiple variables
- Finds projections of the data that maximise the correlation between "views" of the data

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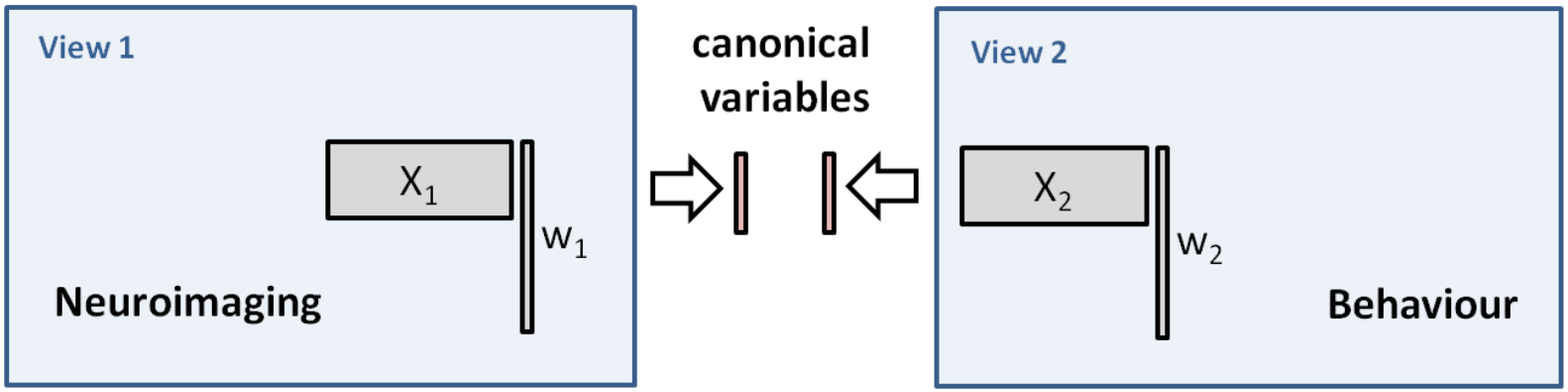

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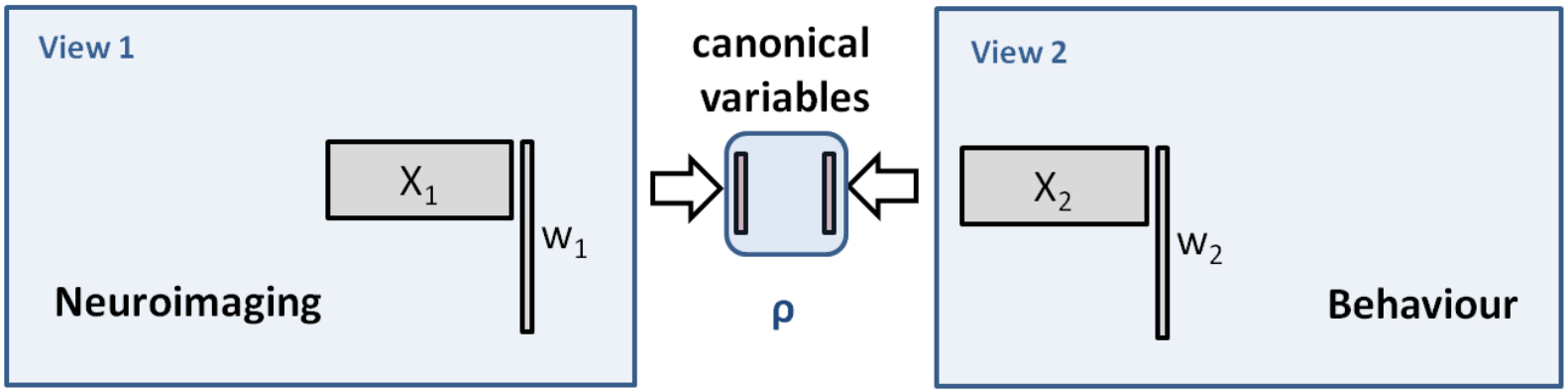

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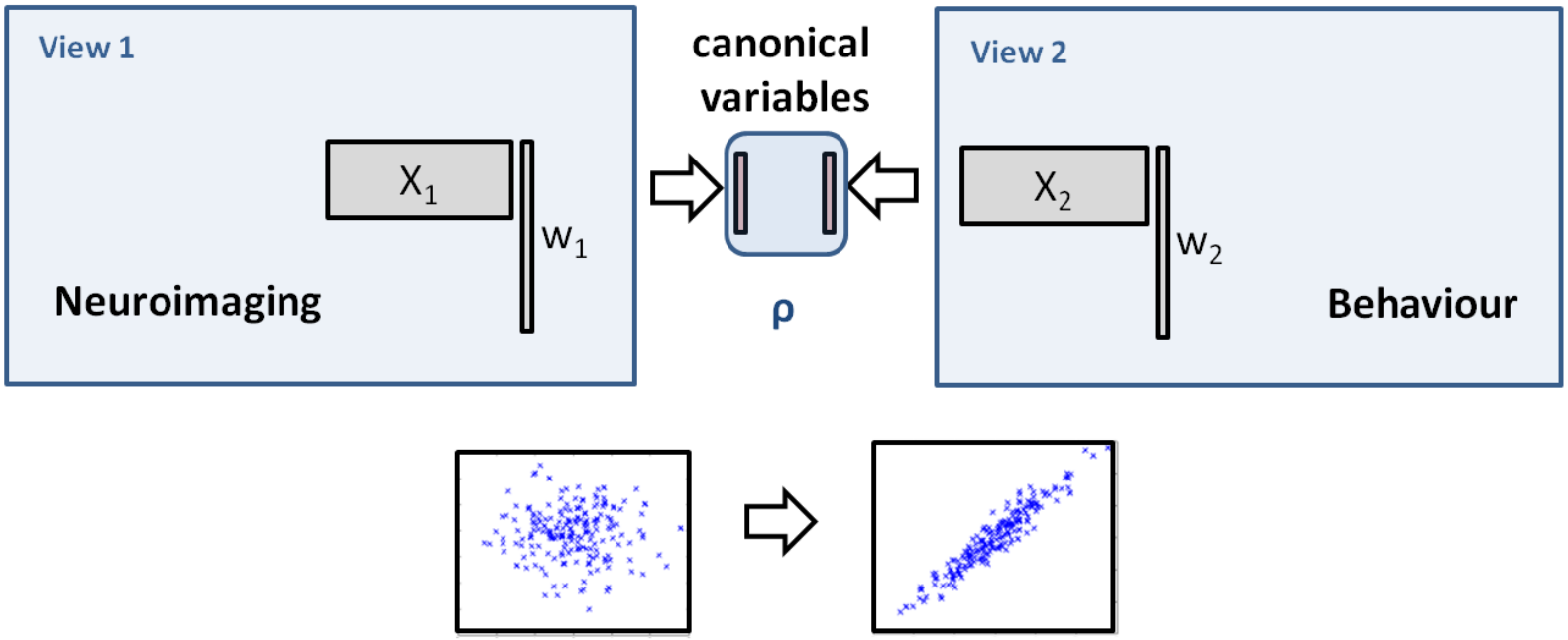

Canonical Correlation Analysis

- CCA is related to techniques such as partial least squares
- Formally, CCA solves the following objective function:

$$\max_{\mathbf{w}_1,\mathbf{w}_2} corr(\mathbf{X}_1\mathbf{w}_1, \mathbf{X}_2\mathbf{w}_2)$$

$$\text{subject to } ||\mathbf{w}_1^T\mathbf{X}_1^T\mathbf{X}_1\mathbf{w}_1|| \leq 1 \text{ and } ||\mathbf{w}_2^T\mathbf{X}_2^T\mathbf{X}_2\mathbf{w}_2|| \leq 1$$

where the constraint is sometimes amended to:

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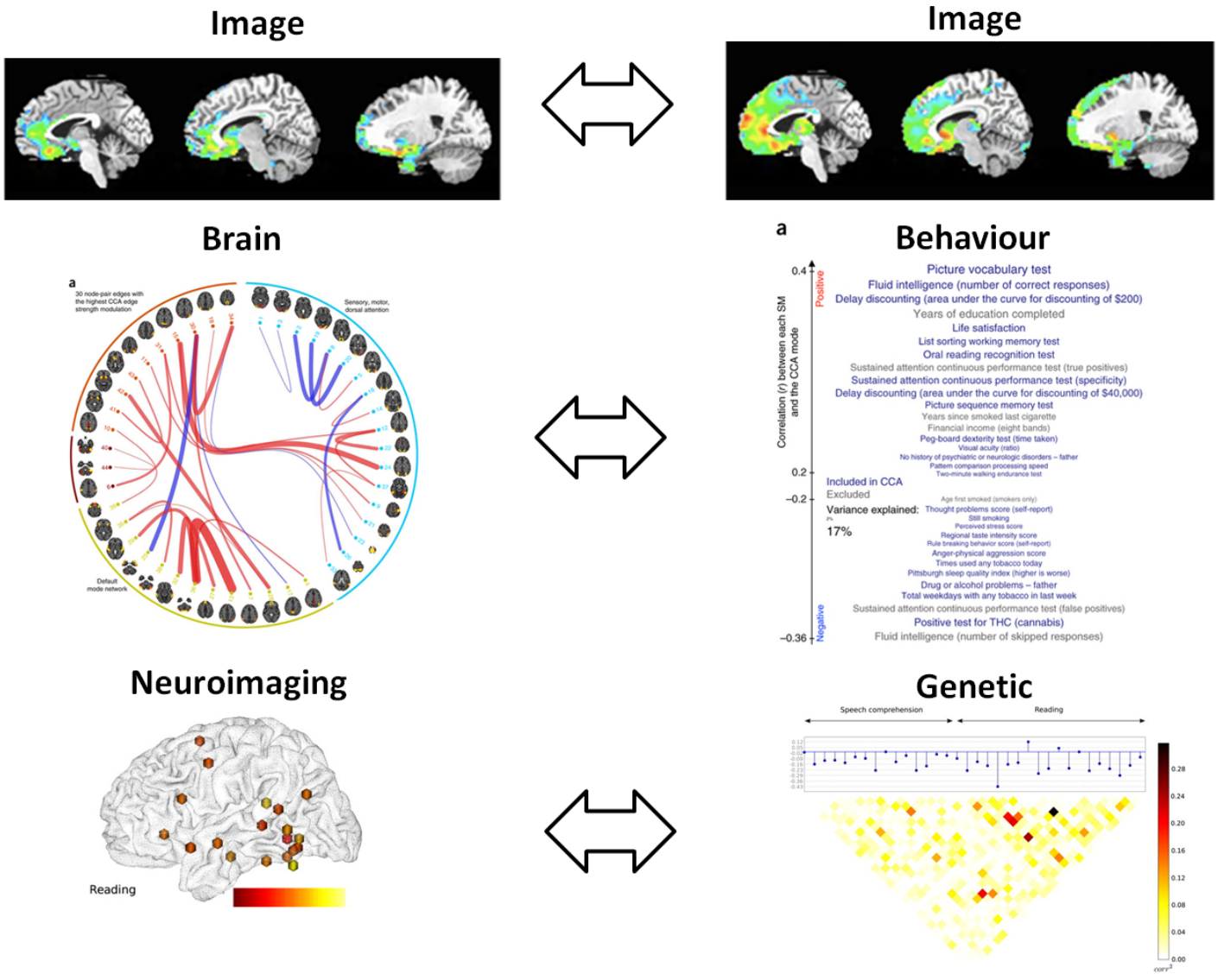
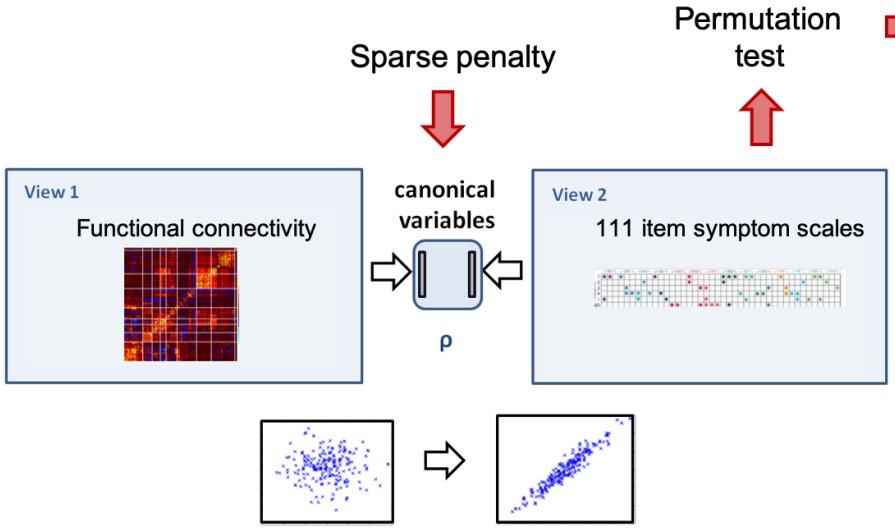
- if $n > p_1$ and p_2, an analytical solution is available
- There are many variants (kernel CCA, Bayesian CCA, deep CCA...)

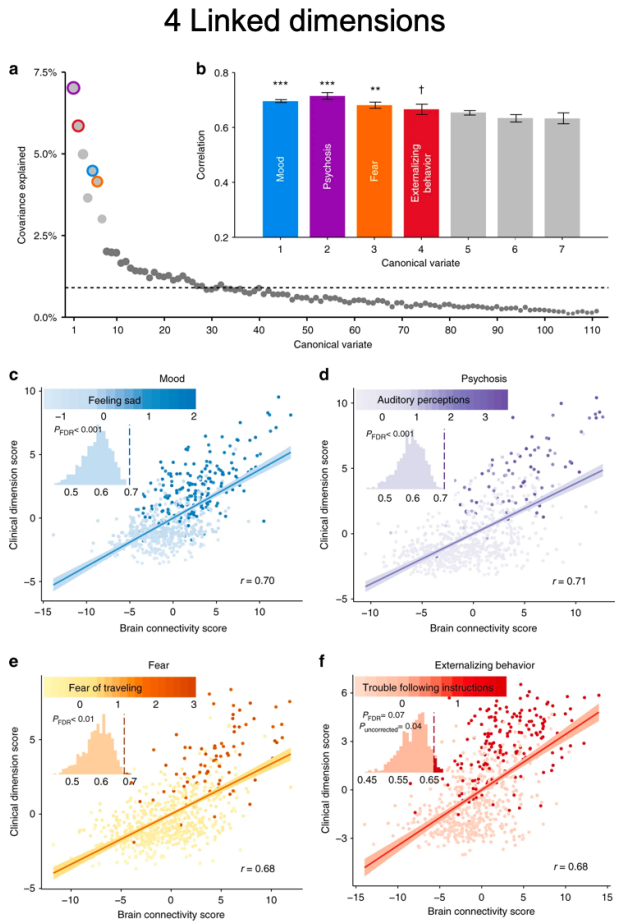
Applications of CCA



Smith et al. (2015); Floch et al. (2012)

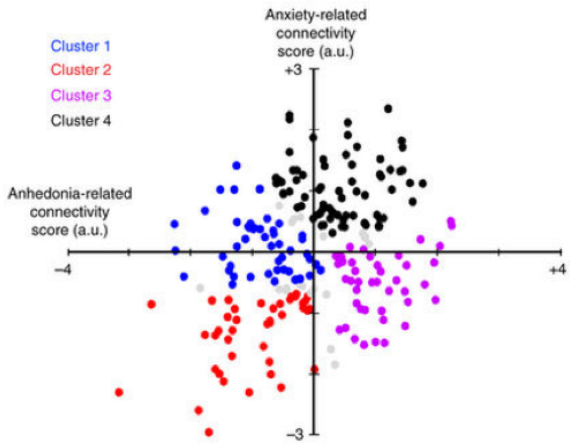
Applications of CCA





Xia et al. (2018)

Stratification of major depression, revisited



Dinga et al. (2019)

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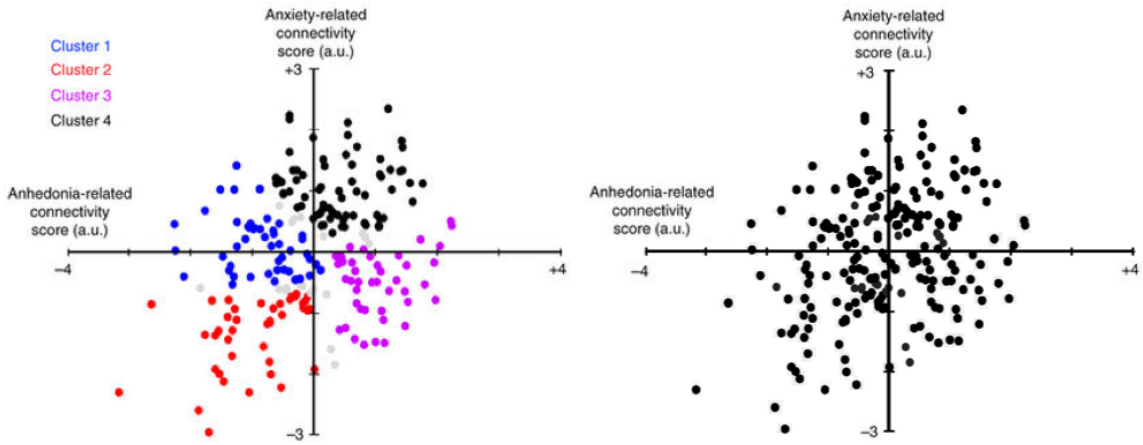

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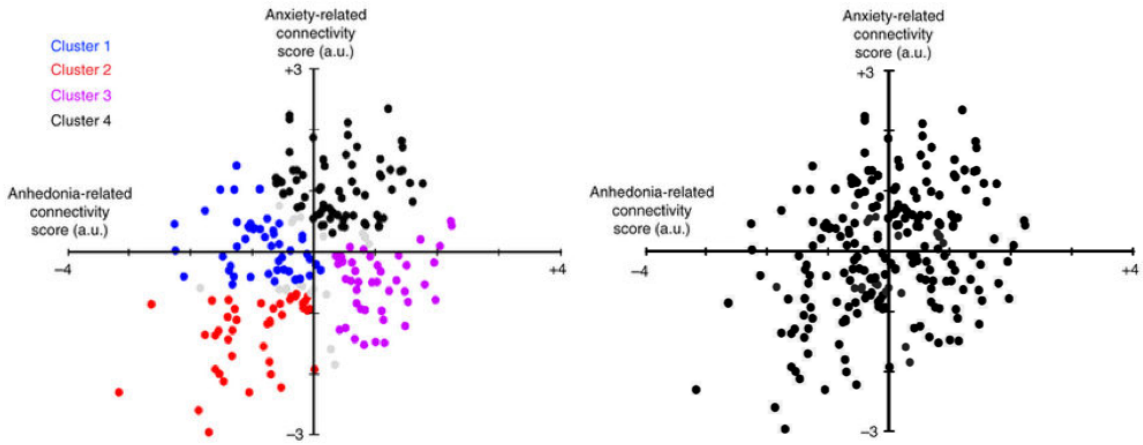
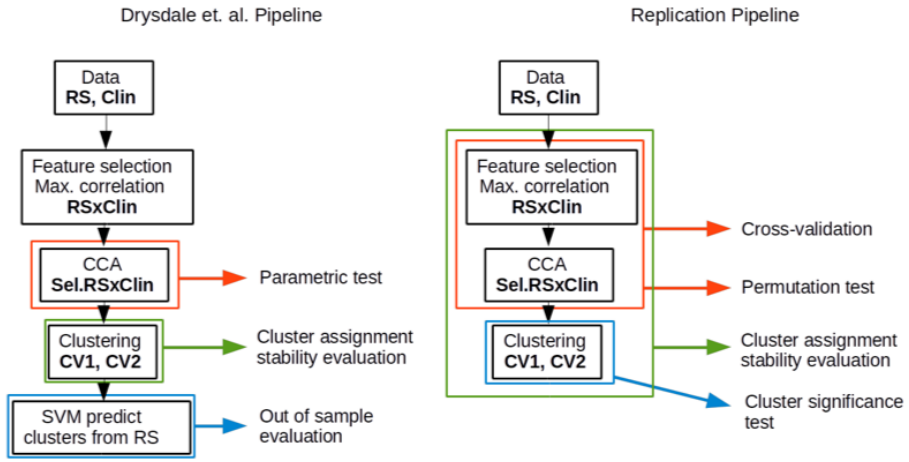


- All tests are in-sample
- No regularization
- Statistical tests are over-optimistic



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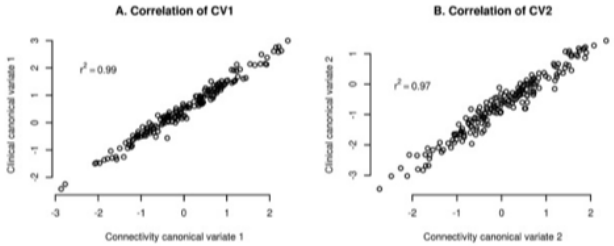

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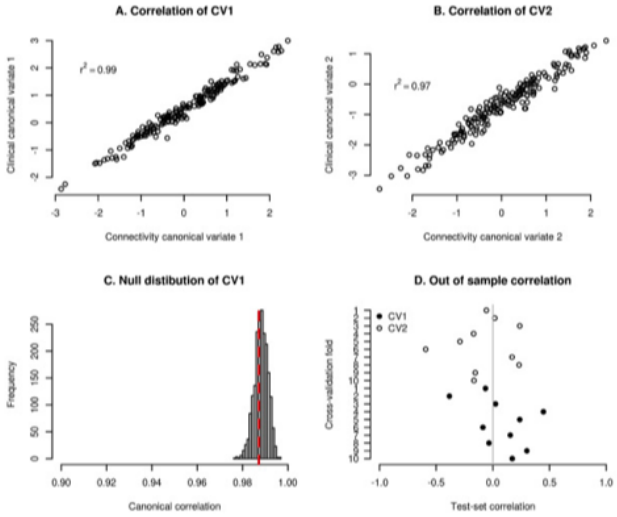

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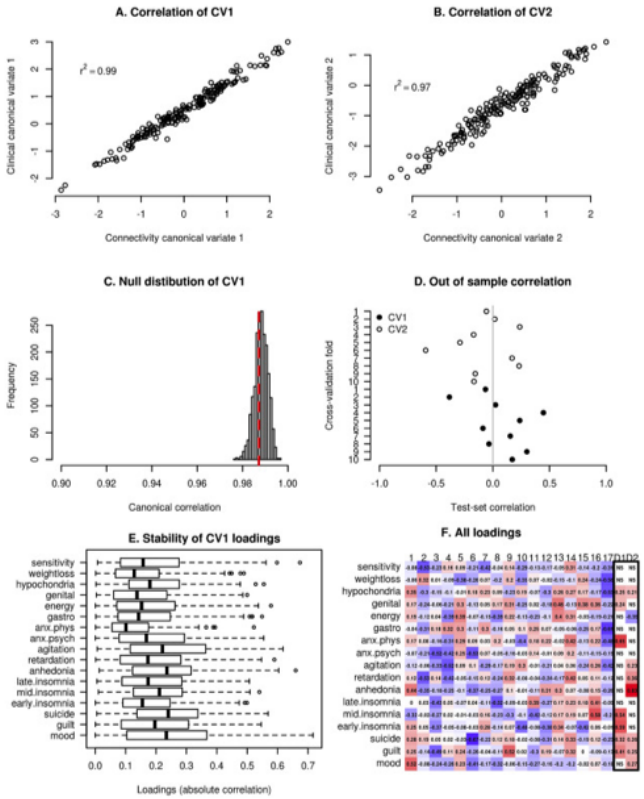

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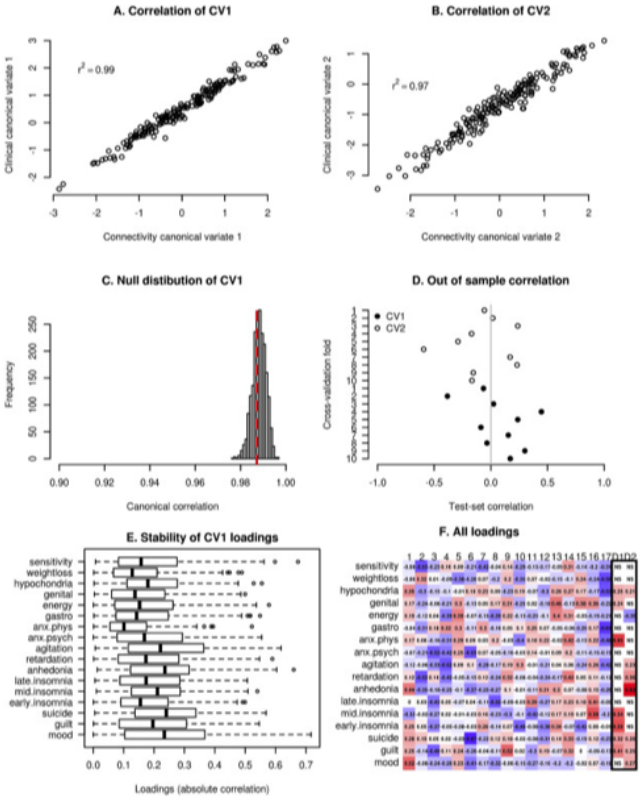

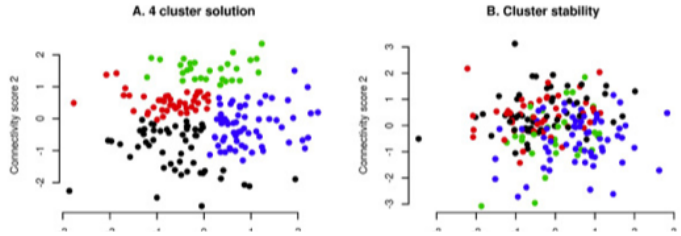

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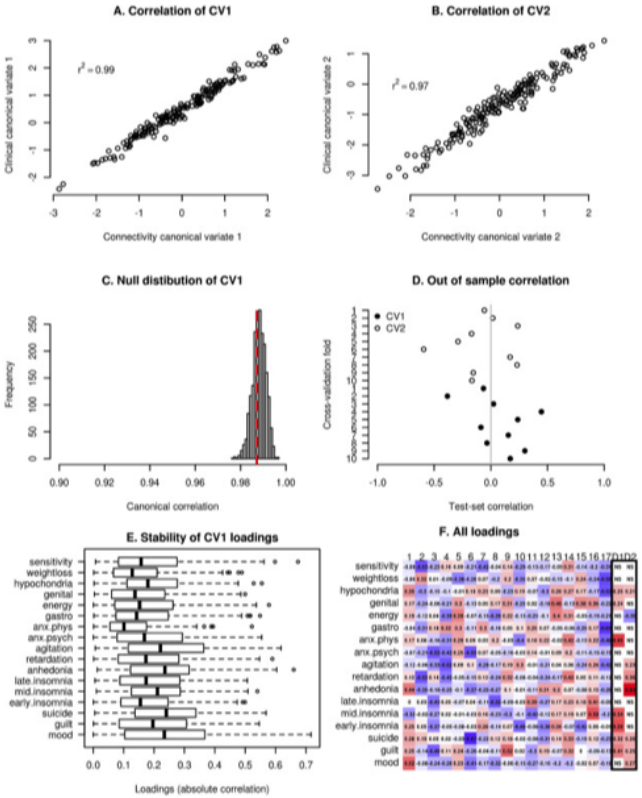
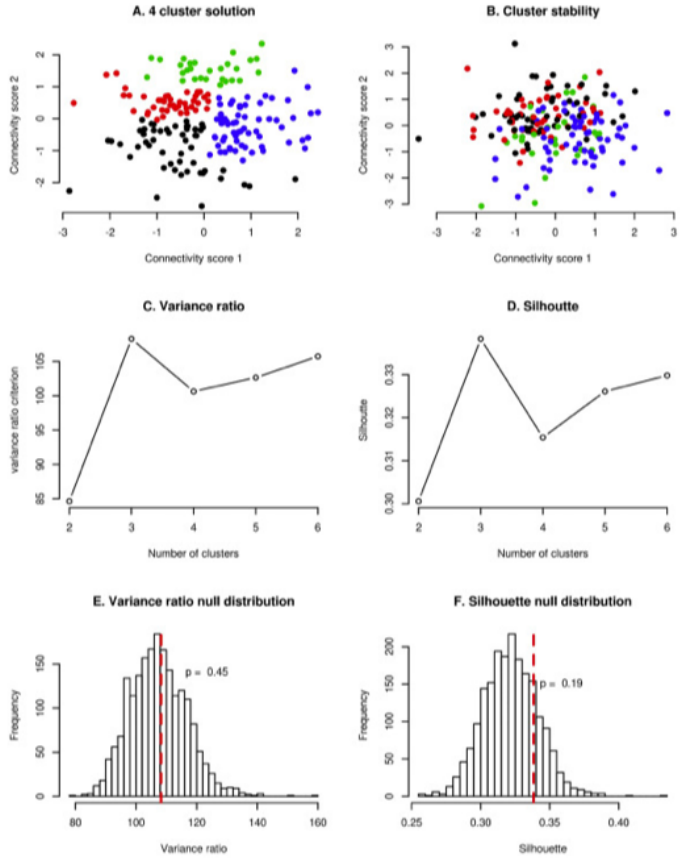
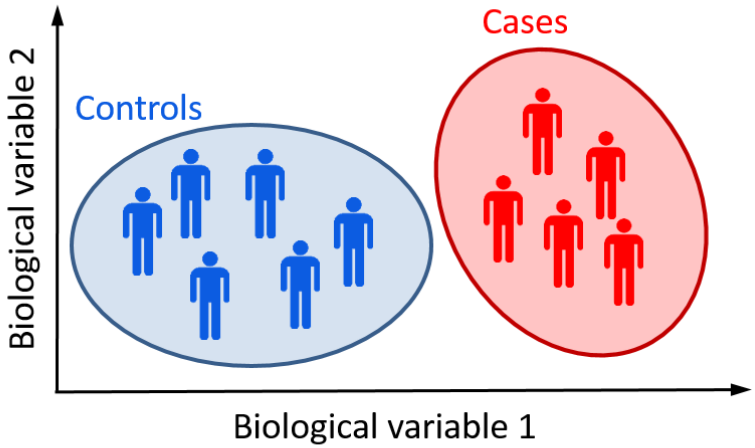




Dinga et al. (2019)

Many types of heterogeneity



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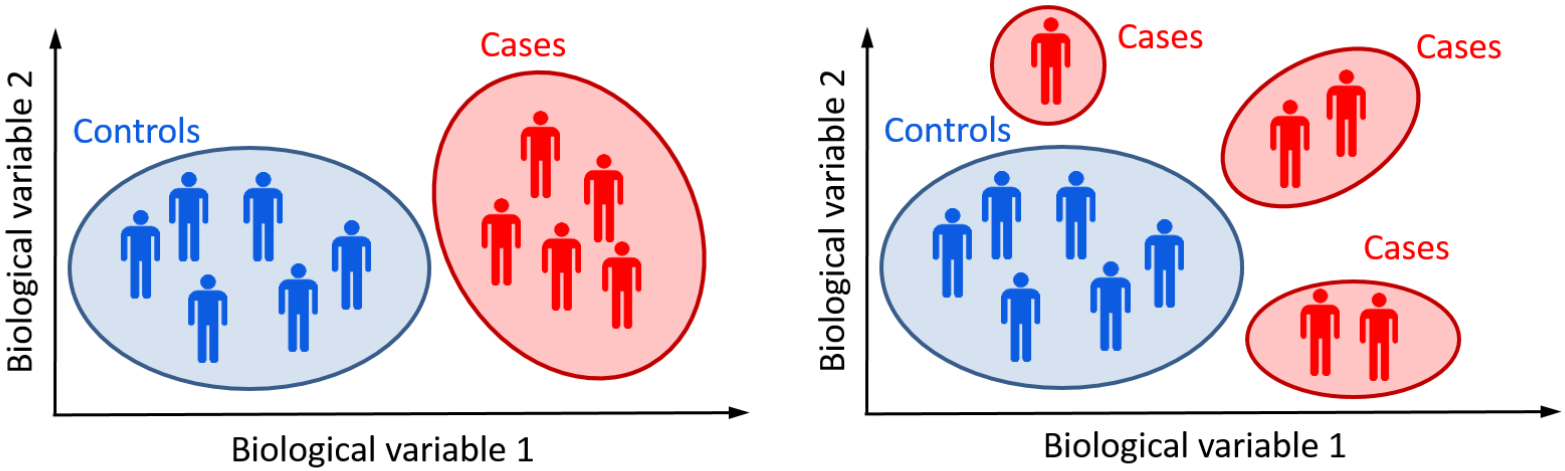

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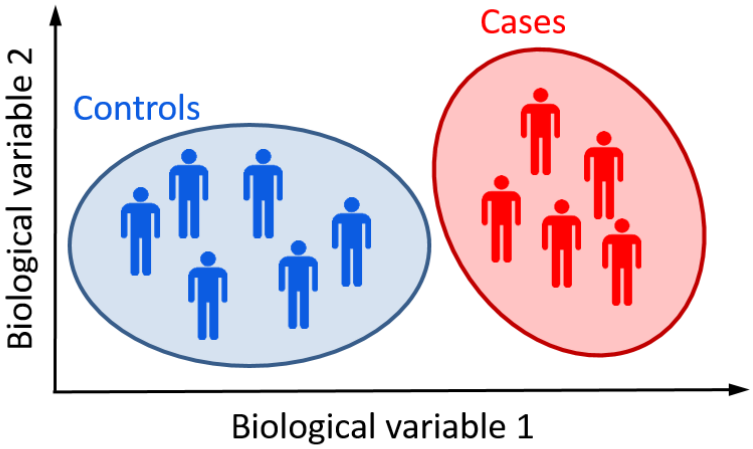

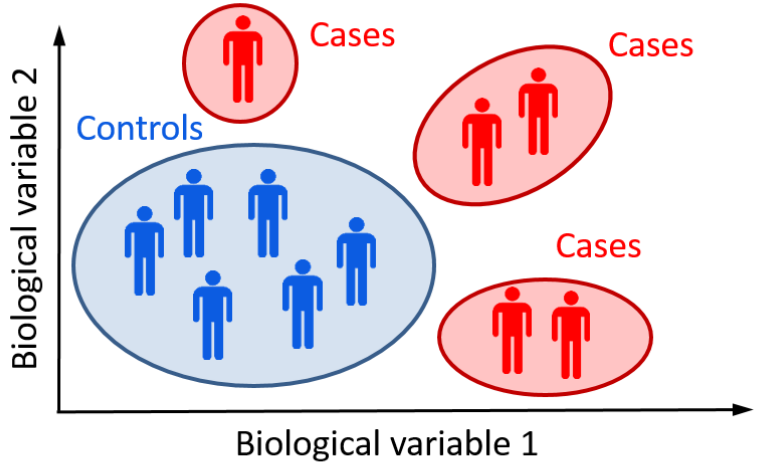

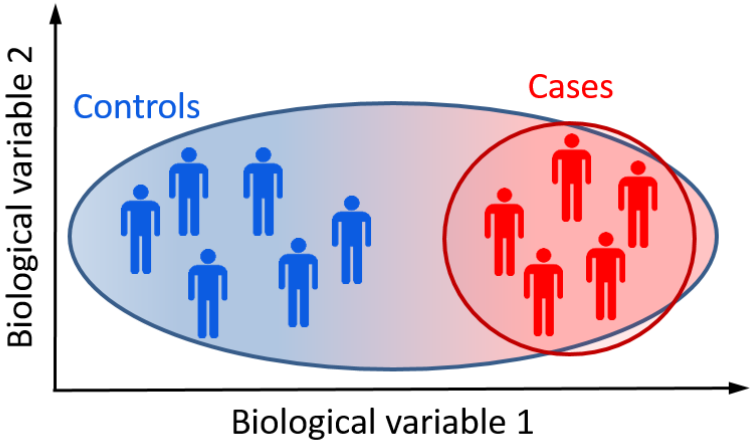

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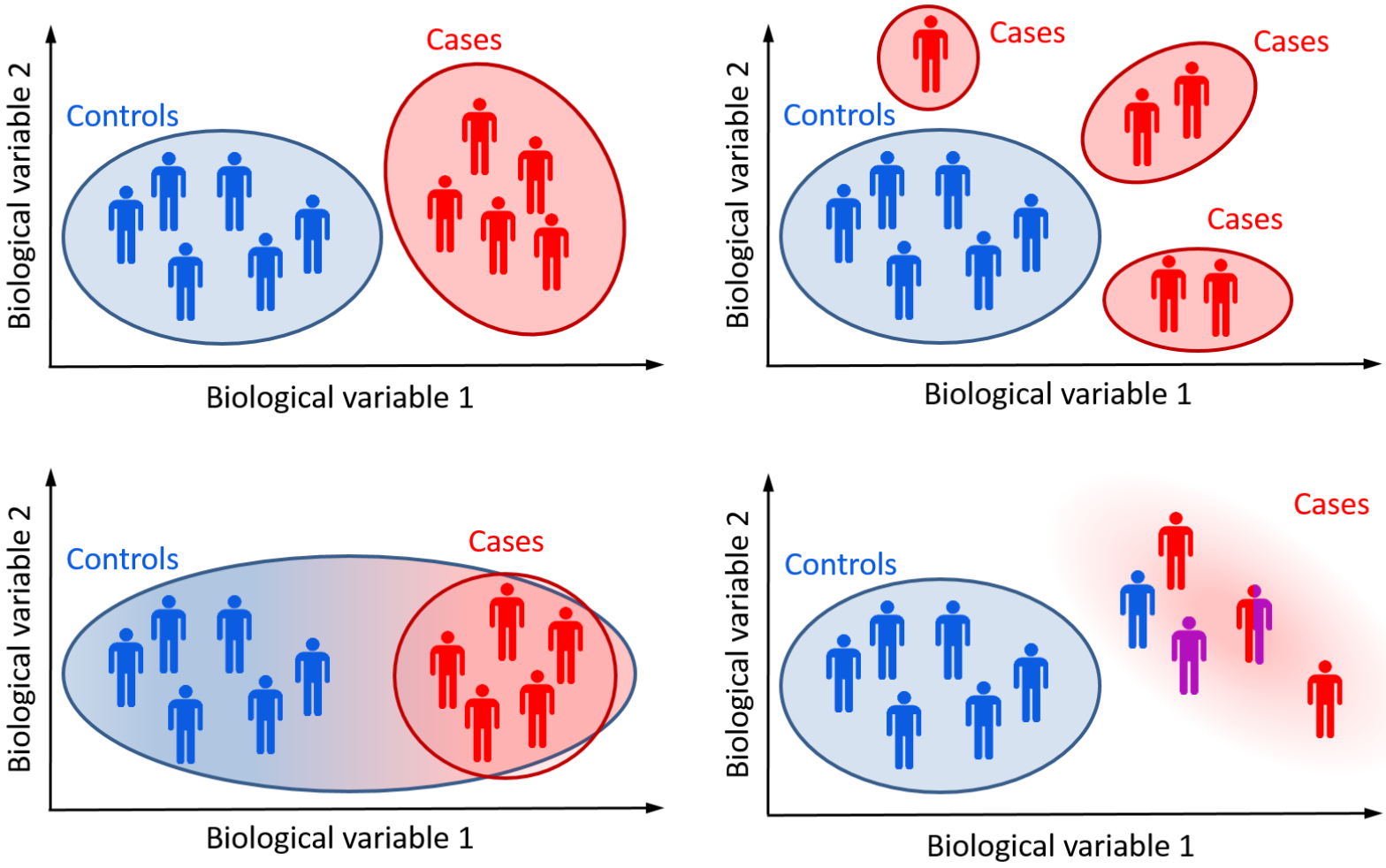

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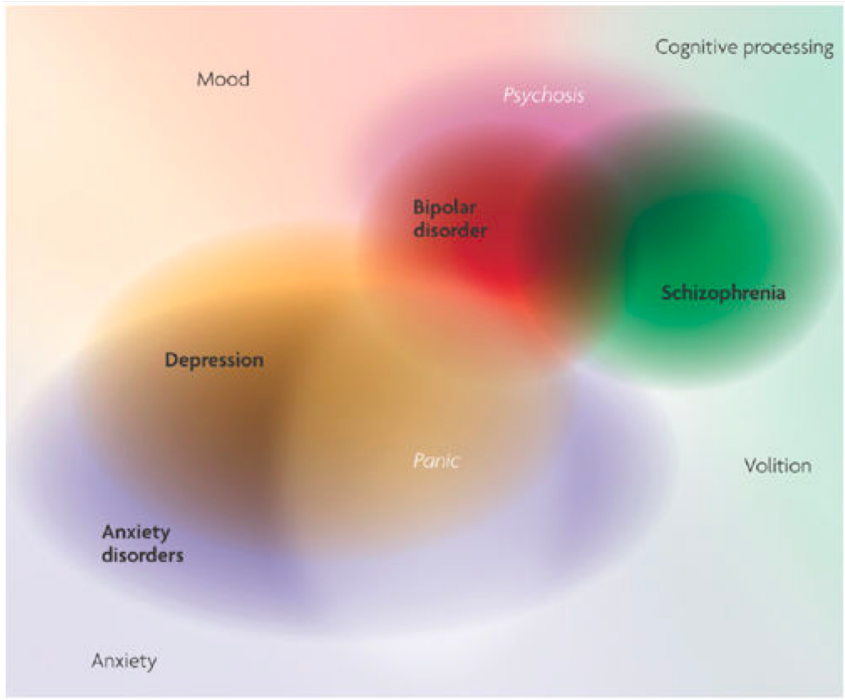
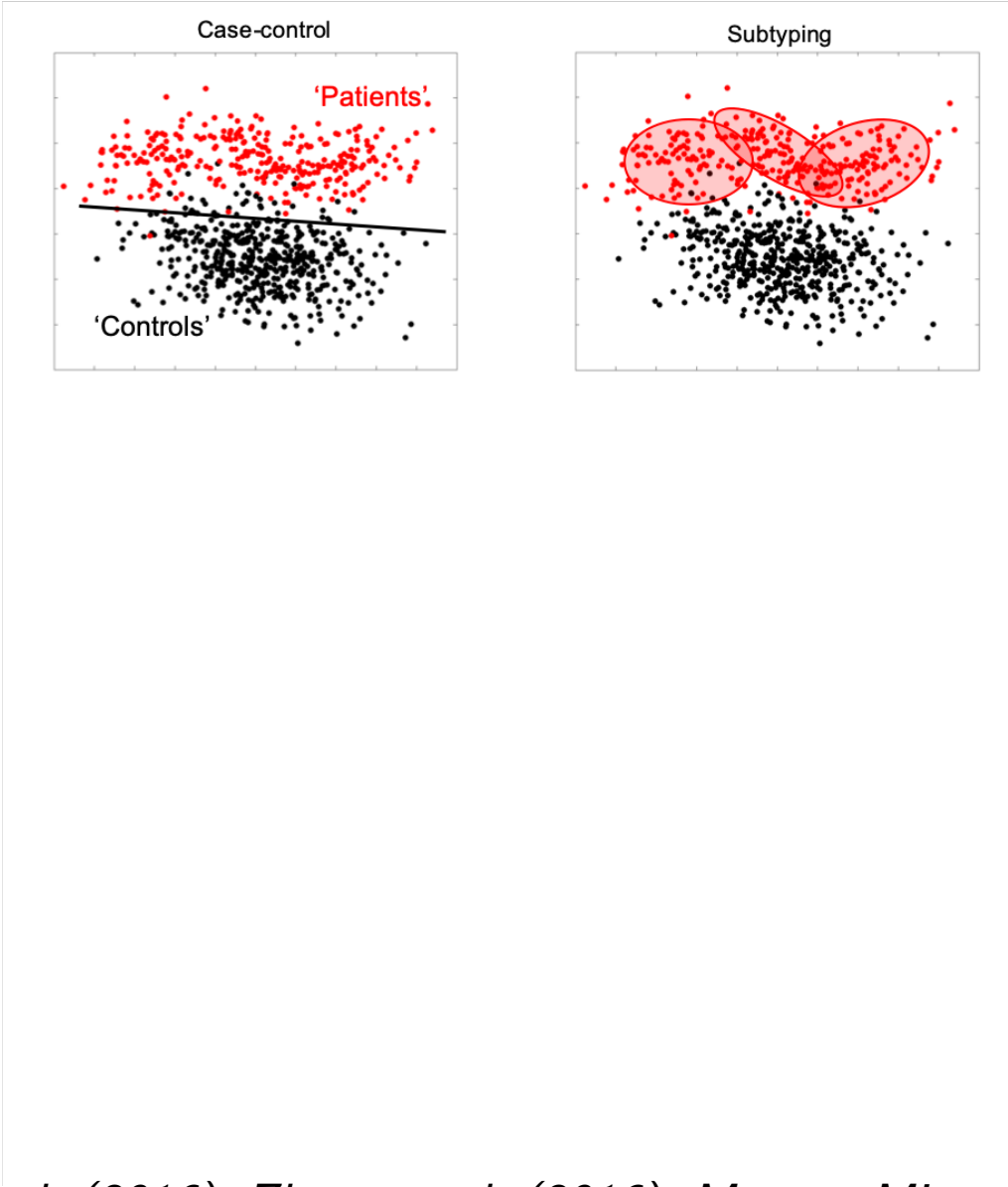


Burmeister et al. (2008)

Methods for addressing heterogeneity



Dong et al. (2016); Zhang et al. (2016); Mourao-Miranda et al. (2011)

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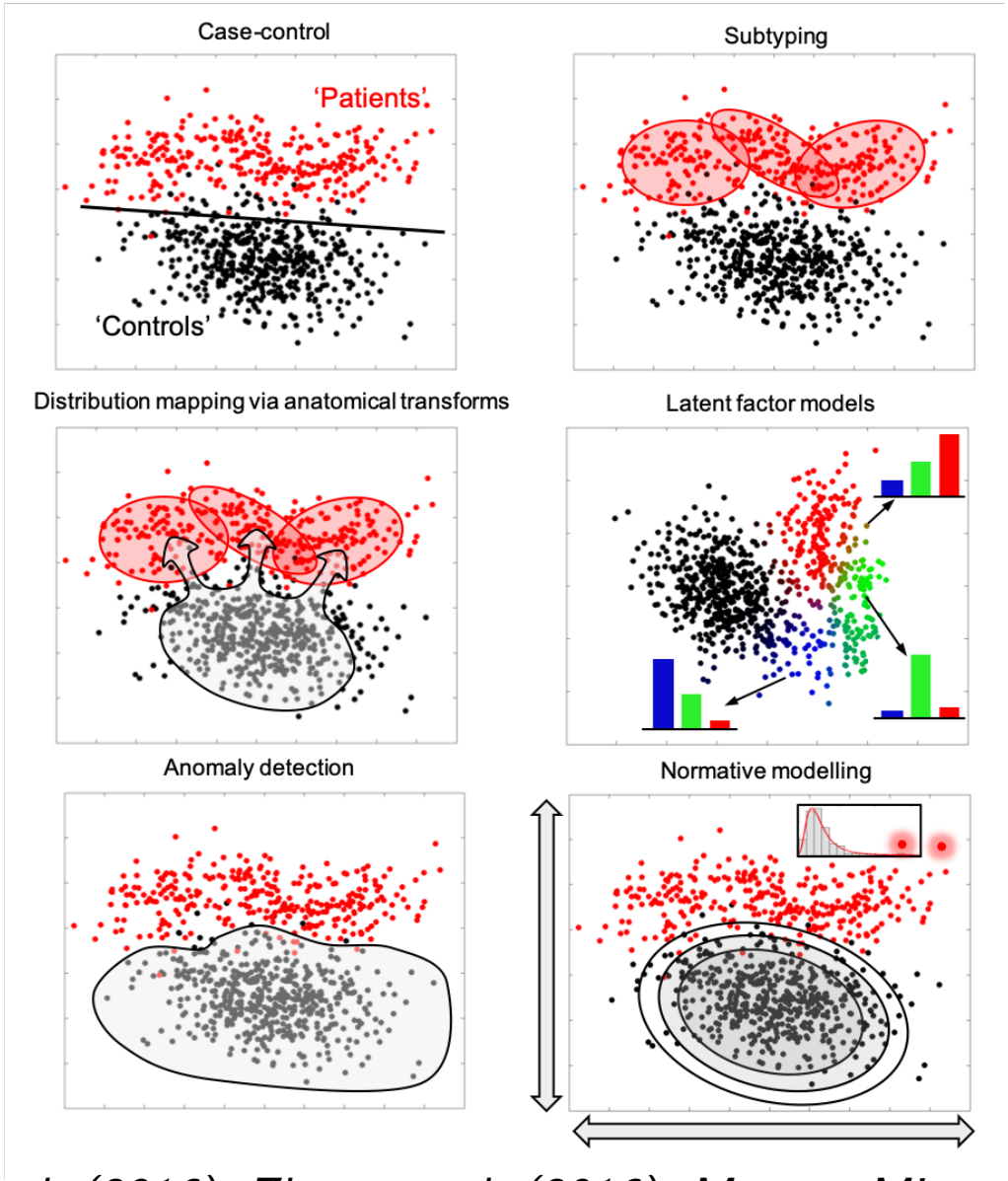

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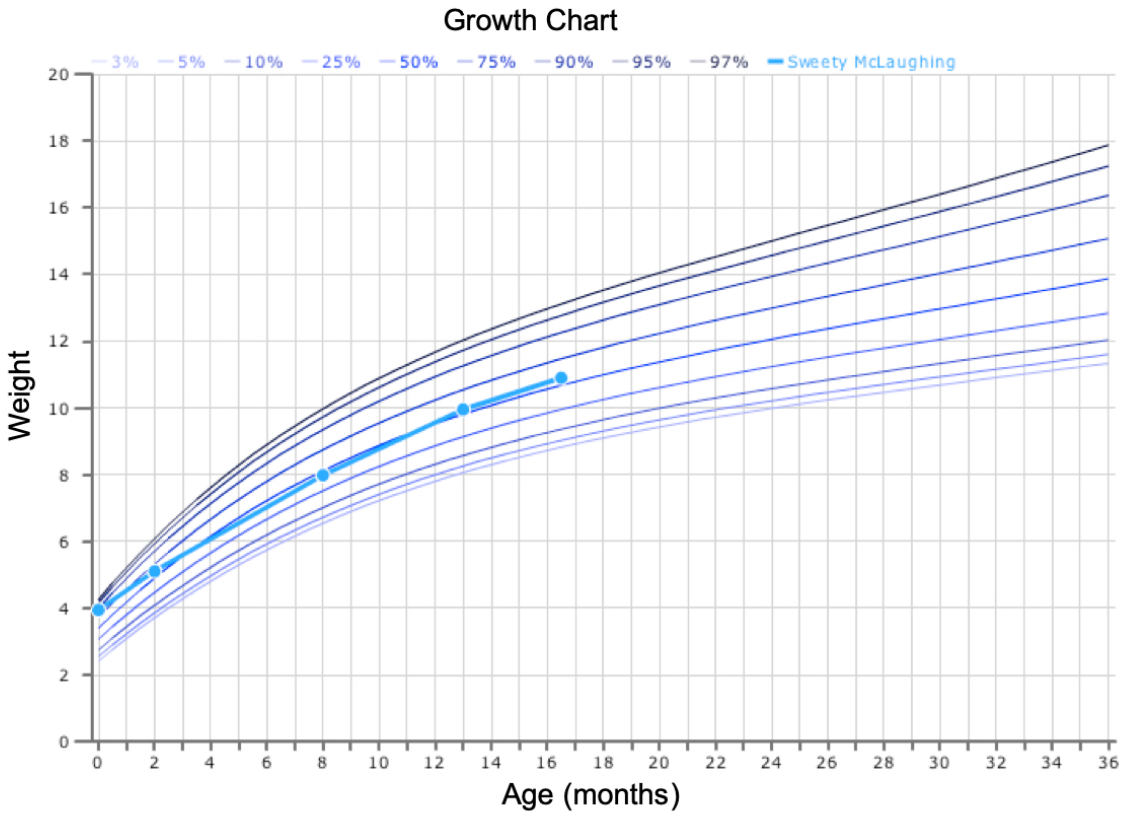
Normative modelling



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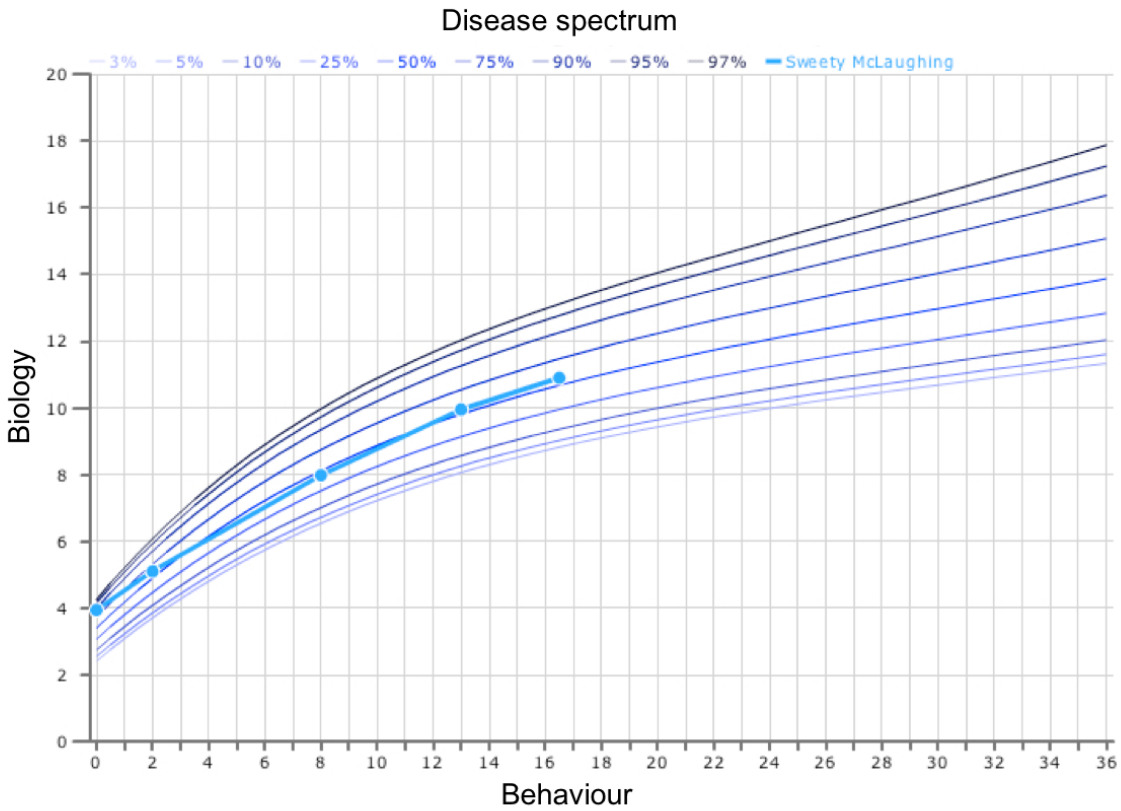

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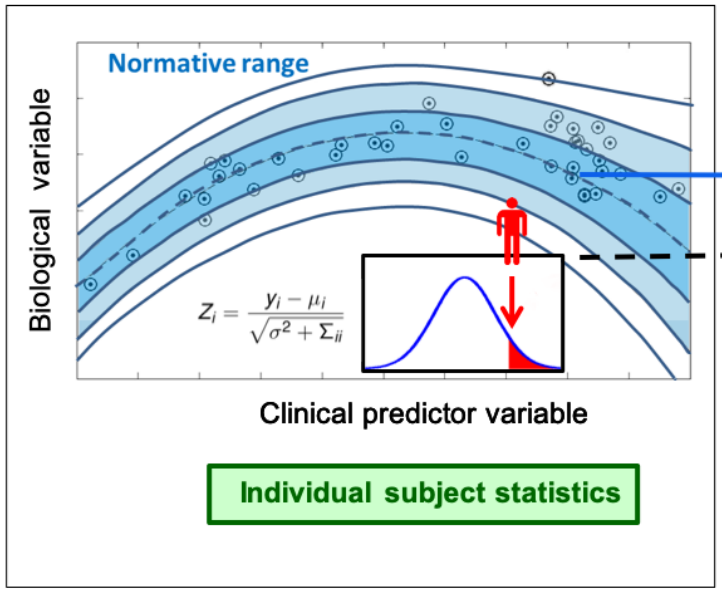


Uncertainty

Error

Gaussian process regression

$$p(y|\mathbf{x}, \sigma^2) = f(\mathbf{x}, \theta) + \epsilon$$

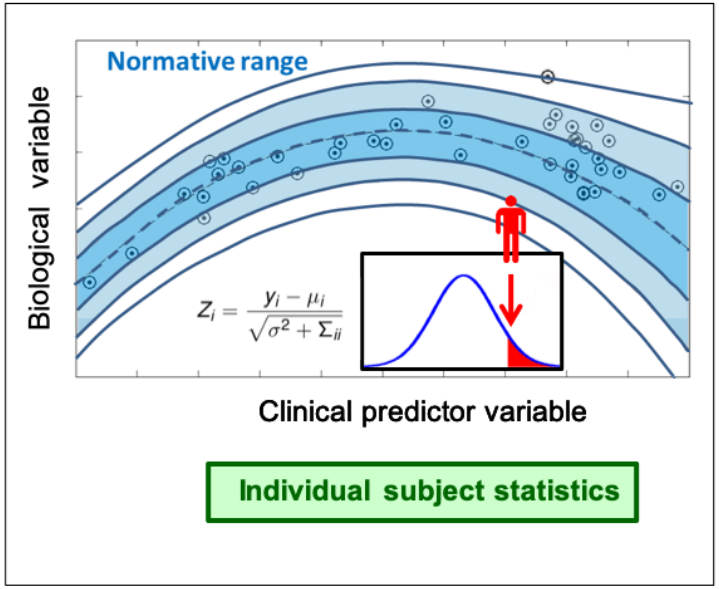
$$p(\epsilon) = \mathcal{N}(0, \sigma^2)$$

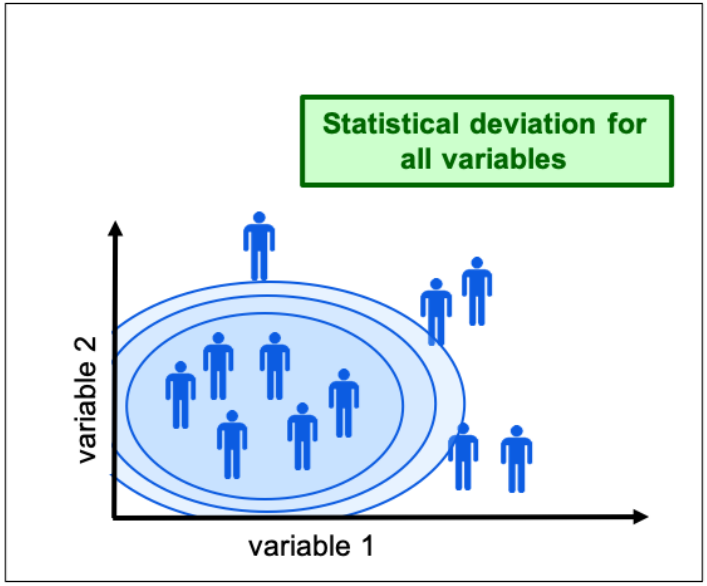
$$p(\mathbf{f}|\theta) = \mathcal{N}(m(\beta), \mathbf{K}(\theta))$$

$$p\left(\begin{bmatrix}\mathbf{y}\\ \mathbf{f}_*\end{bmatrix}\middle|\theta, \beta, \sigma^2\right) \sim \mathcal{N}\left(\begin{bmatrix}\mathbf{m}\\ \mathbf{m}_*\end{bmatrix}, \begin{bmatrix}\mathbf{K}+\sigma^2\mathbf{I} & \mathbf{k}_*{}^T\\ \mathbf{k}_* & \mathbf{k}_{**}\end{bmatrix}\right)$$

Marquand et al. (2016)

Normative modelling





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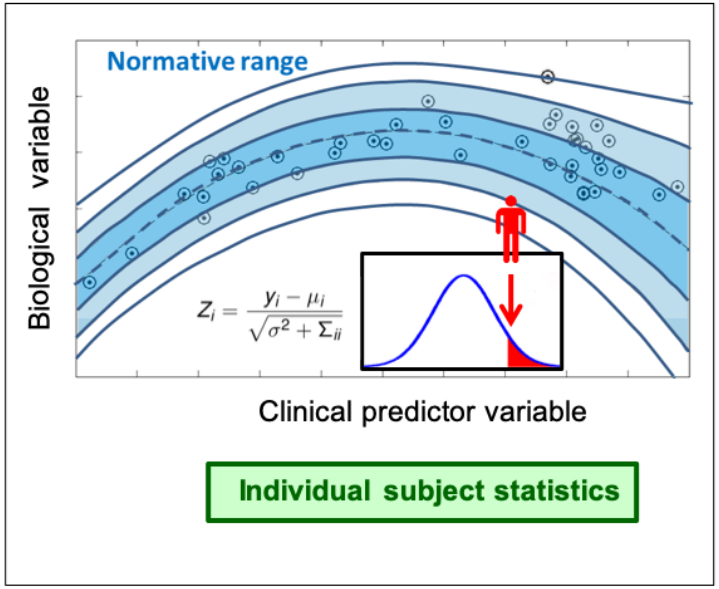

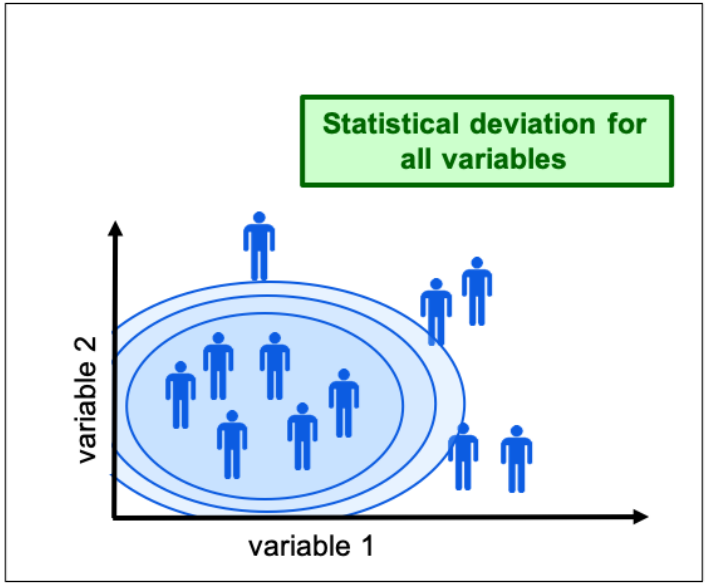

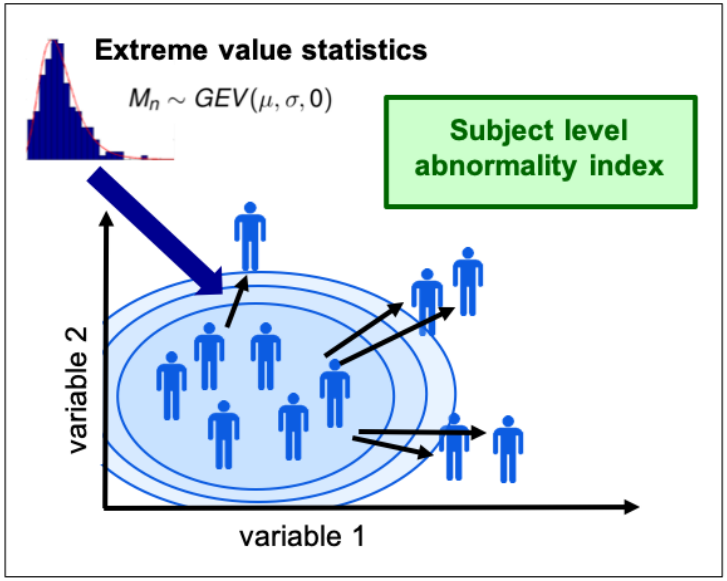

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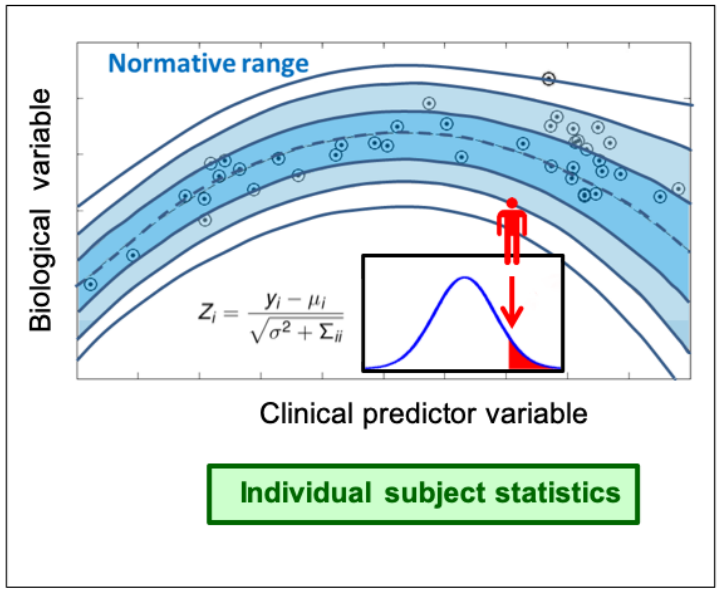
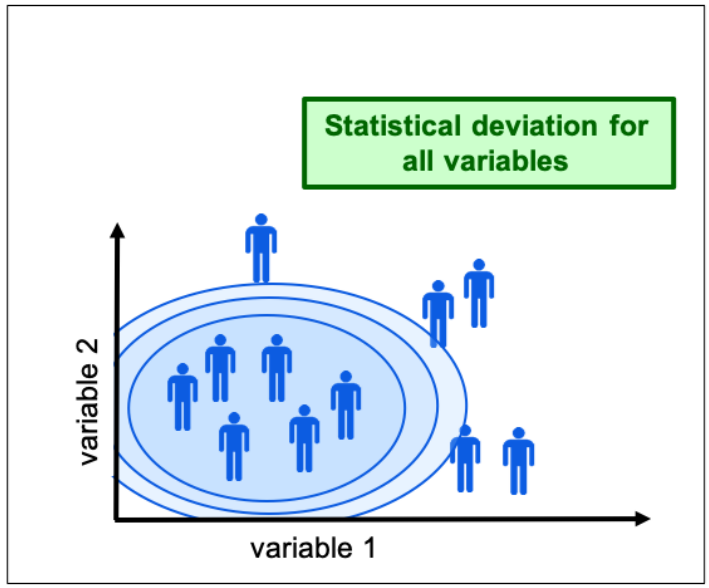
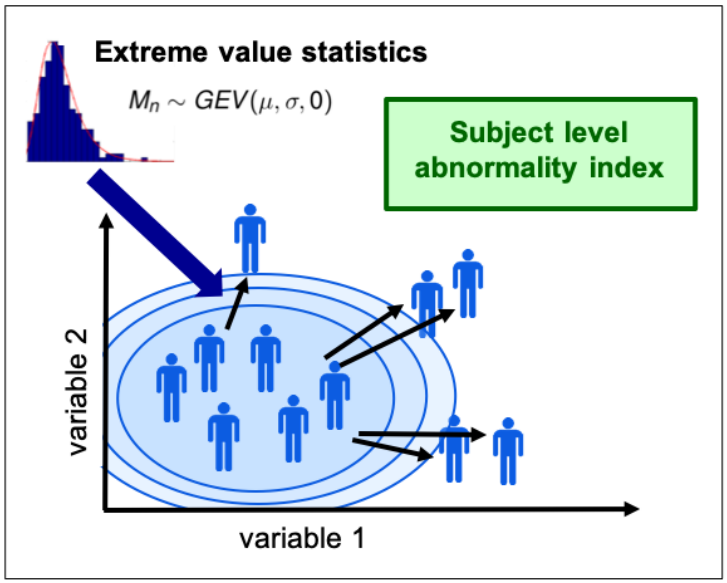
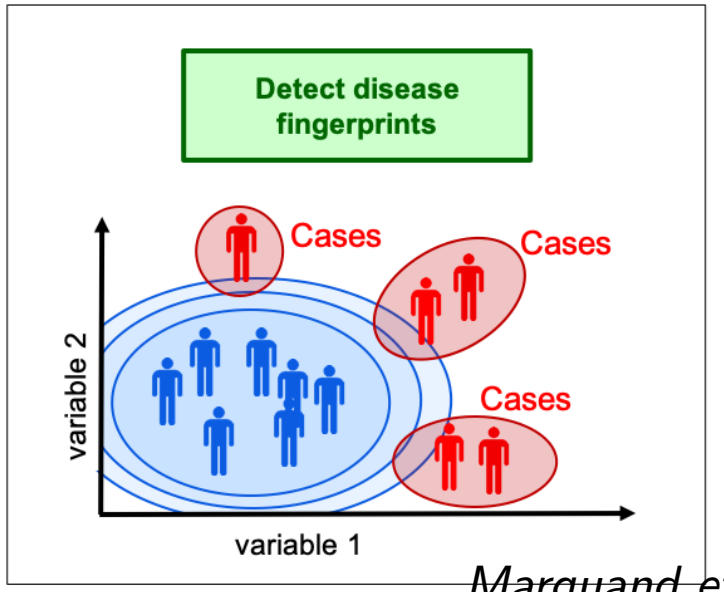


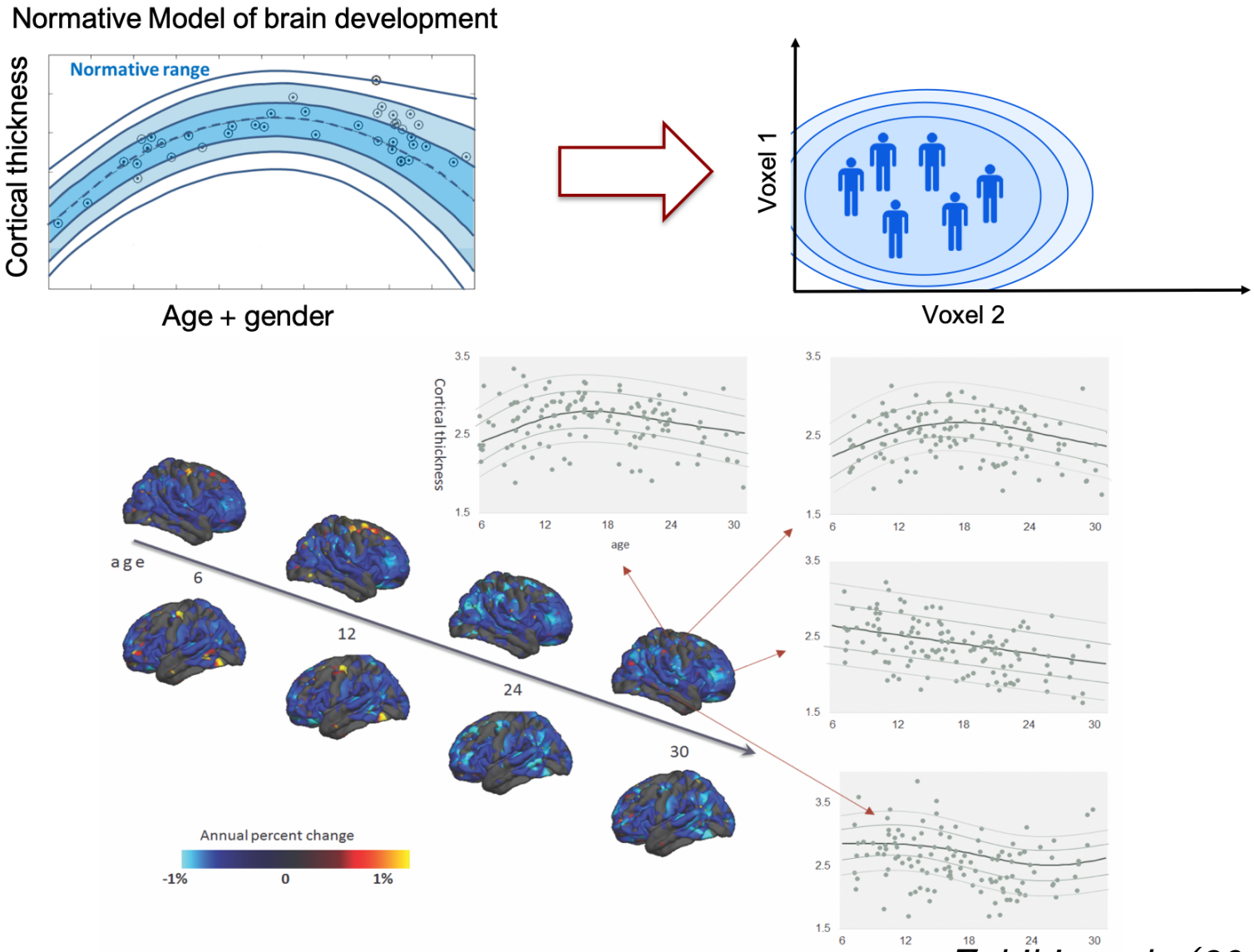






Marquand et al. (2016)

Normative modelling of autism



Zabihi et al. (2019)

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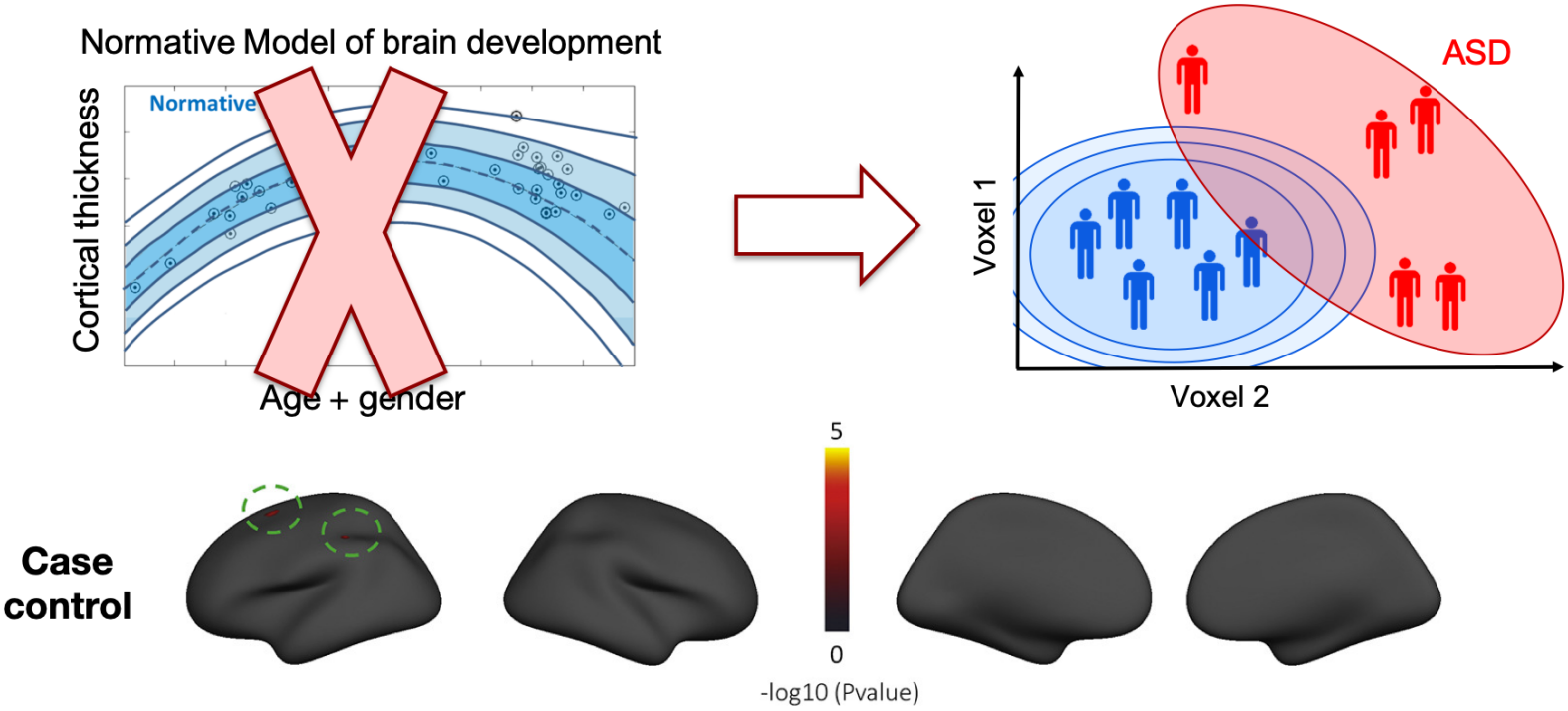

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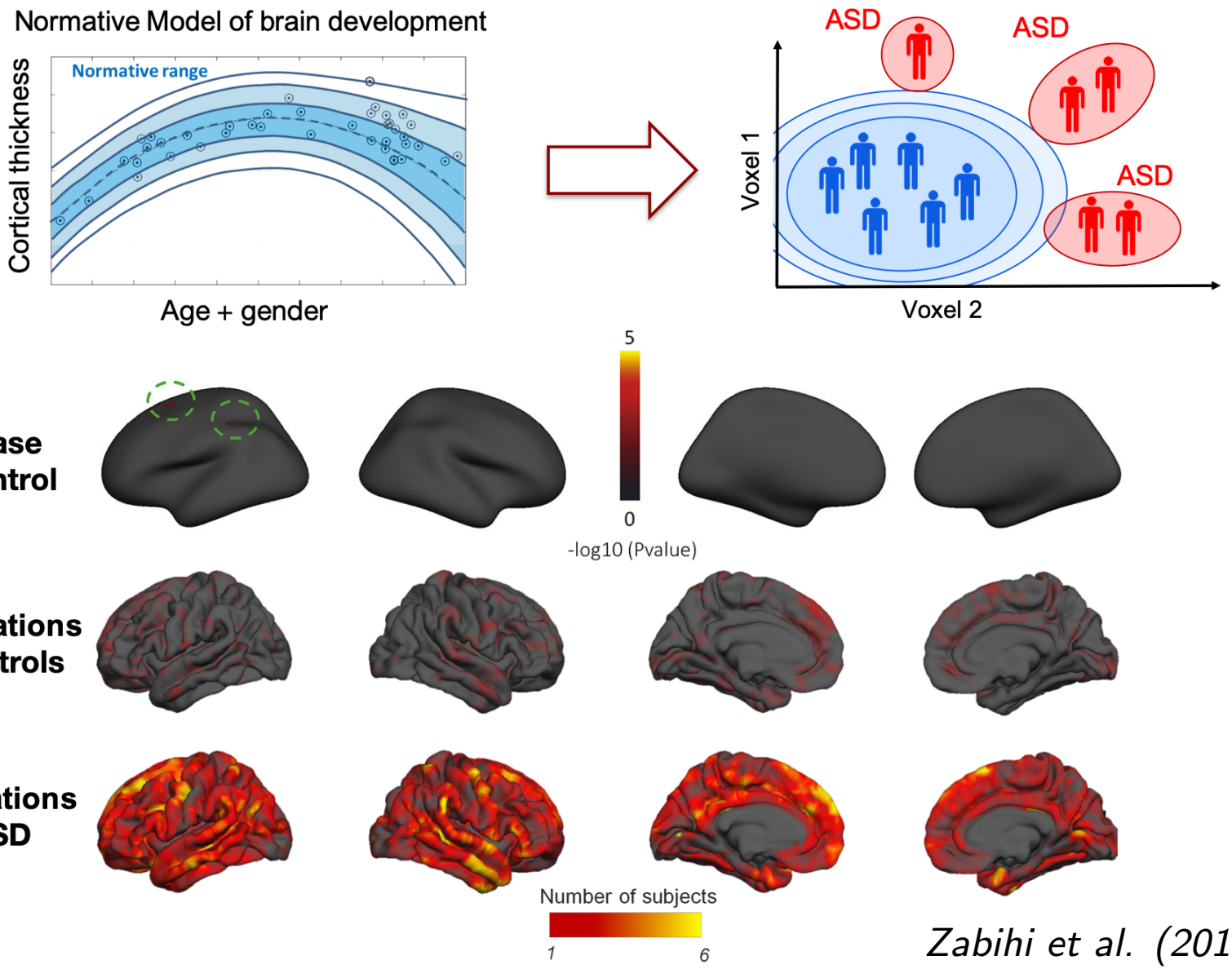

Zabihi et al. (2019)

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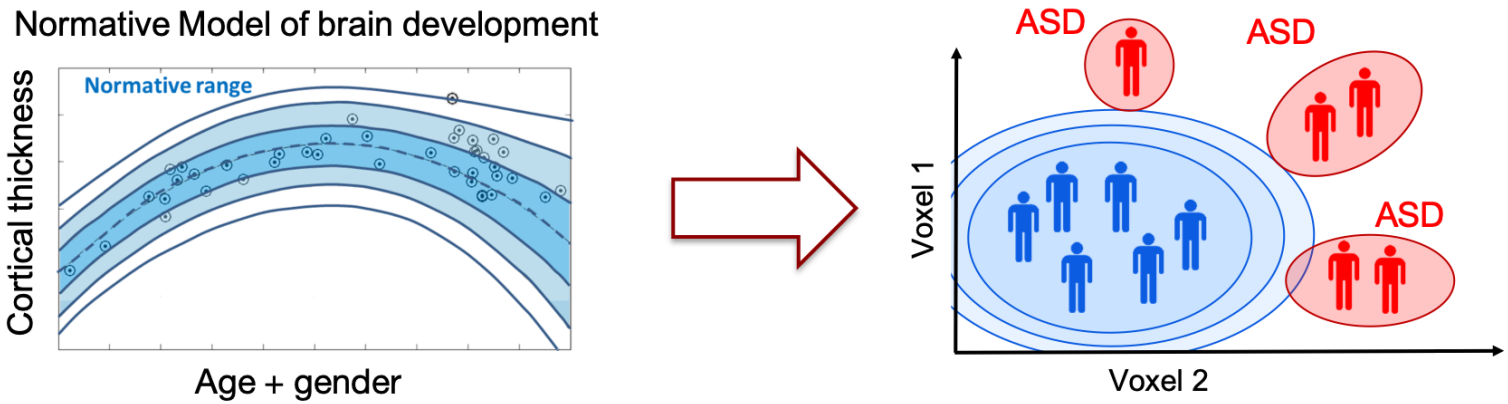
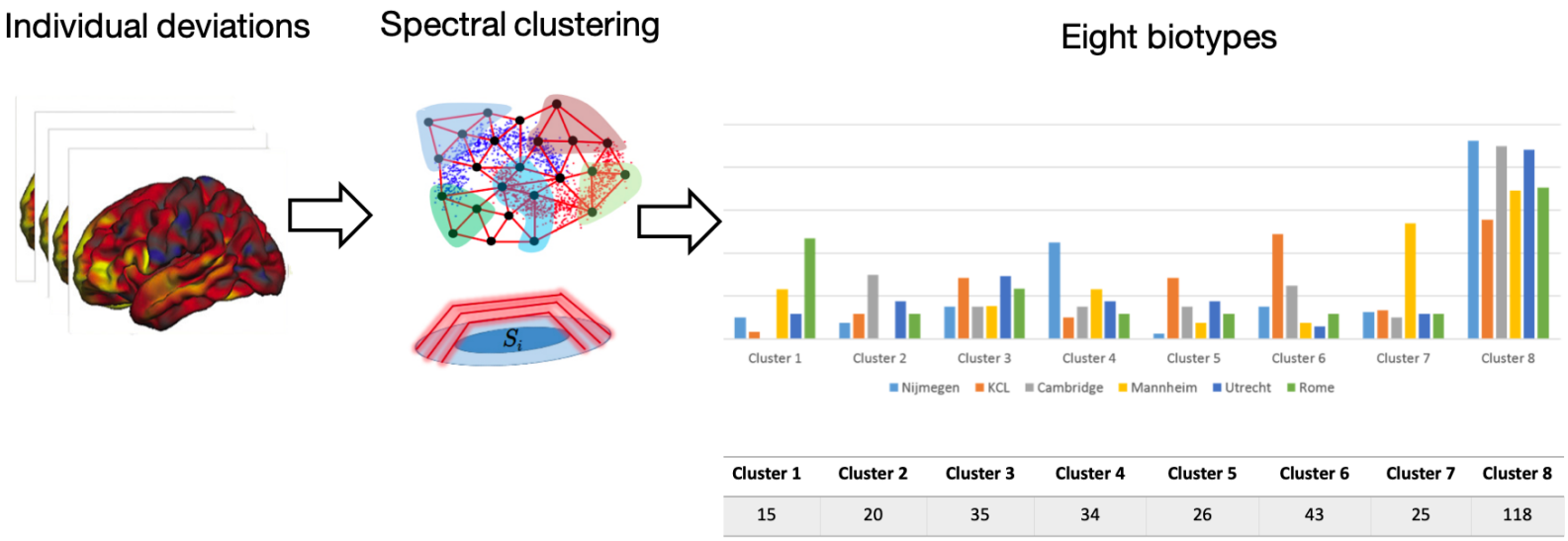




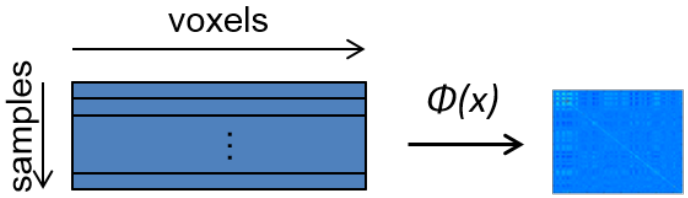
Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	Cluster 8
15	20	35	34	26	43	25	118

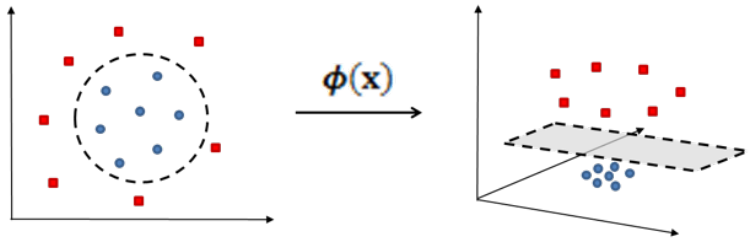
Zabihi et al. (2019)

Outline

Kernels

- Kernel methods (e.g. SVM, GPs) use the "kernel trick" to turn a linear model into a non-linear one





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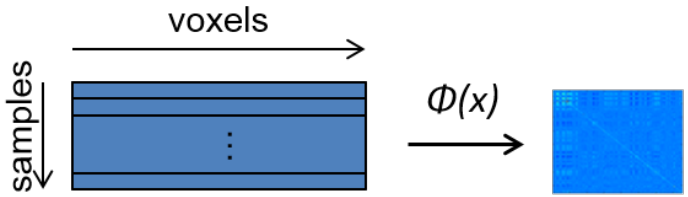

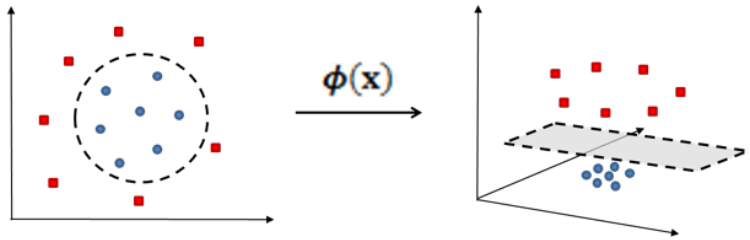

$$\max_{\alpha} \sum_{i=1}^{N} \alpha_i - \frac{1}{2} \sum_{i,j=1}^{N} \alpha_i \alpha_j y_i y_j \mathbf{x}_i^T \mathbf{x}_j$$

$$\text{s.t.:} \sum_i \alpha_i y_i = 0$$

$$0 \leq \alpha_i \leq C$$

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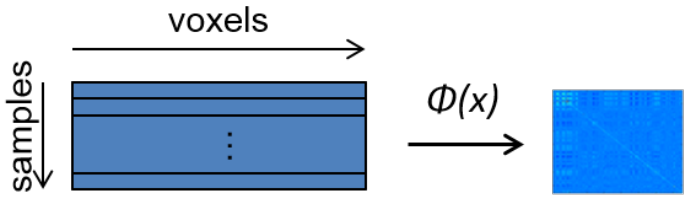

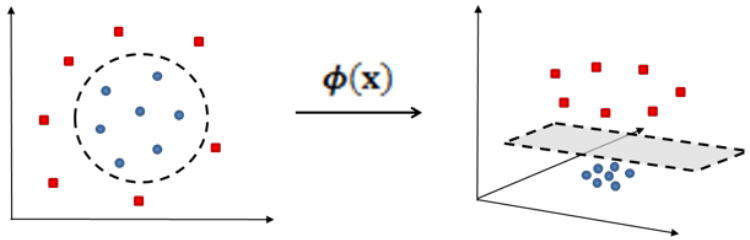

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- In the dual form, the data appear as an inner product, which can be substituted with a kernel function

$$\mathbf{x}_i^T \mathbf{x}_j \Rightarrow k(\mathbf{x}_i, \mathbf{x}_j) \Rightarrow \phi(\mathbf{x}_i)^T \phi(\mathbf{x}_j)$$

Kernels

- Any method that can be written in terms of inner products can be kernelized
- Kernel function must give rise to a positive definite matrix
- Many different functions are admissable

$$\begin{aligned}
\text{linear} &: k(\mathbf{x}, \mathbf{x}') = \mathbf{x}^T \mathbf{x}' \\
\text{RBF} &: k(\mathbf{x}, \mathbf{x}') = \exp(-\gamma ||\mathbf{x} - \mathbf{x}'||^2) \\
\text{polynomial} &: k(\mathbf{x}, \mathbf{x}') = (\gamma \mathbf{x}^T \mathbf{x}' + c)^d \\
\text{sigmoid} &: k(\mathbf{x}, \mathbf{x}') = \tanh(\gamma \mathbf{x}^T \mathbf{x}' + c)
\end{aligned}$$

- linear operations on kernels also yield valid kernels, e.g.

$$k(\mathbf{x}, \mathbf{x}') = k_1(\mathbf{x}, \mathbf{x}') + 2k_2(\mathbf{x}, \mathbf{x}')k_3(\mathbf{x}, \mathbf{x}') + \ldots$$

- This is the basis for *multi-kernel learning*

Multi-Kernel Learning

- Kernels can represent different modalities, different views or different regions

$k(\mathbf{x}, \mathbf{x}') = \sum_{m=1}^{M} d_m k_m(\mathbf{x}, \mathbf{x}')$ with $d_m \geq 0$ and $\sum_m d_m = 1$

- Optimisation problem is a convex combination of kernels

$$\min_{\mathbf{w}} \frac{1}{2} \sum_{m=1}^{M} ||\mathbf{w}_m||^2 + C \sum_{i=1}^{n} \xi_i$$

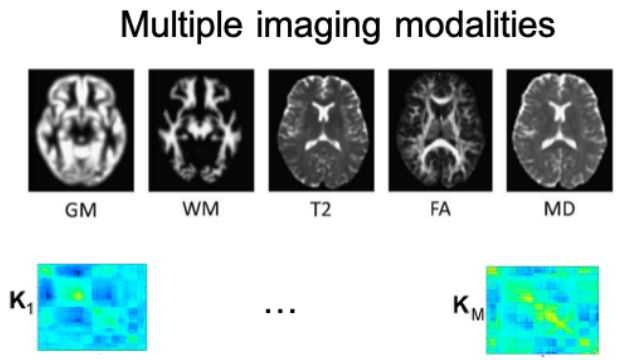
$$\text{subject to: } y_i(\sum_m (\mathbf{x}_i^T \mathbf{w}_m + b)) \geq 1 - \xi_i, \xi_i \geq 0 \; \forall i$$

$$\sum_m d_m = 1 \text{ and } d_m \geq 0$$

Applications of MKL in neuroscience

Multimodal data fusion for predicting brain disorders

$$p(y_{ic}|\mathbf{x}_1 \dots \mathbf{x}_M) = \frac{\exp f_{ic}}{\sum_d \exp f_{id}} \qquad p(\mathbf{y}|\mathbf{x}_1 \dots \mathbf{x}_M) = \mathcal{GP}(\mathbf{0}, \mathbf{K}(\theta))$$



Filippone et al. (2012)

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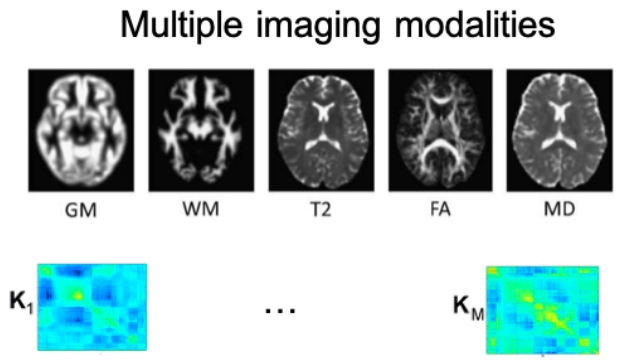
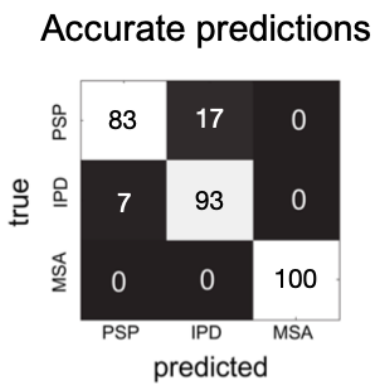
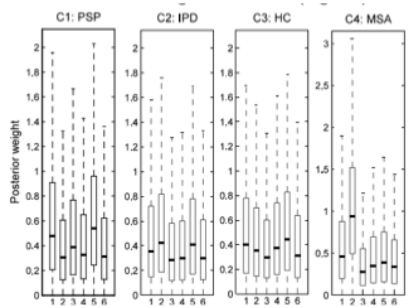


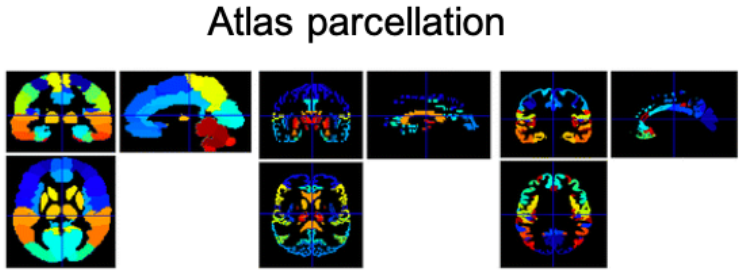


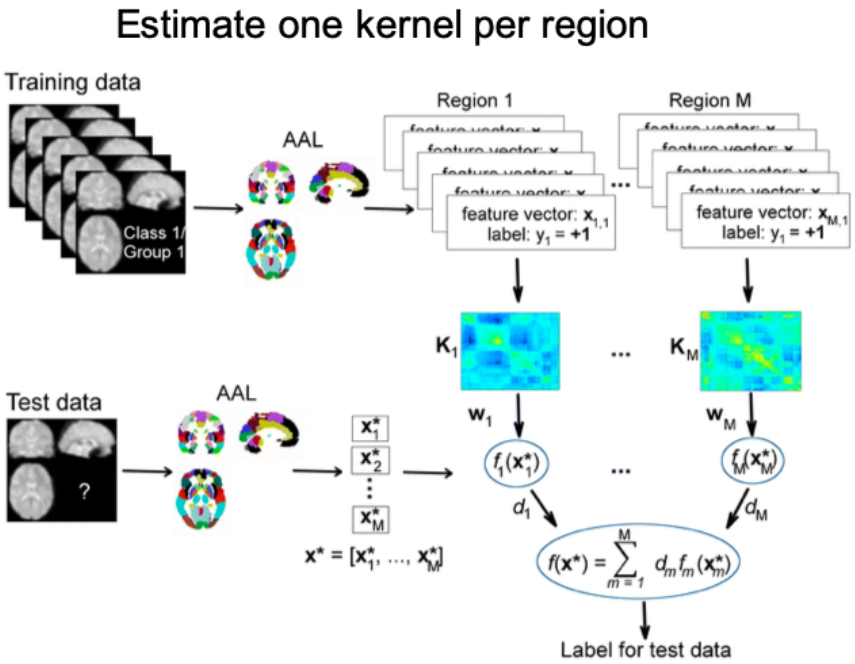


Filippone et al. (2012)

Applications of MKL in neuroscience

Better accommodating spatial variation

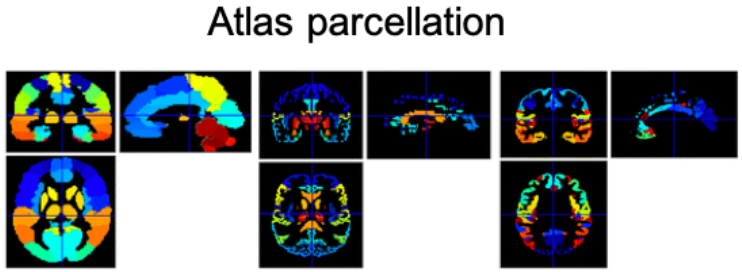


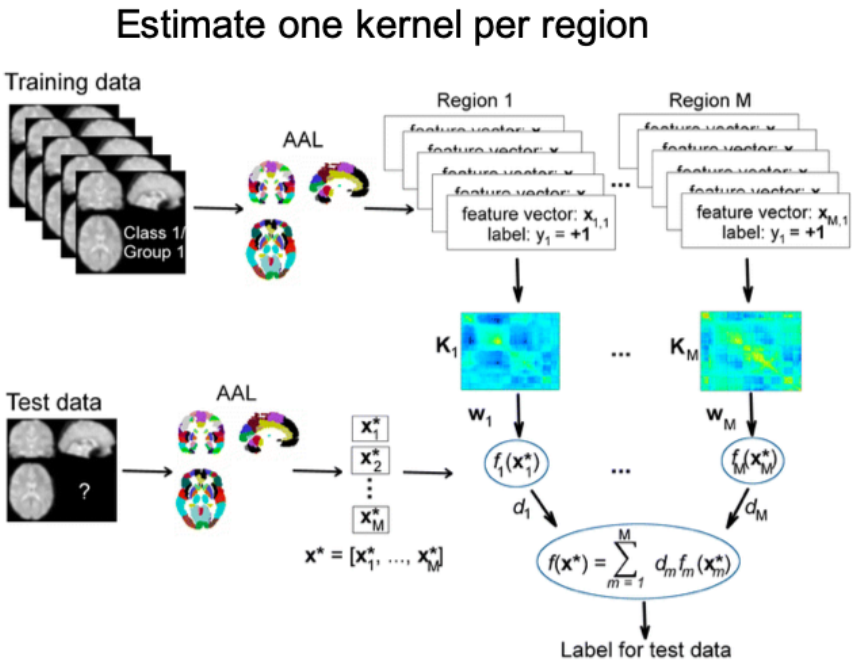


Schrouff et al. (2018)

Applications of MKL in neuroscience

Better accommodating spatial variation



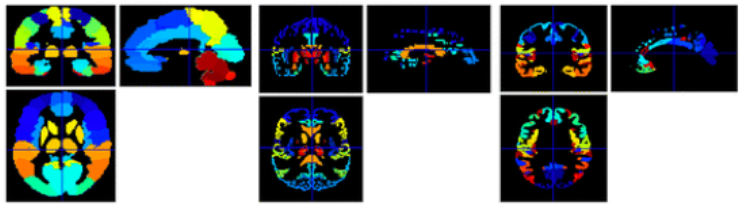


Schrouff et al. (2018)

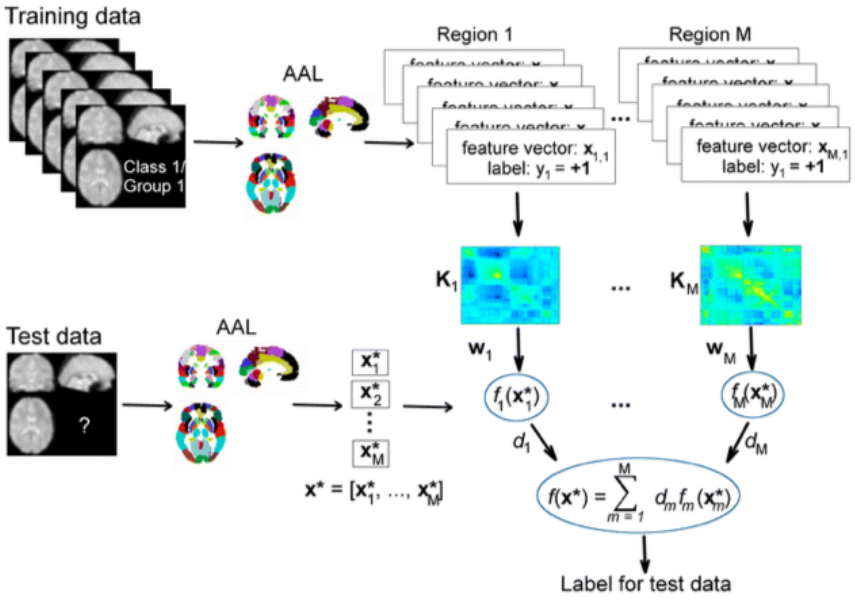
Applications of MKL in neuroscience

Better accommodating spatial variation

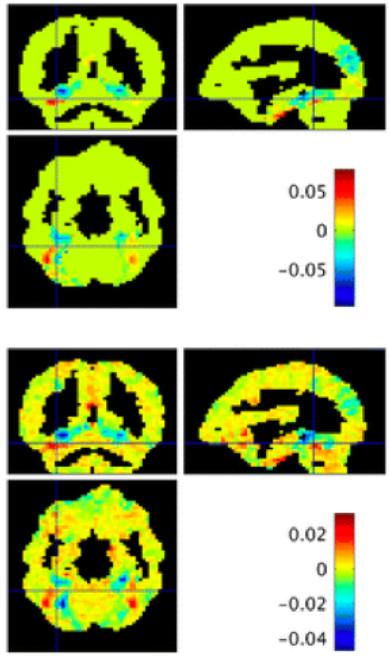
Atlas parcellation



Estimate one kernel per region



Improve SNR



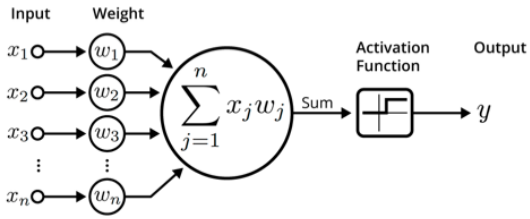
Schrouff et al. (2018)

Deep Learning

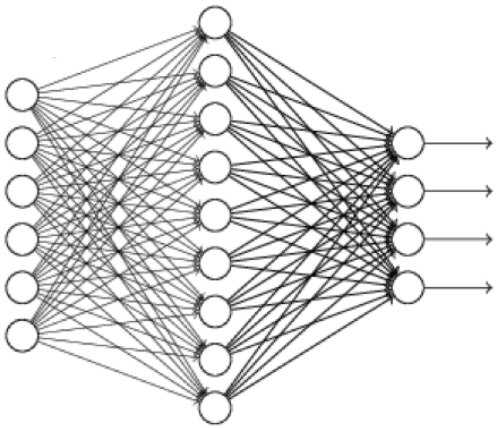
It is helpful to think of deep learning as combining matix products with point-wise linearity, e.g.:

$$f(\mathbf{x}) = \sigma\left(\mathbf{x}\mathbf{W}_1 + \mathbf{b}_1\right)\mathbf{W}_2$$

Artificial neuron
(pointwise non-linearity)



Fully connected



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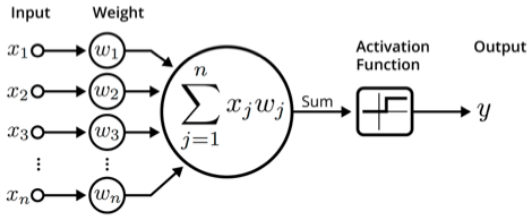
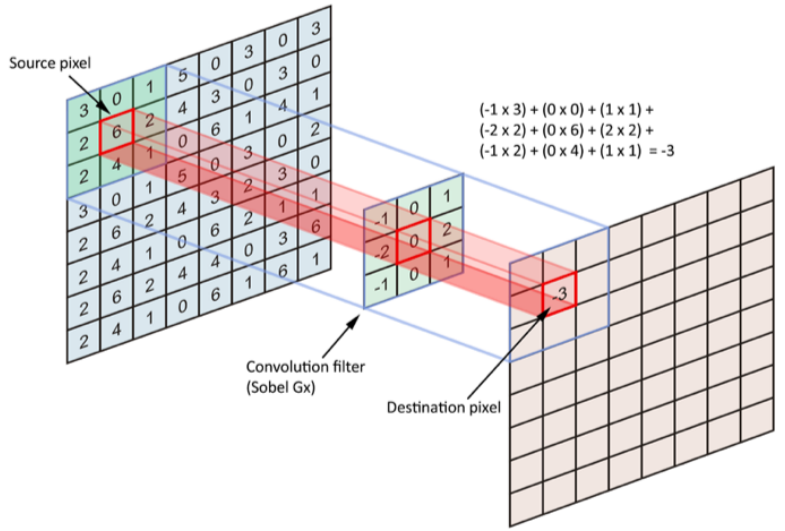


Convolution



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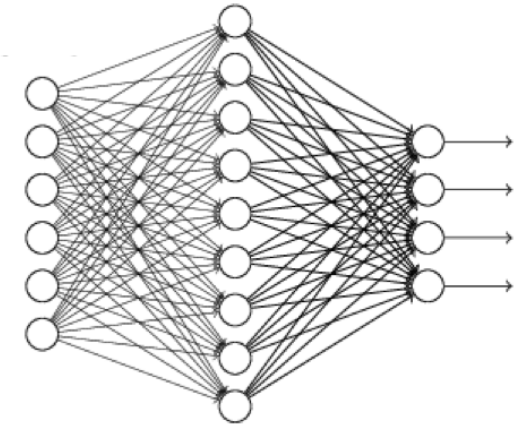
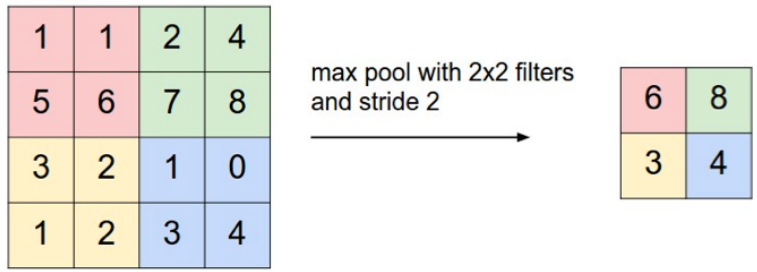
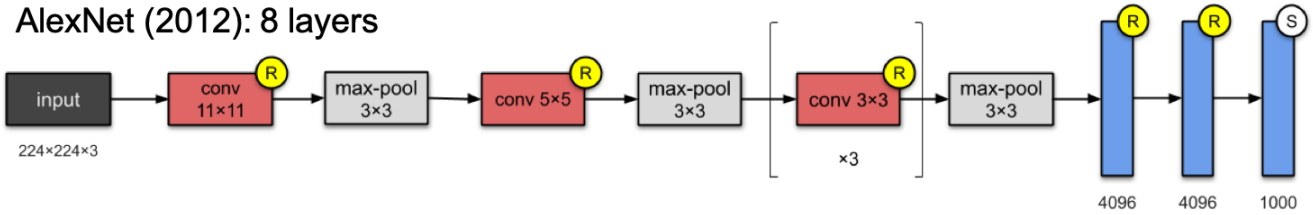


Max pooling



Convolutional Neural Networks



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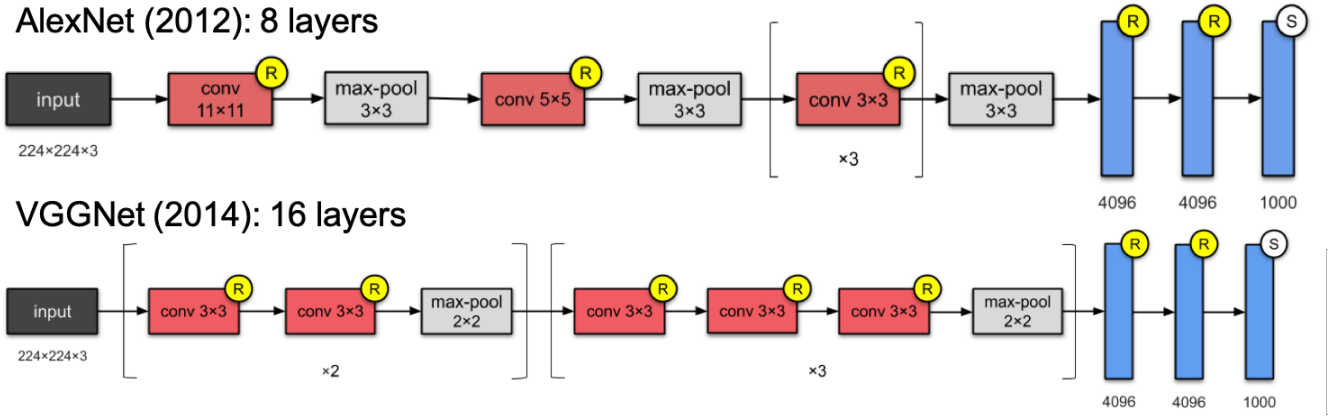

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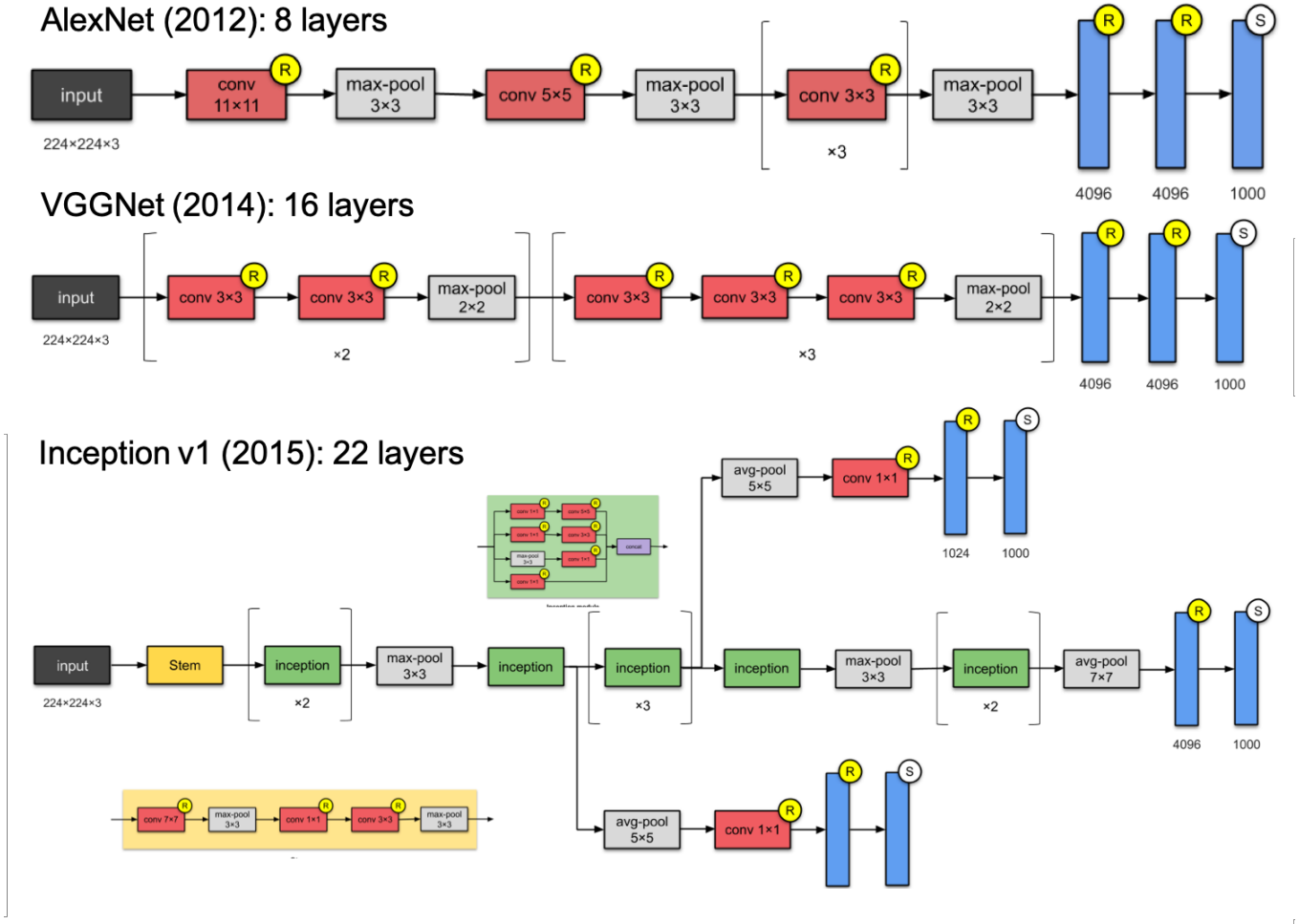

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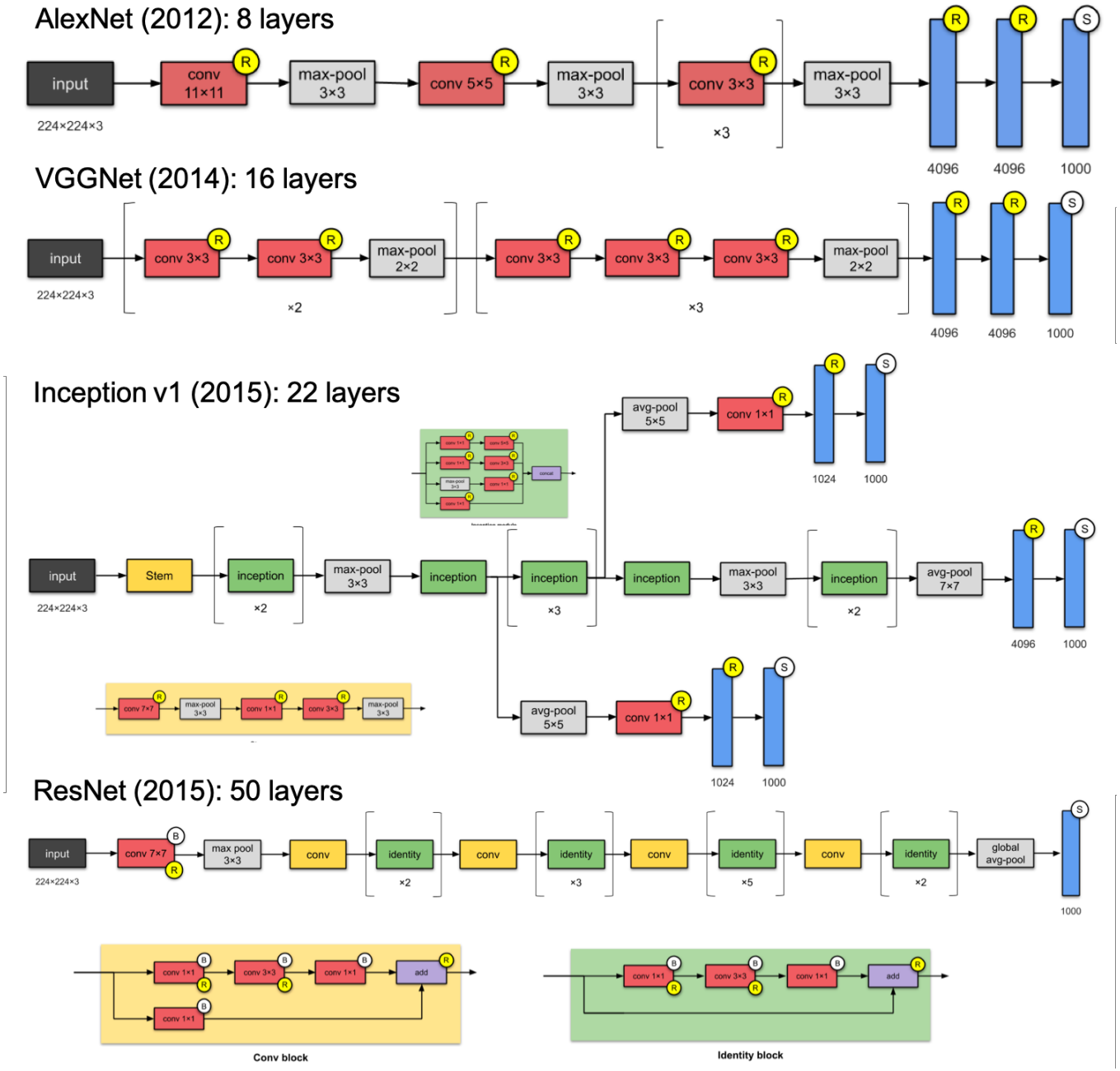
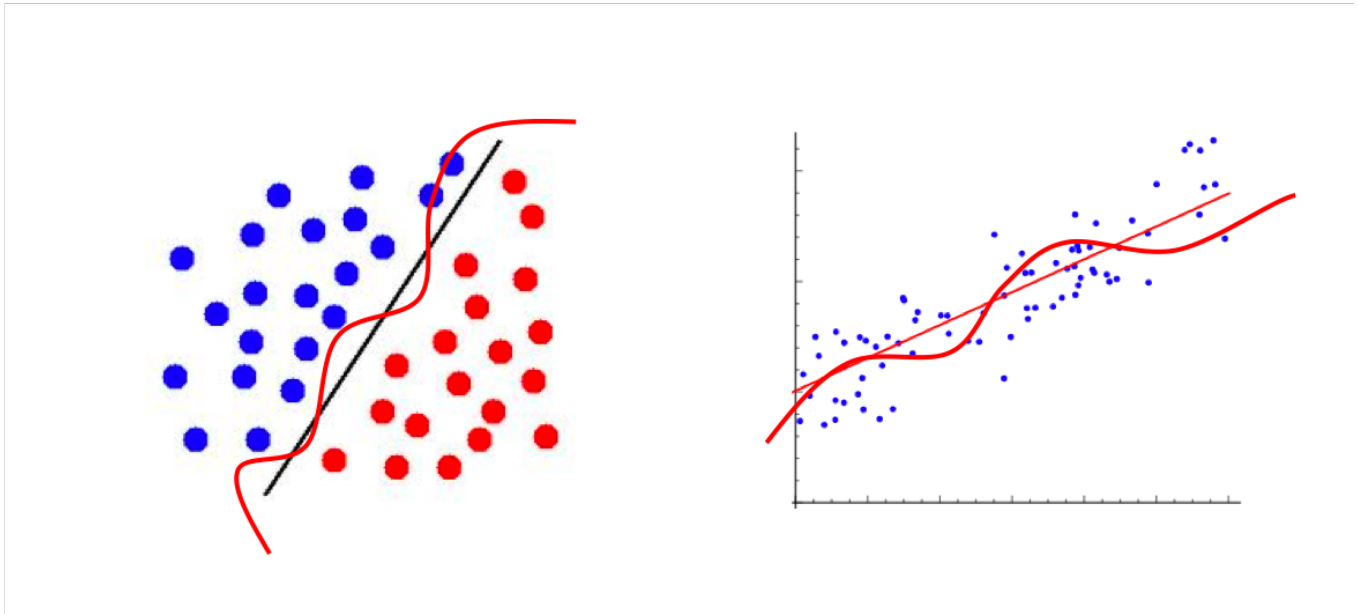


Overfitting (again)

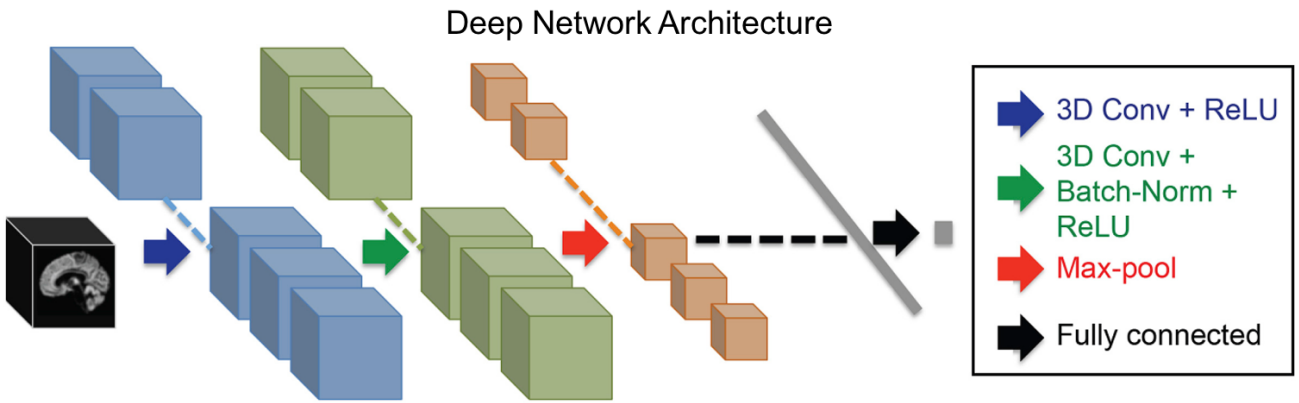
- But if your problem is linear, your fancy nonlinear algorithm will just overfit



- The more complex the model, the easier it is to overfit
- In complex (deep) models it is often not possible to properly optimise all parameters
- This makes validation extremely important!

Deep Learning in Psychiatry?

- Predict age from N= 2001 structural MRI images



Cole et al. (2017)

Deep Learning in Psychiatry?

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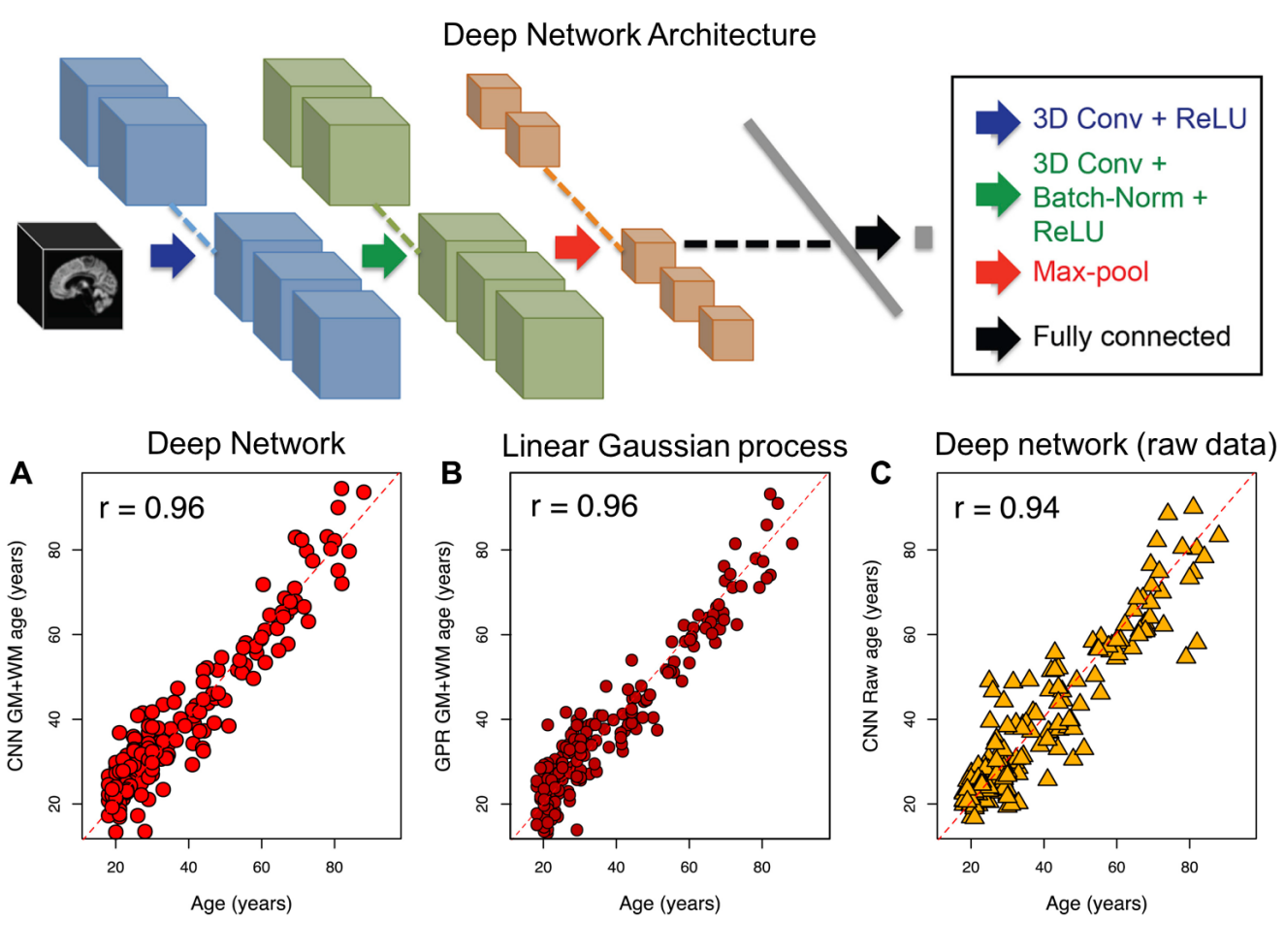

- Similar performance to a linear model on preprocessed data
- Better performance on minimally processed data *Cole et al. (2017)*

Deep Learning in Neuroscience?

Deep Neural Networks and Kernel Regression Achieve Comparable Accuracies for Functional Connectivity Prediction of Behavior and Demographics

Tong He[1,2], Ru Kong[1,2], Avram J. Holmes[3], Minh Nguyen[1,2], Mert R. Sabuncu[4], Simon B. Eickhoff[5,6], Danilo Bzdok[7,8,9], Jiashi Feng[2], B.T. Thomas Yeo[1,2,10,11,12]

He et al. (2019)

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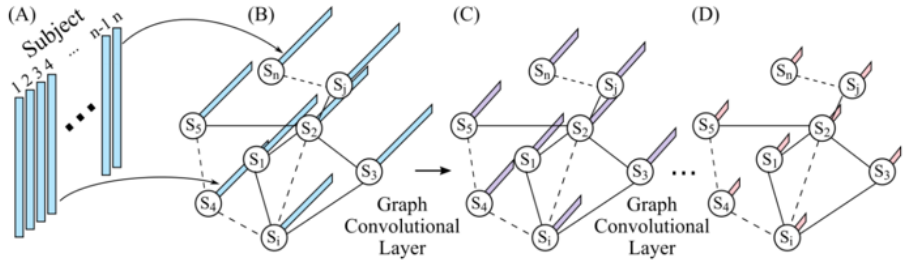
BrainNet CNN

Graph CNN



HUMAN Connectome PROJECT

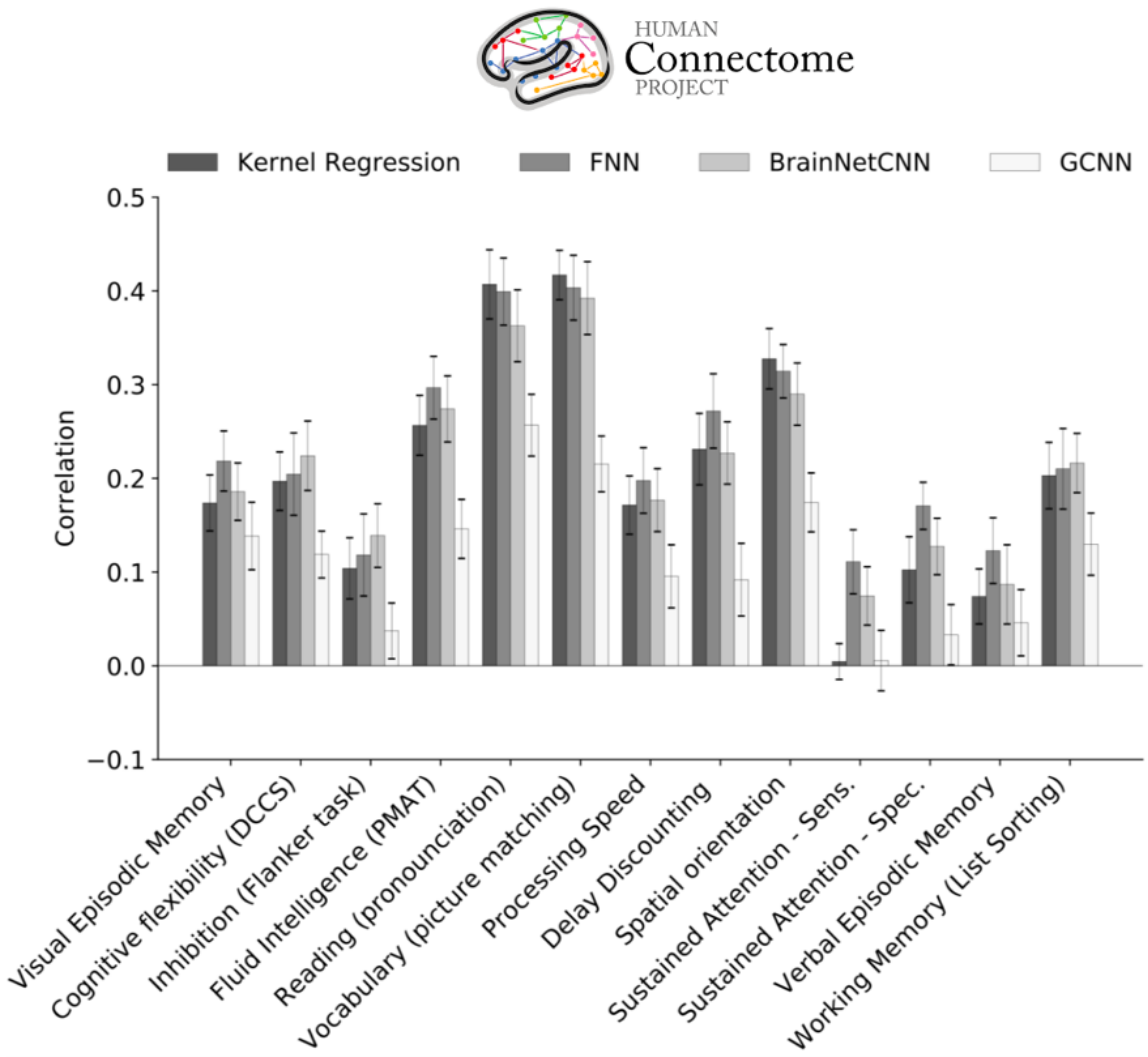
N = 1200

biobank uk

N = 10 000

He et al. (2019)

Deep Learning in Neuroscience?



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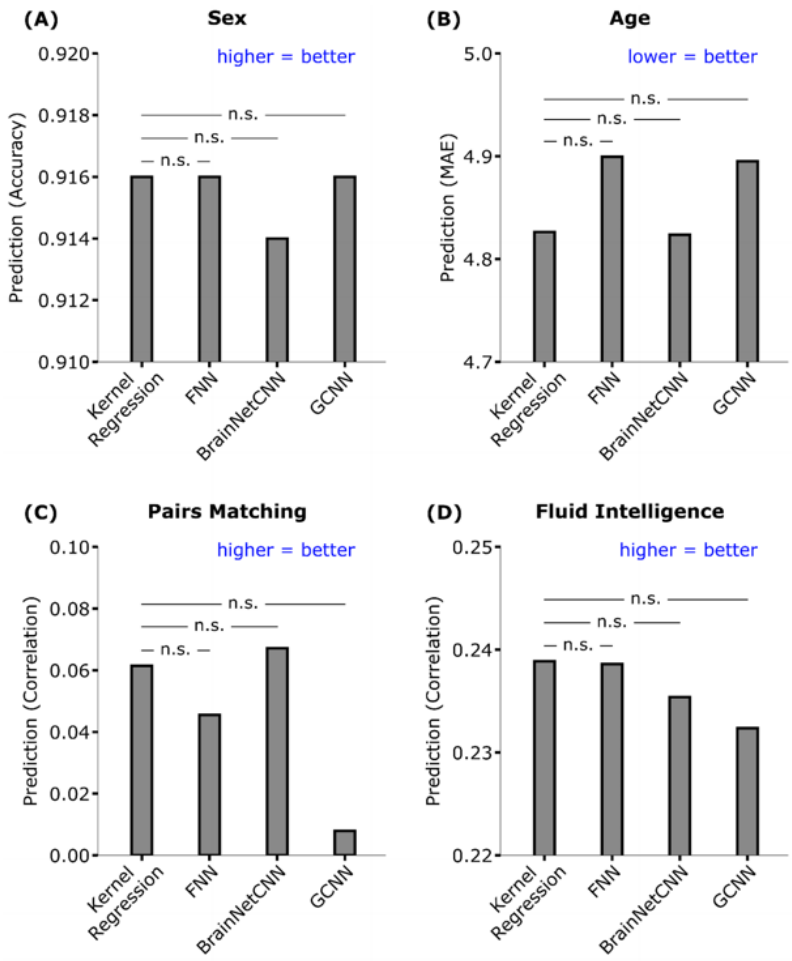
Deep Learning in Neuroscience?



He et al. (2019)

Deep Learning in Medicine?

- Predict mortality from electronic health records

ARTICLE OPEN

Scalable and accurate deep learning with electronic health records

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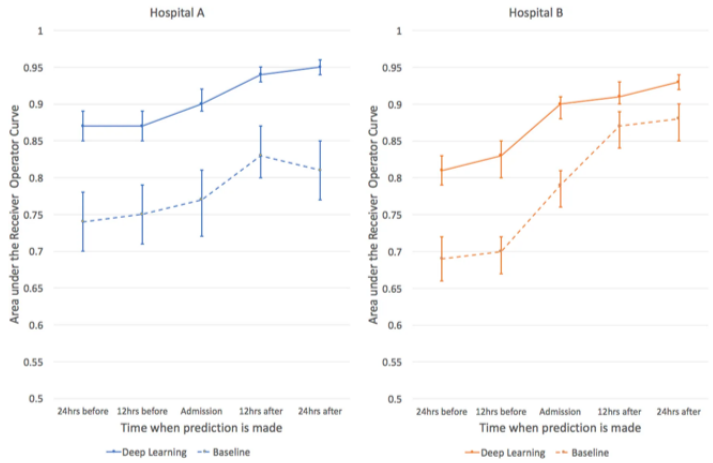

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	Hospital A	Hospital B
Inpatient Mortality, AUROC[1](95% CI)		
Deep learning 24 hours after admission	**0.95**(0.94-0.96)	**0.93**(0.92-0.94)
Full feature enhanced baseline at 24 hours after admission	0.93 (0.92-0.95)	0.91 (0.89-0.92)
Full feature simple baseline at 24 hours after admission	0.93 (0.91-0.94)	0.90 (0.88-0.92)
Baseline (aEWS[2]) at 24 hours after admission	0.85 (0.81-0.89)	0.86 (0.83-0.88)
30-day Readmission, AUROC (95% CI)		
Deep learning at discharge	**0.77**(0.75-0.78)	**0.76**(0.75-0.77)
Full feature enhanced baseline at discharge	0.75 (0.73-0.76)	0.75 (0.74-0.76)
Full feature simple baseline at discharge	0.74 (0.73-0.76)	0.73 (0.72-0.74)
Baseline (mHOSPITAL[3]) at discharge	0.70 (0.68-0.72)	0.68 (0.67-0.69)
Length of Stay at least 7 days AUROC (95% CI)		
Deep learning 24 hours after admission	**0.86**(0.86-0.87)	**0.85**(0.85-0.86)
Full feature enhanced baseline at 24 hours after admission	0.85 (0.84-0.85)	0.83 (0.83-0.84)
Full feature simple baseline at 24 hours after admission	0.83 (0.82-0.84)	0.81 (0.80-0.82)
Baseline (mLiu[4]) at 24 hours after admission	0.76 (0.75-0.77)	0.74 (0.73-0.75)

Deep Learning in Medicine?

- Predict mortality from electronic health records

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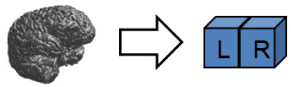
Outline

Mapping the discriminative pattern

For clinical applications it is crucial to infer which variables drive the predictions. There are multiple options:

- Regional classification accuracy as a proxy (searchlight)
- For linear models, the weights can be directly visualised ("discriminative mapping")



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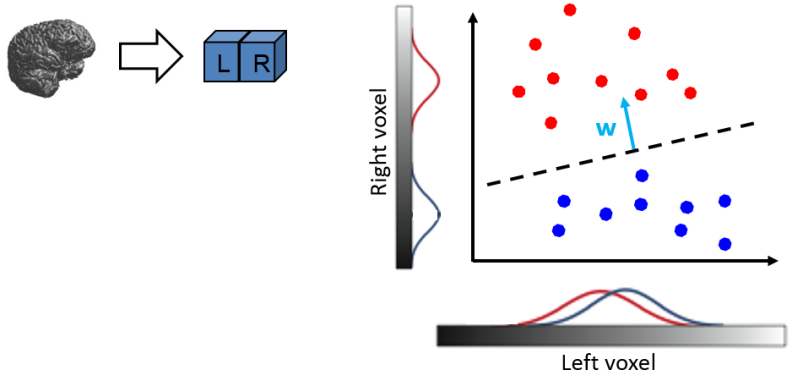

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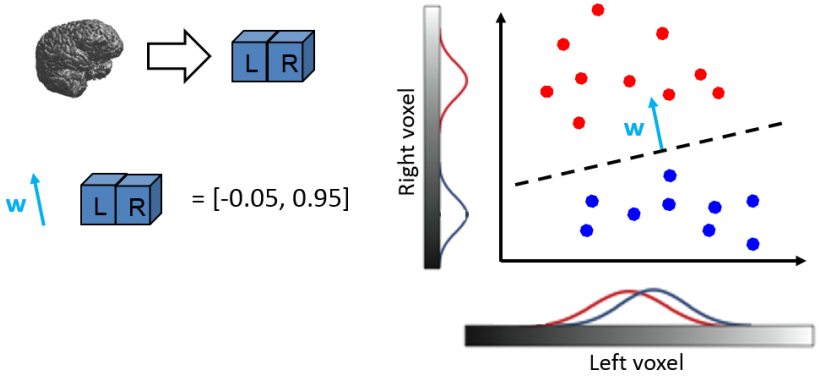

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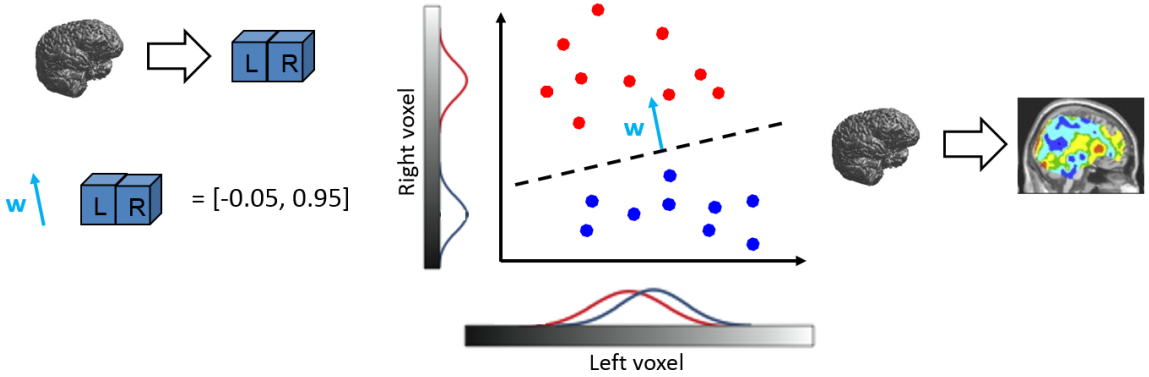

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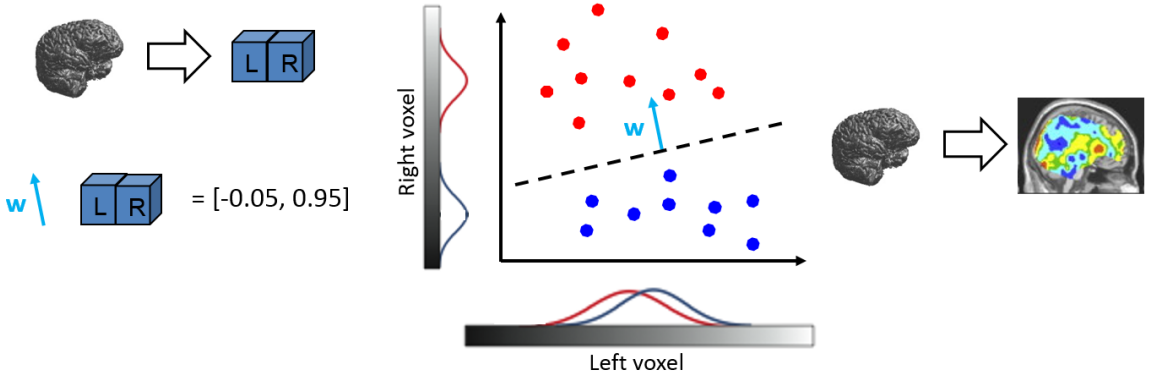
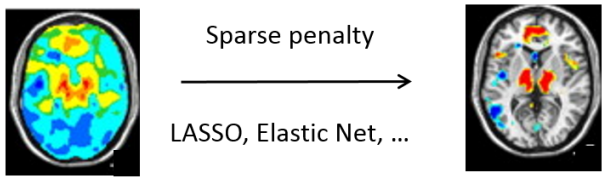


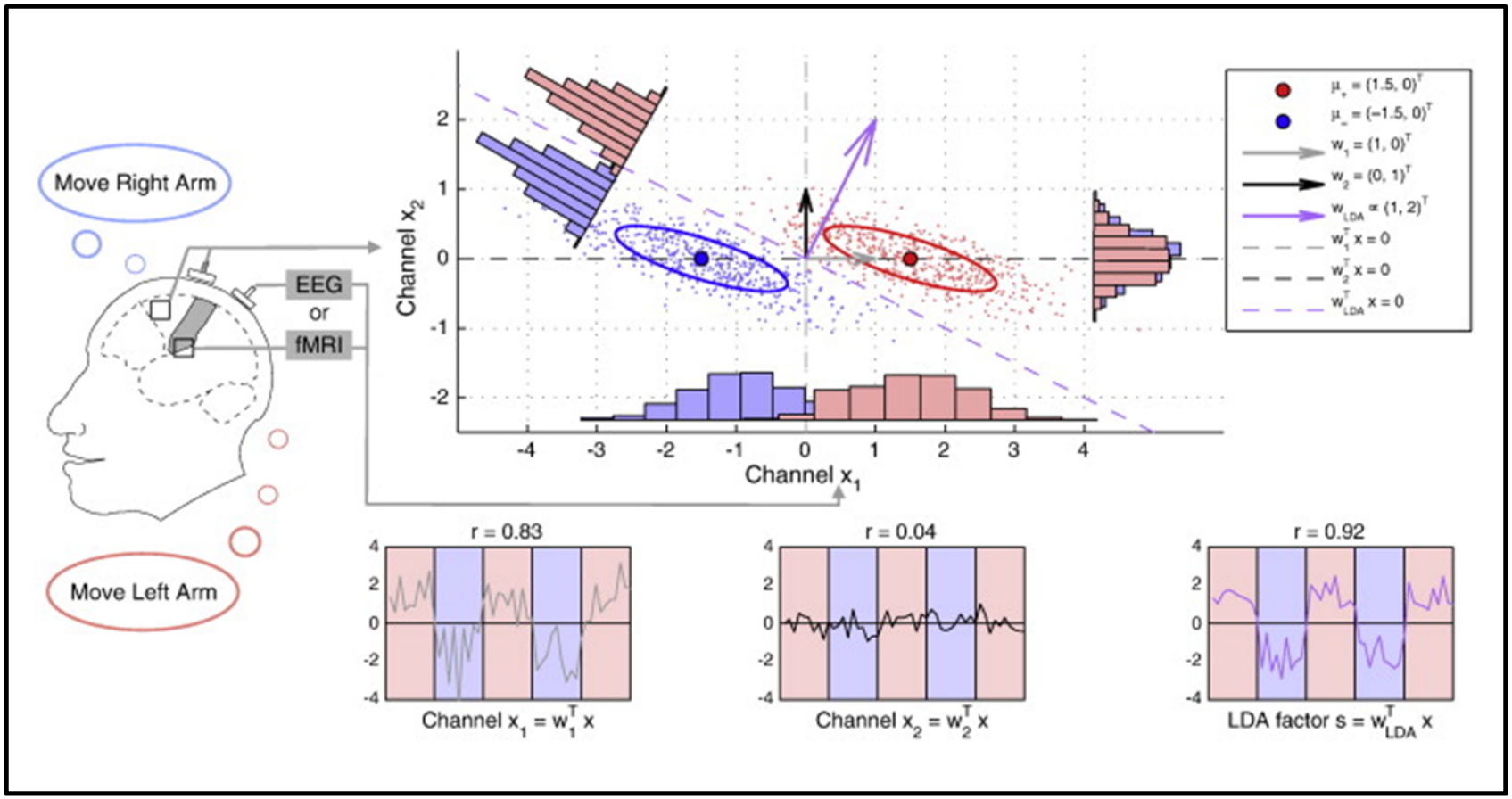
- Can also use regularization to enforce sparse weights



- Weights are often regarded as being difficult to interpret, but this is not always true

Weights do not reflect univariate differences

One proposal is to consider the the weights from a forward model



Construct 'forward maps' by premultiplying by the data covariance

$$\mathbf{a} = \frac{1}{\sigma_y^2}\mathbf{\Sigma}_x\mathbf{w}$$

Haufe et al. (2014)

Understanding weights of discriminative models

- The correct interpretation of the weights is the contribution of each feature to the predictions. This is the same as in a GLM
- Difficulty arises only due to multicollinearity between predictor variables which inflates the variance of the weights
- A variable can have a high weight because:
  1. It is associated with the response variable
  2. It acts as a 'supressor' variable that helps to cancel out noise or mismatch in other covariates

Kraha et al. (2012)

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- To distinguish between these possibilities, we can do the following (assumes standardized data)

$$\mathbf{a} \propto \mathbf{\Sigma}_x \mathbf{w} = \text{cov}\left[\mathbf{X}, \hat{\mathbf{y}}\right] = \text{corr}\left[\mathbf{X}, \hat{\mathbf{y}}\right]$$

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- These are **structure coefficients** from multivariate statistics
- The univariate association between covariate p and the predictions is given simply by:

Kraha et al. (2012)

$$\rho(\mathbf{x}_p, \hat{\mathbf{y}})$$

But what about the penalty?

- Collinearity is well-known in classical GLM settings, where advice is often given to avoid collinearity
- It is true that collinearity impacts on efficiency, but models with collinear predictors are still interpretable
- Collinearity also impacts penalised regression. Recall that:

$$f(\mathbf{x}_i, \mathbf{w}) = \mathbf{x}_i^T \mathbf{w} \quad \Rightarrow \hat{\mathbf{w}} = \min_{\mathbf{w}} \sum_{i=1}^{n} \ell(y_i, f_i) + \lambda J(\mathbf{w})$$

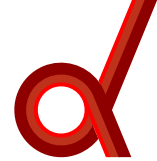
- Considering ridge regression, where the objective function is:

$$\hat{\mathbf{w}} = \min_{\mathbf{w}} \sum_{i=1}^{n} \mathcal{N}(\mathbf{w}^T \mathbf{x}_i, \sigma^2) + \frac{\lambda}{2} ||\mathbf{w}||_2^2$$

- This is eqivalent to maximising the following

$$\min_{\mathbf{w}} -\frac{1}{2\sigma^2} \left(\sum_{i=1}^{n} (y_i - \mathbf{x}_i^T \mathbf{w})^2 + \lambda \mathbf{w}^T \mathbf{w} \right)$$

But what about the penalty?



- This is exactly equivalent to finding the MAP estimate of a posterior distribution over $\mathbf{w}$, with prior:

$$\mathcal{N}(\mathbf{0}, \sigma^2/\lambda\mathbf{I})$$

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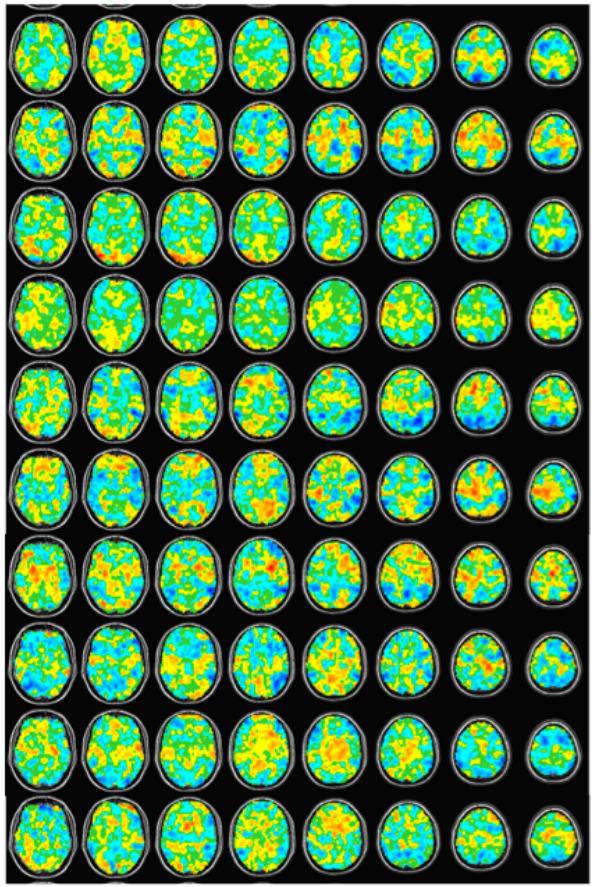
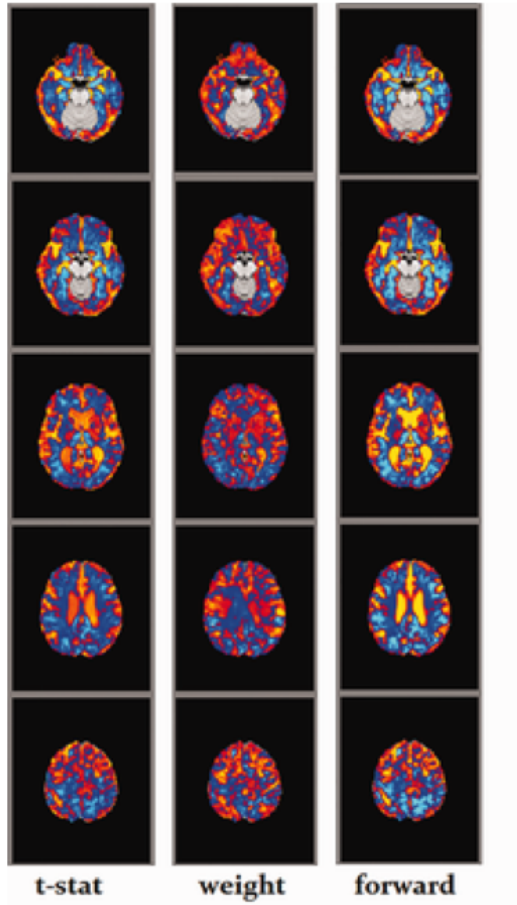
So what does this mean?

- The magnitude and sign of weights are influenced by collinearity
- Including and excluding variables variables can change the magnitude and sign of variables in the model
- It is obvious that when $p > n$, the problem is ill-posed in that there are many ways the same prediction can be achieved.
- Regularisation helps to stabilise coefficients, but this does not eliminate the problem

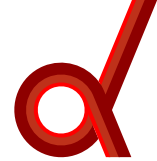
Examples of weights





Aksman et al. (2016)

Stability selection



- It is important to recognise that coefficient stability is largely independent from accuracy

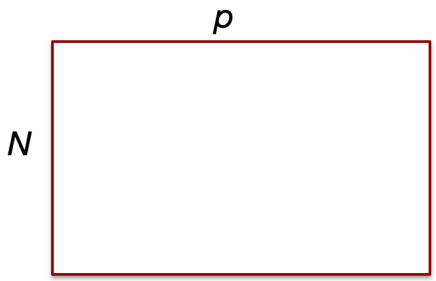
Meinshausen and Buehlmann (2010)

Stability selection

- It is important to recognise that coefficient stability is largely independent from accuracy
- **stability selection** is a method that aims to identify truly important variables by examining stability under perturbation to the data

Lasso

$$\hat{\beta} = \arg\min\left(\|Y - X\beta\|_2^2 + \lambda \sum_{k=1}^{p} |\beta_k| \right)$$



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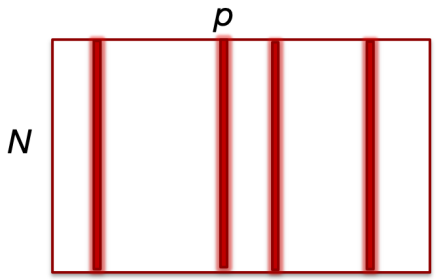

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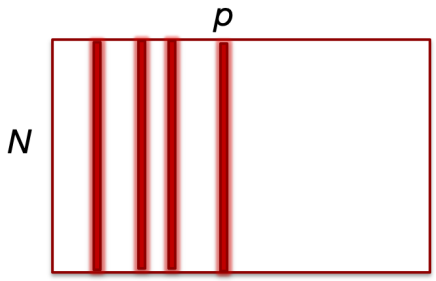

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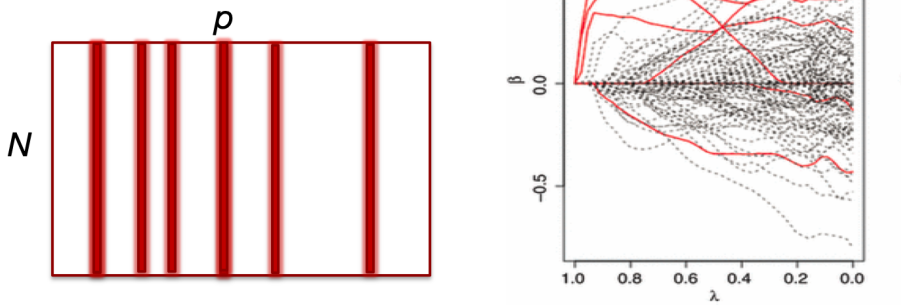

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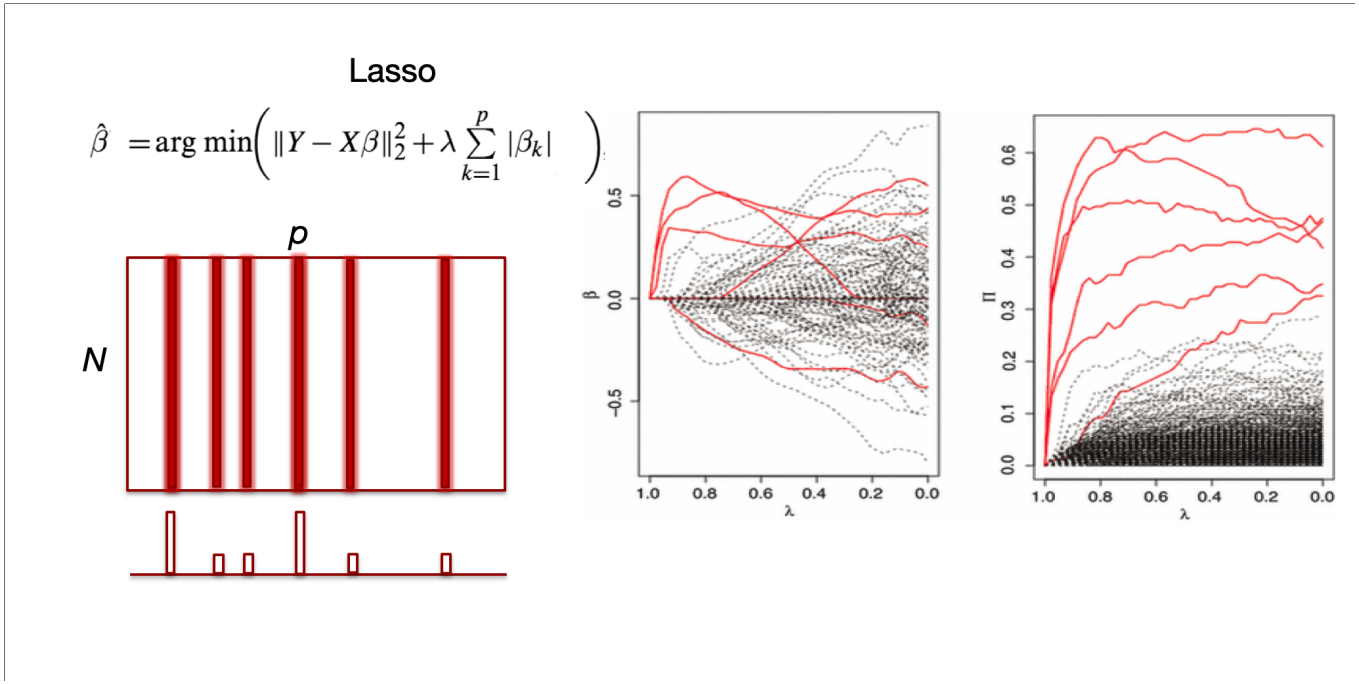

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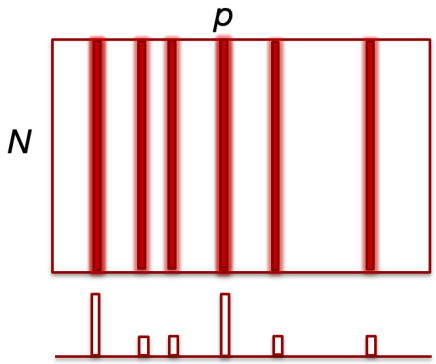
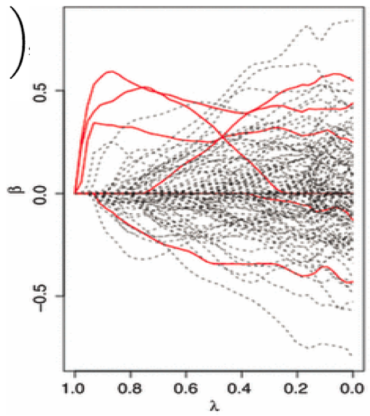
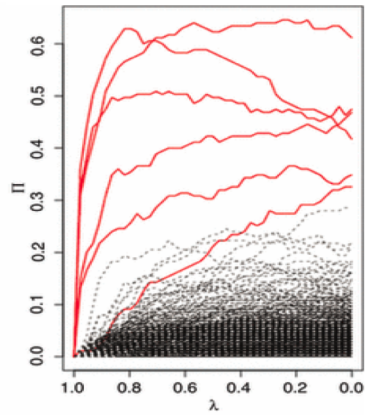




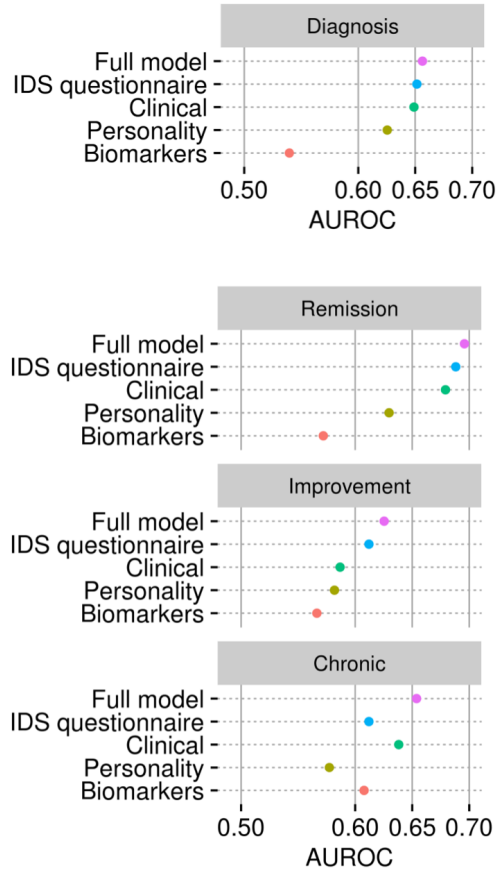


Statistical guarantees against false positives
(controls family-wise error)

Meinshausen and Buehlmann (2010)

Stability selection in major depression

Aim: to identify prognostic markers for depression from an extensive panel (cognition, symptoms, biomarkers...)



Dinga et al. (2018)

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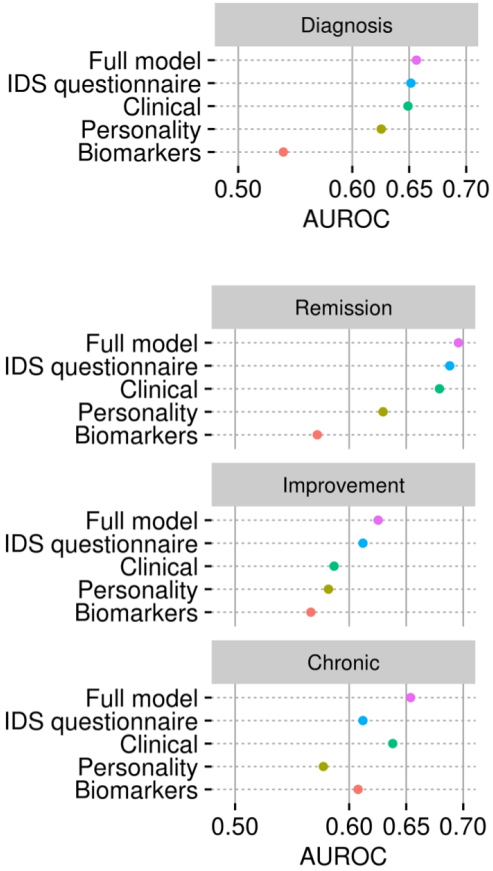
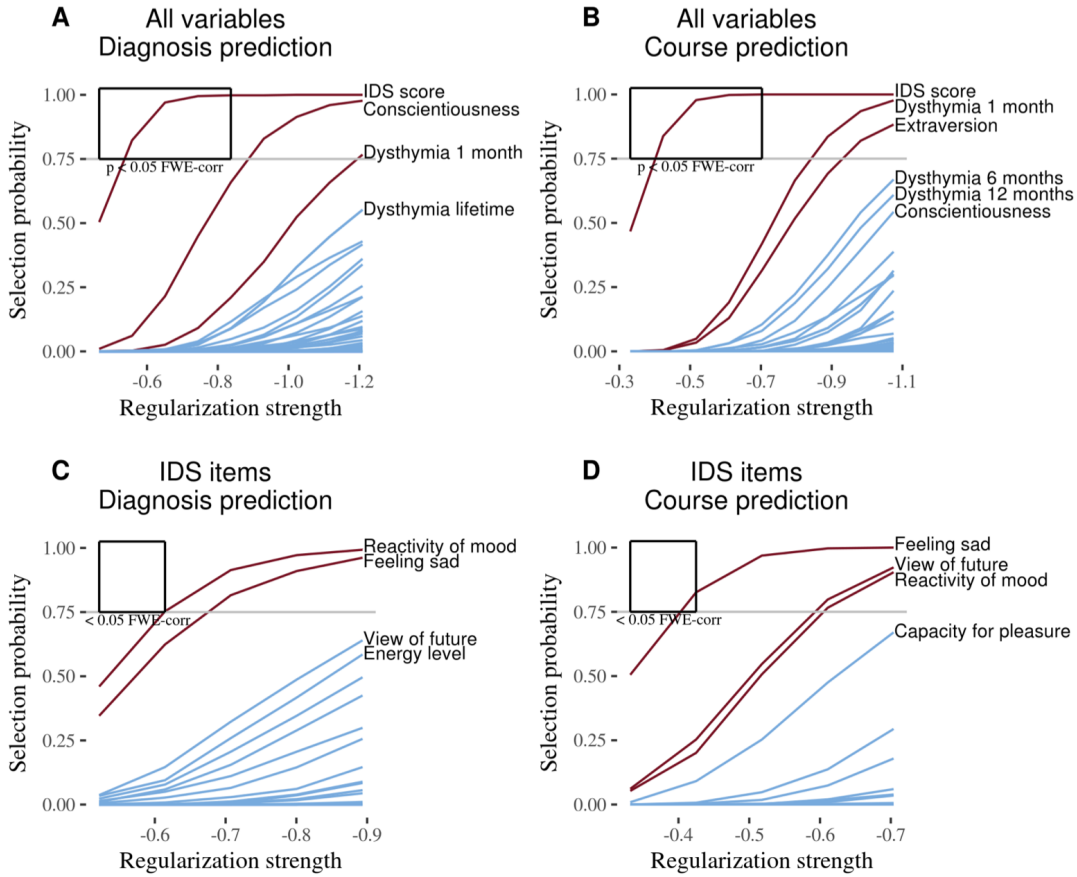
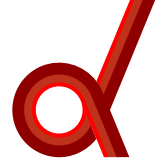


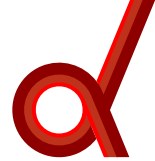


Dinga et al. (2018)

Outline



Take home messages



- Machine learning provides powerful tools for single subject inference and detect spatially distributed effects
- Many different approaches beyond simple notions such as ‘classification’ or ‘clustering’

Take home messages

- Machine learning provides powerful tools for single subject inference and detect spatially distributed effects
- Many different approaches beyond simple notions such as 'classification' or 'clustering'

Recommendations

- Linear models are often sufficient: they are fast, interpretable and often perform as well as non-linear methods
- Careful validation is extremely important for all methods to guard agains overfitting
- Machine learning can be easily integrated with neurocognitive models (e.g. to assess candidate models)

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