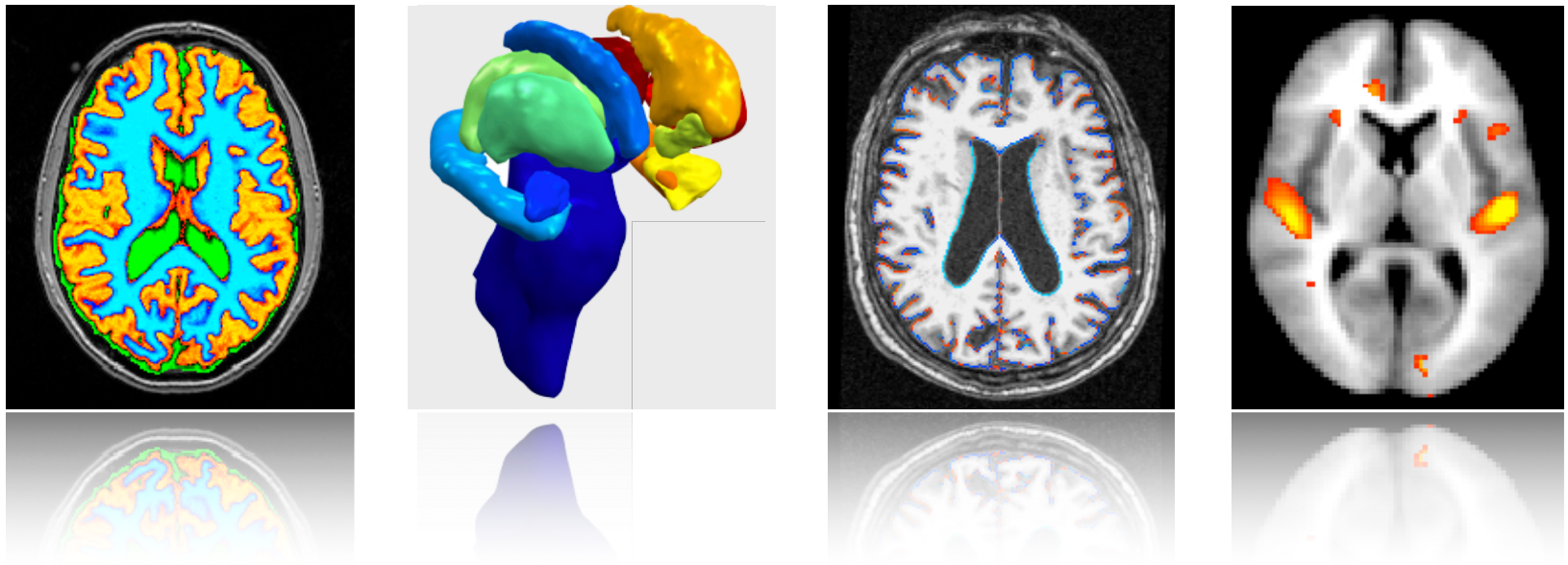
Structural Segmentation



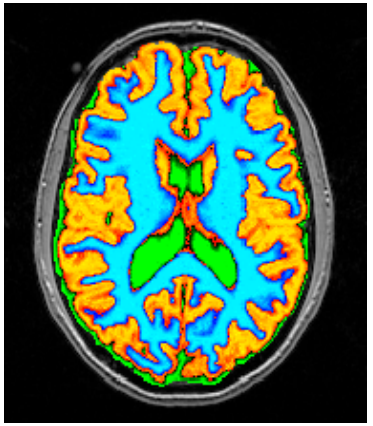
- FAST tissue-type segmentation
- FIRST sub-cortical structure segmentation
- BIANCA segmentation of white matter lesions
- FSL-VBM voxelwise grey-matter density analysis
- SIENA/SIENAX global atrophy estimation

FAST

FMRIB's Automated Segmentation Tool

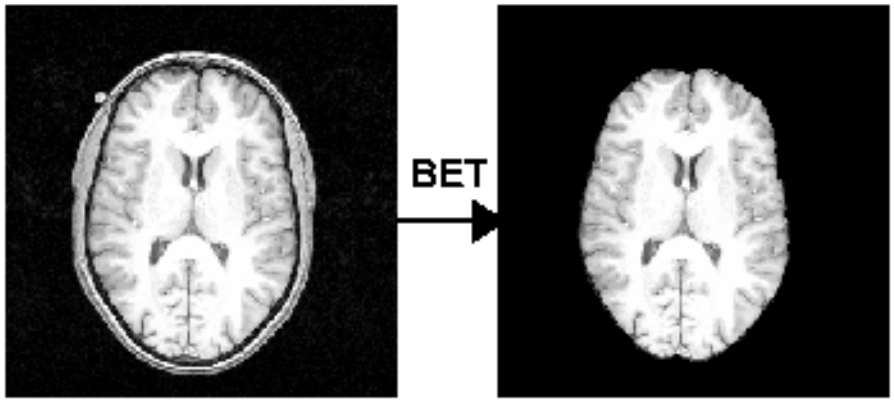
generic tissue-type segmentation and bias field correction

- Input: brain-extracted image(s)
- Segments into different tissue types
- At the same time, estimate bias field
- Robust to noise, because each voxel looks at neighbours



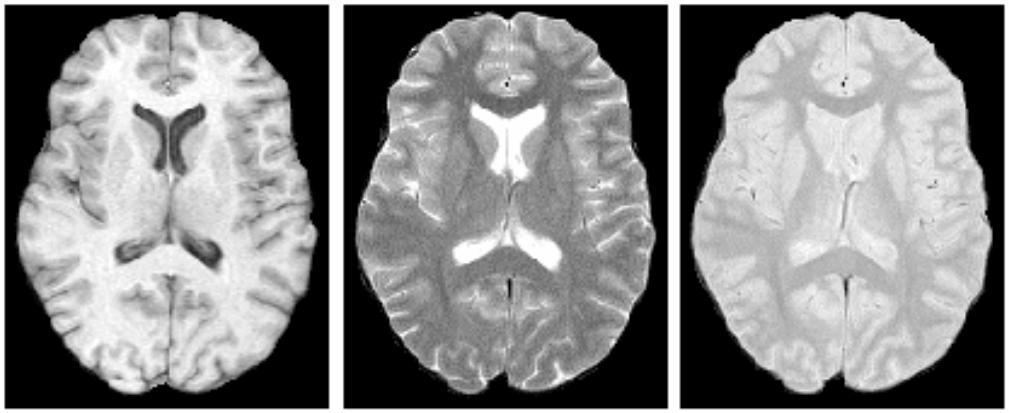
FAST: Input

- First use BET to remove non-brain
  All *volumetric* results are *highly sensitive* to errors here.
  For *bias-field correction alone* the errors do not matter that much



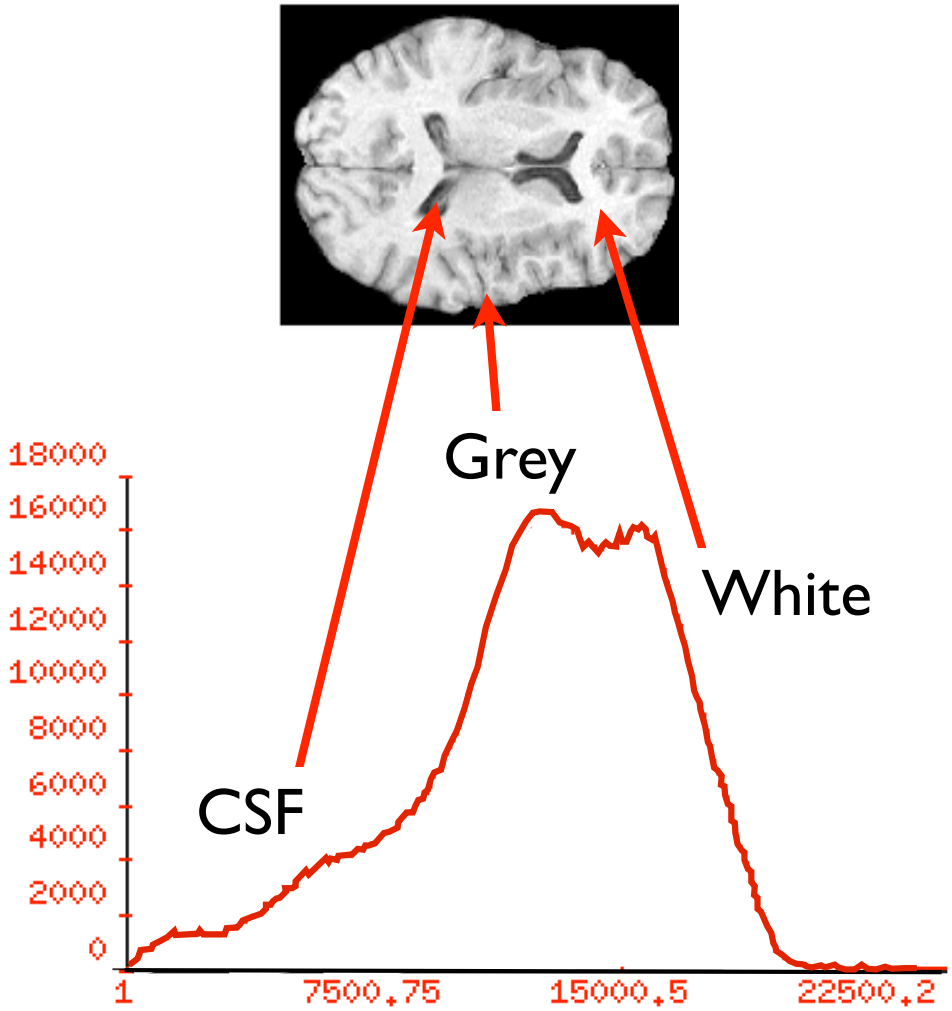
- Input is normally a single image (T1, T2, proton-density....)

- Or several inputs ("multichannel")
- For multi-channel, all must be pre-aligned (FLIRT)



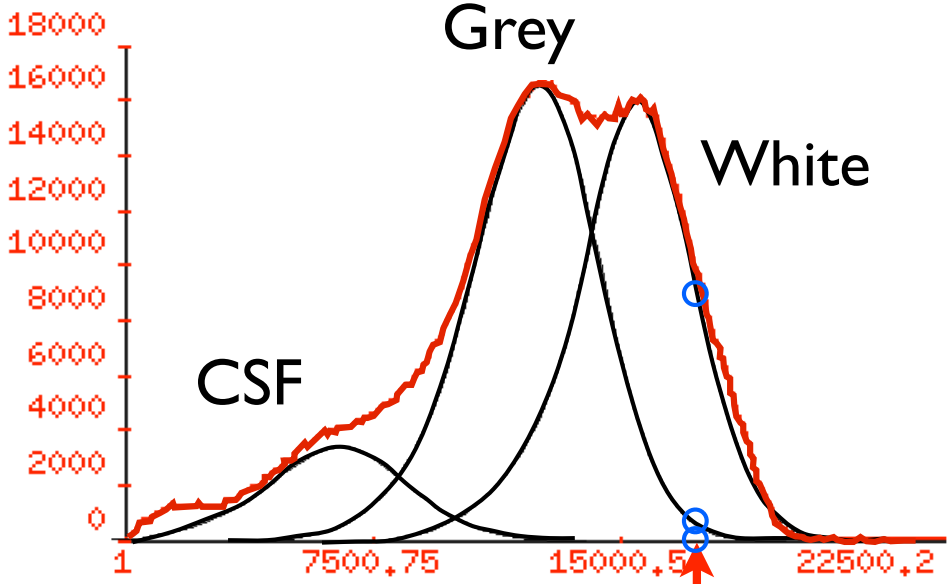
Intensity Model
tissue intensity distributions

- Histogram = voxel count vs. intensity
- Model = mixture of Gaussians
- If well separated, have clear peaks; then segmentation easy
- Overlap worsened by:
  - Bias field
  - Blurring
  - Low resolution
  - Head motion
  - Noise



Probability Model

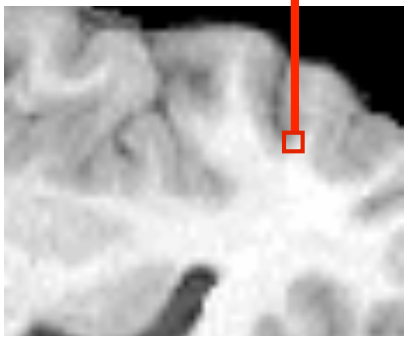
- Histogram = probability distribution function
- Model = mixture of Gaussians
- Probability determined for each tissue class



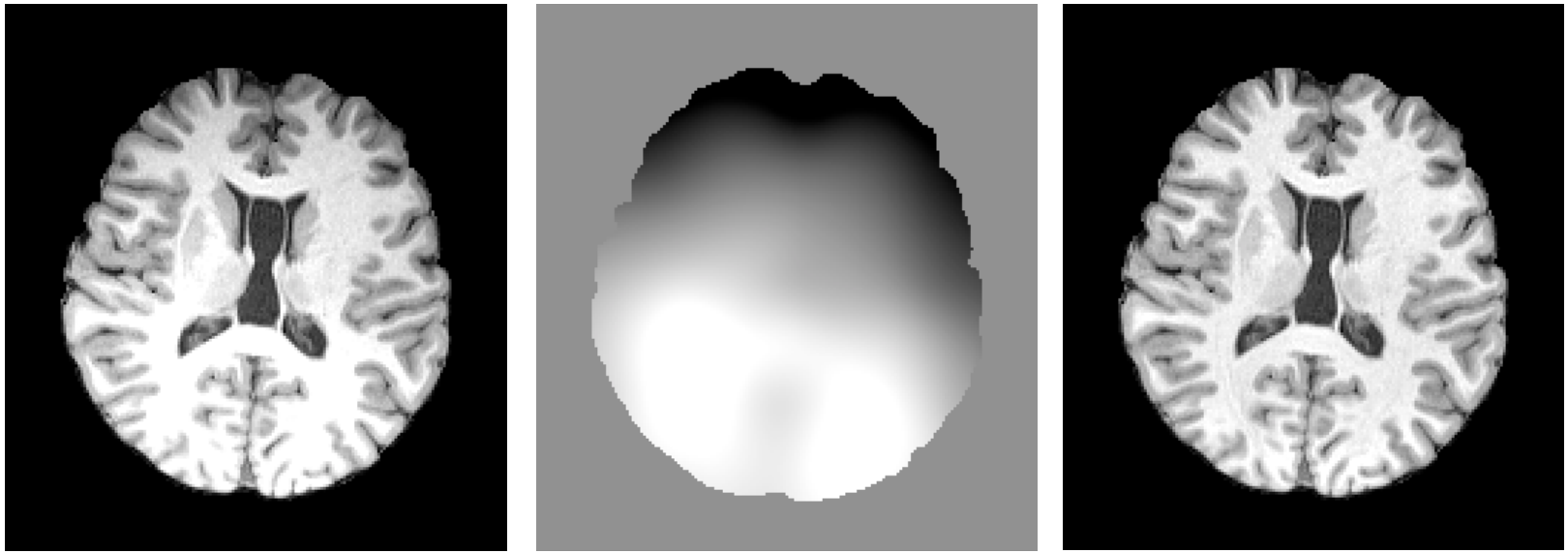
For example:
Voxel near WM/GM border

P(CSF) near zero
P(GM) low
P(WM) moderate

Intensity = 17203



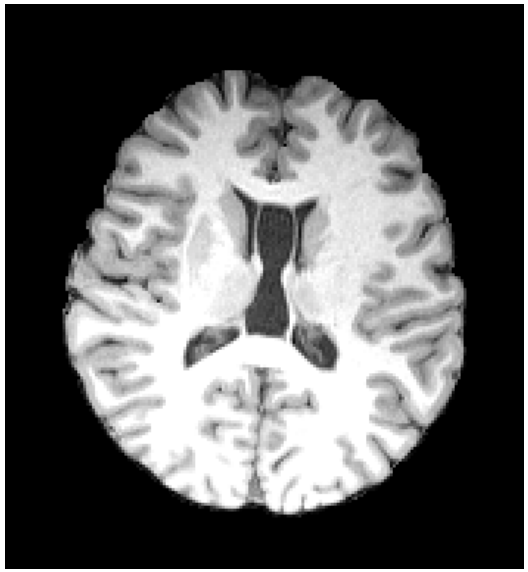
Bias Field Correction



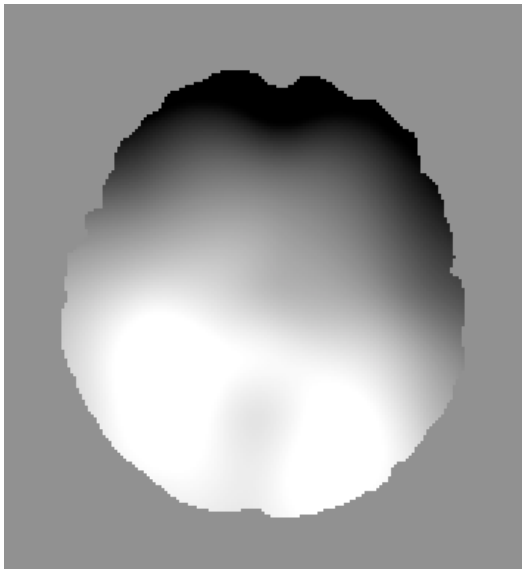
Original Bias Restored

- MRI RF (radio-frequency field) inhomogeneity causes intensity variations across space
- Causes problems for segmentation
- Need to remove bias field before or during segmentation
- Becomes more common and problematic at high field

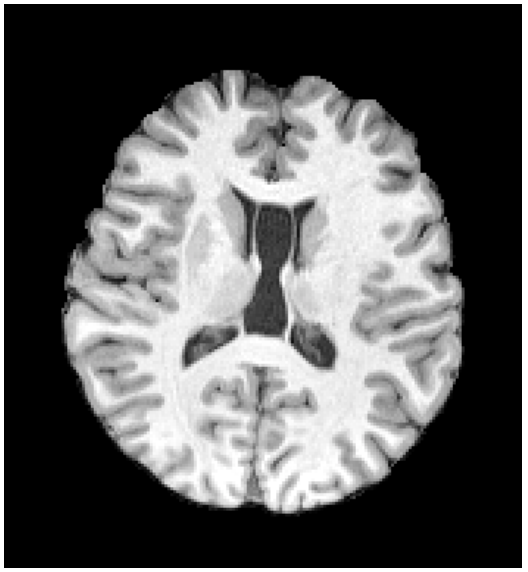
Bias Field Correction



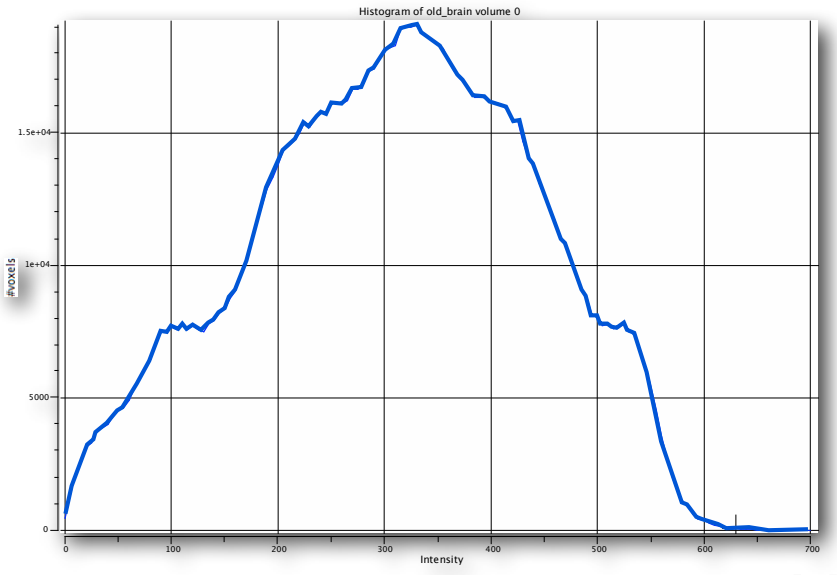
Original

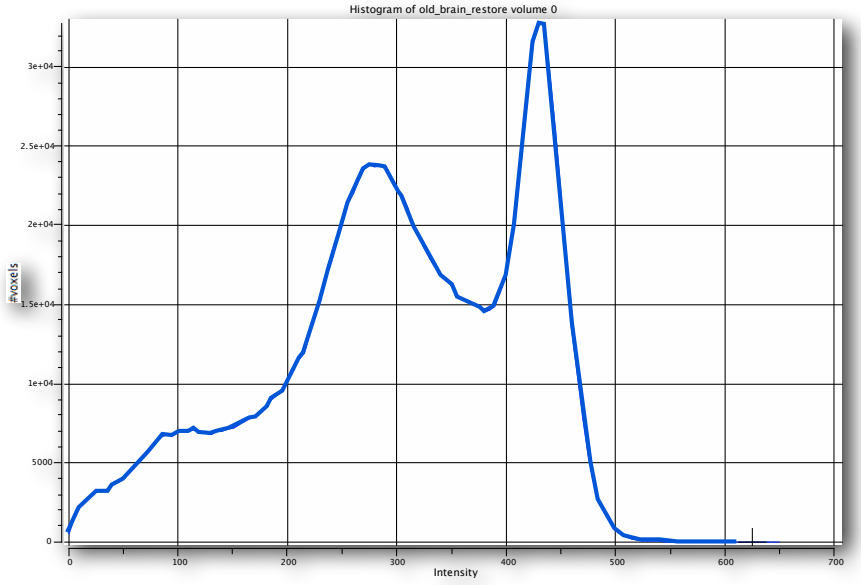


Bias



Restored

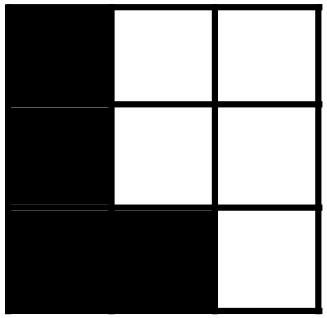




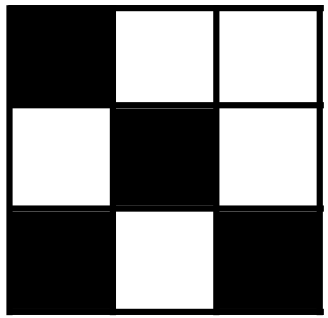
Histograms

Use Spatial Neighbourhood Information (MRF)

- Neighbourhood information: "if my neighbours are grey matter then I probably am too"
- Simple classifiers (like K-means) do not use spatial neighbourhood information
- More robust to noise
- Need the right balance between believing neighbours or intensity



Likely configuration
High probability



Unlikely configuration
Low probability

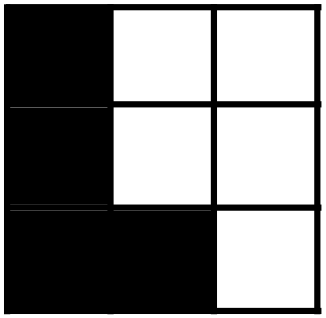
Use Spatial Neighbourhood Information (MRF)

Combine with probability based on Gaussian Mixture Model:

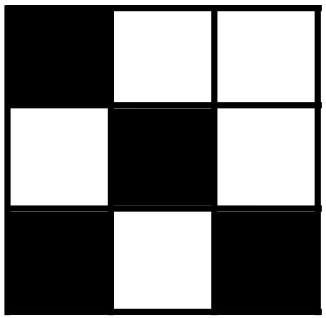
Final log probability =
log p(intensity) + **β** log p(MRF)

Final result depends on β value

This is user-adjustable



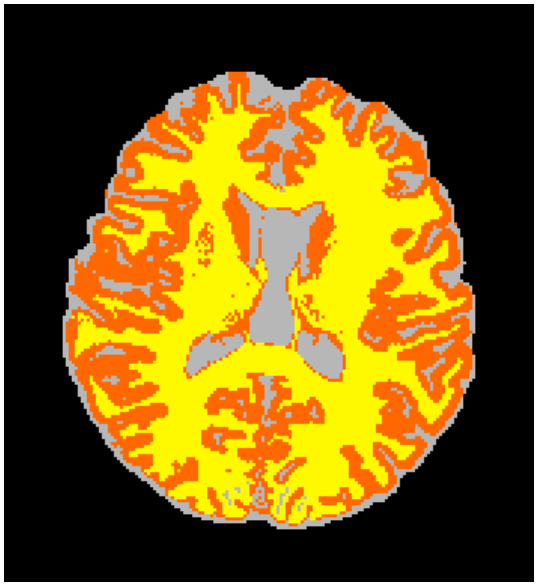
Likely configuration
High probability

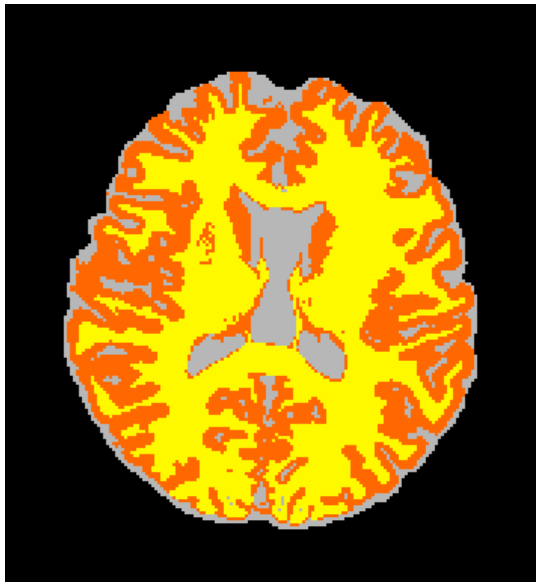


Unlikely configuration
Low probability

Effect of MRF Weighting

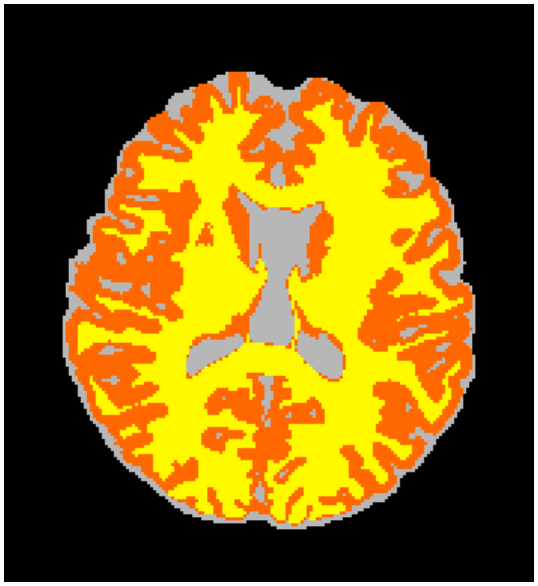
β=0

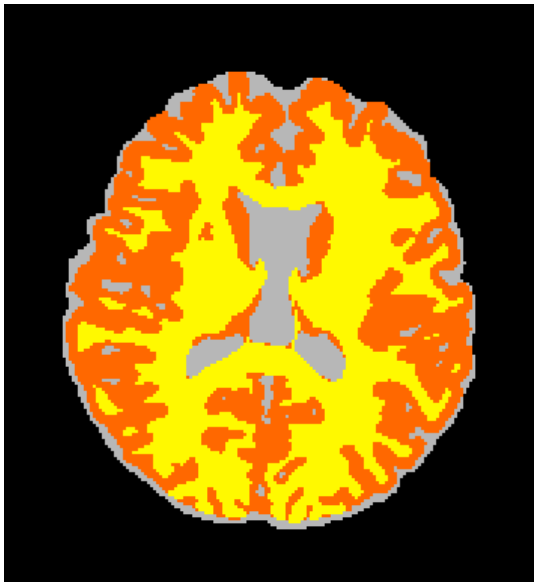




β=0.1

β=0.3

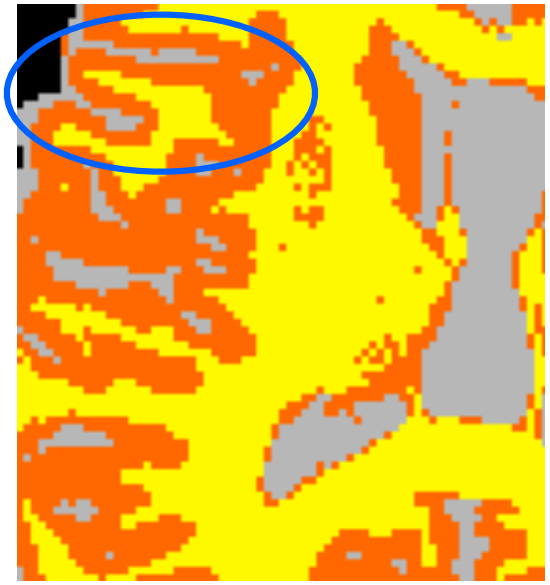




β=0.5

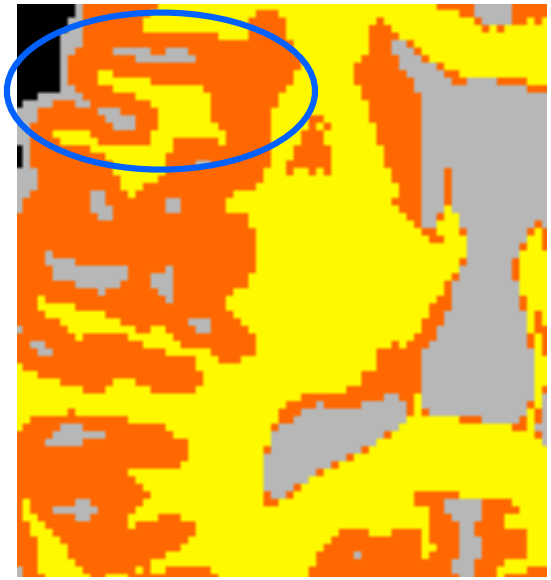
Effect of MRF Weighting

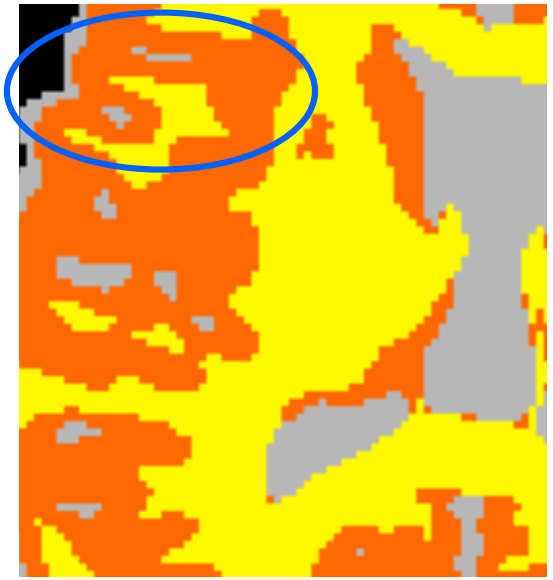
β=0



β=0.1

β=0.3



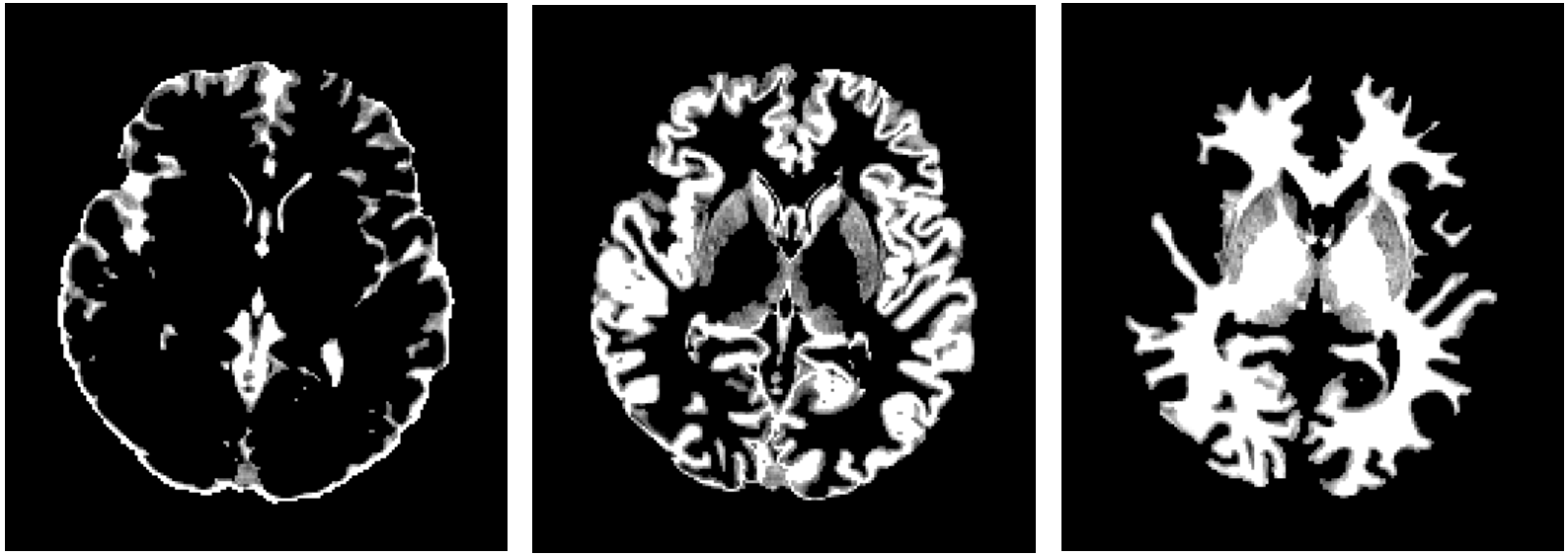


β=0.5

Partial Volume Modelling

- A better model is what fraction of each voxel is tissue X?
- "partial volume" = fraction of CSF, GM or WM

PVE
CSF, GM, WM



Image

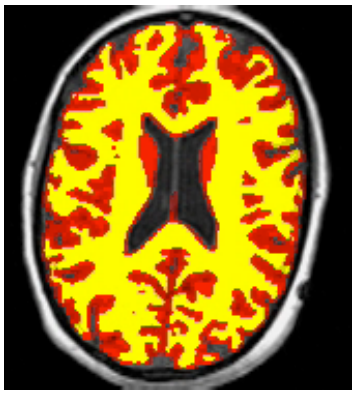
"Hard"
Segmentation

PVE (GM)

- This substantially improves accuracy of volume estimation

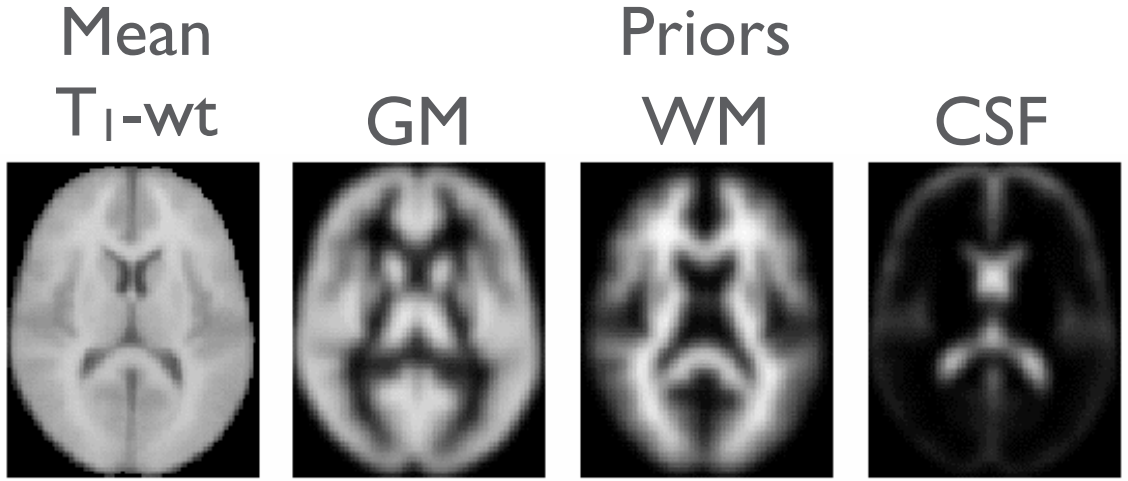
FAST - The Overview

- Initial (approximate) segmentation
  - Tree-K-means
- Iterate
  - Estimate bias field
  - Estimation segmentation; iterate
    - Update segmentation (intensity + MRF)
    - Update tissue class parameters (mean and standard deviation)
- Apply partial volume model
  - MRF on mixel-type (how many tissues)
  - PV Estimation



Optional Use of Priors (tissue probability maps)

- Segmentation priors = average of many subjects' segmentations
- Can use priors to weight segmentation, but can skew results (e.g. due to misalignment)
- FAST does not use priors by default
- If bias field is very bad, priors can be turned on to help initial segmentation (alternatively, do more iterations)
- Can also be turned on to feed into final segmentation (e.g. to aid segmentation of deep grey .... but see FIRST)



Other Options

FAST:

- **Bias field smoothing (-l)**
  - vary spatial smoothing of the bias field
- **MRF beta (-H)**
  - vary spatial smoothness of the segmentation
- **Iterations (-I)**
  - vary number of main loop iterations

fsl_anat:

- This is a new, alternative tool that performs brain extraction and bias field correction (along with other things) in a different way and so is worth trying out too

FAST

FMRIB's Automated Segmentation Tool

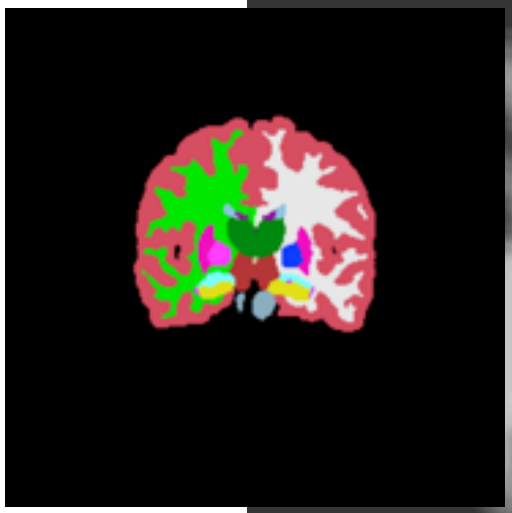
Summary

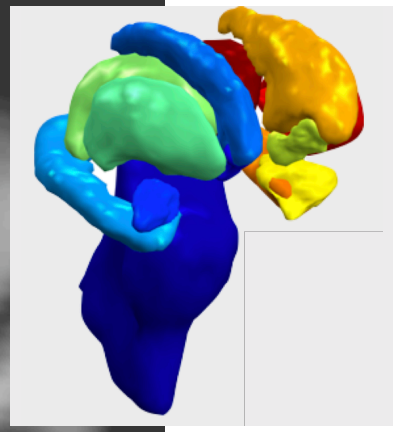
- Typically use a single T1-weighted image
- Multichannel is an option
- Segments into three main tissue-types:
  - Grey Matter, White Matter and CSF
- Models and corrects for bias field
  - Can be used just for bias field correction
- Combines intensity and neighbourhood information
- Partial Volumes Estimates (PVE) are most useful and more accurate for volume calculations
- Can use priors, but can cause bias, so not the default
- Have several adjustable parameters to optimise output

FIRST

FMRIB's Integrated Registration & Segmentation Tool

Segmentation of subcortical brain structures

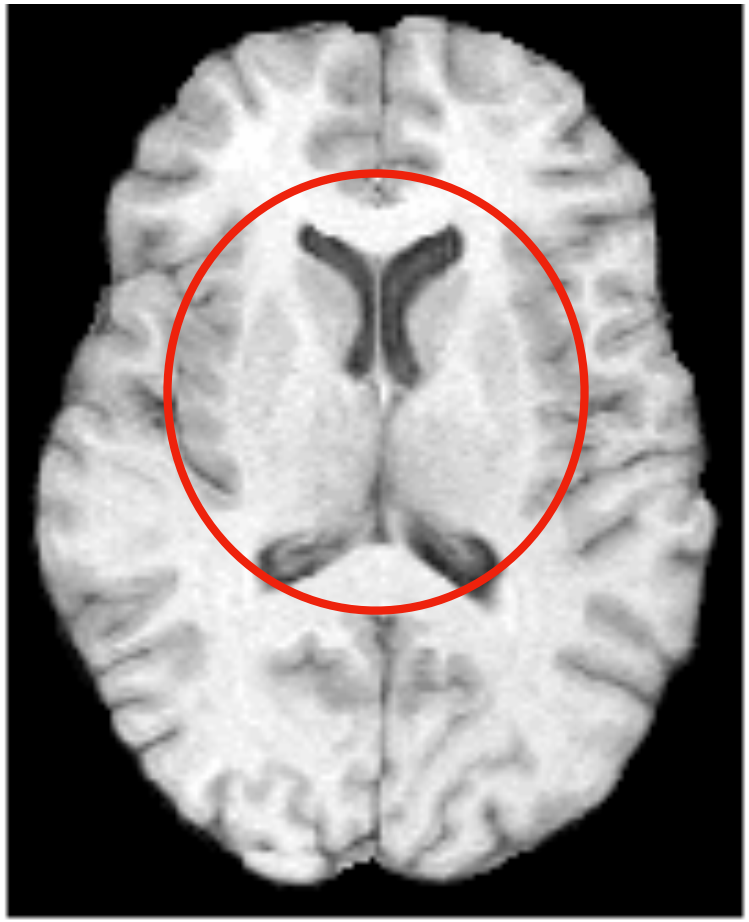




FIRST

FMRIB's Integrated Registration & Segmentation Tool

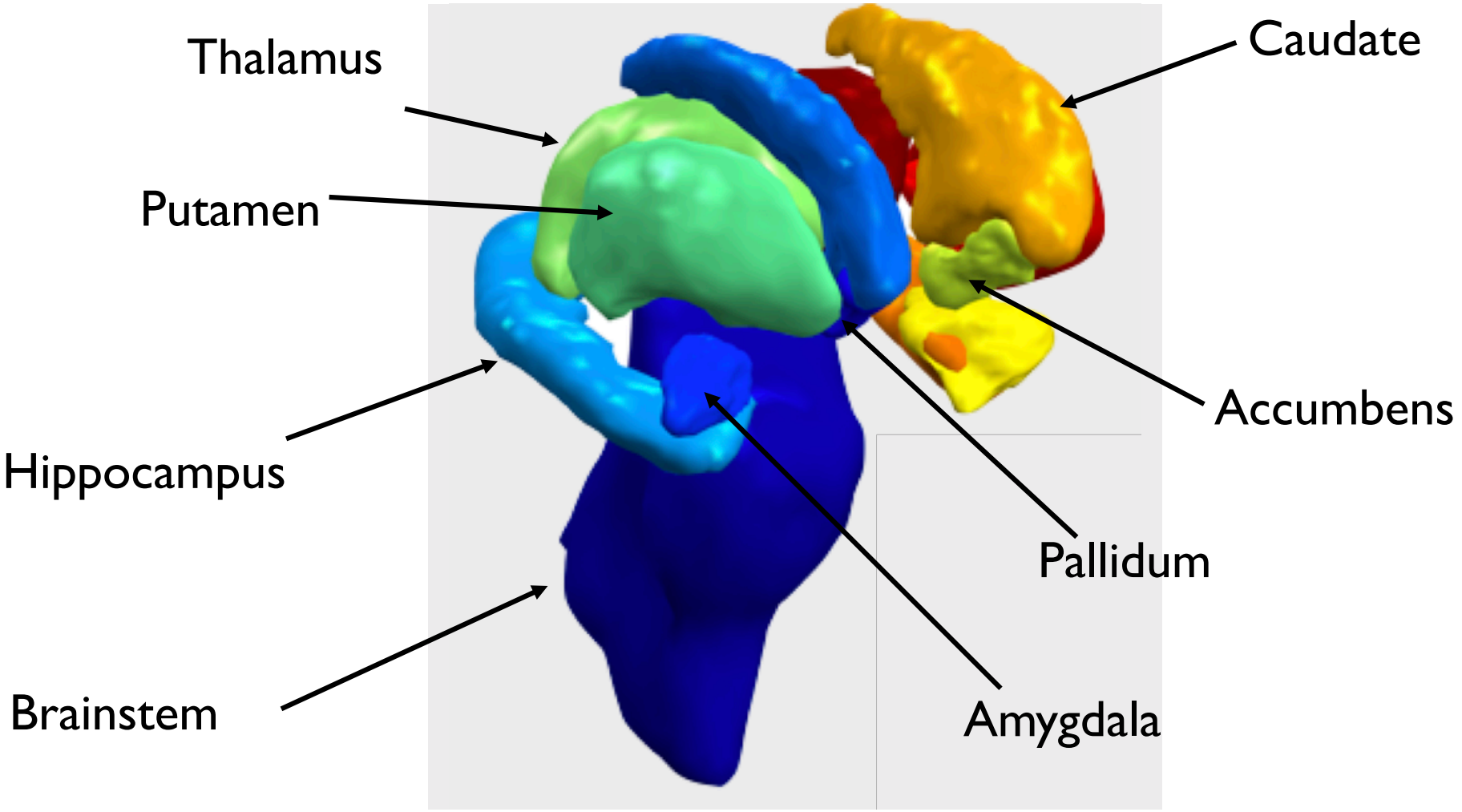
Segmentation of subcortical brain structures



Sub-Cortical Structure Models

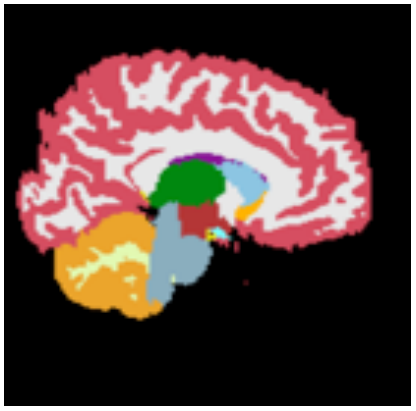
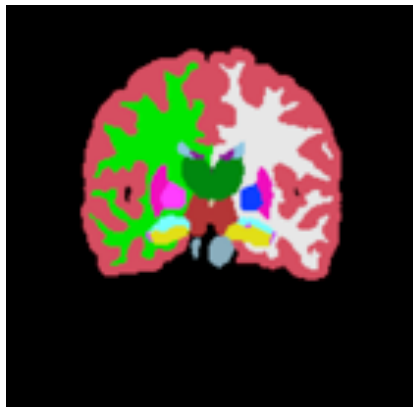
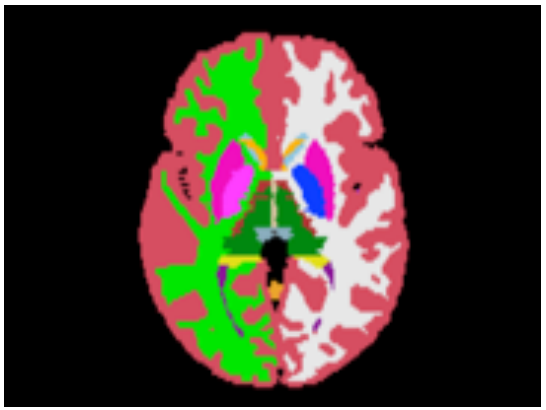
Incorporate prior anatomical information via explicit shape models

Have 15 different sub-cortical structures (left/right separately)



Training Data

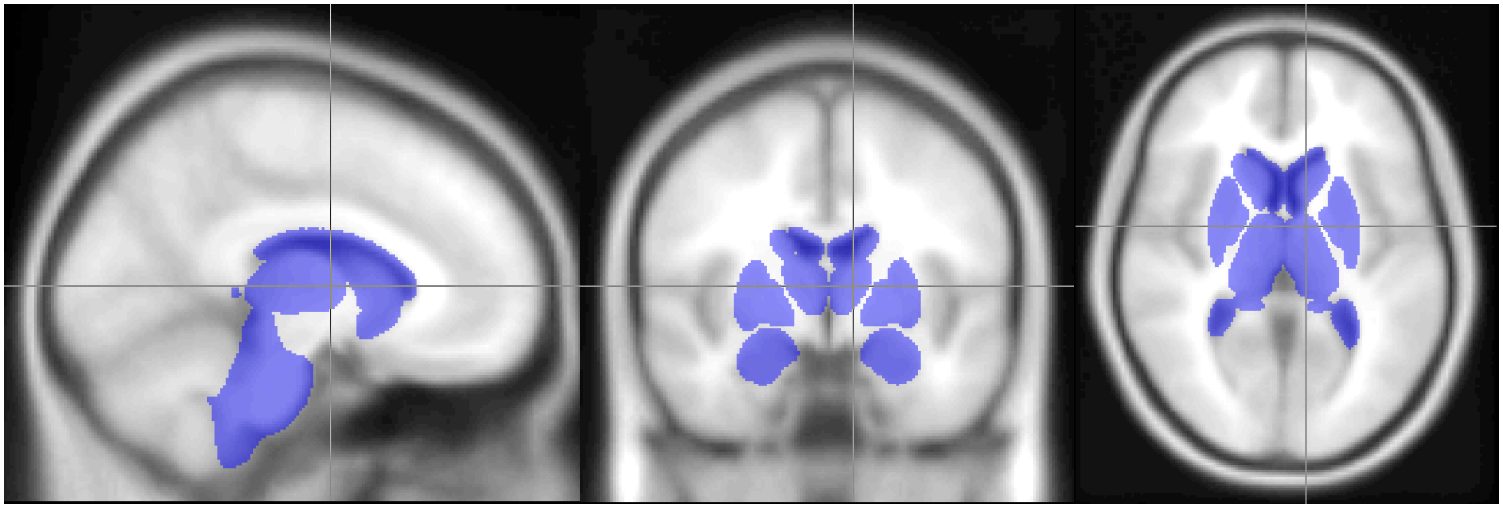
- Manual segmentations courtesy of David Kennedy, Center for Morphometric Analysis (CMA), Boston
- 336 complete data sets
- T_1-weighted images only
- Age range 4 to 87
  - Adults: Ages 18 to 87, Normal, schizophrenia, AD
  - Children: Ages 4 to 18, Normal, ADHD, BP, prenatal cocaine exposure, schizophrenia.

Model Training : Alignment to MNI152 space

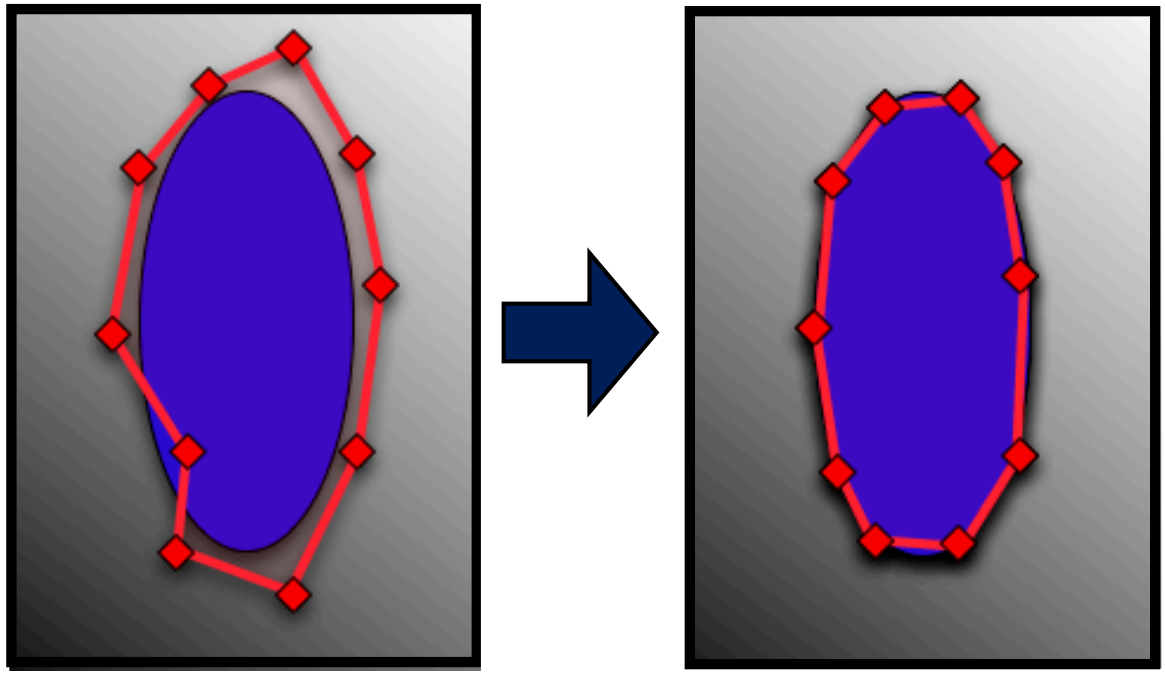
- All CMA data affine-registered to MNI152 space
  - 1mm resolution, using FLIRT

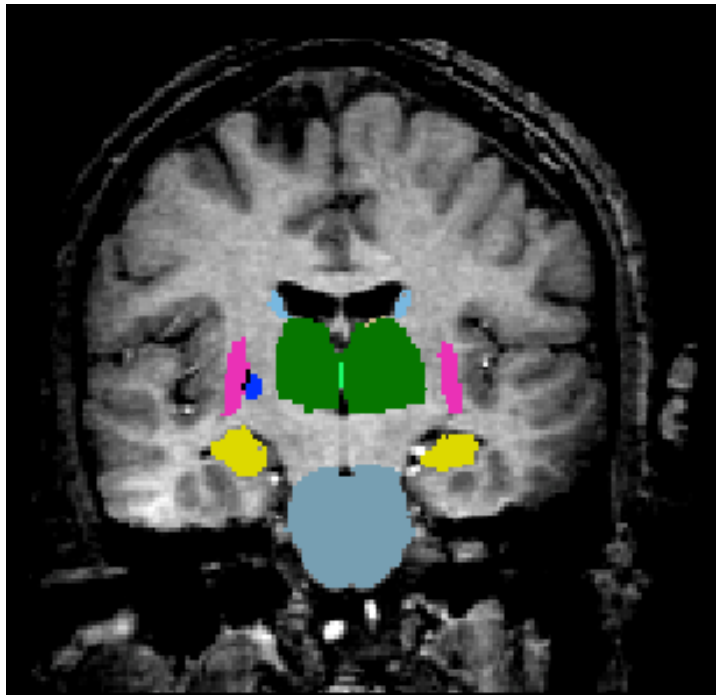
- 2-stage process:
  - Whole head 12 DOF affine
  - 12 DOF affine with MNI-space sub-cortical mask



Deformable Models

- Model: 3D mesh
- Use anatomical info on shape & intensity (from training)
- Deformation: iterative displacement of vertices
- Maintain point (vertex) correspondence across subjects





The Model: Shape

- Model average shape (from vertex locations)
- Also model/learn *likely variations* about this mean
  - modes of variation of the population; c.f. PCA
  - also call eigenvectors
- Average shape and the modes of variation serve as prior information (known before seeing the new image that is to be segmented)
  - formally it uses a Bayesian formulation

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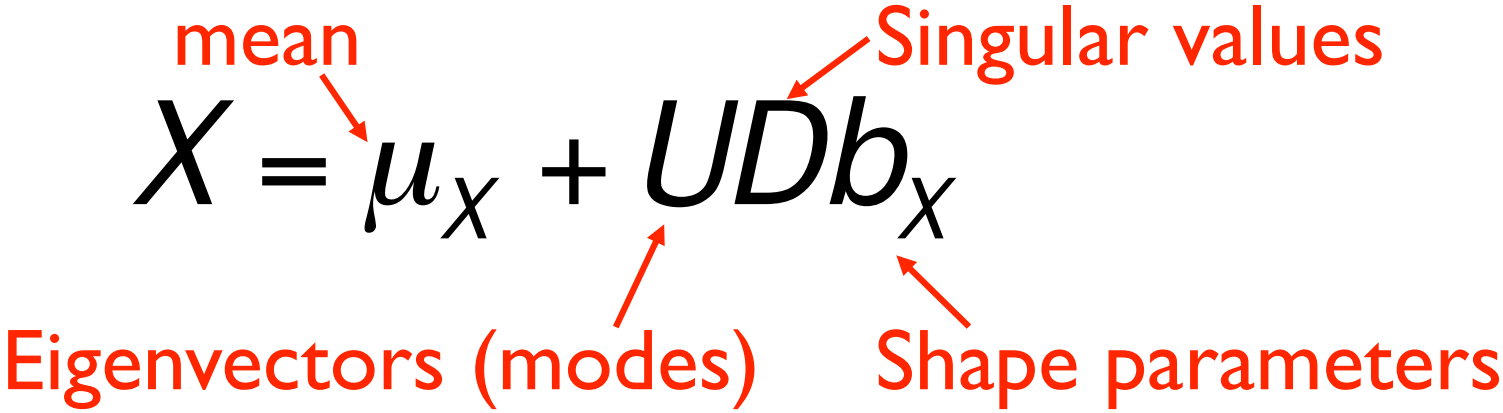
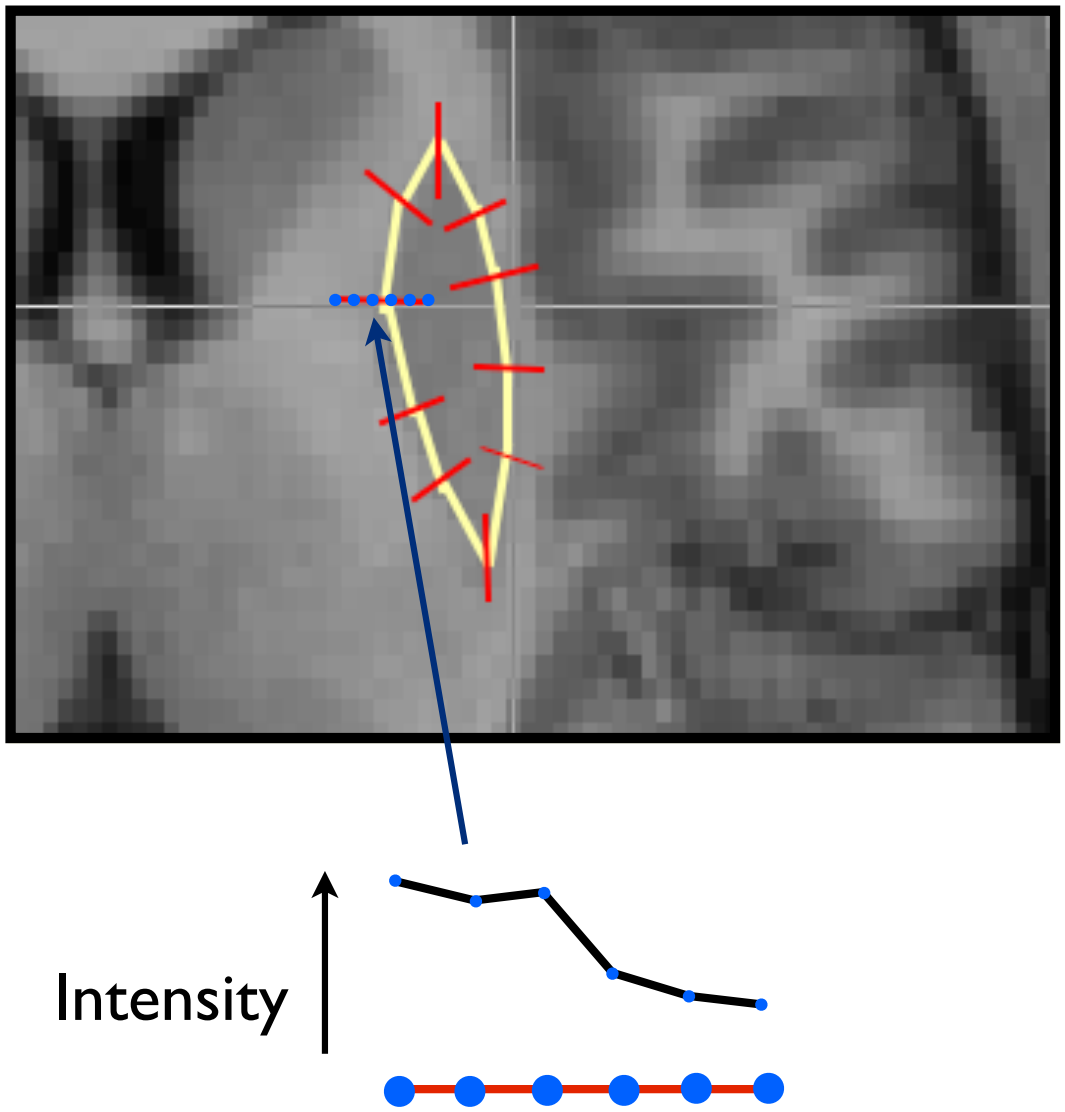


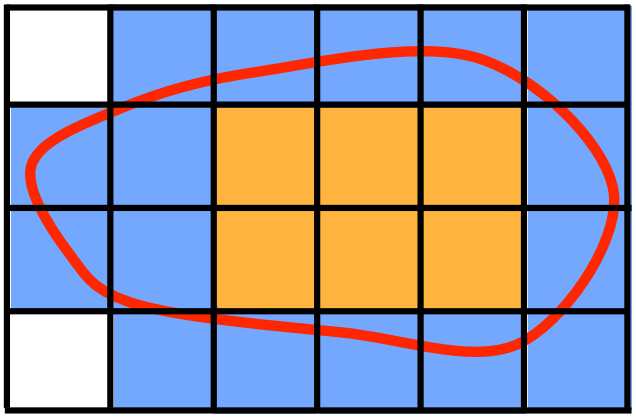
The Model: Intensity

- Intensity is then sampled along the surface normal and stored
- Learn average shape/ intensity and "modes of variation" about both
- Aside: the intensities are re-scaled to a common range and the mode of the intensities in the structure is subtracted



Boundary Correction

- FIRST models all structures by meshes
- Converting from meshes to images gives two types of voxels:
  - boundary voxels
  - interior voxels
- Boundary correction is necessary to decide whether the boundary voxels should belong to the structure or not
- Default correction uses FAST classification method and is run automatically (uncorrected image is also saved)
  - ensures that neighbouring structures do not overlap



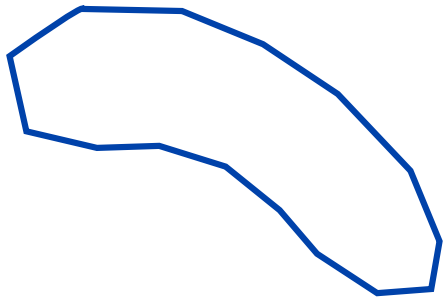
Boundary voxel

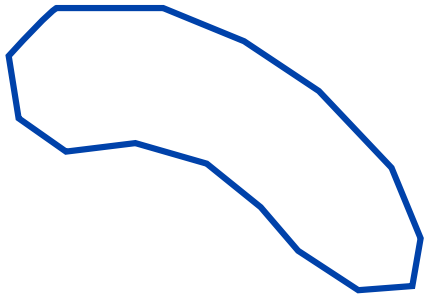
Interior voxel

Vertex Analysis

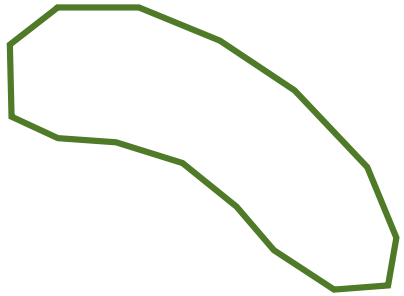
- Use a univariate test at each vertex to measure difference in location (e.g. between means of two groups of subjects)

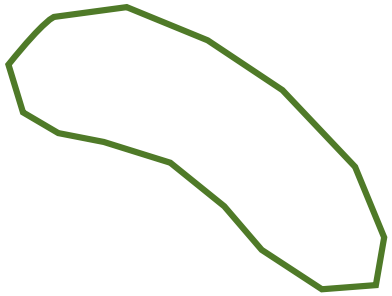
Controls





Disease



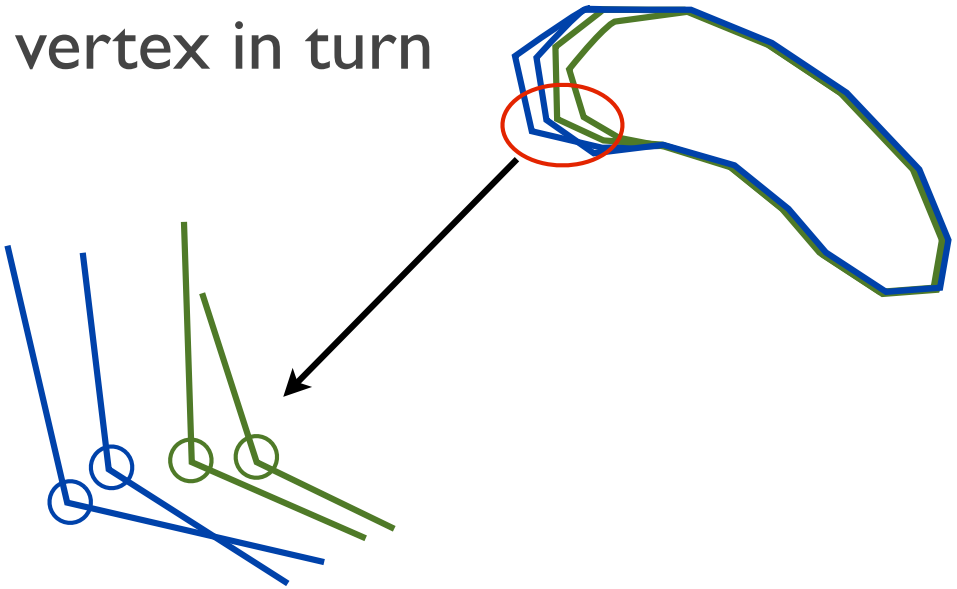


Vertex Analysis

- Use a univariate test at each vertex to measure difference in location (e.g. between means of two groups of subjects)

Controls Disease

Consider each vertex in turn



Vertex Analysis

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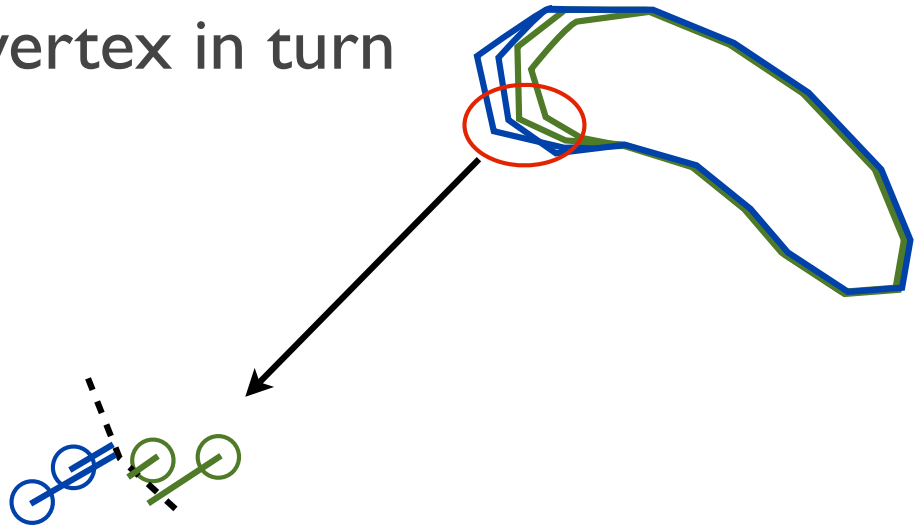
Controls Disease

Consider each vertex in turn



Do a test on distance of these vertices to average shape

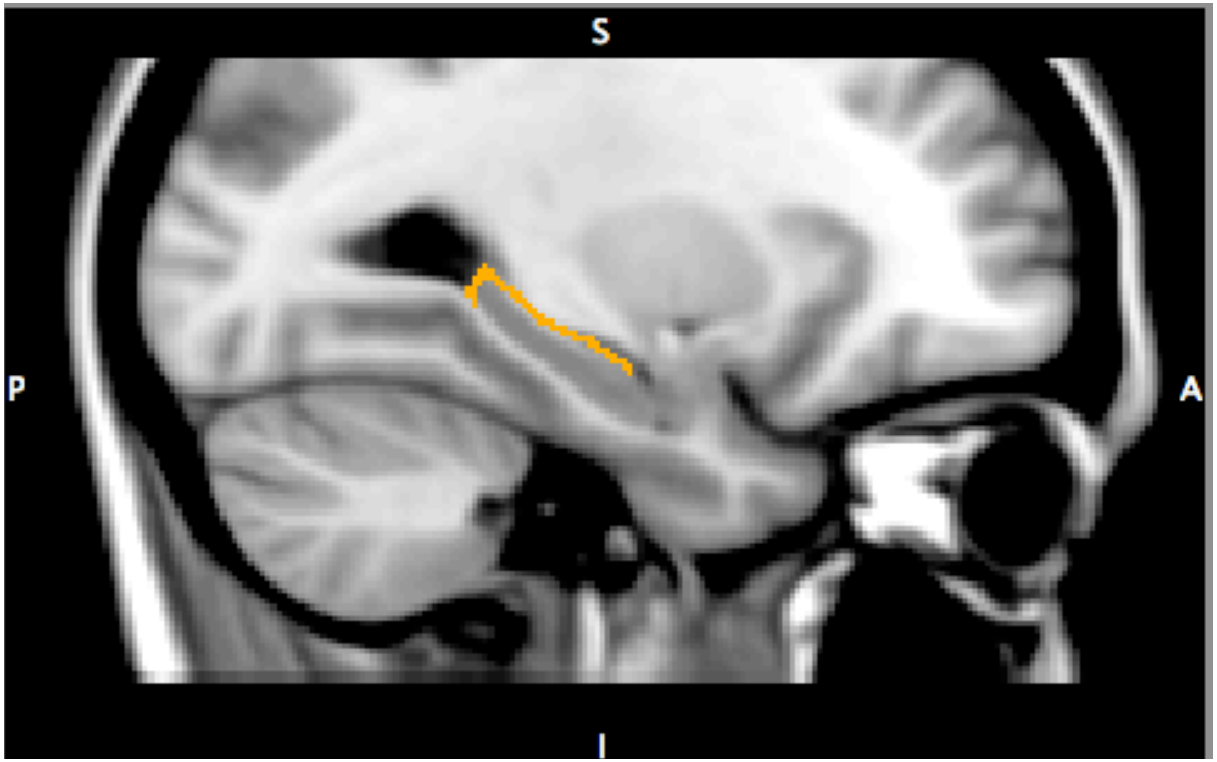
Vertex Analysis

- Use a univariate test at each vertex to measure difference in location (e.g. between means of two groups of subjects) using distance along surface normals

- Results are now given as ***images*** and statistics done with ***randomise***

- Can do analysis in MNI space or native structural space

- MNI space analysis ***normalises for brain size***



Running FIRST

- Inputs:
  - T_1-weighted image
  - Model (built from training data) - provided with FSL

- Applying FIRST
  - A single command: run_first_all
    1. registers image to MNI152 1mm template
    2. fits structure models (meshes) to the image
    3. applies boundary correction (for volumetric output)

- Analysis:
  - Use command: first_utils
    - volumetric analysis (summary over whole structure)
    - vertex analysis (localised change in shape and/or size)
    - randomise (with multiple comparison correction)

FIRST

FMRIB's Integrated Registration & Segmentation Tool

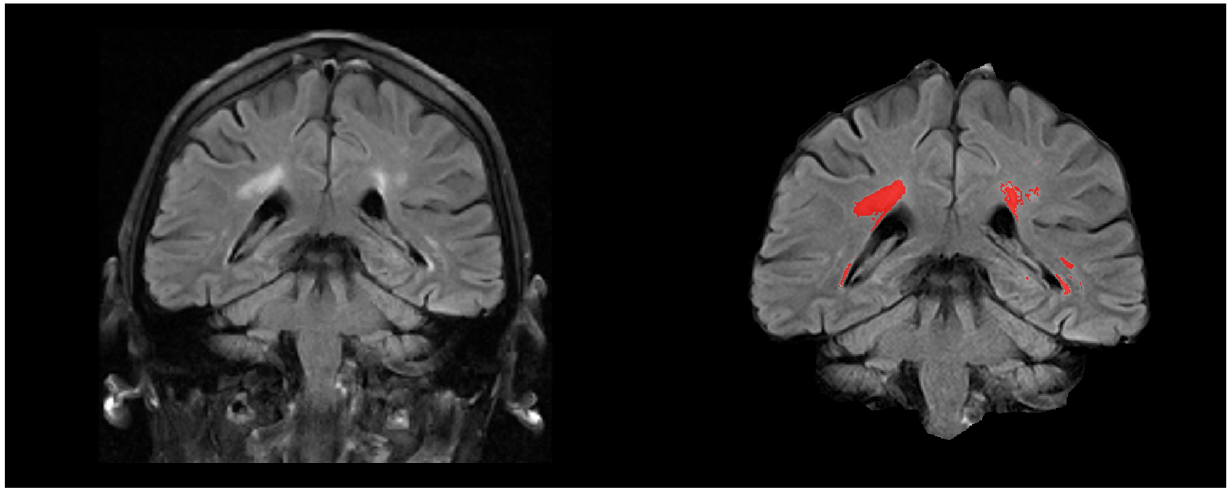
Summary

- Specific to certain deep grey structures
- Uses broad training set - very general demographics
- Can only work with T1-weighted images
- Models average and variations of shape and intensity
- Represents the boundary as a set of points
- Separate boundary correction step to get voxel labels

- Can perform vertex analysis to look at changes in shape and size

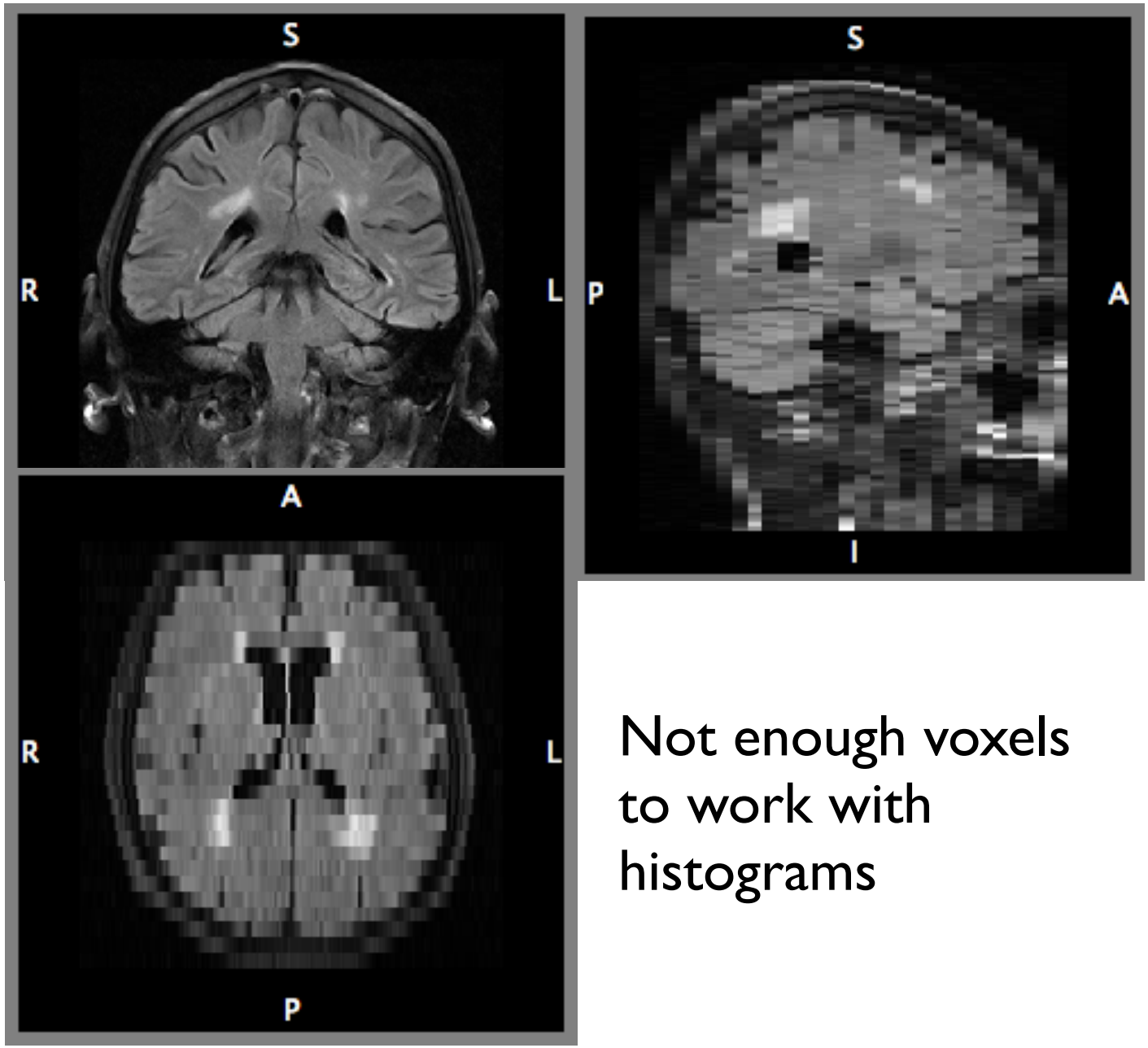
BIANCA

Segmentation of White Matter Hyperintensities / Lesions

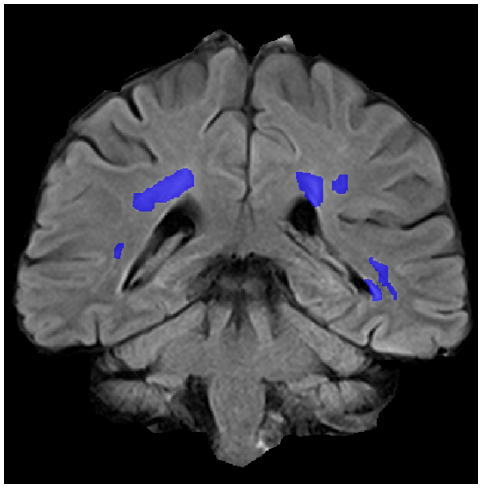


Lesion/WMH Segmentation

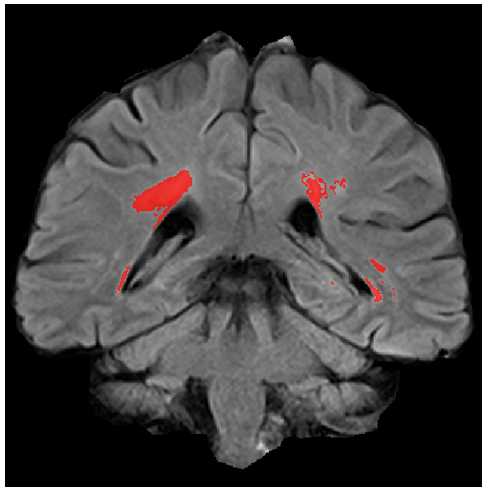
WMH = White Matter Hyperintensities (leukoaraiosis)



Not enough voxels to work with histograms



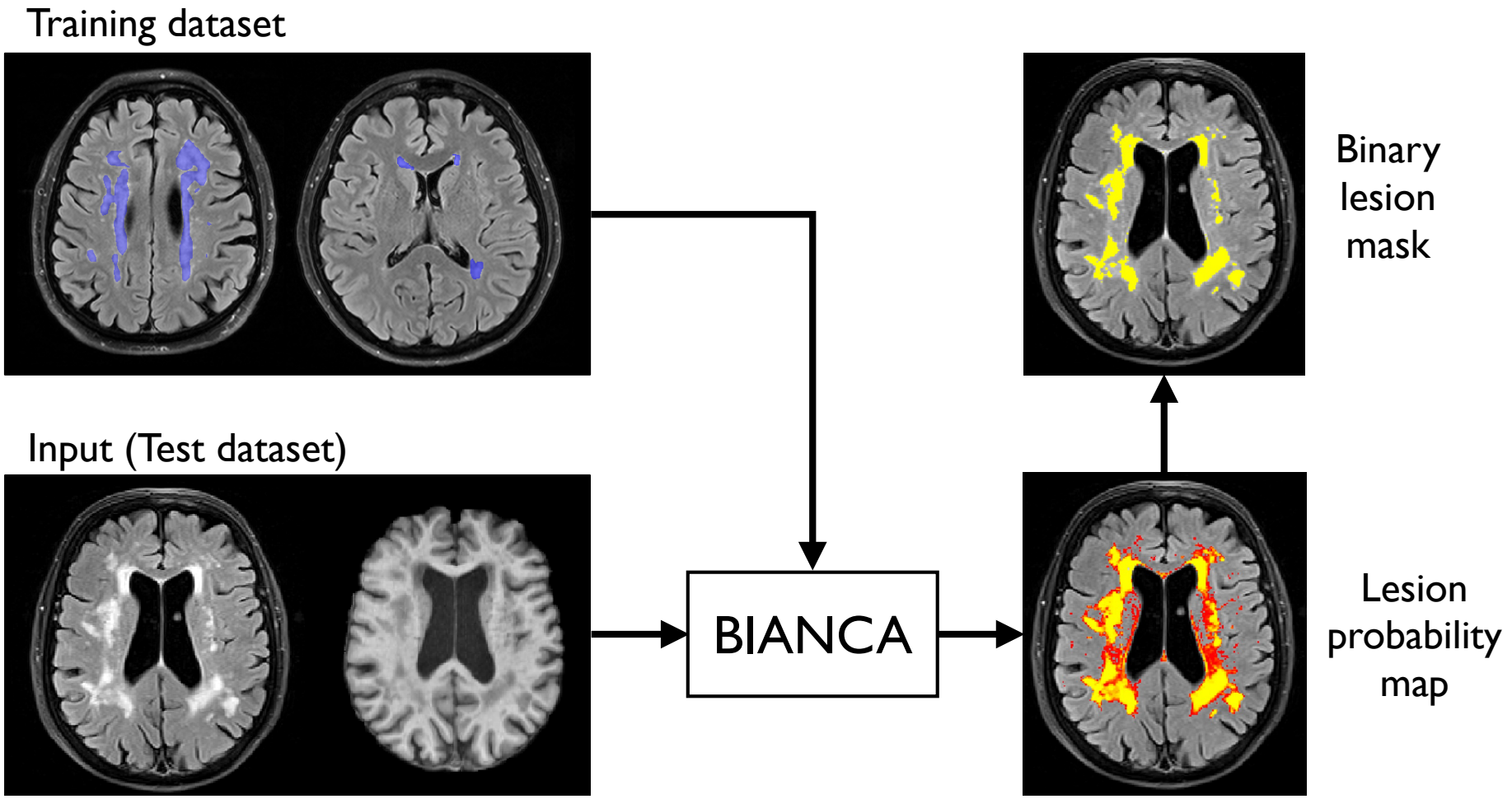
manual



automated

Lesion/WMH Segmentation

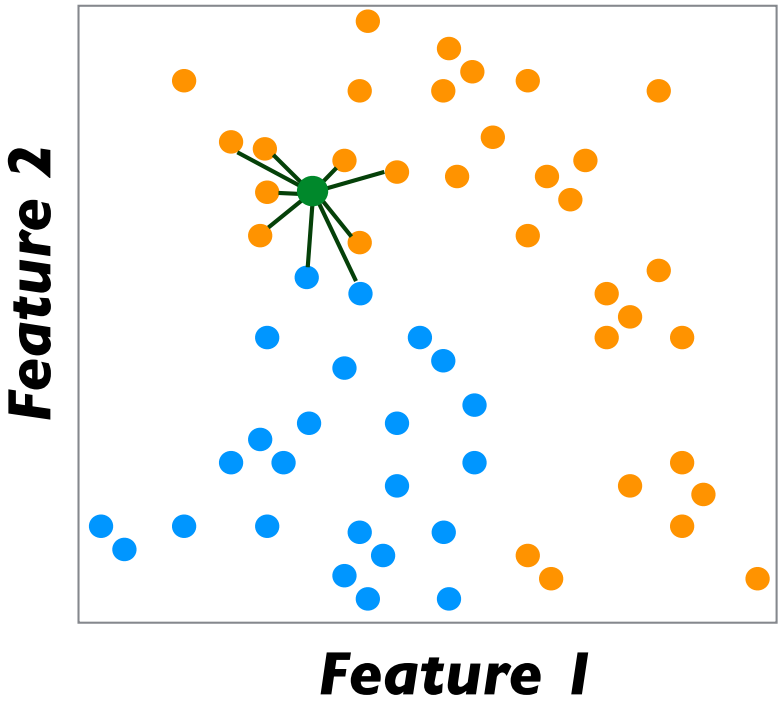
Brain Intensity AbNormalities Classification Algorithm (BIANCA)



Griffanti, et al., NeuroImage 2016

Methodology

- kNN method
  - Anbeek et al, 2004, 2008
  - Steenwijk et al, 2013
- Each point is from one voxel in a training image (labelled lesion or non-lesion)
- Data at each point comprises intensities, coordinates, local averages, etc. (***features***)

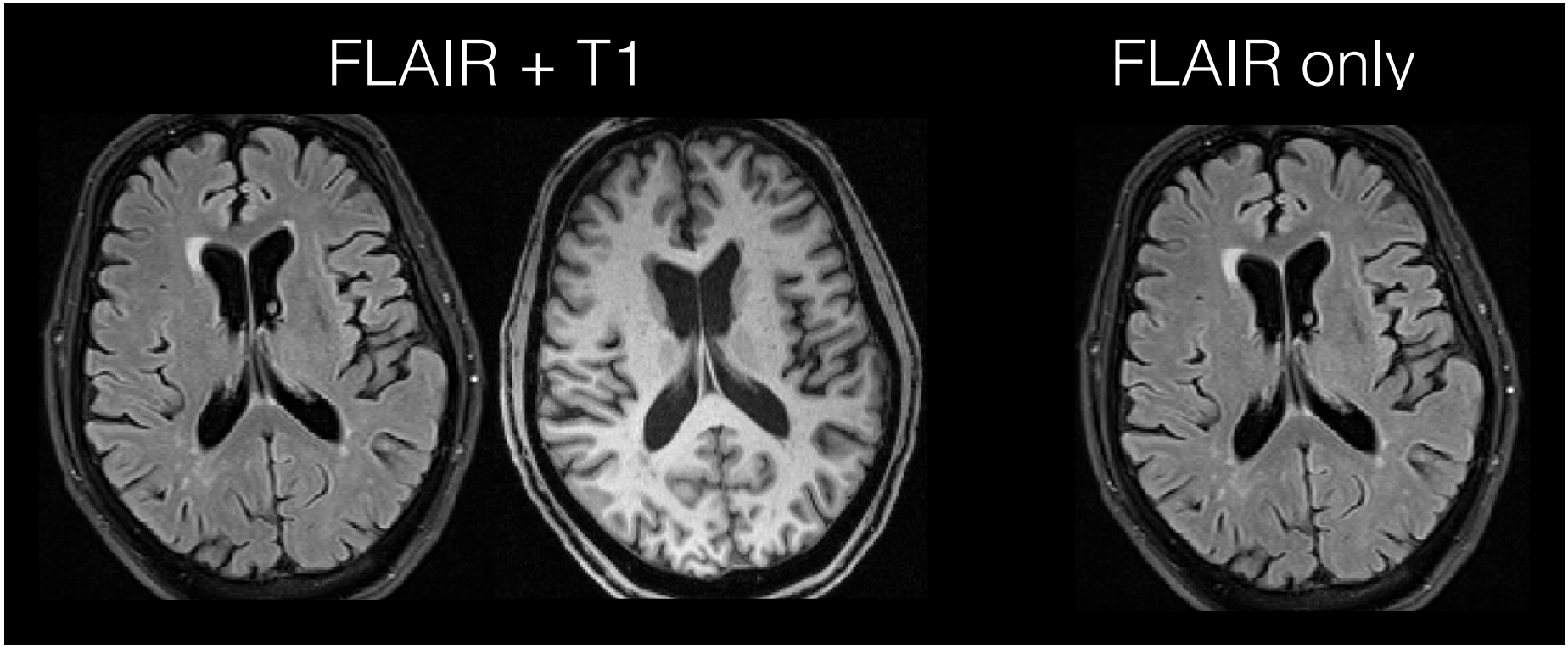


k=9; p(lesion)=7/9=0.78

- **New data point**: kNN picks k nearest neighbours for a voxel of interest and calculates the ratio between those labelled as lesion and non-lesion ➜ **probability** of being lesion

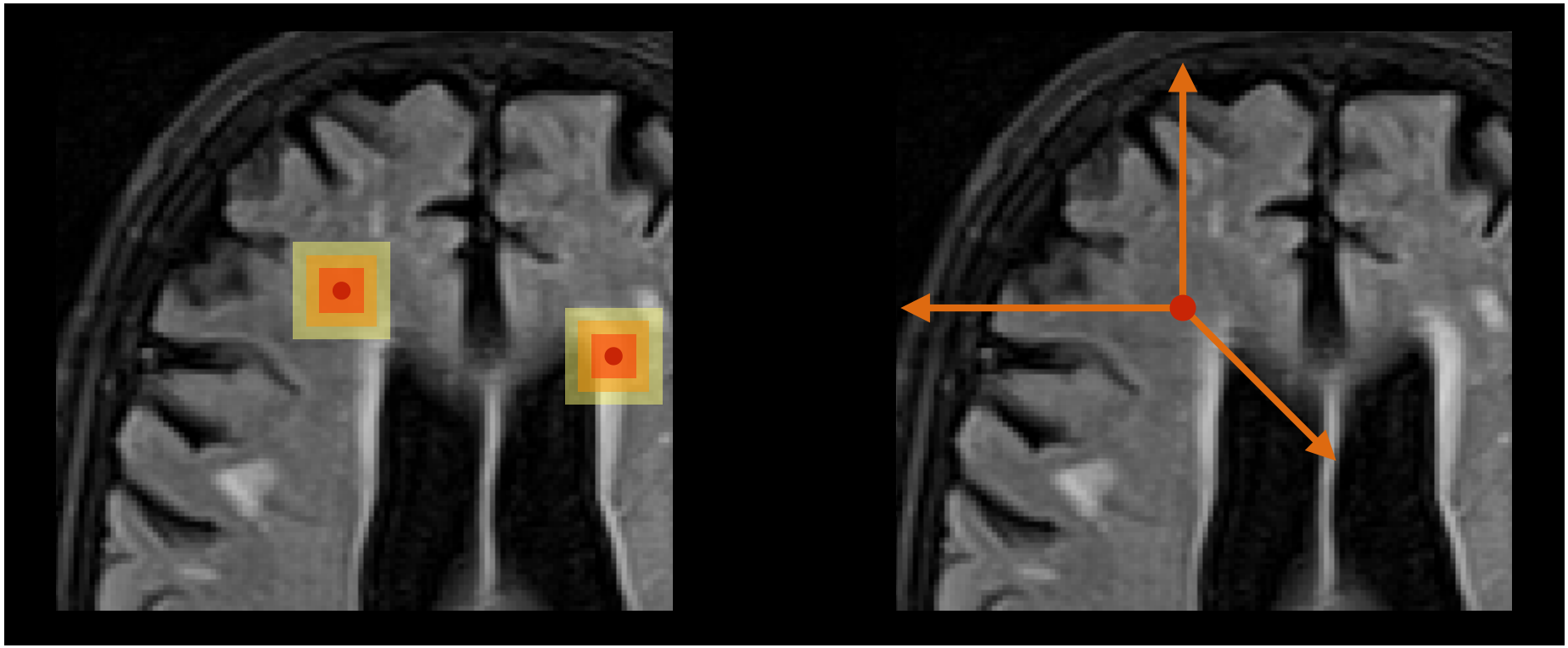
Methodology - options

- Many options exist:
  - **modalities** (e.g. FLAIR, T2w, T1w)



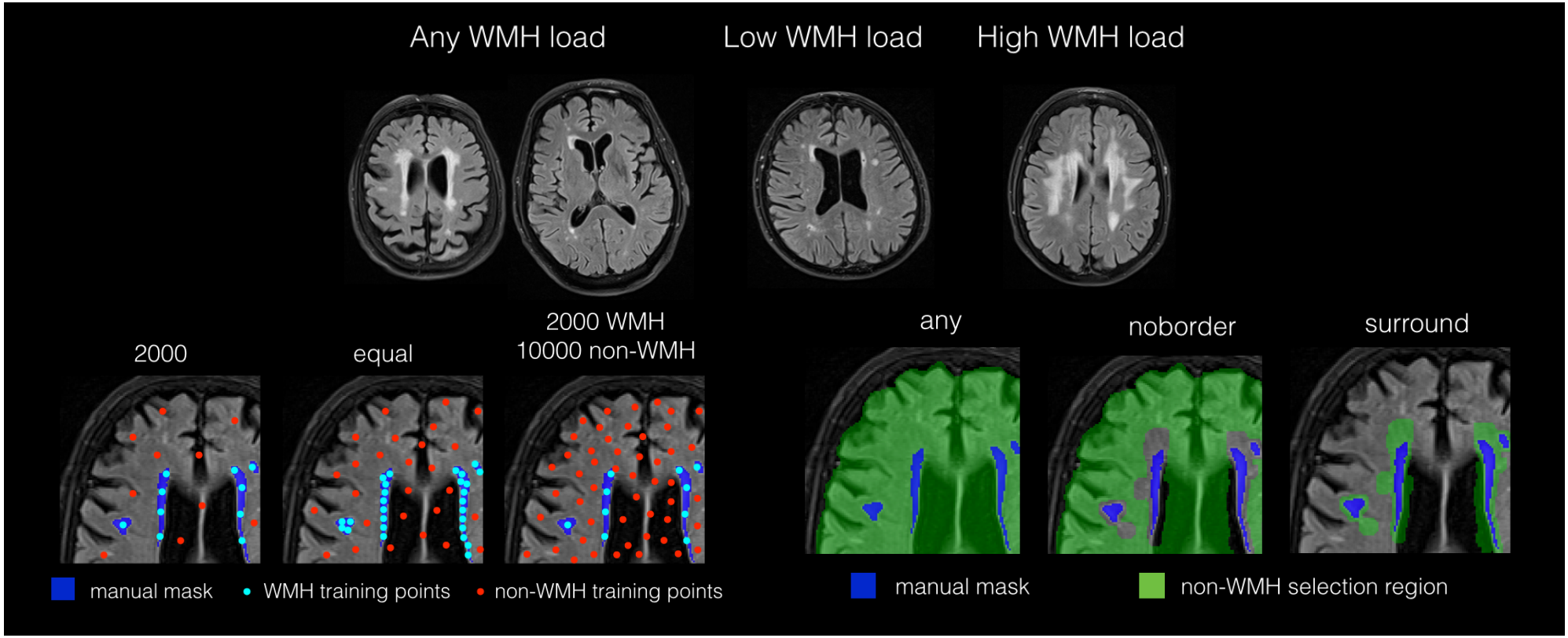
Methodology - options

- Many options exist:
  - modalities (e.g. FLAIR, T2w, T1w)
  - **features** (e.g. local averages, MNI coordinates)



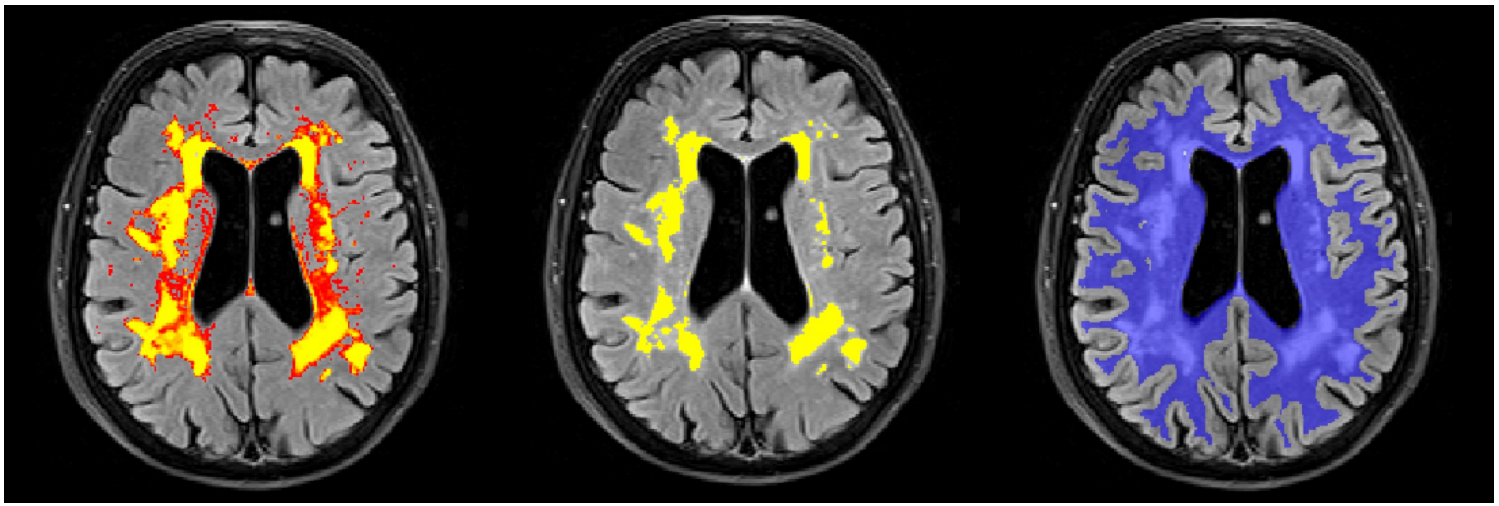
Methodology - options

- Many options exist:
  - modalities (e.g. FLAIR, T2w, T1w)
  - features (e.g. local averages, MNI coordinates)
  - **training** (e.g. type of scans, no. voxels, locations sampled)

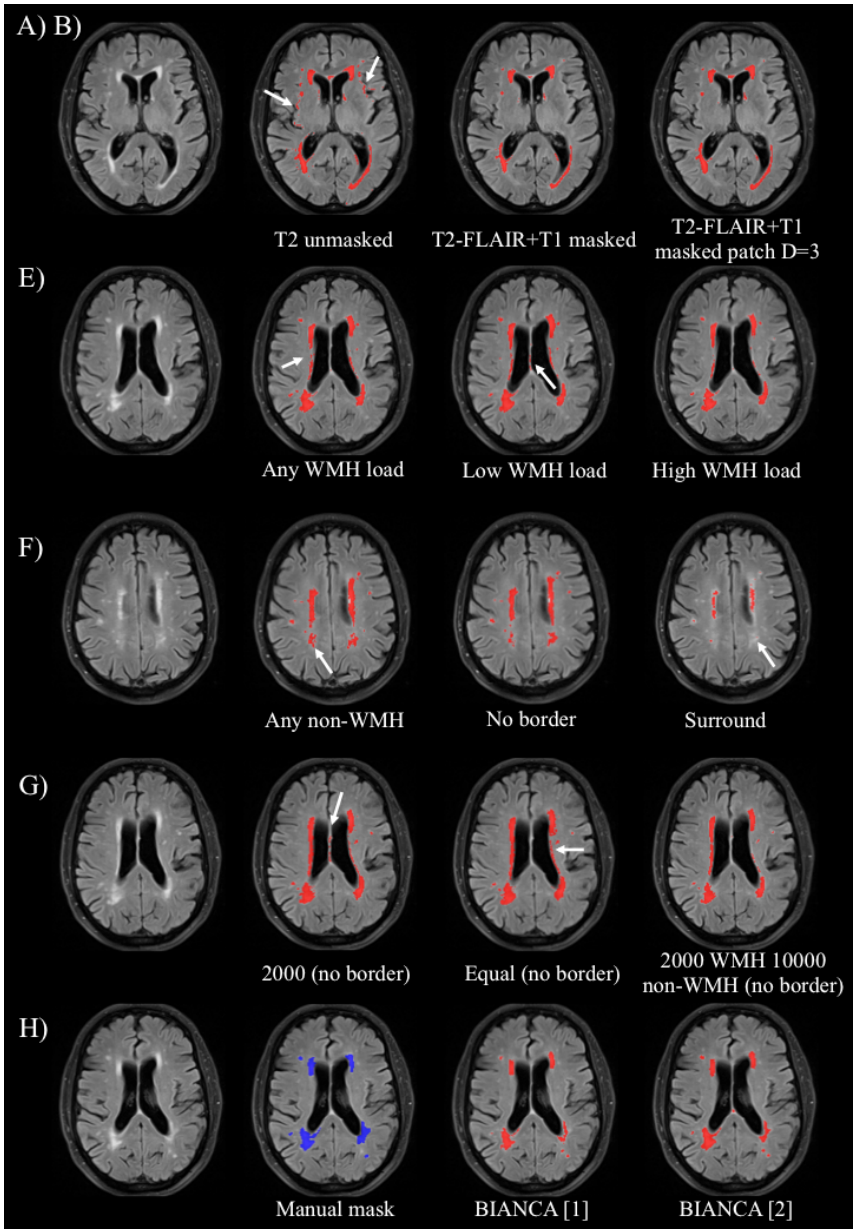


Methodology - options

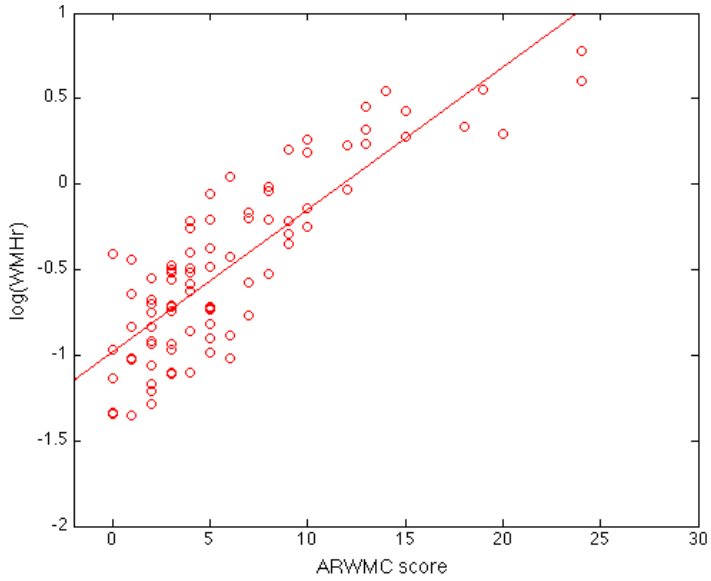
- Many options exist:
  - modalities (e.g. FLAIR, T2w, T1w)
  - features (e.g. local averages, MNI coordinates)
  - training (e.g. type of scans, no. voxels, locations sampled)
  - **post-processing** (Thresholding and Masking: cerebellum, thalamus, inferior deep GM and cortex masked out)



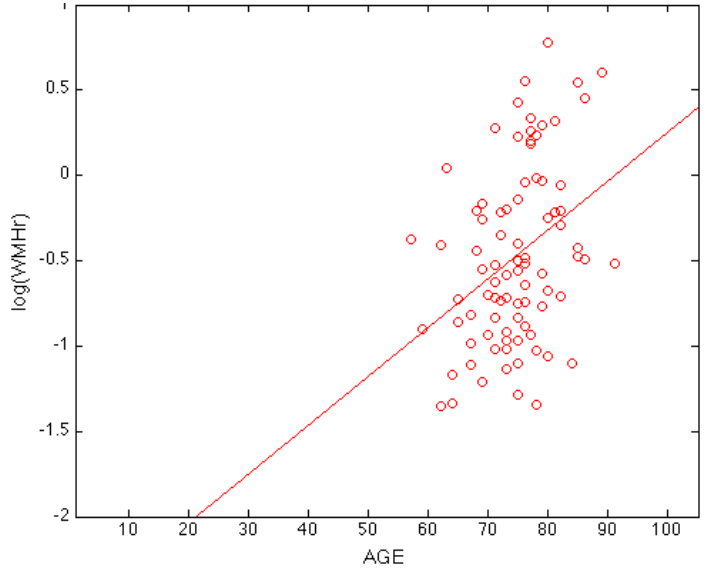
Performance evaluation



Correlation with visual ratings



Correlation with age

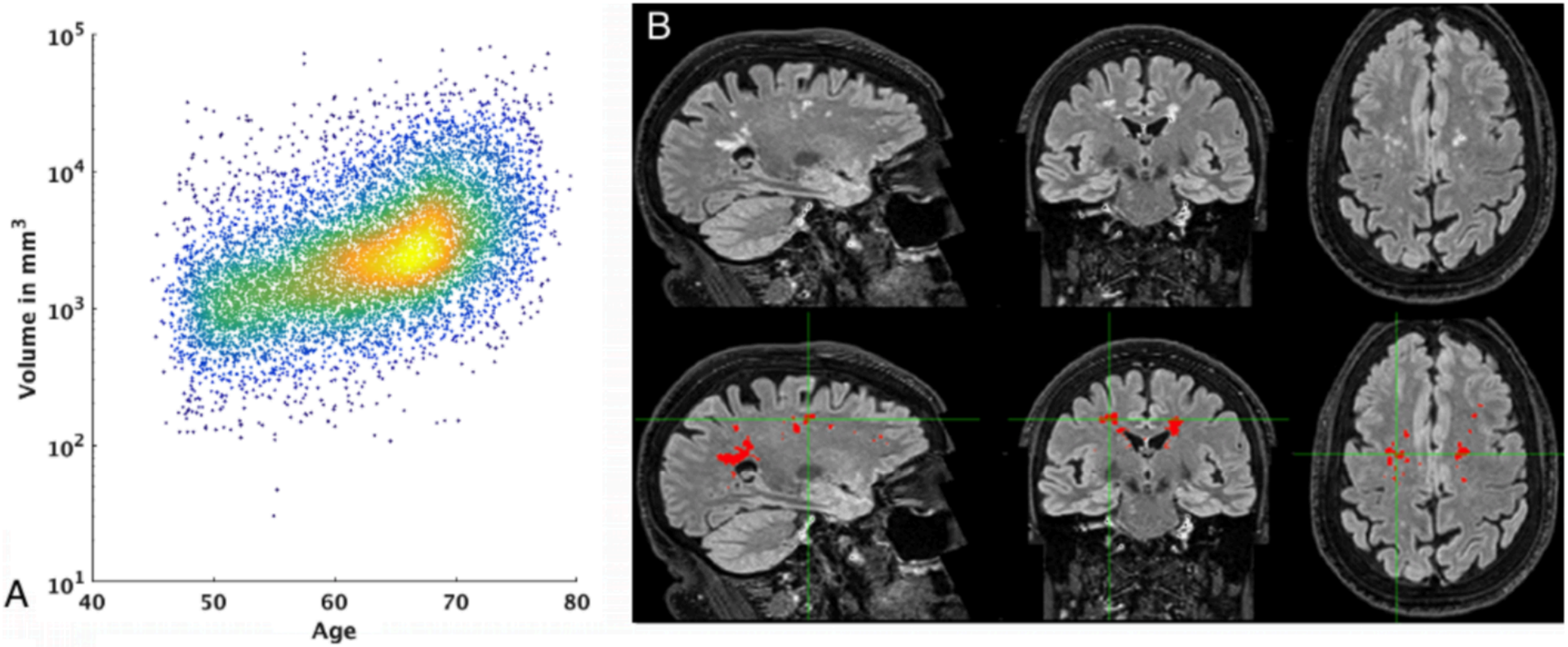


Algorithm optimisation SI = 0.76 ICC = 0.99

Griffanti, et al., NeuroImage 2016

Applications

UK Biobank - 10,000 subjects



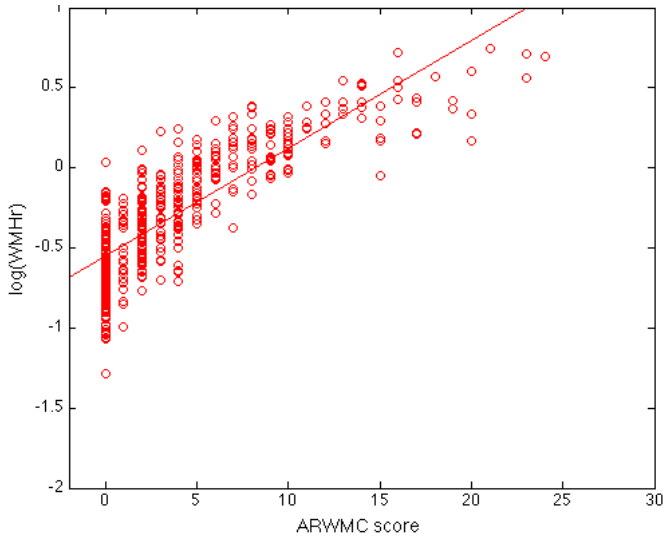
Significant correlations with:

- systolic blood pressure ($r=0.13$, $p<10^{-20}$)
- diastolic blood pressure ($r=0.11$, $p<10^{-15}$)

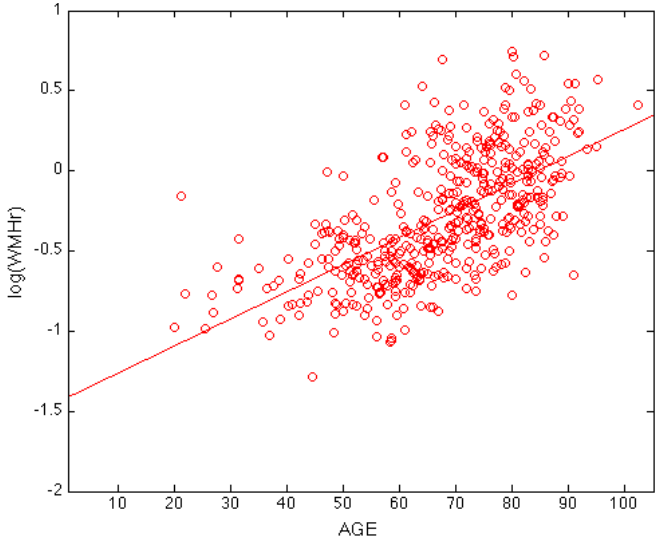
Alfaro-Almagro, et al., NeuroImage 2017

Applications

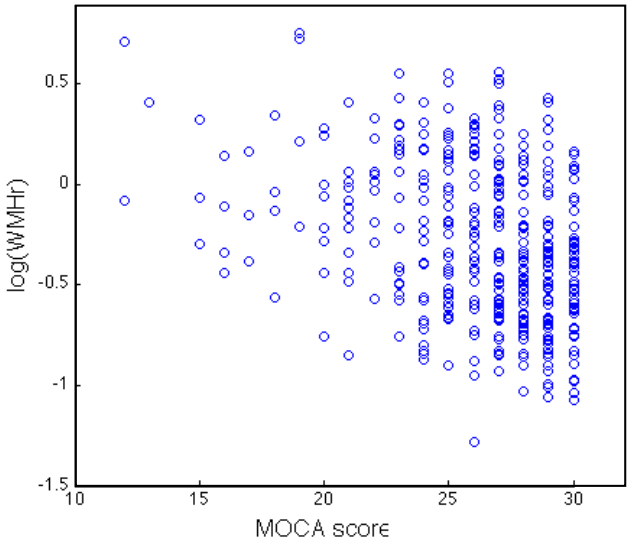
Correlation with visual ratings



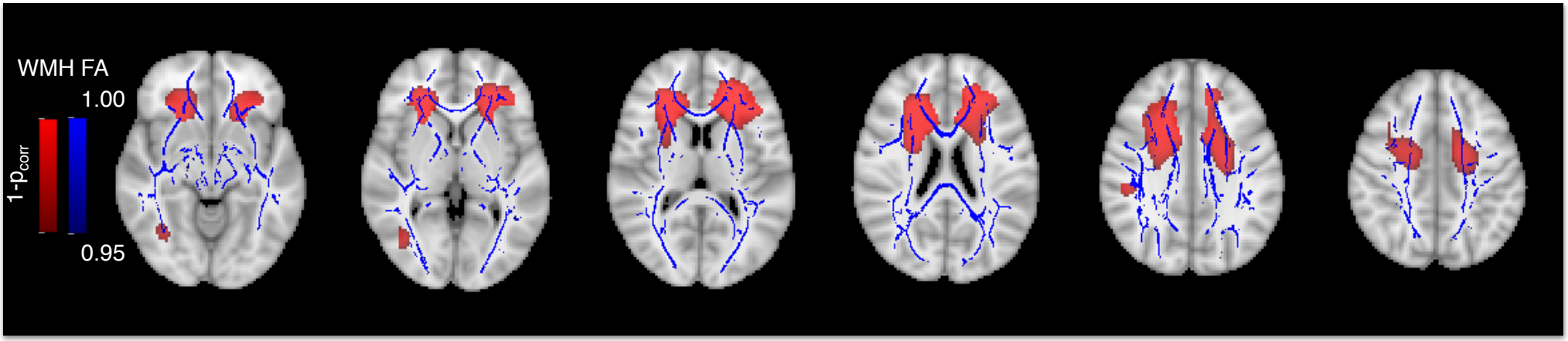
Correlation with age



Correlation with cognitive score



VOXEL-WISE ANALYSIS

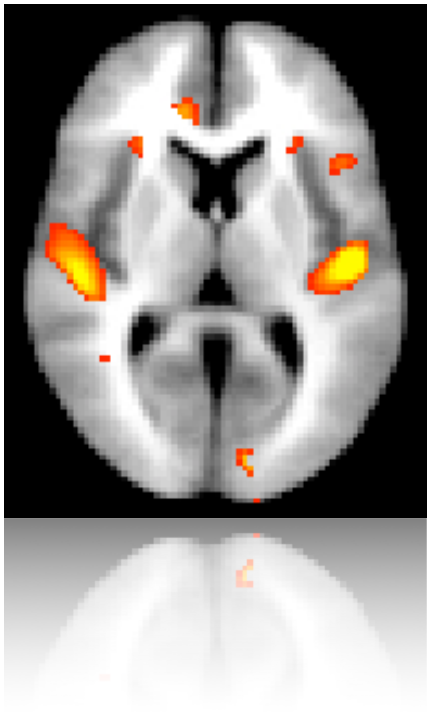


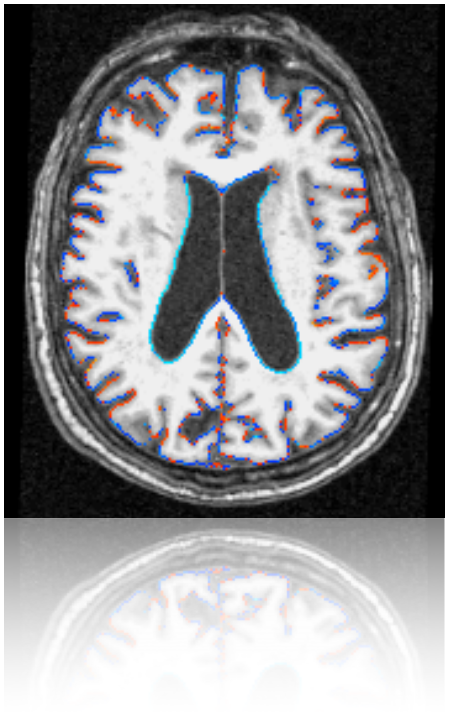
Vascular cohort - Higher WMH and lower FA in subjects with cognitive impairment (CI) according to both MMSE and MoCA vs subjects with no CI.

Zamboni, et al., Stroke 2017

Structural Analysis

FSL-VBM voxelwise grey-matter density analysis
SIENA/SIENAX global atrophy estimation

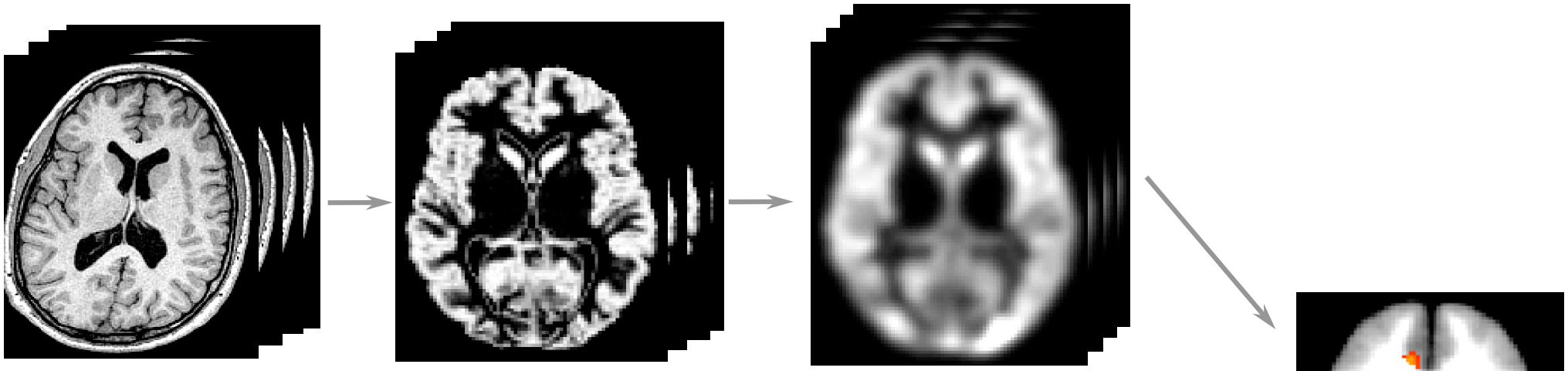




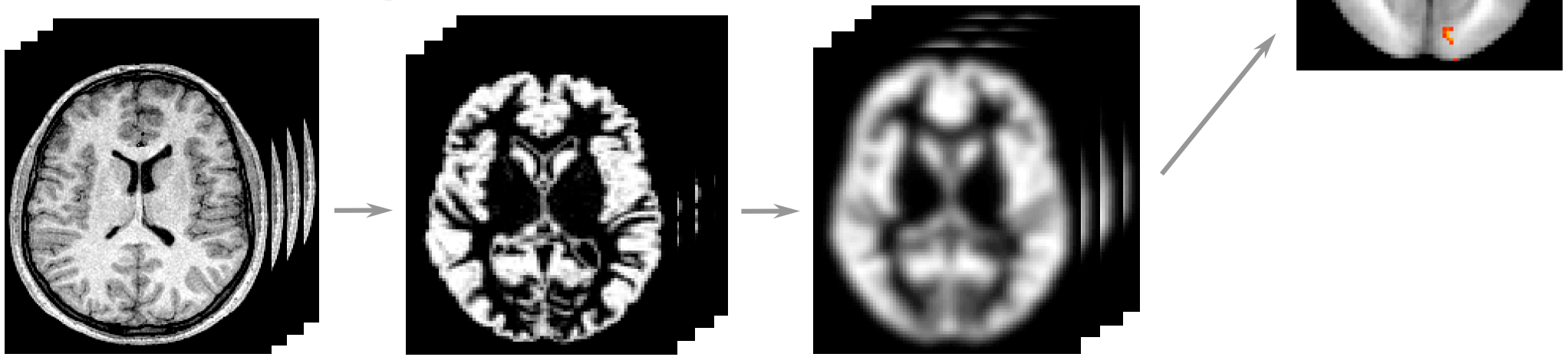
Multiple- and single-timepoint analysis of brain change

	voxelwise local-only estimation (*map*)	global-only estimation (*number*)
single timepoint (atrophy *state*)	FSL-VBM	SIENAX
two timepoints (atrophy *rate*)	Longitudinal FSL-VBM	SIENA

FSL-VBM
Voxel-Based Morphometry with FSL tools



→ To investigate GM volume differences voxel-by-voxel across subjects



Voxel-based analysis of local GM volume

- Somewhat controversial approach
  (e.g. what exactly is it "looking at"?)

- BUT - it gives some clues for:
  - volume/gyrification differences between populations
  - correlations with (e.g.) clinical score
  - fMRI/PET results "caused" by structural changes

- Currently it is very widely used, although some other alternatives exist
  (e.g. surface-based thickness analysis,
  tensor/deformation-based morphometry)

Voxel-based analysis of local GM volume

- No a priori required = whole-brain unbiased analysis
- Automated = Reproducible intra/inter-rater
- Quick

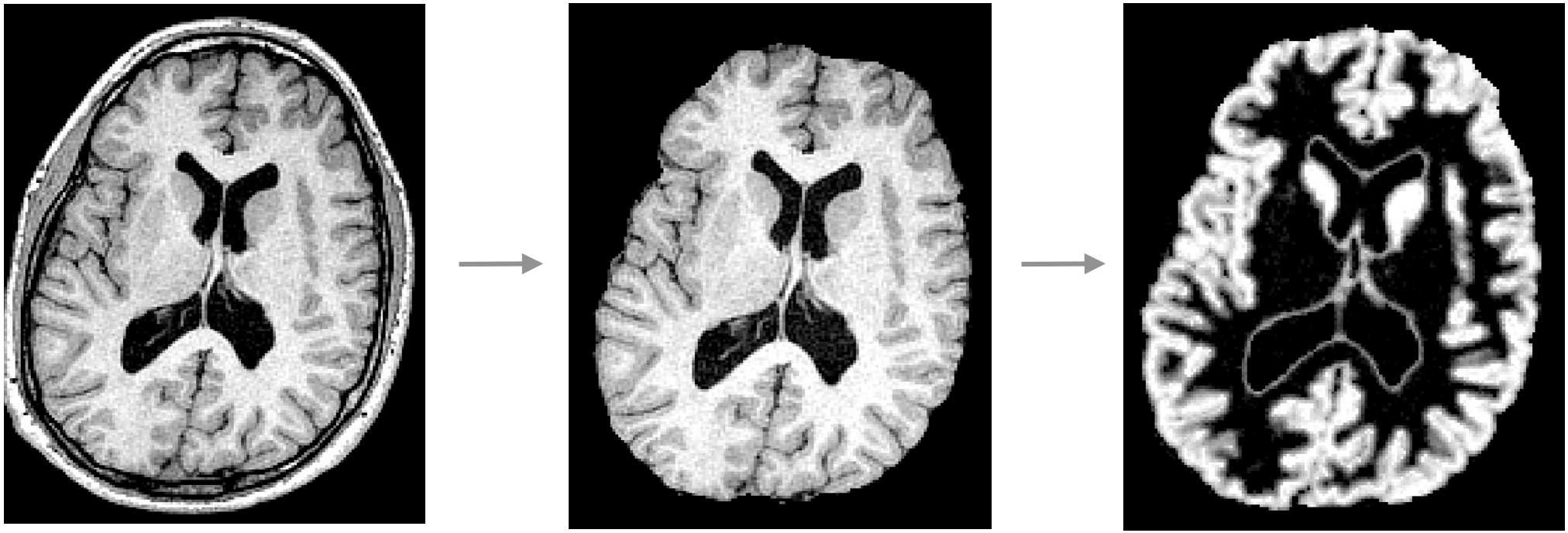
- Localisation of the GM differences across subjects
  ⇒ segmentation + non-linear registration

- Trade-off:
  - not enough non-linear = no correspondence
  - too much non-linear = no difference (in intensities)

Voxel-based analysis of local GM volume

- Optimised protocol (Good et al., 2001)

  1) Segmentation: BET then FAST to get GM partial volume estimate



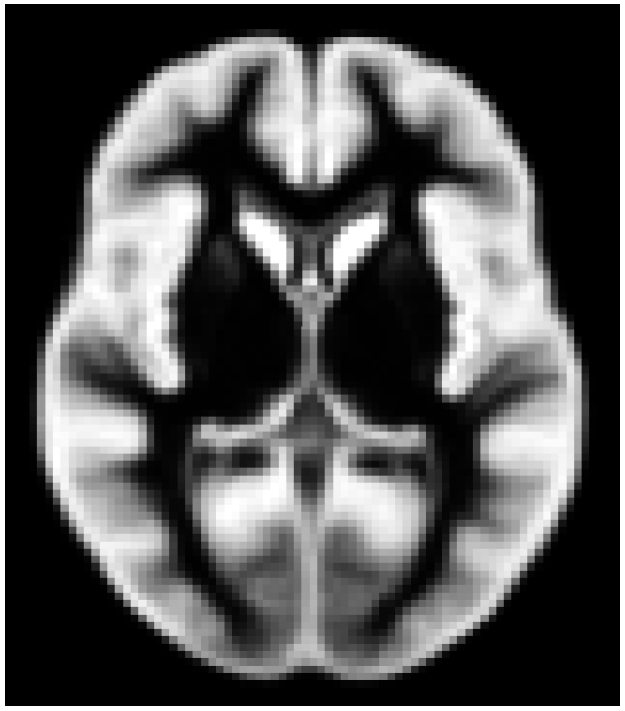
Voxel-based analysis of local GM volume

- Optimised protocol (Good et al., 2001)

  2) Make a study-specific template

  & non-linearly register all images to it (FNIRT)

Make template by iteratively registering images together, starting with a standard template



Want equal numbers of patients and controls

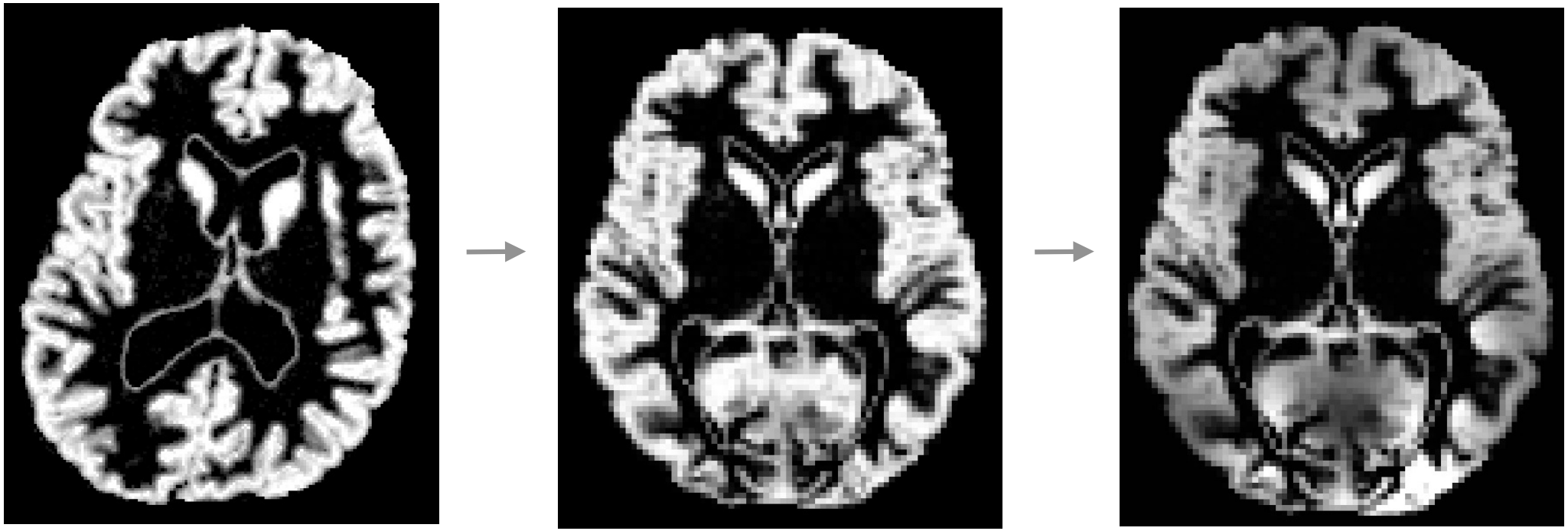
X patients

X controls

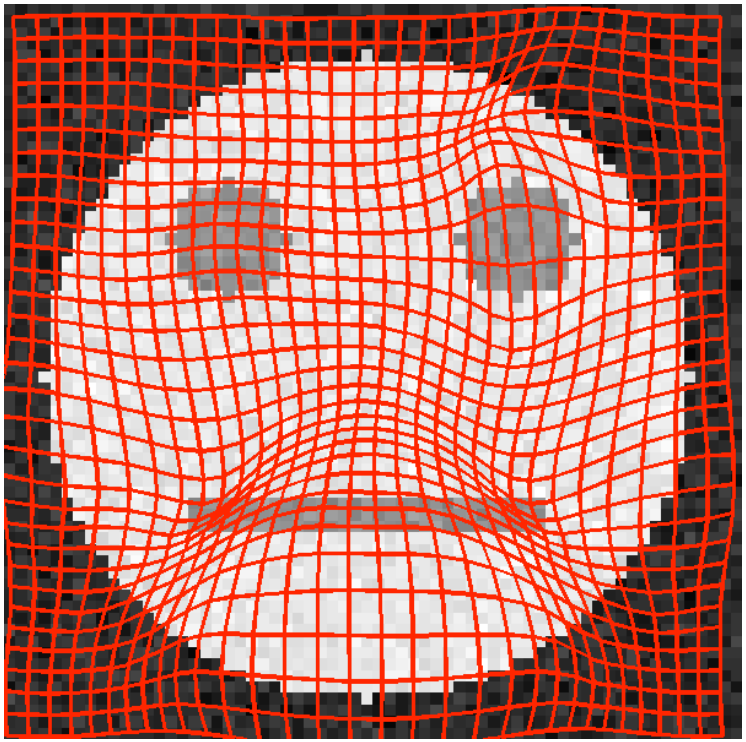
Voxel-based analysis of local GM volume

- Optimised protocol (Good et al., 2001)

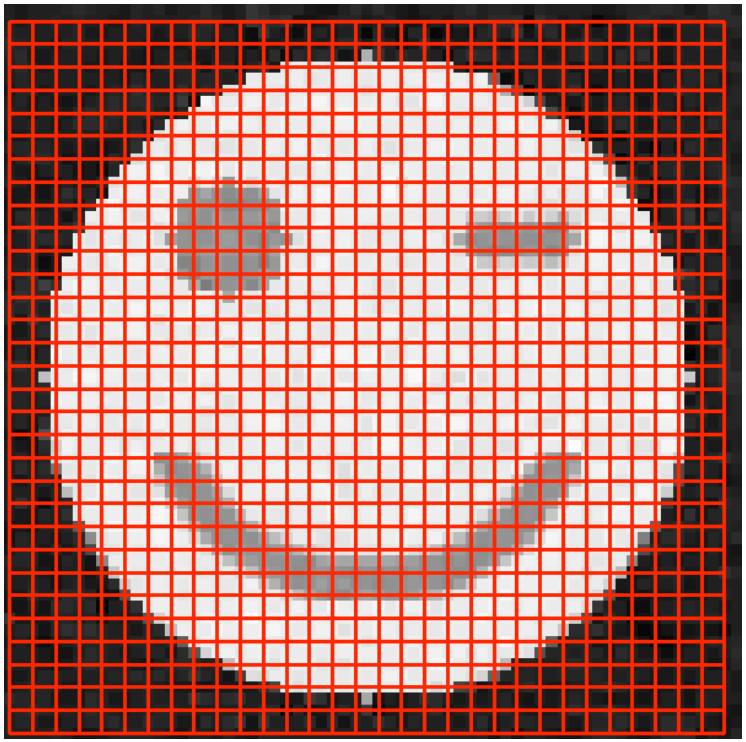
  3) "Modulation": compensates tissue volume for the non-linear part of the registration (FNIRT)



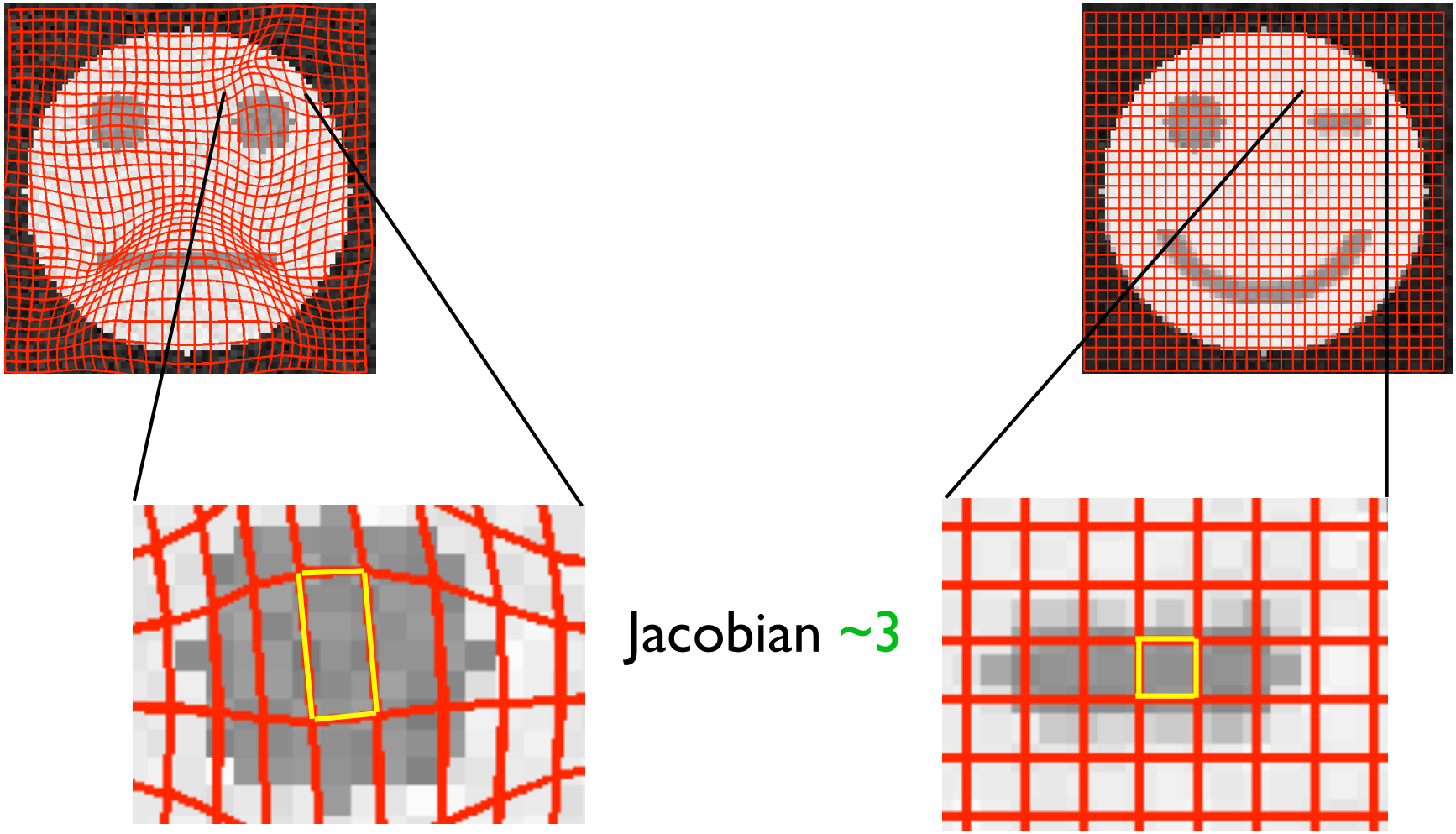
Jacobian modulation



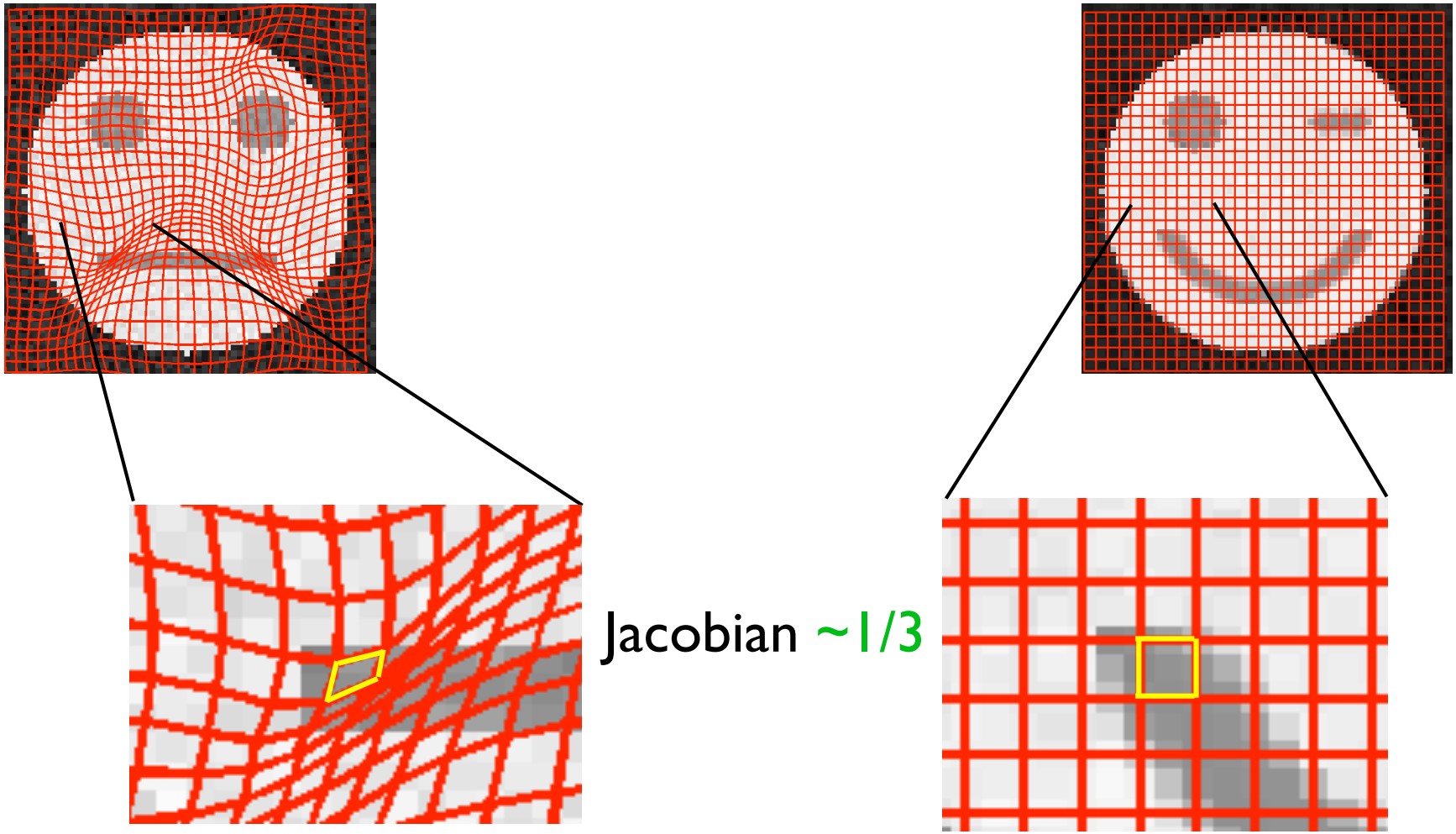
Jacobian modulation



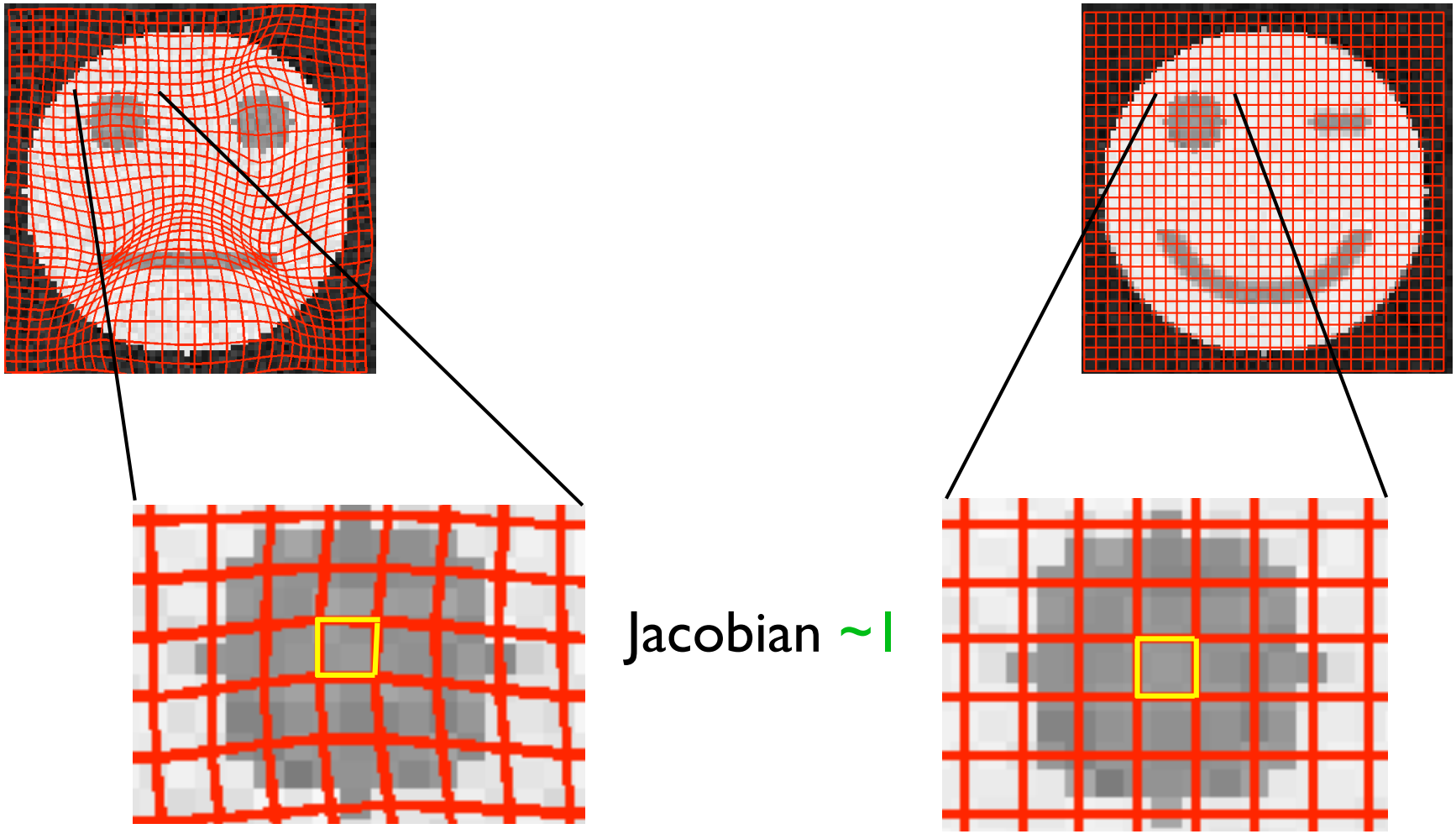
Jacobian modulation



Jacobian modulation



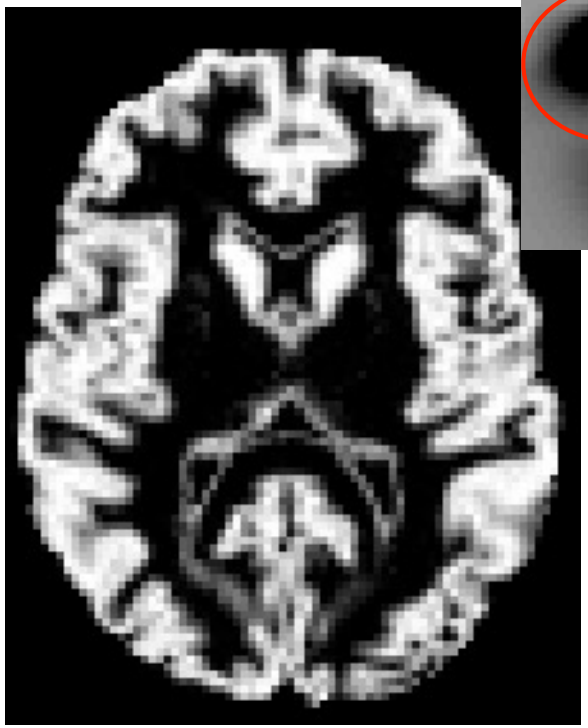
Jacobian modulation

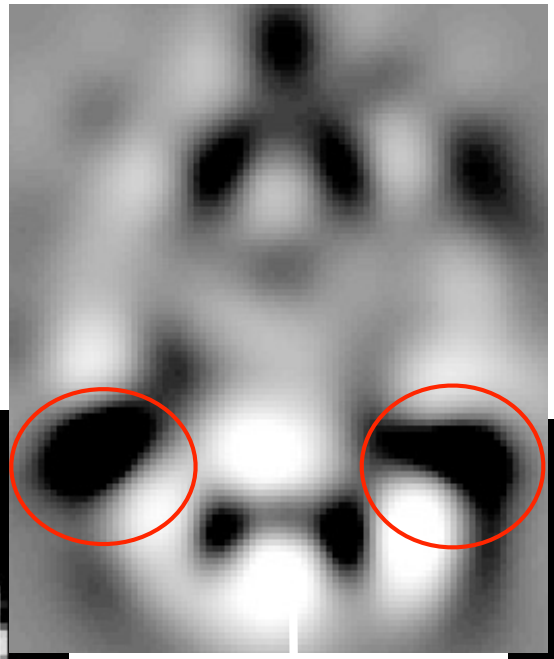


Voxel-based analysis of local GM volume

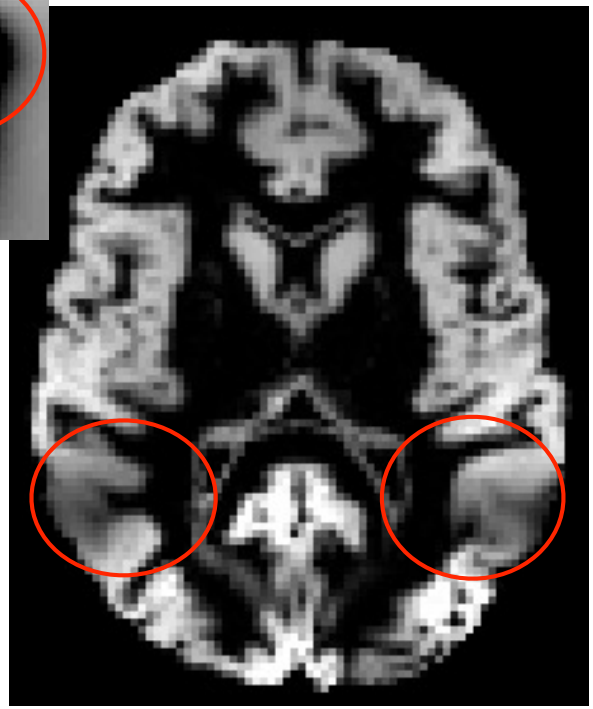
Jacobian map: correction for local expansion/contraction

Uncorrected GM results





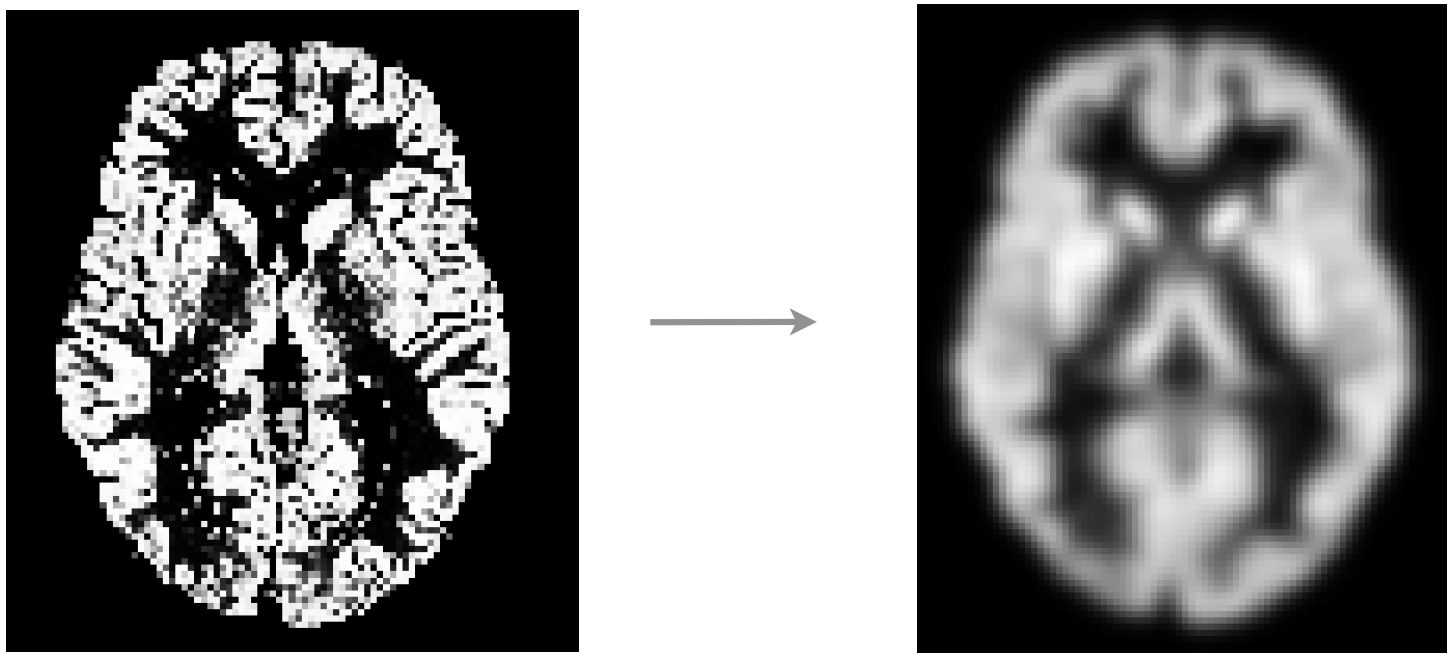
Results in "correct" amount of local GM



Voxel-based analysis of local GM volume

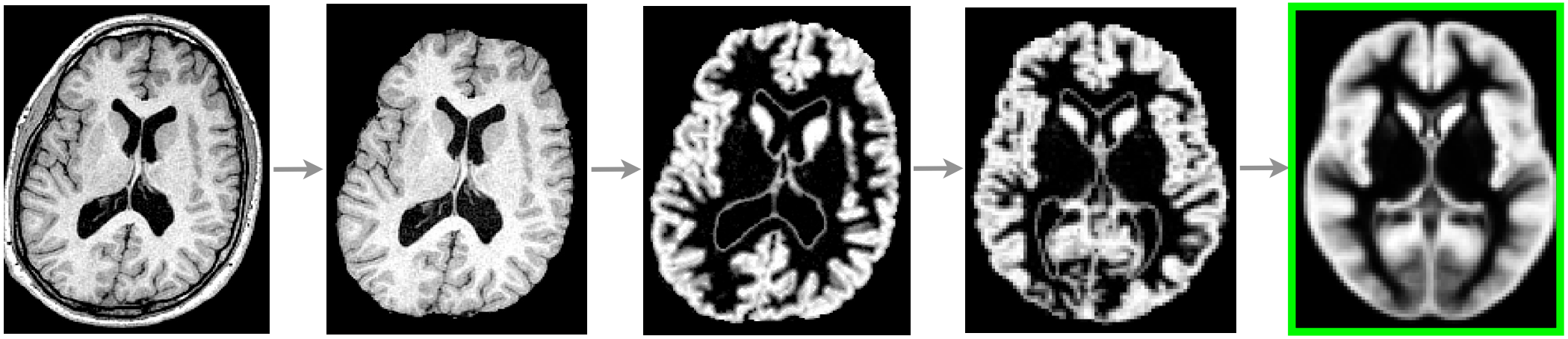
- Optimised protocol (Good et al., 2001)

  4) Smooth with a Gaussian filter

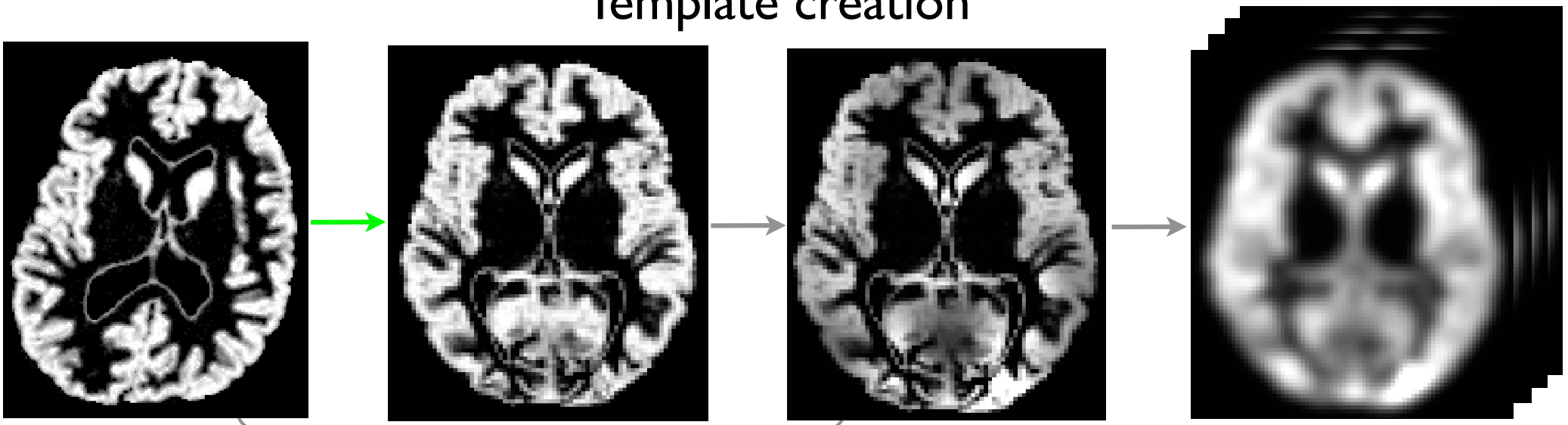


Voxel-based analysis of local GM volume

- Optimised protocol (Good et al., 2001)



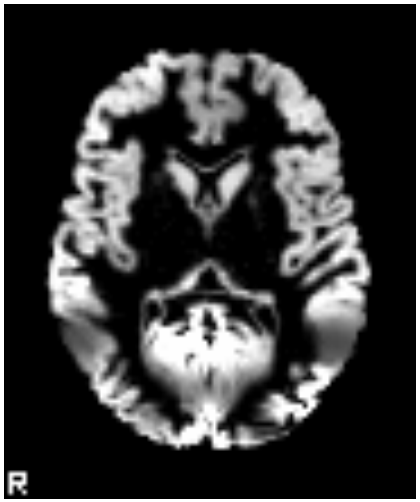
Template creation

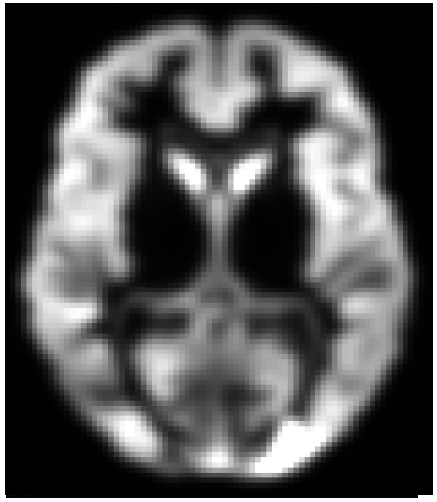


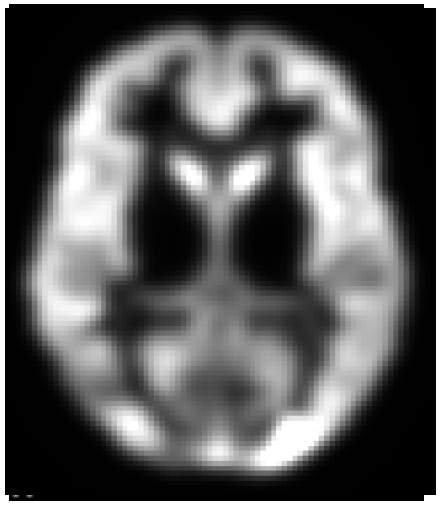
Processing steps

Analysis

Voxel-based analysis of local GM volume

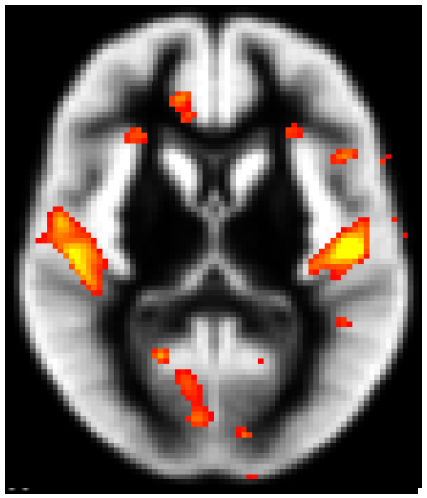


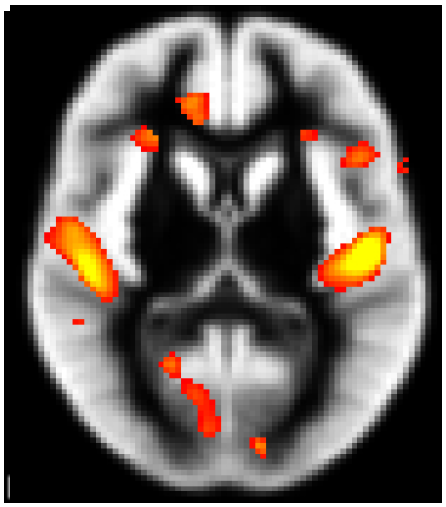




smooth=5mm

smooth=8mm

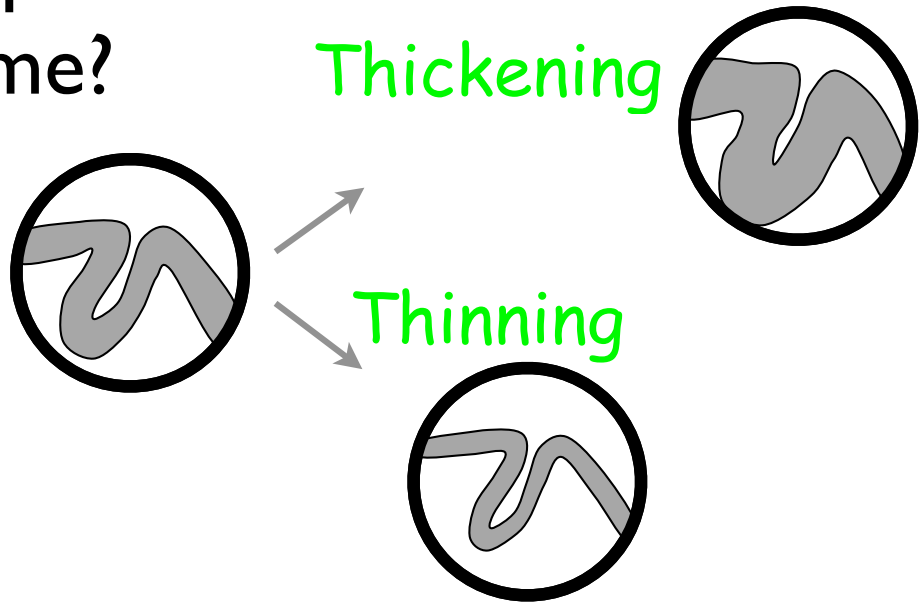




Voxel-based analysis of GM volume

- Controversial approach - back to the issues:

1) Interpretation of the results - real loss/increase of volume?

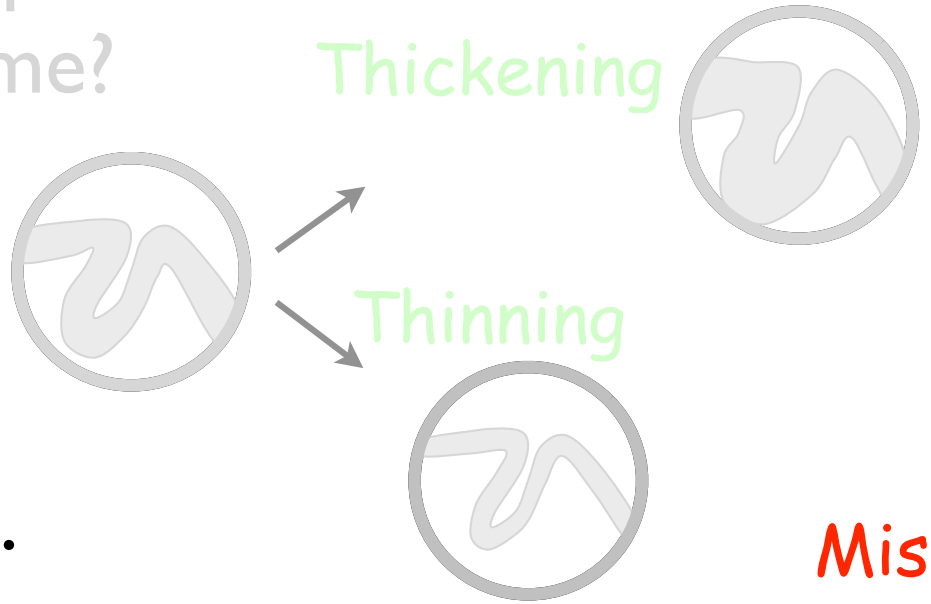


Illustrations courtesy of John Ashburner

Voxel-based analysis of GM volume

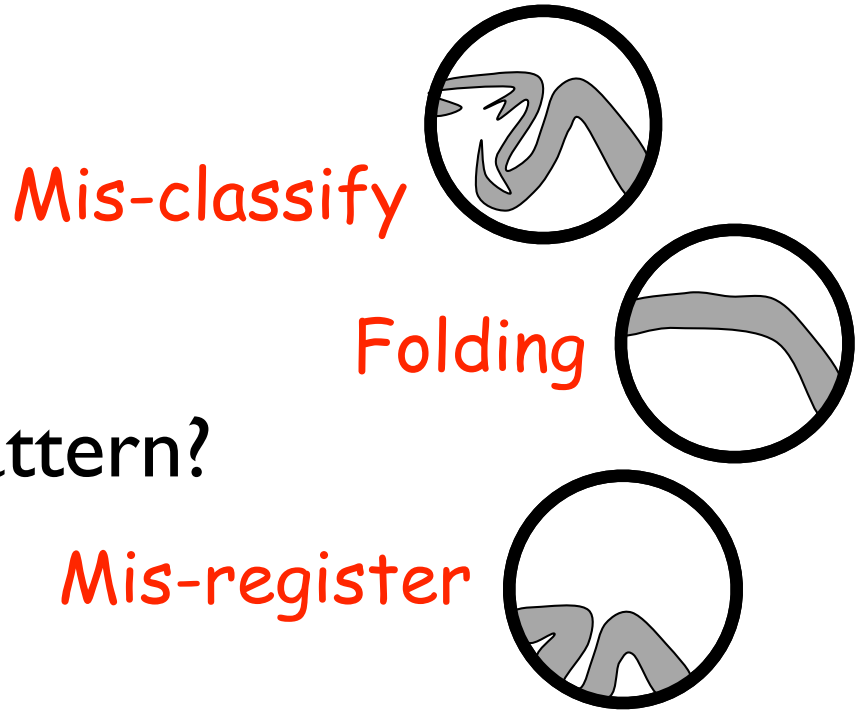
- Controversial approach - back to the issues:

1) Interpretation of the results - real loss/increase of volume?



Or ...

- Difference in the contrast?
- Difference in gyrification pattern?
- Problem with registration?



Illustrations courtesy of John Ashburner

Voxel-based analysis of GM volume

- Controversial approach - back to the issues:

1) Interpretation of the results - real loss of volume?
   - Difference in the contrast?
   - Different in gyrification pattern (developmental)?
   - Problem with registration (Bookstein 2001)?

2) Continuum of results, depending on:
   - Smoothness (Jones 2005)
   - DOF of the nonlinear registration (Crum 2003)
   - Template?
   - Software?

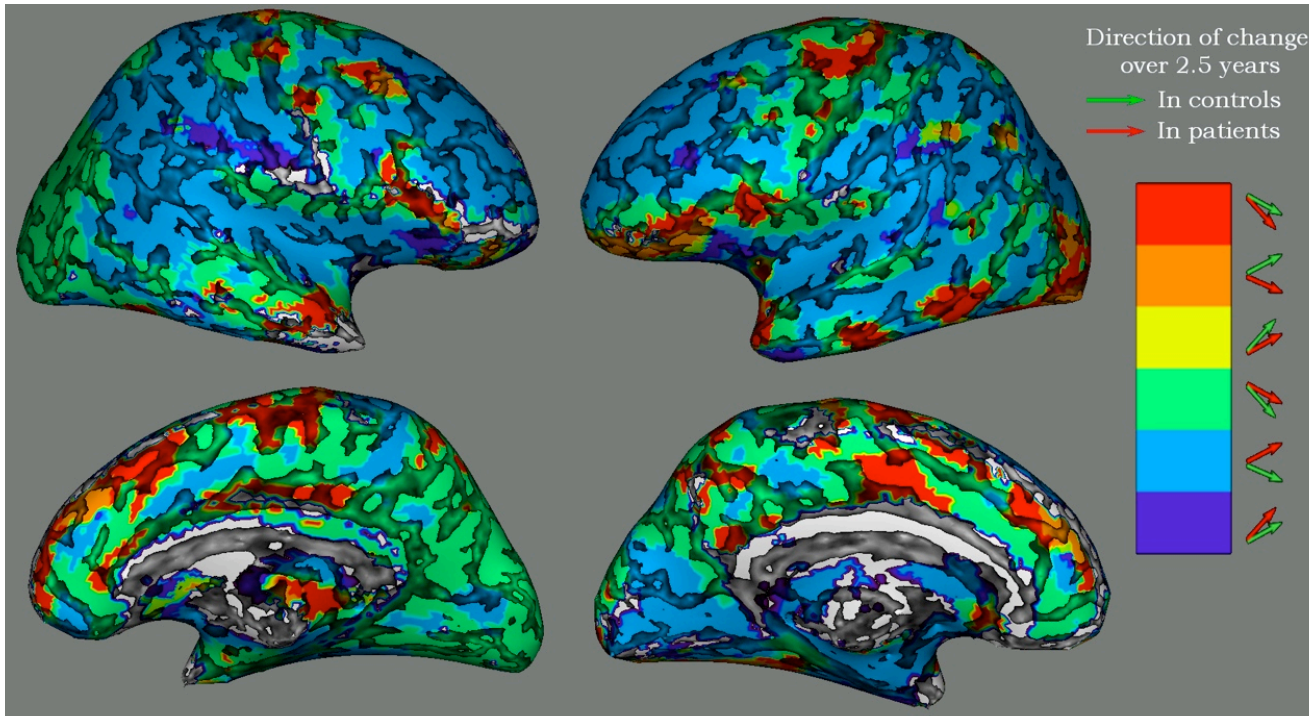
⟶ See Ridgway et al., NeuroImage 2008 for best practice

Multiple- and single-timepoint analysis of brain change

	voxelwise local-only estimation (*map*)	global-only estimation (*number*)
single timepoint (atrophy *state*)	FSL-VBM	SIENAX
two timepoints (atrophy *rate*)	Longitudinal FSL-VBM	SIENA

Voxel-based analysis of GM volume

- Useful literature/examples:
  - Longitudinal protocol in FSL: Douaud et al., Brain 2009



  - Comparisons of longitudinal protocols and softwares: Thomas et al., NeuroImage 2009

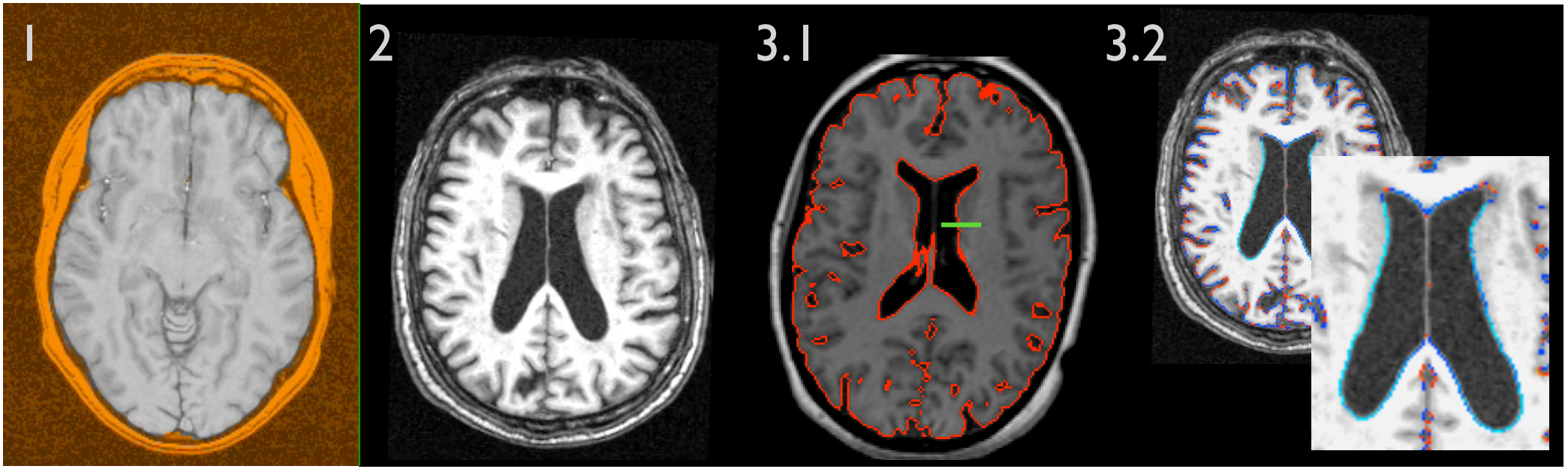
SIENA

Structural Image Evaluation (with Normalisation) of Atrophy

	voxelwise local-only estimation (*map*)	global-only estimation (*number*)
single timepoint (atrophy *state*)	FSL-VBM	SIENAX
two timepoints (atrophy *rate*)	Longitudinal FSL-VBM	SIENA

SIENA Longitudinal atrophy estimation

1. BET: find brain and skull - applied to both time points
2. FLIRT: register to half-way space (similar interpolation for 2 points)
3. Atrophy estimation using edge motion
   3.1. Run FAST, then sample normal profile of brain-non brain boundary
   3.2. Take derivative of both time points' profiles and calculate shift for each boundary point: blue=atrophy, red="growth"
4. Average over all edge points and conversion to % brain volume change (PBVC)



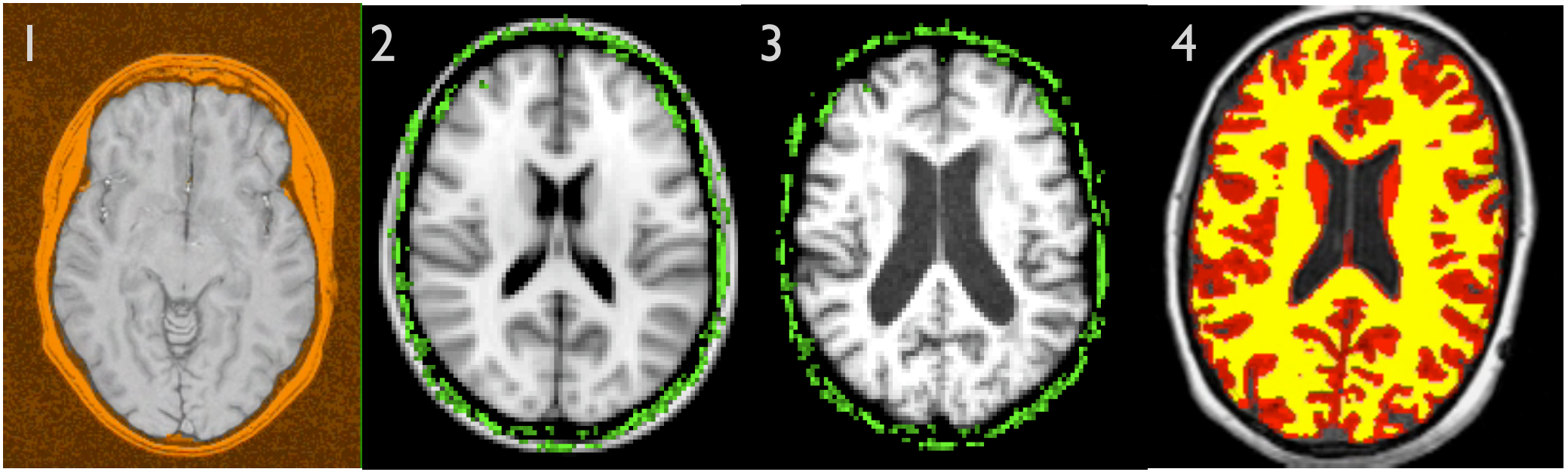
Multiple- and single-timepoint analysis of brain change

	voxelwise local-only estimation (*map*)	global-only estimation (*number*)
single timepoint (atrophy *state*)	FSL-VBM	SIENAX
two timepoints (atrophy *rate*)	Longitudinal FSL-VBM	SIENA

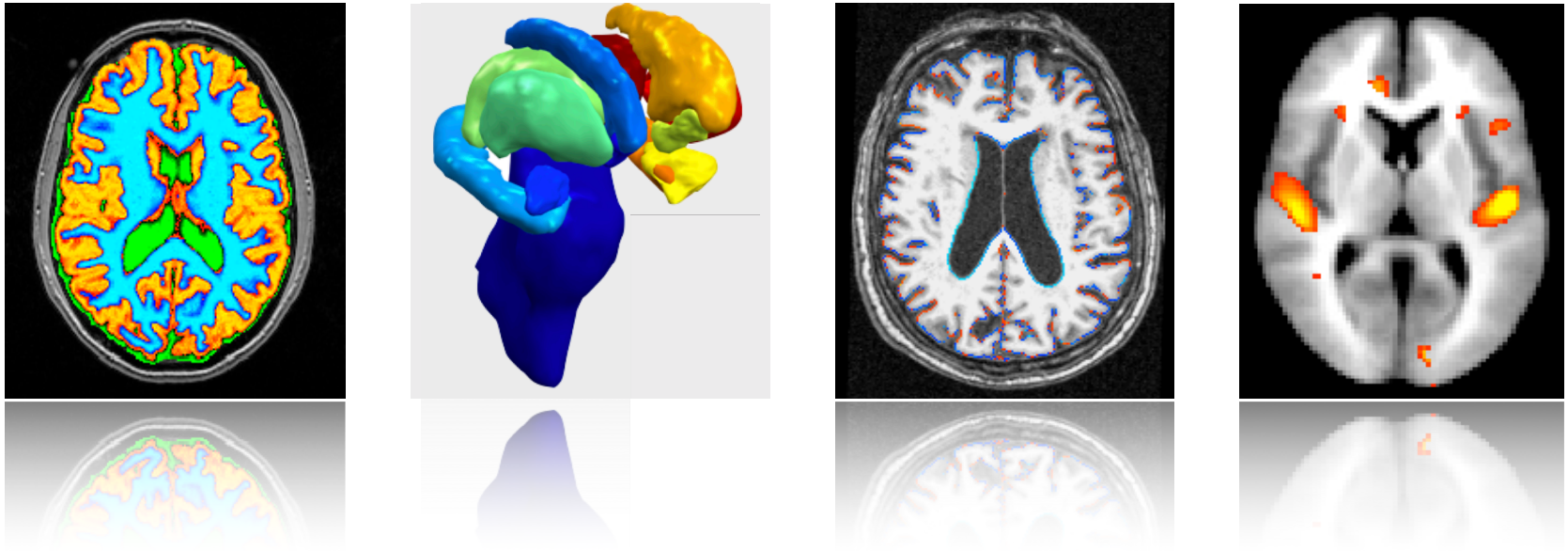
SIENAX Cross-sectional atrophy estimation

1. BET : find brain and skull
2. FLIRT : register to standard space using skull for scaling
3. Use standard-space masking to remove residual eyes/optic nerve
4. FAST : partial volume segmentation of tissues
5. Output : normalised brain volume (NBV)

Note: NBV is useful for including as a *head/brain-size covariate* in other structural analyses (e.g. FIRST, VBM, etc.)



The End



- FAST tissue-type segmentation
- FIRST sub-cortical structure segmentation
- BIANCA segmentation of white matter lesions
- FSL-VBM voxelwise grey-matter density analysis
- SIENA/SIENAX global atrophy estimation