Normative modelling: the what, when and why

Barbora Rehák Bučková
@BarboraRehak

Charlotte Fraza
@CharFraza

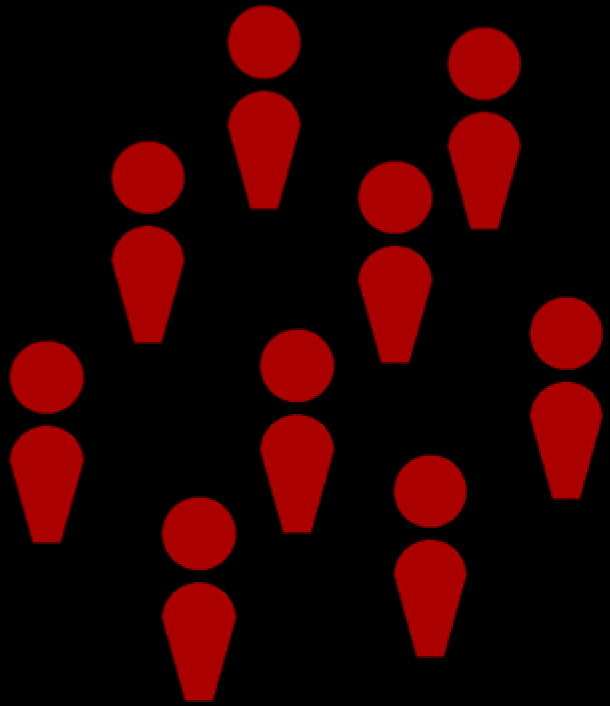
Post Doctoral Researchers
Predictive Clinical Neuroscience Lab

Slides by: @DrHannahSavage

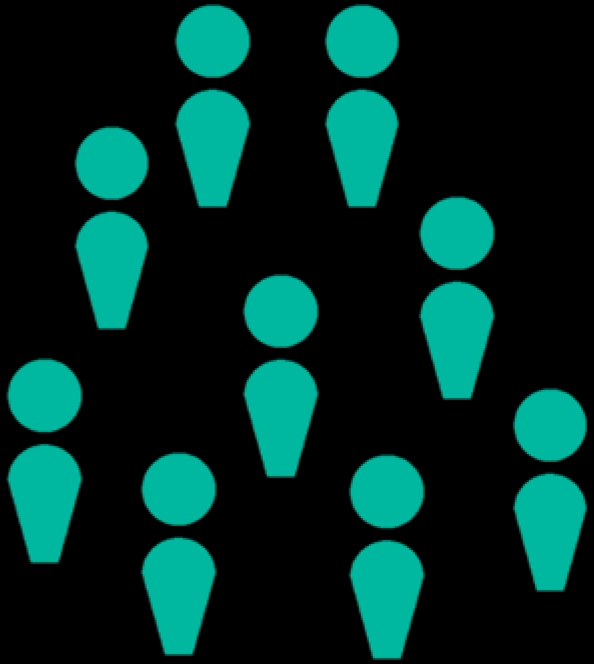
Predictive Clinical Neuroscience Lab

THE SHORTCOMINGS OF CLASSICAL STATISTICS

CASE **CONTROL**

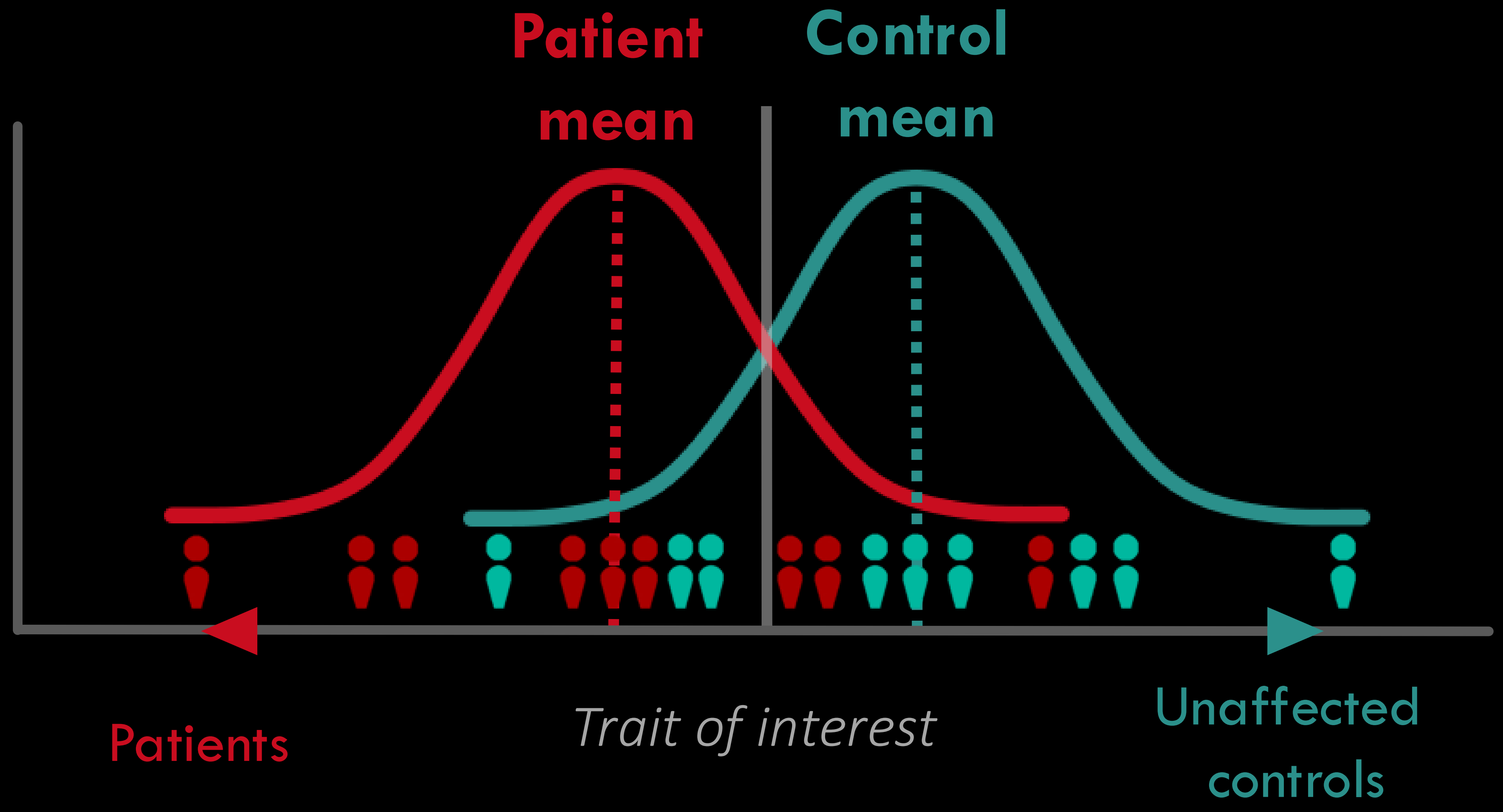


Patients

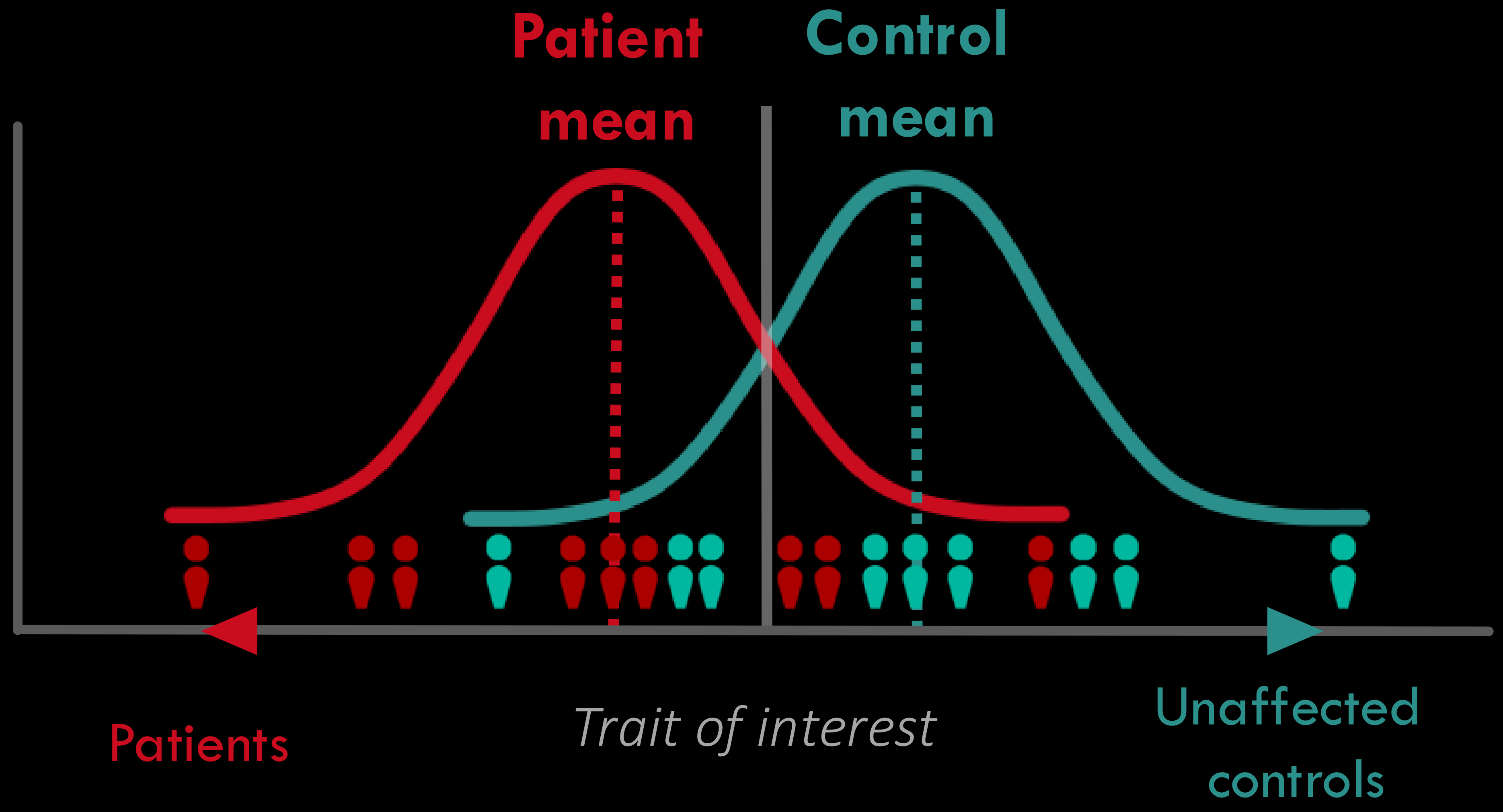


Unaffected controls

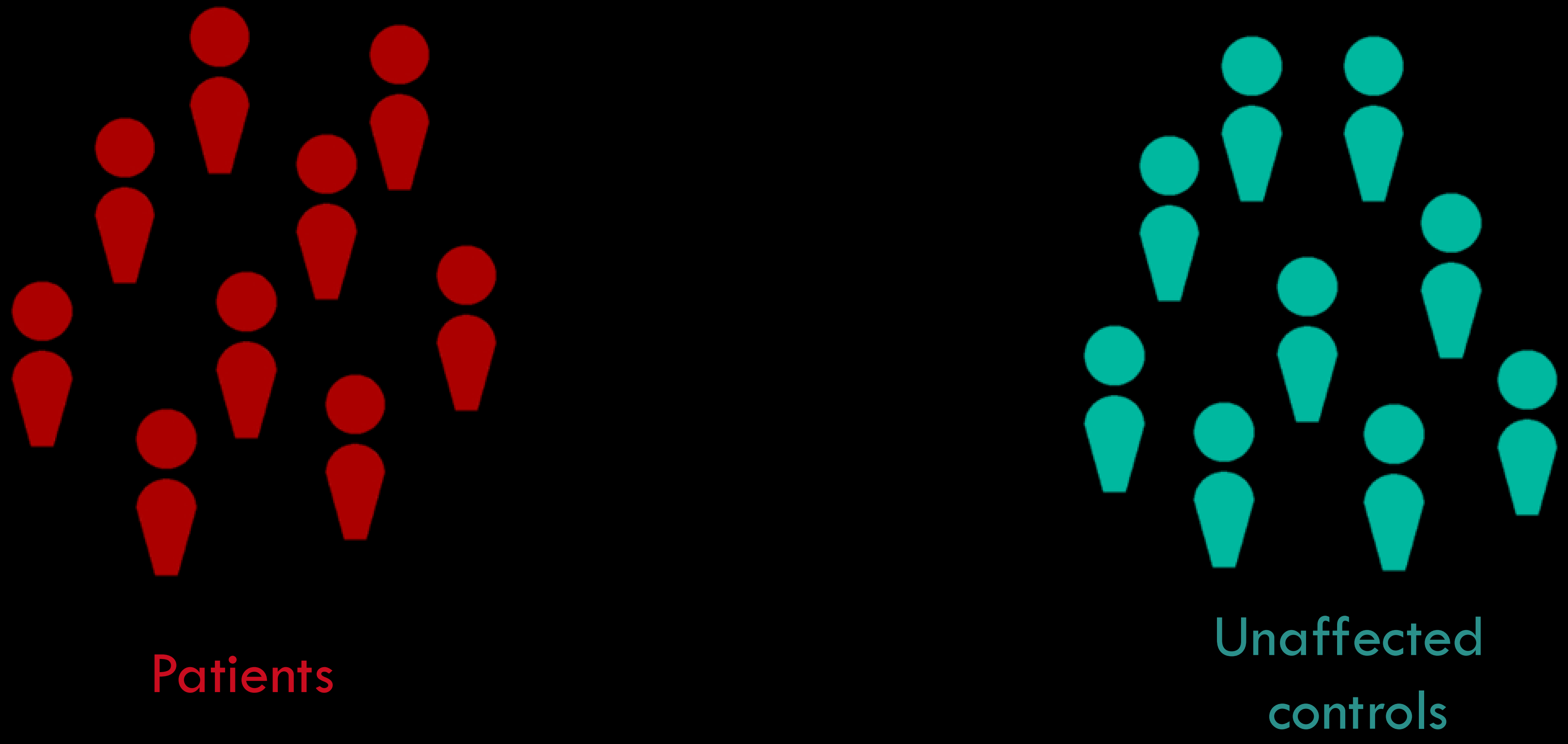
THE SHORTCOMINGS OF CLASSICAL STATISTICS



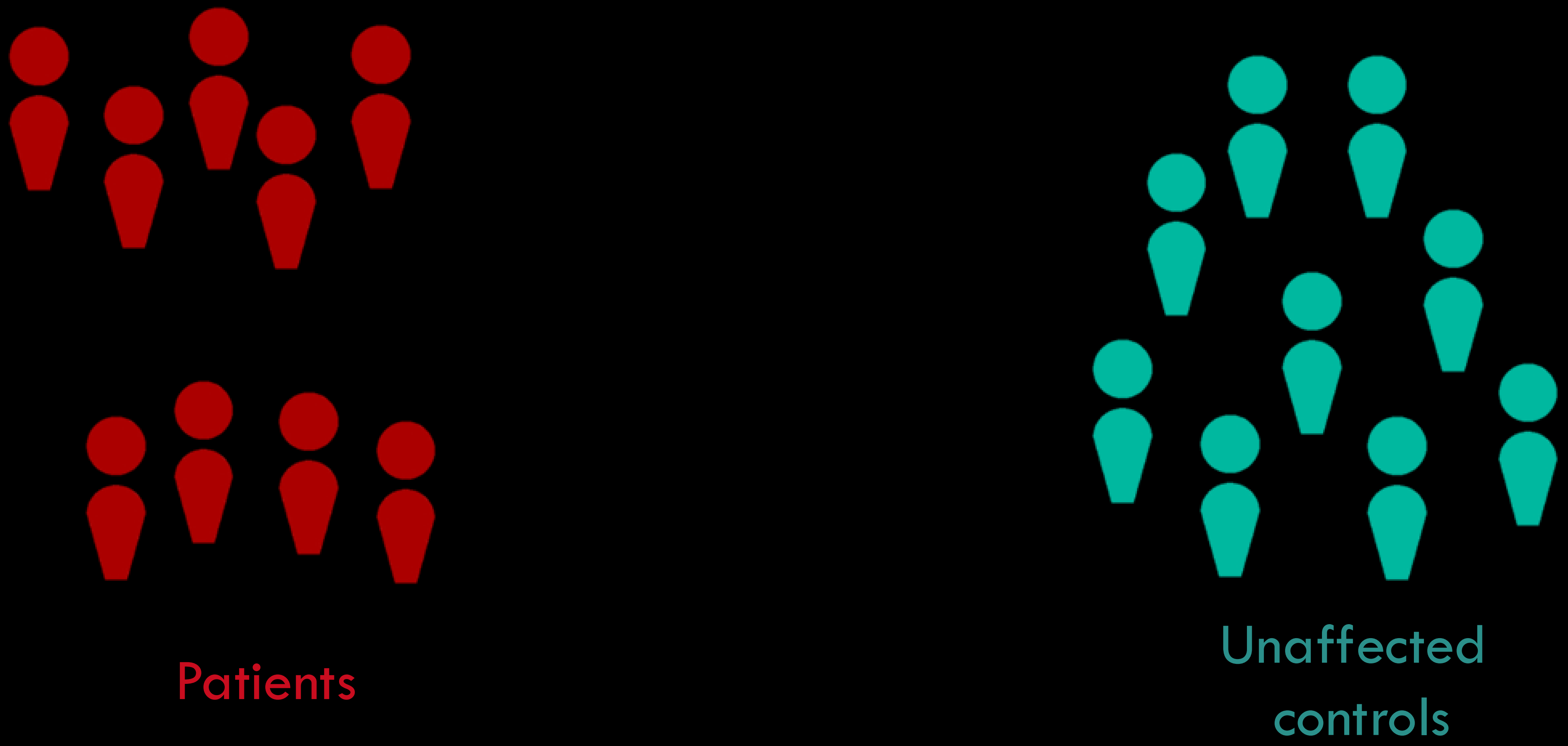
THE SHORTCOMINGS OF CLASSICAL STATISTICS



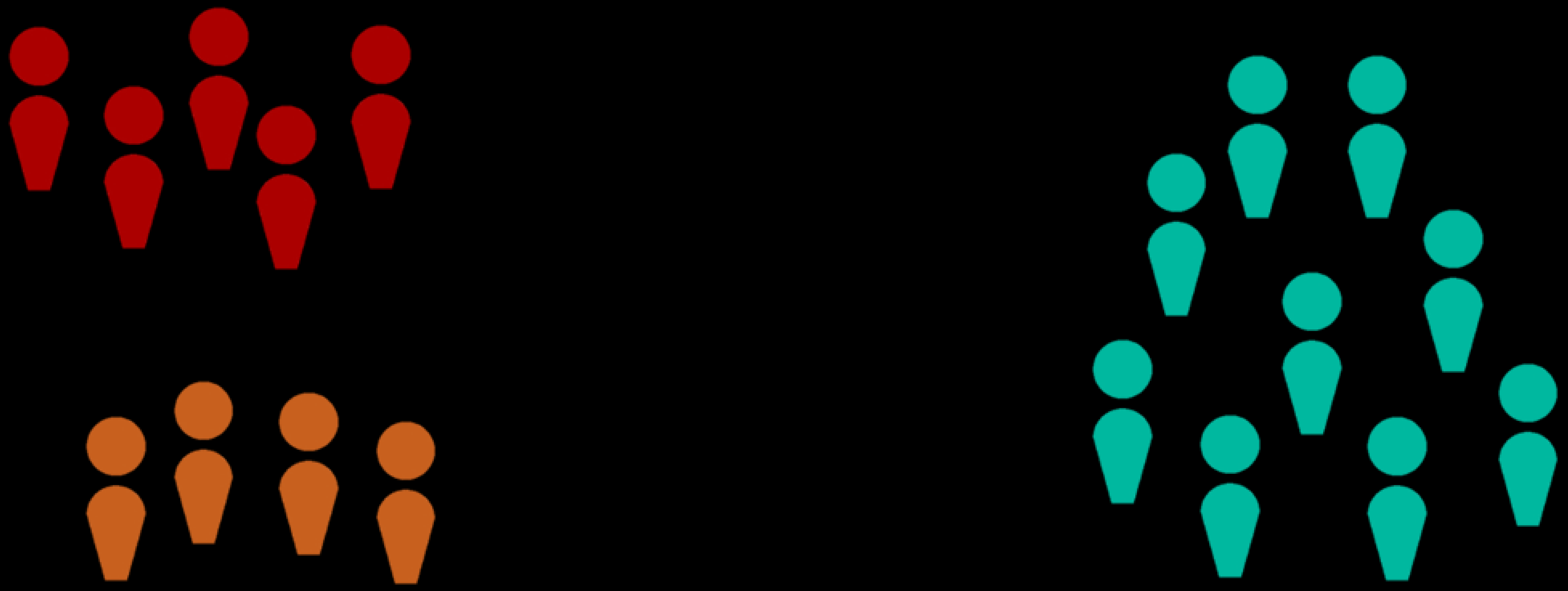
ON HETEROGENEITY



ON HETEROGENEITY



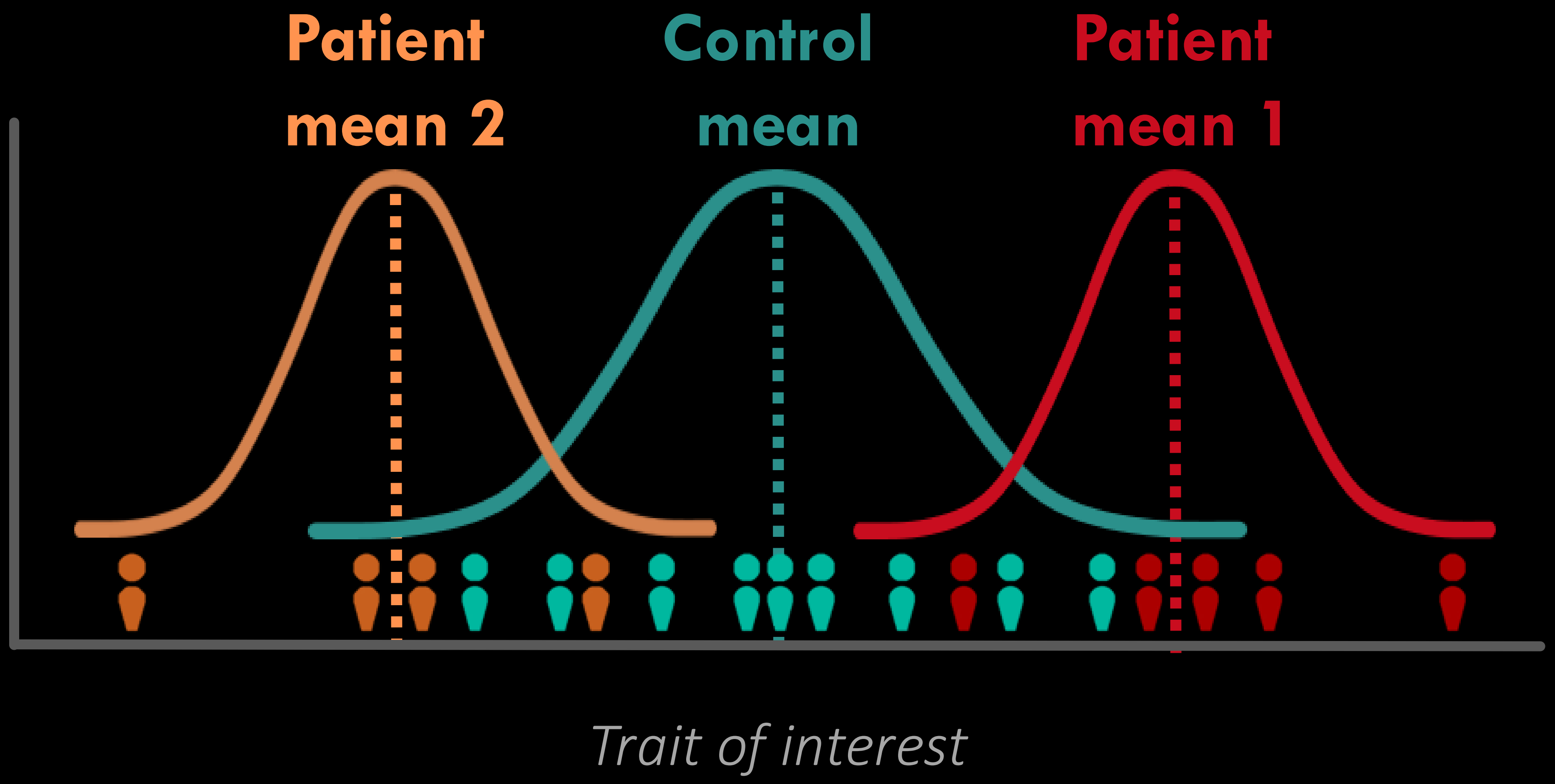
ON HETEROGENEITY



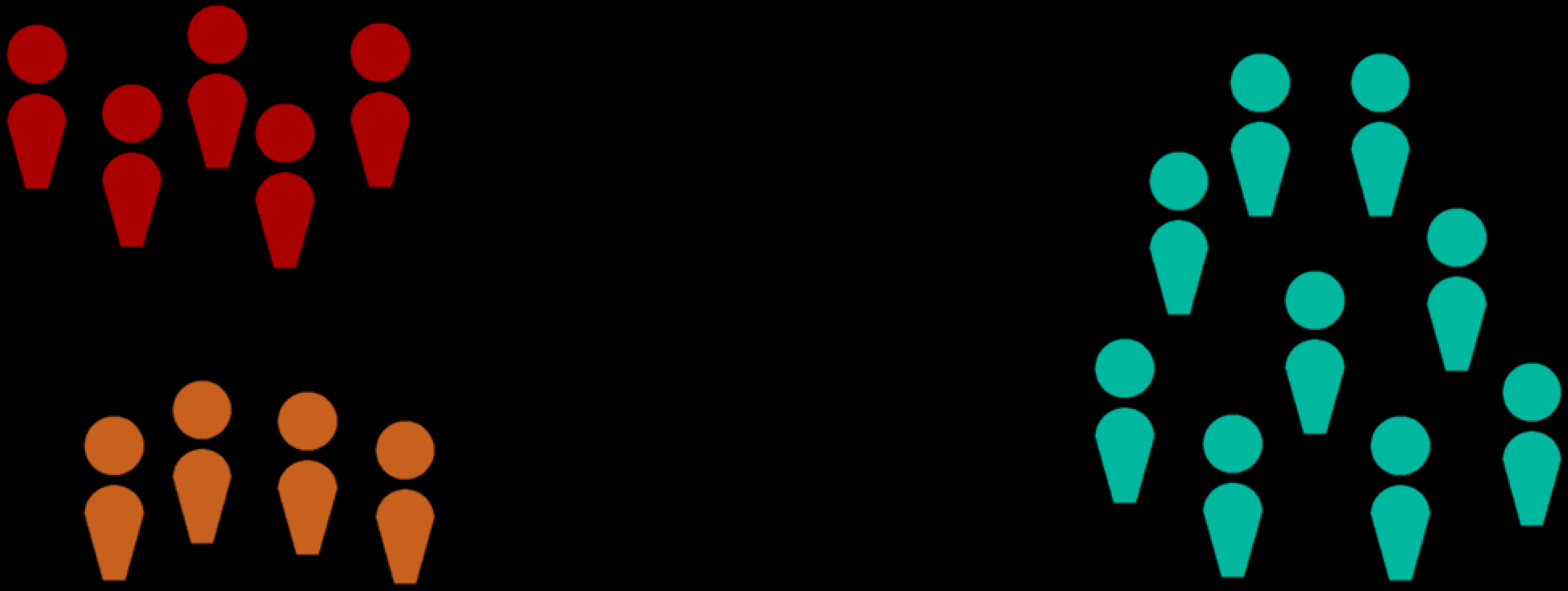
Patients

Unaffected controls

ON HETEROGENEITY



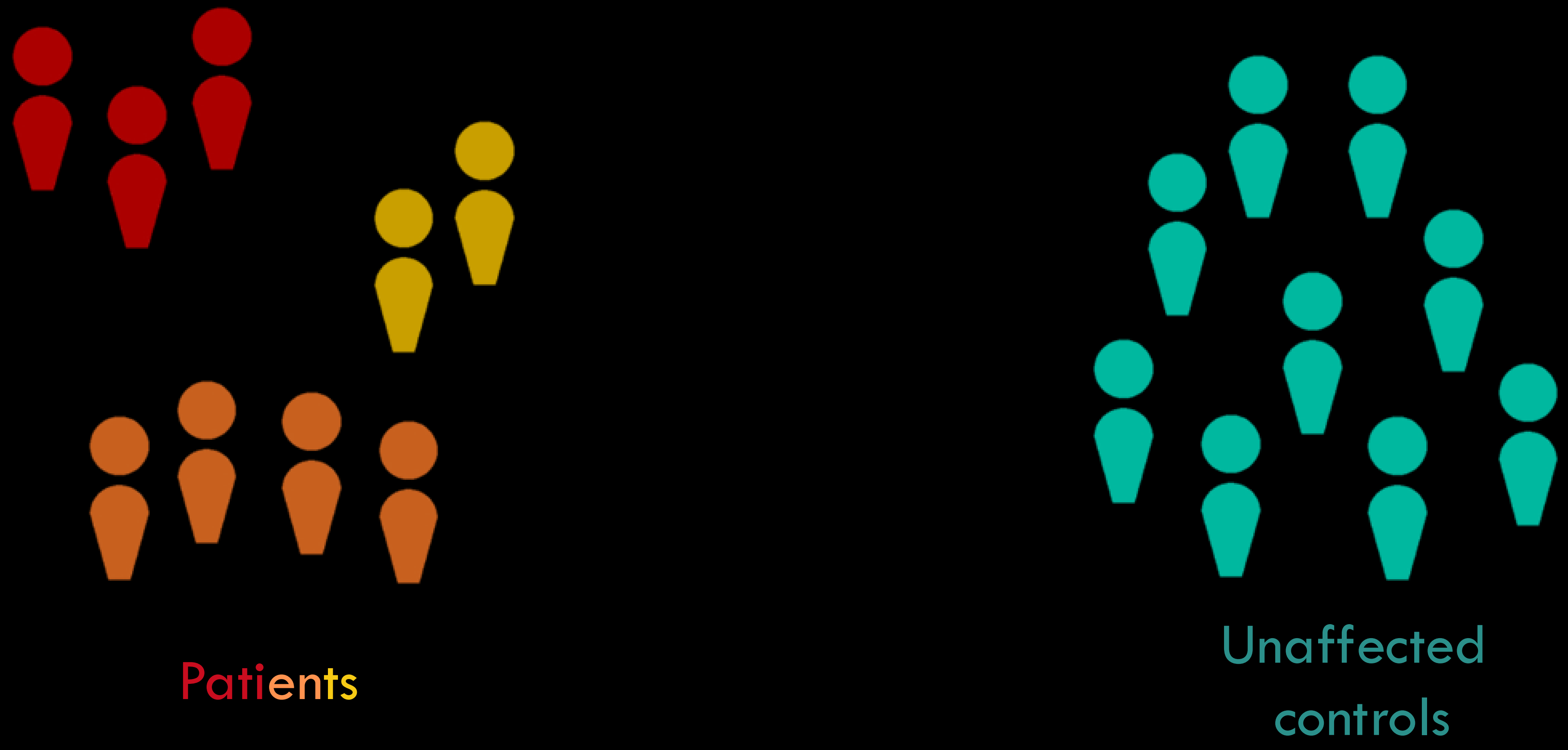
ON HETEROGENEITY



Patients

Unaffected controls

ON HETEROGENEITY

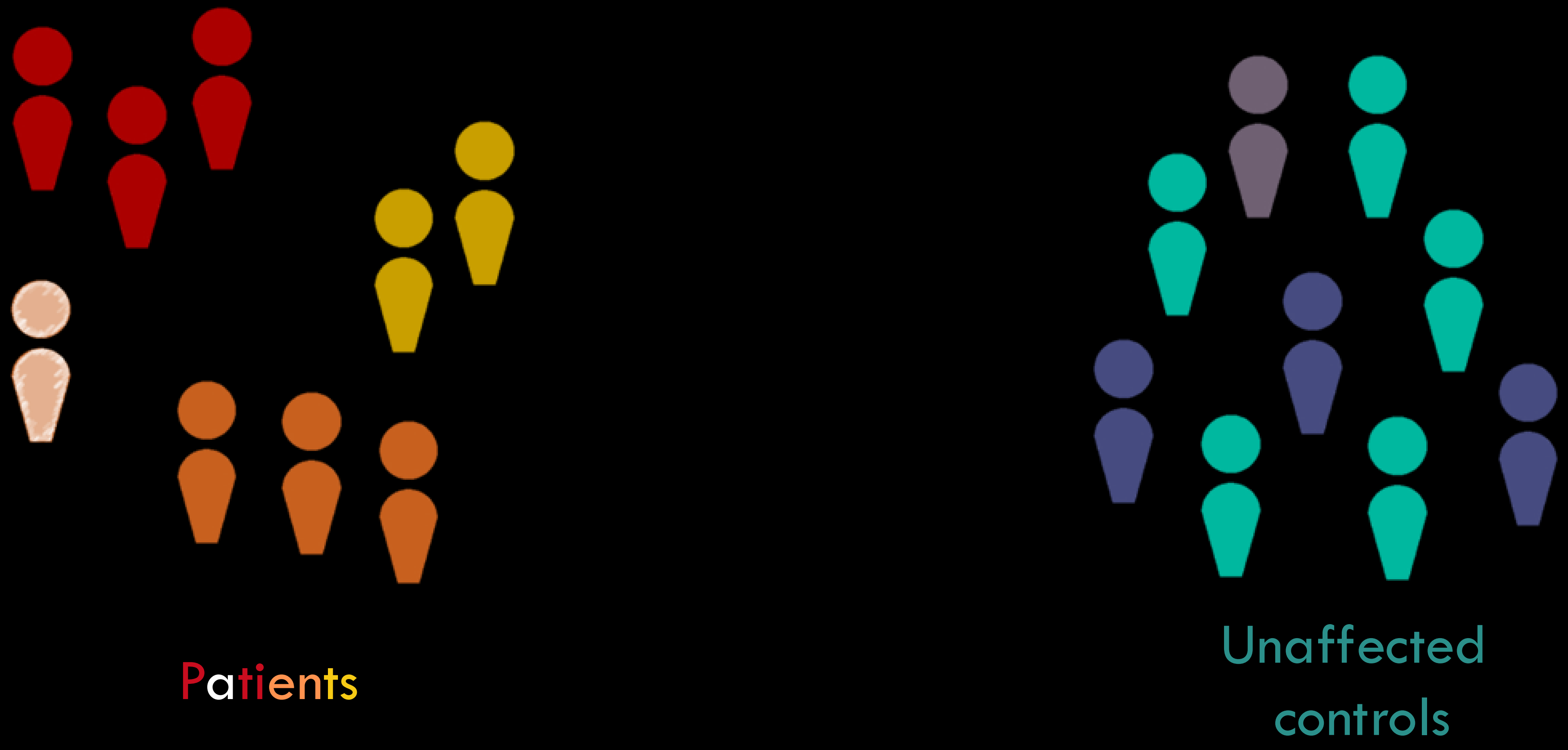


ON HETEROGENEITY

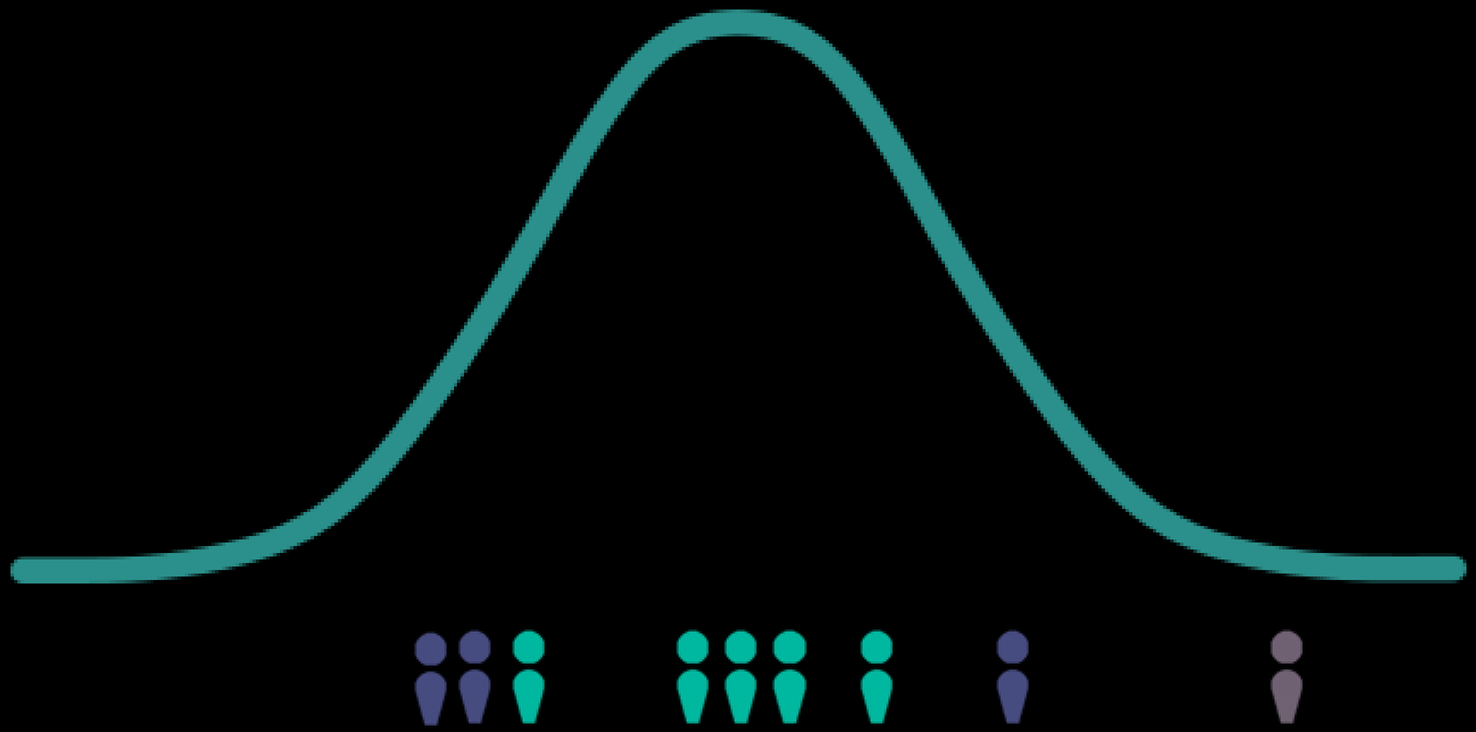
Patients

Unaffected controls

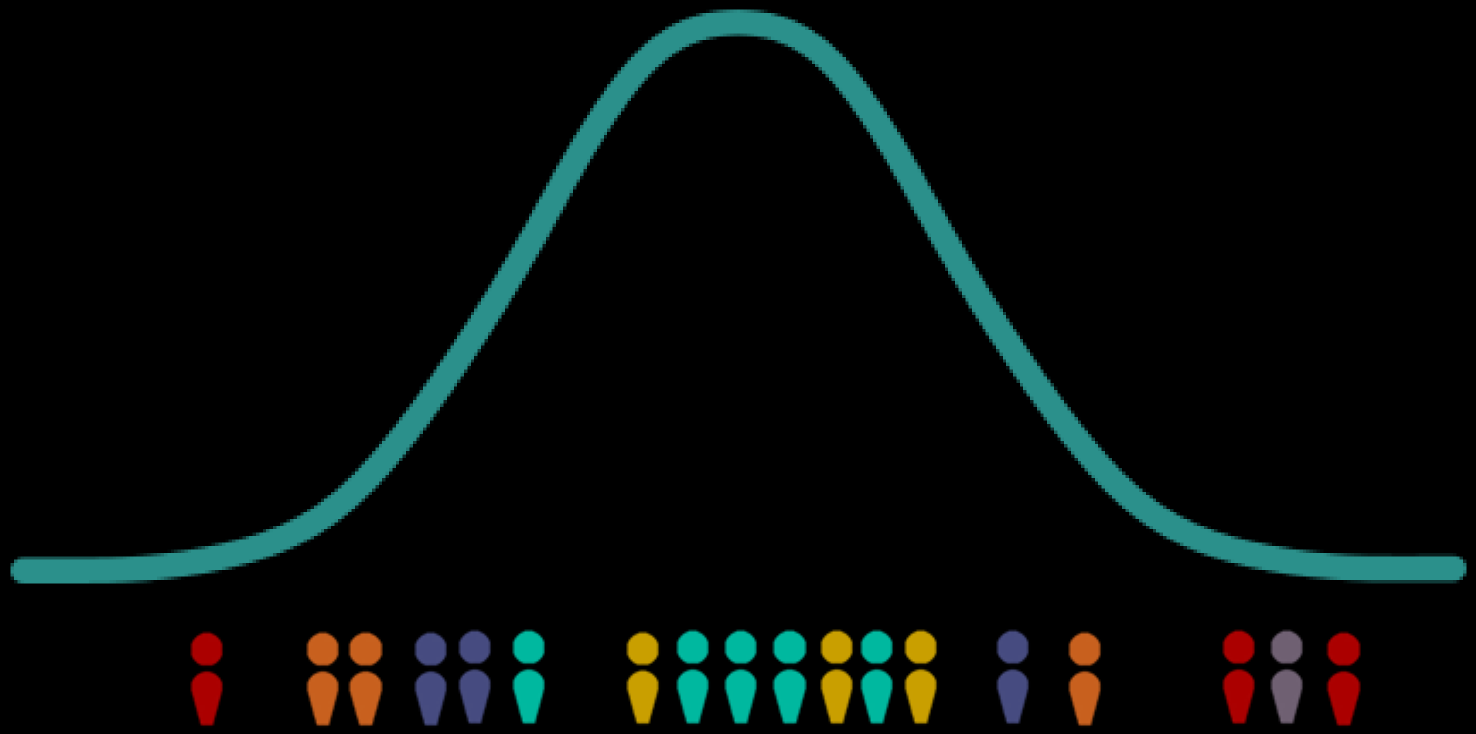
ON HETEROGENEITY



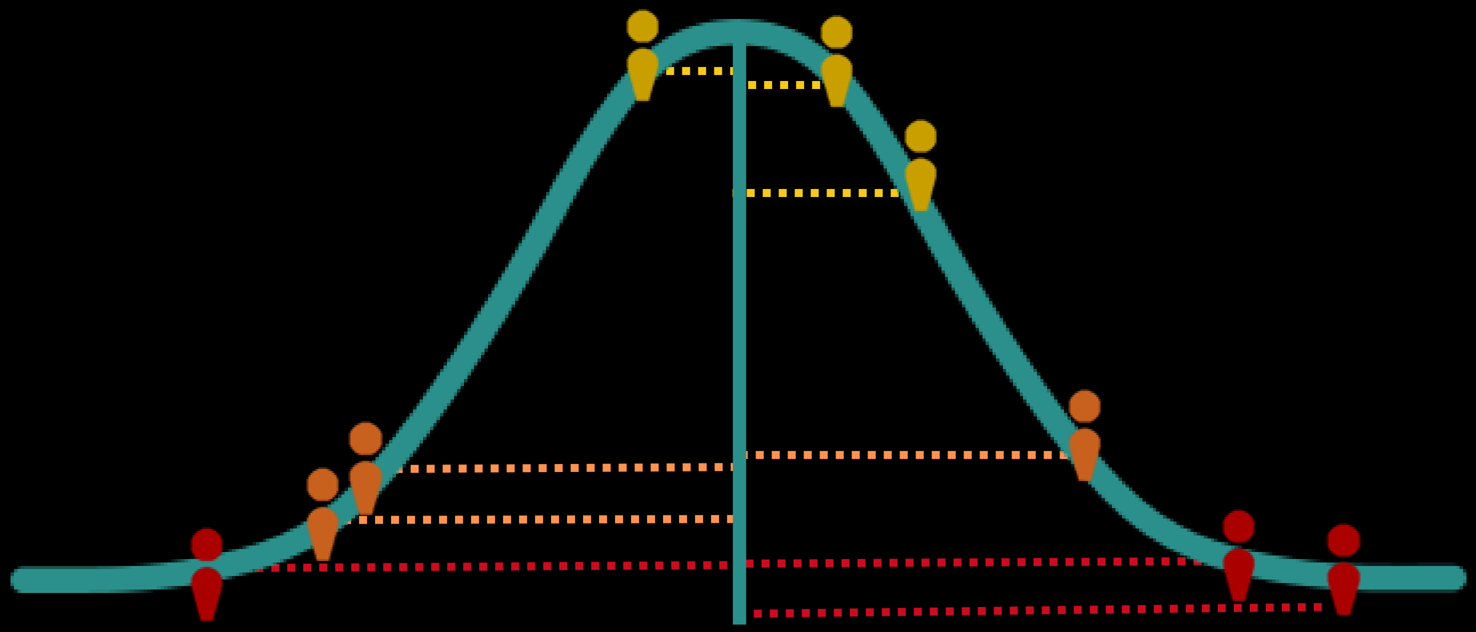
NORMATIVE MODELLING



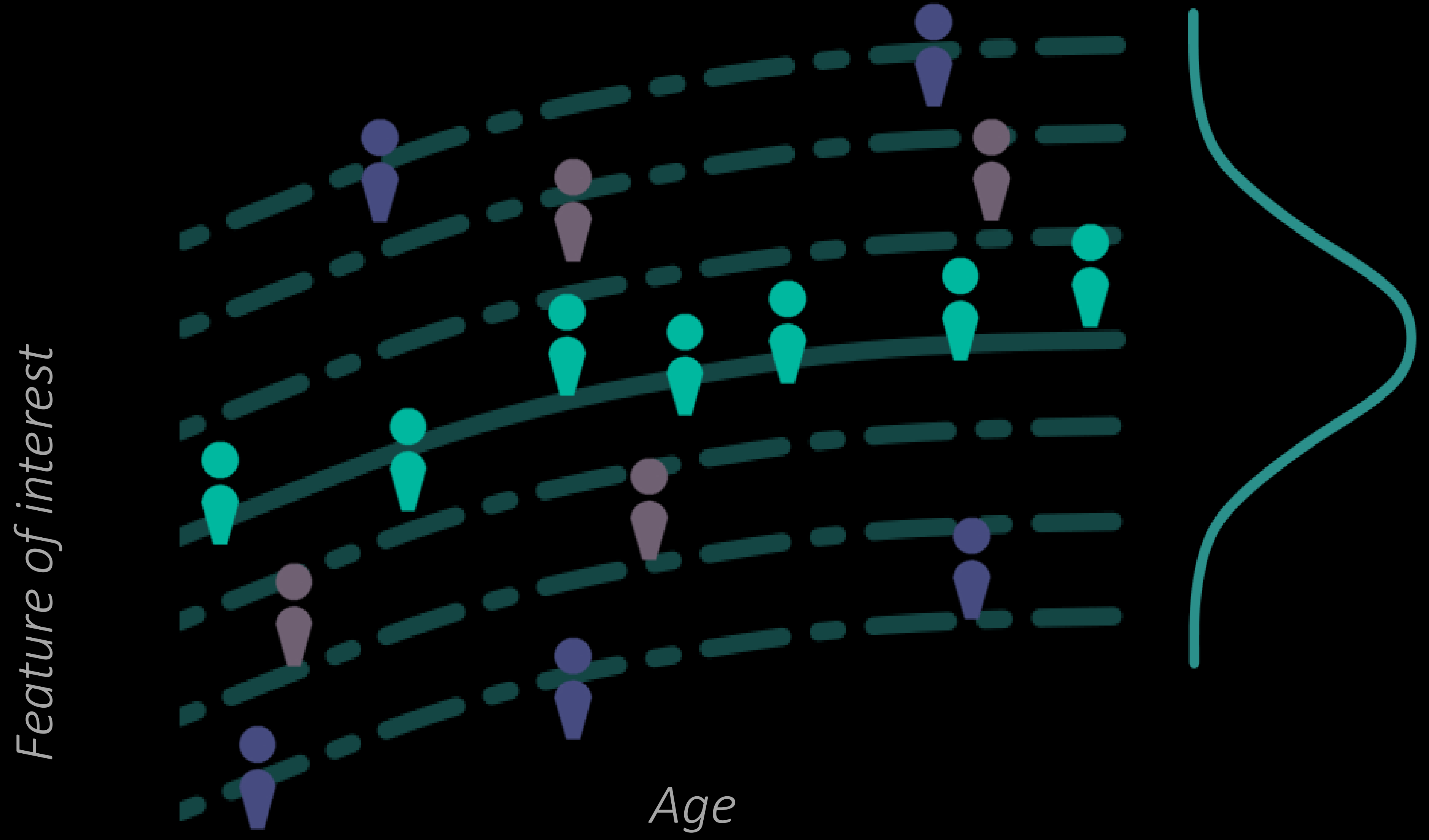
NORMATIVE MODELLING



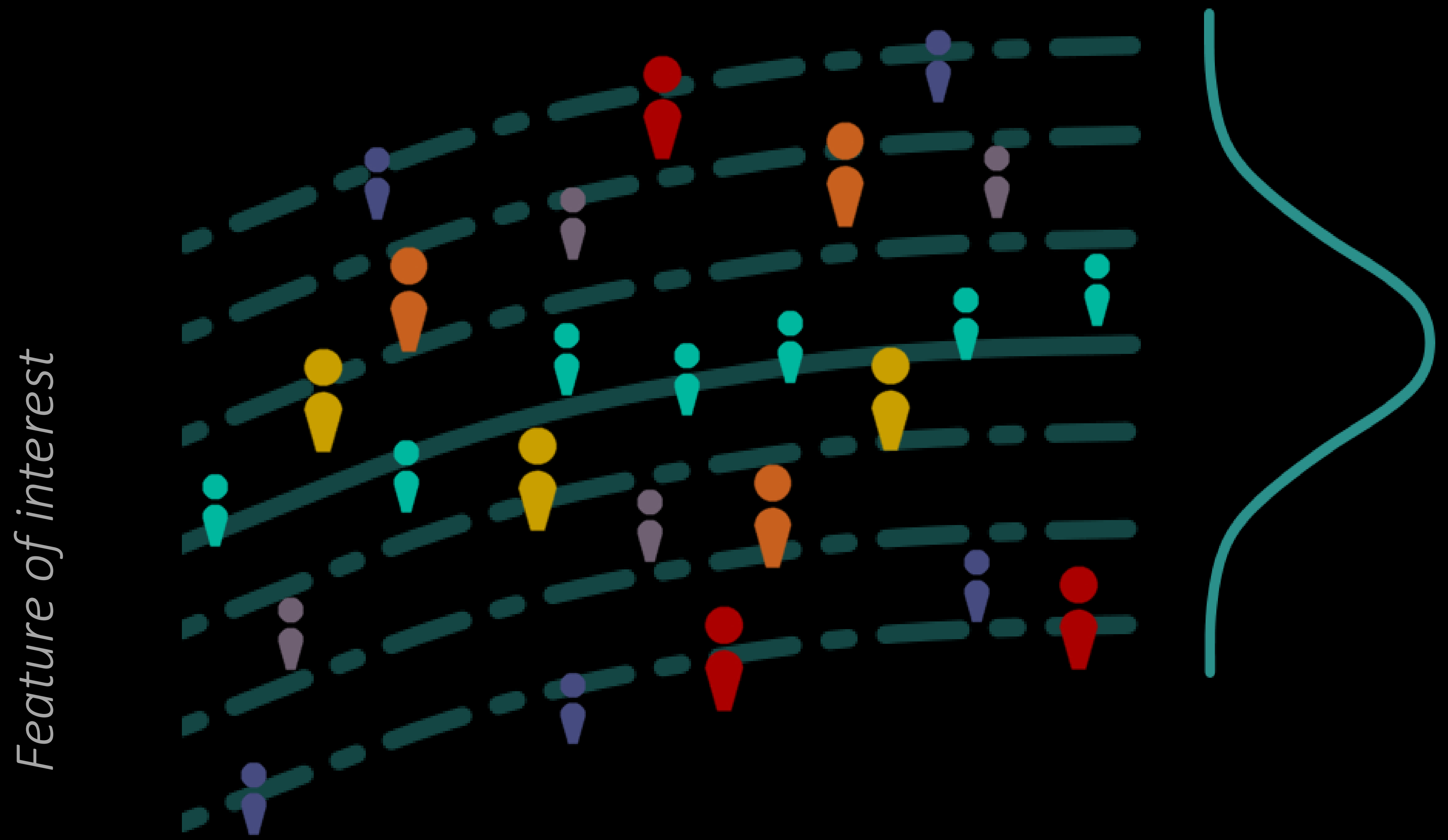
NORMATIVE MODELLING



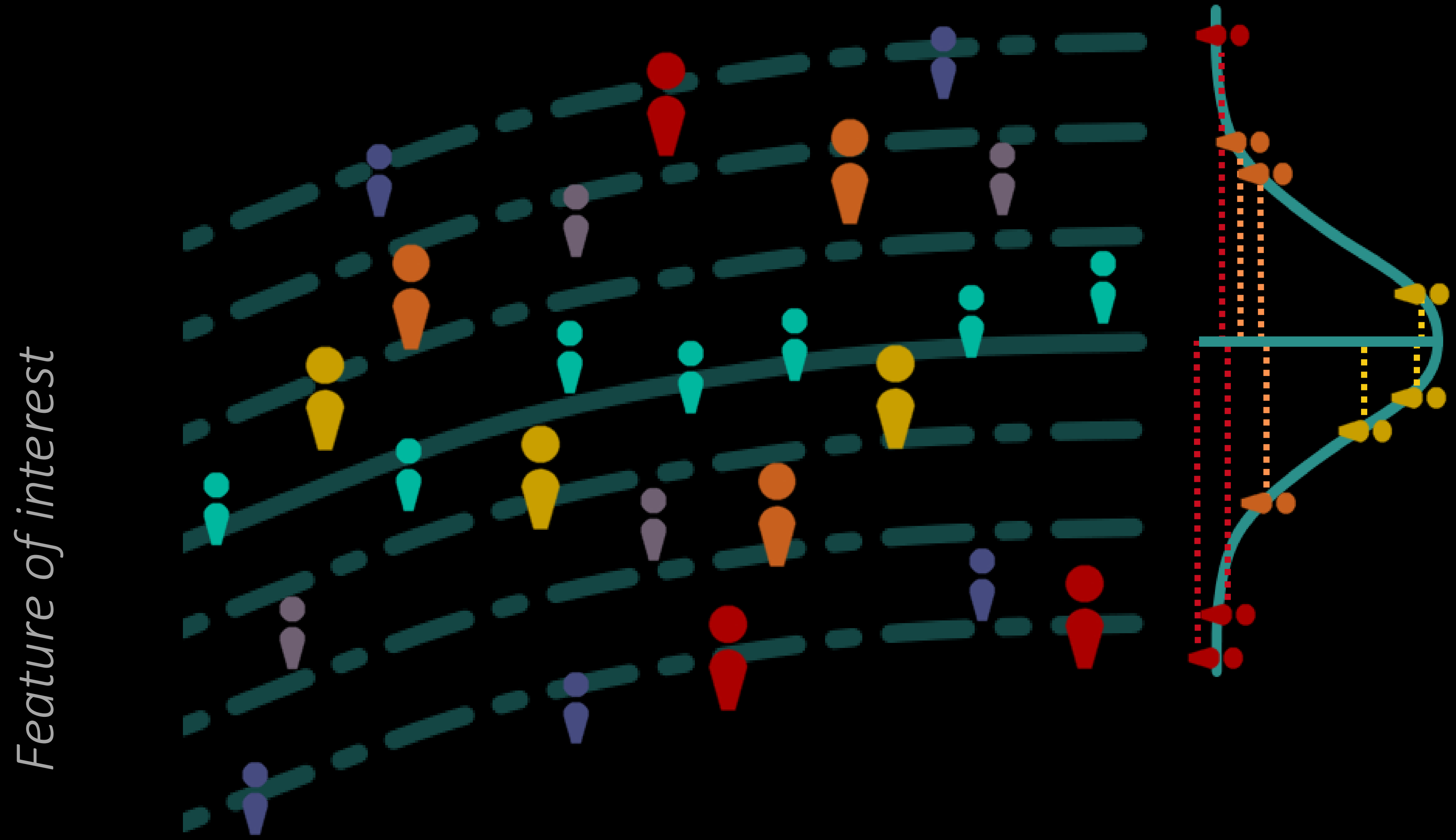
NORMATIVE MODELLING



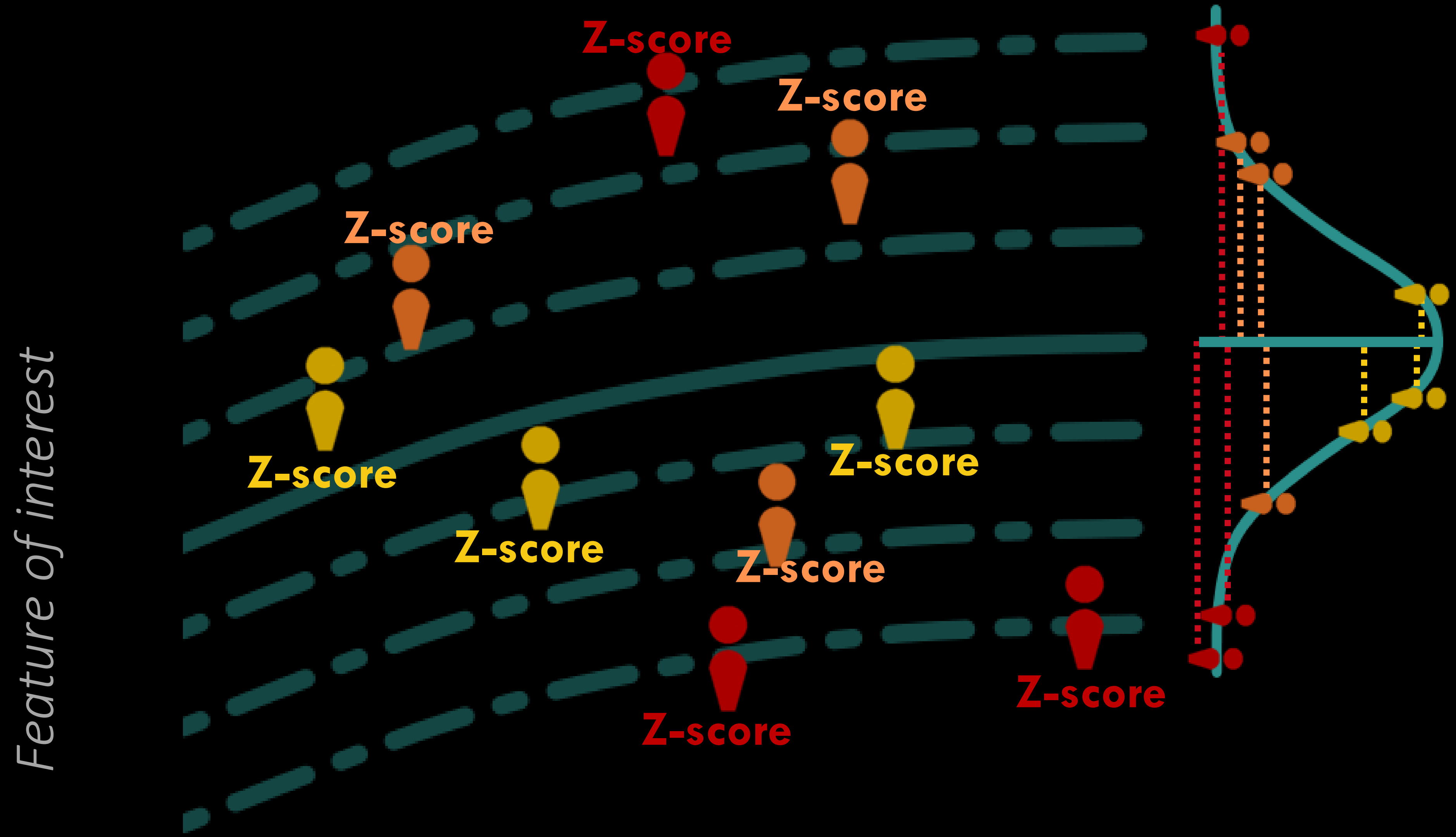
NORMATIVE MODELLING



NORMATIVE MODELLING



NORMATIVE MODELLING



NORMATIVE MODELLING

Y

Brain
(BOLD signal in voxel, ROI)

NORMATIVE MODELLING

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

Brain
(BOLD signal in voxel, ROI)

Covariates
(age, sex, task parameters)

Model parameters

Residuals

NORMATIVE MODELLING

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

Brain
(BOLD signal in voxel, ROI)

Covariates
(age, sex, task parameters)

Model parameters

Residuals

Imaging measures →

Subjects ↑

Responses
(Y)

Predictors →

Subjects ↑

Covariates
(X)

NORMATIVE MODELLING

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

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

APPLICATIONS

Parsing heterogeneity

Neurobiological subtyping

Brain-behavior mappings

Other

APPLICATIONS

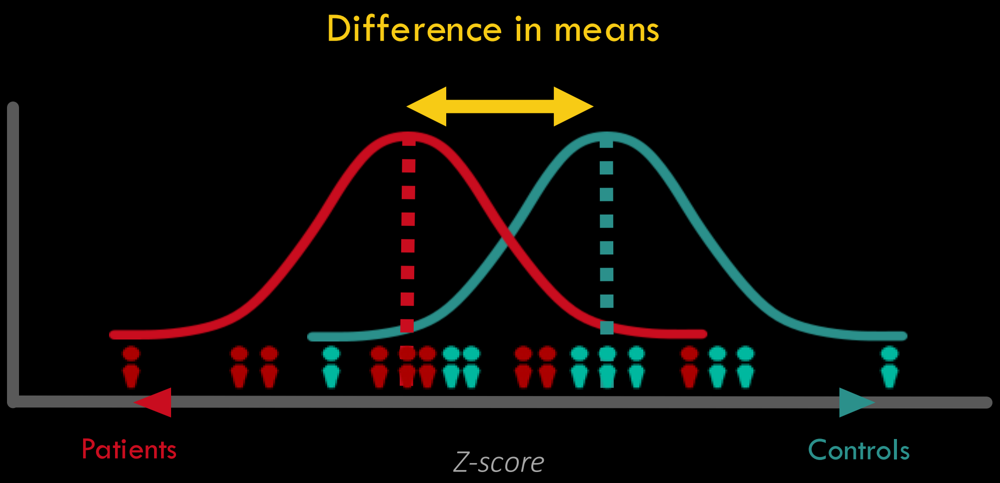
Parsing heterogeneity

Neurobiological subtyping

Brain-behavior mappings

Other

PARSING HETEROGENEITY



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

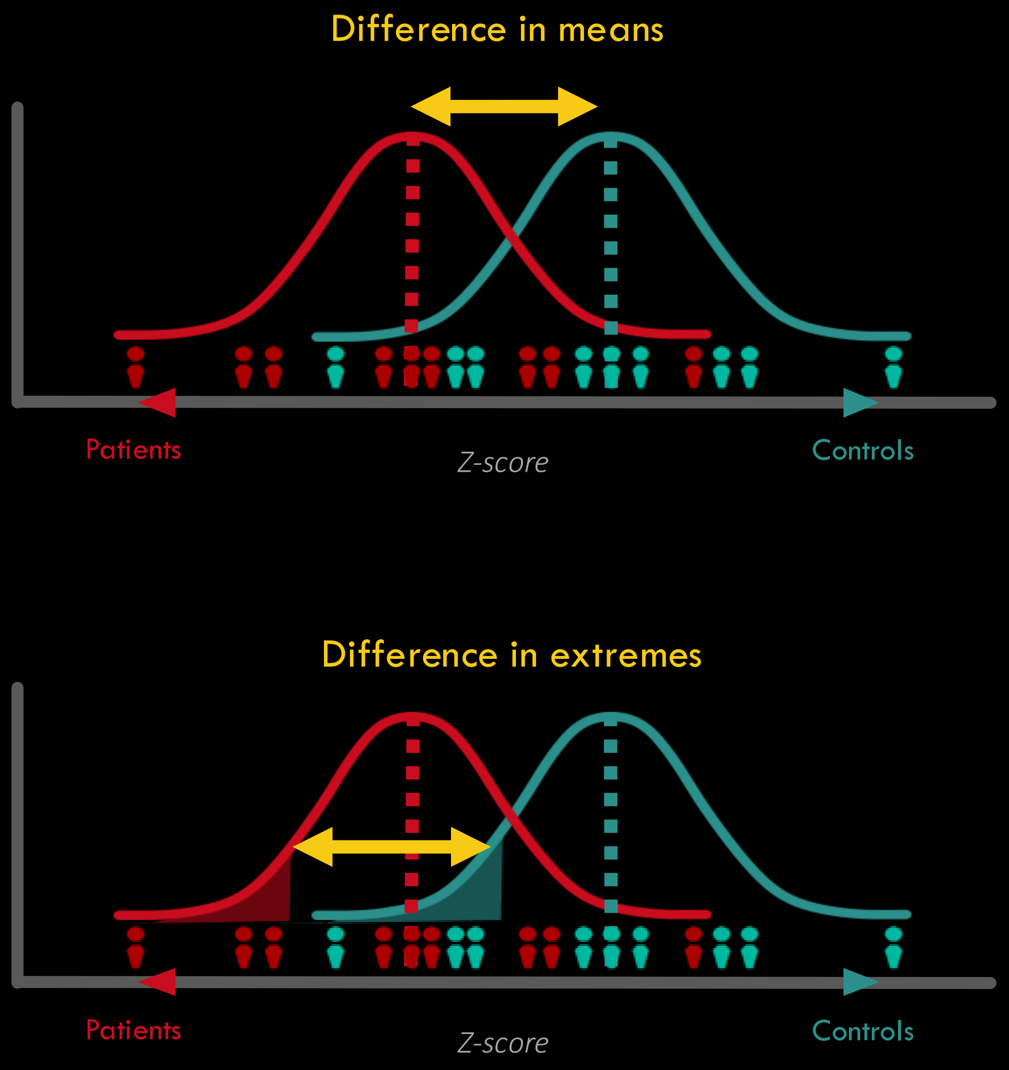
? Do patients show overlapping deviation scores in brain regions significantly different from control group ?

APPLICATIONS

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

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

PARSING HETEROGENEITY



APPLICATIONS

- Training and evaluating the normative model on local dataset

- Using pre-trained models, evaluating on local datasets

PARSING HETEROGENEITY

APPLICATIONS: Structural Imaging

- 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

ROI/Voxels →

Subjects ↑

Cortical thickness/ surface area (Y)

Predictors →

Subjects ↑

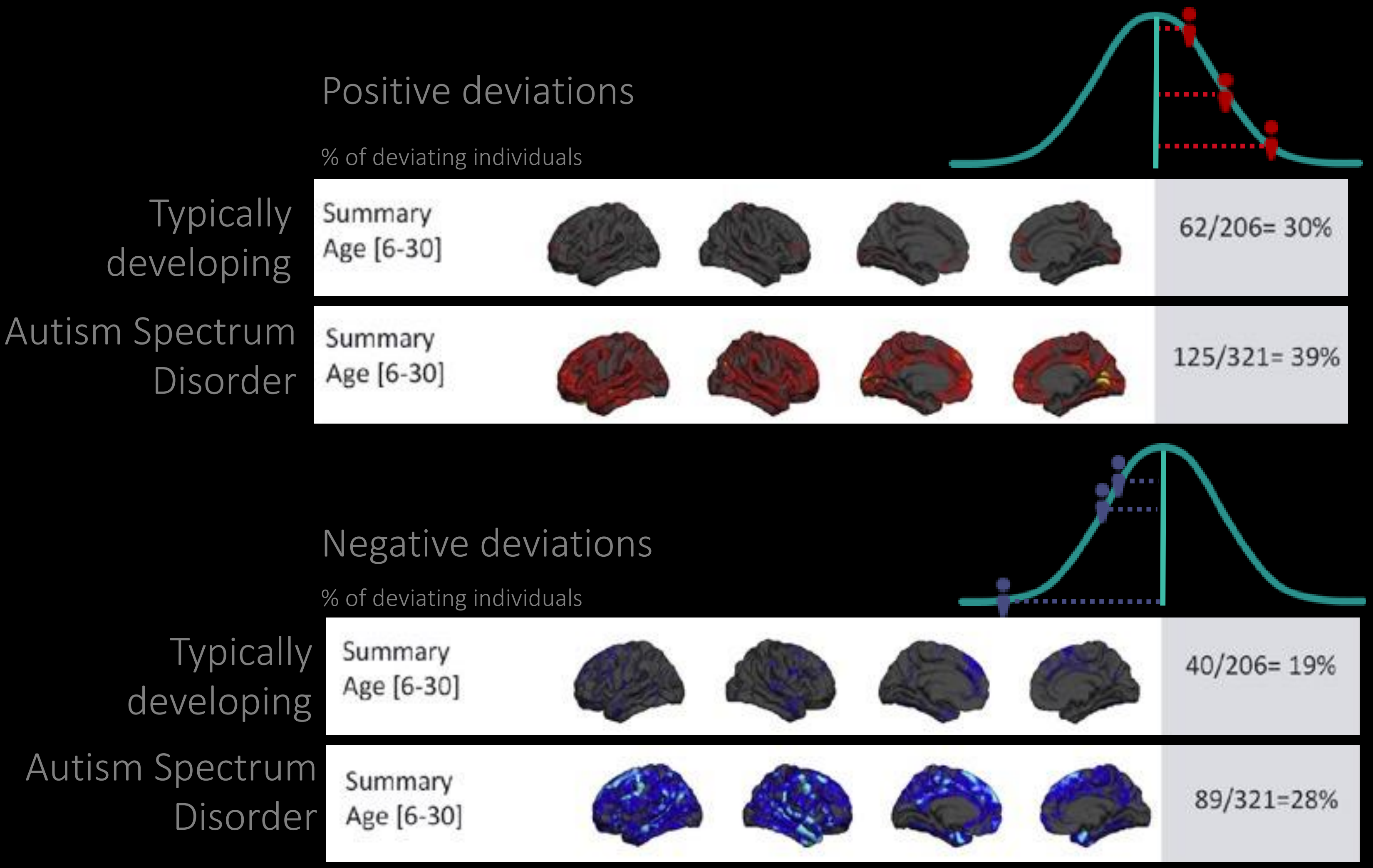
Age
Sex
Site

(X)

PARSING HETEROGENEITY

APPLICATIONS: Structural Imaging

- Training and evaluating the normative model on local dataset



Zabihi, M., et al., (2019) Dissecting the Heterogeneous Cortical Anatomy of Autism Spectrum Disorder Using Normative Models. Biol Psychiatry Cogn Neurosci Neuroimaging, 4(6): 567-578.

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset

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

Bold Signal

Covariates (age, sex, Task parameters)

Model parameters

Residuals

Voxels →

Subjects →

Z-statistic image (Y)

Predictors →

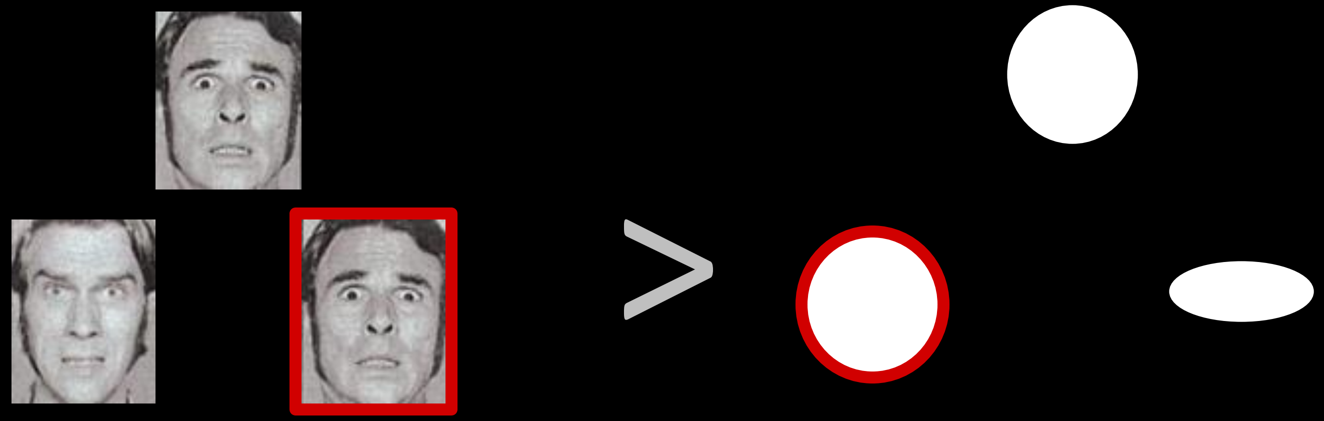
Subjects →

Age	Site
Sex	Scanner strength
	TR
Task length	Multiband-factor
# of target blocks	# of volumes acquired
Instructions	

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset



MATCH FACES/EMOTION MATCH SHAPES

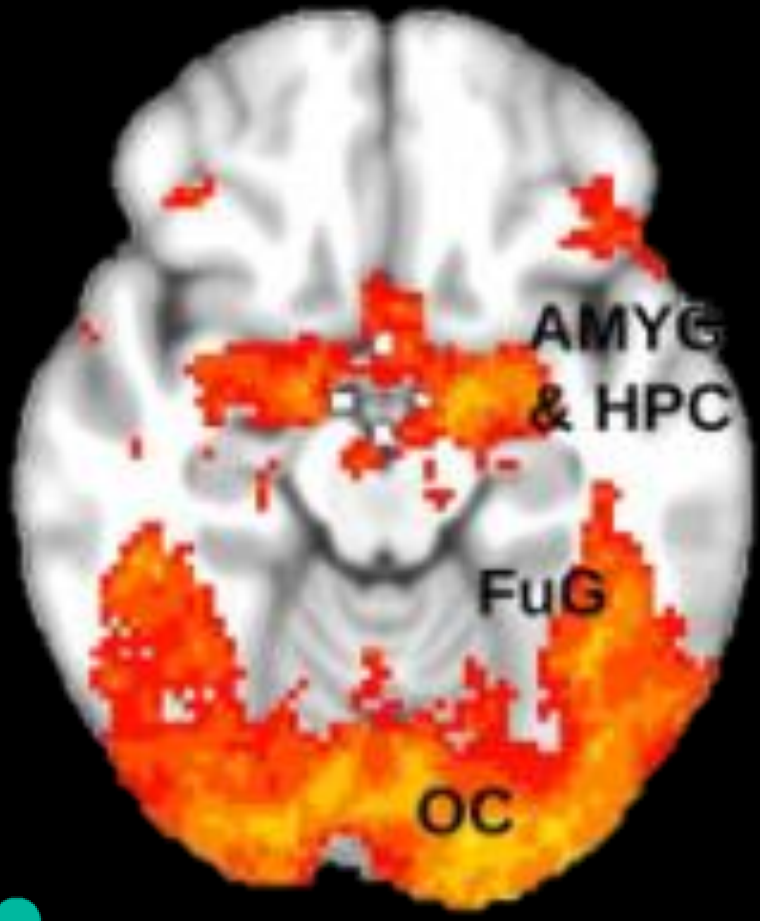
Viering et al (2021) doi: 10.1007/s00787-021-01809-3

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset

FACES/EMOTION SHAPES



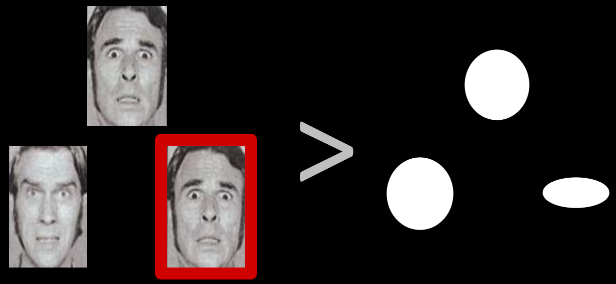
Unaffected controls

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

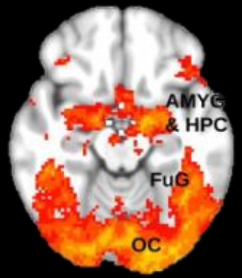
PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

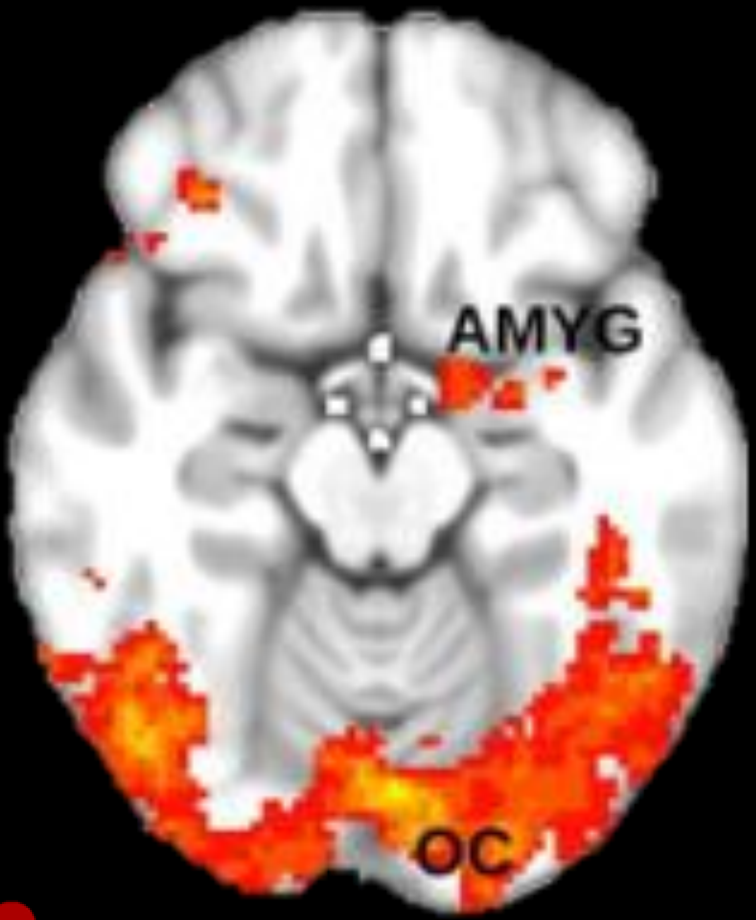
- Training and evaluating the normative model on local dataset



FACES/EMOTION SHAPES



Unaffected controls



Patients

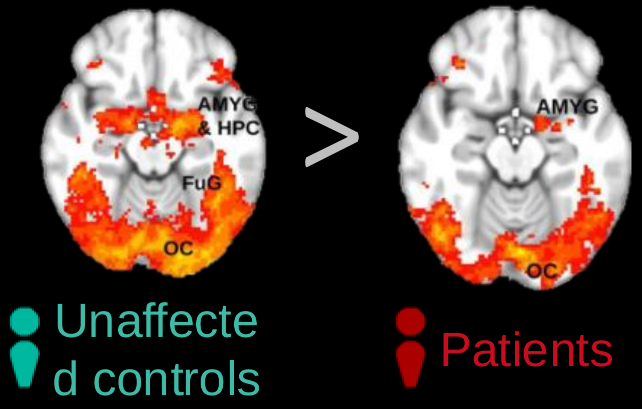
Viering et al (2021) doi: 10.1007/s00787-021-01809-3

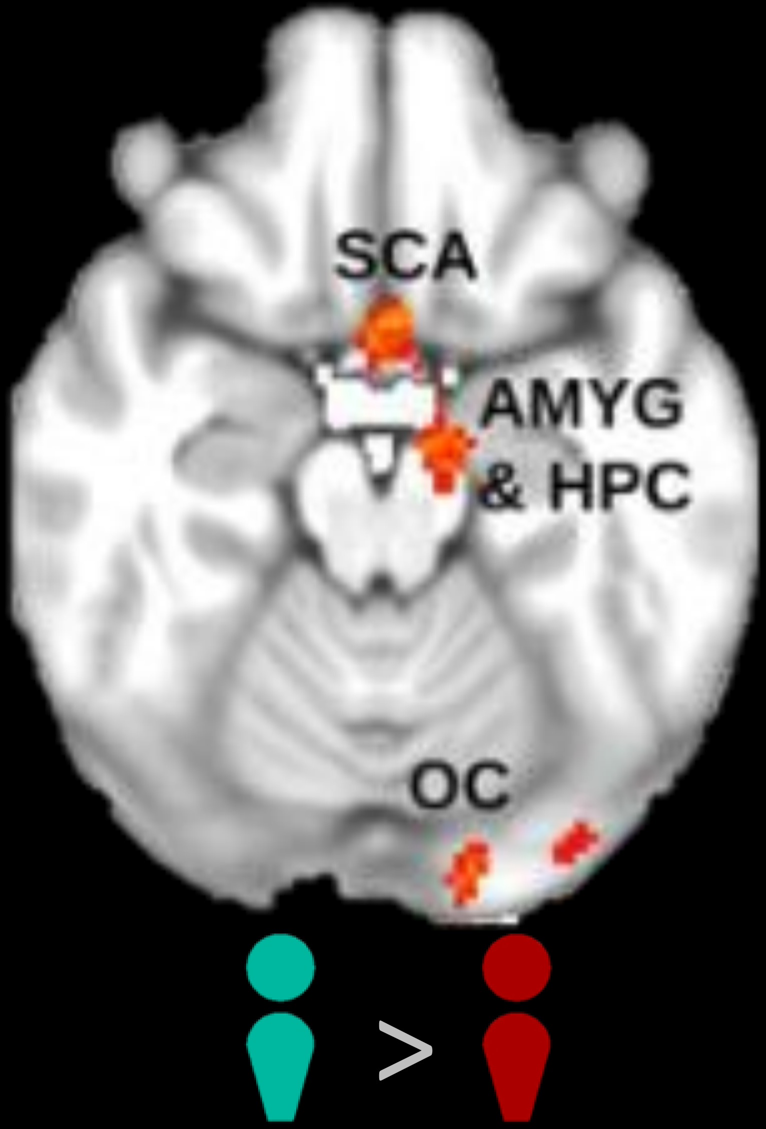
PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset

FACES/EMOTION SHAPES



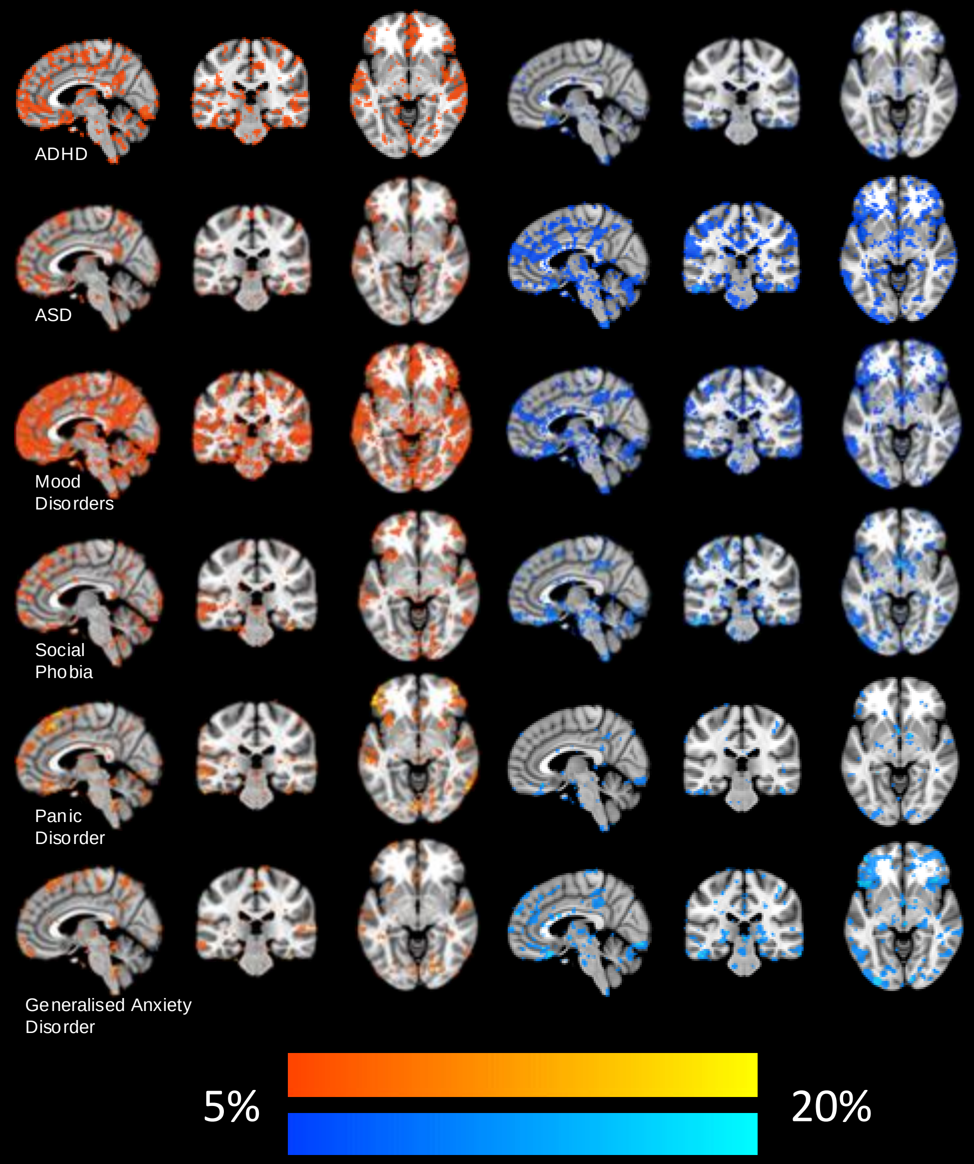


Viering et al (2021) doi: 10.1007/s00787-021-01809-3

PARSING HETEROGENEITY

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.

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Using pre-trained models, evaluating on local datasets

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

Cortical thickness/ surface area

Covariates (age, sex, site)

Model parameters

Residuals

ROI/Voxels →

Subjects ↑

Cortical thickness/ surface area (Y)

Predictors →

Subjects ↑

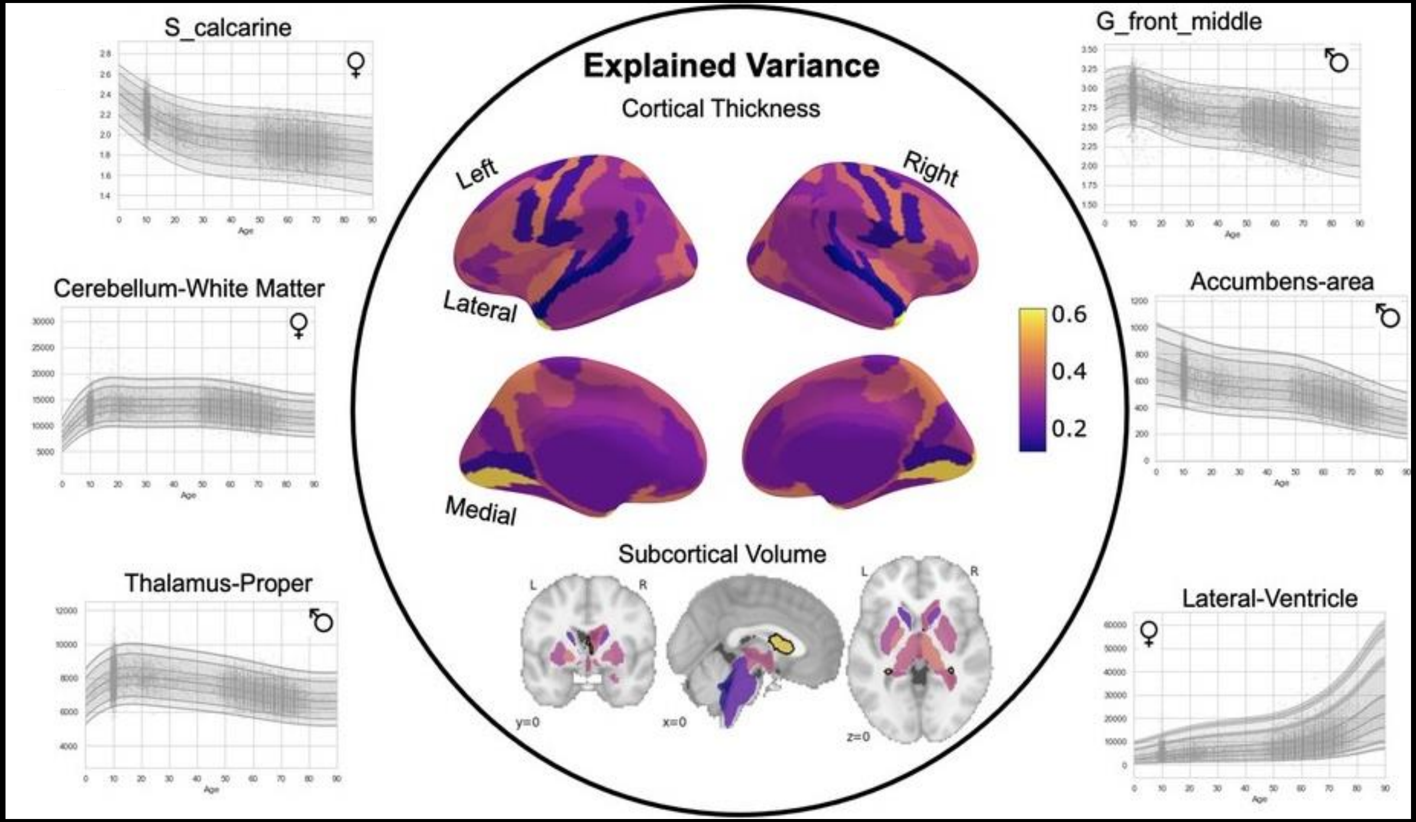
Age
Sex
Site

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- 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

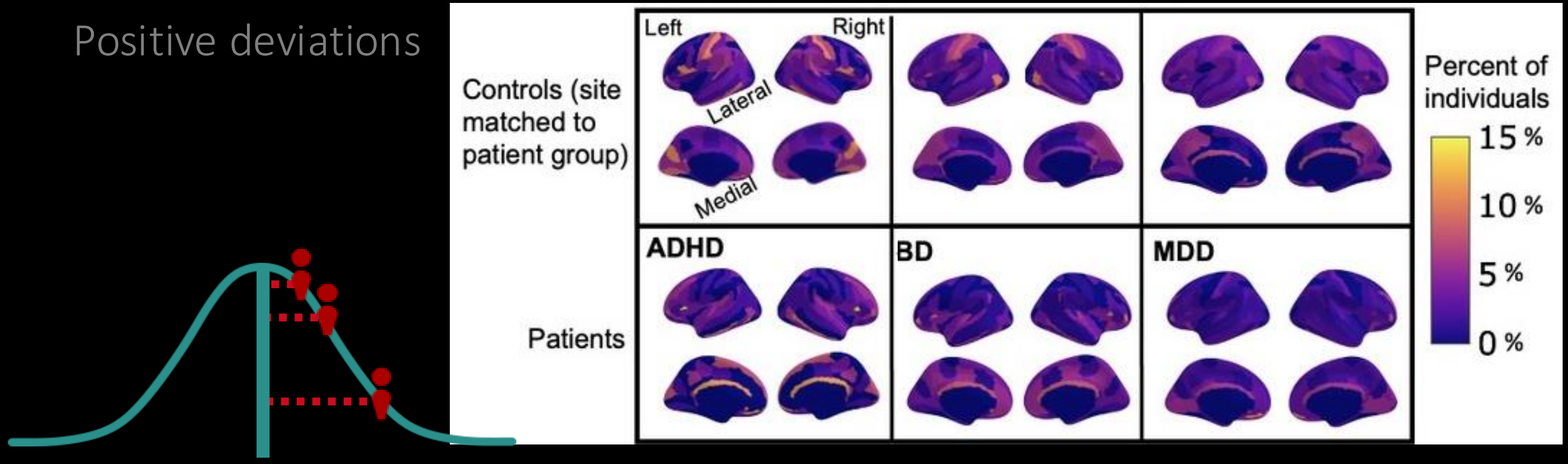
Saige Rutherford et al., (2022) Charting brain growth and aging at high spatial precision. *eLife* **11**:e72904.

PARSING HETEROGENEITY

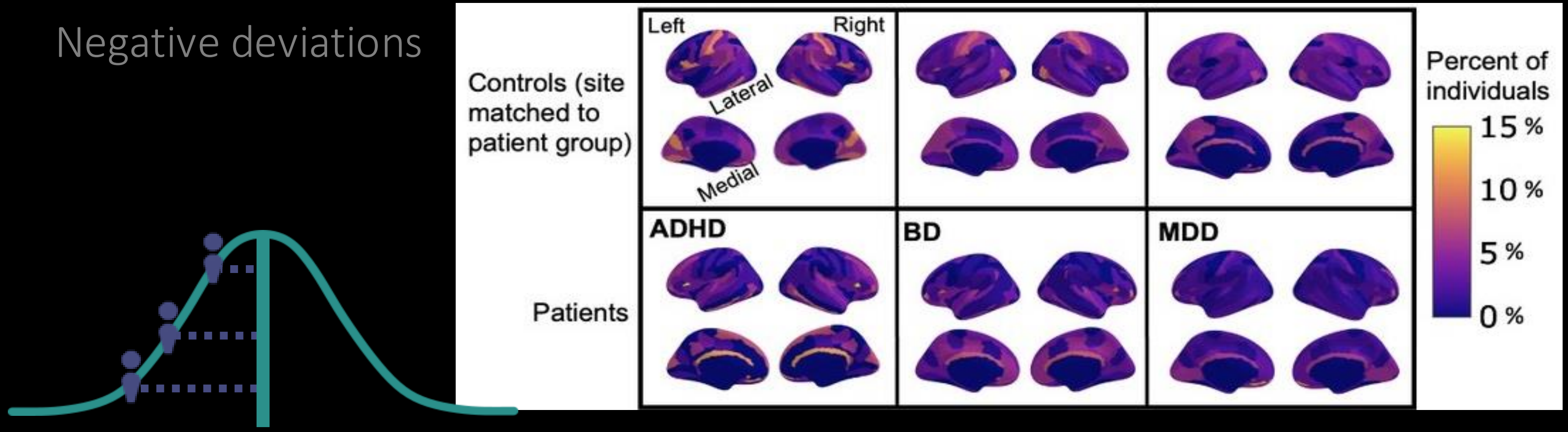
APPLICATIONS: Functional Imaging

- Using pre-trained models, evaluating on local datasets
  - 58,836 individuals
  - 82 scan sites
  - aged 2–100

Positive deviations



Negative deviations



Normative models for cortical thickness and subcortical volumes derived from Freesurfer

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

APPLICATIONS

Parsing heterogeneity

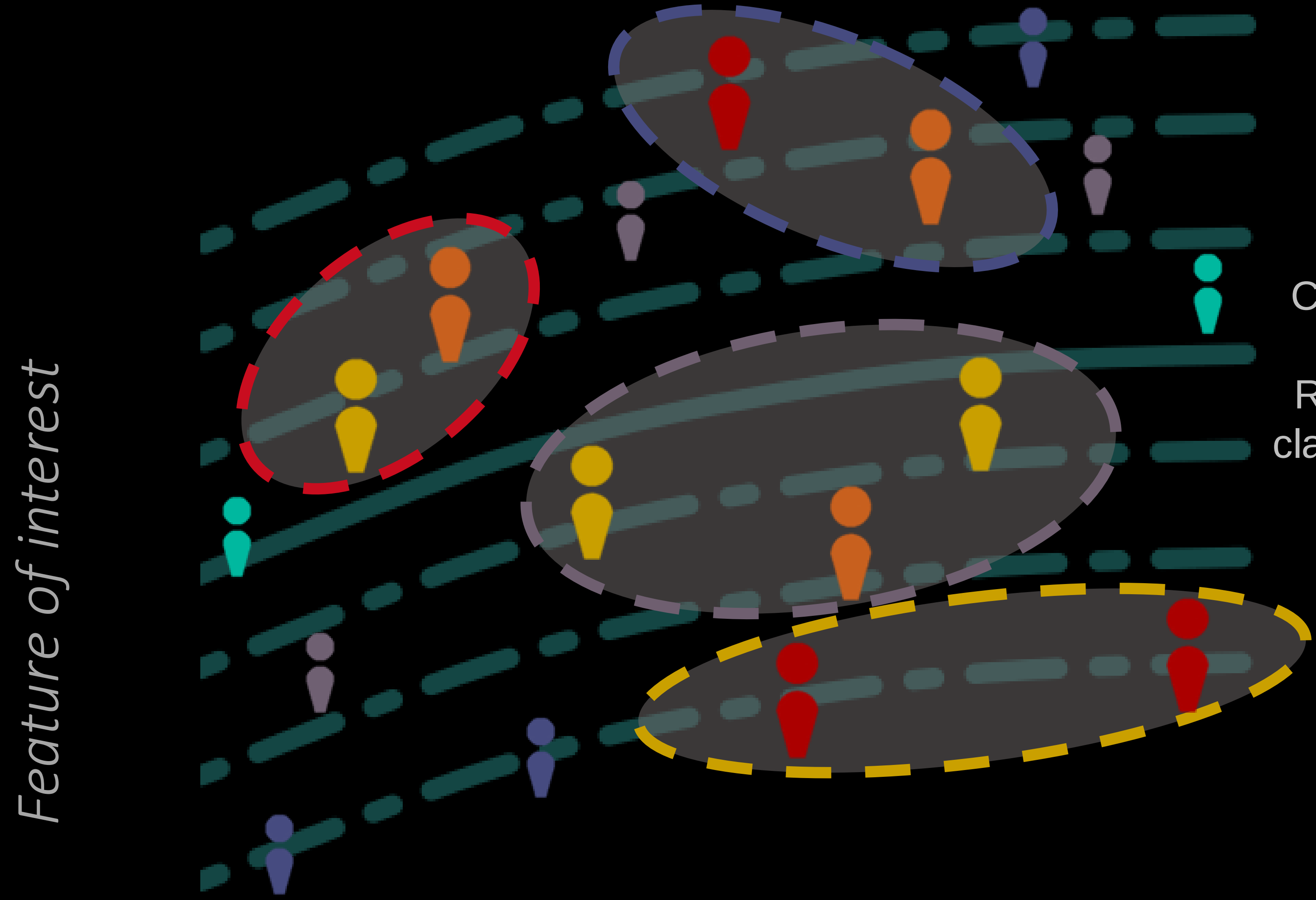
Neurobiological subtyping

Brain-behavior mappings

Other

NEUROBIOLOGICAL SUBTYPING

APPLICATIONS

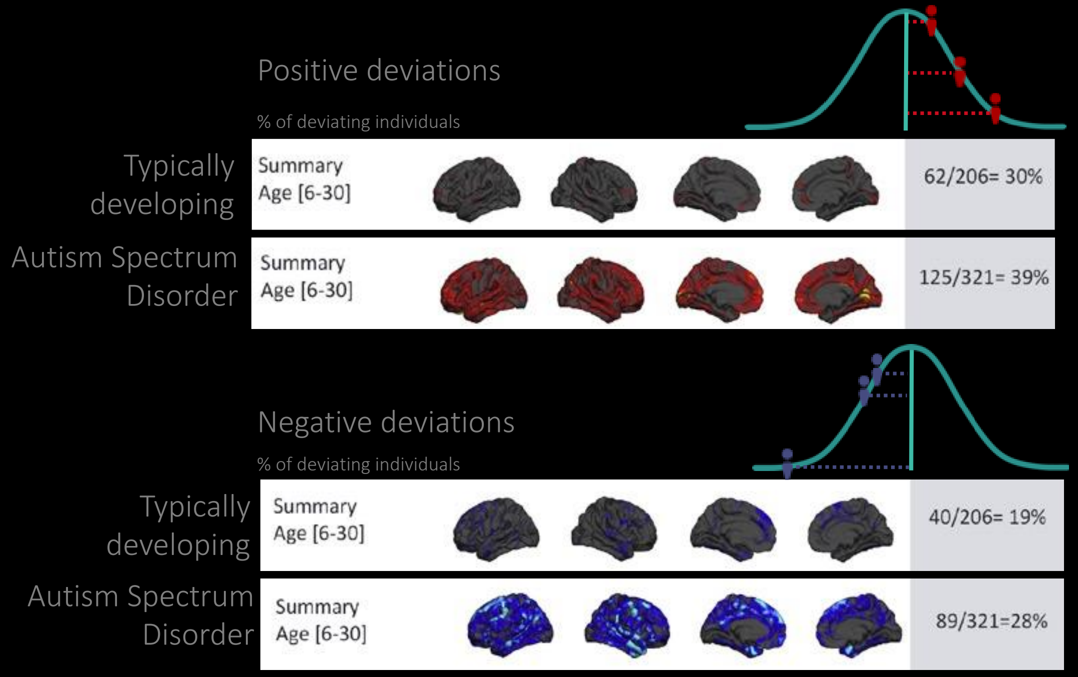


Clustering/
Community detection

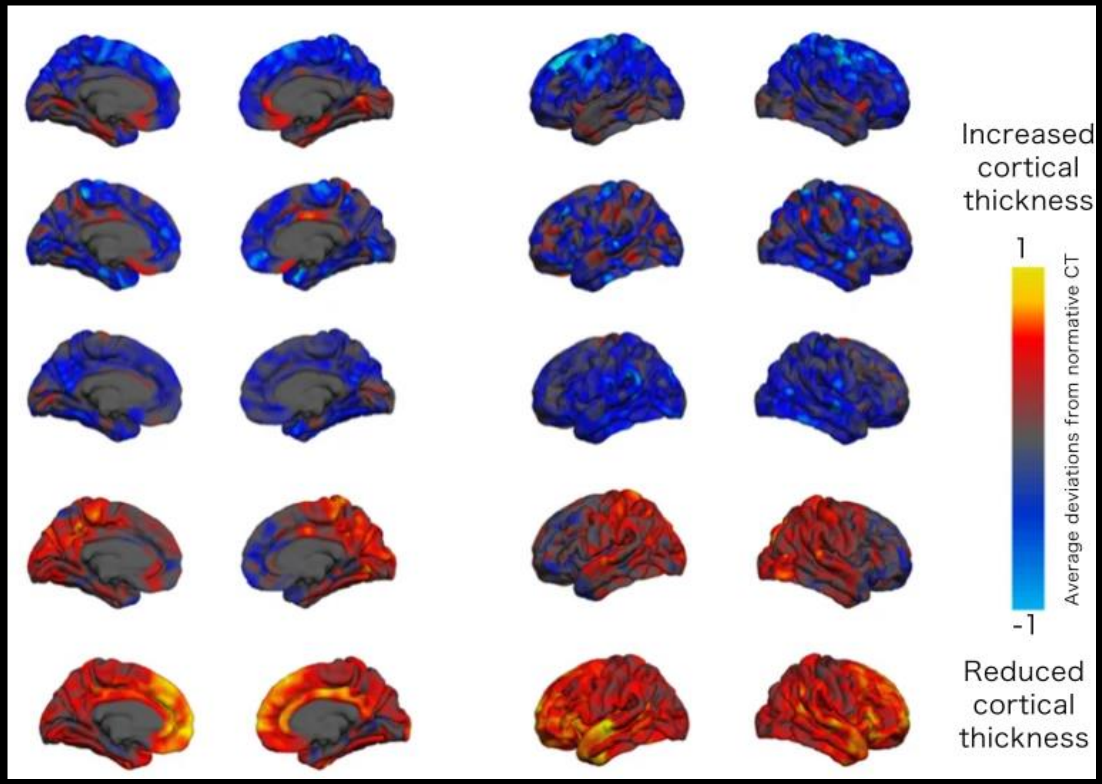
Regression model or
classification prediction
model

NEUROBIOLOGICAL SUBTYPING

APPLICATIONS



5 CLUSTERS



Zabihi, M., et al., (2020) **Fractionating autism based on neuroanatomical normative modeling.** Translational Psychiatry, 10.1: 384.

APPLICATIONS

Parsing heterogeneity

Neurobiological subtyping

Brain-behavior mappings

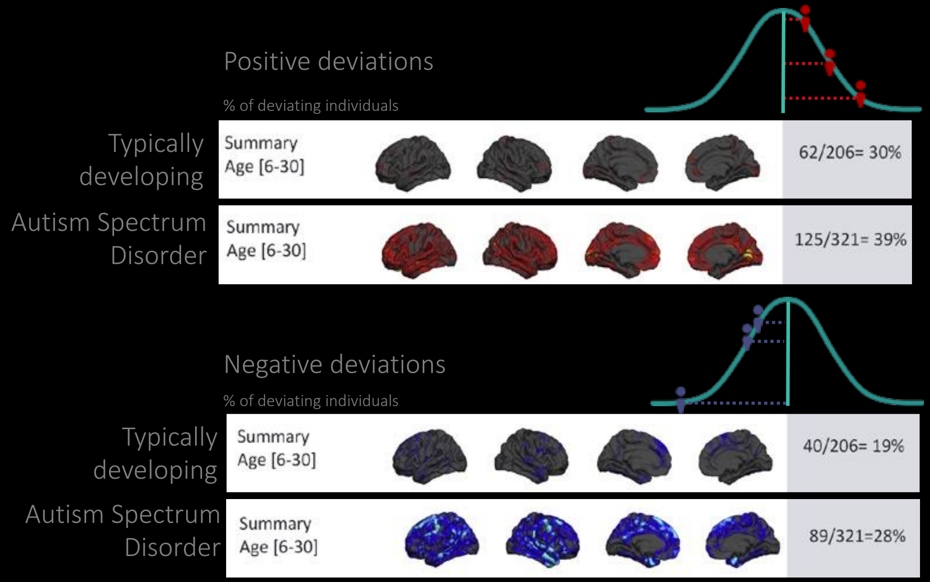
Other

BRAIN-BEHAVIOR MAPPINGS

APPLICATIONS

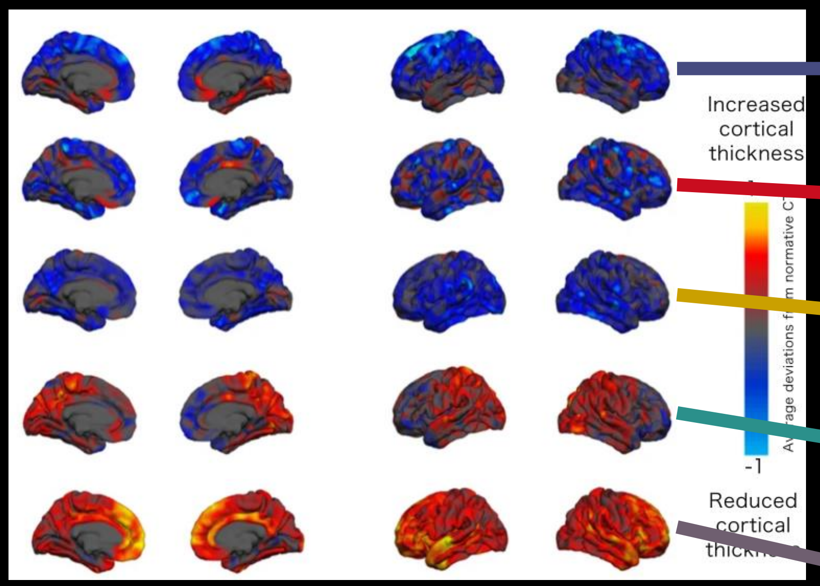
1.

Parse heterogeneity



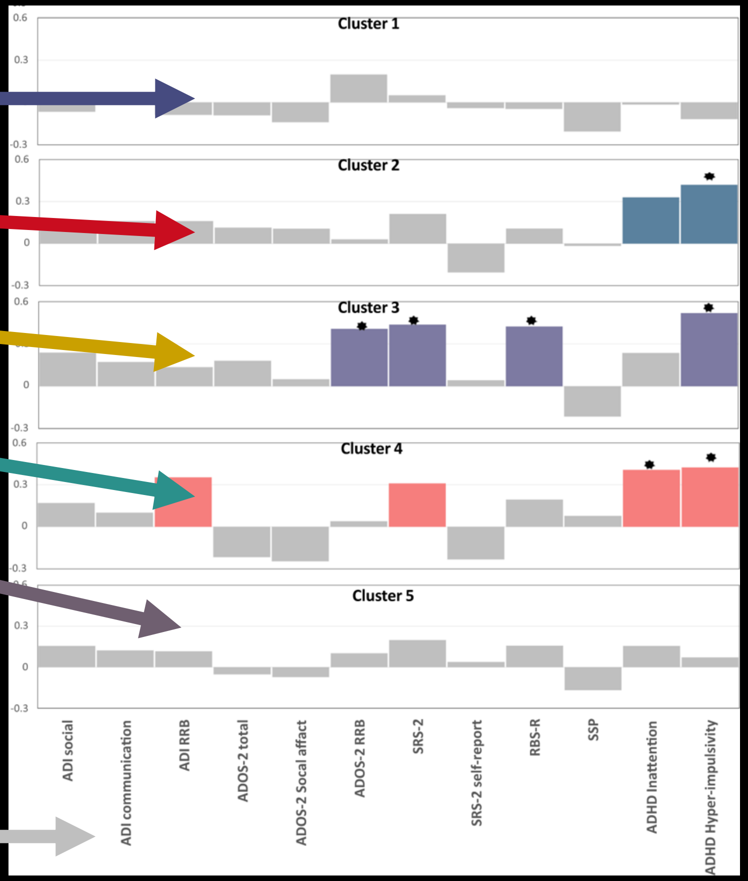
2.

Neurobiological subtyping



3.

Brain-behavior mappings



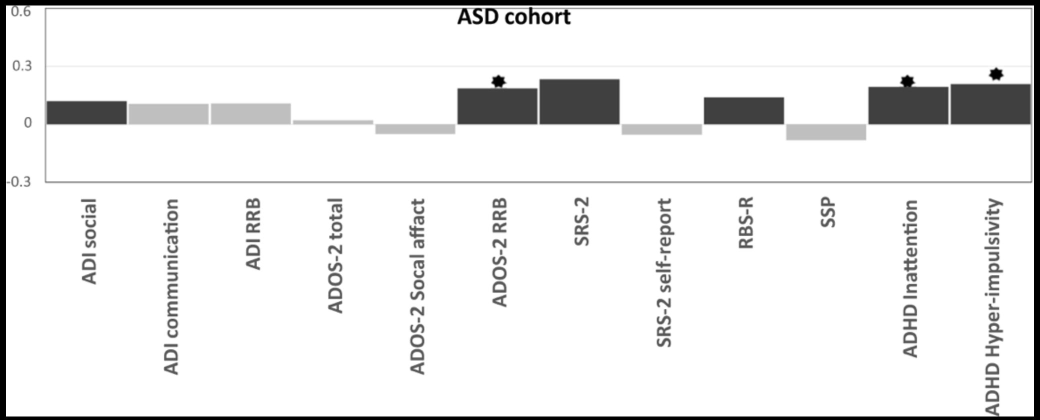
Behavioral scales

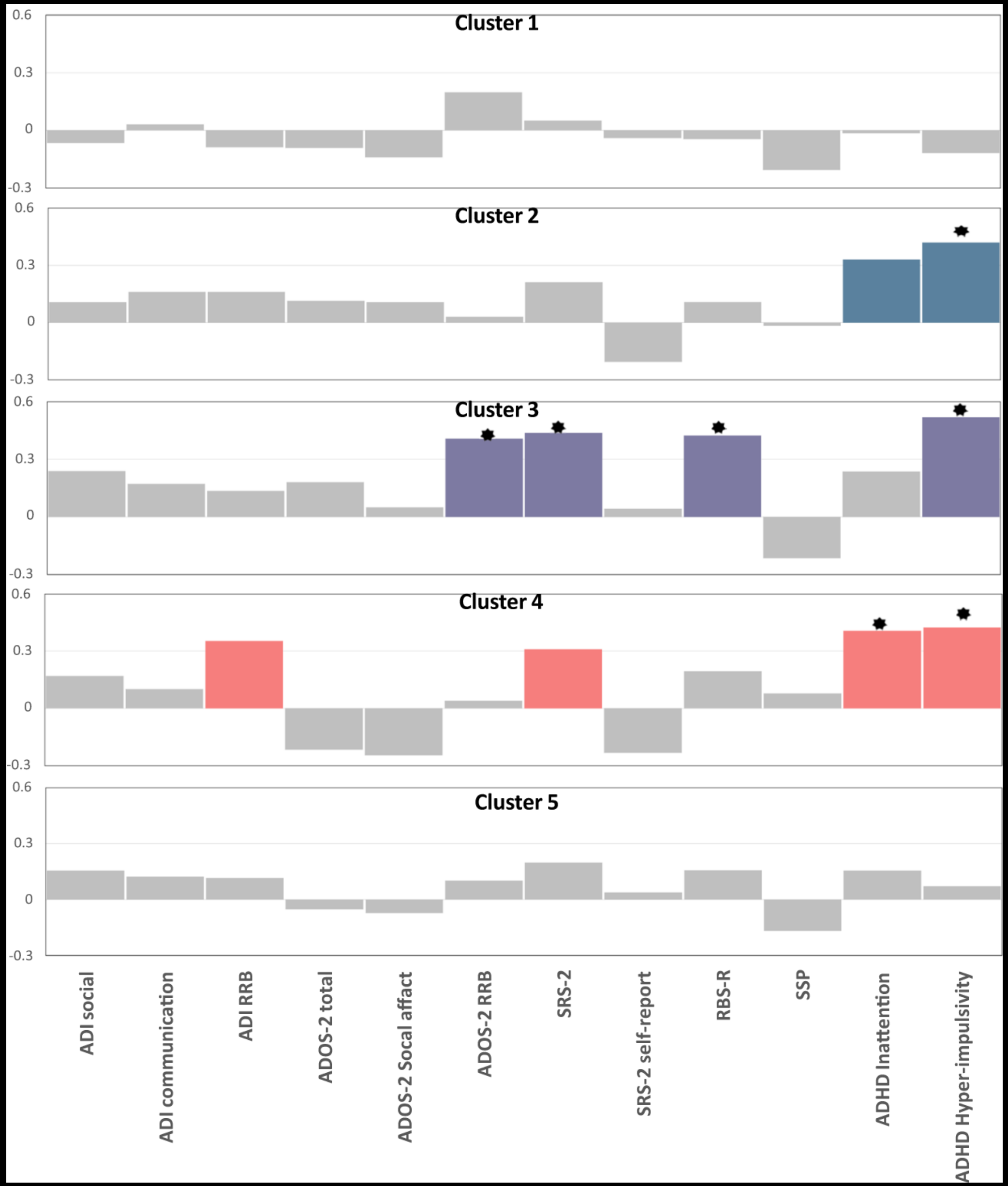
Zabihi, M., et al., (2020) **Fractionating autism based on neuroanatomical normative modeling.** Translational Psychiatry, 10.1: 384.

BRAIN-BEHAVIOR MAPPINGS

APPLICATIONS

- Relate identified deviation scores to behavioral measures related to psychopathology or disease severity



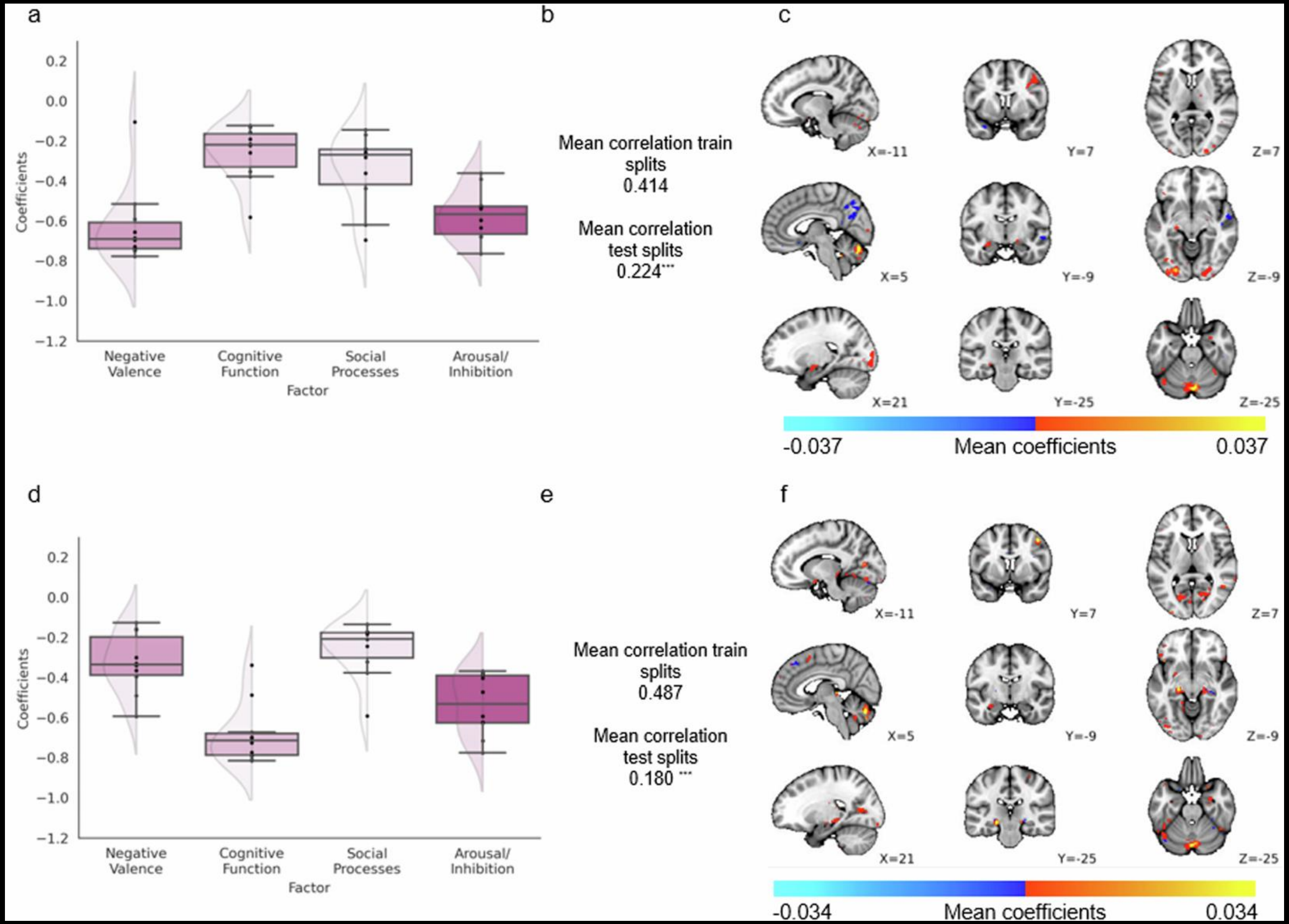


Zabihi, M., et al., (2020) **Fractionating autism based on neuroanatomical normative modeling.** Translational Psychiatry, 10.1: 384.

BRAIN-BEHAVIOR MAPPINGS

APPLICATIONS

- Relate identified deviation scores to behavioral measures related to psychopathology or disease severity



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

Parsing heterogeneity

Neurobiological subtyping

Brain-behavior mappings

Other

OTHER

APPLICATIONS

DTI

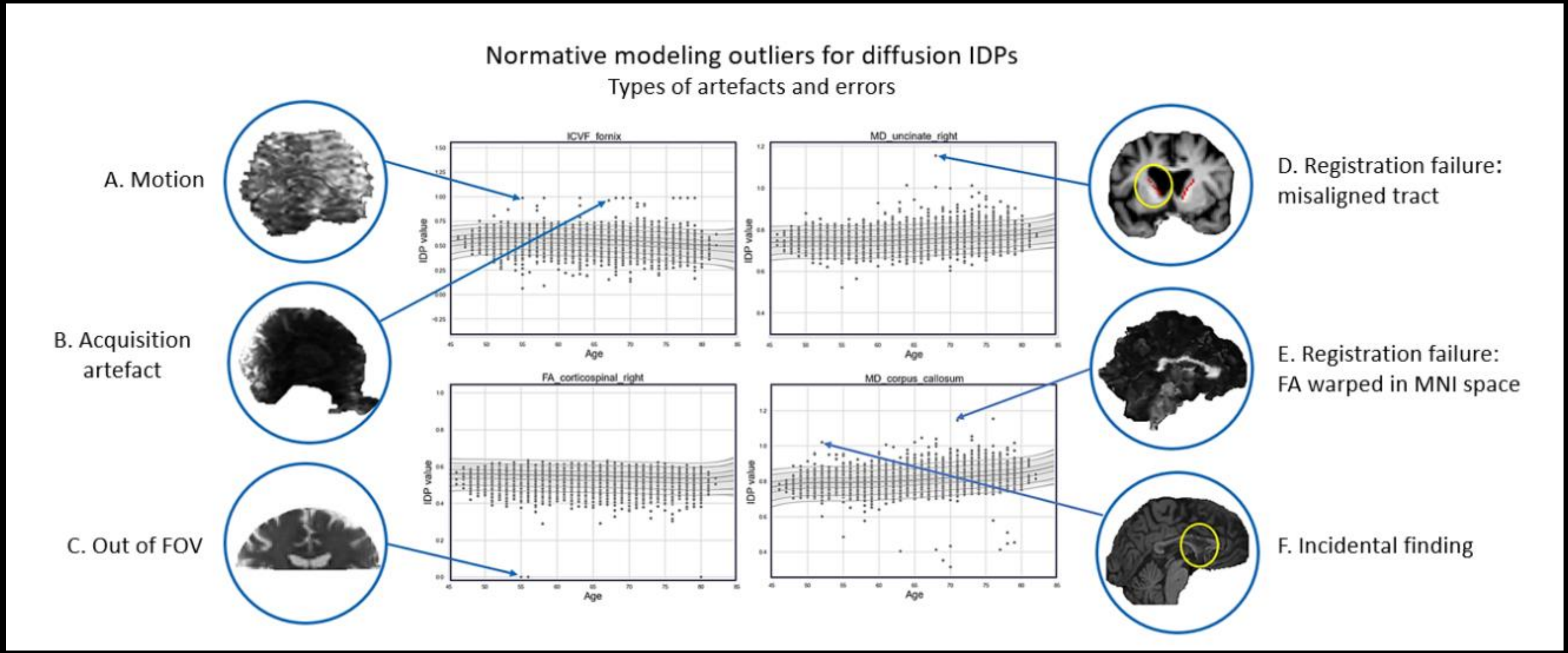
Ramona Cirstian
ramona.cirstian@donders.ru.nl

OTHER

APPLICATIONS

DTI

Ramona Cirstian
ramona.cirstian@donders.ru.nl

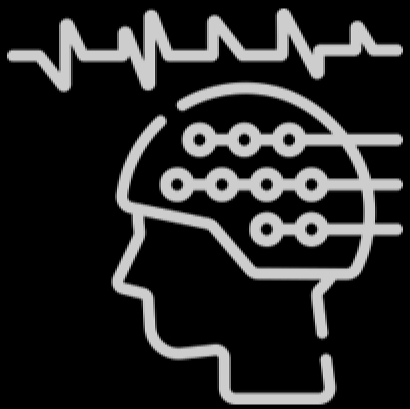


Ramona Cirstian et al., (2024) Objective QC for diffusion MRI data: artefact detection using normative modelling. *Imaging Neuroscience* 2: 1-14.

OTHER APPLICATIONS

DTI

Ramona Cirstian
ramona.cirstian@donders.ru.nl



EEG

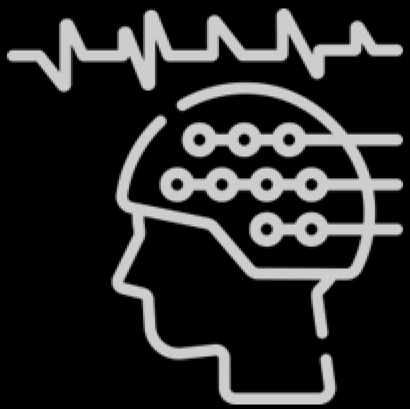
Seyed Mostafa Kia
S.M.Kia@tilburguniversity.edu

OTHER

APPLICATIONS

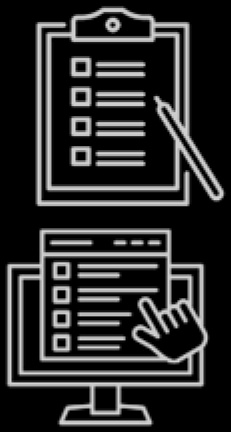
DTI

Ramona Cirstian
ramona.cirstian@donders.ru.nl



EEG

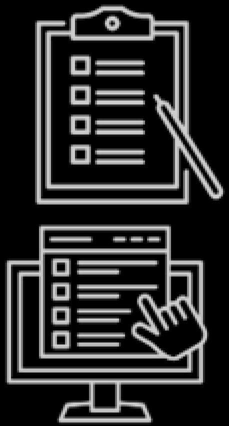
Seyed Mostafa Kia
S.M.Kia@tilburguniversity.edu



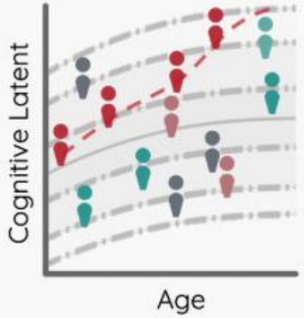
Psychometrics

OTHER

APPLICATIONS



Psychometrics



Focus groups

This project is dedicated to including individuals with **lived experiences of psychosis**, a commitment reflected in our team which comprises experts with firsthand knowledge of psychosis. The cornerstone of our research is in organizing focus groups to understand the lives of people living with psychosis and identify how cognition impacts their daily functioning.

Lifespan Cognitive Models

Driven by the information from focus groups, we aim to **develop lifespan cognitive reference models** that capture various aspects of cognition, such as processing speed, working memory, and verbal learning, among others. These models will be based on existing data resources of tens of thousands of participants across Europe.

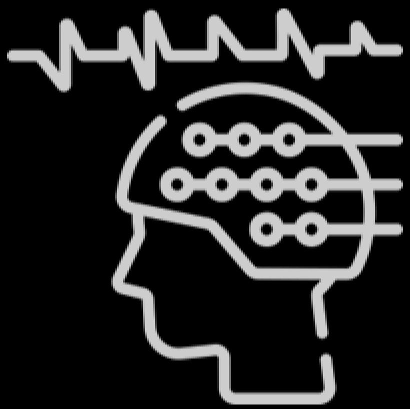
Individual Outcomes

Our overall aim is to **predict functional outcomes in individuals with psychosis** by using the cognitive lifespan models. These models will enable us to understand the progression of the disorder at an individual level and predict the early onset of psychosis. Using our framework, we hope to take the first steps towards individualized disease prediction and understanding.

OTHER APPLICATIONS

DTI

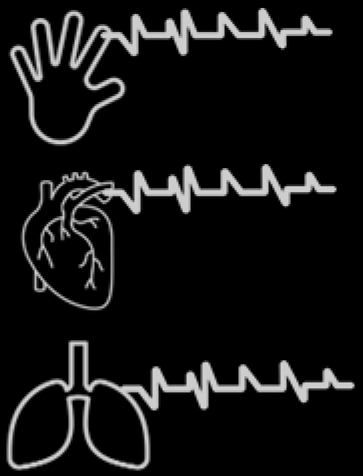
Ramona Cirstian
ramona.cirstian@donders.ru.nl



EEG

Seyed Mostafa Kia
S.M.Kia@tilburguniversity.edu

Psychometrics

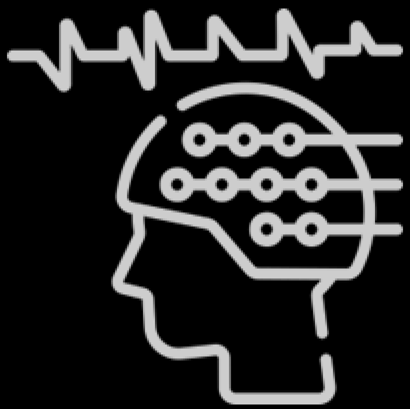


Physiology

OTHER APPLICATIONS

DTI

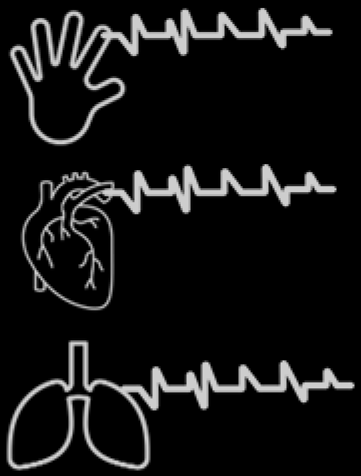
Ramona Cirstian
ramona.cirstian@donders.ru.nl



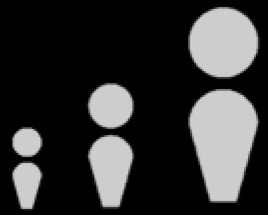
EEG

Seyed Mostafa Kia
S.M.Kia@tilburguniversity.edu

Psychometrics



Physiology



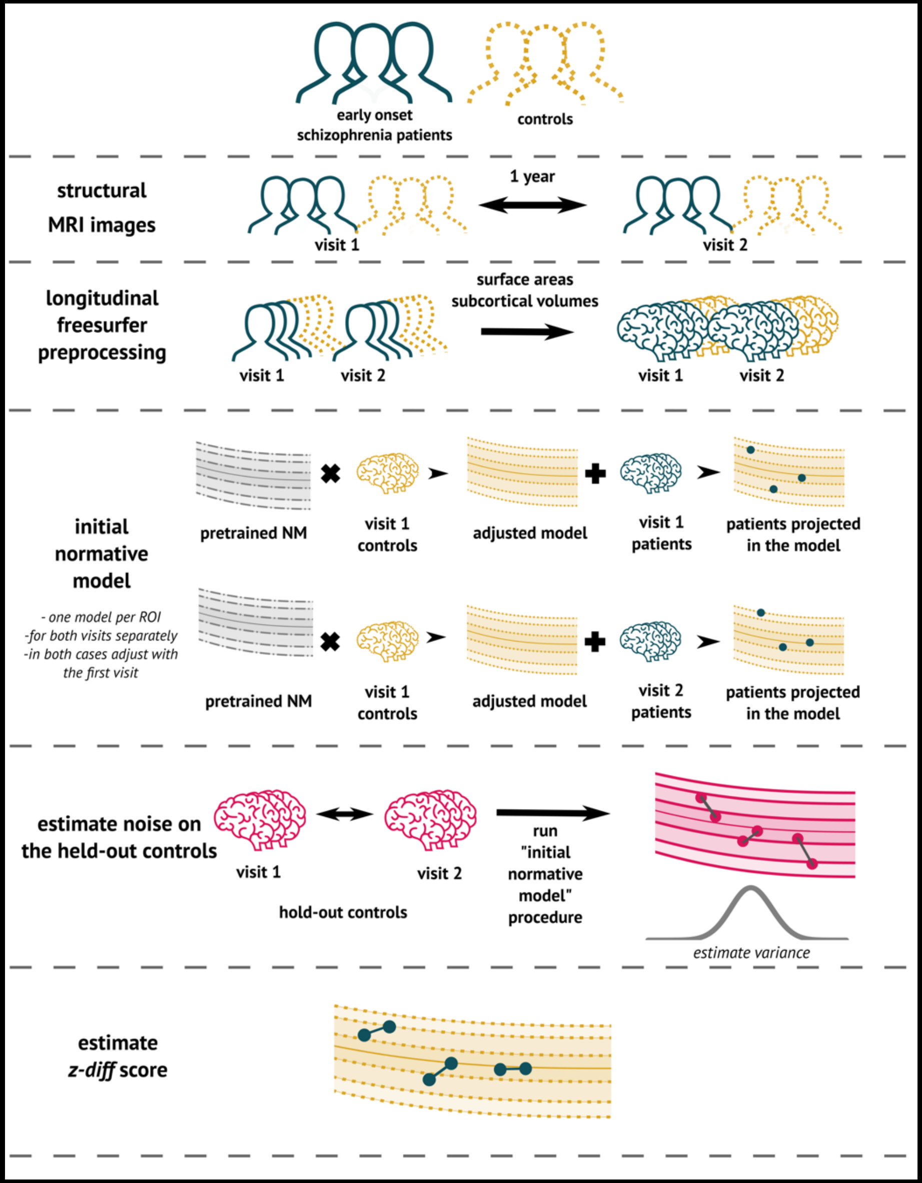
Longitudinal

OTHER

Longitudinal

- Lack of methods for evaluating longitudinal changes
- Lack of resources to construct a fully longitudinal model
- Use pre-trained models and longitudinal controls to estimate a “healthy change”

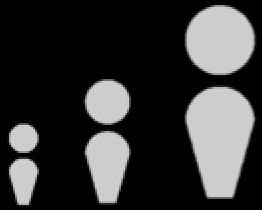
APPLICATIONS



Barbora Rehák Bučková et al., (2024) Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data *BioArxiv.*

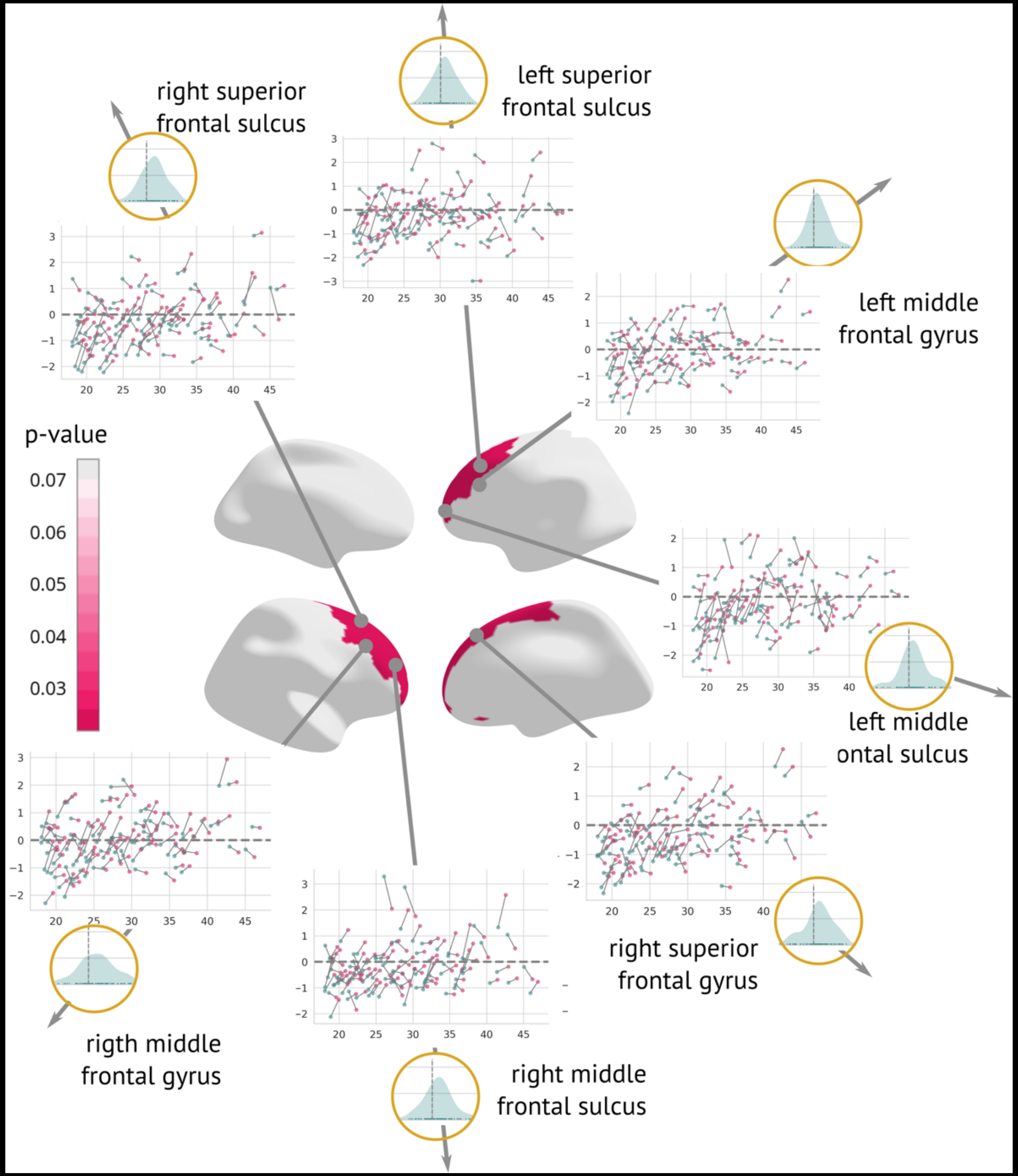
OTHER

APPLICATIONS



Longitudinal

- Lack of methods for evaluating longitudinal changes
- Lack of resources to construct a fully longitudinal model
- Use pre-trained models and longitudinal controls to estimate a "healthy change"



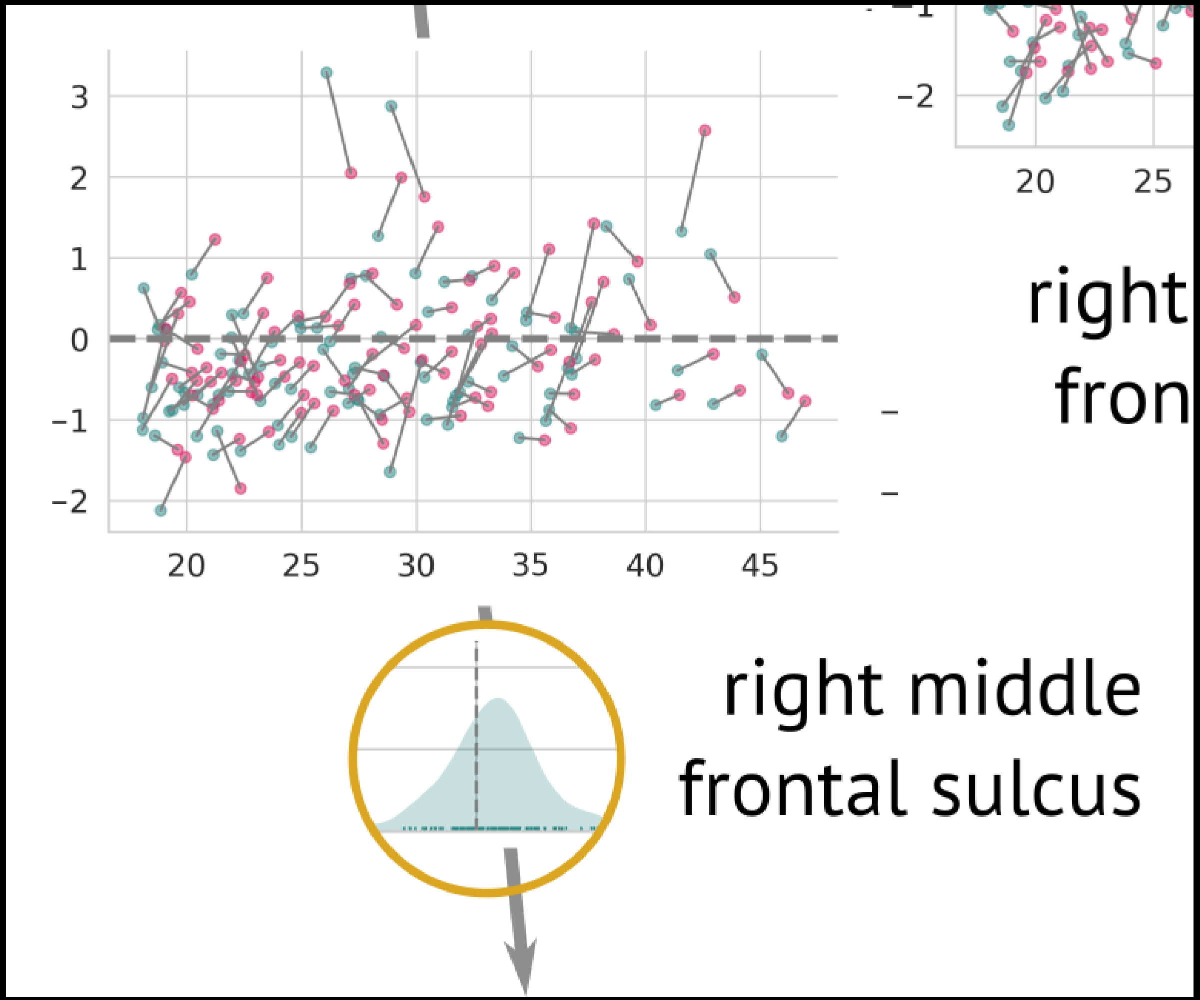
Barbora Rehák Bučková et al., (2024) Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data *BioArxiv.*

OTHER

Longitudinal

- Lack of methods for evaluating longitudinal changes
- Lack of resources to construct a fully longitudinal model
- Use pre-trained models and longitudinal controls to estimate a "healthy change"

APPLICATIONS



Barbora Rehák Bučková et al., (2024) Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data *BioArxiv.*

https://github.com/CharFraza/CPC_ML_tutorial

Tasks

Task 1: Fitting normative models from scratch Open in Colab

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

Task 3: Interpreting and visualizing the outputs of normative models Open in Colab

Task 4: Using the outputs (Z-scores) as features in predictive model Open in Colab

Task 1:	Task 2:	Task 3:	Task 4 :
9:00 - 9:45	10:00 -10:45	10:45 -11:15	11:15- 11:45

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

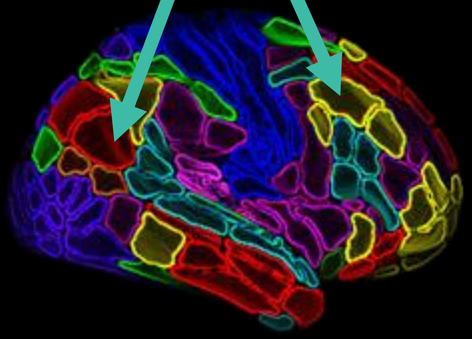
Install and load the packages

Clone the Github directory

Split data into train/test

Select variables for modelling

Select covariates & modelling parameters



TUTORIAL I.

ESTIMATING LIFESPAN NORMATIVE MODELS

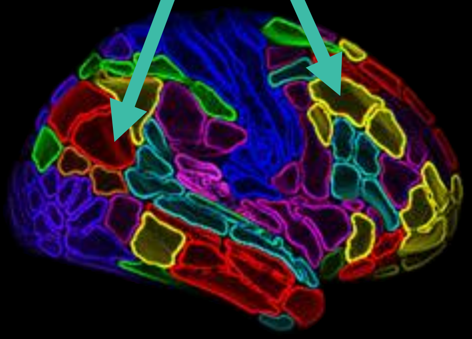
Install and load the packages

Clone the Github directory

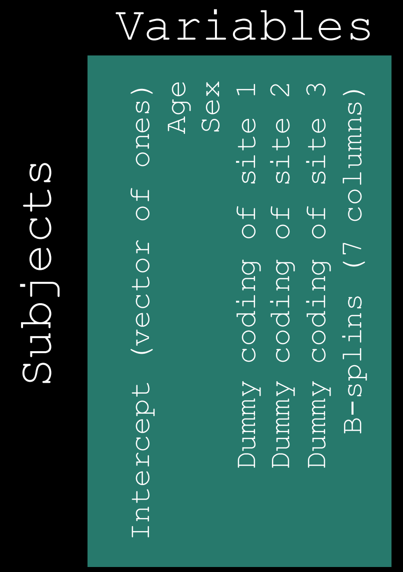
Split data into train/test

Select variables for modelling

Select covariates & modelling parameters



- ["age", "sex"]
- Warp modelled variable?
- Set-up B-spline
- Set-up outlier threshold

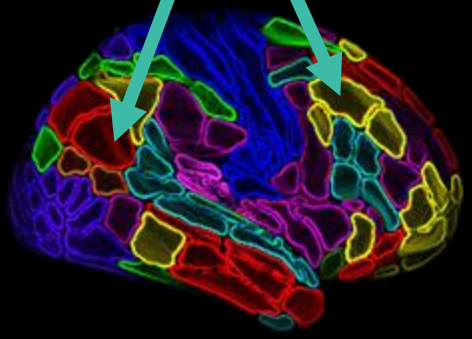


TUTORIAL I.

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



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

External training dataset

↓

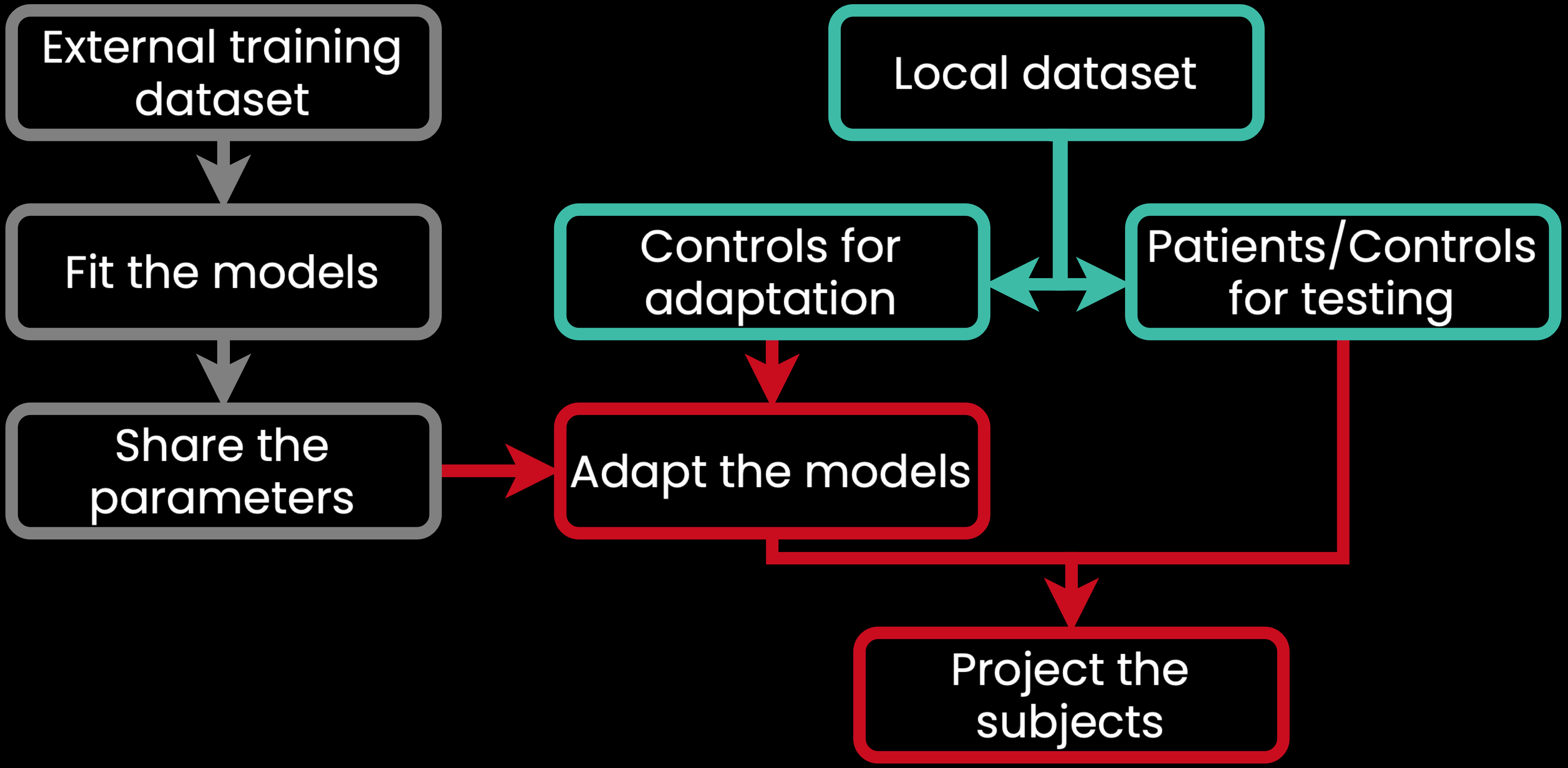
Fit the models

↓

Share the parameters

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS



TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS

- Install and load the packages
- Clone the Github directory
- Clone the pretrained models
- Download adaptation & test data

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
5. Select variables for modelling
6. Select covariates & modelling parameters
7. Adapt the pretrained models & run on test data

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS

Install and load the packages

Clone the Github directory

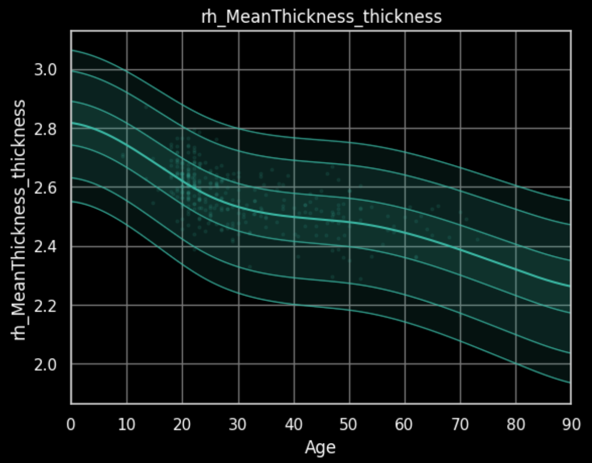
Clone the pretrained models

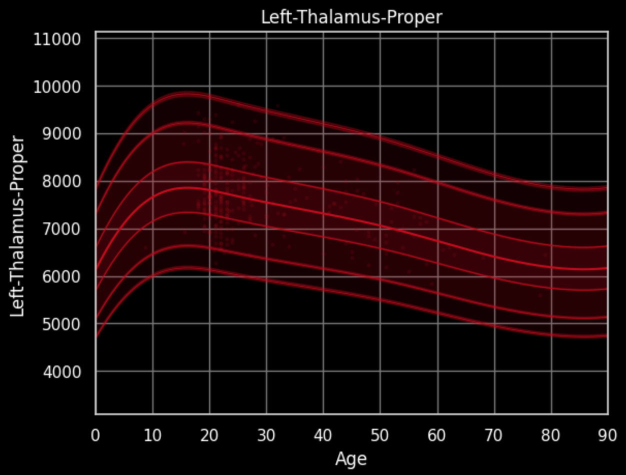
Download adaptation & test data

Select variables for modelling

Select covariates & modelling parameters

Adapt the pretrained models & run on test data





Visualize

TUTORIAL III.

INTERPRETING AND VISUALIZING THE OUTPUTS OF NORMATIVE MODELS

TUTORIAL III.

INTERPRETING AND VISUALIZING THE OUTPUTS OF NORMATIVE MODELS

Load the packages

Clone the Github directory

Download results

Compute statistics on z-scores

TUTORIAL III.

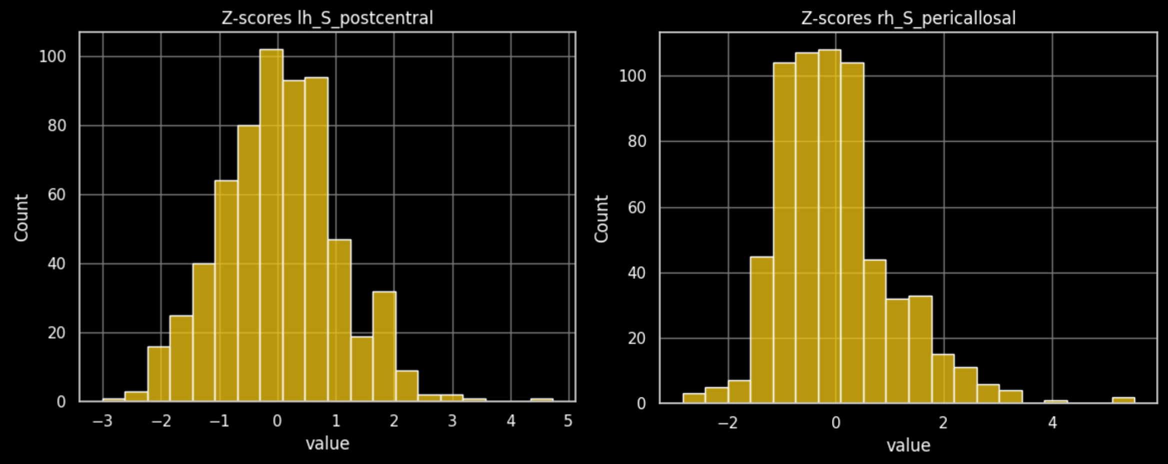
INTERPRETING AND VISUALIZING THE OUTPUTS OF NORMATIVE MODELS

Load the packages

Clone the Github directory

Download results

Compute statistics on z-scores



Visualize individual ROI histograms

TUTORIAL III.

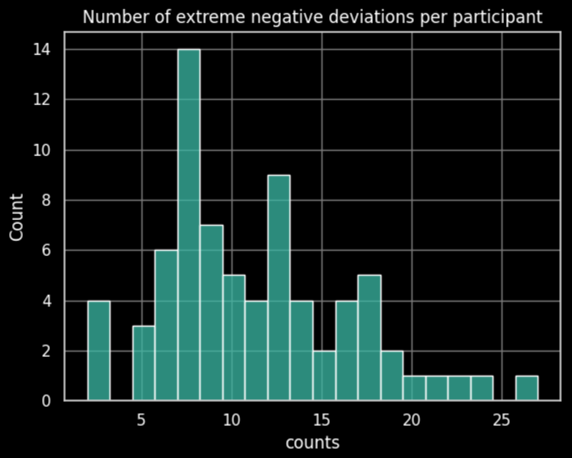
INTERPRETING AND VISUALIZING THE OUTPUTS OF NORMATIVE MODELS

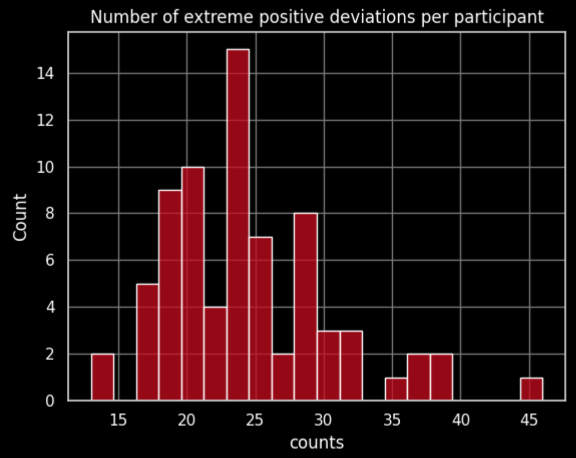
Load the packages

Clone the Github directory

Download results

Compute statistics on z-scores





Visualize individual ROI histograms

TUTORIAL III.

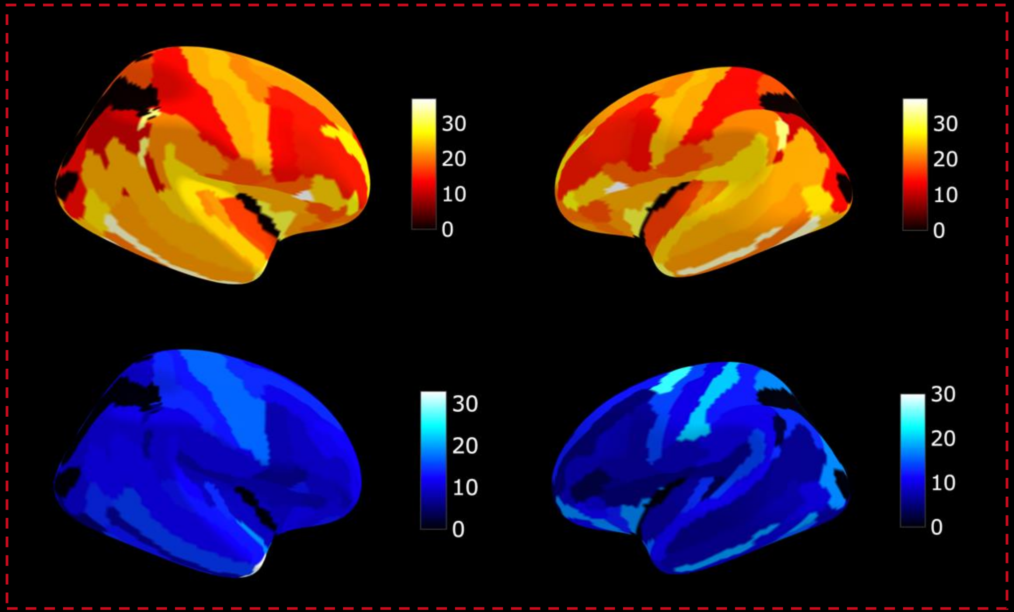
INTERPRETING AND VISUALIZING THE OUTPUTS OF NORMATIVE MODELS

Load the packages

Clone the Github directory

Download results

Compute statistics on z-scores



Visualize individual ROI histograms

Project results on cortical surface

TUTORIAL IV.

USING THE OUTPUTS AS FEATURES IN PREDICTIVE MODEL

- Load the packages
- Clone the Github directory
- Download results
- Train Support Vector Machine Model
- Evaluate

Download the toolbox here:
github.com/amarquand

pcnportal.dccn.nl

https://pcntoolkit.readthedocs.io

Predictive Clinical Neuroscience Lab

Professor Andre Marquand

THANK YOU!

Barbora.Rehak-Buckova@radboudumc.nl
Charlotte.Fraza@radboudumc.nl
Hannah.savage@ucl.ac.uk