Longitudinal TRACULA

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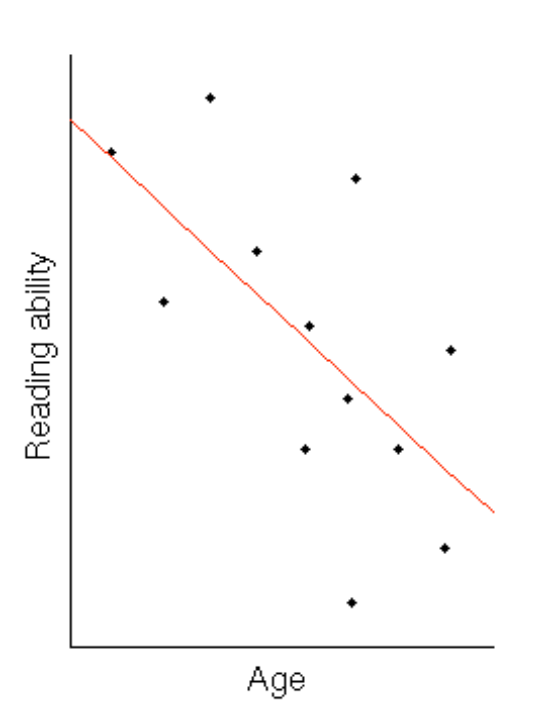
Longitudinal FreeSurfer

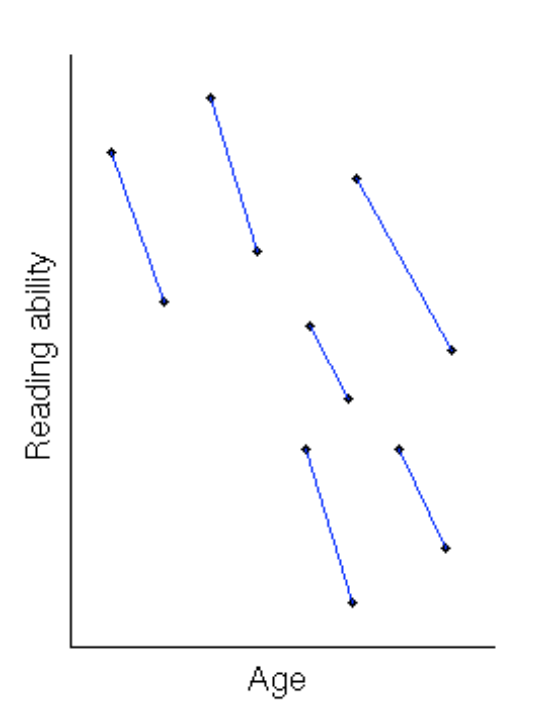
- Detecting changes in brain structure with time (development, aging, effects of treatment):
  - Cross-sectional studies are hampered by between-subject variability, which may dominate the longitudinal effect of interest
  - Longitudinal studies measure within-subject changes directly - each subject is her own control
- Applying cross-sectional image analysis methods to longitudinal data:
  - Performance of methods may degrade as disease progresses
  - Giving a time point special status (mapping other points to it) leads to bias
- Longitudinal stream of FreeSurfer: Unbiased analysis of longitudinal T_1 data, relying on robust within-subject template [Reuter '12]
- Longitudinal stream of TRACULA: Unbiased tractography on longitudinal dMRI data, using the within-subject template from above

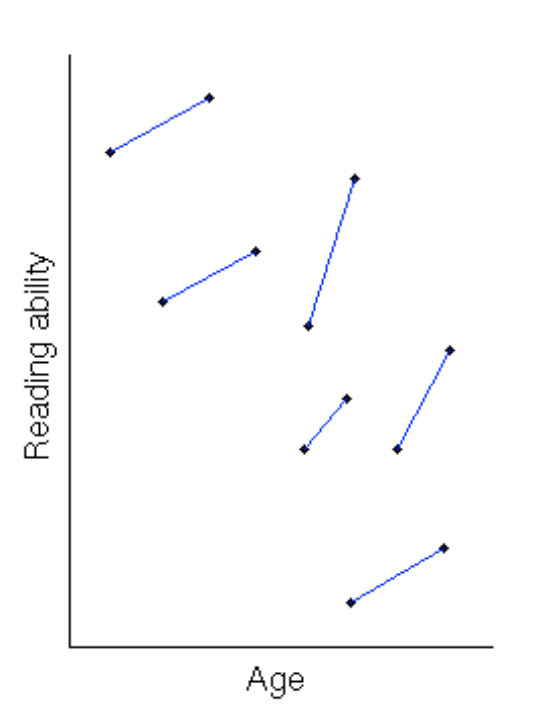
Why longitudinal?

Images courtesy of Martin Reuter

- Between-subject variability is often greater than the longitudinal effects of interest



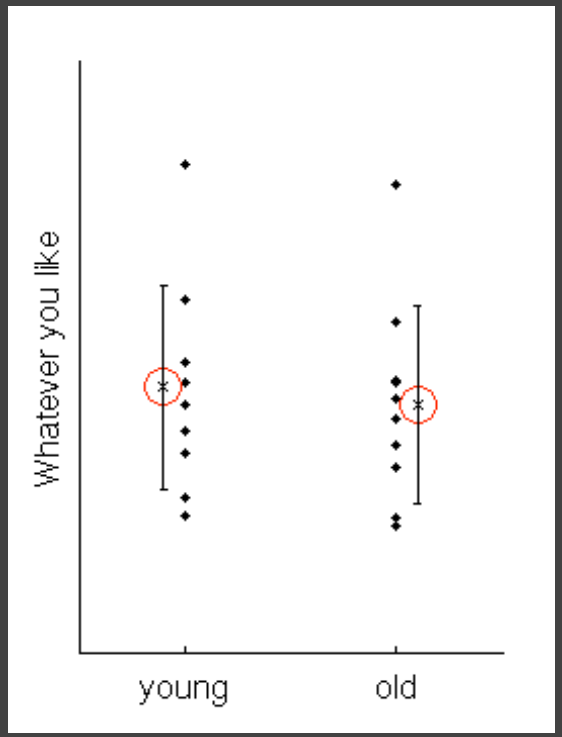


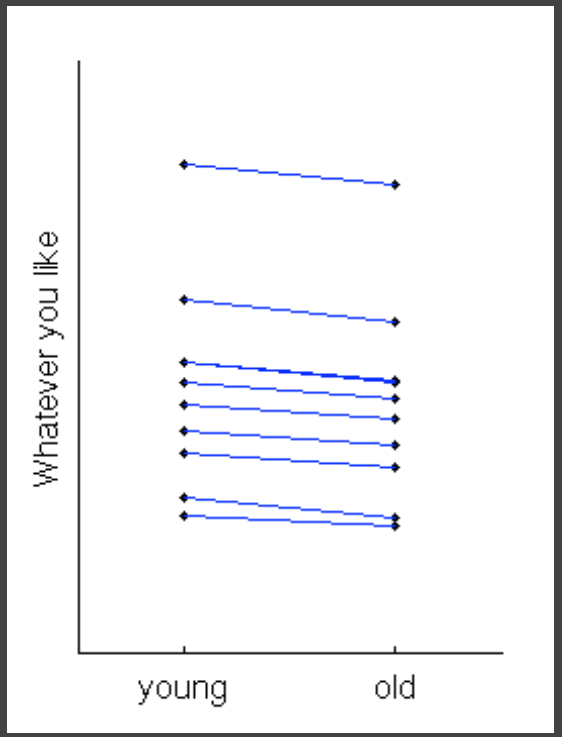


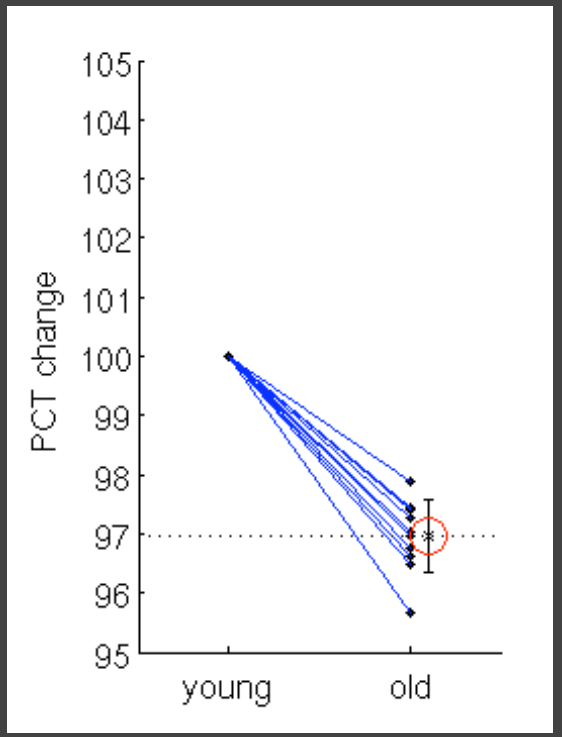
Why longitudinal?

Images courtesy of Martin Reuter

- Within-subject percent change of measure (thickness, volume, etc.) may be more sensitive than absolute values of measure



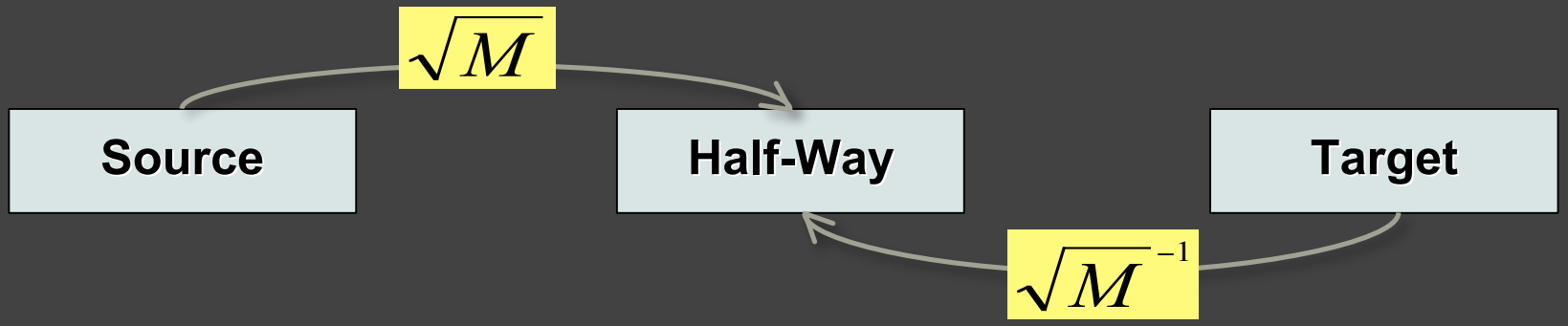




Robust registration

Reuter *et al.*, 2010

- Symmetric
  - Treats source and target image the same
  - Registering source to target results in the inverse of the registration from target to source
  - Resample both source and target to an unbiased half-way space in intermediate steps (square root of registration matrix)



- Robust
  - Cost function that does not penalize large intensity differences
  - Outlier voxels in the images are detected and iteratively filtered out

Robust registration

Reuter *et al.*, 2010

Target

Target

Robust registration

Reuter *et al.*, 2010

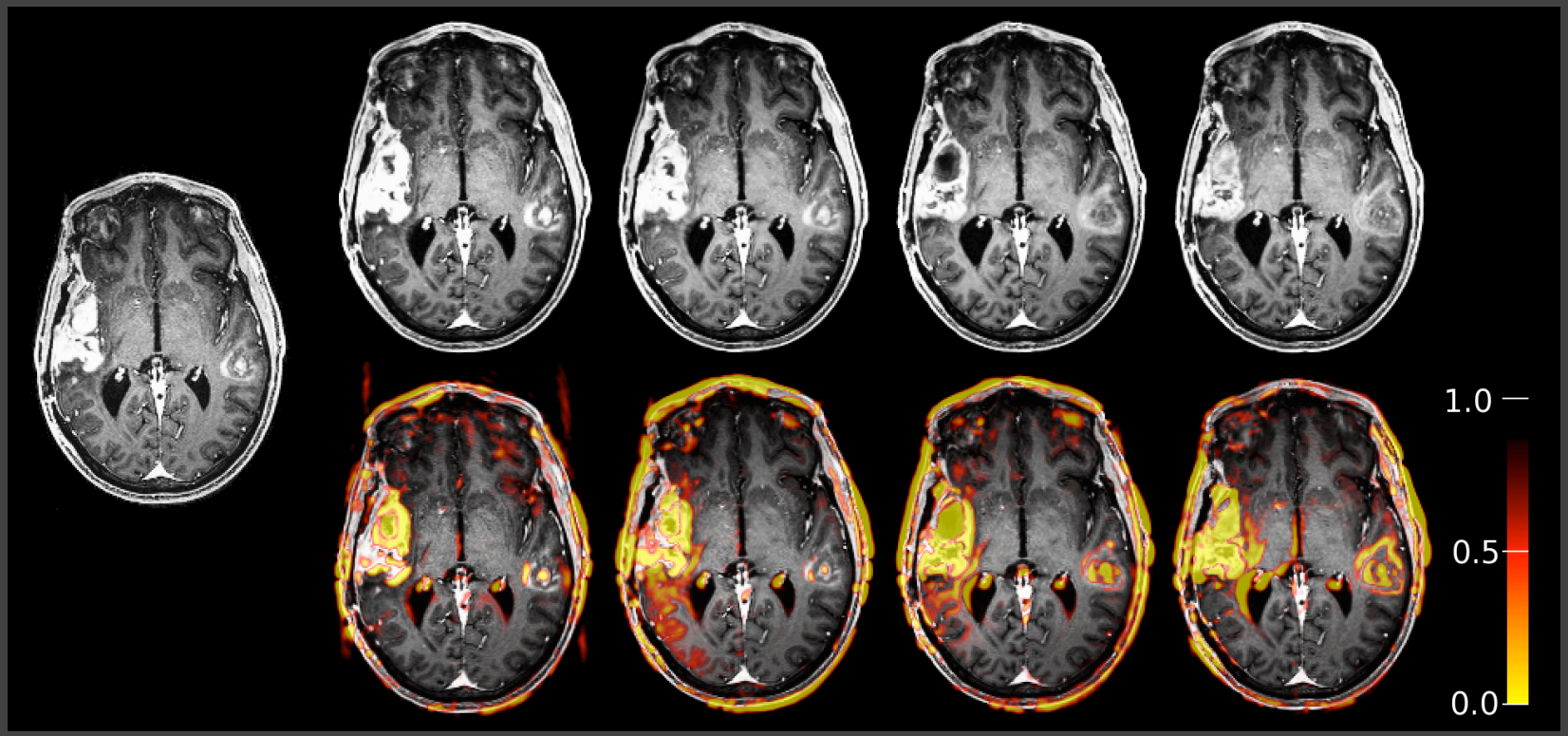
Source, registered by FSL FLIRT

Source, registered by robust

Robust registration

Reuter *et al.*, 2010

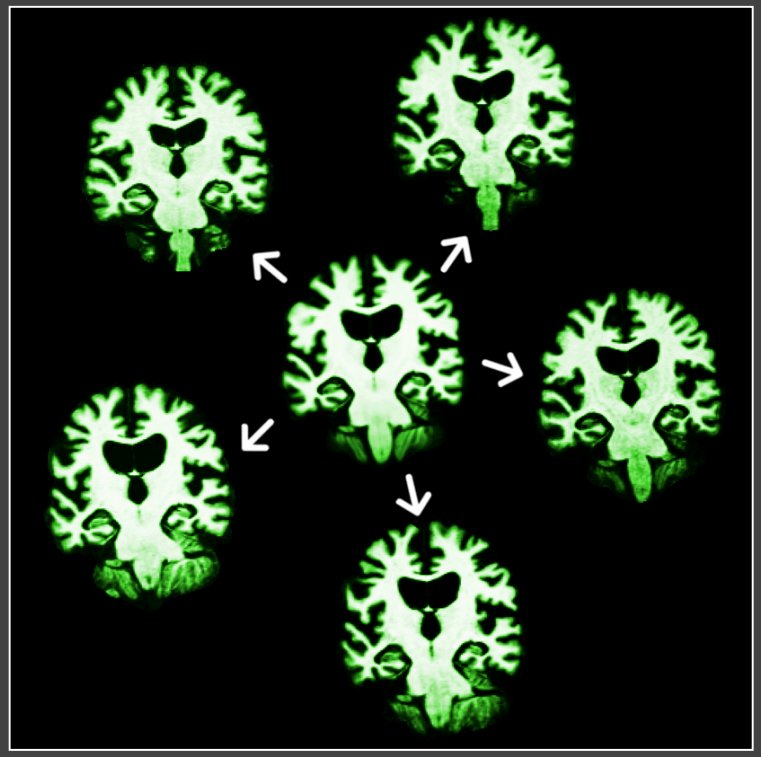
- Tumor patient data, registered to the first time point
- Overlay shows regions detected as outliers, which did not contribute to the robust registration



Tumor data courtesy of Greg Sorensen

Base template

Reuter *et al.*, 2012



1. Create a robust, unbiased, within-subject base template (iterative registration of time points to median)
2. Process base template as a regular scan
3. Transfer information to time points
4. Let processing evolve from there
   - All time points are treated the same
   - No over-regularization, time points evolve freely

Longitudinal FreeSurfer stream

- Assume a subject, bert, with T_1 scans at multiple time points:
  `bert_tp1, bert_tp2, …`
- Step 1: CROSS (run independently for each time point 1, 2, …)

```
recon-all -subjid bert_tp1 -all
recon-all -subjid bert_tp2 -all
…
```

- Step 2: BASE (run once for this subject, creates base template)

```
recon-all -base bert_base -tp bert_tp1 bert_tp2 ... -all
```

- Step 3: LONG (run for each time point 1, 2, …, also specifying the base)

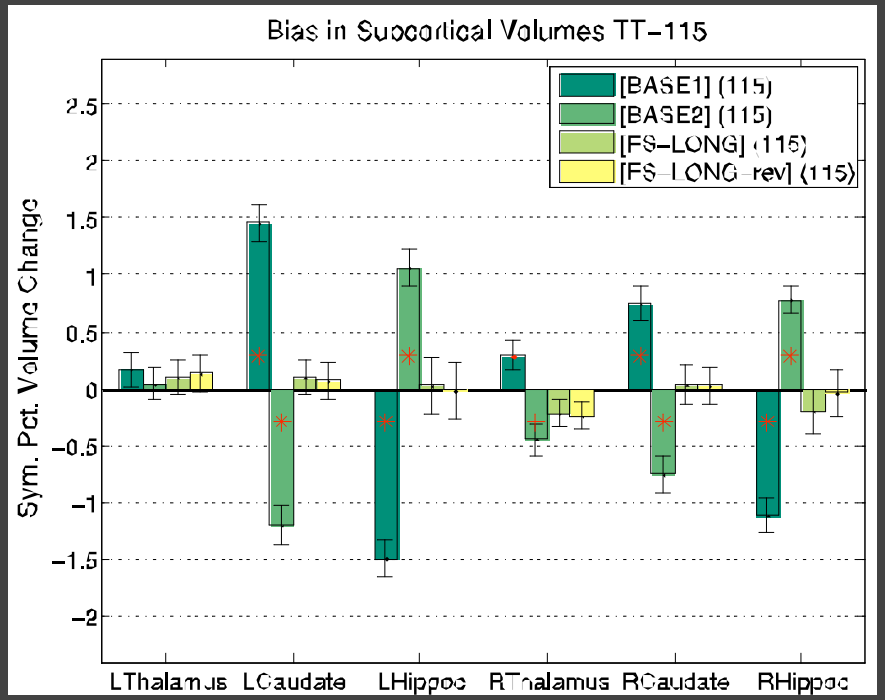
```
recon-all -long bert_tp1 bert_base -all
recon-all -long bert_tp2 bert_base -all
…
```

Biased vs. unbiased

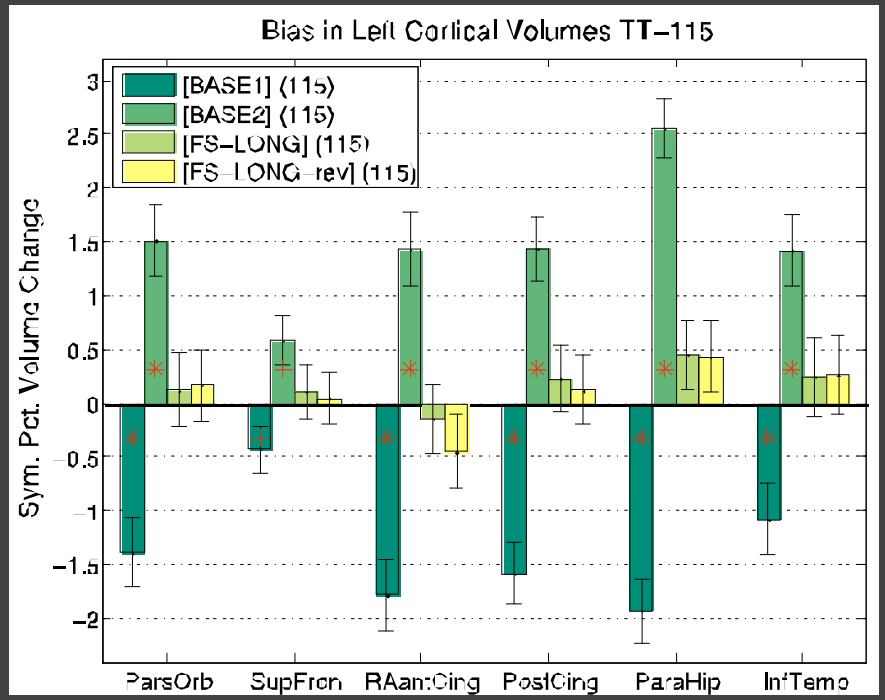
Reuter *et al.*, 2012

- Test-retest scans, treat either test or retest as the base
- Biased information transfer from follow-up to base ([BASE1], [BASE2]) vs. unbiased longitudinal stream ([FS-LONG], [FS-LONG-rev])

Subcortical



Cortical

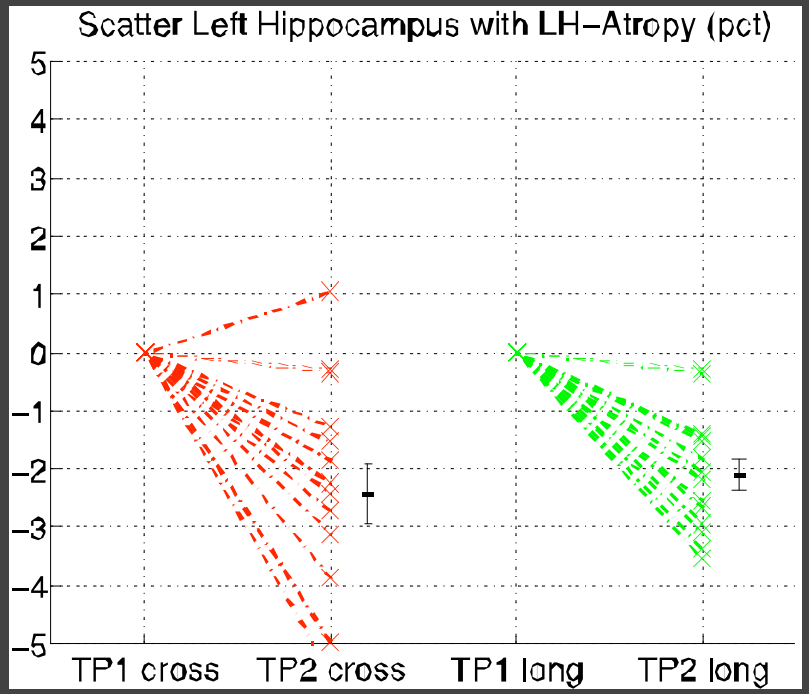


Simulated atrophy

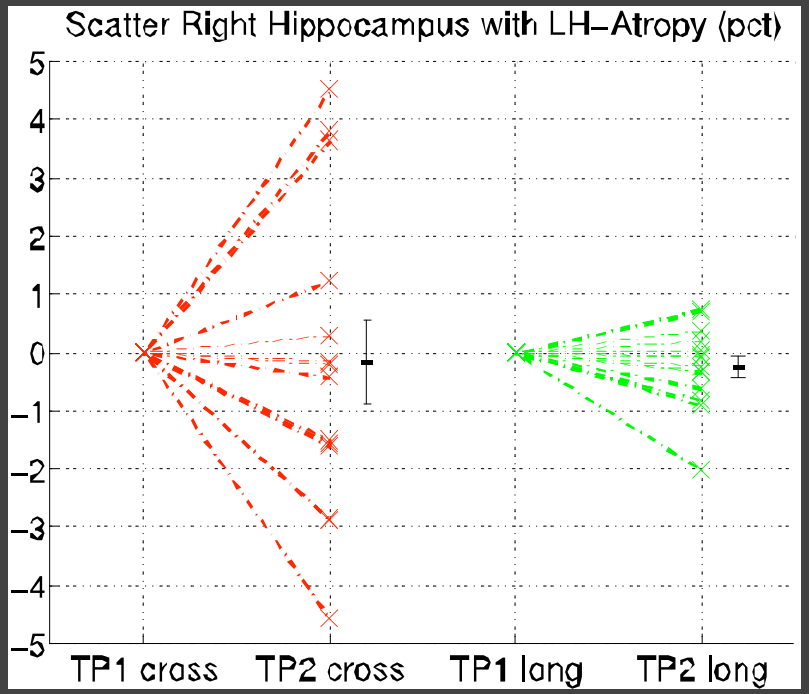
Reuter *et al.*, 2012

- Simulated 2% atrophy in left hippocampus only
- Longitudinal stream significantly improves precision

Subcortical



Cortical

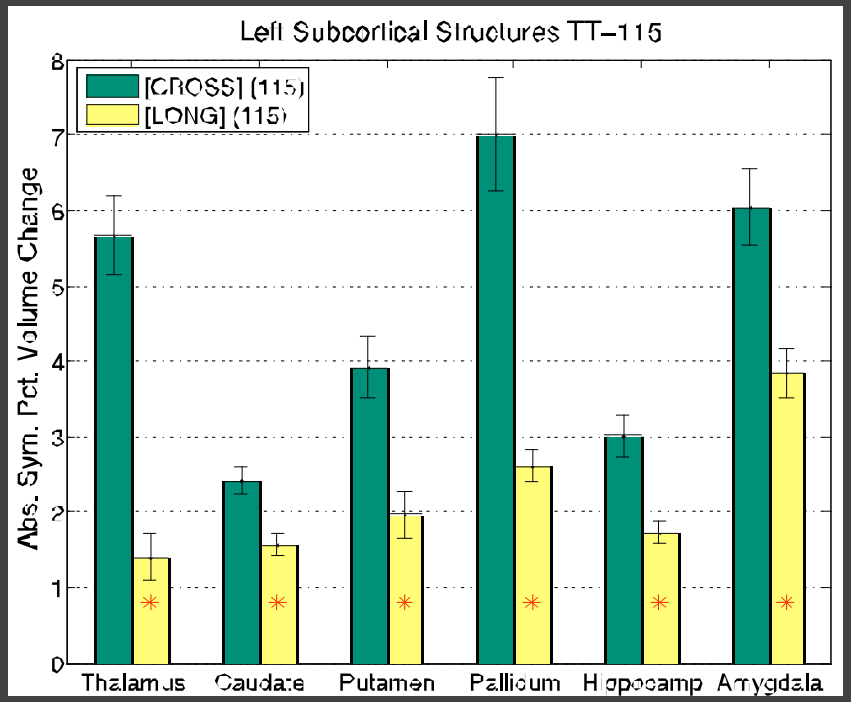


Test-retest reliability

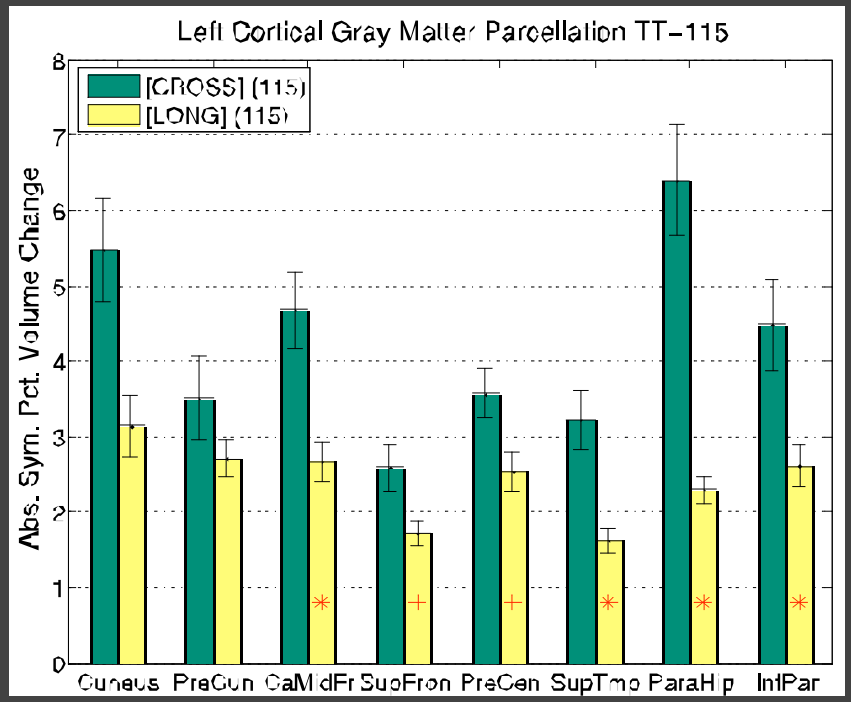
Reuter *et al.*, 2012

- 115 subjects, ME-MPRAGE, 2 scans, same session
- Longitudinal stream significantly improves reliability

Subcortical



Cortical

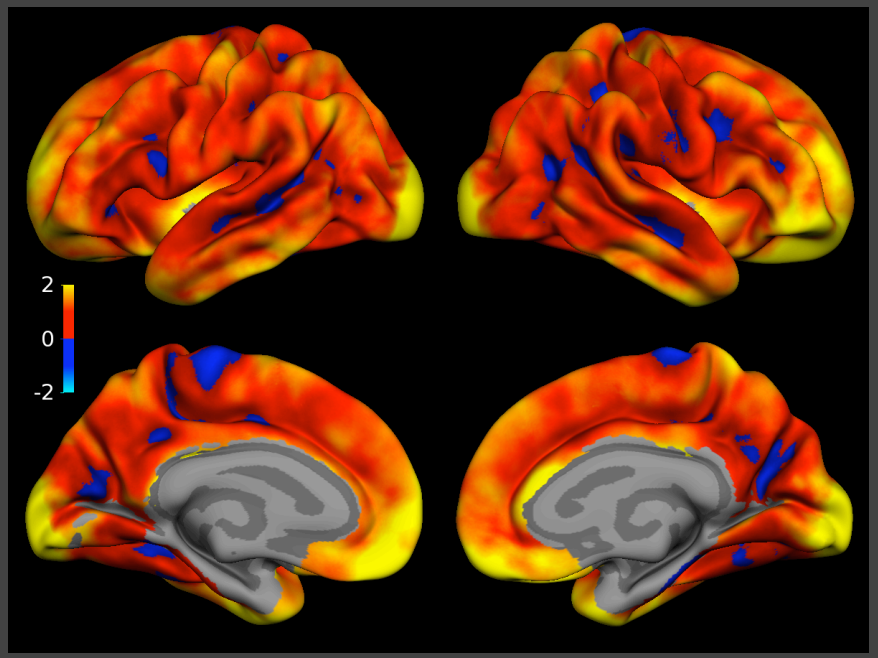


Test-retest reliability

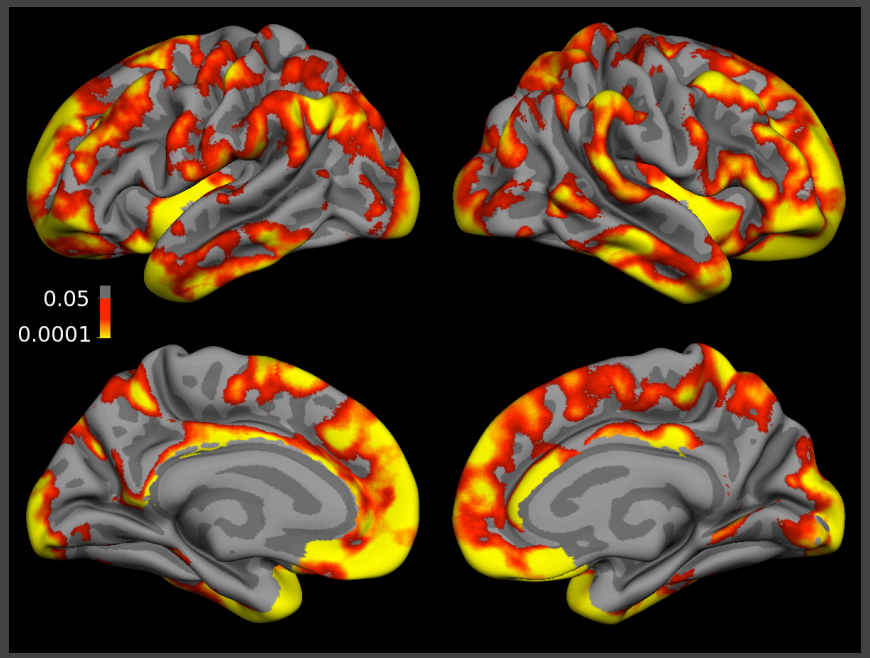
Reuter *et al.*, 2012

- 115 subjects, ME-MPRAGE, 2 scans, same session
- Longitudinal stream significantly improves reliability

Difference of Absolute Thickness Change ([CROSS]-[LONG])



Significance map

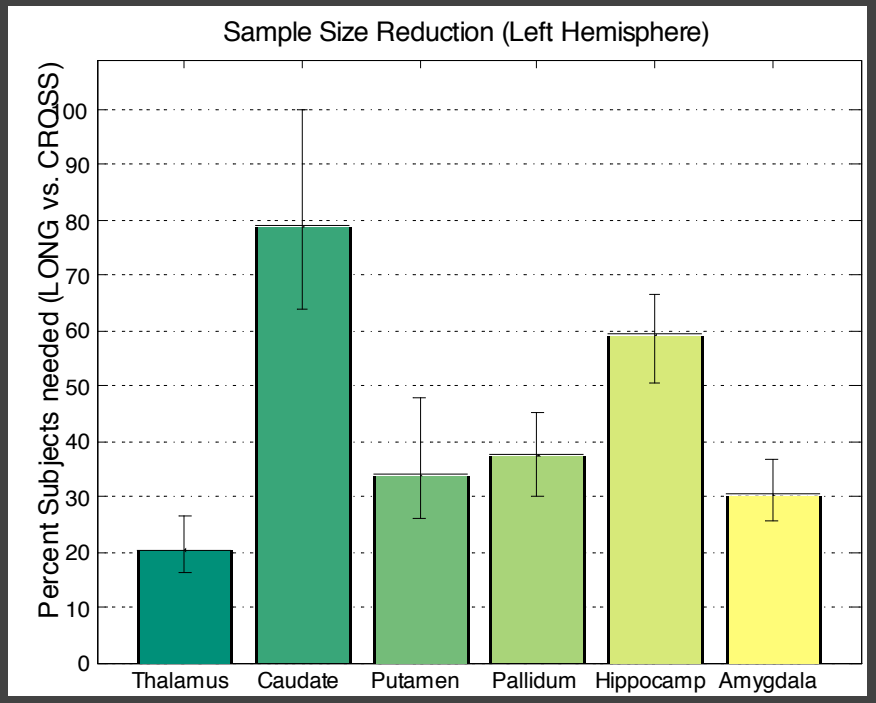


Increased power

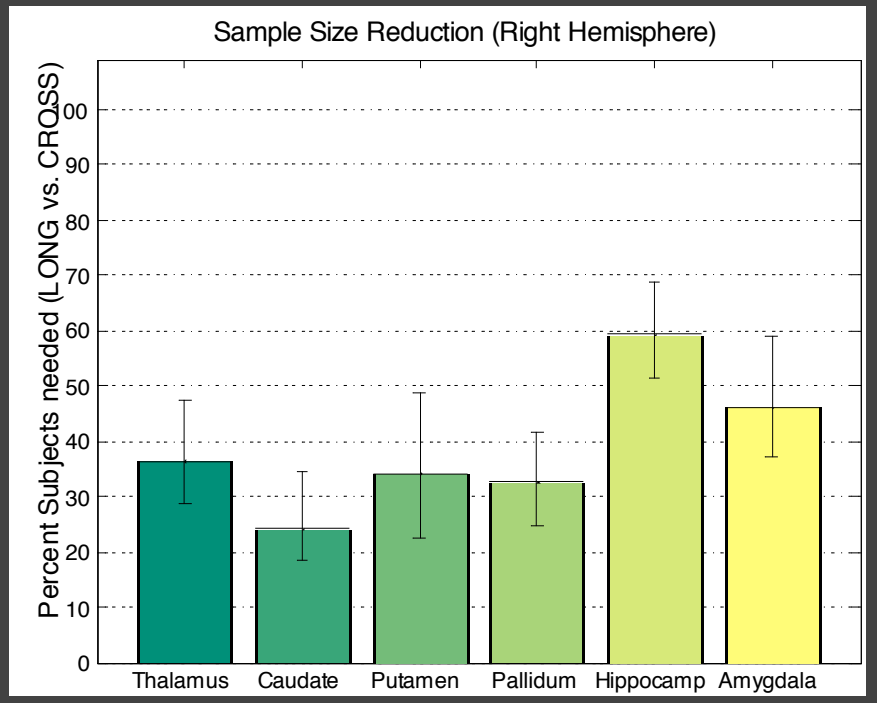
Reuter *et al.*, 2012

- Longitudinal processing requires a fraction of the subjects needed by cross-sectional processing to detect differences

Left hemi



Right hemi

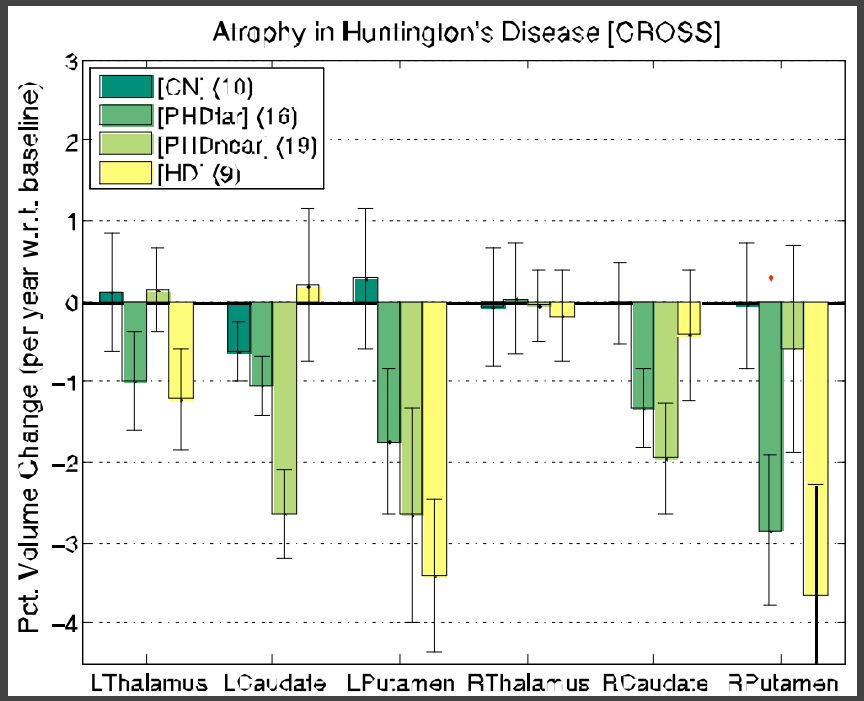


Huntington's Disease (3 visits)

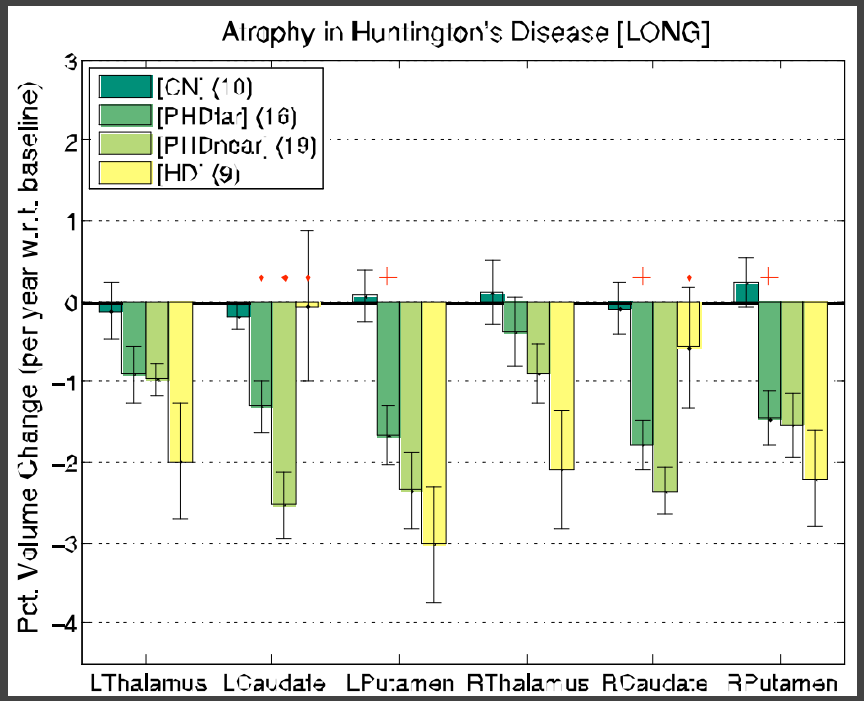
Reuter *et al.*, 2012

- Longitudinal processing leads to higher precision and better discriminating power between groups (specificity and sensitivity)

Independent processing



Longitudinal processing

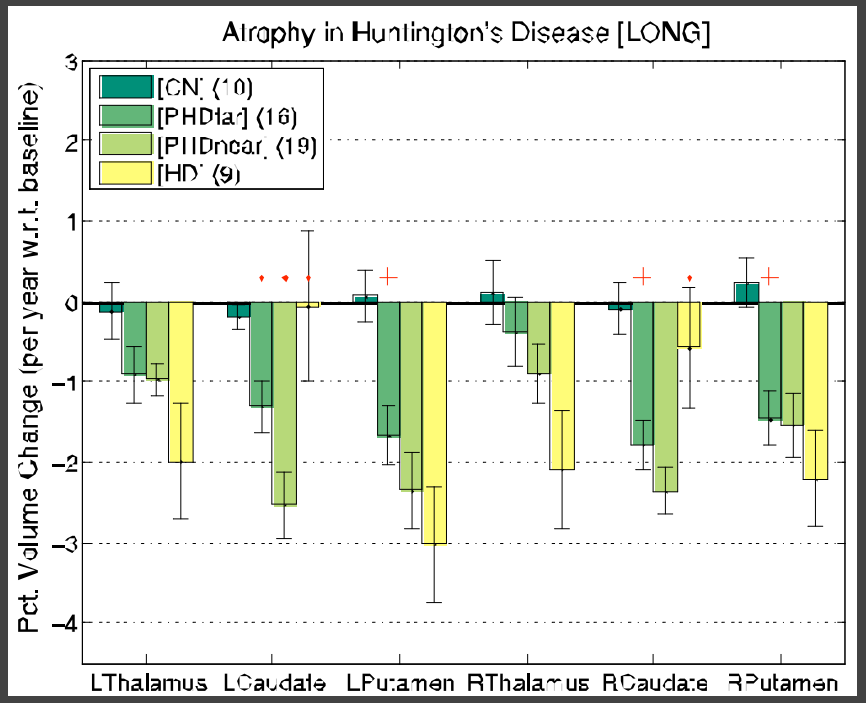


Huntington's Disease (3 visits)

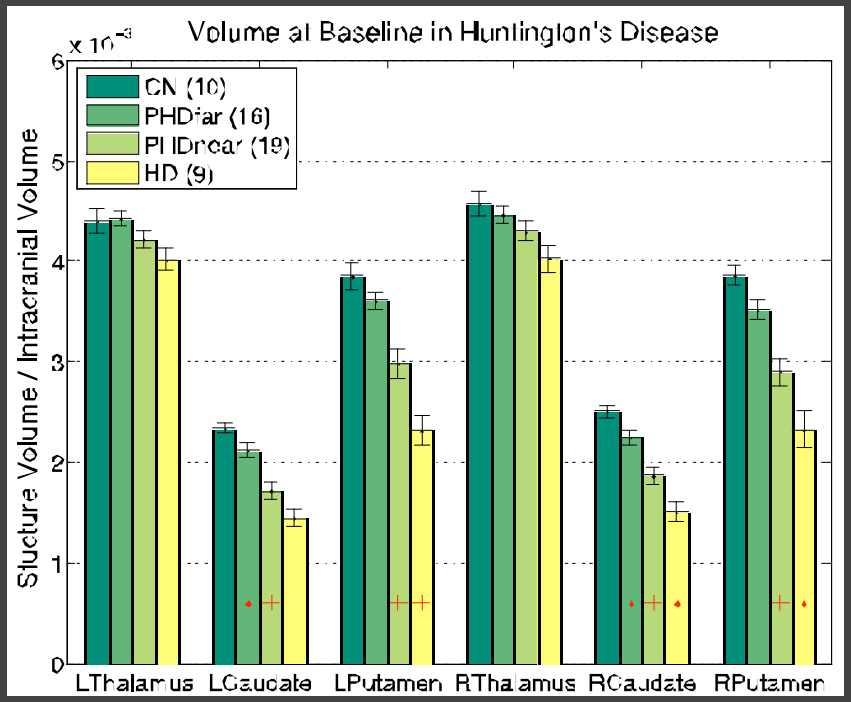
Reuter *et al.*, 2012

- Putamen atrophy rate is significantly different between controls (CN) and pre-HD far from onset (PHDfar)
- Baseline volume is not

Rate of atrophy

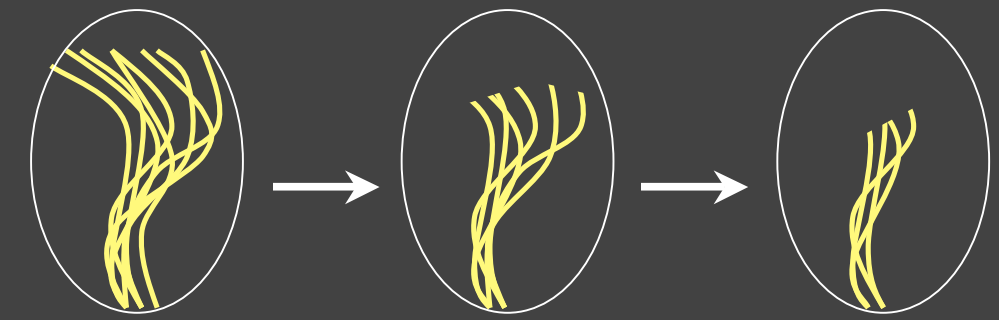


Baseline volume (normalized)



Longitudinal tractography

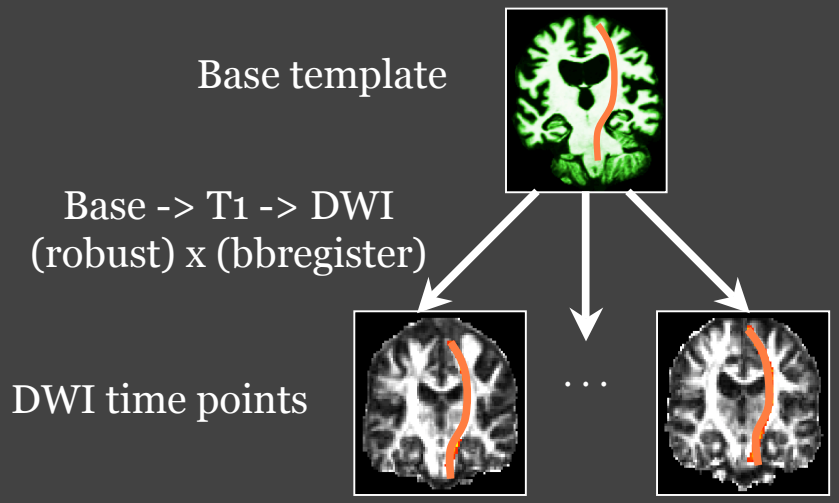
- Goal: Reconstruct a WM pathway consistently among a subject's time points
- Challenging to do when processing time points independently, as if they were cross-sectional data sets



- Different parts of the pathway may be reconstructed in each time point, due to noise or WM degeneration
  - Changes in average anisotropy/diffusivity may be underestimated
  - Point-to-point correspondence difficult to establish for along-the-path analysis of anisotropy/diffusivity

Longitudinal TRACULA

Yendiki *et al.*, In prep



- Reconstruct a subject's pathways simultaneously in all time points:
  - Perturb path in the space of the base template
  - Map to each time point
  - Compute likelihood (fit to the dMRI data) at all time points
  - Anatomical prior info based on aparc+aseg from all time points

- Ensures point-to-point correspondence between time points
- Unbiased, treats all time points the same way

Usage

- Processing steps of trac-all do not change for longitudinal:

```
trac-all -prep -c dmrirc
trac-all -bedp -c dmrirc
trac-all -path -c dmrirc
```

- Only configuration file changes:

```
set subjlist = (bert_1 bert_2 elmo_1 elmo_2 elmo_3)
set baselist = (bert_b bert_b elmo_b elmo_b elmo_b)
```

- Sample configuration file for longitudinal TRACULA:
  `$FREESURFER_HOME/bin/example.dmrirc.long`

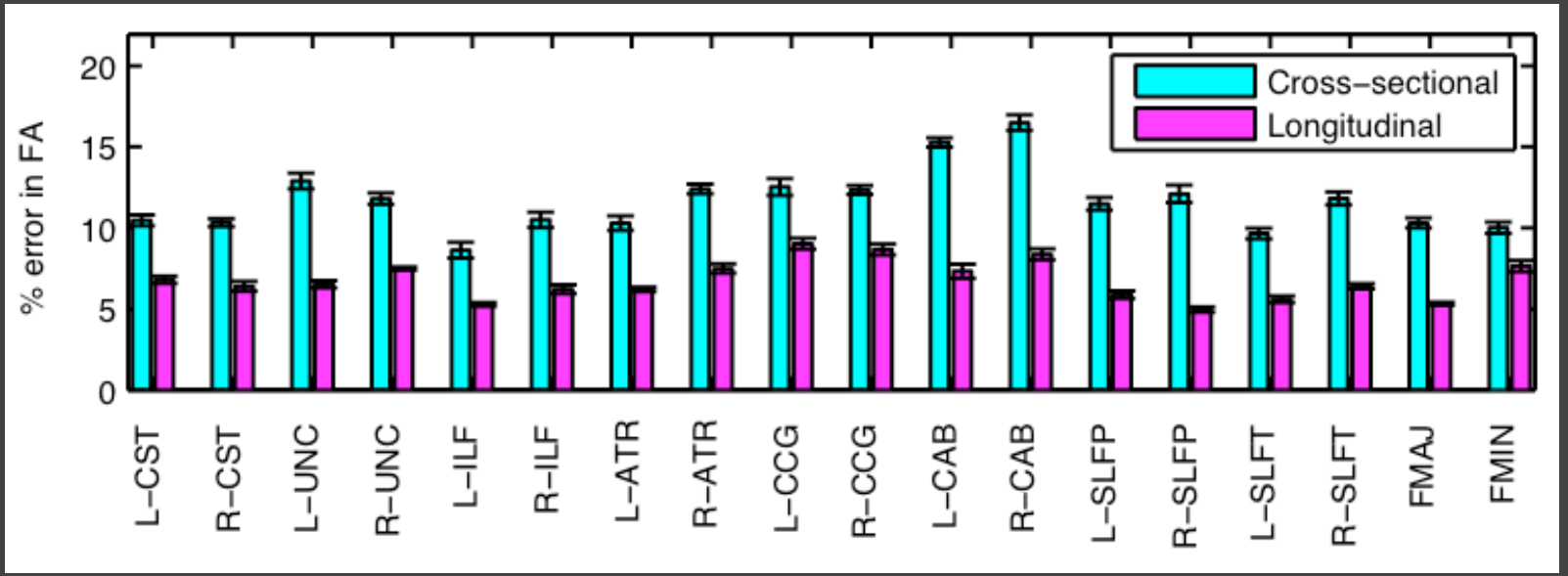
Longitudinal
- Define `baselist` in config file
- Paths saved under `dpathlong/`

Cross-sectional
- Do not define `baselist`
- Paths saved under `dpath/`

Test-retest reliability

Yendiki *et al.,* In prep

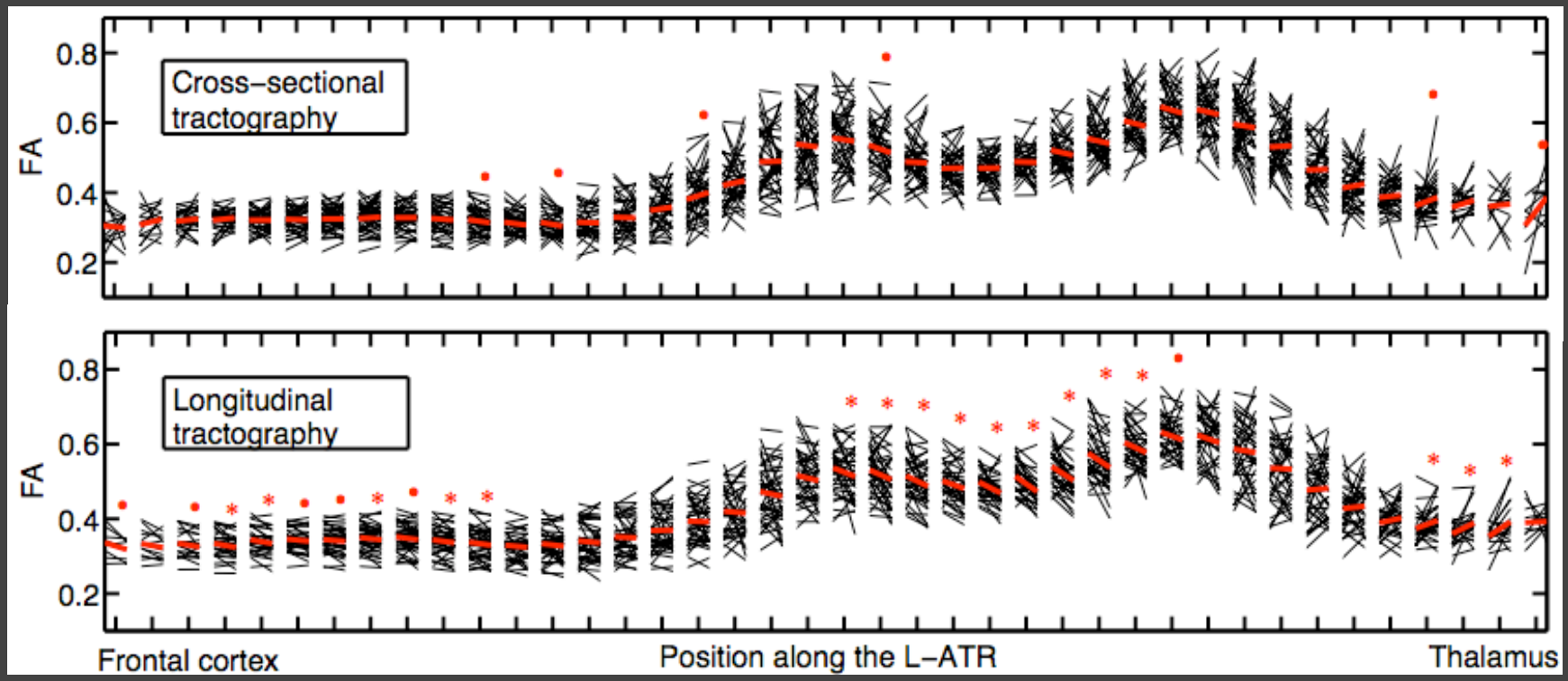
- 9 healthy subjects, scanned twice each (1.5T, 2mm iso, b=700)
- For each subject, pathways reconstructed:
  - Independently from each scan ("cross-sectional")
  - Jointly from both scans ("longitudinal")
- Find FA along the path, compare point to point b/w test-retest



Sensitivity to WM changes

Yendiki *et al.*, In prep

- 43 HD patients, scanned 2-5 times each (3T, 2mm iso, b=700)
- For each subject, pathways reconstructed:
  - Independently from each scan (cross-sectional)
  - Jointly from both scans (longitudinal)
- Find FA along the path, fit linear slope at each point



Sensitivity to WM changes

Yendiki *et al.,* In prep

- Longitudinal changes plotted along each pathway in freeview