Normative modelling:

the what, when and why

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Predictive Clinical Neuroscience Lab

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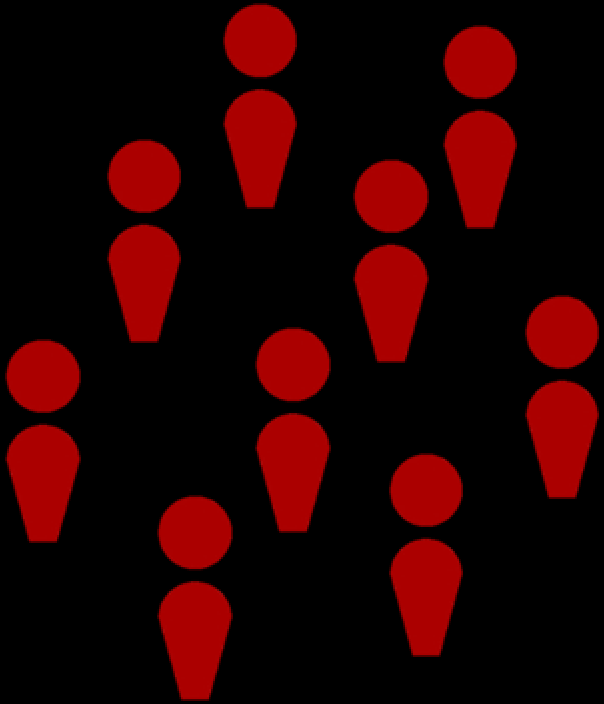
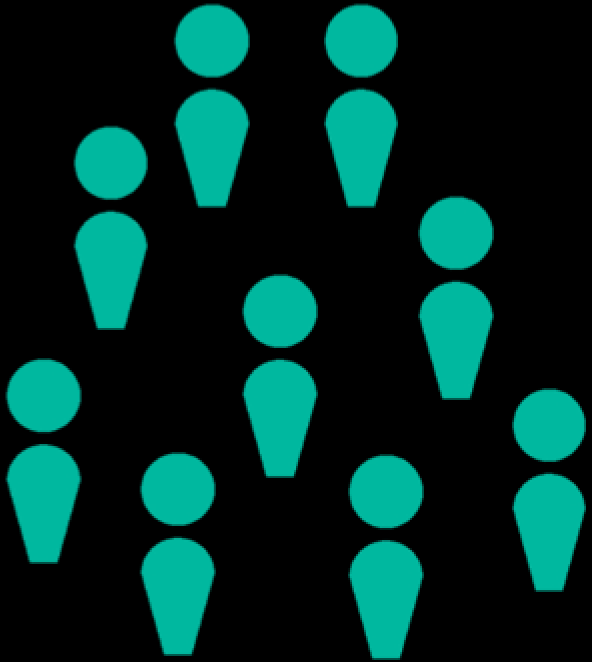
Slides by: @DrHannahSavage Dr. Charlotte Fraza @CharFraza Dr. Barbora Rehák Bučková @BarboraRehak

THE SHORTCOMINGS OF CLASSICAL STATISTICS

CASE **CONTROL**

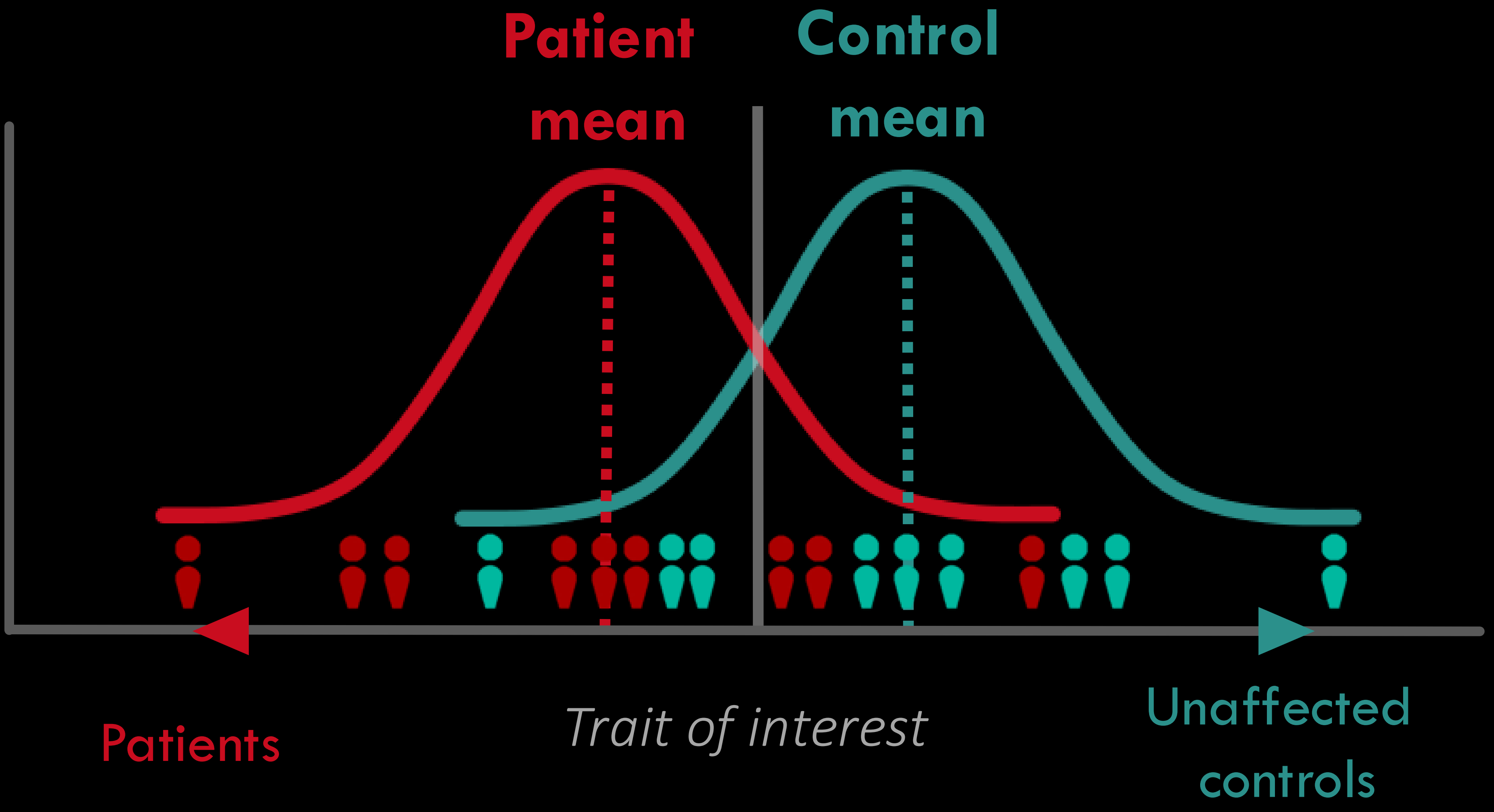


Patients



Unaffected controls

THE SHORTCOMINGS OF CLASSICAL STATISTICS



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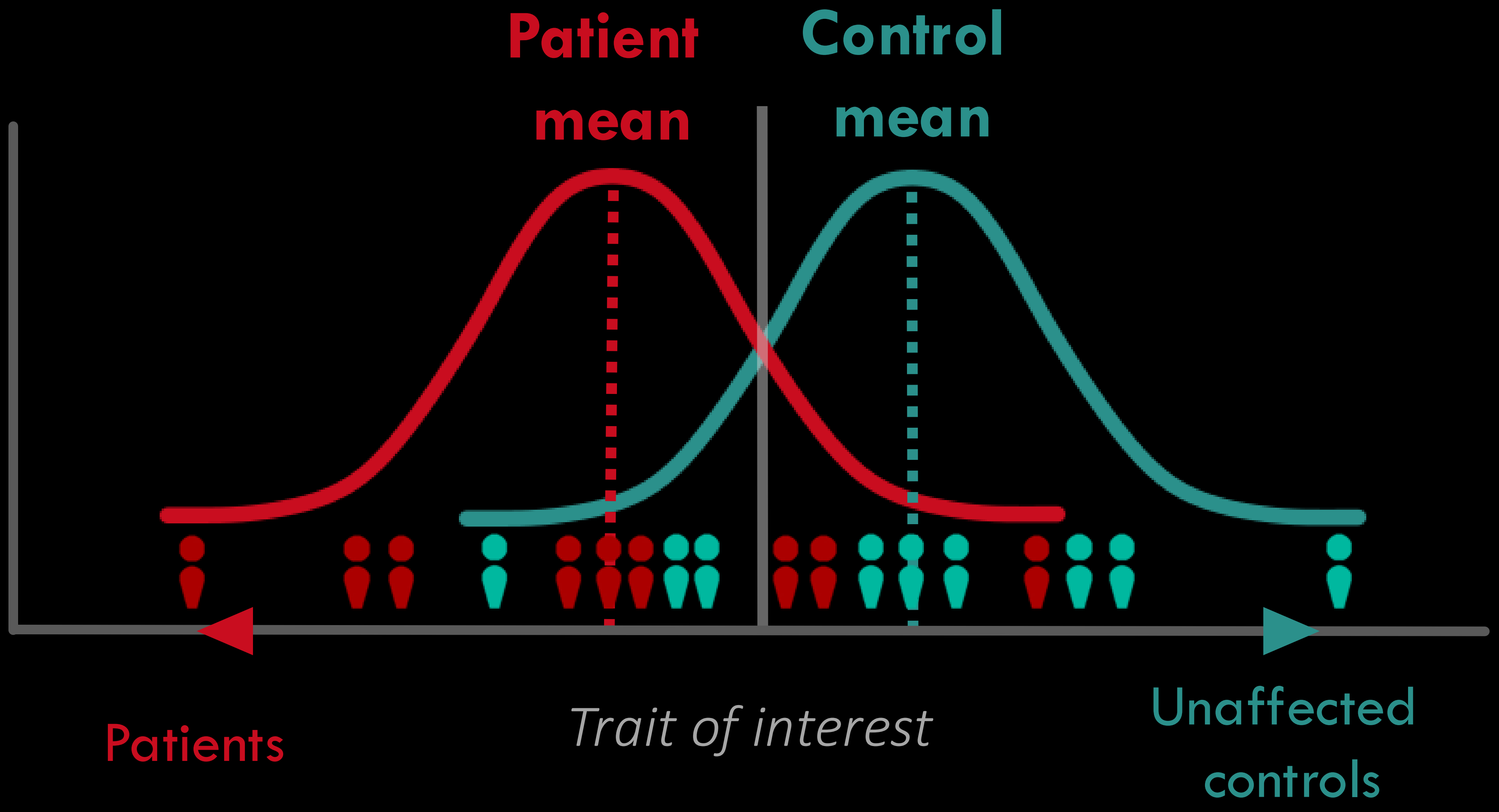
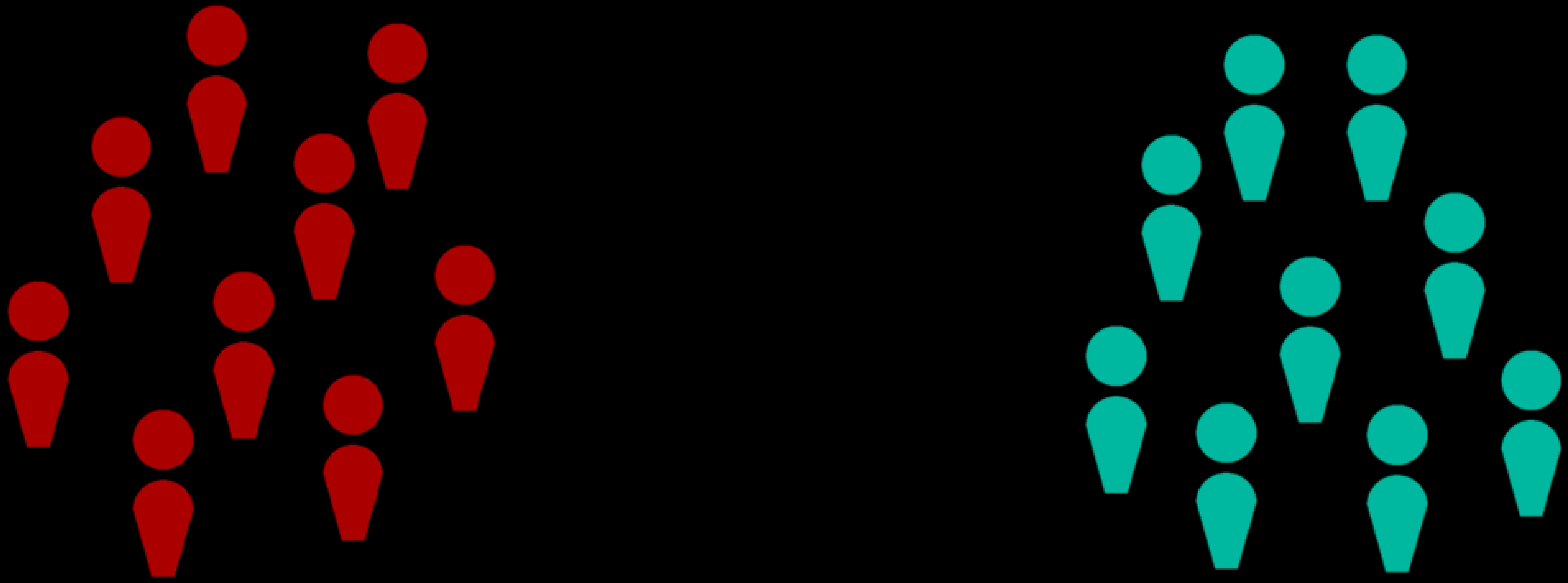


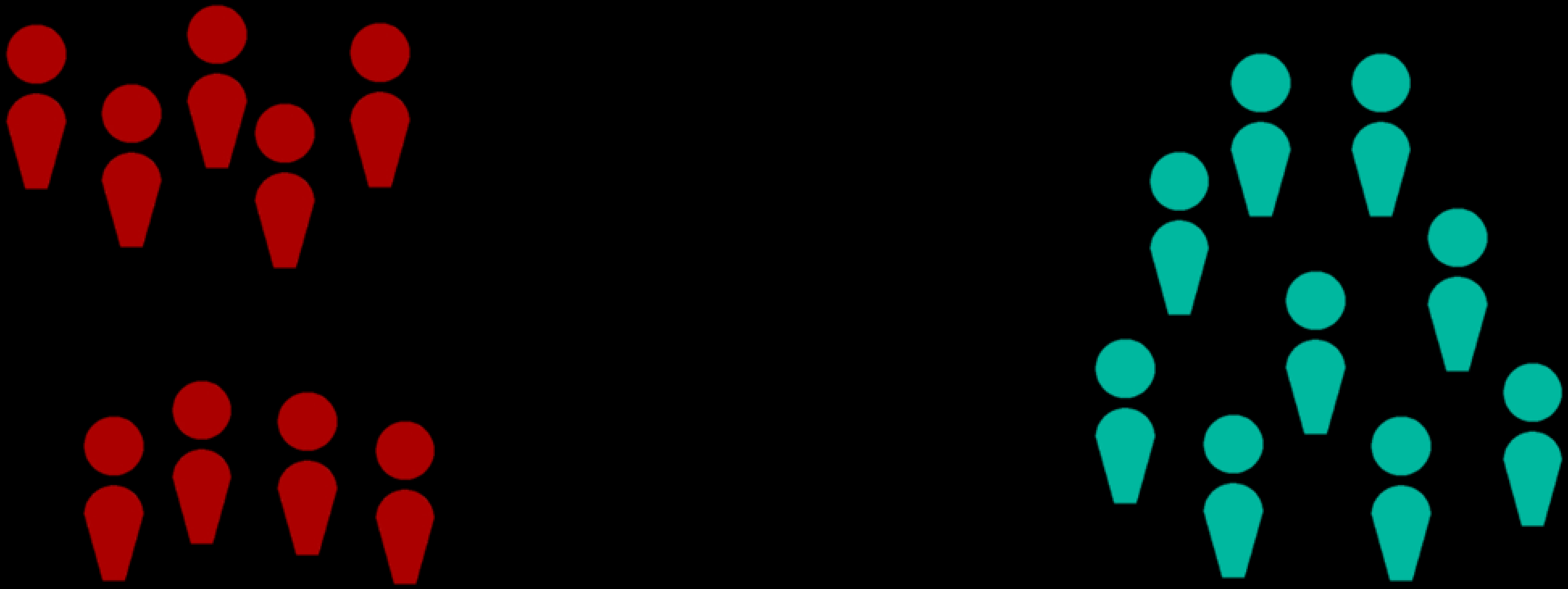
ON HETEROGENEITY



Patients

Unaffected controls

ON HETEROGENEITY



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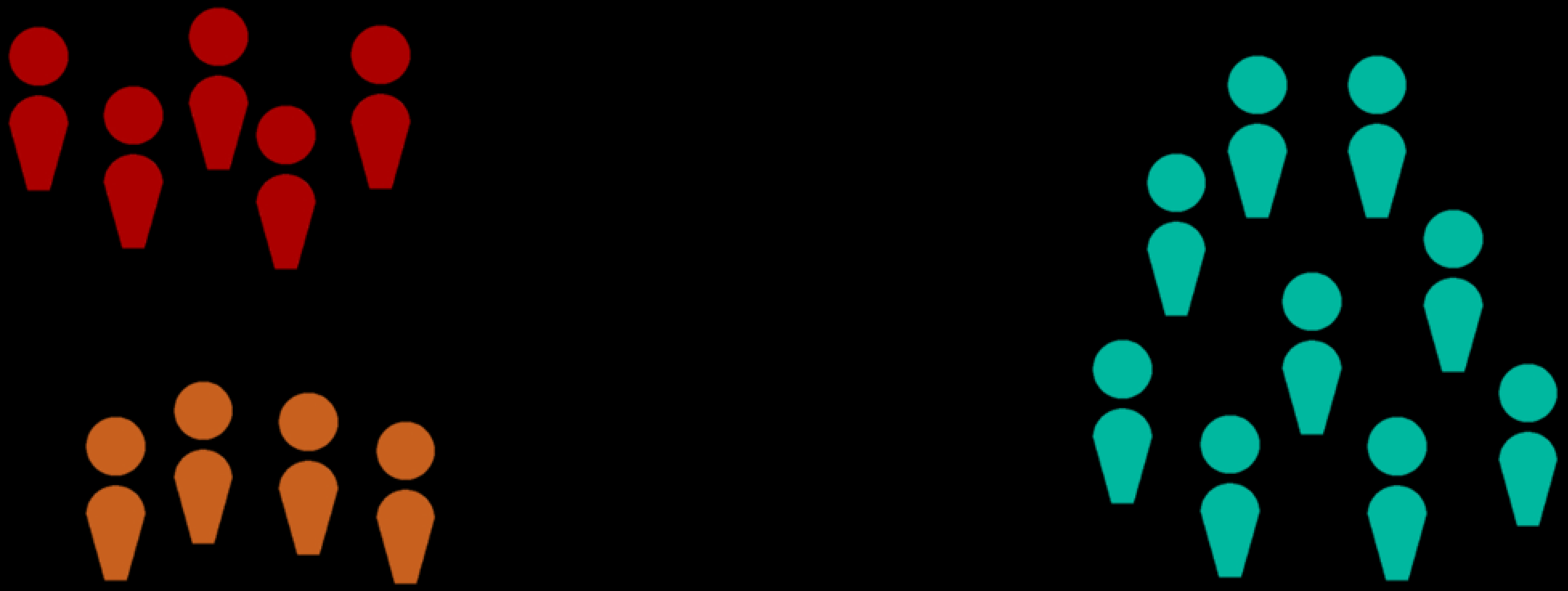

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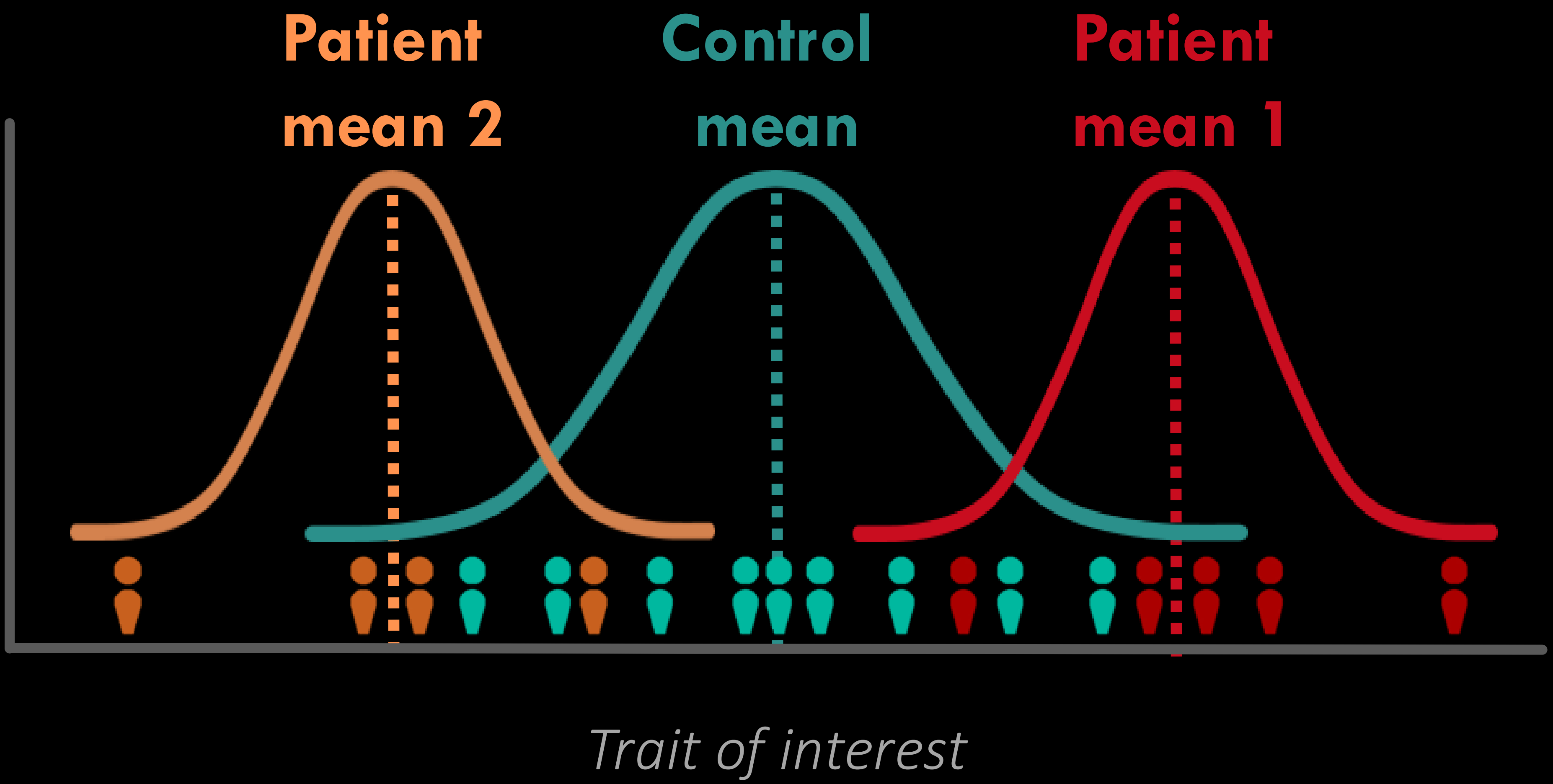

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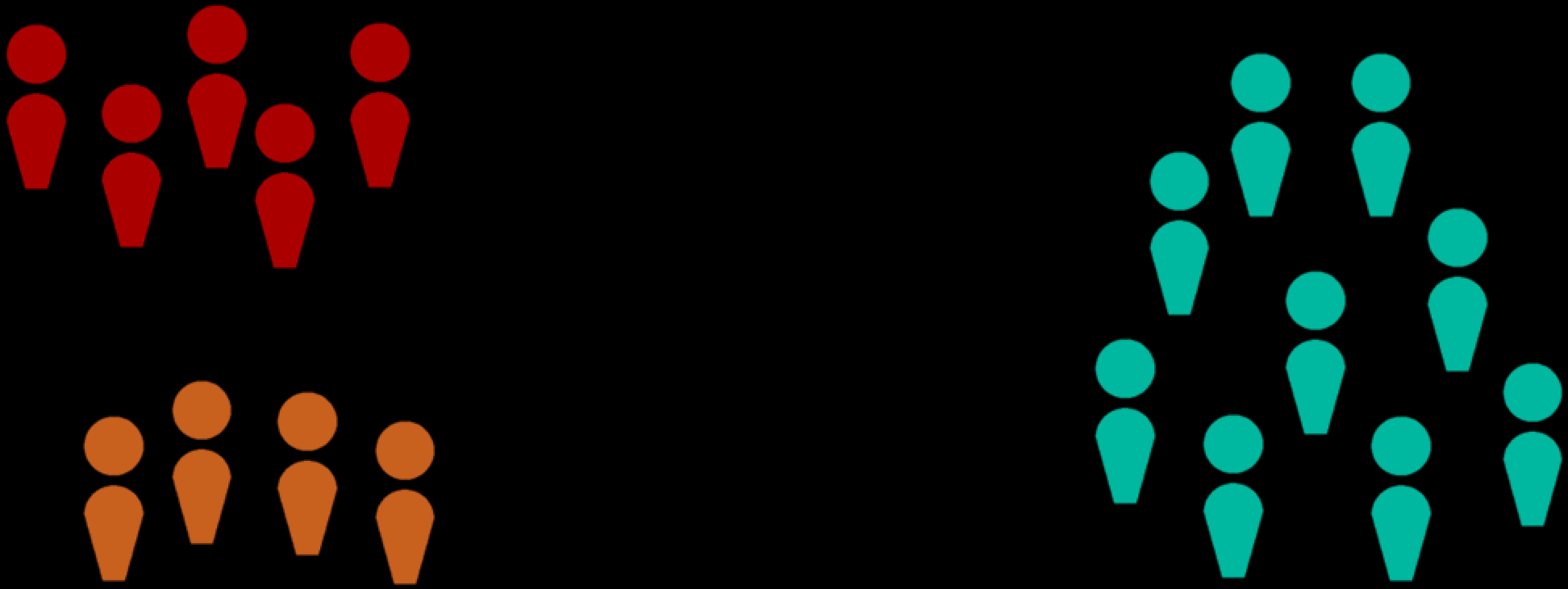

Patients

Unaffected controls

ON HETEROGENEITY

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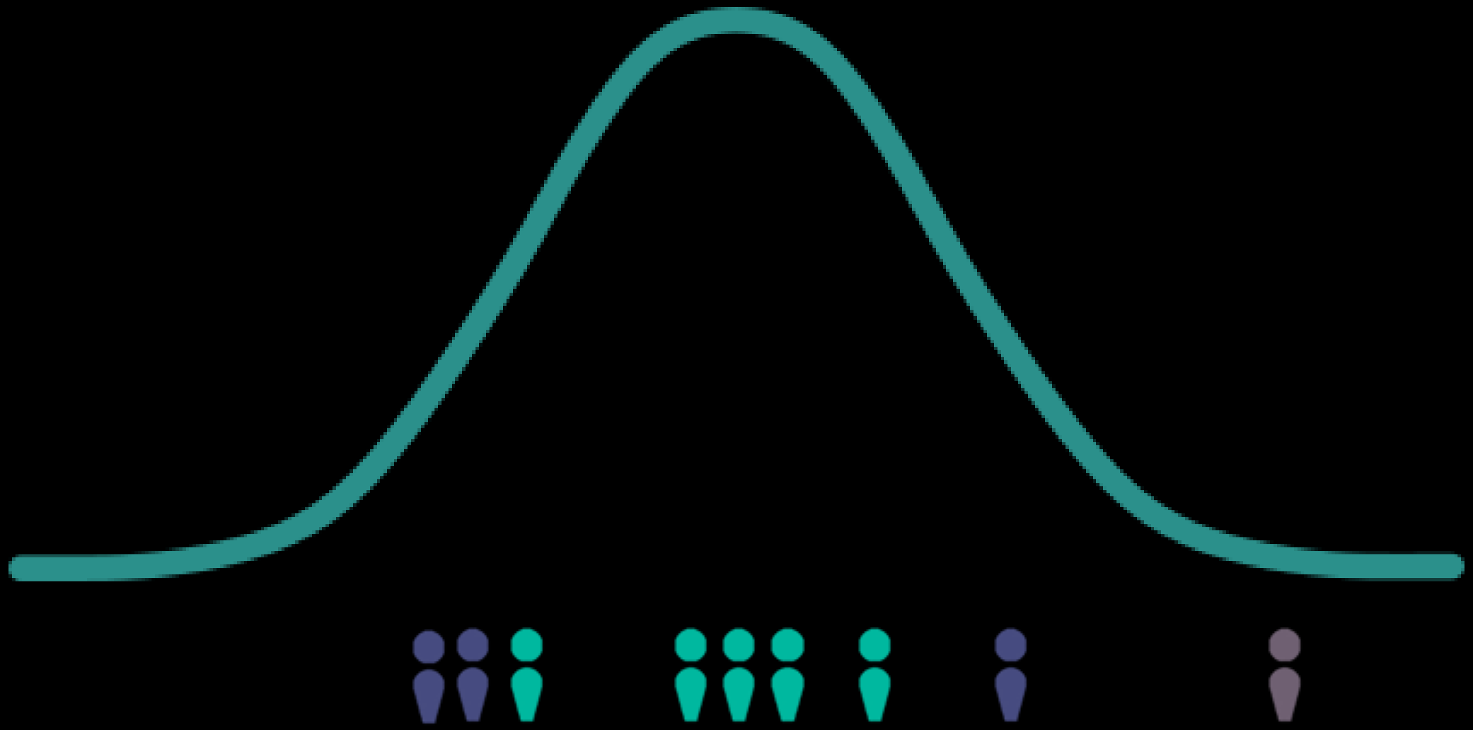
Patients

Unaffected controls

NORMATIVE MODELLING



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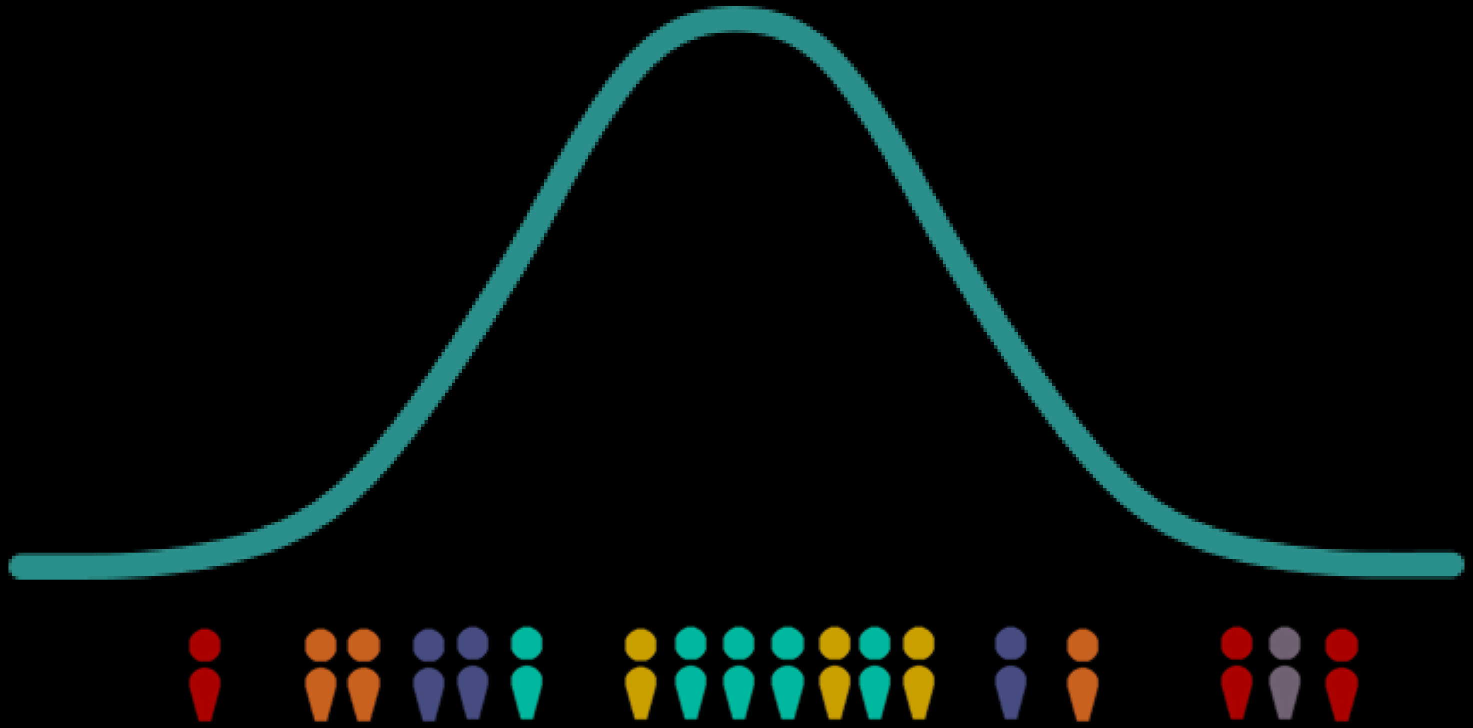

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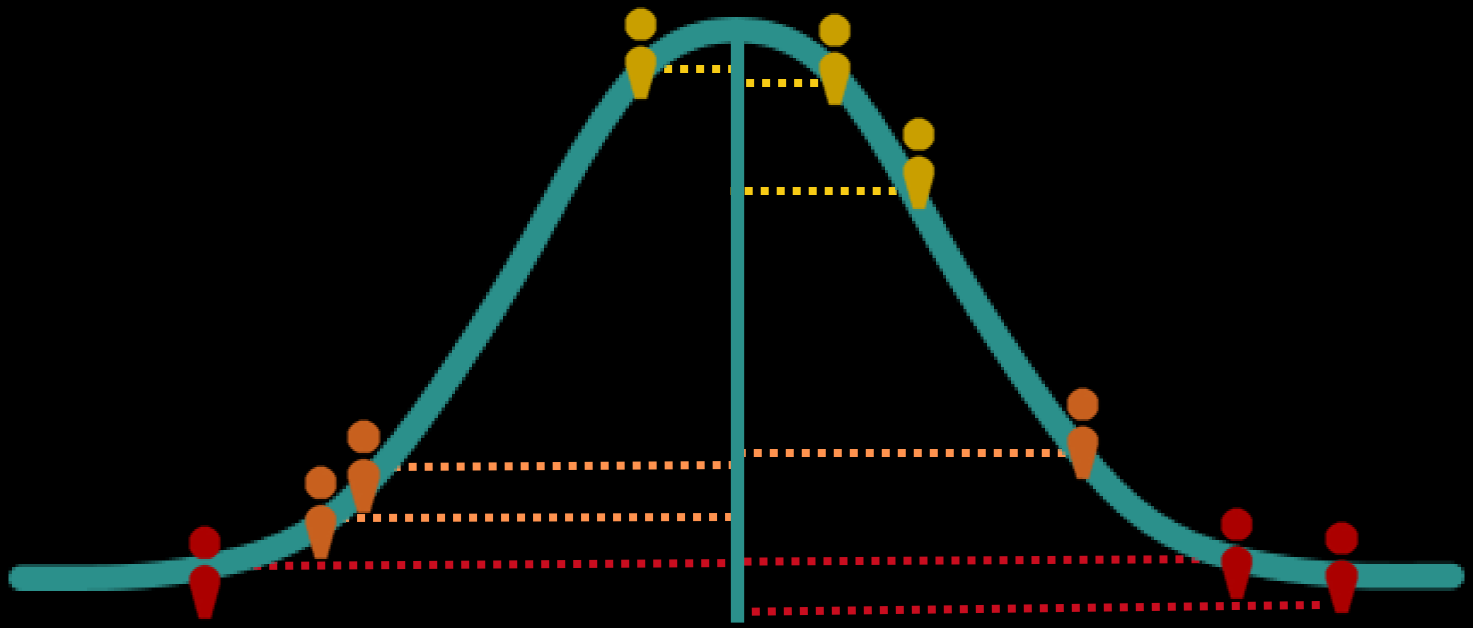

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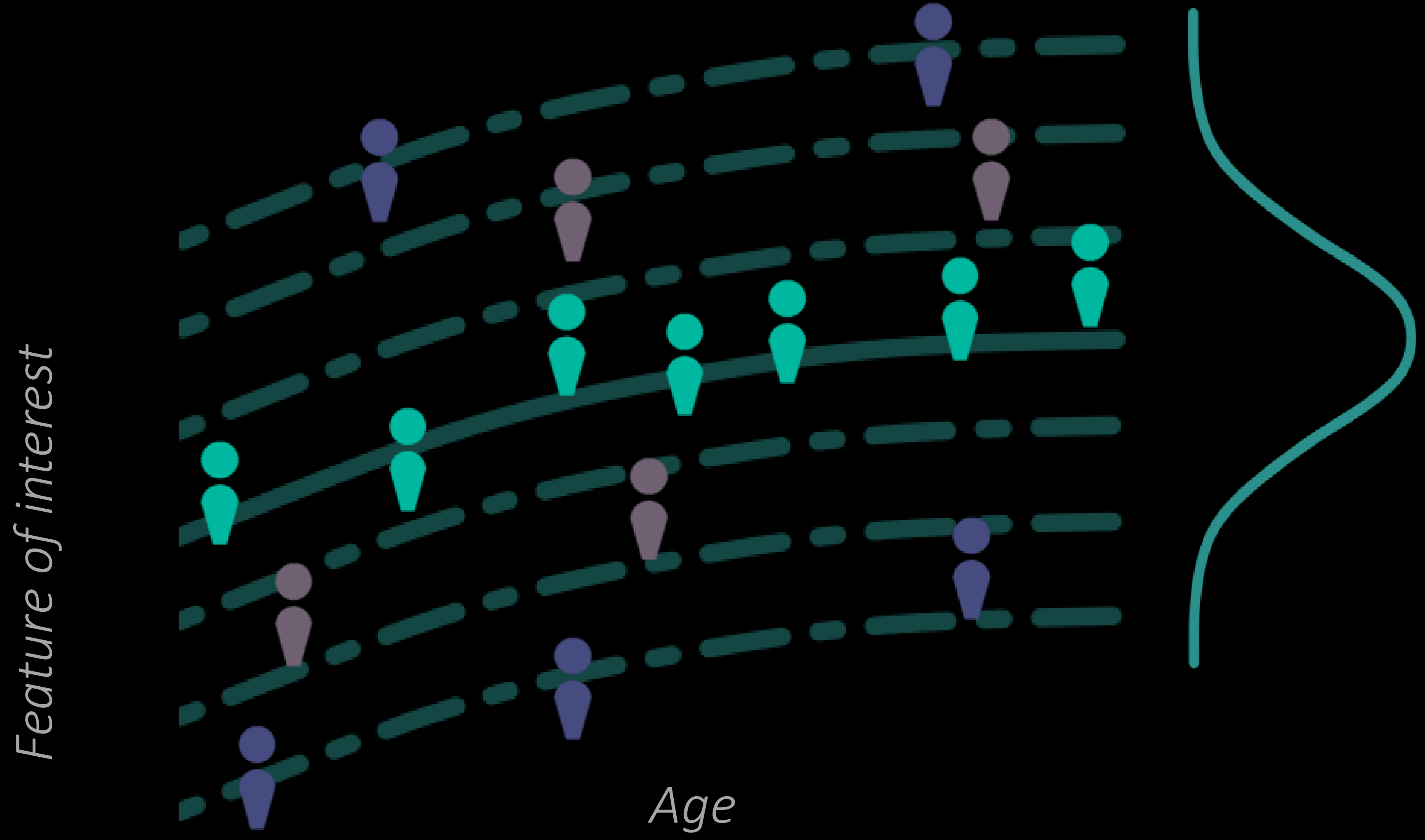

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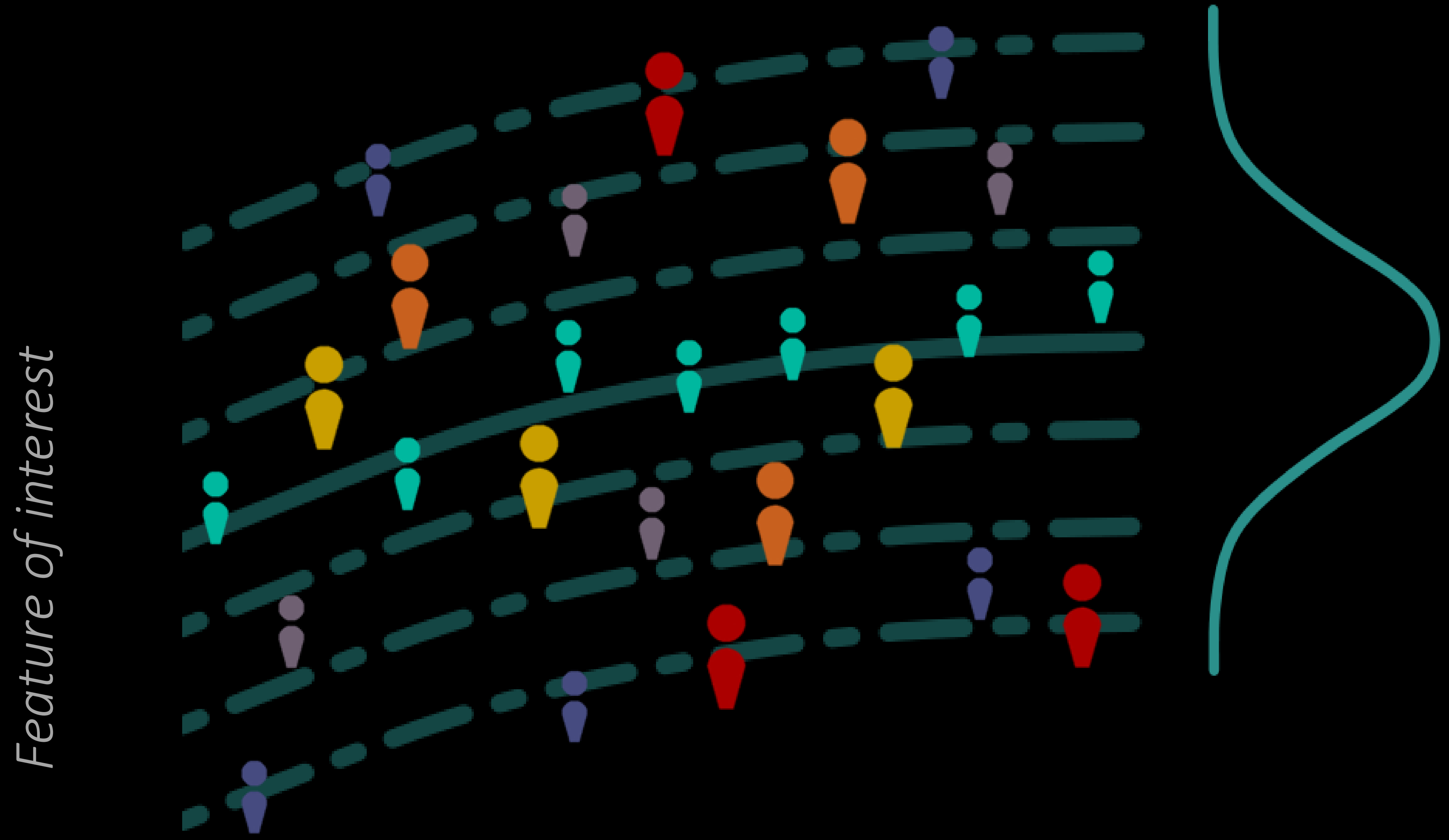

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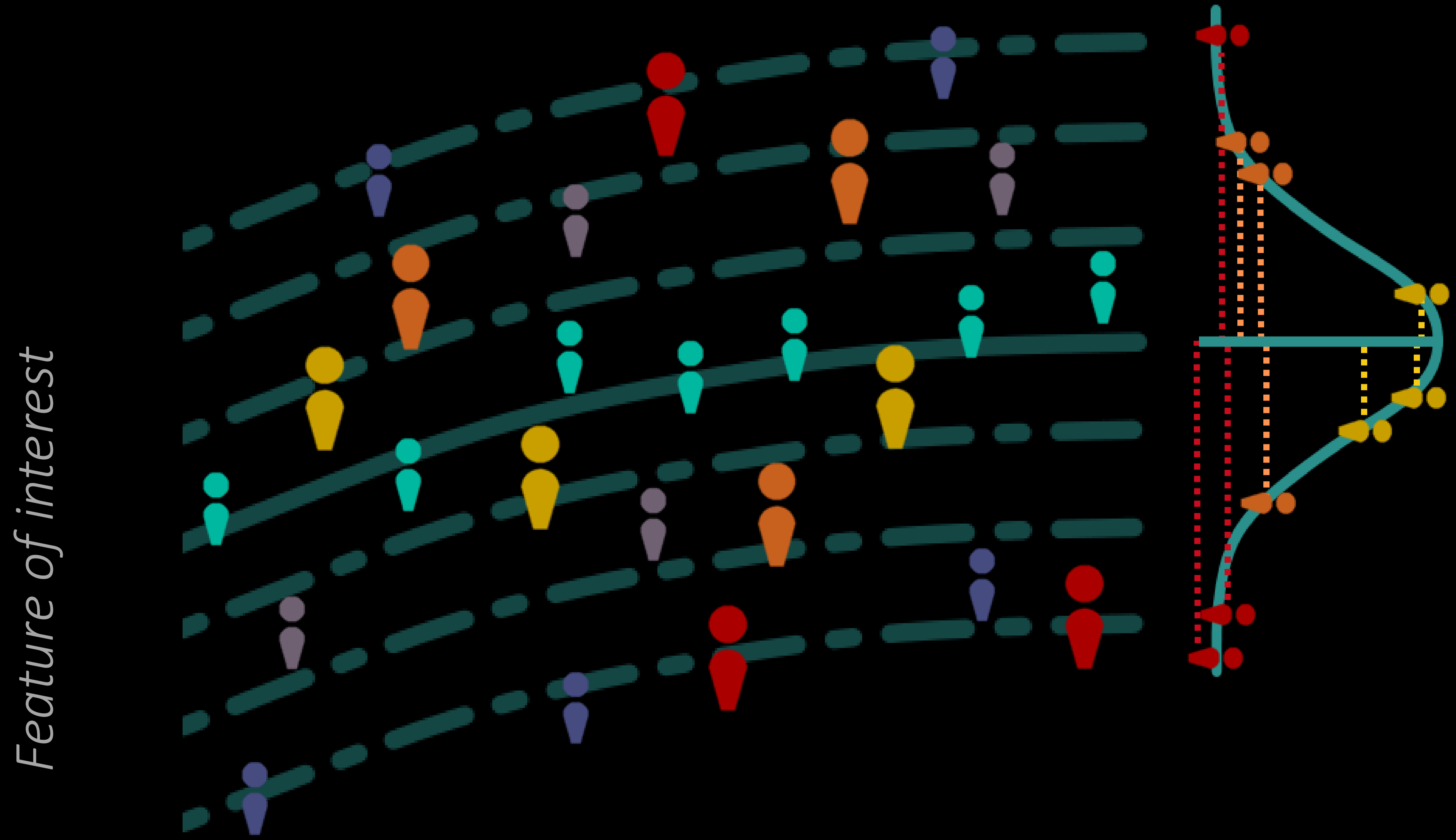

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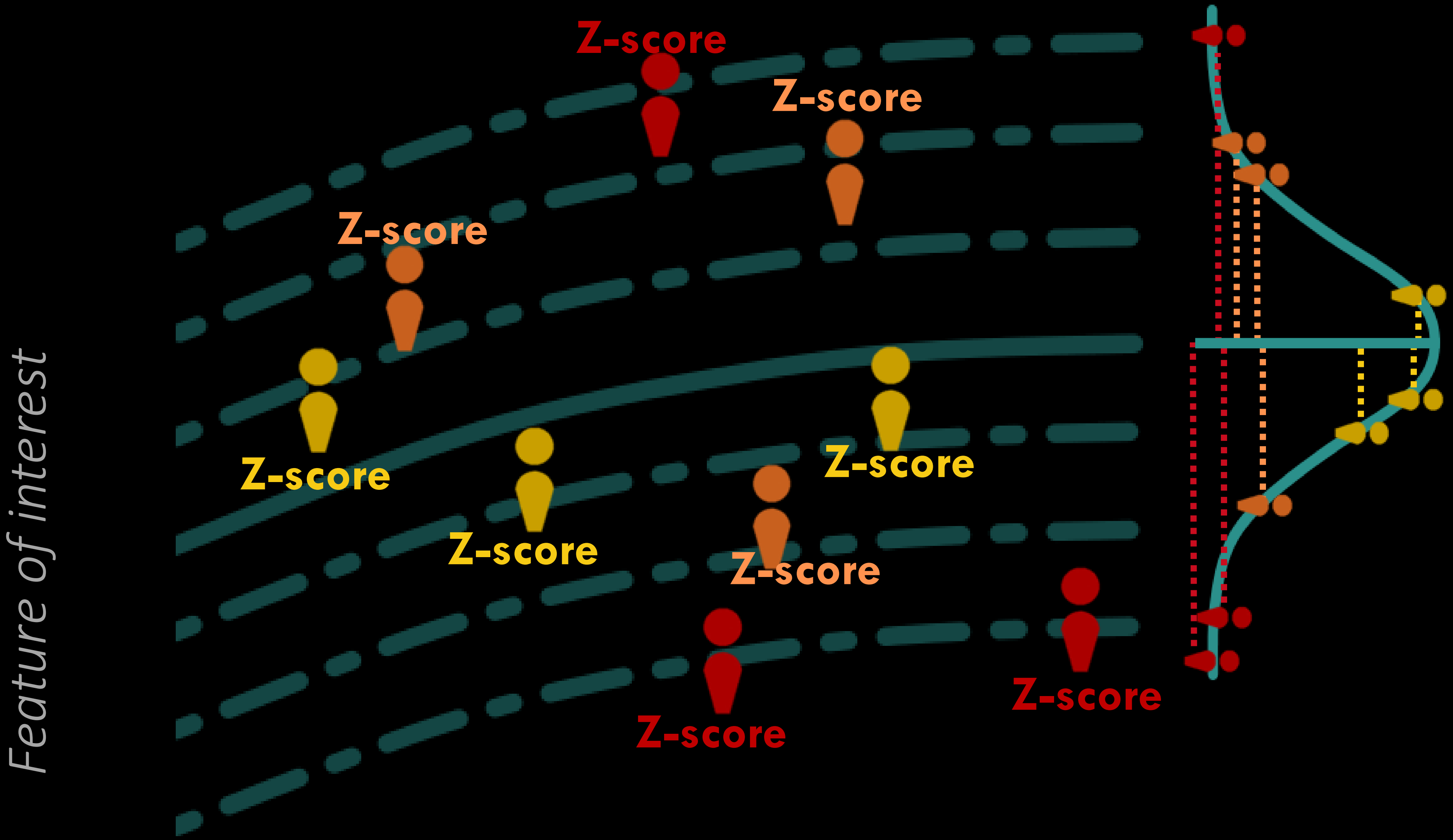


NORMATIVE MODELLING

$$Y$$

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

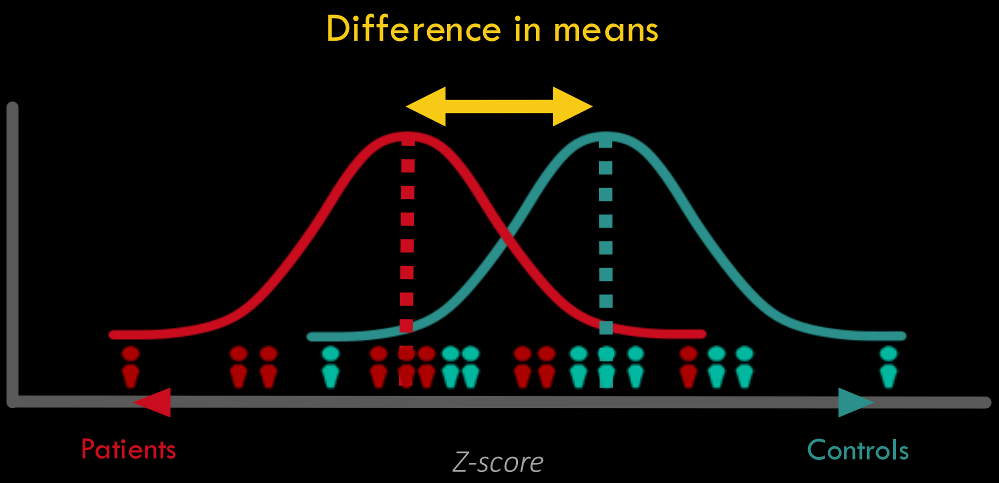
Parsing heterogeneity

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 ?

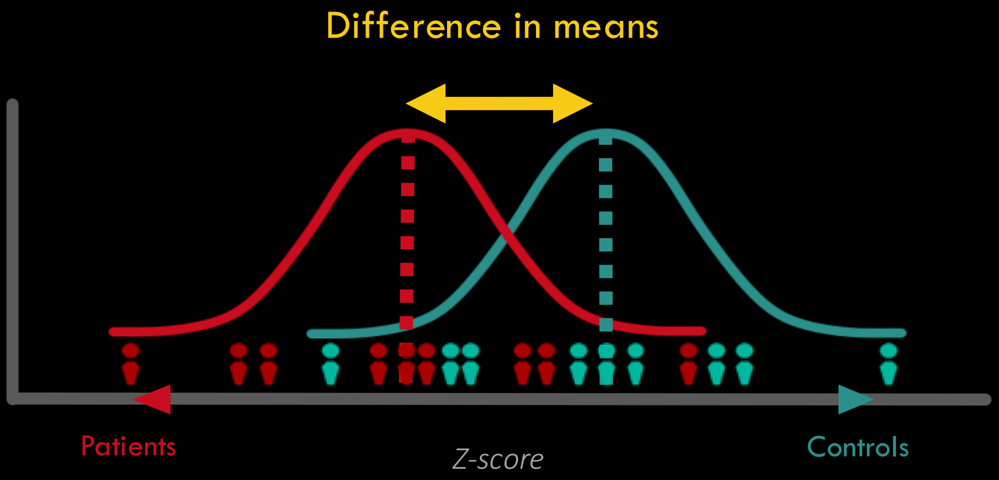
APPLICATIONS

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)

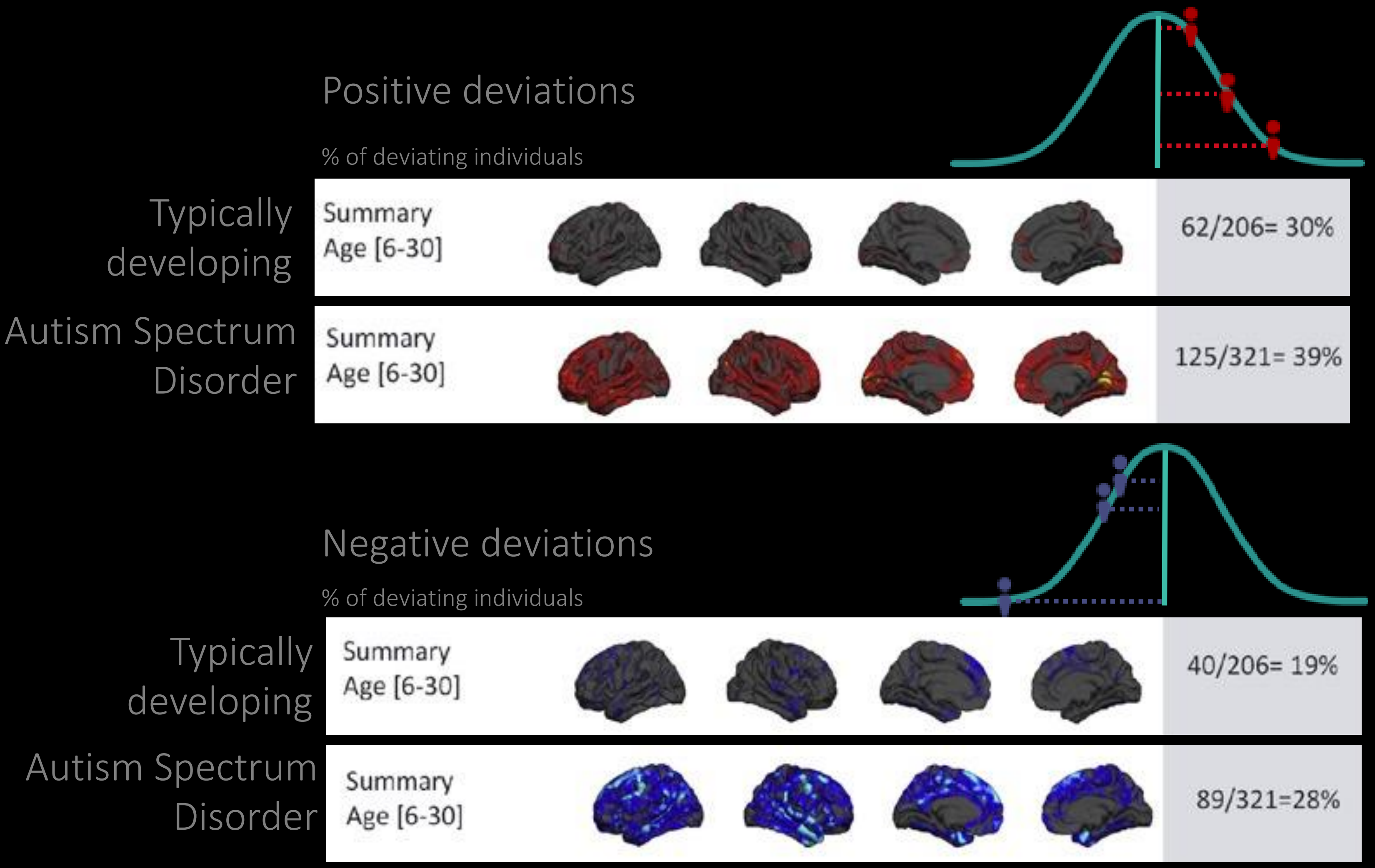
Model parameters

Residuals

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

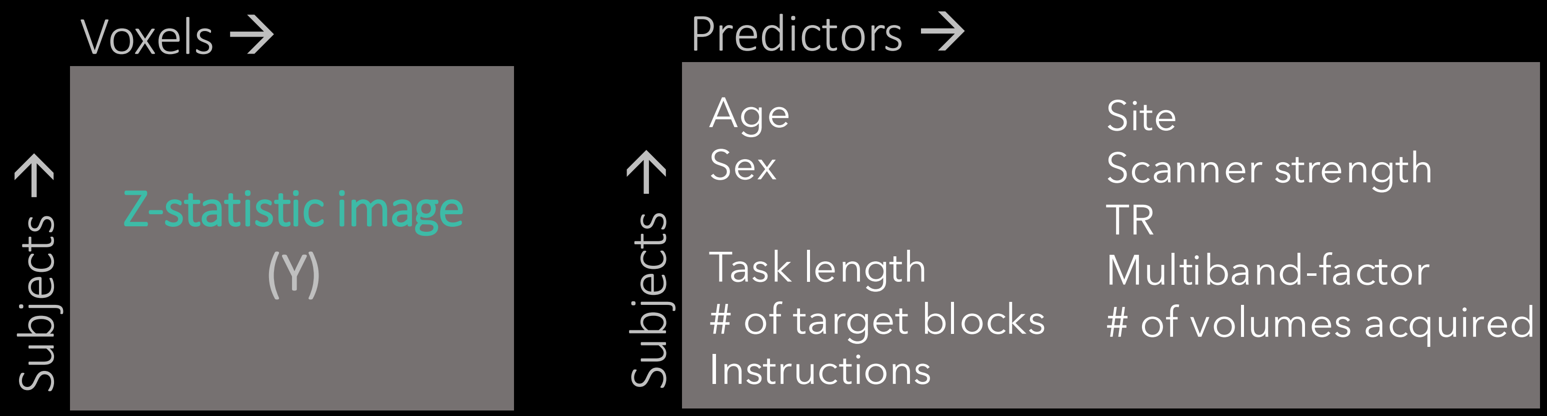
$$Y = f\,(X,\ \theta) + \varepsilon$$

Bold Signal

Covariates
(age, sex,
Task parameters)

Model
parameters

Residuals



Voxels →

Subjects →

Z-statistic image
(Y)

Predictors →

Subjects →

Age
Sex

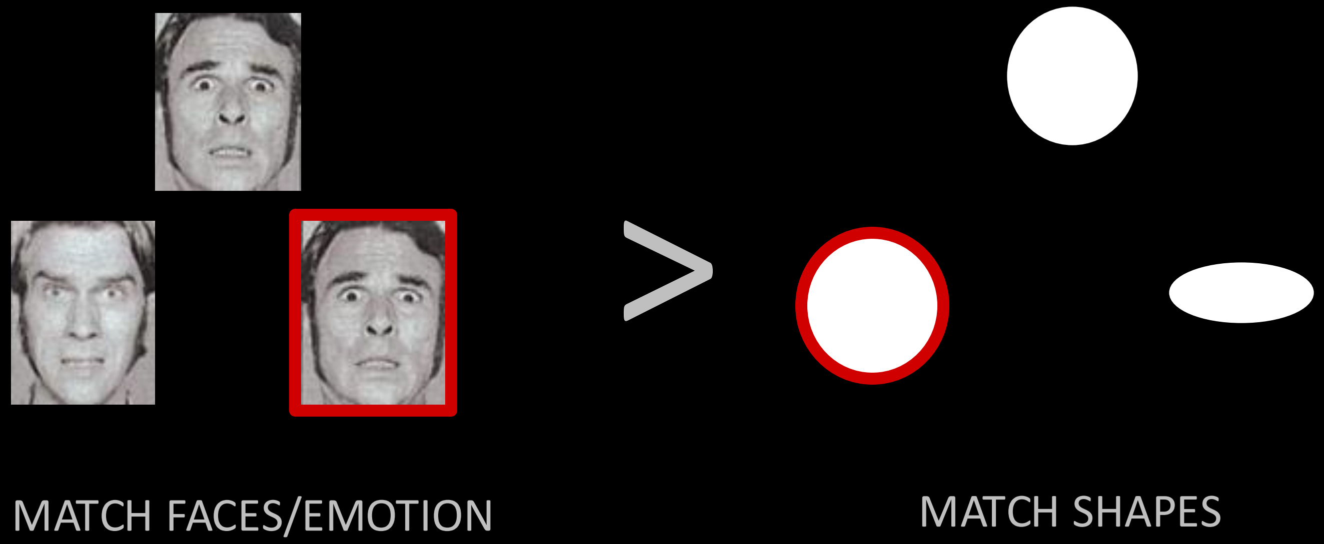
Task length
# of target blocks
Instructions

Site
Scanner strength
TR
Multiband-factor
# of volumes acquired

PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

- Training and evaluating the normative model on local dataset



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

PARSING HETEROGENEITY

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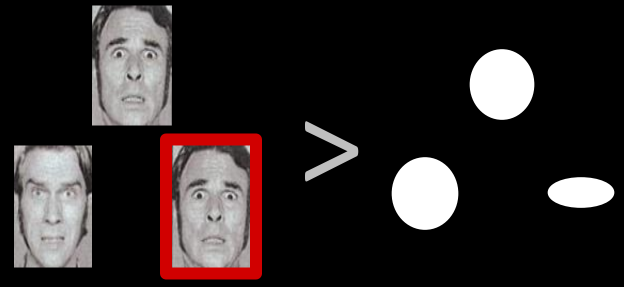

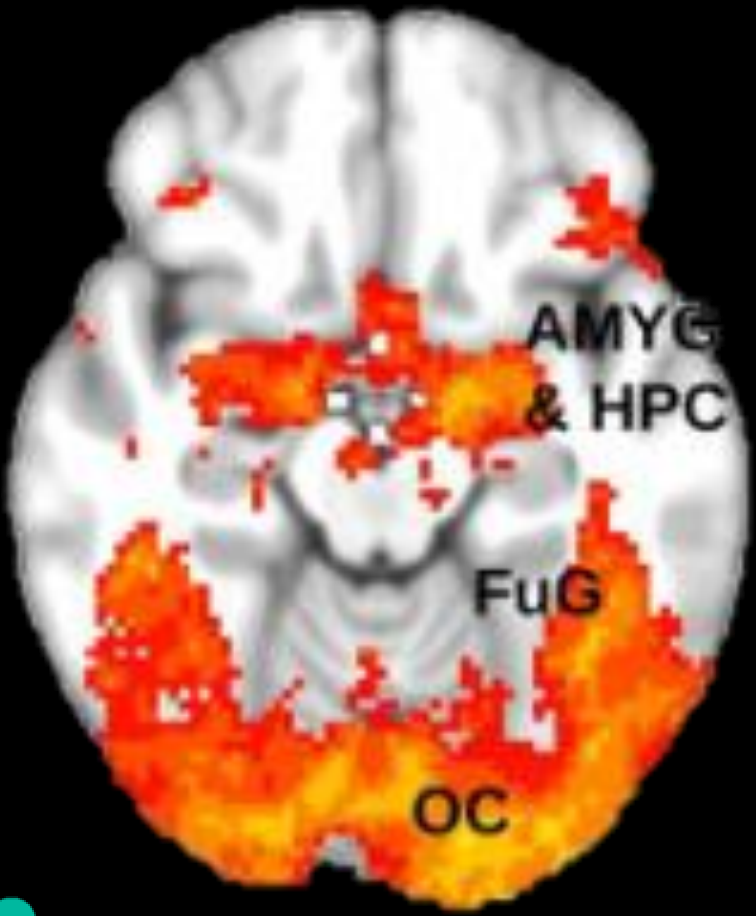

Unaffected controls

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PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

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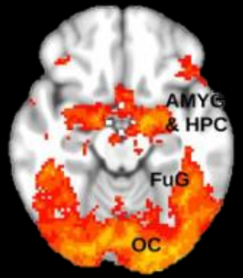
FACES/EMOTION SHAPES



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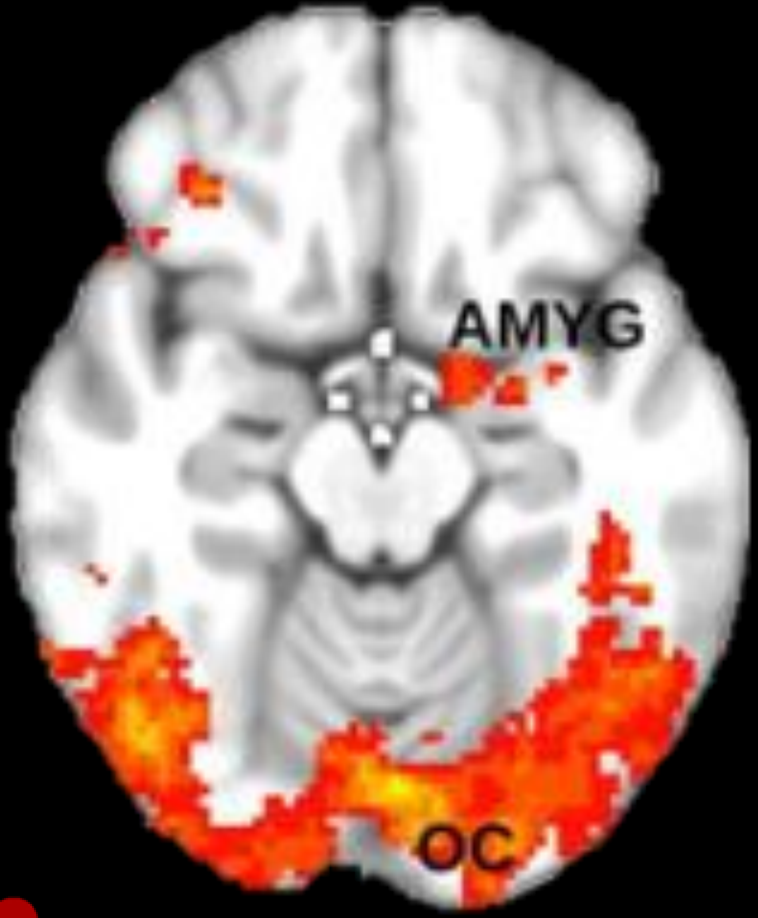

Patients

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PARSING HETEROGENEITY

APPLICATIONS: Functional Imaging

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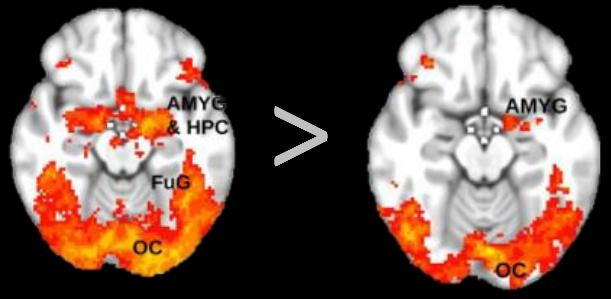
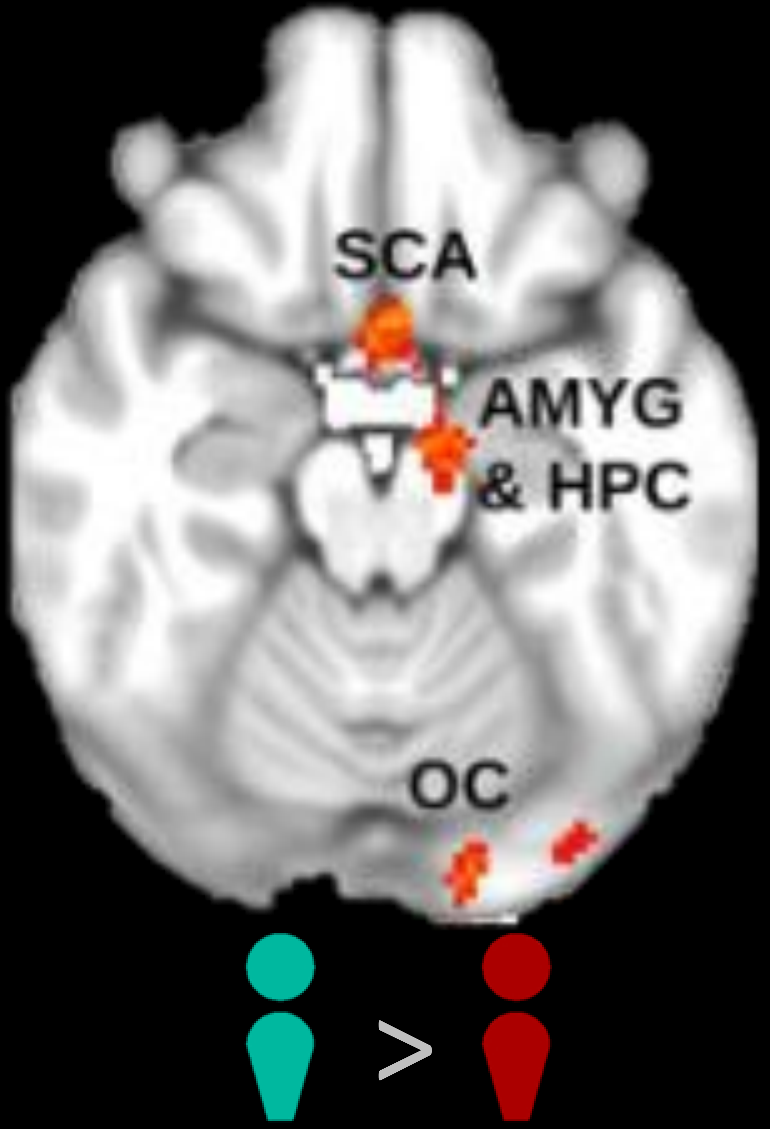


● Unaffected controls ● Patients



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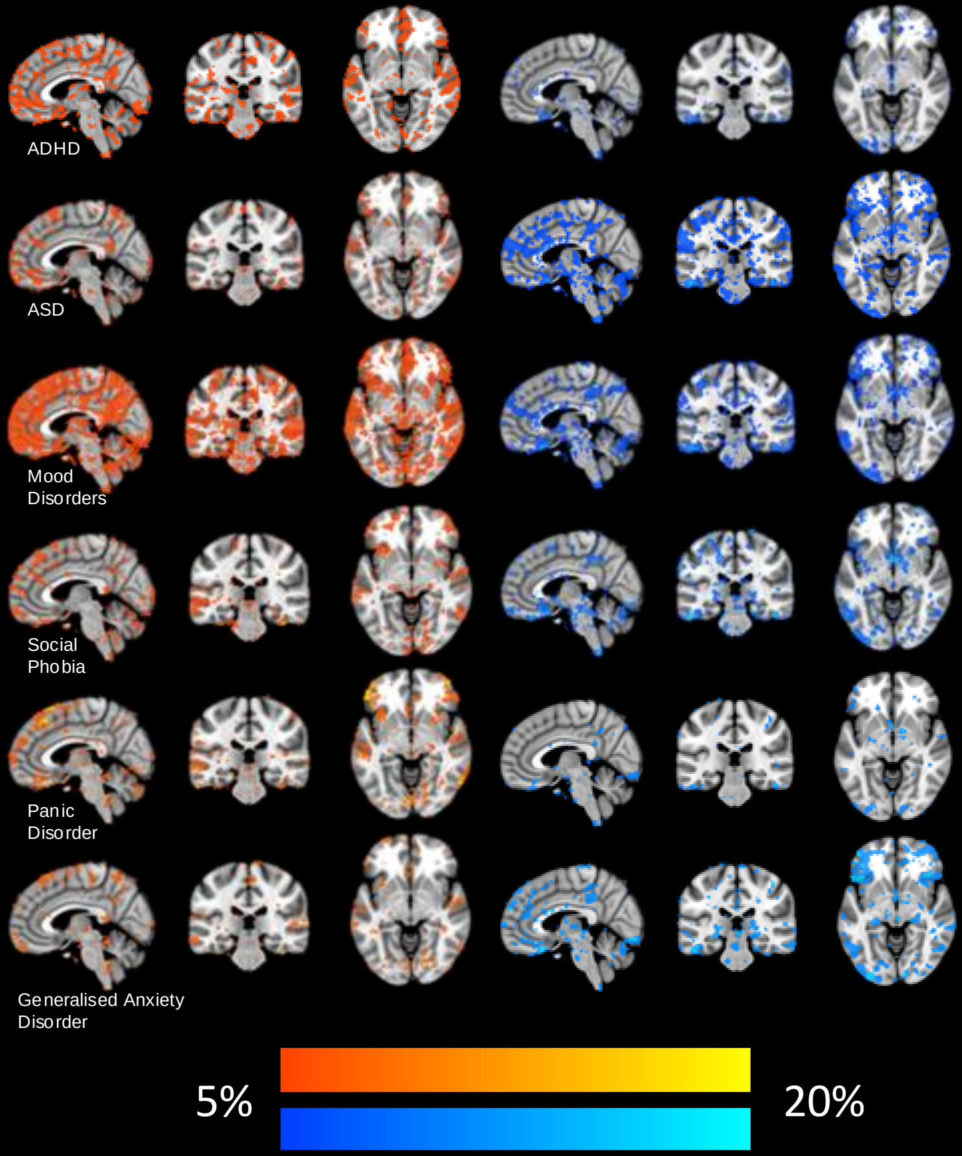

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PARSING HETEROGENEITY

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

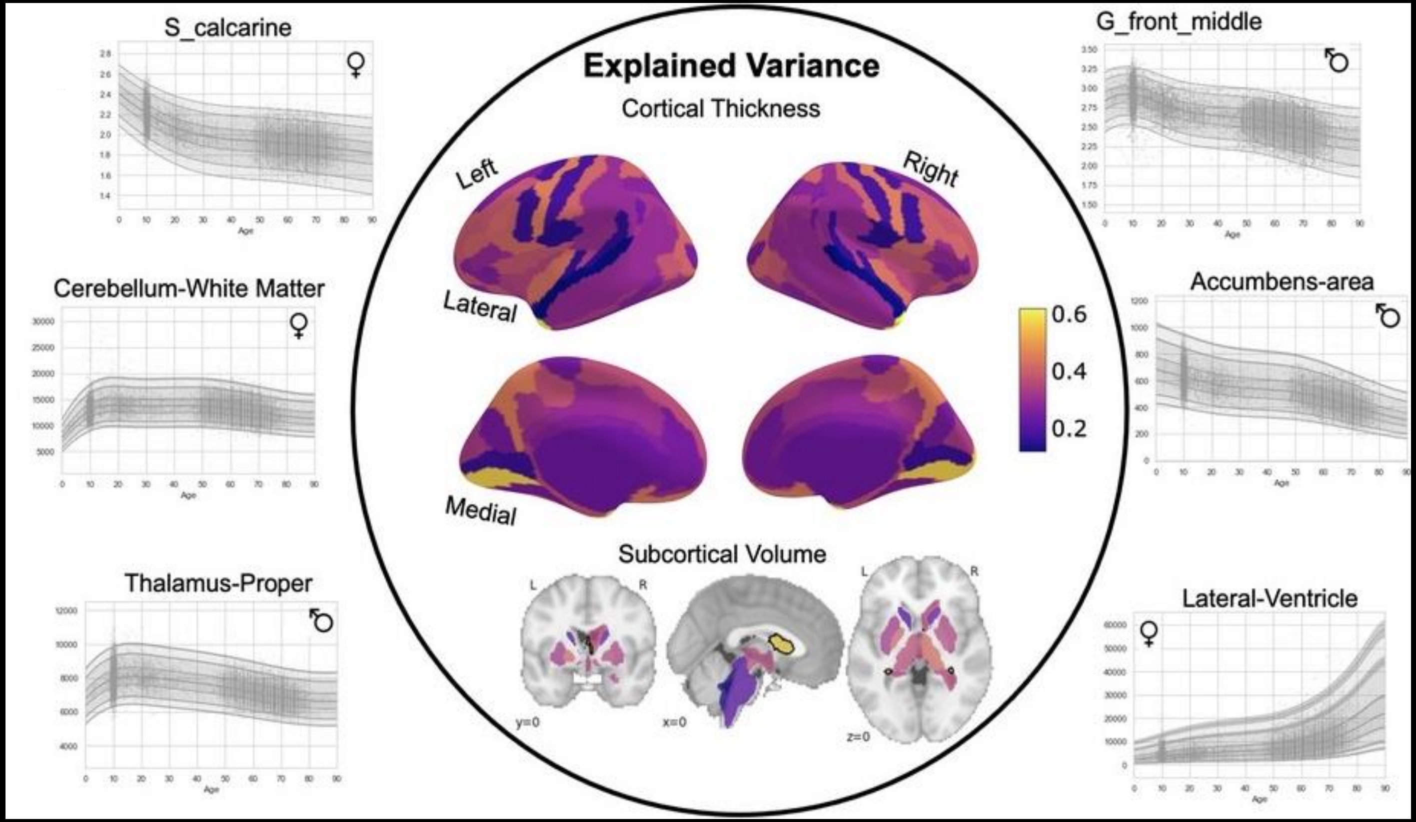
Residuals

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

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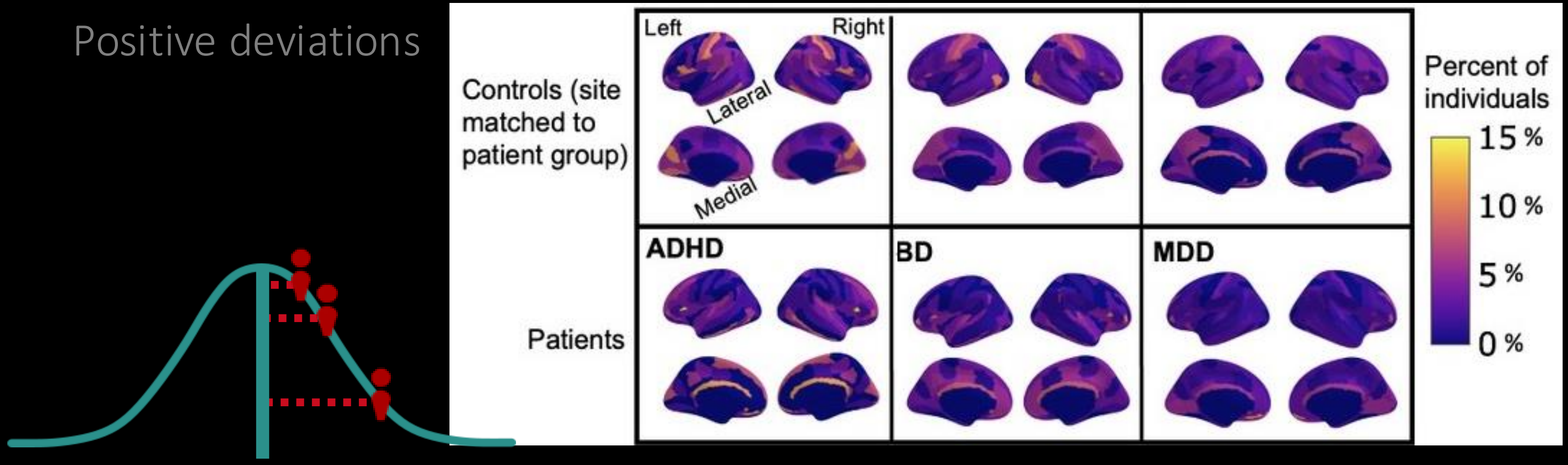
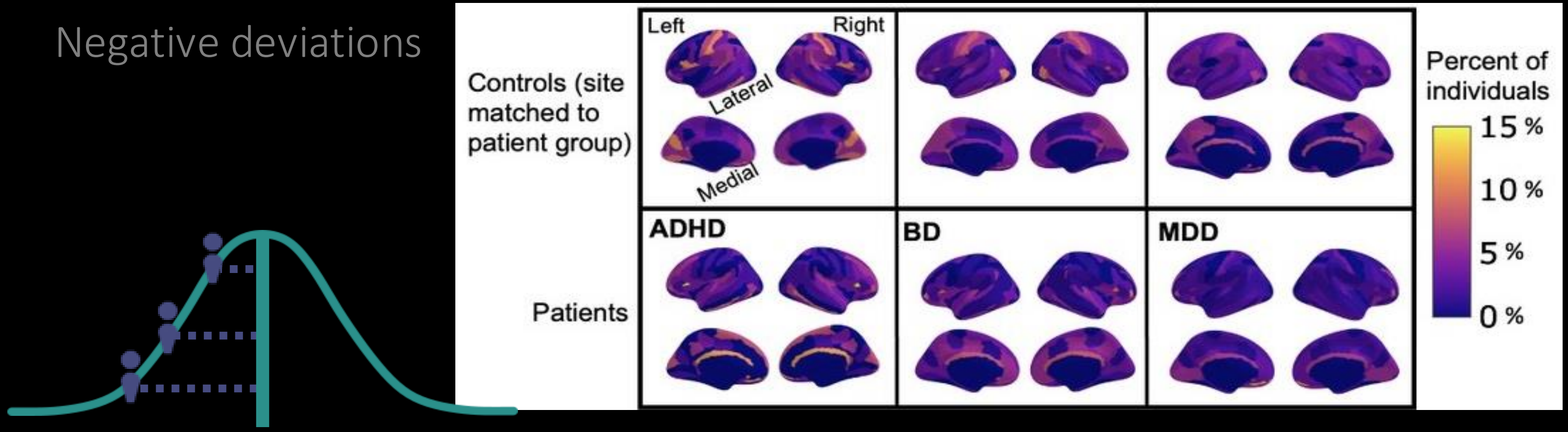
Positive deviations



Negative deviations



APPLICATIONS

Parsing heterogeneity

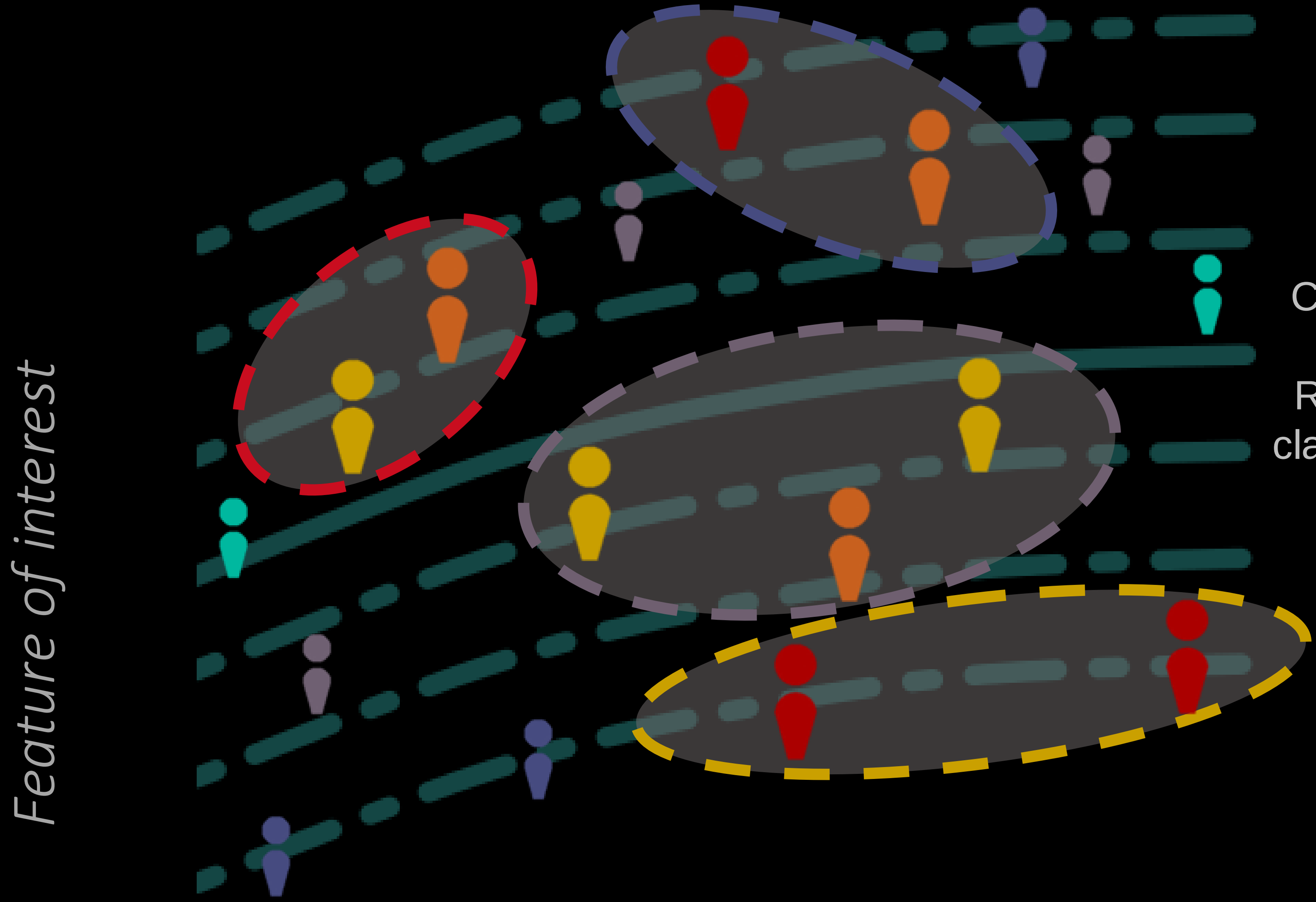
Neurobiological subtyping

Brain-behavior mappings

Other

NEUROBIOLOGICAL SUBTYPING

APPLICATIONS

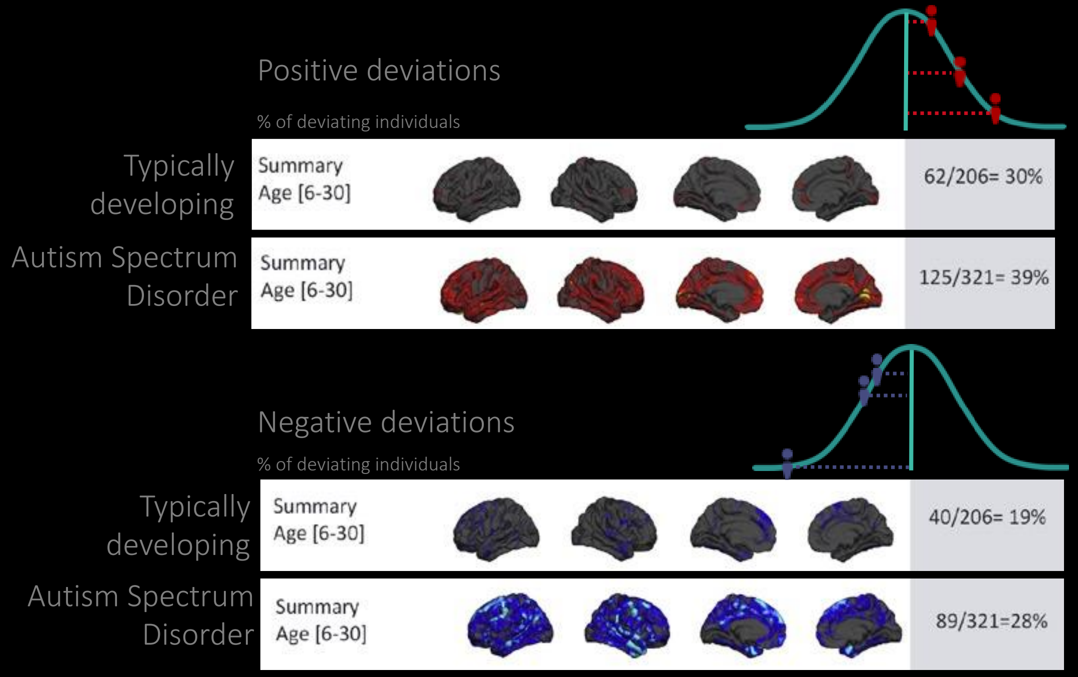


Clustering/
Community detection

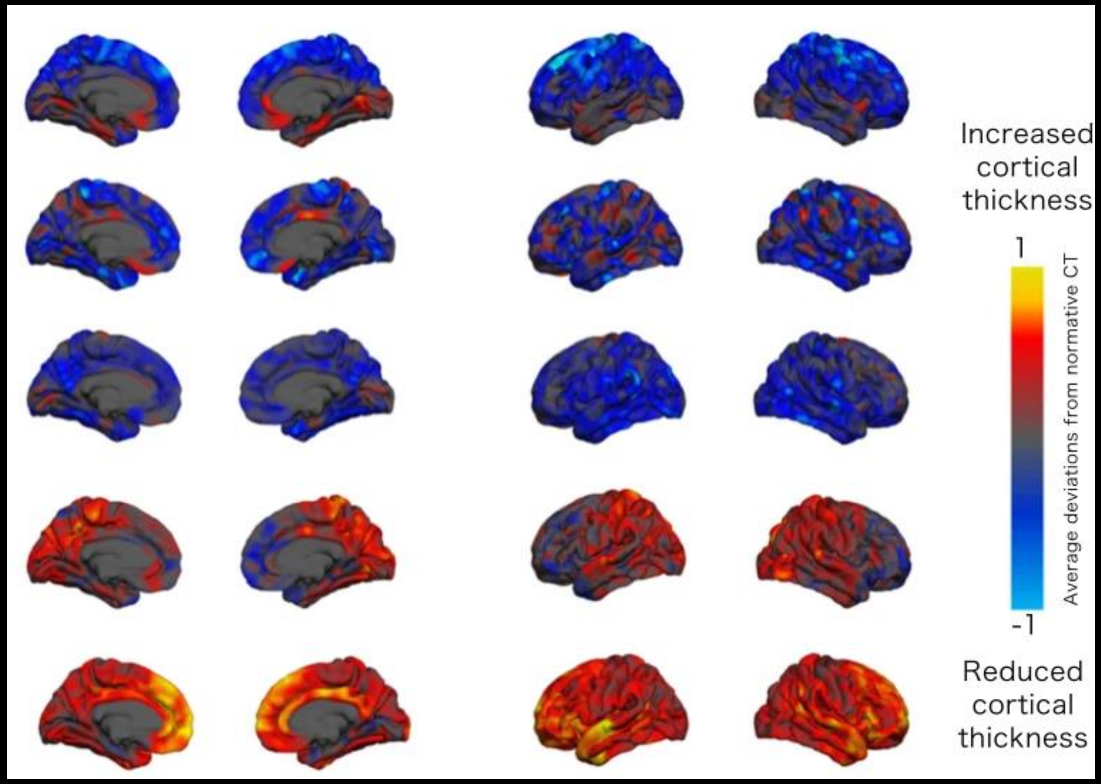
Regression model or
classification prediction
model

NEUROBIOLOGICAL SUBTYPING

APPLICATIONS



5 CLUSTERS



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APPLICATIONS

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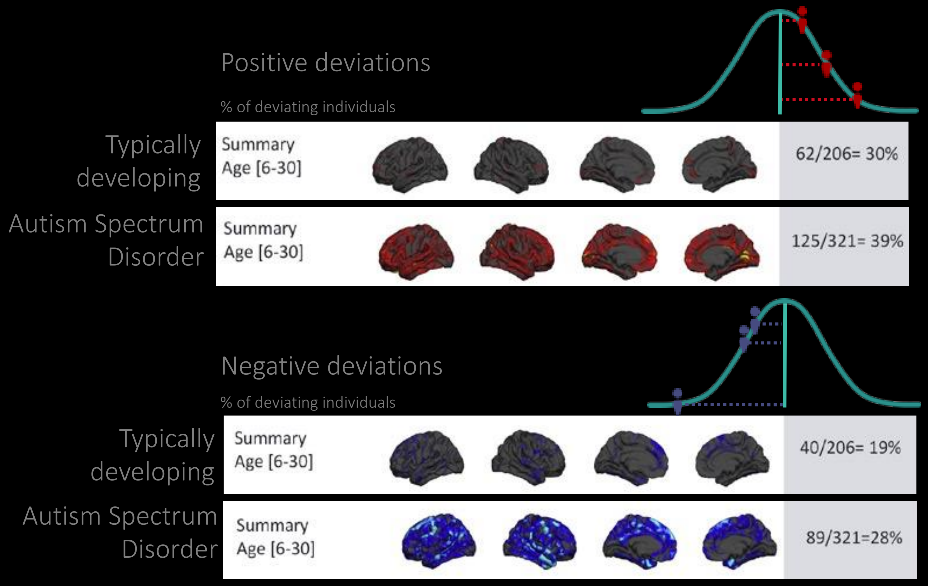
BRAIN-BEHAVIOR MAPPINGS

APPLICATIONS

1.

Parse heterogeneity

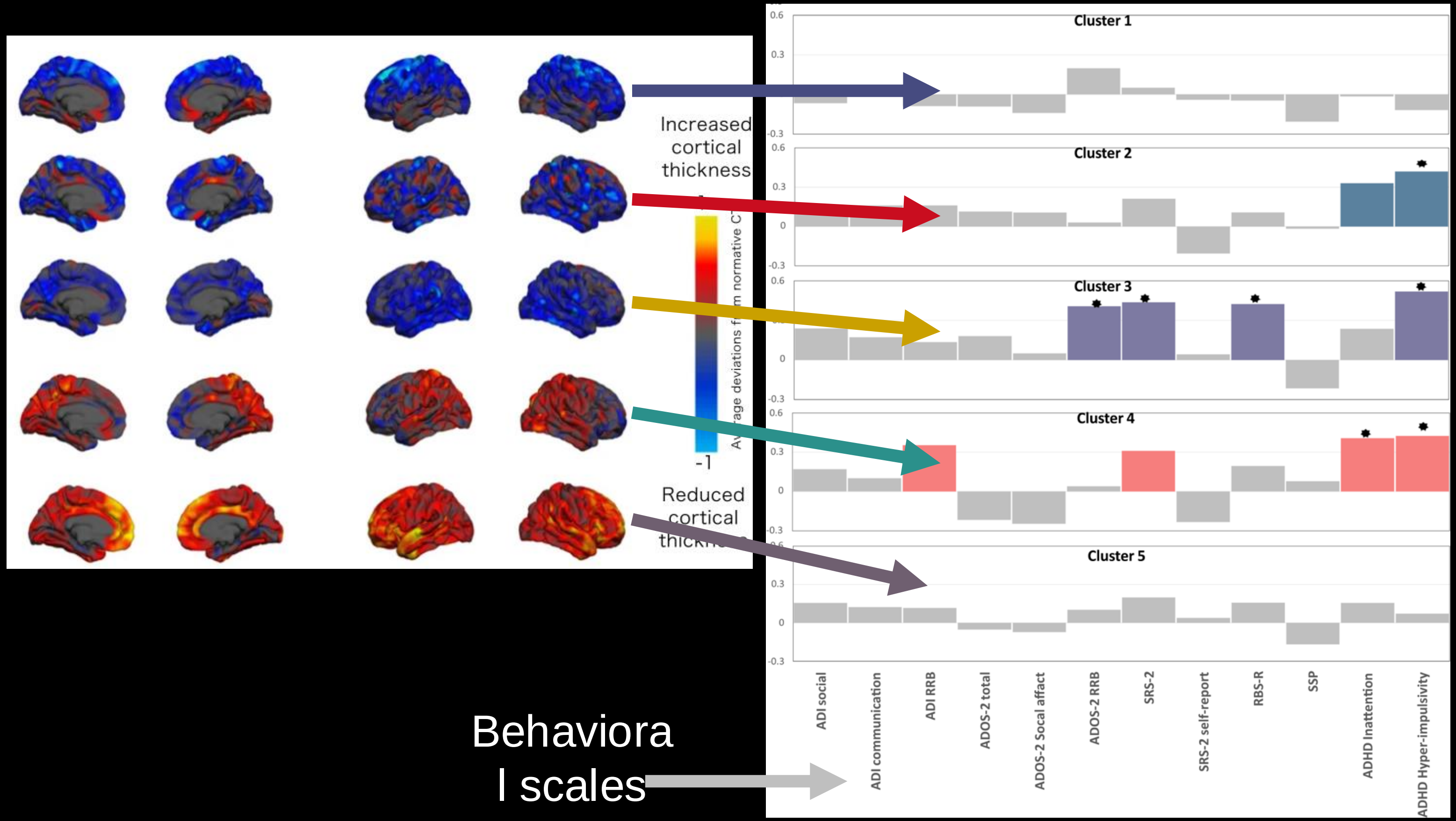


2.

Neurobiological subtyping

3.

Brain-behavior mappings



Behavioral scales

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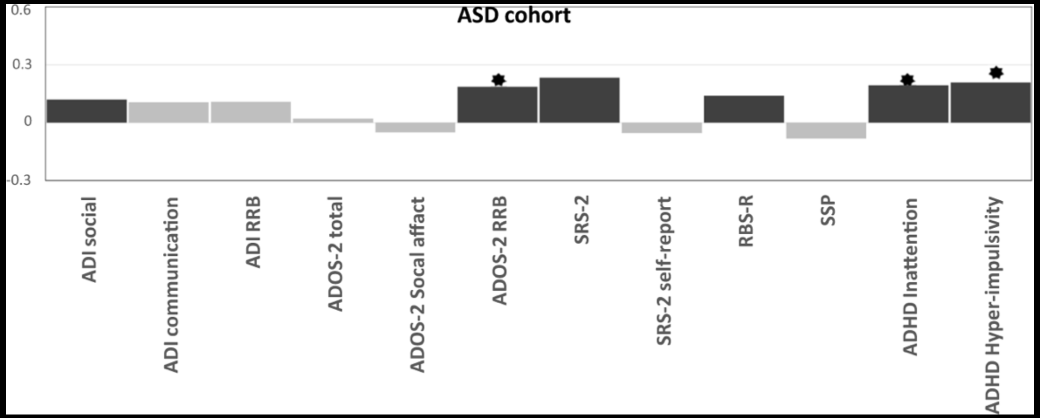
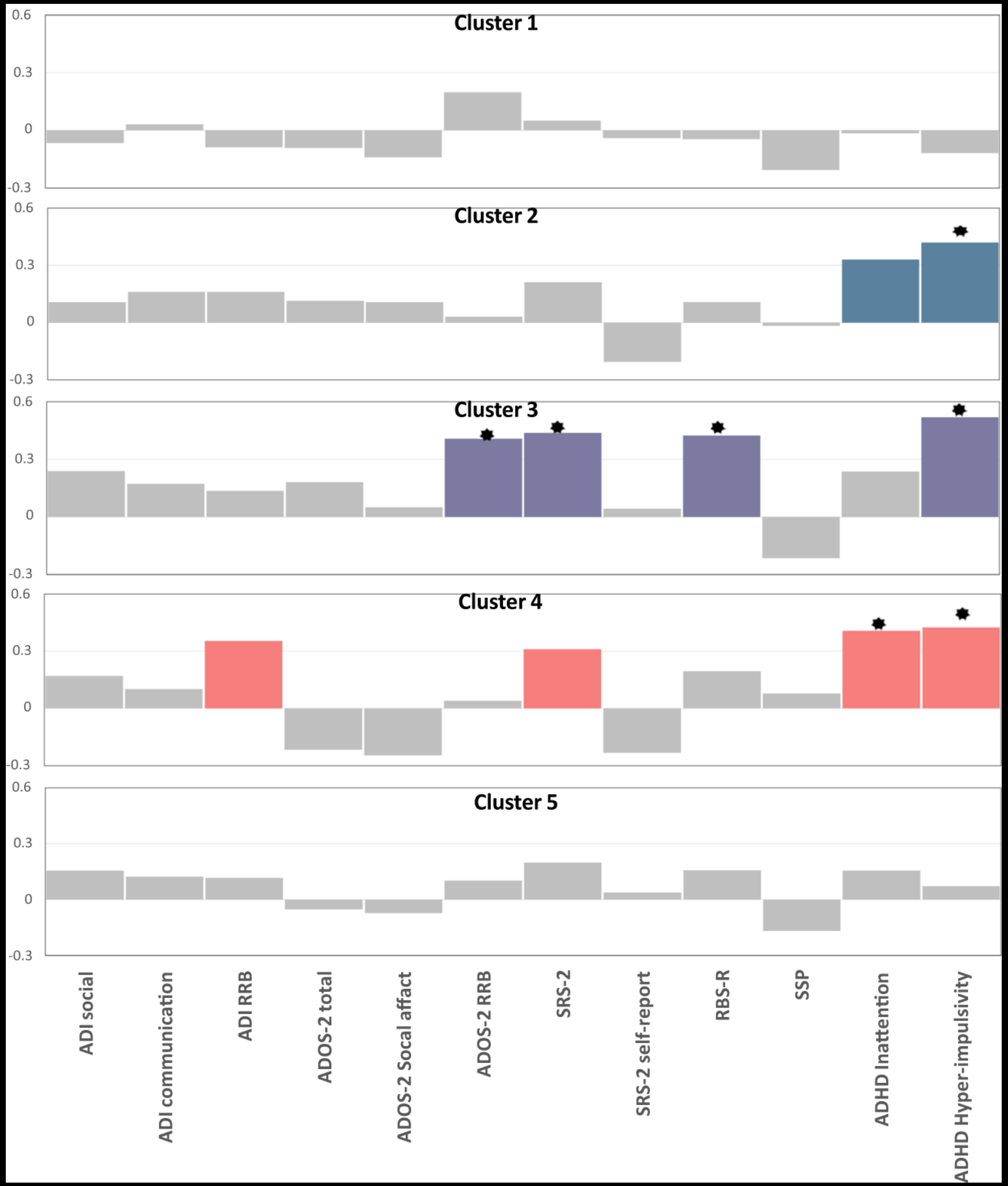
BRAIN-BEHAVIOR MAPPINGS

APPLICATIONS

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





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BRAIN-BEHAVIOR MAPPINGS

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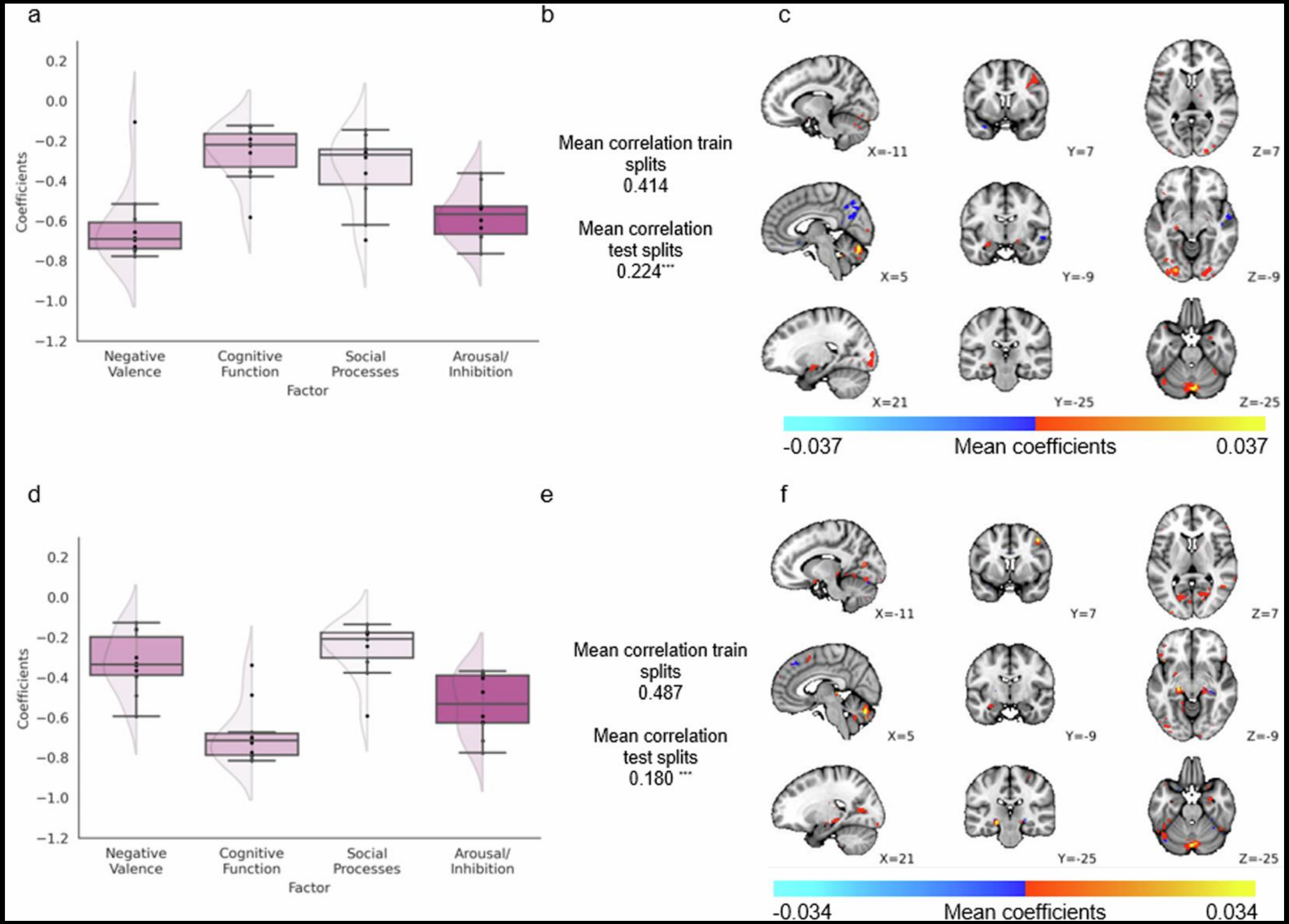

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APPLICATIONS

Parsing heterogeneity

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OTHER

APPLICATIONS

DTI

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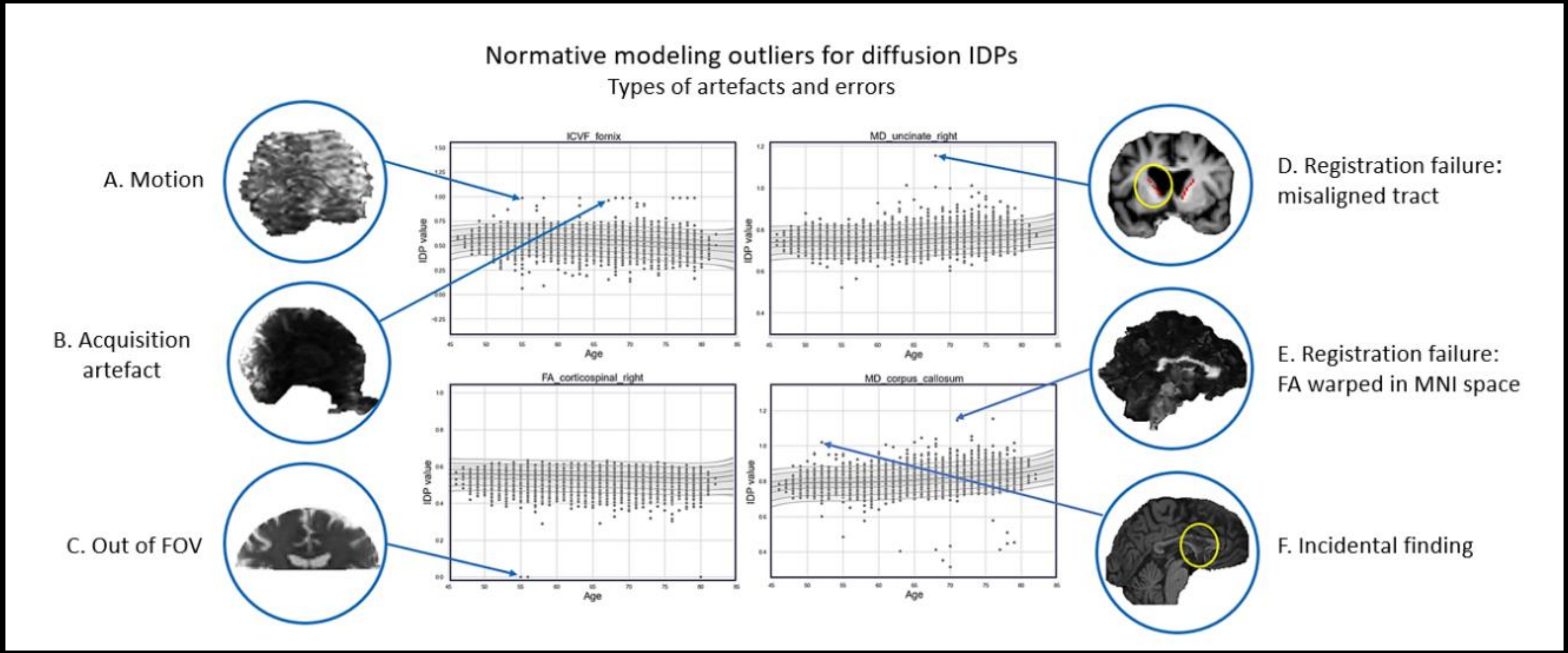
OTHER

APPLICATIONS



DTI

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

OTHER APPLICATIONS

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EEG

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OTHER APPLICATIONS

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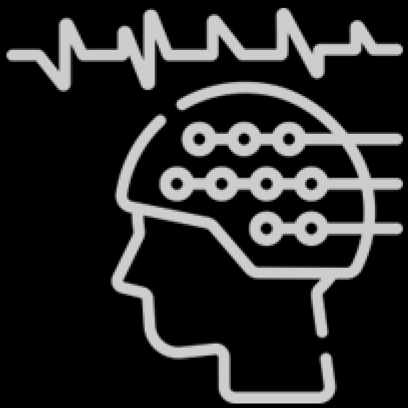

EEG

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Psychometrics

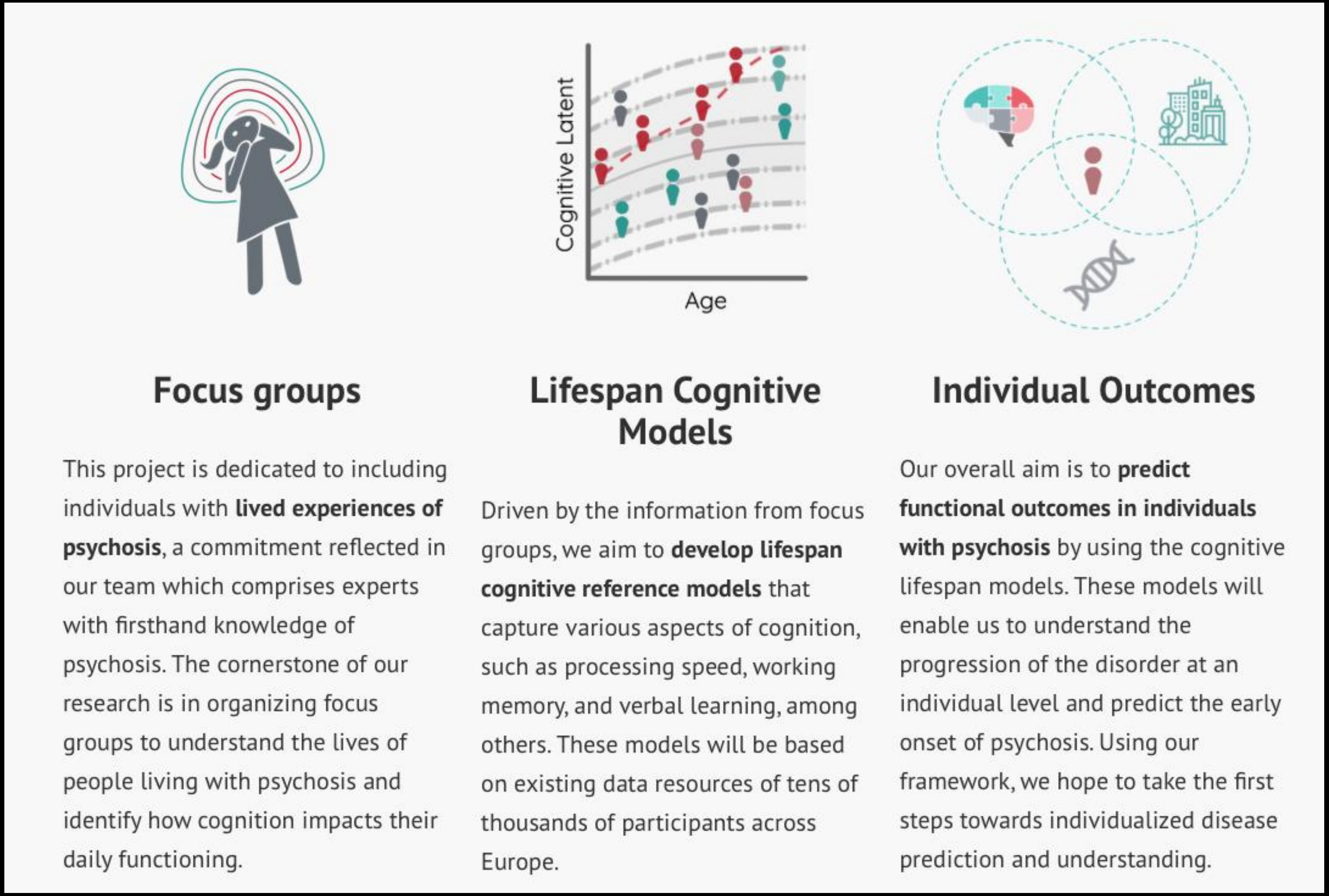
OTHER

APPLICATIONS

PRECOGNITION

Learning Latent Cognitive Profiles to Predict Psychosis

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

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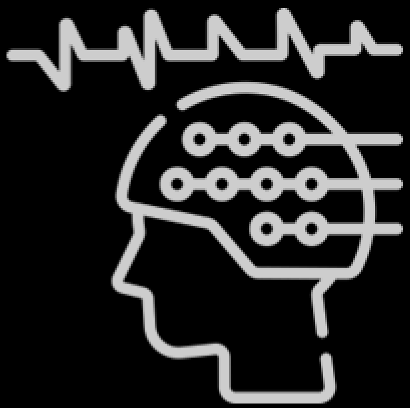

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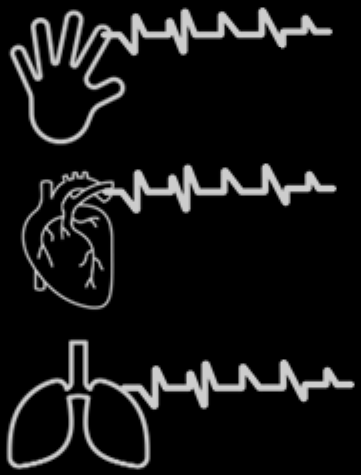
Psychometrics



Physiology

OTHER

APPLICATIONS

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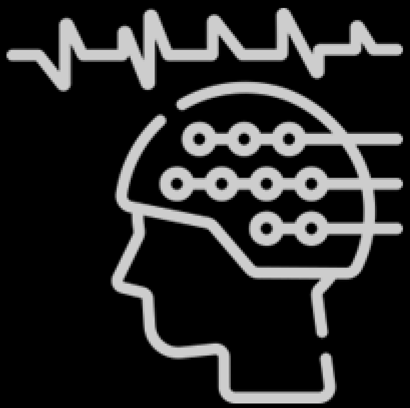

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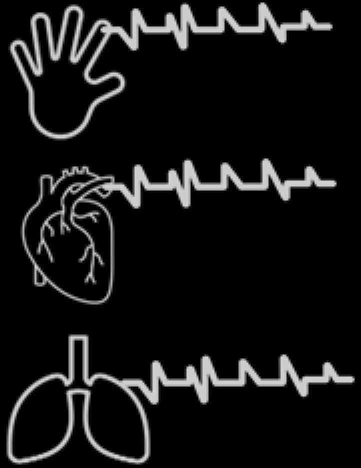
Psychometrics



Physiology

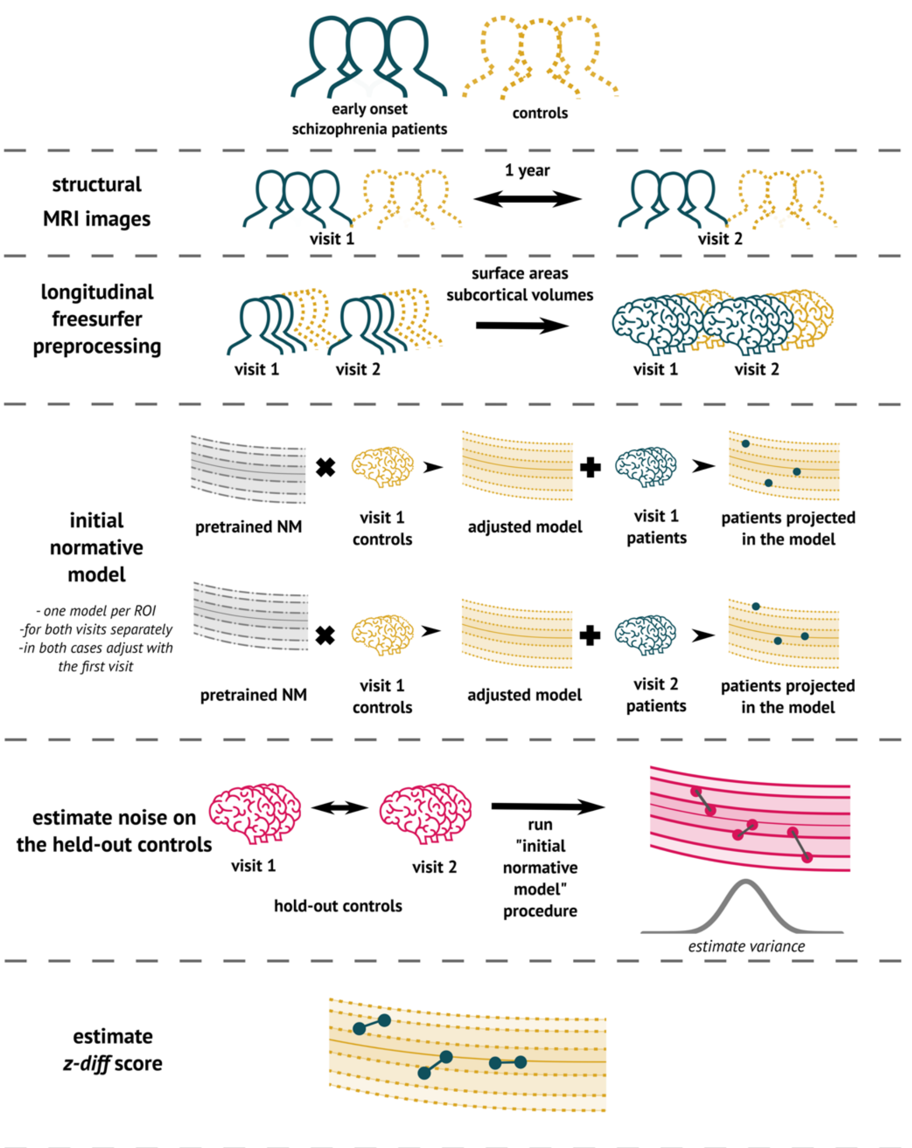
Longitudinal

OTHER

APPLICATIONS

Longitudinal models from cross sectional data

- 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

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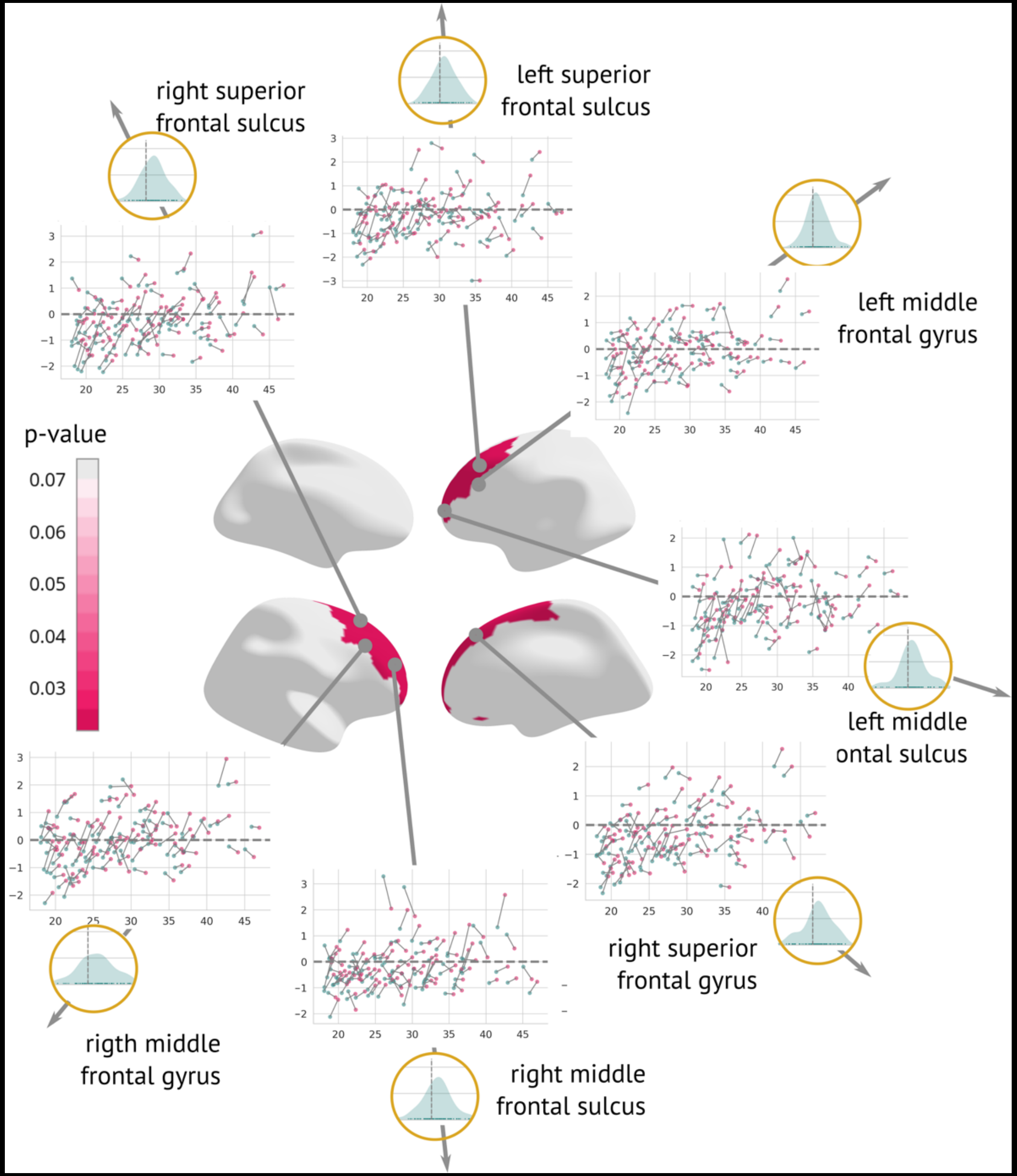
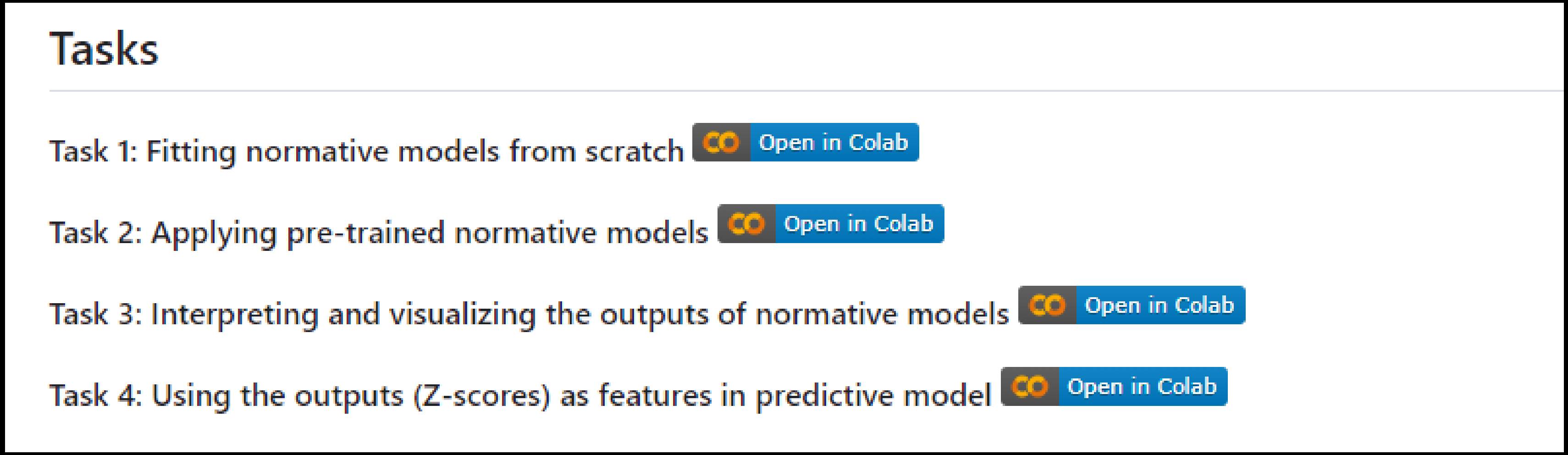


Barbora Rehák Bučková et al., (2024) **Using normative models pre-trained on cross-sectional data to evaluate longitudinal changes in neuroimaging data** *BioArxiv.*

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

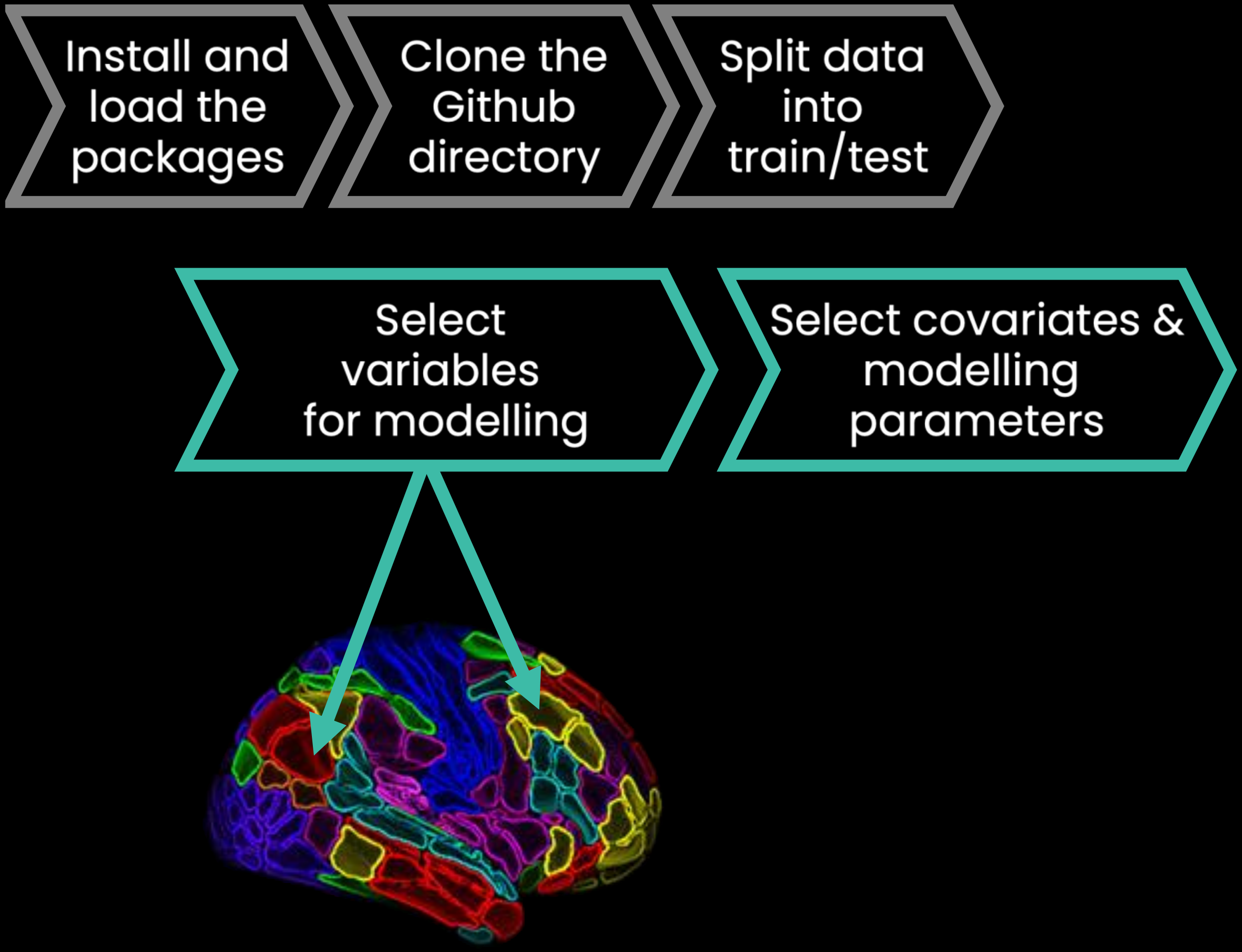
TUTORIAL I.

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

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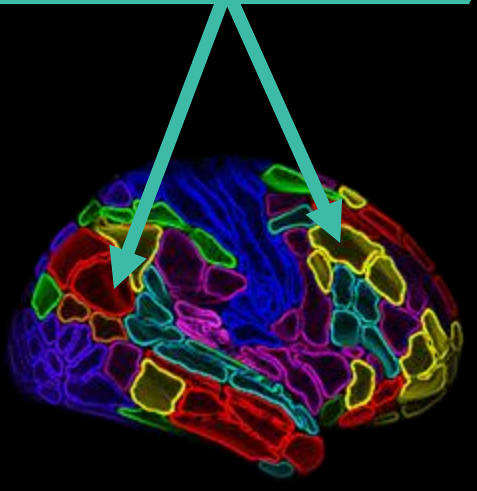
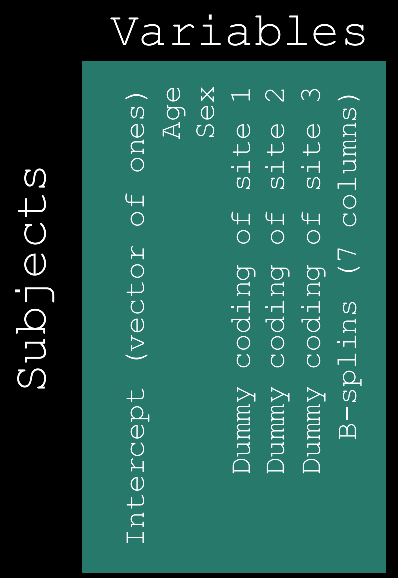
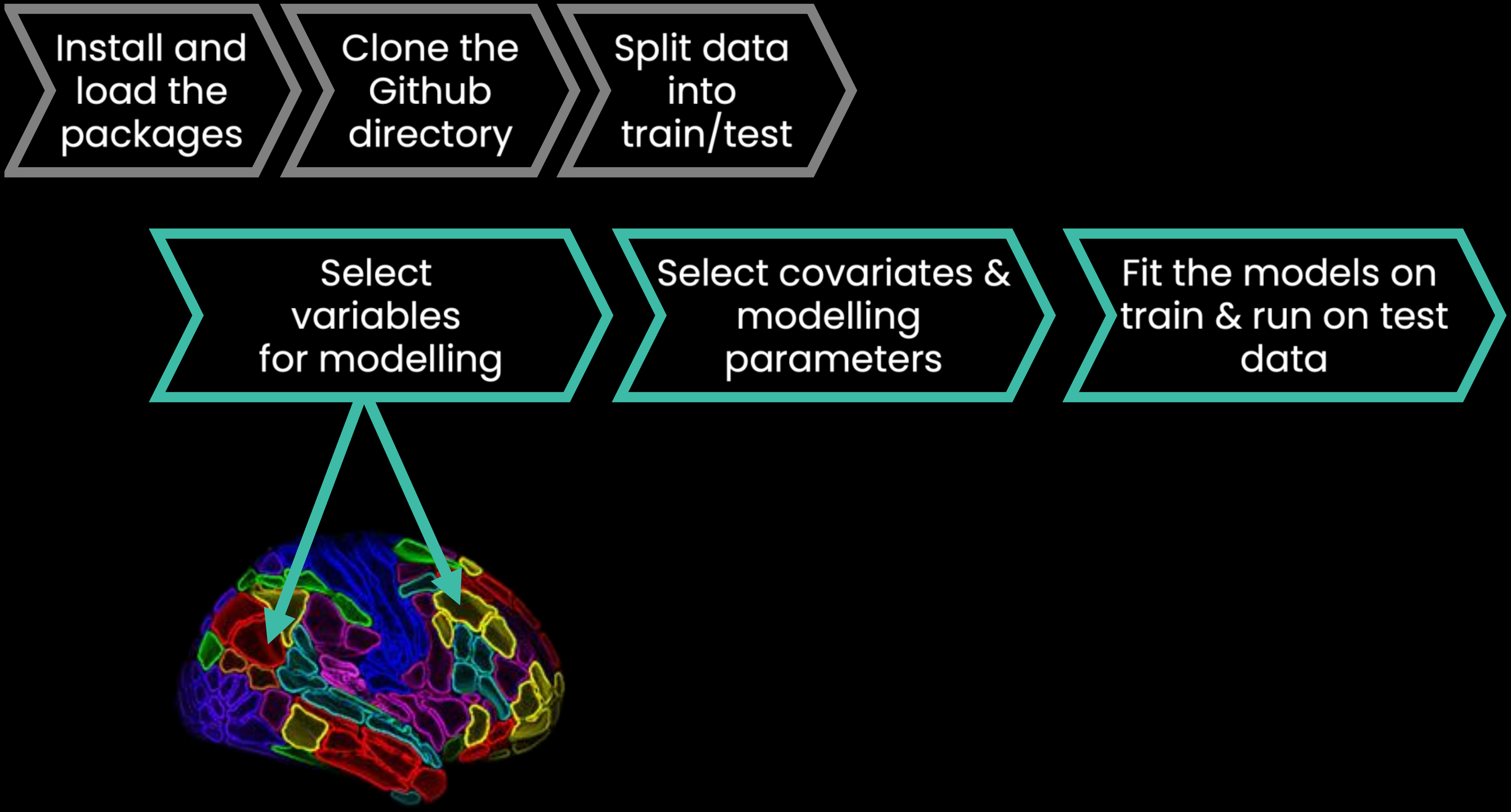
- ["age", "sex"]
- Warp modelled variable?
- Set-up B-spline
- Set-up outlier threshold





TUTORIAL I.

ESTIMATING LIFESPAN NORMATIVE MODELS



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Fit the models on train & run on test data

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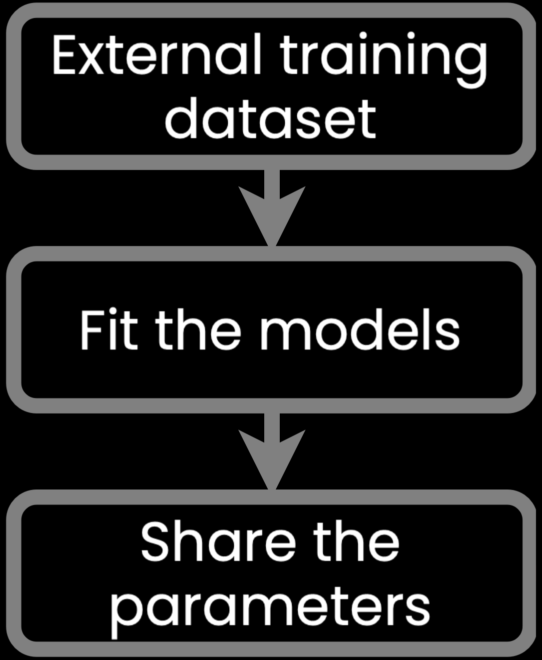
Check the fit of the models

- Negative log likelihood
- Explained variance
- Mean standardized log loss
- Bayesian information criteria
- Skew
- Kurtosis

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS



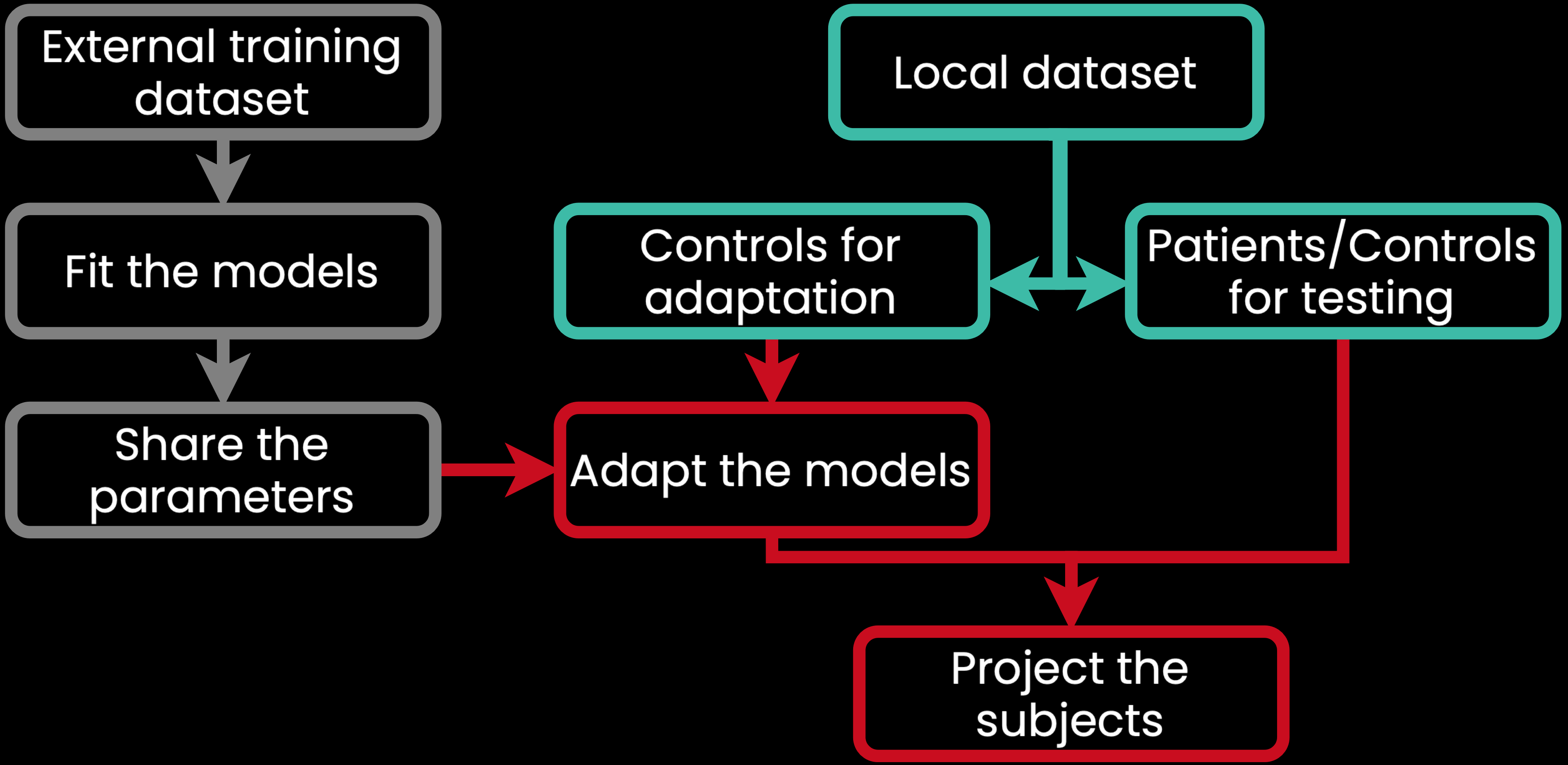
External training dataset

Fit the models

Share the parameters

TUTORIAL II.

APPLYING PRE-TRAINED NORMATIVE MODELS



External training dataset

Fit the models

Share the parameters

Local dataset

Controls for adaptation

Patients/Controls for testing

Adapt the models

Project the subjects

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

- Install and load the packages
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- Select variables for modelling
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- Adapt the pretrained models & run on test data

TUTORIAL II.

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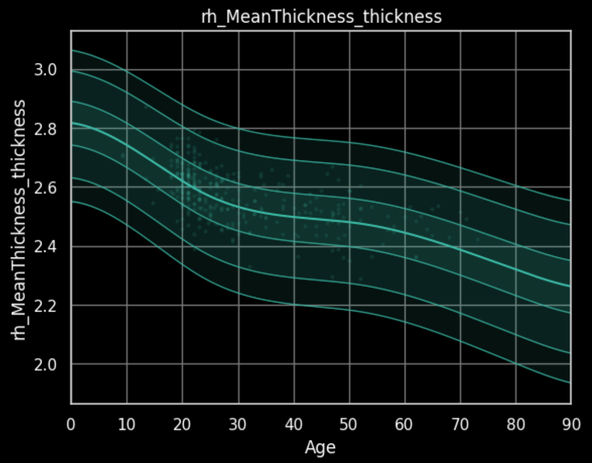

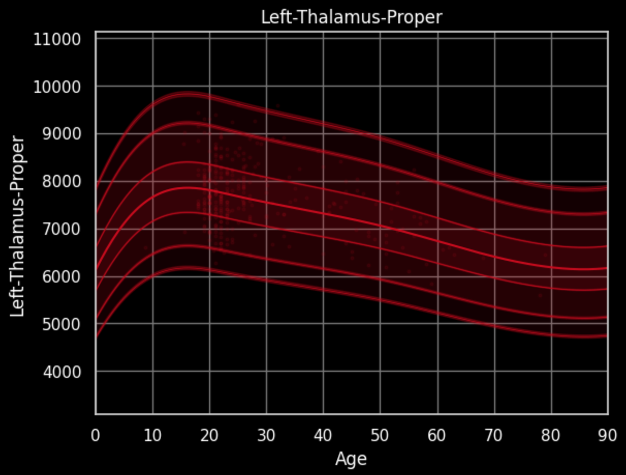

Visualize

Download the toolbox here:
github.com/amarquand

pcnportal.dccn.nl

https://pcntoolkit.readthedocs.io

Predictive Clinical Neuroscience Lab

Professor Andre Marquand

THANK YOU!

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