Zurich SPM Course 2016

Voxel-Based Morphometry

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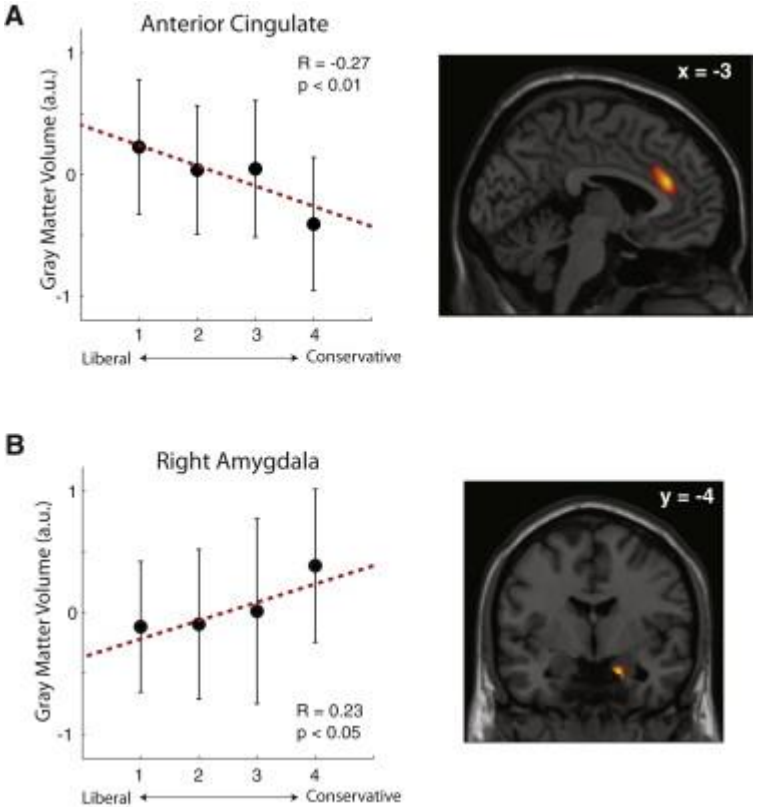
With thanks to John Ashburner
and the FIL Methods Group

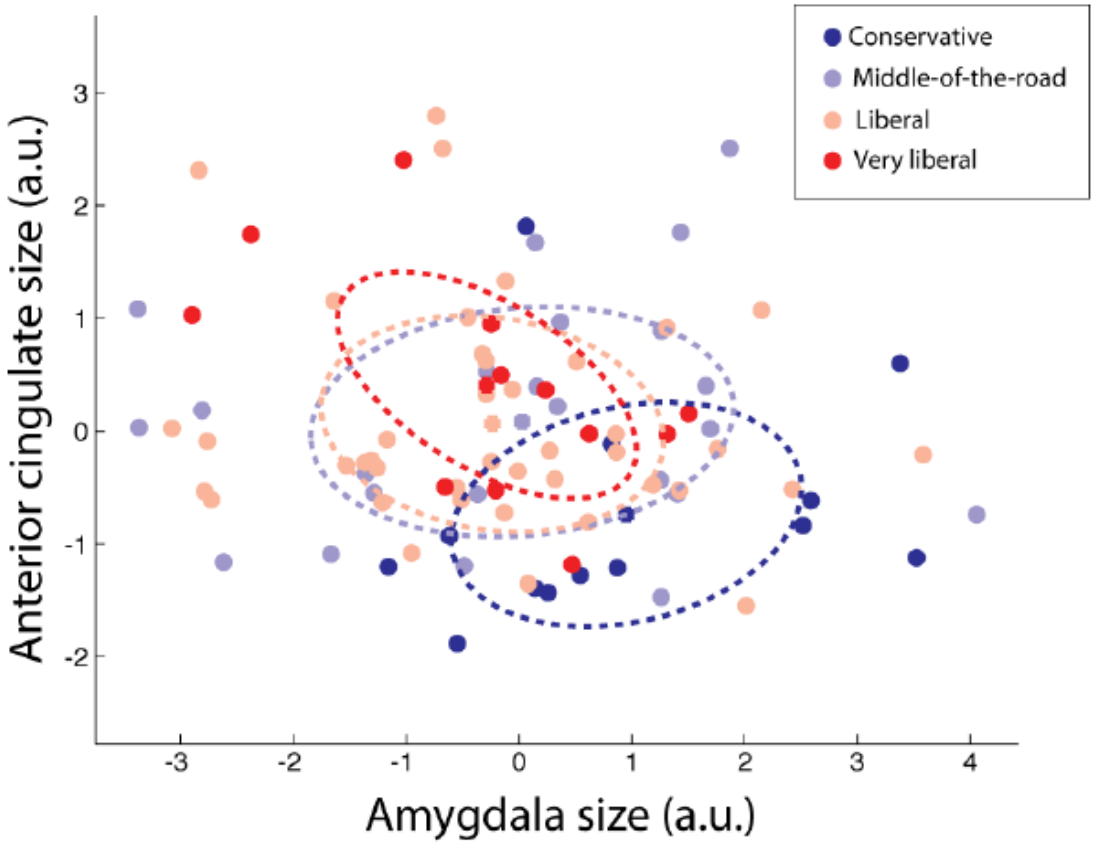
Examples applications of VBM

- Many scientifically or clinically interesting questions might relate to the local volume of regions of the brain
- For example, whether (and where) local patterns of brain morphometry help to:
  - Distinguish groups (demographics, diseases, genetics, …)
  - Explain the changes seen in development and aging
  - Understand plasticity, e.g. when learning new skills
  - Find structural correlates (test scores, traits, …)
  - Identify where an individual is outside a normal range
  - Explain (or not) individual/group differences in fMRI

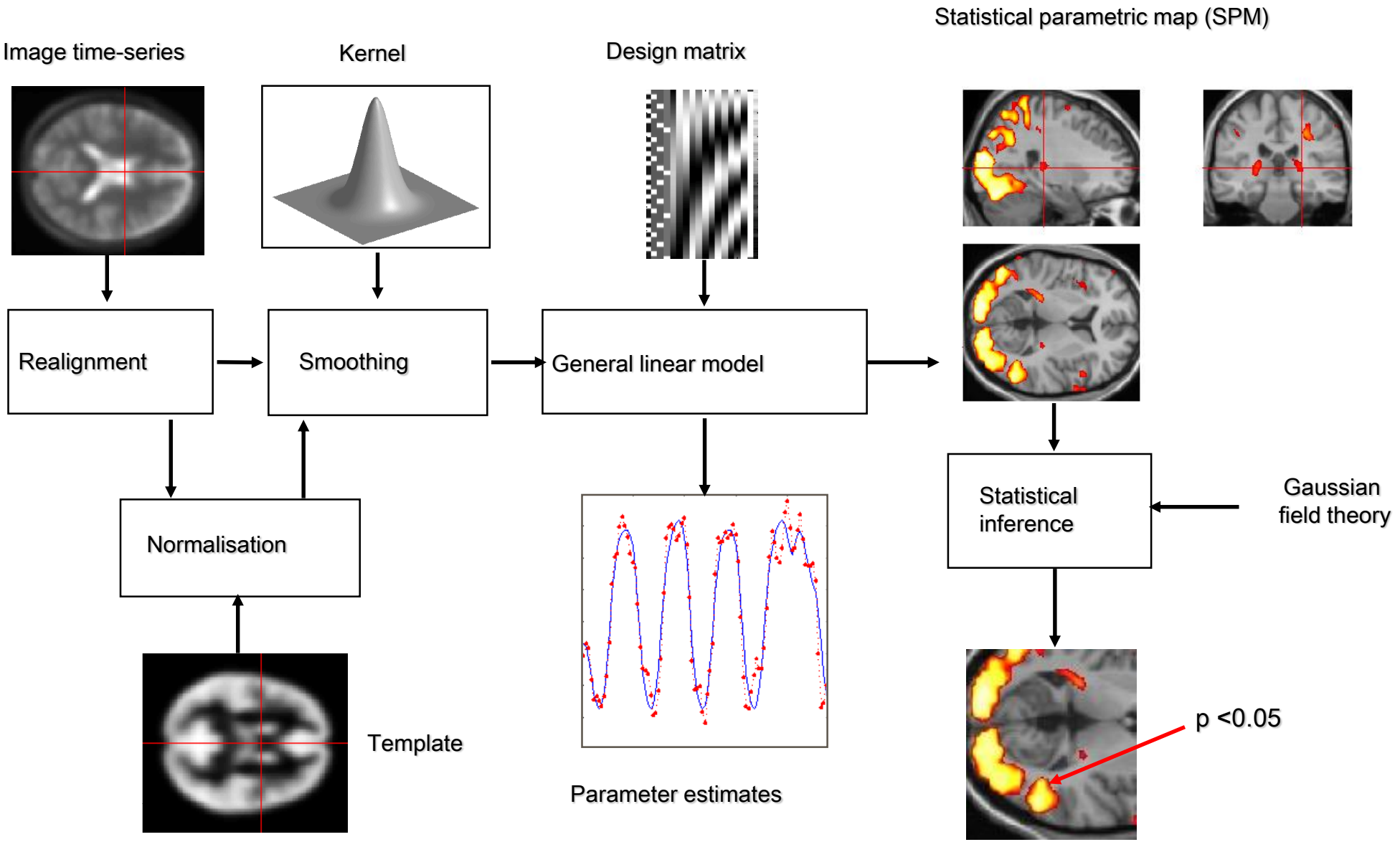
VBM and political orientation

- R. Kanai, T. Feilden, C. Firth, G. Rees
- *Political Orientations Are Correlated with Brain Structure in Young Adults*. DOI:10.1016/j.cub.2011.03.017





Overview of SPM



Tissue segmentation for VBM

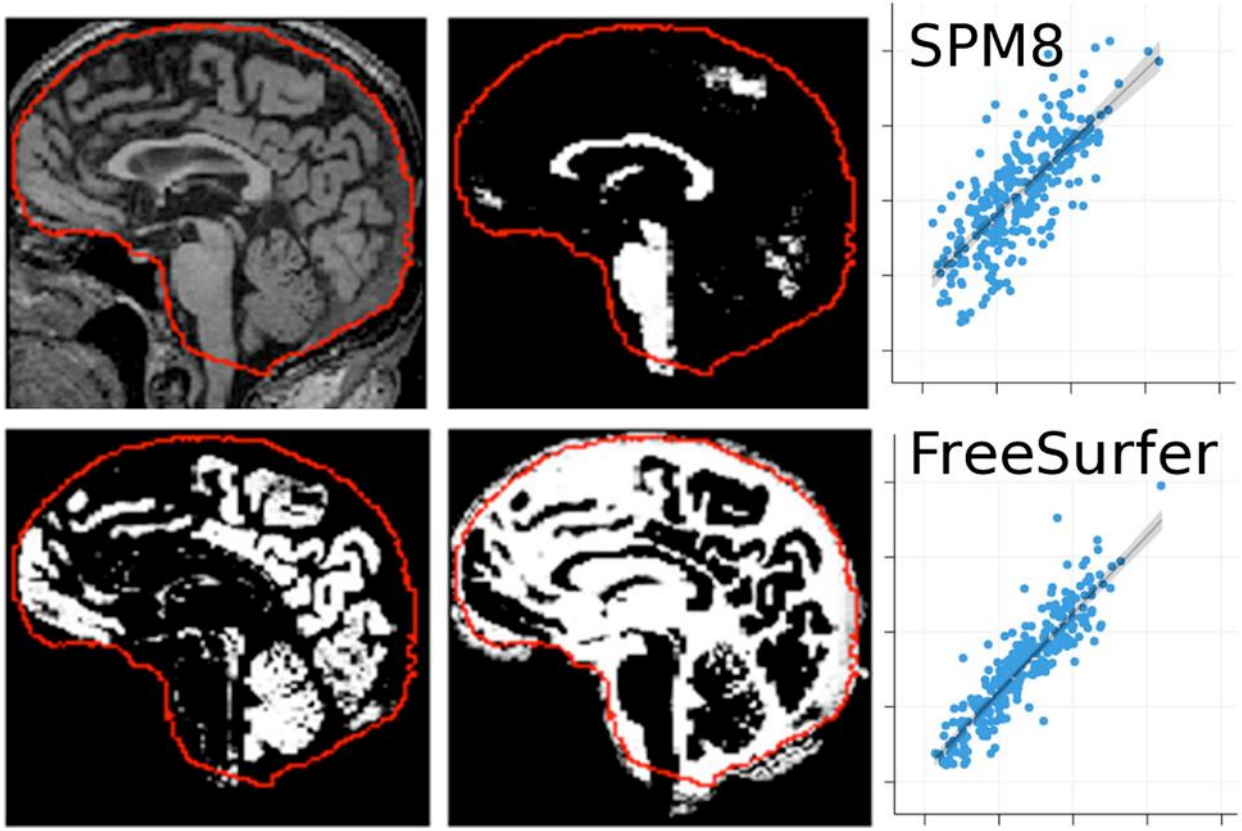
- High-resolution MRI reveals fine structural detail in the brain, but exhibits several challenges
  - Noise, artefacts, intensity-inhomogeneity, complexity, …
- MR Intensity is usually not quantitatively meaningful
  - Or even stable between sessions, sequences or scanners
  - Quantitative MRI is possible though, and promising, see 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 very interesting

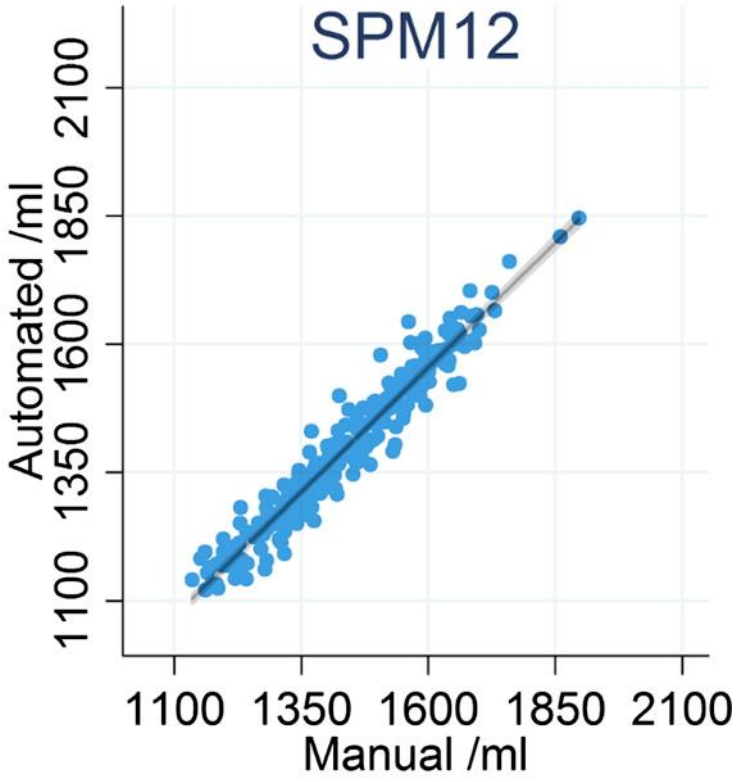
Tissue segmentation in SPM12 vs SPM8

- SPM8 had a “New Segment” toolbox in addition to the main segmentation button
- SPM8’s main segmentation became the “Old Segment” toolbox in SPM12
- SPM8’s New Segment provided the basis for SPM12’s segmentation, but there are several changes…
  - New TPM.nii (from multispectral IXI database)
  - Allowing rescaling of TPMs (like in Old Segment!)
  - For full detail see SPM12 Release Notes and Appendix A in Malone et al. (2015) [PMID:25255942]

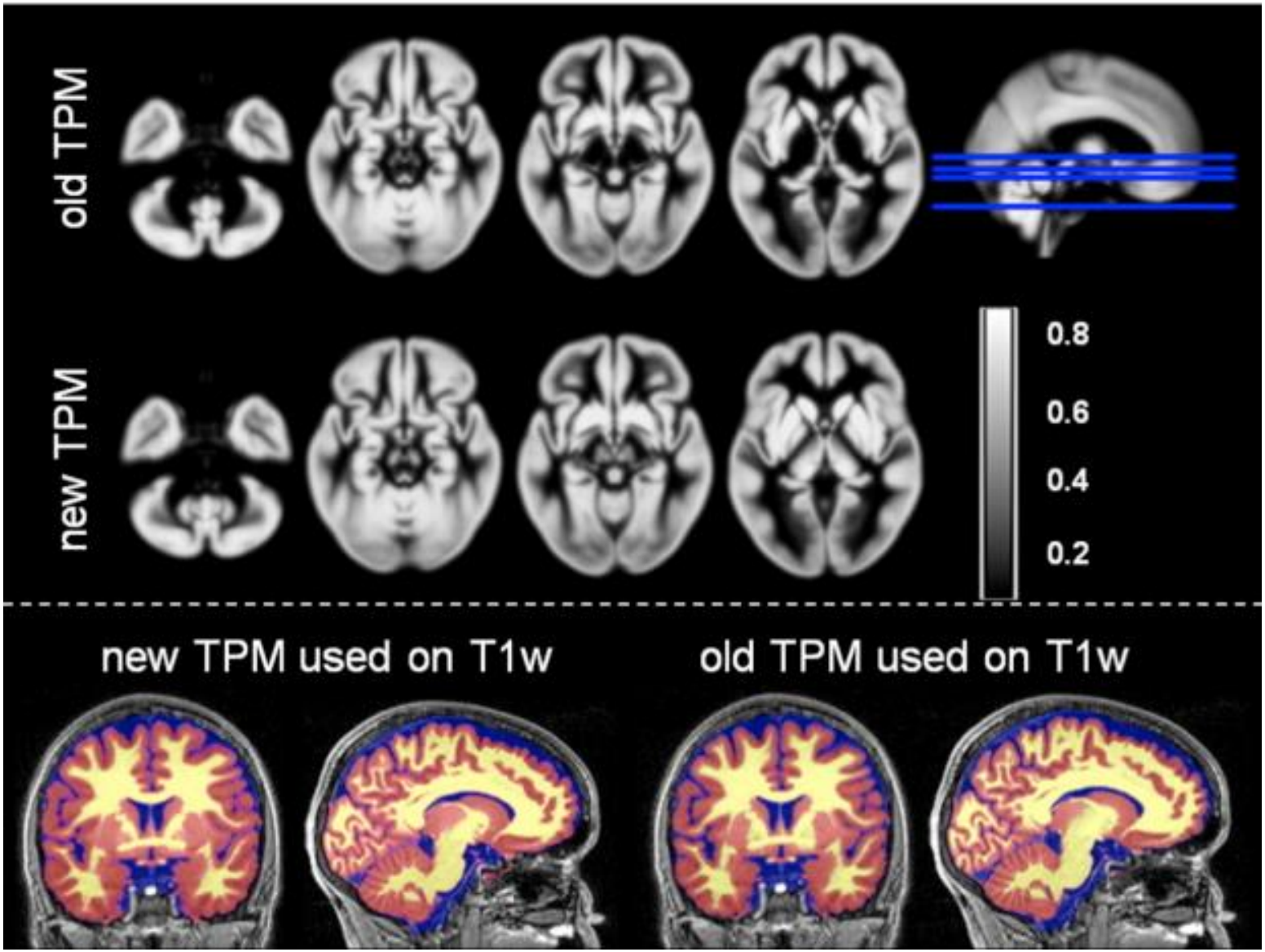
Tissue segmentation in SPM12 vs SPM8

- Evaluation of SPM12 versus SPM8 (Old) in terms of total intracranial volume, compared to manual tracing





Newer (!) tissue priors (Lorio et al., 2016)



Voxel-Based Morphometry

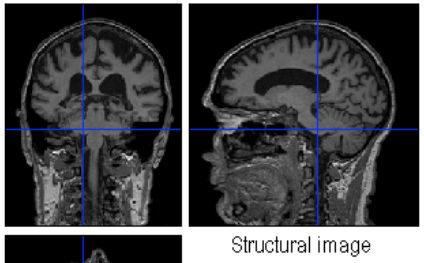
- In essence VBM is Statistical Parametric Mapping of regional segmented tissue density or volume

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

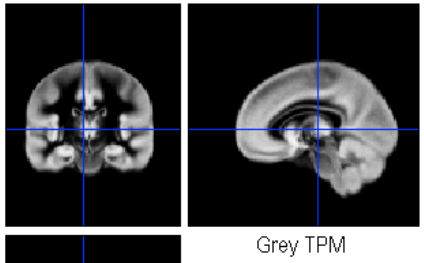
VBM overview

- Unified segmentation and spatial normalisation
  - More flexible group-wise normalisation using DARTEL
- Modulation to preserve tissue volume
  - Otherwise, tissue “density” (harder to interpret)
  - But see also Radua et al. (2014) [PMID:23933042]
- Optional computation of tissue totals/globals
- Gaussian smoothing
- Voxel-wise statistical analysis

VBM in pictures



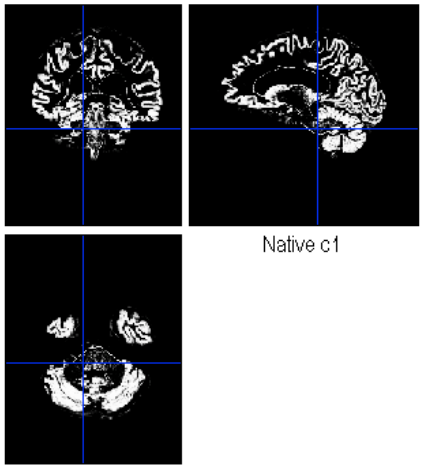
Structural image



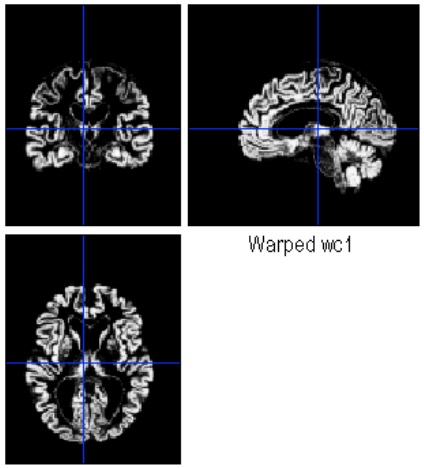
Grey TPM

Segment

Normalise



Native c1



Warped wc1

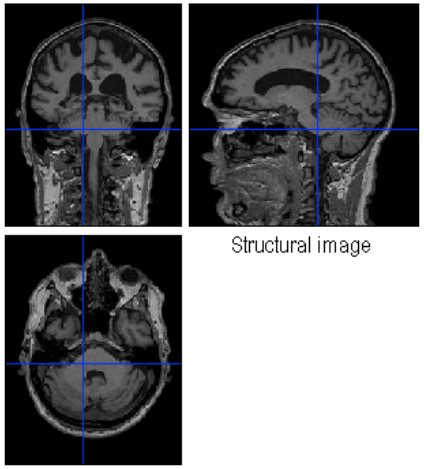
VBM in pictures

Segment

Normalise

Modulate

Smooth



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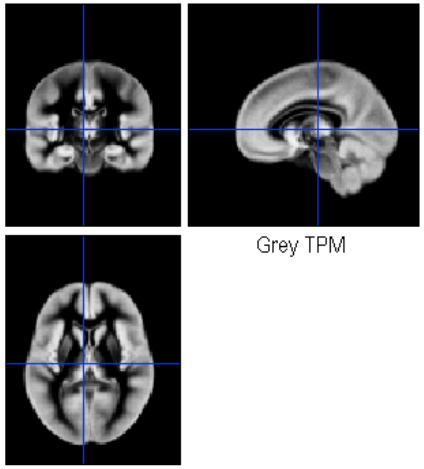
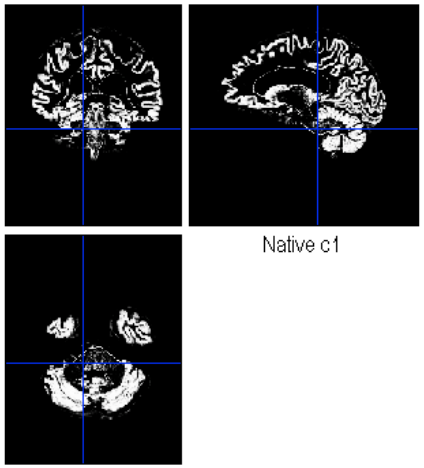
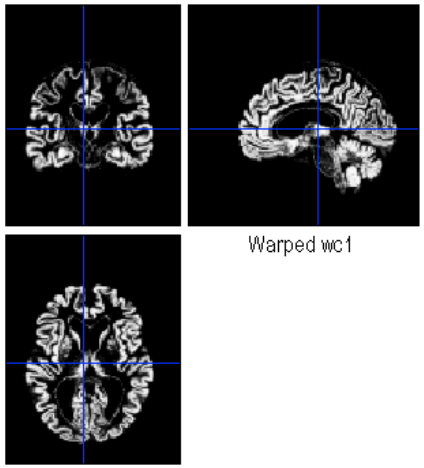


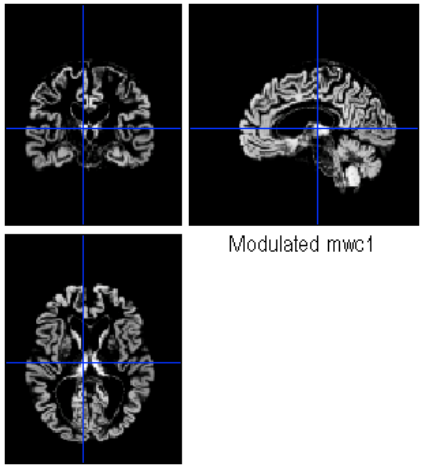
Grey TPM



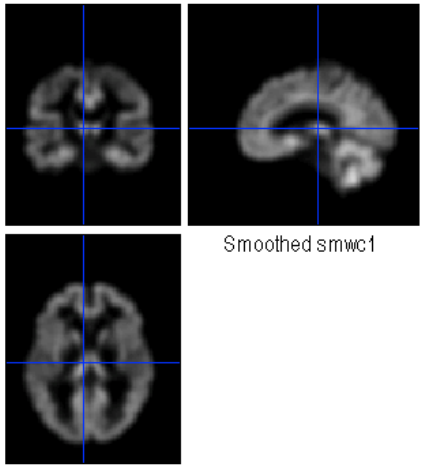
Native c1



Warped wc1



Modulated mwc1



Smoothed smwc1

VBM in pictures

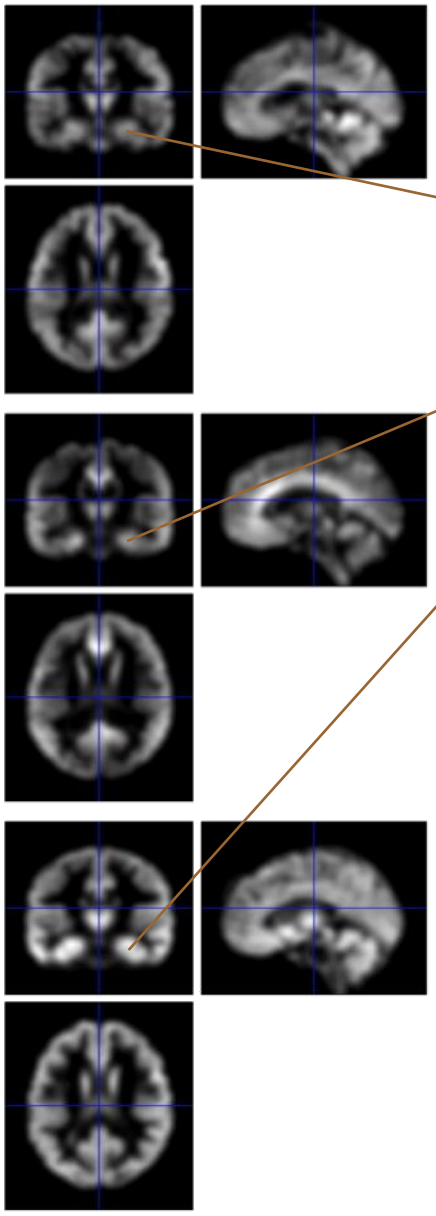
Segment

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

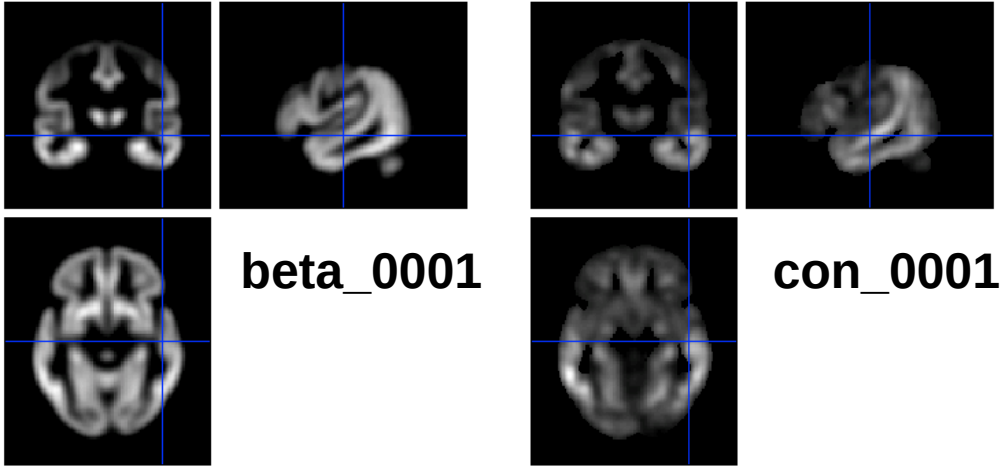
Segment

Normalise

Modulate

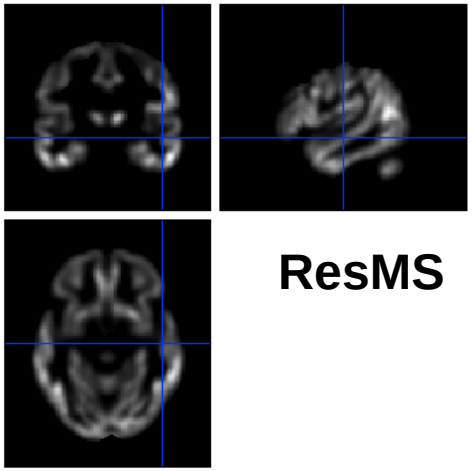
Smooth

Voxel-wise statistics

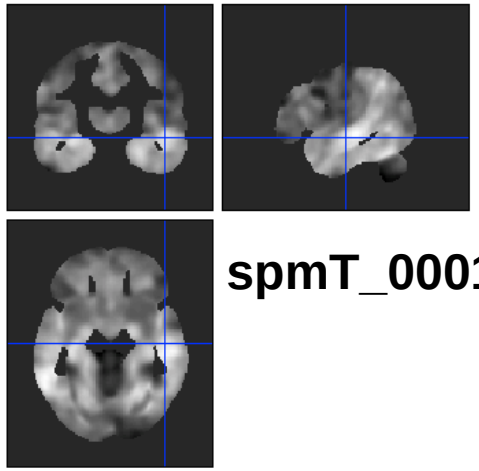


beta_0001

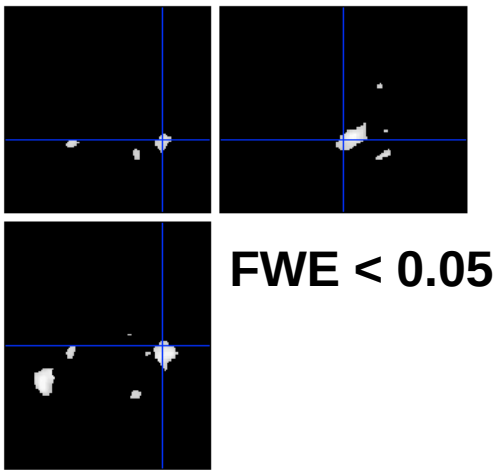
con_0001



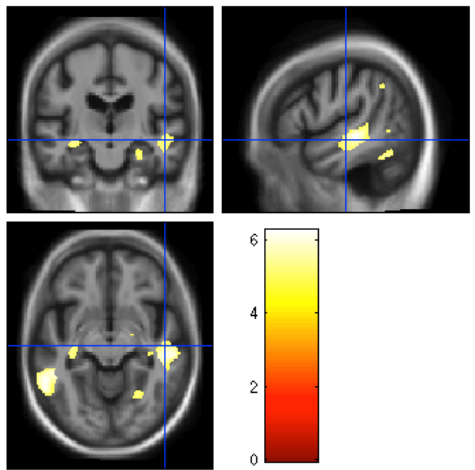
ResMS



spmT_0001



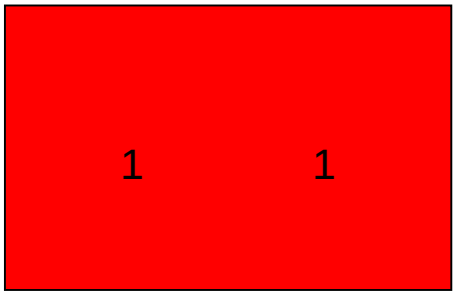
FWE < 0.05



VBM Subtleties

- Modulation
- How much to smooth
- Interpreting results
- Adjusting for total GM or Intracranial Volume
- Statistical validity

Modulation ("preserve amounts")

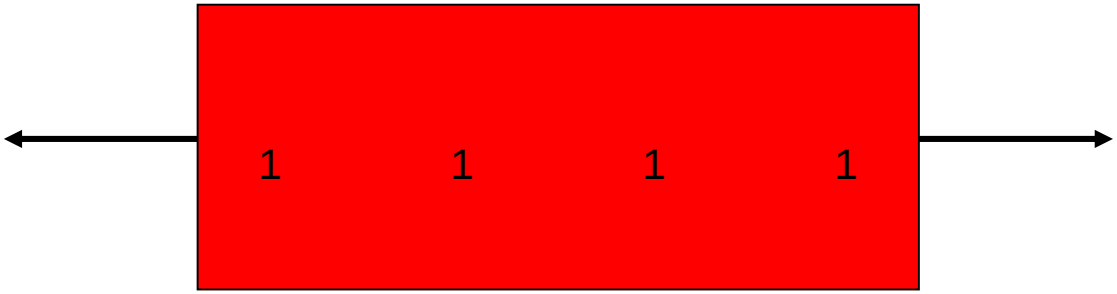


Native

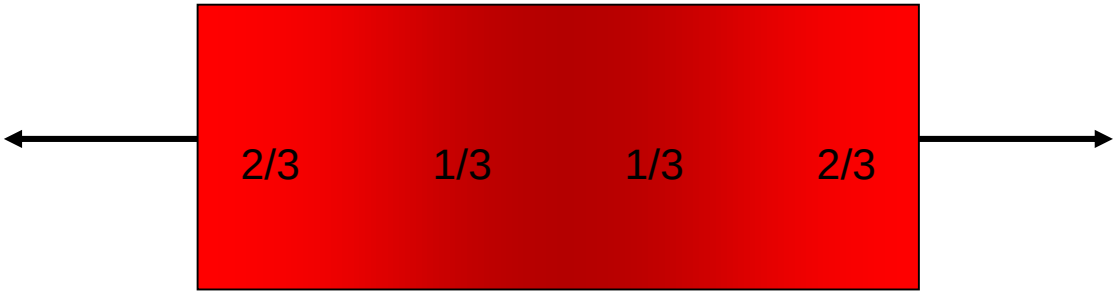
intensity = tissue probability

- Multiplication of warped (normalised) tissue intensities so that their regional total is preserved
  - Can detect differences in completely registered areas
- Otherwise, we *preserve concentrations*, and are detecting *mesoscopic* effects that remain after approximate registration has removed the macroscopic effects
  - Flexible (not necessarily "perfect") warping leaves less

Unmodulated



Modulated

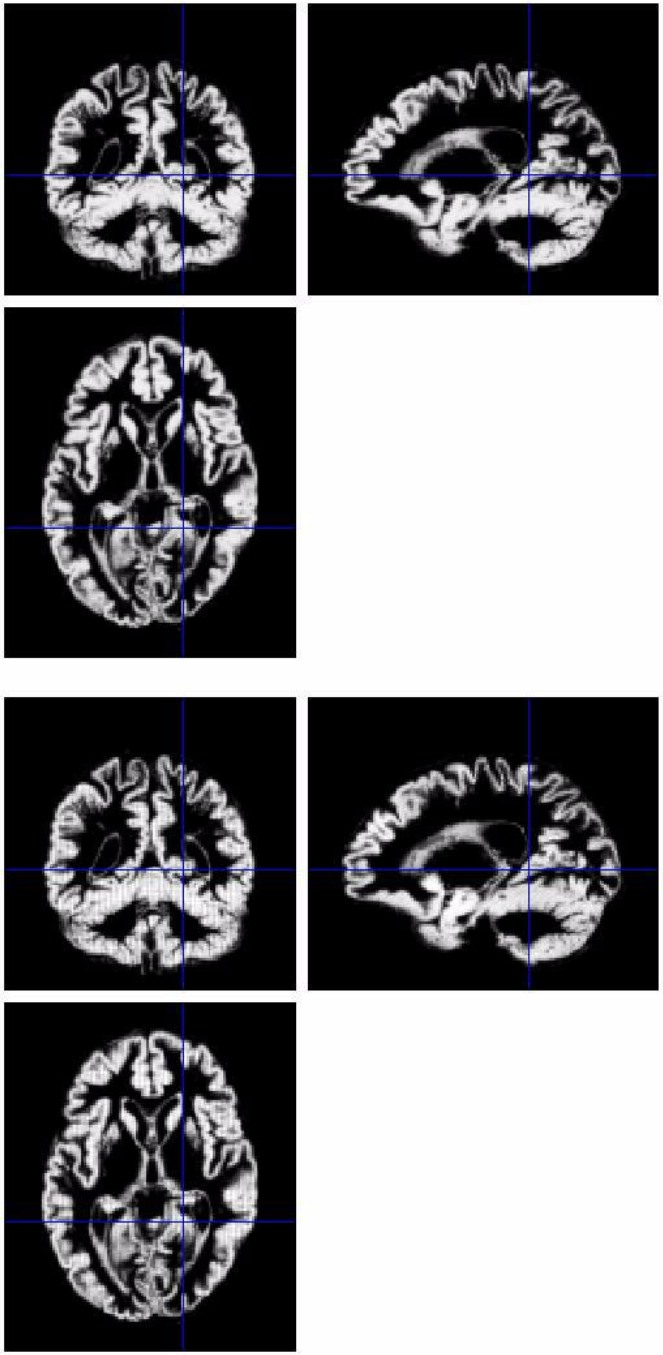


See also http://tinyurl.com/ModulationTutorial

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

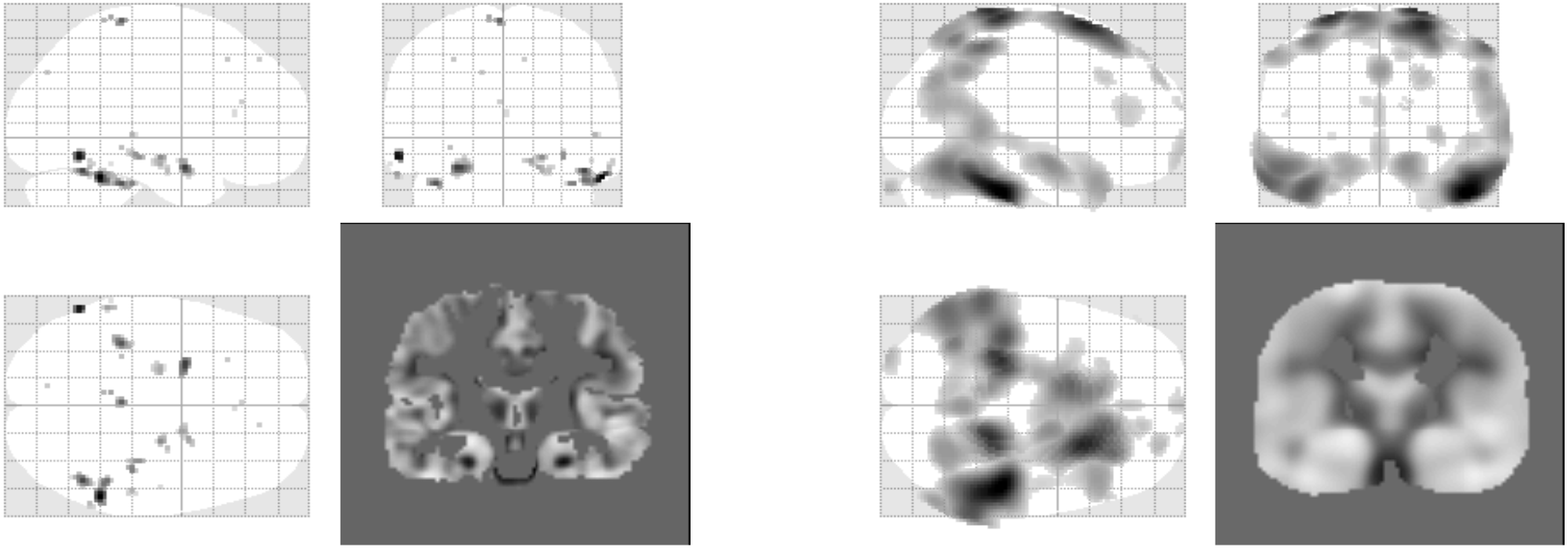


Smoothing

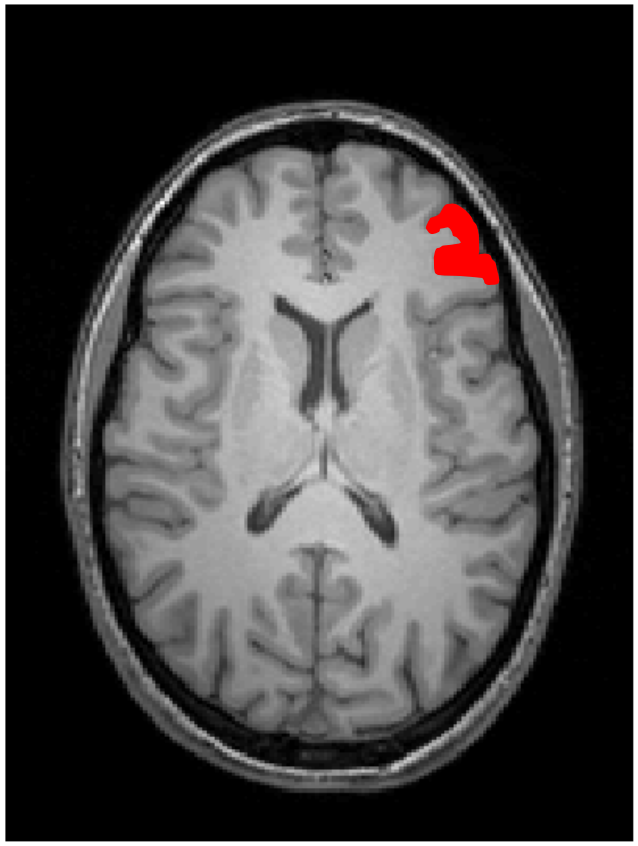
- The analysis will be most sensitive to effects that match the shape and size of the kernel
- Results will be rough and noise-like if too little is used
- The data will be more Gaussian and closer to a continuous random field for larger kernels
  - Usually recommend >= 6mm
- Too much will lead to widespread, indistinct blobs
  - Usually recommend <= 12mm

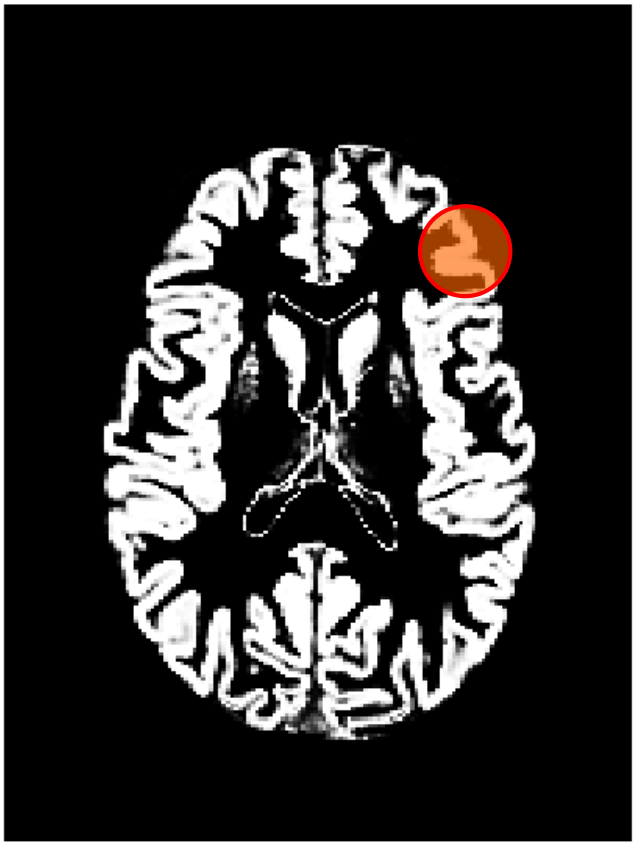
Smoothing

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



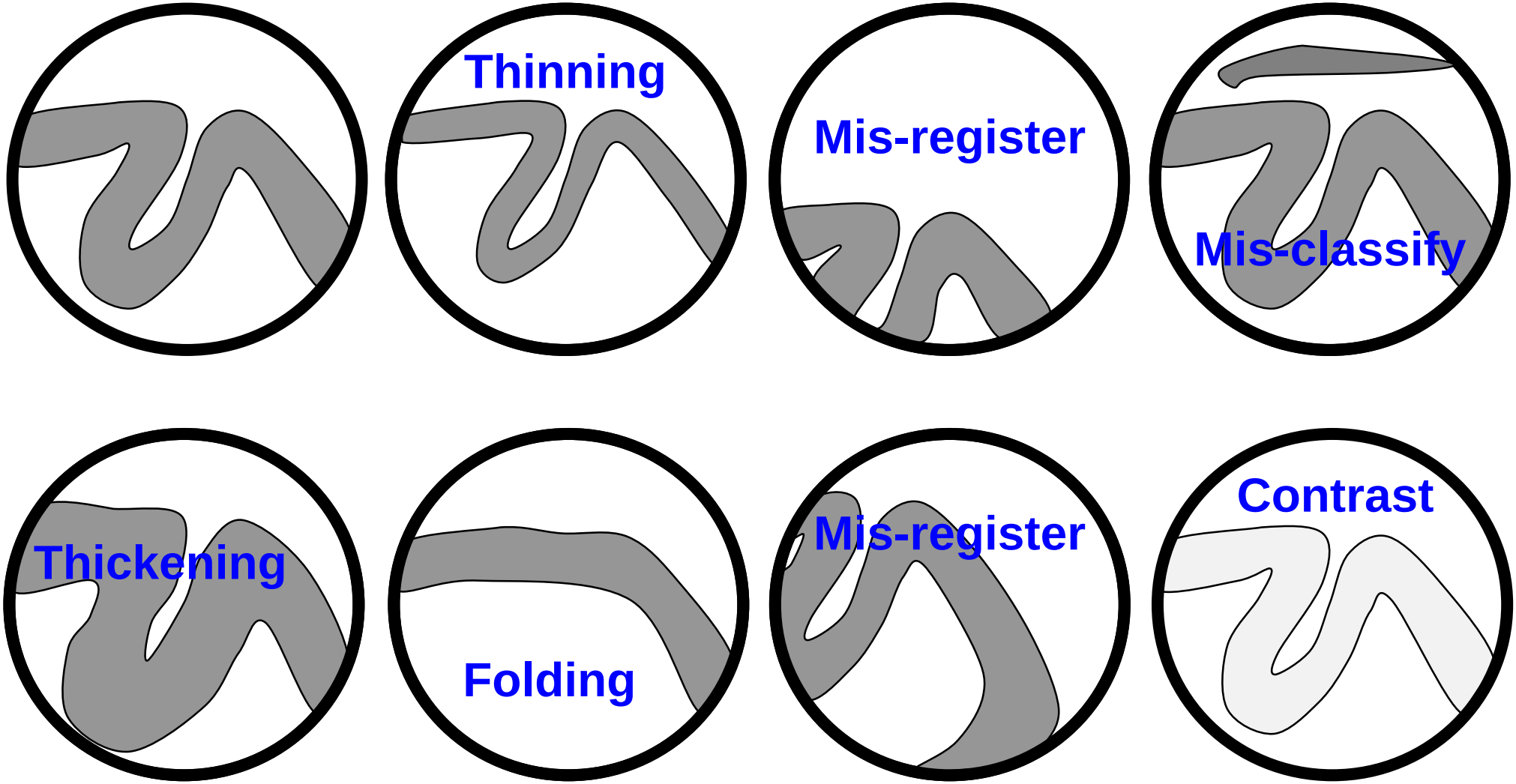
Smoothing as a locally weighted ROI





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

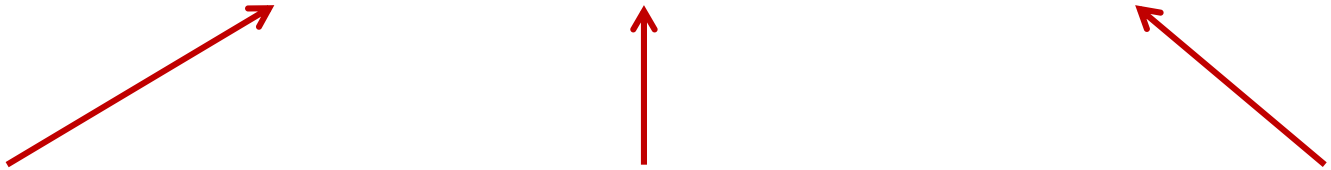
Interpreting findings



Interpreting findings

VBM is sometimes described as

"unbiased whole brain volumetry"



Regional variation in registration accuracy

Segmentation problems, issues with analysis mask

Intensity, folding, etc.

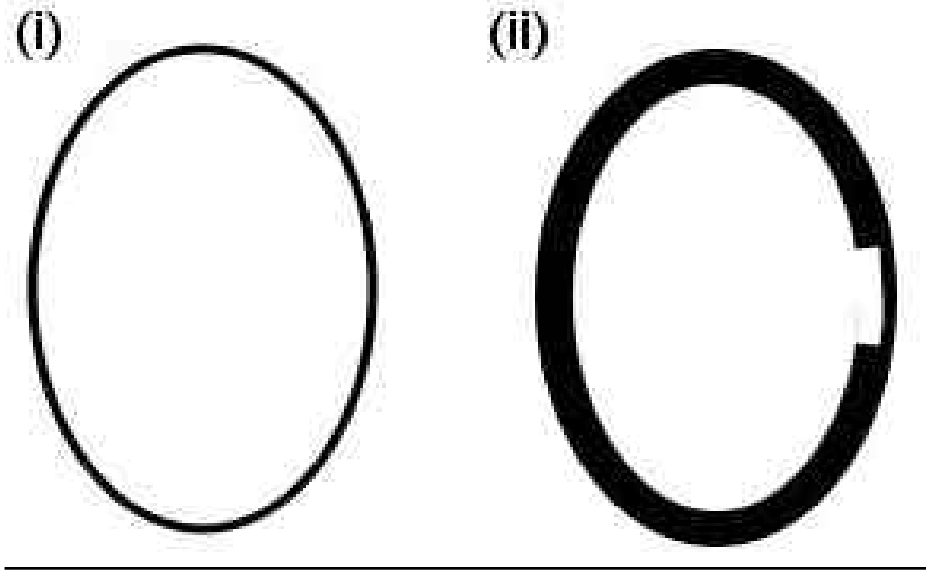
But significant blobs probably still indicate meaningful systematic effects!

Adjustment for “nuisance” variables

- Anything which might explain some variability in regional volumes of interest should be considered
  - Age and gender are obvious and commonly used
    - Consider age + age^2 to allow quadratic effects
  - Site or scanner if more than one
    (Note: model as factor, not covariate; multiple binary columns)
- Total grey matter volume often used for VBM
  - Changes interpretation when correlated with local volumes (shape is a multivariate concept… See next slide)
  - Total intracranial volume (TIV/ICV) sometimes more powerful and/or more easily interpretable, see also Barnes et al. (2010); Malone et al. (2015)

Adjustment for total/global volume

- Shape is really a multivariate concept
  - Dependencies among volumes in different regions
- SPM is mass univariate
  - Combining voxel-wise information with “global” integrated tissue volume provides a compromise
  - Using either ANCOVA or proportional scaling



(ii) is globally thicker, but locally thinner than (i) – either of these effects may be of interest to us.

Fig. from: *Voxel-based morphometry of the human brain…* Mechelli, Price, Friston and Ashburner. Current Medical Imaging Reviews 1(2), 2005.

VBM's statistical validity

- Residuals are not normally distributed
  - Little impact for comparing reasonably sized groups
  - Potentially problematic for comparing single subjects or tiny patient groups with a larger control group
    - (Scarpazza et al, 2013; DOI: 10.1016/j.neuroimage.2012.12.045)
  - Mitigate with large amounts of smoothing
  - Or use nonparametric tests, e.g. permutation testing (SnPM)
    - Though also not suitable for single case versus small control group…

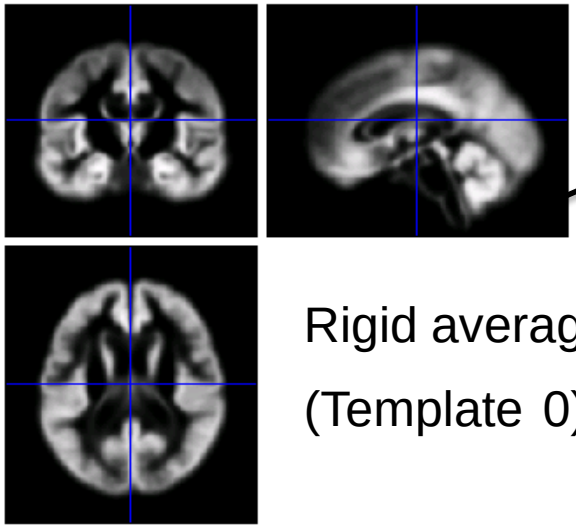
VBM's statistical validity

- Smoothness is not spatially stationary
  - Bigger blobs expected by chance in smoother regions
  - NS toolbox http://www.fil.ion.ucl.ac.uk/spm/ext/#NS
  - Keith Worsley's SurfStat
  - Or nonparametric permutation
- Voxel-wise FDR is common, but not recommended

Spatial normalisation with DARTEL

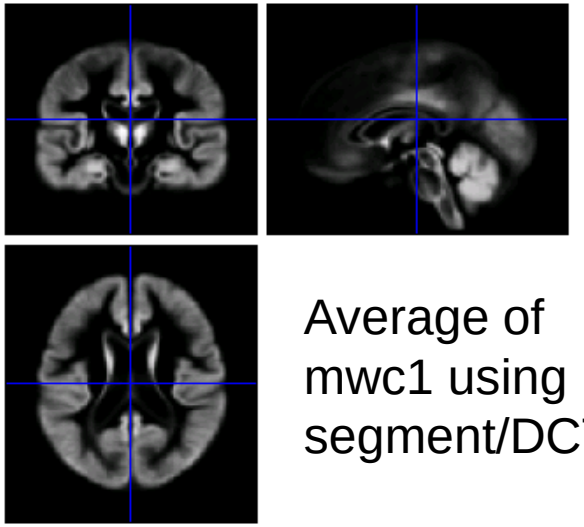
- VBM is crucially dependent on registration performance
  - The limited flexibility of DCT normalisation has been criticised
  - Inverse transformations are useful, but not always well-defined
  - More flexible registration requires careful modelling and regularisation (prior belief about reasonable warping)
  - MNI/ICBM templates/priors are not universally representative
- The 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

DARTEL average template evolution

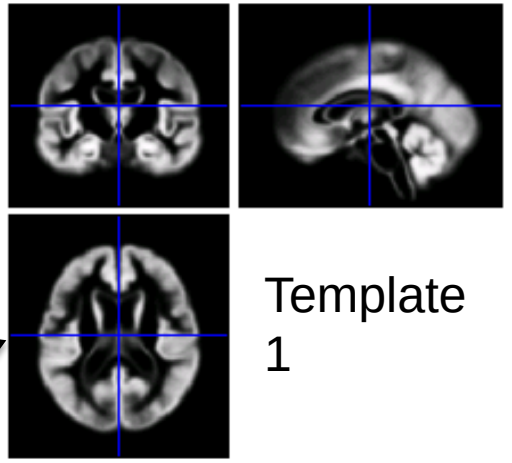


Rigid average

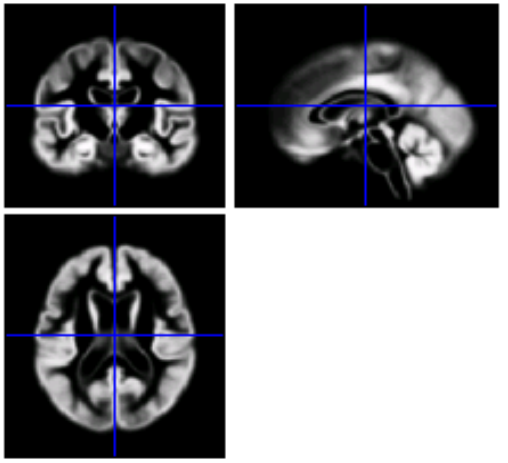
(Template 0)

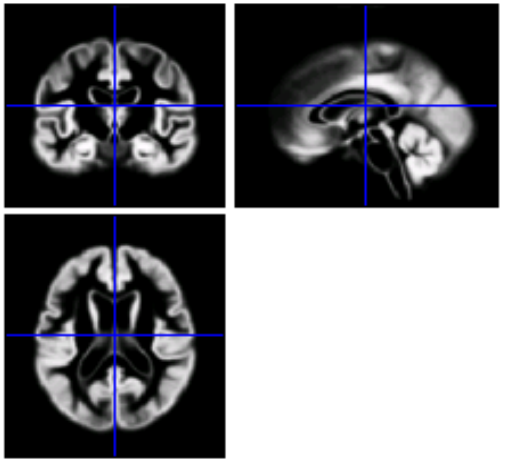


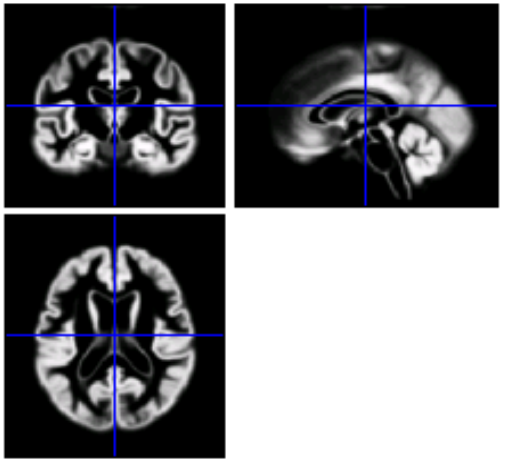
Average of mwc1 using segment/DCT

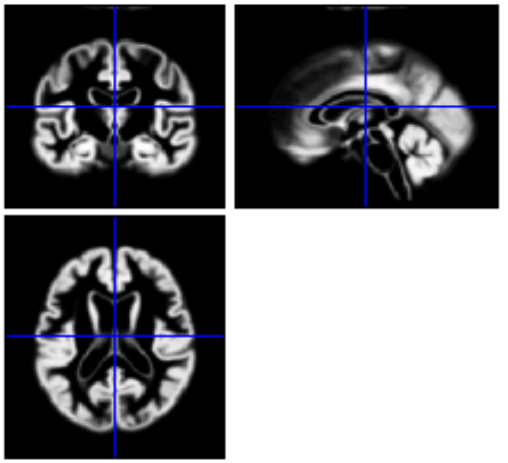


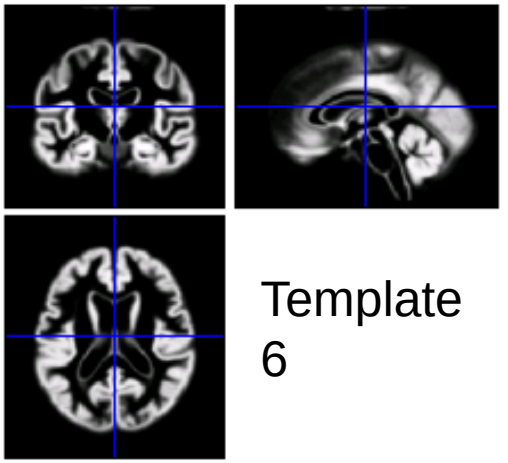
Template 1



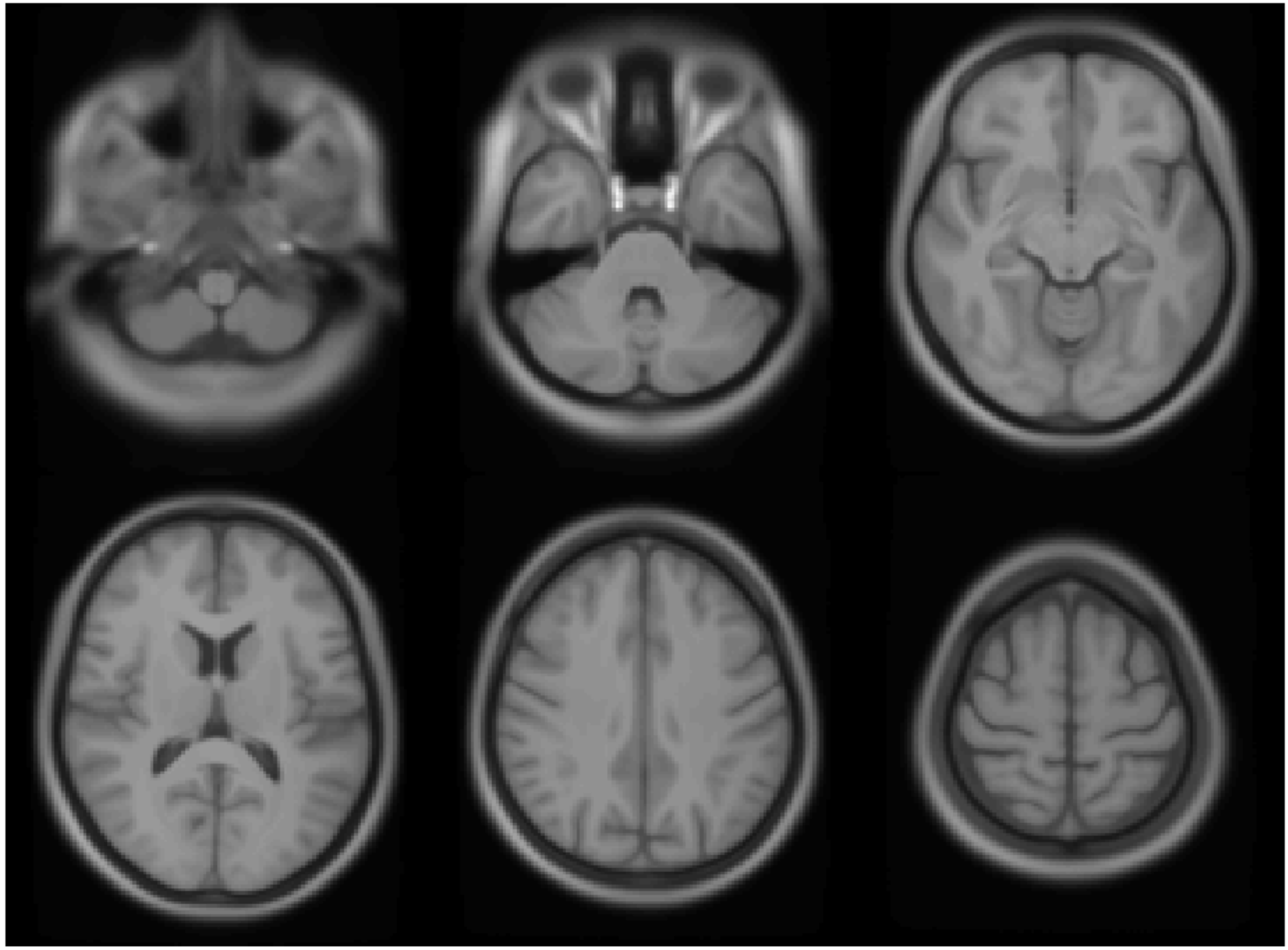


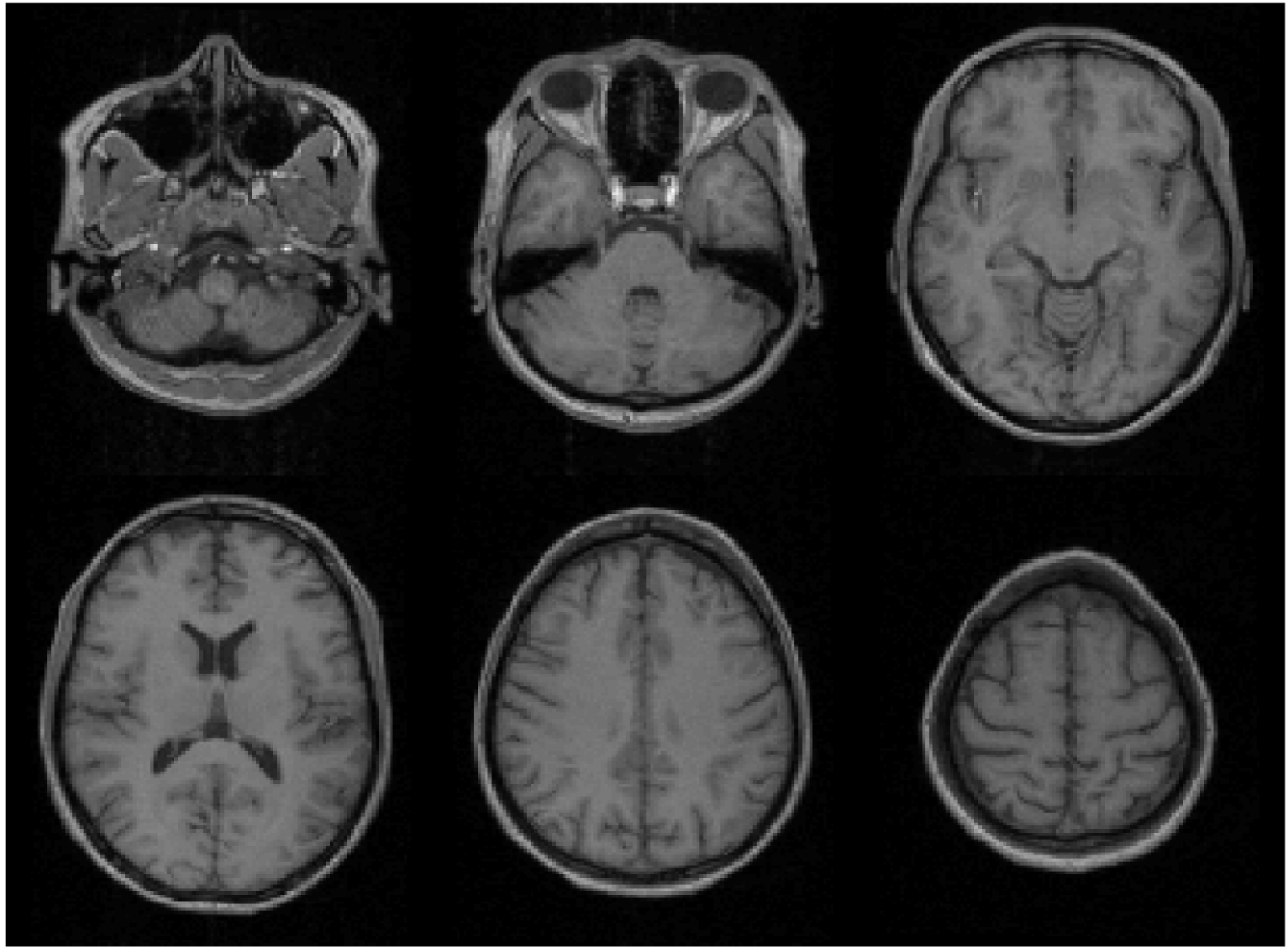


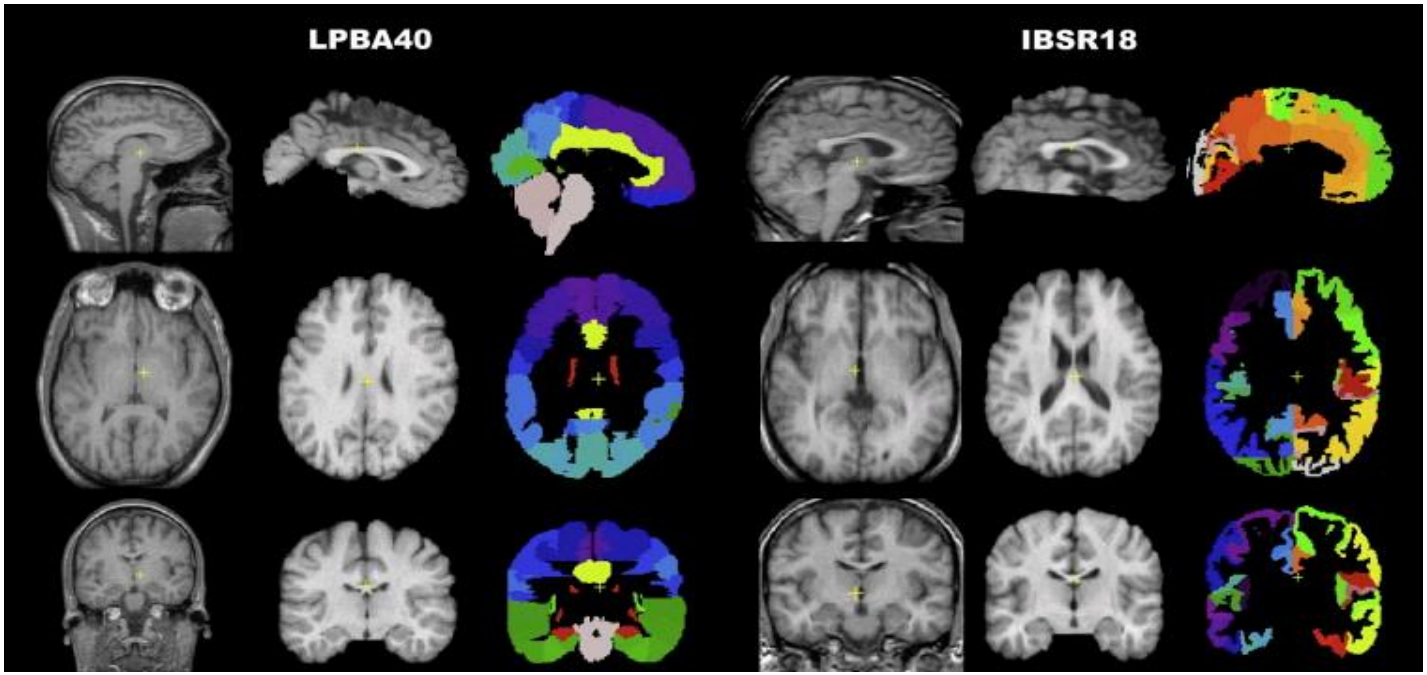




Template 6

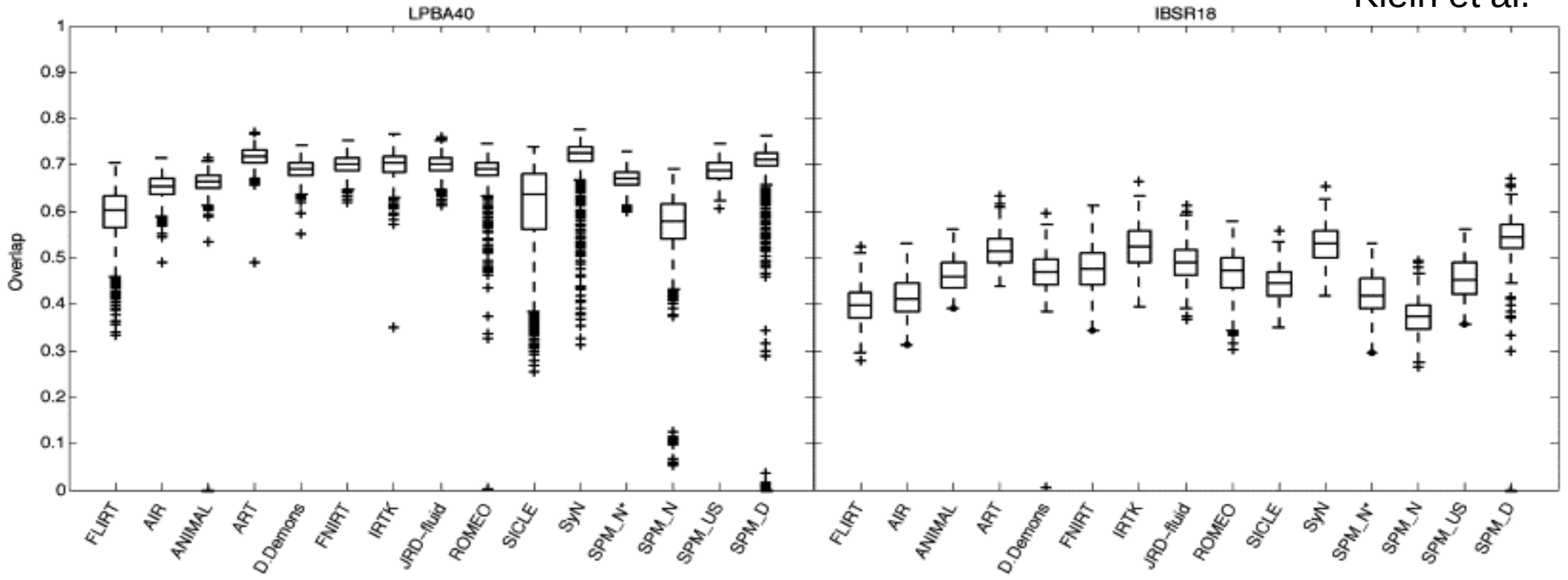






Part of
Fig.1 in
Klein et al.

Part of
Fig.5 in
Klein et al.



Summary

- VBM performs voxel-wise statistical analysis on smoothed (modulated) normalised tissue segments
- SPM performs segmentation and spatial normalisation in a unified generative model
- Subsequent (non-unified) use of DARTEL improves spatial normalisation for VBM
  - (and probably also fMRI...)

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 – preprocessing

- Intra-subject registration over time is much more accurate than inter-subject normalisation
- Simple approach: rigid realignment within-subject
  - Apply one spatial normalisation to all timepoints
  - E.g. Draganski et al (2004) Nature 427: 311-312
- More sophisticated approaches use nonlinear within-subject registration
  - Information transferred to volume-change maps

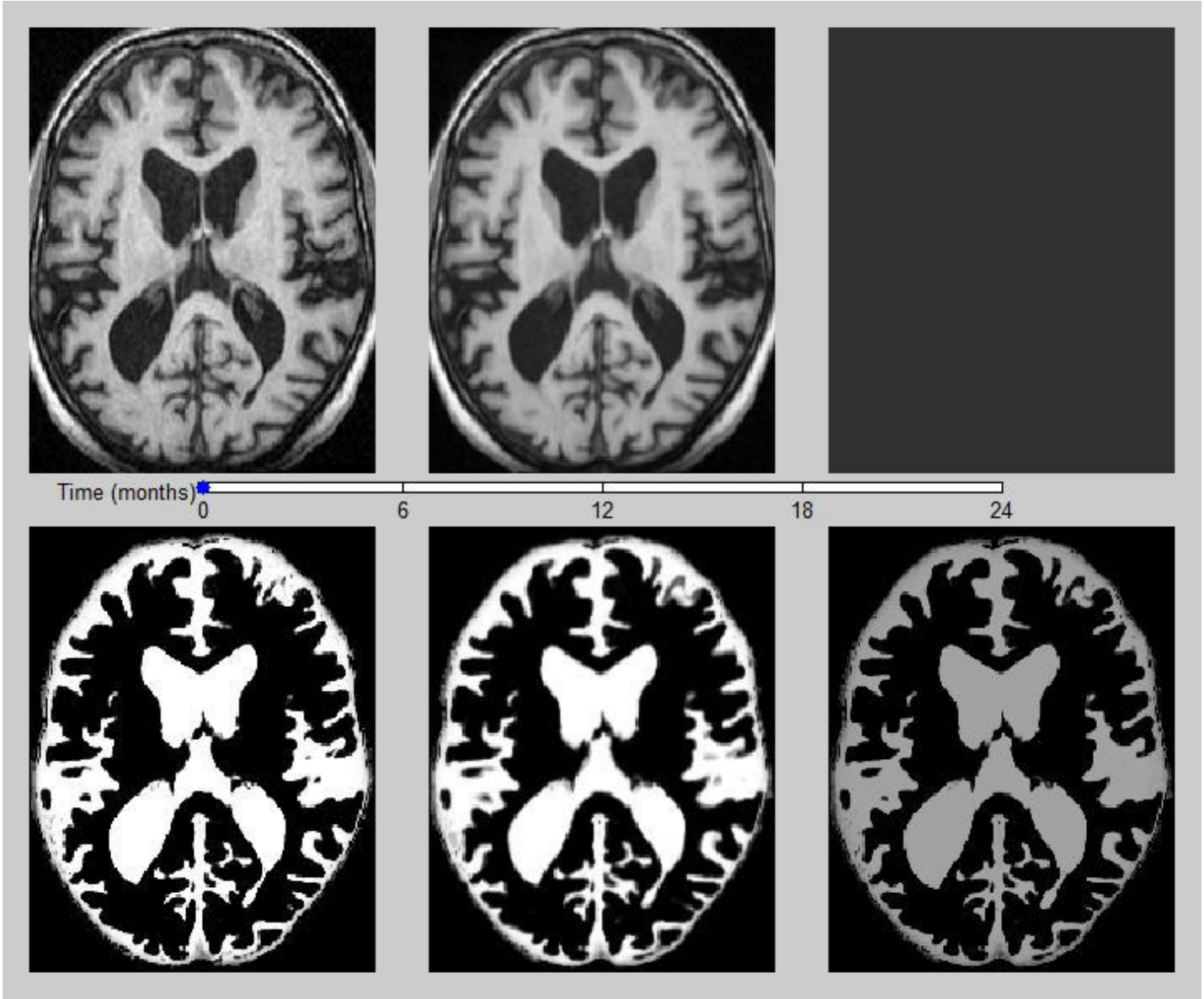
Longitudinal VBM – asymmetry & bias

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

- Ashburner & Ridgway (2013) [PMID: 23386806]
- “Unified” rigid and non-rigid registration with model of differential intensity inhomogeneity (bias)
- “Generative” – each time-point is a reoriented, spatially warped, intensity biased version of avg.
- “Symmetric” with respect to permutation of images
- “Consistent” with direct registration between pair
- “Diffeomorphic” – complex warping without folding

Longitudinal VBM – registration in SPM12



Longitudinal VBM – modelling

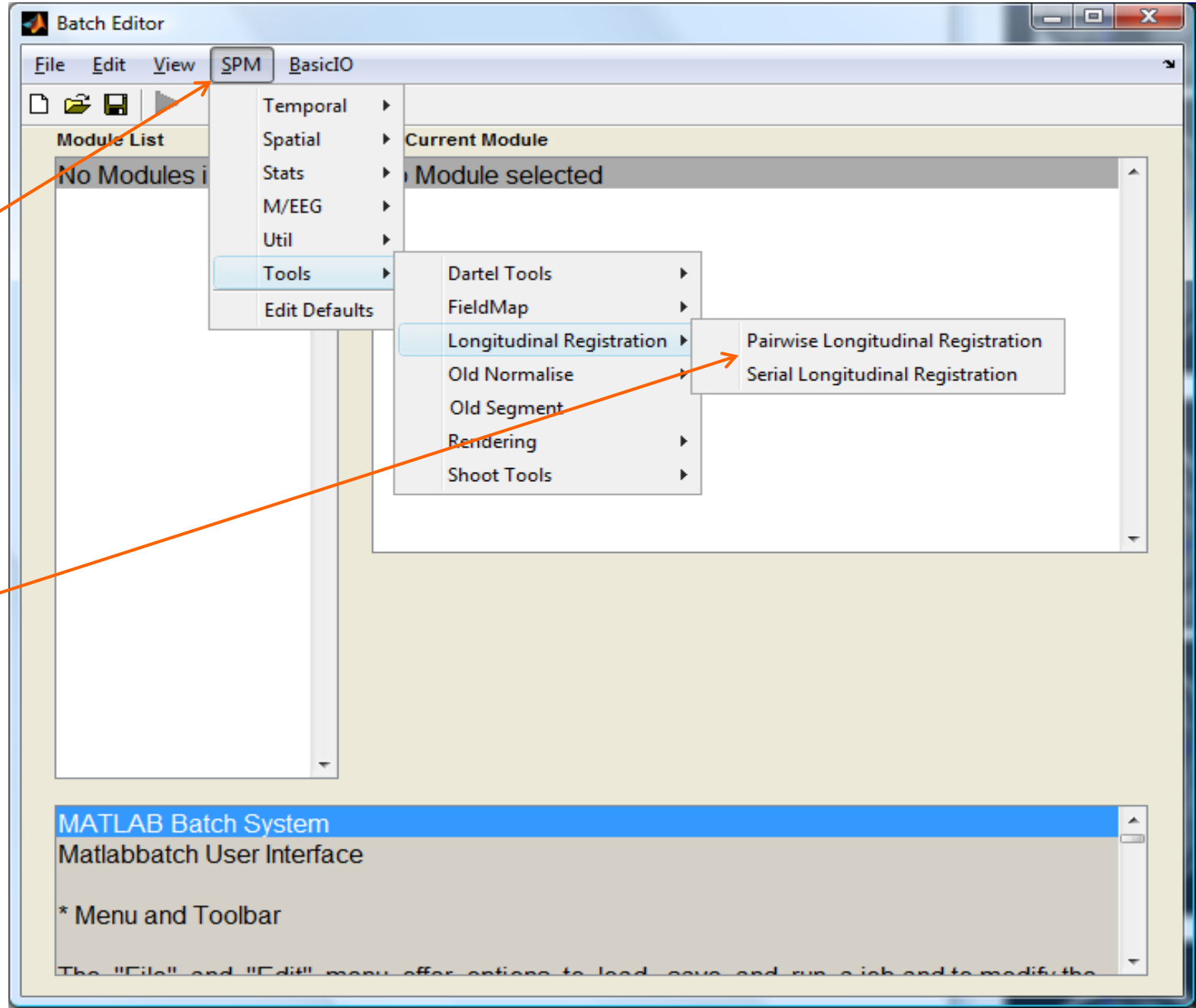
- The longitudinal registration produces a within-subject average and maps of volume change relative to it
  - Can perform cross-sectional VBM (Dartel, etc.) on averages
  - Same spatial normalisation for volume-change maps
  - Optionally multiply volume change with GM before smoothing
- Simplest longitudinal statistical analysis: two-stage summary statistic approach (like in fMRI)
  - Contrast on the slope parameter for a linear regression against time within each subject (usual group analyses of con images)
  - For two time-points with interval approximately constant over subjects, equivalent to simple time2 – time1 difference image

Longitudinal VBM – Getting started…

- The following slides illustrate usage of the longitudinal registration toolbox in the batch interface in SPM12

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

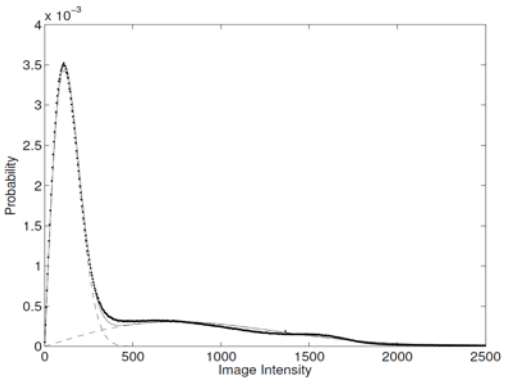
Choice of paired or general serial.
No difference in model, but easier specification and results for pairs.



Specify Time 1 scans for all subjects, then all Time 2 scans (in same order!)

Vector (list) of time intervals (yr)

Default values can be left; NaN to automatically estimate (Rician) noise



Batch Editor

File Edit View SPM BasicIO

Module List

Pairwise Longitudinal

Current Module: Pairwise Longitudinal Registration

Help on: Pairwise Longitudinal Registration	
Time 1 Volumes	<-X
Time 2 Volumes	<-X
Time difference	1
Noise Estimate	NaN
Warping Regularisation	1x5 double
Bias Regularisation	1000000
Save Mid-point average	Save
Save Jacobian Differences	Dont save
Save divergence	Save
Deformation Fields	Dont save

Pairwise Longitudinal Registration

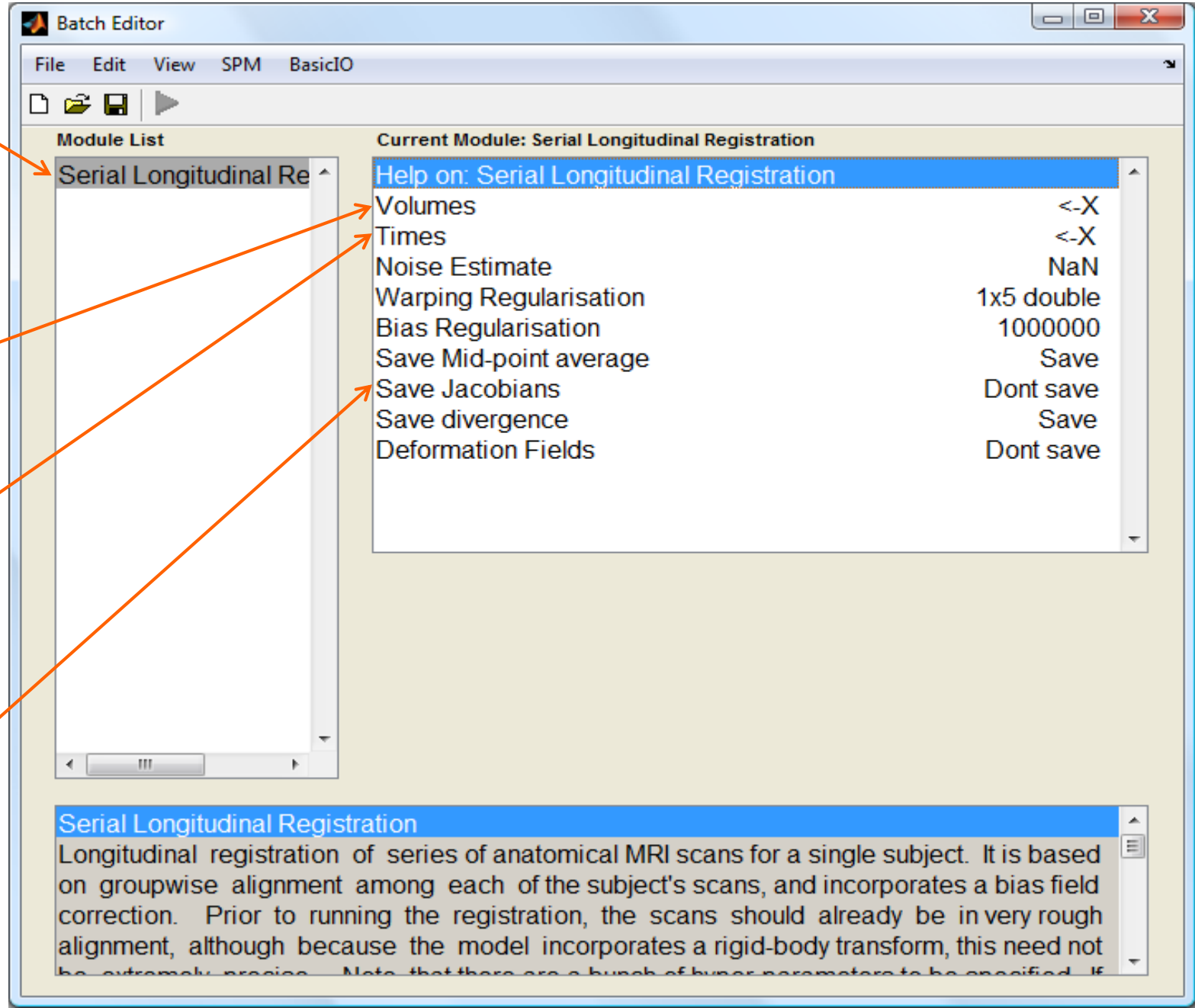
Longitudinal registration of pairs of anatomical MRI scans. It is based on pairwise inverse-consistent alignment between the first and second scan of each subject, and incorporates a bias field correction. Prior to running the registration, the scans should already be in very rough alignment, although because the model incorporates a rigid-body

One module
per subject (scripting
required if many subjects!)

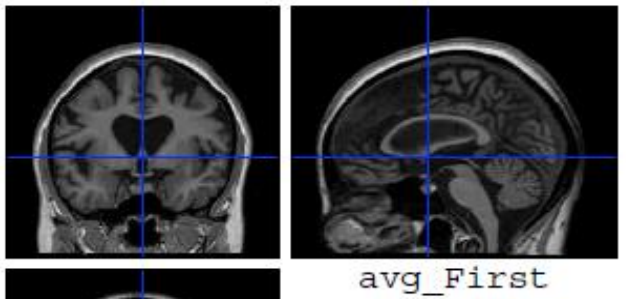
Select all scans for this
subject

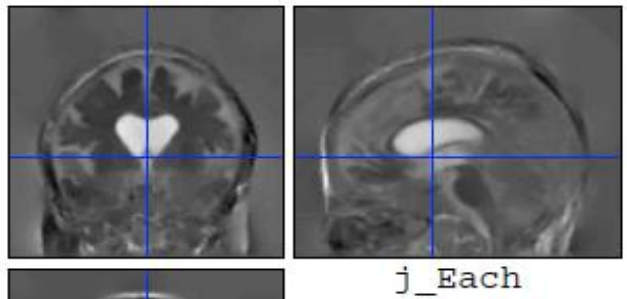
Vector (list) of times
relative to arbitrary datum
(e.g. baseline=0)

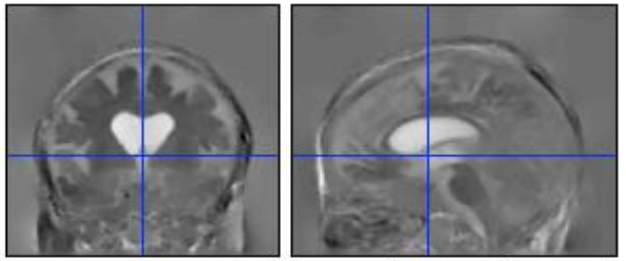
Jacobian output useful to
quantify interpretable ROI
volumes (in litres)

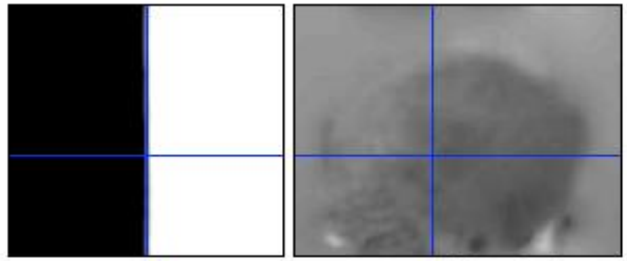


- Output/results
  - Average image
  - Jacobians or divergences
  - Deformations
- Next steps
  - Segment avg
  - Run Dartel/Shoot
  - Warp e.g. dv to standard space
  - SPM stats on dv (TBM)
  - Or combine with seg of avg (VBM)









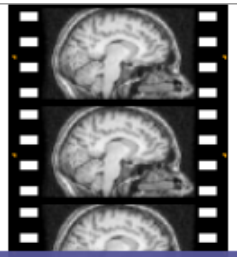
Longitudinal VBM – See also…

- Better statistical modelling for unbalanced data
  - SwE toolbox (Guillaume & Nichols)
  - Hierarchical modelling (Bernal-Rusiel et al; Ziegler et al)

- No longitudinal examples in SPM manual yet…
  - Support on SPM list http://www.fil.ion.ucl.ac.uk/spm/support/
  - Or email me: ged.ridgway@gmail.com

VOXEL-BASED MORPHOMETRY WITH THE MIRIAD DATA

SPM Datasets (not including VBM)



SPM Menu:

- Introduction
- Software
- Documentation
- Courses
- Email list
- Data sets
- Extensions

This page:

- Introduction
- PET
- fMRI: epoch
- fMRI: event-related
- fMRI: DCMs
- fMRI: multi-subject
- EEG: MMN
- LFP: DCM SSR
- Multimodal

UCL SPM

By members & collaborators of the Wellcome Trust Centre for Neuroimaging

Introduction | Software | Documentation | Courses | Email list | Data | Extensions

Data sets and tutorials

Introduction

The following data sets are being made available via anonymous FTP for training and personal education and evaluation purposes. Those wishing to use these data for other purposes, including illustrations or evaluations of methods, should contact the Methods group at the Wellcome Trust Centre for Neuroimaging.

A set of instructions showing how SPM can be used to analyse each data set are also provided. These tutorials show how one can use SPM to implement analyses of PET data, epoch or event-related fMRI data, and data from a group of subjects using Random effects analyses (RFX). They also cover more advanced topics such as Psychophysiological Interactions (PPIs) and Dynamic Causal Modelling (DCM).

PET

The instructions accompanying these data sets show you how to use SPM to analyse PET data.

- Verbal fluency - multiple subjects
- Motor activation - single subject

fMRI: epoch

The instructions accompanying these data sets show you how to implement a block-design fMRI analysis in SPM. They are both single-subject or 'first-level' analyses.

The MIRIAD data

- PubMed PMID: 23274184

Neuroimage. 2012 Dec 28;70C:33-36. doi: 10.1016/j.neuroimage.2012.12.044. [Epub ahead of print]

MIRIAD-Public release of a multiple time point Alzheimer's MR imaging dataset.

Malone IB, Cash D, Ridgway GR, Macmanus DG, Ourselin S, Fox NC, Schott JM.

Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK.

Abstract

The Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) dataset is a series of longitudinal volumetric T1 MRI scans of 46 mild-moderate Alzheimer's subjects and 23 controls. It consists of 708 scans conducted by the same radiographer with the same scanner and sequences at intervals of 2, 6, 14, 26, 38 and 52weeks, 18 and 24months from baseline, with accompanying information on gender, age and Mini Mental State Examination (MMSE) scores. Details of the cohort and imaging results have been described in peer-reviewed publications, and the data are here made publicly available as a common resource for researchers to develop, validate and compare techniques, particularly for measurement of longitudinal volume change in serially acquired MR.

The MIRIAD data

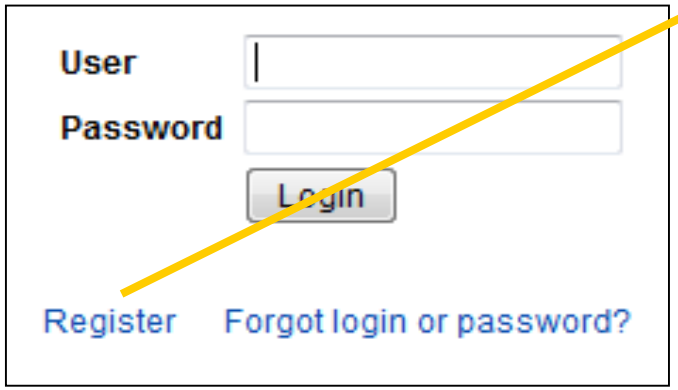
- 46 mild-moderate Alzheimer's patients and 23 controls, with volumetric T1-weighted MRI
  - Suggest dropping miriad_256_AD_F (motion)
- 708 scans at intervals of 2, 6, 14, 26, 38 and 52 weeks, 18 and 24 months from baseline
  - Just baselines used for current practical
- Information on gender, age and Mini Mental State Examination (MMSE)

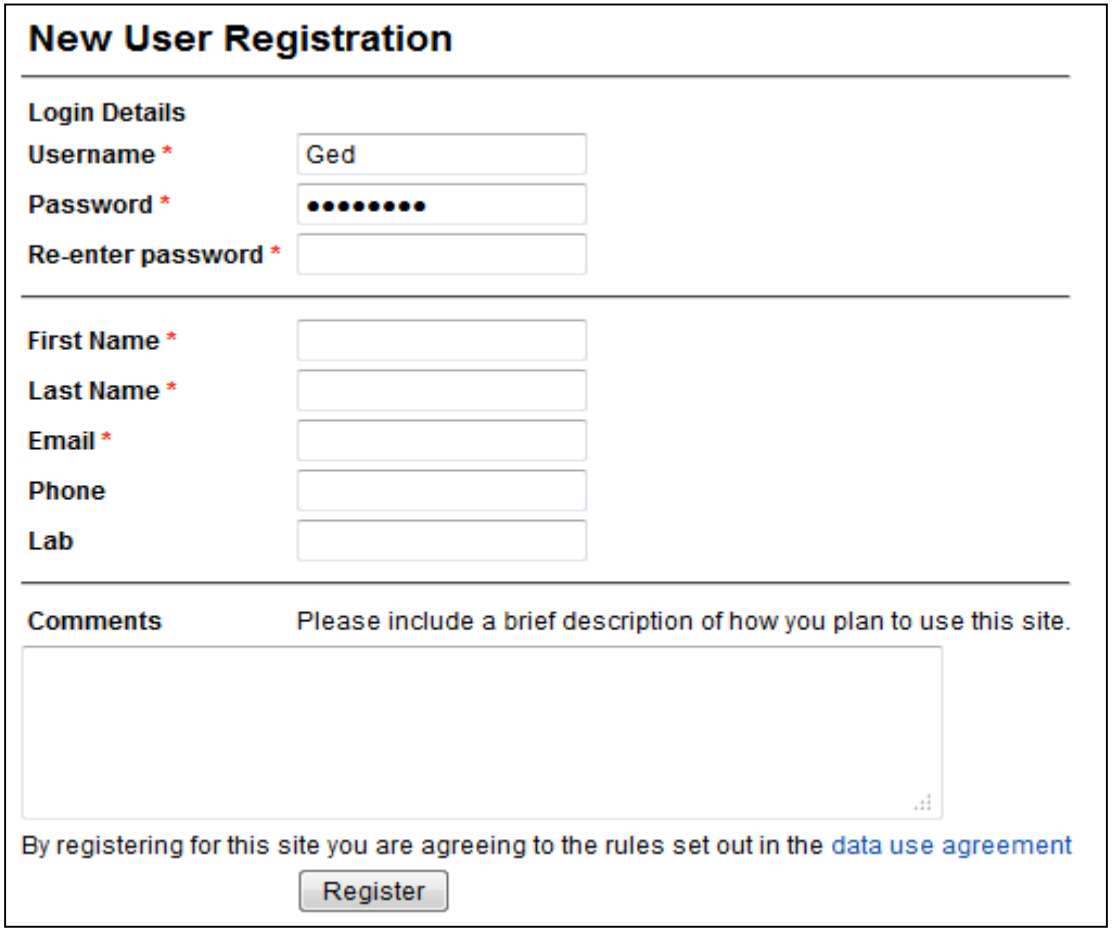
The MIRIAD data

- Available online
  - http://miriad.drc.ion.ucl.ac.uk/
- Data use agreement:
  - Respect privacy of subjects
  - Don’t redistribute without permission
  - No guarantees
  - Acknowledge use
    - Cite reference, acknowledge funding, send copy
    - No need for group authorship cf. ADNI

Registration via XNAT

- miriad.drc.ion.ucl.ac.uk/atrophychallenge
  - (data first used in blinded form for a MICCAI atrophy challenge workshop





Downloading data

- For flexible querying and download, use XNAT
- Shortcut to get entire dataset
  - http://miriad.drc.ion.ucl.ac.uk/atrophychallenge/data/projects/MIRIAD/resources/1682/files/MIRIAD.tgz
  - (not necessary/recommended for VBM practical)
- Shortcut to get baseline images only
  - http://miriad.drc.ion.ucl.ac.uk/miriad-bl.tgz

Extracting data

- Note tgz can be extracted with **tar** for Mac/Linux or e.g. 7-zip for Windows
- Or with **untar** in MATLAB (at its command prompt)

  >> untar('/path/to/miriad-bl.tgz')

  creates **miriad-bl** directory in current working directory