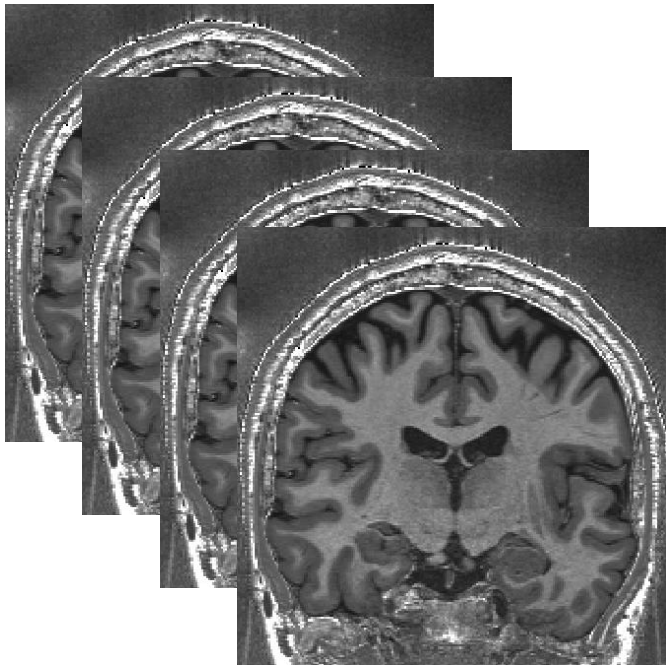
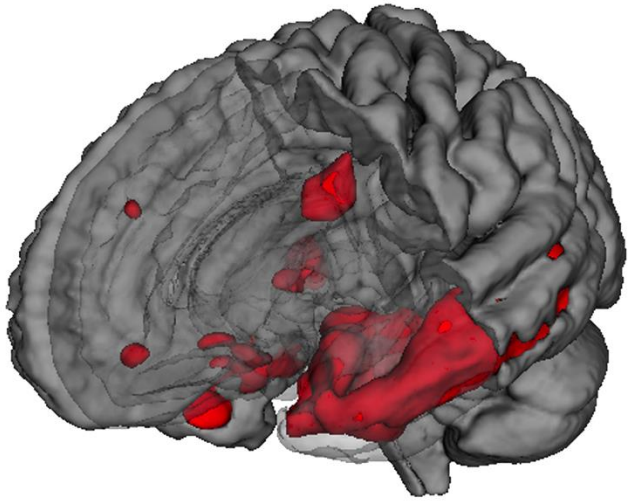
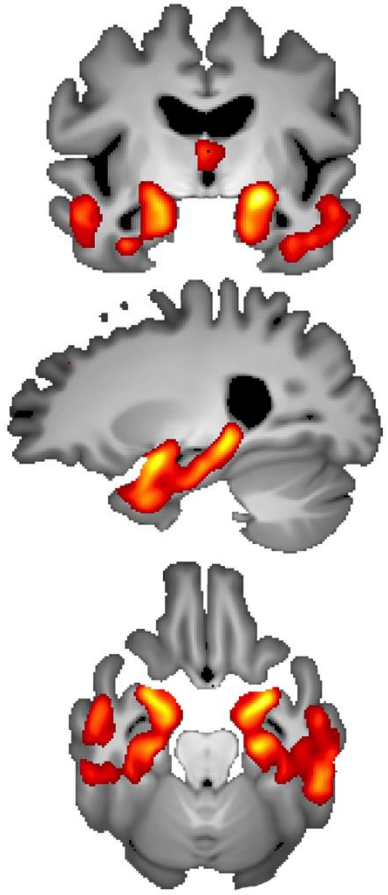
SPM Course November 2020: Voxel-Based Morphometry







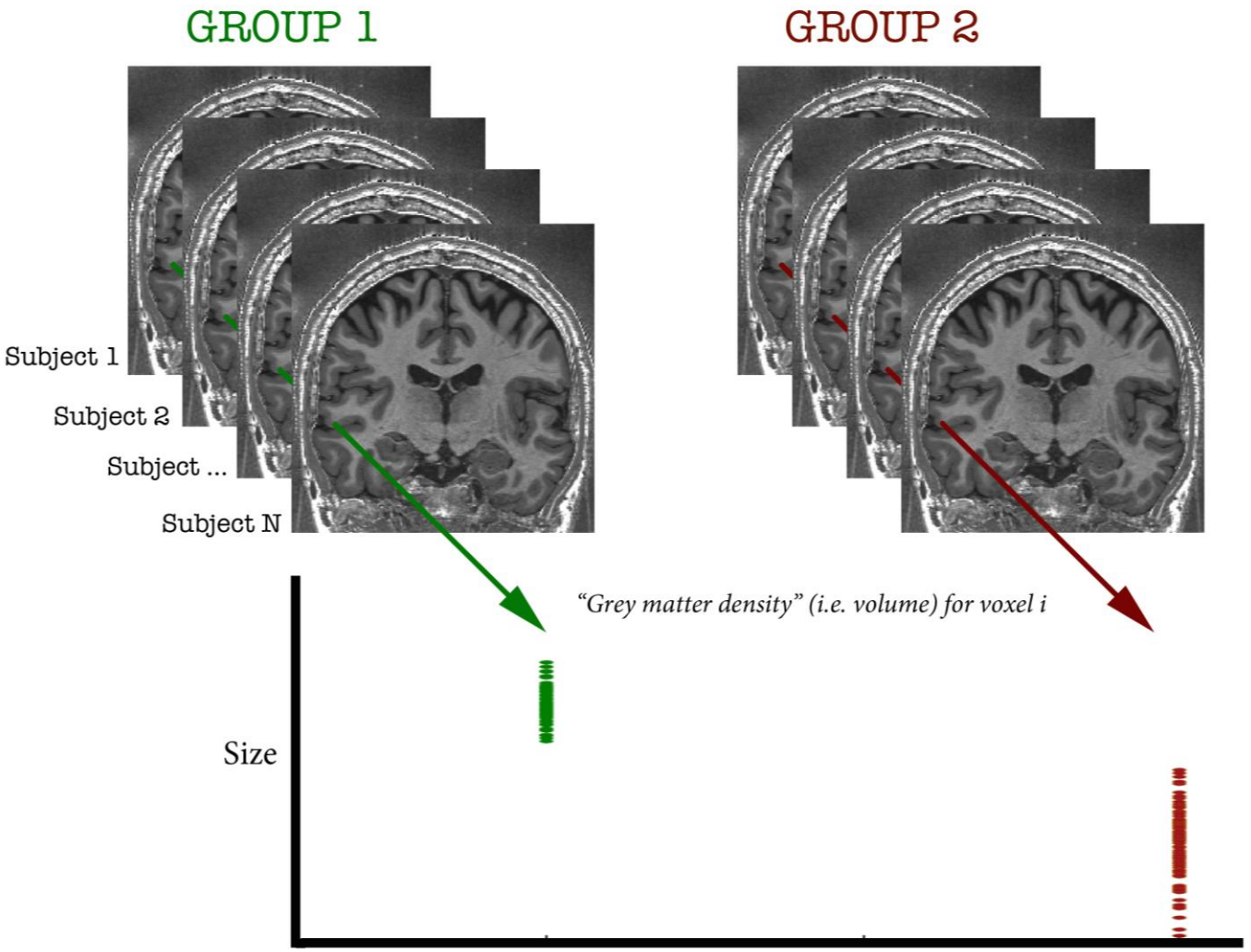
Dr Christian Lambert

+ Prof. John Ashburner & C. Phillips

INTRODUCTION

What is VBM?

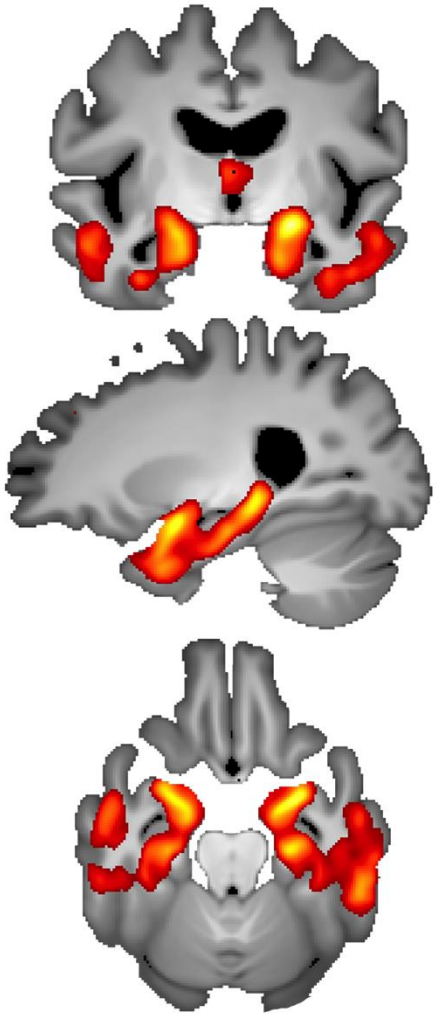
- Voxel-Based Morphometry:
  - Size and shape of the brain and its structures (“*morphometry*”)
  - Compared at a voxel wise level across a population



Examples applications of VBM

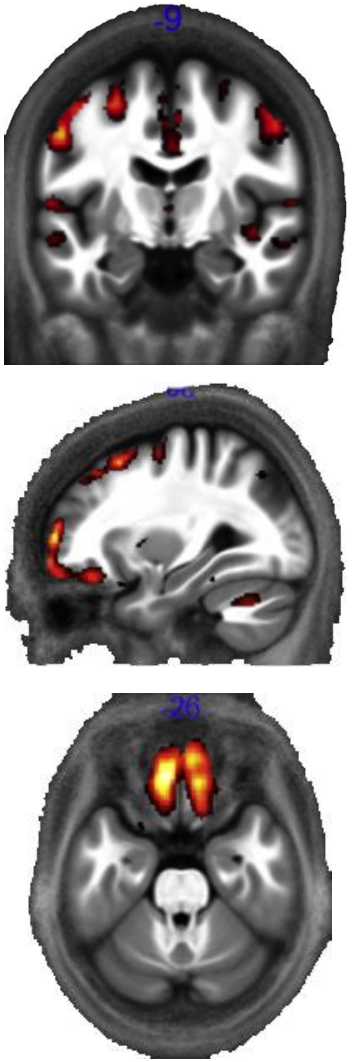
- Many scientifically or clinically interesting questions might relate to changes in local volume of anatomical regions of the brain
- For example, whether (and where) patterns of brain morphometry help to:
  1. Distinguish between groups (e.g. Alzheimer's vs. healthy controls)
  2. Explain changes seen in development and aging
  3. Identify plasticity, e.g. when learning new skills
  4. Find structural correlates (i.e. regions where the size correlates with scores, traits, genotype etc.,)

1. Phenotypic patterns of disease



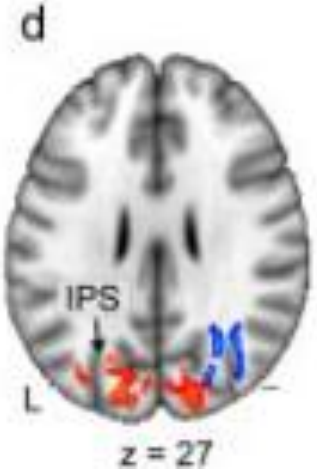
Atrophy - AD vs. healthy Controls (ADNI2 Dataset)

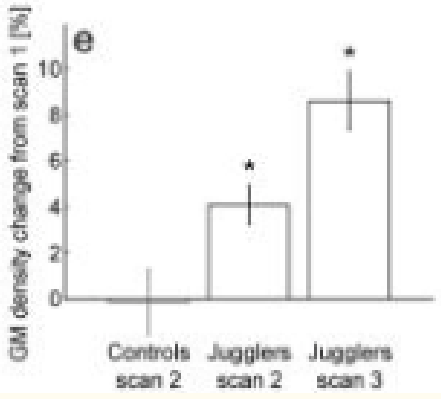
2. Ageing: GM atrophy



Callaghan et al., 2014

3. Plasticity: Juggling

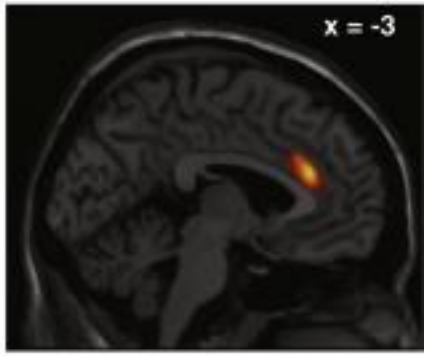




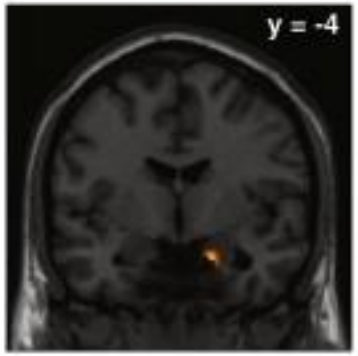
Scholz et al., 2009

4. Correlates: Political orientation

Conservative - Decrease

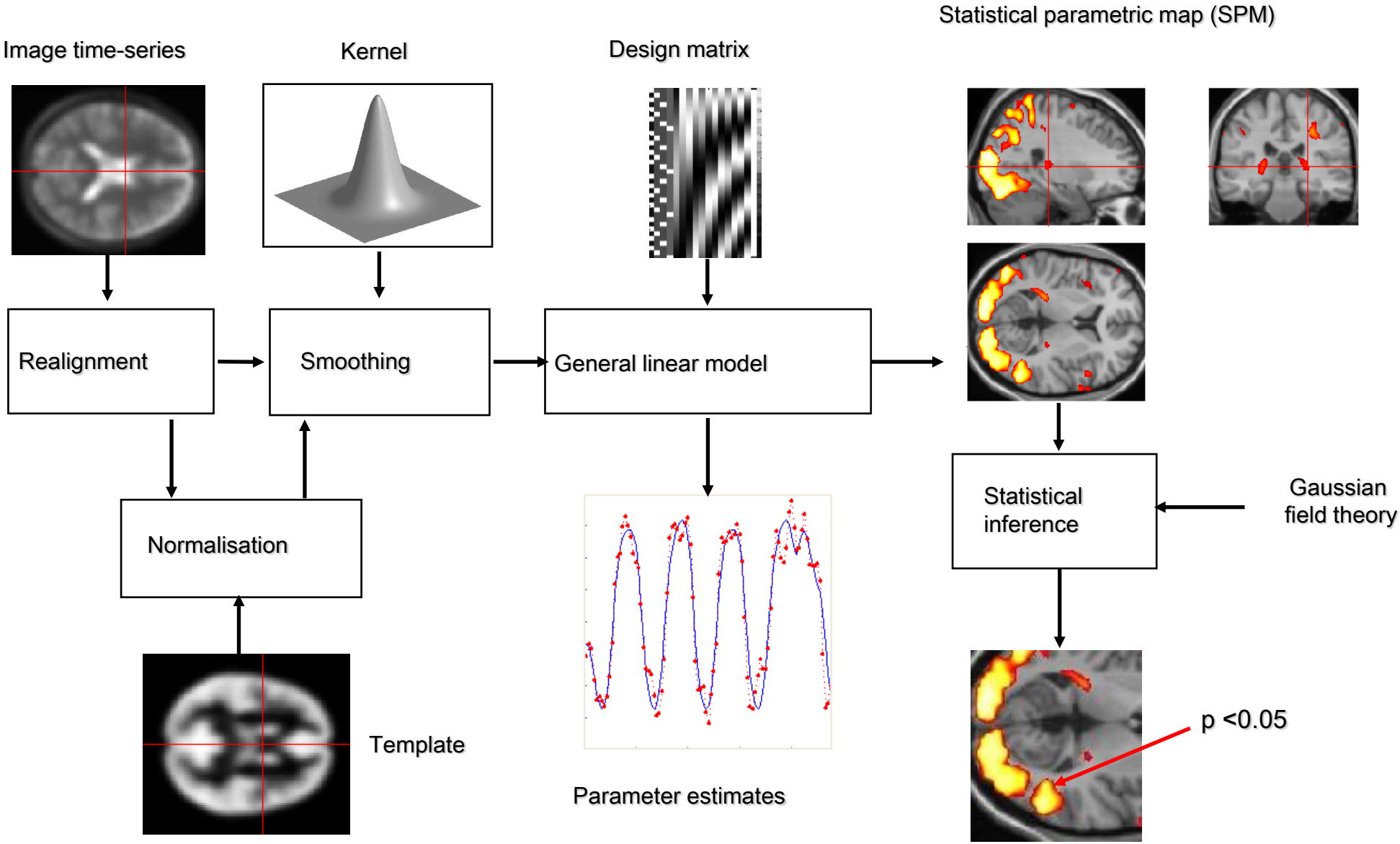


Conservative - Increase

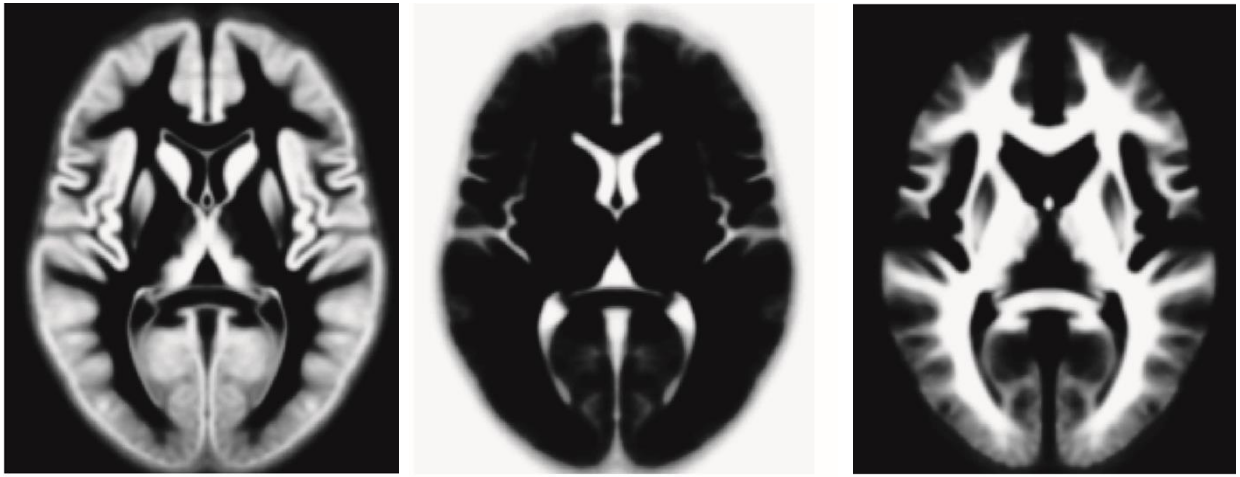


Kanai et al., 2011

Overview of SPM

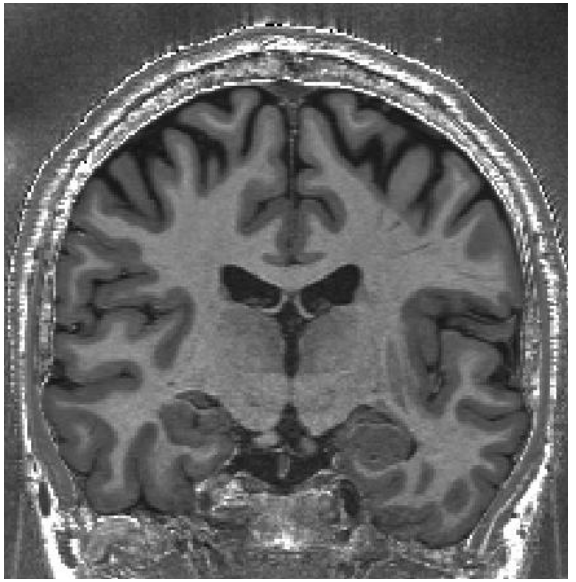


TISSUE SEGMENTATION

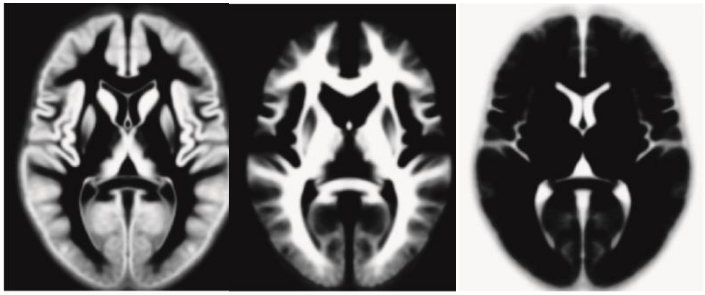


Tissue segmentation for VBM

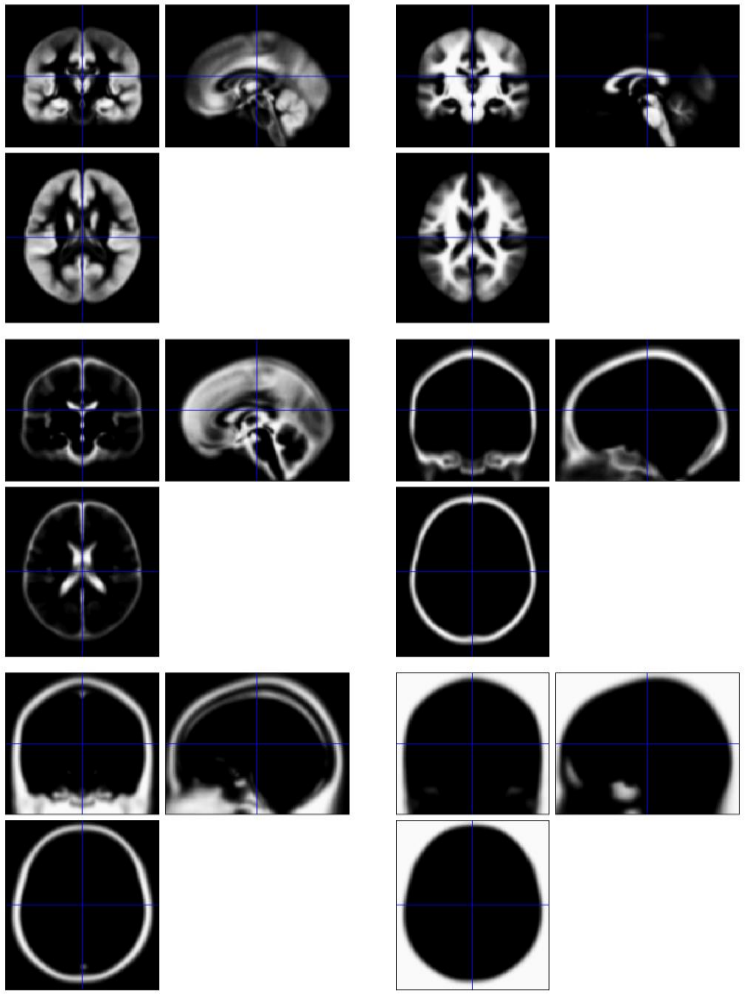
- High-resolution MRI reveals fine structural detail in the brain, but not all of it reliable or interesting
  - Noise, intensity-inhomogeneity, vessels
  - MR Intensity is usually not quantitatively meaningful
  - Quantitative MRI is possible though, and promising, see *Voxel Based Quantification* (VBQ)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

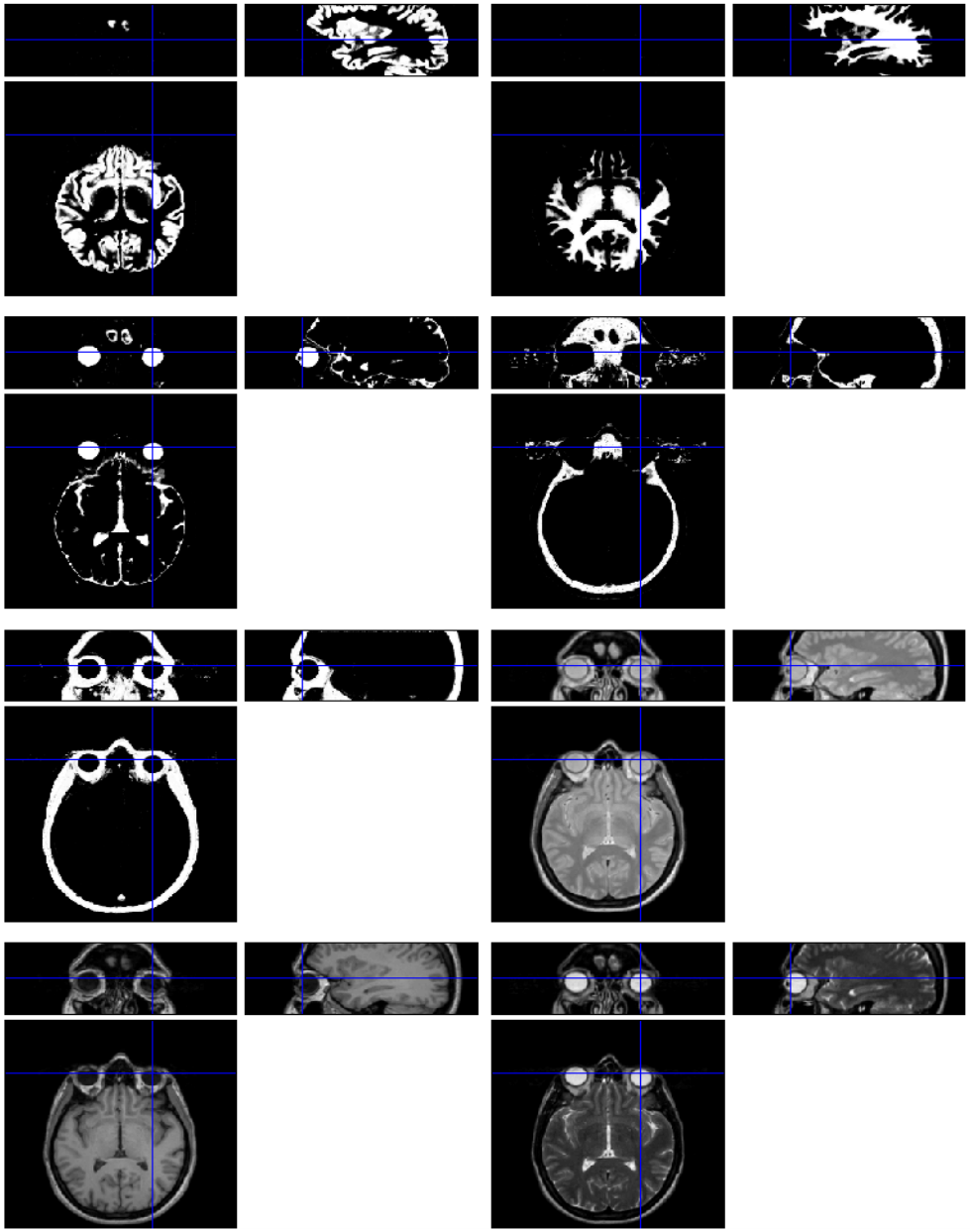


- Regional volumes of the three main tissue types: gray matter, white matter and CSF, are well-defined and potentially very interesting



Multi-spectral

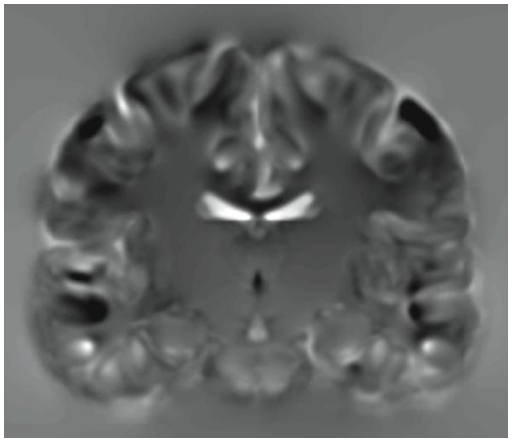


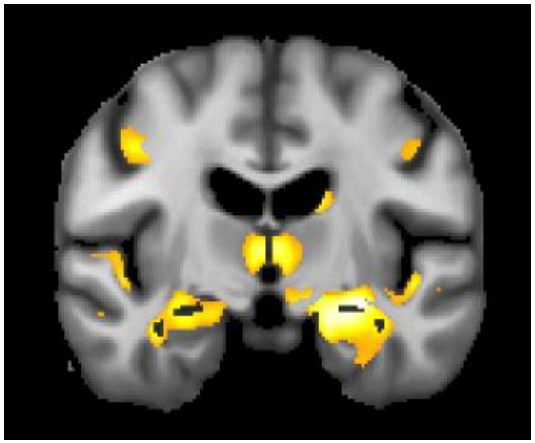


Limitations of the current model

- 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.

VOXEL BASED MORPHOMETRY



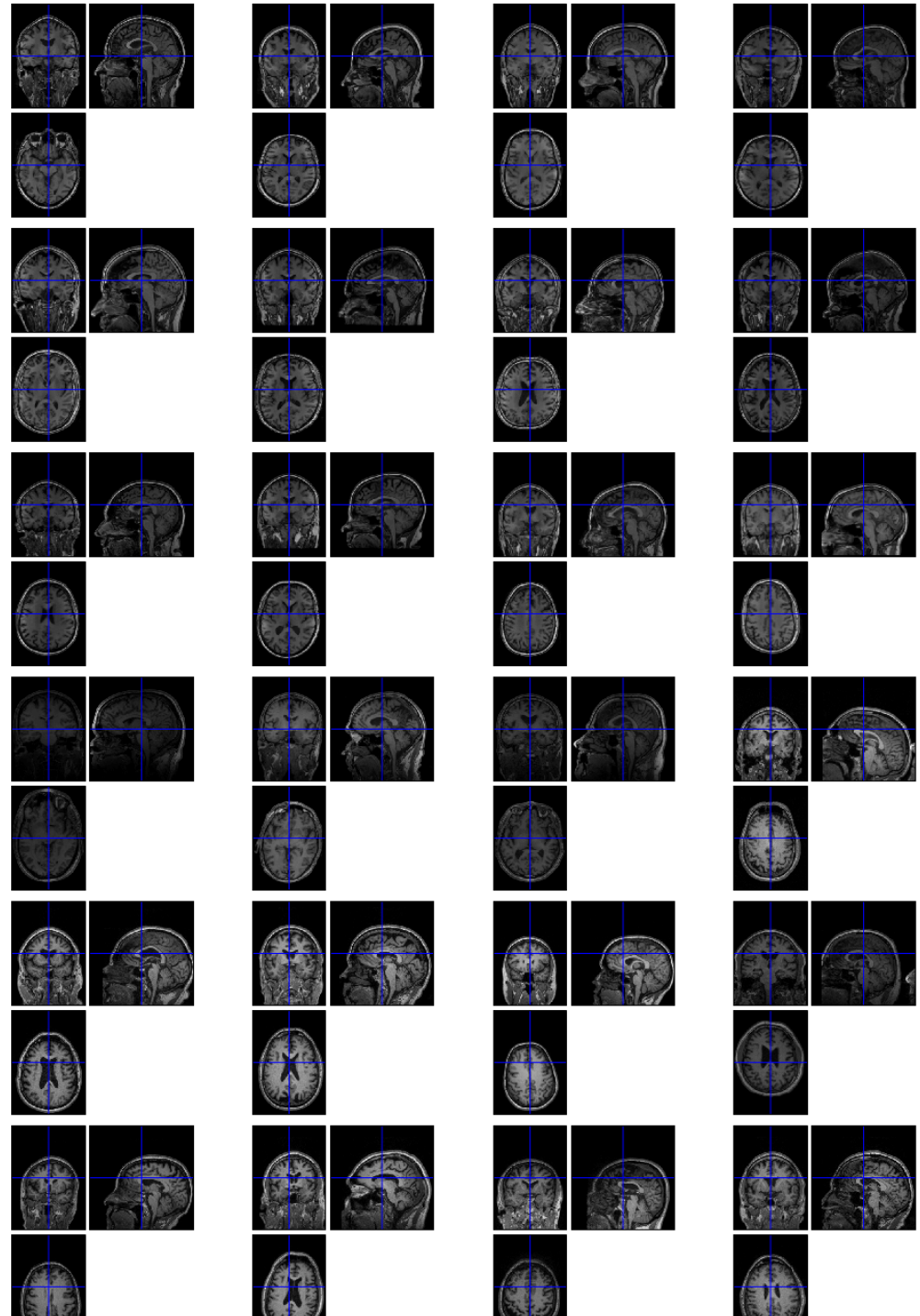


Voxel-Based Morphometry

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

- The exact interpretation of gray matter density or volume is complicated, and depends on the preprocessing steps used
  - It is not interpretable as neuronal packing density or other cytoarchitectonic tissue properties
  - The hope is that changes in these microscopic properties may lead to macro- or mesoscopic VBM-detectable differences
  - One technique is to use VBM in combination with other quantitative structural measures (diffusion, MT, R2*, SWI) to make biophysical inferences (example later)

VBM: Step-by-step overview



VBM overview

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

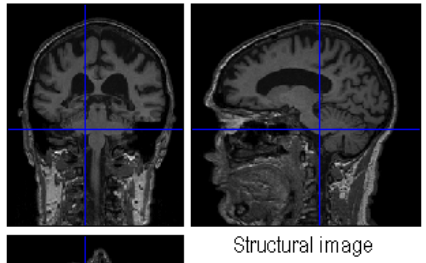
- Poor scan quality, artefacts, abnormal tissue (ischaemia, dural thickening), abnormal brains (hydrocephalus) relatively close rigid alignment (header issues)

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

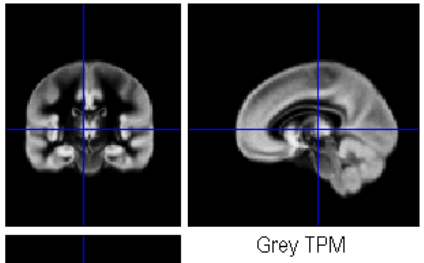
VBM in pictures

Segment

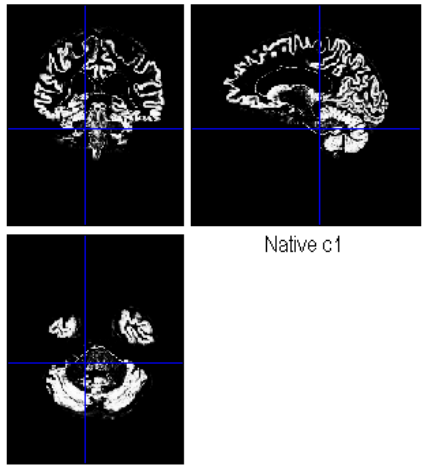
Normalise



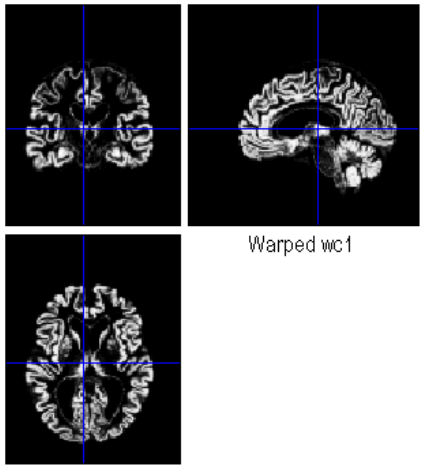
Structural image



Grey TPM



Native c1



Warped wc1

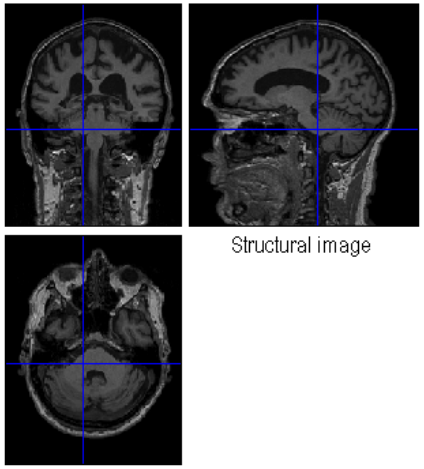
VBM in pictures

Segment

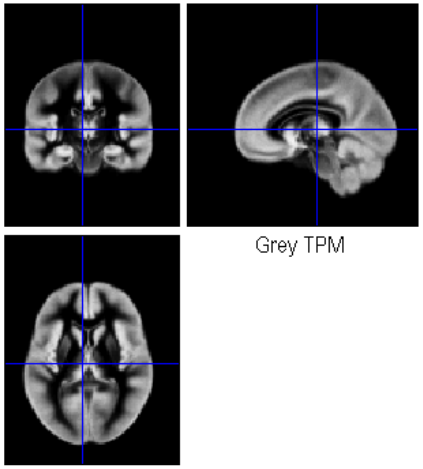
Normalise

Modulate

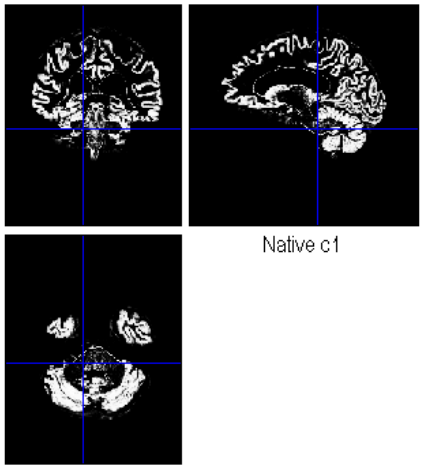
Smooth



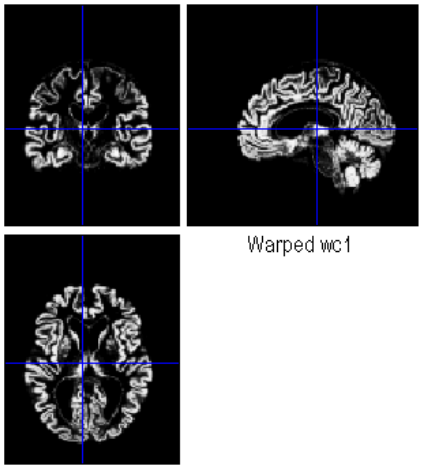
Structural image



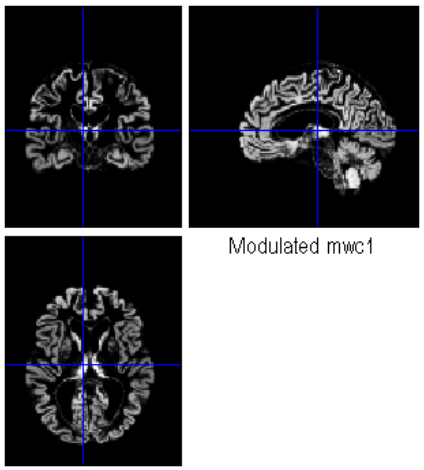
Grey TPM



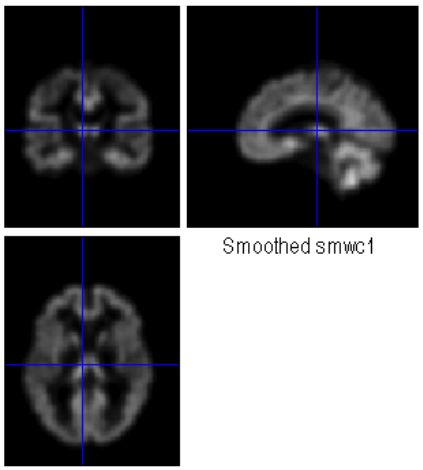
Native c1



Warped wc1



Modulated mwc1



Smoothed smwc1

VBM in pictures

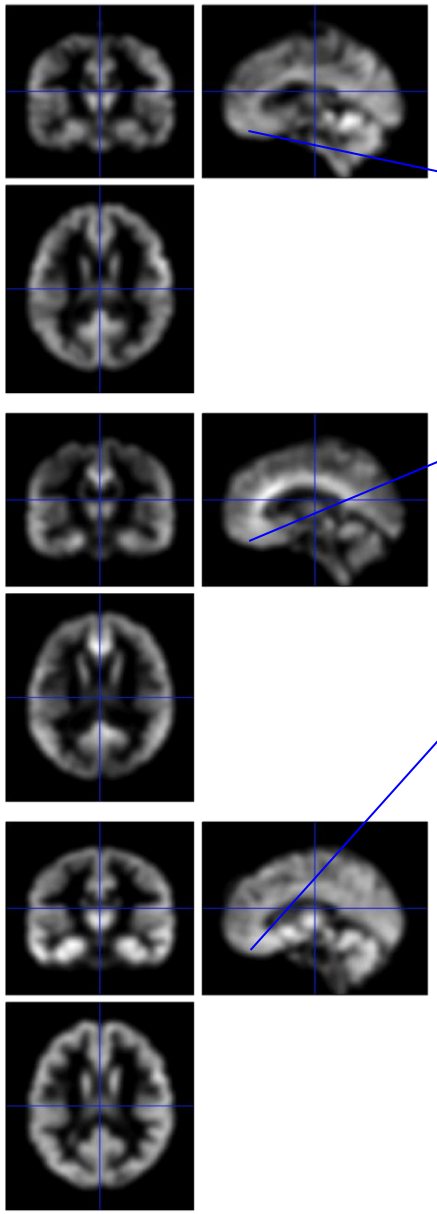
Segment

Normalise

Modulate

Smooth

Voxel-wise statistics



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

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

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

VBM in pictures

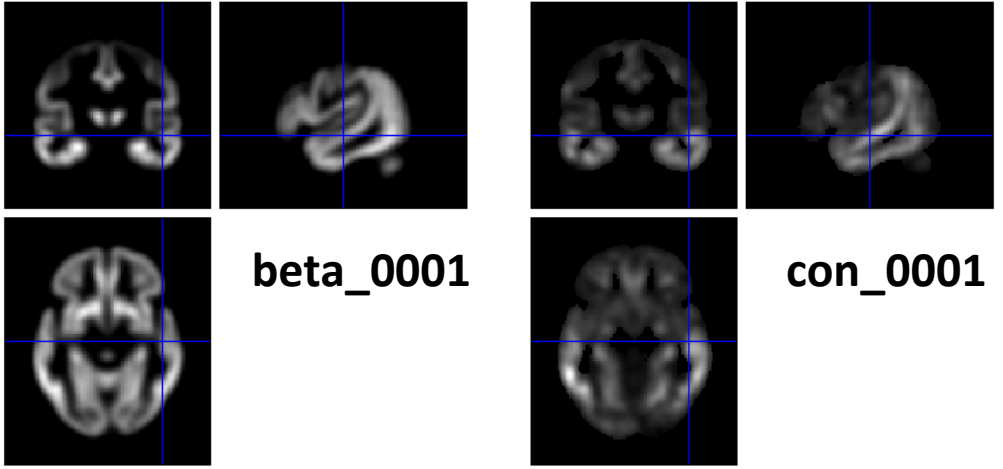
Segment

Normalise

Modulate

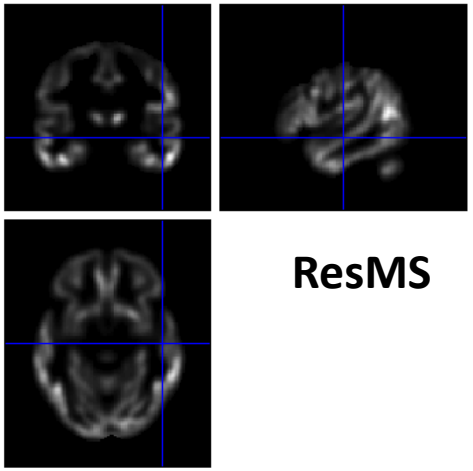
Smooth

Voxel-wise statistics

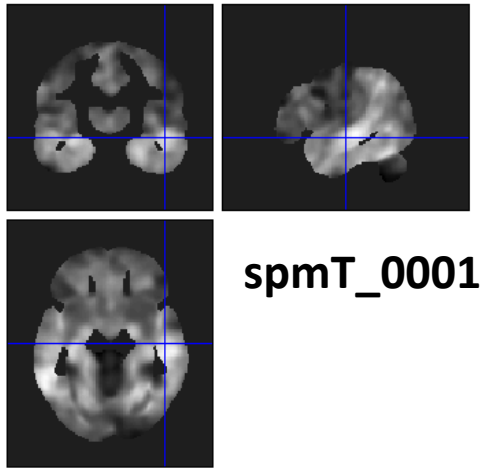


beta_0001

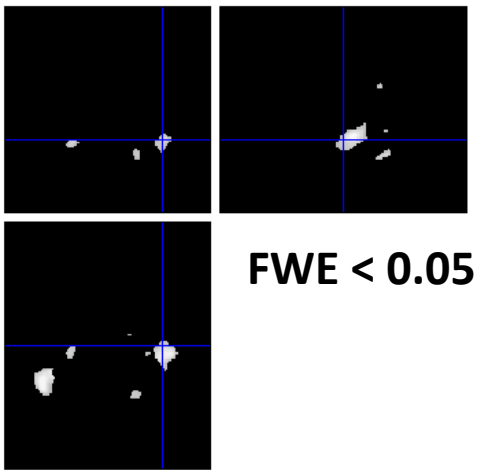
con_0001



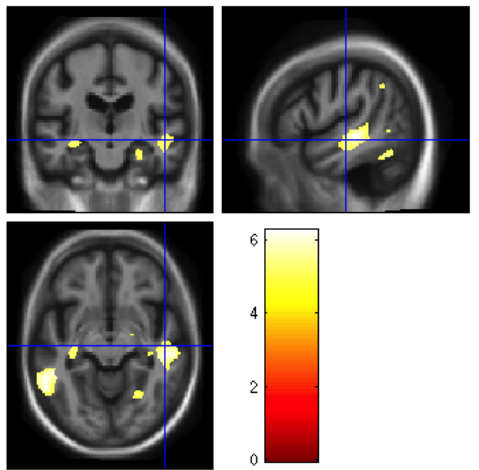
ResMS



spmT_0001



FWE < 0.05



VBM SUBTLETIES

Modulation

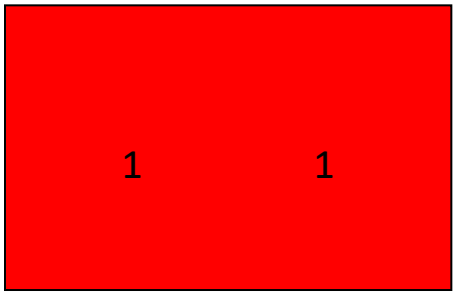
How much to smooth

Interpreting results

Adjusting for total GM or Intracranial Volume

Statistical validity

Modulation ("preserve amounts")

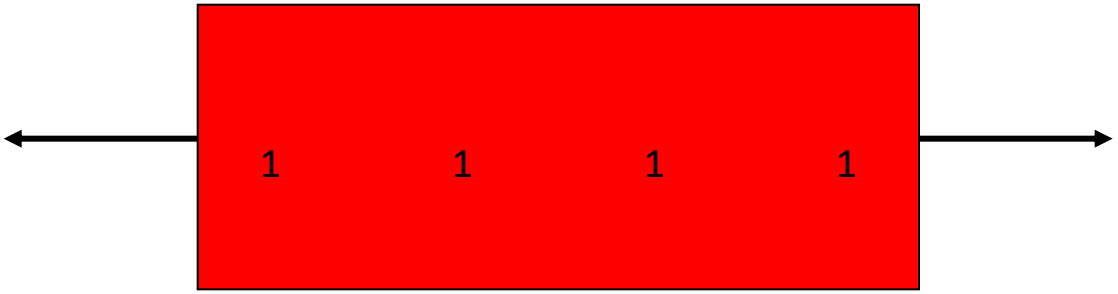


Native

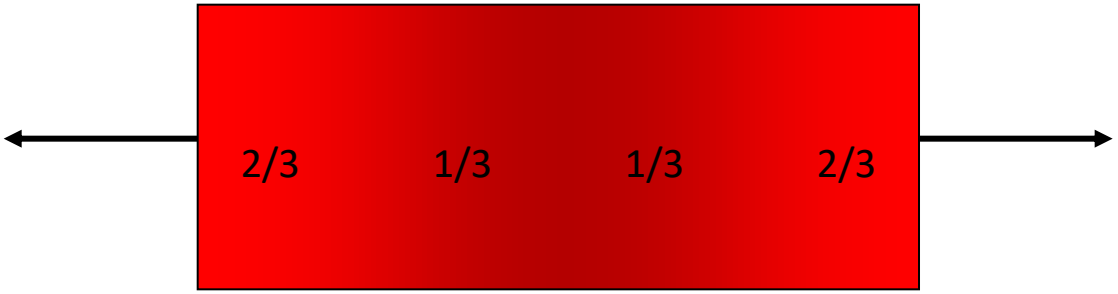
intensity =
tissue probability

- 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

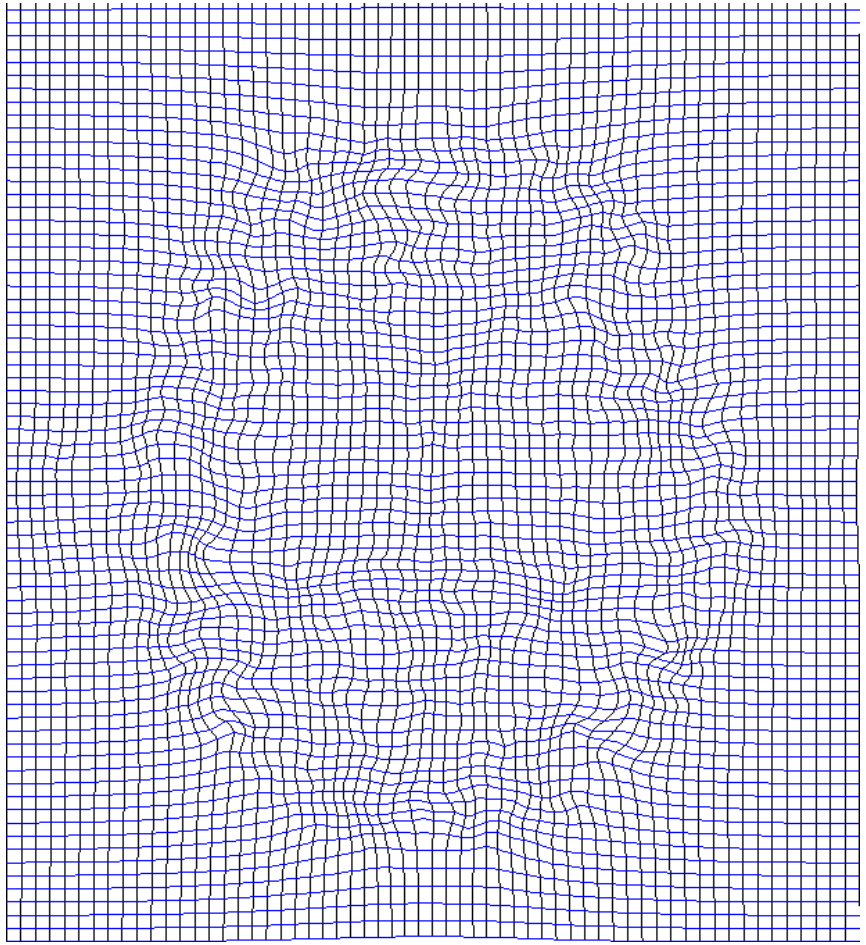


Modulated

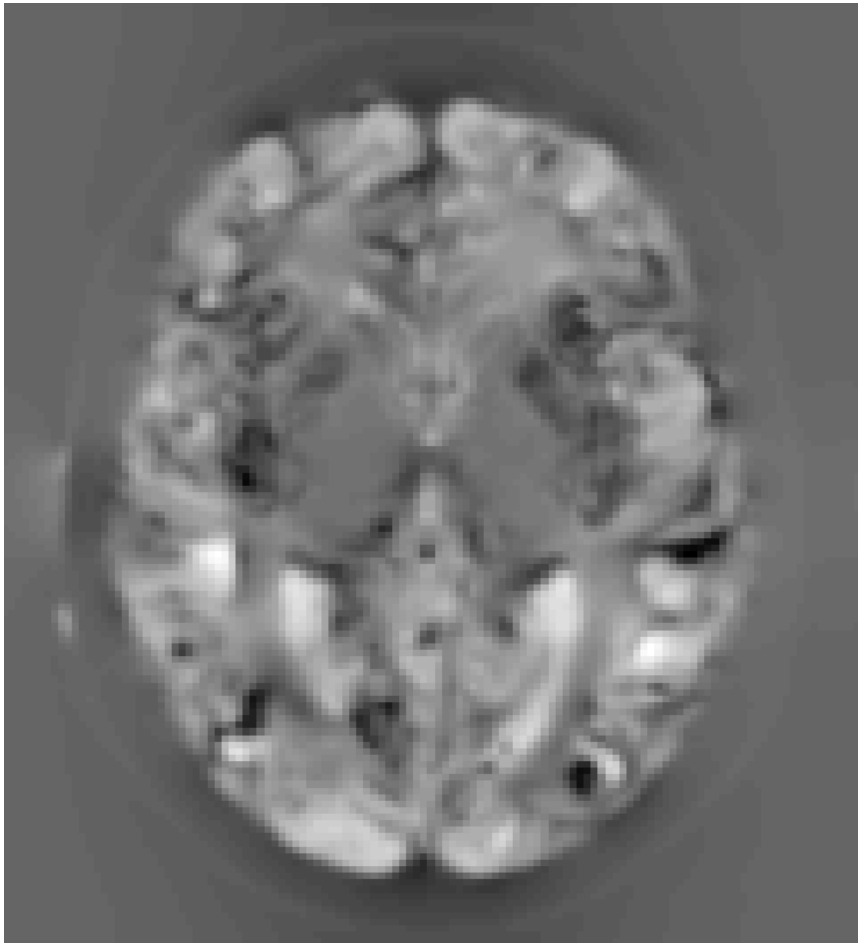


See also http://tinyurl.com/ModulationTutorial

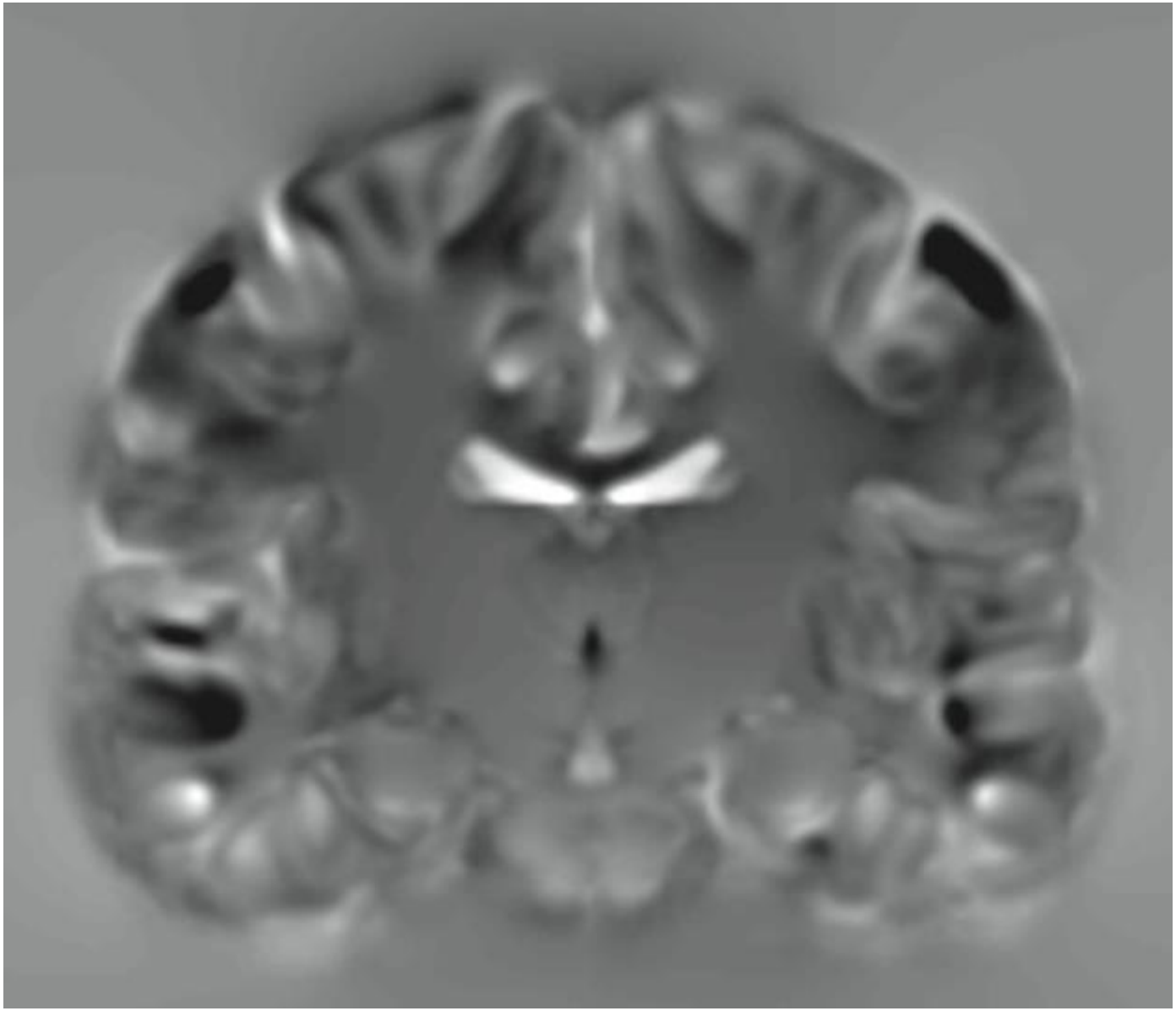
“Modulation” – change of variables.



Deformation Field



Jacobians determinants
Encode relative volumes.



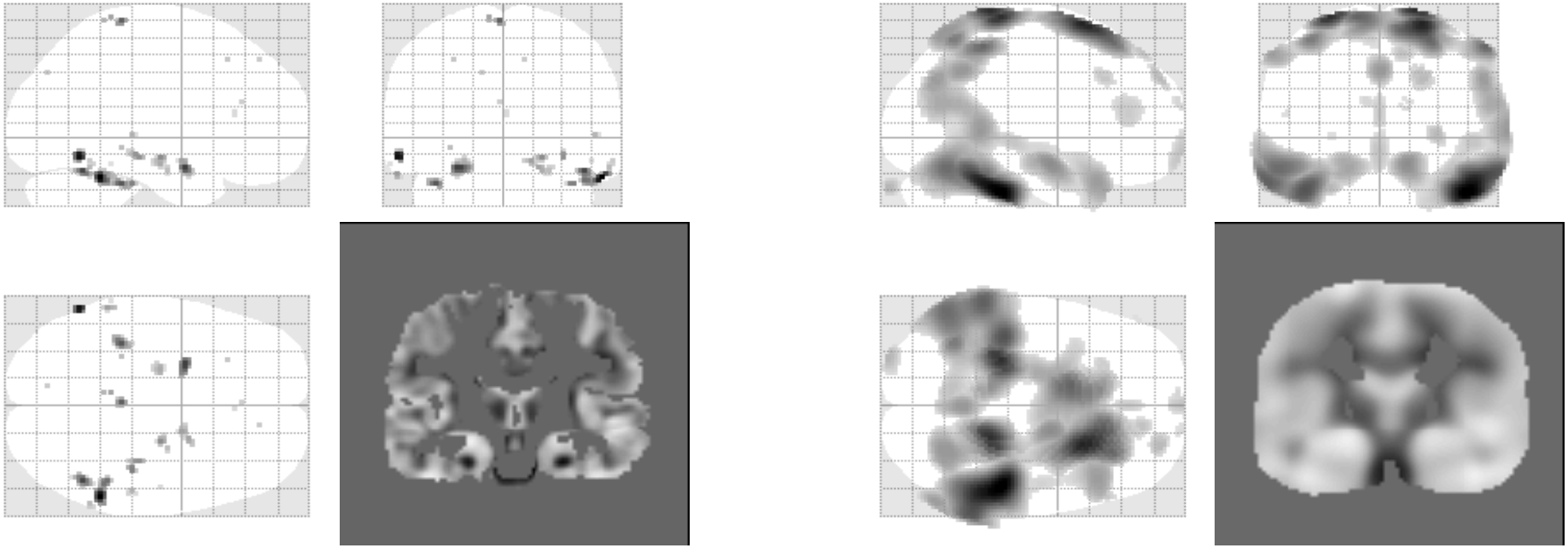
JACOBIAN DETERMINANT IMAGE (j_<image>.nii)

Smoothing

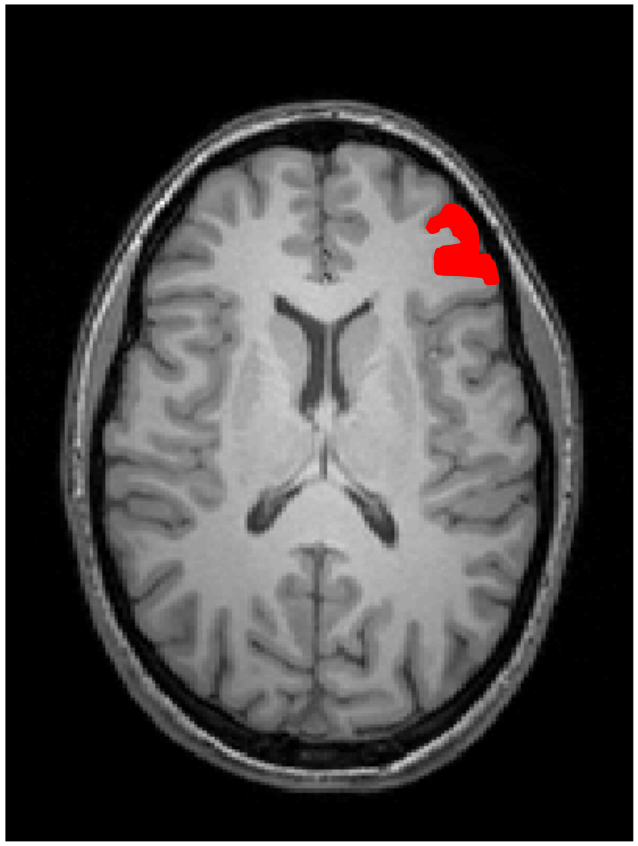
- The analysis will be most sensitive to effects that match the shape and size of the kernel
- The data will be more Gaussian and closer to a continuous random field for larger kernels
  - Usually recommend >= 6mm
- Results will be rough and noise-like if too little smoothing is used
- Too much will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

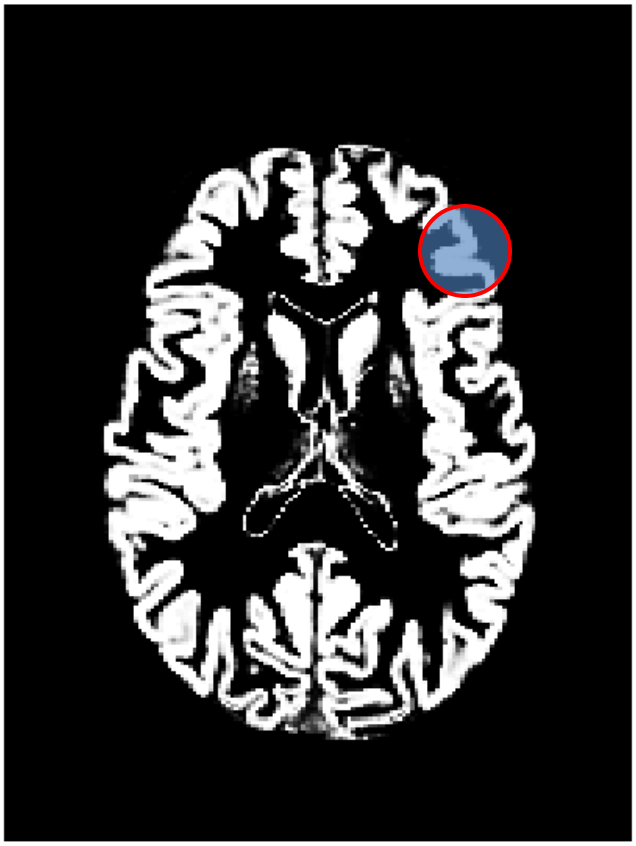
Smoothing

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



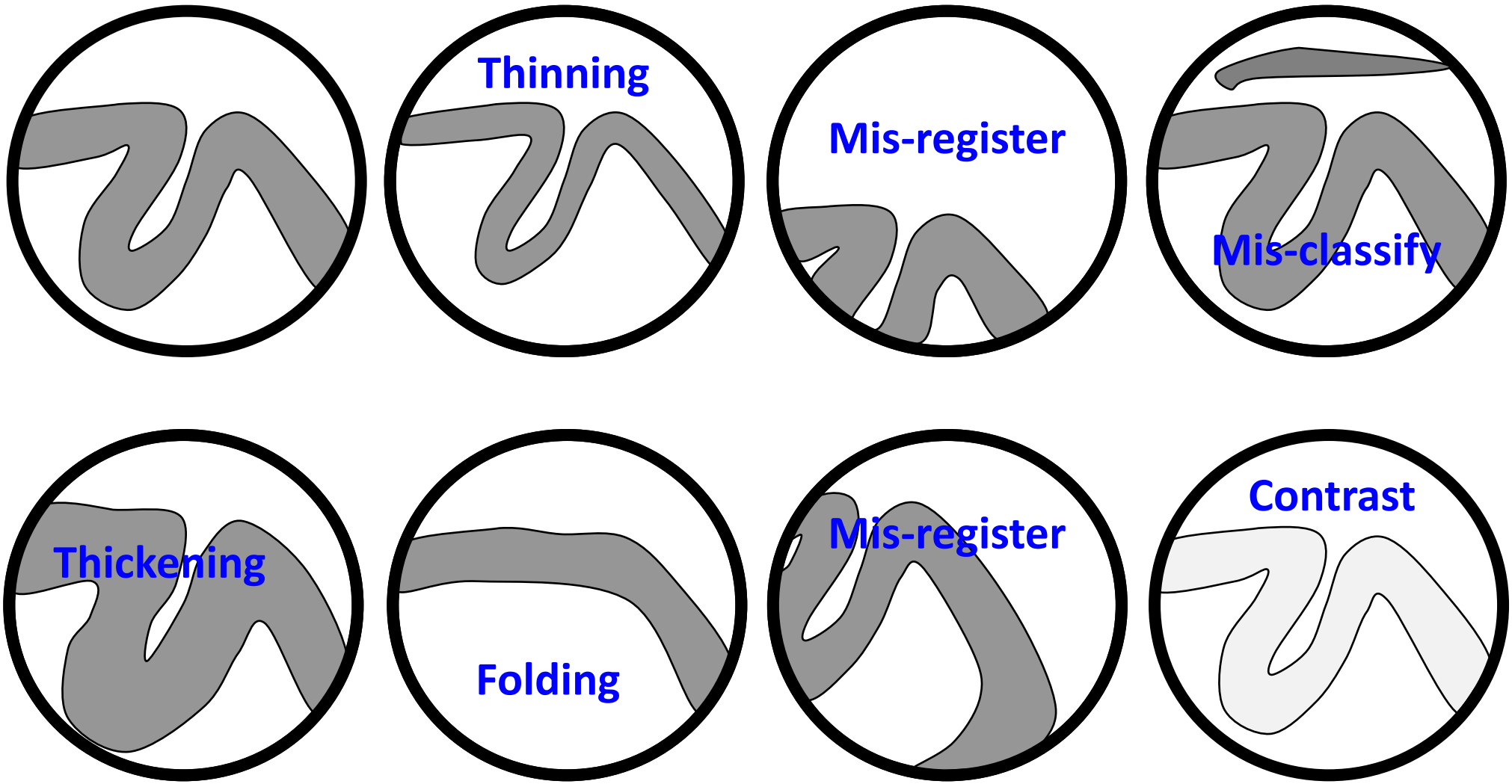
Smoothing as a locally weighted ROI





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

Interpreting findings



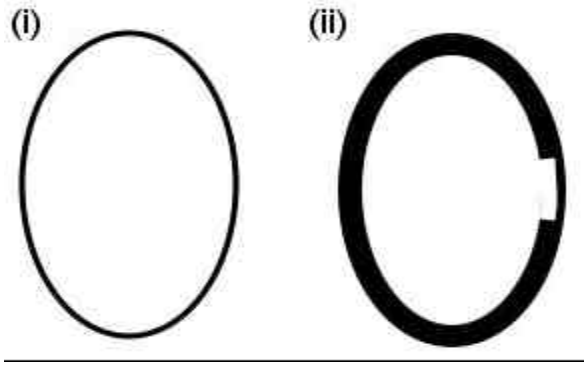
Adjustment for “nuisance” variables

- 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 intracranial volume (TIV/ICV) often used for VBM
  - Changes interpretation when correlated with local volumes (shape is a multivariate concept… See next slide)
  - See also Barnes et al. (2010); Malone et al. (2015)

“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.



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

- 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

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 control group…
- 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
- Voxel-wise FDR is common, but not recommended

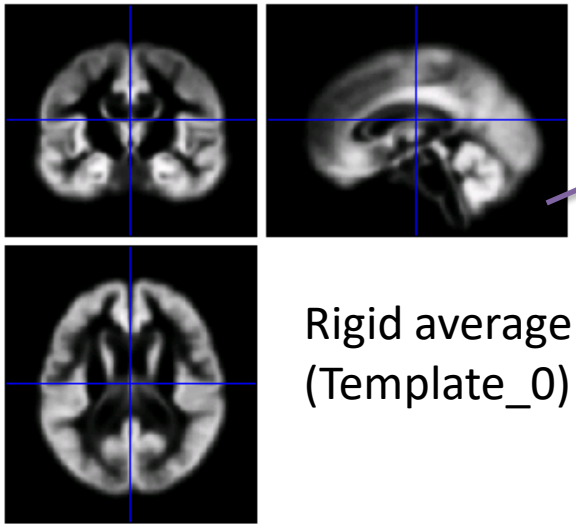
NORMALISATION

Spatial normalisation with DARTEL/Shoot

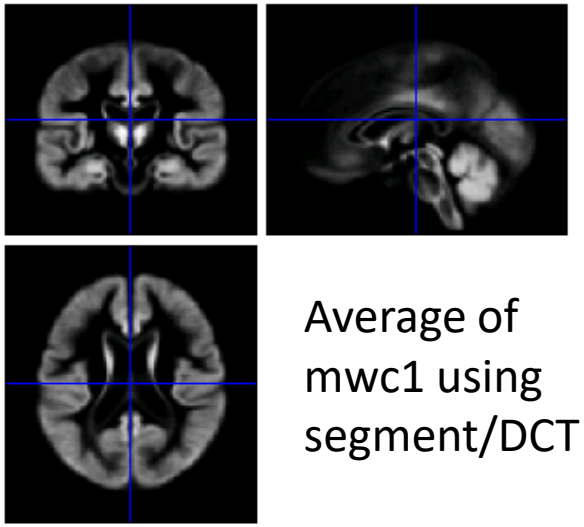
- VBM is crucially dependent on registration performance
  - The limited flexibility of DCT normalisation has been criticised
  - Inverse transformations are useful, but not always well-defined
  - More flexible registration requires careful modelling and regularisation (prior belief about reasonable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

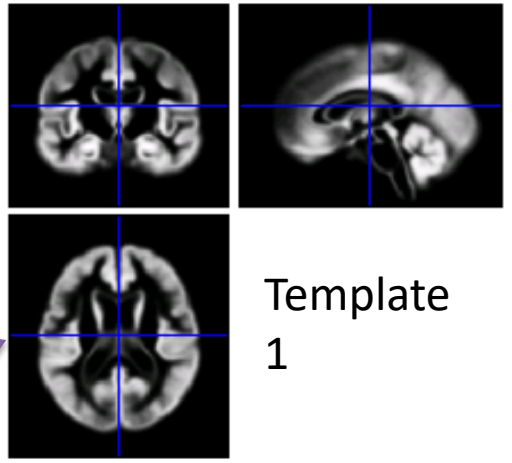
DARTEL average template evolution



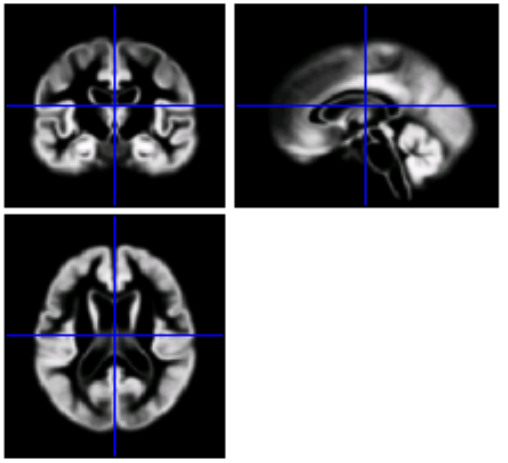
Rigid average (Template_0)

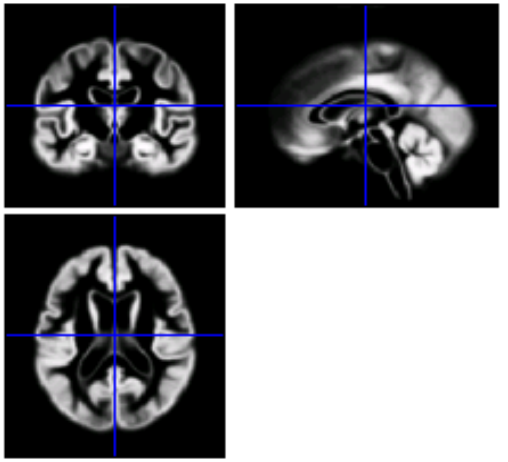


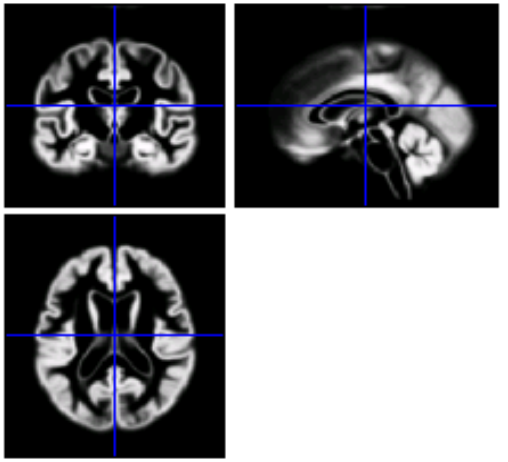
Average of mwc1 using segment/DCT

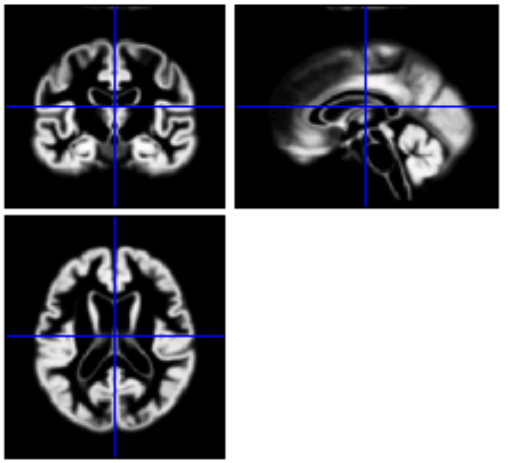


Template 1

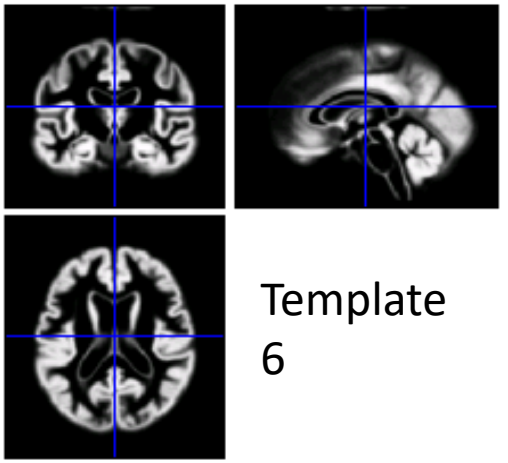




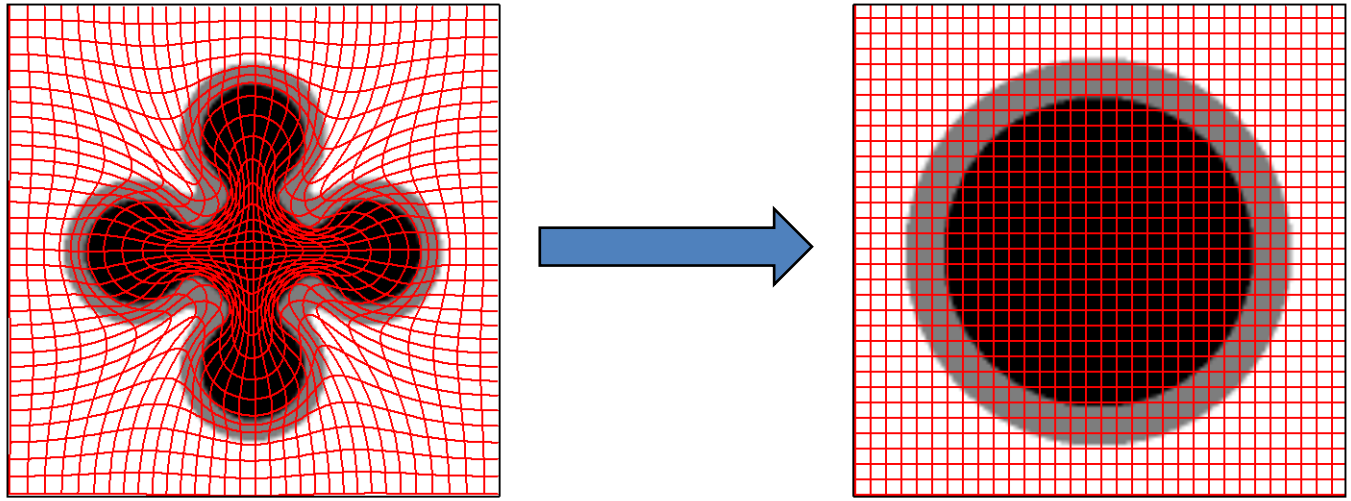


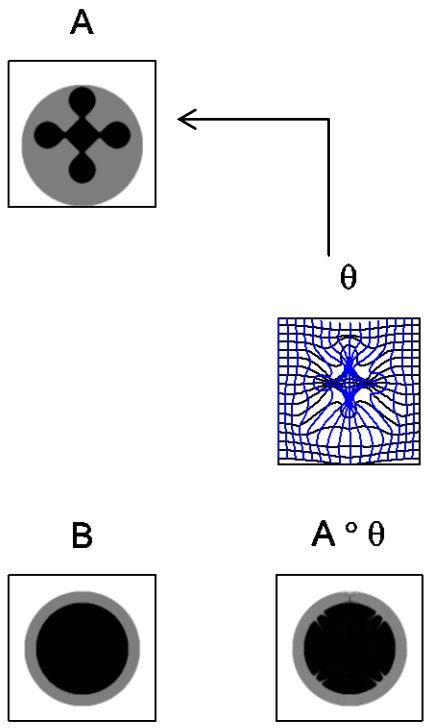


Template 6



Diffeomorphic Deformations





Composition

Diffeomorphic Image Registration

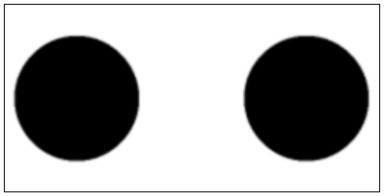
- Minimises two terms:

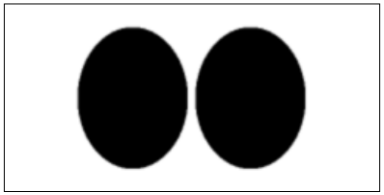
1. A measure of distance between images
2. A measure of the amount of distortion.

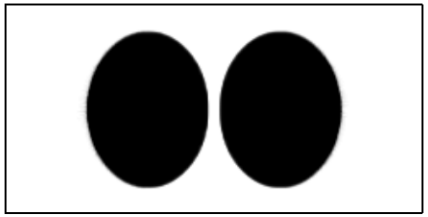
Because we can not simply add displacement fields, large deformations are generated by composing many small deformations.

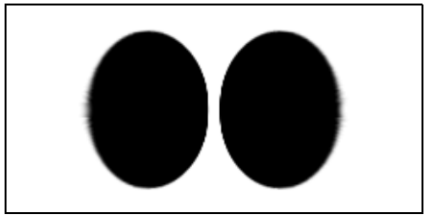
The amount of distortion is computed by summing up the distortion measures from the small displacements.

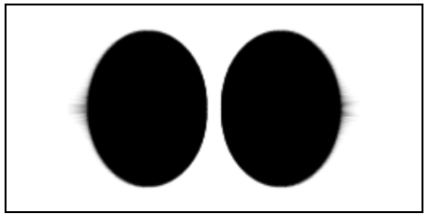
Effect of Different Distortion Measures

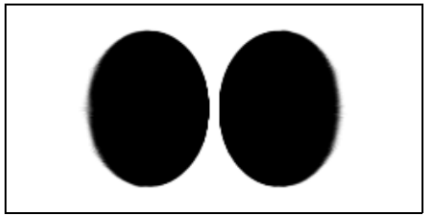


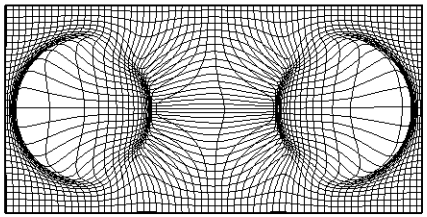


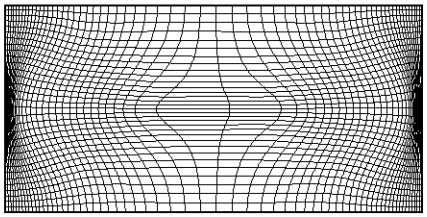


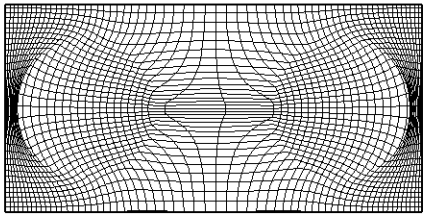


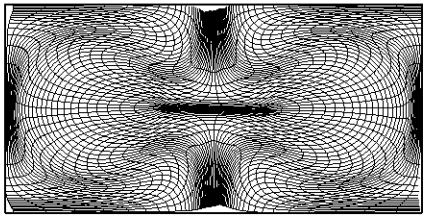


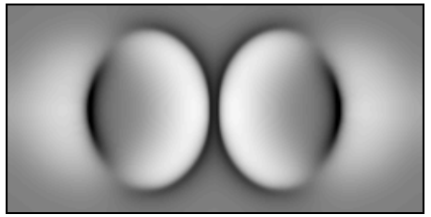


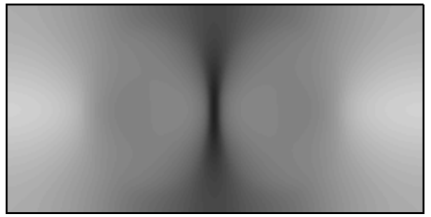


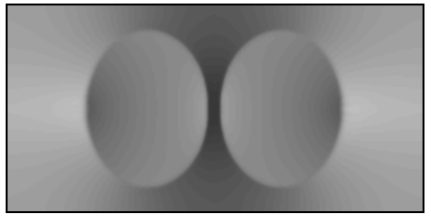




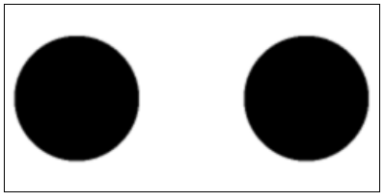


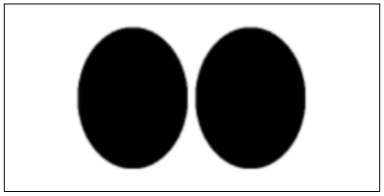


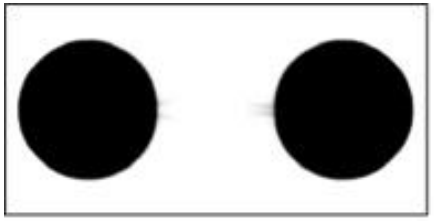


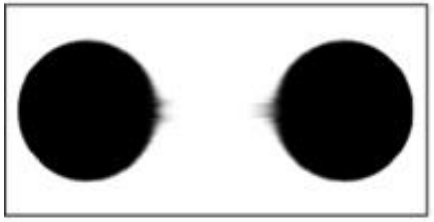


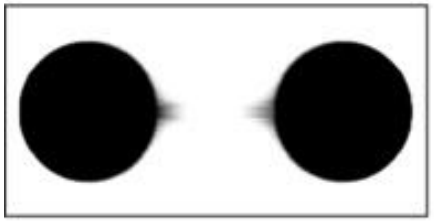
Effect of Different Distortion Measures

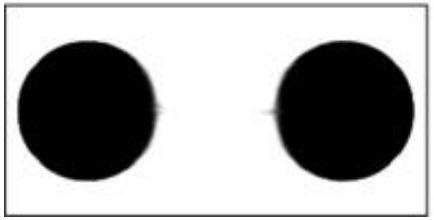


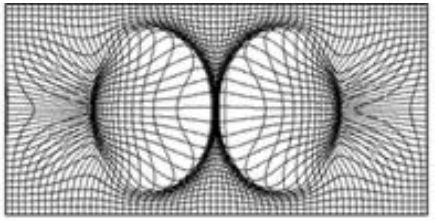


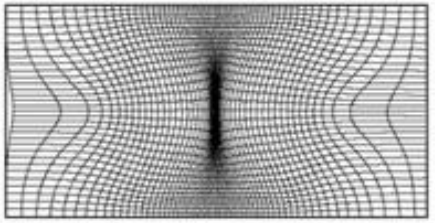


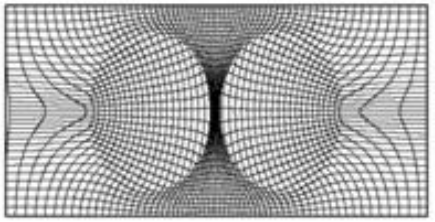


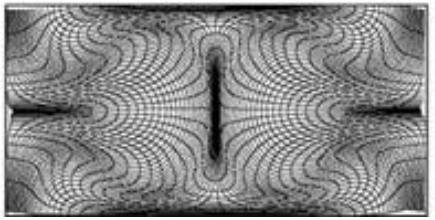


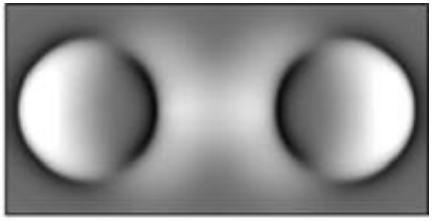


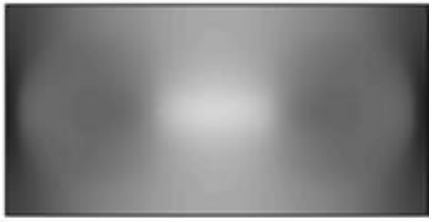


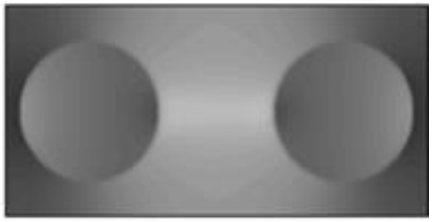












Two diffeomorphic approaches in SPM

Dartel.

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

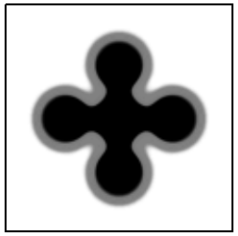
Geodesic Shooting

- 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

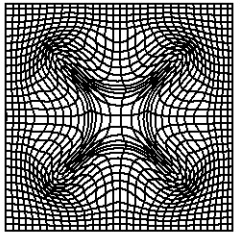
Dartel

$\mu \circ \chi$

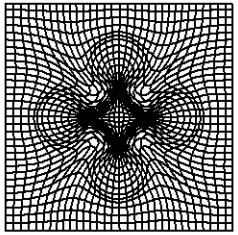


$f \circ \chi^{-1}$

χ

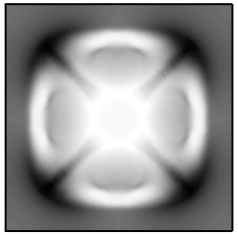


χ^{-1}



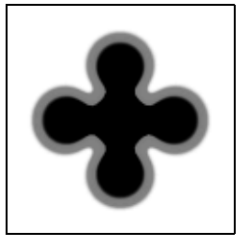
$|J^{\chi}|$

$|J^{\chi^{-1}}|$



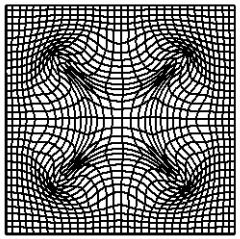
Geodesic Shooting

$\mu \circ \theta$

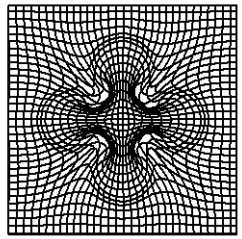


$f \circ \phi$

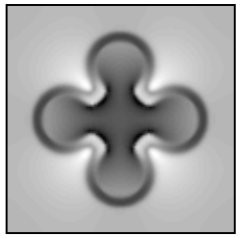
θ



ϕ

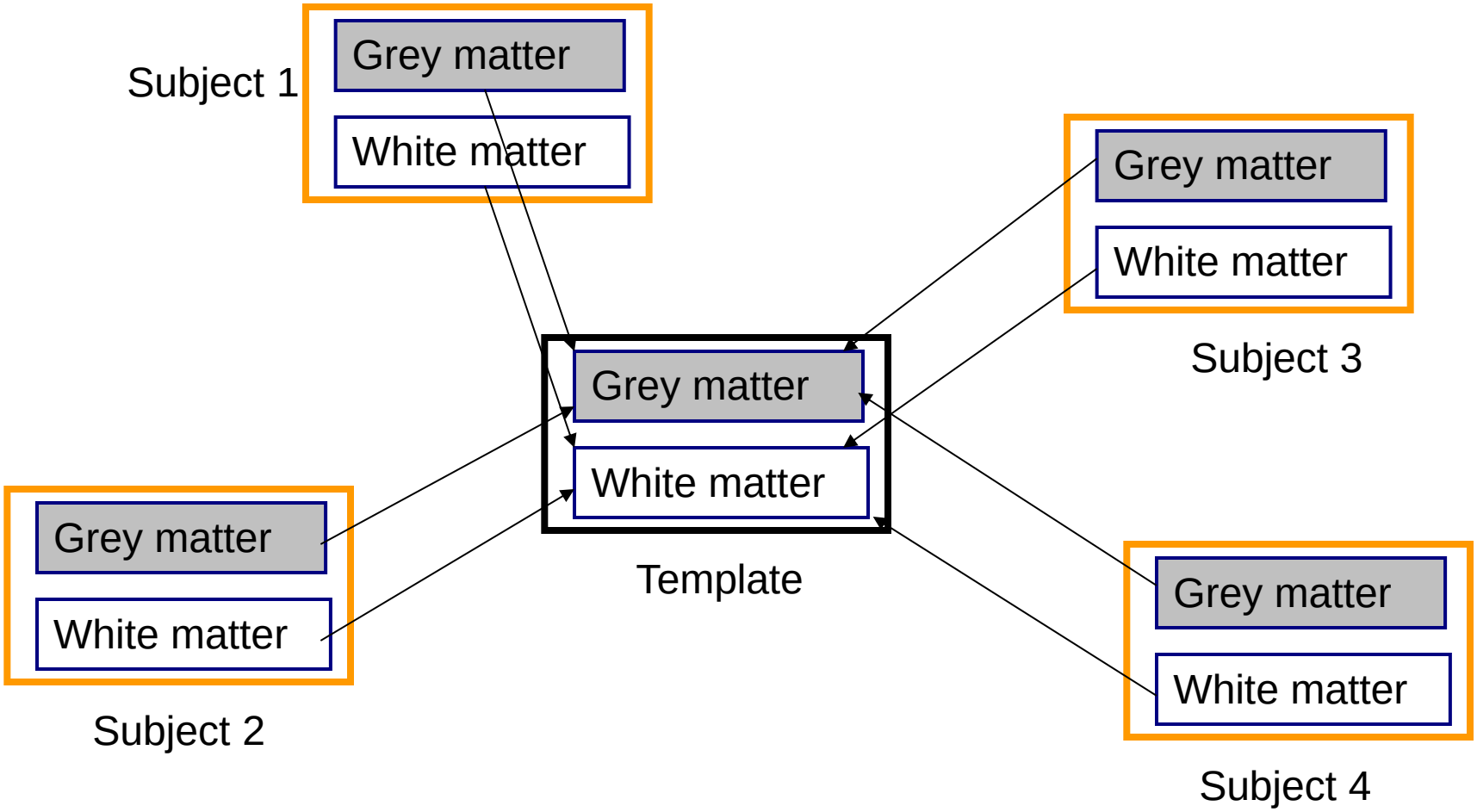


$|J^{\theta}|$



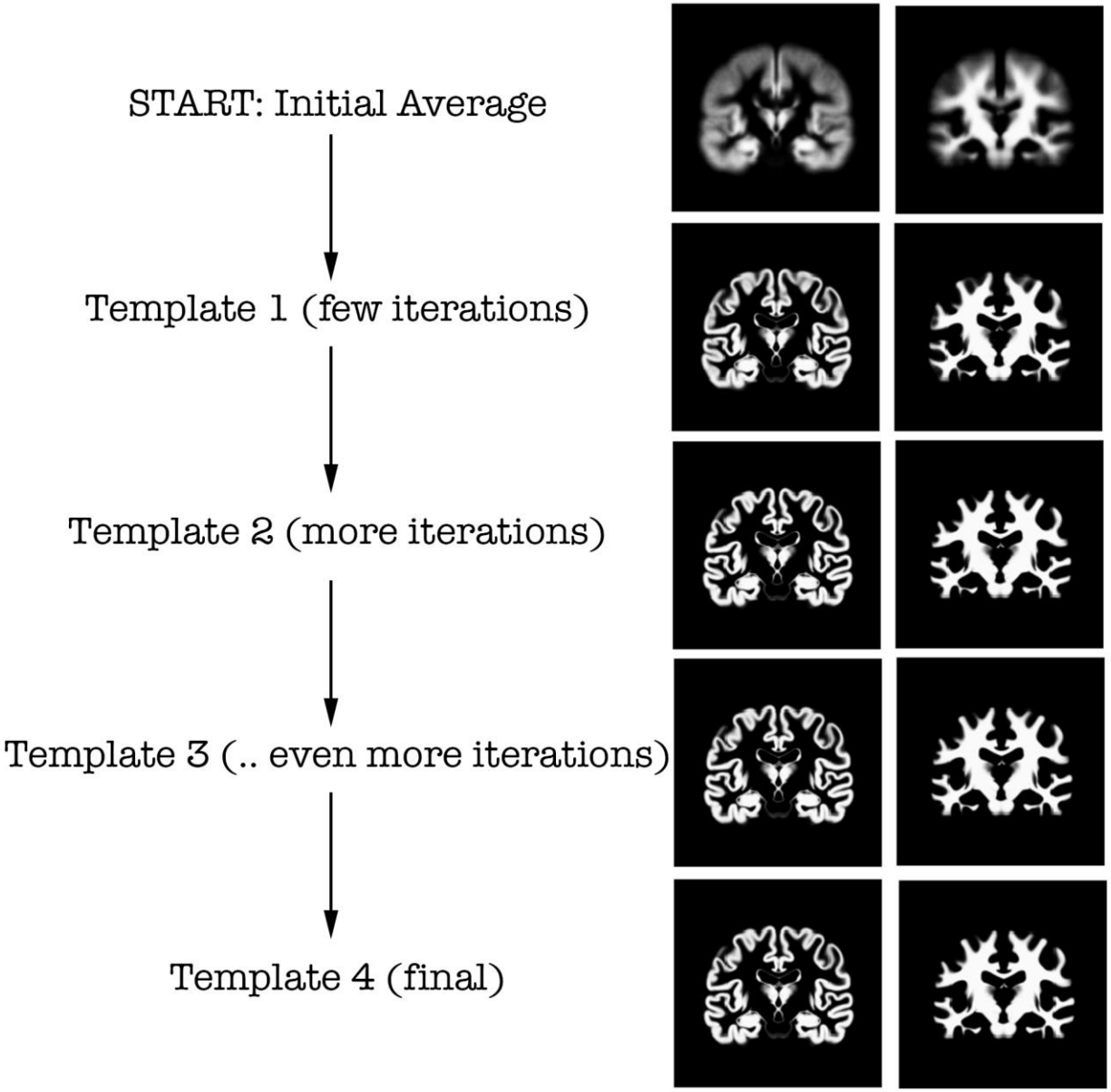
$|J^{\phi}|$

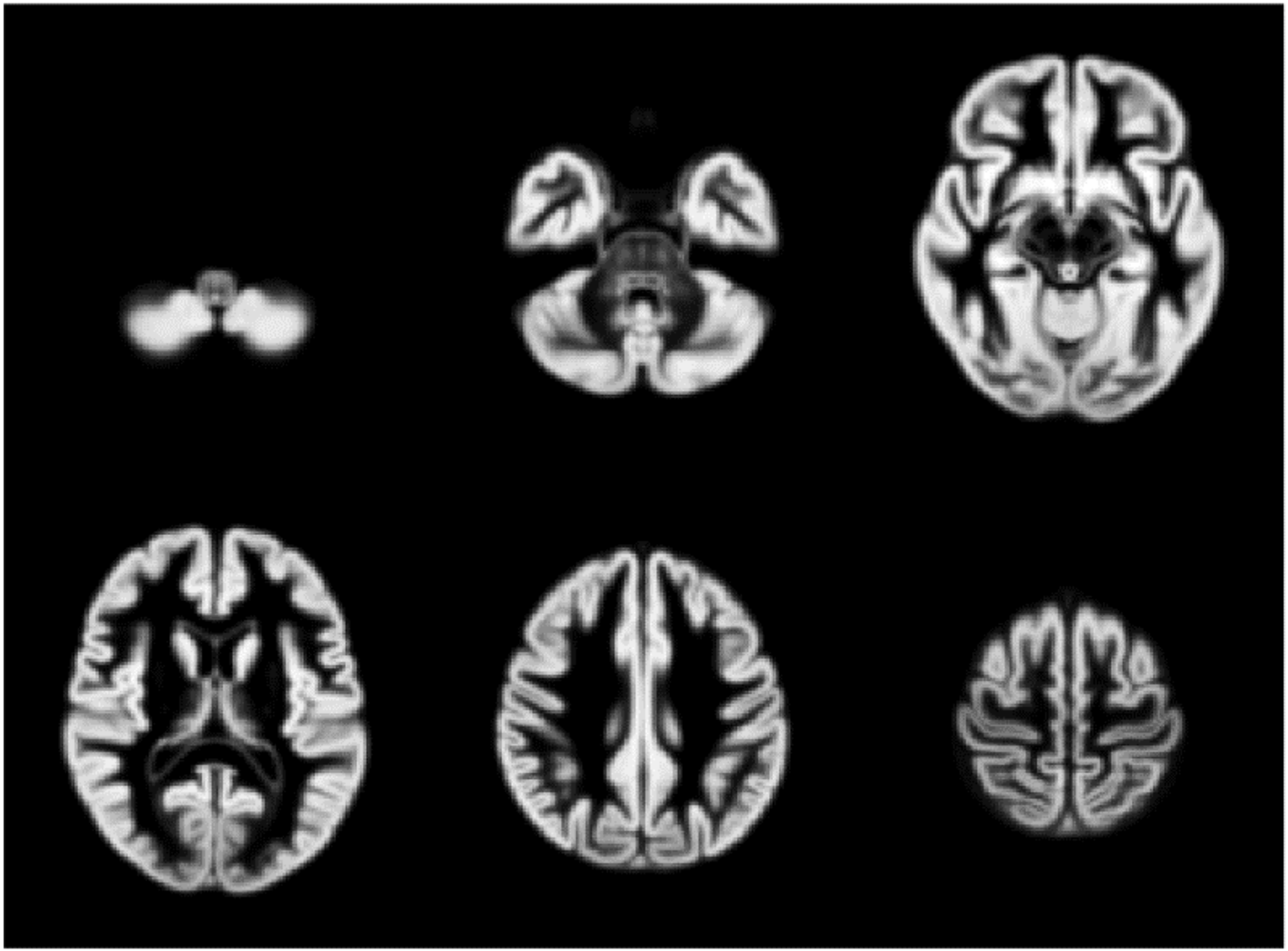
Simultaneous registration of GM to GM and WM to WM



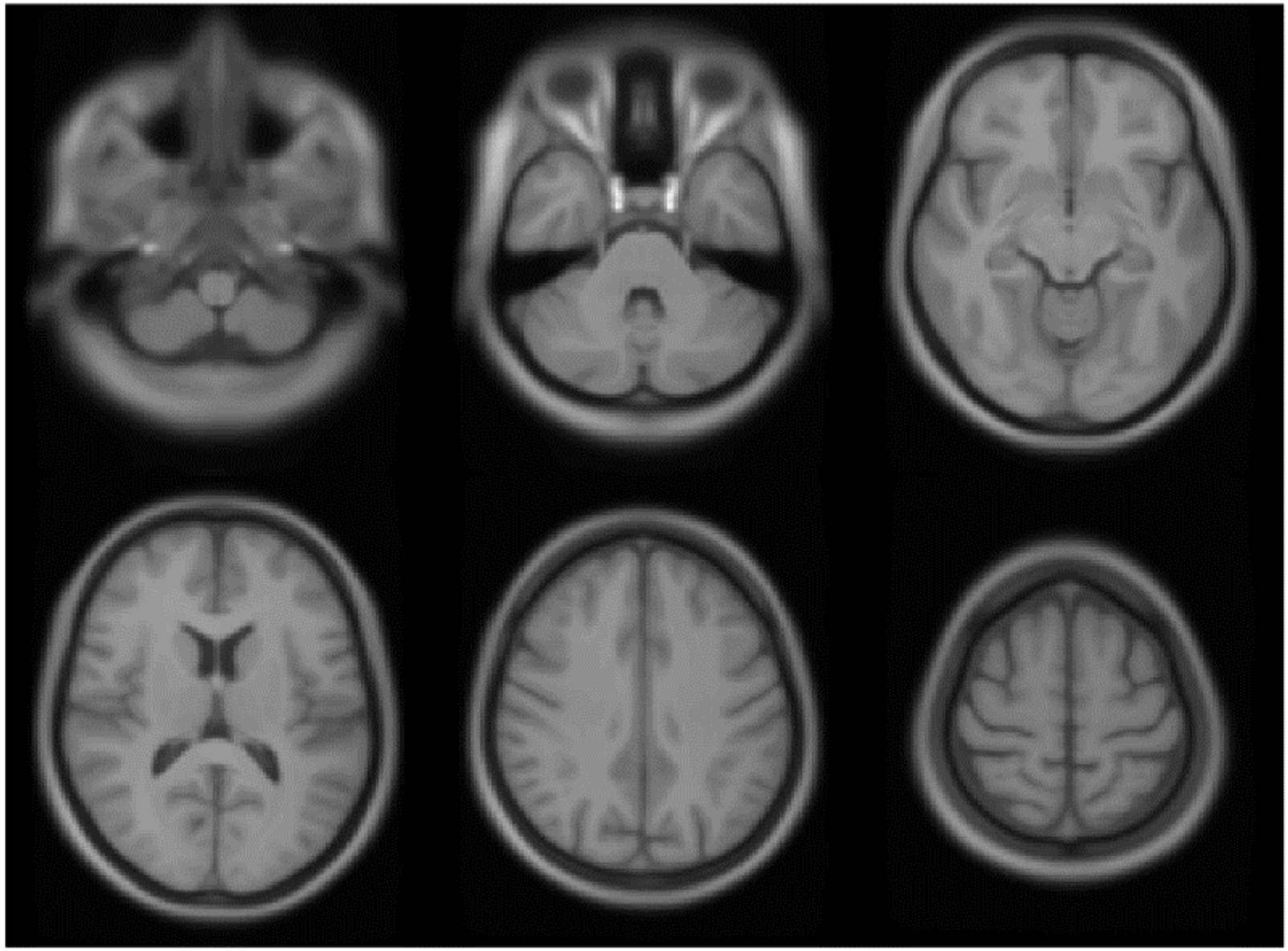
Group-wise alignment

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

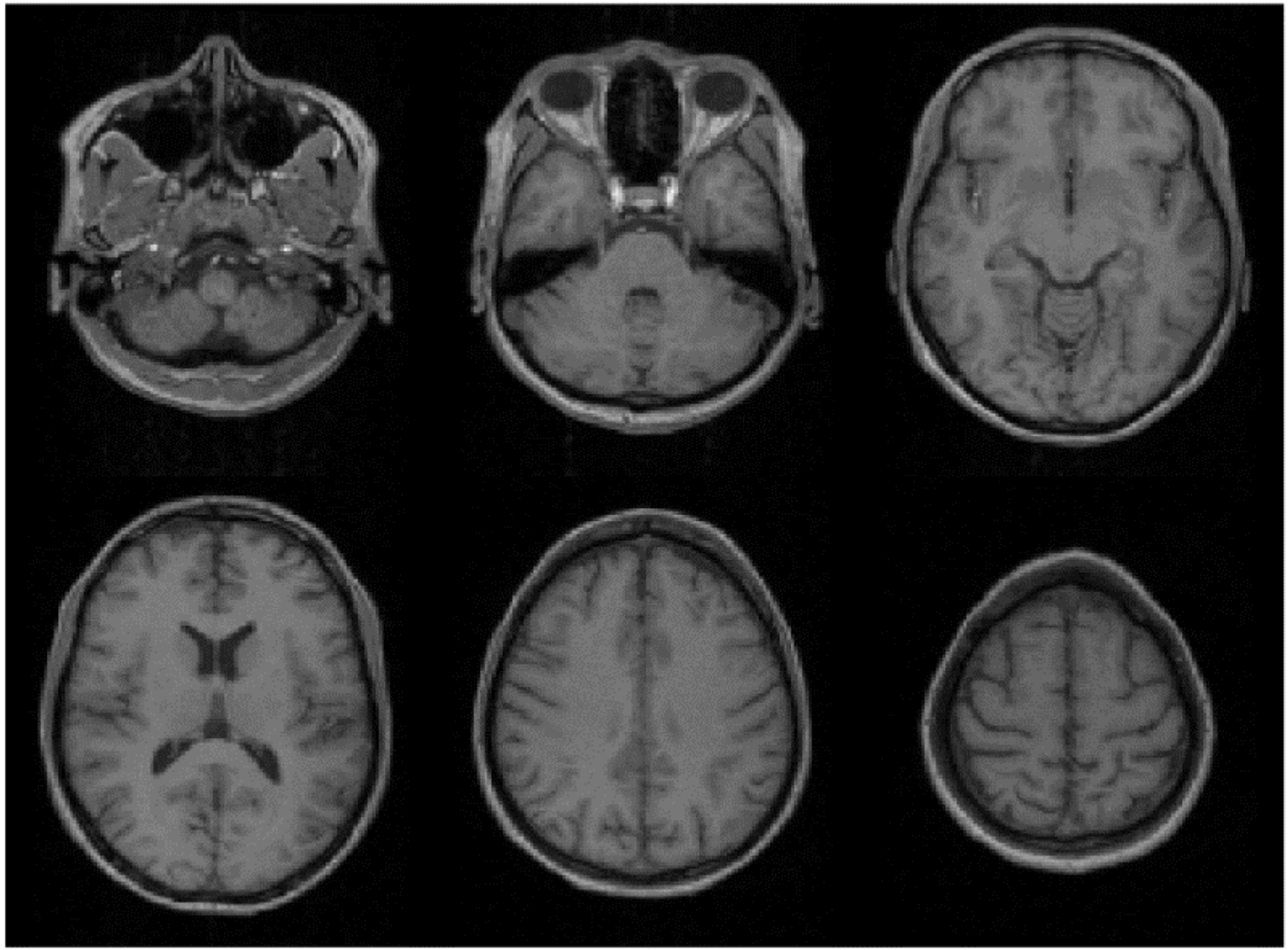




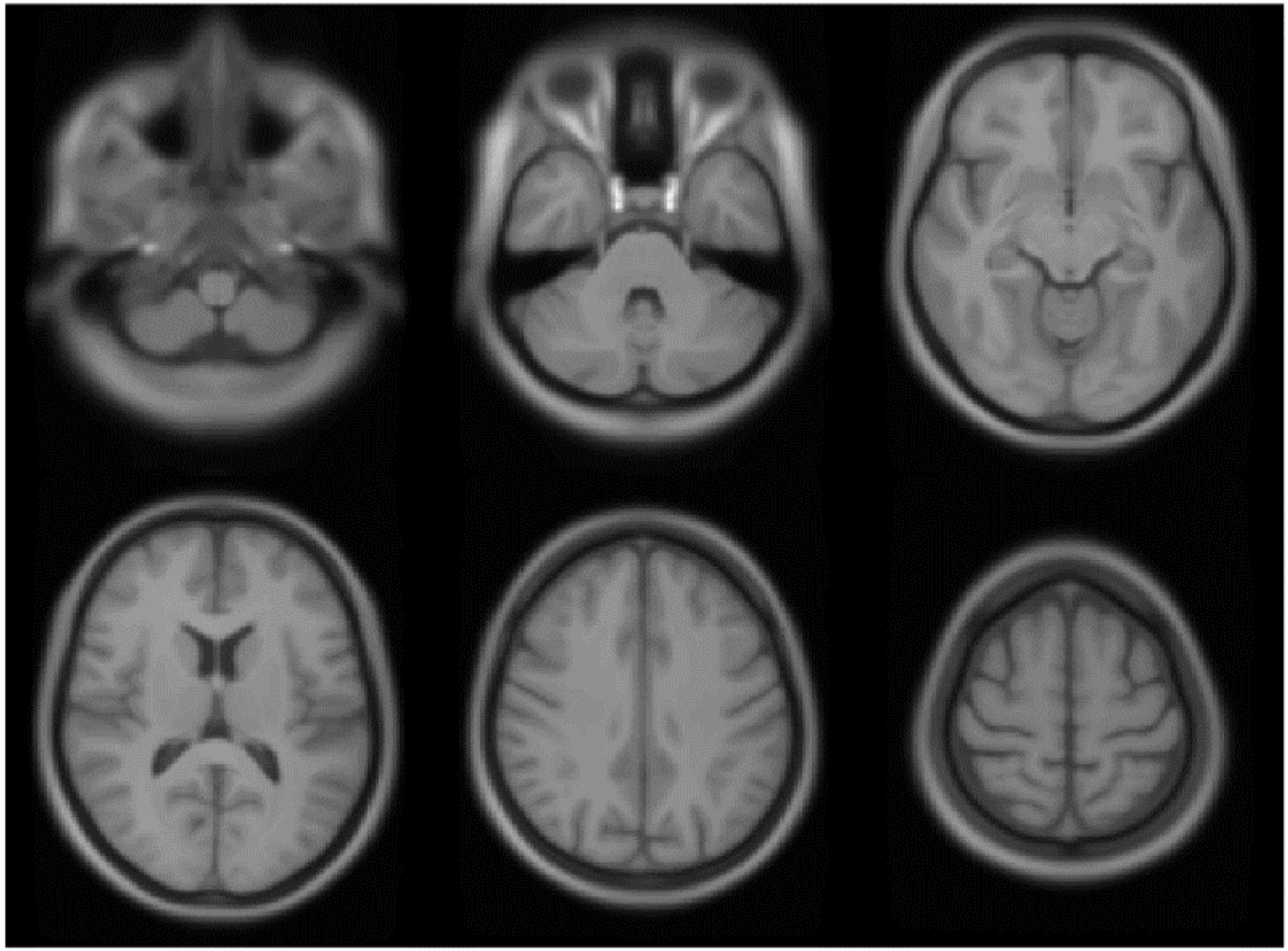
471 Subject Average (DARTEL)



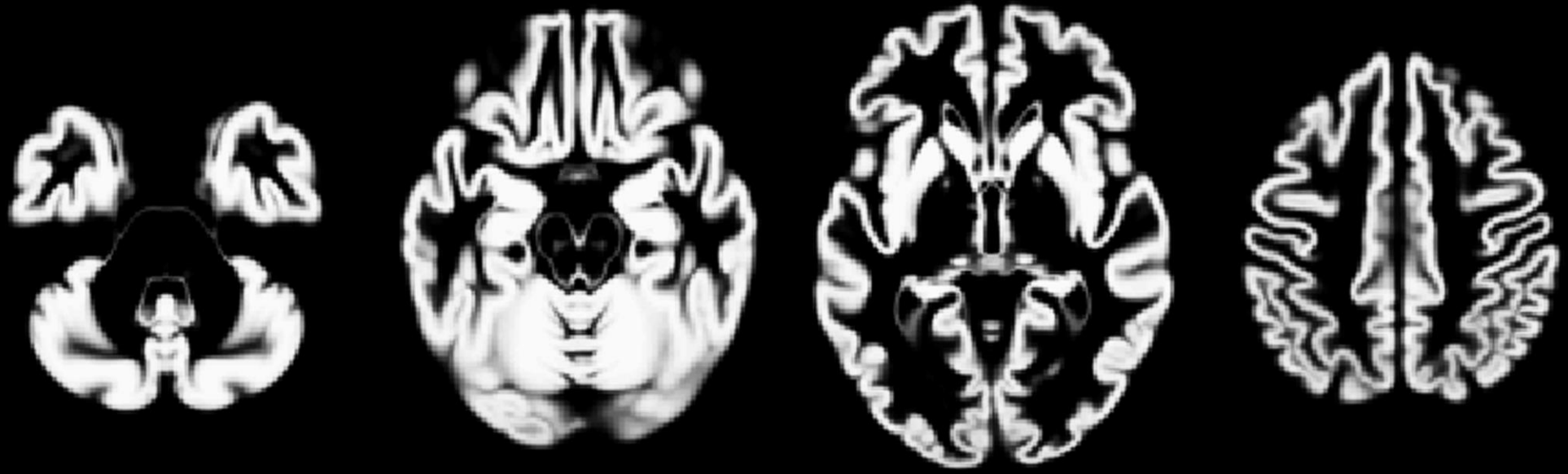
471 Subject Average



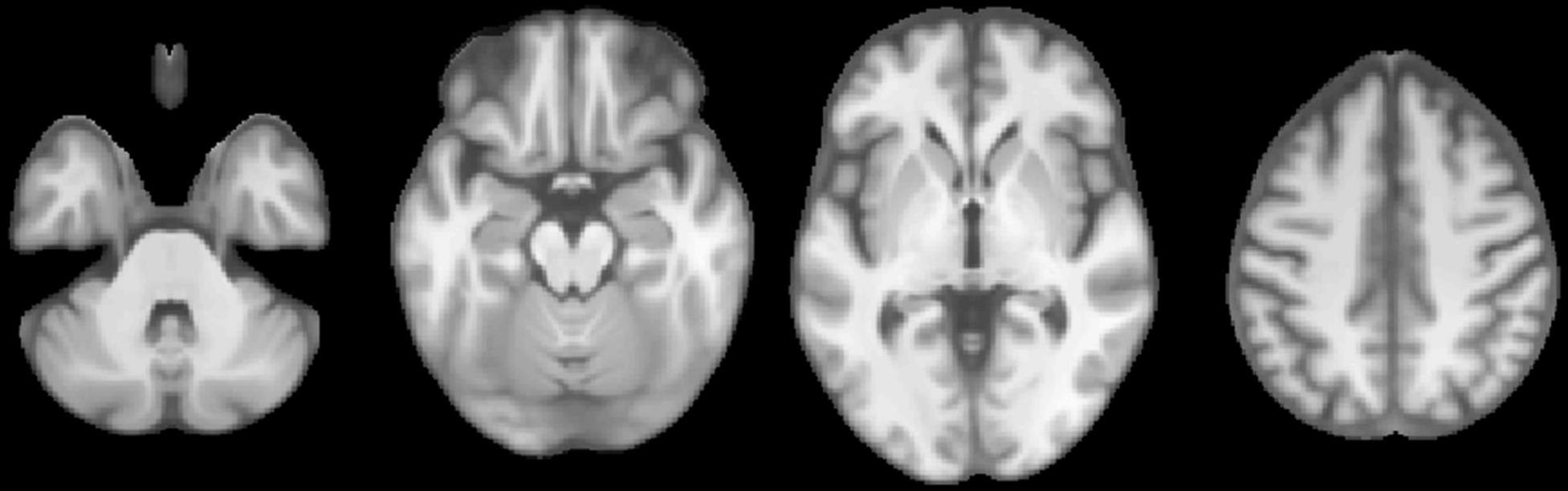
Subject 1



471 Subject Average



Shoot Group Average Template
N = 5632

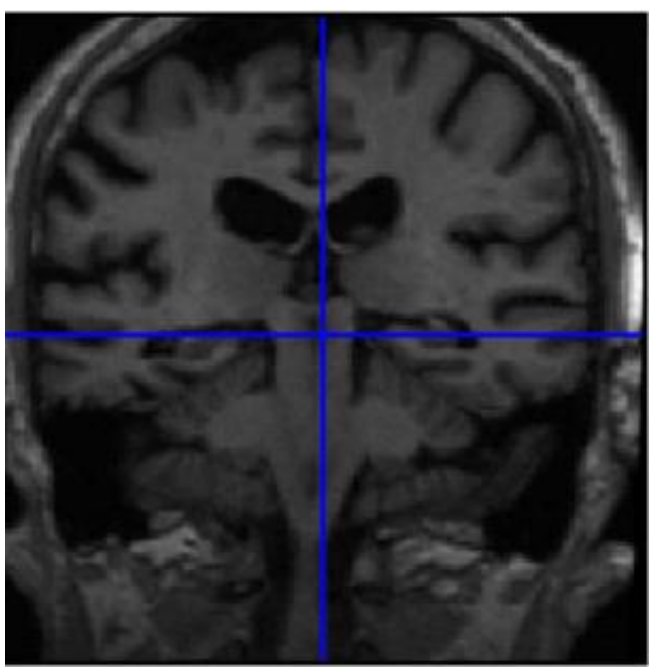
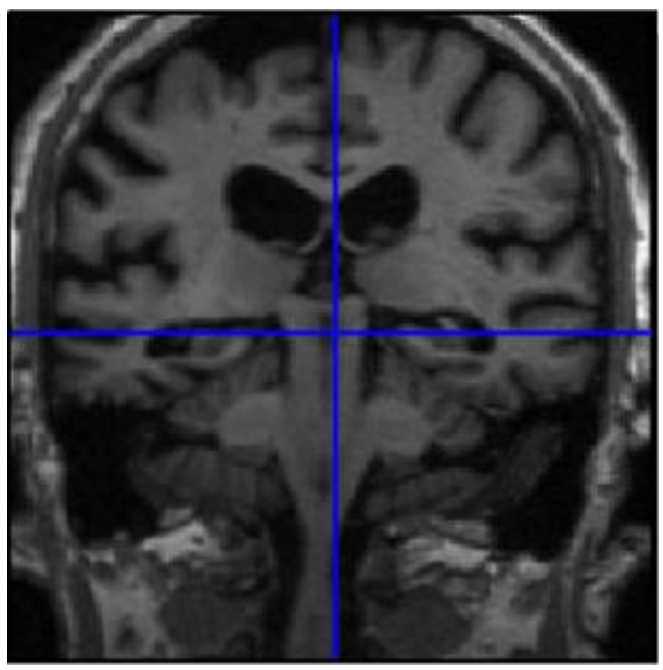
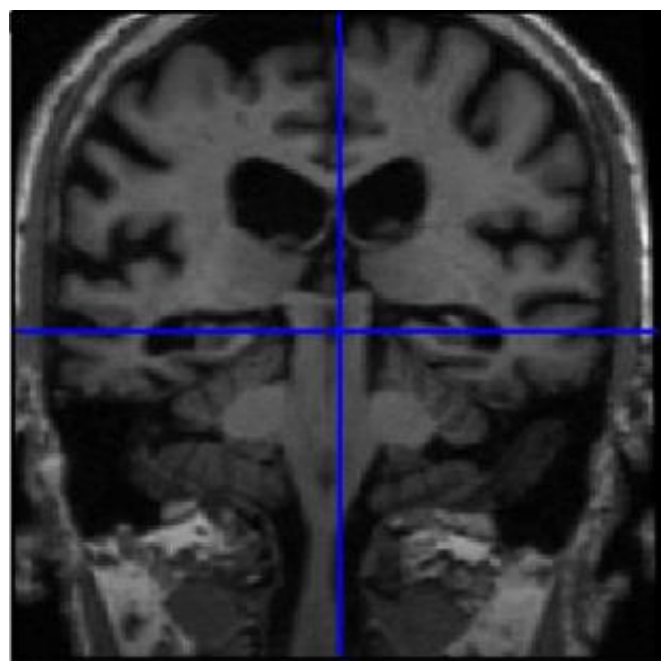


Shoot Group Average Template
N = 5632

Summary

- VBM performs voxel-wise statistical analysis on smoothed (modulated) normalised tissue segments
- SPM performs segmentation and spatial normalisation in a unified generative model
  - Based on Gaussian mixture modelling, with warped spatial prior probability maps, and multiplicative bias field
- Subsequent (non-unified) use of DARTEL or SHOOT toolboxes improves spatial normalisation for VBM
  - (and probably also fMRI...)

LONGITUDINAL ANALYSIS

Longitudinal VBM – motivation

- Development, growth, plasticity, aging, degeneration, and treatment-response are inherently longitudinal
- Serial data have major advantages over multiple cross-sectional samples at different stages
- Increasing power
  - Subtlety of change over time vs. inter-individual variation
- Reducing confounds
  - Separating within-subject changes from cohort effects
  - Demonstrating causality with interventions

Longitudinal VBM – 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

- 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

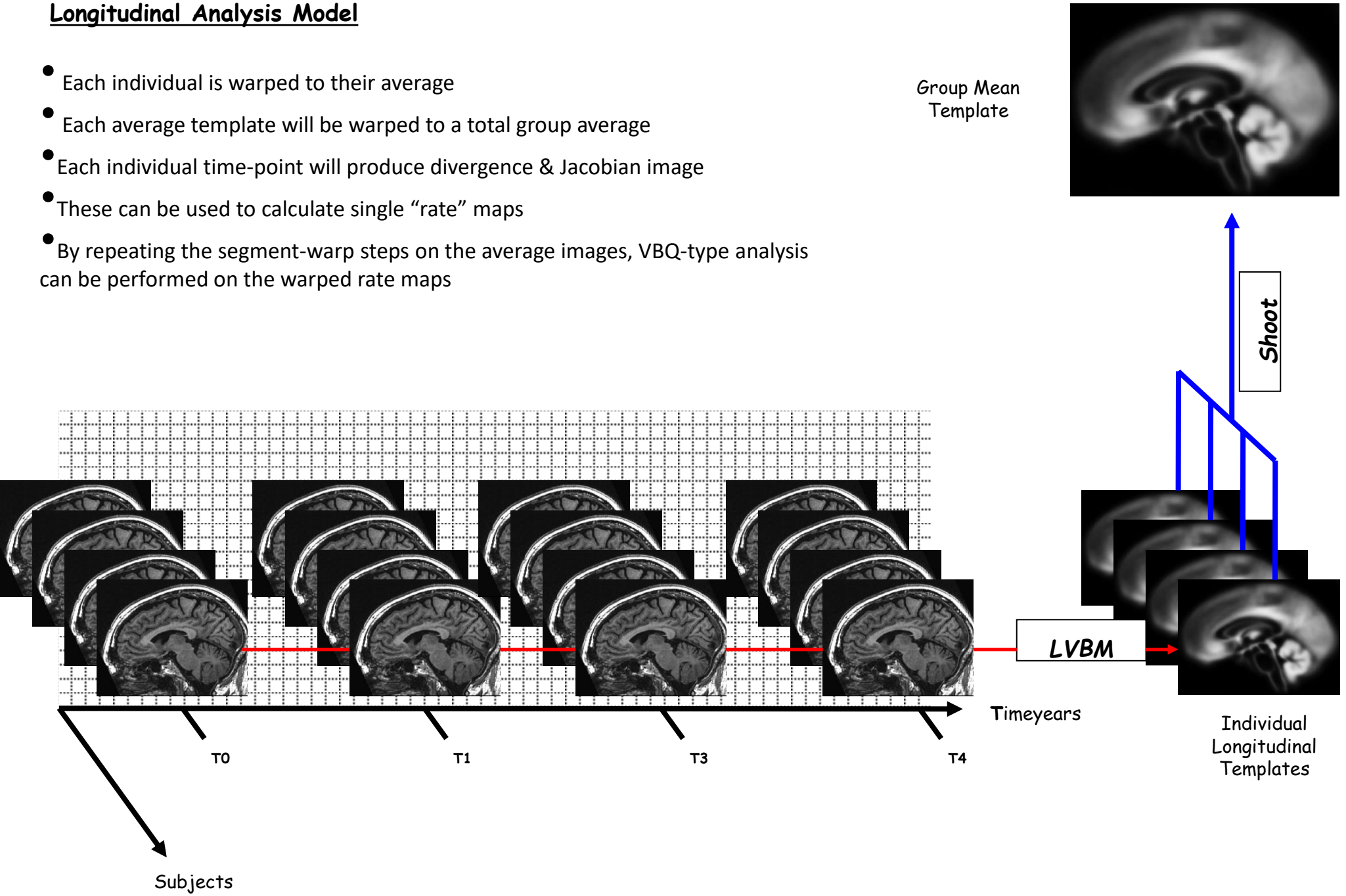
- Ashburner & Ridgway (2013) [PMID: 23386806]
- “Unified” rigid and non-rigid registration with model of differential intensity inhomogeneity (bias)
- “Generative” – each time-point is a reoriented, spatially warped, intensity biased version of avg.
- “Symmetric” with respect to permutation of images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

Longitudinal VBM – 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
  - Can multiply volume change with GM, then smooth
- 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

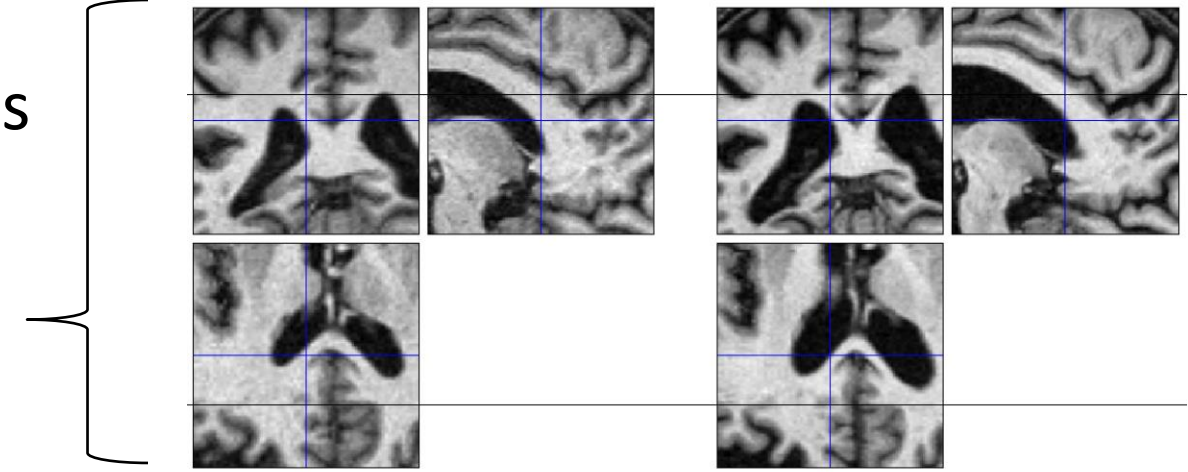
Longitudinal Analysis Model

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



Two Longitudinal Scans

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



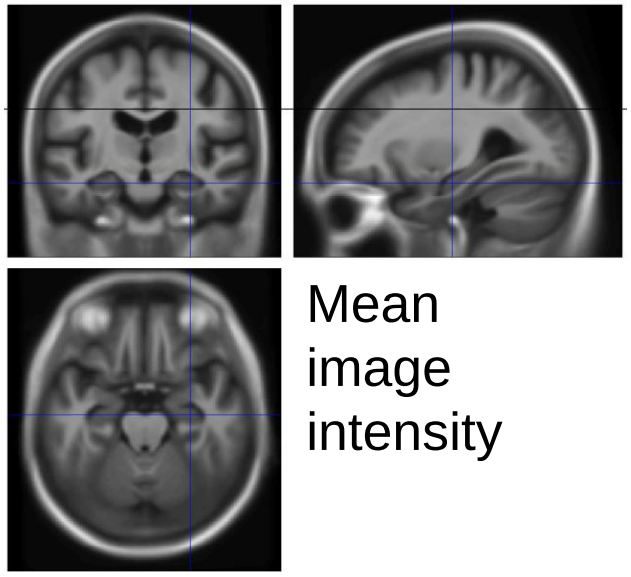
Oasis Data

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

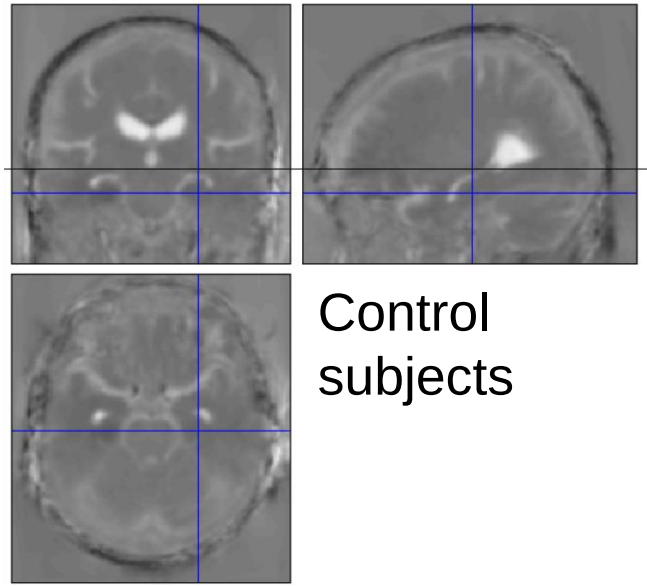
Computed average expansion/contraction rates for each subject.

Warped all data to common anatomical space.

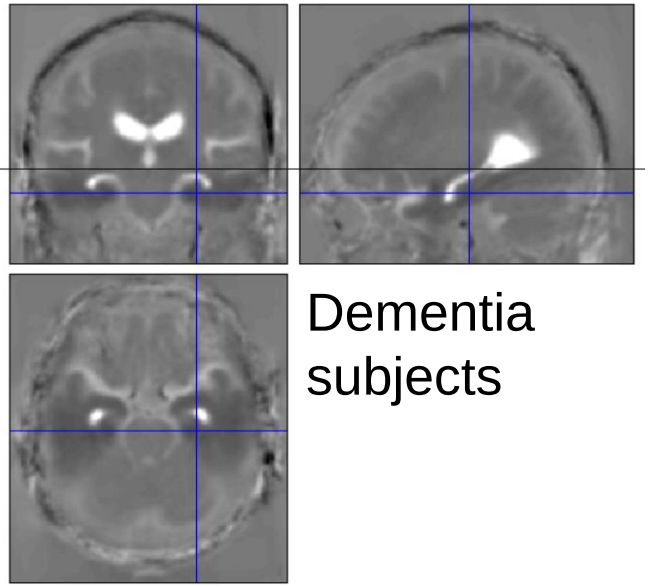
Generated averages.



Mean image intensity



Control subjects

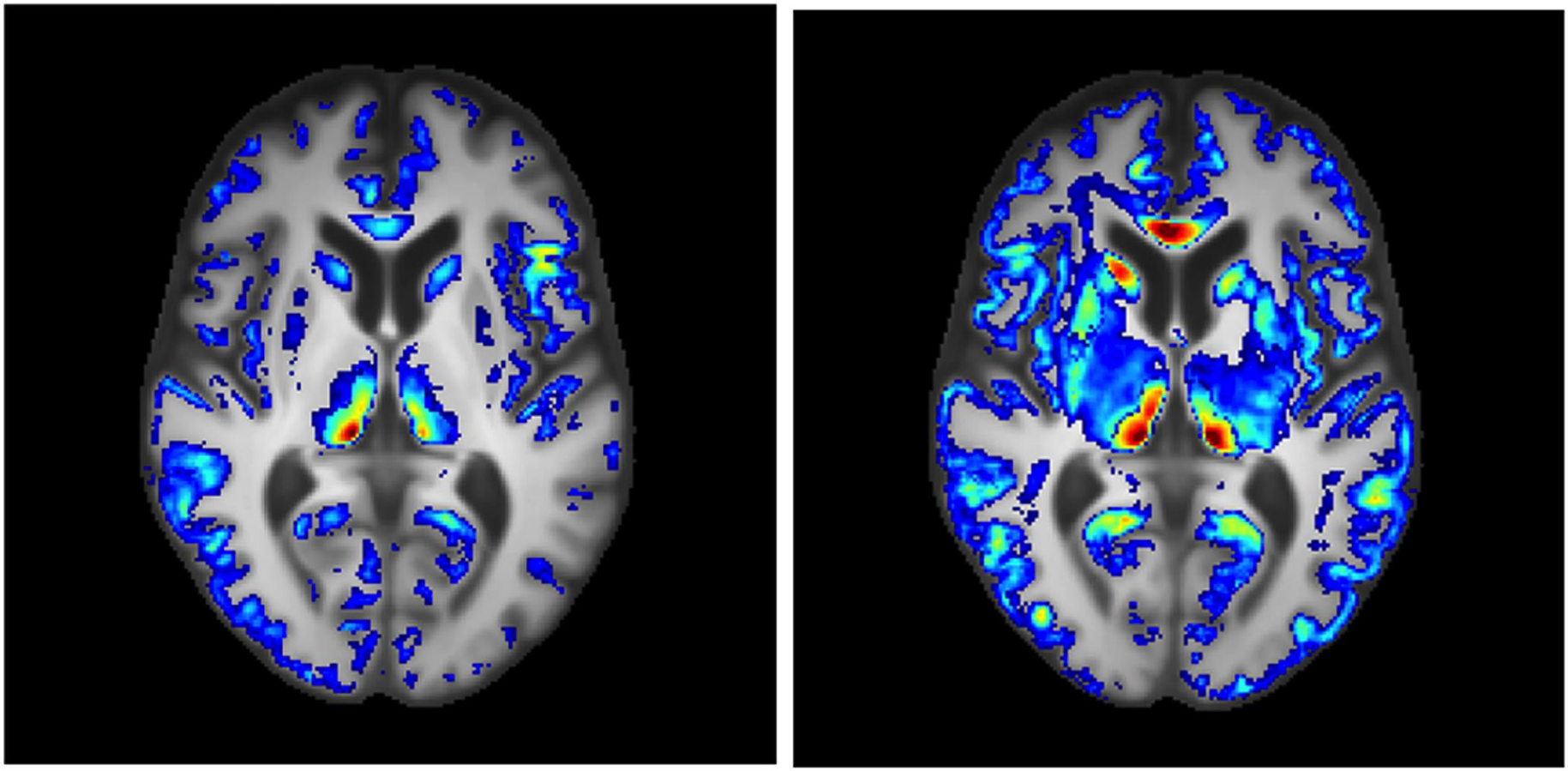


Dementia subjects

RATE OF BRAIN TISSUE LOSS

NORMAL AGEING

PARKINSON'S DISEASE



0.005 0.020 0.035

CONCLUSION

Introduced VBM & Potential uses

Tissue Segmentation

Statistics

VBM Subtleties

Normalisation via DARTEL/SHOOT

Longitudinal Toolbox

There is a lot more(!):

Quantitative MRI, Voxel based quantification, Cortical thickness analysis, lesion analysis, structural covariance, combining with multivariate machine learning techniques.. etc.,