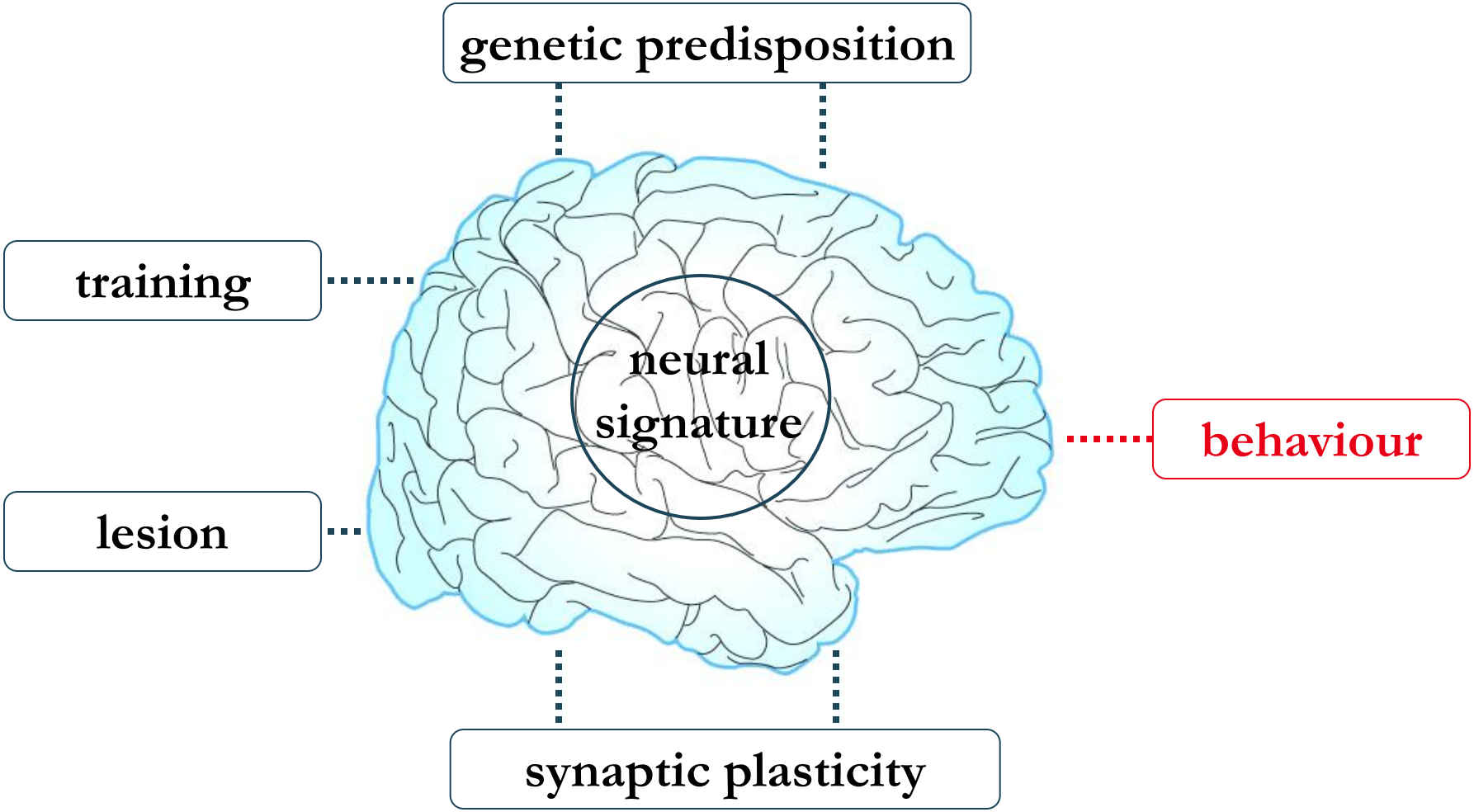
SPM course 2012 Lausanne

Computational Anatomy

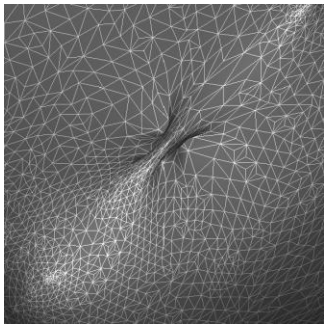
synapsy
bringing together brain research and psychiatry
National Center of Competences in Research

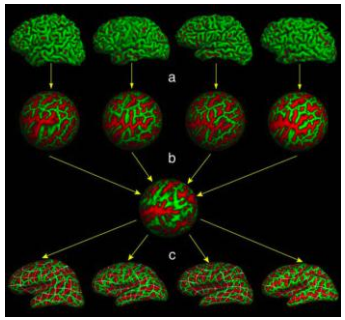
Motivation


genetic predisposition
training
neural signature
behaviour
lesion
synaptic plasticity

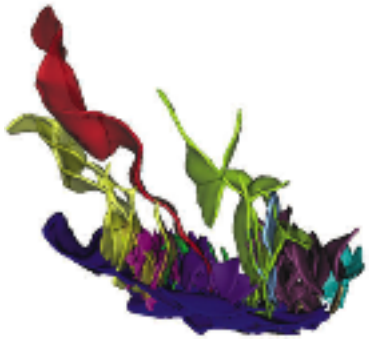
Methods

surface



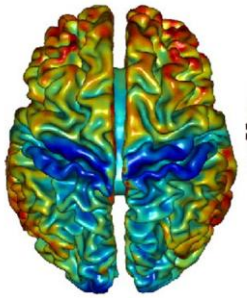


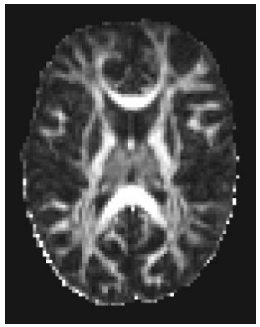
shape



Fischl et al., 1999 *Neuroimage*
Cykowski et al., 2008 *Cer Cortex*

voxel-based





Ashburner & Friston, 2000 *Neuroimage*
Jones et al., 2005 *Neuroimage*
Hutton et al., 2009 *Neuroimage*

Prerequisites

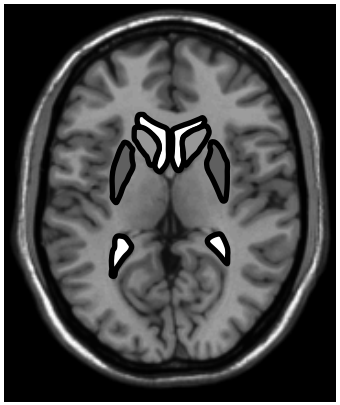
- Anatomical scans can also help us infer brain function.
  - Do people with chronic depression show brain atrophy?
  - Which brain regions atrophy with age?
  - Do people with good spatial memory (taxi drivers) have different anatomy than other people?
- Voxel-based morphometry is a tool to relate grey matter volume with medical history and behaviour

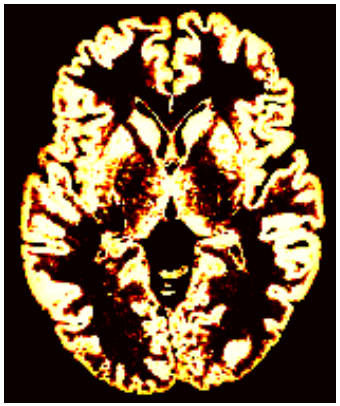
Prerequisites

- Cross-sectional studies
  - Can compare two distinct populations
  - Can also examine atrophy through time, though will require more people than longitudinal VBM.
- Longitudinal VBM
  - Sensitive way to detect atrophy through time. Using the same individual reduces variability.
- VBM findings are first step in understanding structural changes.

Prerequisites

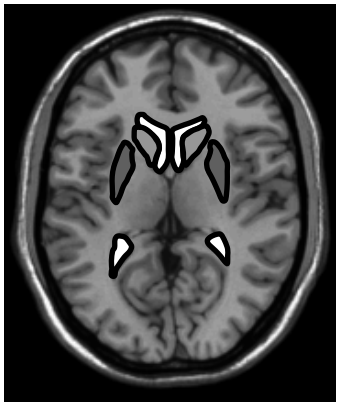
- Morphometry examines the shape, volume and integrity of structures.
- Classically, morphometry was conducted by manually segmenting a few regions of interest.
- Voxel based morphometry conducts an independent statistical comparison for each voxel in the brain.

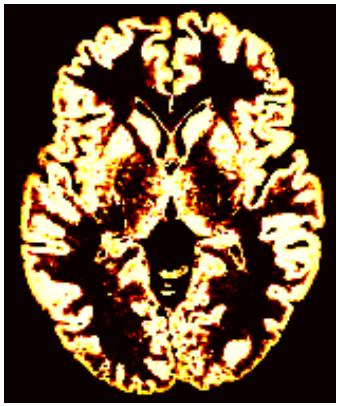




Prerequisites

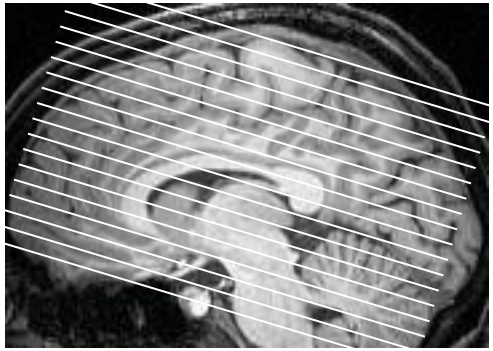
- VBM has some advantages over manual tracing:
  - Automated: fast and not subject to individual bias.
  - Able to examine regions that are not anatomically well defined.
  - Able to see the whole brain
  - Normalisation compensates for overall differences in brain volume, which can add variance to manual tracing of un-normalised images.



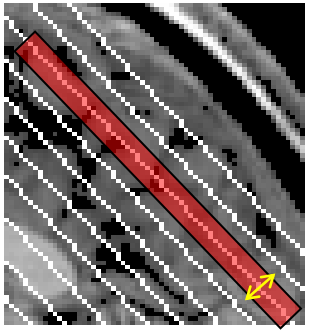


Terminology

Scan Volume:
Field of View
(FOV),
e.g. 192 mm



Axial slices



Slice thickness
e.g., 1 mm

Matrix Size
e.g., 192 x 192

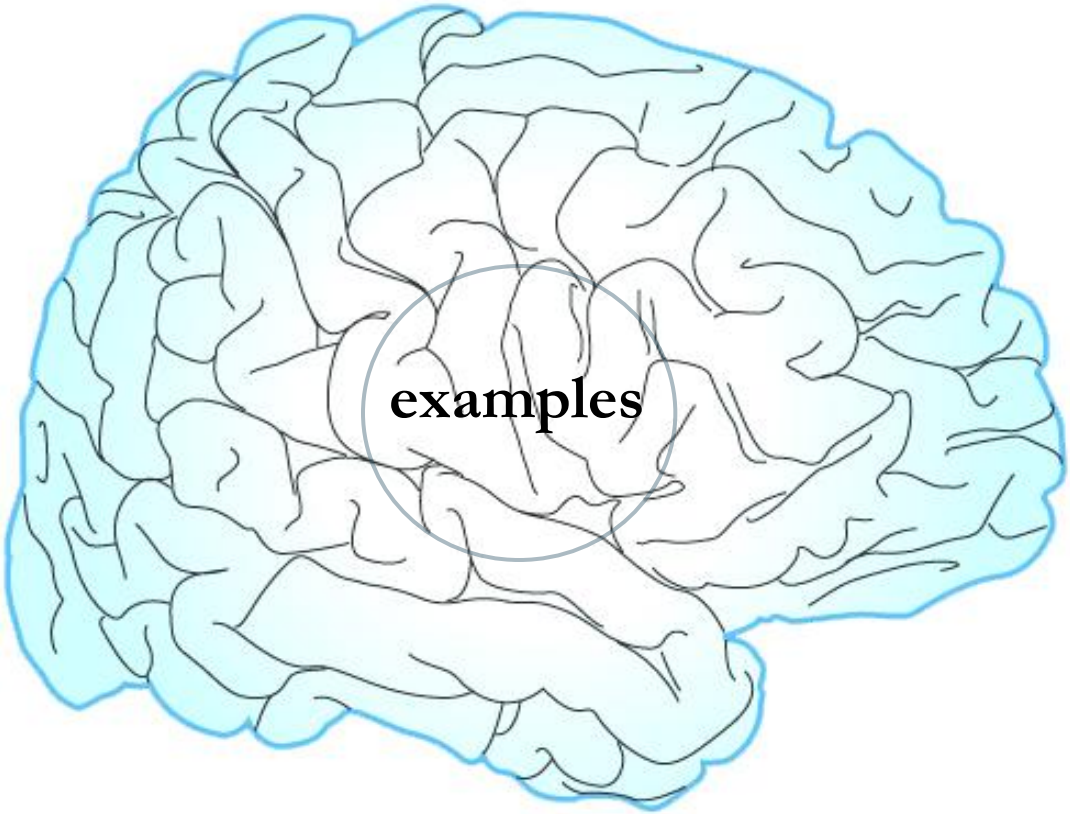
In-plane resolution
192 mm / 192
= 1 mm

1 mm

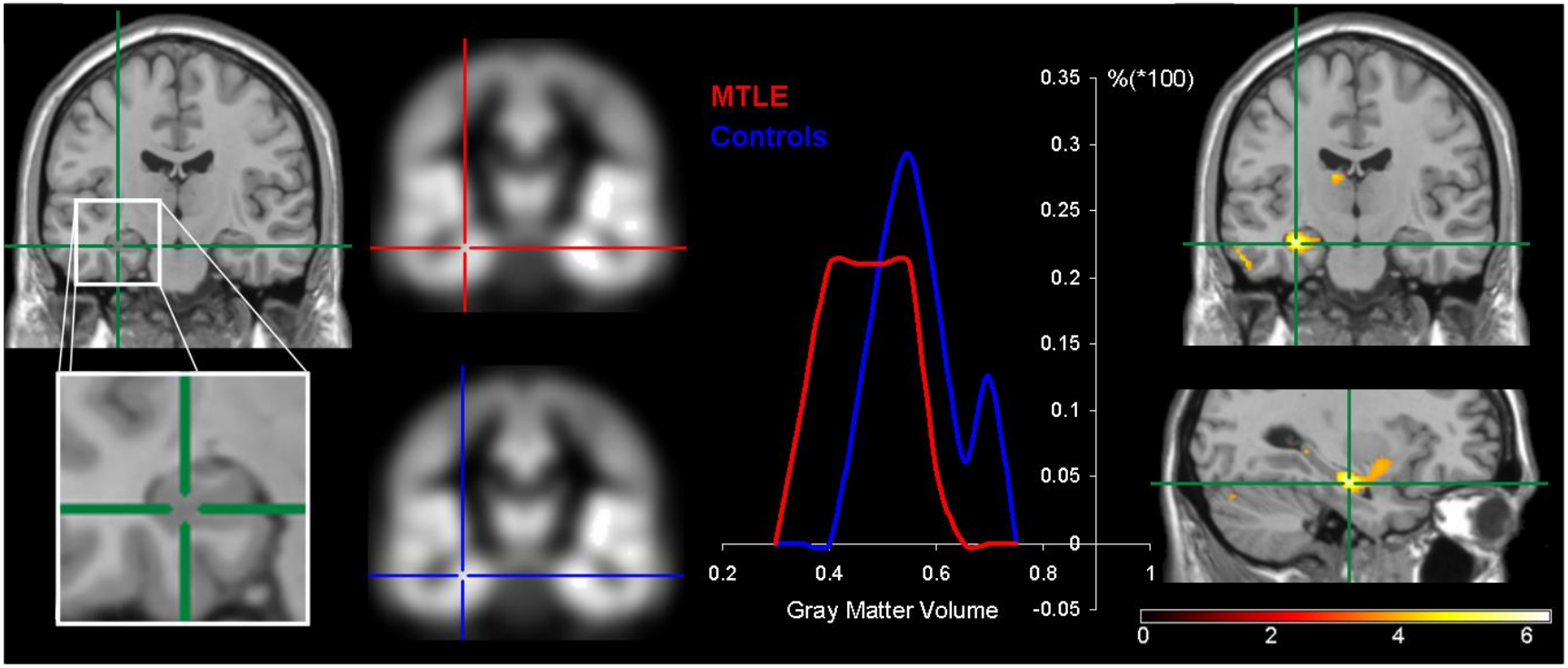
1 mm

1 mm

Voxel Size
(volumetric pixel)

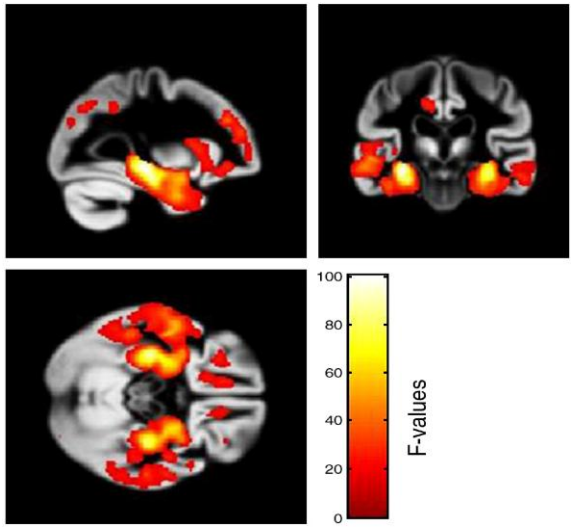

examples

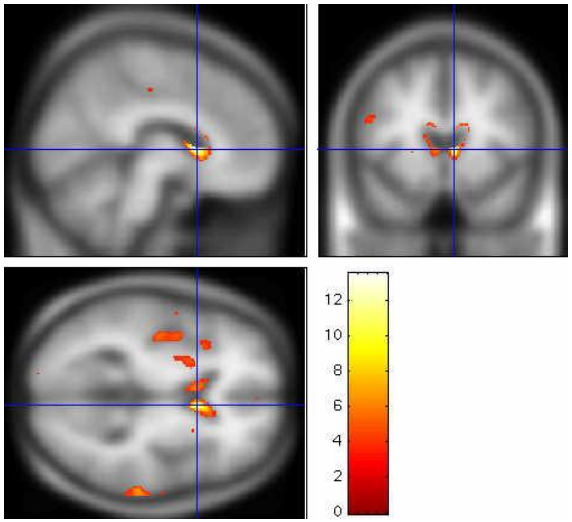
We can statistically analyze gray matter atrophy



Neurodegenerative diseases

- Alzheimer's disease
  - 6 different MR scanner
  - Major software updates
  - 10 years of data acquisition
- Chorea Huntington
  - Pre-symptomatic stage





Stonnington et al., 2008 *Neuroimage*
Thieben et al., 2002 *Brain*

Higher cognitive functions

Science/AAAS | Fleming et al. 329 (5998): 1541 Figure 3 - Mozilla F...

http://www.sciencemag.org/cgi/content-nw/full/329/5998/1541/F3

http://www.sciencemag.org/cgi/content-nw/full/329/5998/1541/F3

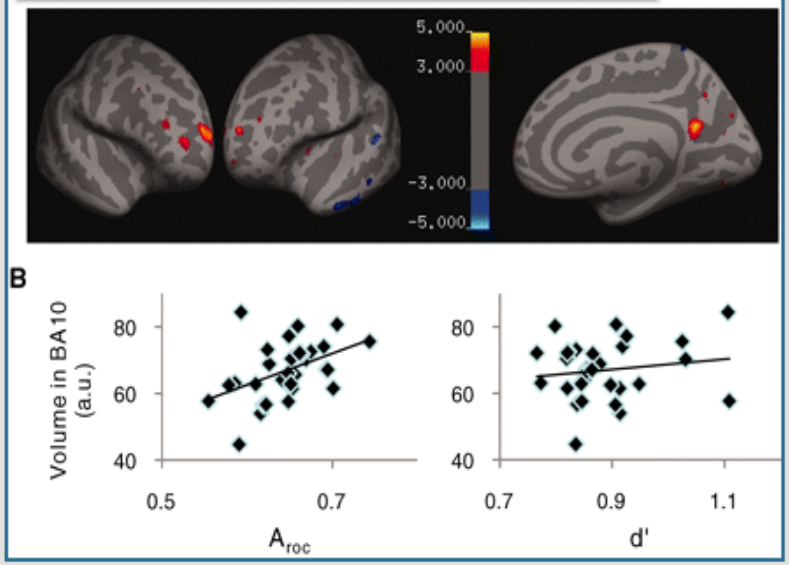


Fig. 3 Gray-matter volume correlated with introspective ability. (**A**) Projection of statistical (T) maps for positive (hot color map: red, orange, yellow) and negative (cool color map: blue) correlations with A_{roc} onto an inflated cortical surface (T1-weighted template, thresholded at $T > 3$ for display purposes). Significant clusters ($P < 0.05$, corrected for multiple comparisons) where metacognitive ability correlated with gray-matter volume (see SOM methods) were found in right anterior PFC (BA 10; positive correlation) and the left inferior temporal gyrus (negative correlation), accompanied by contralateral homologous clusters at $P < 0.001$, uncorrected. (**B**) Plot of gray-matter volume in the right BA 10 cluster against both A_{roc} and d' (see SOM methods for full details), indicating that the correlation with metacognitive ability was independent of task performance. a.u., arbitrary units.

Done

BBC Mobile | News | Sport | Weather | iPlayer | TV

NEWS SCIENCE & ENVIRONMENT

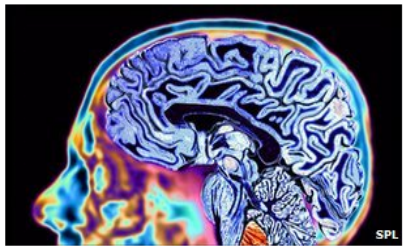
Home | World | UK | England | N. Ireland | Scotland | Wales | Business | Politics | Health | Education | Sci/Envi

17 September 2010 Last updated at 10:52

It's good to think - but not too much, scientists say

By Katie Alcock
Science reporter, BBC News

People who think more about whether they are right have more cells in an area of the brain known as the frontal lobes.



People who think more about their decisions have more brain cells in their frontal lobes

UK scientists, writing in Science, looked at how brain size varied depending on how much people thought about decisions.

But a nationwide survey recently found that some people think too much about life.

These people have poorer memories, and they may also be depressed.

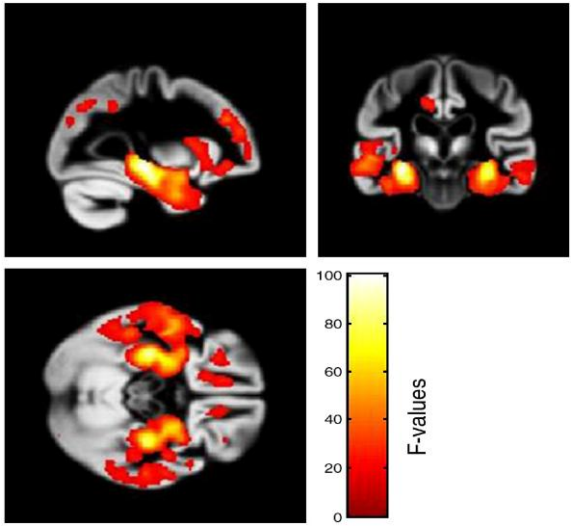
Stephen Fleming, a member of the University College London (UCL) team that carried out the research, said: "Imagine you're on a game show such as 'Who Wants to Be a Millionaire' and you're uncertain of your answer. You can use that knowledge to ask the audience, ask for help."

The London group asked 32 volunteers to make difficult decisions. They had to look at two very similar black and grey pictures and say which one had a lighter spot.

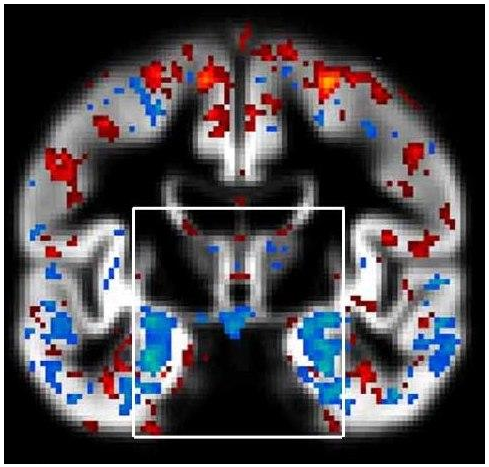
They then had to say just how sure they were of their answer, on a scale of one to six. Although it was hard to tell the difference, the pictures were adjusted to make sure that no-one found the task harder than anyone else.

People who were more sure of their answer had more brain cells in the front-most part of the brain - known as the anterior prefrontal cortex.

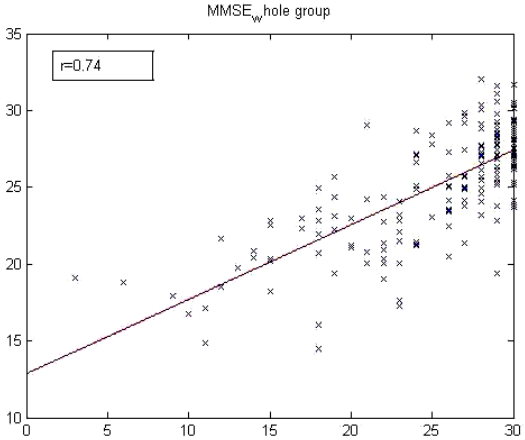
Univariate goes multivariate



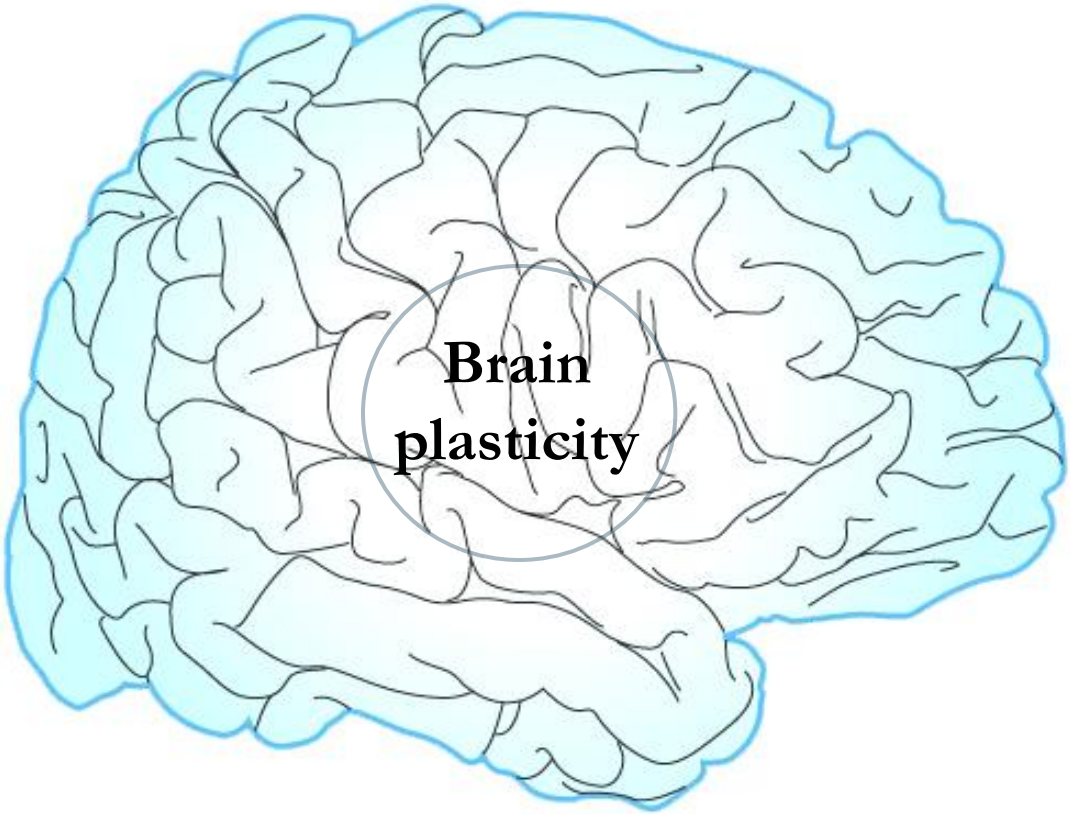
mass-univariate



multivariate

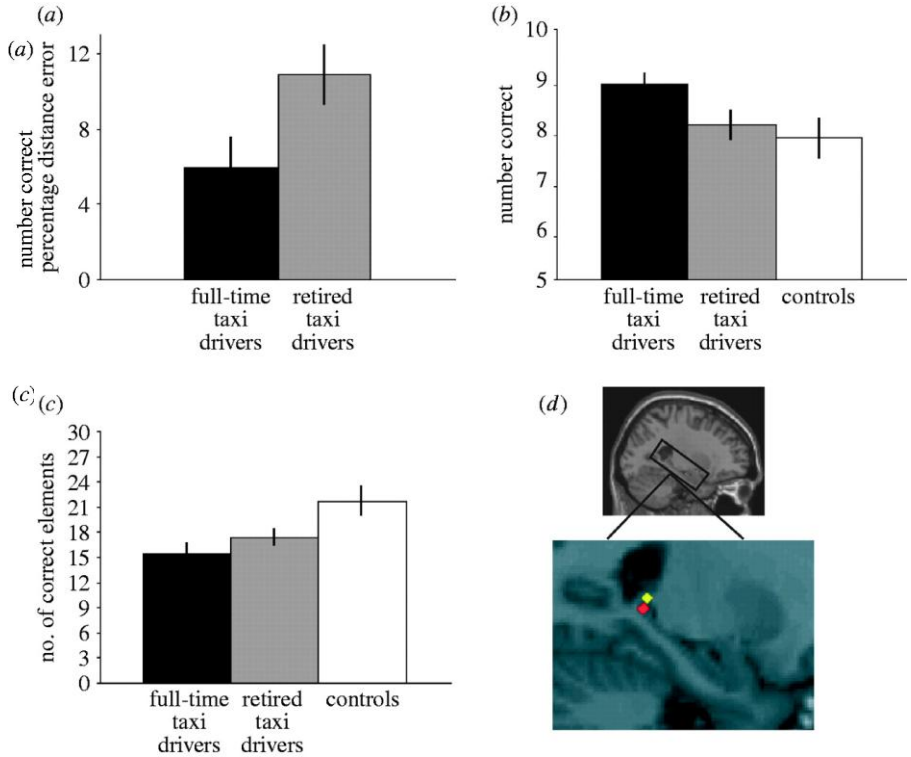


Stonnington et al., 2008 *Neuroimage*
Klöppel et al., 2007 *Brain*

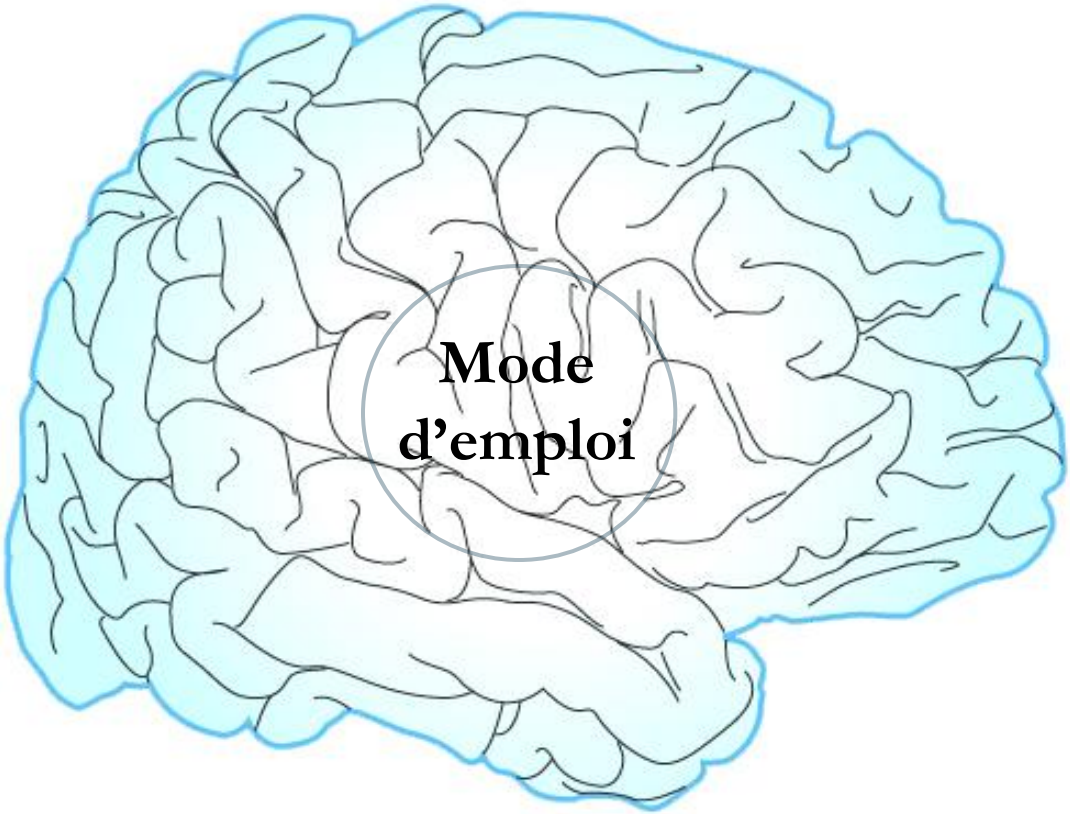

Brain
plasticity

Brain plasticity

- Taxi drivers – London
- Training = „the Knowledge“
- Posterior HC volume increase
- Positive correlation with navigation experience



Maguire et al. 2000 *PNAS*
Woollett et al., 2009 *PTRSB*


Mode
d'emploi

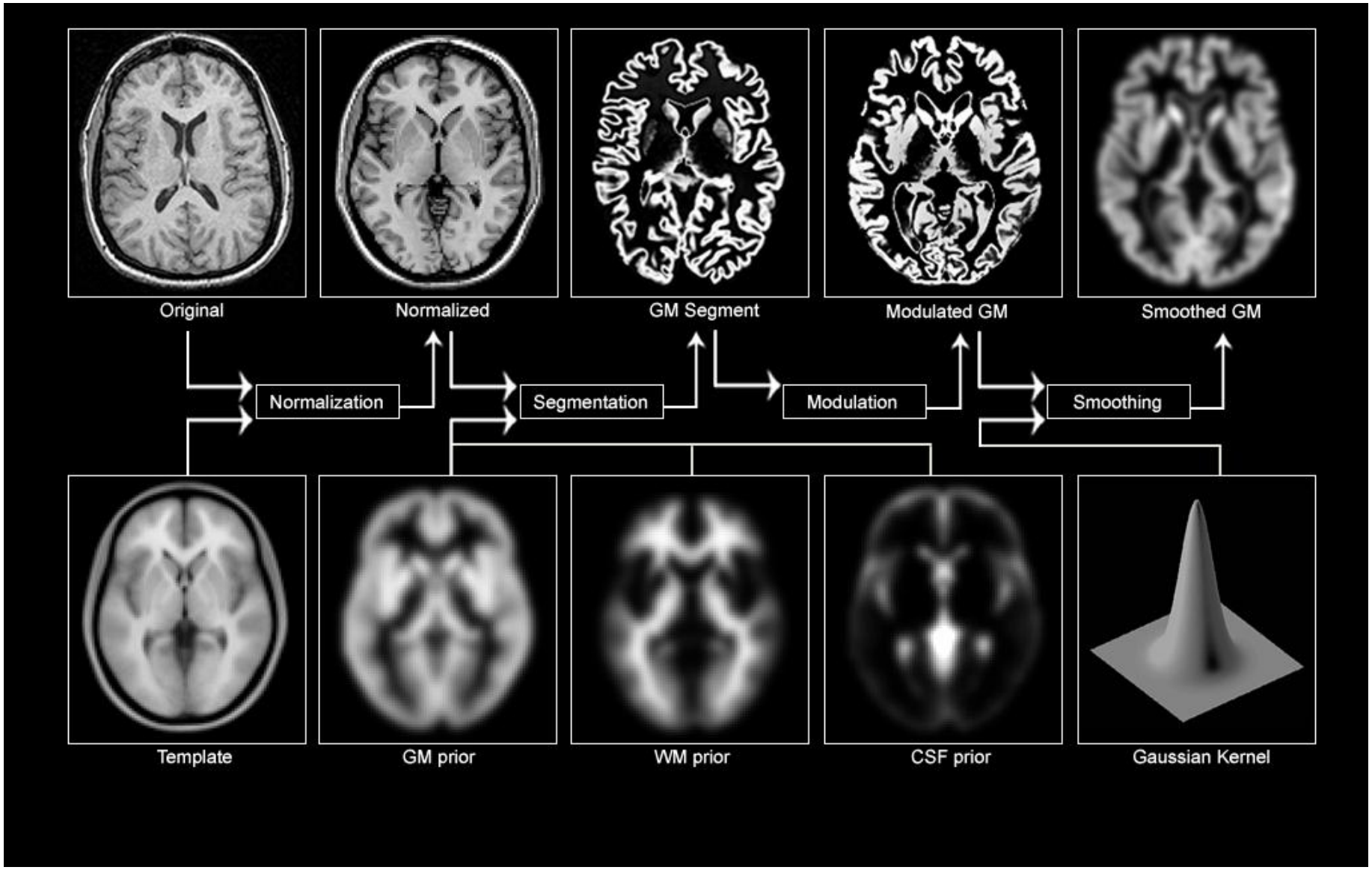
The FIL – home of SPM

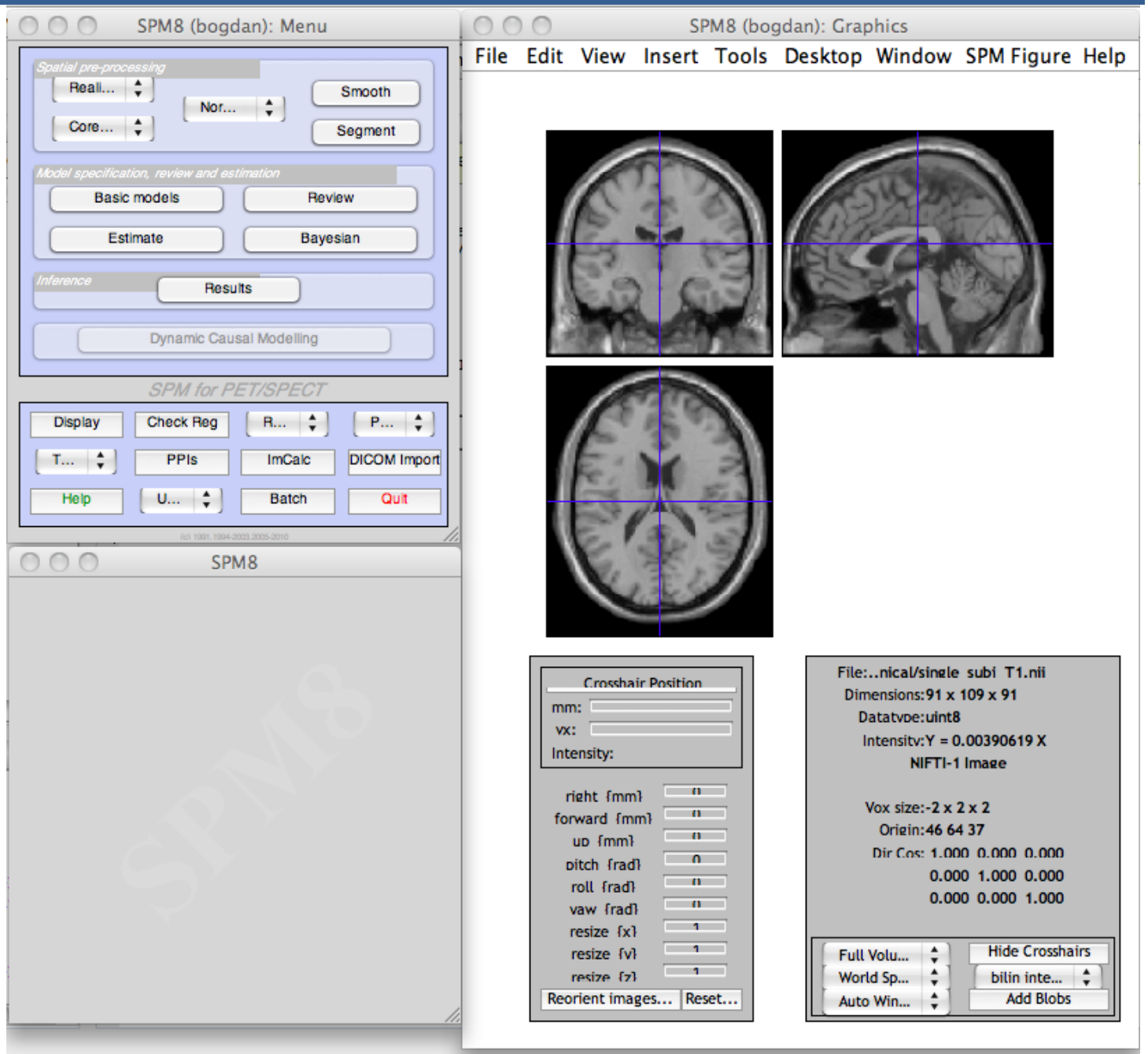
Wellcome Trust Centre for Neuroimaging

http://www.fil.ion.ucl.ac.uk/spm/

https://www.jiscmail.ac.uk/

Data processing




SPM8 (bogdan): Menu
Spatial pre-processing
Reali...
Core...
Nor...
Smooth
Segment
Model specification, review and estimation
Basic models
Review
Estimate
Bayesian
Inference
Results
Dynamic Causal Modelling
SPM for PET/SPECT
Display
Check Reg
R...
P...
T...
PPIs
ImCalc
DICOM Import
Help
U...
Batch
Quit
SPM8
SPM8 (bogdan): Graphics
File Edit View Insert Tools Desktop Window SPM Figure Help
Crosshair Position
mm:
vx:
Intensity:
right [mm]
forward [mm]
up [mm]
pitch [rad]
roll [rad]
yaw [rad]
resize [x]
resize [y]
resize [z]
Reorient images...
Reset...
File:..nical/single_subj_T1.nii
Dimensions:91 x 109 x 91
Datatype:uint8
Intensity:Y = 0.00390619 X
NIFTI-1 Image
Vox size:-2 x 2 x 2
Origin:46 64 37
Dir Cos: 1.000 0.000 0.000
0.000 1.000 0.000
0.000 0.000 1.000
Full Volu...
World Sp...
Auto Win...
Hide Crosshairs
bilin inte...
Add Blobs

VBM preprocessing

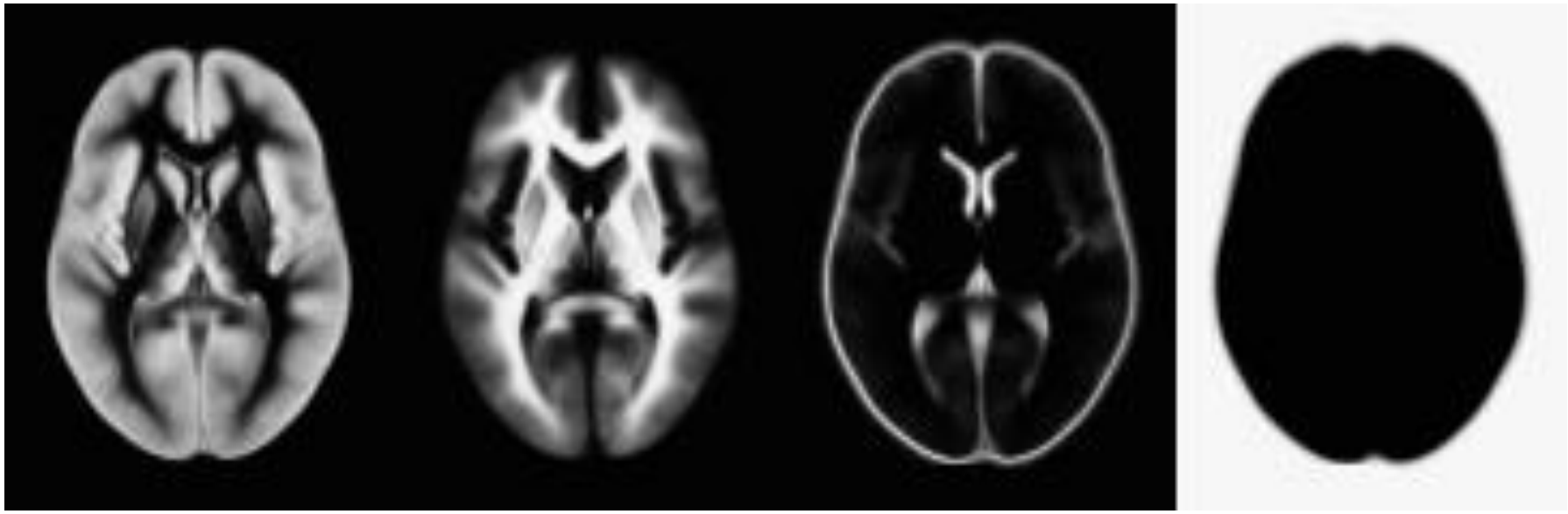
- Unified Segmentation
  - New Segment
  - Smooth
- DARTEL (alternative)
  - New Segment
  - Create Template
  - Normalise to MNI

Segmentation

- High-resolution MRI reveals fine structural detail in the brain, but not all of it reliable or interesting
  - Noise, intensity-inhomogeneity, vasculature, …
- MR Intensity is usually not quantitatively meaningful (in the same way that e.g. CT is)
- Regional volumes of the three main tissue types: gray matter, white matter and CSF, are well-defined and potentially very interesting

Segmentation

- Uses information from tissue probability maps (TPMs) and the intensities of voxels in the image to work out the probability of a voxel being GM, WM or CSF



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.

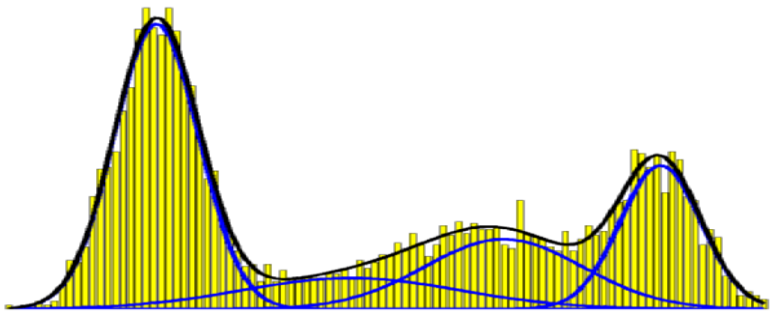
Segmentation

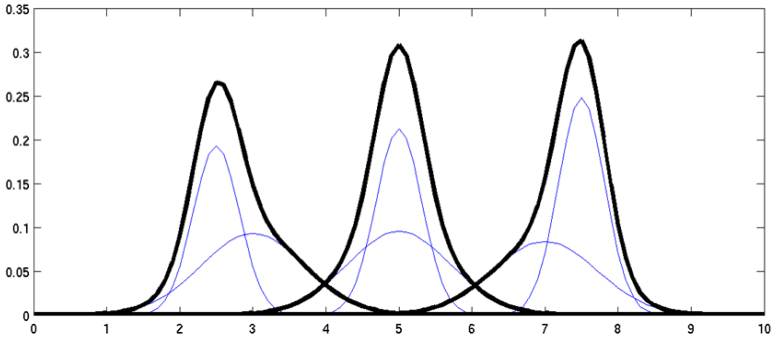
- VBM segments image into three tissue types: grey matter, white matter and CSF.
  - Typically done on T1 scans (best spatial resolution, good grey-white contrast).
  - Only three tissue types: will not cope with large lesions.
  - Probability map: each voxel has a 0..100% chance of being one of the 3 tissue types.

T_1 gray white CSF

Segmentation

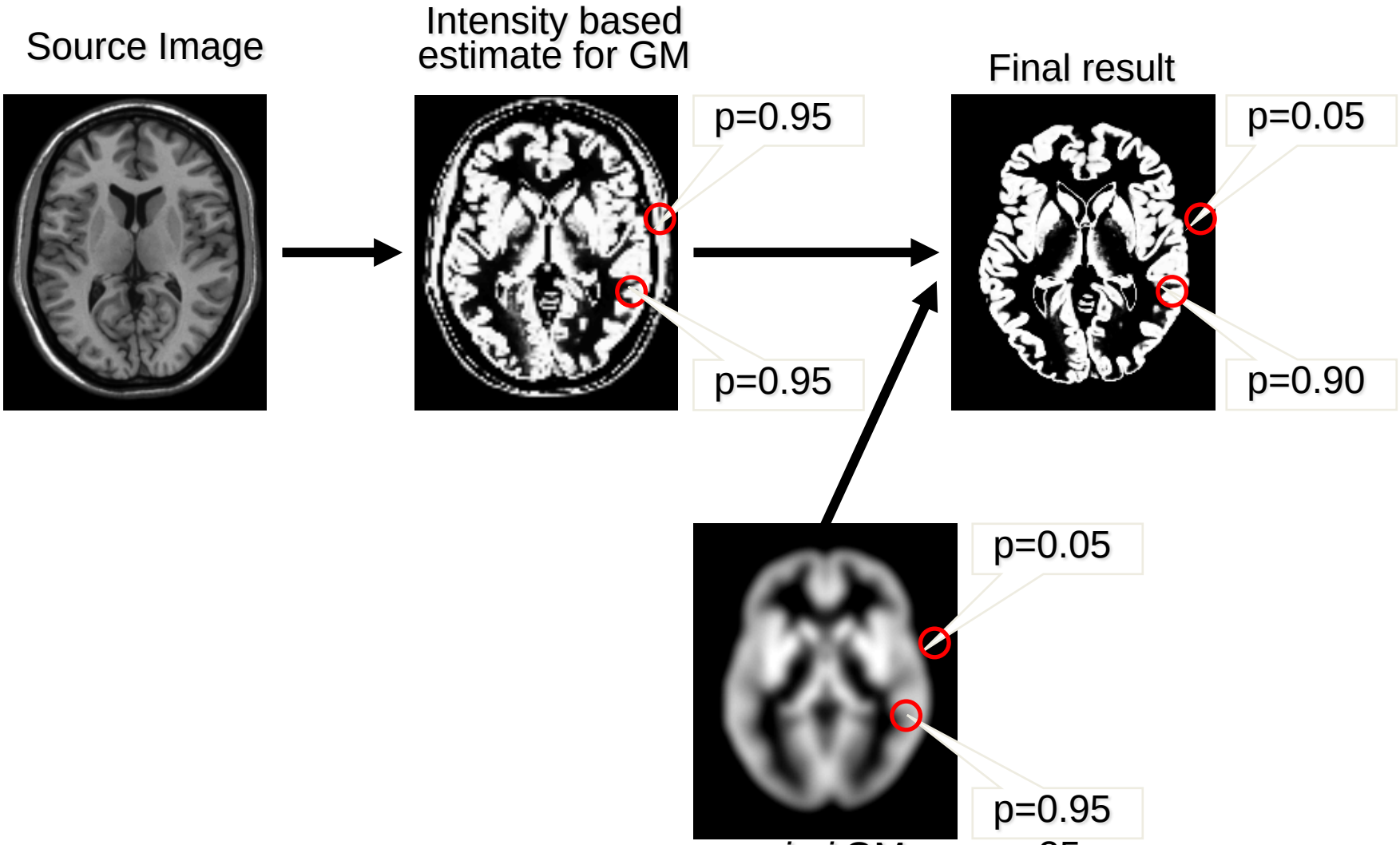
- Intensities are modelled by a Gaussian Mixture Model (aka Mixture Of Gaussians)
- With a specified number of components
- Parameterised by means, variances and mixing proportions (prior probabilities for components)





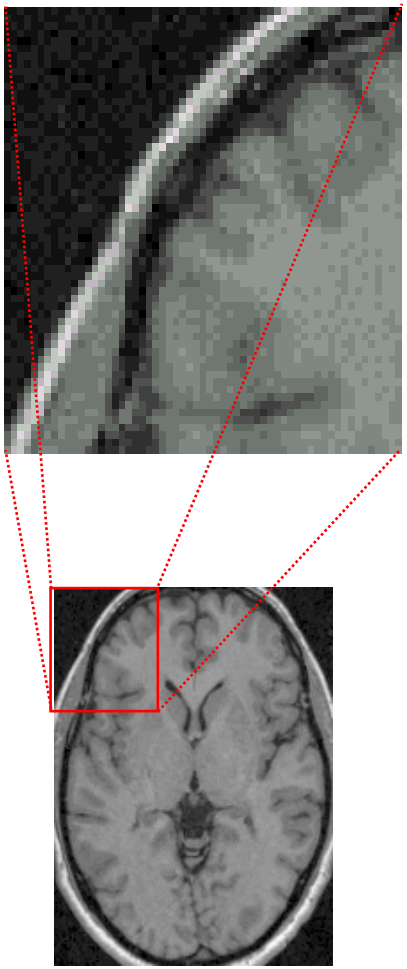
- Multiple MoG components per tissue class allow non-Gaussian distributions to be modelled
  - E.g. accounting for partial volume effects
  - Or possibility of deep GM differing from cortical GM

Segmentation



Segmentation clean-up

T_1

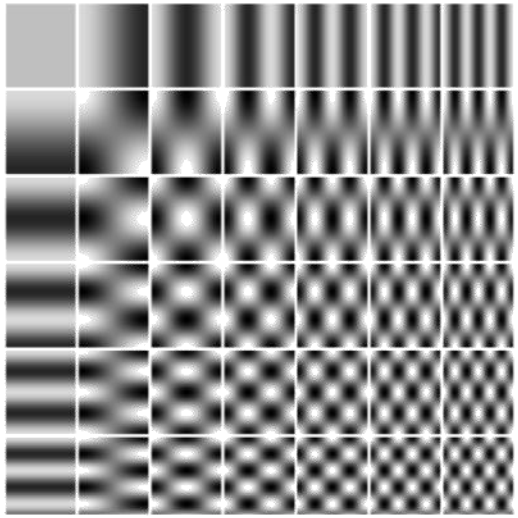


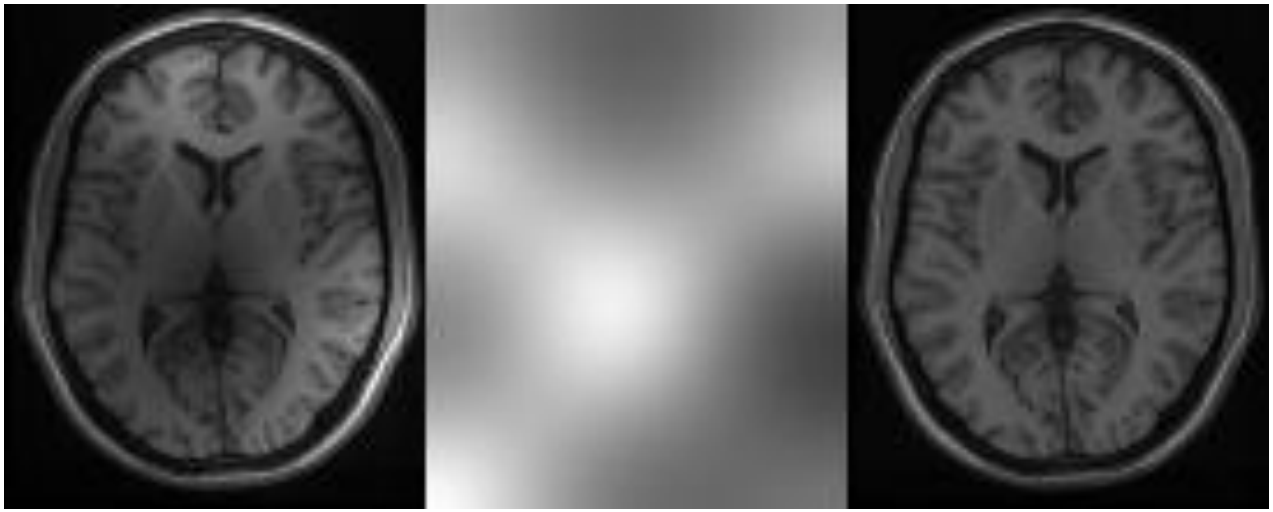
masked

mask

Inhomogeneity correction

- MR Images are corrupted by smoothly varying intensity **inhomogeneity** caused by magnetic field imperfections and subject-field interactions
  - Would make intensity distribution spatially variable
- A smooth intensity **correction** can be modelled by a linear combination of DCT basis functions

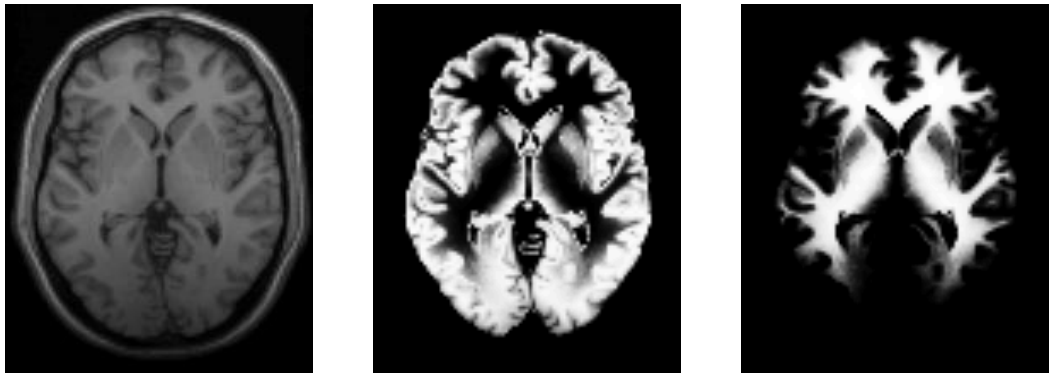


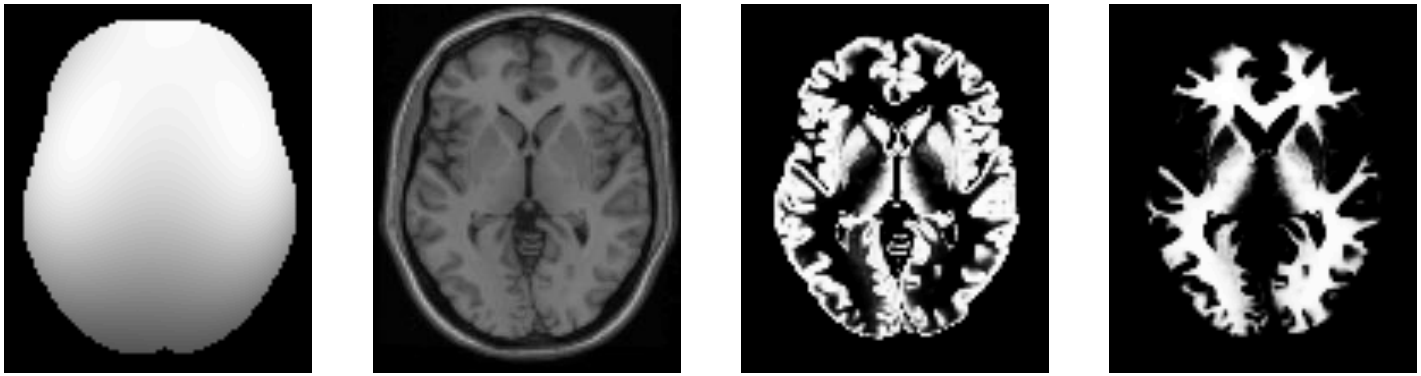


Inhomogeneity correction

- Field inhomogeneity will disrupt intensity based segmentation
- Bias correction required

no correction





Estimate T_1 GM WM

The generative model

- Keeps doing these steps iteratively until the objective function is minimised

- Results in images that are segmented, bias-corrected, and registered into standard space

Summary of the unified model

- SPM5/SPM8 implements a **generative model**
  - Principled Bayesian probabilistic formulation
- Combines deformable tissue probability maps with Gaussian mixture model segmentation
  - The inverse of the transformation that aligns the TPMs can be used to normalise the original image
- Bias correction is included within the model

VBM preprocessing

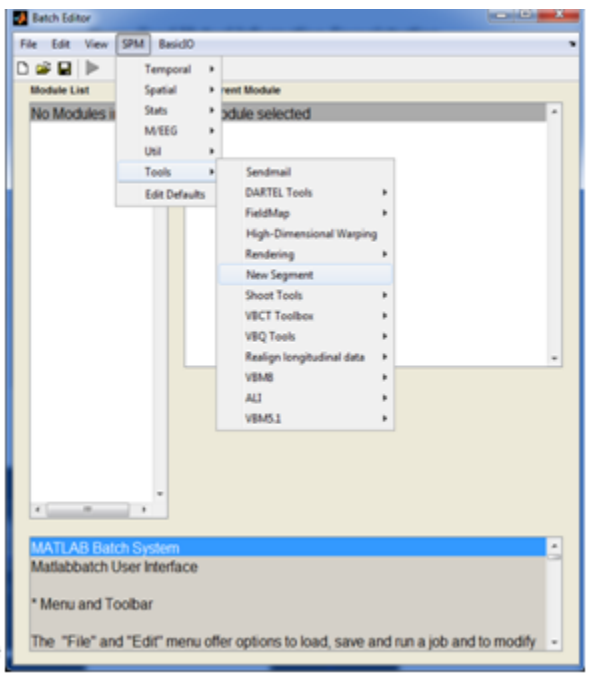
New Segment

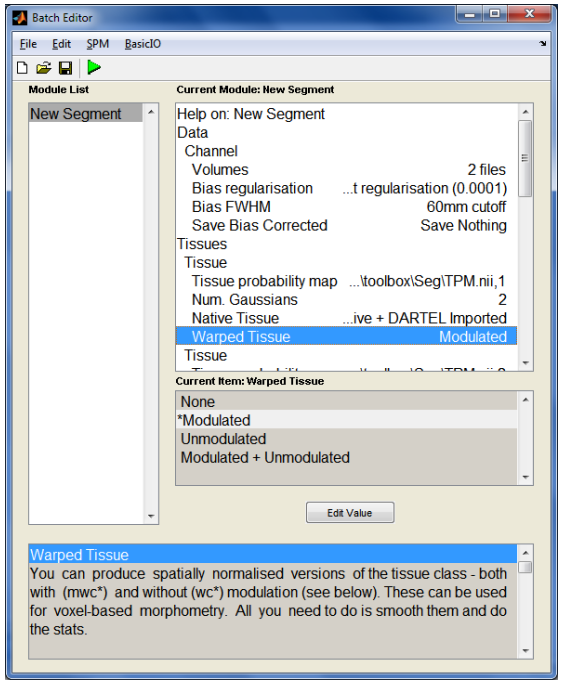
- Select: Batch→SPM→Tools→New Segment

- Volumes to Segment (Data:Channel:Volumes) – select structural MRI scans

Optional: for DARTEL pre-processing select Tissues:Tissue{1}:Native Tissue: **Native+DARTEL Imported**

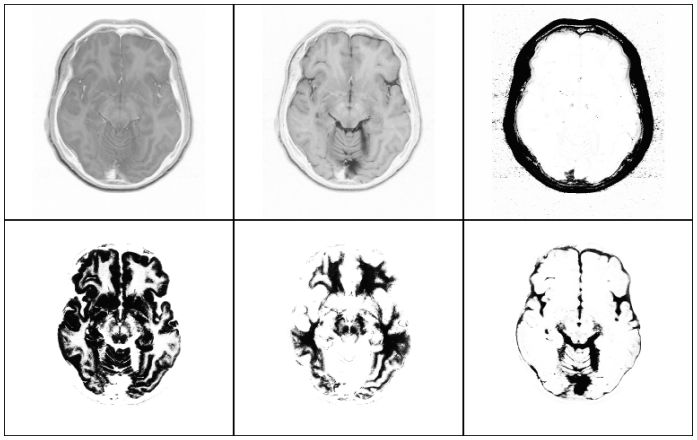
- To obtain spatially normalized modulated (preserve amount of signal) images select option: Tissues:Tissue{1}:Warped Tissue: **Modulated**





New segmentation

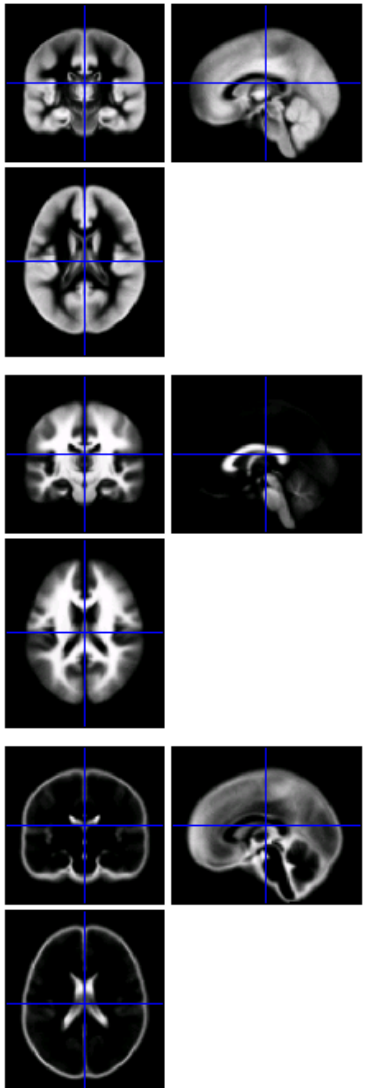
- An extended work-in-progress algorithm
- Multi-spectral $\mu_k \rightarrow \boldsymbol{\mu}_k, \sigma_k \rightarrow \boldsymbol{\sigma}_k, \rho \rightarrow \{\rho_s\}$
- New TPMs including different tissues
  - Reduces problems in non-brain tissue



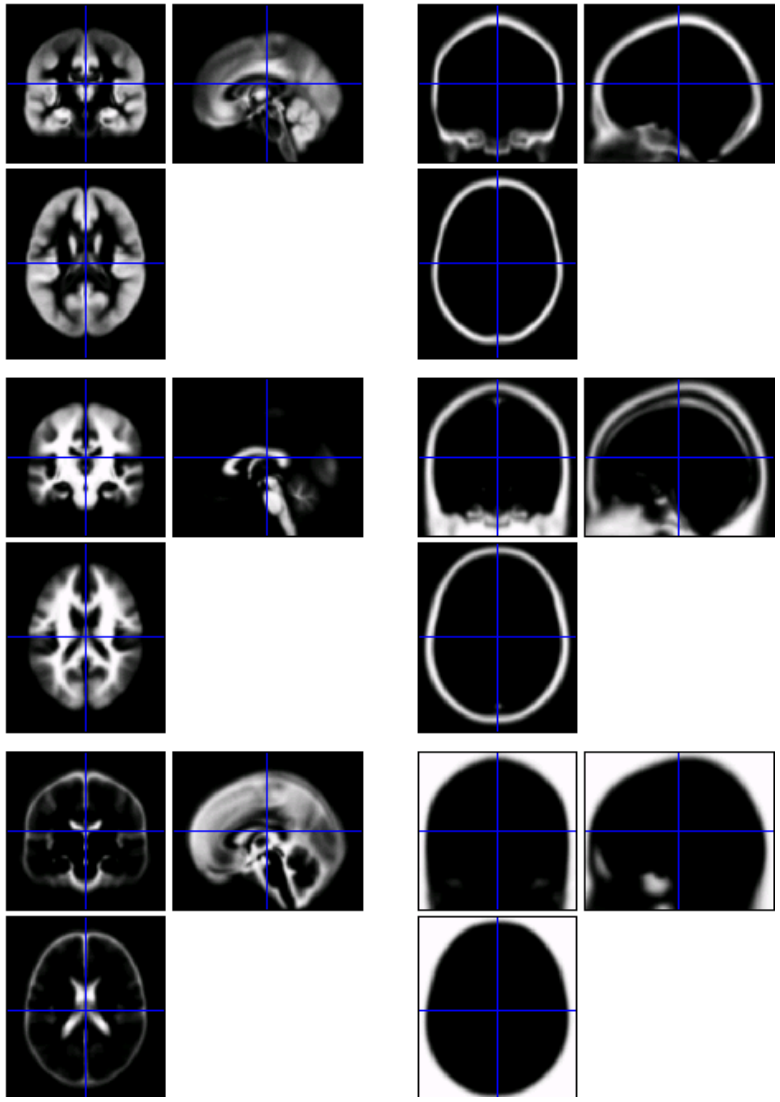
- New more flexible warping of TPMs
  - More precise and more "sharp/contrasty" results

New segmentation – tissue probability maps

Segment button

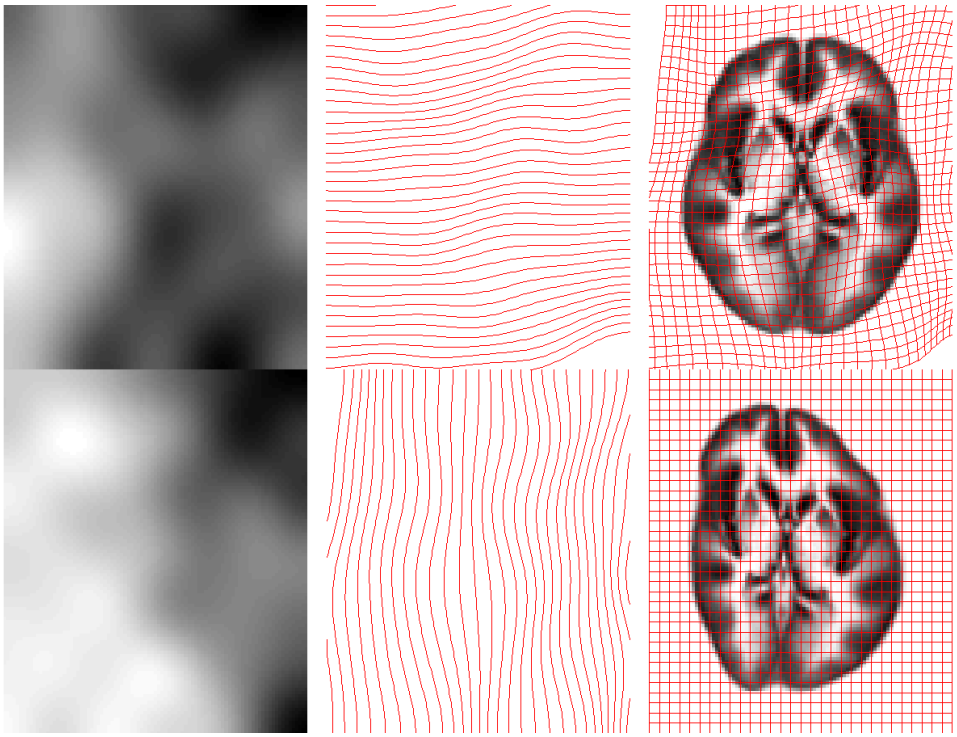


New Seg Toolbox



Normalisation

- The tissue probability maps (which are in standard space) are warped to match the image
  - this gives parameters for registering the image into standard space later



Diffeomorphic registration

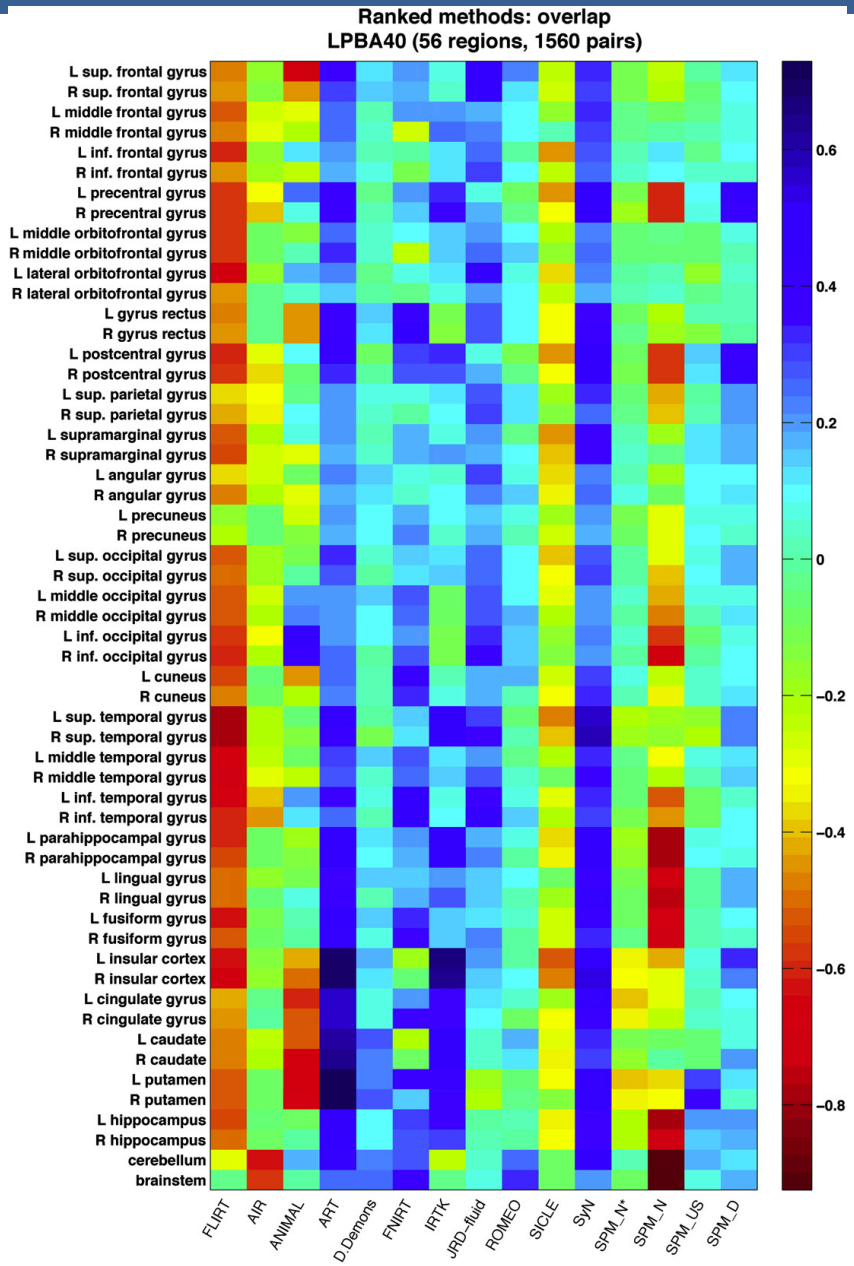
- VBM is crucially dependent on registration performance
  - The limited flexibility of DCT normalisation has been criticised
  - Inverse transformations are useful, but not always well-defined
  - More flexible registration requires careful modelling and regularisation (prior belief about reasonable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

Ashburner (2007) NeuroImage 38:95-113

DARTEL

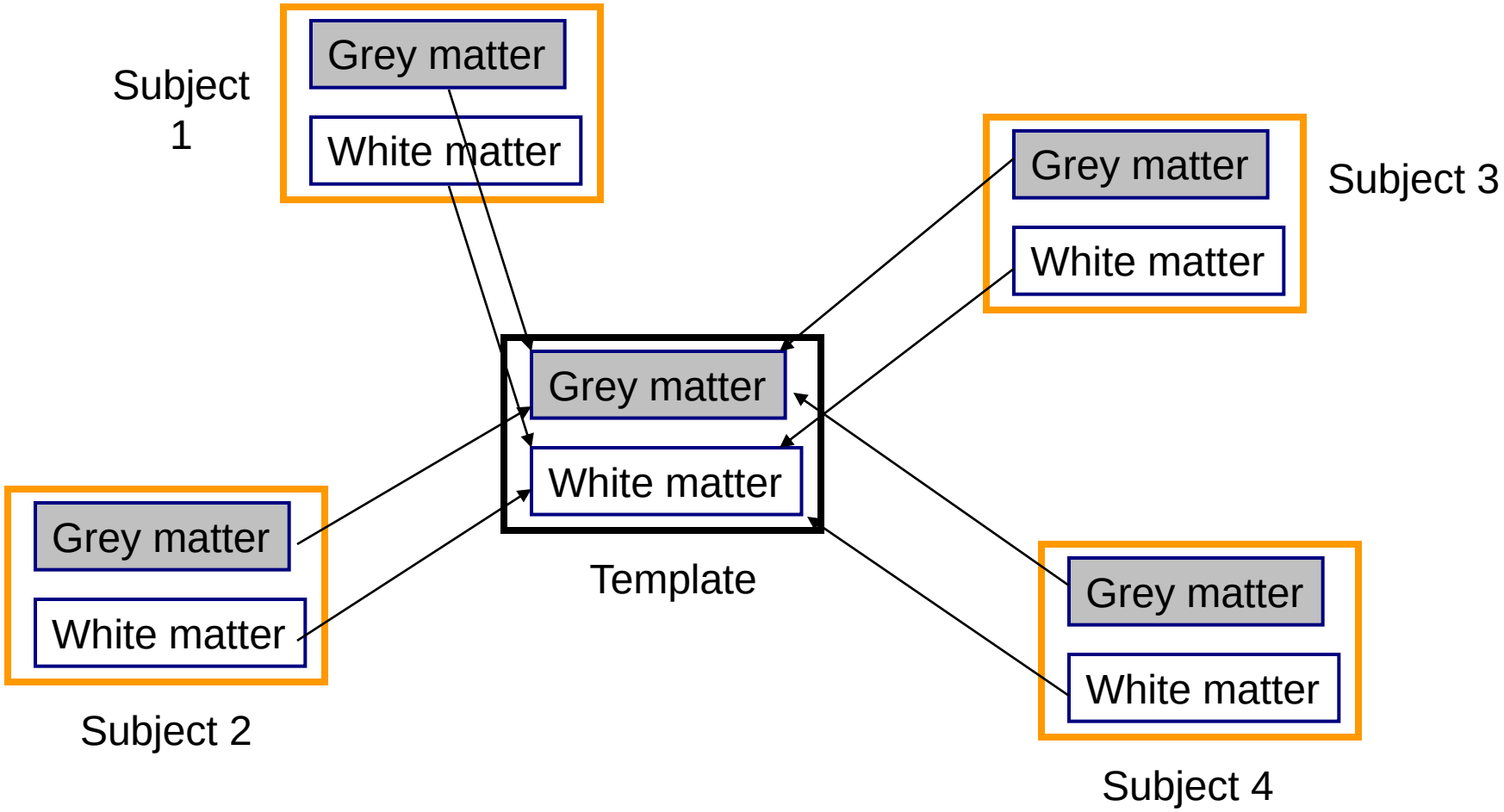
- Recent papers comparing different approaches have favoured more flexible methods
- DARTEL usually outperforms DCT normalisation
  - Also comparable to the best algorithms from other software packages (though note that DARTEL and others have many tunable parameters...)
- Klein et al. (2009) is a particularly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

DARTEL

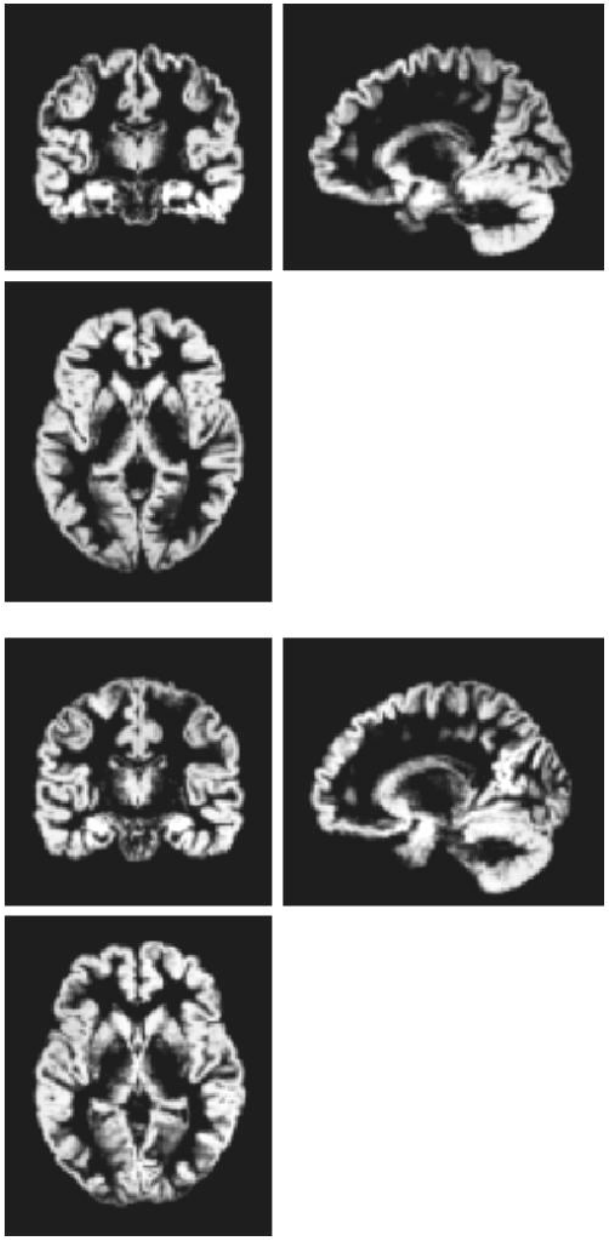


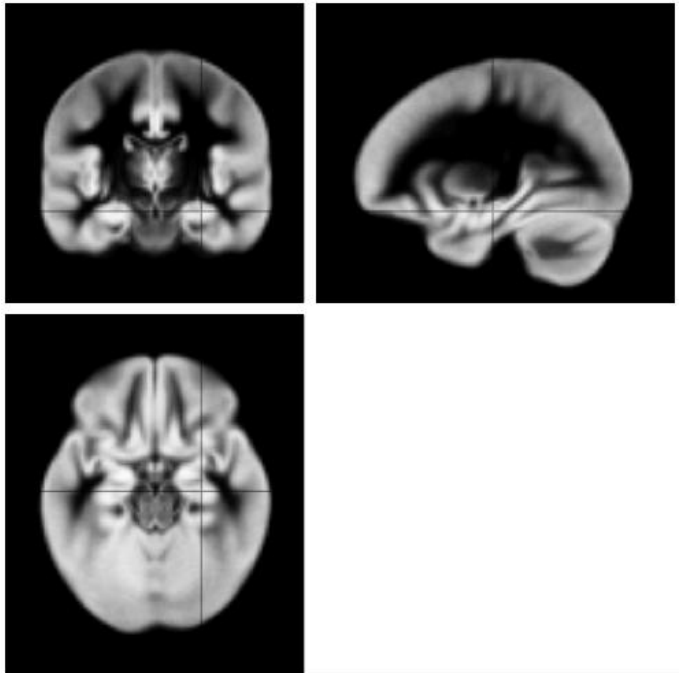
Klein et al., 2009 *Neuroimage*

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

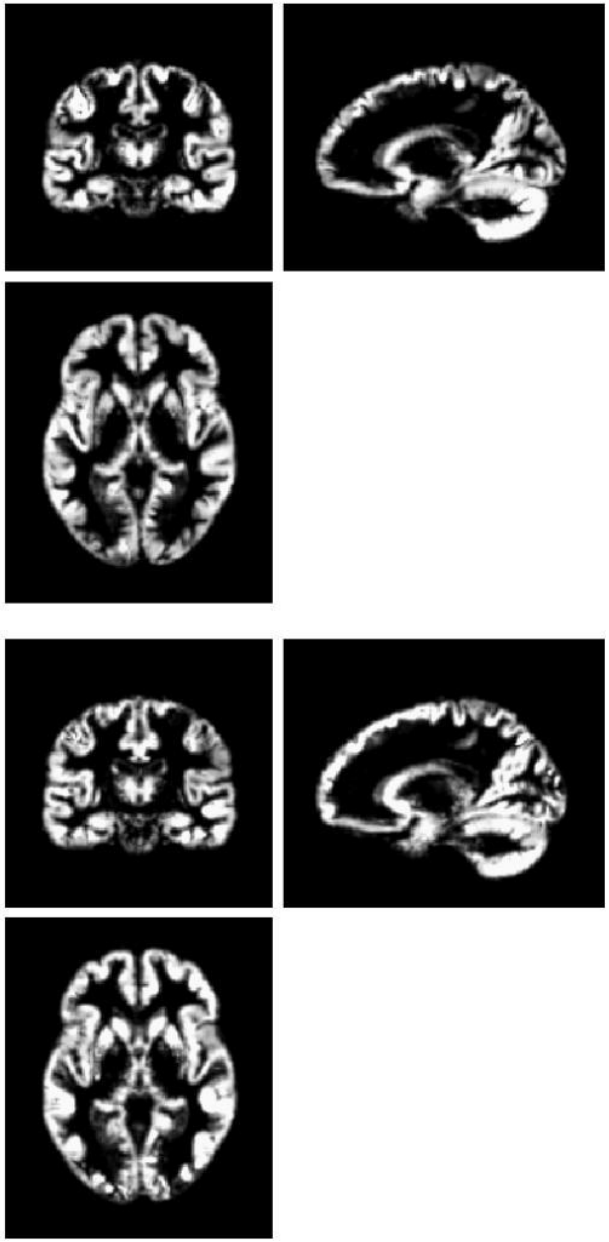


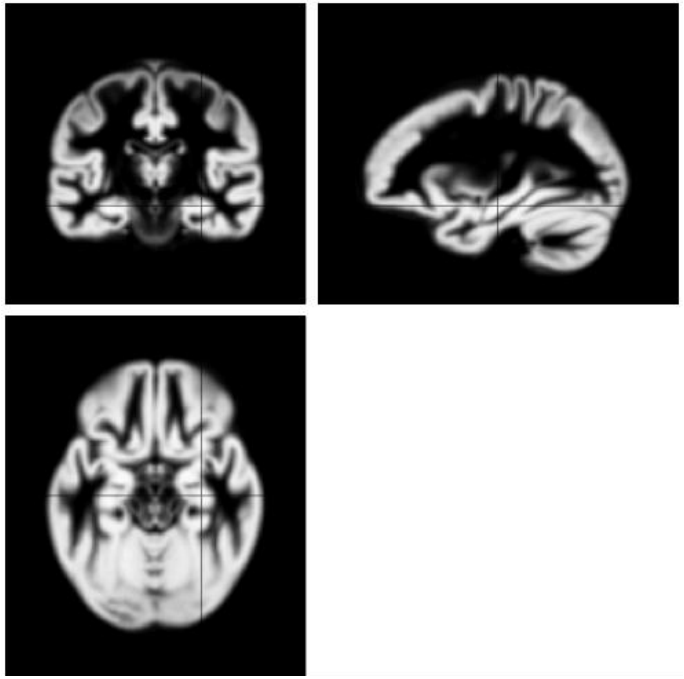
Unified segmentation





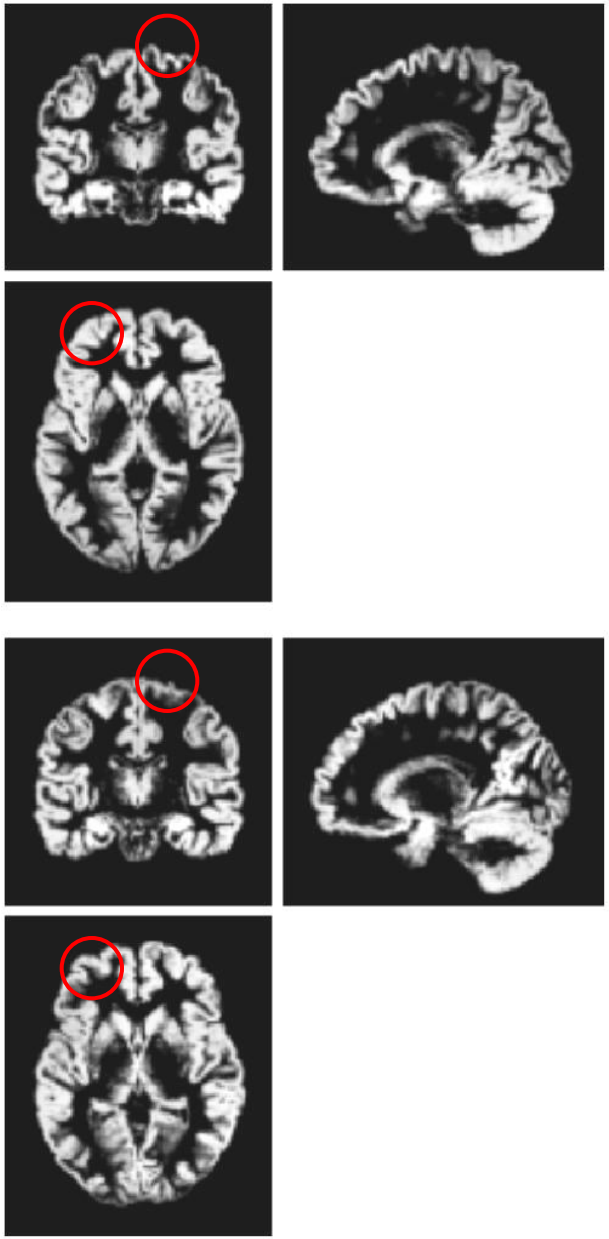
DARTEL

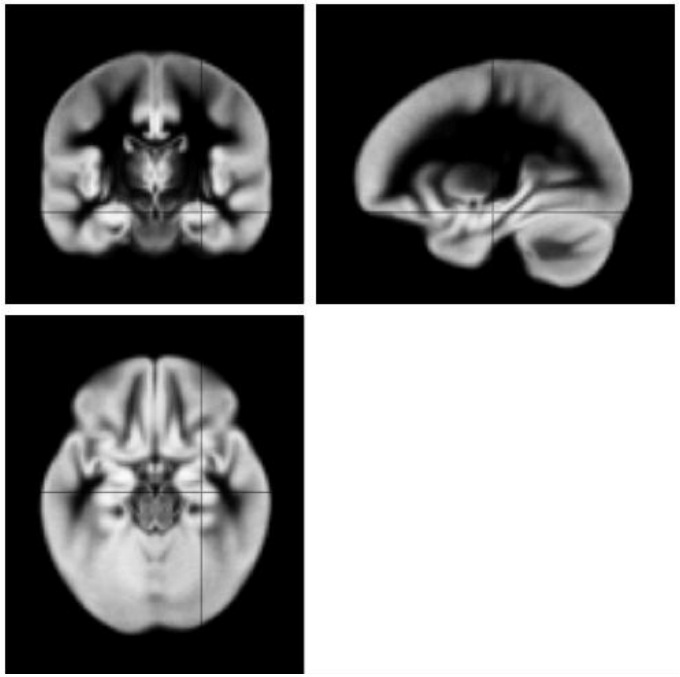




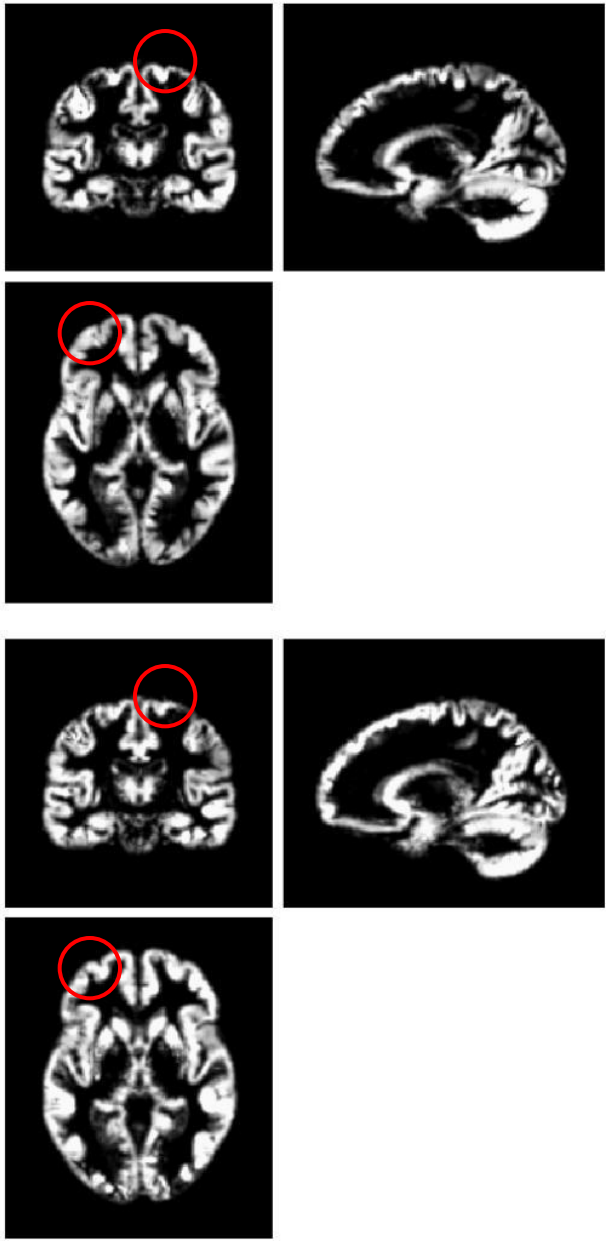
Ashburner 2007 *Neuroimage*

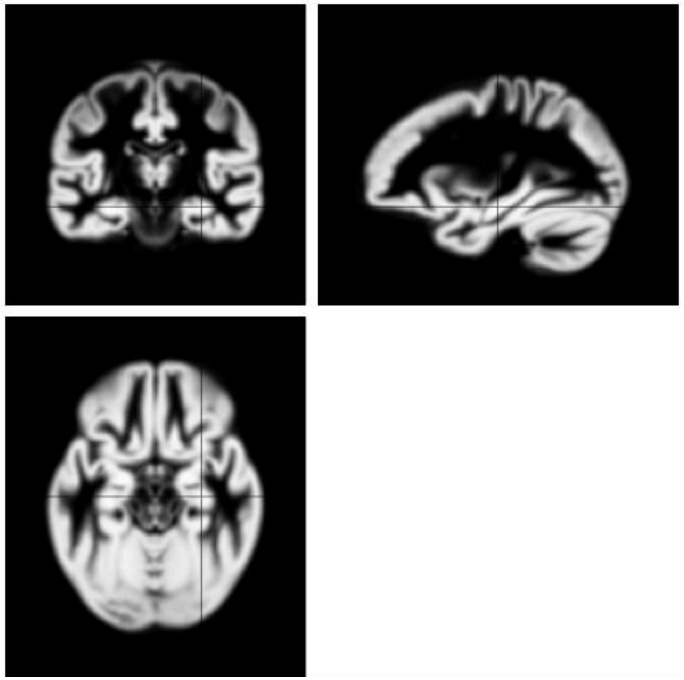
Unified segmentation





DARTEL





Ashburner 2007 *Neuroimage*

Limitations

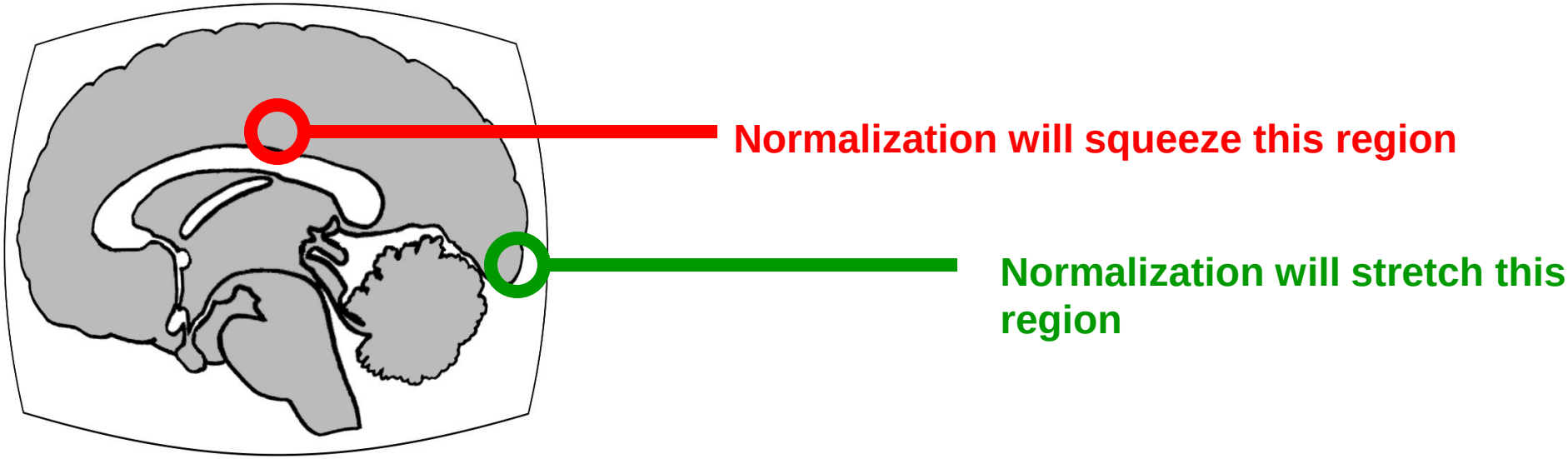
- Assumes that the brain consists of only the tissues modelled by the TPMs
  - No allowance for lesions (stroke, tumours, etc)
- Prior probability model is based on relatively young and healthy brains
  - Less appropriate for subjects outside this population
- Needs reasonable quality images to work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

VBM subtleties

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

Modulation

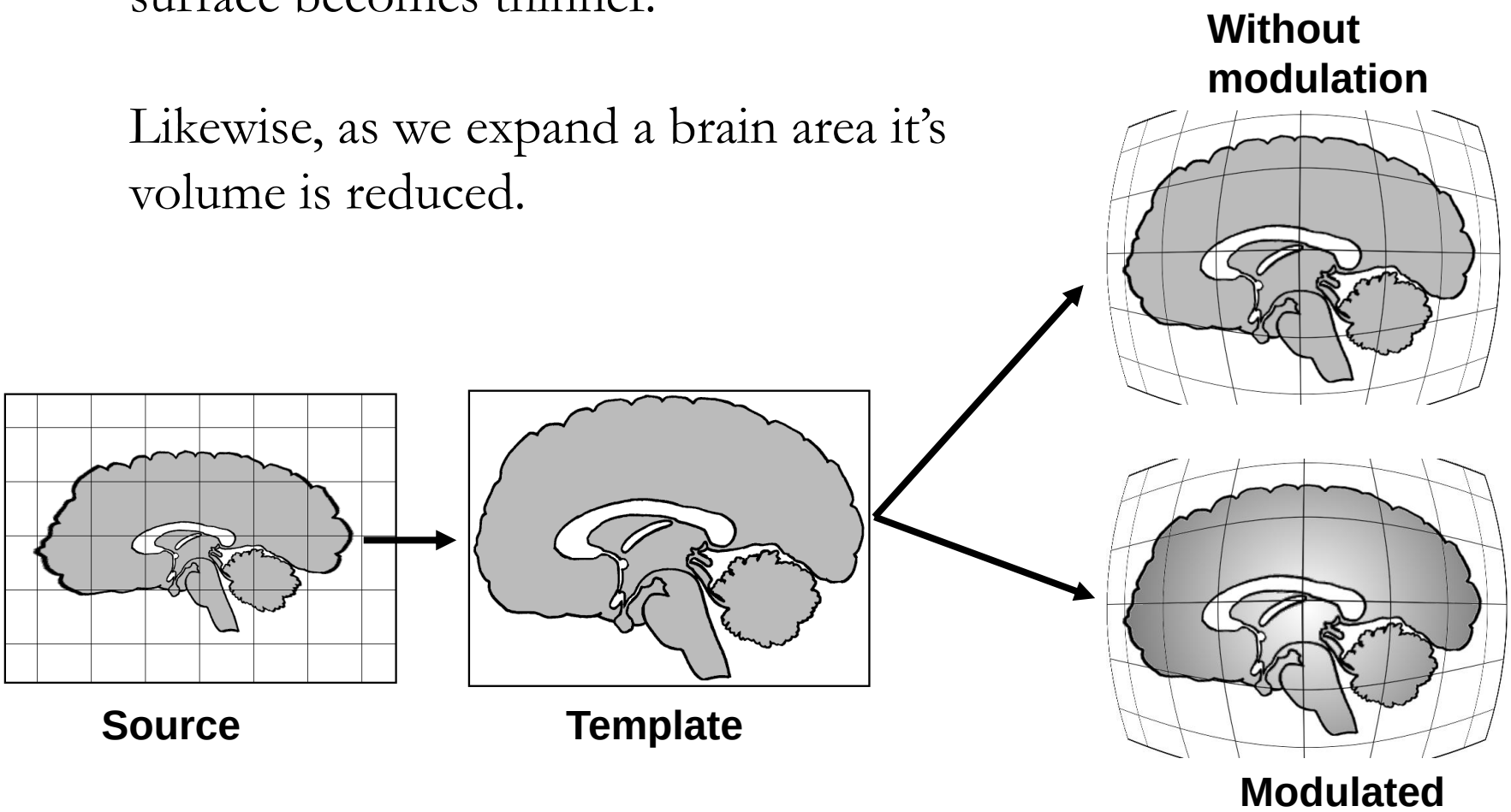
- If someone has atrophy, normalisation will stretch grey matter to make brain match healthy template
- This will reduce ability to detect differences



Modulation

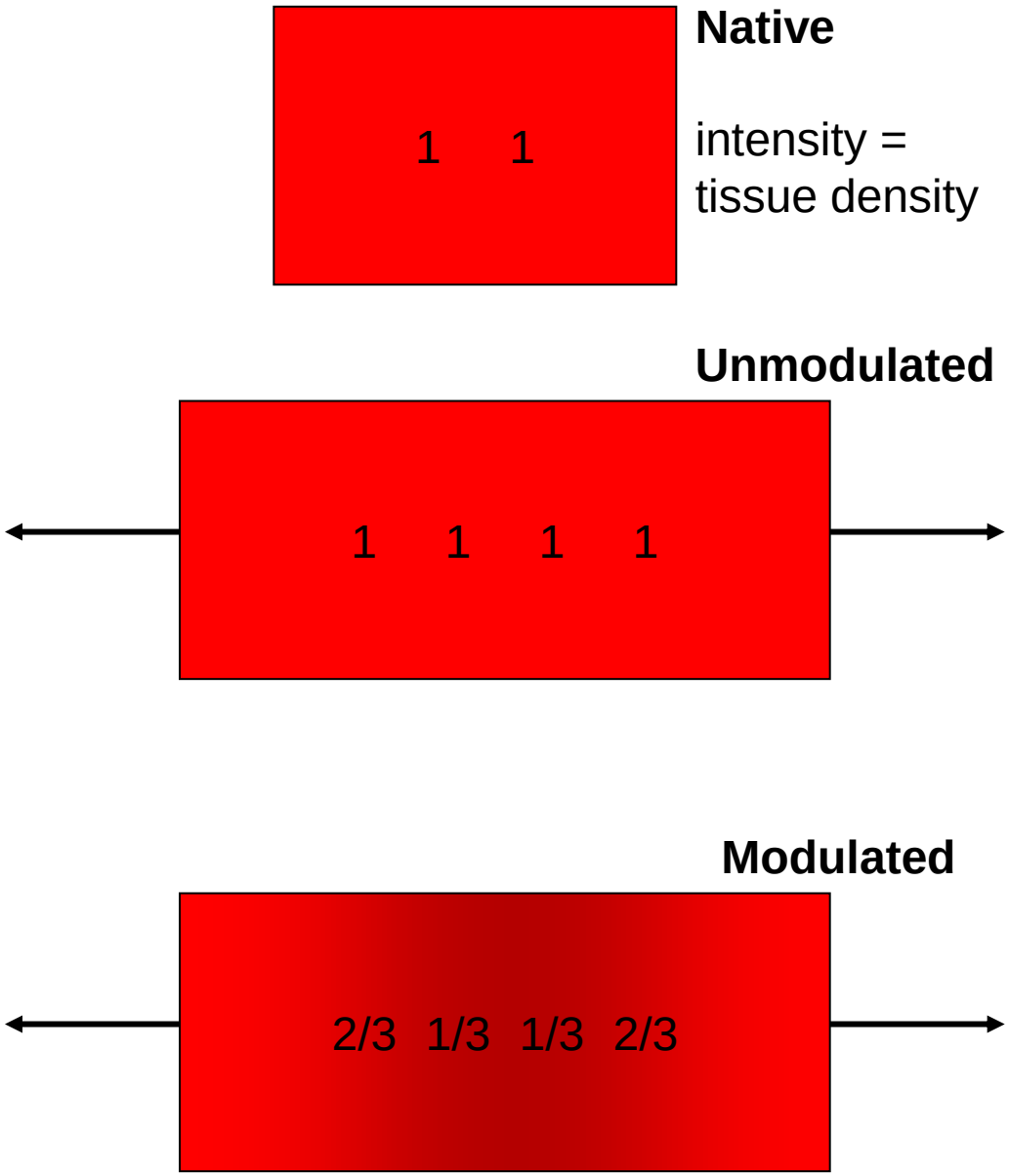
Analogy: as we blow up a balloon, the surface becomes thinner.

Likewise, as we expand a brain area it's volume is reduced.



Modulation

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



VBM subtleties

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

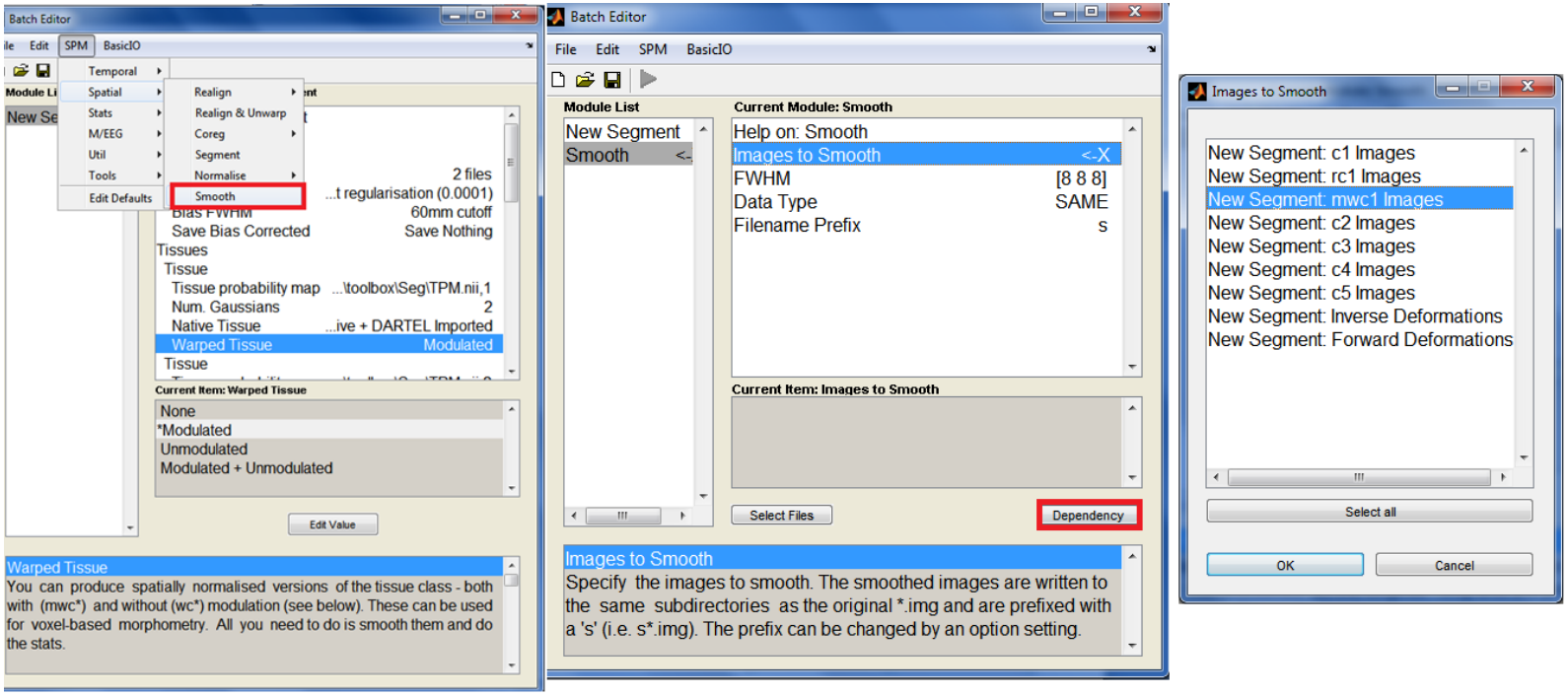
VBM preprocessing

Smooth

- To get smoothed images select: SPM→Spatial→Smooth

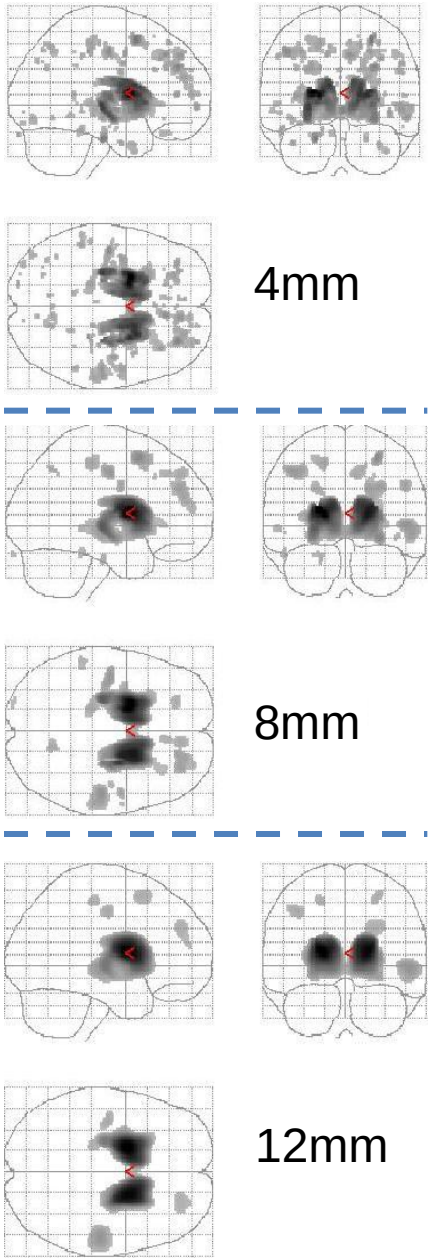
- Click on "Images to Smooth"→ Select "Dependency"(bottom right)→Select "New Segment: mwc1 Images"

- Click on "Run batch" (green button)



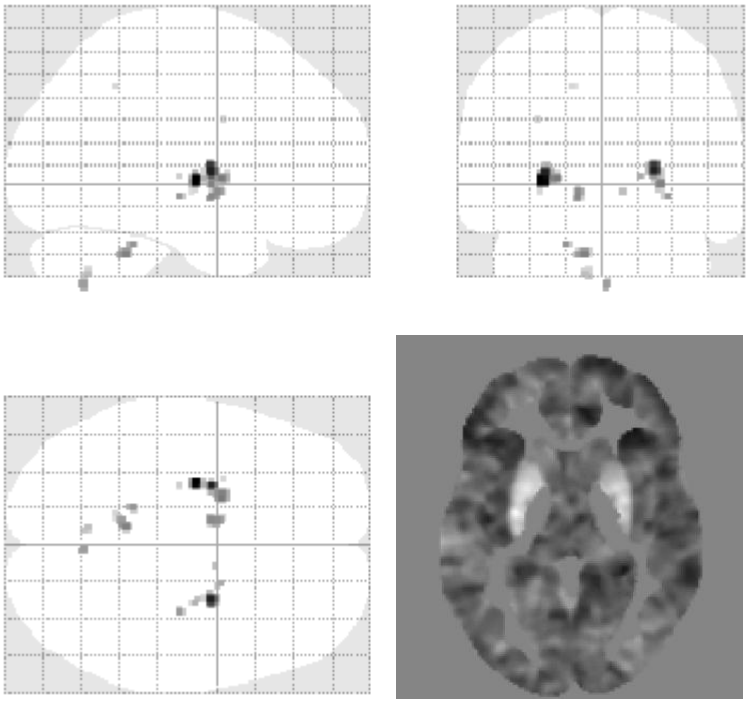
Smoothing

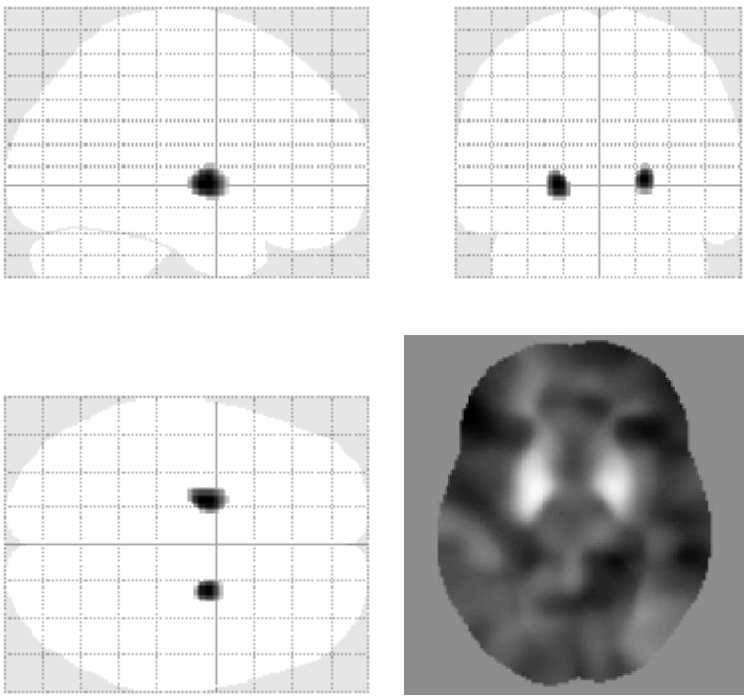
- Smoothing kernel - should match the shape and size of the expected effect
- Benefits
  - more "Gaussian distribution" of the data
  - Smooth out incorrect registration
- RFT requires FWHM > 3 voxels



Smoothing

- Between 7 and 14mm is probably best
  - (lower is okay with better registration, e.g. DARTEL)





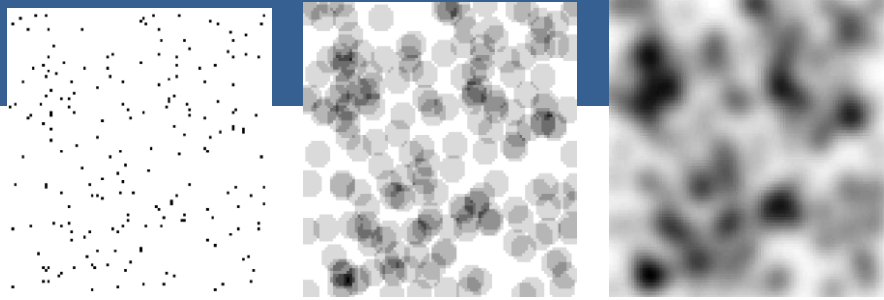
Smoothing

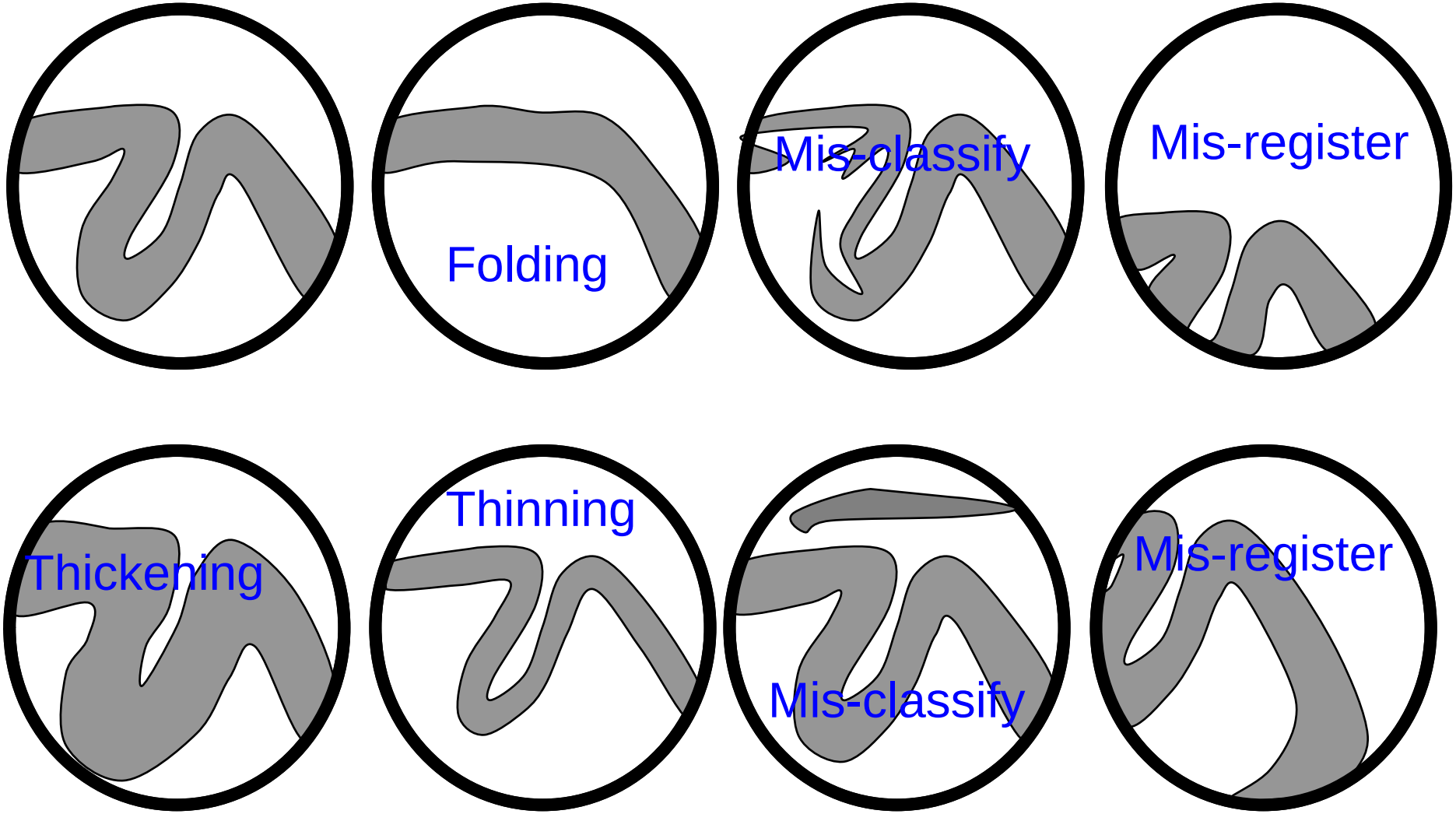
- The analysis will be most sensitive to effects that match the shape and size of the kernel
- The data will be more Gaussian and closer to a continuous random field for larger kernels
- Results will be rough and noise-like if too little smoothing is used
- Too much will lead to distributed, indistinct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

VBM subtleties

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

Interpretation





Interpretation

- Microstructural changes could cause intensity changes
  - T1-weighted imaging not quantitative (cf. T1-quant, MT, etc.)
  - Still potential explanation of findings (or lack thereof)
- Complicated phenomenon…
  - Increased T1w intensity in cortex =>
    - Lower GM prob, prob shifted to WM class
    - Higher GM prob, prob taken from CSF class
- Significant differences still *generally* interpretable

VBM subtleties

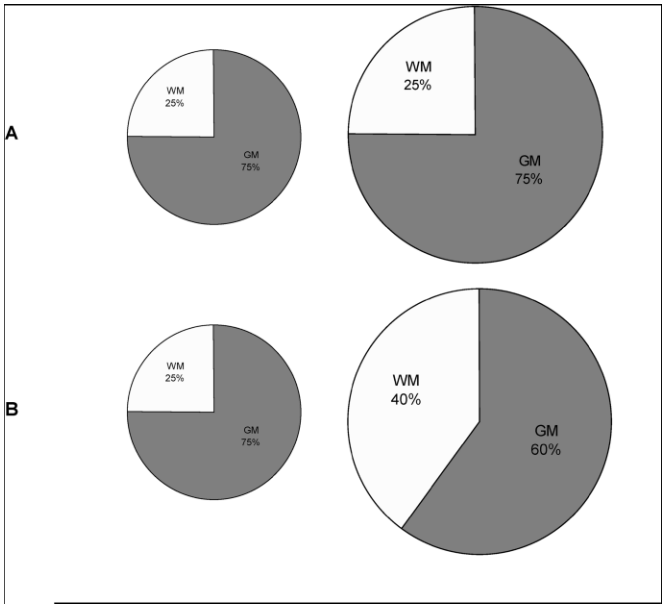
- Whether to modulate
- How much to smooth
- Interpreting results
- **Adjusting for total GM or Intracranial Volume**
- Limitations of linear correlation
- Statistical validity

Global normalisation

- Total intracranial volume integrates GM, WM and CSF, or attempts to measure the skull-volume directly
  - Not sensitive to global reduction of GM+WM (cancelled out by CSF expansion – skull is fixed!)
- Correcting for TIV in VBM statistics **may** give more powerful and/or more interpretable results
  - See also http://dx.doi.org/10.1016/j.neuroimage.2010.06.025

Global normalisation

- **Generic issue** in neuroimaging
  - to ensure that the analysis identifies regionally specific "non-global" effects
- Changes in dimension or shape as a function of size
  - "global" model
  - "mosaic" model

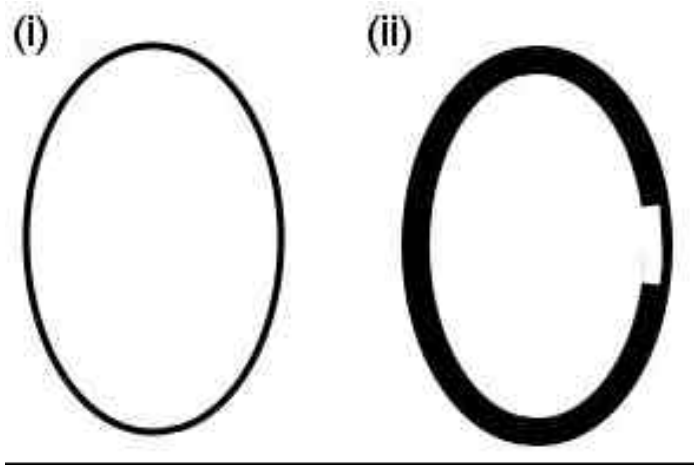


	Total Brain	White Matter	Gray Matter
A	Increase	Proportional increase	Proportional increase
B	Increase	Disproportionate increase	Relative decrease

Figure from: *Adjustment for Whole Brain…* O'Brian et al, 2006

Global normalisation

- Shape is really a multivariate concept
  - Dependencies among volumes in different regions
- SPM is mass univariate
  - Combining voxel-wise information with "global" integrated tissue volume provides a compromise



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

Below: The two "cortices" on the right both have equal volume…

Figures from: *Voxel-based morphometry of the human brain*… Mechelli et al, 2005

Summary

- VBM uses the machinery of SPM to localise patterns in regional volumetric variation
- The procedure involves
  - Unified tissue segmentation (Gaussian mixture modelling with bias correction and spatially registered priors)
  - Spatial normalisation using Dartel, with preservation of volume
  - Smoothing
  - SPM analysis
    - Typically with covariates for age, gender, perhaps TIV and/or total GM
- Interpretation is challenging, and caution is advised
  - But Science papers and BBC News articles await!

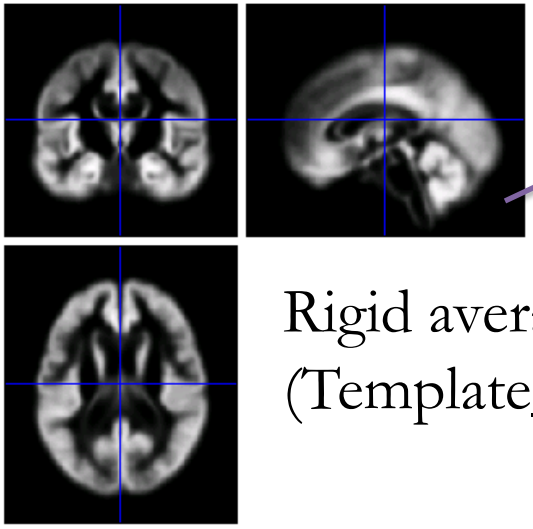
References

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

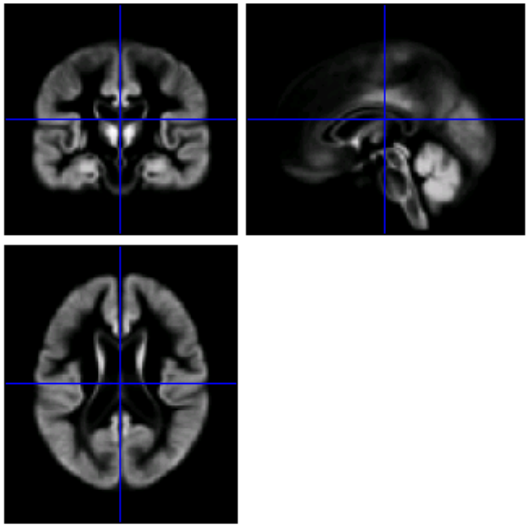
Thank you

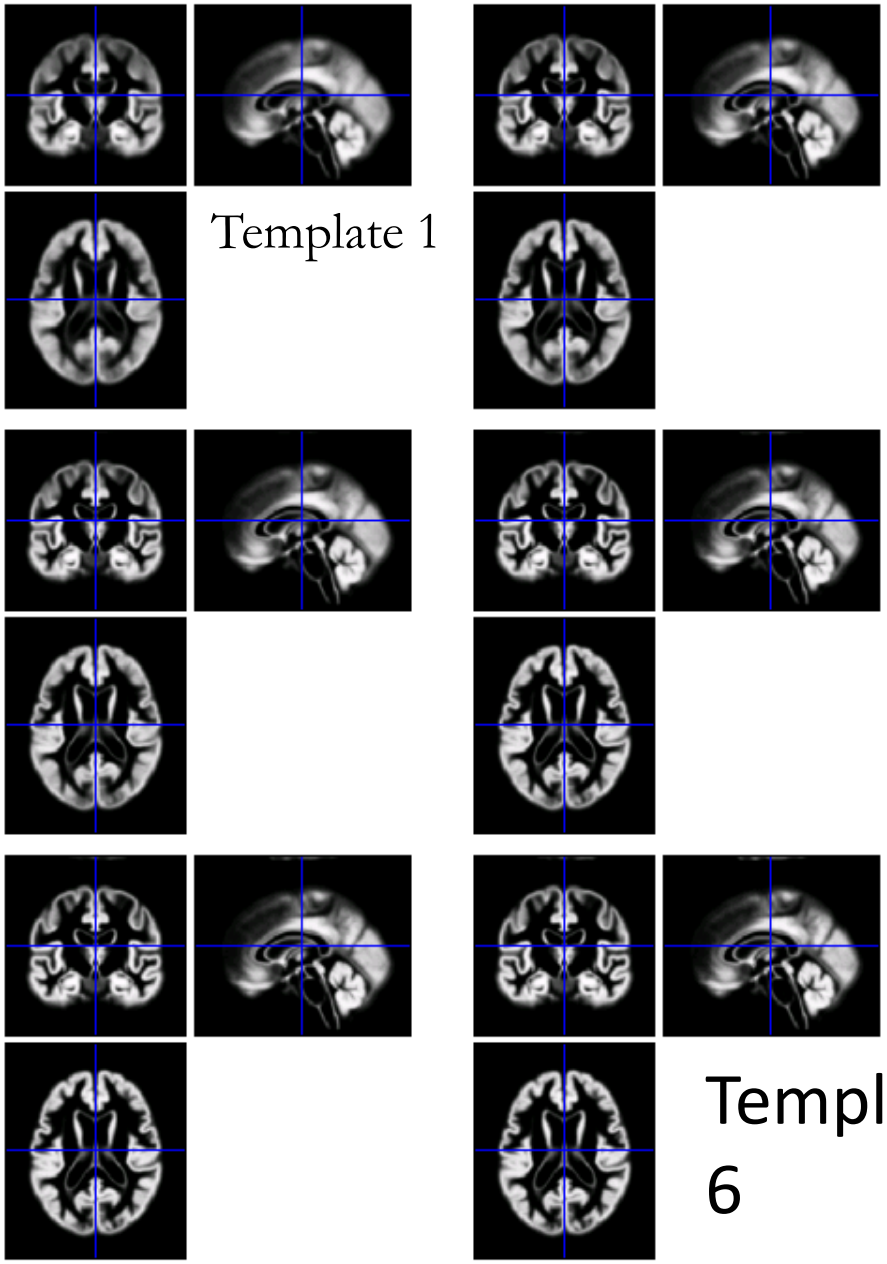
LREN

Laboratoire de Recherche en Neuro-Imagerie



Rigid average
(Template_0)



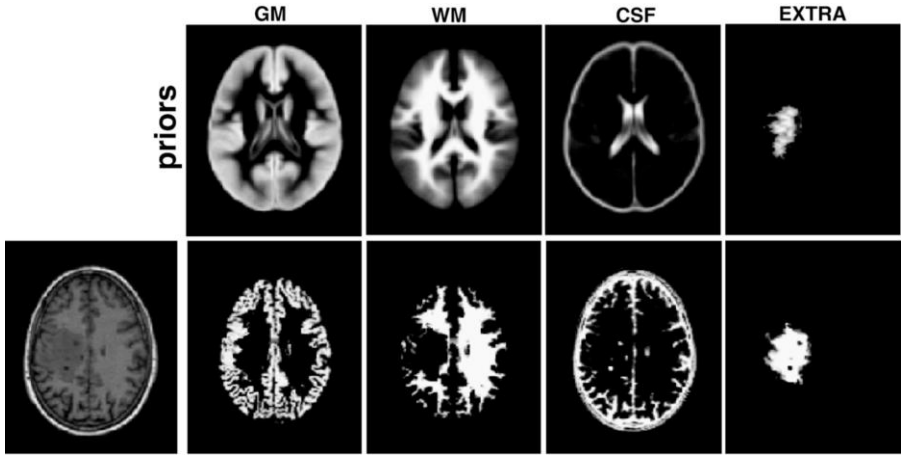


Template 1

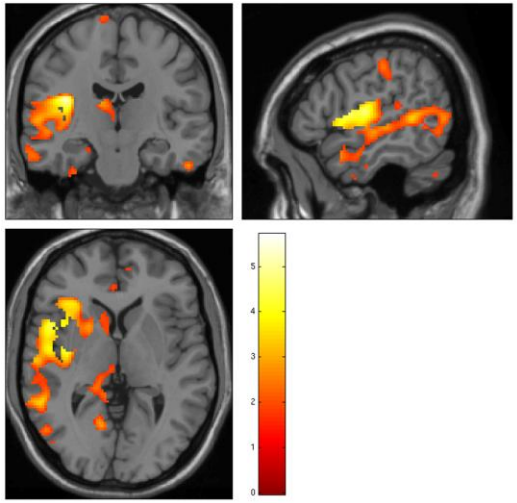
Templat
6

Lesion mapping

- Automated detection
  - SPM8 „unified segmentation“
  - Fuzzy clustering



- Analysis
  - GM volume
  - Binary & probabillistic lesion maps



Seghier et al., 2008 *Neuroimage*

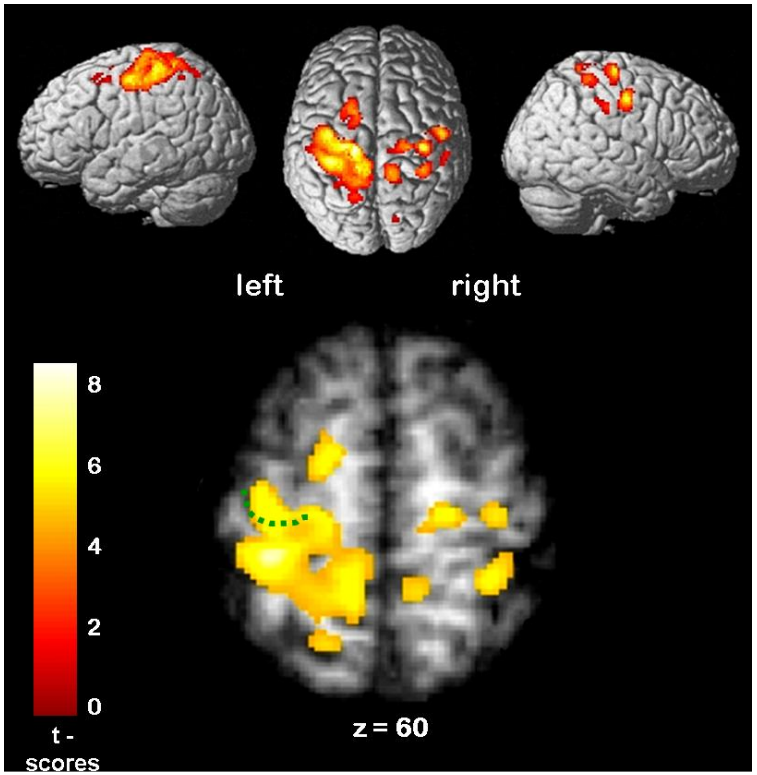
Short-term changes

- Study design

  - Motor learning paradigm – 10-digit sequence

  - 3 subjects, 9 weeks

  - 15 min/d training @ home



Ward et al., *in preparation*