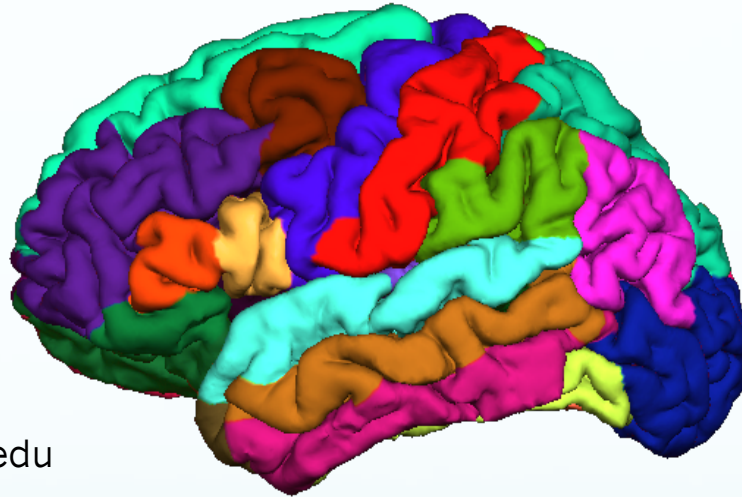


# Longitudinal FreeSurfer

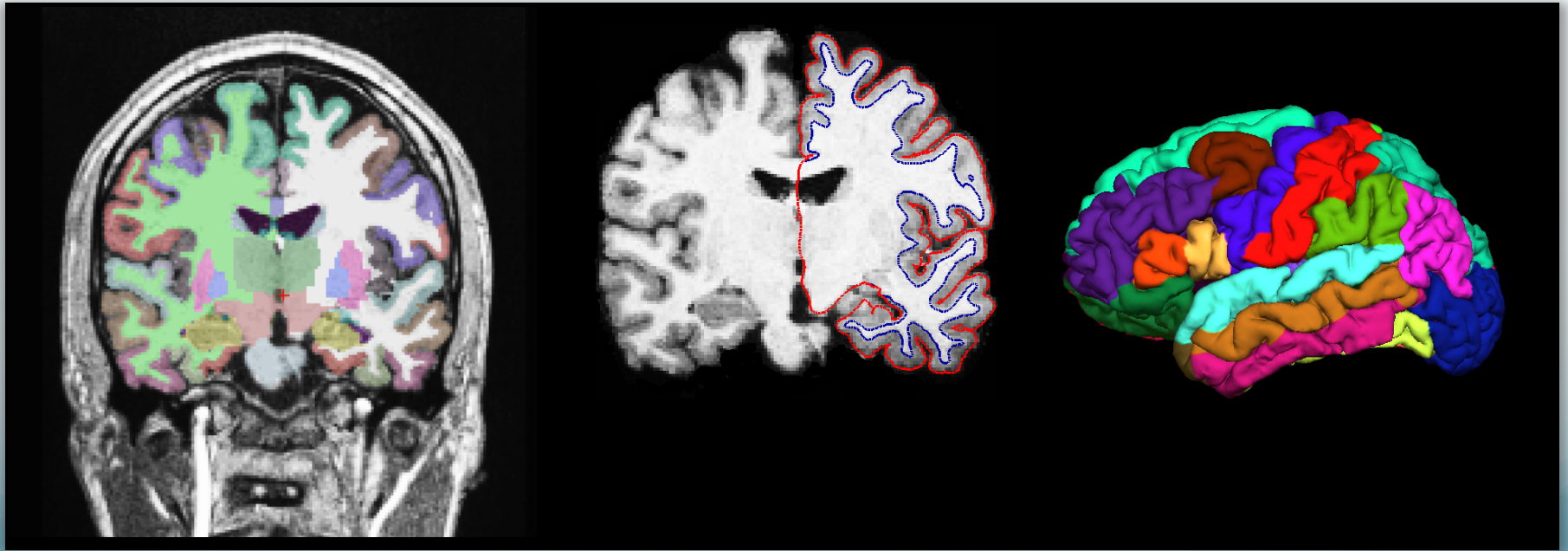


Martin Reuter  
[mreuter@nmr.mgh.harvard.edu](mailto:mreuter@nmr.mgh.harvard.edu)  
<http://reuter.mit.edu>

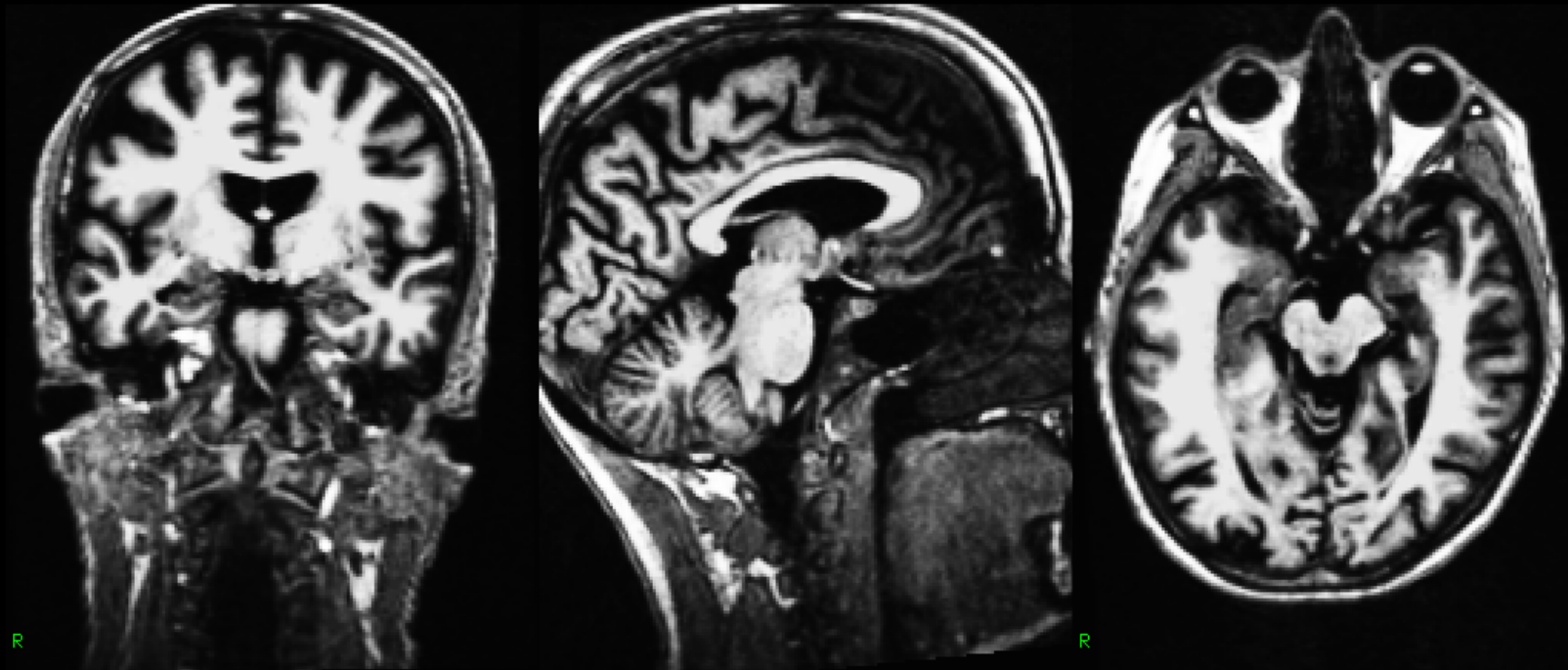
**MGH/HST Athinoula A. Martinos  
Center for Biomedical Imaging**

# What can we do with FreeSurfer?

- measure volume of cortical or subcortical structures
- compute thickness (locally) of the cortical sheet
- study differences of populations (diseased, control)



# Neurodegenerative disease:



14 time points, 6 years, Huntington's Disease

# We'd like to:

- exploit longitudinal information  
(same subject, different time points)

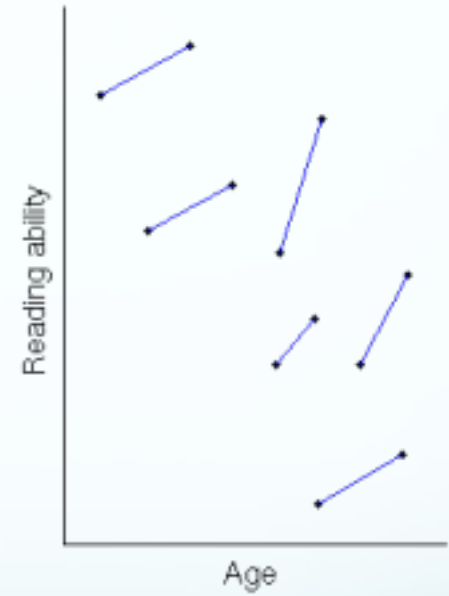
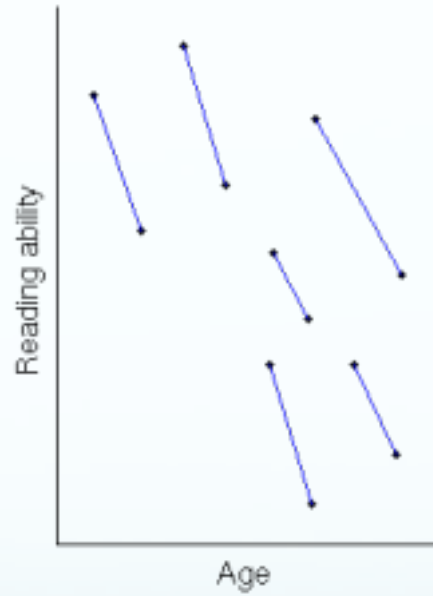
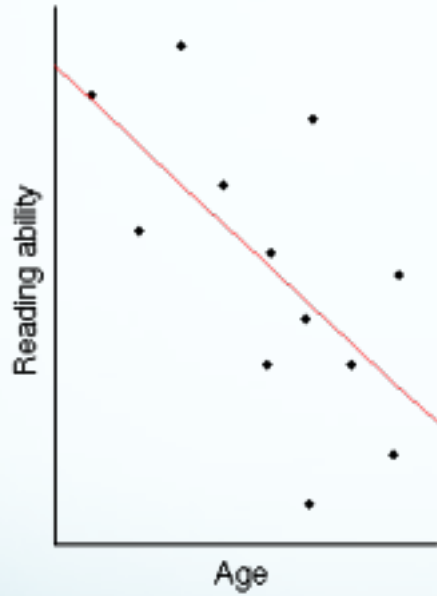
## Why longitudinal?

- to reduce variability on intra-individual morph. estimates
- to detect small changes, or use less subjects (power)
- for marker of disease progression (atrophy)
- to better estimate time to onset of symptoms
- to study effects of drug treatment

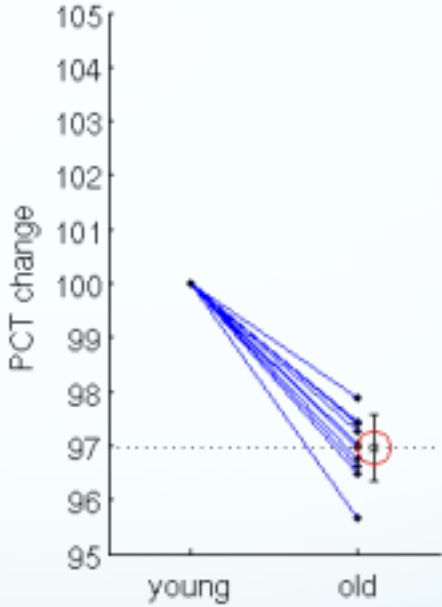
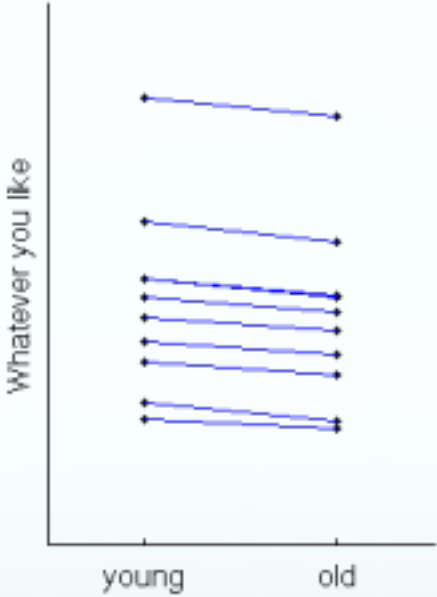
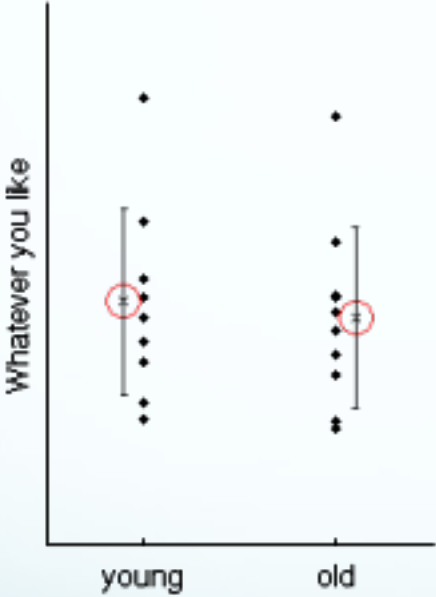
...

[Reuter et al, NeuroImage 2012]

# Example 1



# Example 2



# Challenges in Longitudinal Designs

## 1. **Over-Regularization:**

- Temporal smoothing
- Non-linear warps
- Potentially underestimating change

## 2. **Bias** [Reuter and Fischl 2011] , [Reuter et al. 2012]

- Interpolation Asymmetries [Yushkevich et al. 2010]
- Asymmetric Information Transfer
- Often overestimating change

## 3. **Limited designs:**

- Only 2 time points
- Special purposes (e.g. only surfaces, WM/GM)

# How can it be done?

- Stay *unbiased* with respect to any specific time point by treating all the same
- Create a within subject *template* (base) as an initial guess for segmentation and reconstruction
- *Initialize* each time point with the template to reduce variability in the optimization process
- For this we need a **robust registration** (rigid) and **template estimation**



# Robust Registration

# Robust Registration

**Goal:** Highly accurate inverse consistent registrations

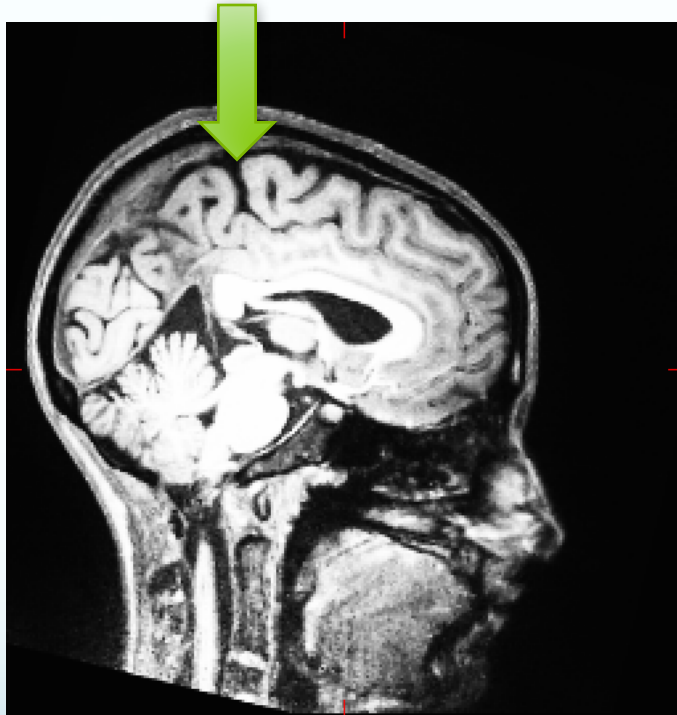
• In the **presence** of:

- Noise
- Gradient non-linearities
- Movement: jaw, tongue, neck, eye, scalp ...
- Cropping
- Atrophy (or other longitudinal change)

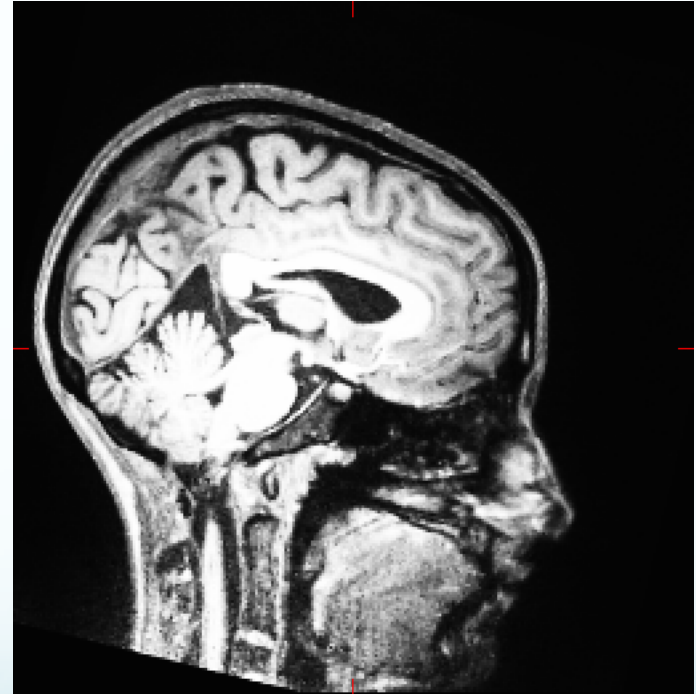
**We need:**

- **Inverse consistency** keep registration **unbiased**
- **Robust statistics** to **reduce** influence of outliers

# Robust Registration

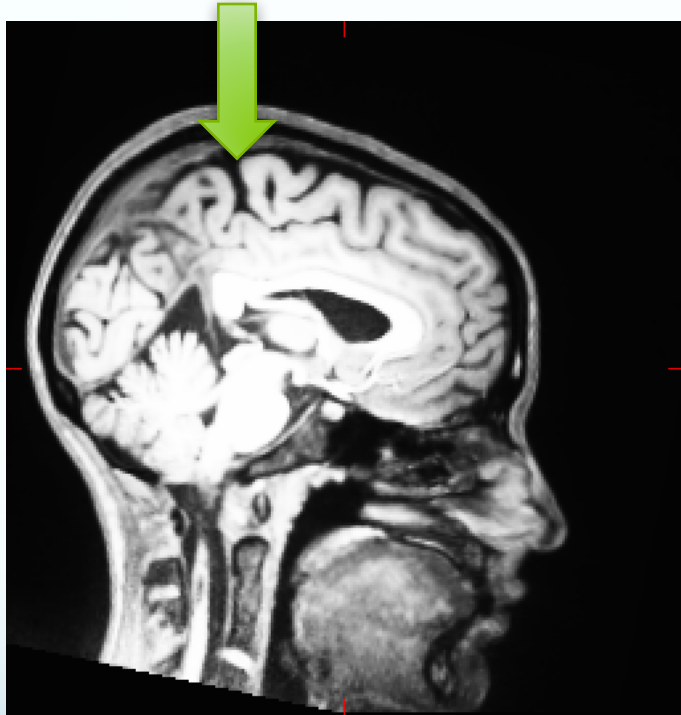


Target

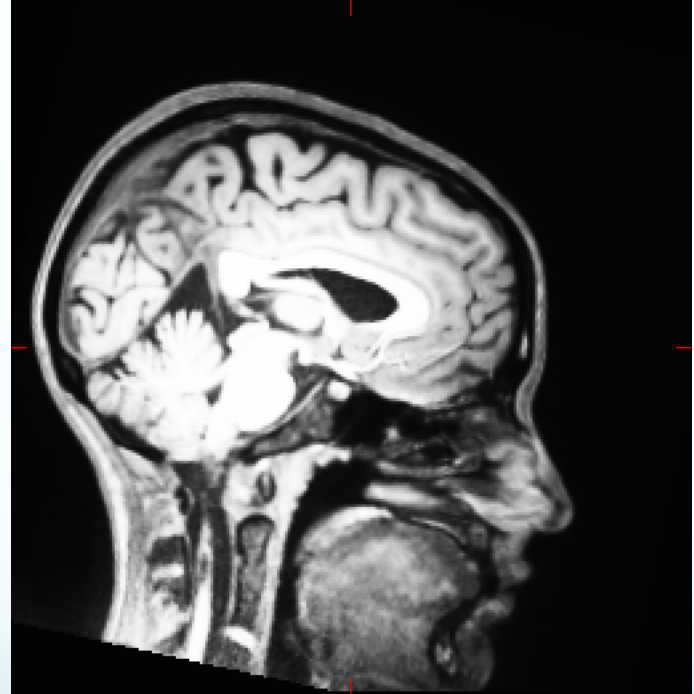


Target

# Robust Registration



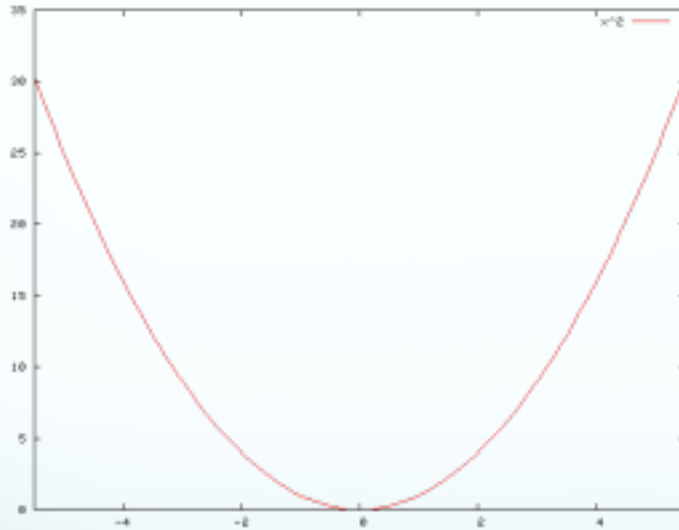
Registered Src FSL FLIRT



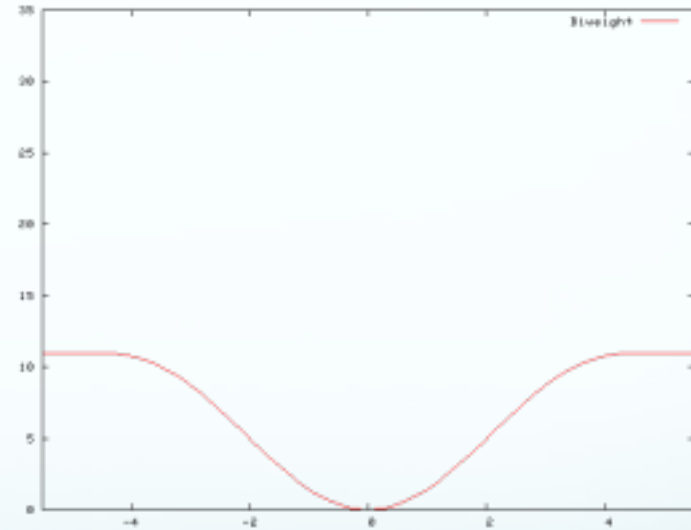
Registered Src Robust

# Robust Registration

Limited contribution of outliers *[Nestares&Heeger 2000]*

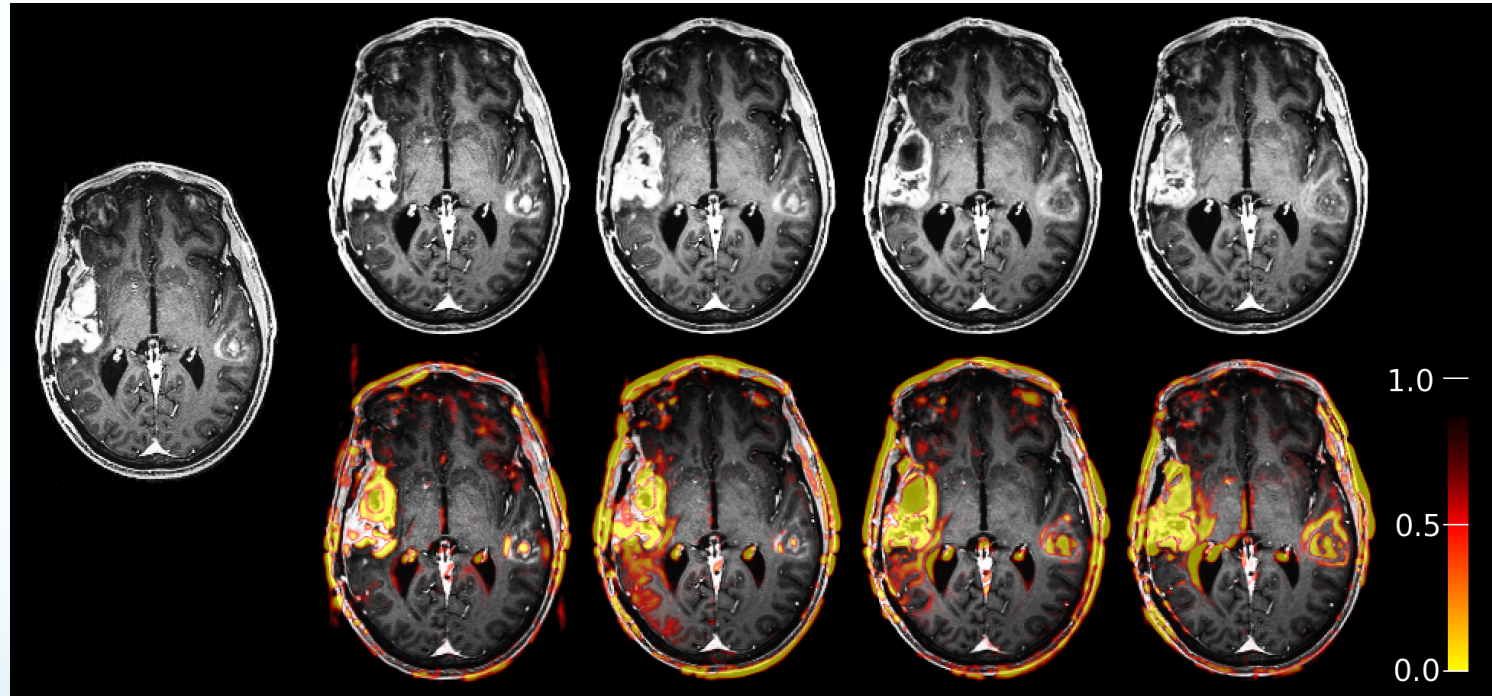


Square



Tukey's Biweight

# Robust Registration



Tumor data with significant intensity differences in the brain, registered to first time point (left).

# Robust Registration

## Inverse consistency:

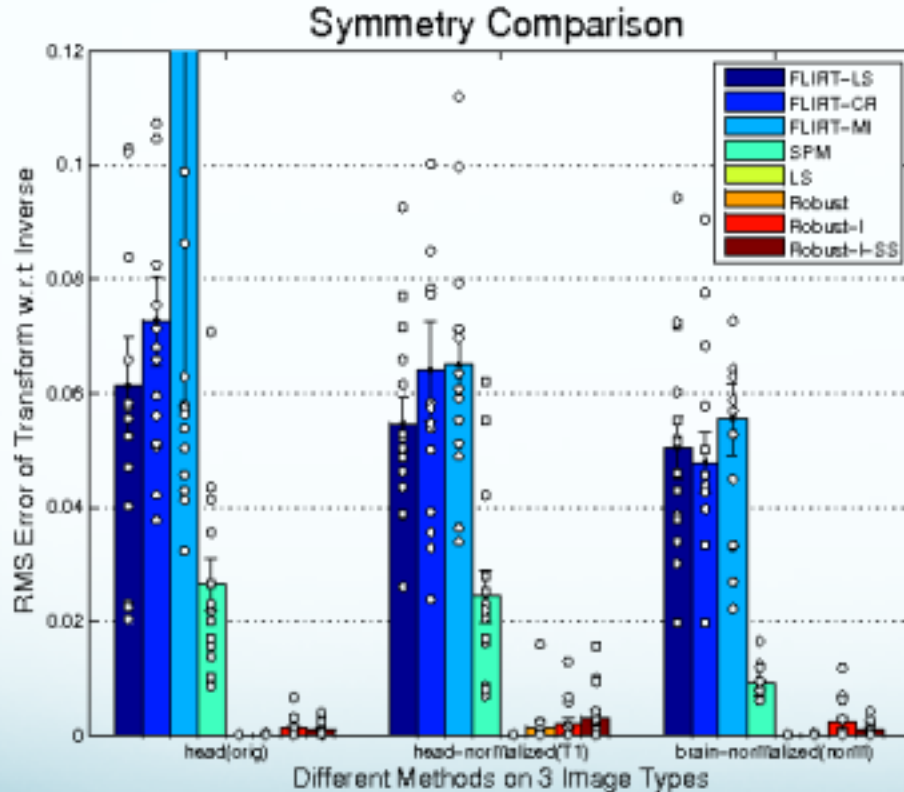
- a **symmetric displacement** model:

$$r(p) = I^T \bar{x} - \frac{1}{2} \vec{d}(\vec{p}) \quad I^S \bar{x} + \frac{1}{2} \vec{d}(\vec{p})$$

- resample both source and target to an **unbiased half-way space** in intermediate steps (matrix square root)



# Robust Registration



**Inverse consistency** of different methods on original (orig), intensity normalized (T1) and skull stripped (norm) images.

## LS and Robust:

- nearly perfect symmetry (worst case RMS < 0.02)

## Other methods:

- several alignments with RMS errors > 0.1



# Robust Registration

- ***mri\_robust\_register*** is part of FreeSurfer
- can be used for pair-wise registration (optimally within subject, within modality)
- can output results in half-way space
- can output ‘outlier-weights’
- see also Reuter et al. “*Highly Accurate Inverse Consistent Registration: A Robust Approach*”, NeuroImage 2010. <http://reuter.mit.edu/publications/> for comparison with FLIRT (FSL) and SPM coreg.
- for more than 2 images use: ***mri\_robust\_template***

# Robust Template Estimation

- Minimization problem for N images:

$$\{\hat{I}, \hat{\varphi}_i\} := \operatorname{argmin}_{I, \varphi_i} \sum_{i=1}^N E(I_i \circ \varphi_i, I) + D(\varphi_i)^2$$

- Image Dissimilarity:

$$E(I_1, I_2) = \int_{\Omega} |I_1(x) - I_2(x)| dx$$

- Metric of Transformations:

$$D(\vec{t}, r)^2 = \|\vec{t}\|^2 + \|R - \mathbf{1}\|_F^2$$

# Longitudinal Processing Challenges

## 1. **Over-Regularization (limited flexibility):**

- Will avoid by only initializing processing

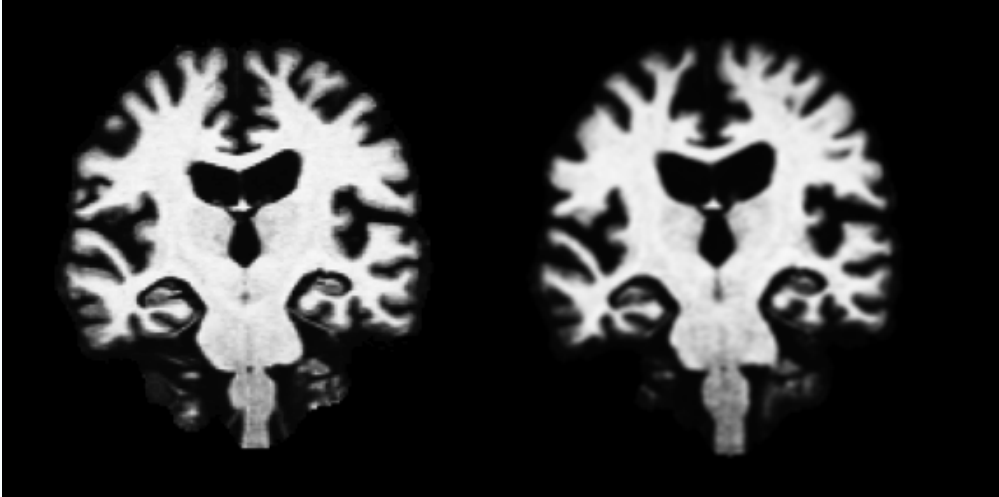
## 2. **Bias** [Reuter and Fischl 2011] , [Reuter et al. 2012]

- Interpolation Asymmetries [Yushkevich et al. 2010]
- Asymmetric Information Transfer
- Will avoid by treating time points the same

## 3. **Limited designs:**

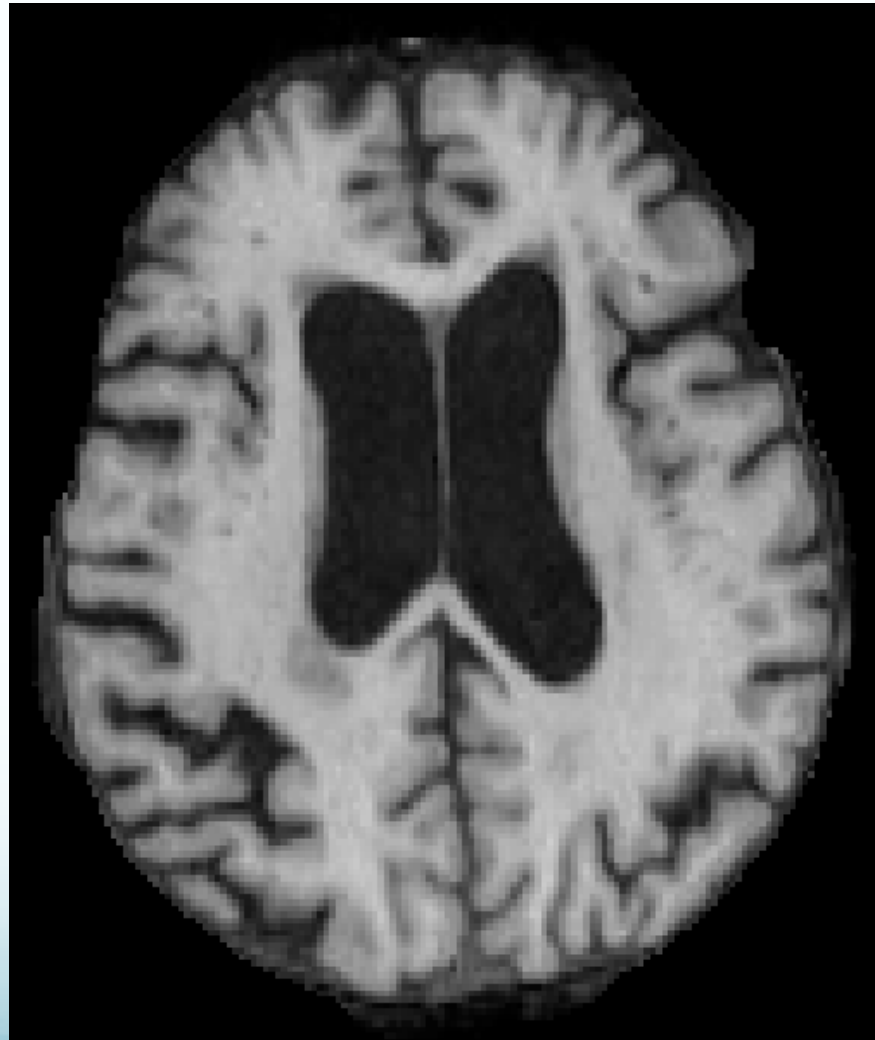
- Allow n time points
- Reliably estimate all of FS measurements

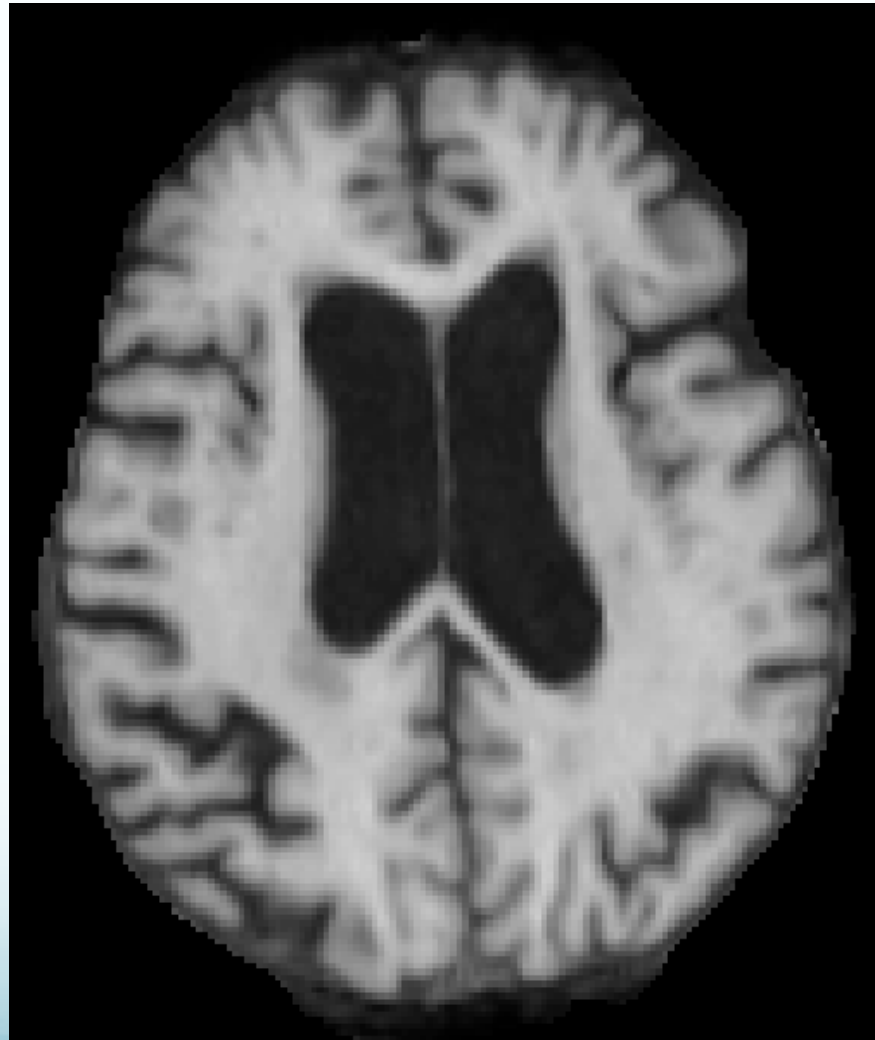
# (i) Interpolation Asymmetries (Bias)

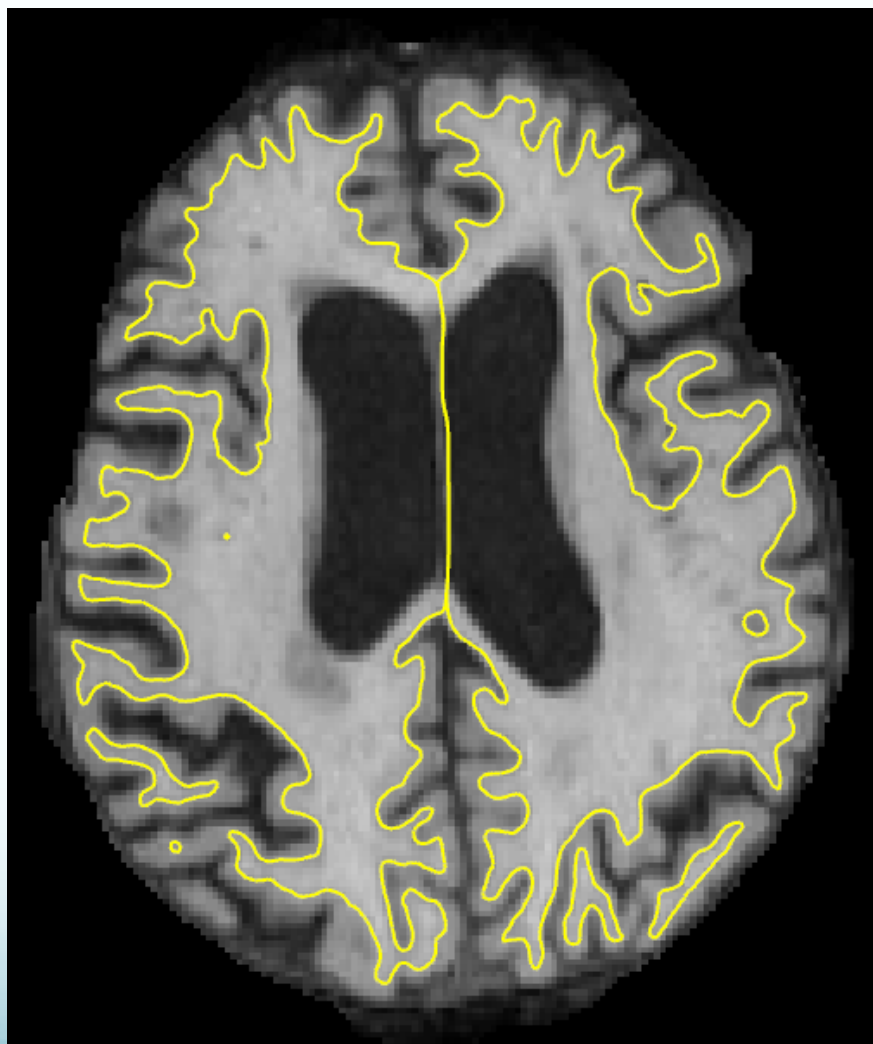


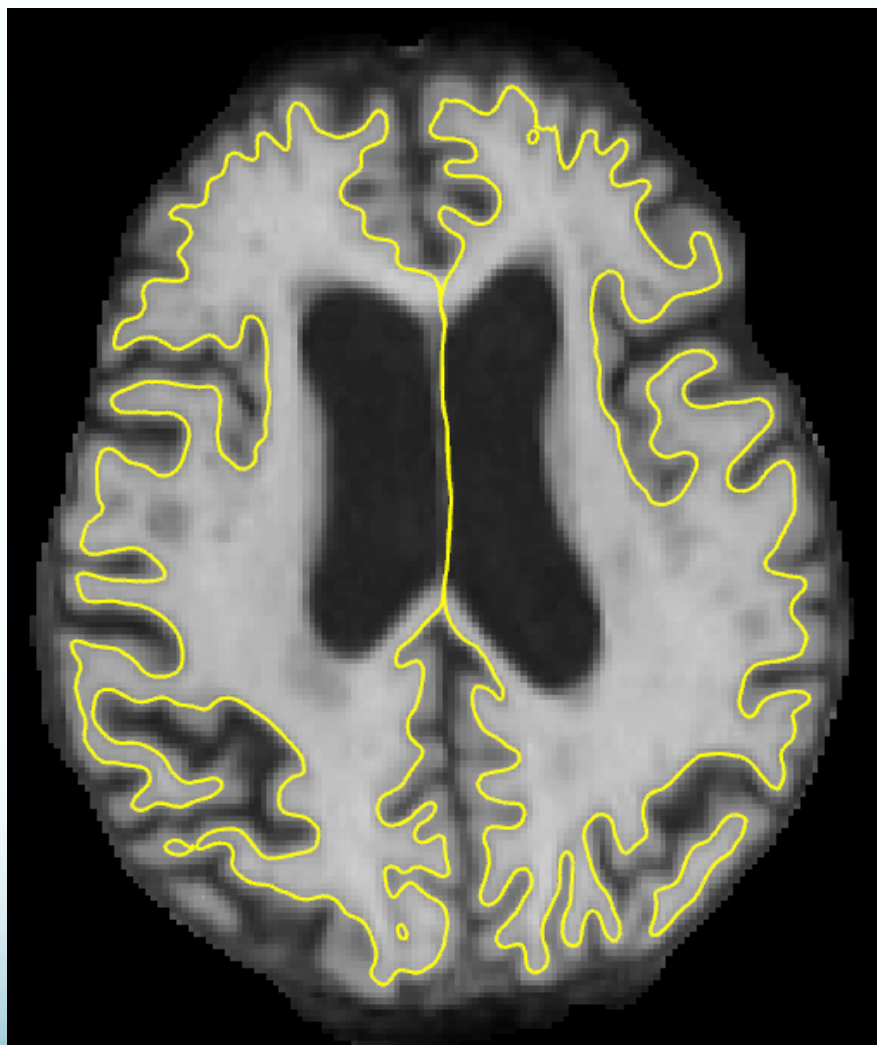
## **Mapping follow-up to baseline:**

- Keeps baseline image fixed (crisp)
- Causes interpolation artefacts in follow-up (smoothing)
- Often leads to overestimating change



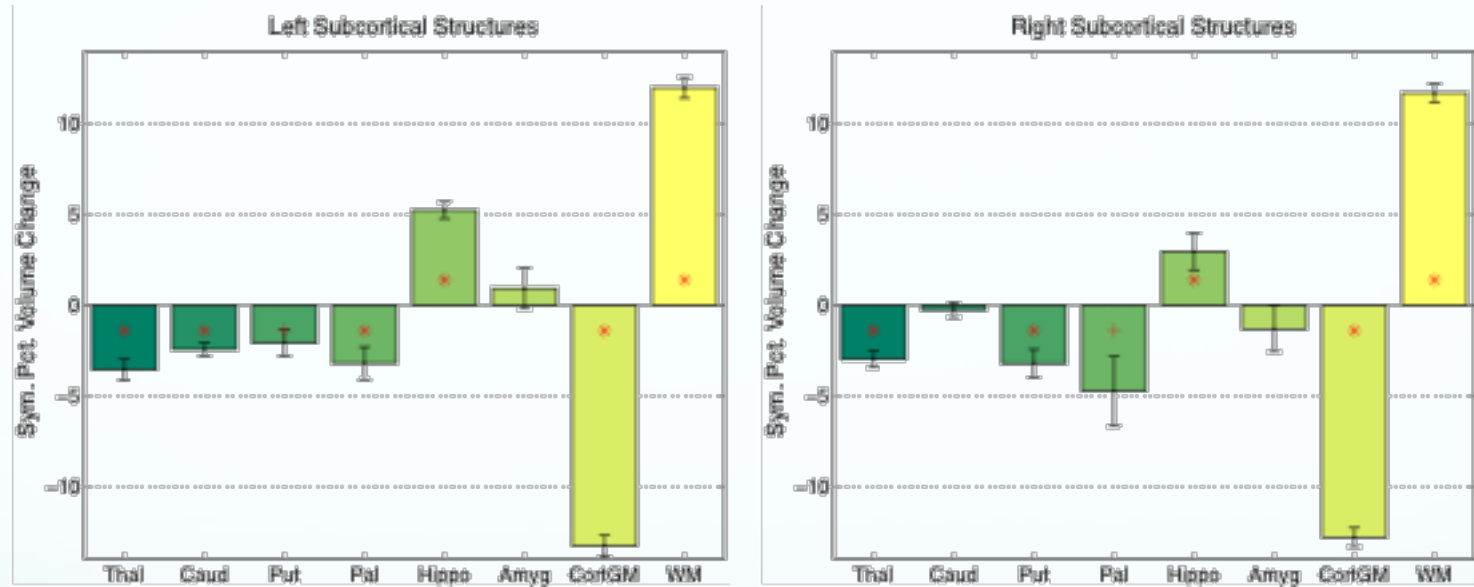








# (i) Interpolation Asymmetries (Bias)

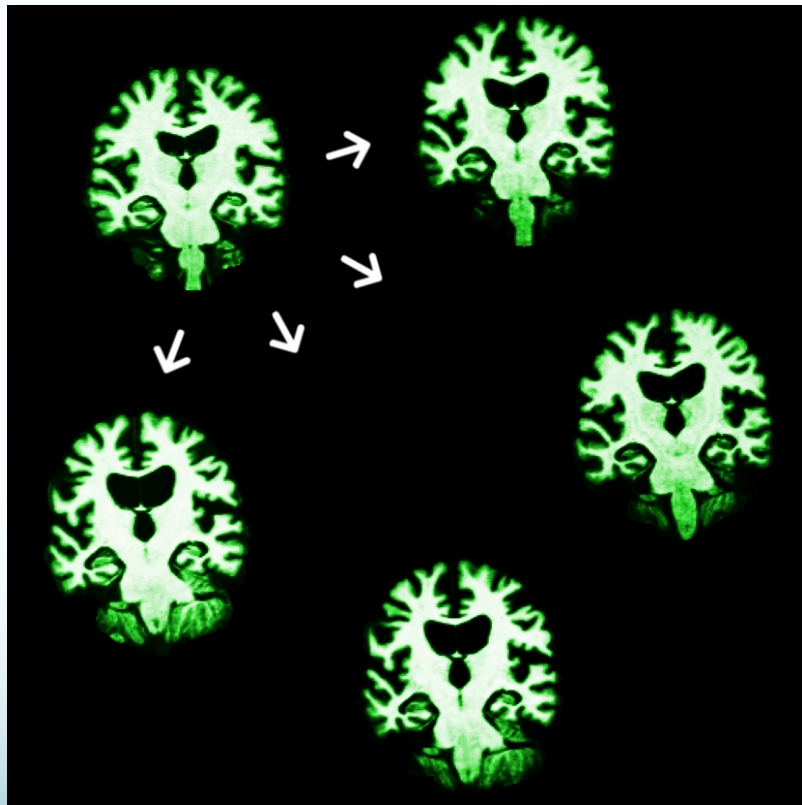


MIRIAD dataset: 65 subjects

First session first scan compared to twice interpolated image.

Regional: not finding it does not mean it is not there.

## (ii) Asymmetric Information Transfer



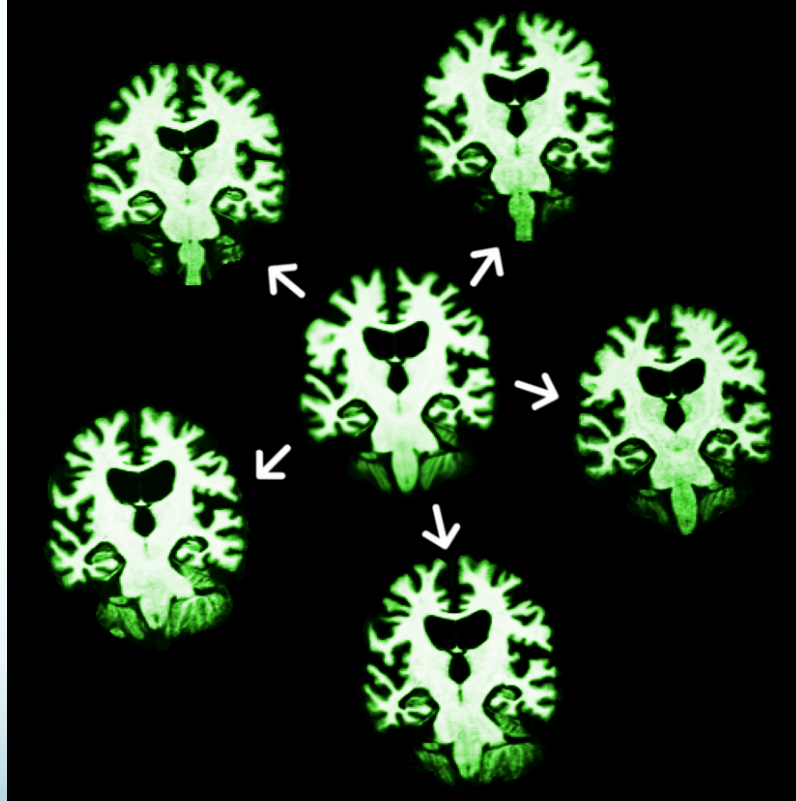
Example:

1. Process baseline
2. Transfer results from baseline to follow-up
3. Let procedures evolve in follow-up

(or construct skullstrip in baseline, or Talairach transform ...)

Can introduce bias!

# Robust Unbiased Subject Template

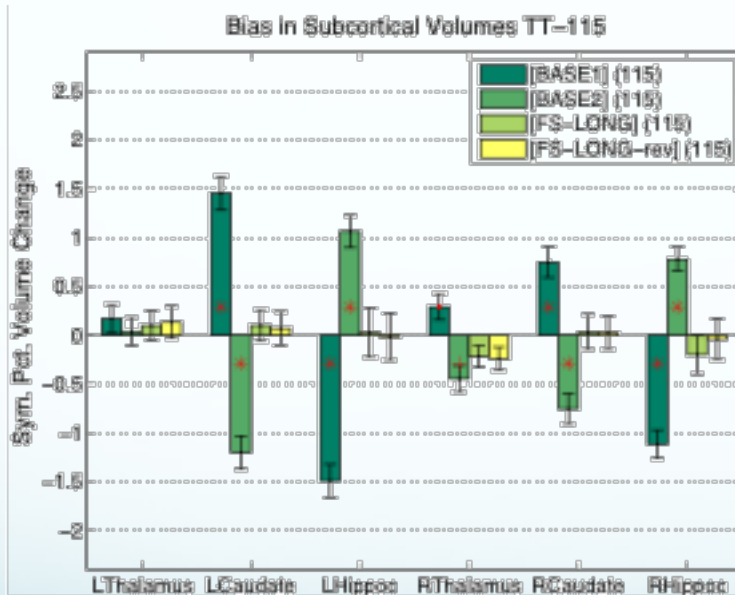


1. Create subject template (iterative registration to median)
2. Process template
3. Transfer to time points
4. Let it evolve there
  - All time points are treated the same
  - Minimize over-regularization by letting tps evolve freely

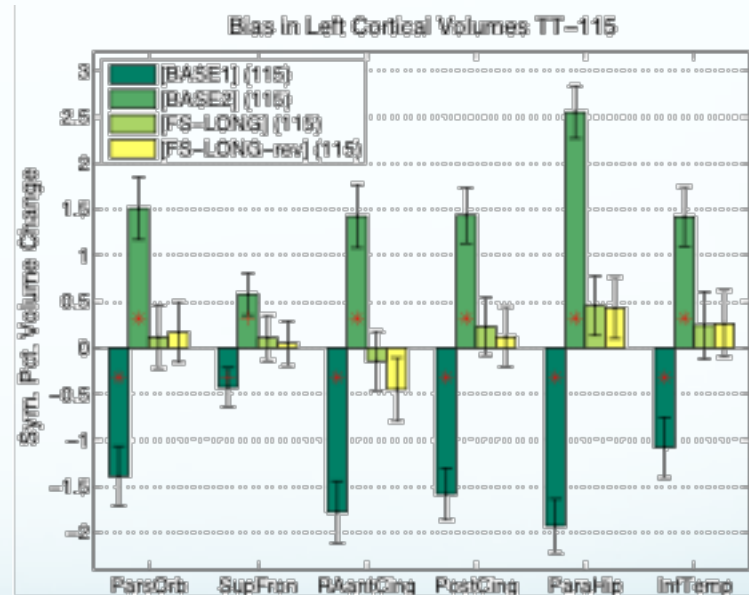
# (ii) Asymmetric Information Transfer

Test-Retest (115 subjects, 2 scans, same session)

Subcortical



Cortical



Biased information transfer: [BASE1] and [BASE2].  
Our method [FS-LONG] [FS-LONG-rev] shows no bias.

# Review the central ideas

Idea: *Would like to include some information that much of the anatomy is the same over time, but don't want to lose sensitivity to disease effects.*

How to minimize over regularization:

- ✓ Only initialize processing, evolve freely

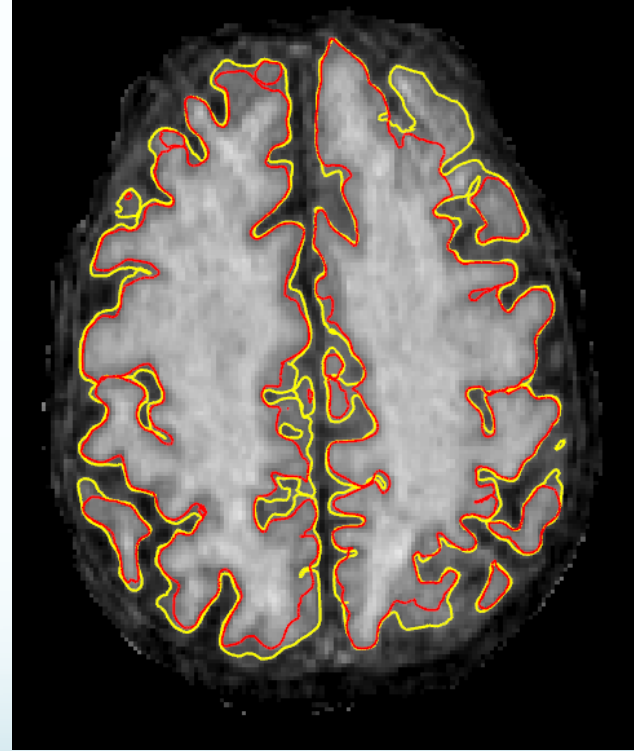
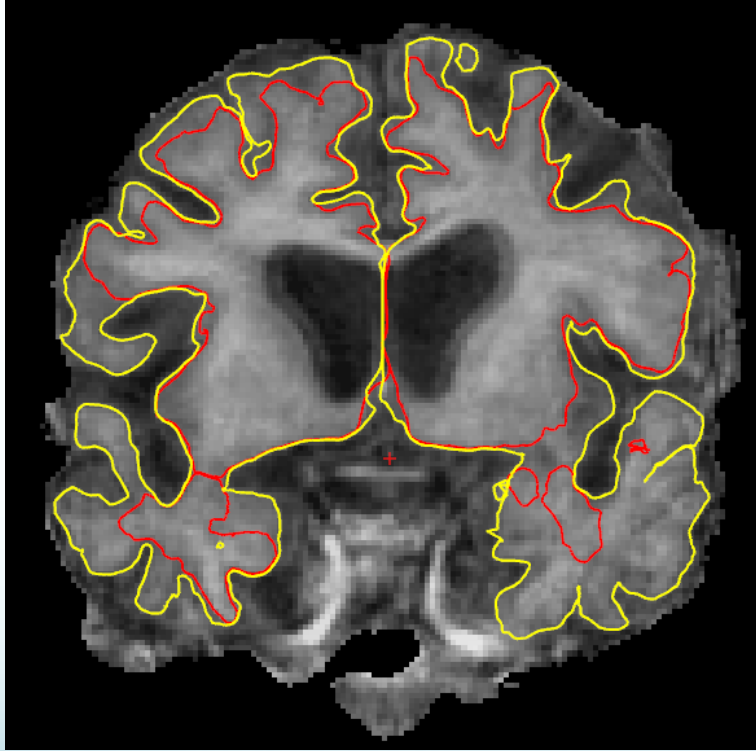
How to avoid processing bias:

- ✓ Treat all time points the same

Why not simply do independent processing then?

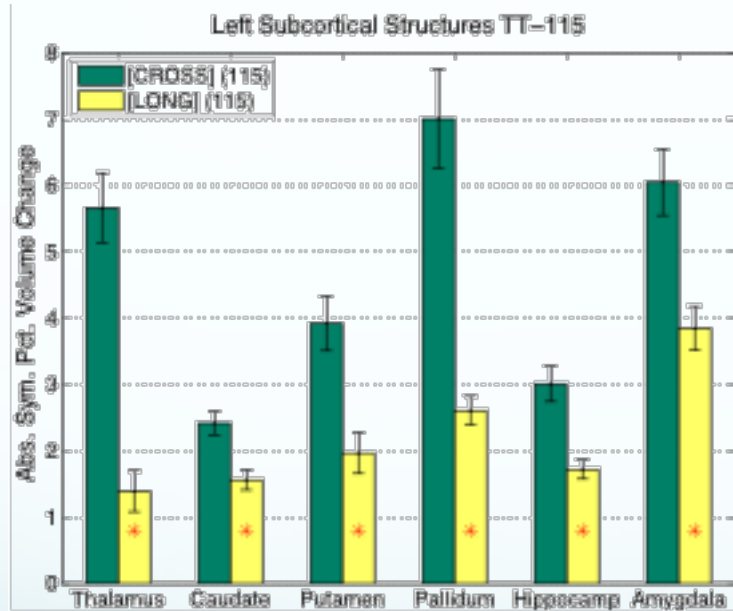
- Sharing information across time points increases reliability, statistical power!

# Improved Surface Placement

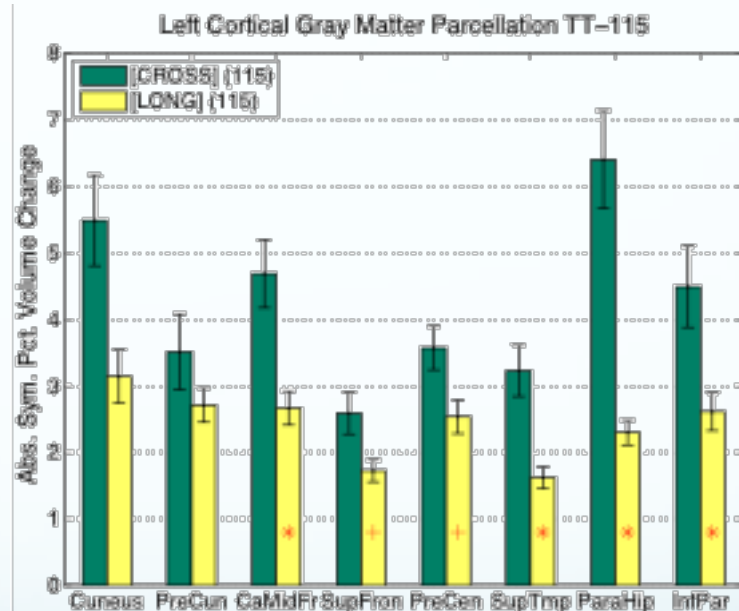


# Test-Retest Reliability

Subcortical



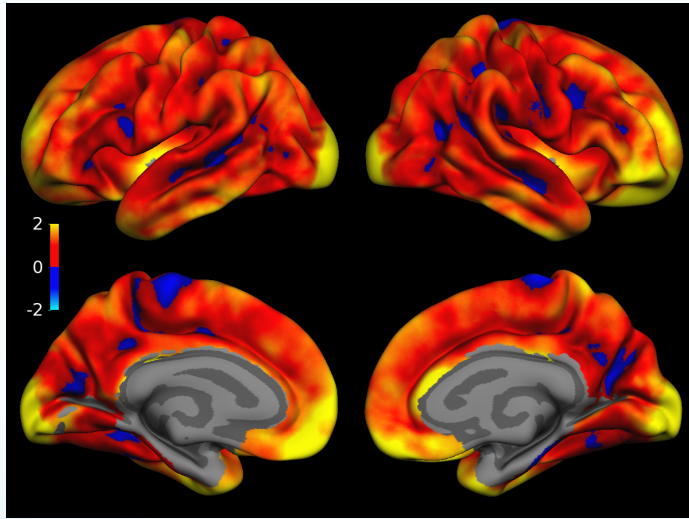
Cortical



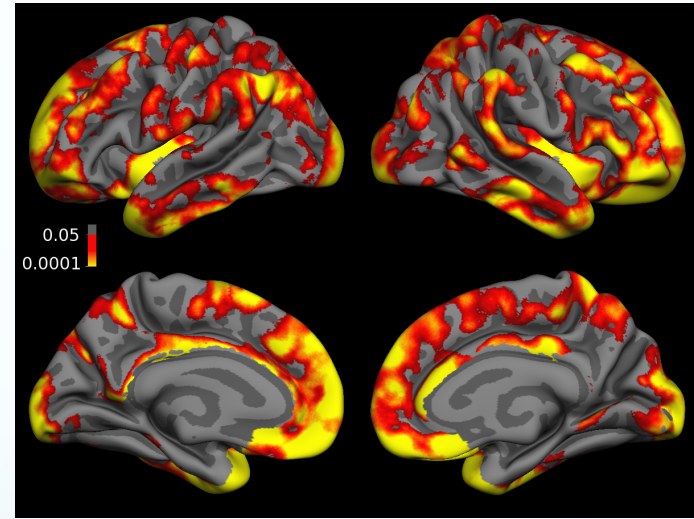
[LONG] significantly improves reliability  
115 subjects, MEMPRAGE, 2 scans, same session

# Test-Retest Reliability

Diff. ([CROSS]-[LONG])  
of Abs. Thick. Change:



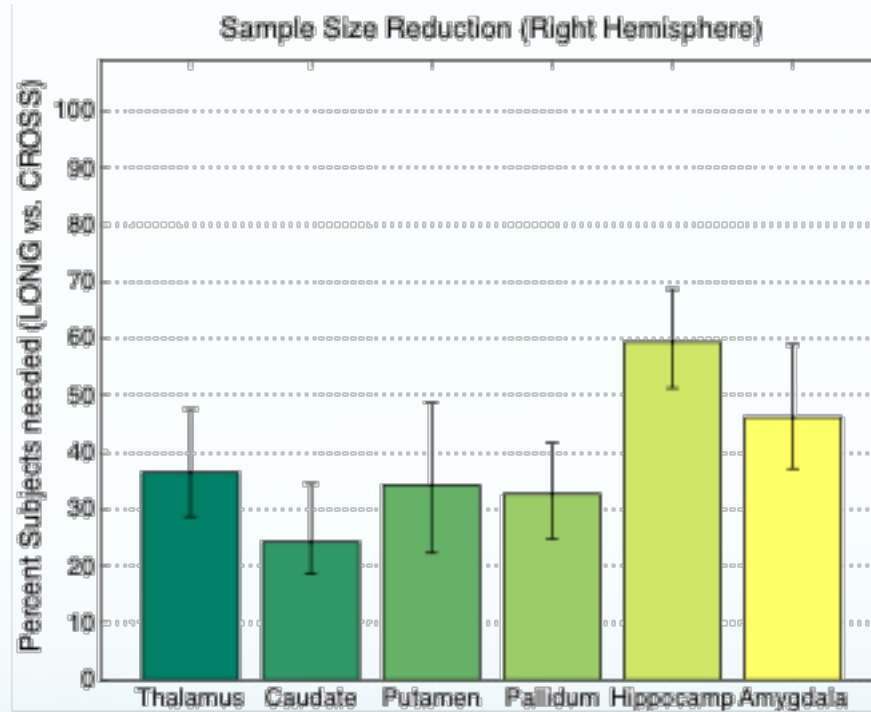
Significance Map



[LONG] significantly improves reliability  
115 subjects, ME MPRAGE, 2 scans, same session



# Increased Power



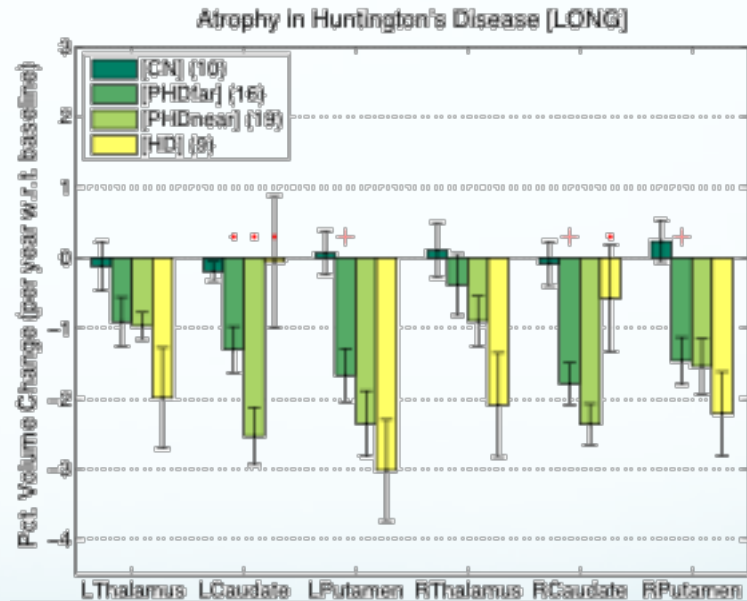
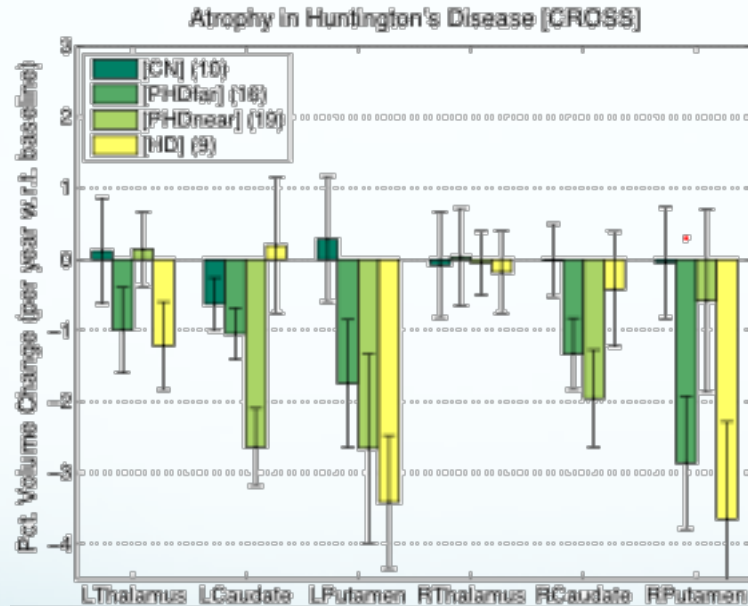
Sample Size Reduction when using [LONG]  
(based on test-retest 14 subjects, 2 weeks)

# Huntington's Disease (3 visits)

(with D. Rosas)

Independent Processing

Longitudinal Processing

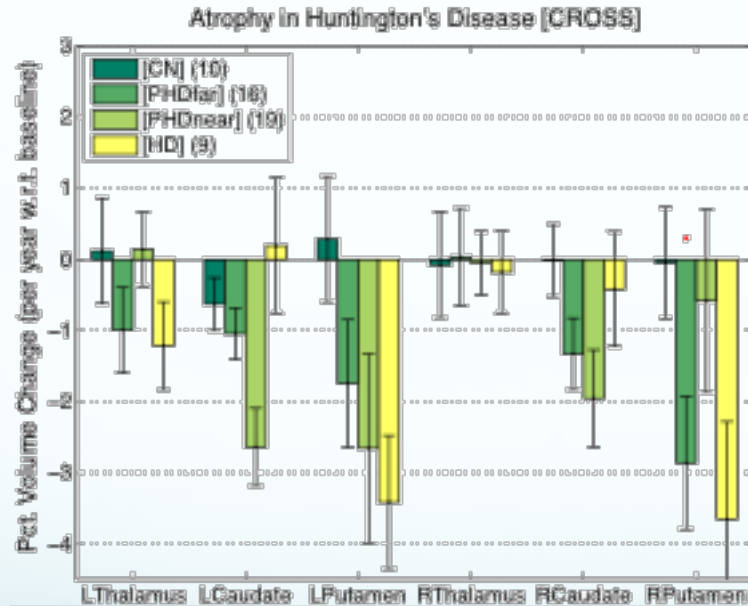


[LONG] shows higher precision and better discrimination power between groups (specificity and sensitivity).

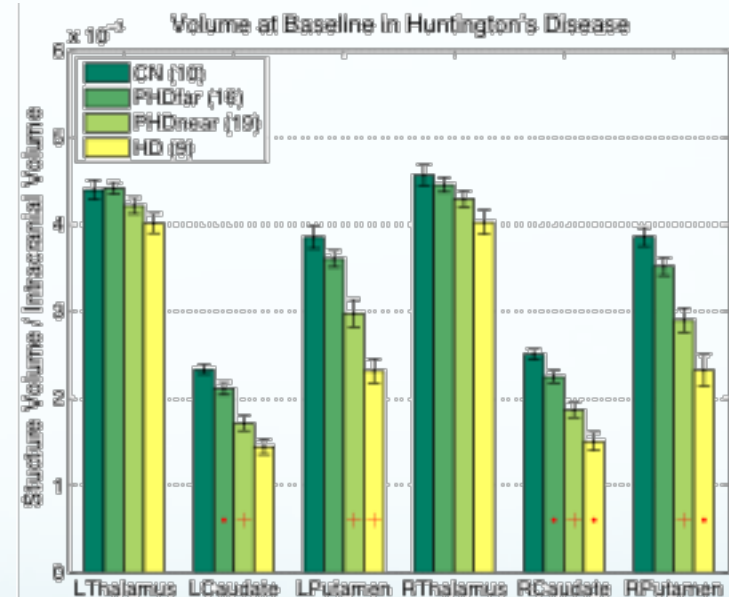
# Huntington's Disease (3 visits)

(with D. Rosas)

## Rate of Atrophy

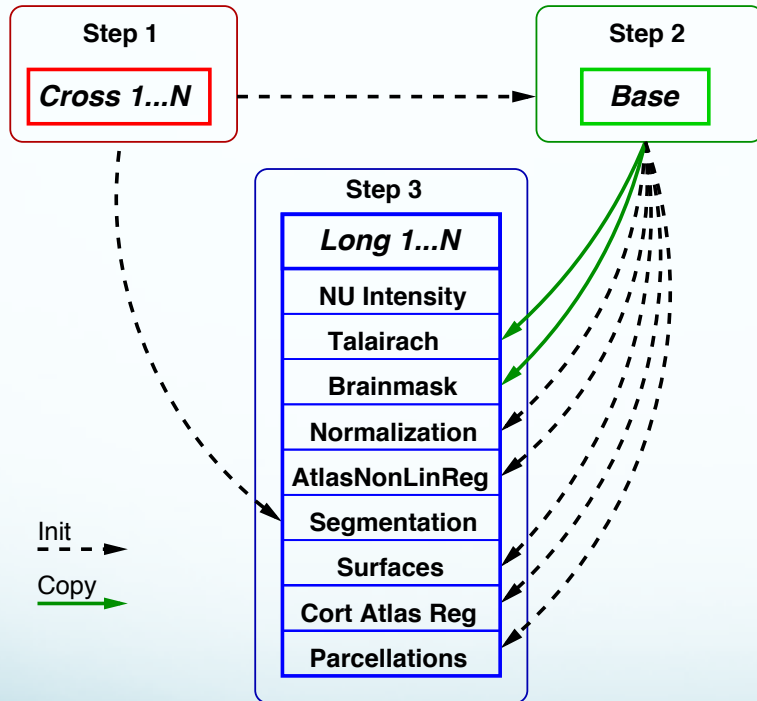


## Baseline Vol. (normalized)



Putamen Atrophy Rate can be significantly different between CN and PHD far, but baseline volume is not.

# Robust Template for Initialization



- Unbiased
- Reduces Variability
- Common space for:
  - TIV estimation
  - Skullstrip
  - Affine Talairach Registration
- Basis for:
  - Intensity Normalization
  - Non-linear Registration
  - Surfaces / Parcellation

# FreeSurfer Commands (recon-all)

1. CROSS (independently for each time point tpNid):

```
recon-all -subjid tpNid -all
```

2. BASE (creates template, one for each subject):

```
recon-all -base baseid -tp tp1id \  
-tp tp2id ... -all
```

3. LONG (for each time point tpNid, passing baseid):

```
recon-all -long tpNid baseid -all
```

This creates the final directories **tpNid.long.baseid**

# Directory Structure

Contains all CROSS, BASE and LONG data:

- me1
- me2
- me3
- me\_base
- me1.long.me\_base
- me2.long.me\_base
- me3.long.me\_base
- you1
- ...

# Single time point

Since FS5.2 you can run subjects with a single time point through the longitudinal stream!

- Mixed effects models can use single time point subjects to estimate variance (increased power)
- This assures identical processing steps as in a subject with several time points
- Commands same as above:

```
recon-all -subjid tp1id -all  
recon-all -base baseid -tp tp1id -all  
recon-all -long tp1id baseid -all
```

# Final Remarks ...



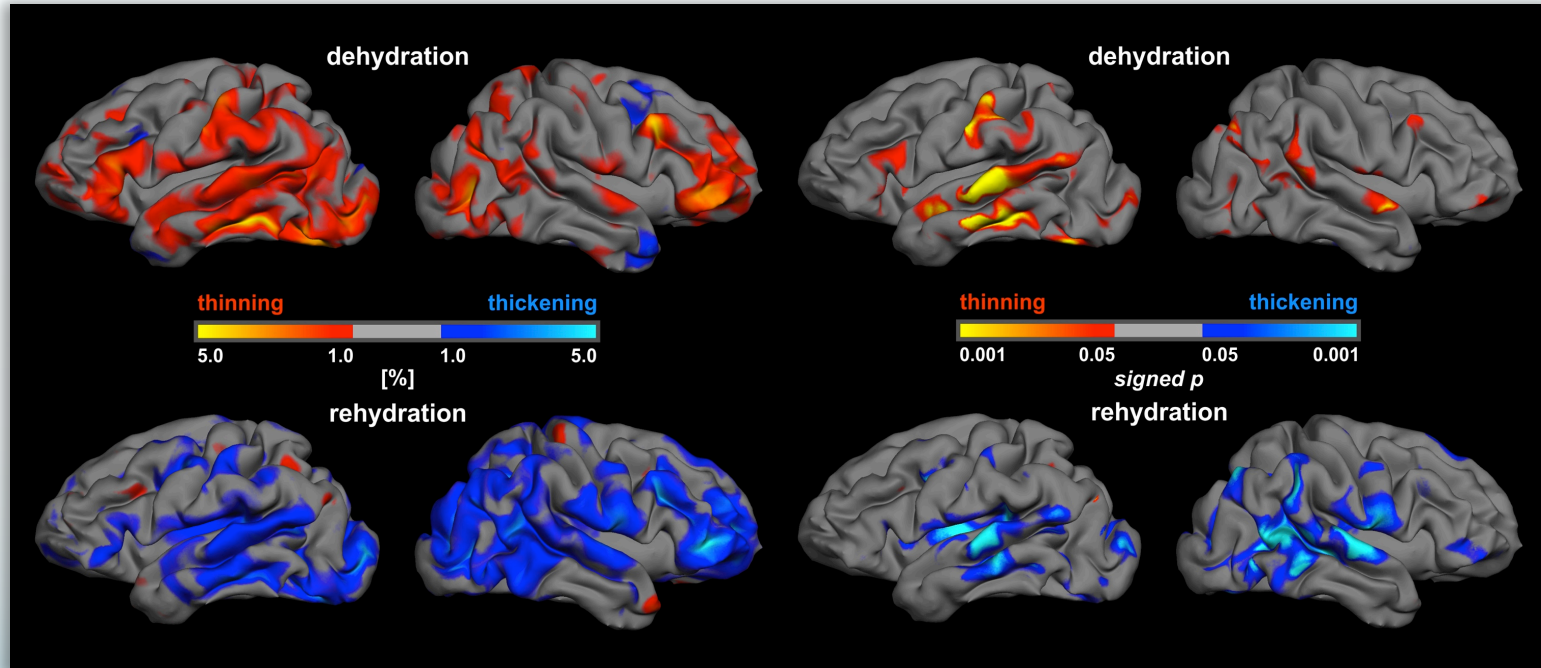
# Sources of Bias during Acquisition

**BAD:** influence images directly and cannot be easily removed!

- **Different Scanner Hardware** (Headcoil, Pillow?)
- **Different Scanner Software** (Shimming Algorithm)
- **Scanner Drift and Calibration**
- **Different Motion Levels Across Groups**
- **Different Hydration Levels** (season, time of day)

# Hydration Levels

14 subjects, 12h dehydration (over night)

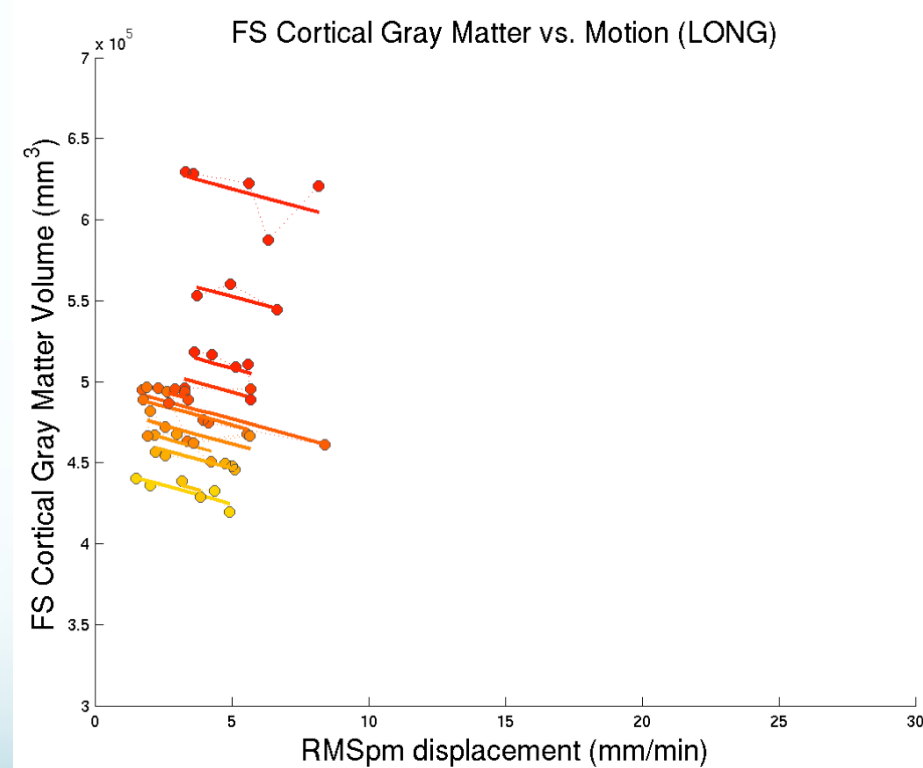


rehydration 1L/h

# Motion Biases GM Estimates

- 12 volunteers
- 5 motion types:
  - 2 Still
  - Nod
  - Shake
  - Free
- Duration:
  - 5-15 s/min

*Effect:*  
roughly 0.7-1%  
volume loss per  
1mm/min increase  
in motion



# Still to come ...

- Common warps (non-linear)
- Optimized intracranial volume estimation
- Joint intensity normalization
- New thickness computation
- Joint spherical registration

<http://freesurfer.net/fswiki/LongitudinalProcessing>

<http://reuter.mit.edu/publications>

Thanks to: the FreeSurfer Team

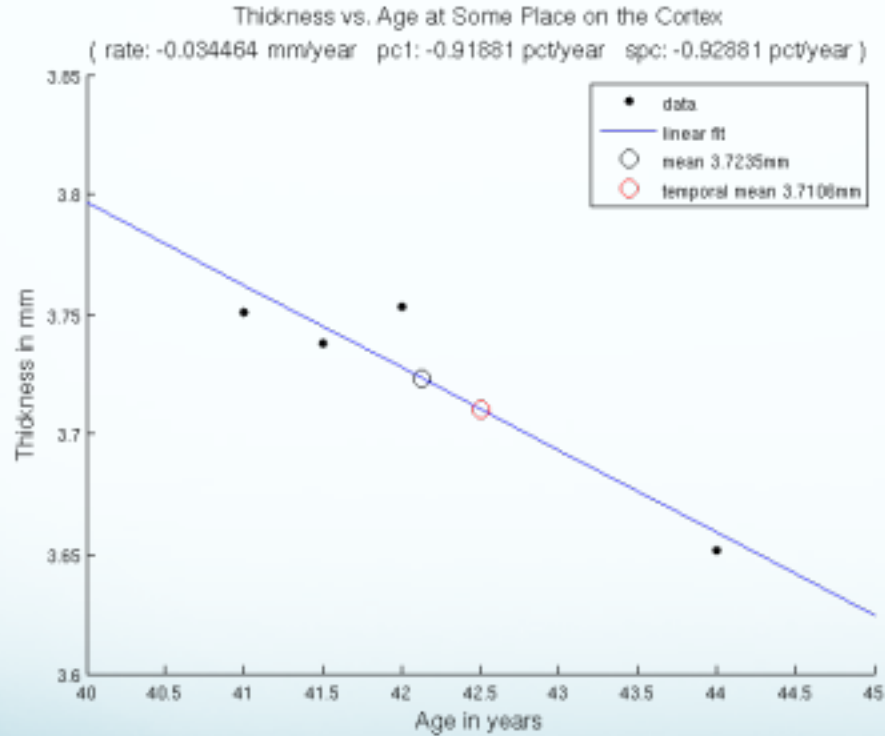
# Longitudinal Tutorial

The background of the slide features a light blue gradient. At the bottom, there are several overlapping, semi-transparent wavy lines in shades of blue, creating a sense of depth and movement.

# Longitudinal Tutorial

1. How to process longitudinal data
  - Three stages: CROSS, BASE, LONG
2. Post-processing (statistical analysis):
  - (i) compute atrophy rate within each subject
  - (ii) group analysis (average rates, compare)
  - here: two time points, rate or percent change
3. Manual Edits
  - Start in CROSS, do BASE, then LONGs should be fixed automatically
  - Often it is enough to just edit the BASE
  - See <http://freesurfer.net/fswiki/LongitudinalEdits>

# Longitudinal Tutorial



- Temporal Average
- Rate of Change
- Percent Change (w.r.t. time 1)
- Symmetrized Percent Change (w.r.t. temp. avg.)