Longitudinal FreeSurfer

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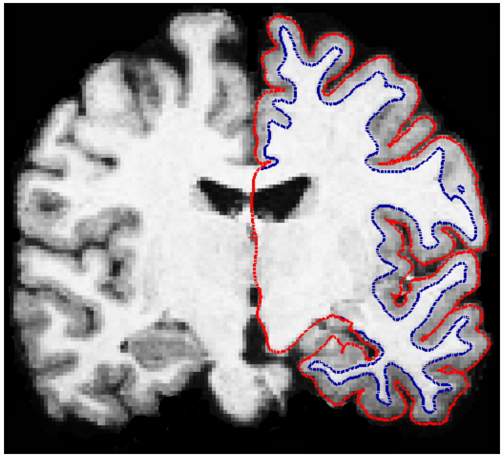
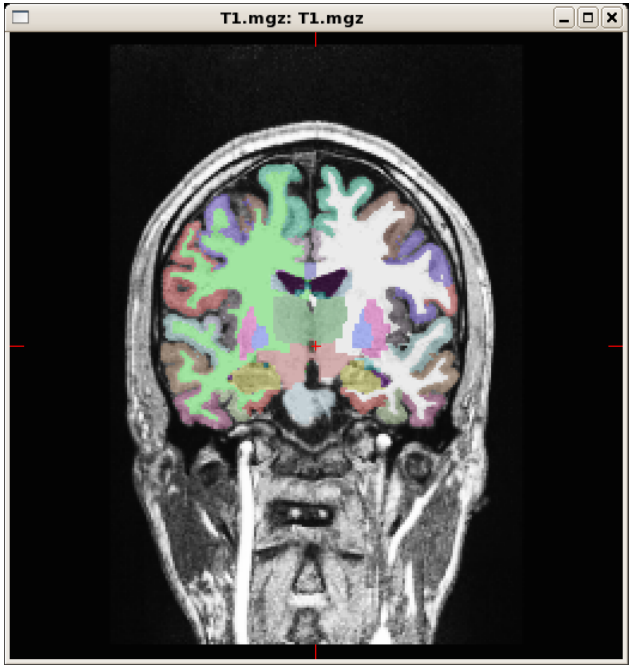
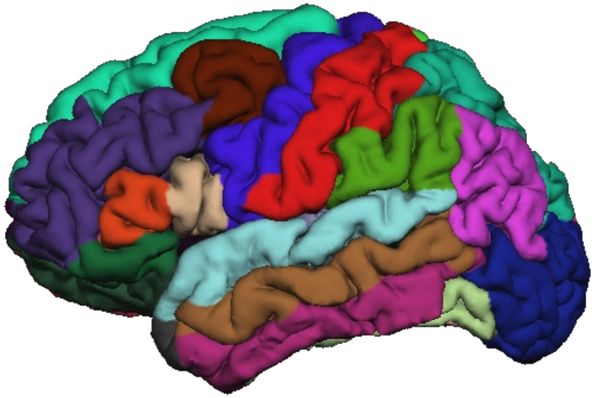
What can we do with FreeSurfer?

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







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

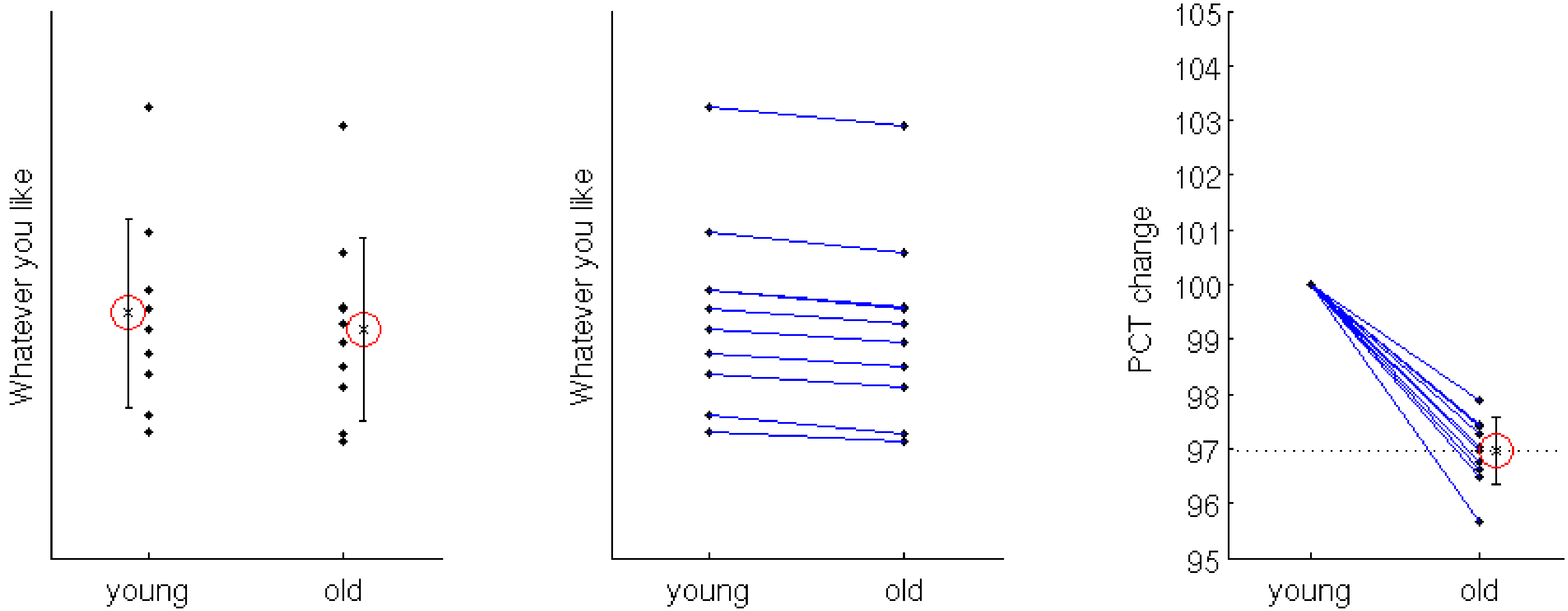
...

[Reuter et al, NeuroImage 2012]

Example 1


Reading ability
Age
Reading ability
Age
Reading ability
Age

Example 2



Whatever you like
young
old
Whatever you like
young
old
PCT change
105
104
103
102
101
100
99
98
97
96
95
young
old

Challenges in Longitudinal Designs

- **Over-Regularization:**
  - Temporal smoothing
  - Non-linear warps
  - ➢ Potentially underestimating change
- **Bias** [Reuter and Fischl, NeuroImage 2011] , [Reuter et al. NeuroImage 2012]
  - Interpolation Asymmetries [Yushkevich et al. 2010]
  - Asymmetric Information Transfer
  - ➢ Often overestimating change
- **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

[Reuter et al., NeuroImage, 2010]

Robust Registration

[Reuter et al., NeuroImage, 2010]

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

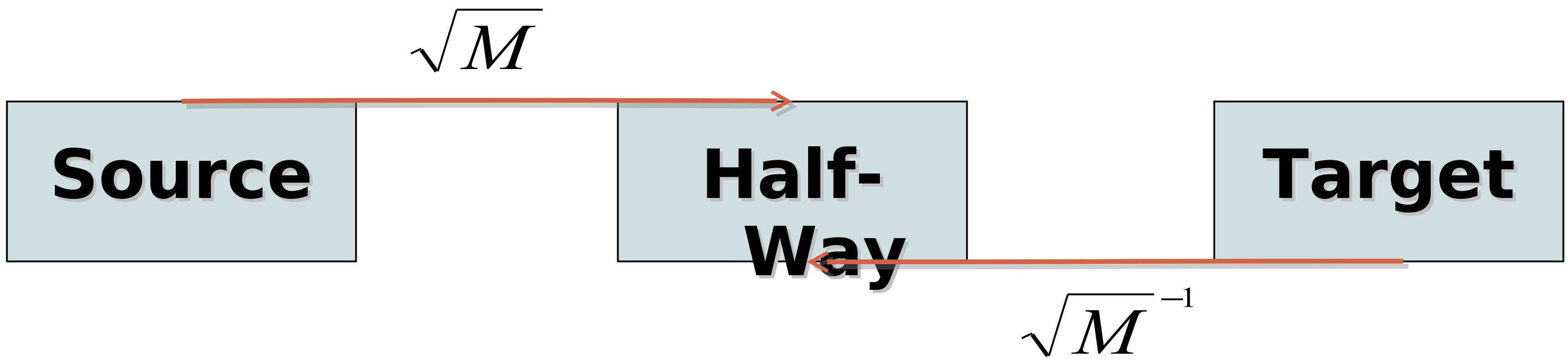
[Reuter et al., NeuroImage, 2010]

Inverse consistency:

- a **symmetric displacement** model:

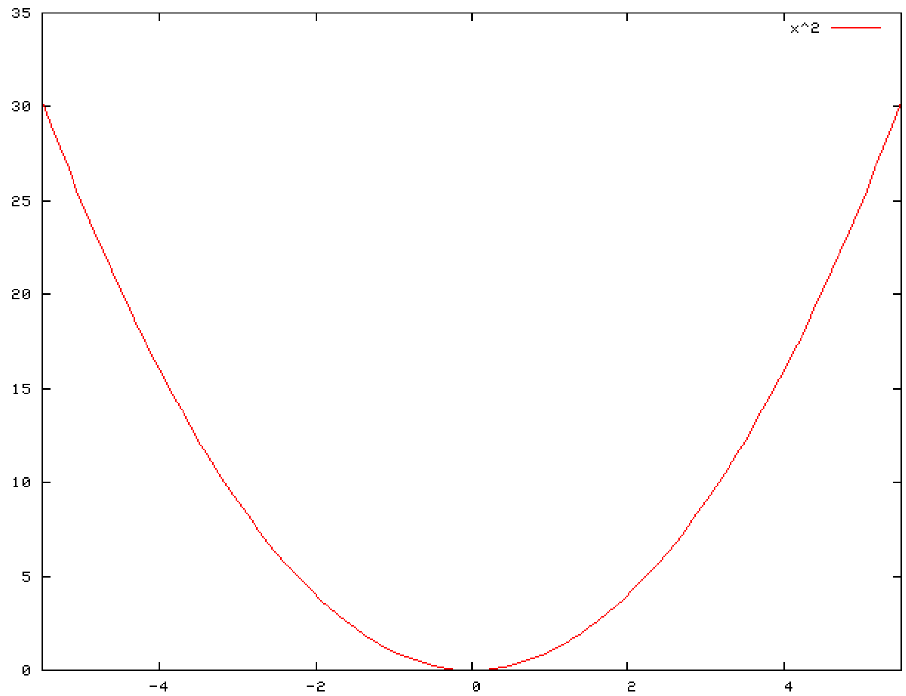
$$r(\vec{p}) = I^T\left(\vec{x} - \frac{1}{2}\vec{d}(\vec{p})\right) - I^S\left(\vec{x} + \frac{1}{2}\vec{d}(\vec{p})\right)$$

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

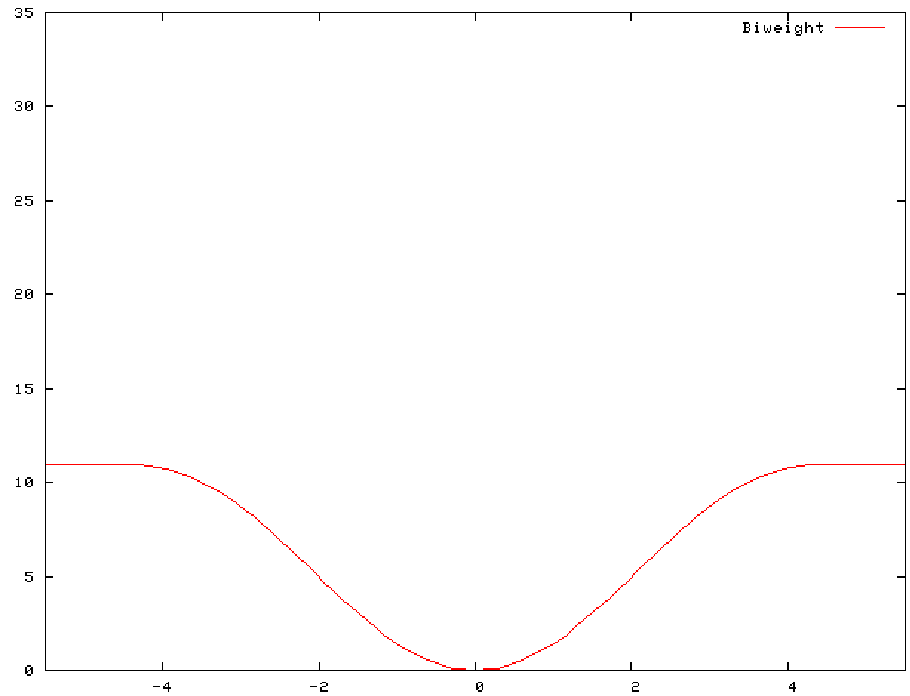


Robust Registration
[Reuter et al., NeuroImage, 2010]

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



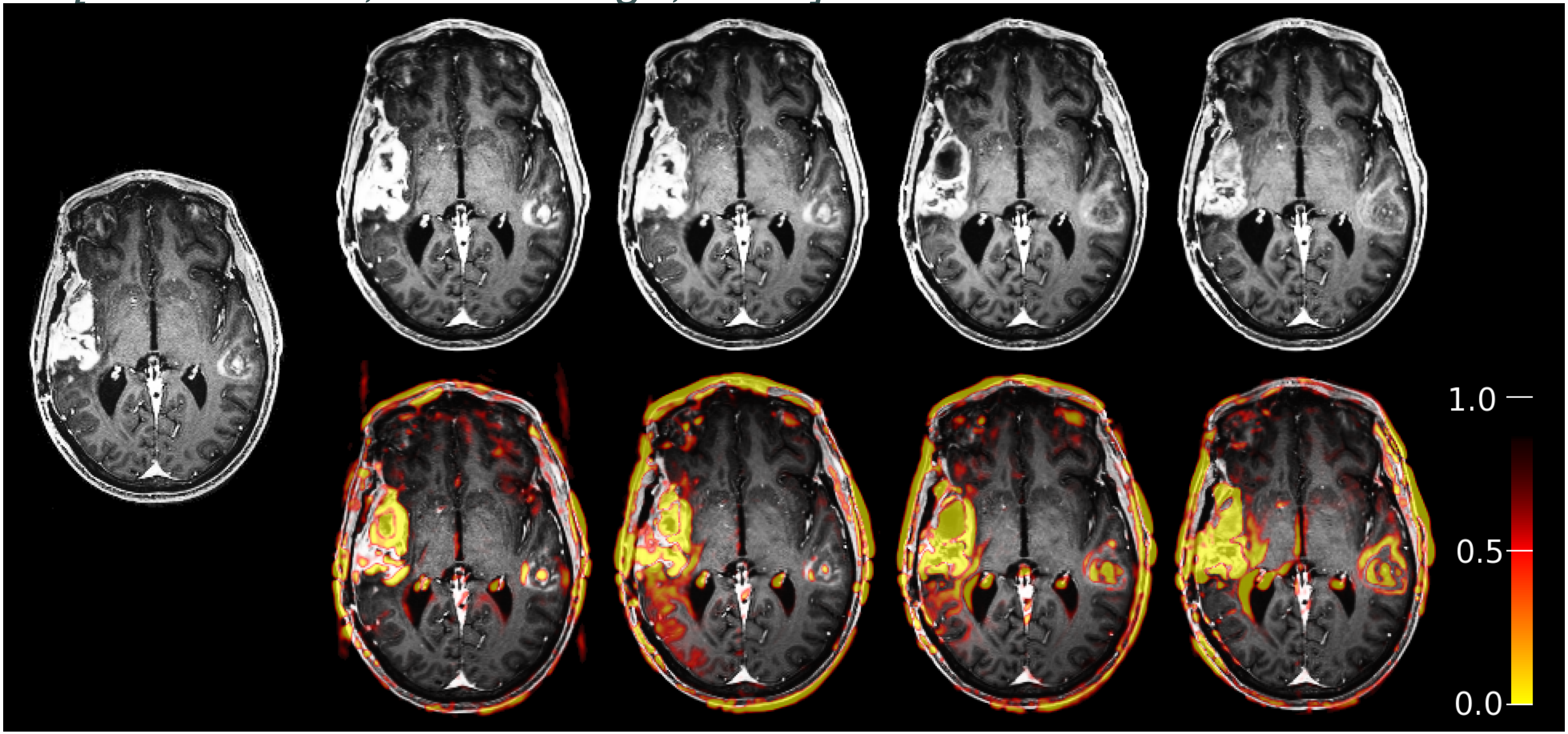
Square



Tukey's Biweight

Robust Registration

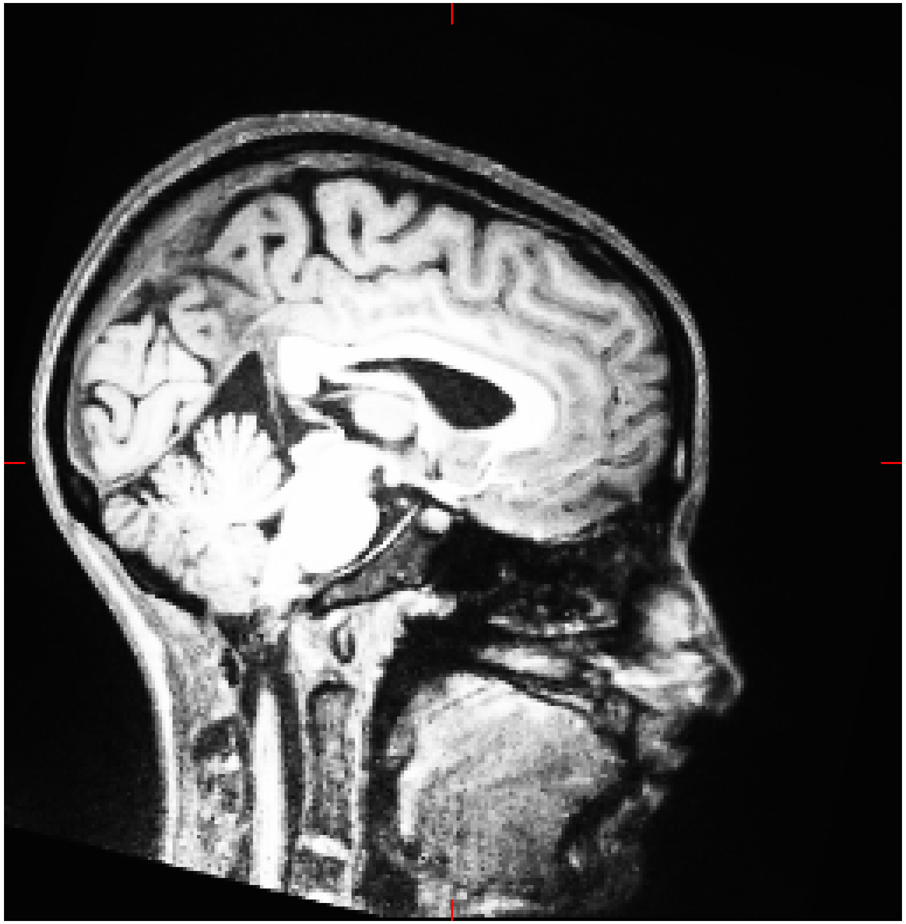
[Reuter et al., NeuroImage, 2010]



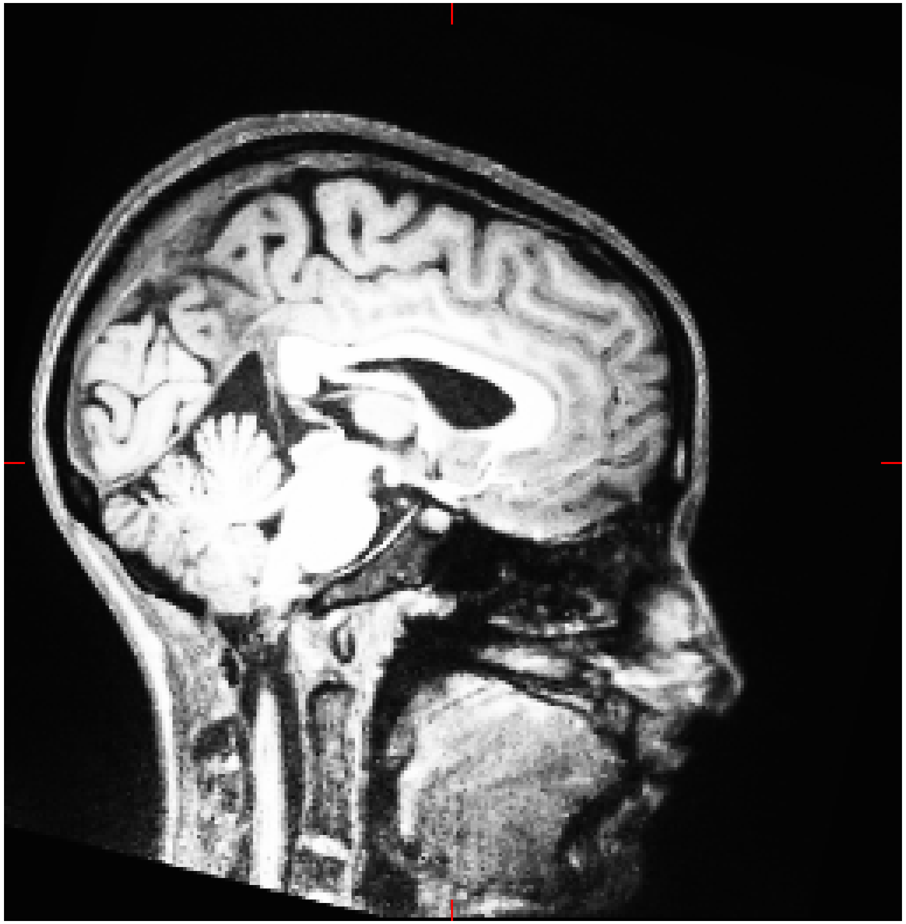
Tumor data courtesy of Dr. Greg Sorensen

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

Robust Registration [Reuter et al 2010]

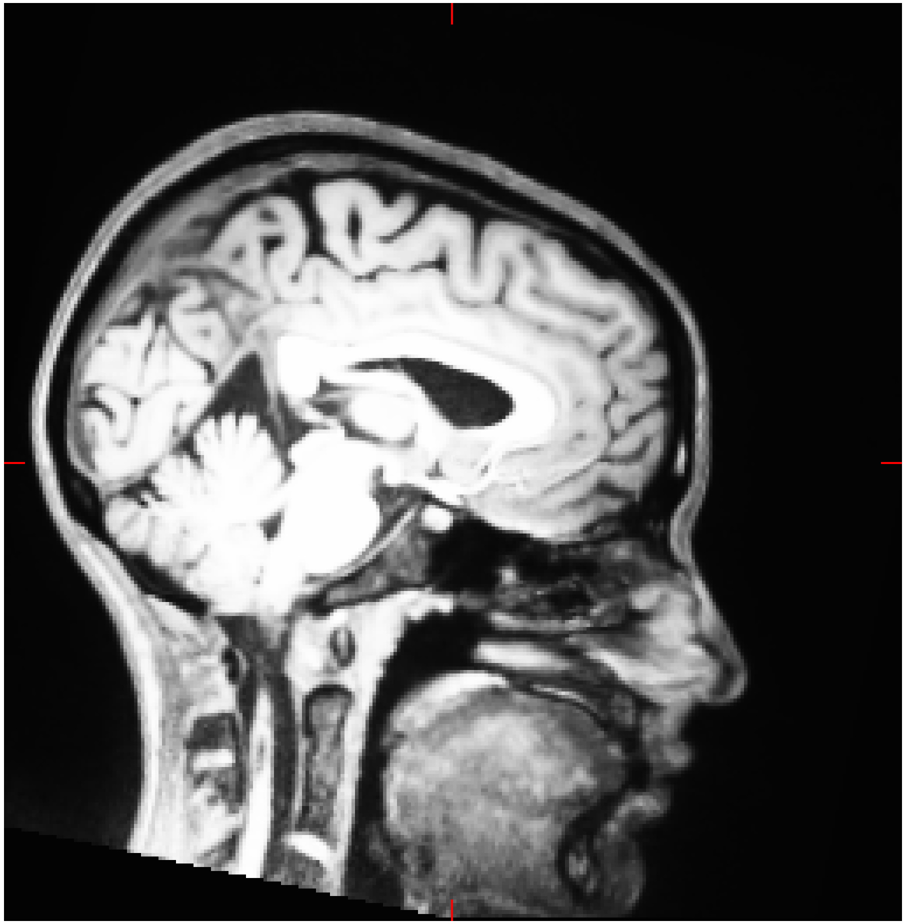


Target

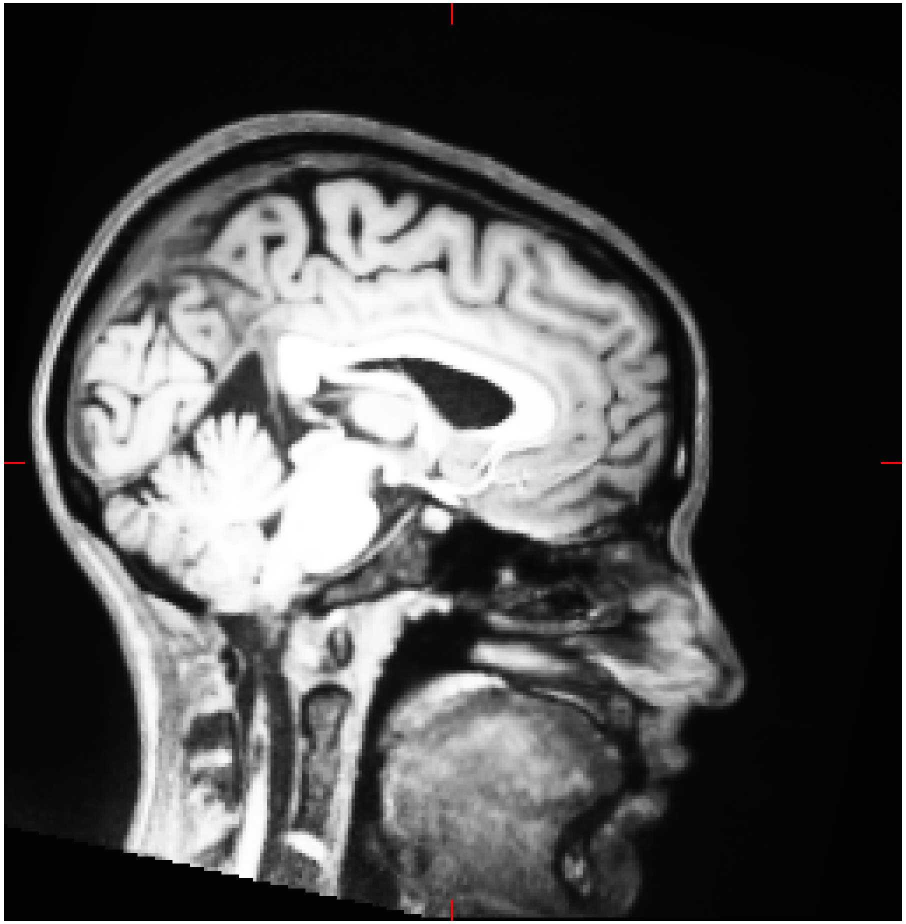


Target

Robust Registration *[Reuter et al 2010]*

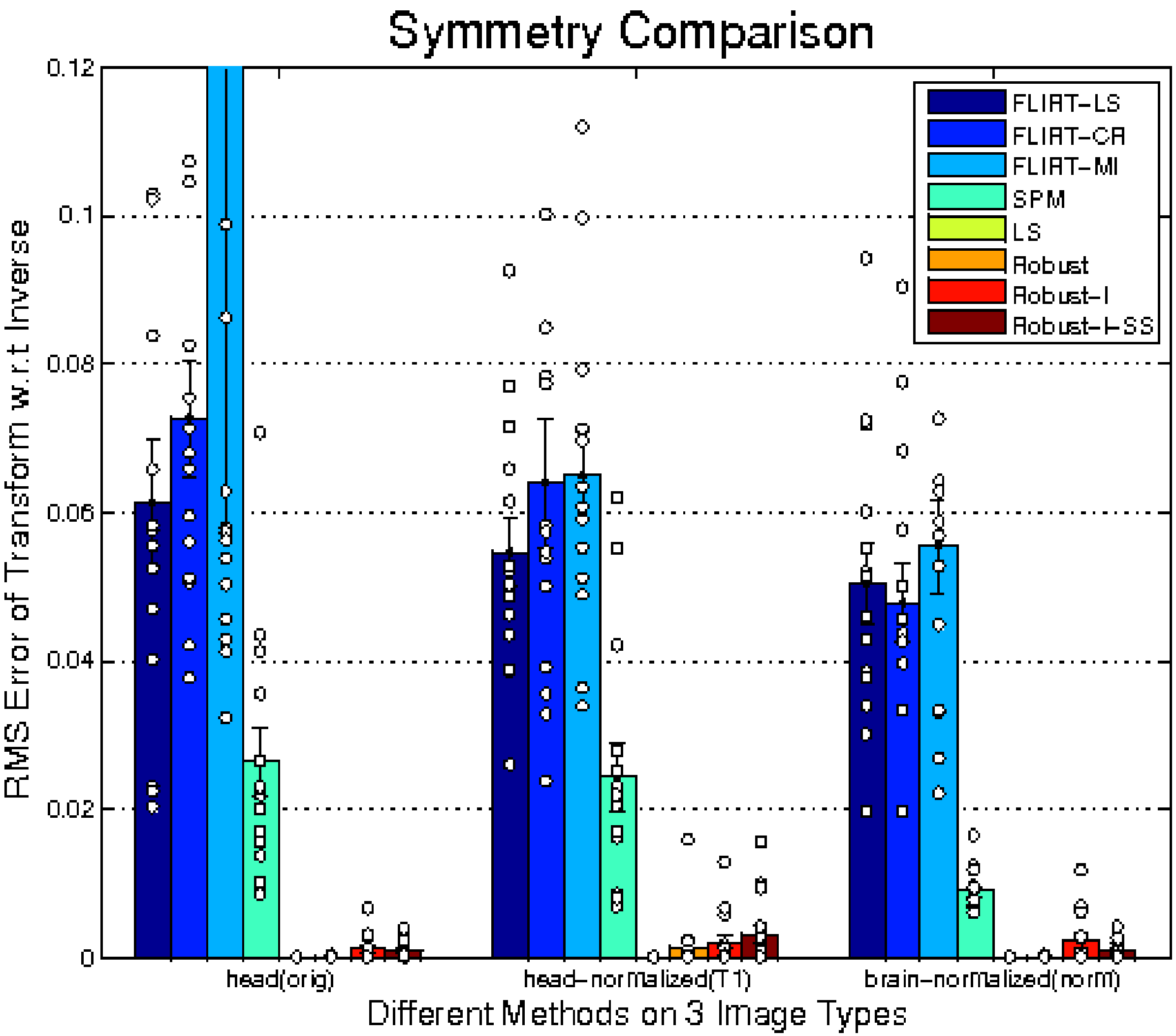


Registered Src FSL FLIRT



Registered Src Robust

Inverse Consistency of mri_robust_register



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

LS and Robust:

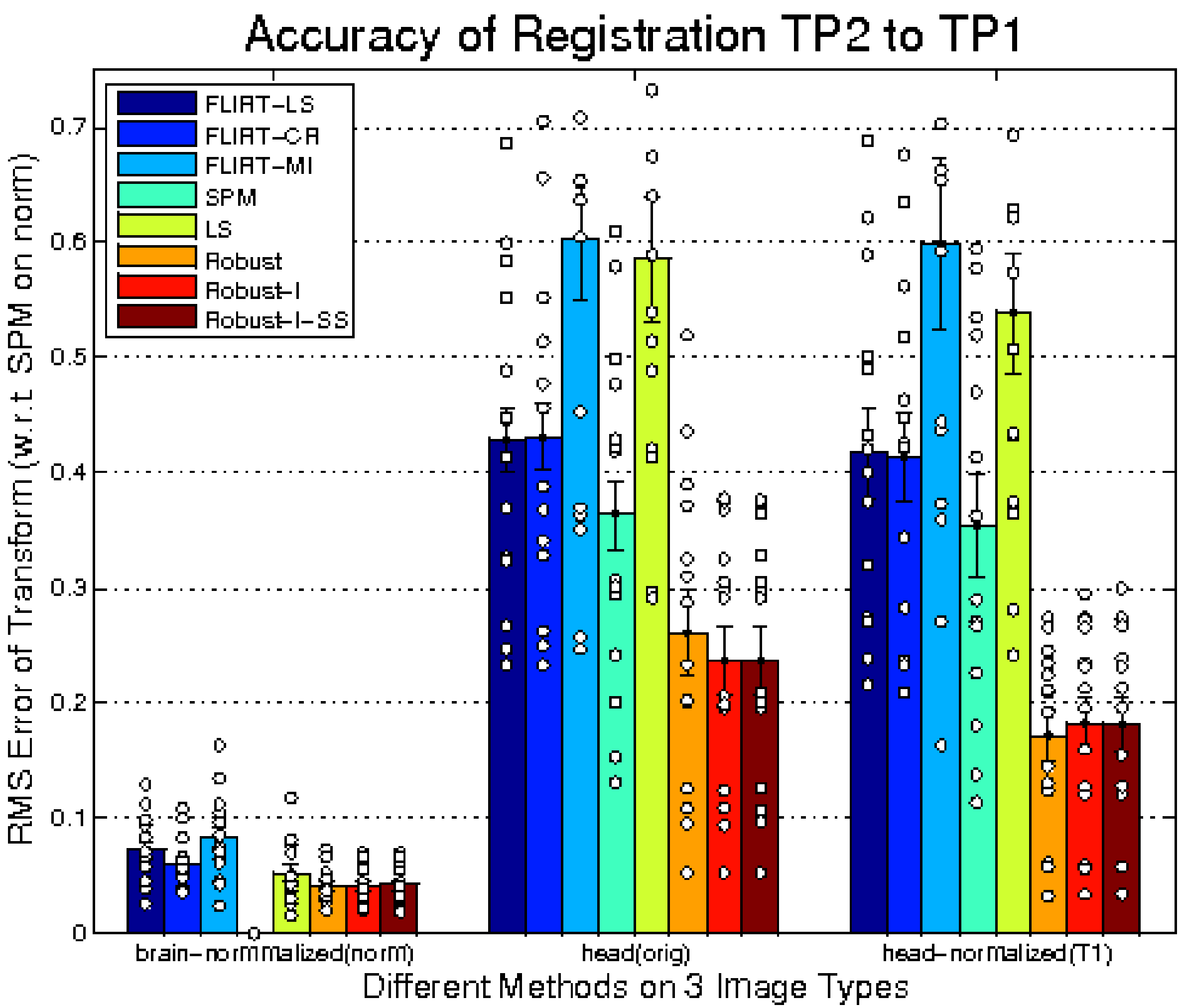
• nearly perfect symmetry (worst case RMS < 0.02)

Other methods:

• several alignments with RMS errors > 0.1

[Reuter et al., NeuroImage, 2010]

Accuracy of mri_robust_register



Performance of different methods on **test-retest scans**, with respect to SPM skull stripped brain registration (norm).

- The brain-only registrations are very similar
- Robust shows better performance for original (orig) or normalized (T1) full head images

[Reuter et al., NeuroImage, 2010]

mri_robust_register

- *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 more than 2 images: *mri_robust_template*

Robust Template Estimation

- Minimization problem for N images:

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

- Image Dissimilarity:

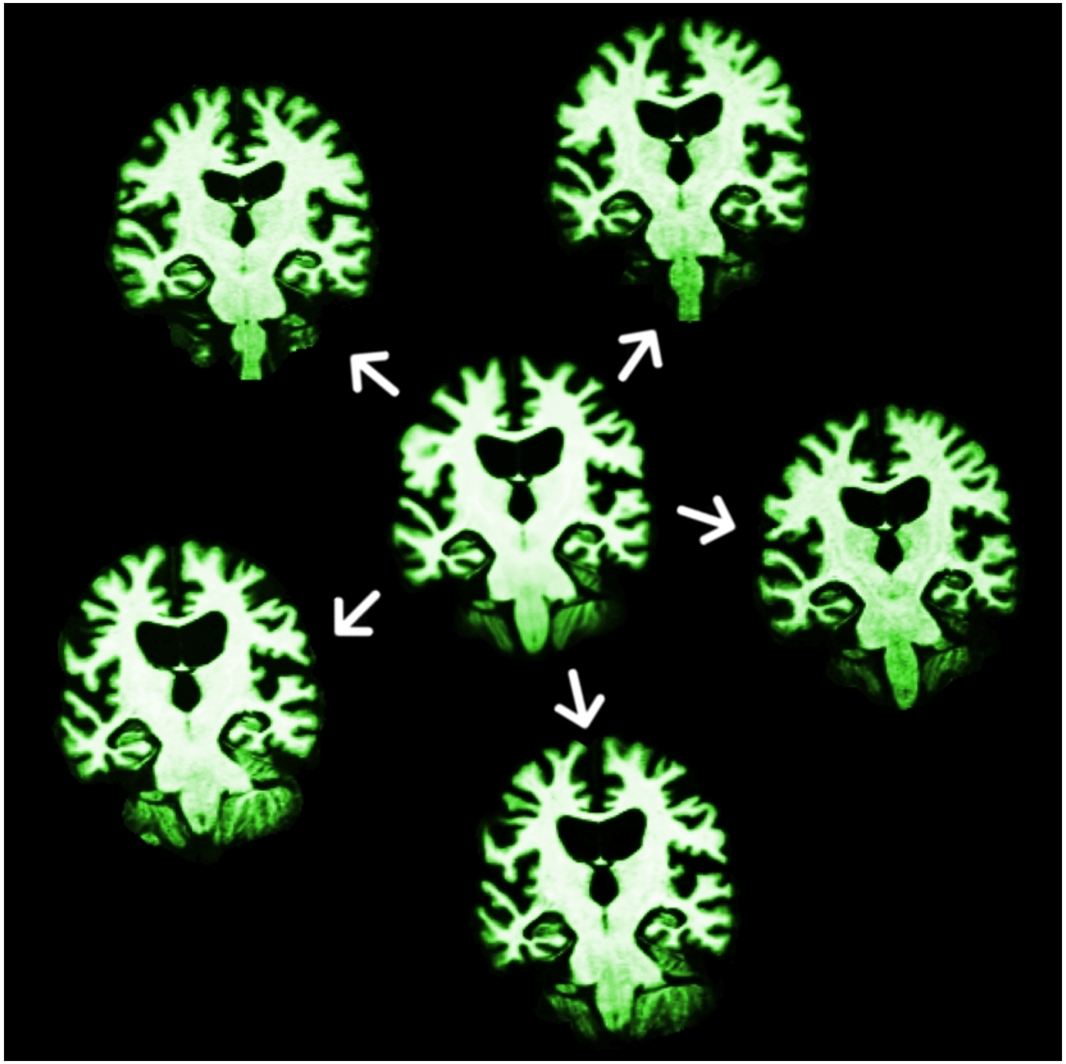
$$E(I_1, I_2) = \int_{\Omega} |I_1(x) - I_2(x)| \, dx$$

- Metric of Transformations:

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

Longitudinal Processing

Robust Unbiased Subject Template

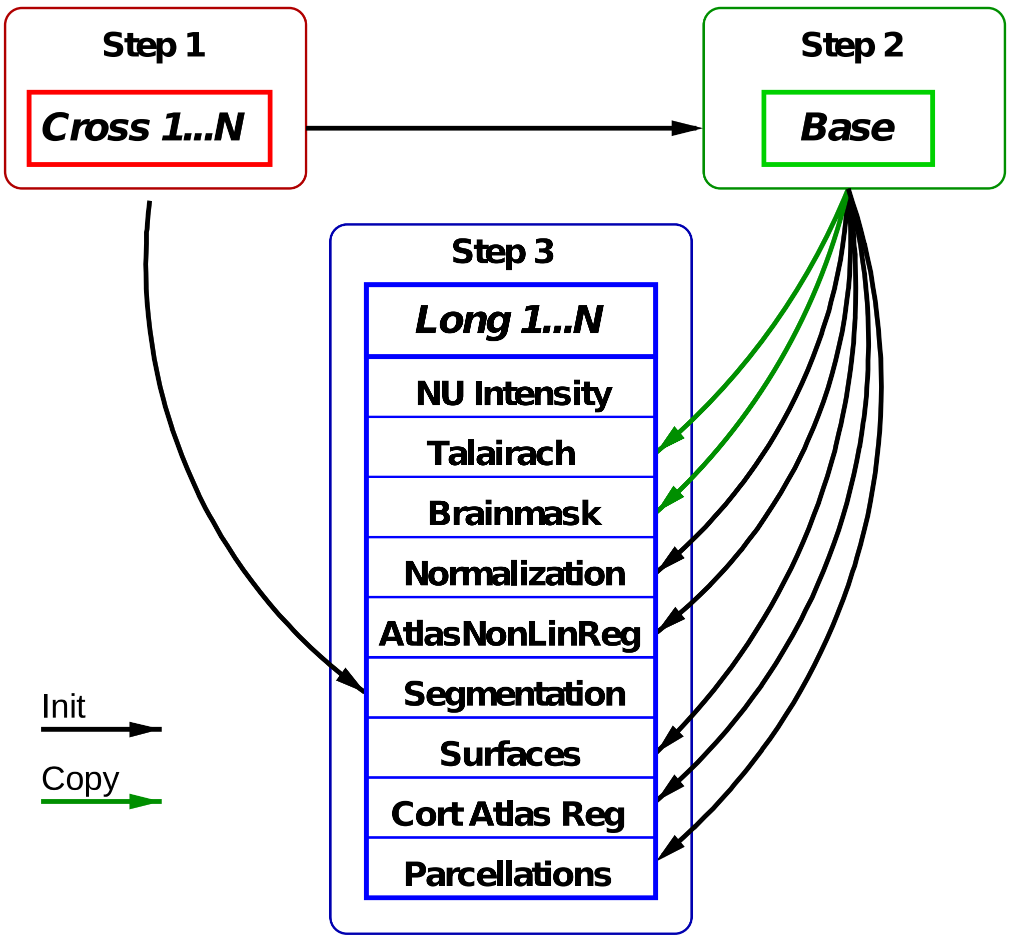


1. Create subject template (iterative registration to median)
2. Process template
3. Transfer to time points
4. Let it evolve there

- All time points are treated the same
- Minimize over-regularization by letting tps evolve freely

[Reuter et al., NeuroImage, 2012]

Robust Template for Initialization



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

FreeSurfer Commands (recon-all)

1.CROSS (independently for each time point tpNi

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

2. BASE (creates template, one for each subje

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

3. LONG (for each time point tpNid, passing basei

```
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!

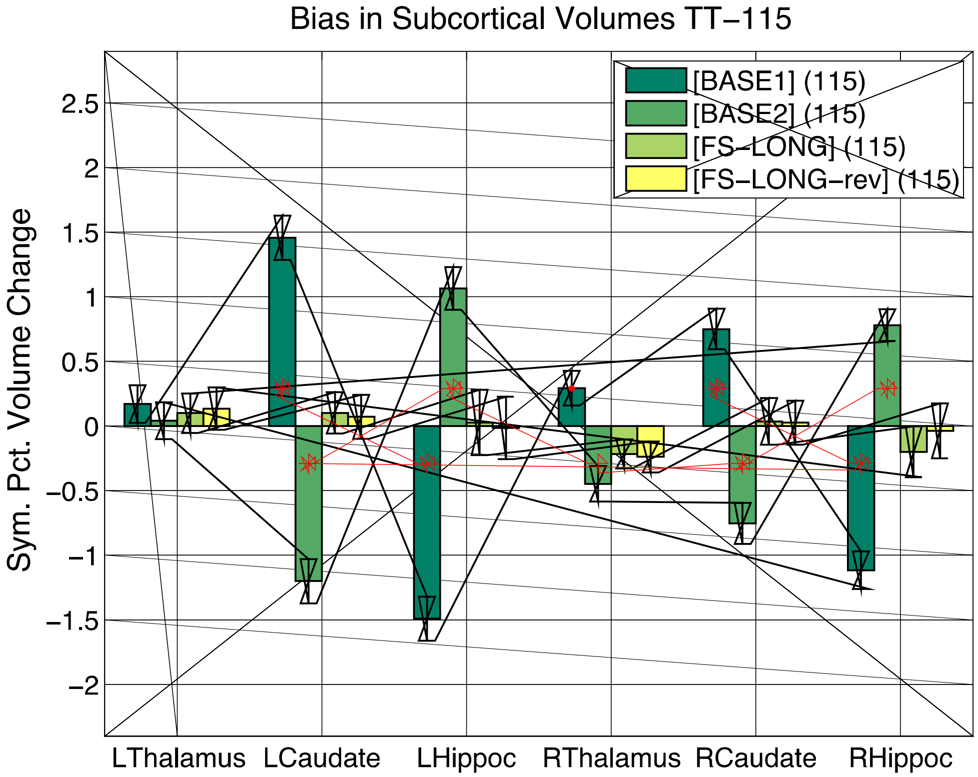
- Mixed effects models can use single tp subjects to estimate variance (increased power)
- This assures identical processing steps as in a subject with several time points
- Commands same as above:

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

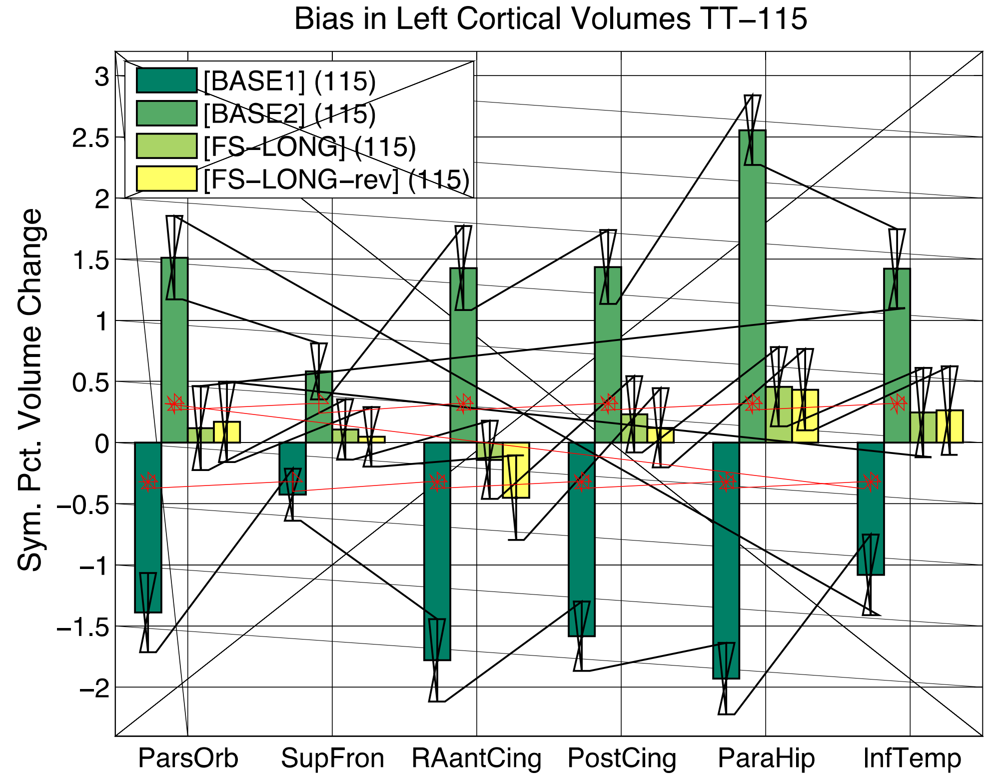
Biased Information Transfer

[Reuter et al., NeuroImage, 2012]

Subcortical



Cortical



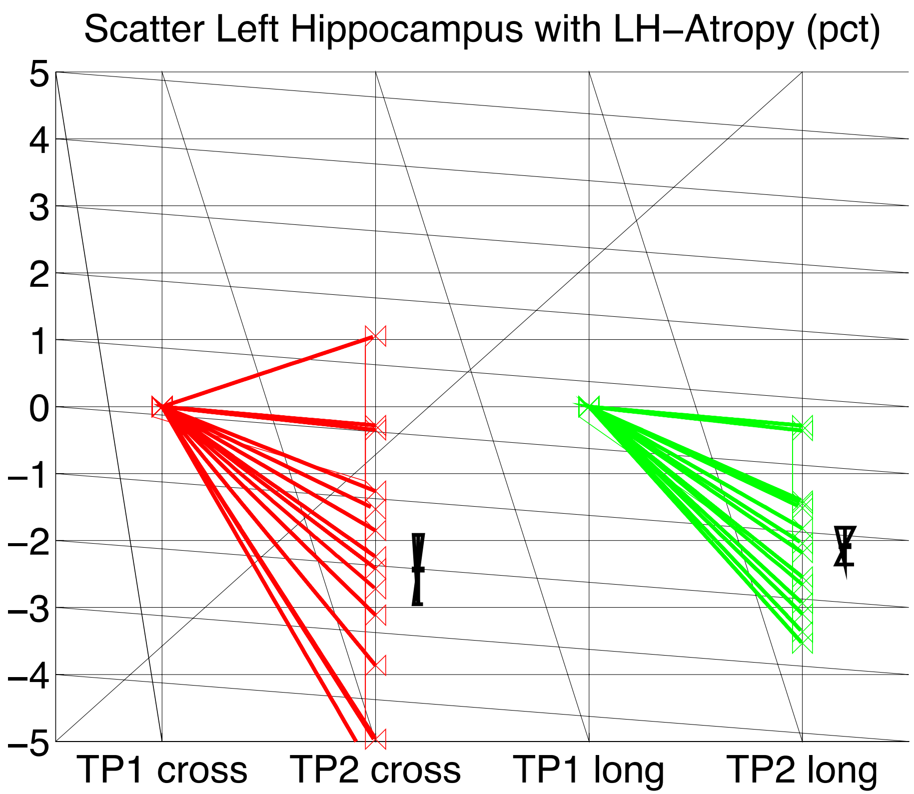
Biased information transfer: [BASE1] and [BASE2].

Our method [FS-LONG] [FS-LONG-rev] shows no bias.

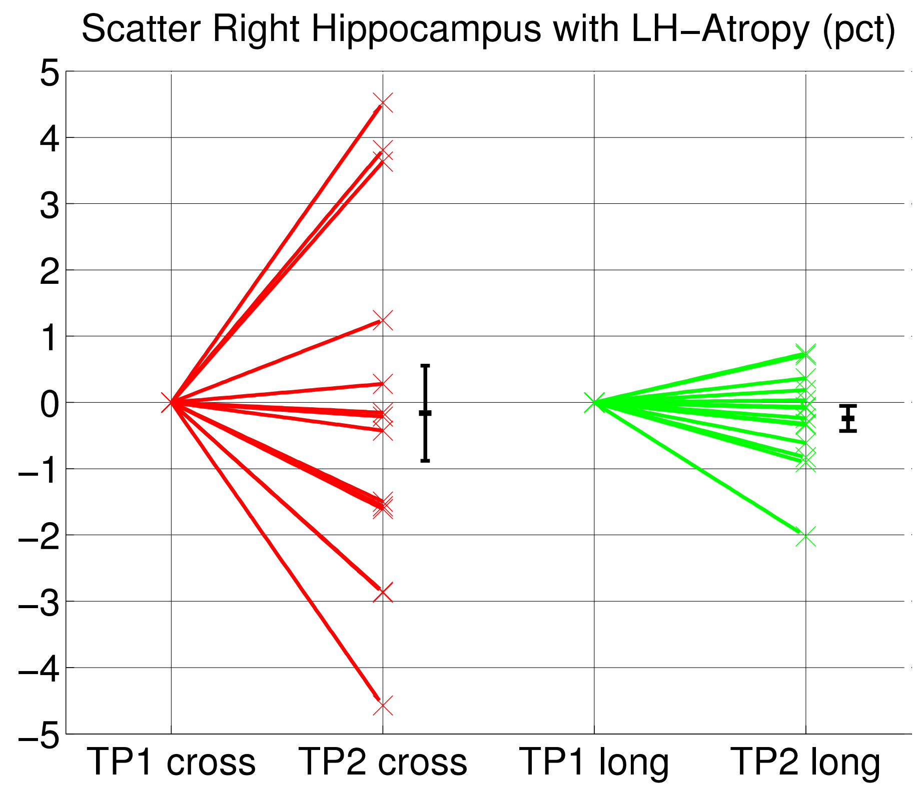
Simulated Atrophy (2% left Hippo.)

[Reuter et al., NeuroImage, 2012]

Left Hippocampus



Right Hippocampus



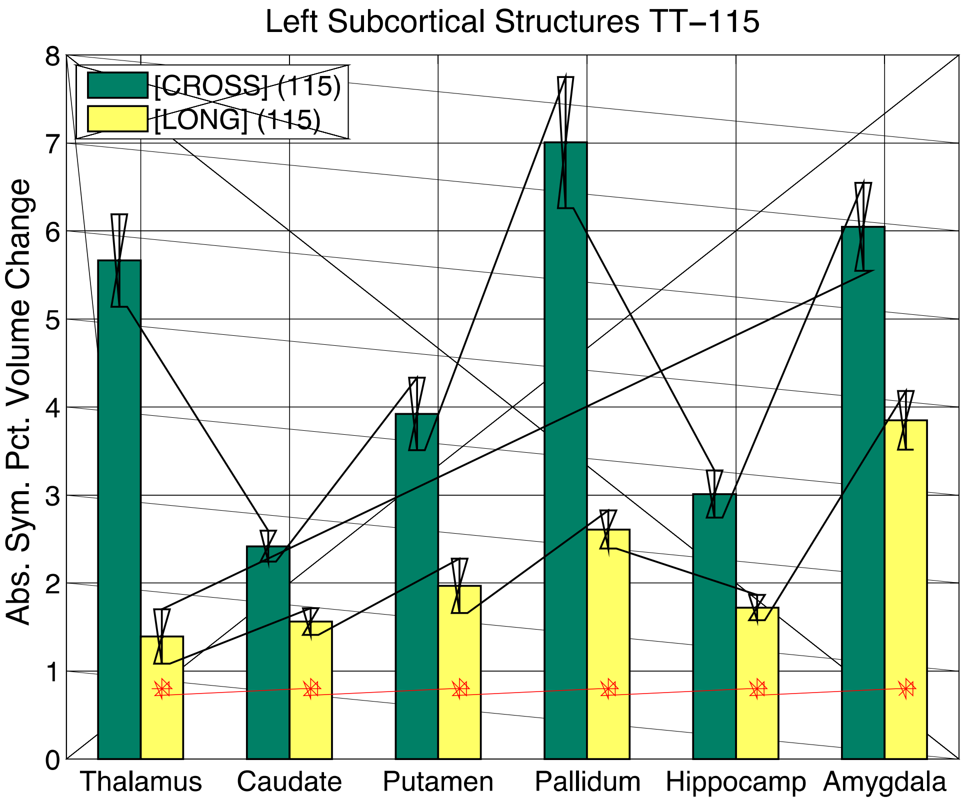
Cross sectional RED, longitudinal GREEN

Simulated atrophy was applied to the left hippocampus only

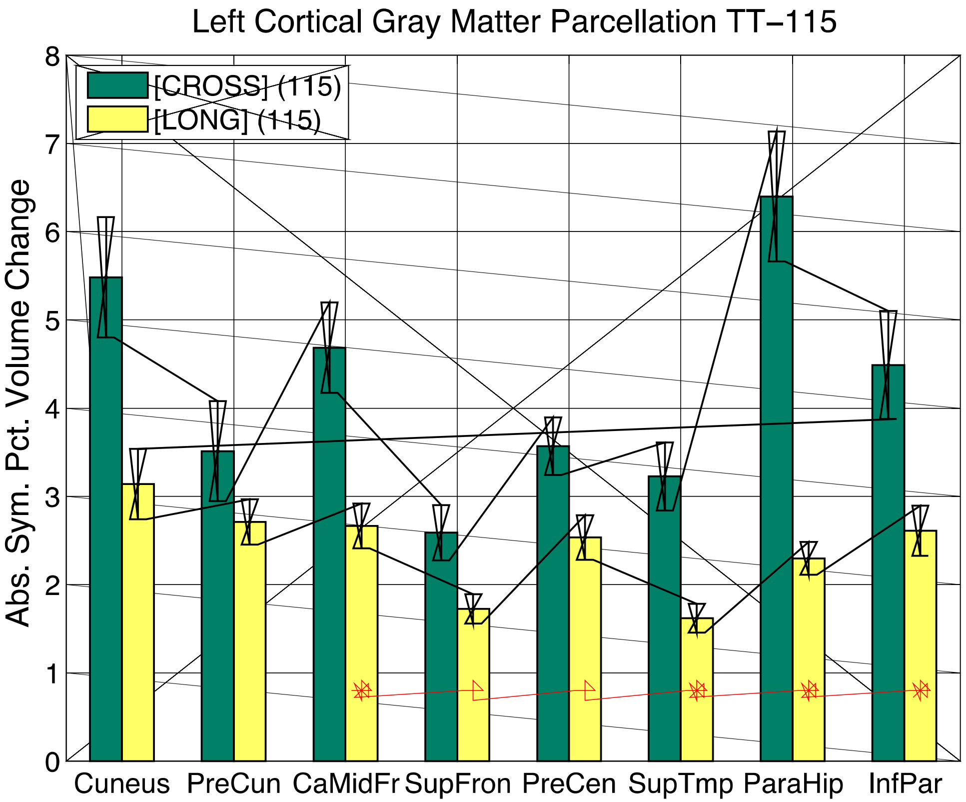
Test-Retest Reliability

[Reuter et al., NeuroImage, 2012]

Subcortical



Cortical



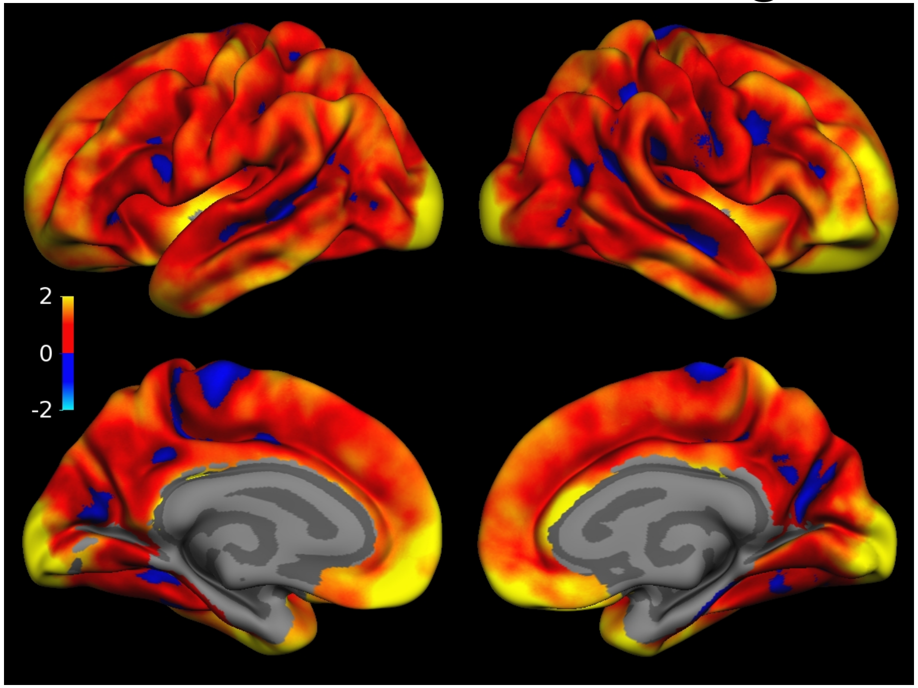
[LONG] significantly improves reliability

115 subjects, ME MPRAGE, 2 scans, same session

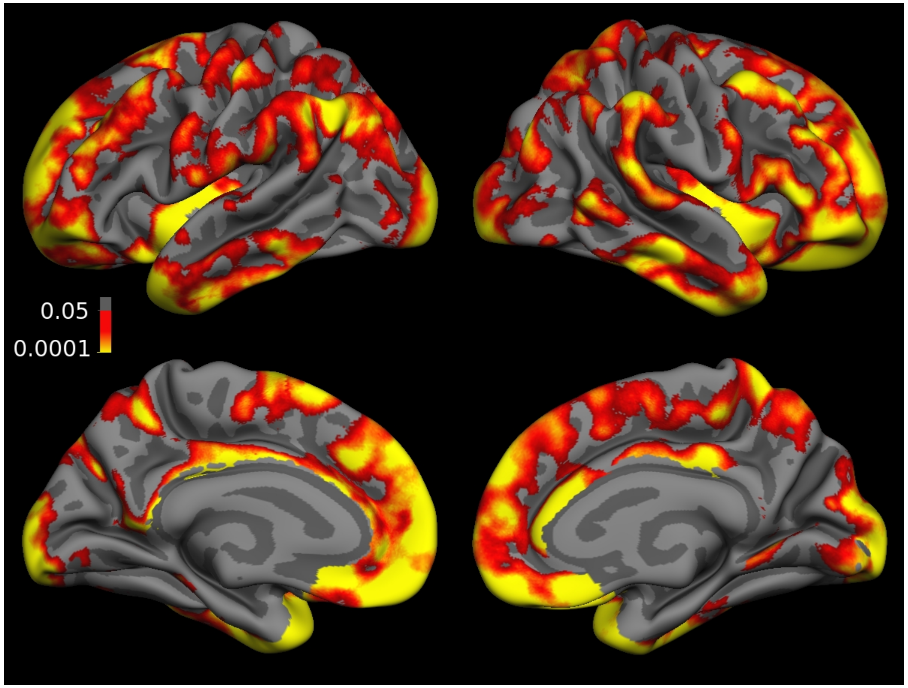
Test-Retest Reliability

[Reuter et al., NeuroImage, 2012]

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



Significance Map

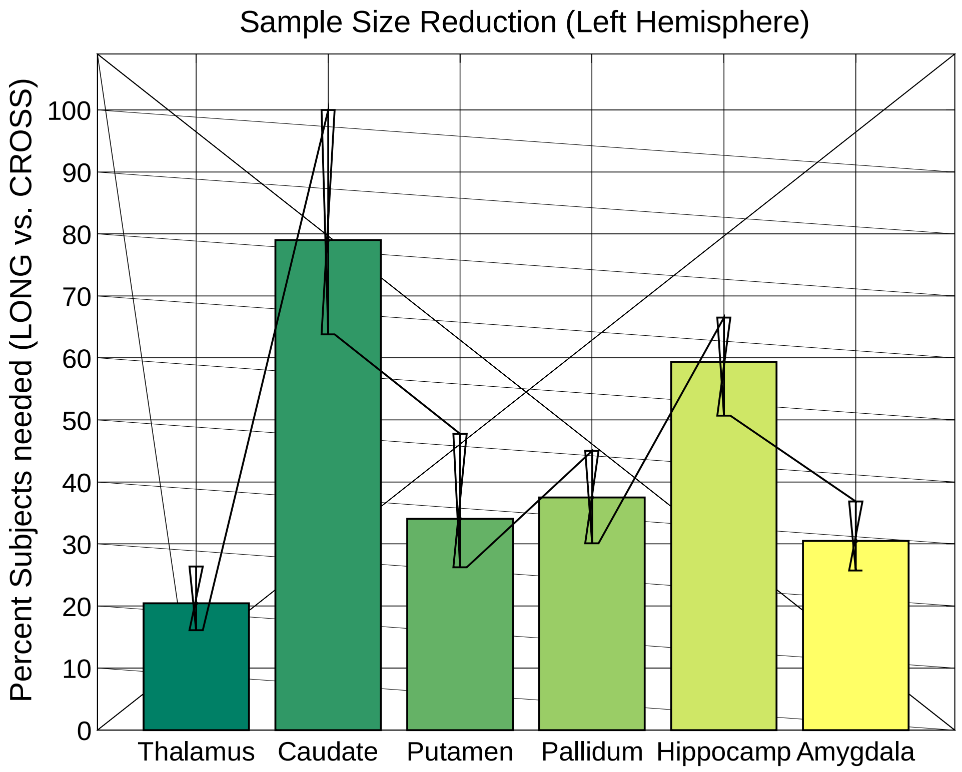


[LONG] significantly improves reliability

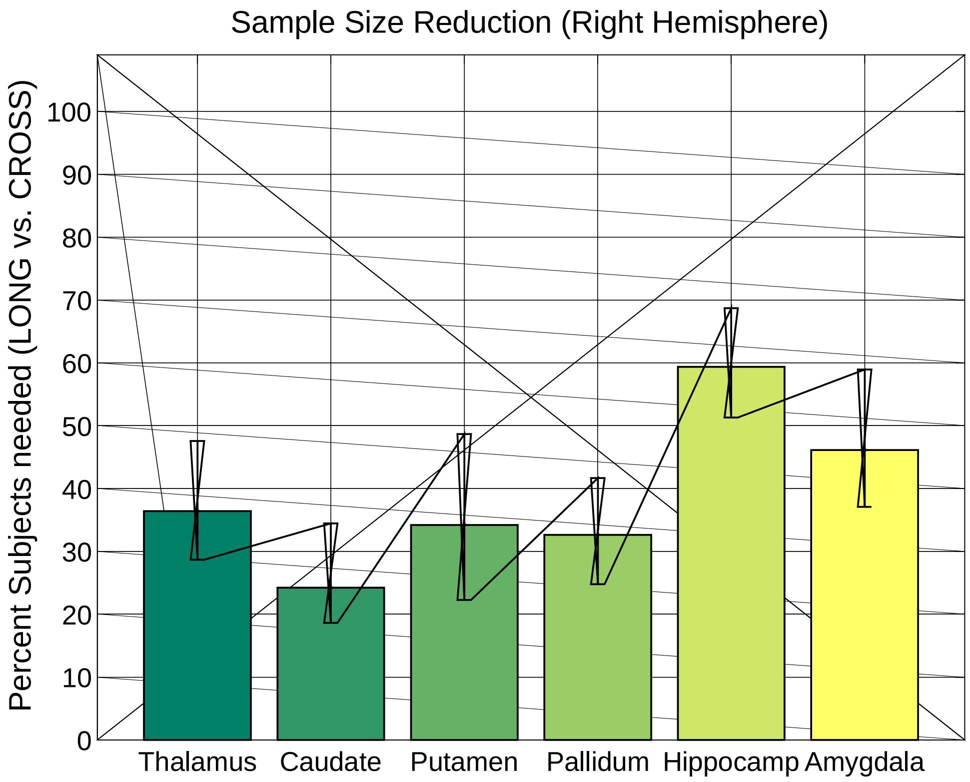
115 subjects, ME MPRAGE, 2 scans, same session

Increased Power
[Reuter et al., NeuroImage, 2012]

Left Hemisphere:



Right Hemisphere

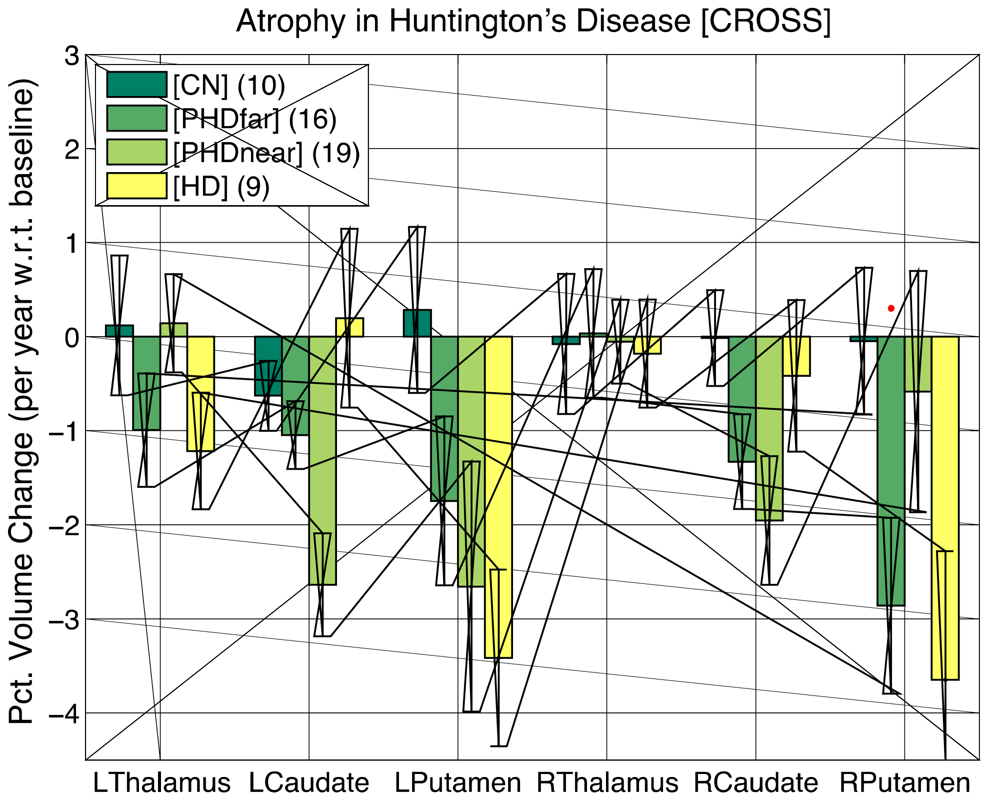


Sample Size Reduction when using [LONG]

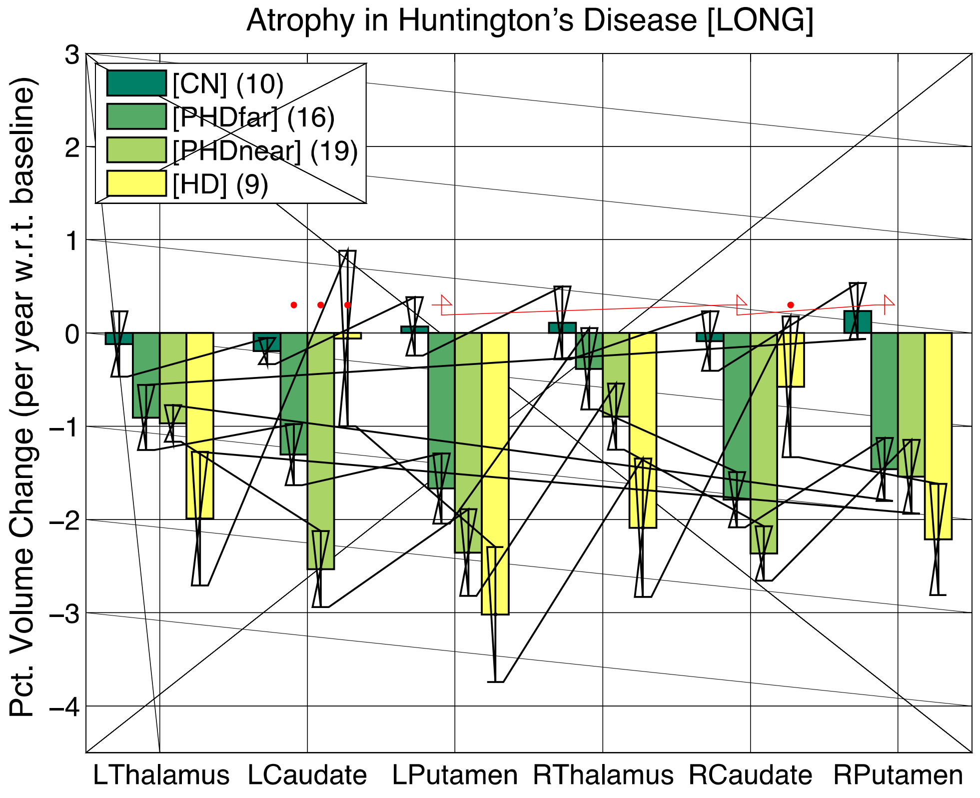
Huntington's Disease (3 visits)

[Reuter et al., NeuroImage, 2012]

Independent Processing



Longitudinal Processing

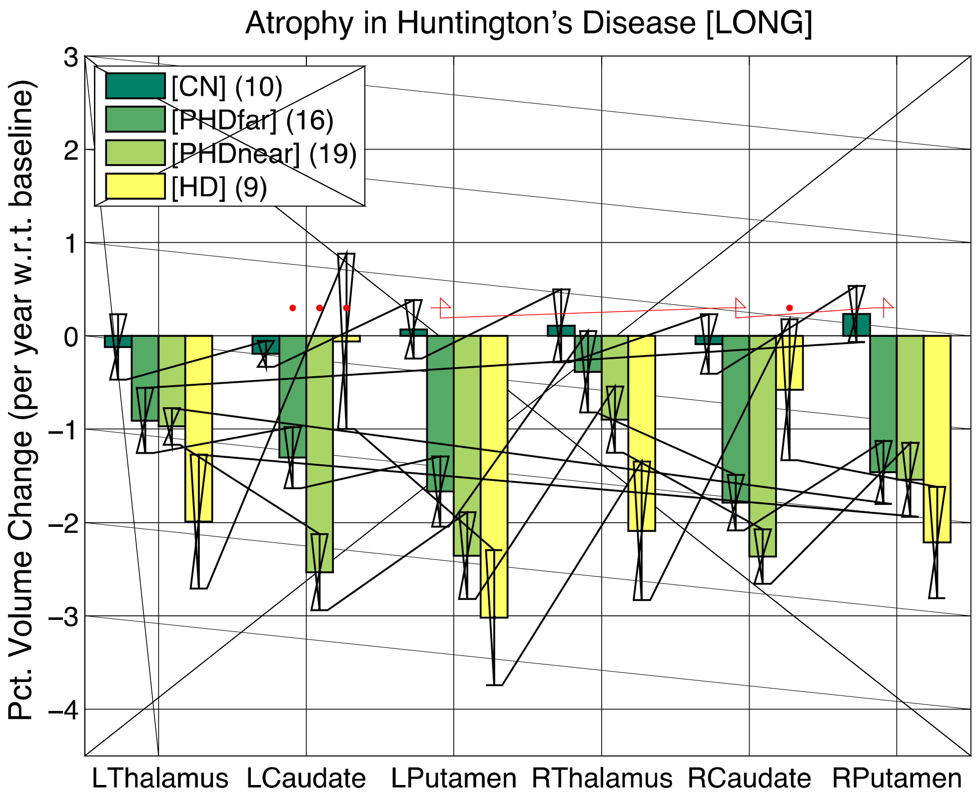


[LONG] shows higher precision and better discrimination power between groups (specificity and sensitivity).

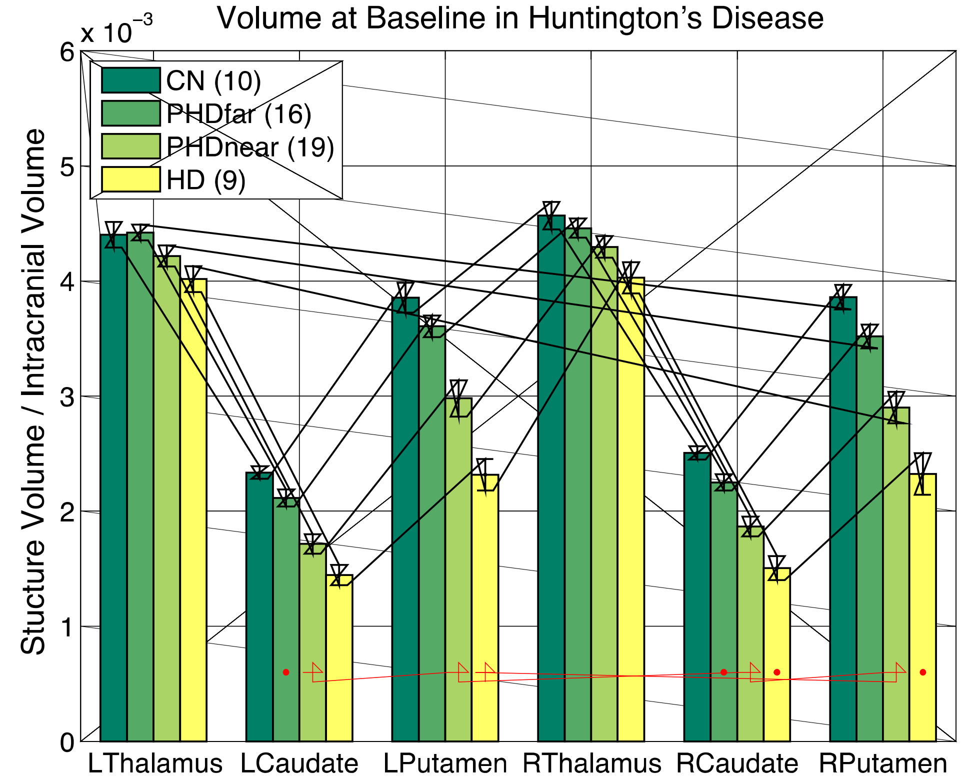
Huntington's Disease (3 visits)

[Reuter et al., NeuroImage, 2012]

Rate of Atrophy



Baseline Vol. (normalized)



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

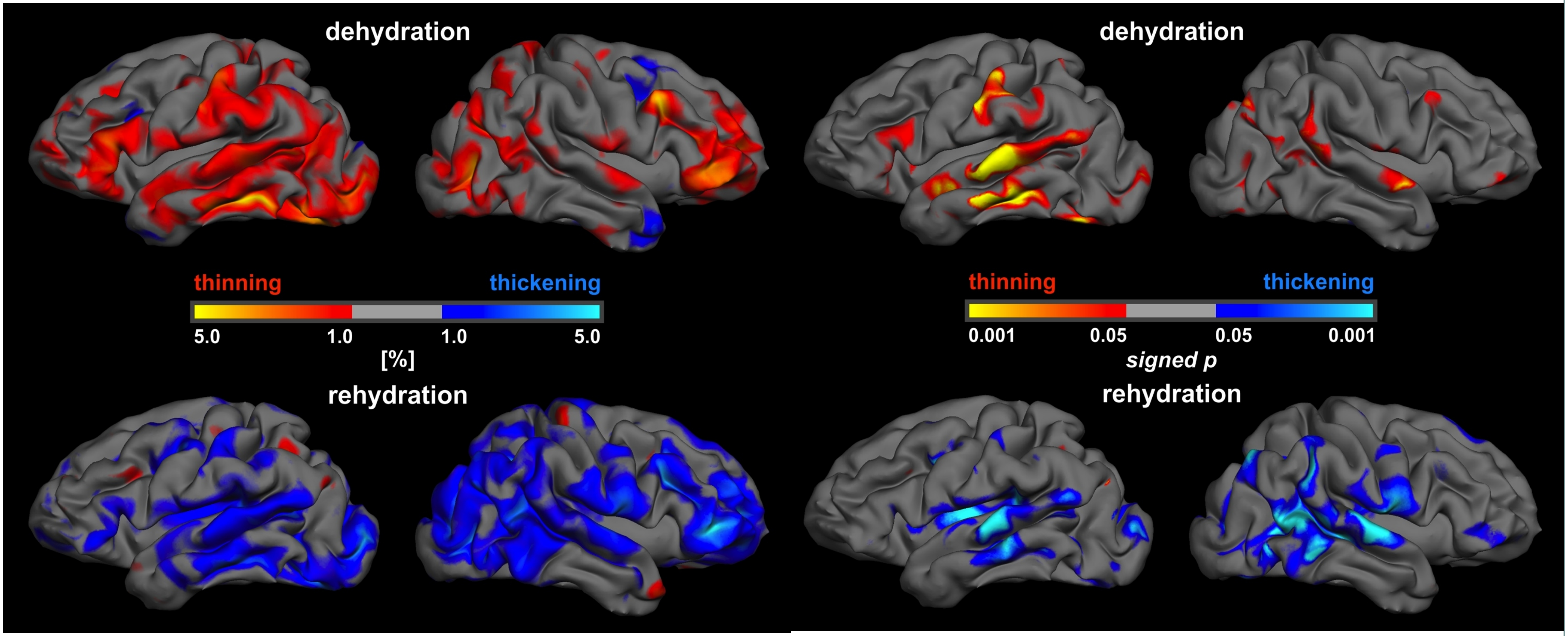
Final Remarks …

Sources of Bias during Acquisition

BAD: these influence the 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, rehydration 1L/h

[with A. Bartsch et al. – submitted]

Still to come …

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

http://freesurfer.net/fswiki/**LongitudinalProcessing**

http://reuter.mit.edu/publications

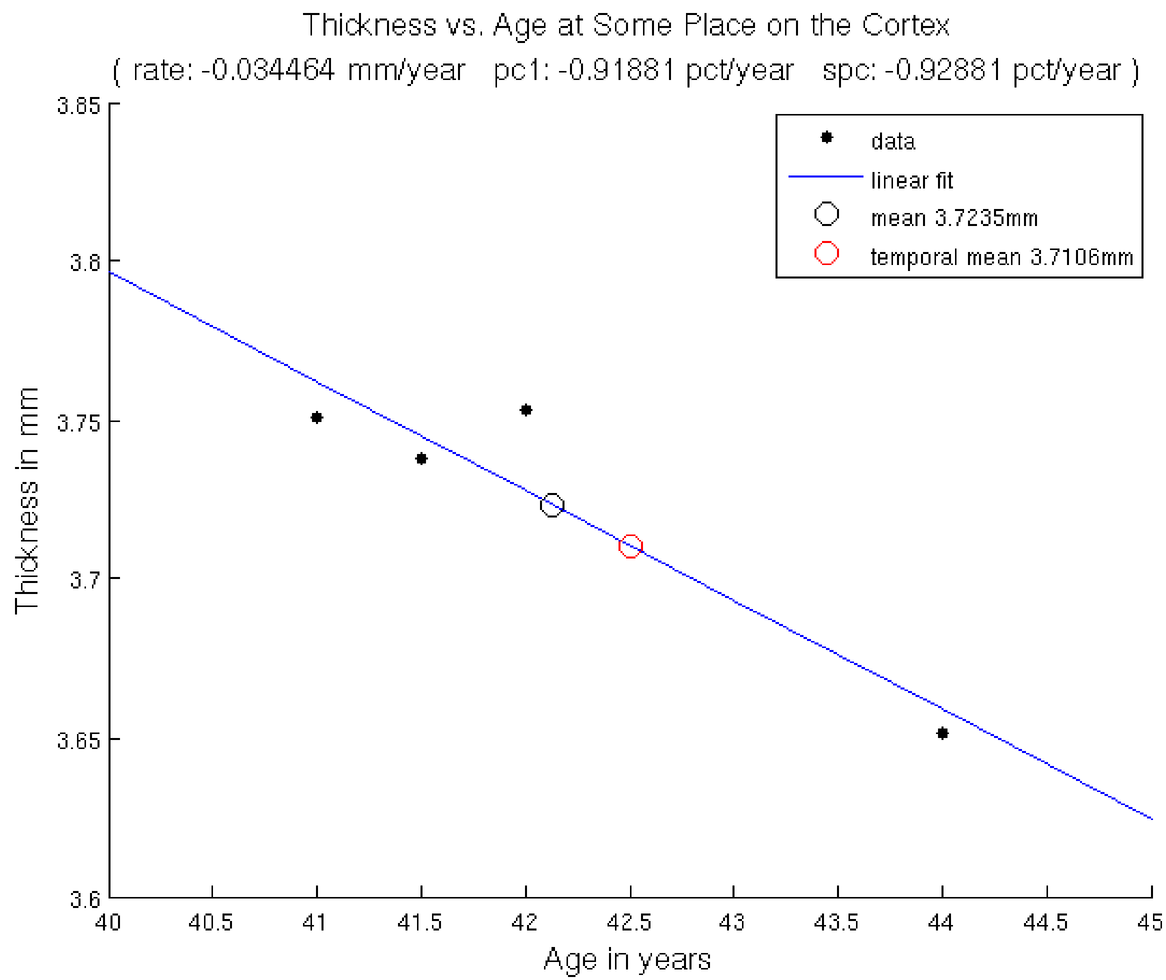
Thanks to: the FreeSurfer Team

Longitudinal Tutorial

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.)