# NON-RIGID REGISTRATION & ATLAS BUILDING IN MEDICAL IMAGE ANALYSIS

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# Where is non-rigid registration needed in medical imaging?

- Correcting/accounting for imaging distortions
  - Scanner induced geometric changes
- Resolving differences between subjects:
  - Spatial normalization to compare image data across populations
- Correcting tissue deformations
  - Subject related anatomical changes
- Capturing tissue growth or loss within a subject
  - Studying dementia or tissue growth: Deformation Based Morphometry (DBM)

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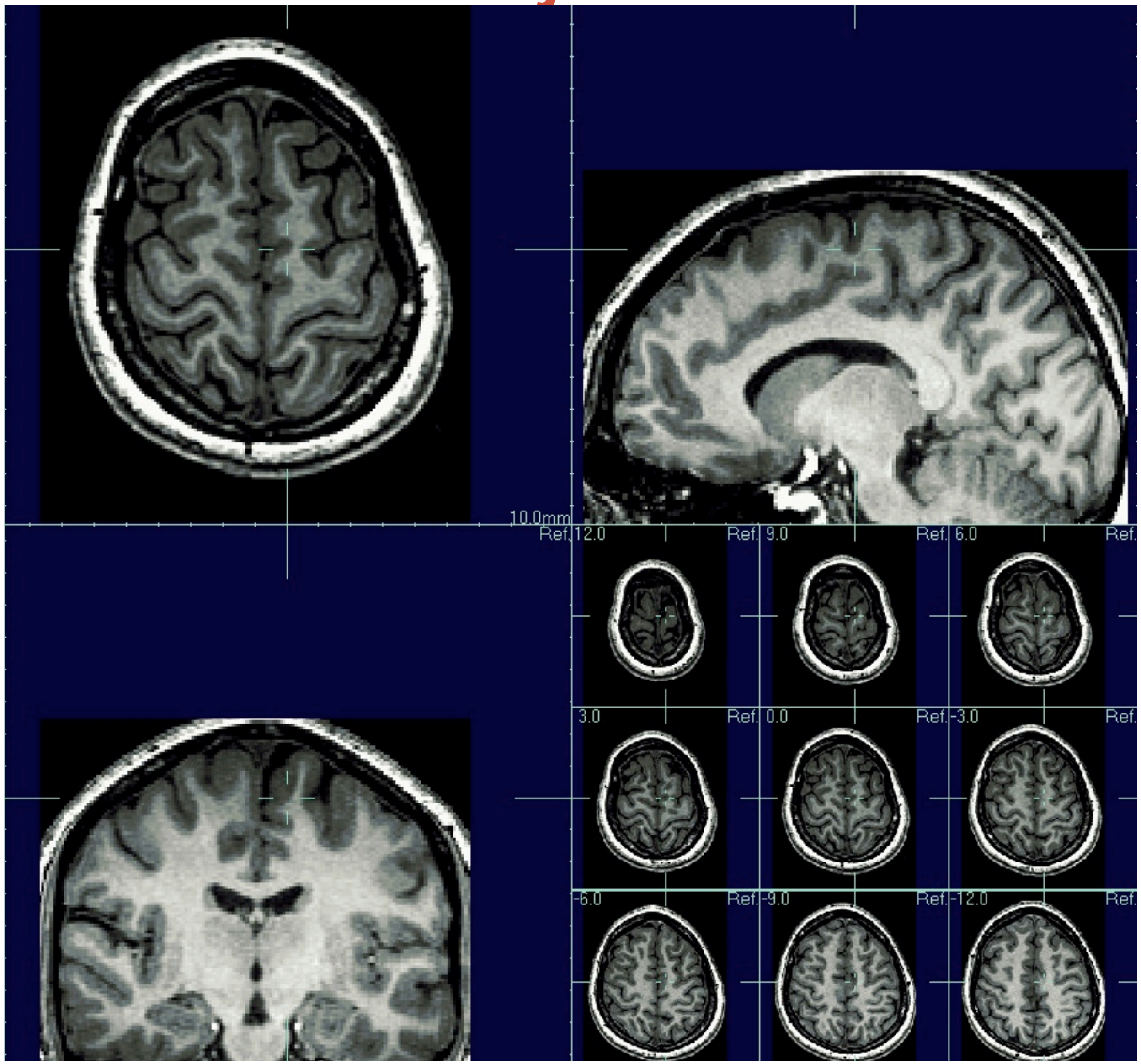
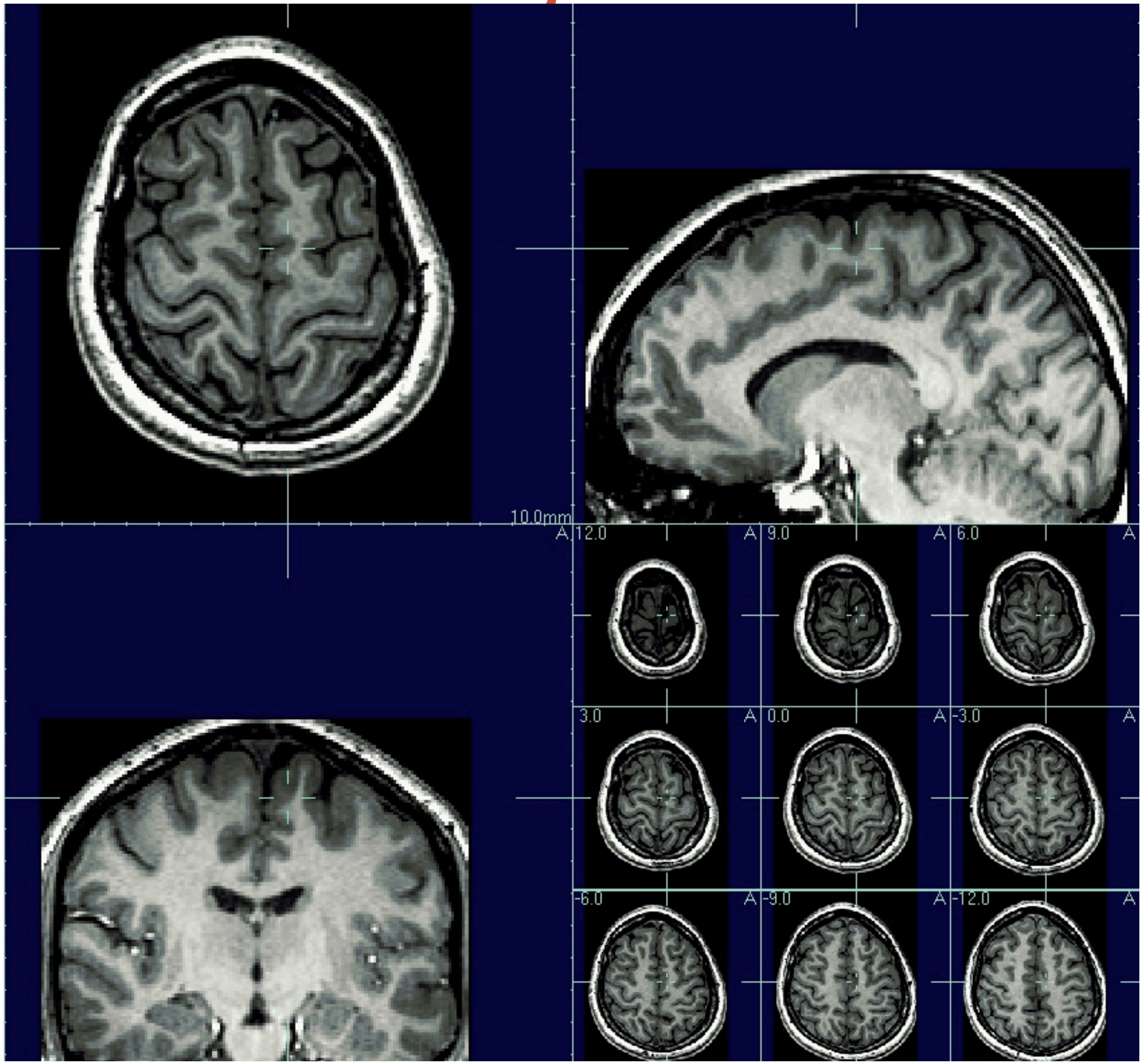
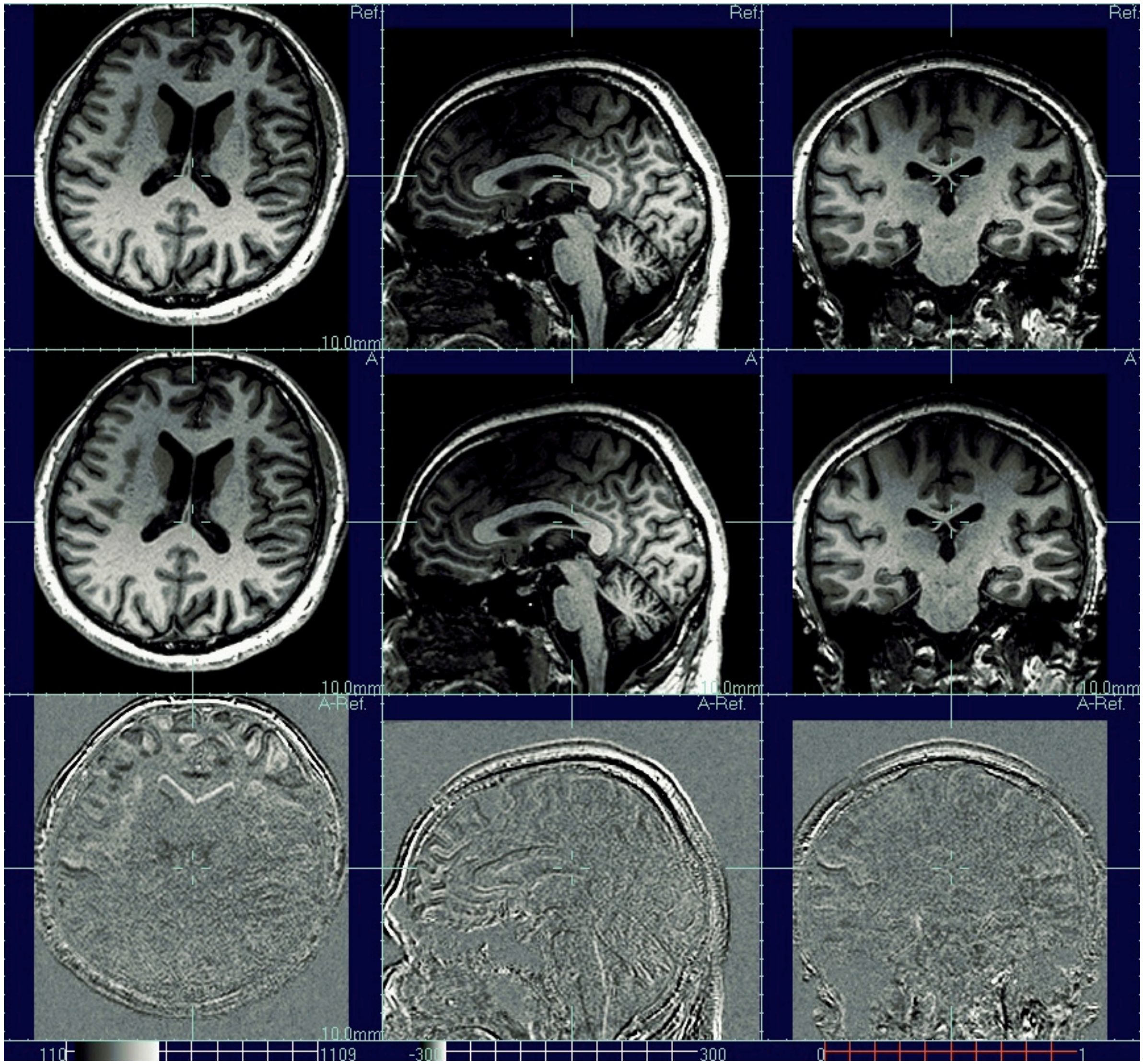
# GE 3T control subject at Time Point 1



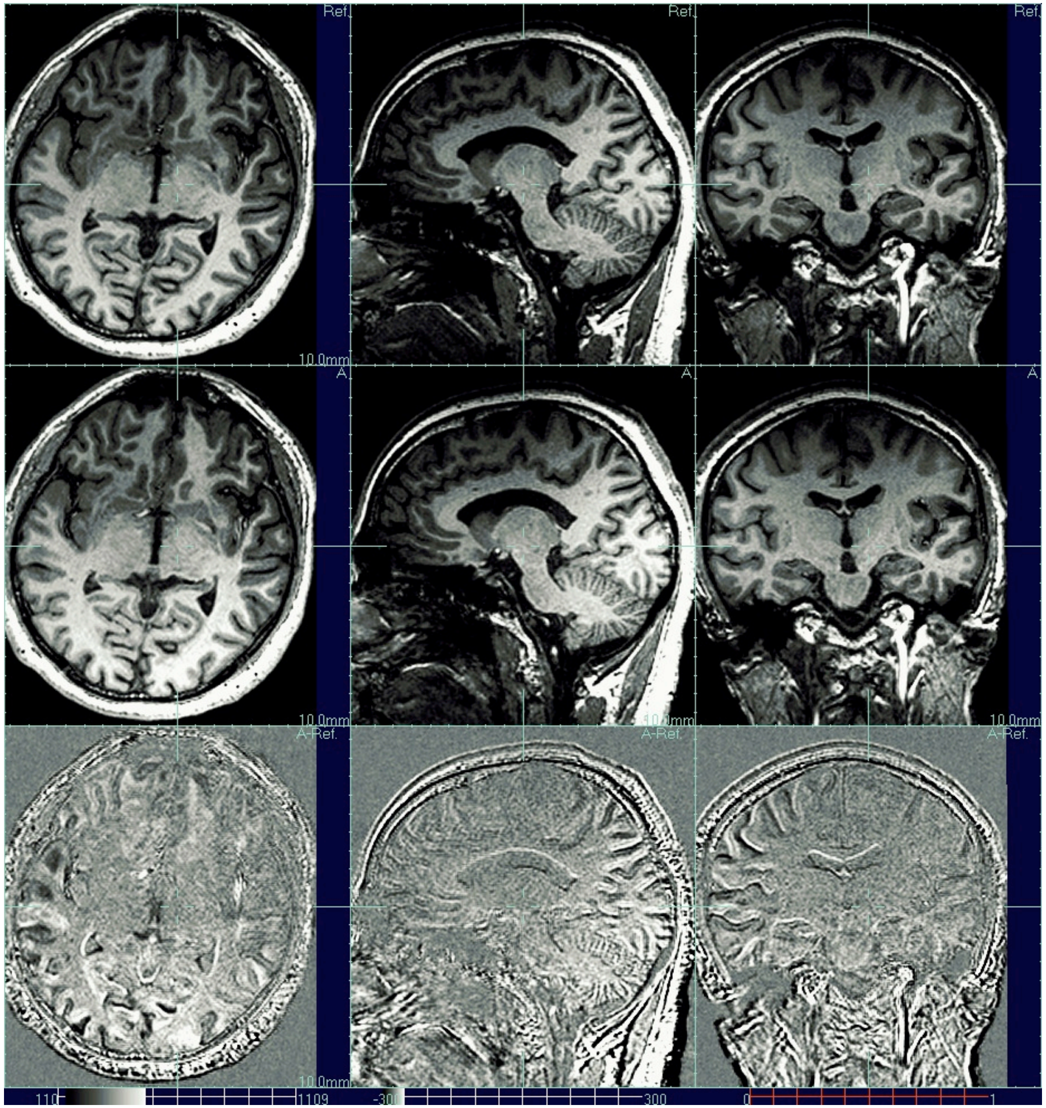
# GE 3T control subject at Time Point 2



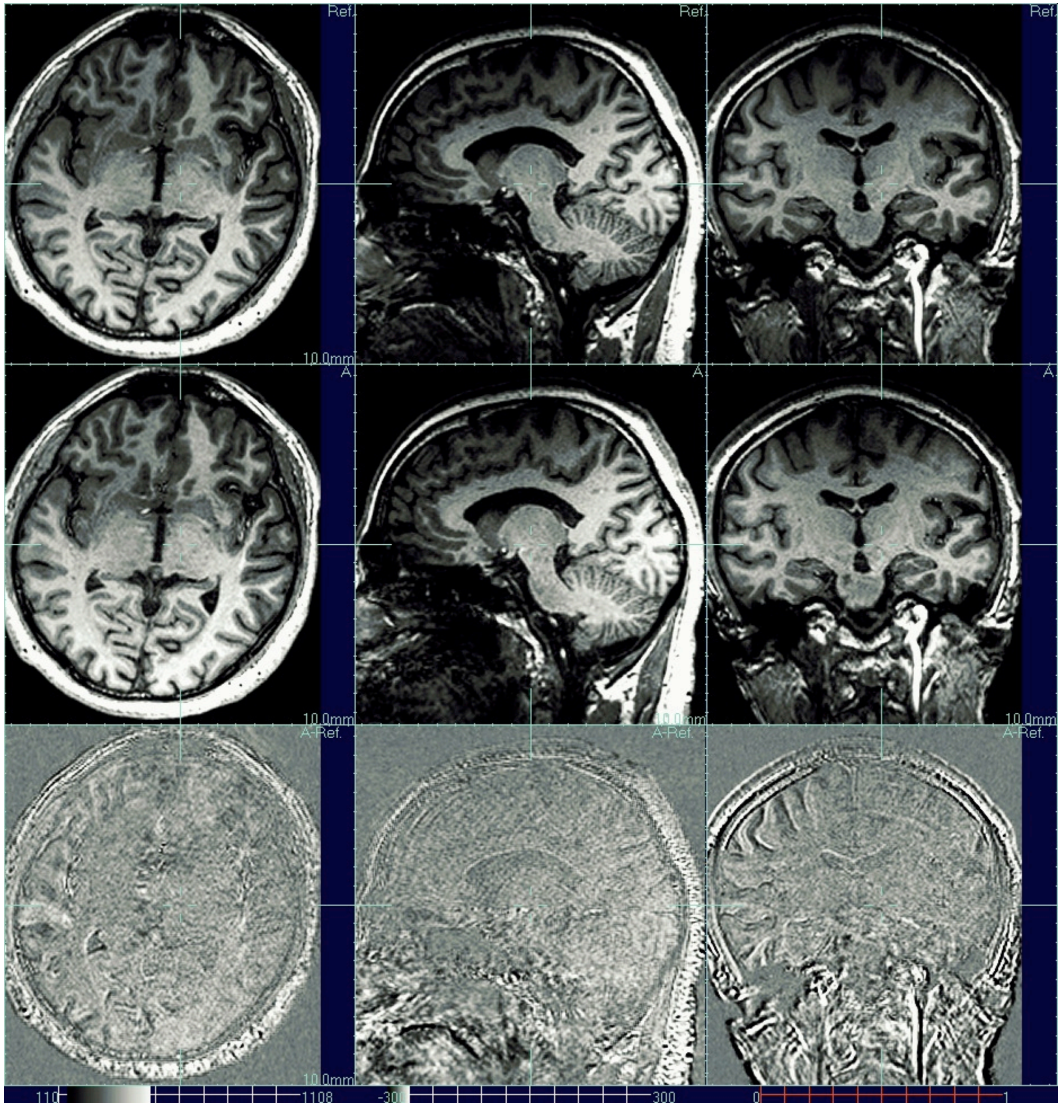
# With and without gradient correction: No movement, positioned centrally in the magnet



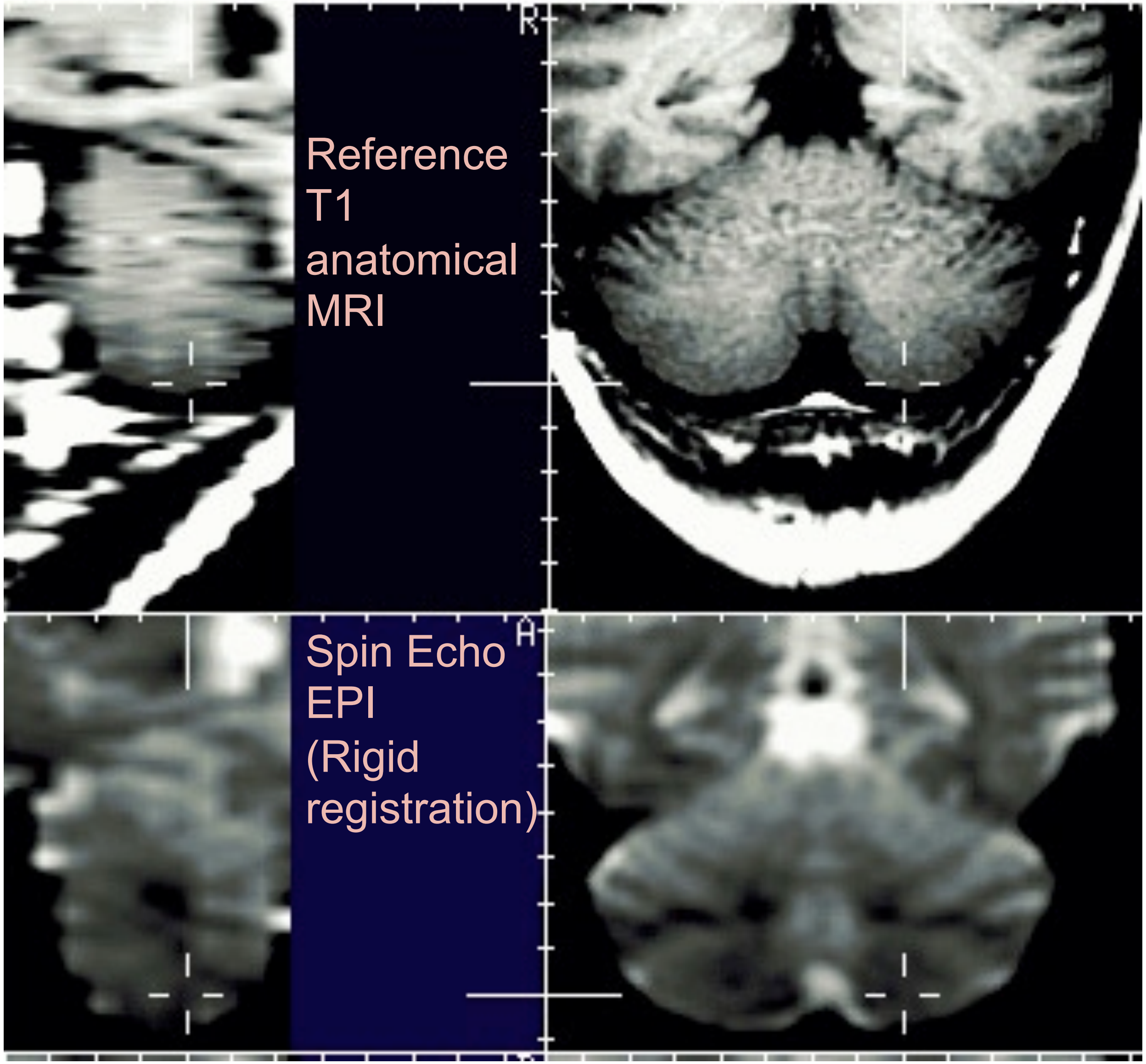
# Change in positioning (~ 3.4 cm shift along the bore); no gradient correction



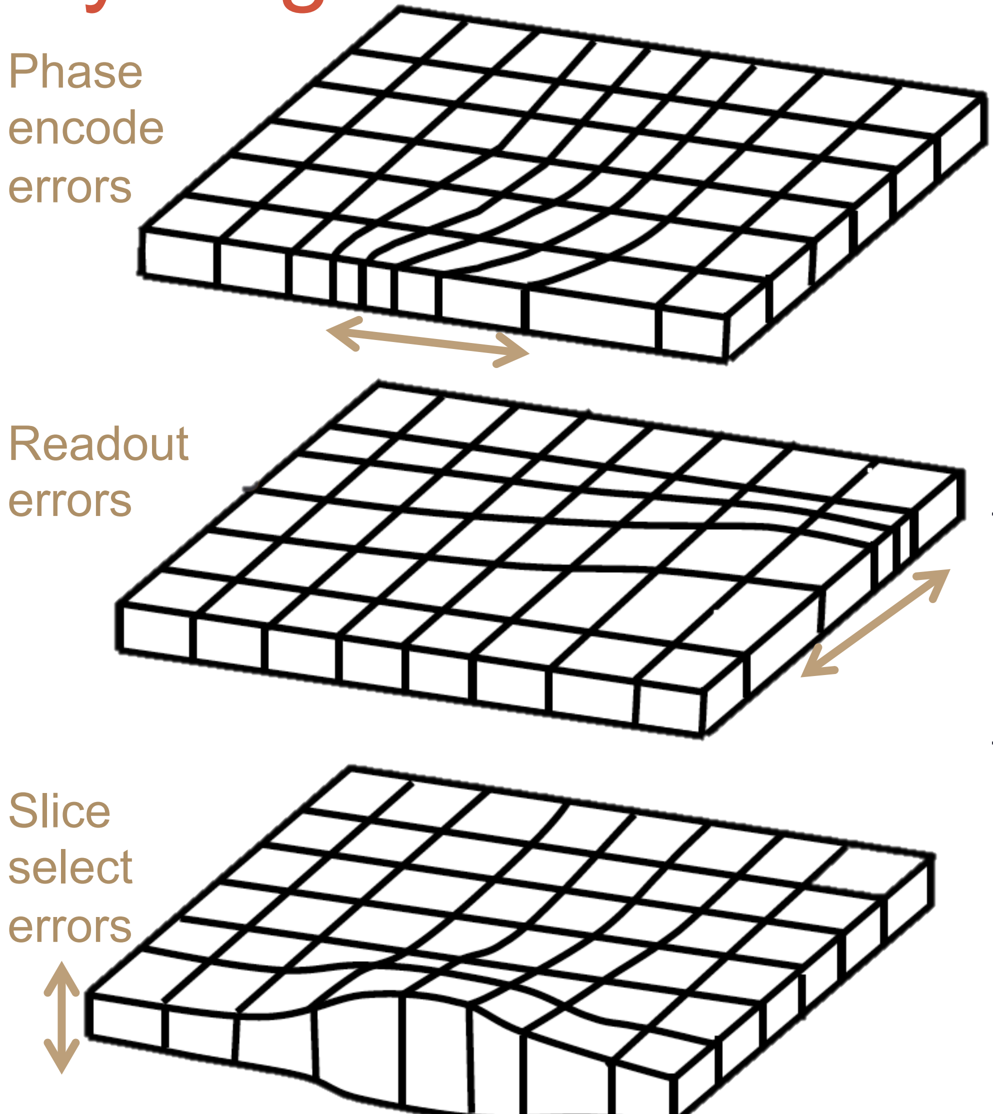
# Change in positioning (~3.4cm shift along bore) with gradient correction for both images

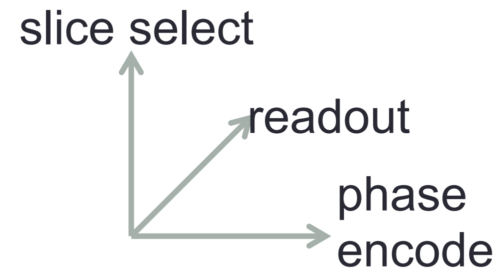


# Larger scale geometric and intensity distortion



# Components of spatial distortion induced by magnetic field inhomogeneity



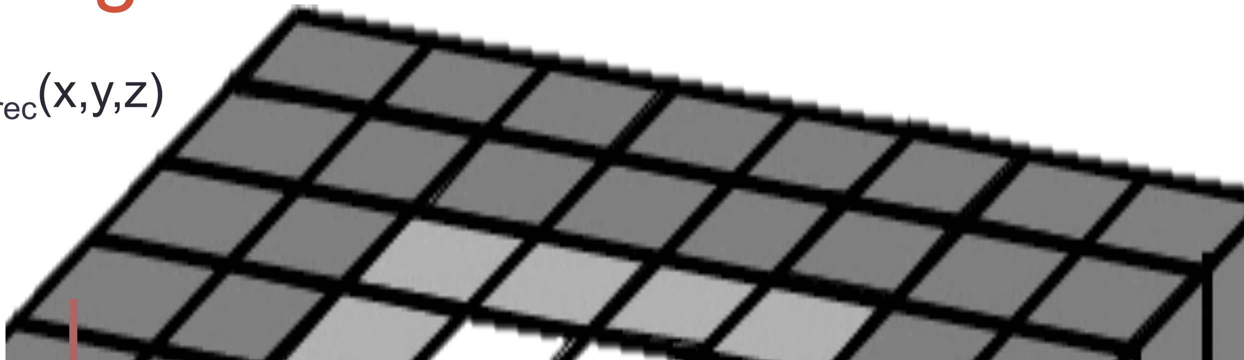




<u>Conventional Spin Echo MRI:</u>
Displacements occur in the readout and slice select axes.

<u>In mapping EPI to anatomical MRI:</u>
The primary ***relative*** error to recover is along phase encode axis of EPI data.

# Using a model of spin echo signal conservation and intensity distortion when estimating registration

$I_{rec}(x,y,z)$

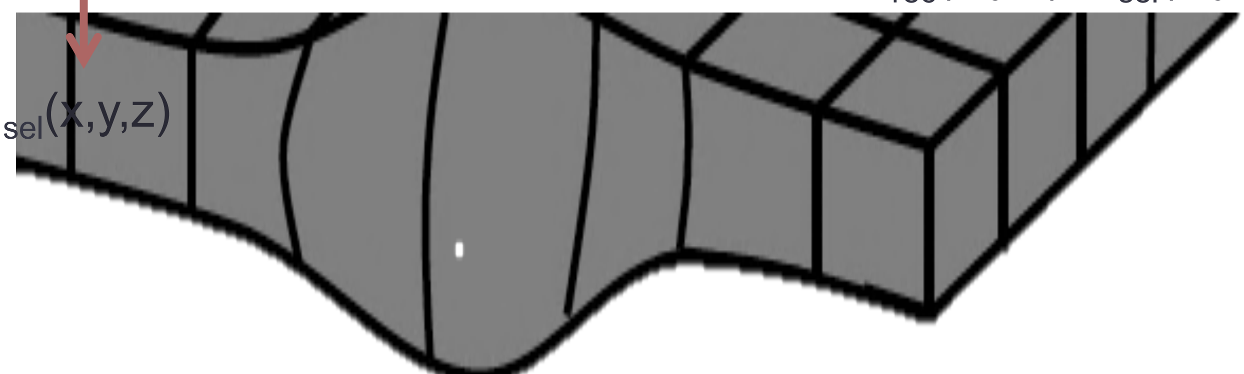


Reconstructed spin echo image with intensity distortion

$T_{dist}$

If we have a spatial registration estimate of EPI to anatomy, we can use its Jacobian to estimate an EPI intensity correction.

$$I_{rec}(x,y,z) = I_{sel}(x,y,z)/J_{dist}(x,y,z)$$

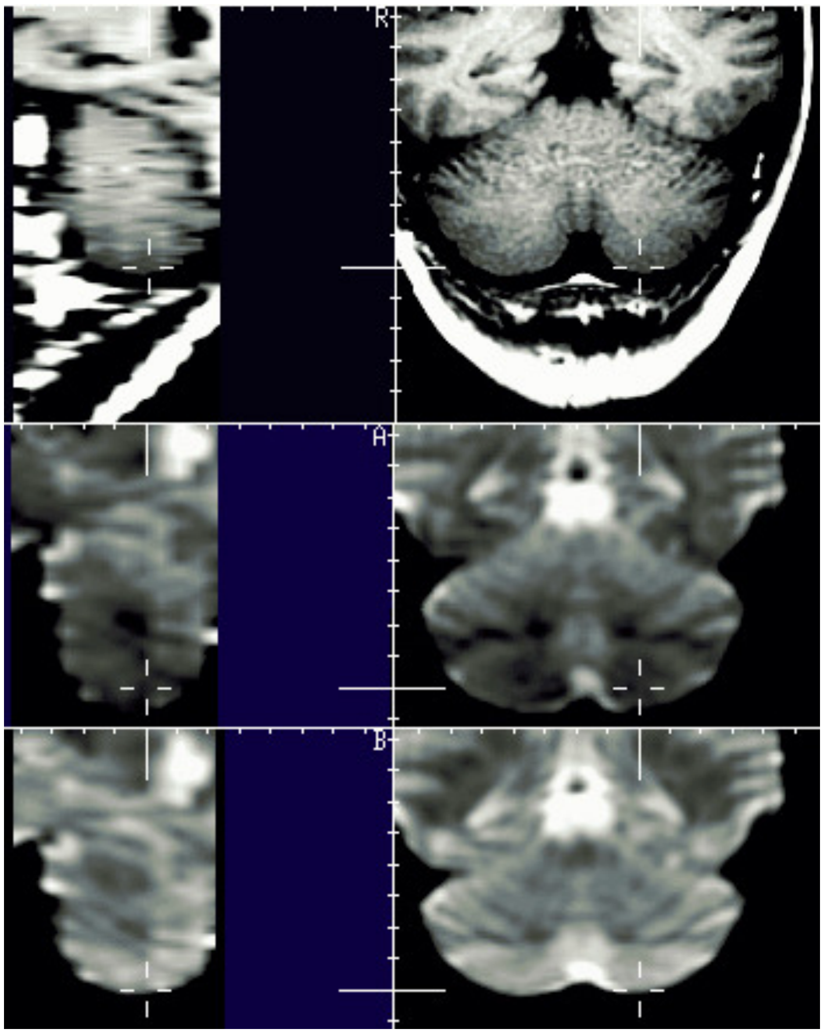


$I_{sel}(x,y,z)$

Distorted voxel selection due to magnetic field inhomogeneity

[C. Studholme, T.C. Constable, J.S. Duncan, Non-Rigid Spin Echo MRI Registration Incorporating an Image Distortion Model: Application to Accurate Alignment of fMRI to Conventional MRI, IEEE Trans. Med. Imaging, Vol 19, No 11. Nov 2000.]

# Correction of larger scale geometric and intensity distortion



Reference T1 anatomical MRI

Spin Echo EPI (Rigid registration)

Spin Echo EPI (10mm Spline estimate) incorporating Jacobian intensity correction

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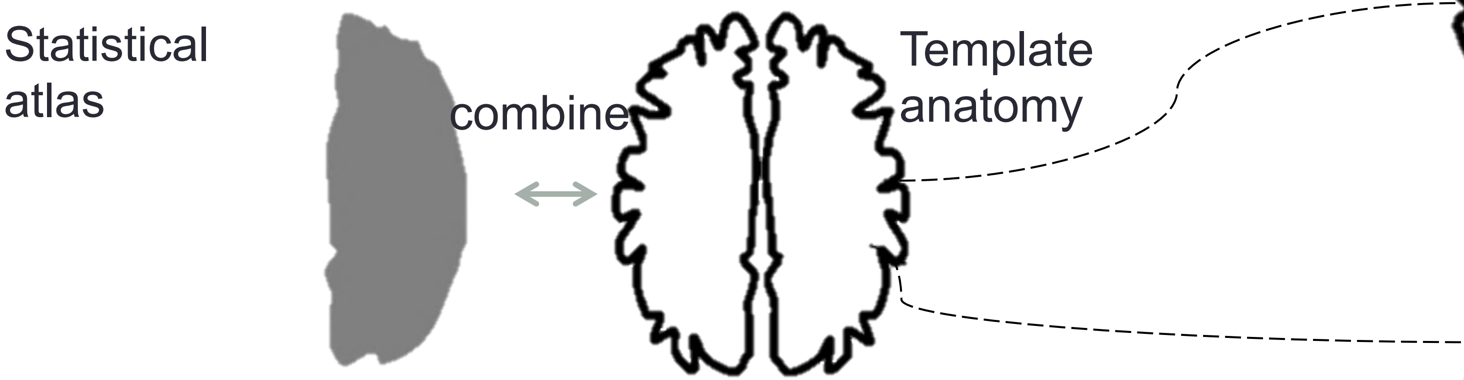
# Bringing image data into a common coordinate system

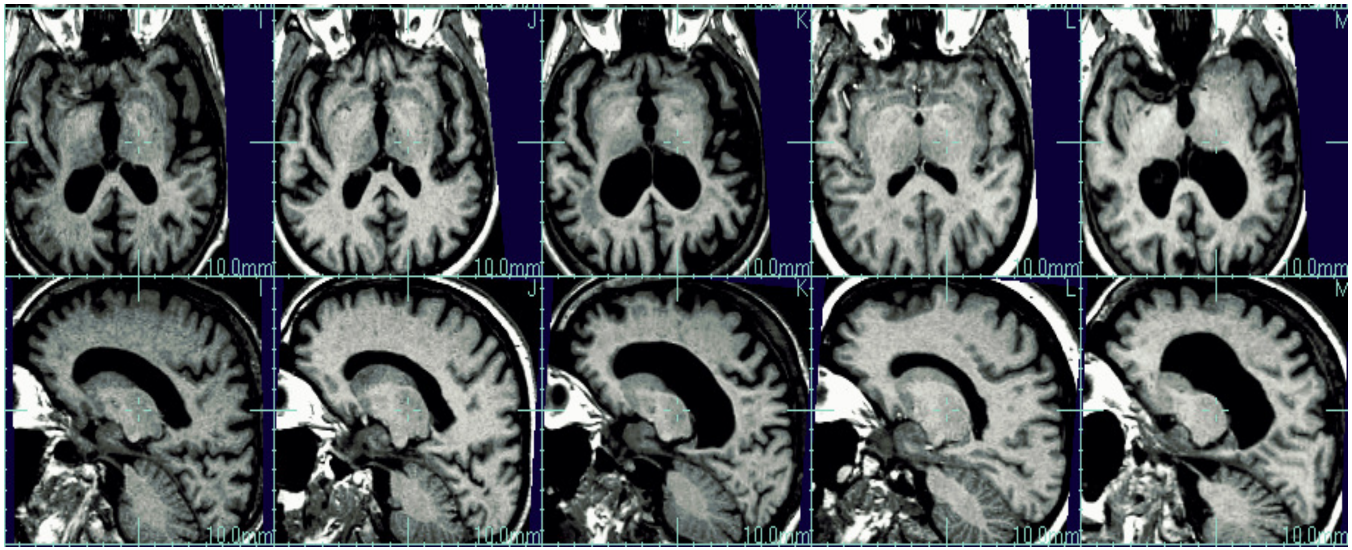
- Collecting data from different individual anatomies not trivial
- Need to locate corresponding location in atlas for a given measurement in the subject anatomy

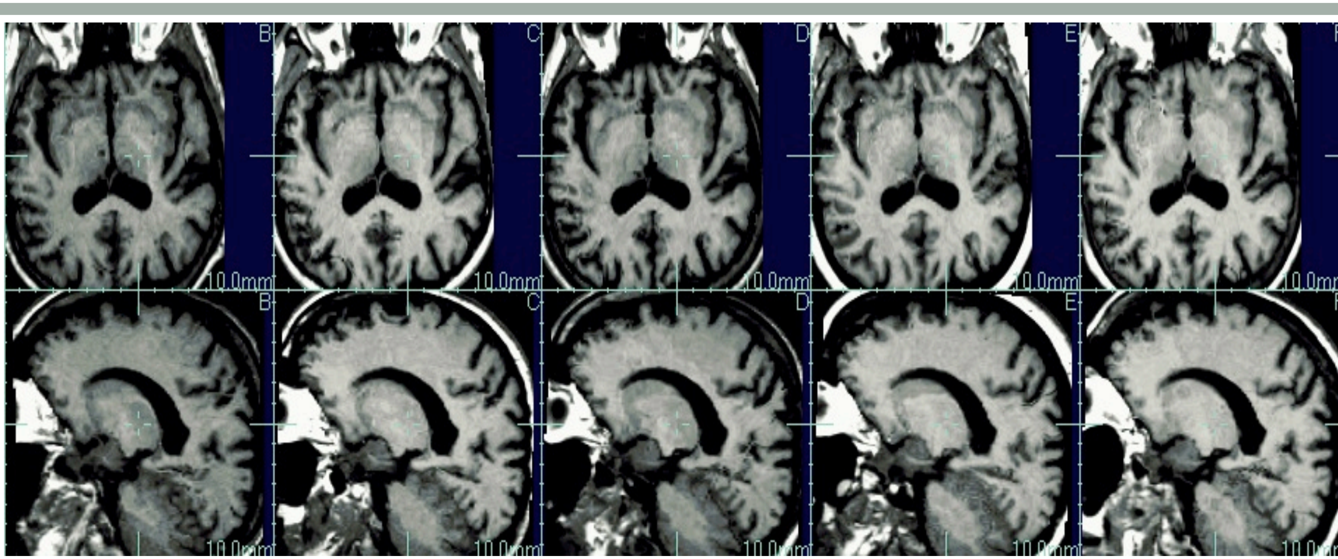


- Need a **Template** (in atlas space) to match subject anatomy to
- *How do we derive a correspondence or mapping?*
  - Estimate the warp that takes us from template to subject
  - Requires a non-rigid registration algorithm for -> "*Spatial Normalization*"

# Ex: Group spatial normalization



Global **affine** normalized



**Spatial normalization** of brain anatomy

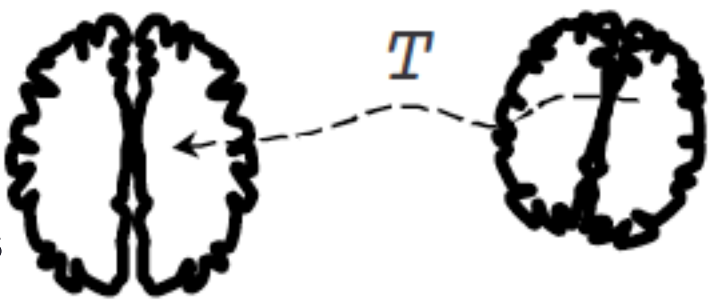
# Components of a non-rigid registration algorithm

- Model or parameterization of the transformation $T$
  - What structural differences we can resolve

- Registration (similarity) measure $S(T)$
  - provide an absolute or relative measure of the quality of match

- Geometric constraints $C(T)$
  - prevent unwanted or physically meaningless deformations
  - so... need to vary $T$ to find optimum (here maximum) value for

$$F = S(T) - \alpha C(T)$$




- Optimization method
  - Continuous refinement of many parameters
  - Often high dimensional search space
  - Constrained by corresponding spatial structures

# Mathematical models for spatial transformations of image data

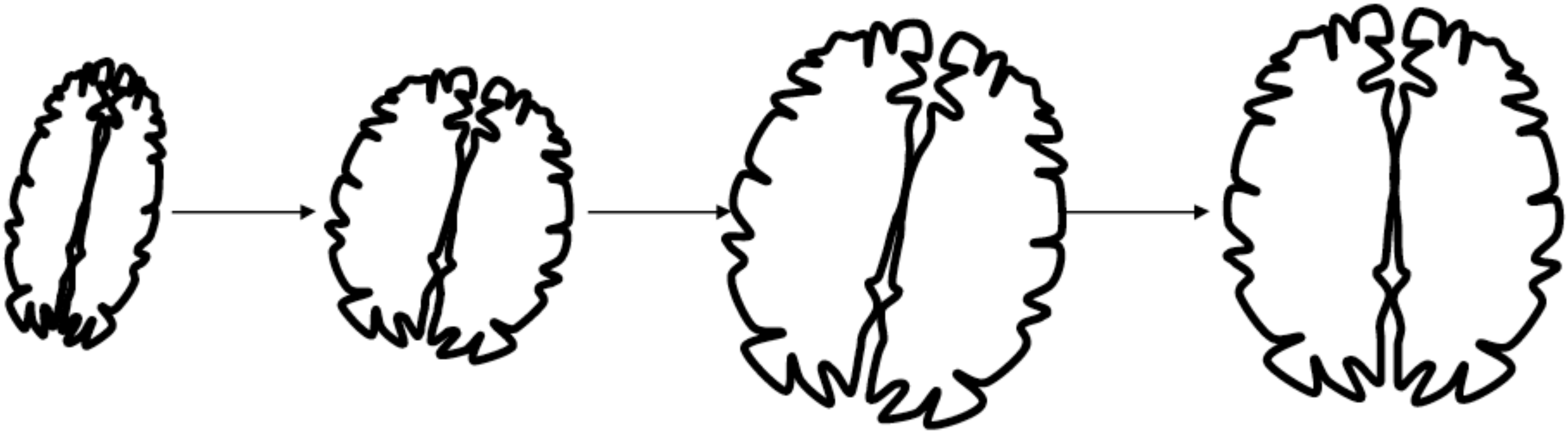
- Global affine
- Non-linear global parameterizations
- Spatially local parameterizations
- Dense field techniques

# Simplest methods…

- Use global linear or affine model
- Describing only global
  - Translations, rotations, scaling, and skew

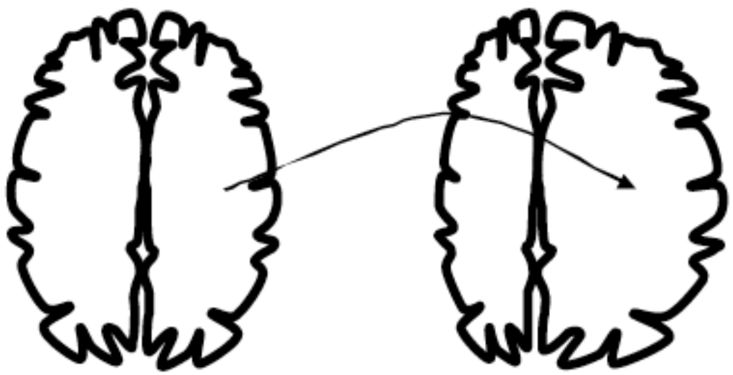
$$x' = a * x + t$$

$$\begin{bmatrix} x' \\ y' \\ z' \\ 1 \end{bmatrix} = \begin{bmatrix} a_{11} & a_{12} & a_{13} & t_x \\ a_{21} & a_{22} & a_{23} & t_y \\ a_{31} & a_{32} & a_{33} & t_z \\ 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \\ 1 \end{bmatrix}$$



# More complex deformations…

- Globally parameterize the deformation field:
  e.g. Polynomial function of location (here 1D)
  $T(x) = a.x^3 + b.x^2 + cx + d$



- Modify parameters $a, b, c$ and $d$ so global similarity $F(T)$ maximized

[Woods et al, Automated Image registration,JCAT 1998.]

# Cosine basis functions

$$T(x_i) = x_i - \sum_{j=1\ldots J} t_{jd} b_{ij}(x_i)$$

$$T(y_i) = y_i - \sum_{j=1\ldots J} t_{jd} b_{ij}(y_i)$$

$$T(z_i) = z_i - \sum_{j=1\ldots J} t_{jd} b_{ij}(z_i)$$

$$b_{ml}(x_i) = \begin{cases} \dfrac{1}{\sqrt{M}} \text{ for } j = 1, m = 1, \ldots, M \\ \dfrac{\sqrt{2}}{\sqrt{M}} \cos\left[\dfrac{\pi(2m-1)(j-1)}{2M}\right] \text{ for } j = 2, \ldots, M, m = 1, \ldots, M \end{cases}$$

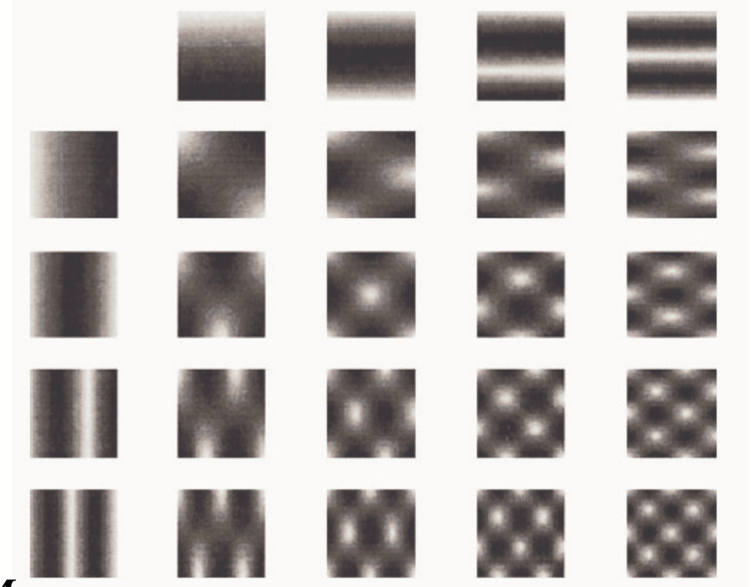
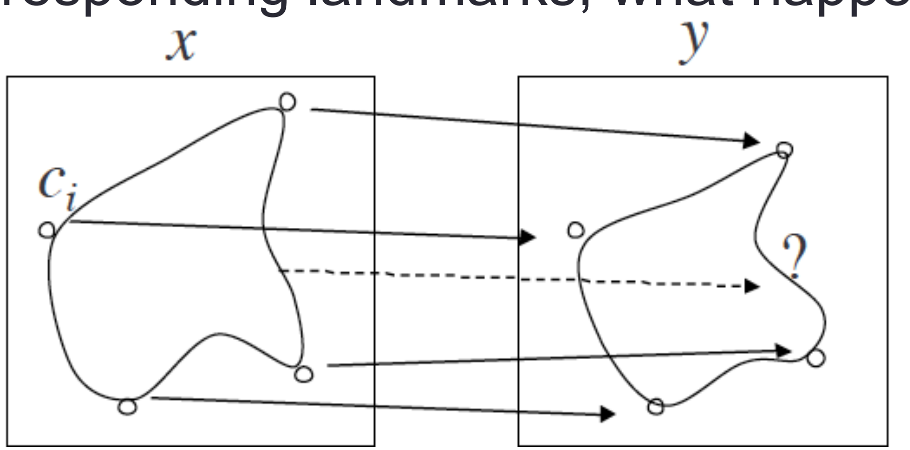


**Figure 1.**
The lowest-frequency basis functions of a two-dimensional discrete cosine transform.

[Ashburner and Friston, Nonlinear Spatial Normalisation Using Basis Functions, Human Brain Mapping, 7:254-266, 1999]

# Radial basis functions (RBF)

- Given a set of corresponding landmarks, what happens between?




- An RBF estimates mapping for points not at landmarks
- For a given point `x`, it combines mappings from neighboring landmarks `c_i` weighted by a function of distance

$$\phi : \Re^+ \rightarrow \Re \qquad\qquad y(x) = \sum_{i=1}^{N} w_i \phi\left(\left\| x - c_i \right\|\right)$$

- where the basis function determines the form of the warp:

[F. L. Bookstein. Principal Warps: Thin-Plate Splines and the Decomposition of Deformations. IEEE Trans. on Pattern Anal. and Machine Intell., 11(6):567-585, 1989.]

# Different forms of RBF

- Thin plate spline

$$\phi(r) = r^2 \log(r)$$

- Gaussian

$$\phi(r) = \exp(-cr^2)$$

- Multiquadric

$$\phi(r) = \sqrt{r^2 + c^2}$$

[D. Ruprecht and H. Muller. Free form deformation with scattered data interpolation methods. Comp. Suppl., 8:267-281, 1993.]
[J. A. Little, D. L. G. Hill, and D. J. Hawkes. Deformations Incorporating Rigid Structures. Computer Vision and Image Understanding, 66(2):223-232,1997.]

# Properties of RBF

- Many of the common forms (e.g. thin plate) provide optimally smooth deformations
- Generally stable to estimate weights for many different configurations of points
- Change location of any landmark and whole deformation field changes
  - Expensive to re-evaluate whole image match

# Limitations of global parametrizations

$$T(x) = f(x, a, b, c)$$

- Each parameter $a, b, c...$ modifies entire image
  - Expensive to evaluate gradients of $T$ with respect to parameters
- Complex brain shape differences requires a fine scale deformation
- Fine scale deformation requires MANY parameters
  - High spatial frequencies for cosine parameters
  - or: high order polynomial

So.. Need a way to simplify problem

# Alternatives: Local models

- Rather than having
  - many parameters
  - where each influences the image deformation over the whole space

- Need parameters that have localized influence on the deformation
  - faster to evaluate image match

- Forms of Spline can provide spatially localized deformation control

# Spline-based deformations with local support

- Thin-Plate splines can be adapted to have local support

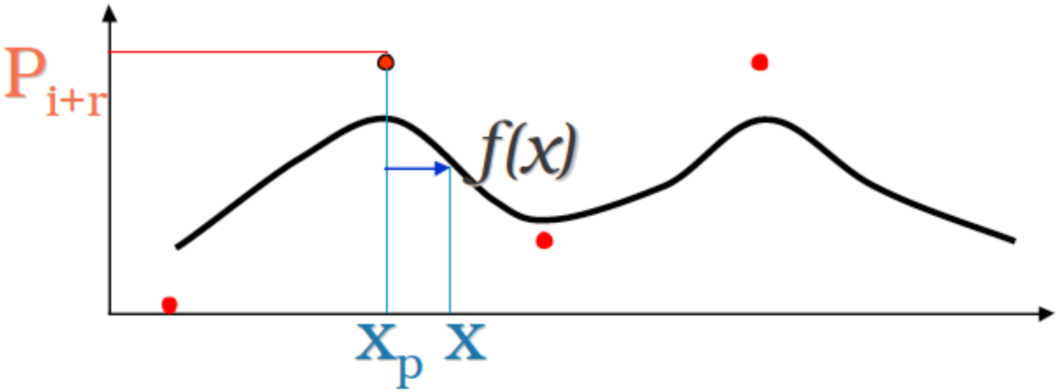
  [Mike Fornefett, Karl Rohr, and H. Siegfried Stiehl, Elastic Registration of Medical Images Using Radial Basis Functions with Compact Support, Computer Vision and Pattern Recognition, 1999]

- Other forms using specialized regular control knots can provide faster evaluation

  [S. Lee, G. Wolberg, K.Y. Chwa and S.Y. Shin IEEE Trans Vis. Comp. Graph.,1996 and 1997]

# B-Spline models for registration

- B-Spline Model: $T(x)$ function of sparse knot values



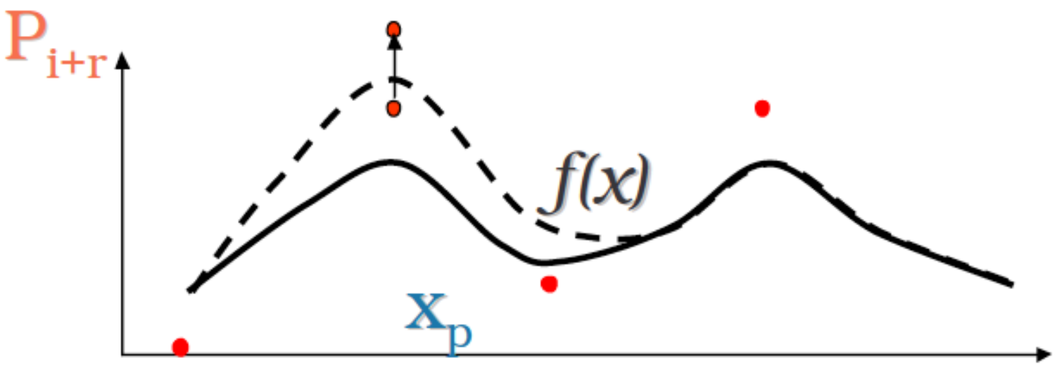

$$f(x) = \Sigma_{r=0,N} P_{i+r} B_r(x-x_p)$$

- Sum of contributions from local knots $r=0..N$ only
- The Basis functions $B_r()$ are specific polynomials e.g. Cubic B-Spline with 4 controlling knots:

$$B_0(t)=(1-t)^3/6$$
$$B_1(t)=(3t^3-6t^2+4)/6$$
$$B_2(t)=(-3t^3+3t^2+3t+1)/6$$
$$B_3(t)=t^3/6$$

[S. Lee, G. Wolberg, K.Y. Chwa and S.Y. Shin IEEE Trans Vis. Comp. Graph., 1996 and 1997]

# B-Spline models for registration




$$f(x) = \Sigma_{r=0,N} \; P_{i+r} \cdot B_r(x - x_p)$$

Move one knot and deformation changes only within a given range of knot locations.

A B-Spline approximates. It does not interpolate!

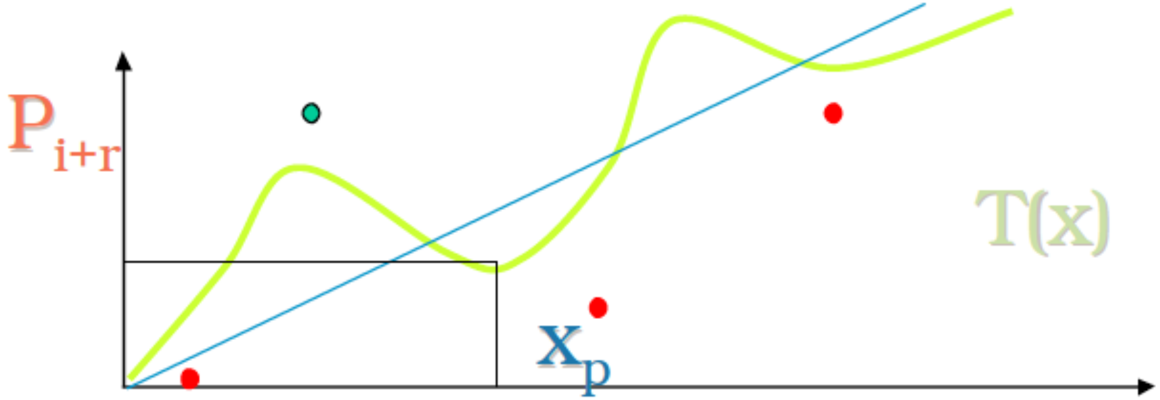
Functions do not have to pass through knot values

# B-Spline models for registration

B-Spline transformation model

$$T(x) = x + \sum_{r=0,N} P_{i+r} \cdot B_r(x - x_p)$$

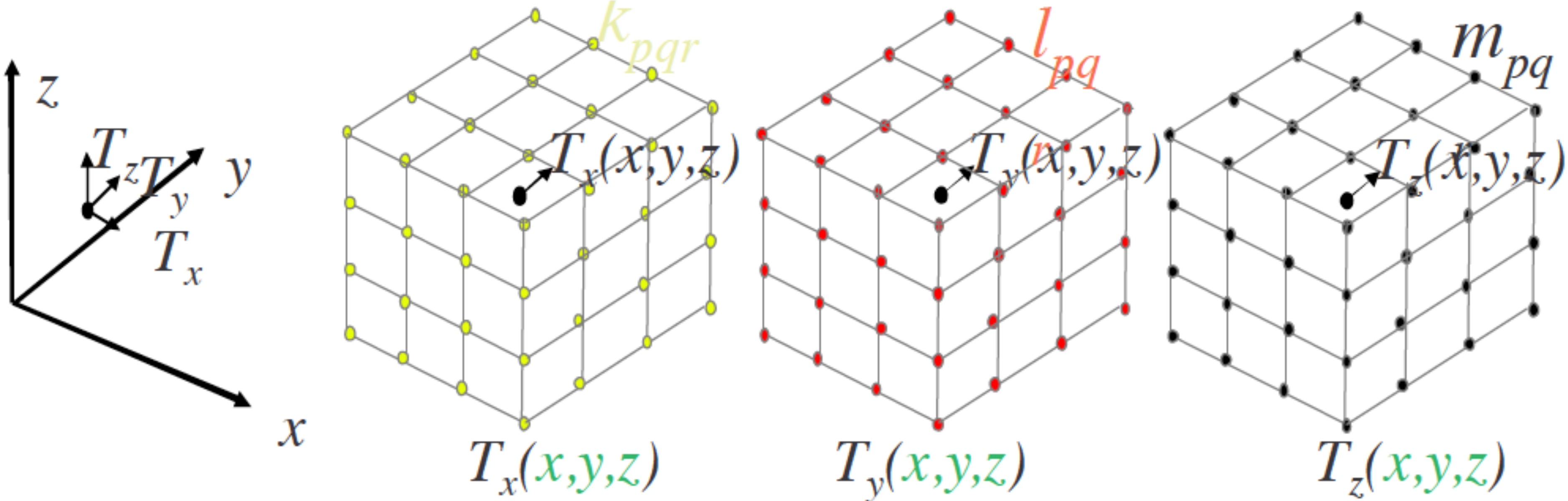
B-Spline can still fold! (e.g. multiple $x$'s map to the same value of $T(x)$




Can test for folding based on distance between knot values.

Can prevent folding by adding a smoothness penalty term.

# Extend to 3D displacement…

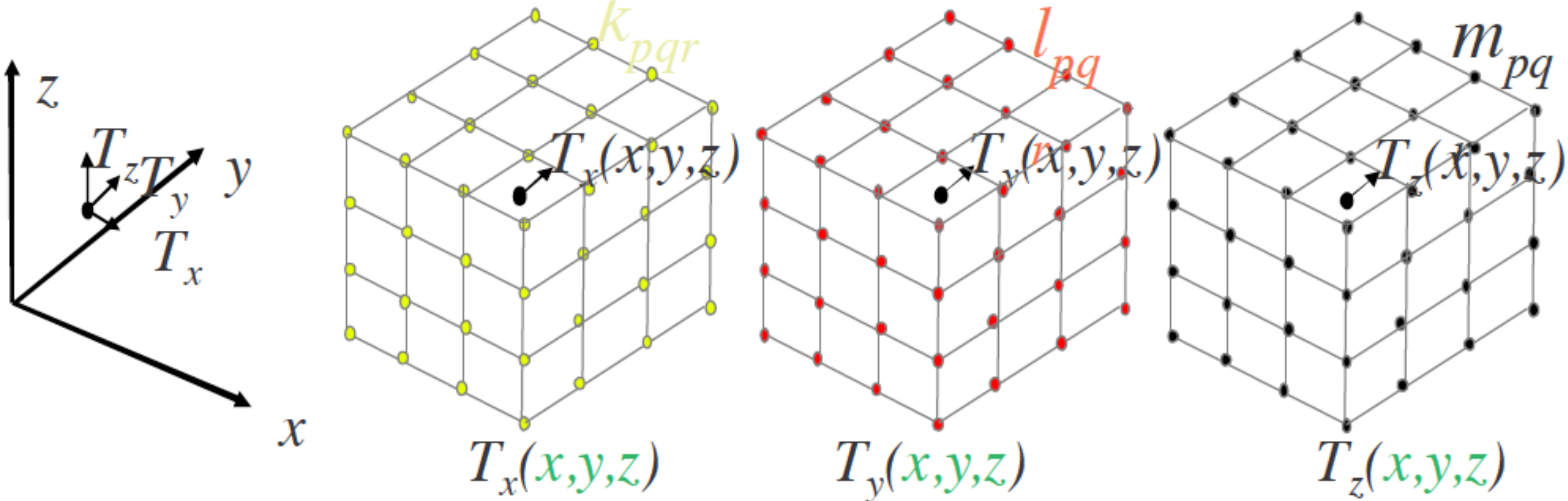



Describe transformation $\boldsymbol{T}()$ in directions $x$, $y$ and $z$ for each point in $\{x,y,z\}$

Parameterized by a Lattice of control parameters (knots)

$$\boldsymbol{Q}_{pqr}=\{k_{pqr},l_{pqr},m_{pqr}\}$$

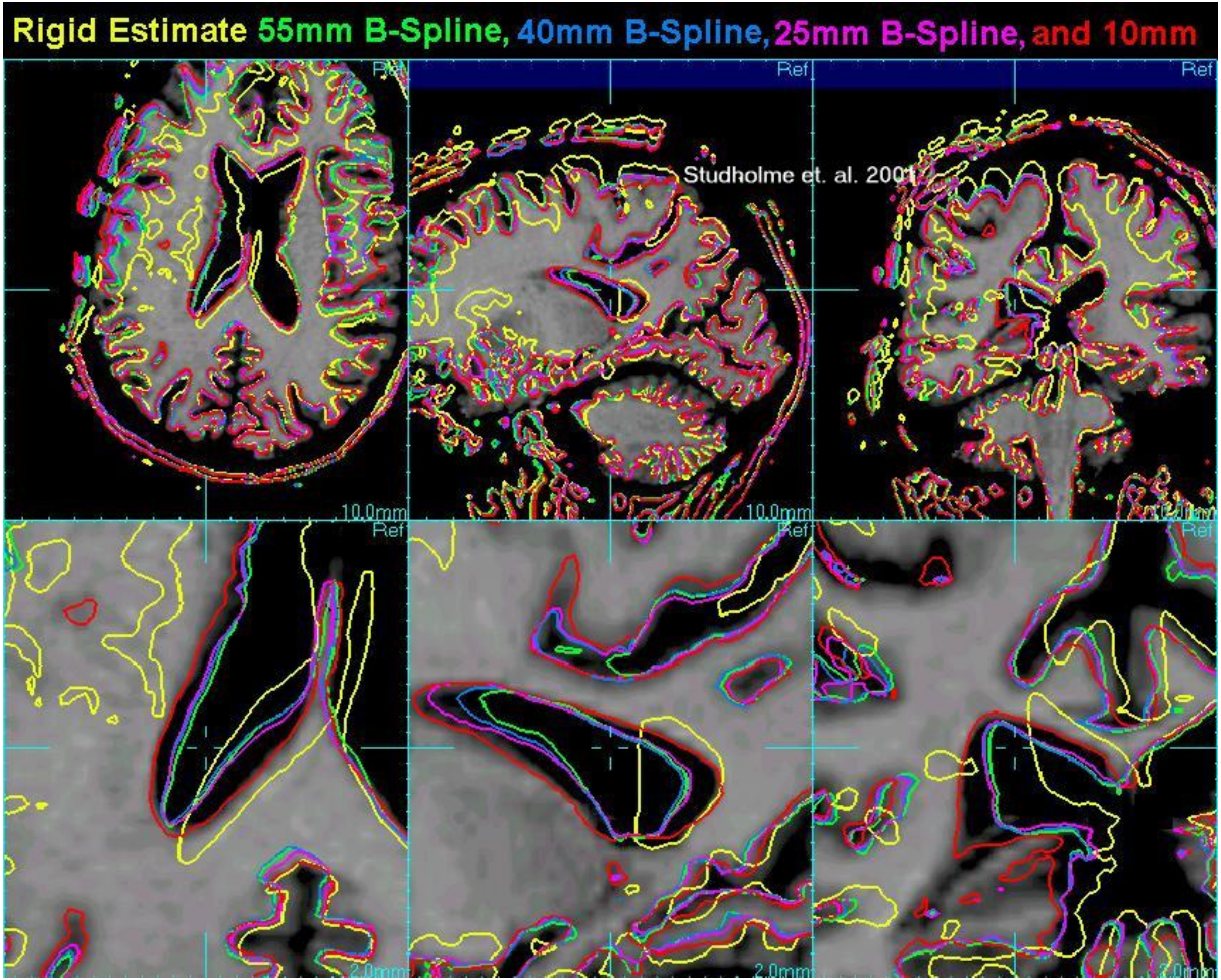
# Extend to 3D displacement…



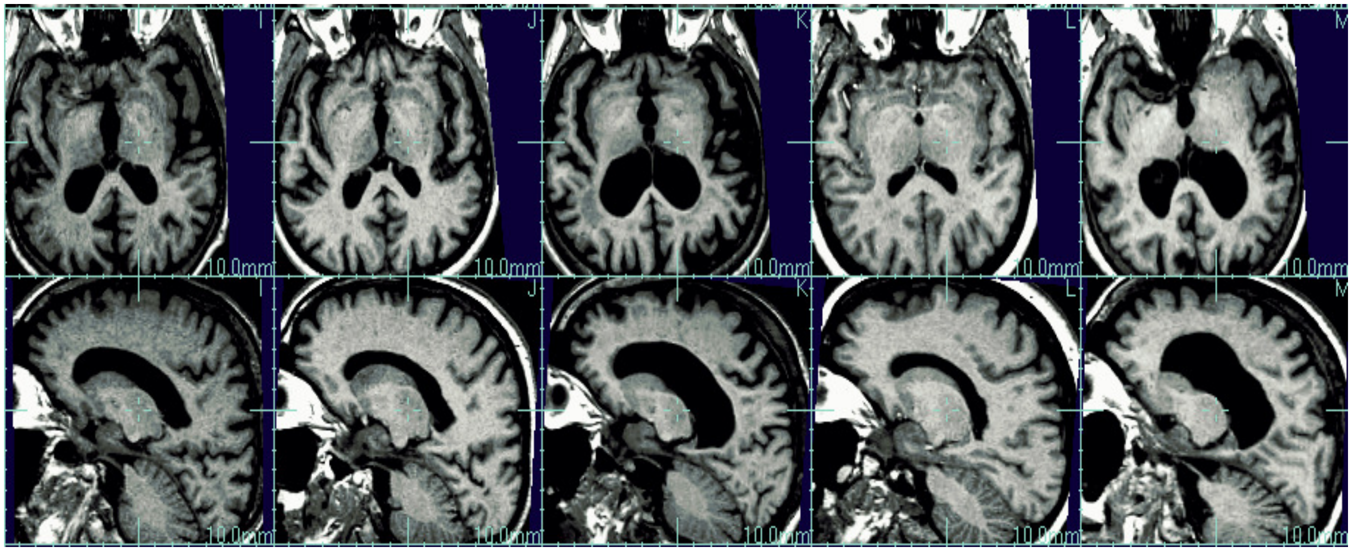

Maximize image similarity w.r.t. $Q_{pqr}$

$$R\left(Q_{pqr}\right) = Y\left(Q_{pqr}\right) - \lambda \sum_{x} \frac{\partial^2 T(x, Q_{pqr})}{\partial^2 x}$$

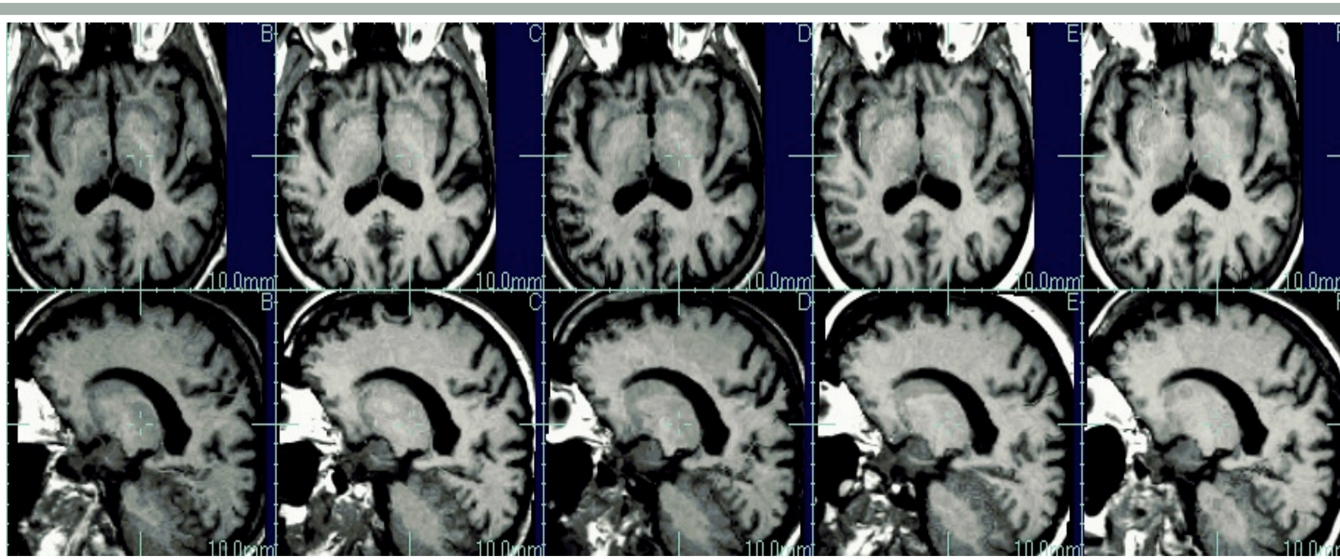
Registration criteria Regularization penalty


Rigid Estimate 55mm B-Spline, 40mm B-Spline, 25mm B-Spline, and 10mm
Studholme et. al. 2001
Ref
10.0mm
2.0mm

# Example group spatial normalization



Global **affine** normalized



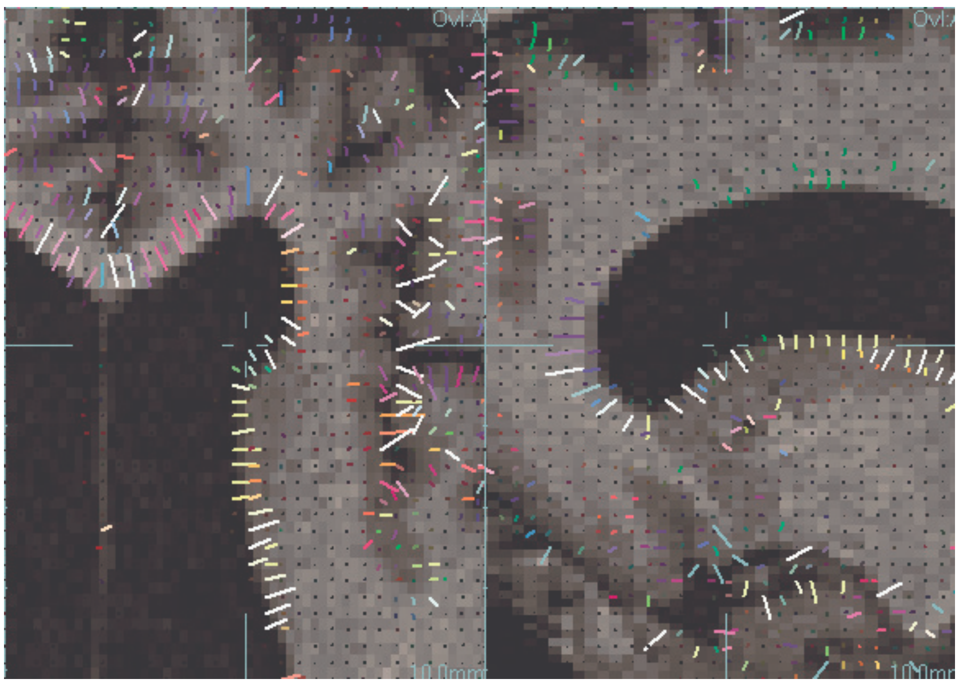
Mutual information driven B-Spline **spatial normalization** of brain anatomy

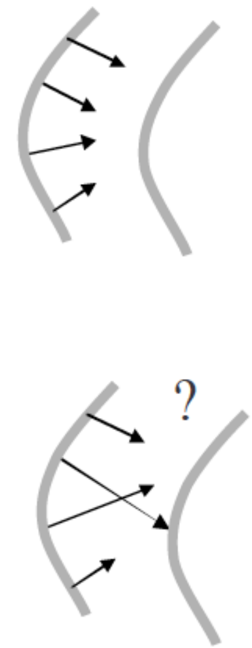
# CAPTURING MORE DETAILS…

Dense field models!

# Dense field methods

- Derive a voxel by voxel force field making images more similar
  (local gradient of similarity measure with respect to individual voxel location)
- Move in the direction of the force field and re-evaluate






- Need a model to describe how image responds to registration force

# Elastic deformation

- ***Early approach*** applied to 3D brain images [Bajcsy, JCAT, 1983]
  - Applying a marked template to a new individual

$$T(\mathbf{x}) = \mathbf{x} + u(\mathbf{x})$$

- Find a displacement field $u(x)$ which balances the elastic energy of $u(x)$ with the registration criteria $S(x)$

- Elastic deformation model is given by

$$\mu \nabla^2 u(x) + (\lambda + \mu)\nabla(\nabla^T u(x)) = S(x)$$

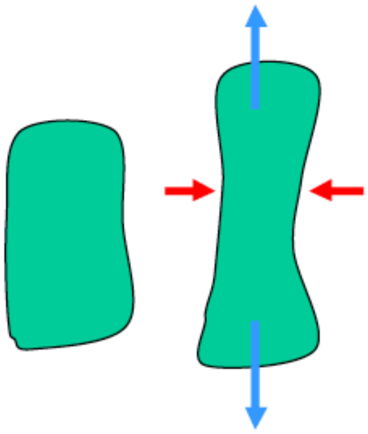
- μ and λ are *Lame's elasticity* constants

# Lame's elasticity constants

$$\mu\nabla^2 u(x) + (\lambda + \mu)\nabla(\nabla^T u(x)) = S(x)$$

- μ and λ relate applied forces to the resulting strains, by the Poisson's Ratio:

$$\sigma = \frac{\lambda}{\lambda + \mu}$$



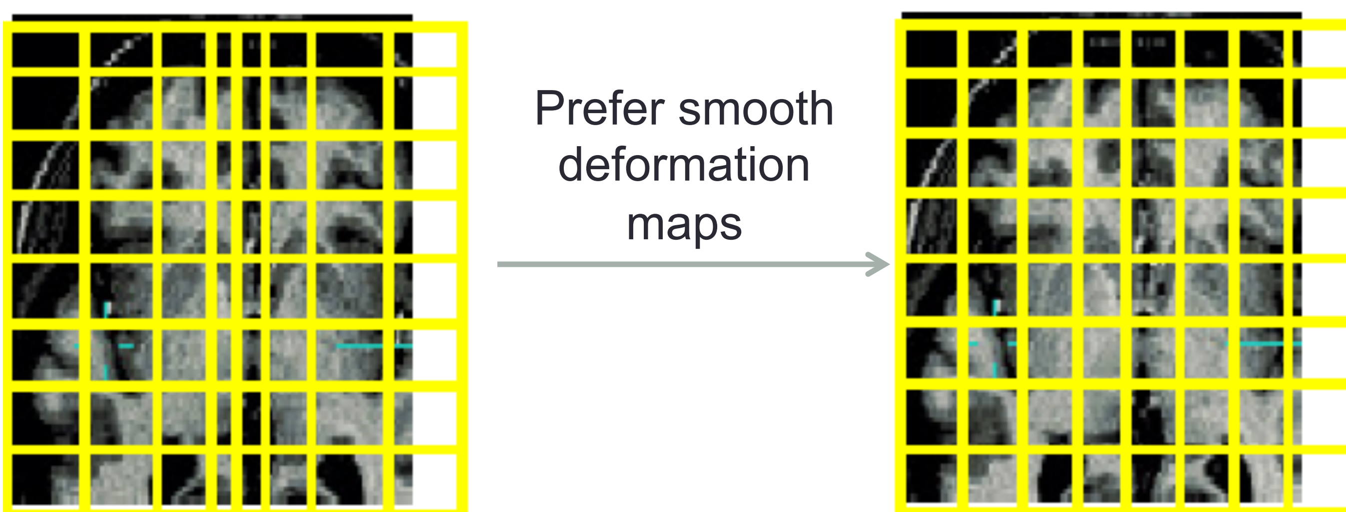
- Ratio of lateral shrink to extensional strain
- Generally for registration λ=0
- So registration force in one axis does not influence other axes

# Elastic deformation

$$\mu \nabla^2 u(x) + (\lambda + \mu)\nabla(\nabla^T u(x)) = S(x)$$

- Key Idea: The force balancing registration criteria is a function of the derivatives of the deformation field

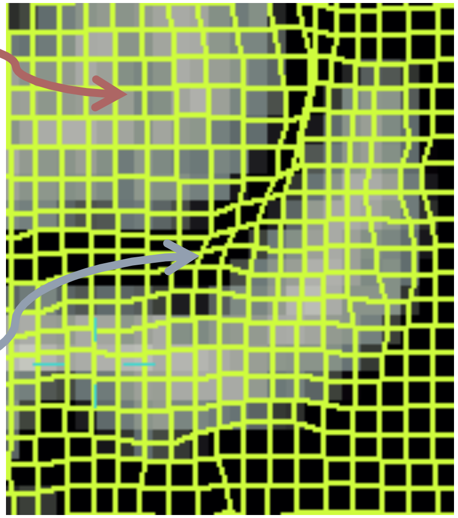
… rates of change of displacements $u(x)$ w.r.t. location $x$



# … rates of change of displacements

$$\mu\nabla^2 u(x) + (\lambda + \mu)\nabla(\nabla^T u(x)) = S(x)$$

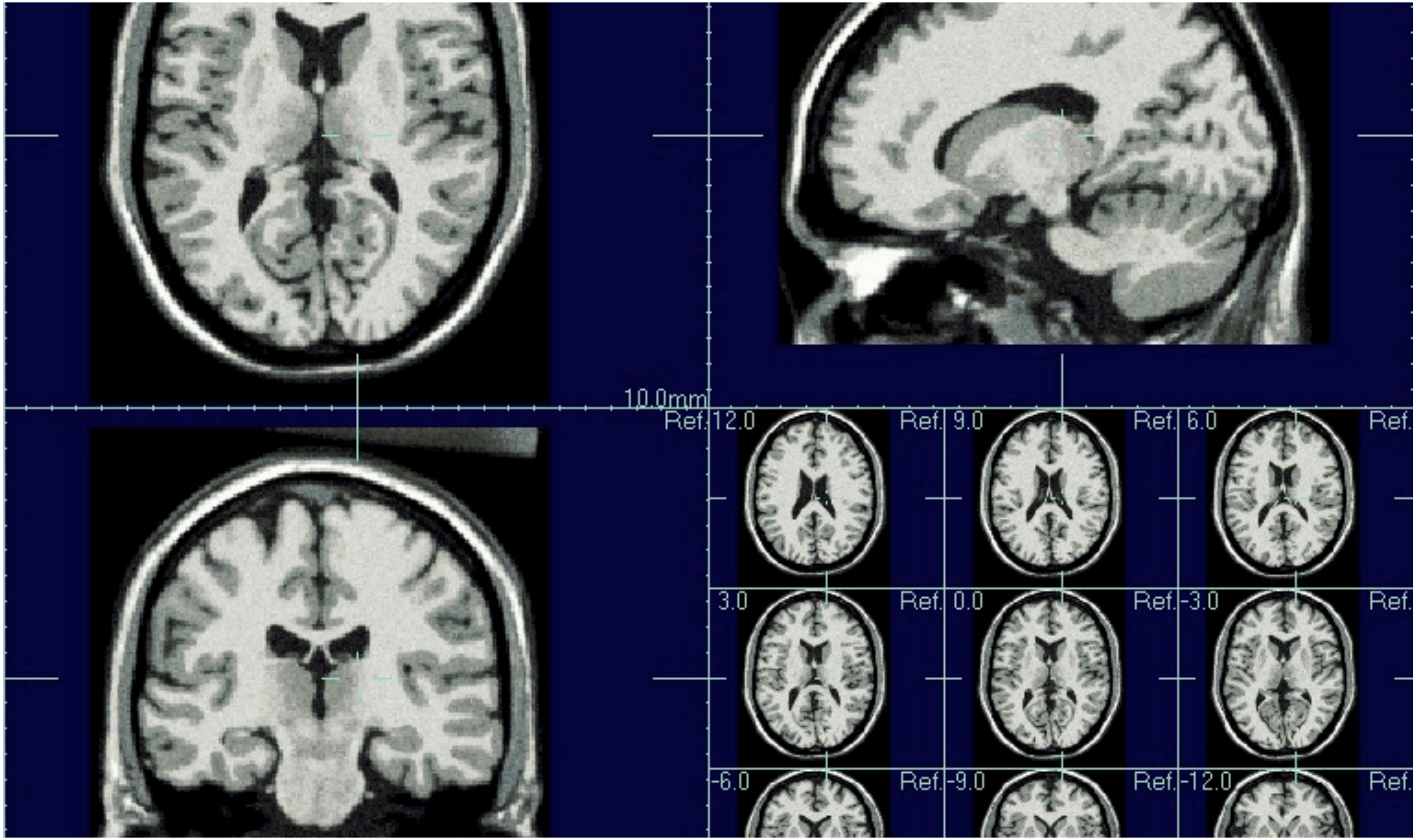
If neighboring displacements are similar:
Local relative size is similar across image.



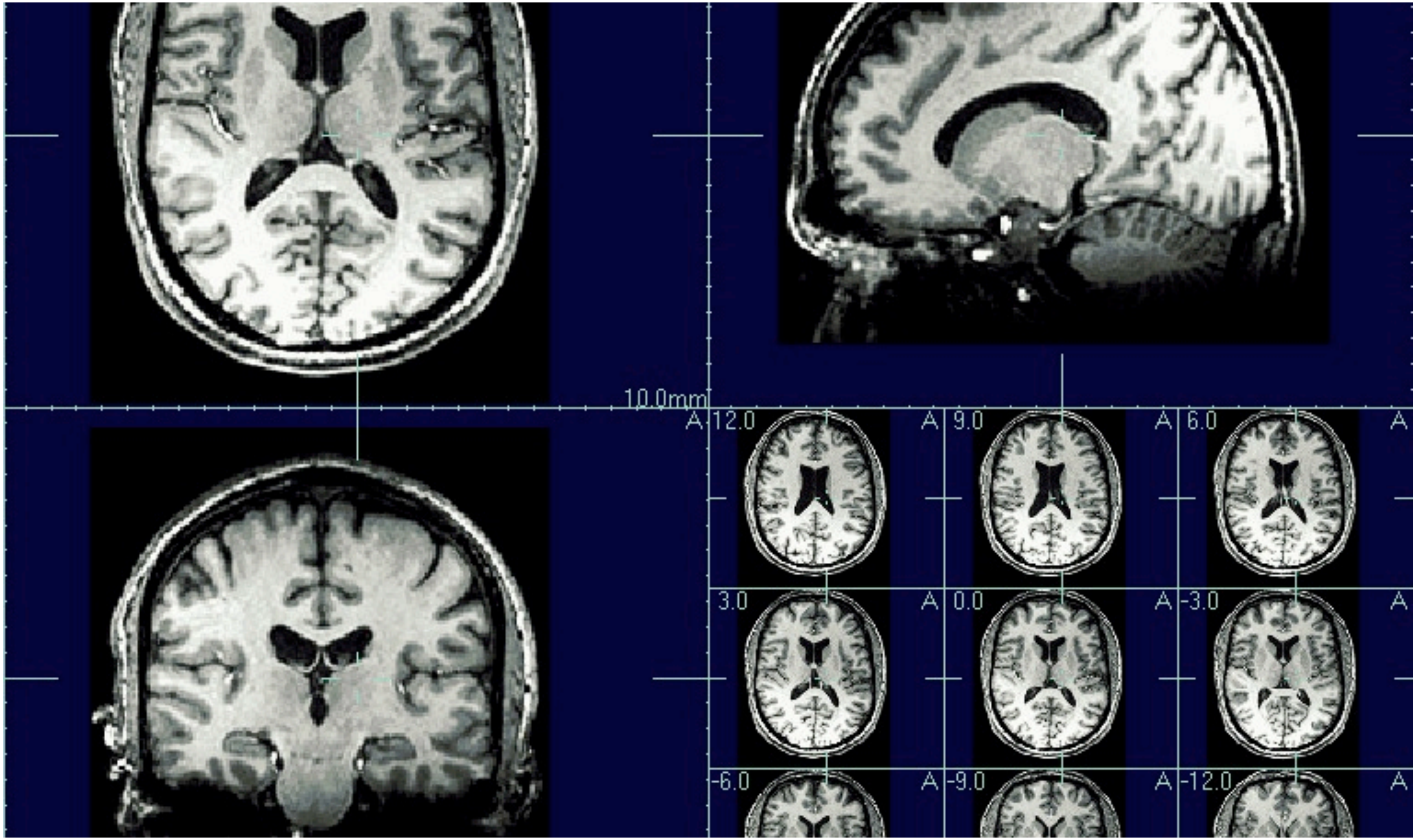
If neighboring displacements are different:
local relative size is changing.

When anatomical differences very localized (e.g. voxels in cortex) registration force balancing smoothness may under-estimate local contractions

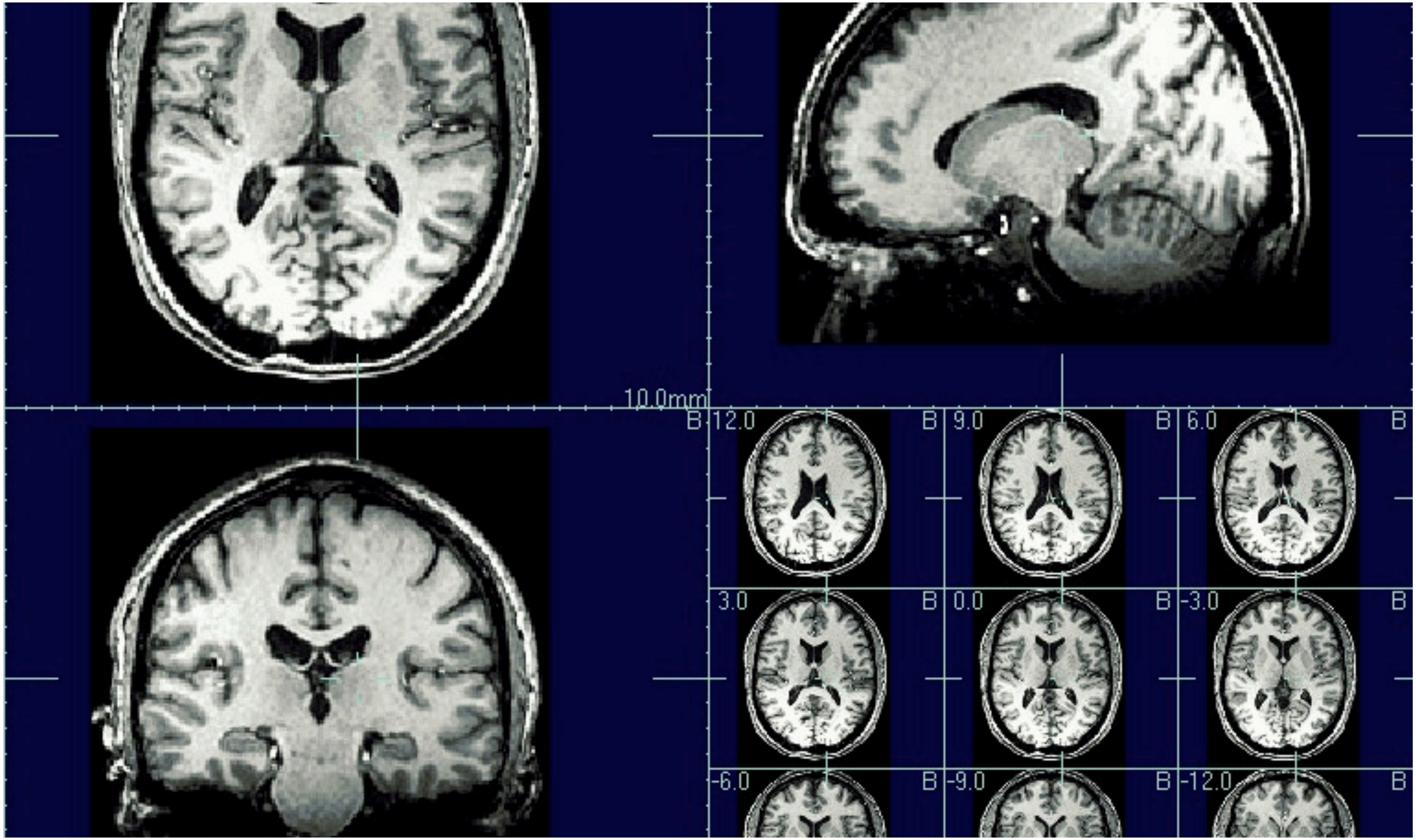
# Template (MNI)

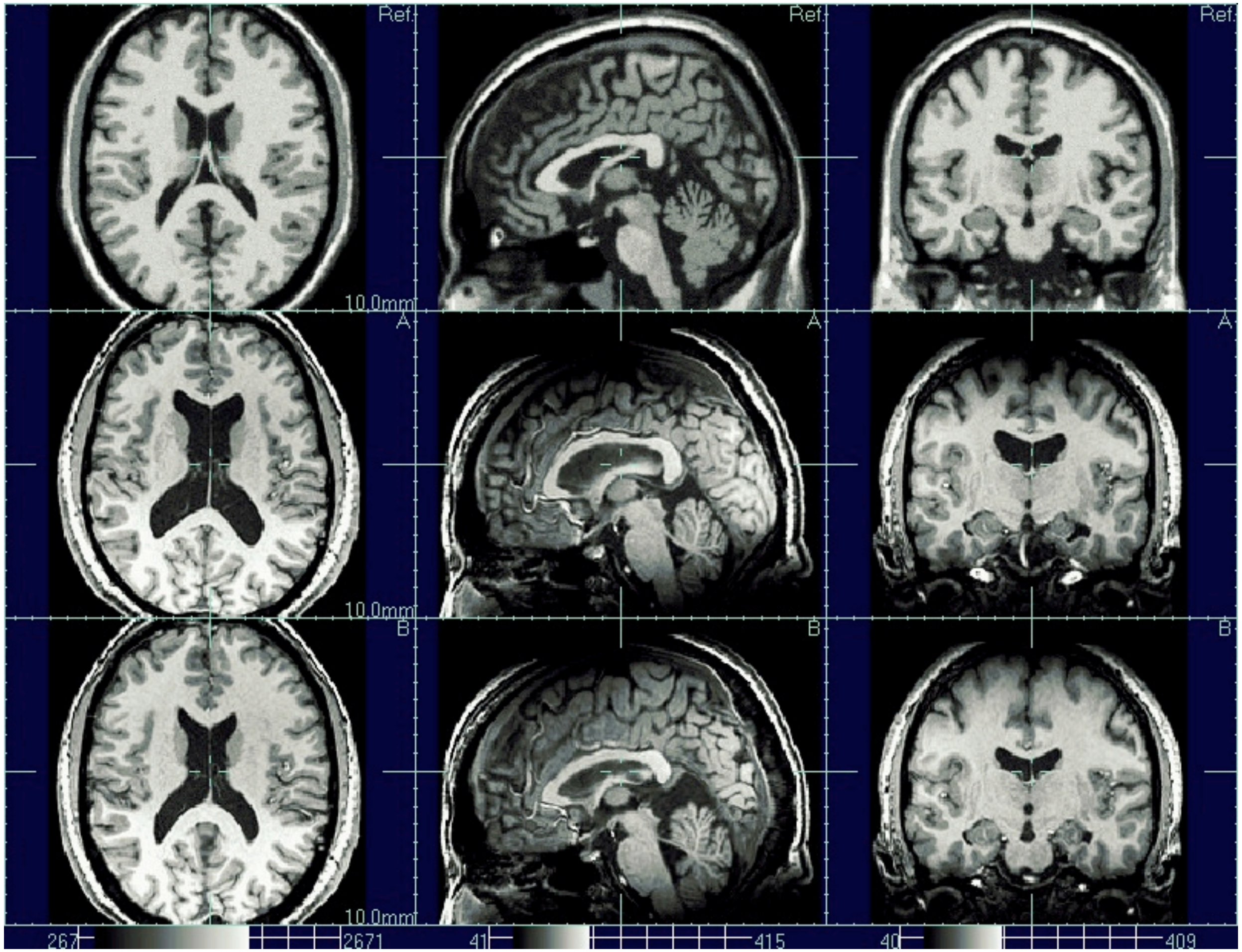


# Subject (affine)



# Subject (Elastic Warp)






Template (MNI27)

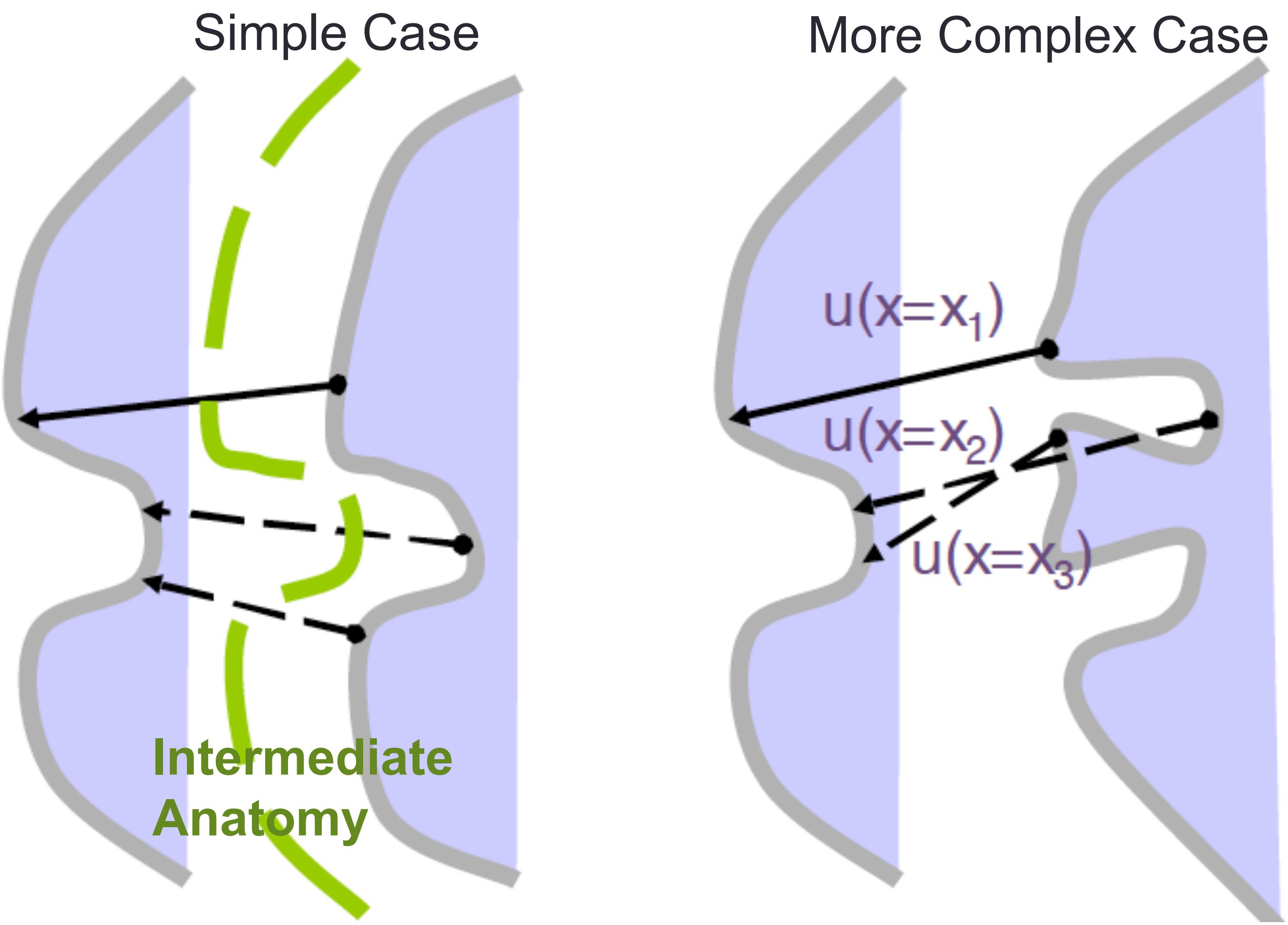
Subject

Elastic warp of subject to template

# Elastic deformation

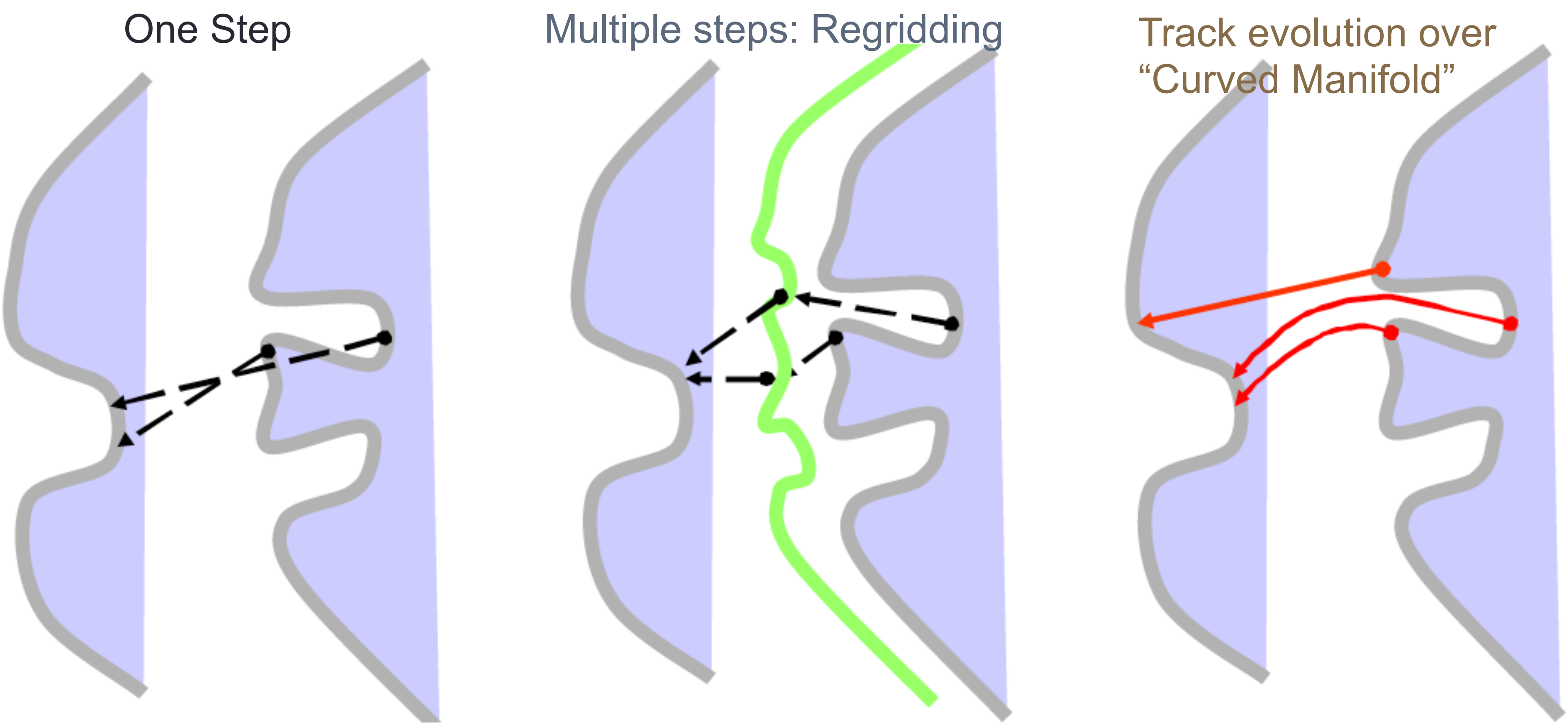
- Can be used to prevent singularities or folding
- But as displacement field evolves deformation energy builds up
- For extreme differences in anatomies deformation energy will prevent complete registration → “Large deformation” problem

# Regularization and large deformations



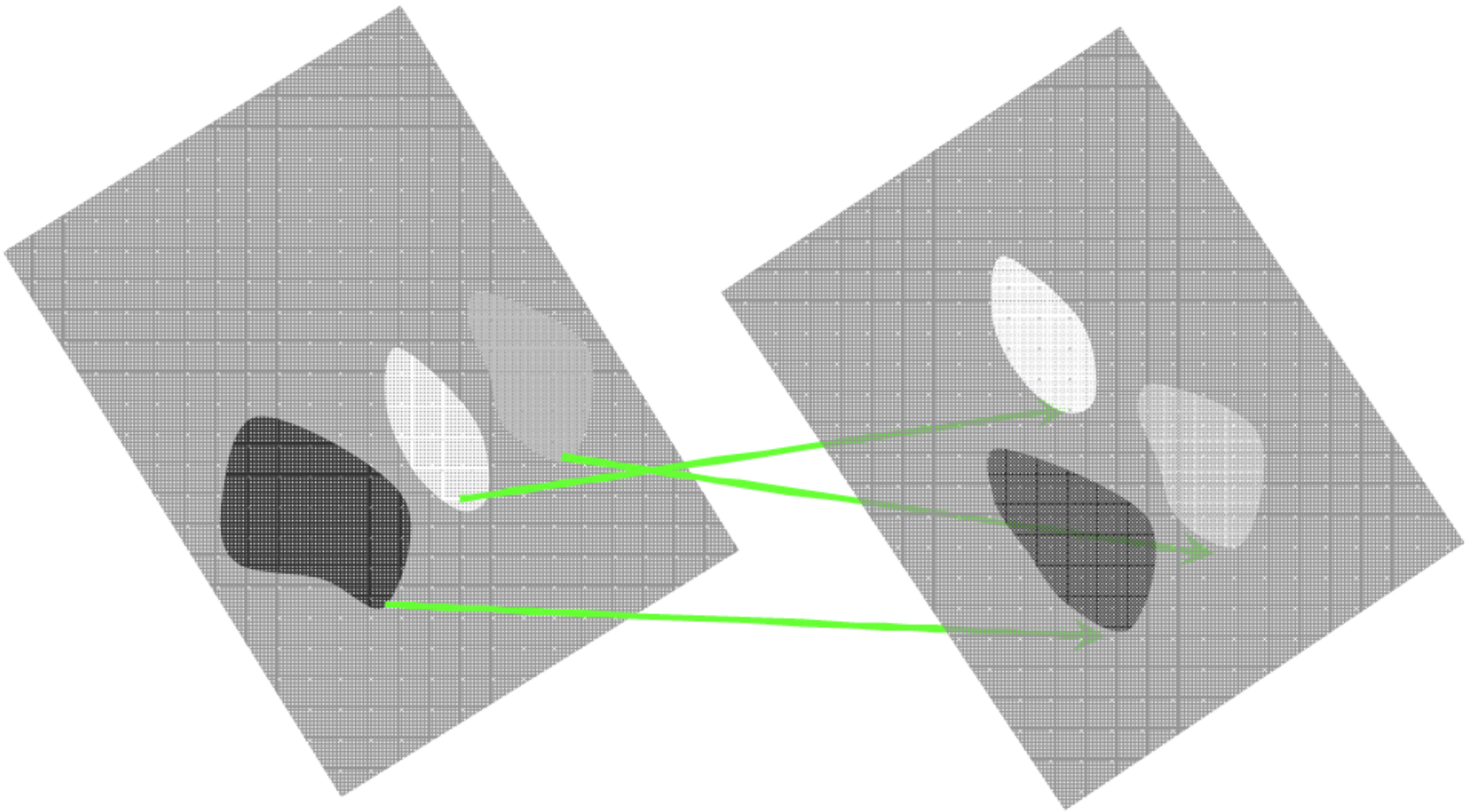

For "Large Deformations" when evaluating "distance" of deformation for regularization linear distance can fail or limit our shape alignment

# Regularization and large deformations

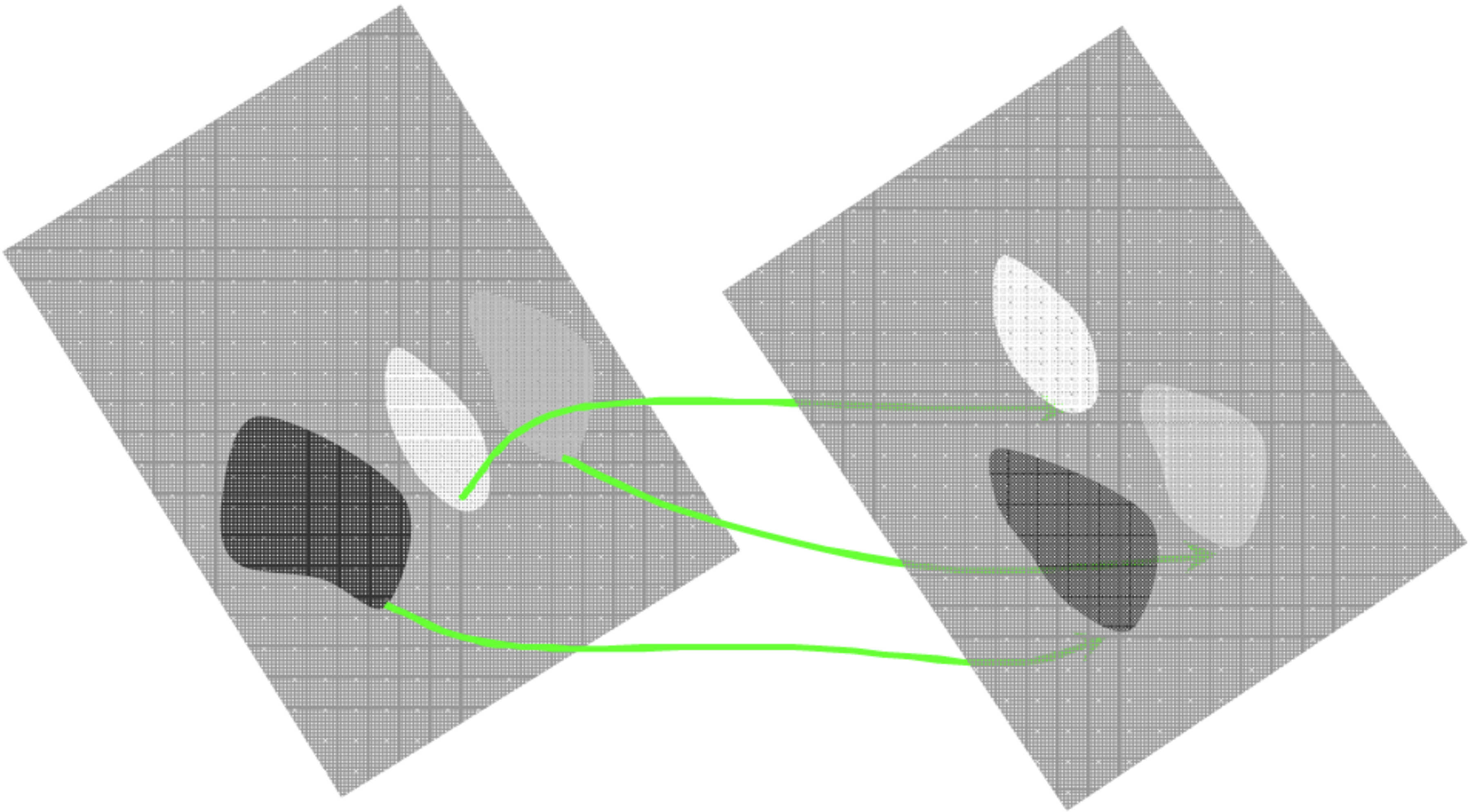



[Christensen, Miller et al, IEEE trans Image Processing, 1996]

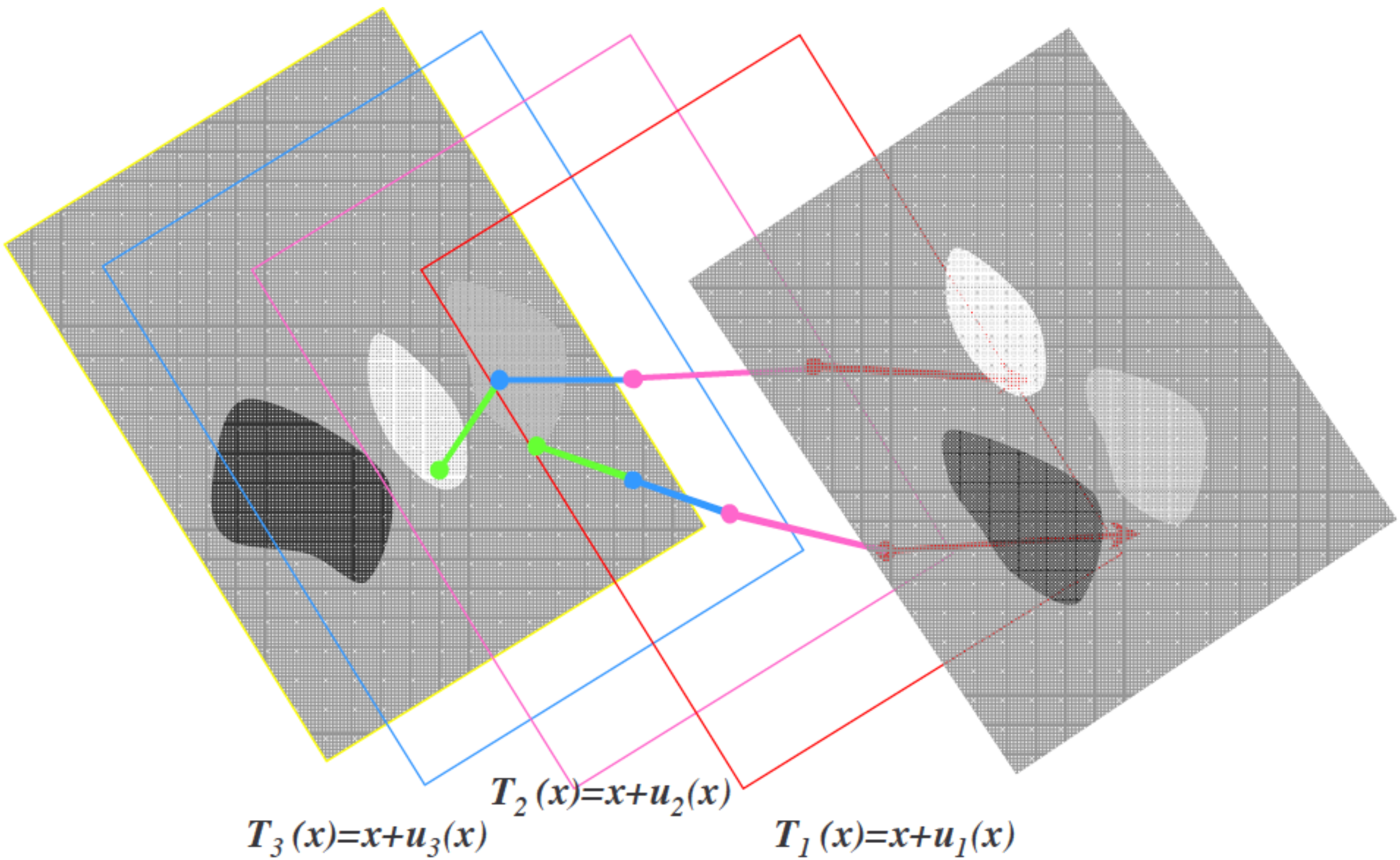
# Mapping between anatomies: Describing correspondence



# Curved diffeomorphic mapping: Describing large deformations



# Discrete large diffeomorphic mapping: Composing sequences of small deformations



# Viscous fluid deformation

- ***Best known approach*** [Christensen,TIP,1996; Freeborough&Fox98]
- For current deformation, evaluate velocity field:

$$\mu\nabla^2 v(x) + (\lambda+\mu)\nabla\left(\nabla^T v(x)\right) = S\left(u(t,x)\right)$$

μ is Shear Modulus, λ is Lame's Modulus

- Evaluate a fractional update ($\Delta t$ 'seconds') of the displacement field along current velocity field:

$$u'(x) = u(x) + R\Delta t$$

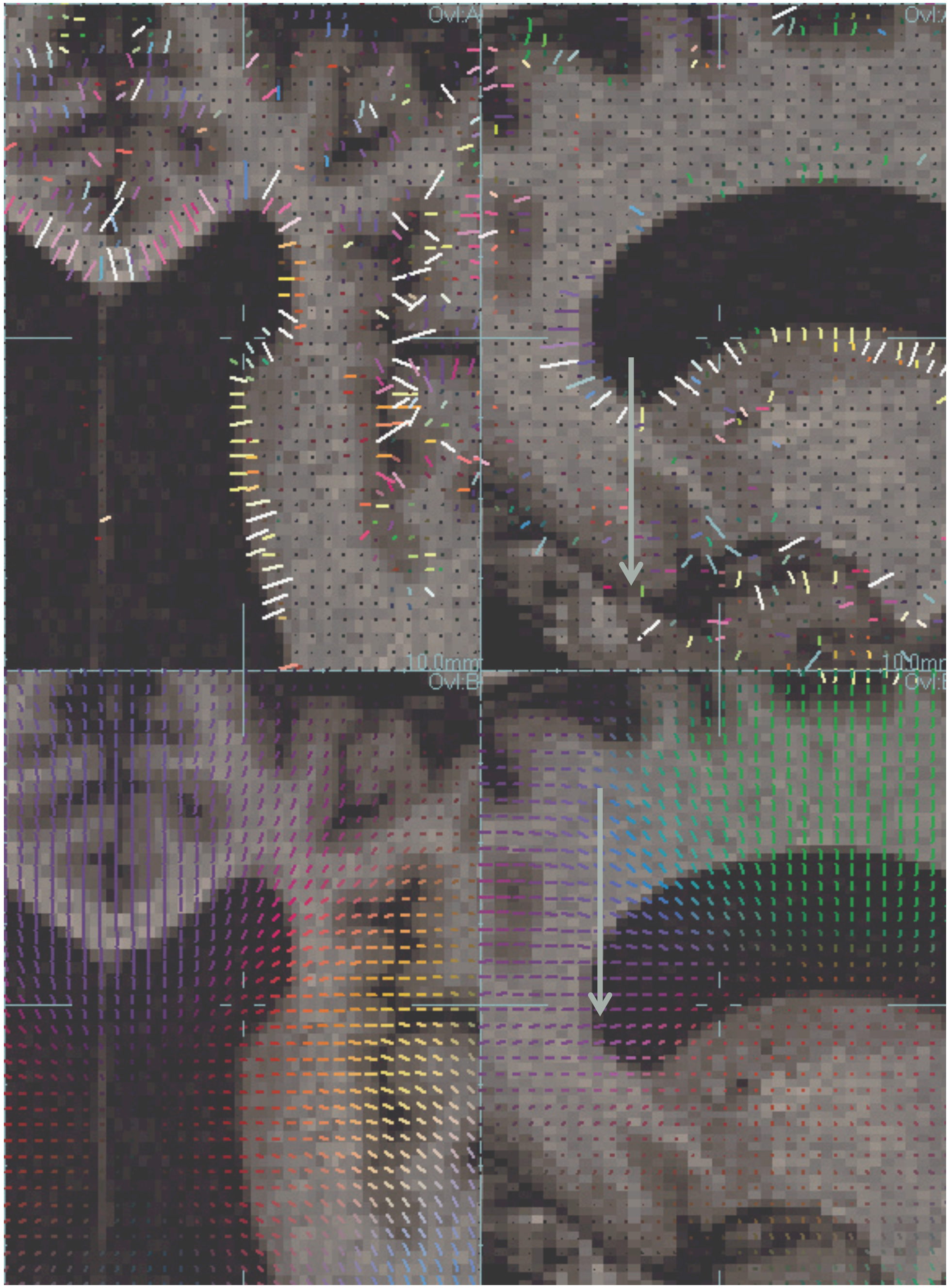
where

$$R = v(x) - v(x).\left[\frac{\partial u}{\partial x}\right]^T$$

- Then update the force field $S(u(x,t))$ and iterate

## Sparse Registration Force Field

- Driving points into better alignment
- In regions of misaligned tissue force>0



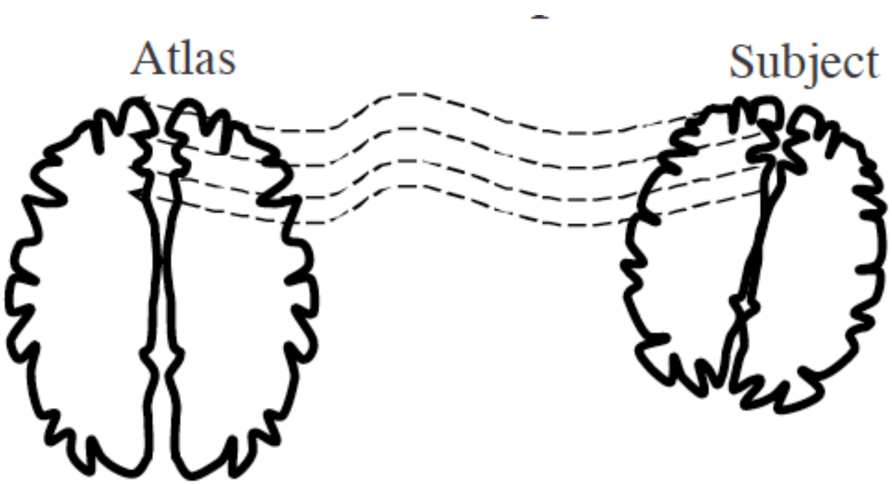

## 'Velocity' Field

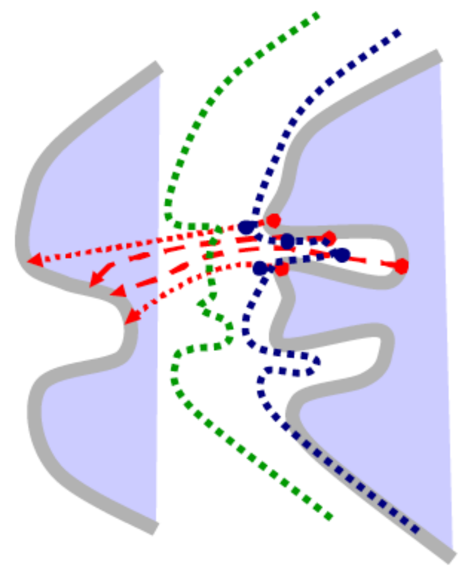
- Smooth and well-behaved i.e. no singularity points or folding
- Then: Update displacement estimate $u(x)$ along $v(x)$

# Viscous fluid deformation model

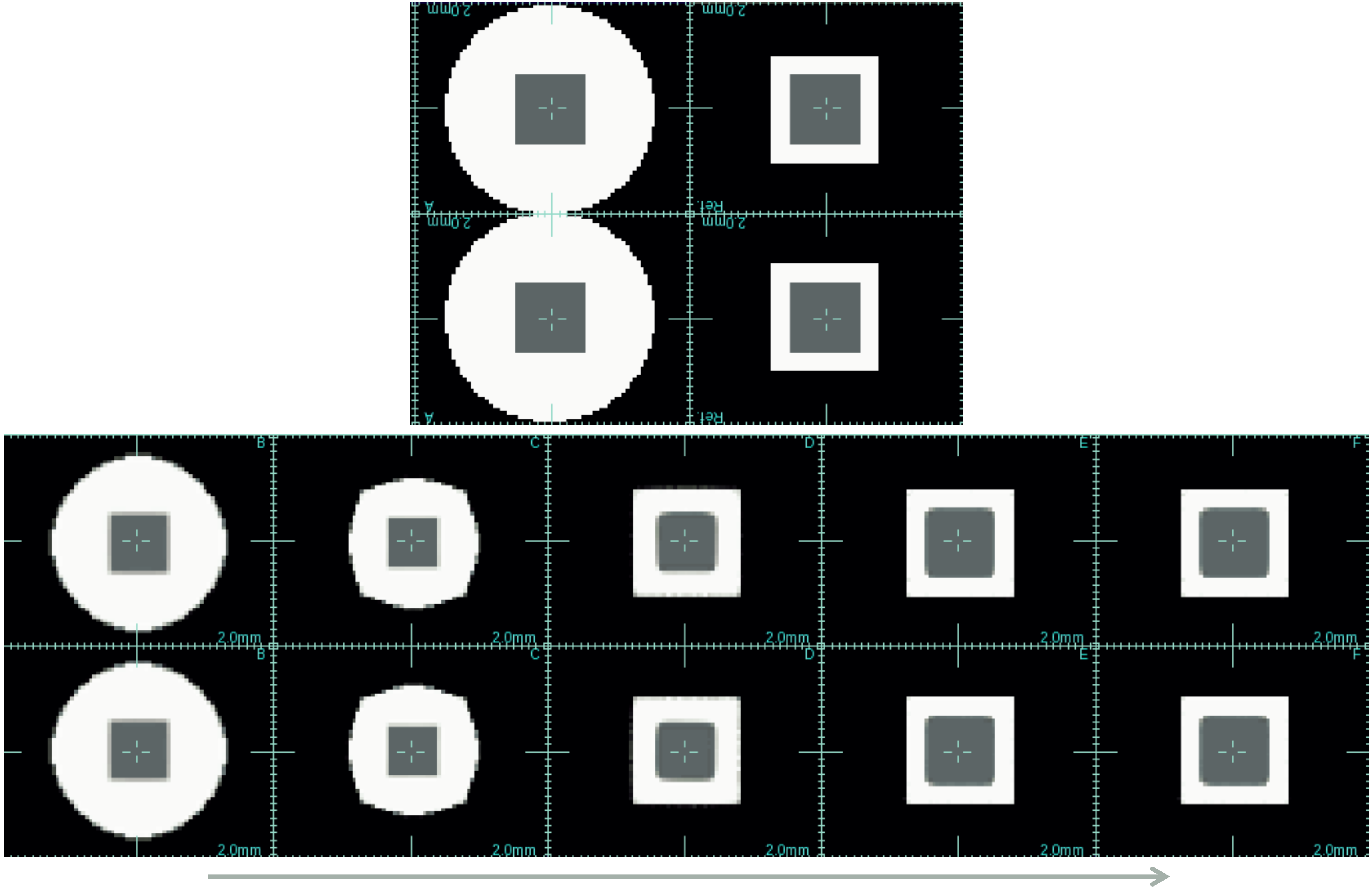
i. Evaluate velocity field $v(x)$ for current force
ii. Propagate mapping along velocity field (update $u(x)$)
iii. Update force field $F(u(t,x))$ for current deformation

Key Idea: The fluid model ensures that the deformation preserves topology at each step: “two points don’t map to one point”



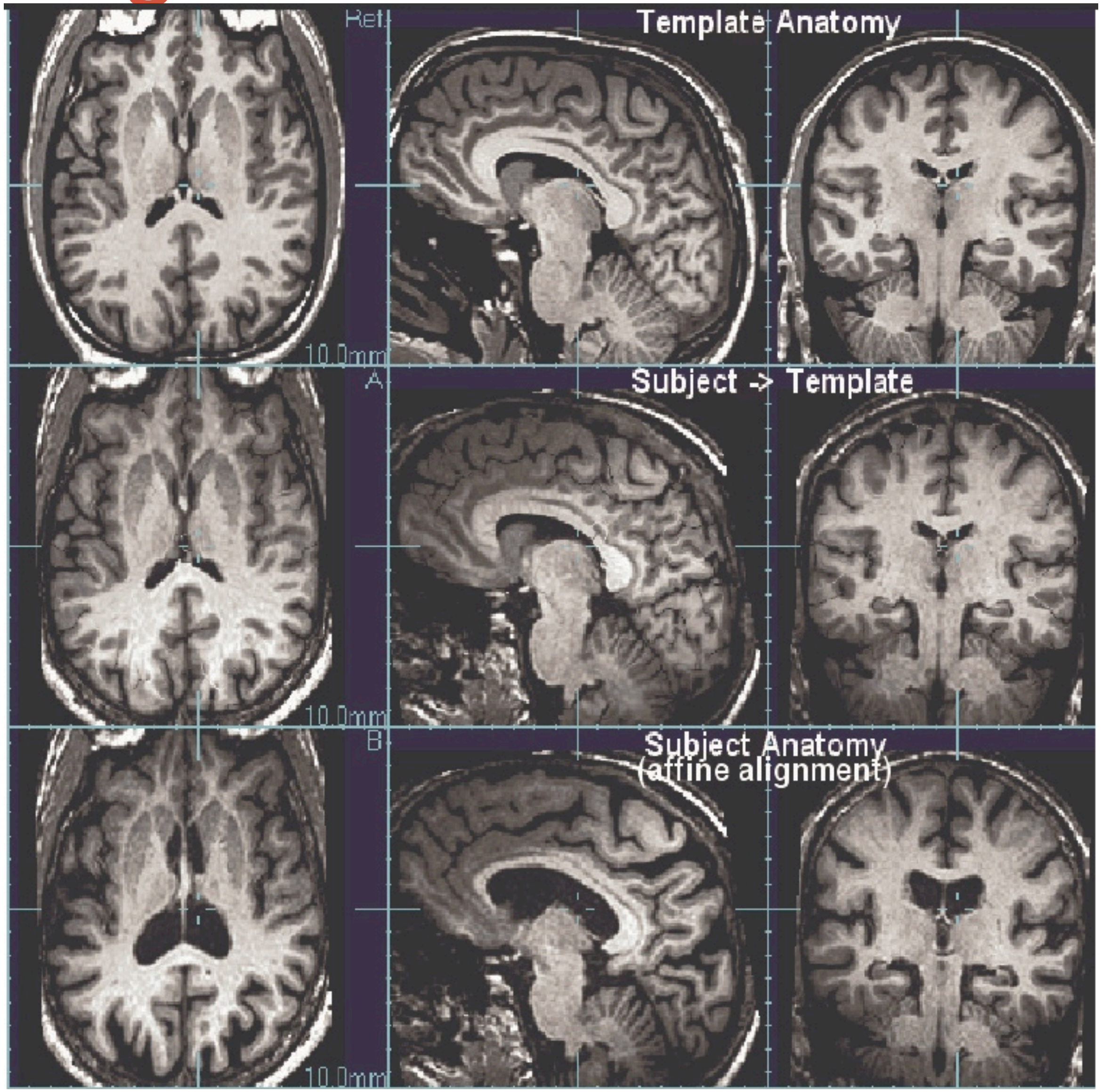



# Large deformation example

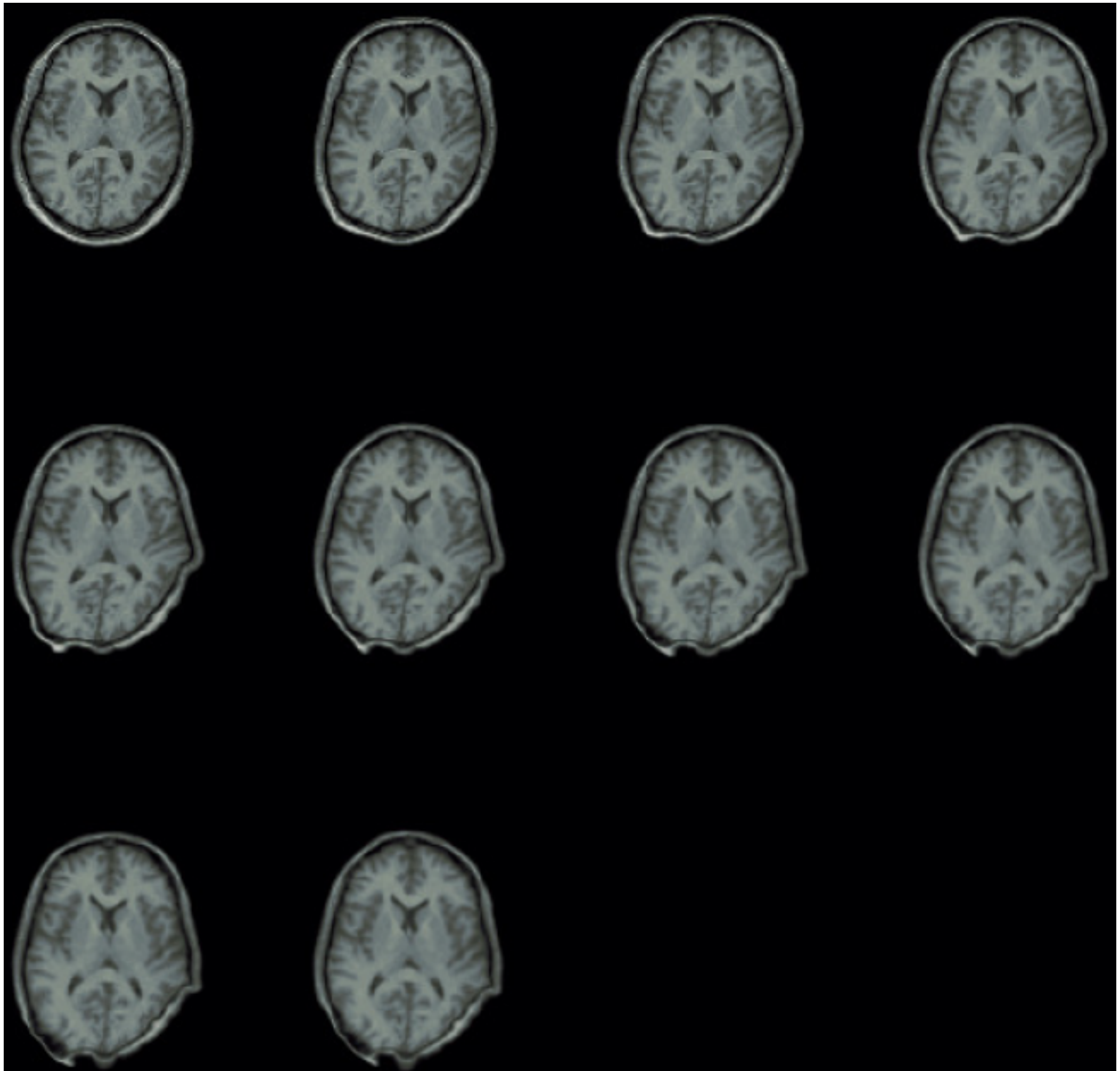


# Viscous fluid registration

Many cortical structures deformed (intensities/ tissue… look the same) BUT not necessarily registered!



# Fluid registration can be dangerous..



Can be critically dependent on initialization, pre-registration, and constraints on region applied to.

Key factor: Lots of engineering rather than mathematics

[H. Lester, S. Arridge, A survey of hierarchical nonlinear medical image registration., Pattern recognition, vol 32(1), 1999, page 129-149.]

# ATLASES AND TEMPLATES FOR SPATIAL NORMALIZATION OF ANATOMIES

# What is an atlas?

In practice we might say an atlas is a map or spatial record of what we know about a region

# Characteristics of an atlas

1) The type information we record in it
2) How we place that information within the atlas
3) How we display/project/extract that information

# Atlases in medical imaging

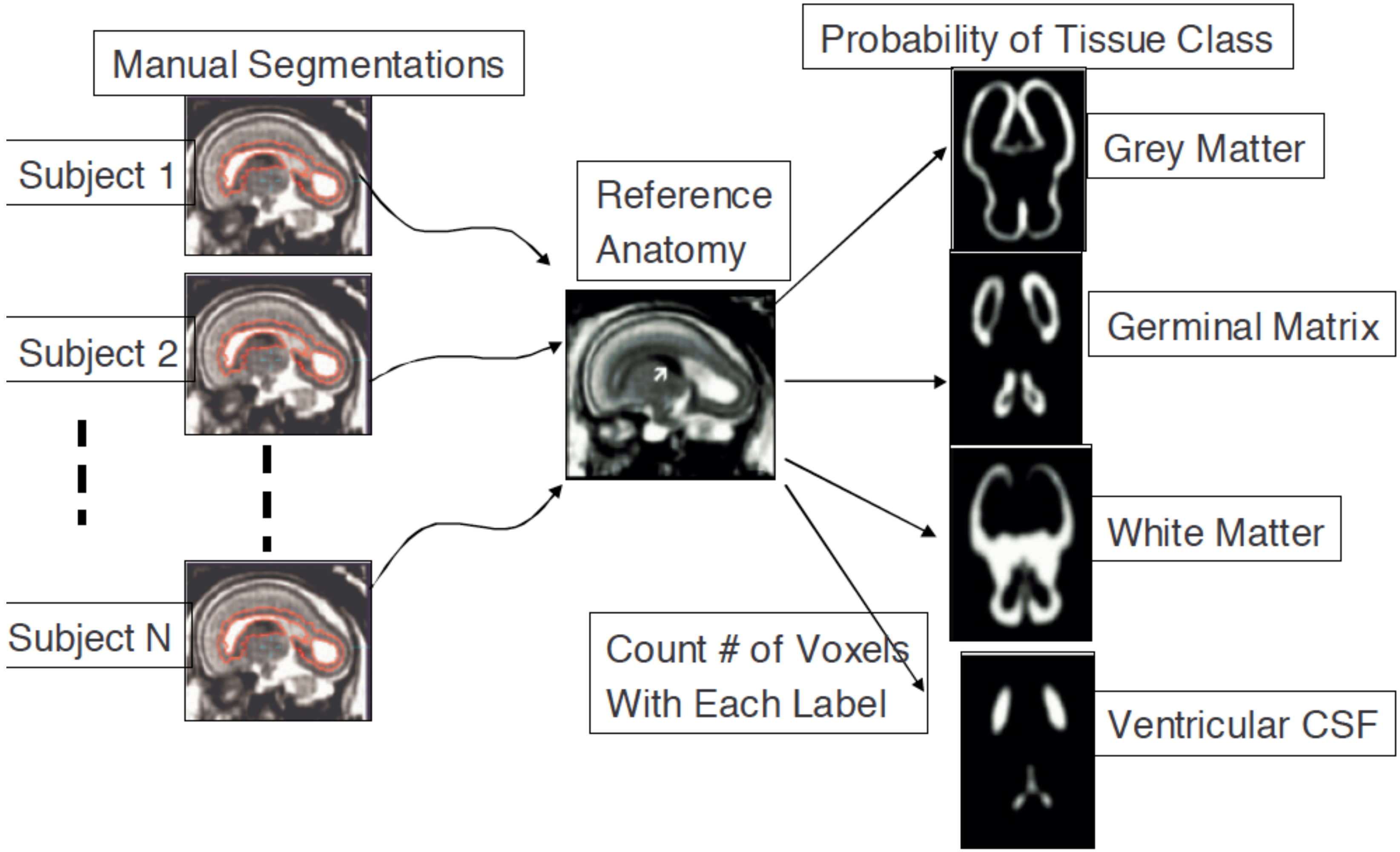
- An atlas usually refers to a (often probabilistic) model of a population of spatial data (images)

- Parameters determining the model are learned from a set of training data.
  - One or more subjects: e.g. atlas of brain regions

- Simplest form is a template or average intensity.
  - e.g. Mean grey matter density, mean PET tracer uptake

- More complex forms capture
  - Higher order statistics: variance, or other model of distribution
  - Complex parameterized models: e.g. age

# Example: Statistical model of tissue distribution in fetal brain




[P. A. Habas,et al, "Atlas-based segmentation of the germinal matrix from in utero clinical MRI of the fetal brain," in MICCAI, LNCS, vol. 5241, part I, pp. 351-358, September 2008.]

# Example Atlas: Complex Parameterized Models


Age-specific tissue probability maps generated in average space

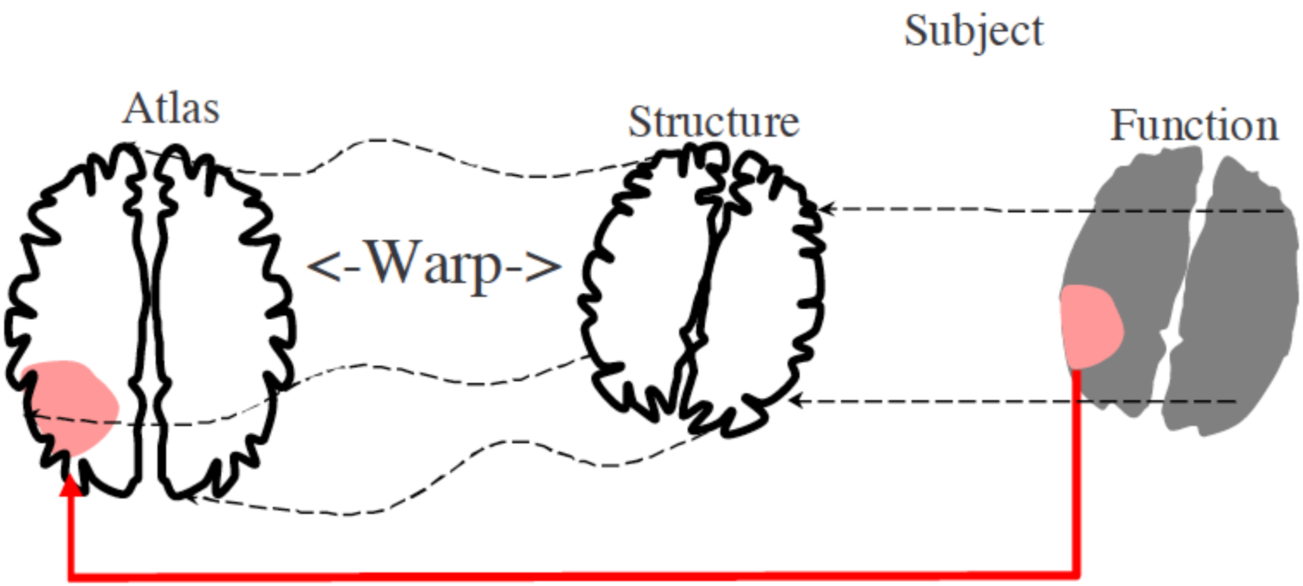
# HOW DO WE PLACE INFORMATION INTO AN ATLAS?

# Independent modalities

Use ‘structure’ to place ‘functional’ measurements within the atlas

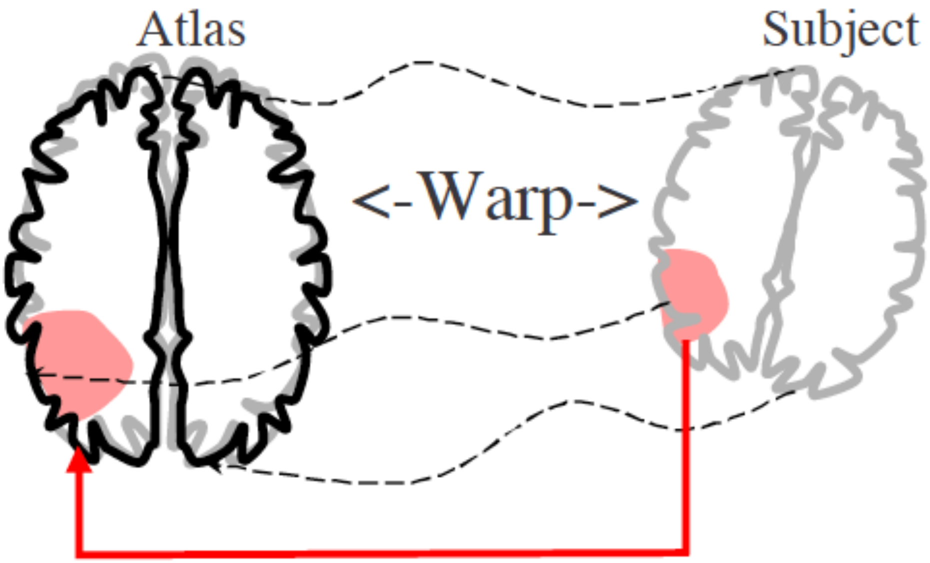
– Use MRI to normalize subject anatomy to a template anatomy

– Apply anatomical transformations to bring functional measurements in a subject into the atlas



# Same modality

Use neighboring structure to locate and place measurements within an atlas of the same type of measurements

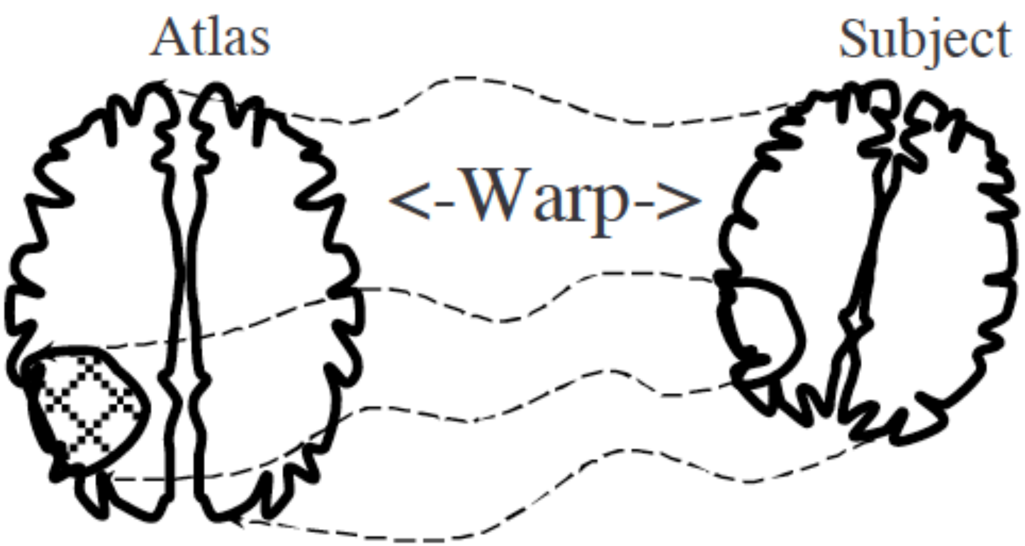



– How accurately do we place that information?
– How does that neighboring information influence placement?

# Shape mapping: Morphometric atlases

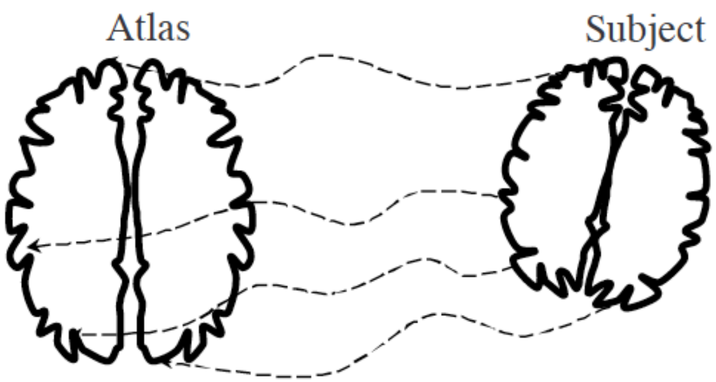
Do not record imaging measurements (e.g., function, parcellation) in subject BUT record how subject was spatially re-arranged to fit the atlas

– Record how the shape of Subject and Atlas differ (e.g., atrophy)



# “Templates” for atlas mapping

- What structure do we use as a target or template?
- Needs to contain information relevant to problem
  - Where are the gyri delineating functional brain regions?
- Needs to exclude irrelevant information:
  - Template should not contain a tumor if studying normal anatomy




- Need to have a representative shape:
  - Don’t use a brain with rare sulcal patterns to study normal anatomy

# Templates and atlases

- Early Atlases for presentation/visualization:
  - were often manually drawn [Broadmann]
  - ‘idealized’ anatomies created by sketching features of interest
  - difficult to compare results

- Modern templates for spatial normalization can be optimized for use with registration method

[Broadmann, K: On the Comparative Localization of the Cortex 201-230]

# Optimizing templates

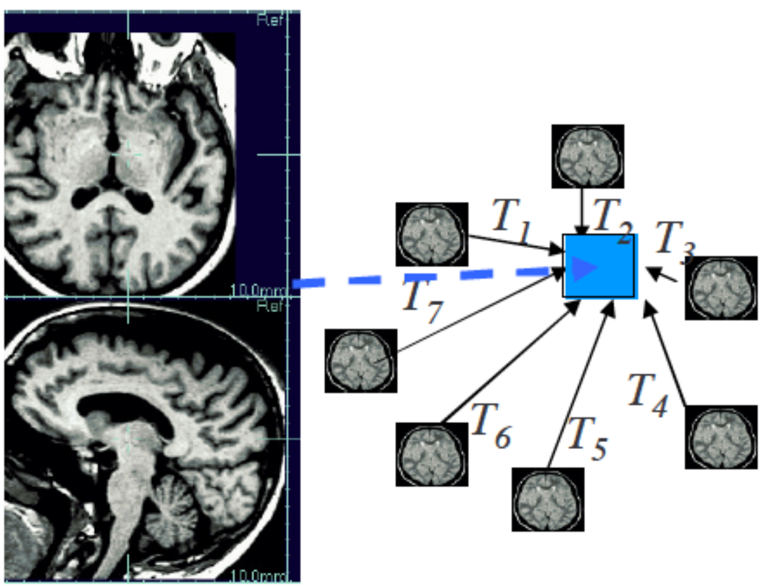
- Contrast/Intensity properties
  - High signal to noise (average brain of MNI colin27?)
  - Show Imaging structures of interest:
    - T1W template for T1W matching -> structure
    - T2W template for T2W matching -> fMRI?
- Resolution
  - High isotropic resolution
    - Minimize loss of fine structure/tissue boundary
- Spatial mathematical properties
  - Average ‘shape’ of anatomies studied
    - aid in visualization of results
    - improve registration algorithm?

# Optimal template for matching

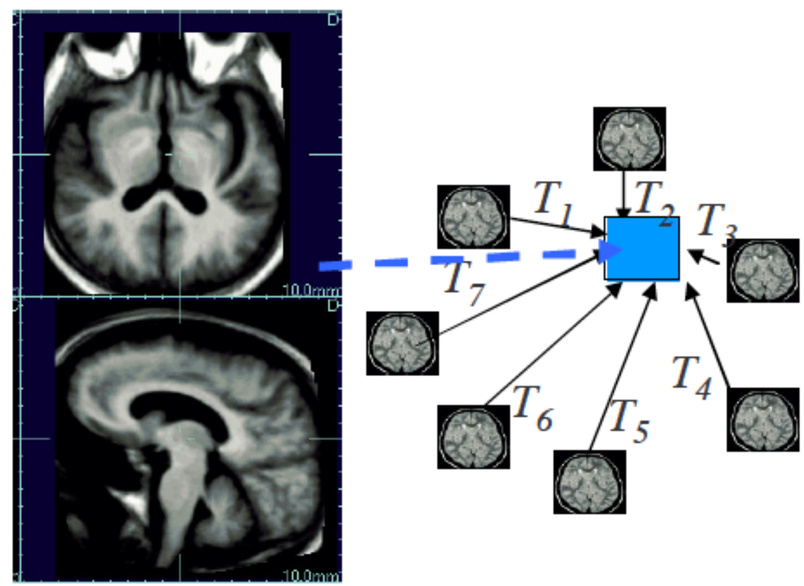
- Average intensity? (older SPM/VBM analyses)

– register a set of MRI's to a single subject MRI

– and average intensities to form a new template

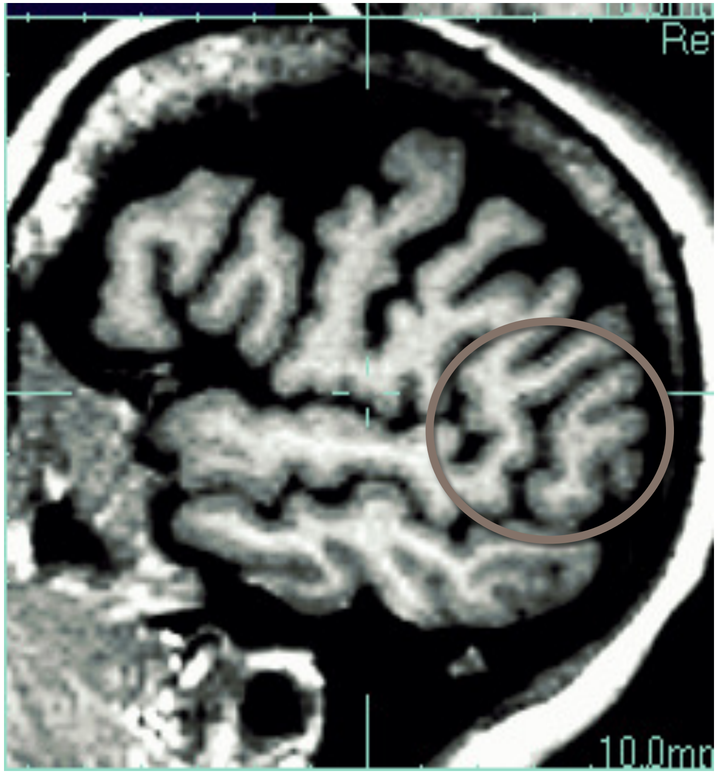



Single subject MRI




'Average' subject MRI

Single Subject



Average of 14 subjects
(Coarse deformation)

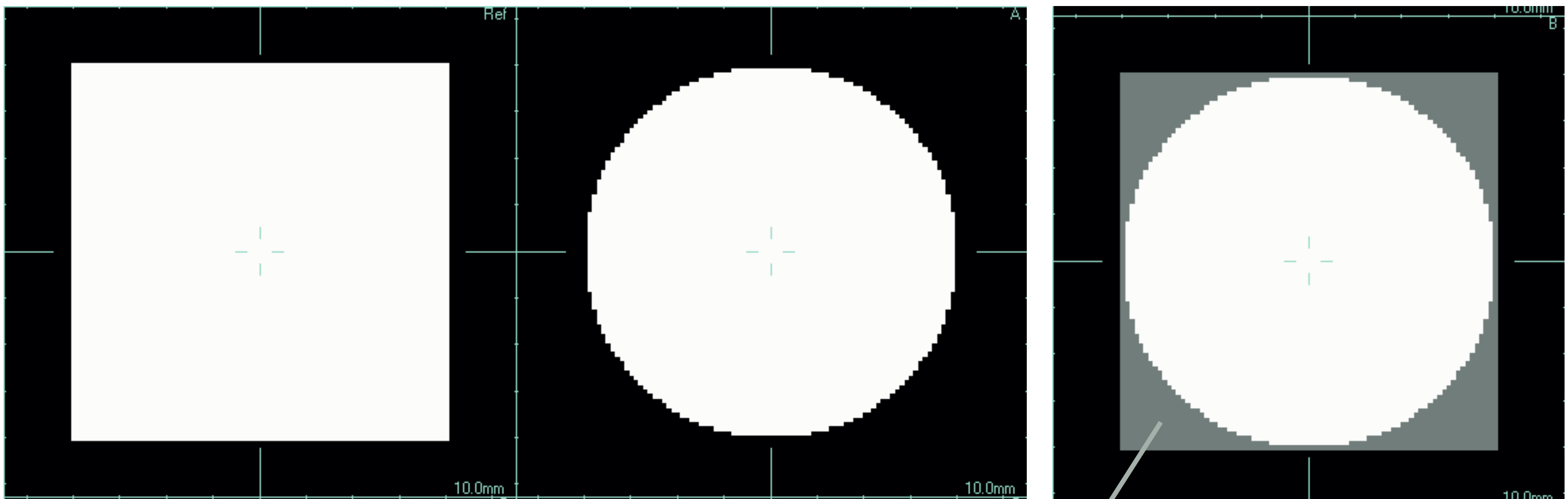
•Since images imperfectly aligned there is a fundamental problem.

•Resulting ‘average’ image is not necessarily an example of **a real anatomy** which has been blurred.

•May even be **topologically different** (e.g. sulci covered over)

•So... deforming an individual to it may be impossible!

# Average shape between a cube and a sphere

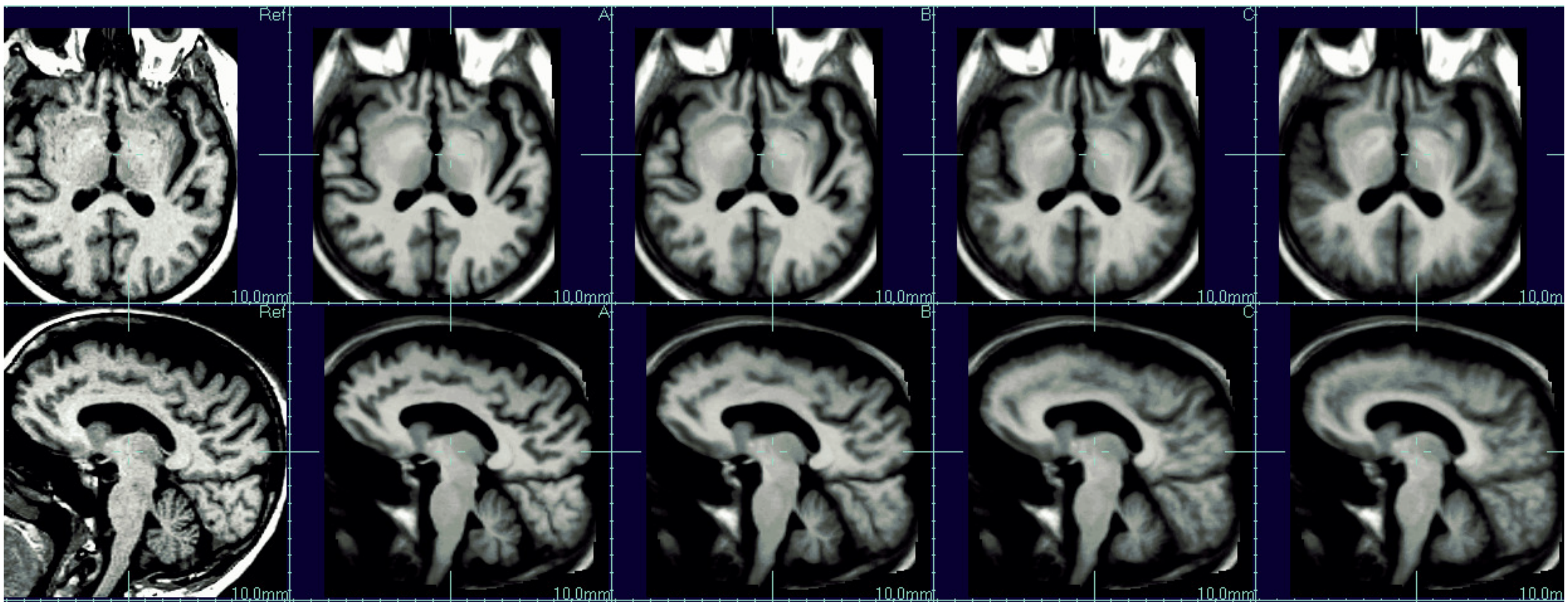



Linear average

Unreal intensities

# Improving average through fine scale registration

Reference MRI Average of 14 Controls Mapped to Reference MRI




2.4mm B-Spline 4.8mm B-Spline 9.6mm B-Spline 19.2mm B-Spline

# How to define average anatomical geometry?

- “Template is most similar in shape to a given group being studied”
- Makes registration easier?
- Need a definition of distance between anatomies

# Linear averaging: ‘Unbiased atlases’

Evaluate a common space such that the average displacements of a given point to a set of subjects is zero.

Can do this

1) Group-iteratively during registration:

• register group to template

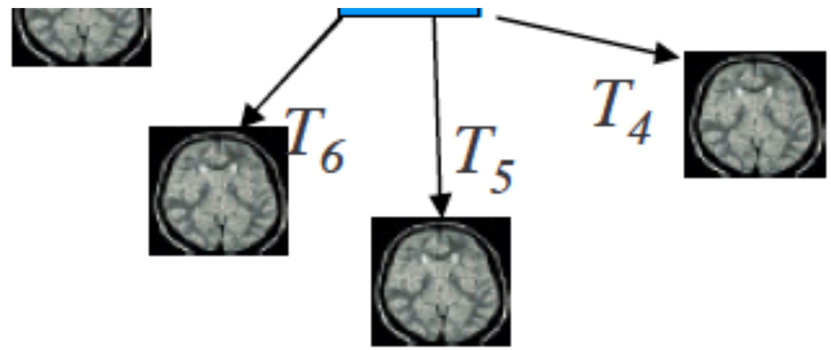
• warp template to linear average

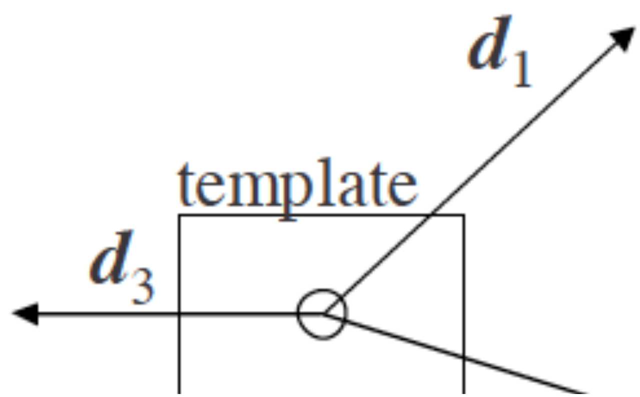
• re-warp subject to template

[Guimond, A., Meunier, J., Thirion, J.P.: Average brain models: a convergence study. Comput. Vis. Image Underst. 77(2)(2000) 192–210]

2) Collectively during group-wise registration

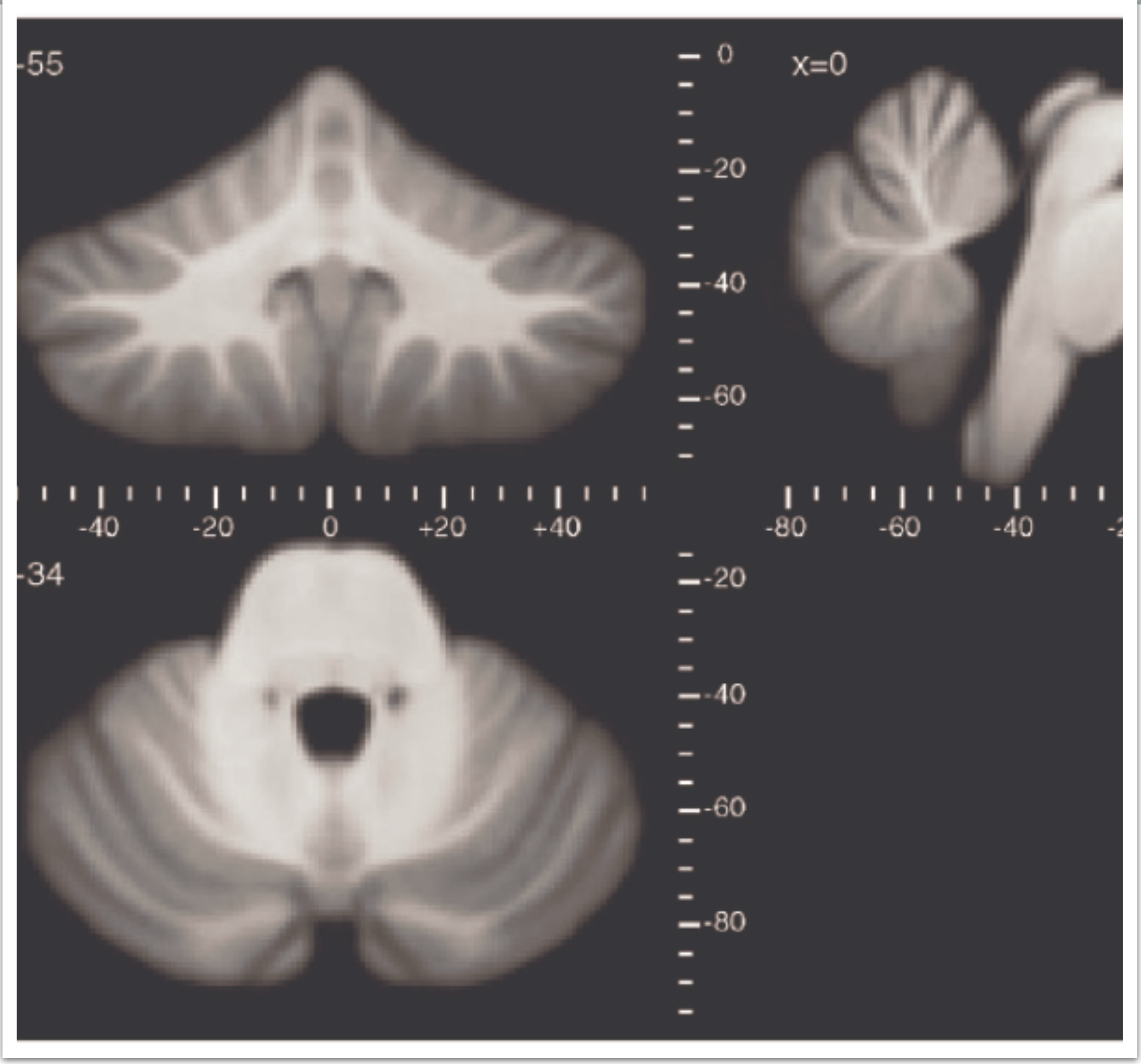
• Use distance as a constraint



# Spatially unbiased infra-tentorial (SUIT) template

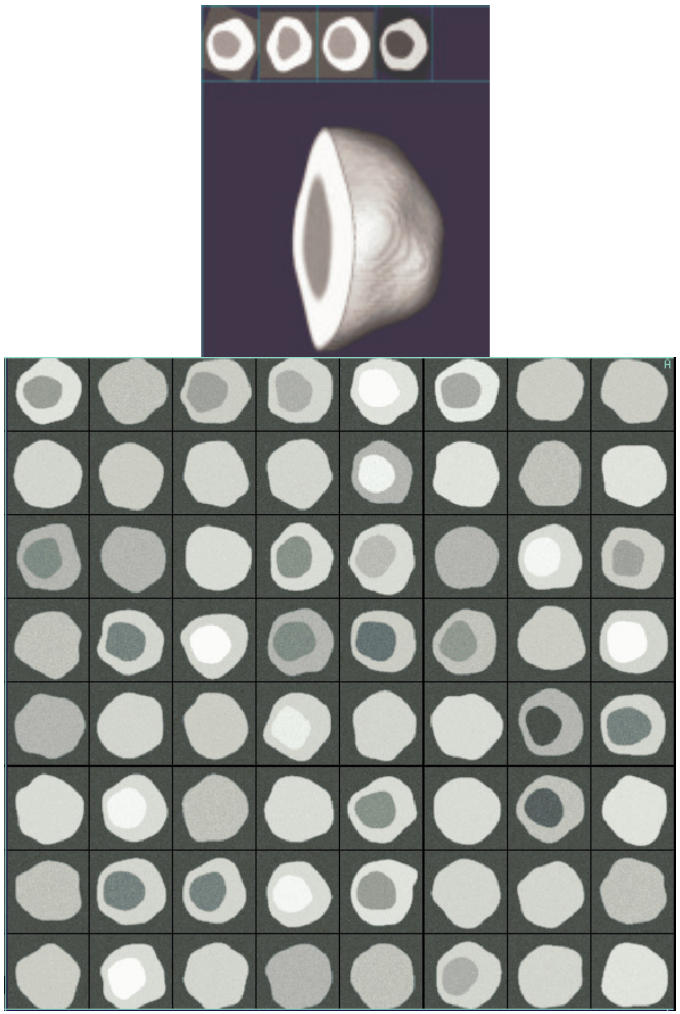
The coordinate system is defined by the ICBM 152 template. Each structure is at the same coordinate as it would be on average after affine alignment to the generally accepted MNI reference frame. The template image is based on the average anatomical image of 20 individuals.



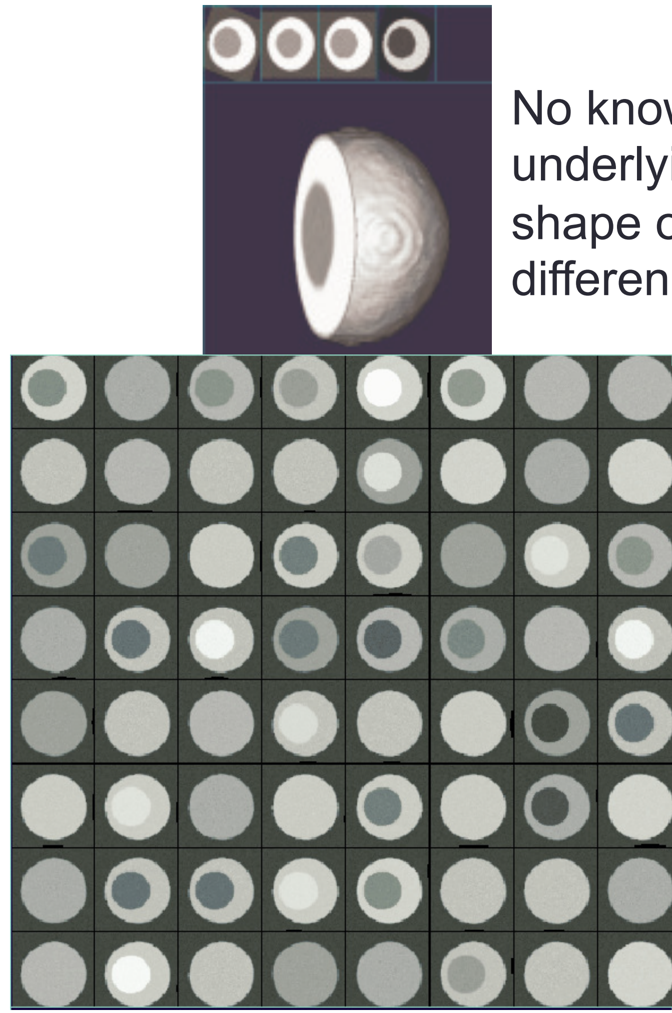

[A spatially unbiased atlas template of the human cerebellum, Jörn Diedrichsen , Neuroimage vol 33, issue 1, 2006]

# Elastic averaging of group (driven by entropy)

Starting Population



Populations Deformed Toward Each other

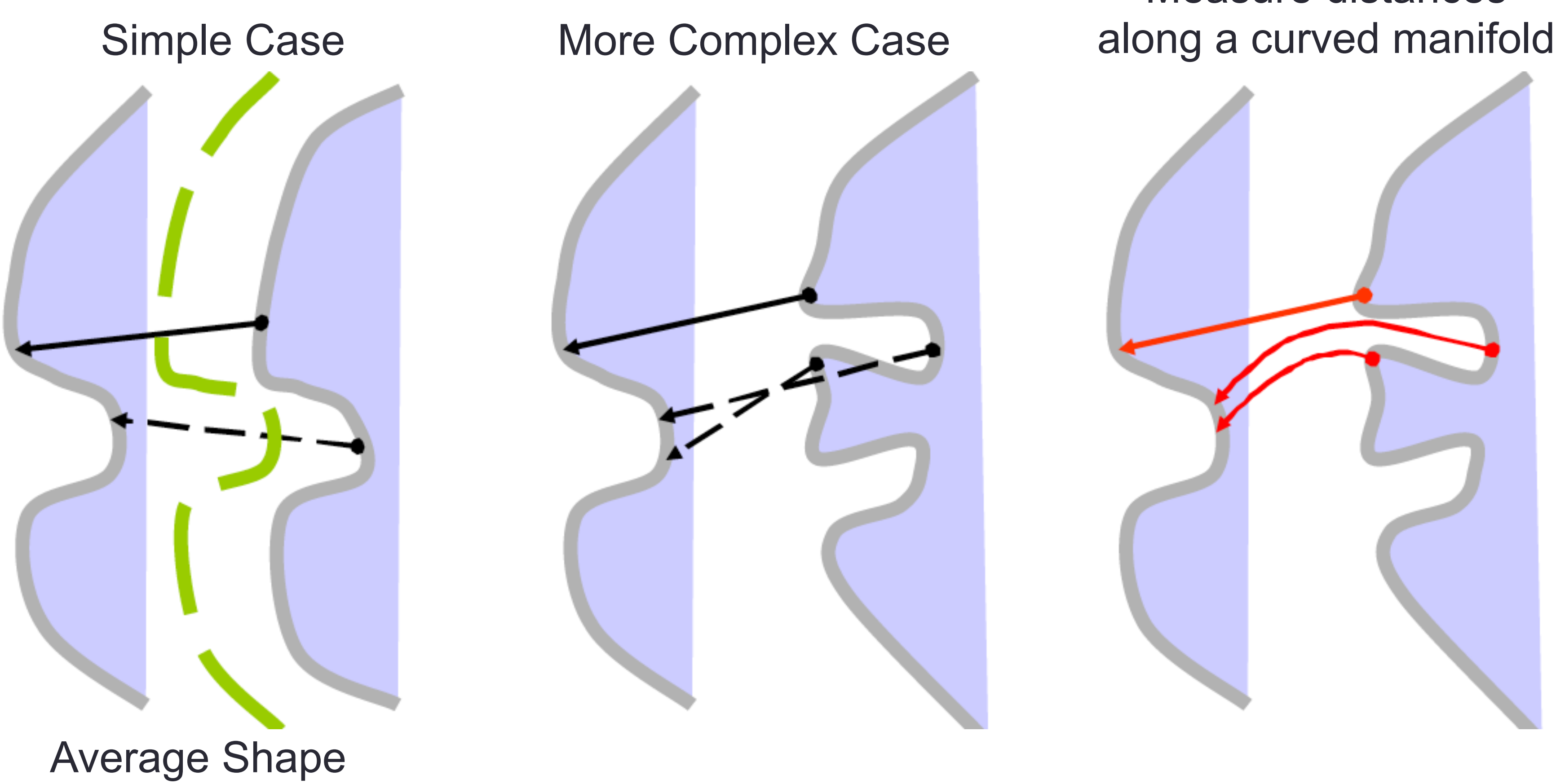


No knowledge of underlying average shape or contrast differences!

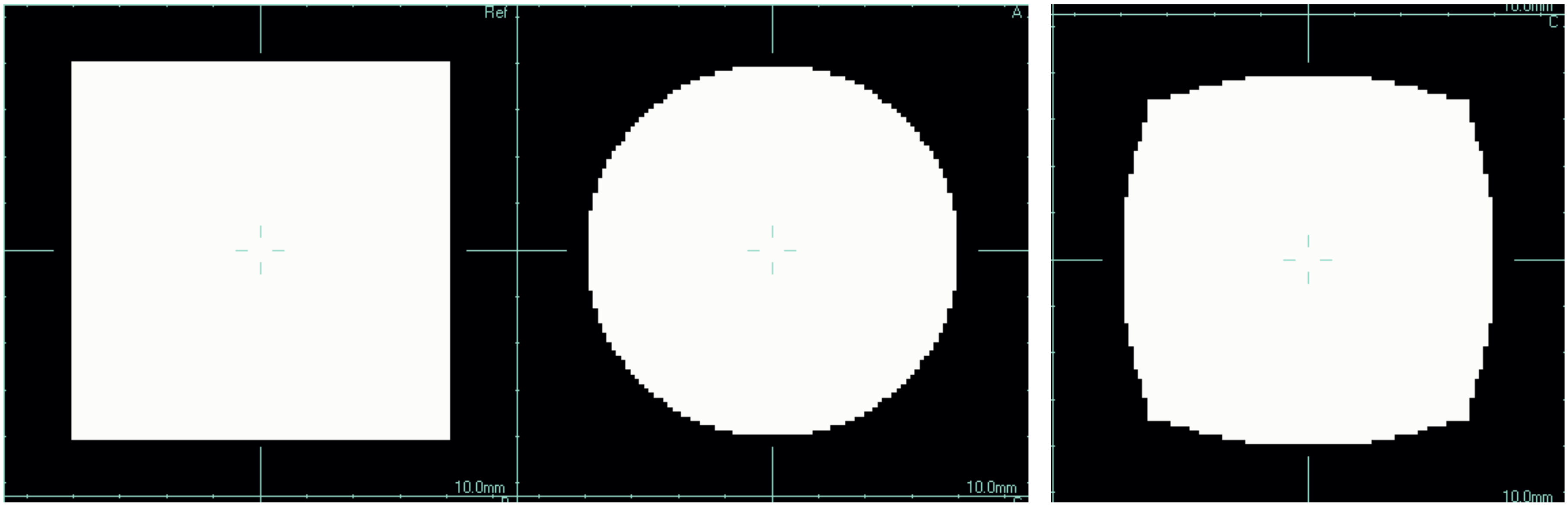
Subpopulation with internal spheres collectively aligned

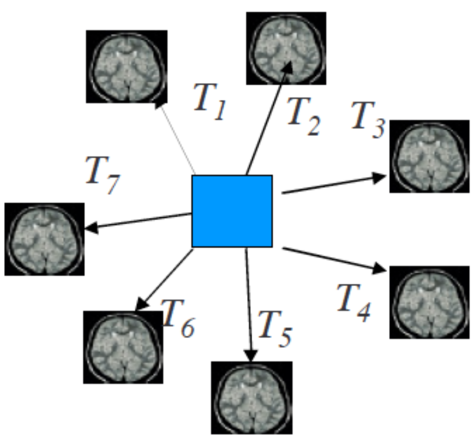
# Non-linear shape averaging

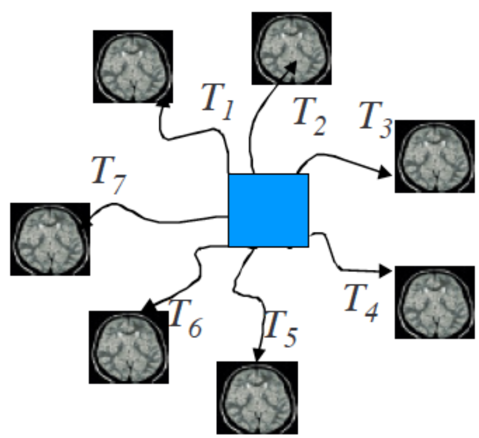
The shape distance problem (same as in regularization)



# Large deformation non-linear average shape between a cube and a sphere

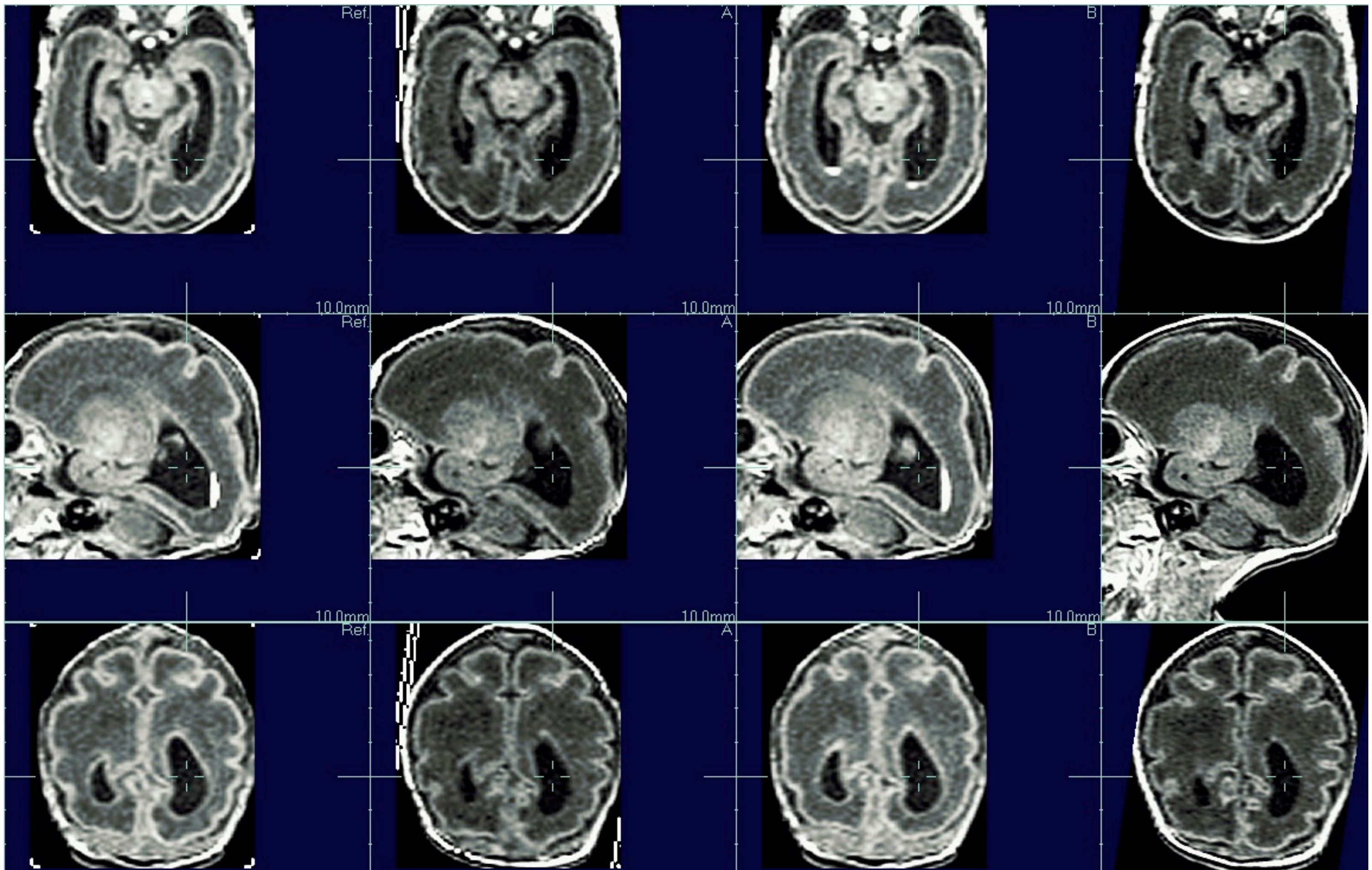



Distance measured along curved manifold then averaged over population

# Symmetric warping between developing anatomies

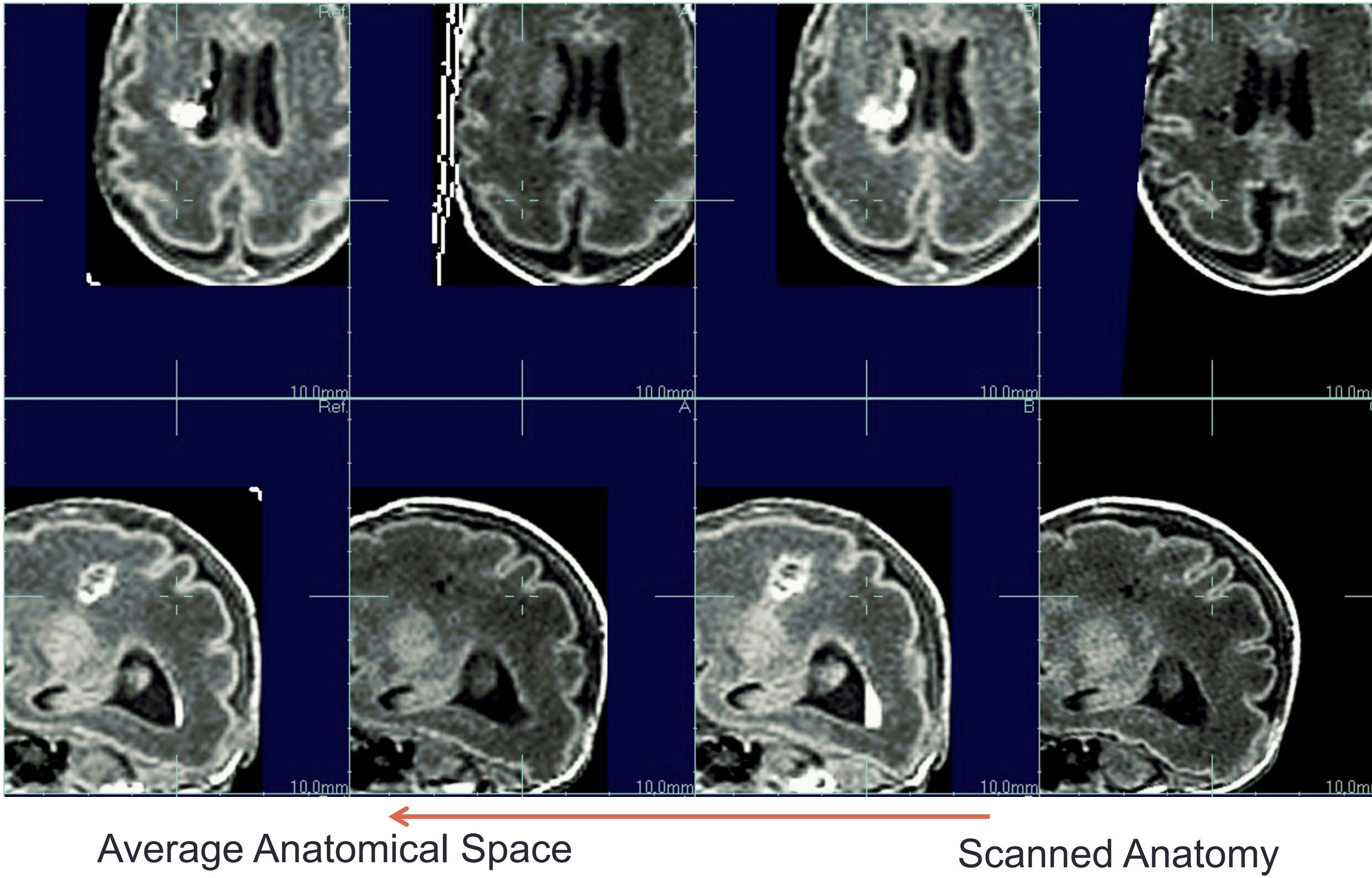



Warp Image Pair Into Alignment

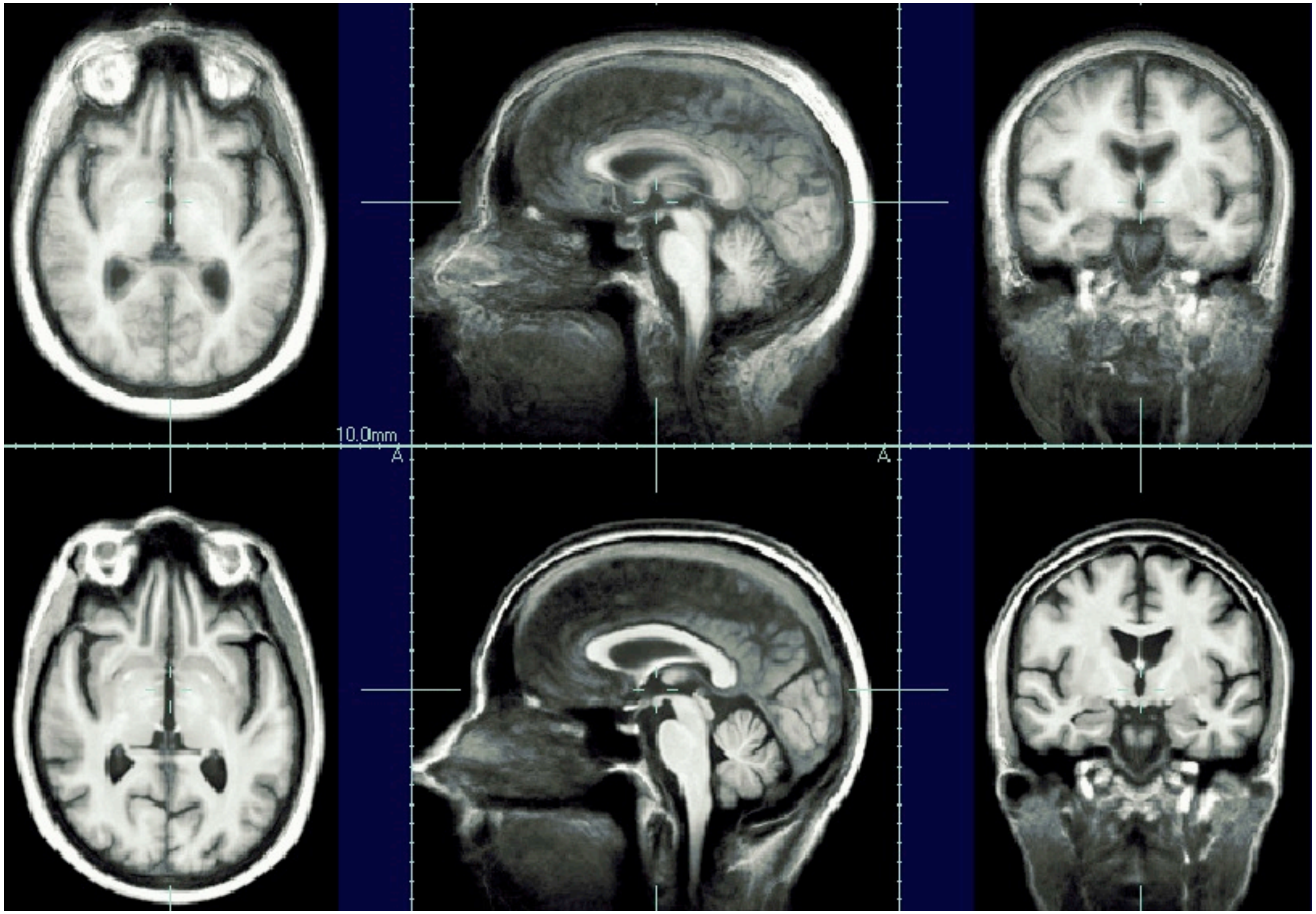
Average Anatomical Space

Scanned Anatomy

# Symmetric warping between developing anatomies



# Linear and non-linear averages of 23 subjects




[S. Joshi, B. Davis, M. Jomier, and G. Gerig, "Unbiased Diffeomorphic Atlas Construction for Computational Anatomy", NeuroImage; Supplement issue on Mathematics in Brain Imaging, Volume 23, Supplement 1, Pages S151-S160, Elsevier, 2004.]

- Many different factors in atlas based analysis
- Critical issues in registration algorithm
  - How accurately can you relate individuals to atlas?
    - for atlas construction and atlas use
  - Importance depends on application
- Very active area of research