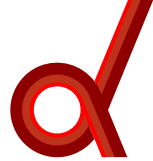
DONDERS INSTITUTE

Machine Learning 2: advanced

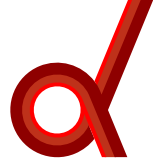
Andre F. Marquand
a.marquand@donders.ru.nl

Radboud University Radboudumc

Outline

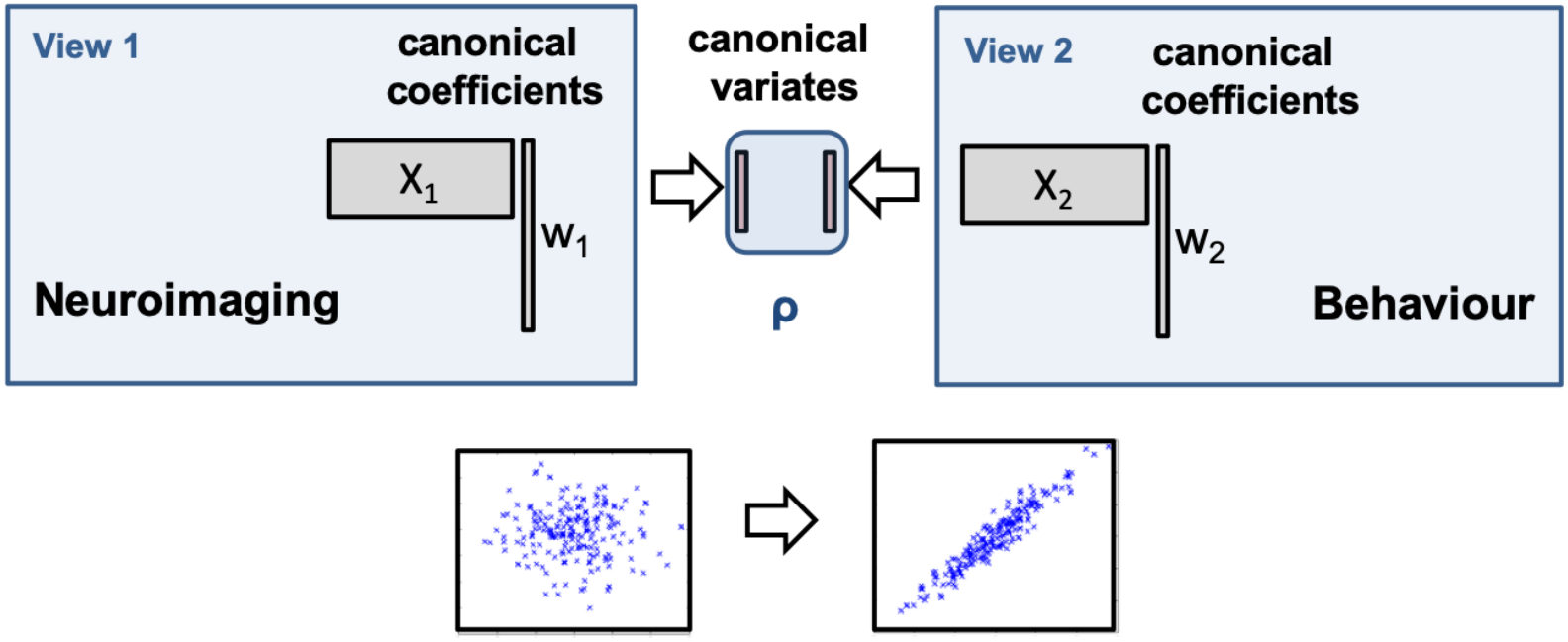


Outline



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



Canonical Correlation Analysis

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

$$\max_{w_1,w_2} corr(X_1 w_1, X_2 w_2)$$

$$\text{subject to } ||w_1^T X_1^T X_1 w_1|| \leq 1 \text{ and } ||w_2^T X_2^T X_2 w_2|| \leq 1$$

where the constraint is sometimes amended to:

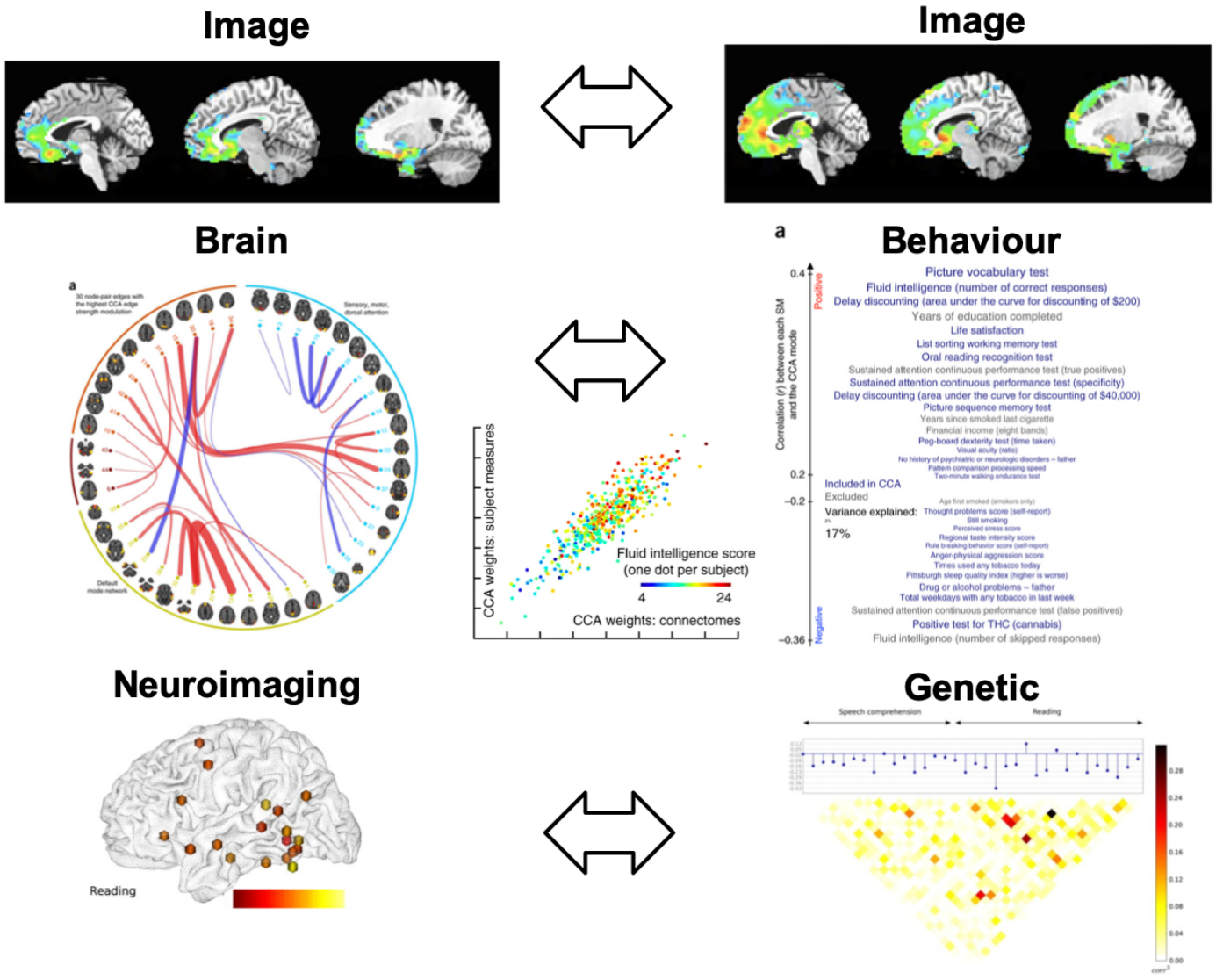
$$\text{subject to } ||w_1||^2 \leq 1 \text{ and } ||w_2||^2 \leq 1$$

...and other constraints can be added (e.g. to promote sparsity)

$$P(w_1) < c_1 \text{ and } P(w_2) < c_2$$

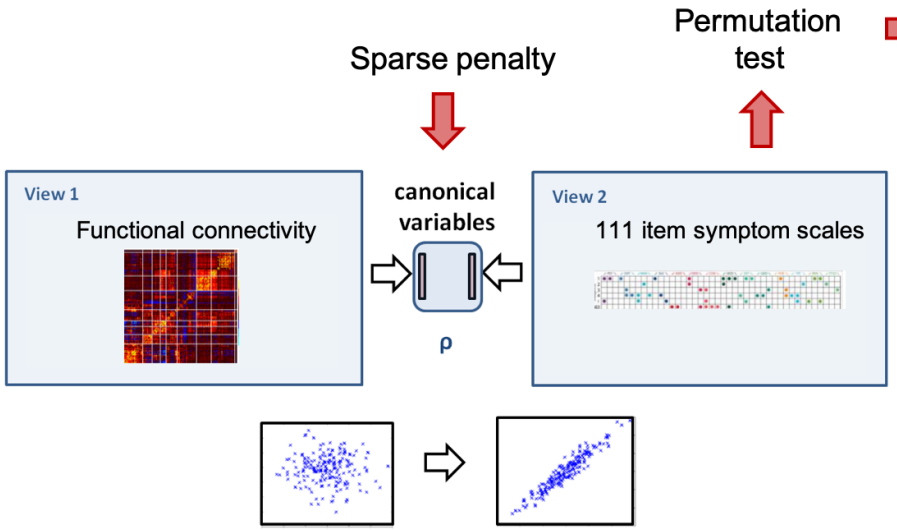
- if $n > p_1$ and p_2, an analytical solution is available
- There are many variants (kernel CCA, Bayesian CCA, deep CCA...)

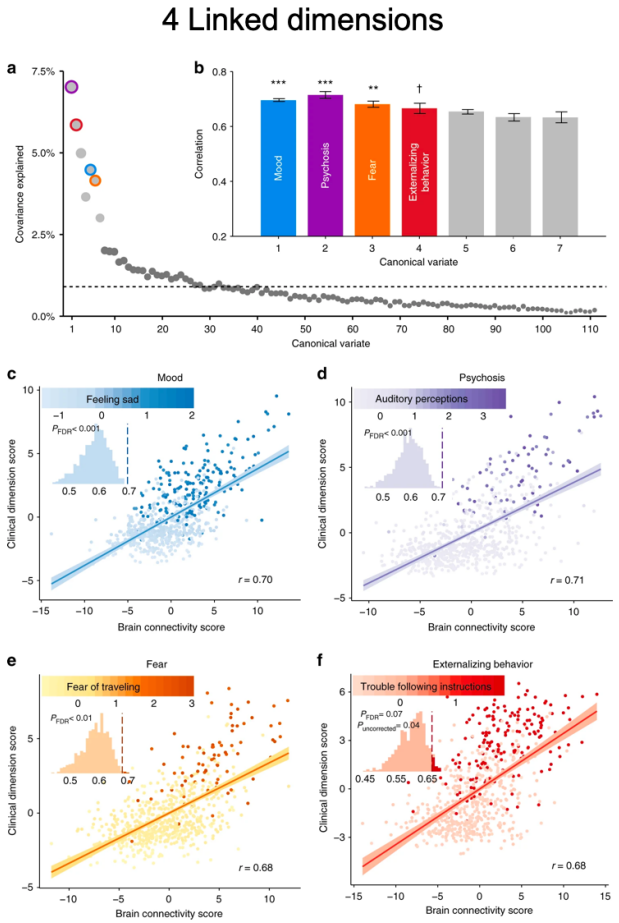
Applications of CCA



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

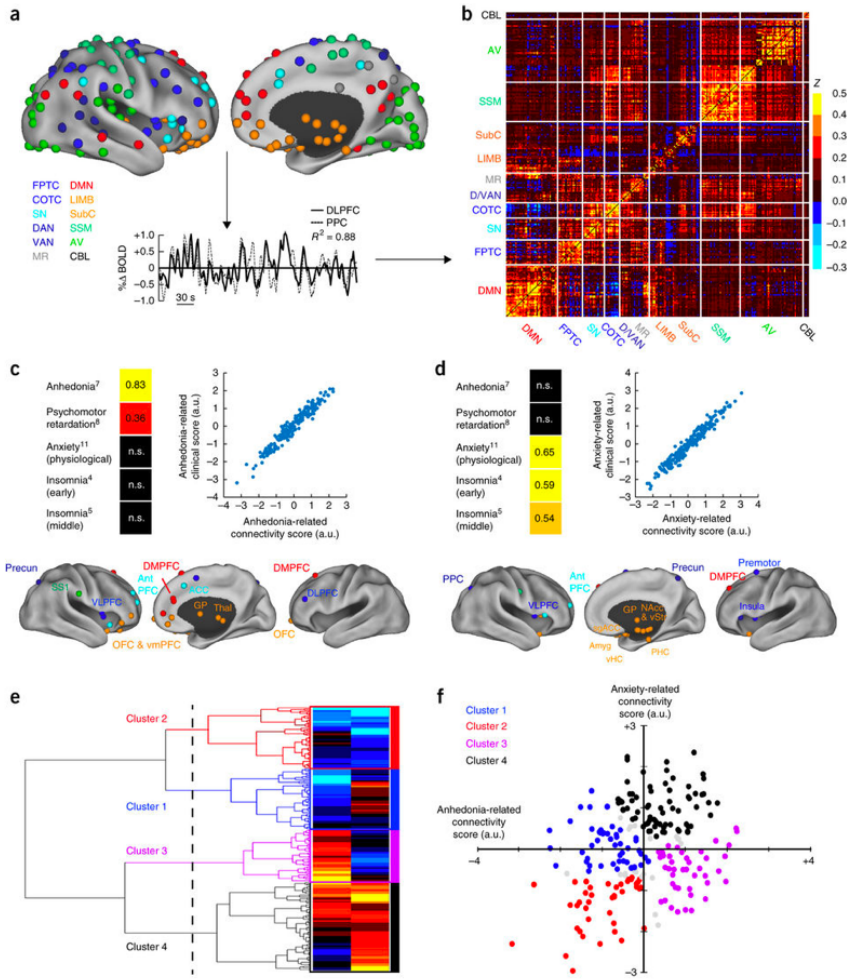
Applications of CCA



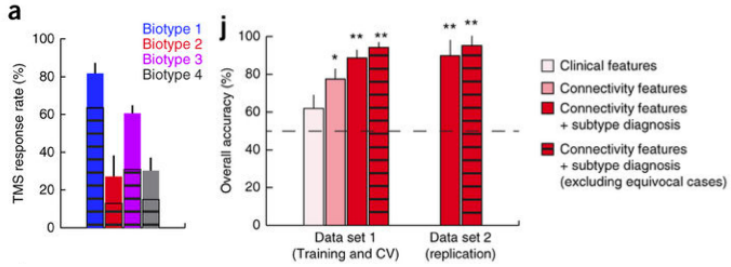


Xia et al. (2018)

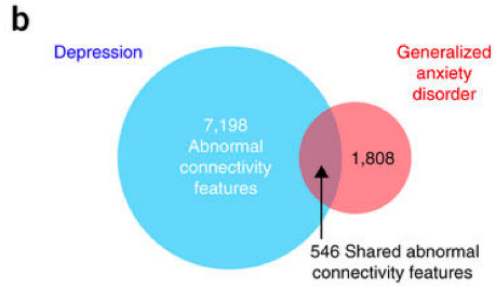
Stratification of major depression



- Extensive validation
- Predict treatment response (TMS)

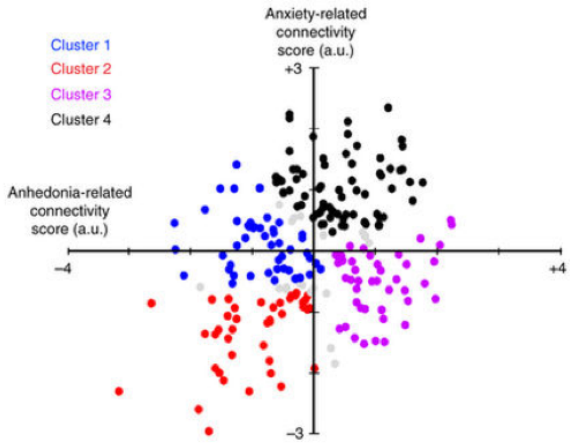


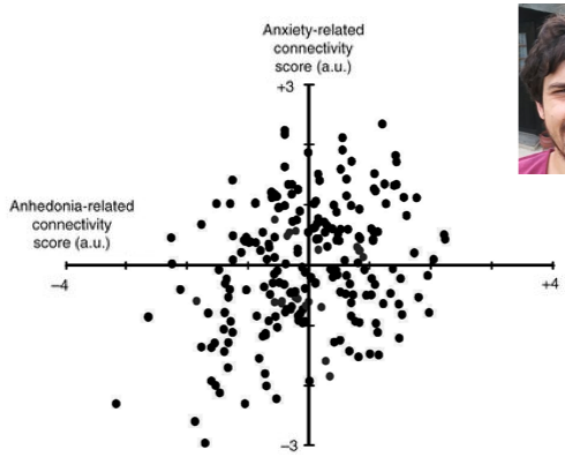
- Cut across diagnoses



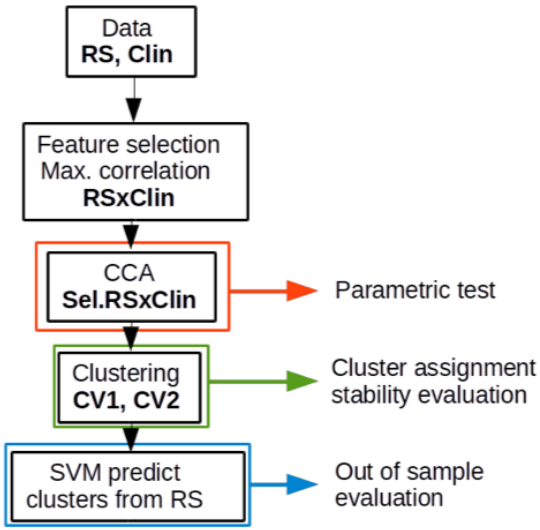
Drysdale et al. (2017)

Stratification of major depression

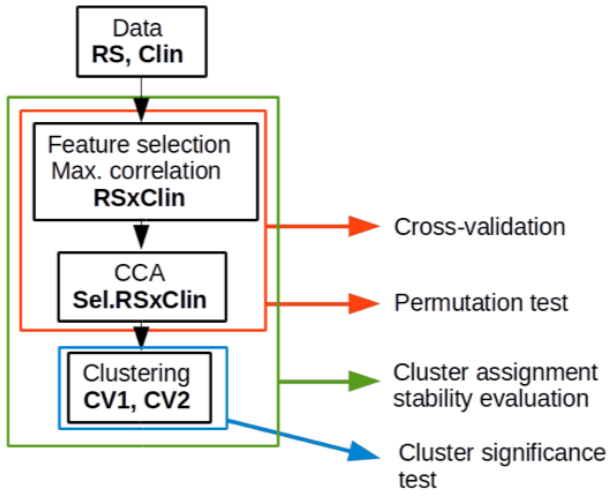




Drysdale et. al. Pipeline

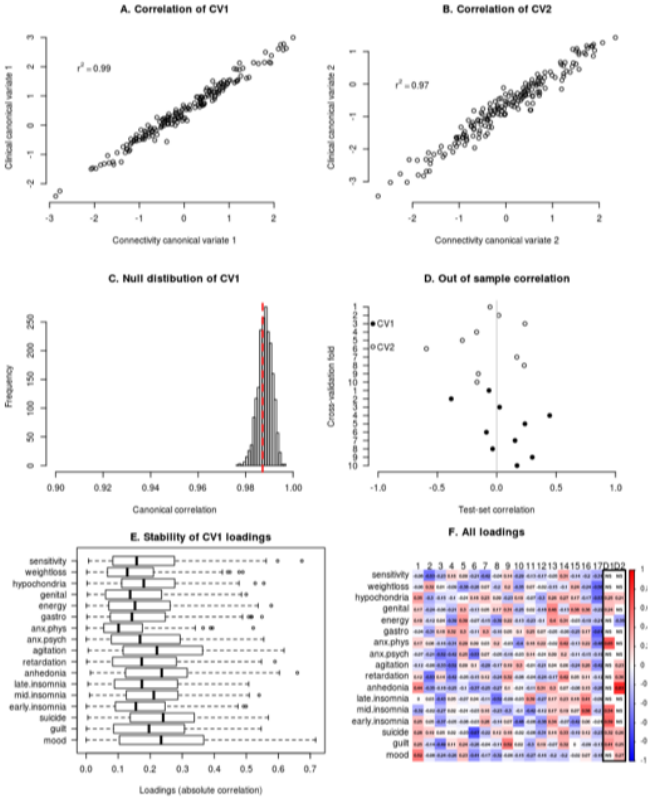


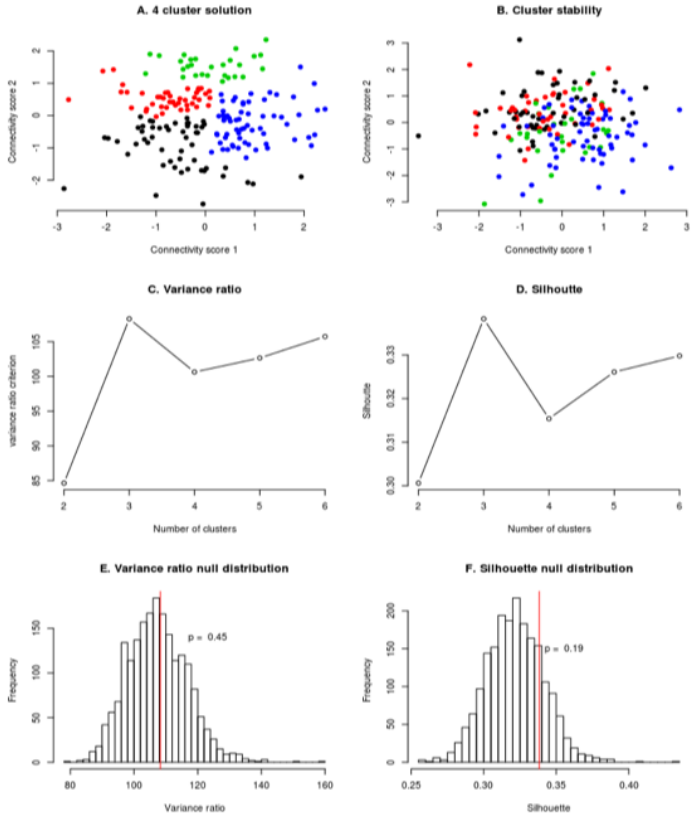
Replication Pipeline



Dinga et al. (2019)

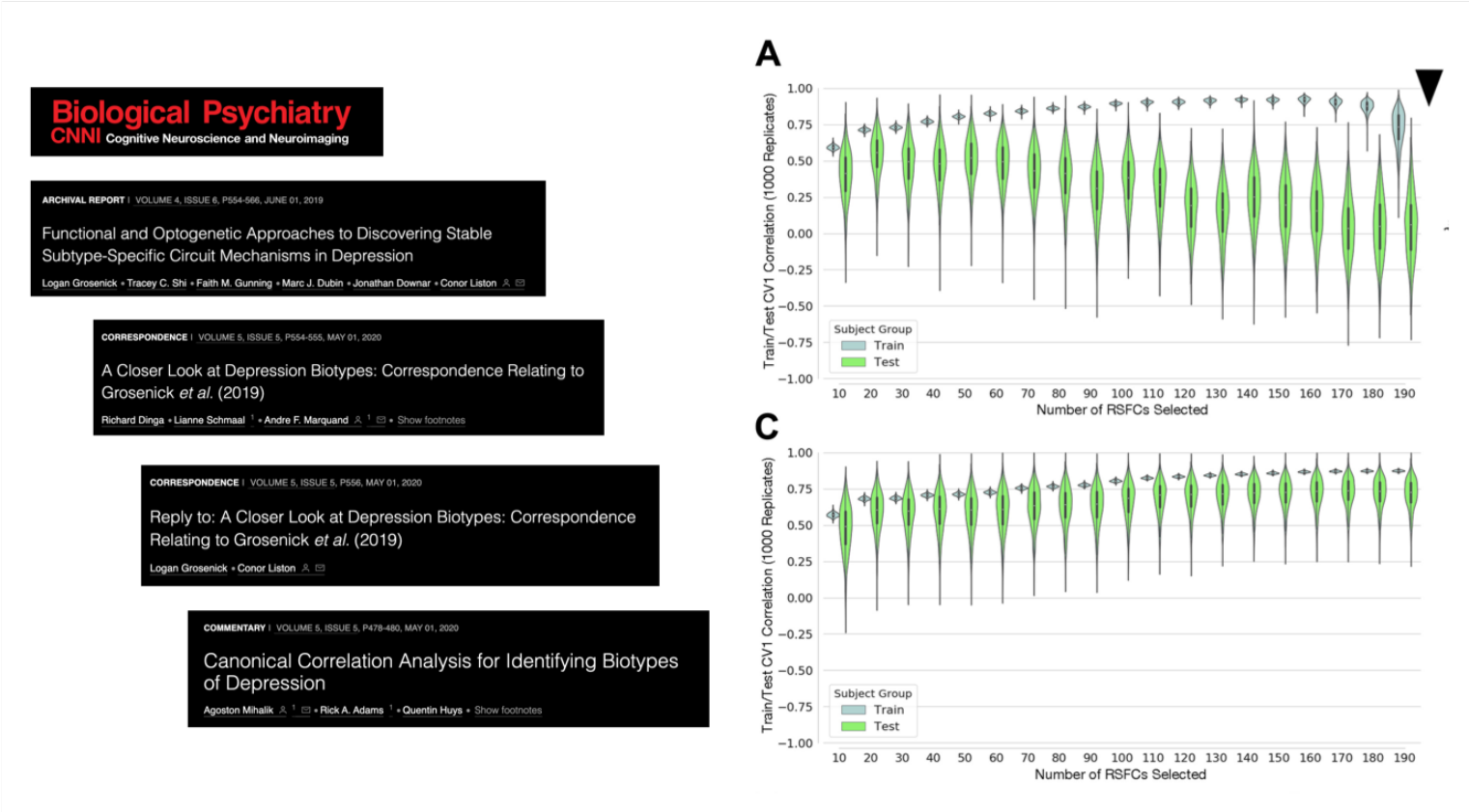
Stratification of major depression





Dinga et al. (2019)

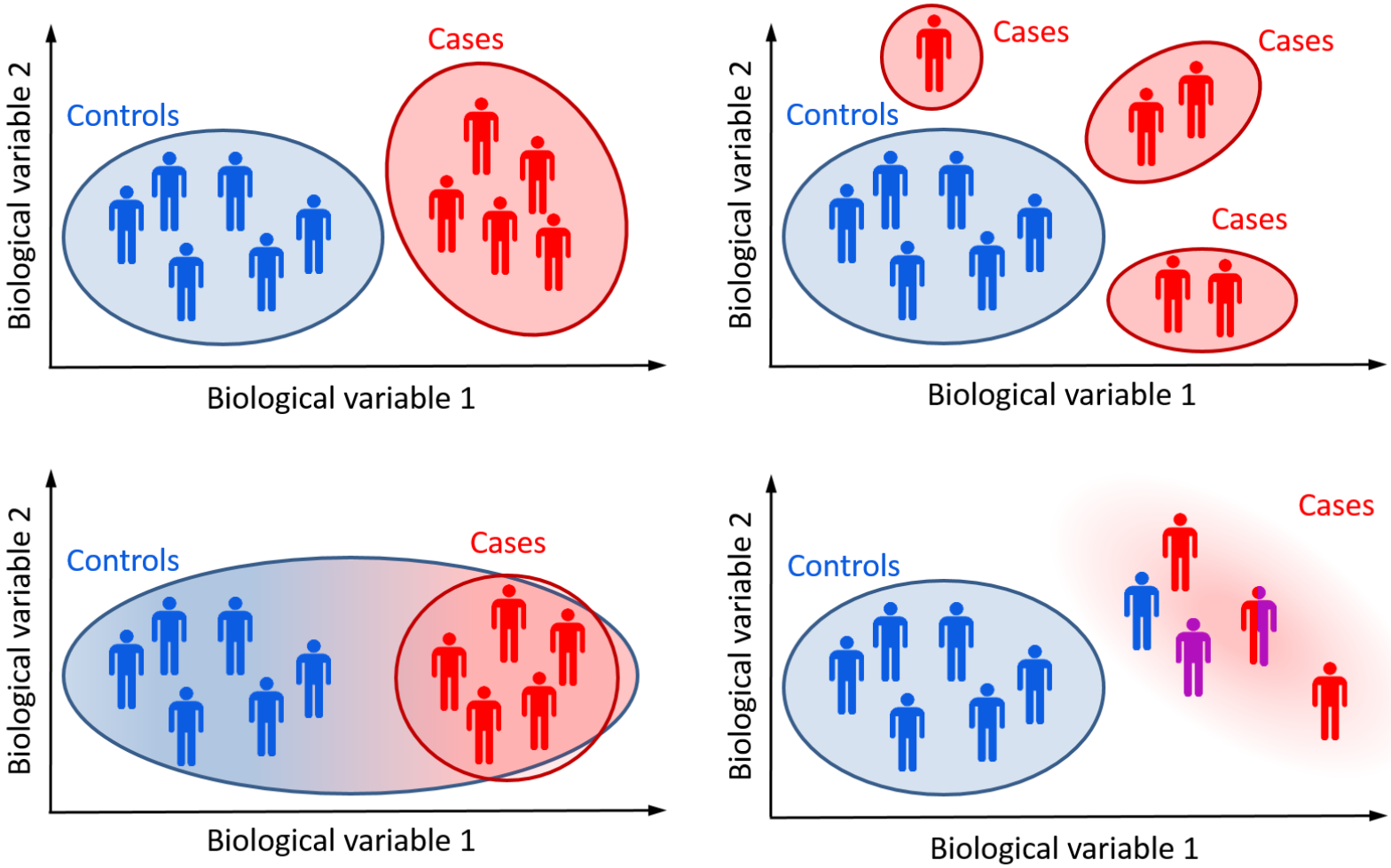
Applications of CCA



- CCA easily overfits, even when $N > p$
- Magnitude of in-sample canonical correlation is meaningless!
- Regularization and/or feature selection is very important
- Statistical evaluation should include the whole pipeline

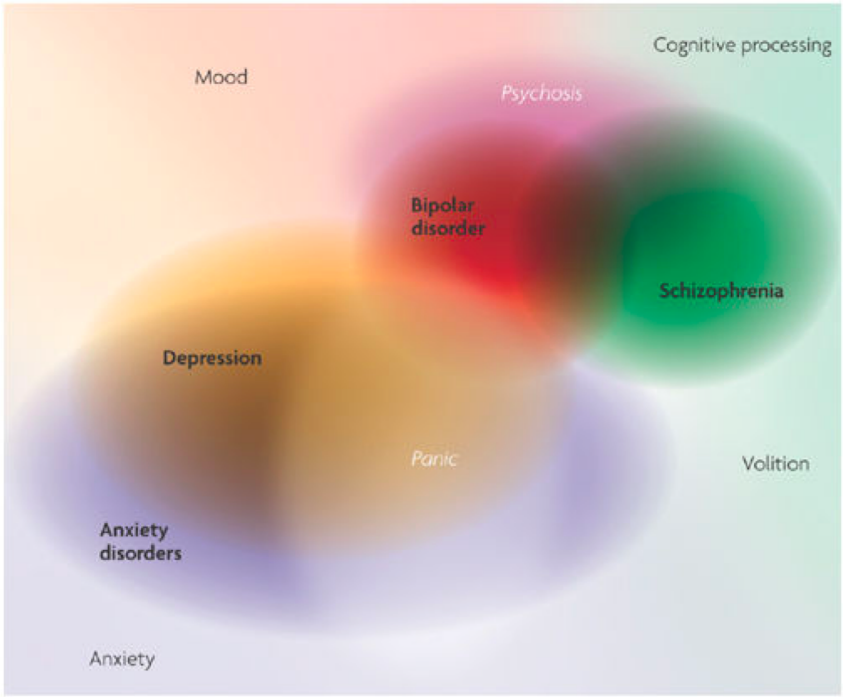
Dinga et al. (2020); Grosenick and Liston (2020); Mihalik et al. (2020)

Many types of heterogeneity



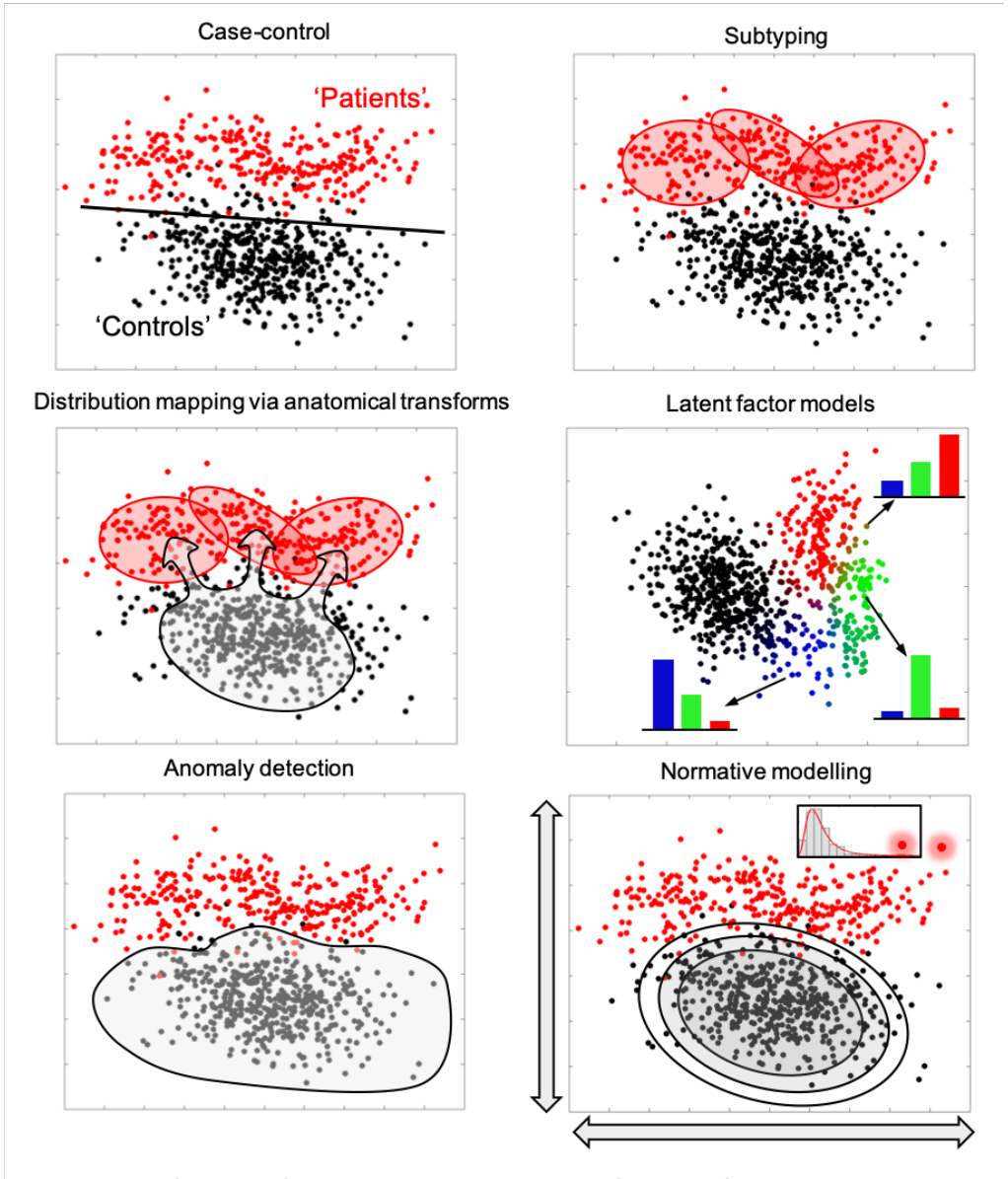
Marquand et al. (2016)

Many types of heterogeneity



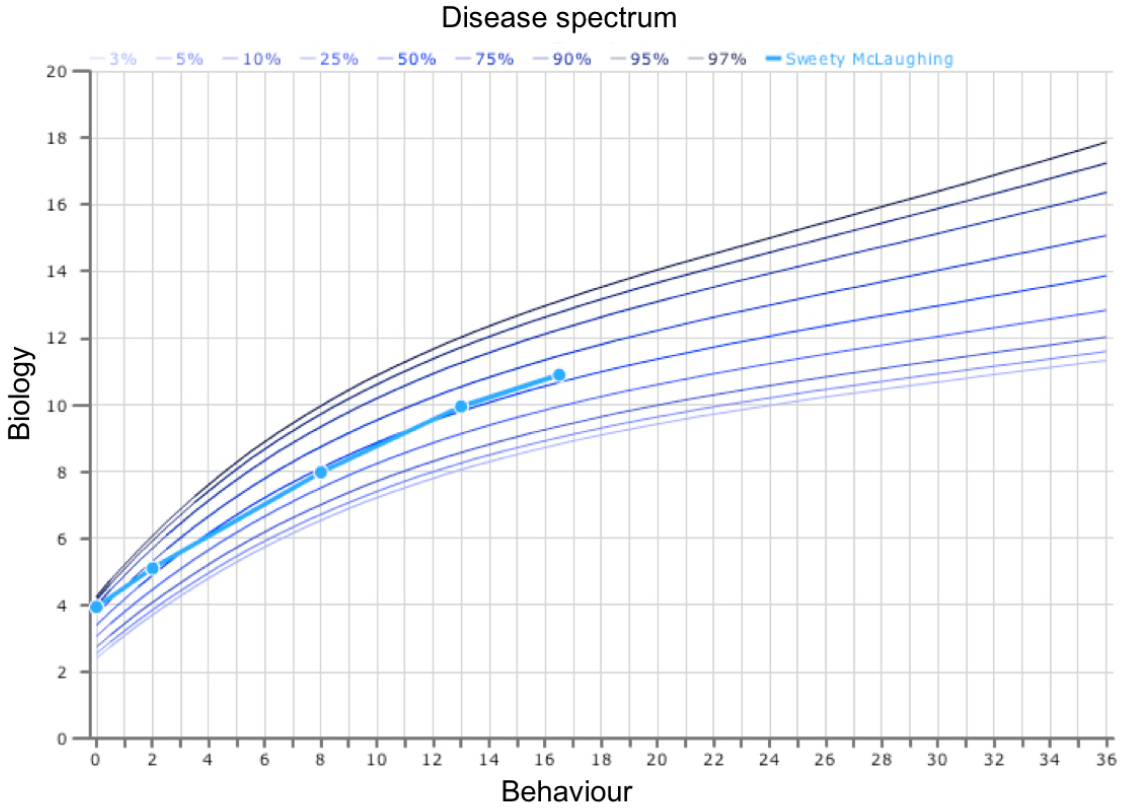
Burmeister et al. (2008)

Methods for addressing heterogeneity



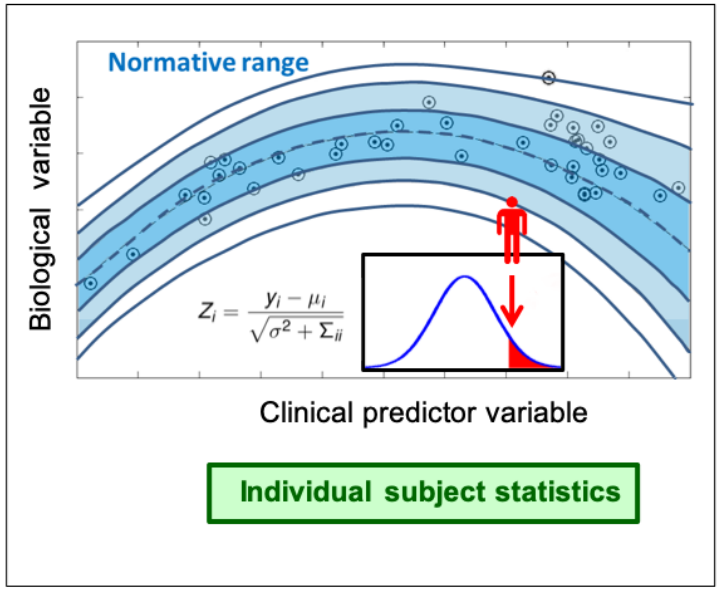
Dong et al. (2016); Zhang et al. (2016); Mourao-Miranda et al. (2011)

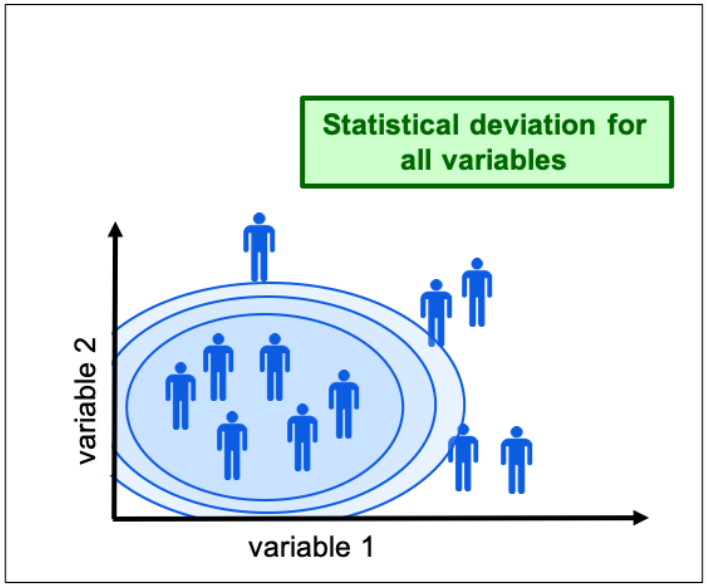
Normative modelling

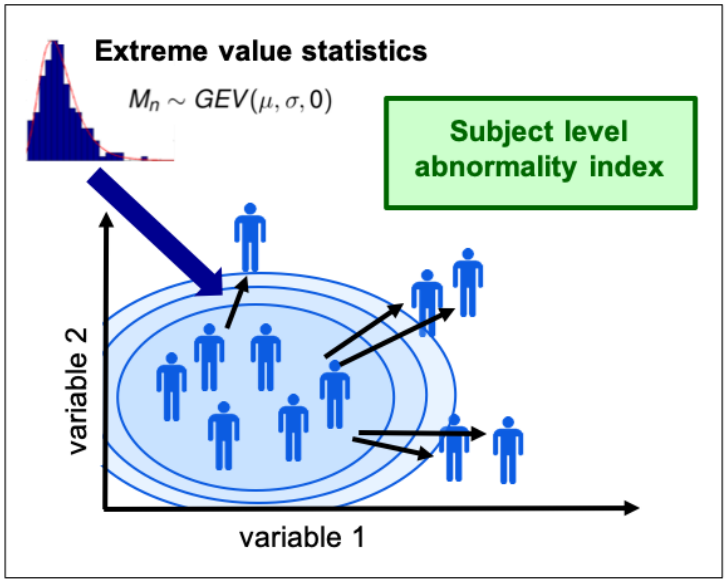


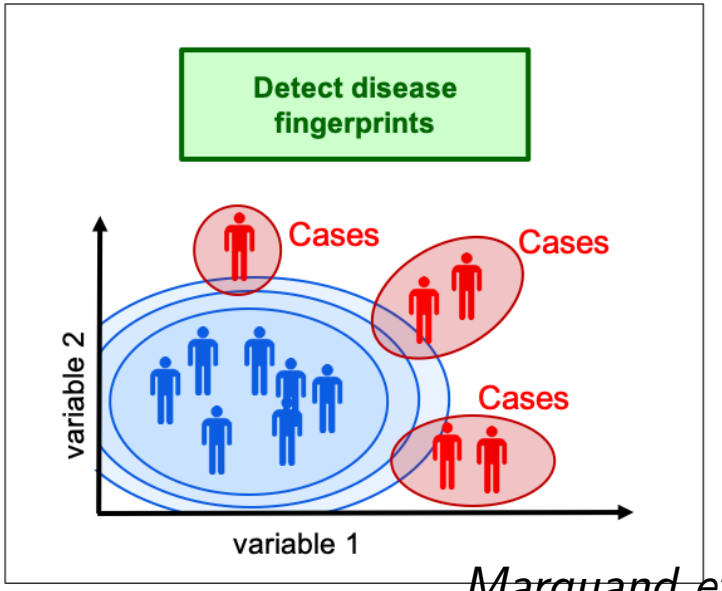
Marquand et al. (2016)

Normative modelling



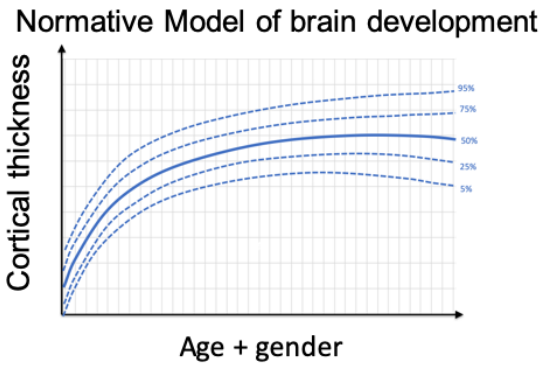


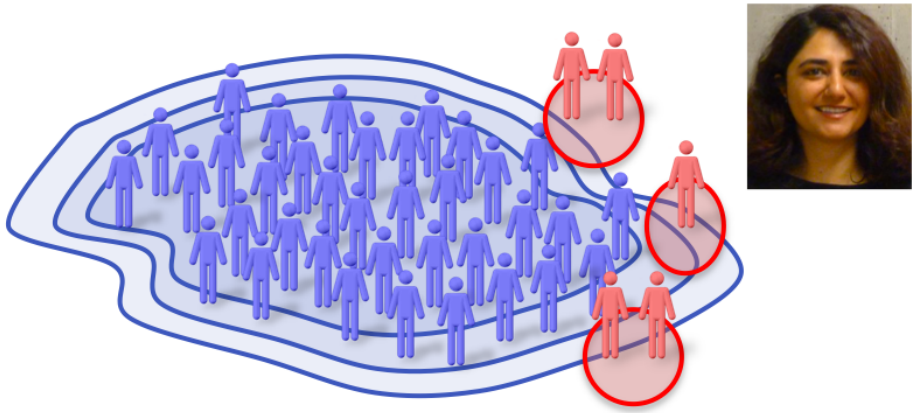


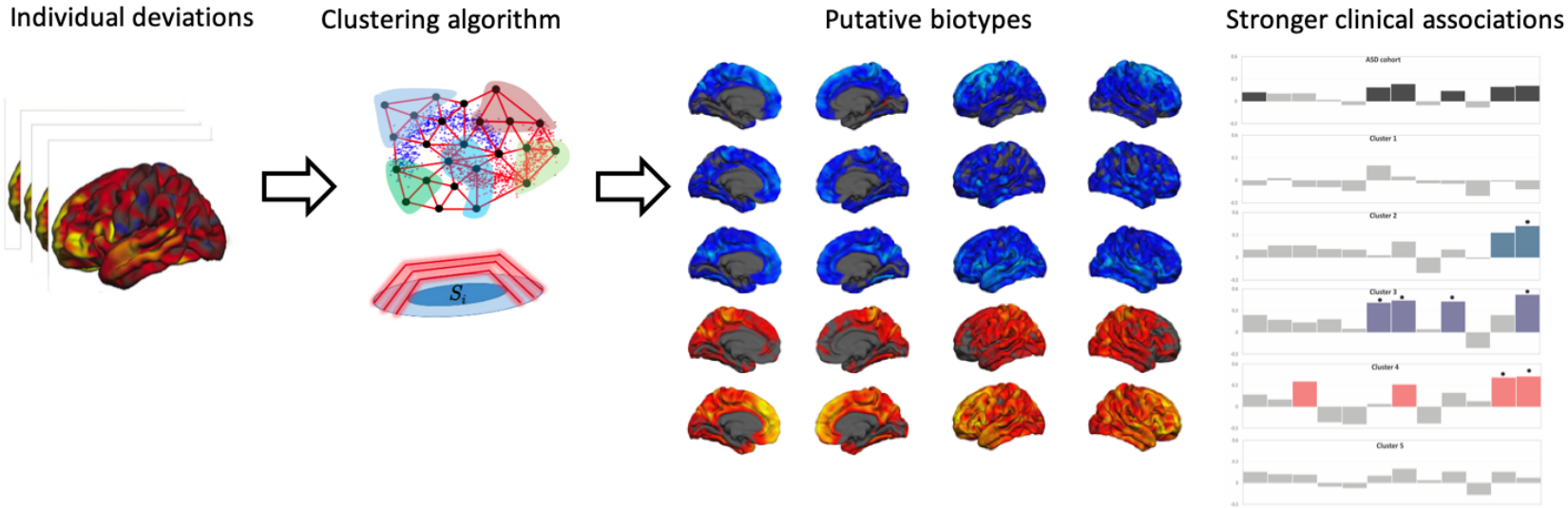


Marquand et al. (2016)

Normative modelling of autism



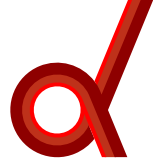




Tutorial: https://github.com/saigerutherford/CPC_2020

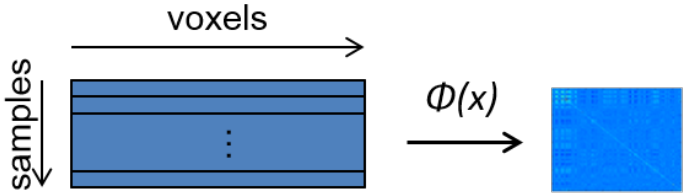
Zabihi et al. (2019)

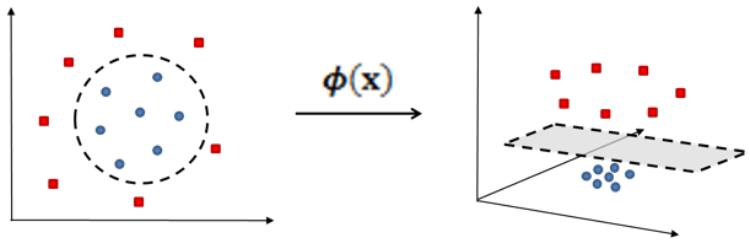
Outline



Kernels

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





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

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

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

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

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

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

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

- Optimisation problem is a convex combination of kernels

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

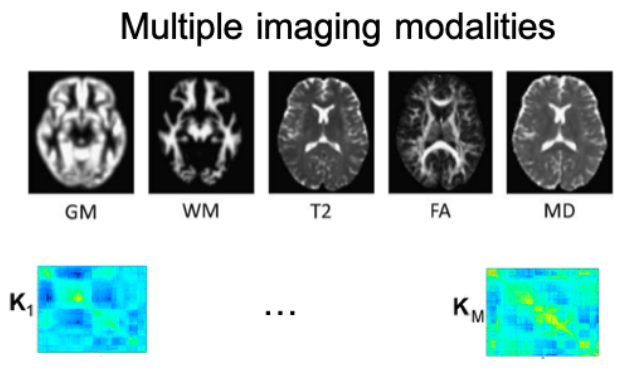
$$\text{subject to: } y_i(\sum_m (\mathrm{x}_i^T \mathrm{w}_m + b)) \geq 1 - \xi_i, \xi_i \geq 0 \; \forall i$$

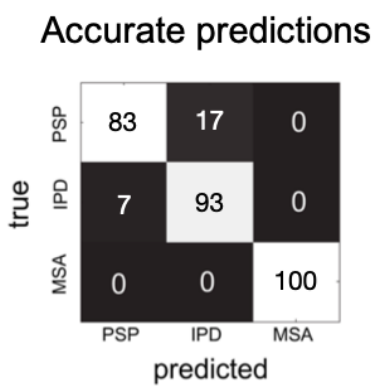
$$\sum_m d_m = 1 \text{ and } d_m \geq 0$$

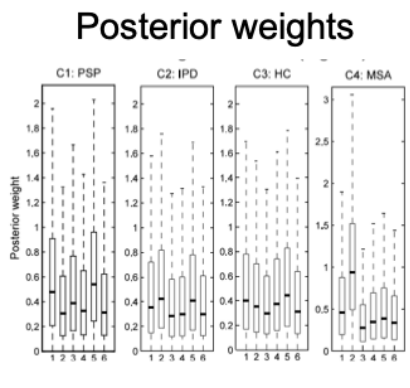
Applications of MKL in neuroscience

Multimodal data fusion for predicting brain disorders

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





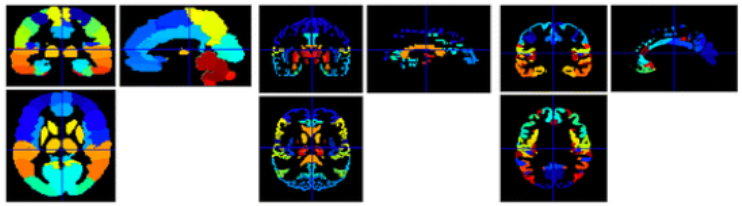


Filippone et al. (2012)

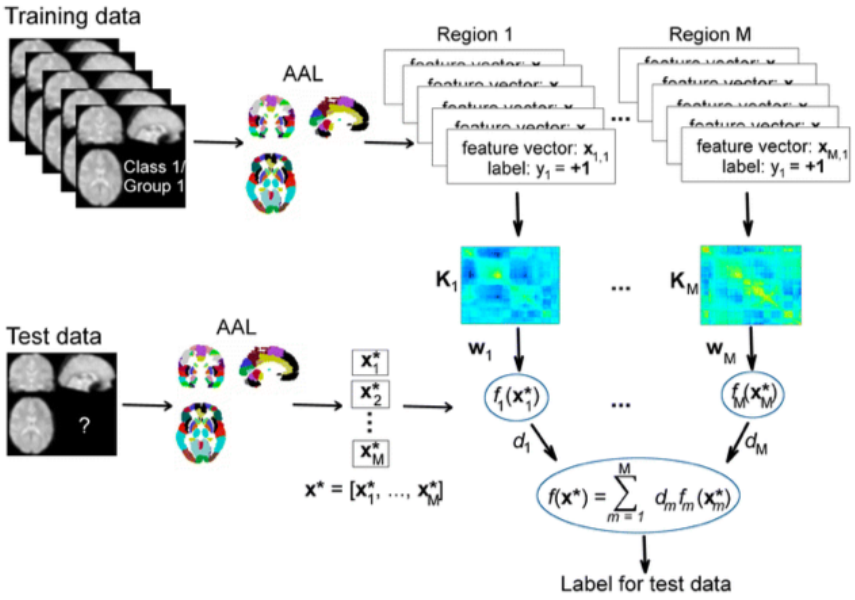
Applications of MKL in neuroscience

Better accommodating spatial variation

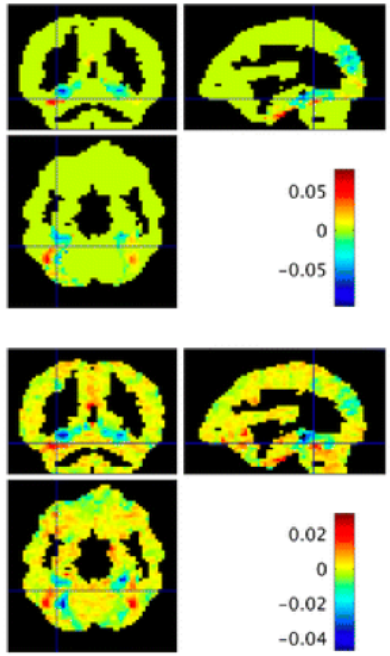
Atlas parcellation



Estimate one kernel per region



Improve SNR



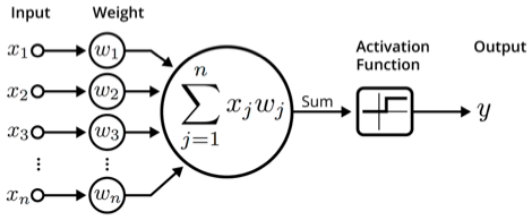
Schrouff et al. (2018)

Deep Learning

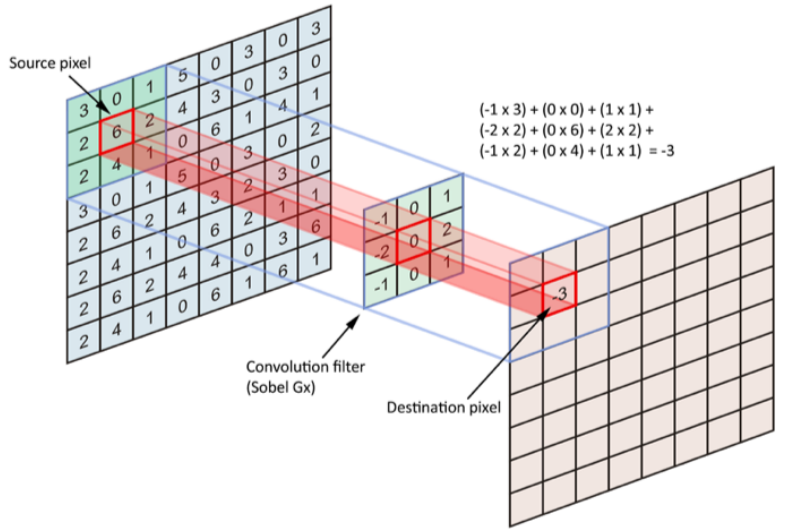
It is helpful to think of deep learning as combining matix products with point-wise linearity, e.g.:

$$f(x) = \sigma\left(xW_1 + b_1\right)W_2$$

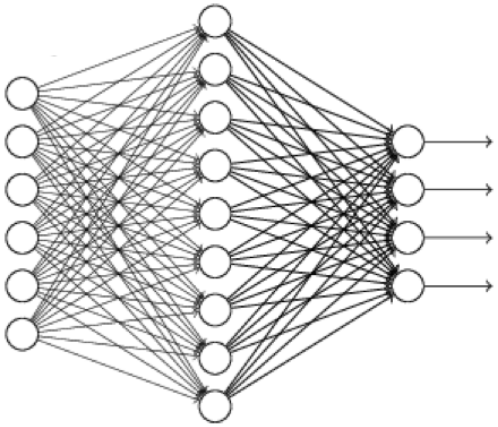
Artificial neuron
(pointwise non-linearity)



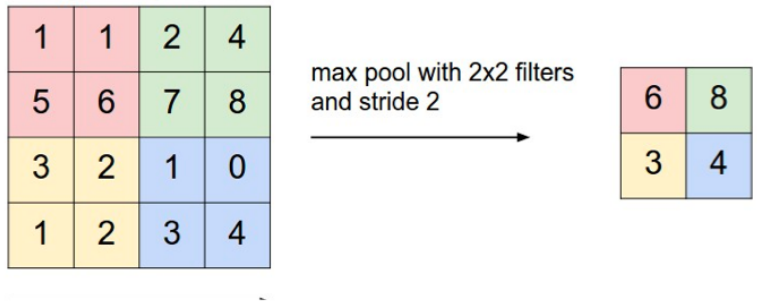
Convolution



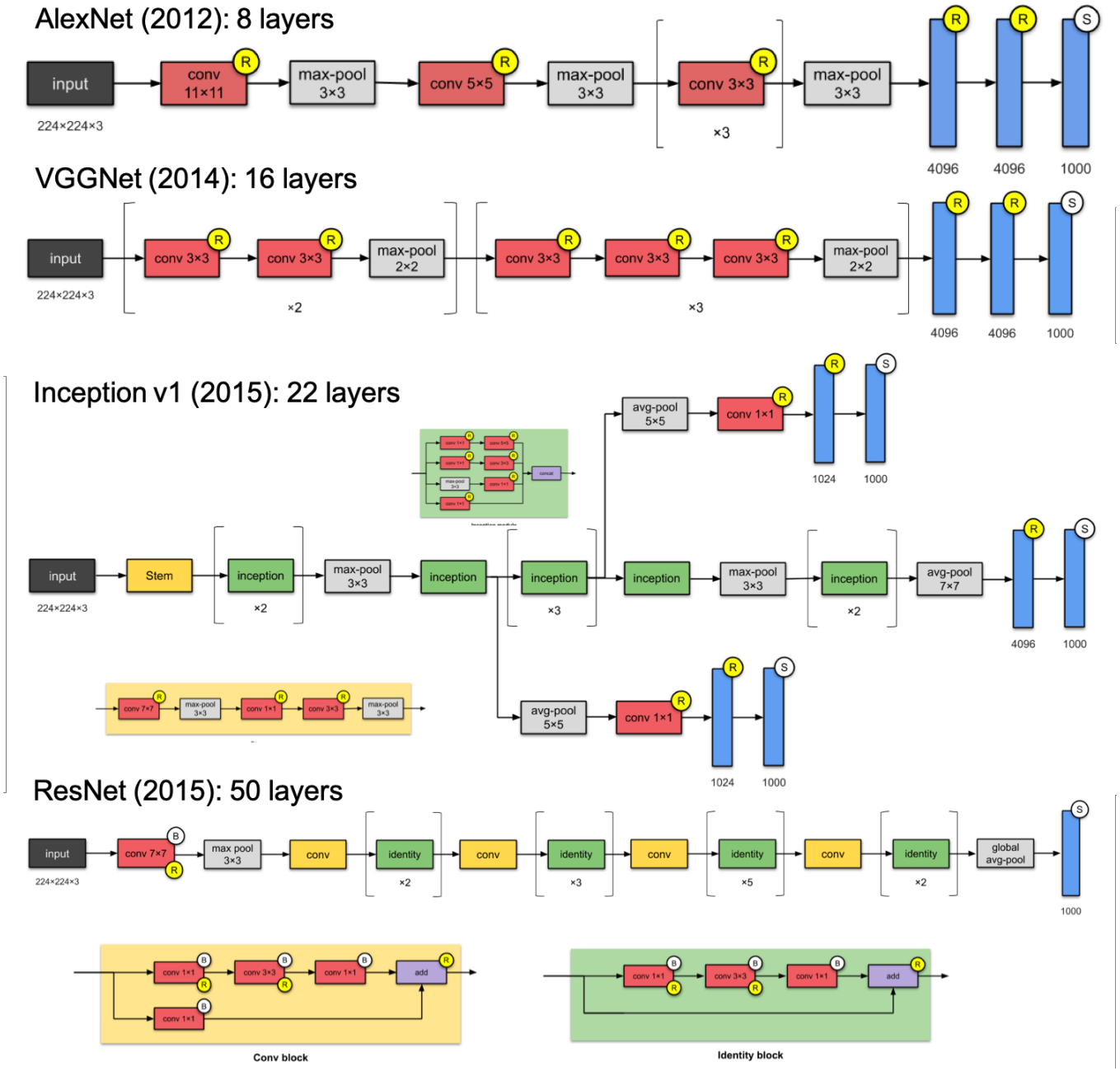
Fully connected



Max pooling

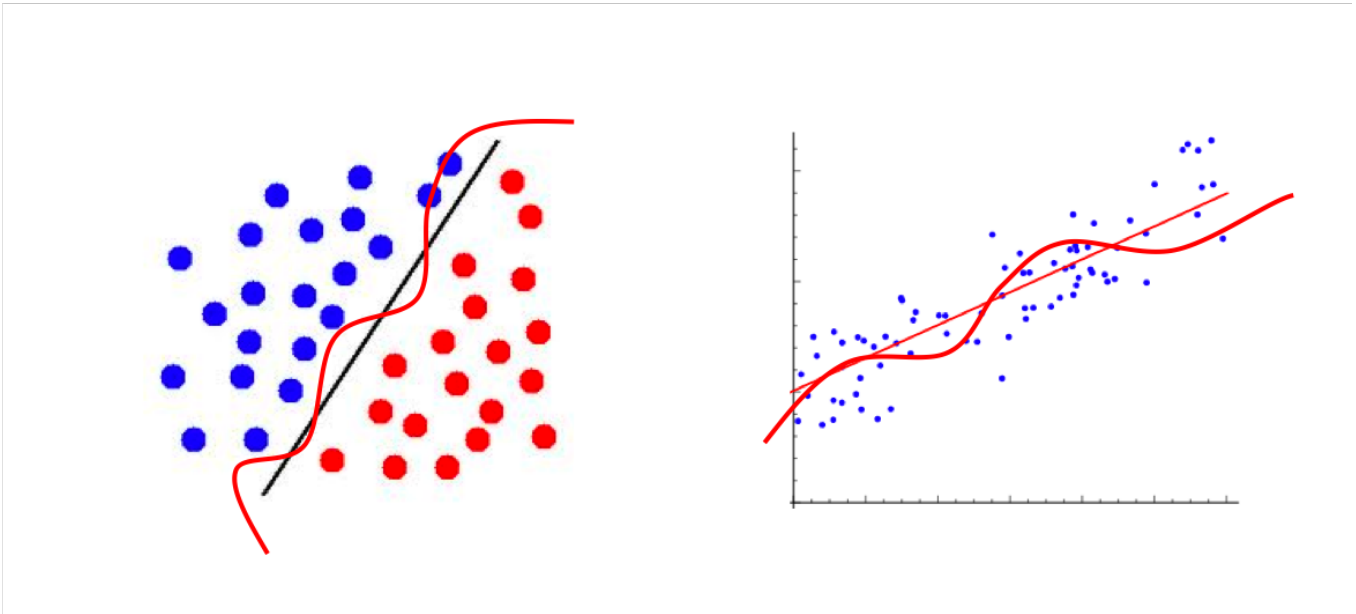


Convolutional Neural Networks



Overfitting (again)

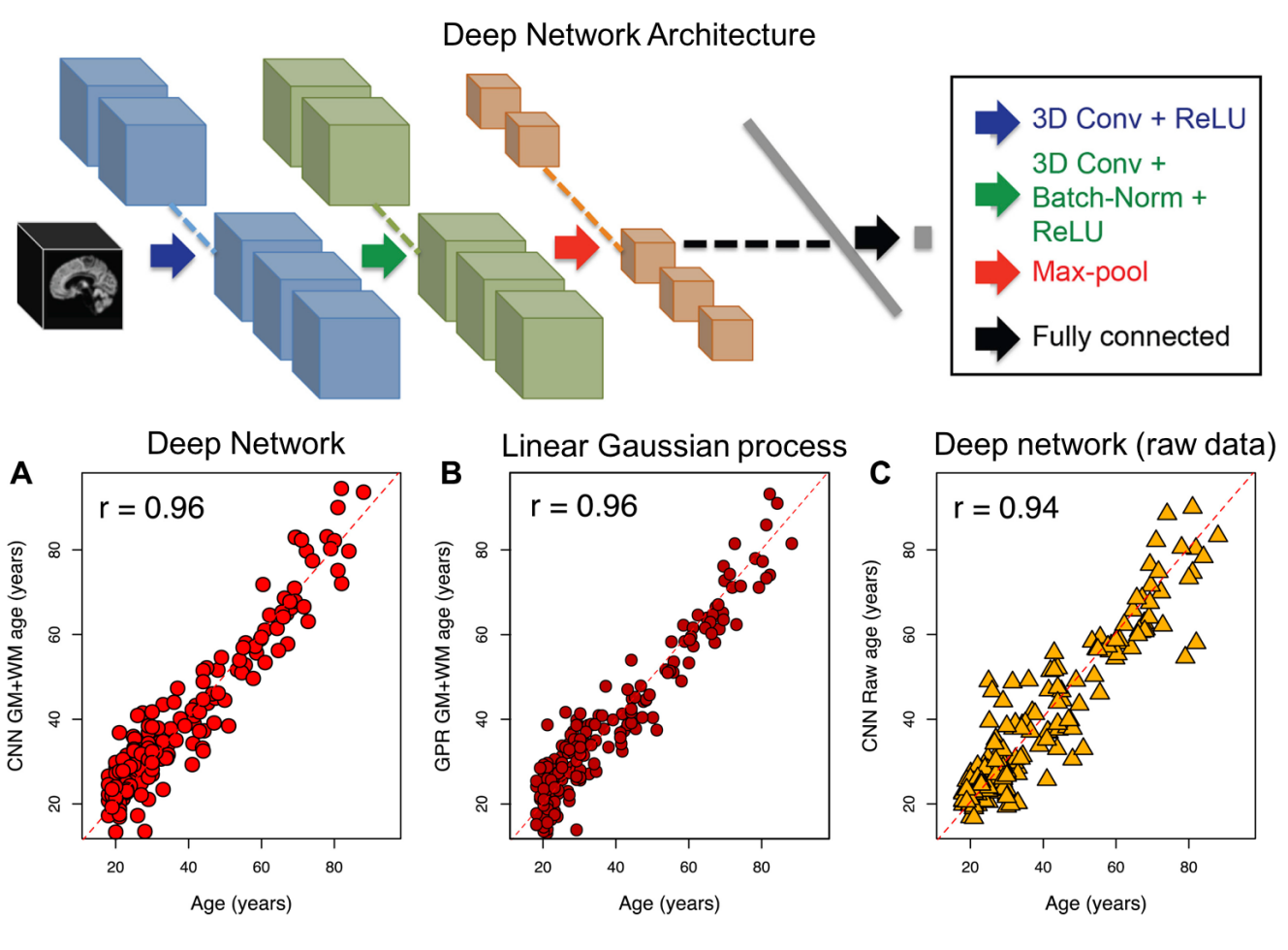
- But if your problem is linear, your fancy nonlinear algorithm will just overfit



- 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!

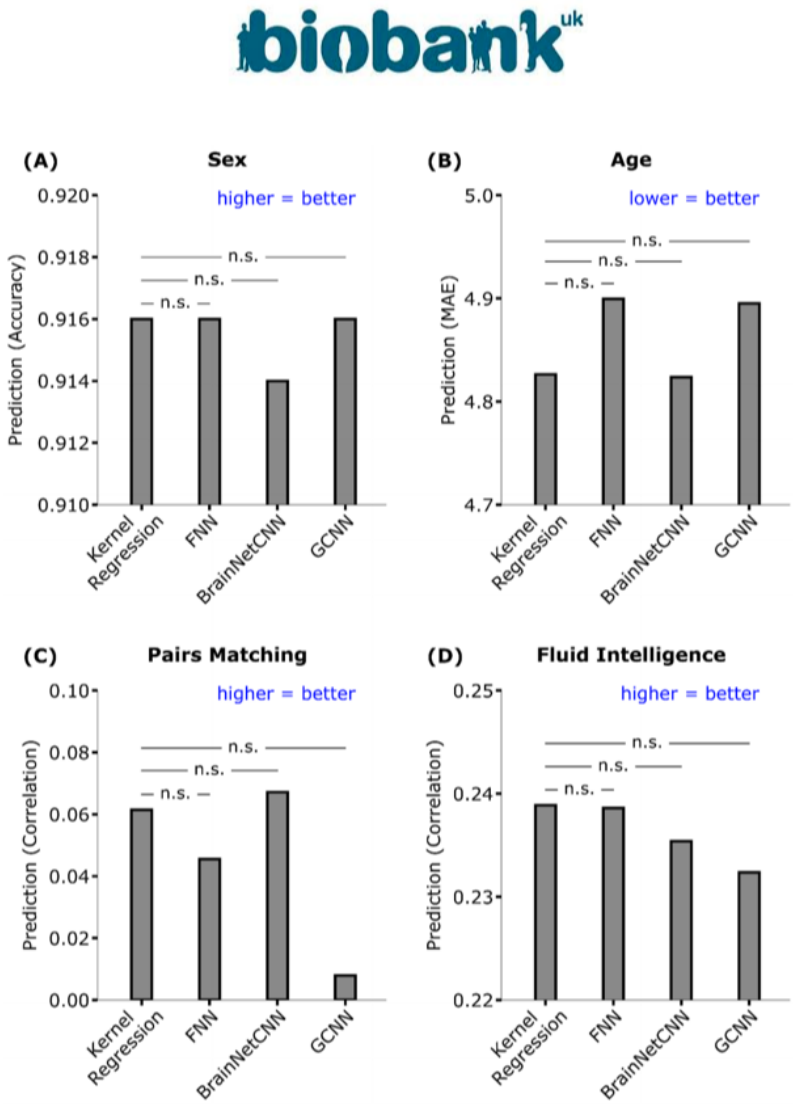
Deep Learning in Neuroscience?

- Predict age from N= 2001 structural MRI images



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

Deep Learning in Neuroscience?



He et al. (2019)

Deep Learning in Neuroscience?

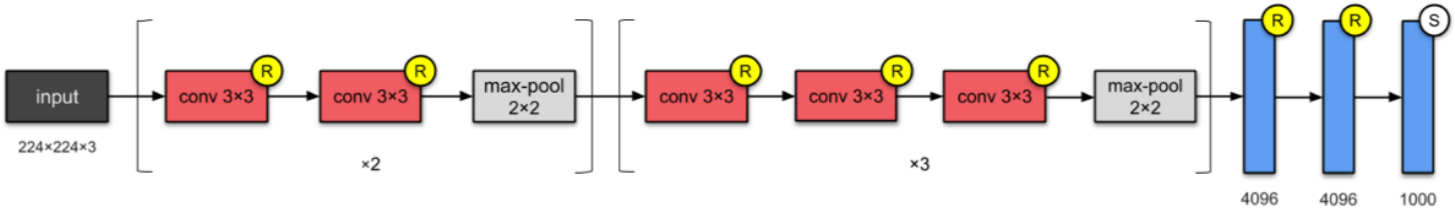
New Results

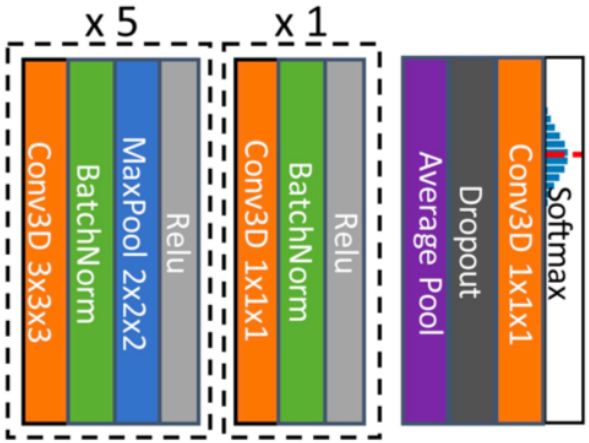
Comment on this paper

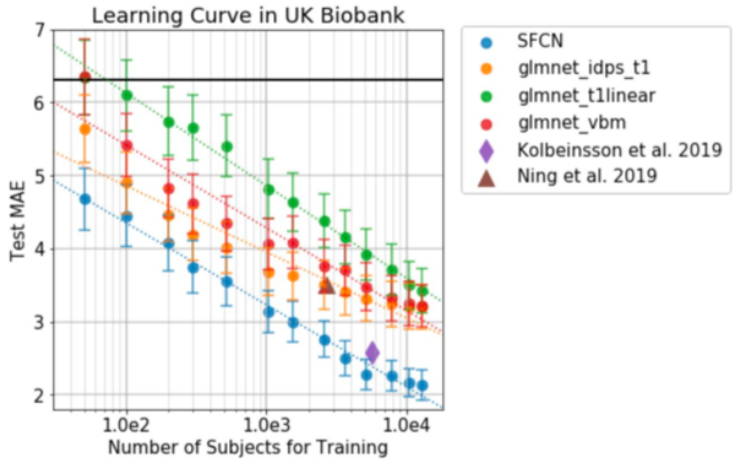
Accurate brain age prediction with lightweight deep neural networks

Han Peng, Weikang Gong, Christian F. Beckmann, Andrea Vedaldi, Stephen M. Smith

doi: https://doi.org/10.1101/2019.12.17.879346



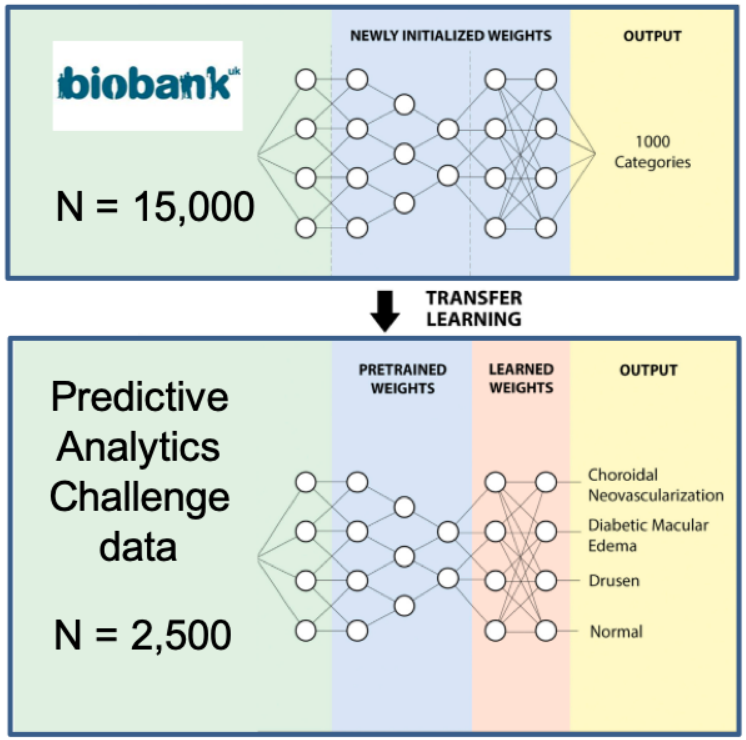




Won the 2019 PAC 'brainage' challenge

Peng et al. (2019)

Transfer Learning



- Basic idea: transfer knowledge (i.e. weights) from a large dataset to a small one (where it is harder to learn)
- Different variants depending on whether the targets are the same, similiar or different

Deep Learning in Medicine?

- Predict mortality from electronic health records

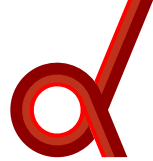
ARTICLE OPEN

Scalable and accurate deep learning with electronic health records

Alvin Rajkomar[1,2], Eyal Oren[1], Kai Chen[1], Andrew M. Dai[1], Nissan Hajaj[1], Michaela Hardt[1], Peter J. Liu[1], Xiaobing Liu[1], Jake Marcus[1], Mimi Sun[1], Patrik Sundberg[1], Hector Yee[1], Kun Zhang[1], Yi Zhang[1], Gerardo Flores[1], Gavin E. Duggan[1], Jamie Irvine[1], Quoc Le[1], Kurt Litsch[1], Alexander Mossin[1], Justin Tansuwan[1], De Wang[1], James Wexler[1], Jimbo Wilson[1], Dana Ludwig[2], Samuel L. Volchenboum[3], Katherine Chou[1], Michael Pearson[1], Srinivasan Madabushi[1], Nigam H. Shah[4], Atul J. Butte[2], Michael D. Howell[1], Claire Cui[1], Greg S. Corrado[1] and Jeffrey Dean[1]

	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)

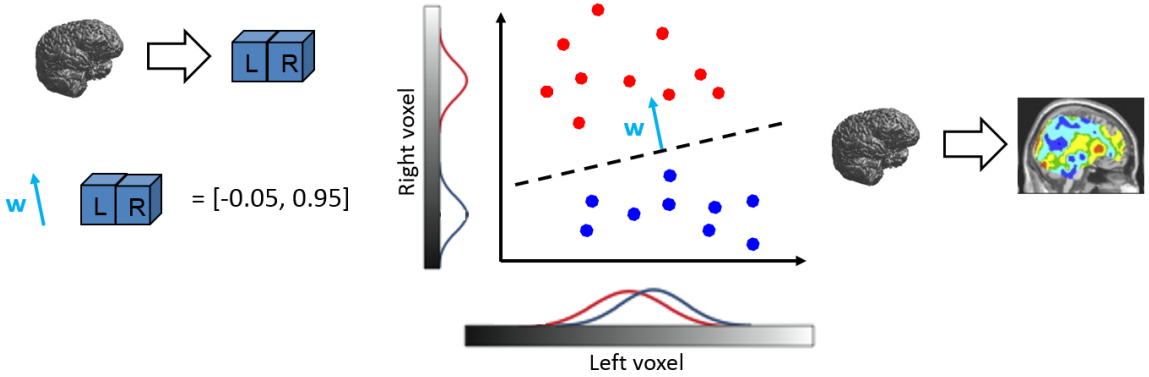
Outline



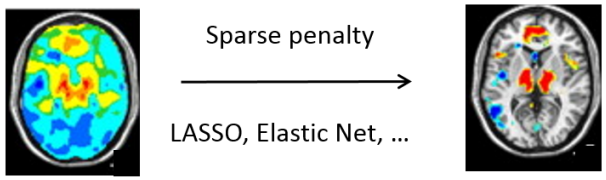
Mapping the discriminative pattern

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")



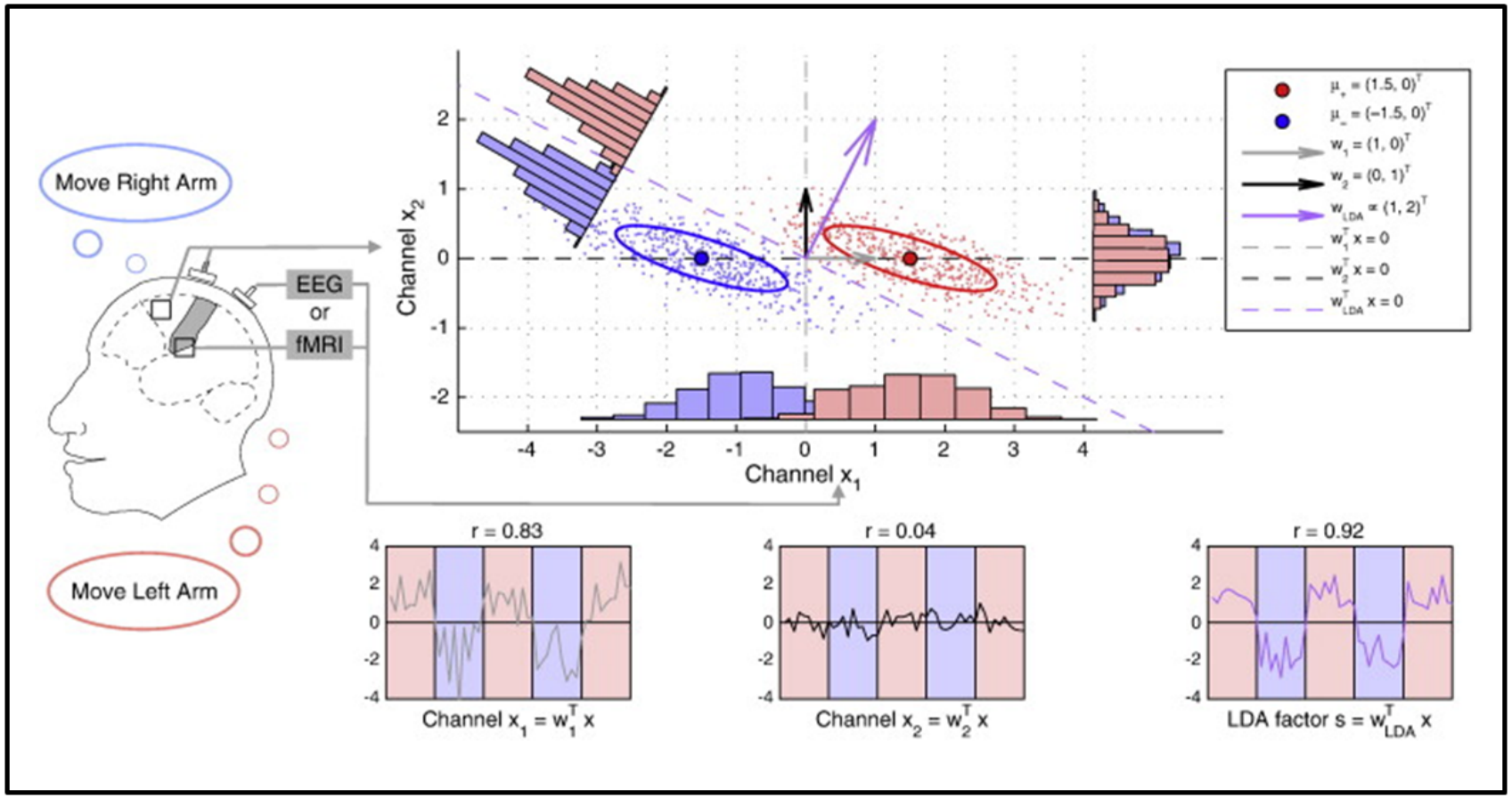
- Can also use regularization to enforce sparse weights



- 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

$$\mathsf{a} = \frac{1}{\sigma_y^2}\Sigma_x \mathsf{w}$$

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

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

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

Kraha et al. (2012)

$$\rho(x_p, \hat{y})$$

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:

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

- Considering ridge regression, where the objective function is:

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

- This is eqivalent to maximising the following

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

But what about the penalty?

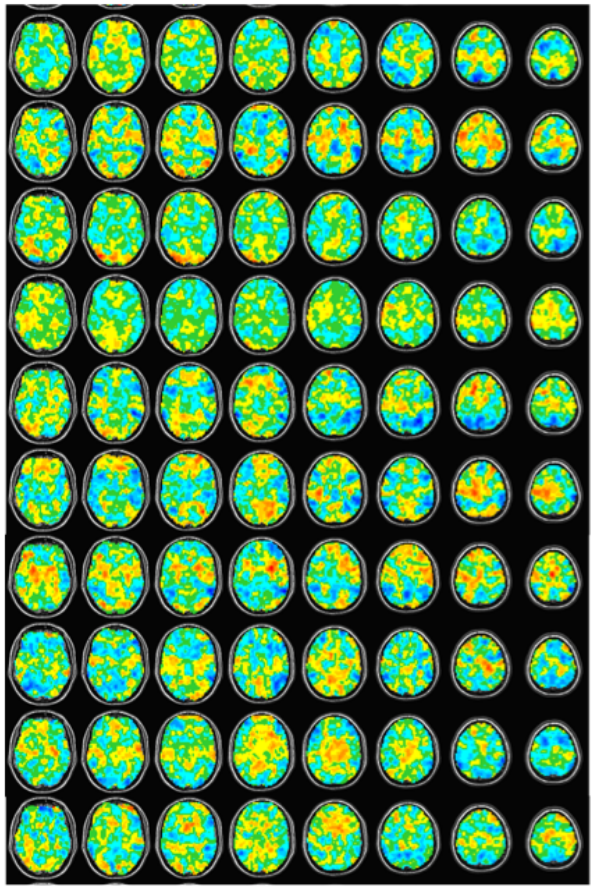
- This is exactly equivalent to finding the MAP estimate of a posterior distribution over w, with prior:

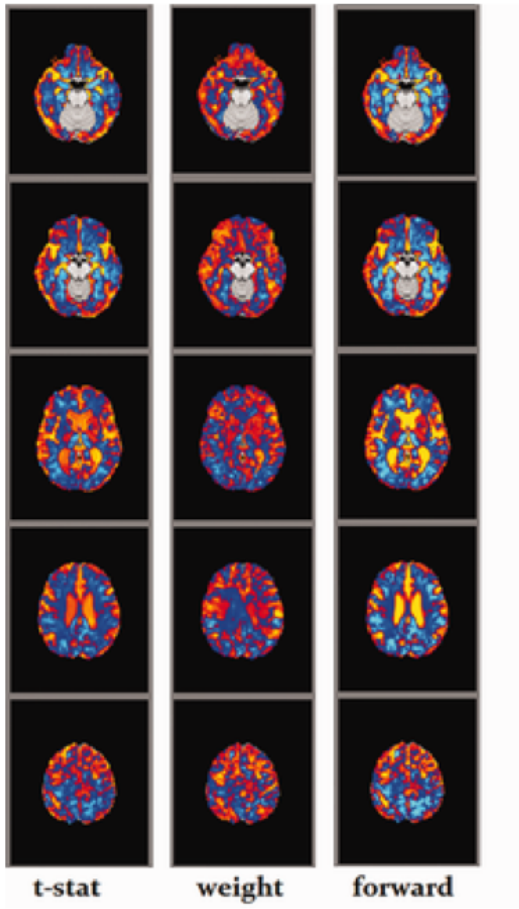
$$\mathcal{N}(0, \sigma^2/\lambda \mathrm{I})$$

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





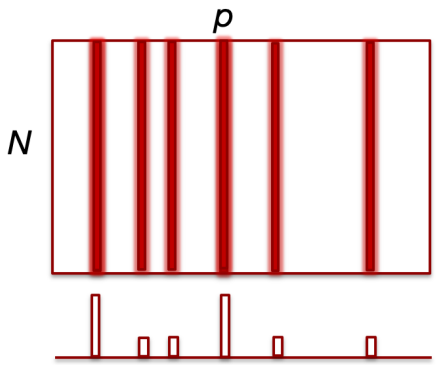
Aksman et al. (2016)

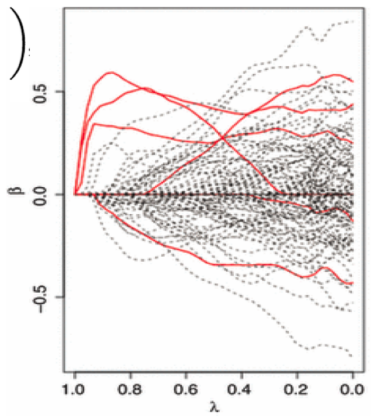
Stability selection

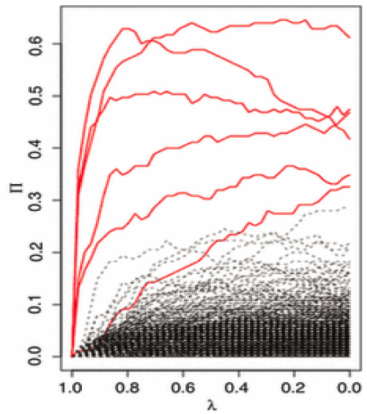
- It is important to recognise that coefficient stability is largely independent from accuracy, especially if features are correlated
- **stability selection** is a method that aims to identify truly important variables by examining stability under perturbation to the data

Lasso

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





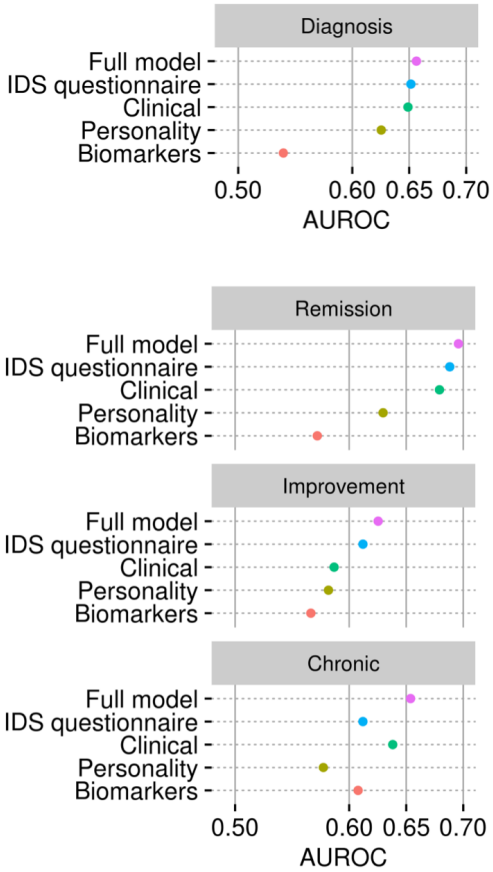


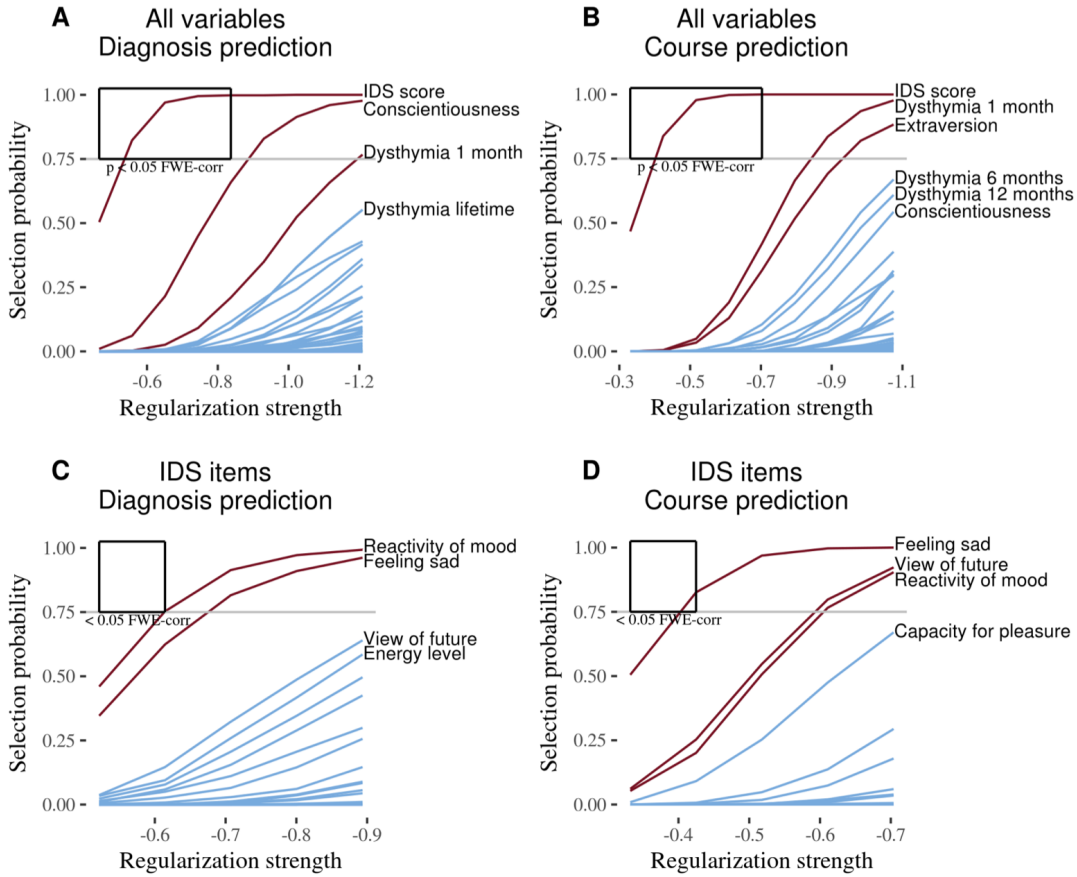
Statistical guarantees against false positives
(controls family-wise error)

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)

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'

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)

Acknowledgments

Mariam Zabihi

Richard Dinga

Thomas Wolfers

Saige Rutherford

Predictive Clinical Neuroscience Lab

We are hiring!

Tutorial on Normative modelling:

`https://github.com/saigerutherford/CPC_2020`

References I

Leon Aksman, David J. Lythgoe, Steven C.R. Williams, Martha Jokisch, Christoph Moenninghoff, Johannes Streffer, Karl Heinz Joeckel, Christian Weimar, and Andre F. Marquand. Making use of longitudinal information in pattern recognition. *Human Brain Mapping*, 37(12):4385–4404, 2016. doi: 10.1002/hbm.23317. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/hbm.23317.

James Cole, Rudra Poudel, Dimosthenis Tsagkasoullis, Matthan Caan, Claire Steves, Tim Spector, and Giovanni Montana. Predicting brain age with deep learning from raw imaging data results in a reliable and heritable biomarker. *Neuroimage*, (In Press), 2017.

Richard Dinga, Andre F. Marquand, Dick J. Veltman, Aartjan T. F. Beekman, Robert A. Schoevers, Albert M. van Hemert, Brenda W. J. H. Penninx, and Lianne Schmaal. Predicting the naturalistic course of depression from a wide range of clinical, psychological, and biological data: a machine learning approach. 2018.

Richard Dinga, Lianne Schmaal, Brenda W.J.H. Penninx, Marie Jose van Tol, Dick J. Veltman, Laura van Velzen, Maarten Mennes, Nic J.A. van der Wee, and Andre F. Marquand. Evaluating the evidence for biotypes of depression: Methodological replication and extension of drysdale et al. (2017). *NeuroImage: Clinical*, 22: 101796, 2019. ISSN 2213-1582. doi: https://doi.org/10.1016/j.nicl.2019.101796. URL http://www.sciencedirect.com/science/article/pii/S2213158219301469.

Richard Dinga, Lianne Schmaal, and Andre F. Marquand. A closer look at depression biotypes: Correspondence relating to grosenick et al. (2019). *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(5):554 – 555, 2020. ISSN 2451-9022. doi: https://doi.org/10.1016/j.bpsc.2019.09.011. URL http://www.sciencedirect.com/science/article/pii/S245190221930299X.

A. Dong, N. Honnorat, B. Gaonkar, and C. Davatzikos. Chimera: Clustering of heterogeneous disease effects via distribution matching of imaging patterns. *IEEE Transactions on Medical Imaging*, 35(2):612–621, Feb 2016. ISSN 0278-0062. doi: 10.1109/TMI.2015.2487423.

Andrew T Drysdale, Logan Grosenick, Jonathan Downar, Katharine Dunlop, Farrokh Mansouri, Yue Meng, Robert N Fetcho, Benjamin Zebley, Desmond J Oathes, Amit Etkin, Alan F Schatzberg, Keith Sudheimer, Jennifer Keller, Helen S Mayberg, Faith M Gunning, George S Alexopoulos, Michael D Fox, Alvaro Pascual-Leone, Henning U Voss, BJ Casey, Marc J Dubin, and Conor Liston. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine*, (23):28–38, 2017.

Maurizio Filippone, Andre Marquand, Camilla Blain, Steven Williams, Janaina Mourao-Miranda, and Mark Girolami. Probabilistic prediction of neurological disorders with a statistical assessment of neuroimaging data modalities. *Annals of Applied Statistics*, 6:1883–1905, 2012.

References II

Edith Le Floch, Vincent Guillemot, Vincent Frouin, Philippe Pinel, Christophe Lalanne, Laura Trinchera, Arthur Tenenhaus, Antonio Moreno, Monica Zilbovicius, Thomas Bourgeron, Stanislas Dehaene, Bertrand Thirion, Jean-Baptiste Poline, and Edouard Duchesnay. Significant correlation between a set of genetic polymorphisms and a functional brain network revealed by feature selection and sparse partial least squares. *NeuroImage*, 63 (1):11 – 24, 2012. ISSN 1053-8119.

Logan Grosenick and Conor Liston. Reply to: A closer look at depression biotypes: Correspondence relating to grosenick et al (2019). *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(5):556, 2020. ISSN 2451-9022. doi: https://doi.org/10.1016/j.bpsc.2019.11.002. URL http://www.sciencedirect.com/science/article/pii/S2451902219302988.

Stefan Haufe, Frank Meinecke, Kai Goergen, Sven Daehne, John-Dylan Haynes, Benjamin Blankertz, and Felix Biessmann. On the interpretation of weight vectors of linear models in multivariate neuroimaging. *NeuroImage*, 87(0):96 – 110, 2014.

Tong He, Ru Kong, Avram Holmes, Minh Nguyen, Mert Sabuncu, Simon Eickhoff, Danilo Bzdok, Jiashi Feng, and B. T. Thomas Yeo. Deep neural networks and kernel regression achieve comparable accuracies for functional connectivity prediction of behavior and demographics. *BioRxiv*, 2019.

Amanda Kraha, Heather Turner, Kim Nimon, Linda Zientek, and Robin Henson. Tools to support interpreting multiple regression in the face of multicollinearity. *Frontiers in Psychology*, 3:44, 2012. ISSN 1664-1078. doi: 10.3389/fpsyg.2012.00044. URL https://www.frontiersin.org/article/10.3389/fpsyg.2012.00044.

Andre F. Marquand, Iead Rezek, Jan Buitelaar, and Christian F. Beckmann. Understanding heterogeneity in clinical cohorts using normative models: beyond case control studies. In Press, 2016.

Agoston Mihalik, Rick A. Adams, and Quentin Huys. Canonical correlation analysis for identifying biotypes of depression. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(5):478 – 480, 2020. ISSN 2451-9022. doi: https://doi.org/10.1016/j.bpsc.2020.02.002. URL http://www.sciencedirect.com/science/article/pii/S245190222030032X.

Janaina Mourao-Miranda, David R. Hardoon, Tim Hahn, Andre F. Marquand, Steve C.R. Williams, John Shawe-Taylor, and Michael Brammer. Patient classification as an outlier detection problem: An application of the one-class support vector machine. *NeuroImage*, 58(3):793 – 804, 2011. ISSN 1053-8119. doi: https://doi.org/10.1016/j.neuroimage.2011.06.042. URL http://www.sciencedirect.com/science/article/pii/S1053811911006872.

References III

Han Peng, Weikang Gong, Christian F. Beckmann, Andrea Vedaldi, and Stephen M. Smith. Accurate brain age prediction with lightweight deep neural networks. *bioRxiv*, 2019. doi: 10.1101/2019.12.17.879346. URL https://www.biorxiv.org/content/early/2019/12/18/2019.12.17.879346.

Stephen M Smith, Thomas E Nichols, Diego Vidaurre, Anderson M Winkler, Timothy E J Behrens, Matthew F Glasser, Kamil Ugurbil, Deanna M Barch, David C Van Essen, and Karla L Miller. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. 18:1565–1567, 2015.

Cedric Xia, Zongming Ma, Rastko Ciric, Shi Gu, Richard F. Betzel, Antonia N. Kaczkurkin, Monica E. Calkins, Philip A. Cook, Angel Garcia de la Garza, Simon N. Vandekar, Zaixu Cui, Tyler M. Moore, David R. Roalf, Kosha Ruparel, Daniel H. Wolf, Christos Davatzikos, Ruben C. Gur, Raquel E. Gur, Russell T. Shinohara, Danielle S. Bassett, and Theodore D. Satterthwaite. Linked dimensions of psychopathology and connectivity in functional brain networks. *Nature Communications*, 9, 2018.

Mariam Zabihi, Marianne Oldehinkel, Thomas Wolfers, Vincent Frouin, David Goyard, Eva Loth, Tony Charman, Julian Tillmann, Tobias Banaschewski, Guillaume Dumas, Rosemary Holt, Simon Baron-Cohen, Sarah Durston, Sven Boelte, Declan Murphy, Christine Ecker, Jan K. Buitelaar, Christian F. Beckmann, and Andre F. Marquand. Dissecting the heterogeneous cortical anatomy of autism spectrum disorder using normative models. 4(6):567 – 578, 2019. ISSN 2451-9022. doi: https://doi.org/10.1016/j.bpsc.2018.11.013. URL http://www.sciencedirect.com/science/article/pii/S245190221830329X. The Bridging of Scales: Techniques for Translational Neuroscience.

Xiuming Zhang, Elizabeth C. Mormino, Nanbo Sun, Reisa A. Sperling, Mert R. Sabuncu, and B. T. Thomas Yeo. Bayesian model reveals latent atrophy factors with dissociable cognitive trajectories in alzheimer's disease. *Proceedings of the National Academy of Sciences*, 113(42):E6535–E6544, 2016. ISSN 0027-8424. doi: 10.1073/pnas.1611073113. URL https://www.pnas.org/content/113/42/E6535.