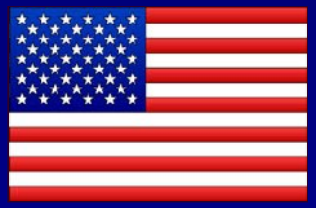
Comparing Brains

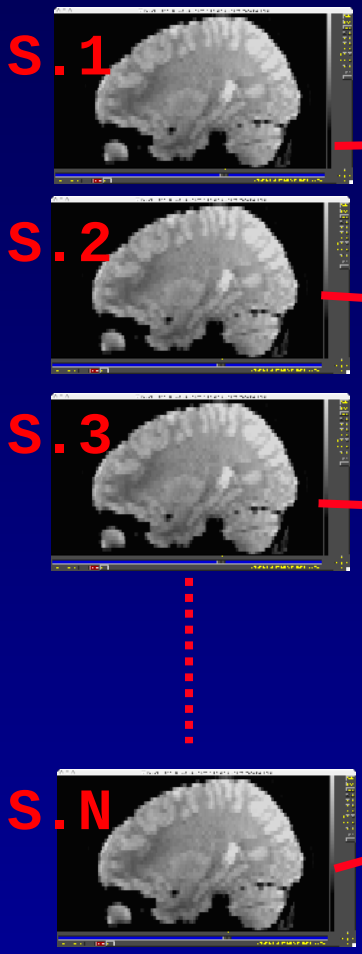
Ziad S Saad, PhD

SSCC / NIMH & NINDS / NIH / DHHS / USA / EARTH



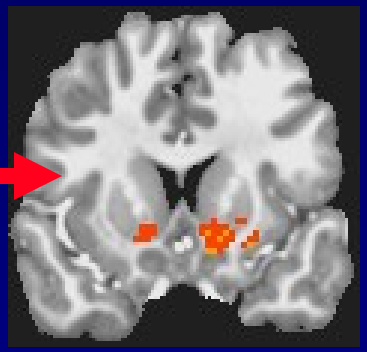
Comparing Brains: Finding Commonalities

Single subject data

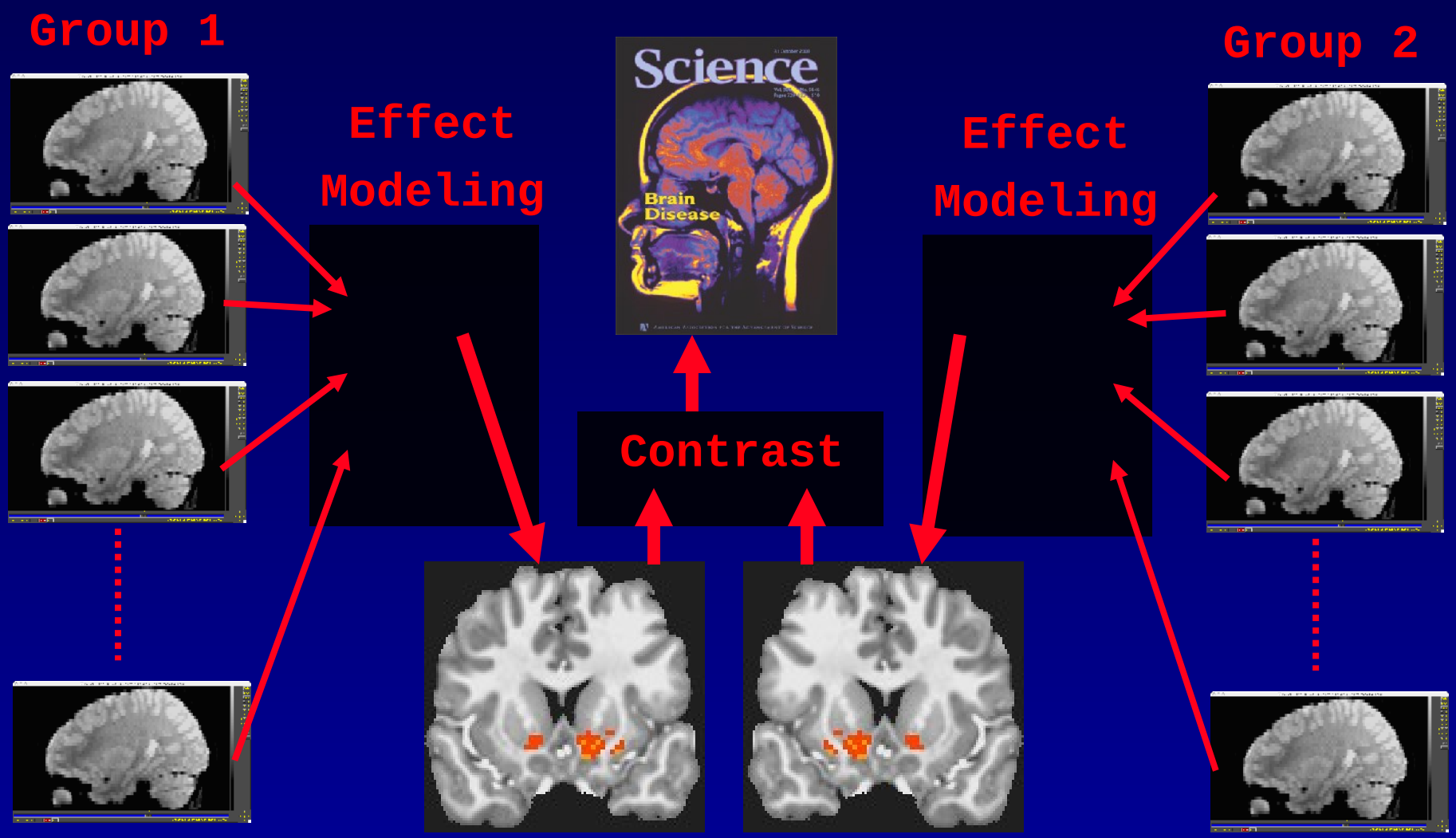


Effect Modeling

Group Results



Comparing Brains:
Finding Group Differences



Cross Species Normalization

- Cross-species normalization *when appropriate* can be useful in understanding commonalities.
- Use of functional instead of anatomical reference

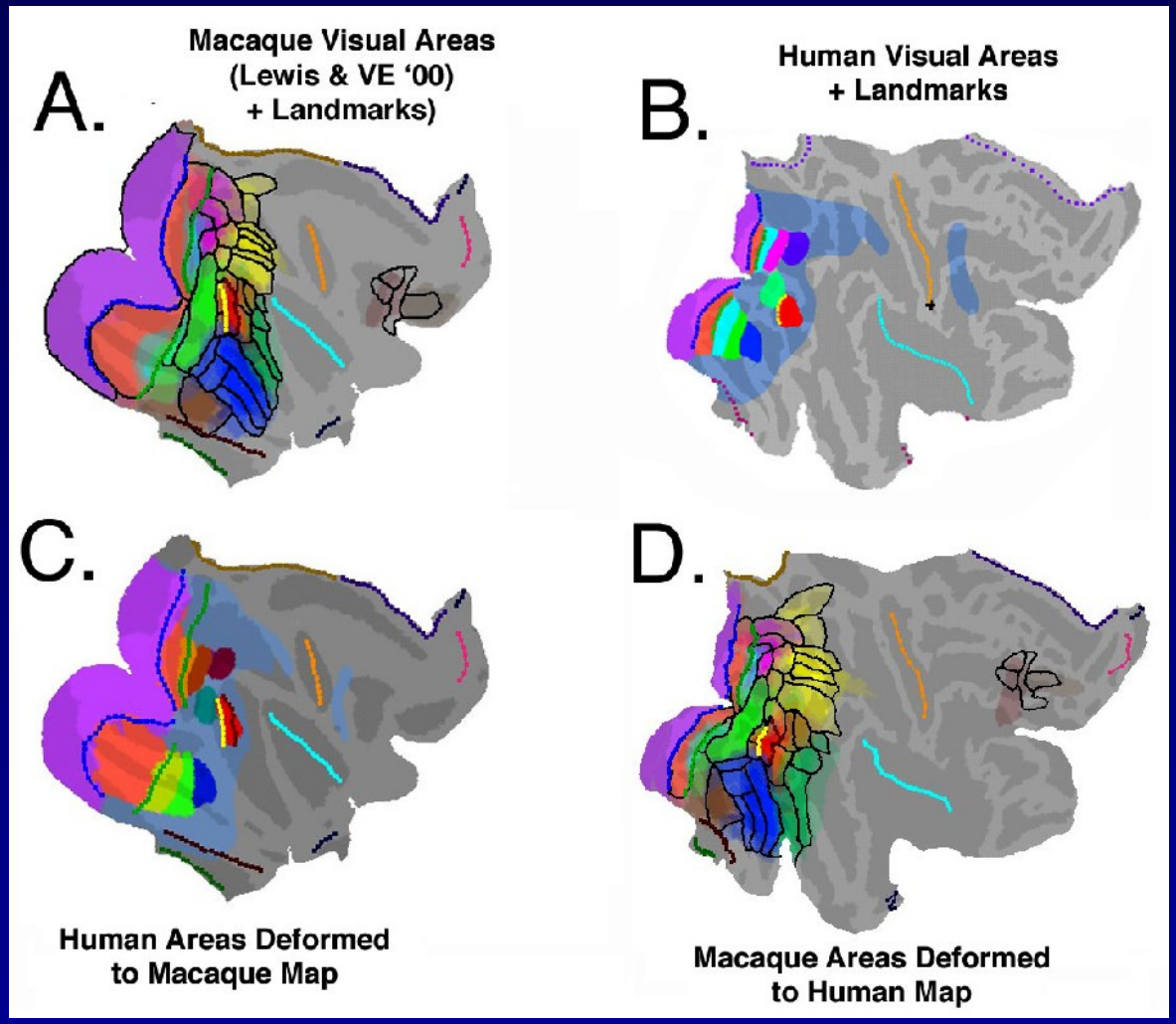
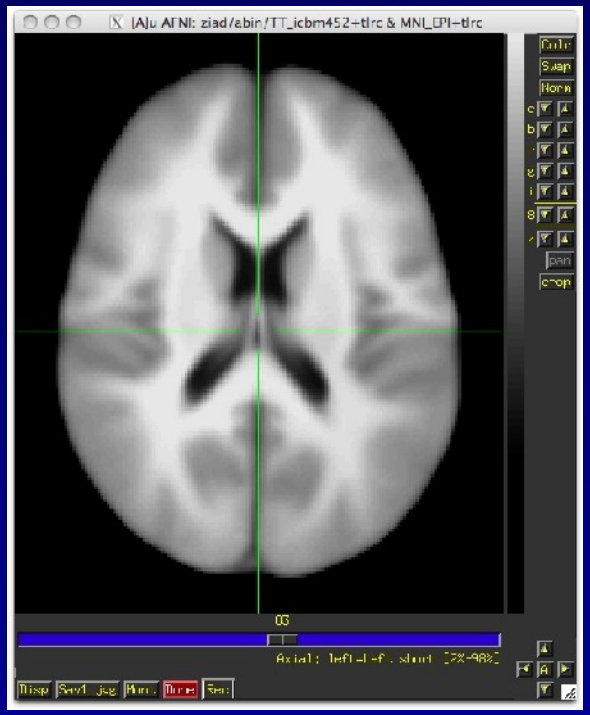
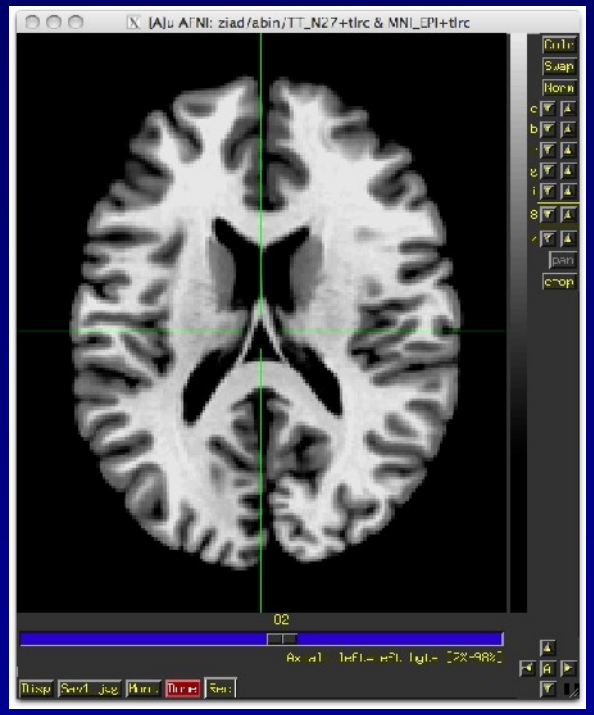


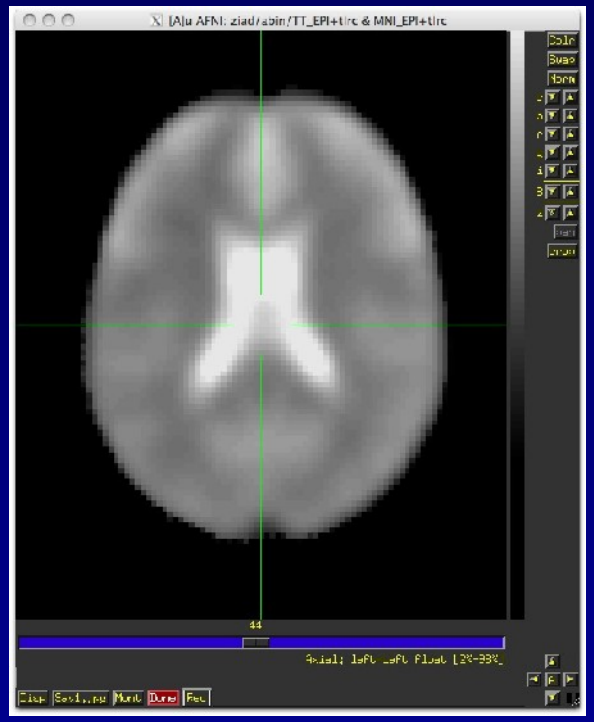
Fig.6 from D.C. VanEssen, Organization of Visual Areas in Macaque and Human Cerebral Cortex. In: Visual Neurosciences (L. Chalupa and J. Werner, eds.)

A Common Domain

- Voxel-wise brain comparison require data from multiple subjects to be defined, or mapped onto a common domain.

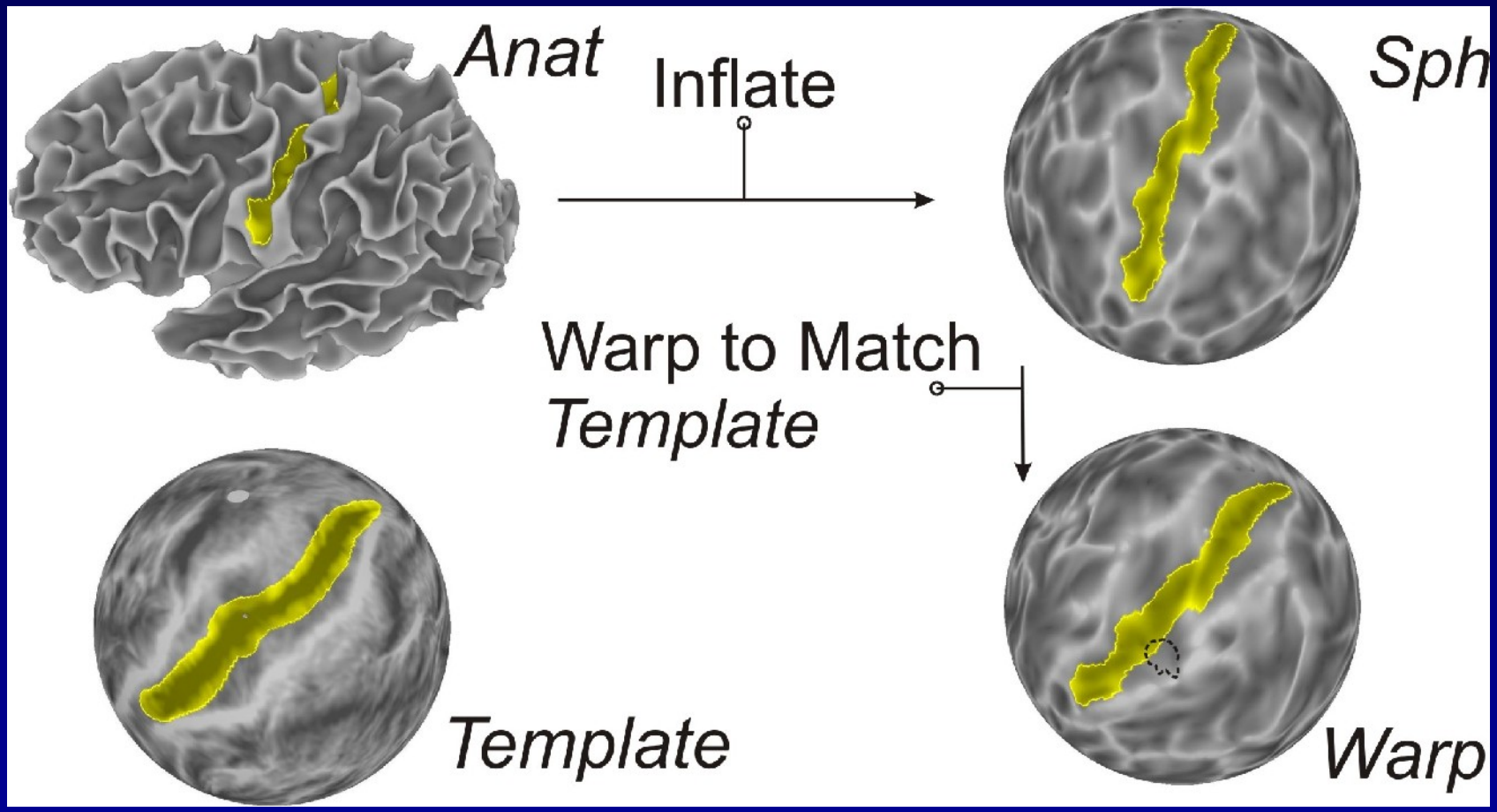






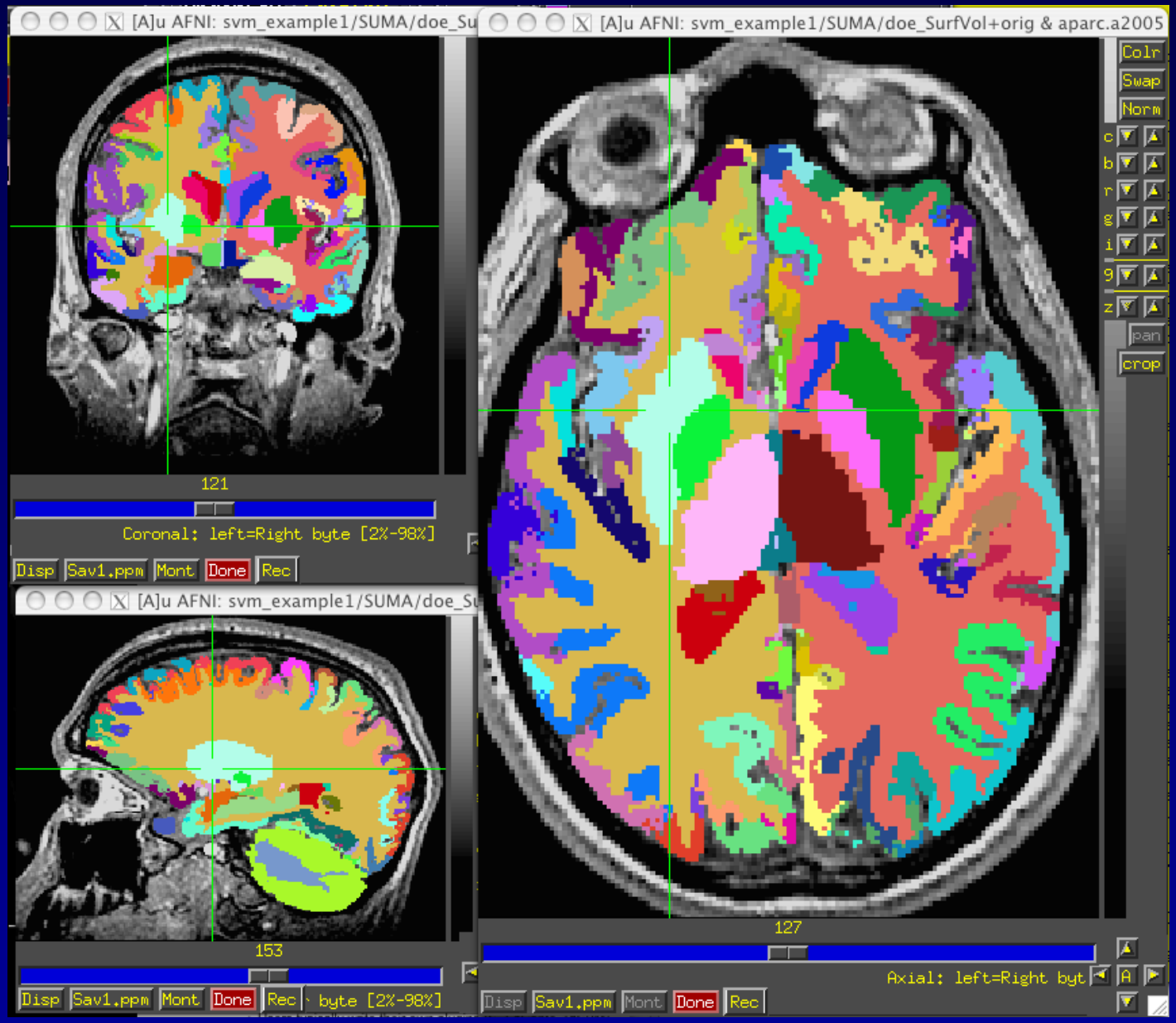
A Common Domain

- On surfaces, the domain is typically defined on a spherical template



A Common Domain

Alternately, commonality can be defined with ROIs

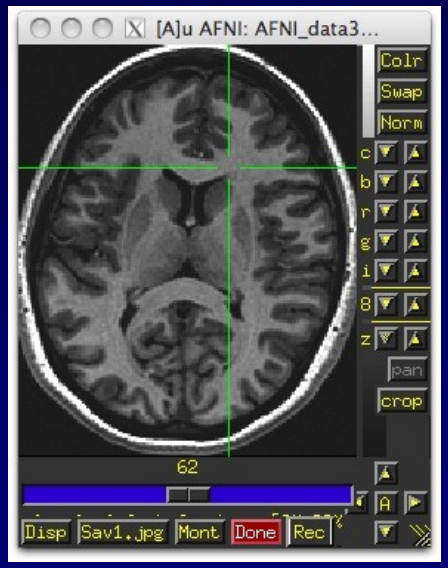


Outline

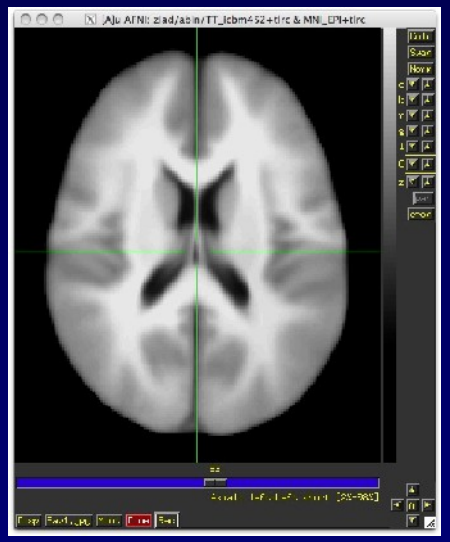
- Functional MRI
  - Volume-based analyses
  - Atlases
  - Covariates, and centering
- Anatomical MRI
  - Deformation Based Morphometry
  - Tensor Based Morphometry
  - Voxel Based Morphometry
  - Surface-based analyses thickness/morphometry
  - ROI based analyses

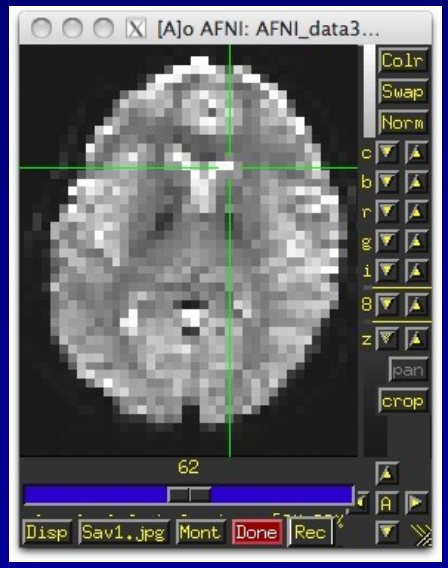
Single Subject to template

Anat



Template

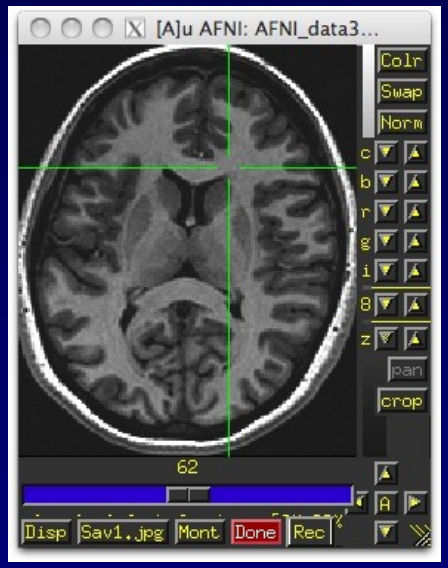




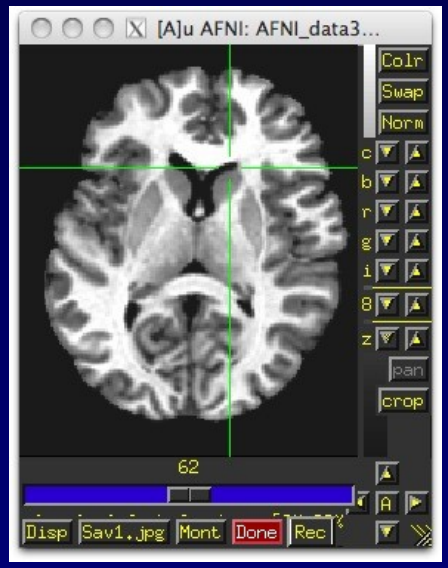
EPI

Single Subject to template

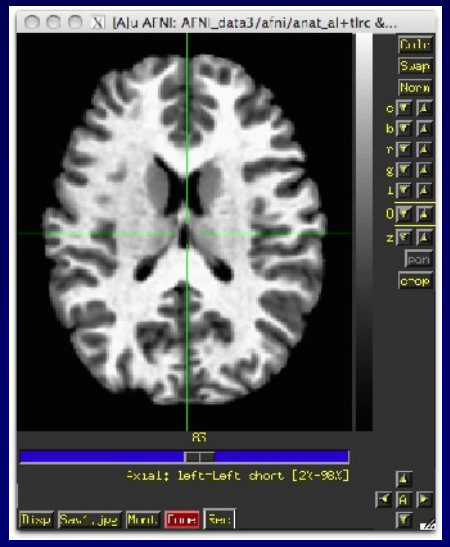
Anat

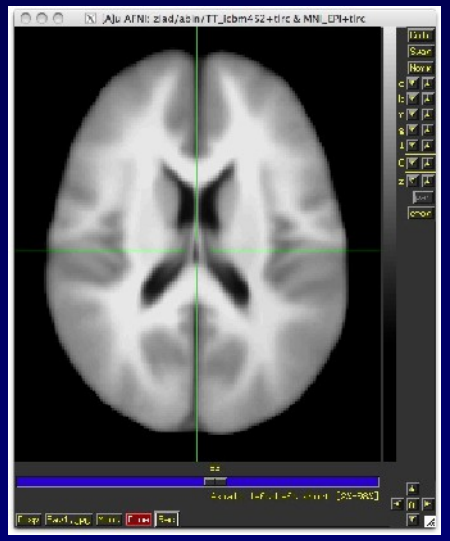


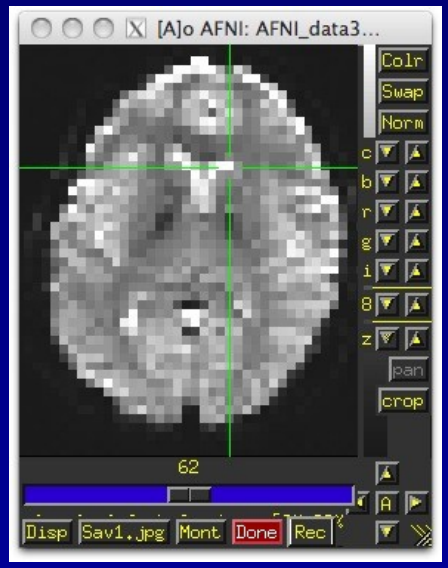
Anat aligned to EPI



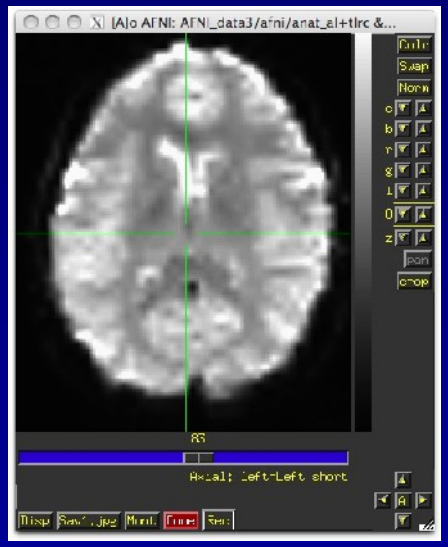
Anat aligned to Template





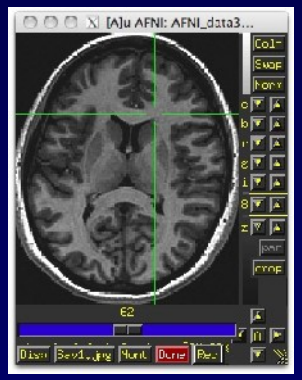


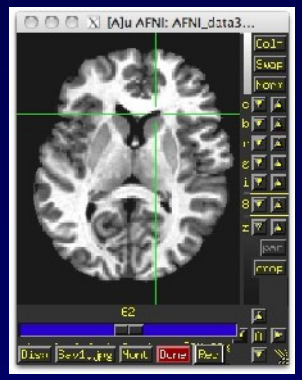
EPI

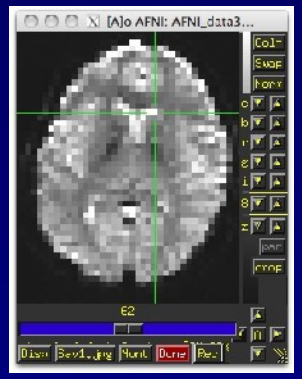


EPI aligned to Template

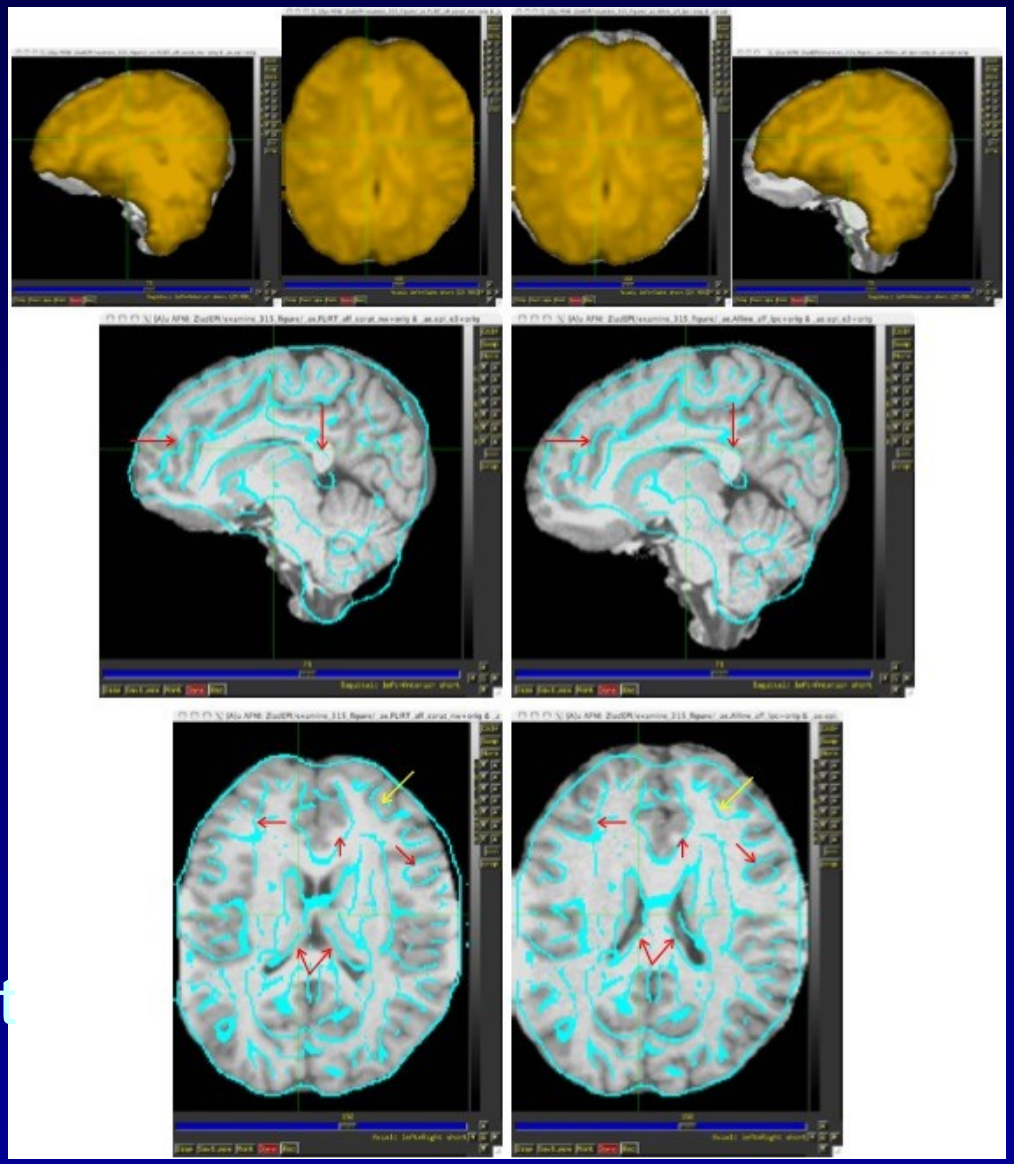
Get close to your data





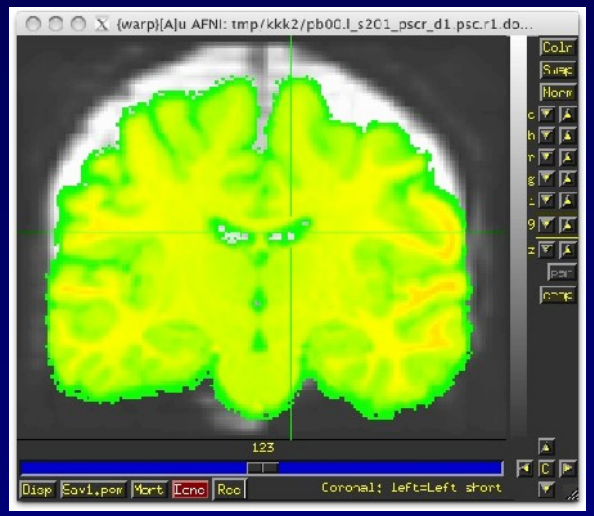


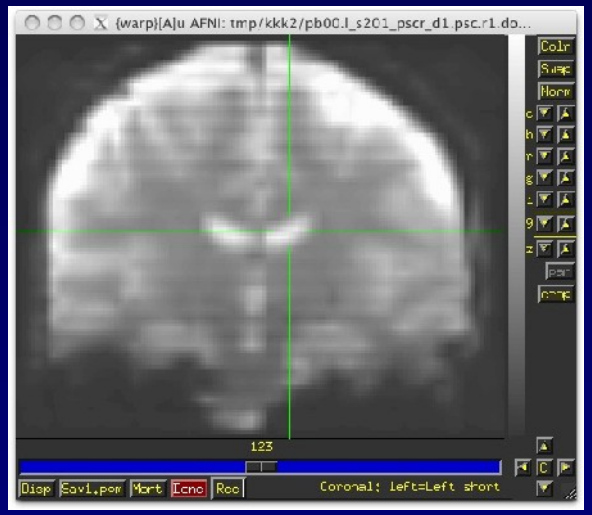
- Cursory checks not enough
- Normally, misalignment errors reduce power

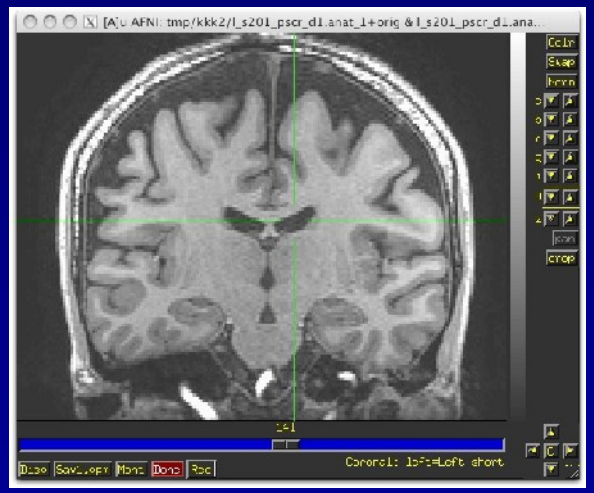


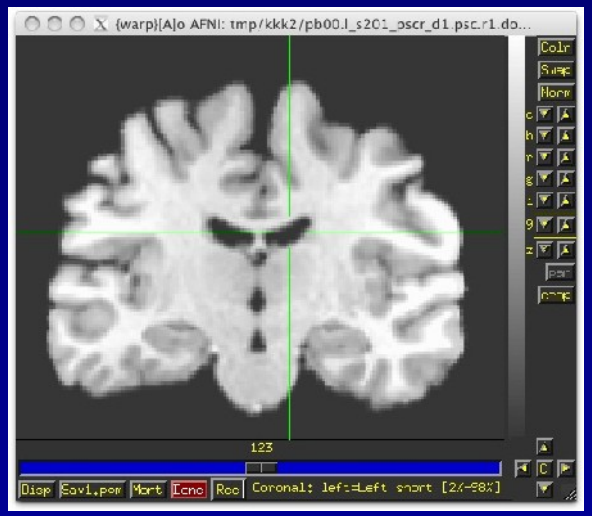
Saved by the contrast

- However, bias may result in erroneous group differences

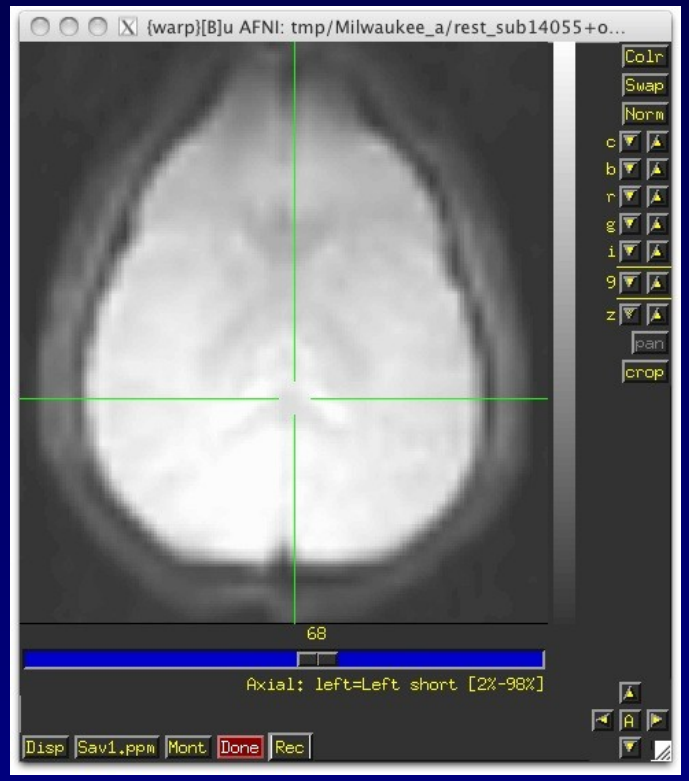


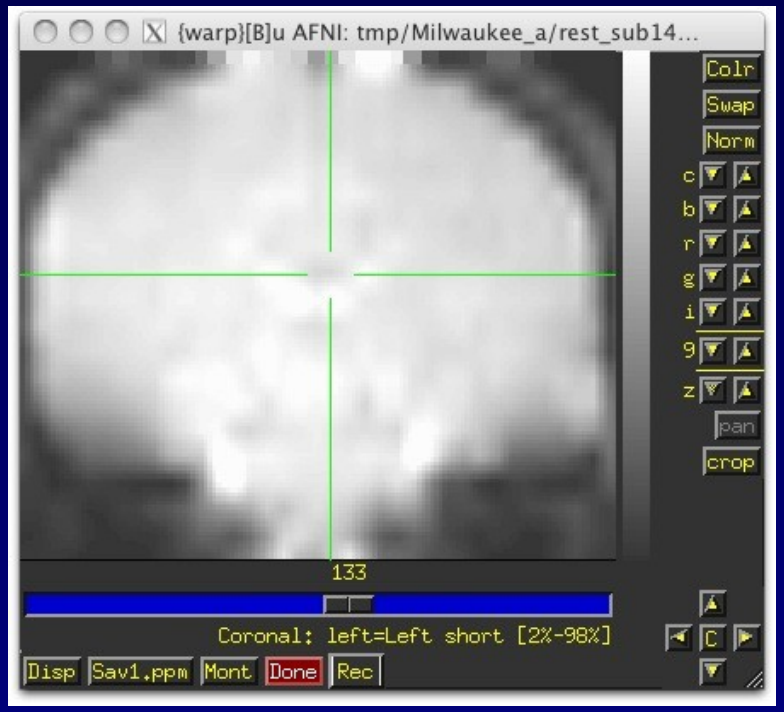






Poor contrast = sketchy alignment



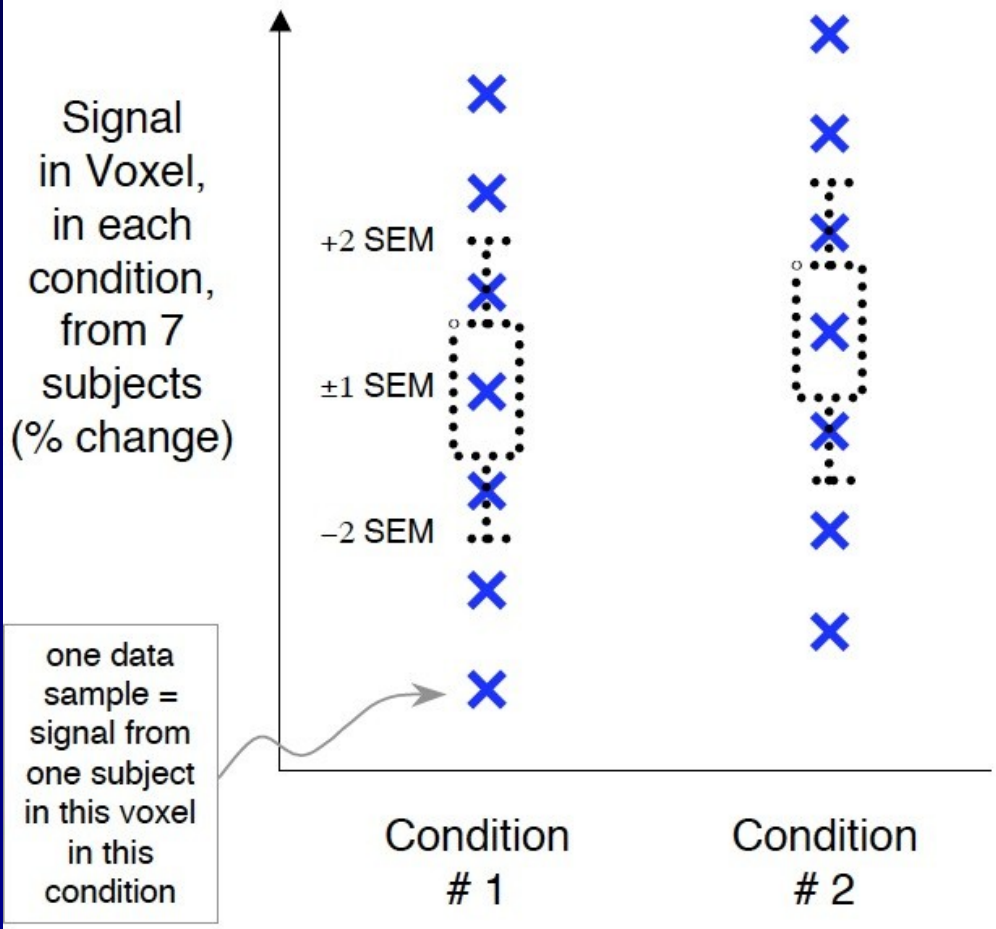


- PRESERVE pre-steady state images
- Use lower flip angles with short TR (< 2s)
  - Talk to your friendly physicist (Vinai/Souheil)

Group Statistics

- The subject of numerous hours of discourse
  - Unless physicists plan the course
  - I will touch on the ttest, mostly as a gateway to discussing the importance of covariates
- Most FMRI group tests involve massively univariate tests.
  - This means running the same type of test at each of the voxels
- With morphometric tests, multivariate tests are at time used.
    - Not to be confused with spatial multivariate methods.

Unpaired 2 Sample *t*-Test: Cartoon Data



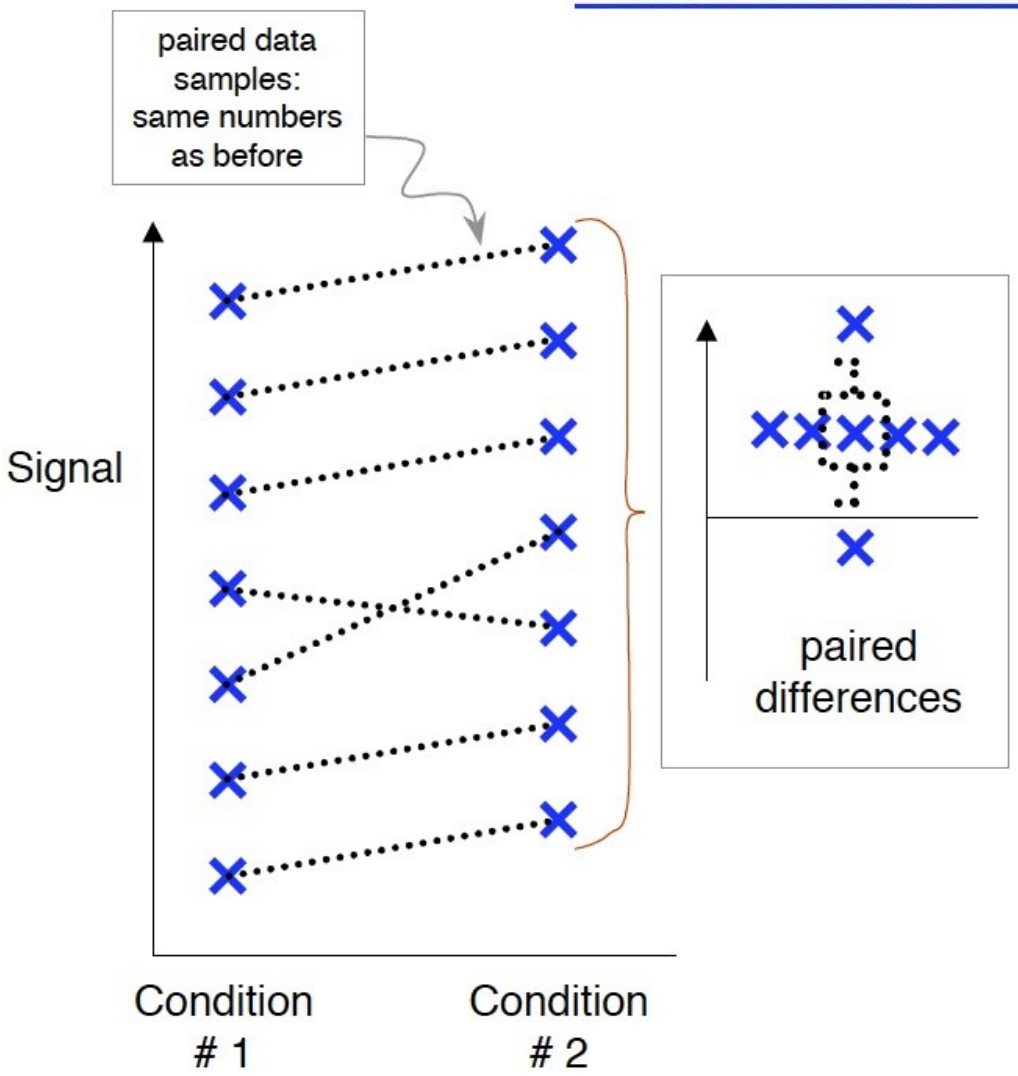
- Not significantly different!

- Condition = some way to categorize data (*e.g.*, stimulus type, drug treatment, day of scanning, subject type, …)

- SEM = Standard Error of the Mean = standard deviation of sample divided by square root of number of samples
= estimate of uncertainty in sample mean

- Unpaired *t*-test determines if sample means are "far apart" compared to size of SEM
  - *t* statistic is difference of means divided by SEM

Paired *t*-Test: Cartoon Data



- Paired means that samples in different conditions should be linked together (*e.g.*, from same subjects)

- Test determines if differences between conditions in each pair are "large" compared to SEM of the differences

- Paired test can detect systematic *intra*-subject differences that can be hidden in *inter*-subject variations

- Lesson: properly separating ***inter***-subject and ***intra***-subject signal variations can be very important!

- Significantly different!
- Condition #2 > #1, per subject

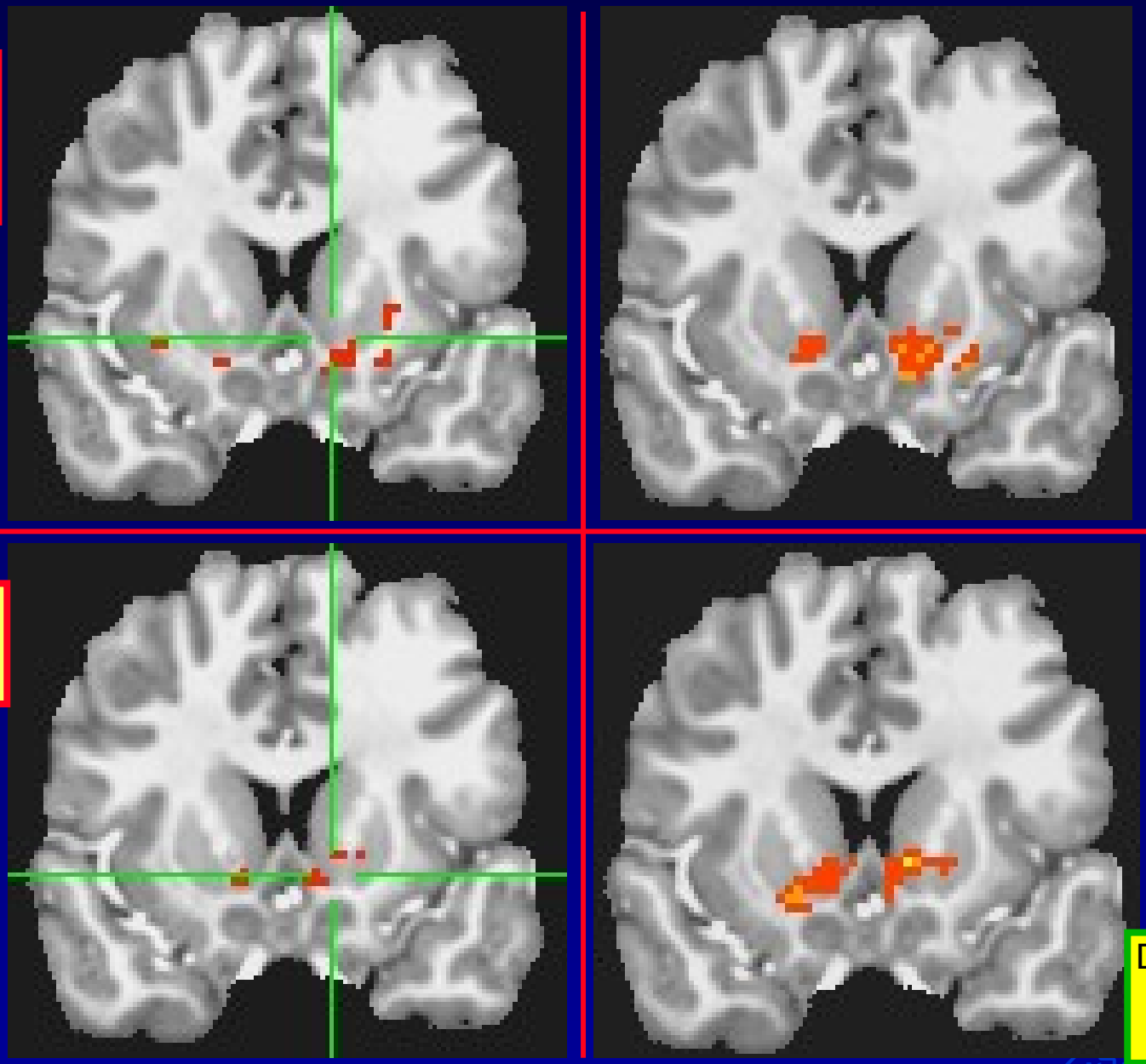
Results: 3dANOVA vs. 3dMEMA

ANOVA: 12 Control subjects

MEMA: Control subjects

ANOVA: 12 Patients

MEMA: Patients



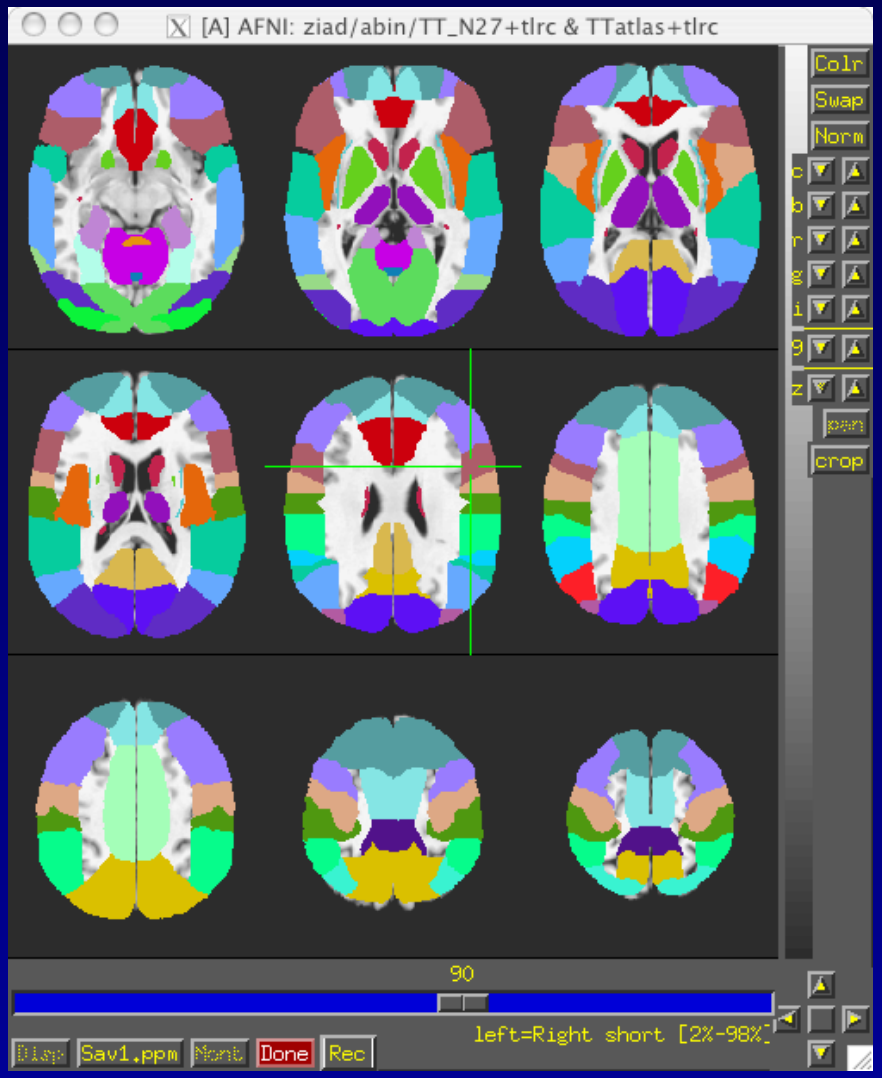
Data courtesy James Bjork NIDA/NIH

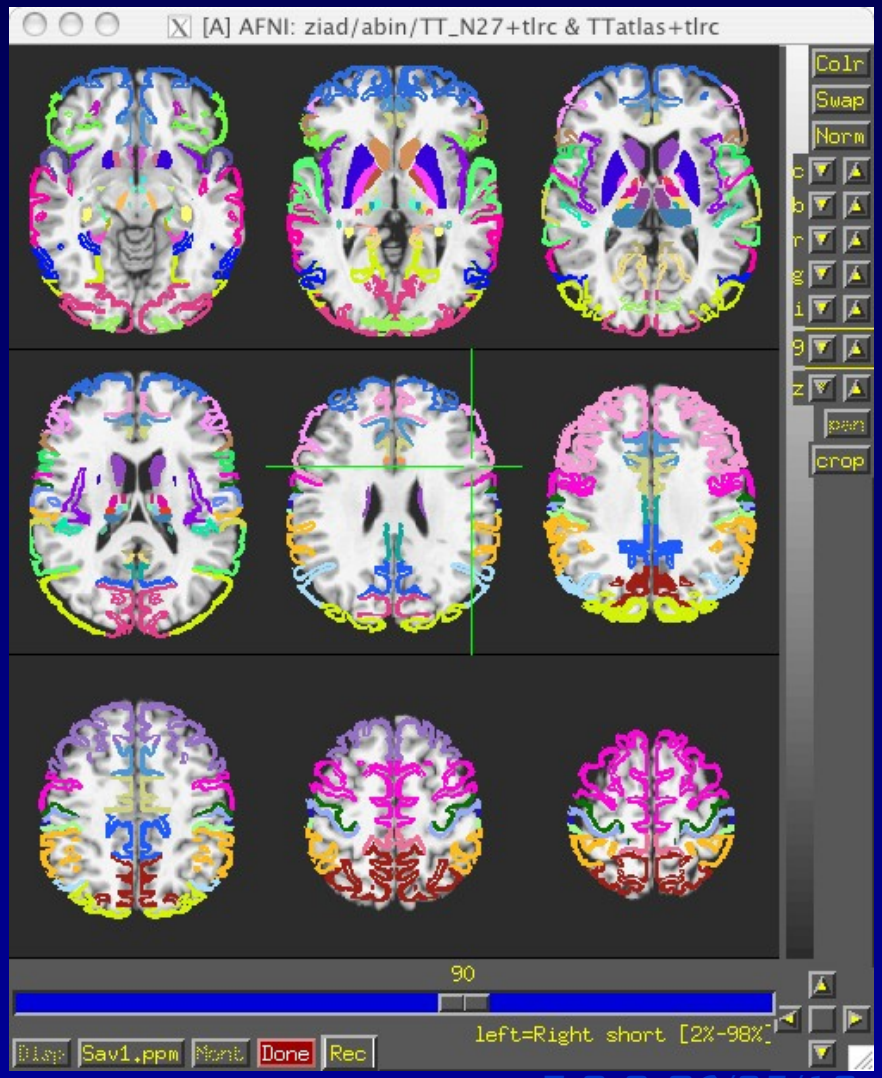
Outline

- Functional MRI
  - Volume-based analyses
  - Atlases
  - Covariates, and centering
- Anatomical MRI
  - Deformation Based Morphometry
  - Tensor Based Morphometry
  - Voxel Based Morphometry
  - Surface-based thickness/morphometry
  - ROI based analyses

The bounty of standard spaces

- TT_Daemon : Created by tracing Talairach and Tournoux brain illustrations.
  - Generously contributed by Jack Lancaster and Peter Fox of RIC UTHSCSA)

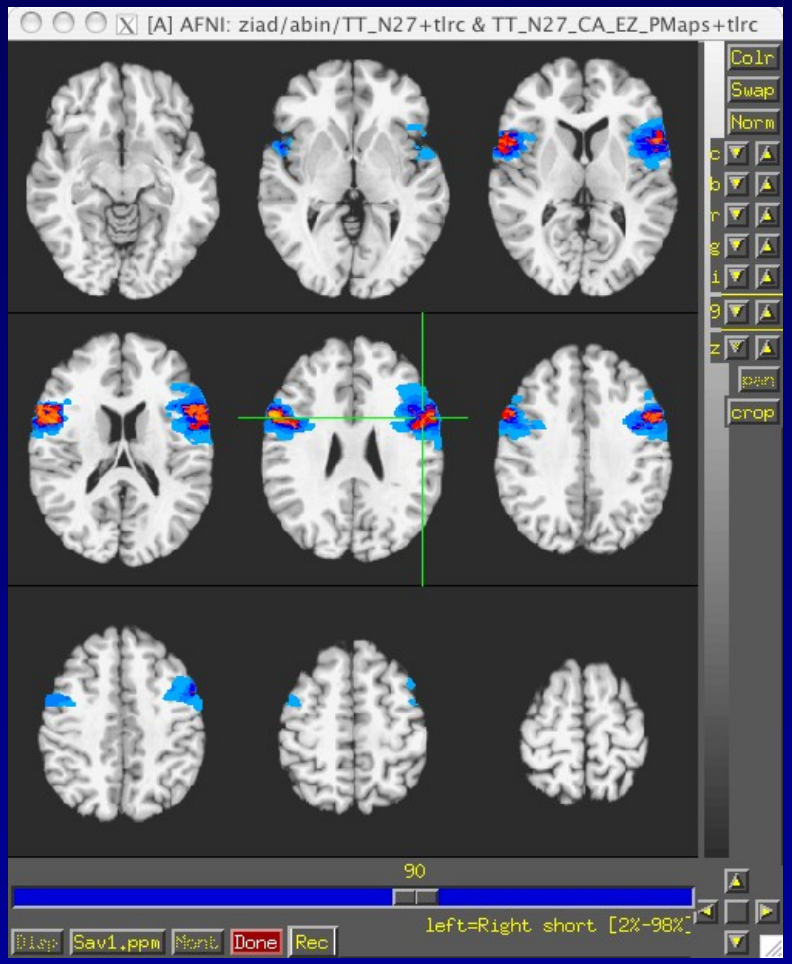


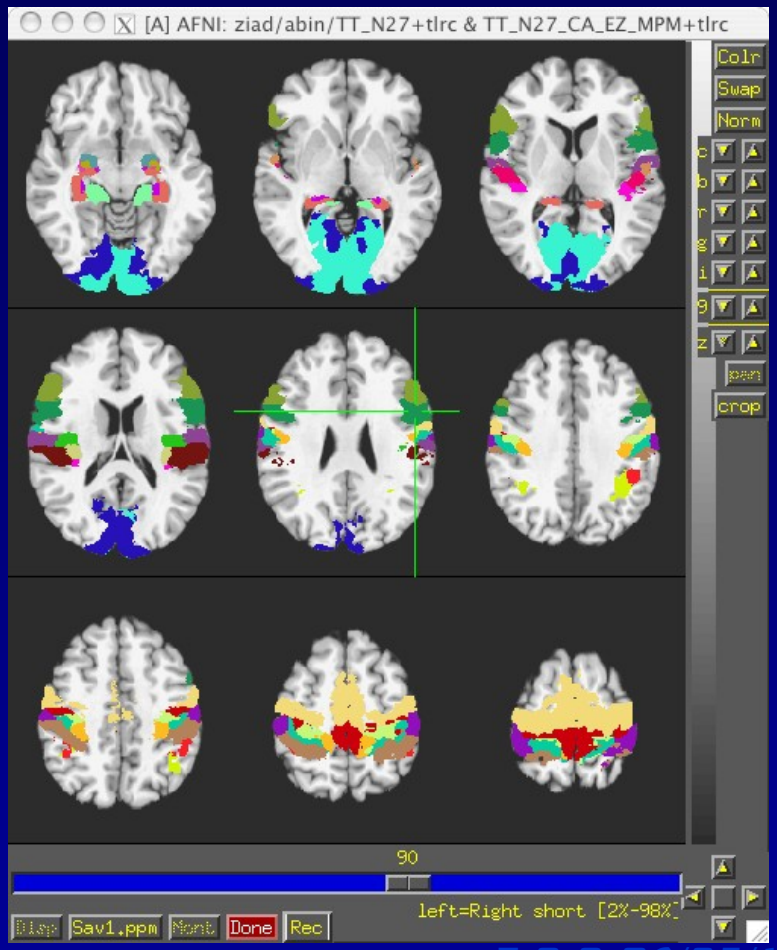


More bounty
Anatomy Toolbox: Prob. Maps, Max. Prob. Maps

- CA_N27_MPM, CA_N27_ML, CA_N27_PM: Anatomy Toolbox's atlases with some created from cytoarchitectonic studies of 10 human post-mortem brains
  - Generously contributed by Simon Eickhoff, Katrin Amunts and Karl Zilles of IME, Julich, Germany

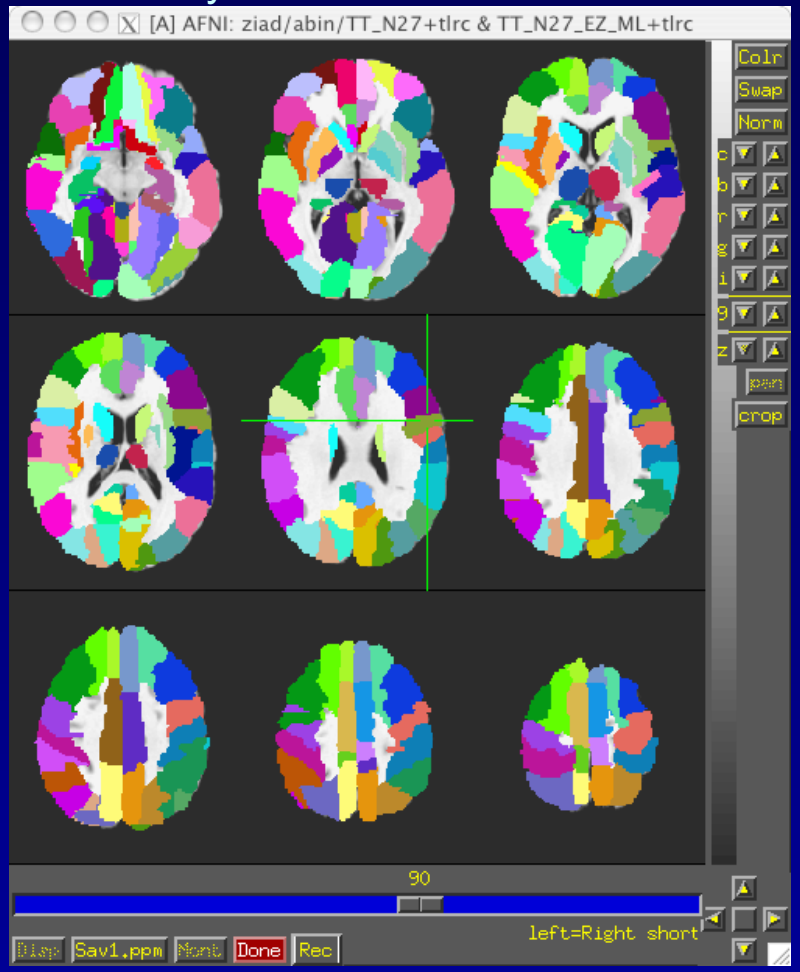
Eickhoff S. et al. 05

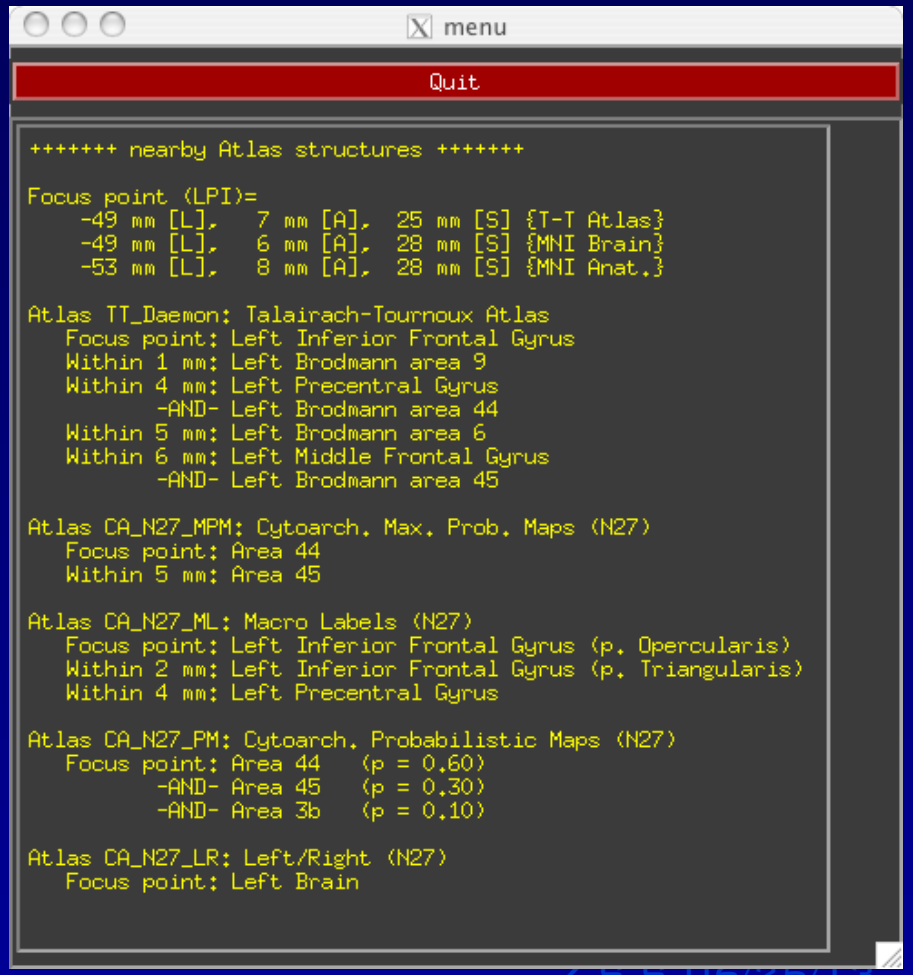




And some more
Anatomy Toolbox: MacroLabels

- CA_N27_MPM, CA_N27_ML, CA_N27_PM: Anatomy Toolbox's atlases with some created from cytoarchitectonic studies of 10 human post-mortem brains
  - Generously contributed by Simon Eickhoff, Katrin Amunts and Karl Zilles of IME, Julich, Germany





[Where am I?]

Shows you where you are in various atlases.

(works in `+orig` too, if you have a TT transformed parent)

For atlas installation, and much much more, see help in command line version:

`whereami -help`

menu

Quit

```
+++++++ nearby Atlas structures +++++++

Focus point (LPI)=
    -12 mm [L], -76 mm [P],   9 mm [S] {T-T Atlas}
    -12 mm [L], -79 mm [P],   6 mm [S] {MNI Brain}
    -13 mm [L], -84 mm [P],  16 mm [S] {MNI Anat.}

Atlas TT_Daemon: Talairach-Tournoux Atlas
   Focus point: Left  Cuneus
   Within 1 mm: Left  Brodmann area 17
   Within 2 mm: Left  Brodmann area 23
   Within 3 mm: Left  Brodmann area 18
   Within 4 mm: Left  Lingual Gyrus
   Within 6 mm: Left  Brodmann area 30

Atlas CA_N27_MPM: Cytoarch. Max. Prob. Maps (N27)
   Focus point: Area 17
   Within 7 mm: Area 18

Atlas CA_N27_ML: Macro Labels (N27)
   Focus point: Left Calcarine Gyrus
   Within 2 mm: Left Cuneus
   Within 3 mm: Left Superior Occipital Gyrus
   Within 7 mm: Left Middle Occipital Gyrus
           -AND- Left Linual Gyrus

Atlas CA_N27_PM: Cytoarch. Probabilistic Maps (N27)
   Focus point: Area 17   (p = 0.90)
           -AND- Area 18   (p = 0.10)

Atlas CA_N27_LR: Left/Right (N27)
   Focus point: Left Brain
```

The blob table

- In this example, 4 ROI clusters were found that fit the criteria designated by the **`3dclust`** command. Below is an explanation of the output:

0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
#Volume	CM RL	CM AP	CM IS	minRL	maxRL	minAP	maxAP	minIS	maxIS	Mean	SEM	Max Int	MI RL	MI AP	MI IS
#------	-----	-----	-----	-----	-----	-----	-----	-----	-----	-------	-------	-------	-----	-----	-----
387	-37.2	29.1	1.4	-61.4	-16.4	-1.3	58.7	-19.4	26.1	16.064	0.5	94.727	-38.9	28.7	-1.9
348	34.2	31.3	3.1	9.8	47.3	-1.3	58.7	-12.4	26.1	16.24	0.5369	80.252	32.3	28.7	1.6
75	-26.6	24.8	37.8	-42.7	-20.2	17.5	32.5	26.1	54.1	12.647	0.5967	29.788	-23.9	28.7	40.1
66	16.8	26.3	40.9	9.8	24.8	17.5	36.2	29.6	54.1	11.69	0.4156	22.931	17.3	21.2	40.1
#------	-----	-----	-----	-----	-----	-----	-----	-----	-----	-------	-------	-------	-----	-----	-----
# 876	-3.7	29.6	6.9							15.512	0.3164				

- Volume: Size of each cluster volume
- CM RL: Center of mass (CM) for each cluster in the Right-Left direction
- CM AP: Center of mass for each cluster in the Anterior-Posterior direction
- CM IS: Center of mass for each cluster in the Inferior-Superior direction
- minRL,maxRL: Bounding box for cluster, min & max coordinates in R-L direction
- minAP,maxAP: Bounding box for cluster, min & max coordinates in A-P direction
- minIS, maxIS: Bounding box for cluster, min & max coordinates in I-S direction
- Mean: Mean value for each volume cluster
- SEM: Standard error of the mean for the volume cluster
- Max Int: Maximum Intensity value for each volume cluster
- MI RL: Maximum Intensity value in the R-L direction of each volume cluster
- MI AP: Maximum intensity value in the A-P direction of each volume cluster
- MI IS: Maximum intensity value in the I-S direction of each volume cluster

Know the anatomy, appreciate limitation of atlases

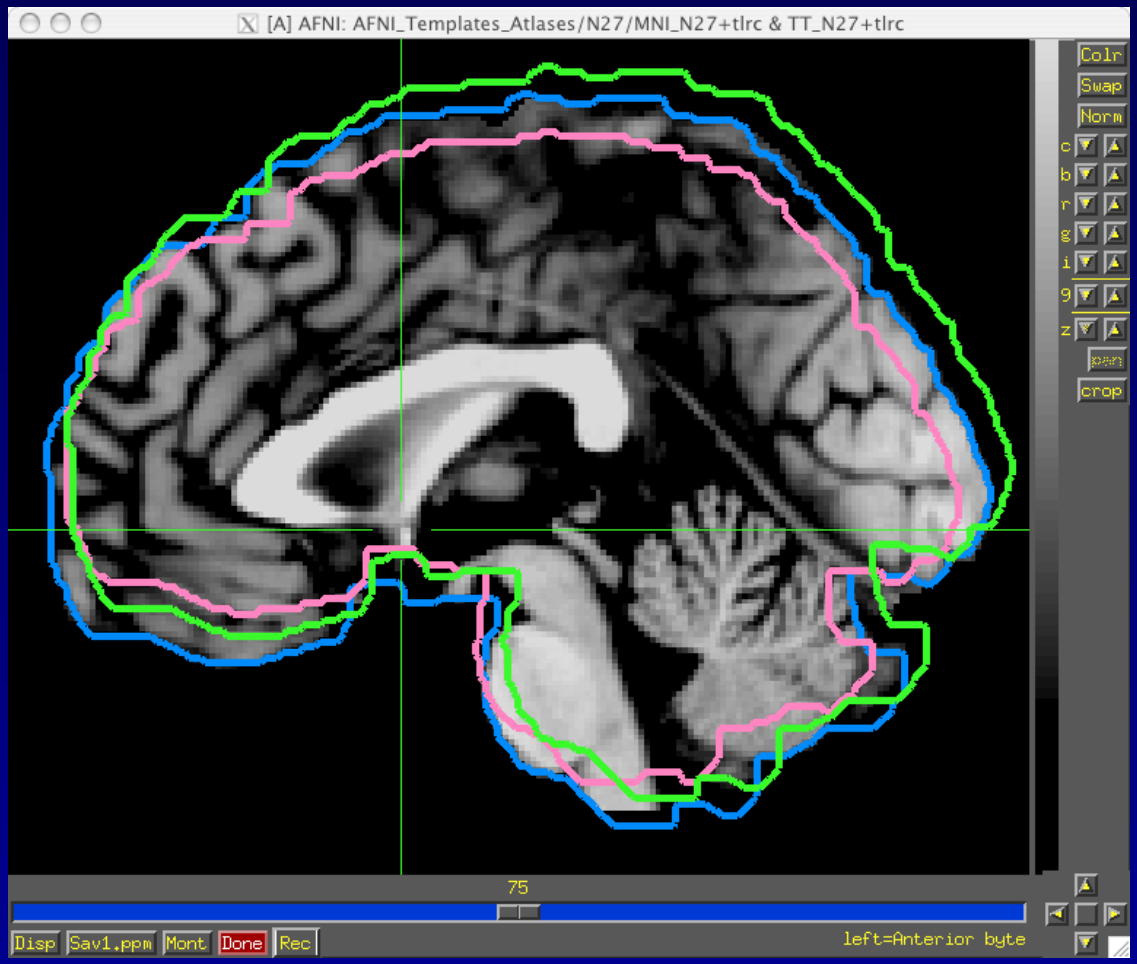
- More than a coordinate to your blob.
- Consider describing how a blob overlaps atlas areas.
- Specify template, and space
- Look at data, know the anatomy

```
Intersection of ROI (valued 1) with atlas TT_Daemon (sb0):
   89.2 % overlap with Middle Occipital Gyrus, code 33
   6.7  % overlap with Middle Temporal Gyrus, code 35
   -----
   95.9 % of cluster accounted for.

Intersection of ROI (valued 1) with atlas TT_Daemon (sb1):
   19.5 % overlap with Brodmann area 37, code 113
   1.5  % overlap with Brodmann area 19, code 96
   -----
   21.0 % of cluster accounted for.

++    195 voxels in atlas-resampled mask
Intersection of ROI (valued 1) with atlas CA_N27_MPM (sb0):
   1.5  % overlap with hOC5 (V5 / MT+), code 110
   -----
   1.5  % of cluster accounted for.

++    195 voxels in atlas-resampled mask
Intersection of ROI (valued 1) with atlas CA_N27_ML (sb0):
   61.0 % overlap with Right Middle Occipital Gyrus, code 52
   20.0 % overlap with Right Middle Temporal Gyrus, code 86
   -----
   81.0 % of cluster accounted for.
```

- **`whereami`** can report on the overlap of ROIs with atlas-defined regions

```
whereami -omask anat_roi+tlrc
```

The curse of multiple spaces



TLRC
MNI
MNI-Anat.

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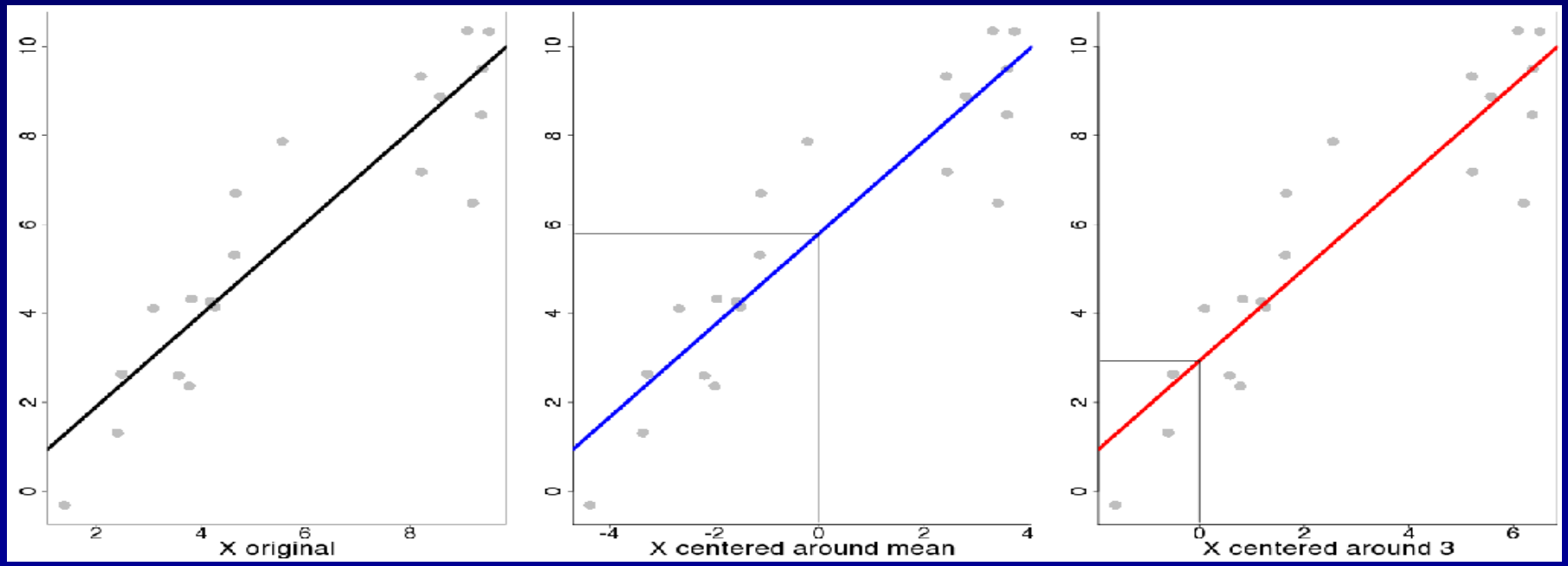
  - ROI based analyses

Covariates

- Covariates
  - May or may not be of direct interest
  - Confounding, nuisance, or interacting variables
  - Subject-level
  - Continuous or discrete
  - One-sample model $y_i = \alpha_0 + \alpha_1 x_i + \delta_i + \varepsilon_i$, for ith subject
  - Two-sample model $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + \varepsilon_i$
- Examples
  - Age, IQ, brain volume, cortex thickness
  - Behavioral data

Handling covariates: one group

- Centering:
  - $y_i = \alpha_0 + \alpha_1 x_i + \delta_i + \varepsilon$, for ith subject
  - Interested in group effect α_0 (x=0) while controlling (partialling out) x
  - α_1 - slope (change rate): % signal change per unit of x
  - Interpretability: group effect α_0 at what value of x: mean or any other value?

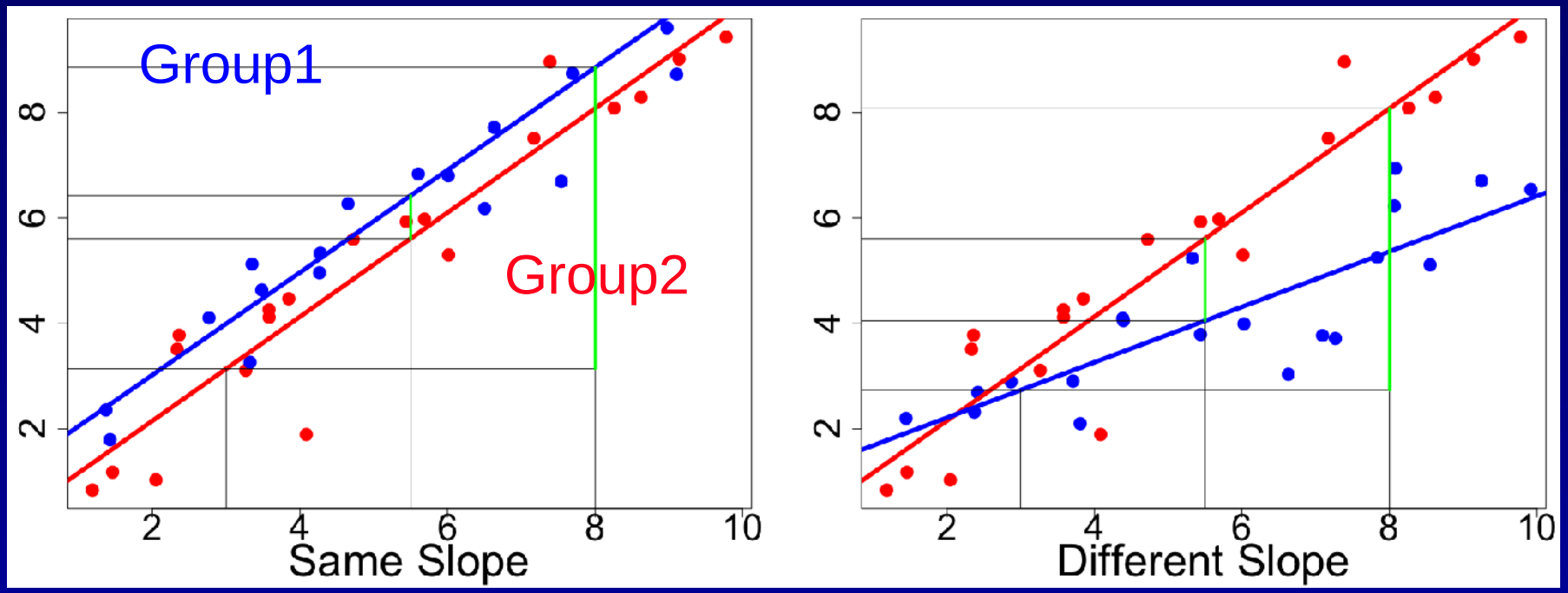


Covariates: trickier with > 1 group

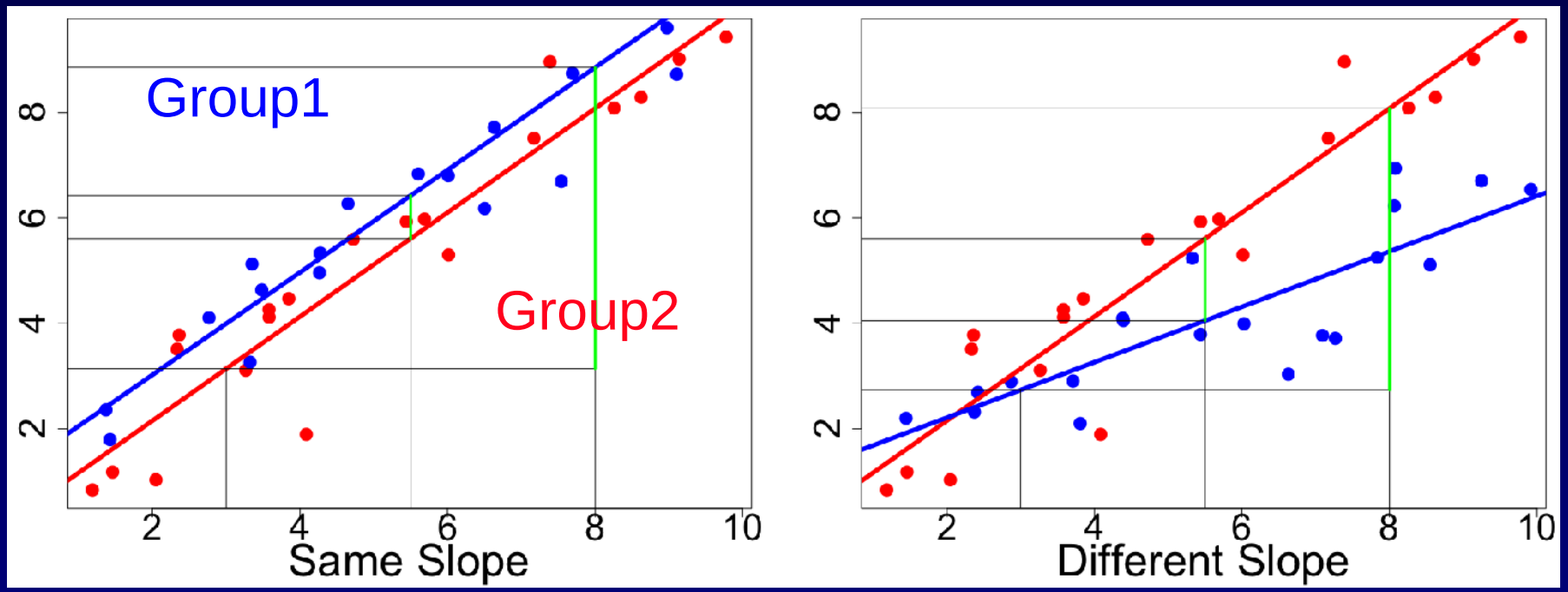
- Center and slope
  - $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + \varepsilon_i$, for ith subject
    - x_1: group indicator
    - x_2: covariate
    - x_3: group effect in slope (interaction btw group and covariate)
  - What we're interested in
    - Group effects α_0 and α_1 while controlling covariate
  - Interpretability
    - Center
      - Group effect α_0 and α_1 at what covariate value?
      - Same or different center across groups?
    - Slope
      - same ($\alpha_3=0$) or different ($\alpha_3 \neq 0$) slope across groups

Covariates: scenarios with 2 groups

- Center and slope
  - $y_i = \alpha_0 + \alpha_1 x_{1i} + \alpha_2 x_{2i} + \alpha_3 x_{3i} + \delta_i + e_i$, for ith subject
  - Interpretability
    - Same center and same slope ($\alpha_3=0$)
    - Different center with same slope ($\alpha_3=0$)
    - Same center with different slope ($\alpha_3 \neq 0$)
    - Different center and different slope ($\alpha_3 \neq 0$)

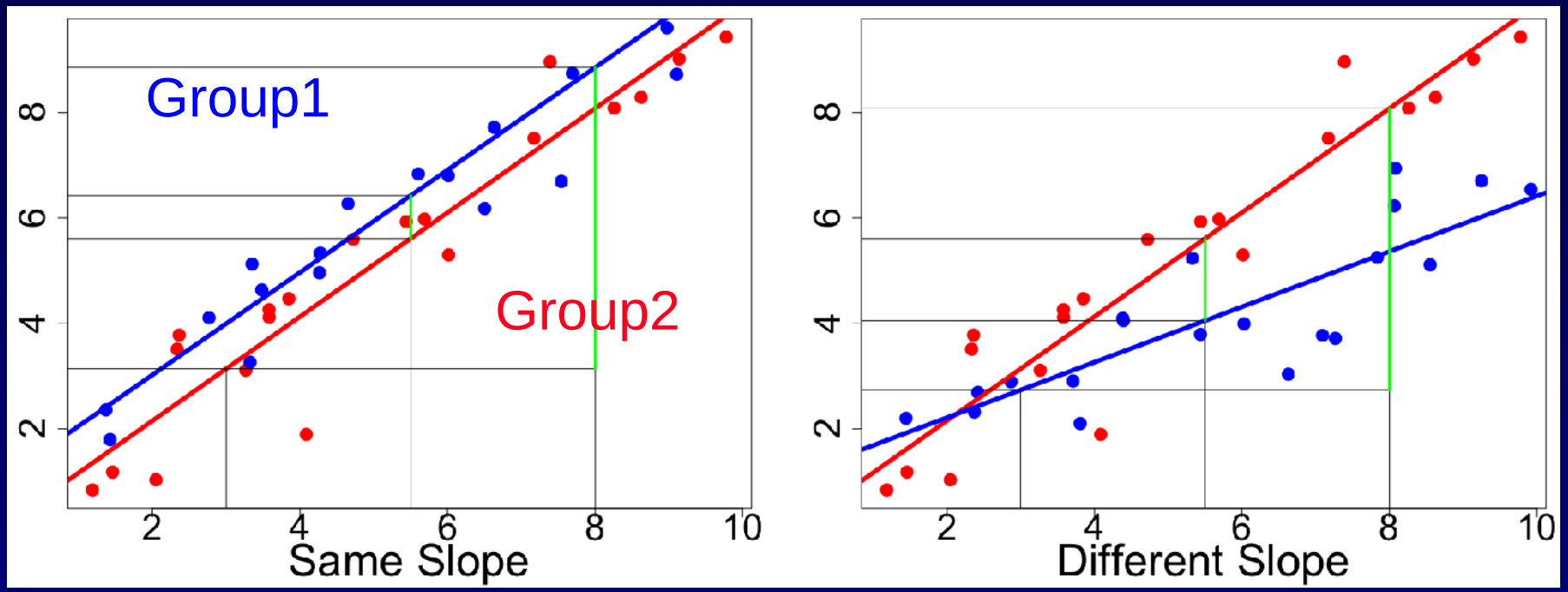


Covariates: scenarios with 2 groups



- If covariate for each group is centered on same value
  - Group effect constant regardless of that value
- Else group effect depends on centering difference
- When slopes are different:
  - Group effect depends on covariate value, even when centering is properly done

Covariates: scenarios with 2 groups



- Just "Regressing Out" a covariate is not enough!
  - Need to center properly
  - Need to consider covariate value (if $_3$ significant)

Outline

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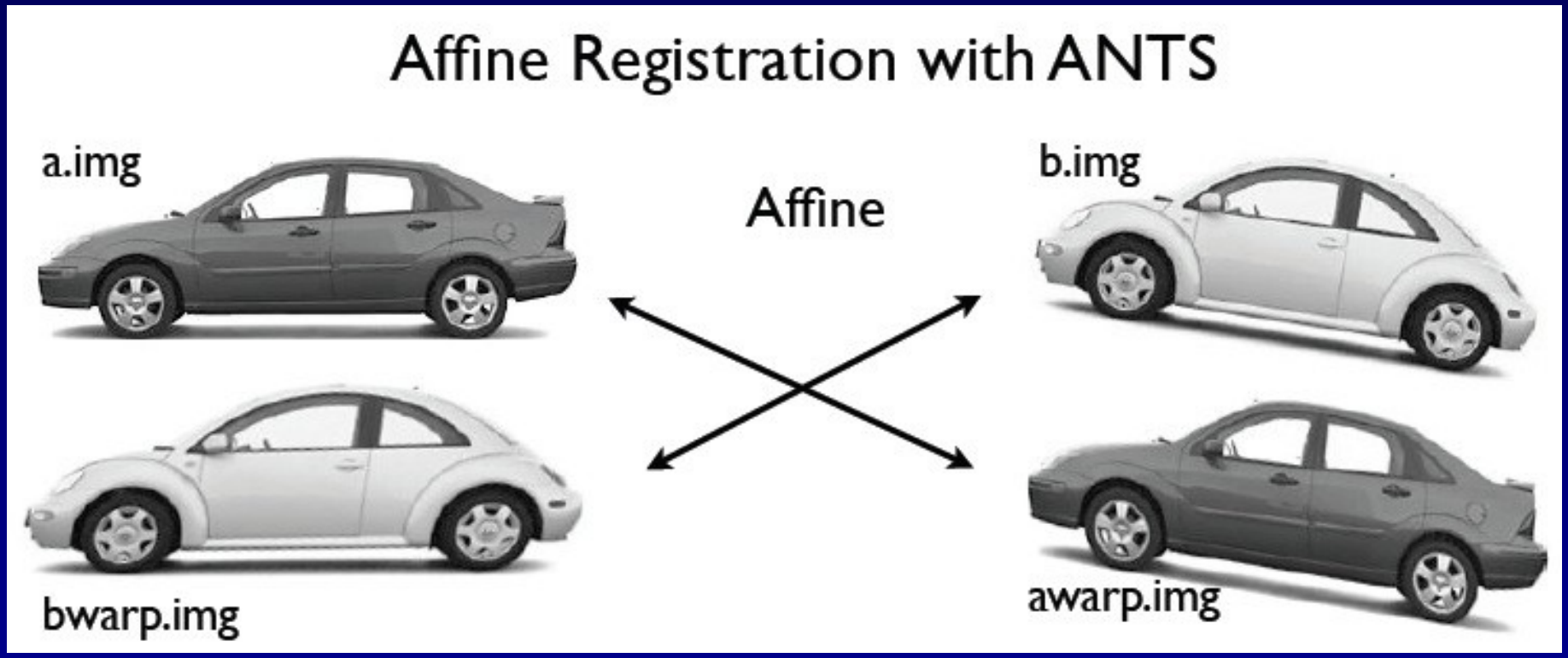
  - ROI based analyses

Linear, and non linear registration

- With FMRI affine registration is sufficient



From: Practical Guide to ANTS, Penn Image Computing and Science Lab
Brian B. Avants, Nick Tustison and Gang Song

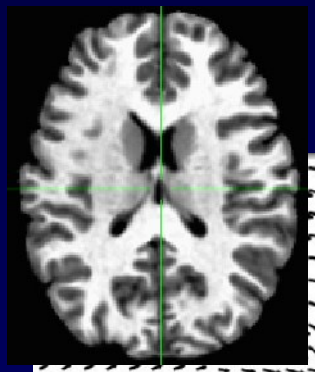
Linear, and non linear registration

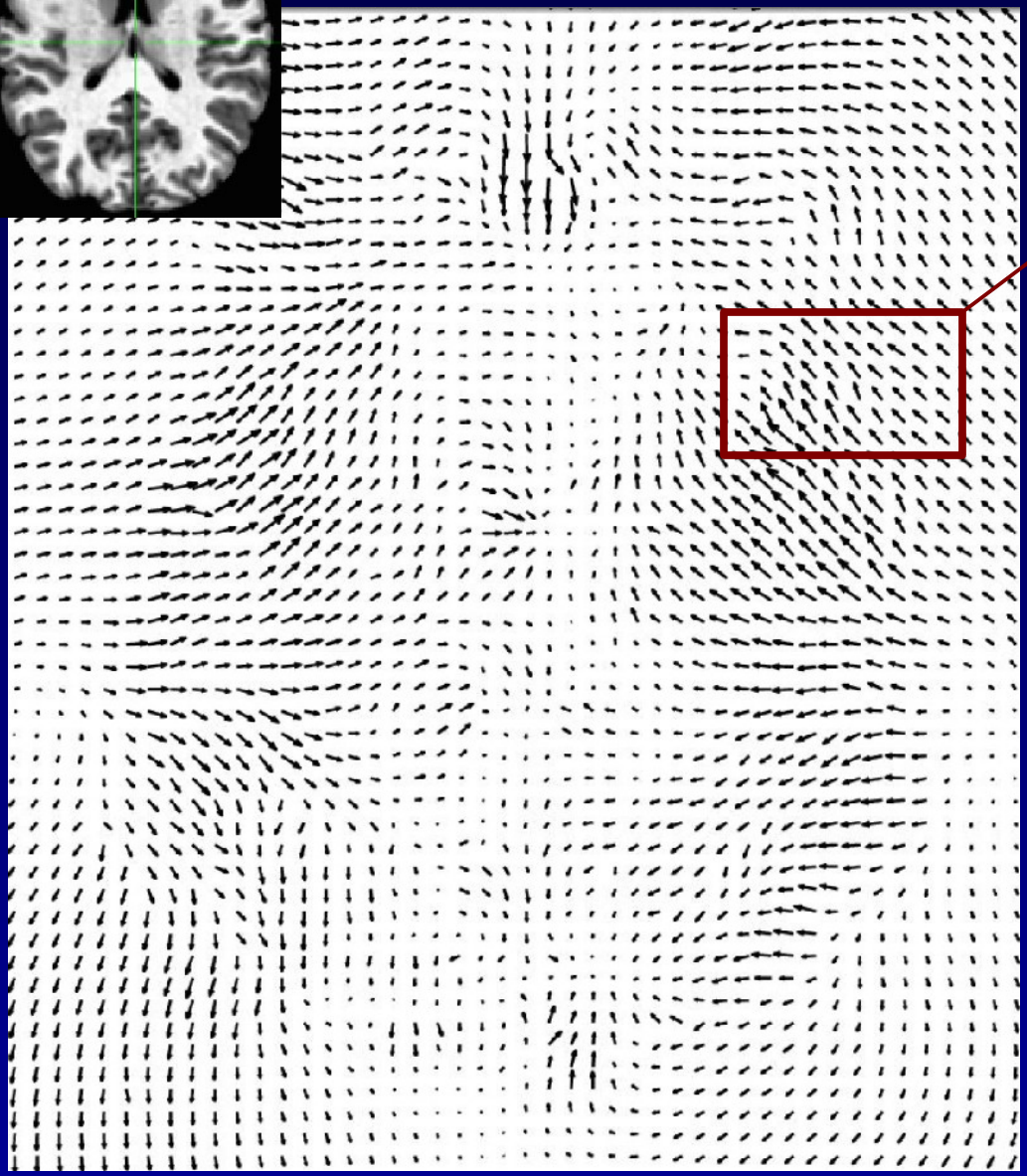
- For anatomical morphometrics, non linear registration is de rigeur

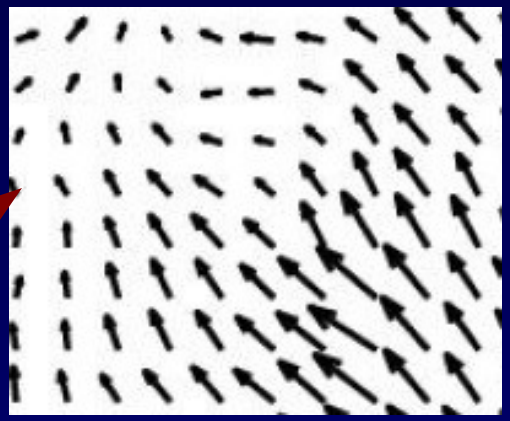
Figure 4: This example shows the degree to which the beetle (b.img) may be deformed to the ford (a.img) under different transformation models. Left to right increases the degrees of freedom in the mapping and thus the registration accuracy.

From: Practical Guide to ANTS, Penn Image Computing and Science Lab
Brian B. Avants, Nick Tustison and Gang Song

Deformations, and DBM



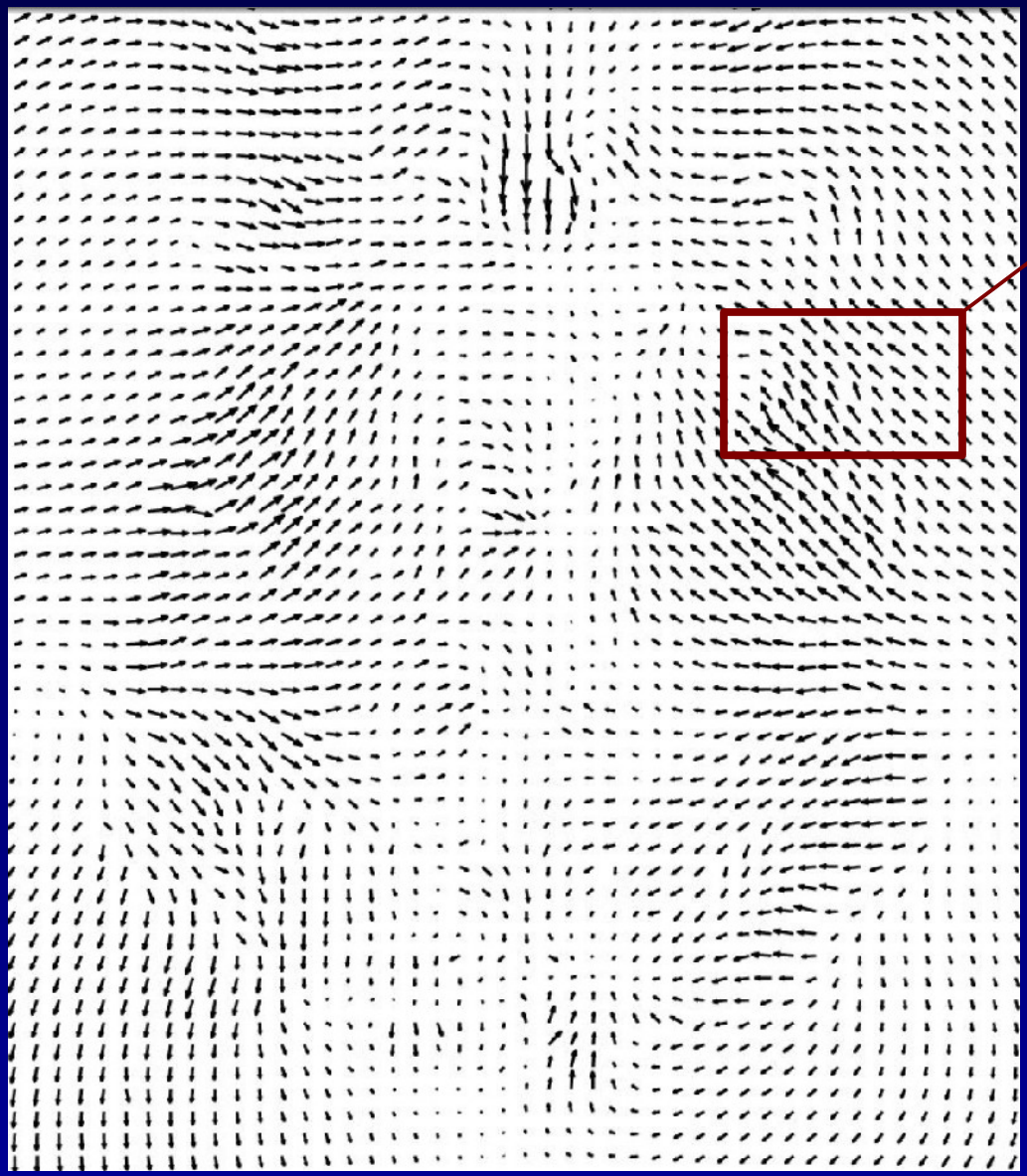


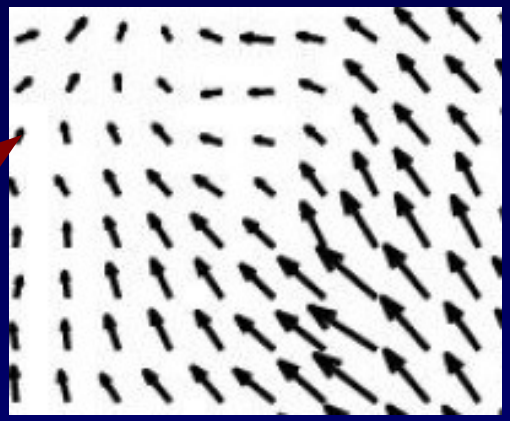


- Deformations can be compared between groups
- Tests can be done at each voxel, or on summary global deformation descriptors
- However, tests reflect changes in relative position, rather than shape

Image from: Functional Imaging, John Ashburner & Karl J. Friston

Deformation, and Jacobian Fields





$$\mathbf{J} = \begin{bmatrix} \partial y_1/\partial x_1 & \partial y_1/\partial x_2 & \partial y_1/\partial x_3 \\ \partial y_2/\partial x_1 & \partial y_2/\partial x_2 & \partial y_2/\partial x_3 \\ \partial y_3/\partial x_1 & \partial y_3/\partial x_2 & \partial y_3/\partial x_3 \end{bmatrix}$$

Image from: Functional Imaging,
John Ashburner & Karl J. Friston

Jacobian Matrix

- Describes local spatial partial derivatives of deformation
- Its determinant describes local expansion or compression
- Decomposition of Jacobian can also yield stretching, shearing, and rotation.

$$\mathbf{J} = \begin{bmatrix} \partial y_1/\partial x_1 & \partial y_1/\partial x_2 & \partial y_1/\partial x_3 \\ \partial y_2/\partial x_1 & \partial y_2/\partial x_2 & \partial y_2/\partial x_3 \\ \partial y_3/\partial x_1 & \partial y_3/\partial x_2 & \partial y_3/\partial x_3 \end{bmatrix}$$

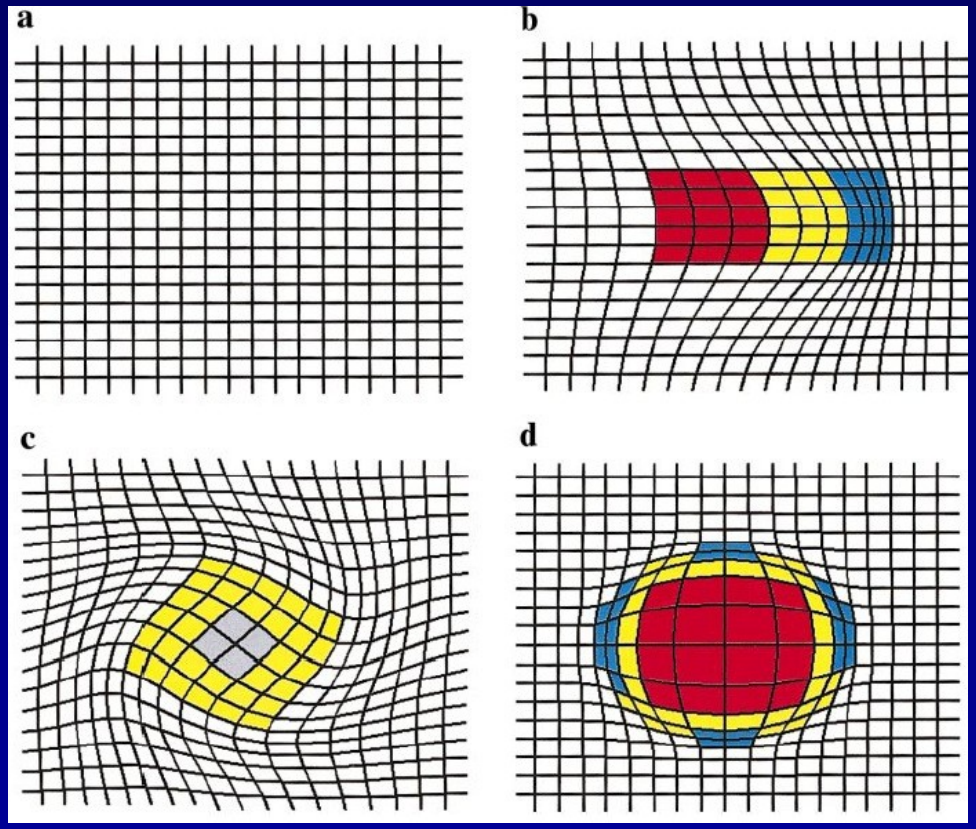


FIG. 2. From Chung et al. Neuroimage 2001

Red, volume increase;
Blue, volume decrease;
Gray, rotation;
Yellow, translation.

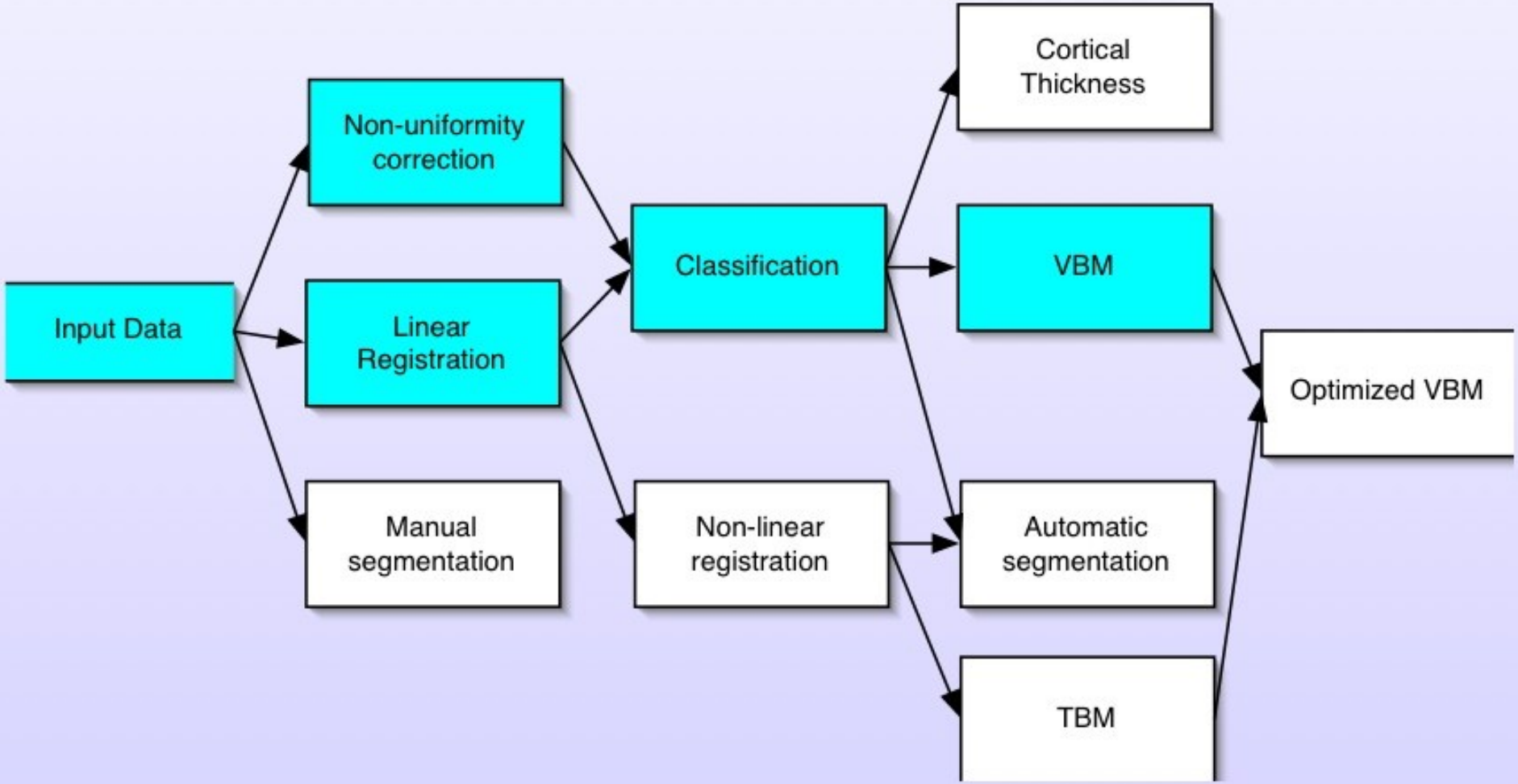
TBM

- Stats based on the tensor field
  - Is there volume expansion/compression ?
  - Can also include strain, translation, rotation.
    - Requires multivariate stats
- TBM describes shape differences, rather than positional differences as the deformations would.
- If perfect homologies were possible, then deformations and their gradients would capture differences at large, medium, and small spatial scales.
  - However this is not possible even with infinite degrees of freedom. Brains are not exactly alike.

VBM

- Considered a tool to allow small scale morphology, looking for local voxel proportion of a tissue type.
  - Older versions looked for local density/concentration but that is no longer advocated
    - USE NEWEST recommendations in this field. For example use SPM8, not SPM99 – even if your blobs disappear

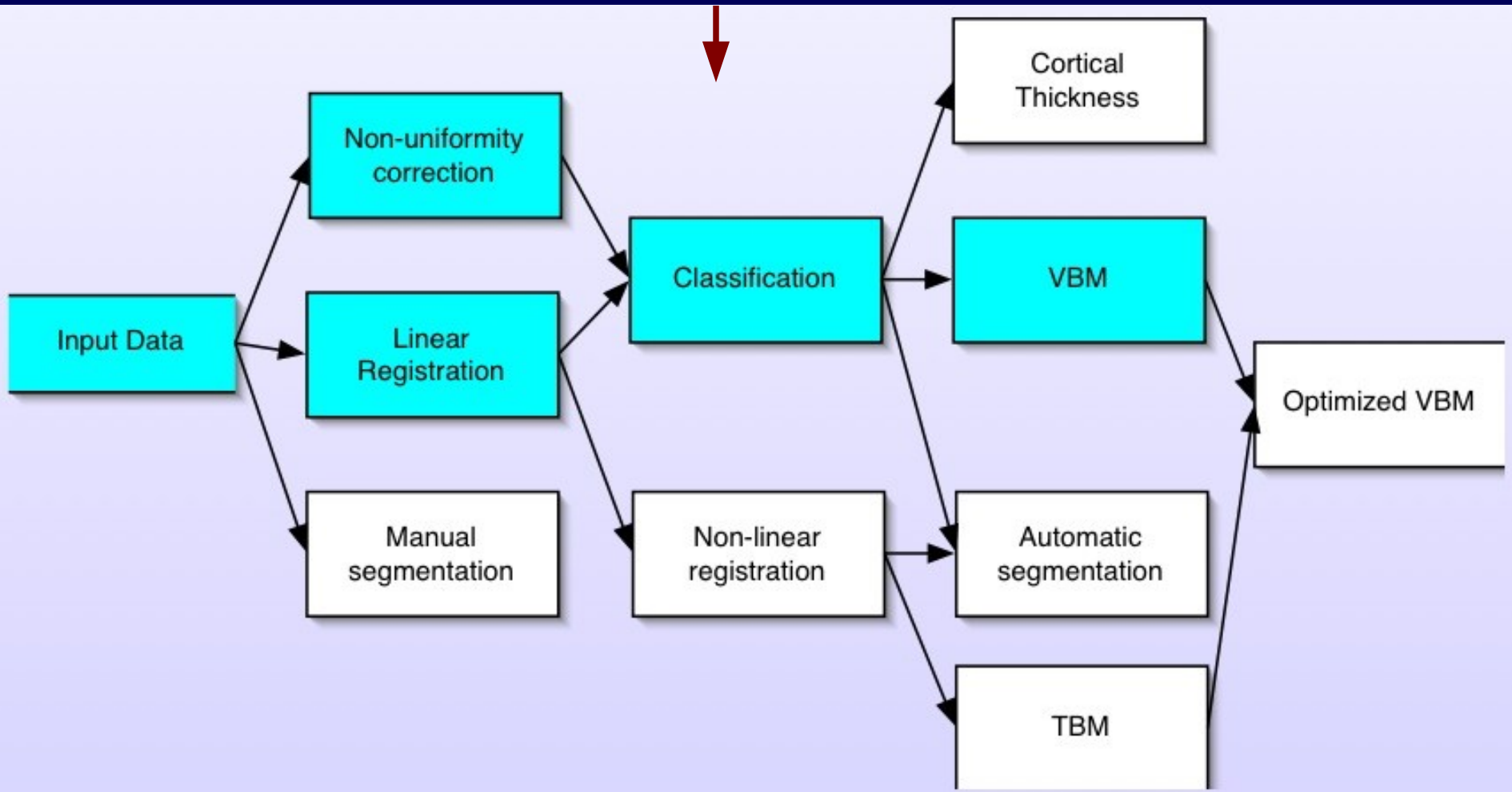
VBM of Yore



Courtesy of Jason Lerch

VBM of Yore

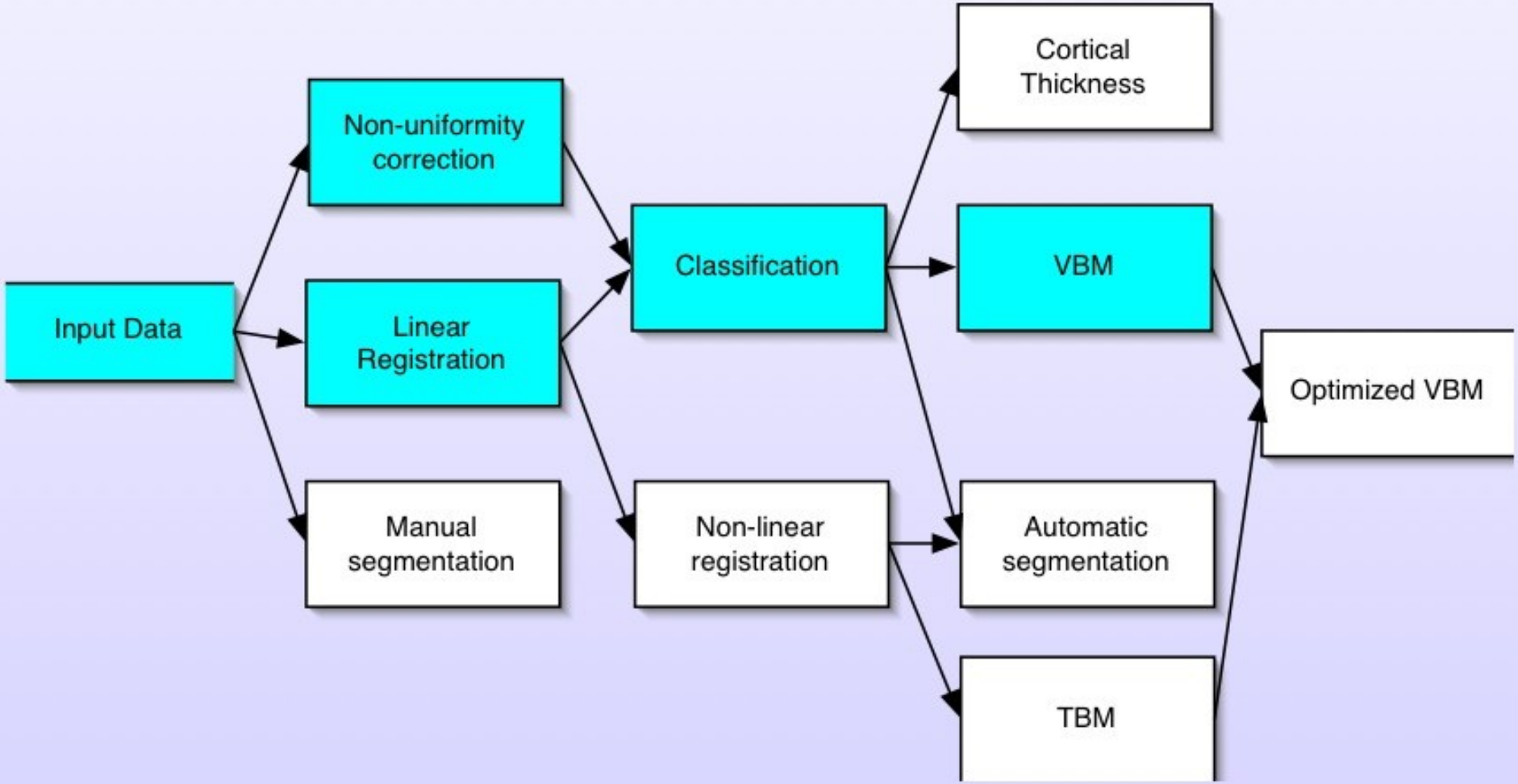
Template Choice
Warping DOF



Courtesy of Jason Lerch

VBM of Yore

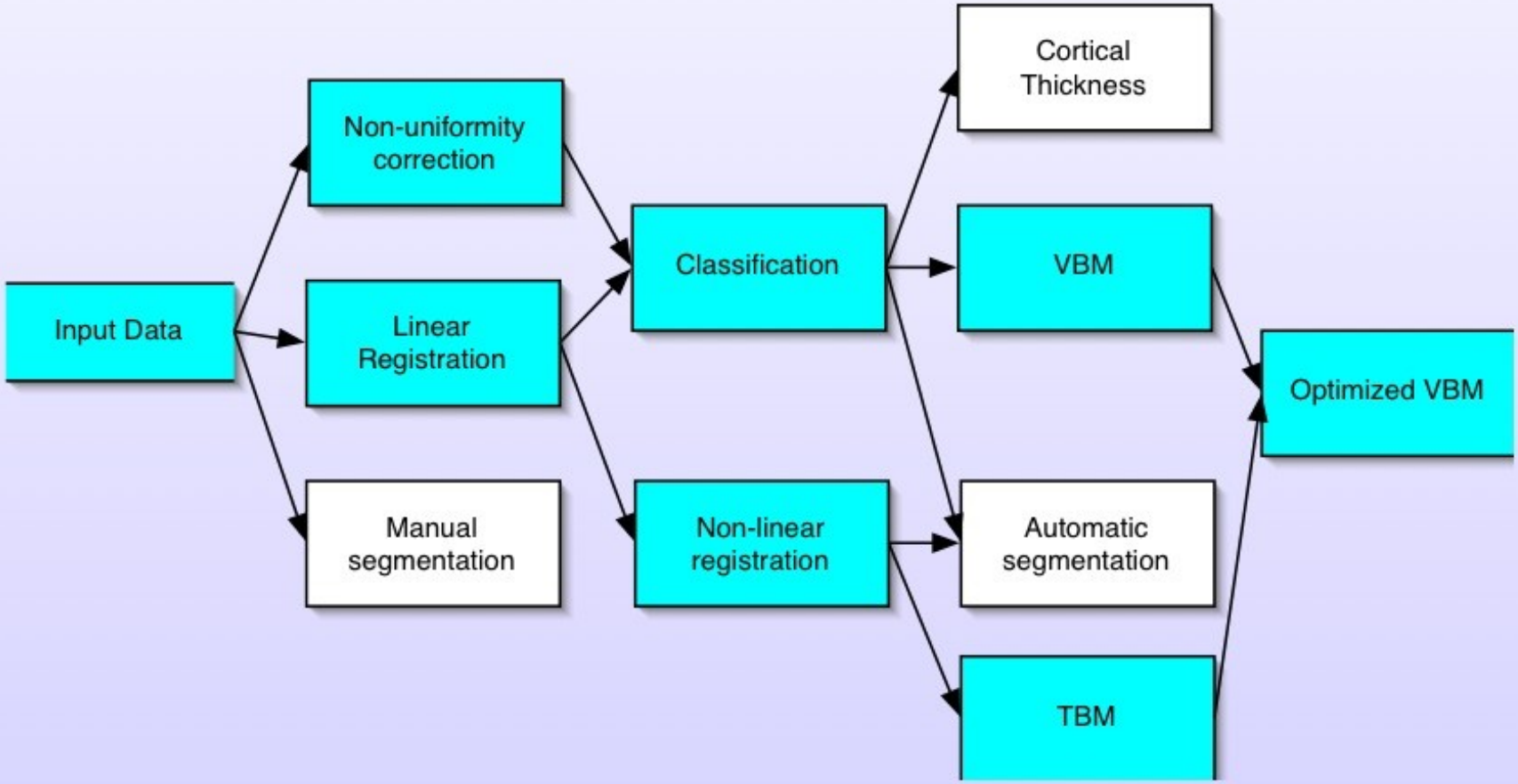
Tissue Class
Smoothness



Courtesy of Jason Lerch

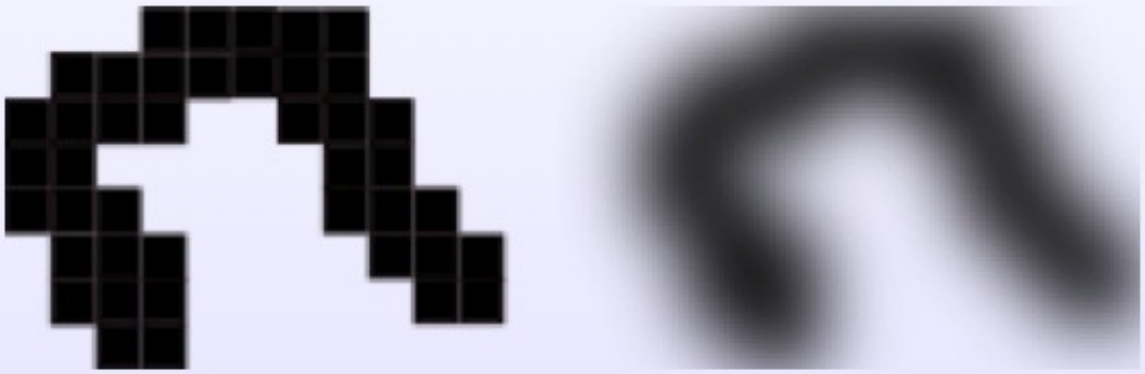
Optimized VBM

- The goal: combine the best of VBM and TBM

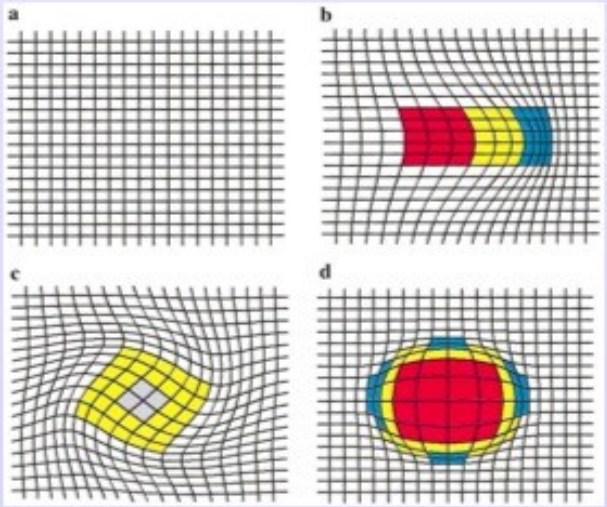


Courtesy of Jason Lerch

Optimized VBM



X



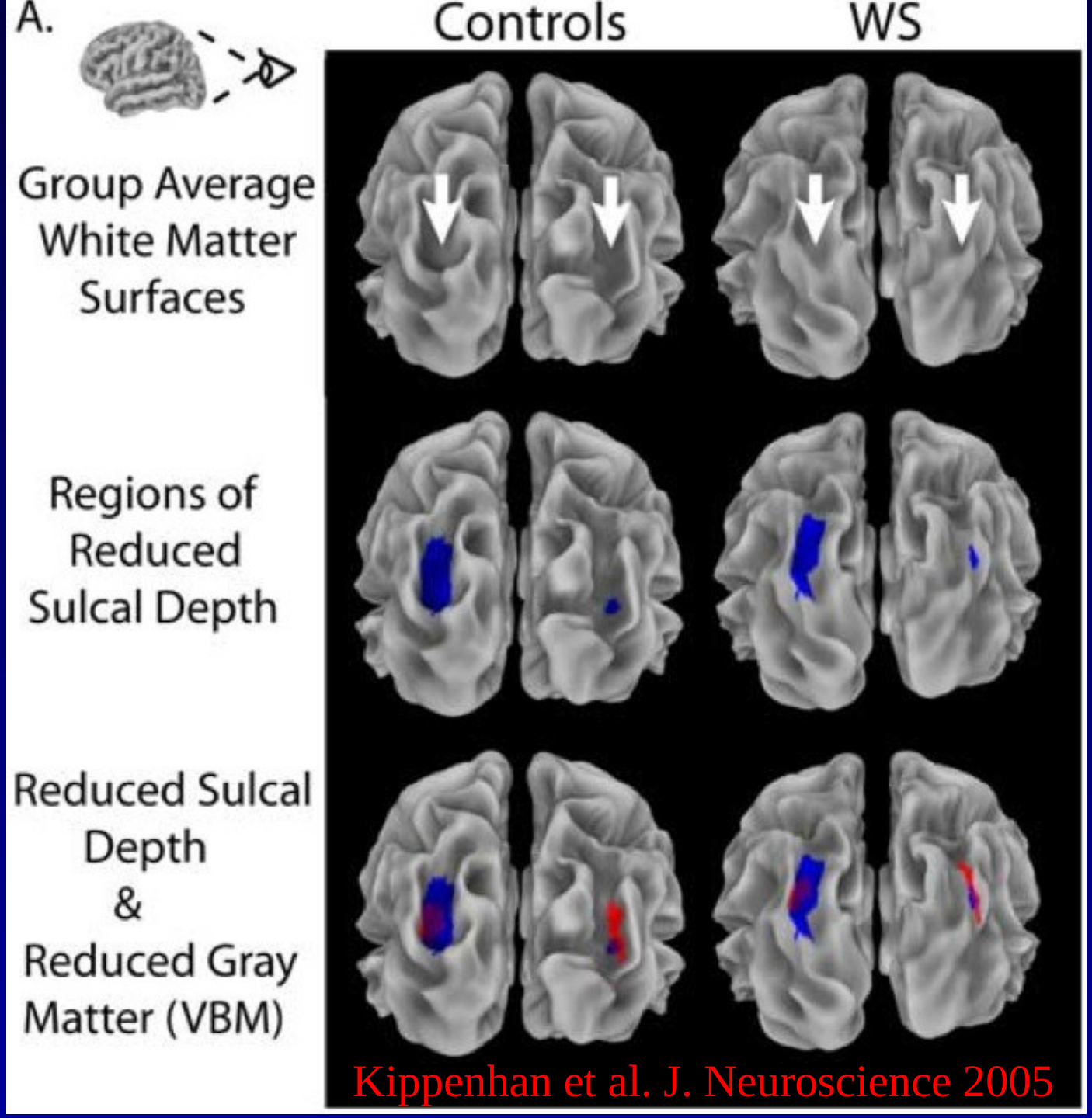
- det(J) modulation
- Registration to tissue of interest
- Improved segmentation+ registration
- Permutation statistics

SPM, FSL

Courtesy of Jason Lerch

Optimized VBM

- Very appealing because results highly localized.
- Nice to see changes in VBM coinciding with other morphometrics such as cortical thickness, or shape.
- Be composed interpreting the results.
  - Could be difference in cortical thickness, sulcal shape, or knowable and unknowable unknowns affecting segmentation
- Literature quite lively on the topic – but improvements are constantly made in response
  - USE NEWEST implementations



Kippenhan et al. J. Neuroscience 2005

Outline

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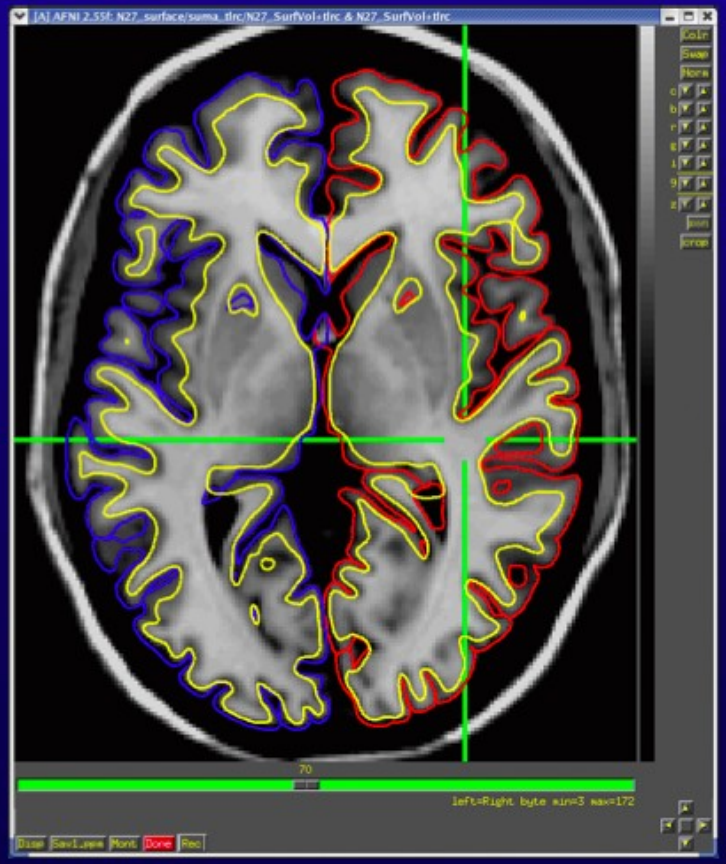
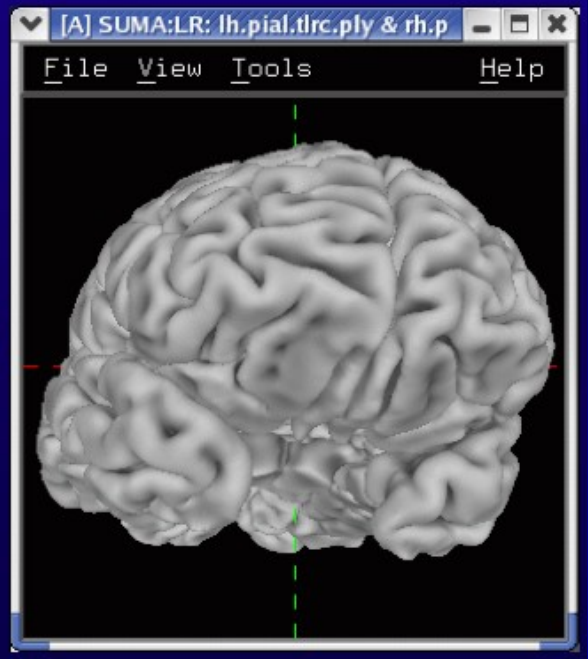
Surface-based Analyses

- 3D models of cortical sheet are created from high resolution MRI.





Models automatically generated by FreeSurfer

Thickness Measures

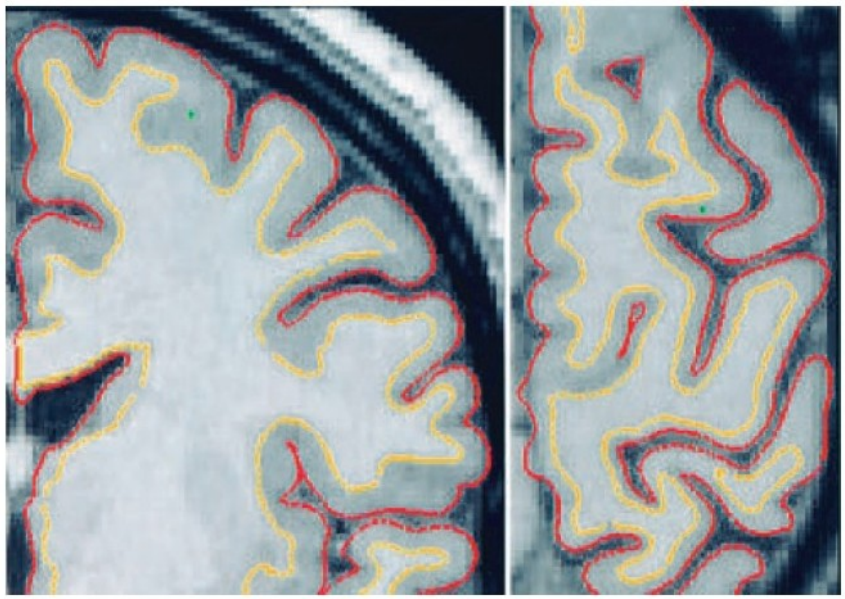


Fig. 1. Coronal (*Left*) and horizontal (*Right*) slices of the left hemisphere with gray/white (yellow) and pial (red) surfaces overlaid. The green crosses indicate a point at which using the coronal view only would result in a dramatic overestimation of the thickness of the cortex.

Bruce Fischl and Anders M. Dale , PNAS 2000

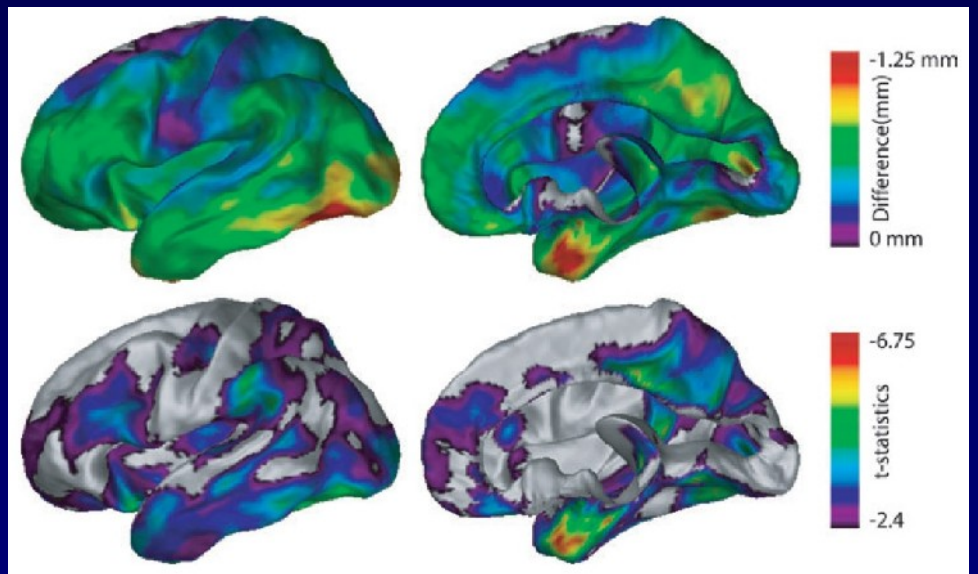


Figure 3. *t*-statistical (lower panel) and cortical thickness (upper panel) difference maps in 19 AD subjects versus 17 controls (age effect removed by regression). The display emphasizes the differences in the left lateral and right medial views. Significant differences can be seen in the posterior and anterior cingulate, the left dorsolateral prefrontal cortex, most of the temporal lobes, and the left supramarginal gyrus.

Jason P. Lerch, Cerebral Cortex 2005

- Easy to obtain – once surfaces are created

Surface-based morphometry

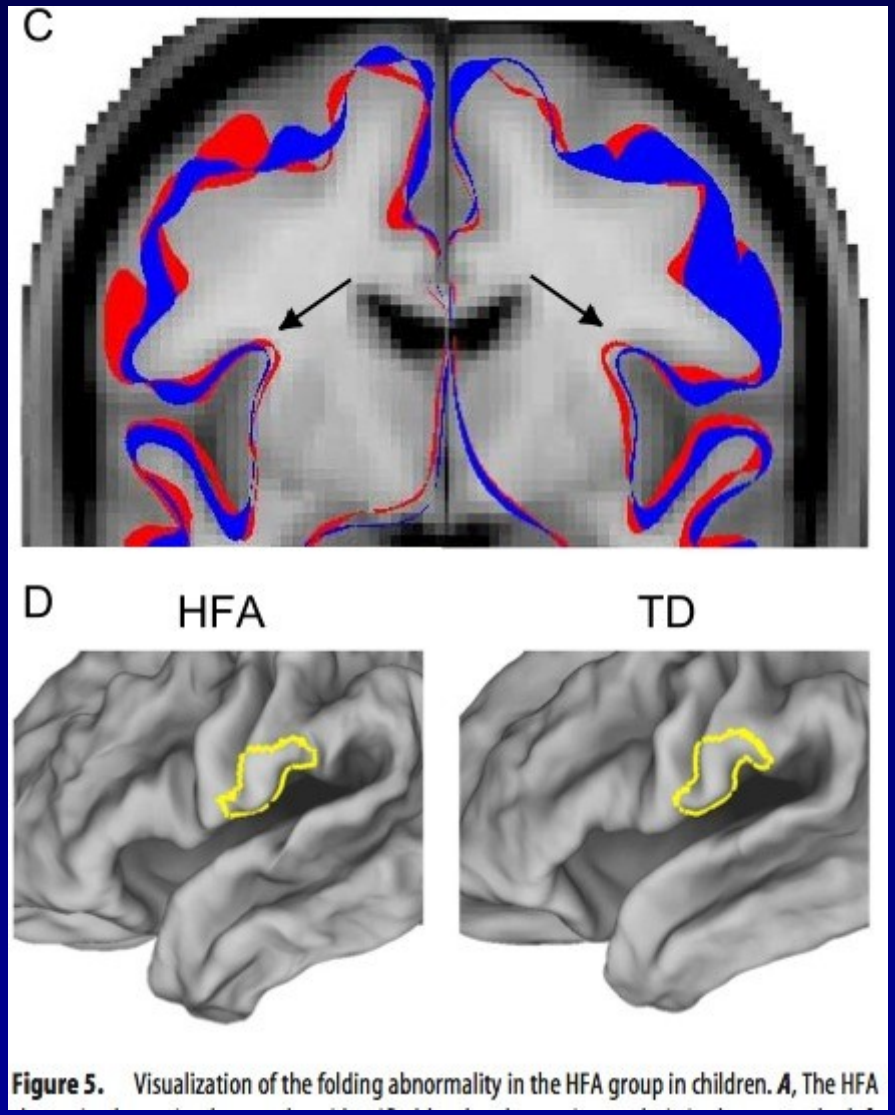


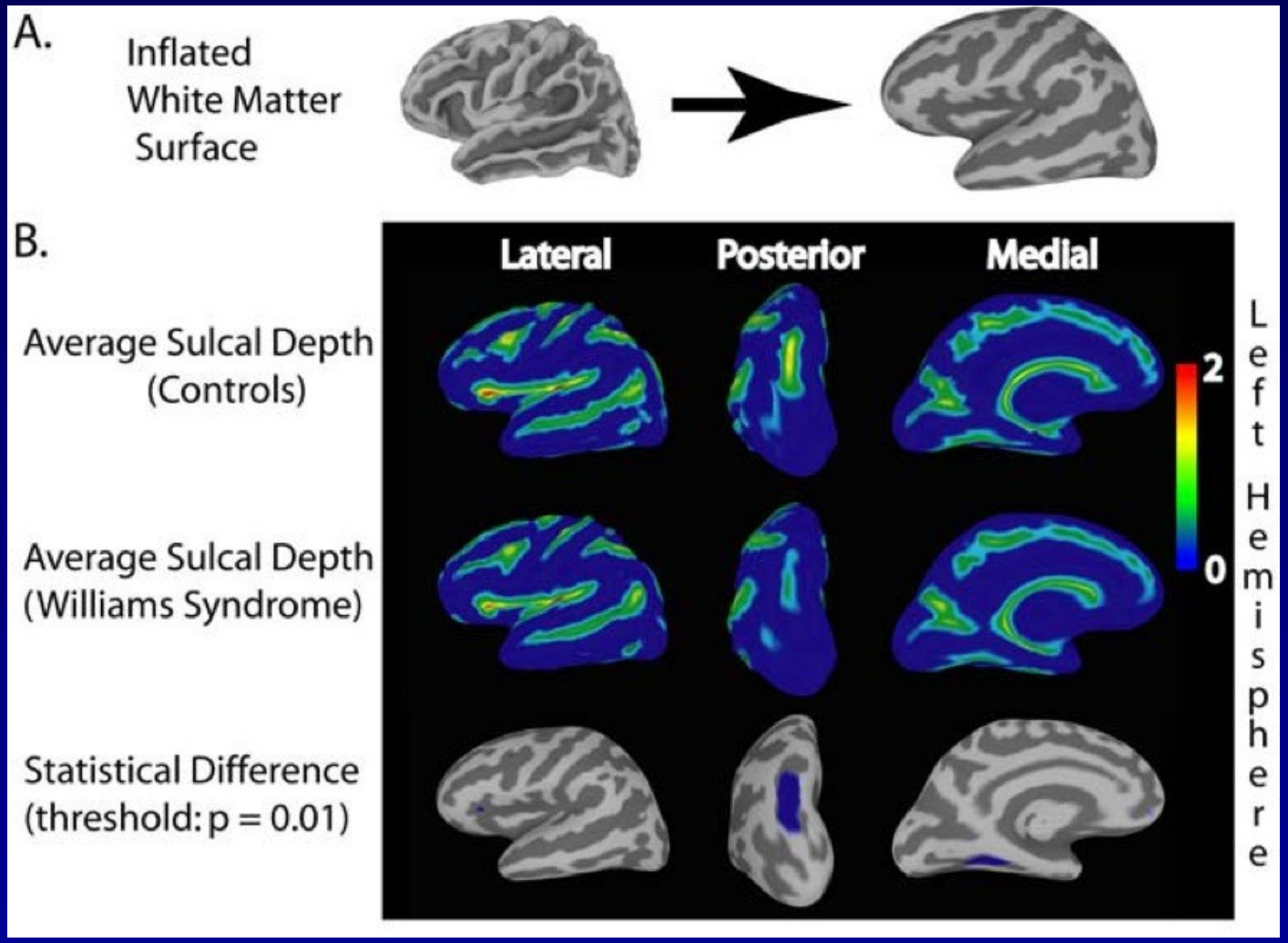
Figure 5. Visualization of the folding abnormality in the HFA group in children. ***A***, The HFA

- Or depth differnces:
  - Sulcal depth differences between HFA and TD children.

From Christine Wu Nordahl et al. J. Neuroscience 2007

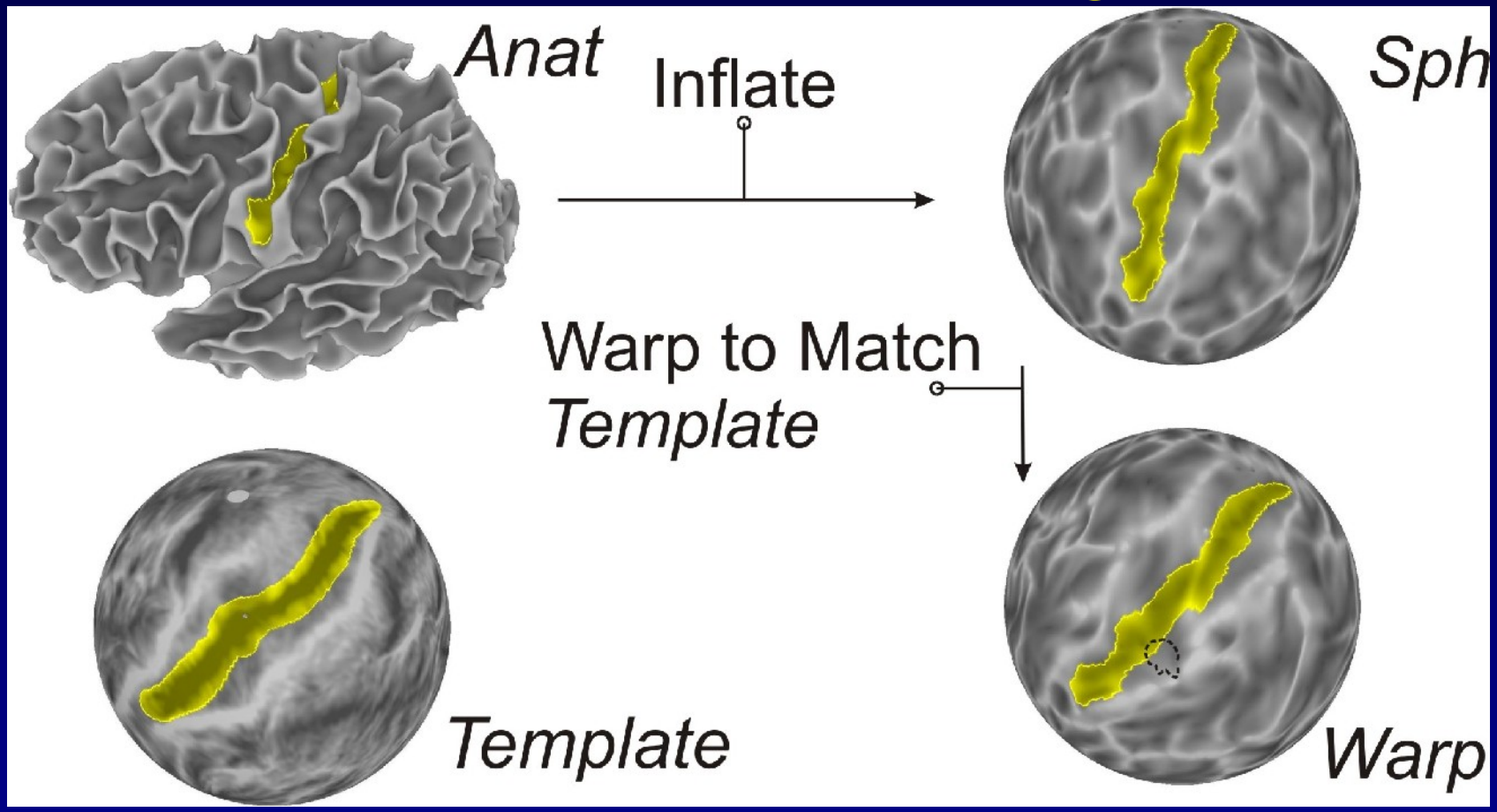
Surface-based morphometry

- Sulcal depth differences between Williams Syndrome and TD children.



From Shane Kippenhan et al. J. Neuroscience 2007

Spherical Warping



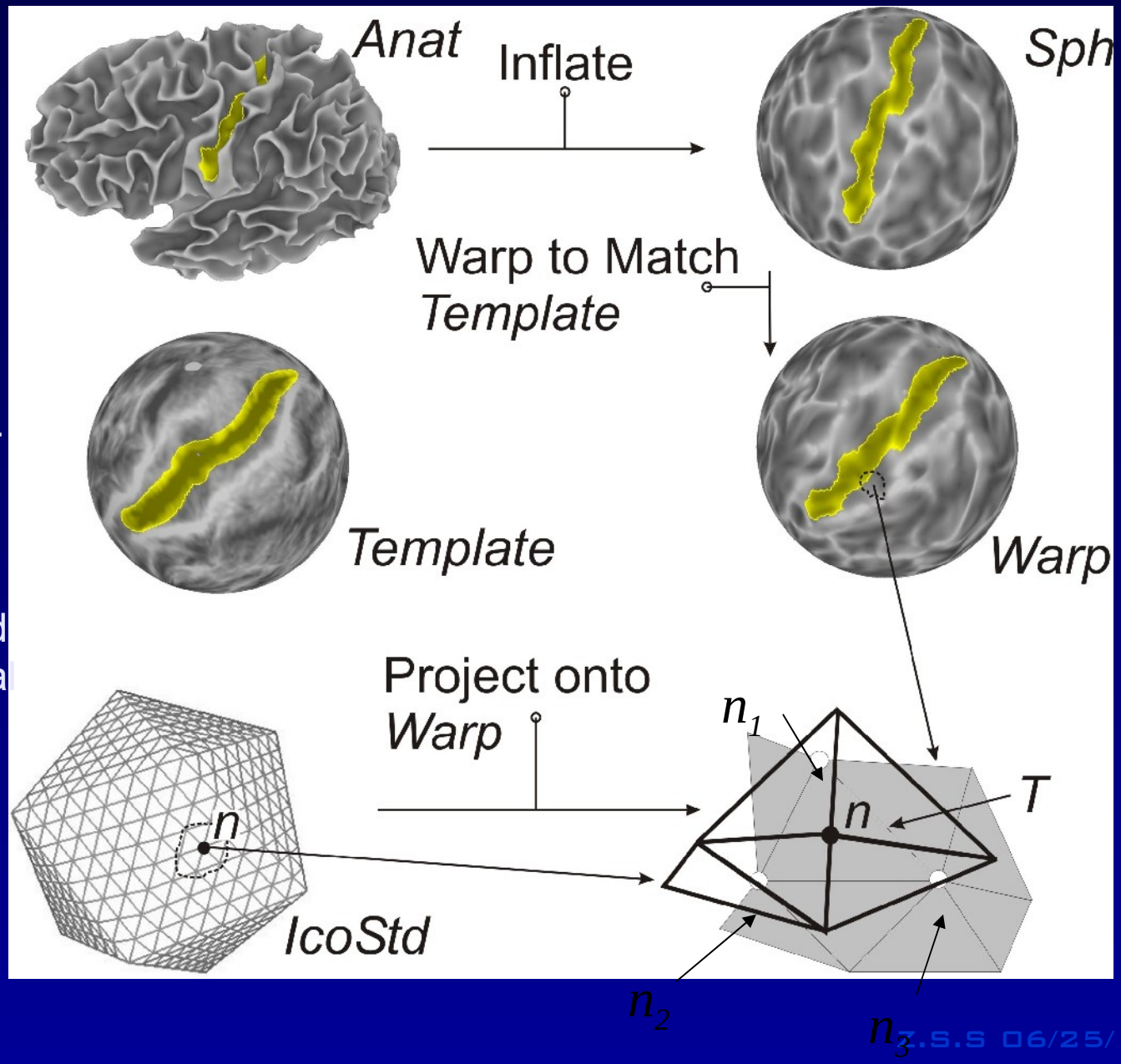
Surface-based warping is more accurate than the more common low order Talairach volume-based analysis because it preserves the topology of the cortical sheet and uses more landmarks for the warping

Mapping data onto common domain

Problem is that surfaces from different subjects are not topologically isomorphic (different meshes).

Data from each subject are mapped onto the icosahedral surface for group analysis

Cumbersome and unnecessary interpolation

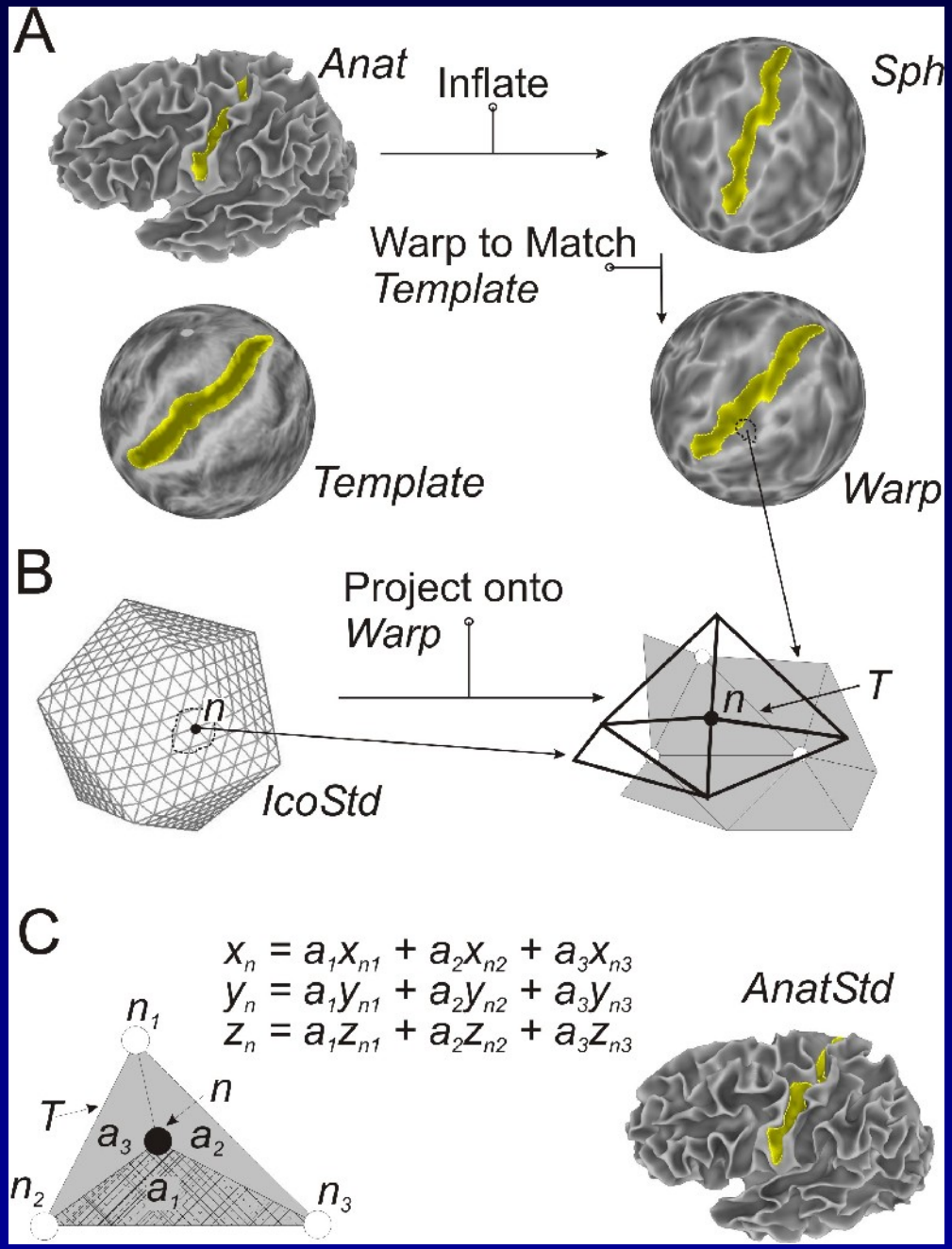


Our twist

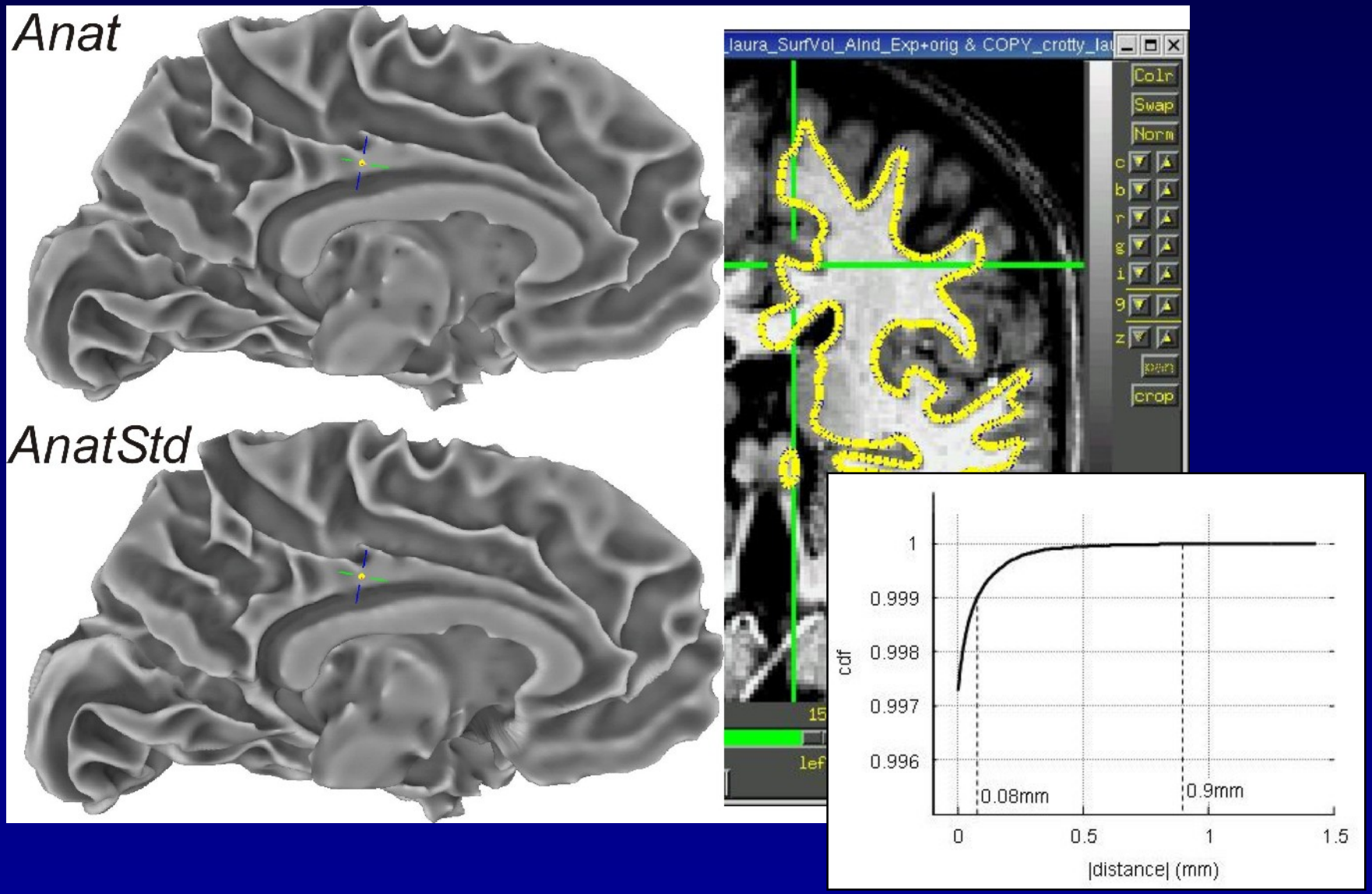
Instead of interpolating data values to the icosahedral nodes, interpolate using the coordinates of the original surface's node.

This results in a surface that is virtually identical in geometry to the original surface but with the mesh of the icosahedron.

Cross-subject surface based analysis is thus reduced to node-based analysis

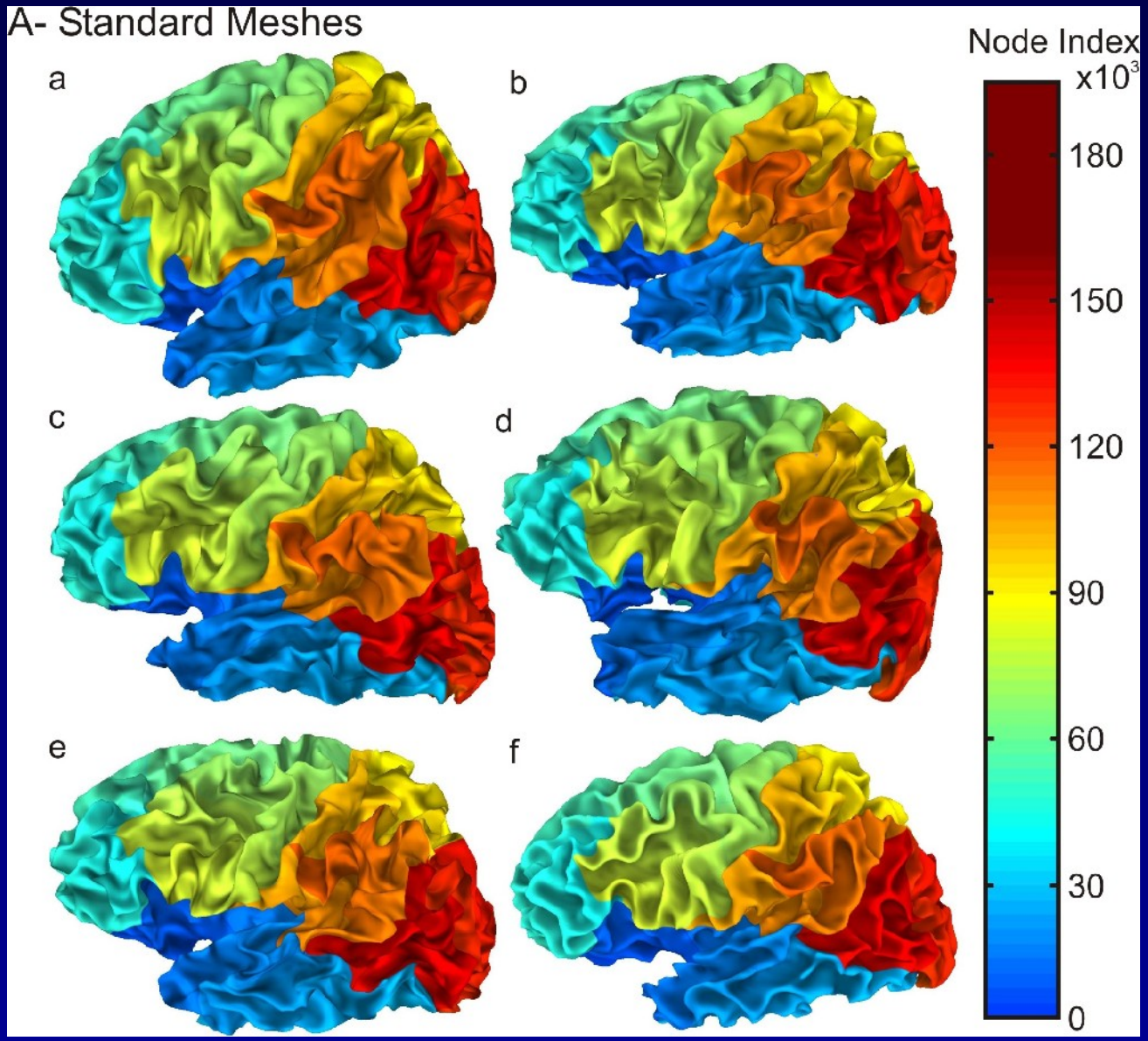


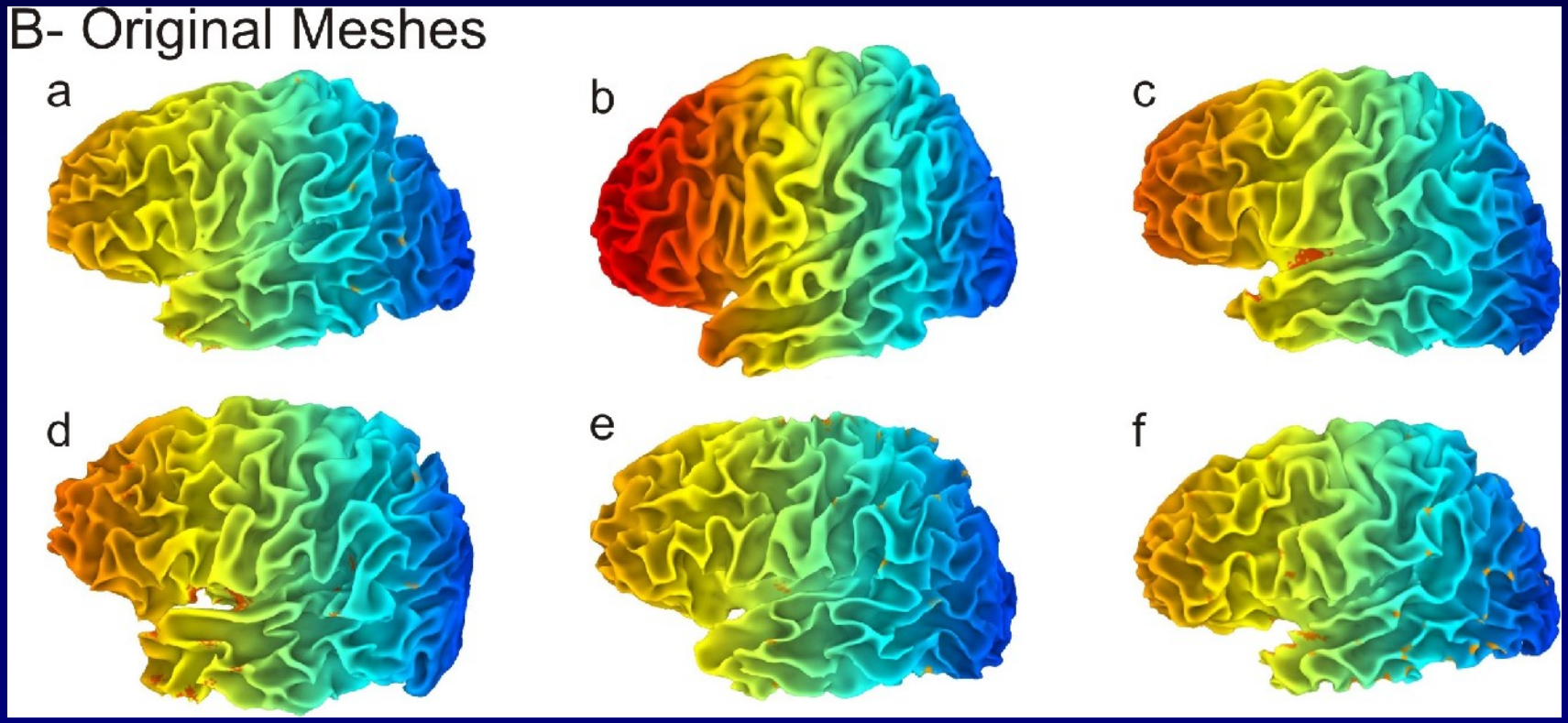
Compare surfaces



Standard meshes for 6 subjects

- 6 standard-mesh surface models from different subjects.
- Node colors encode for node index *n* on the standard mesh.
- Nodes with similar indices correspond to comparable sulcal landmarks despite anatomical variability across subjects.
- Some tools generate standard meshes from the outset. e.g. MacDonald et al., 2000





- Original-mesh versions of standard-mesh surfaces with same coloration scheme
- Surfaces have differing numbers of nodes, some colors may not be represented
- Nodes with similar indices no longer correspond to comparable anatomical areas
- Small clusters of red color show new nodes later added to correct topological errors

Better on the surface?

+ Easier to match domains (2D object)
+ Focused on grey matter – won't mix data from other tissues
+ Easy to visualize & gorgeous

- Only cortex, only gray matter
- Spatial computations more complicated

From Lukas Pezawas et al. J. Neuroscience 2004

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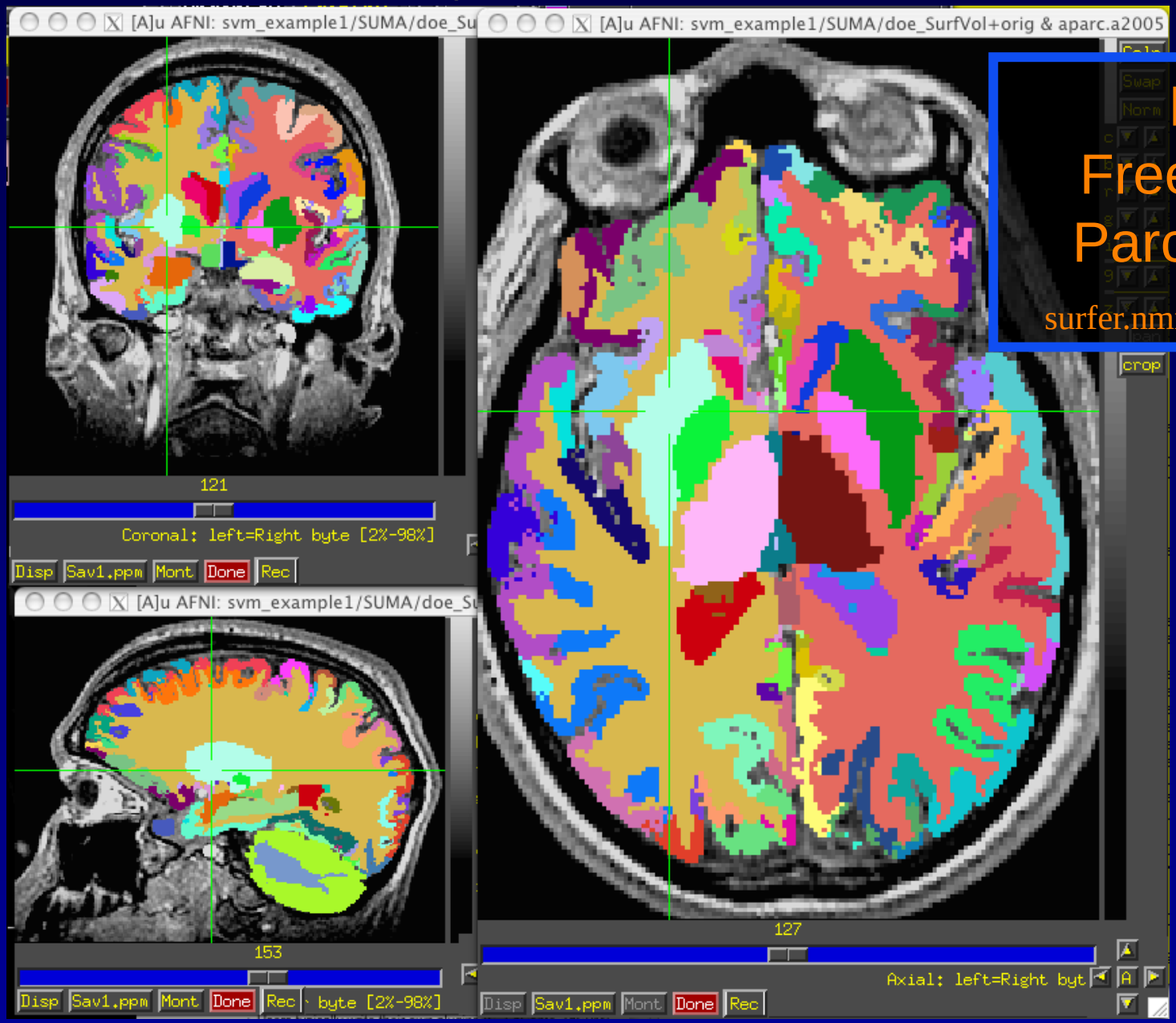
Full Circle Back To ROIs

- ROI methods are usually shunned
  - Operator variability
  - The tedium
- However results easier to interpret
- Subject-based automated parcellation (as with FreeSurfer), both on the surface, and in the volume, removes the downsides
  - Quite simple to compare GM volumes, etc.

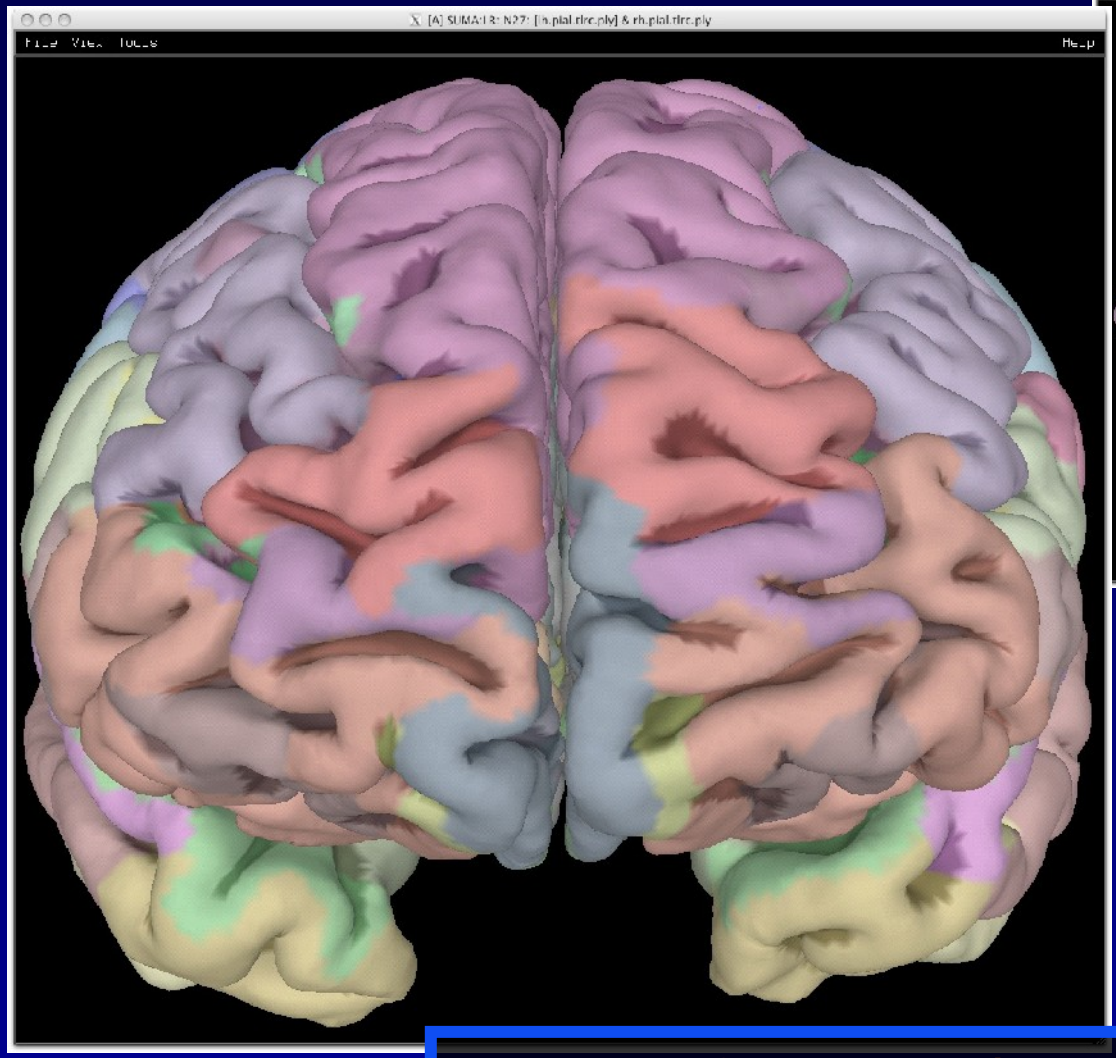
Subject-based Anatomical ROIs

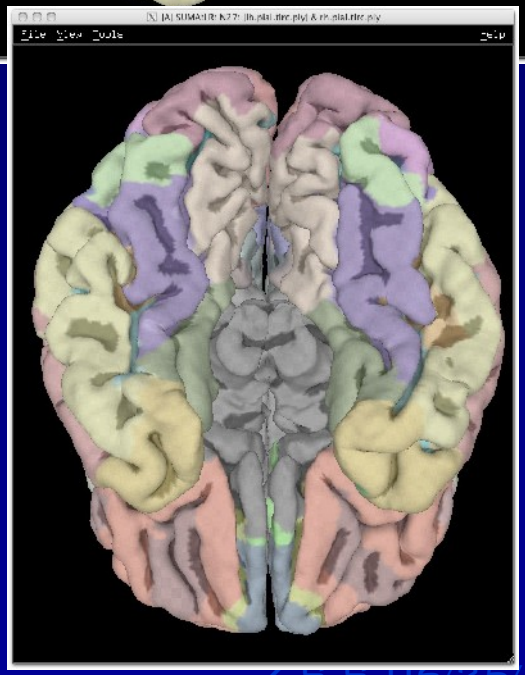


From FreeSurfer's Parcellations

surfer.nmr.mgh.harvard.edu

Surface-based ROIs





FreeSurfer annotations

surfer.nmr.mgh.harvard.edu

Acknowledgments

Robert Cox
Gang Chen

Jason Lerch
Adam Thomas

But Wait! There's more

- What about white matter FA comparisons?
  - VBM methods deemed touchy for FA
    - Dependent on smoothing levels: Jones et al. 2005
    - Imperfect alignment too much for voxel wise stats
  - One approach is to restrict analysis to certain bundles, or project FA values to a skeleton of the white matter [TBSS, Smith et al. 2006]
    - Voxels with largest weighted FA have their FA mapped to the skeleton.
    - Group stats computed on the skeleton

[TBSS, Smith et al. 2006]

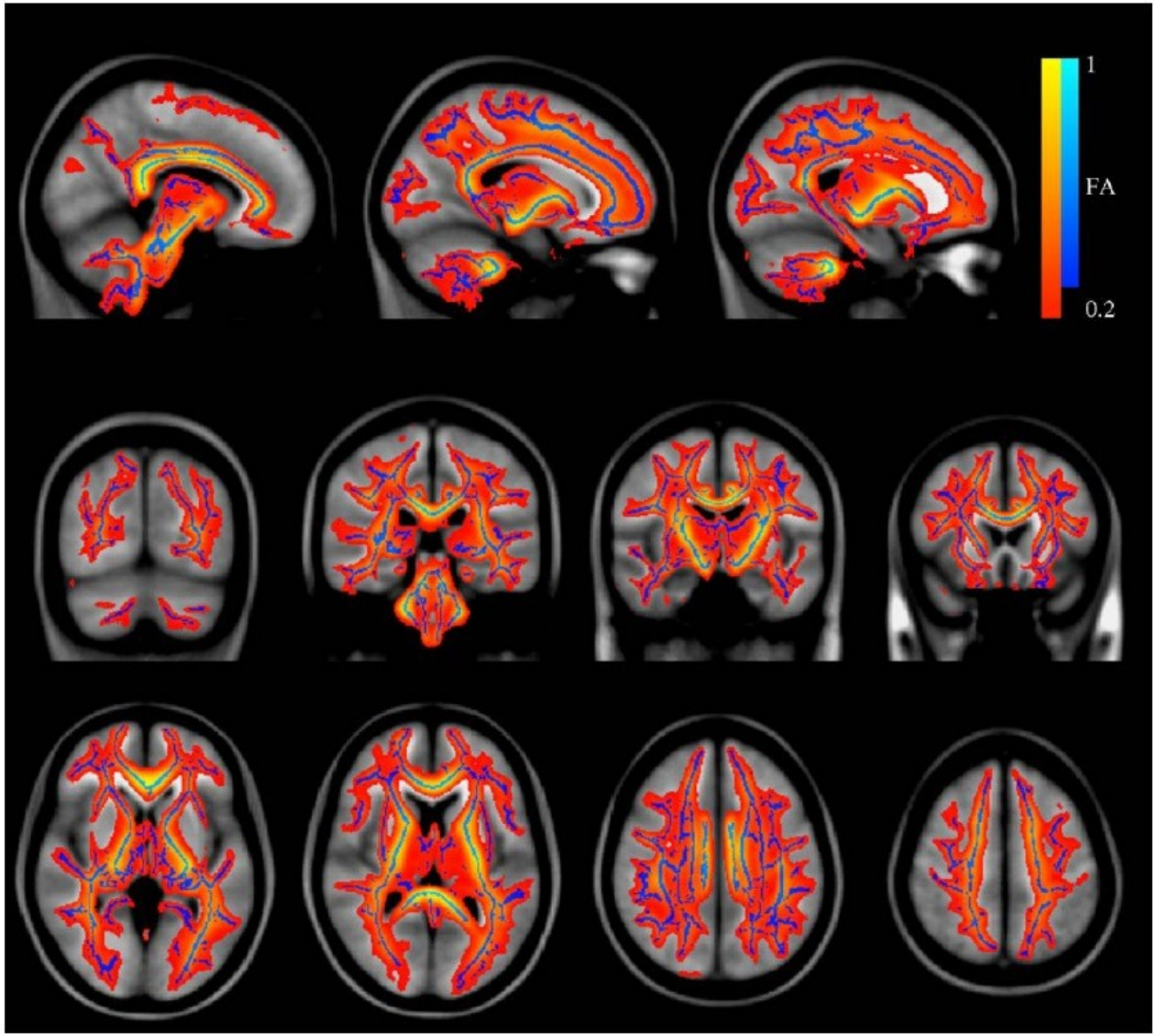


Fig. 8. Example overlay of mean FA map from 20 controls and 13 ALS patients, after each subject has been nonlinearly aligned to the target subject in MNI152 space. The mean FA, shown in red–yellow, is thresholded at 0.2 and overlaid onto the MNI152. The skeleton, shown in blue, is thresholded at 0.3.