Normative modelling: the what, when and why

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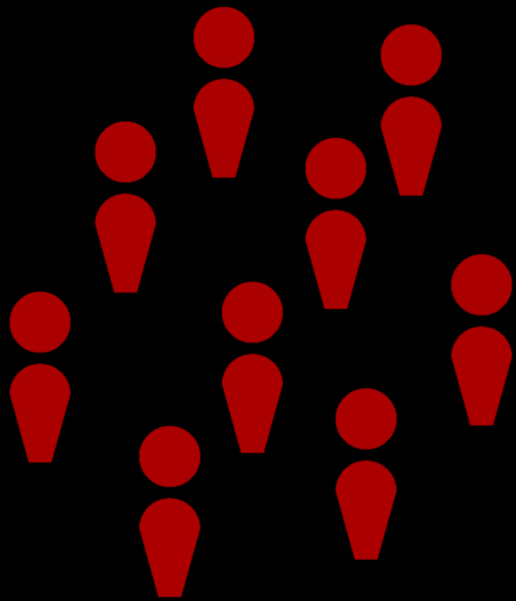
OUTLINE

1. Short and conceptual introduction to normative modelling
2. How to train your own normative models
3. How to use our pretrained models
4. Methodological developments
5. Tutorial (Jupyter notebooks)

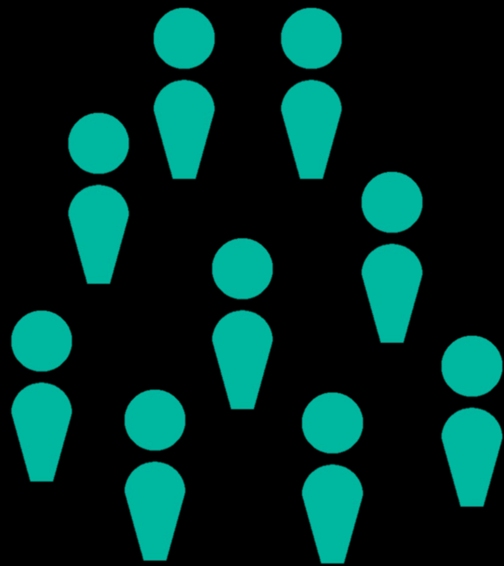
Resources:
- PCN Toolkit: https://pcntoolkit.readthedocs.io/en/latest/
- PCN Portal: https://pcnportal.dccn.nl/
- Tutorials and Repository for this talk: https://github.com/likeajumprope/Tutorial_normative_modelling/blob/master/README.md
- Pre-fitted models: https://github.com/predictive-clinical-neuroscience/braincharts
- More tutorials: https://github.com/predictive-clinical-neuroscience/PCNtoolkit-demo

THE SHORTCOMINGS OF CLASSICAL STATISTICS

CASE CONTROL

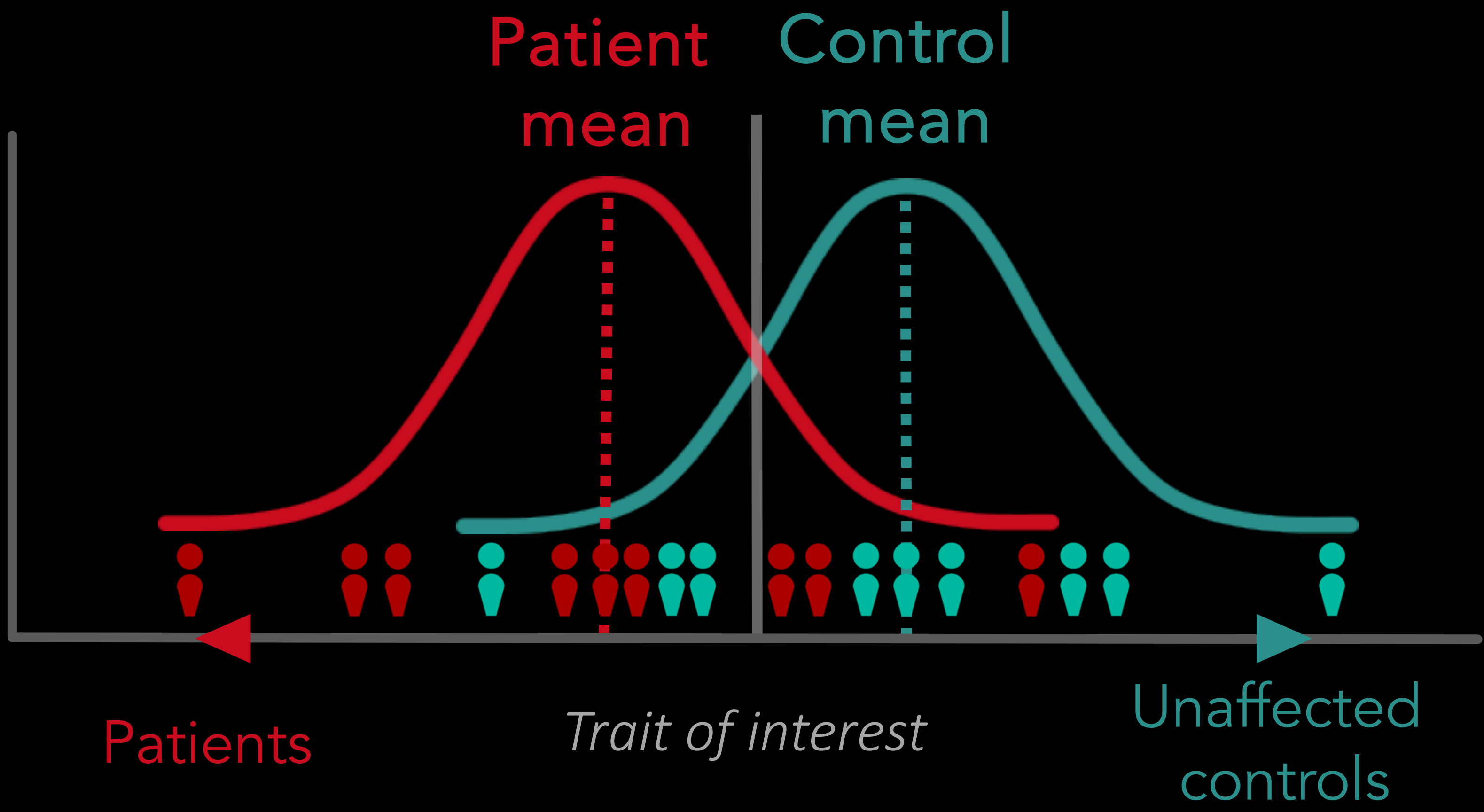


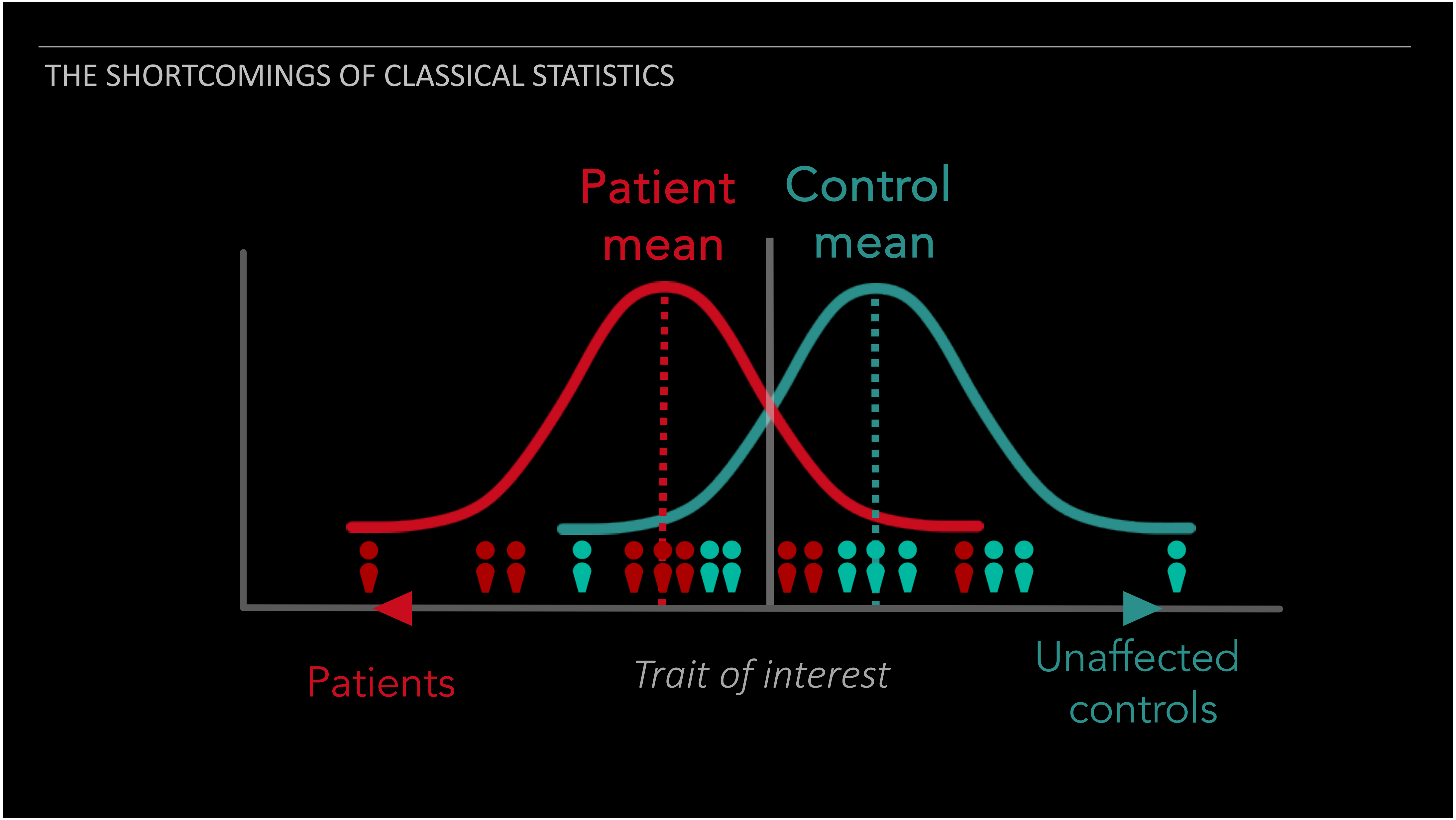
Patients



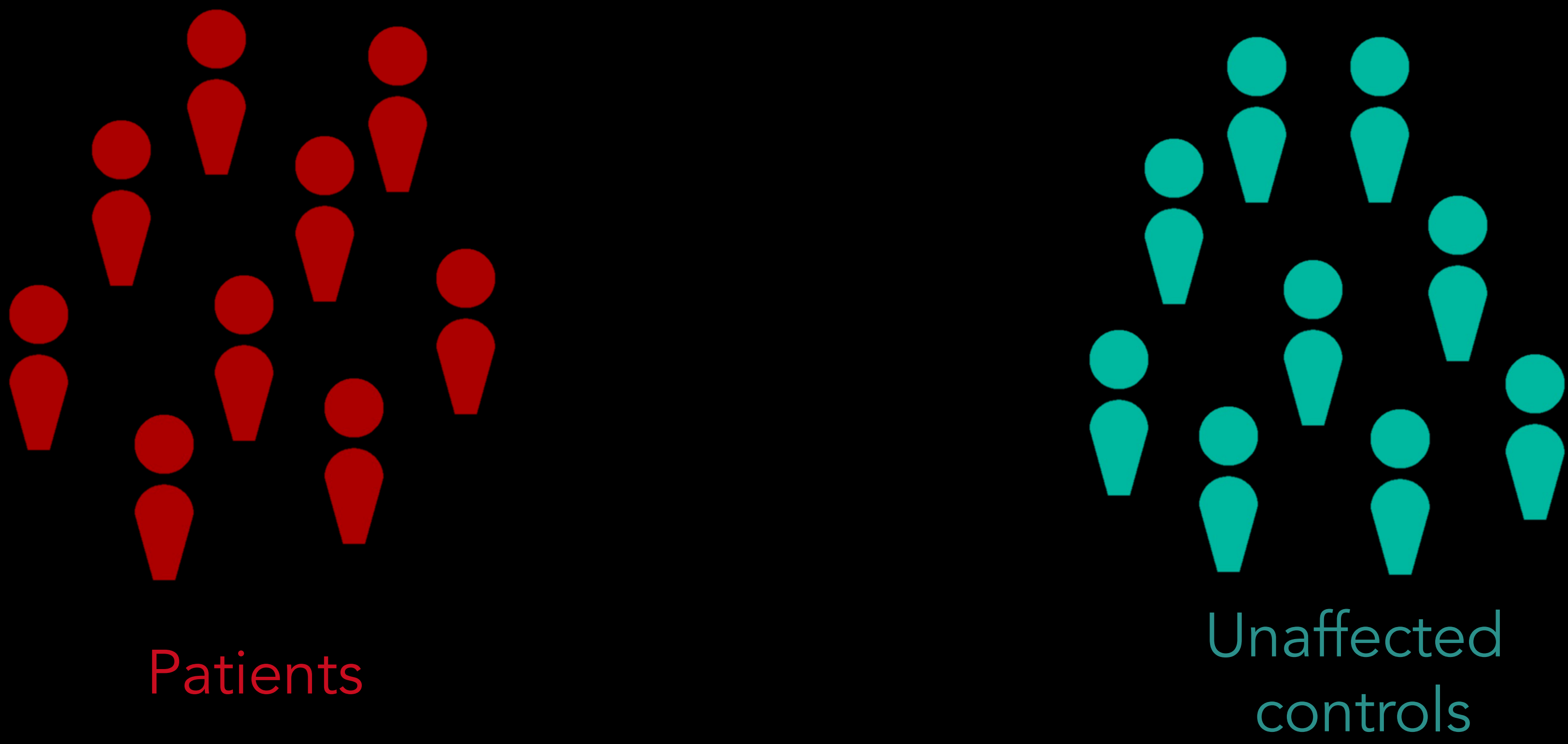
Unaffected controls

THE SHORTCOMINGS OF CLASSICAL STATISTICS

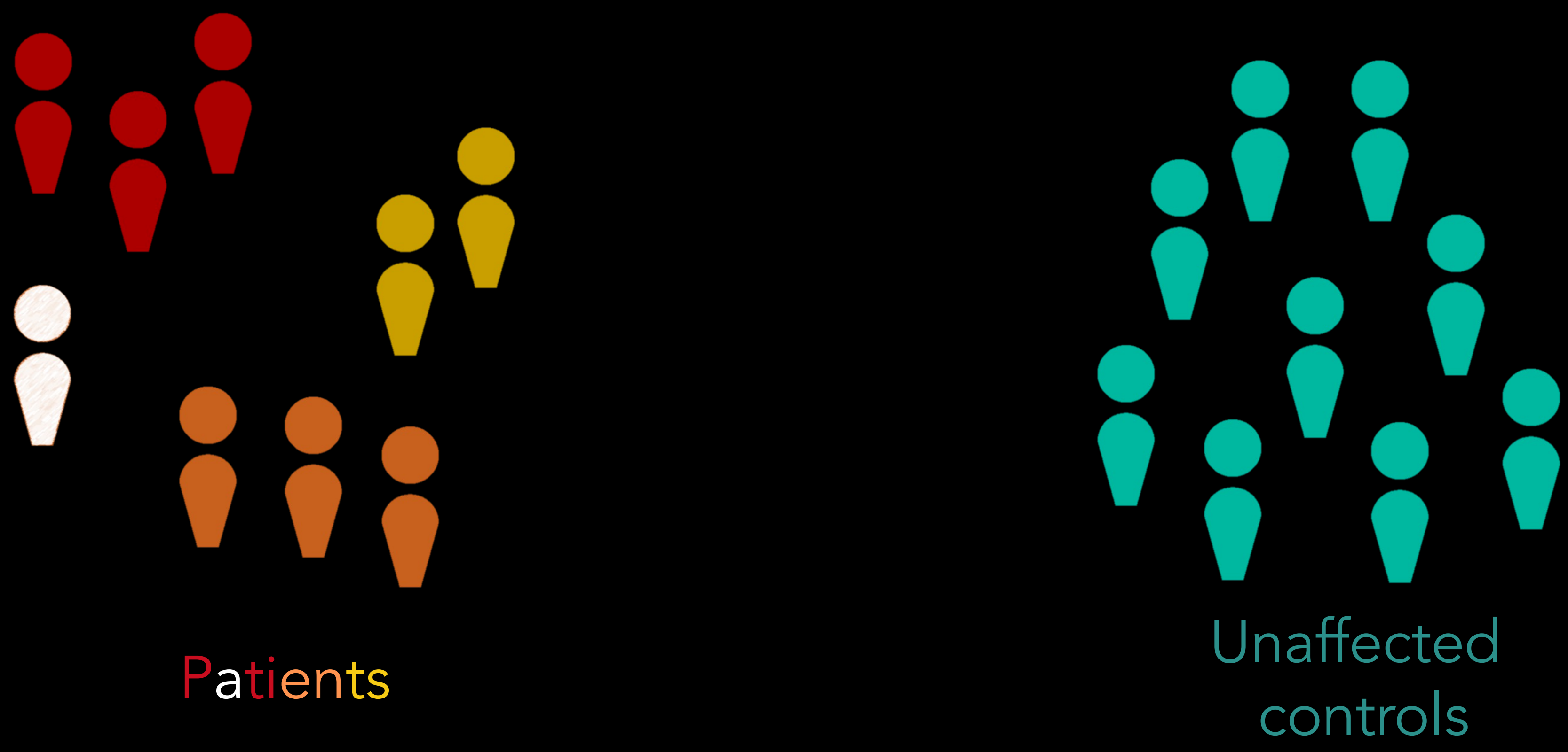



THE SHORTCOMINGS OF CLASSICAL STATISTICS
Patient mean
Control mean
Patients
Trait of interest
Unaffected controls

ON HETEROGENEITY

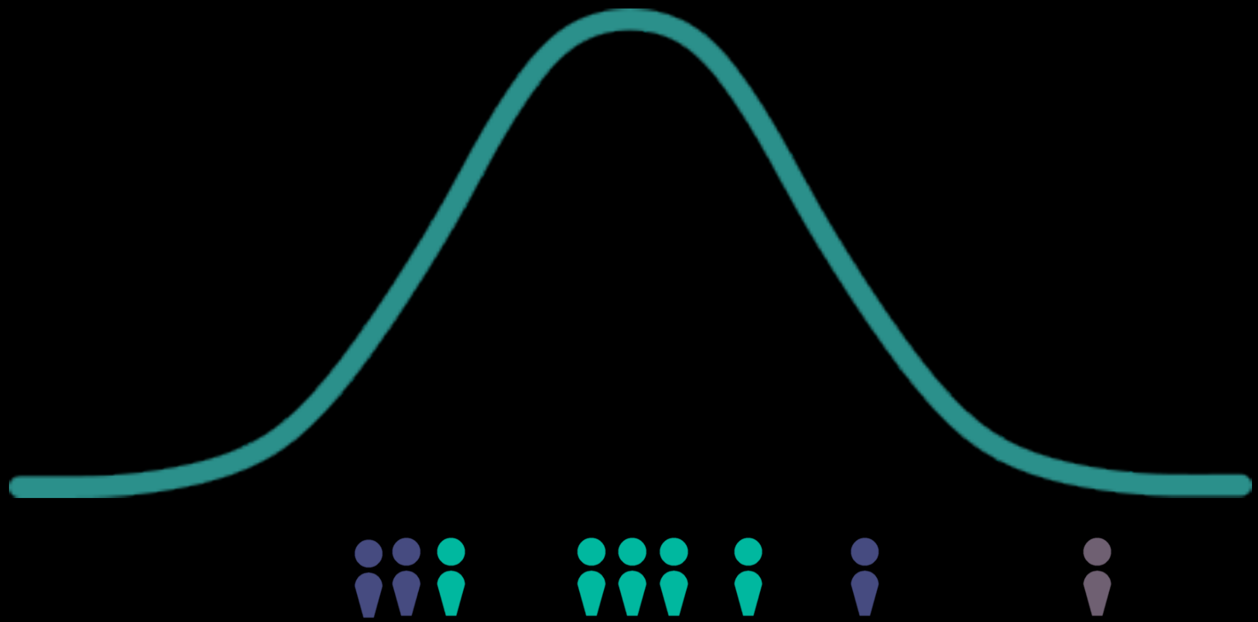


ON HETEROGENEITY

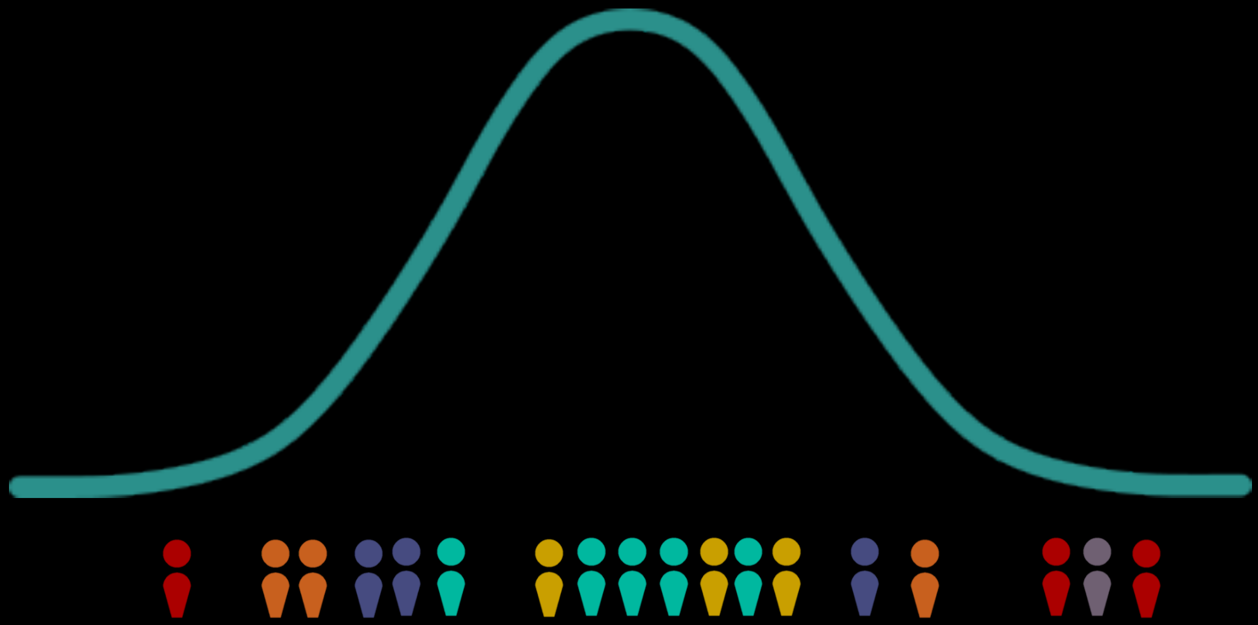


ON HETEROGENEITY

NORMATIVE MODELLING

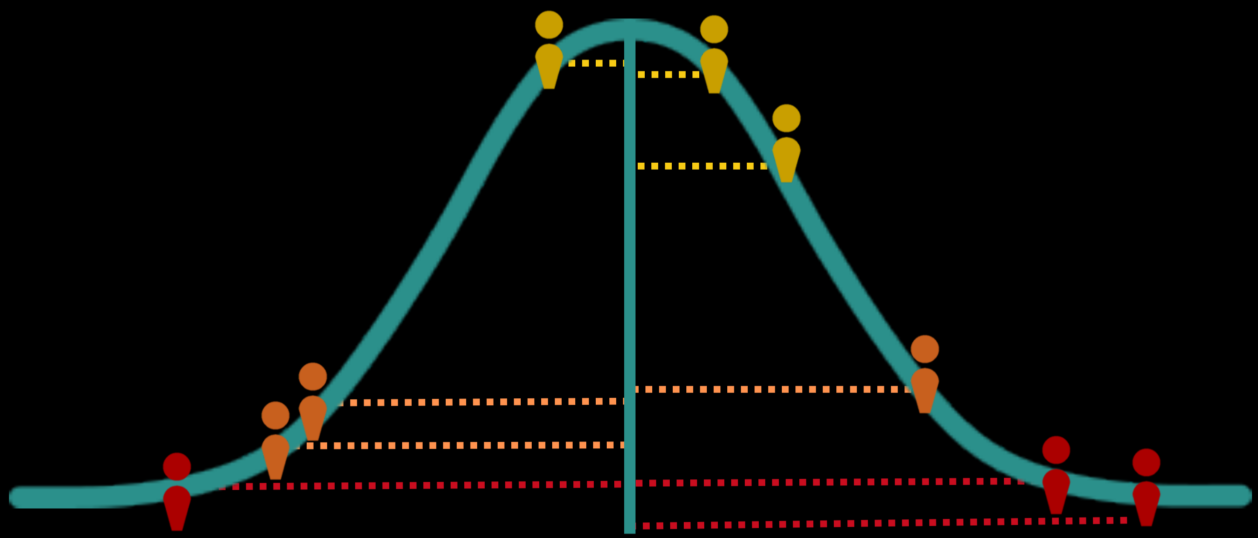


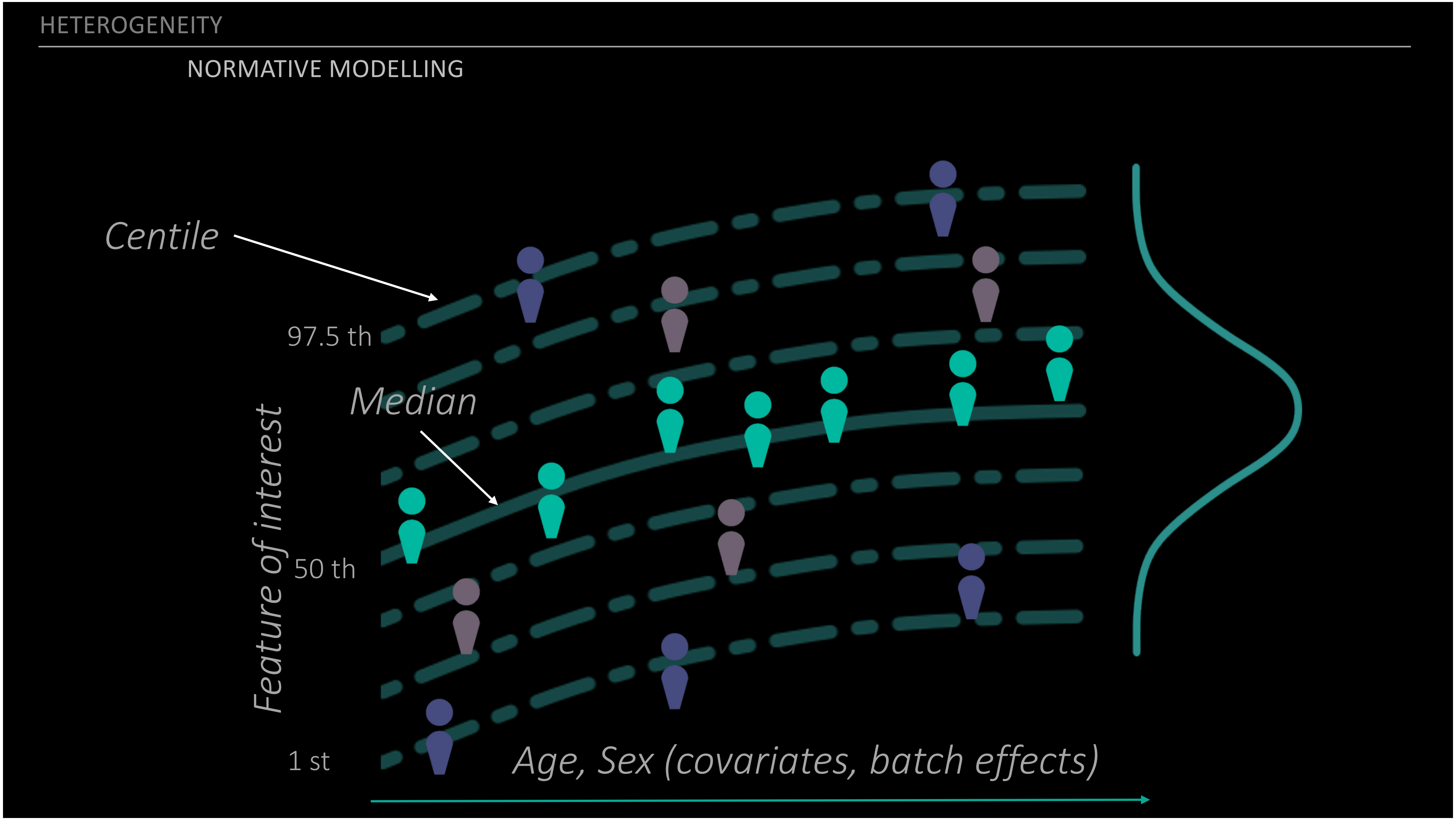
NORMATIVE MODELLING



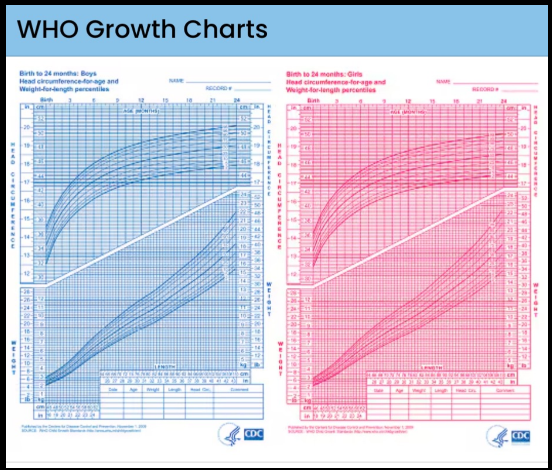
HETEROGENEITY

NORMATIVE MODELLING



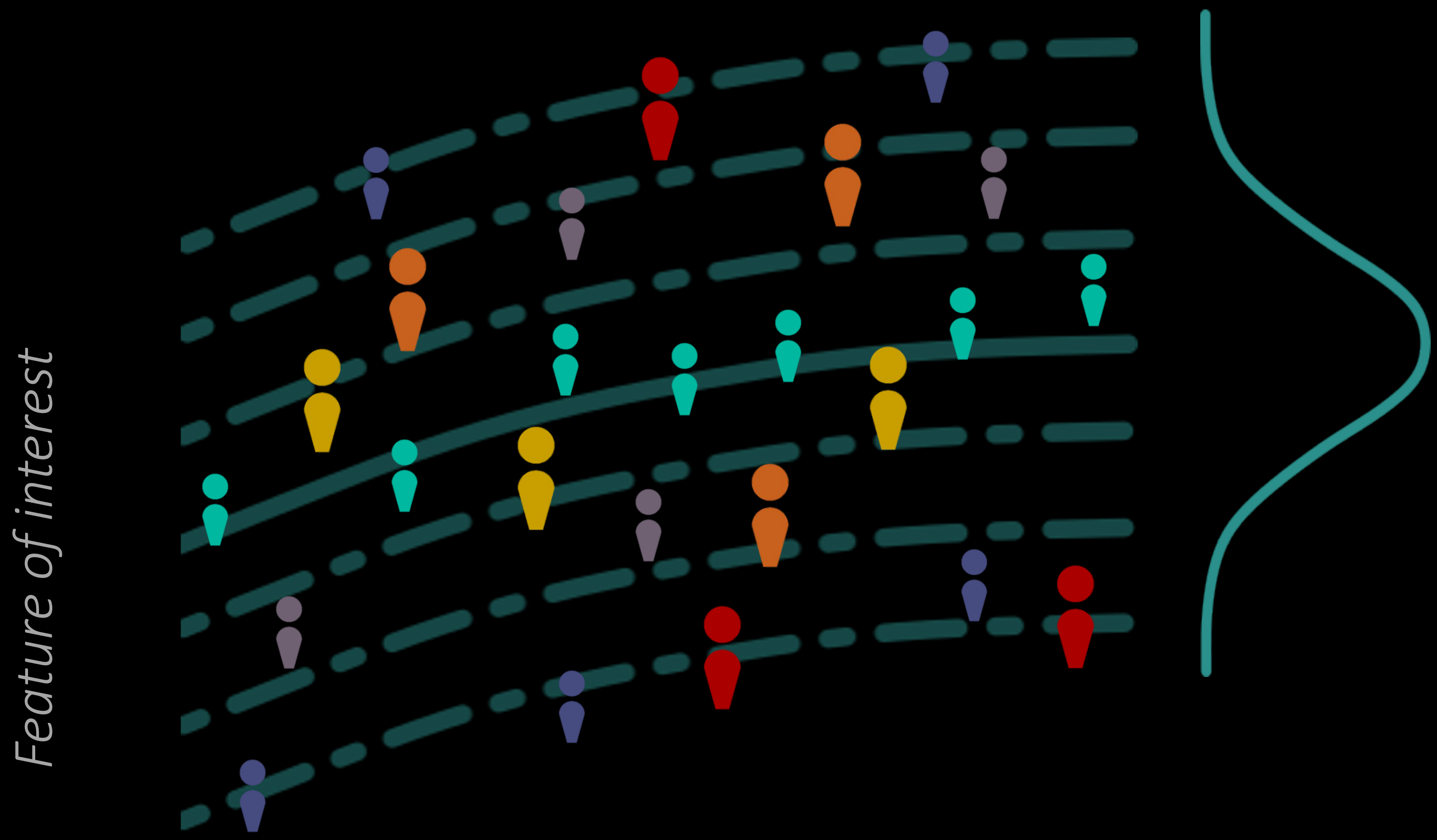

HETEROGENEITY
NORMATIVE MODELLING
Centile
97.5 th
Median
50 th
Feature of interest
1 st
Age, Sex (covariates, batch effects)

NORMATIVE MODELLING



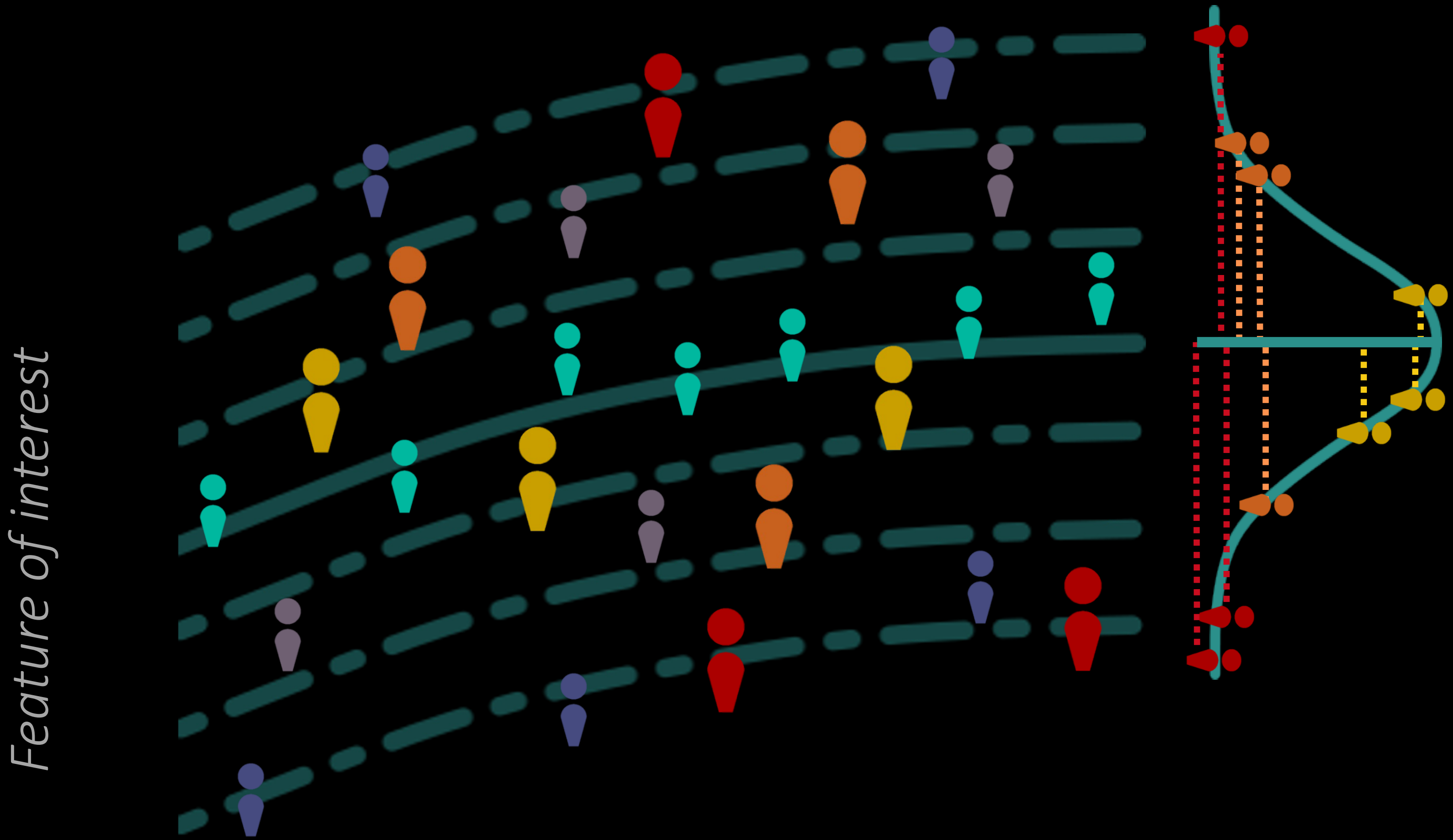
HETEROGENEITY

NORMATIVE MODELLING



HETEROGENEITY

NORMATIVE MODELLING



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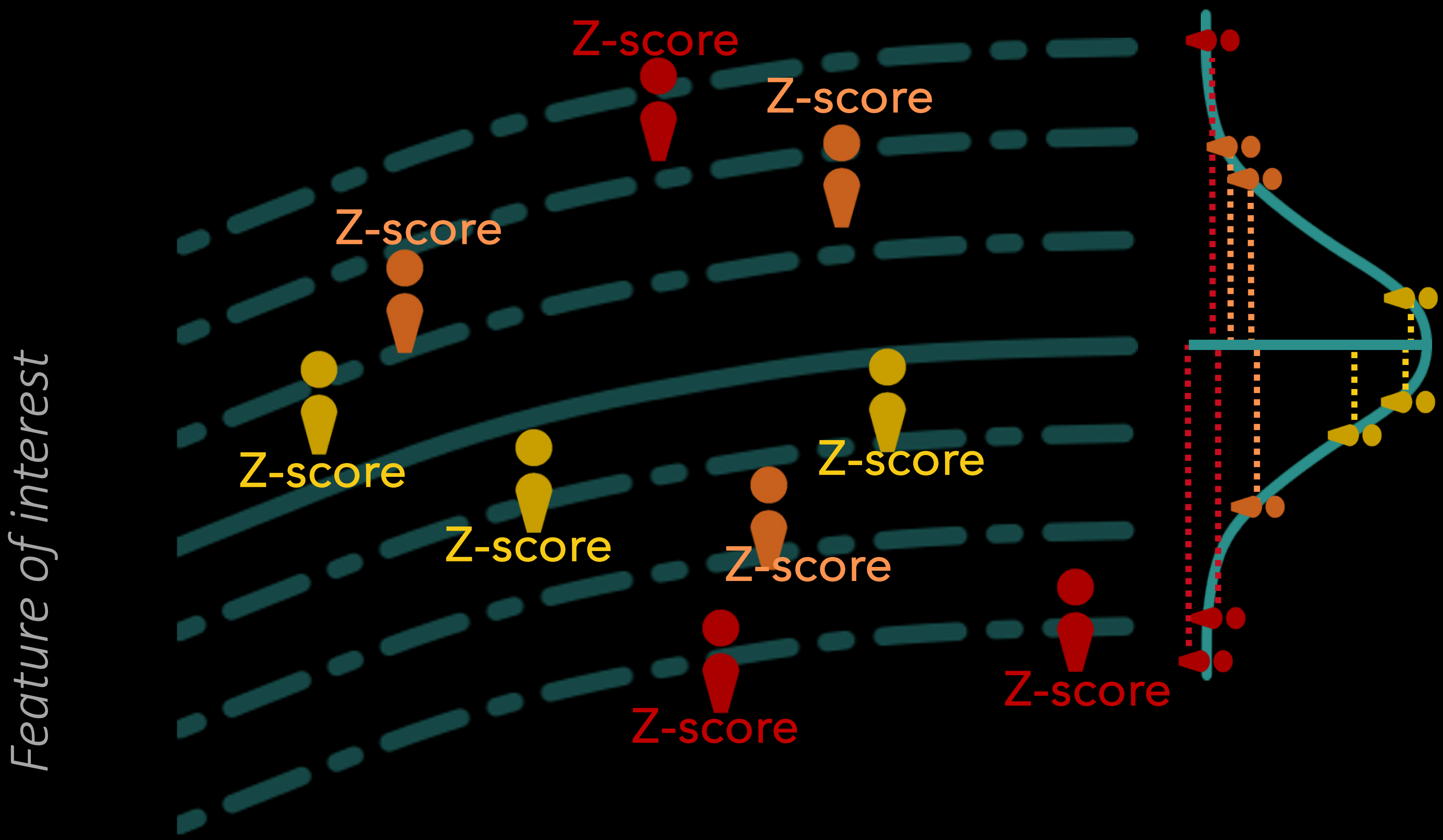


APPLICATIONS & DEVELOPMENT

Training your own models

Applying pre-trained models

Methodology

APPLICATIONS & DEVELOPMENT

Training your own models

Applying pre-trained models

Methodology

APPLICATIONS & DEVELOPMENT

Y

Brain
(BOLD signal in voxel, ROI)

APPLICATIONS & DEVELOPMENT

$$Y = f\,(X,\ \theta) + \varepsilon$$

Brain (BOLD signal in voxel, ROI)

Covariates (age, sex, task parameters)

Model parameters

Residuals

APPLICATIONS & DEVELOPMENT

$$Y = f\,(X,\ \theta) + \varepsilon$$

Brain
(BOLD signal in voxel, ROI)

Covariates
(age, sex, task parameters)

Model parameters

Residuals

Imaging measures →

Subjects ↑

Responses (Y)

Predictors →

Subjects ↑

Covariates (X)

- Training and evaluating the normative model on local dataset

$$Y = f\,(X, \theta) + \varepsilon$$

Cortical thickness/ surface area — Covariates (age, sex, site) — Model parameters — Residuals

- Training and evaluating the normative model on local dataset

$$Y = f\,(X,\ \theta) + \varepsilon$$

Cortical thickness/ surface area

Covariates (age, sex, site)

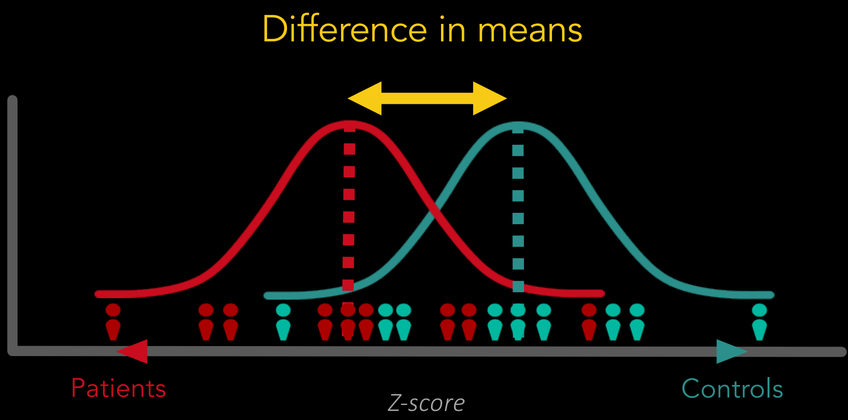
Model parameters

Residuals

$$\hat{Y}, \sigma_S, \sigma_\epsilon = f\,(X, \theta) + \varepsilon$$

$$Z = \frac{\hat{Y} - Y}{\sqrt{\sigma_S + \sigma_\epsilon}}$$

APPLICATIONS: Structural Imaging



Reminiscent of case-control design, but controlling for individual variation

Charlotte Fraza et al., (2024) Reconceptualizing psychopathology as extreme deviations from a normative reference model. BioRxiv

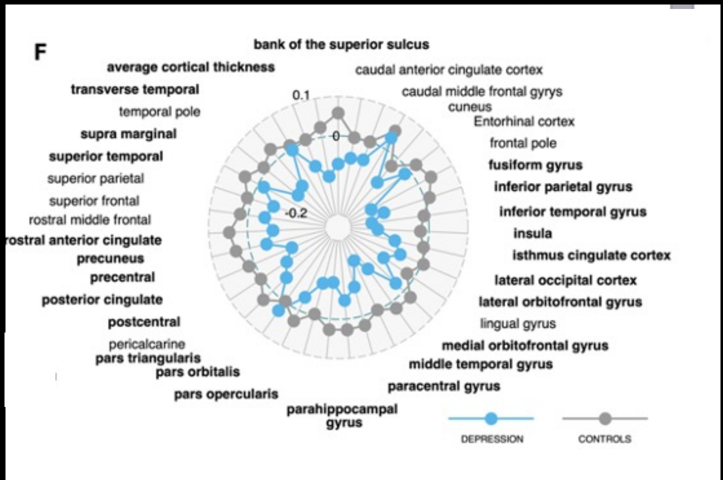
? Do patients show overlapping deviation scores in brain regions significantly different from control group ?

? Are patients more likely to lie in the tails of distribution of (cortical thickness) ?

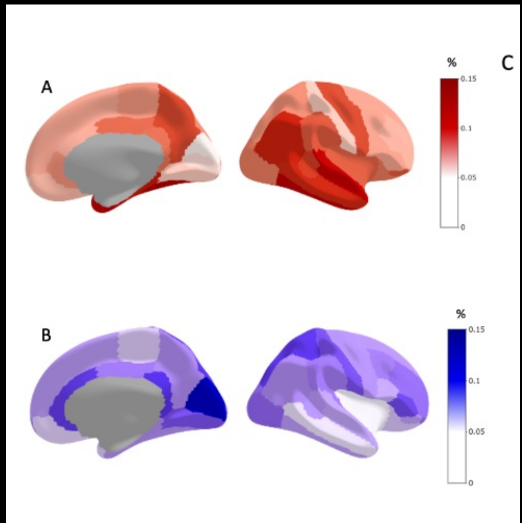
APPLICATIONS: Structural Imaging

1.

Parse heterogeneity



Extreme negative deviations



Extreme positive deviations

2.

Brain-behavior mappings

- earlier onset of depression
- more severe depressive symptoms
- higher BMI

- being remitted
- not taking antidepressants
- less severe symptoms

Bayer, J. M. M. et al. Dissecting heterogeneity in cortical thickness in major depressive disorder: a large scale normative modelling study. (2025) submitted to JAMA Network Open

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset

$$Y = f\,(X, \theta) + \varepsilon$$

Bold Signal (Y)

Covariates (X) (age, sex, Task parameters)

Model parameters (θ)

Residuals (ε)

Voxels →

Subjects ↑

Z-statistic image (Y)

Predictors →

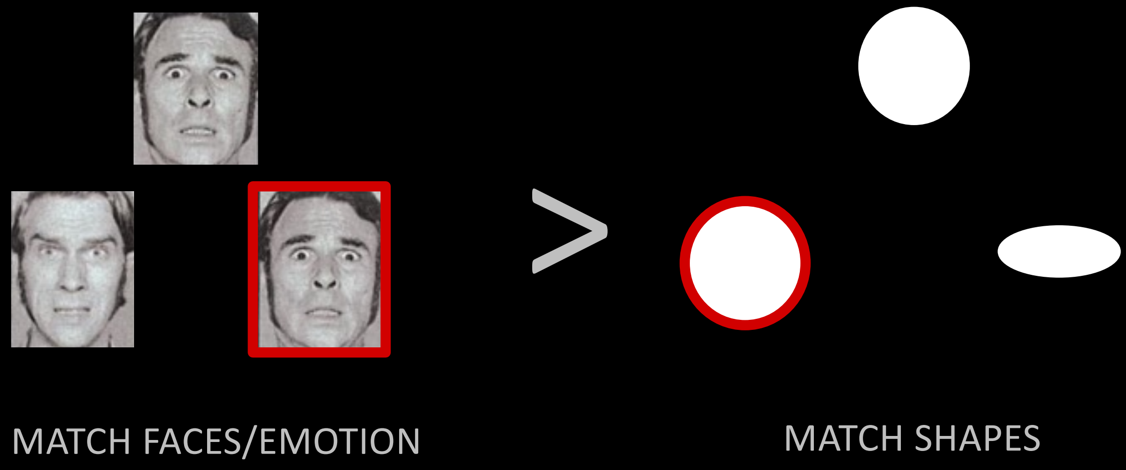
Subjects ↑

Age
Sex
Task length
# of target blocks
Instructions

Site
Scanner strength
TR
Multiband-factor
# of volumes acquired

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset



Viering et al (2021) doi: 10.1007/s00787-021-01809-3

APPLICATIONS: Functional Imaging

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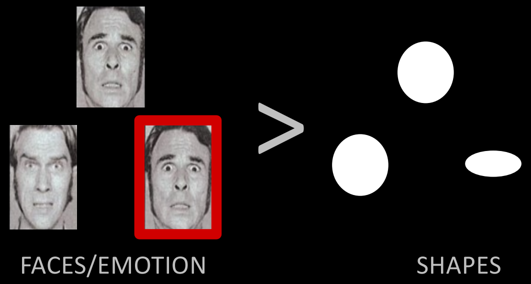

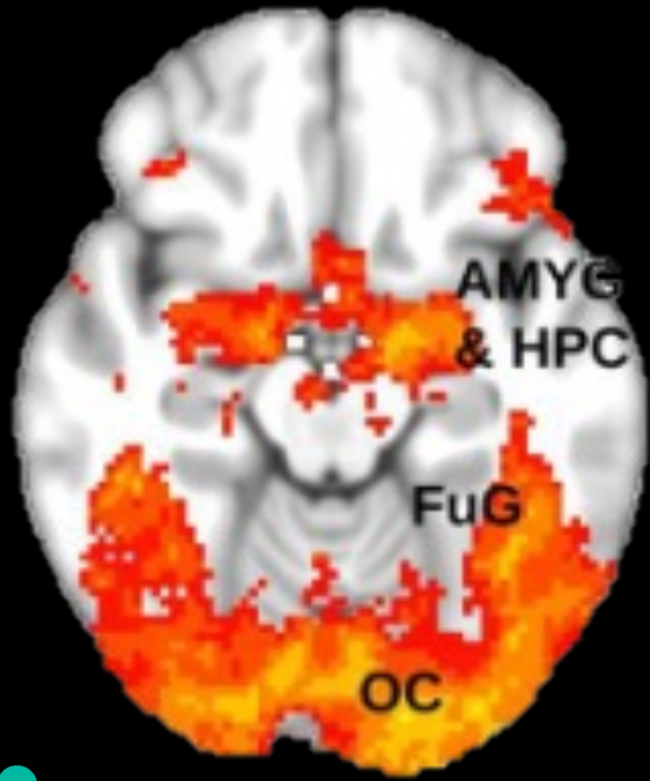

Unaffected controls

Viering et al (2021) doi: 10.1007/s00787-021-01809-3

APPLICATIONS: Functional Imaging

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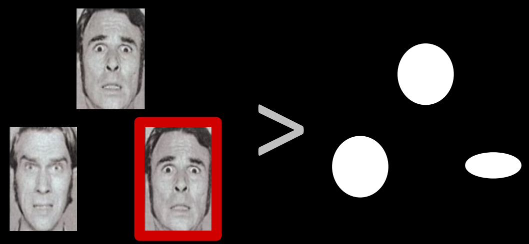
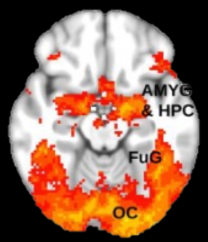
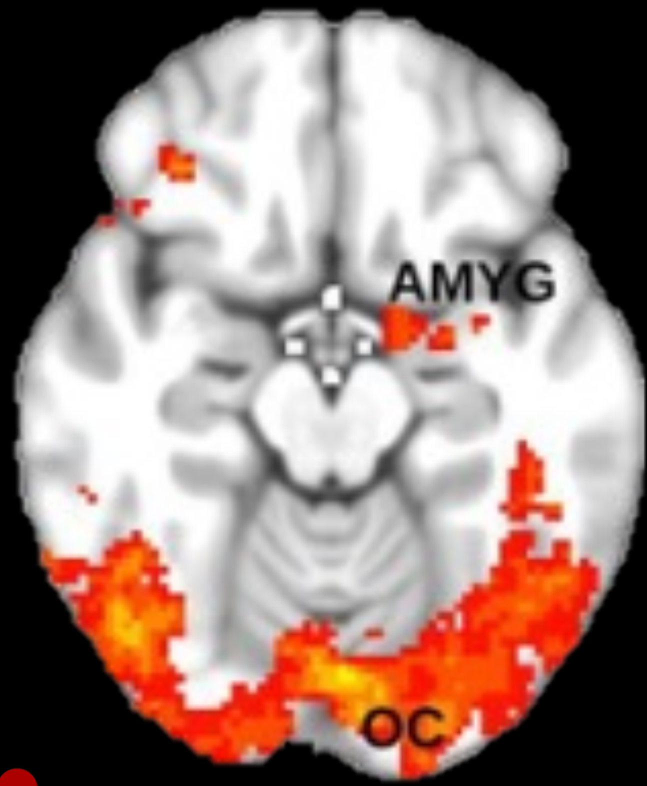


FACES/EMOTION > SHAPES



Unaffected controls

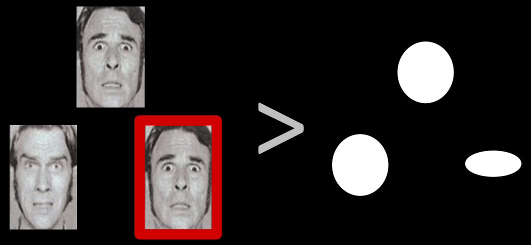


Patients

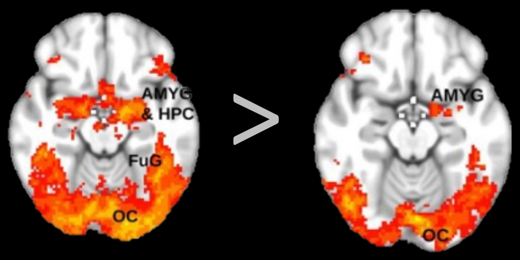
Viering et al (2021) doi: 10.1007/s00787-021-01809-3

APPLICATIONS: Functional Imaging

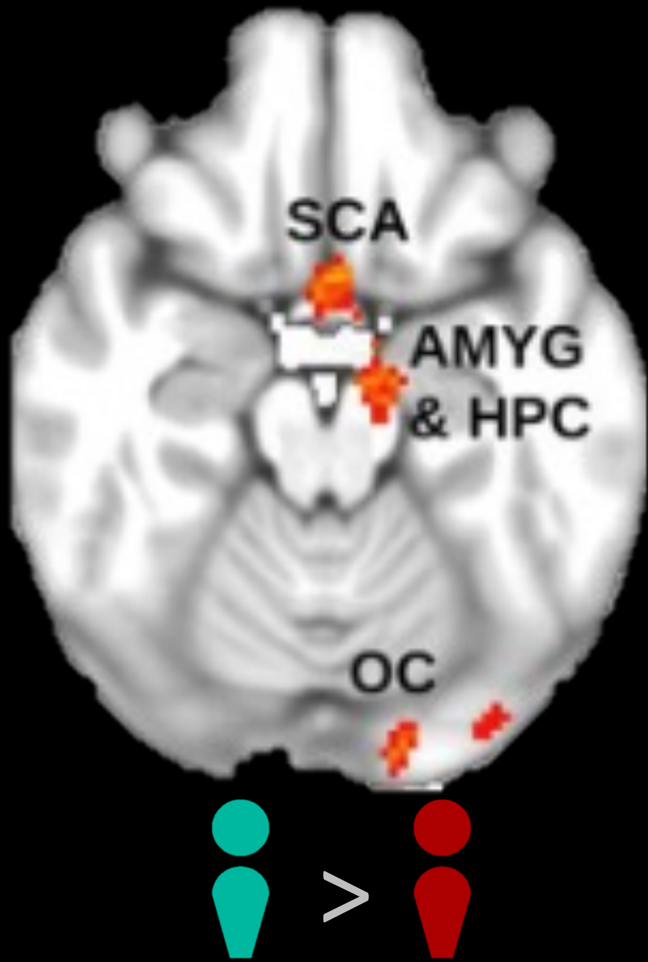
- Training and evaluating the normative model on local dataset



FACES/EMOTION SHAPES



Unaffected controls Patients



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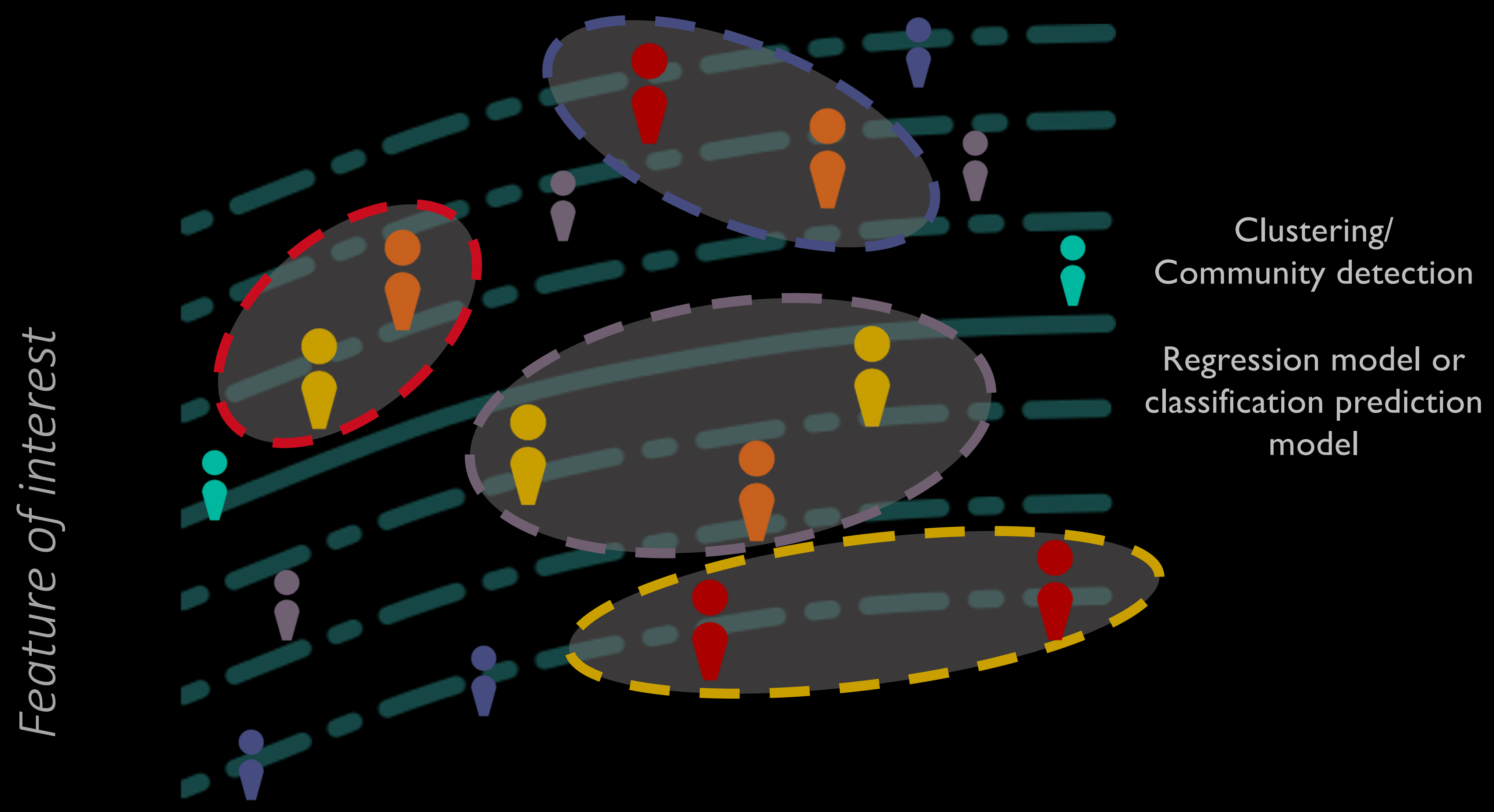
HETEROGENEITY NORMATIVE MODELLING

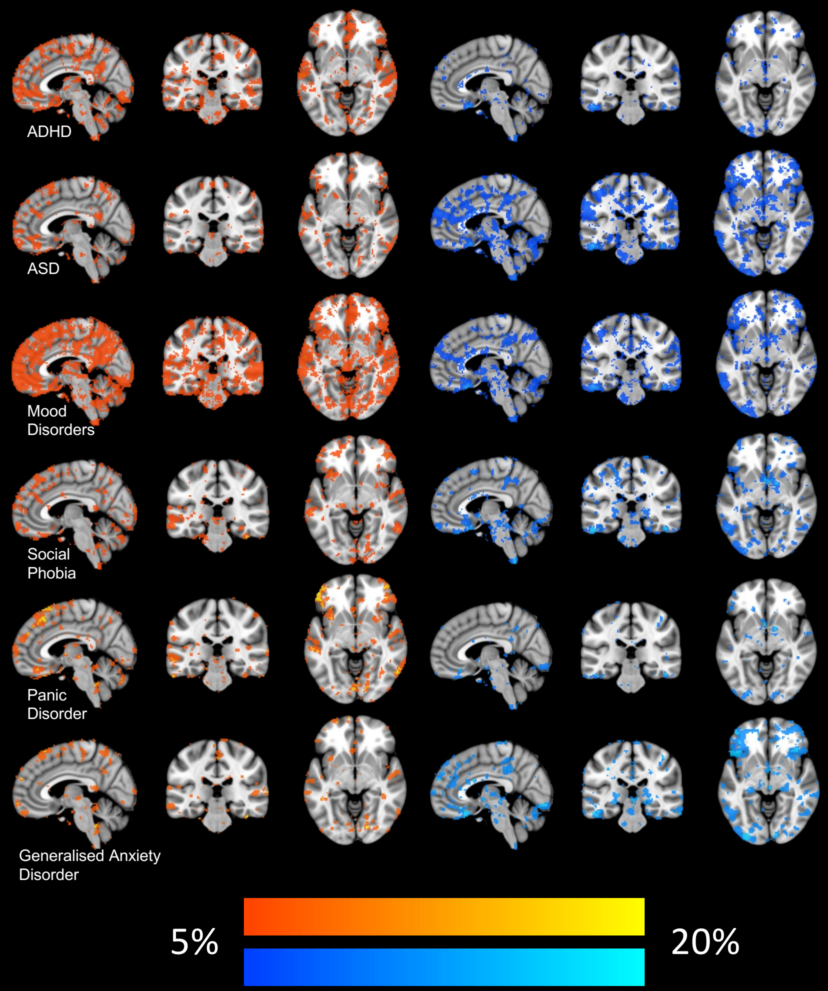
NEUROBIOLOGICAL SUBTYPING

APPLICATIONS



APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset



Hannah Savage et al., (2024) **Dissecting task-based fMRI activity using normative modelling: an application to the Emotional Face Matching Task.** *Communications Biology* 7.1: 888.

APPLICATIONS & DEVELOPMENT

Training your own models

Applying pre-trained models

Methodology

APPLICATIONS & DEVELOPMENT

Training your own models

Applying pre-trained models

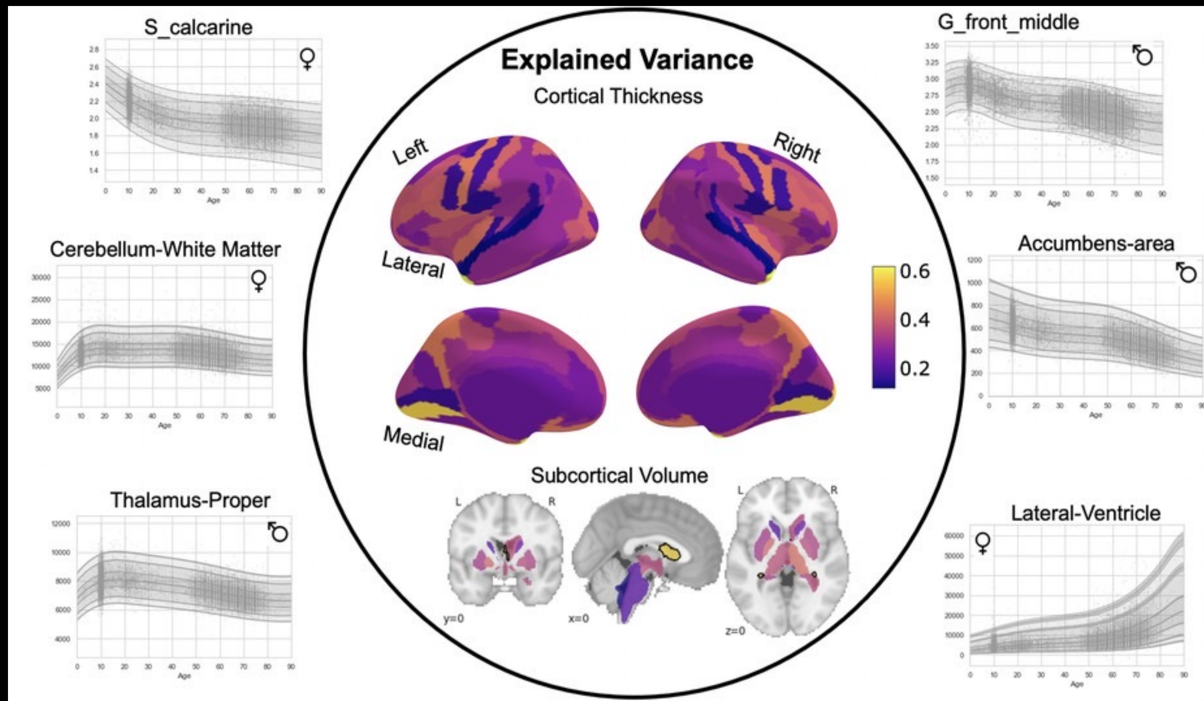
Methodology

USE PRETRAINED MODELS

- Using pre-trained models, evaluating on local datasets

- 58,836 individuals
- 82 scan sites
- aged 2–100

Normative models for cortical thickness and subcortical volumes derived from Freesurfer



$$\hat{Y}, \sigma_S, \sigma_\epsilon = f(X, \theta) + \varepsilon$$

Saige Rutherford et al., (2022) Charting brain growth and aging at high spatial precision. *eLife* 11:e72904.

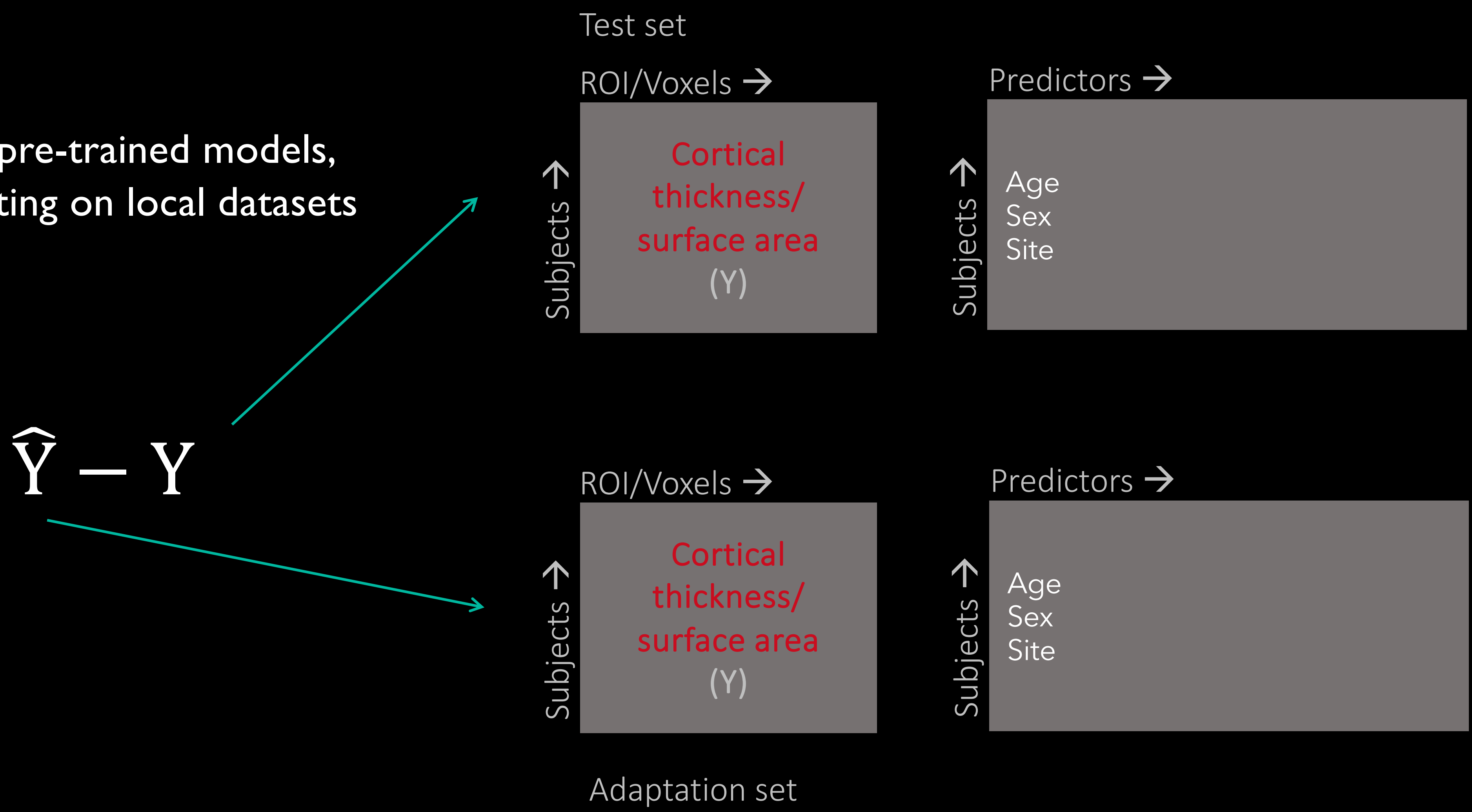
USE PRETRAINED MODELS

- Using pre-trained models, evaluating on local datasets

$$Z = \frac{\hat{Y} - Y}{\sqrt{\sigma_s + \sigma_\epsilon}}$$

USE PRETRAINED MODELS

- Using pre-trained models, evaluating on local datasets



Training your own models

Applying pre-trained models

Methodology

Training your own models

Applying pre-trained models

Methodology

METHODOLOGICAL ADVANCES

$$Y = f\,(X, \theta) + \varepsilon$$

Brain
(BOLD signal in voxel, ROI)

Covariates
(age, sex, task parameters)

Model parameters

Residuals

Gaussian process regression

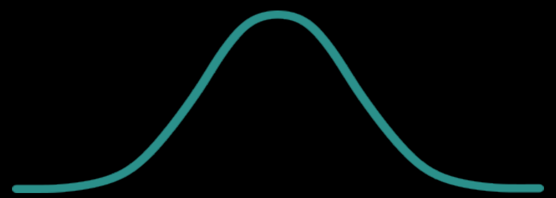
Warped Bayesian linear regression

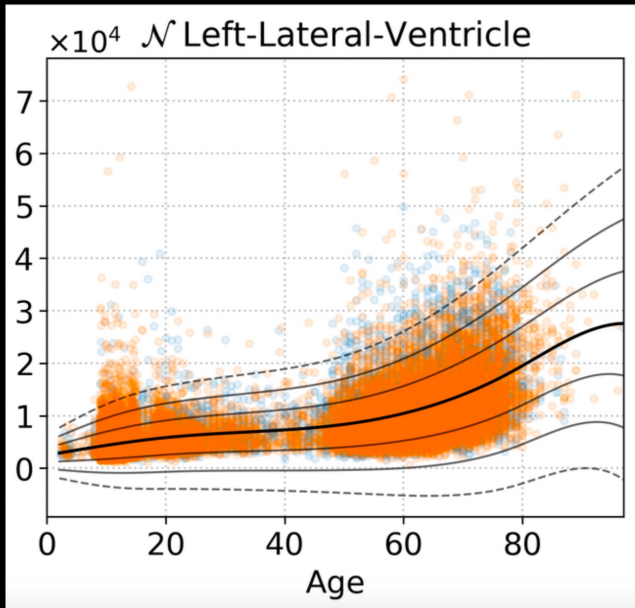
Generalized additive models of location scale and shape

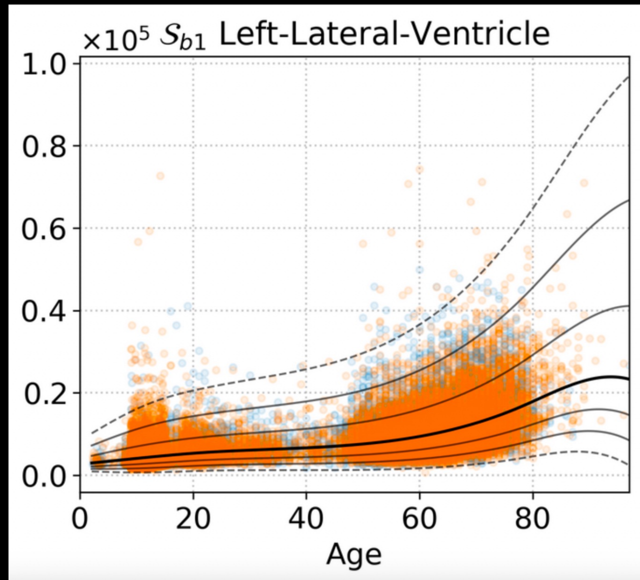
Hierarchical Bayesian regression

COMPLEX PHENOTYPES

- Hierarchical Bayesian Regression with non-gaussian SHASH likelihood allows to model skewed and heteroscedastic distributions



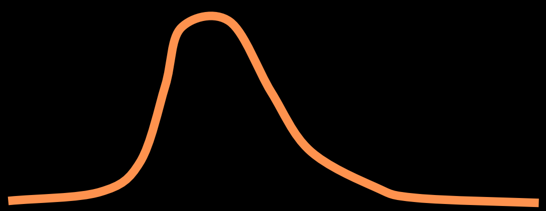


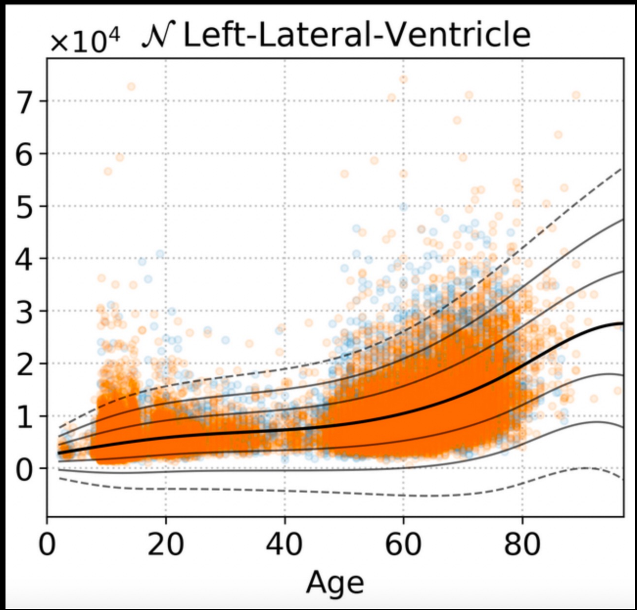


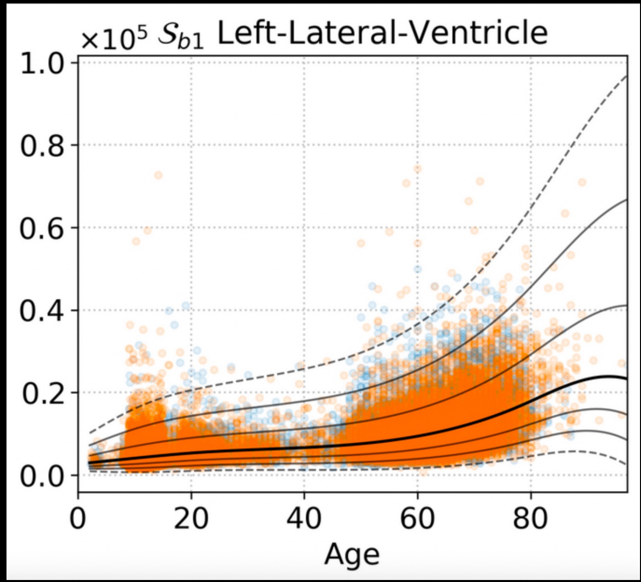
de Boer, A. A. A. Bayer, J. M. M. *et al.* (2024) **Non-Gaussian normative modelling with hierarchical Bayesian regression**. *Imaging Neuroscience* **2**, 1–36.

COMPLEX PHENOTYPES

- Hierarchical Bayesian Regression with non-gaussian SHASH likelihood allows to model skewed and heteroscedastic distributions







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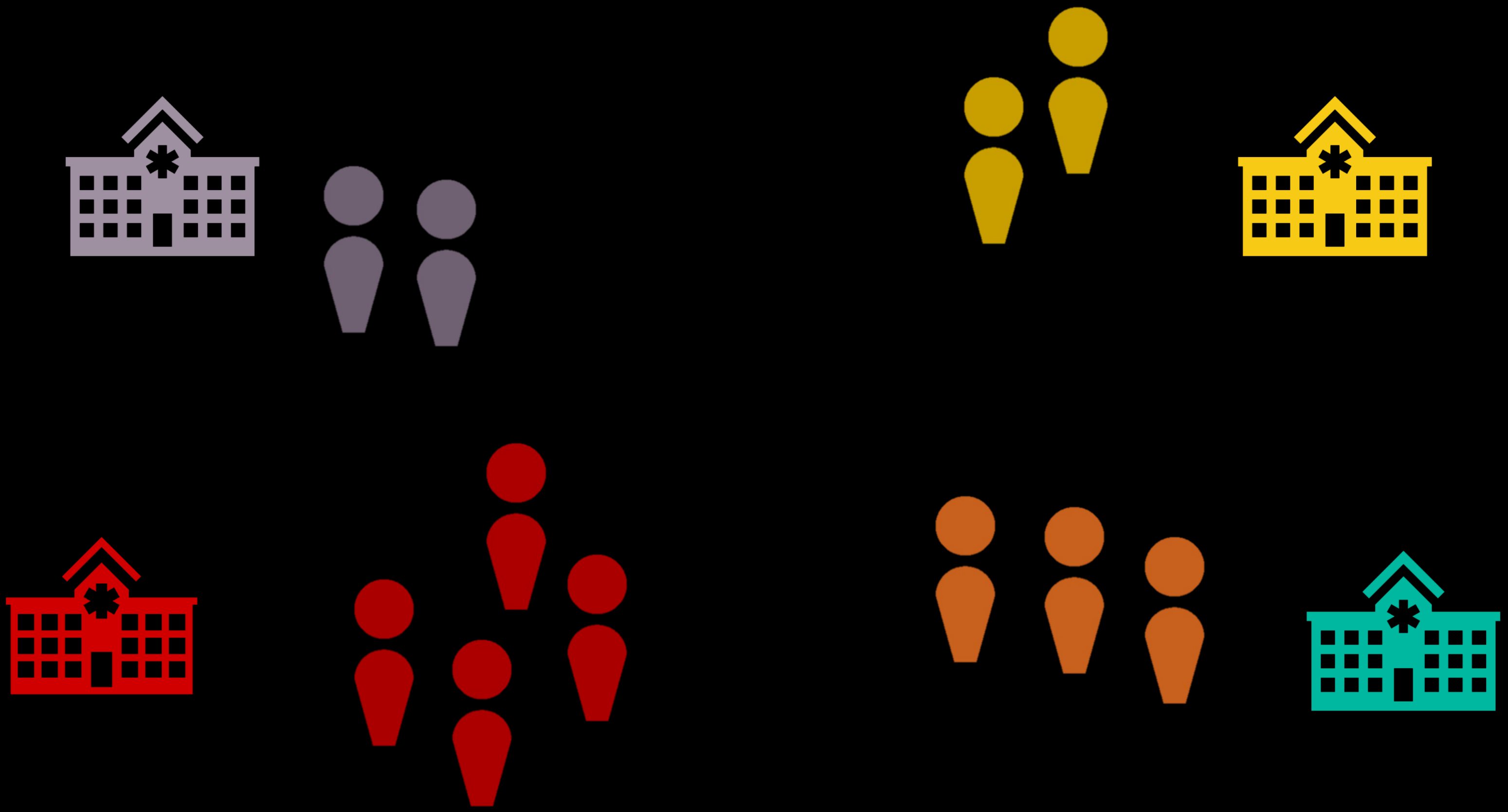
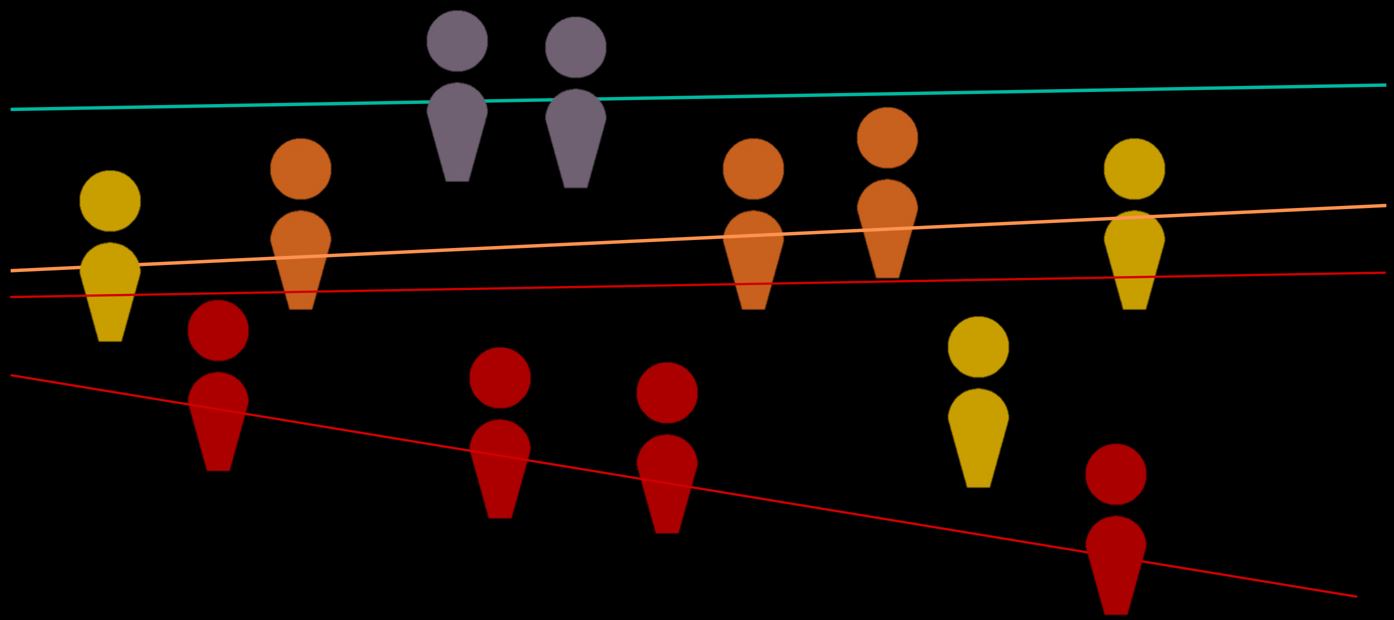
SITE EFFECTS



Bayer, J. M. M. *et al.* Site effects how-to and when: An overview of retrospective techniques to accommodate site effects in multi-site neuroimaging analyses. *Front. Neurol.* **13**, (2022).

SITE EFFECTS



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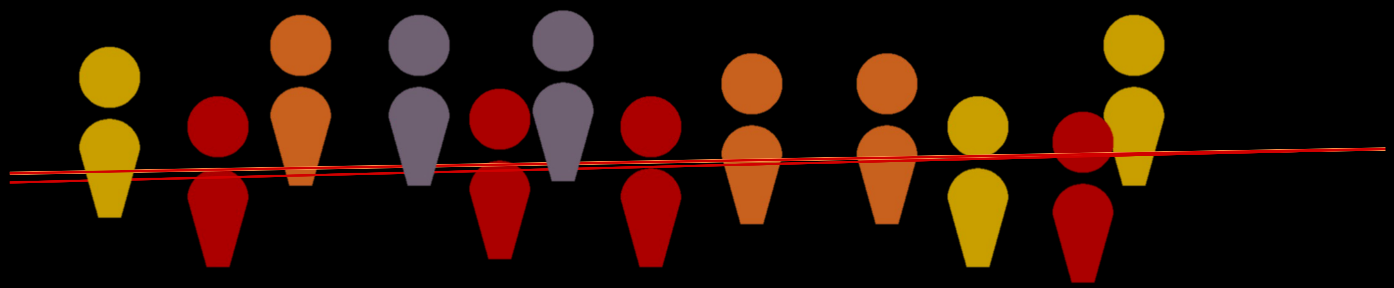
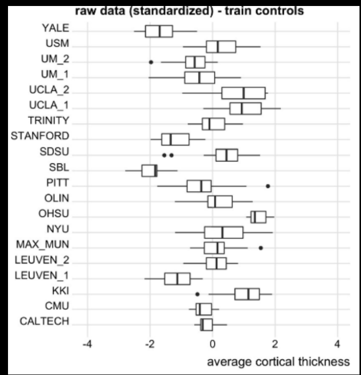
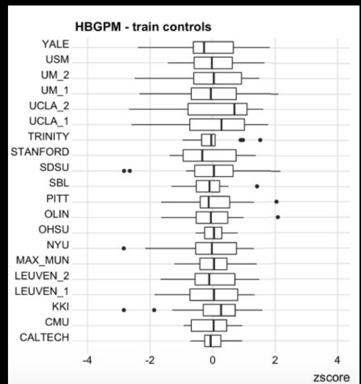


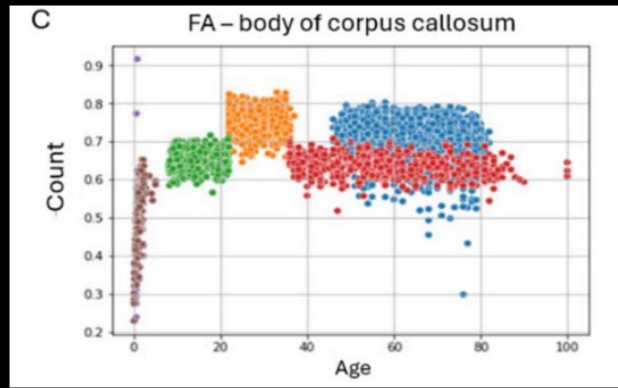
Bayer, J. M. M. *et al.* Site effects how-to and when: An overview of retrospective techniques to accommodate site effects in multi-site neuroimaging analyses. *Front. Neurol.* **13**, (2022).

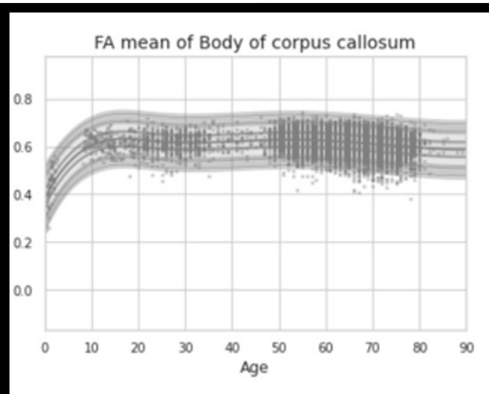
SITE EFFECTS

- Including site as batch effect into normative model
- Inverting z-scores between sites





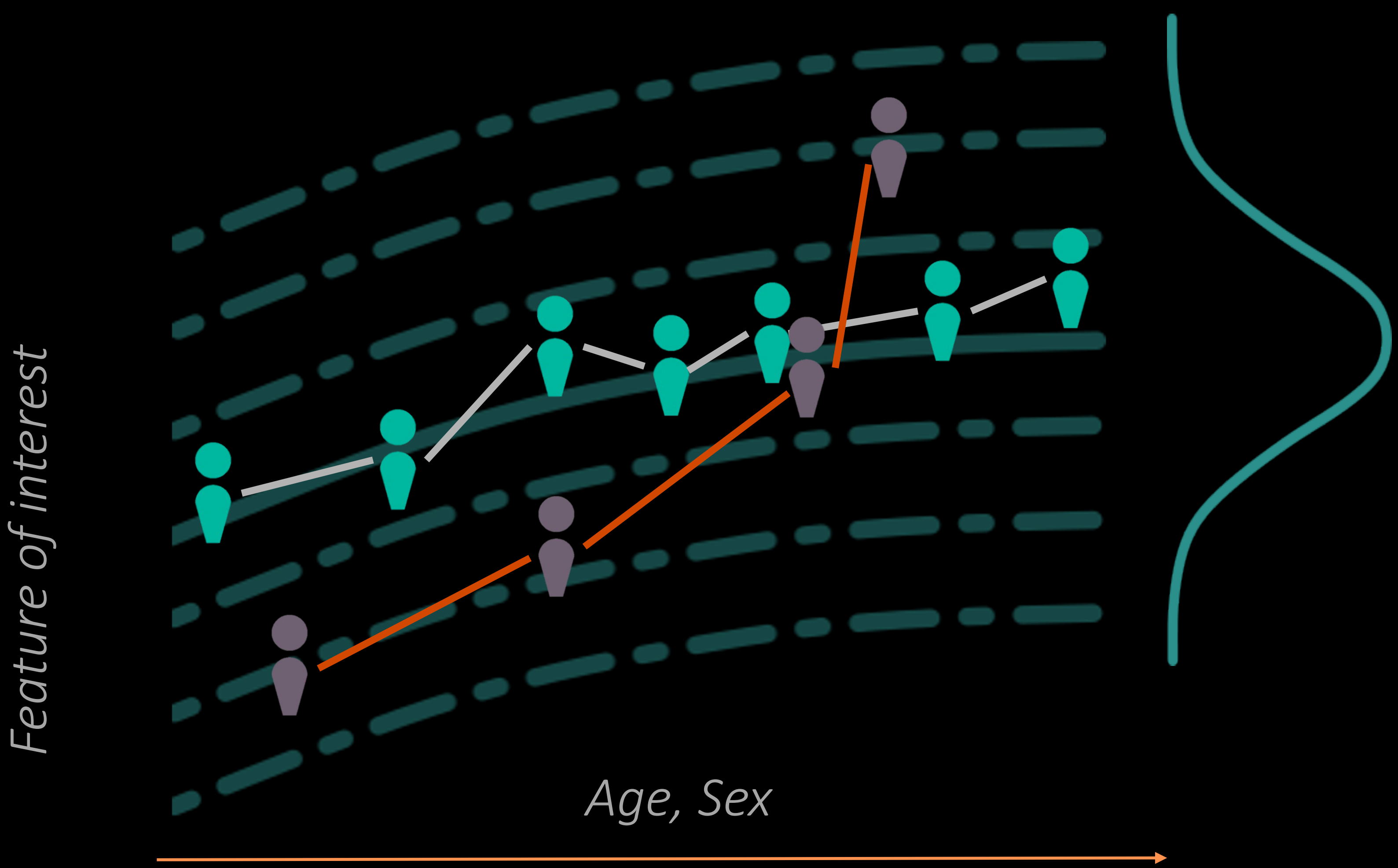




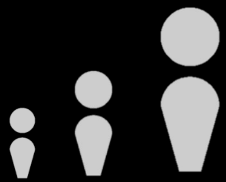
Bayer, J. M. M. *et al.* Accommodating site variation in neuroimaging data using normative and hierarchical Bayesian models. *Neuroimage* **264**, 119699 (2022).

Cirstian, R. *et al.* Lifespan normative models of white matter fractional anisotropy: Applications to Early Psychosis. *bioRxivorg* 2024.12.11.627897 (2024) doi:10.1101/2024.12.11.627897.

LONGITUDINAL NORMATIVE MODELLING

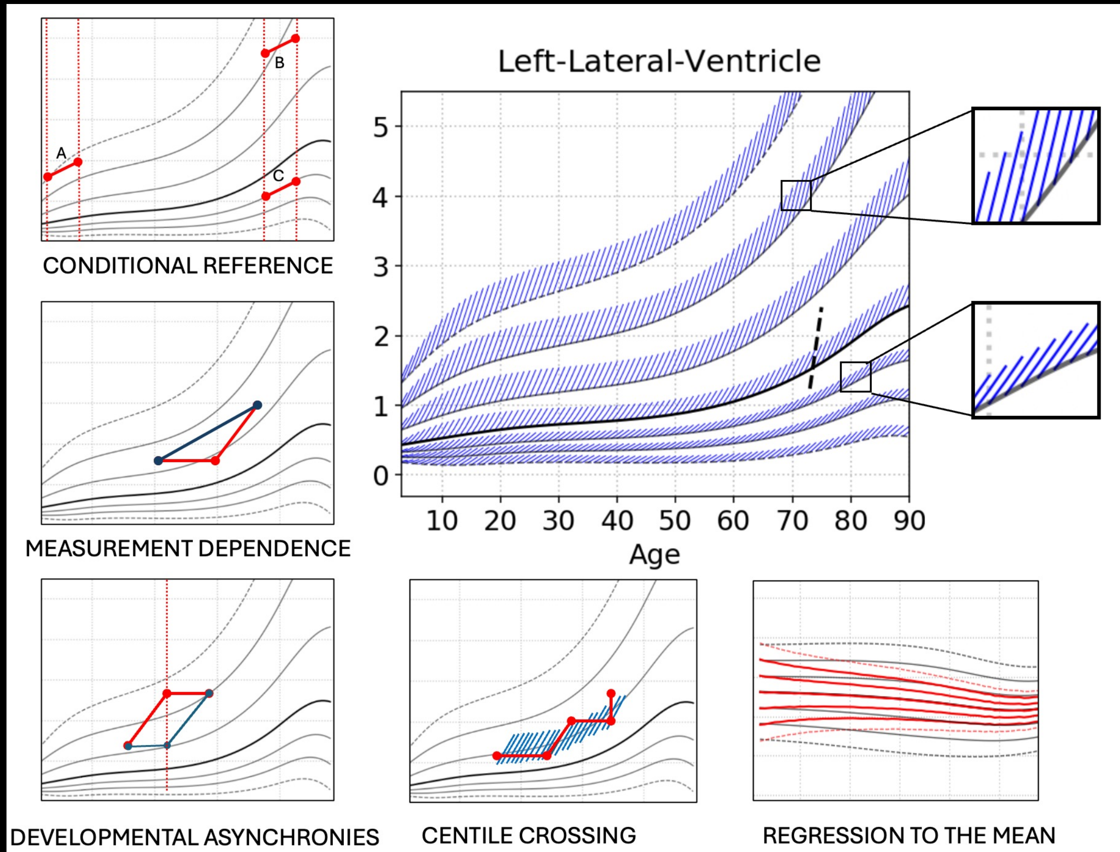


LONGITUDINAL NORMATIVE MODELLING



Longitudinal models –
From longitudinal data
Thrive lines

- 22000 longitudinal data points
- Age range: 7 days – 97 years
- Thrive lines: estimate the point of failure to thrive
- Allow for true longitudinal predictions and an estimate of centile crossing
- Normal rate of change varies with age



Bayer 2024, in prep.

TUTORIALS

https://github.com/likeajumprope/Tutorial_normative_modelling

Tasks

Task 1: Fitting normative models from scratch Open in Colab

Task 2: Applying pre-trained normative models Open in Colab

TUTORIAL I.

ESTIMATING LIFESPAN NORMATIVE MODELS

Install and load the packages → Clone the Github directory → Split data into train/test

TUTORIAL I.

ESTIMATING LIFESPAN NORMATIVE MODELS

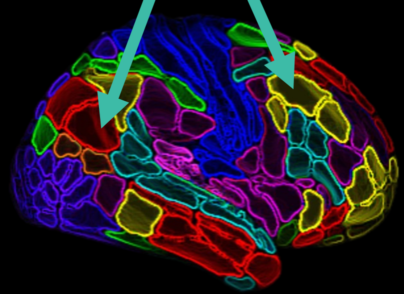
Install and load the packages

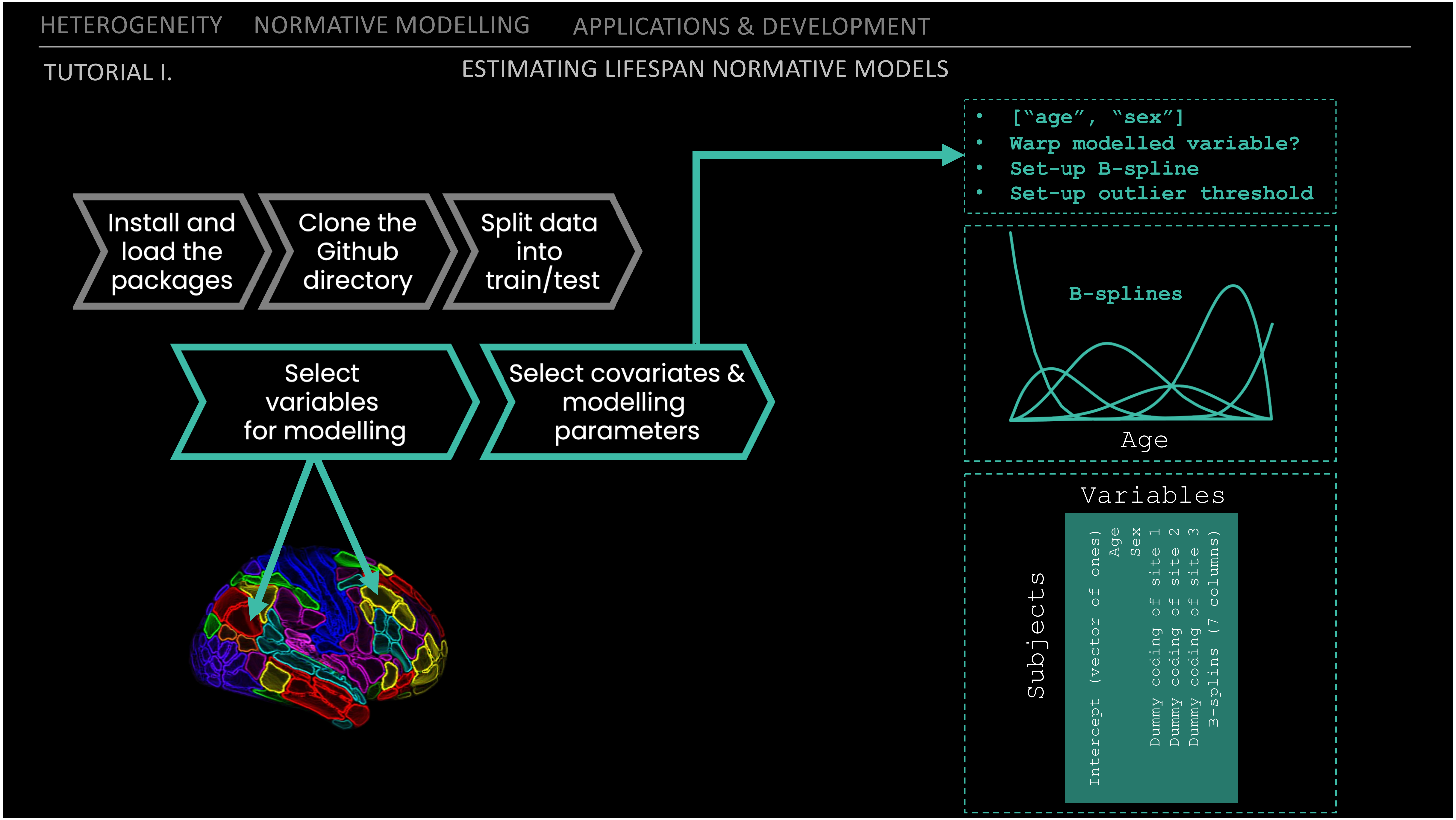
Clone the Github directory

Split data into train/test

Select variables for modelling

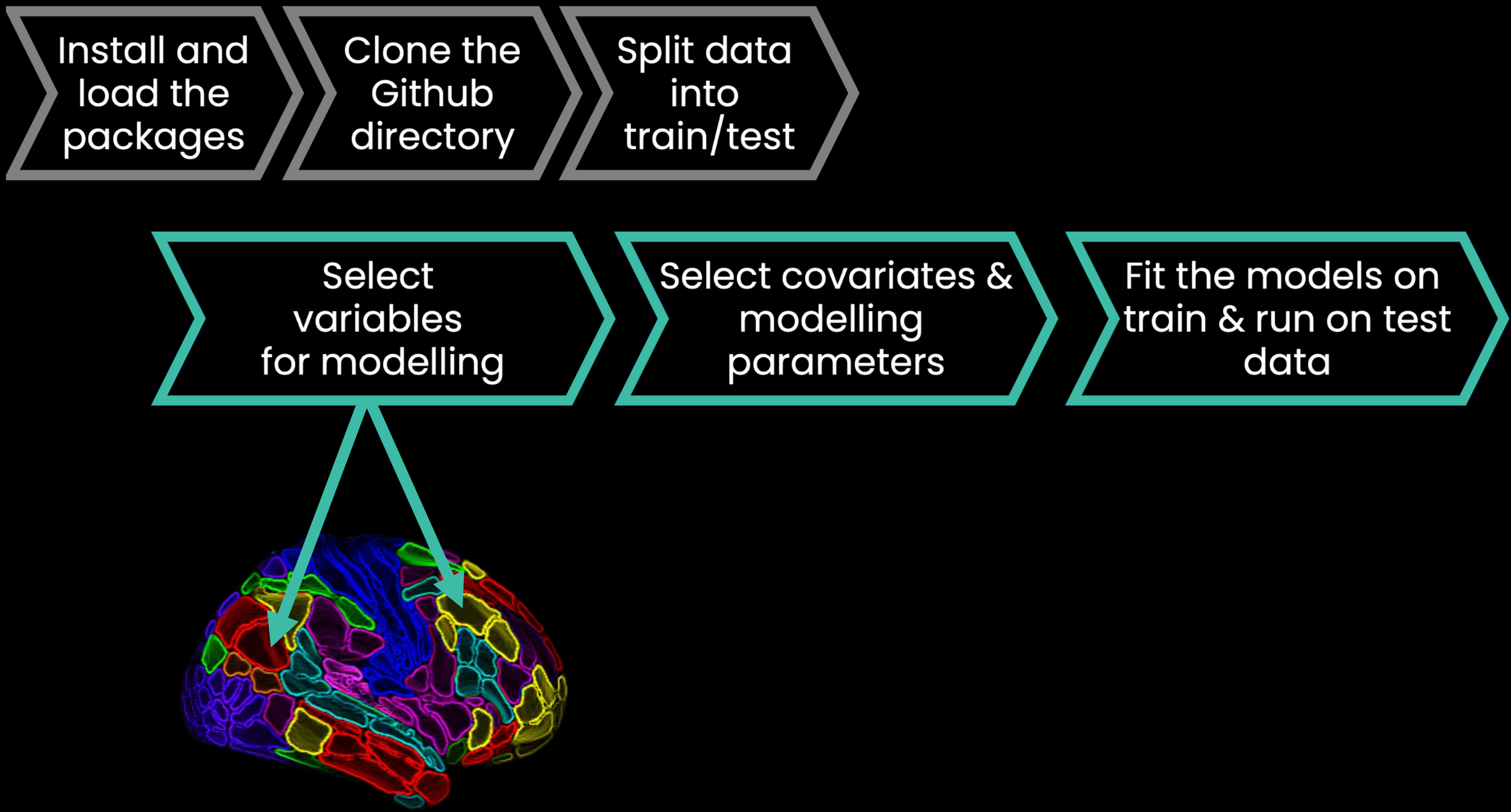
Select covariates & modelling parameters

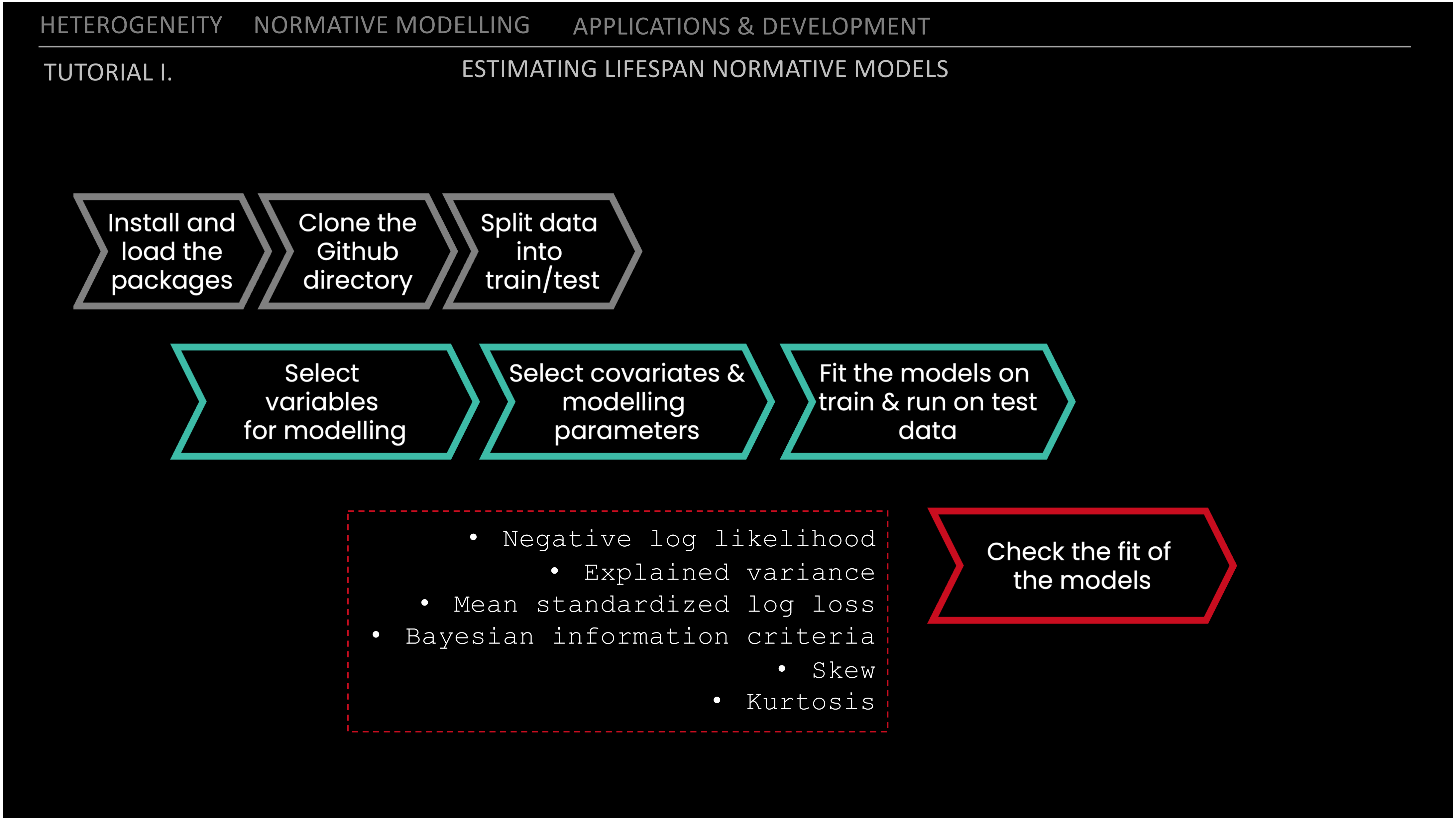



HETEROGENEITY
NORMATIVE MODELLING
APPLICATIONS & DEVELOPMENT
TUTORIAL I.
ESTIMATING LIFESPAN NORMATIVE MODELS
Install and load the packages
Clone the Github directory
Split data into train/test
Select variables for modelling
Select covariates & modelling parameters
• ["age", "sex"]
• Warp modelled variable?
• Set-up B-spline
• Set-up outlier threshold
B-splines
Age
Variables
Subjects
Intercept (vector of ones)
Age
Sex
Dummy coding of site 1
Dummy coding of site 2
Dummy coding of site 3
B-splins (7 columns)

TUTORIAL I.

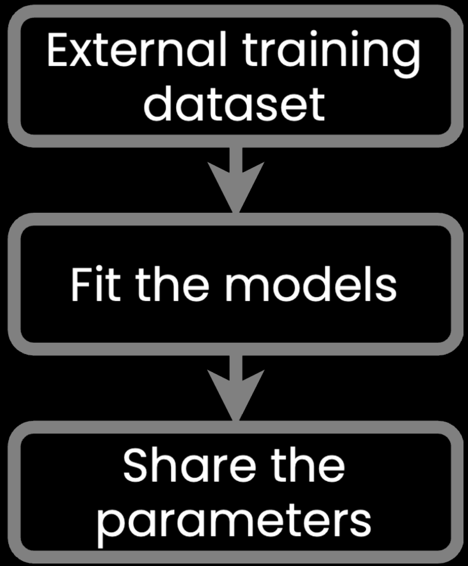
ESTIMATING LIFESPAN NORMATIVE MODELS




HETEROGENEITY
NORMATIVE MODELLING
APPLICATIONS & DEVELOPMENT
TUTORIAL I.
ESTIMATING LIFESPAN NORMATIVE MODELS
Install and load the packages
Clone the Github directory
Split data into train/test
Select variables for modelling
Select covariates & modelling parameters
Fit the models on train & run on test data
• Negative log likelihood
• Explained variance
• Mean standardized log loss
• Bayesian information criteria
• Skew
• Kurtosis
Check the fit of the models

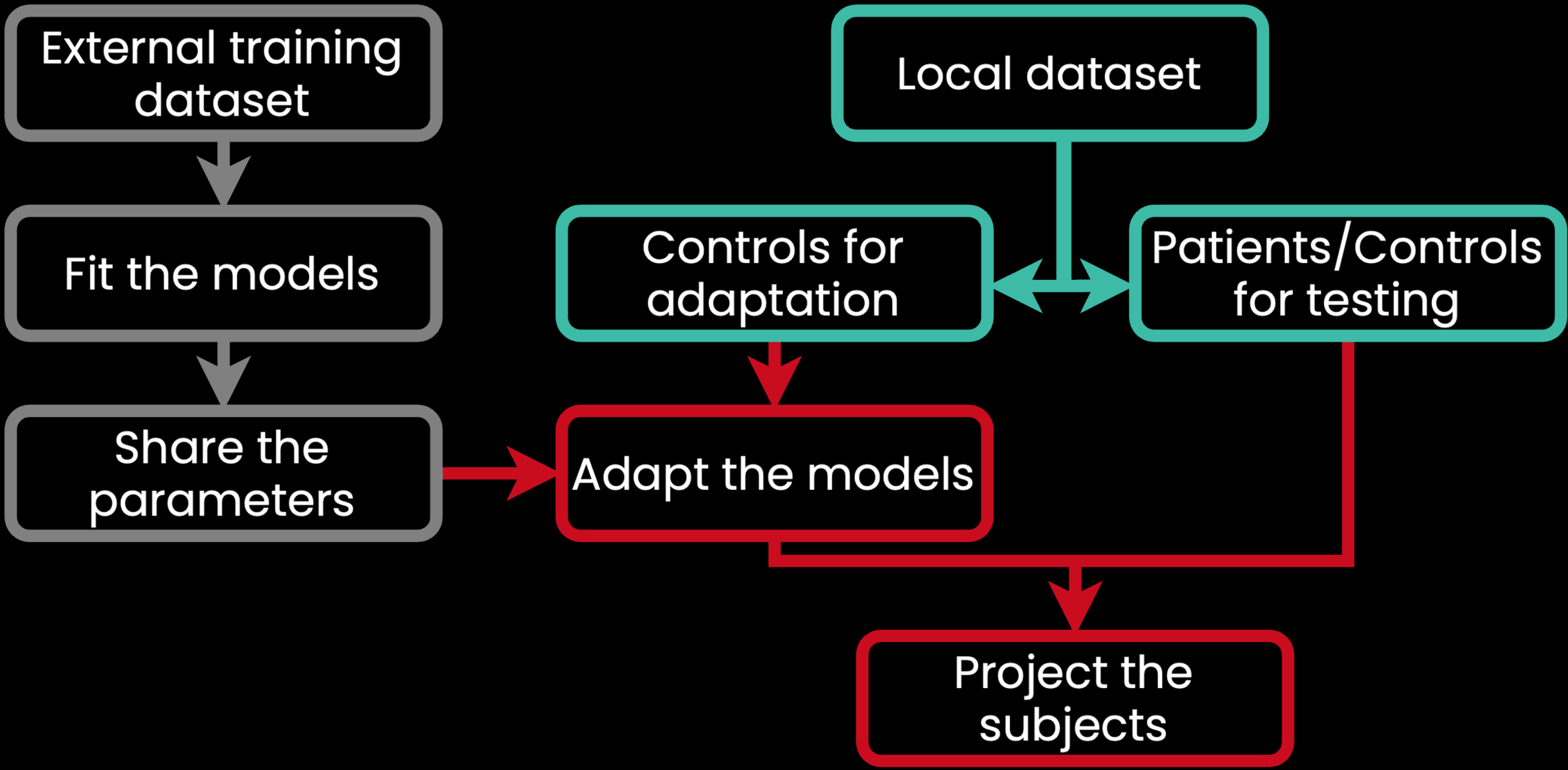
TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS



TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS



TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS

1. Install and load the packages
2. Clone the Github directory
3. Clone the pretrained models
4. Download adaptation & test data

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS

Install and load the packages

Clone the Github directory

Clone the pretrained models

Download adaptation & test data

Select variables for modelling

Select covariates & modelling parameters

Adapt the pretrained models & run on test data

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS

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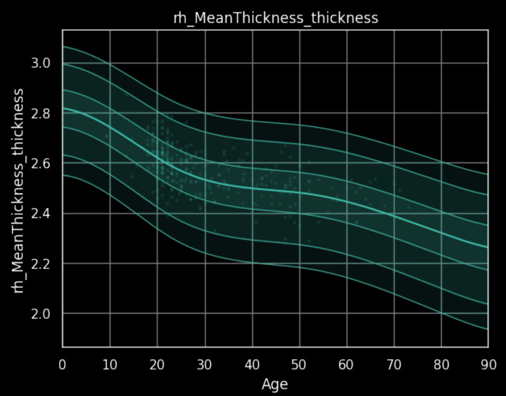

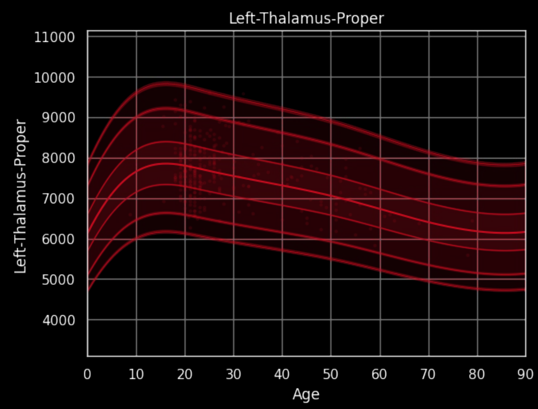

Visualize

Download the toolbox here:
github.com/amarquand

pcnportal.dccn.nl

https://pcntoolkit.readthedocs.io

Predictive Clinical Neuroscience Lab

Professor Andre Marquand

Radboudumc

THANK YOU!

https://github.com/likeajumprope/Tutorial_normative_modelling

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