SECOND-LEVEL ANALYSIS OF PET AND MRI DATA

Turku PET Centre Brain Imaging Course 2024

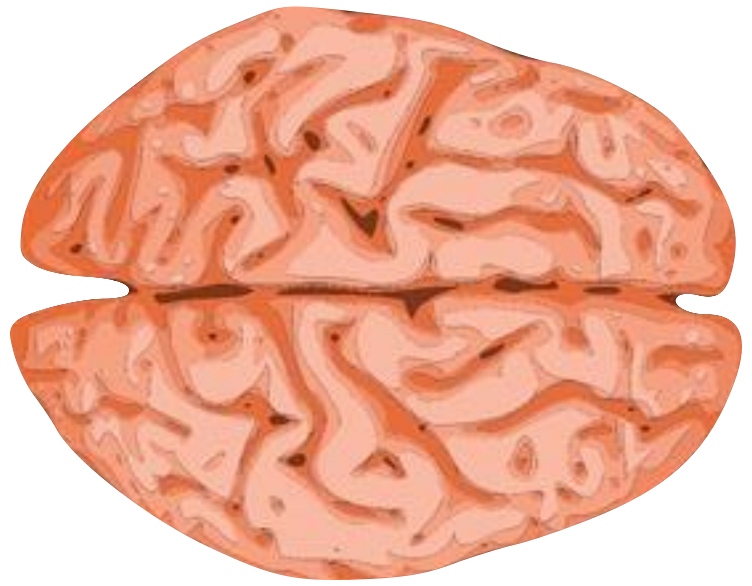
Lauri Nummenmaa, Turku PET Centre

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)

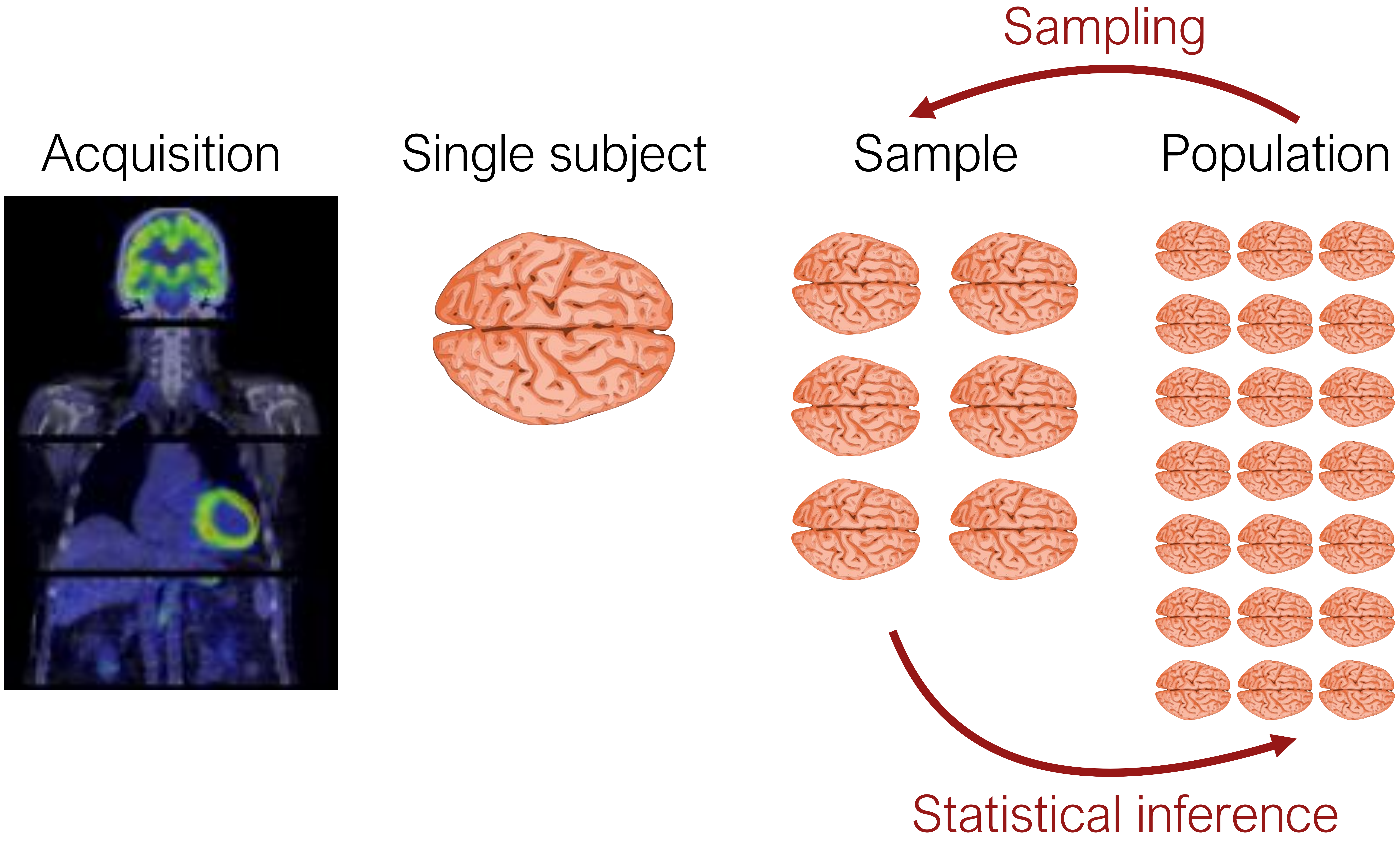


OBSERVED SCORE (Outcome measure such as BPND)

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)

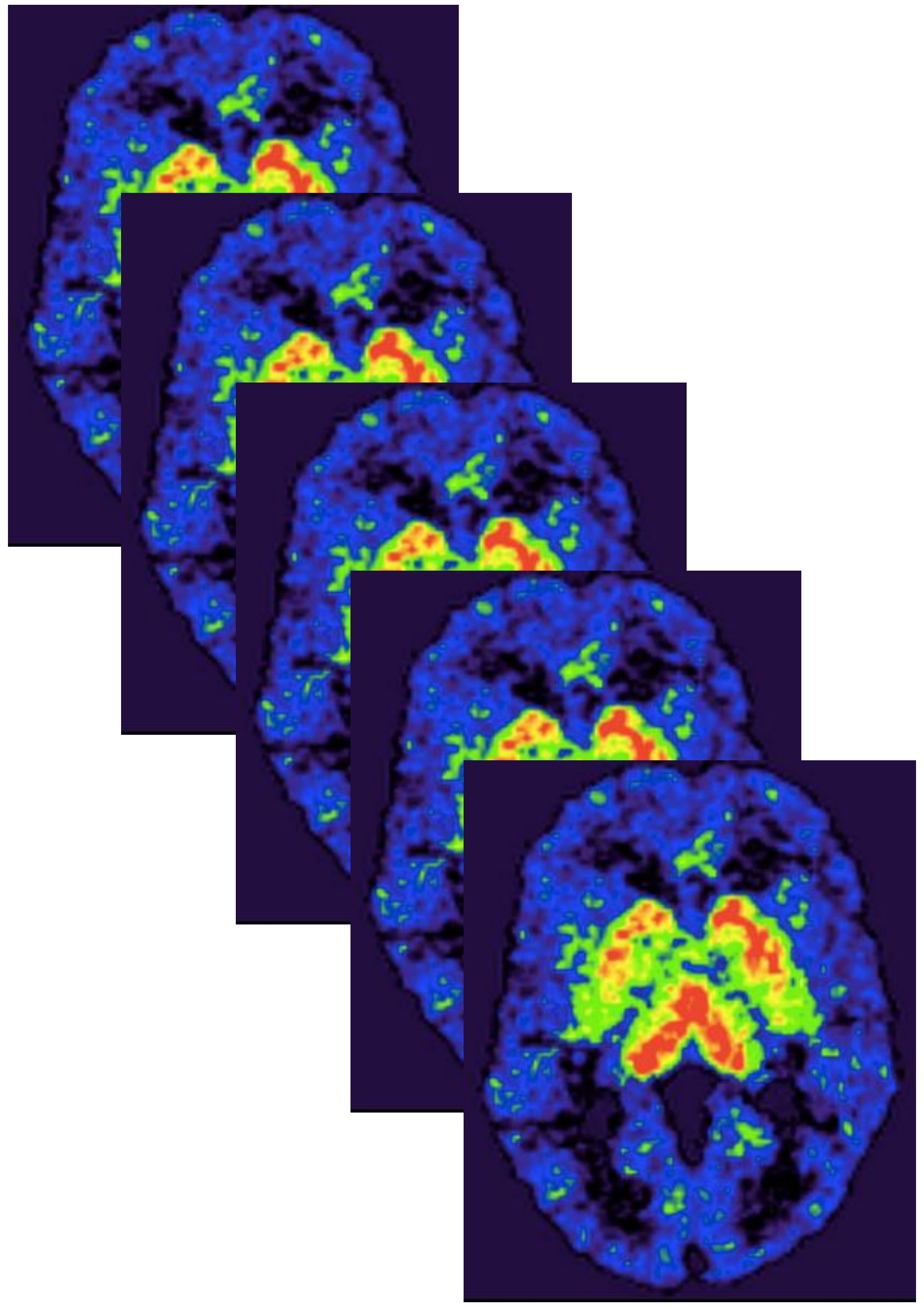
Making inferences about the population

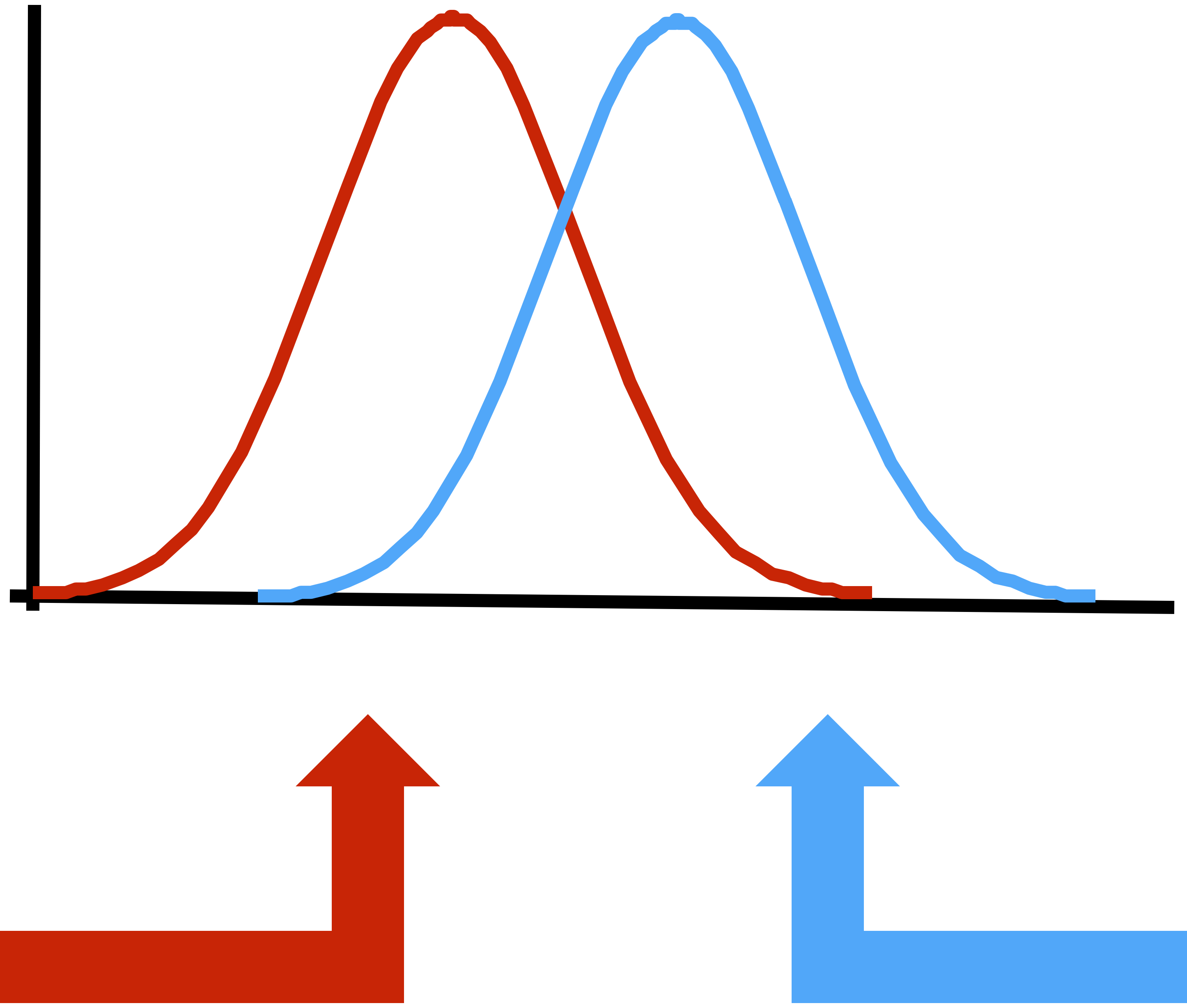


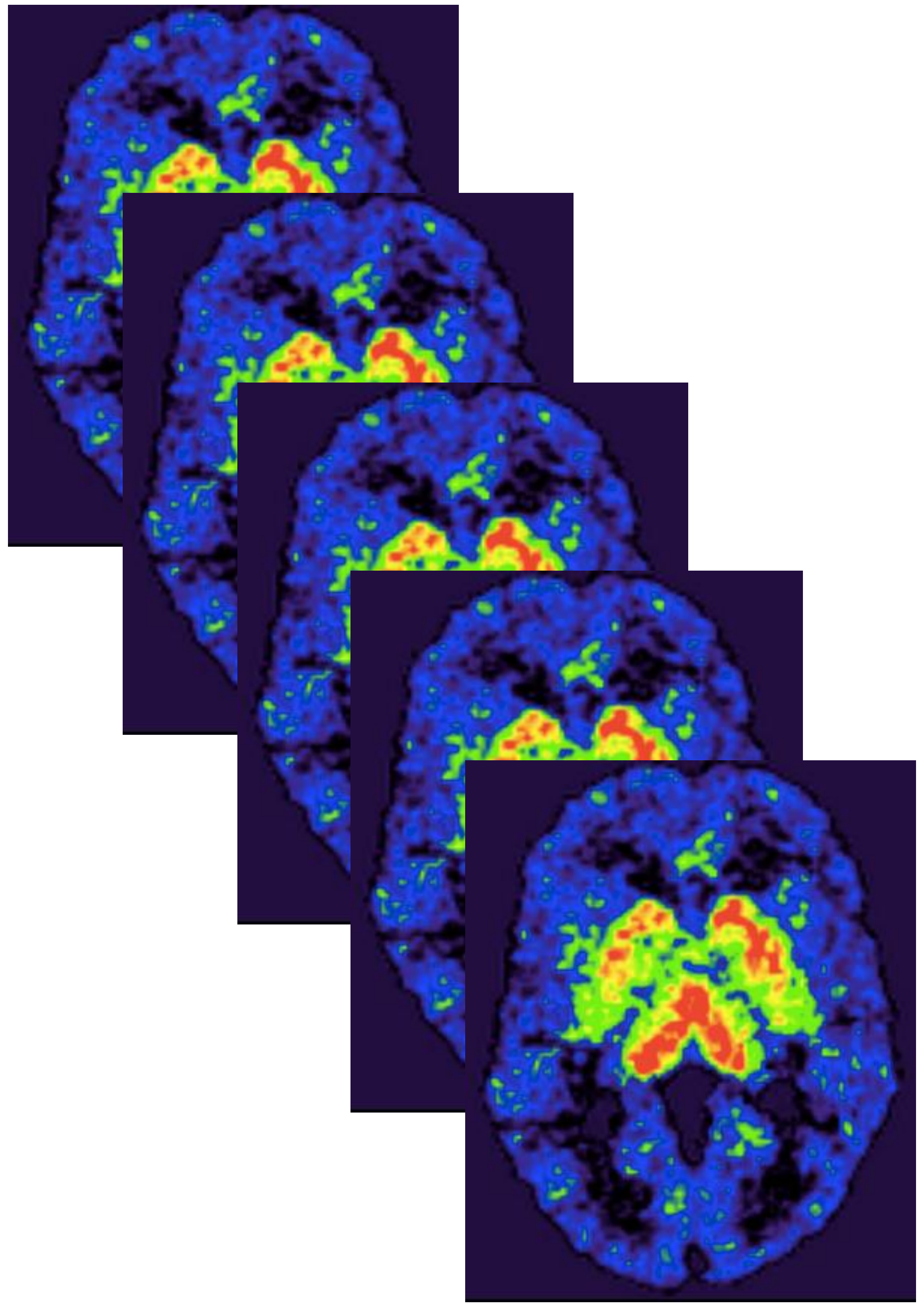
CONTROLS

ARE THESE BRAINS STATISTICALLY DIFFERENT?

PATIENTS







Starting point: Images where voxel intensities reflect the outcome measure

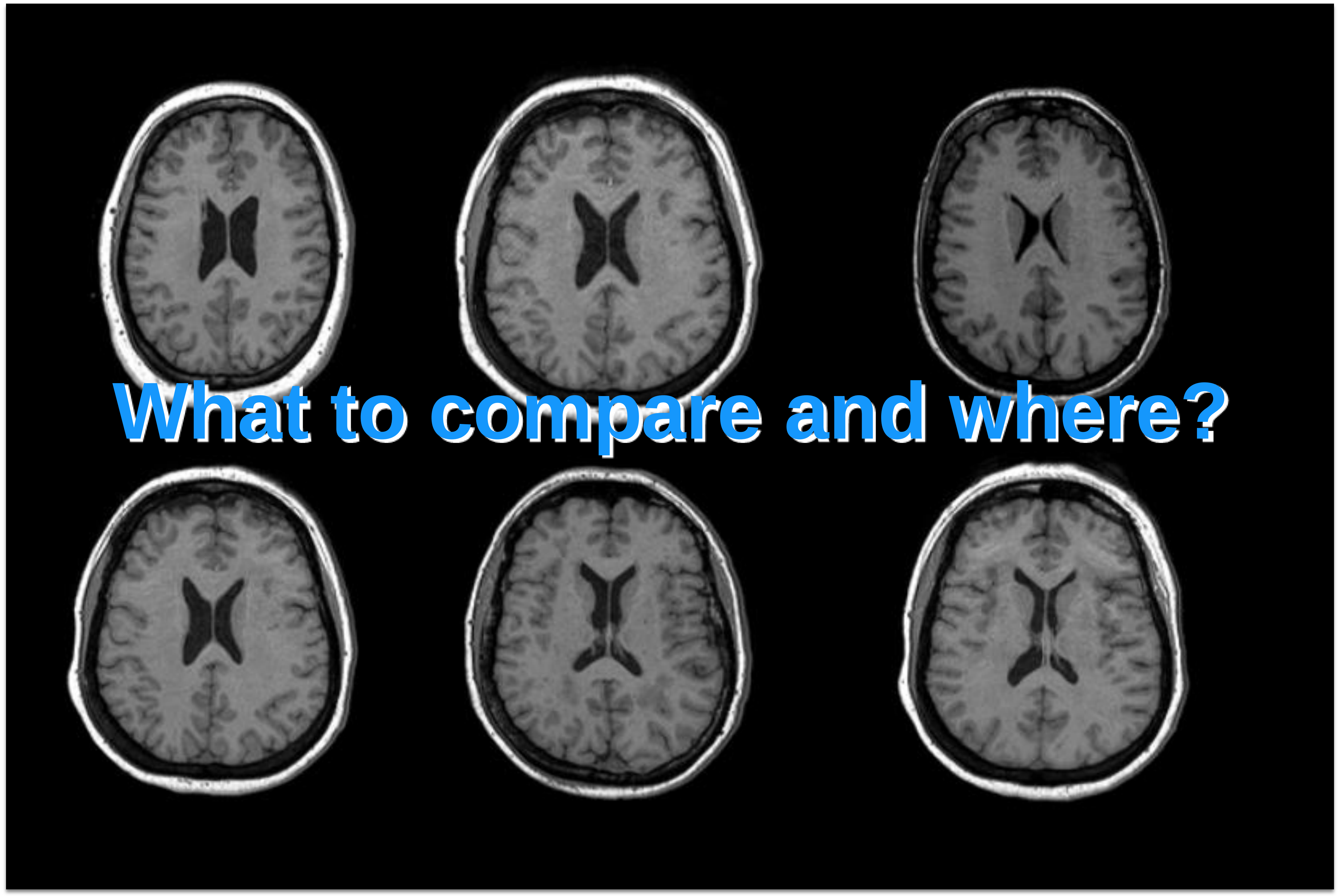
Sneak peek: Analysis of PET vs. fMRI data

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

Univariate data
Regularly shaped

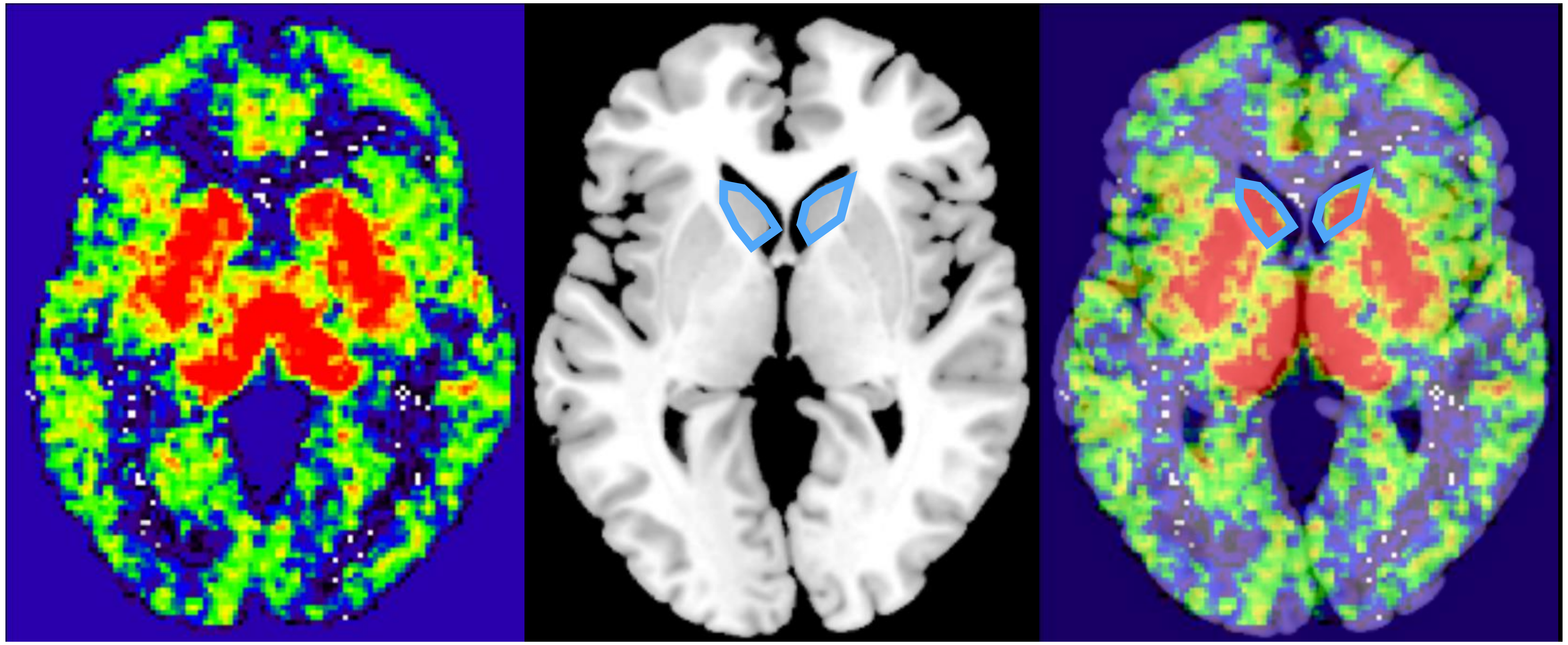
Controls		Patients
3		5
4	t-test	4
5		6
6		7
3		6
2		5
3		2
5		6
2		8

3D neuroimaging data
Irregularly shaped



ROI-based analyses

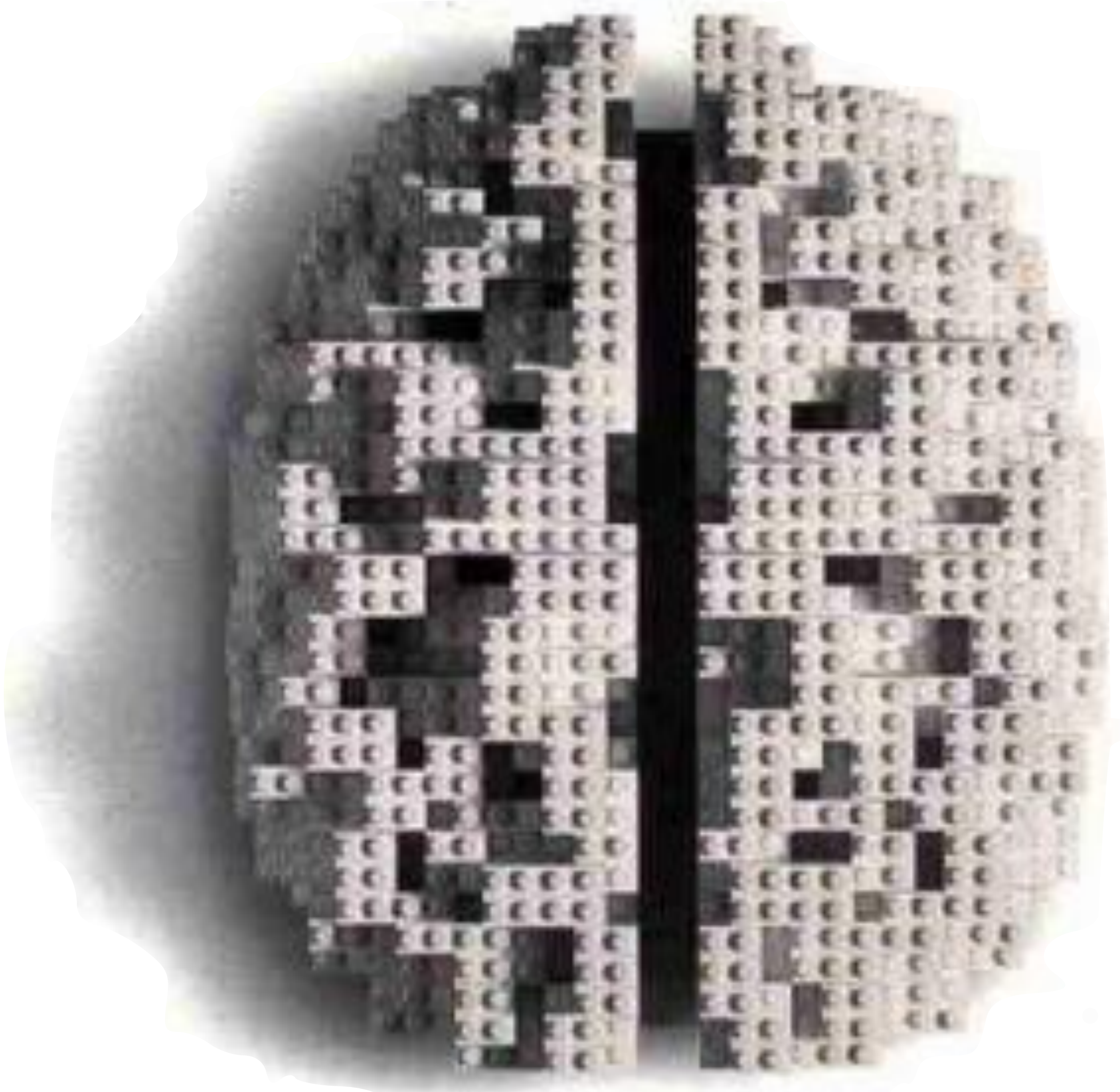
Univariate data
regularly shaped
can use univariate stats

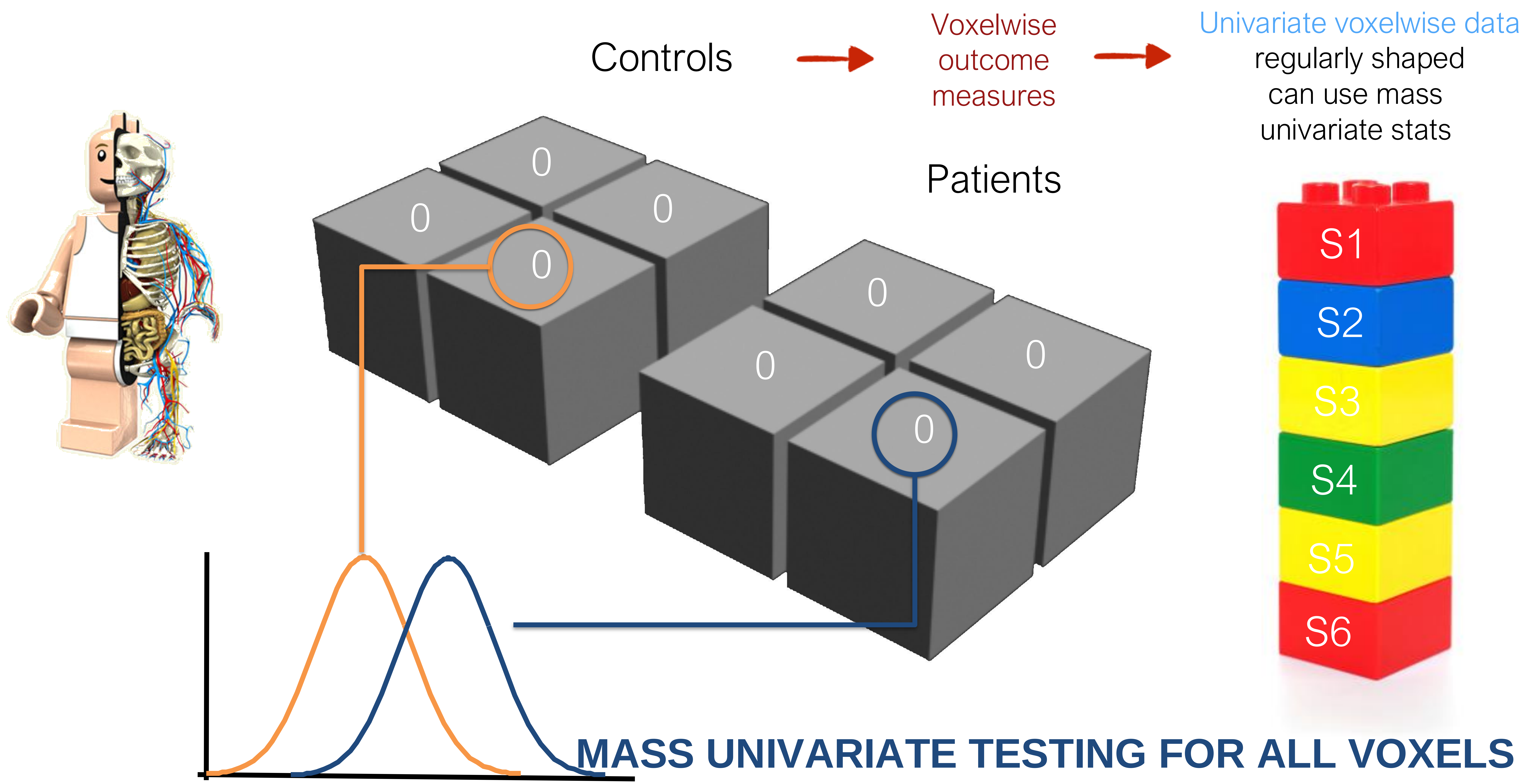


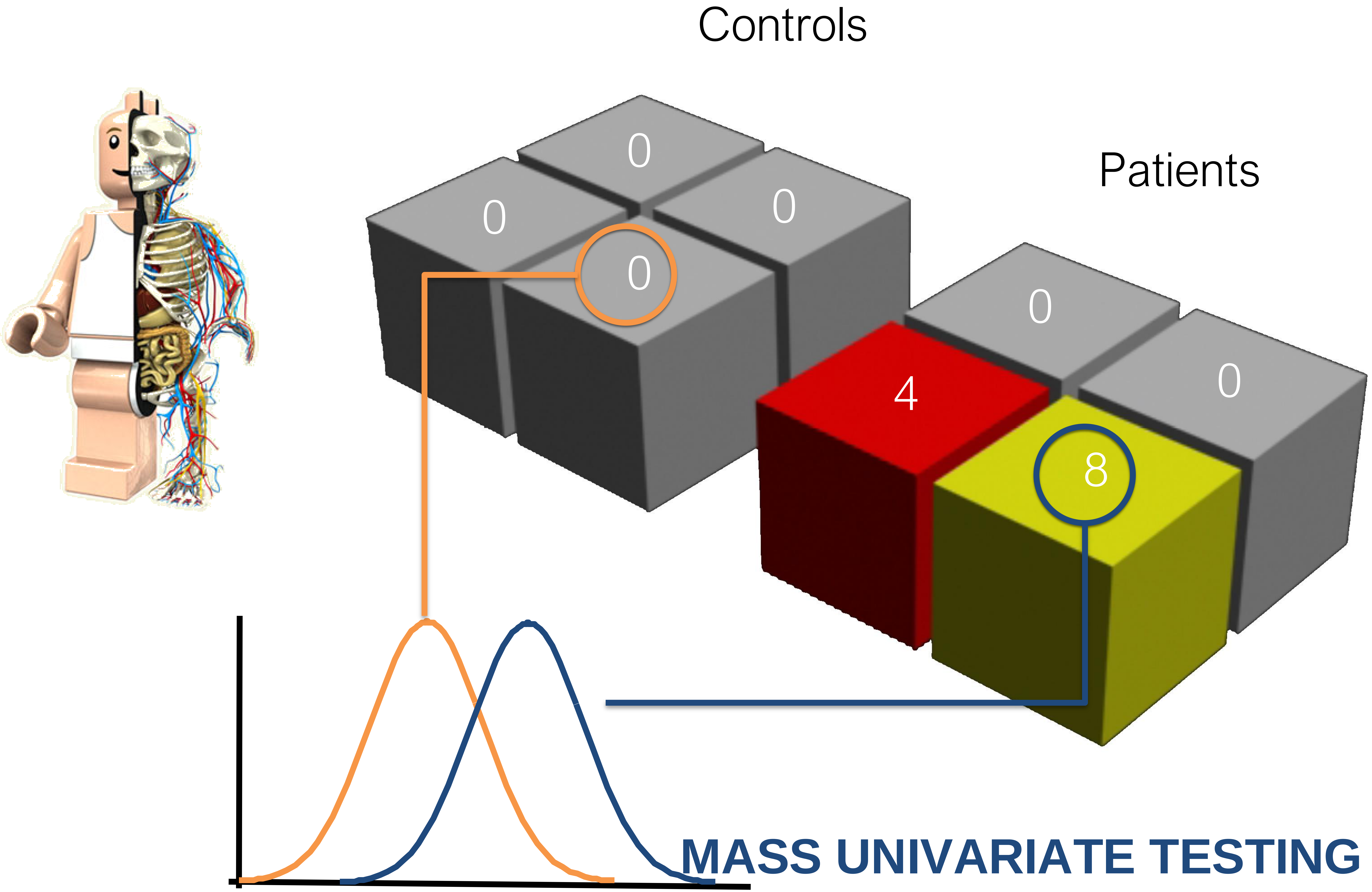
Extract outcome measure in ROI

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

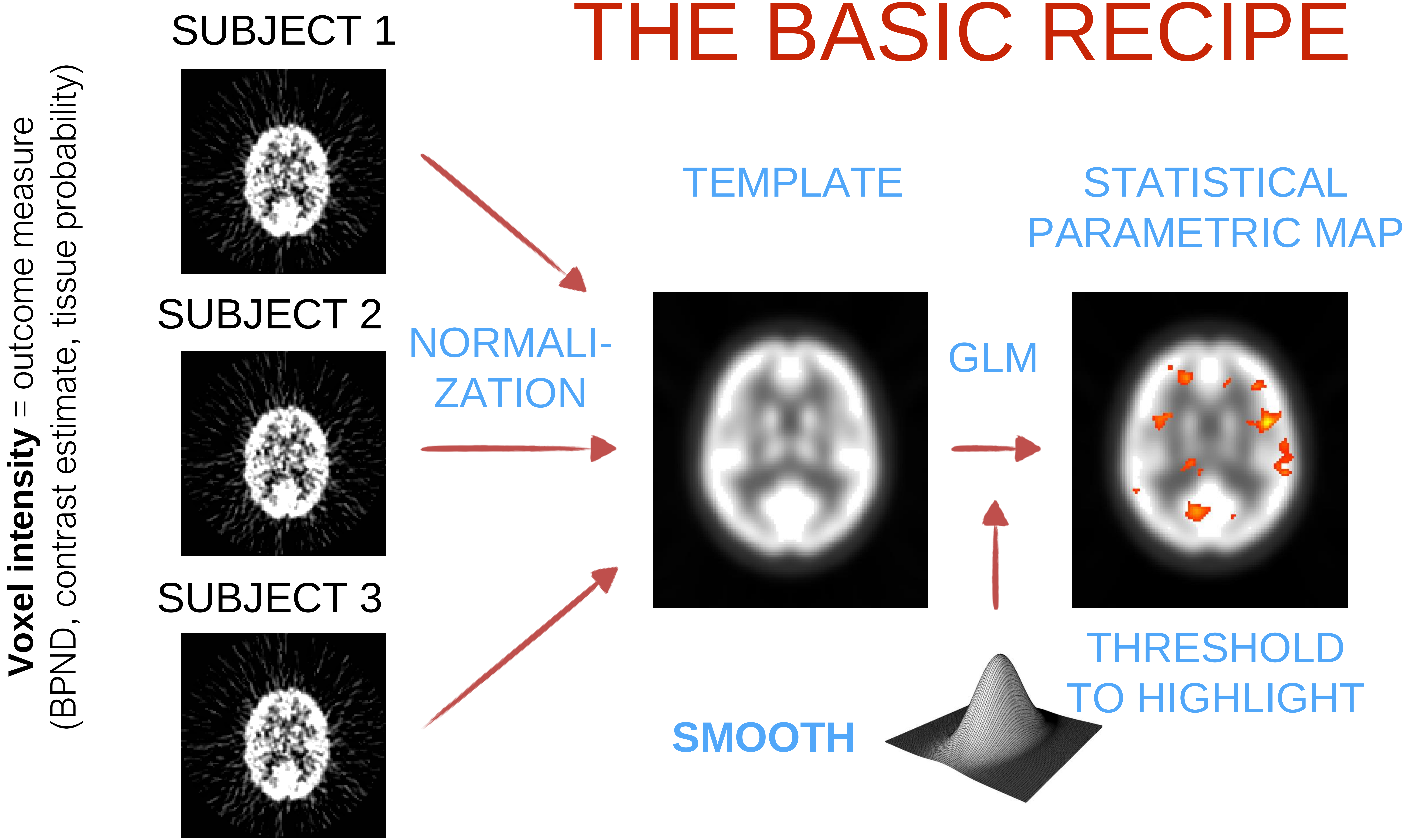



Controls
Voxelwise
outcome
measures
Univariate voxelwise data
regularly shaped
can use mass
univariate stats
Patients
S1
S2
S3
S4
S5
S6
MASS UNIVARIATE TESTING FOR ALL VOXELS



MASS UNIVARIATE TESTING FOR ALL VOXELS

THE BASIC RECIPE

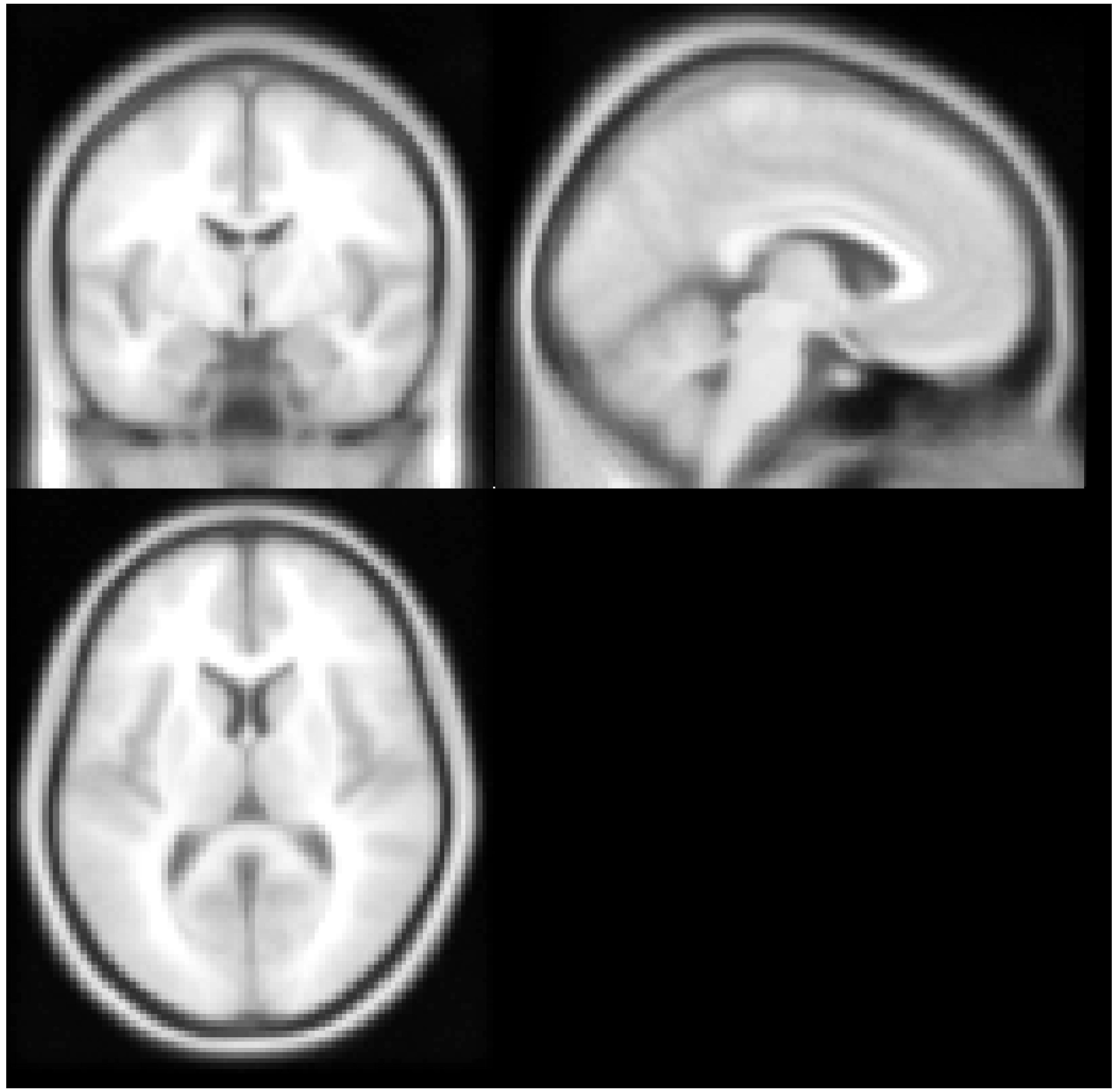


Full-volume analyses with real brains

- 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

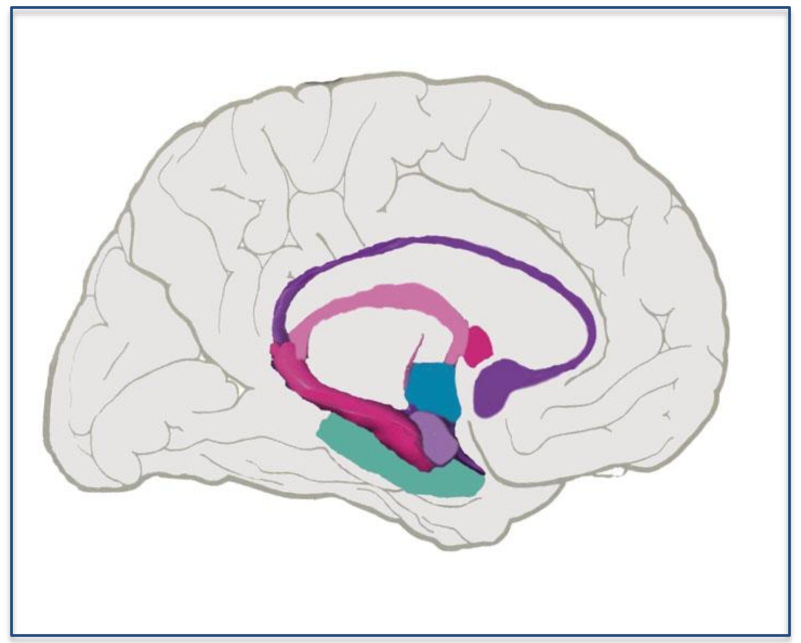
- **ICBM 152 template**
- Based on average of 152 brains that have been spatially normalized
- Statistical average of the typical western adult brain
- Problem: not necessarily representative of study sample
- In fMRI can also use e.g. spherical models



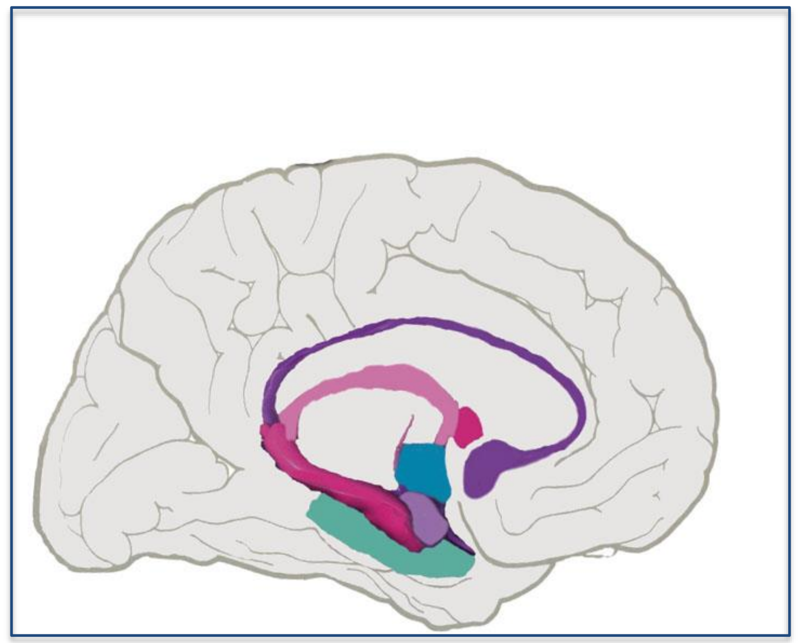
Spatial normalization in practice

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

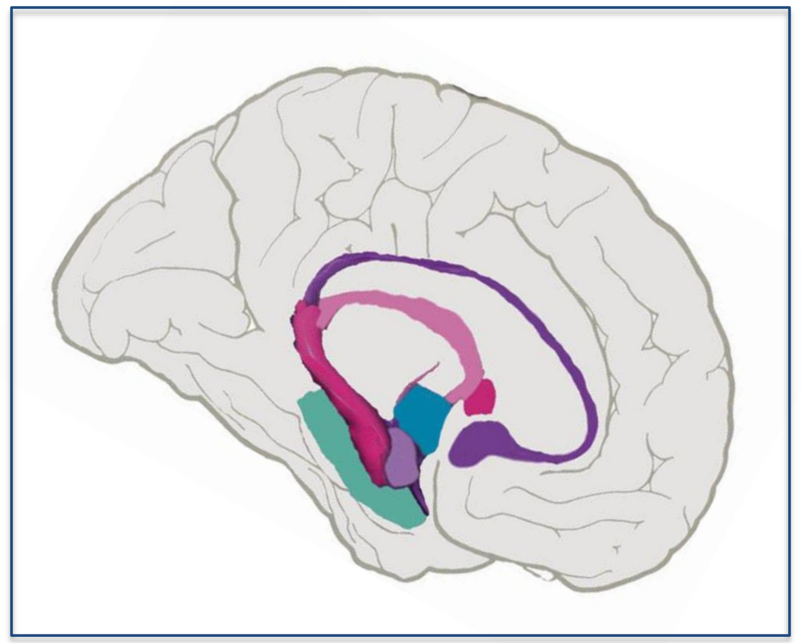
NATIVE



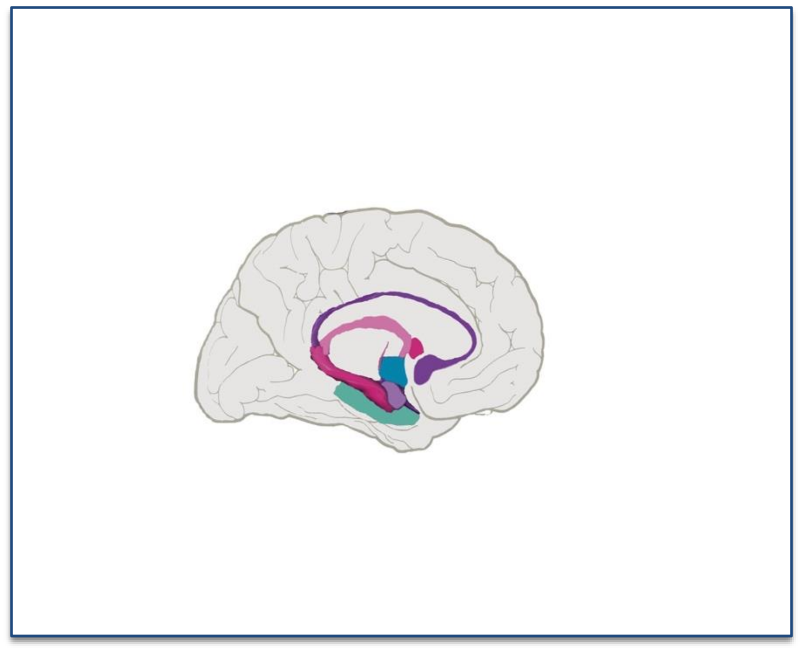
TRANSLATION



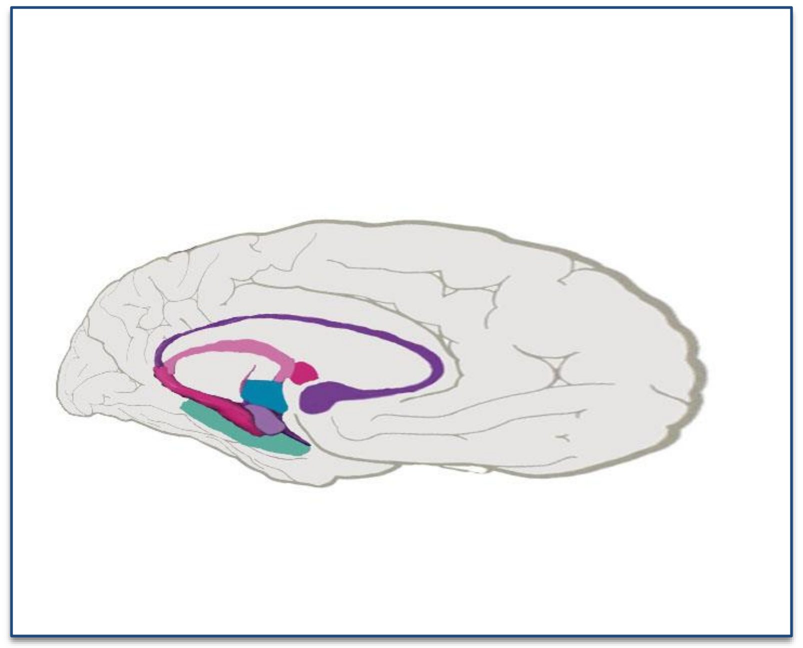
ROTATION



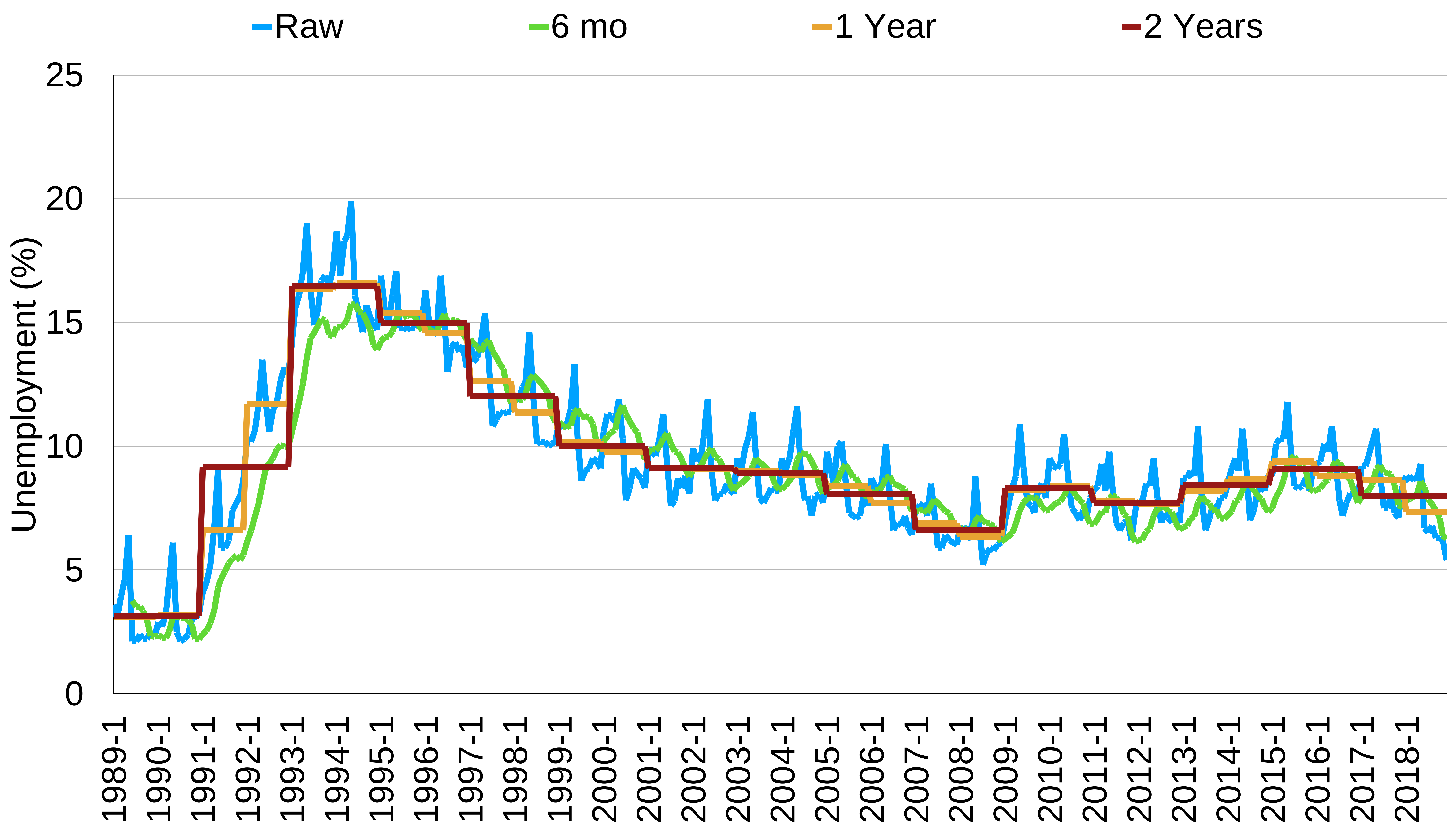
ZOOM



SHEAR



AFFINE NORMALIZATION: 4*3 PARAMETERS



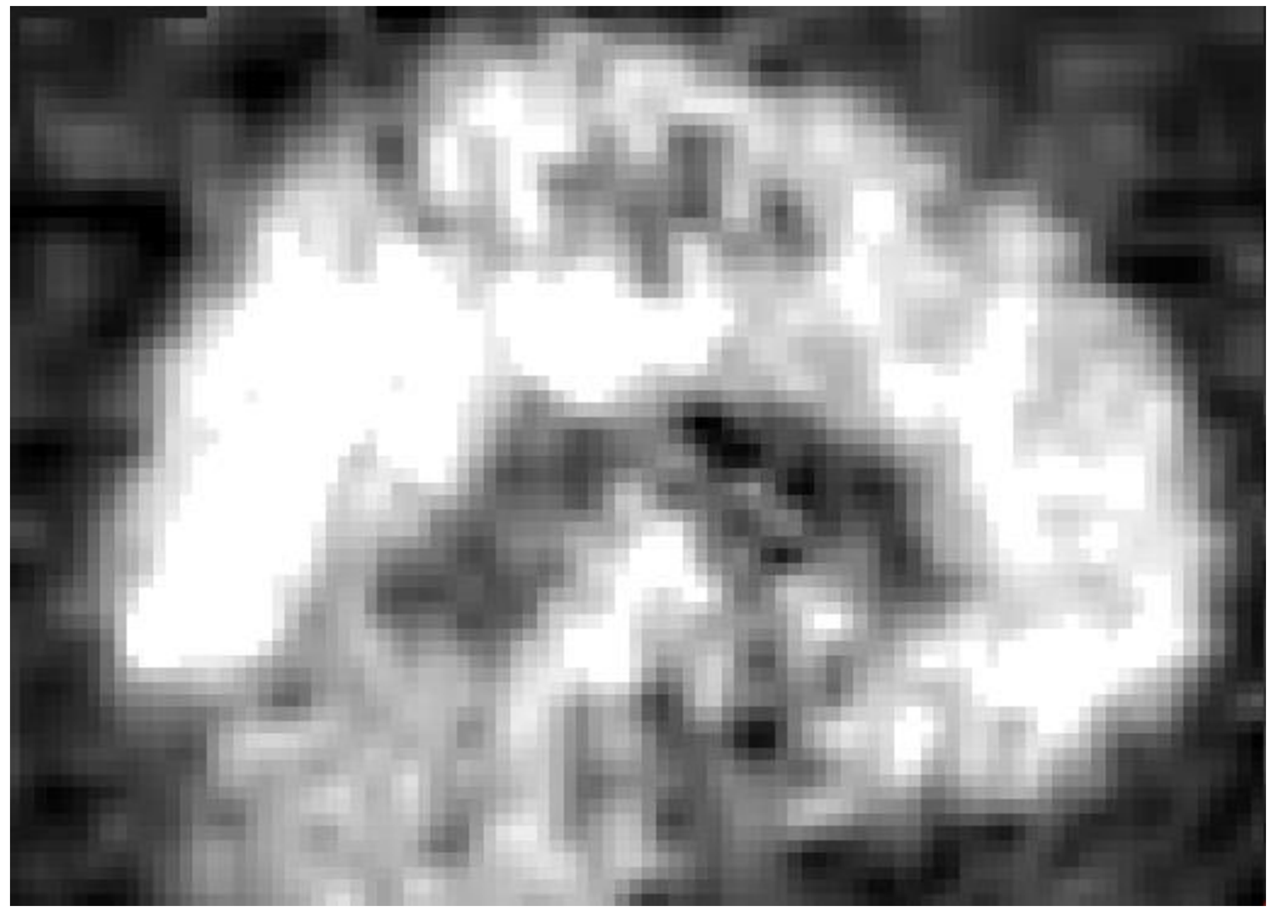
Raw
6 mo
1 Year
2 Years
Unemployment (%)
25
20
15
10
5
0
1989-1
1990-1
1991-1
1992-1
1993-1
1994-1
1995-1
1996-1
1997-1
1998-1
1999-1
2000-1
2001-1
2002-1
2003-1
2004-1
2005-1
2006-1
2007-1
2008-1
2009-1
2010-1
2011-1
2012-1
2013-1
2014-1
2015-1
2016-1
2017-1
2018-1

Smoothing

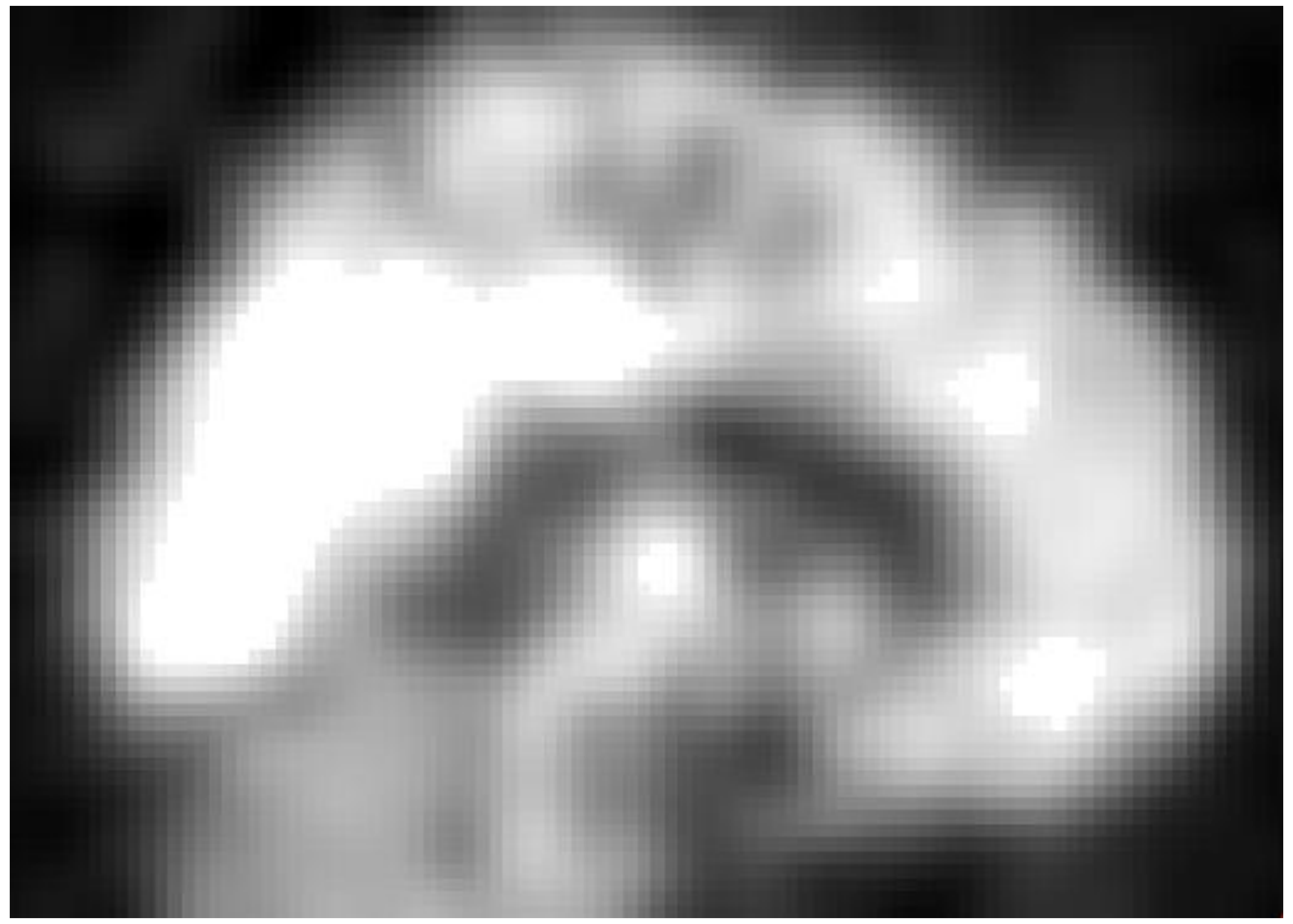
FWHM = spatial extent of the filter

Example on smoothing brain-PET images

UNSMOOTHED

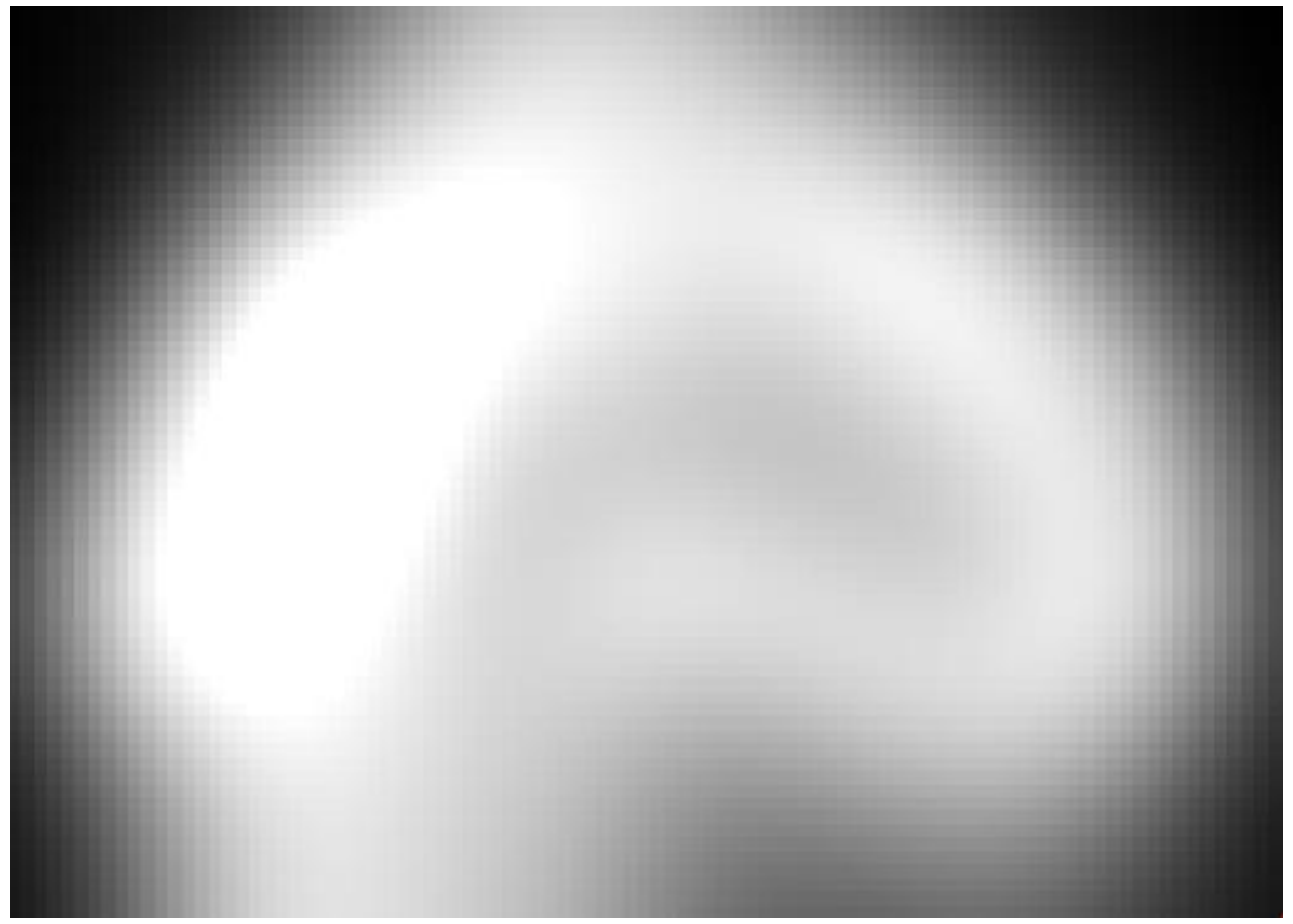


12mm FWHM



16mm FWHM

32mm FWHM



Why smooth?

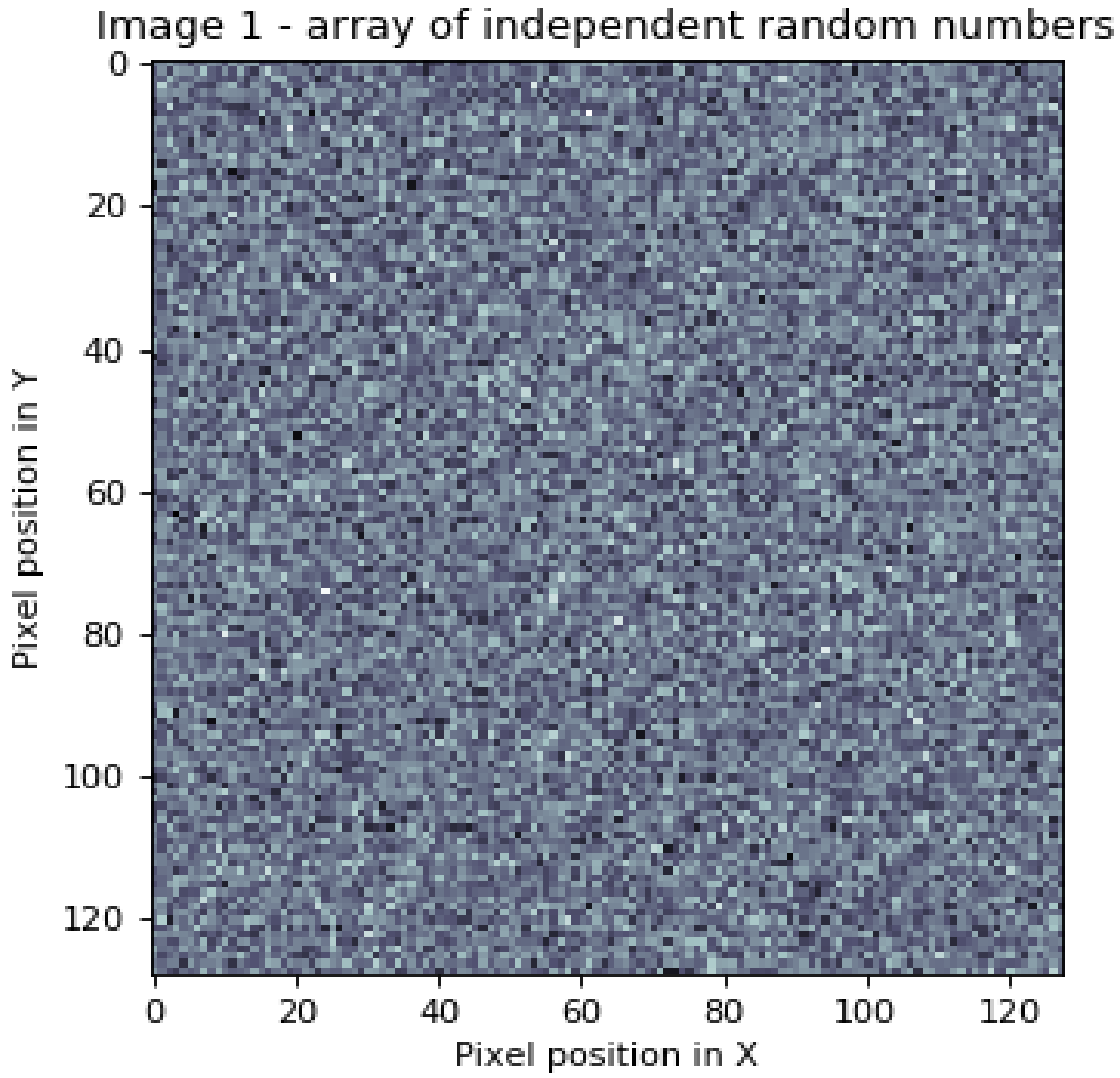
- Smoothing neuroimaging data: reduces noise and anatomical discrepancies

- Assumption: error terms are roughly Gaussian; FWHM greater than voxel size

- Enables hypothesis testing and dealing with multiple comparison problem in functional imaging

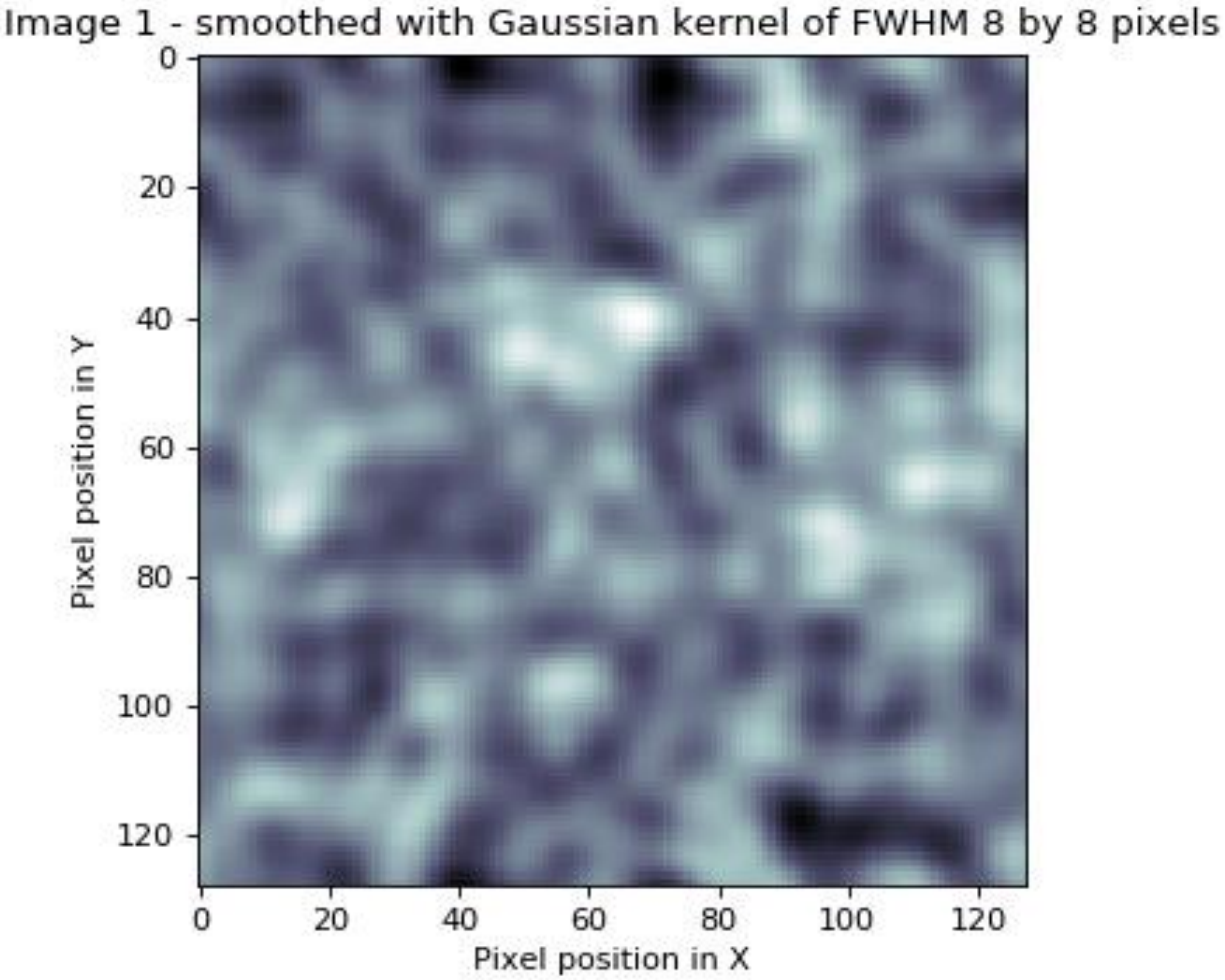
- However introduces problem of how to correct for multiple comparisons

Raw data: 16384 independent numbers



8 by 8 square smooth

Kernel-based smoothing
How many independent numbers?

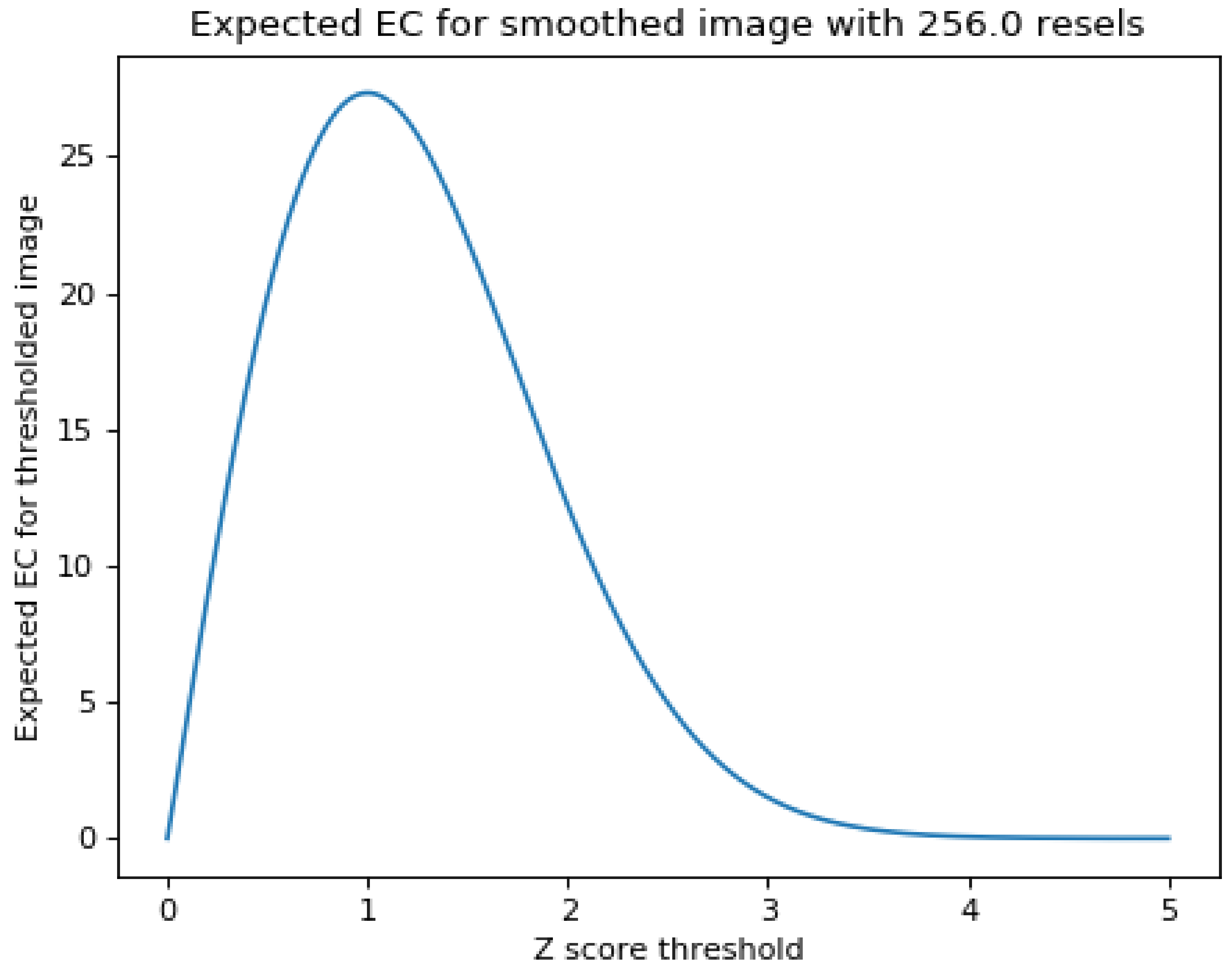


Problem with kernel-based smoothing: How many numbers are independent?

https://matthew-brett.github.io/teaching/random_fields.html

Random Field Theory in nutshell

- Estimate the number of resels in the image
  - Resel= block of pixels / voxels of the same size as the FWHM of the smoothness of the image. Depends on both image size and FWHM
- Work out the Euler characteristic (EC) of the image
  - Property of the image after it has been thresholded. Roughly number of blobs in image after thresdholfing
- Resels and EC are linked: when Z thresholds increases and EC drops the expected EC approximates the probability of observing one or more blobs at that threshold.



What sort of voxelwise model to fit?

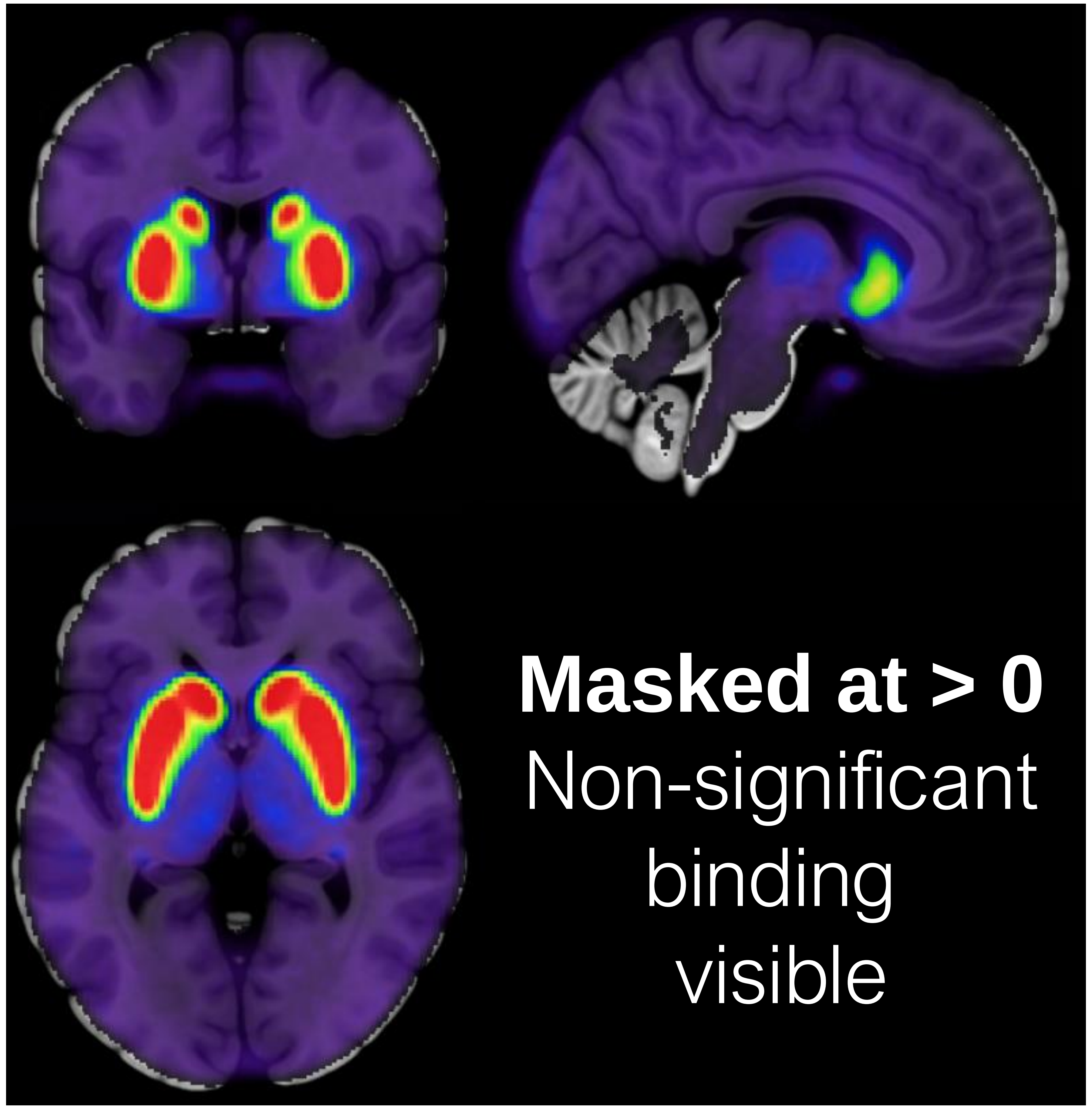
GLM

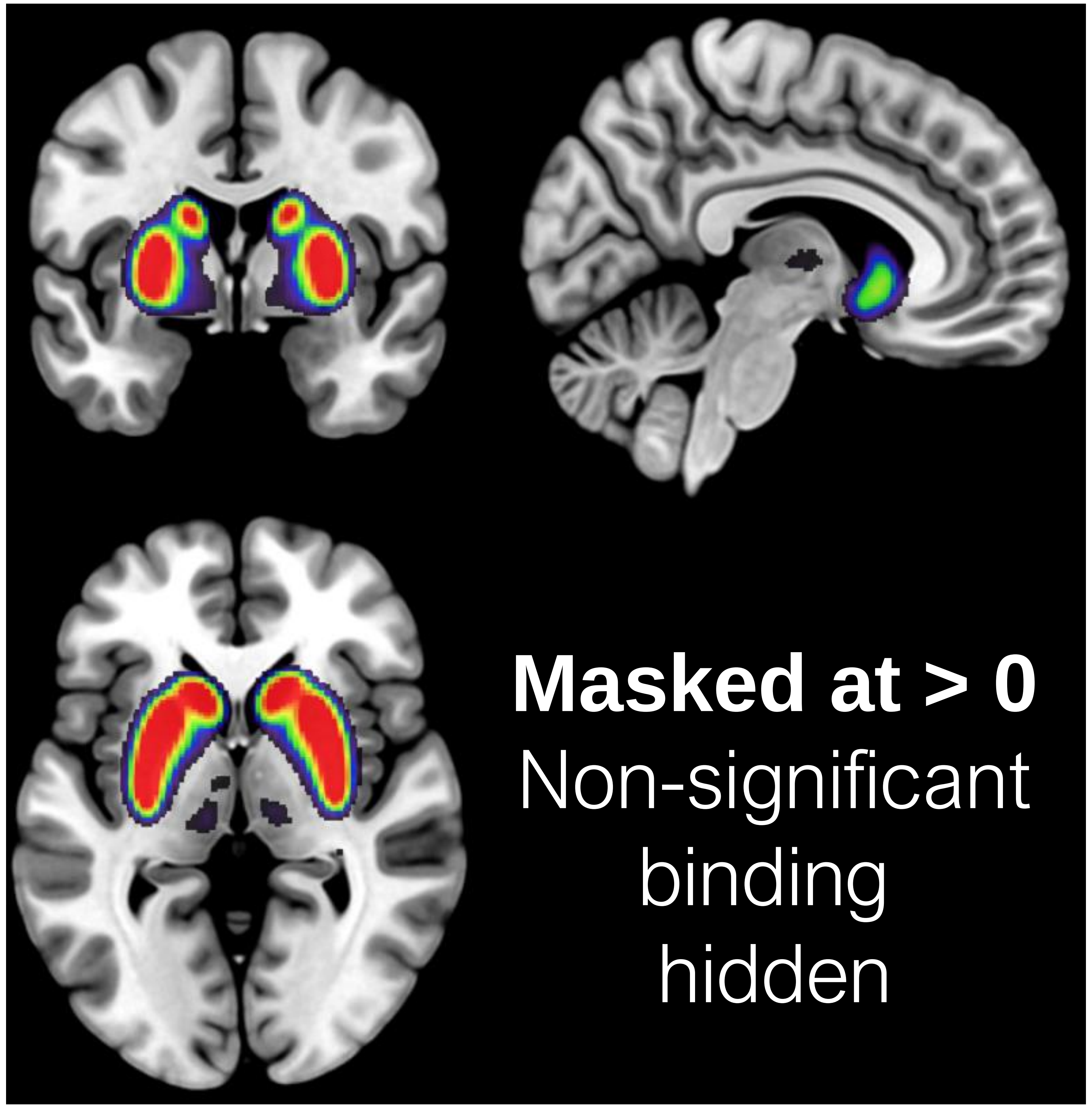
ANOVA, ANCOVA, linear regression…

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i$$

- Dependent Variable: Y_i
- Population Y intercept: β_0
- Population Slope Coefficient: β_1
- Independent Variable: X_i
- Random Error term: ε_i
- Linear component: $\beta_0 + \beta_1 X_i$
- Random Error component: ε_i

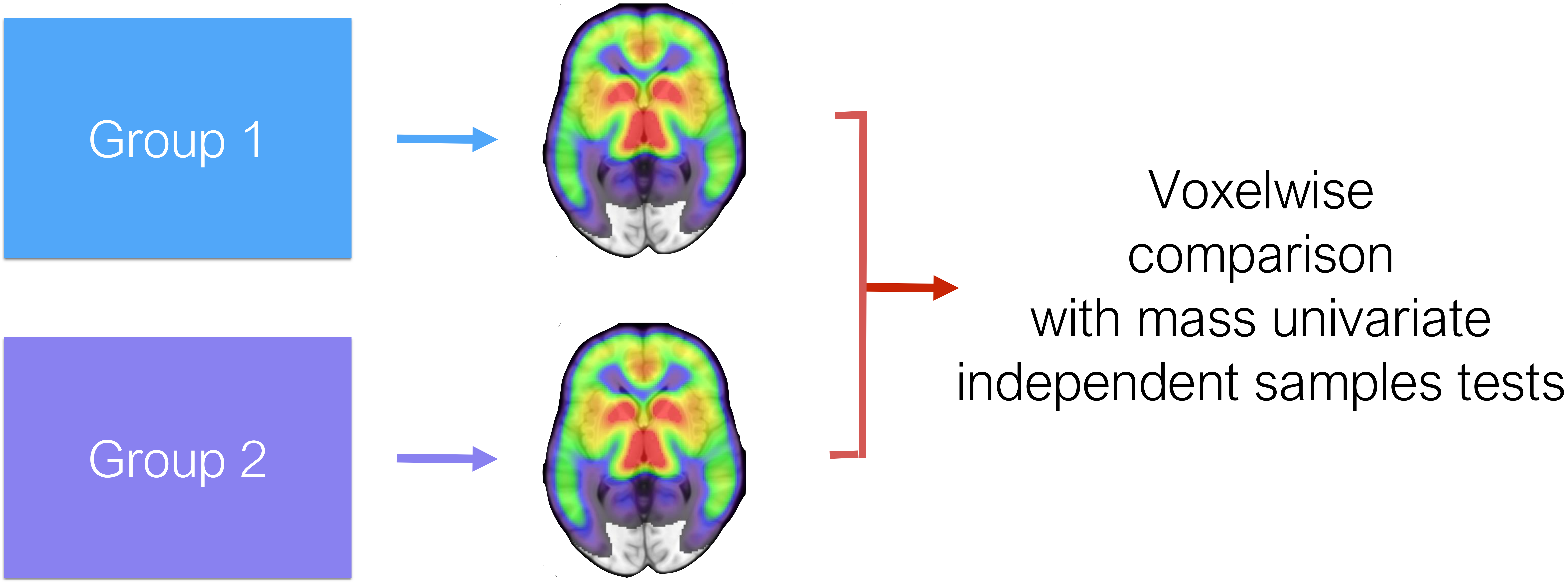
Masking the data



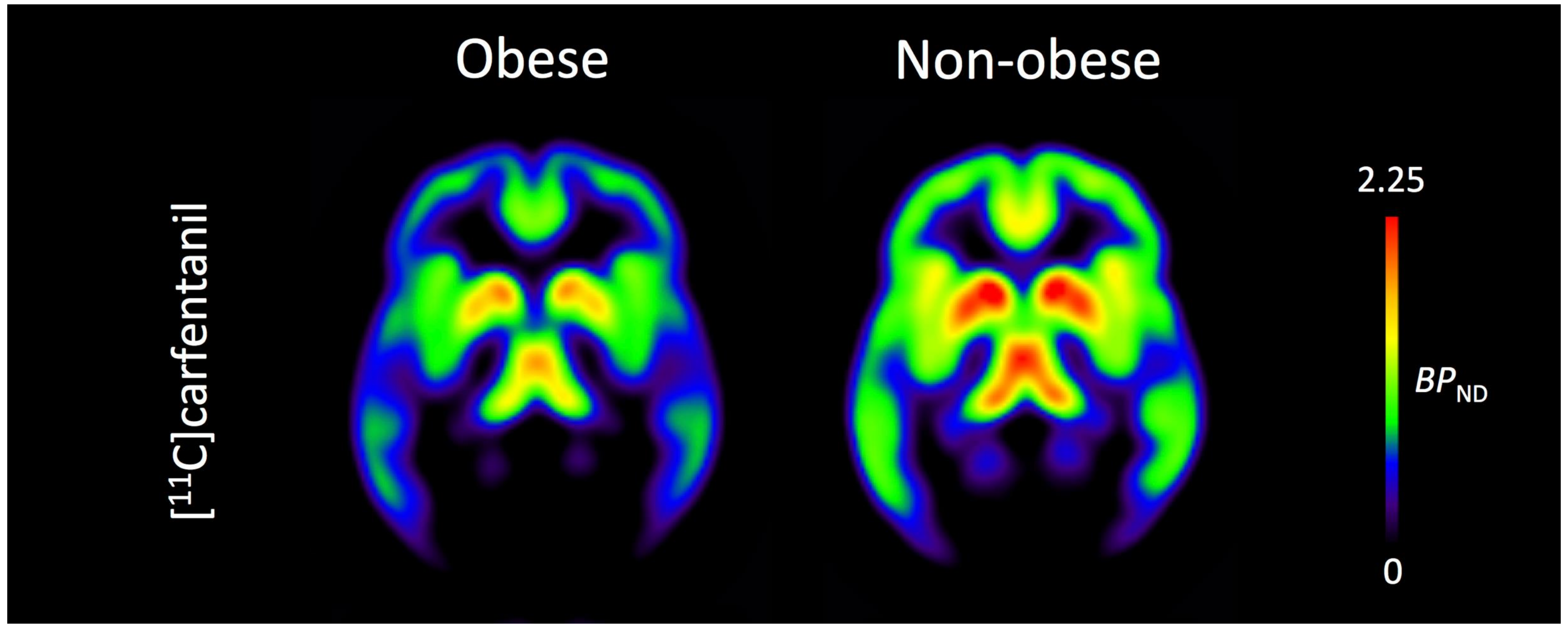


Applying explicit / threshold mask is necessary to avoid fitting model to noise

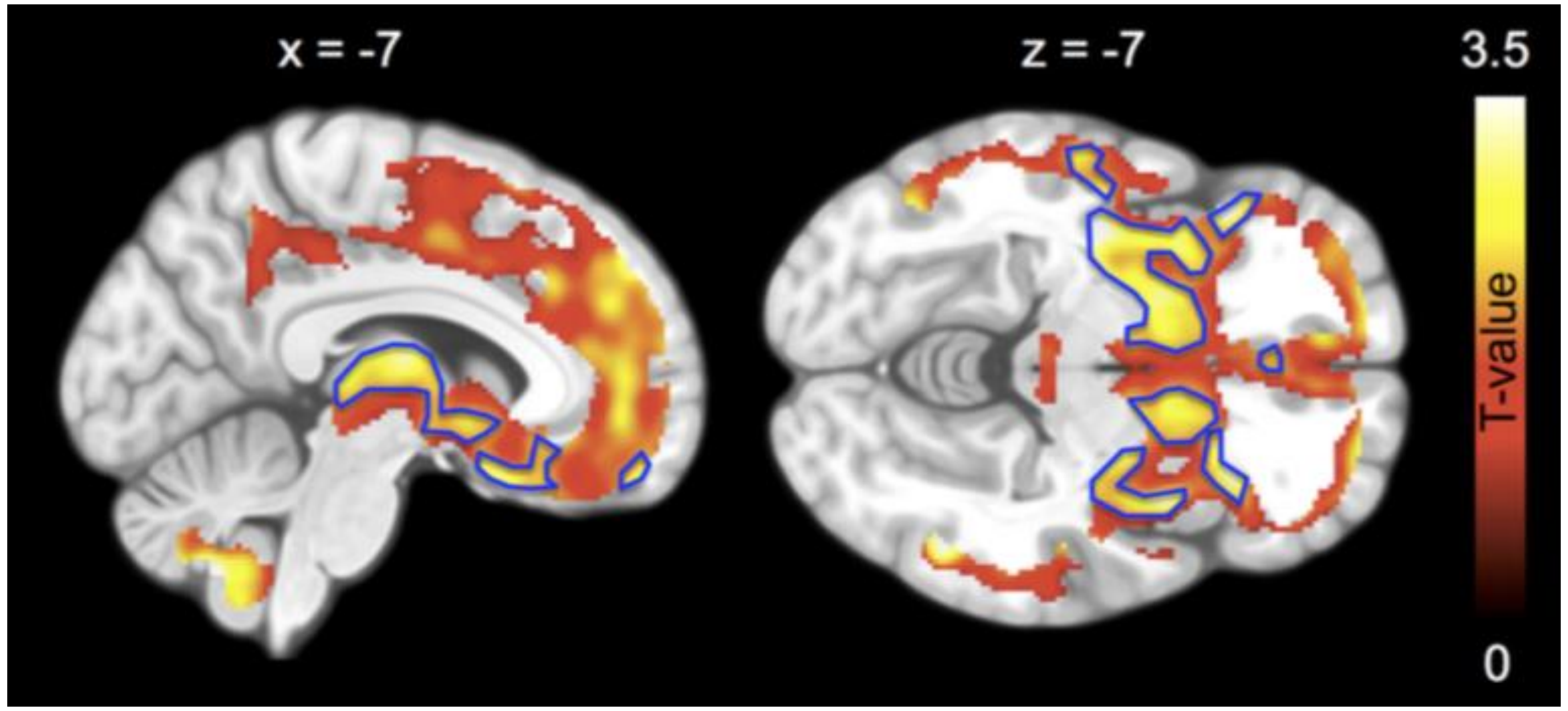
Between-groups design



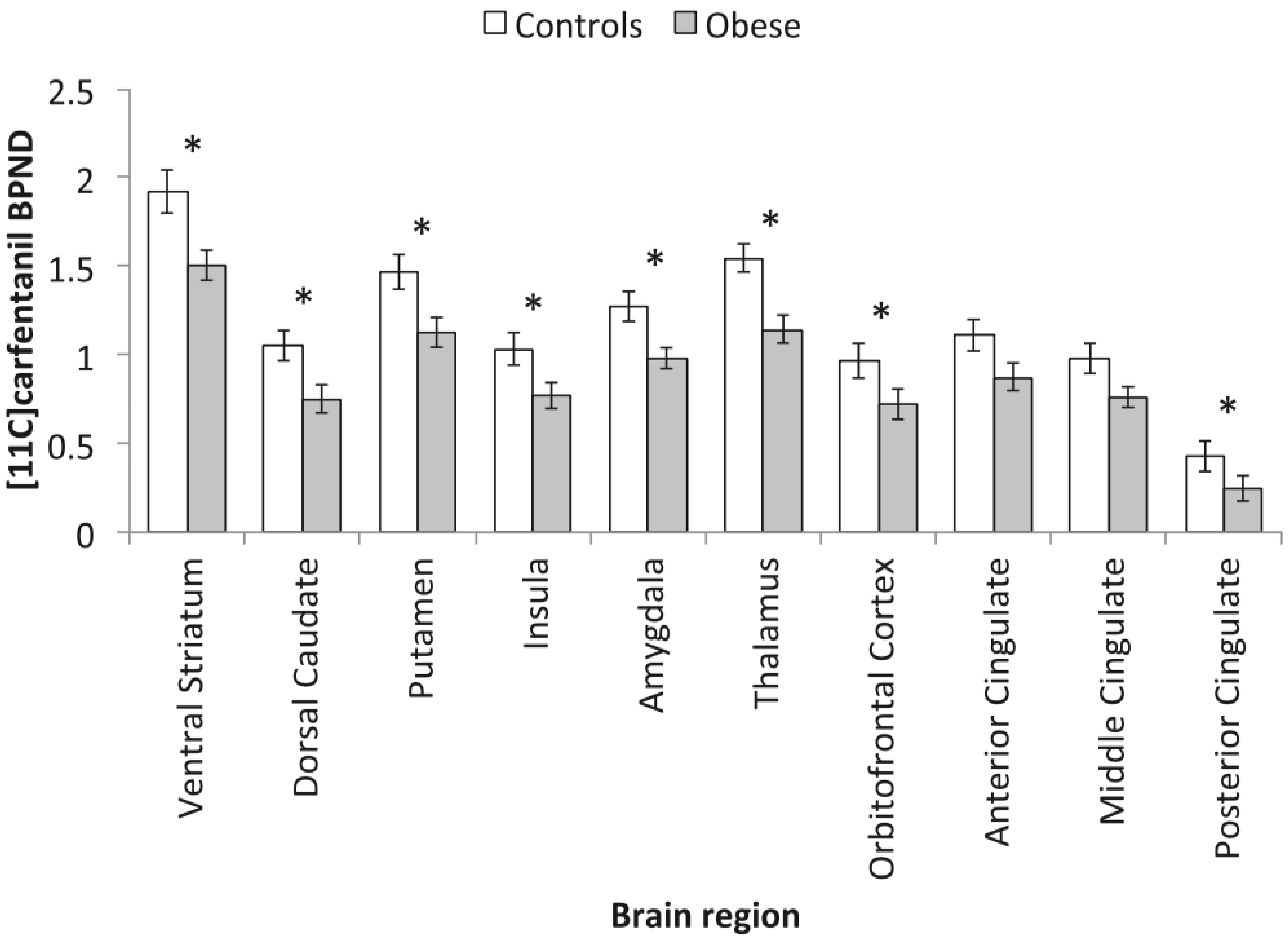
1) Mean images for each group



2) Statistical differences (t-map)



3) Region-of-interest data



Karlsson et al (2015 J Neurosci)

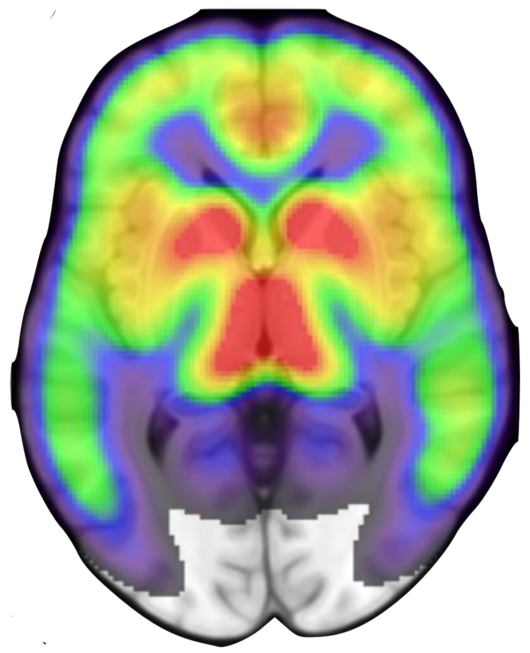
Challenge / longitudinal design

Lag hours or days

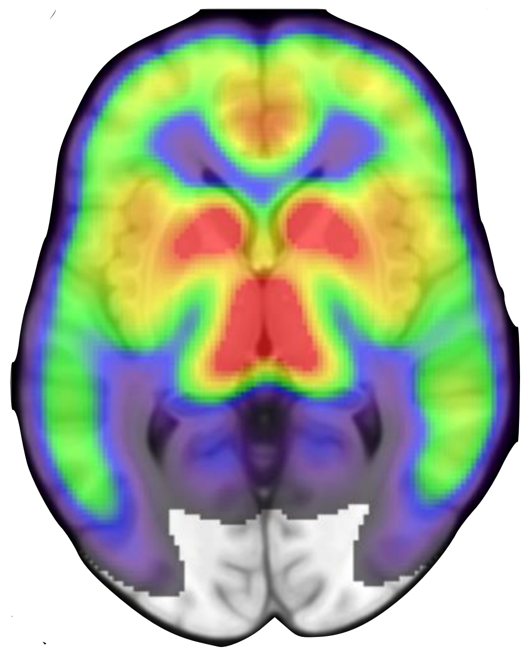
Scan 1

Challenge:
Task, drug, etc.

Scan 2



Voxelwise comparison with mass univariate repeated measures tests

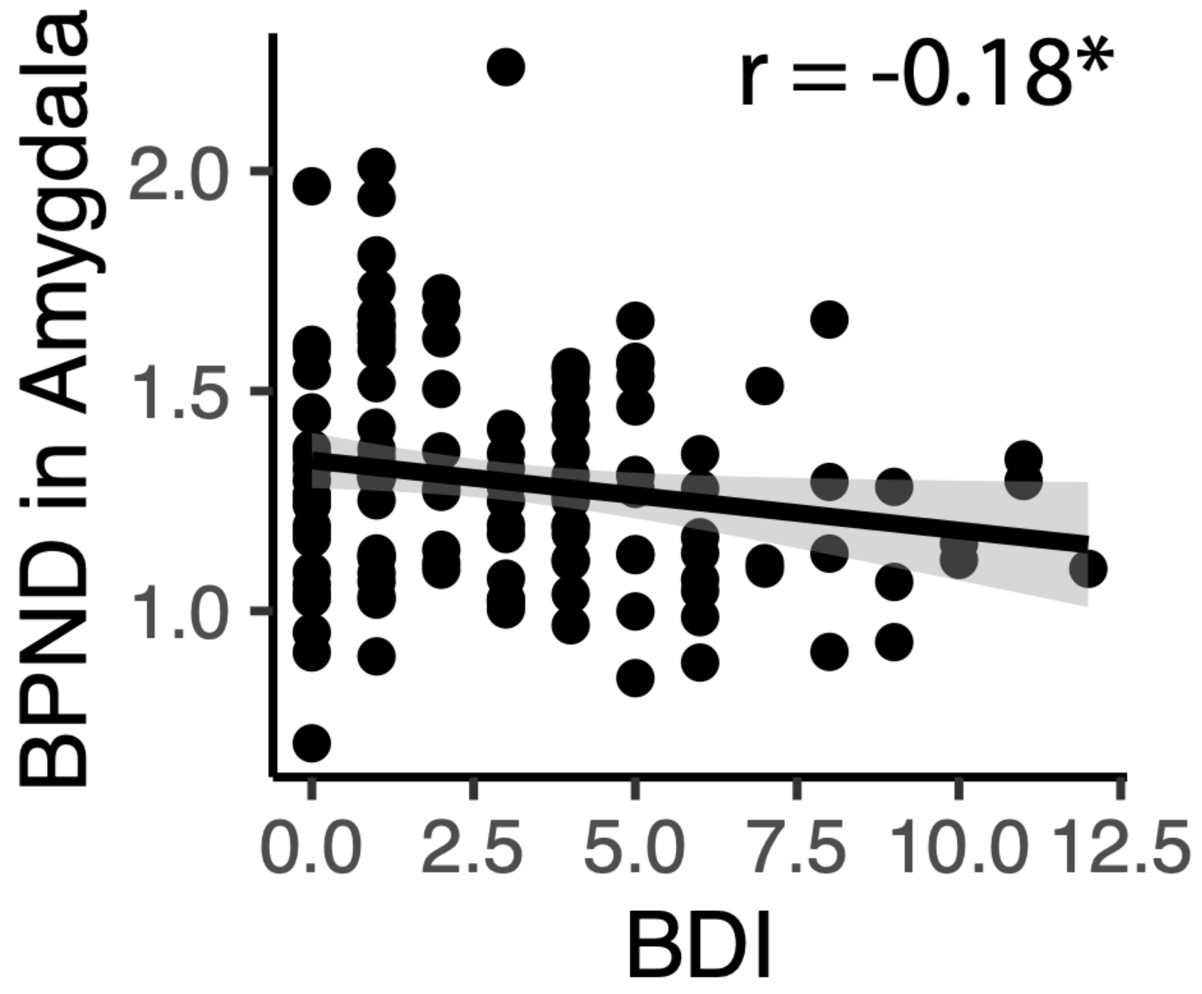


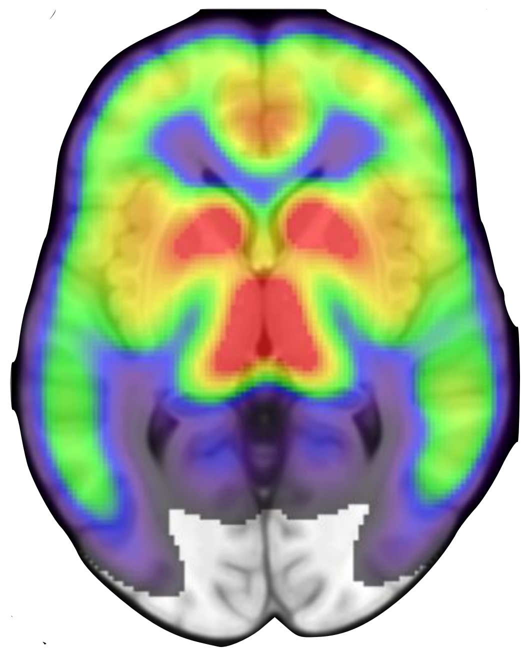
Tuulari et al (2018 J Neurosci)

Correlational design

Baseline scan

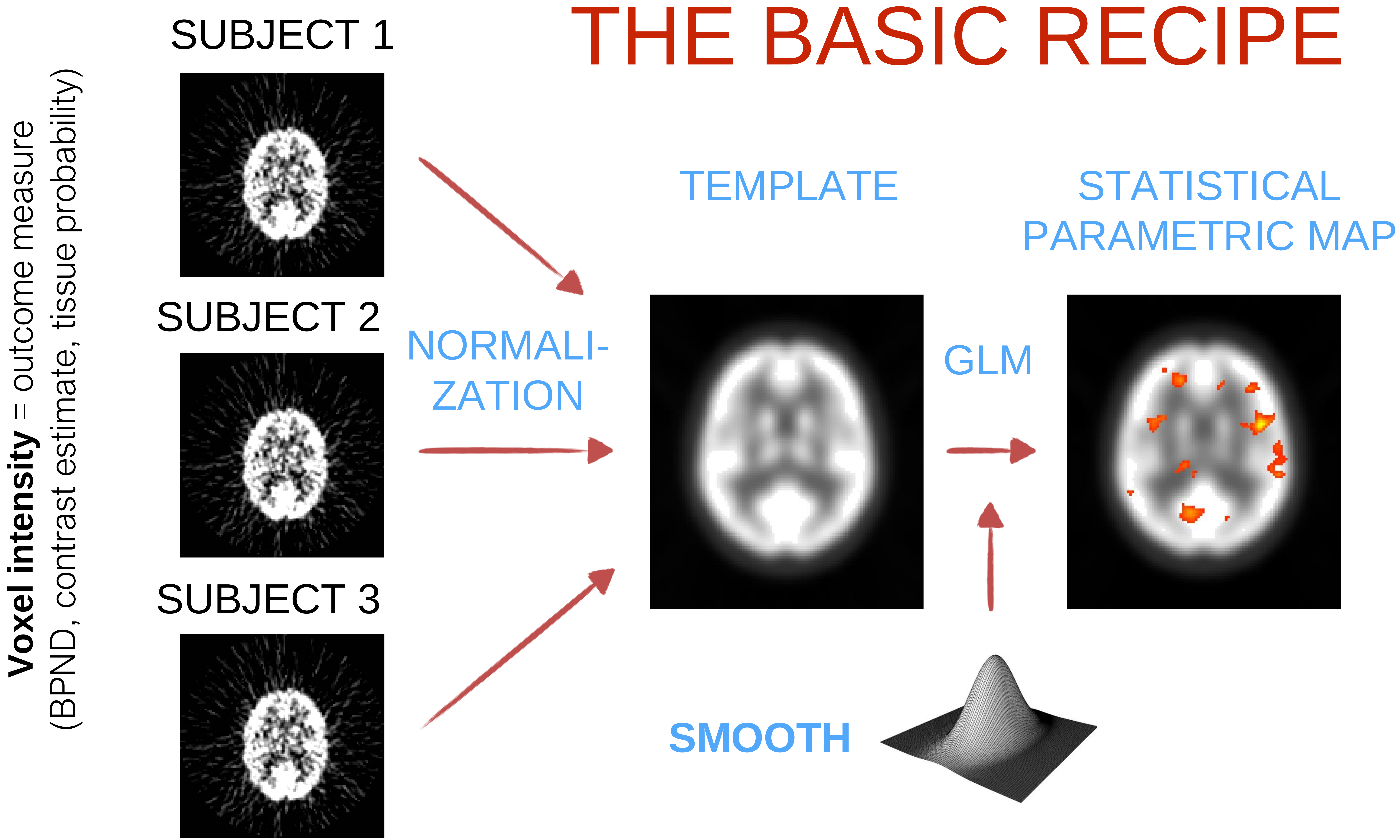
Univariate biological variable





Lowered mu-opioid receptor levels in subclinical depression

Nummenmaa et al (2020 Neuropsychopharmacology)


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