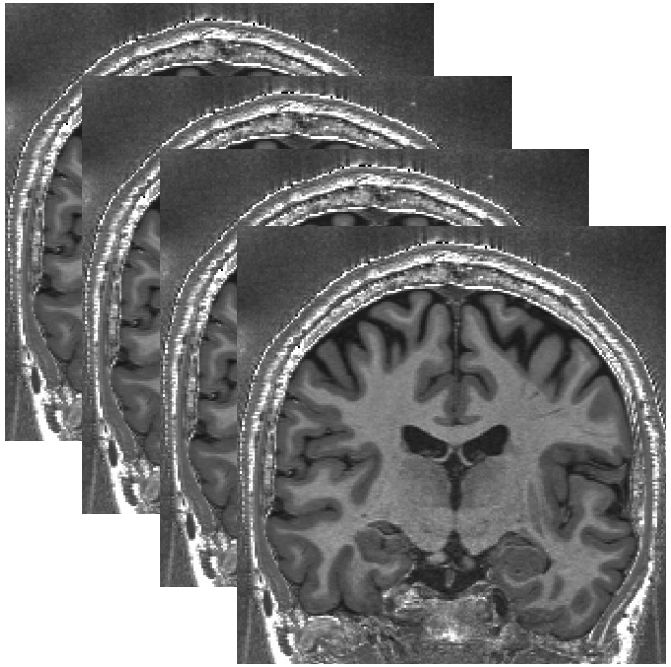
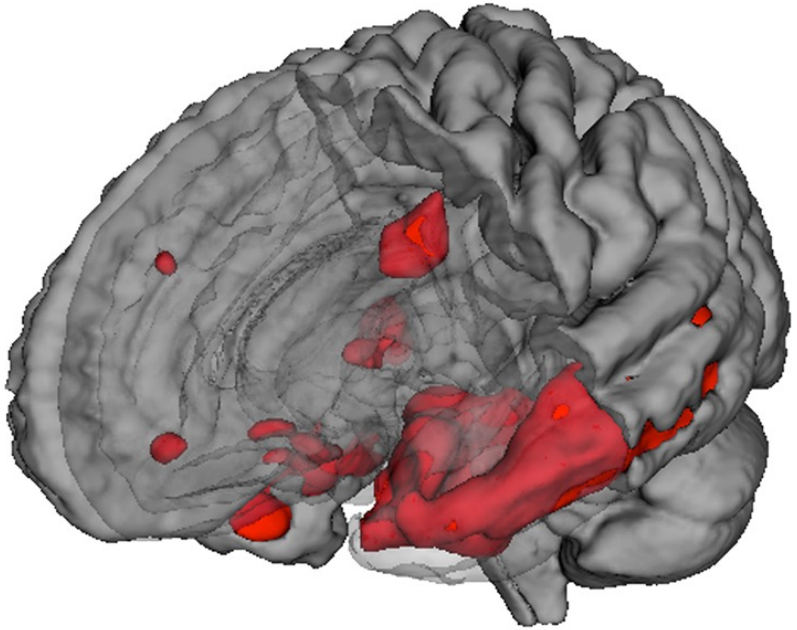
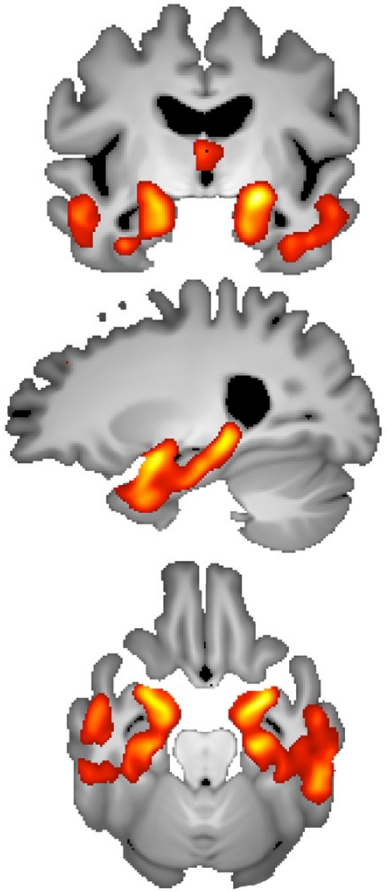
Voxel-Based Morphometry







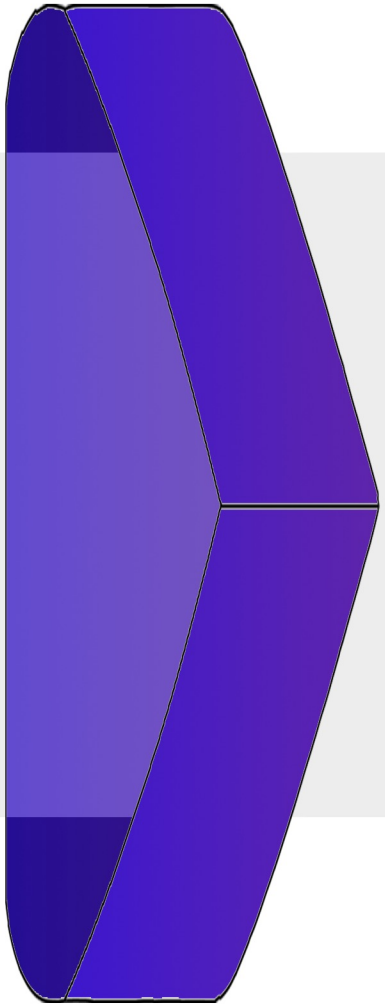
Dr Christian Lambert

Wellcome Centre for Human Neuroimaging, UCL

PART I

A. Introduction to structural brain analysis

B. What is VBM?

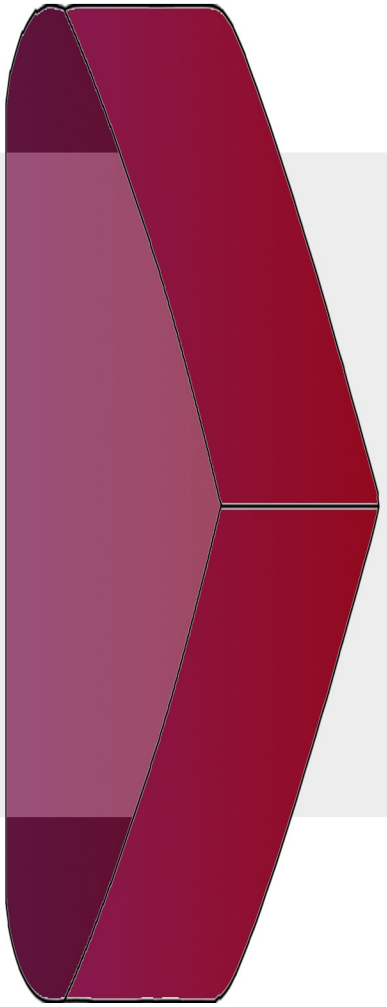


PART II

A. Pre-processing fundamentals

B. Step-by-step guide

C. Pitfalls and hints



PART III

A. Longitudinal analyses

B. Quantitative MRI & voxel base quantification

INTRODUCTION

ANATOMICAL ANALYSIS
Structural properties accross homologous (i.e. like-for-like) regions

WHOLE BRAIN PROPERTIES

REGIONAL SHAPE PROPERTIES

Manually defined region of interest (ROI) volumes

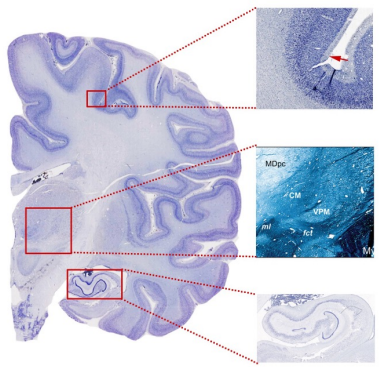
Voxel-wise tissue “density”
Voxel based morphometry

TISSUE MICROSTRUCTURE MRI PROPERTIES

Average signal in manually defined ROIs

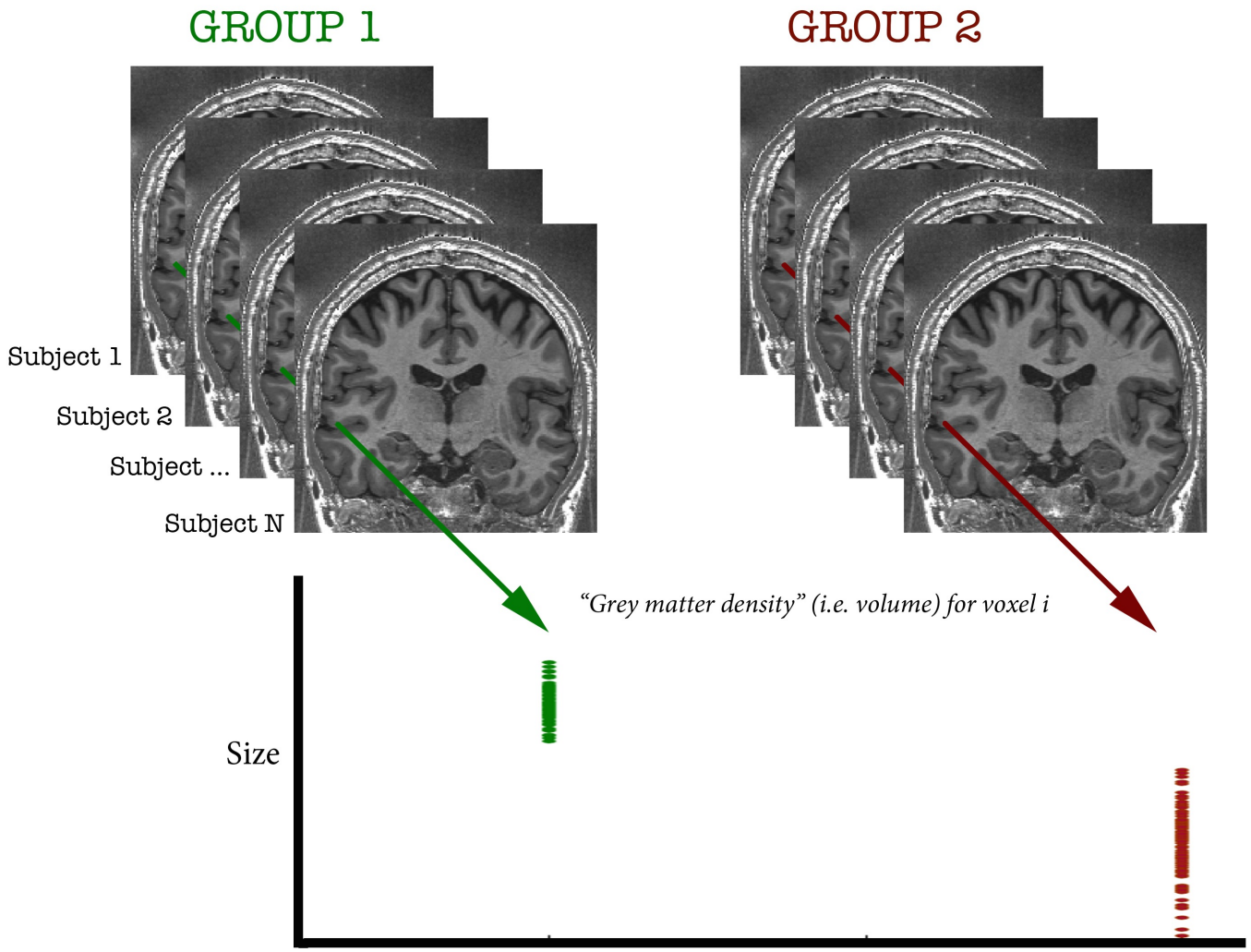
Voxel-wise tissue maps:
Voxel based quantification

HISTOLOGY



What is VBM?

- Voxel-Based Morphometry:
  - Size and shape of the brain and its structures (“*morphometry*”)
  - Compared at a voxel wise level across a population



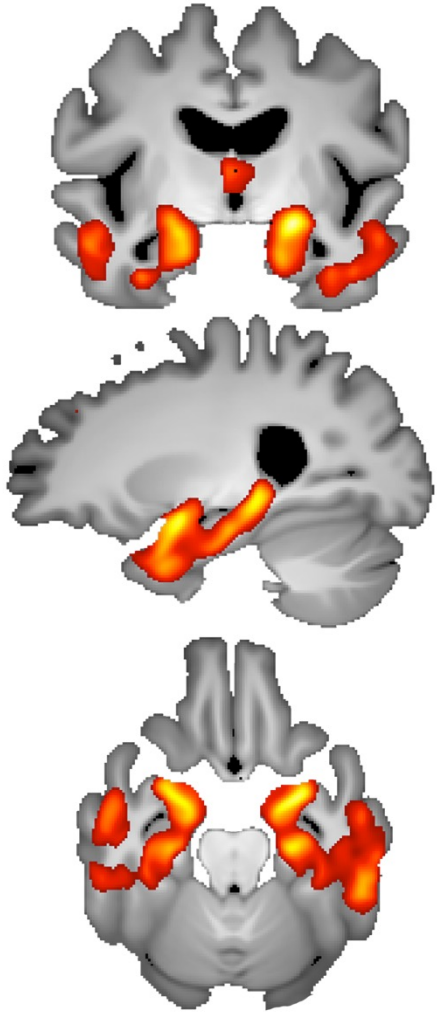
Examples applications of VBM

- Many scientifically or clinically interesting questions might relate to changes in local volume of anatomical regions of the brain

- For example, whether (and where) patterns of brain morphometry help to:

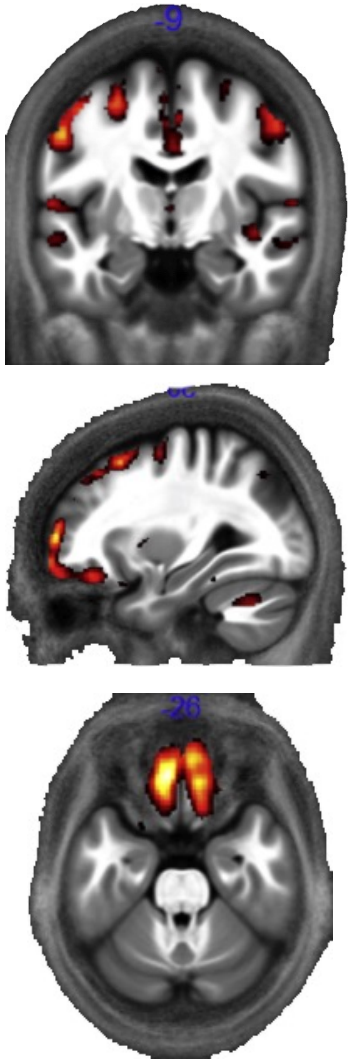
1. Distinguish between groups (e.g. Alzheimer's vs. healthy controls)
2. Explain changes seen in development and aging
3. Identify plasticity, e.g. when learning new skills
4. Find structural correlates (i.e. regions where the size correlates with scores, traits, genotype etc.,)

1. Phenotypic patterns of disease



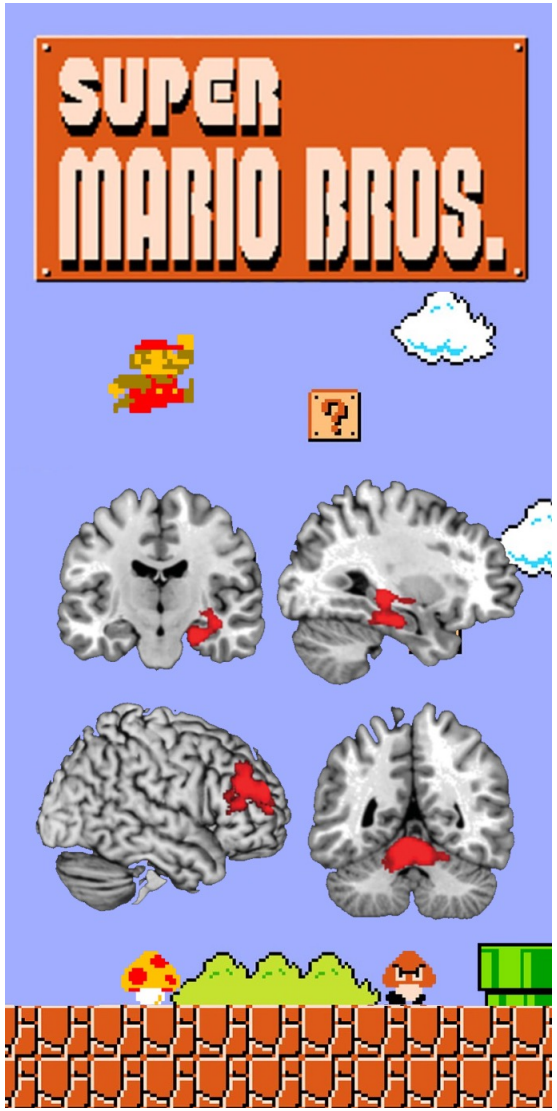
Atrophy - AD vs. healthy Controls (ADNI2 Dataset)

2. Ageing: GM atrophy



Callaghan et al., 2014

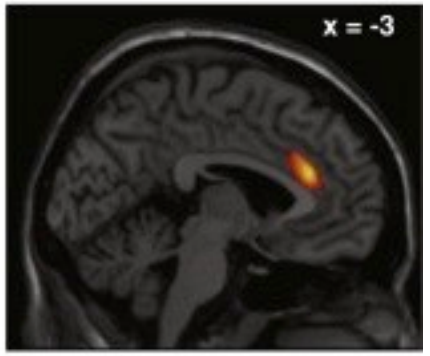
3. Plasticity: Computer game



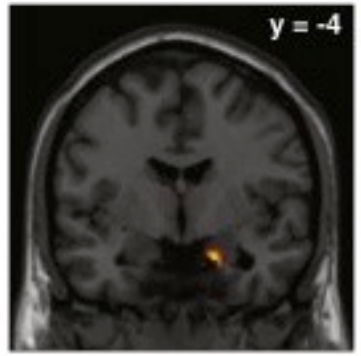
Ku¨hn et al., 2014

4. Correlates: Political orientation

Conservative - Decrease

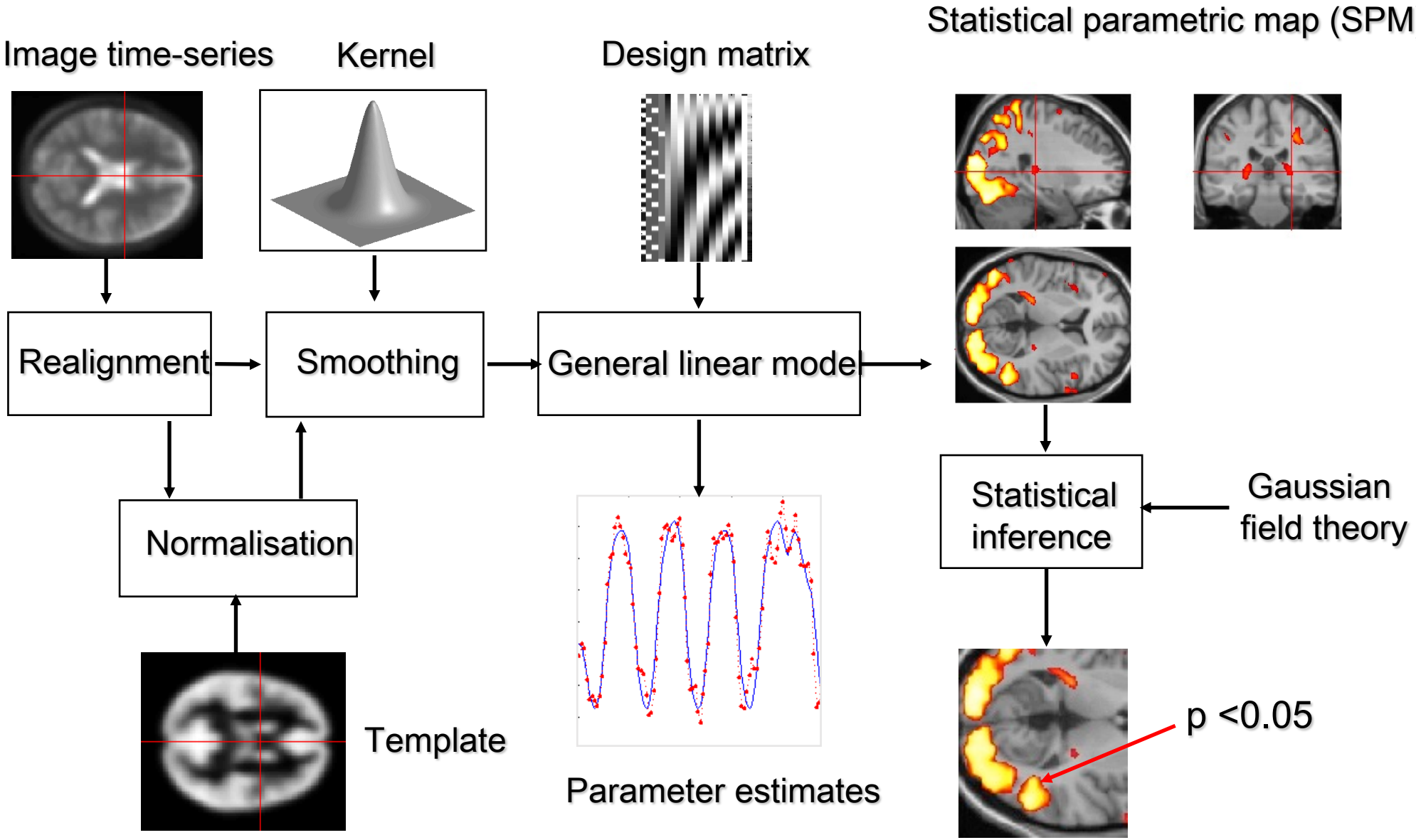


Conservative - Increase

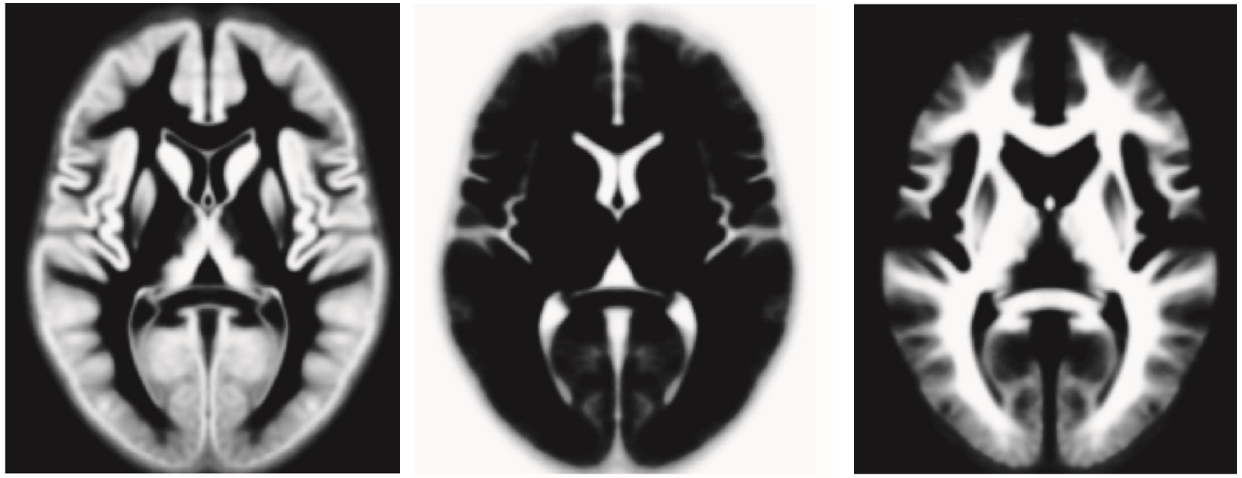


Kanai et al., 2011

Overview of SPM

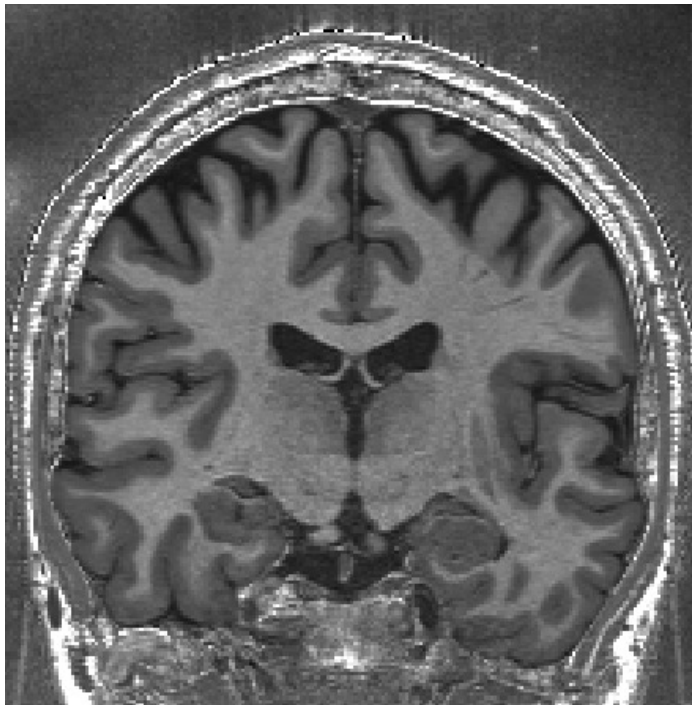


TISSUE SEGMENTATION

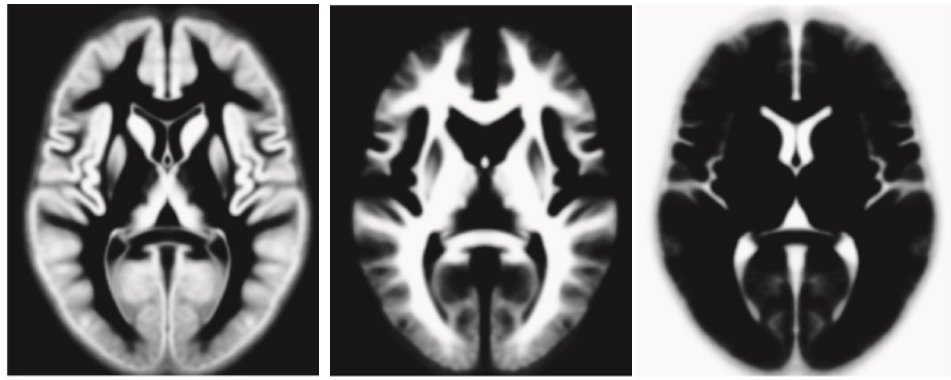


Tissue segmentation for VBM

- High-resolution MRI reveals fine structural detail in the brain, but not all of it reliable or interesting
  - Noise, intensity-inhomogeneity, vessels
  - MR Intensity is usually not quantitatively meaningful
  - Quantitative MRI is possible though, and promising, see *Voxel Based Quantification* (VBQ) e.g. Draganski et al. (2011) PMID:21277375

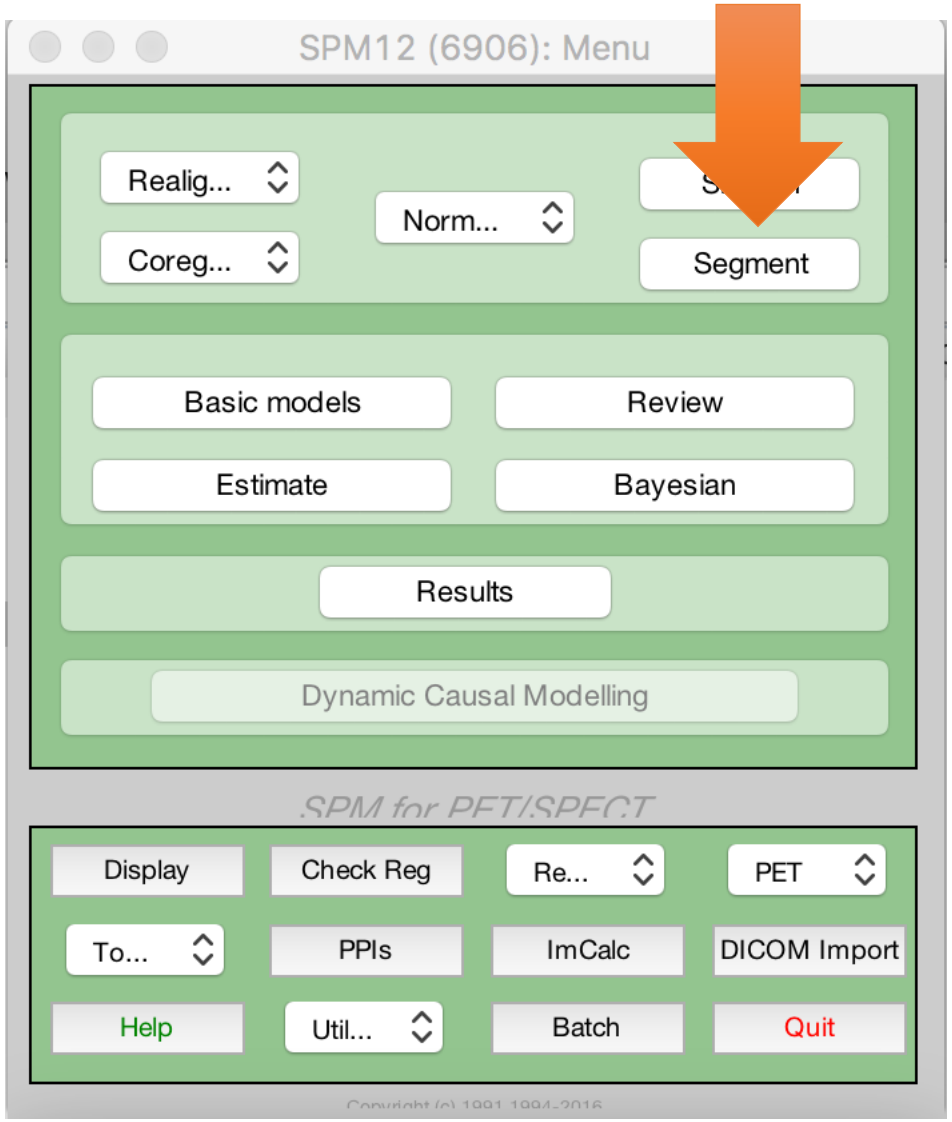


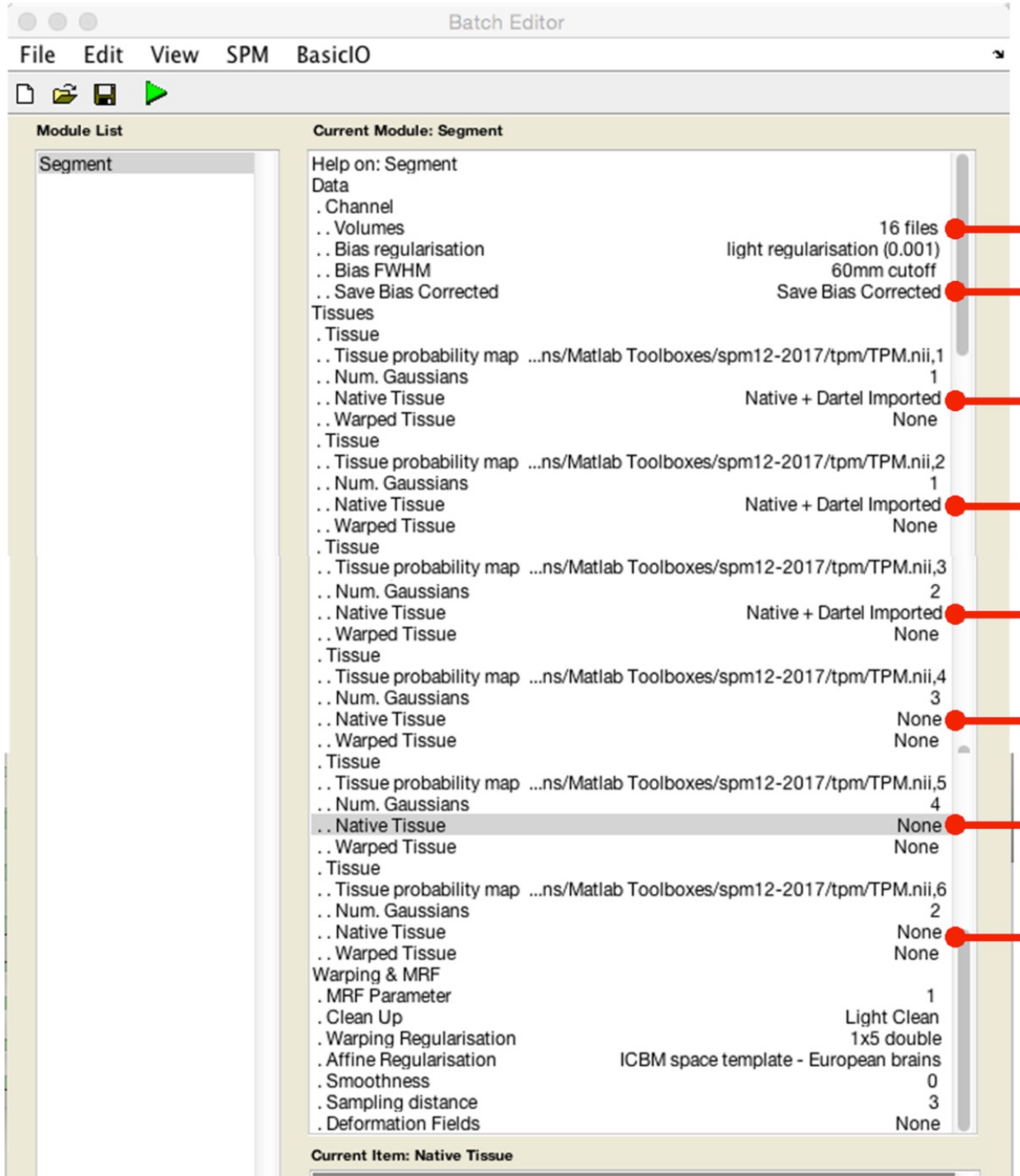
- Regional volumes of the three main tissue types: gray matter, white matter and CSF, are well-defined and potentially have interesting properties



Tissue segmentation in SPM12

- Main Segmentation button on the SPM GUI



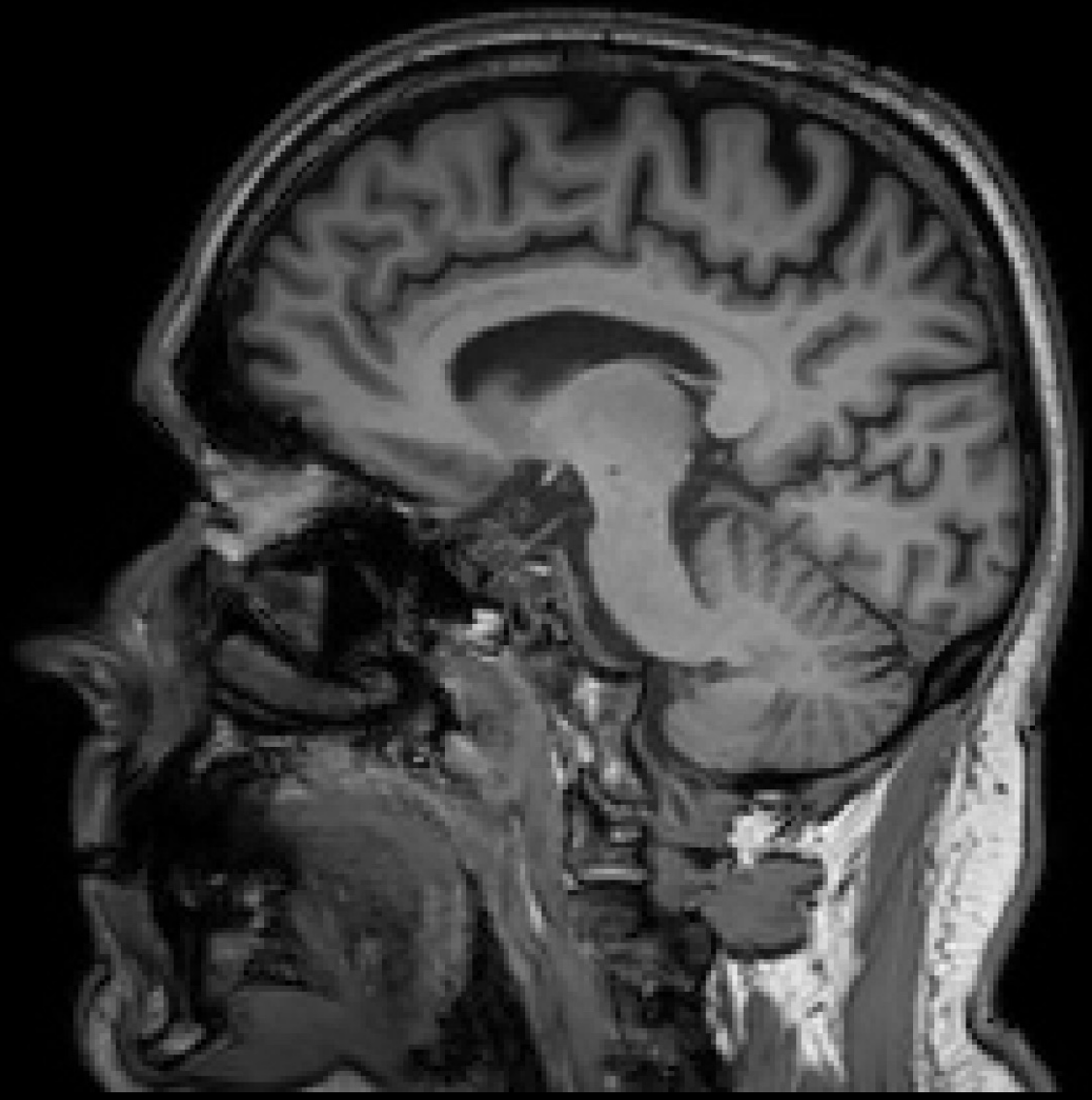


Structural MRI (e.g. T1 weighted MRI)

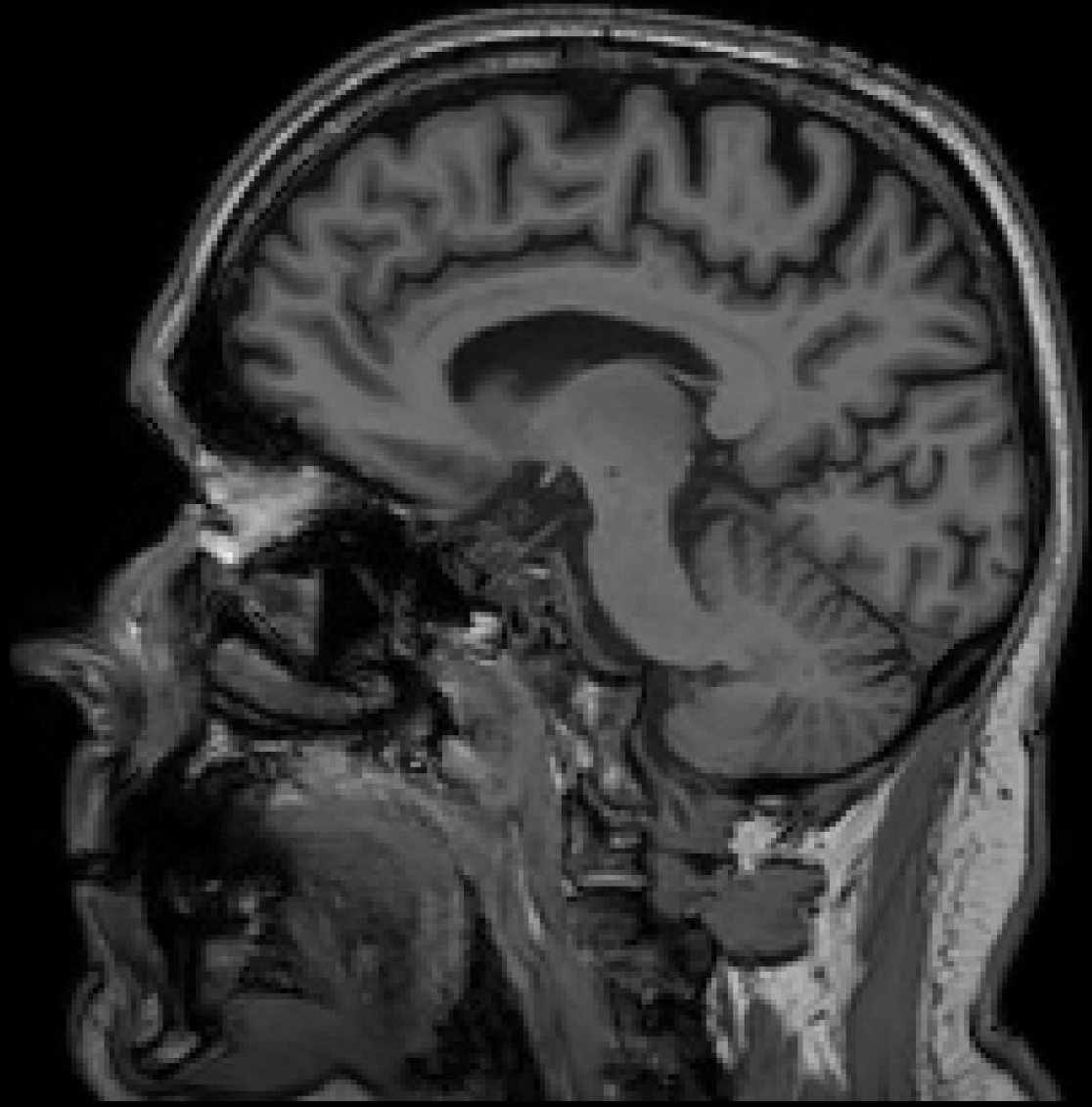
Output T1 with bias field inhomogeneities removed

Tissue segmentations (c1->c6)
Can output *"native"* or *"dartel imported"*, make sure to select what you want.
Can use either, but if native make sure the data is all well aligned across subjects (see later example)

Native T1 MRI



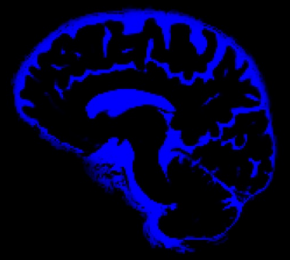
Bias corrected T1 MRI

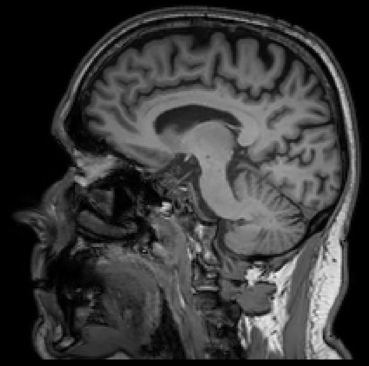


WHITE MATTER
c2[filename].nii

GREY MATTER
c1[filename].nii

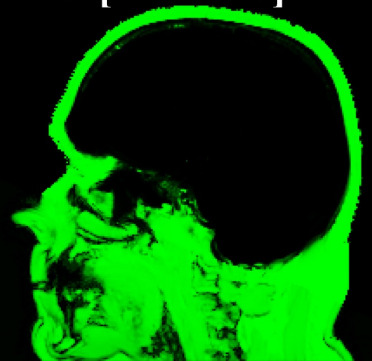
CSF
c3[filename].nii





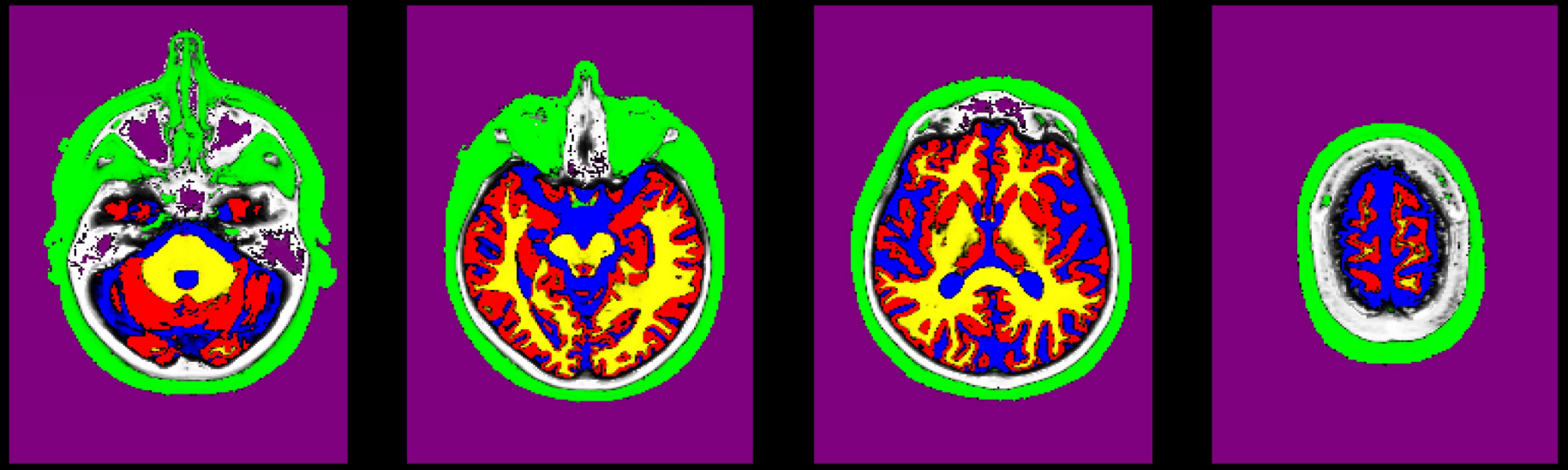
AIR
c6[filename].nii

SOFT-TISSUE
c5[filename].nii



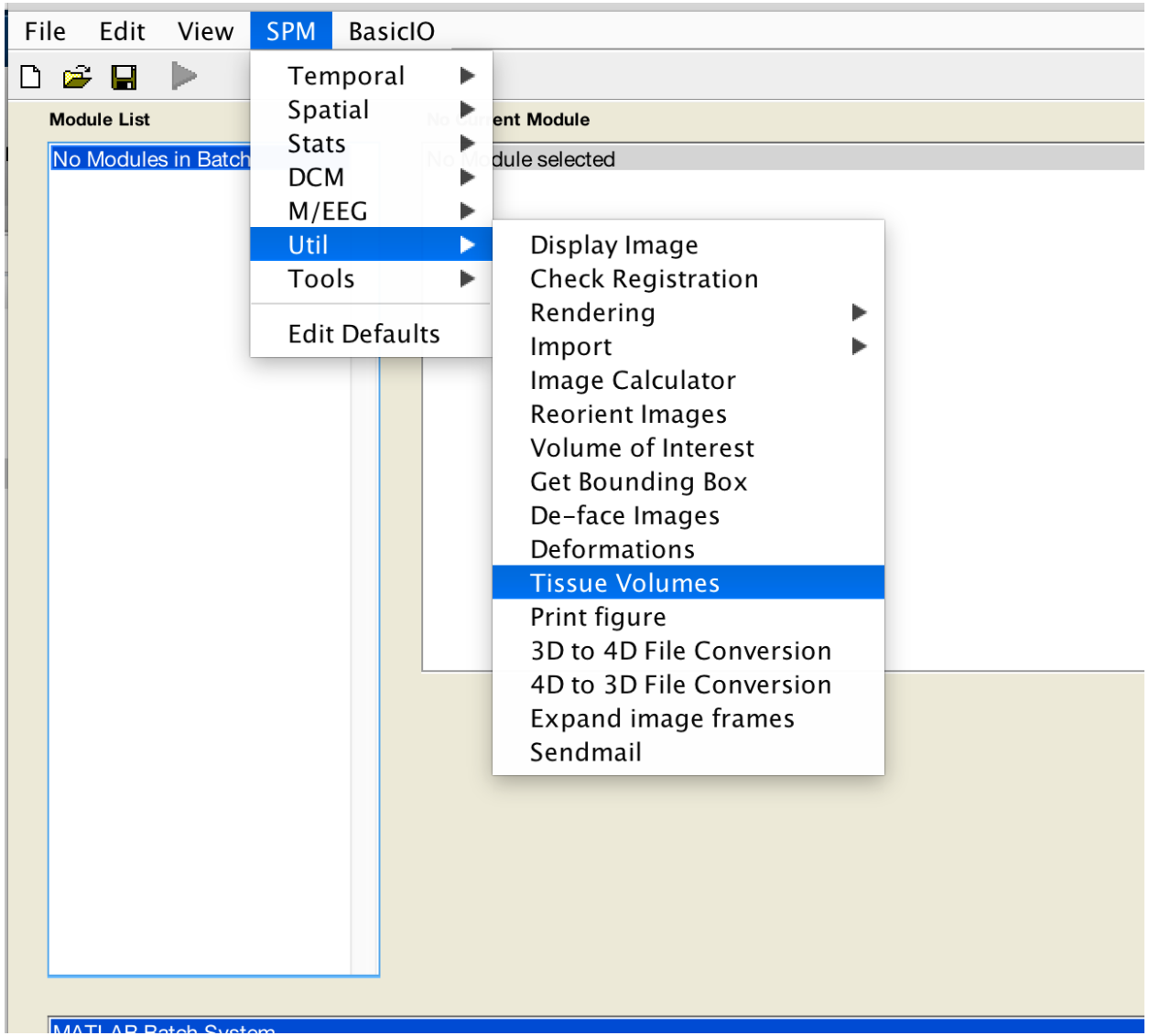
BONE
c4[filename].nii

Tissue segmentations

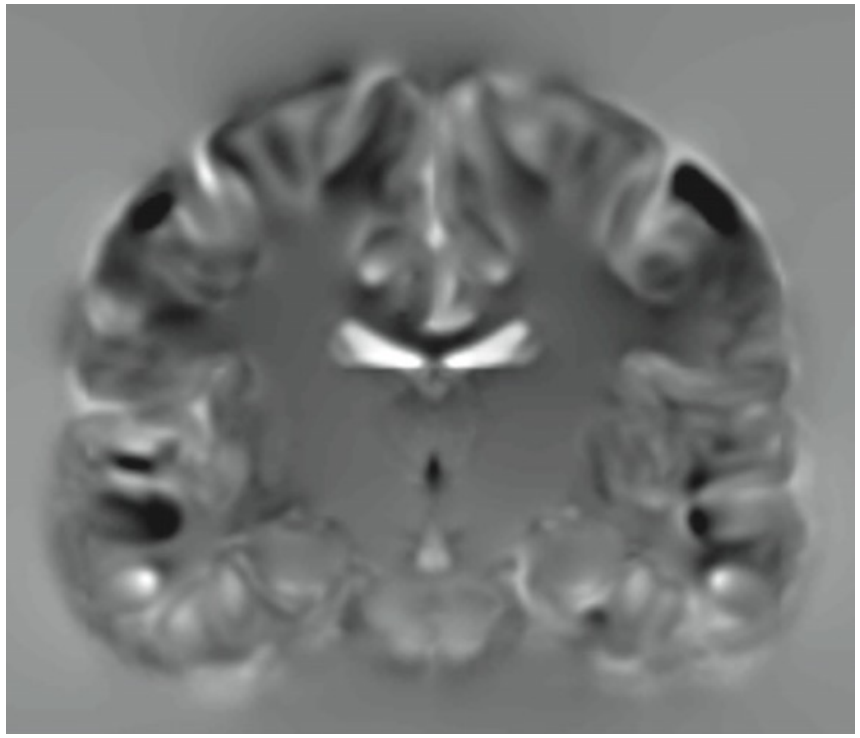


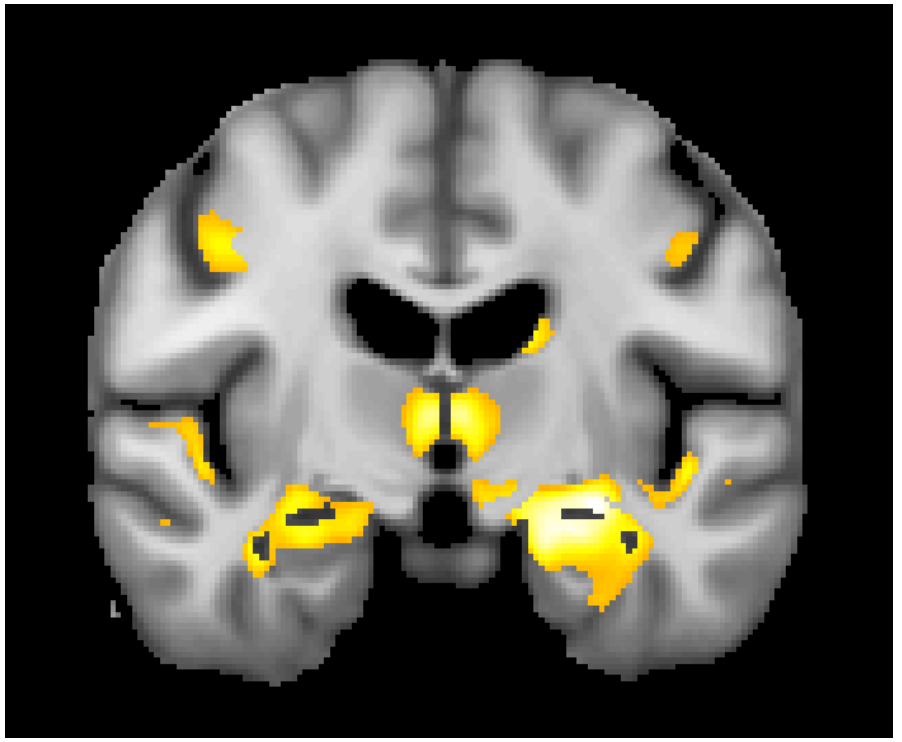
Total intracranial volume (TIV)

- TIV is a useful measure, as the regional size of brain structures correlate with overall brain size.
- Used as a covariate in VBM analysis
- Once you have run SPM SEGMENT, each subject will have a "_seg8.mat" file
- Can use this in "Tissue Volumes" function
- Output – Volume (mm^3) of each tissue class



VOXEL BASED MORPHOMETRY





Voxel-Based Morphometry

- In essence VBM is Statistical Parametric Mapping of regional segmented tissue density or volume

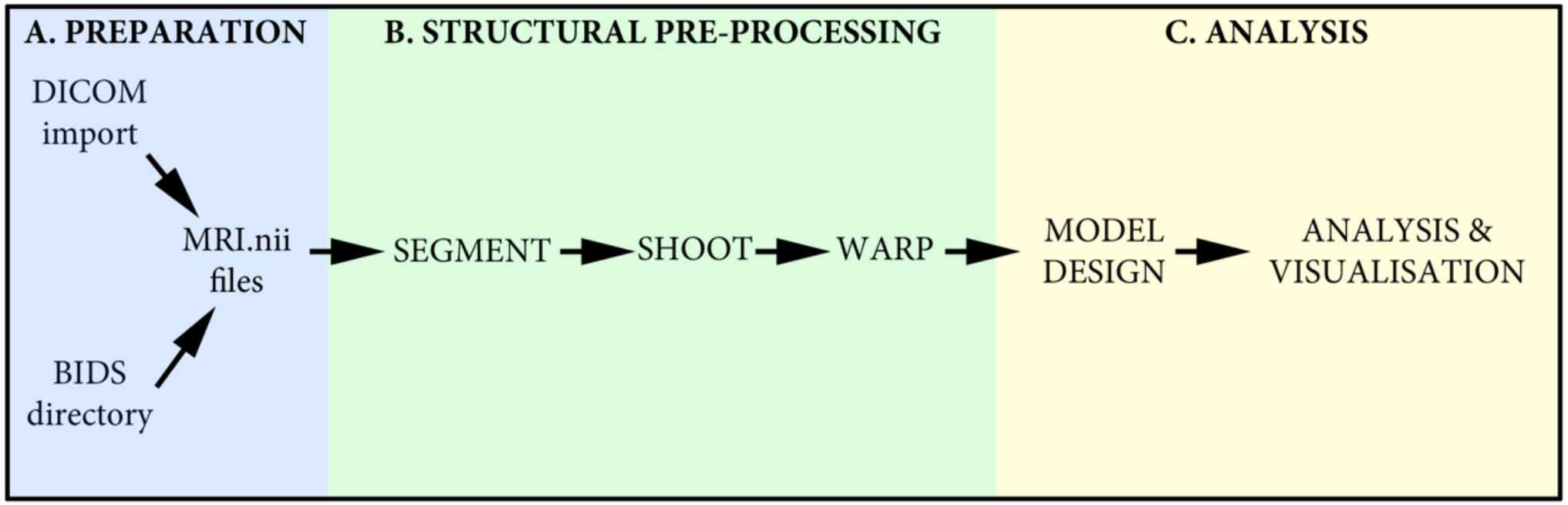
- The exact interpretation of gray matter density or volume is complicated, and depends on the preprocessing steps used:

  - It is not interpretable as neuronal packing density or other cytoarchitectonic tissue properties

  - The hope is that changes in these microscopic properties may lead to macro- or mesoscopic VBM-detectable differences

  - One technique is to use VBM in combination with other quantitative structural measures (diffusion, MT, R2*, SWI) to make biophysical inferences (see later)

Overview of VBM



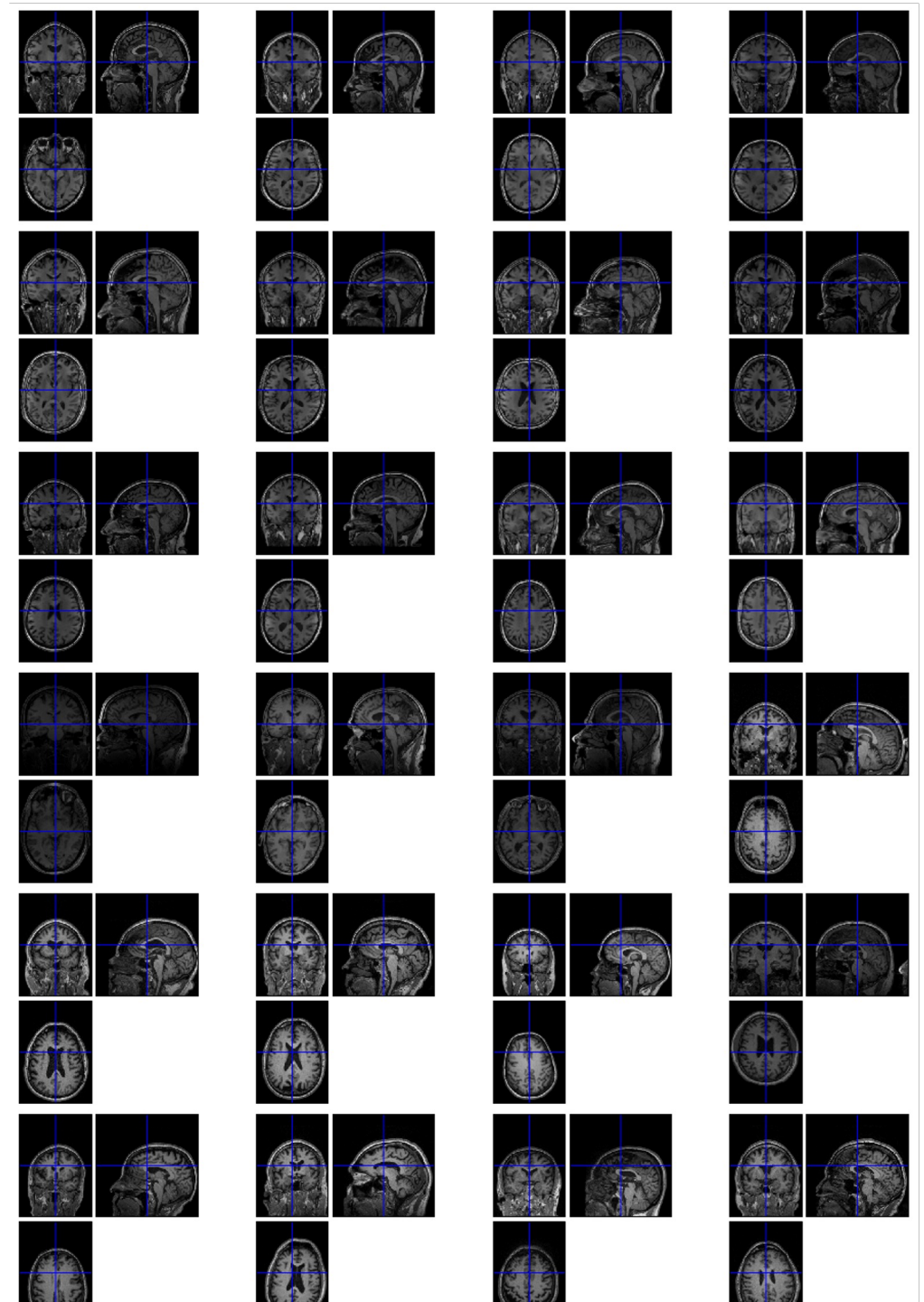
- Anatomical analyses in SPM (VBM, VBQ) use the same standard SPM pipeline, but with a few adaptations to allow us to derive and use morphometric properties

VBM
Step-by-step overview

STEP 1!

** ALWAYS VISUALLY CHECK YOUR DATA**

Examples: Poor scan quality, artefacts, abnormal tissue (ischaemia, dural thickening, lesions), abnormal brains (hydrocephalus), alignment (need to be relatively close), header issues (flipped brains), missing data



VBM overview

**** ALWAYS VISUALLY CHECK YOUR DATA****

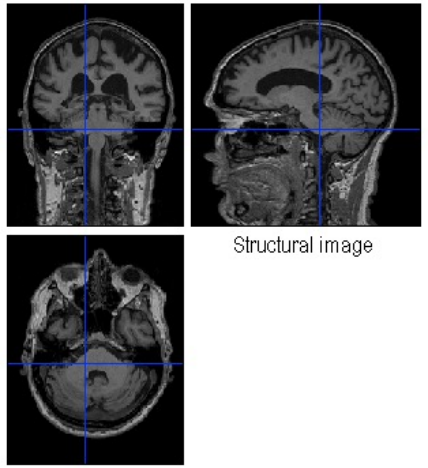
Poor scan quality, artefacts, abnormal tissue (ischaemia, dural thickening, lesions), abnormal brains (hydrocephalus), alignment (need to be relatively close), header issues (flipped brains), missing data

1. Unified segmentation and spatial normalisation
   i. More flexible groupwise normalisation using Shoot (supersedes DARTEL)
2. Modulation to preserve tissue volume
   i. Otherwise, tissue "density" (harder to interpret, registration errors)
   ii. See also Radua et al. (2014) [PMID:23933042]
3. Compute tissue totals/globals
4. Gaussian smoothing
5. Voxel-wise statistical analysis

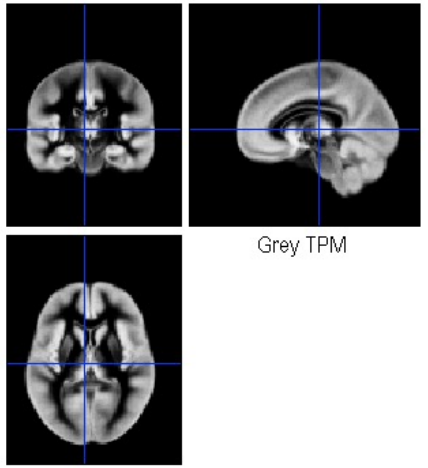
VBM in pictures

Segment

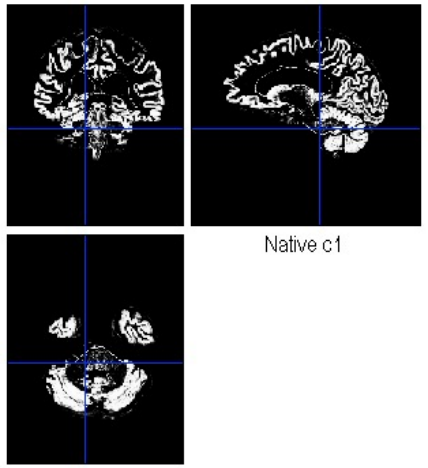
Normalise



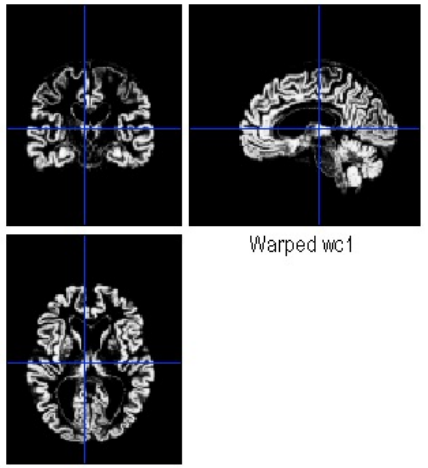
Structural image



Grey TPM



Native c1



Warped wc1

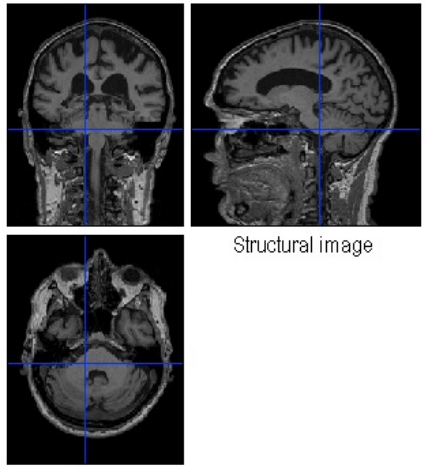
VBM in pictures

Segment

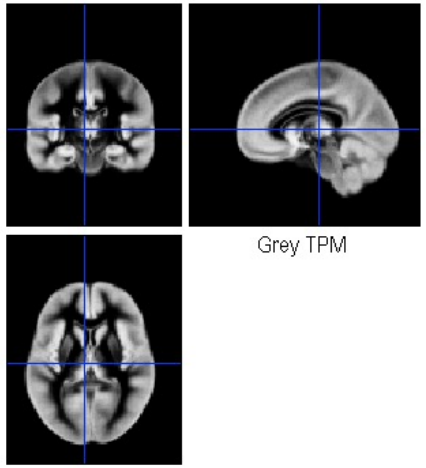
Normalise

Modulate

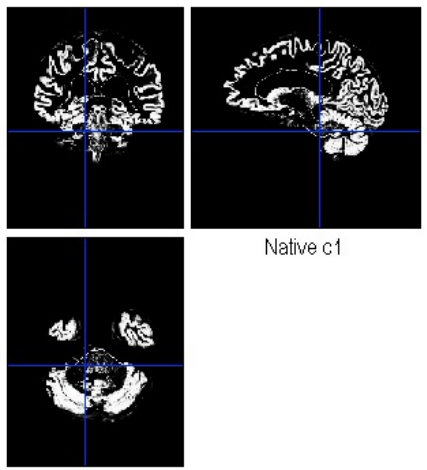
Smooth



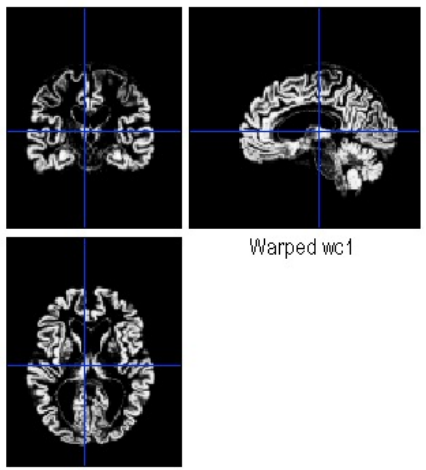
Structural image



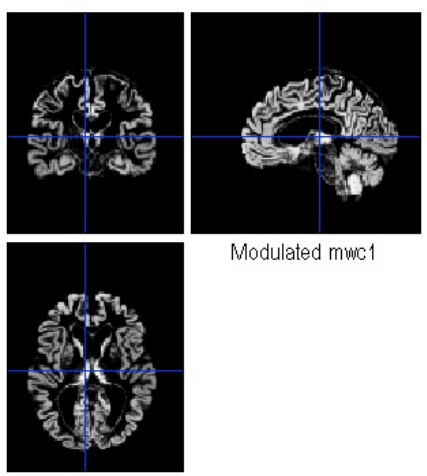
Grey TPM



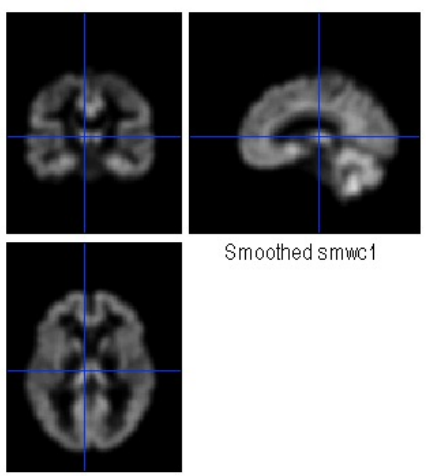
Native c1



Warped wc1



Modulated mwc1



Smoothed smwc1

VBM in pictures

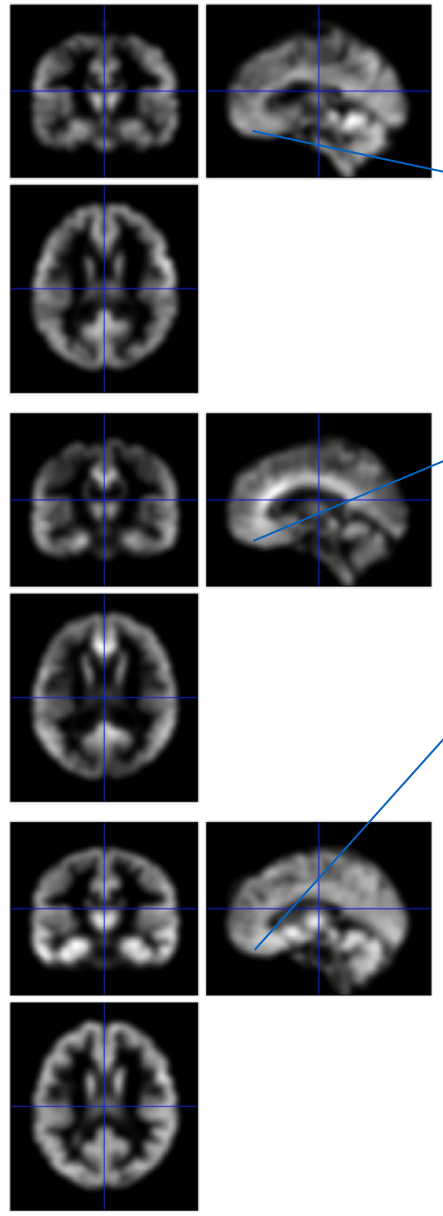
Segment

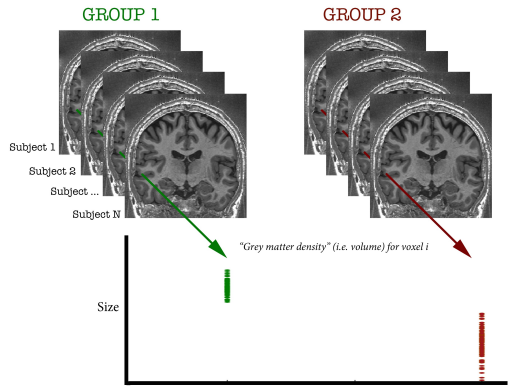
Normalise

Modulate

Smooth

Voxel-wise statistics





$$\begin{bmatrix} a1xyz \\ a2xyz \\ \vdots \\ aNxyz \end{bmatrix} = Y = X\beta_{xyz} + e_{xyz}$$

$$e_{xyz} \sim N(0, \sigma^2_{xyz} V)$$

$$X = \begin{bmatrix} 1 & 0 \\ 1 & 0 \\ \vdots & \vdots \\ 0 & 1 \\ 0 & 1 \end{bmatrix}$$

VBM in pictures

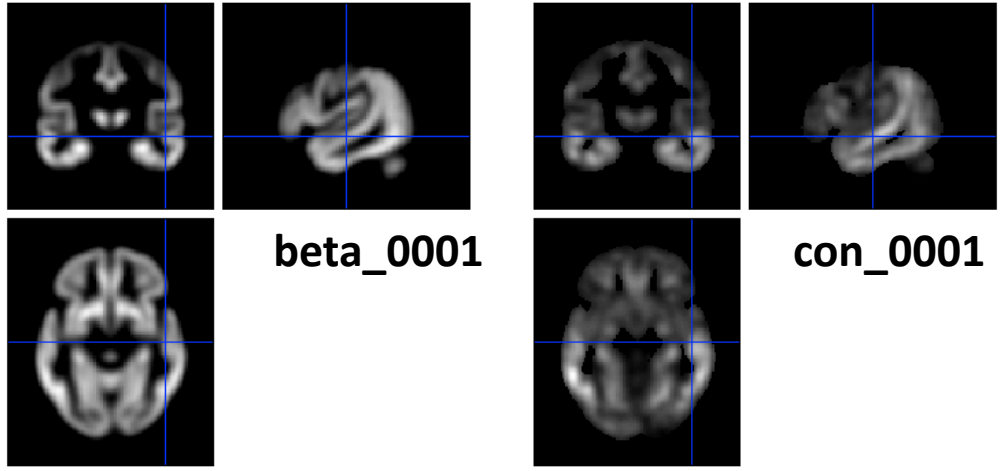
Segment

Normalise

Modulate

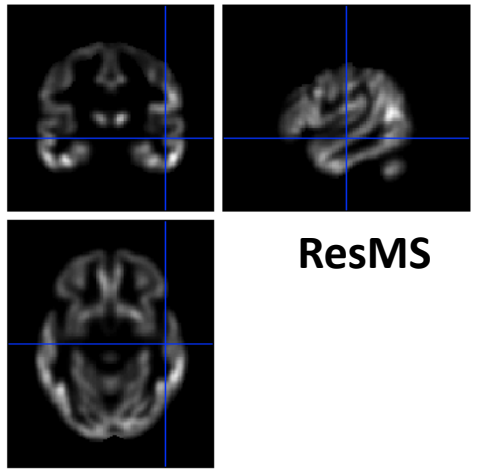
Smooth

Voxel-wise statistics

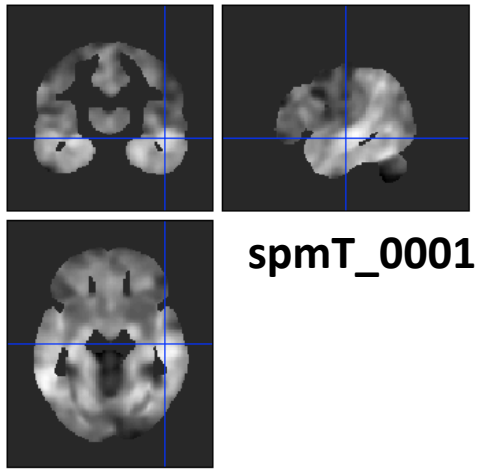


beta_0001

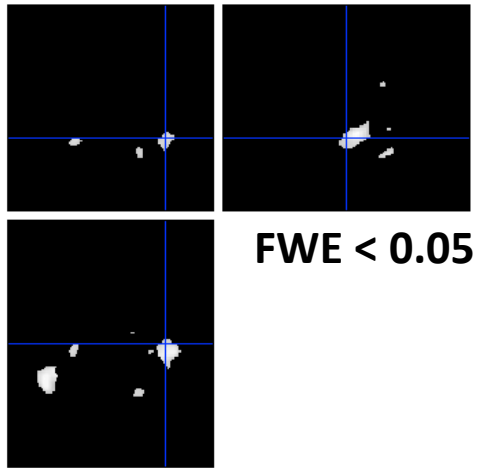
con_0001



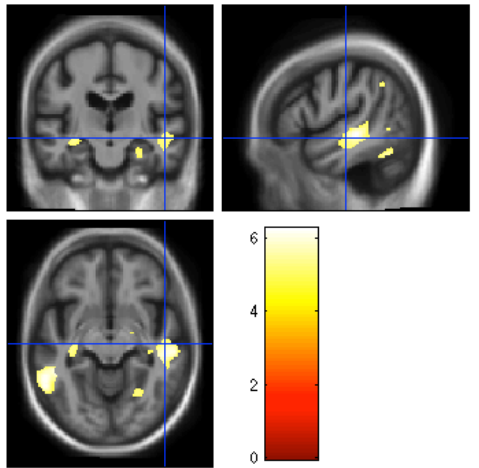
ResMS



spmT_0001



FWE < 0.05



VBM SUBTLETIES

Modulation

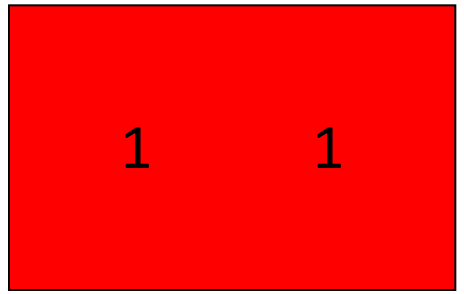
How much to smooth

Interpreting results

Adjusting for total GM or Intracranial Volume

A priori regions of interest

Modulation (“*preserve amounts*”)

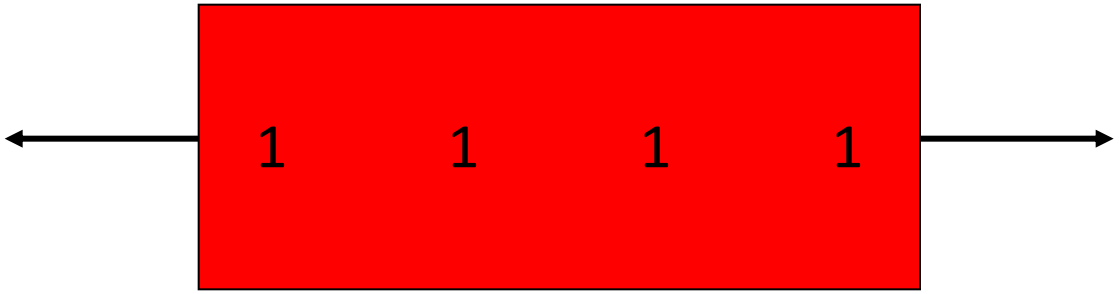


Native

intensity =
tissue probability

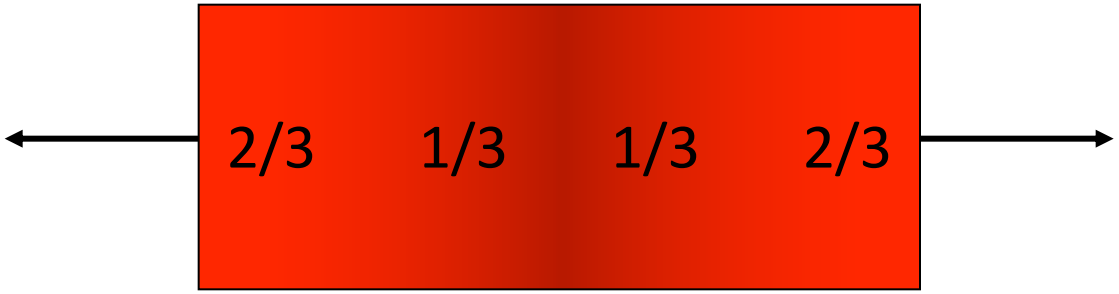
- Multiplication of warped (normalised) tissue intensities so that their regional total is preserved
  - Can detect differences in completely registered areas
  - E.g. Focal atrophy

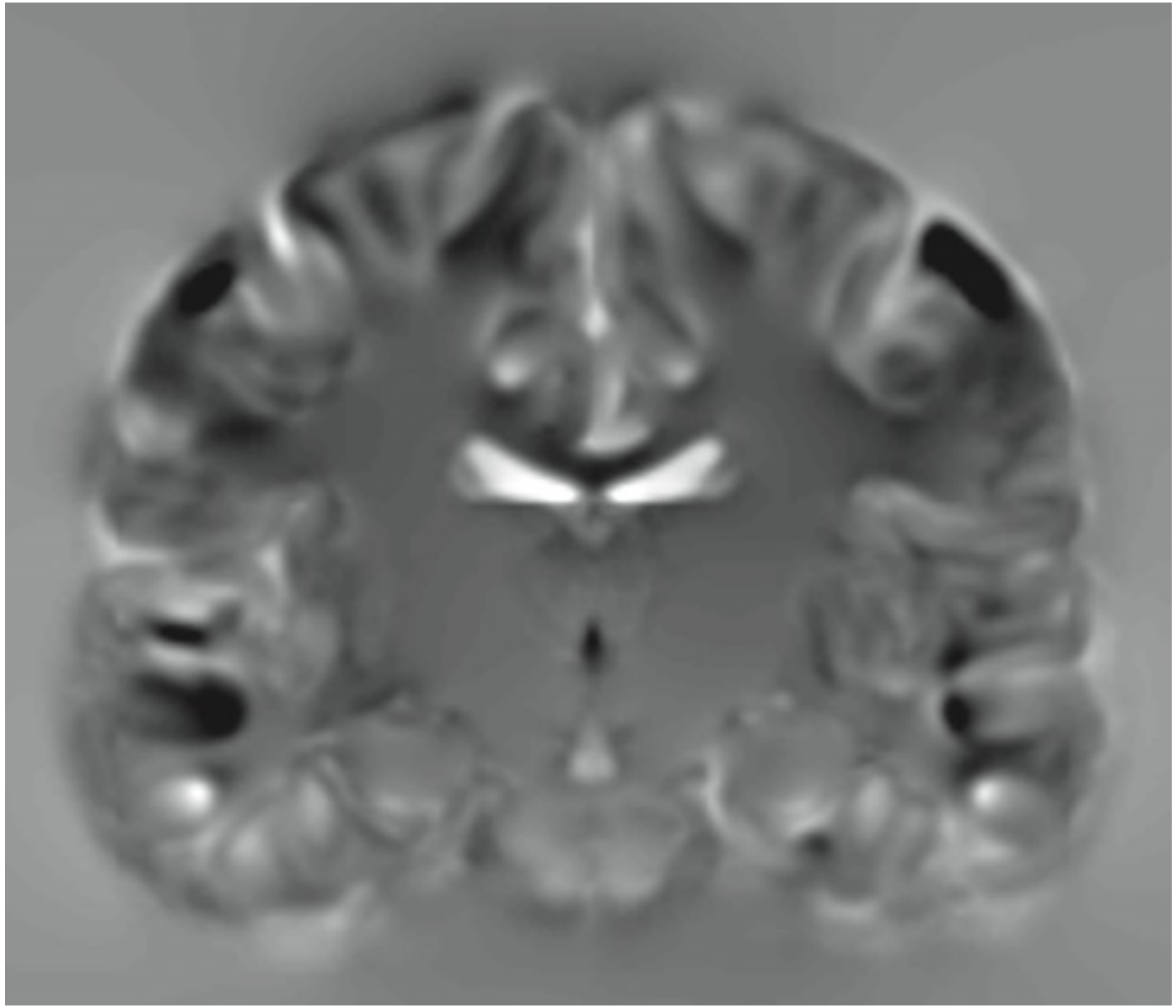
Unmodulated



- Otherwise, we *preserve concentrations*, and are detecting *mesoscopic* effects that remain after approximate registration has removed the macroscopic effects
  - For example, gross folding differences in sulci but not focal atrophy

Modulated



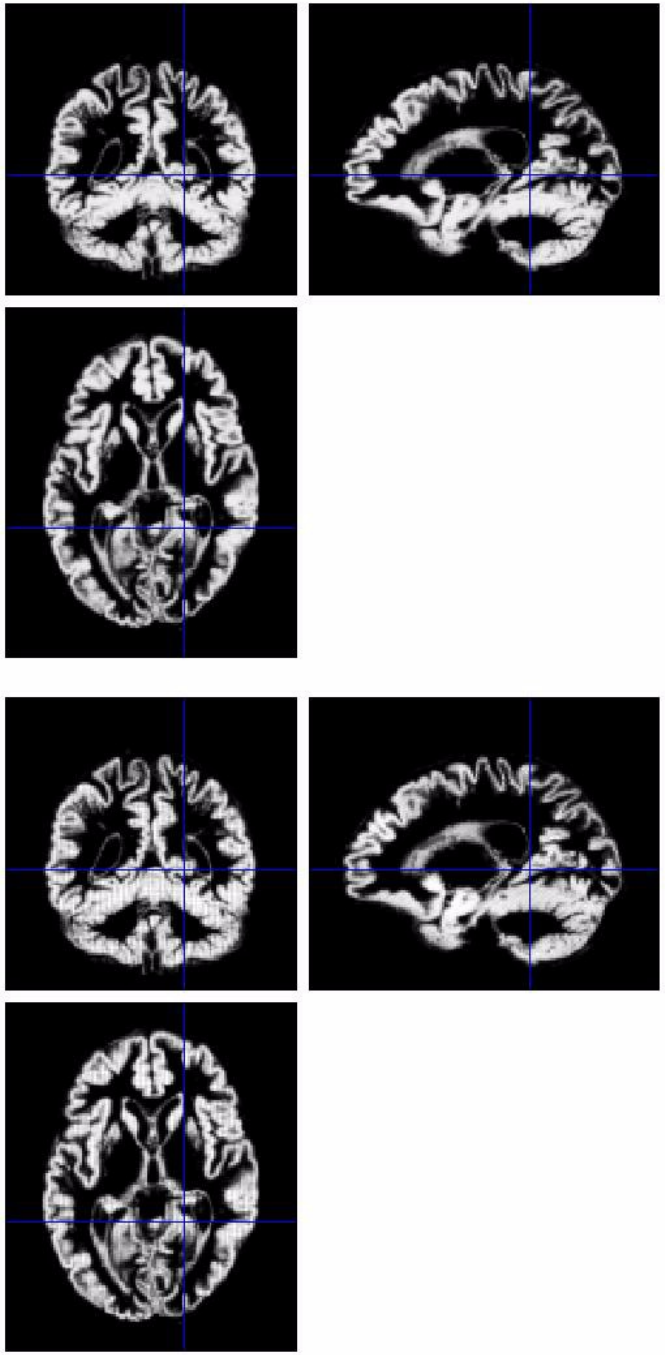


JACOBIAN DETERMINANT IMAGE
(j_<image>.nii)

Modulation (“*preserve amounts*”)

- Top shows “unmodulated” data (wc1), with intensity or concentration preserved
  - Intensities are constant

- Below is “modulated” data (mwc1) with amounts or totals preserved
  - The voxel at the cross-hairs brightens as more tissue is compressed at this point

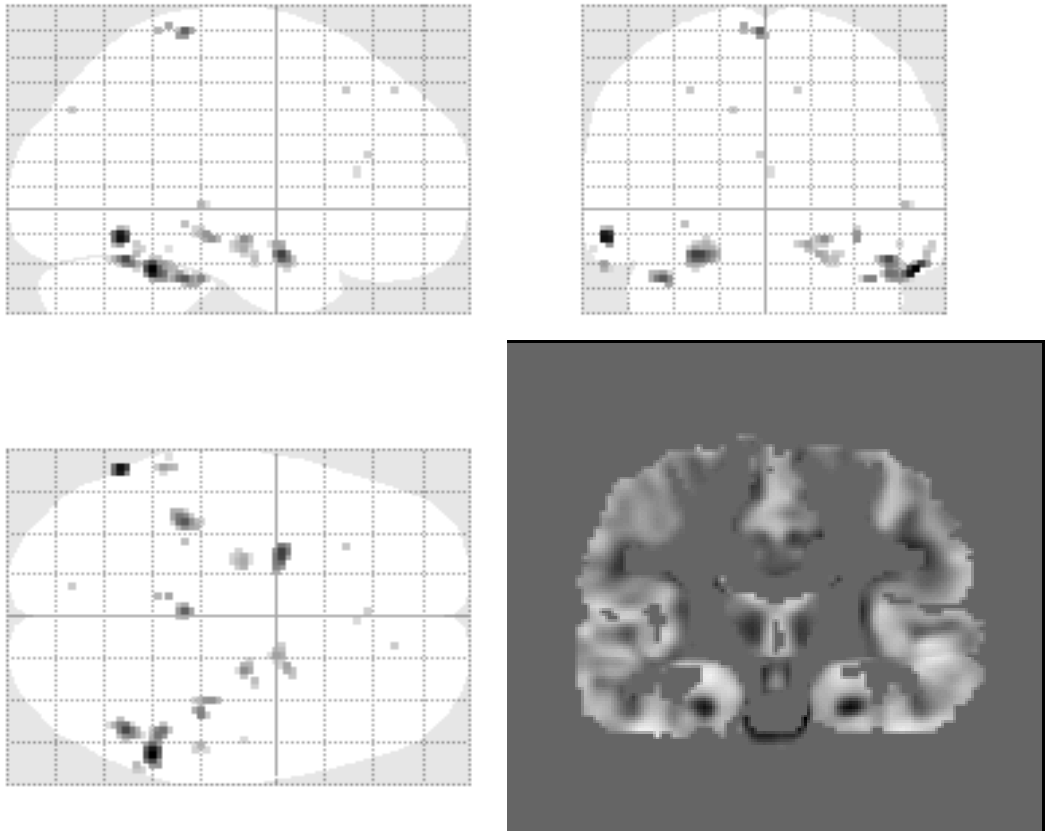


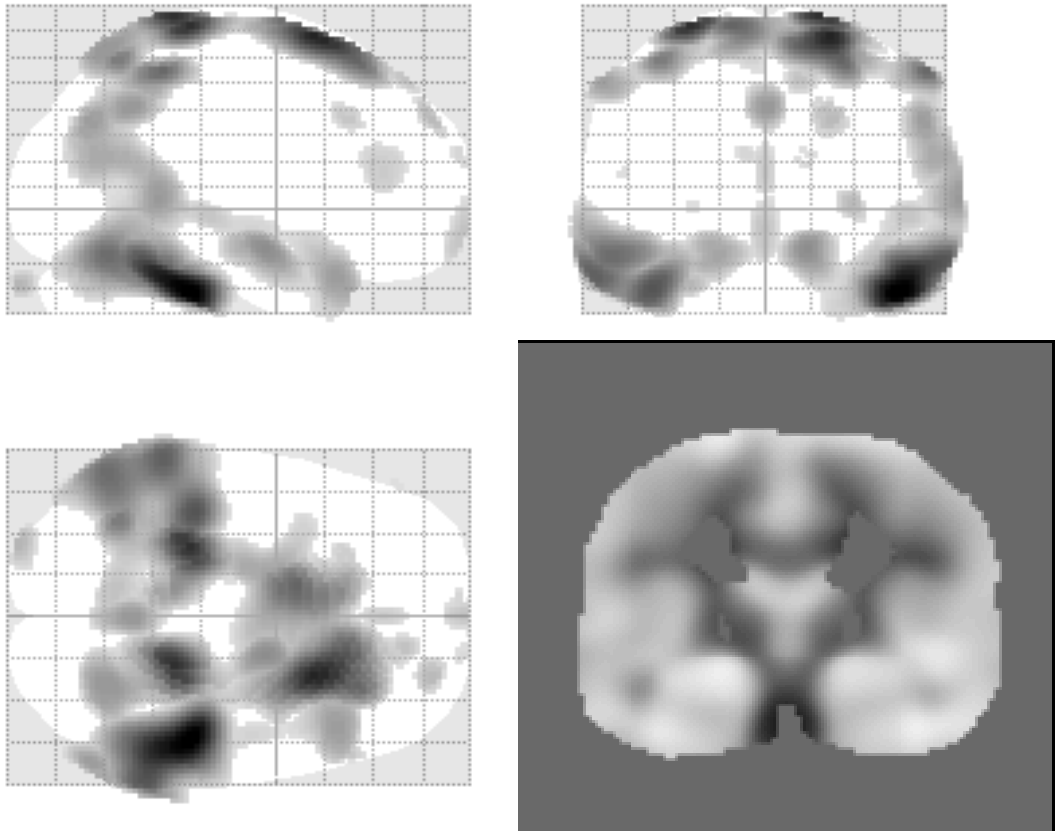
Smoothing

- Analysis will be most sensitive to effects matching shape and size of the kernel
- The data will be more Gaussian and closer to a continuous random field for larger kernels
  - Usually recommend >= 6mm
- Results will be rough and noise-like if too little smoothing is used
- Too much will lead to distributed, indistinct blobs (i.e. loss of spatial sensitivity)
  - Usually recommend <= 12mm
- Small subcortical nuclei (e.g. STN/SN) represent a special case where <<4mm may be warranted (see de Hollander *et al.,* 2015)

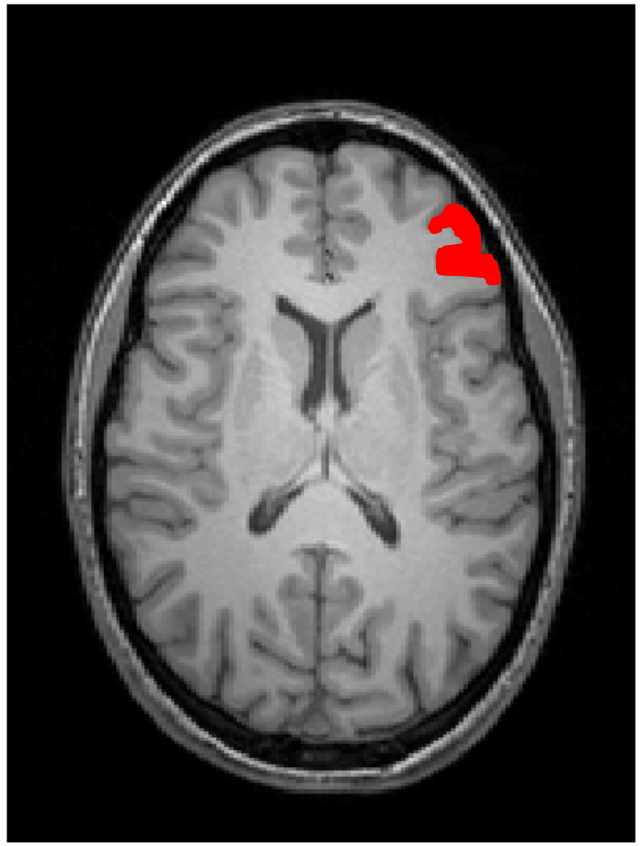
Smoothing

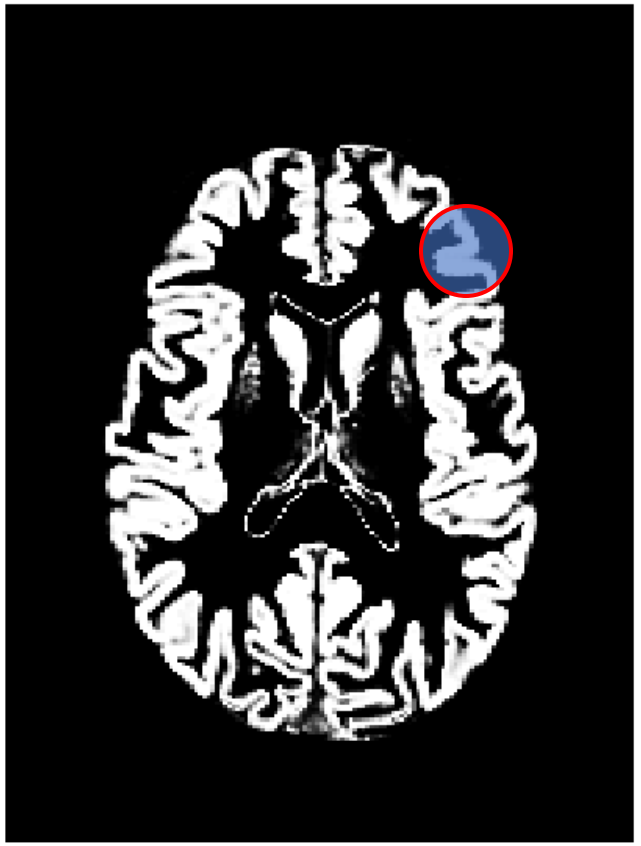
- The results below show two fairly extreme choices on the same data
  - 5mm on the left, and 16mm on the right





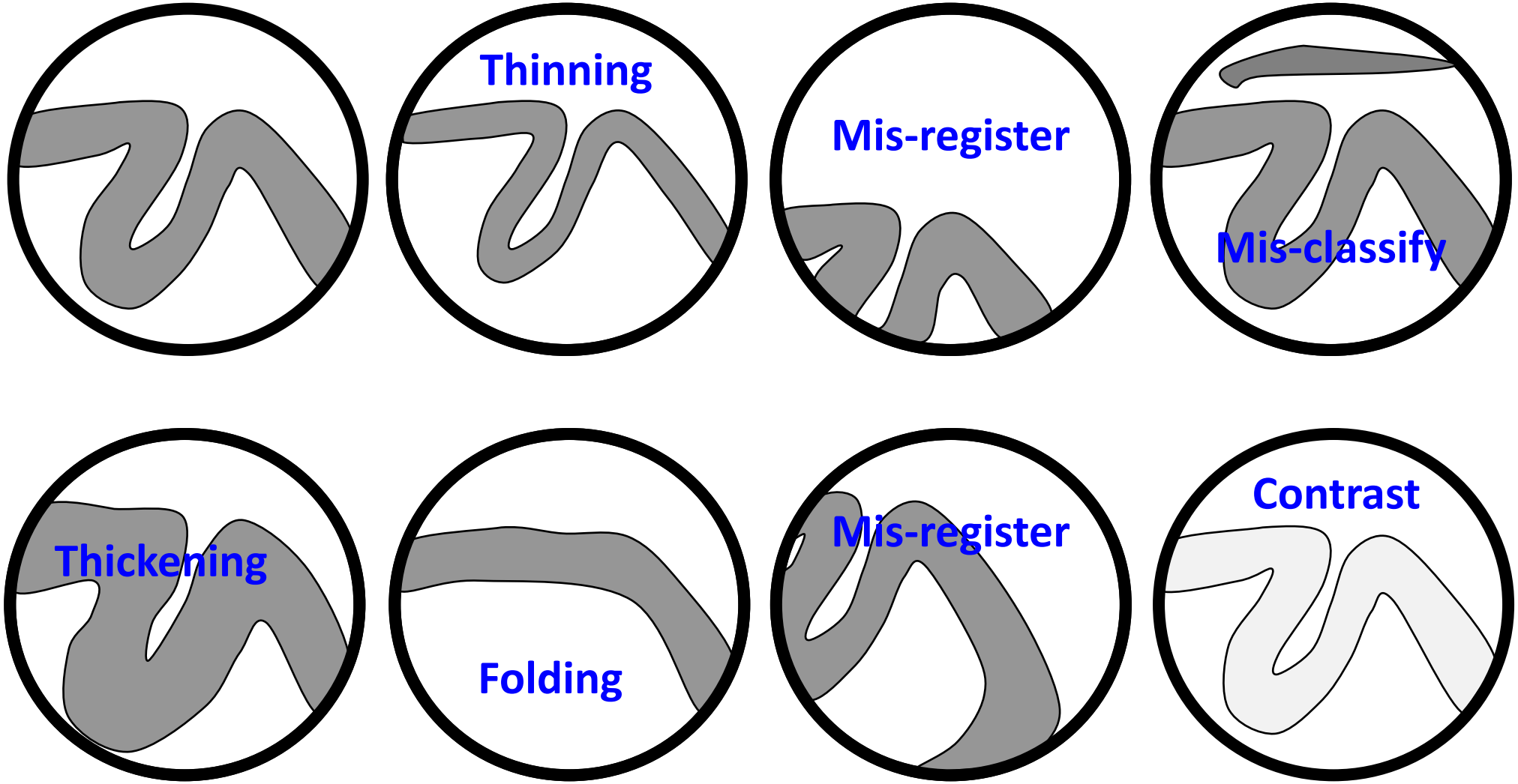
Smoothing is a *locally weighted ROI*





- VBM > ROI: no subjective (or arbitrary) boundaries
- VBM < ROI: harder to interpret blobs & characterise error

Interpreting findings

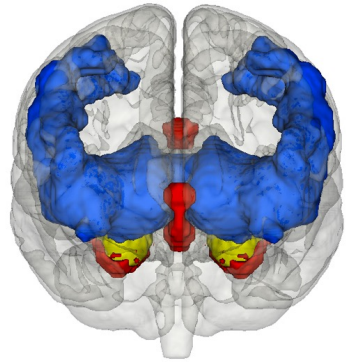


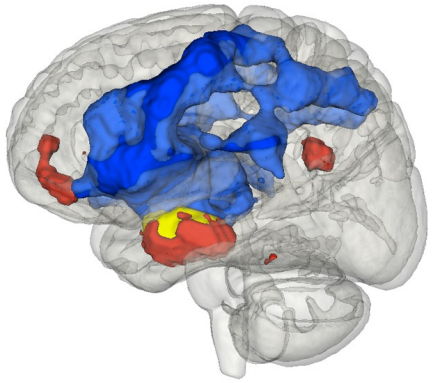
Adjustment for "*nuisance*" variables

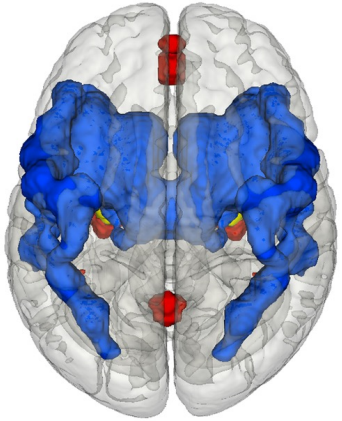
- Anything which might explain some variability in regional volumes of interest should be considered:
  - Total intracranial volume (TIV/ICV)
  - Age and biological sex are commonly used (i.e. brain size *biases* that may confound)
    - Consider age & age^2 to allow quadratic effects
  - Site or scanner if more than one
    (Note: model as factor, not covariate; multiple binary columns)

HINT: Define *a priori* regions of interest before analysis

- Before starting any analyses, you should try to identify brain regions where you expect to see structural changes:
  - Formal review of the literature (e.g., fMRI, VBM, functional networks, histopathology etc.,)
  - MRI-based meta-analyses tools
- Clearly defining *a priori* regions in advanced allows you to accept $P < 0.001$ uncorrected in those regions, if peak voxel $FWE < 0.05$ fails
- You can also conduct small volume analysis in these regions to try and boost statistical sensitivity.
- Consider pre-registering ROIs in advance to clearly demarcate hypothesis testing from exploratory analyses



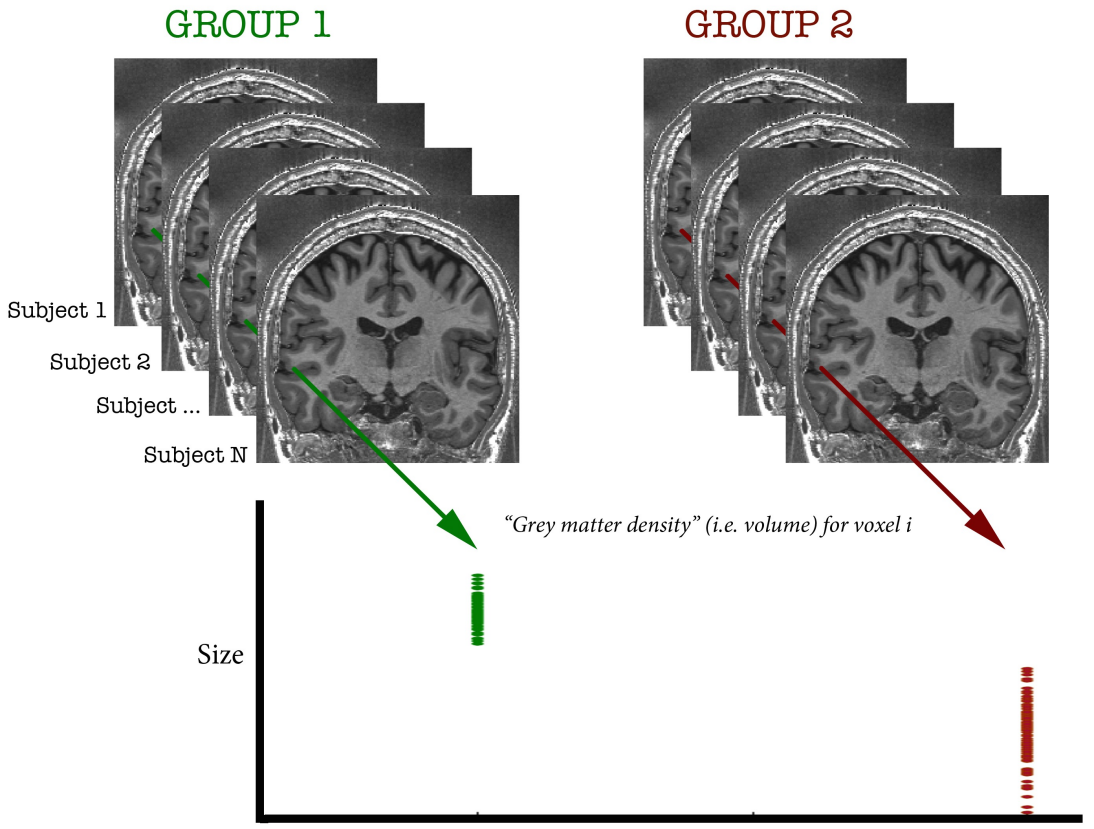




NORMALISATION
(warping)

NORMALISATION (warping)

- To analyse our data, we need to accurately align identical structures voxel wise
- To do this, we calculate the transformation to a "*Template space*"
- Calculating these transformations (warps) also encodes regional information about the amount of compression or expansion required compared to the average – Which are used for VBM



Spatial normalisation with Shoot

- VBM is crucially dependent on registration performance
  - The limited flexibility of DCT *normalisation* has been criticised
  - Inverse transformations are useful, but not always well-defined
  - MNI/ICBM templates/priors are not universally representative

- The Shoot (& DARTEL) toolbox combines several methodological advances to address these limitations
  - Voxel-wise DF, integrated flows, group-wise registration of GM & WM tissue segments to their (iteratively evolving) average

Two diffeomorphic approaches in SPM

“Dartel Tools” (SPM 8-12)

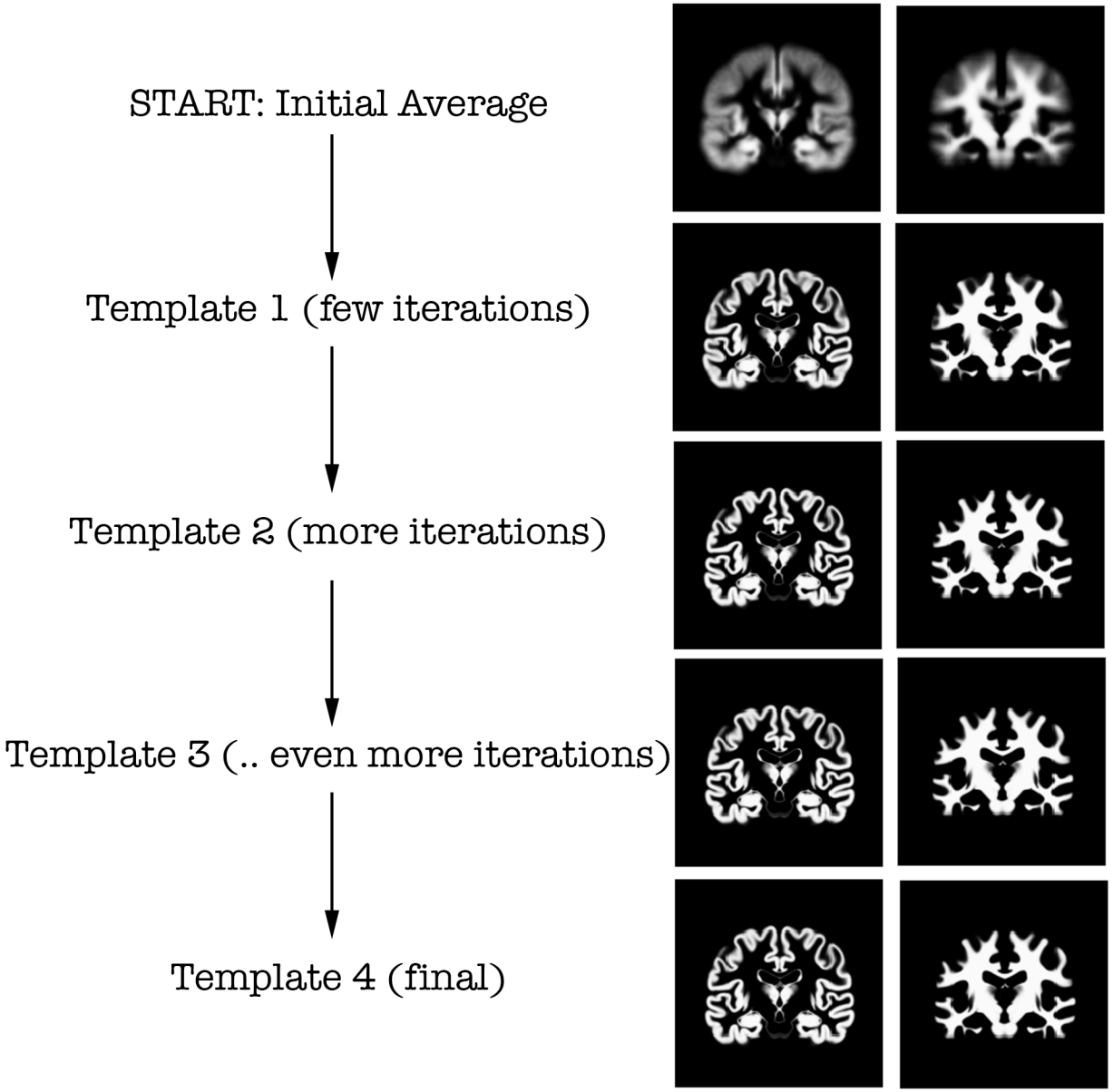
- Uses the same small deformation composed multiple times.
- Faster than Geodesic Shooting.
- Gives similar deformations to Geodesic Shooting.
- Currently more additional utilities.

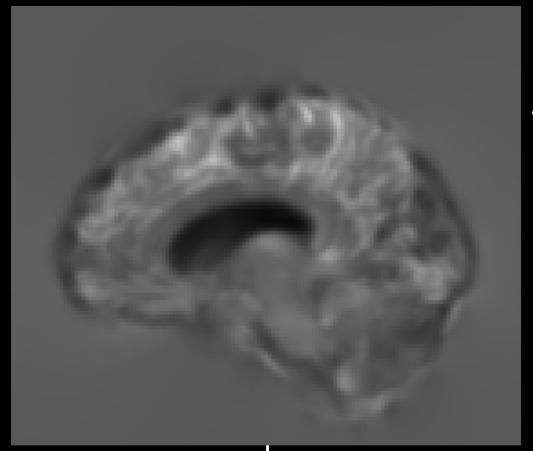
Geodesic Shooting (SPM 12 onwards)

- Uses the optimal series of small deformations, which are composed together.
- More mathematically correct than Dartel.
- Gives nicer maps of volume change than Dartel.
- Growing number of utilities
- Recommended to use this instead of Dartel

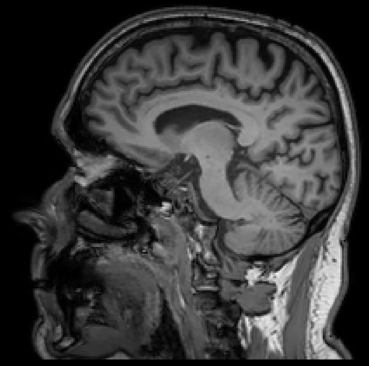
Group-wise alignment in shoot

- Template implicitly generated from data in study.
- Findings less biased by choice of template.

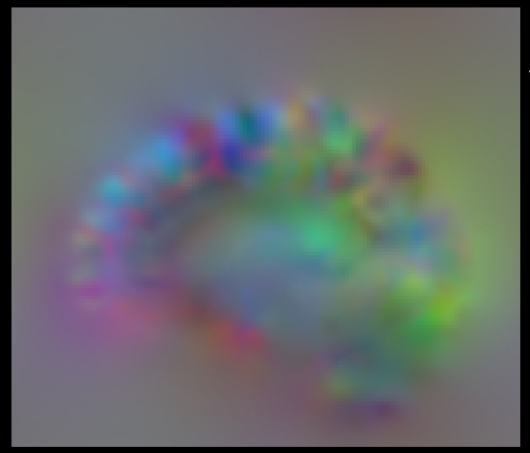




Jacobian determinant
j[filename].nii
voxel wise volumetric information

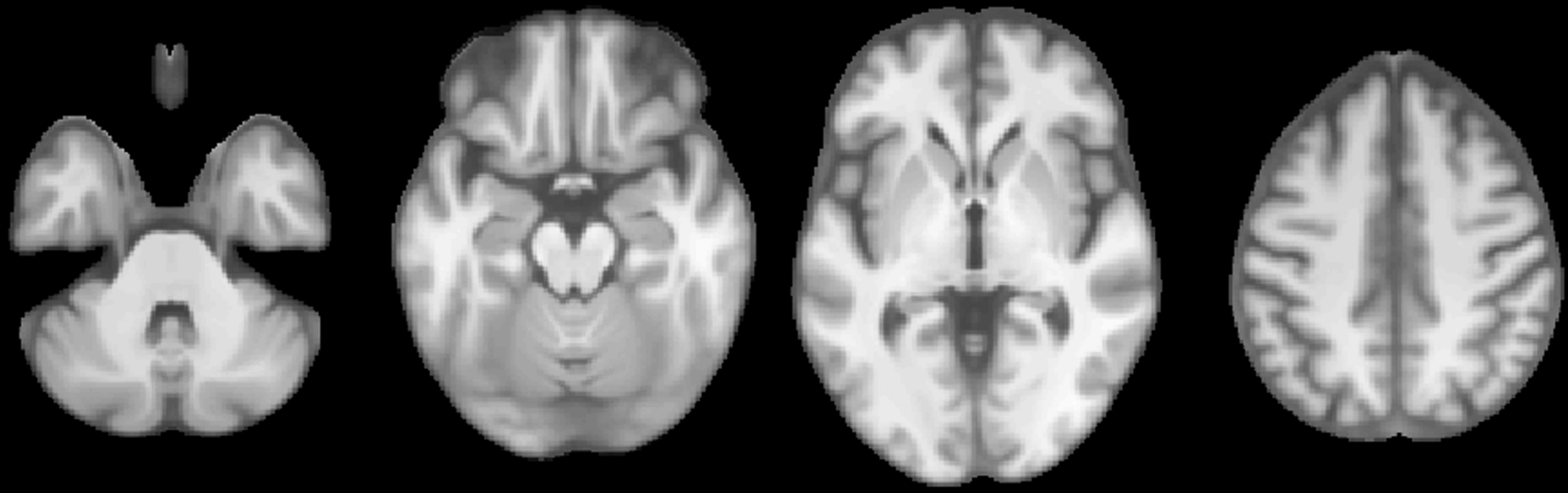


Velocity field
v[filename].nii
4D file



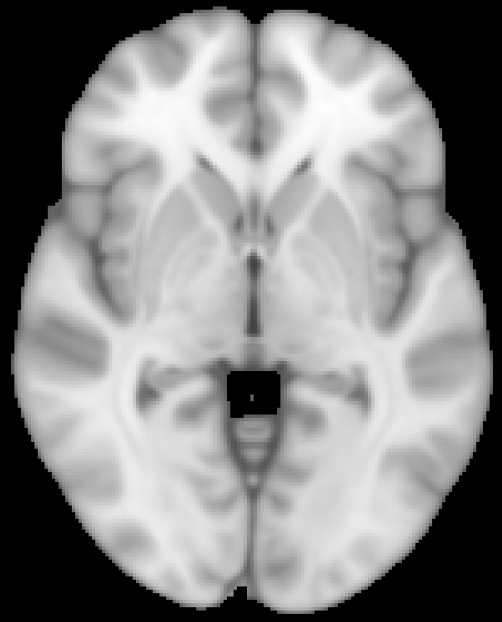
Deformation field
y[filename].nii
4D file

Shoot Group Average Template
N = 5632

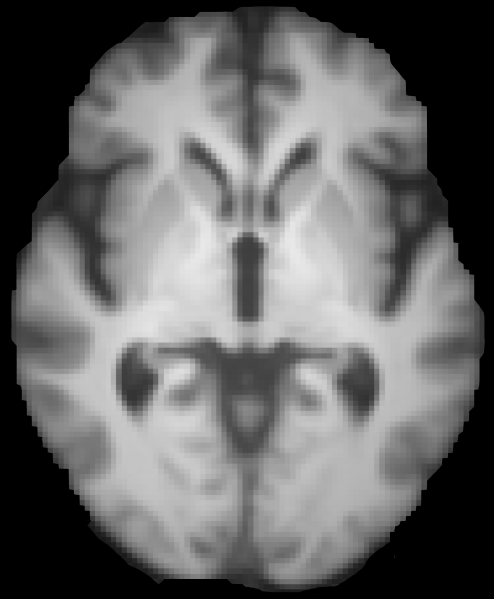


Shoot Group Average Template
N = 5632

WHICH TEMPLATE SPACE?



MNI

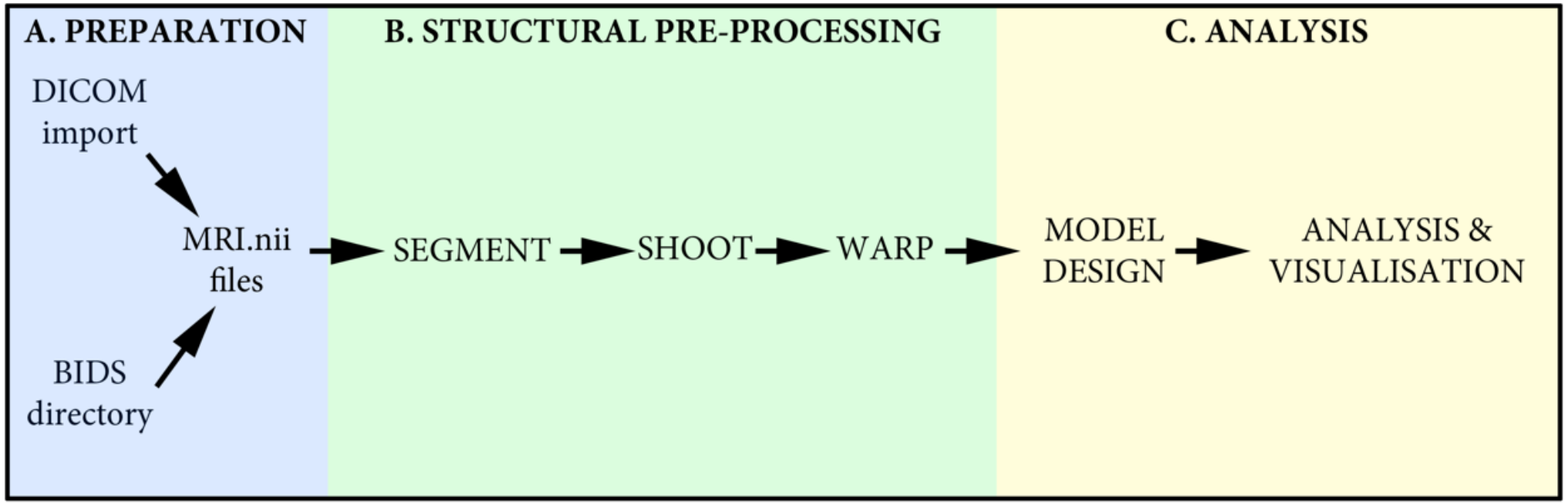


ADNI
(Alzheimer's)

PPMI
(Parkinson's)

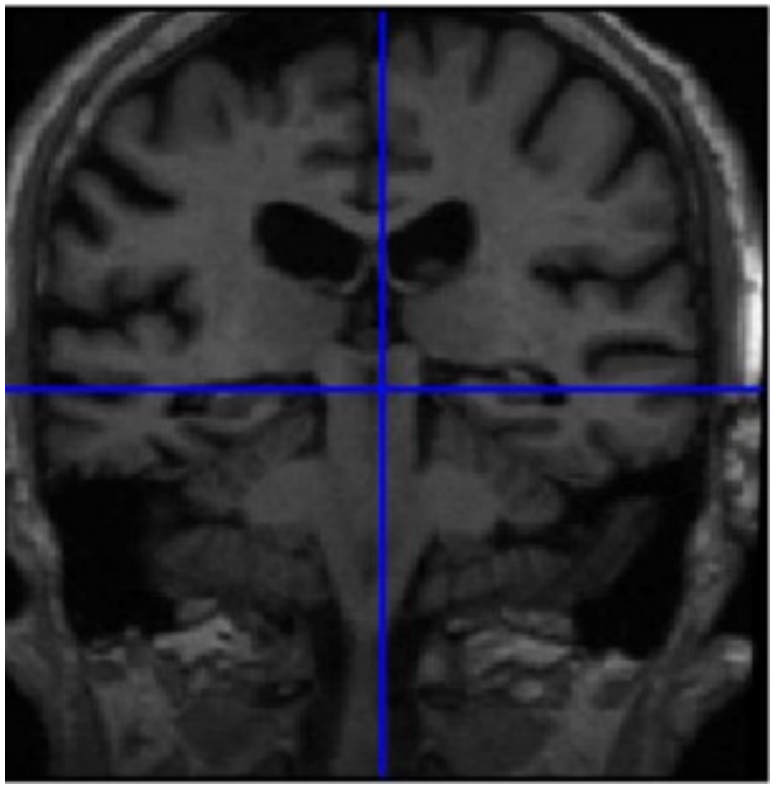
- There are lots of examples of "*Template*" or "*Group average*" spaces e.g. MNI
- However, each space represents the population from which it was created, which may bias your results (e.g. MNI tends to be larger than most)
- Creating specific "*Group average space*" for your study population will avoid this.
- You can always transform your coordinates (i.e. peak results) to MNI for reporting if needed (e.g. for meta-analysis).

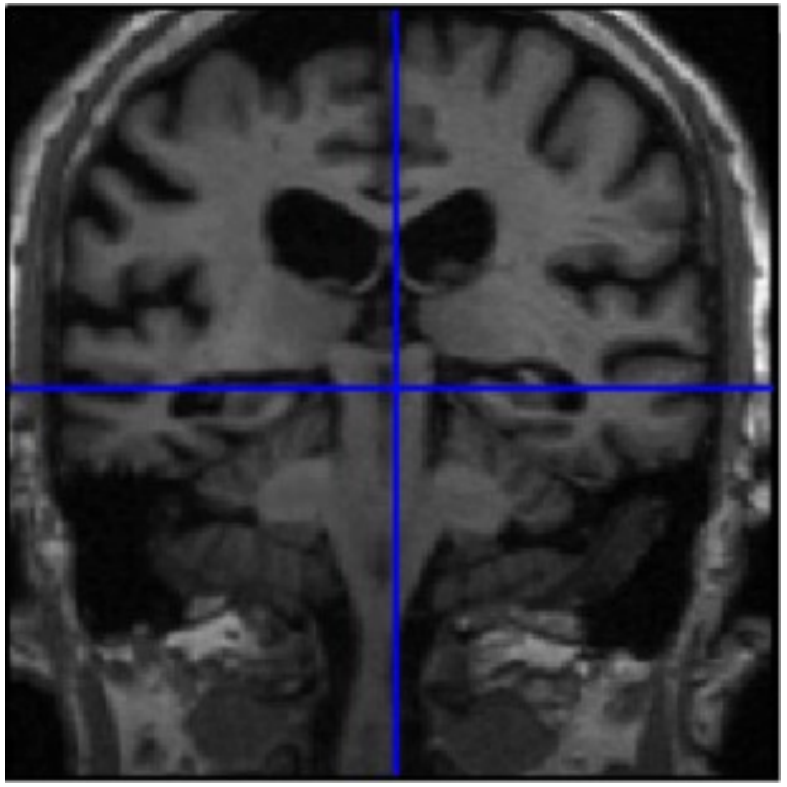
Summary

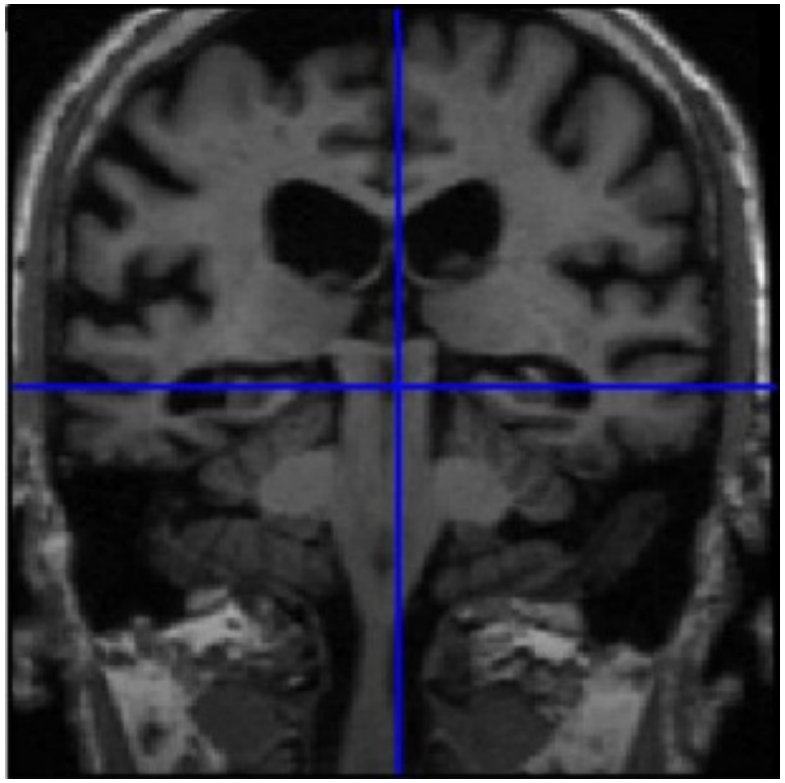


- VBM performs voxel-wise statistical analysis on smoothed (modulated) normalised tissue segments
- SPM performs segmentation and spatial normalisation in a unified generative model
- The SHOOT (or DARTEL) toolboxes improves spatial normalisation for VBM (and probably also fMRI...)
- More specific details in the demo and practical sessions

LONGITUDINAL ANALYSIS







Longitudinal VBM – motivation

- Development, growth, plasticity, aging, degeneration, and treatment-response are inherently longitudinal

- Serial data have major advantages over multiple cross-sectional samples at different stages

- Increasing power
  - Subtlety of change over time vs. inter-individual variation

- Reducing confounds
  - Separating within-subject changes from cohort effects
  - Demonstrating causality with interventions

Longitudinal VBM – asymmetry & bias

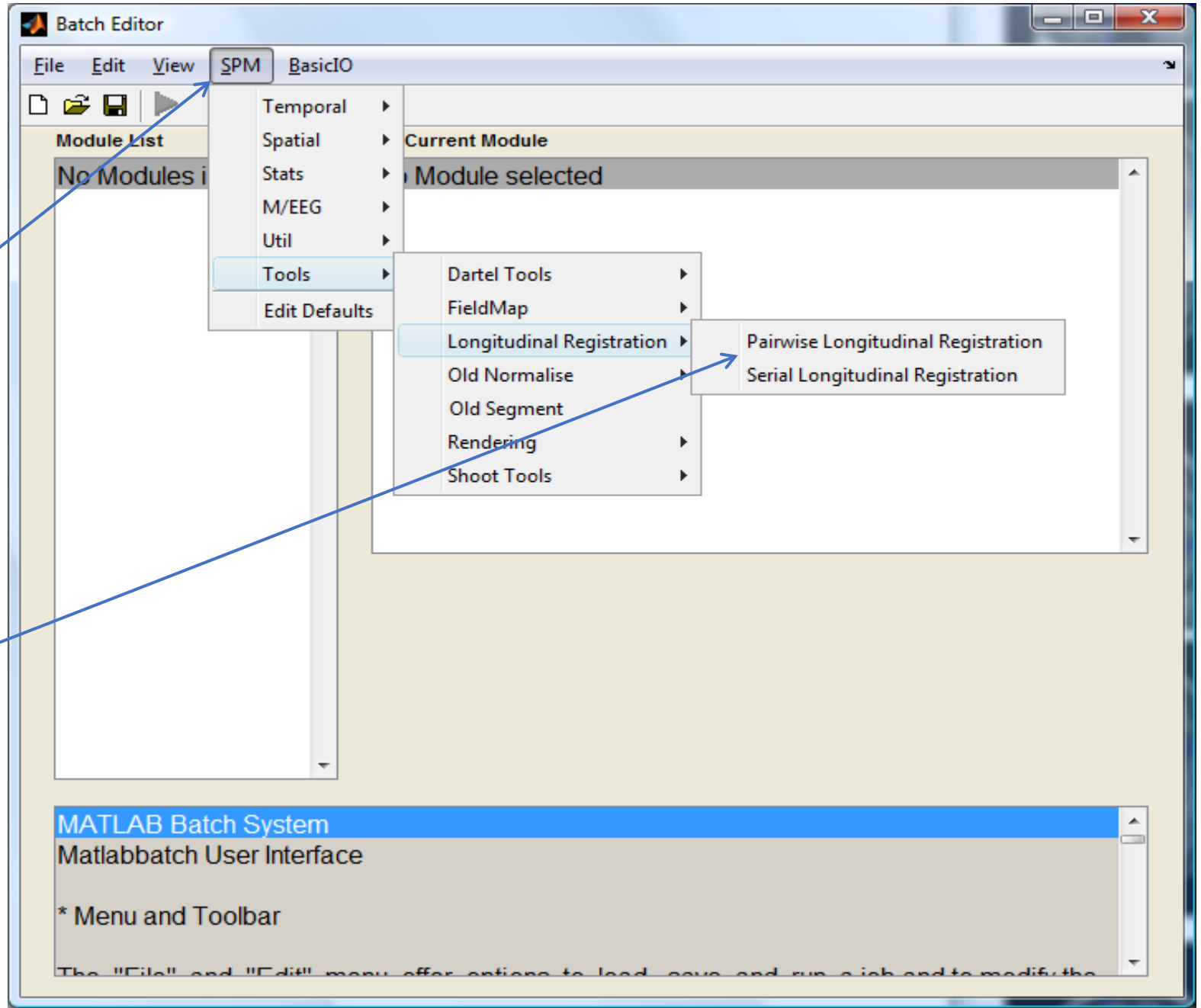
- Within-subject image processing often treats one time-point differently from the others
  - Later scans registered (rigidly or non-rigidly) to baseline

- Asymmetry can introduce methodological biases
  - E.g. only baseline has no registration interpolation error
  - Baseline seg. more accurate than propagated segs.
  - Change in later intervals more regularised/constrained

Longitudinal VBM – registration in SPM12

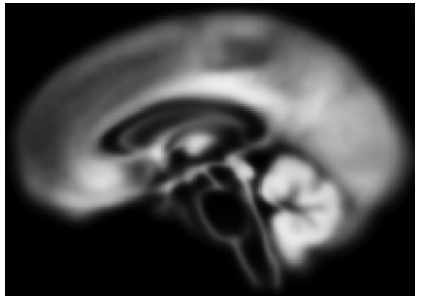
No Longitudinal button, but found in Batch menu, like Dartel, etc.

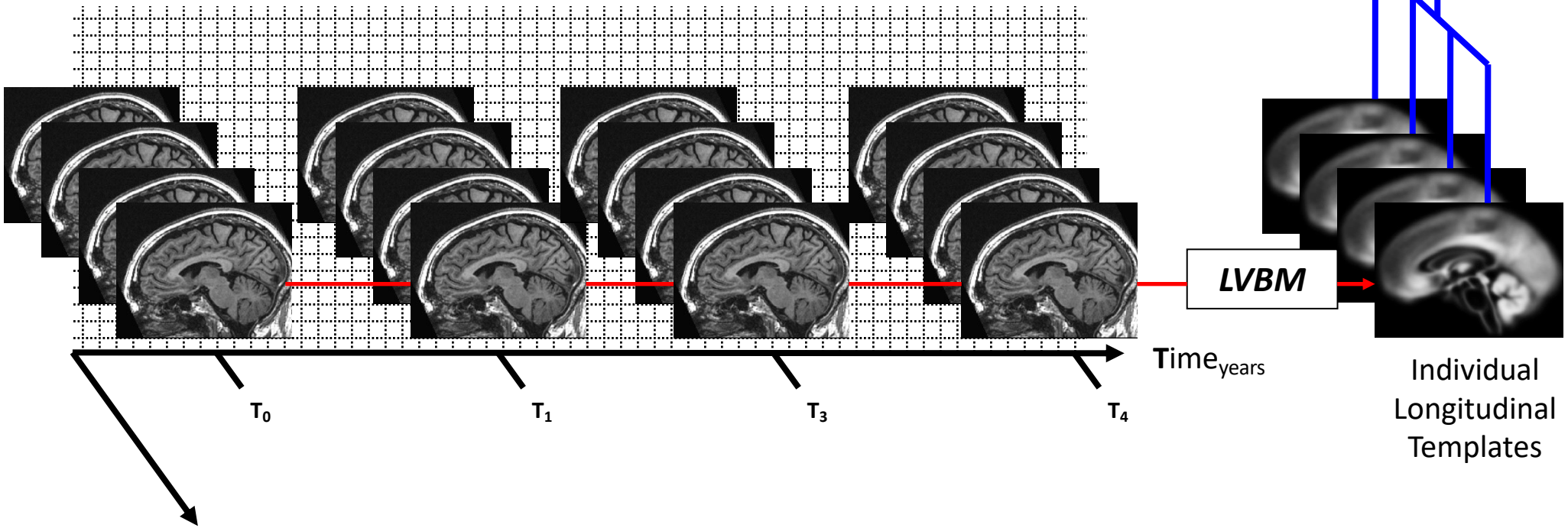
Choice of paired or general serial.
No difference in model, but easier specification and results for pairs.



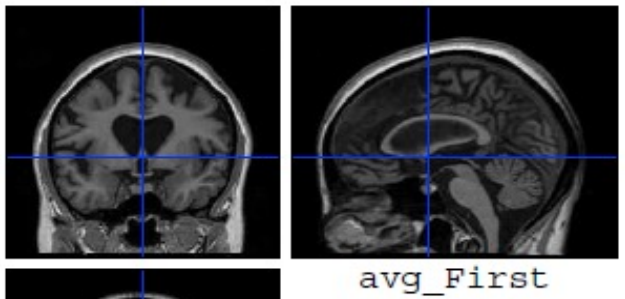
Longitudinal Analysis Model

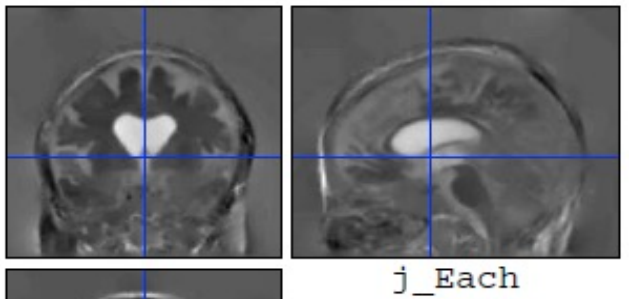
- Each individual is warped to their average
- Each average template will be warped to a total group average
- Each individual time-point will produce divergence & jacobian image
- These can be used to calculate single "rate" maps
- By repeating the segment-warp steps on the average images, VBQ-type analysis can be performed on the warped rate maps

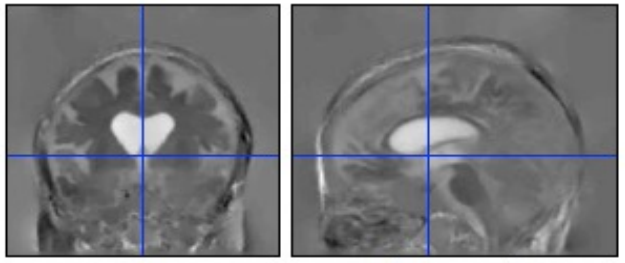


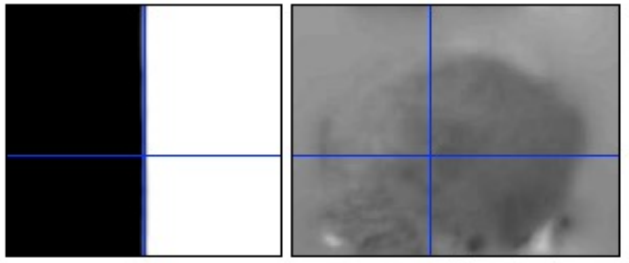


- Output/results
  - Average image
  - Jacobians or divergences
  - Deformations
- Next steps
  - Segment avg
  - Run Shoot
  - Warp e.g. dv to standard space
  - SPM stats on dv (TBM)
  - Or combine with seg of avg (VBM)



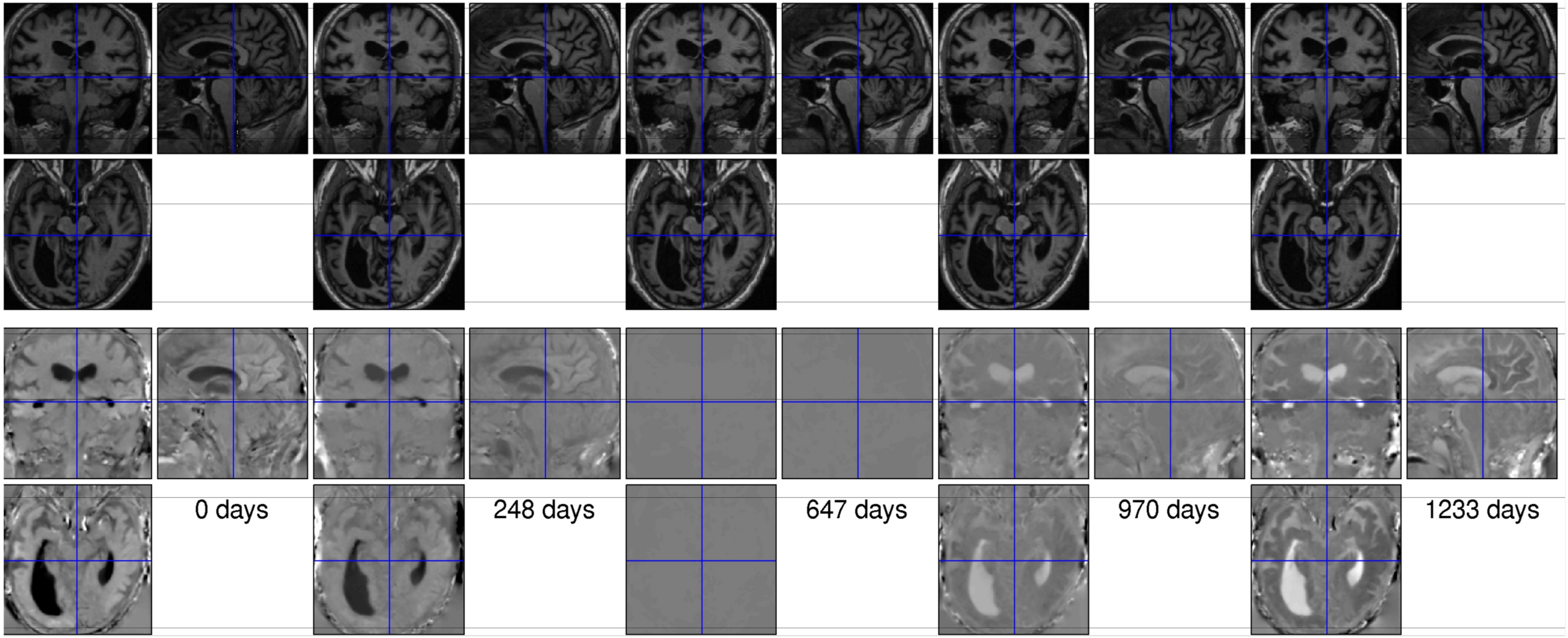






Oasis Data

66 year old male, with MCI (MMSE=19, CDR=1).



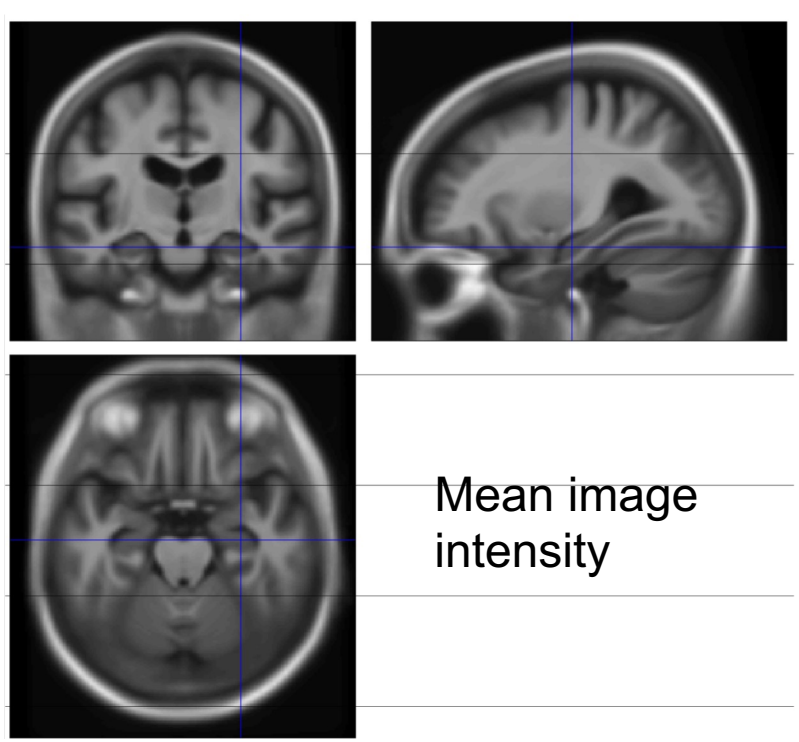
Oasis Data

Data from first 82 subjects (OAS2 0001 to OAS2 0099).

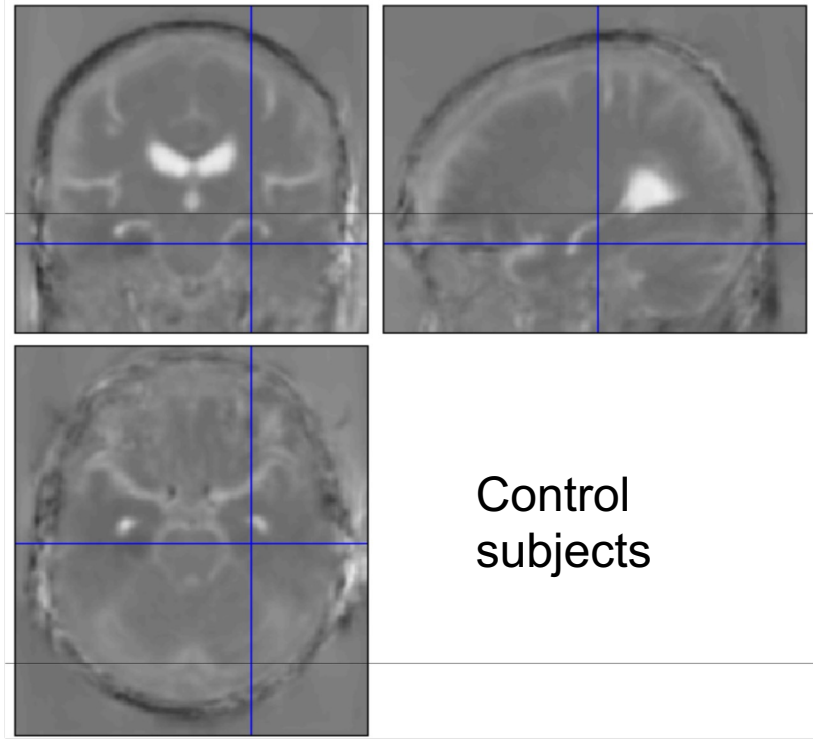
Computed average expansion/contraction rates for each subject.

Warped all data to common anatomical space.

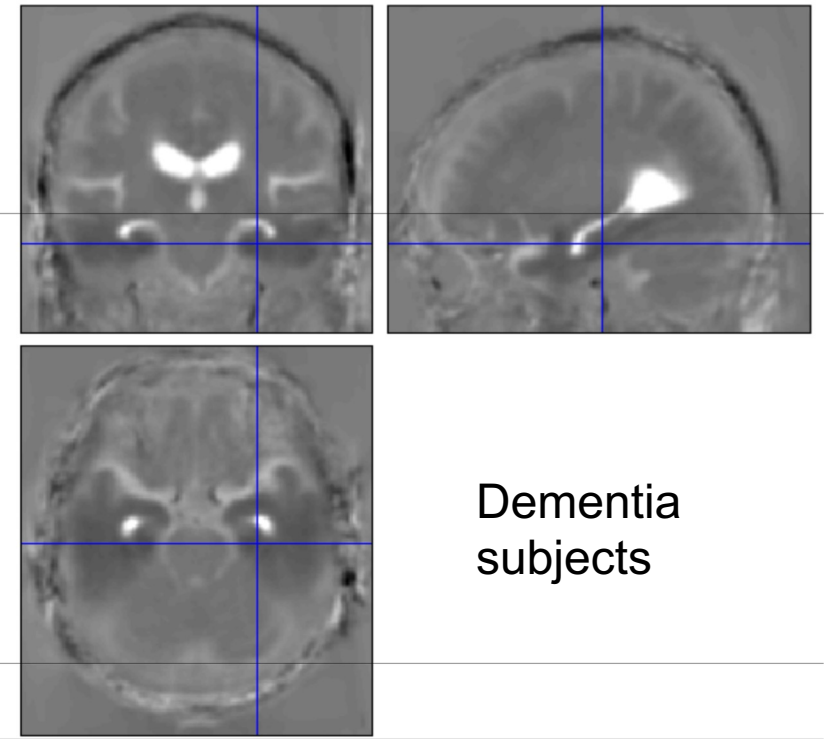
Generated averages.



Mean image intensity



Control subjects

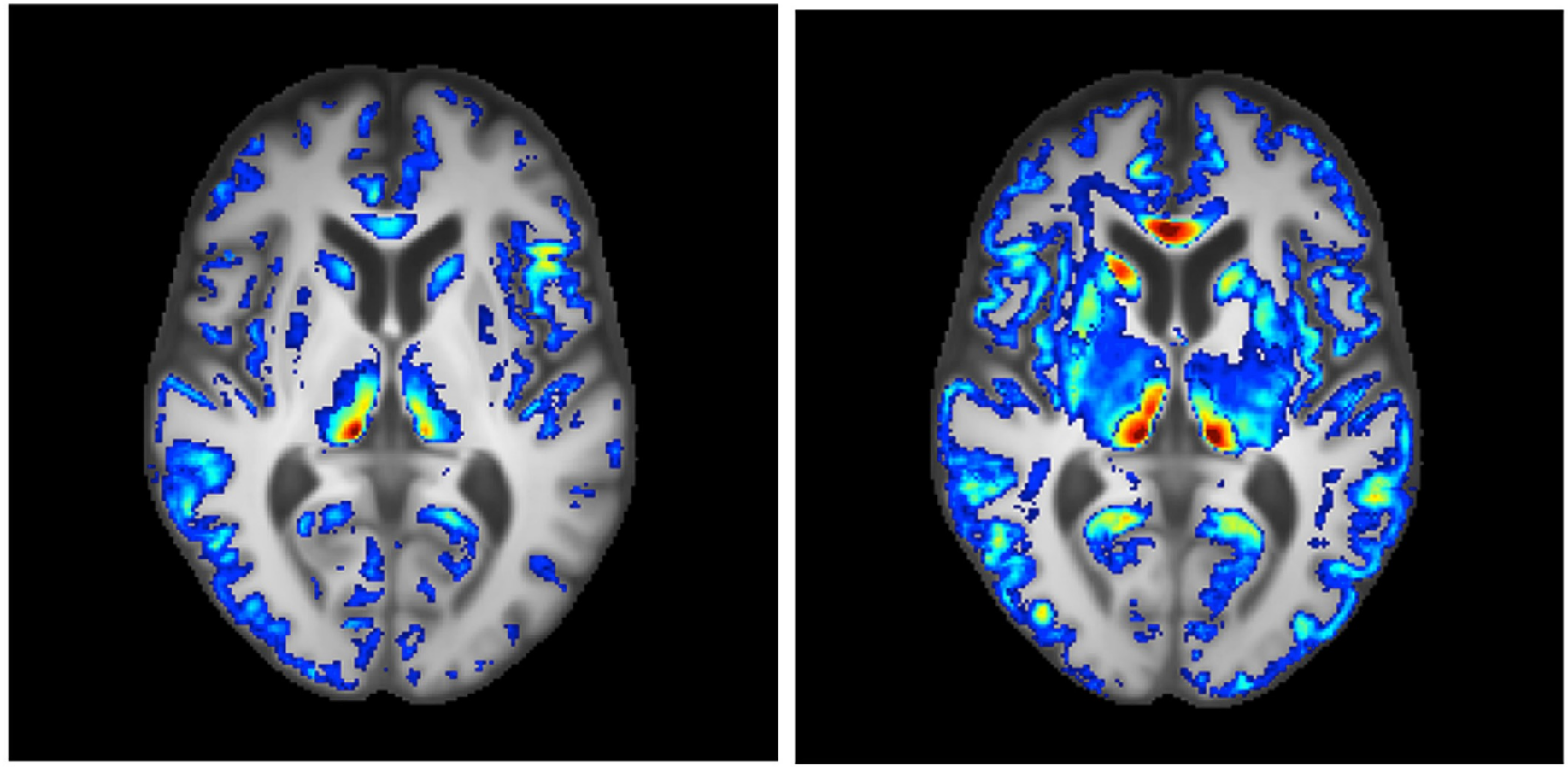


Dementia subjects

RATE OF BRAIN TISSUE LOSS

NORMAL AGEING

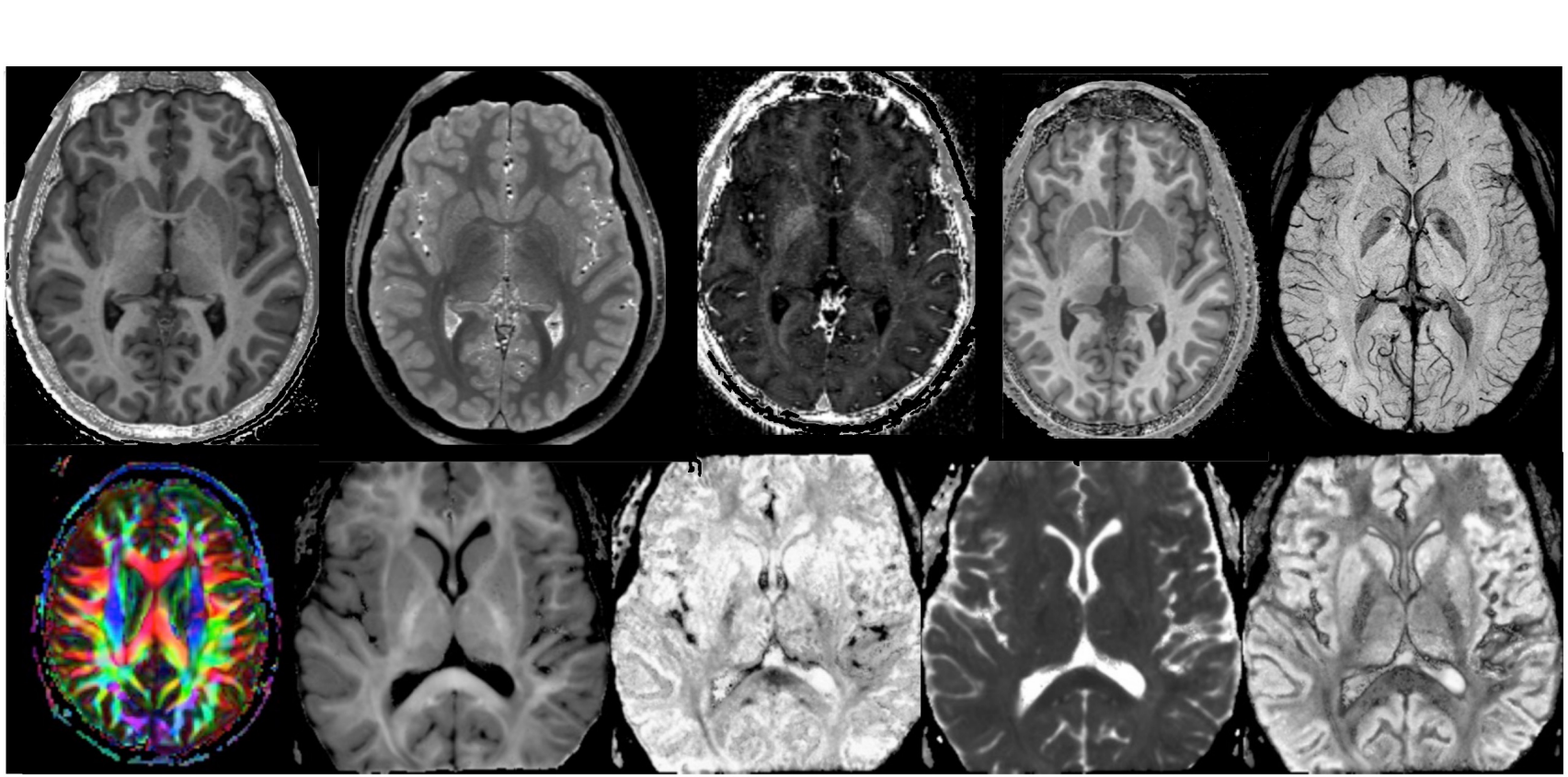
PARKINSON'S DISEASE

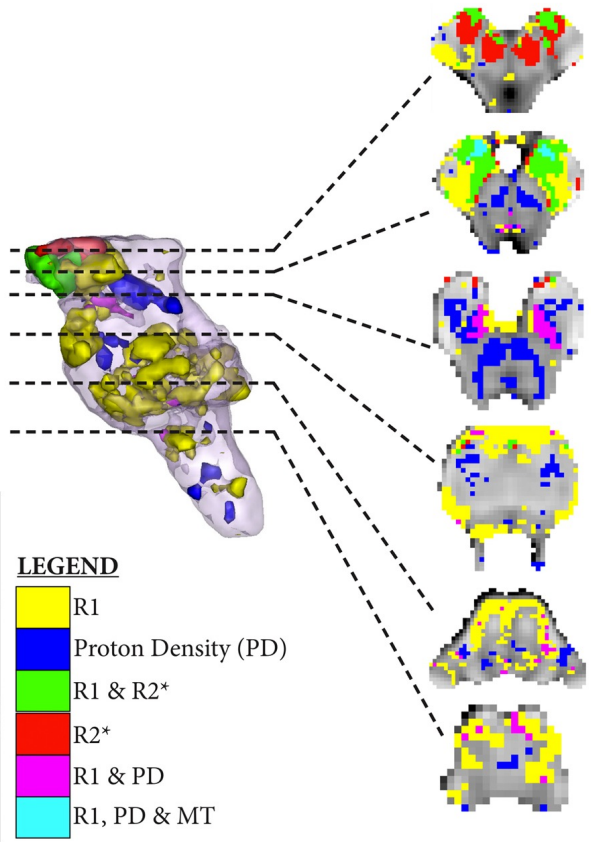


0.005 0.020 0.035

AUGMENTING VBM:

Quantitative MRI &
Voxel Based Quantification



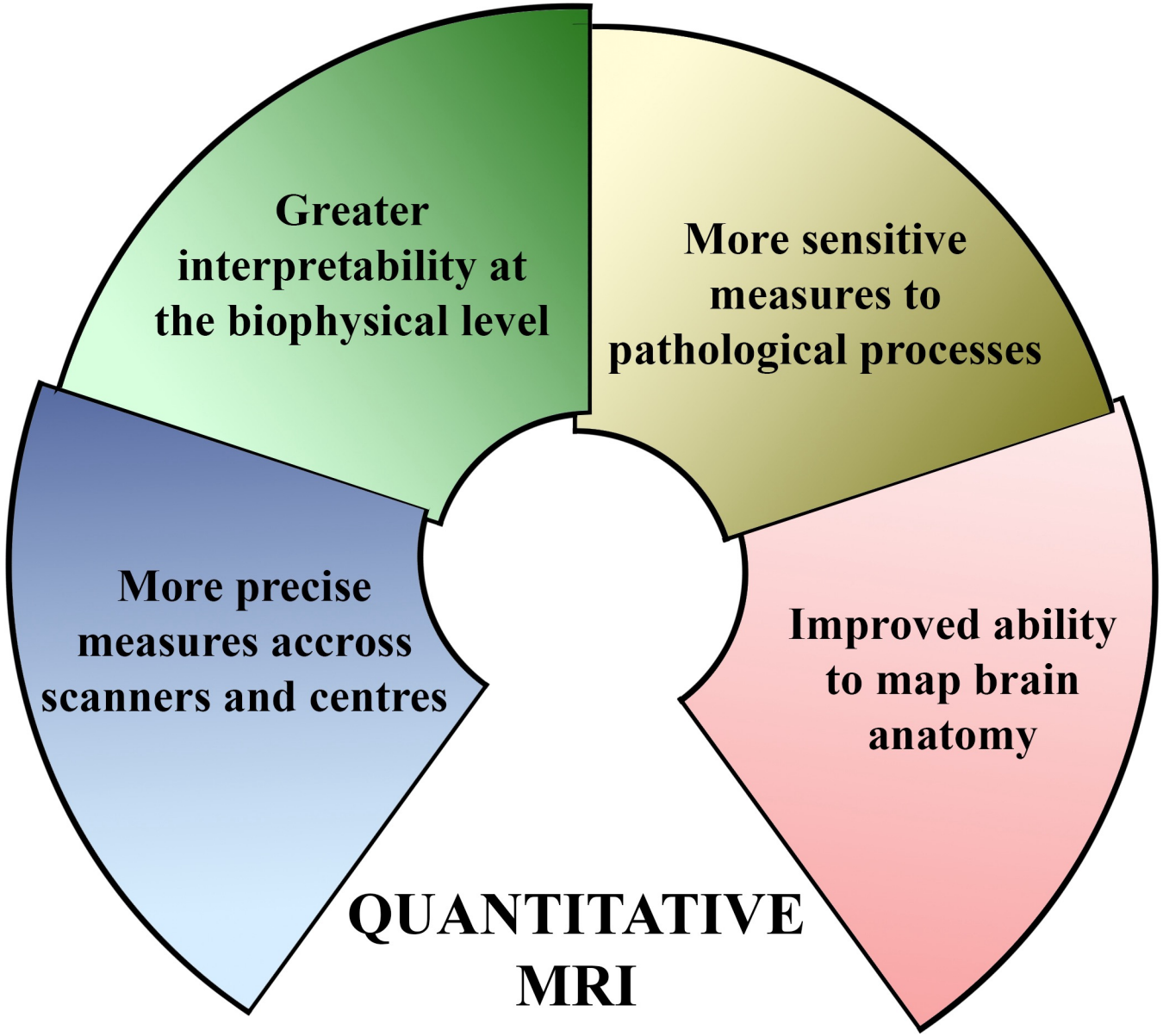


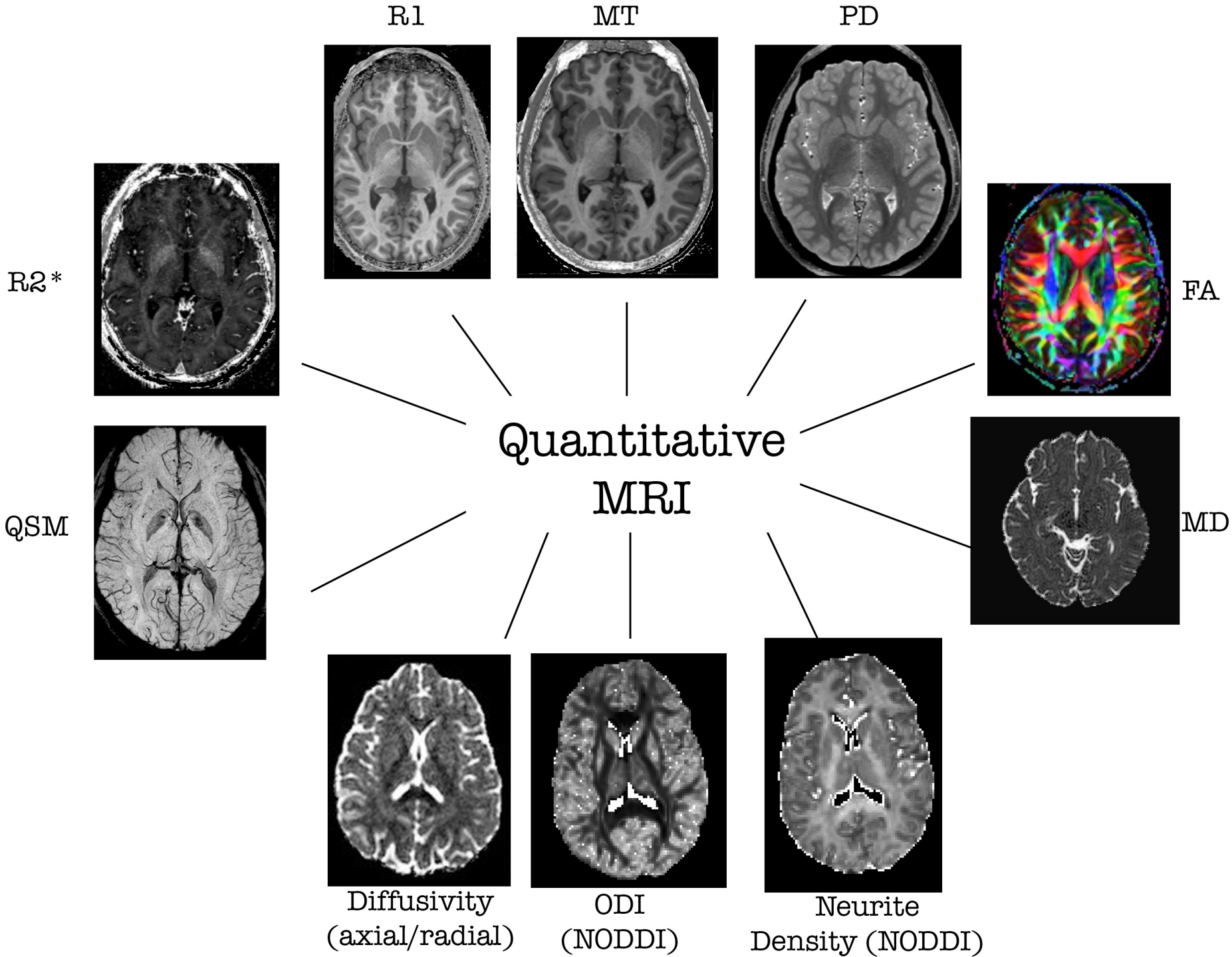
What is quantitative MRI?

- Standard MRI acquisitions have signal intensities that depend on many factors (both biological and scanner related) – Provide pictures of the brain rather than accurate voxel wise measurements

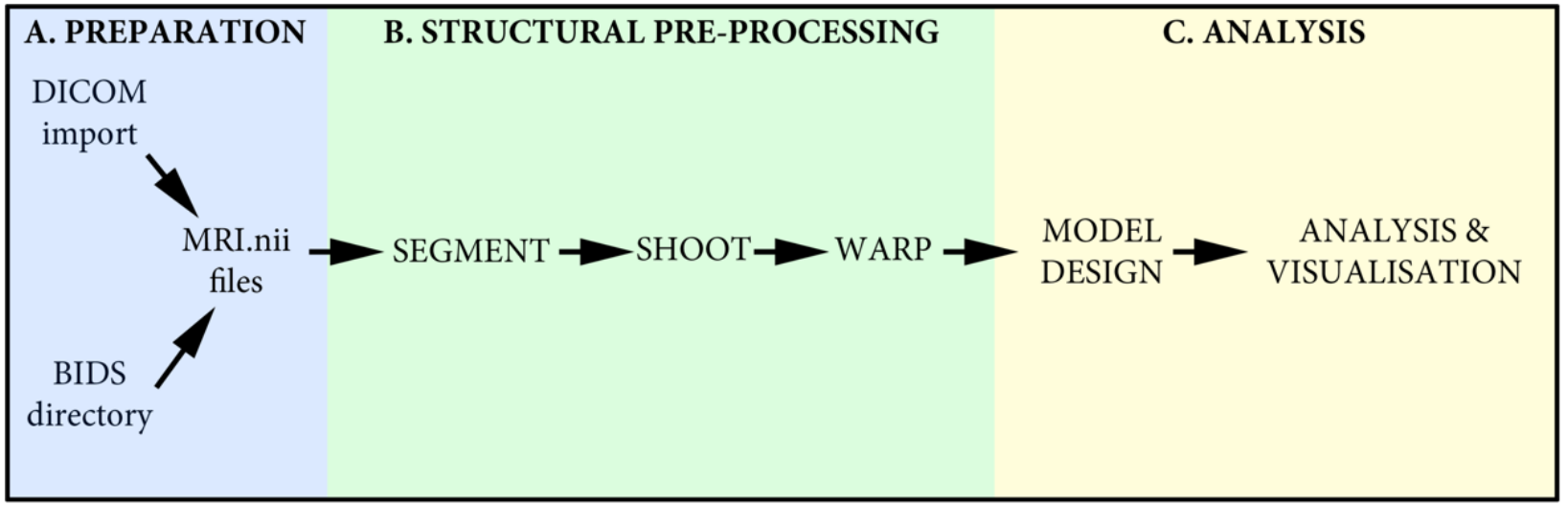
- There are a number of dedicated MRI acquistions that allow specific tissue properties to be quantified aka. quantitative MRI (qMRI)

- In addition to these, there are derived parameter maps that can also be treated as quantitative maps e.g. Cortical thickness, longitudinal rate maps/divergence maps


Greater interpretability at the biophysical level
More sensitive measures to pathological processes
More precise measures accross scanners and centres
Improved ability to map brain anatomy
QUANTITATIVE MRI


R1
MT
PD
R2*
FA
Quantitative
MRI
QSM
MD
Diffusivity
(axial/radial)
ODI
(NODDI)
Neurite
Density (NODDI)

Voxel based Quantification



- This can be considered an extension of VBM, designed to allow quantitative MRI to be analysed in a voxel-wise manner using the SPM framework
- All of the VBM pre-processing steps are identical, the only difference comes in creating "*weighted averages*" when applying the spatial smoothing (to limit partial volume effects)
- Can be implemented directly or using an SPM extension in the "The hMRI toolbox"
- Analysis of these quantitative weighted averages then uses standard SPM approach

wellcome centre human neuroimaging

UCL

Combining the advances in anatomical mapping with the biophysical insights provided by qMRI measures allows us to go beyond VBM and understand the basis for structural brain changes

TBM

MT

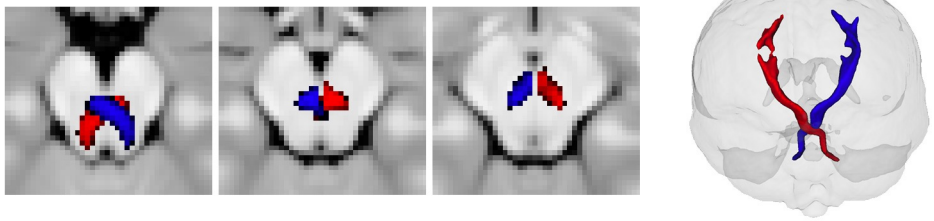
BRAINSTEM AGEING

Focal regions of volume loss

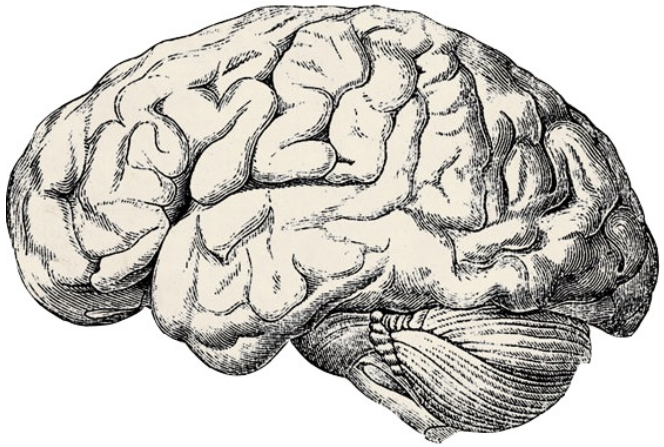
Focal regions of reduced myelin density

(also associated with increased proton density)

Location[↓Volume + ↓Myelin + ↑Free water]
= Cerebellothalamic tract degeneration



CONCLUSION



Introduced VBM & Potential uses

Tissue Segmentation

Statistics

VBM Subtleties

Normalisation via SHOOT

Templates (e.g., MNI, population average etc.,)

Longitudinal Toolbox

Quantitative MRI and voxel based quantification

There is a lot more(!): *In vivo histology, Cortical thickness, lesion analysis, structural covariance, combining with multivariate machine learning techniques.. etc.,*

BASIC VBM HOW TO GUIDE: http://qmaplab.com/resources/how-to-guides