



# Morphometry

John Ashburner

Wellcome Trust Centre for Neuroimaging,  
12 Queen Square, London, UK.

# Overview

- **Voxel-Based Morphometry**
  - Morphometry in general
  - Volumetrics
  - **VBM preprocessing followed by SPM**
- Tissue Segmentation
- Diffeomorphic Registration
- Longitudinal Registration
- Multivariate Shape Models
- Current Work

# Measuring differences with MRI

- What are the significant differences between populations of subjects?
  - What effects do various genes have on the brain?
  - What changes occur in the brain through development or aging?
- 
- A significant amount of the difference (measured with MRI) is anatomical.

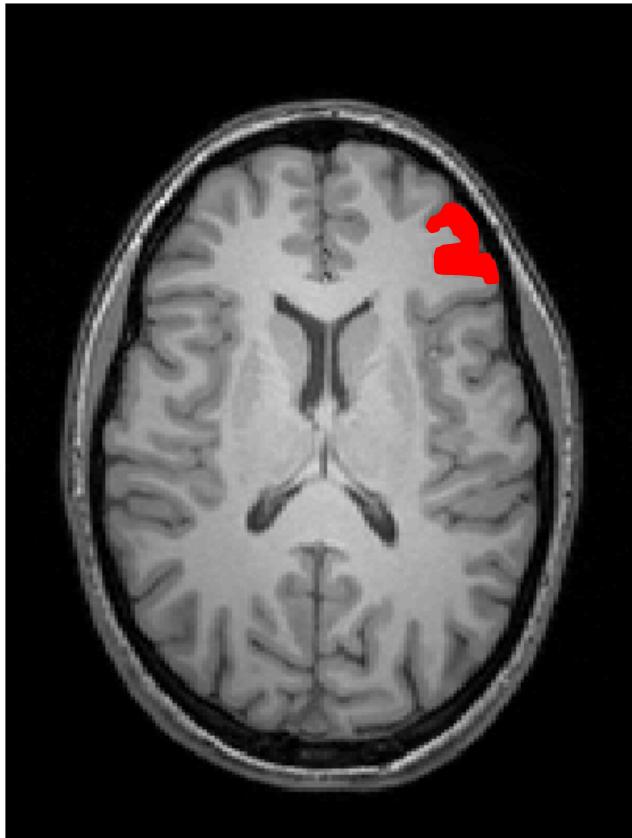
# There are many ways to model differences.

- Usually, we try to localise regions of difference.
  - **Univariate models.**
  - Using methods similar to SPM
  - Typically localising volumetric differences
- 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?
- Need to select the best model of difference to use, before trying to fill in the details.

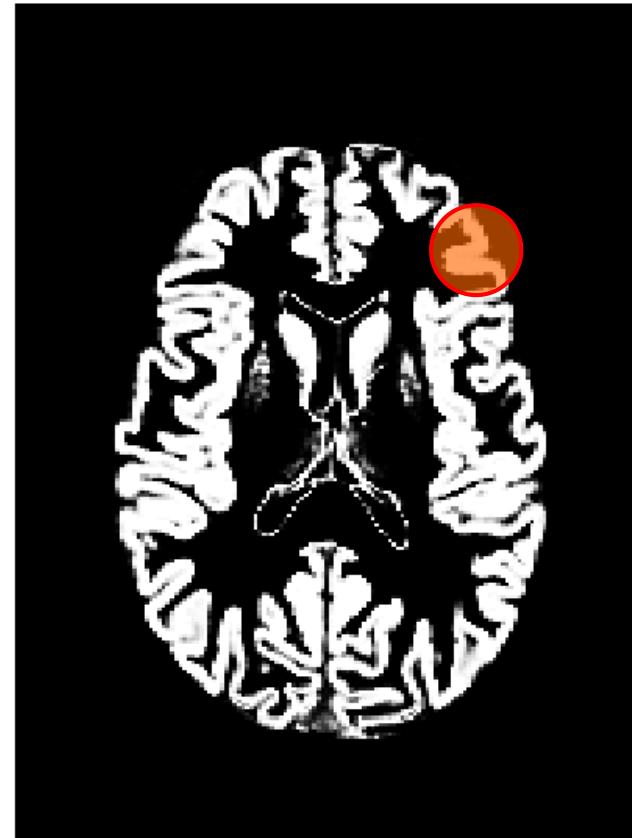
# Voxel-Based Morphometry

- Based on comparing **regional volumes of tissue**.
- Produce a map of statistically significant differences among populations of subjects.
  - e.g. compare a patient group with a control group.
  - or identify correlations with age, test-score etc.
- The data are pre-processed to sensitise the tests to regional tissue volumes.
  - Usually grey or white matter.
- Suitable for studying focal volumetric differences of grey matter.

# Volumetry

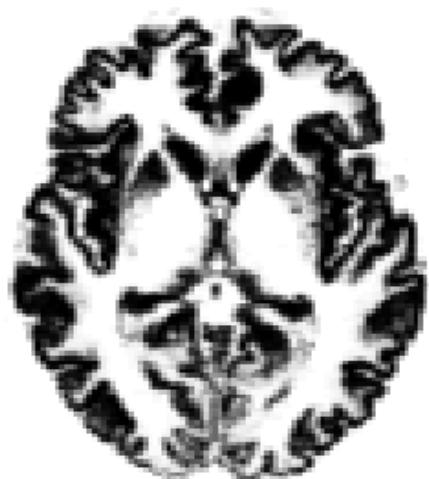


T1-Weighted MRI



Grey Matter

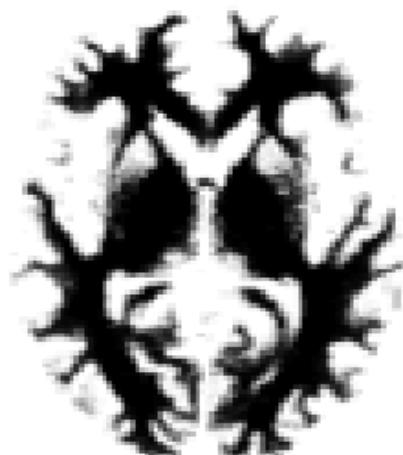
Original



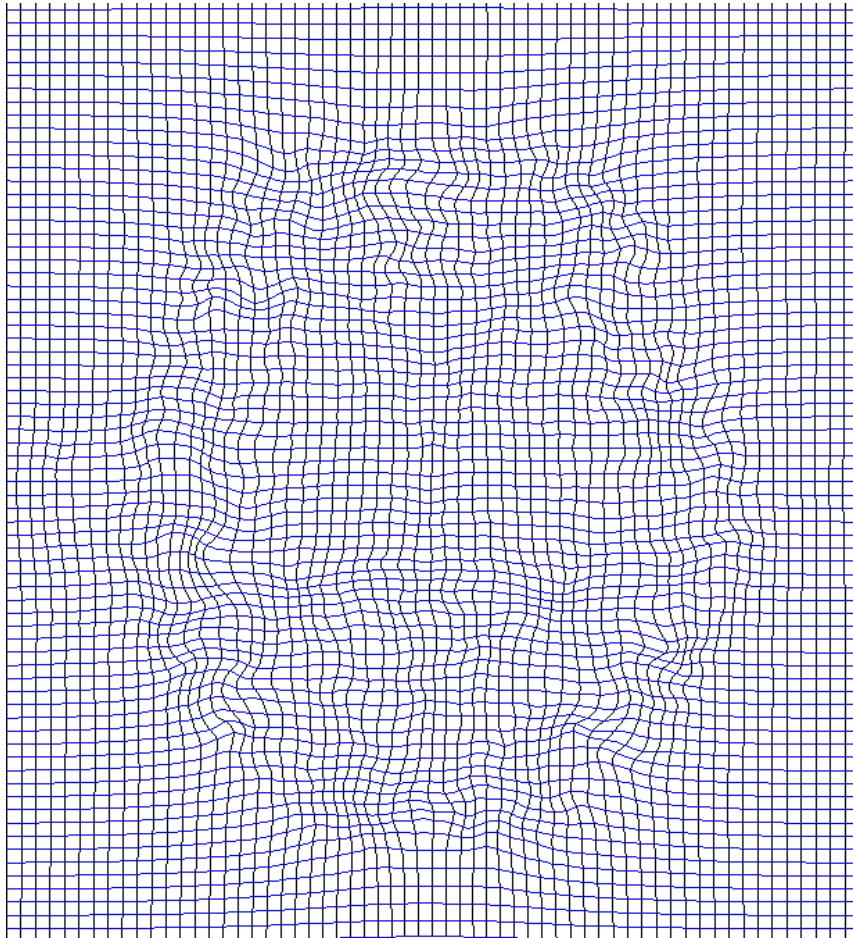
Warped



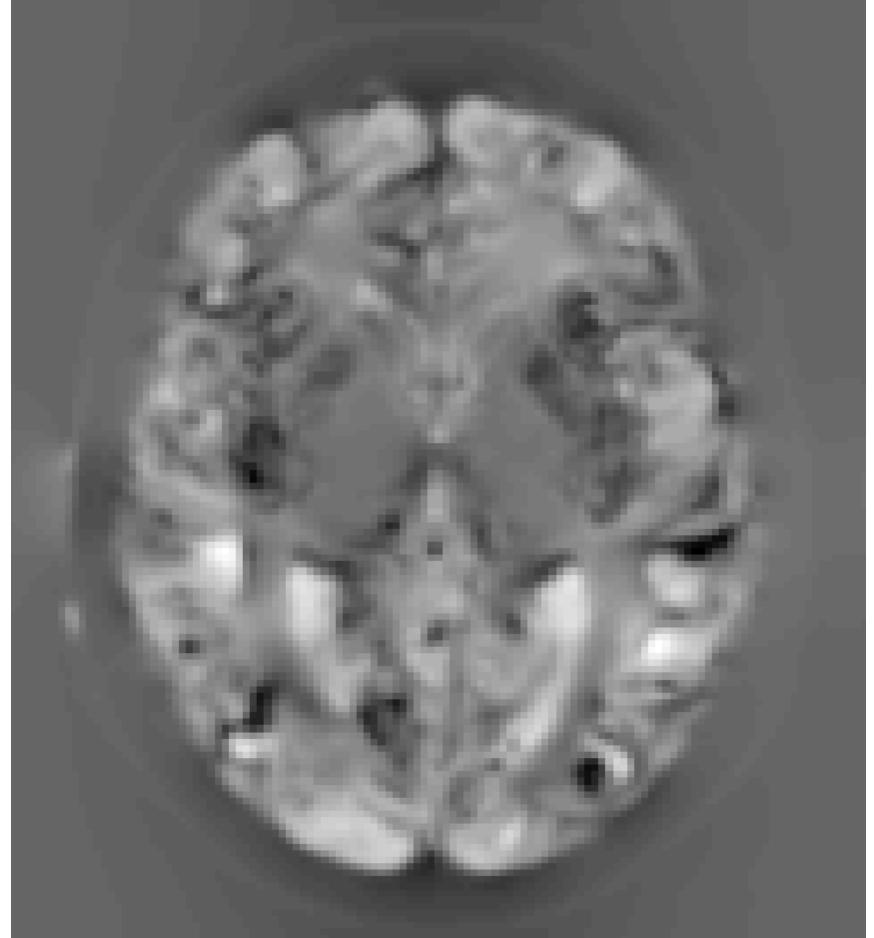
Template



# “Modulation” – change of variables.



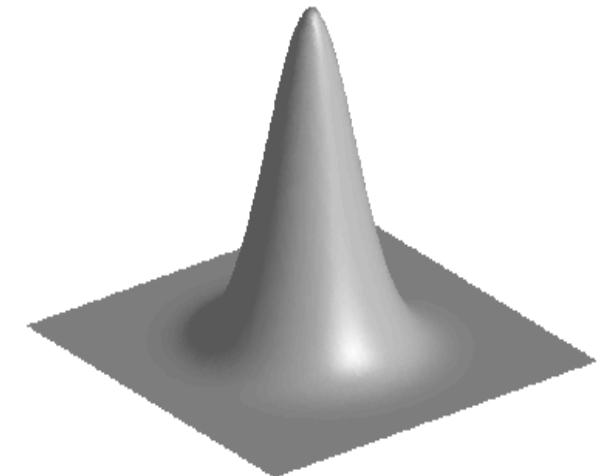
Deformation Field



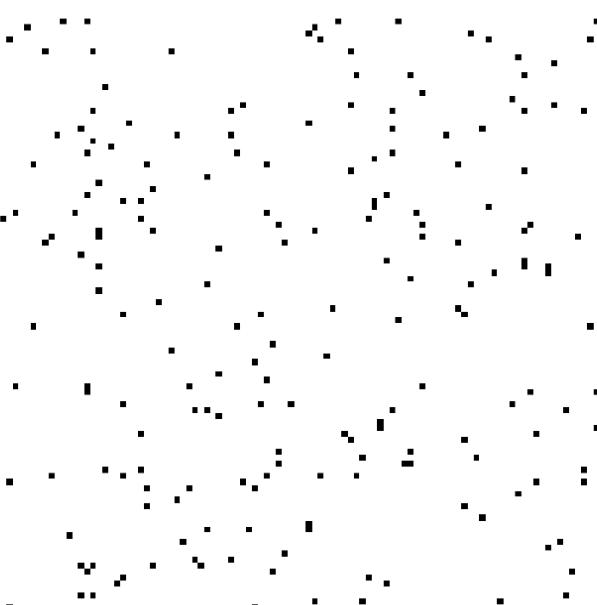
Jacobians determinants  
Encode relative volumes.

# Smoothing

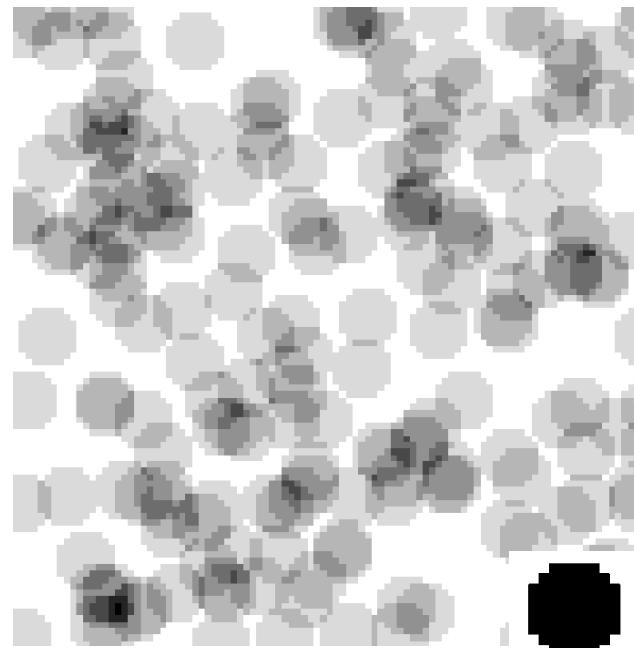
Each voxel after smoothing effectively becomes the result of applying a weighted region of interest (ROI).



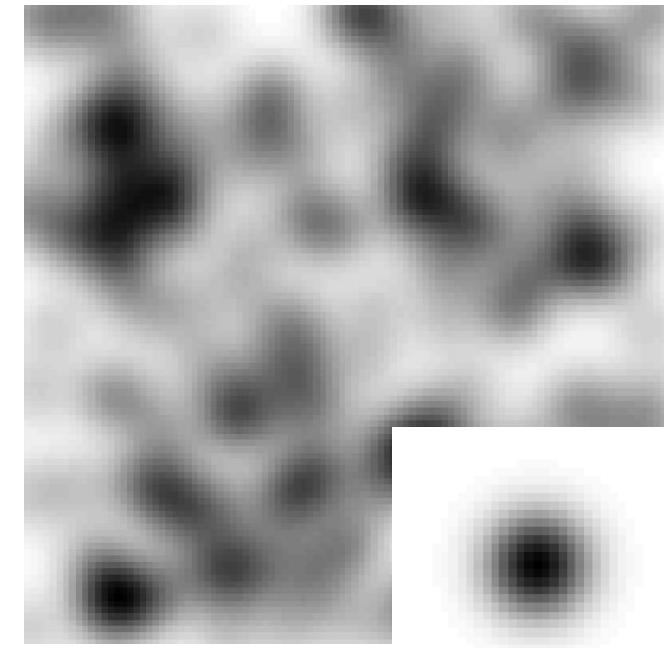
Before convolution



Convolved with a circle

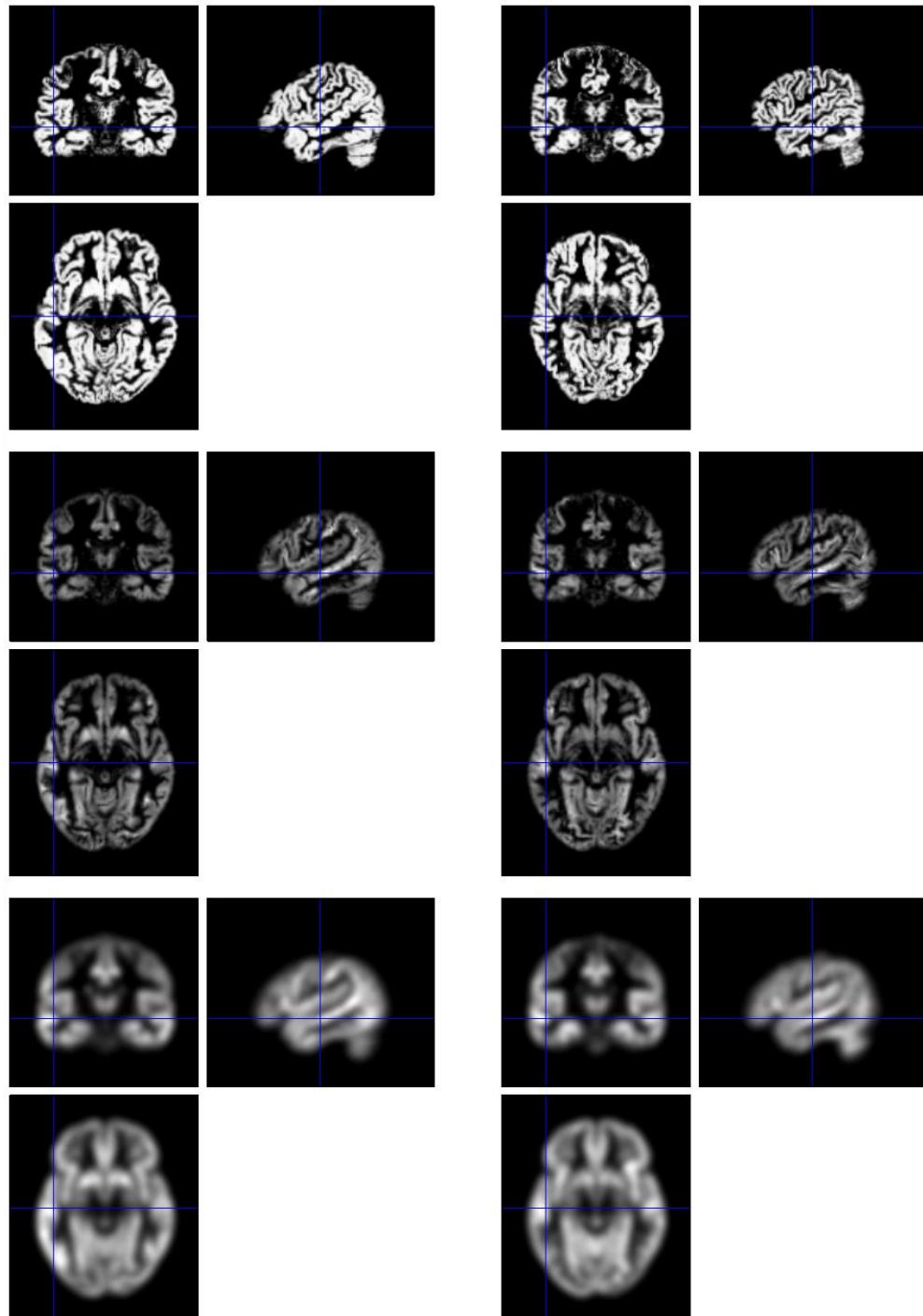


Convolved with a Gaussian



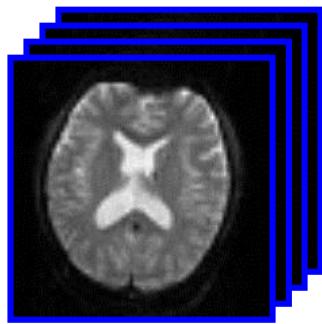
# VBM Pre-processing in SPM12

- Use Segment for characterising intensity distributions of tissue classes, and writing out “imported” images that Dartel can use.
- Run Dartel to estimate all the deformations.
- Dartel warping to generate smoothed, “modulated”, warped grey matter.
- Statistics.

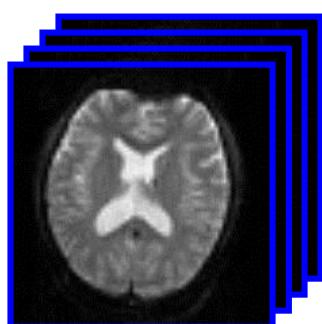


# SPM for group fMRI

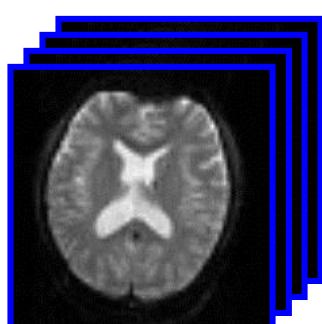
fMRI time-series



fMRI time-series



fMRI time-series



Analysis

Group-wise  
statistics

Spatially Normalised  
“Contrast” Image

Preprocessing

Spatially Normalised  
“Contrast” Image

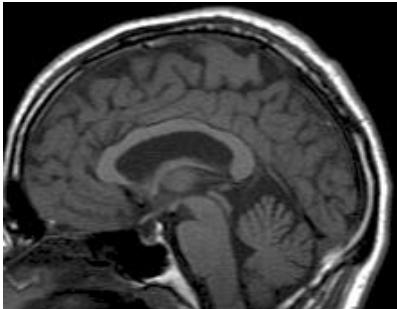
Preprocessing

Spatially Normalised  
“Contrast” Image



# SPM for Anatomical MRI

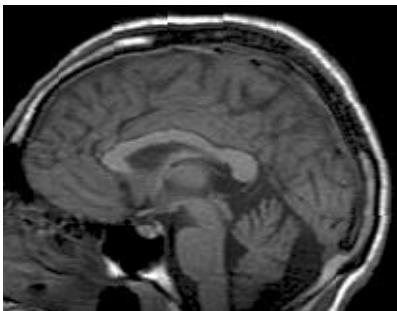
Anatomical MRI



Preprocessing

Group-wise  
statistics

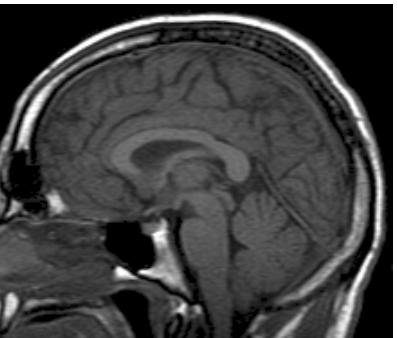
Anatomical MRI



Preprocessing

Spatially Normalised  
Grey Matter Image

Anatomical MRI

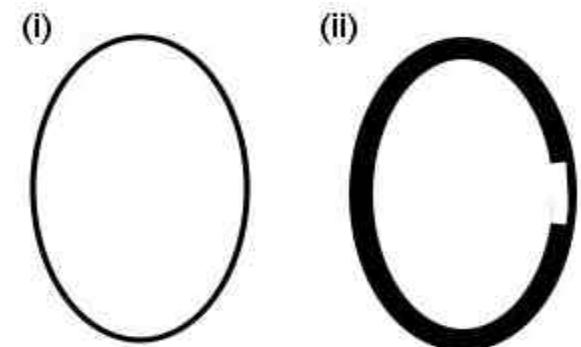


Preprocessing

Spatially Normalised  
Grey Matter Image

# “Globals” for VBM

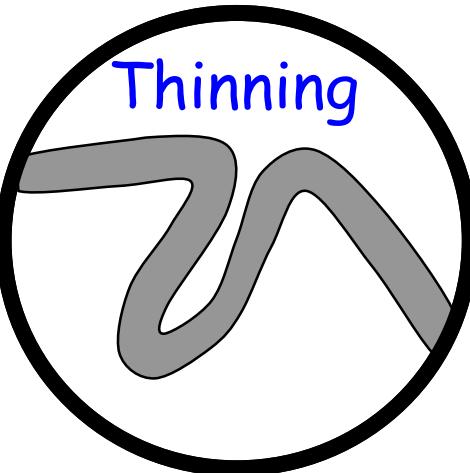
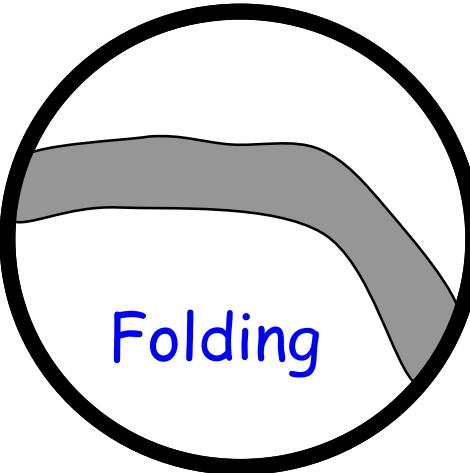
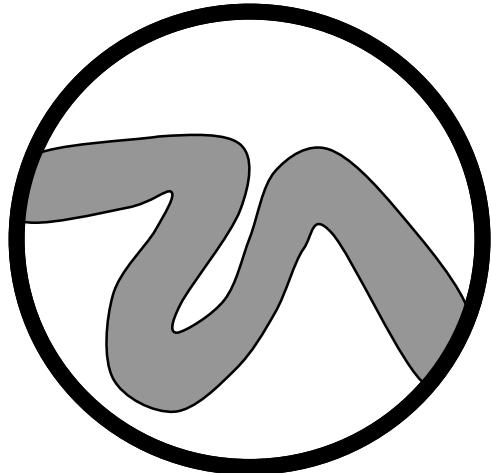
- Shape is really a multivariate concept
  - Dependencies among different regions
- SPM is mass univariate
  - Combining voxel-wise information with “global” integrated tissue volume provides a compromise
  - Either ANCOVA or proportional scaling.
- Total intracranial volume (TIV) integrates GM, WM and CSF, or attempts to measure the skull-volume directly
  - Can still identify global brain shrinkage (skull is fixed!)
  - Can give more powerful and/or more interpretable results
  - See also Pell et al (2009) doi:10.1016/j.neuroimage.2008.02.050



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

# Some Explanations of the Differences



# Selected References

- Wright et al. A voxel-based method for the statistical analysis of gray and white matter density applied to schizophrenia. *Neuroimage* 2(4):244-252 (1995).
- Ashburner & Friston. Voxel-based morphometry - the methods. *Neuroimage* 11:805-821 (2000).
- Mechelli et al. Voxel-based morphometry of the human brain: Methods and applications. *Current Medical Imaging Reviews* 1:105-103 (2005).
- Ashburner. Computational Anatomy with the SPM software. *Magnetic Resonance Imaging* 27:1163-1174 (2009).

# Overview

- Voxel-Based Morphometry

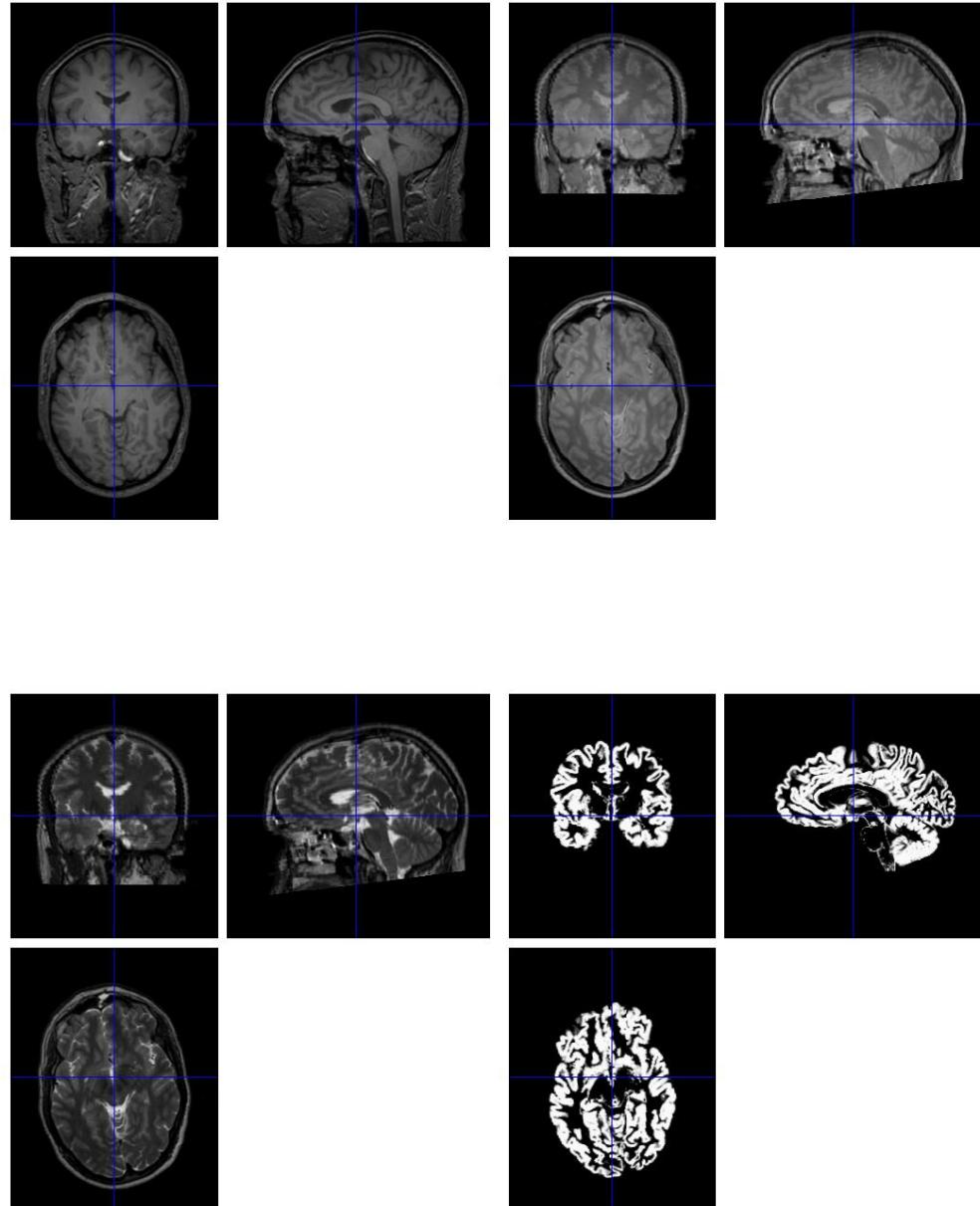
## • **Tissue Segmentation**

- **Gaussian mixture model**
- **Intensity non-uniformity correction**
- **Deformed tissue probability maps**

- Diffeomorphic Registration
- Longitudinal Registration
- Multivariate Shape Models
- Current Work

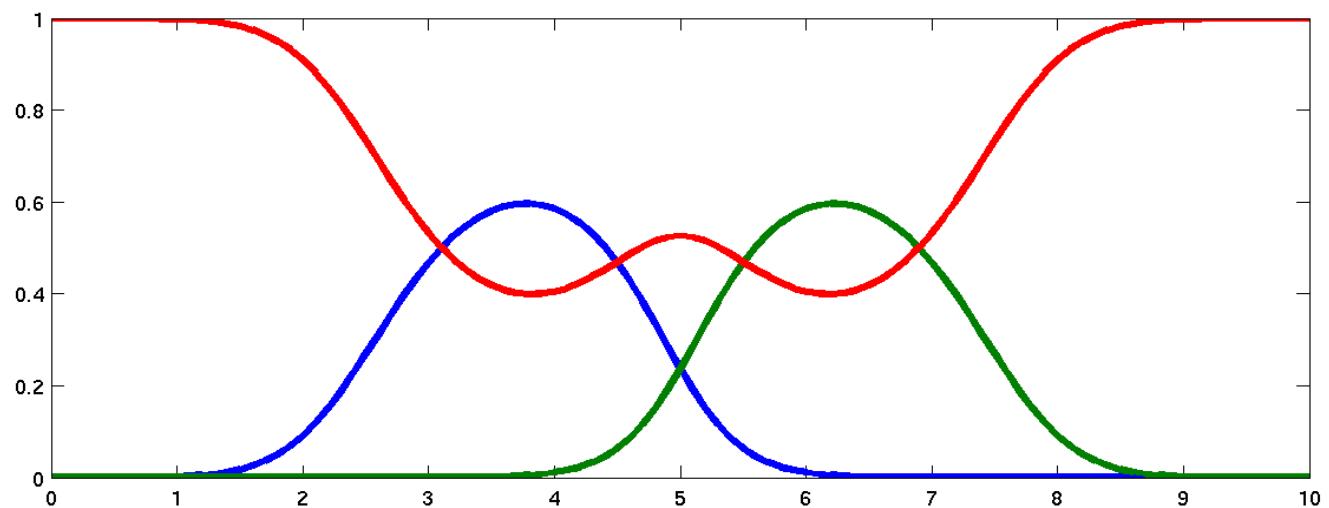
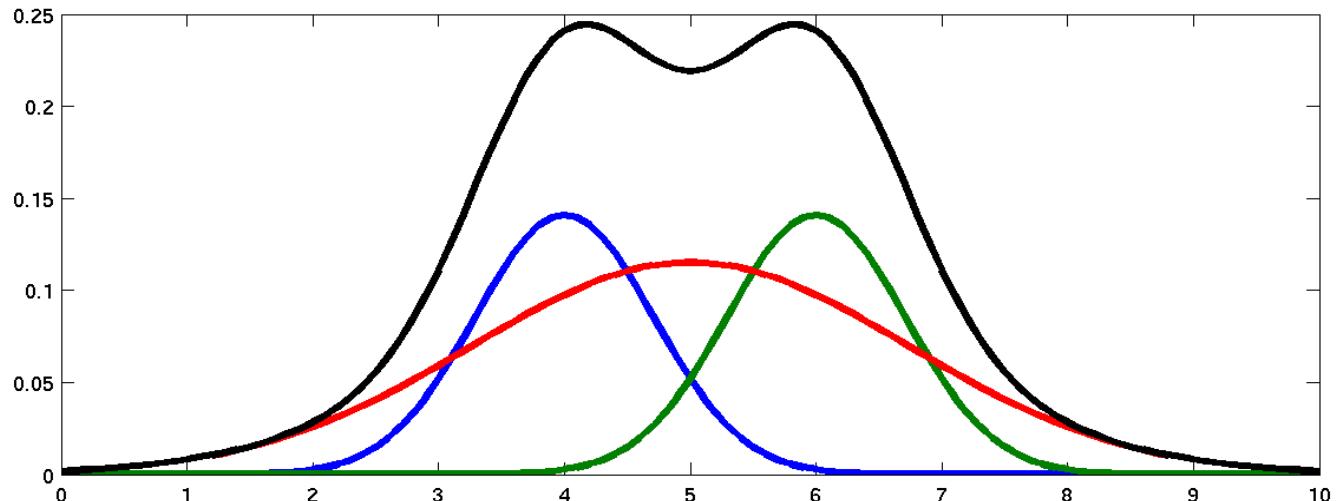
# Tissue Segmentation

- It uses a **generative model**, which involves:
  - Mixture of Gaussians (MOG)
  - Bias Correction Component
  - Warping (Non-linear Registration) Component



# Belonging Probabilities

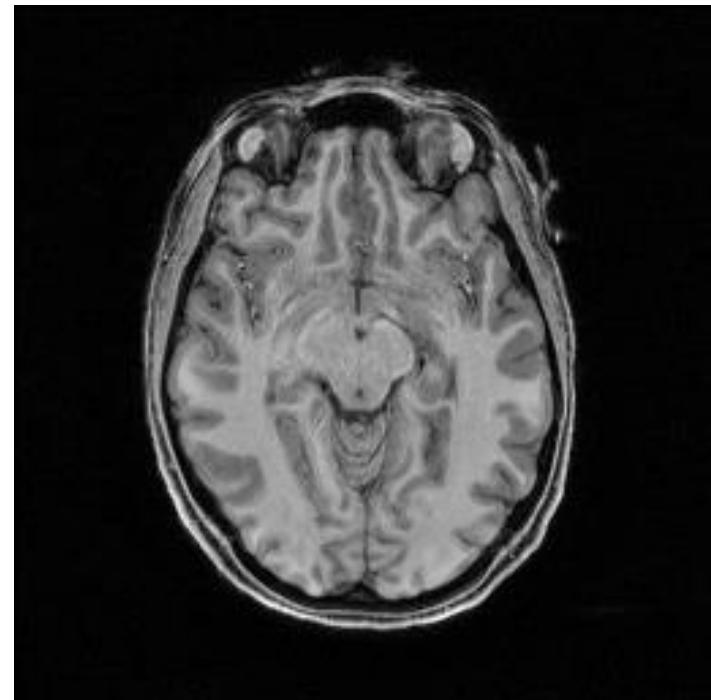
Belonging probabilities are assigned by normalising to one.



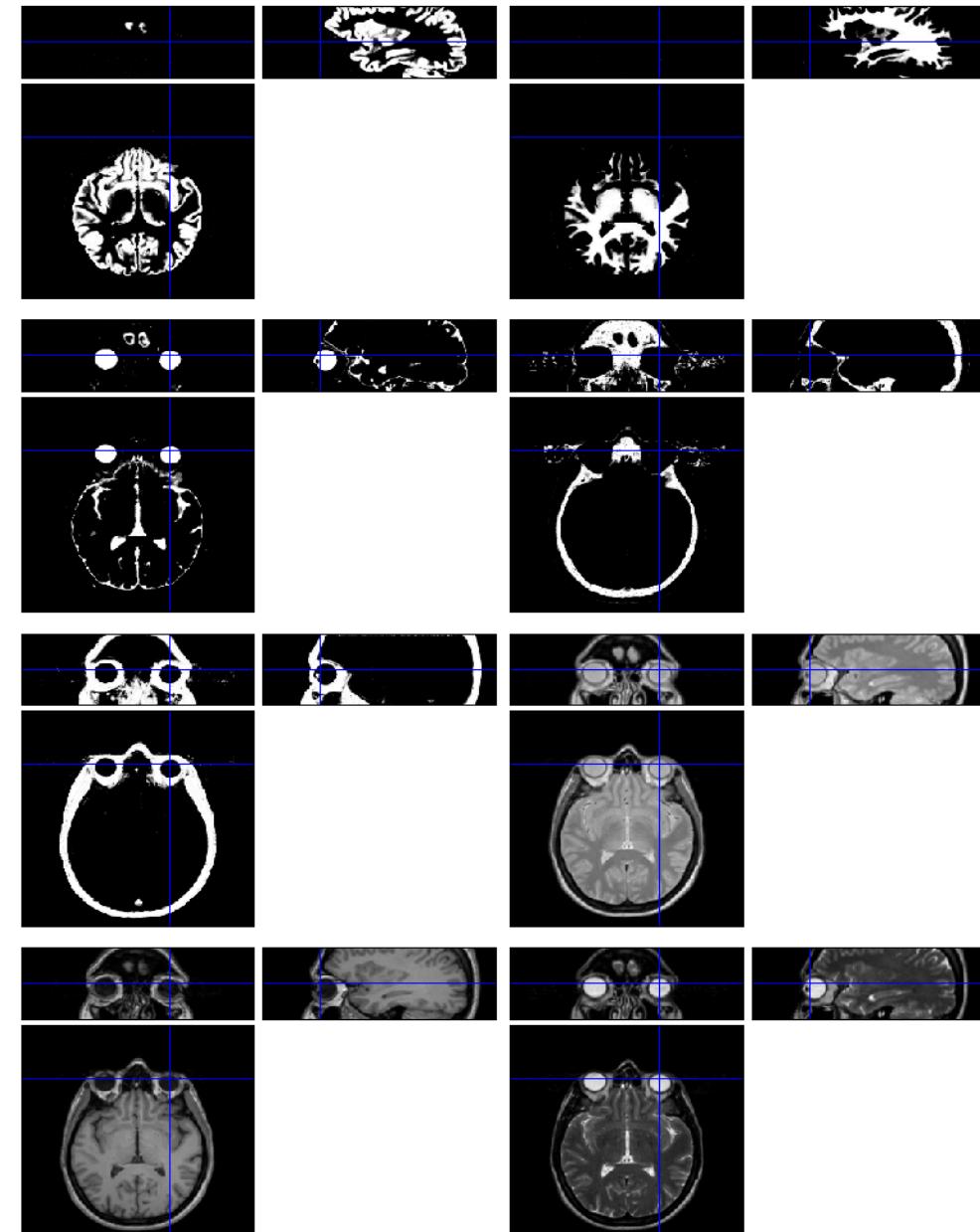
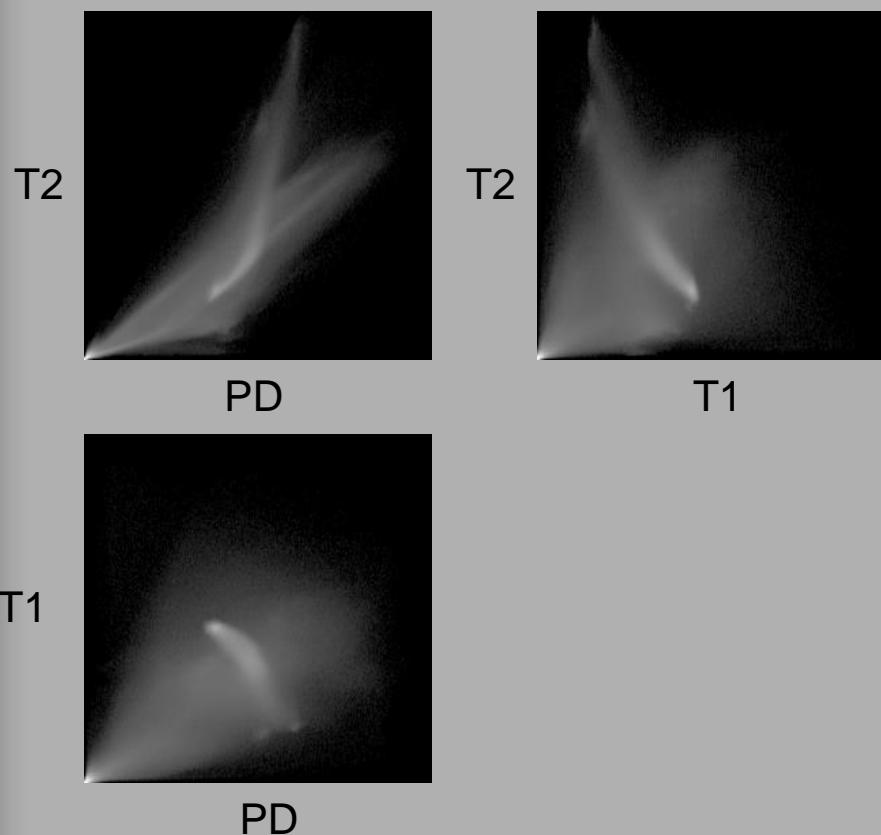
# Belonging Probabilities



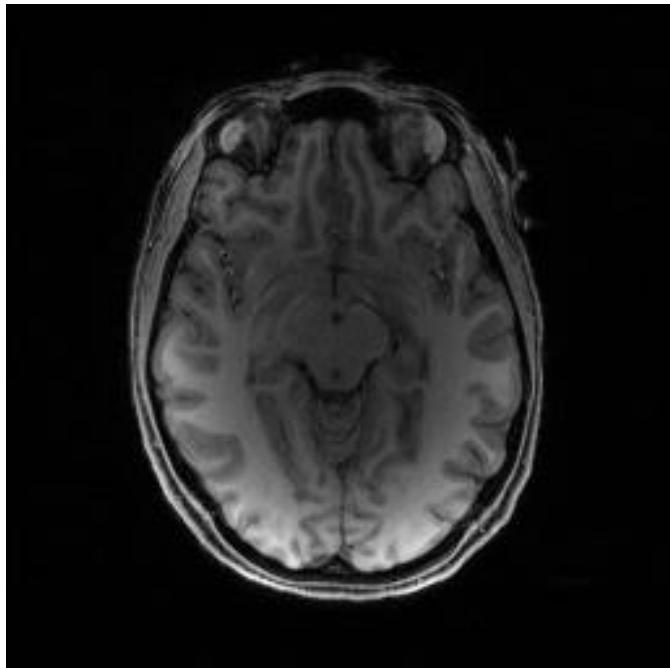
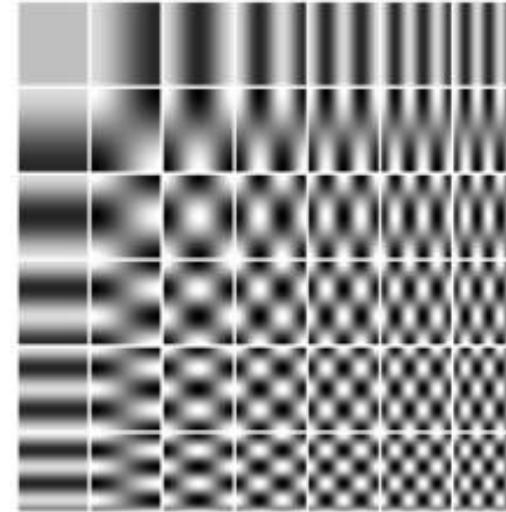
Skull-stripping not needed because information outside the brain is modelled.



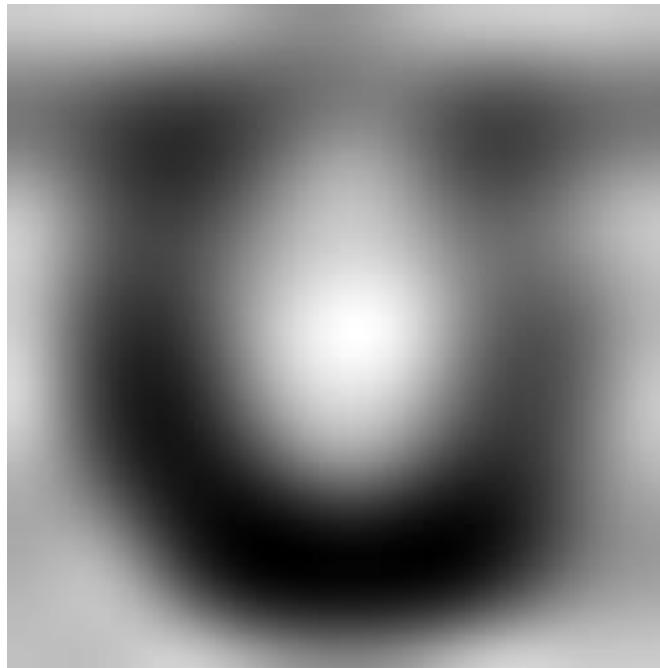
# Multi-spectral



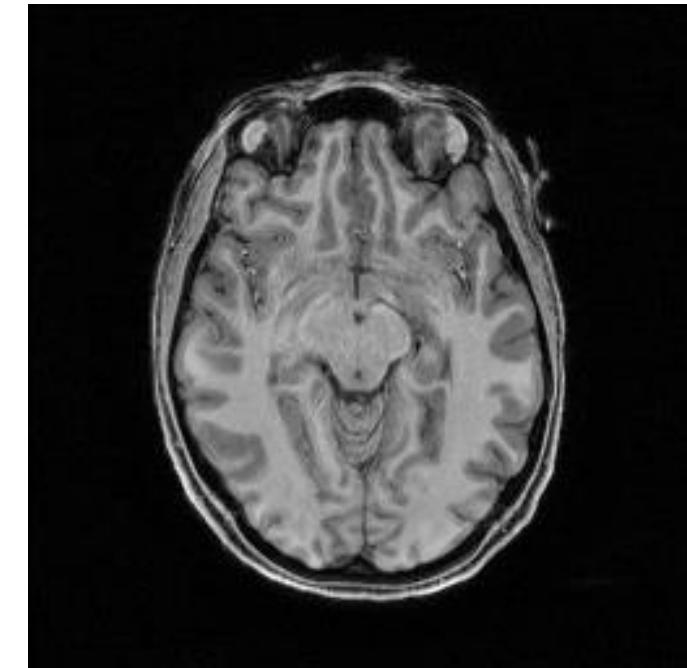
# Modelling a bias field



Corrupted image



Bias Field



Corrected image

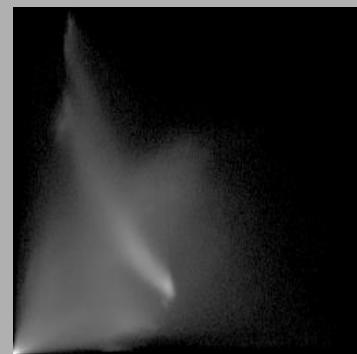
# Modelling a bias field

## With bias correction



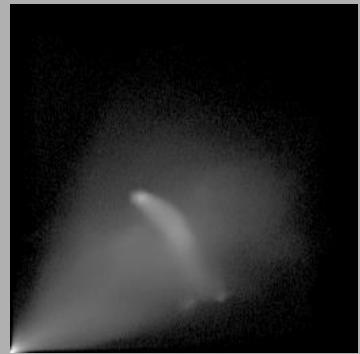
T2

PD



T2

T1



T1

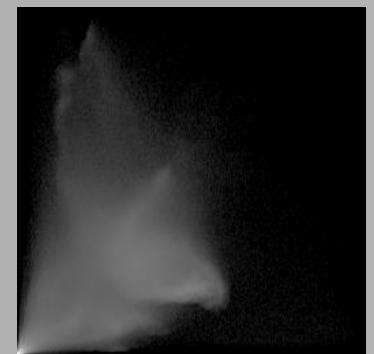
PD

## Without bias correction



T2

PD



T2

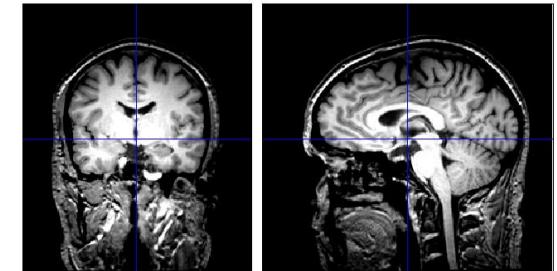
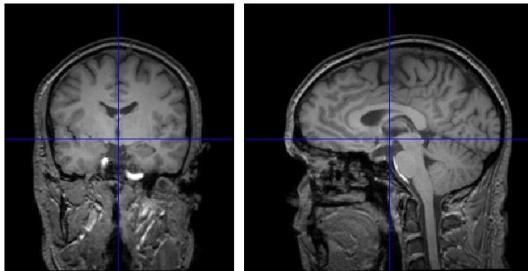
T1



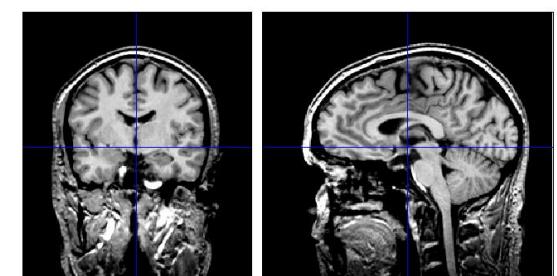
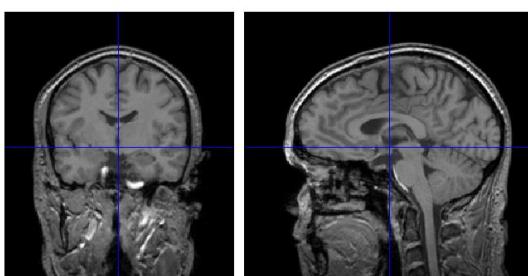
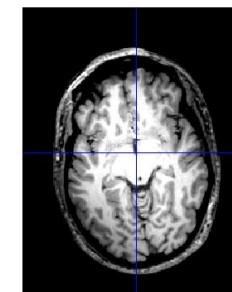
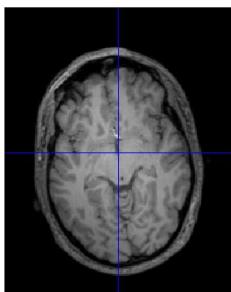
T1

PD

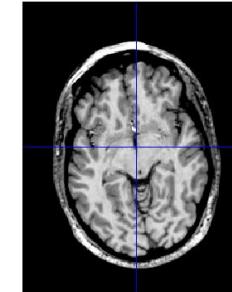
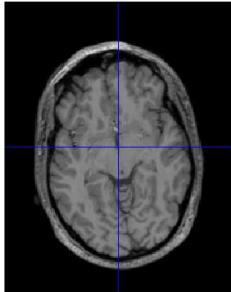
# Modelling a bias field



**Without bias correction**

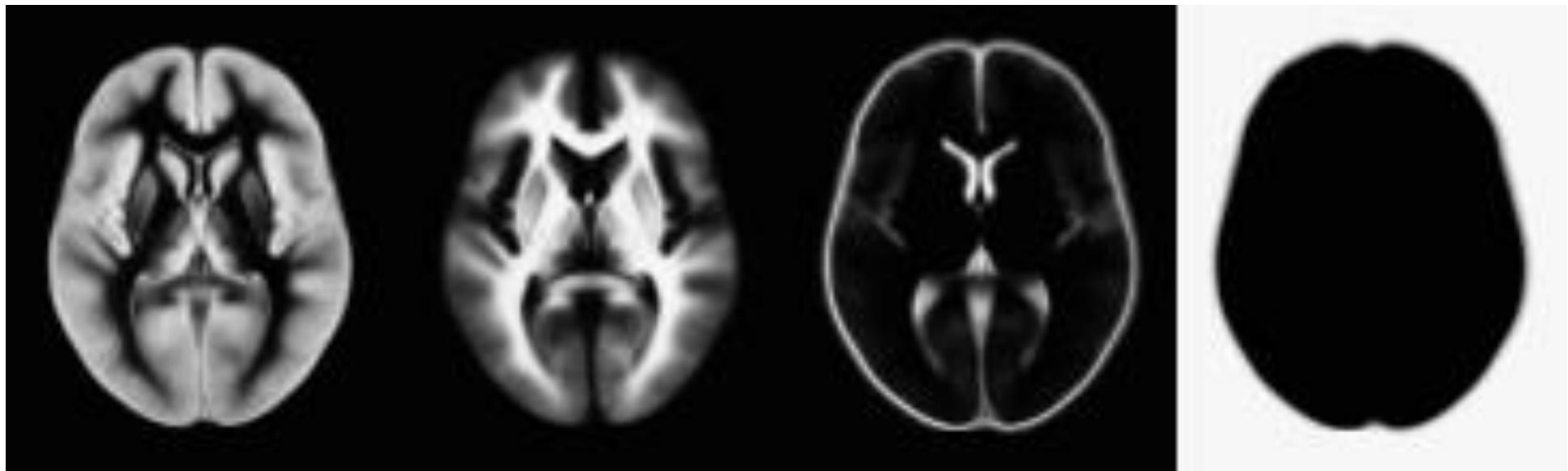


**With bias correction**



# Tissue probability priors

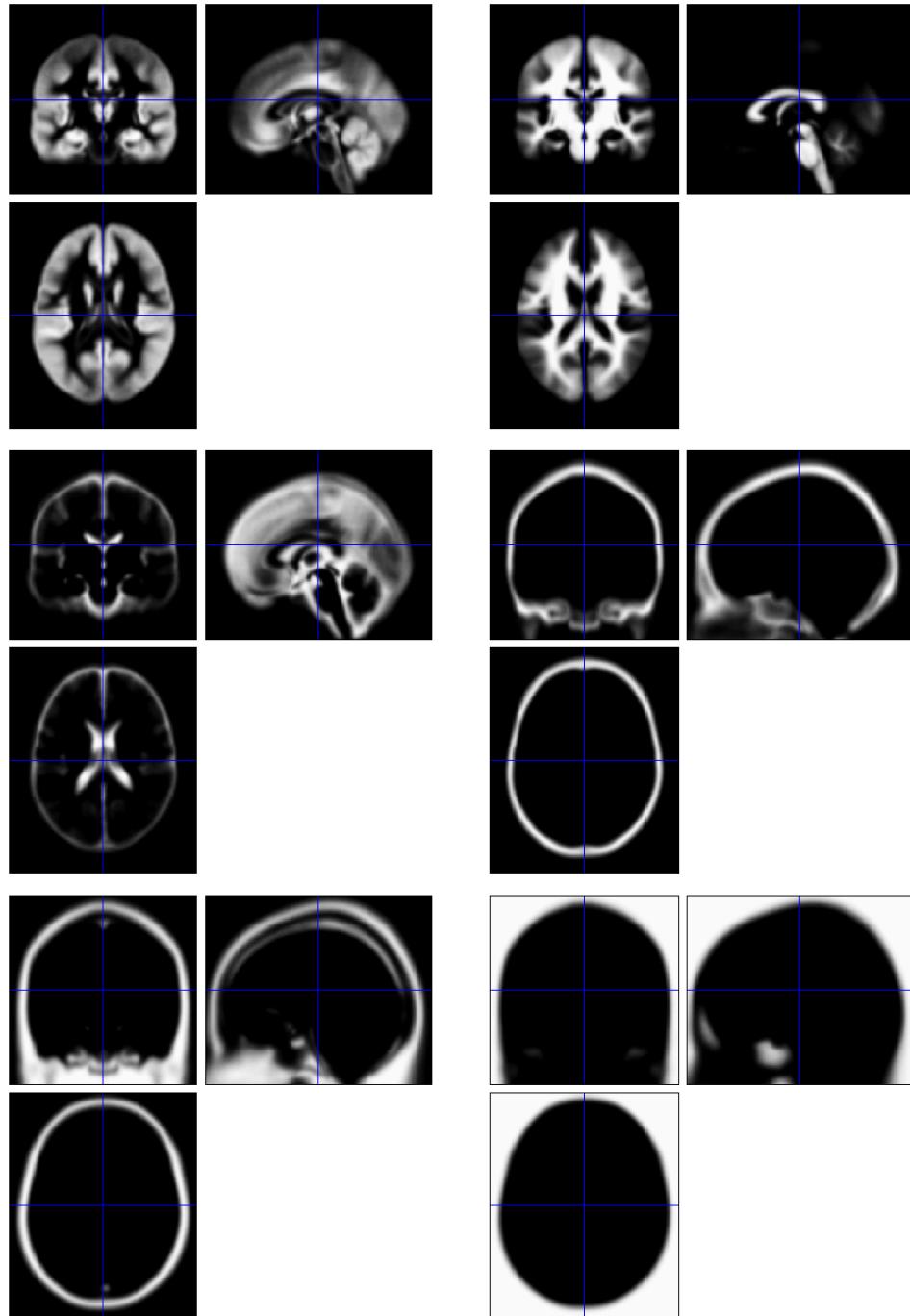
- Tissue probability maps (TPMs) are used instead of the proportion of voxels in each Gaussian as the prior.

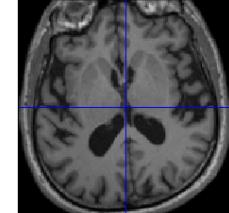
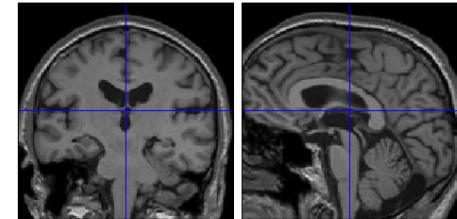
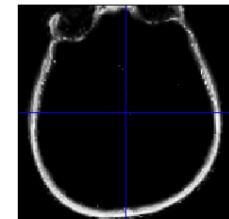
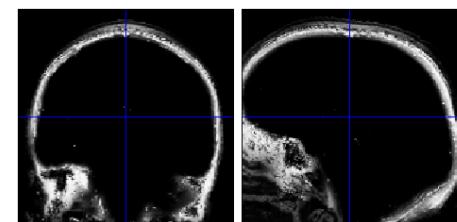
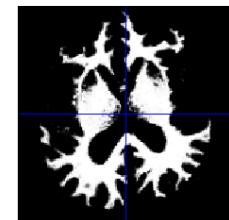
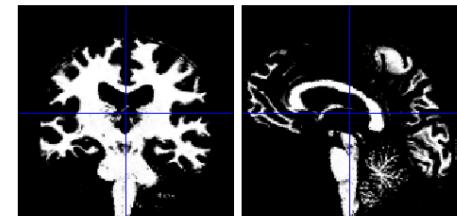
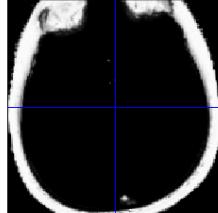
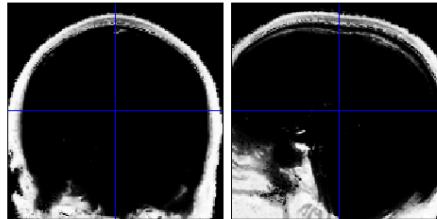
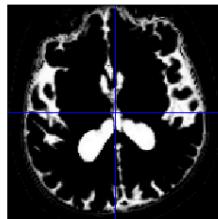
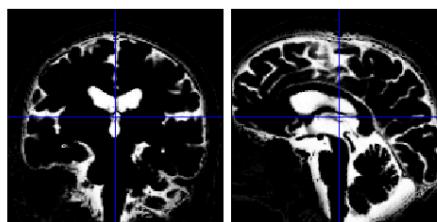
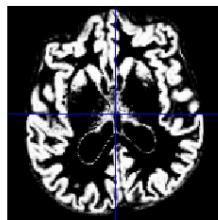
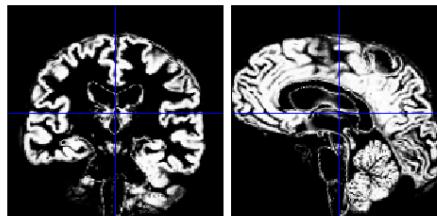
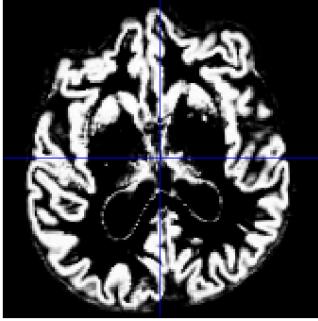
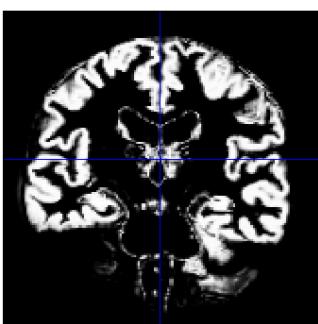
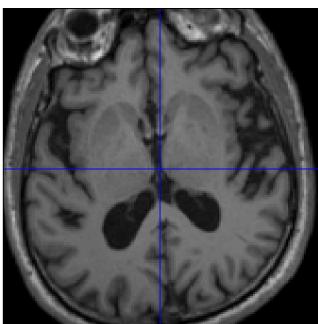
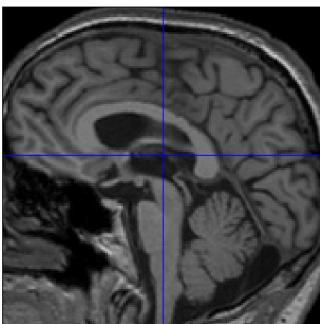
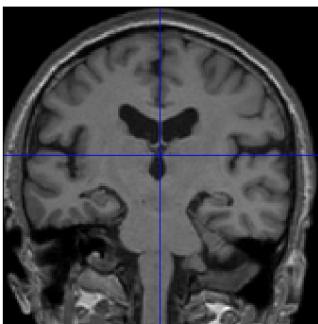


**ICBM Tissue Probabilistic Atlases.** These tissue probability maps are kindly provided by the International Consortium for Brain Mapping, John C. Mazziotta and Arthur W. Toga.

# Tissue probability priors in SPM12

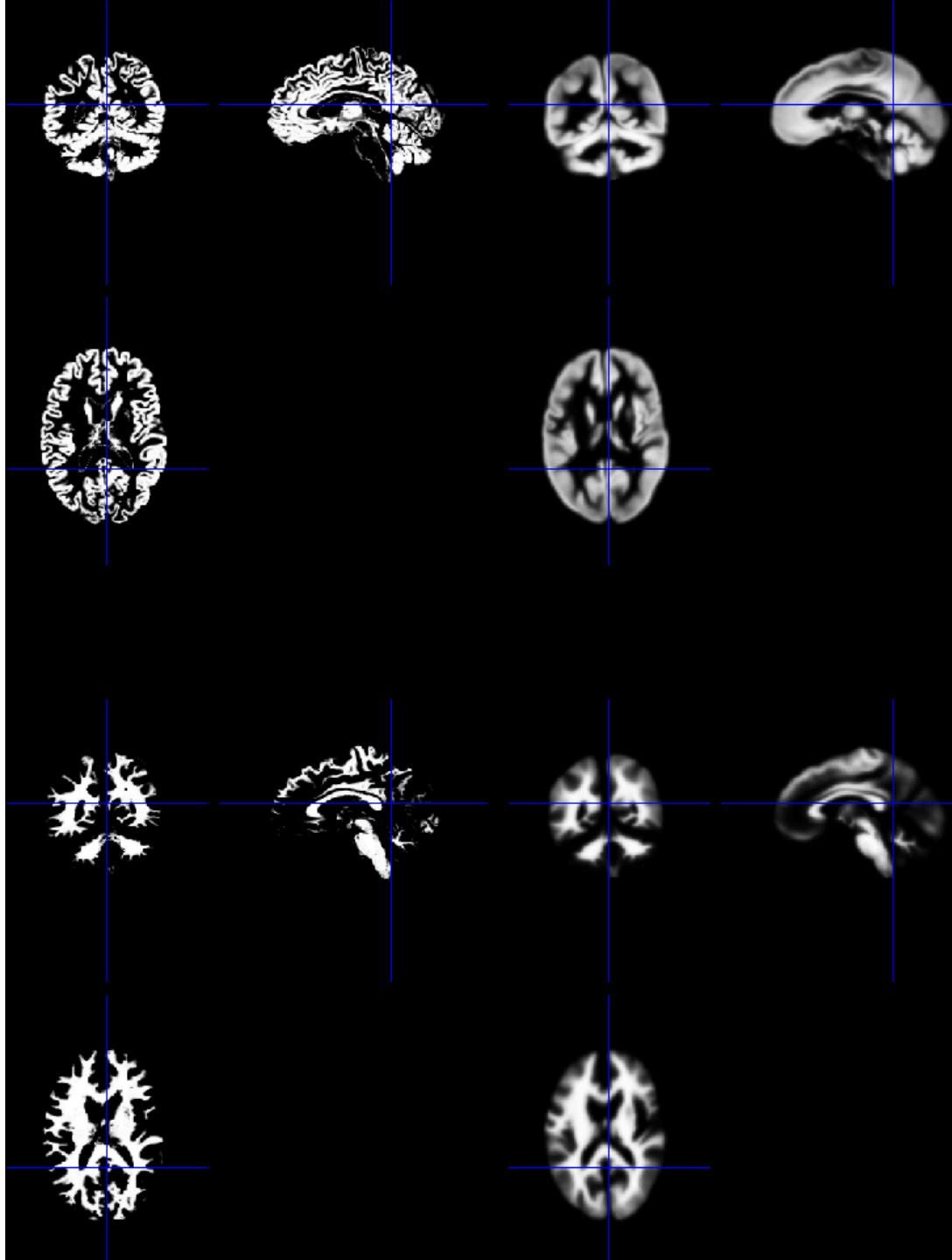
Includes additional non-brain tissue  
classes (bone, and soft tissue)



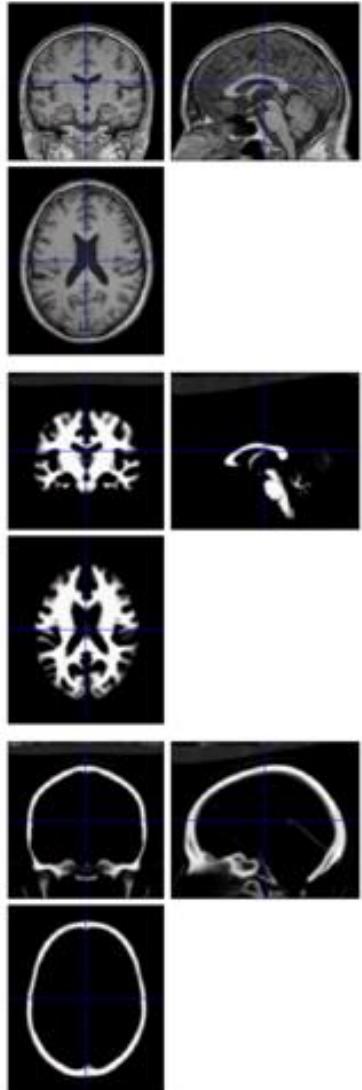


# Deformable tissue probability priors

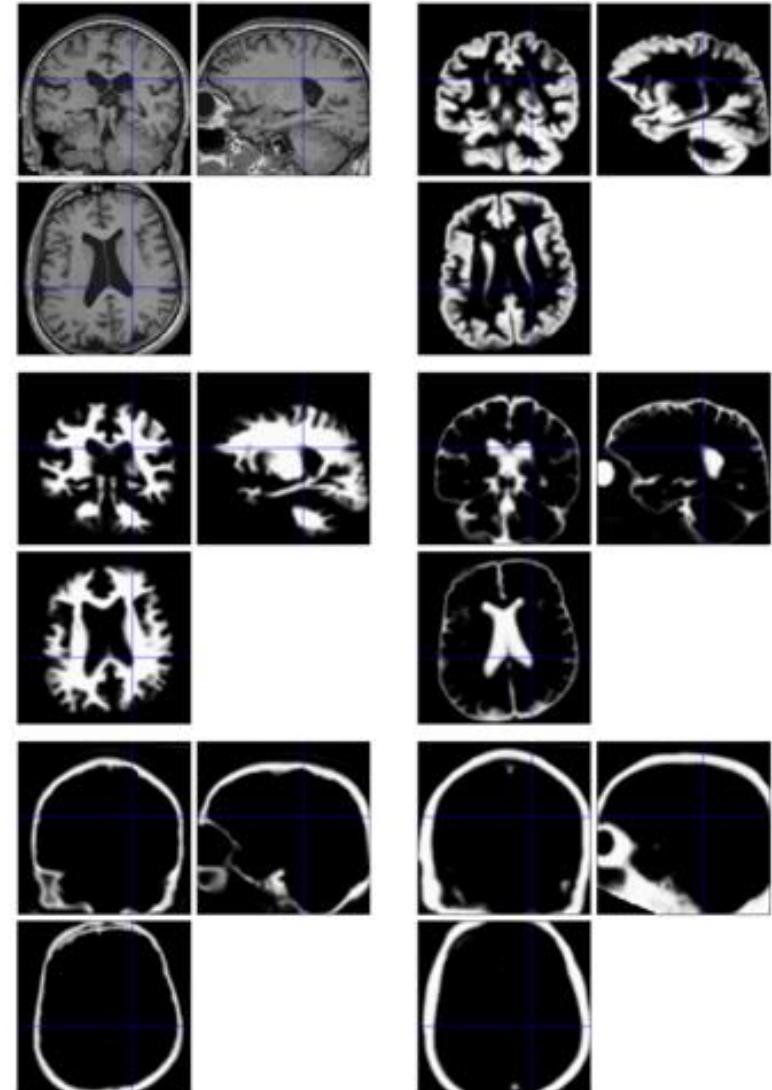
- Tissue probability maps are warped to align with tissues identified in image.



## Warping individual to match atlas (spatial normalisation)



## Warping atlas to match individual

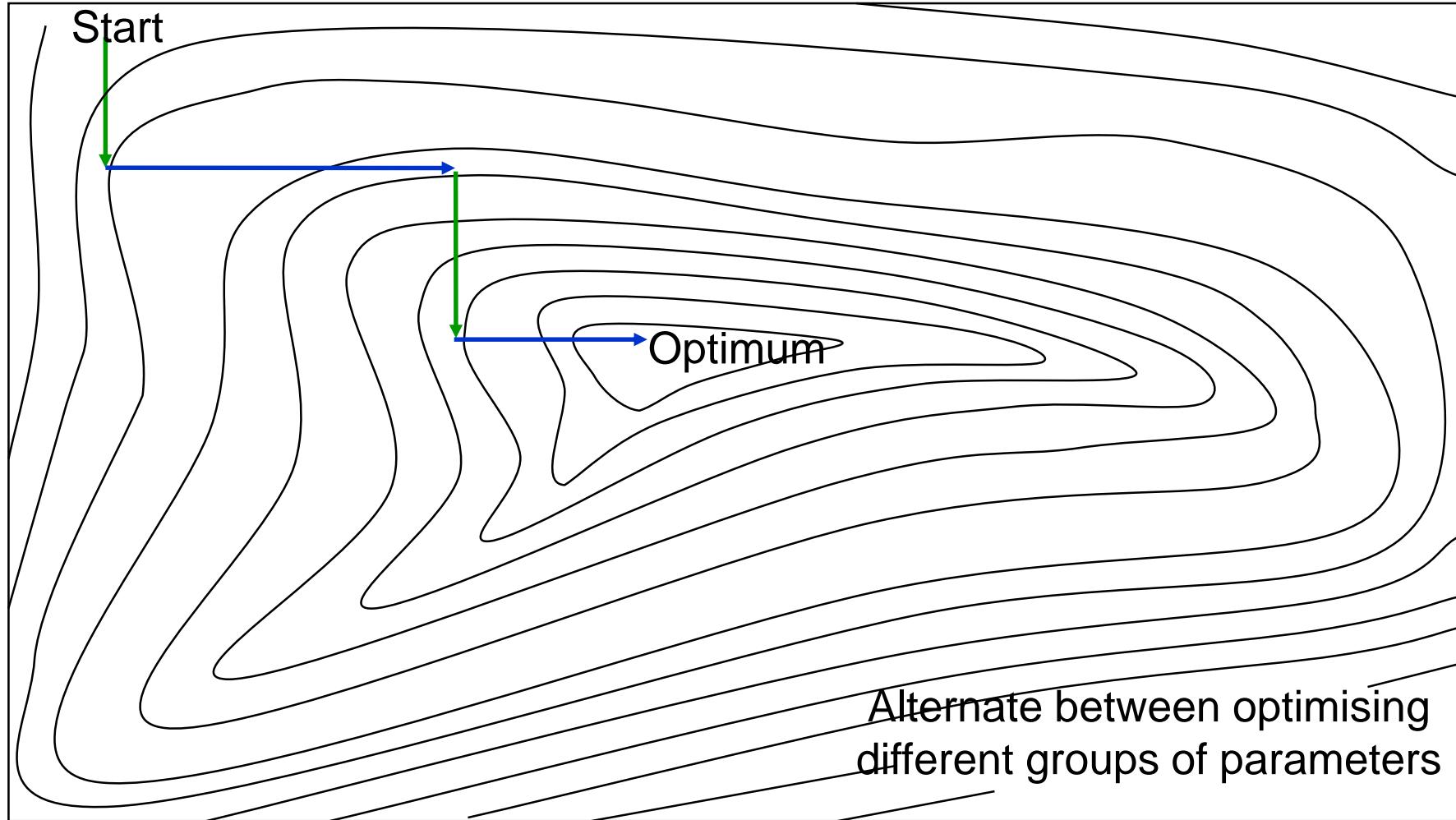


# Optimisation

- The “best” parameters are those that minimise this objective function.
- Optimisation involves finding them.
- Begin with starting estimates, and repeatedly change them so that the objective function decreases each time.

$$E = -\sum_{i=1}^I \log \left[ p_i \beta \sum_{k=1}^K \frac{\gamma_k b_{ik}(\alpha)}{\sum_{j=1}^K \gamma_j b_{ij}(\alpha)} \frac{1}{\sqrt{2\pi\sigma_k^2}} \exp \left( -\frac{(p_i \beta y_i - \mu_k)^2}{2\sigma_k^2} \right) \right]$$

# Descent scheme



# 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 healthy brains (IXI dataset from London).
  - Less accurate for subjects outside this population
- Needs reasonable quality images to work with
  - No severe artefacts
  - Good separation of intensities
  - Reasonable initial alignment with TPMs.

# Selected References

- Ashburner & Friston. *Unified Segmentation*. NeuroImage 26:839-851 (2005).
- Blaiotta et al. *Variational inference for medical image segmentation*. Computer Vision and Image Understanding 151:14-28 (2016).

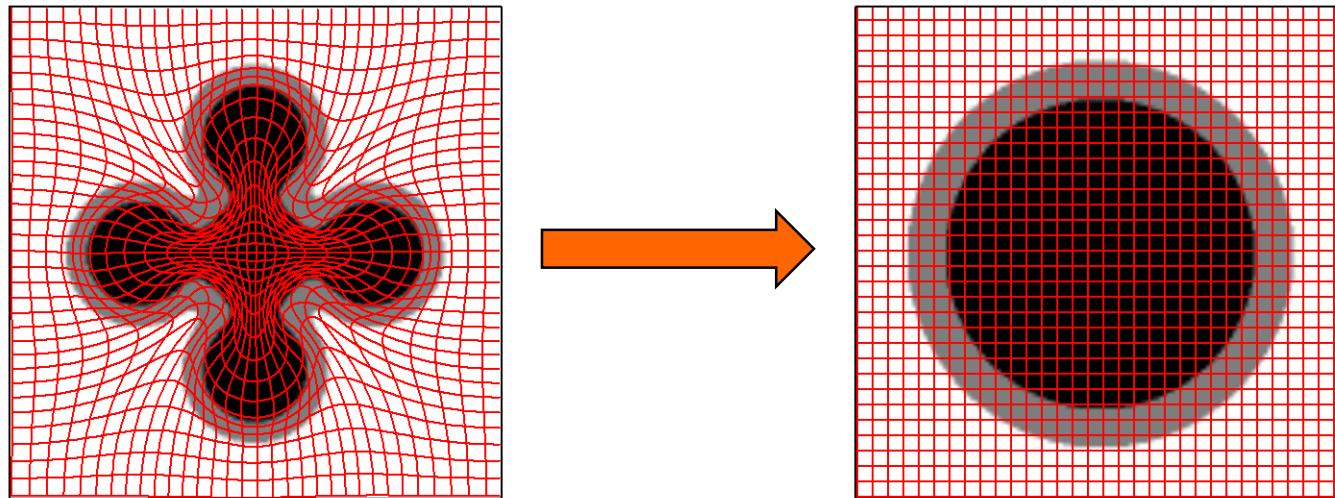
# Overview

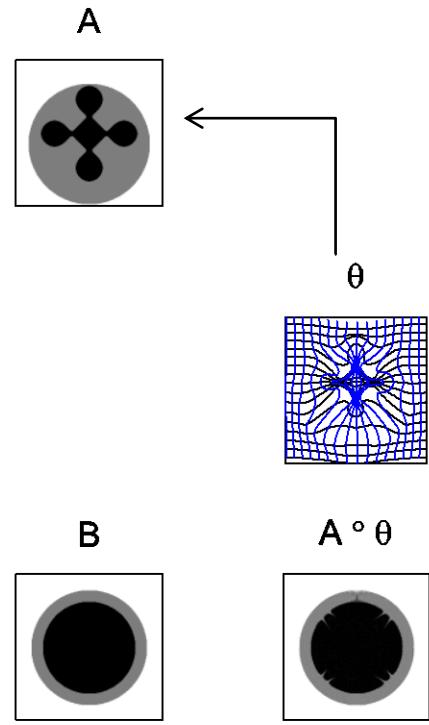
- Voxel-Based Morphometry
- Tissue Segmentation

## • **Diffeomorphic Registration**

- Compositions
- Objective function
- Template creation
- Longitudinal Registration
- Multivariate Shape Models
- Current Work

# Diffeomorphic Deformations





# Composition

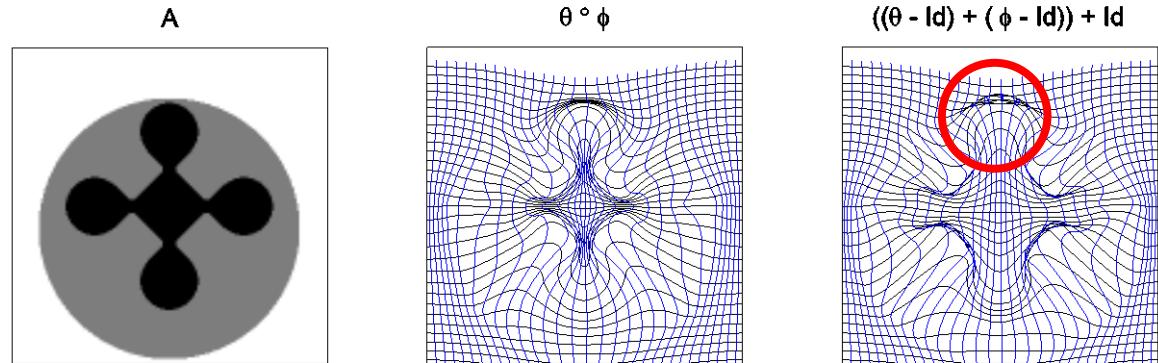
# Small Deformation Approximation

The composition:

$$\vartheta \circ \varphi$$

Would be approximated with:

$$\text{Id} + ((\vartheta - \text{Id}) + (\varphi - \text{Id}))$$

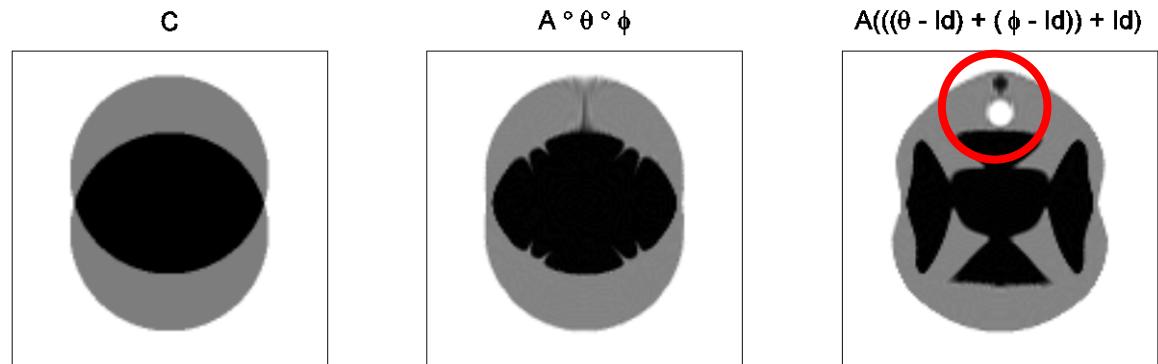


The inversion:

$$\varphi^{-1}$$

Would be approximated with:

$$\text{Id} - (\varphi - \text{Id})$$



Not good approximations for large deformations.

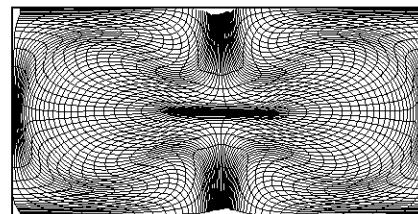
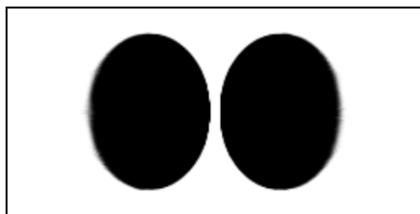
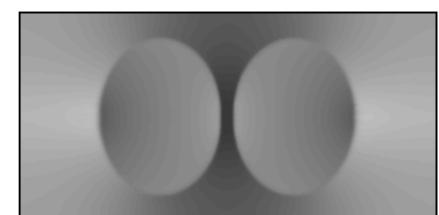
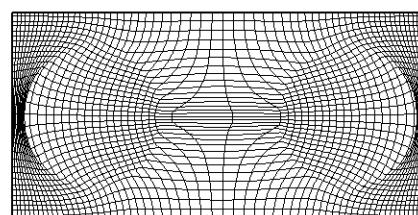
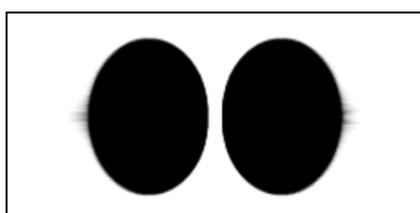
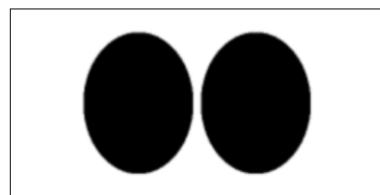
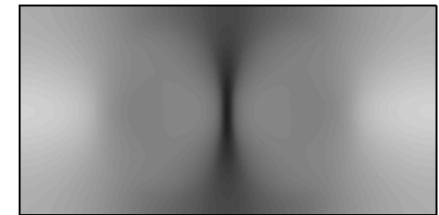
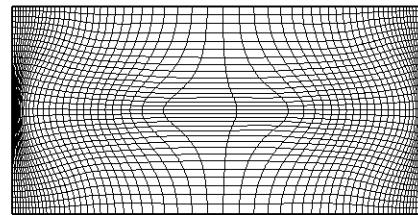
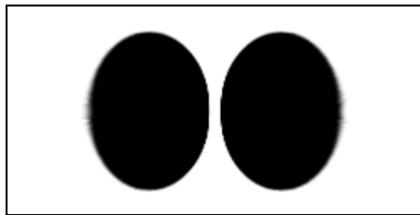
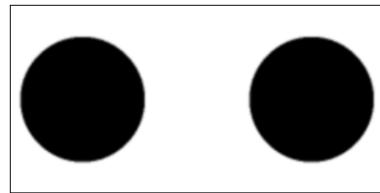
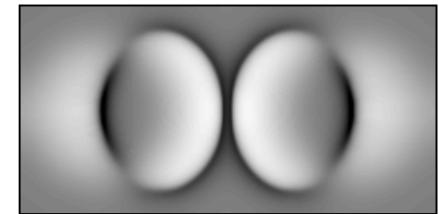
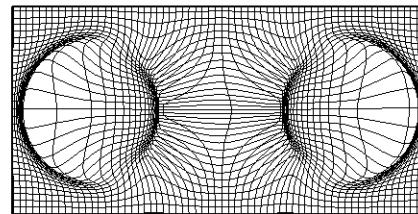
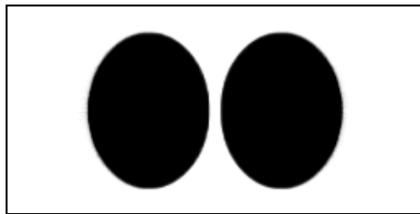
# Diffeomorphic Image Registration

- Minimises two terms:
  1. A measure of distance between images
  2. A measure of the amount of distortion.

Because we can not simply add displacement fields, large deformations are generated by composing many small deformations.

The amount of distortion is computed by summing up the distortion measures from the small displacements.

# Effect of Different Distortion Measures



# Two diffeomorphic approaches in SPM

## Dartel.

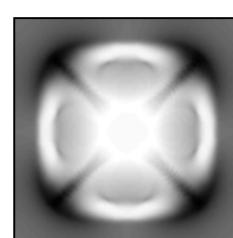
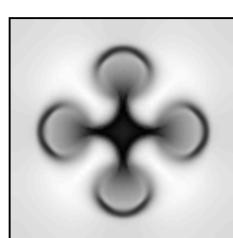
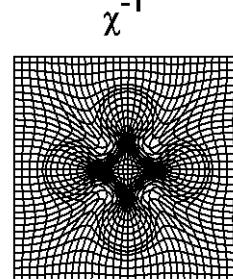
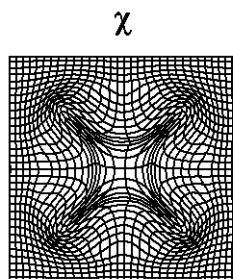
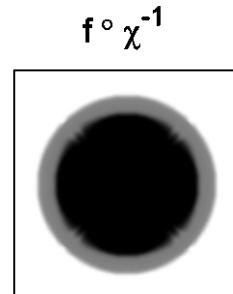
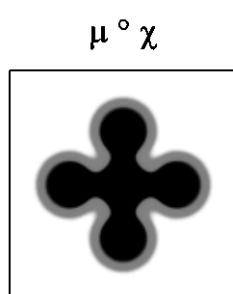
- Uses the same small deformation composed multiple times.
- Faster than Geodesic Shooting.
- Gives similar deformations to Geodesic Shooting.
- Currently more additional utilities.

## Geodesic Shooting

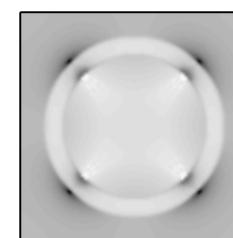
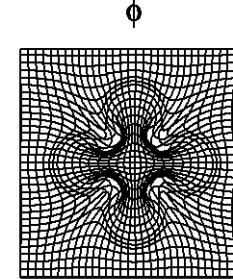
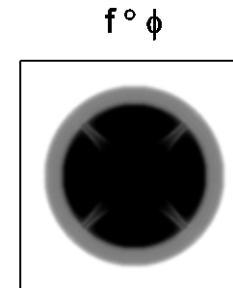
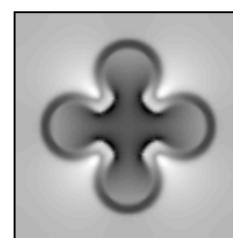
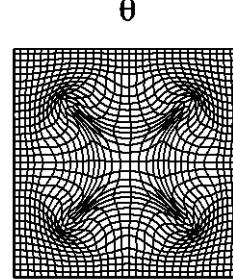
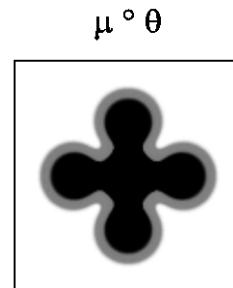
- Uses the optimal series of small deformations, which are composed together.
- More mathematically correct than Dartel.
- Gives nicer maps of volume change than Dartel.
- Likely to replace Dartel in future.

# Dartel & GS Compared

Dartel

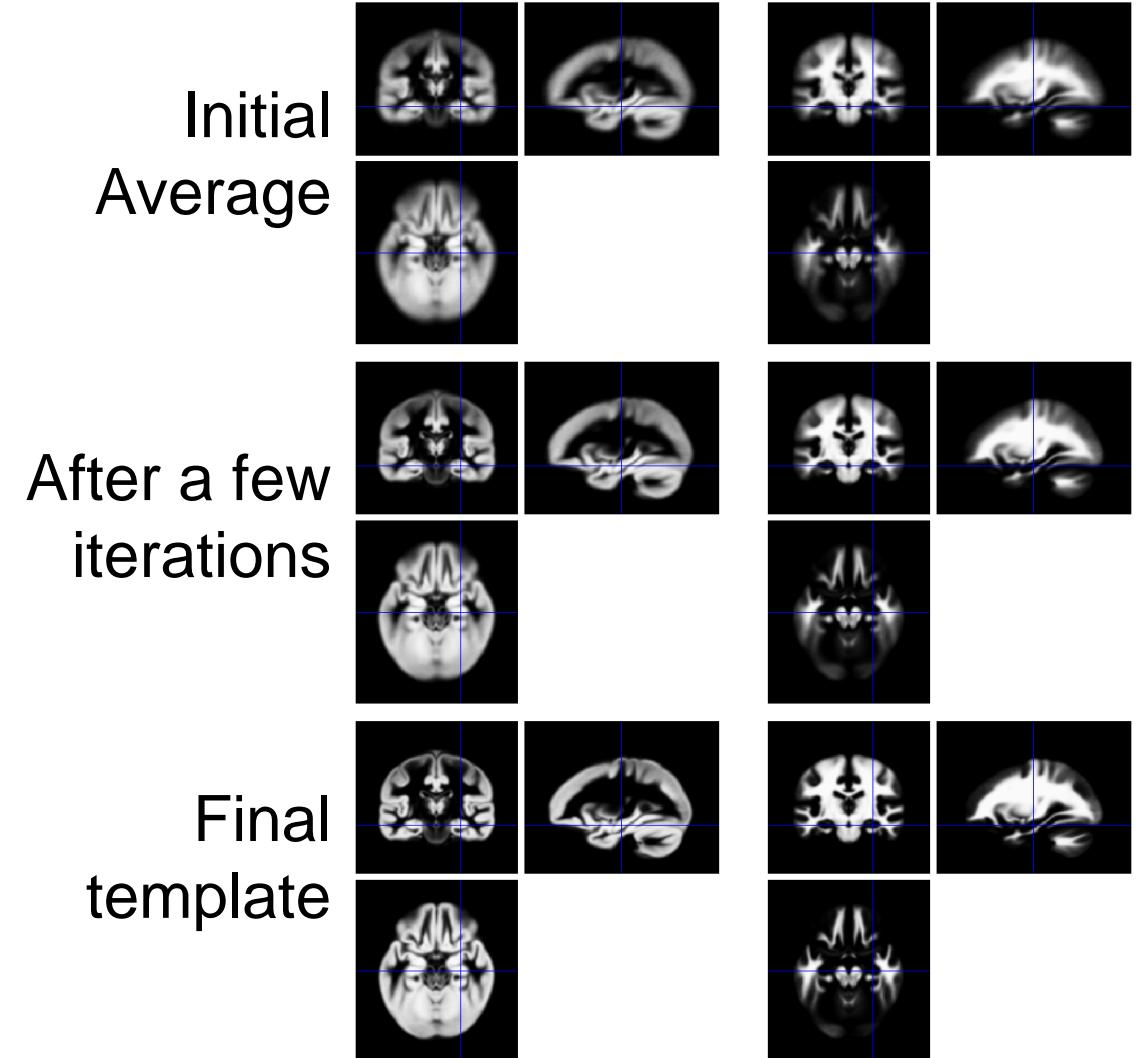


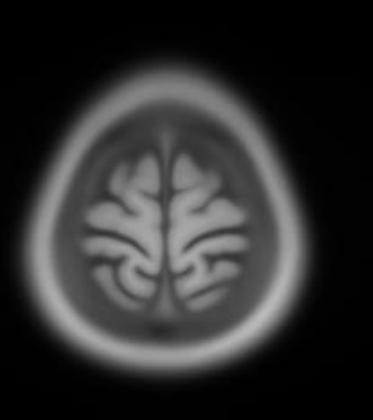
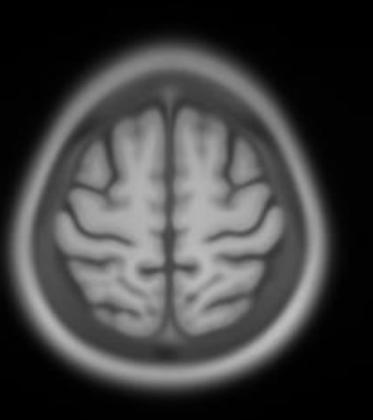
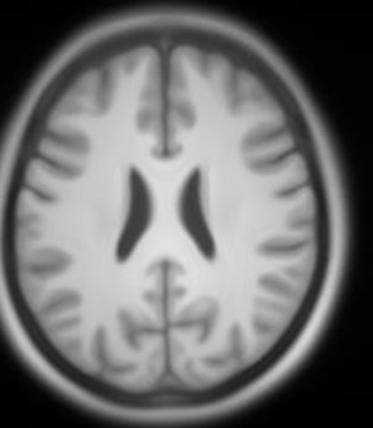
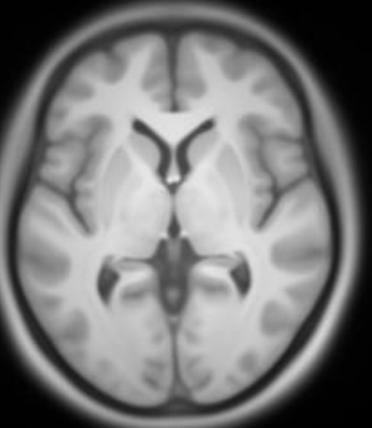
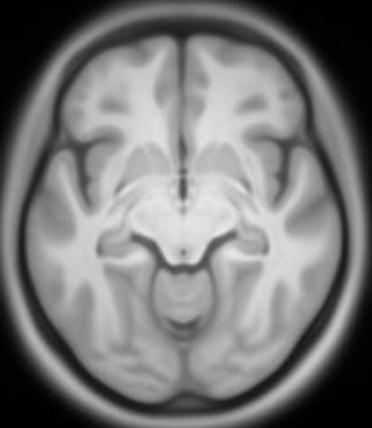
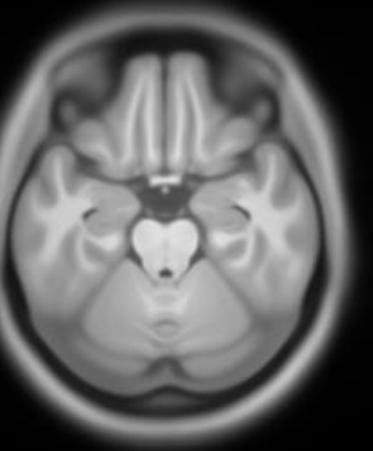
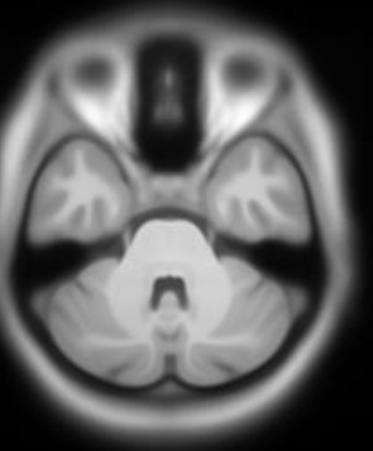
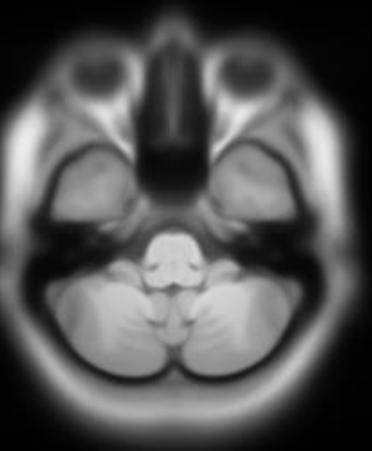
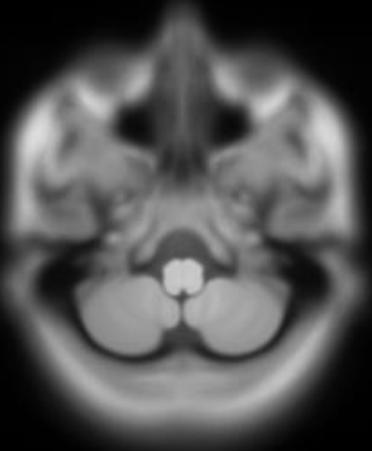
Geodesic Shooting



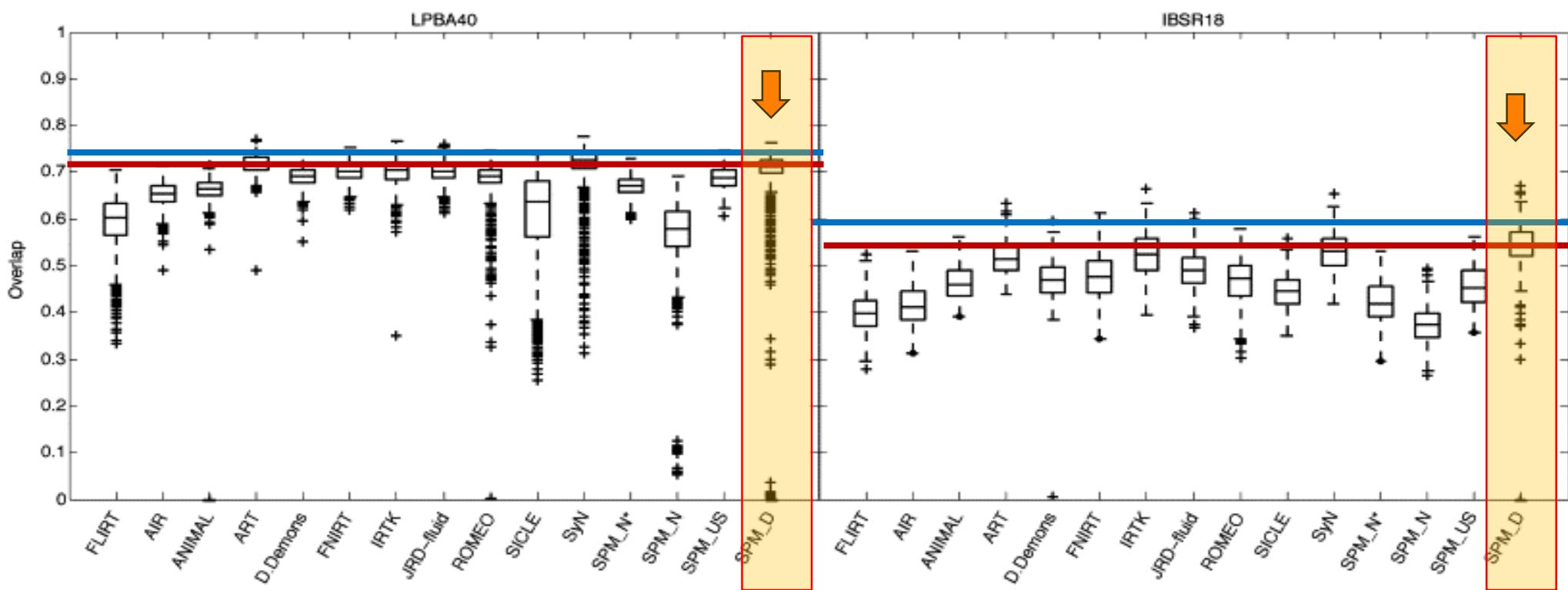
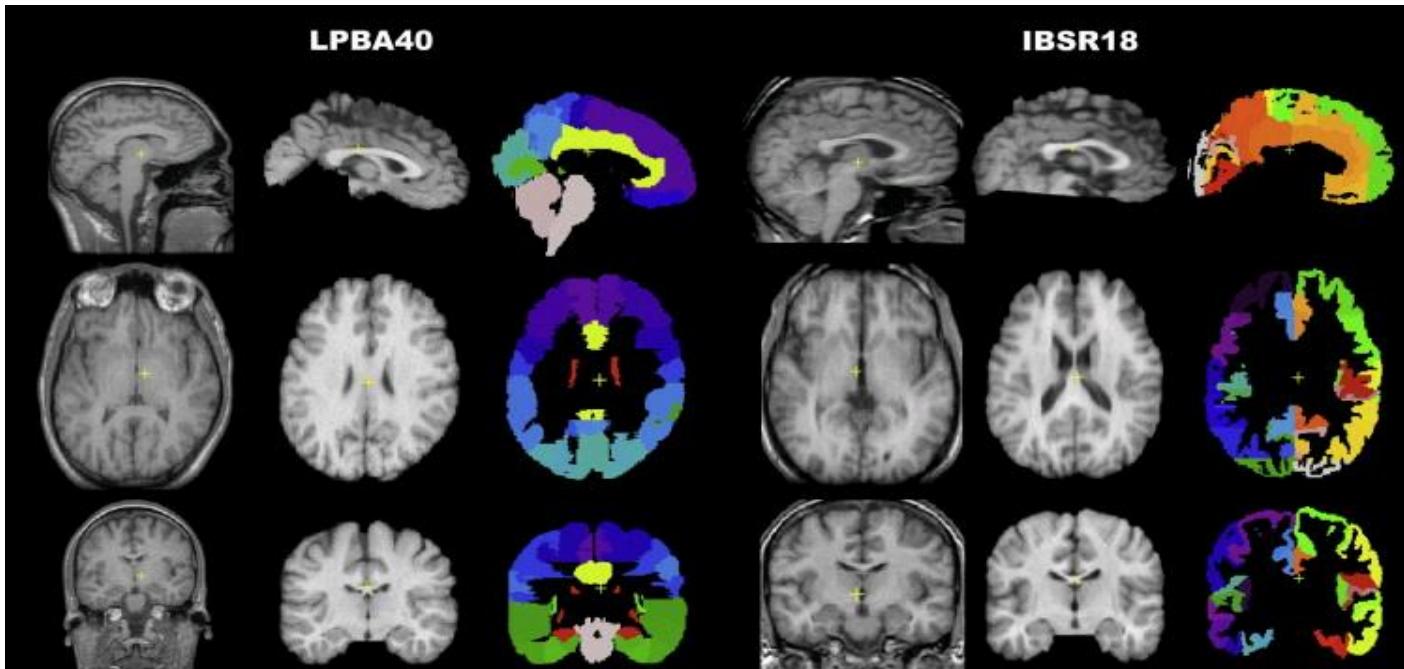
# Group-wise alignment

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



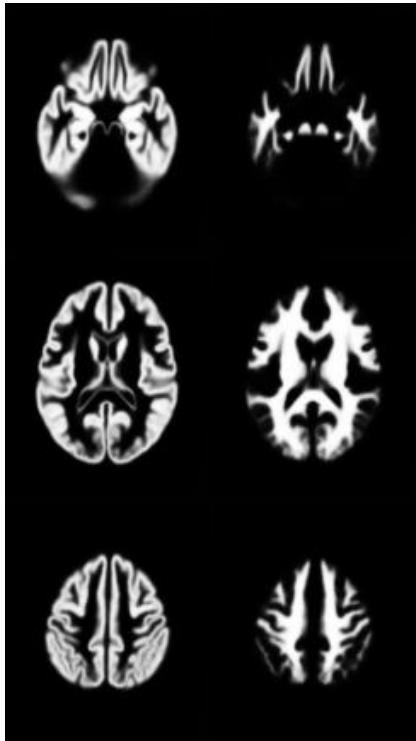


# Evaluations of nonlinear registration algorithms

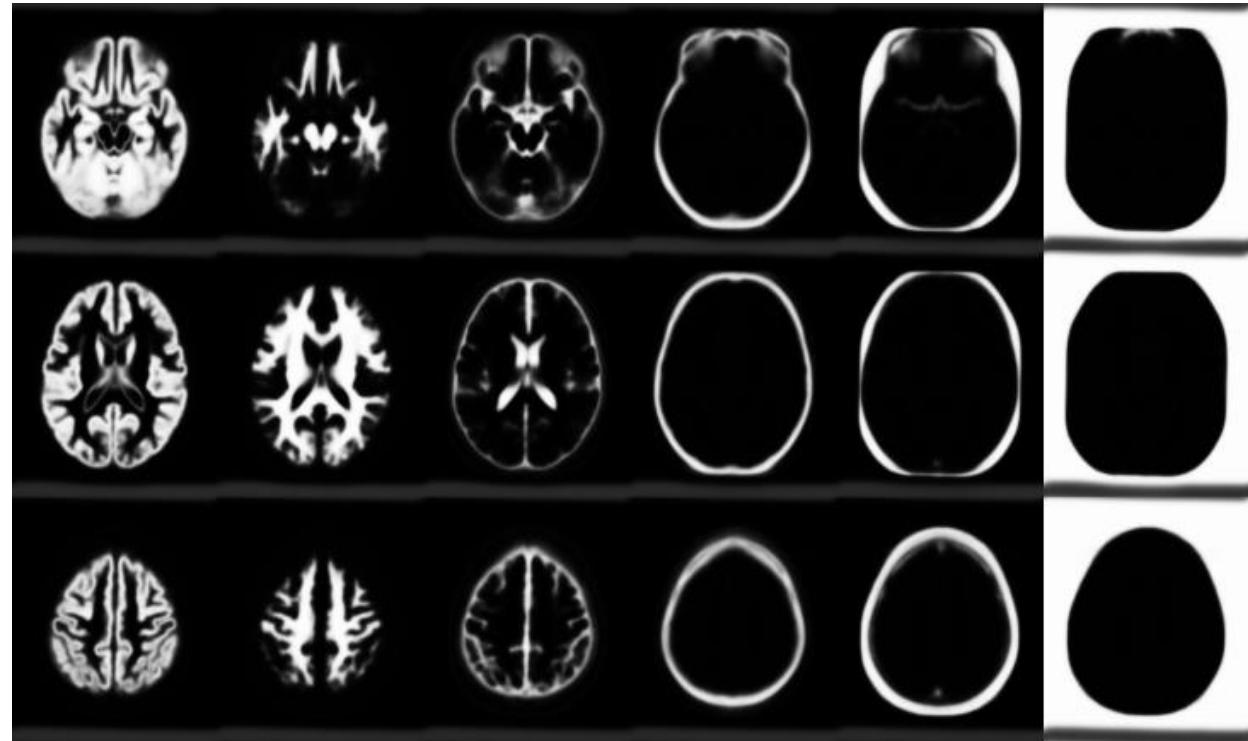


# Tissue map averages

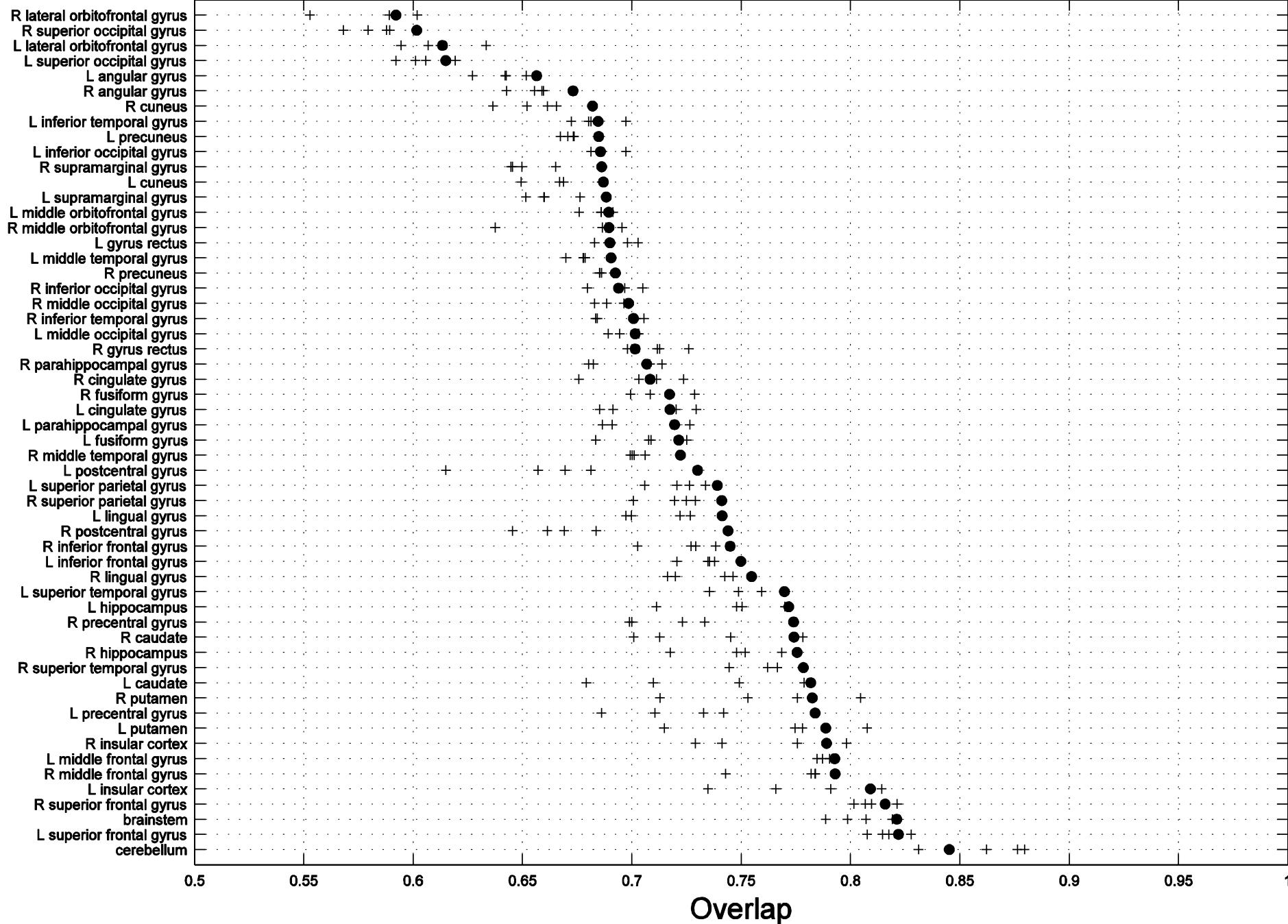
LPBA40



IBSR18



# LPBA40



# Limitations of spatial normalisation

- Cortical folding variability precludes accurate one-to-one mapping.
- Assumptions that we must “spatially normalise” may be impeding progress.
- Should instead be thinking about how best to model the data generatively.



# Selected References

- Beg et al. *Computing large deformation metric mappings via geodesic flows of diffeomorphisms*. International journal of computer vision 61:139-157 (2005).
- Ashburner. *A Fast Diffeomorphic Image Registration Algorithm*. NeuroImage 38:95-113 (2007).
- Ashburner & Friston. *Computing Average Shaped Tissue Probability Templates*. NeuroImage 45:333-341 (2009).
- Klein et al. *Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration*. NeuroImage 46:786-802 (2009).
- Ashburner & Friston. *Diffeomorphic registration using geodesic shooting and Gauss-Newton optimisation*. NeuroImage 55:954-967 (2011).

# Overview

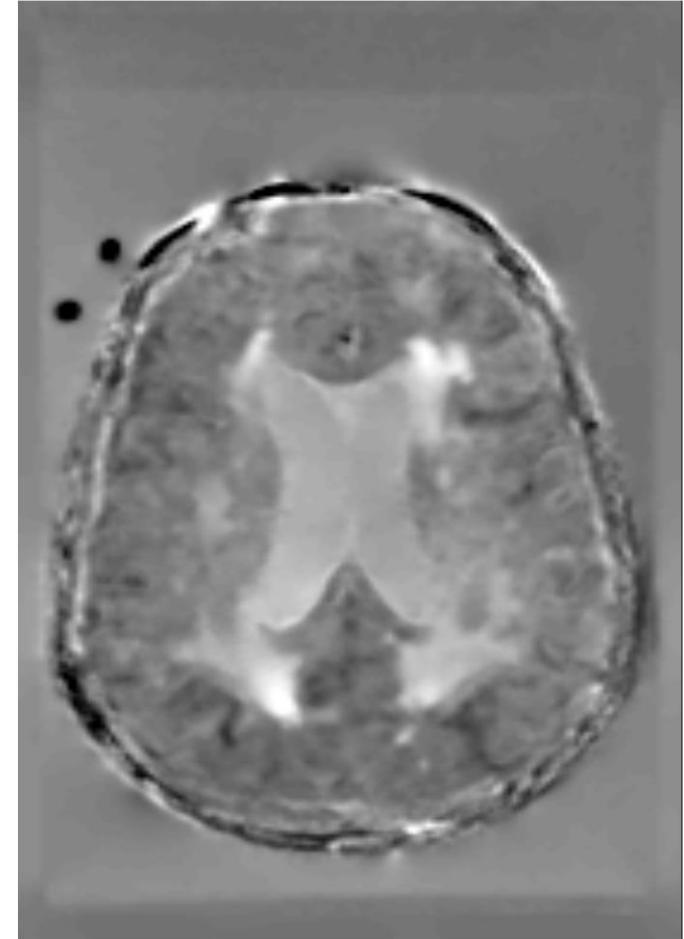
- Voxel-Based Morphometry
- Tissue Segmentation
- Diffeomorphic Registration

# • **Longitudinal Registration**

- Multivariate Shape Models
- Current Work

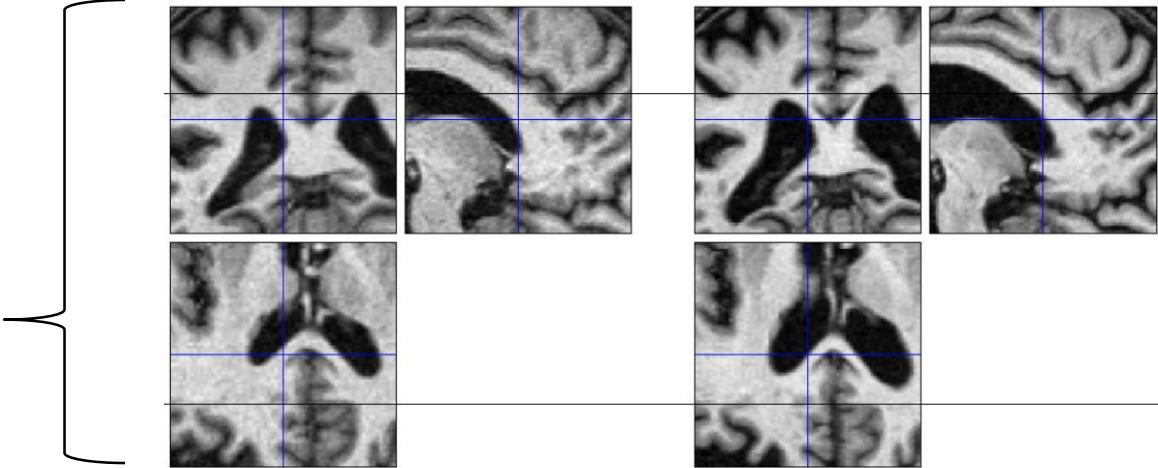
# Longitudinal Registration

- Unified model combines:
  - Nonlinear diffeomorphic registration.
  - Rigid-body registration.
  - Intensity inhomogeneity correction.



# Two Longitudinal Scans

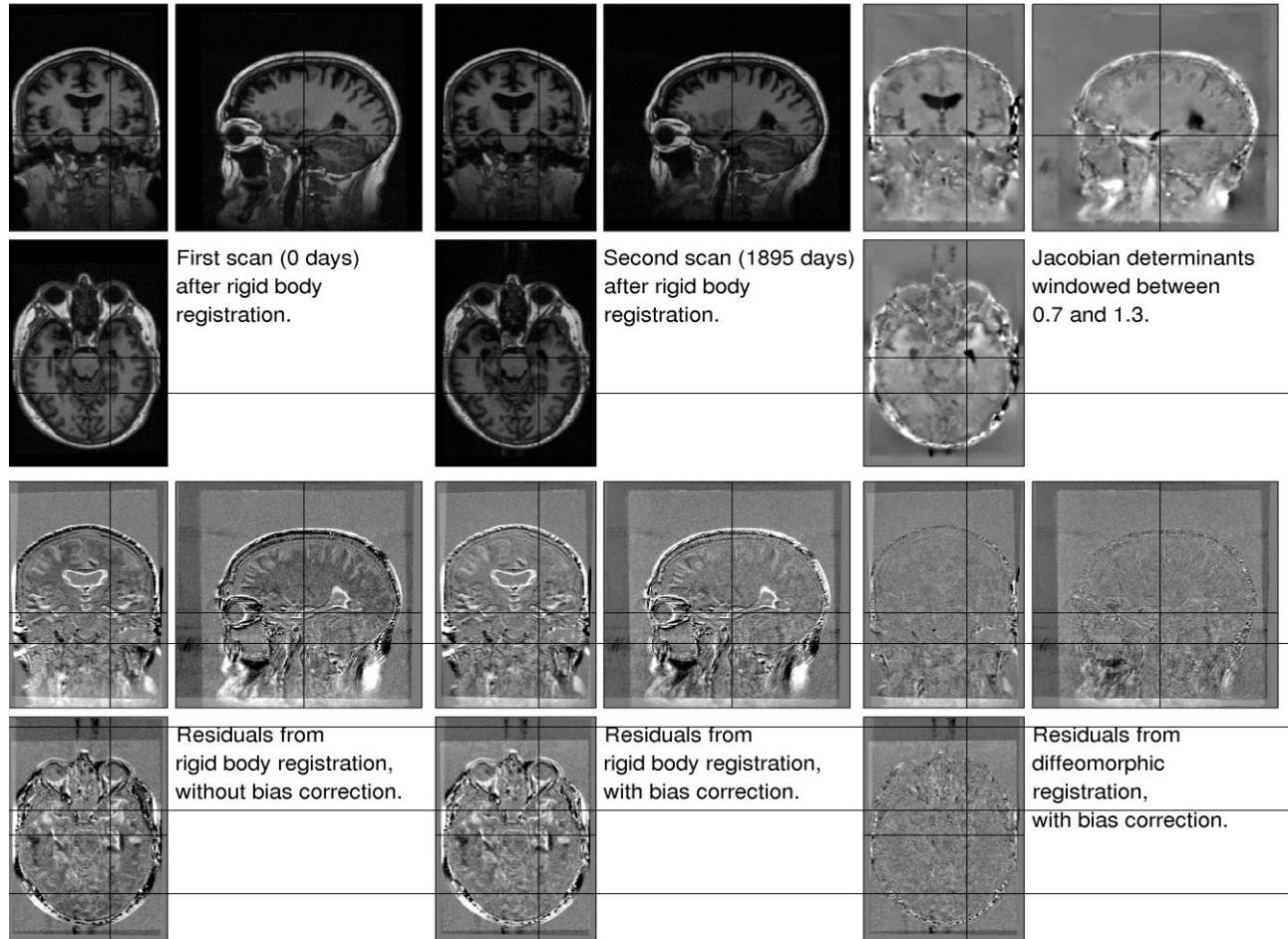
Two scans taken 6 years apart  
(after rigid registration).



# Oasis Data

## OAS2 0002

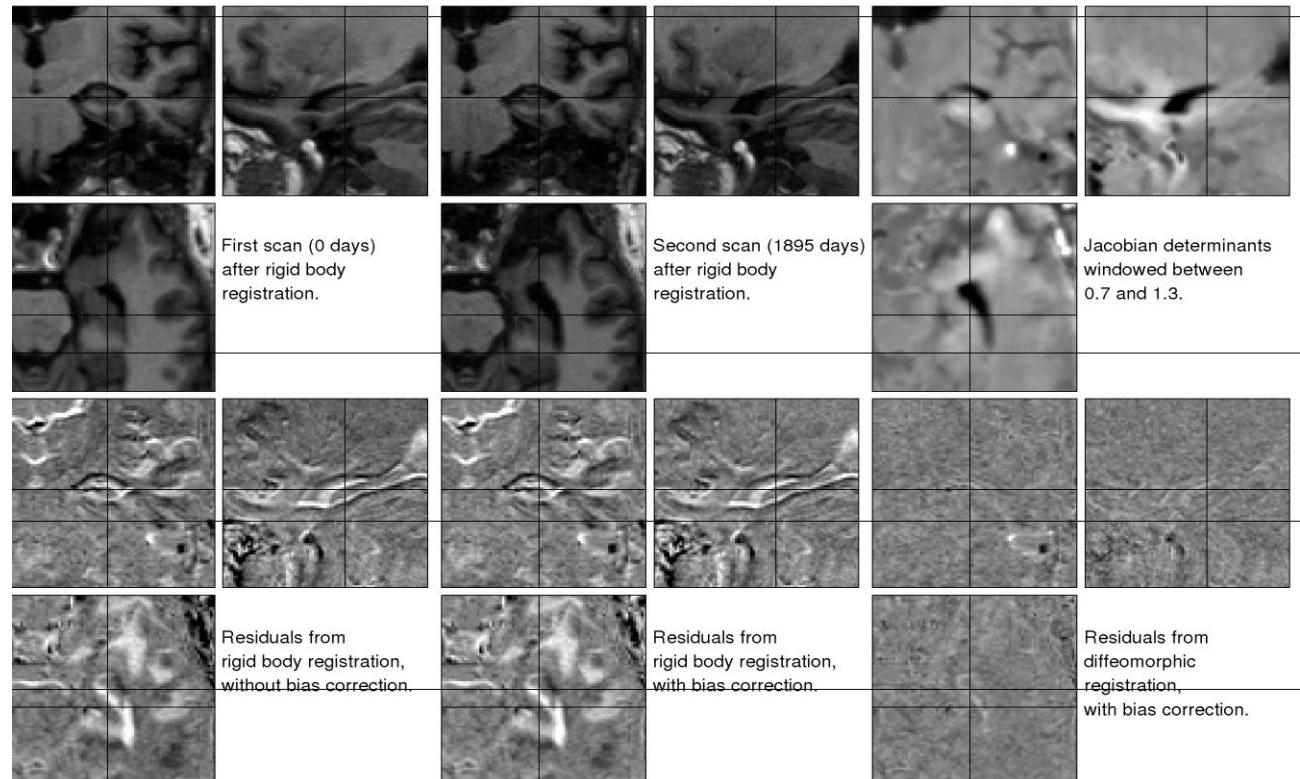
75 year old male,  
with MCI  
(MMSE=22,  
CDR=0.5).



# Oasis Data

## OAS2 0002

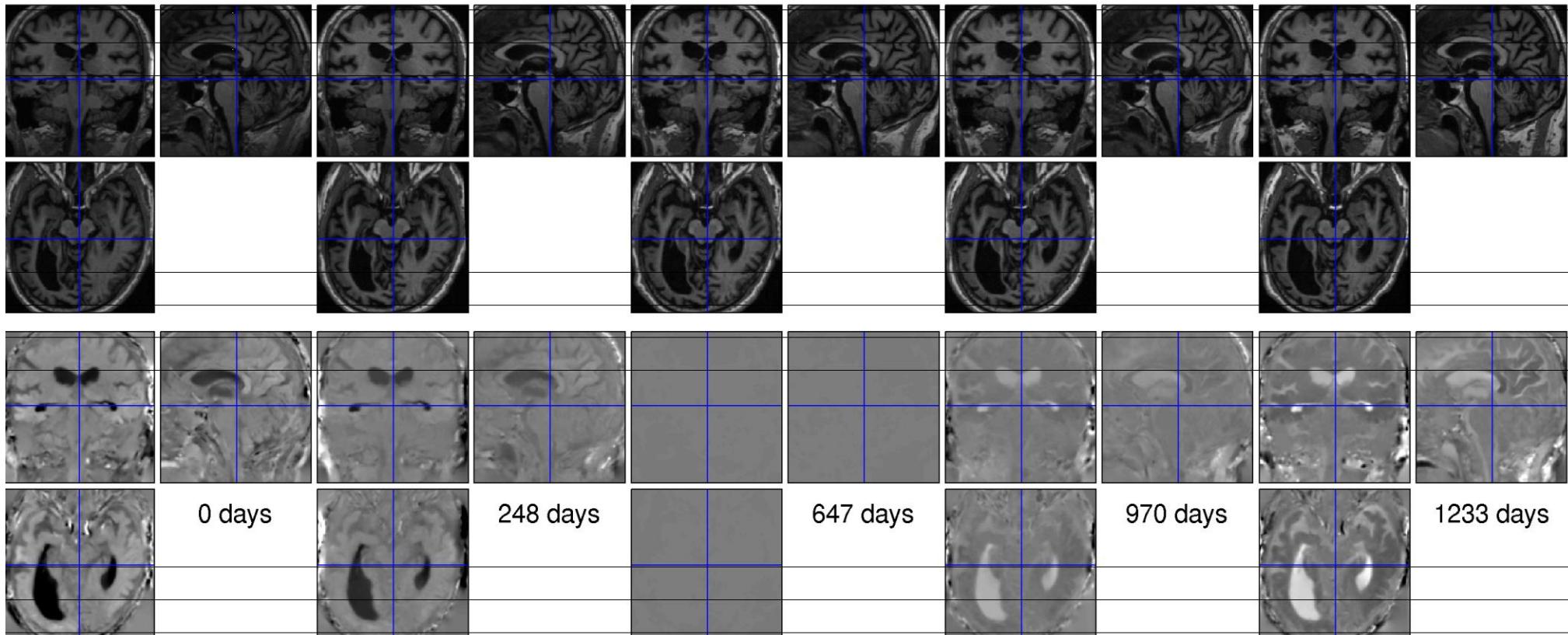
75 year old male,  
with MCI  
(MMSE=22,  
CDR=0.5).



# Oasis Data

## OAS2 0048

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



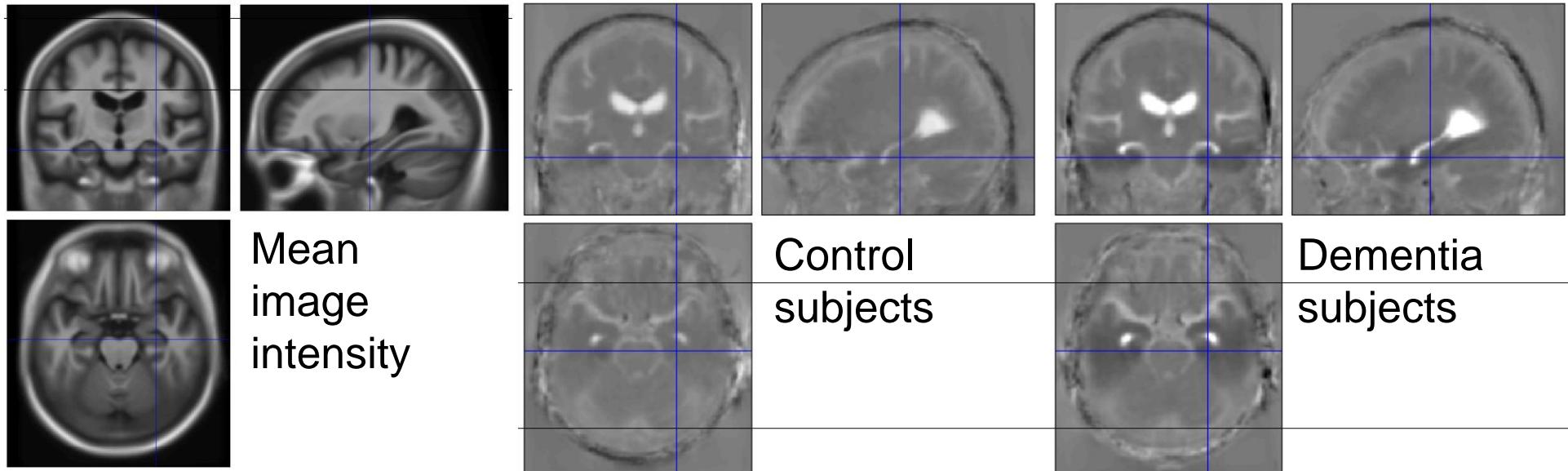
# Oasis Data

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.



# Selected References

- Fox, Ridgway & Schott. *Algorithms, atrophy and Alzheimer's disease: cautionary tales for clinical trials*. Neuroimage 57:15-18 (2011).
- Ashburner & Ridgway. *Symmetric diffeomorphic modelling of longitudinal structural MRI*. Frontiers in Neuroscience 6(197) (2013).

# Overview

- Morphometry
- Voxel-Based Morphometry
- Tissue Segmentation
- Diffeomorphic Registration
- Longitudinal Registration
- **Multivariate Shape Models**
  - Multivariate nature of shape
  - “Scalar momentum”
  - Some evaluations
- Current Work

# Multivariate shape models

- In theory, assumptions about structural covariance among brain regions are more biologically plausible.  
Form determined (in part) by spatio-temporal modes of gene expression.
- Empirical evidence in (eg)  
[Mechelli, Friston, Frackowiak & Price. \*Structural covariance in the human cortex\*. Journal of Neuroscience 25\(36\):8303-8310 \(2005\).](#)
- We should work with the most accurate modelling assumptions available.
  - If a model is accurate, it will make accurate predictions.

*“The morphologist, when comparing one organism with another, describes the differences between them point by point, and “character” by “character”. If he is from time to time constrained to admit the existence of “correlation” between characters, yet all the while he recognises this fact of correlation somewhat vaguely, as a phenomenon due to causes which, except in rare instances, he cannot hope to trace ; and he falls readily into the habit of thinking and talking of evolution as though it had proceeded on the lines of his own descriptions, point by point, and character by character.”*

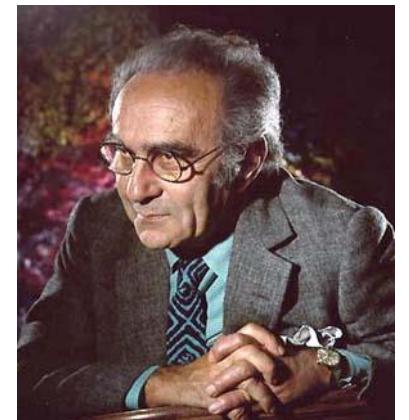
D'Arcy Thompson (Growth and Form, 1917).

*“This unhappy result can be traced to the piecemeal tests which have hitherto been used. A bone or a tooth is a unit ; it is not a discrete assembly of independent measurements.”*

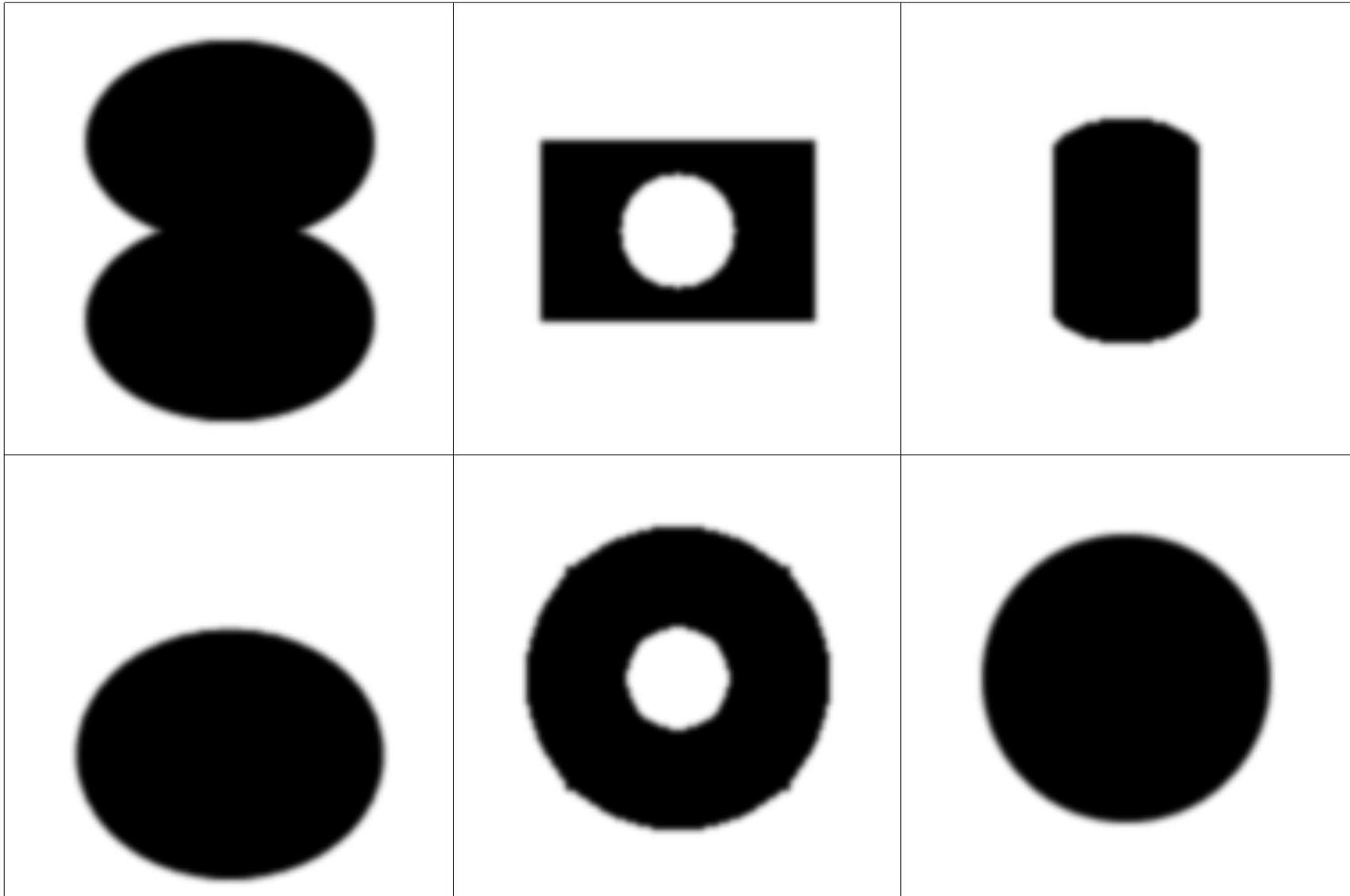
Jacob Bronowski & W.M. Long (Nature, 1951).

*“The right statistical method must treat the set of variates as a single coherent matrix ; and this is, in fact, the technique of multivariate analysis.”*

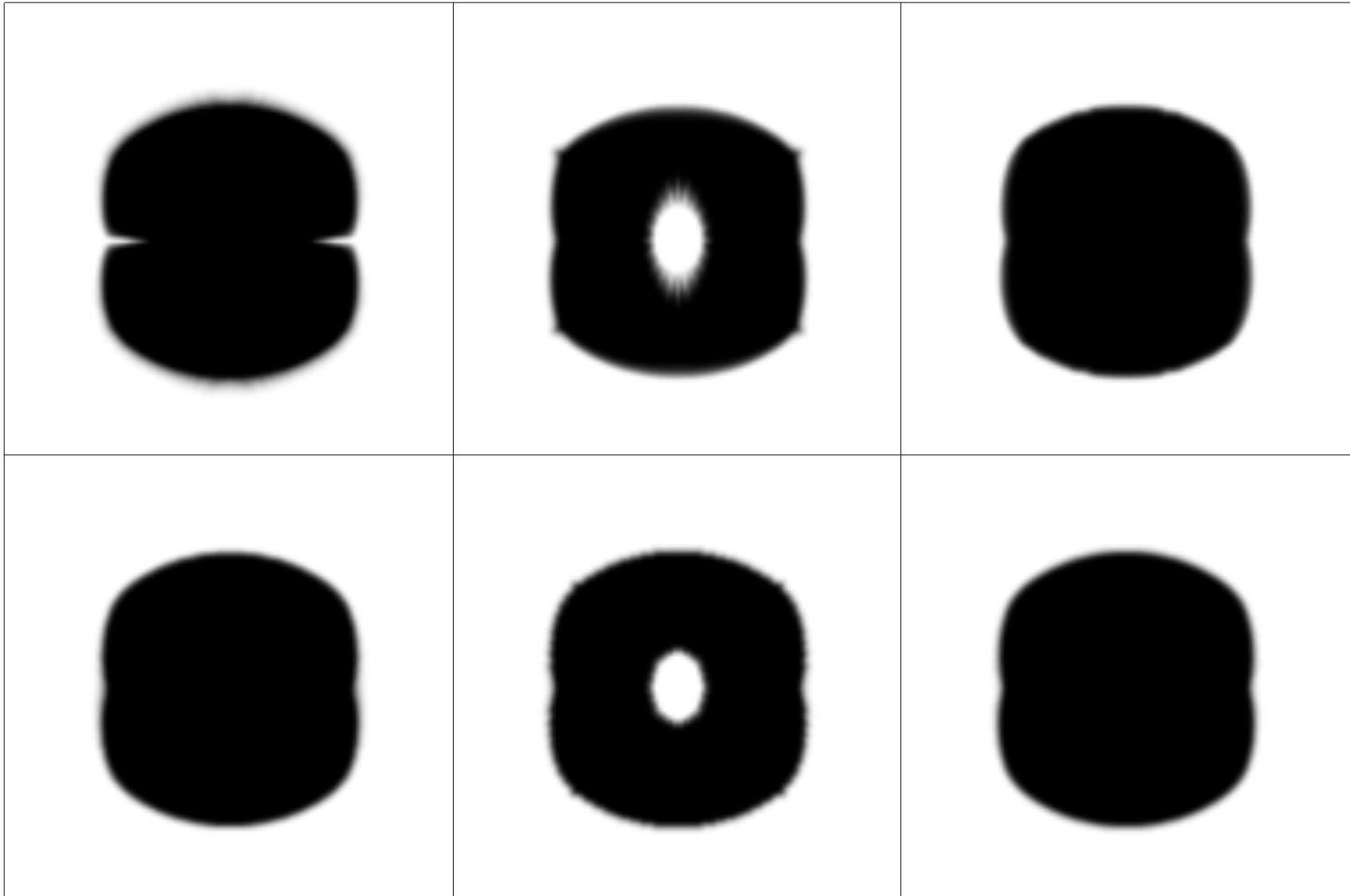
Jacob Bronowski & W.M. Long (Nature, 1951).



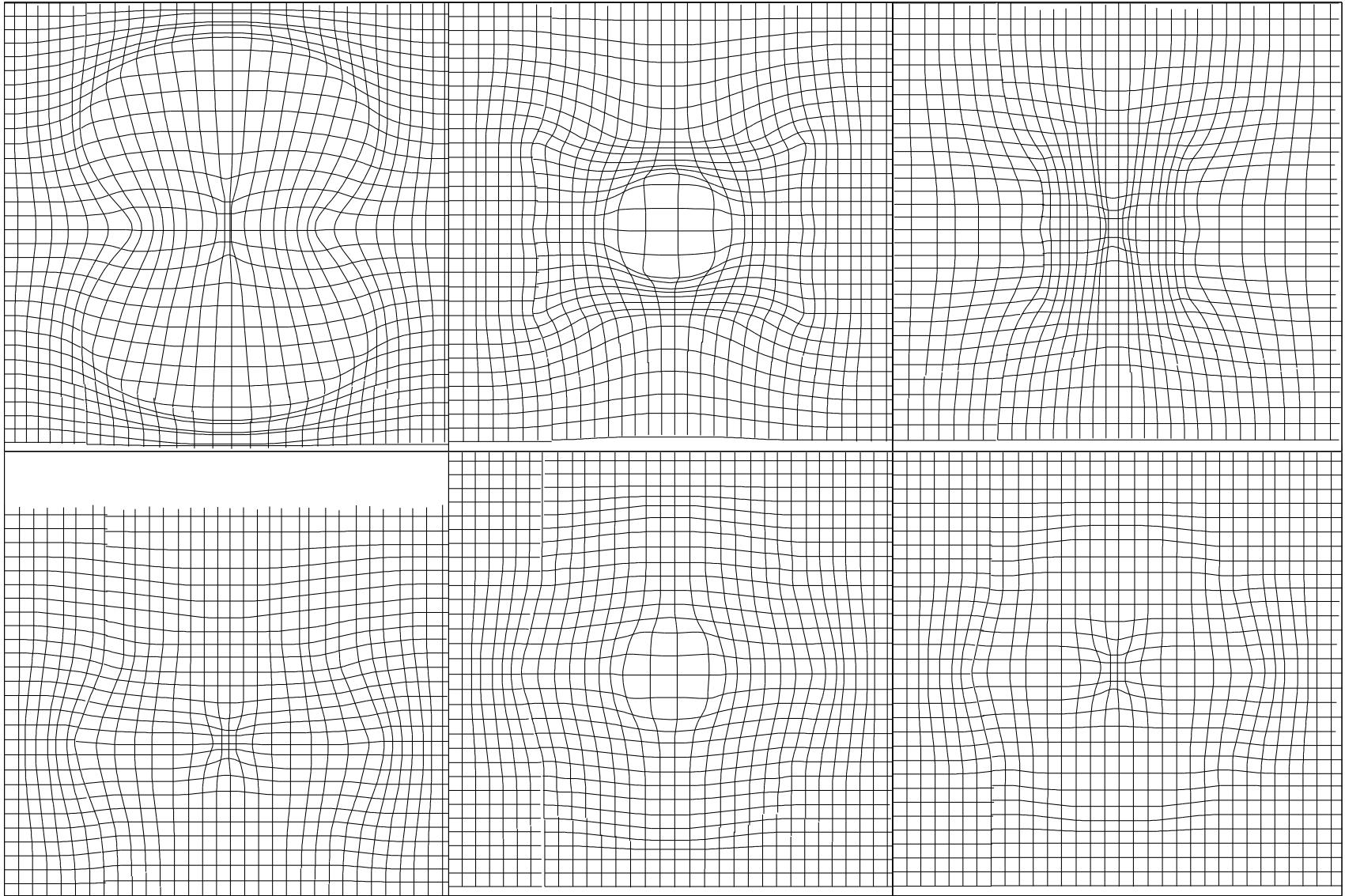
# Some 2D Shapes



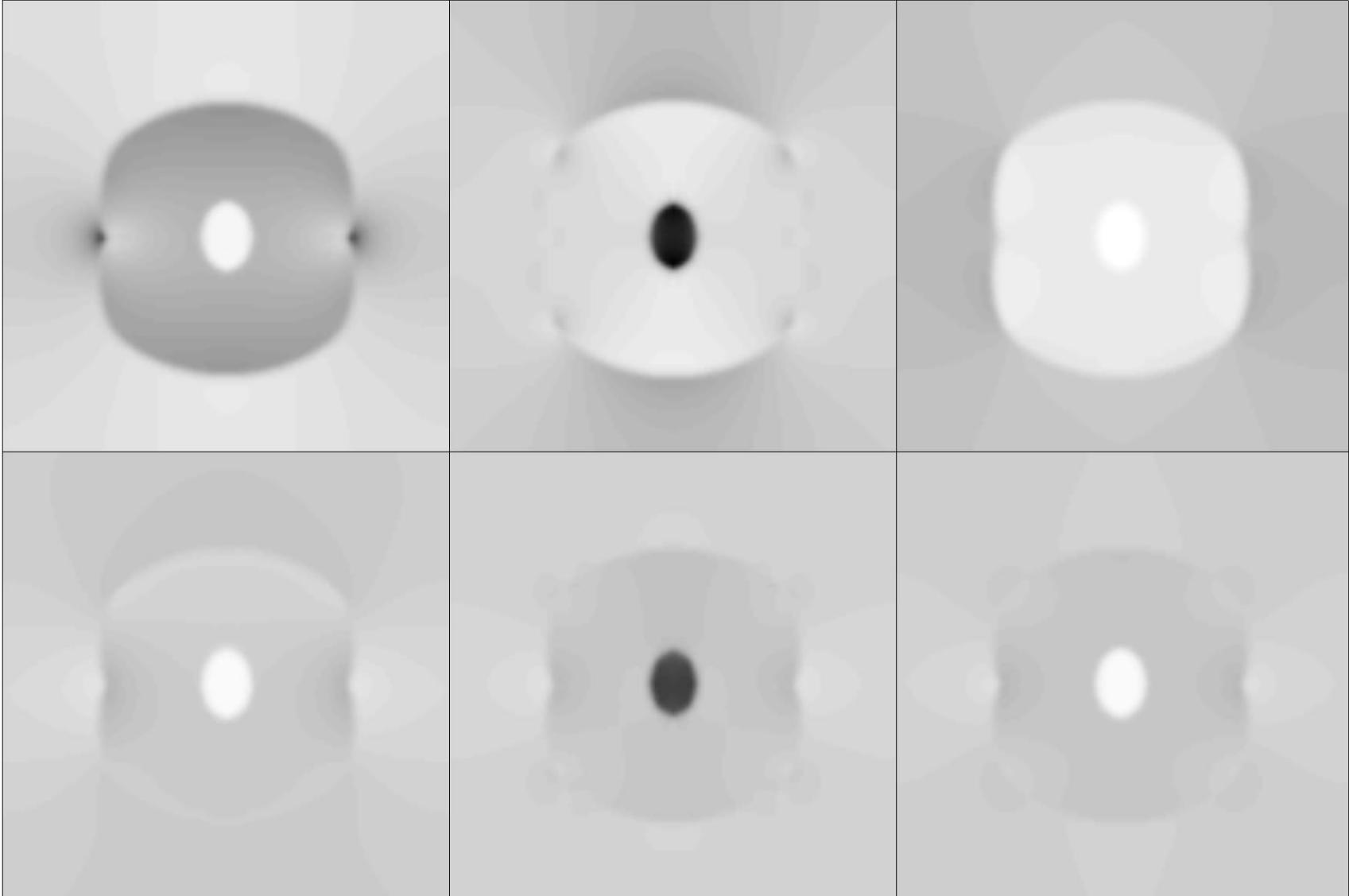
# Shapes aligned to their average



These were the deformations for that

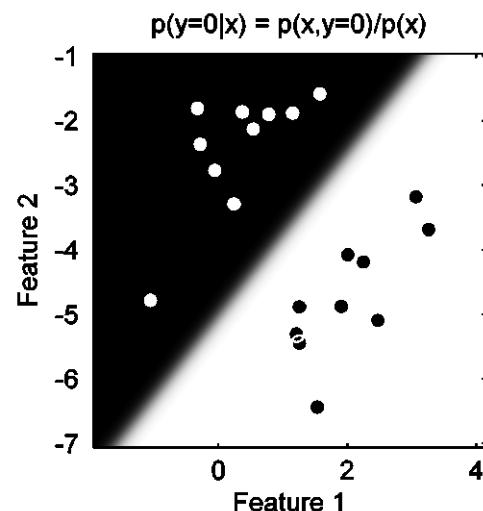
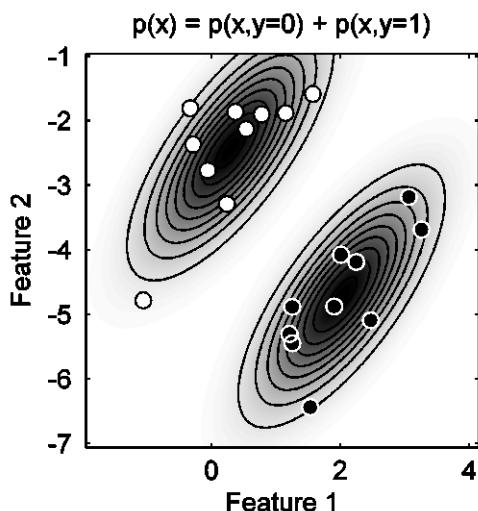
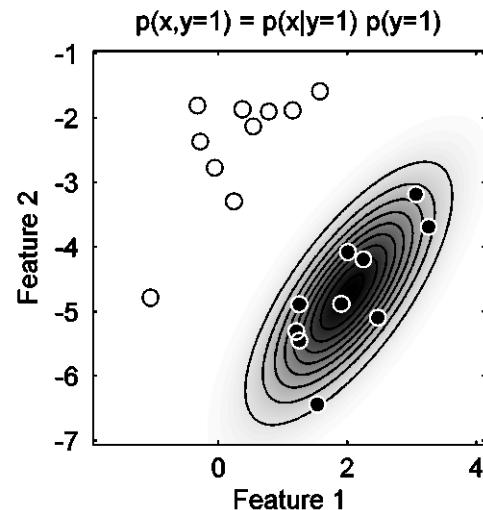
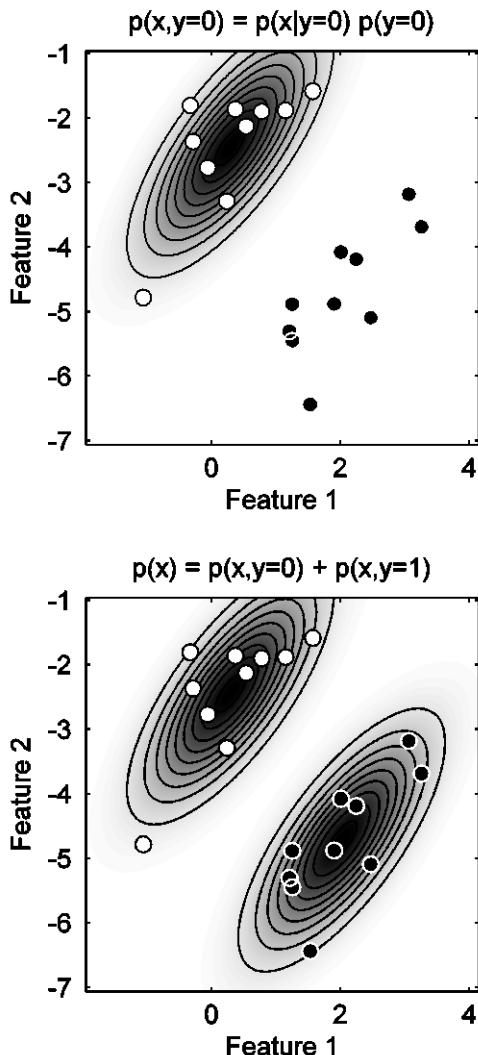


and these are the Jacobian determinants



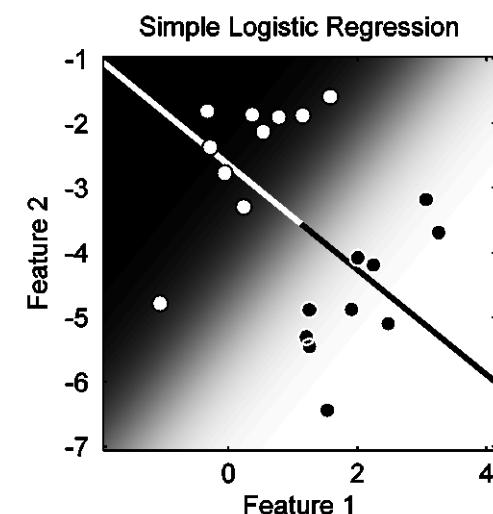
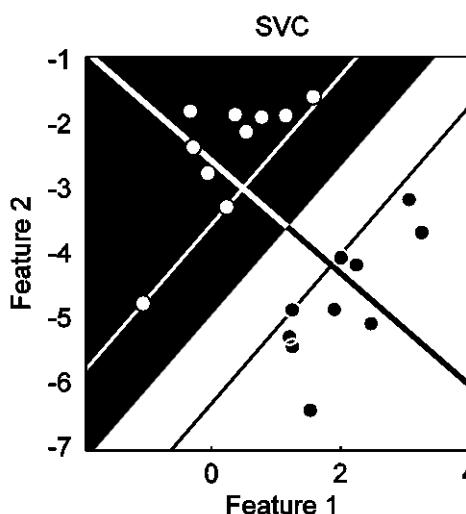
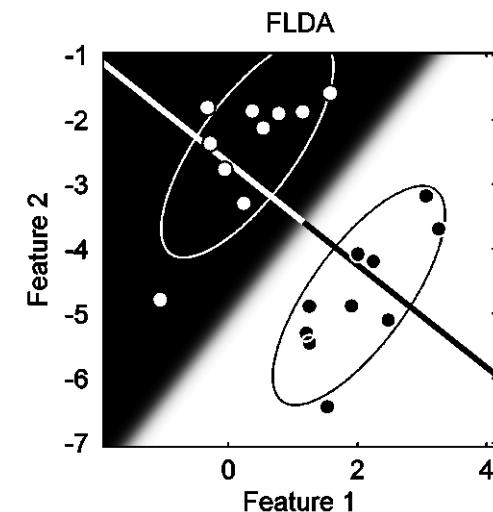
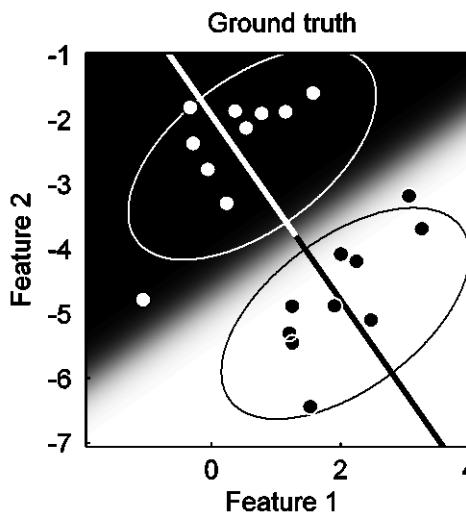
# Fisher's Linear Discriminant Analysis

- A multivariate model.
- Special case of canonical variates analysis.
- A **generative** model.



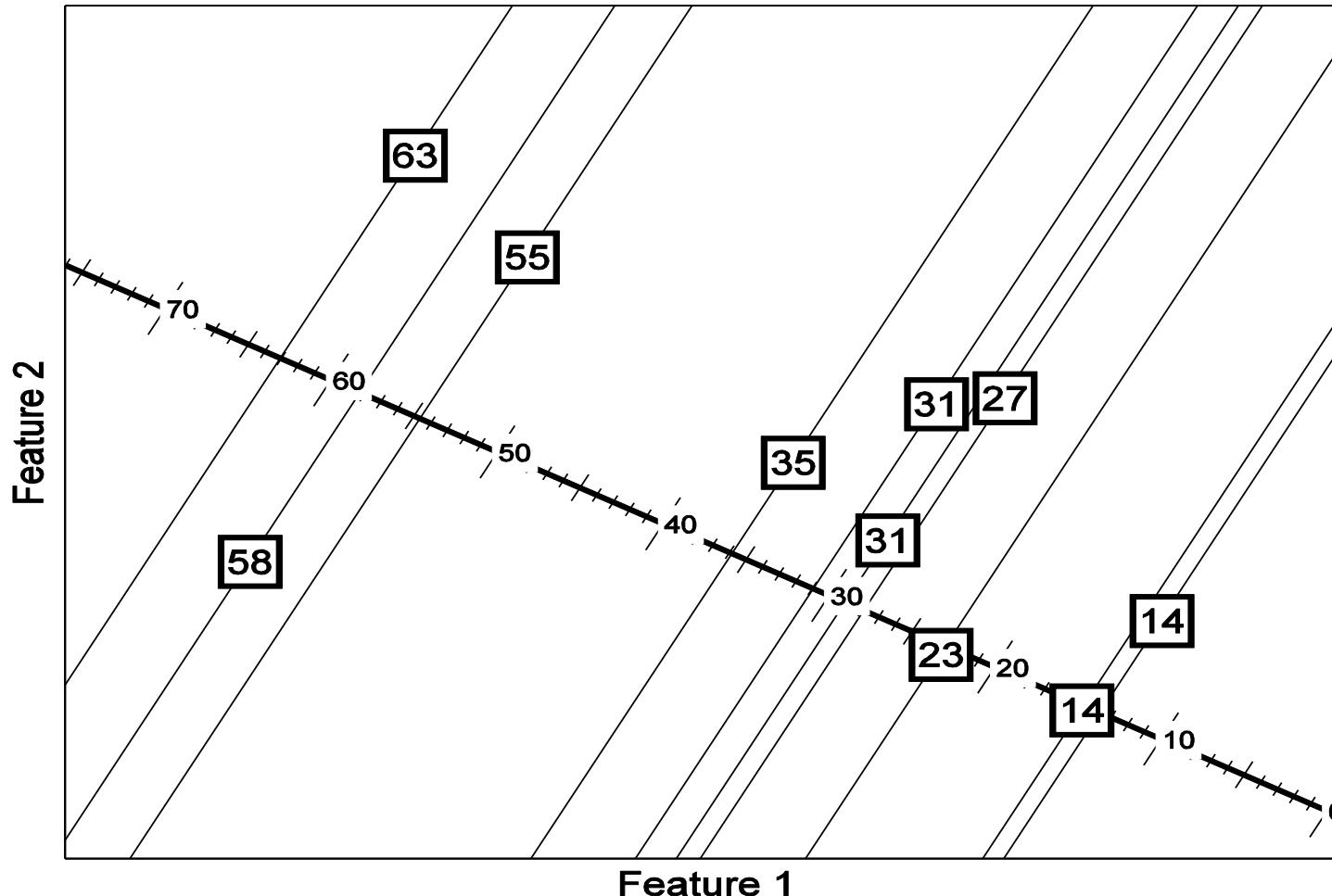
# Other linear discrimination approaches

- Can also use **discriminative models**.
- Anatomical differences are encoded by the vector orthogonal to the separating hyper-plane.
- The most accurate model of difference is the one that best separates the groups.



# Regression

- For predicting a continuous variable



# Weight Map

For linear classifiers, predictions are made by:

$$y = a_1 \times x_1 + a_2 \times x_2 + a_3 \times x_3 + \dots + b$$

where:  $y$  is the prediction

$x_1, x_2, x_3$  etc are voxels in the image to classify

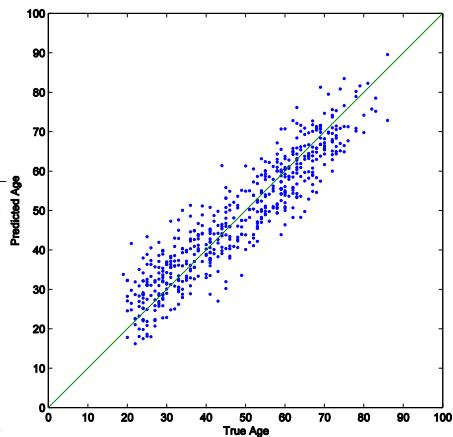
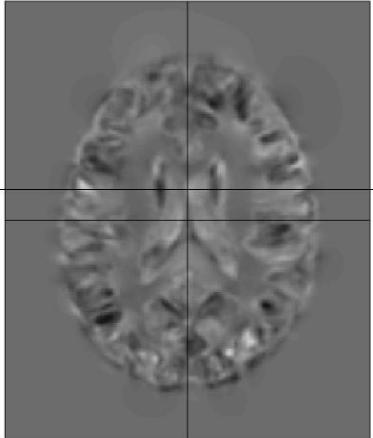
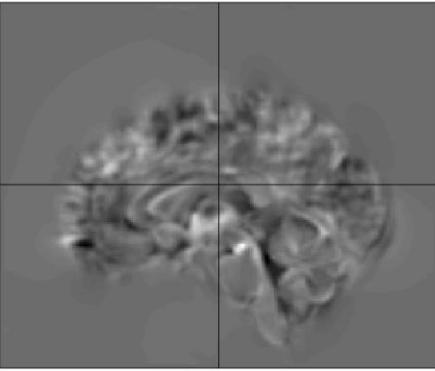
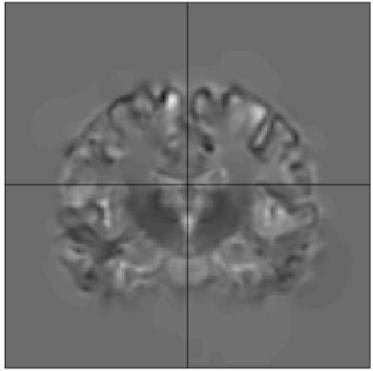
$a_1, a_2, a_3$  etc are voxels in a weight map

$b$  is a constant offset.

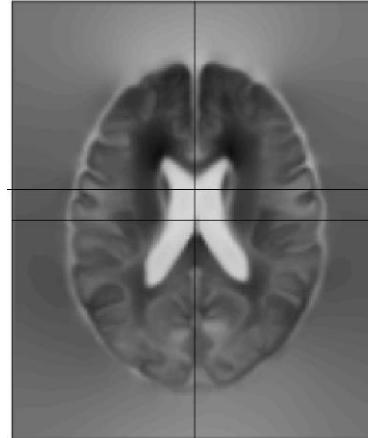
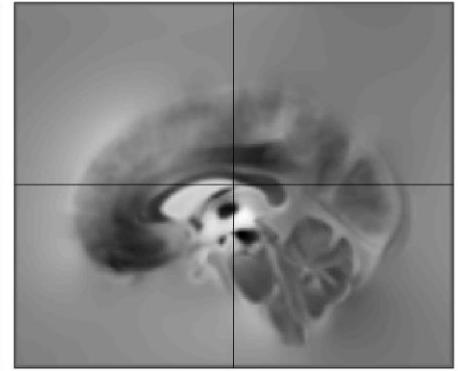
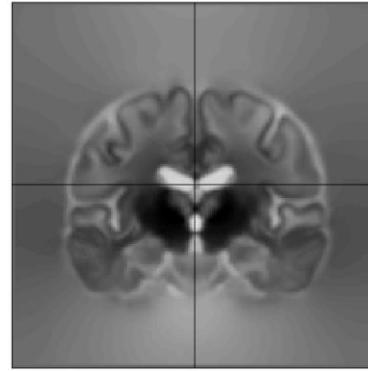
The weight map can be visualised

# Maps

Multivariate weight map



Simple T statistic image



Prettier – but  
does not  
accurately  
characterise the  
effects of age.

# “Scalar Momentum”

- For diffeomorphic registration by least-squares matching, the warps ( $\varphi$ ) are encoded by an initial velocity ( $v(0)$ ):

$$Lv(0) = \frac{1}{\sigma^2} |\det d\varphi| (I_0 - I_1 \circ \varphi) \nabla I_0$$

Initial Momentum

Jacobian determinants

Template

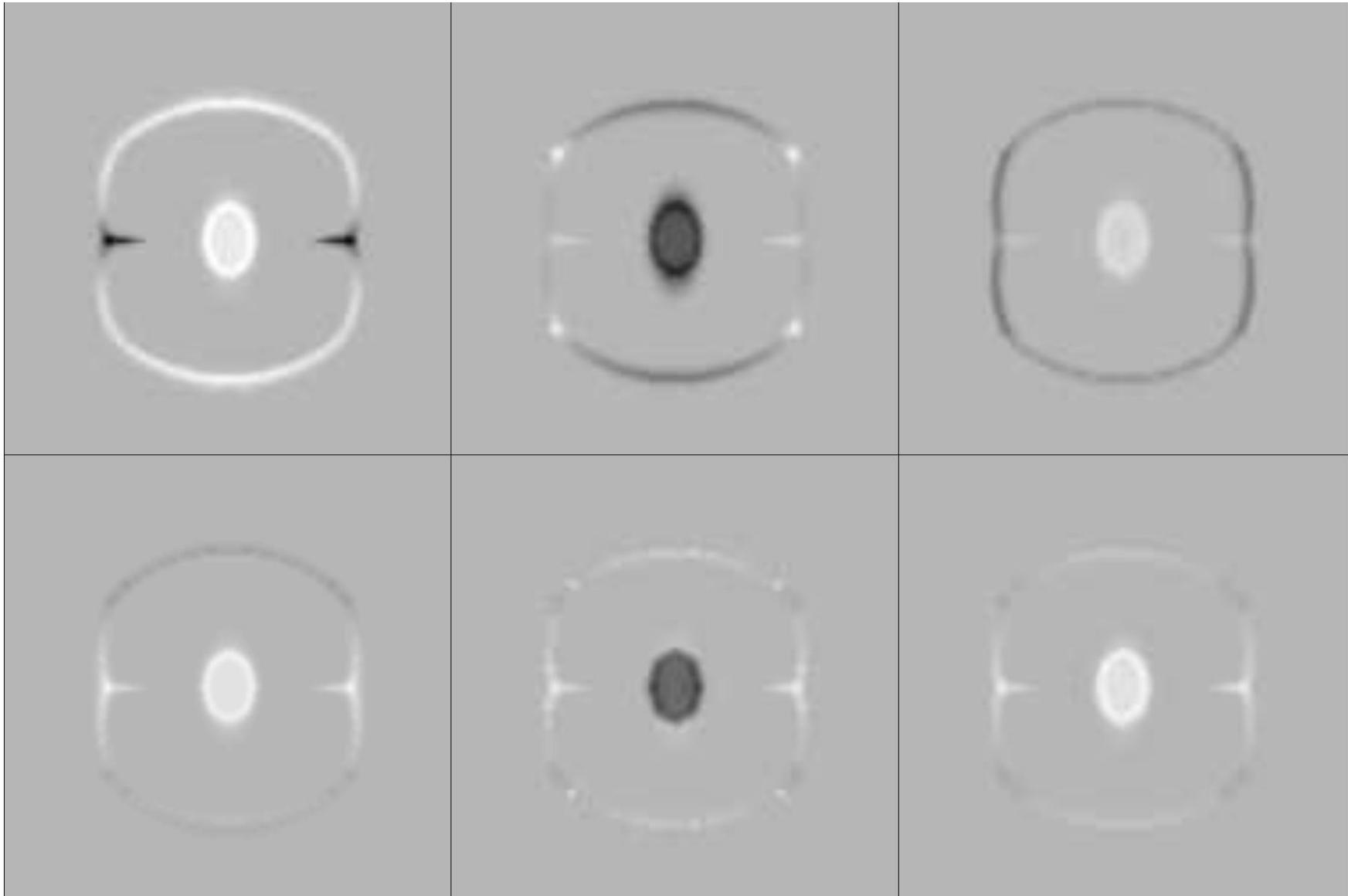
Warped individual

Gradient of template

# The 2D shapes (again)



“Scalar momentum”  $|\det d\varphi|(I_0 - I_1 \circ \varphi)$



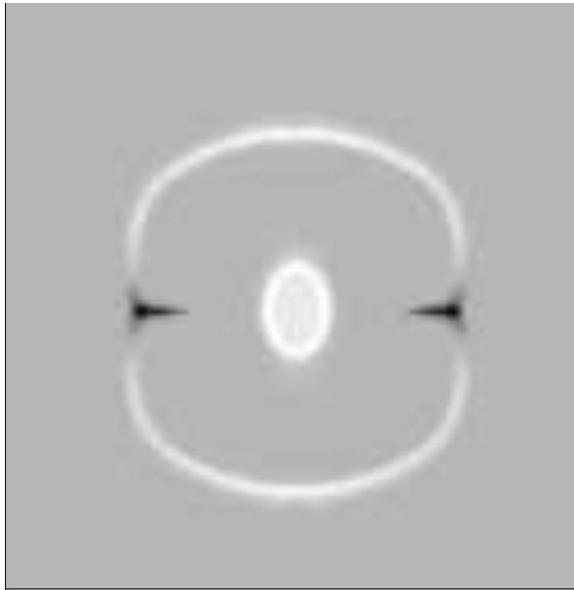
# The 2D shapes (yet again)



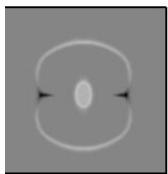
Reconstructed from scalar momentum and template.



“Scalar momentum” – encodes the original shapes

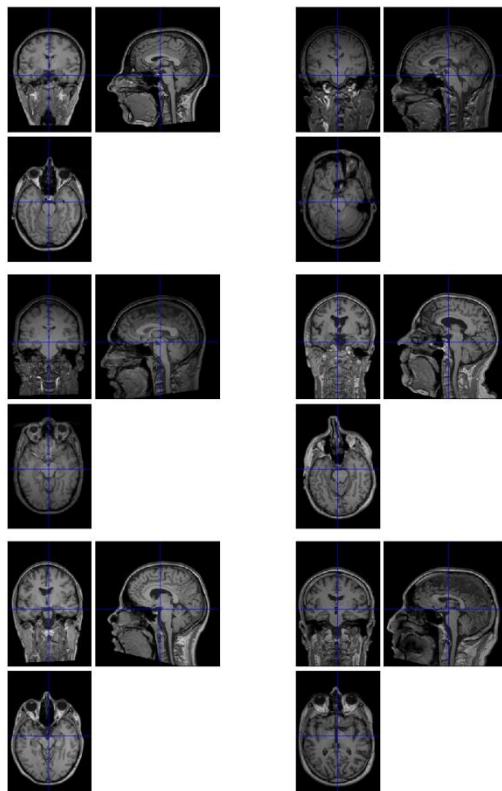


Residuals

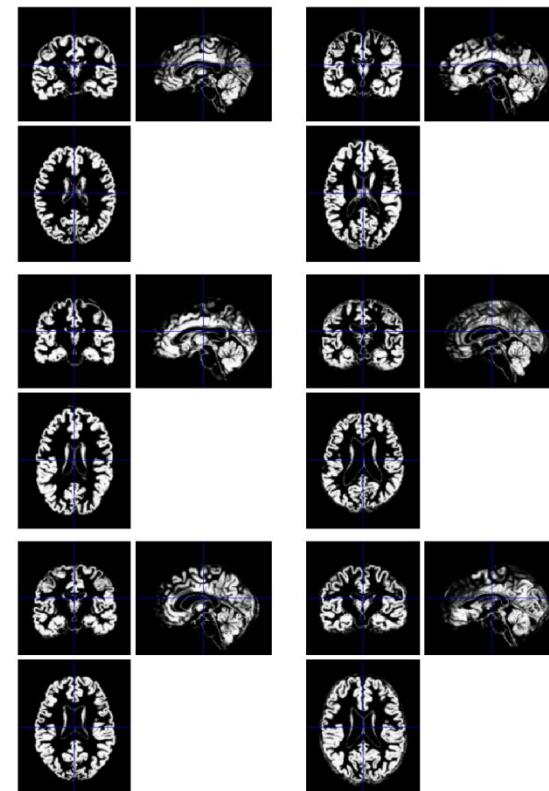


# IXI Data

## Original Images

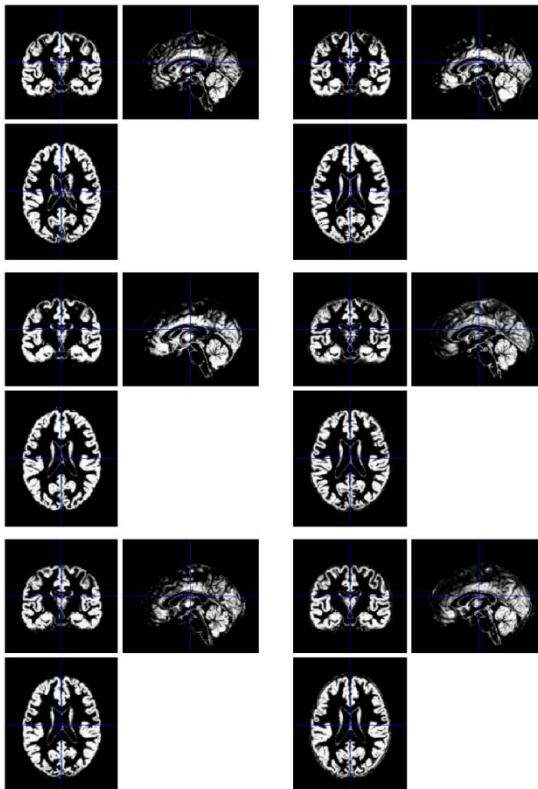


## Rigidly Aligned Grey Matter

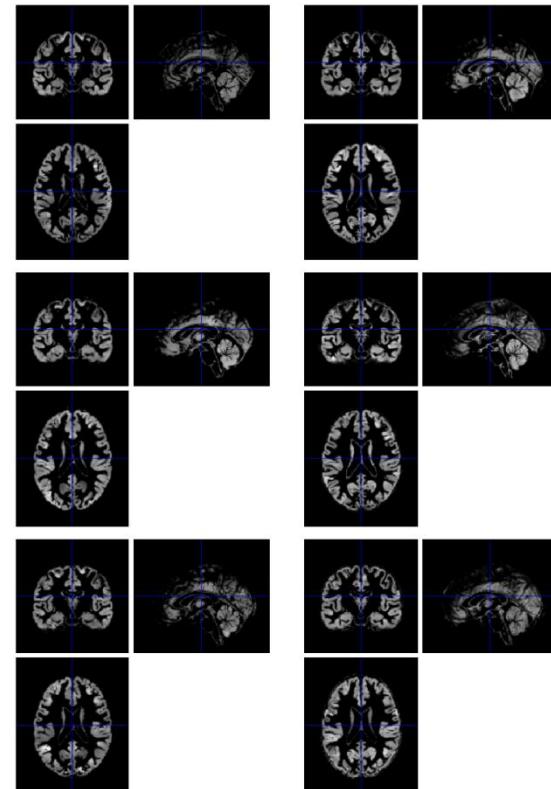


# VBM-type Features

## Warped Grey Matter

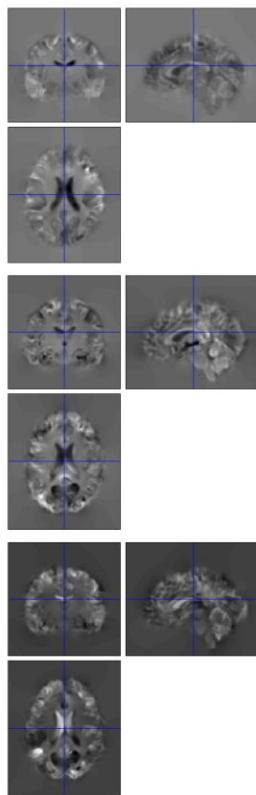


## “Modulated” Warped GM

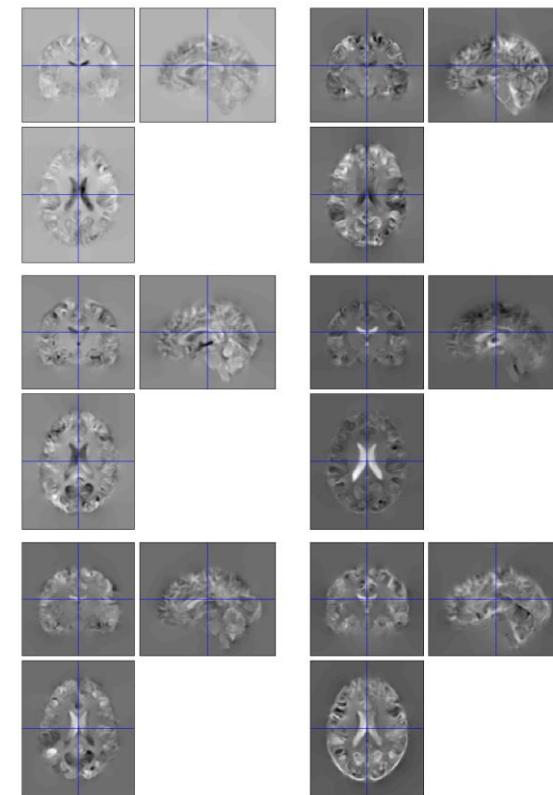


# Volumetric Measures from Deformation Fields

**Jacobian determinants**

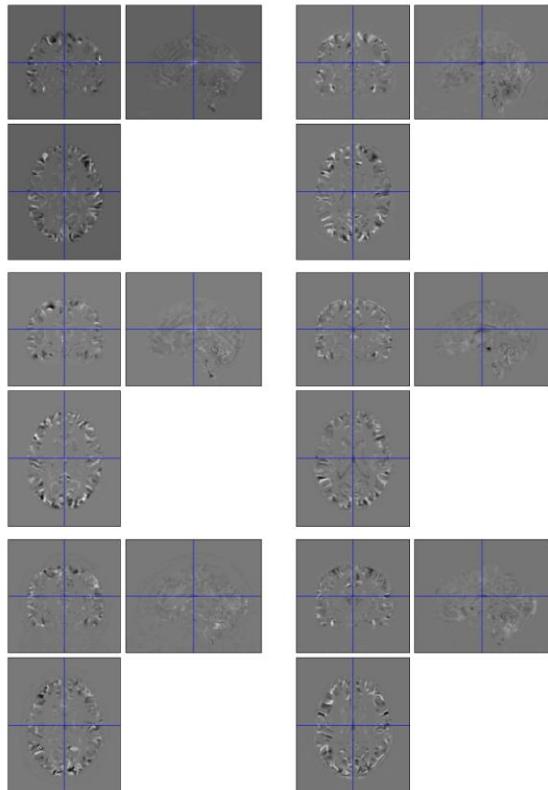


**Initial Velocity Divergence**

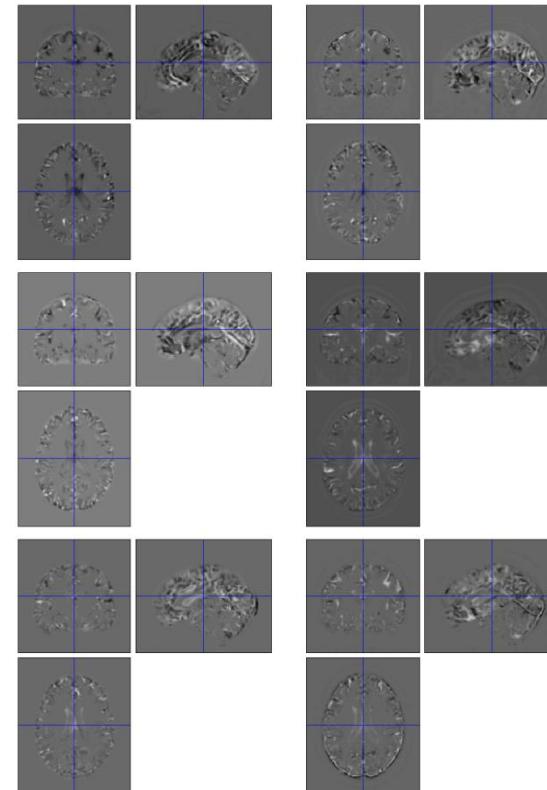


# Scalar Momentum

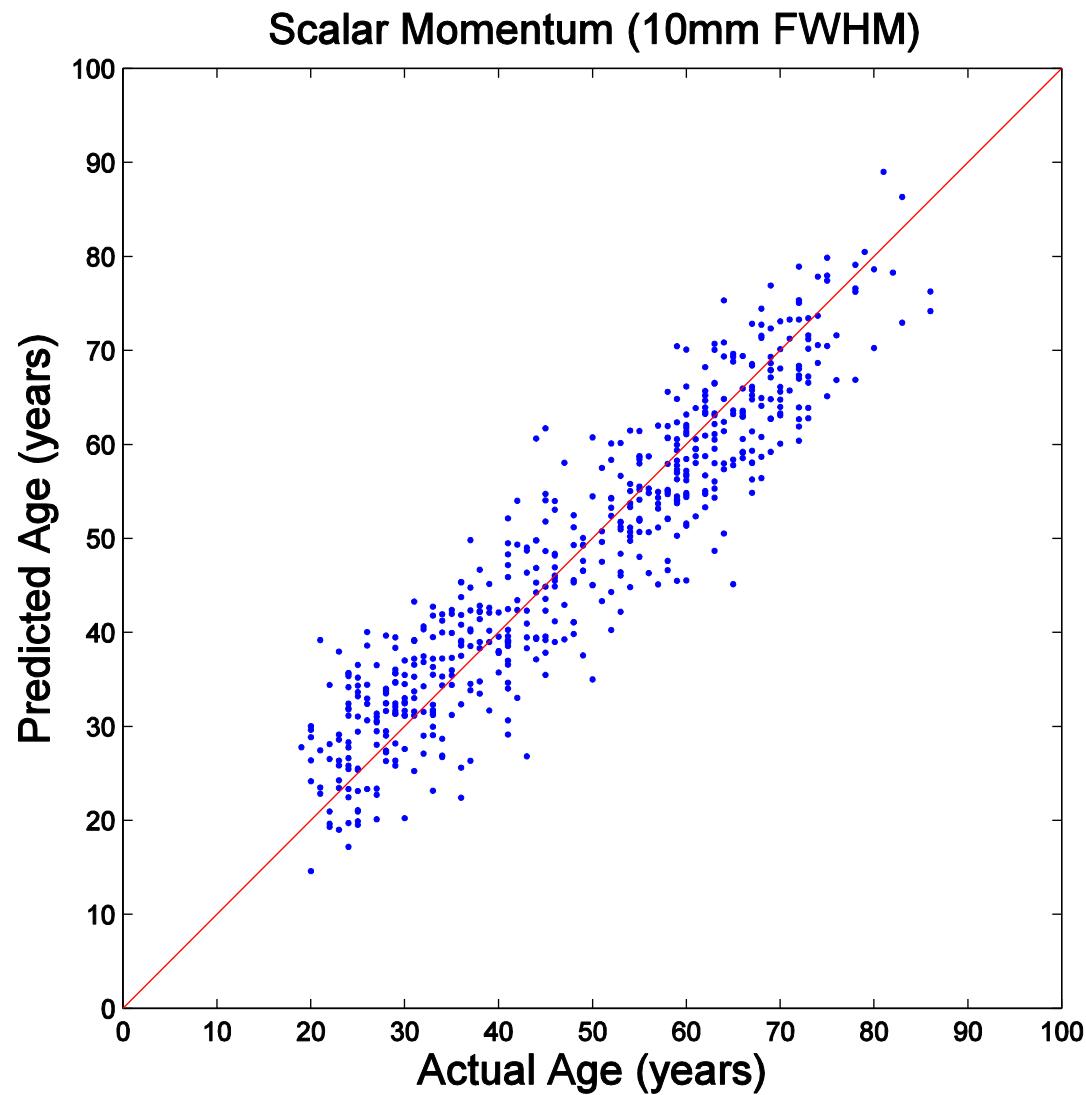
## 1<sup>st</sup> Component



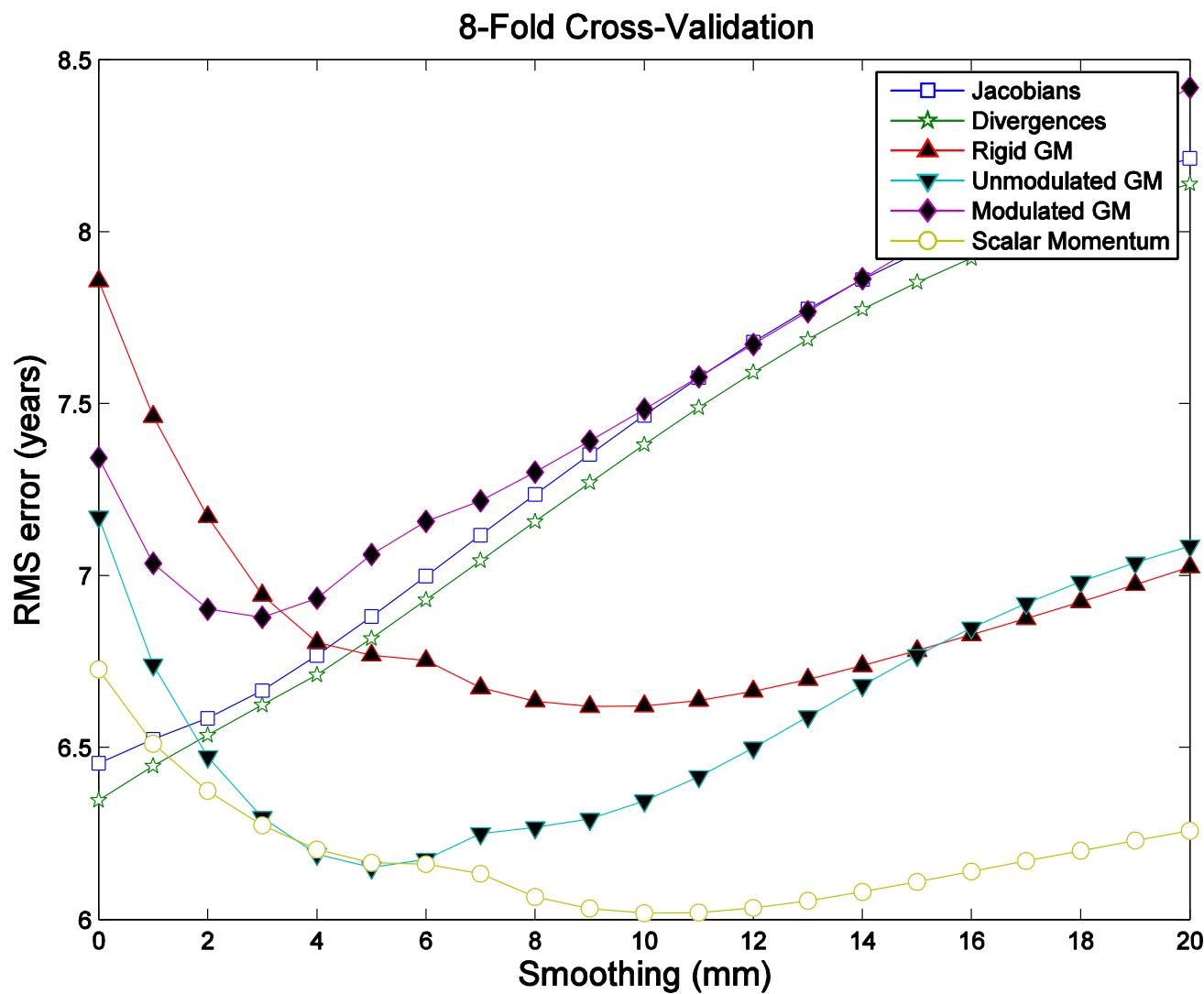
## 2<sup>nd</sup> Component



# Age Prediction - Best Result

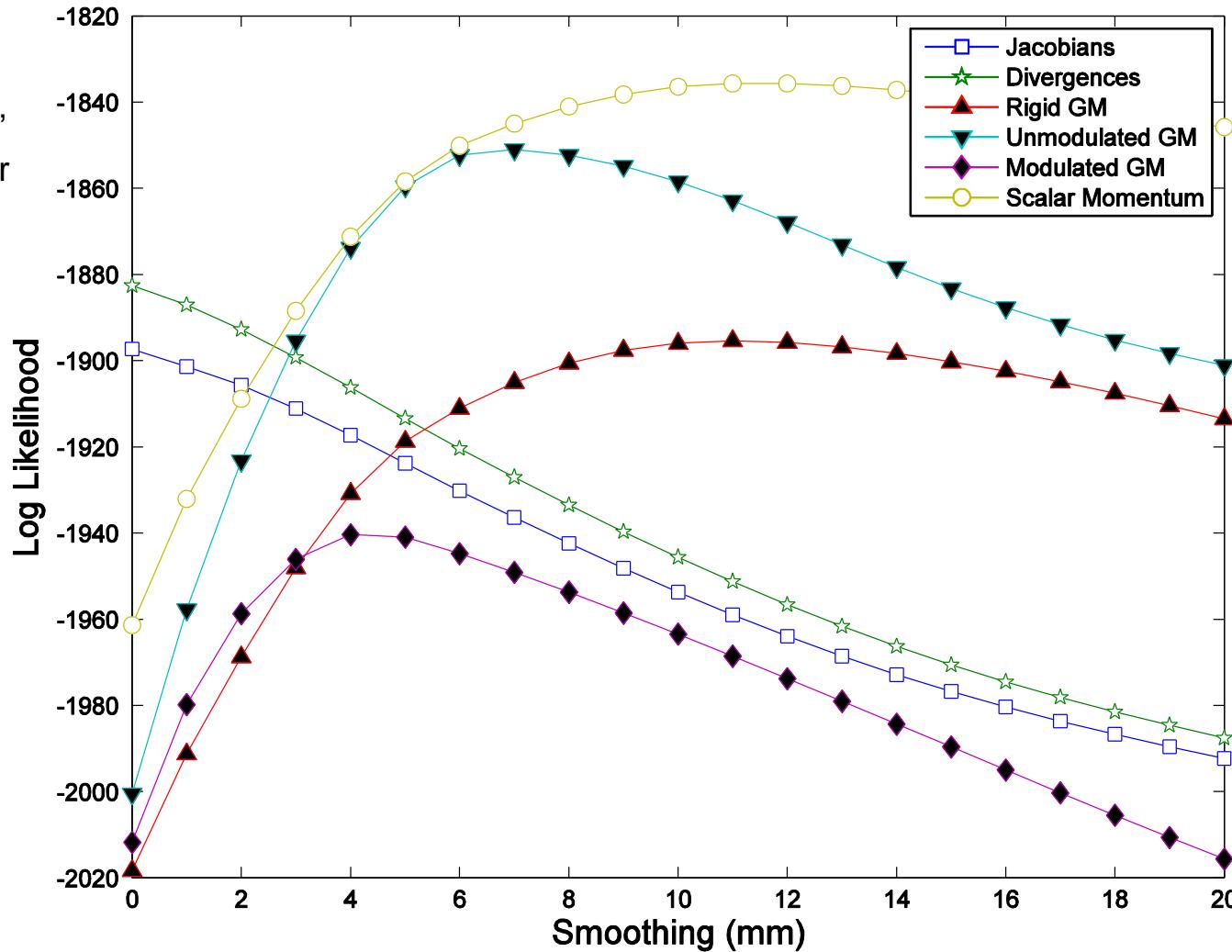


# Age Prediction – Comparison Among Features

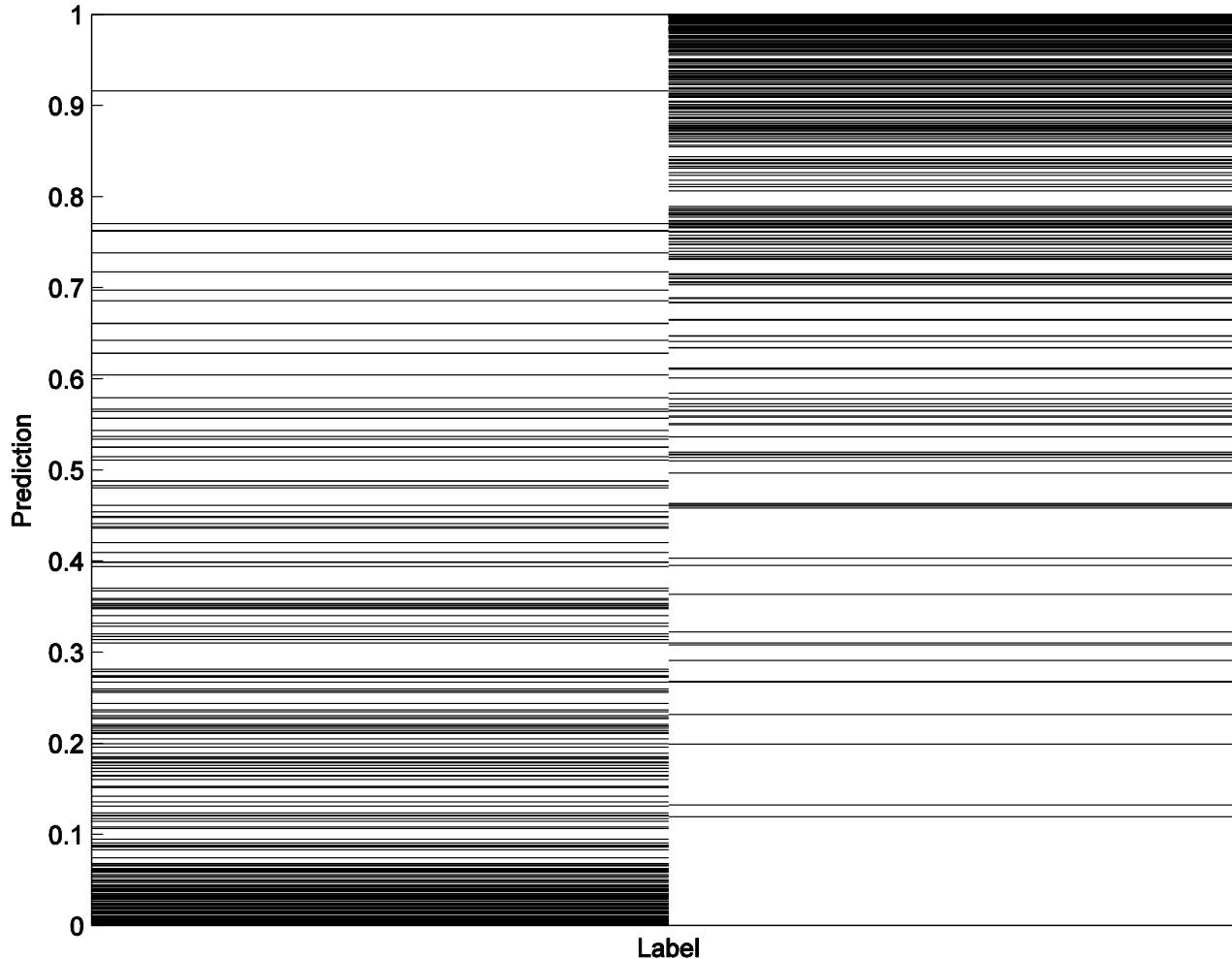


# Age Prediction – Model Log Likelihoods

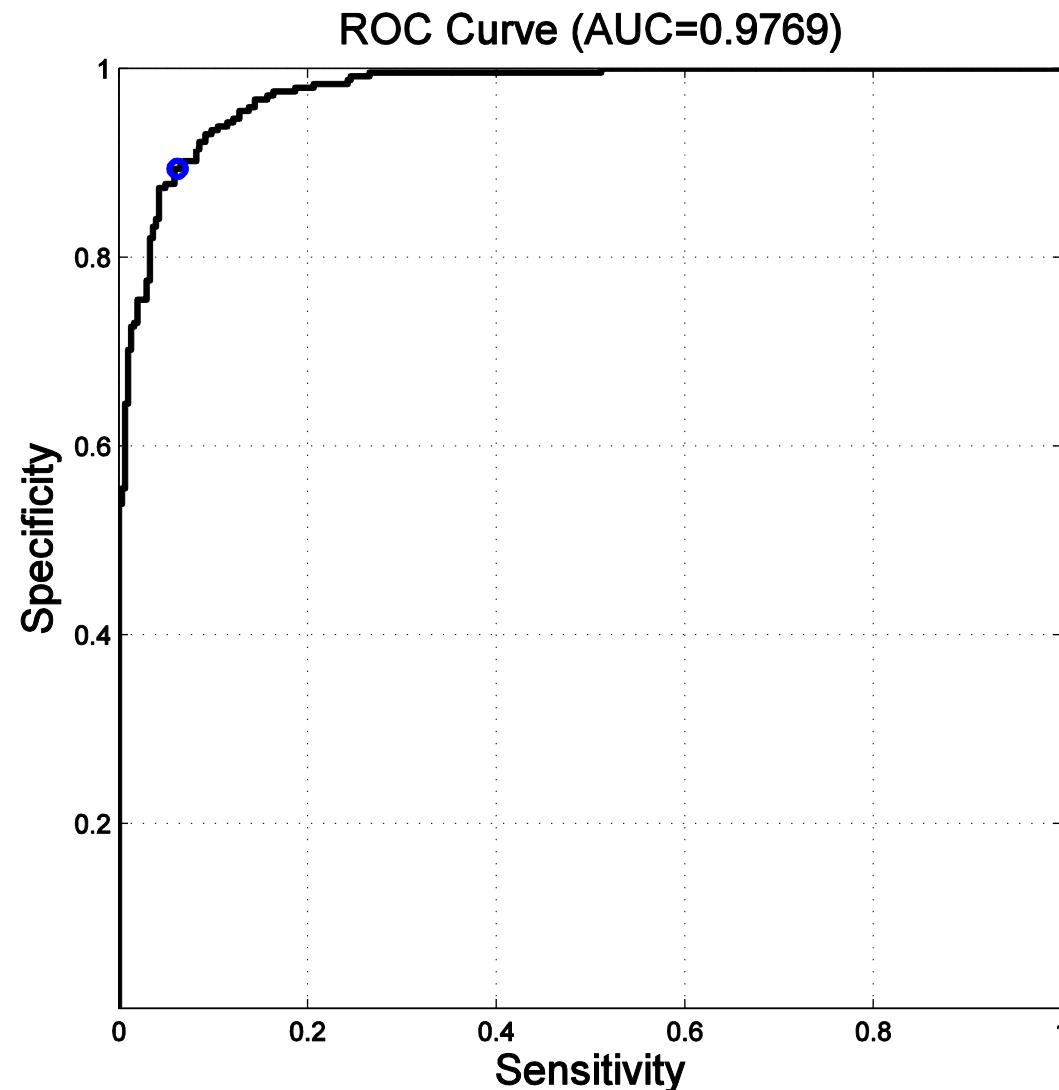
Differences > 4.6 indicate “decisive” evidence in favour of one approach over another.



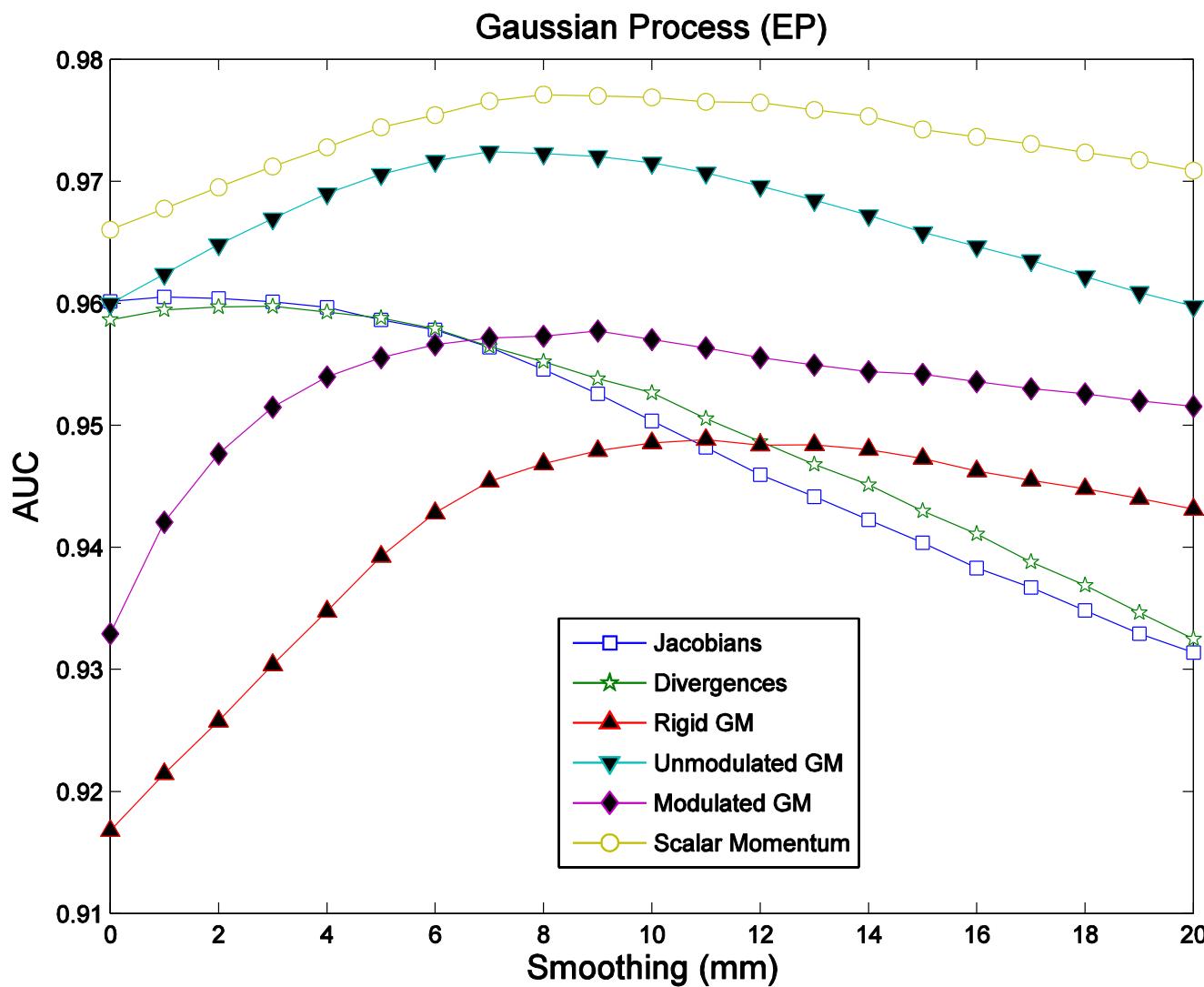
# Sex Prediction – Best Result



# Sex Prediction – Best Result

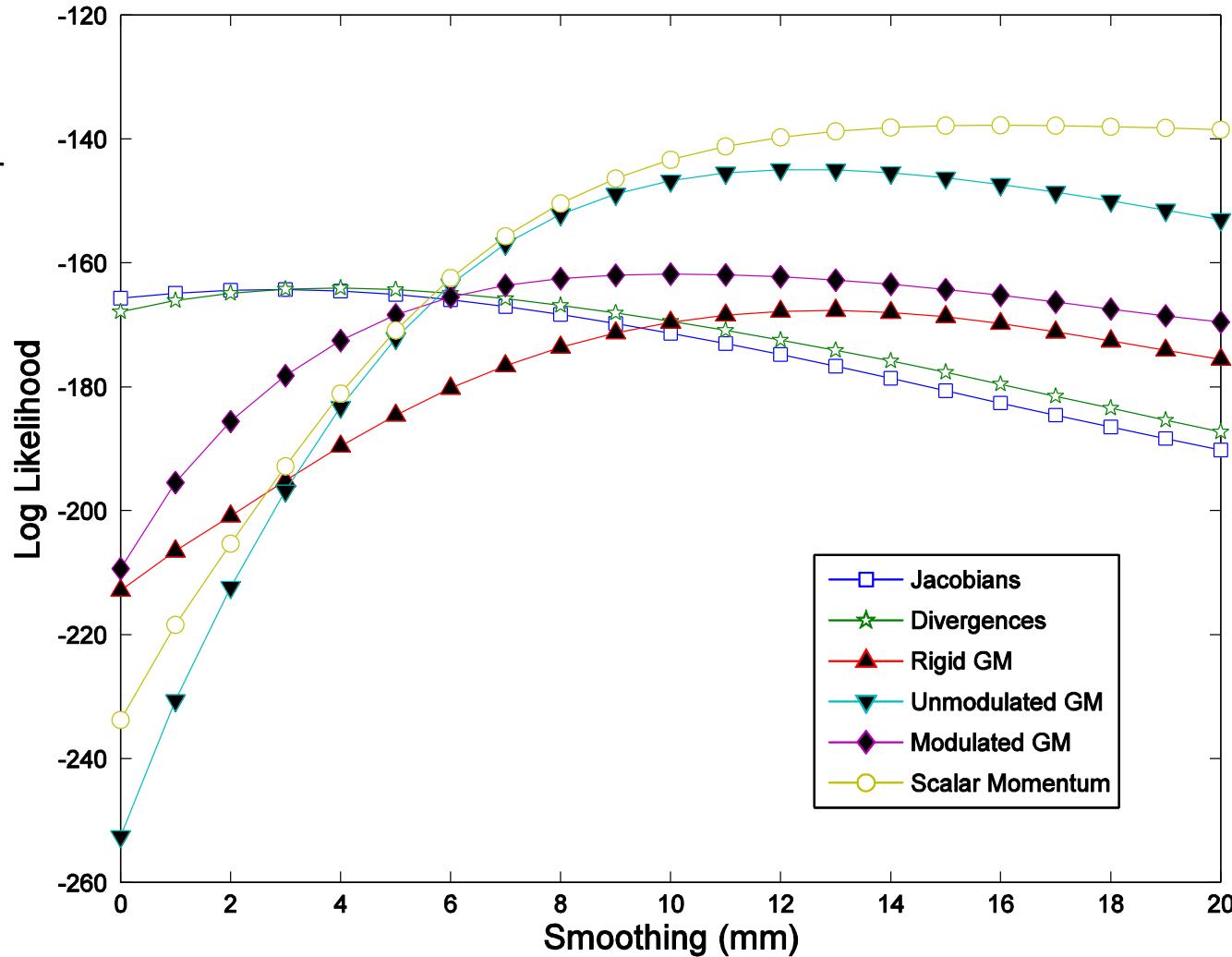


# Sex Prediction – Comparison Among Features



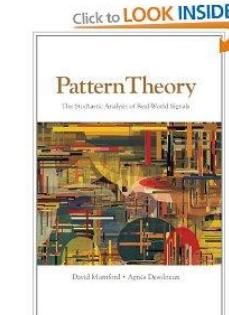
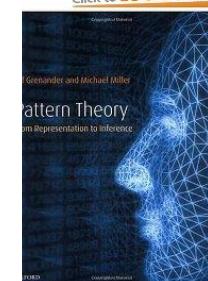
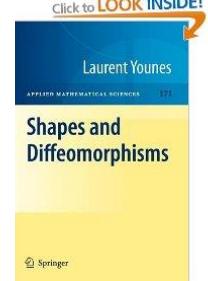
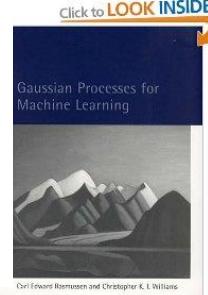
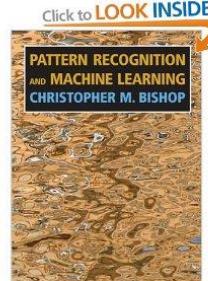
# Sex Prediction – Model Log Likelihoods

Differences > 4.6 indicate “decisive” evidence in favour of one approach over another.



# Selected References

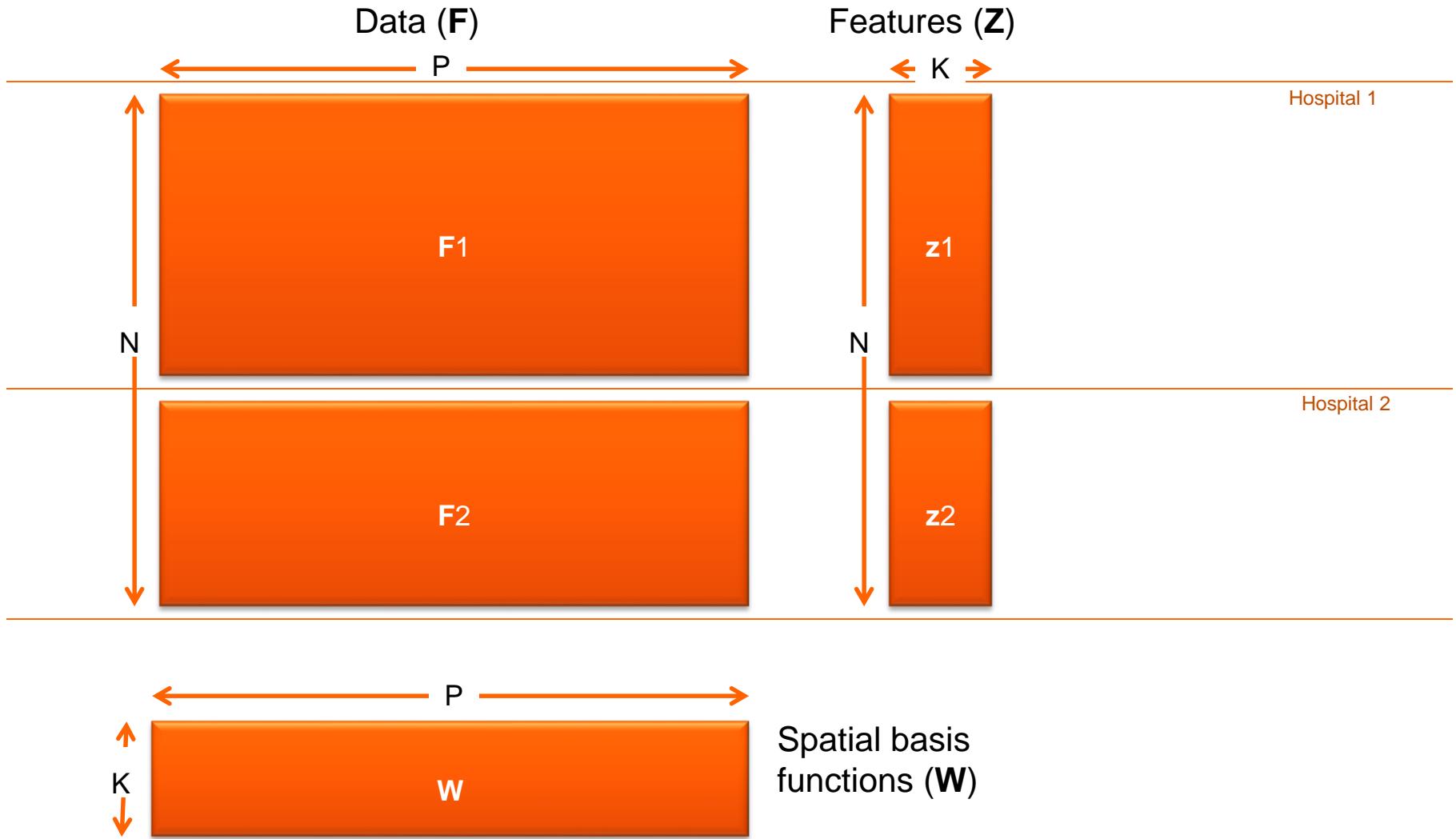
- Bishop. *Pattern Recognition and Machine Learning*. 2006.
- Rasmussen & Williams. *Gaussian Processes for Machine Learning*. MIT Press, 2006. ISBN-10 0-262-18253-X, ISBN-13 978-0-262-18253-9.  
<http://www.gaussianprocess.org/gpml/>
- Younes et al. *Evolutions equations in computational anatomy*. NeuroImage 45:S40-S50 (2009).
- Singh et al. *Multivariate Statistical Analysis of Deformation Momenta Relating Anatomical Shape to Neuropsychological Measures*. MICCAI 2010, Part III, LNCS 6363, pp. 529–537, 2010.
- Ashburner & Klöppel. *Multivariate models of inter-subject anatomical variability*. NeuroImage 56:422-439 (2011).



# Overview

- Voxel-Based Morphometry
- Tissue Segmentation
- Diffeomorphic Registration
- Longitudinal Registration
- Multivariate Shape Models
- **Current Work**
  - Privacy-preserving factorisation of large image datasets

# Privacy-preserving image factorisation



# Shape and appearance “eigen-modes”

**First of 50 eigenmodes**

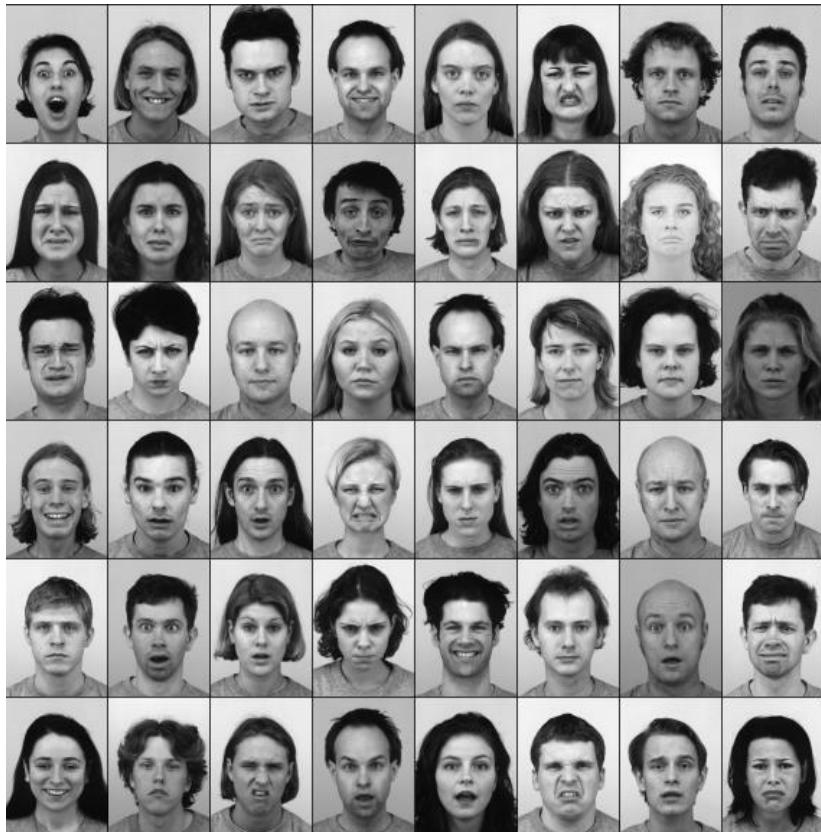


**First of 64 eigenmodes**

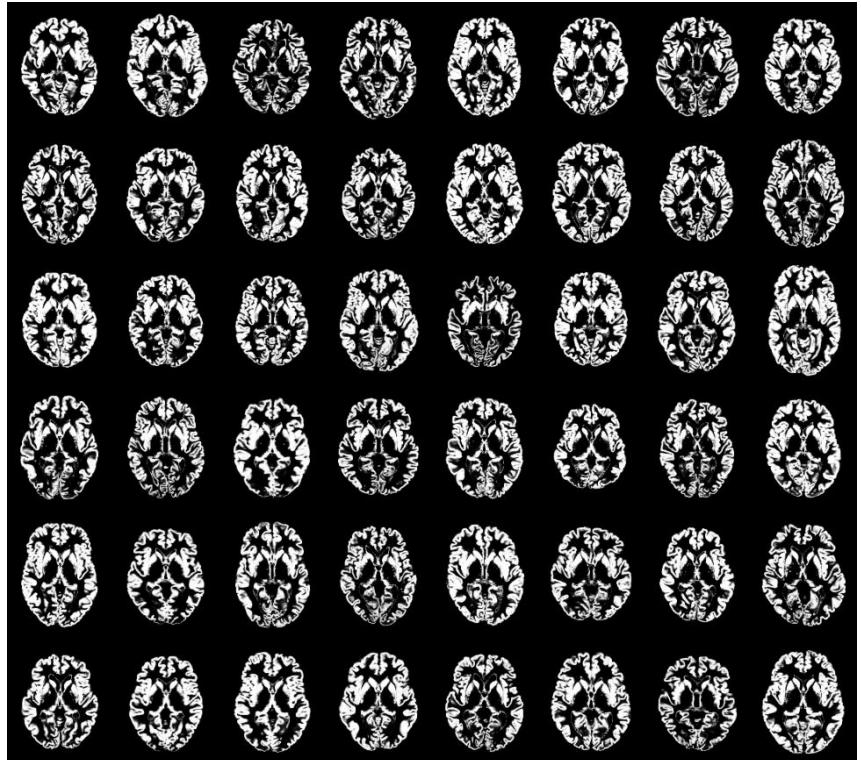


# Data (only 2D)

**Faces (64 out of 490)**

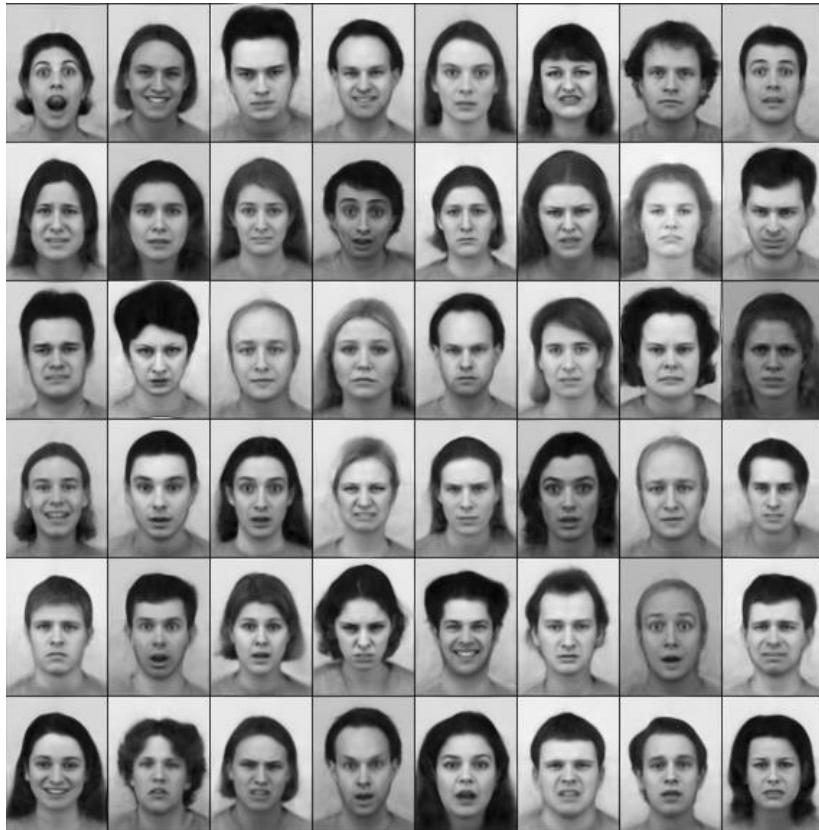


**Grey matter maps (64 of 581)**

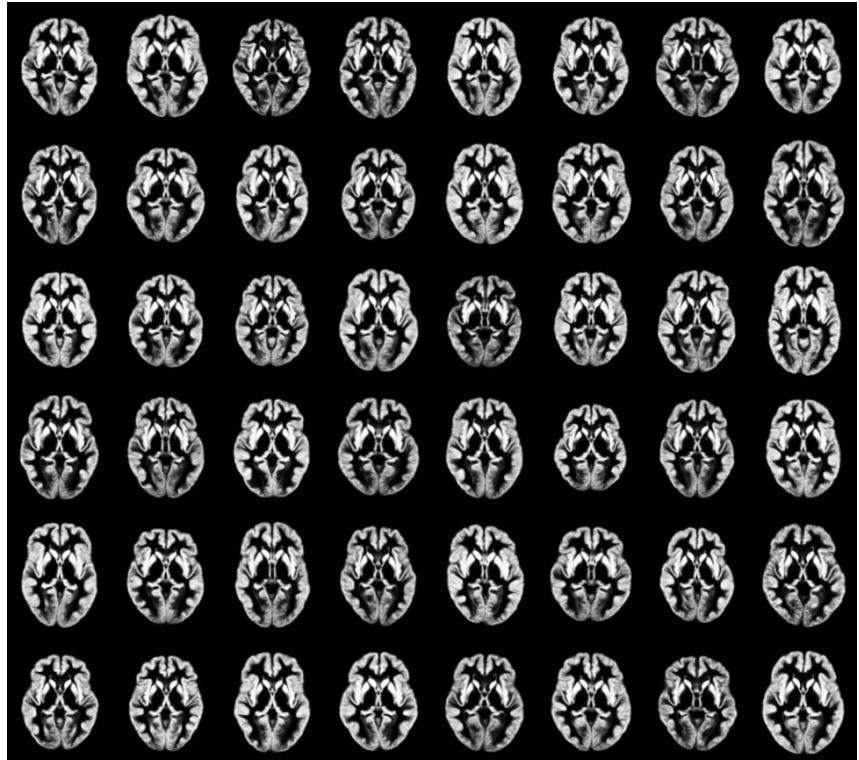


# Full model fit

## Shape and appearance



## Shape and appearance (logistic)

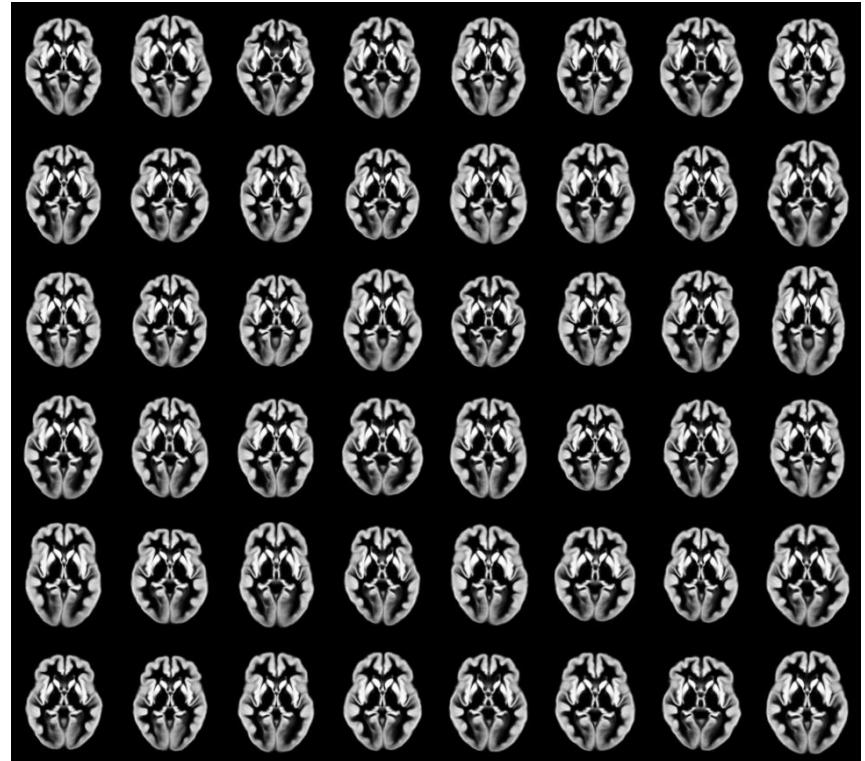


# Shape model only

Warped average face

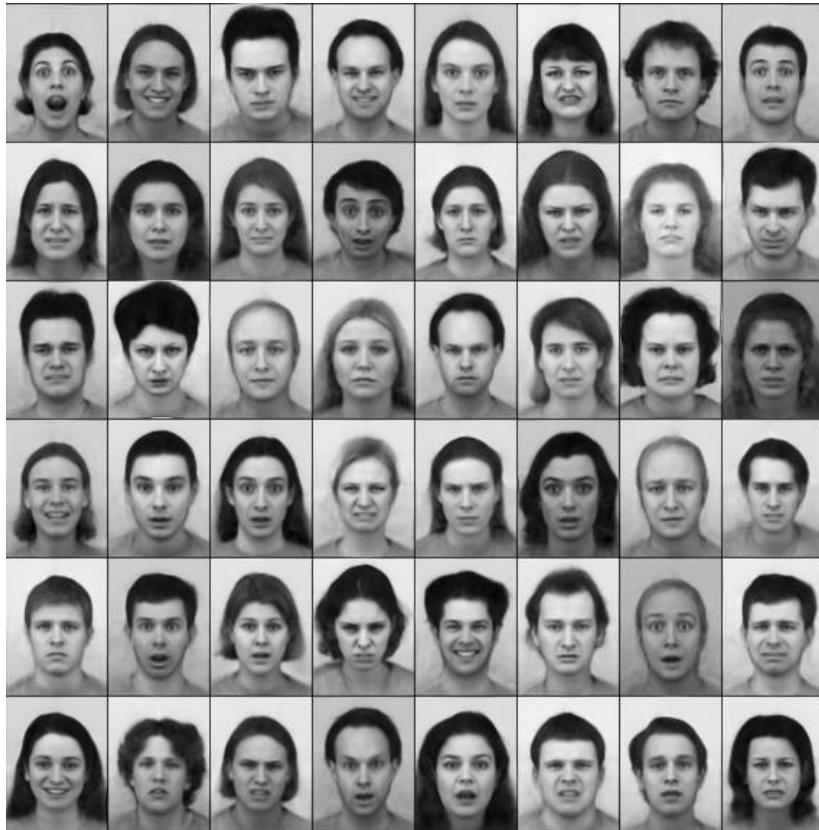


Warped average GM

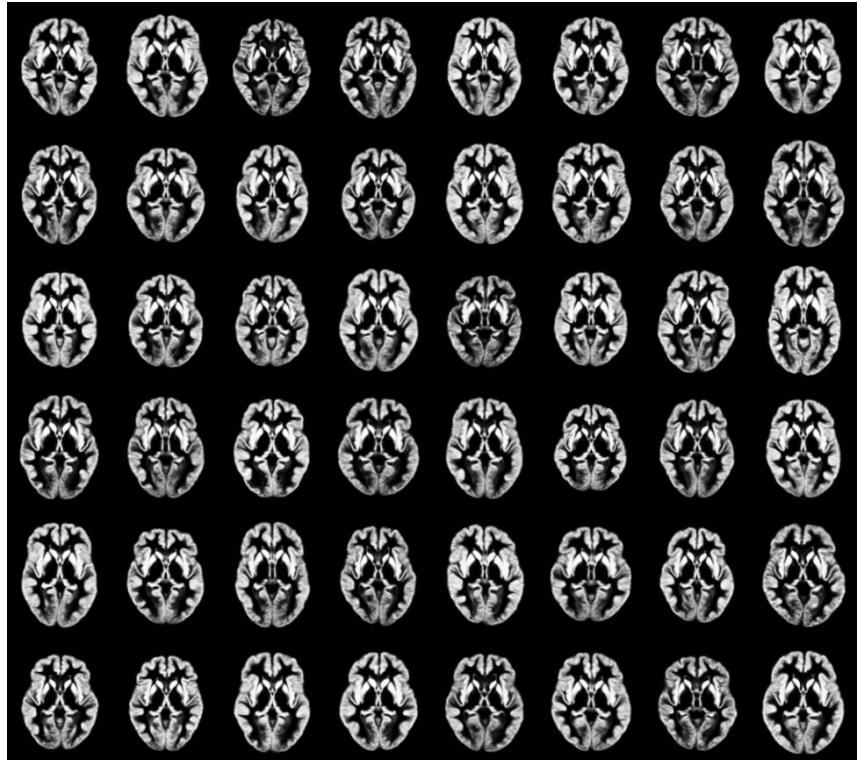


# Full model fit

## Shape and appearance



## Shape and appearance (logistic)

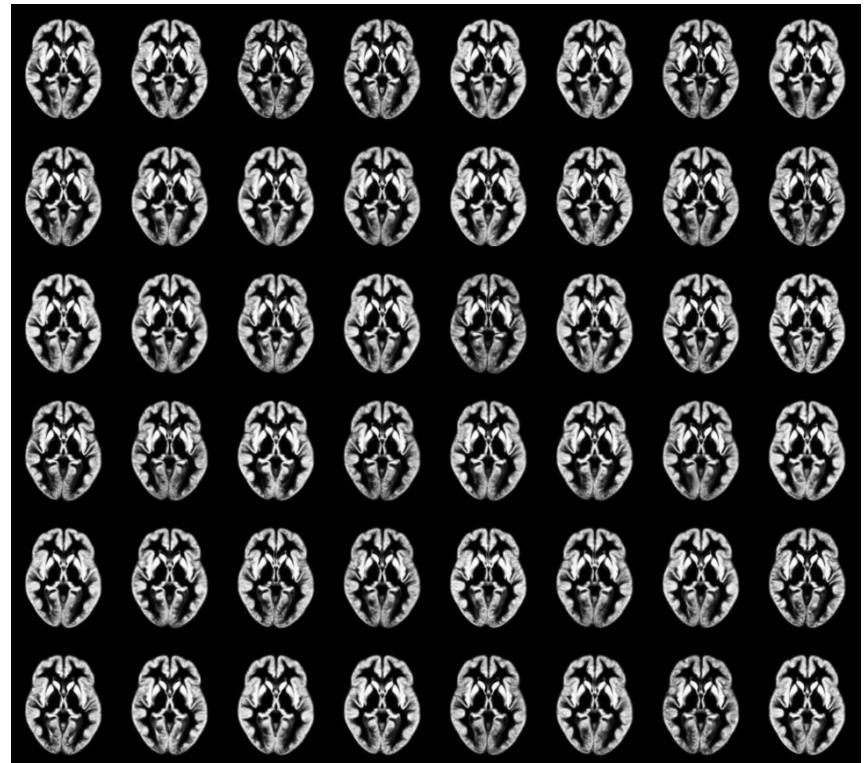


# Appearance model only

**Appearance fit (no warping)**



**Appearance fit (no warping)**



For the harmony of  
the world is made  
manifest in Form and  
Number, and the heart  
and soul and all the  
poetry of Natural  
Philosophy are embodied  
in the concept of  
mathematical beauty.

D'Arcy Thompson  
*On Growth and Form*  
(Dundee, 1917)