Statistical analysis of PET data

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Basic problems associated with scientific measurement

ERRORS PRESENT AT ALL LEVELS; THEY ALSO ACCUMULATE FROM LEVEL TO LEVEL

TARGET
(e.g. specific neuro-receptor)

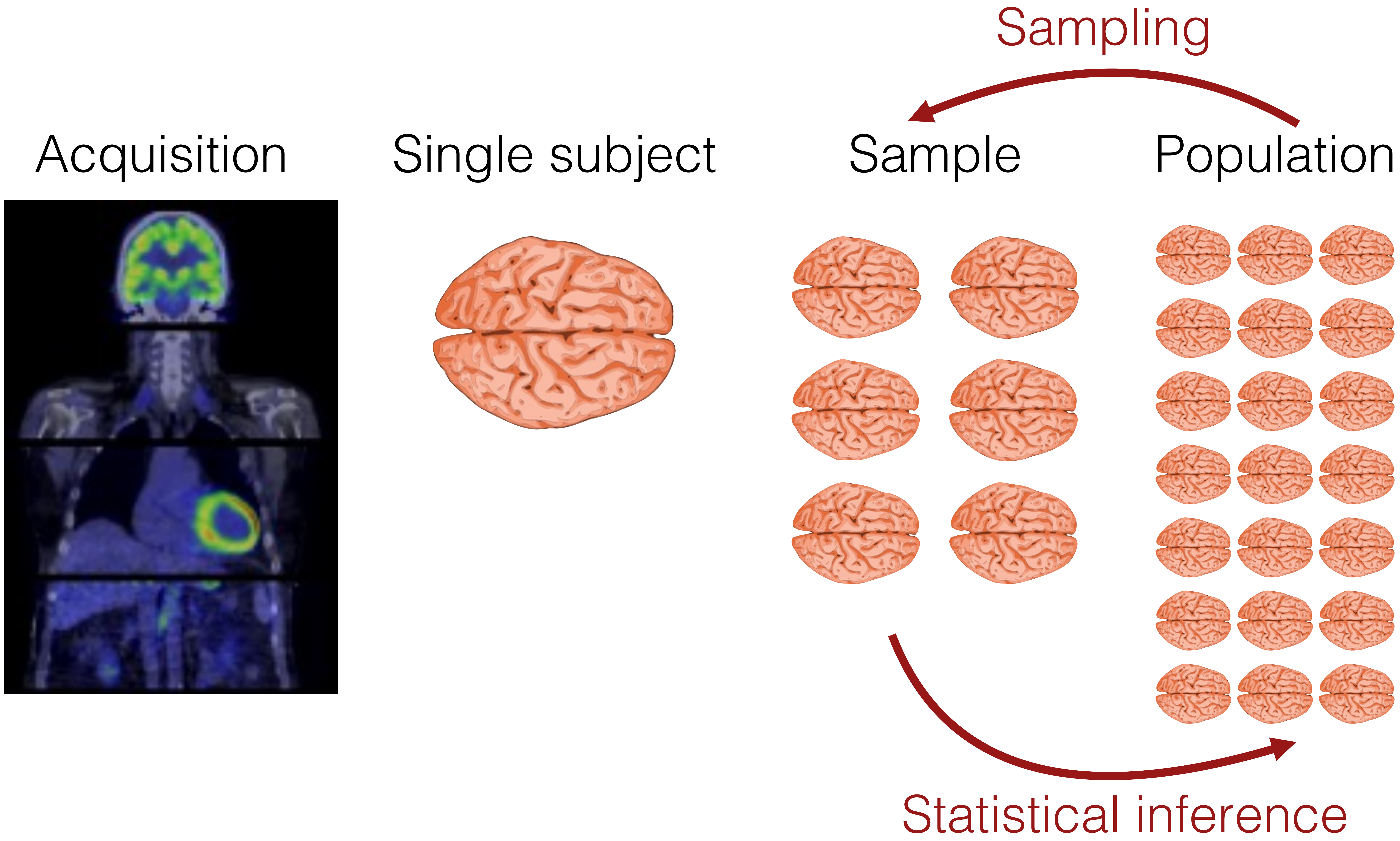
TRUE SCORE (T)
How target is defined
(e.g. number of receptors)

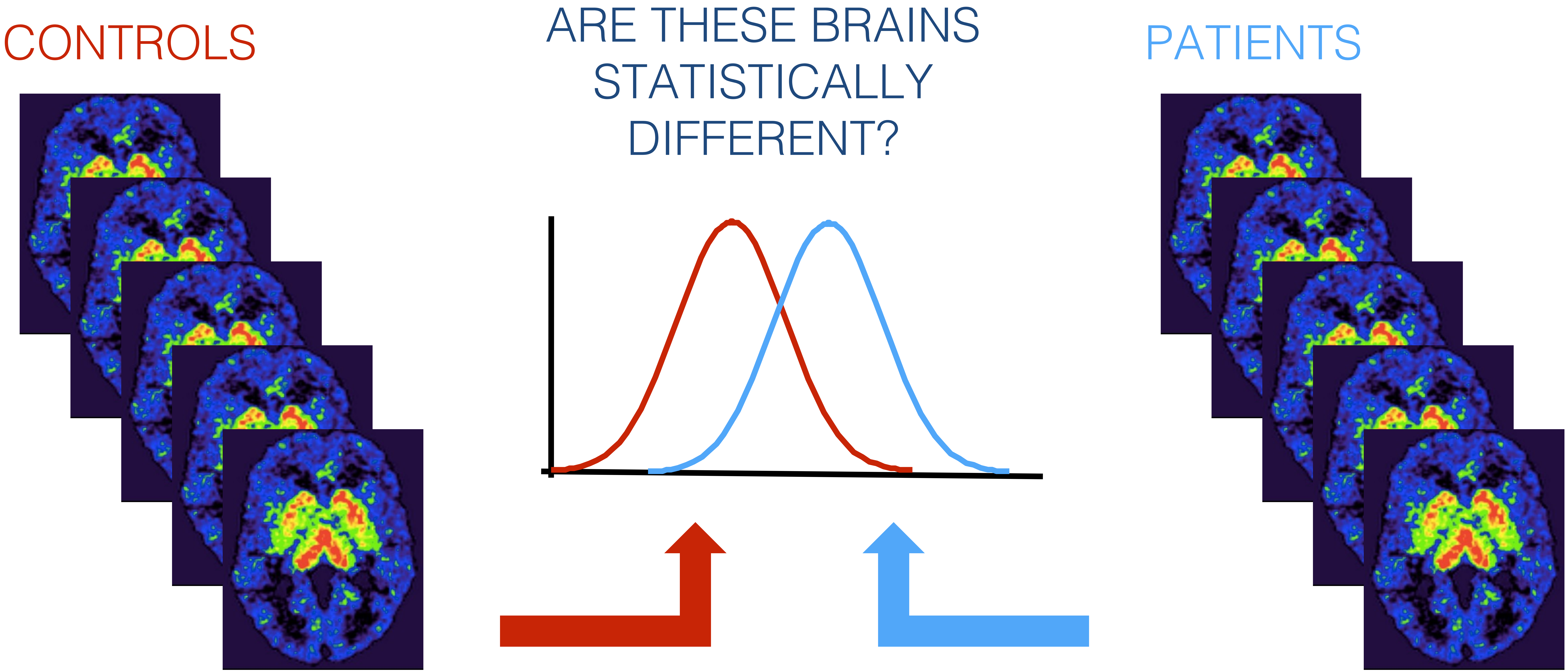
OBSERVED SCORE
(Outcome measure such as BPND)

PREDICTION OF BEHAVIOR
(e.g. anxiety-like behaviour)

- How well is target variable reflected in true scroe (construct validity)
- How well true score is reflected in observed score? (reliability)
- How well does observed score predict behaviour? (criterion-based validity)

Making inferences about the population





Starting point: Images where voxel intensities reflect the outcome measure

Sneak peek: Analysis of PET vs. fMRI data

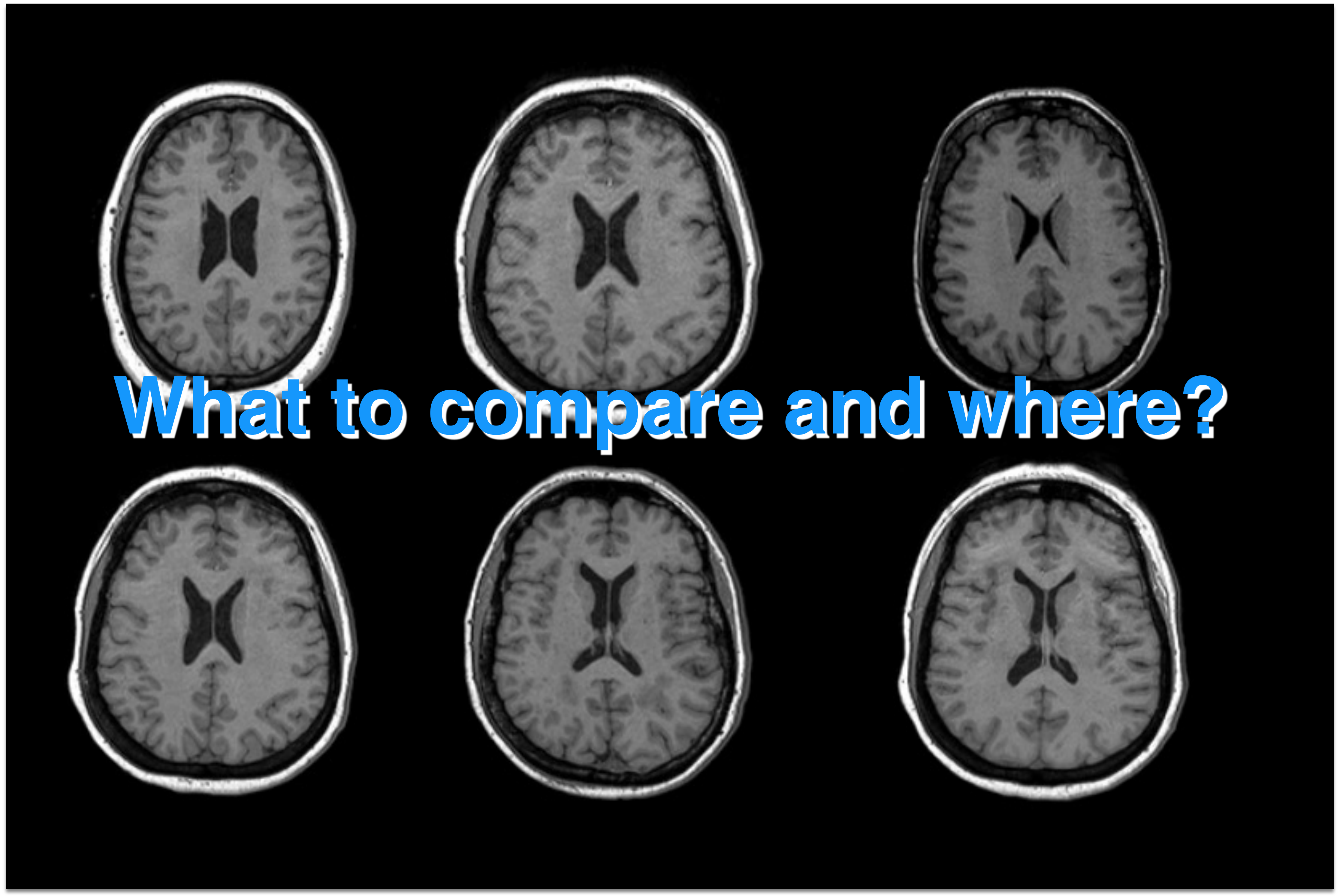
- **PET data needs to be modelled** before population level inference
  - Dynamic 4D image or static 3D image —> 3D image
  - Voxel intensities reflect outcome measure (receptor density, metabolism….)
- **Similarly, EPI data needs to be modelled** before population level inference
  - Dynamic 4D image —> 3D image
  - Voxel intensities reflect the fit of the stimulation model to the BOLD time series

Univariate data
Regularly shaped

3D neuroimaging data
Irregularly shaped

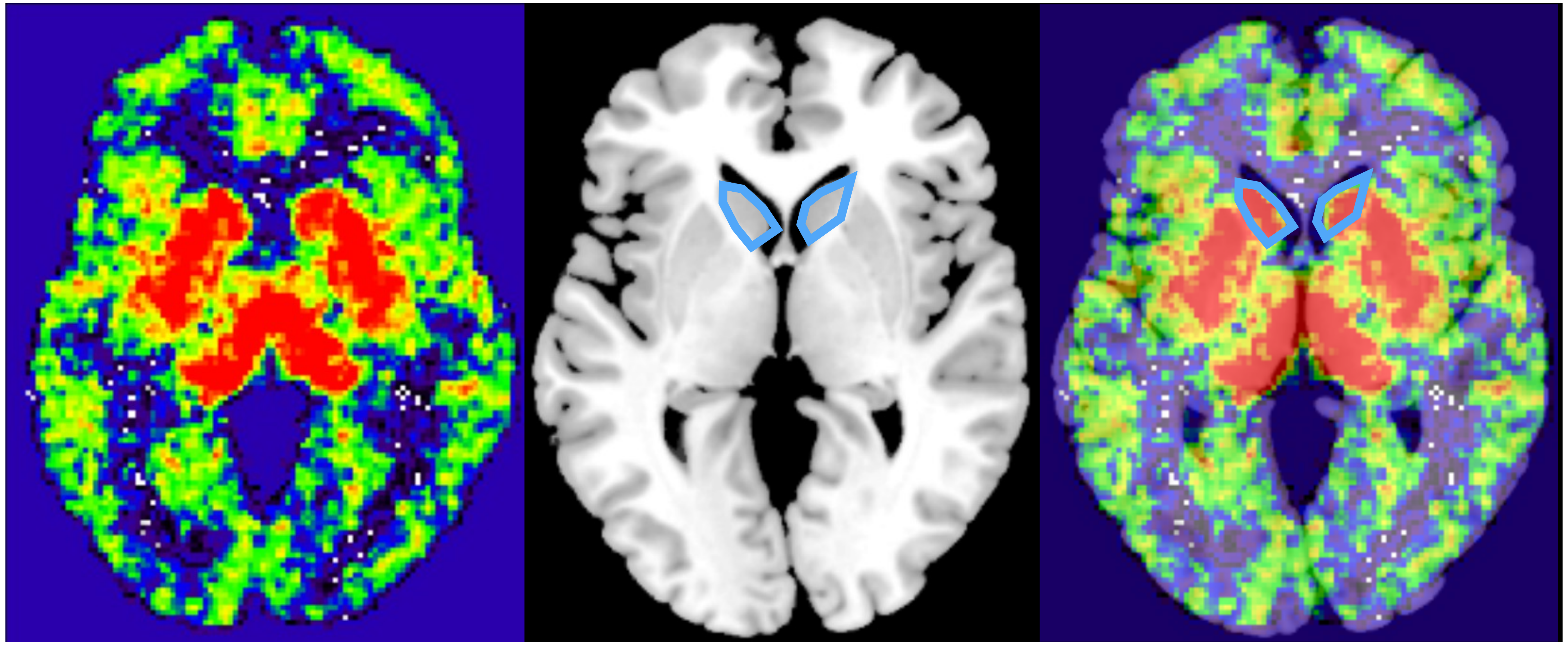
t-test

Controls	Patients
3	5
4	4
5	6
6	7
3	6
2	5
3	2
5	6
2	8



ROI-based analyses

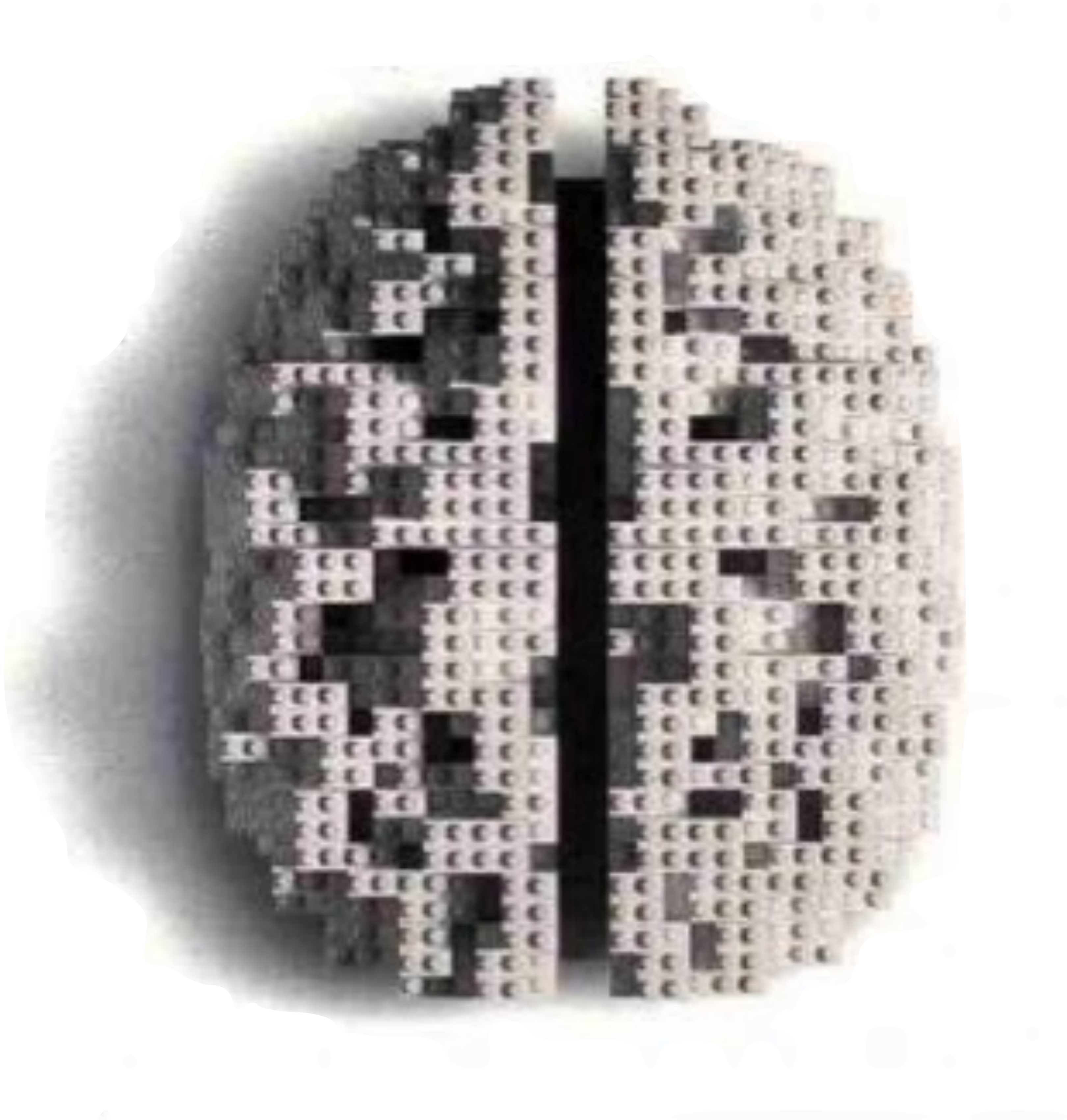
Univariate data
regularly shaped
can use univariate stats

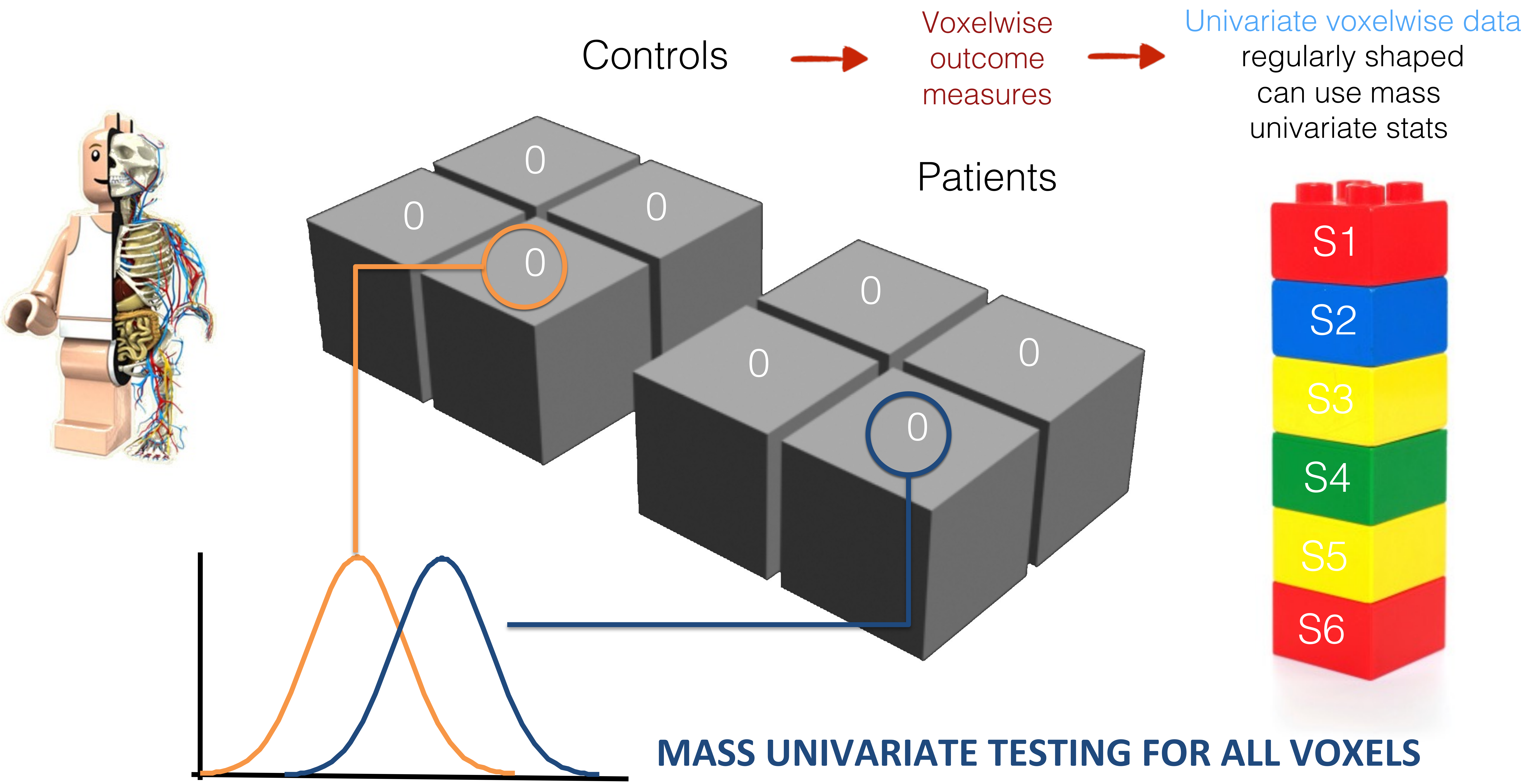


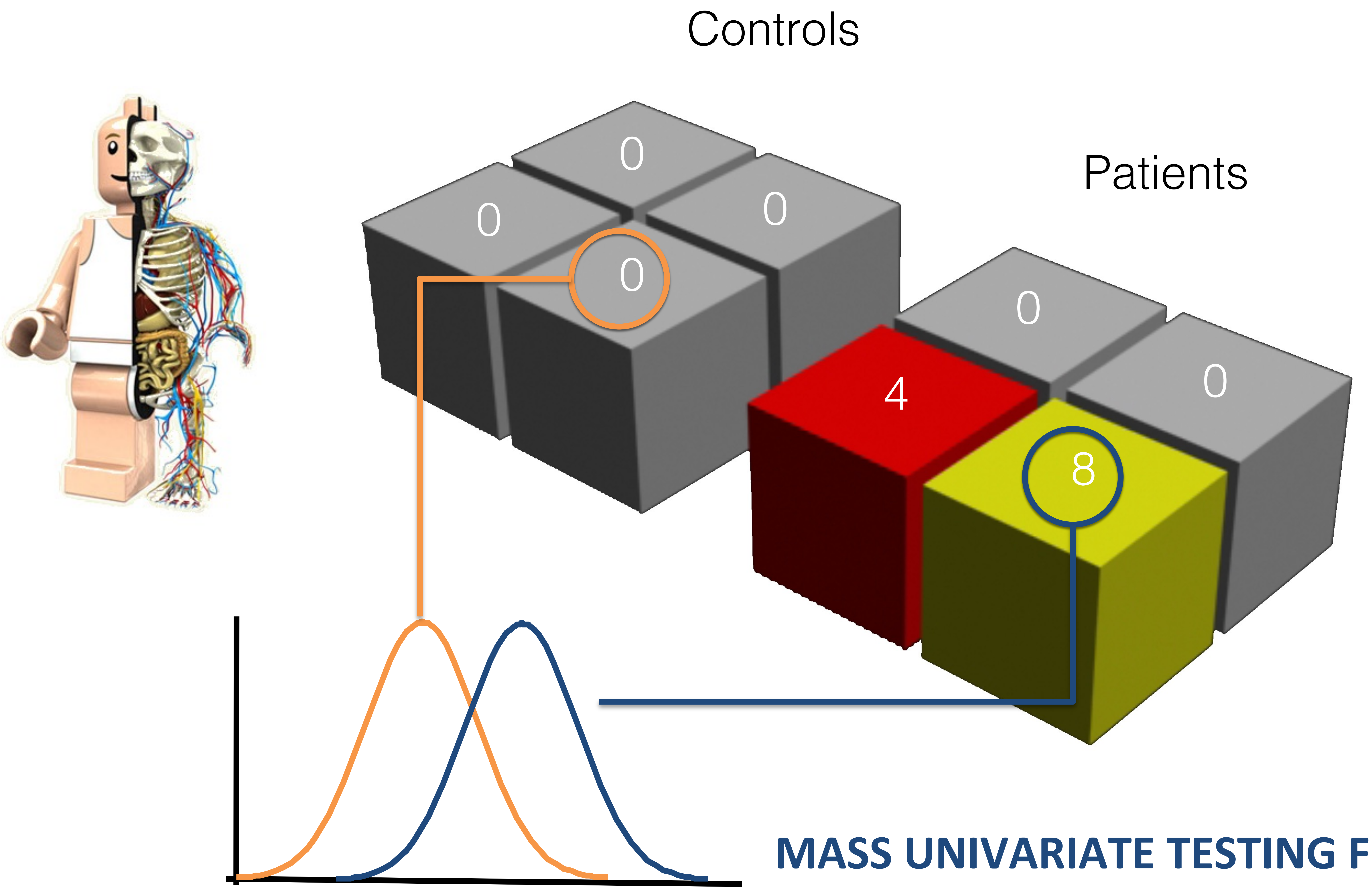
Extract outcome measure in ROI

Controls	Patients
3	5
4	4
5	6
6	7
3	6
2	5
3	2
5	6
2	8

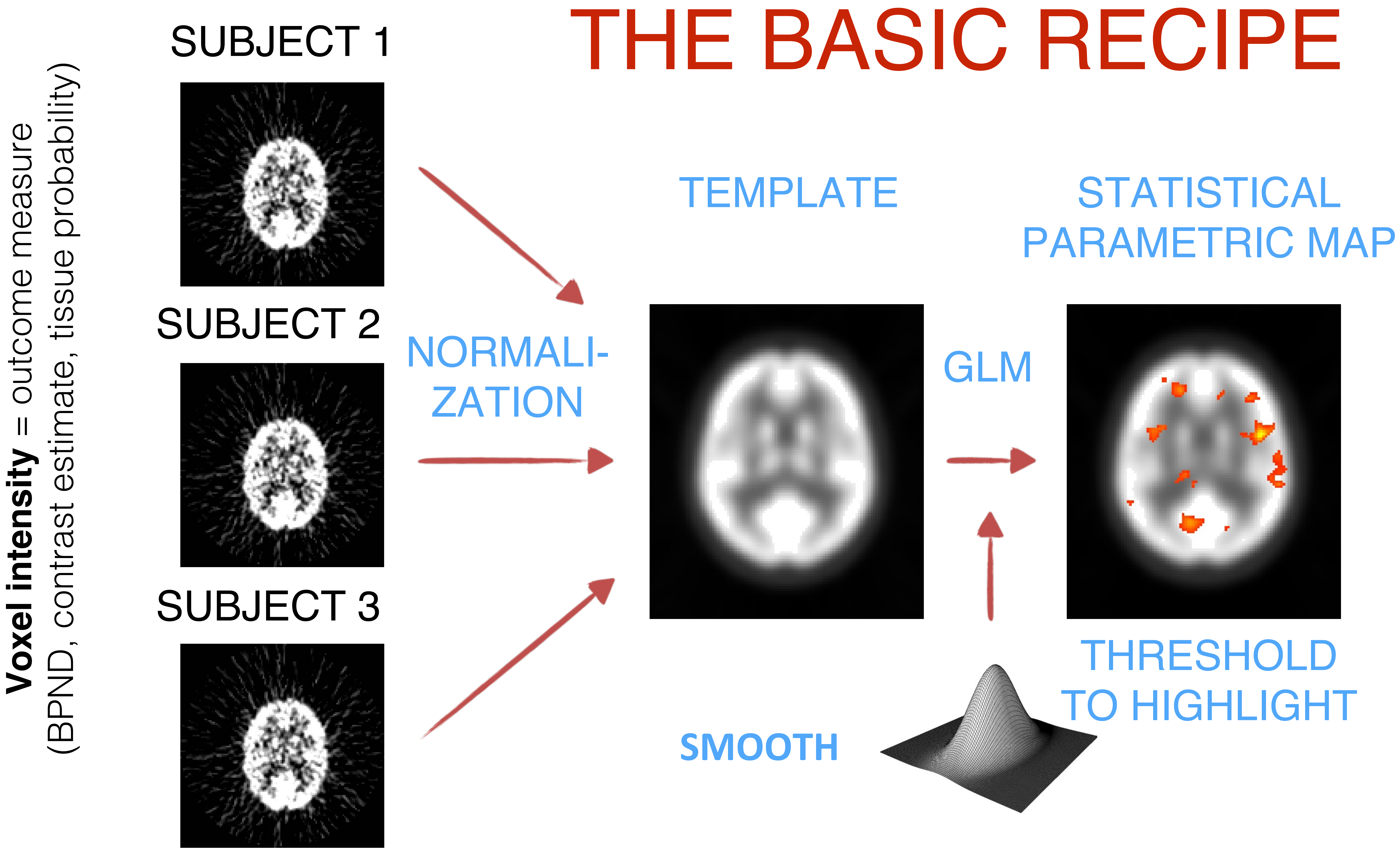
- Pros: Anatomically accurate if ROIs well definied, data can be analyzed with simple univariate statistical tests
- Cons: Laborious, using many ROIs not feasible, averaging within ROI not always appropriate




Controls
Voxelwise
outcome
measures
Univariate voxelwise data
regularly shaped
can use mass
univariate stats
Patients
0
0
0
0
0
0
0
0
S1
S2
S3
S4
S5
S6
MASS UNIVARIATE TESTING FOR ALL VOXELS



MASS UNIVARIATE TESTING FOR ALL VOXELS

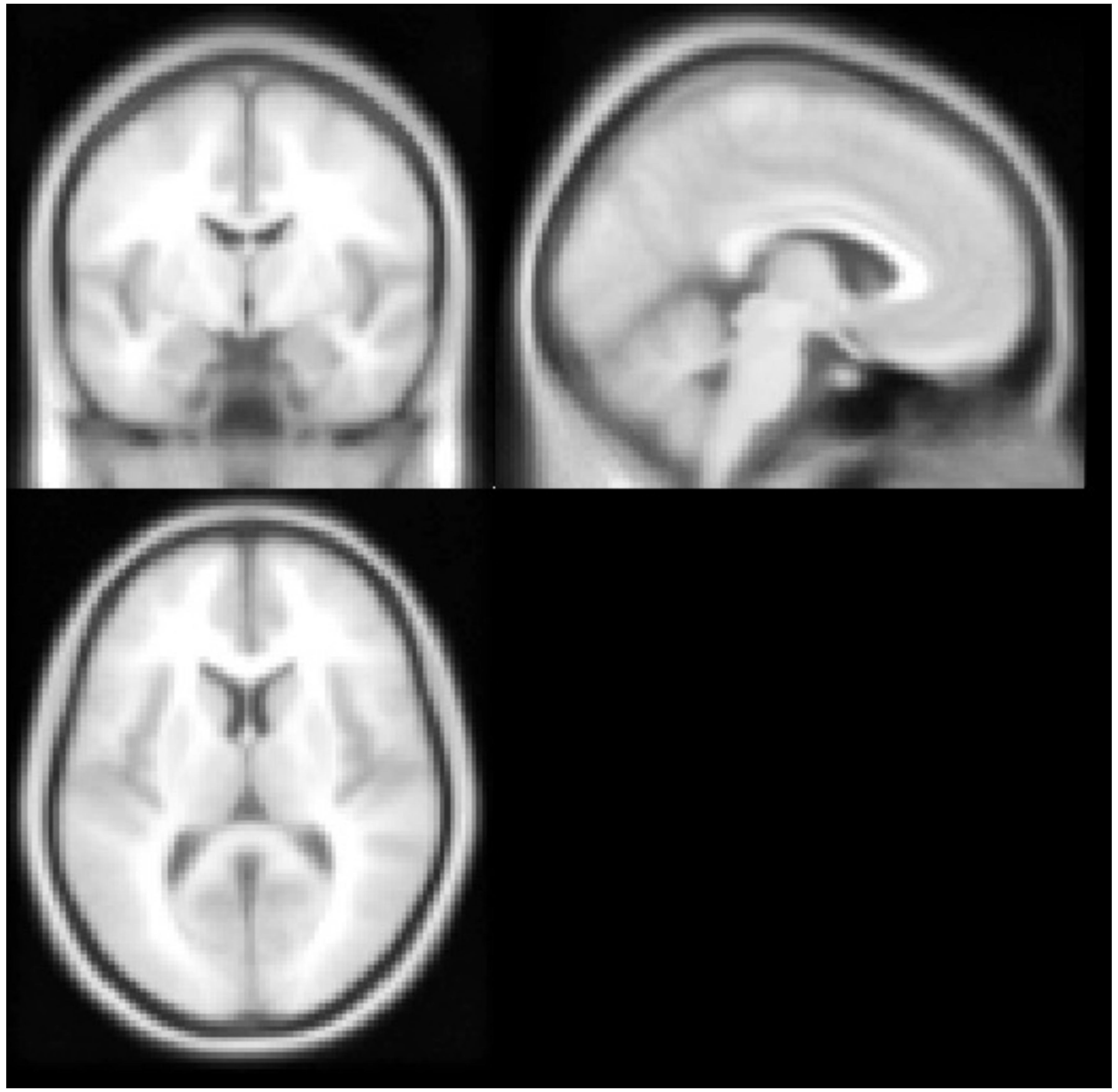

THE BASIC RECIPE
Voxel intensity = outcome measure
(BPND, contrast estimate, tissue probability)
SUBJECT 1
SUBJECT 2
SUBJECT 3
NORMALI-
ZATION
TEMPLATE
GLM
STATISTICAL
PARAMETRIC MAP
SMOOTH
THRESHOLD
TO HIGHLIGHT

Full-volume analyses with real brains

- Basic problem: Individual brains differ in size and shape
- Solution to the problem: Make brains similar by warping them
- Problems with the solution
  - Warps distort anatomy
  - Anatomical information is not the precise anyway
  - How should we warp the brains?

The MNI space as the target

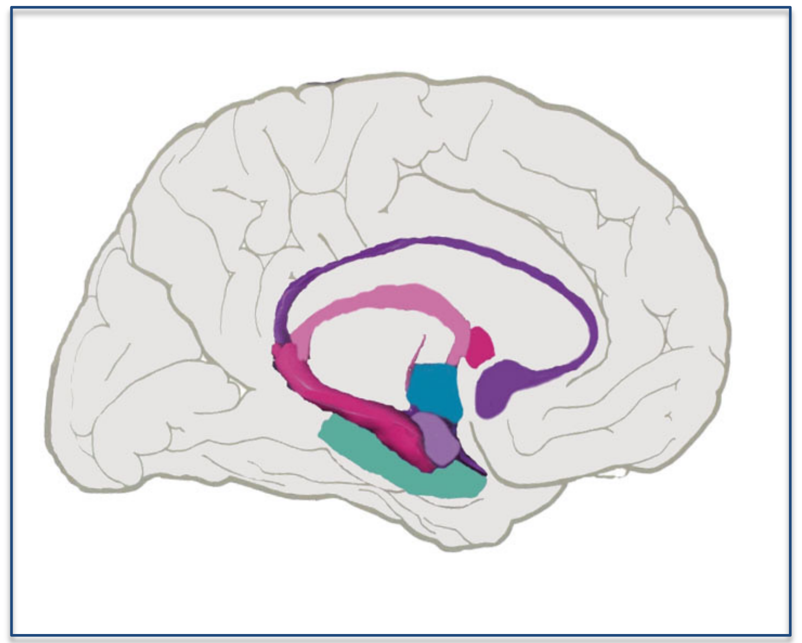
- **ICBM 152 template**
- Based on average of 152 brains that have been spatially normalized
- Statistical average of the typical western adult brain
- Problem: not necessarily representative of study sample
- In fMRI can also use e.g. spherical models



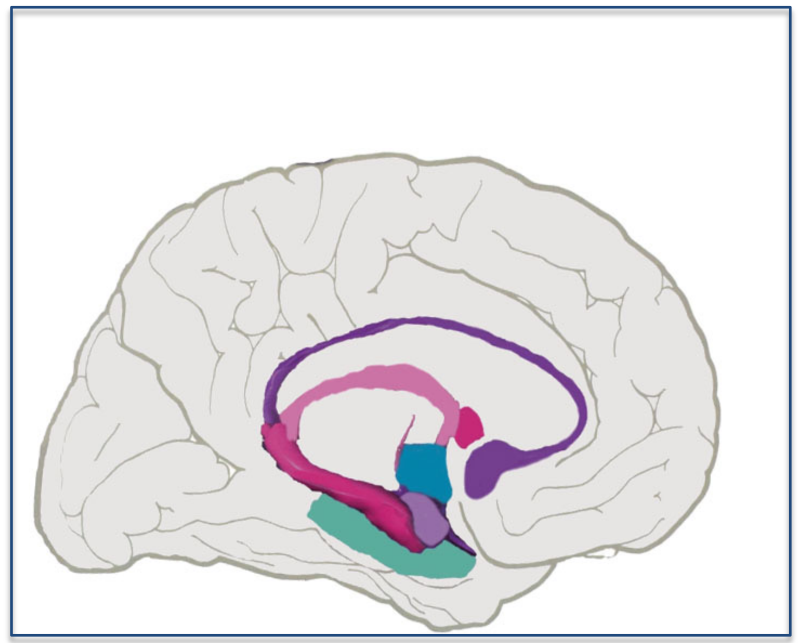
Spatial normalization in practice

1. Linear (12-parameter affine) normalization
   - Match size and position
2. Nonlinear normalization
   - Linear combinations of smooth discrete cosine basis functions

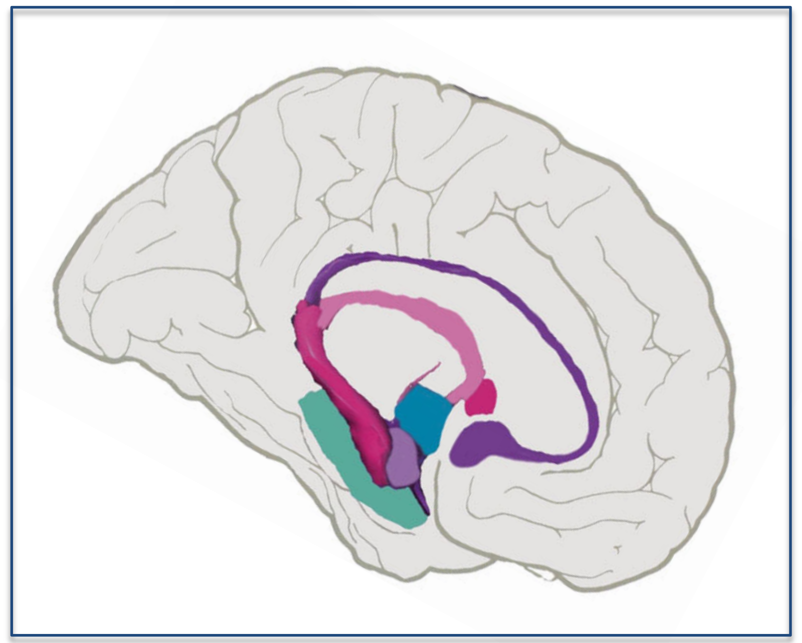
NATIVE



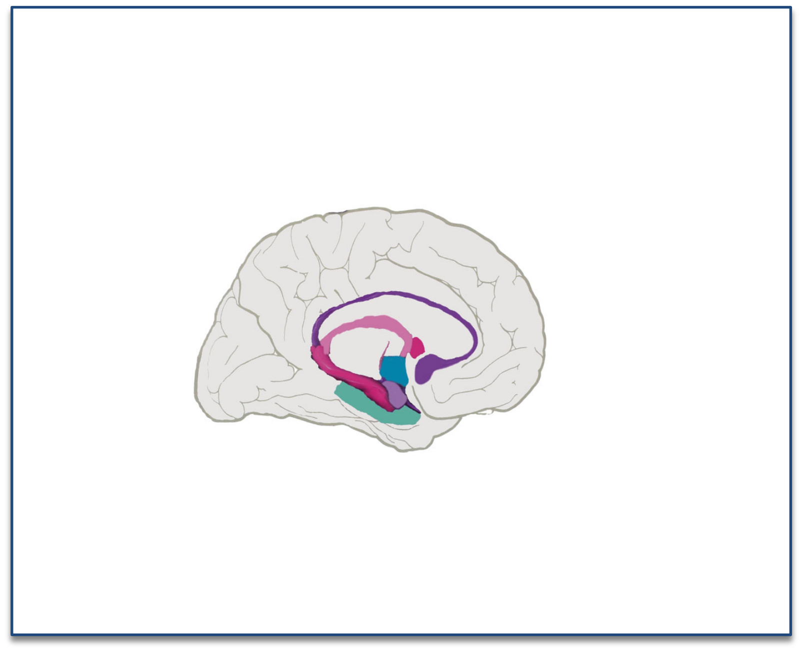
TRANSLATION



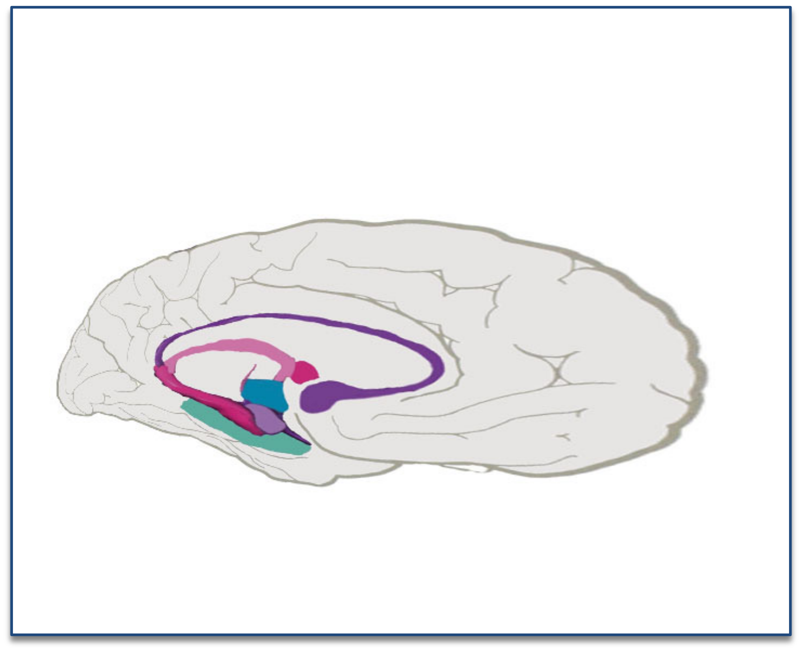
ROTATION



ZOOM

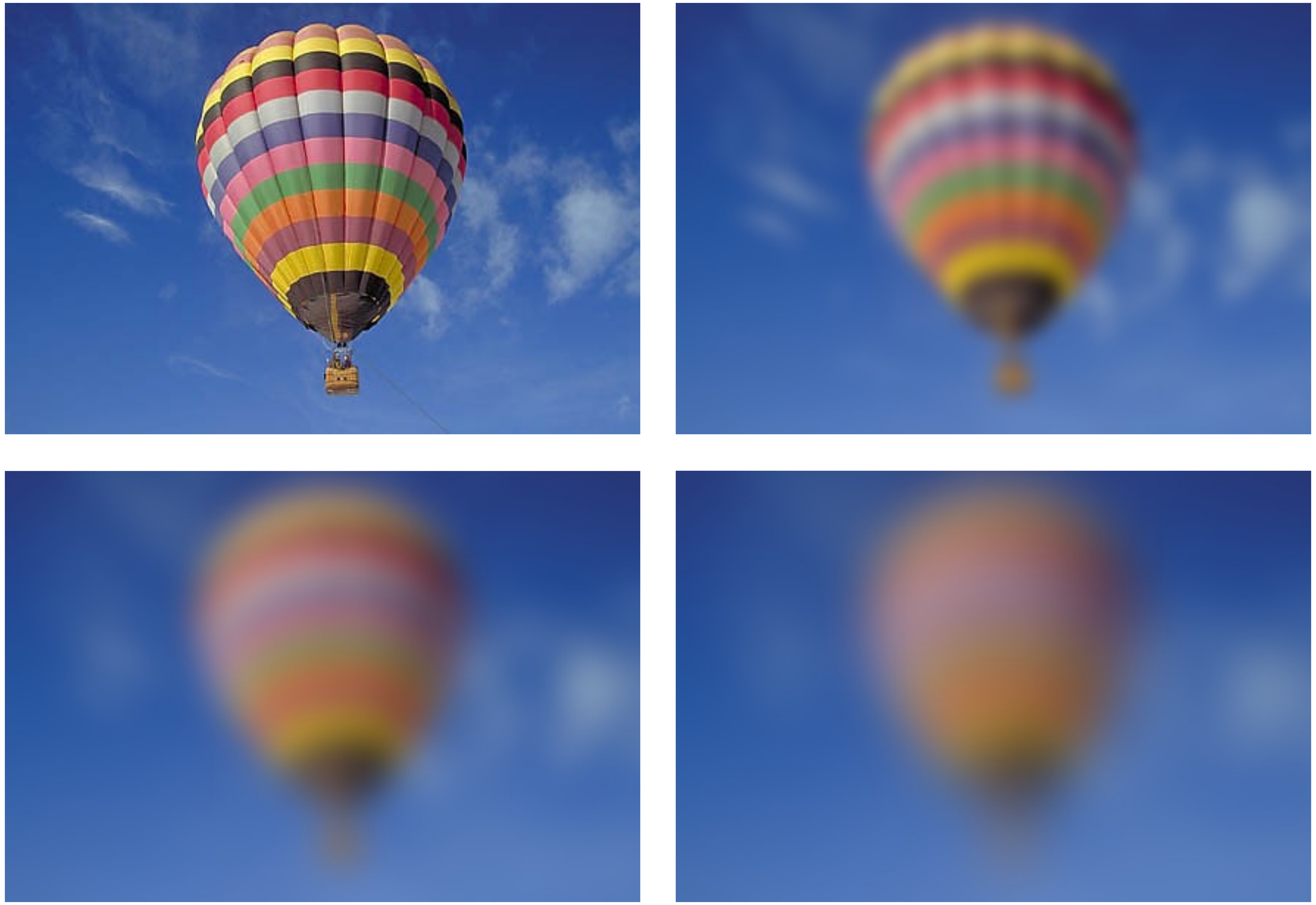


SHEAR



AFFINE NORMALIZATION: 4*3 PARAMETERS

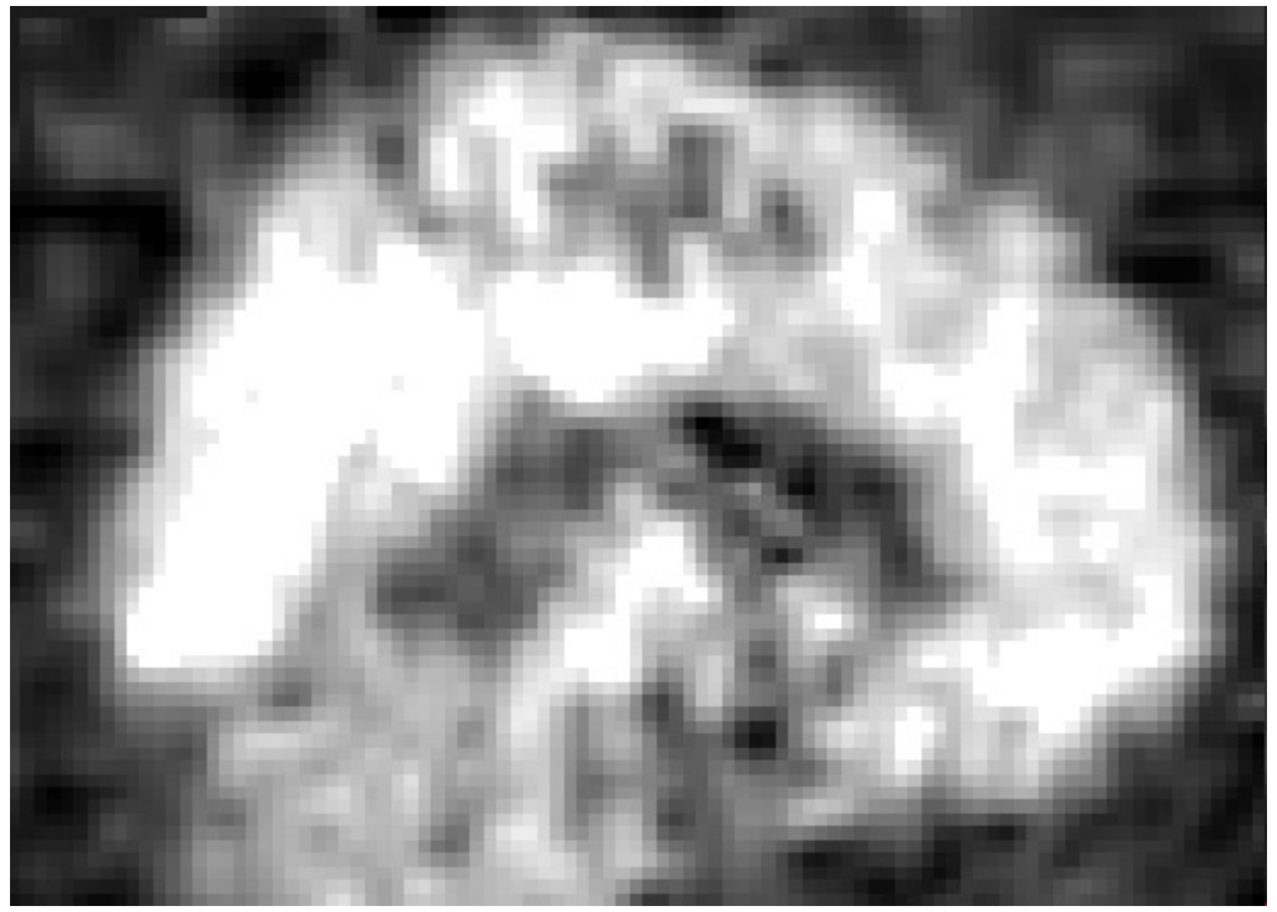
Smoothing



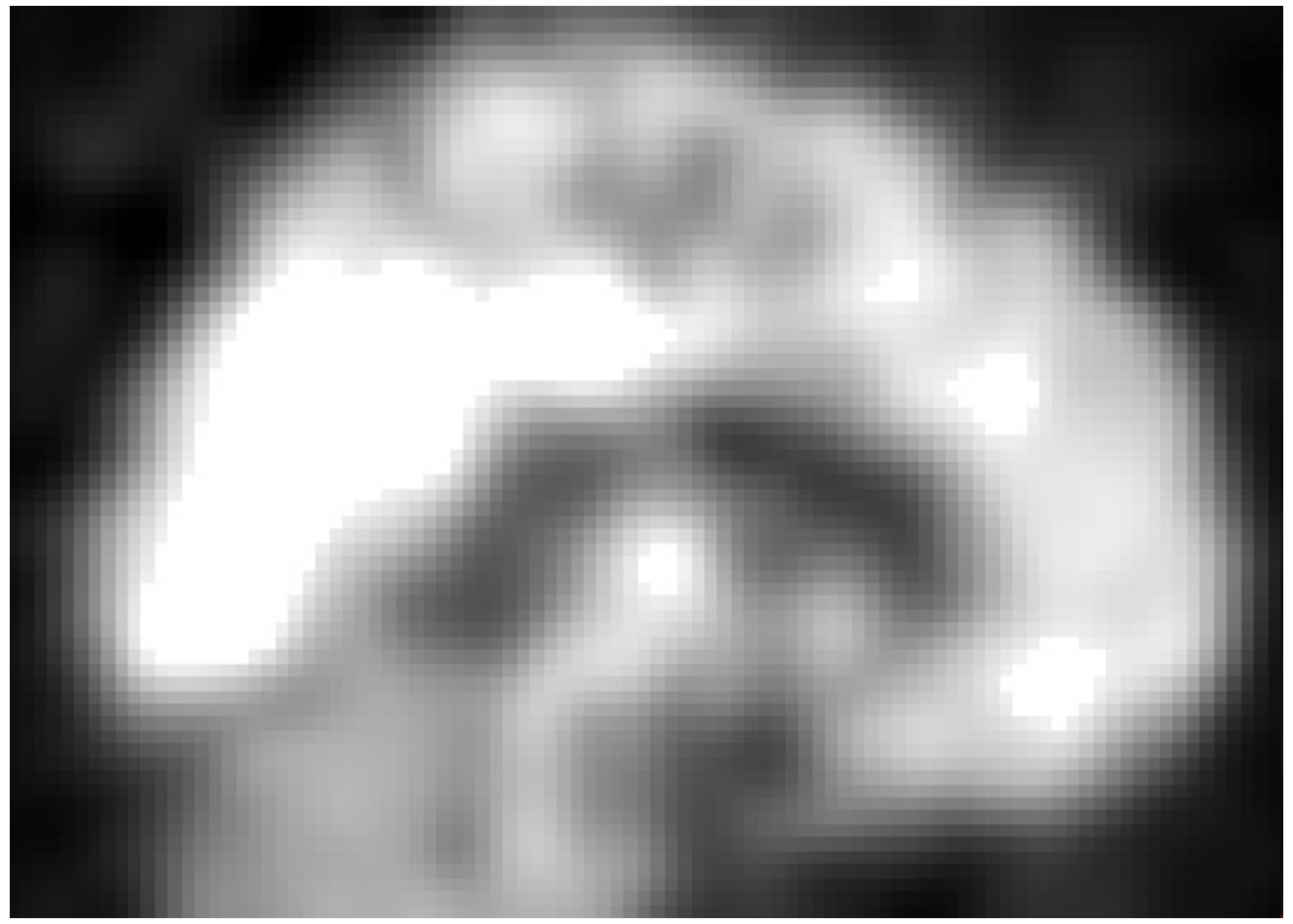
FWHM = spatial extent of the filter

Example on smoothing brain-PET images

UNSMOOTHED

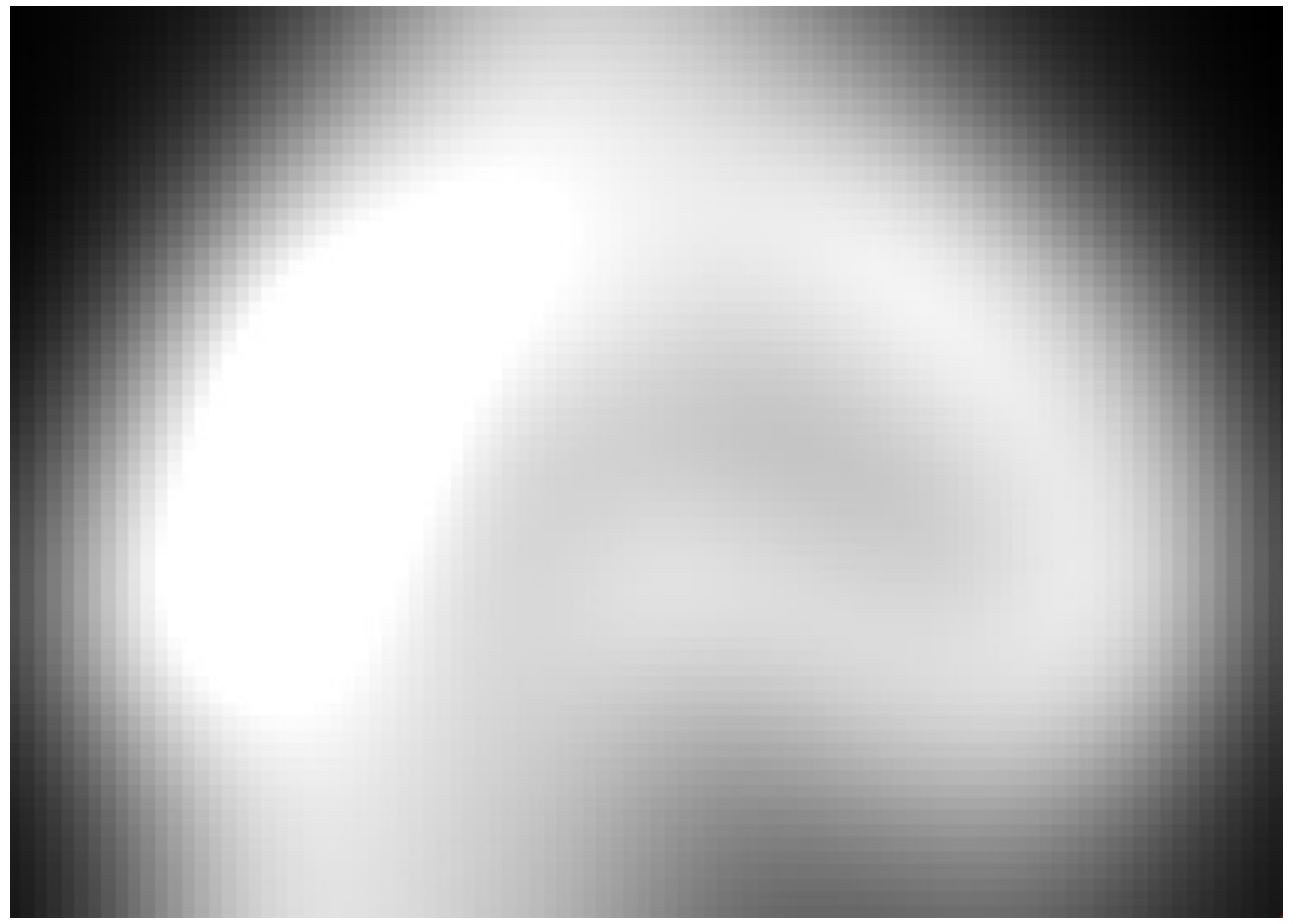


12mm FWHM

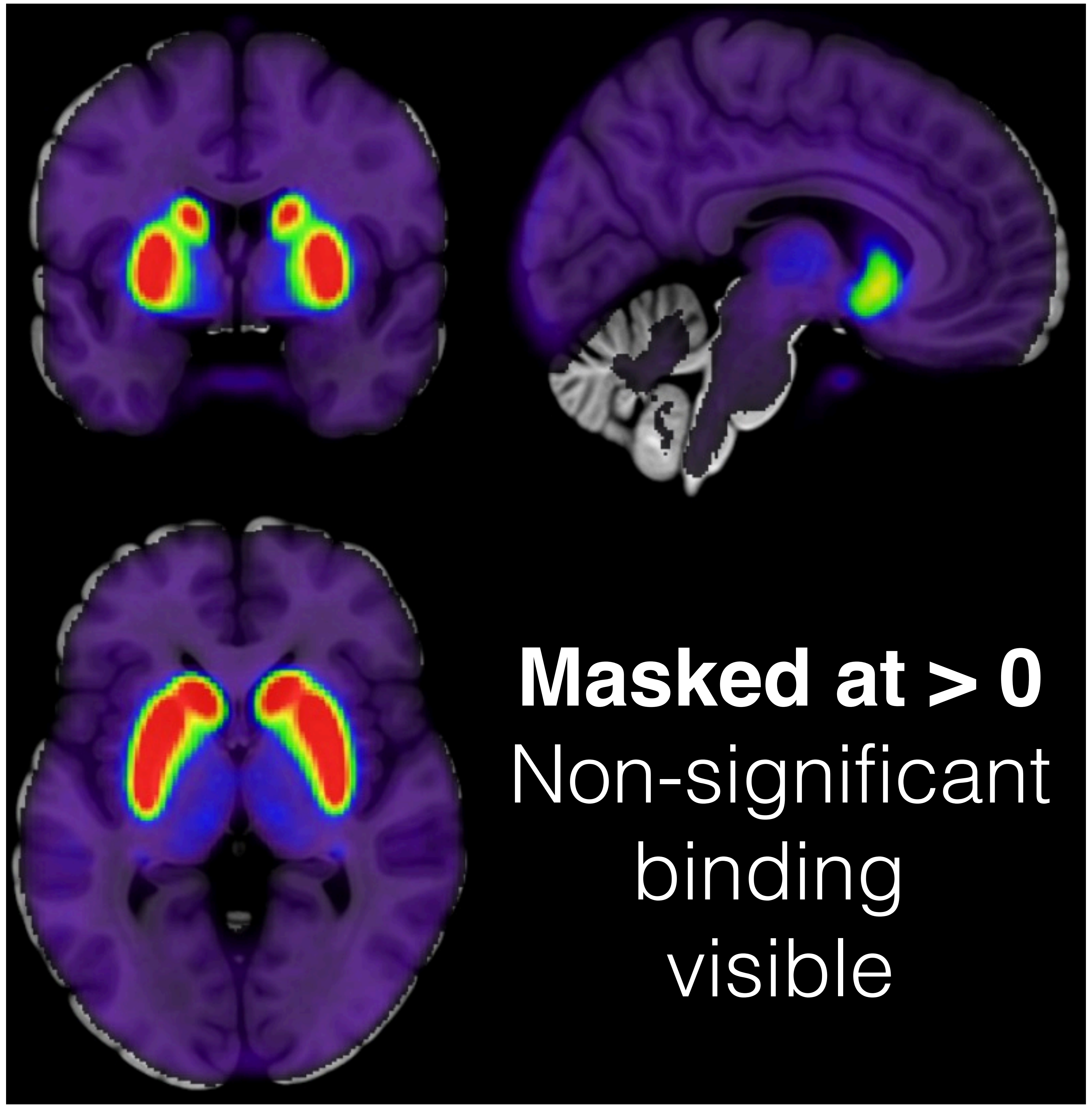


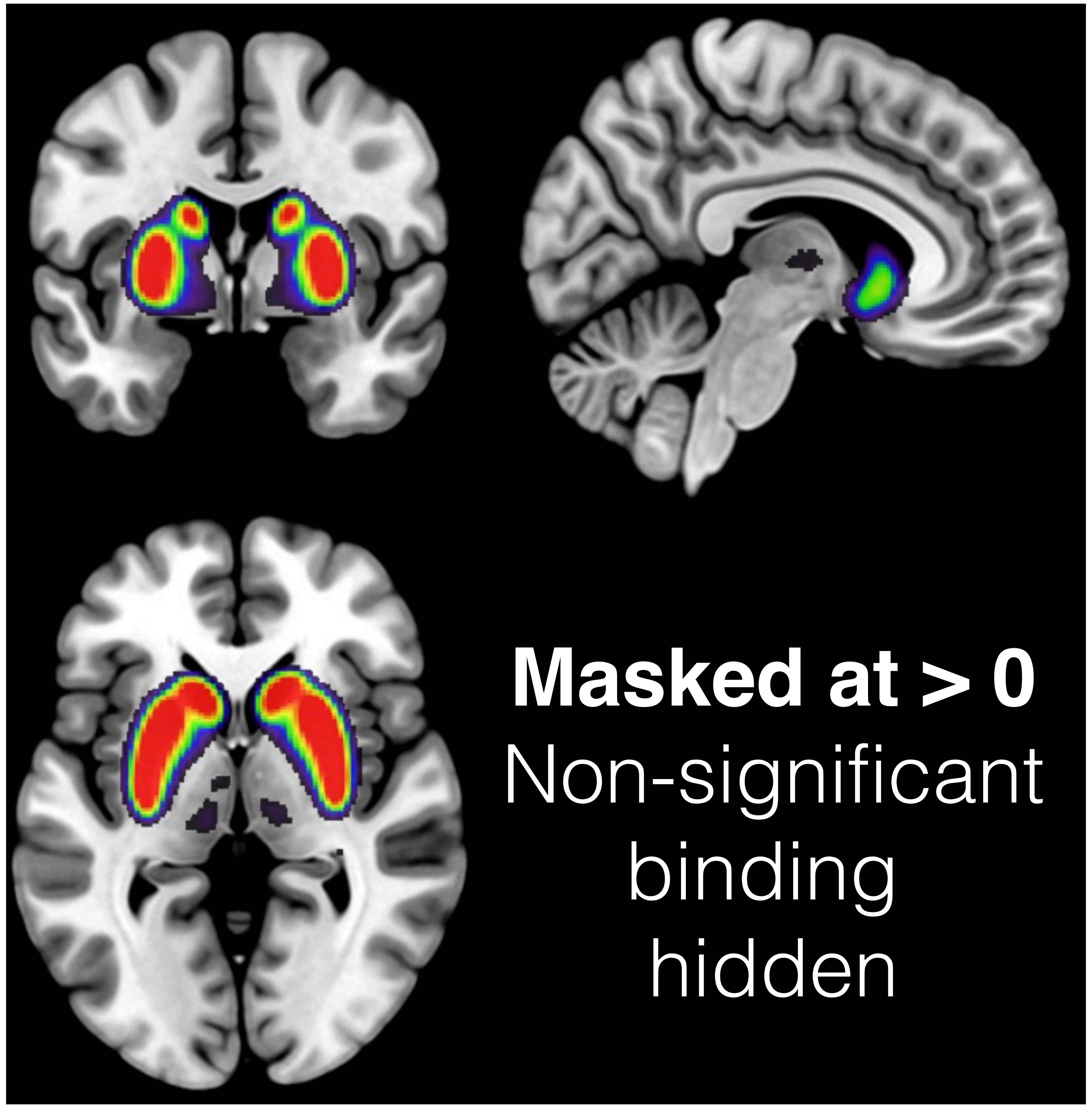
16mm FWHM

32mm FWHM



Masking the data





Applying explicit / threshold mask is necessary to avoid modelling noise

What sort of voxelwise model to fit?

GLM

ANOVA, ANCOVA, linear regression…

Dependent Variable

Population Y intercept

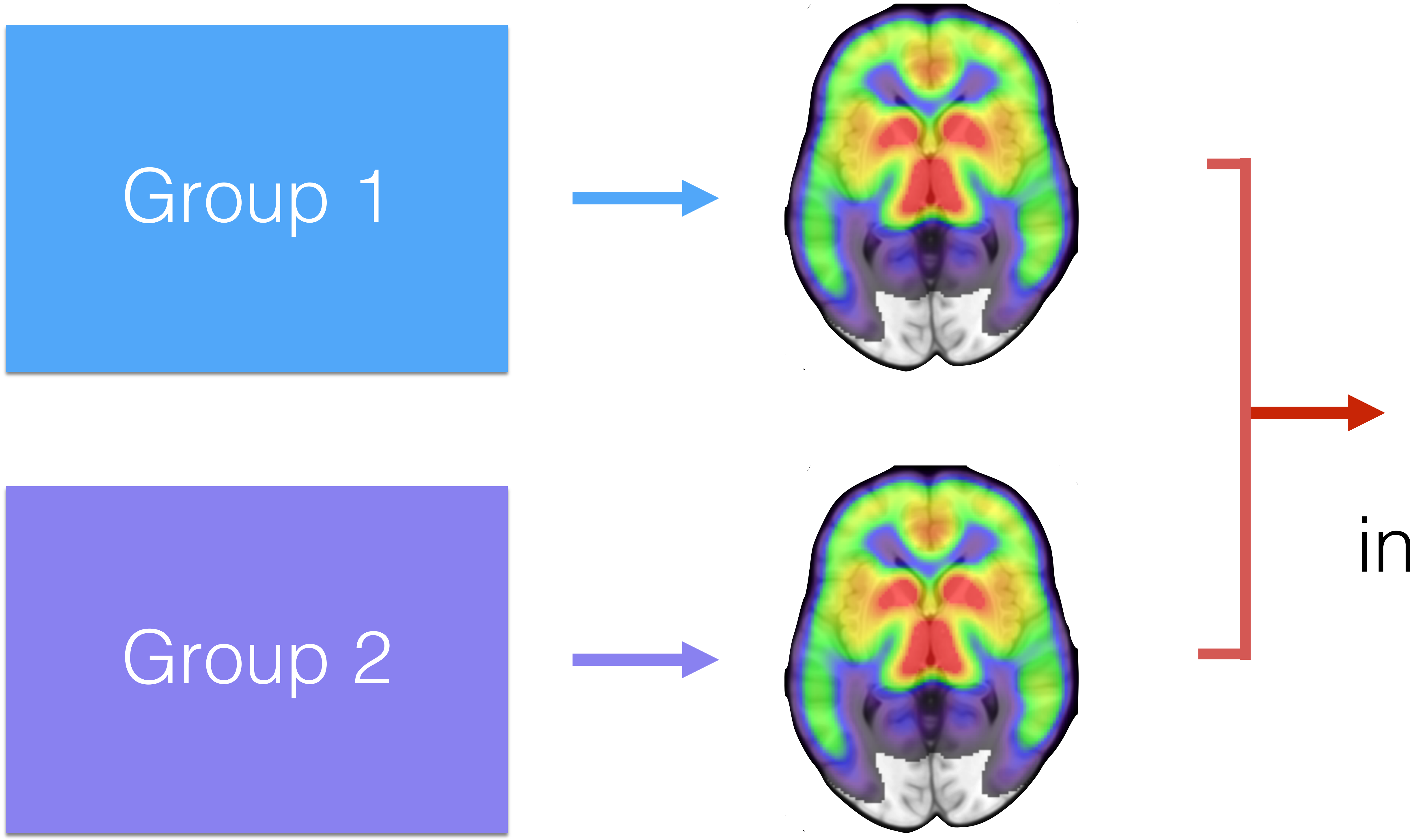
Population Slope Coefficient

Independent Variable

Random Error term

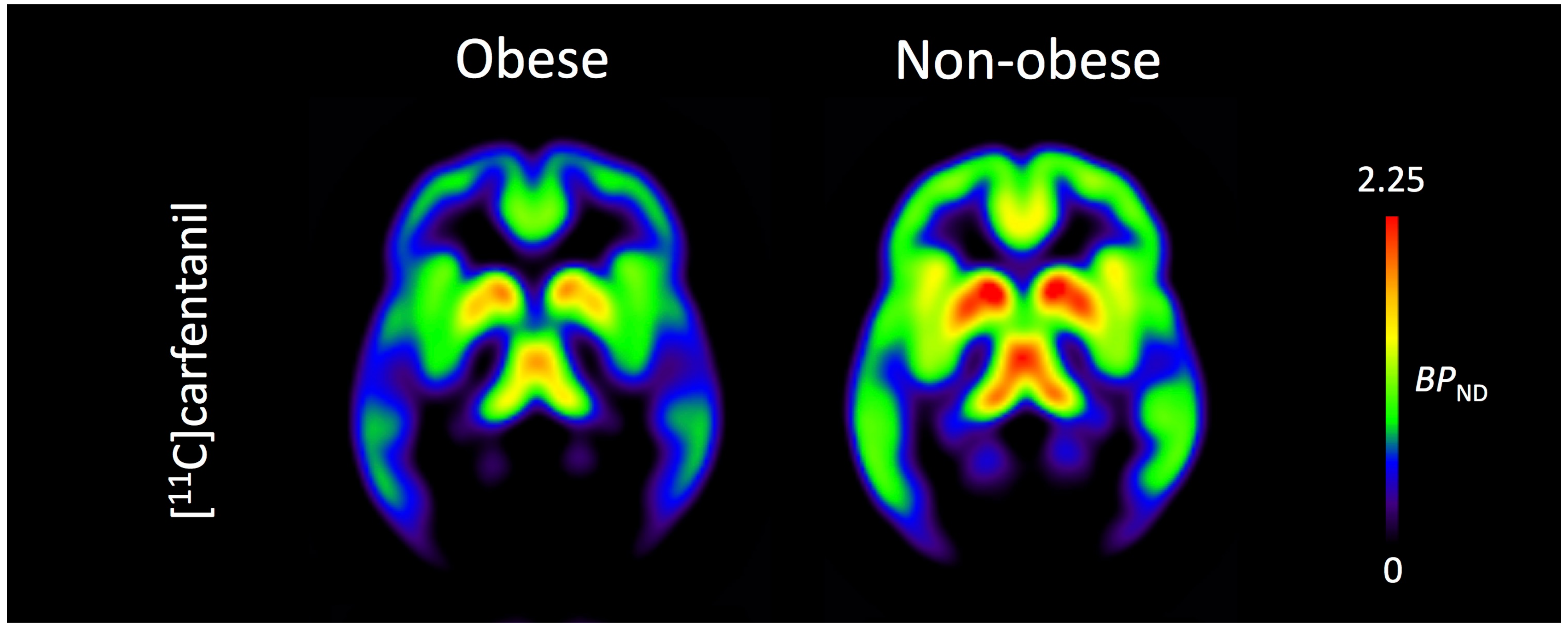
$$Y_i = \underbrace{\beta_0 + \beta_1 X_i}_{\text{Linear component}} + \underbrace{\varepsilon_i}_{\text{Random Error component}}$$

Between-groups design

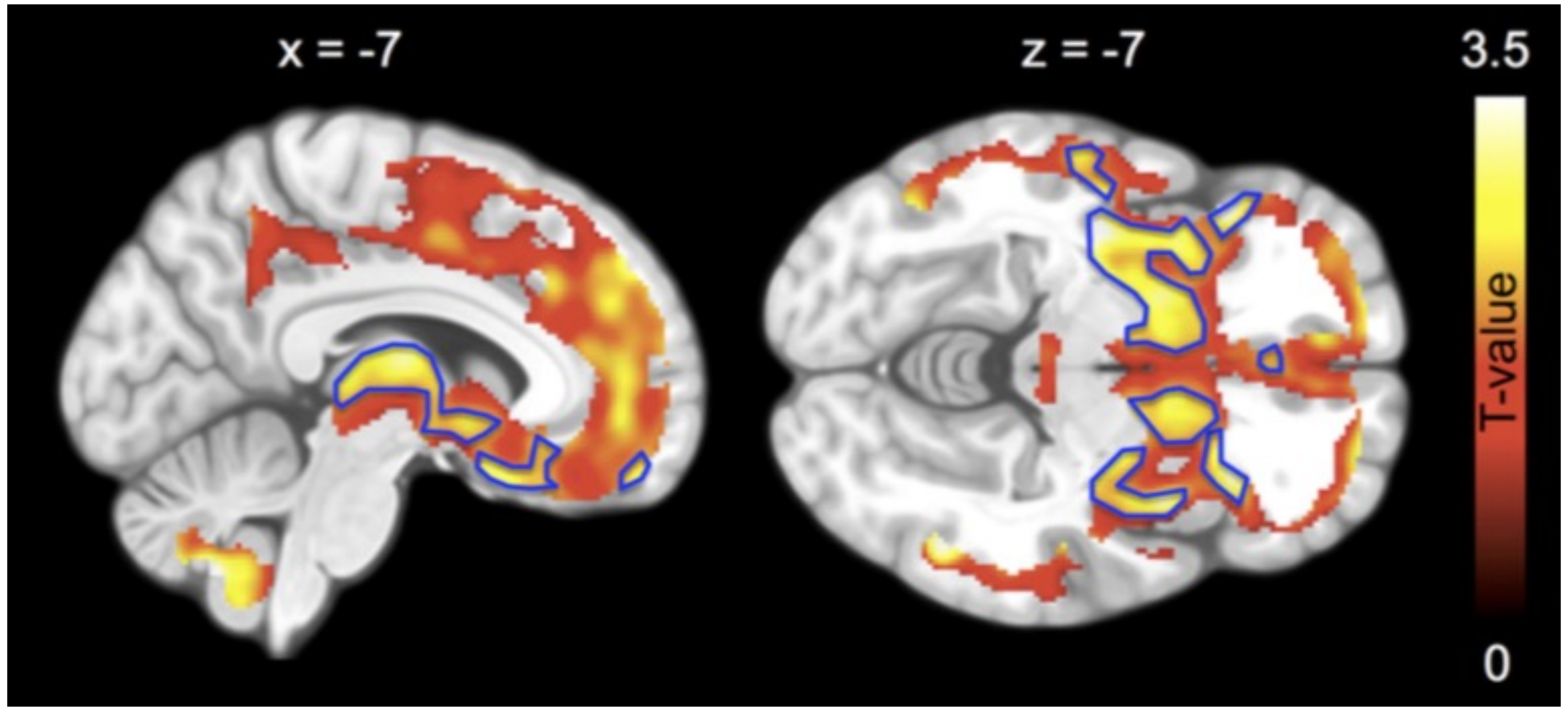


Voxelwise
comparison
with mass univariate
independent samples tests

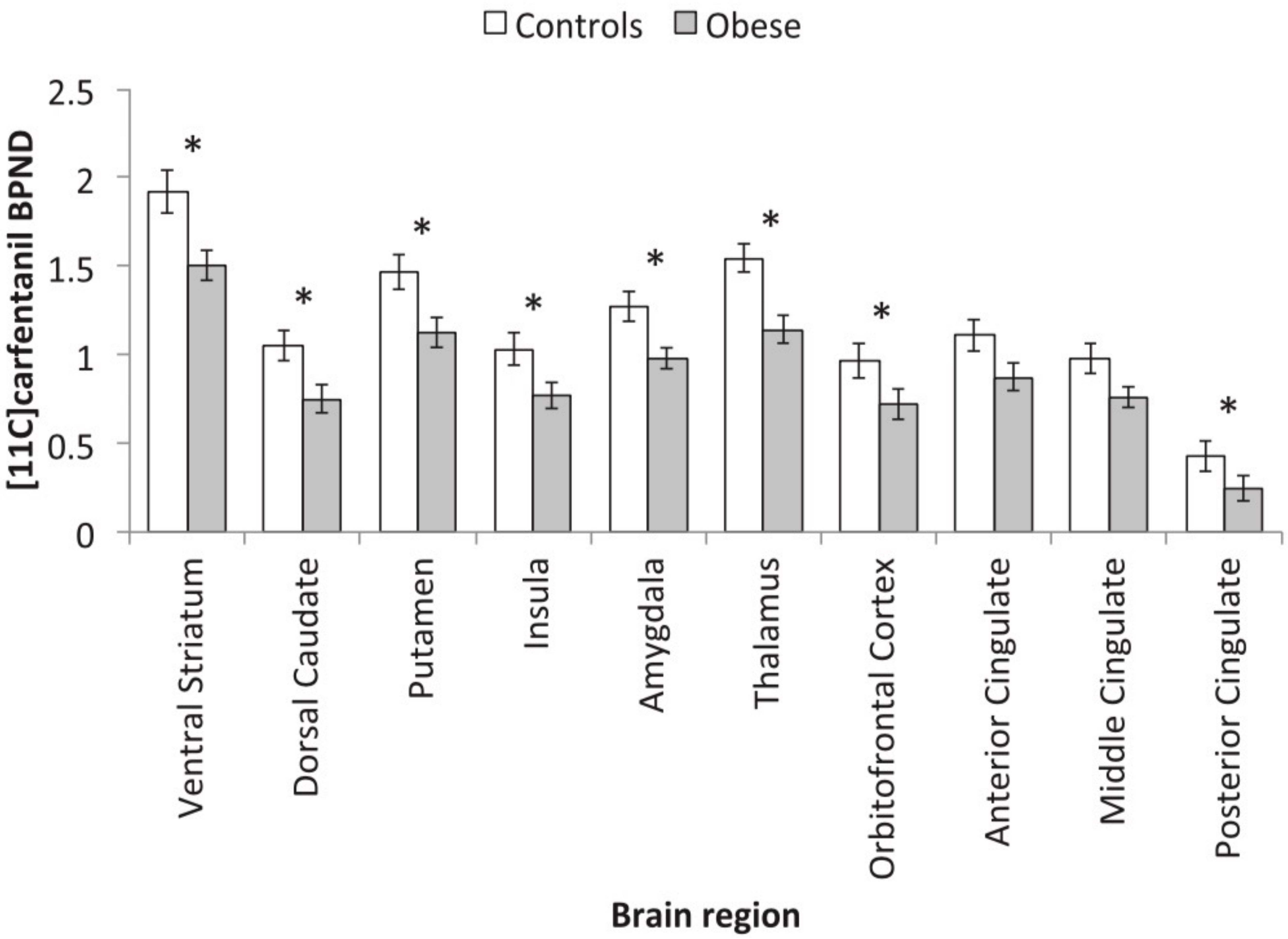
1) Mean images for each group



2) Statistical differences (t-map)



3) Region-of-interest data



Karlsson et al (2015 J Neurosci)

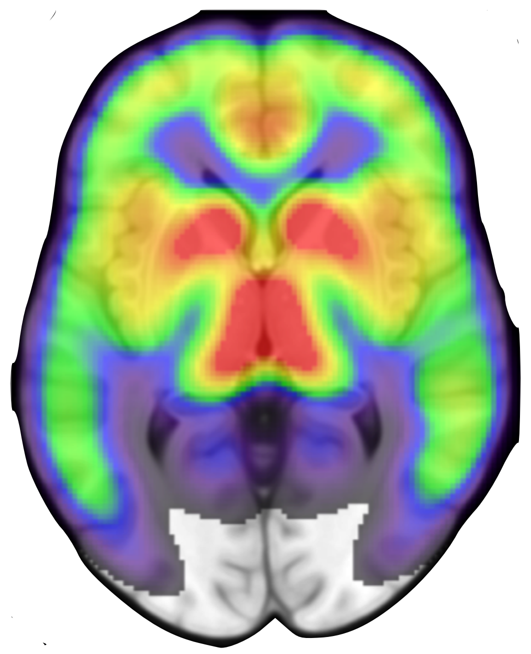
Challenge / longitudinal design

Lag hours or days

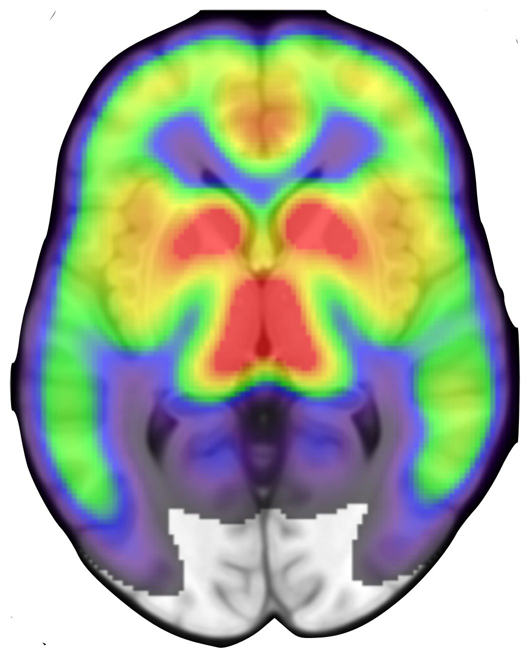
Scan 1

Challenge:
Task, drug, etc.

Scan 2



Voxelwise comparison with mass univariate repeated measures tests

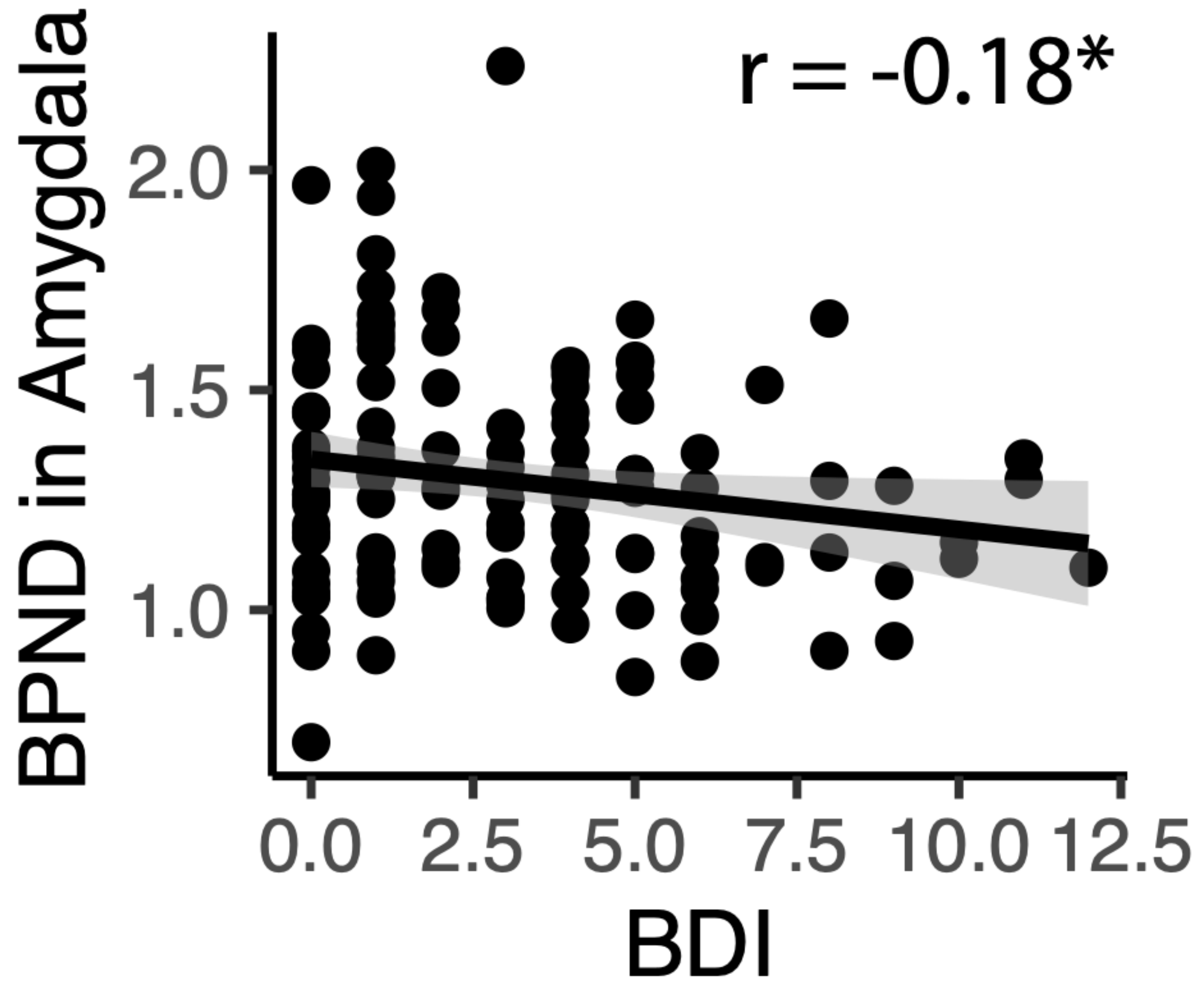


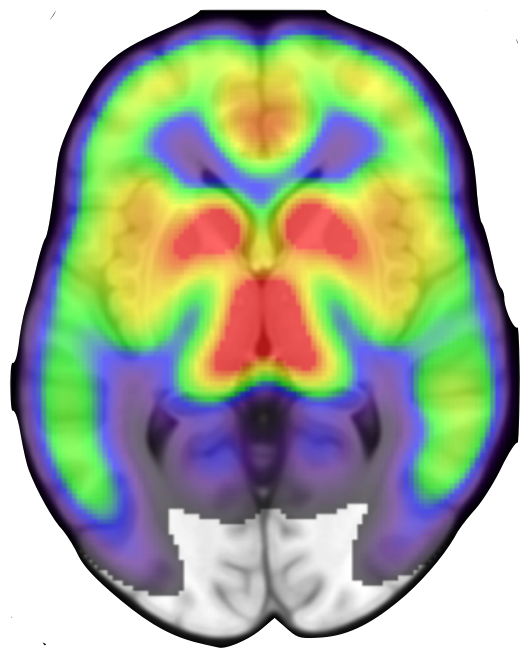
Tuulari et al (2018 J Neurosci)

Correlational design

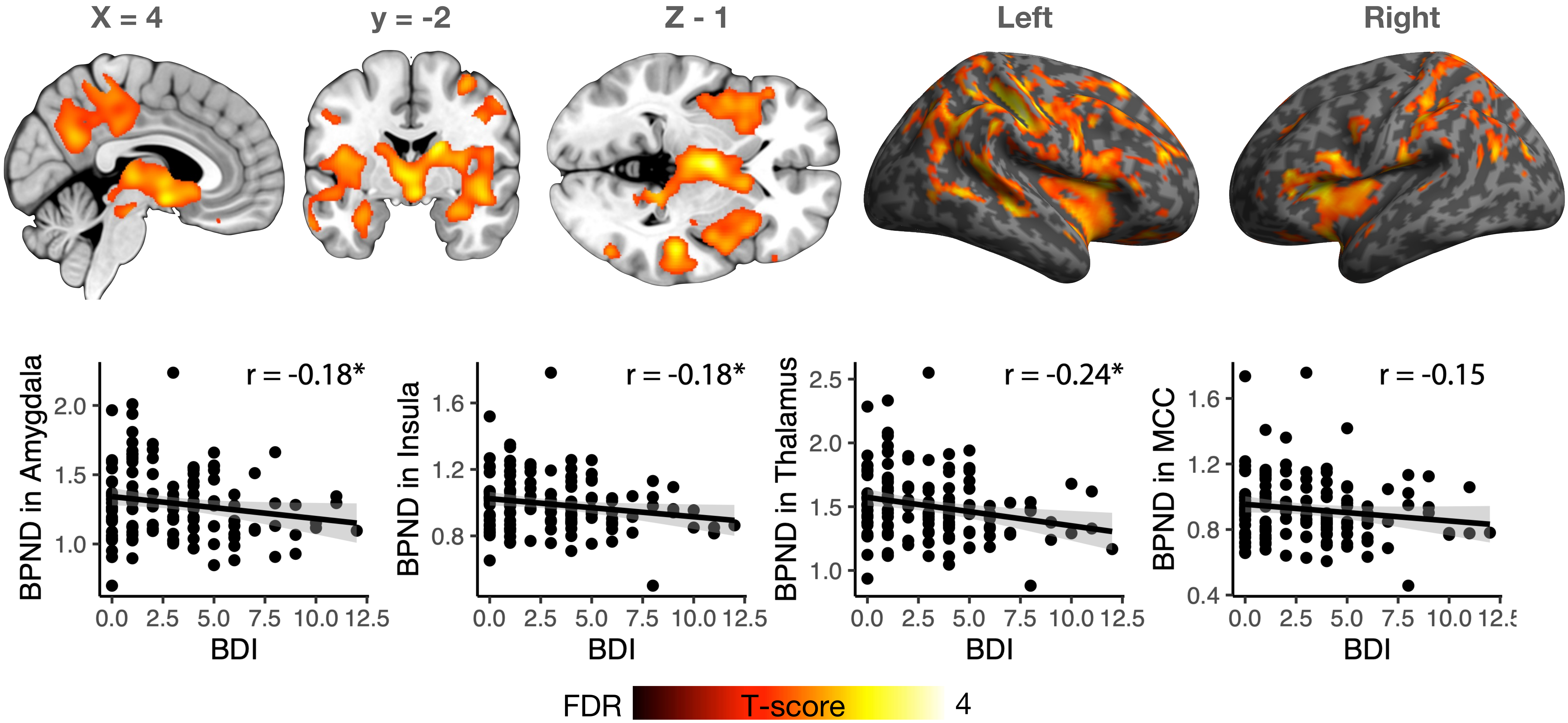
Baseline scan

Univariate biological variable





Lowered mu-opioid receptor levels in subclinical depression



Nummenmaa et al (2020 Neuropsychopharmacology)

THE BASIC RECIPE