

# Introduction à la statistique médicale

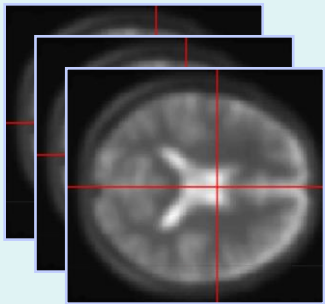
## Statistical Parametric Mapping short course

### Course 1: spatial pre-processing

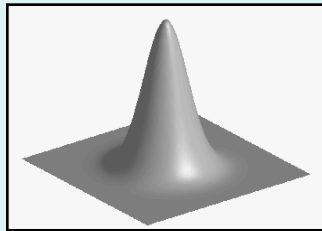
Christophe Phillips, Ir PhD  
GIGA – CRC *In Vivo* Imaging &  
GIGA – *In Silico* Medicine

# SPM work flow

Image time-series



Spatial filter

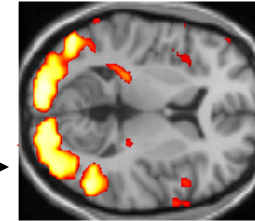
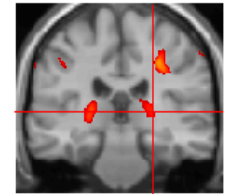
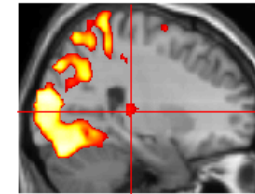


Realignment

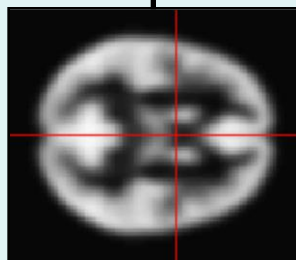
Smoothing

General Linear Model

Statistical Parametric Map

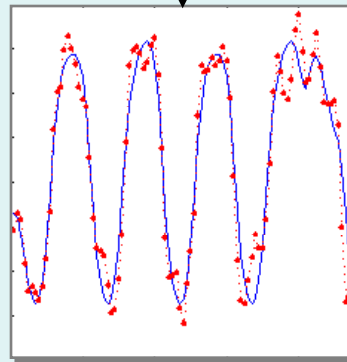
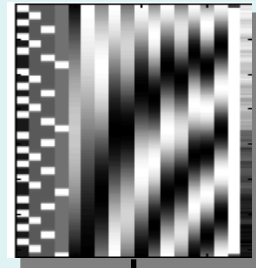


Normalisation



Anatomical reference

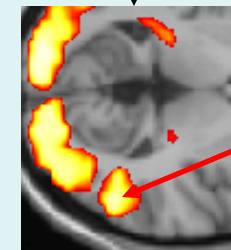
Design matrix



Parameter estimates

Statistical Inference

RFT



$p < 0.05$

# Content

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- **Preliminaries**
- **Within-subject**
- **Between-subject**
- **Smoothing**
- **Conclusion**

# Content

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- **Preliminaries**

- **Introduction**
- **Rigid-body & affine transformation**
- **Function optimisation**
- **Transformations and interpolation**
- **Pre-processing overview**

- **Within-subject**

- **Between-subject**

- **Smoothing**

- **Conclusion**

# Image registration

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Most “preprocessing” involves aligning images together.

## **Two components:**

- *Registration* - i.e. Optimise the parameters that describe spatial transformations between the images.
- *Transformation* - i.e. Re-sample according to the determined transformation parameters.

# *Label based* techniques

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- Homologous labels (points, lines, surfaces) in the source and the reference images
  - find transformations that best superpose them
- Labels are identified (manually/semi-automatically)
  - time consuming and subjective process
  - few identifiable discrete points in the brain
- Lines and surfaces, e.g. contours, can be extracted (semi-)automatically
- Best match = minimal distance
  - Q: how do you measure “distance”?

# *Intensity based* techniques

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By minimizing a “**distance**” between the whole *source* image and the whole *reference* image:

- Need a scalar measure (=distance) to optimize
- Susceptible to poor starting estimates

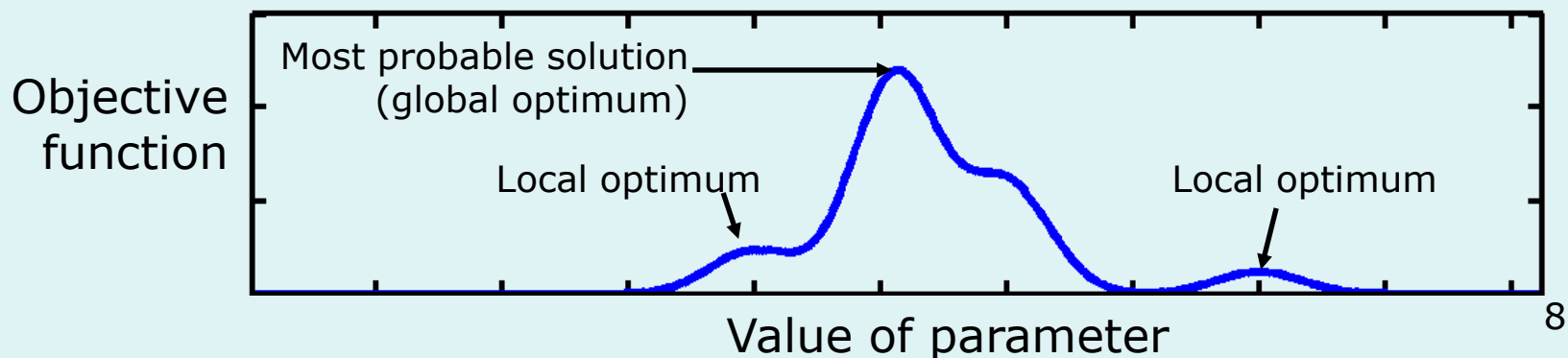
➔ Hybrid approaches :

label/manual + intensity based methods

# Optimisation

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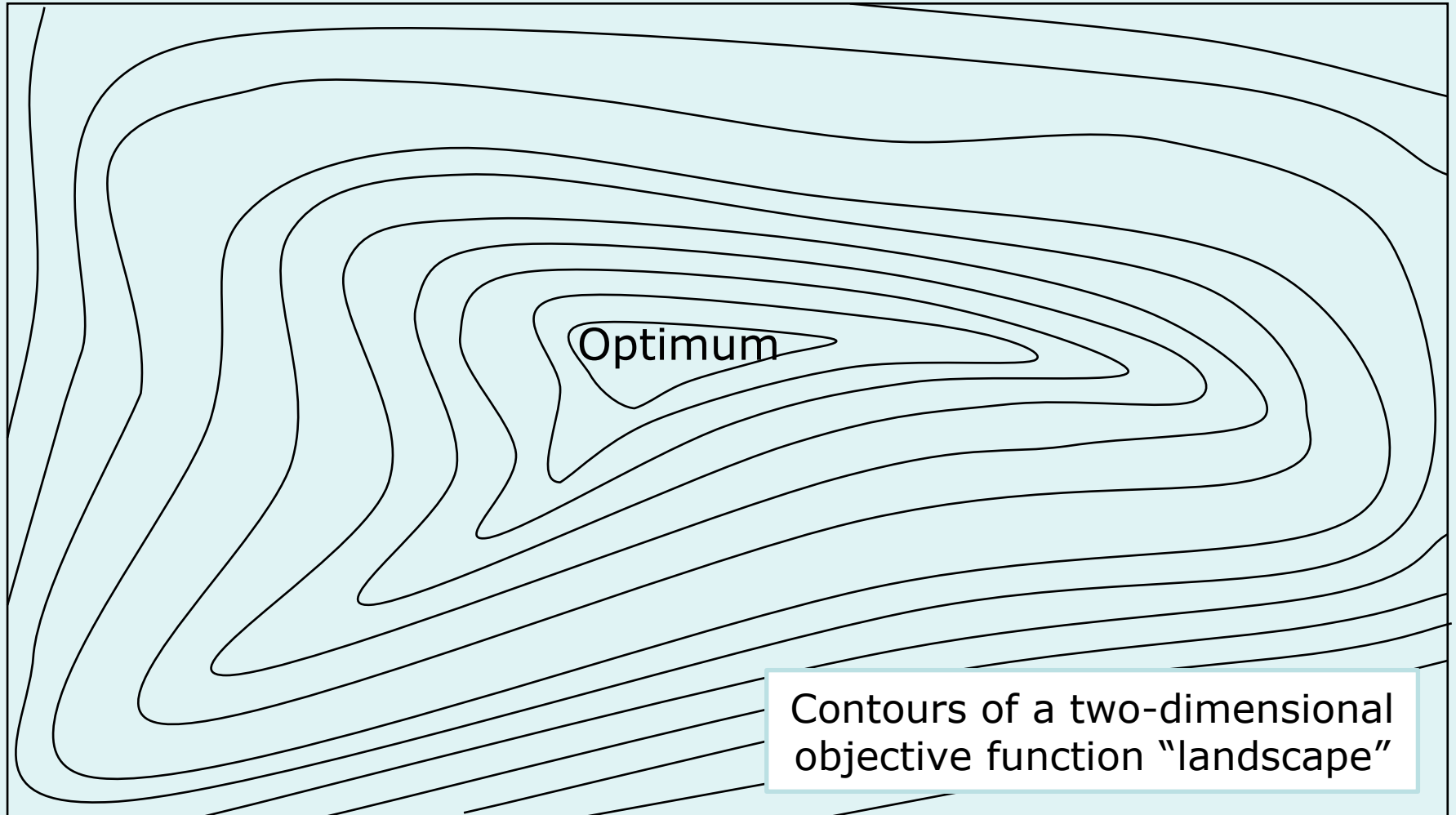
- Image registration is done by **optimisation**.
- Optimisation involves finding some “best” parameters according to an “objective function”, which is either minimised or maximised
- The “objective function” is often related to a probability based on some model





# Optimisation, multiple parameters

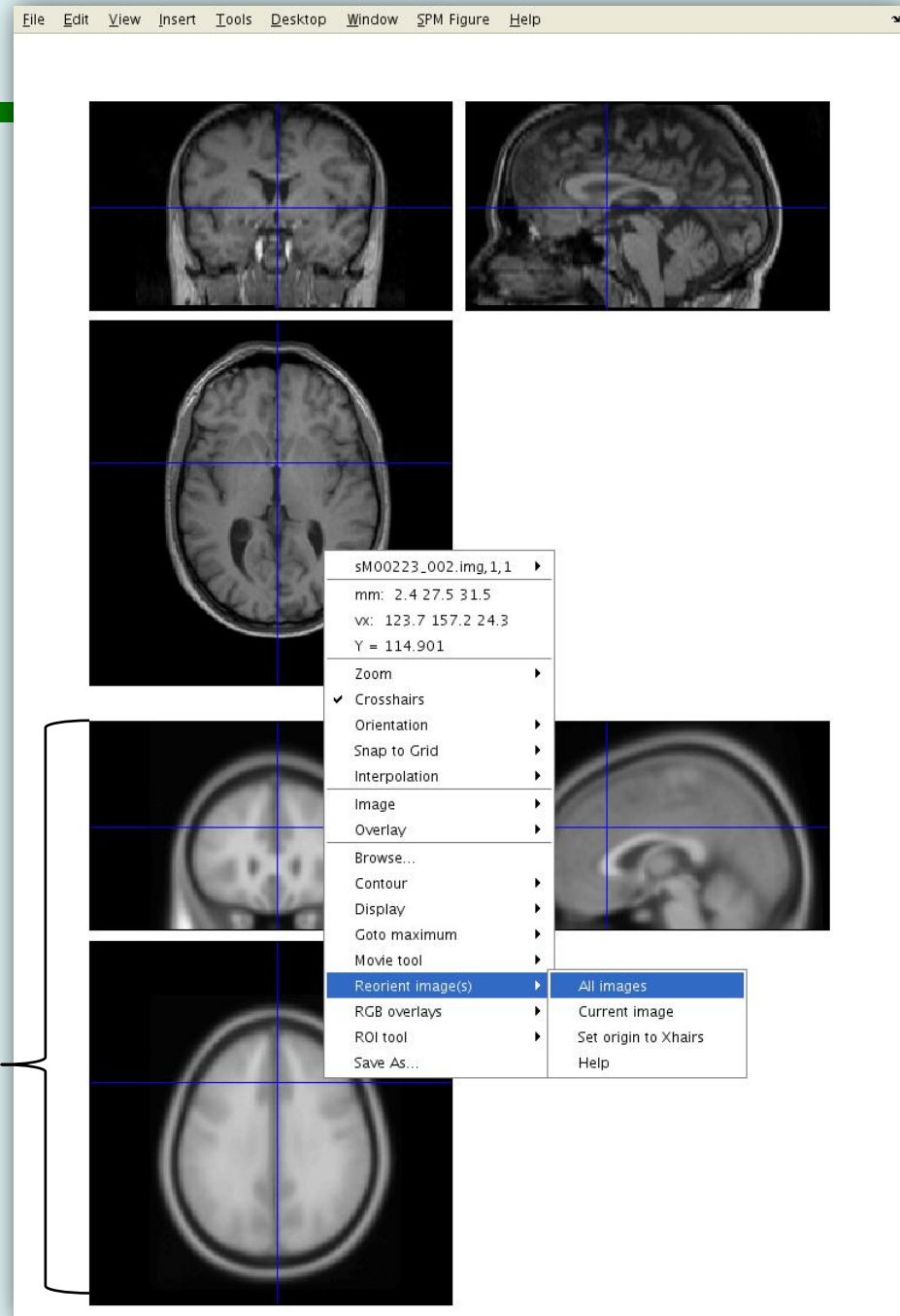
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# Optimisation

Because registration only finds a *local optimum*, some manual reorienting of the images may be needed before doing anything else in SPM.

An MNI-space image from `spm12/canonical` directory.



# 2D Affine Transforms

- Translations by  $t_x$  and  $t_y$

$$x_1 = x_0 + t_x$$

$$y_1 = y_0 + t_y$$

- Rotation around the origin by  $\Theta$  radians

$$x_1 = \cos(\Theta) x_0 + \sin(\Theta) y_0$$

$$y_1 = -\sin(\Theta) x_0 + \cos(\Theta) y_0$$

- Zooms by  $s_x$  and  $s_y$ :

$$x_1 = s_x x_0$$

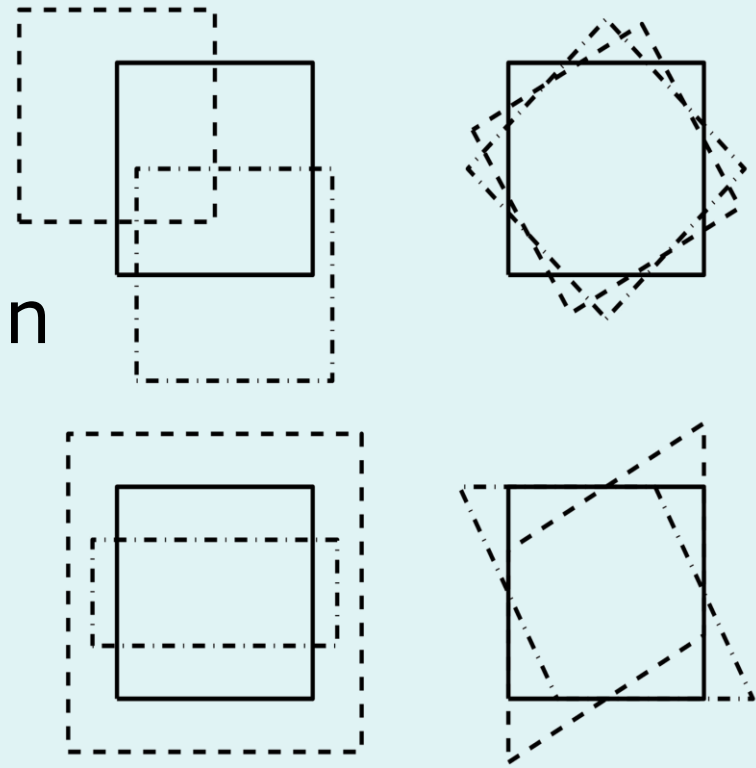
$$y_1 = s_y y_0$$

- Shear  $h_x$

$$x_1 = x_0 + h_x y_0$$

$$y_1 = y_0$$

Same for  $h_y$



# 2D Affine Transforms

- Translations by  $t_x$  and  $t_y$

$$x_1 = 1 x_0 + 0 y_0 + t_x$$

$$y_1 = 0 x_0 + 1 y_0 + t_y$$

- Rotation around the origin by  $\Theta$  radians

$$x_1 = \cos(\Theta) x_0 + \sin(\Theta) y_0 + 0$$

$$y_1 = -\sin(\Theta) x_0 + \cos(\Theta) y_0 + 0$$

- Zooms by  $s_x$  and  $s_y$ :

$$x_1 = s_x x_0 + 0 y_0 + 0$$

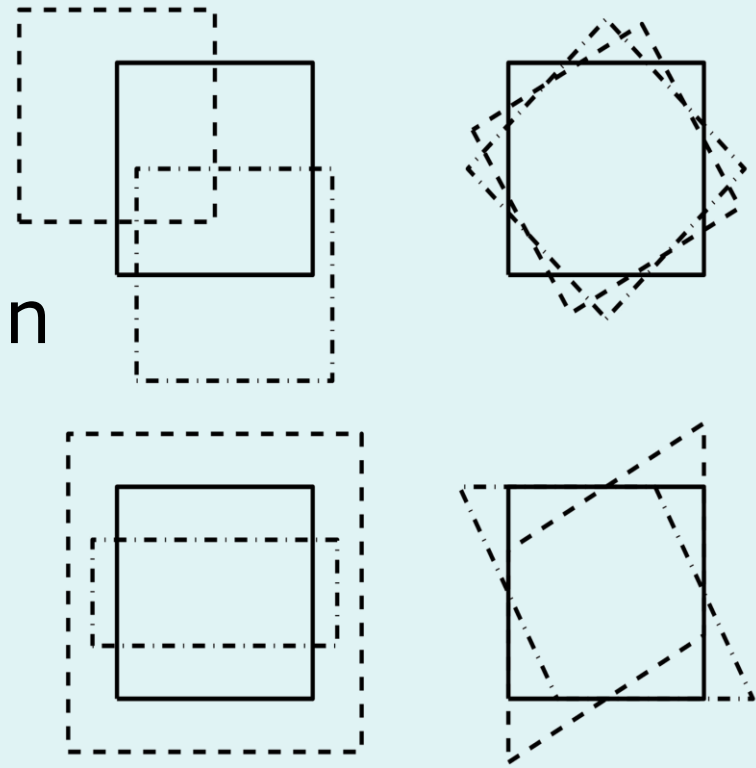
$$y_1 = 0 x_0 + s_y y_0 + 0$$

- Shear  $h_x$

$$x_1 = 1 x_0 + 0 y_0 + h_x y_0$$

$$y_1 = 0 x_0 + 1 y_0 + 0$$

Same for  $h_y$



# 2D Affine transform

- Rigid-body transformations are a subset of “affine transformation”
- Parallel lines remain parallel
- Operations can be represented by:

$$x_1 = m_{11}x_0 + m_{12}y_0 + m_{13}$$

$$y_1 = m_{21}x_0 + m_{22}y_0 + m_{23}$$

- Or as matrices:

$$\mathbf{p}_1 = \mathbf{M} \mathbf{p}_0$$

$$\begin{bmatrix} x_1 \\ y_1 \\ 1 \end{bmatrix} = \begin{bmatrix} m_{11} & m_{12} & m_{13} \\ m_{21} & m_{22} & m_{23} \\ 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} x_0 \\ y_0 \\ 1 \end{bmatrix}$$

# 3D Affine transform

- Rigid-body transformations are a subset of “affine transformation”
- Parallel lines remain parallel
- Operations can be represented by:

$$x_1 = m_{11}x_0 + m_{12}y_0 + m_{13}z_0 + m_{14}$$

$$y_1 = m_{21}x_0 + m_{22}y_0 + m_{23}z_0 + m_{24}$$

$$z_1 = m_{31}x_0 + m_{32}y_0 + m_{33}z_0 + m_{34}$$

- Or as matrices:

$$\mathbf{y} = \mathbf{M} \mathbf{x}$$

$$\begin{bmatrix} x_1 \\ y_1 \\ z_1 \\ 1 \end{bmatrix} = \begin{bmatrix} m_{11} & m_{12} & m_{13} & m_{14} \\ m_{21} & m_{22} & m_{23} & m_{24} \\ m_{31} & m_{32} & m_{33} & m_{34} \\ 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} x_0 \\ y_0 \\ z_0 \\ 1 \end{bmatrix}$$

# Rigid-body transformations

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- Assume that brain of the same subject doesn't change shape or size in the scanner.
  - Head can move, but remains the same shape and size.
  - Some exceptions:
    - Image distortions.
    - Brain slops about slightly because of gravity.
    - Brain growth or atrophy over time.
- If the subject's head moves, we need to correct the images.
  - Do this by image registration.

# 3D Rigid-body Transform

- A 3D rigid body transform is an affine transform defined by:
  - 3 translations - in X, Y & Z directions
  - 3 rotations - about X, Y & Z axes
- The order of the operations matters

$$R = \begin{pmatrix} 1 & 0 & 0 & X_{\text{trans}} \\ 0 & 1 & 0 & Y_{\text{trans}} \\ 0 & 0 & 1 & Z_{\text{trans}} \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos f & \sin f & 0 \\ 0 & -\sin f & \cos f & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos q & 0 & \sin q & 0 \\ 0 & 1 & 0 & 0 \\ -\sin q & 0 & \cos q & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos \Omega & \sin \Omega & 0 & 0 \\ -\sin \Omega & \cos \Omega & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Translations                      Pitch  
about x axis                      Roll  
about y axis                      Yaw  
about z axis



# Voxel-to-world transformation

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“Voxel-to-world transforms” =

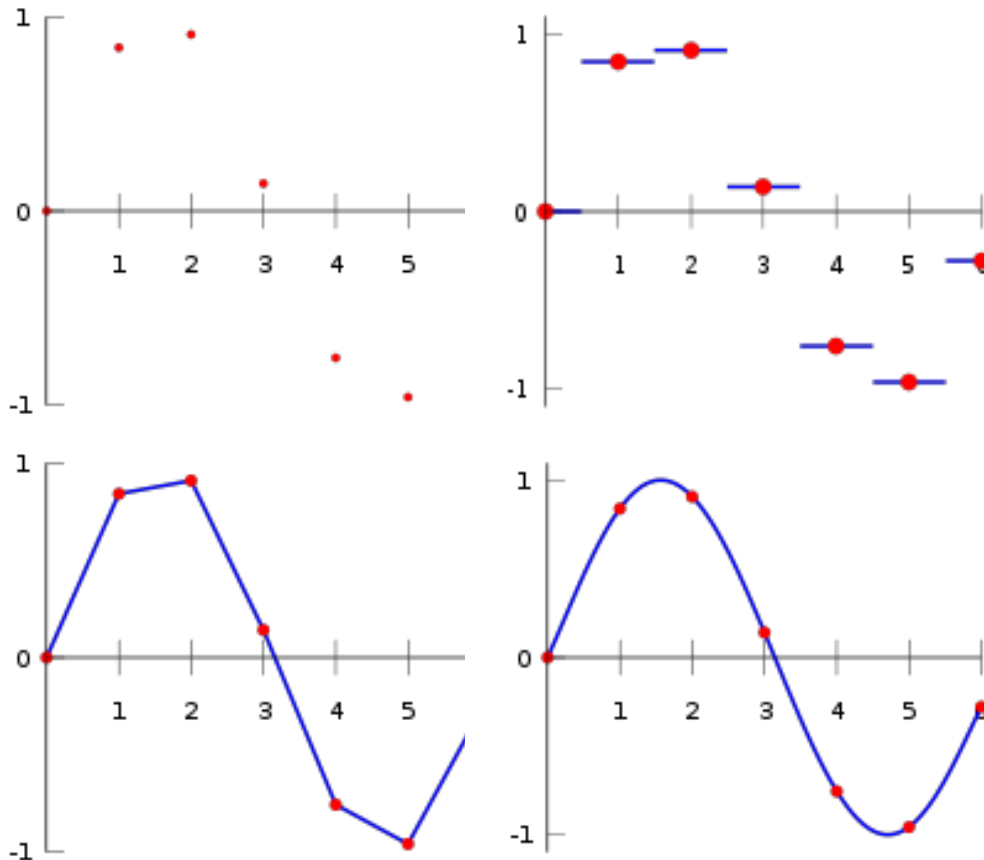
*Affine transform* **M** associated with each image such that

- Maps from voxels ( $\mathbf{x}=[1\dots N_x]$ ,  $\mathbf{y}=[1\dots N_y]$ ,  $\mathbf{z}=[1\dots N_z]$ ) to some world co-ordinate system. e.g.,
  - Scanner co-ordinates - images from DICOM toolbox
  - T&T/MNI coordinates - spatially normalised
- World coordinates are (usually) in millimetres!

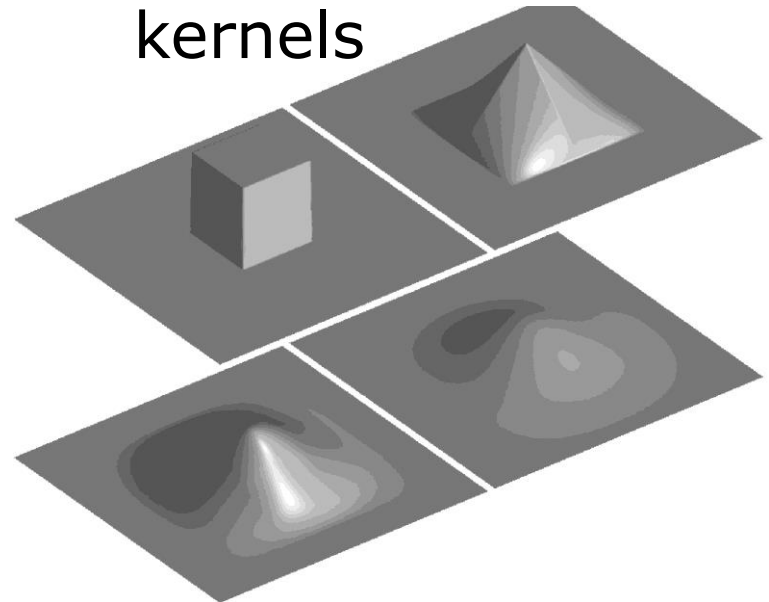
# Image resampling

A continuous function is represented by a linear combination of basis functions

## 1D interpolation

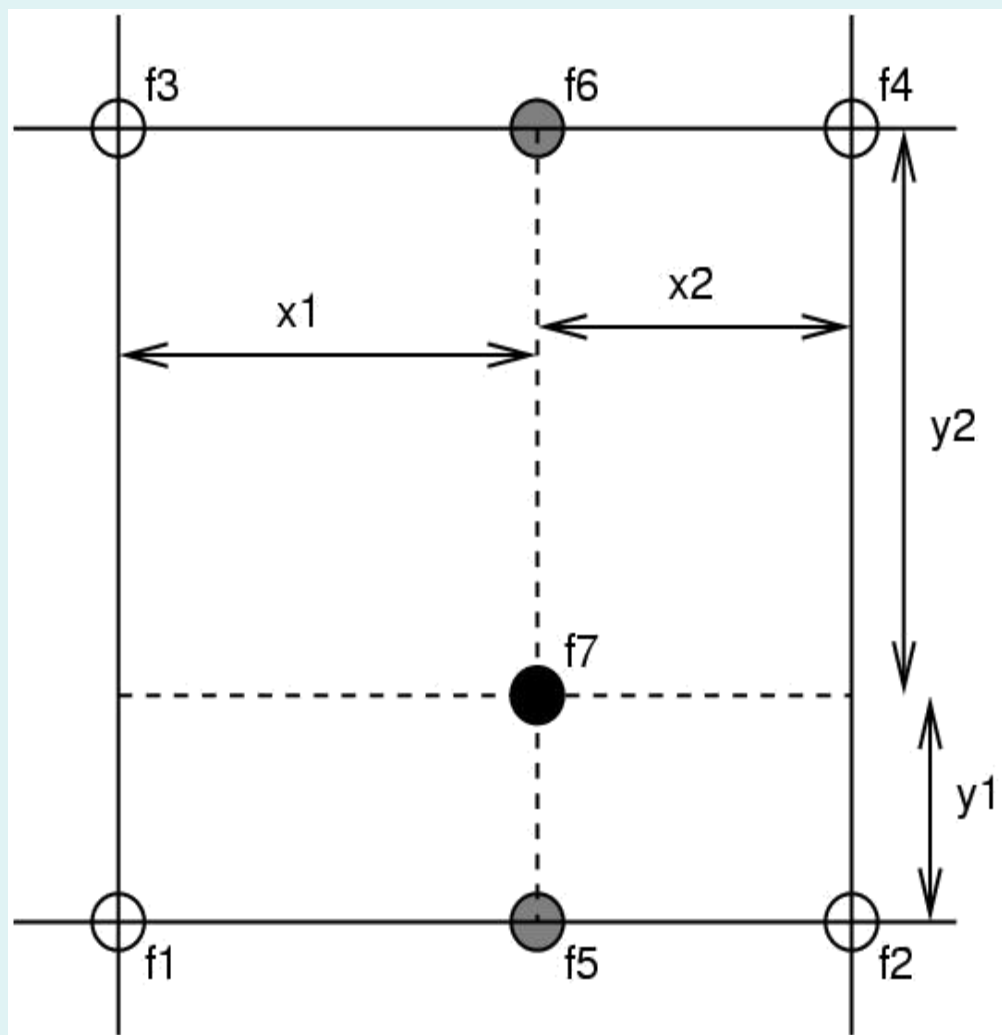


2D  
interpolation  
kernels



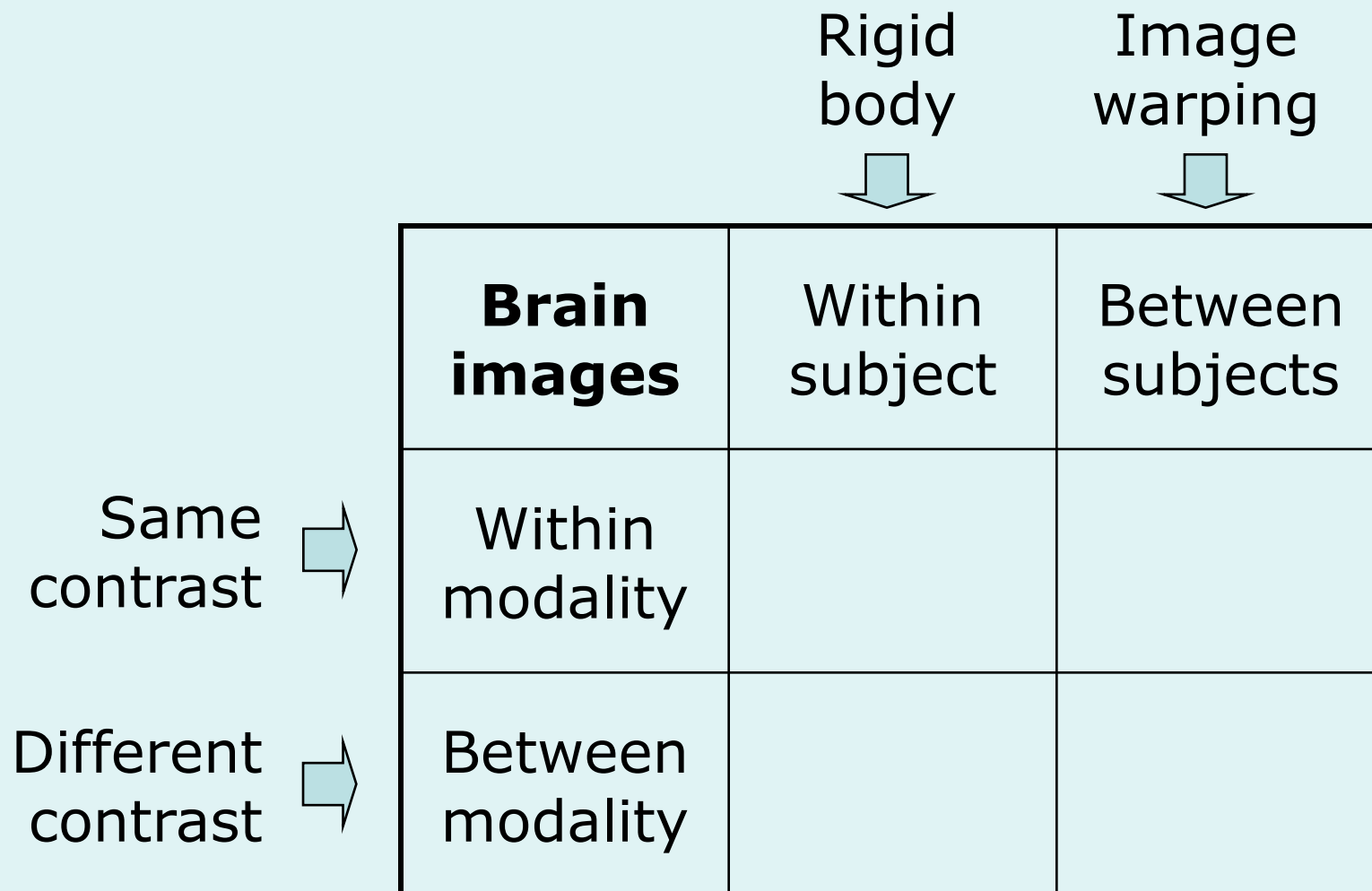
# Image resampling

- Nearest neighbour
  - Take the value of the closest voxel
- Tri-linear
  - Just a weighted average of the neighbouring voxels
  - $f_5 = f_1 x_2 + f_2 x_1$
  - $f_6 = f_3 x_2 + f_4 x_1$
  - $f_7 = f_5 y_2 + f_6 y_1$

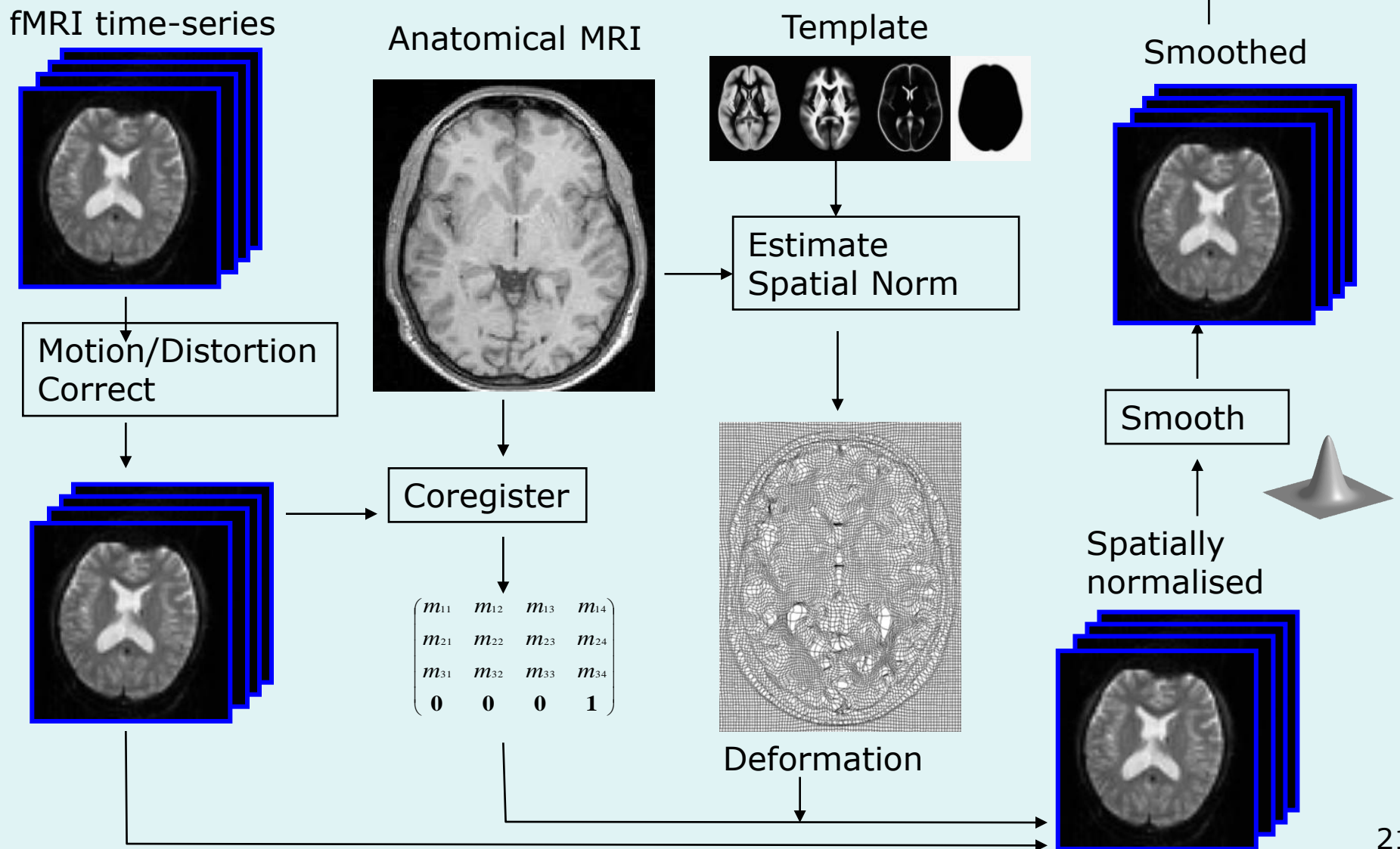


# Various problems

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# Pre-processing overview

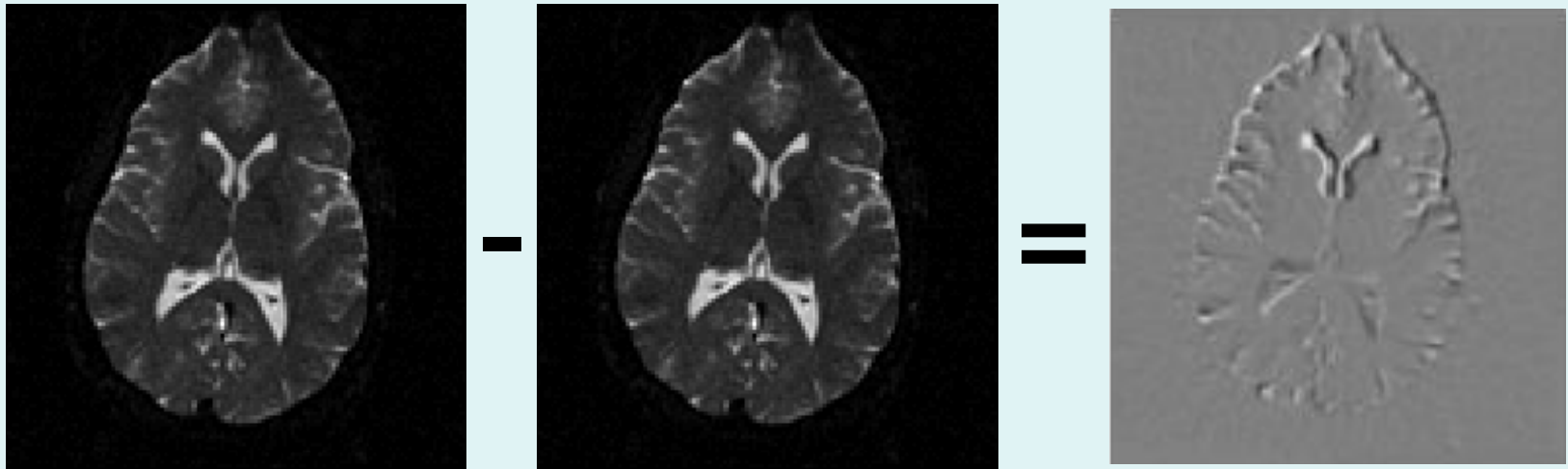


# Content

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- **Preliminaries**
- **Within-subject**
  - **Realignment**
    - **Minimising mean-squared difference / Residual artifacts**
  - **EPI Distortion correction**
    - **FieldMap Toolbox / Movement by distortion interaction**
  - **Coregistration**
    - **Maximising mutual information**
- **Between-subject**
- **Smoothing**
- **Conclusion**

# Mean-squared difference



- Minimising mean-squared difference works for intra-modal registration (realignment)

$$c(I, J) = \sum_{n=1}^N (I_n - J_n)^2$$

- Simple relationship between intensities in one image, versus those in the other  
(Assumes normally distributed differences, i.e. residuals)

# Within-subject registration

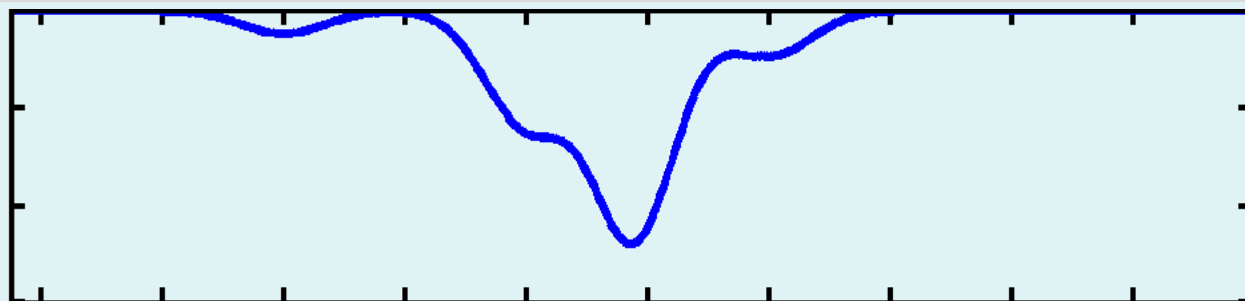
- Realign images  $I$  (fixed) and  $J$  (moving):
- Criteria to optimize:

$$\rightarrow c(I, J) = \sum_{n=1}^N (I_n - J_n)^2$$

- $c(I, J)$  depends on  $J$ 's orientation, which depends on  $R$ 's 6 parameters
  - Optimize  $c(I, J)$  according to those 6 parameters !

$$R = \begin{pmatrix} 1 & 0 & 0 & X_{\text{trans}} \\ 0 & 1 & 0 & Y_{\text{trans}} \\ 0 & 0 & 1 & Z_{\text{trans}} \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos f & \sin f & 0 \\ 0 & -\sin f & \cos f & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos q & 0 & \sin q & 0 \\ 0 & 1 & 0 & 0 \\ -\sin q & 0 & \cos q & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos \Omega & \sin \Omega & 0 & 0 \\ -\sin \Omega & \cos \Omega & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

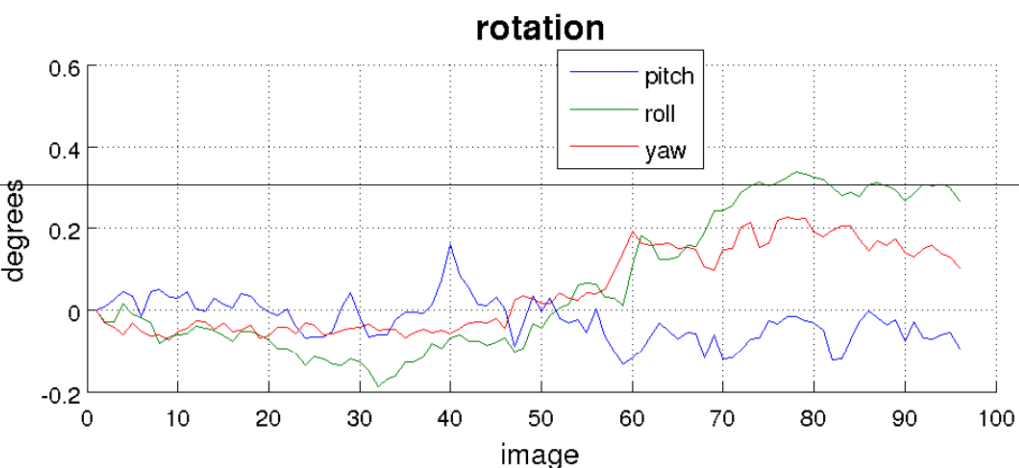
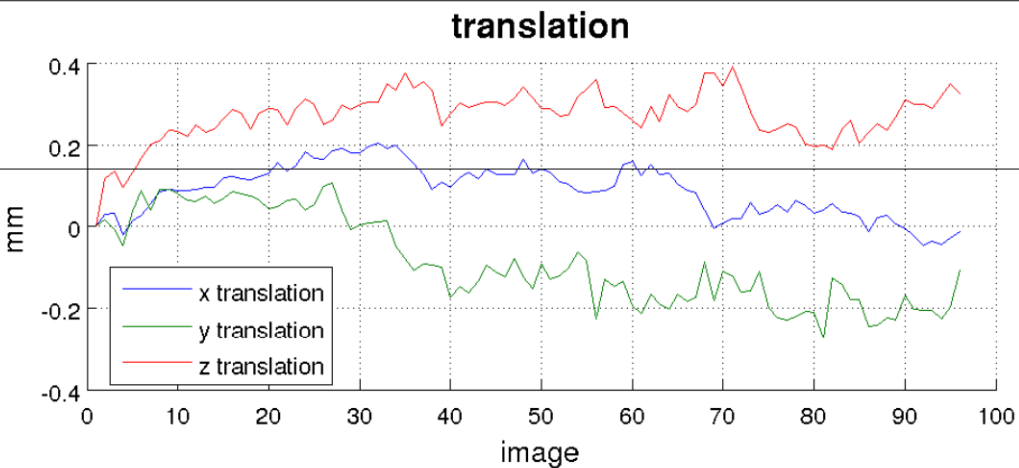
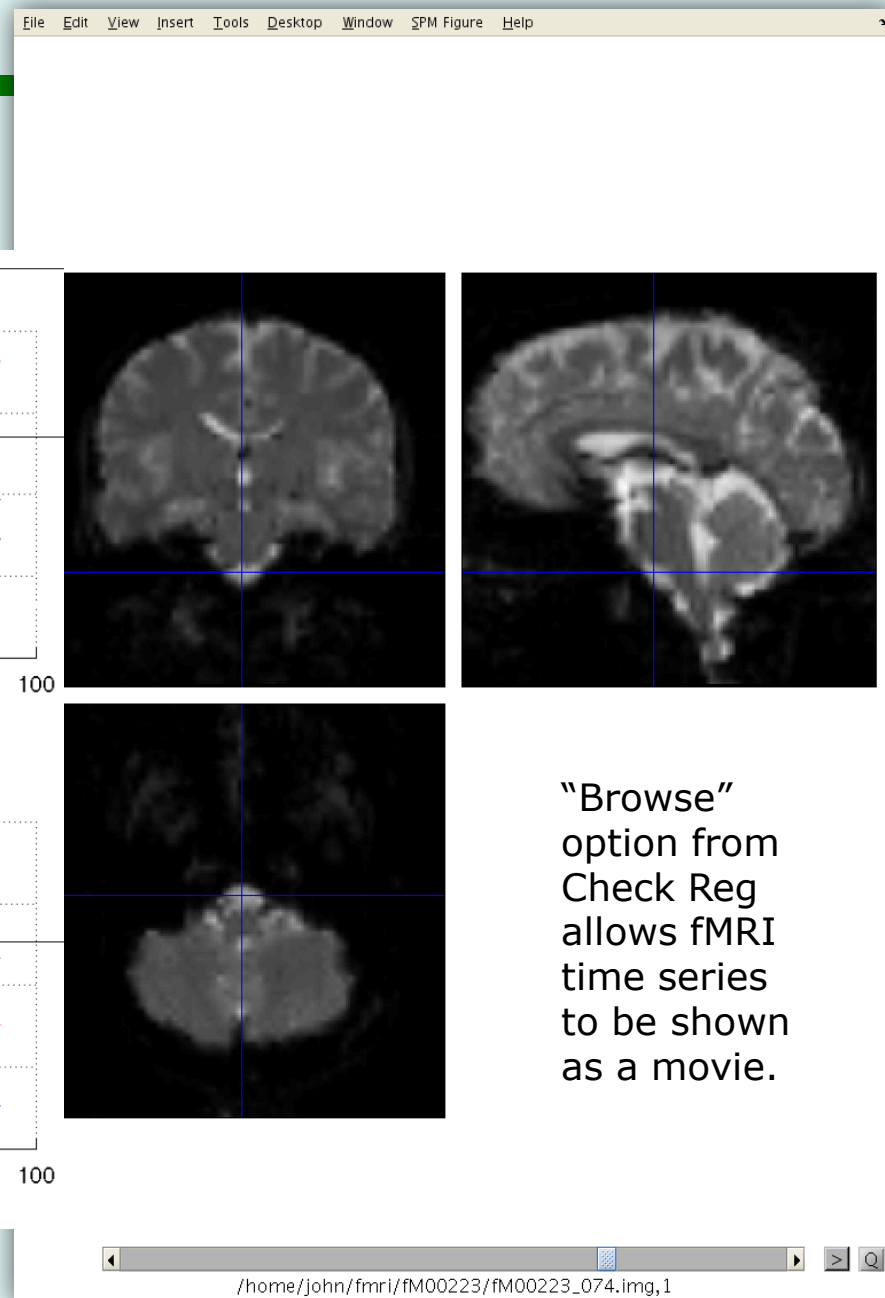
Objective function



Value of parameter



# Motion estimates



“Browse” option from Check Reg allows fMRI time series to be shown as a movie.

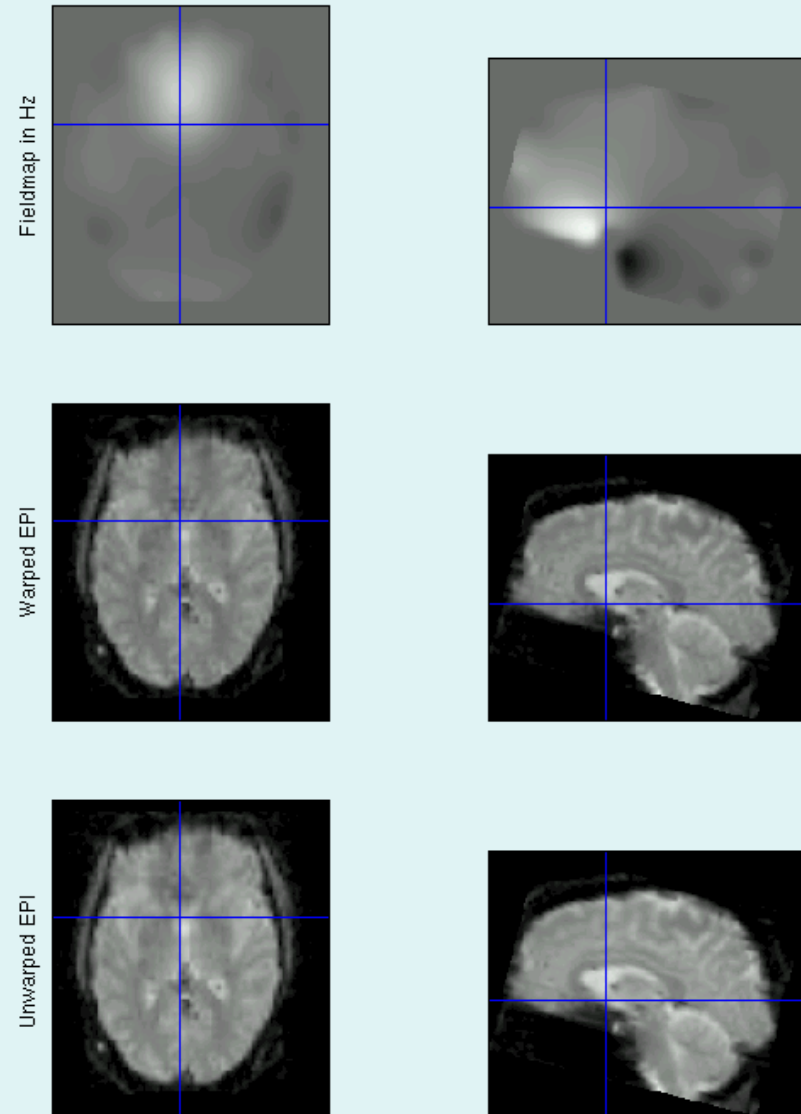
# Residual errors from aligned fMRI

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- Re-sampling can introduce interpolation errors
  - especially tri-linear interpolation
- Gaps between slices can cause aliasing artefacts
- Slices are not acquired simultaneously
  - rapid movements not accounted for by rigid body model
- Image artefacts may not move according to a rigid body model
  - image distortion, image dropout, Nyquist ghost
- BOLD signal changes influence the estimated motion.
- Functions of the estimated motion parameters can be modelled as confounds in subsequent analyses

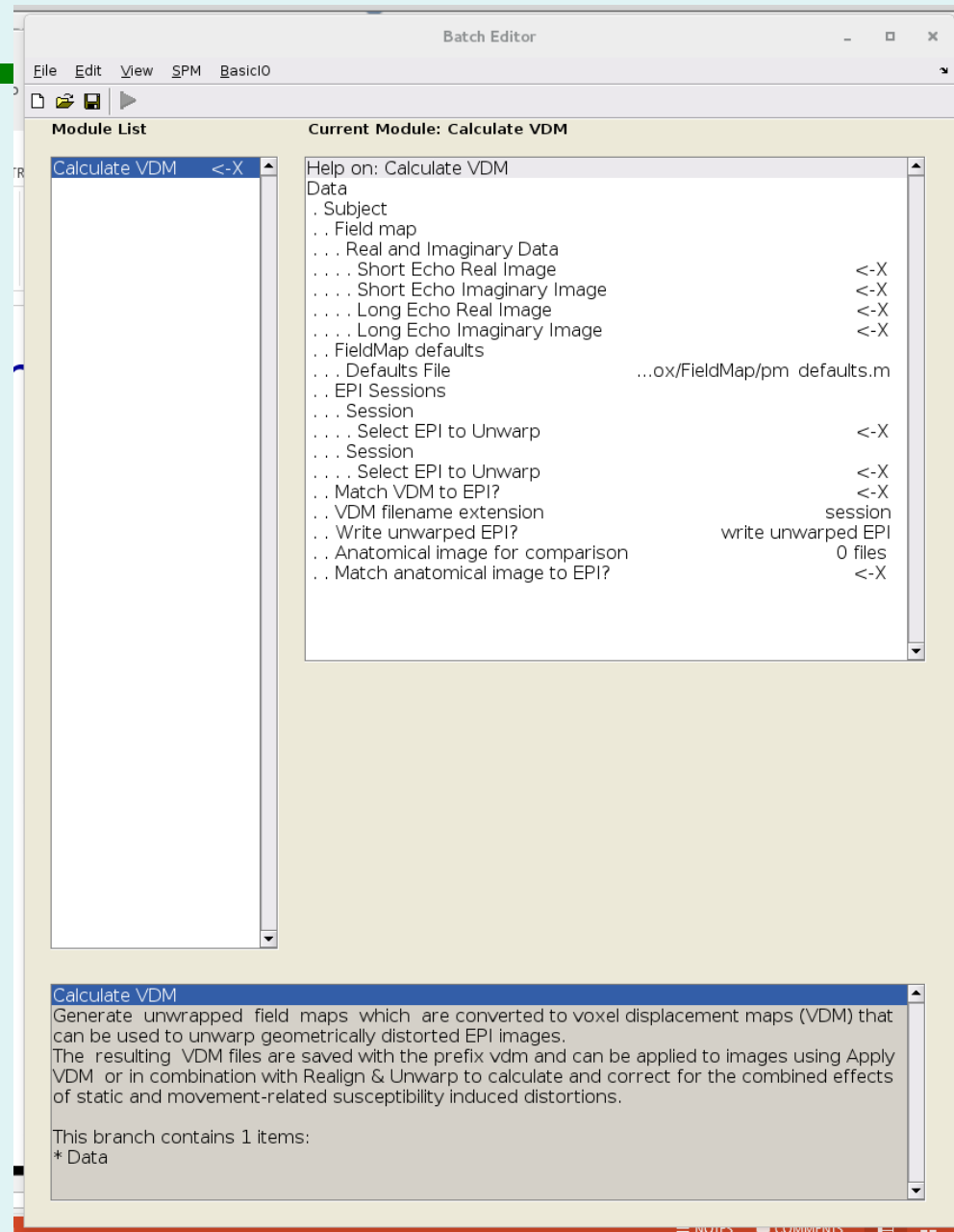
# EPI distortion

- Magnetic susceptibility differs among tissues.
- Greatest difference is between air and tissue.
- Subject disrupts B0 field, rendering it inhomogeneous
- Distortions in phase-encode direction



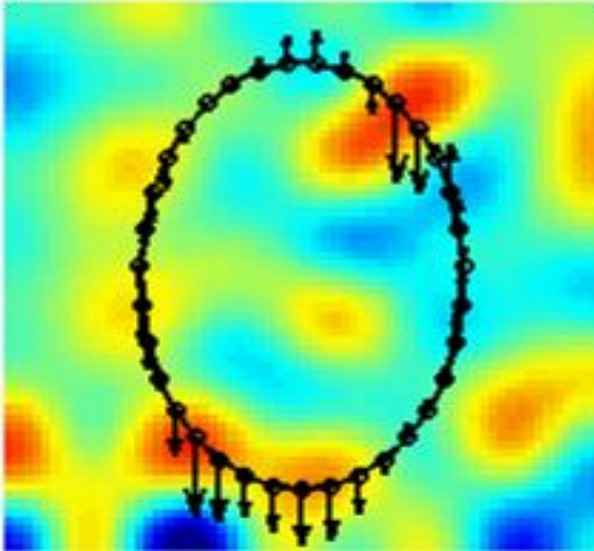
# FieldMap toolbox

- Computes a voxel-displacement map (VDM) from “fieldmap” scans.
- Used to correct distortions in EPI.

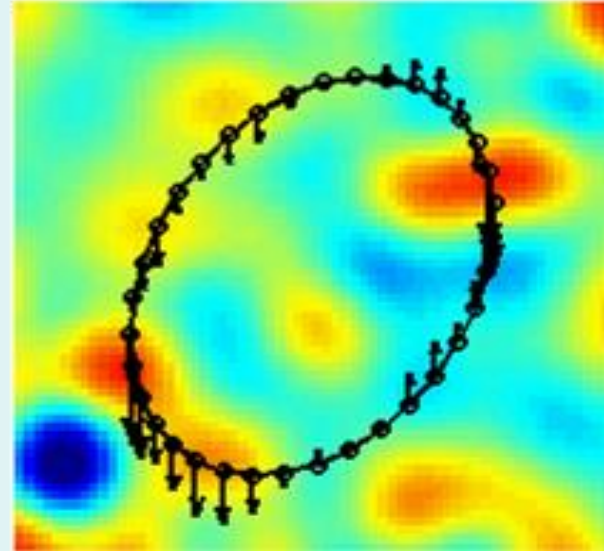


# Movement-by-distortion interaction

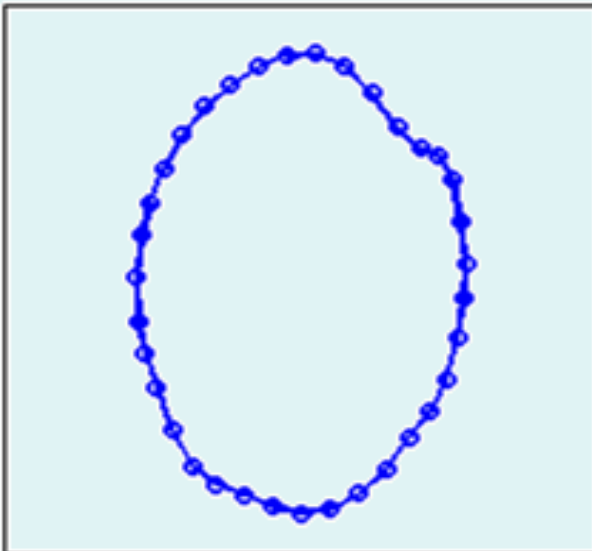
Original position



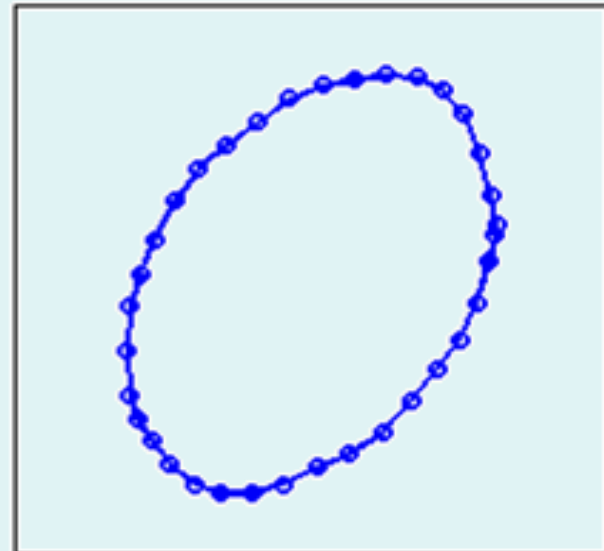
After rotation



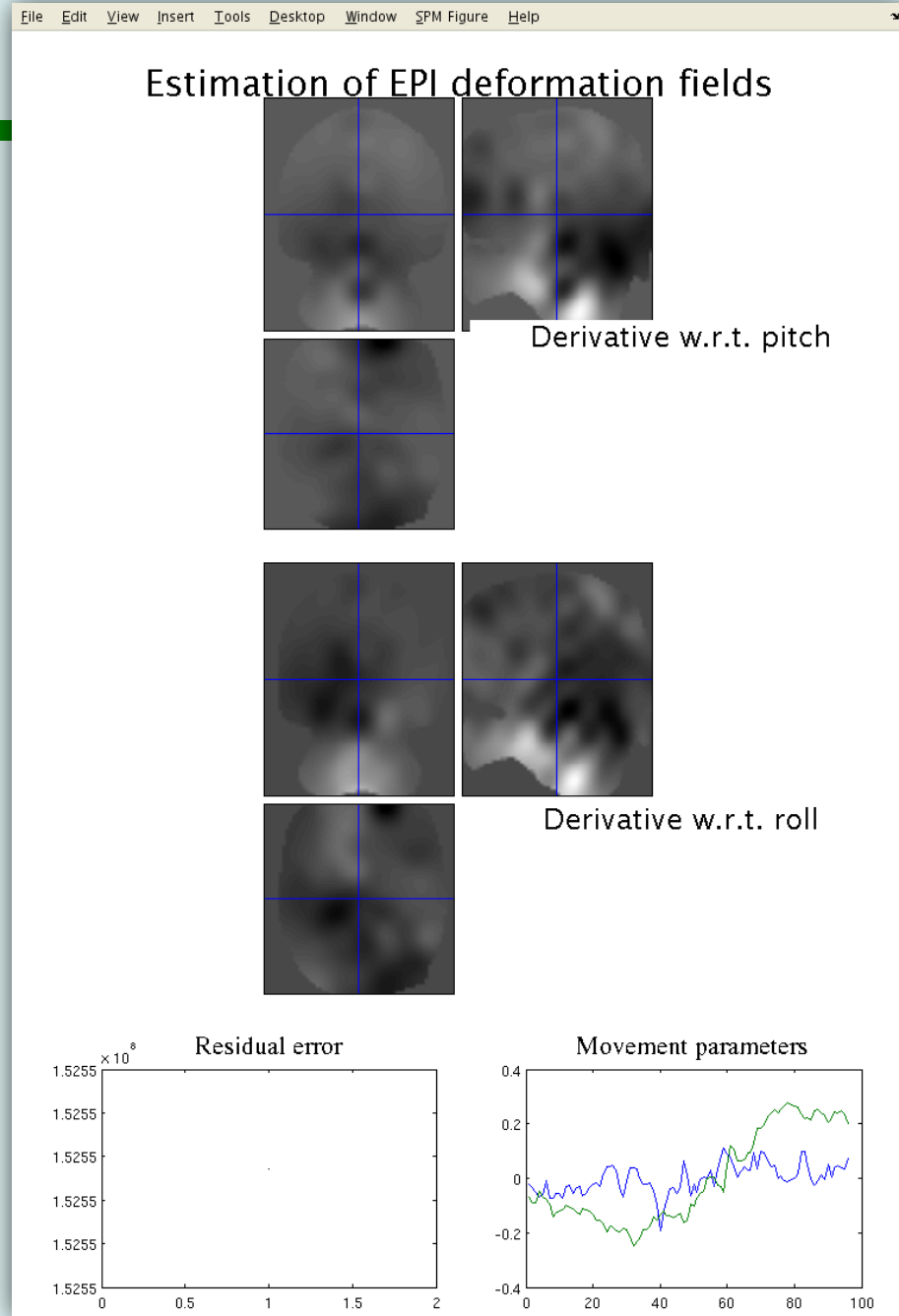
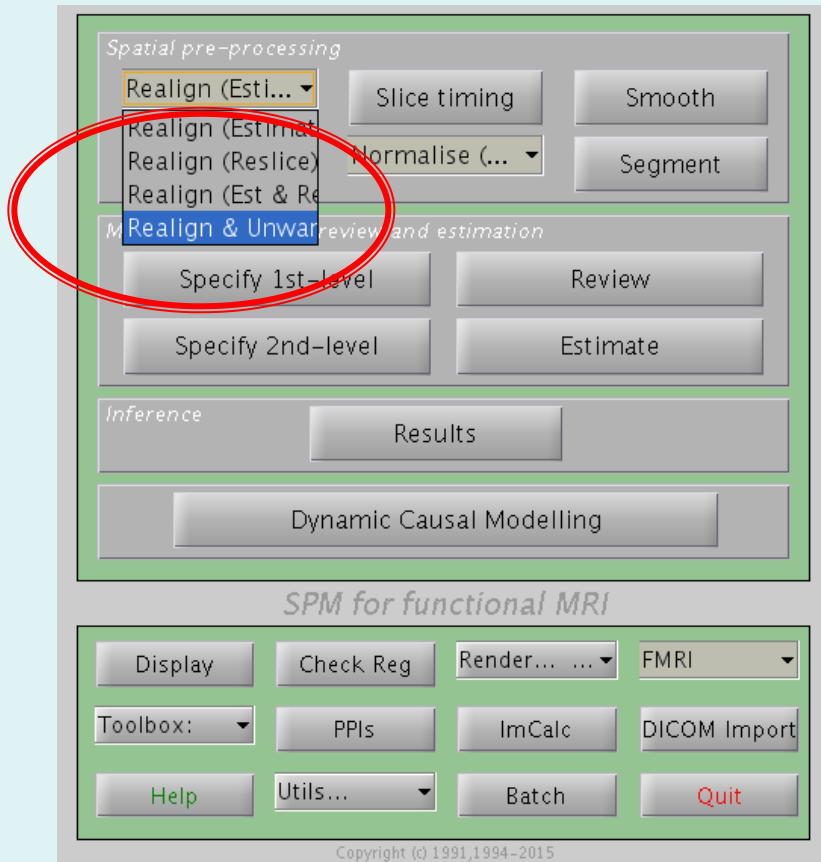
Original position



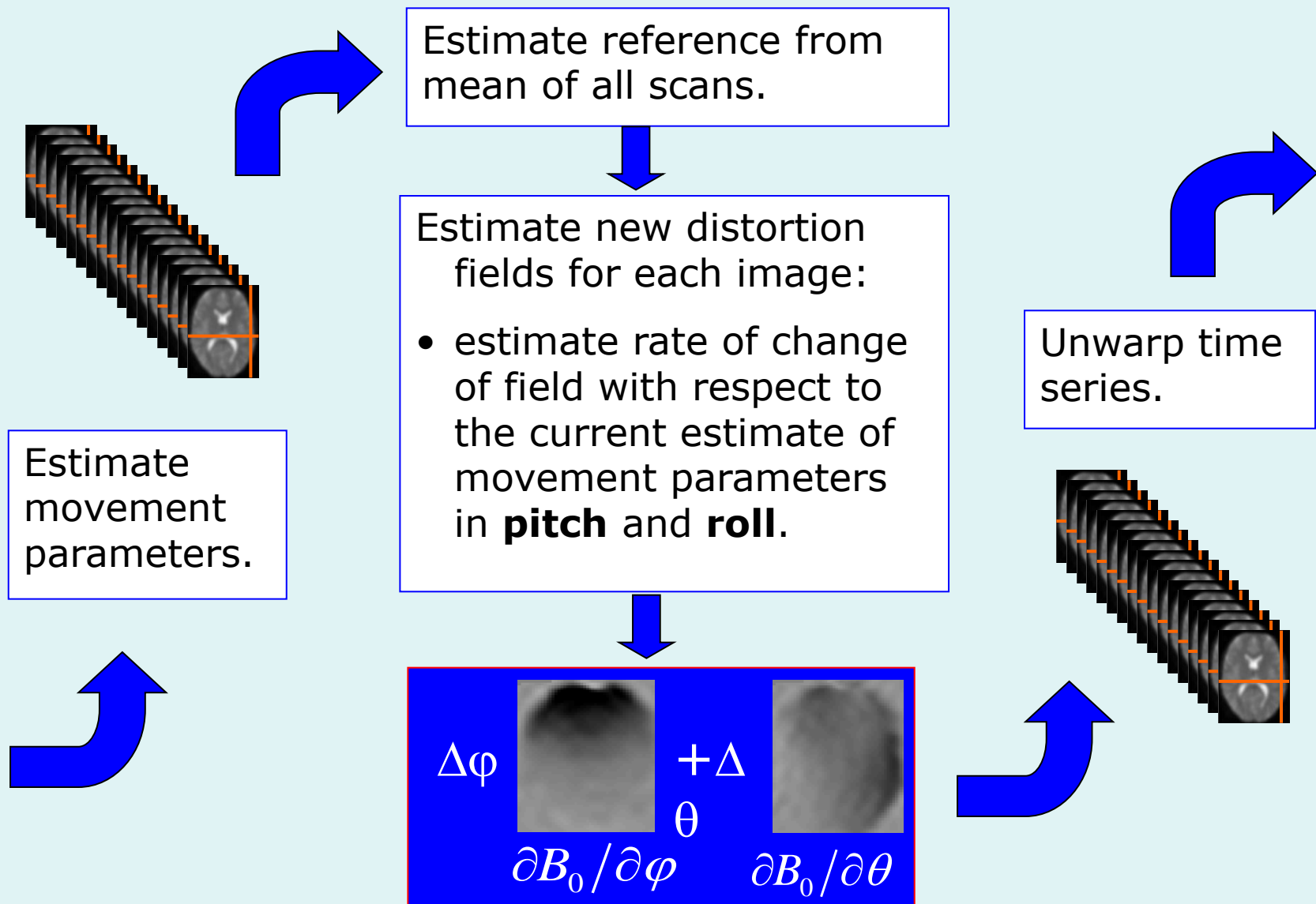
After rotation



# “Realign & Unwarp”



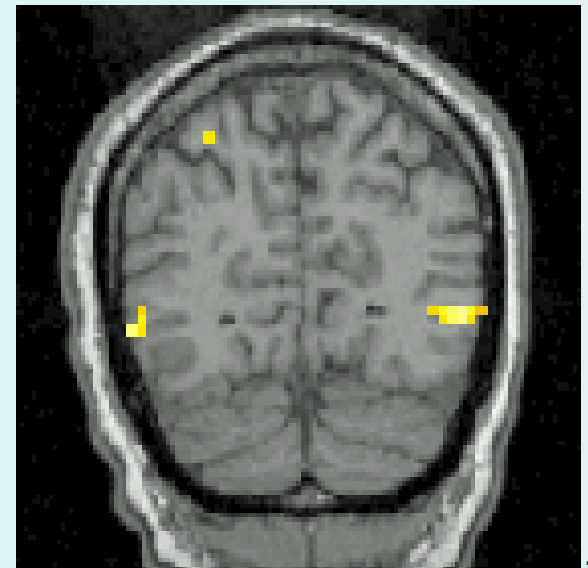
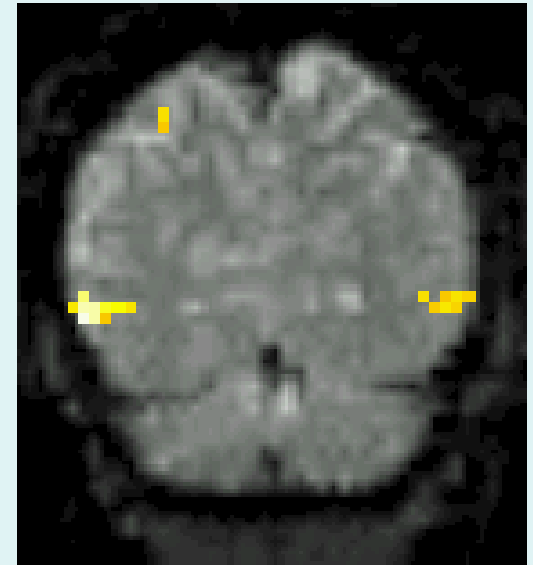
# Correcting for distortion changes



# “Coregistration”

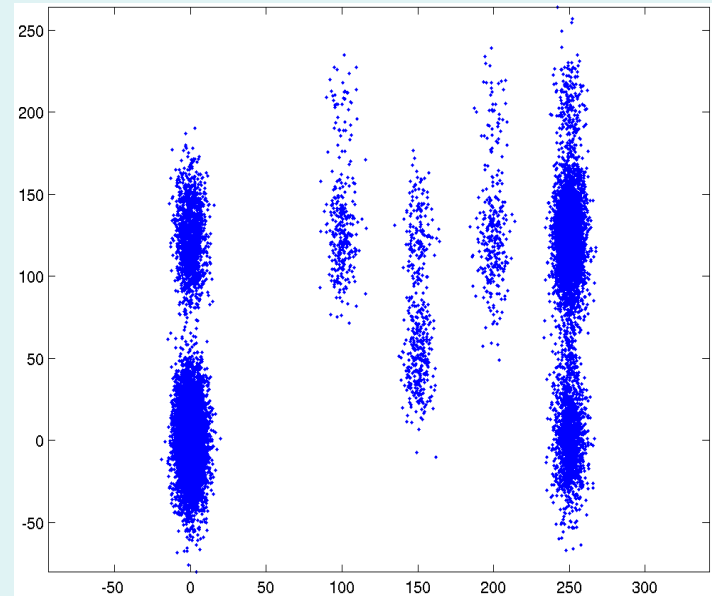
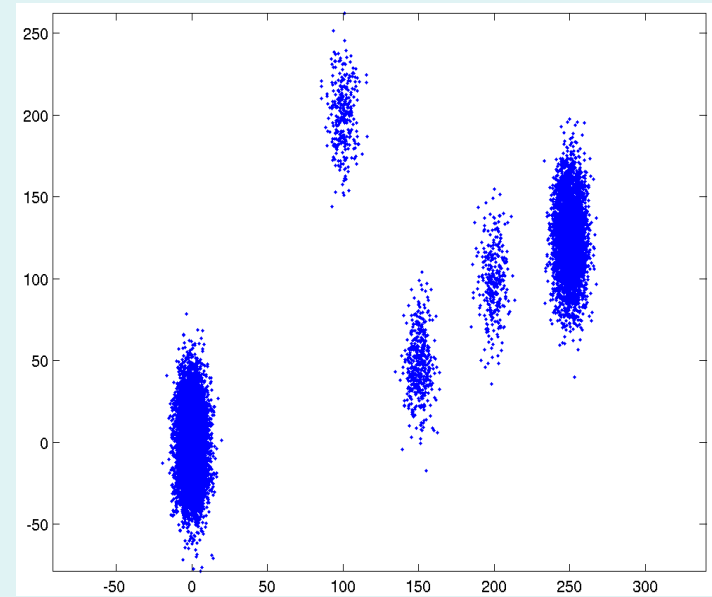
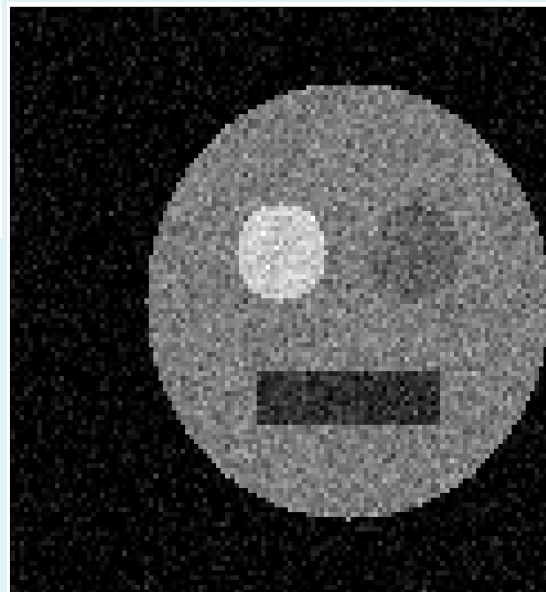
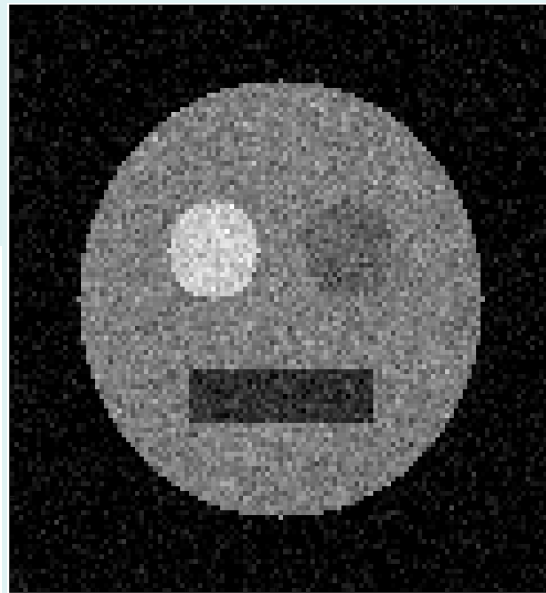
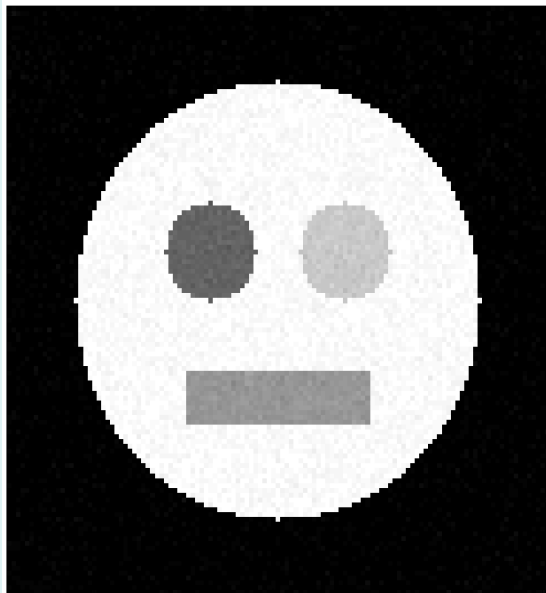
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- Inter-modal registration.
- Match images from same subject but different modalities:
  - anatomical localisation of single subject activations
  - achieve more precise spatial normalisation of functional image using anatomical image.

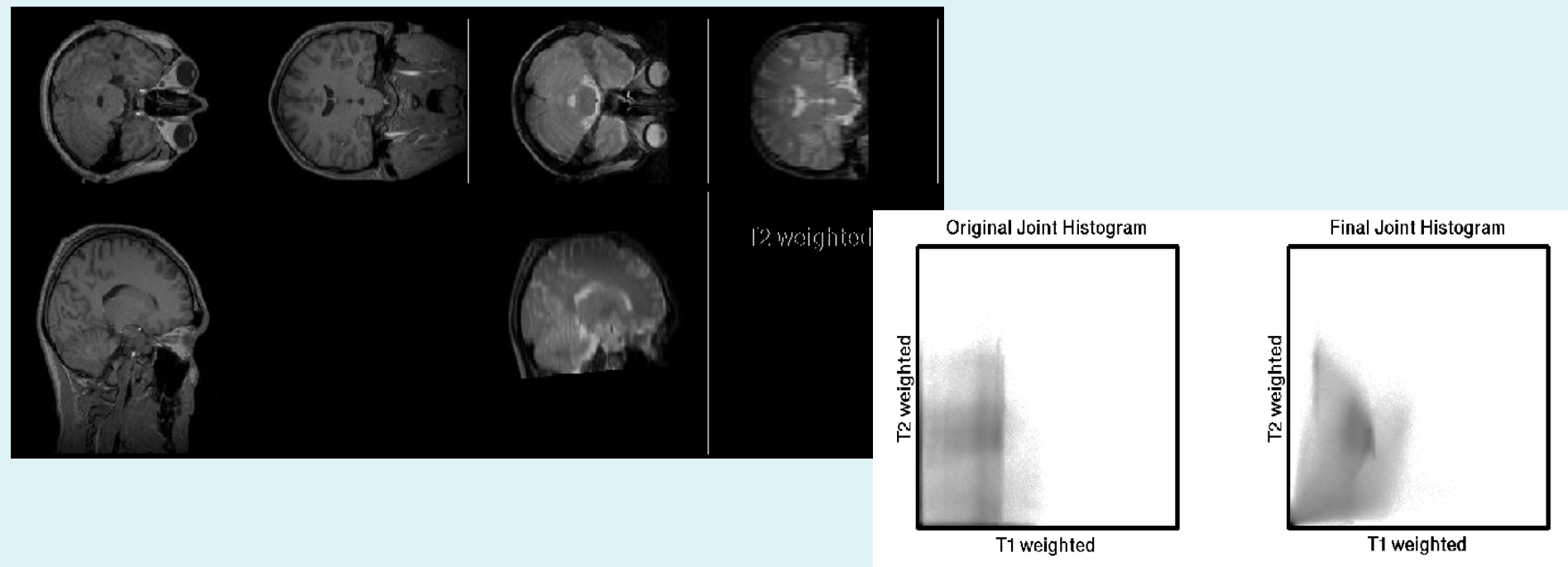




# Mutual Information, example



# Mutual Information, real case



- Used for between-modality registration
- Derived from joint histograms
- $MI = \int_{ab} P(a,b) \log_2 [P(a,b) / (P(a) P(b))]$ 
  - Related to entropy:  $MI = -H(a,b) + H(a) + H(b)$   
Where  $H(a) = -\int_a P(a) \log_2 P(a)$  and  $H(a,b) = -\int_{ab} P(a,b) \log_2 P(a,b)$

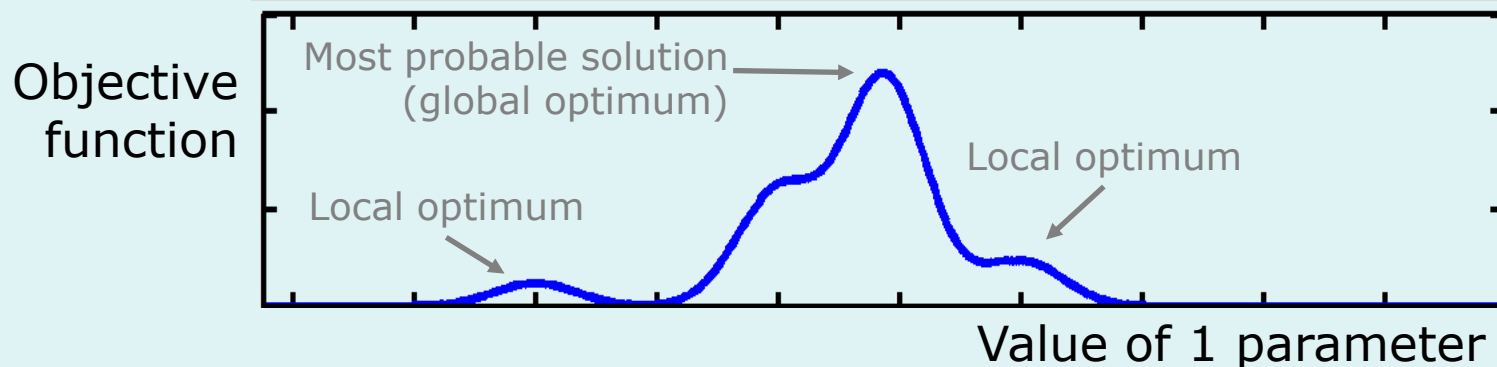
# Within-subject registration

- Realign images  $I$  (fixed) and  $J$  (moving):
- Criteria to optimize:

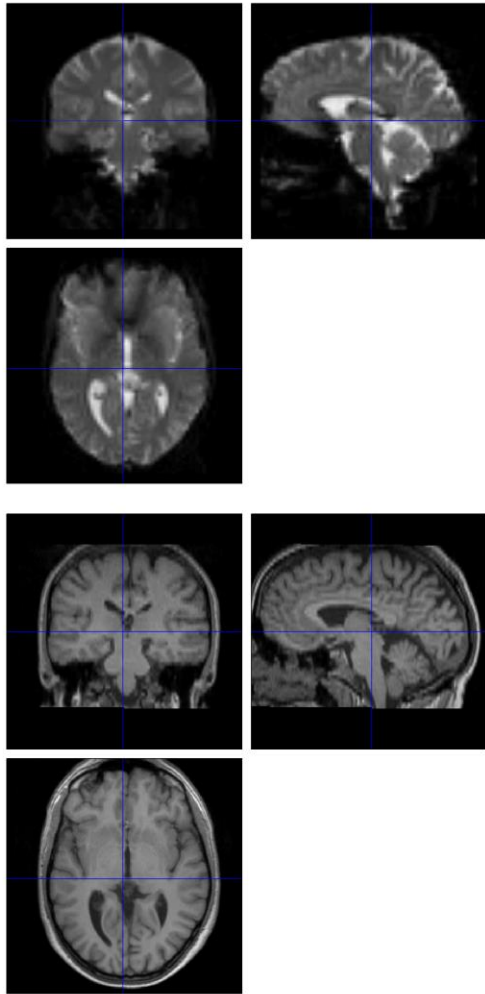
$$\rightarrow c(I, J) = MI(I, J)$$

- $c(I, J)$  depends on  $J$ 's orientation, which depends on  $R$ 's 6 parameters
  - Optimize  $c(I, J)$  according to those 6 parameters !

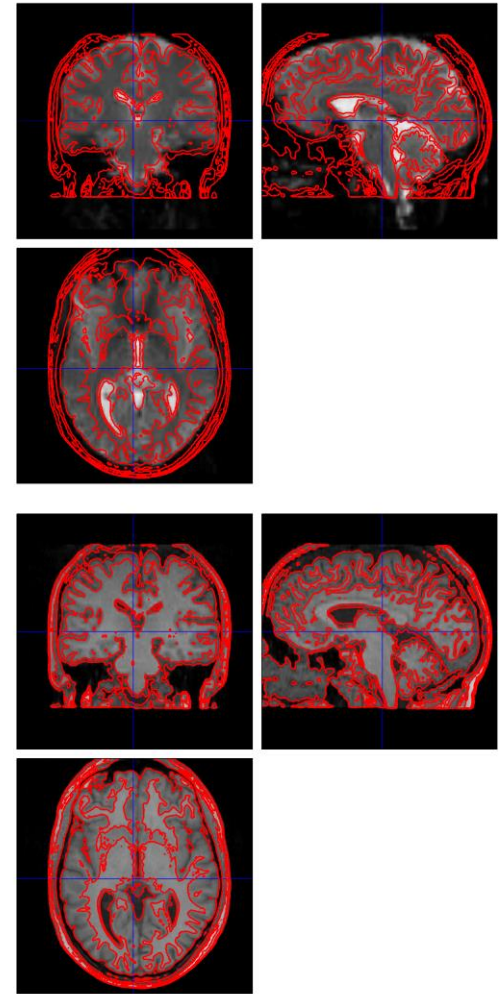
$$R = \begin{pmatrix} 1 & 0 & 0 & X_{\text{trans}} \\ 0 & 1 & 0 & Y_{\text{trans}} \\ 0 & 0 & 1 & Z_{\text{trans}} \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & \cos f & \sin f & 0 \\ 0 & -\sin f & \cos f & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos q & 0 & \sin q & 0 \\ 0 & 1 & 0 & 0 \\ -\sin q & 0 & \cos q & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} \cos \Omega & \sin \Omega & 0 & 0 \\ -\sin \Omega & \cos \Omega & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$



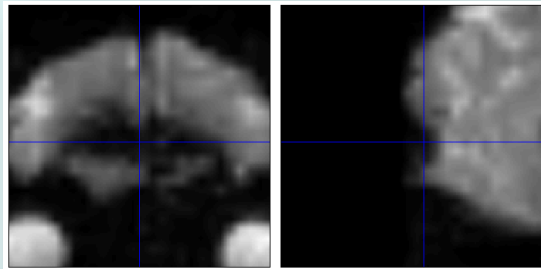
# “CheckReg” to assess alignment



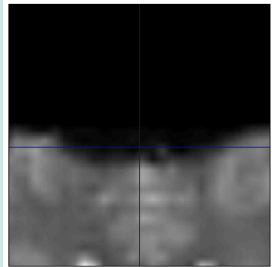
CheckReg allows contours from one image to be shown superimposed on another



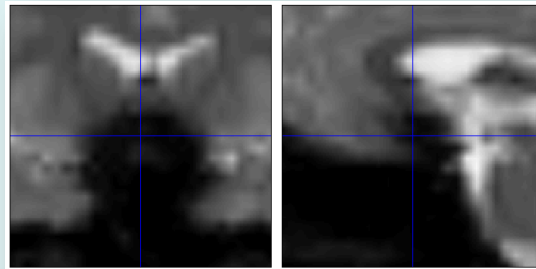
# EPI dropout and distortion



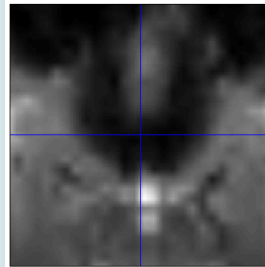
EPI



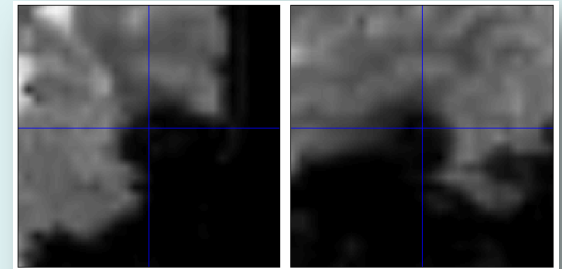
structural



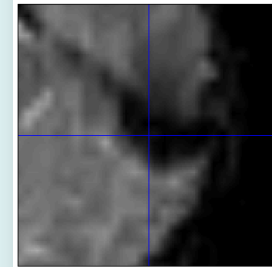
EPI



structural



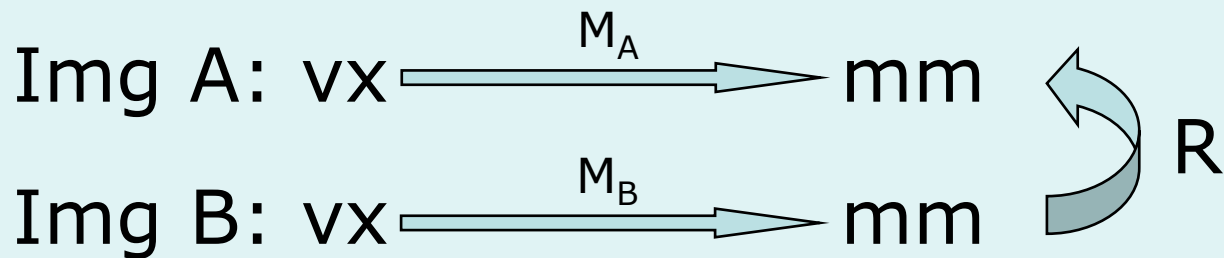
EPI



structural

# Voxel-to-world transformation

- Registering image B (source) to image A (target) will update B's voxel-to-world mapping.



- Mapping from voxels in B to voxels in A is by combining  $M_B$  and R:  $M_B^* = M_B R$ 
  - B-to-world using  $M_B^*$ , then world-to-A using  $M_A^{-1} \Rightarrow M_B^* M_A^{-1}$

# Content

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- **Preliminaries**
- **Within-subject**
- **Between-subject**
  - Unified segmentation for spatial normalisation**
    - **Gaussian mixture model**
    - **Intensity non-uniformity correction**
    - **Deformed tissue probability maps**
- **Smoothing**
- **Conclusion**

# Between subjects

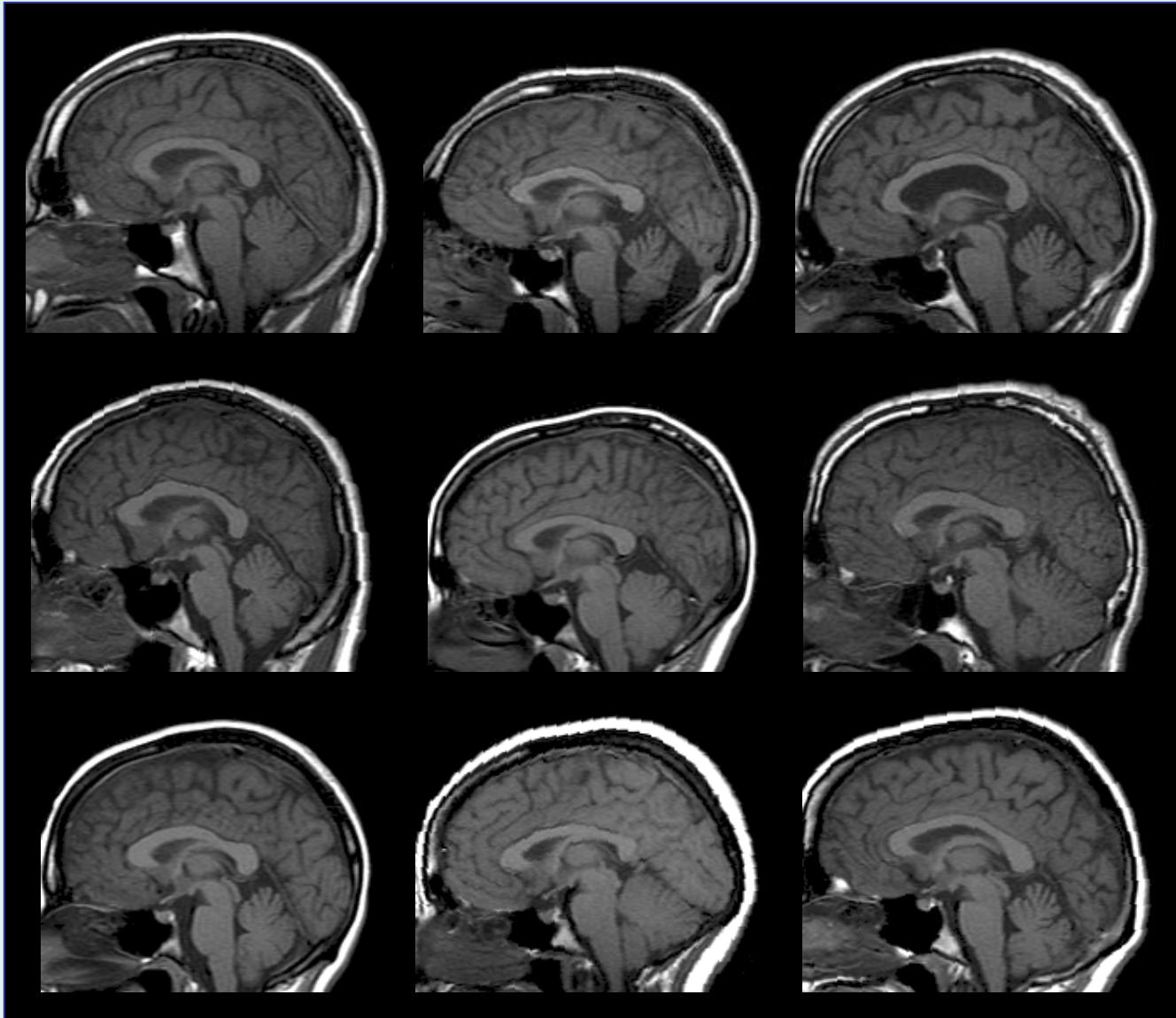
---

Brains of different subjects vary in *shape* and *size*.



# Between subjects

---



# Between subjects

---

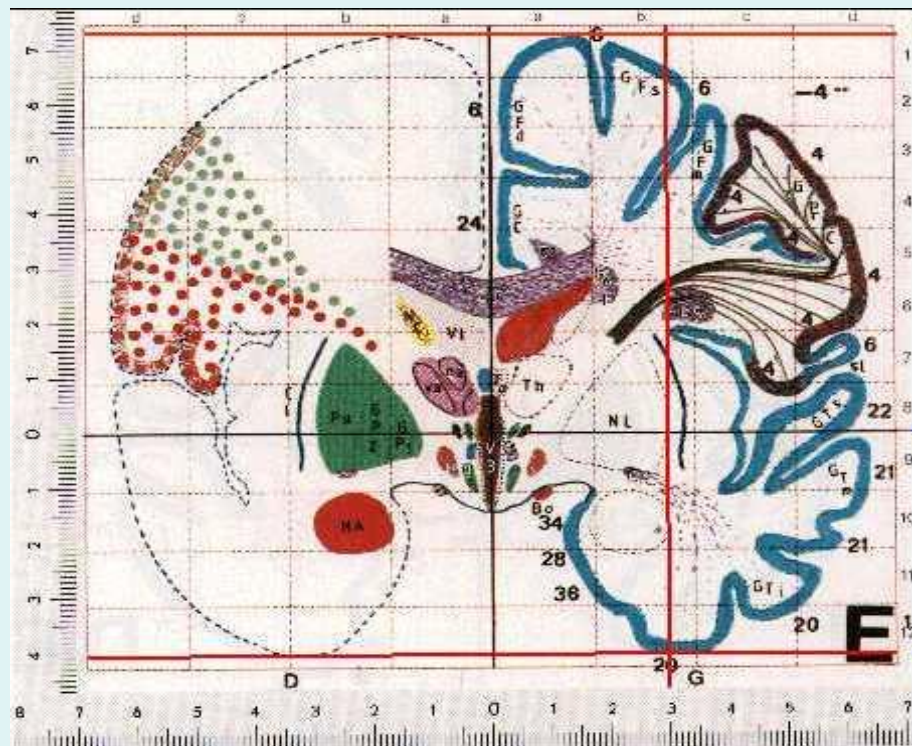
Brains of different subjects vary in *shape* and *size*.

- Need to bring them all into a common anatomical space.
  - Examine homologous regions across subjects
    - Improve anatomical specificity
    - Improve sensitivity
  - Report findings in a common anatomical space (e.g. MNI space)

# Between subjects

The Talairach Atlas

The MNI/ICBM AVG152 Template



The MNI template follows the *convention* of T&T, but does NOT match the *particular brain*

Recommended reading: <http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>

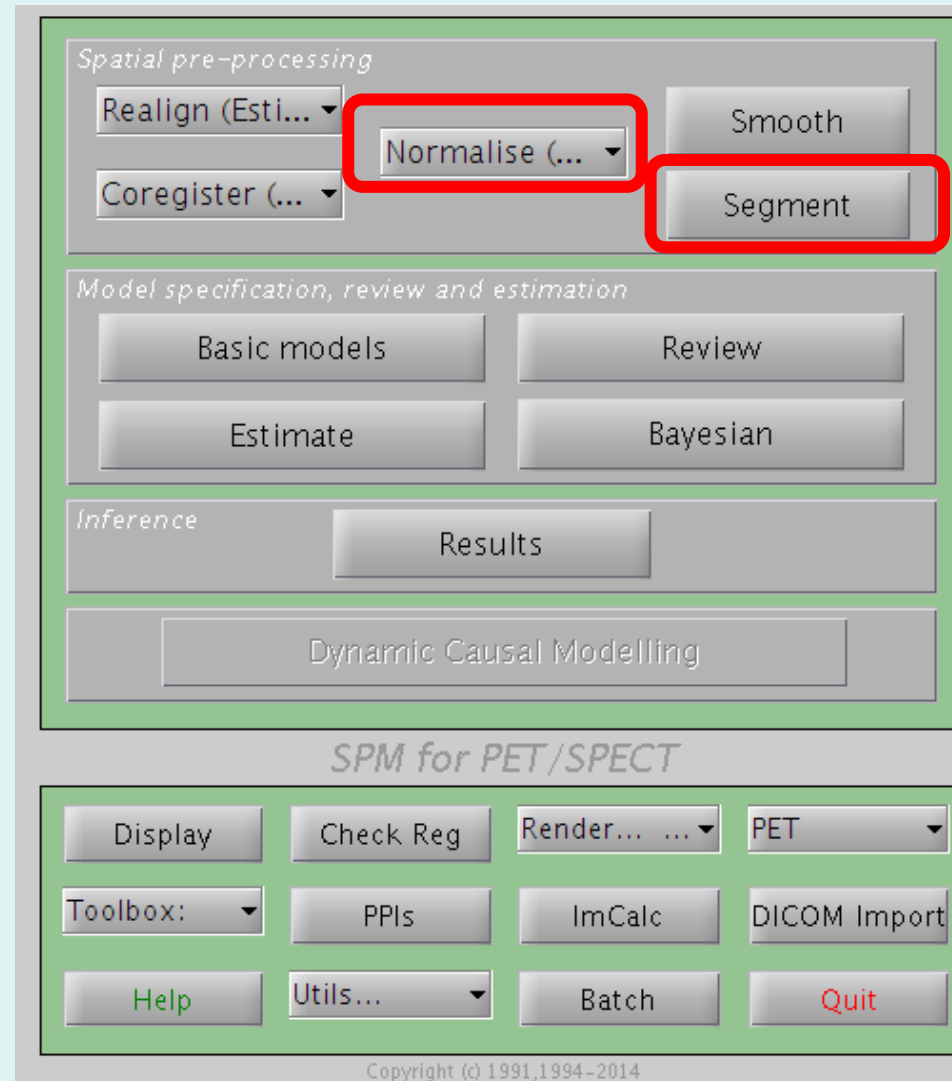
# Between subjects

---

- Brains of different subjects vary in *shape* and *size*.
  - Need to bring them all into a common anatomical space.
  - Examine homologous regions across subjects
    - Improve anatomical specificity
    - Improve sensitivity
  - Report findings in a common anatomical space (e.g. MNI space)
- In SPM12, alignment is achieved by matching tissue classes, i.e. GM with GM, WM with WM,...

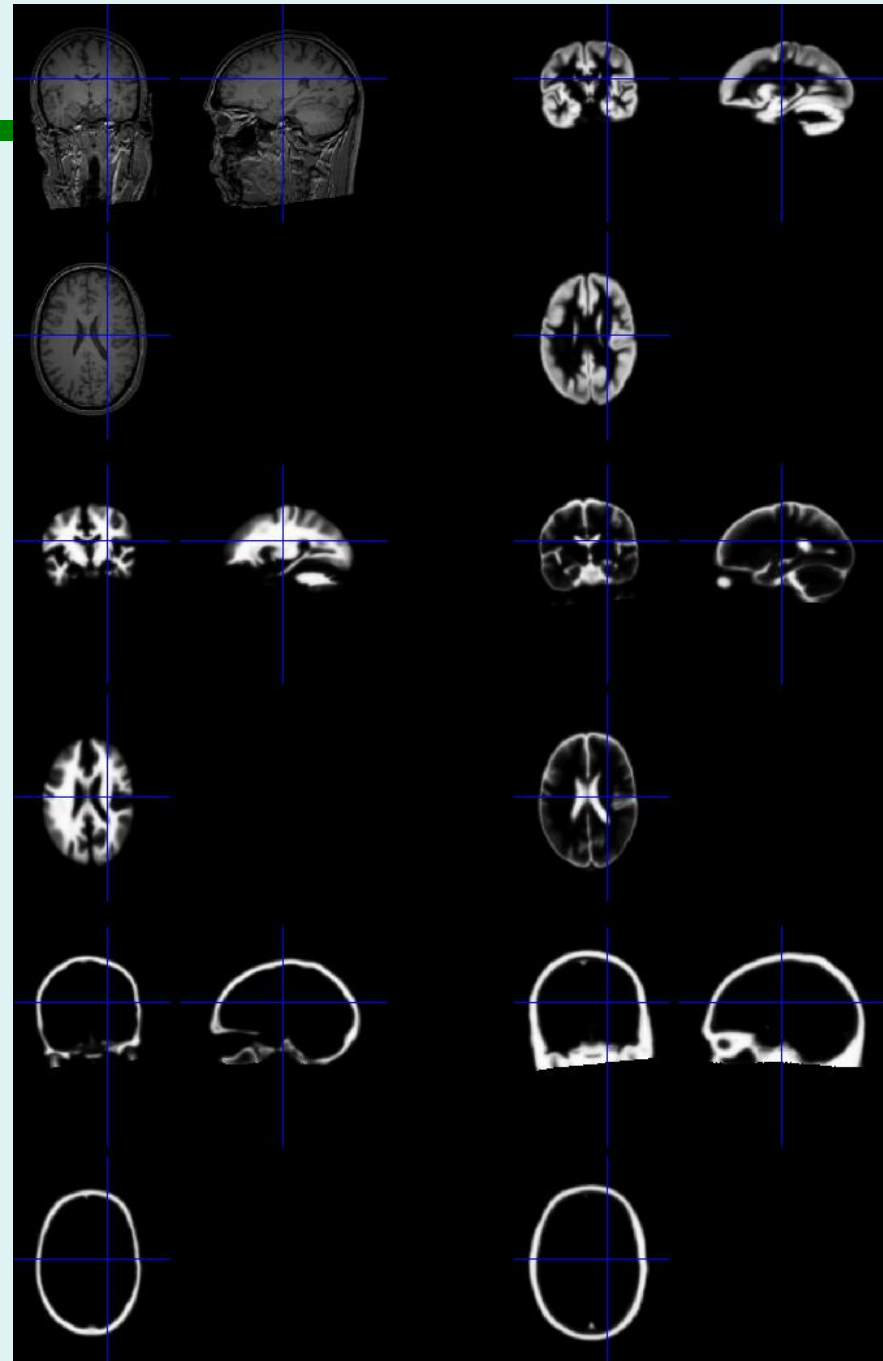
# Normalise/Segment

- This is the same algorithm as for tissue segmentation.
- Combines:
  - Mixture of Gaussians (MOG)
  - Bias Correction Component
  - Warping (Non-linear Registration) Component



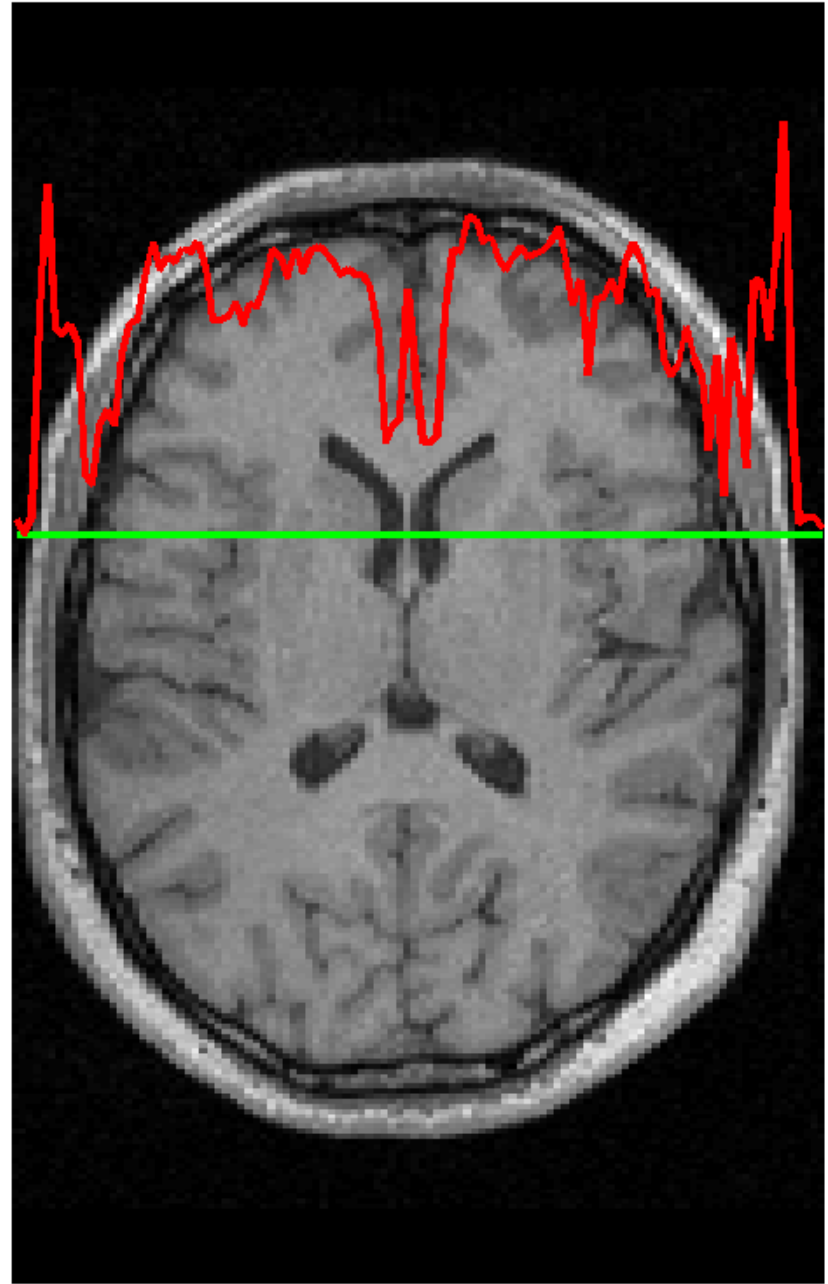
# Spatial normalisation

- Default spatial normalisation in SPM12 estimates nonlinear warps that match tissue probability maps to the individual image.
- Spatial normalisation achieved using the inverse of this transform.



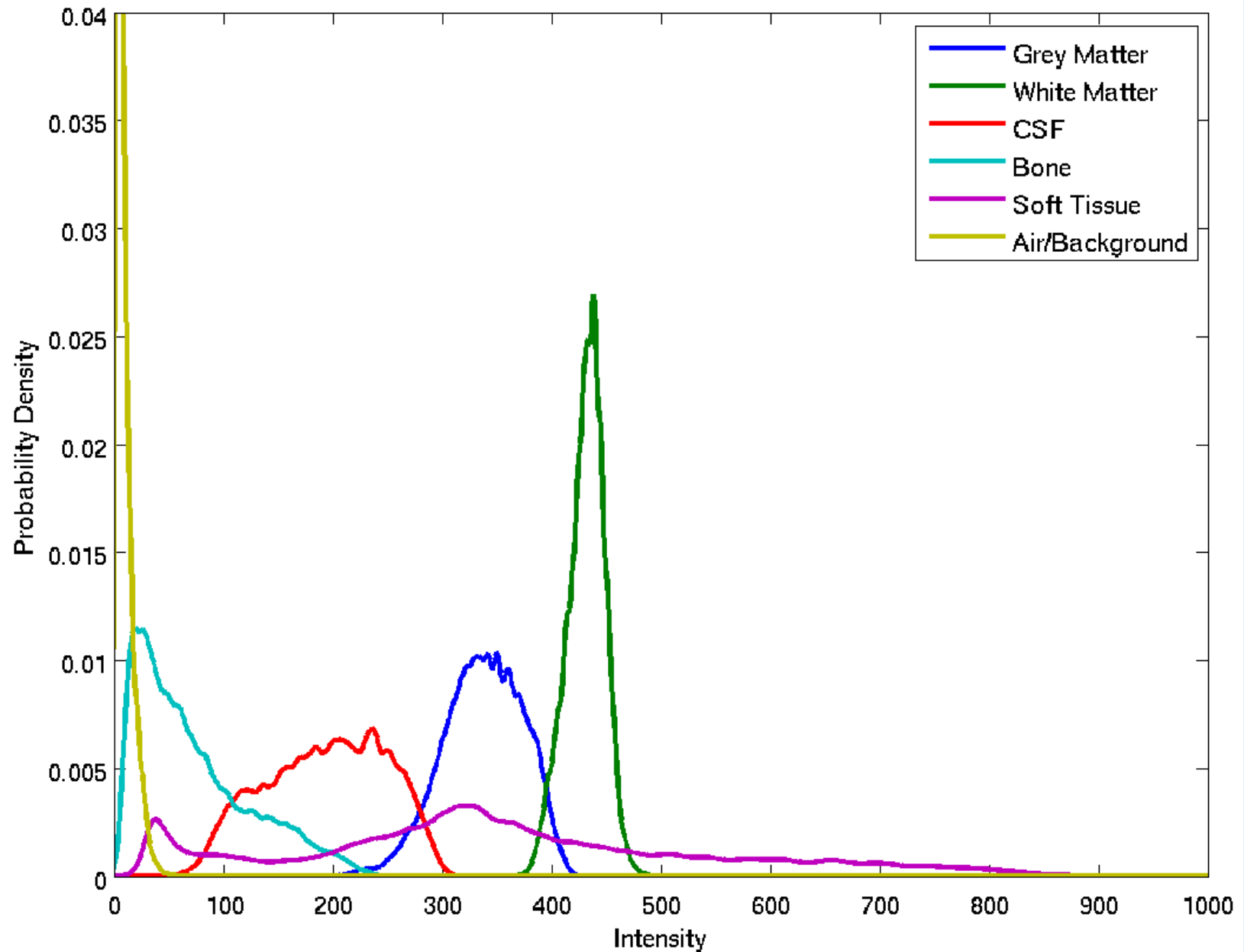
# Segmentation

- Segmentation in SPM12 also estimates a spatial transformation that can be used for spatially normalising images.
- It uses a **generative model**, which involves:
  - Mixture of Gaussians (MOG)
  - Warping (Non-linear Registration) Component
  - Bias Correction Component





# Tissue intensity distributions (T1w-MRI)



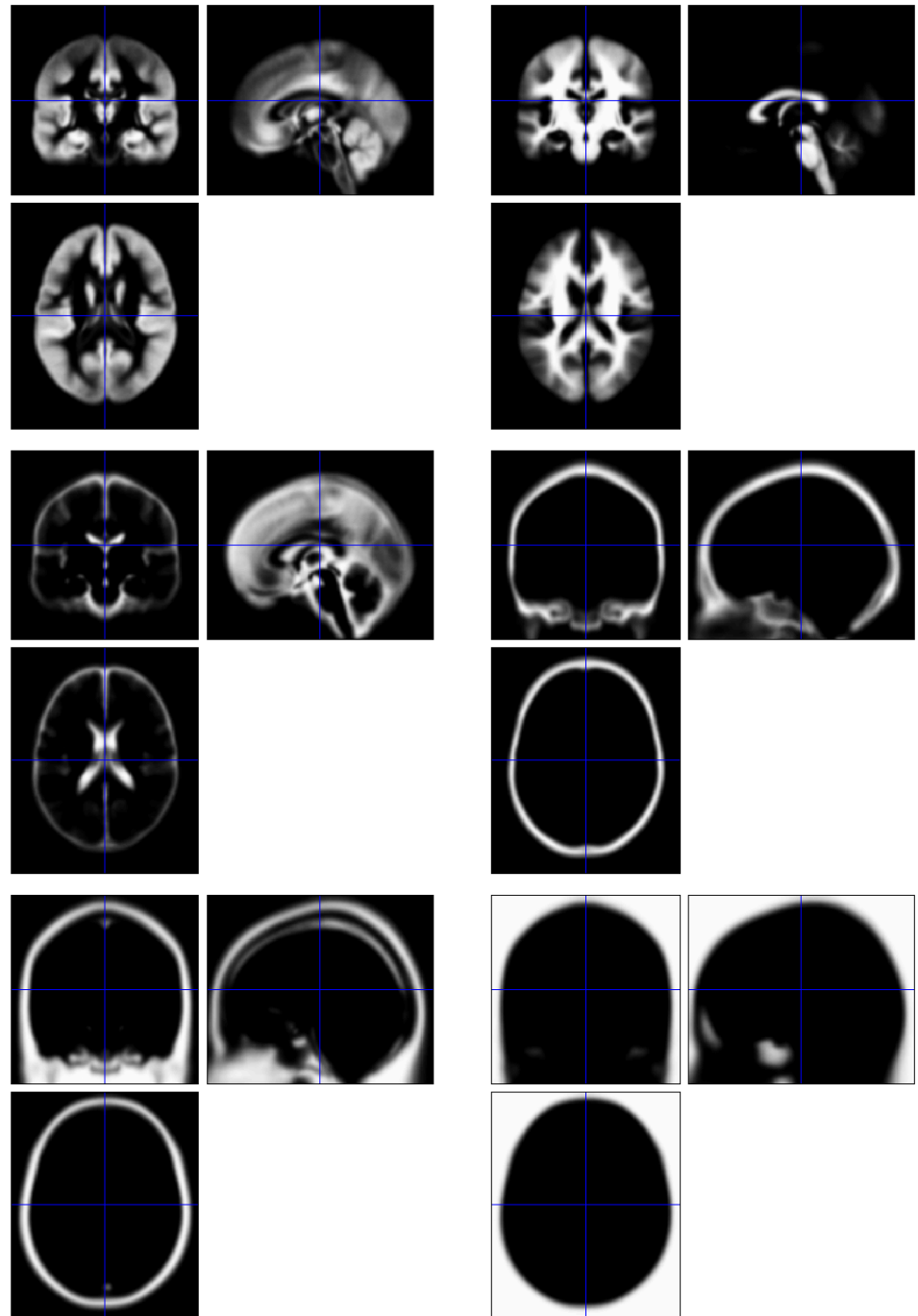


# TPM's

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Tissue probability maps in SPM12.

- GM, WM & CSF
- Additional non-brain tissue classes



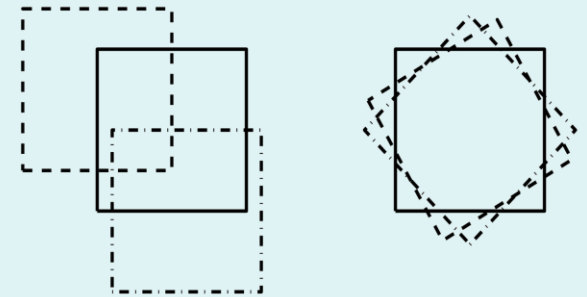
# Modelling deformations, affine transform

## 12 parameter affine transform

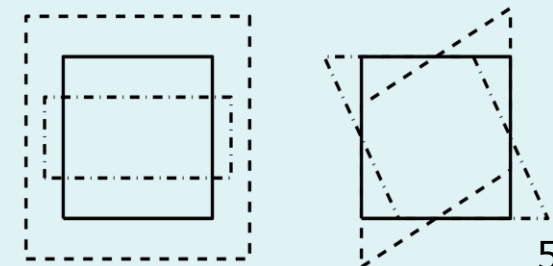
- 3 translations
- 3 rotations
- 3 zooms
- 3 shears

$$\begin{bmatrix} x_1 \\ y_1 \\ z_1 \\ 1 \end{bmatrix} = \begin{bmatrix} m_{11} & m_{12} & m_{13} & m_{14} \\ m_{21} & m_{22} & m_{23} & m_{24} \\ m_{31} & m_{32} & m_{33} & m_{34} \\ 0 & 0 & 0 & 1 \end{bmatrix} \times \begin{bmatrix} x_0 \\ y_0 \\ z_0 \\ 1 \end{bmatrix}$$

→ Fits **overall** shape and size

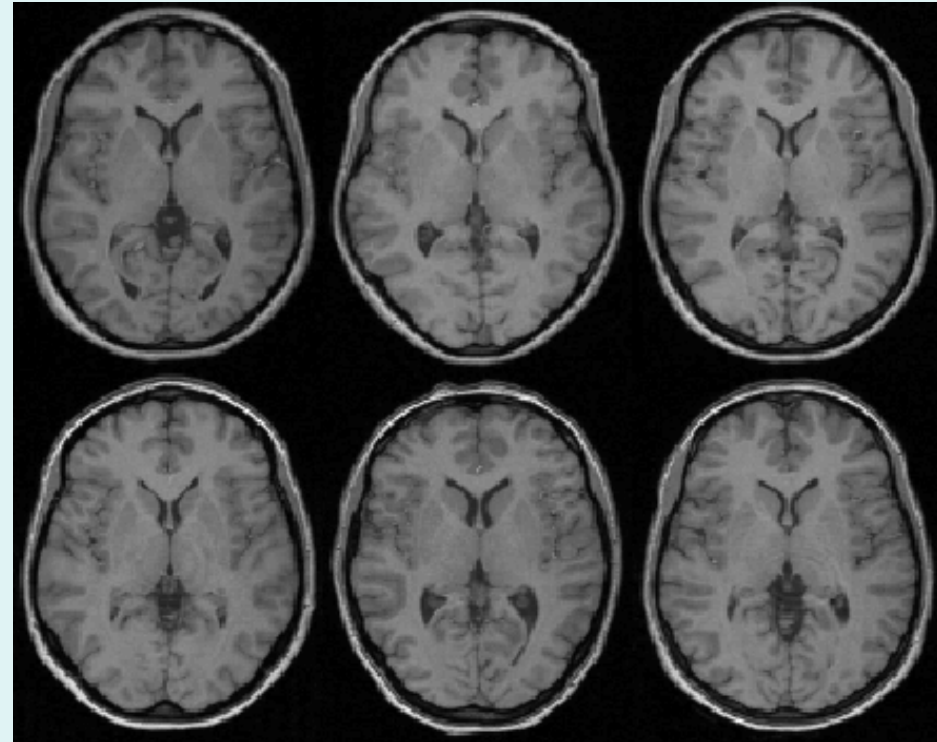


→ Need *warping* for local deformation



# Spatial normalisation results

---

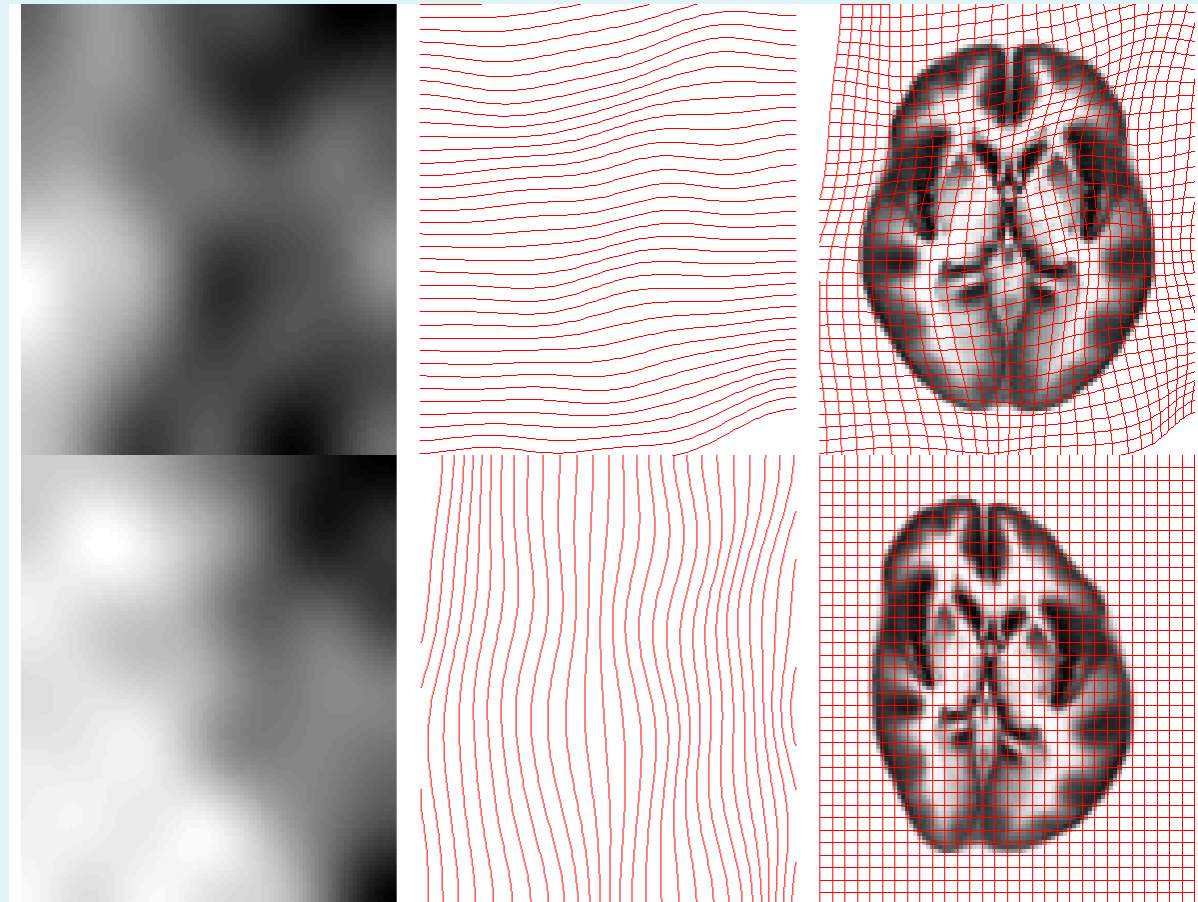


Affine registration

# Modelling deformations, warps

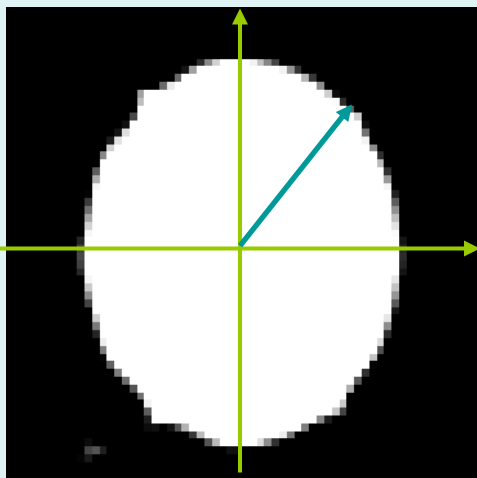
---

- Tissue probability images are warped to match the subject
- The inverse transform warps to the TPMs
- Warps are constrained to be reasonable by penalising various distortions (energies)

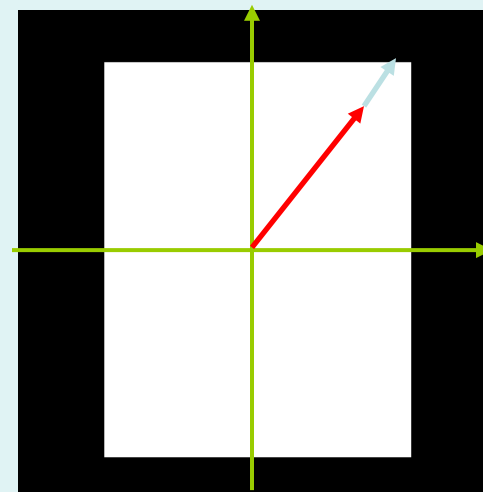


# Non-linear warping, example

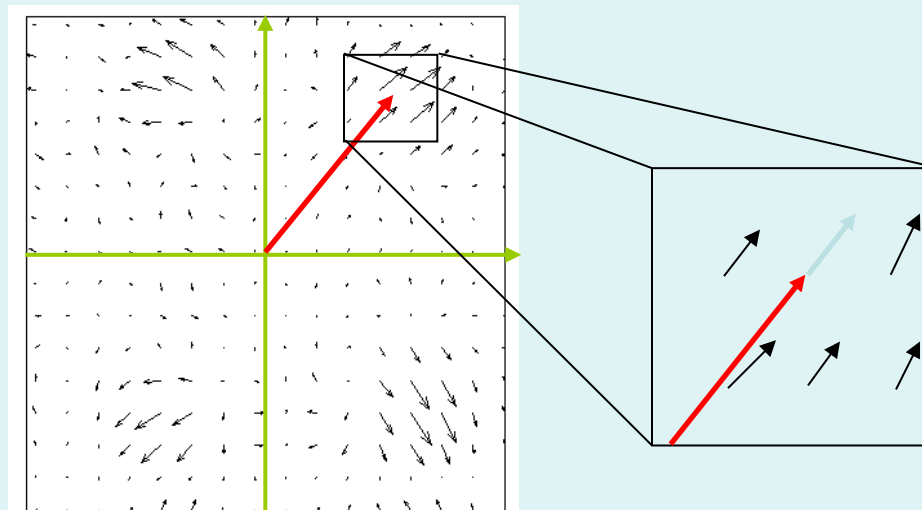
For every voxel position in blank sheet



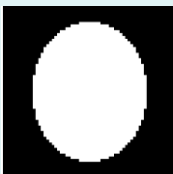
Go to original image and find intensity at warped co-ordinate



Get position in original space by adding pertinent displacement

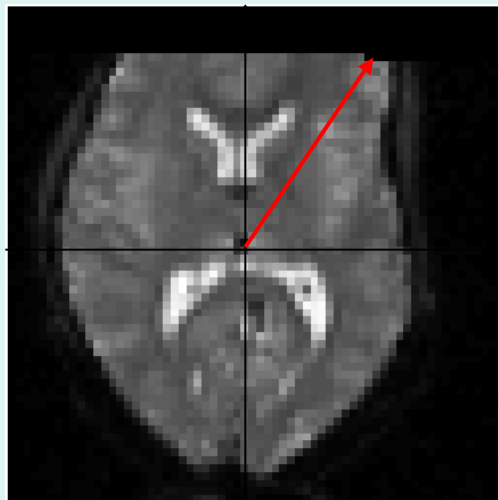


Template

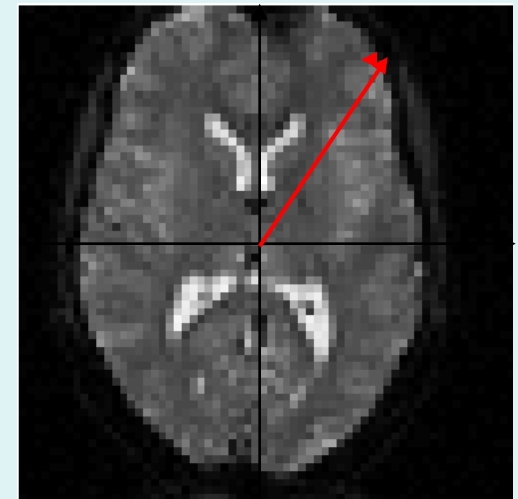


# Non-linear warping, example

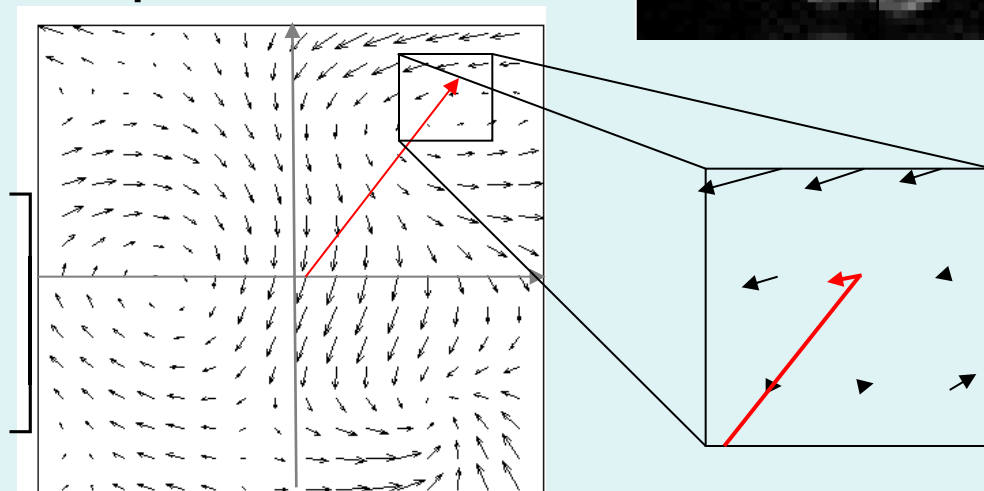
For each voxel-centre in blank sheet.



Go to original image and find intensity at "warped" co-ordinate

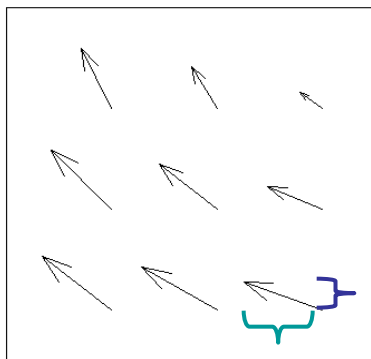
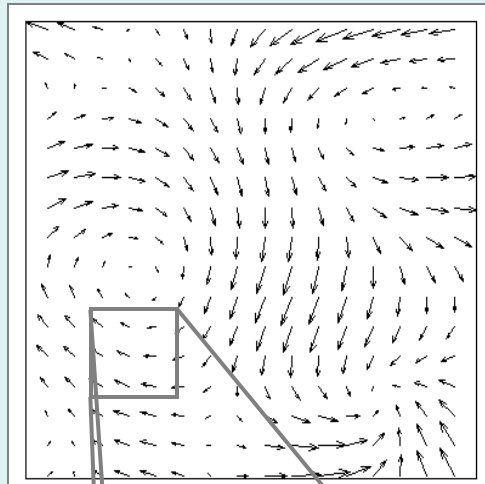


Get position in original space by adding pertinent displacement.



$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} d_x(x, y) \\ d_y(x, y) \end{bmatrix}$$

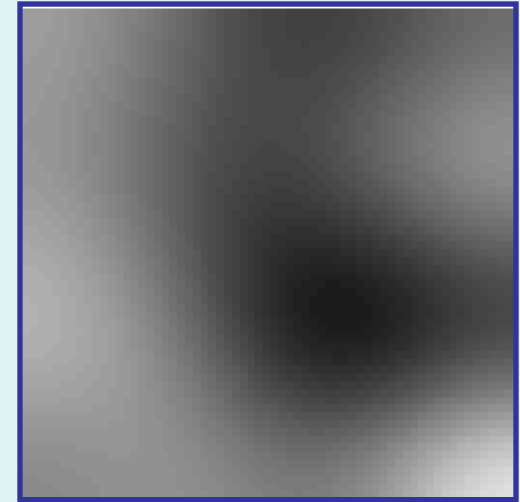
# Displacement map



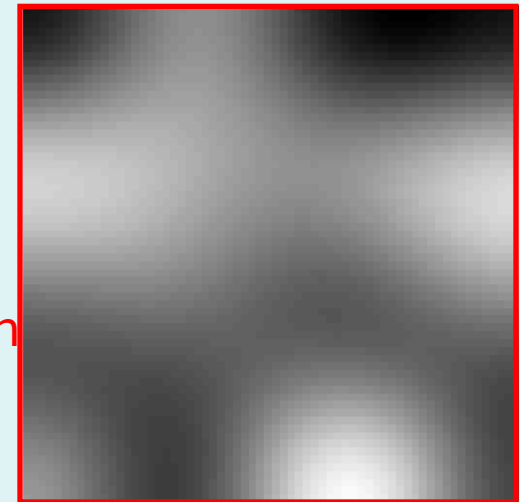
x-displacement

y-displacement

y-displacement,  
**black**: downward translation  
**white**: upward translation  
**grey**: no translation

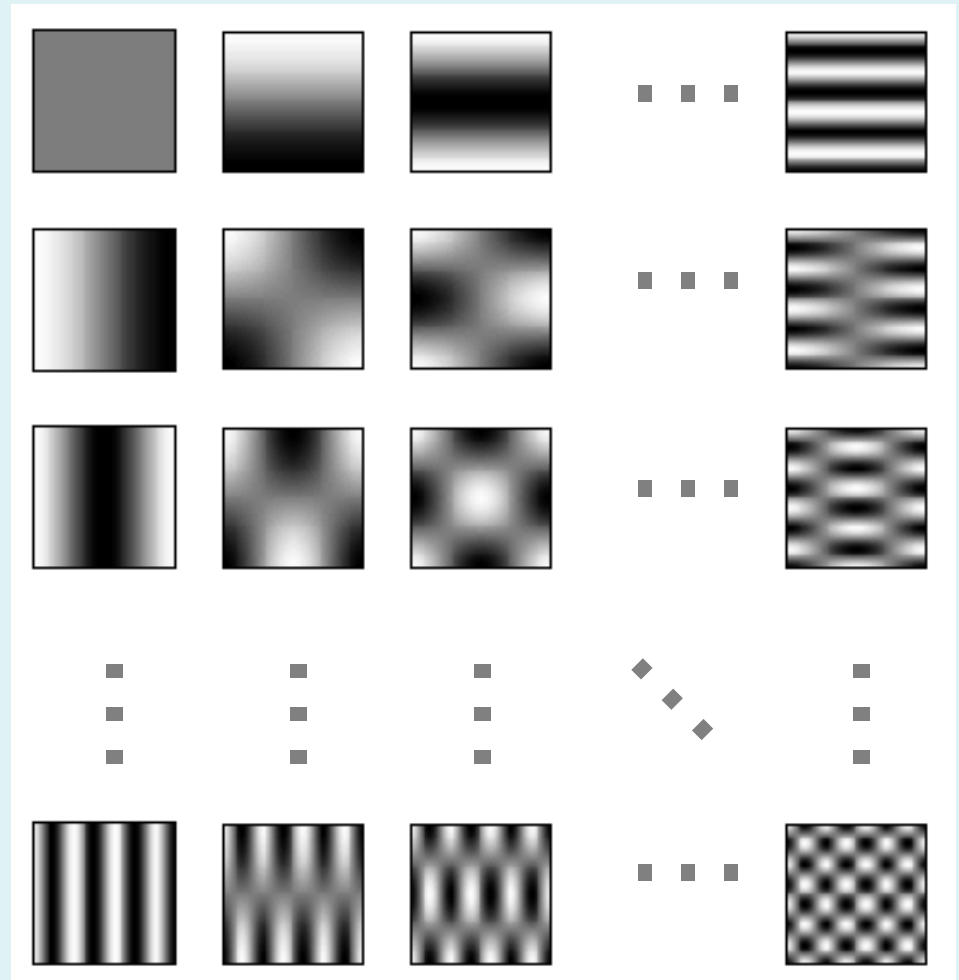


x-displacement,  
**black**: leftward translation  
**white**: rightward translation  
**gray**: no translation



# Displacement map modelling

- To prevent impossible deformations we restrict it to be a linear combination of permitted basis-warps.
- For example use the discrete cosine set  $\rightarrow$  smooth deformation!

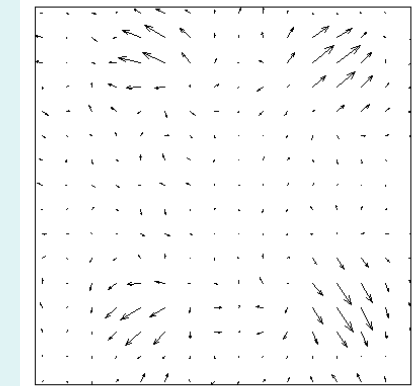
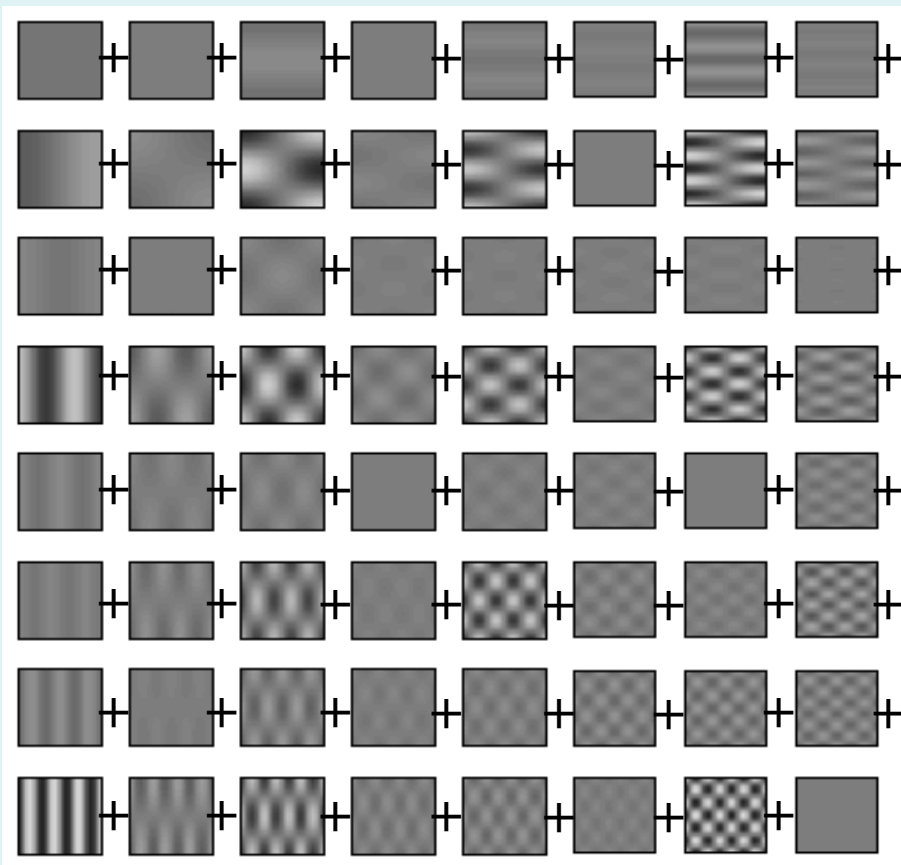




# Displacement maps, example

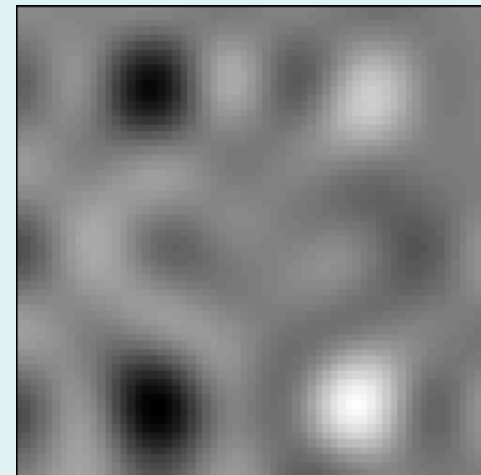
Square-to-ellipse map

Each basis-warp multiplied by a weight



x-component of  
square-to-ellipse map

=

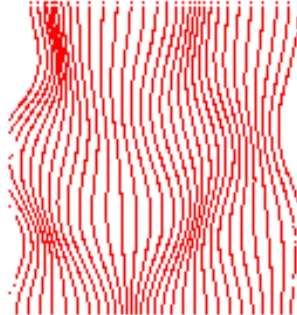


# Displacement maps, example

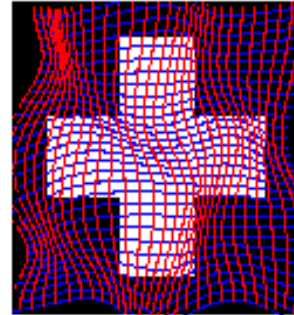
Dark - shift left, Light - shift right



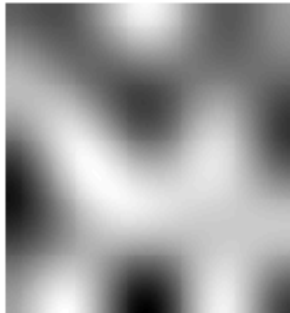
Deformation Field in X



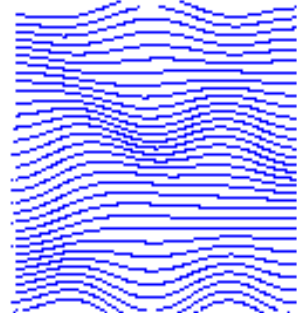
Field Applied To Image



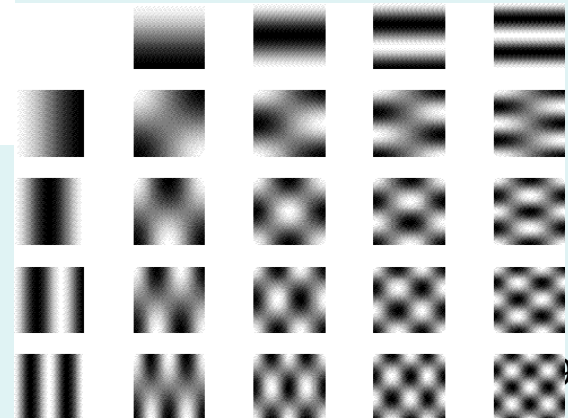
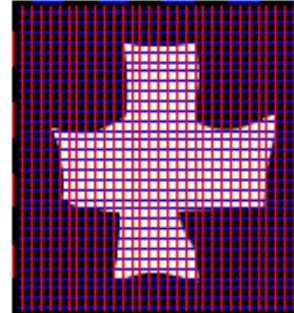
Dark - shift down, Light - shift up



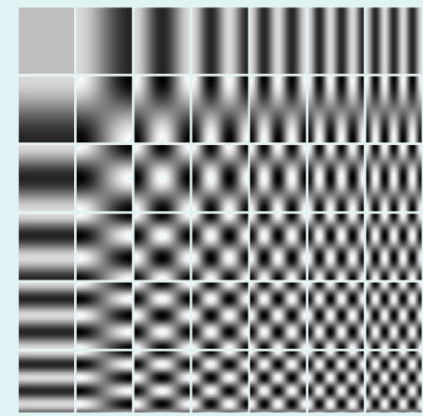
Deformation Field in Y



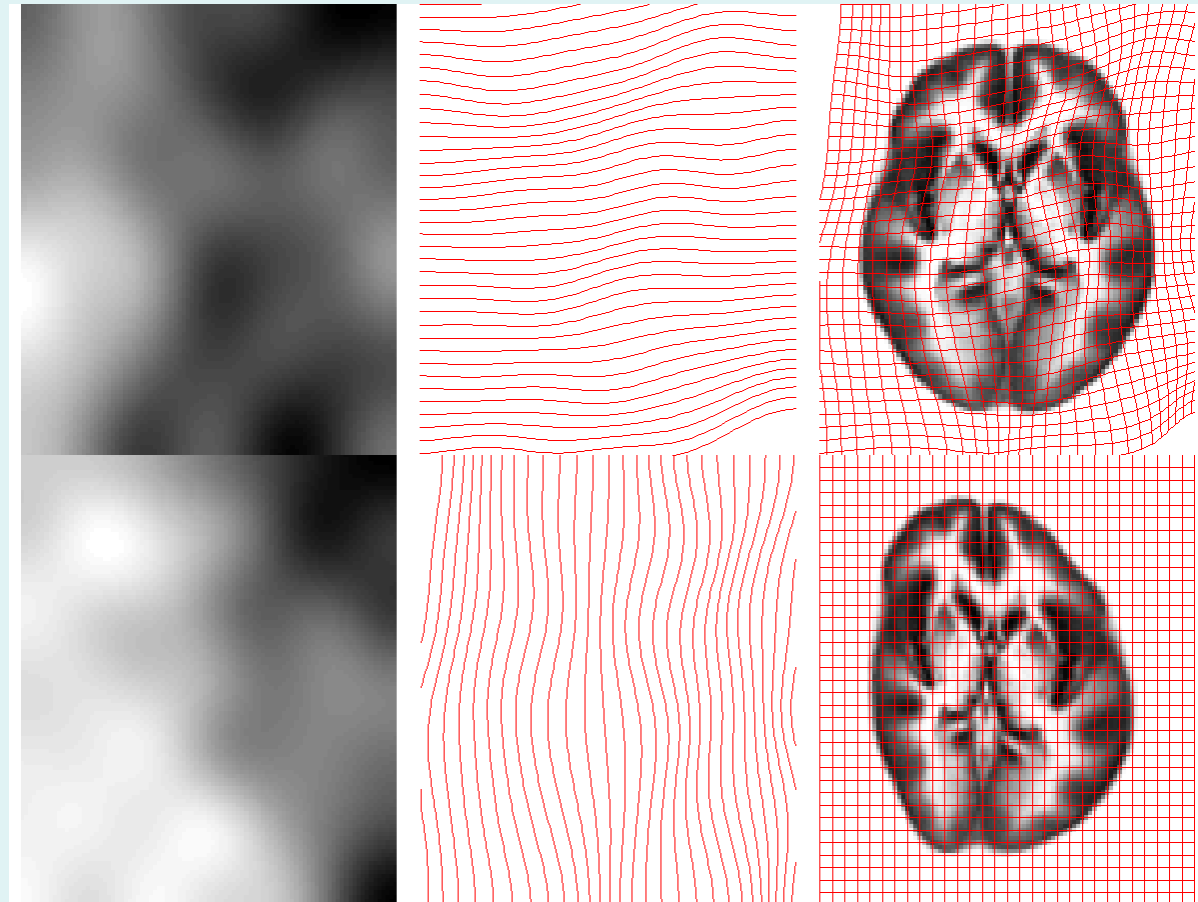
Deformed Image



# Modelling deformations, warps

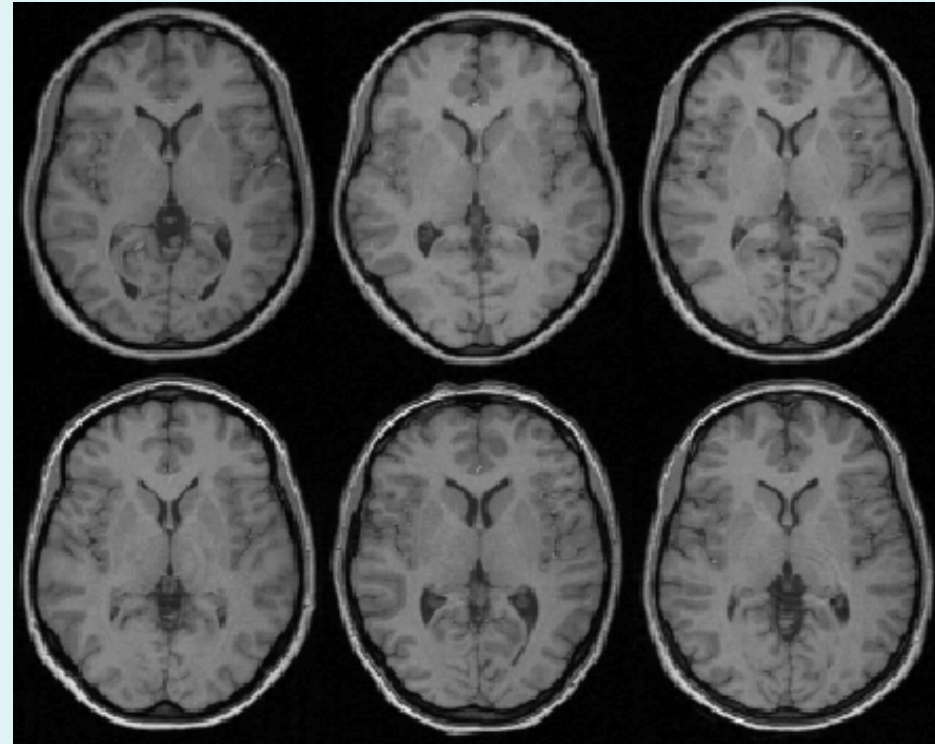


- Tissue probability images are warped to match the subject
- The inverse transform warps to the TPMs
- Warps are constrained to be reasonable by penalising various distortions (energies)

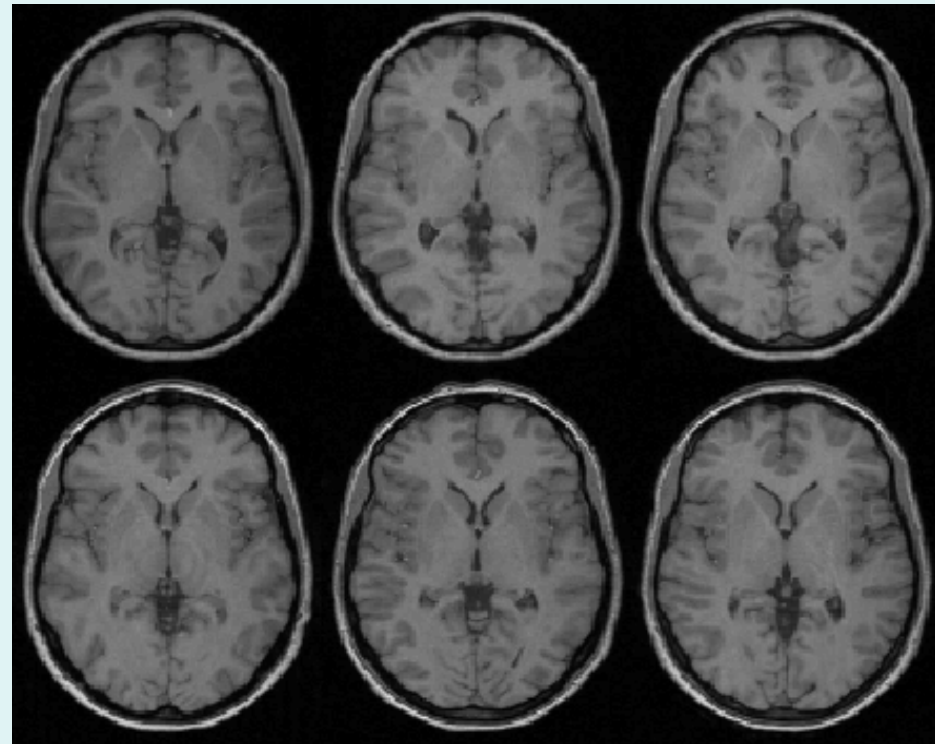


# Spatial normalisation results

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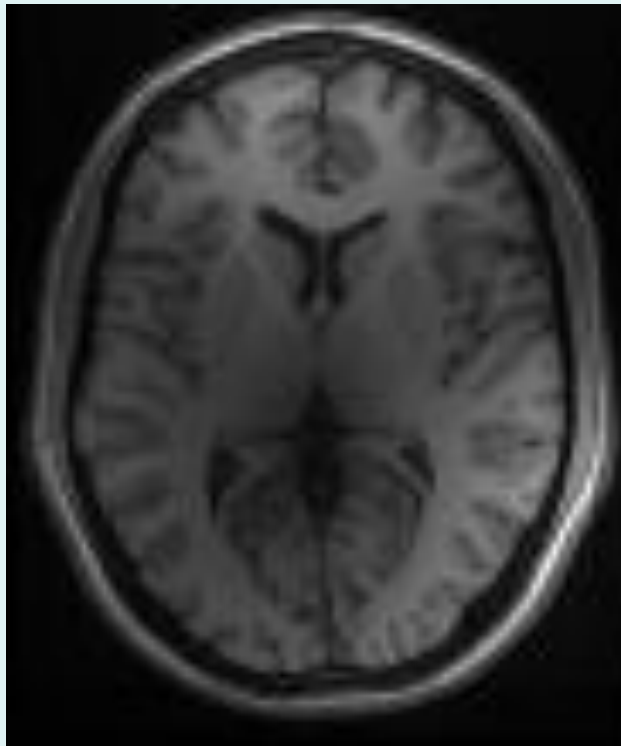
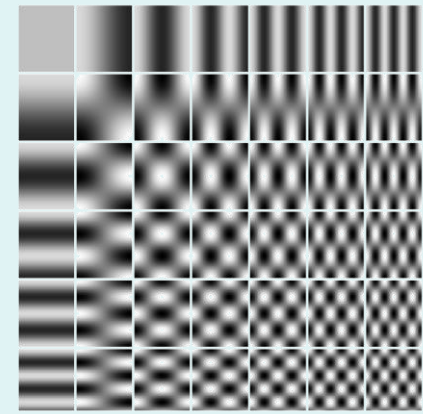
Affine registration



Non-linear registration

# Modelling inhomogeneity

A multiplicative bias field is modelled as a spatially smooth image



**Corrupted image**



**Bias Field**



**Corrected image**

# Normalisation & Unified Segmentation

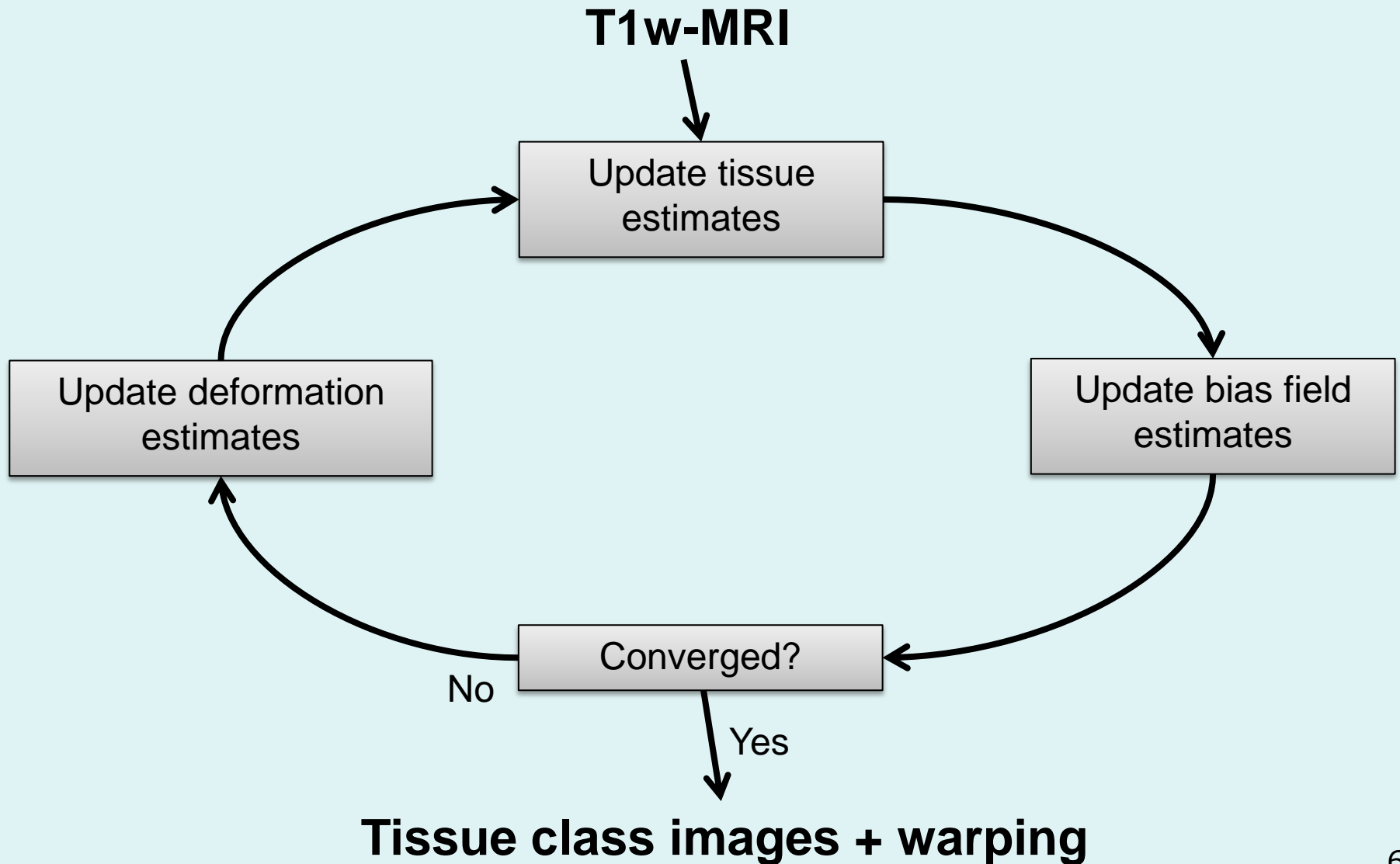
---

- MRI imperfections make normalisation harder
  - Differences between sequences, artefacts
  - Intensity inhomogeneity or “bias” field
- Normalising *segmented tissue maps* should be more robust and precise than using the original images ...
- ... Tissue segmentation benefits from spatially-aligned *prior tissue probability maps* (from other segmentations)

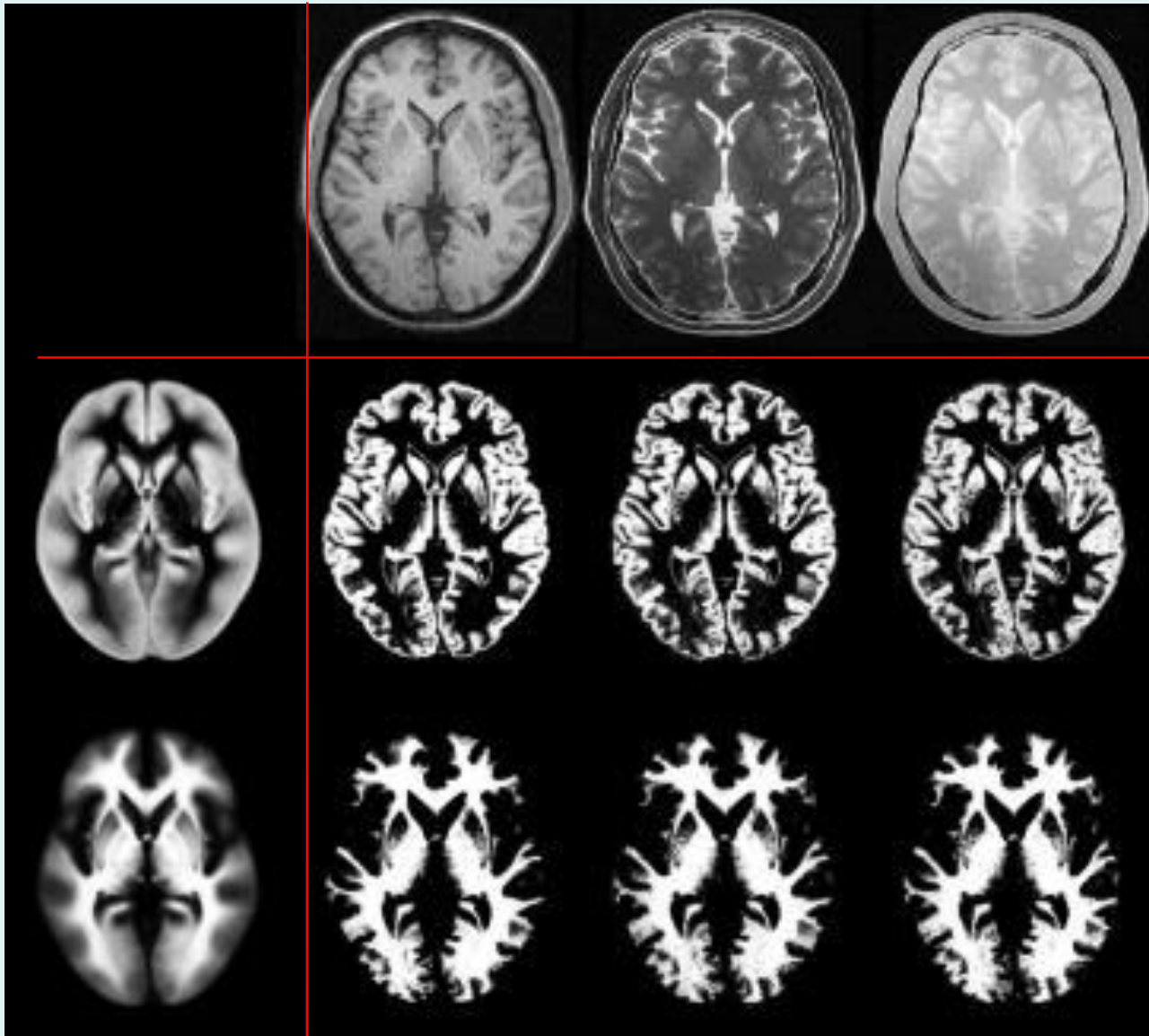
→ Circular reasoning!

# Iterative optimisation scheme

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# Segmentation results



Spatially  
normalised  
BrainWeb  
phantoms  
(T1, T2,  
PD)

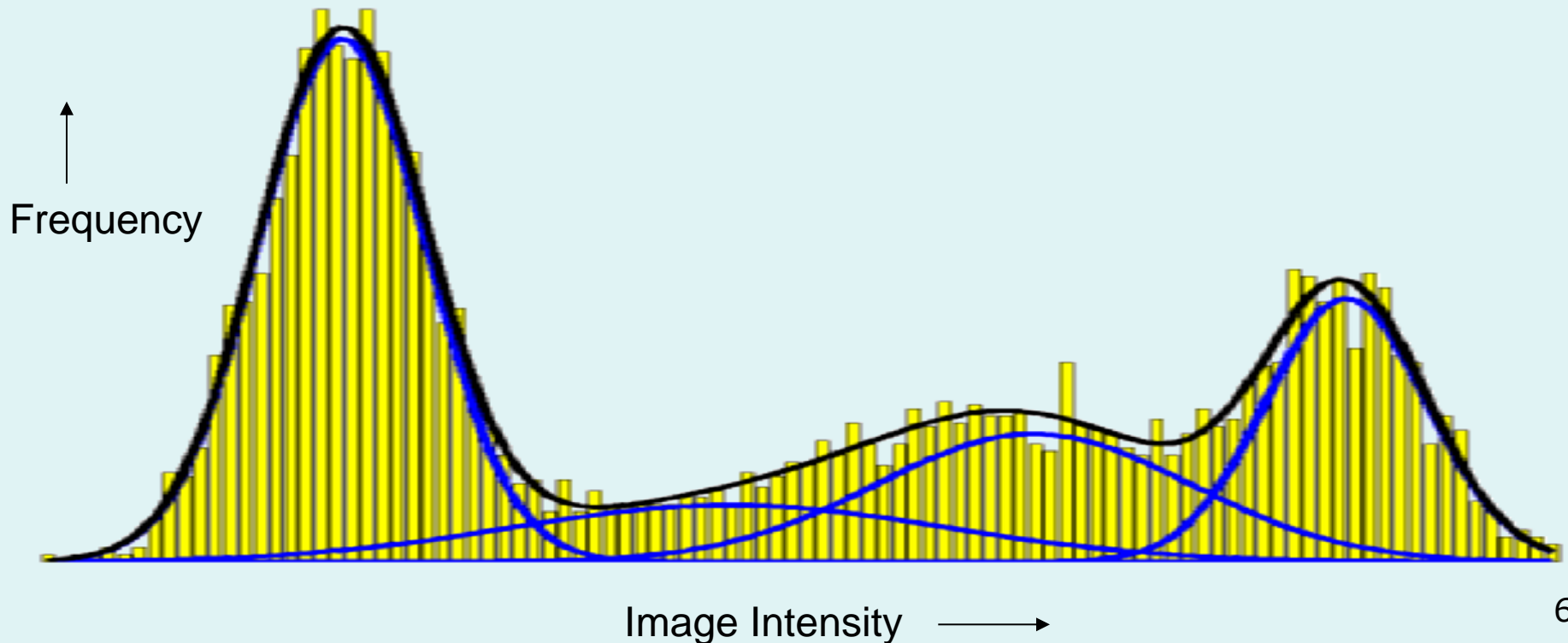
Tissue  
probability  
maps of  
GM and  
WM



# Mixture of Gaussians (MoG)

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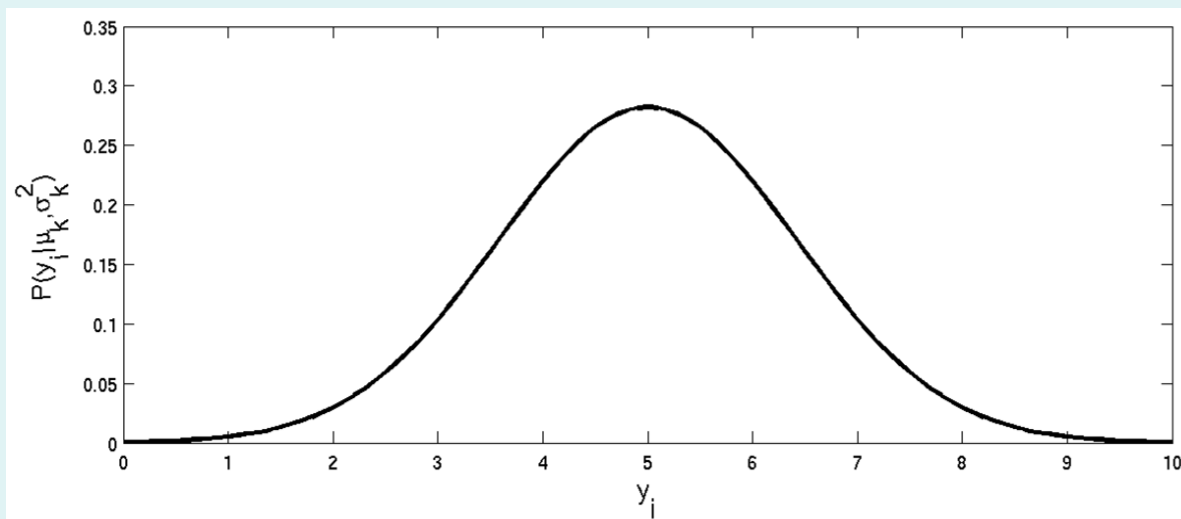
Classification is based on a Mixture of Gaussians model (MOG), which represents the intensity probability density by a number of Gaussian distributions.



# Gaussian probability density

If intensities are assumed to be Gaussian of mean  $\mu_k$  and variance  $\sigma_k^2$ , then the probability of a value  $y_i$  is:

$$P(y_i | \mu_k, \sigma_k^2) = \frac{1}{\sqrt{2\pi\sigma_k^2}} \exp\left(-\frac{(y_i - \mu_k)^2}{2\sigma_k^2}\right)$$

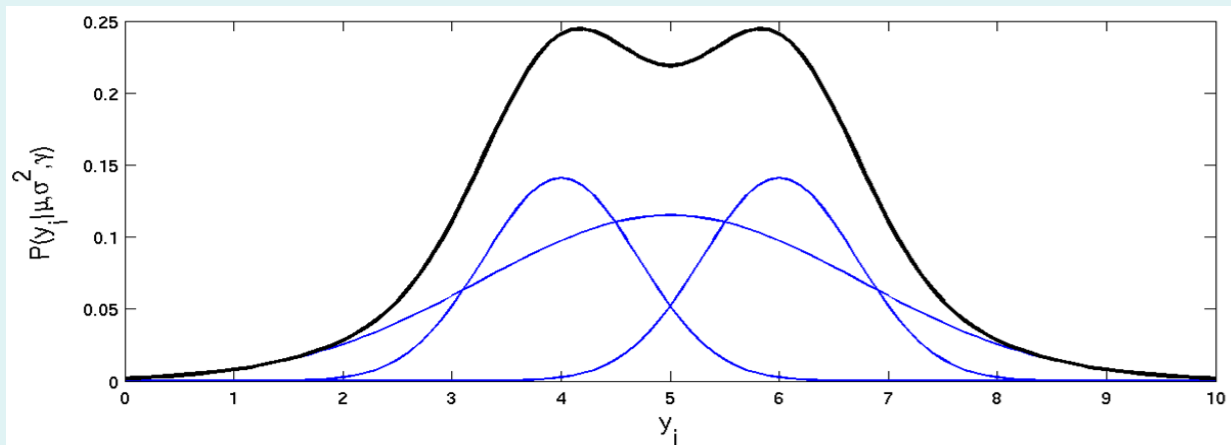


# Non-Gaussian probability density

A non-Gaussian probability density function can be modelled by a Mixture of Gaussians (MOG):

$$P(y_i | \mu, \sigma^2, \gamma) = \sum_{k=1}^K \gamma_k \frac{1}{\sqrt{2\pi\sigma_k^2}} \exp\left(-\frac{(y_i - \mu_k)^2}{2\sigma_k^2}\right)$$

Mixing proportion - positive and sums to one

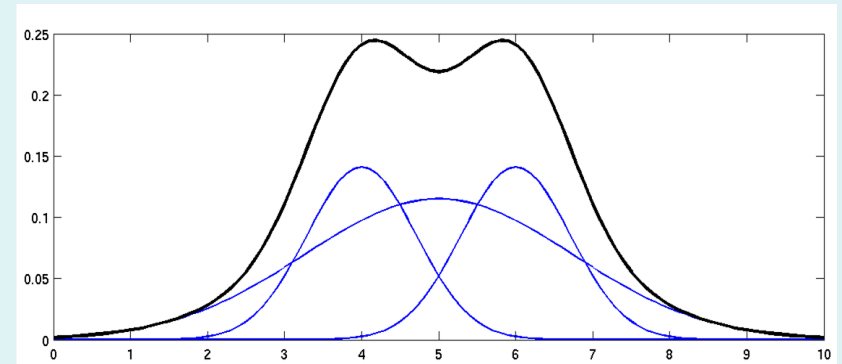


# Mixing proportions

- The mixing proportion  $\gamma_k$  represents the prior probability of a voxel being drawn from class  $k$  - irrespective of its intensity.

$$P(c_i = k | \gamma) = \gamma_k$$

- So:



$$\begin{aligned} P(y_i | \mu, \sigma^2, \gamma) &= \sum_{k=1}^K P(y_i, c_i = k | \mu, \sigma^2, \gamma) \\ &= \sum_{k=1}^K P(c_i = k | \gamma) P(y_i | c_i = k, \mu, \sigma^2) \end{aligned}$$

# Probability of whole image

- If the voxels are assumed to be independent, then the probability of the whole image is the product of the probabilities of each voxel:

$$P(\mathbf{y} \mid \mu, \sigma^2, \gamma) = \prod_{i=1}^I P(y_i \mid \mu, \sigma^2, \gamma)$$

- It is often easier to work with negative log-probabilities:

$$-\log(P(\mathbf{y} \mid \mu, \sigma^2, \gamma)) = -\sum_{i=1}^I \log(P(y_i \mid \mu, \sigma^2, \gamma))$$

# Modelling a bias field

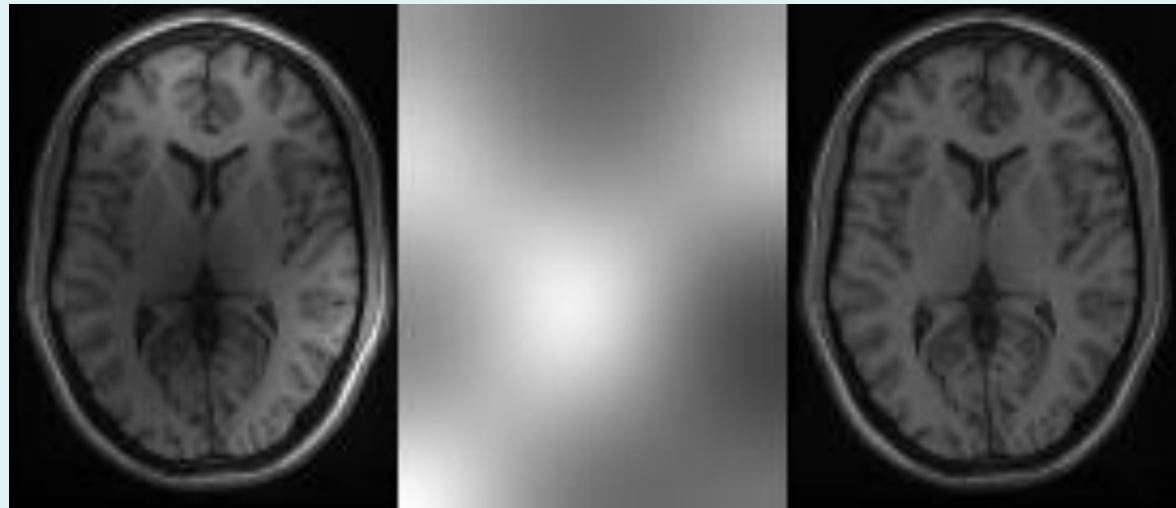
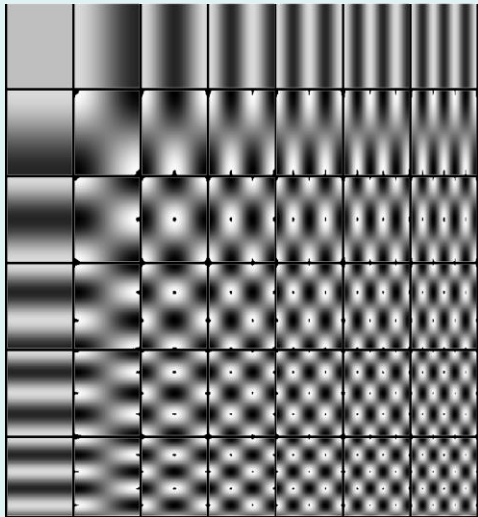
- A bias field is included, such that the required scaling at voxel  $i$ , parameterised by  $\beta$ , is  $\rho_i(\beta)$ .
- Replace the means by  $\mu_k / \rho_i(\beta)$
- Replace the variances by  $(\sigma_k / \rho_i(\beta))^2$

$$P(y_i | c_i = k, \mu, \sigma^2, \beta) = \frac{1}{\sqrt{2\pi(\sigma_k / \rho_i(\beta))^2}} \exp\left(-\frac{(y_i - \mu_k / \rho_i(\beta))^2}{2(\sigma_k / \rho_i(\beta))^2}\right)$$

# Modelling a bias field

After rearranging:

$$P(y_i | c_i = k, \mu, \sigma^2, \beta) = \frac{\rho(\beta)}{\sqrt{2\pi\sigma_k^2}} \exp\left(-\frac{(y_i\rho_i(\beta) - \mu_k)^2}{2\sigma_k^2}\right)$$



$y$

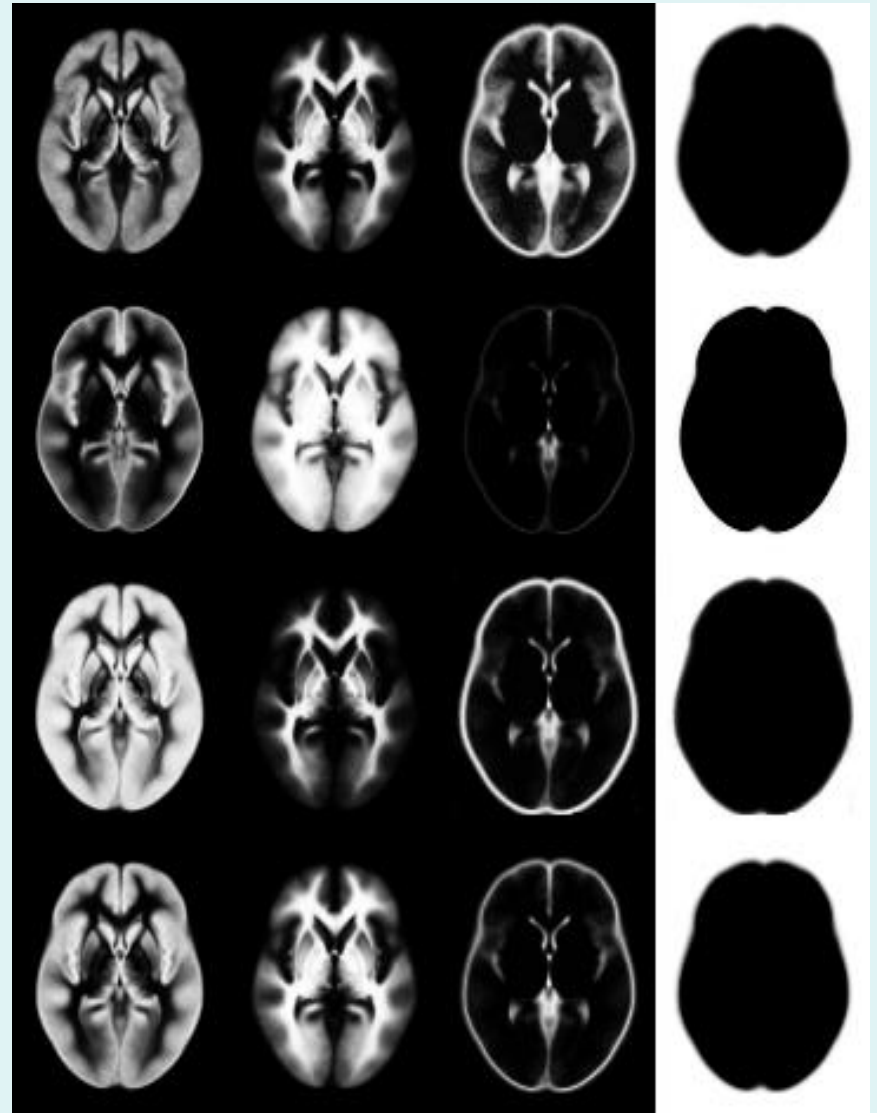
$\rho(\beta)$

$y \rho(\beta)$

# “Mixing proportions”

- Tissue probability maps for each class are included.
- The probability of obtaining class  $k$  at voxel  $i$ , given weights  $\gamma$  is then:

$$P(c_i = k | \gamma) = \frac{\gamma_k b_{ik}}{\sum_{j=1}^K \gamma_j b_{ij}}$$

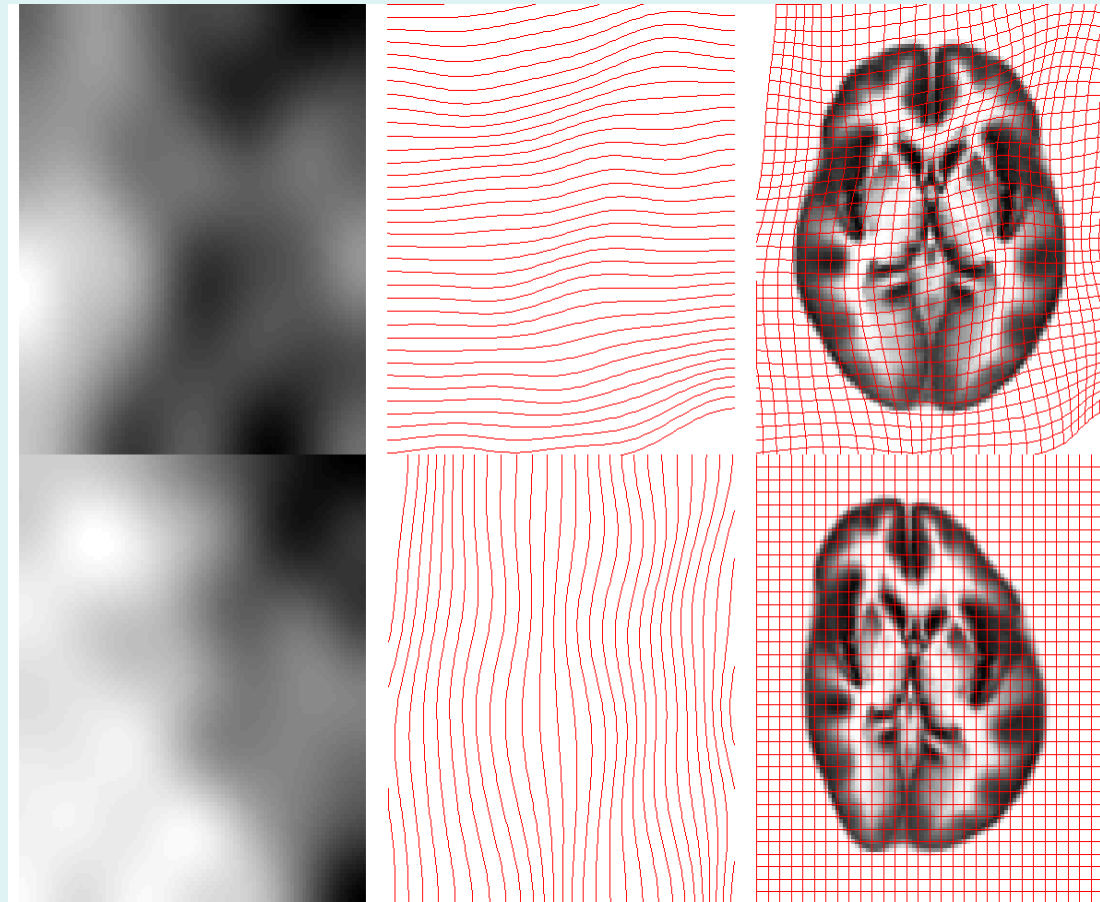




# TPMs deformation

- Tissue probability images are deformed according to parameters  $\alpha$ .
- The probability of obtaining class  $k$  at voxel  $i$ , given weights  $\gamma$  and parameters  $\alpha$  is then:

$$P(c_i = k \mid \gamma, \alpha) = \frac{\gamma_k \mathbf{b}_{ik}(\alpha)}{\sum_{j=1}^K \gamma_j \mathbf{b}_{ij}(\alpha)}$$



# The extended US model

- By combining the modified  $P(c_i=k|\theta)$  and  $P(y_i|c_i=k,\theta)$ , the overall objective function (E) becomes:

$$E = -\sum_{i=1}^I \log [P(y_i|\theta)] = -\sum_{i=1}^I \log \left[ \sum_{k=1}^K P(c_i = k | \theta) P(y_i | c_i = k, \theta) \right]$$

$$= -\sum_{i=1}^I \log \left[ \rho_i(\beta) \sum_{k=1}^K \frac{\gamma_k \mathbf{b}_{ik}(\alpha)}{\sum_{j=1}^K \gamma_j \mathbf{b}_{ij}(\alpha)} \frac{1}{\sqrt{2\pi\sigma_k^2}} \exp \left( -\frac{(\rho_i(\beta)\gamma_i - \mu_k)^2}{2\sigma_k^2} \right) \right]$$

**The Objective Function**

# Optimisation

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

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

# Optimisation strategy

---

Repeat until convergence...

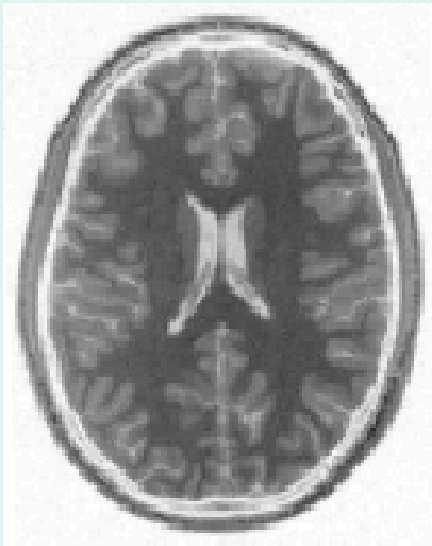
- Hold  $\gamma$ ,  $\mu$ ,  $\sigma^2$  and  $\alpha$  constant, and minimise  $E$  w.r.t.  $\beta$   
Levenberg-Marquardt strategy, using  $dE/d\beta$  and  $d^2E/d\beta^2$
- Hold  $\gamma$ ,  $\mu$ ,  $\sigma^2$  and  $\beta$  constant, and minimise  $E$  w.r.t.  $\alpha$   
Levenberg-Marquardt strategy, using  $dE/d\alpha$  and  $d^2E/d\alpha^2$
- Hold  $\alpha$  and  $\beta$  constant, and minimise  $E$  w.r.t.  $\gamma$ ,  $\mu$  and  $\sigma^2$   
Use an Expectation Maximisation (EM) strategy.

end

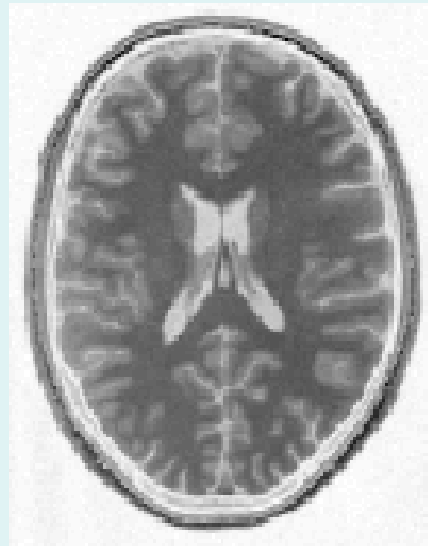
# Spatial normalisation, overfitting

Without regularisation, the non-linear spatial normalisation can introduce unnecessary warps.

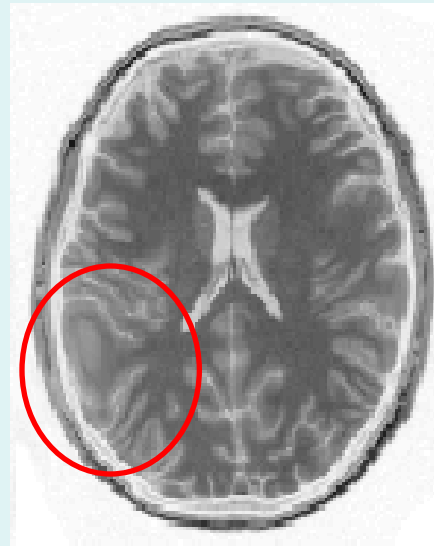
Template image



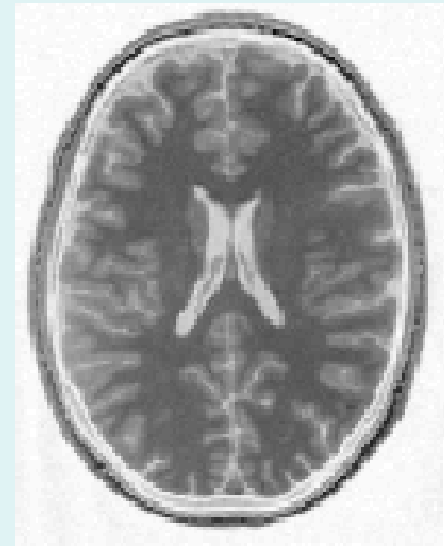
Affine registration.



Non-linear registration without regularisation.



Non-linear registration using regularisation.



# Linear regularisation

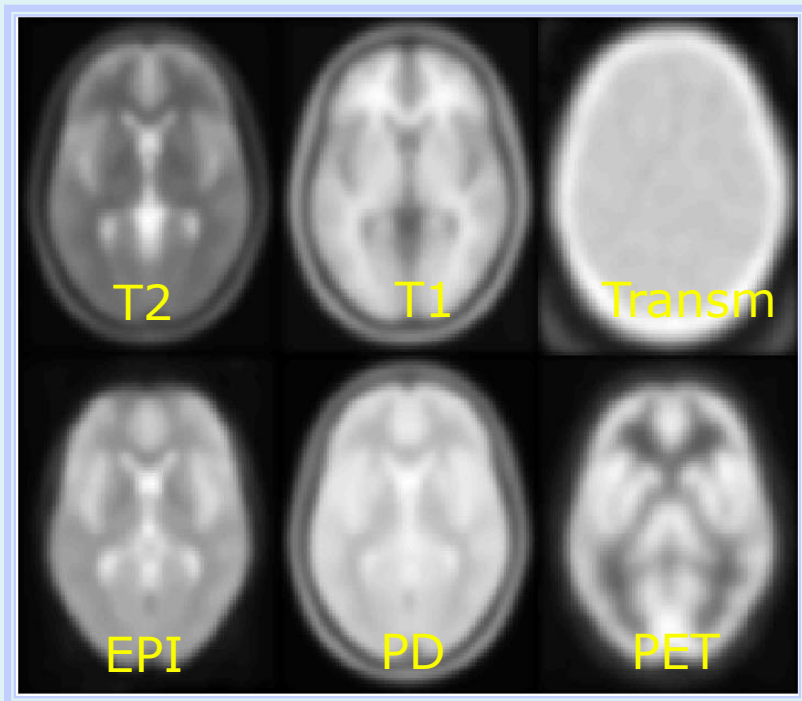
- Some bias fields and distortions are more probable (a priori) than others.
- Encoded using Bayes rule:

$$-\log [P(\theta, \mathbf{y})] = -\log [P(\mathbf{y} | \theta)] - \log [P(\theta)]$$

- Prior probability distributions can be modelled by a multivariate normal distribution.
  - Mean vector  $\mu_a$  and  $\mu_b$
  - Covariance matrix  $\Sigma_a$  and  $\Sigma_b$
  - $-\log[P(\mathbf{a})] = (\mathbf{a} - \mathbf{m}_a)^T \mathbf{S}_a^{-1} (\mathbf{a} - \mathbf{m}_a) + \text{const}$

# Old fashioned template matching

Minimise mean squared difference from image to template image(s)



Template Images



Spatial normalisation can be weighted so that non-brain voxels do not influence the result.

Similar weighting masks can be used for normalising lesioned brains.

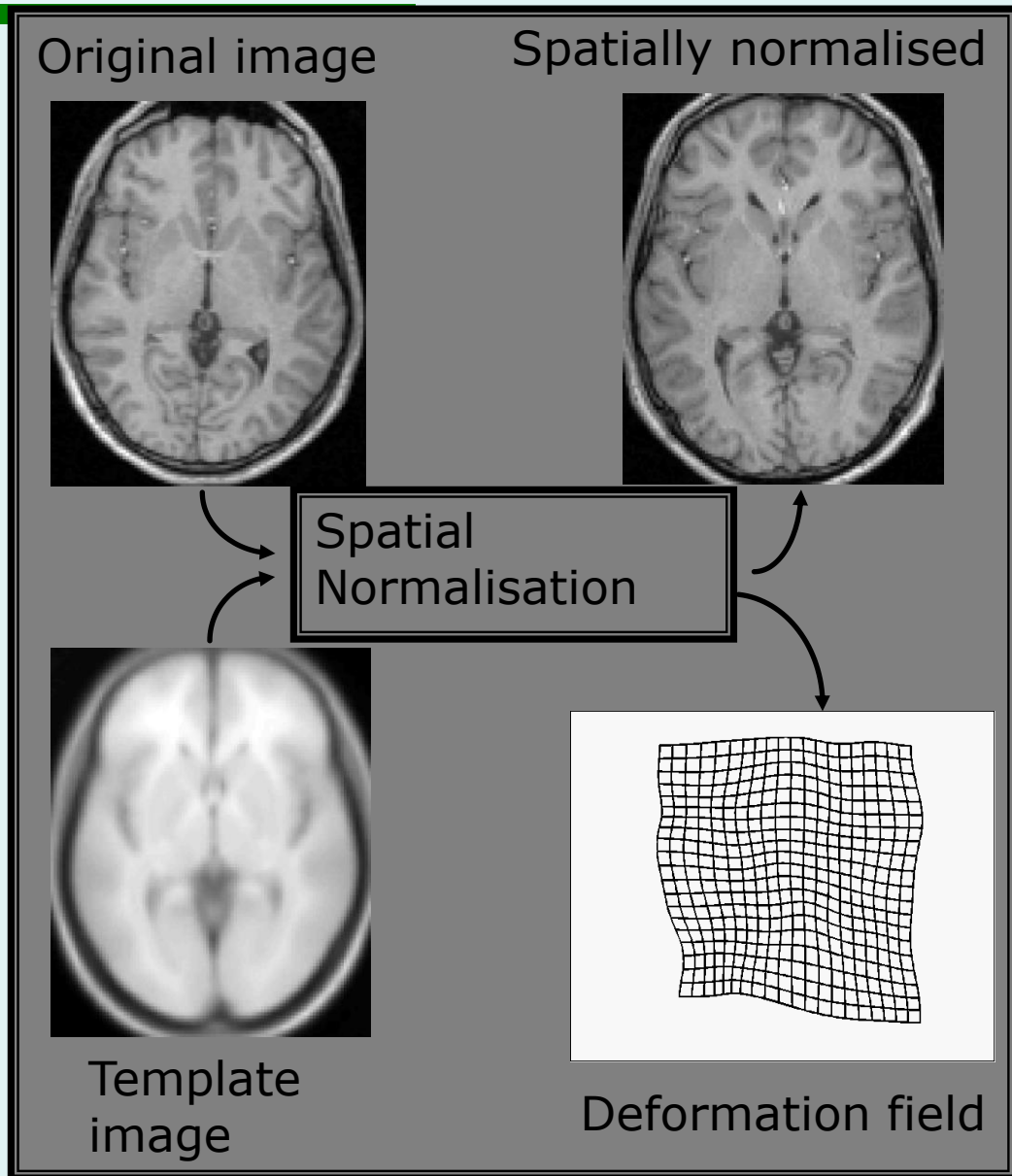
# Old fashioned template matching

Determine the spatial transformation that minimises the sum of squared difference between an image and a linear combination of one or more templates.

Begins with an affine registration to match the size and position of the image.

Followed by a global non-linear warping to match the overall brain shape.

Uses a Bayesian framework to simultaneously minimize the bending energies of the warps.





# Content

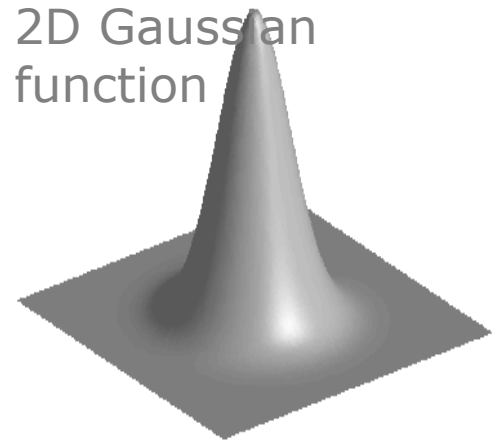
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- **Preliminaries**
- **Within-subject**
- **Between-subject**
- **Smoothing**
- **Conclusion**

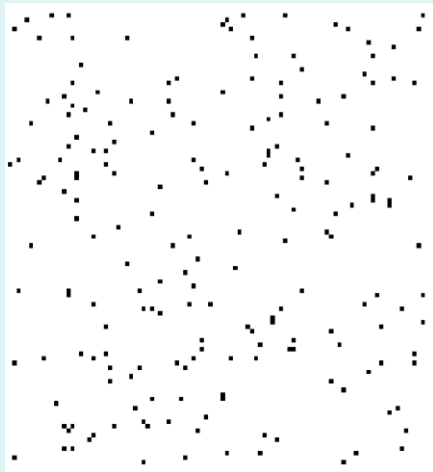
# Smoothing, principle

- Smoothing is done by convolution.
- Each voxel after smoothing effectively becomes the result of applying a weighted region of interest (ROI).
- Gaussian function, defined by its “*full width at half maximum*” (FWHM)

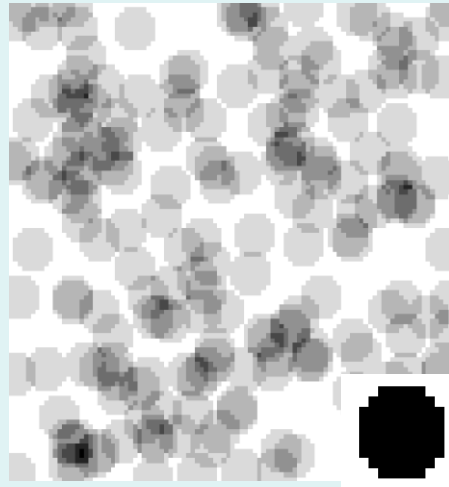
2D Gaussian function



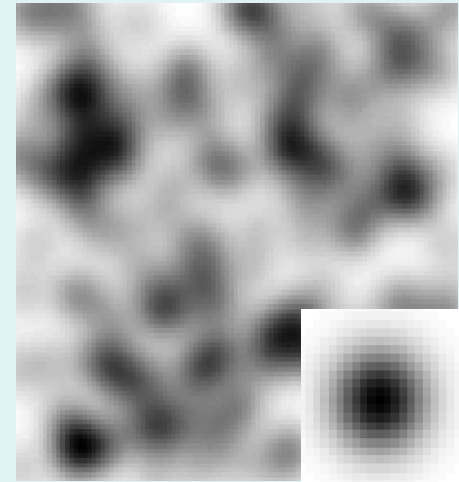
Before convolution



Convolved with a circle

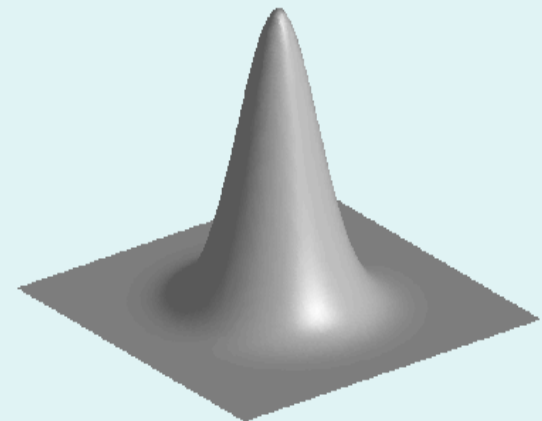


Convolved with a Gaussian



# Smoothing, why blur the data?

- Improves spatial overlap by blurring over minor anatomical differences and registration errors
- Averaging neighbouring voxels suppresses noise (matched filter theorem)
- Makes data more normally distributed (central limit theorem)
- Reduces the effective number of multiple comparisons

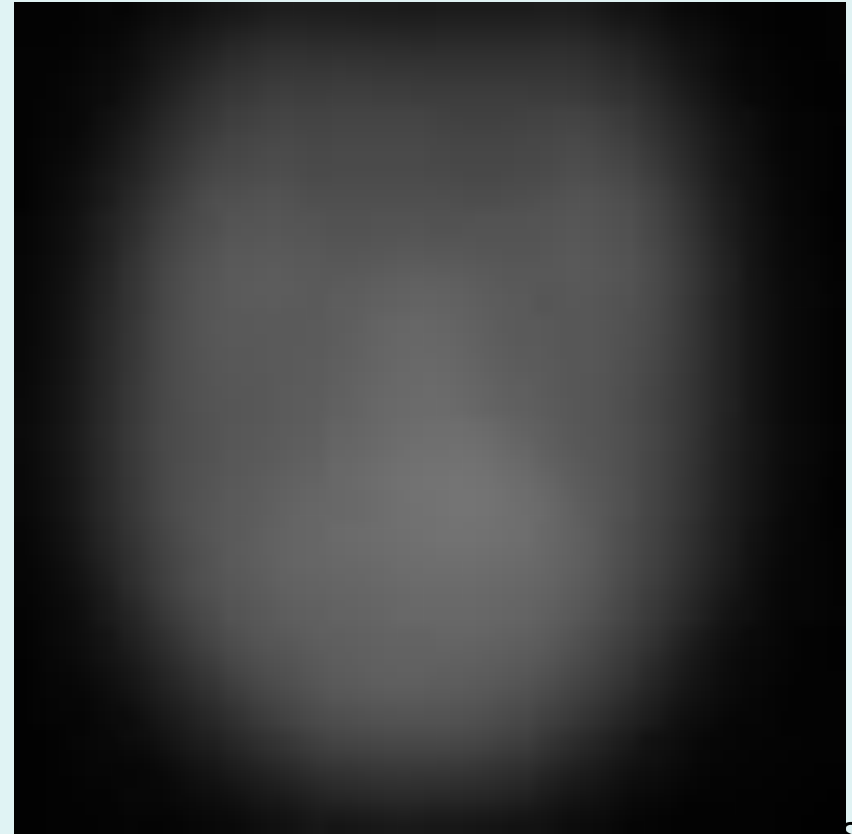
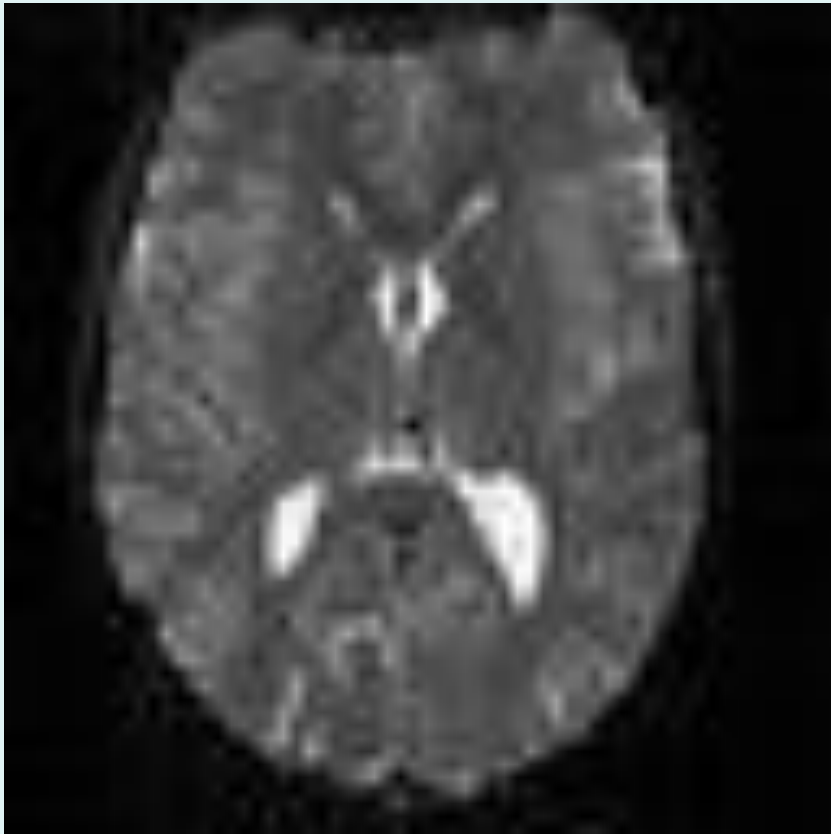


# Smoothing, kernel size

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Decide *a priori*, based on:

- Population, i.e. noise & inter-subject variability
- Expected activation size

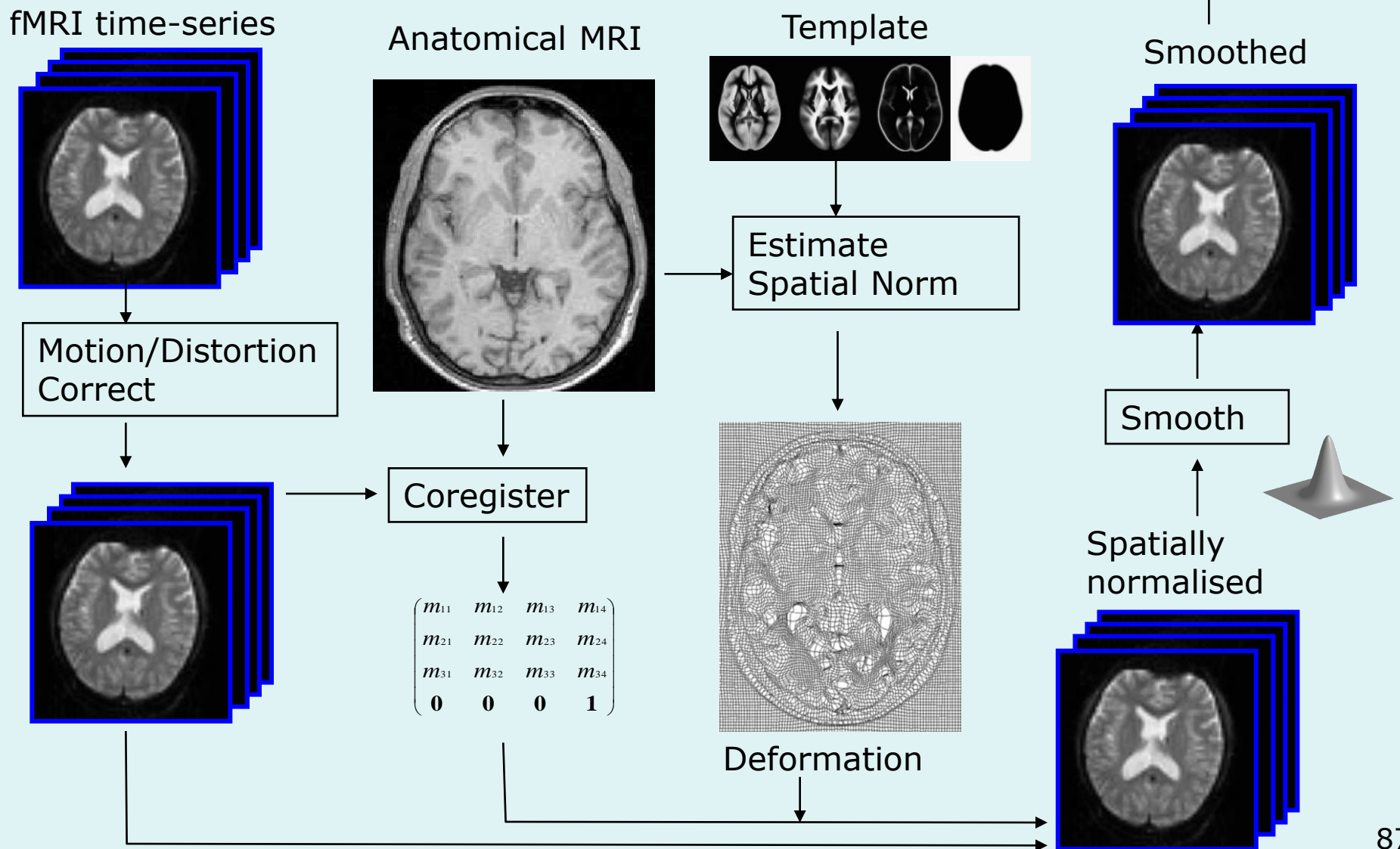


# Content

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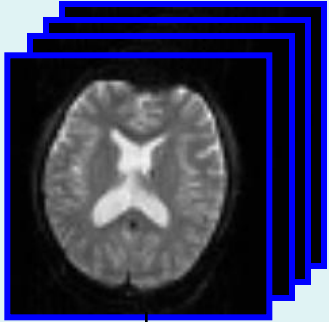
- **Preliminaries**
- **Within-subject**
- **Between-subject**
- **Smoothing**
- **Conclusion**

# Pre-processing overview

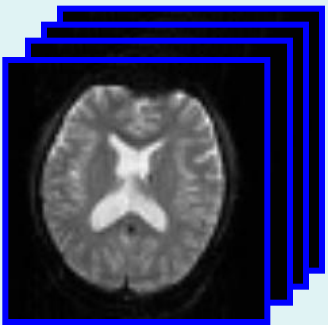


# Alternative pipeline

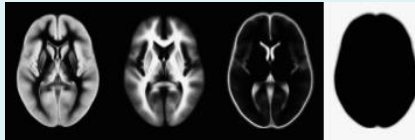
fMRI time-series



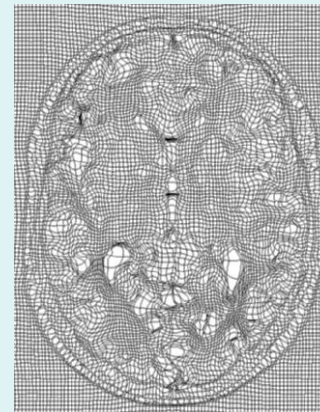
Motion/Distortion Correct



Template



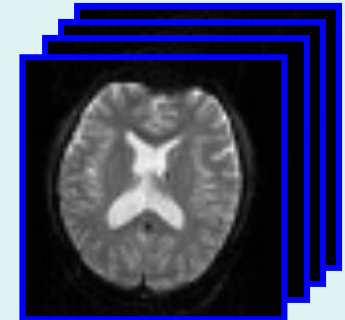
Estimate Spatial Norm



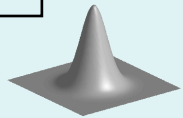
Deformation

Statistics or whatever

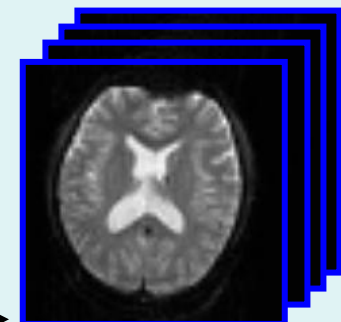
Smoothed



Smooth



Spatially normalised



# References

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