UBC SPM Course 2010

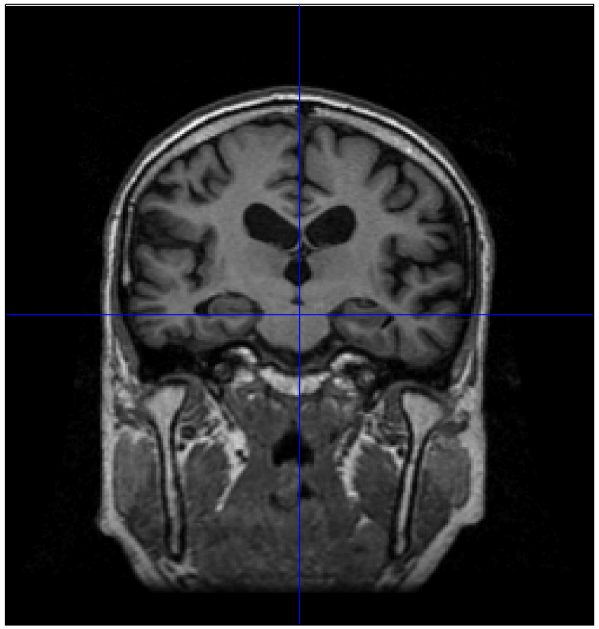
Voxel-Based Morphometry & DARTEL

Ged Ridgway

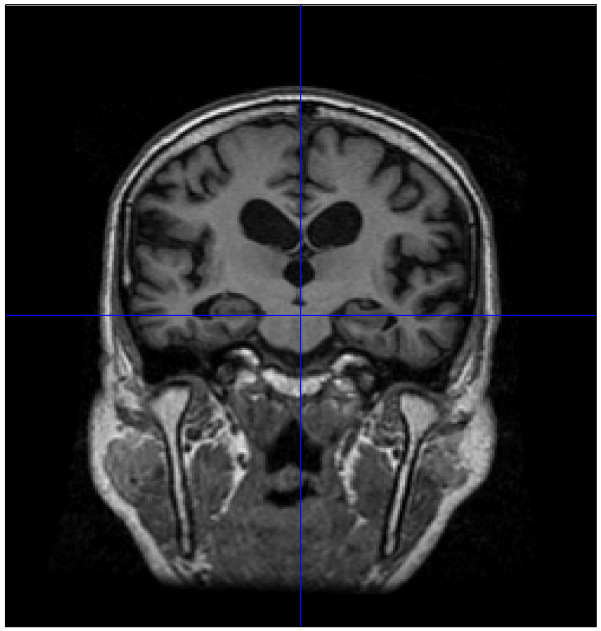
Aims of computational neuroanatomy

* Many interesting and clinically important questions might relate to the shape or local size of regions of the brain
* For example, whether (and where) local patterns of brain **morphometry** help to:
  - ? Distinguish schizophrenics from healthy controls
  - ? Understand plasticity, e.g. when learning new skills
  - ? Explain the changes seen in development and aging
  - ? Differentiate degenerative disease from healthy aging
  - ? Evaluate subjects on drug treatments versus placebo

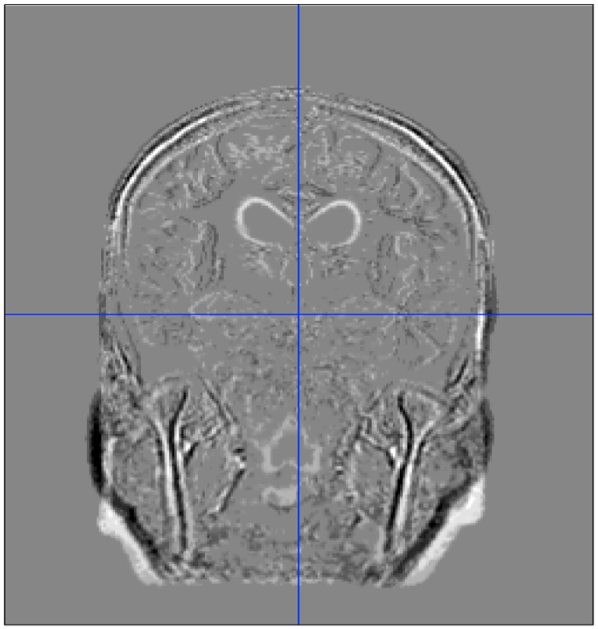
Alzheimer's Disease example



Baseline Image
Standard clinical MRI
1.5T T1 SPGR
1x1x1.5mm voxels



Repeat image
12 month follow-up
rigidly registered

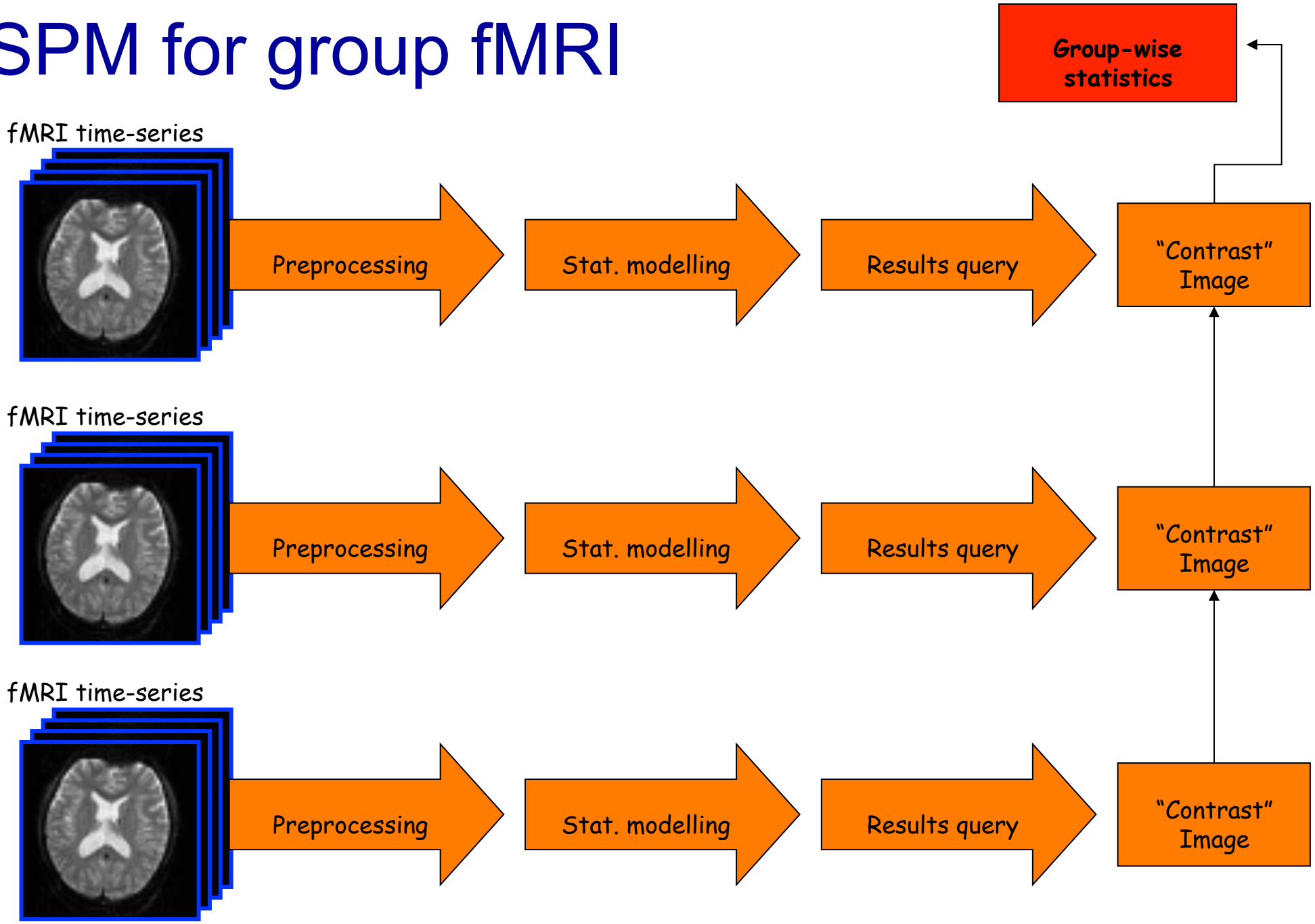


Subtraction image

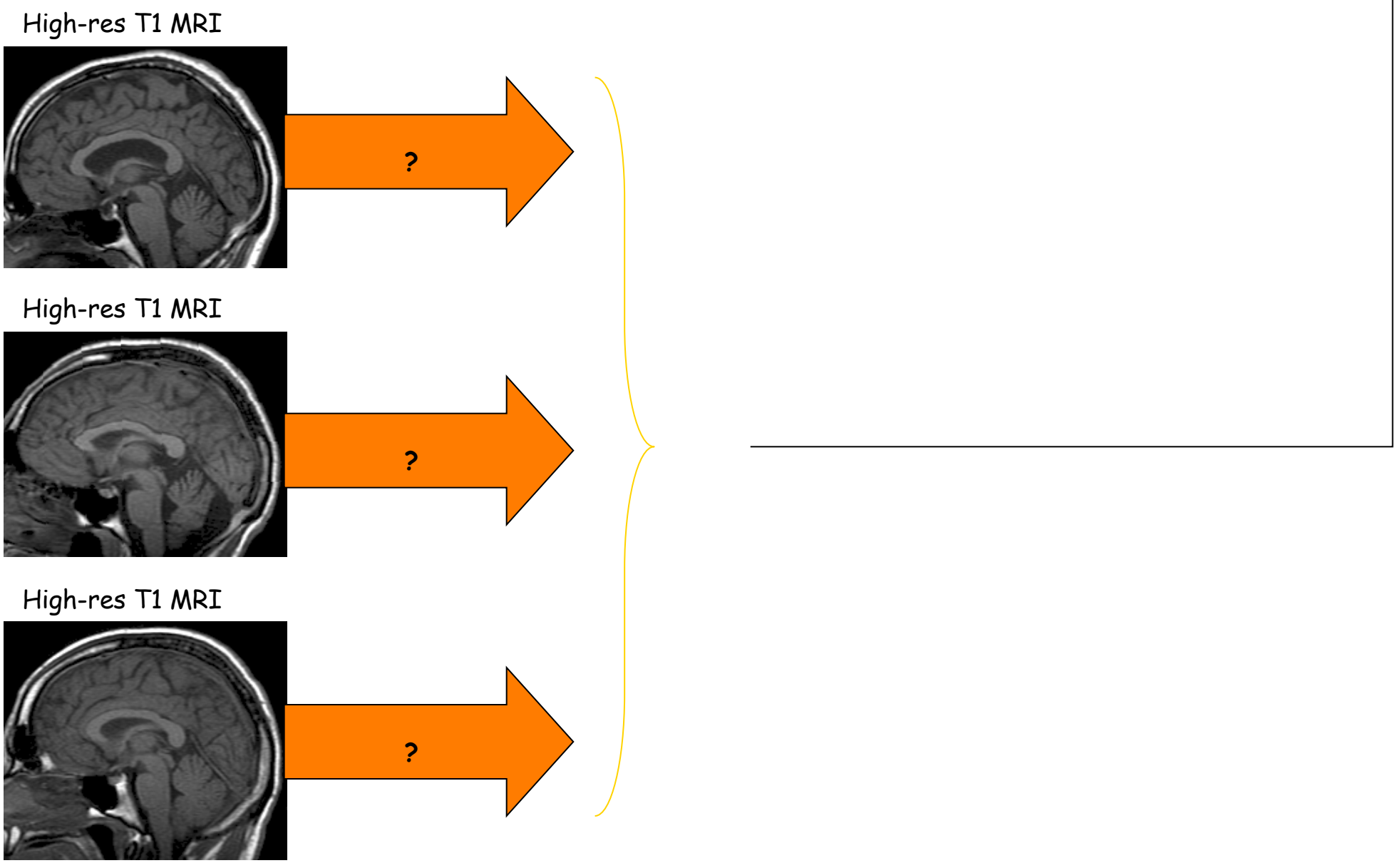
Alzheimer's Disease example

* Some changes are apparent in this patient...
  * Some might be noise or misregistration
  * Perhaps confounding biological effects like hydration changes
  * But some might genuinely reflect underlying AD pathology...
* If we acquired more than two time-points, we could rule out some of the potential confounds
  * Would changes generalise from the patient to the disease?
  * Many morphological questions are not longitudinal, e.g. IQ, sex
* It is appealing to try a "second-level" SPM analysis of structural data variation over subjects
  * E.g. AD vs. healthy, male vs. female or a correlation with IQ

SPM for group fMRI



SPM for structural MRI



The need for tissue segmentation

* High-resolution MRI reveals fine structural detail in the brain, but not all of it reliable or interesting
  * Noise, intensity-inhomogeneity, vasculature, …
* MR Intensity is usually not quantitatively meaningful (in the same way that e.g. CT is)
  * fMRI time-series allow signal *changes* to be analysed statistically, compared to baseline or global values
* Regional volumes of the three main tissue types: gray matter, white matter and CSF, are well-defined and potentially very interesting
  * Other aspects (and other sequences) can also be of interest

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

A brief history of VBM

* *A Voxel-Based Method for the Statistical Analysis of Gray and White Matter Density…* Wright, McGuire, Poline, Travere, Murrary, Frith, Frackowiak and Friston. NeuroImage 2(4), 1995 (!)
  * Rigid reorientation (by eye), semi-automatic scalp editing and segmentation, 8mm smoothing, SPM statistics, global covars.
* *Voxel-Based Morphometry – The Methods*. Ashburner and Friston. NeuroImage 11(6 pt.1), 2000
  * Non-linear spatial normalisation, automatic segmentation
  * Thorough consideration of assumptions and confounds

A brief history of VBM

* *A Voxel-Based Morphometric Study of Ageing…* Good, Johnsrude, Ashburner, Henson and Friston. NeuroImage 14(1), 2001
  * Optimised GM-normalisation (“a half-baked procedure”)
* *Unified Segmentation.* Ashburner and Friston. NeuroImage 26(3), 2005
  * Principled generative model for segmentation using deformable priors
* *A Fast Diffeomorphic Image Registration Algorithm*. Ashburner. Neuroimage 38(1), 2007
  * Large deformation normalisation to average shape templates
* …

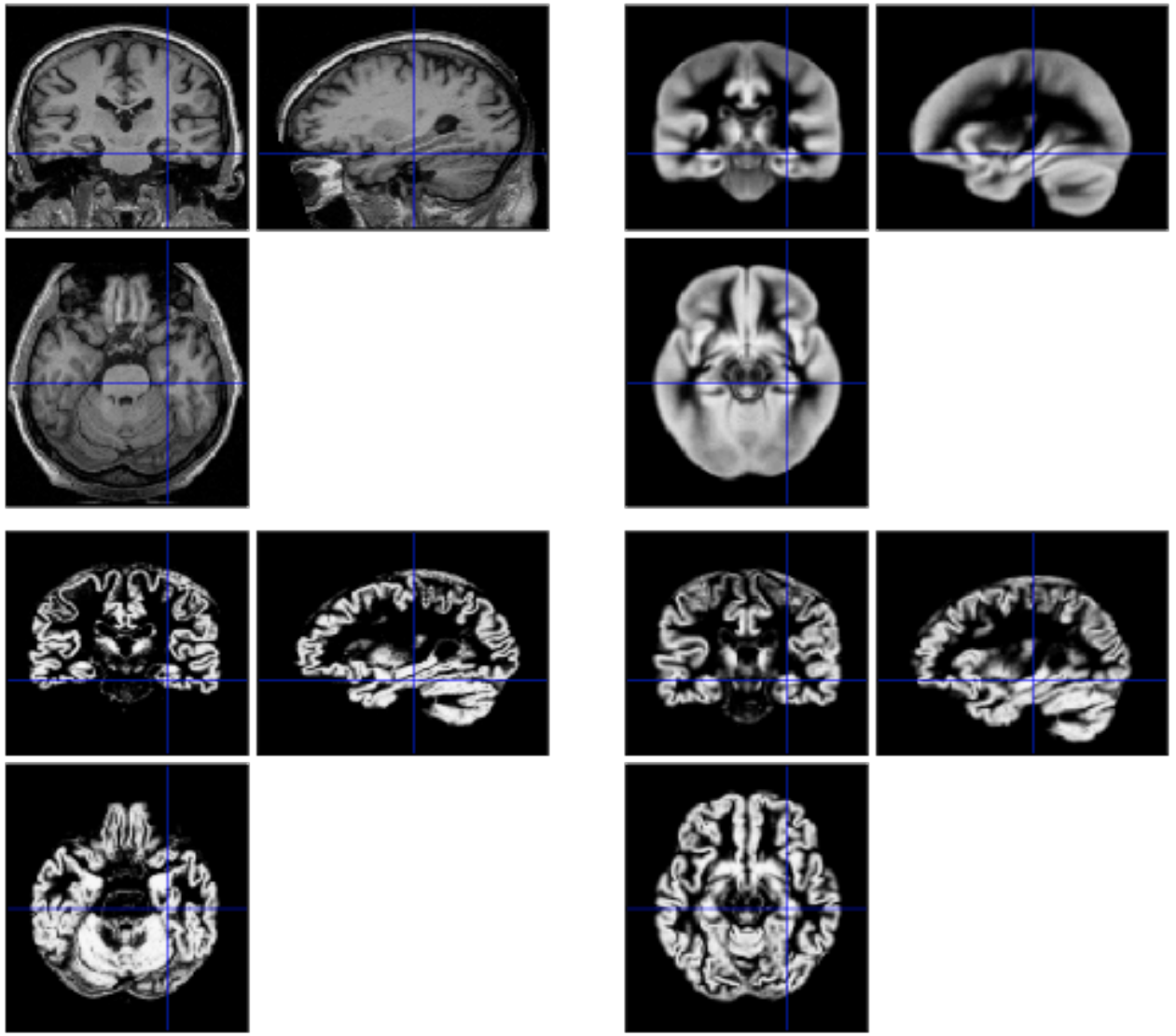
VBM overview

* Unified segmentation and spatial normalisation
  * More flexible groupwise normalisation using DARTEL
* [Optional] modulation with Jacobian determinant
* Optional computation of tissue totals/globals
* Gaussian smoothing
* Voxel-wise statistical analysis

VBM in pictures

Segment

Normalise



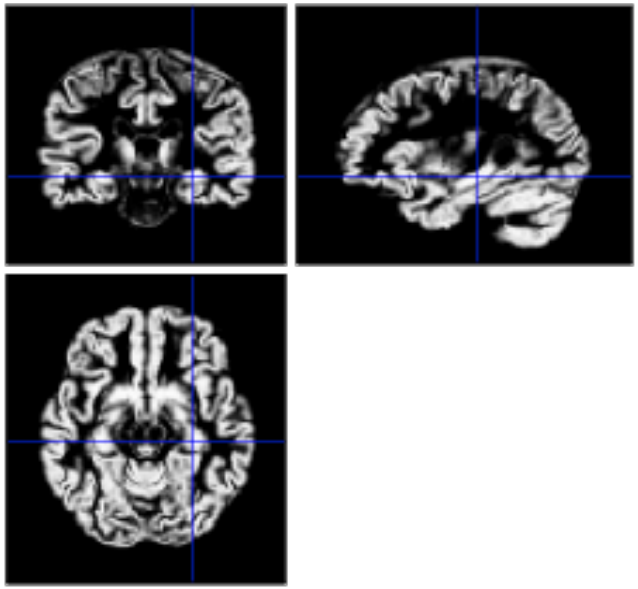
VBM in pictures

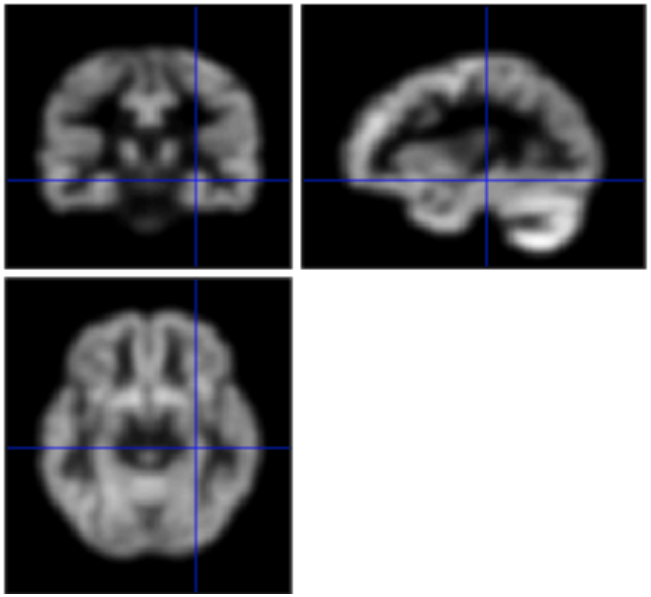
Segment

Normalise

Modulate (?)

Smooth





VBM in pictures

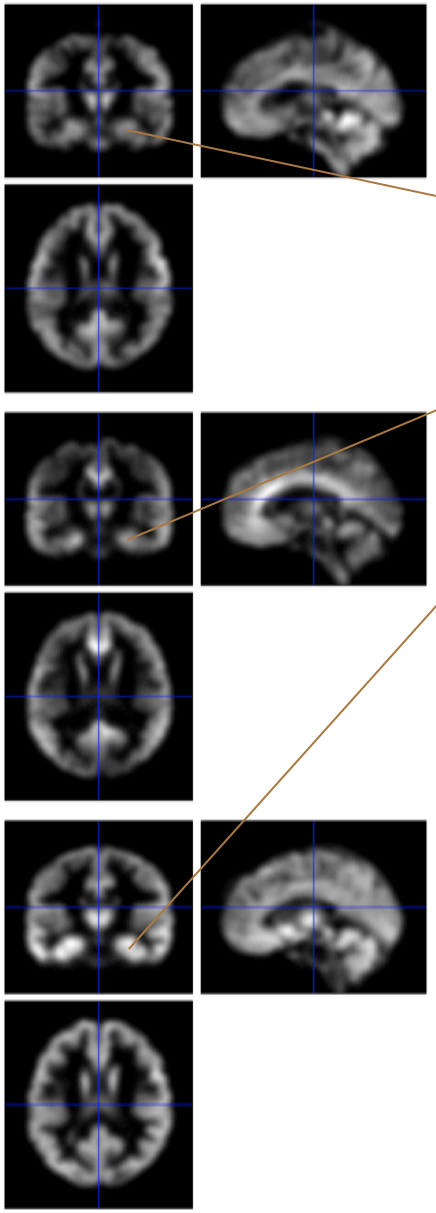
Segment

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

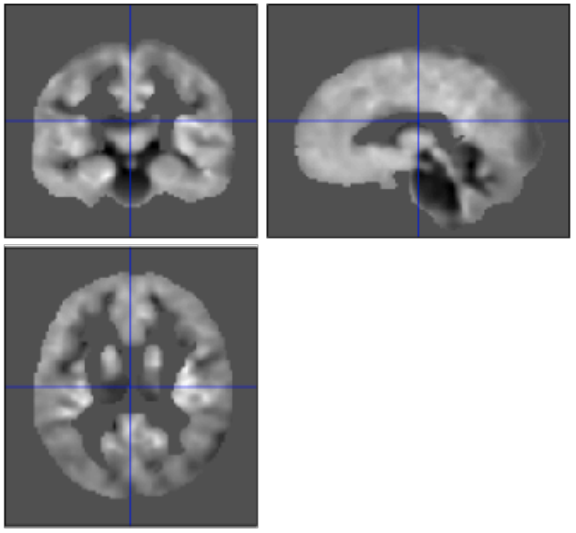
Segment

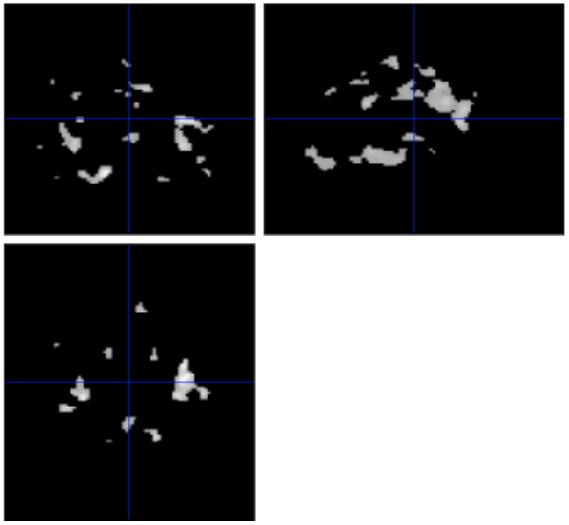
Normalise

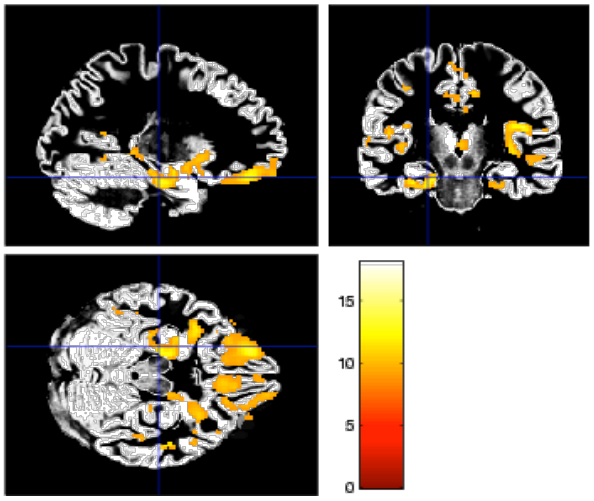
Modulate (?)

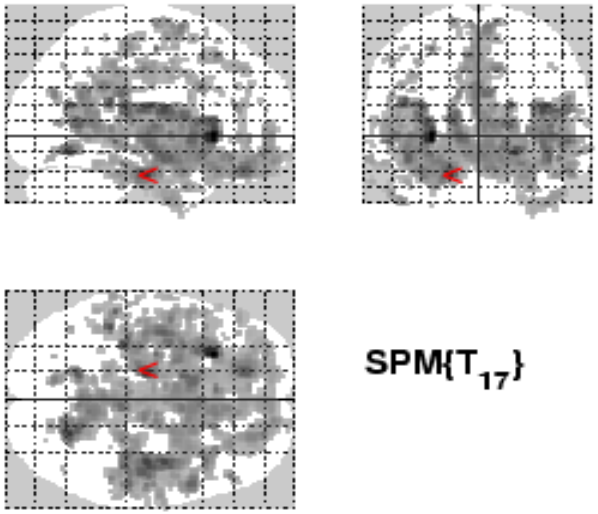
Smooth

Voxel-wise statistics





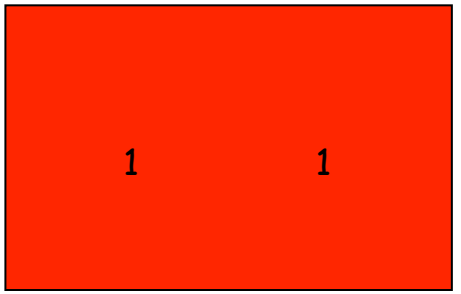




VBM Subtleties

* **Whether to modulate**
* How much to smooth
* Interpreting results
* Adjusting for total GM or Intracranial Volume
* Limitations of linear correlation
* Statistical validity

Modulation

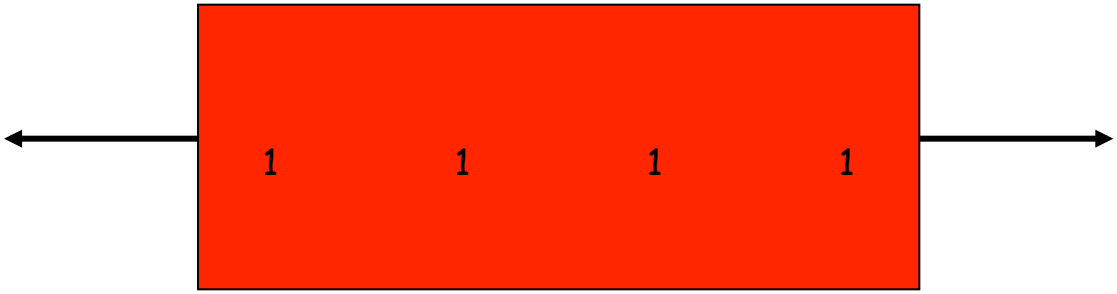


Native

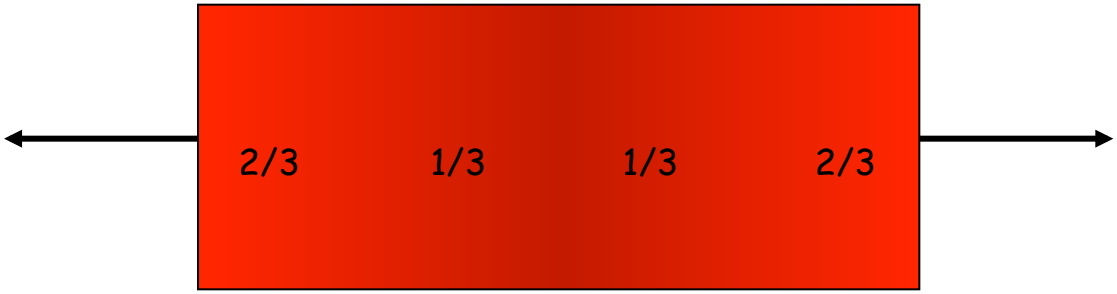
intensity = tissue density

* Multiplication of the warped (normalised) tissue intensities so that their regional or global volume 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") registration may not leave any such differences

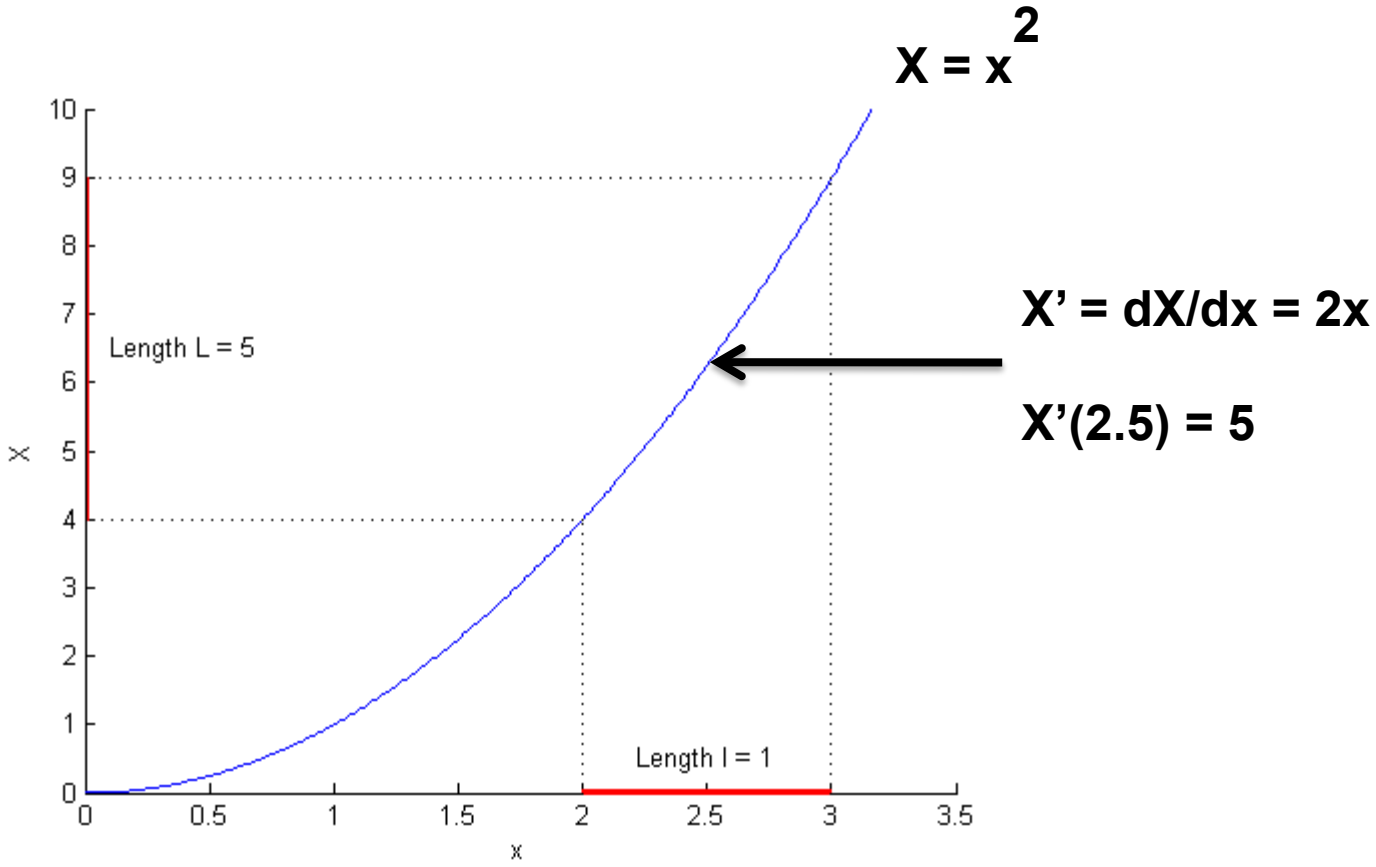
Unmodulated



Modulated

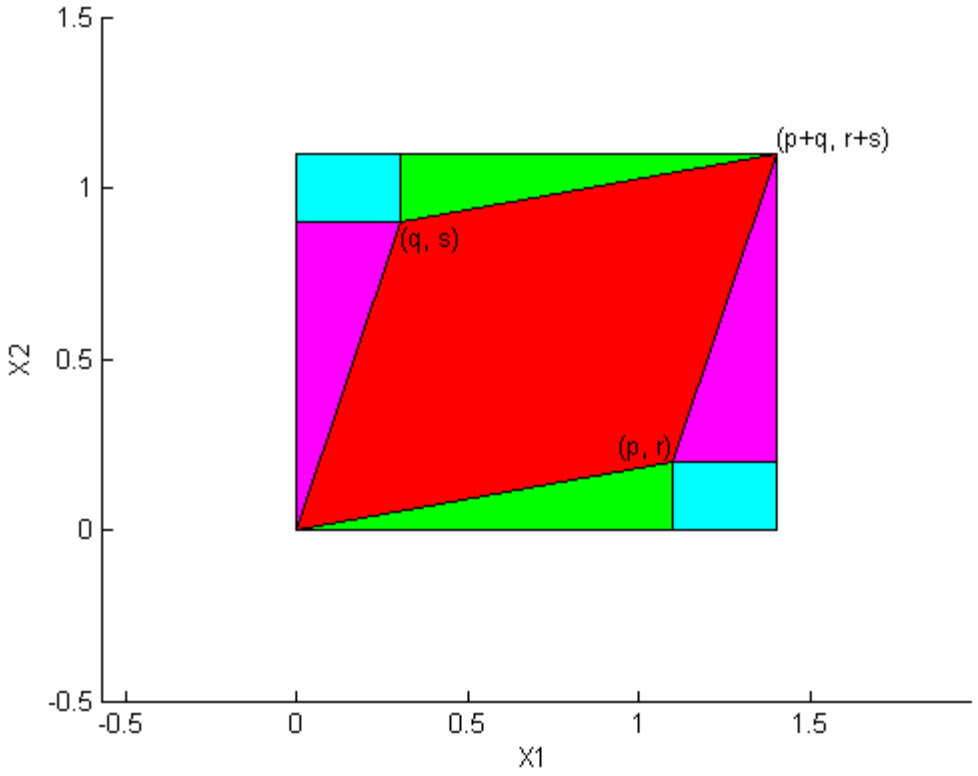


Modulation tutorial



Available from http://www.mathworks.co.uk/matlabcentral/fileexchange/26884

Modulation tutorial



$$T = \begin{bmatrix} p & q \\ r & s \end{bmatrix}$$

Square area = (p+q)(r+s) = pr+ps+qr+qs

$$x \rightarrow X(x)$$

$$dX/dx = \begin{bmatrix} dX_1/dx_1 & dX_1/dx_2 \\ dX_2/dx_1 & dX_2/dx_2 \end{bmatrix}$$

Red area =
Square – cyan – magenta – green =
pr+ps+qr+qs – 2qr – qs – pr = ps – qr

VBM Subtleties

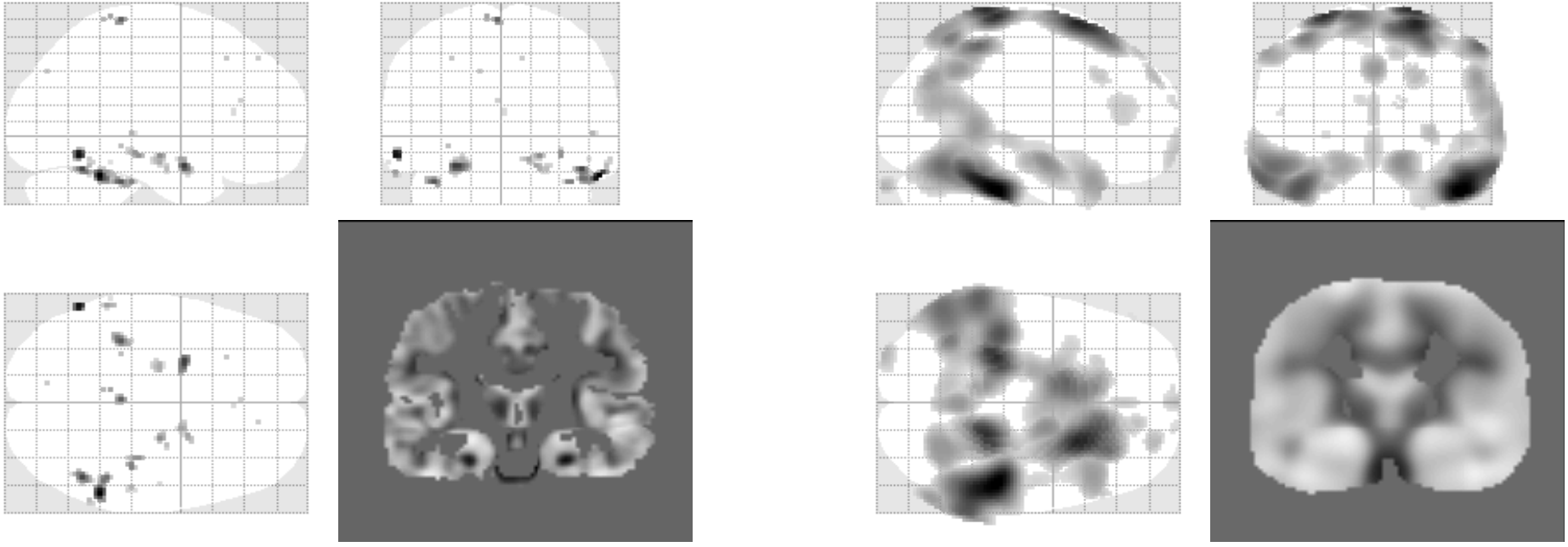
* Whether to modulate
* How much to smooth
* Interpreting results
* Adjusting for total GM or Intracranial Volume
* Limitations of linear correlation
* Statistical validity

Smoothing

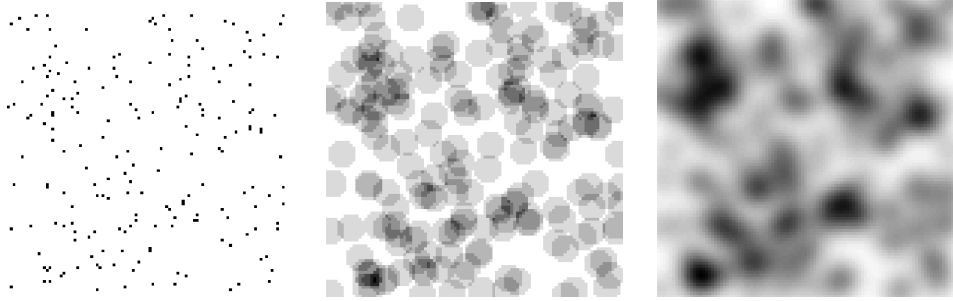
* The analysis will be most sensitive to effects that match the shape and size of the kernel
* The data will be more Gaussian and closer to a continuous random field for larger kernels
* Results will be rough and noise-like if too little smoothing is used
* Too much will lead to distributed, indistinct blobs

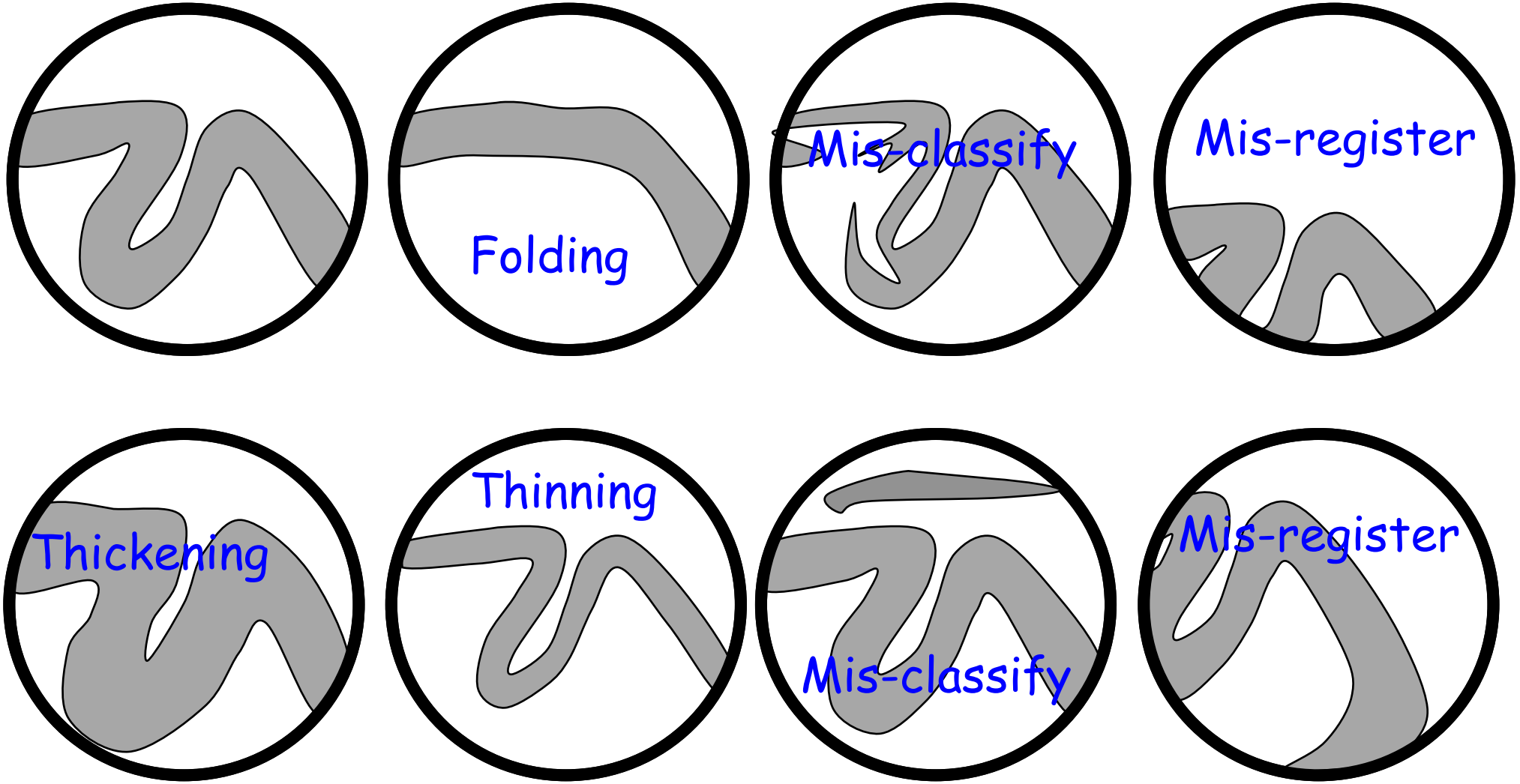
Smoothing

* Between 7 and 14mm is probably reasonable
  * (DARTEL's greater precision allows less smoothing)
  * The results below show two fairly extreme choices, 5mm on the left, and 16mm, right



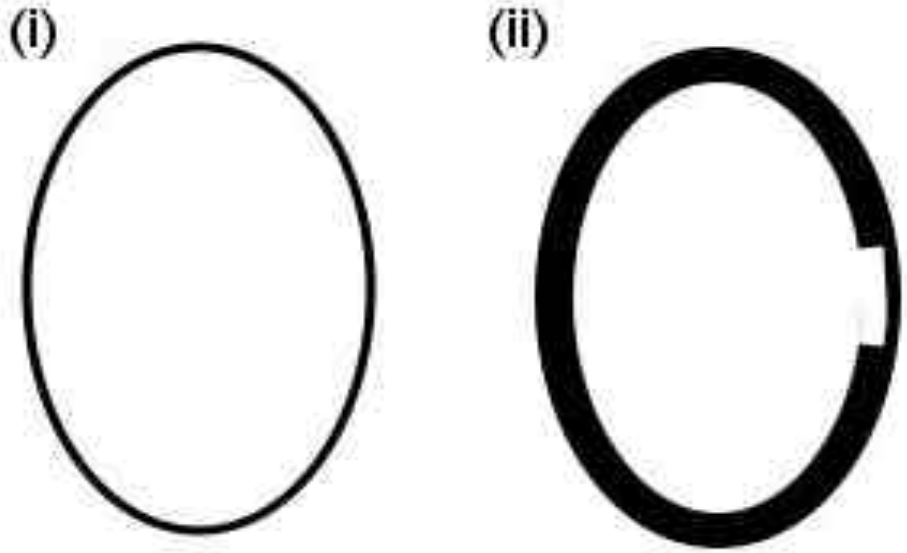
Interpreting findings





“Globals” for VBM

* 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.

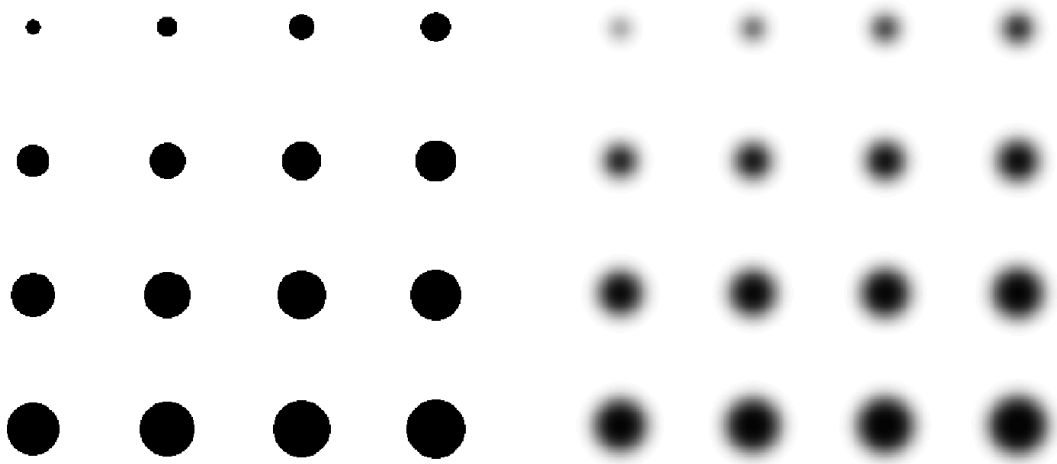
Fig. from: *Voxel-based morphometry of the human brain…* Mechelli, Price, Friston and Ashburner. Current Medical Imaging Reviews 1(2), 2005.

Total Intracranial Volume (TIV/ICV)

* "Global" integrated tissue volume may be correlated with interesting regional effects
  * Correcting for globals in this case may overly reduce sensitivity to local differences
  * Total intracranial volume integrates GM, WM and CSF, or attempts to measure the skull-volume directly
    * Not sensitive to global reduction of GM+WM (cancelled out by CSF expansion – skull is fixed!)
  * Correcting for TIV in VBM statistics **may** give more powerful and/or more interpretable results
    * See also Pell et al (2009) doi:10.1016/j.neuroimage.2008.02.050

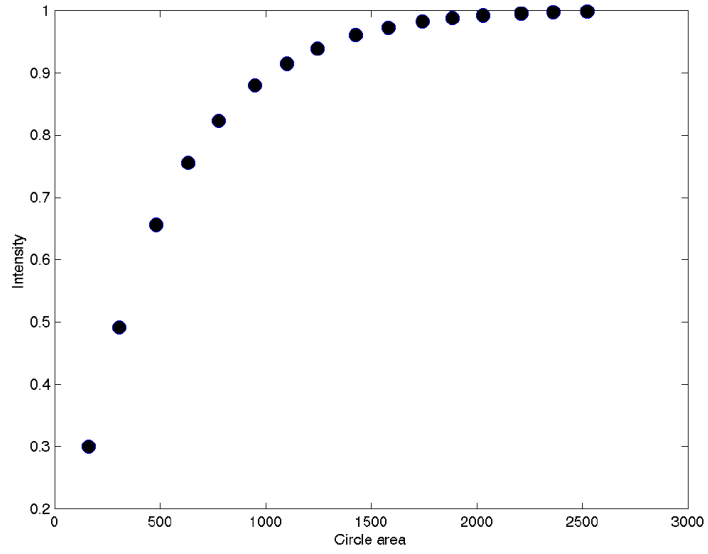
Nonlinearity

Caution may be needed when interpreting linear relationships between grey matter concentrations and some covariate of interest.



Circles of uniformly increasing area.

Smoothed



Plot of intensity at circle centres versus area

VBM's statistical validity

* Residuals are not normally distributed
  * Little impact on uncorrected statistics for experiments comparing reasonably sized groups
  * Probably invalid for experiments that compare single subjects or tiny patient groups with a larger control group
  * Mitigate with large amounts of smoothing
  * Or use nonparametric tests that make fewer assumptions, e.g. permutation testing with SnPM

VBM's statistical validity

* Correction for multiple comparisons
  * RFT correction based on peak heights should be fine
* Correction using cluster extents is problematic
  * SPM usually assumes that the smoothness of the residuals is spatially stationary
    * VBM residuals have spatially varying smoothness
    * Bigger blobs expected in smoother regions
  * Cluster-based correction accounting for nonstationary smoothness is under development
    * See also Satoru Hayasaka's nonstationarity toolbox http://www.fmri.wfubmc.edu/cms/NS-General

VBM's statistical validity

* False discovery rate
  * Less conservative than FWE
  * Popular in morphometric work
    * (almost universal for cortical thickness in FreeSurfer)
  * Recently questioned…
* Topological FDR (for clusters and peaks)
  * See SPM8 release notes and Justin's papers
  * http://dx.doi.org/10.1016/j.neuroimage.2008.05.021
  * http://dx.doi.org/10.1016/j.neuroimage.2009.10.090

Longitudinal VBM

* The simplest method for longitudinal VBM is to use cross-sectional preprocessing, but longitudinal statistical analyses
  * Standard preprocessing not optimal, but unbiased
  * Non-longitudinal statistics would be severely biased
    * (Estimates of standard errors would be too small)
  * Simplest longitudinal statistical analysis: two-stage summary statistic approach (common in fMRI)
    * Within subject longitudinal differences or beta estimates from linear regressions against time

Longitudinal VBM variations

* Intra-subject registration over time is much more accurate than inter-subject normalisation
  * Different approaches suggested to capitalise
* A simple approach is to apply one set of normalisation parameters (e.g. Estimated from baseline images) to both baseline and repeat(s)
  * Draganski et al (2004) Nature 427: 311-312
* “Voxel Compression mapping” – separates expansion and contraction before smoothing
  * Scahill et al (2002) PNAS 99:4703-4707

Longitudinal VBM variations

* Can also multiply longitudinal volume change with baseline or average grey matter density
  * Chételat et al (2005) NeuroImage 27:934-946
  * Kipps et al (2005) JNNP 76:650
  * Hobbs et al (2009) doi:10.1136/jnnp.2009.190702
* Note that use of baseline (or repeat) instead of average might lead to bias
  * Thomas et al (2009) doi:10.1016/j.neuroimage.2009.05.097
  * Unfortunately, the explanations in this reference relating to interpolation differences are not quite right... there are several open questions here...

Spatial normalisation with DARTEL

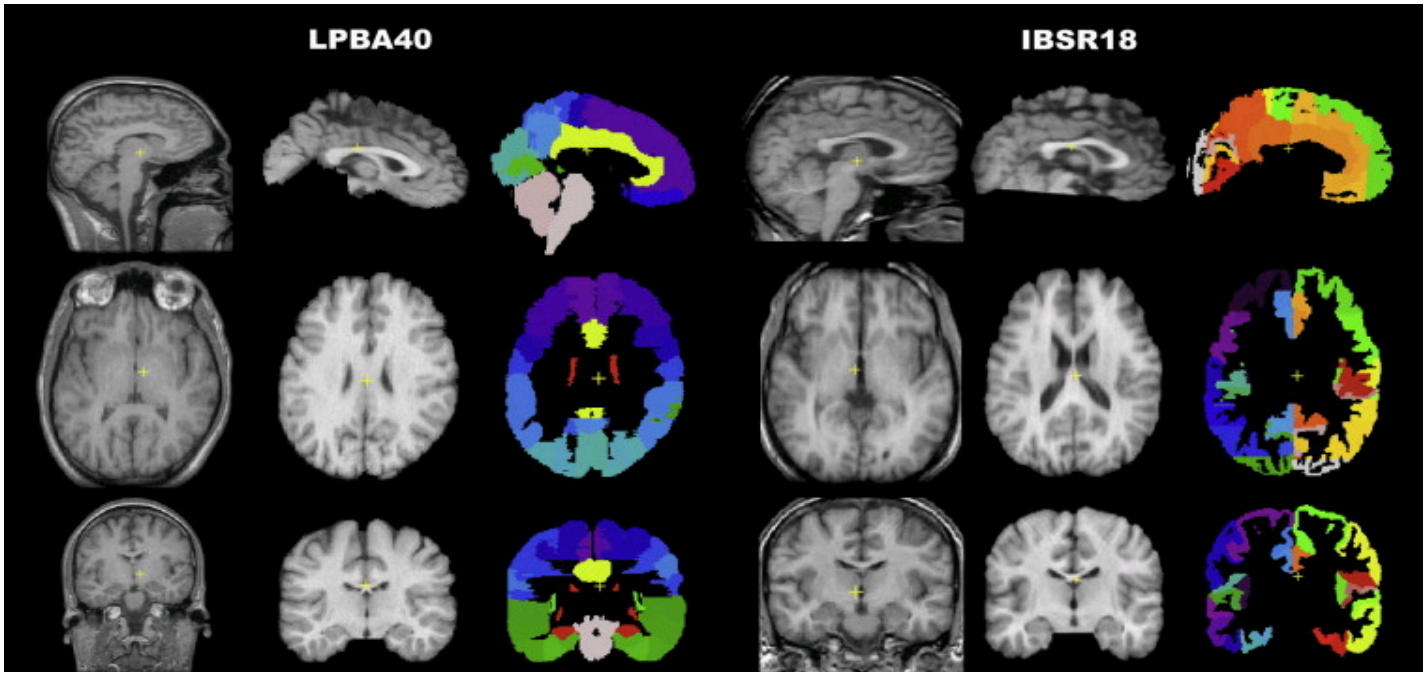
* VBM is crucially dependent on registration performance
  * The limited flexibility of DCT normalisation has been criticised
  * Inverse transformations are useful, but not always well-defined
  * More flexible registration requires careful modelling and regularisation (prior belief about reasonable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

Mathematical advances in registration

* Large deformation concept
  * Regularise velocity not displacement
    * (syrup instead of elastic)
* Leads to concept of geodesic
  * Provides a metric for distance between shapes
  * Geodesic or Riemannian average = mean shape
* If velocity assumed constant computation is fast
  * Ashburner (2007) NeuroImage 38:95-113
  * DARTEL toolbox in SPM8
    * Currently initialised from unified seg_sn.mat files

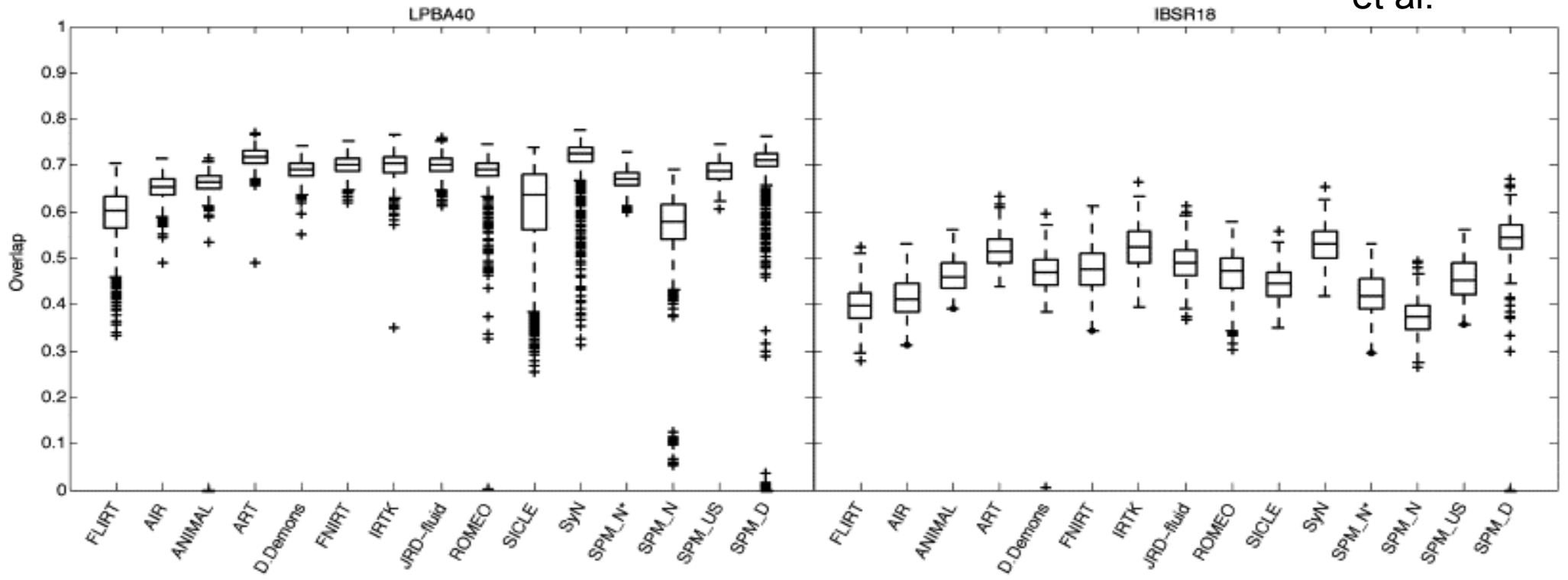
Motivation for using DARTEL

* Recent papers comparing different approaches have favoured more flexible methods
* DARTEL usually outperforms DCT normalisation
  * Also comparable to the best algorithms from other software packages (though note that DARTEL and others have many tunable parameters...)
* Klein et al. (2009) is a particularly thorough comparison, using expert segmentations
  * Results summarised in the next slide



Part of Fig. 1 in Klein et al.

Part of Fig. 5 in Klein et al.

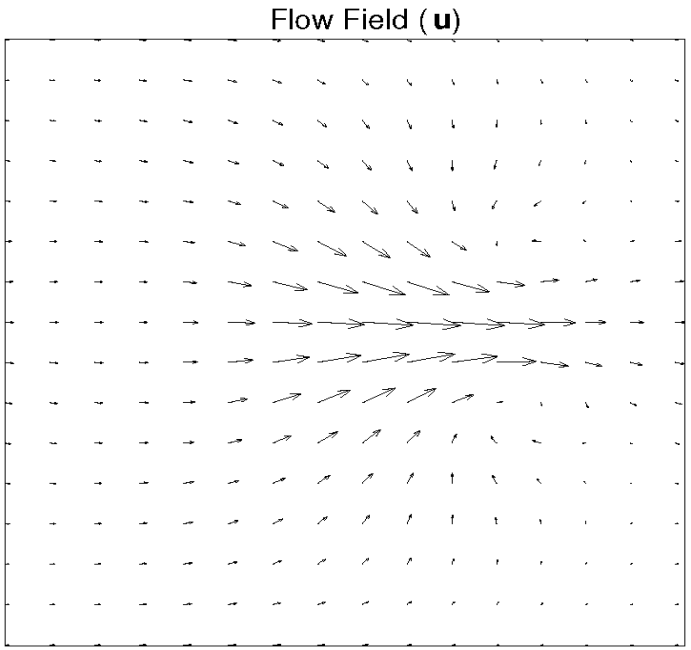


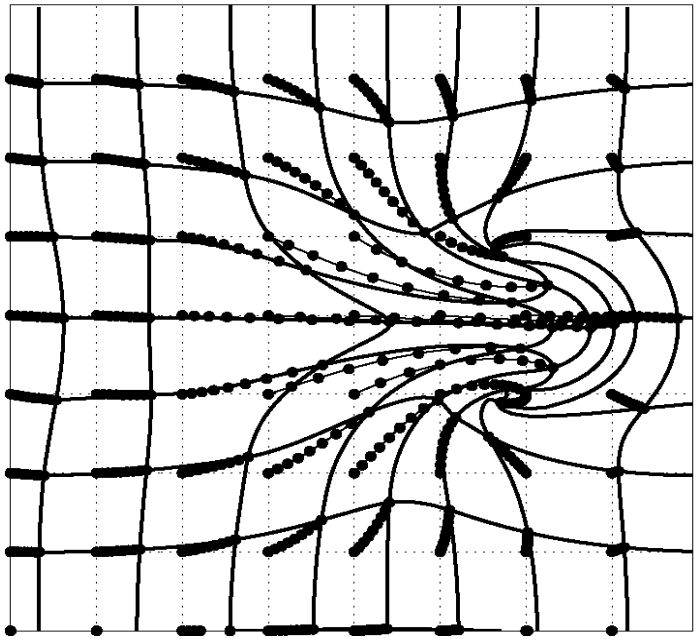
Spatial normalisation with DARTEL

* 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

DARTEL

* Parameterising the deformation
* **u** is a flow field to be estimated
  * 3 (x,y,z) DF per 1.5mm cubic voxel
  * 10^6 DF vs. 10^3 DCT bases
* $\boldsymbol{\varphi}^{(0)}(\mathbf{x}) = \mathbf{x}$
* $\boldsymbol{\varphi}^{(1)}(\mathbf{x}) = \int_{t=0}^{1} \mathbf{u}(\boldsymbol{\varphi}^{(t)}(\mathbf{x}))dt$
* Scaling and squaring is used to generate deformations
* Inverse simply integrates -u





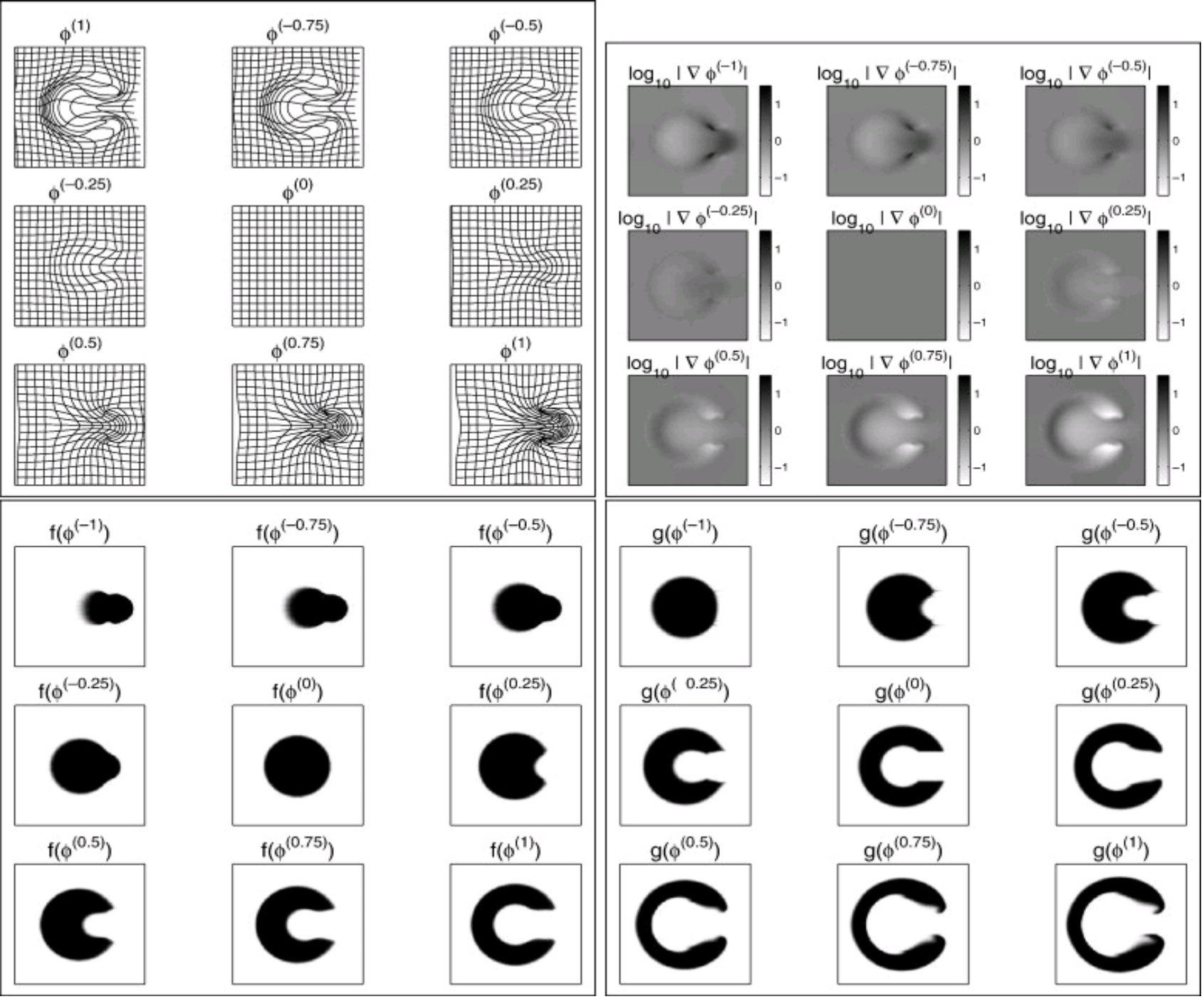


Fig.5 in DARTEL paper

Registration objective function

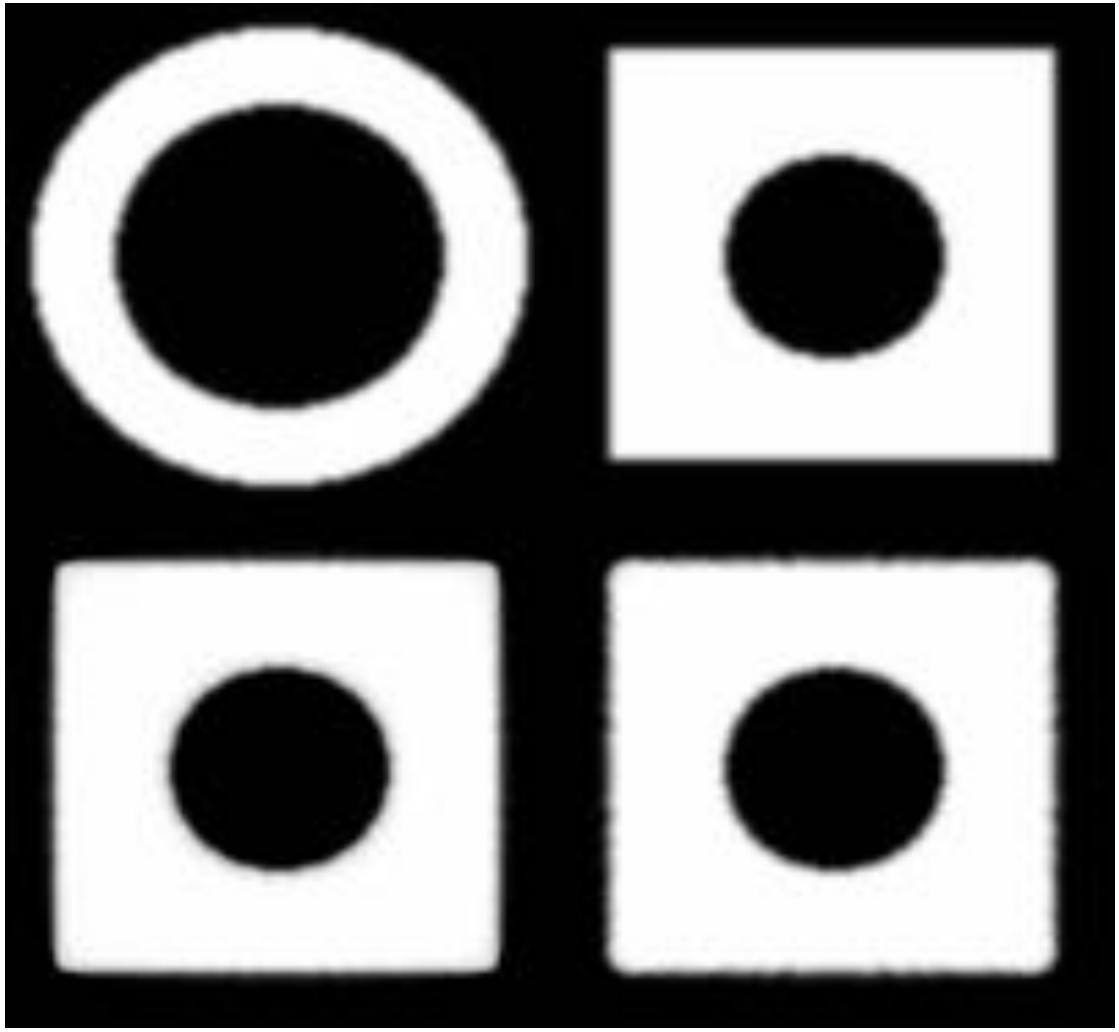
* Likelihood component
  * Drives the matching of the images.
  * Multinomial assumption
* Prior component
  * A measure of deformation roughness
  * Regularises the registration
  * $\frac{1}{2}\mathbf{u}^T\mathbf{H}\mathbf{u}$

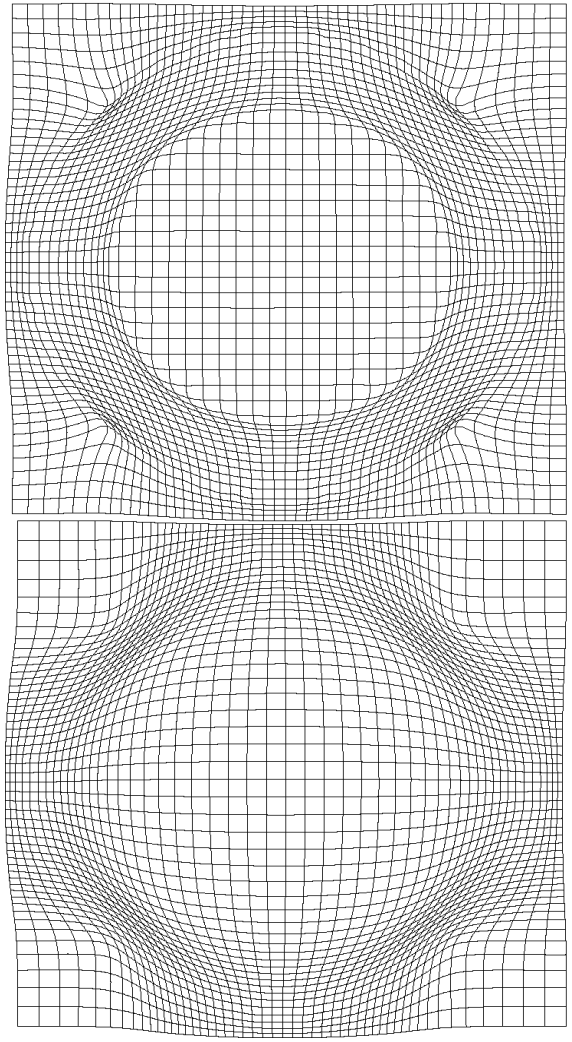
* Need to choose H and a balance between the two terms

Likelihood Model

* Current DARTEL model is *multinomial* for matching tissue class images.
* Template represents probability of obtaining different tissues at each point.
* $\log p(\mathbf{t}|\boldsymbol{\mu},\boldsymbol{\phi}) = \Sigma_j \Sigma_k \, t_{jk} \log(\mu_k(\phi_j))$
  - $\mathbf{t}$ – individual GM, WM and background
  - $\boldsymbol{\mu}$ – template GM, WM and background
  - $\boldsymbol{\phi}$ – deformation

Prior Models



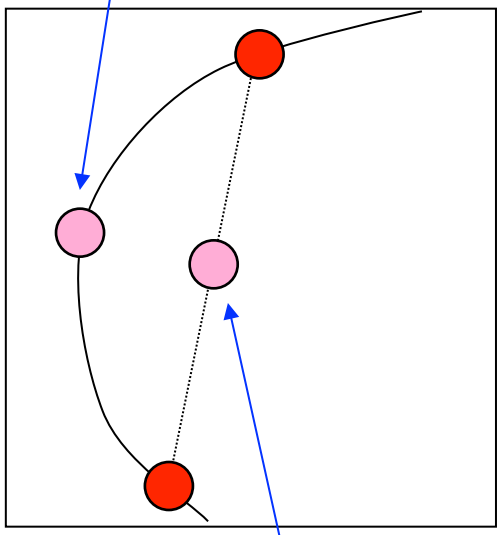


A word of caution…

* Different models have different parameterisations and will therefore give different findings
* Shape models (image registration models) are no exception
* Need to have a good model to reliably report details about differences among parameters
* Not always easy to determine good/best model
  * Bayesian model comparison not yet feasible for Dartel
  * Classification or prediction are useful; work in progress...

Example geodesic shape average

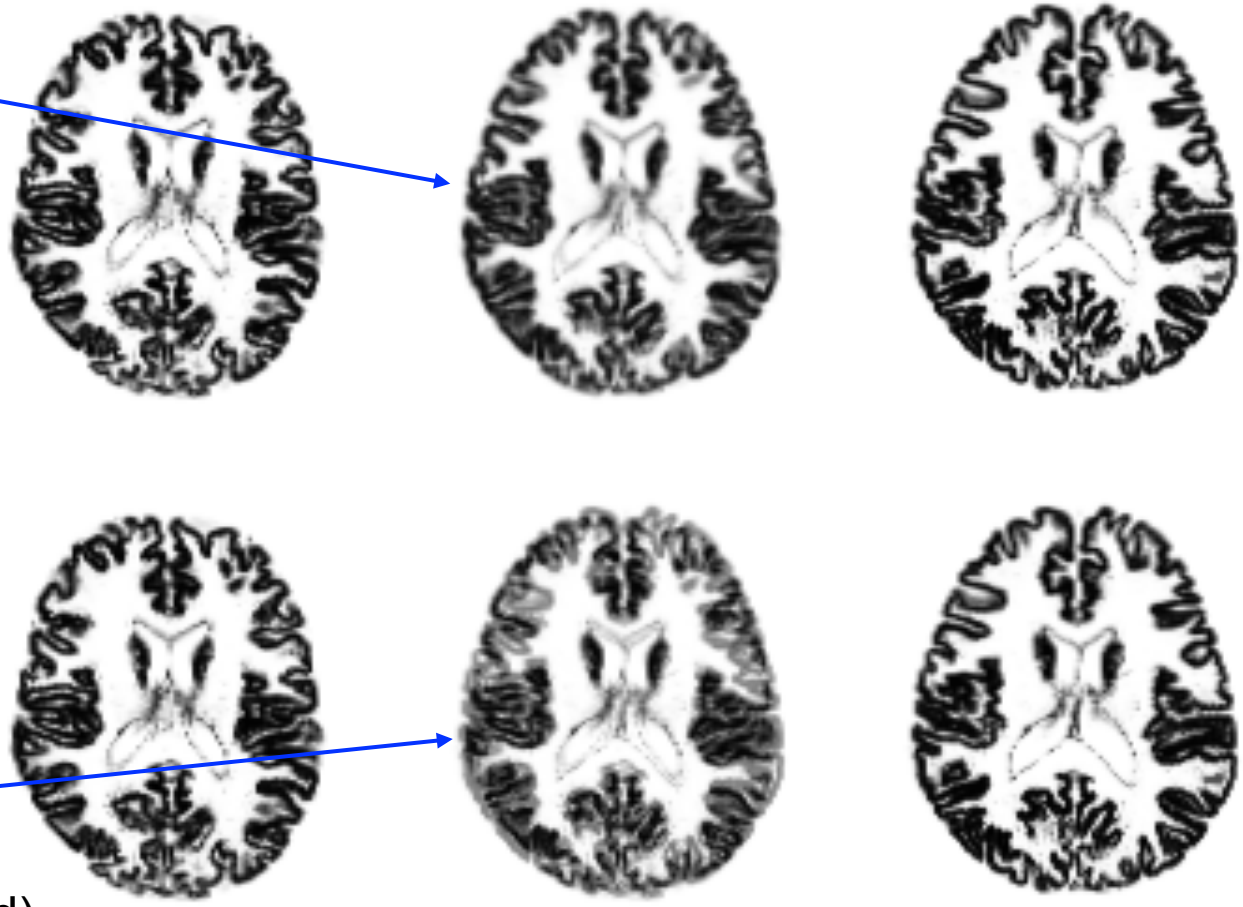
Average on Riemannian manifold



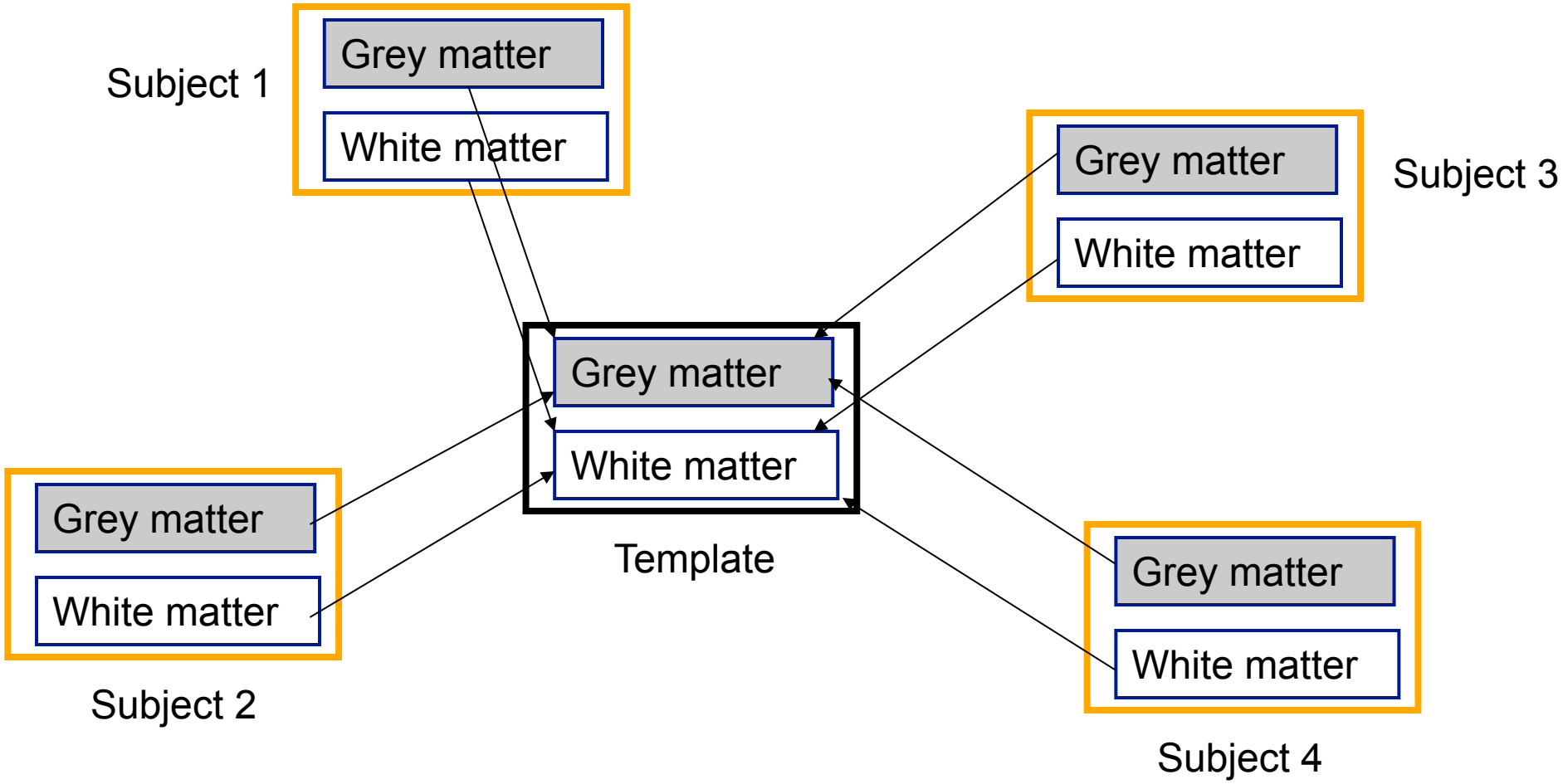
Linear Average

(Not on Riemannian manifold)

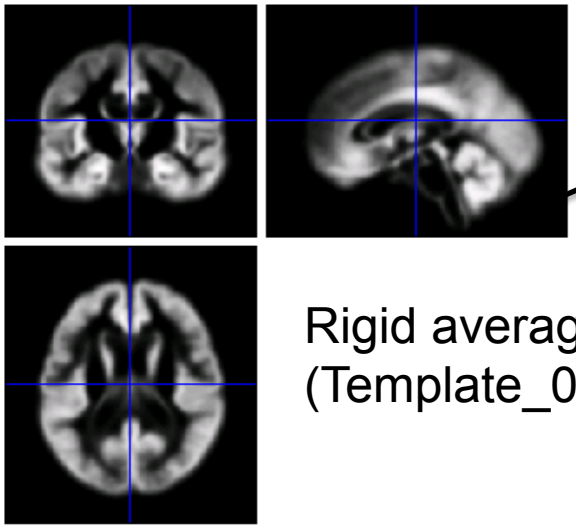
Uses average flow field



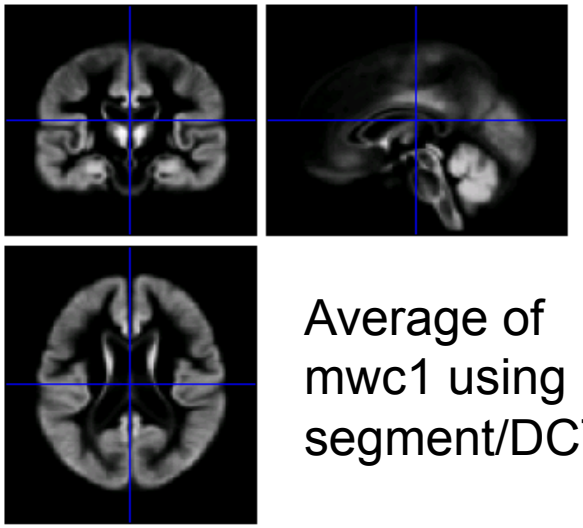
Simultaneous registration of GM to GM and WM to WM, for a group of subjects



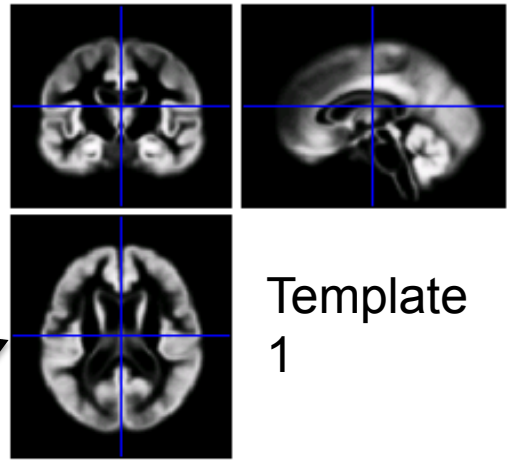
DARTEL average template evolution



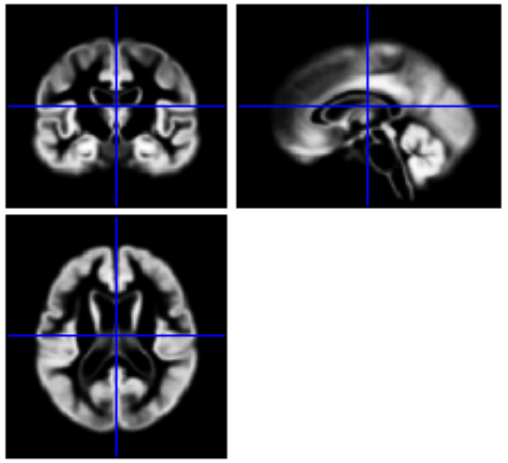
Rigid average
(Template_0)

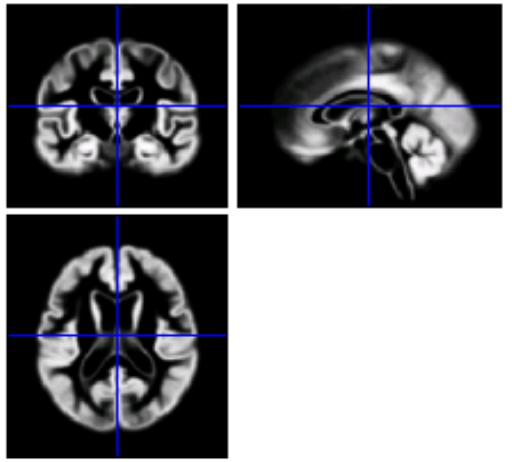


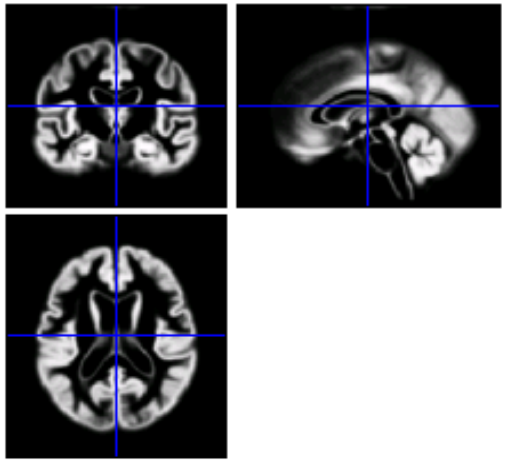
Average of
mwc1 using
segment/DCT

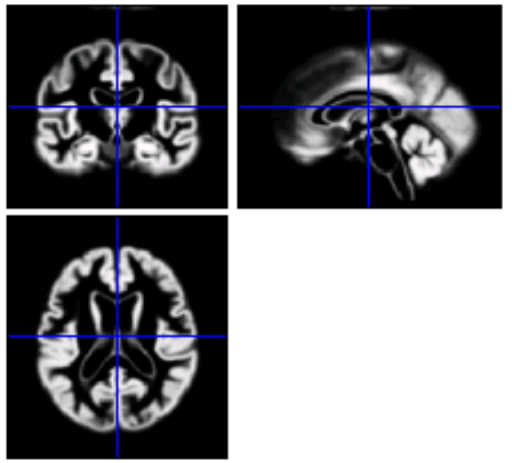


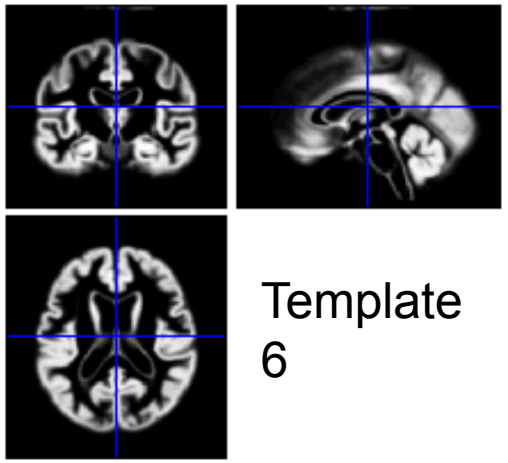
Template
1



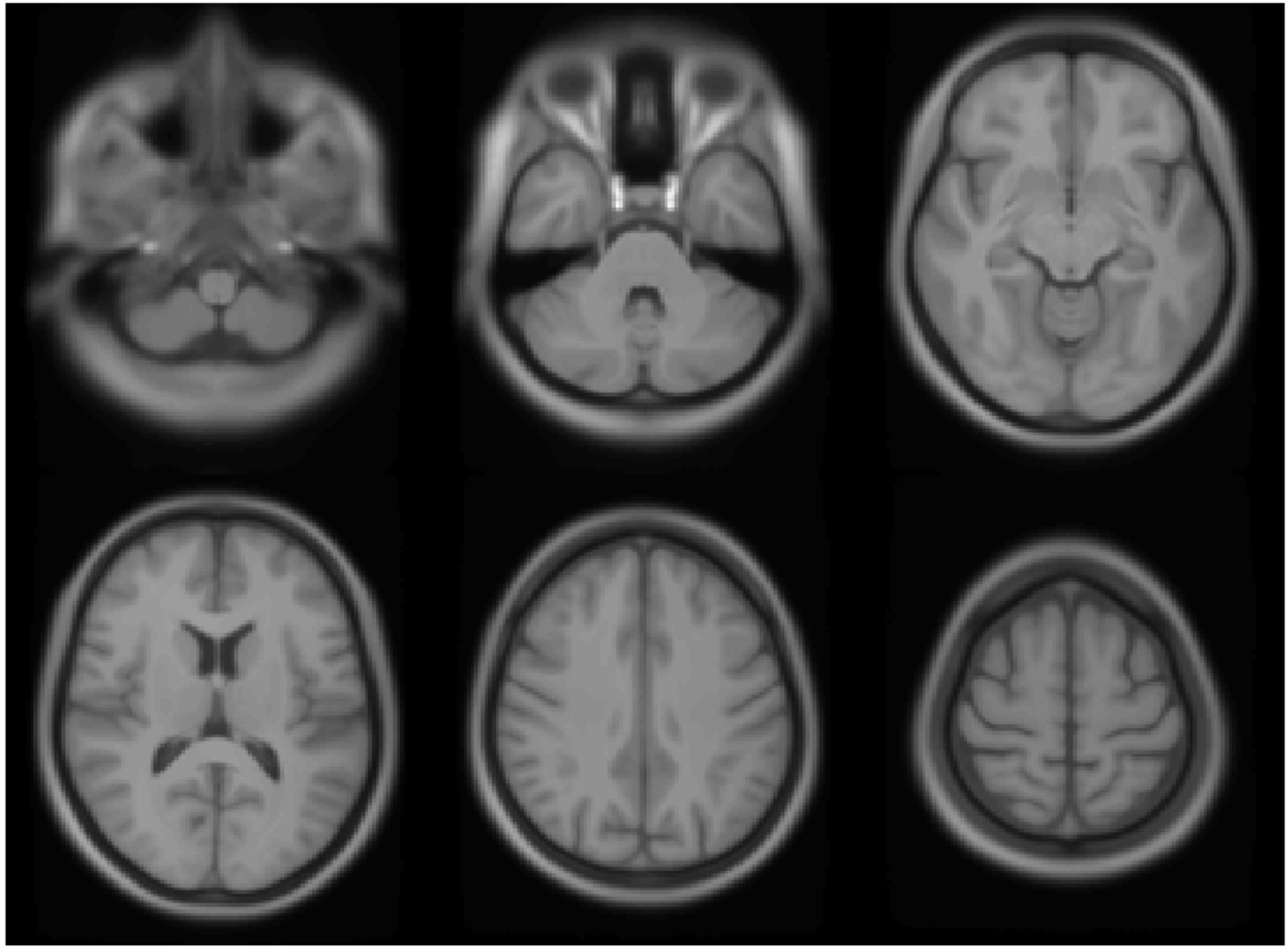


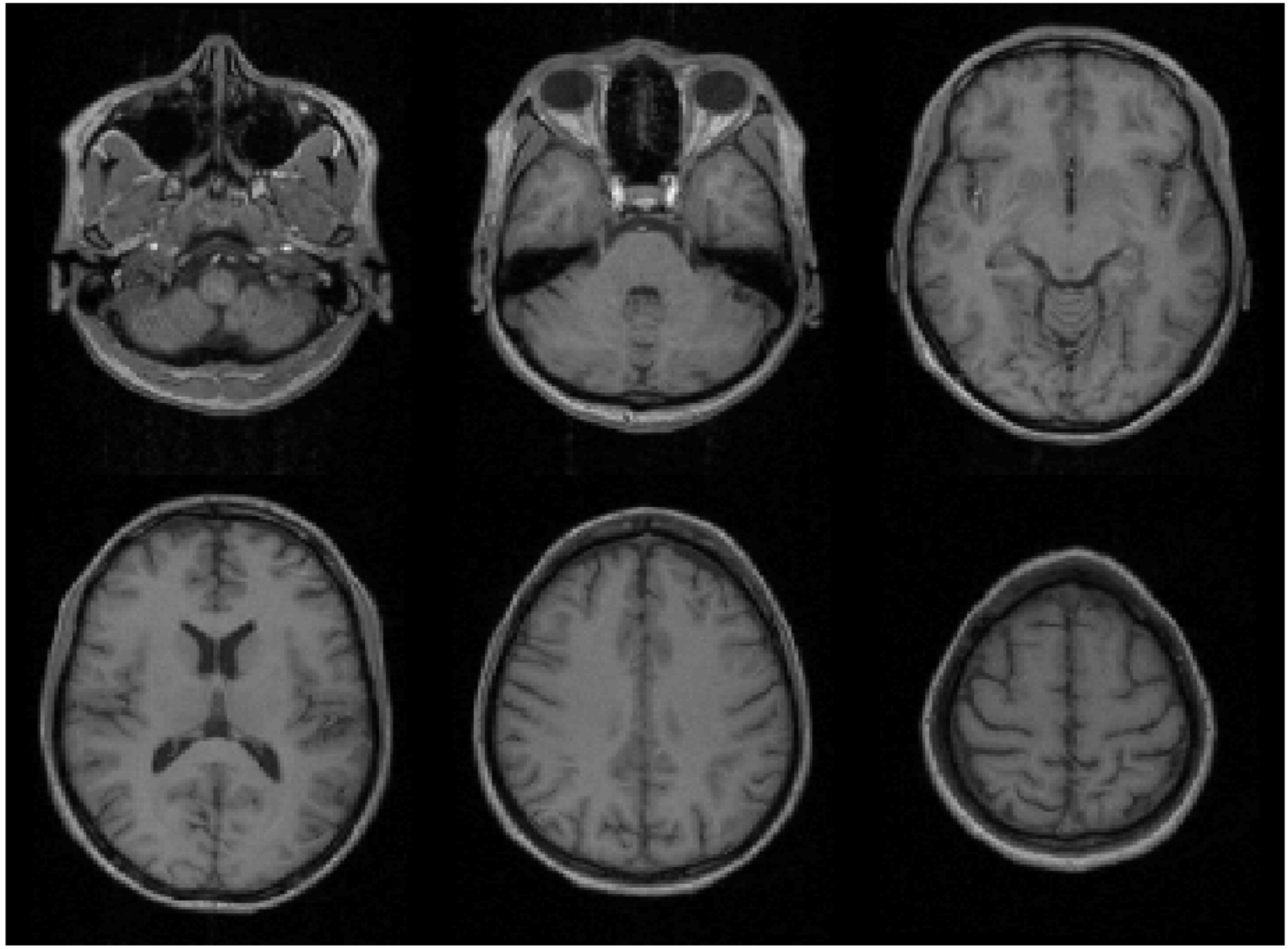






Template
6

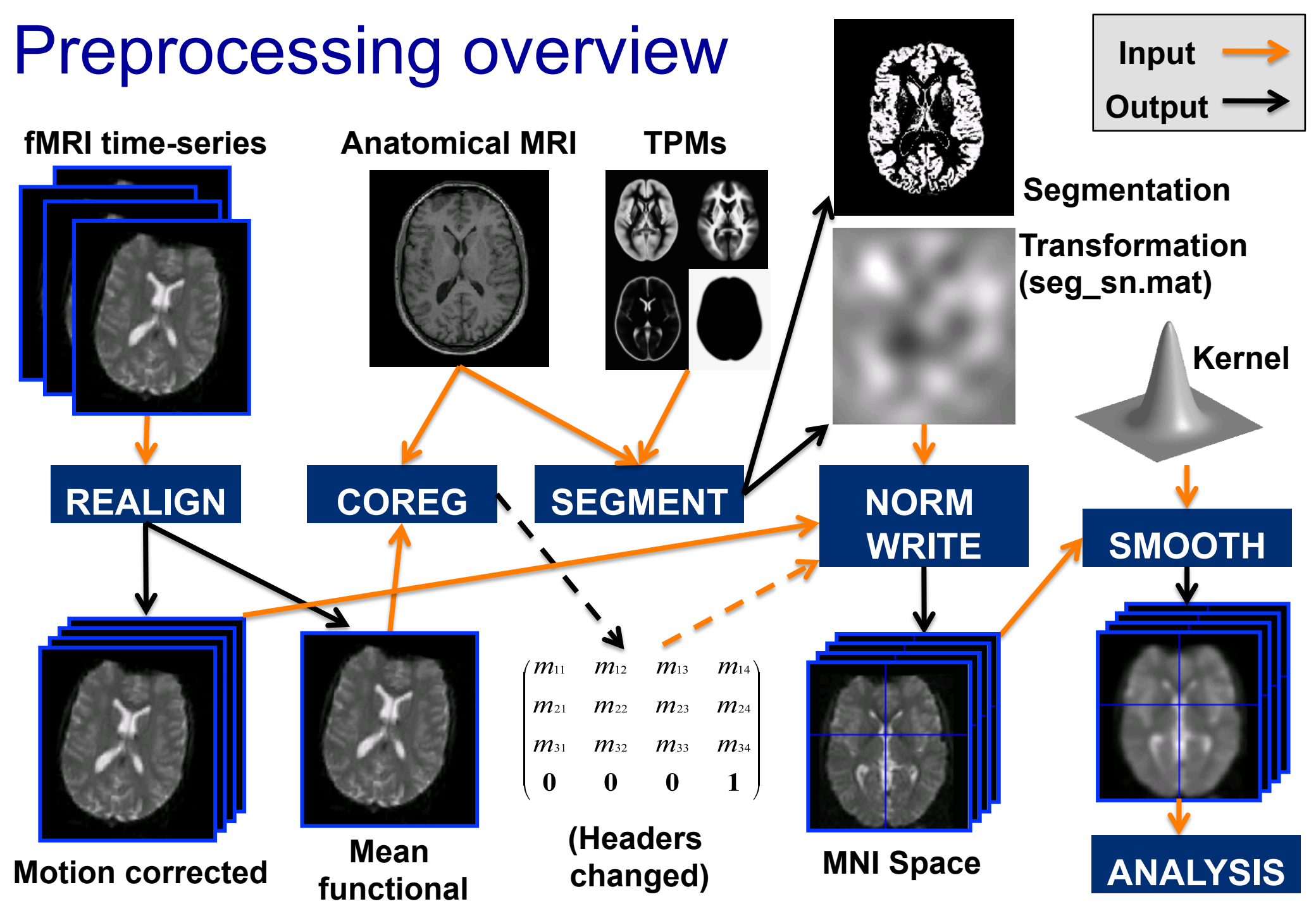




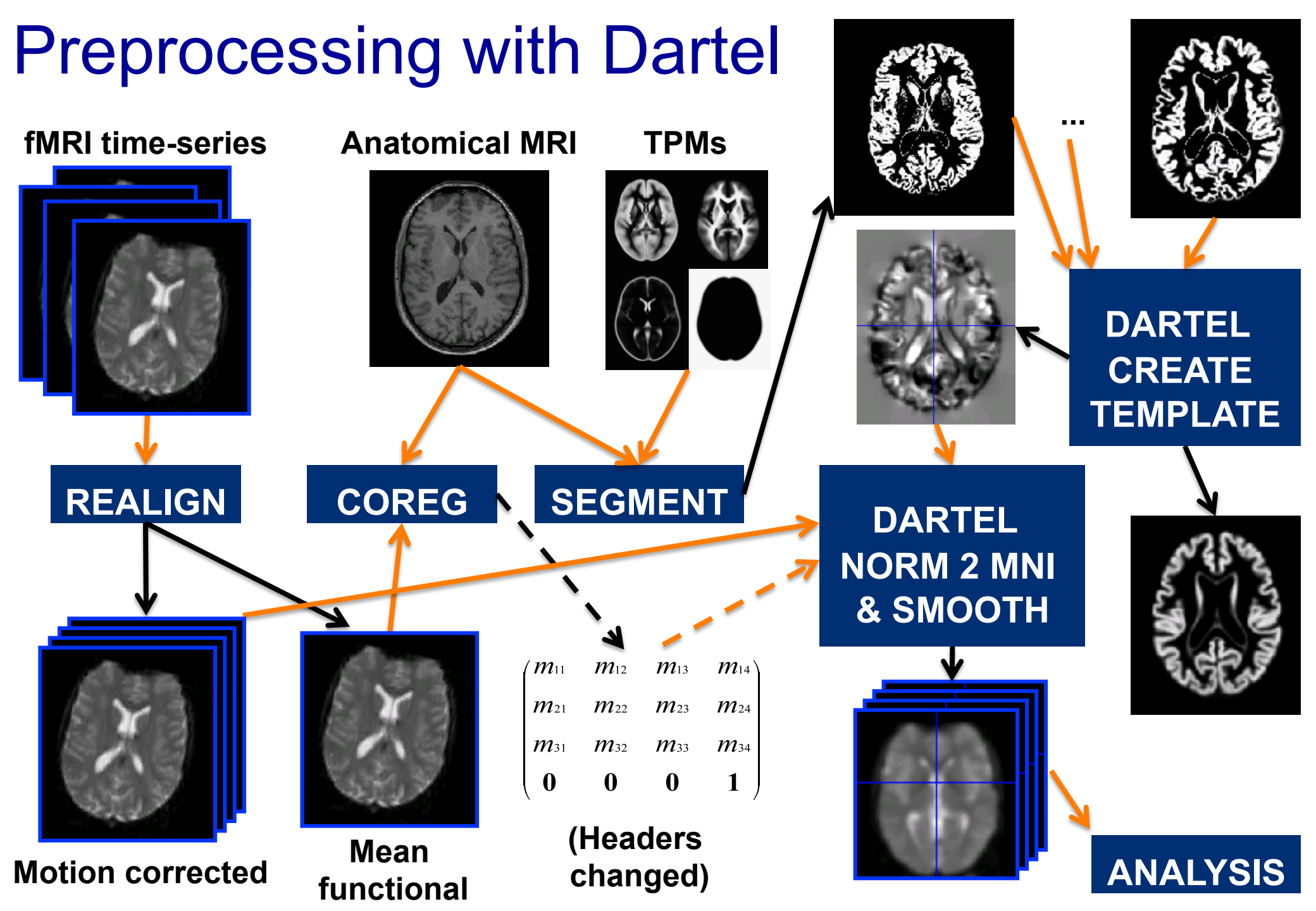
Summary

* VBM performs voxel-wise statistical analysis on smoothed (modulated) normalised tissue segments
* SPM8 performs segmentation and spatial normalisation in a unified generative model
  * Based on Gaussian mixture modelling, with DCT-warped spatial priors, and multiplicative bias field
  * The new segment toolbox includes non-brain priors and more flexible/precise warping of them
* Subsequent (currently non-unified) use of DARTEL improves normalisation for VBM
  * And perhaps also fMRI...

Preprocessing overview



Preprocessing with Dartel



Mathematical advances in computational anatomy

* VBM is well-suited to find focal volumetric differences
* Assumes independence among voxels
  * Not very biologically plausible
  * But shows differences that are easy to interpret
* Some anatomical differences can not be localised
  * Need multivariate models
  * Differences in terms of proportions among measurements
  * Where would the difference between male and female faces be localised?

Mathematical advances in computational anatomy

* In theory, assumptions about structural covariance among brain regions are more biologically plausible
  * Form influenced by spatio-temporal modes of gene expression
* Empirical evidence, e.g.
  * Mechelli, Friston, Frackowiak & Price. *Structural covariance in the human cortex*. Journal of Neuroscience 25:8303-10 (2005)
* Recent introductory review:
  * Ashburner & Klöppel. "*Multivariate models of inter-subject anatomical variability*". NeuroImage, In press.

Conclusion

* VBM uses the machinery of SPM to localise patterns in regional volumetric variation
  * Use of “globals” as covariates is a step towards multivariate modelling of volume and shape
* More advanced approaches typically benefit from the same preprocessing methods
  * New segmentation and DARTEL close to state of the art
  * Though possibly little or no smoothing
* Elegant mathematics related to transformations (diffeomorphism group with Riemannian metric)
* VBM – easier interpretation – complementary role

Key references for VBM

* Ashburner & Friston. *Unified Segmentation*. NeuroImage 26:839-851 (2005).
* Mechelli et al. *Voxel-based morphometry of the human brain…* Current Medical Imaging Reviews 1(2) (2005).
* Ashburner. *A Fast Diffeomorphic Image Registration Algorithm*. NeuroImage 38:95-113 (2007).
* Ashburner & Friston. *Computing average shaped tissue probability templates*. NeuroImage 45(2): 333-341 (2009).

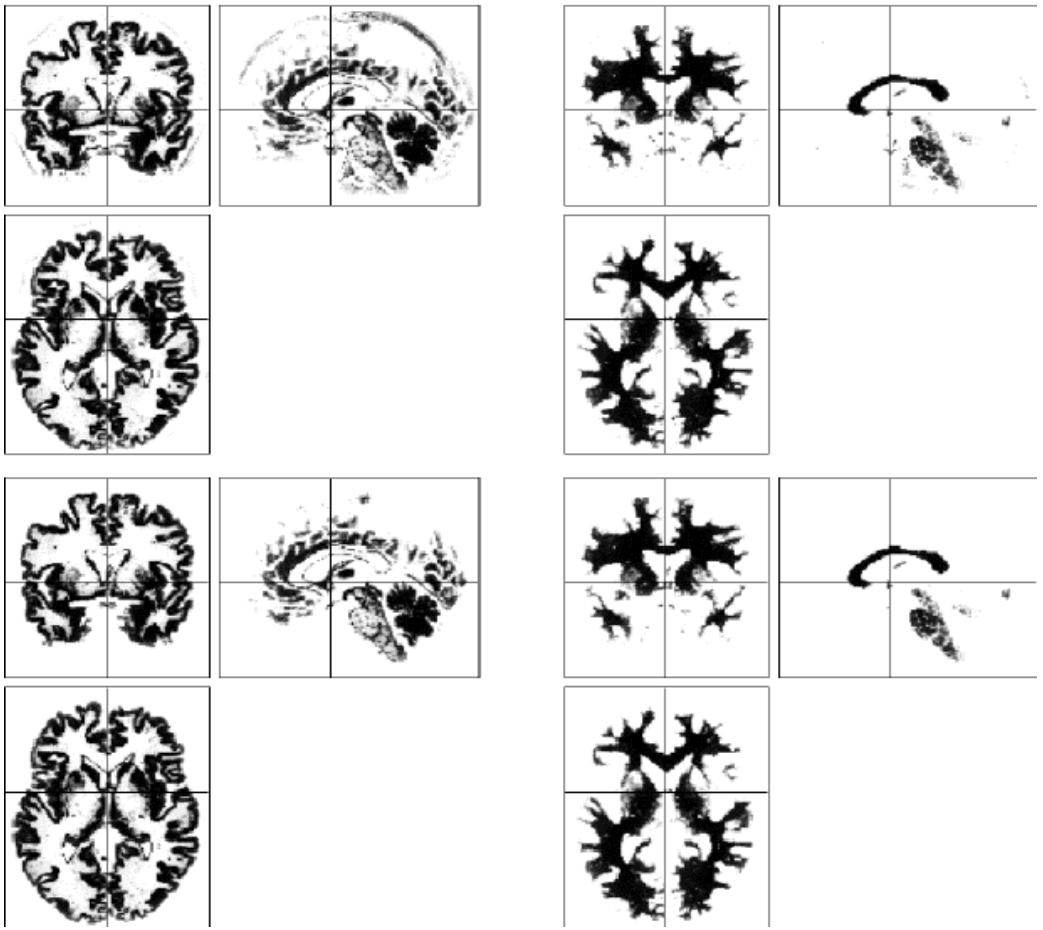
References for more advanced computational anatomy

* Ashburner, Hutton, Frackowiak, Johnsrude, Price & Friston. "*Identifying global anatomical differences: deformation-based morphometry*". Human Brain Mapping 6(5-6):348-357, 1998.
* Bishop. *Pattern recognition and machine learning*. 2006.
* Younes, Arrate & Miller. "*Evolutions equations in computational anatomy*". NeuroImage 45(1):S40-S50, 2009.
* Ashburner & Klöppel. "*Multivariate models of inter-subject anatomical variability*". NeuroImage, In press.

EXTRA MATERIAL

Segmentation clean-up

* Results may contain some non-brain tissue (dura, scalp, etc.)
* This can be removed automatically using simple morphological filtering operations
  * Erosion
  * Conditional dilation

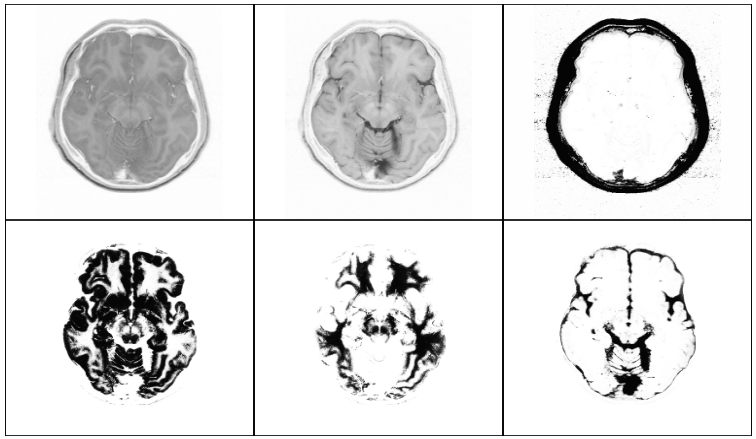


Lower segmentations have been cleaned up

The new segmentation toolbox

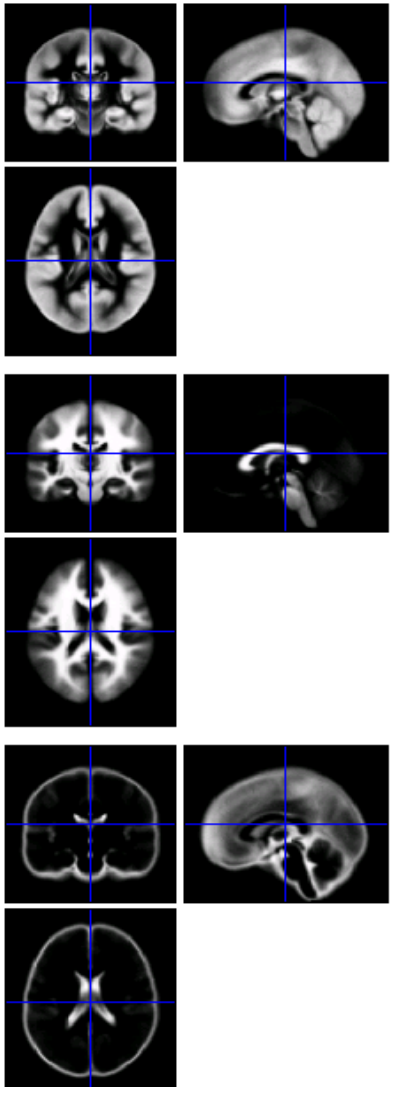
* An extended work-in-progress algorithm
* Multi-spectral
* New TPMs including different tissues
  * Reduces problems in non-brain tissue
* New more flexible warping of TPMs
  * More precise and more “sharp/contrasty” results

$$\mu_k \rightarrow \mathbf{\mu}_k, \sigma_k \rightarrow \mathbf{\sigma}_k, \rho \rightarrow \{\rho_s\}$$

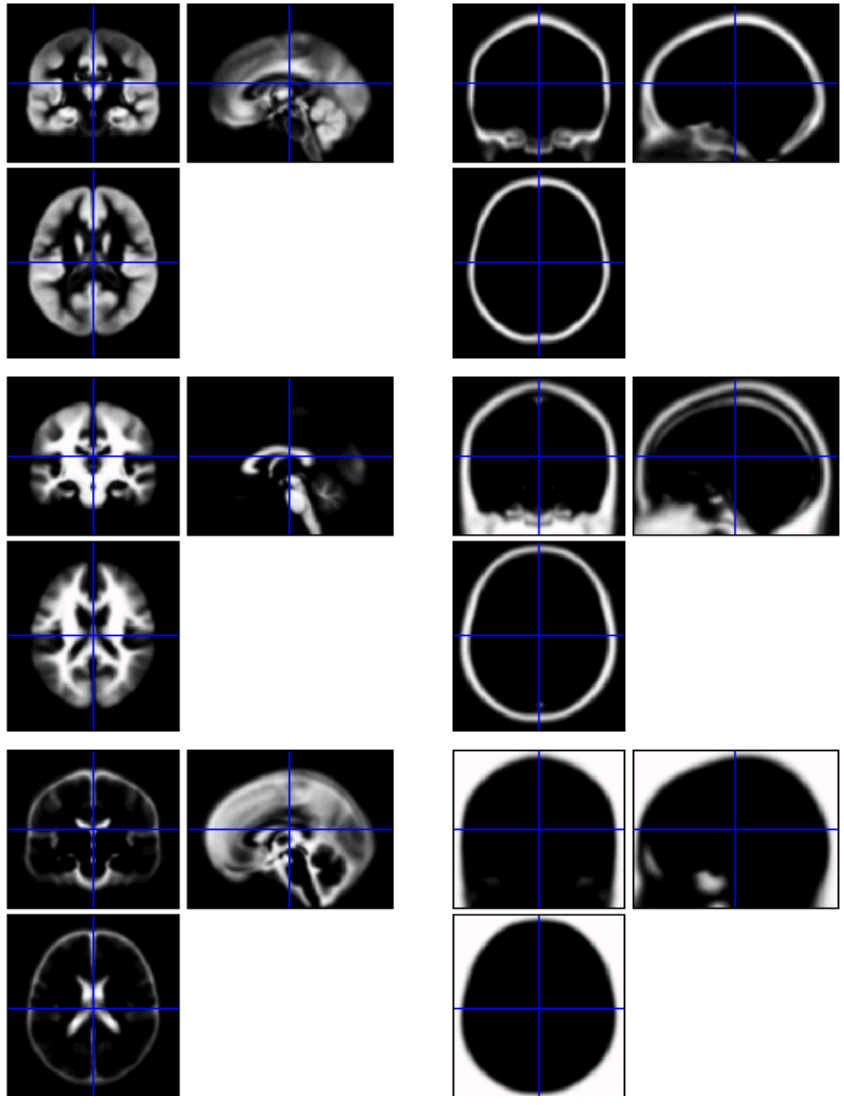


New Segmentation – TPMs

Segment button



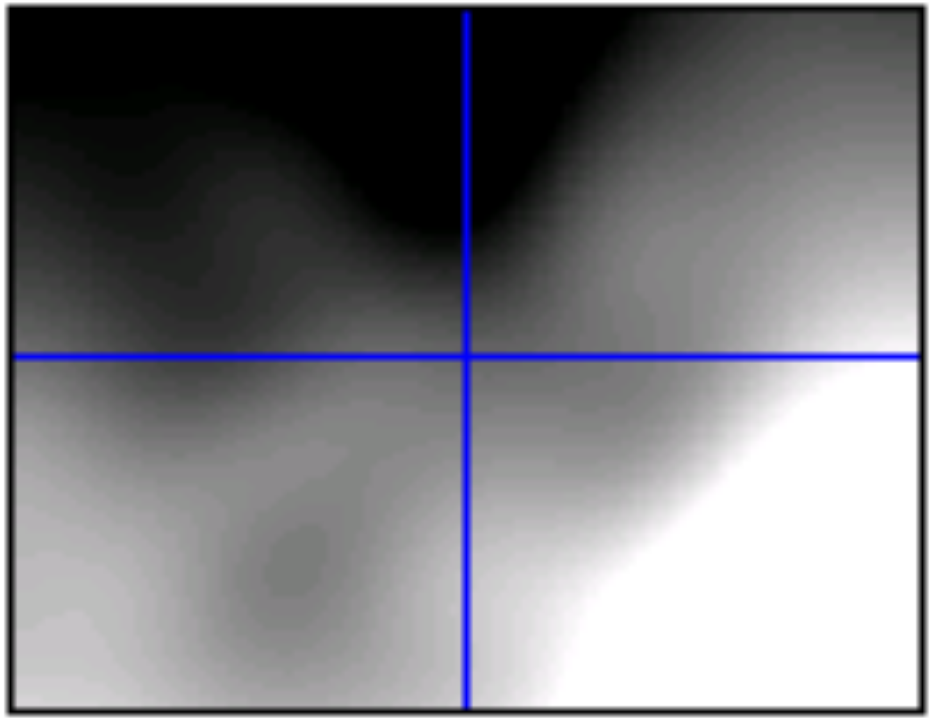
New Seg Toolbox



New Segmentation – registration

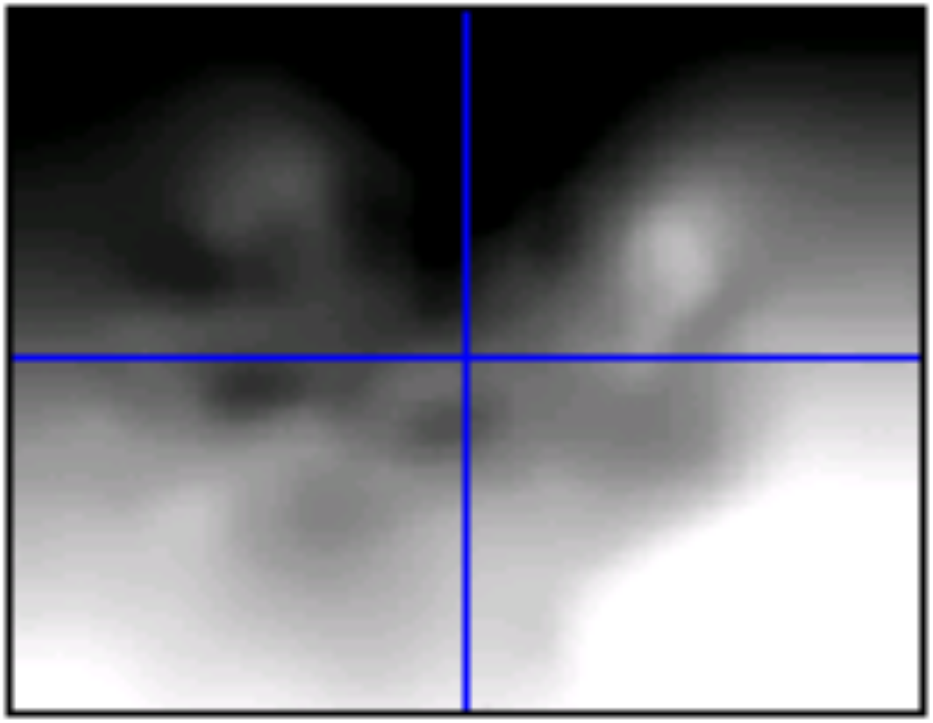
Segment button

* 9*10*9 * 3 = 2430



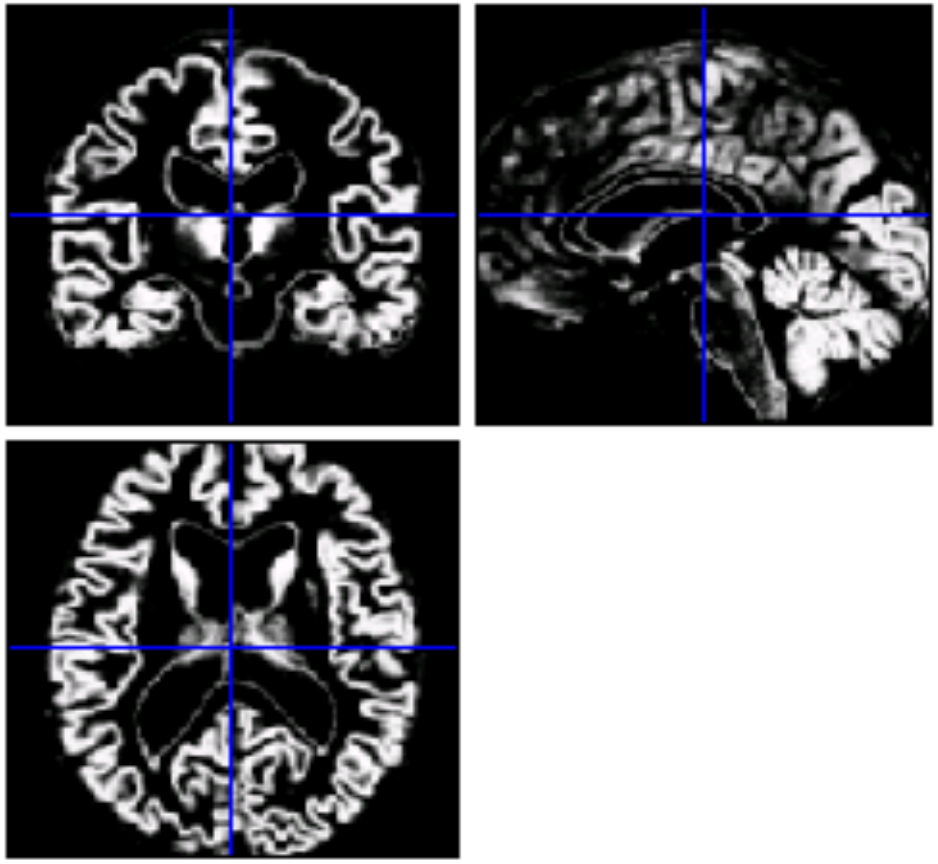
New Seg Toolbox

* 59*70*59 * 3 = 731010

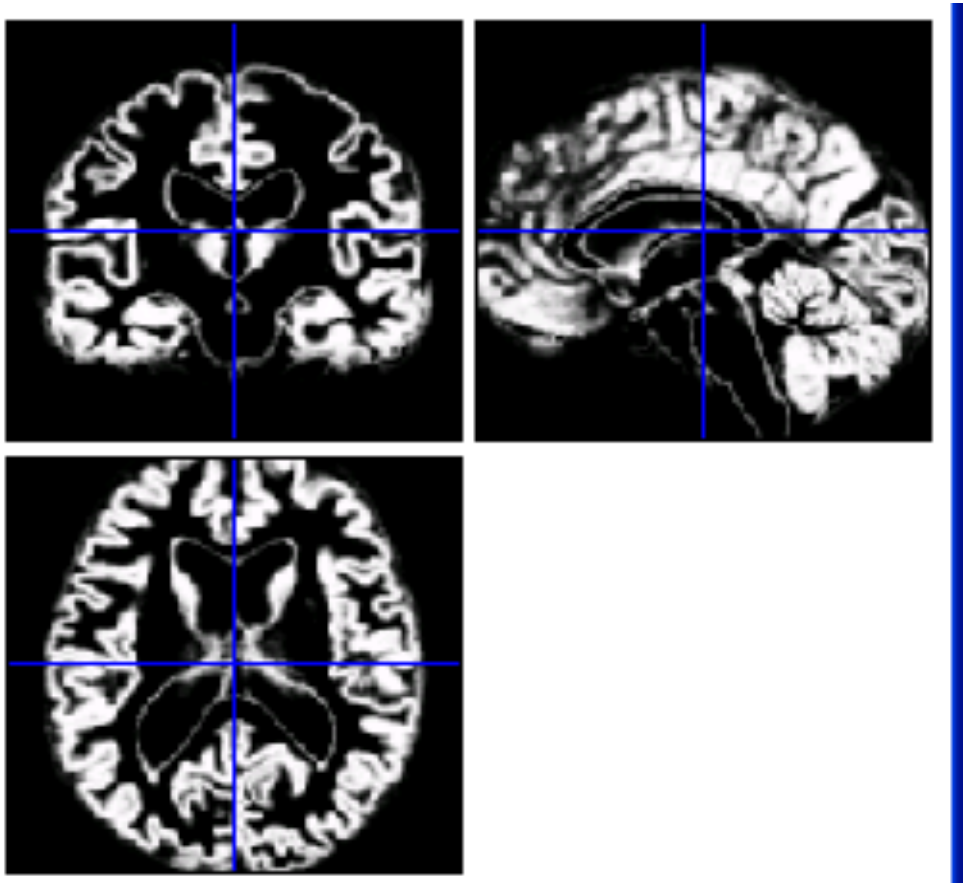


New Segmentation – results

Segment button



New Seg Toolbox



Limitations of the current model

* Assumes that the brain consists of only the tissues modelled by the TPMs
  * No spatial knowledge of lesions (stroke, tumours, etc)
* Prior probability model is based on relatively young and healthy brains
  * Less appropriate for subjects outside this population
* Needs reasonable quality images to work with
  * No severe artefacts
  * Good separation of intensities
  * Good initial alignment with TPMs...

Possible future extensions

* Deeper Bayesian philosophy
  * E.g. priors over means and variances
  * Marginalisation of nuisance variables
  * Model comparison, e.g. for numbers of Gaussians
* Groupwise model (enormous!)
* Combination with DARTEL (see later)
* More tissue priors e.g. deep grey, meninges, etc.
* Imaging physics
  * See Fischl et al. (2004), as cited in A&F (2005) introduction