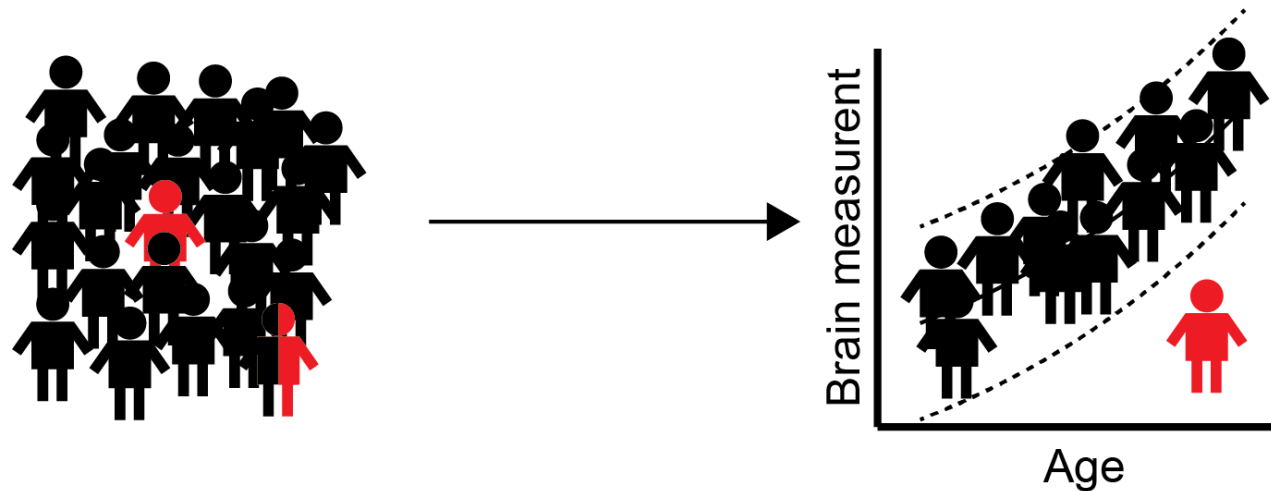


FUNCOIN: A whole-brain functional connectivity regression method for normative modelling

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Professor Diego Vidaurre, Center of Functionally Integrative Neuroscience, Aarhus University

Analysis workshop, May 26 2025, Aarhus University

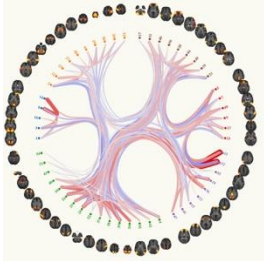


Motivation:

Brain function biomarkers of disease/disorder

- Challenges:

- Complex nature



- Heterogenous symptoms



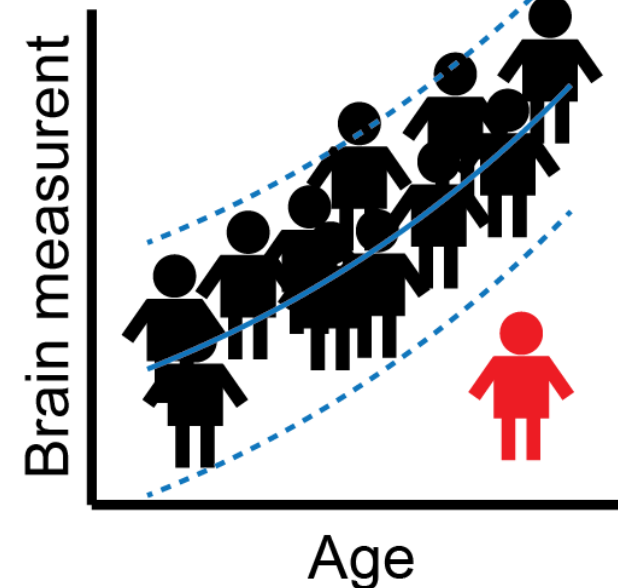
- Described on a spectrum



- Hard to recruit cases

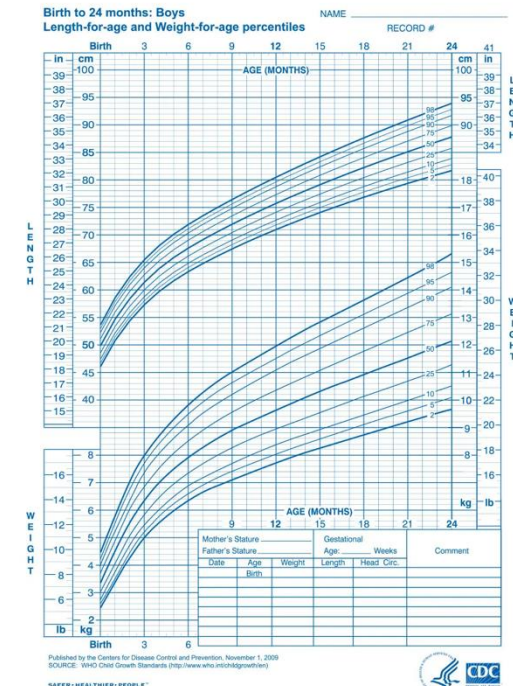
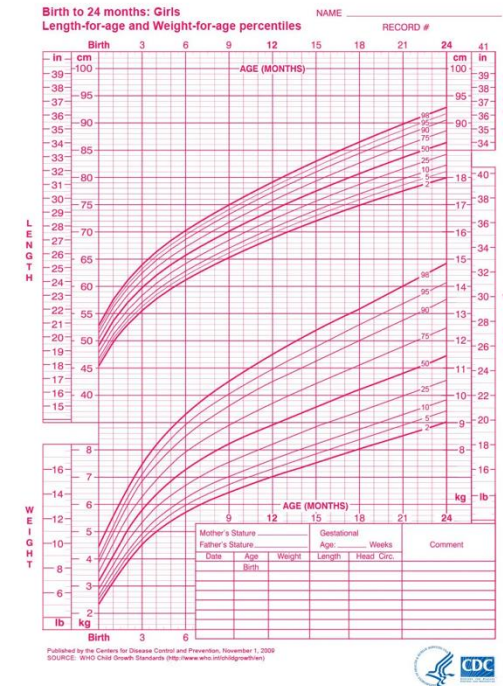
- Suggestion:

Normative modelling



Normative modelling

- Like growth charting of children
- Describes the normal variation in height and weight given sex and age
- Individual measures are evaluated as percentiles or Z-scores
- Allows identifying outliers or spotting longitudinal effects



The W.H.O. growth charts for girls (left) and boys (right) from birth to age 2, published by the C.D.C. (Centers for Disease Control and Prevention), 2009

Elements in normative modelling

1. A large dataset of healthy subjects and (possibly fewer) subjects with diagnoses
2. A method to predict the brain measure from sex and age

1.

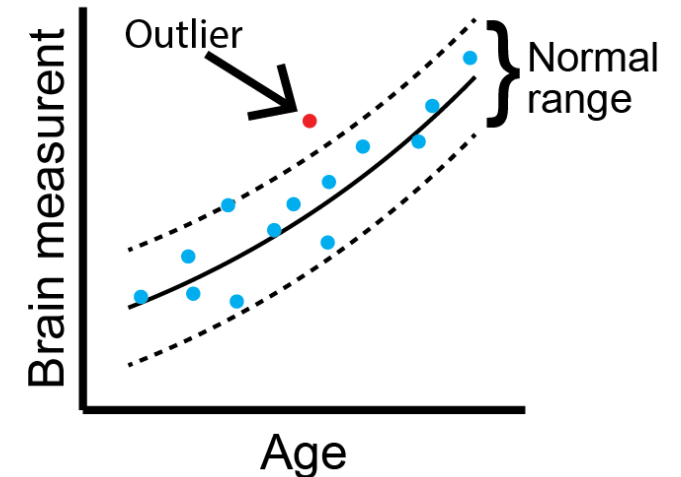
Dataset subjects



Grouping

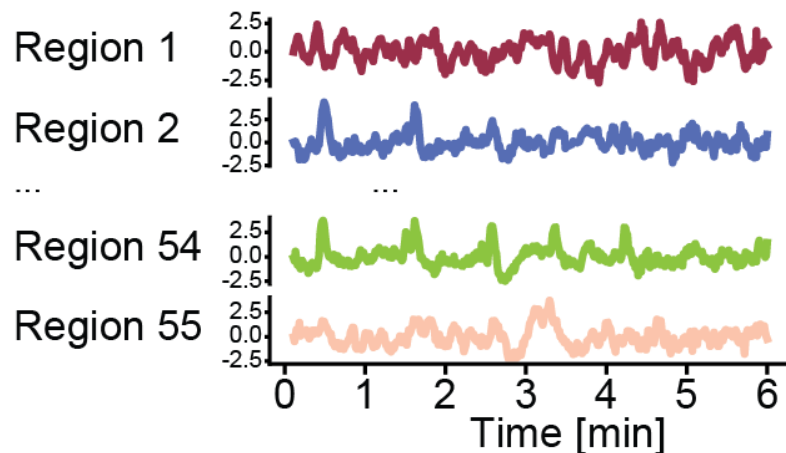


2.

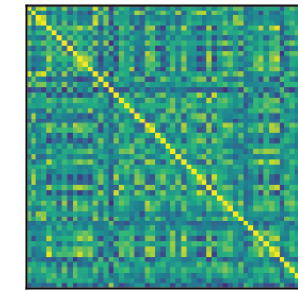
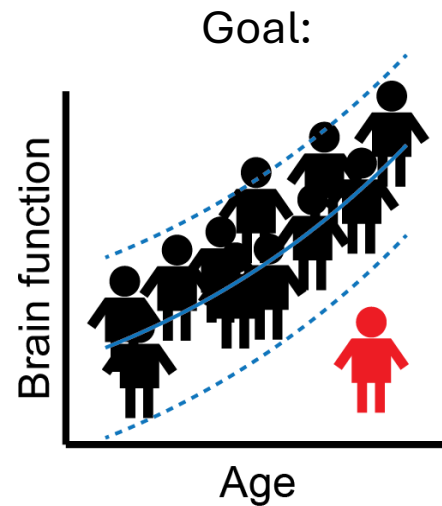


UK Biobank, fMRI data

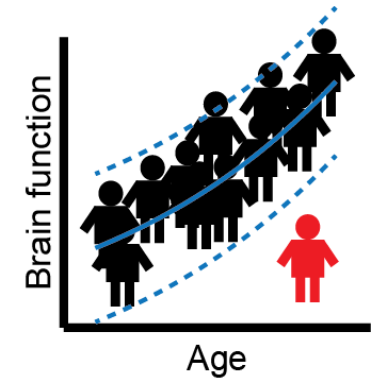
- rs-fMRI from >60k subjects
 - 10684 with diagnoses in ICD10 F or G
 - 49721 with no diagnoses in ICD10 F or G
- Scan time 6 minutes (TR = 0.735 s)
- Network parcellations from ICA (p=55)



Normative modelling of brain function



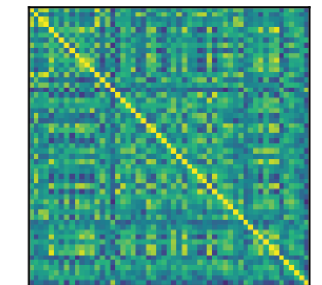
?



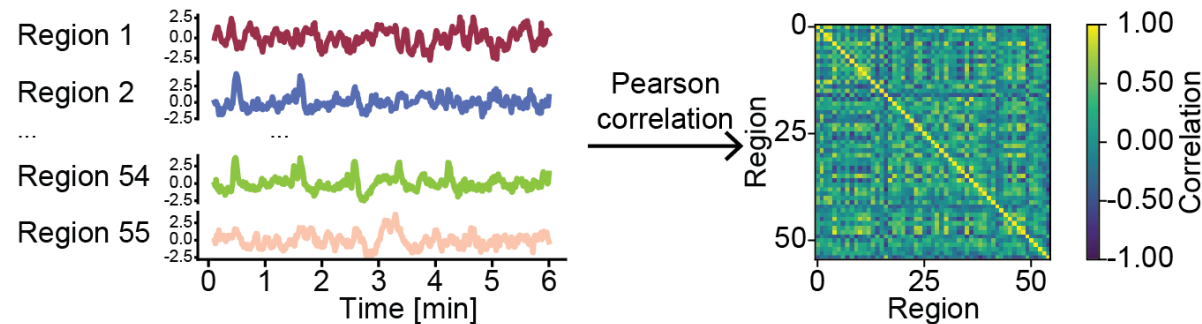
that is:

(age, sex)

?



Assessing brain function with functional connectivity (FC)



FUNCOIN: Functional Connectivity Integrative Normative Modelling¹

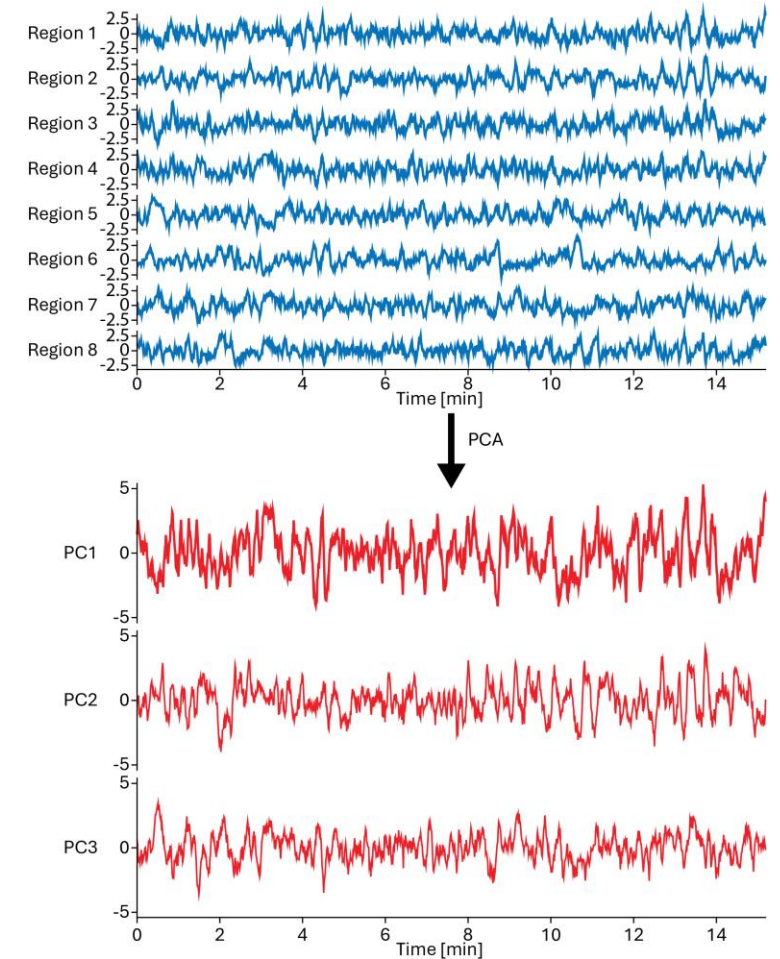
- A novel framework for network-level normative modelling
- An adaptation of a recently developed covariance regression method: Covariate Assisted Principal Regression²
 - Modified for normative modelling
 - Dimensionality reduction and regression in one go
- Released as a ready-to-use Python package

¹: Kobbersmed, J.R.L. et al. (2025). 'One-shot normative modelling of whole-brain functional connectivity', *BioRxiv*.

²: Zhao, Y. et al. (2021). 'Covariate Assisted Principal regression for covariance matrix outcomes', *Biostatistics*, 22(3), pp. 629-45.

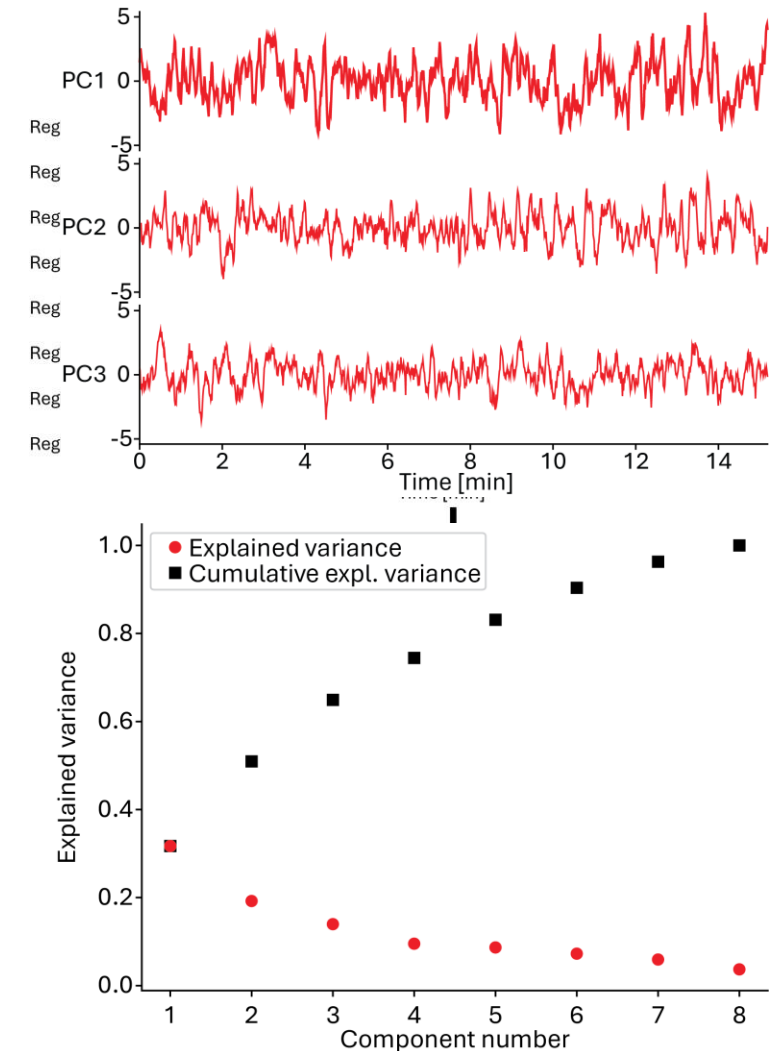
Background: Principal components analysis

- We identify the components that **capture most variation** in the data
- => Benefits:
 - We **reduce data to fewer dimensions**
 - The component loadings reveal **which brain regions contribute most** to each component



Background: Principal components analysis

- We identify the components that **capture most variation** in the data
- => Benefits:
 - We **reduce data to fewer dimensions**
 - The component loadings reveal **which brain regions contribute most** to each component
 - From the **strength** of a component we can compute how much variance the component explains



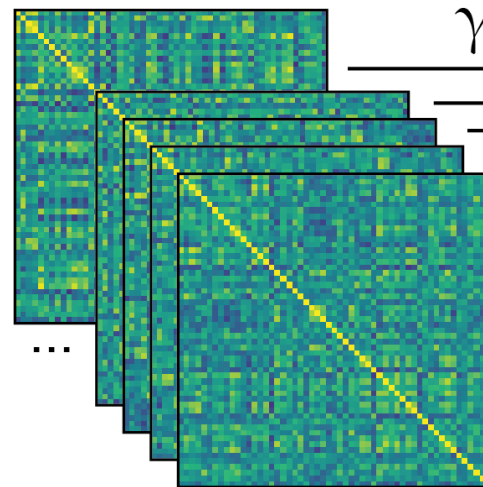
Functional Connectivity Integrative Normative Modelling (FUNCOIN)

- Identifies **components** in a way similar to PCA
- The identified components are **shared** among the subjects
- The **strength** of the components **depend on covariates** (e.g. sex and age)

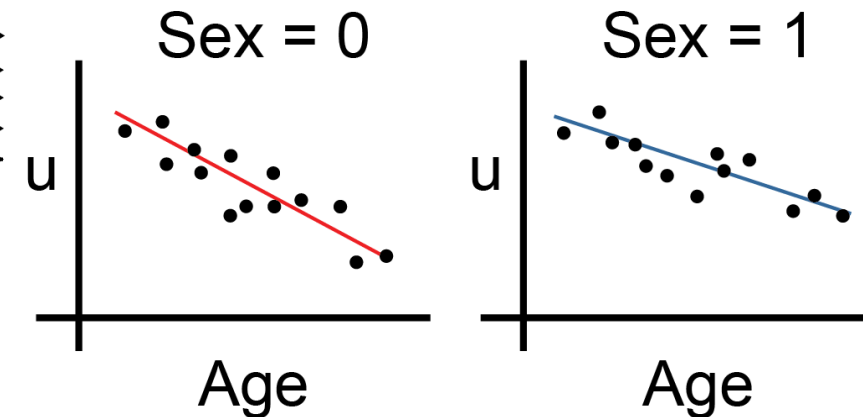
Model:

$$u_i = \log(\boldsymbol{\gamma}^T \boldsymbol{\Sigma}_i \boldsymbol{\gamma}) = \beta_0 + \mathbf{X}_i^T \boldsymbol{\beta}$$

FC data:



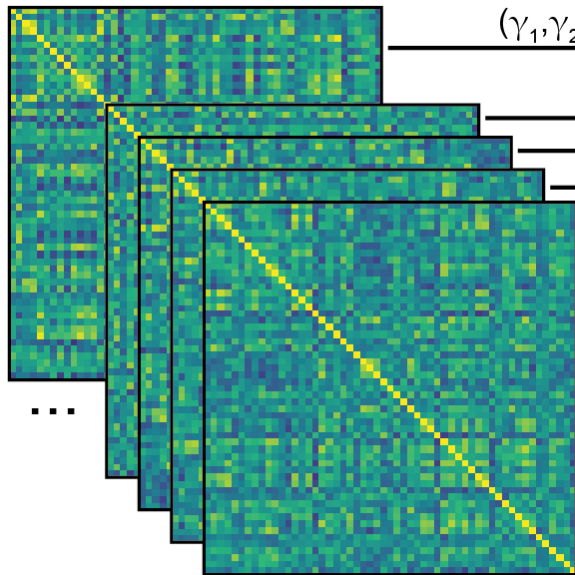
Normative model:



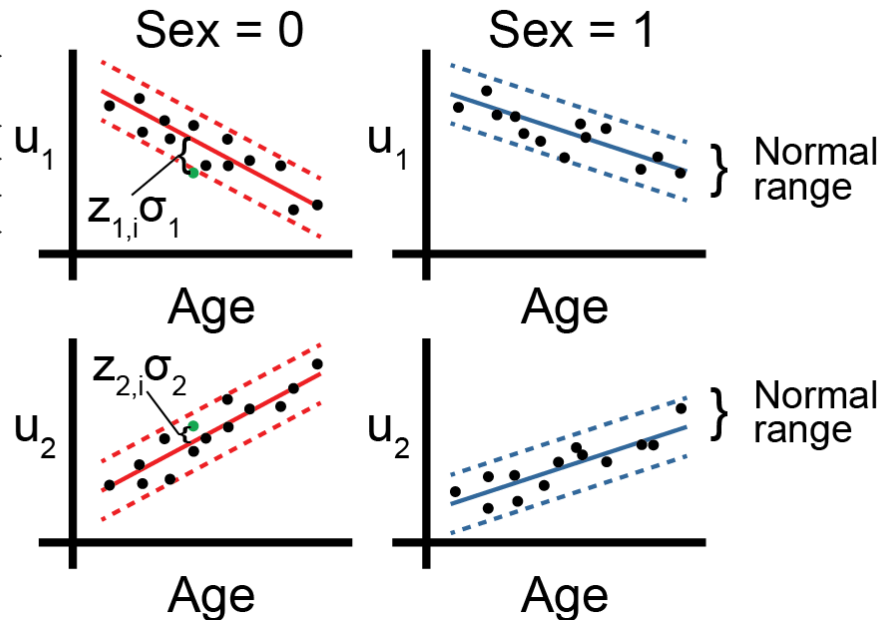
Normative modelling of FC

- Healthy training: $n=32000$; healthy test: $n=14000$
- Deviation is assessed as two Z-scores

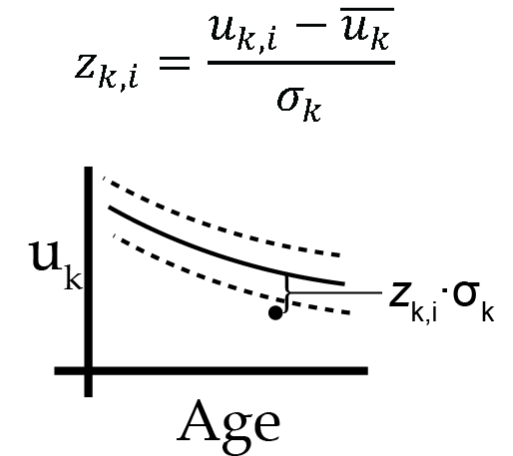
Healthy training FC:



Normative model:

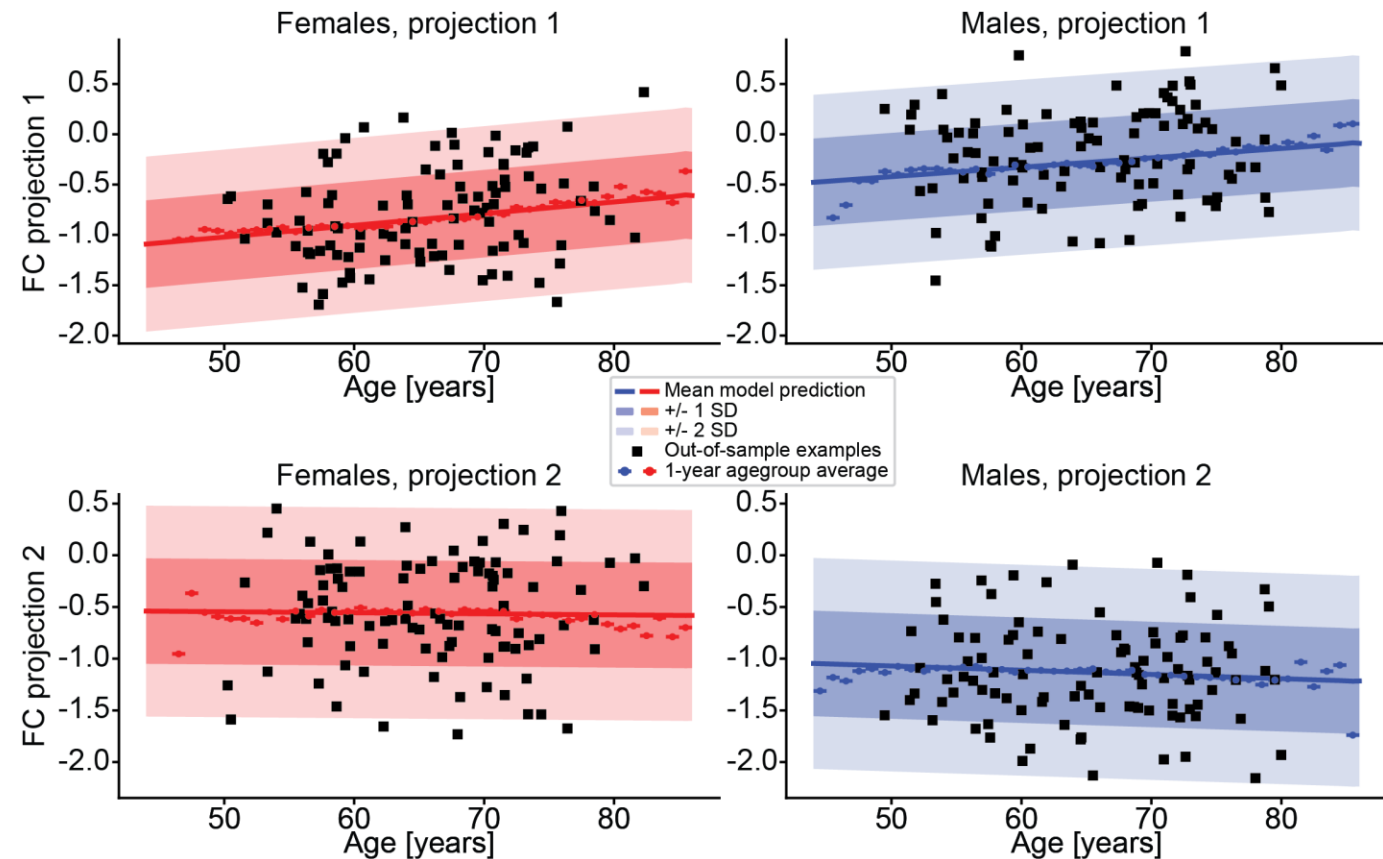


Individual deviation:



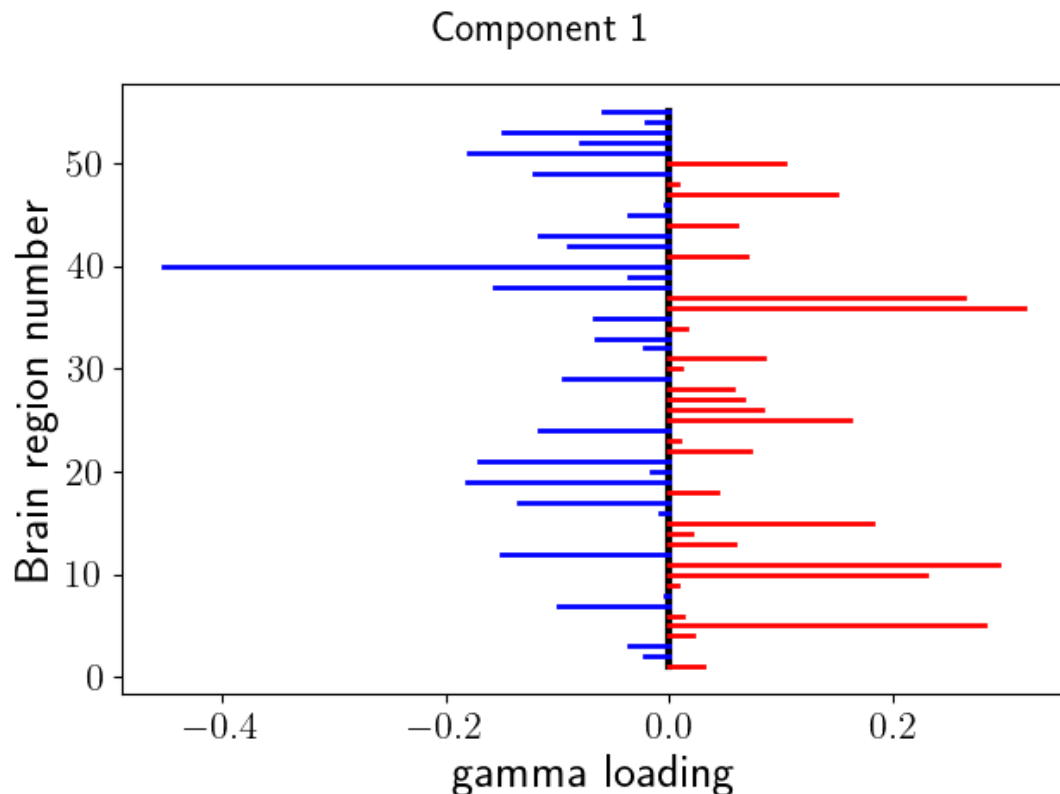
Results: Normative models with FUNCOIN

- We identify 2 components:
 - 1: Depends on sex and age
 - 2: Depends (mainly) on sex



Results: Inspecting components and coefficients

- The weighting of the brain regions are the values of γ s
- The association with covariates is seen from the β coefficients

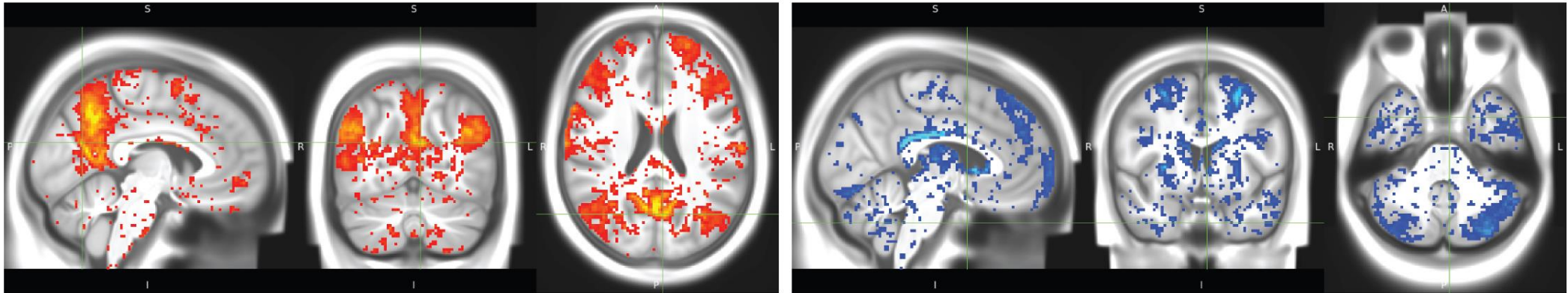


	Coeff.	Variable	Estimate (SE)	95%-CI
First projection	$\beta_{1,0}$	Intercept	-1.085 (0.010)	[-1.101; -1.066]
	$\beta_{1,1}$	Sex	0.6129 (0.014)	[0.585; 0.641]
	$\beta_{1,2}$	Age	0.4755 (0.018)	[0.440; 0.511]
	$\beta_{1,3}$	Sex-age	-0.0935 (0.026)	[-0.145; -0.043]

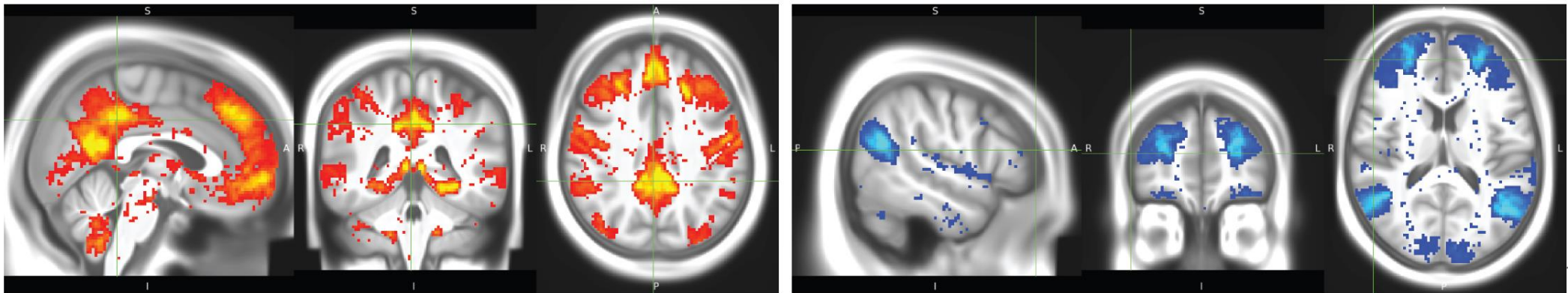
Results: Sex and age components

- Components illustrated with brain maps:

Projection 1: Depends on sex and age

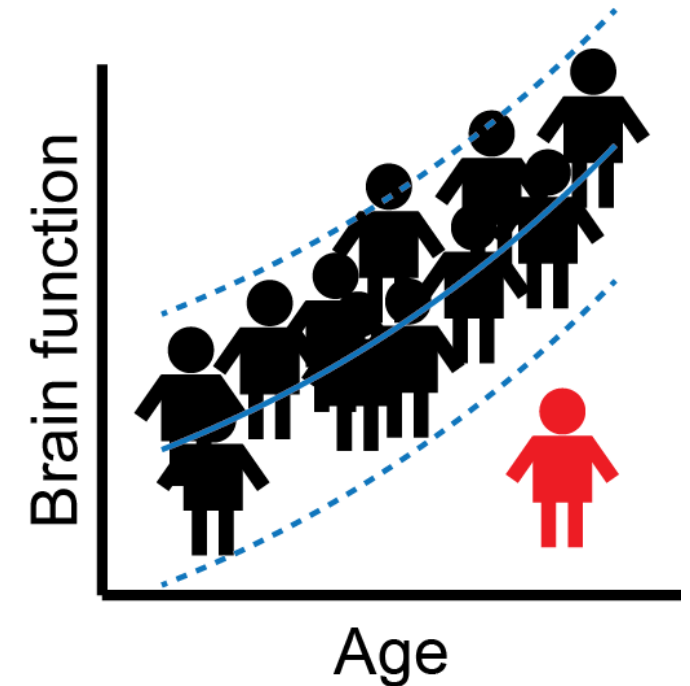


Projection 2: Depends on sex



Diagnosis prediction

- We consider $|Z| > 2$ as an outlier
 - Expect 2,3 % of healthy subjects to be outliers in each direction
- Reasons for being an outlier
 - Coincidence
 - Non-identified pathology
 - Brain disease/disorder



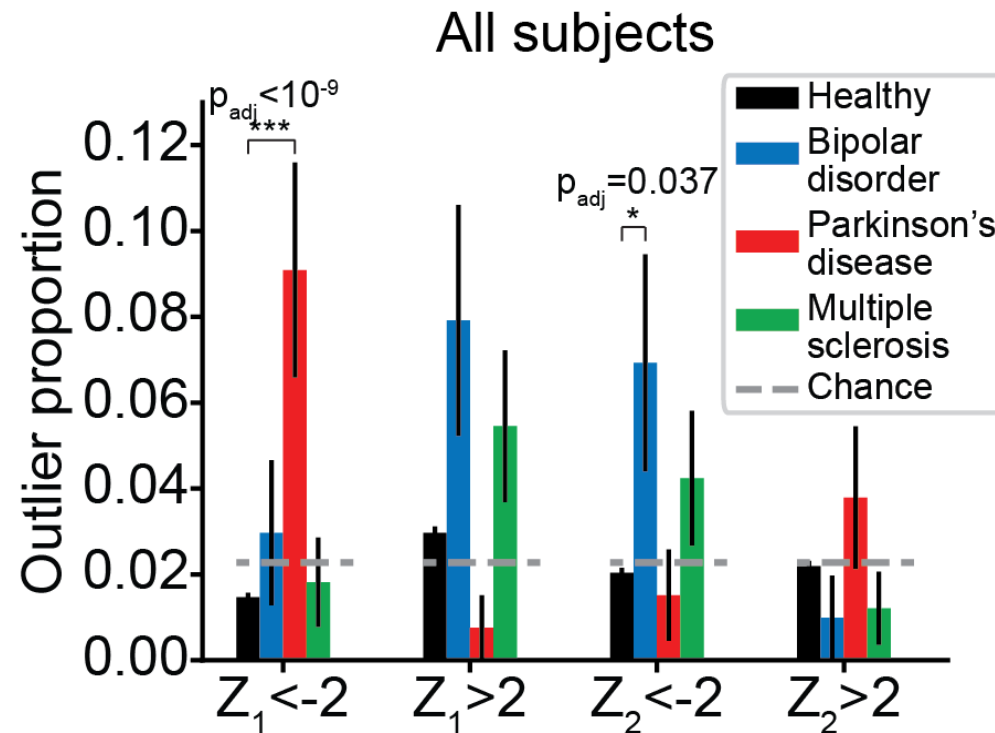
Diagnosis data

- Focus on chronic conditions
- Focus on N>100

Diagnosis	N
Alzheimer's dementia (F00)	34
Vascular dementia (F01)	25
Unspecified dementia (F03)	55
Mild cognitive impairment (F06)	28
Schizophrenia (F20)	33
Bipolar disorder (F31)	101
Autism/Asperger's (F840 and F845)	24
Parkinson's disease (G20)	132
Alzheimer's disease (G30)	48
Multiple sclerosis (G35)	164

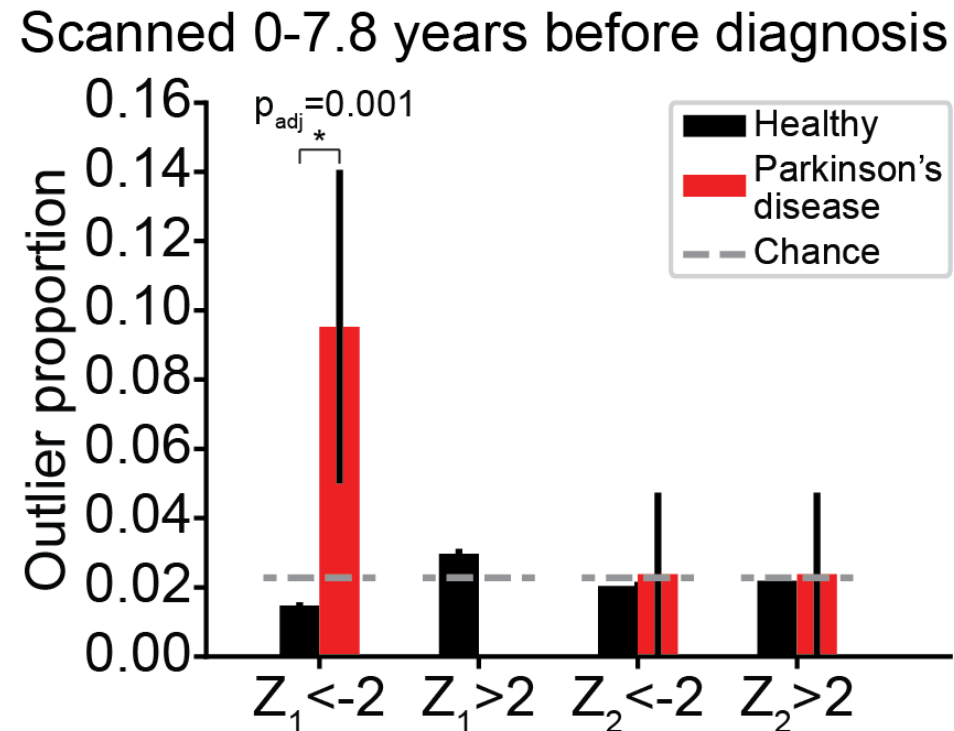
Diagnosis prediction

- FUNCOIN reveals significant FC alterations in Parkinson's disease and bipolar disorder
- Subjects with bipolar disorder divided into two groups



Early diagnosis prediction

- Some subjects were diagnosed with PD years after their scan
 - 54 subjects were scanned 0-8 years before PD diagnosis (average ~3.7 years before)



What can I do with the FUNCOIN package?

- Normative modelling of FC
- Identify components that depend on covariates
 - => Identify brain networks that capture covariate-related changes
- Apply the model on out-of-sample data
- Apply statistical analysis and testing on model coefficients
 - Parametric (t-tests, confidence intervals)
 - Non-parametrics (bootstrap confidence intervals)

Example study questions for FUNCOIN

- Whole-brain normative modelling of FC
- How does FC change between healthy subjects and subjects with a certain diagnosis?
- Which brain regions/networks are involved in the FC changes seen with increasing symptom score?
- How does FC relate to other measures (e.g. blood samples, IQ, test scores...)?

Future work

- Currently finishing a version of FUNCOIN for MEG/EEG
 - Spectral properties
 - High dimensionality (large p)
 - Large amount of time points

See more:

- Paper:
<https://www.biorxiv.org/content/10.1101/2025.01.13.632752v1>
- The FUNCOIN Python package:
<https://github.com/kobbersmed/funcoin>
- FUNCOIN tutorial for this workshop:
https://github.com/CFIN-analysis/analysis_workshop_26May/blob/main/Notebooks/4_Tutorial_funcoin.ipynb

Extra slides (leftout but feel free to ask)

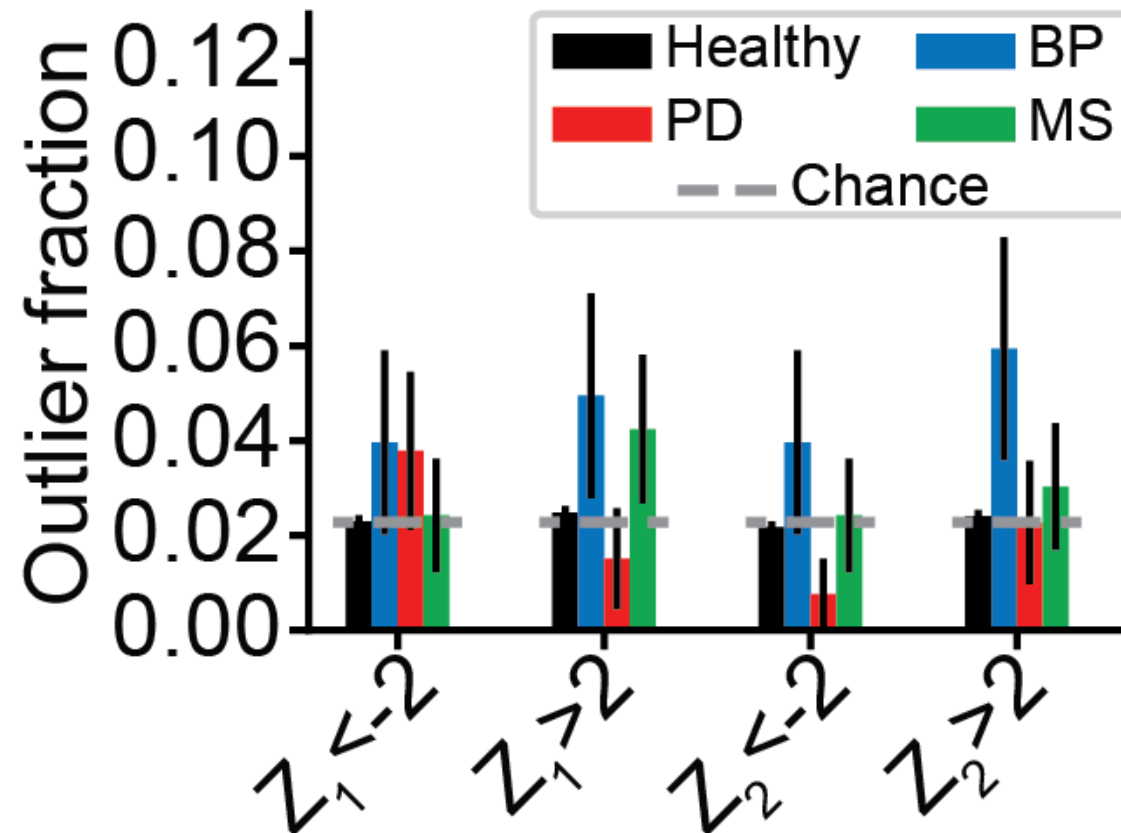
Covariate-assisted principal regression

- For each subject, i , let $y_{it} \in \mathbb{R}^p$, $t = 1, \dots, T_i$ be independent, identically distributed multivariate, normal random variables with mean zero and variance Σ_i
- Assume that there exists a vector, $\gamma \in \mathbb{R}^p$, such that $z_{it} = \gamma^T y_{it}$ satisfies the following multiplicative heteroscedasticity model:

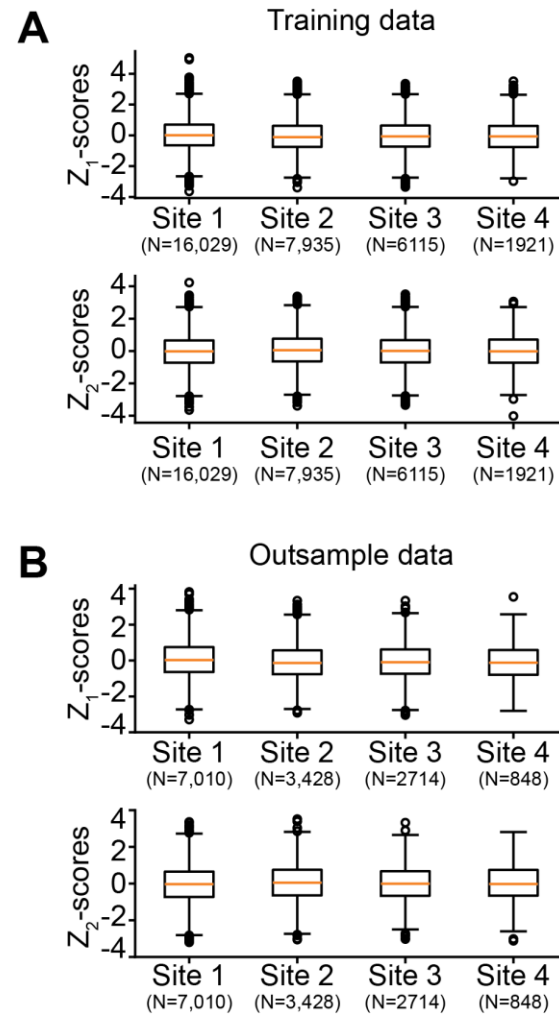
$$\log(\text{Var}(z_{it})) = \log(\boldsymbol{\gamma}^T \boldsymbol{\Sigma}_i \boldsymbol{\gamma}) = \beta_0 + \mathbf{X}_i^T \boldsymbol{\beta}$$

where $\beta_0 \in \mathbb{R}$ and $\boldsymbol{\beta} \in \mathbb{R}^{q-1}$ model coefficients.

Disease prediction – elementwise model



Taking scanning site into account

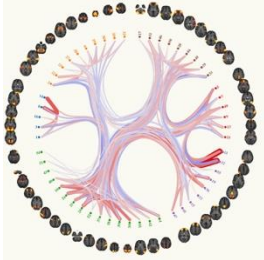


Benefits of normative modelling

Brain function biomarkers of disease/disorder

- Challenges:

- Complex nature



- Heterogenous symptoms



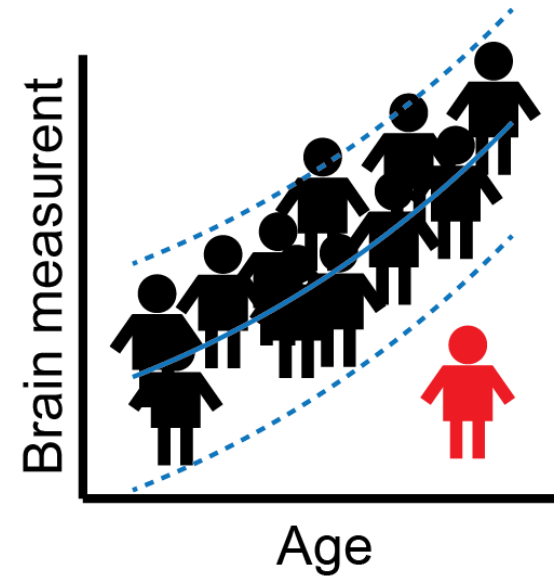
- Described on a spectrum



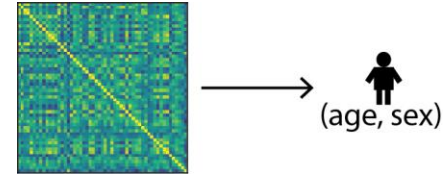
- Hard to recruit cases

- Benefits of normative models:

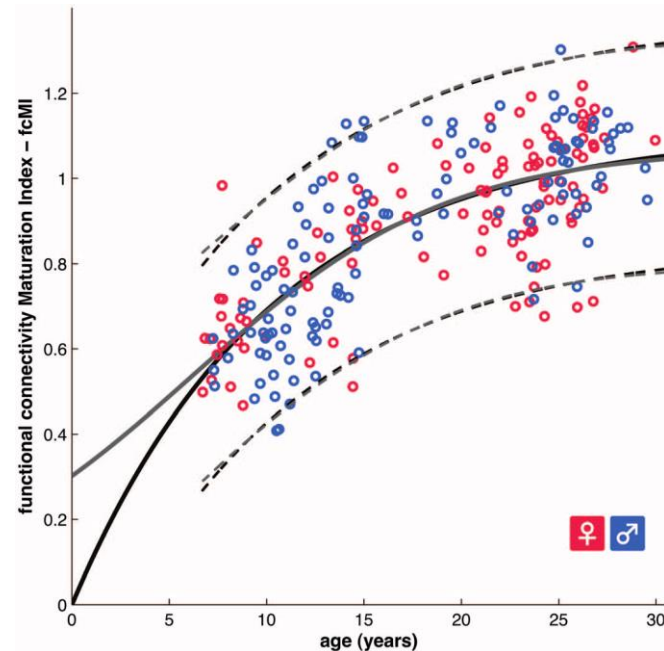
- Subject-level inference
- Inference is per definition on a spectrum
- Does not require a large number of cases



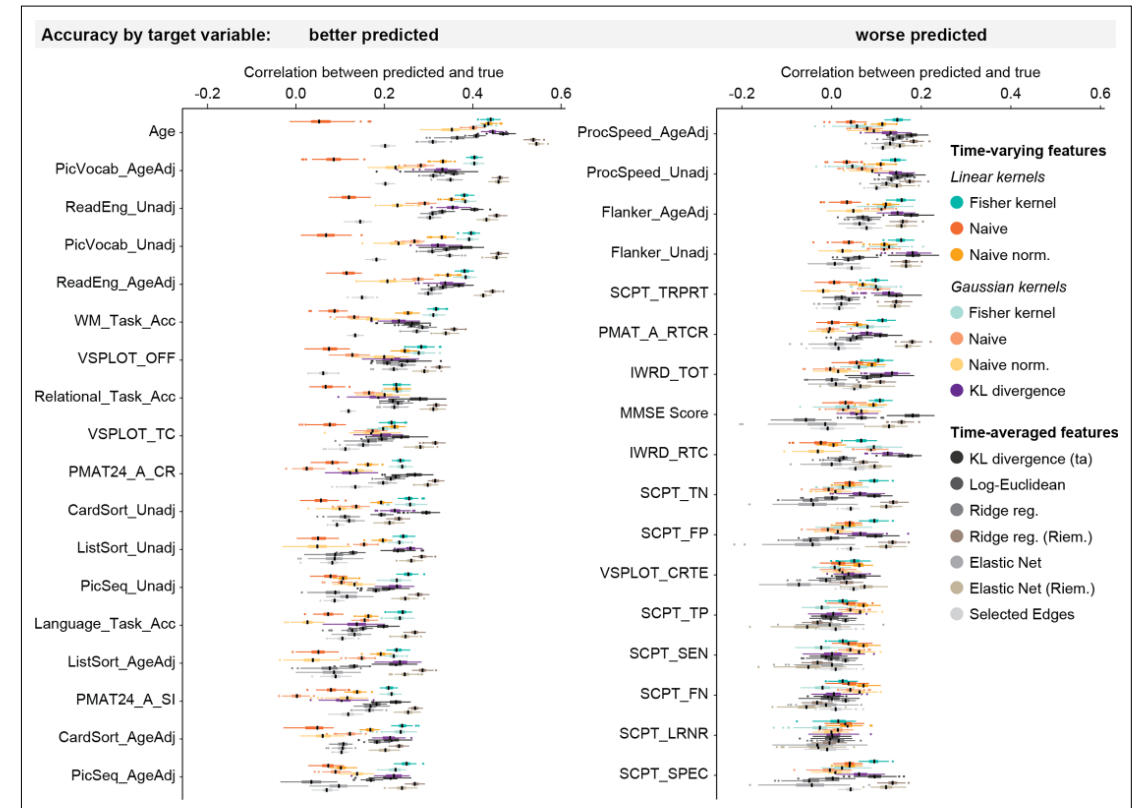
Prediction from FC



- Age and other traits can be predicted from rsfMRI FC, e.g. with
 - Linear models
 - SVMs (and other ML)
 - HMM



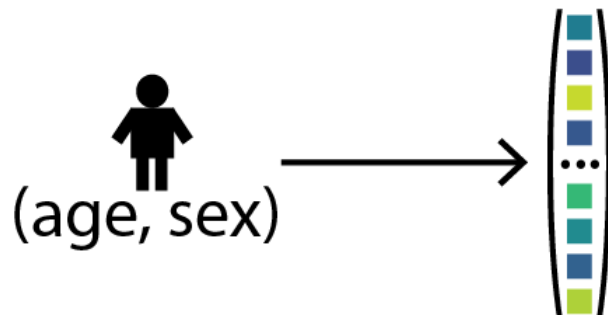
From: Dosenbach, N.U. et al. (2010). Prediction of individual brain maturity using fMRI. Science.



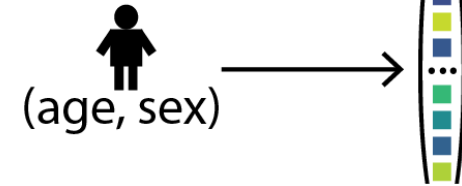
From: Ahrends, C. et al. (2025). Predicting individual traits from models of brain dynamics accurately and reliably using the Fisher kernel. eLife.

Previous normative models in rsfMRI FC

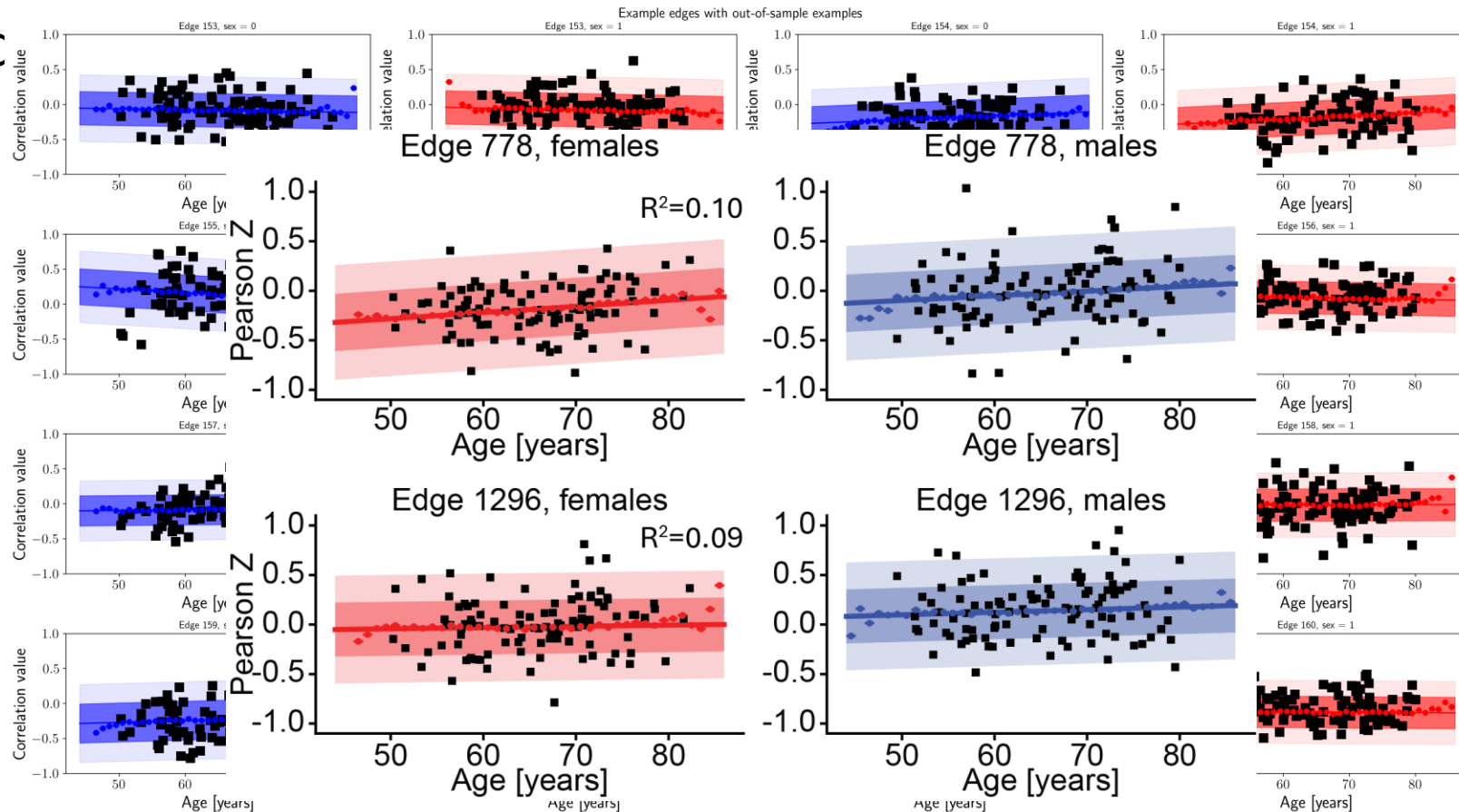
- Normative models of FC have predicted **individual connections**
 - Gaussian-Gamma mixed models (Looden et al, *Molecular Autism*, 2022)
 - Warped Bayesian Linear Regression (e.g. Fraza et al, *Neuroimage*, 2021)
 - Gaussian Processes (e.g. Marquand et al, *Biological Psychiatry*, 2016)
- Good overview in: Marquand et al, *Molecular Psychiatry*, 2019



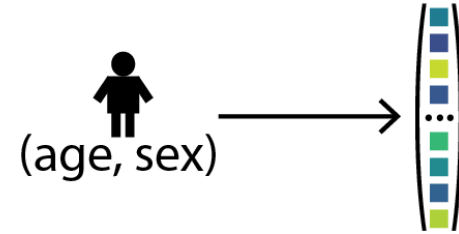
Elementwise FC prediction



- Predicting each correlation value (Fisher z) from sex and age
- Best ec

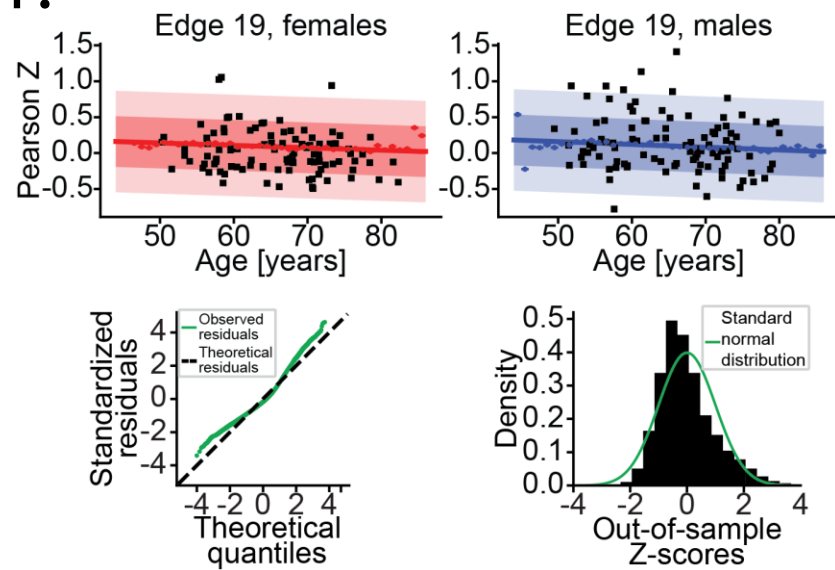


Problems in elementwise FC prediction

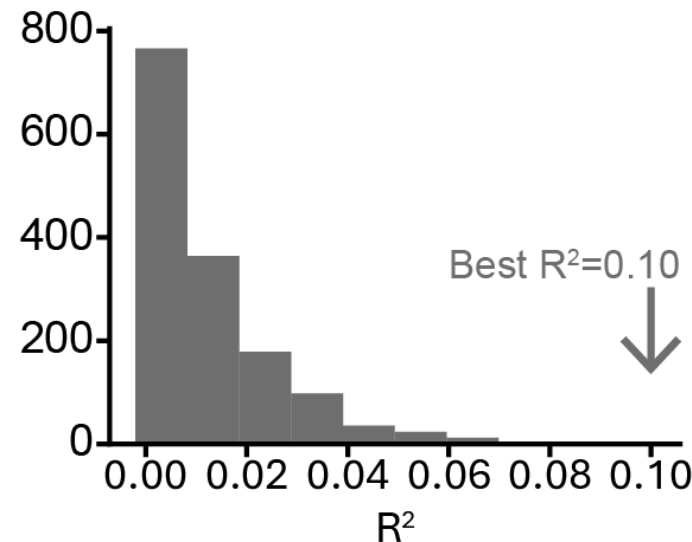


1. Massive amount of models to validate
2. Each element holds little information about sex and age
3. Massive hypothesis testing
4. Not predicting valid FC matrices

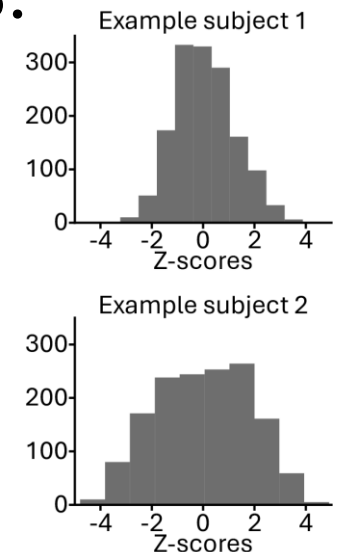
1:



2:



3:



Z-score distribution

- The out-of-sample Z-scores from healthy subjects follow a standard normal distribution

