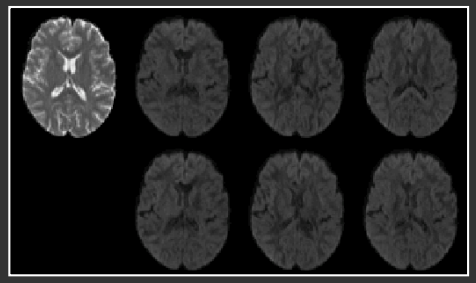
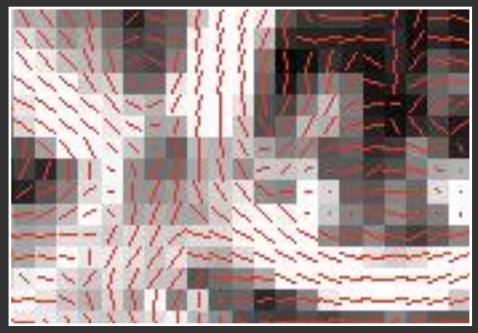
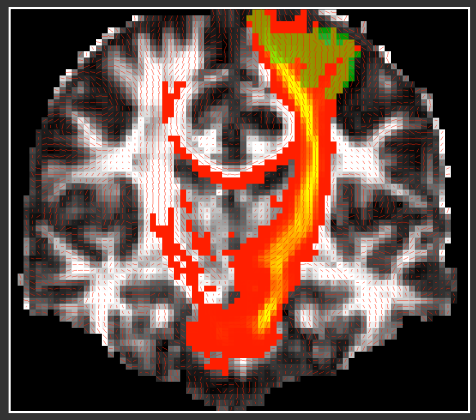
TRACULA

Data analysis steps

- Pre-process images to reduce distortions
  - Either register distorted DW images to an undistorted (non-DW) image
  - Or use information on distortions from separate scans (field map, residual gradients)
- Fit a diffusion model at every voxel
  - DTI, DSI, Q-ball, …
- Do tractography to reconstruct pathways and/or
- Compute measures of anisotropy/diffusivity and compare them between populations
  - Voxel-based, ROI-based, or tract-based statistical analysis

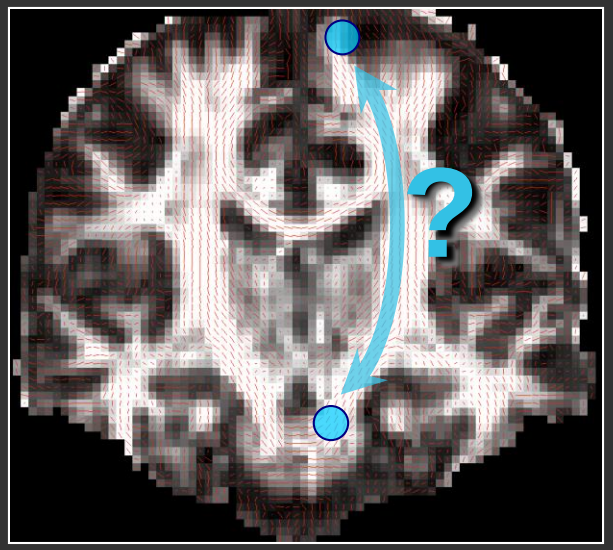






Tractography studies

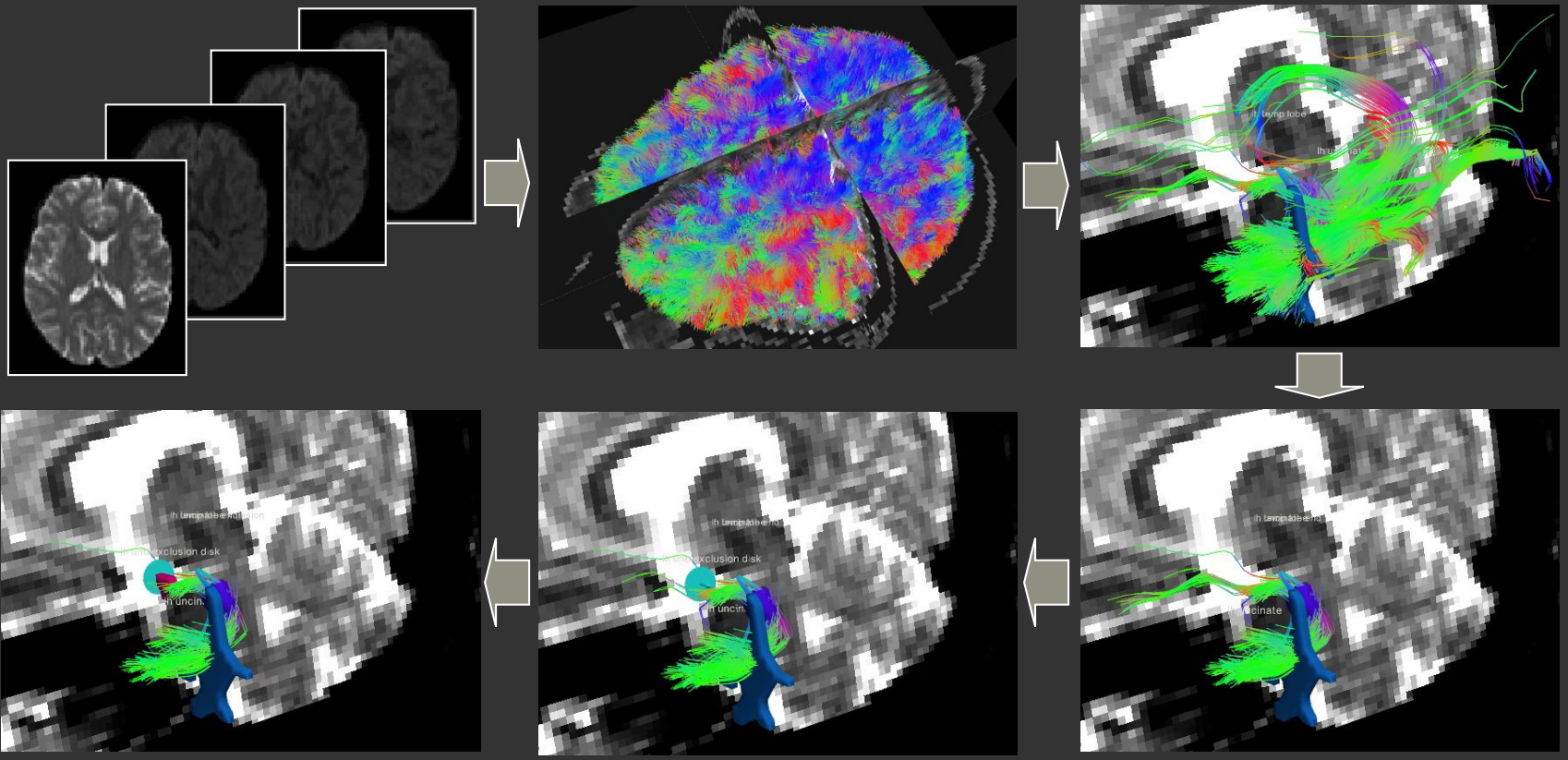
- Exploratory tractography:
  - Example: *Show me all regions that the motor cortex is connected to.*
  - Seed region can be anatomically defined (motor cortex) or functionally defined (region activated in an fMRI finger-tapping task)



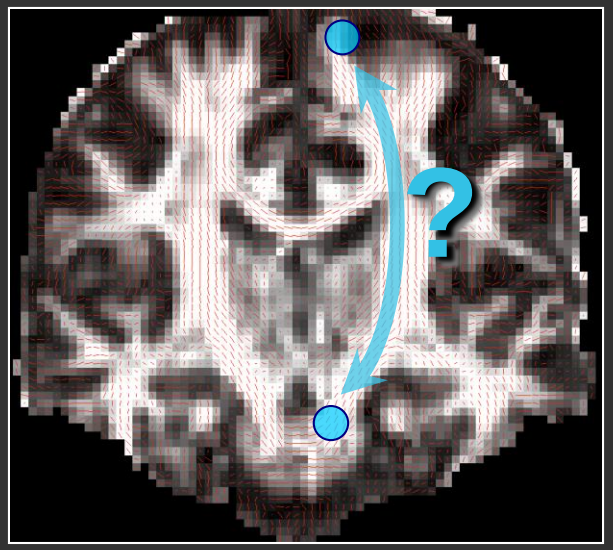
- Tractography of known pathways:
  - Example: *Show me the corticospinal tract.*
  - Use prior anatomical knowledge of the pathway's terminations and trajectory (connects motor cortex and brainstem through capsule)

Tractography takes time

- Get whole-brain tract solutions, edit manually
- Use knowledge of anatomy to isolate specific pathways



Tractography methods



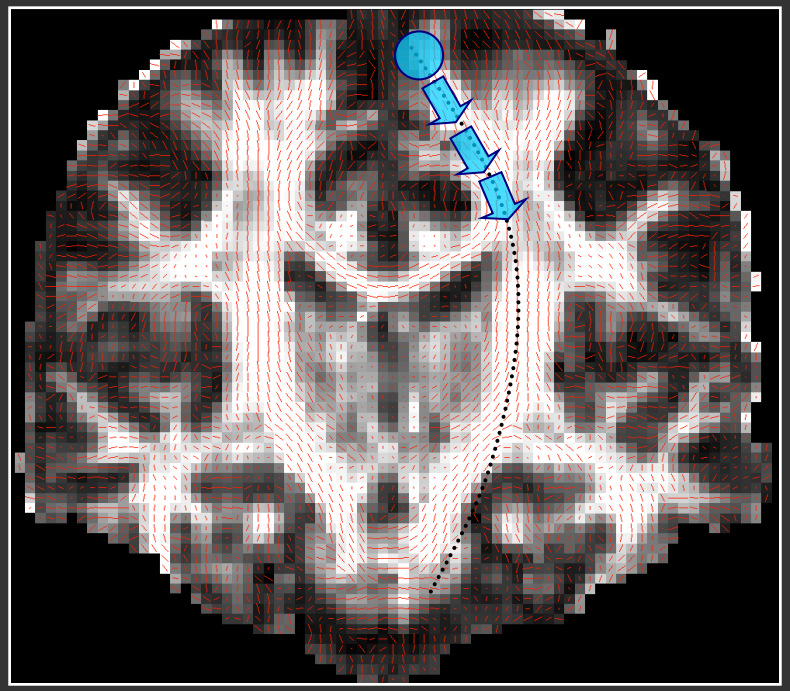
- Use local diffusion orientation at each voxel to determine pathway between distant brain regions
- Local orientation comes from diffusion model fit (tensor, ball-and-stick, etc.)
- Deterministic vs. probabilistic tractography:
  - Deterministic assumes a single orientation at each voxel
  - Probabilistic assumes a distribution of orientations
- Local vs. global tractography:
  - Local fits the pathway to the data one step at a time
  - Global fits the entire pathway at once

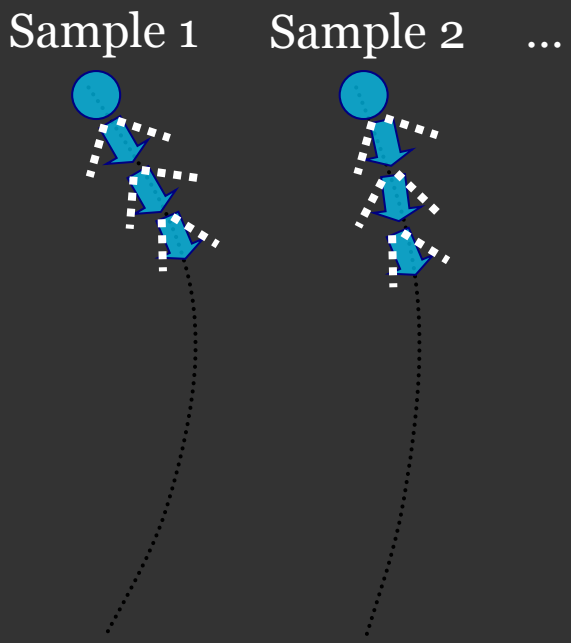
Deterministic vs. probabilistic

- Deterministic methods give you an estimate of model parameters

- Probabilistic methods give you the uncertainty (probability distribution) of the estimate

Deterministic vs. probabilistic

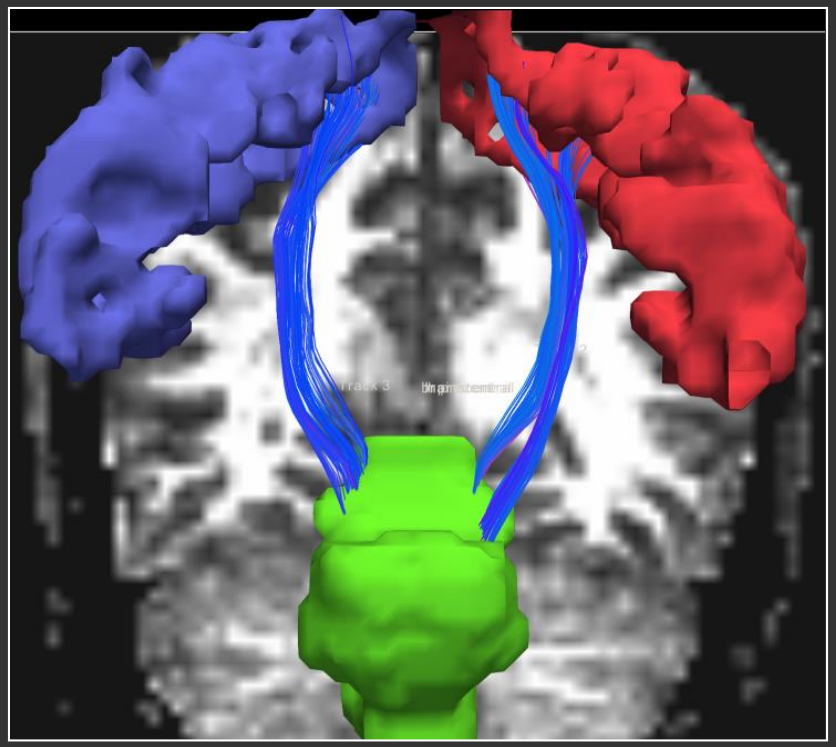


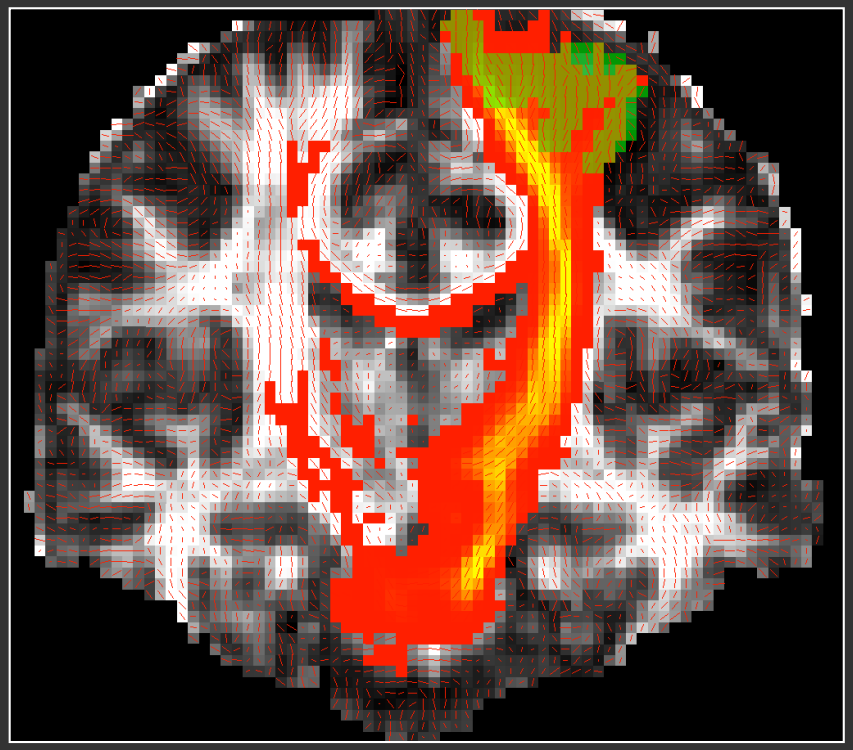


Deterministic tractography:
One streamline per seed voxel

Probabilistic tractography:
Multiple streamline samples per seed voxel (drawn from probability distribution)

Deterministic vs. probabilistic





Deterministic tractography:

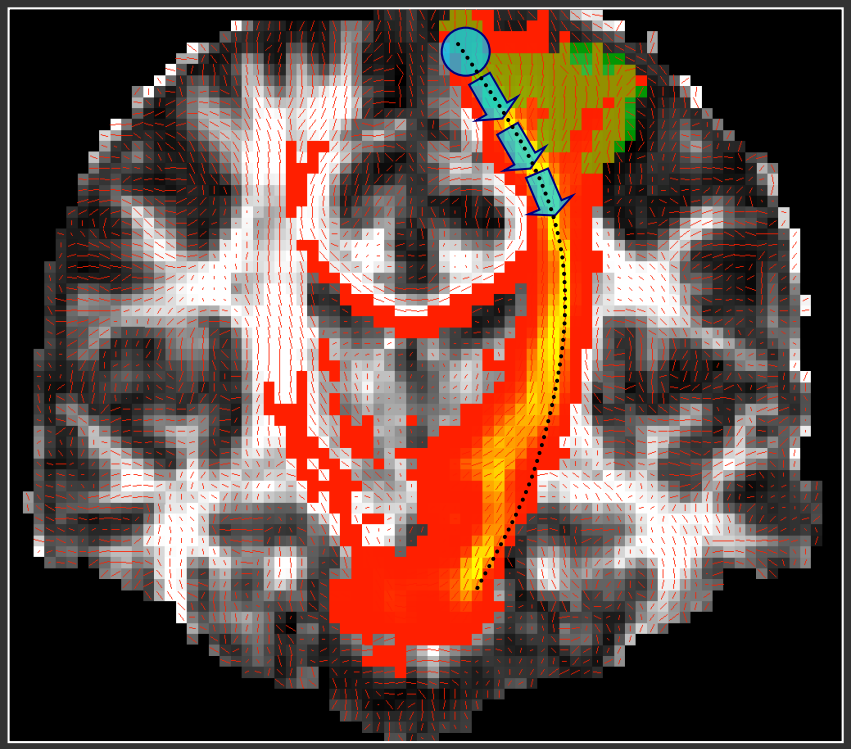
One streamline per seed voxel

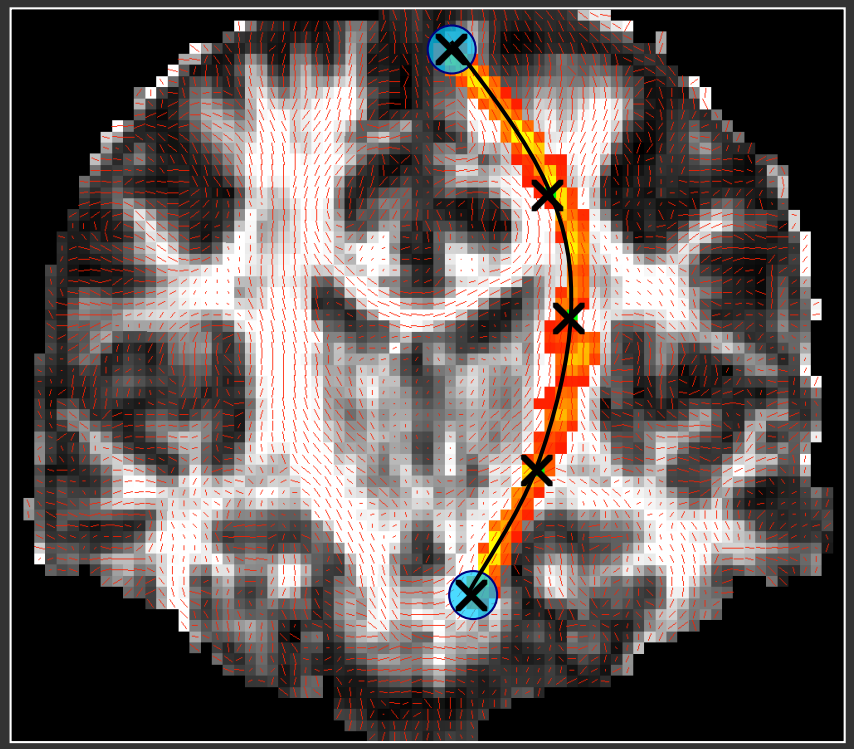
Probabilistic tractography:

A probability distribution

(sum of all streamline samples from all seed voxels)

Local vs. global





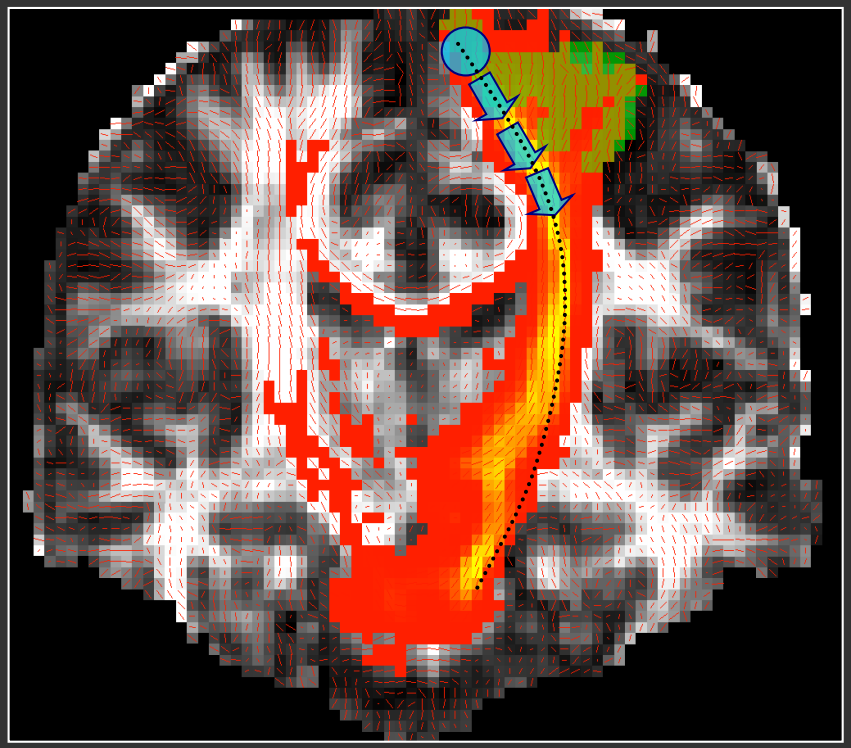
Local tractography:

Fits pathway step-by-step, using local diffusion orientation at each step

Global tractography:

Fits the entire pathway, using diffusion orientation at all voxels along pathway length

Local tractography

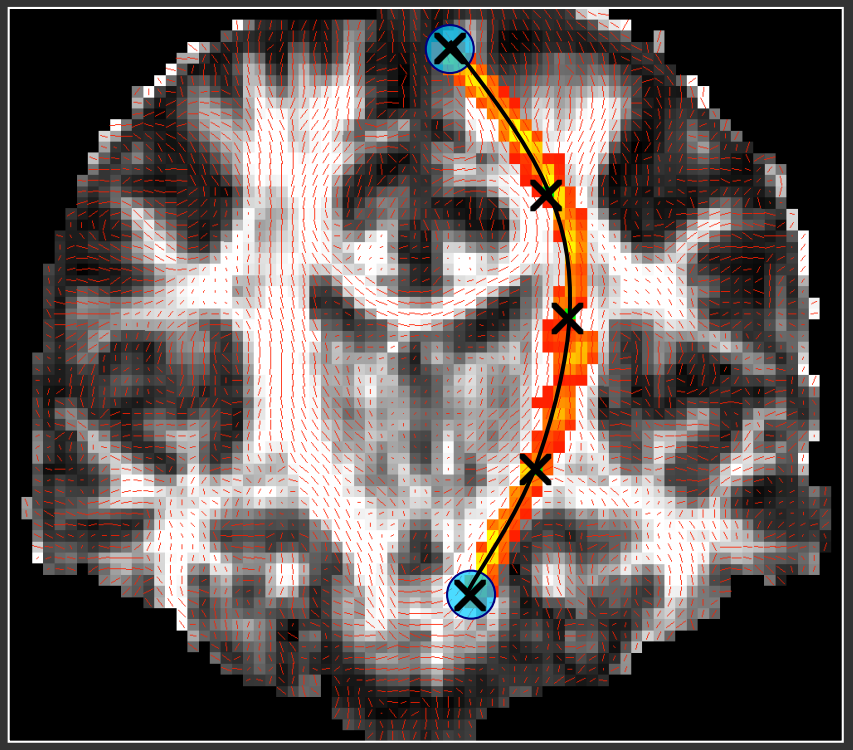


- Best suited for exploratory study of connections

- All connections from a seed region, not constrained to a specific target region
- How do we isolate a specific white-matter pathway?
  - Thresholding?
  - Intermediate masks?
- Non-dominant connections are hard to reconstruct

- Results are not symmetric between “seed” and “target” regions
- Sensitive to areas of high local uncertainty in orientation (*e.g.*, pathaway crossings), errors propagate from those areas

Global tractography



- Best suited for reconstruction of known white-matter pathways

- Constrained to connection of two specific end regions
- Not sensitive to areas of high local uncertainty in orientation, integrates over entire pathway
- Symmetric between “seed” and “target” regions

- Need to search through a large solution space of all possible connections between two regions:
  - Computationally expensive
  - Sensitive to initialization

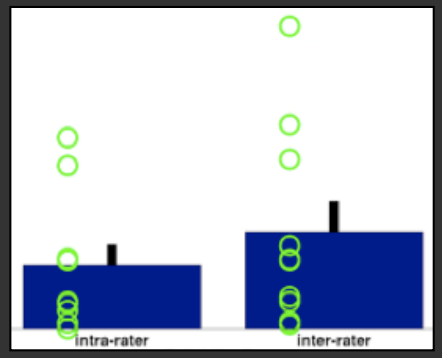
TRACULA

- TRActs Constrained by UnderLying Anatomy
- Global probabilistic tractography with prior information on tract anatomy from training subjects
- Learn from training subjects which anatomical regions each pathway typically goes through/next to
- Constrain pathway in new subject based on this prior anatomical knowledge
- Reconstruct 18 major white-matter pathways
  - No manual intervention in new subjects
  - Robustness with respect to pathway initialization
  - Anatomically plausible solutions
- Ad-hoc anatomical constraints are often used by other methods: constraints on path bending angle or length, WM masks, ...

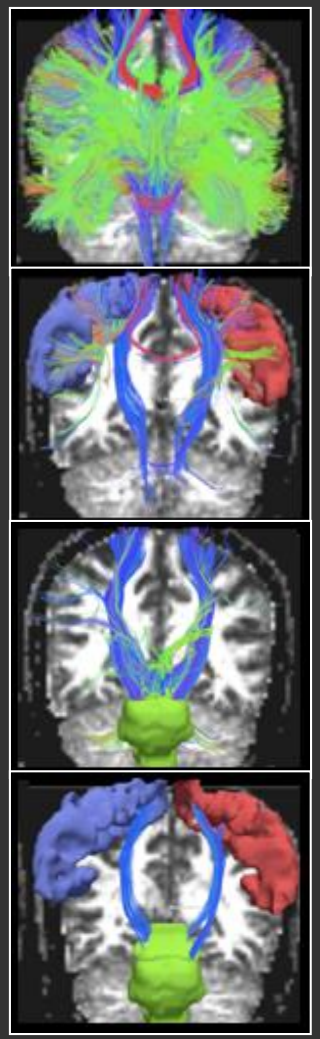
White-matter pathway atlas

- Labeling based on an established protocol [Wakana '07]

- Corticospinal tract
- Inferior longitudinal fasciculus
- Uncinate fasciculus
- Corpus callosum
  - Forceps major
  - Forceps minor
- Anterior thalamic radiation
- Cingulum
  - Cingulate (supracallosal)
  - Angular (infracallosal)
- Superior longitudinal fasciculus
  - Parietal
  - Temporal

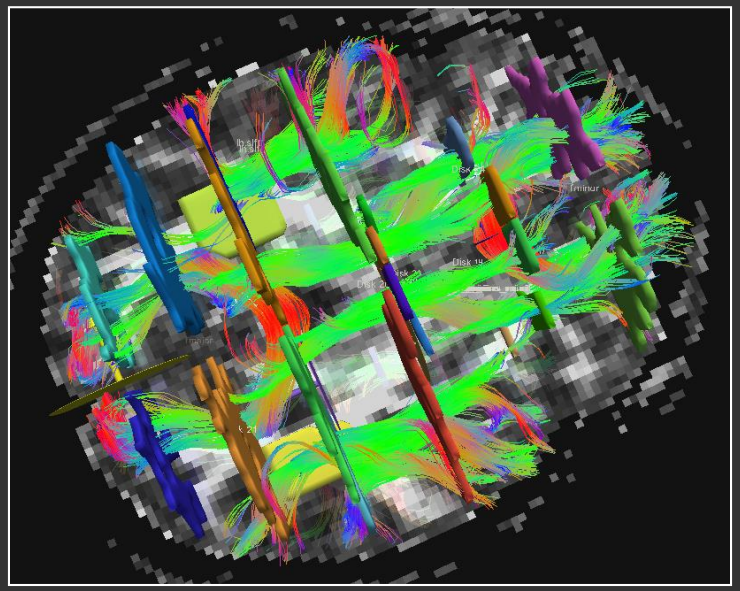


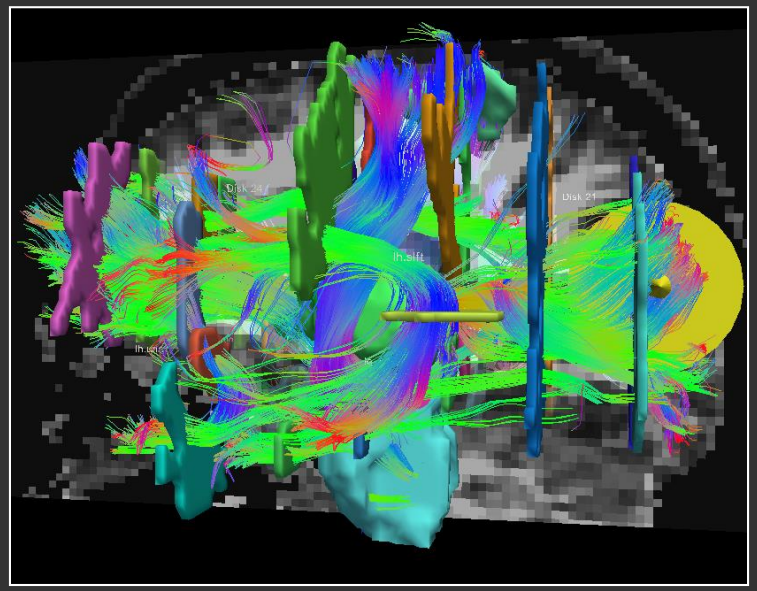
Intra/inter-rater errors:
1mm/2mm on average



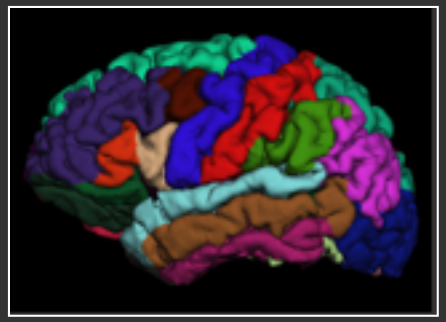
White-matter pathway atlas

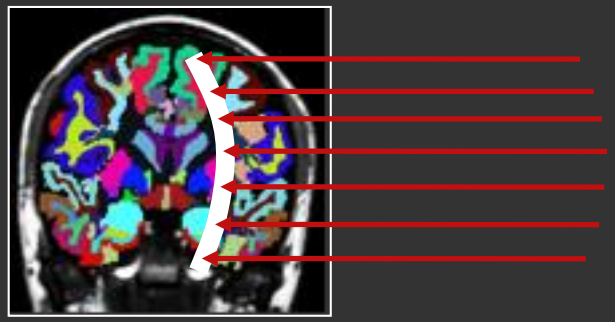
- Manual labeling of paths in training subjects performed in Trackvis





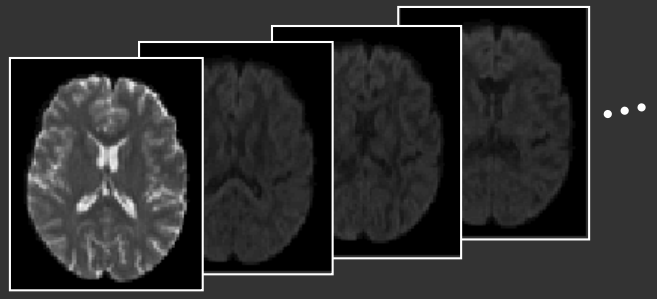
- Anatomical segmentation maps of training subjects from FreeSurfer



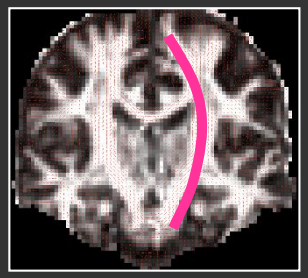


Automated pathway reconstruction

Have image data $\boldsymbol{Y}$



Want most probable path F

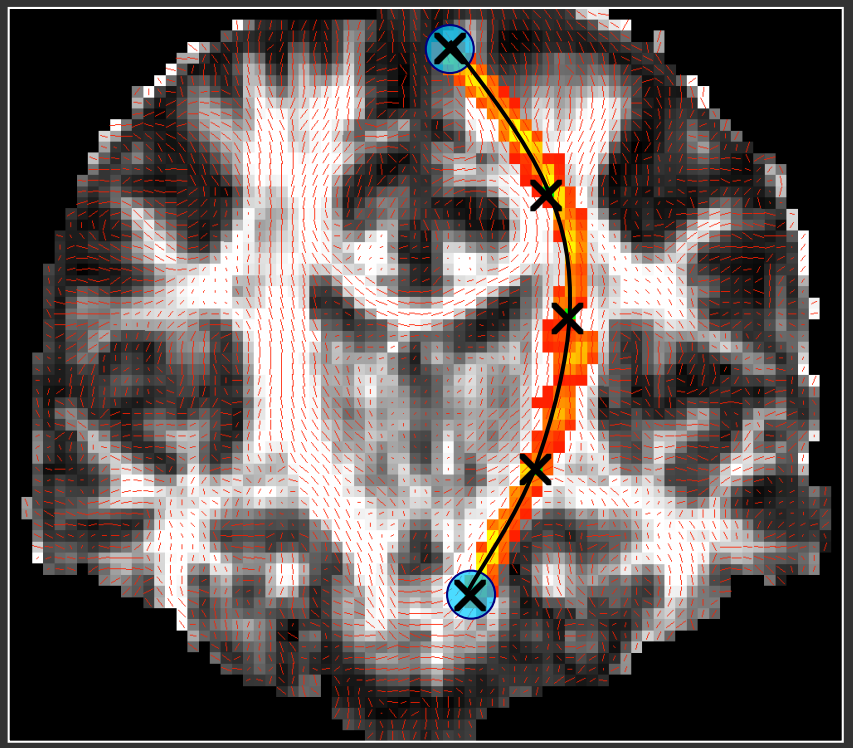


- Determine the most probable path based on:
  - What the images tell us about the path
  - What we already know about the path
- Estimate posterior probability of path F given images $\boldsymbol{Y}$

$$p(F \mid \boldsymbol{Y}) \;\propto\; p(\boldsymbol{Y} \mid F)\; p(F)$$

  - $p(\boldsymbol{Y} \mid F)$: Uncertainty due to imaging noise
    Fit of pathway orientation to ball-and-stick model parameters
  - $p(F)$: Uncertainty due to anatomical variability
    Fit of pathway to prior anatomical knowledge from training set

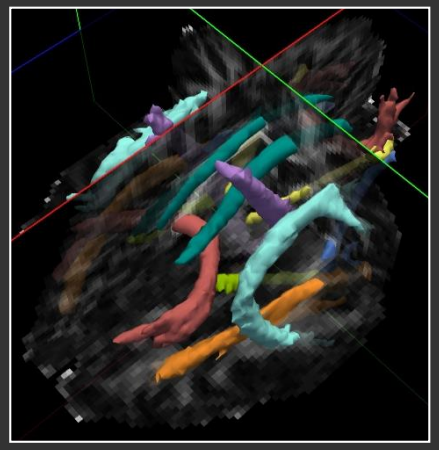
Tract-based measures

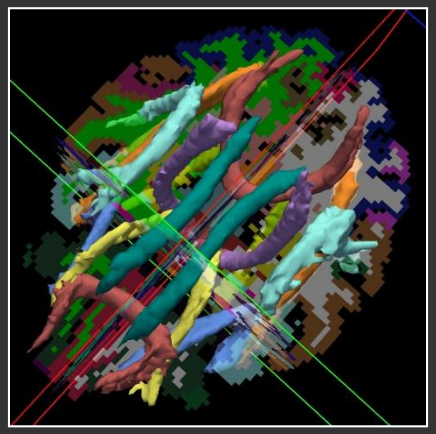


- Reconstruction outputs:
  - Posterior probability distribution of pathway given data (3D)
  - Maximum *a posteriori* pathway (1D)
- Tract-based diffusion measures (FA, MD, RD, AD, etc):
  - Average over pathway distribution
  - Weighted average over pathway distribution
  - Average over MAP pathway
  - As a function of arc length along MAP pathway

Schizophrenia study

Yendiki *et al.*, *Frontiers* 2011





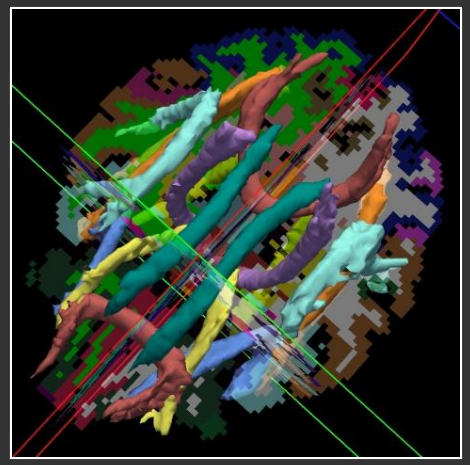
QuickTime™ and a
H.264 decompressor
are needed to see this picture.

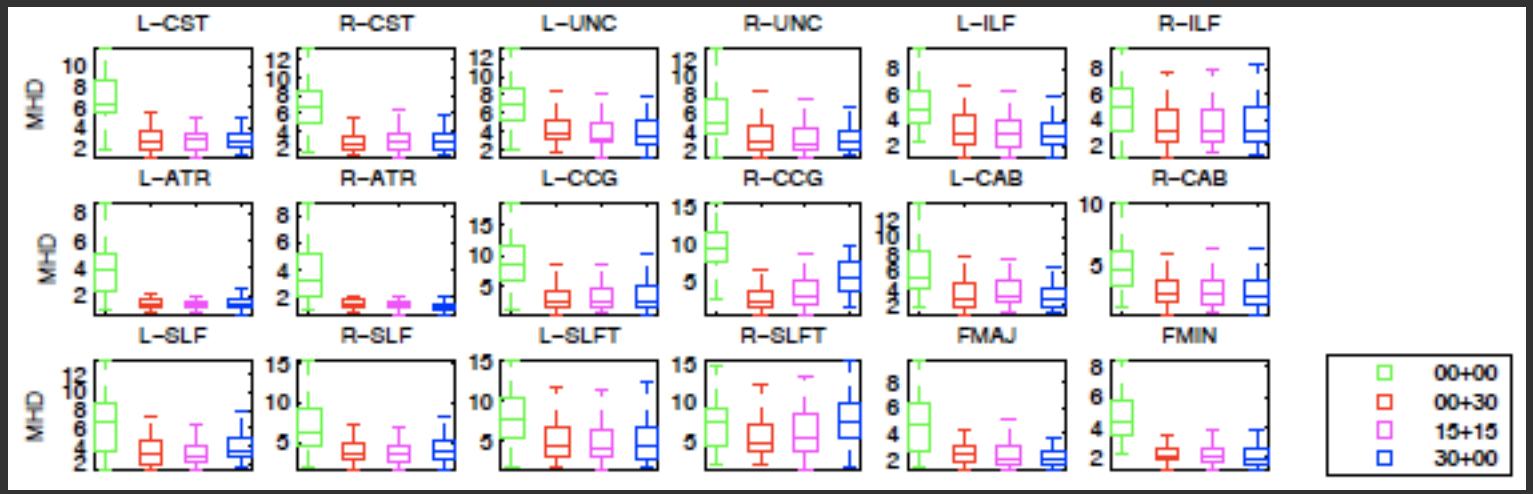
Pathway distributions reconstructed automatically in a SZ patient using 30 healthy training subjects

Schizophrenia study

Yendiki *et al.*, *Frontiers* 2011

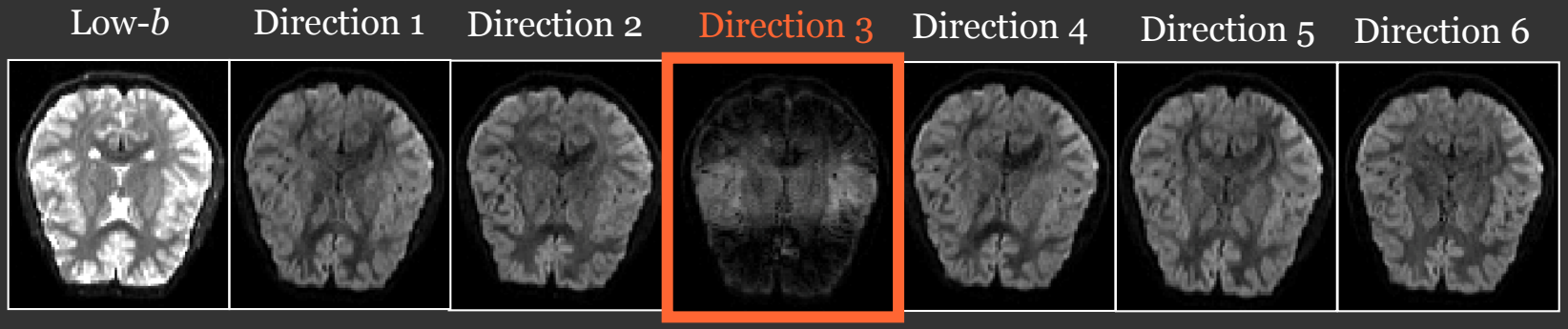
- Reconstruct pathways in 34 SZ patients and 23 healthy controls with
  - No training subjects
  - 30 healthy training subjects
  - 15 healthy / 15 SZ training subjects
  - 30 SZ training subjects
- Evaluate distance b/w automatically reconstructed and manually labeled pathways





Head motion in diffusion MRI

- Head motion during a dMRI scan can lead to:
  - Misalignment between consecutive DWI volumes in the series
  - Attenuation in the intensities of a single DWI volume/slice, if the motion occurred during the diffusion-encoding gradient pulse
  - The former can be corrected with rigid registration, *the latter can't*

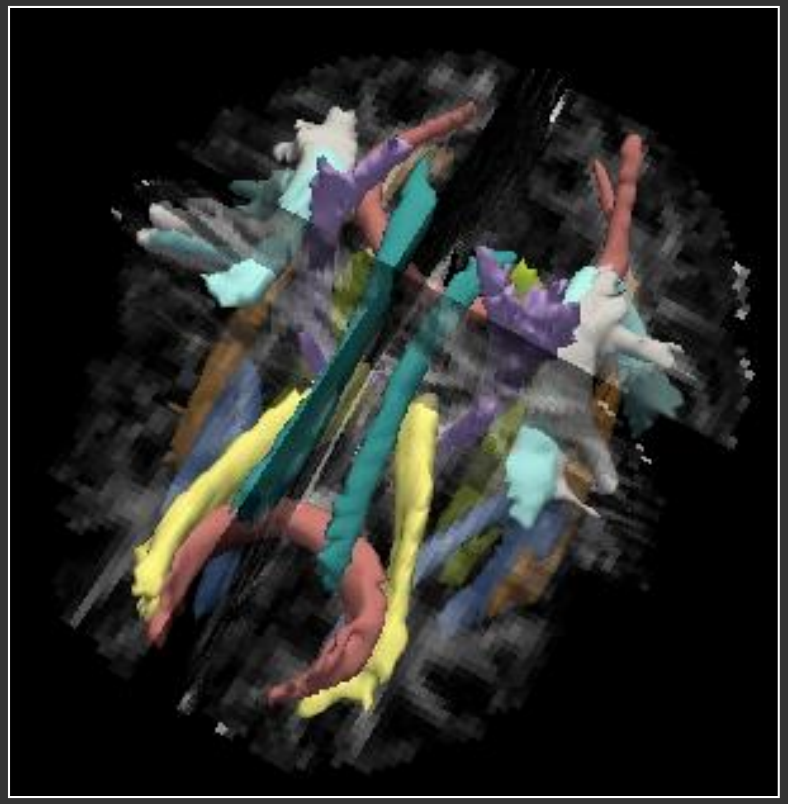


- Conventional EPI sequences for dMRI ignore the problem
  - If motion in several directions ⇒ underestimation of anisotropy
  - False positives in group studies where one group moves more
  - Effects more severe when higher *b*-values, more directions acquired

Motion in a dMRI group study

Yendiki *et al.*, *Neuroimage* 2014

- 57 children with autism spectrum disorder (ASD)
- 73 typically developing children (TD)
- Ages 5-12
- 195 total scans (some retest)
- DWI: 3T, 2mm isotropic, 30 directions, b=700 s/mm^2
- Translation, rotation, intensity drop-out due to motion assessed
- Outlier data sets excluded
- Pathways reconstructed automatically with TRACULA

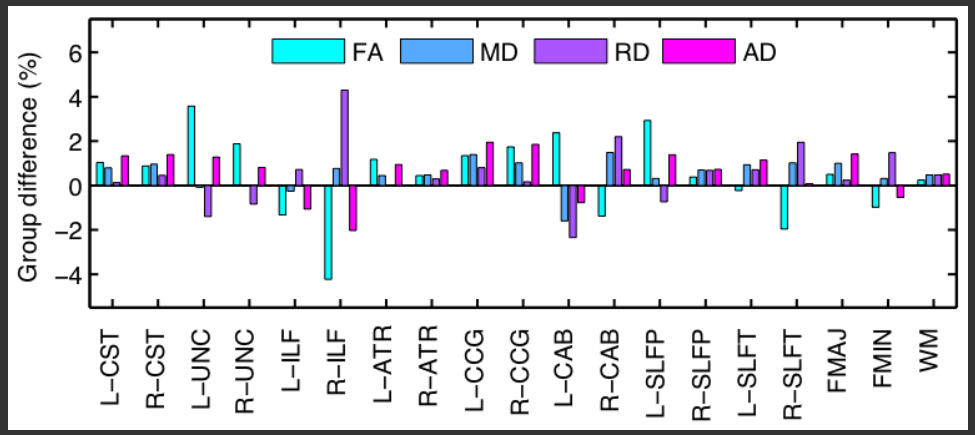


Data courtesy of Dr. Nancy Kanwisher and Ellison autism study

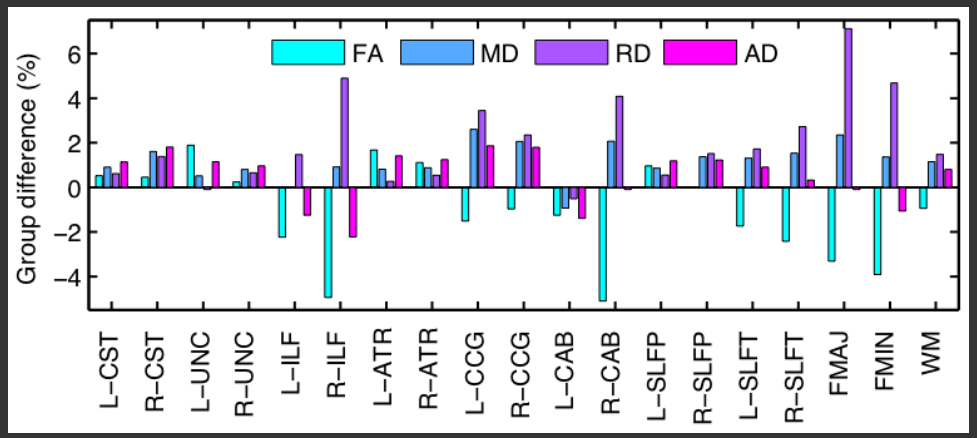
ASD vs. TD

Yendiki *et al.*, *Neuroimage* 2014

Differences in dMRI measures between groups with low differences in head motion



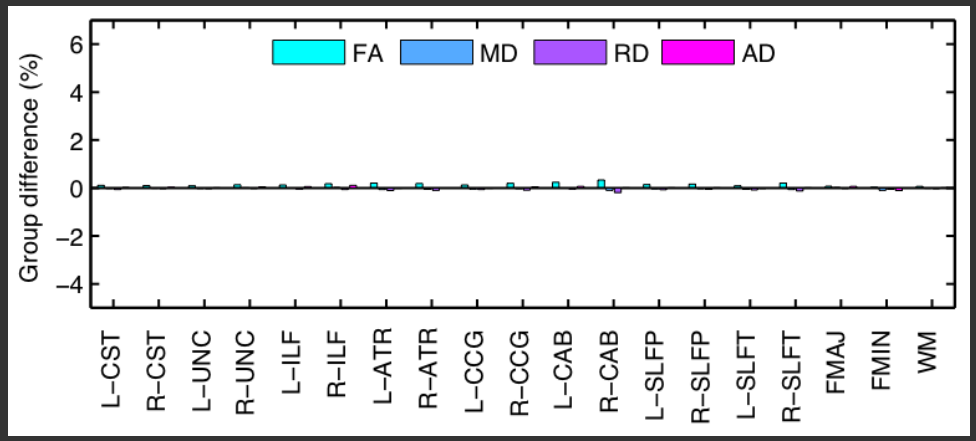
Differences in dMRI measures between groups with high differences in head motion



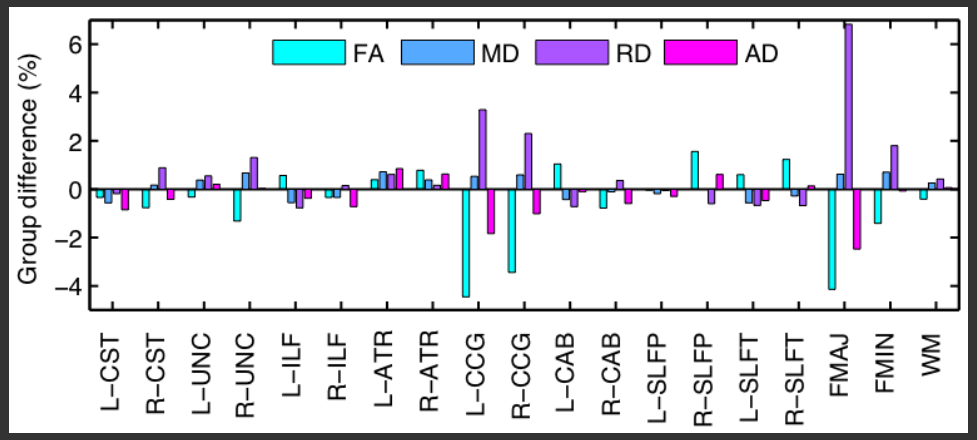
TD vs. TD

Yendiki *et al.*, *Neuroimage* 2014

Differences in dMRI measures between groups with low differences in head motion



Differences in dMRI measures between groups with high differences in head motion



Head motion, in summary

Yendiki *et al.*, *Neuroimage* 2014

- Differences in head motion between groups can induce spurious group differences in diffusivity and anisotropy
- General trend: Head motion↑ ⇒ RD↑, AD↓, MD –, FA↓
- This is *after* registration-based motion correction
- Match motion between groups and/or use a motion score as a nuisance regressor
- Note that all this will address *false positives*, but not *false negatives* due to head motion in the data
- Methods for tackling the problem during data acquisition are needed

TRACULA usage

- All processing options are defined in a configuration file, **`dmrirc`**
- Step 1: Pre-processing (distortion compensation, registration, etc.)
  `trac-all -prep -c dmrirc`
- Step 2: Fitting of ball-and-stick model (FSL's bedpostx)
  `trac-all -bedp -c dmrirc`
- Step 3: Reconstruct pathways
  `trac-all -path -c dmrirc`

Configuration file

- Example configuration file:
  `$FREESURFER_HOME/bin/dmrirc.example`

- The simplest configuration file possible, using all default options and only defining inputs:

```
setenv SUBJECTS_DIR /path/to/fs/output/directory
set subjlist = (subjA subjB …)
set dcmlist = (/path/to/A/1.dcm /path/to/B/011-1.dcm …)
set bvecfile = /path/to/bvecs.txt
set bvalfile = /path/to/bvals.txt
```

- Same gradient vectors and b-values assumed for all scans

- Can specify trac-all output directory different from recon-all `$SUBJECTS_DIR`:

```
set dtroot = /path/to/tracula/output/directory
```

Pre-processing

```
trac-all -prep -c dmrirc
```

- Includes the following steps:
  - Image corrections: `-corr`
  - NEW: Quality assessment (motion scores): `-qa`
  - Intra-subject registration (DWI to T1) : `-intra`
  - Inter-subject registration (T1 to template) : `-inter`
  - Anatomical masks and labels : `-mask`
  - Tensor fit : `-tensor`
  - Anatomical priors : `-prior`

- Can do some of the steps only (assuming previous steps have been done):
  - `trac-all -corr -qa -c dmrirc`

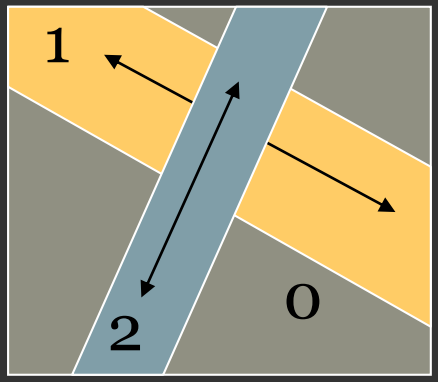
- Or exclude some of the steps (assuming they have been done previously):
  - `trac-all -prep -nocorr -noqa -c dmrirc`

Ball-and-stick model fit

```
trac-all -bedp -c dmrirc
```

- This step simply runs FSL bedpostX to fit the ball-and-stick model of diffusion to every voxel in the brain mask
- This can take a while, but it's possible to run every slice in parallel
- To specify the maximum number of anisotropic compartments per voxel (default: 2)

  ```
  set nstick = 3
  ```



Pathway reconstruction

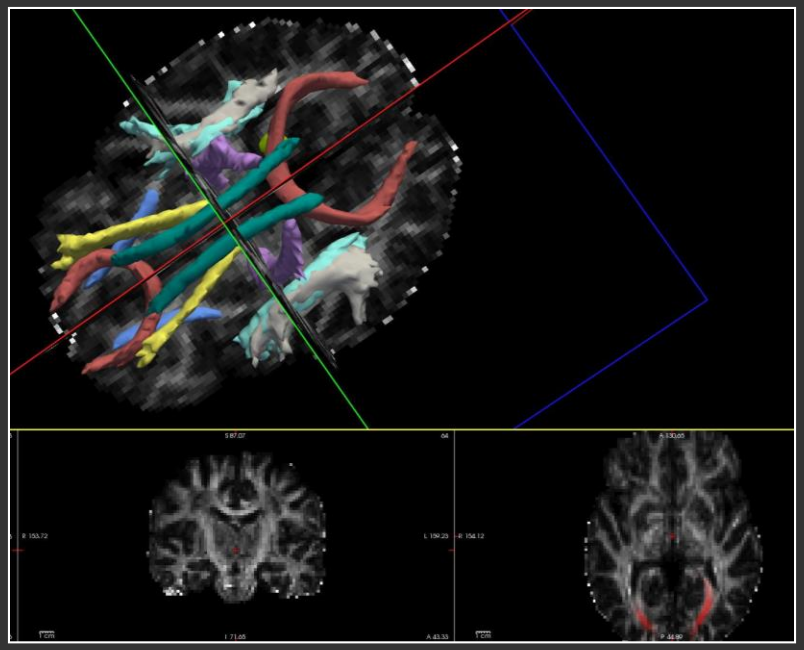
```
trac-all -path -c dmrirc
```

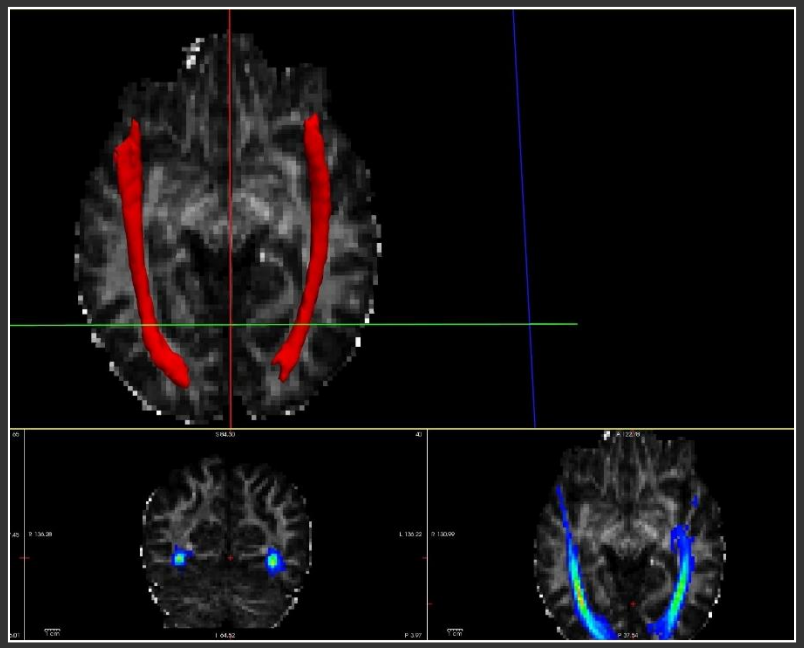
- Reconstruct the 18 pathways (or a subset) using a random sampling algorithm:
- Pick an initial guess for the path from the training subjects in the atlas (the only step that requires decent alignment between individual and atlas!)
- At every iteration, perturb control points of path and compute its fit to diffusion data and to anatomical priors from atlas
- To specify number of paths to sample (default: 7500)

```
set nsample = 10000
```

Visualization with freeview

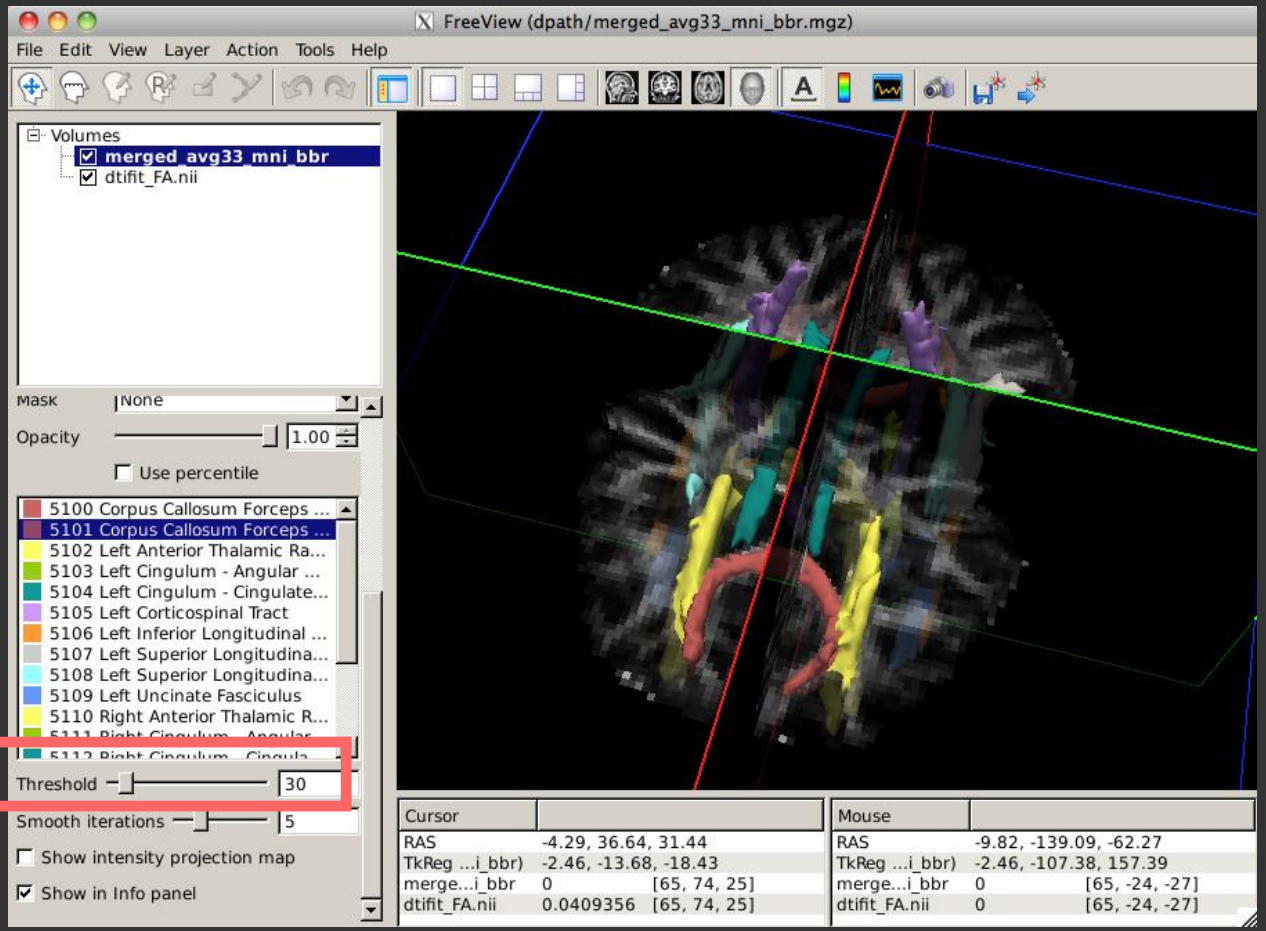
- There is a 4D volume where all the pathway distributions that were estimated have been merged
- Opening this file in freeview will display all distributions as isosurfaces, thresholded at 20% of their maximum value.





Visualization: 3D view

- `freeview dmri/dtifit_FA.nii.gz \`
  `-tv dpath/merged_avg33_mni_bbr.mgz`

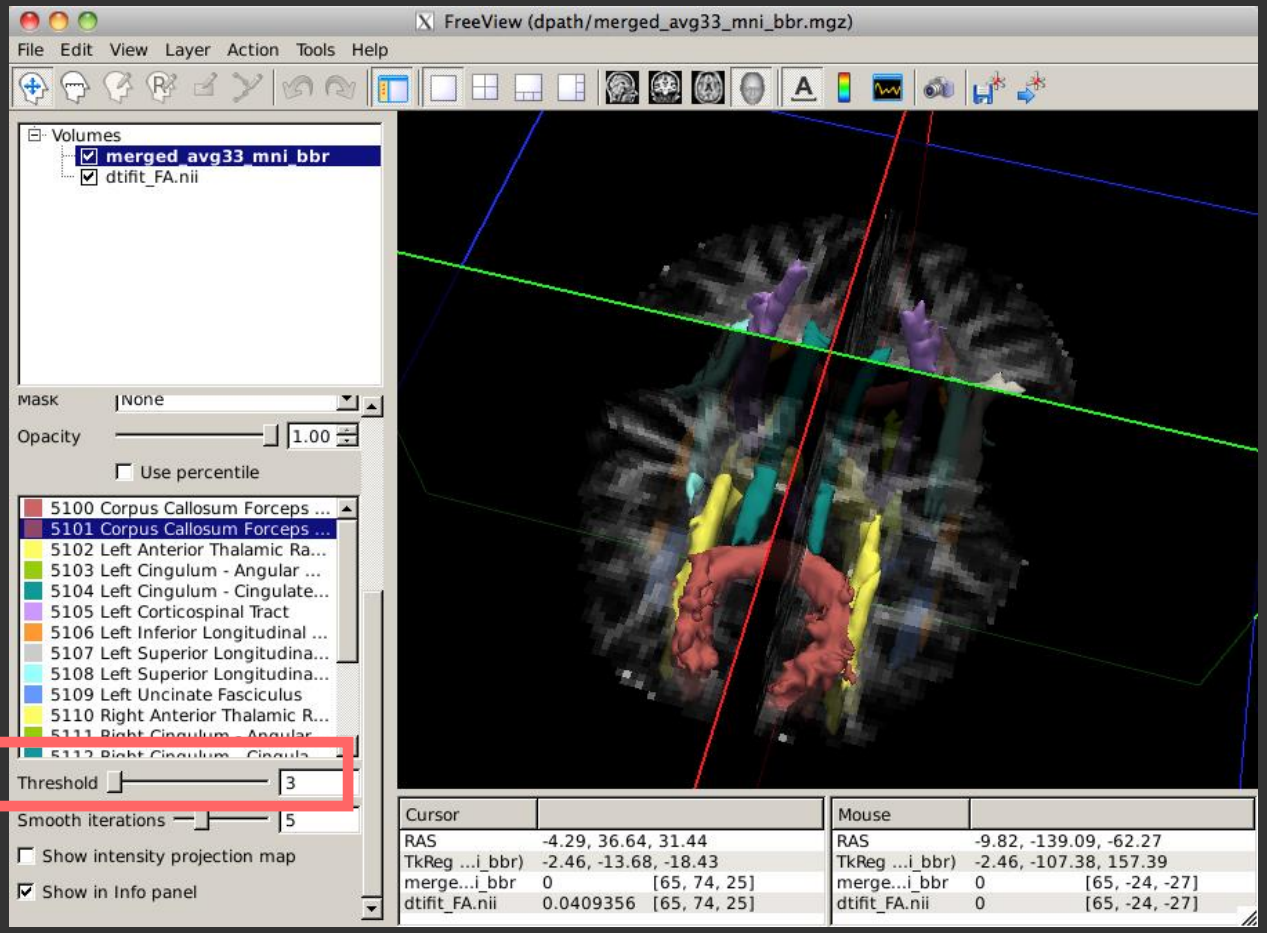


Change threshold for display

Visualization: 3D view

- `freeview dmri/dtifit_FA.nii.gz \`
  `-tv dpath/merged_avg33_mni_bbr.mgz`

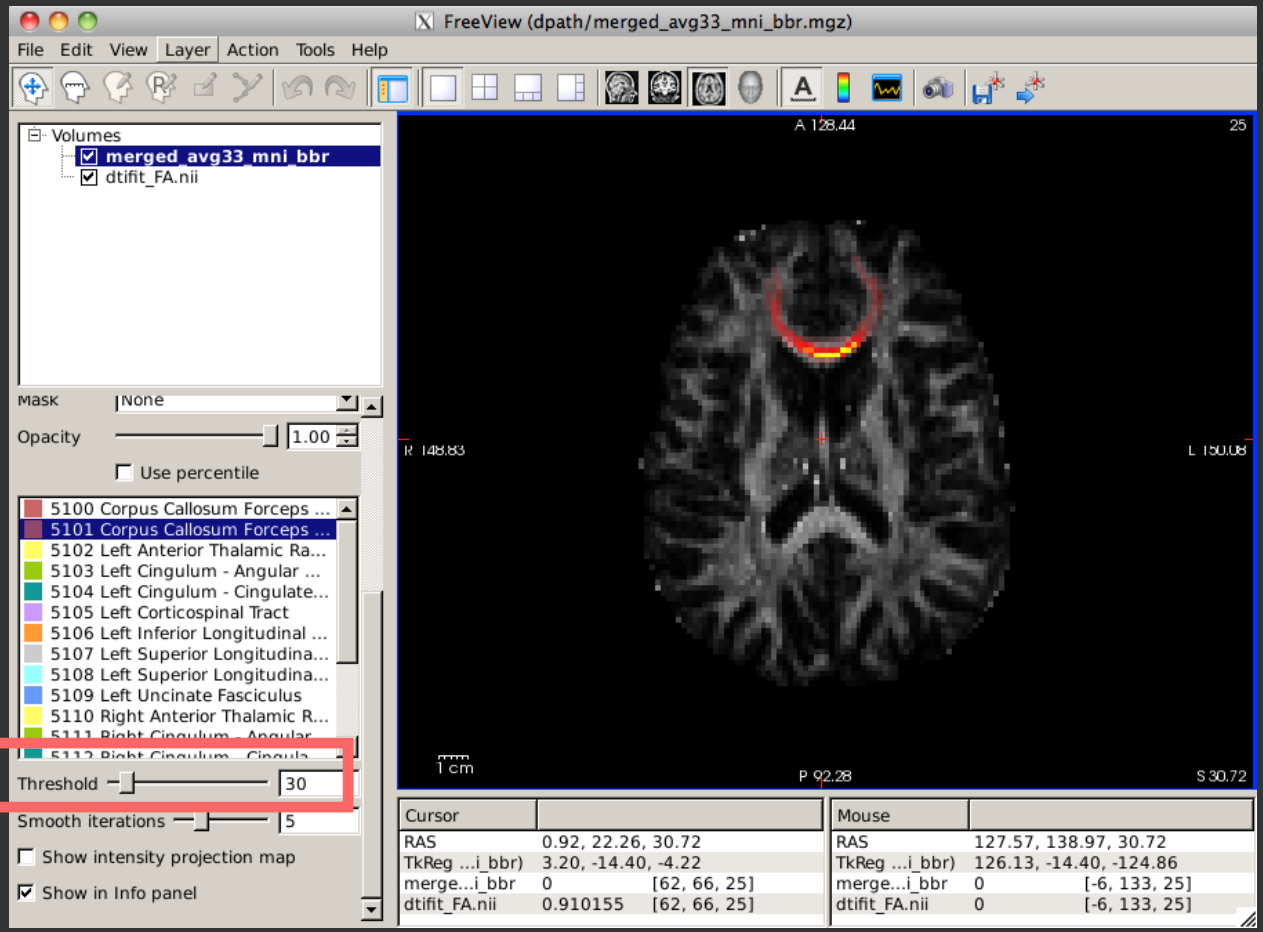
Change threshold for display



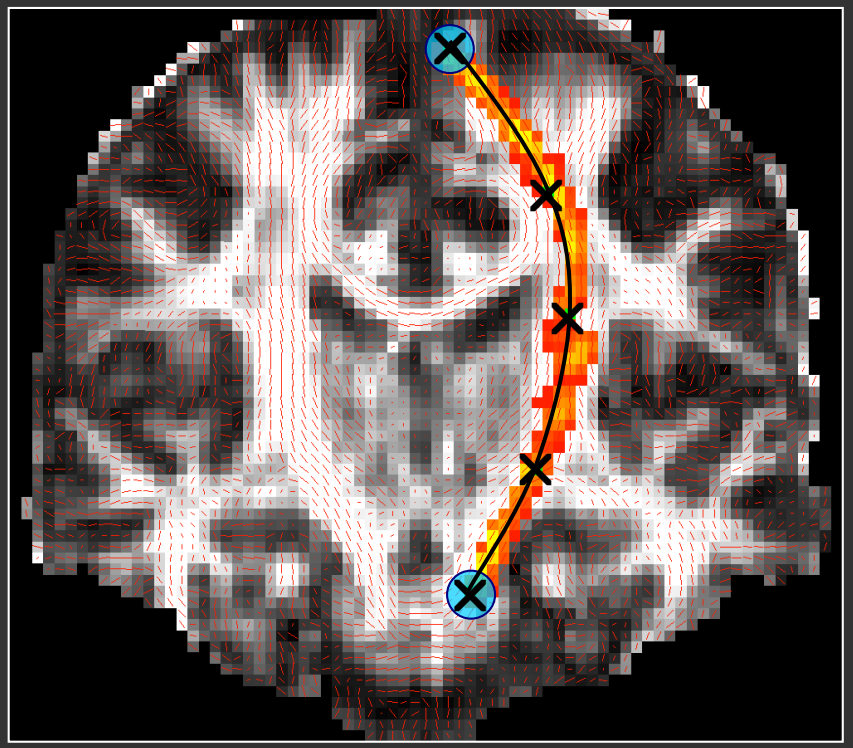
Visualization: Slice view

- `freeview dmri/dtifit_FA.nii.gz \`
  `-tv dpath/merged_avg33_mni_bbr.mgz`

Change threshold for display



Tract-based measures



- Reconstruction outputs
  - Posterior probability distribution of pathway given data (3D):

    `paths.pd.nii.gz`
  - Maximum *a posteriori* pathway (1D):

    `path.map.nii.gz`
- Tract-based diffusion measures (FA, MD, RD, AD)
  - Averaged over the entire pathway distribution:

    `pathstats.overall.txt`
  - As a function of position along the pathway:

    `pathstats.byvoxel.txt`

Path stats (average values)

pathstats.overall.txt

```
# subjectname Diff001
# pathwayname lh.cst
#
Count 1000
Volume 327
Len_Min 35
Len_Max 70
Len_Avg 53.119
Len_Center 48
AD_Avg 0.00106102
AD_Avg_Weight 0.00108794
AD_Avg_Center 0.00105527
RD_Avg 0.000438781
RD_Avg_Weight 0.000430744
RD_Avg_Center 0.000441464
MD_Avg 0.000646195
MD_Avg_Weight 0.000649809
MD_Avg_Center 0.000646067
FA_Avg 0.519271
FA_Avg_Weight 0.539241
FA_Avg_Center 0.511358
```

- `*_Avg`: Average values of every voxel with probability > 20% of the maximum
- `*_Avg_Weight`: Multiply value at voxel with the probability at that voxel, sum over every voxel with probability > 20% of the maximum
  - This is closest to the notion of mean/expected value
- `*_Center`: Average values only on the 1-D path with the highest probability

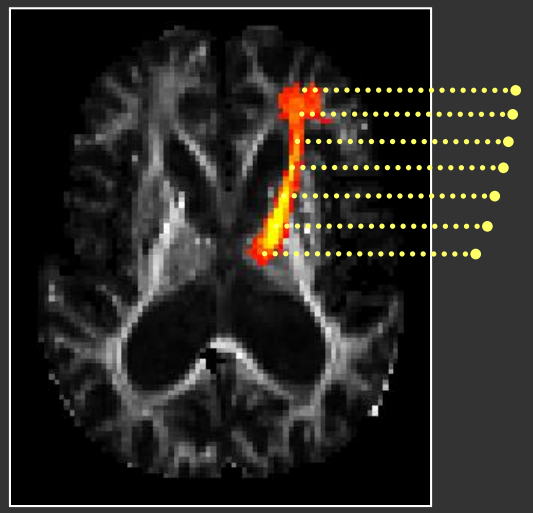
Path stats (values along the path)

pathstats.byvoxel.txt

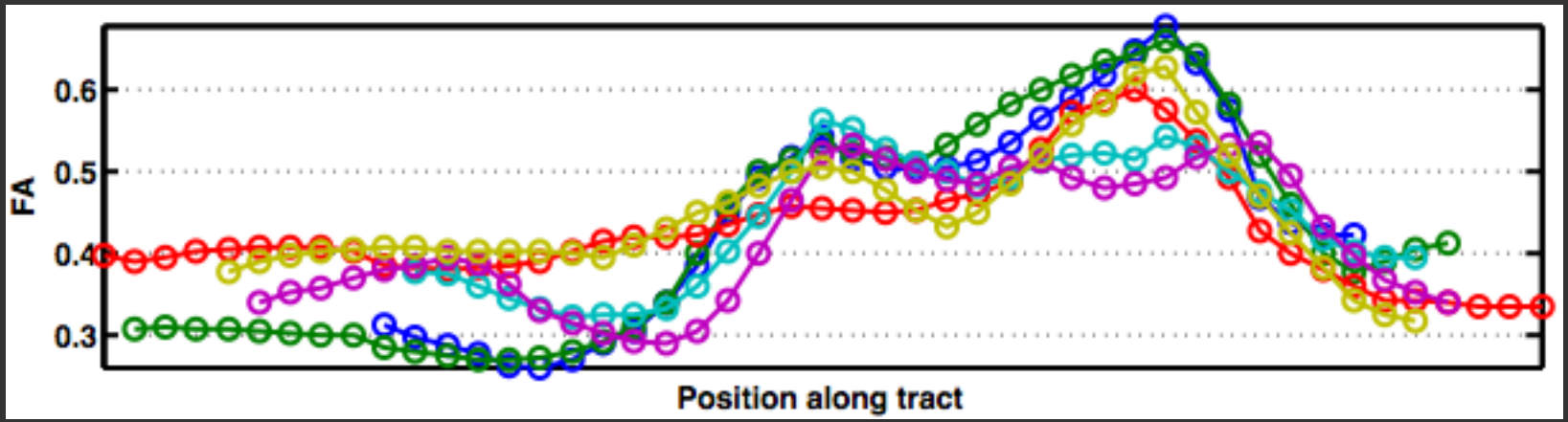
```
# subjectname Diff001
# pathwayname lh.cst
#
# pathway start
x y z AD RD MD FA AD_Avg RD_Avg
66 63 13 0.00103657 0.000574918
66 63 14 0.00100453 0.000480365
67 64 15 0.000816154 0.00035986
67 64 16 0.000946625 0.00042132
68 64 17 0.000967142 0.00030569
68 64 18 0.00114626 0.000333594
69 65 19 0.00152806 0.000740932
69 65 20 0.00126399 0.000470638
69 65 21 0.00140243 0.000482392
70 65 21 0.00143949 0.000480912
70 65 22 0.00116007 0.000156374
70 66 23 0.00138642 0.000415134
71 66 24 0.00134187 0.000385197
71 66 25 0.00108983 0.000289931
71 66 26 0.00111074 0.000307493
```

- At each position along the path
  - Value on 1-D path with the highest probability
  - `*_Avg`: Average value over nearest points from all sampled paths
- Coordinates are given in native diffusion space
- Paths from different subjects generally have different number of positions along path

Along-the-path analysis



- Compute average FA/MD/RD/AD at each cross-section of the pathway
- Plot as a function of position along the pathway
- Correspondence of points between subjects based on Euclidean distance in MNI space



New: Assemble group stats

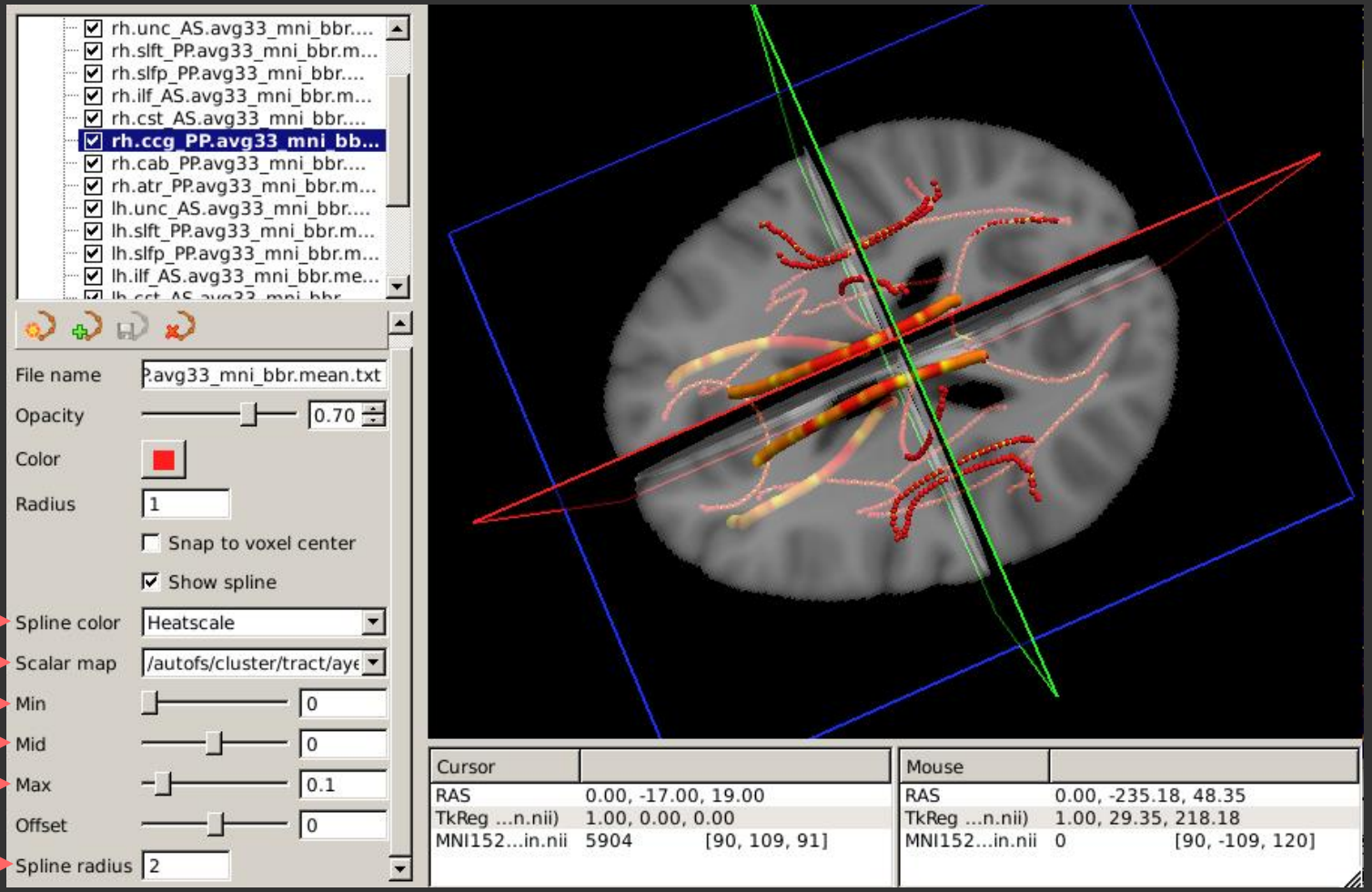
```
trac-all -stat -c dmrirc
```

- Combine files of stats along the path from multiple subjects:
  - Interpolate values of FA/MD/… at the same arc lengths for all paths
  - Find mean path for visualizing group results

- Outputs can be used for group studies on FA, MD, RD, AD along the pathway
  - One text file per pathway per measure (FA, MD, RD, AD)
  - Coordinates of mean path for visualization in freeview
  - Log file shows which subjects are outliers (shape-wise)

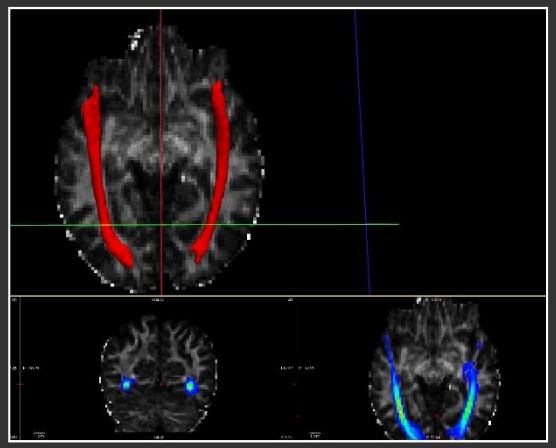
Example: *p*-values along each tract

- Save *p*-values in a simple text file, load it as a "scalar map"



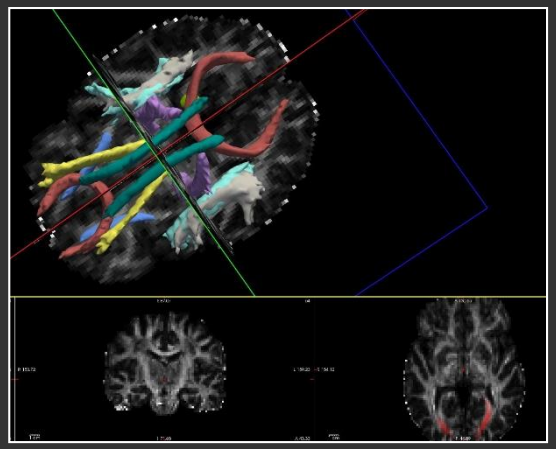
Tutorial

- How to run TRACULA and view outputs:
  - Set up configuration file (input images, gradient directions, b-values, registration method, etc.)
  - "Run" trac-all (*don't actually run it!*)
  - Look at pathways in freeview
  - Look at FA, MD, and other stats for each pathway



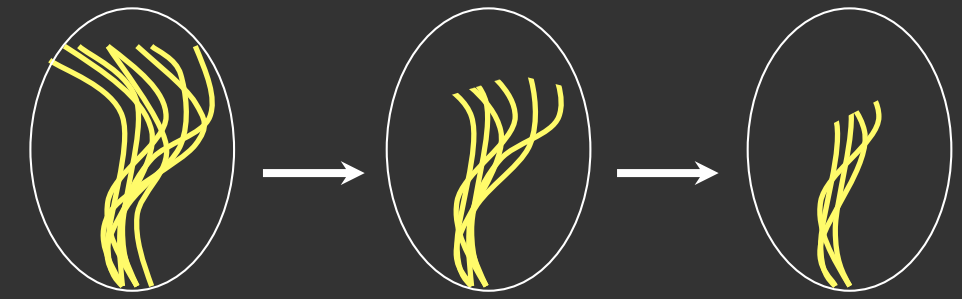
```
# subjectname Diff001
# pathwayname lh.cst
#
Count 1000
Volume 327
Len_Min 35
Len_Max 70
Len_Avg 53.119
Len_Center 48
AD_Avg 0.00106102
AD_Avg_Weight 0.00108794
AD_Avg_Center 0.00105527
RD_Avg 0.000438781
RD_Avg_Weight 0.000430744
RD_Avg_Center 0.000441464
MD_Avg 0.000646195
MD_Avg_Weight 0.000649809
MD_Avg_Center 0.000646067
FA_Avg 0.519271
FA_Avg_Weight 0.539241
FA_Avg_Center 0.511358
```

```
# subjectname Diff001
# pathwayname lh.cst
#
# pathway start
x y z AD RD MD FA
66 63 13 0.00103657 0.000574918 0.000728804 0.374774
66 63 14 0.00100453 0.000480365 0.000655088 0.478045
67 64 15 0.000816154 0.000359865 0.000511961 0.547635
67 64 16 0.000946625 0.000421327 0.000596426 0.521222
68 64 17 0.000967142 0.000305692 0.000526175 0.646745
68 64 18 0.00114626 0.000333594 0.000604484 0.658591
69 65 19 0.00152806 0.000740932 0.00100331 0.426333
69 65 20 0.00126399 0.000470638 0.000735089 0.57121
69 65 21 0.00140243 0.000482392 0.000789071 0.611696
70 65 21 0.00143949 0.000480912 0.000800438 0.618516
70 65 22 0.00116007 0.000156374 0.000490939 0.858895
70 66 23 0.00138642 0.000415134 0.000738896 0.650657
71 66 24 0.00134187 0.000385197 0.000704089 0.678151
71 66 25 0.00108983 0.000289931 0.000556565 0.729769
71 66 26 0.00111074 0.000307493 0.000575241 0.693343
72 66 27 0.00117242 0.000398032 0.00065616 0.619191
72 66 28 0.00118738 0.000448541 0.000694819 0.568624
```



New: Longitudinal tractography

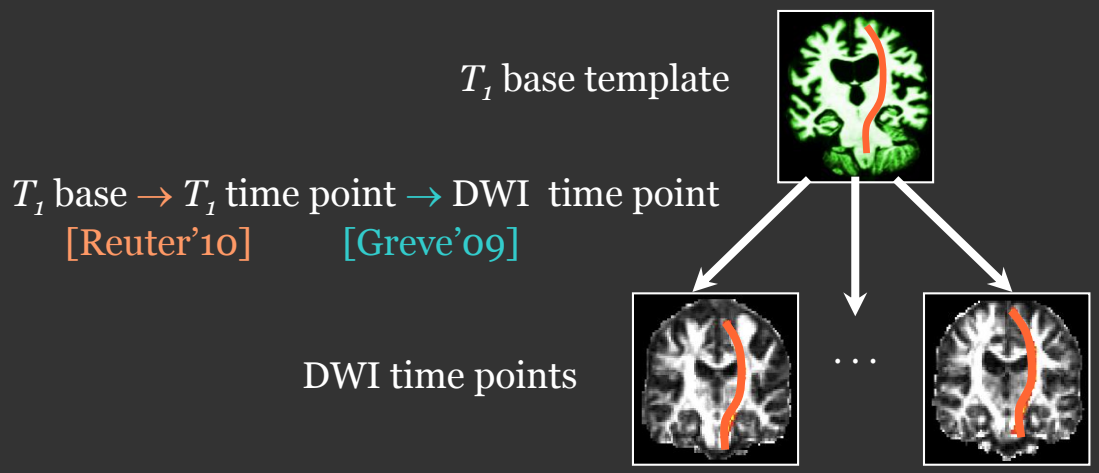
- Goal: Reconstruct a white-matter pathway consistently among all time points of a subject
- Challenging to do when processing each time point independently, as if it were a cross-sectional data point



- Different parts of the pathway may be reconstructed in each time point, due to noise or white matter 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.*, *ISMRM* 2014



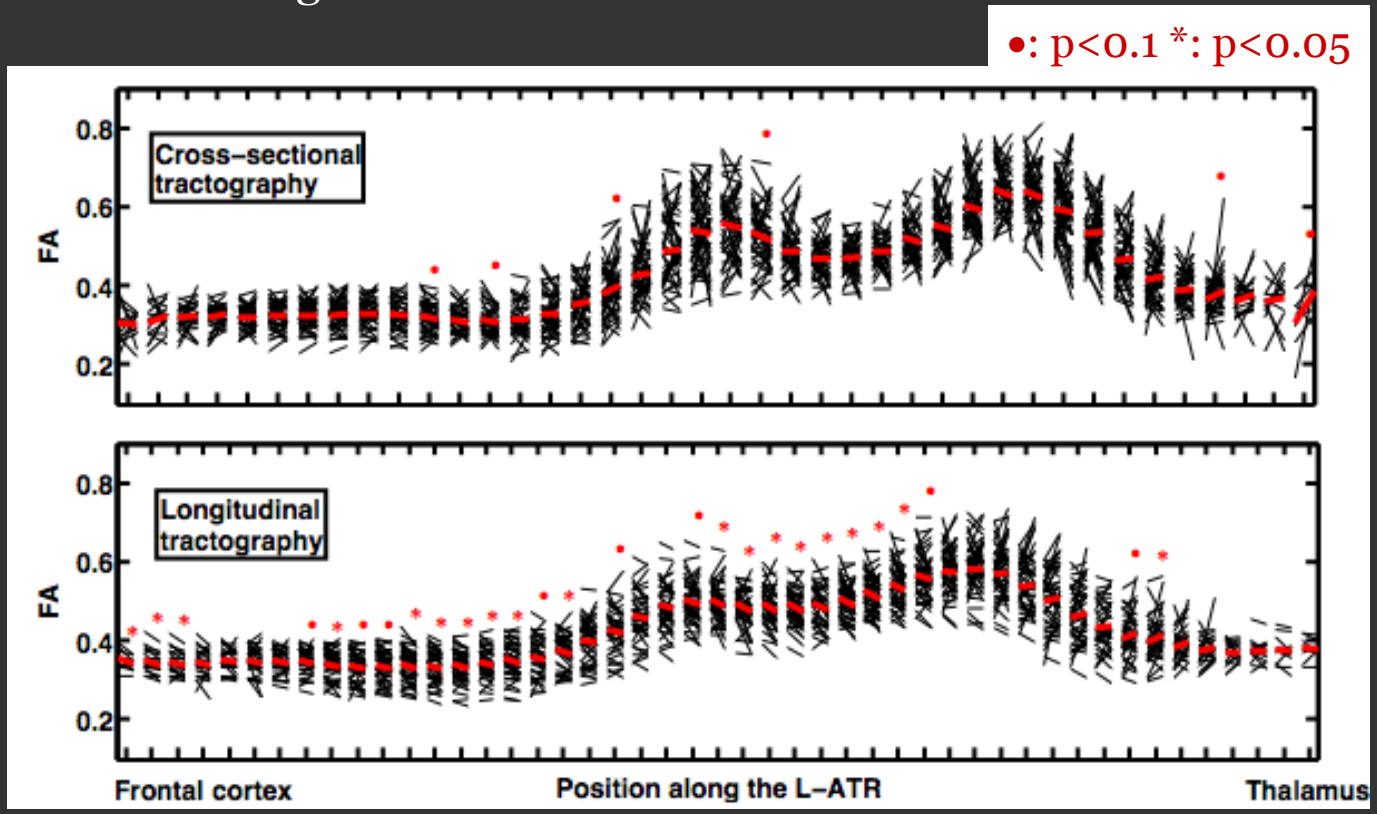
- Reconstruct a subject's pathways simultaneously in all time points:
  - Perturb path in the space of the base template
  - Map to each time point
  - Compute likelihood of DWI data at all time points
  - Compute anatomical prior based on segmentations of all time points

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

Longitudinal TRACULA: Sensitivity

Yendiki *et al.*, *ISMRM* 2014

- Improved sensitivity to longitudinal changes in FA in Huntington's disease with longitudinal TRACULA



Longitudinal TRACULA : Usage

- Example configuration file:
  `$FREESURFER_HOME/bin/dmrirc.long.example`

- List all time points and their corresponding base templates:

```
set subjlist = (subjA-tp1 subjA-tp2 … subjB-tp1 subjB-tp2 …)
set baselist = (subjA-base subjA-base .. subjB-base subjB-base …)
```

- If `baselist` is not specified, data will be processed cross-sectionally

- The same 3 steps of trac-all must be run for either cross-sectional or longitudinal stream (the only difference is in the configuration file)