# Neuroimaging with ANTs as a model for the pulmonary community

Jim Gee

# Significance

# E. A. Hoffman et al., JMRI 2015.

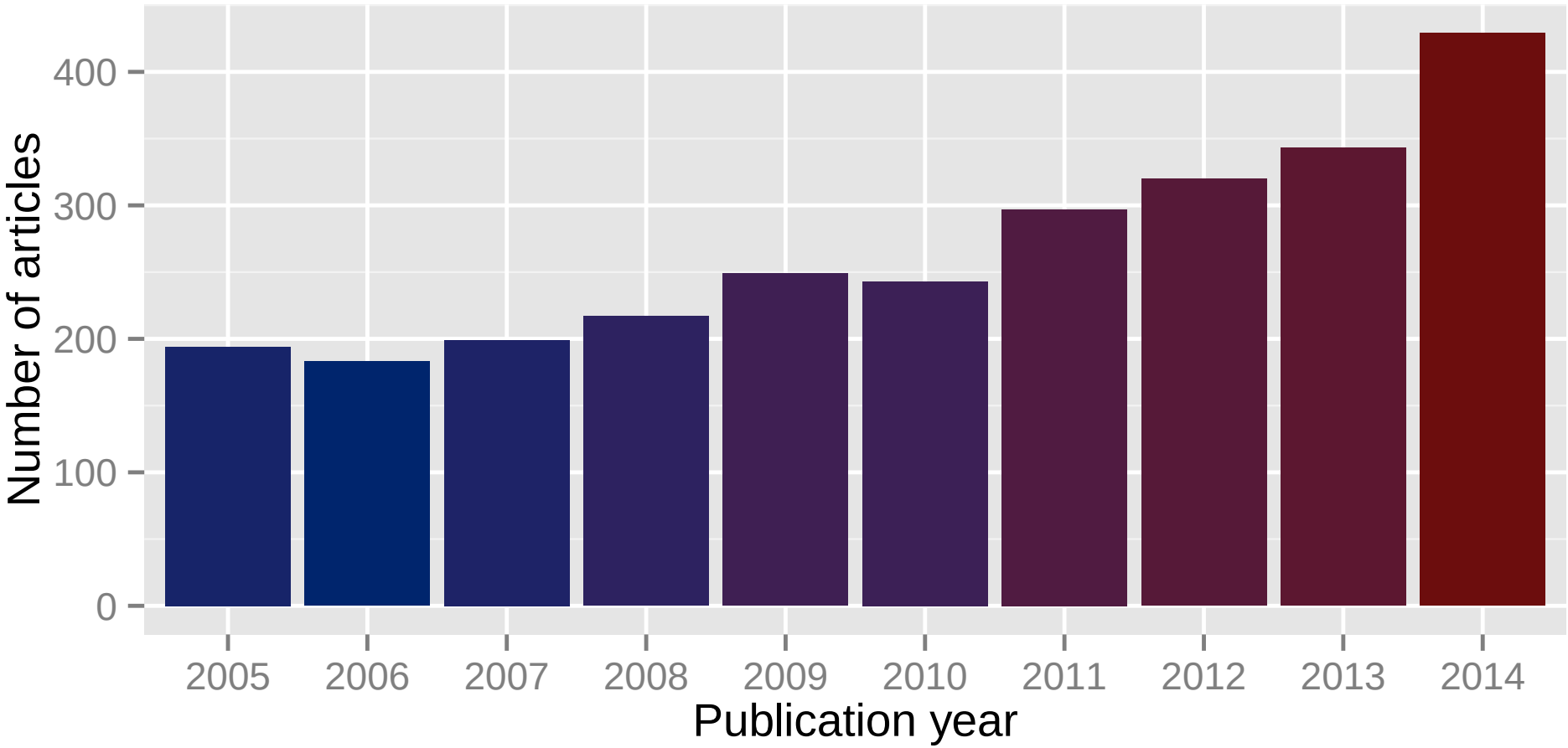
*"More widespread use of all [pulmonary] imaging biomarkers has been limited for a number of key reasons, including: 1) lack of support to harmonize image acquisition software;* ***2) universally available image analysis software;*** *3) regulatory boundaries for emerging approaches; and 4) historically weak links between respiratory and radiology clinical programs."*

# What does the neuroimaging community offer?

Great packages such as:

- AFNI
- FSL
- FreeSurfer
- SPM

# Public & robust software $\longrightarrow$ research output



# Benefits of open-source:

- Motivates community-based support:
  - bug fixes (*"Given enough eyeballs, all bugs are shallow."*),
  - new features,
  - reproducibility verification, and
  - community tech support.
- Learn directly from journal manuscripts *and* implementations.
- Tremendous cost-savings.

# Innovation

# Preliminary data

# ANTs functionality

# Donoho?

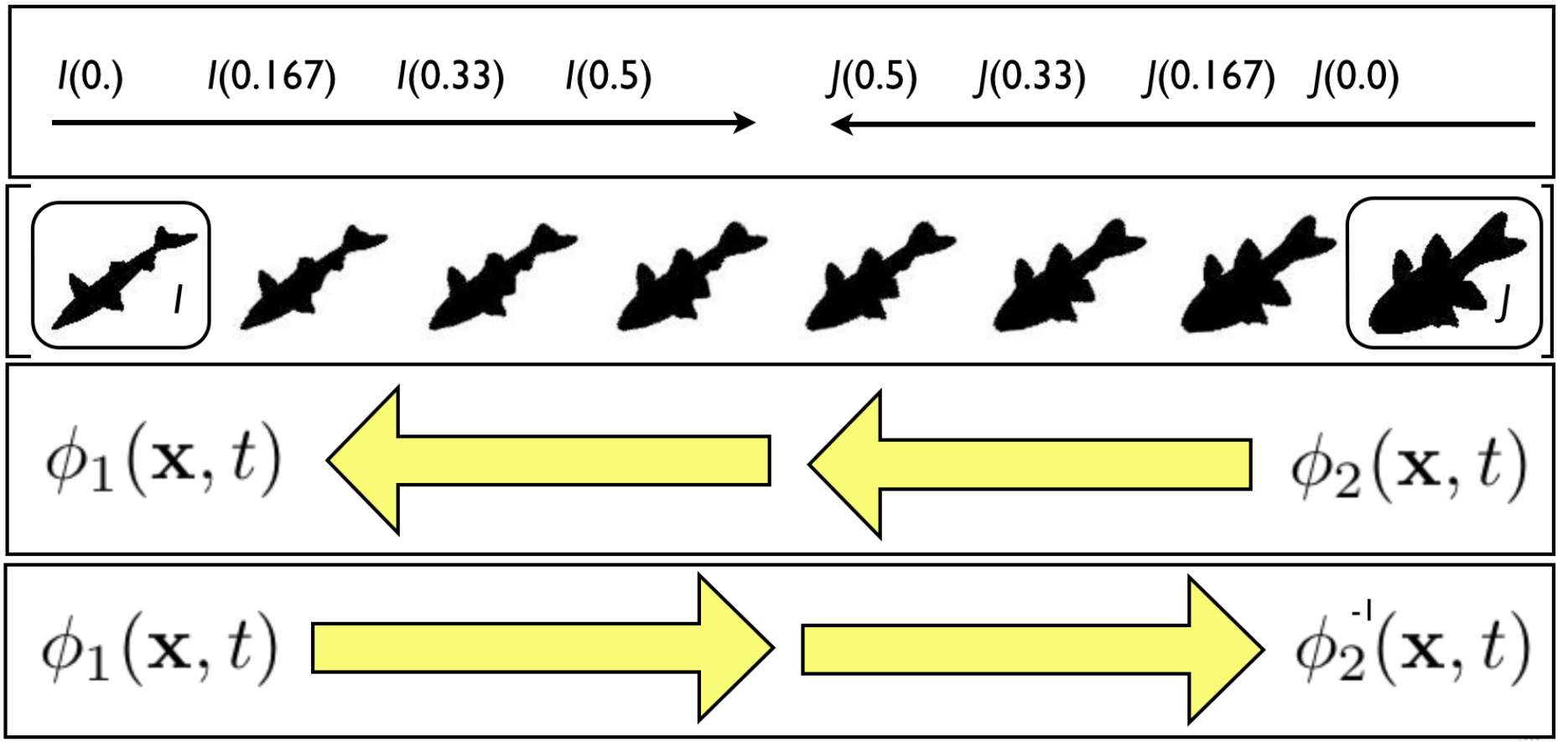
*“Papers are just advertisements for the science.”*

# ANTs core tools

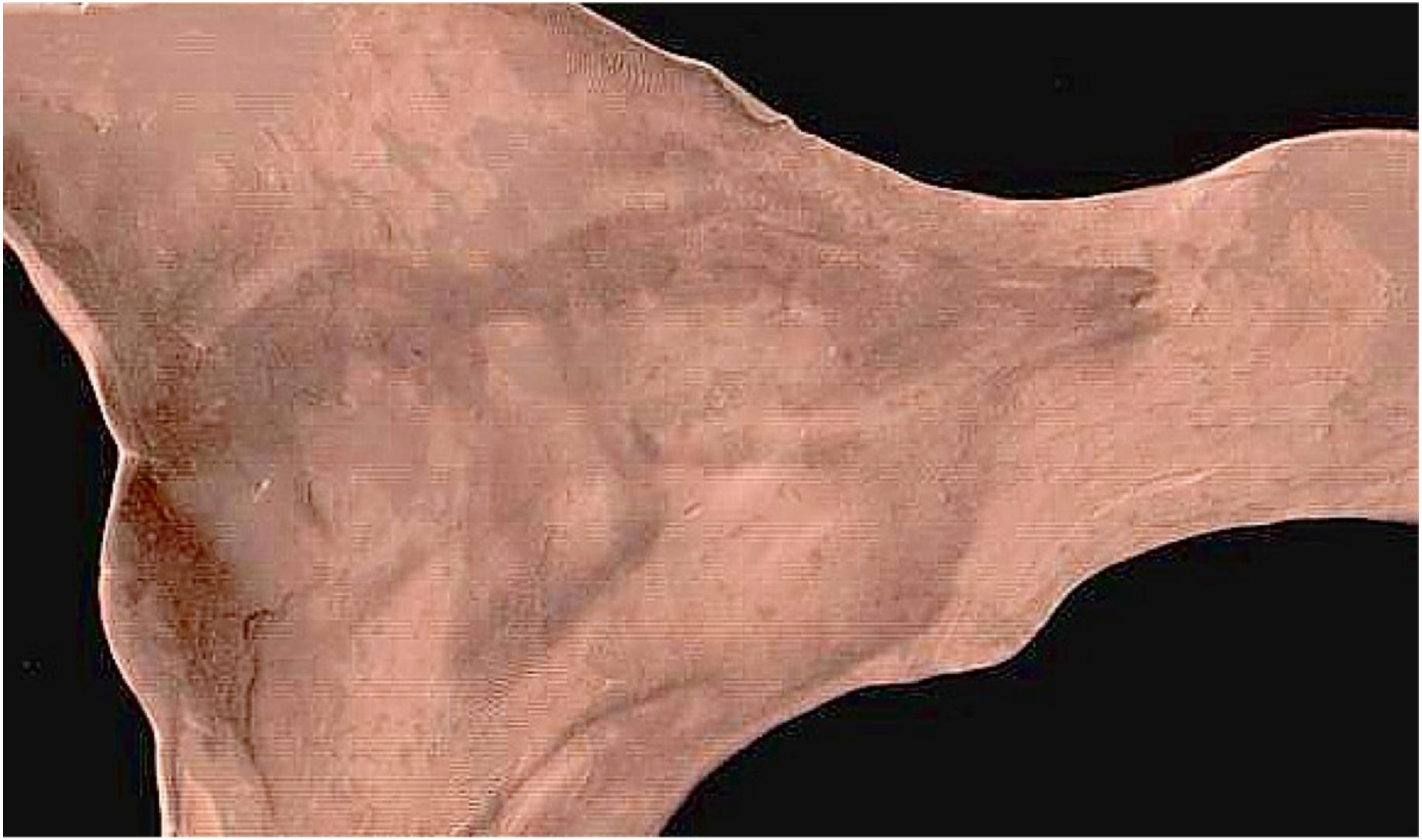
- image registration
- template building
- Bayesian segmentation with priors
- N4 bias correction
- joint label fusion
- spatially adaptive denoising

# Symmetric Normalization (SyN)

$$\int_{t=0}^{0.5} \left( \|\mathbf{v}_1(x,t)\|_L^2 + \|\mathbf{v}_2(x,t)\|_L^2 \right) dt + \| I\left(\phi_1(x,0.5)\right) - J_i\left(\phi_2(x,0.5)\right) \|^2$$

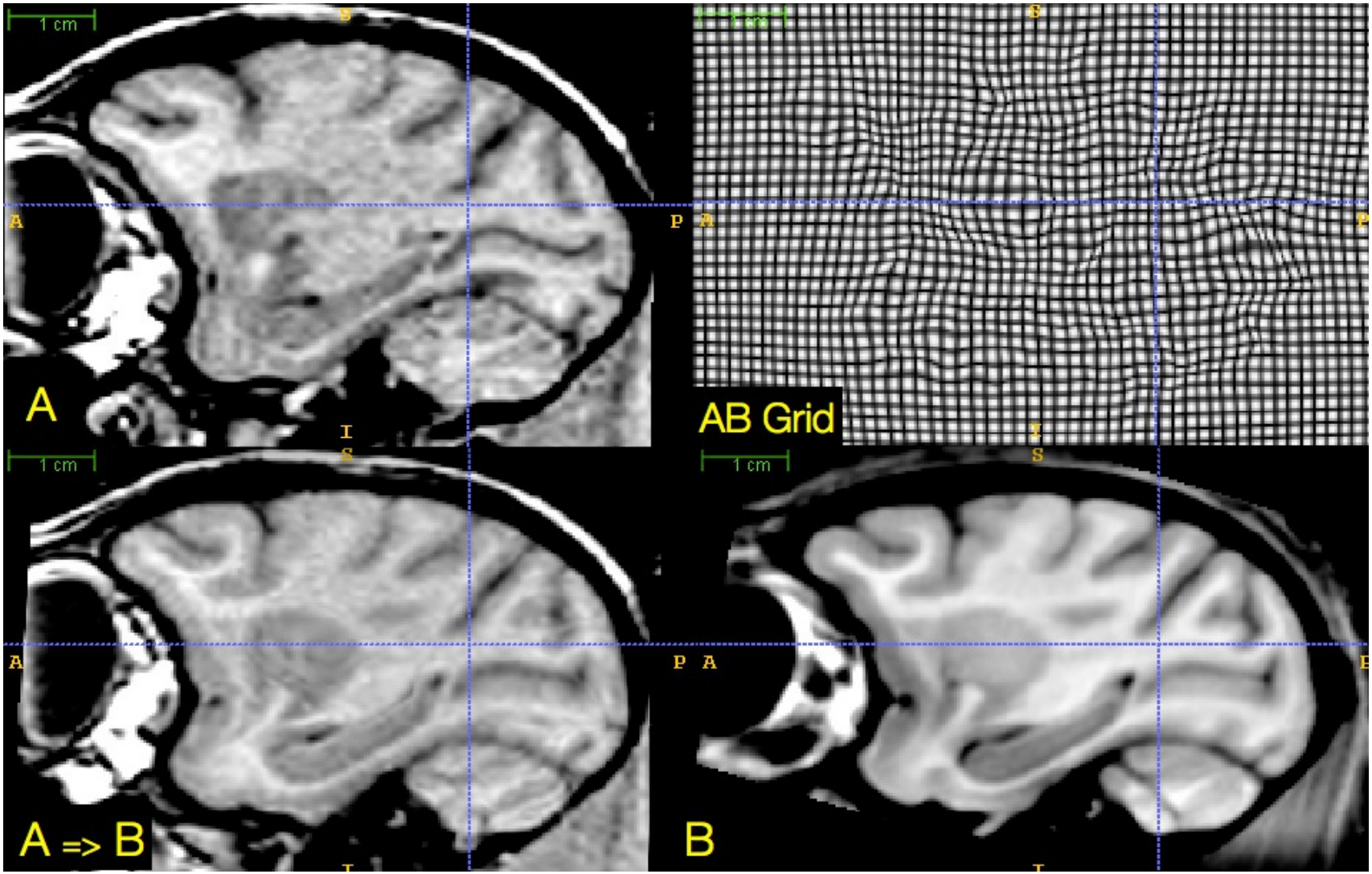


# Diffeomorphisms: Occam's razor modeling



*differentiable map with differentiable inverse*

# Diffeomoprhisms: fine-grained and flexible maps



# Beyond original SyN

frontiers in NEUROINFORMATICS

ORIGINAL RESEARCH ARTICLE
published: 28 April 2014
doi: 10.3389/fninf.2014.00044

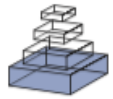
## The Insight ToolKit image registration framework

***Brian B. Avants[1]*, Nicholas J. Tustison[2], Michael Stauffer[1], Gang Song[1], Baohua Wu[1] and James C. Gee[1]***

[1] *Penn Image Computing and Science Laboratory, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA*
[2] *Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, VA, USA*

frontiers in NEUROINFORMATICS

METHODS ARTICLE
published: 23 December 2013
doi: 10.3389/fninf.2013.00039



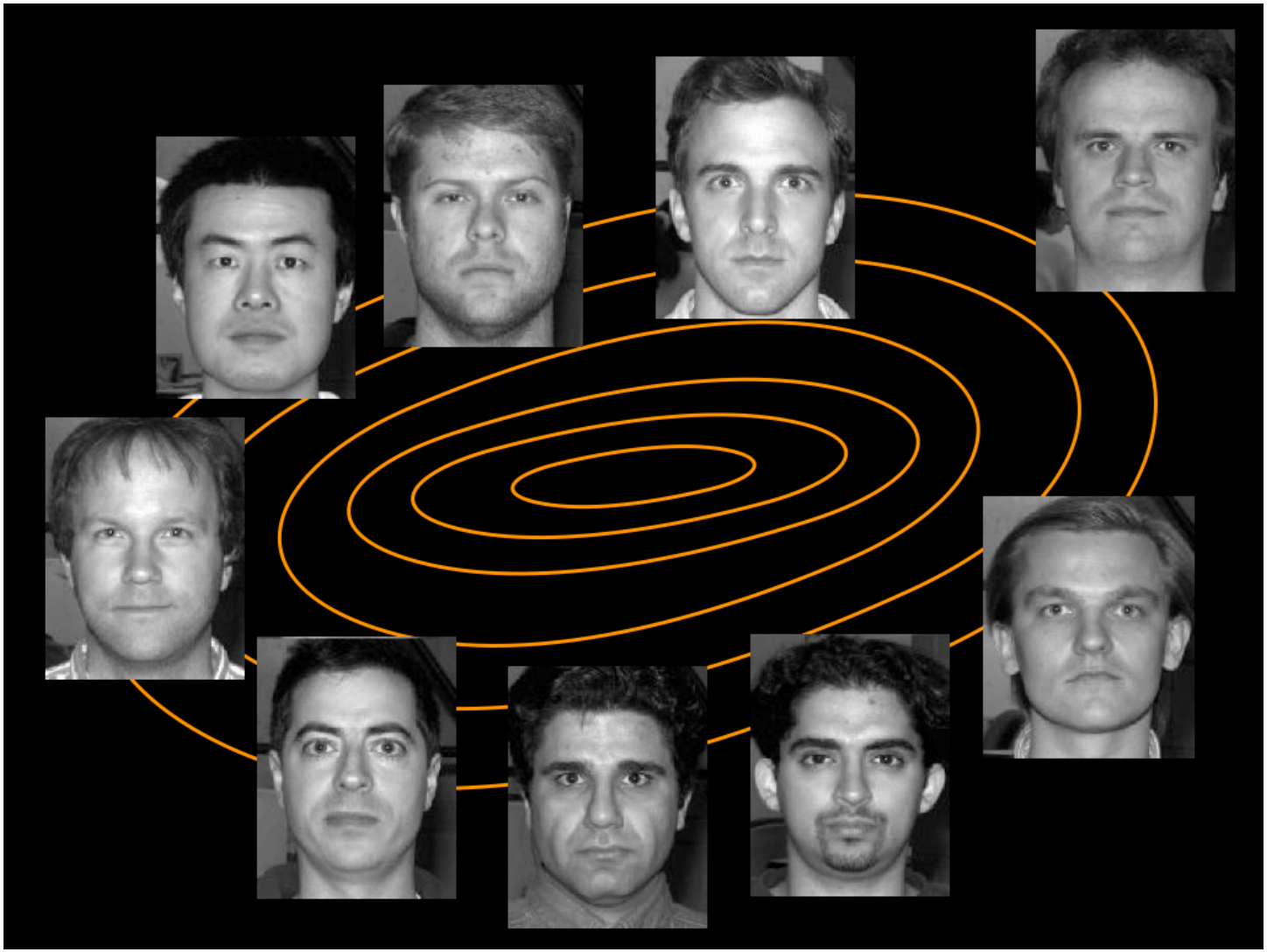
## Explicit B-spline regularization in diffeomorphic image registration

***Nicholas J. Tustison[1]* and Brian B. Avants[2]***

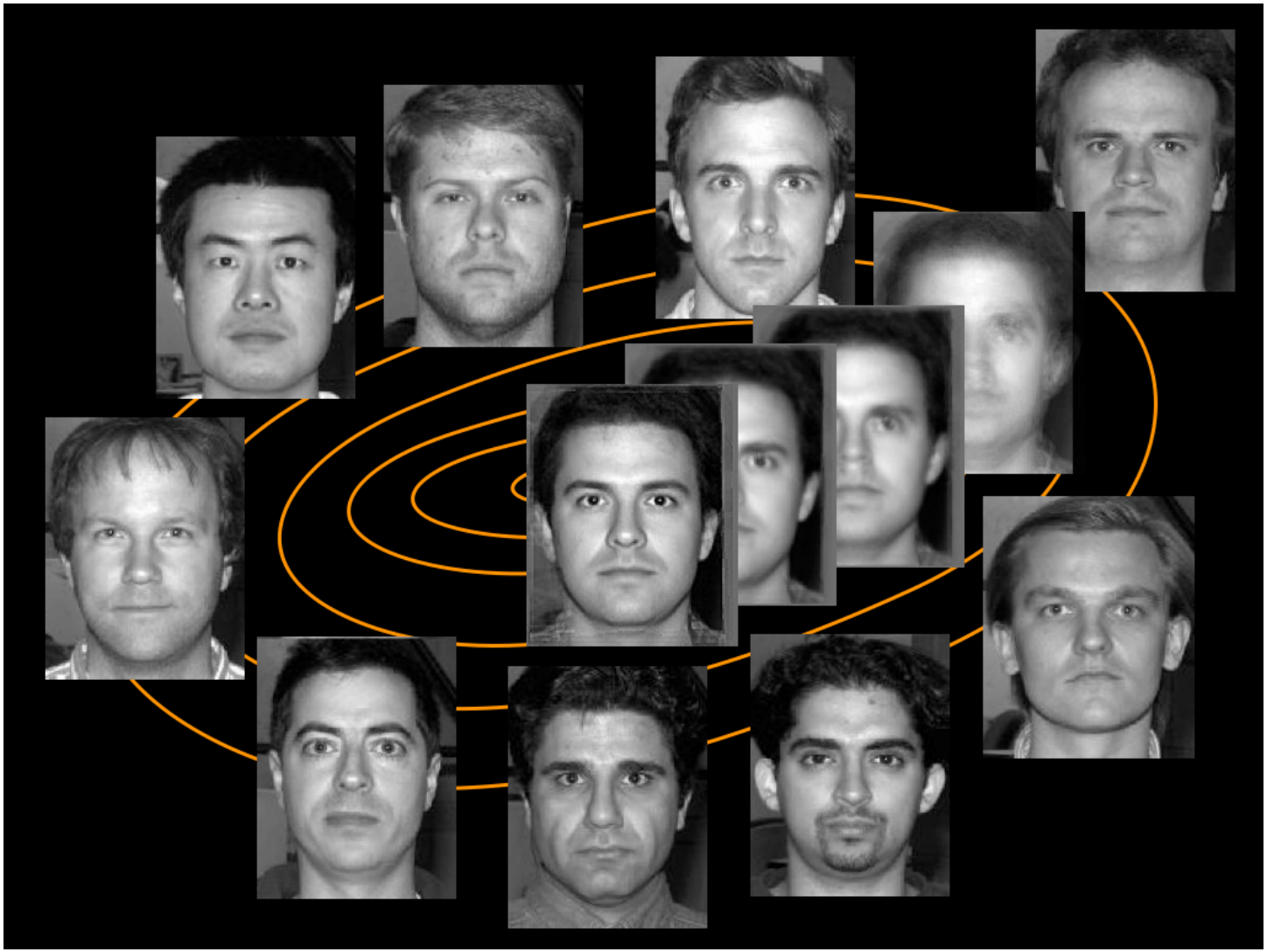
# antsRegistration

```
$ antsRegistration -h

COMMAND:
     antsRegistration

OPTIONS:
     --version
     -d, --dimensionality 2/3
     -o, --output outputTransformPrefix
                 [outputTransformPrefix,<outputWarpedImage>,<
     -j, --save-state saveSateAsTransform
     -k, --restore-state restoreStateAsATransform
     -a, --write-composite-transform 1/(0)
     -p, --print-similarity-measure-interval <unsignedIntegerV
     --write-interval-volumes <unsignedIntegerValue>
     -z, --collapse-output-transforms (1)/0
```

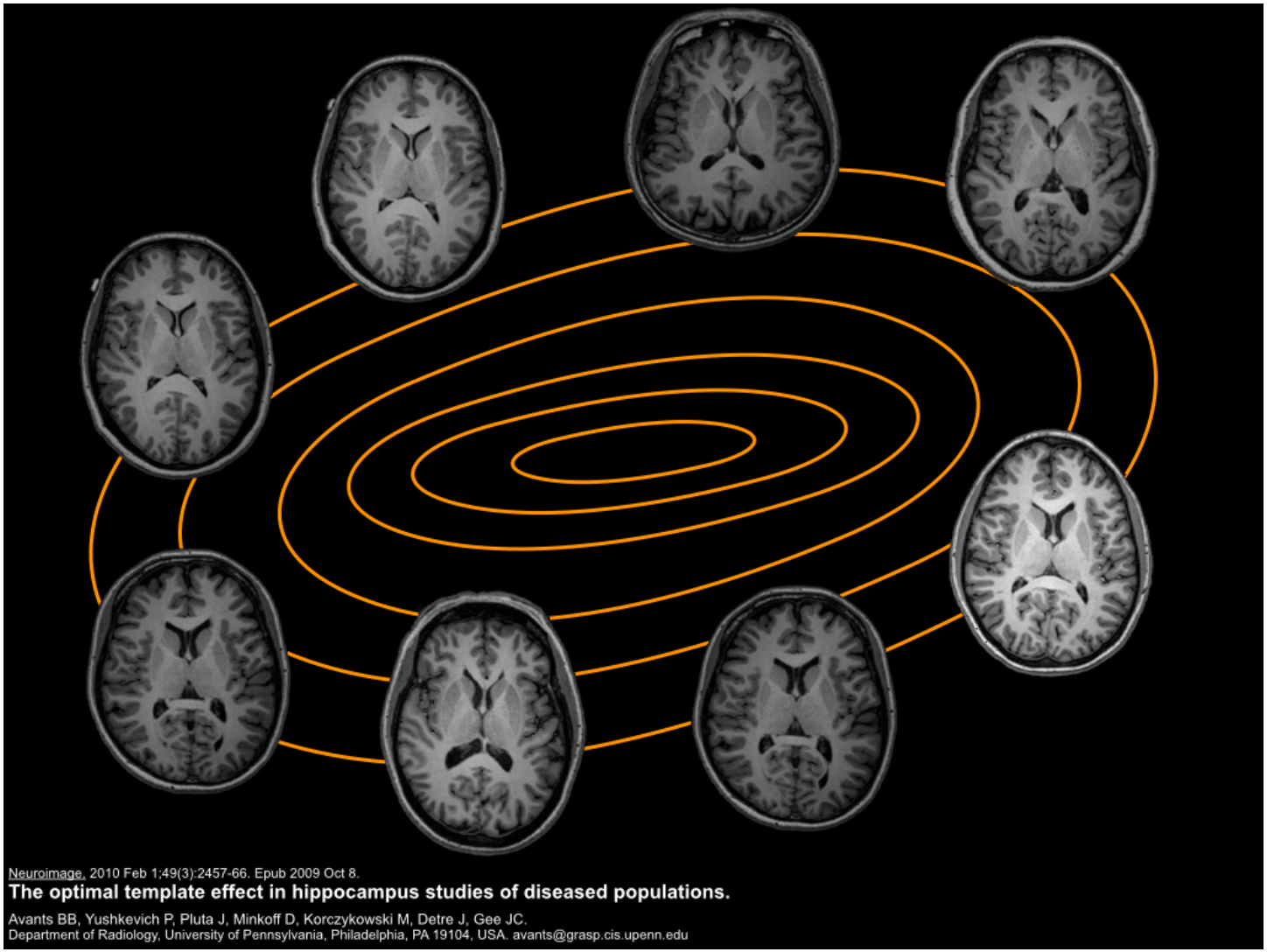
# Template building: creating the average Joe



# “Attractiveness” → mental processing?

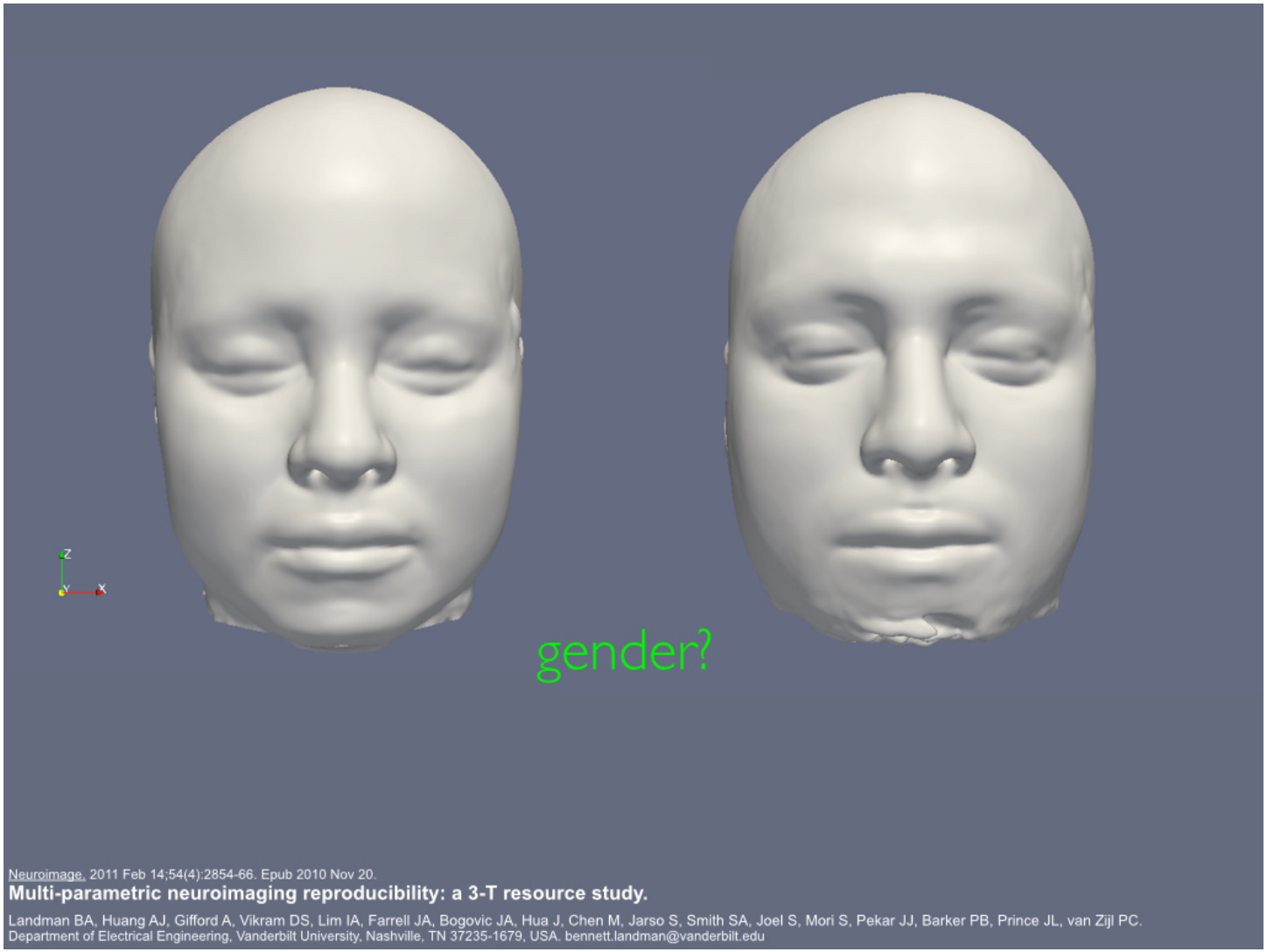


# What about brains?



# Templates facilitate computation

# Gender discernibility?



# antsMultivariateTemplateConstruction2.sh

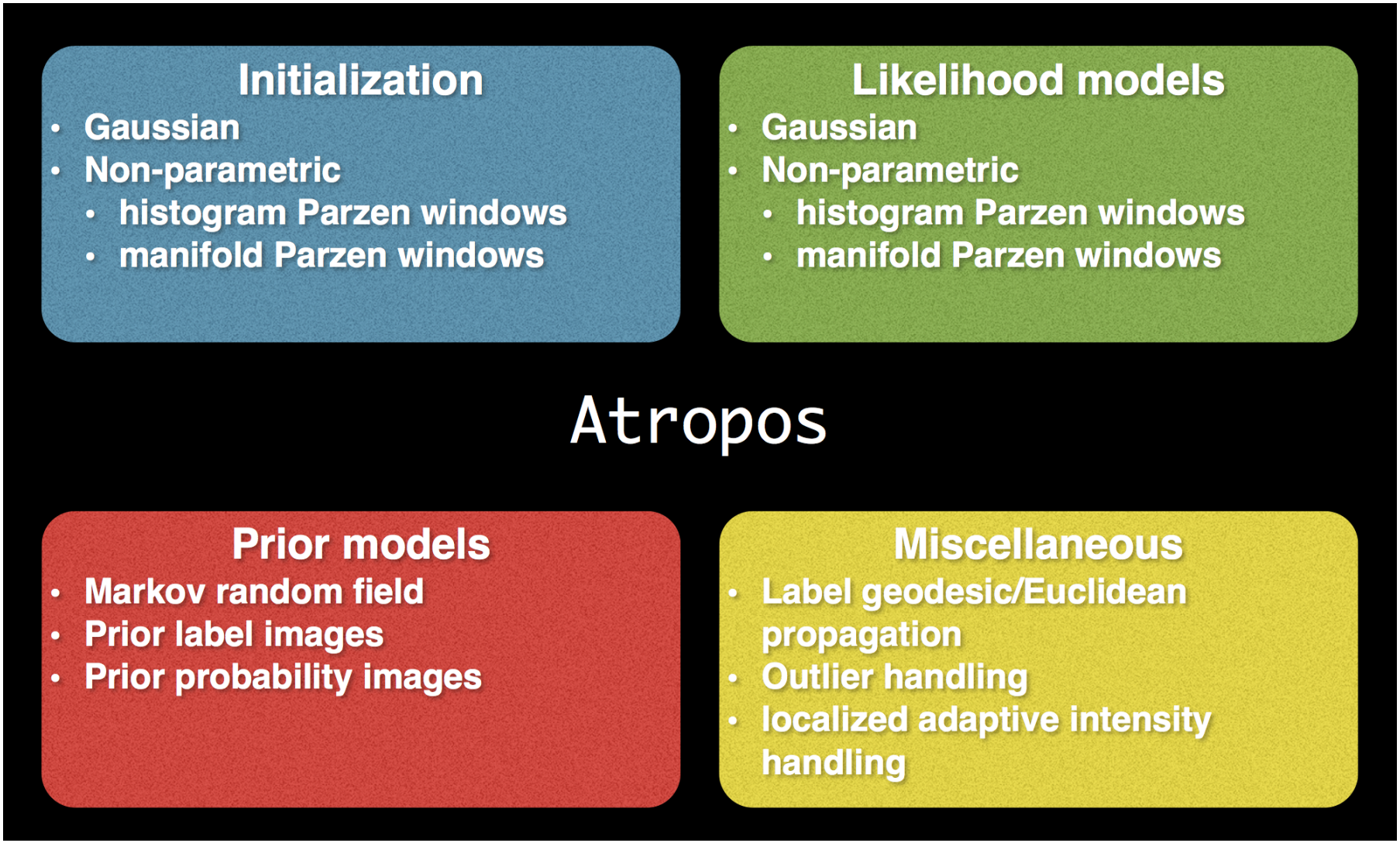
```
$ antsMultivariateTemplateConstruction2.sh

Usage:

antsMultivariateTemplateConstruction2.sh -d ImageDimension -o

Compulsory arguments (minimal command line requires SGE/PBS cl
  -j options):

     -d:  ImageDimension: 2 or 3 (for 2 or 3 dimensional regis
   ImageDimension: 4 (for template generation of time-series c

     -o:  OutputPrefix; A prefix that is prepended to all outp

<images>  List of images in the current directory, eg *_t1.nii
          of the command.  Optionally, one can specify a .csv
```

# Bayesian segmentation with spatial/MRF priors

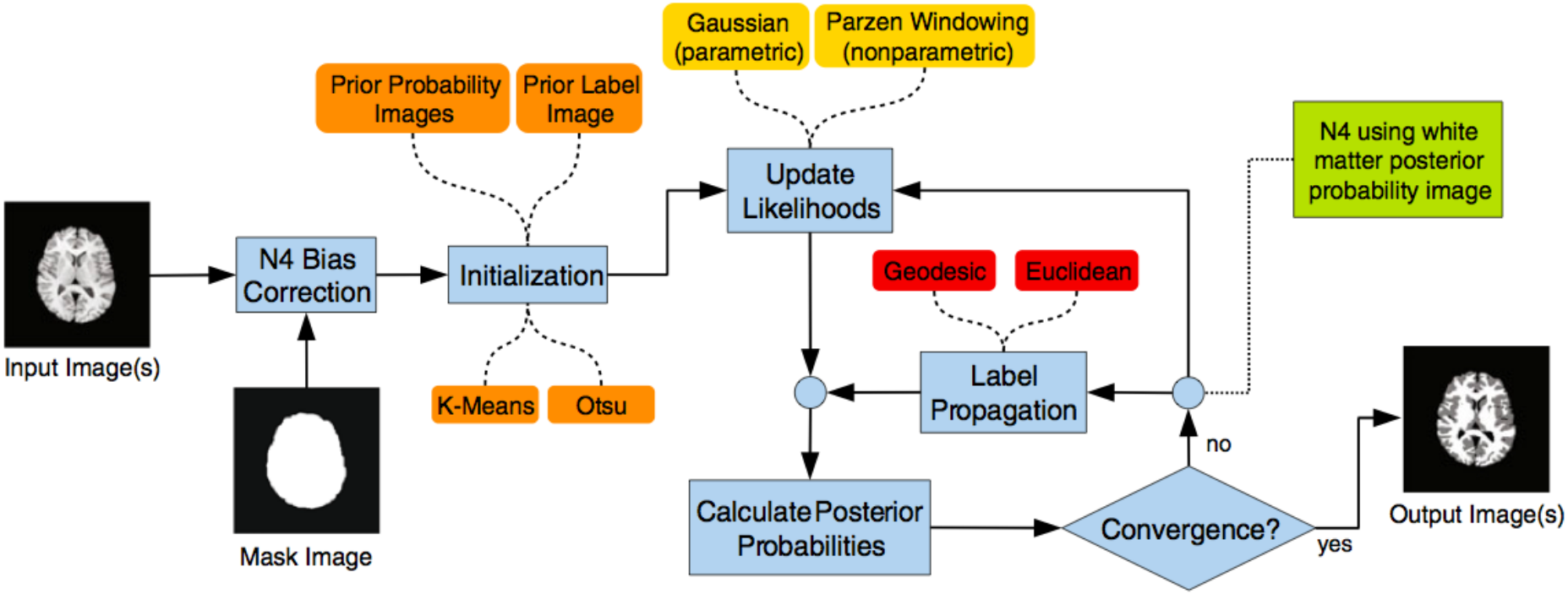
# "20+ years of development. *Show me the code!*"

Brian Avants, MICCAI workshop

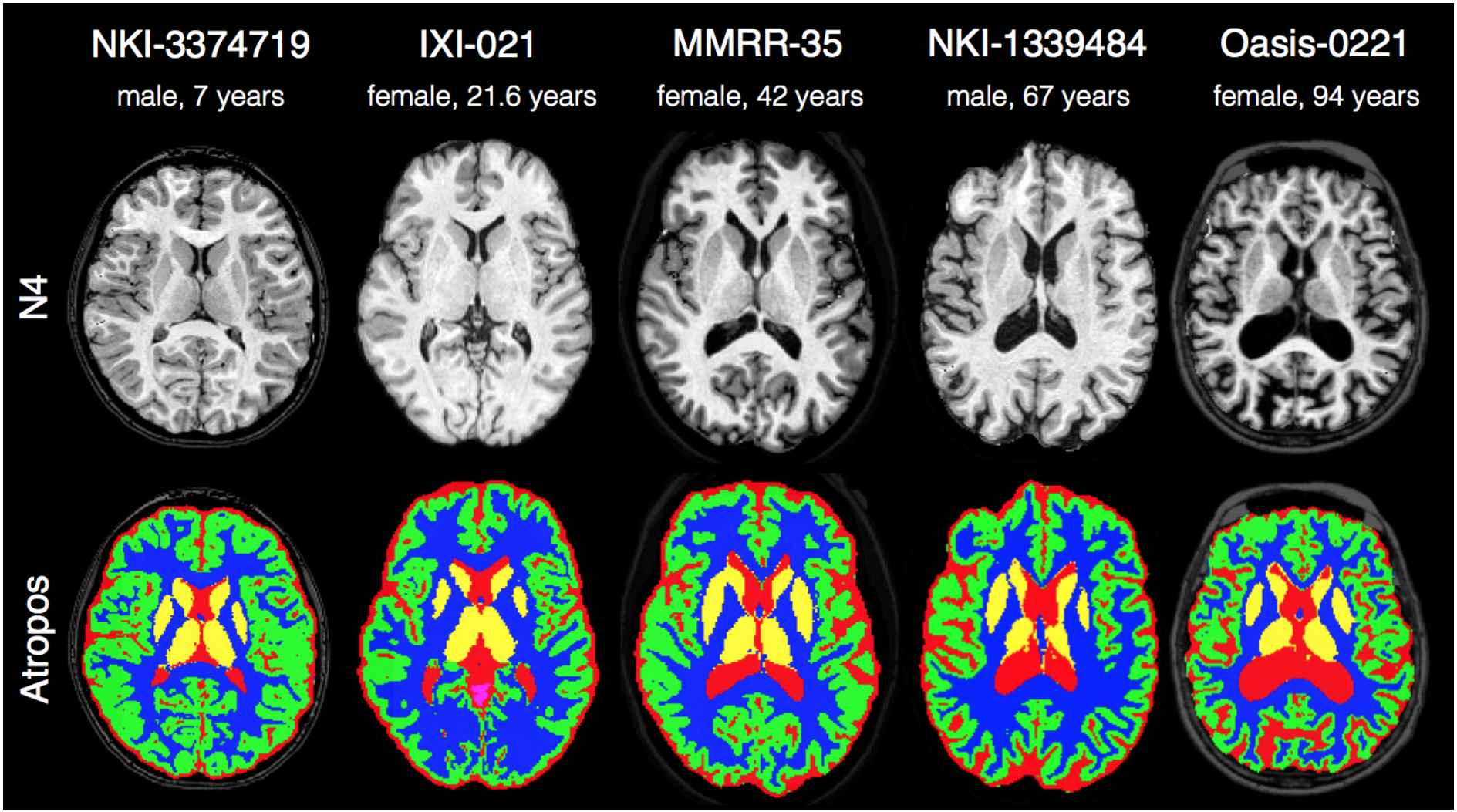
# Atropos


Initialization
• Gaussian
• Non-parametric
• histogram Parzen windows
• manifold Parzen windows
Likelihood models
• Gaussian
• Non-parametric
• histogram Parzen windows
• manifold Parzen windows
Atropos
Prior models
• Markov random field
• Prior label images
• Prior probability images
Miscellaneous
• Label geodesic/Euclidean propagation
• Outlier handling
• localized adaptive intensity handling

# Algorithmic workflow(Atropos + N4)



# Sample results from public data



# Command line help

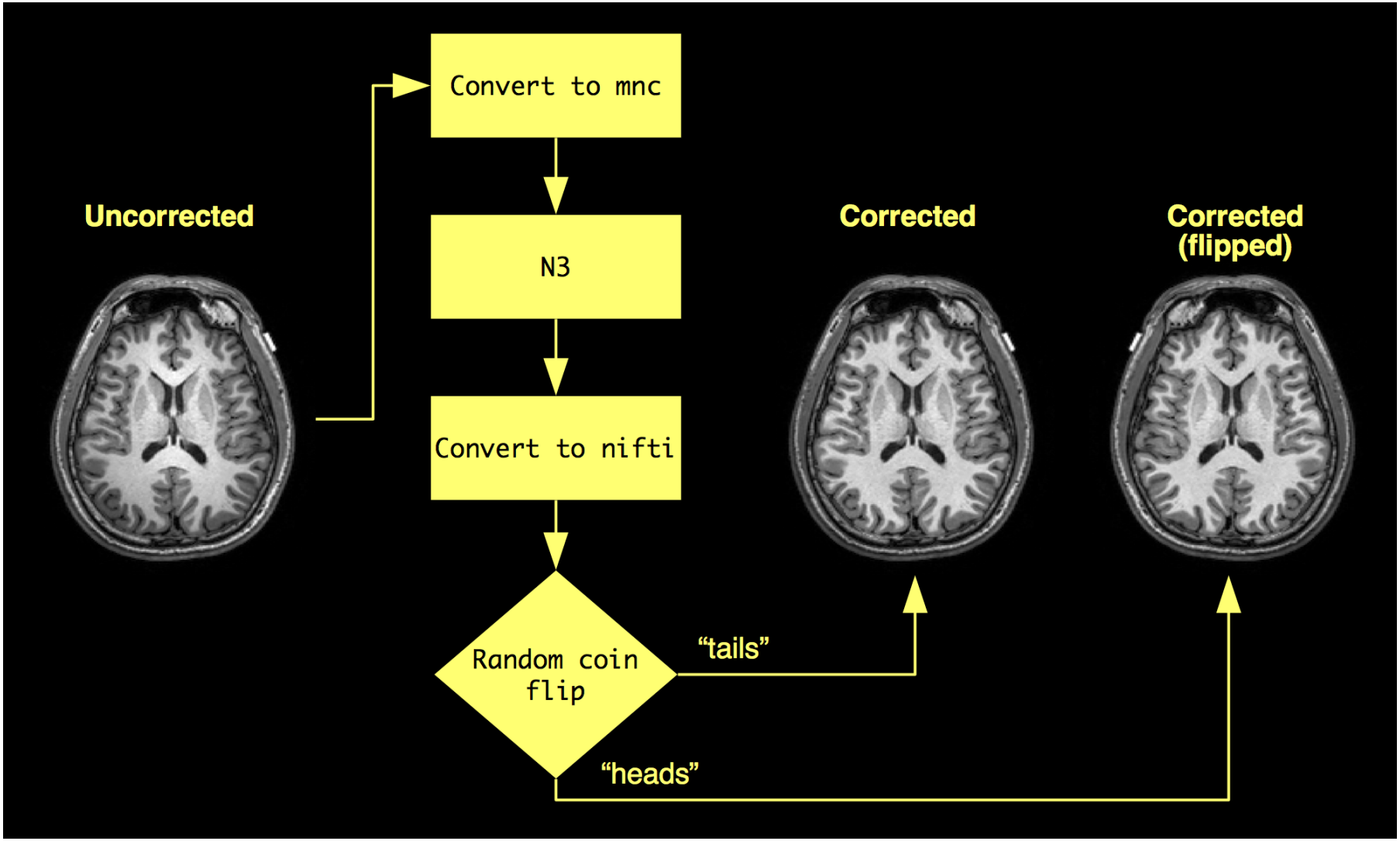
```
$ Atropos -h

COMMAND:
     Atropos

OPTIONS:
     -d, --image-dimensionality 2/3/4
     -a, --intensity-image [intensityImage,<adaptiveSmoothingW
     -b, --bspline [<numberOfLevels=6>,<initialMeshResolution=
     -i, --initialization Random[numberOfClasses]
                          Otsu[numberOfTissueClasses]
                          KMeans[numberOfTissueClasses,<cluste
                          PriorProbabilityImages[numberOfTissu
                          PriorLabelImage[numberOfTissueClasse
     -s, --partial-volume-label-set label1xlabel2xlabel3
     --use-partial-volume-likelihoods 1/(0)
```

# N4 bias correction

# Nonparametric nonuniform intensity normalization (N3)

- Developed at the Montreal Neurological Institute (John Sled, 1998)
- Part of the standard preprocessing protocol in large scale projects such as ADNI
- The traditional de facto standard in MRI bias correction
  - good performance
  - *public availability*
- Public availability — set of perl scripts coordinating various C++ programs
- "*Let's incorporate N3 into ANTs!*"

# N3 adoption issues



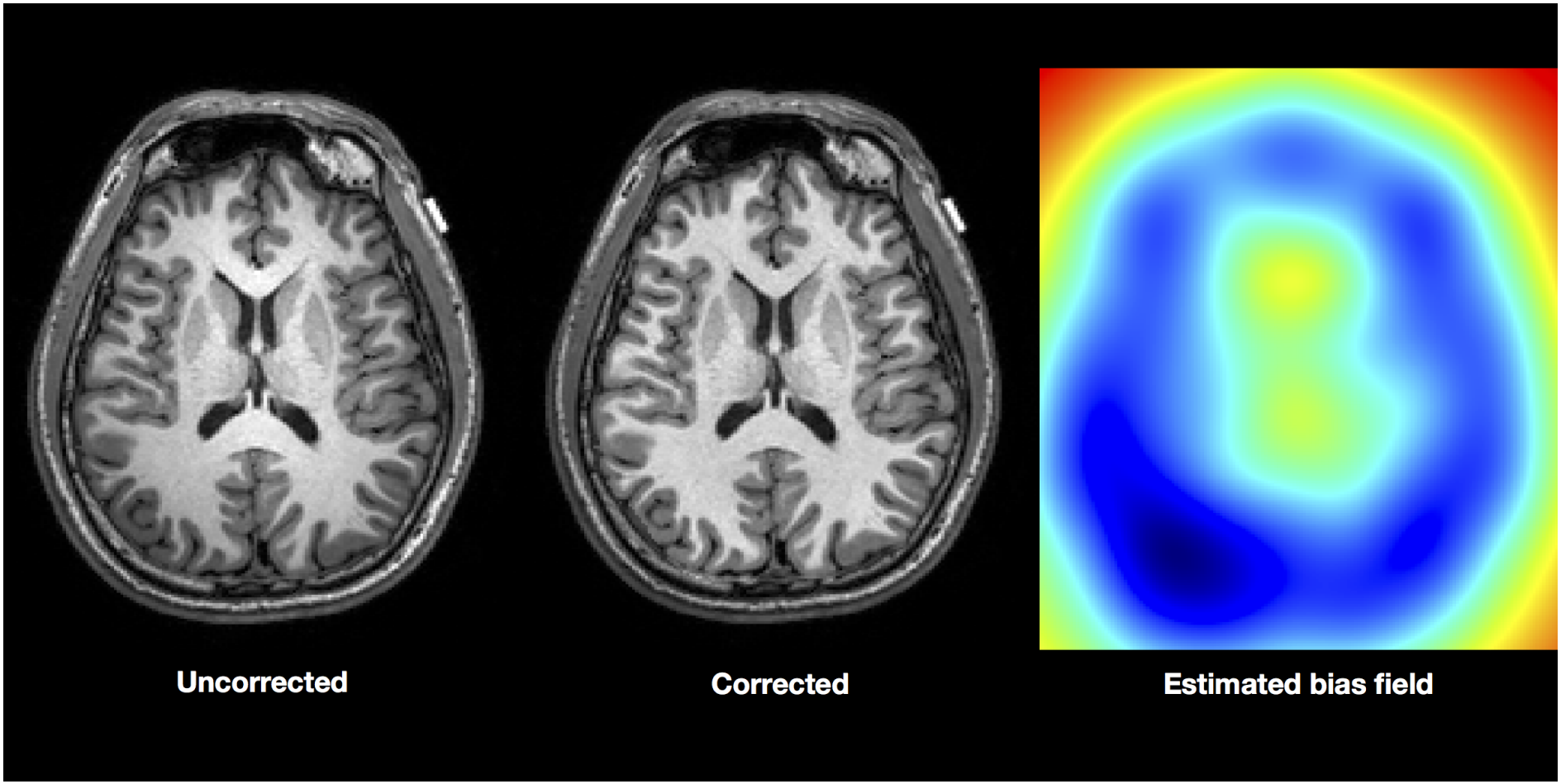

*"So let's re-implement N3 in ITK for ANTs users."*

# N3 -> N4*

*Nick's N3

- comparative evaluation
- smaller spline distances (useful for higher magnet strengths)
- multiresolution
- weighted regional mask (used in `antsAtroposN4.sh`)
- faster execution times
- less susceptible to noise
- *publicly available*

# N4 example

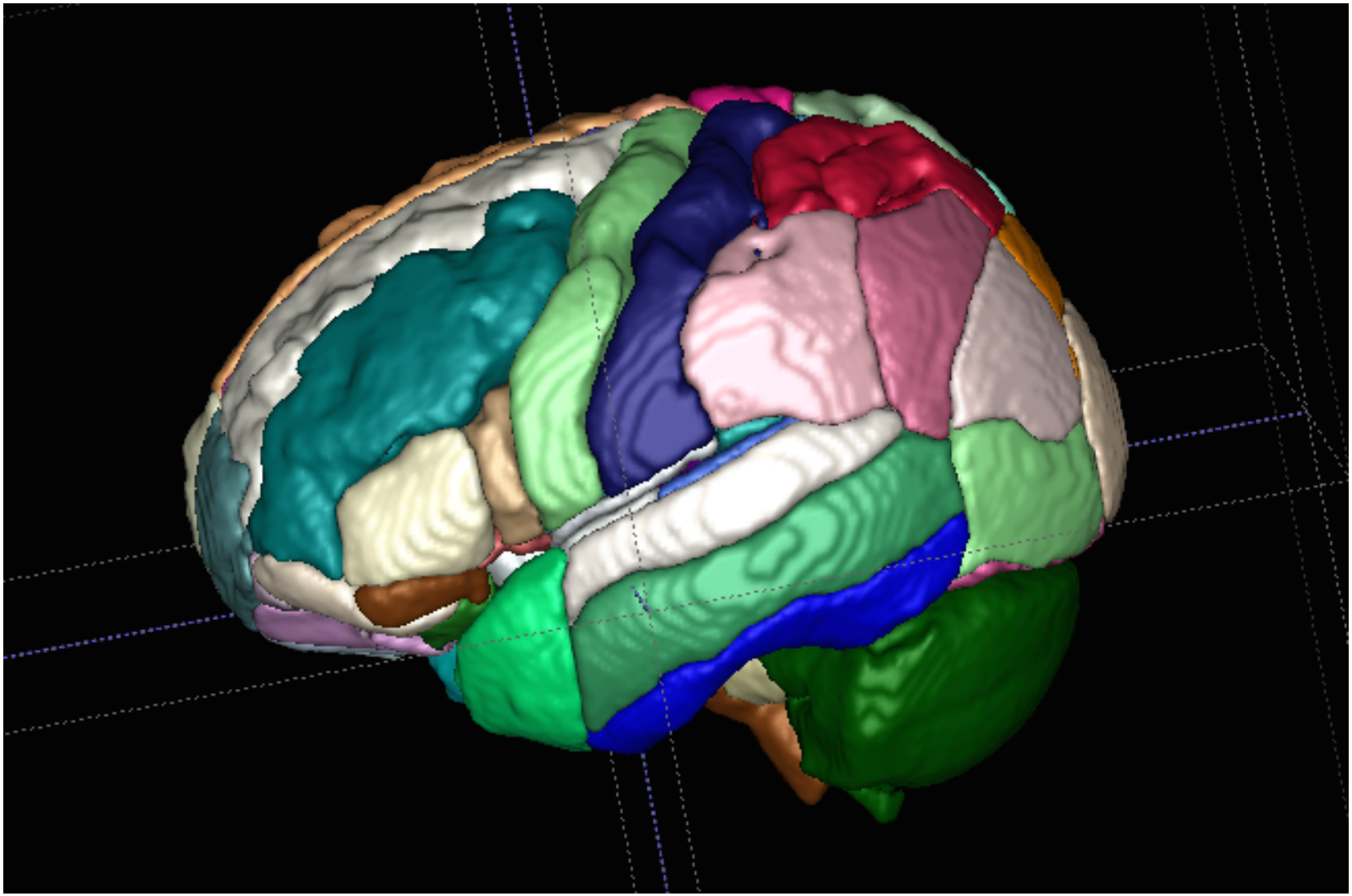


# Command line help

```
$ N4BiasFieldCorrection -h

COMMAND:
     N4BiasFieldCorrection

OPTIONS:
     -d, --image-dimensionality 2/3/4
     -i, --input-image inputImageFilename
     -x, --mask-image maskImageFilename
     -r, --rescale-intensities 0/(1)
     -w, --weight-image weightImageFilename
     -s, --shrink-factor 1/2/3/4/...
     -c, --convergence [<numberOfIterations=50x50x50x50>,<conv
     -b, --bspline-fitting [splineDistance,<splineOrder=3>]
                           [initialMeshResolution,<splineOrder
     -t, --histogram-sharpening [<FWHM=0.15>,<wienerNoise=0.01
```

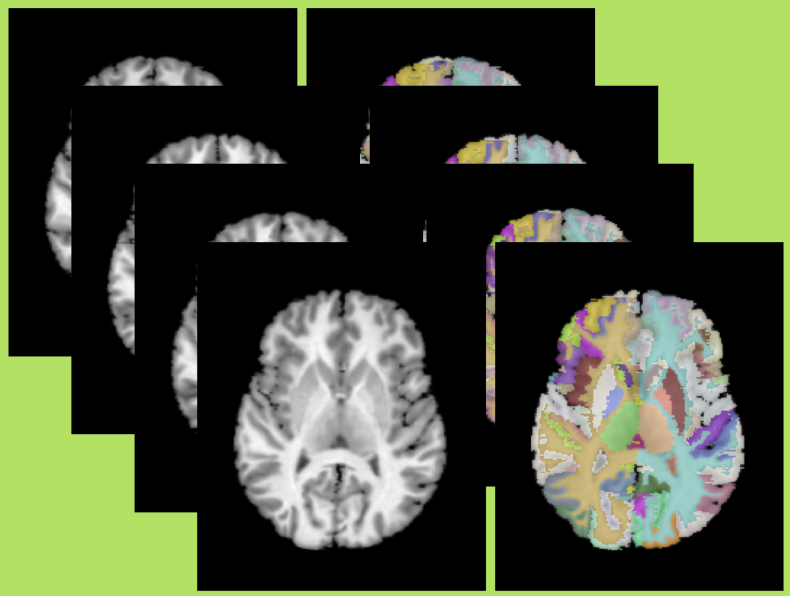
# Joint label fusion

# Multi-atlas labeling

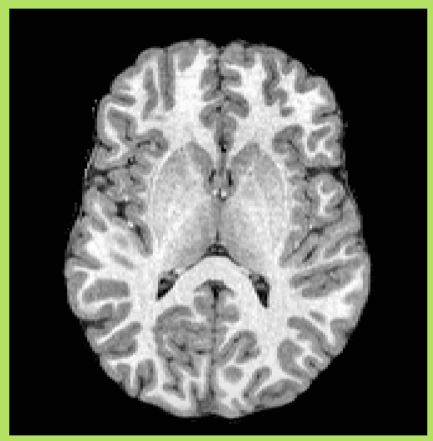


# Multi-atlas segmentation

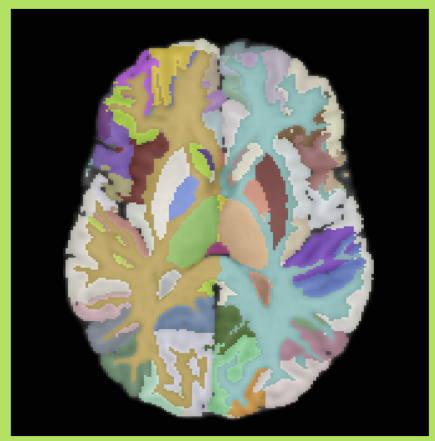
## Joint label fusion



Atlases
(grayscale + segmentation)



Target image



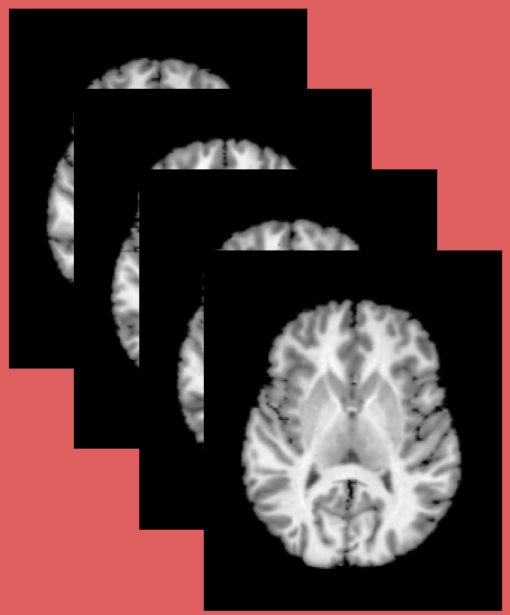
Target segmentation

# Multi-atlas 2012 results

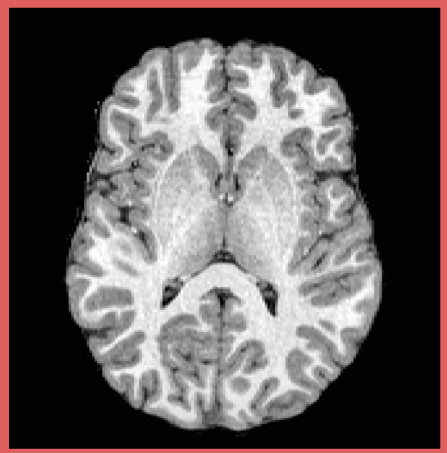
| Overall Rank † | Repro. Rank‡ | Team Name | Mean DSC Overall | Mean DSC Cortical | Mean DSC Non-Cortical |
|---|---|---|---|---|---|
| 1 | 1 | PICSL_BC | 0.7654 | 0.7388 | 0.8377 |
| 2 | 2 | NonLocalSTAPLE | 0.7581 | 0.7318 | 0.8296 |
| 3 | 3 | MALP_EM | 0.7576 | 0.7328 | 0.8252 |
| 4 | 4 | PICSL_Joint | 0.7499 | 0.7216 | 0.8271 |
| 5 | 6 | MAPER | 0.7413 | 0.7144 | 0.8144 |
| 6 | 7 | STEPS | 0.7372 | 0.7107 | 0.8095 |
| 7 | 5 | SpatialSTAPLE | 0.7372 | 0.7093 | 0.8130 |
| 8 | 9 | CIS_JHU | 0.7357 | 0.7131 | 0.7971 |
| 9 | 8 | CRL_Weighted_STAPLE ANTS+Baloo | 0.7344 | 0.7122 | 0.7950 |
| 10 | 10 | CRL_Weighted_STAPLE ANTS | 0.7308 | 0.7066 | 0.7966 |

# New work: joint intensity fusion

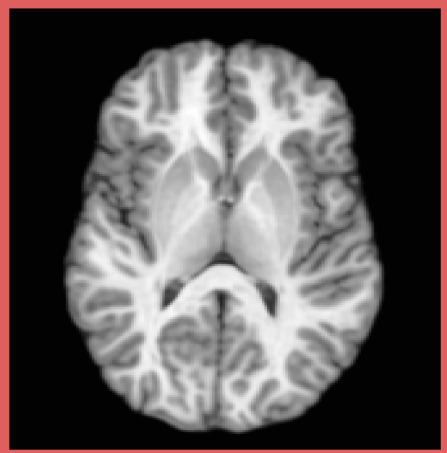
## Joint intensity fusion



Atlases
(grayscale only)



Target image



Target fusion image

# Command line help

```
$ antsJointFusion -h

COMMAND:
     antsJointFusion

OPTIONS:
     -d, --image-dimensionality 2/3/4
     -t, --target-image targetImage
                        [targetImageModality0,targetImageModal
     -g, --atlas-image atlasImage
                       [atlasImageModality0,atlasImageModality
     -l, --atlas-segmentation atlasSegmentation
     -a, --alpha 0.1
     -b, --beta 2.0
     -r, --retain-label-posterior-images (0)/1
     -f, --retain-atlas-voting-images (0)/1
```

# Spatially adaptive denoising

# Command line help

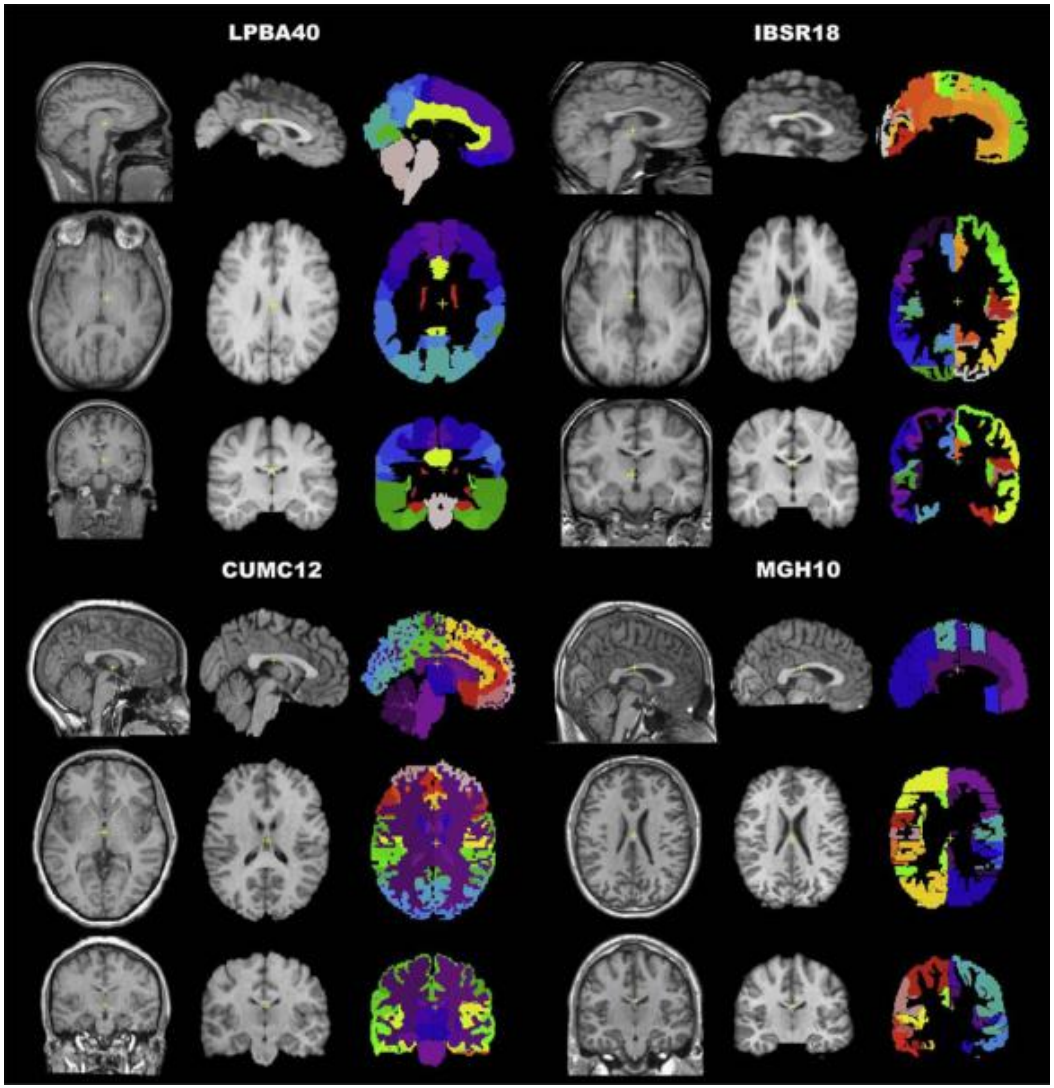
```
$ DenoiseImage -h

COMMAND:
     DenoiseImage

OPTIONS:
     -d, --image-dimensionality 2/3/4
     -i, --input-image inputImageFilename
     -n, --noise-model Rician/(Gaussian)
     -s, --shrink-factor (1)/2/3/...
     -o, --output correctedImage
                    [correctedImage,<noiseImage>]
     --version
     -v, --verbose (0)/1
     -h
     --help
```

# Algorithmic competition

# International competitions

- Klein 2009
- EMPIRE 2010
- Multi-Atlas Label Challenge 2012
- SATA Challenge 2013
- BRATS 2013
- STACOM 2014 MoCo Challenge

# Klein, NeuroImage 2009



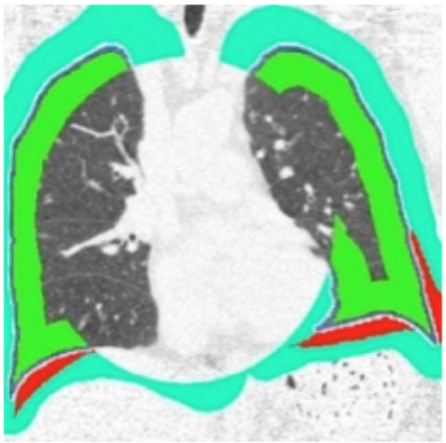
# Klein results

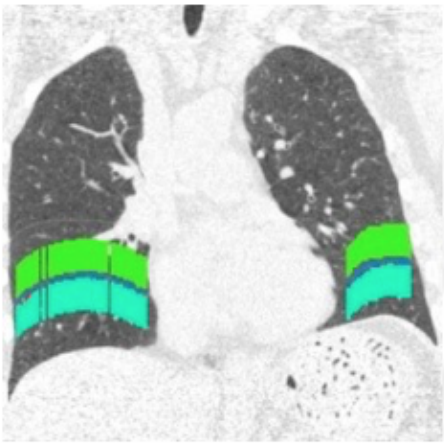
| | LPBA40 | $\mu$ (SD) | IBSR18 | $\mu$ (SD) | CUMC12 | $\mu$ (SD) | MGH10 | $\mu$ (SD) |
|---|---|---|---|---|---|---|---|---|
| rank 1 | ART | .82 (.35) | SPM_D | .83 (.27) | SPM_D | .76 (.24) | SyN | .77 (.37) |
| | SyN | .60 (.38) | SyN | .72 (.51) | SyN | .74 (.51) | ART | .72 (.45) |
| | FNIRT | .49 (.66) | IRTK | .67 (.53) | IRTK | .74 (.50) | IRTK | .61 (.51) |
| | JRD-fluid | .49 (.66) | ART | .60 (.70) | ART | .60 (.70) | | |
| 2 | IRTK | .43 (.63) | JRD-fluid | .30 (.82) | | | SPM_D | .27 (.23) |
| | D.Demons | .13 (.82) | | | | | D.Demons | .27 (.69) |
| | SPM_US | .11 (.83) | | | | | JRD-fluid | .24 (.66) |
| | | | | | | | ROMEO | .06 (.63) |
| 3 | ROMEO | .08 (.73) | FNIRT | .16 (.82) | D.Demons | .20 (.84) | | |
| | SPM_D | .07 (.29) | D.Demons | .05 (.84) | FNIRT | .18 (.81) | | |
| | | | | | JRD-fluid | .17 (.81) | | |

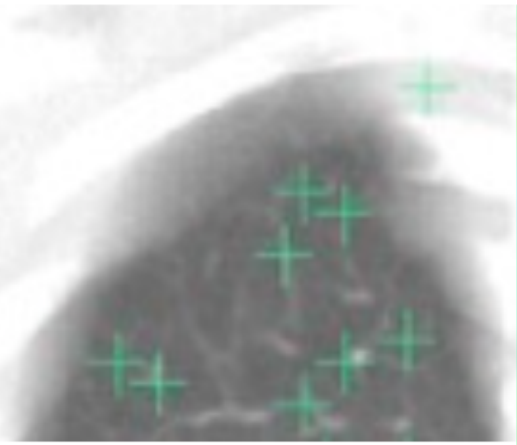
# Take-away message

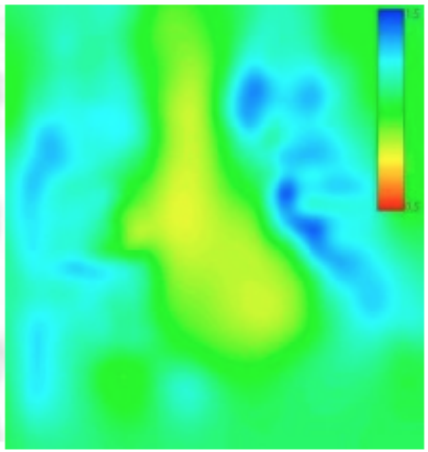
*"One of the most significant findings of this study is that the relative performances of the registration methods under comparison appear to be little affected by the choice of subject population, labeling protocol, and type of overlap measure. . . . ART, SyN, IRTK, and SPM's DARTEL Toolbox gave the best results according to overlap and distance measures, with ART and SyN delivering the most consistently high accuracy across subjects and label sets."*

# EMPIRE 2010


boundaries


fissures


landmarks

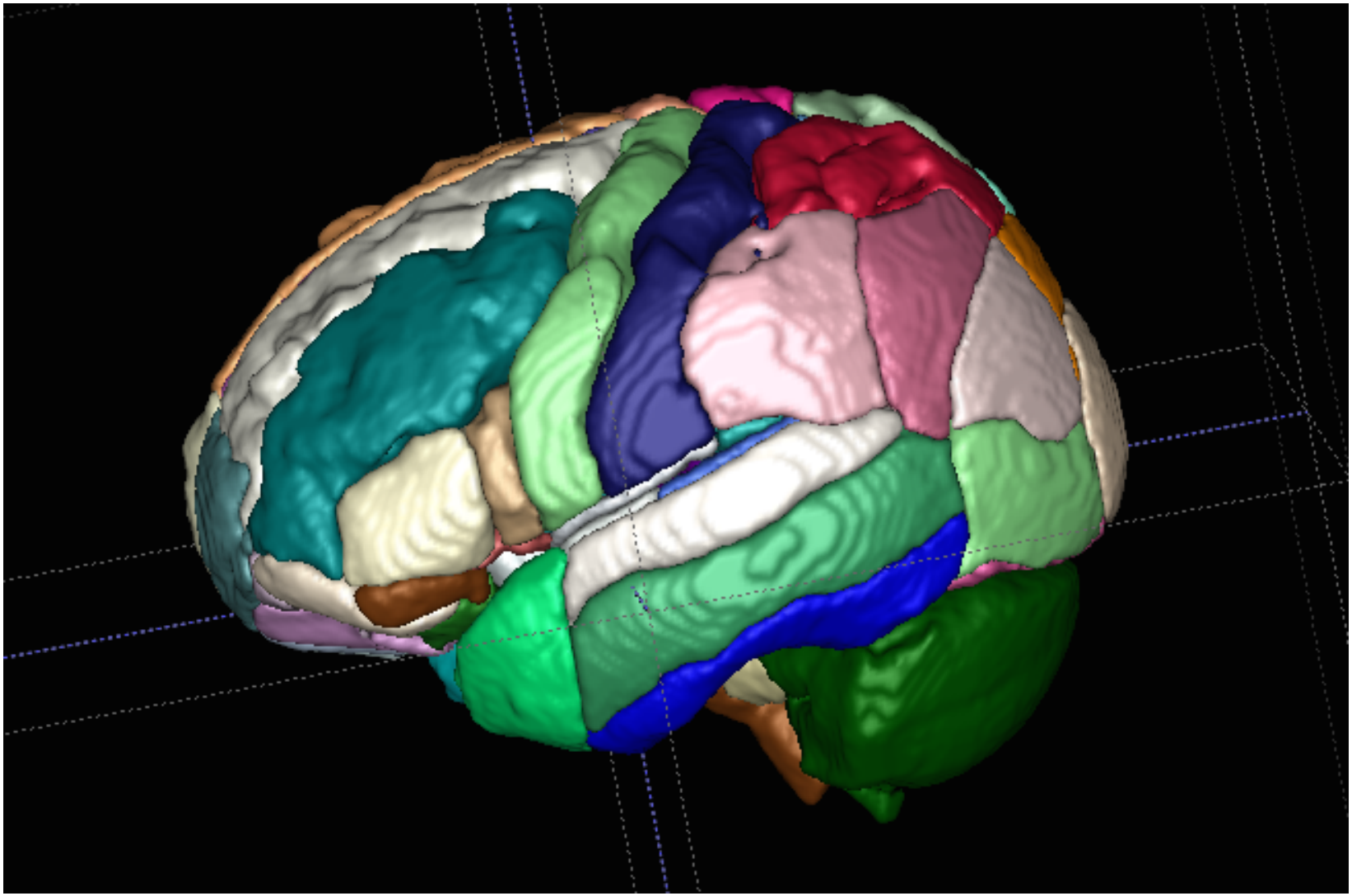

jacobian

- Alignment of lung boundaries,
- major fissures,
- annotated landmark pairs, and
- topology of displacement field.

# EMPIRE 2010 results

| | Lung Boundaries | | Fissures | | Landmarks | | Folding | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Team Name | Avg Score | Avg Rank | Avg Score | Avg Rank | Avg Score | Avg Rank | Avg Score | Avg Rank | Avg Rank | Placed | Last Update | Method Type |
| picsl gsyn | 0.12 | 8.00 | 0.03 | 9.52 | 0.75 | 3.65 | 0.00 | 13.77 | 8.73 | 1 | 25 Jun 2010 | Fully Auto |
| Nifty Reggers | 0.00 | 7.57 | 0.27 | 12.30 | 0.75 | 7.25 | 0.00 | 12.50 | 9.90 | 2 | 26 Jun 2010 | Fully Auto |
| Iowa sstvd | | | | | | | | | | | 26 Jun | Fully |

# Multi-atlas 2012



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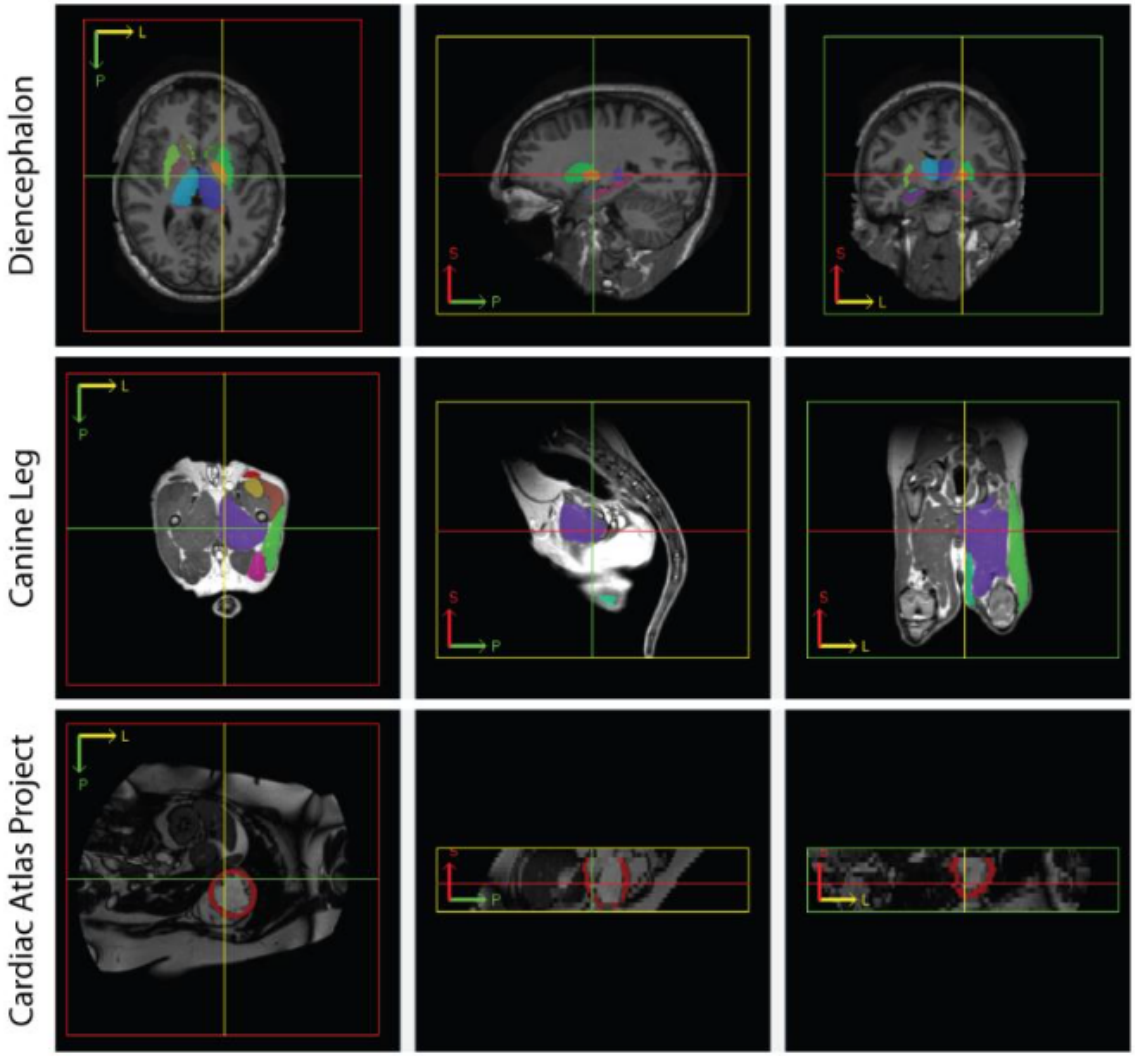
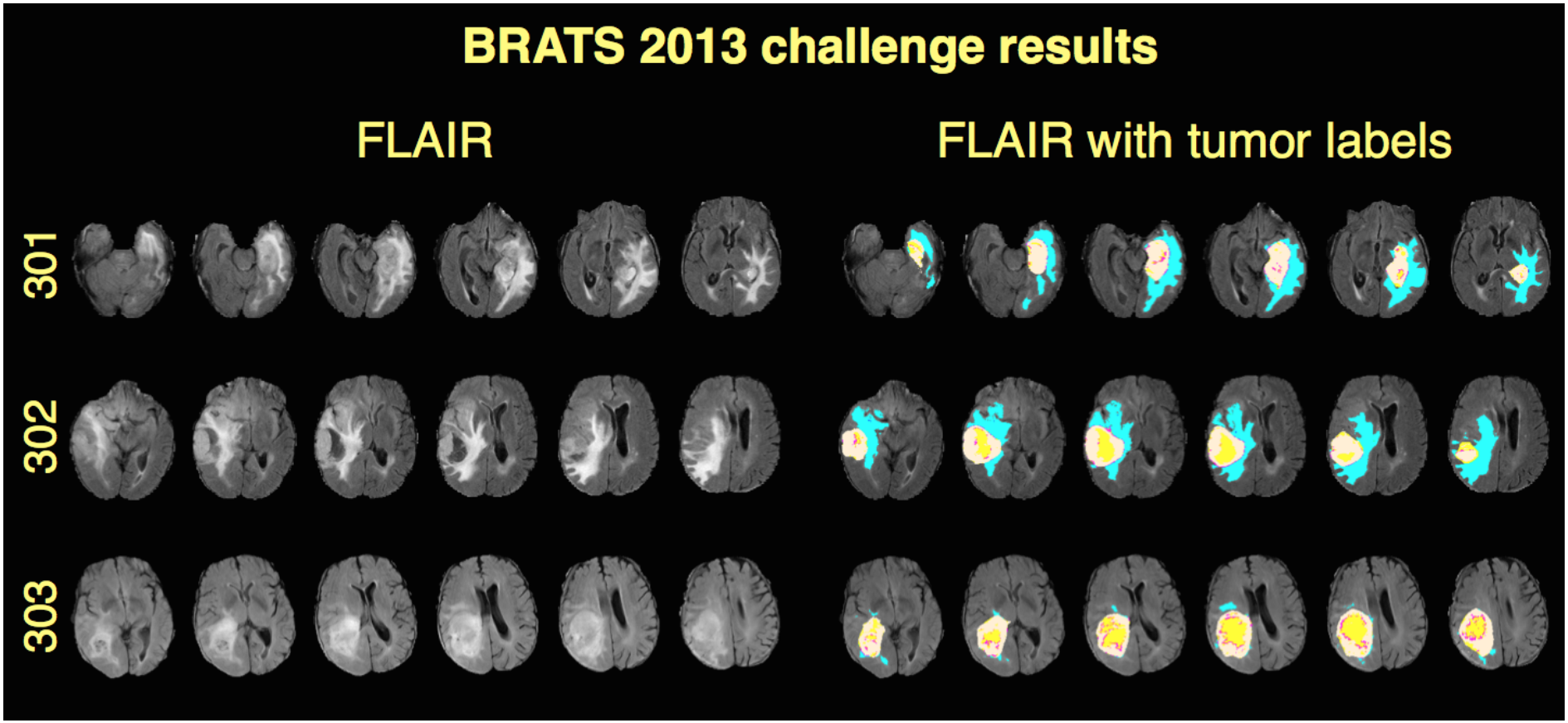
# SATA 2013

Three very different problem domains



# BRATS 2013


BRATS 2013 challenge results
FLAIR
FLAIR with tumor labels
301
302
303

# BRATS 2013 results

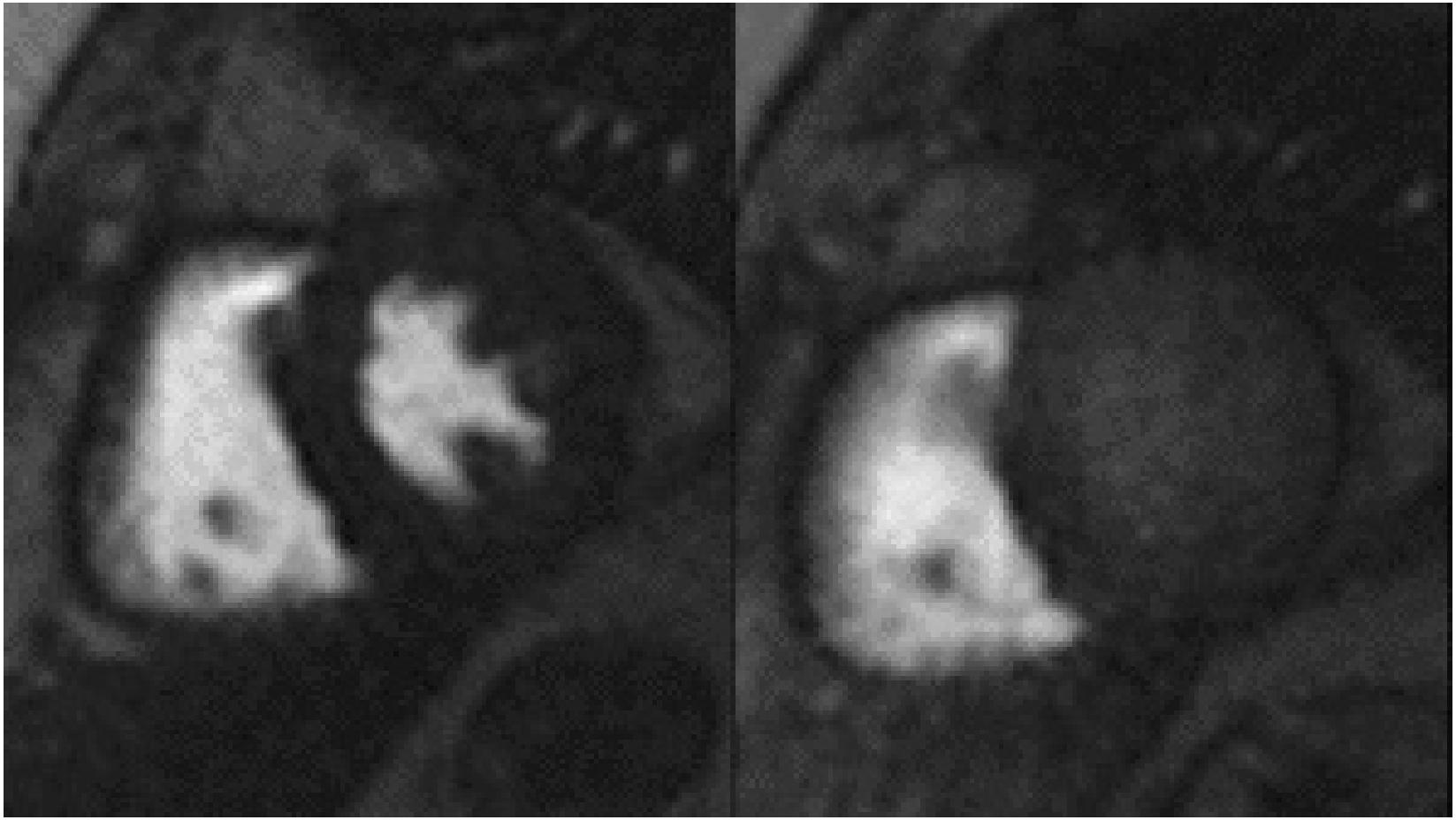
## Results

Patient

| Position | User | Dice | | | Positive Predictive Value | | | Sensitivity | | | Kappa | Complete tumor Rank | Tumor core Rank | Enhancing tumor Rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | complete | core | enhancing | complete | core | enhancing | complete | core | enhancing | | | | |
| 1 | Nick Tustison | 0.87 (1) | 0.78 (1) | 0.74 (1) | 0.85 (2) | 0.74 (4) | 0.69 (4) | 0.89 (2) | 0.88 (1) | 0.83 (1) | 0.99 (1) | 1.67 | 2.00 | 1.89 |
| 2 | Raphael Meier | 0.82 (5) | 0.73 (2) | 0.69 (3) | 0.76 (6) | 0.78 (2) | 0.71 (1) | 0.92 (1) | 0.72 (4) | 0.73 (3) | 0.99 (4) | 4.00 | 2.67 | 3.00 |
| 3 | Syed Reza | 0.83 (4) | 0.72 (3) | 0.72 (2) | 0.82 (3) | 0.81 (1) | 0.70 (3) | 0.86 (5) | 0.69 (6) | 0.76 (2) | 0.99 (3) | 4.00 | 3.33 | 3.22 |
| 4 | Liang Zhao | 0.84 (3) | 0.70 (4) | 0.65 (5) | 0.80 (4) | 0.67 (5) | 0.65 (6) | 0.89 (3) | 0.79 (3) | 0.70 (4) | 0.99 (5) | 3.33 | 4.00 | 4.11 |
| 5 | Nicolas Cordier | 0.84 (2) | 0.68 (5) | 0.65 (6) | 0.88 (1) | 0.63 (6) | 0.68 (5) | 0.81 (6) | 0.82 (2) | 0.66 (6) | 0.99 (2) | 3.00 | 4.33 | 4.33 |
| 6 | Joana Festa | 0.72 (6) | 0.66 (6) | 0.67 (4) | 0.77 (5) | 0.77 (3) | 0.70 (2) | 0.72 (7) | 0.60 (7) | 0.70 (5) | 0.98 (6) | 6.00 | 5.33 | 5.00 |
| 7 | Senan Doyle | 0.71 (7) | 0.46 (7) | 0.52 (7) | 0.66 (7) | 0.38 (7) | 0.58 (7) | 0.87 (4) | 0.70 (5) | 0.55 (7) | 0.98 (7) | 6.00 | 6.33 | 6.44 |

Optimal symmetric multimodal templates and concatenated random forests for supervised brain tumor segmentation (simplified) with ANTsR, *Neuroinformatics*.

# STACOM 2014



# ANTs for neuroimaging

# Putting it all together—the ANTs cortical thickness pipeline

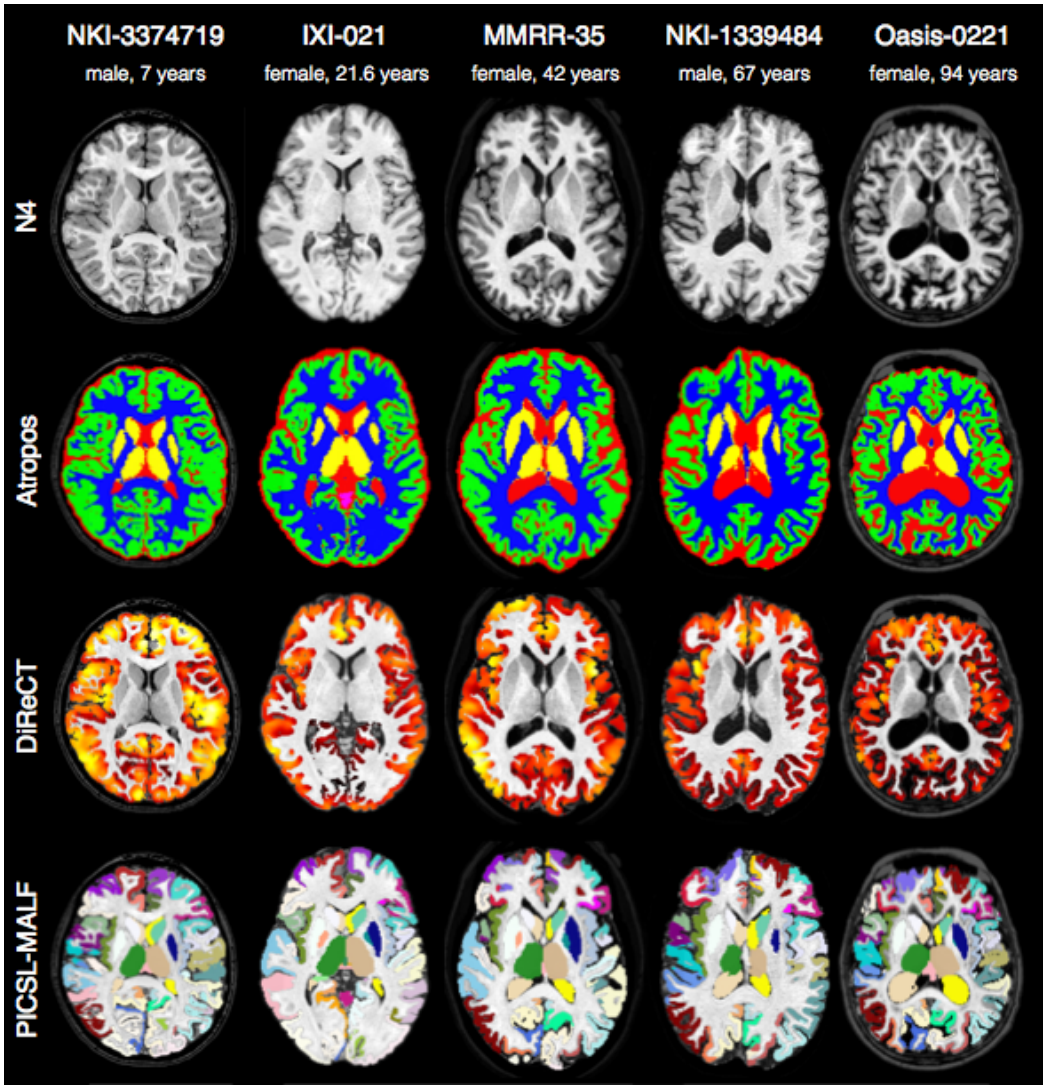
# Cortical thickness studies

| Column1 | Column2 |
|---|---|
| Tetris-playing ability | chronic pancreatitis |
| Huntington's disease | obsessive-compulsive disorder |
| schizophrenia | ADHD |
| bipolar disorder | obesity |
| Alzheimer's disease | heritable depression |
| frontotemporal dementia | elderly depression |
| Parkinson's disease | age |
| Williams syndrome | gender |
| multiple sclerosis | handedness |
| autism | intelligence |

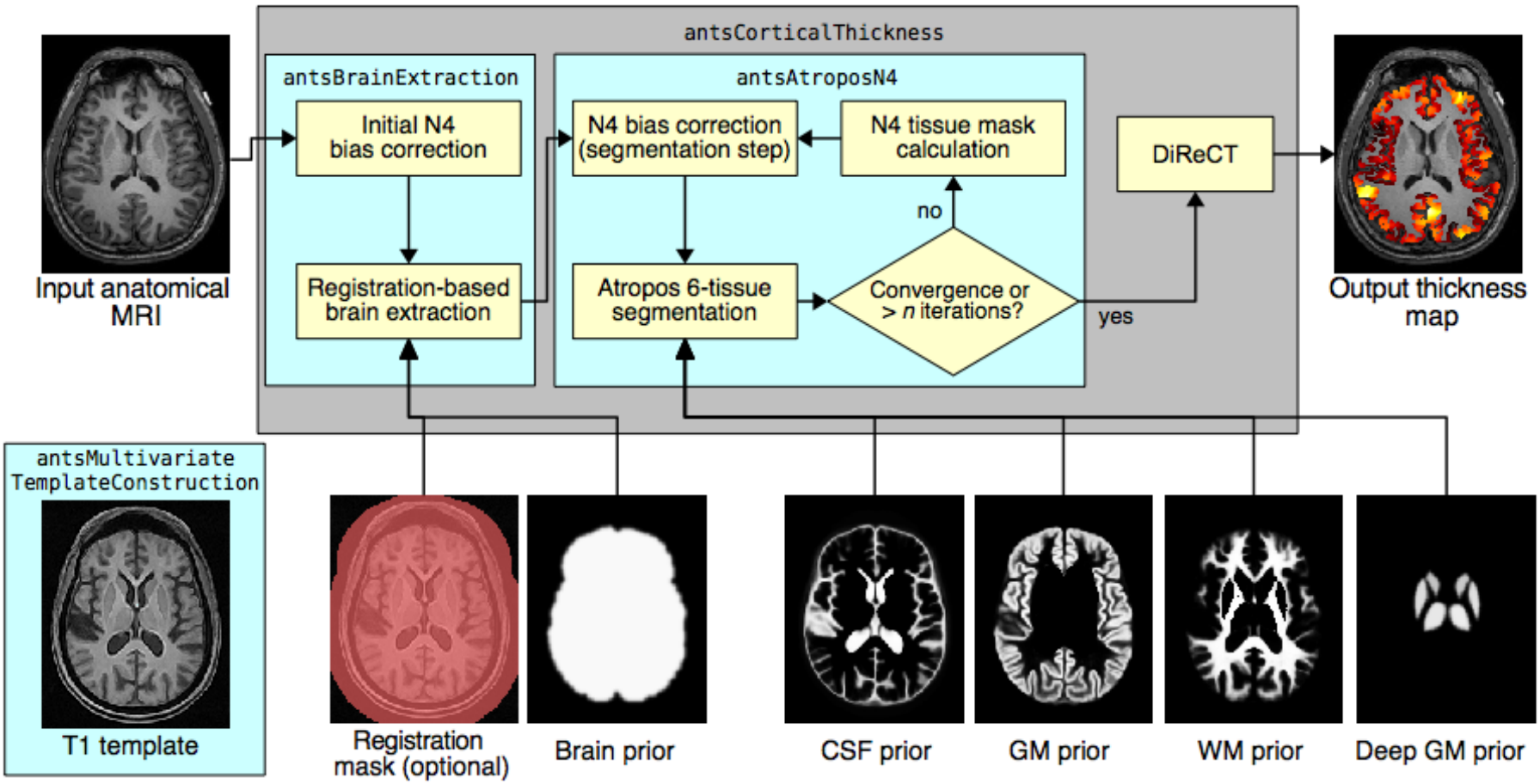
# Basic components of the pipeline

1. template building (offline)
2. brain extraction
3. cortical thickness estimation
4. cortical parcellation

# Sample results

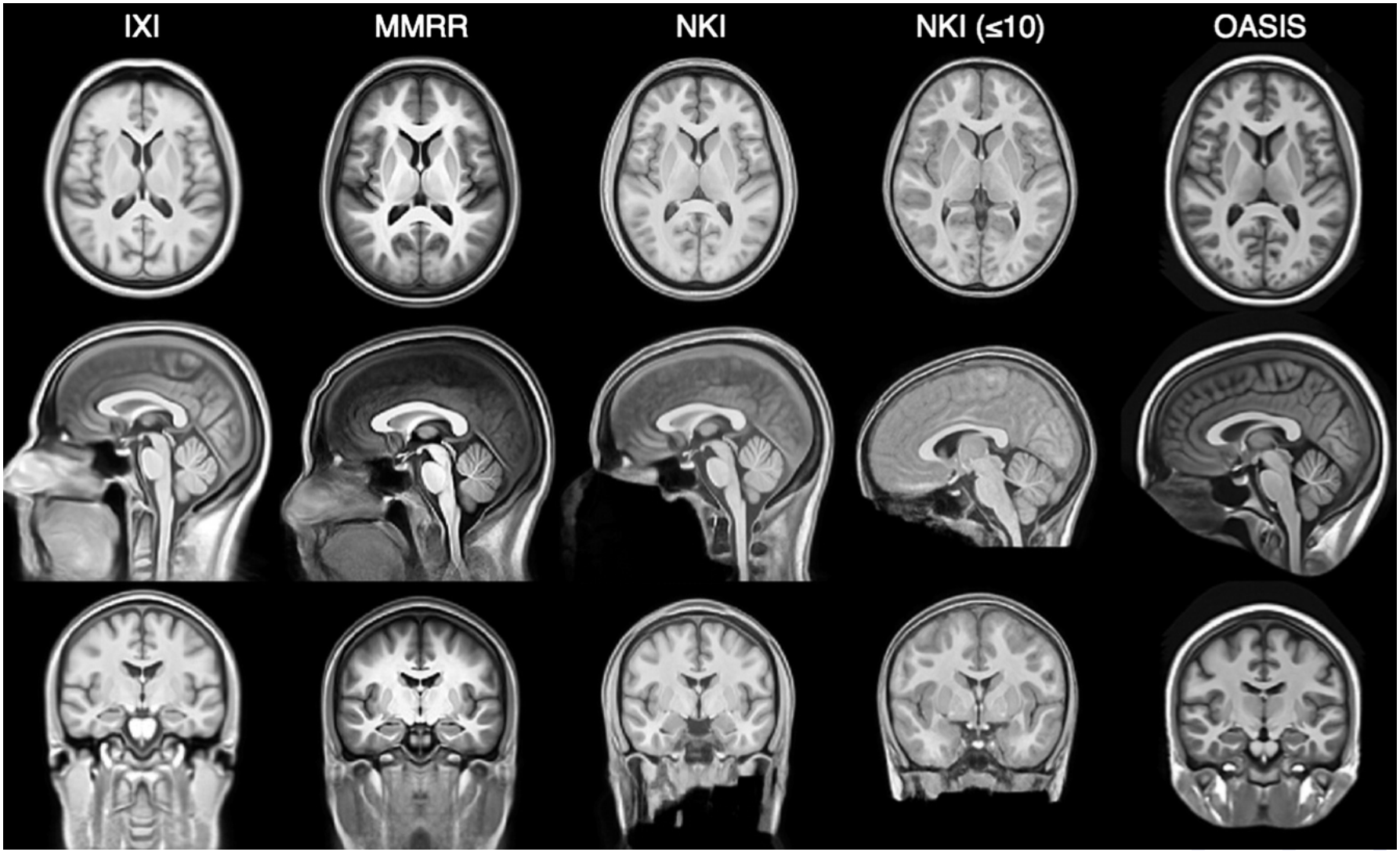


# The ANTs structural brain mapping workflow

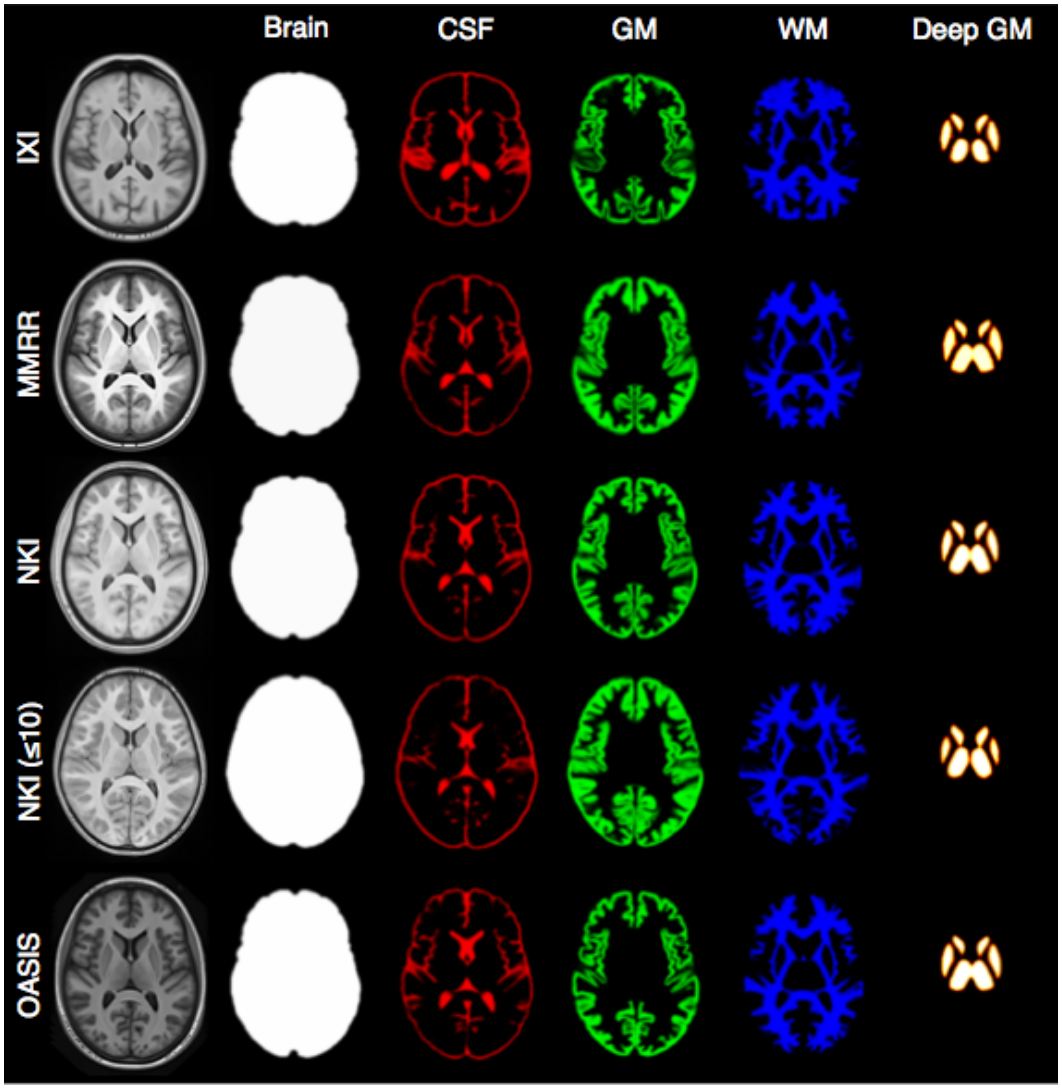


# Template building

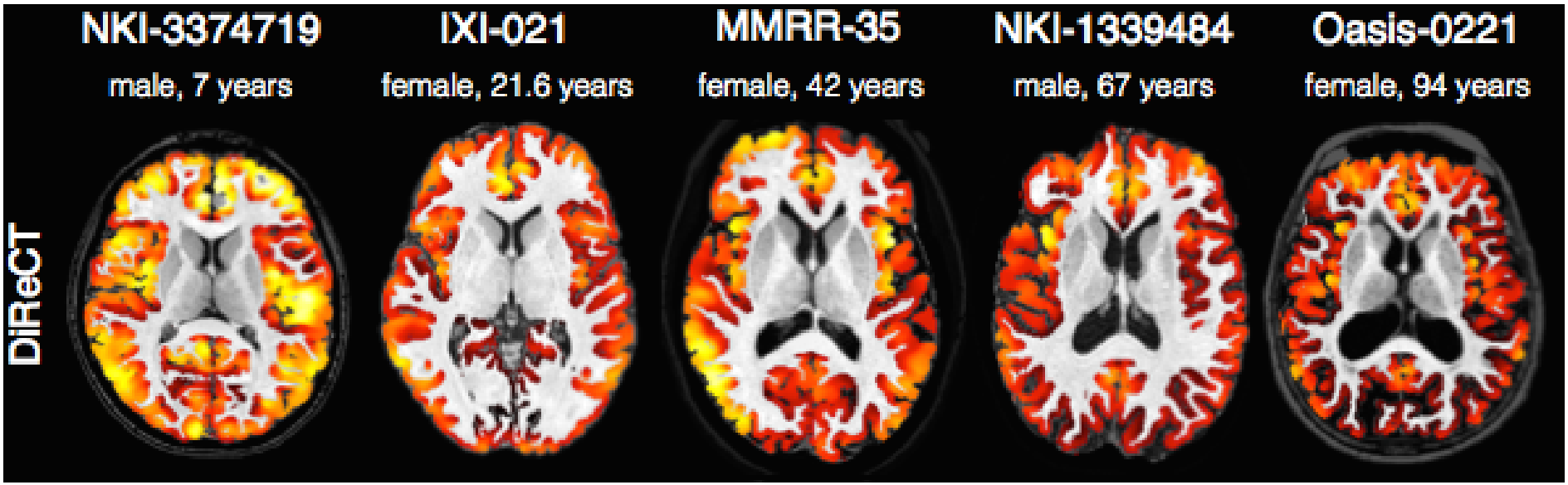
*Tailor data to your specific cohort*



# Template priors



# Cortical thickness estimation

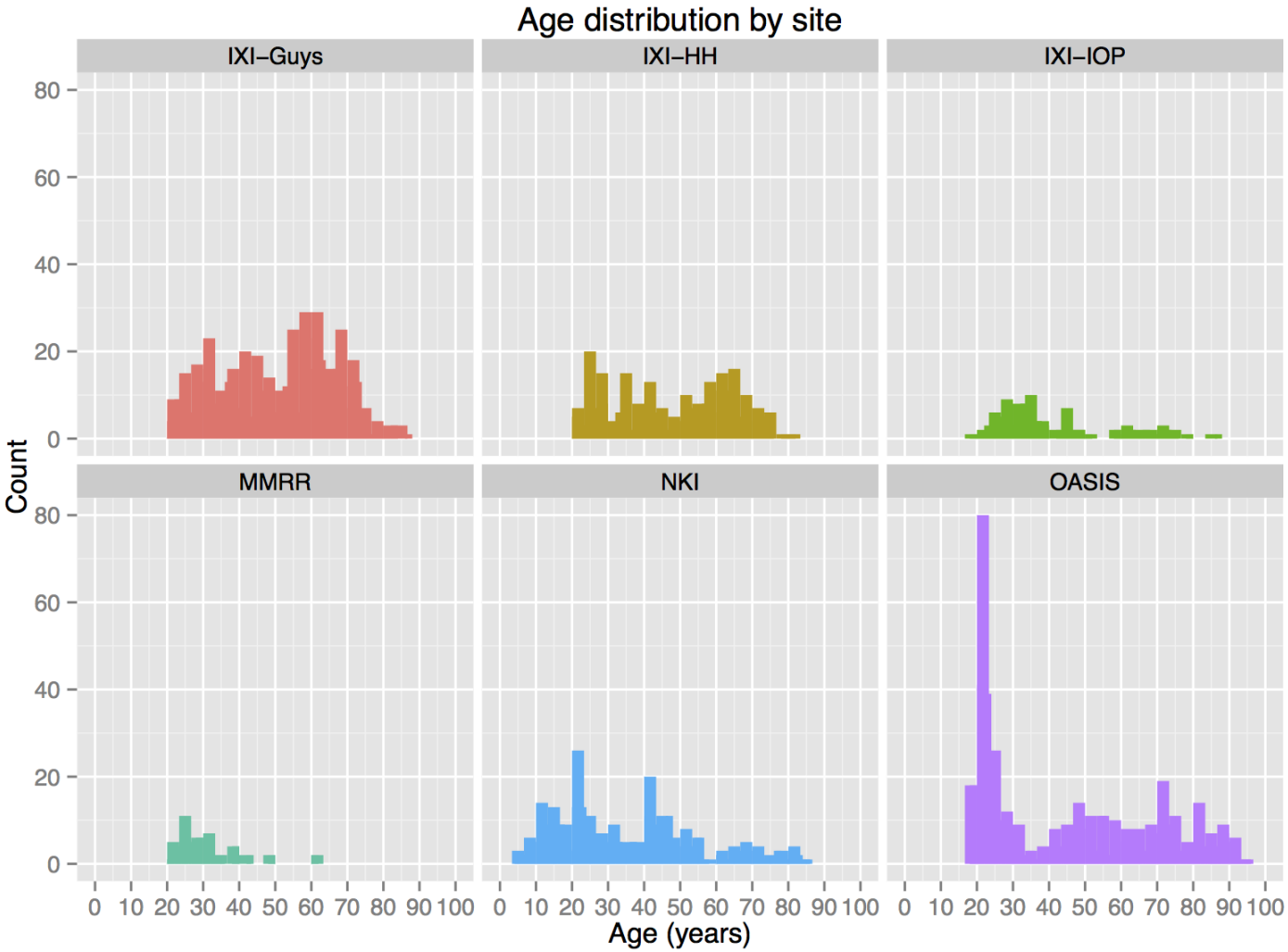


# *But without ground truth, how does one evaluate the pipeline?*

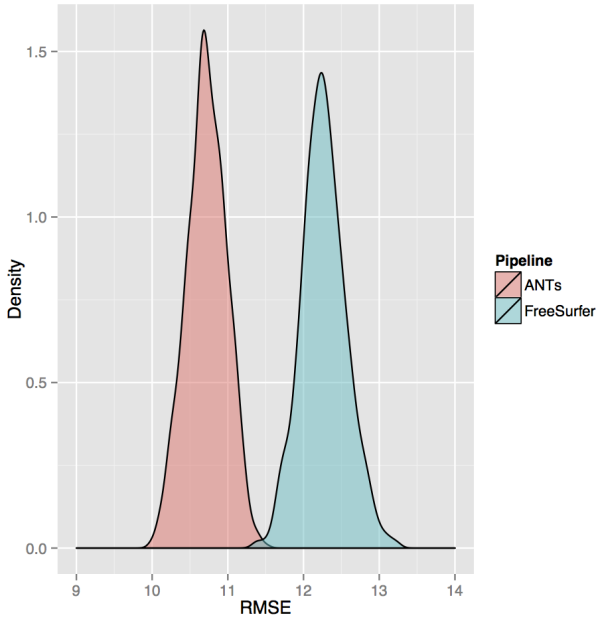
# Predict age and gender

$$AGE \sim VOLUME + GENDER + \sum_{i=1}^{62} T(DKT_i)$$

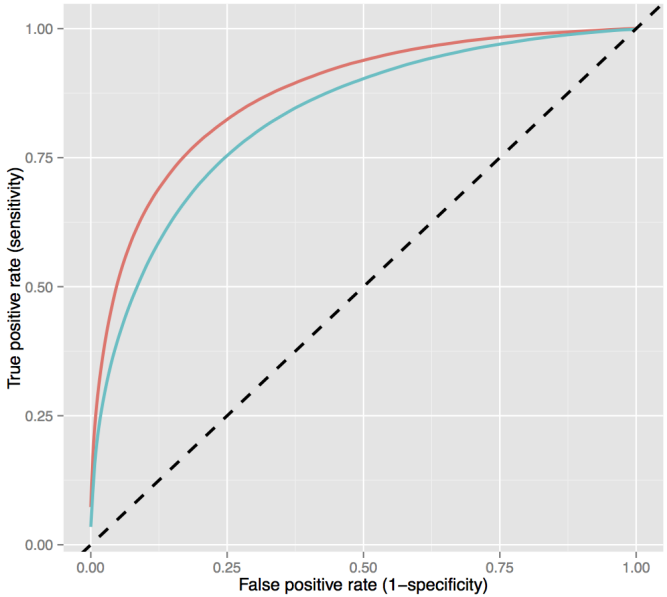
# Open science principles

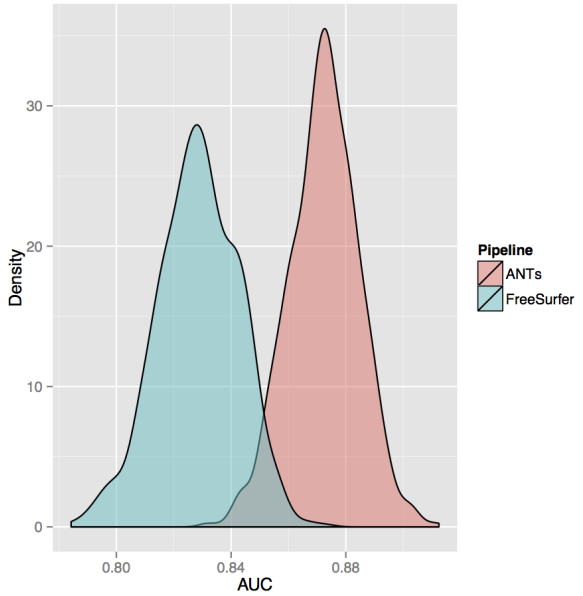


# Prediction from cortical thickness data




**Age**




**Gender**

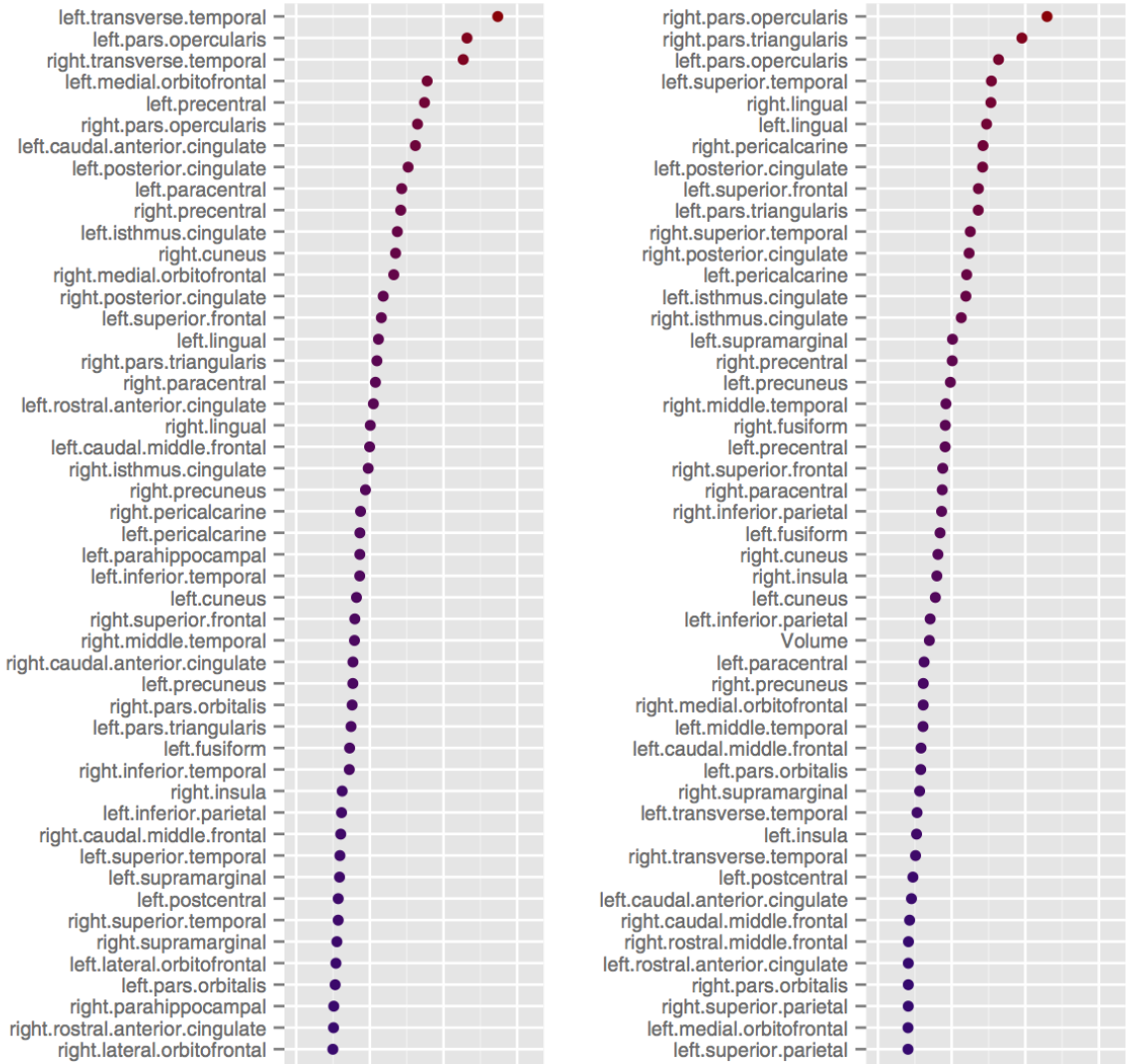
# Age prediction per site

**Table 3**
Mean RMSE for age prediction in years.

| | Linear model | Random forest |
|---|---|---|
| ANTs (combined) | 10.7 | 10.2 |
| FreeSurfer (combined) | 12.3 | 11.9 |
| ANTs (IXI) | 9.3 | 8.6 |
| FreeSurfer (IXI) | 12.3 | 11.7 |
| ANTs (NKI) | NA[a] | 10.9 |
| FreeSurfer (NKI) | NA[a] | 13.3 |
| ANTs (OASIS) | 15.0 | 12.4 |
| FreeSurfer (OASIS) | 15.0 | 11.4 |

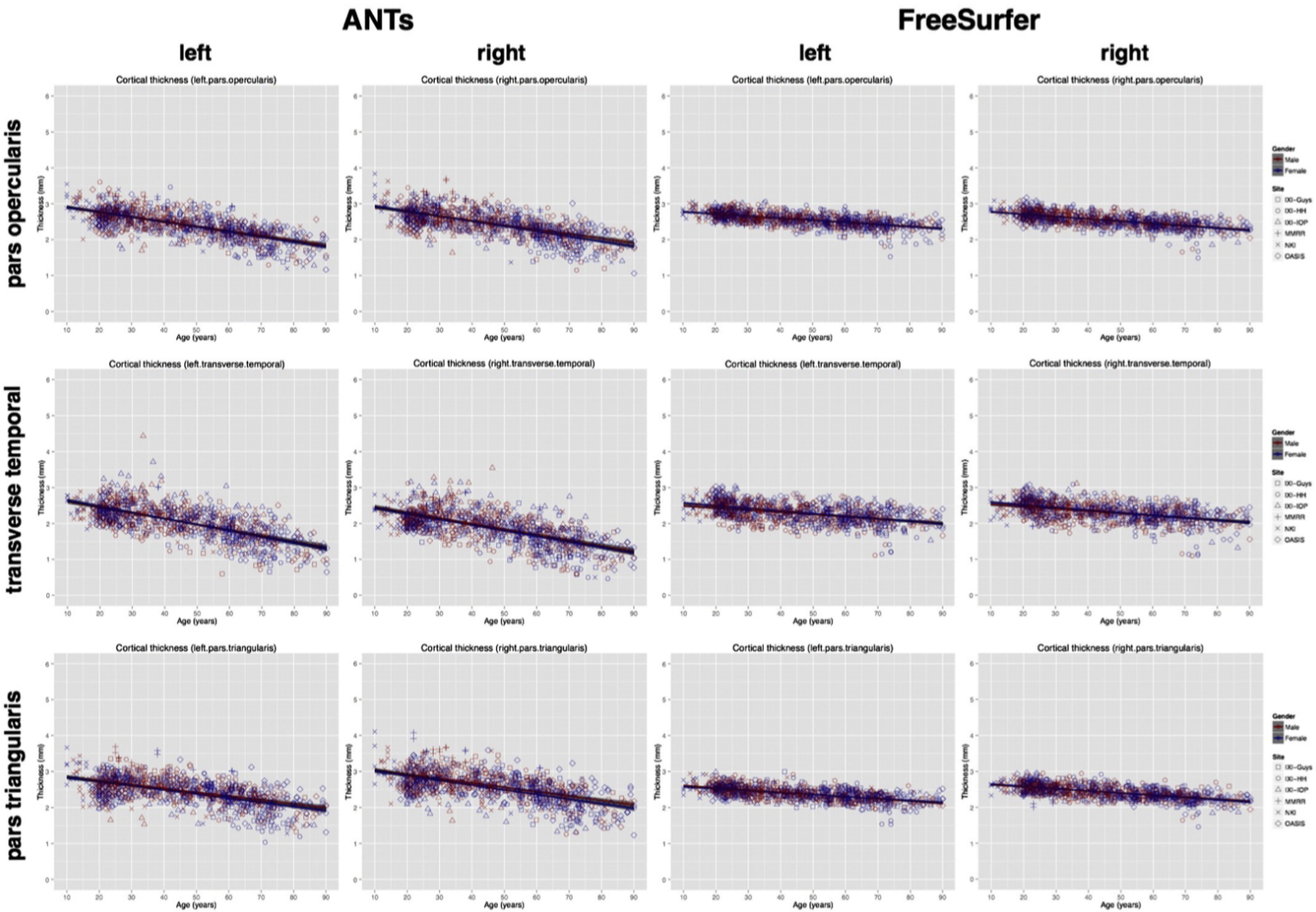
[a] Fitting error.

# Regional importance comparison



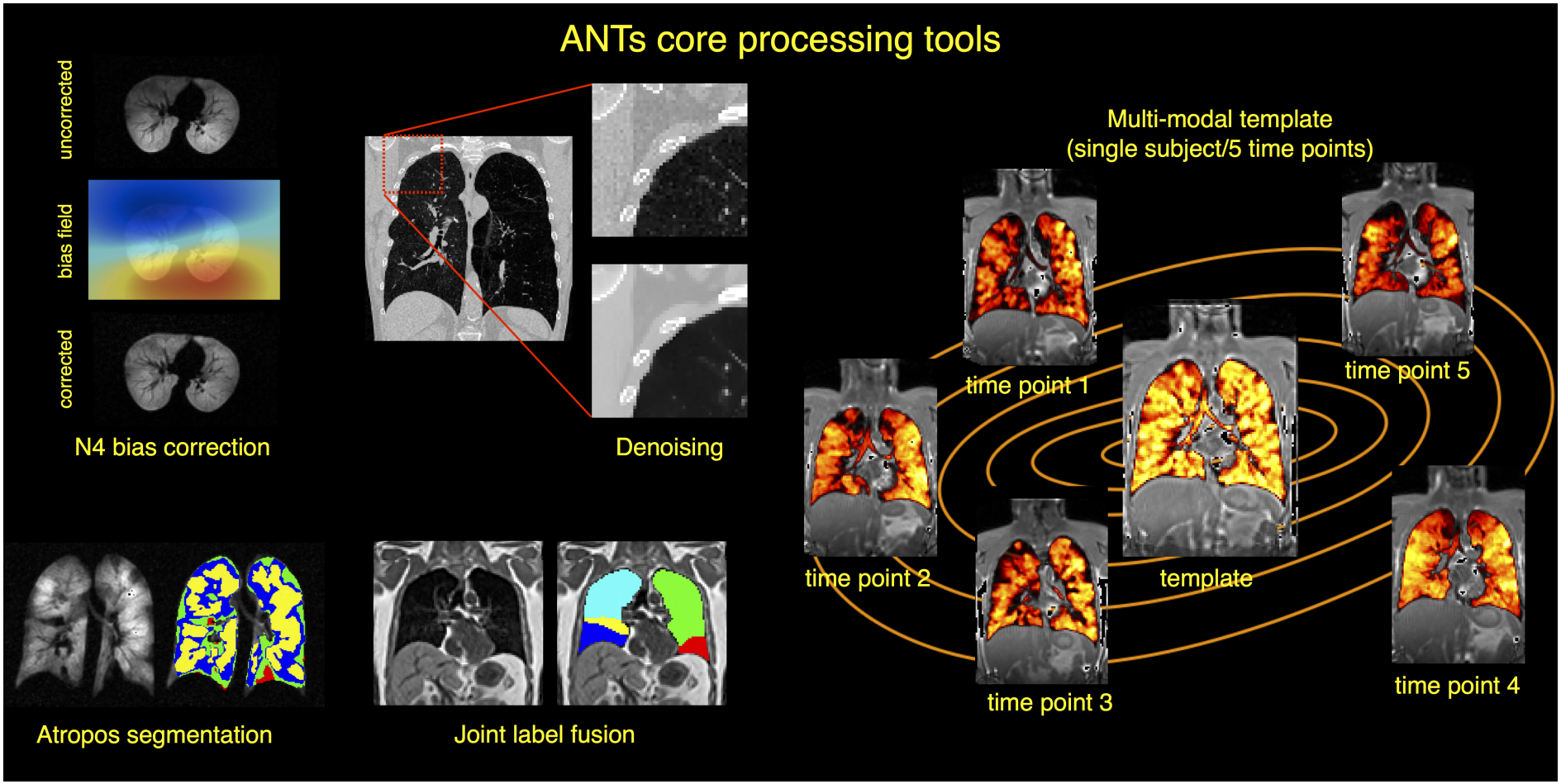

ANTs (left) vs. FreeSurfer (right)

# Regional measurements

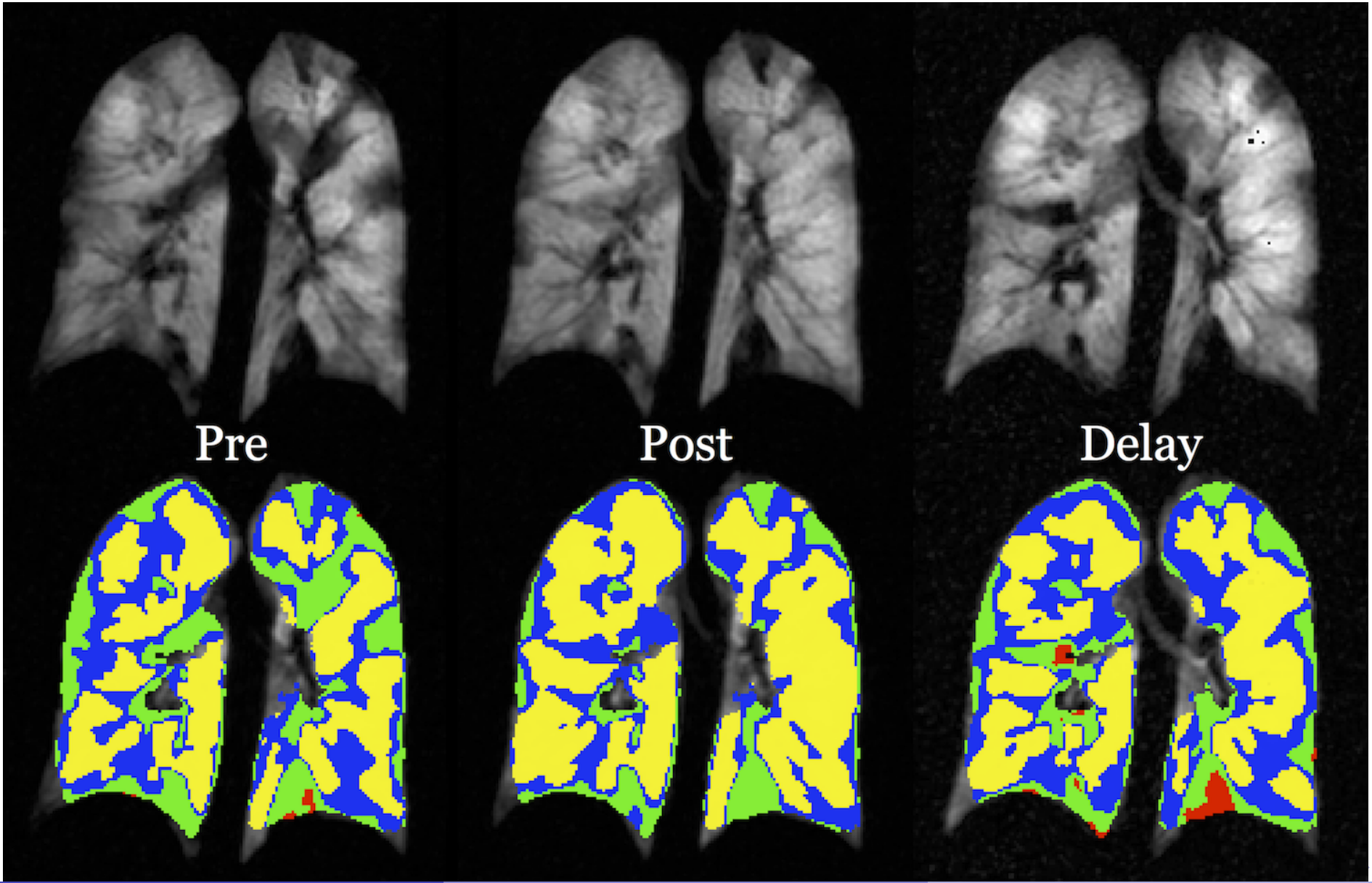


# ANTs for pulmonary imaging

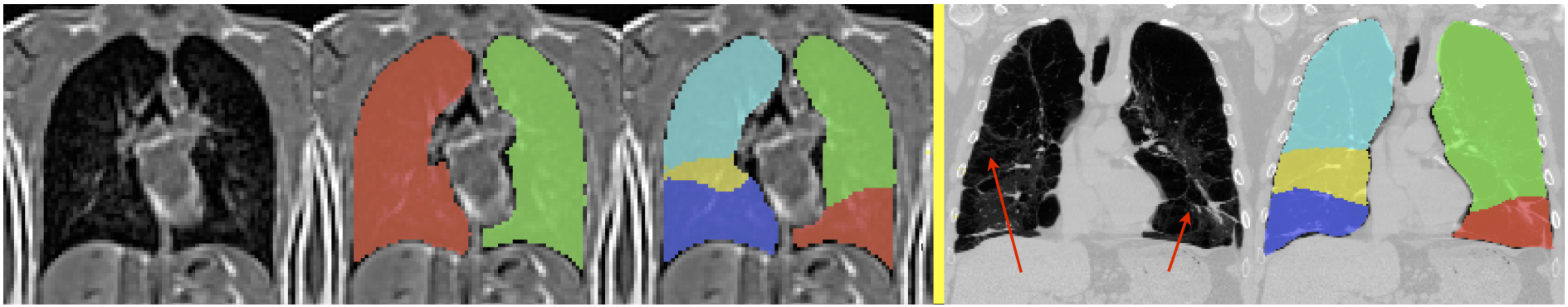
# ANTs core tools for lung image analysis



# Functional ventilation



# Lung and lobe estimation



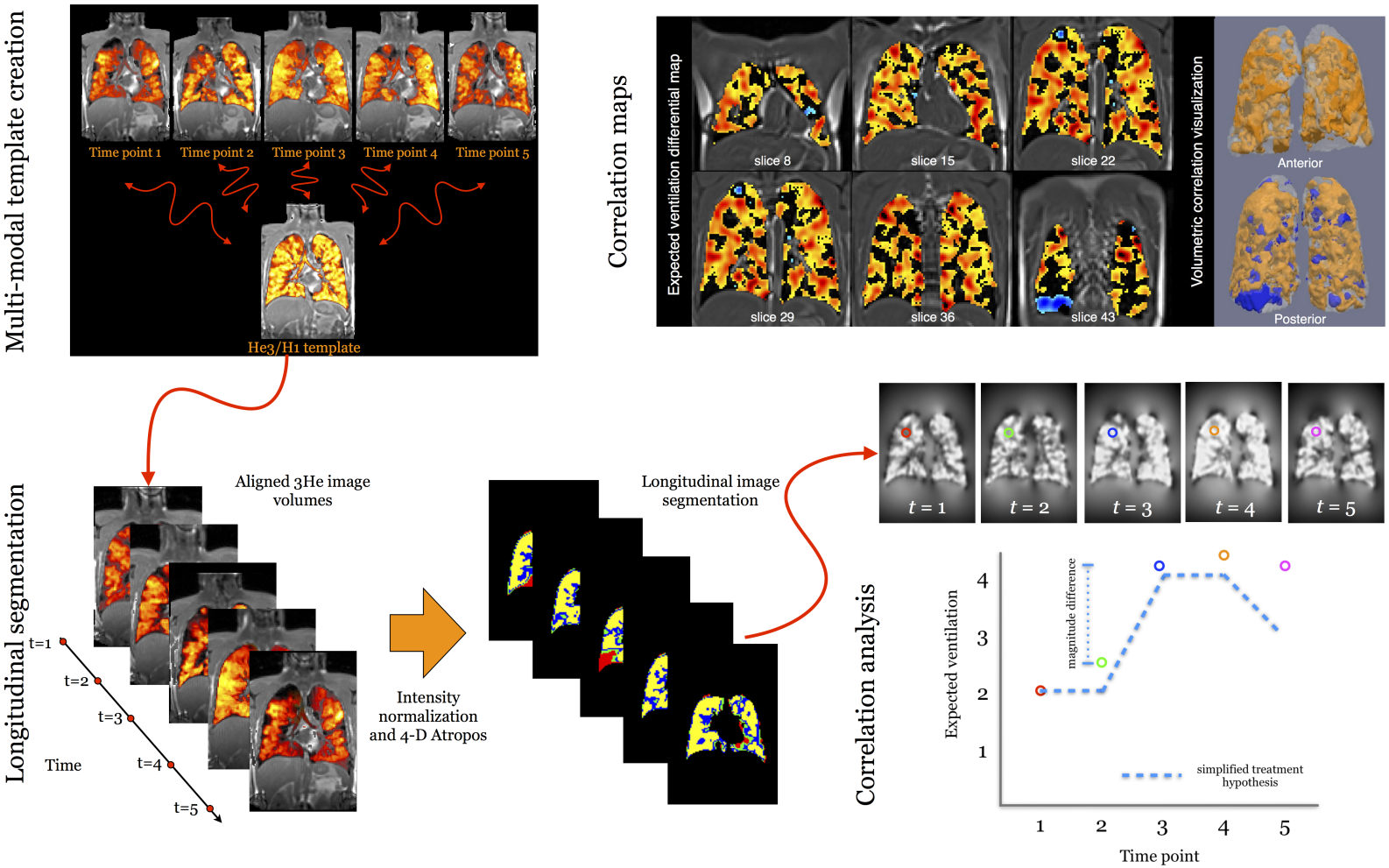
# Good results on 1H MRI

| | Mean | SD | Median |
|---|---|---|---|
| **Left lung** | 0.963 (0.974) | 0.013 (0.097) | 0.964 (0.992) |
| **Right lung** | 0.968 (0.972) | 0.012 (0.135) | 0.970 (0.996) |
| **Left upper** | 0.882 (0.922) | 0.059 (0.163) | 0.894 (0.978) |
| **Left lower** | 0.868 (0.885) | 0.06 (0.229) | 0.892 (0.964) |
| **Right upper** | 0.852 (0.921) | 0.067 (0.088) | 0.875 (0.96) |
| **Right middle** | 0.657 (0.765) | 0.130 (0.299) | 0.696 (0.886) |
| **Right lower** | 0.873 (0.914) | 0.063 (0.176) | 0.900 (0.968) |

(*) Comparison with state-of-the-art in both 1H MRI and CT

# Combining ANTs lung functionality I

## Longitudinal voxelwise analysis of ventilation data



# Combining ANTs lung functionality II