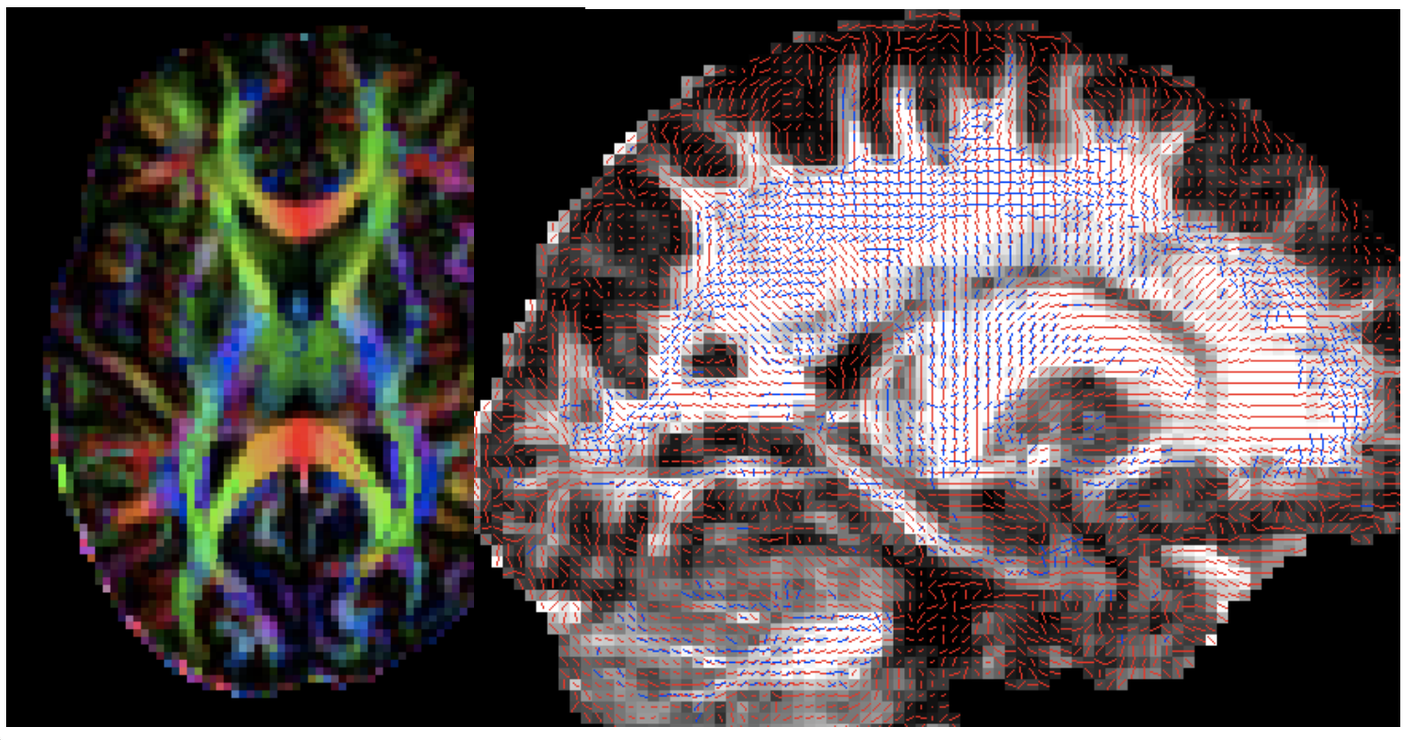
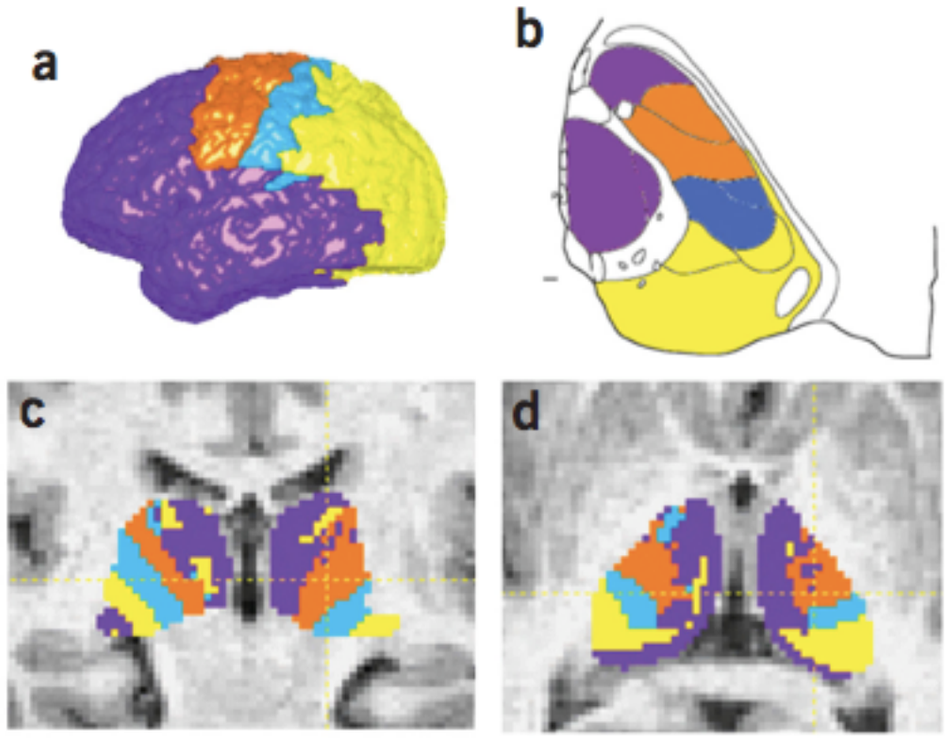
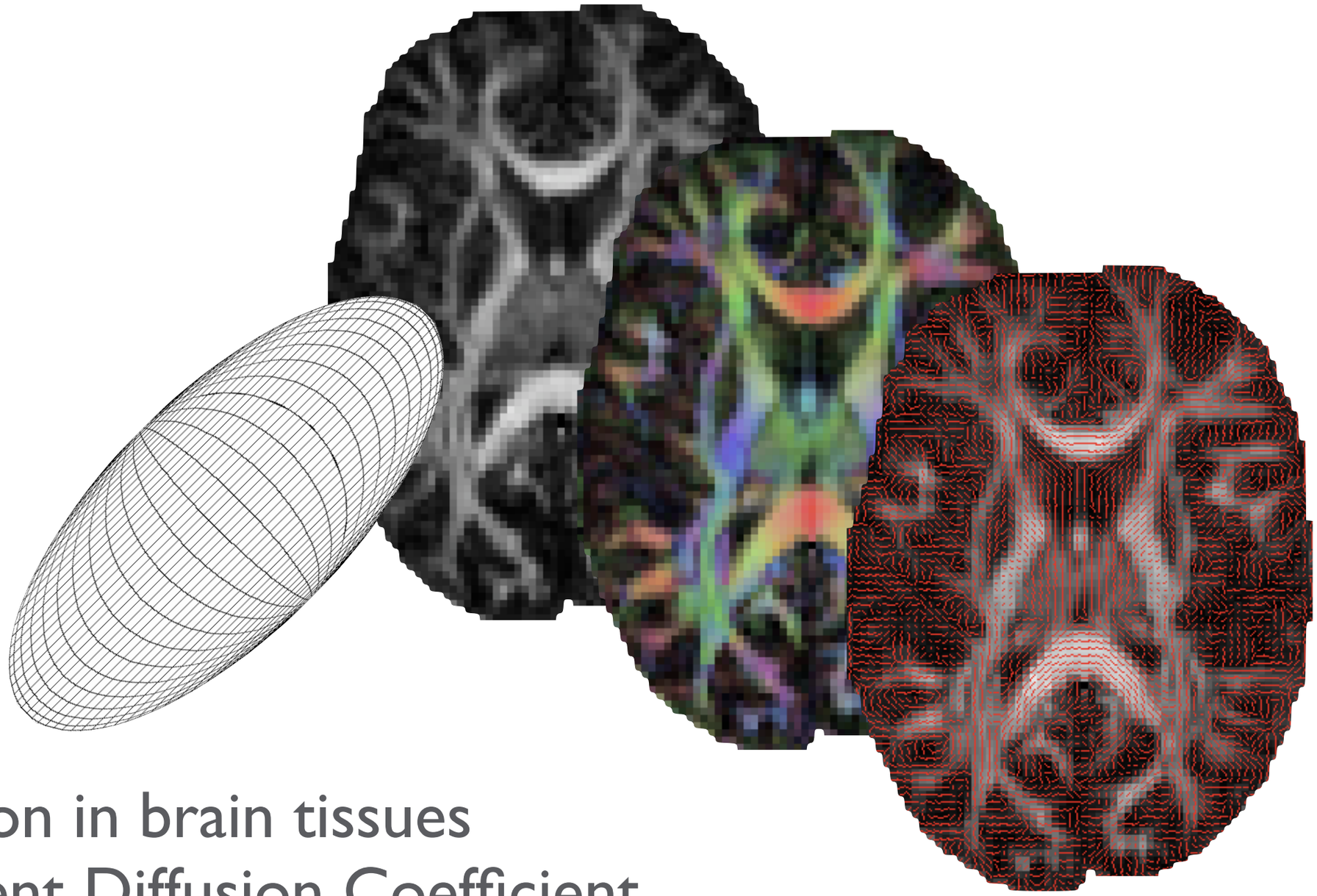
FMRIB Diffusion Toolbox

- DTI model fit
- Eddy current correction
- Voxel-Based diffusion analysis (TBSS)
- BEDPOSTX modelling crossing fibres
- PROBTRACKX propagating uncertainty in tractography





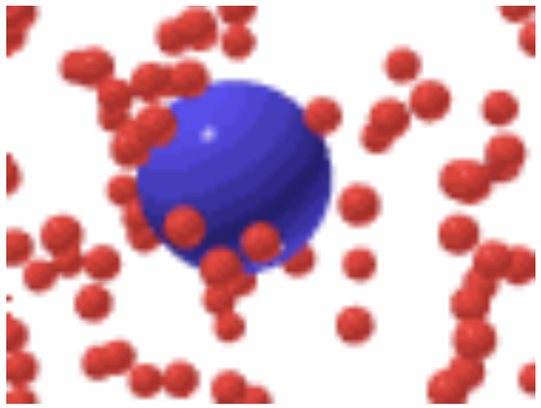
Diffusion Tensor Imaging - basic principles



- Diffusion in brain tissues
- Apparent Diffusion Coefficient
- Diffusion Tensor model
- Tensor-derived measures

Diffusion - Brownian Motion

Robert Brown (1773-1858)



Molecules are in constant motion in non-zero absolute temperatures…

Diffusion = A molecular transport process that involves thermally-driven random motions

Diffusion - Brownian Motion

Albert Einstein (1879-1955)

How can we describe this motion?
For an ensemble of molecules, in *n*-dimensional space:

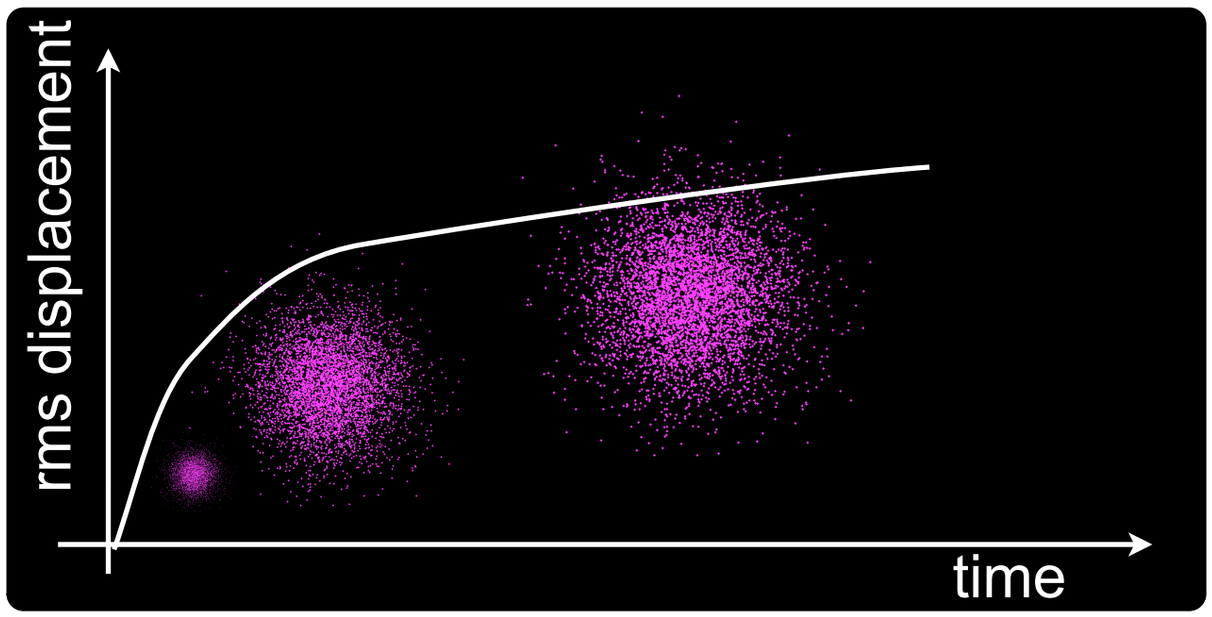
$$< x^2 >= 2nDt$$

displacement

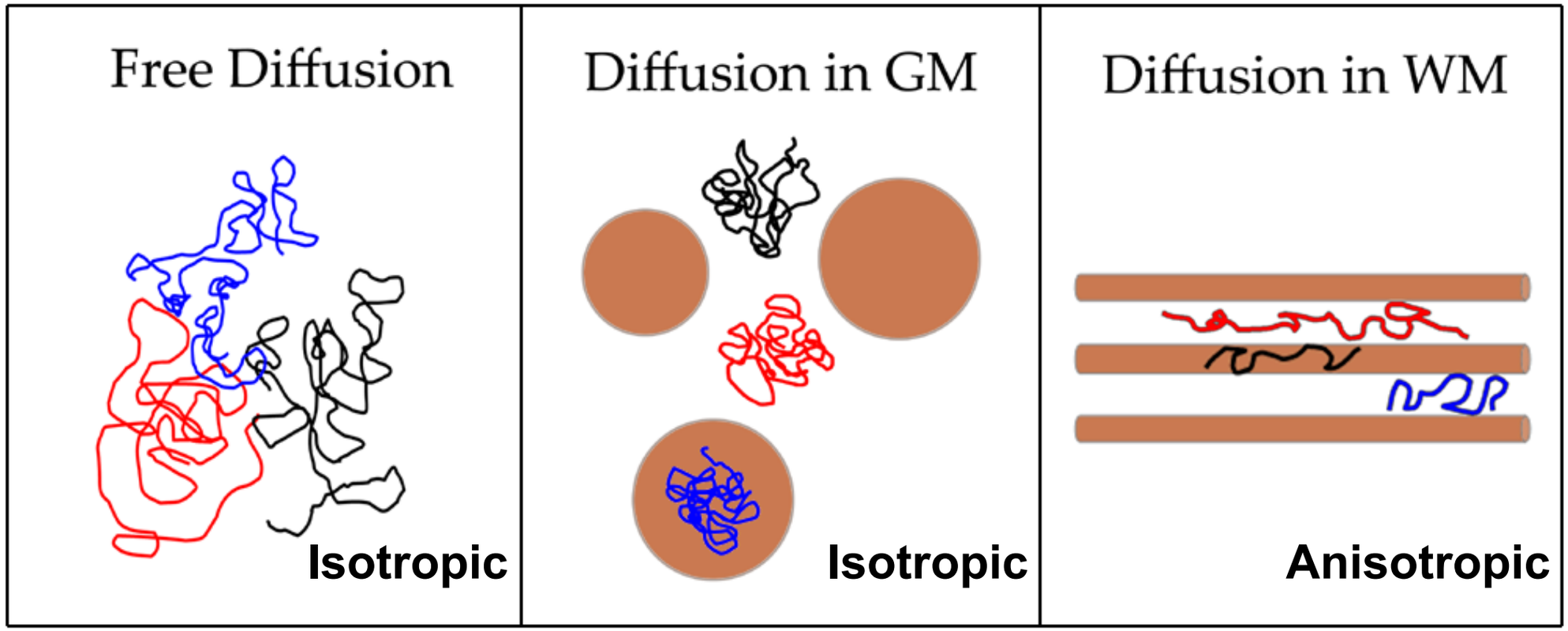
time

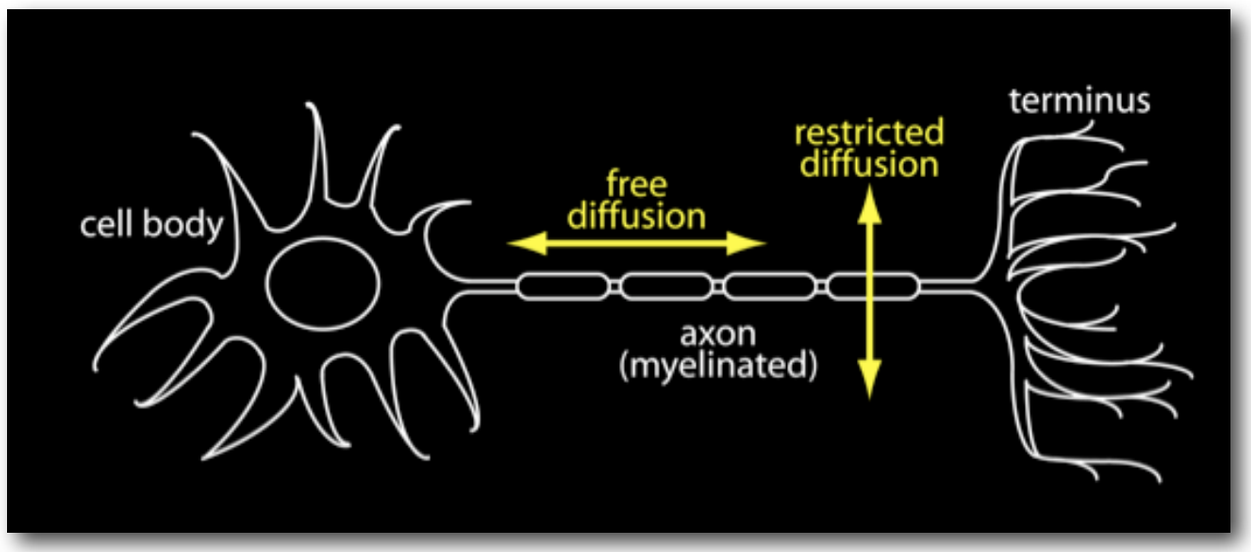
Diffusion coefficient

Valid for a homogeneous, barrier-free medium.



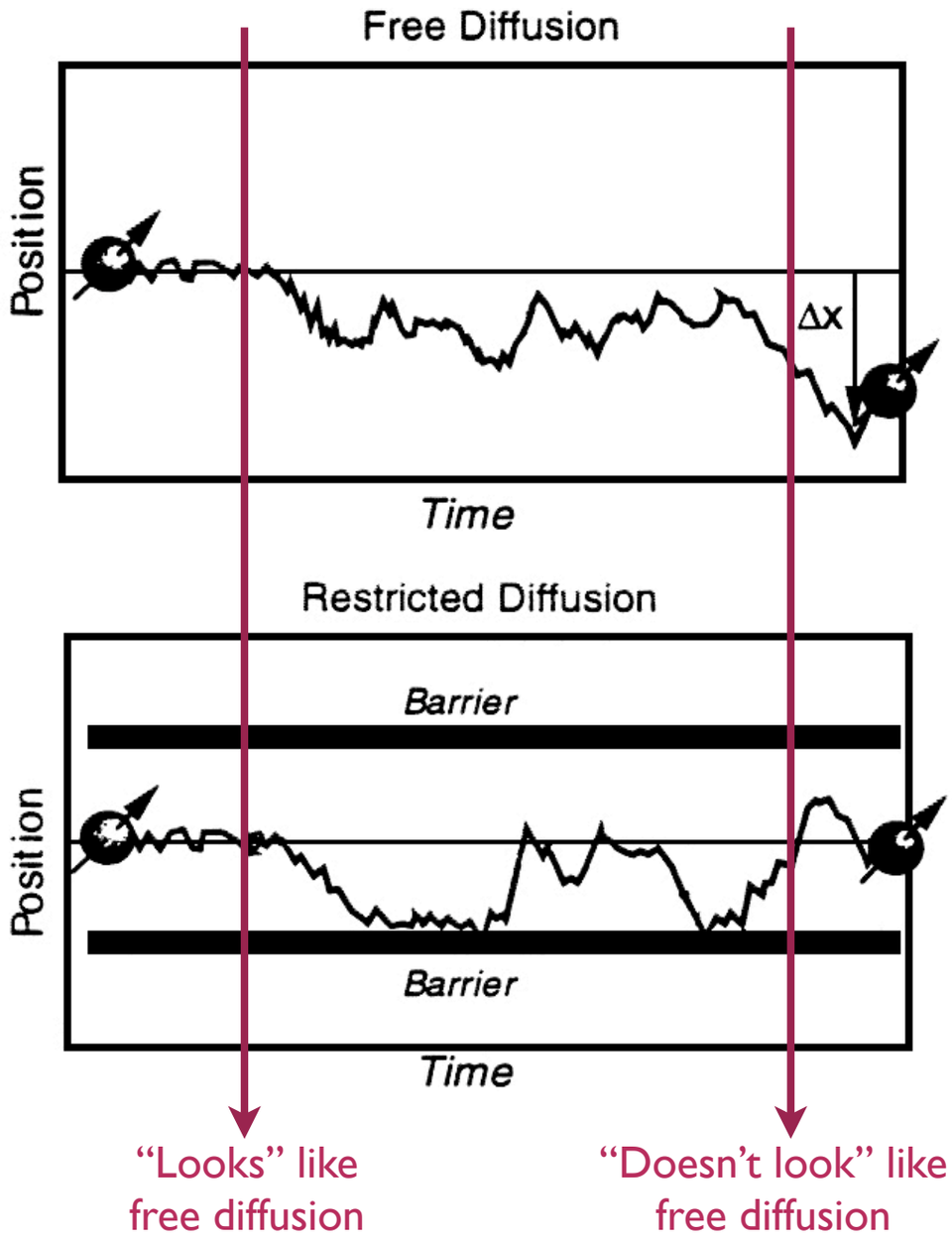
Diffusion in the Brain. Why is it Interesting?

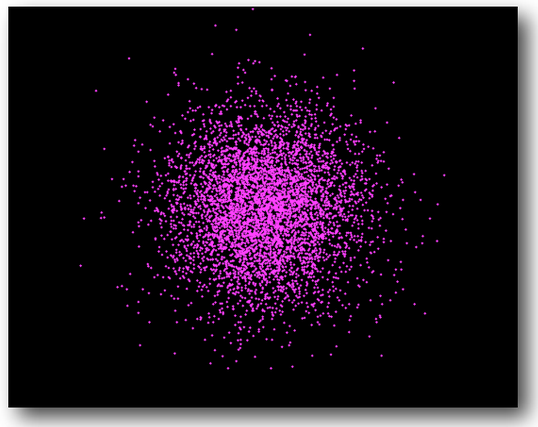


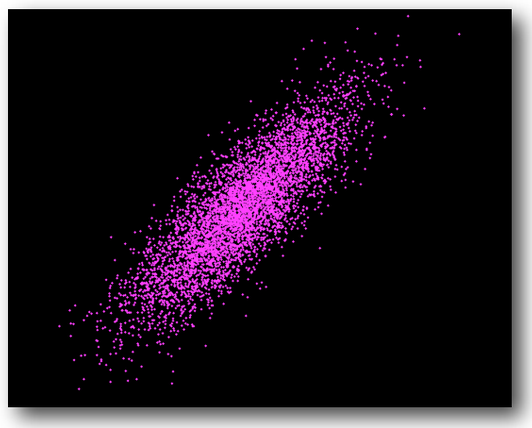


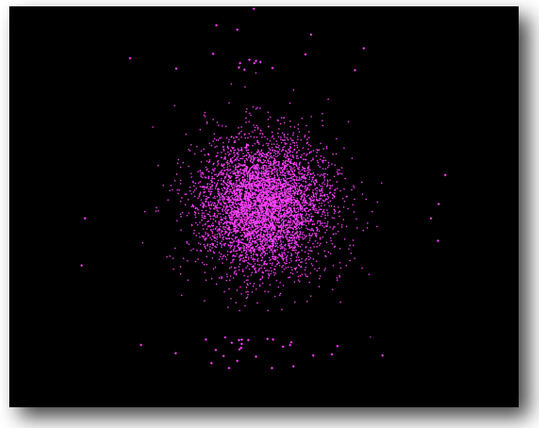
Diffusion is hindered by tissue boundaries, membranes, etc.
Marker for tissue microstructure (healthy and pathology)
Diffusion is anisotropic in white matter

Apparent Diffusion



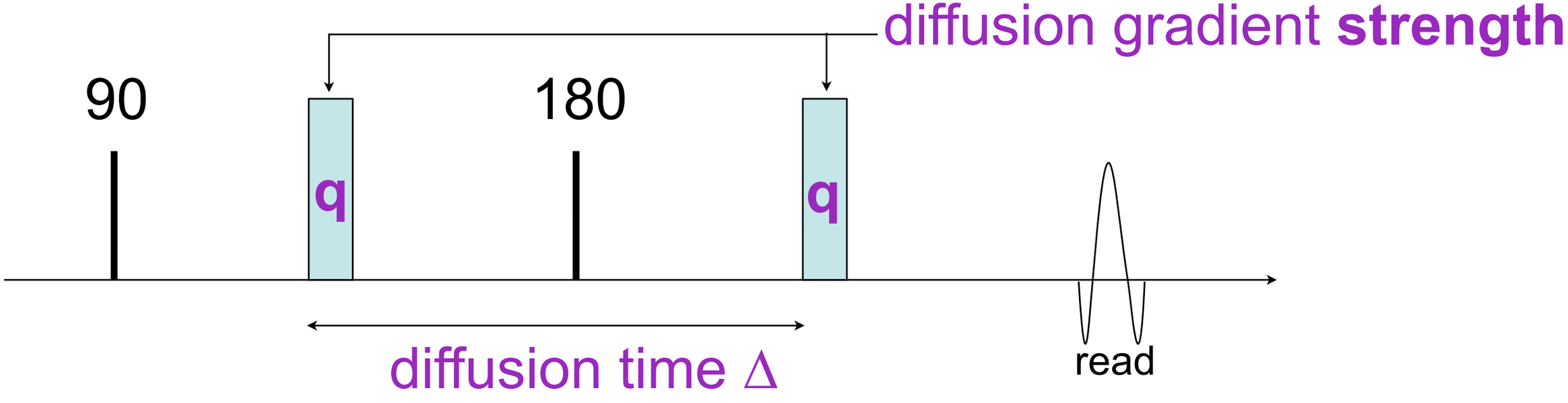




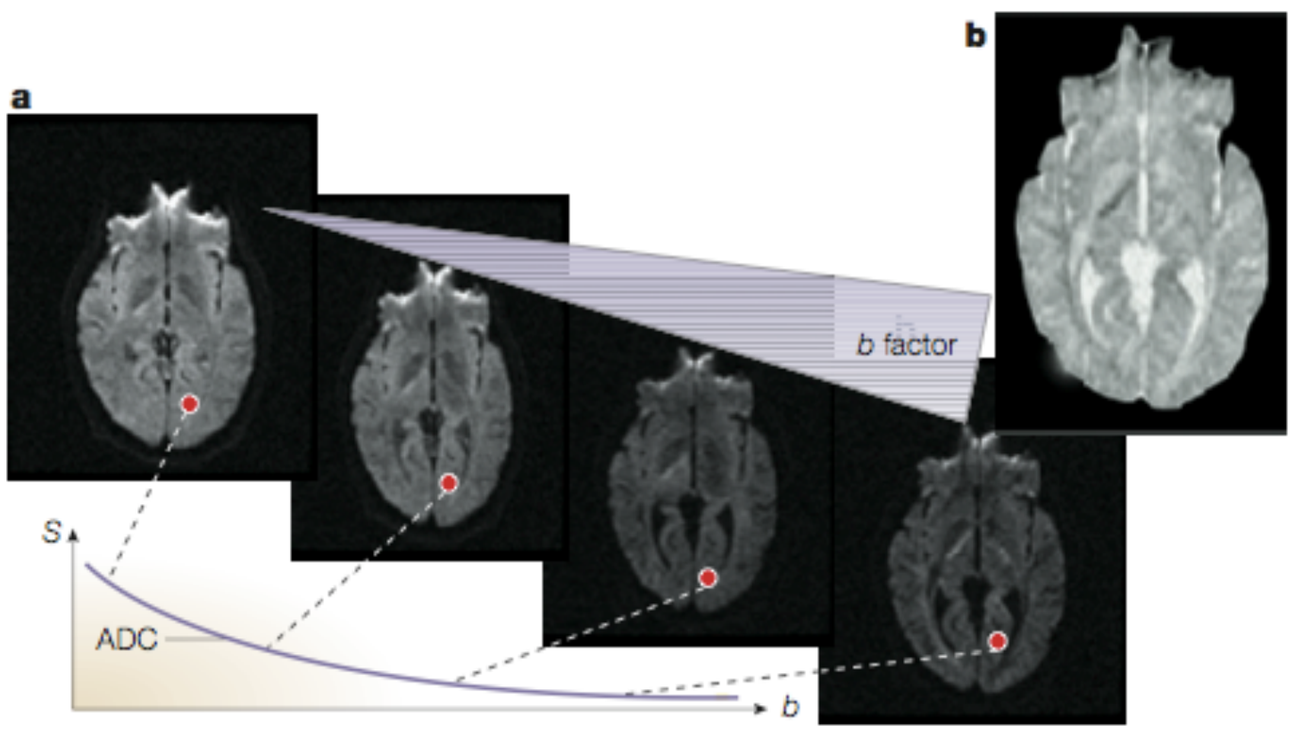


Observed diffusion in tissues depends on the experiment =
"Apparent diffusion" &
"Apparent diffusion coefficient" (ADC)

Measuring diffusion with MRI: Diffusion-Weighted MRI



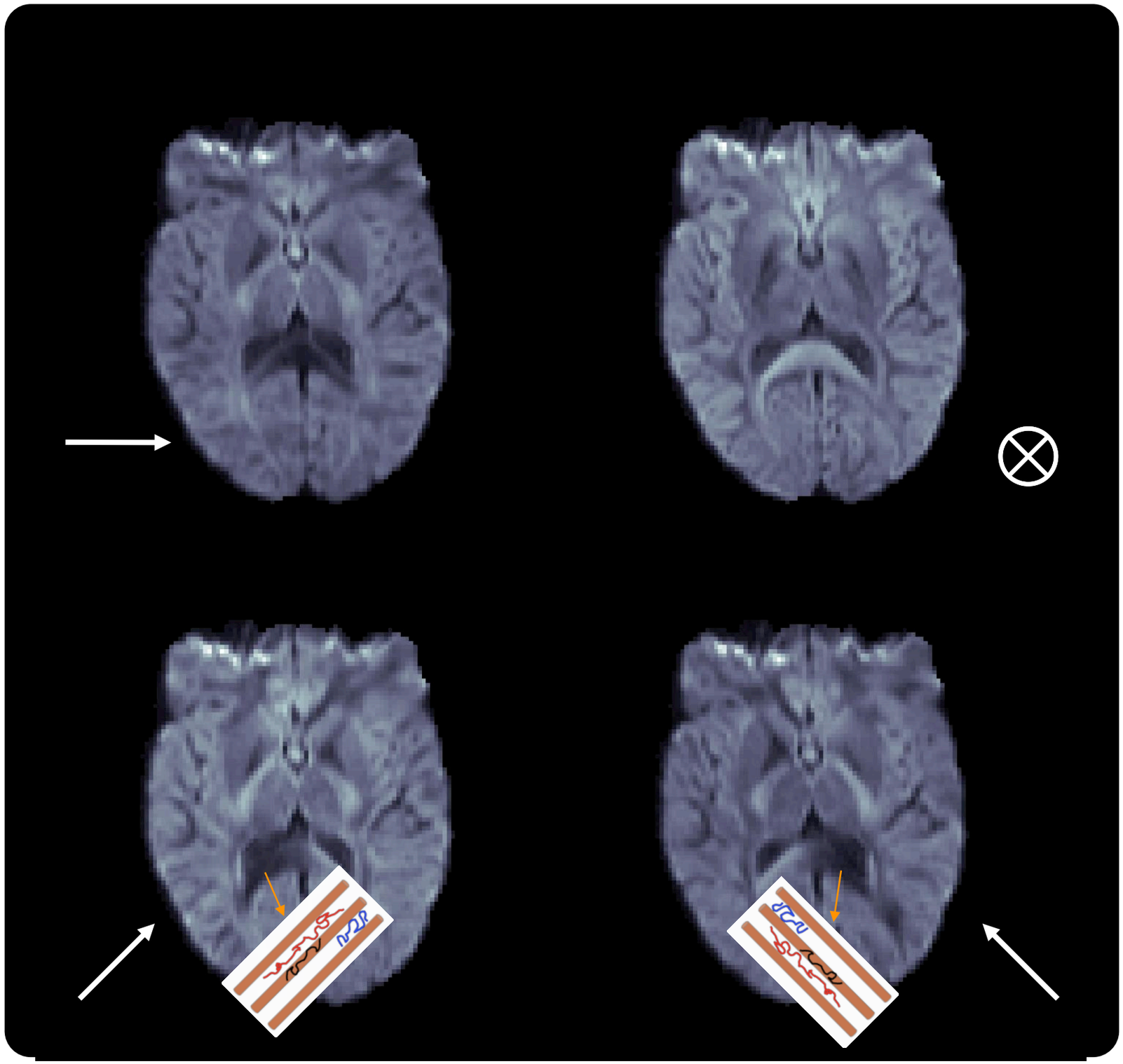
- If diffusion occurs along the direction of the applied gradient, signal is attenuated compared to the signal obtained with no diffusion gradients applied (b=0).



$$b \text{ value} \sim q^2.\Delta$$

Summary of diffusion gradient features. Controls how much diffusion-weighted contrast we introduce to the image.

Orientation Contrast in DWI



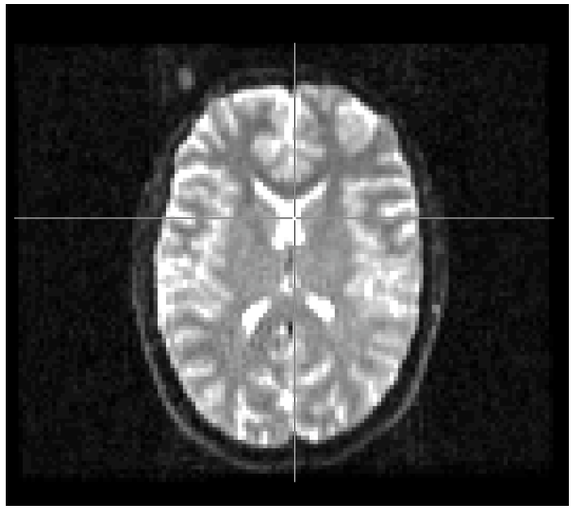
Because diffusion is anisotropic in WM, applying a gradient G along different directions **x**, gives different contrast in WM.

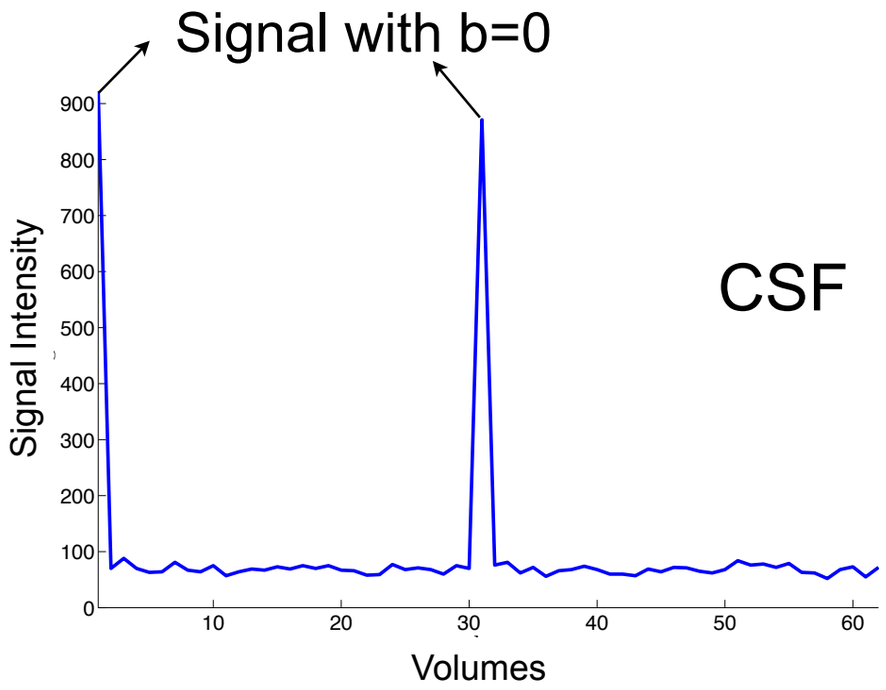
Anisotropic measurements in WM!

Roughly **Isotropic** in GM and CSF.

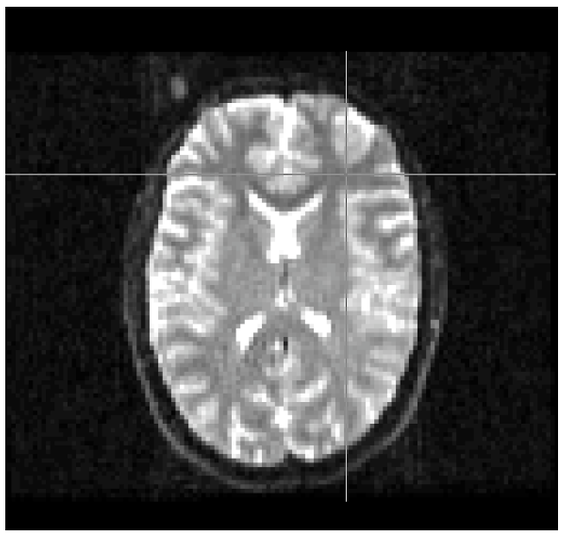
A Typical DWI Protocol

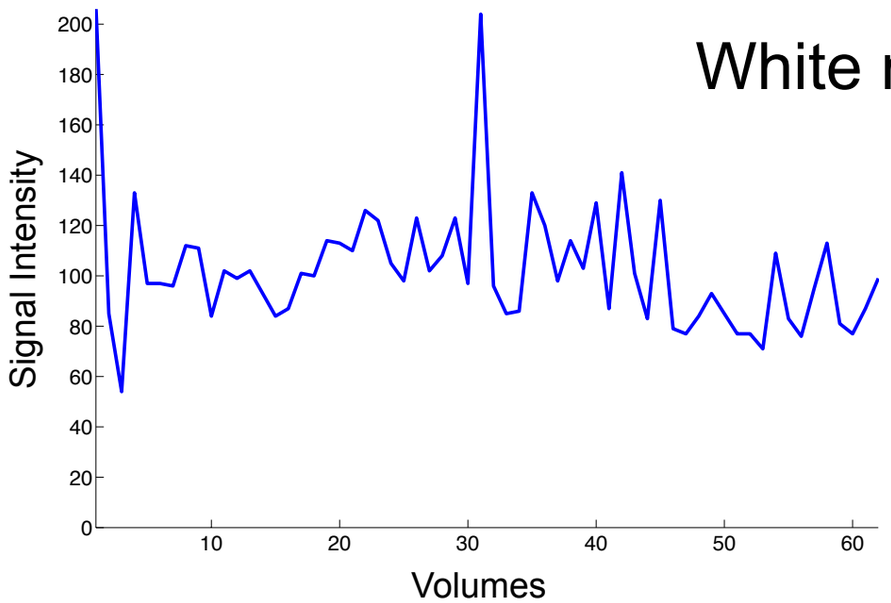
- Normally a few (at least one) b=0 volumes acquired, along with volumes at high b (~1000 s/mm^2).
- Different gradient directions are applied for the high b volumes.





CSF

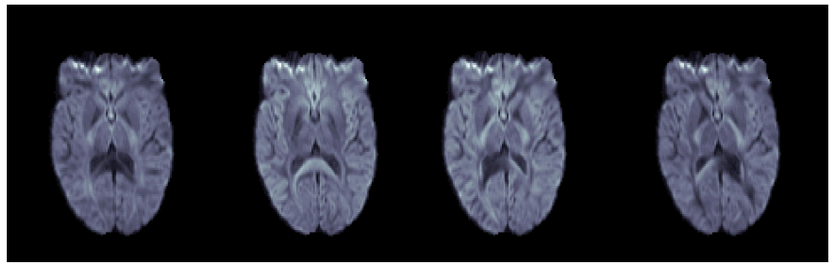




White matter

Diffusion Tensor Imaging (DTI)

- Apply **the diffusion tensor model** to a set of DWI images.



<u>Model Assumptions</u>

- The tensor model assumes that diffusion within tissues is Gaussian (barrier-free) diffusion!
But instead of a homogeneous medium (scalar variance), assumes anisotropic behaviour (covariance).

=> Instead of a scalar diffusion coefficient, use the **Diffusion Tensor: a 3x3 matrix that describes anisotropic diffusion.**

Diffusion displacements ~ N_3 (0, 2t**D**)

Diffusion Tensor Imaging (DTI)

Diffusion Tensor Model. In each voxel:

b-factor for gradient *j* (known)

Unit vector representing the direction of gradient *j* (known)

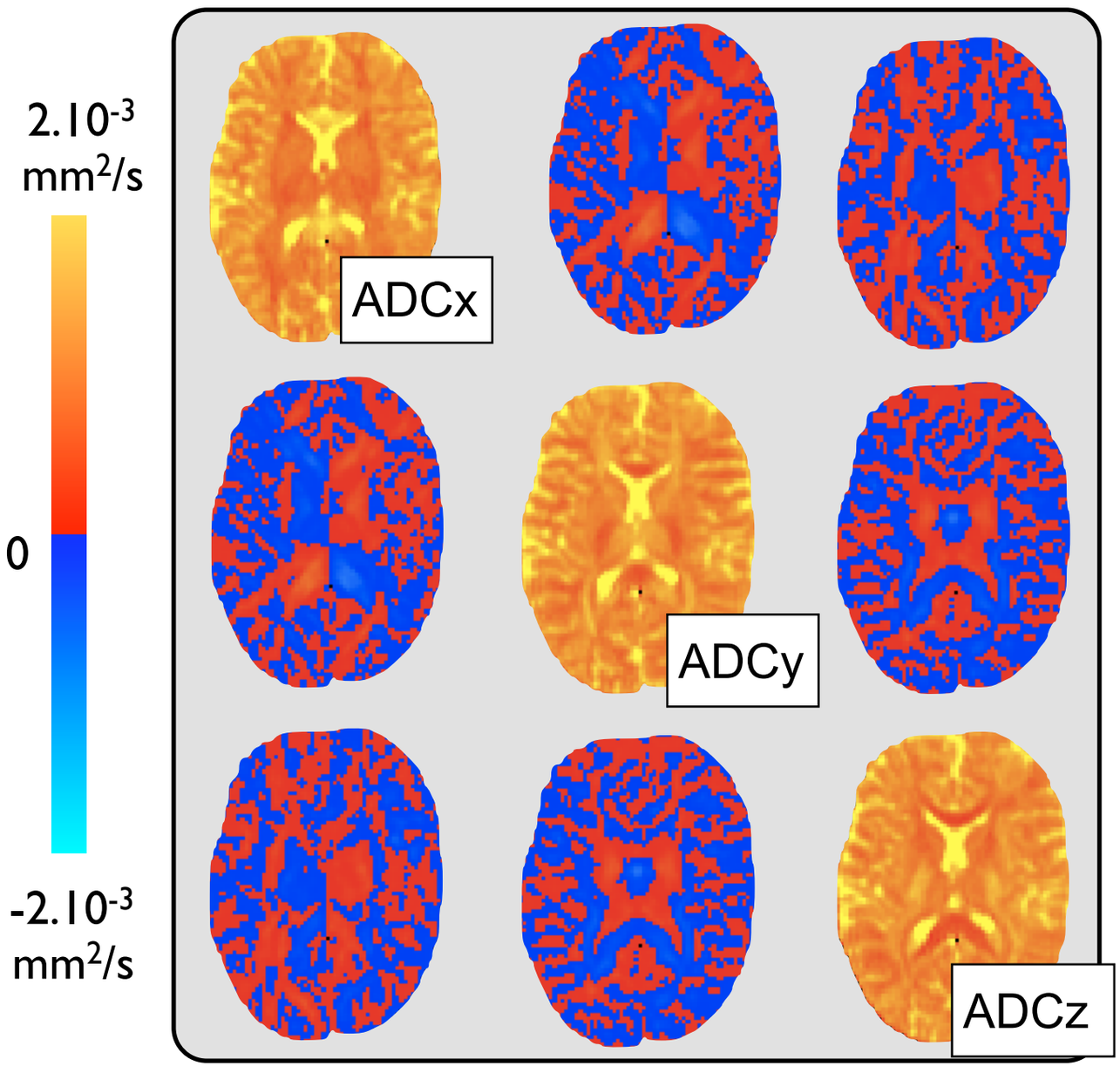
$$s_j = s_0 \exp(-b_j \, \boldsymbol{x}_j^T \, \boldsymbol{D} \, \boldsymbol{x}_j)$$

Signal measured after applying a Gradient *j* with direction $\boldsymbol{x}_j$ and b-factor b_j (measured)

3x3 Diffusion Tensor (unknown)

Signal measured with no diffusion gradient applied

The Elements of the Diffusion Tensor



$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

- Tensor is **symmetric** (6 unknowns)

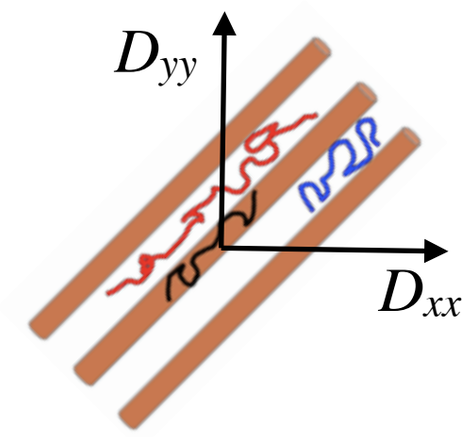
- **Diagonal Elements** are proportional to the diffusion displacement variances (**ADCs**) along the three directions of the experiment coordinate system

-**Off-diagonal Elements** are proportional to the **correlations** (covariances) of displacements along these directions

N_3 (0, 2t**D**)

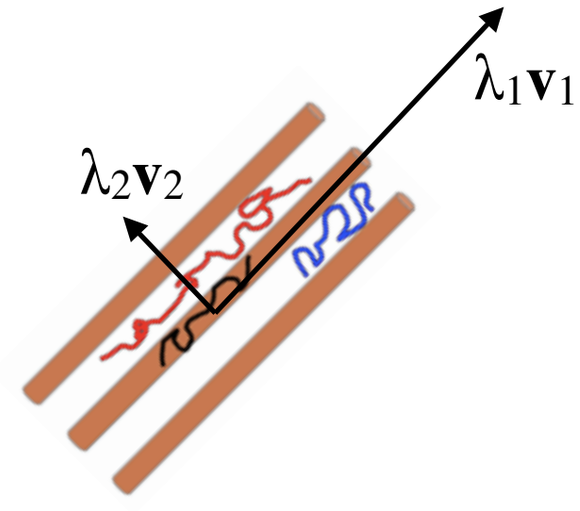
The Diffusion Tensor Eigenspectrum

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$



Once D is estimated, we get ADCs along the scanner's coordinate system. But we want ADCs along a local coordinate system in each voxel, determined by the anatomy.

Diagonalize the estimated tensor in each voxel



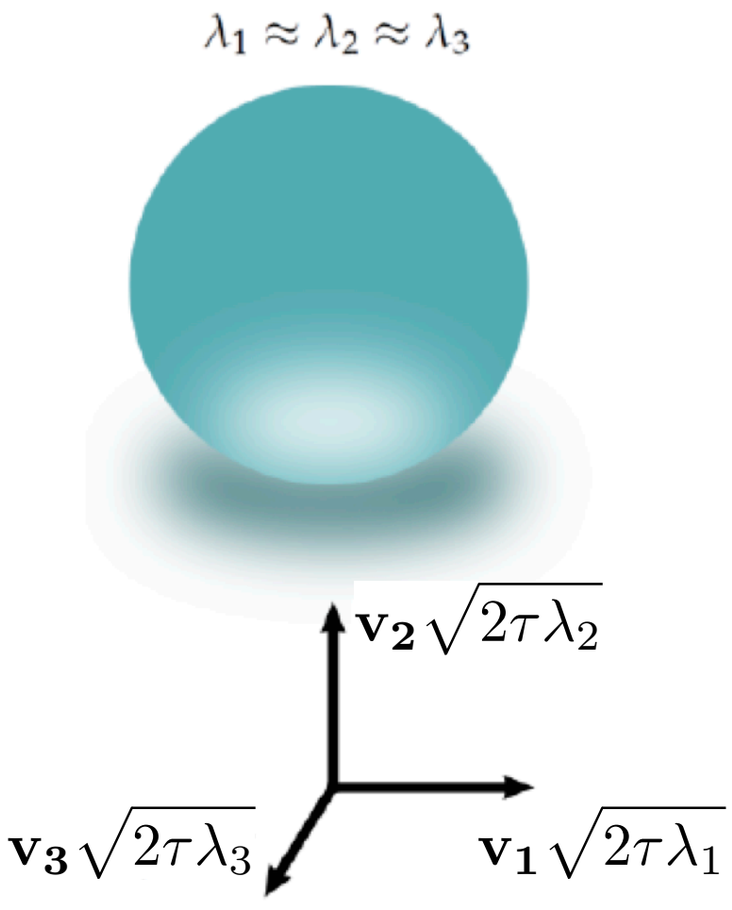
$$\mathbf{D} = [\mathbf{v_1}|\mathbf{v_2}|\mathbf{v_3}]^{\mathrm{T}} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} [\mathbf{v_1}|\mathbf{v_2}|\mathbf{v_3}]$$

eigenvectors - $\mathbf{v}_1$=direction of max diffusivity

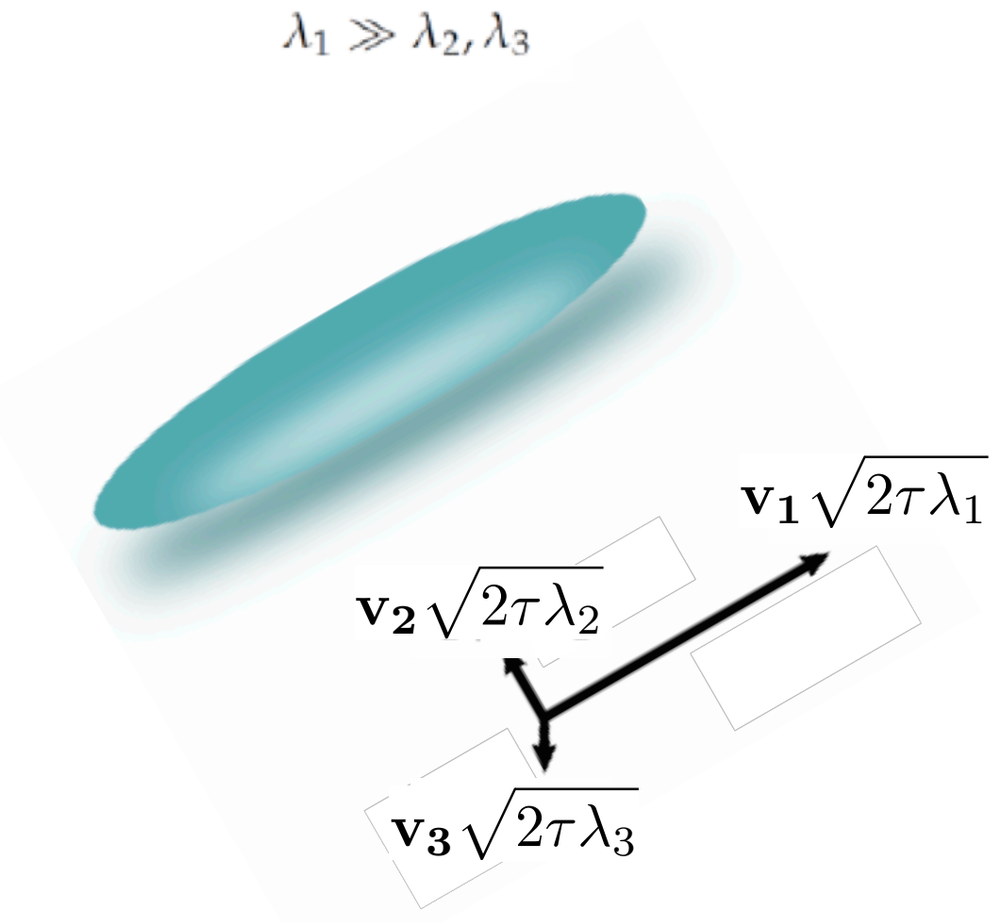
eigenvalues: ADCs along $\mathbf{v}_1$,$\mathbf{v}_2$,$\mathbf{v}_3$

The Diffusion Tensor Ellipsoid

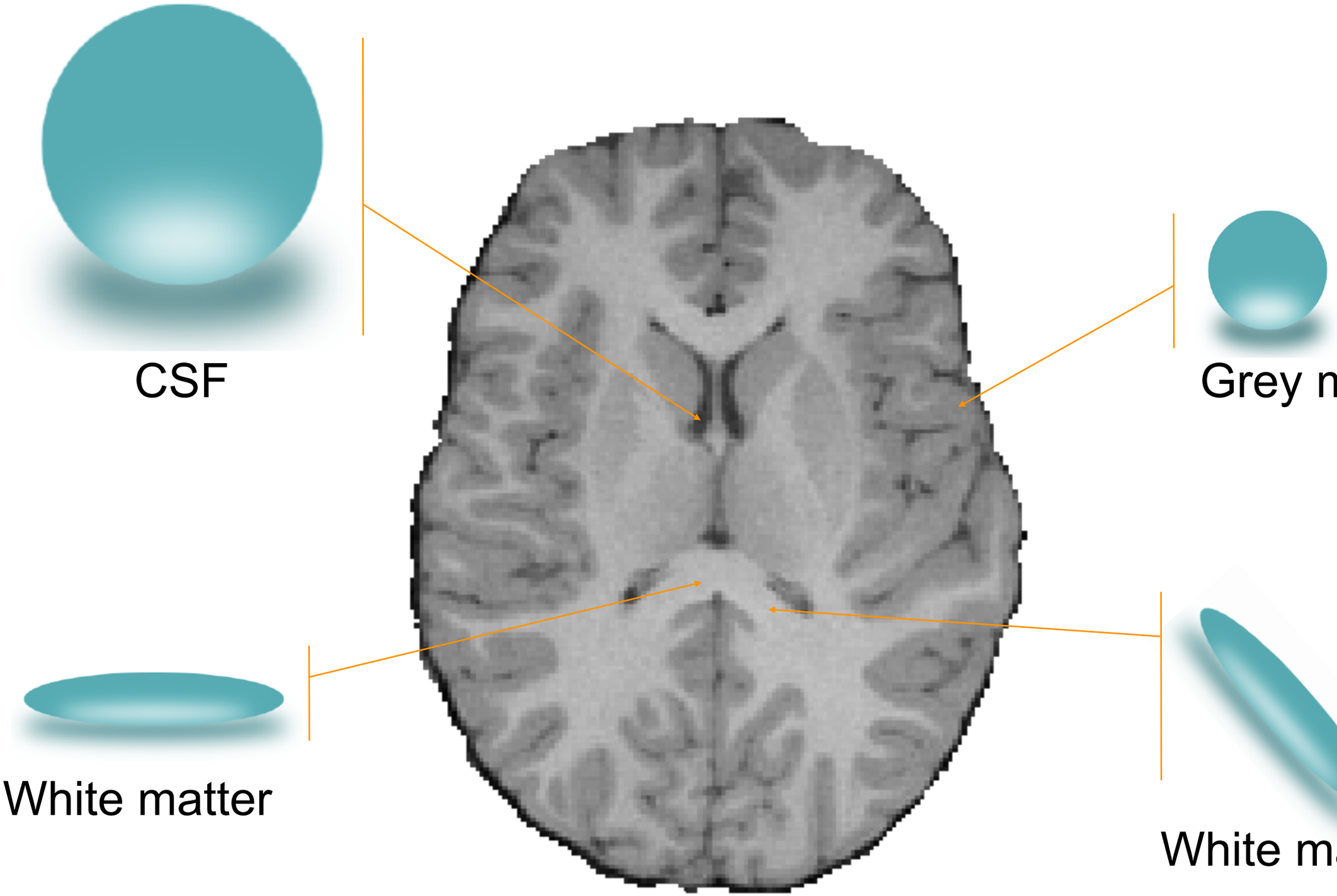
Isotropic voxel



Anisotropic voxel

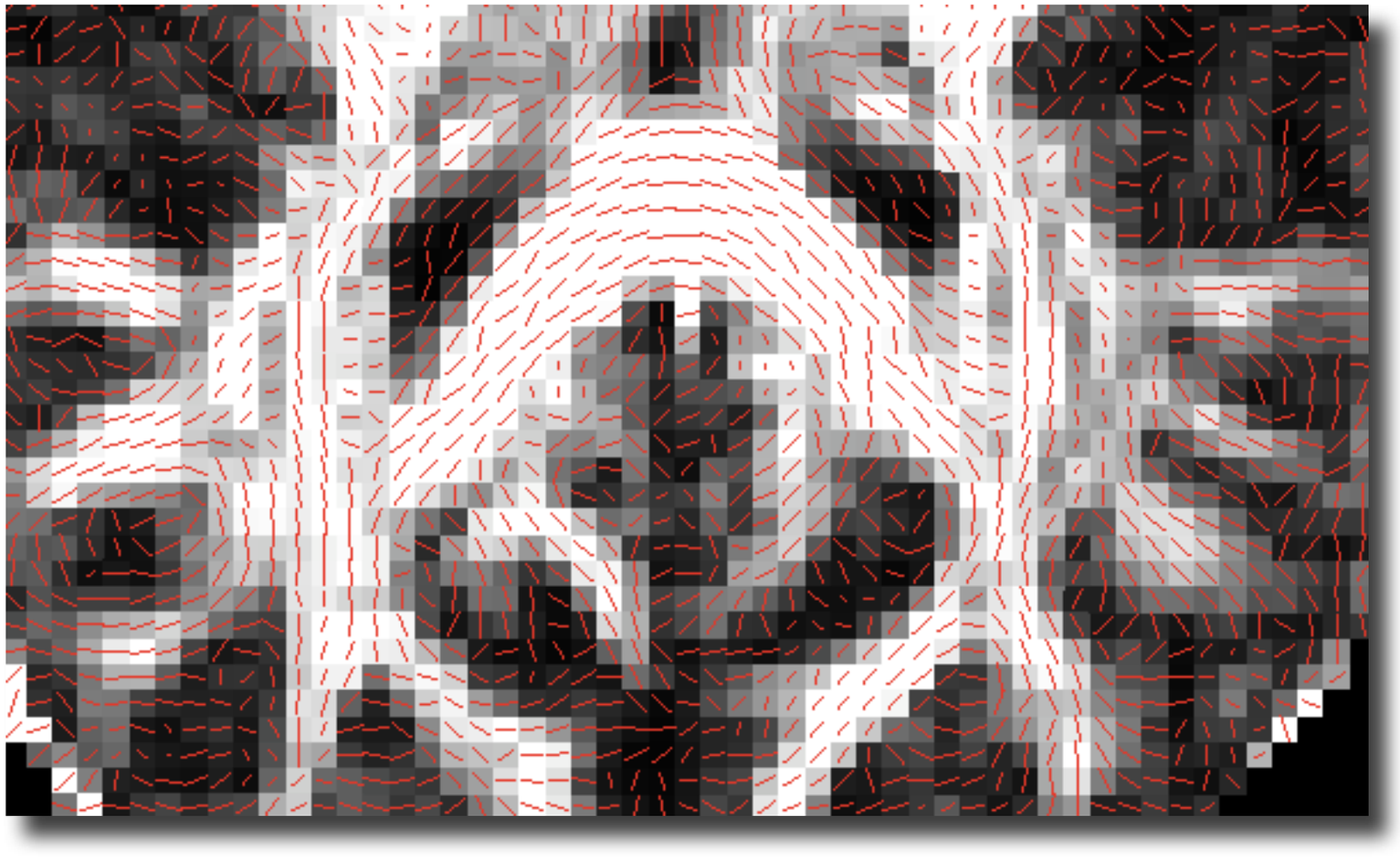


The Diffusion Tensor Ellipsoid

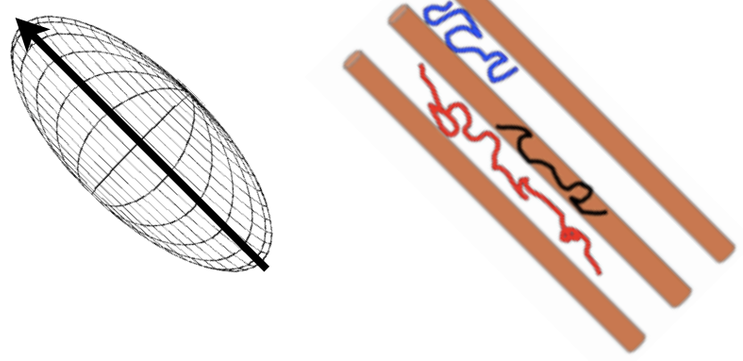


Estimates of Principle Fibre Orientation in WM

$\mathbf{v}_1$ map
Principal Diffusion Direction



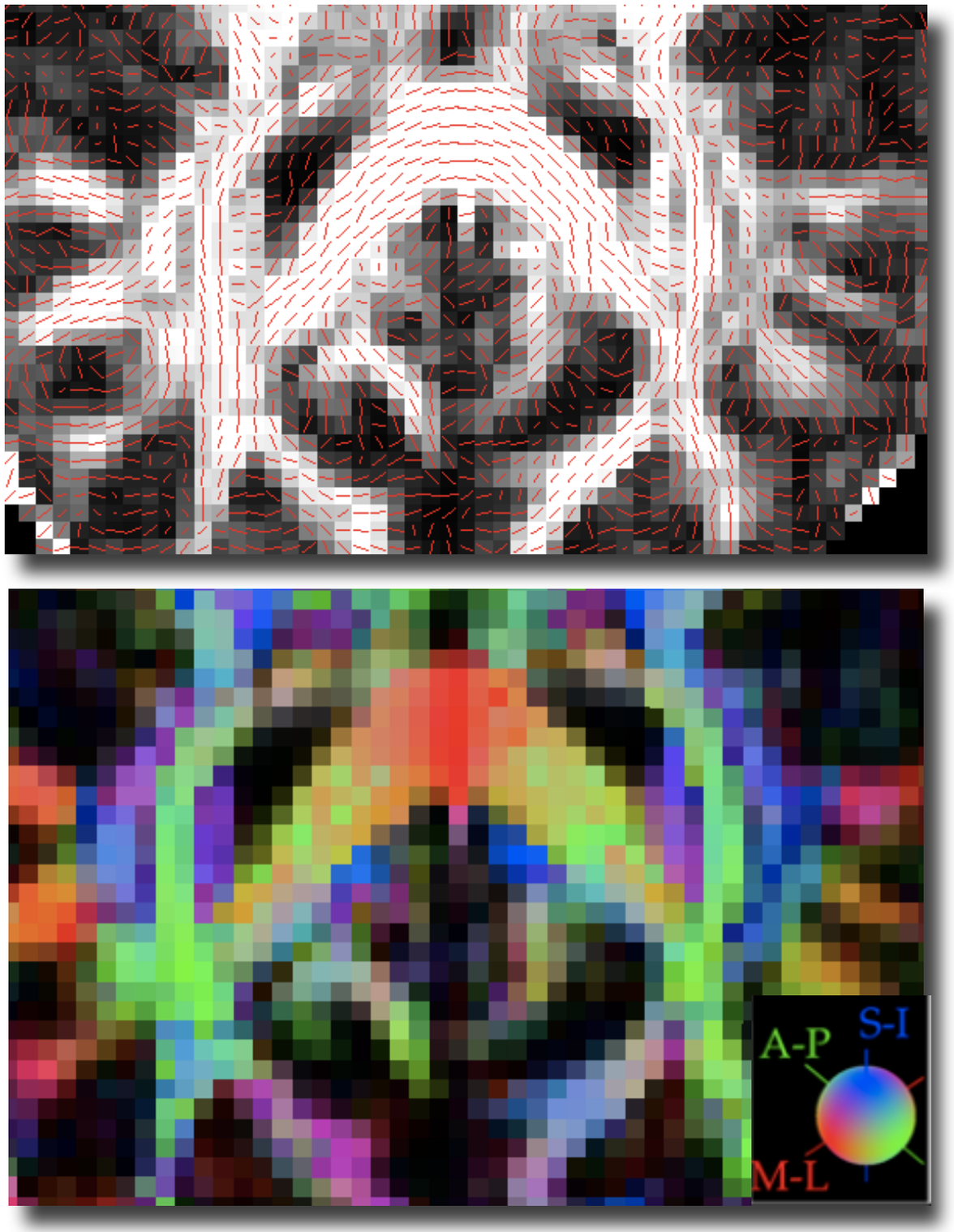
Principal Diffusion Direction



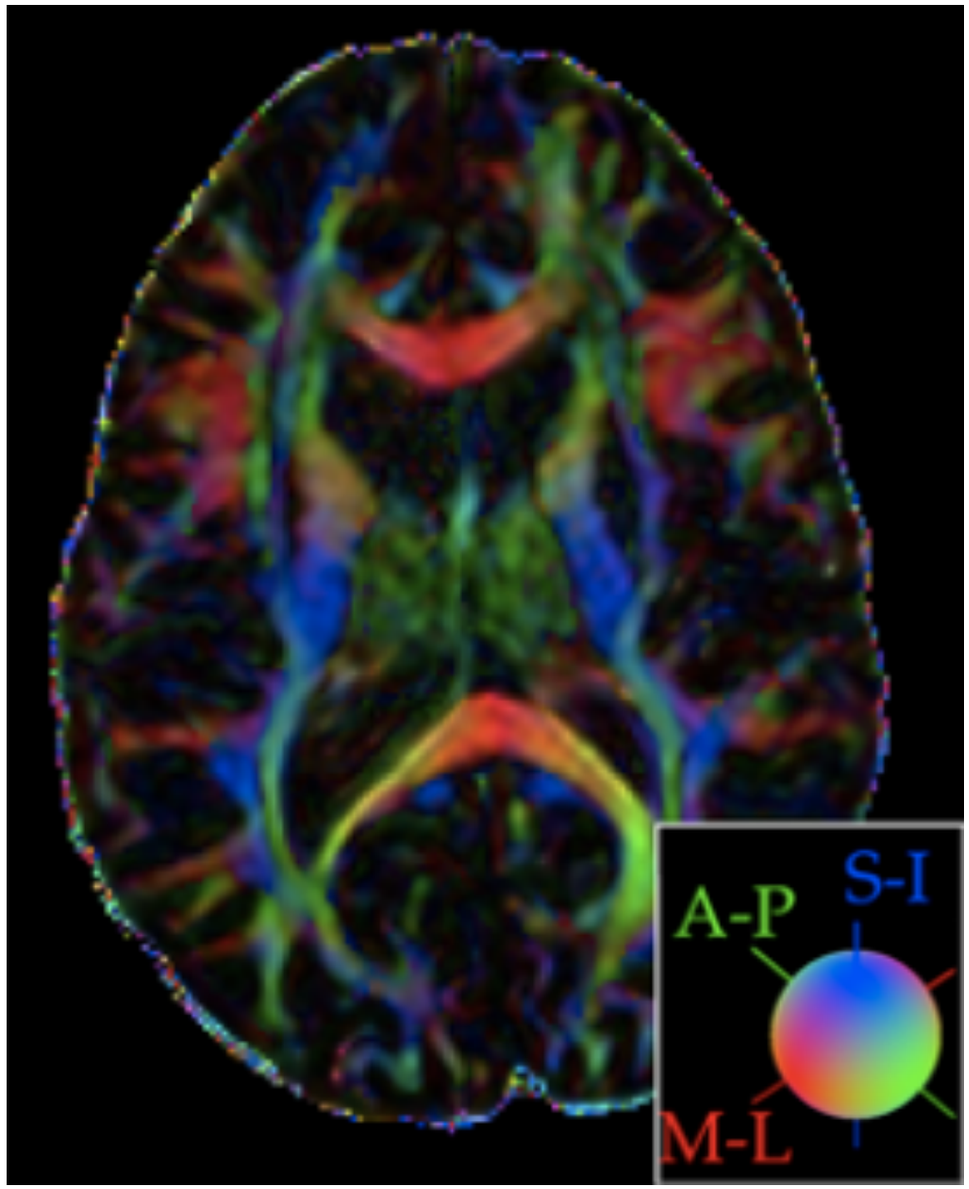
Assumption!!

Direction of maximum diffusivity in voxels with anisotropic profile is an **estimate of the major fibre orientation**.

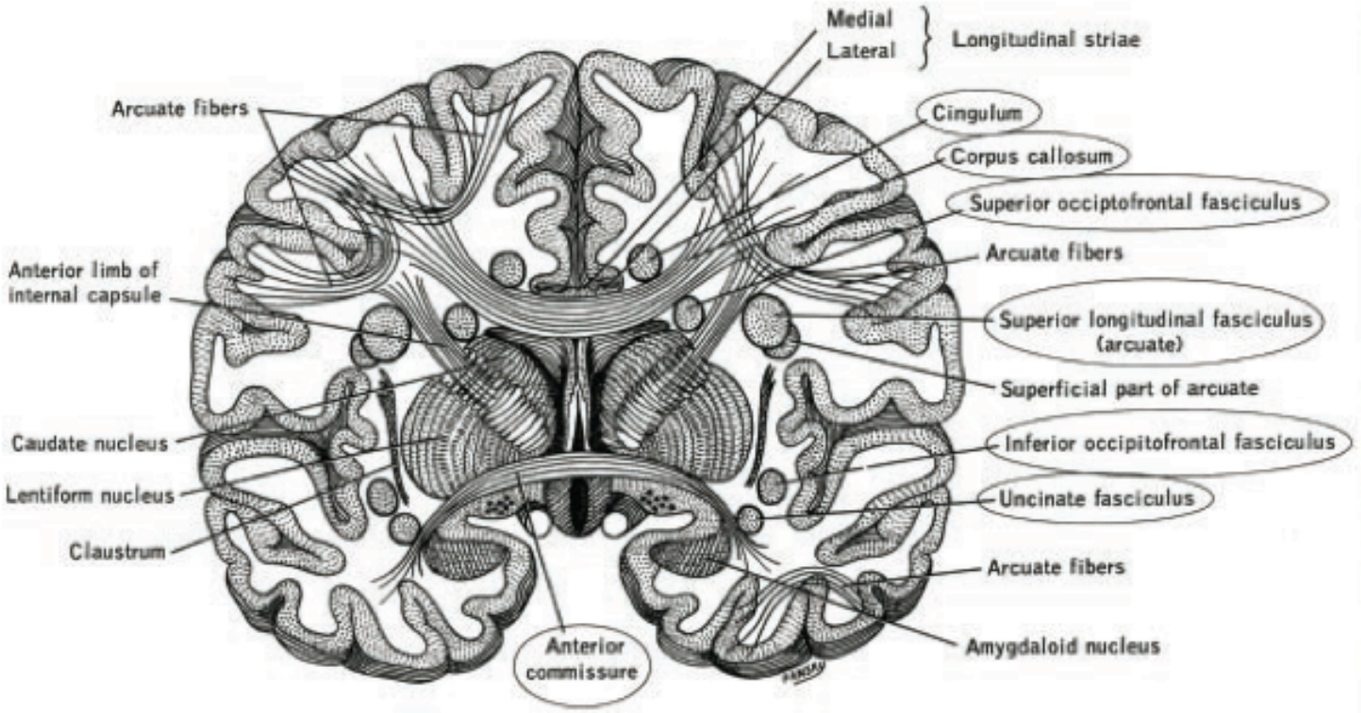
Estimates of Principle Fibre Orientation in WM

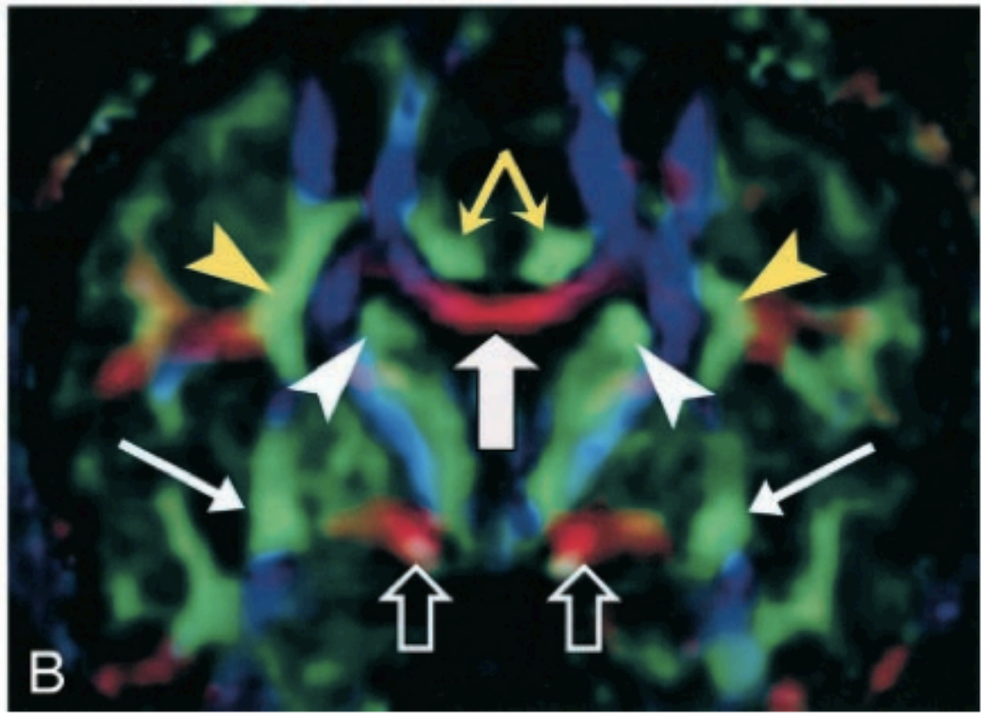


Colour-coded $\mathbf{v}_1$ map



Estimates of Principle Fibre Orientation in WM





Quantitative Diffusion Maps

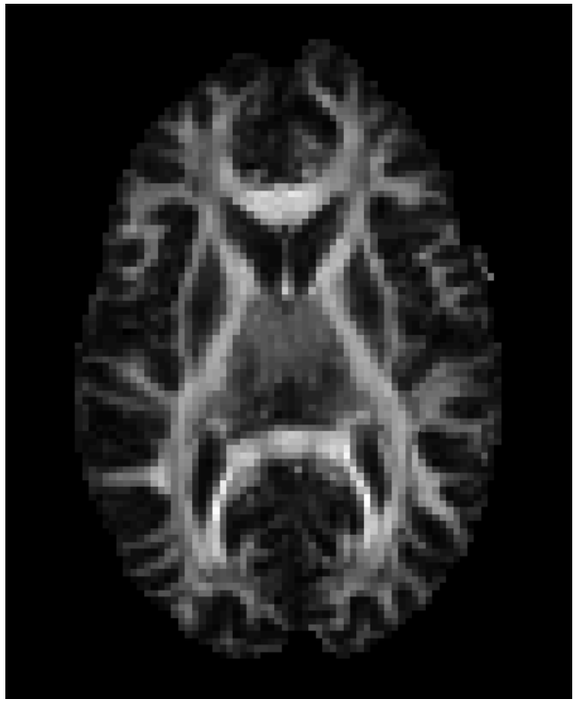
Fractional Anisotropy (FA) ~ Eigenvalues Variance (normalised!)
Mean Diffusivity (MD) = Eigenvalues Mean

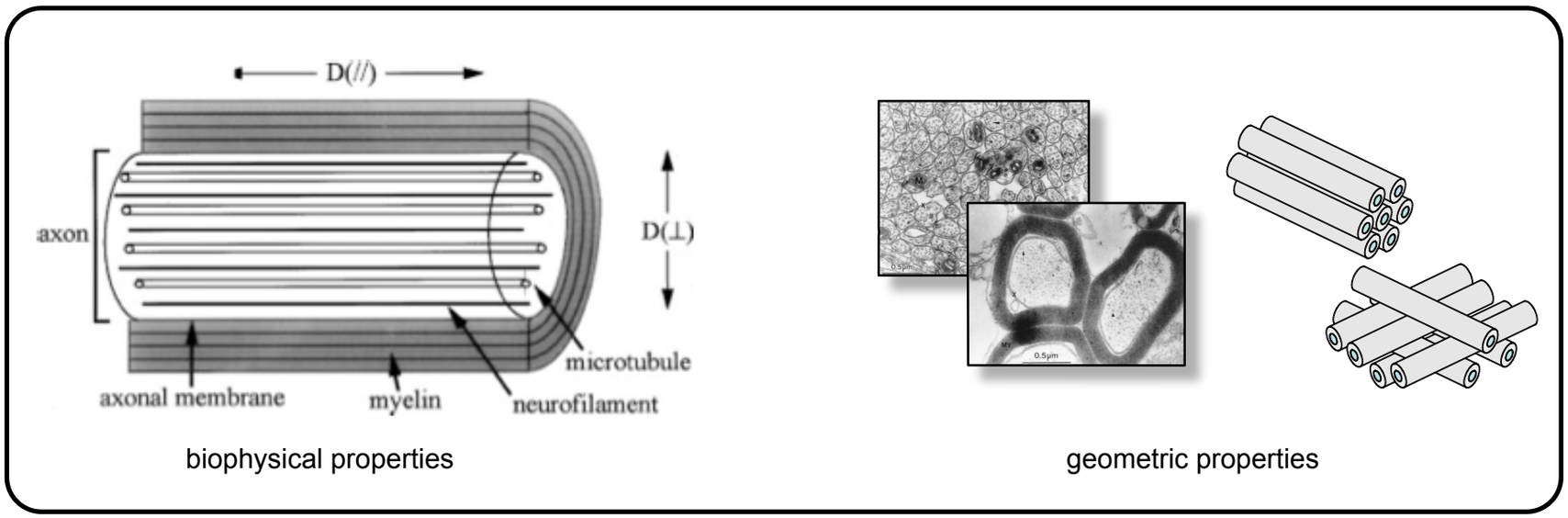
$$FA = \sqrt{\frac{3\sum_{i=1}^{3}(\lambda_i - \overline{\lambda})^2}{2\sum_{i=1}^{3}\lambda_i^2}}, \qquad FA \text{ in } [0,1]$$

$$MD = \frac{D_{xx} + D_{yy} + D_{zz}}{3} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Quantitative Diffusion Maps

FA

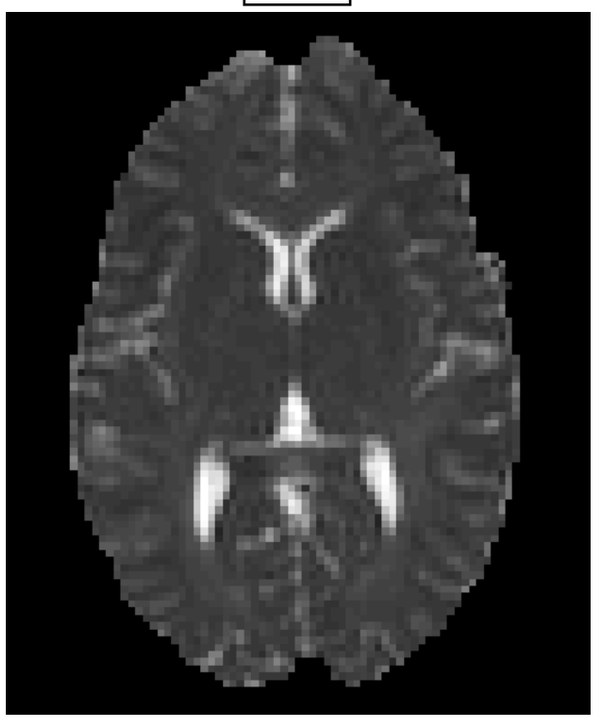




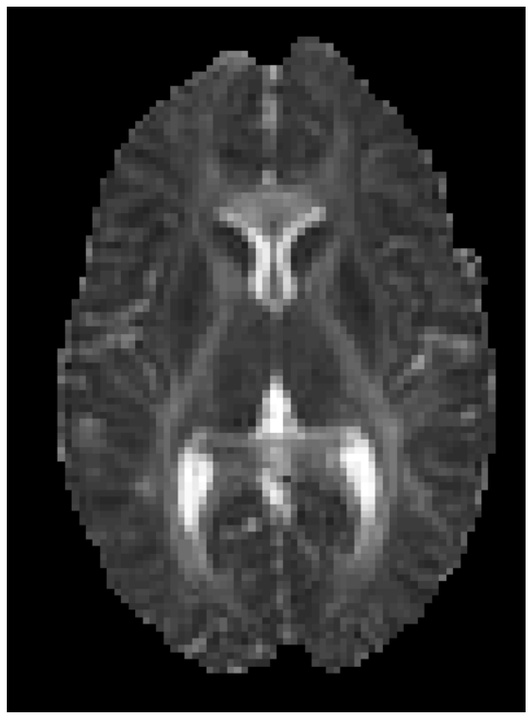
biophysical properties

geometric properties

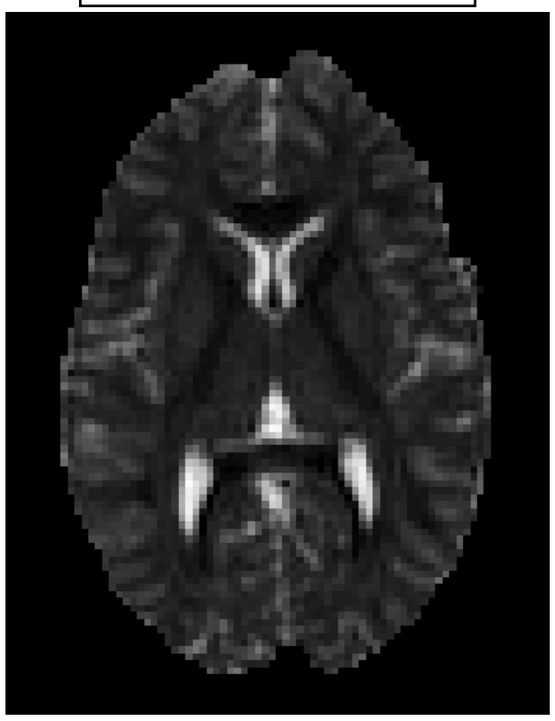
MD



Longitudinal ADC
(λ_1)

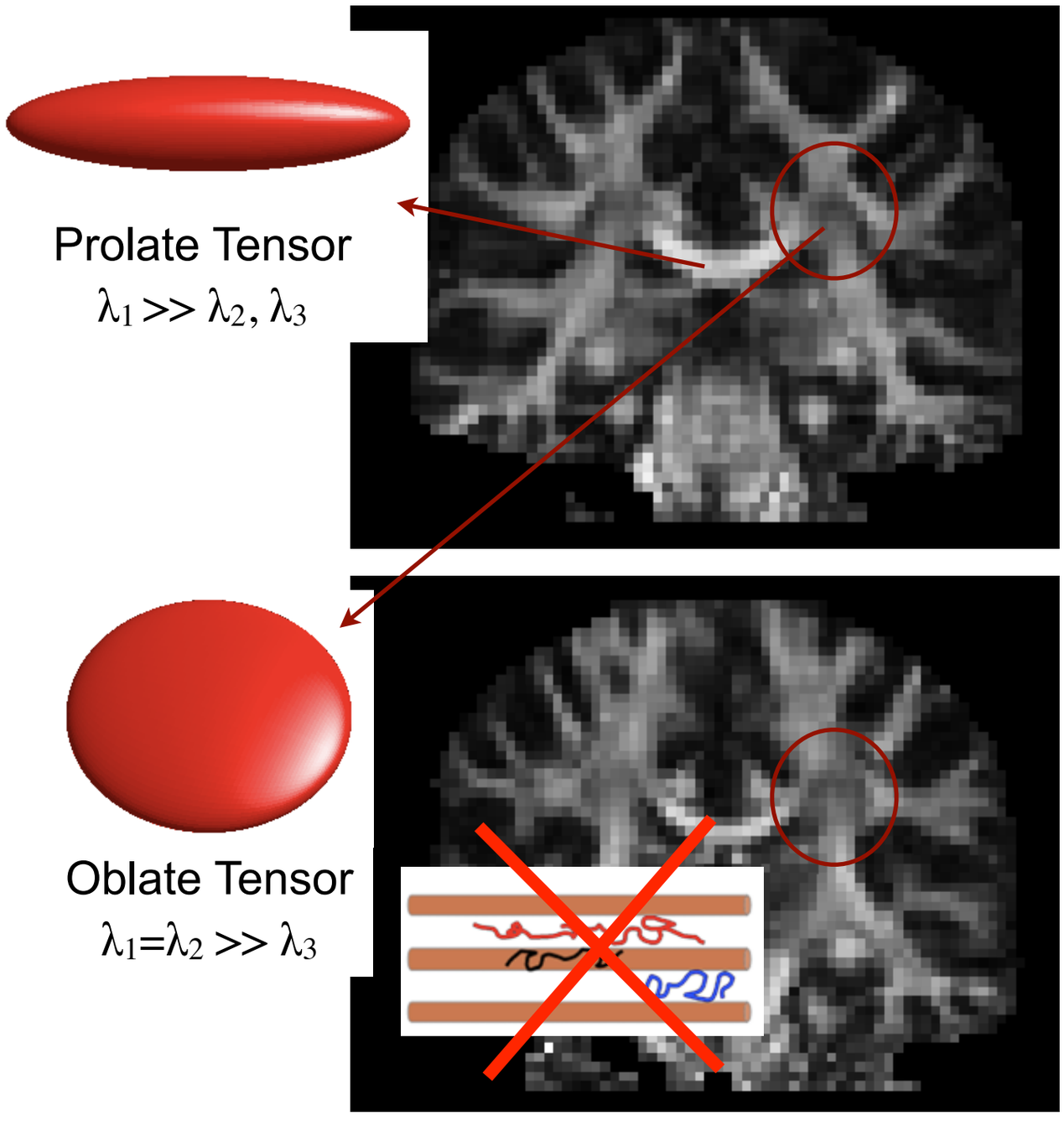


Transverse ADC
($\lambda_2+\lambda_3$)/2



Tensor and FA in Crossing Regions

- In voxels containing two crossing bundles, the FA is artificially low and the tensor ellipsoid is pancake-shaped (oblate, planar tensor).
- FA changes difficult to interpret: Changes in one or both crossing bundles?



- The DTI model is an oversimplification of reality

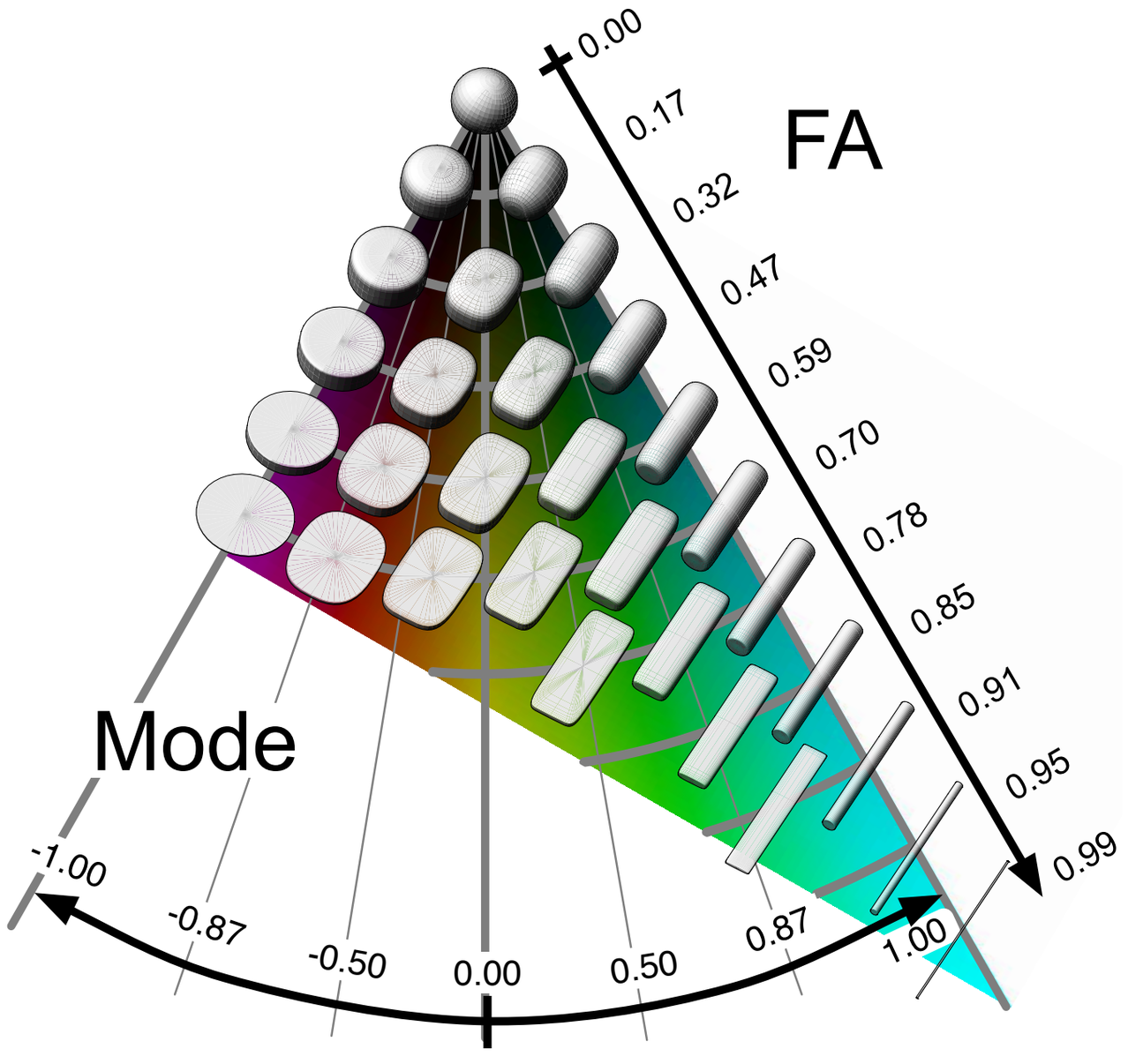
Quantitative Diffusion Maps: Tensor Mode

In voxels with two crossing fibres, the tensor ellipsoid tends to have a planar shape.

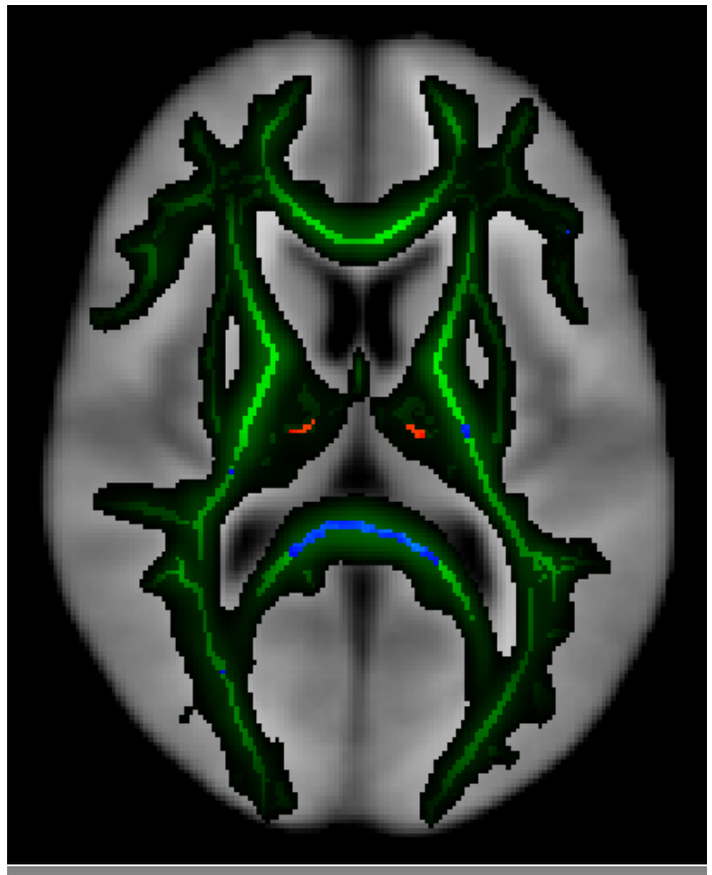
Mode

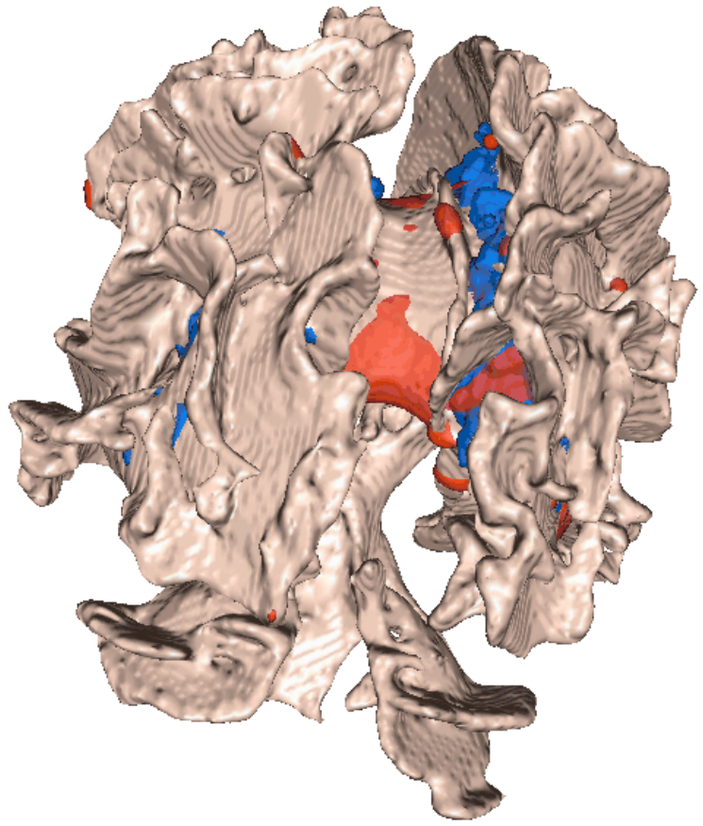
- Quantifies whether the tensor has a tubular (mode=1) (one strong fibre) or planar shape (mode=-1) (two strong fibres)?
- Estimated from the tensor eigenvalues.

- Combined with the FA can help us understand better the underlying structure, especially where ambiguities exist.



TBSS : Tract-Based Spatial Statisics



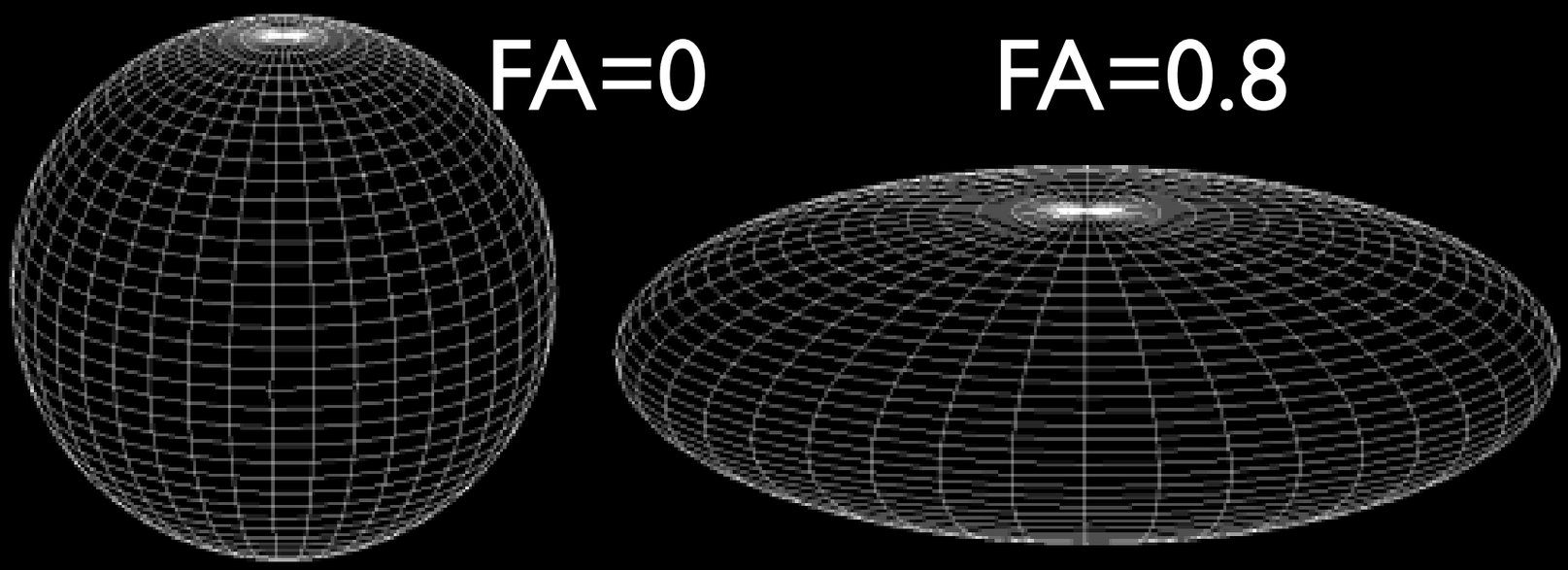


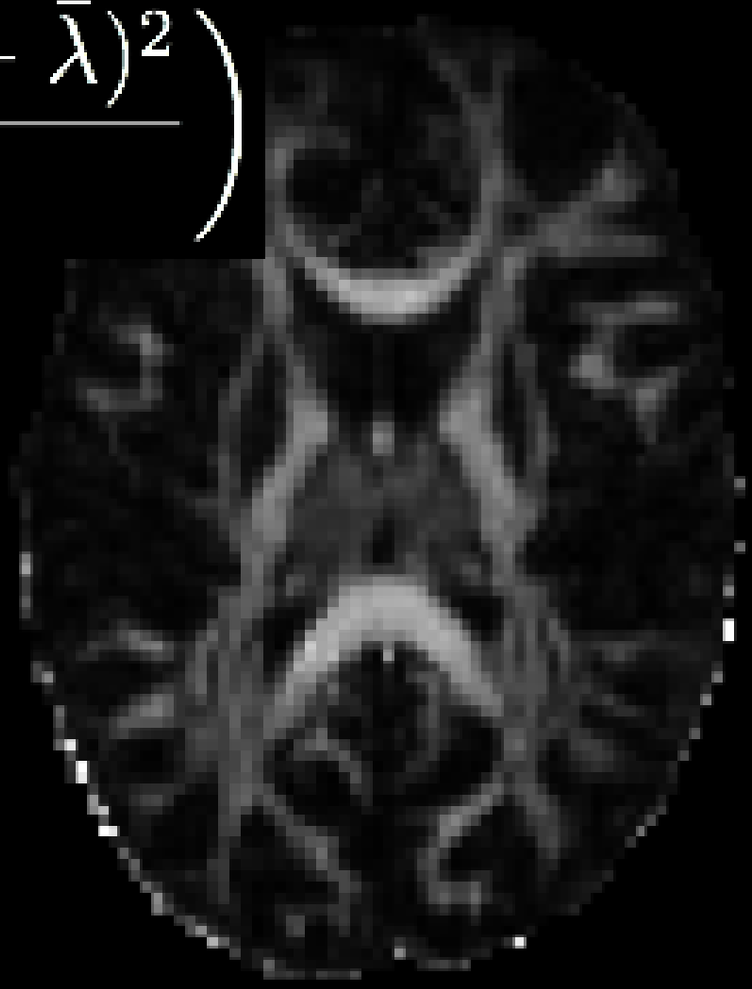
- Need: robust “voxelwise” cross-subject stats on DTI
- Problem: alignment issues confound valid local stats
- TBSS: solve alignment using alignment-invariant features:
- Compare FA taken from tract centres (via skeletonisation)

Tensor-derived parameters: Fractional Anisotropy

- FA encodes how strongly directional diffusion is
  - (derived from diffusion tensor eigenvalues)
- Hence good marker for WM integrity
  - i.e., good marker for disease, development, etc.

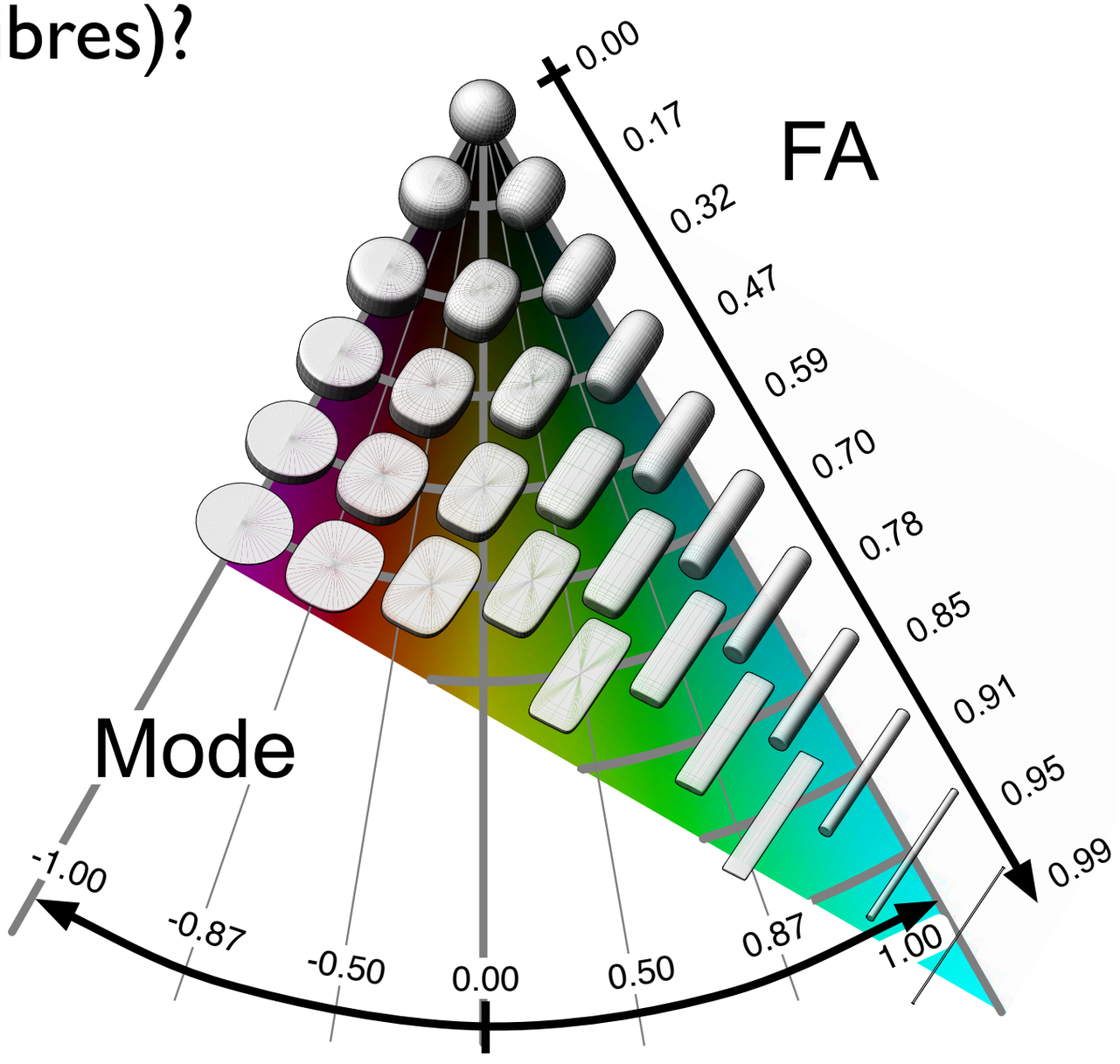
$$\mathrm{FA} = \sqrt{\frac{3}{2}\left(\frac{(\lambda_1 - \bar{\lambda})^2 + (\lambda_2 - \bar{\lambda})^2 + (\lambda_3 - \bar{\lambda})^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}\right)}$$





Orthogonal Tensor Invariants (Kindlmann, TMI 2007)

- Nice to have 3 orthogonal (independent) tensor-derived measures: MD, FA & "Mode"
- Mode: is the tensor tubular (one strong fibre) or flat-cylindrical (two strong fibres)?

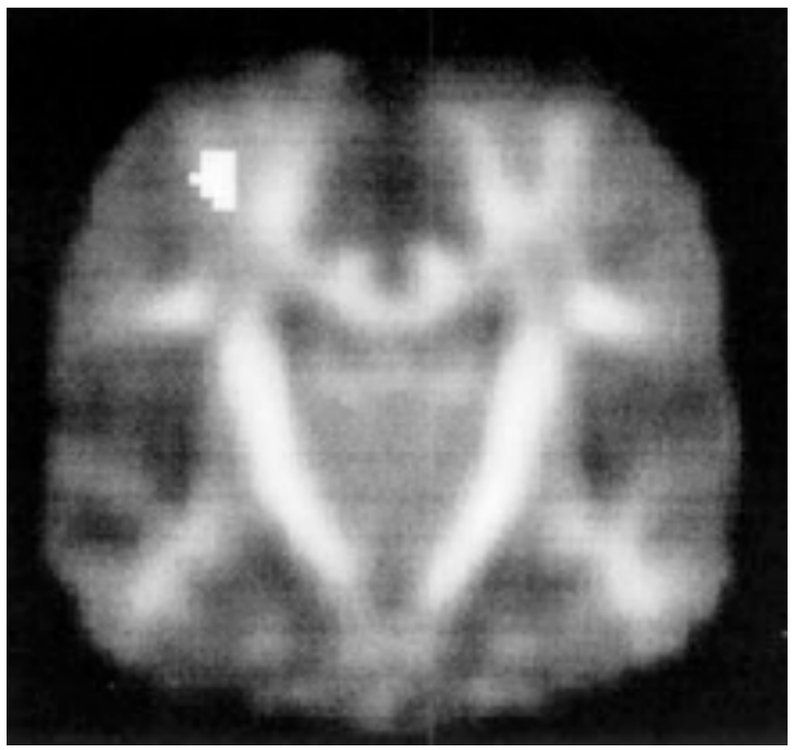


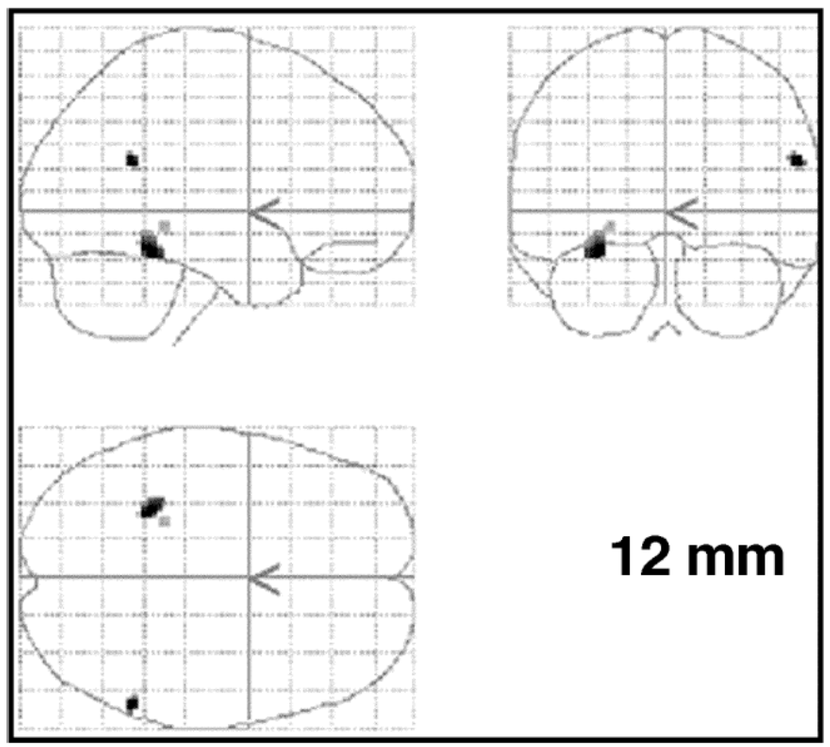
VBM-style Analysis of FA

- VBM [Ashburner 2000, Good 2001]
- Align all subjects' data to standard space
- Segment -> grey matter segmentation
- Smooth GM
- Do voxelwise stats (e.g. controls-patients)

- VBM on FA [Rugg-Gunn 2001, Büchel 2004, Simon 2005]
- Like VBM but no segmentation needed

Büchel 2004



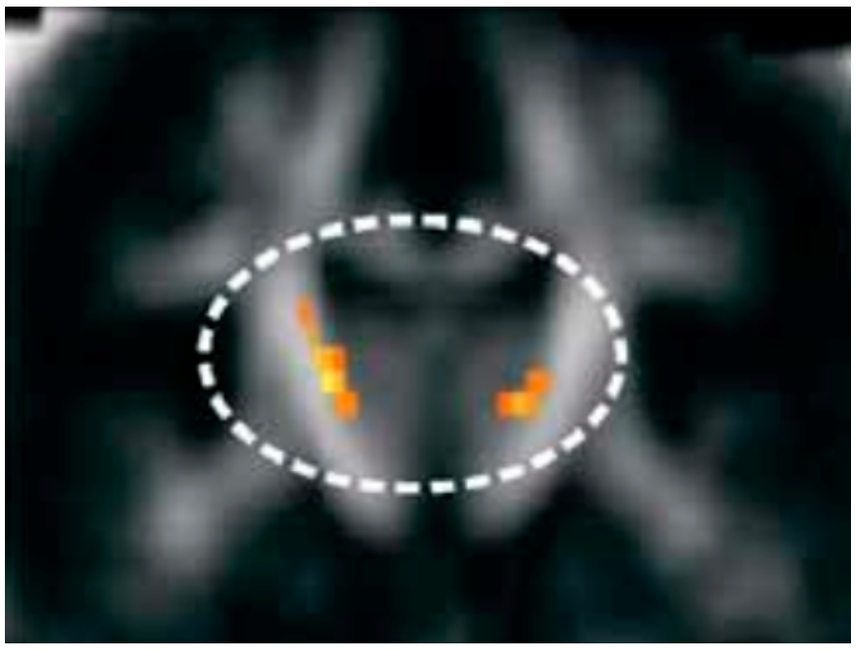
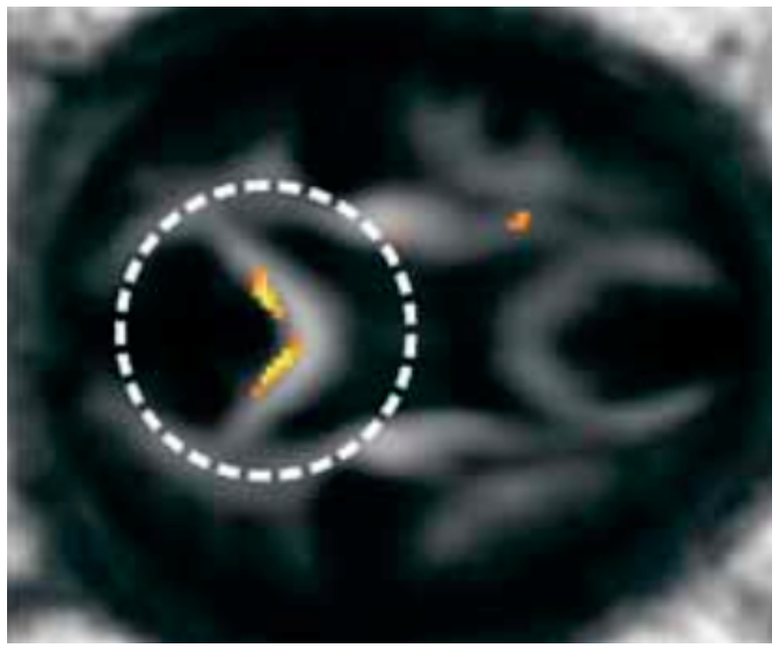
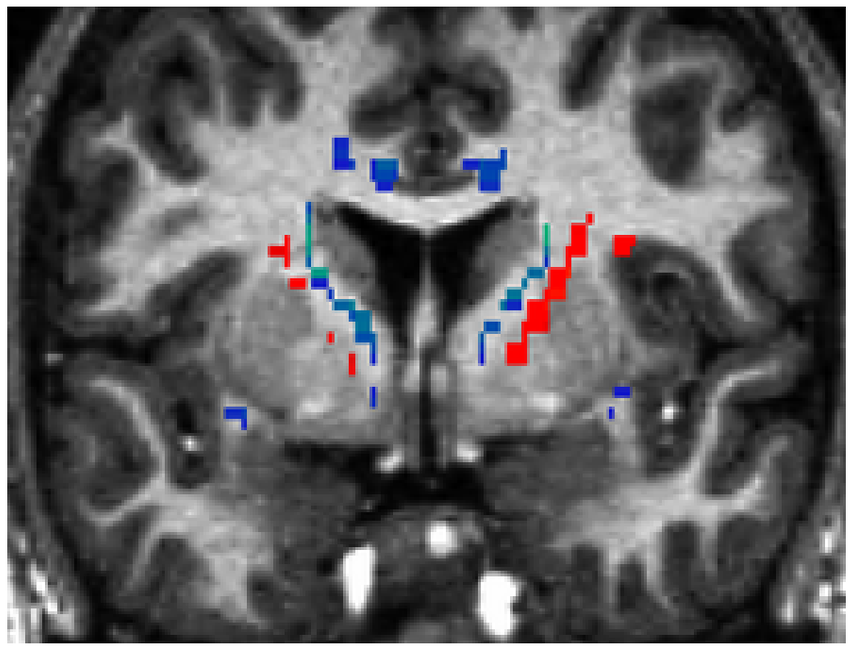


Jones 2005

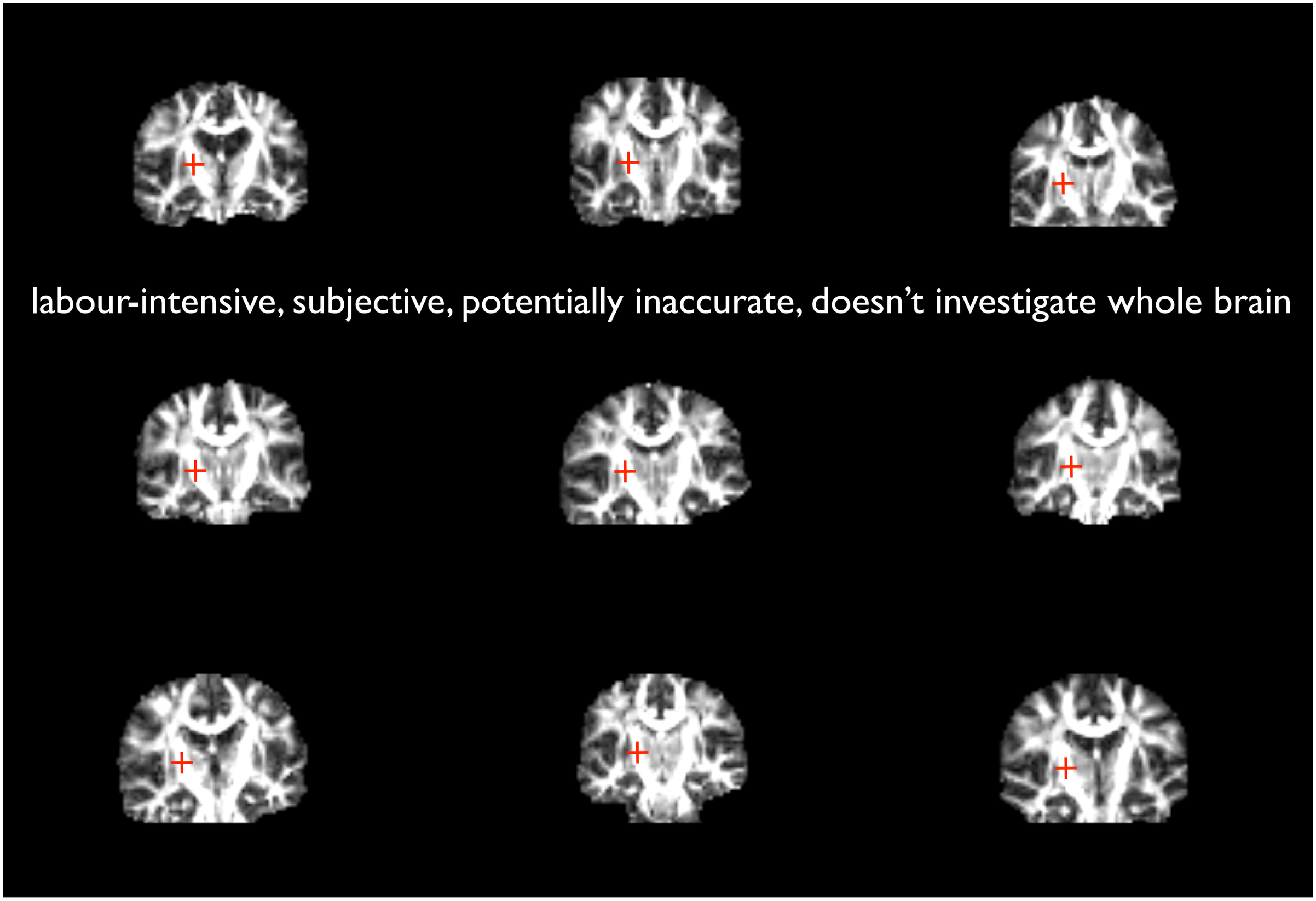
VBM-style Analysis of FA

- Strengths
  - Fully automated & quick
  - Investigates whole brain

- Problems [Bookstein 2001, Davatzikos 2004, Jones 2005]
  - Alignment difficult; smallest systematic shifts between groups can be incorrectly interpreted as FA change
  - Needs smoothing to help with registration problems
  - No objective way to choose smoothing extent

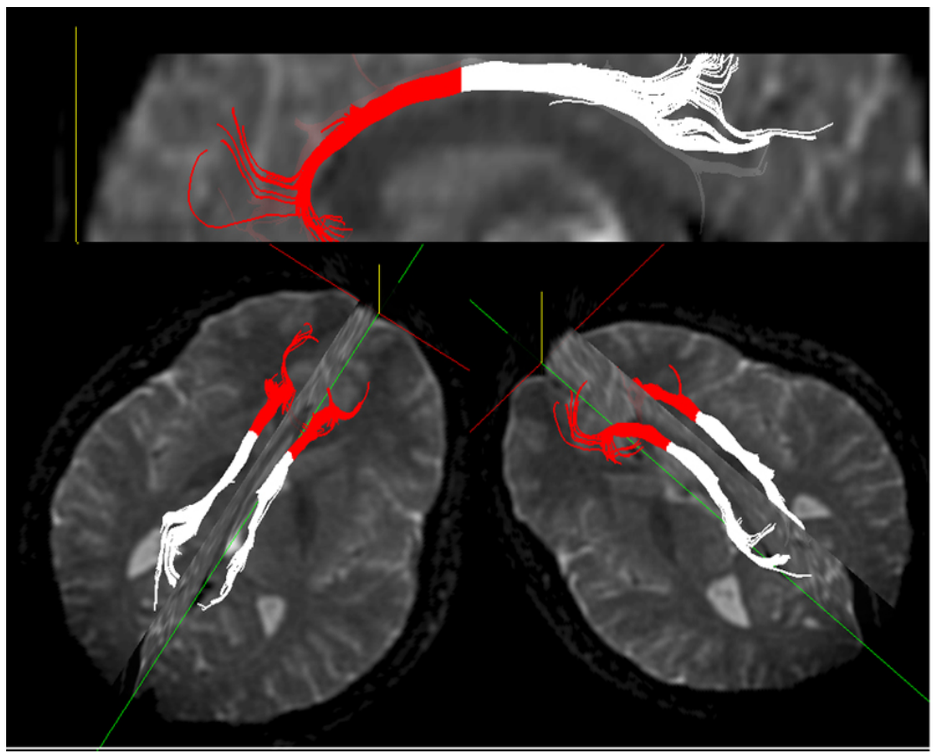




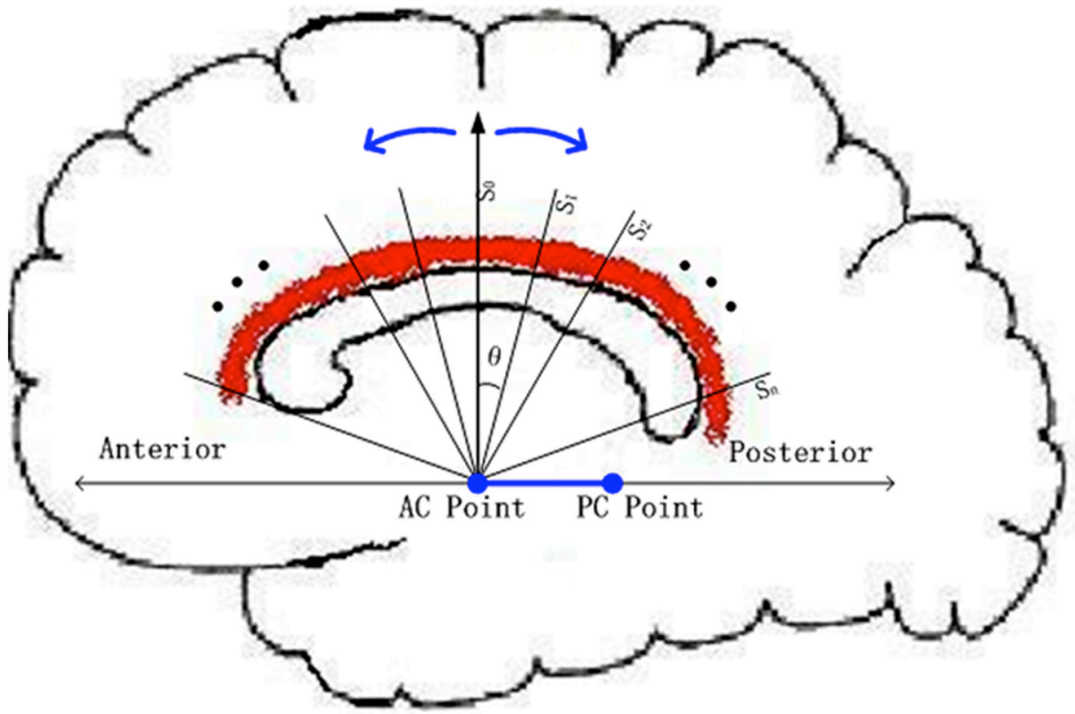
Hand-placed voxel/ROI-based FA Comparison



labour-intensive, subjective, potentially inaccurate, doesn't investigate whole brain

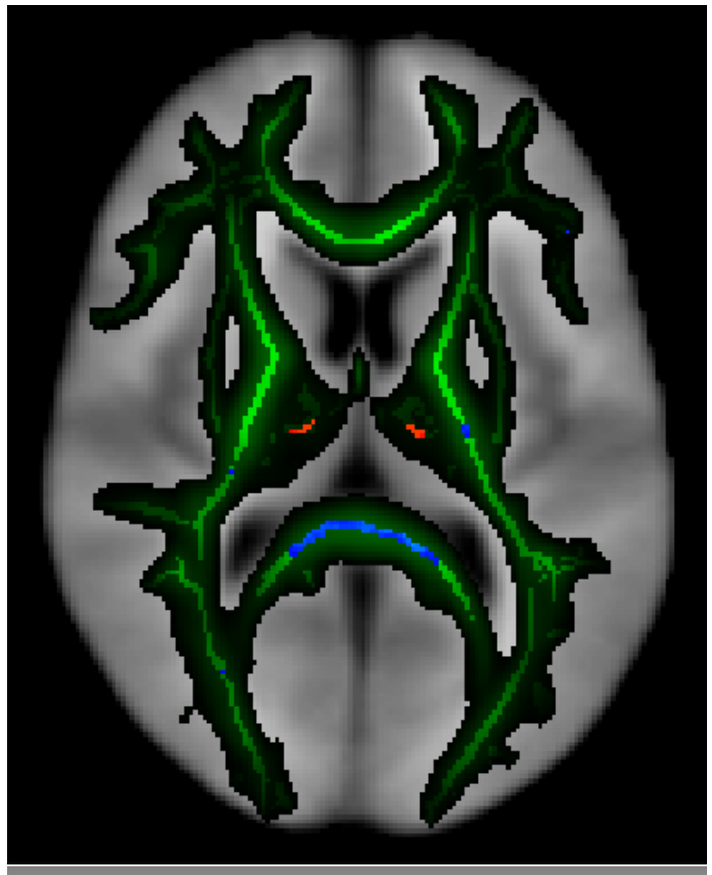
Tractography-Based FA Comparison

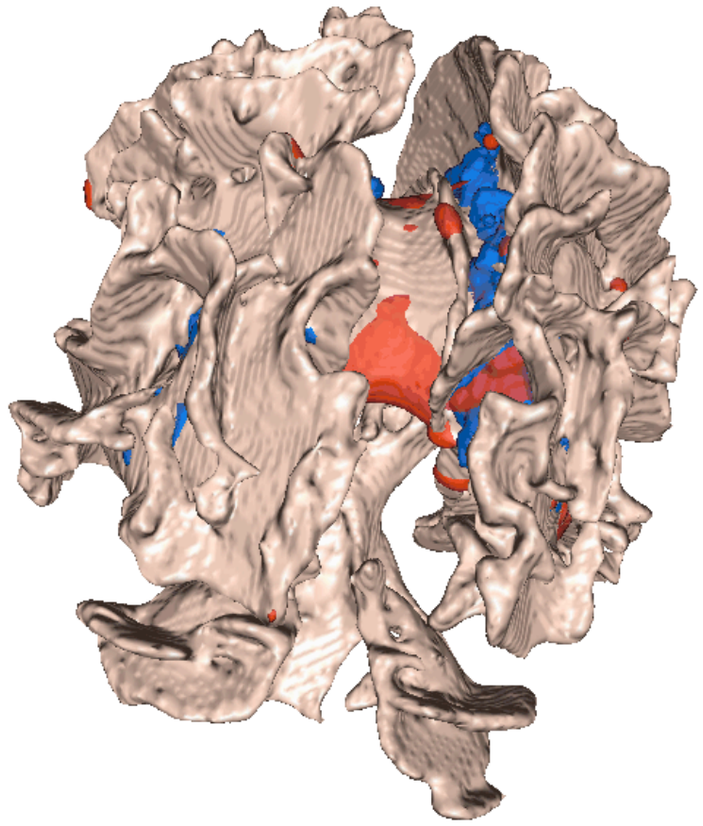




- Method [Gong 2005, Corouge 2006]
  - Define a given tract in all subjects
  - Parameterise FA along tract
  - Compare between subjects
- Strength: correspondence issue hopefully resolved
- Problems
  - Currently requires manual intervention to specify tract
  - Hence doesn't investigate whole brain
  - Projection of FA onto tract needs careful thought

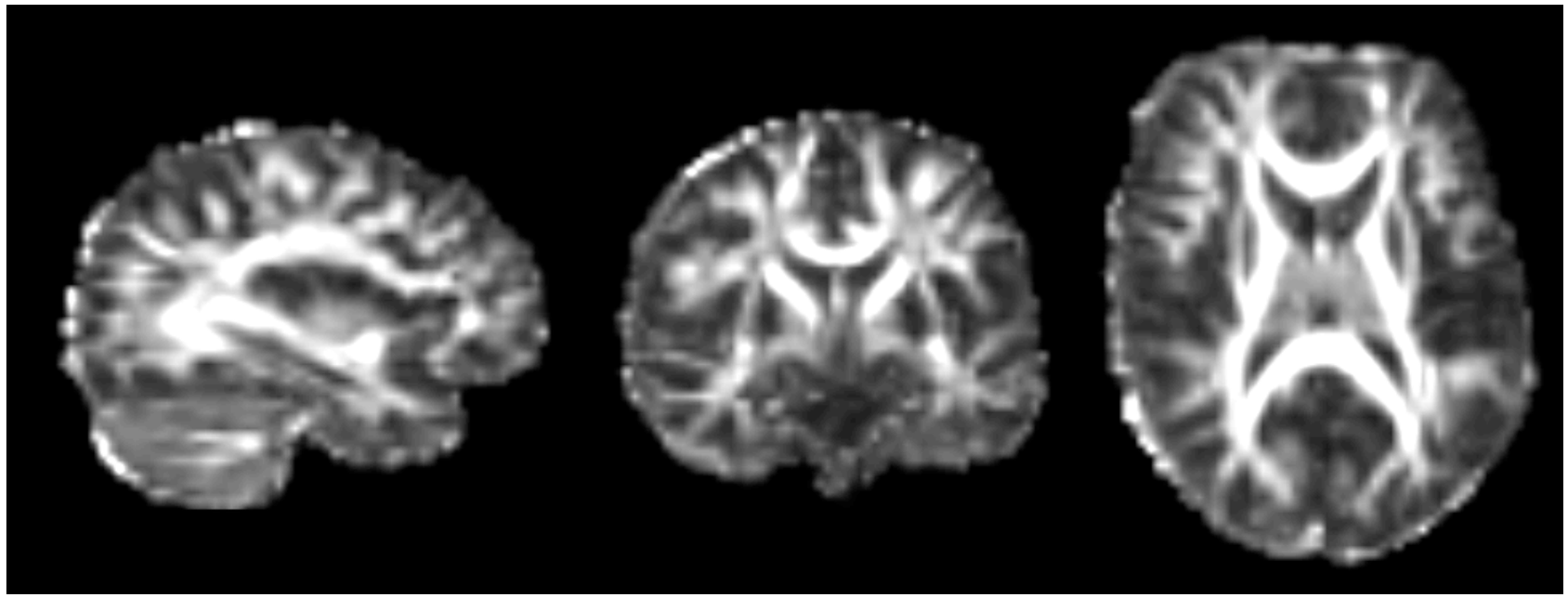
TBSS : Tract-Based Spatial Statisics



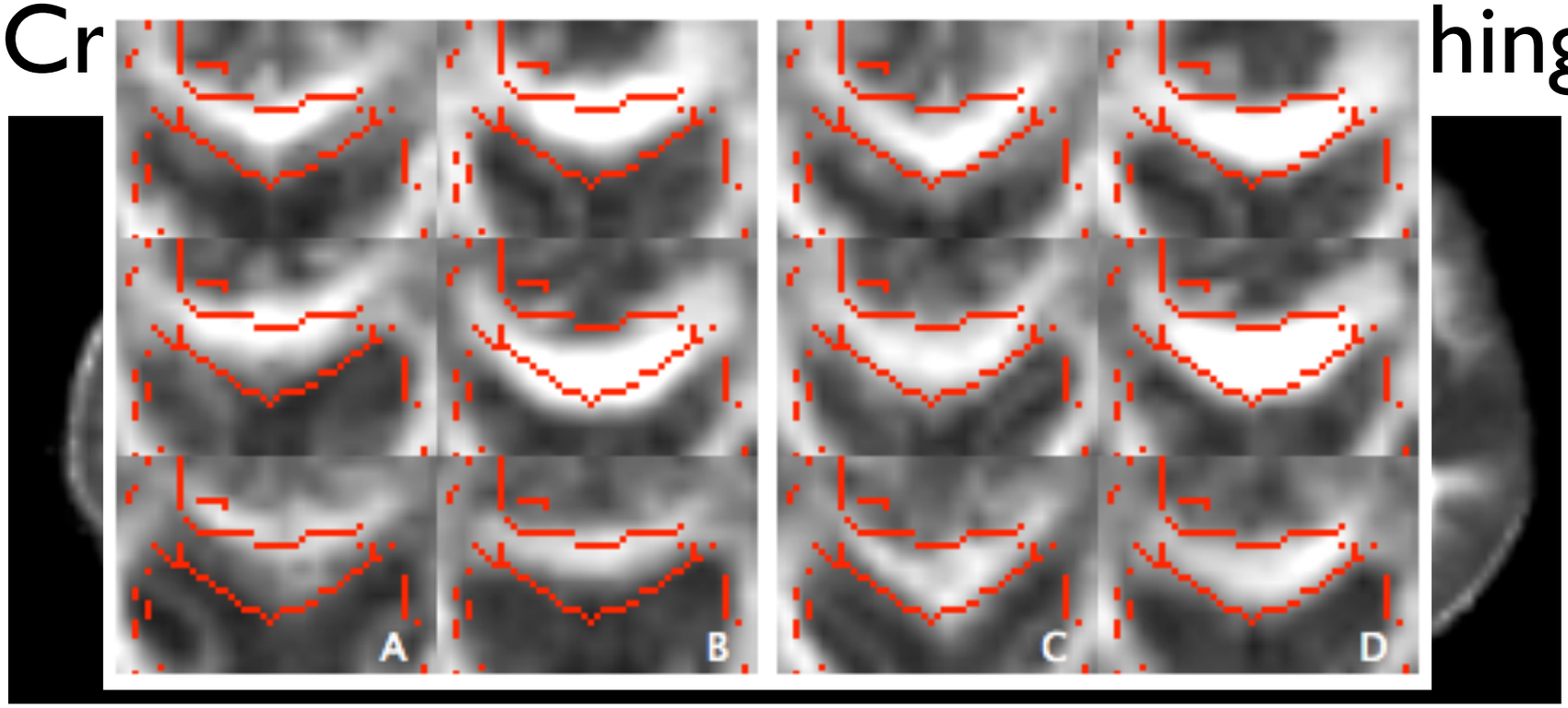


- Need: robust “voxelwise” cross-subject stats on DTI
- Problem: alignment issues confound valid local stats
- TBSS: solve alignment using alignment-invariant features:
- Compare FA taken from tract centres (via skeletonisation)

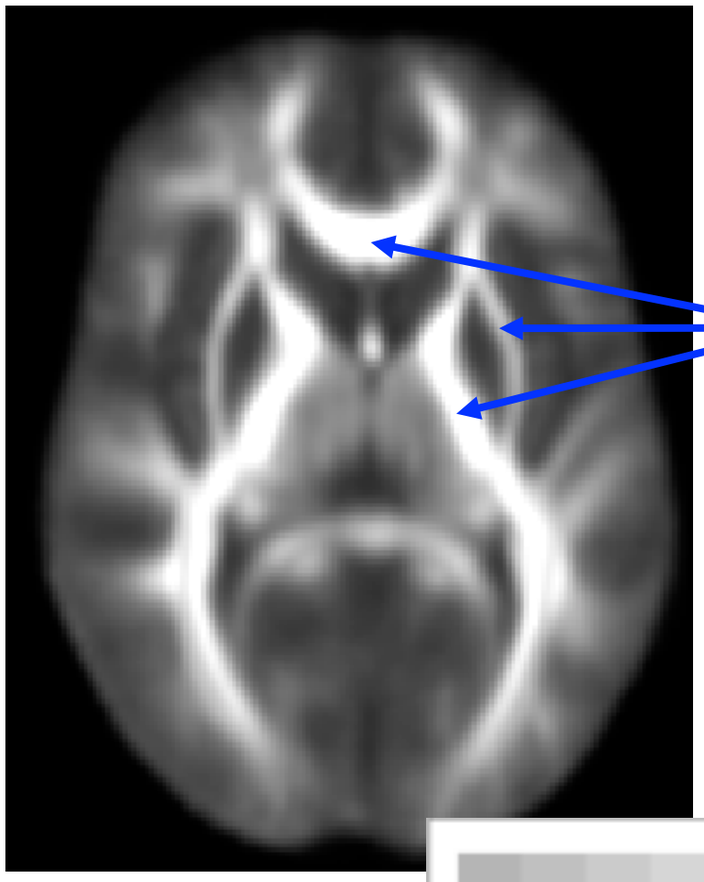
1. Use medium-DoF nonlinear reg to pre-align all subjects' FA
(nonlinear reg: FNIRT)

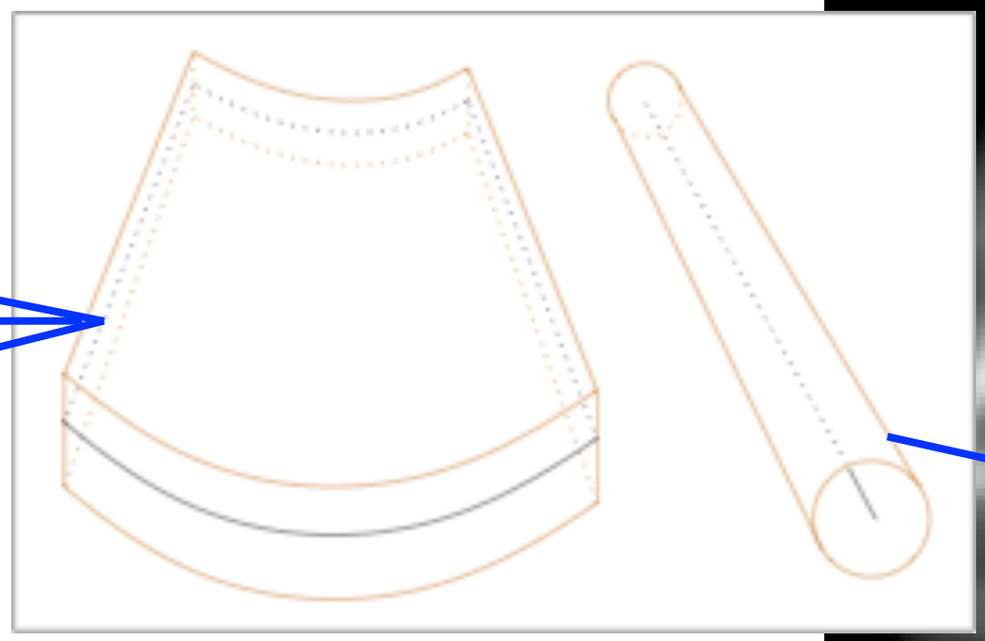


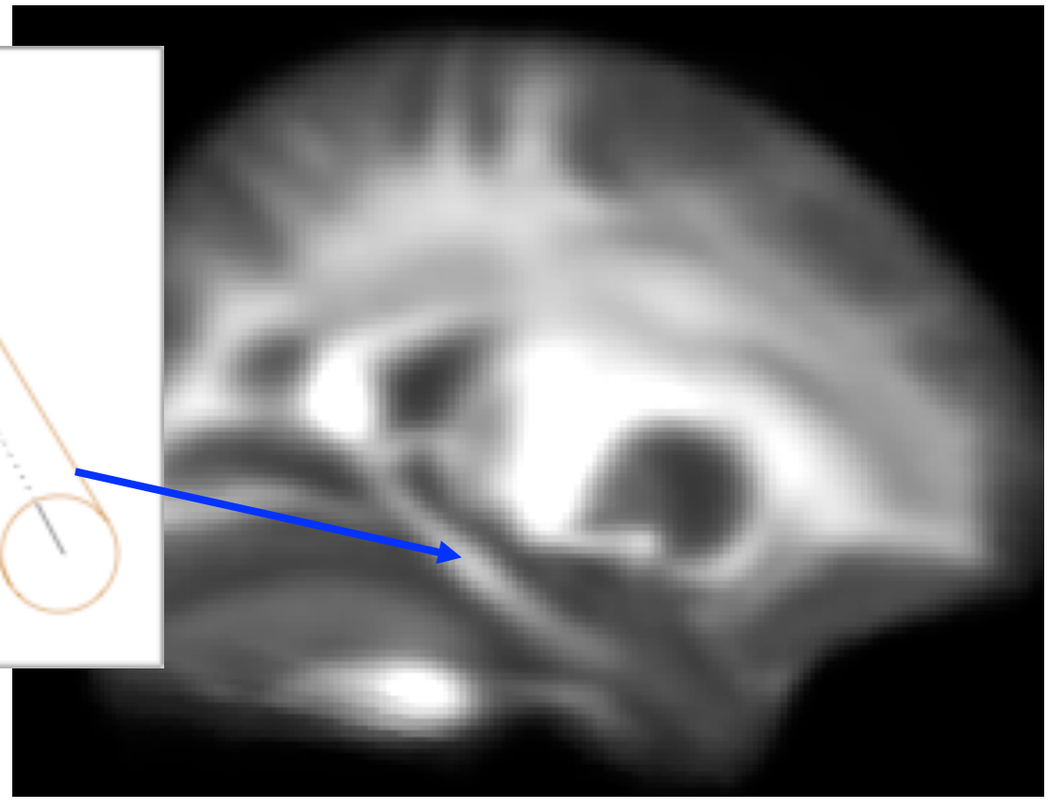
2. Cr hing)

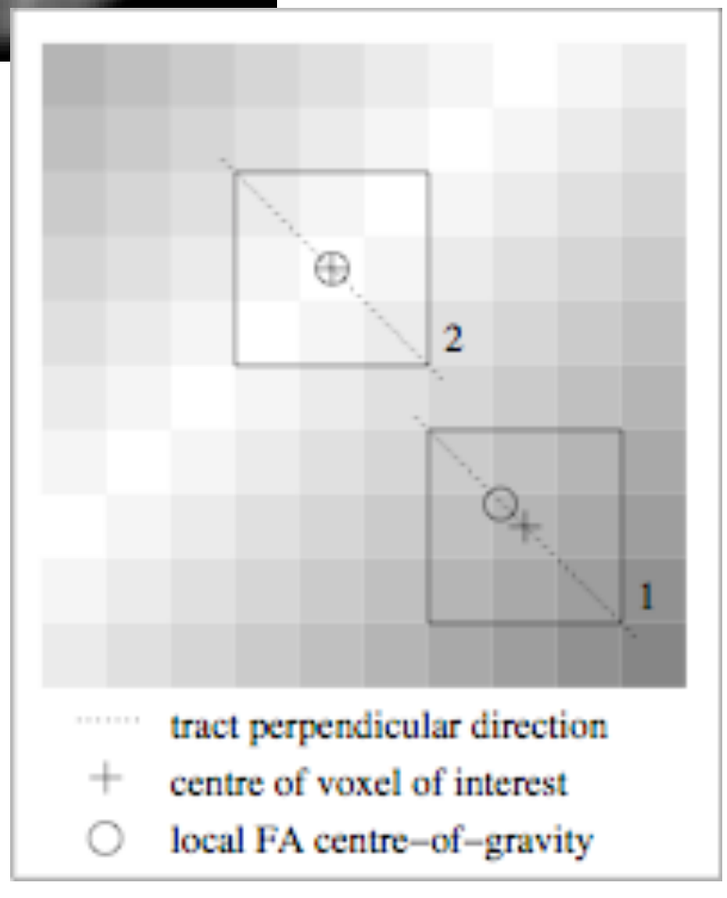


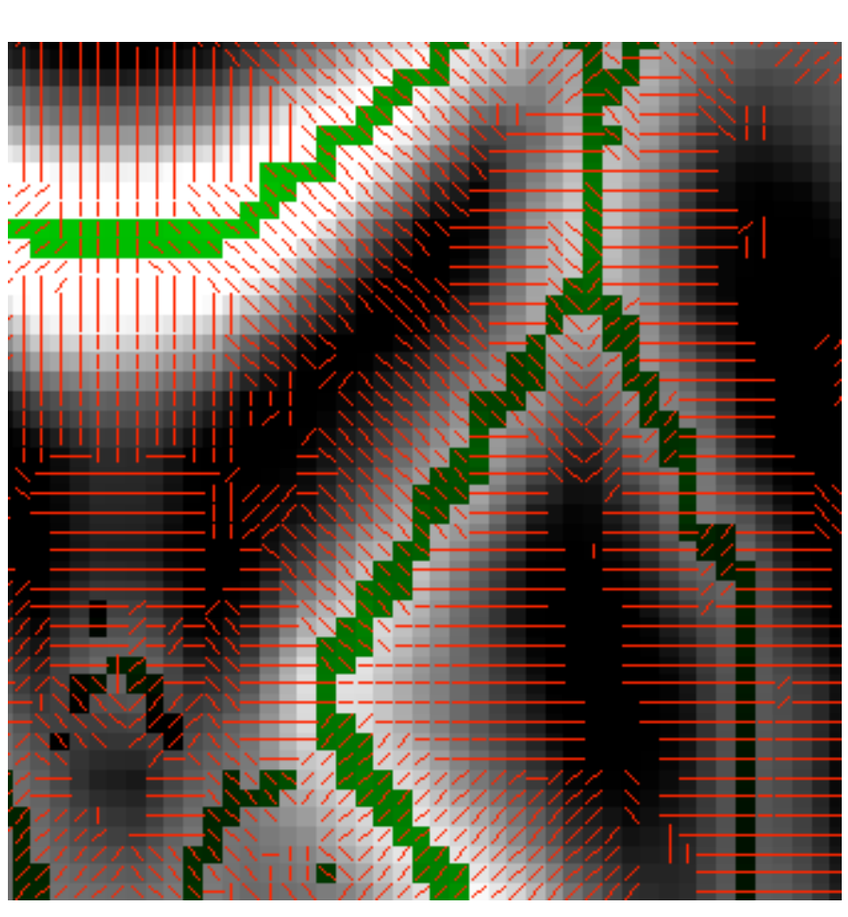
2. “Skeletonise” Mean FA





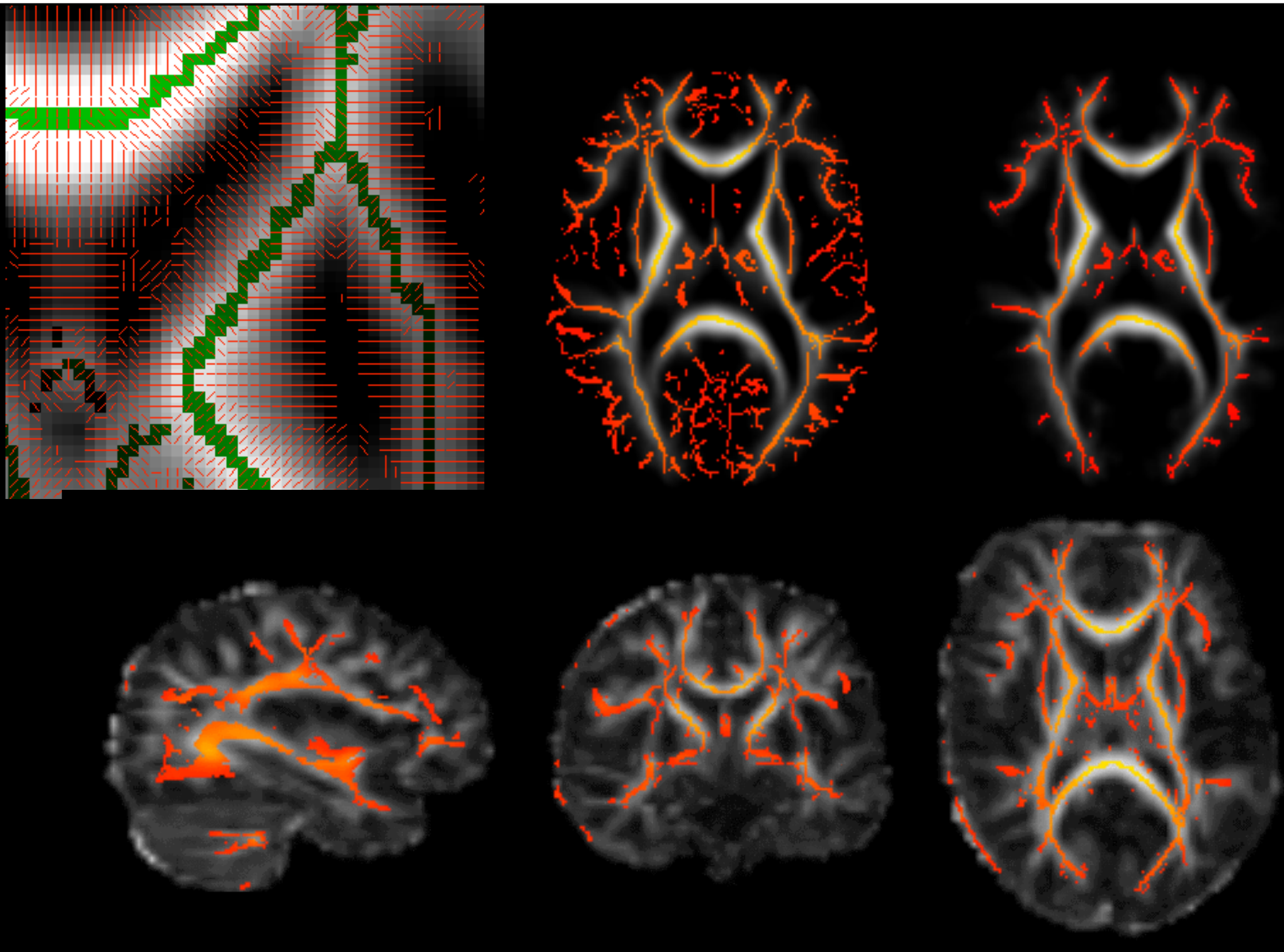






3. Threshold Mean FA Skeleton

giving "objective" tract map



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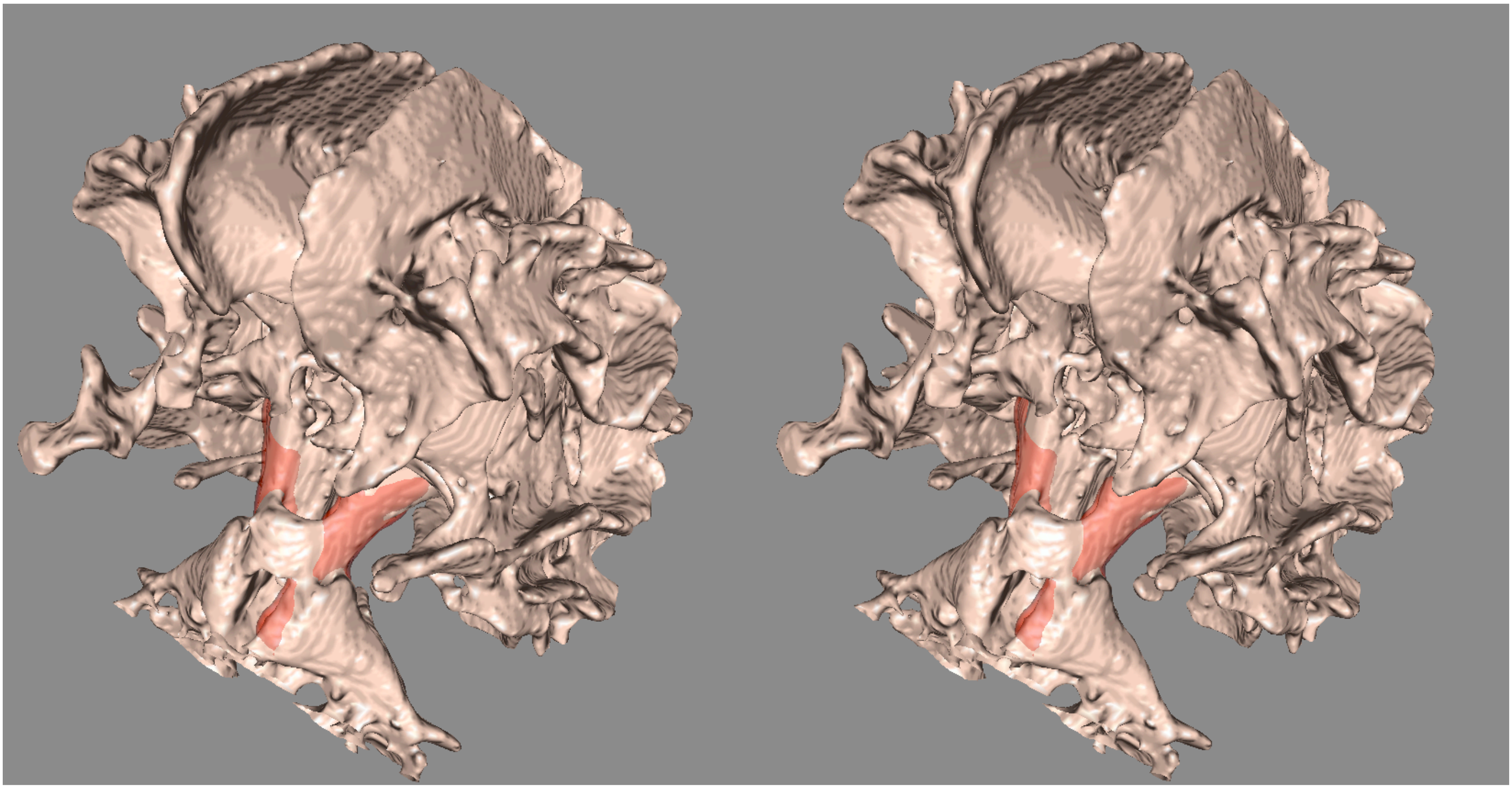
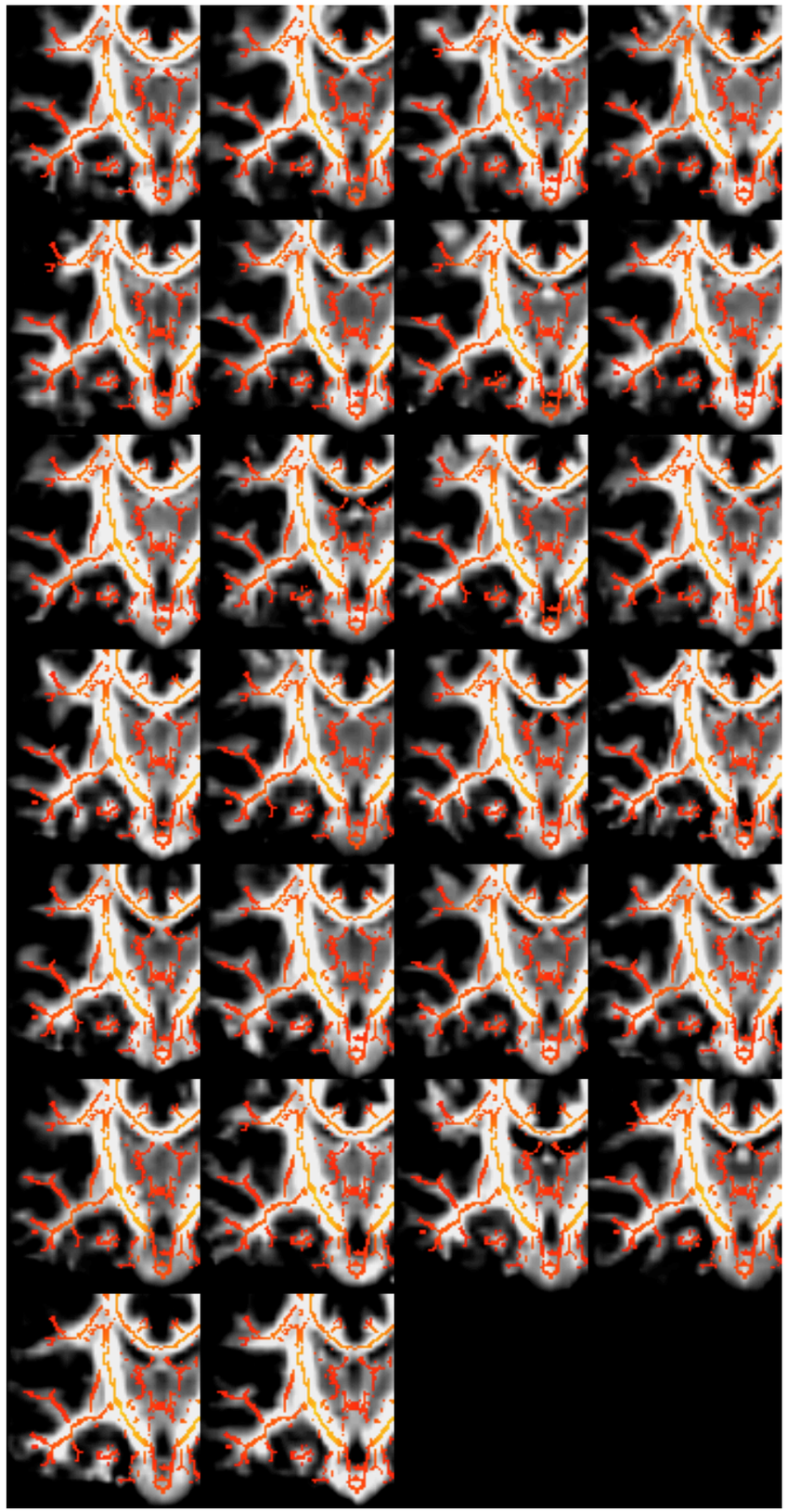
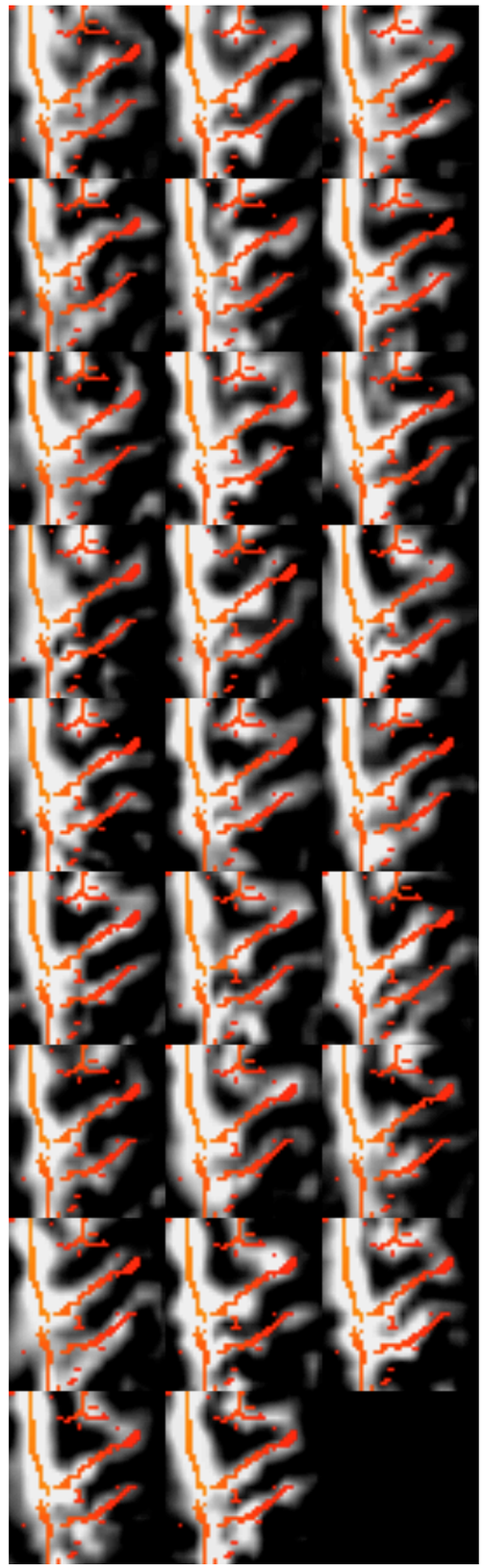
giving "objective" tract map



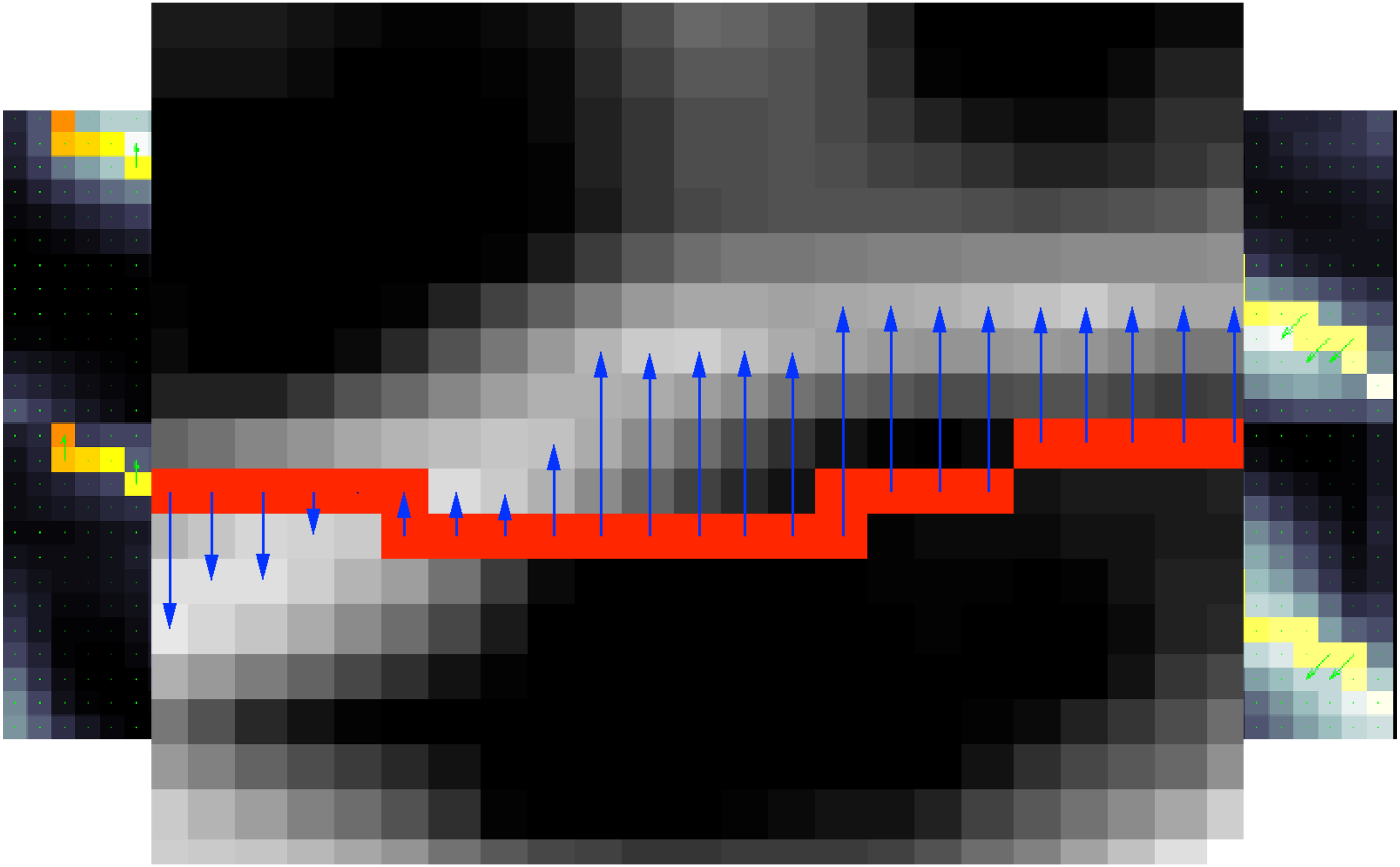
3. Threshold Mean FA Skeleton

giving "objective" tract map

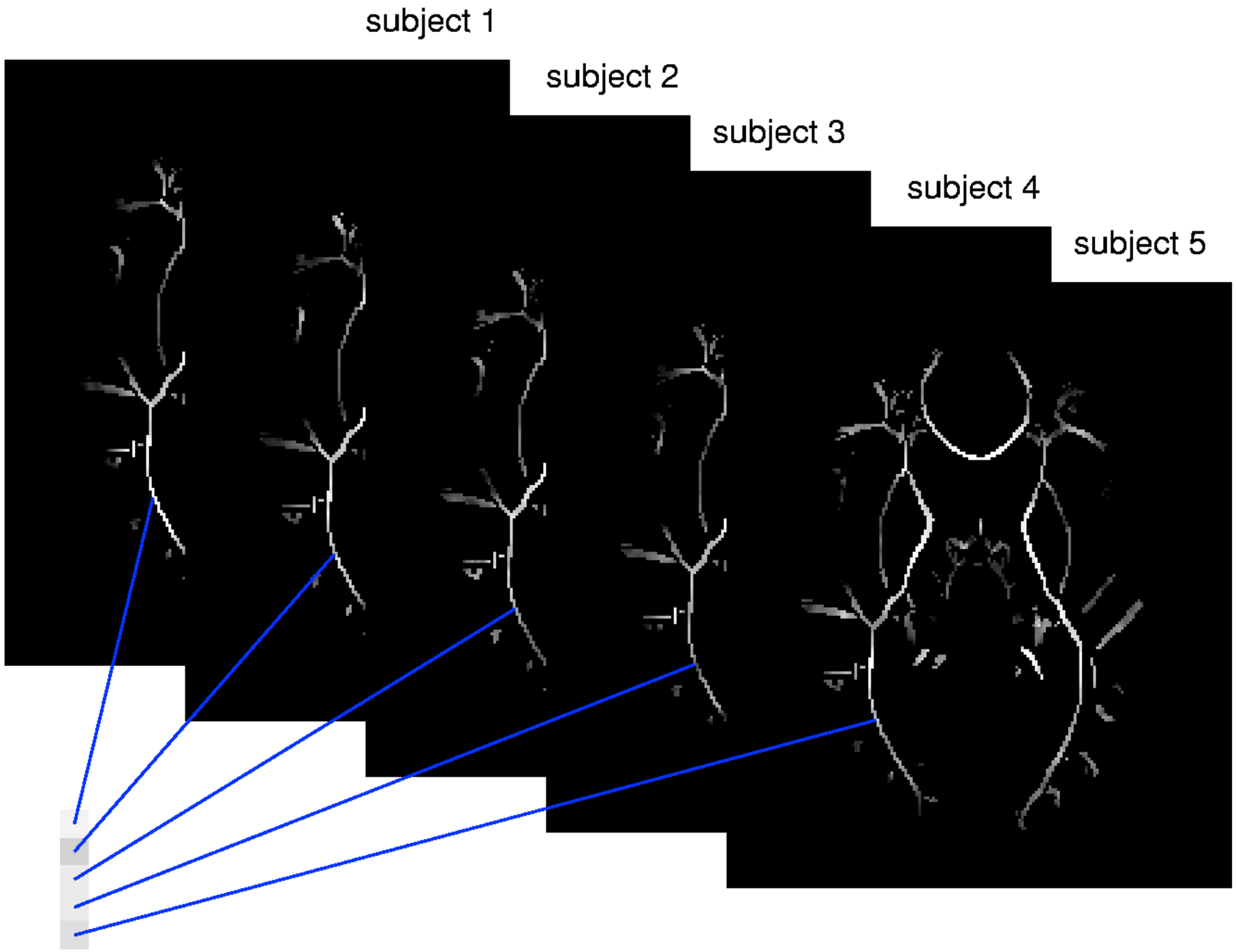




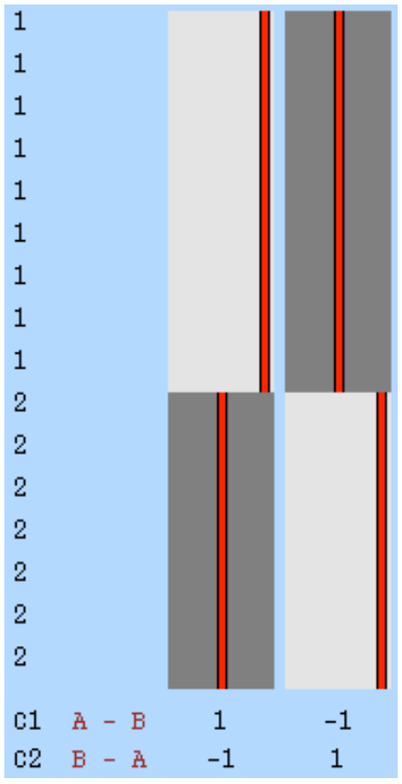
4. For each subject's warped FA, fill each point on the mean-space skeleton with nearest maximum FA value (i.e., from the centre of the subject's nearby tract)

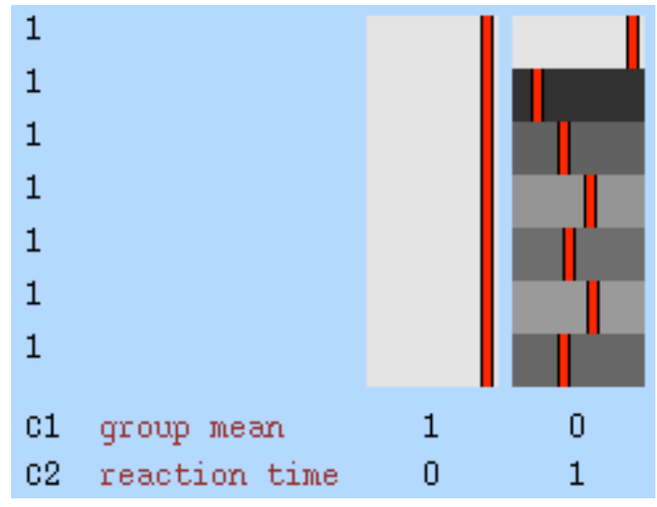


5. Do cross-subject voxelwise stats on skeleton-projected FA
6. Threshold, (e.g., permutation testing, including multiple comparison correction)



one skeleton voxel's data vector (to be fed into GLM)

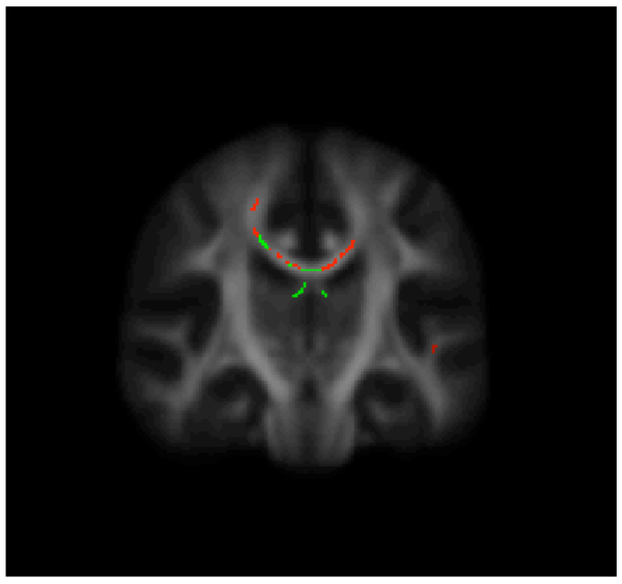


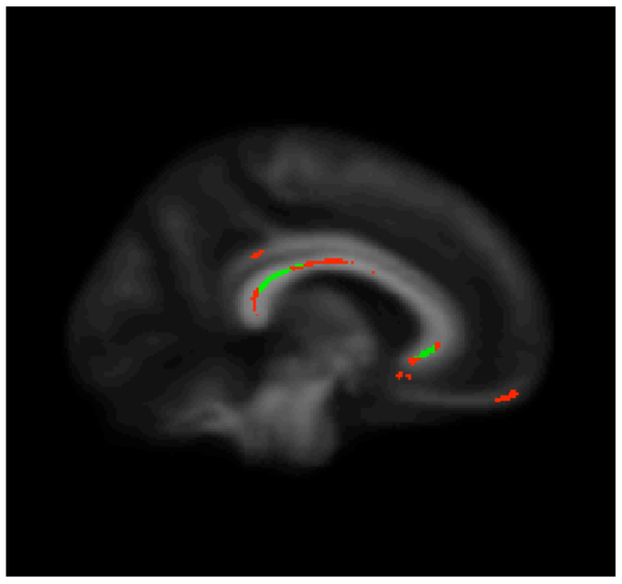


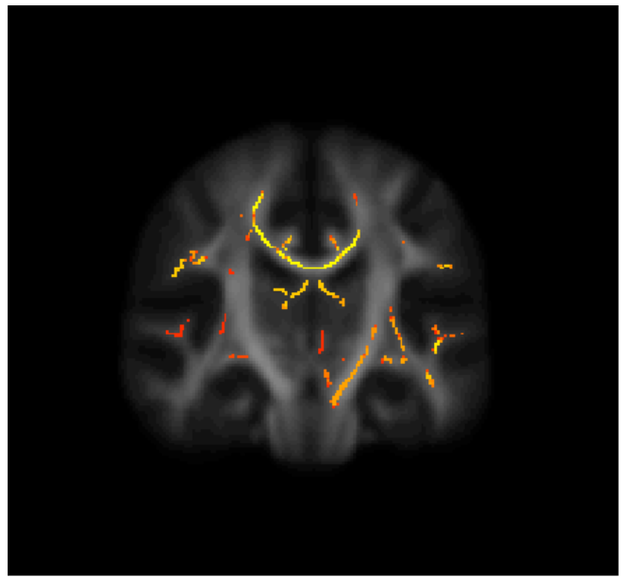
TFCE for TBS

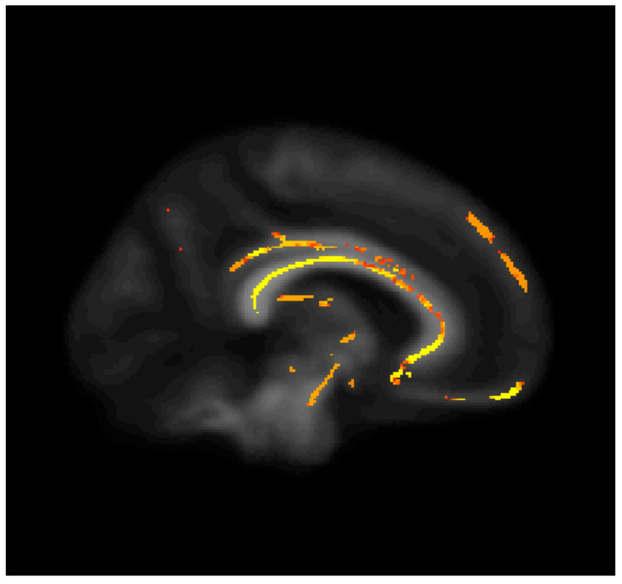
controls > schizophrenics

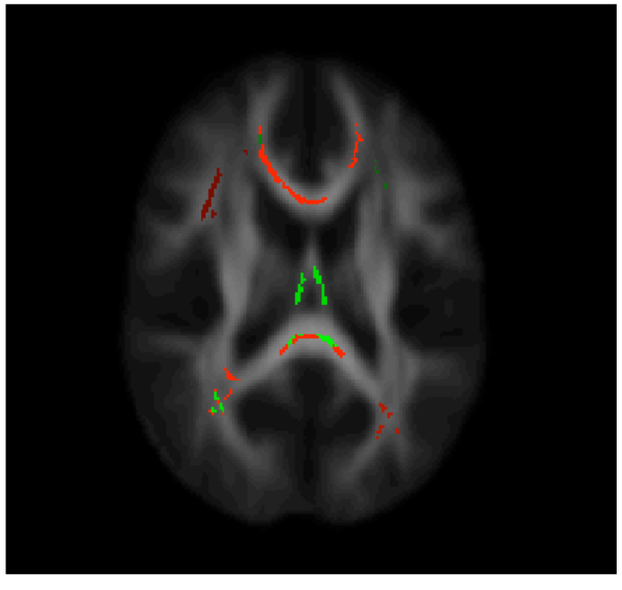
p<0.05 corrected for multiple comparisons across space, using randomise



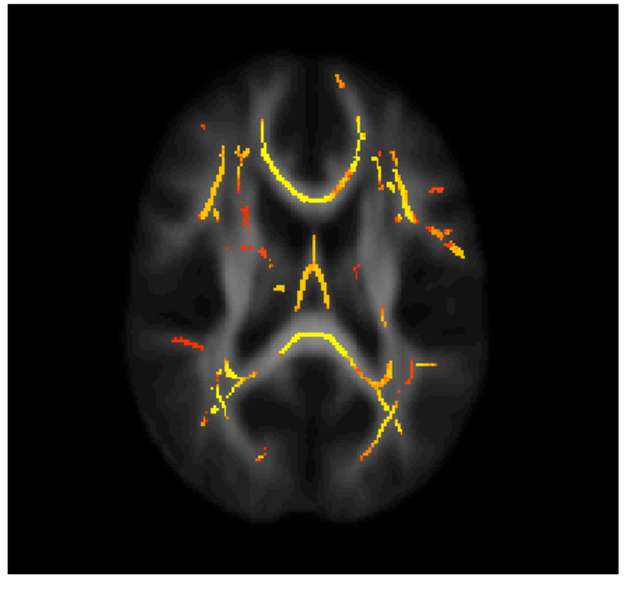








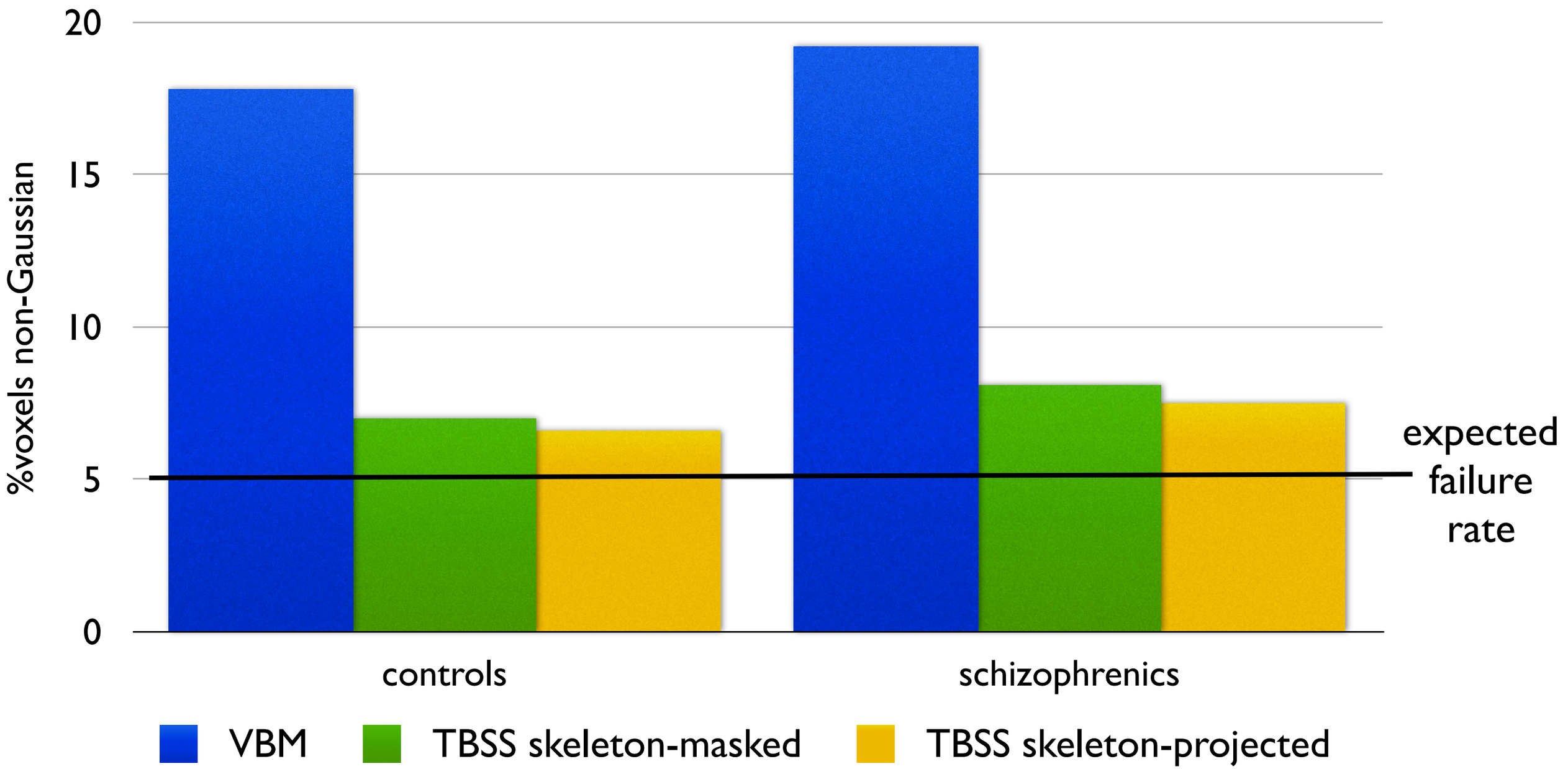
cluster-based:
cluster-forming
threshold =
2 or 3



TFCE

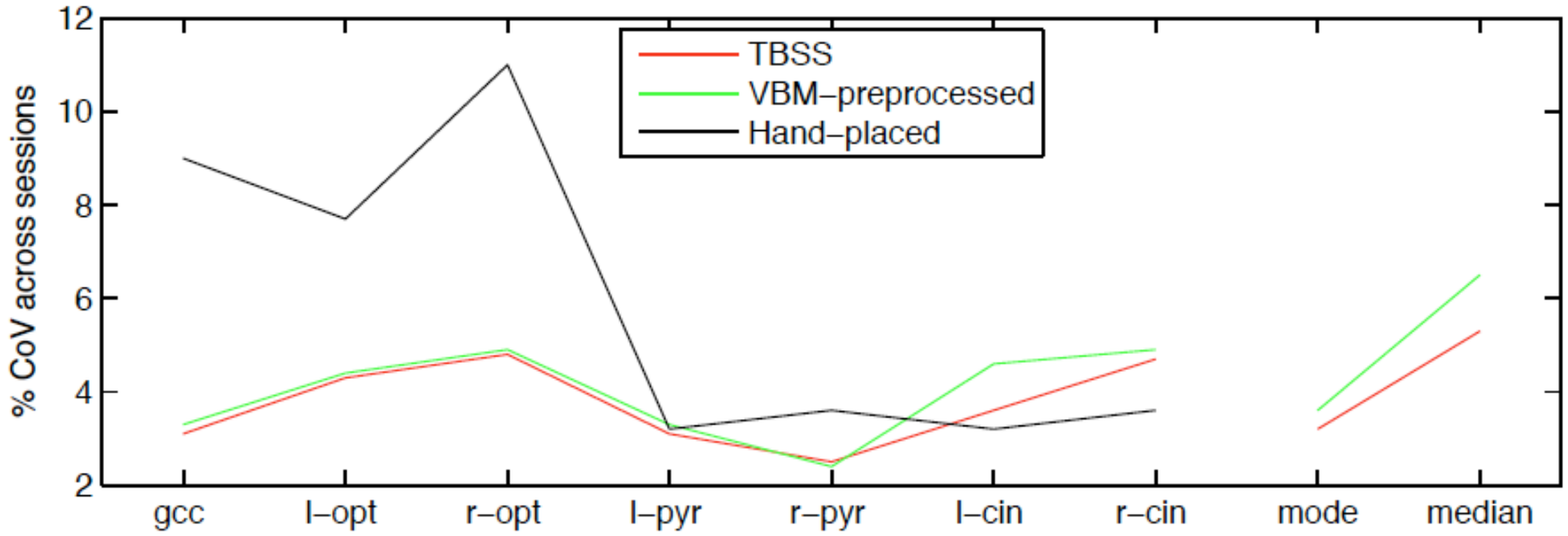
Testing for Gaussianity

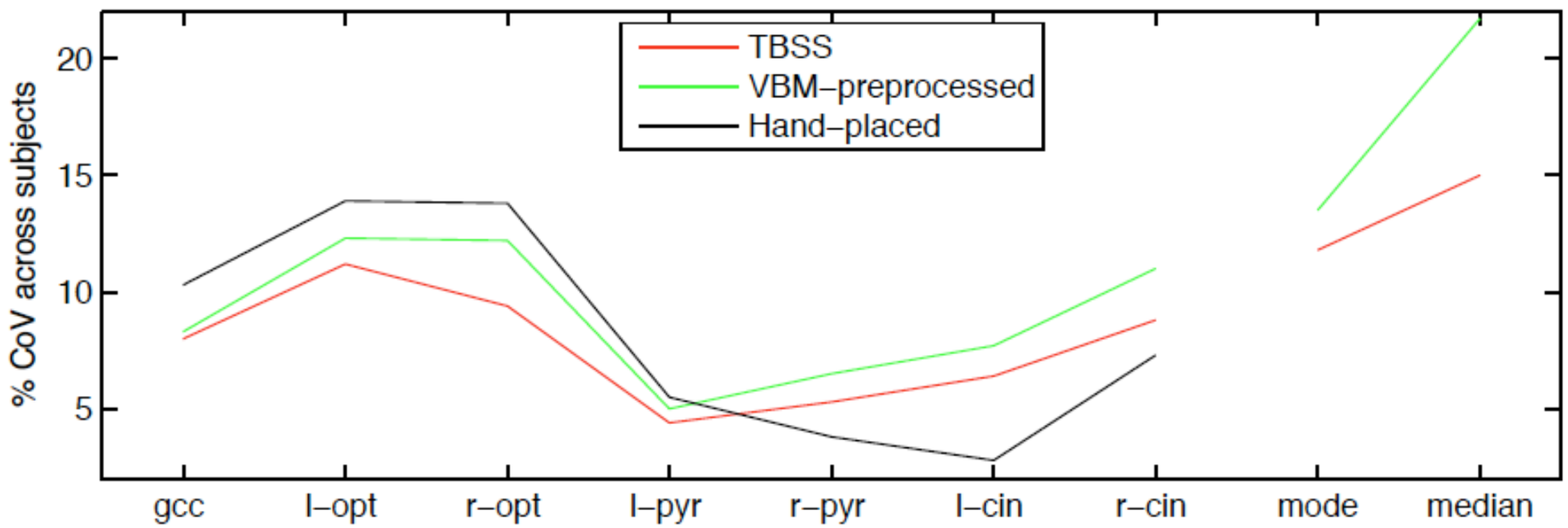
- 36 controls & 33 schizophrenics (Mackay)
- Test each voxel across subjects for Gaussianity using Lilliefors at 5%
- No smoothing with any preprocessing method



Repeatability Tests

- 8 controls scanned twice each
- Measure %CoV across sessions & subjects
- Test hand-placed points and global mode & median

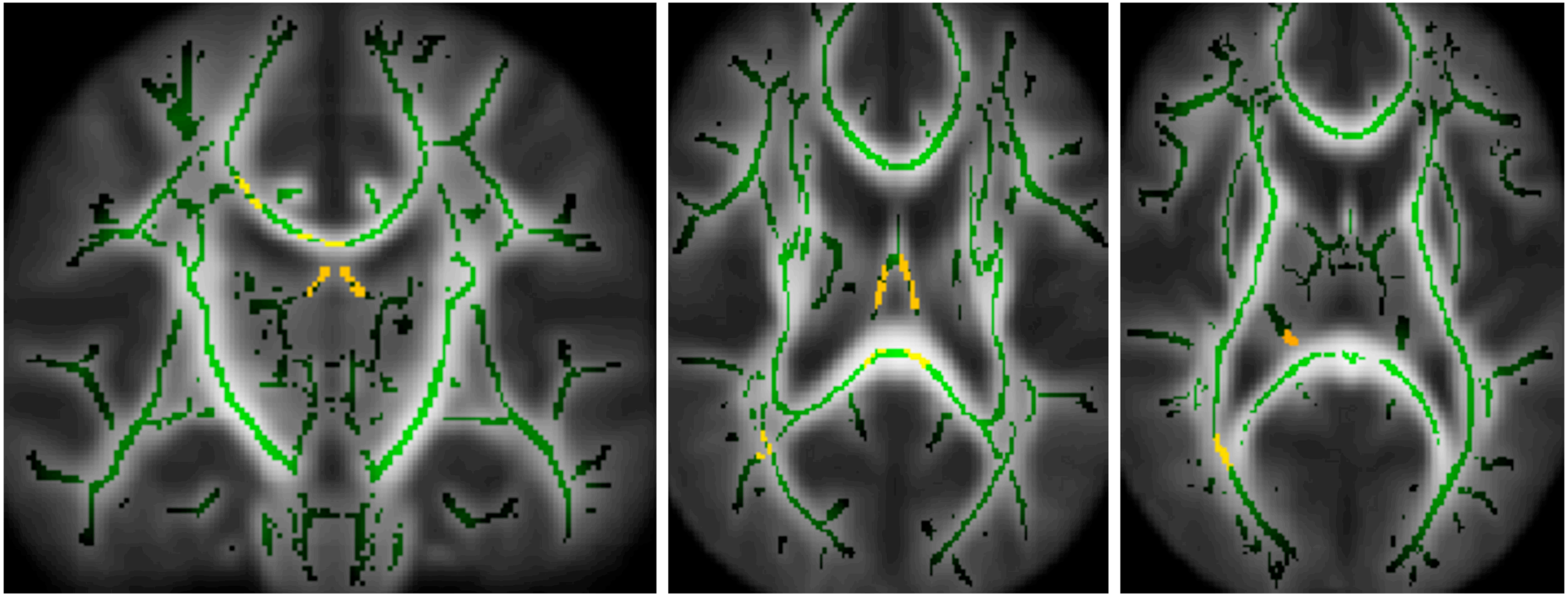




Schizophrenia (Mackay)

TBSS & VBM show reduced FA in corpus callosum & fornix
VBM shows spurious result in thalamus due to increased ventricles in schiz.

TBSS | VBM | mean FA (controls) | mean FA (schiz.)



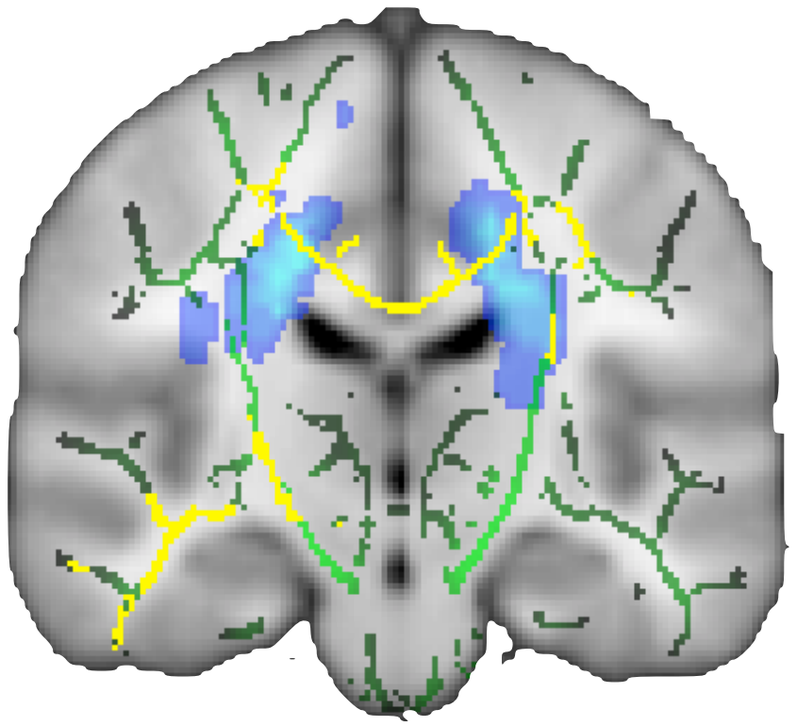
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)

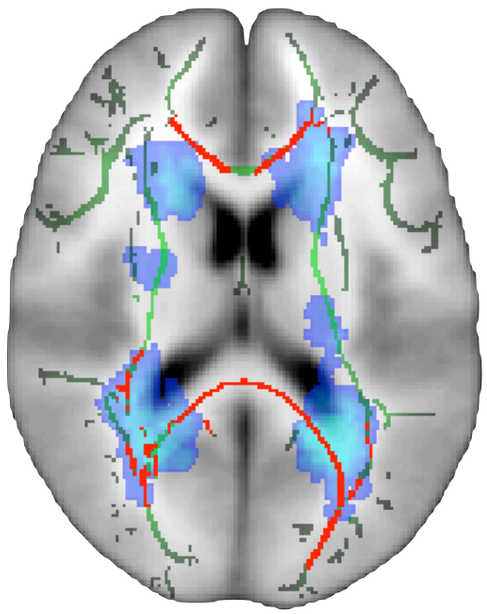
- 15 MS patients

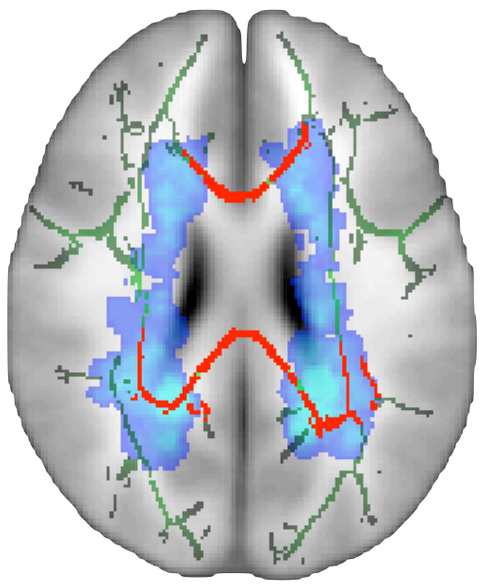
- Yellow = -ve corr. FA vs EDSS

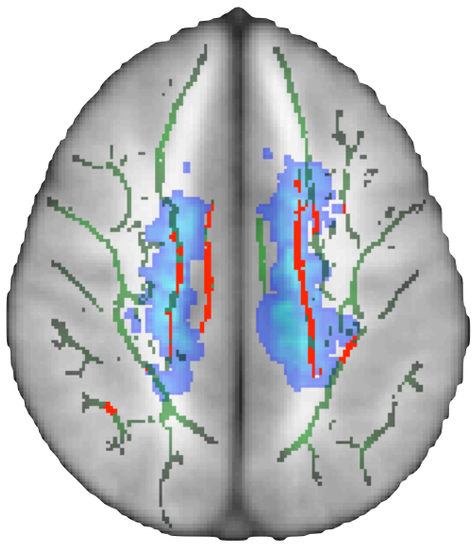
- Blue = group lesion probability (50%)
- Red = -ve corr. FA vs lesion volume

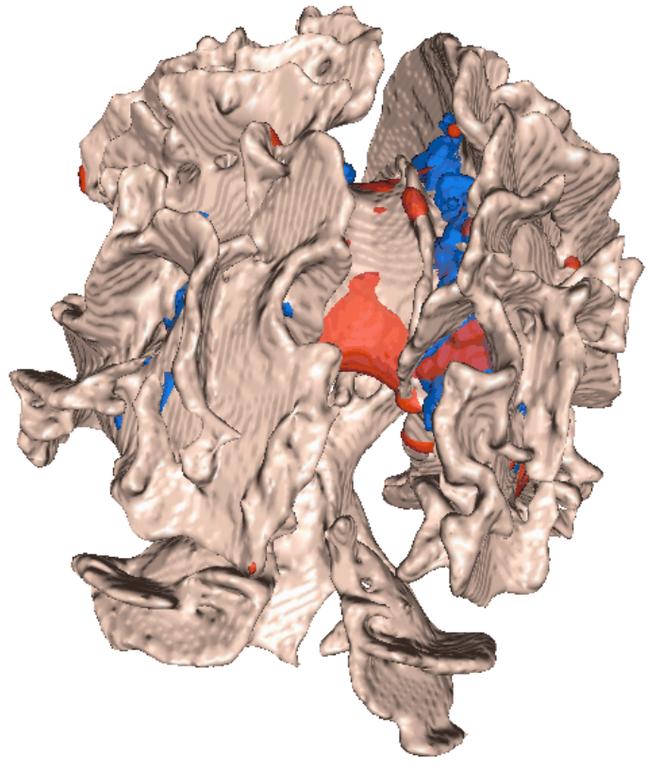
Note reduced FA away from lesions



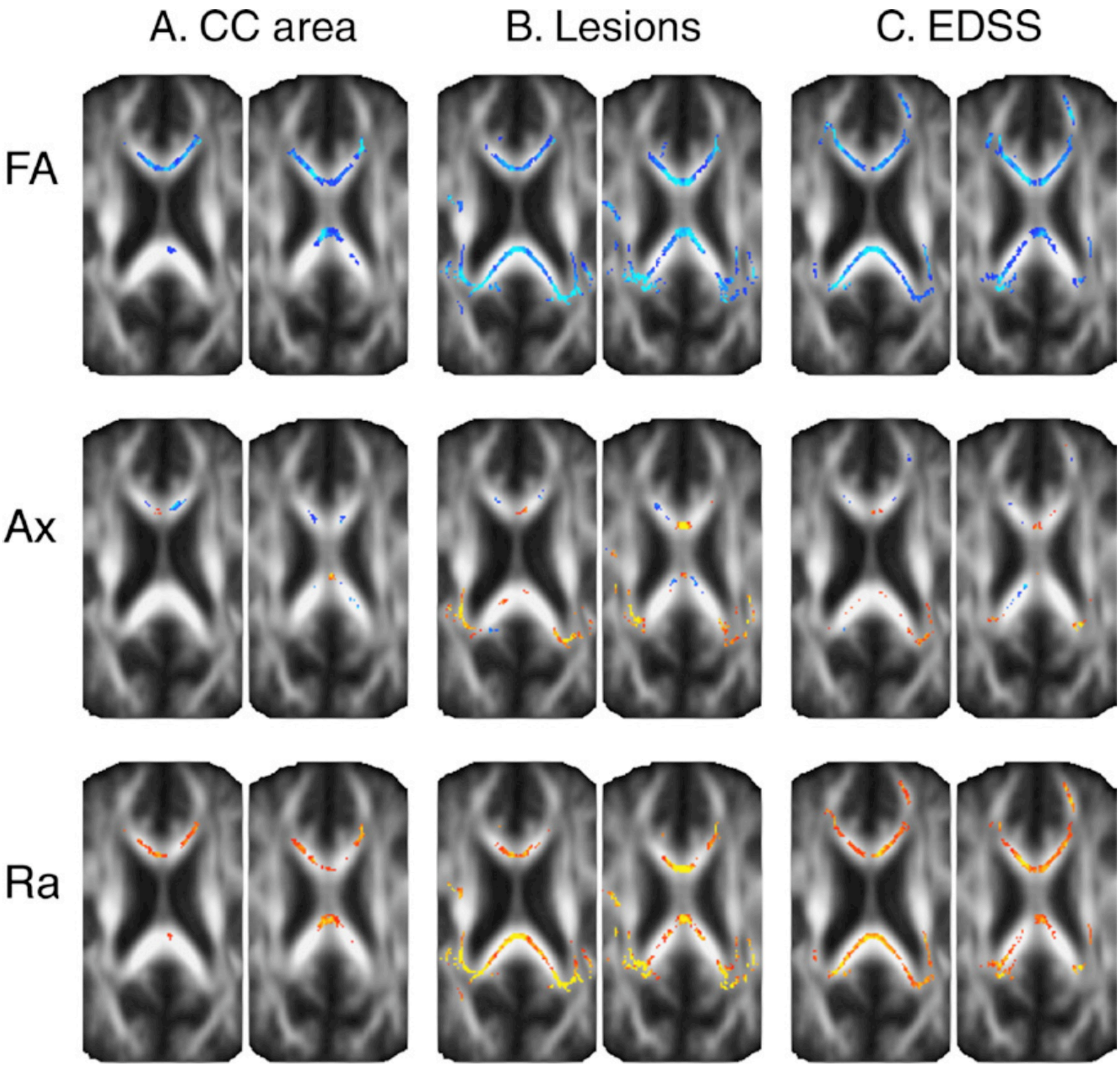




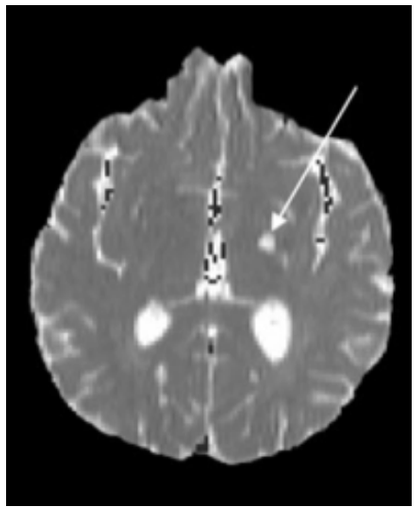




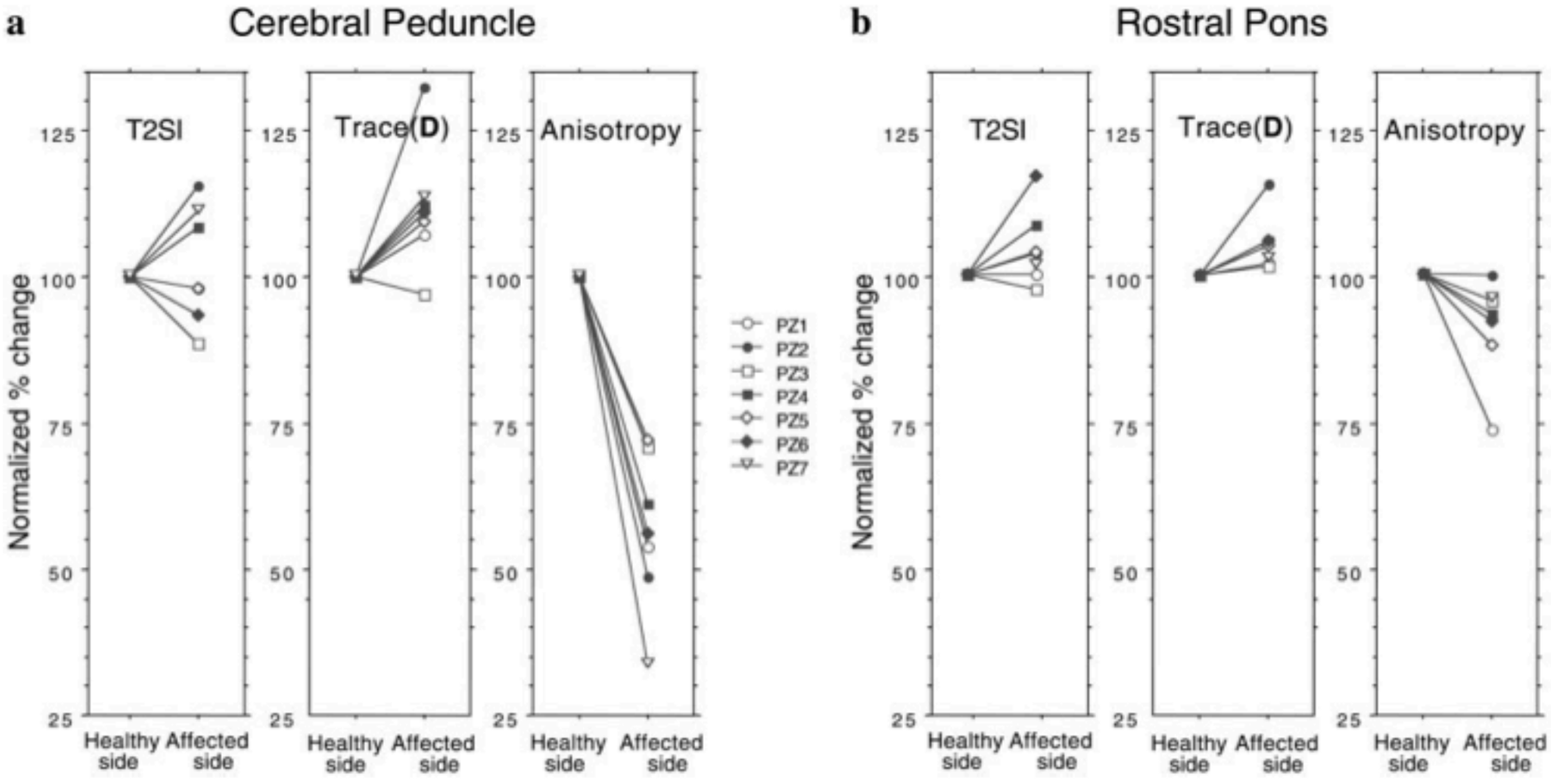
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)



Crossing fibres



Lesion in the internal capsule



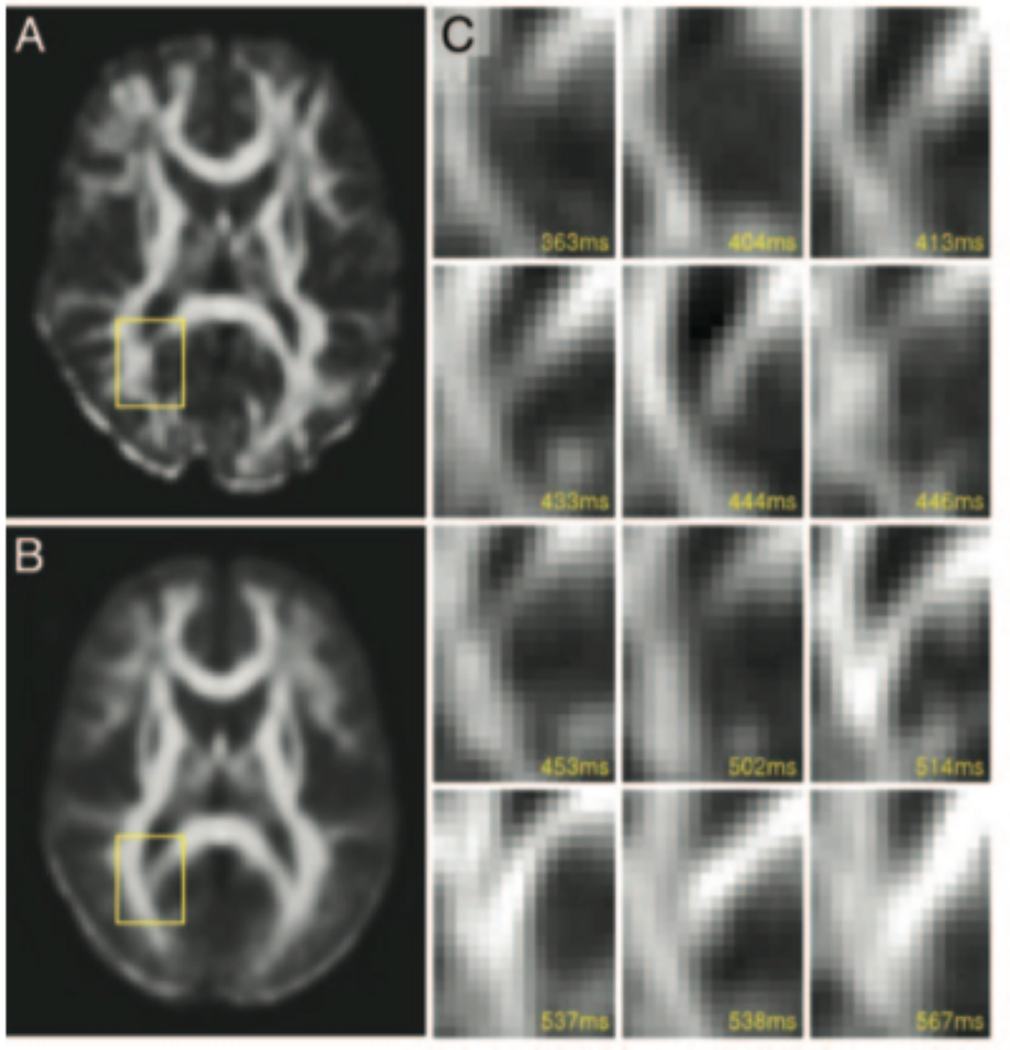
no crossing fibres

crossing fibres

Wallerian degeneration along the cortico-spinal tract.
The effect is "washed out" in crossing fibre regions.

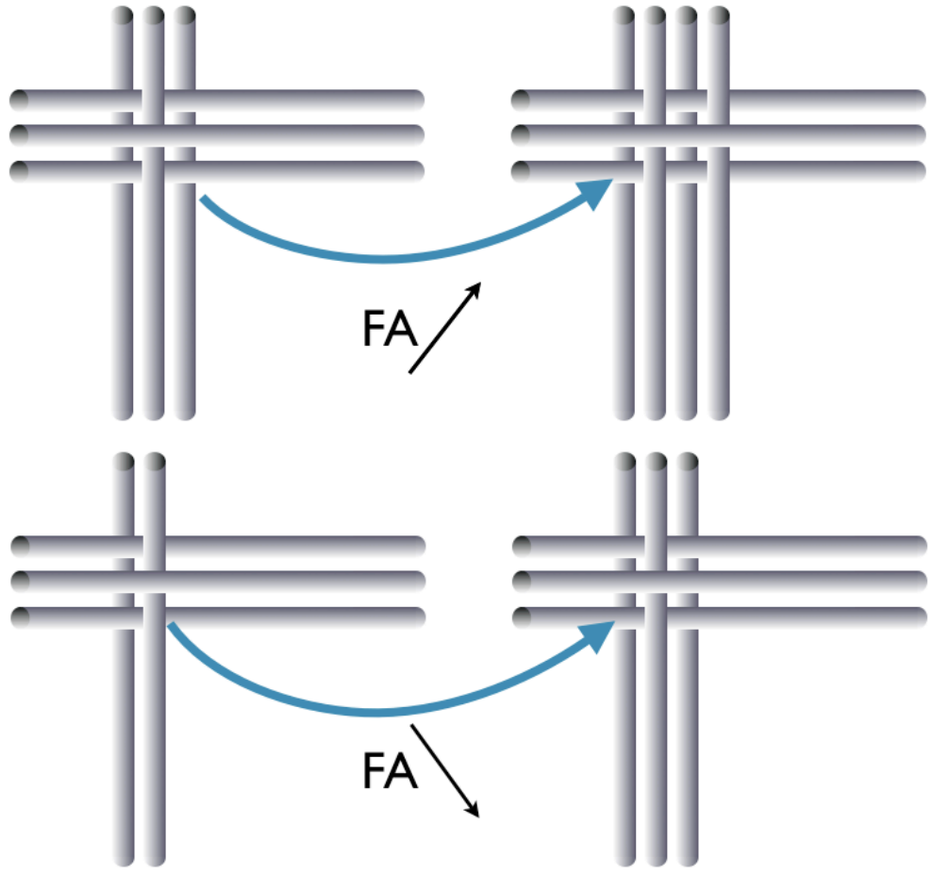
Pierpaoli et al, 2001

Crossing fibres



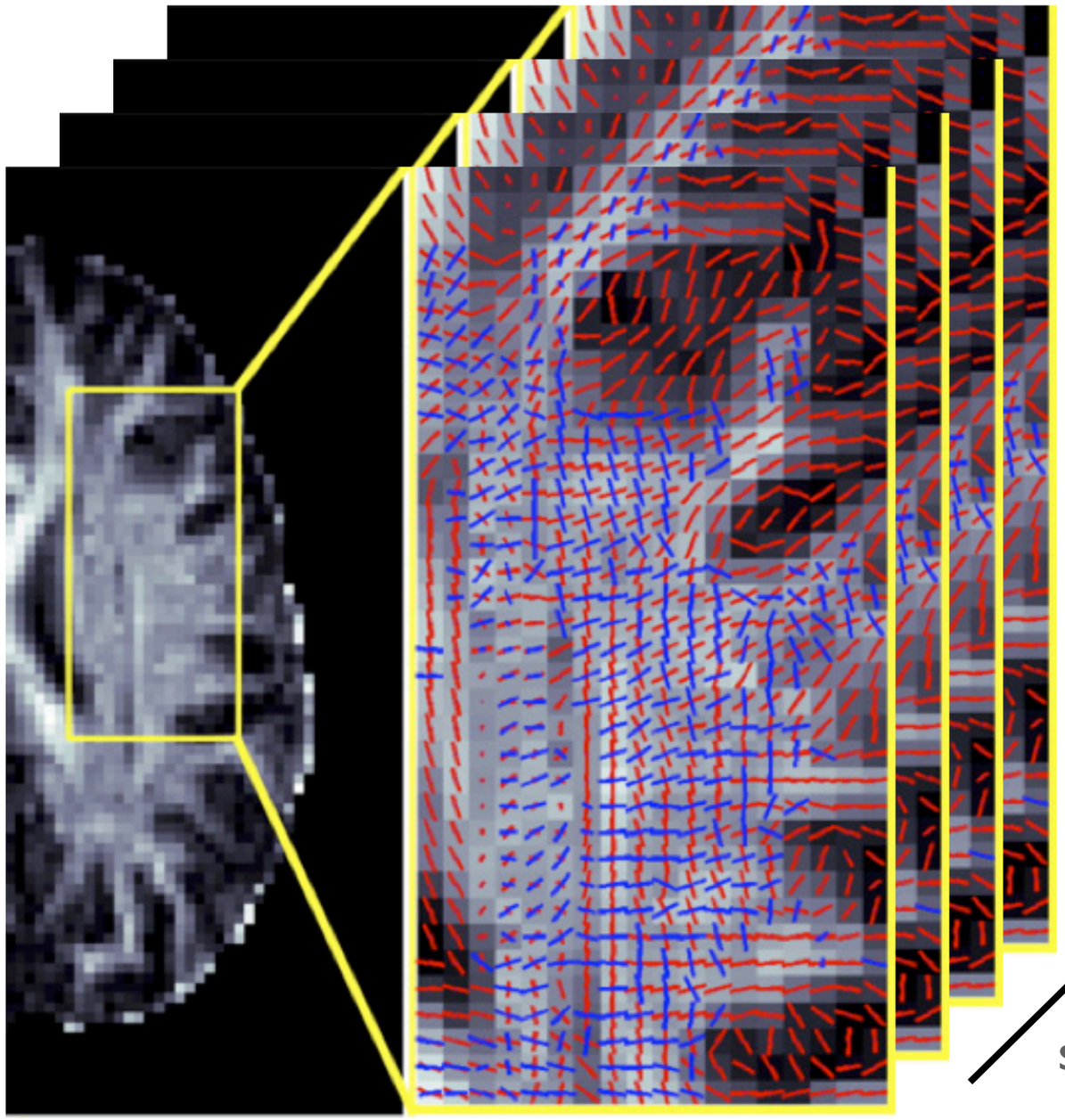
Tuch et al, 2005

FA *decreases* dramatically with *increasing* performance at a visio-motor task. Crossing fibres?



Simplified illustration: the same underlying effect (increased fibre density) gives ≠ FA effects depending on xfibre architecture

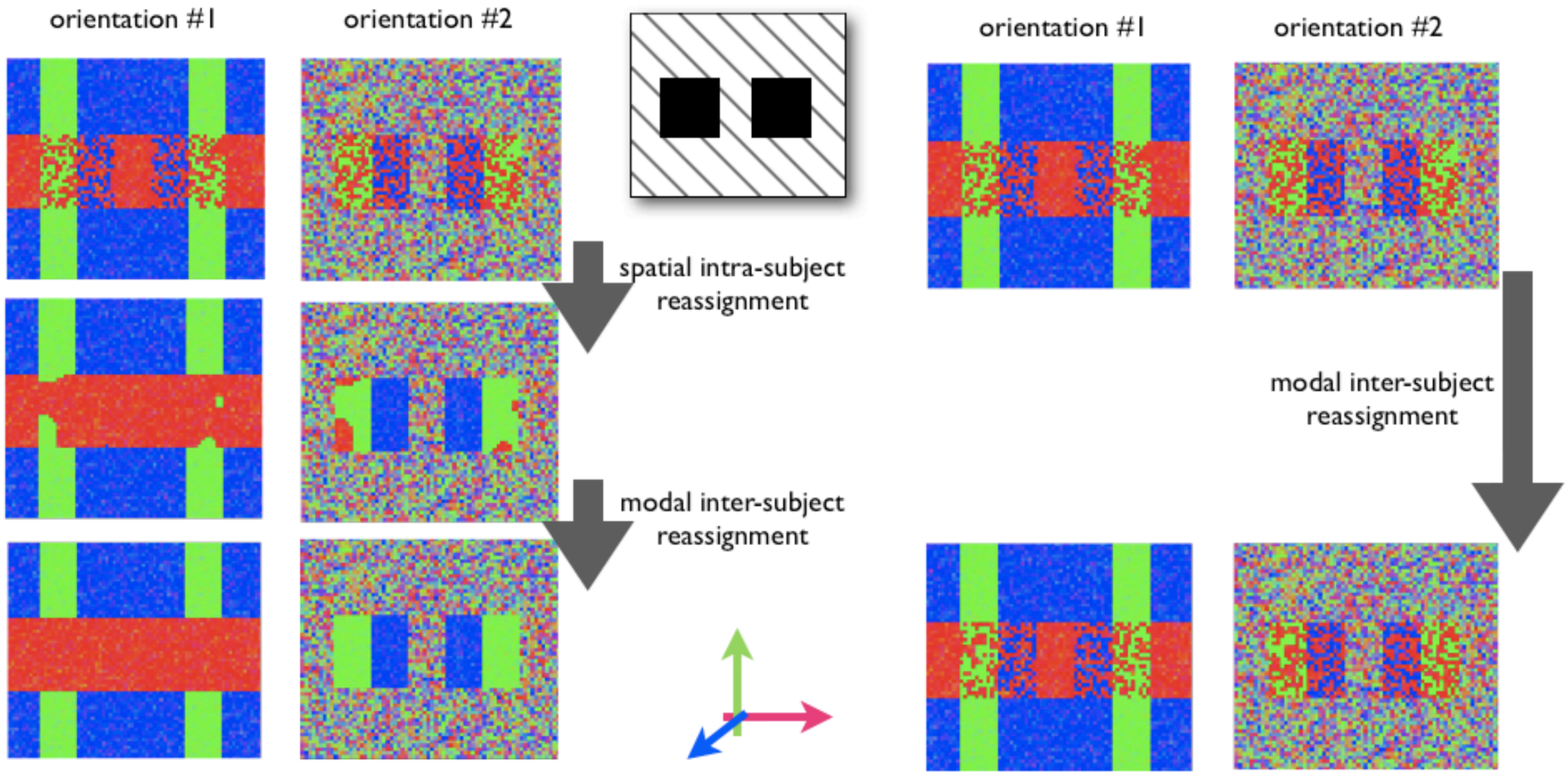
Matching fibres across space and subjects



$$data = f_1.S_1 + f_2.S_2 + Iso$$

Do the red fibres always refer to the SLF across subjects?
Do the blue fibres always refer to the callosal connections across subjects?

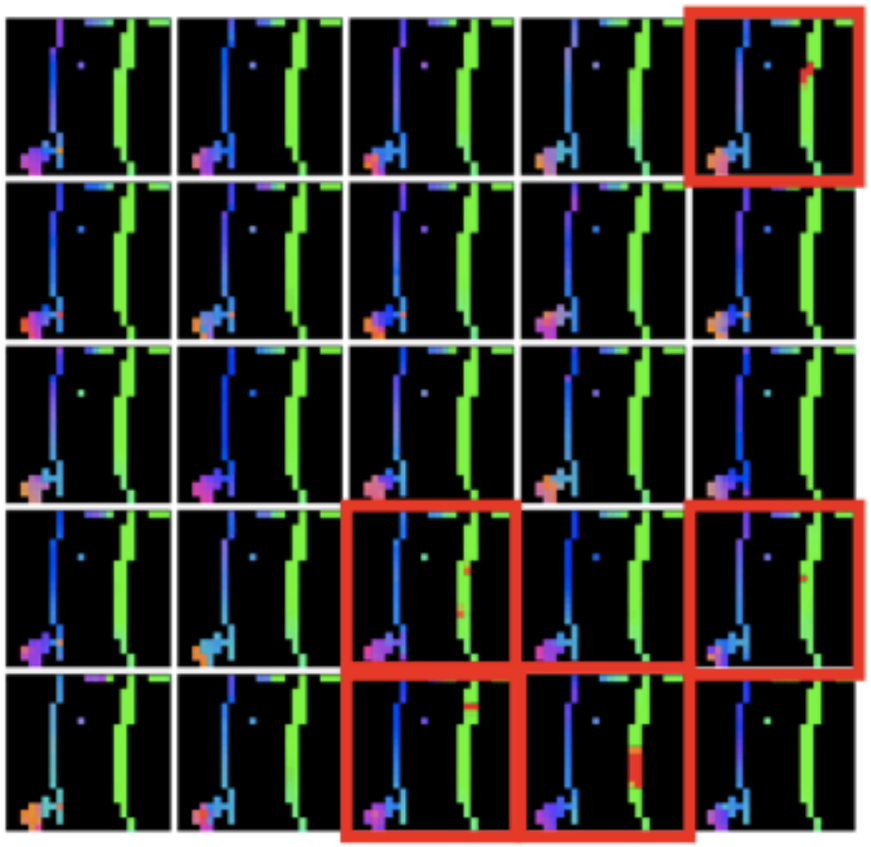
Relabelling fibres across space and subjects



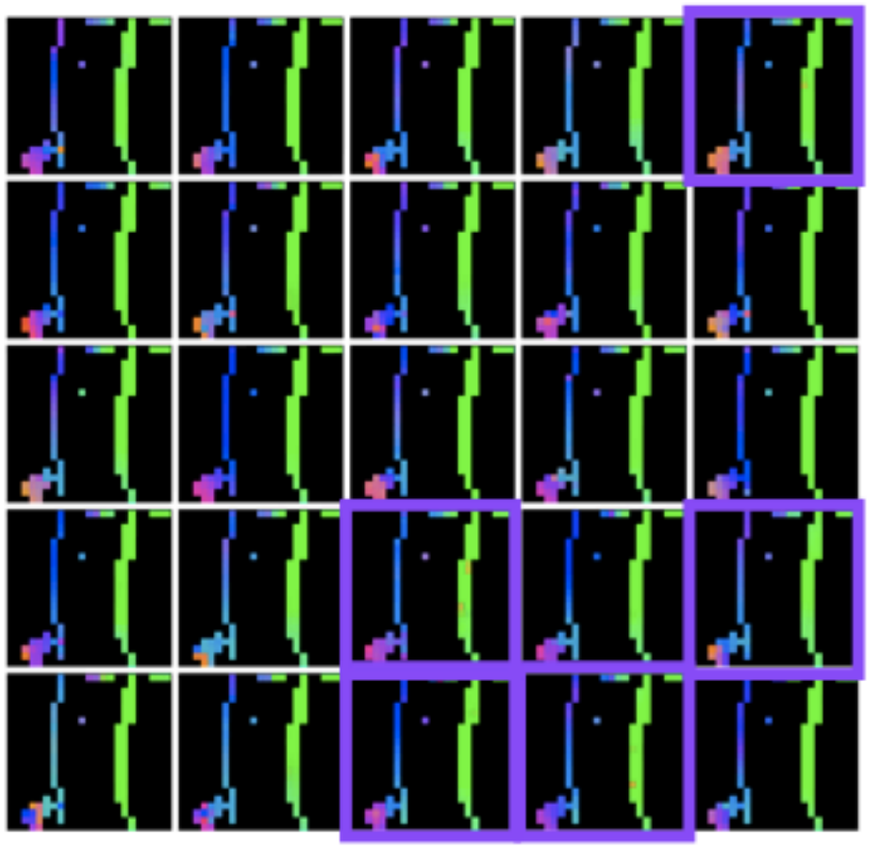
Across space: front propagation - nearby voxels are more likely to have same labels - better spatial statistics

Across subjects: match to the subject-wise mode - better sensitivity and specificity

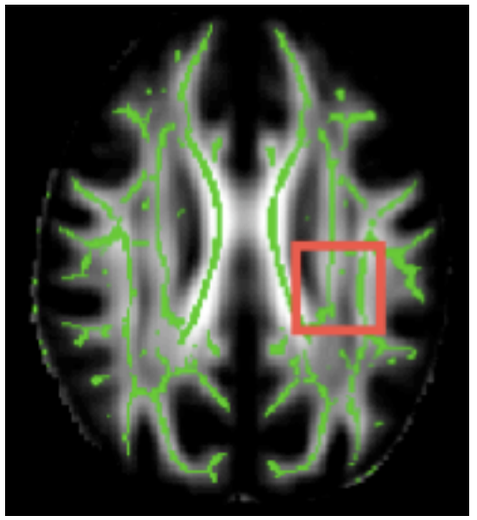
Relabelling fibres across space and subjects



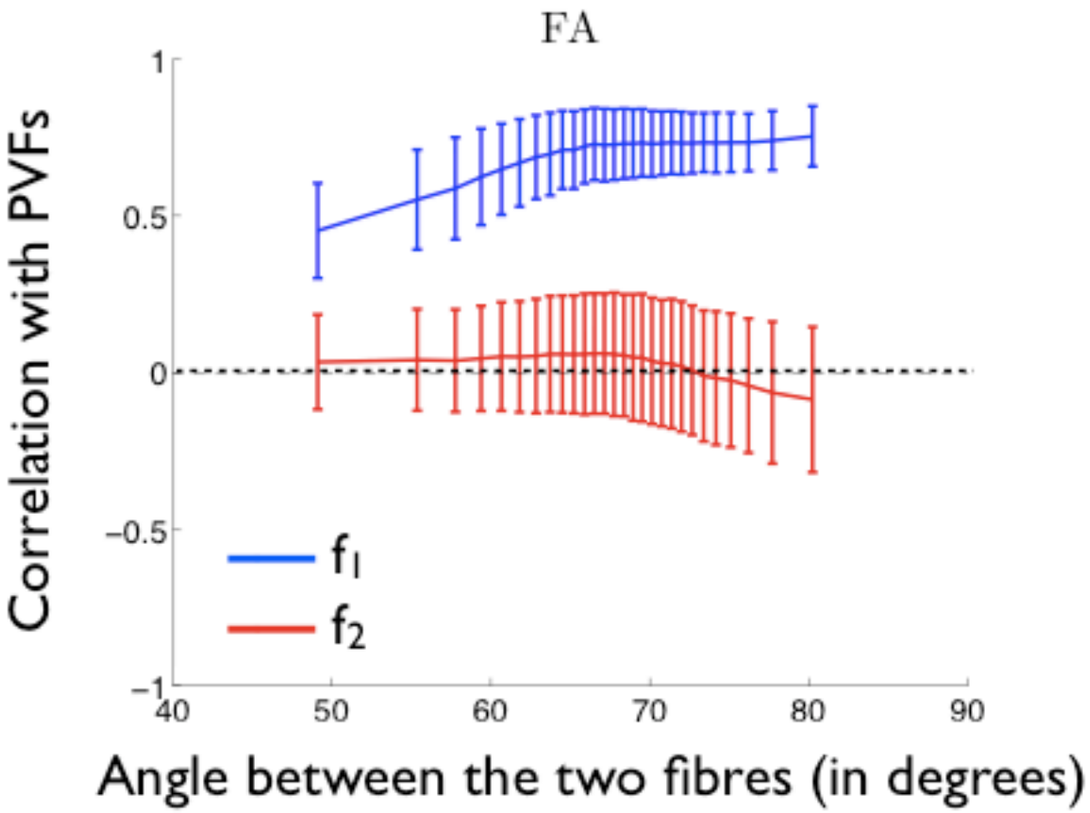
before relabelling



after relabelling

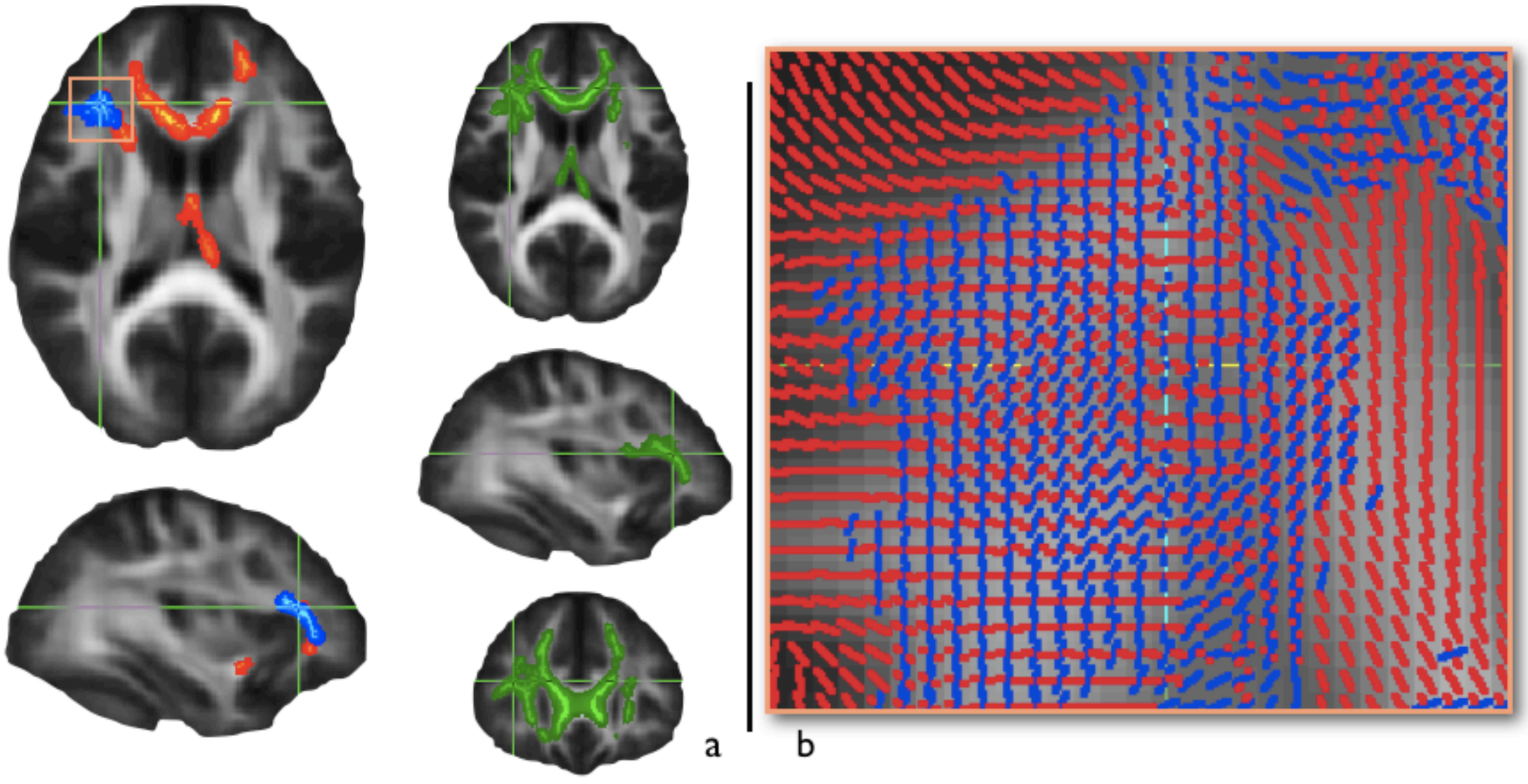


FA vs PVFs



FA correlates with major fibre, but not with minor one

Example



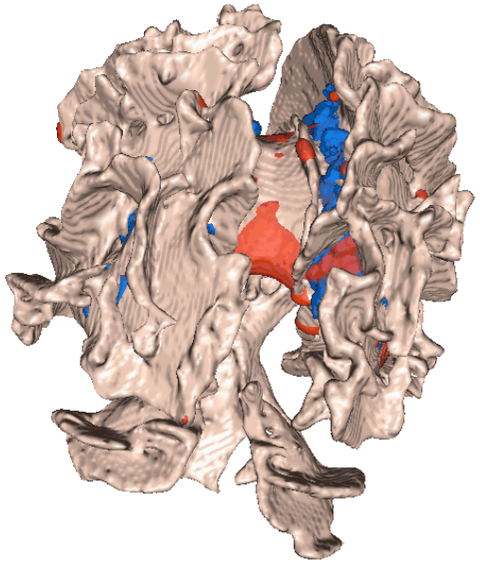
65 subjects - negative correlation with age
FA more sensitive (but maybe less specific)
f_1 vs age in red, f_2 vs age in blue
we can associate age correlation with the frontal connections in blue

TBSS - Conclusions

- Attempting to solve correspondence/smoothing problems
- Less ambiguity of interpretation / spurious results than VBM
- Easier to test whole brain than ROI / tractography

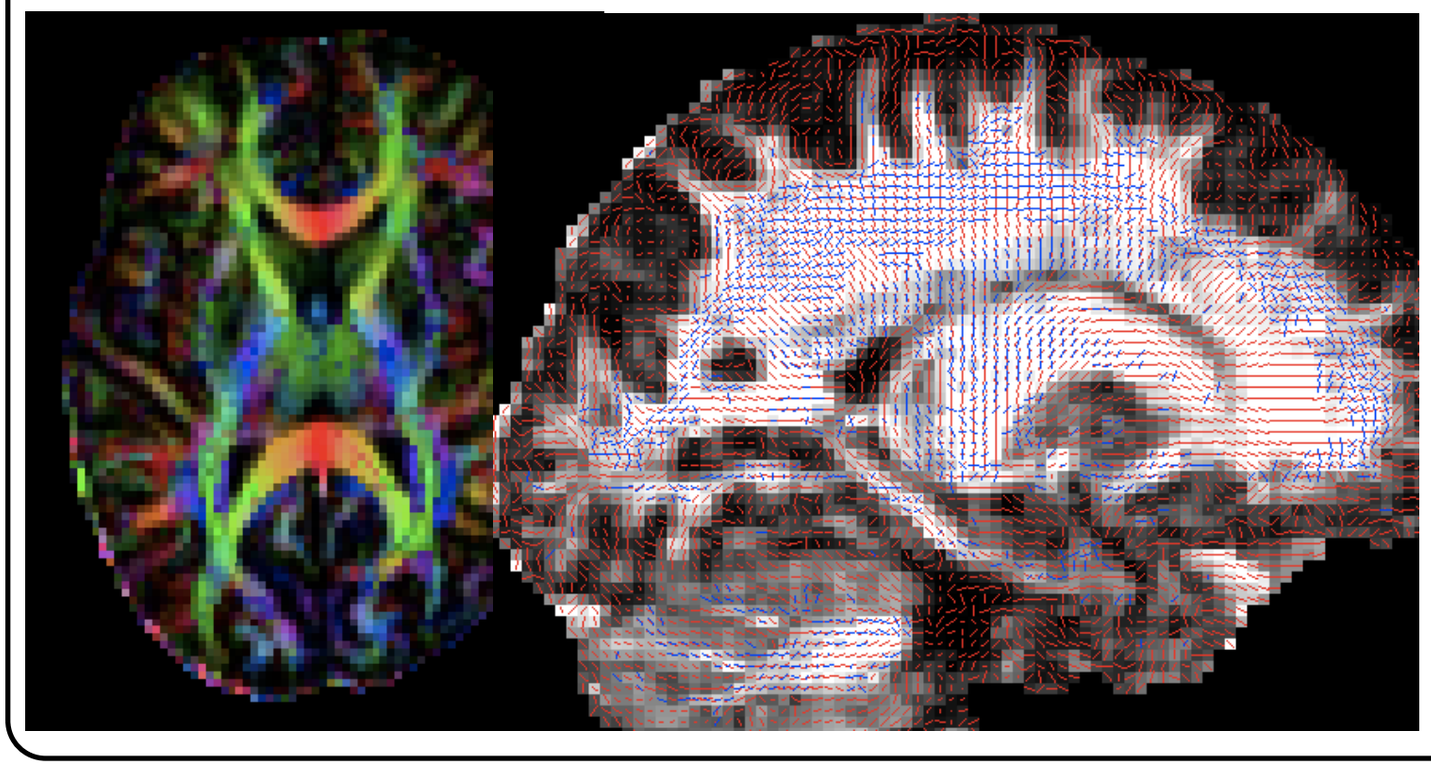
- Limitations & Dangers
  - Interpretation of partial volume tracts still an issue
  - Crossing tracts?

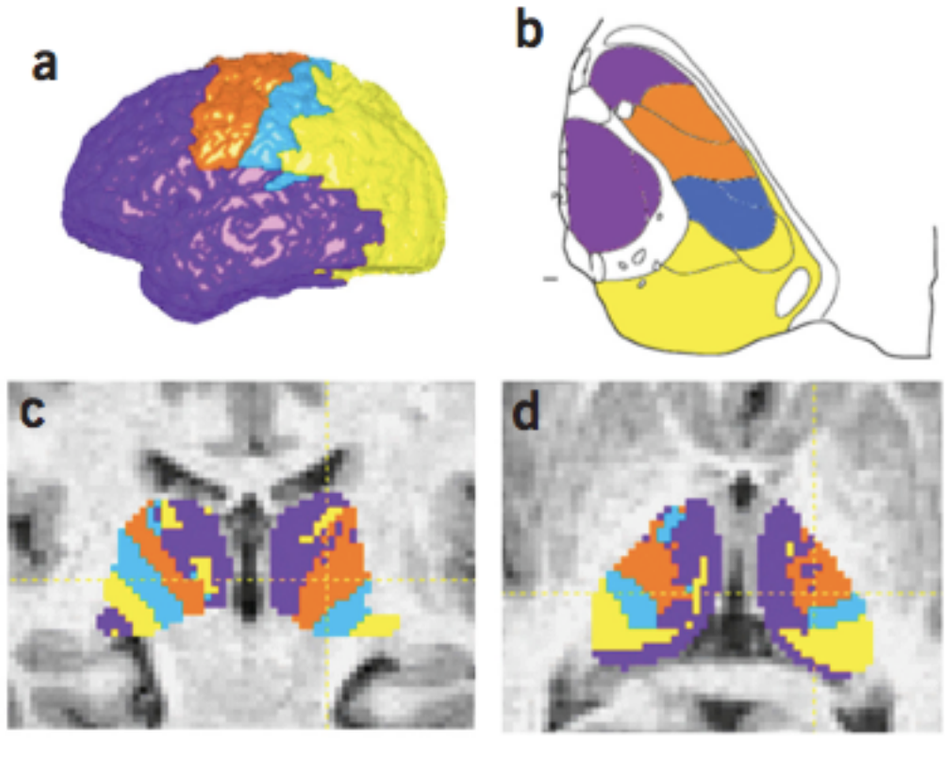
- Future work
  - Use full tensor (for registration and test statistic)
  - Use other test statistics (MD, PDD, width)
  - Multivariate stats (across voxels and/or different diffusion measures) & discriminant (ICA, SVM)



FMRIB Diffusion Toolbox

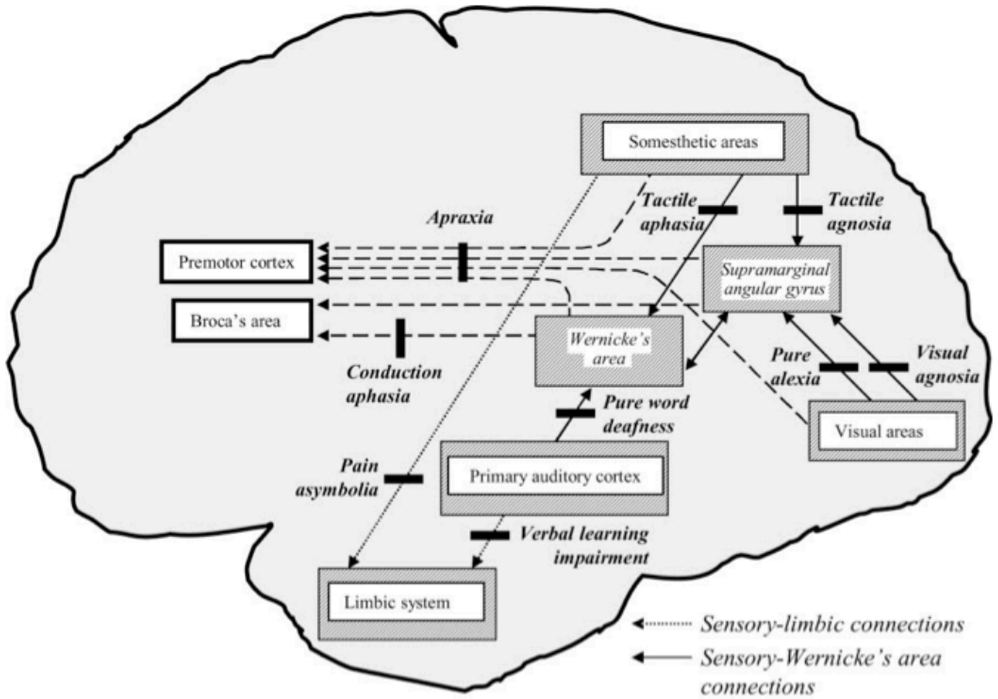
- DTI model fit
- Eddy current correction
- Voxel-Based diffusion analysis (TBSS)
- BEDPOSTX modelling crossing fibres
- PROBTRACKX propagating uncertainty in tractography





Connectivity - Why do we care?

- White matter (dys)connectivity is thought to form the substrate for many different neurological and psychiatric disorders.

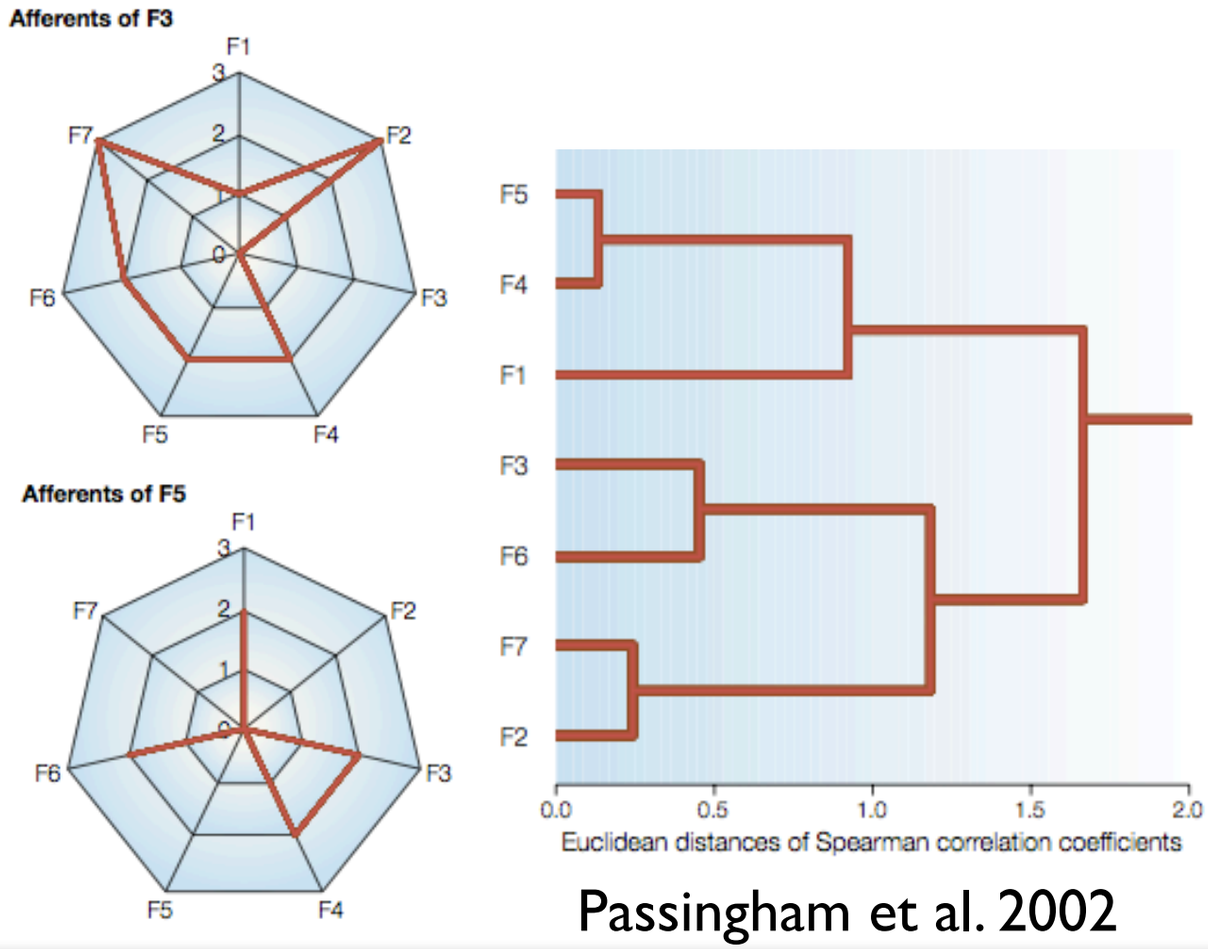


Catani and Ffytche 2005

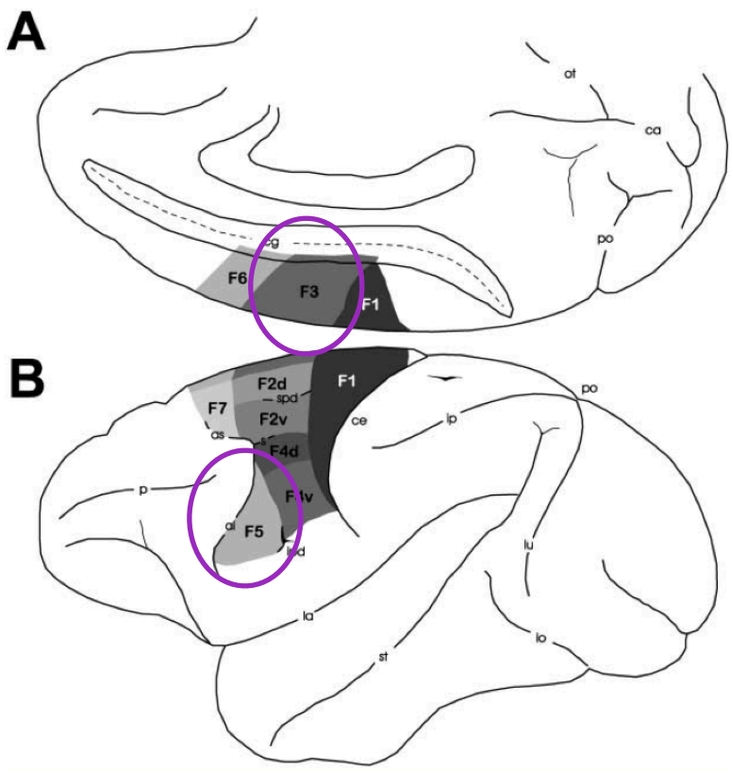
Connectivity - Why do we care?

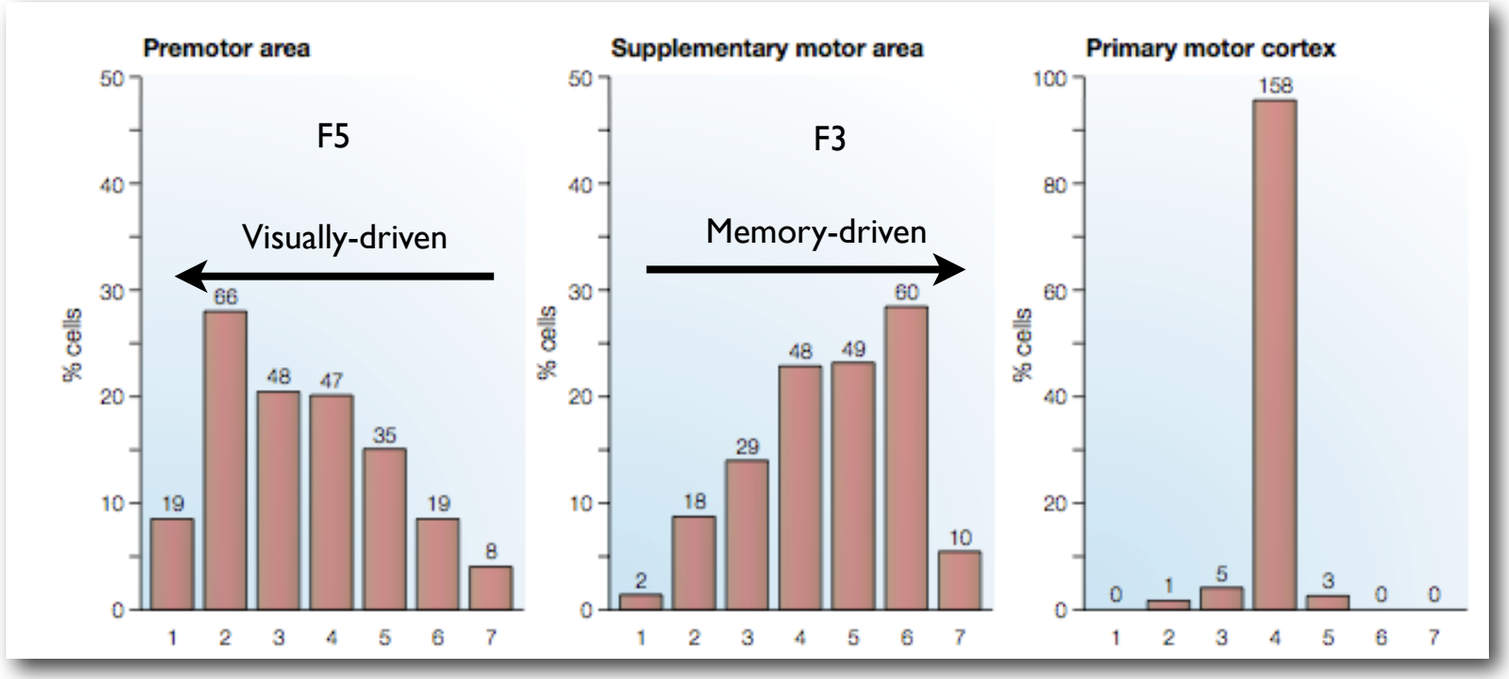
- Connections constrain function

- Different regions have distinct connectivity fingerprints



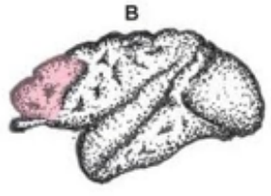
Passingham et al. 2002

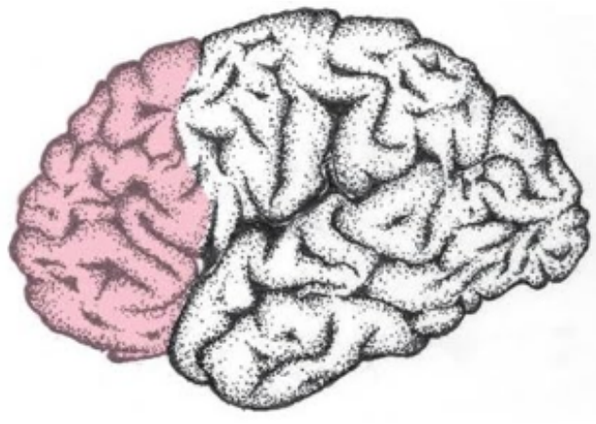


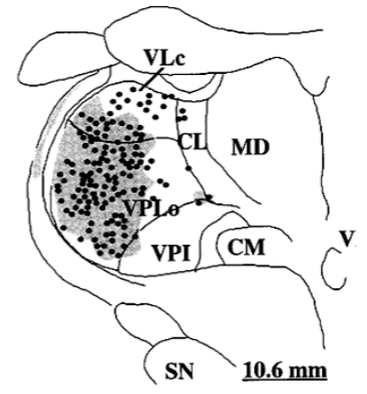


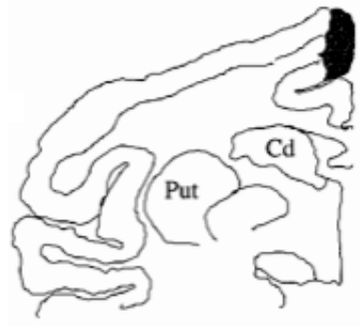
Investigating connectivity

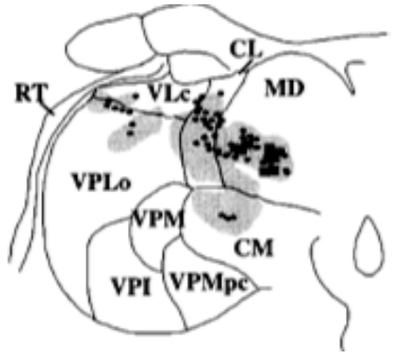
- Tracer studies in non-human animals











Rouiller et al 1998

Post-mortem

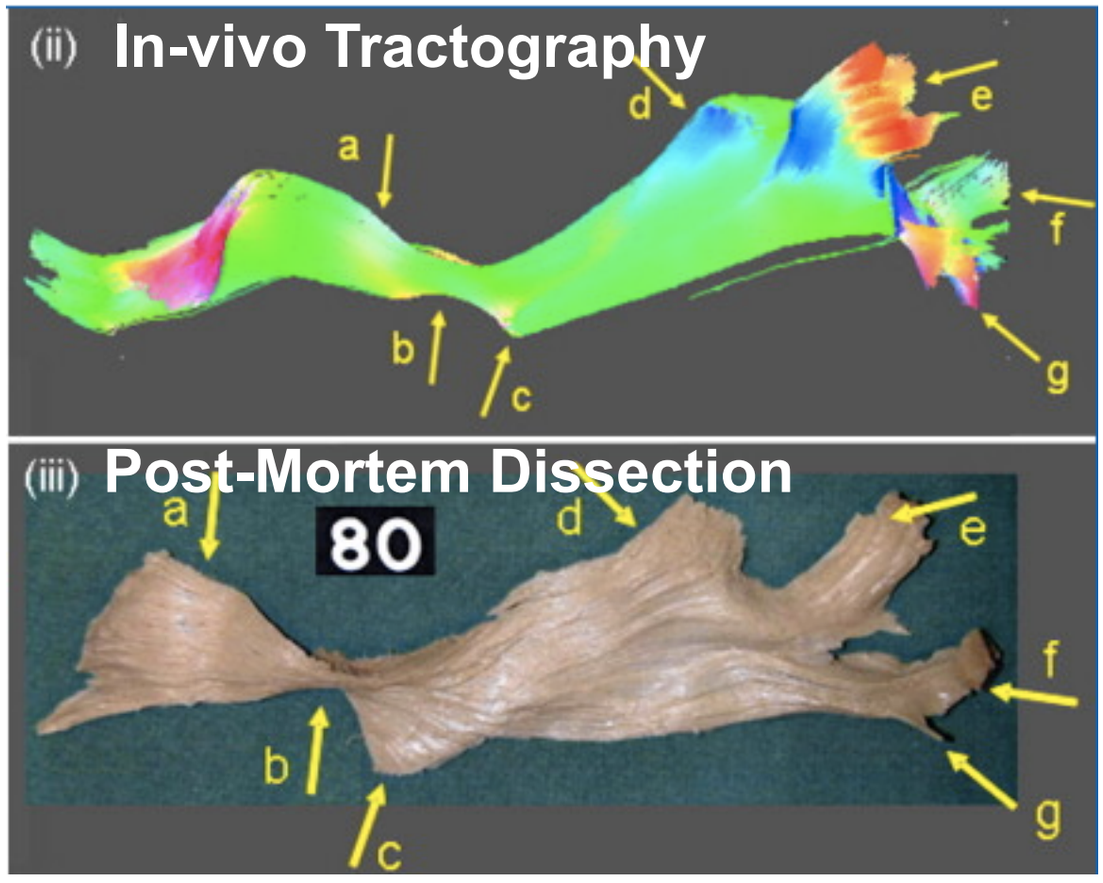
In human

Post-mortem dissection reveals large tracts

Post-mortem histology shows degeneration after remote lesions

What does tractography offer?

+ non-invasive
+ in-vivo
+ whole brain
+ can address new questions

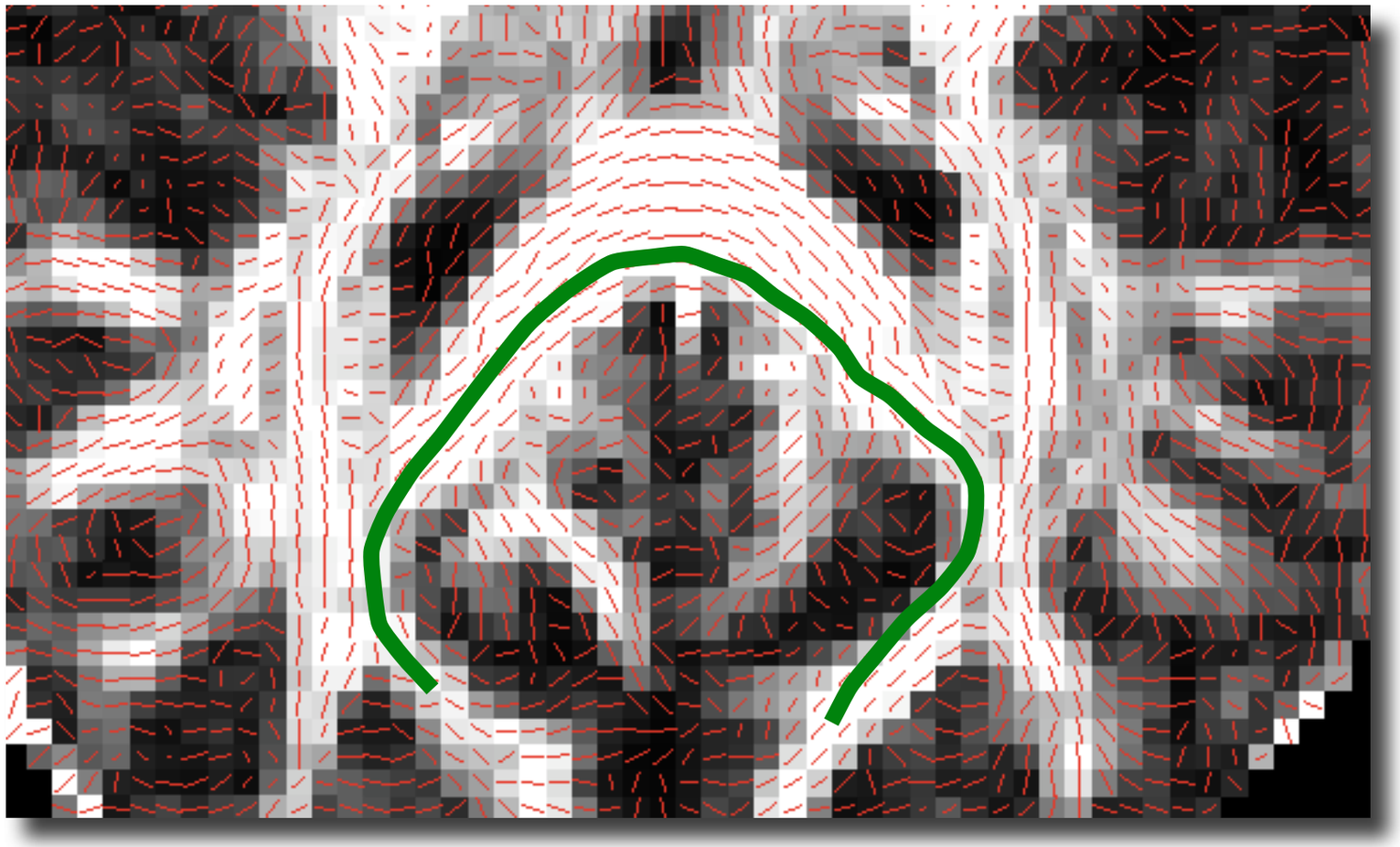


Lawes et al. 2008

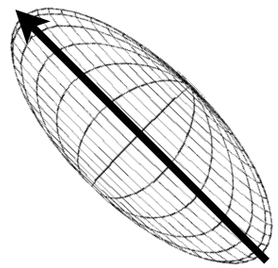
...But
- low resolution (large bundles)
- indirect (diffusion paths)
- error prone (MRI is noisy)
- difficult to interpret quantitatively

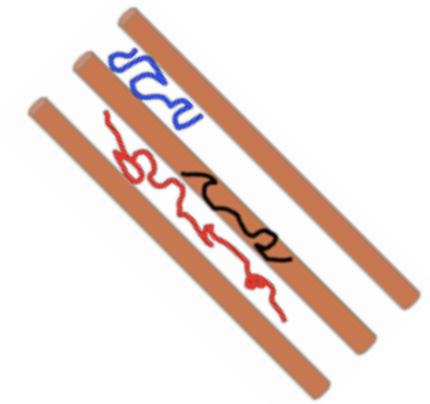
Estimates of Principle Fibre Orientation in WM

$\mathbf{v}_1$ map
Principal Diffusion Direction



Principal Diffusion Direction



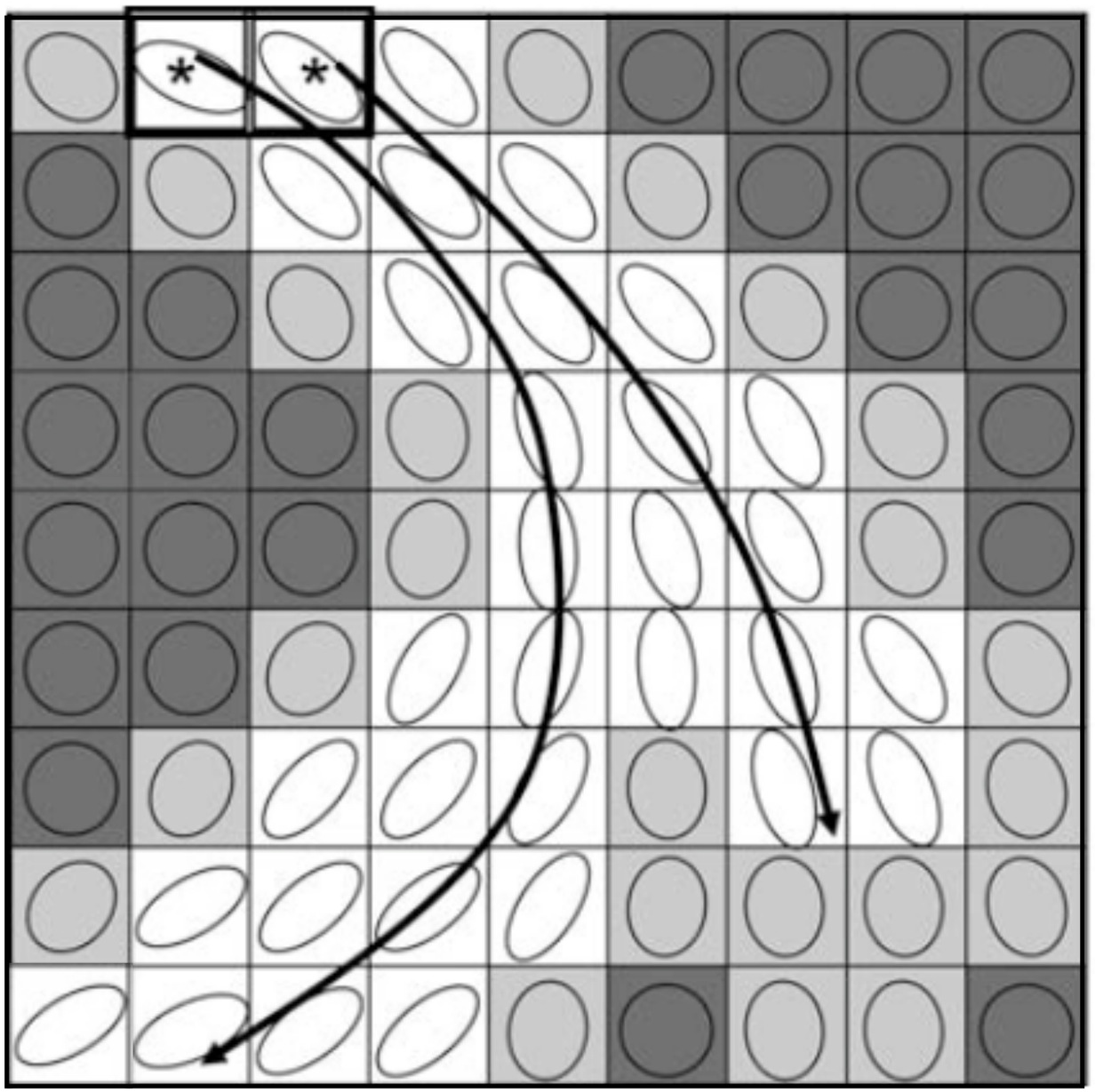


<u>Assumption</u>:

Direction of maximum diffusivity
(in anisotropic voxels)
is an **<u>estimate</u> of the major fibre orientation**.

DTI Streamline Tractography

Seed region



following $\mathbf{v_1}$

Effectively, we solve numerically the differential equation:

$$\frac{d\mathbf{r}(s)}{ds} = \mathbf{v_1}(\mathbf{r}(s)), \quad \mathbf{r}(0) = \mathbf{r}_0$$

- $\frac{d\mathbf{r}(s)}{ds}$: Position along a curve
- $\mathbf{v_1}(\mathbf{r}(s))$: Principal eigenvector $\mathbf{v_1}$ at position $\mathbf{r}(s)$
- $\mathbf{r}_0$: Starting Position

Benefits:

- Established numerical integration methods
- Control error propagation using more complex schemes (e.g. Runge-Kutta)

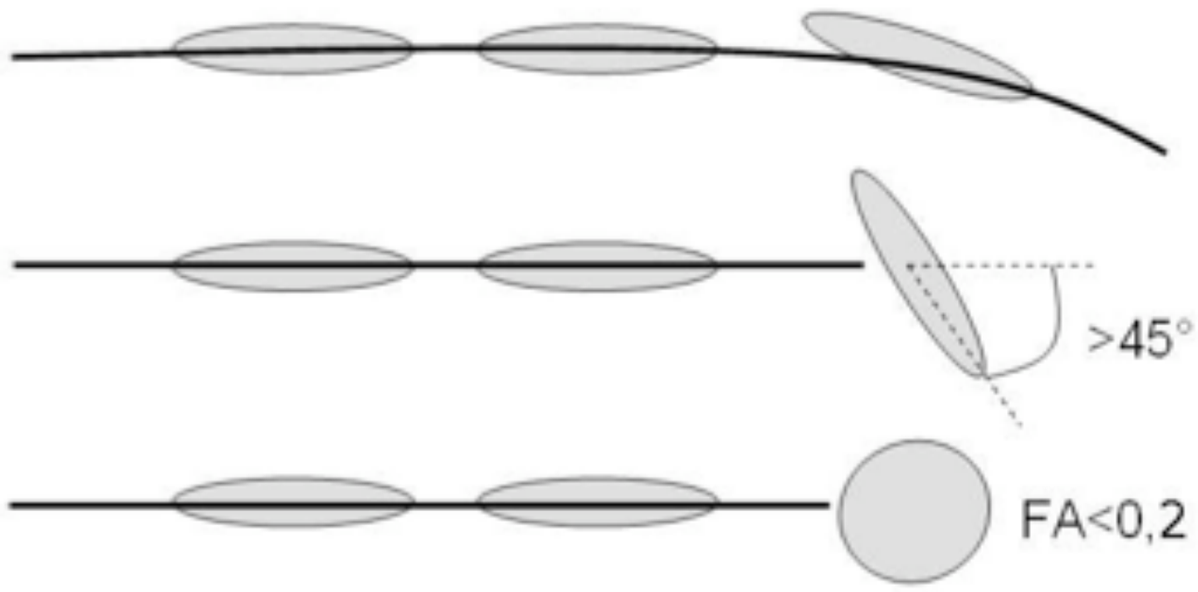
DTI Streamline Tractography

But When to Stop?
Heuristics to avoid error propagation.
+ Knowledge of the anatomy

Curvature Change Threshold: To avoid crossings of boundaries and very bended trajectories, impose a smoothness criterion.

Anisotropy Threshold: To avoid propagating in regions where $\mathbf{v}_1$ is meaningless.

Anatomical criteria (e.g. reach grey matter)



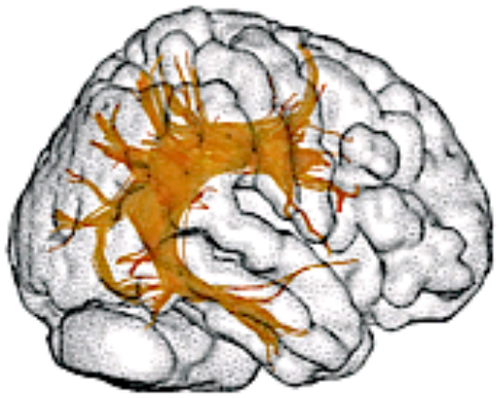
DTI Streamline Tractography Summary

- Use the major axis of the DTI ellipsoid as a fibre orientation estimate.

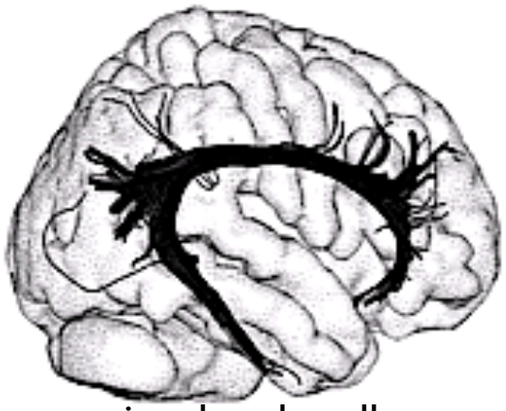
- Propagate curves within this vector field until empirical thresholds are exceeded.

- Major fibre bundles can be reconstructed.

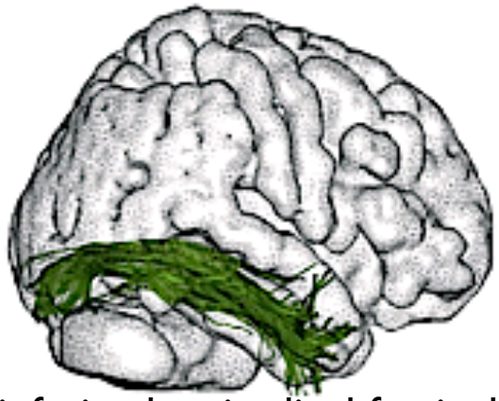
Streamline tractography can dissect major bundles



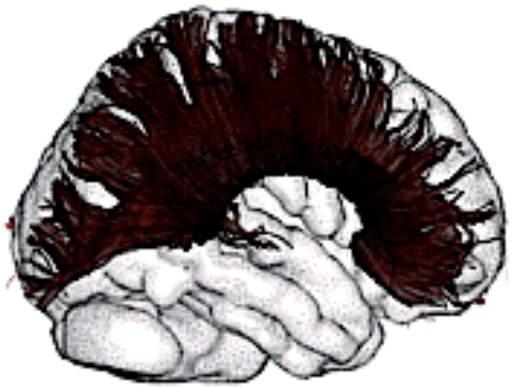
arcuate fasciculus



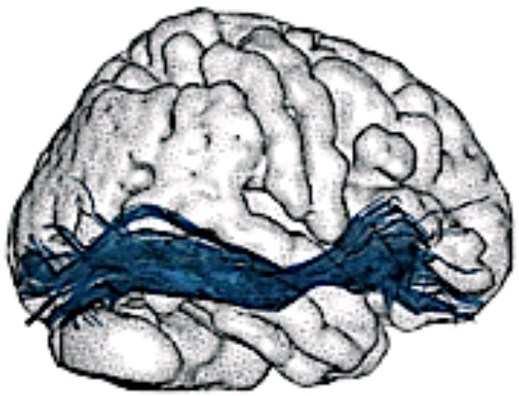
cingulum bundle



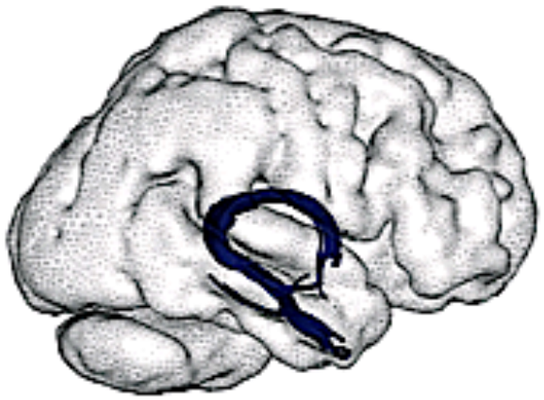
inferior longitudinal fasciculus



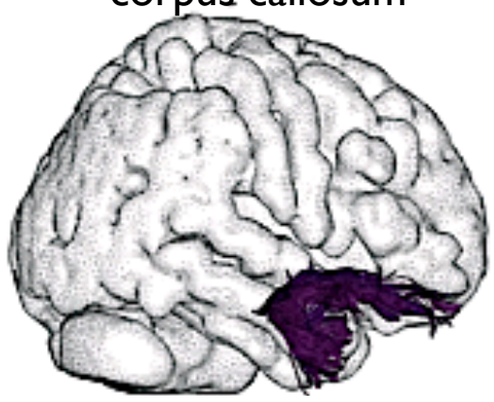
corpus callosum



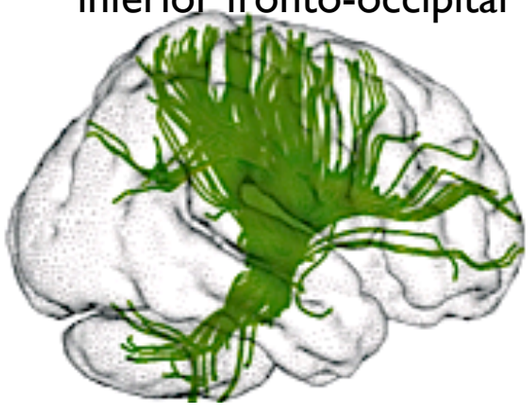
inferior fronto-occipital



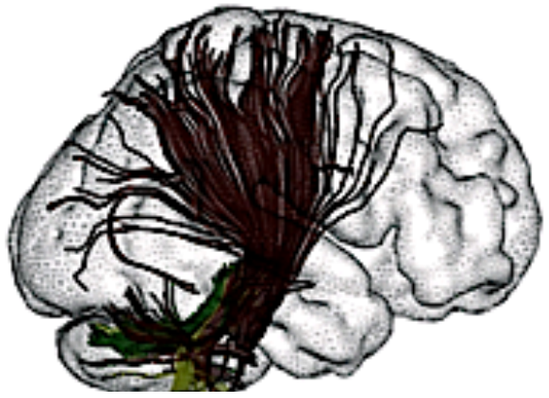
fornix



uncinate fasciculus



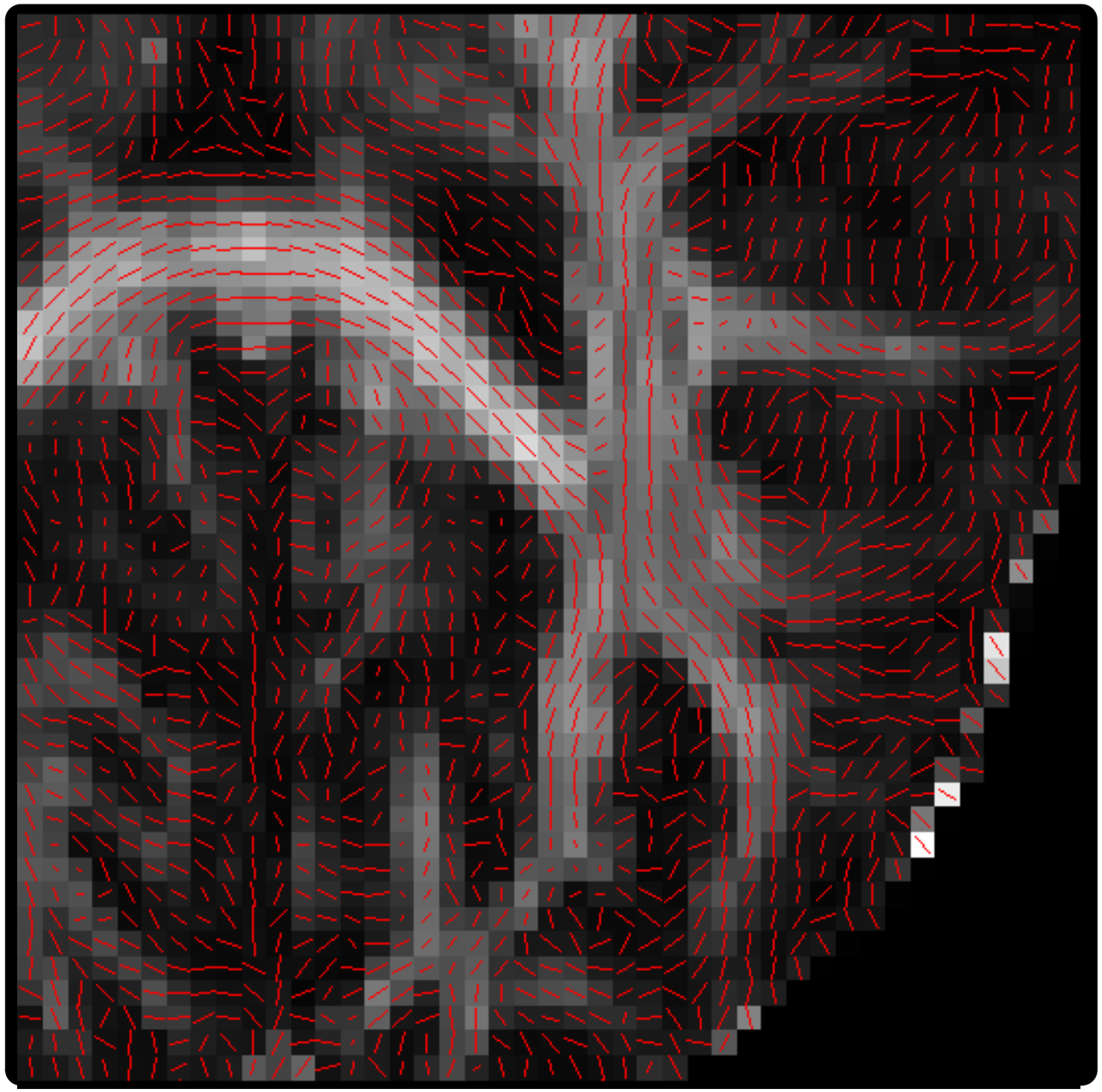
corona radiata



cerebellar tracts

Catani and Thiebaut de Schotten 2008

But How Confident Are We?



Fibre orientations from DTI

DWI is very noisy.

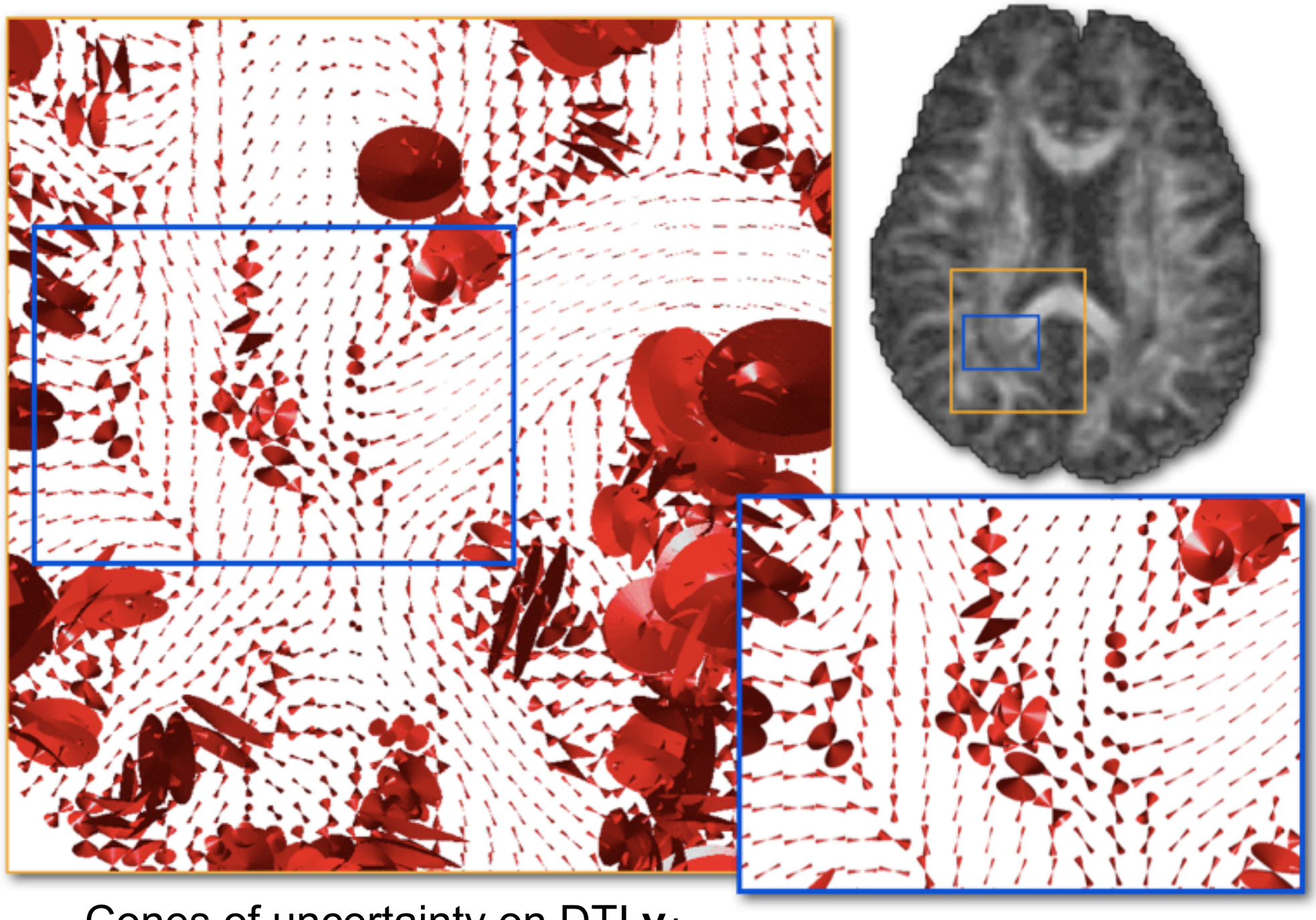
If we scan a subject repeatedly, will we get the same result?

Uncertainty on Fibre Orientation Estimates

Repeat an acquisition many times and obtain the variability in $\mathbf{v}_1$ from the different datasets.

Uncertainty Sources

- Noise
- Modelling errors



Cones of uncertainty on DTI $\mathbf{v}_1$

Jones, 2002

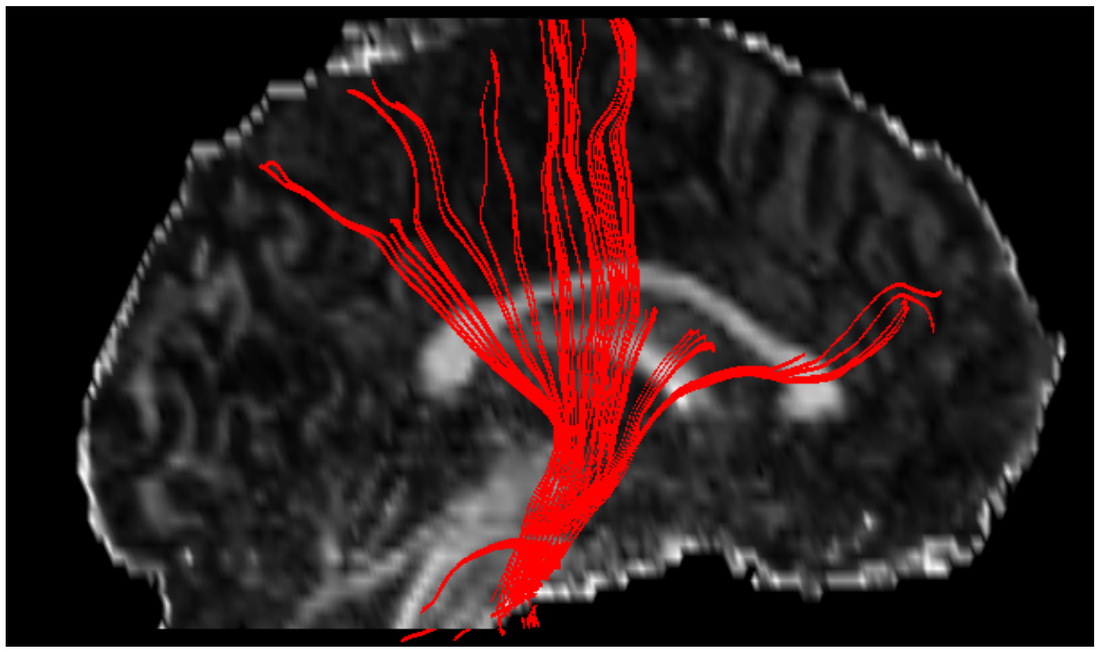
Reproducibility of Tracking Results

Repeat an acquisition many times and repeat streamline tracking.

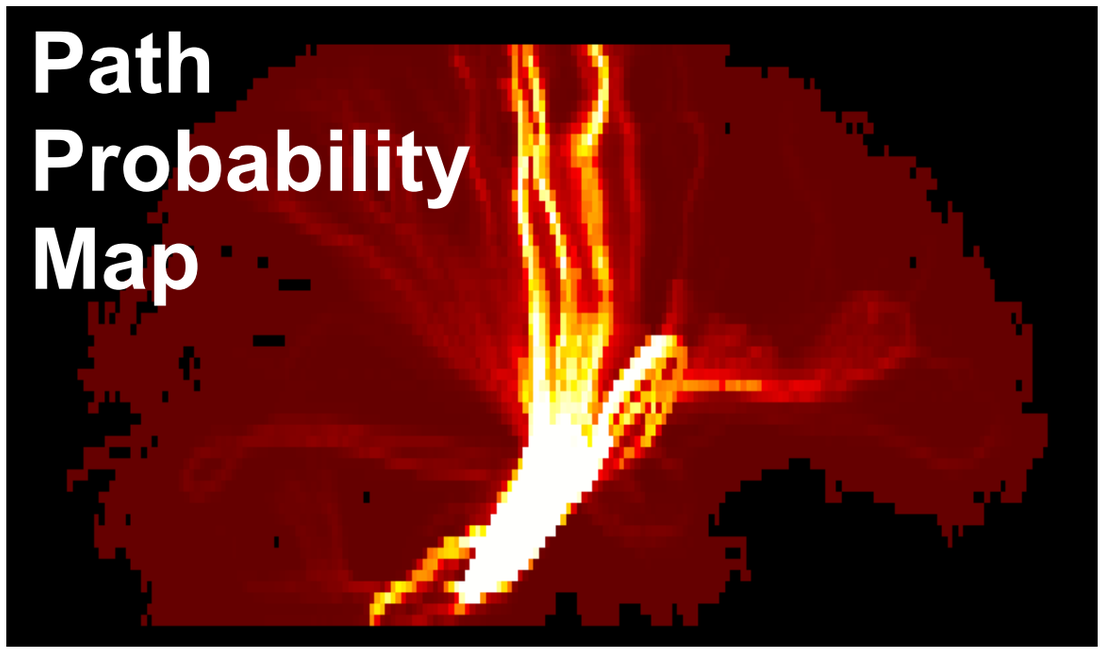
Due to uncertainty in $\mathbf{v}_1$, curves will not perfectly overlap

Create a map that shows the degree of overlap across the trials.

Streamlines from a single dataset



Map that shows where results across datasets overlap



Low Reproducibility — High Reproducibility

Probabilistic Tractography

- We normally have one dataset per subject, not many.

- Probabilistic Tractography as a two-step process:

a) Use DWI data and a model to infer a fibre orientation **and its uncertainty** in each voxel.

b) Use the estimates **and the uncertainty to build a path probability map** to a seed.

How can we estimate uncertainty?

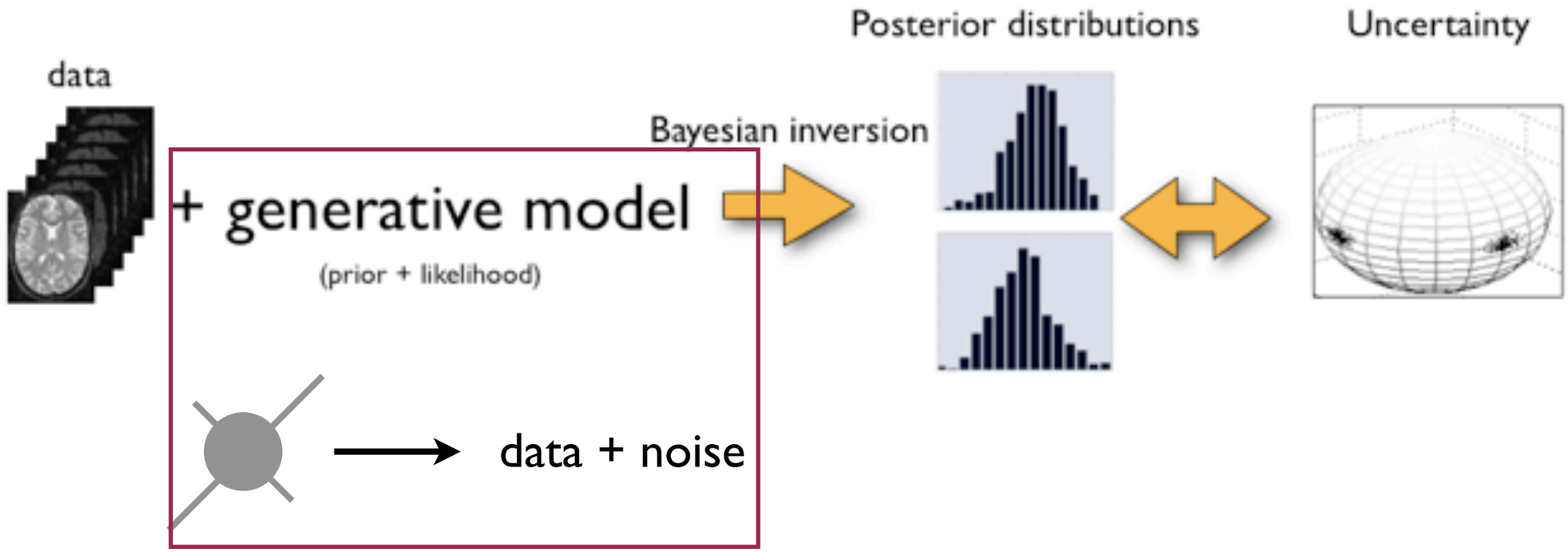
- Remember ... a long time ago in the world of fMRI ...

- We estimated two things:
  - A cope file (the parameters)
  - A varcope file (uncertainty in these parameters)

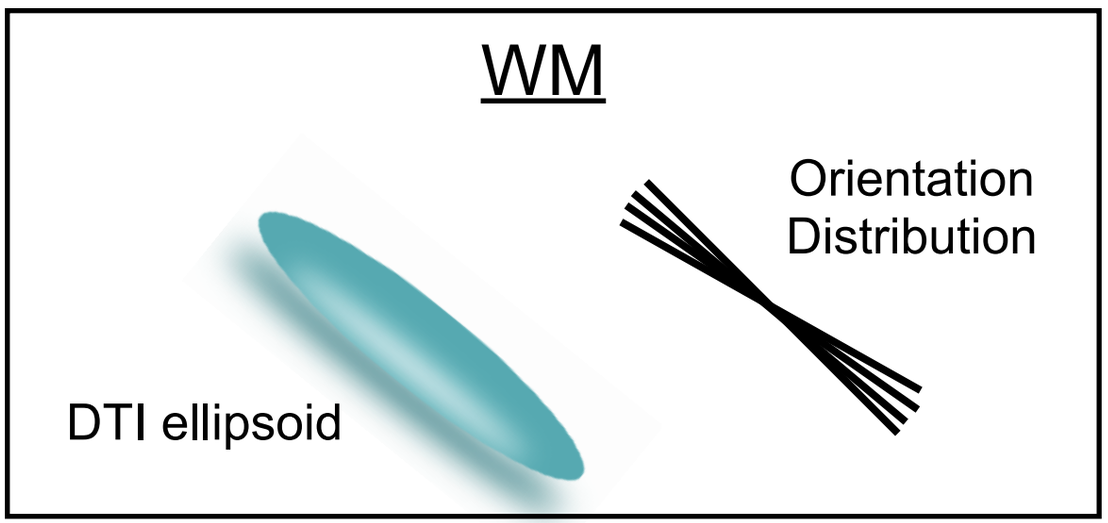
- We estimated our parameters, and their uncertainty from a single dataset.

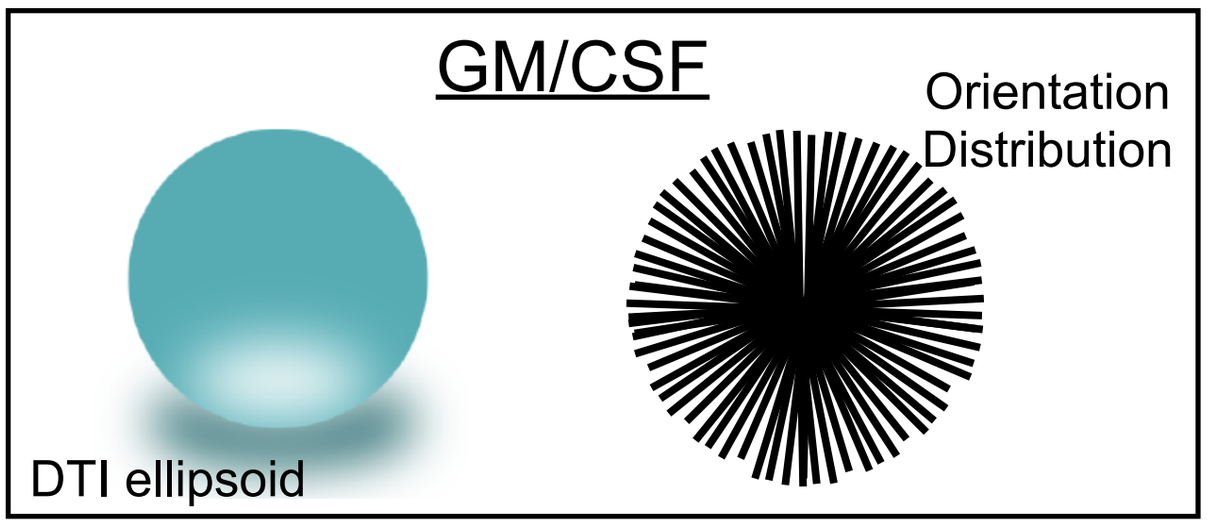
- Can we do a similar thing with Diffusion parameters?
  - In the context of GLM, we have analytic formulas
  - For diffusion (especially orientations) we don't

Quantifying Uncertainty
Bayesian Modelling (FDT BedpostX)

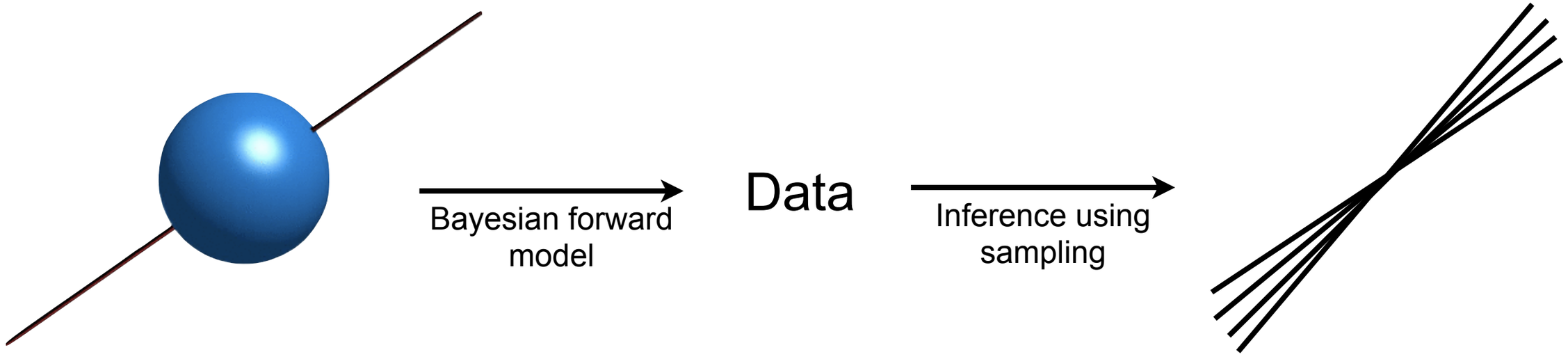


- Uncertainty can be quantified from a single data set
- Instead of a single orientation estimate, infer a distribution of orientations in each voxel.





Diffusion Model in FDT BedpostX



* Simple model of local diffusion (ball and stick). Alternative to DTI model.
- A single anisotropic direction (stick) with isotropic background diffusion (ball)
- Direction modelled explicitly and separated from isotropic partial volumes
- Can be easily extended to model multiple orientations within a voxel.

Anisotropic Volume Fraction (unknown)

Diffusivity (unknown)

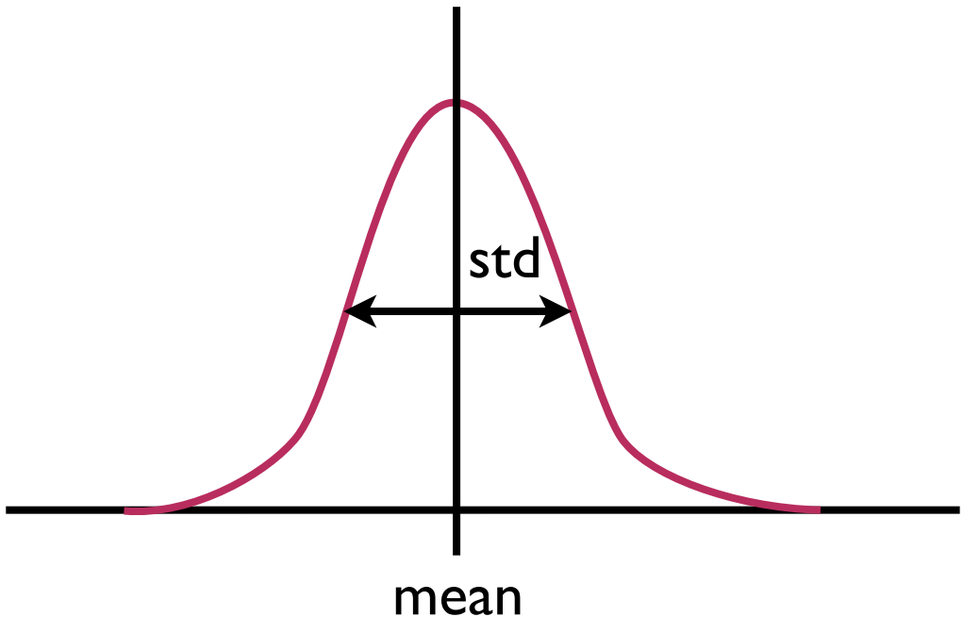
Fibre Orientation (unknown)

$$s_j = s_0 \left[(1-f)\exp(-b_j\, d) + f \exp(-b_j\, d(\boldsymbol{x}_j^{\mathrm{T}} \boldsymbol{v})^2)\right]$$

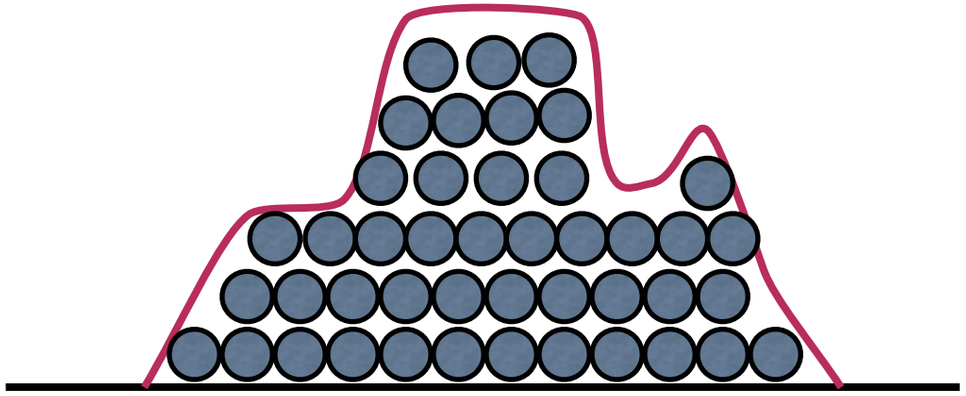
Measured Signal for Gradient *j*

b-factor for gradient *j* (known - bvals)

Unit vector representing the direction of gradient *j* (known - bvecs)

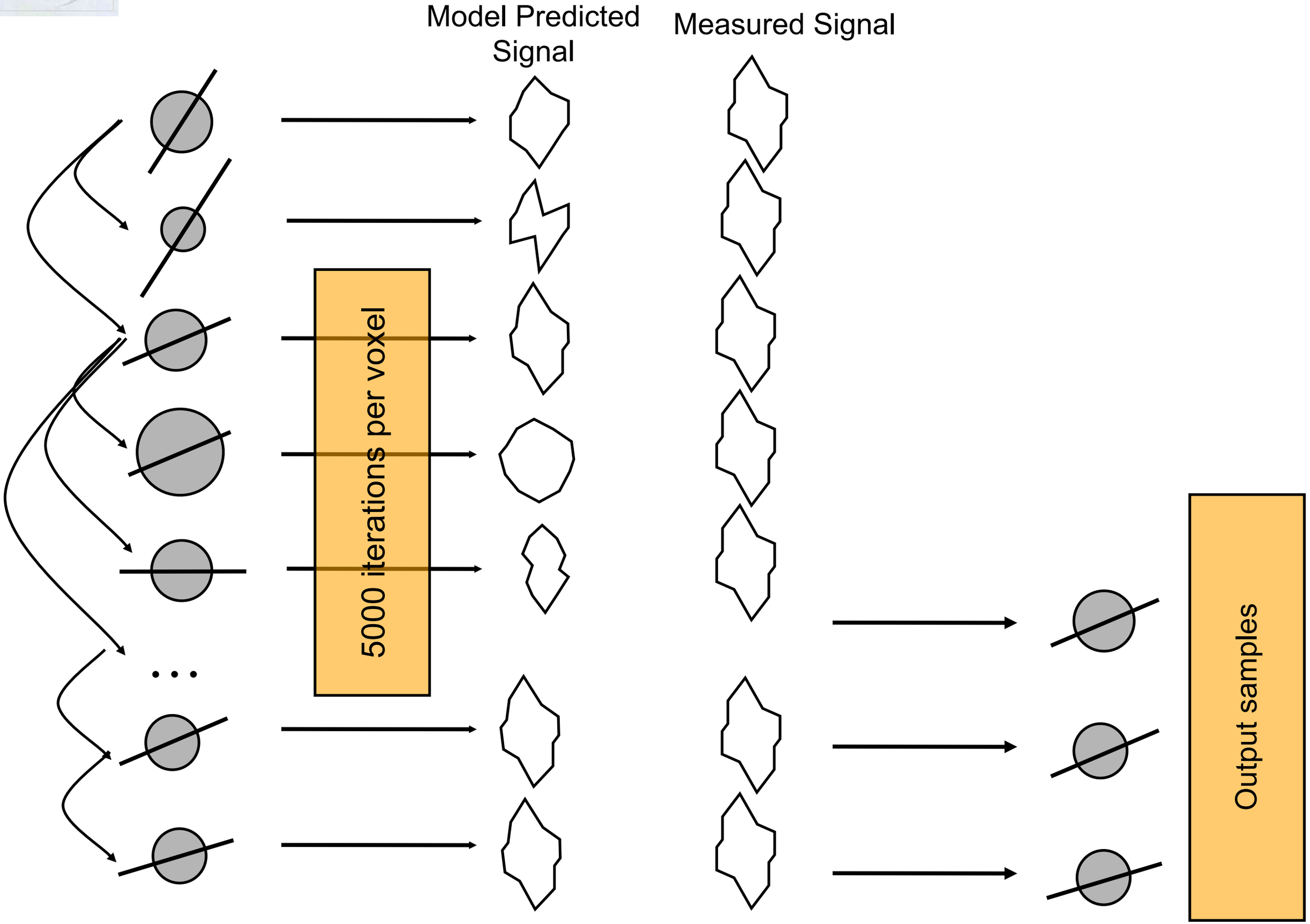


Distribution entirely characterised by a few parameters

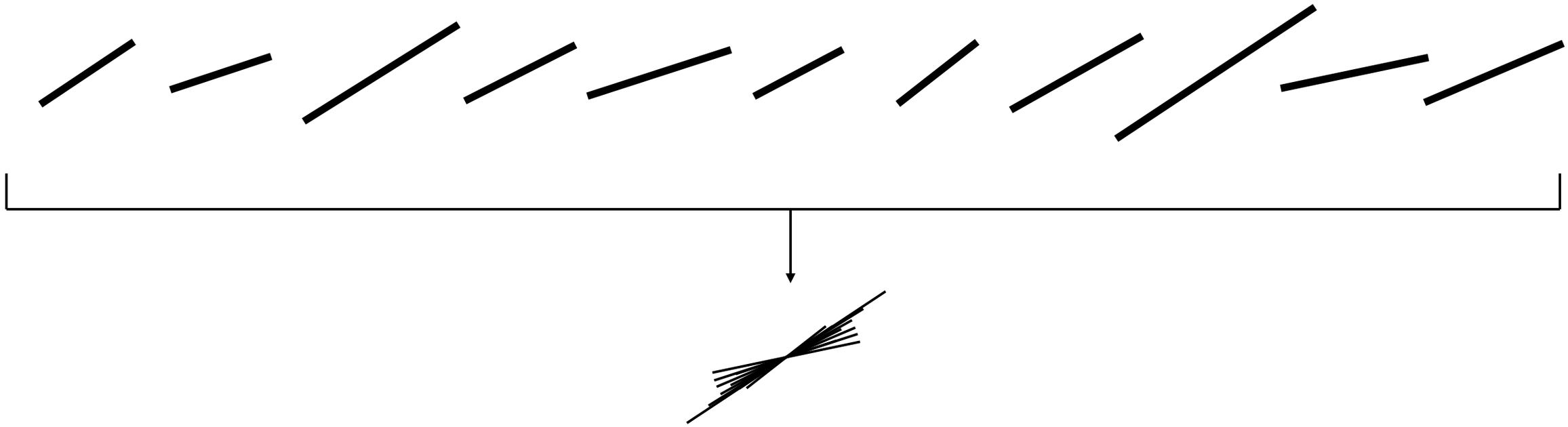


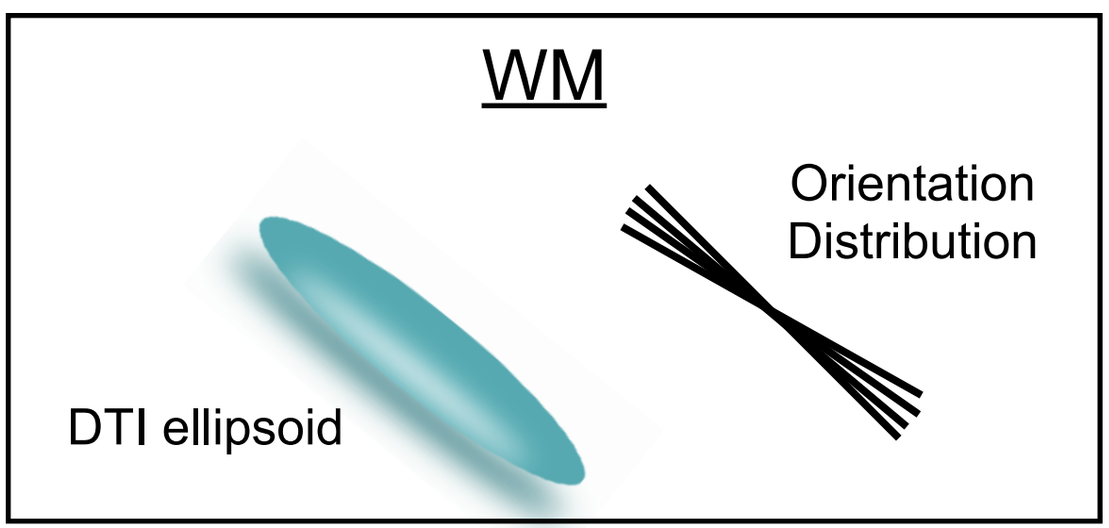
Complex distribution approximated using samples

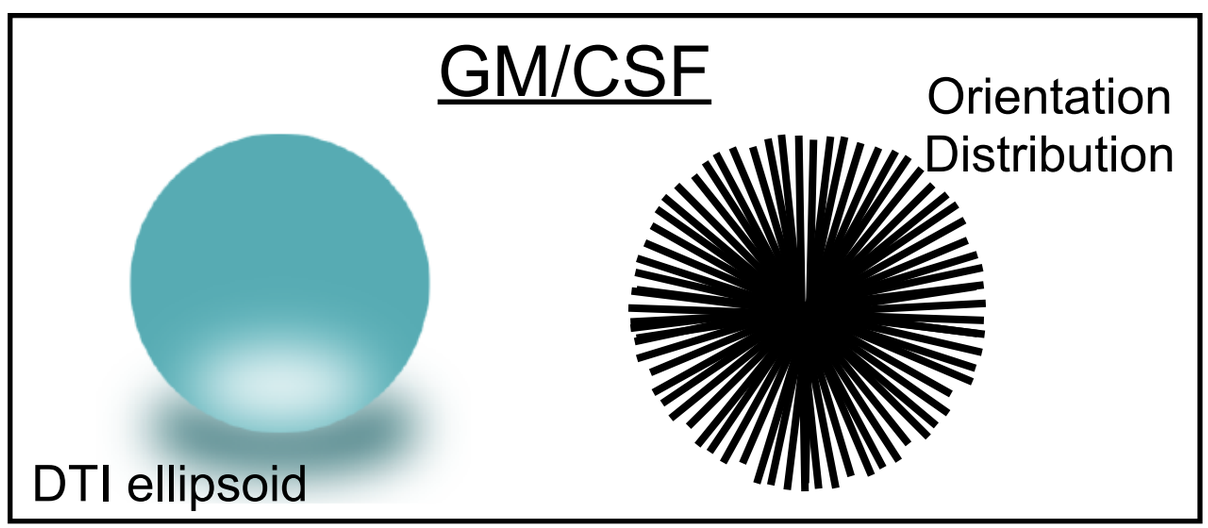
Metropolis Hastings MCMC Sampling



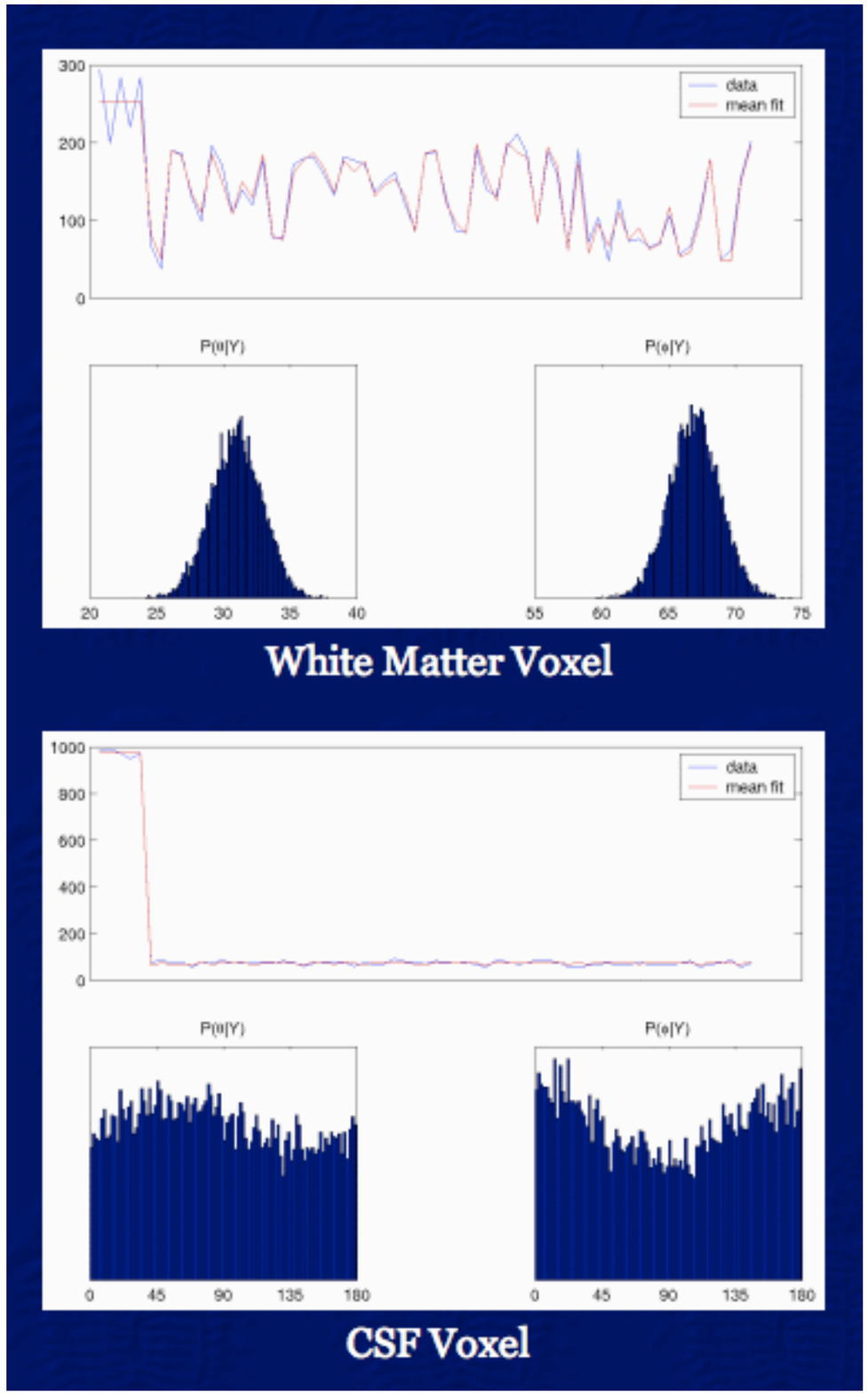
Output in Each voxel = Distributions of Parameters

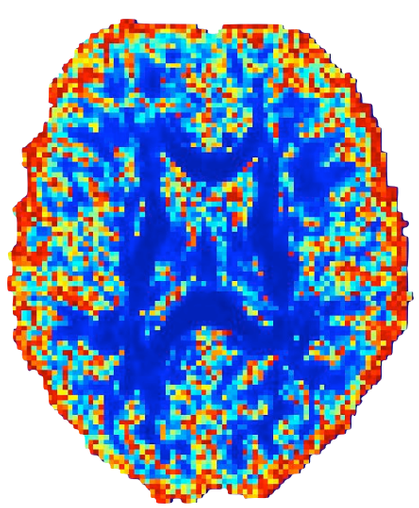




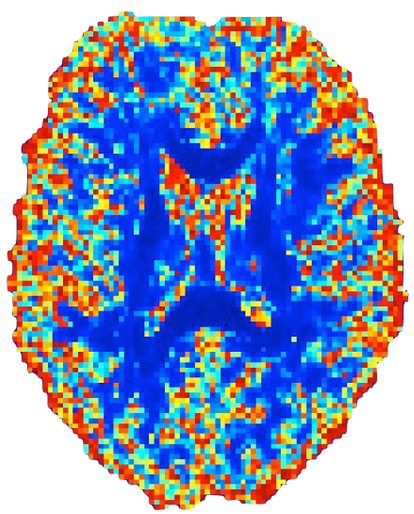


Uncertainty from a single dataset





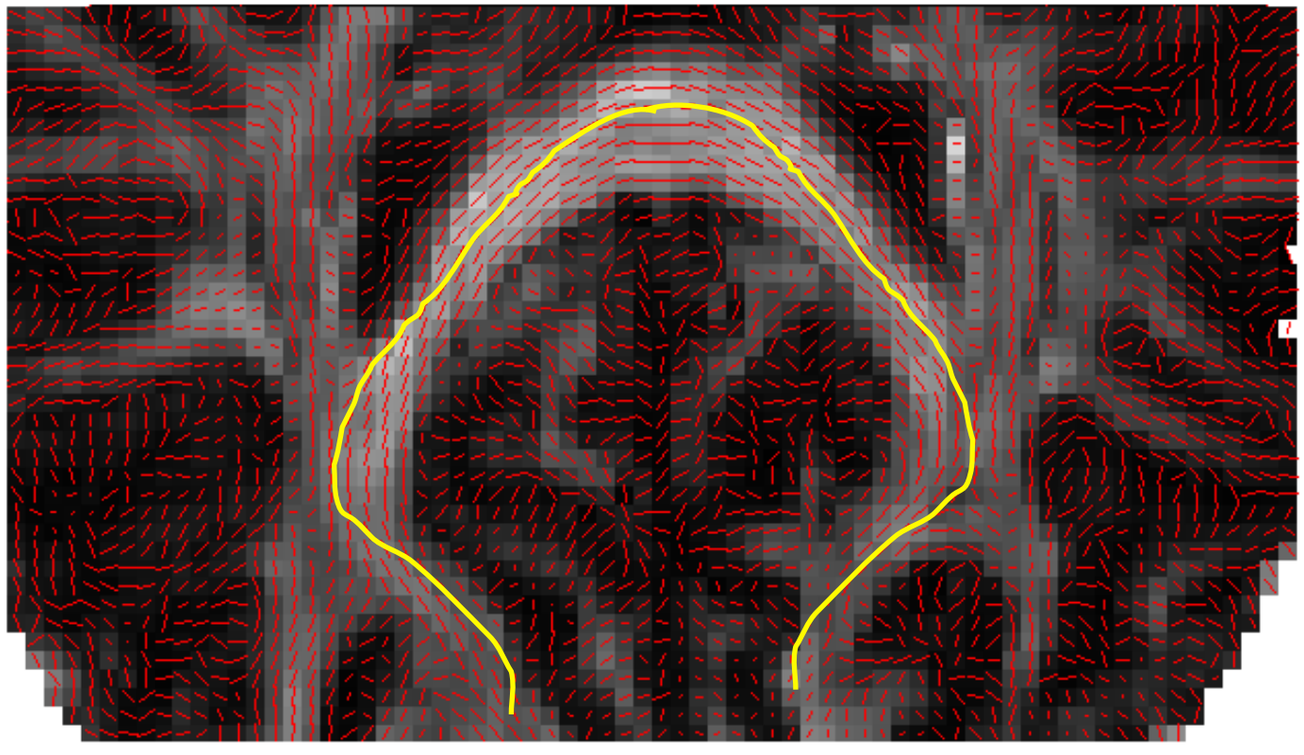
Empirical



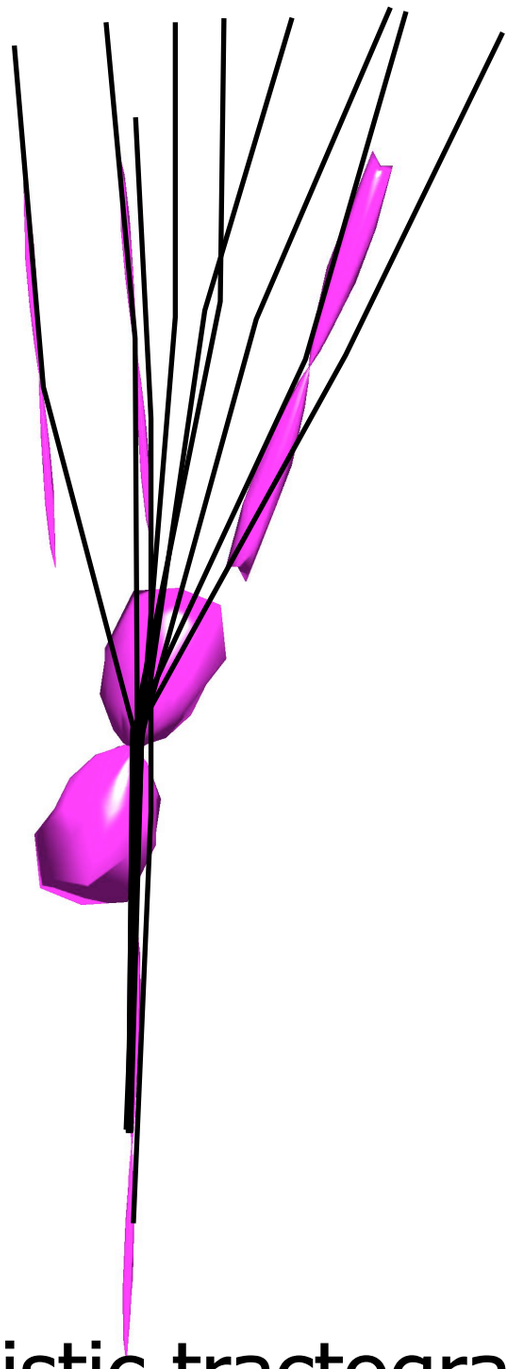
Bayesian

Probabilistic tractography

- But now, we no longer have a single direction at each voxel. How can we do tractography?



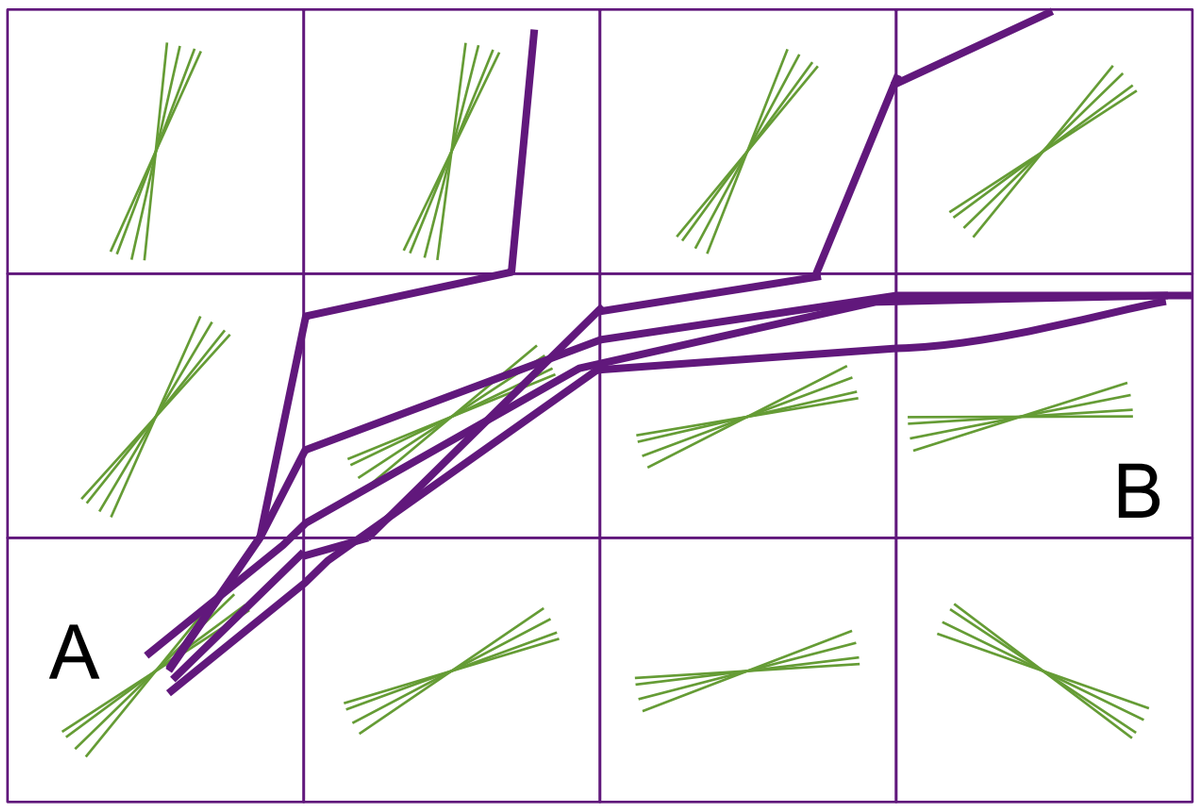
'Streamlining'



Probabilistic tractography

Behrens et al, 2003, Parker et al. 2003, Hagmann et al 2003, Jones et al. 2004

Probabilistic Tractography - Propagating the Uncertainty

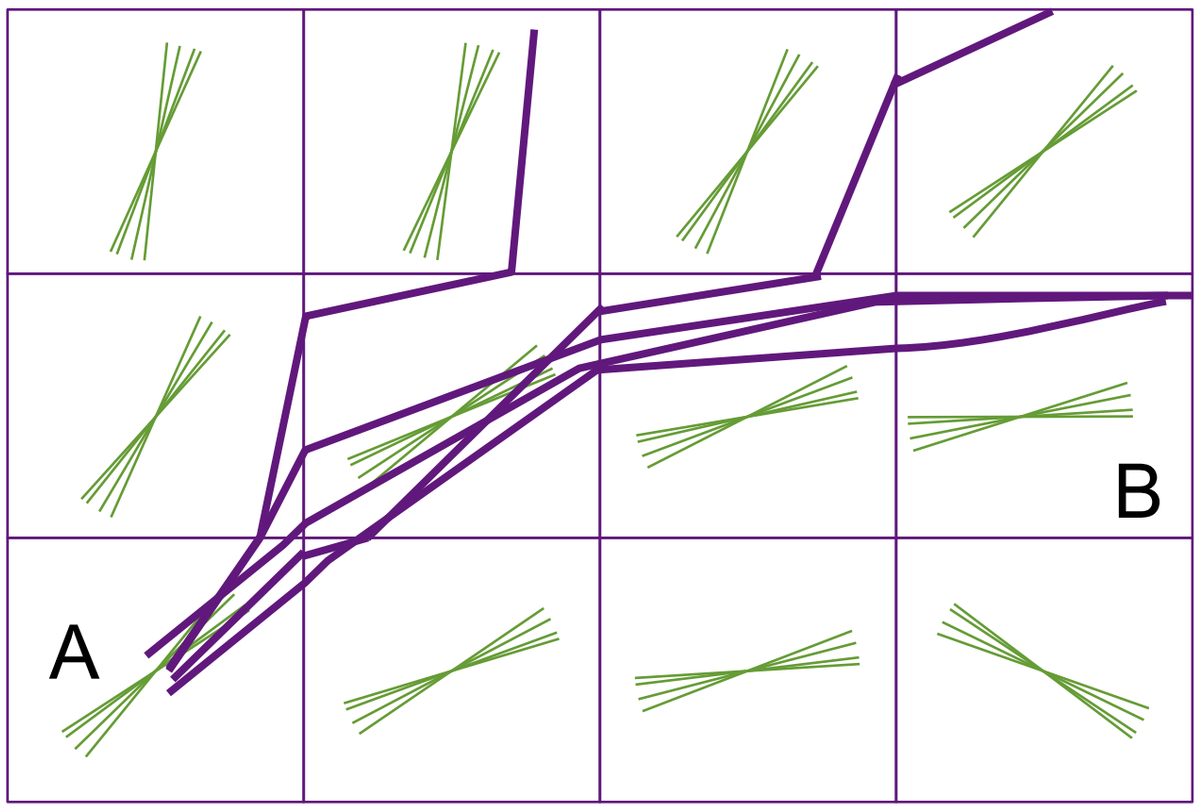


Behrens et al, 2003
Parker et al, 2003

- Propagate N streamlines from a seed, but for each propagation step choose randomly an orientation from the underlying distribution.

- Build a spatial distribution of curves that mimics the overlapped results from multiple deterministic tracking on multiple scans

Probabilistic Tractography - Propagating the Uncertainty



Behrens et al, 2003
Parker et al, 2003

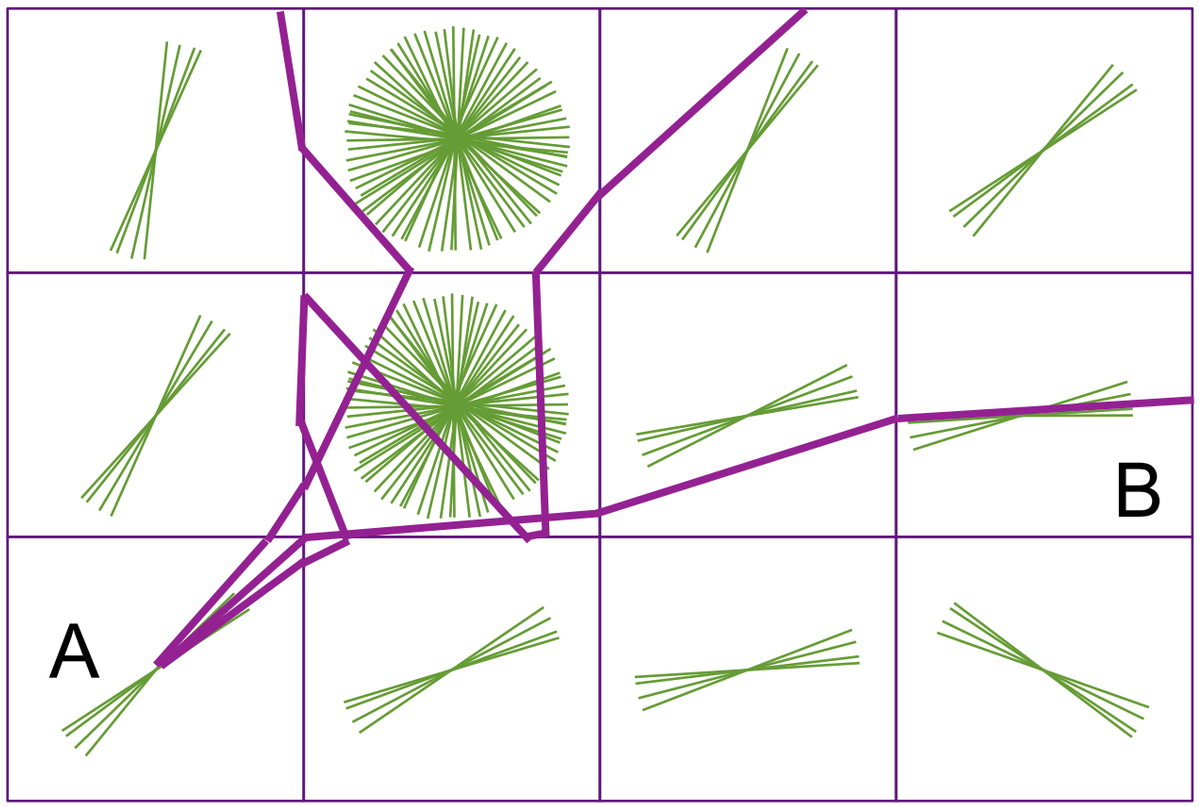
Define the degree of overlap at each location B, as:

$$P_{AB} = M/N$$

M:number of streamlines that go through B
N: total streamlines generated from A

This is the probability of a curve starting at A and going through B.

Probabilistic Tractography - Propagating the Uncertainty



Behrens et al, 2003
Parker et al, 2003

- Can now propagate through isotropic regions (e.g. GM).

- Do not need to stop when anisotropy is low, as in deterministic tracking.

- The high uncertainty will be reflected in the probability map.

-Still impose a curvature threshold to avoid swirled trajectories.

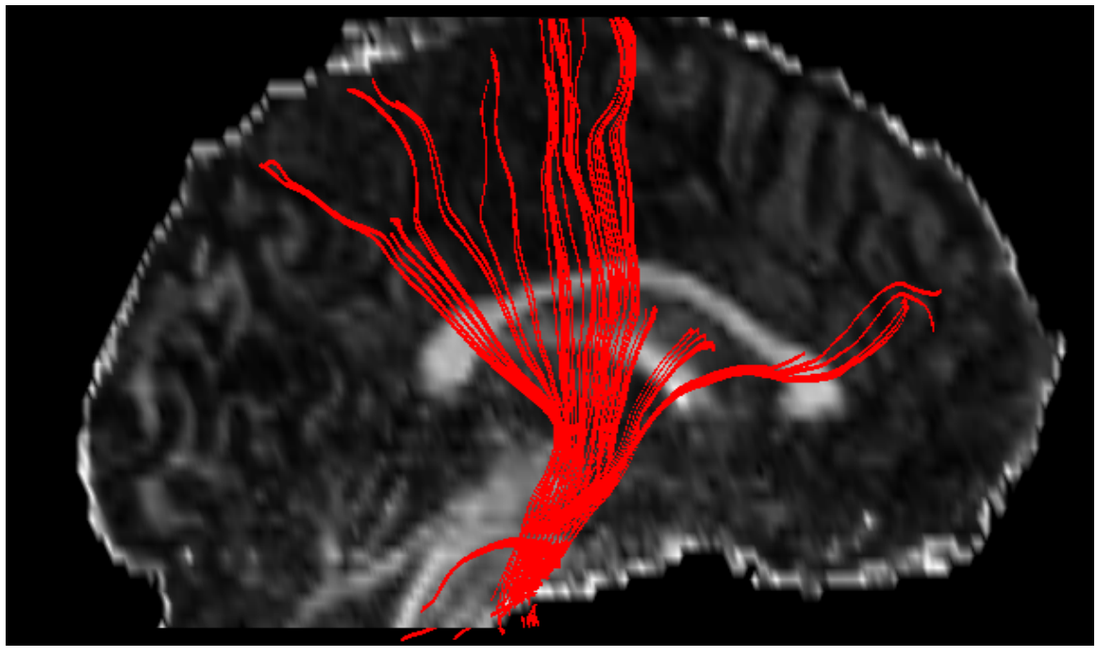
Path Probability Map

- Recall that it assesses how reproducible results are

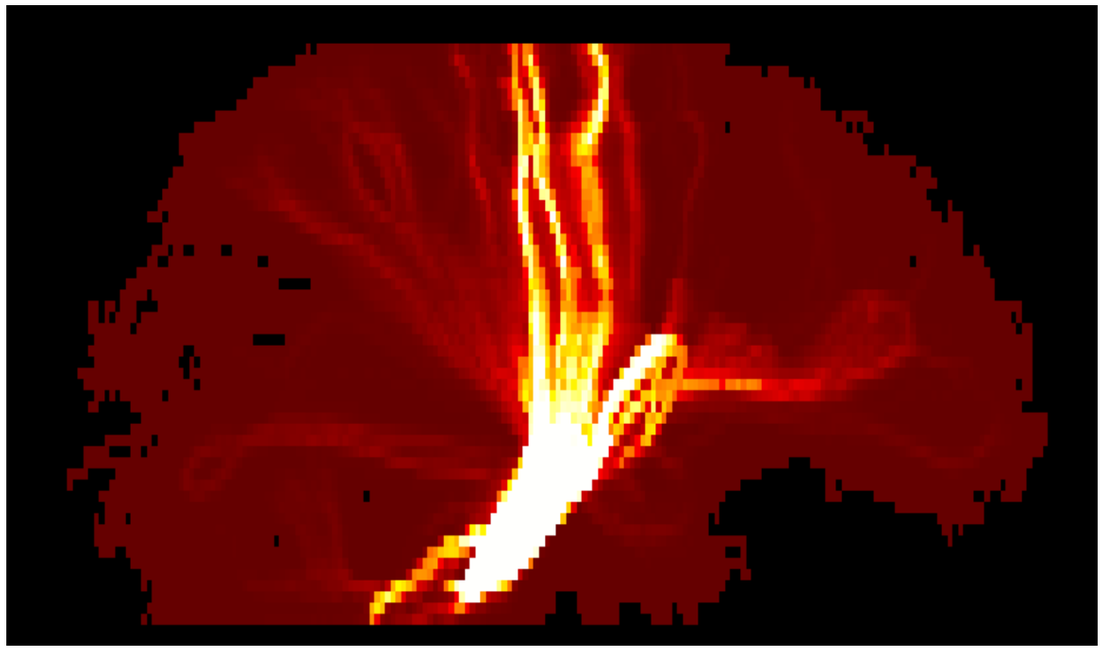
- Often called “connection probability”, “connectivity index”, “connectivity strength”. But it does not quantify how strong a connection is...

- Rather, how robust it is against noise

Deterministic Tractography



Probabilistic Tractography



Low Probability

High Probability

What is a quantitative measure of connectivity?

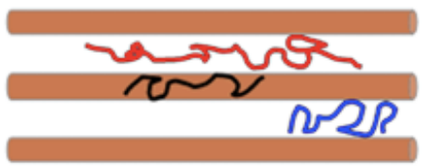
- Number of axons connecting 2 areas?
- Proportion of axons from a seed that reach a target?
- "Integrity" of the connecting white matter …
  - Effective conductivity?
  - Degree of myelination?
  - Packing density?
- What are we measuring?
  - The probability that the **dominant** path through the diffusion field passes through this region.

Probabilistic Streamline Tractography Summary

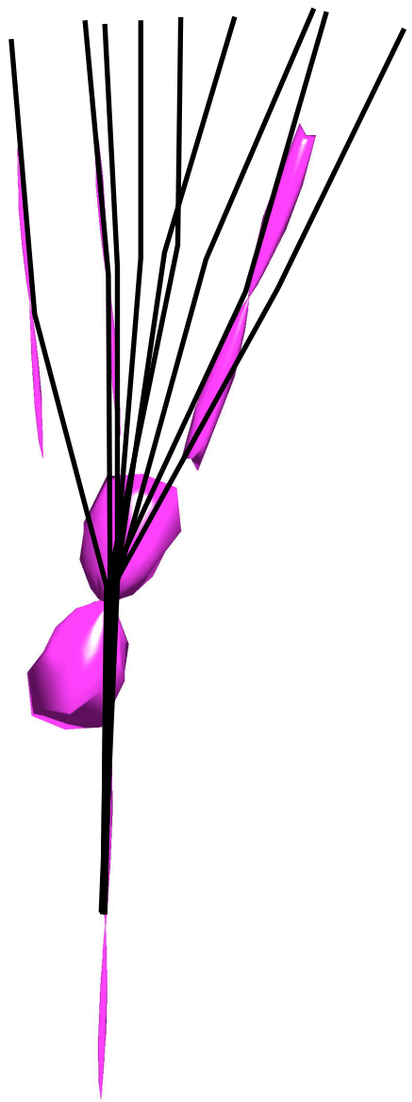
- Needs apart from orientation estimates, an estimate of their uncertainty. Does not need to be the ball and stick model, the DTI model can be used instead!

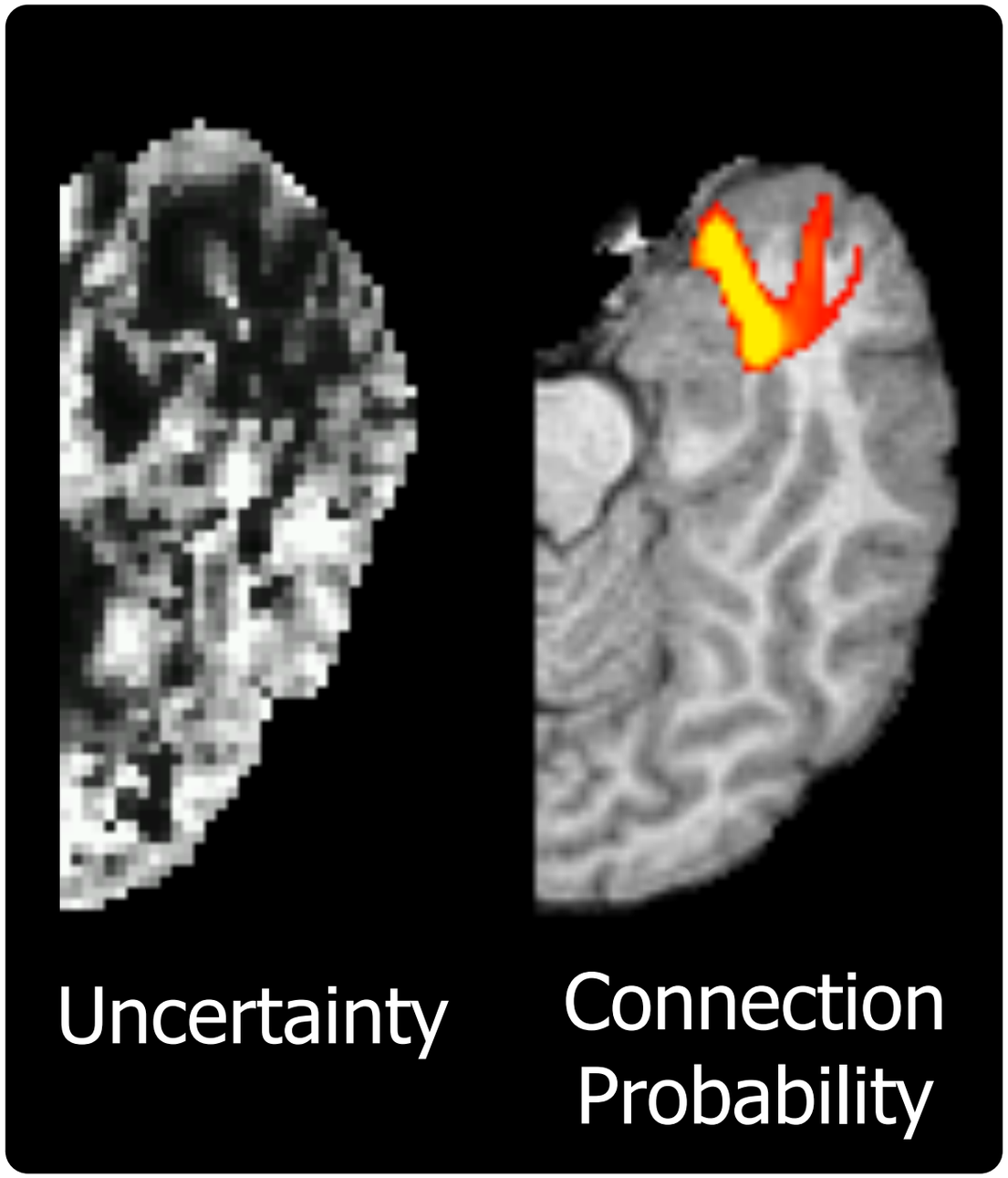
- Propagate streamlines repeatedly from a seed, but the orientation field is no longer deterministic. In each propagation step choose randomly an orientation from the underlying distribution.

- A connection probability value>=0 can be obtained from a seed A to any voxel in the brain B. This assesses **the reproducibility of the path from A to B, along which water molecules preferably diffuse.**



Probabilistic Tractography

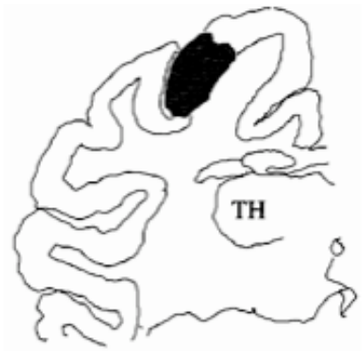


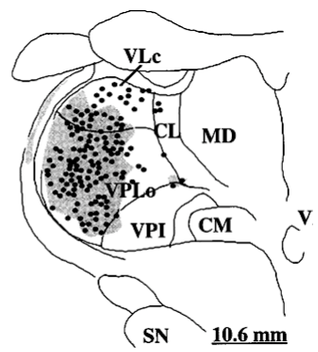


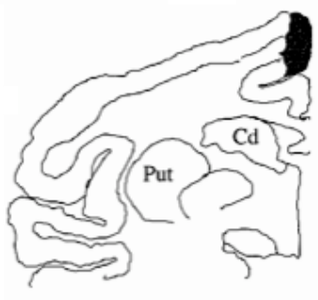
- Allows you to track into regions of low anisotropy, eg grey matter
- Provides quantitative probability of connection from A to B

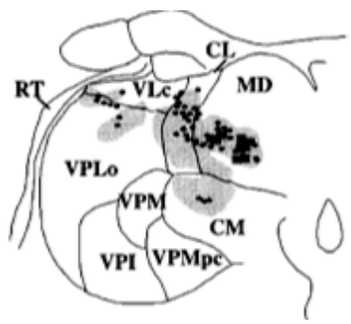
Behrens et al, MRM, 2003

Thalamic connections with cortex





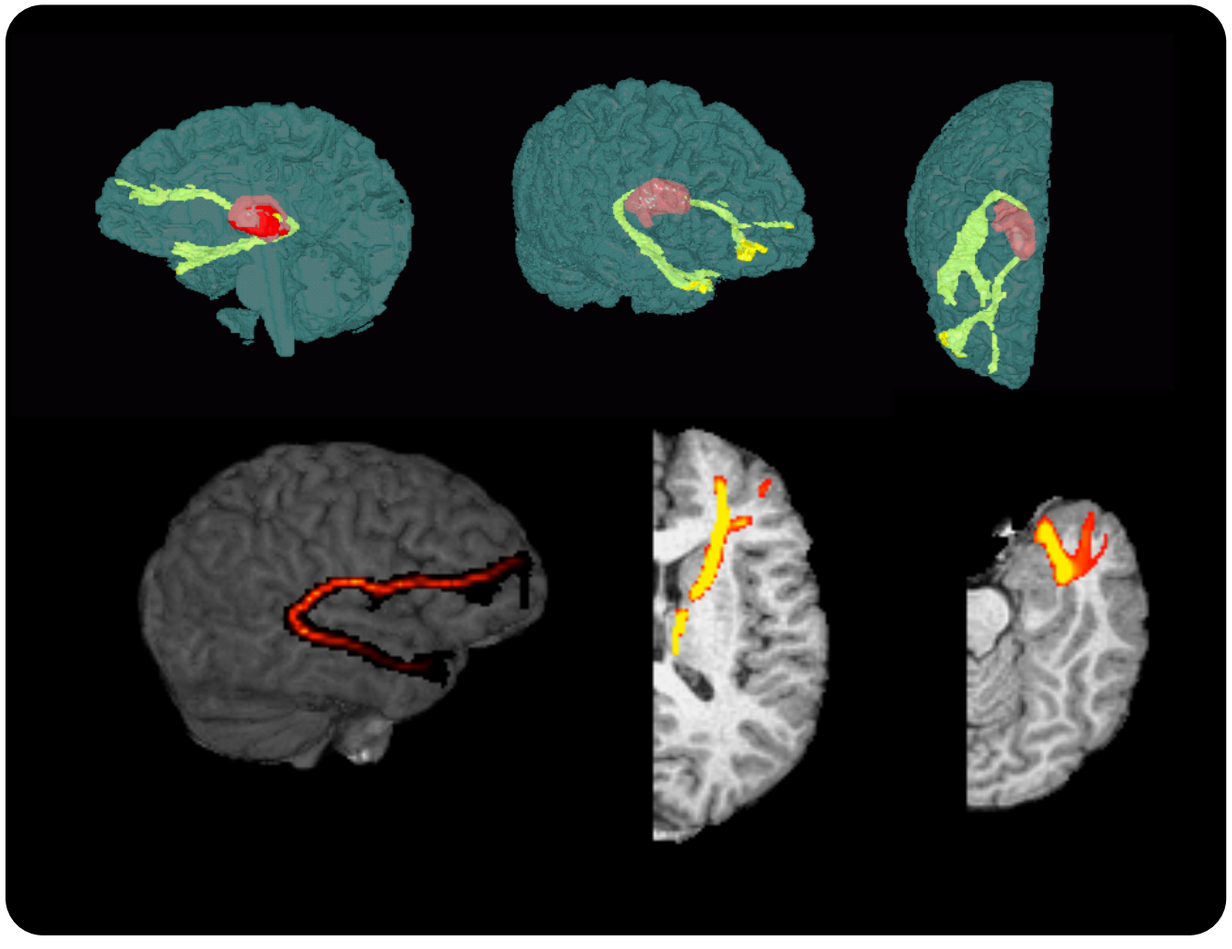


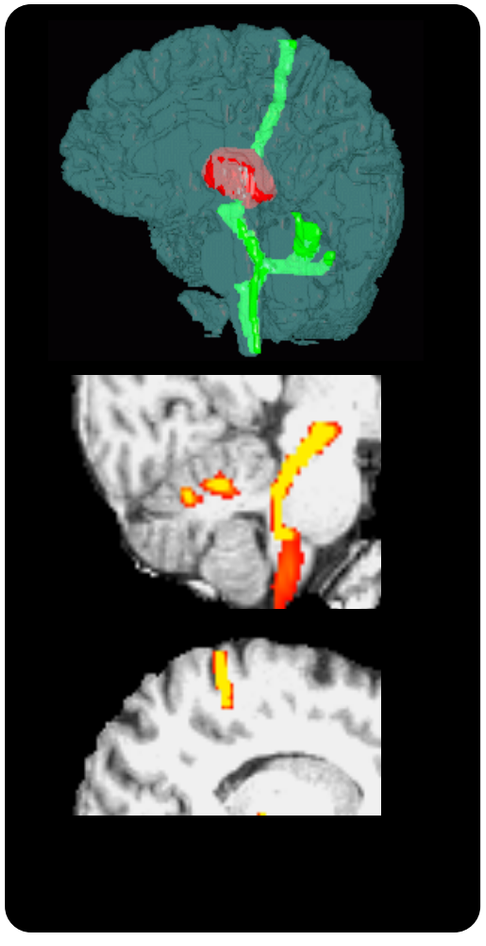


MD -> PFC

VL –> M1

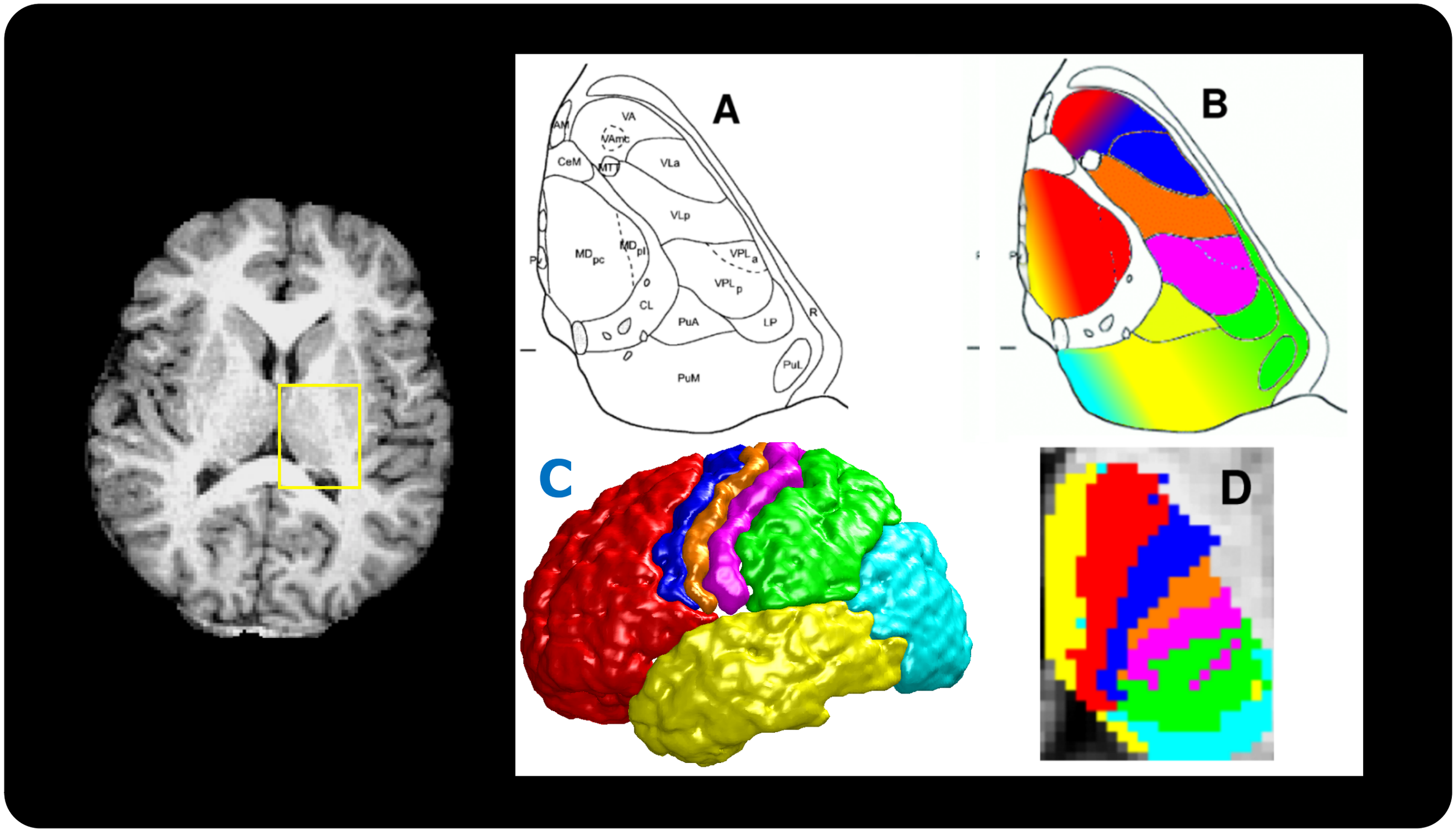
Rouiller et al 1998





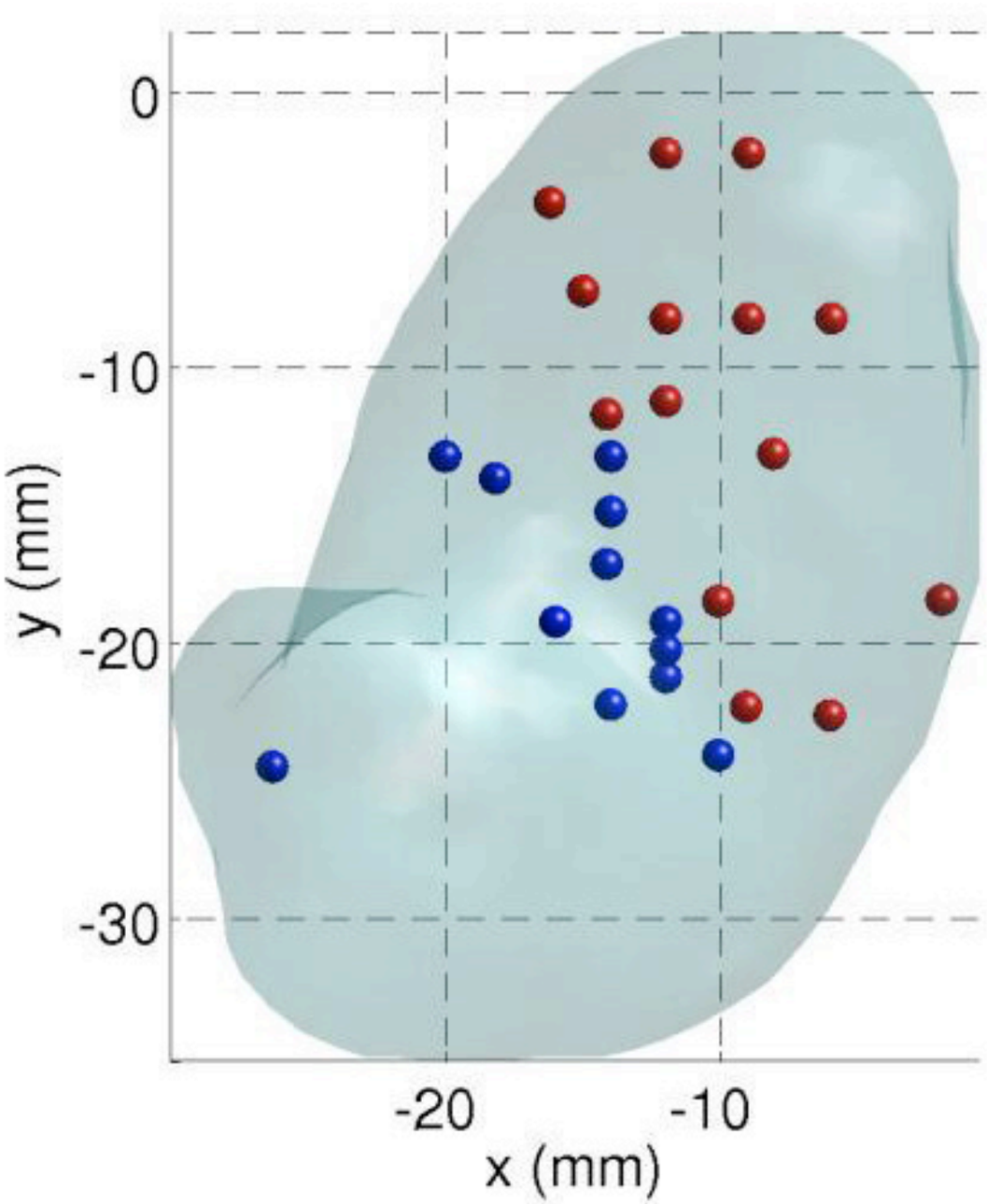
Behrens et al 2003

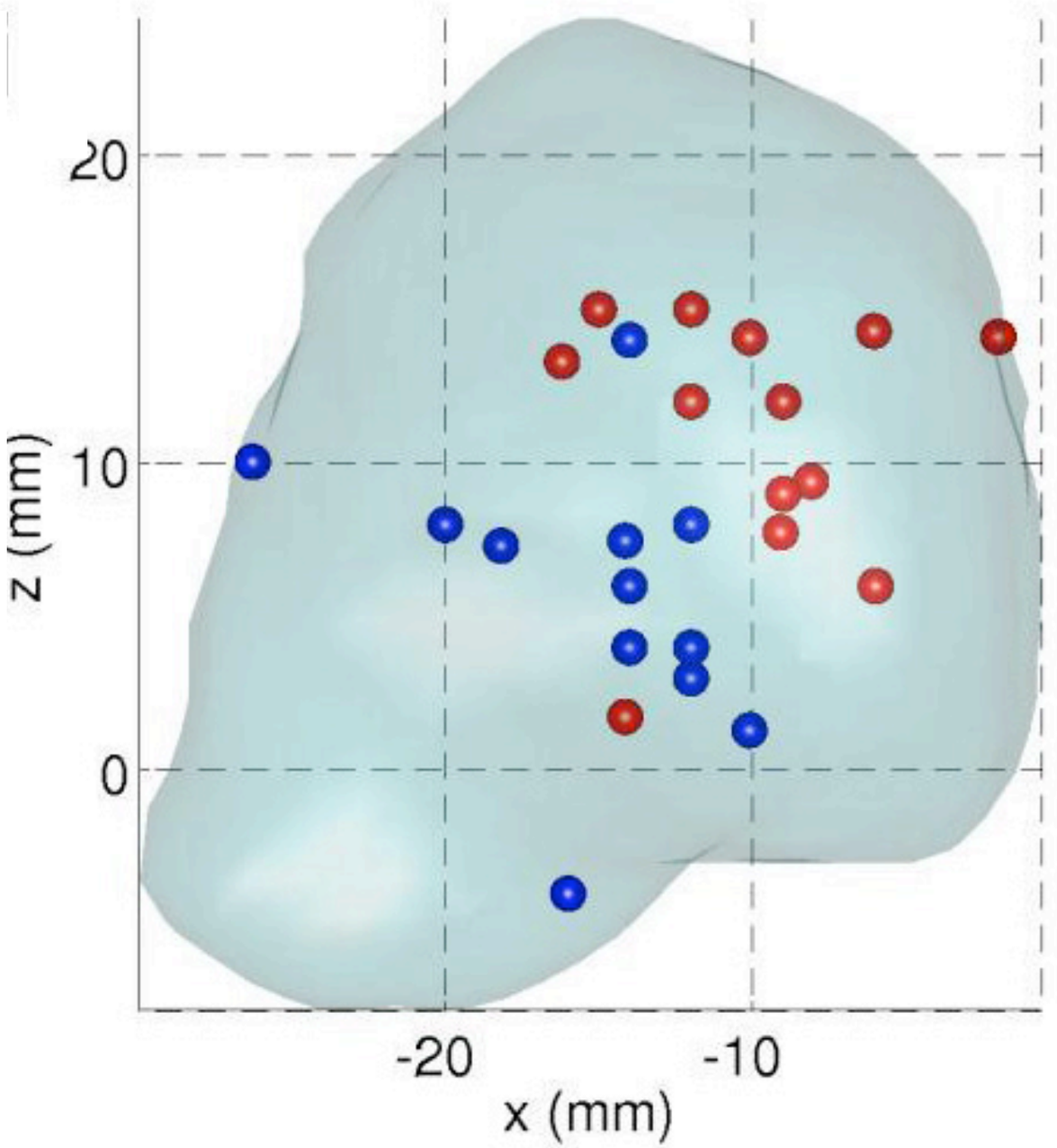
Connectivity-based classification of thalamic voxels produces clusters



Behrens, Johansen-Berg et al, Nature Neuroscience, 2003

Functional validation: meta-analysis of FMRI activations within thalamus



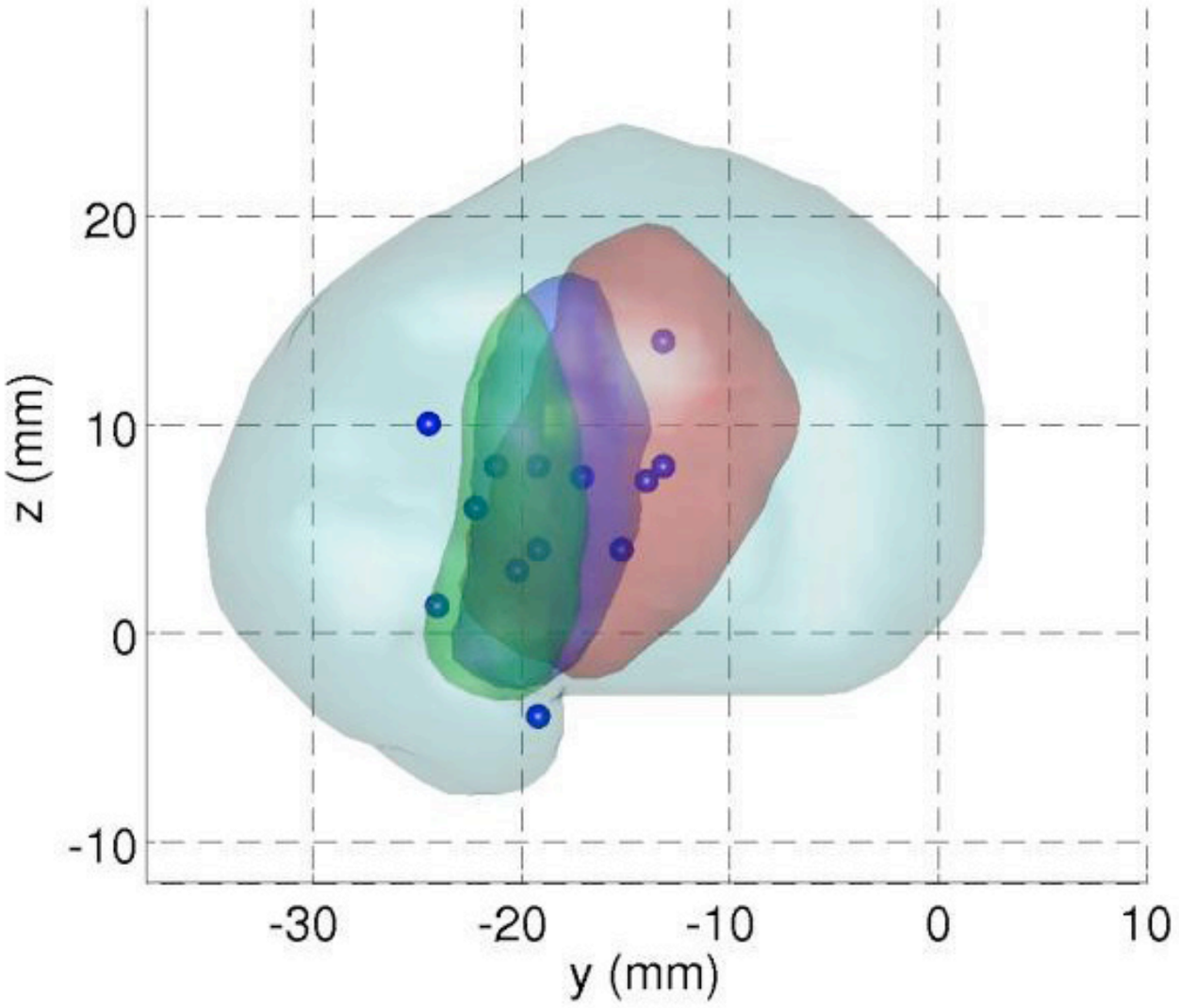


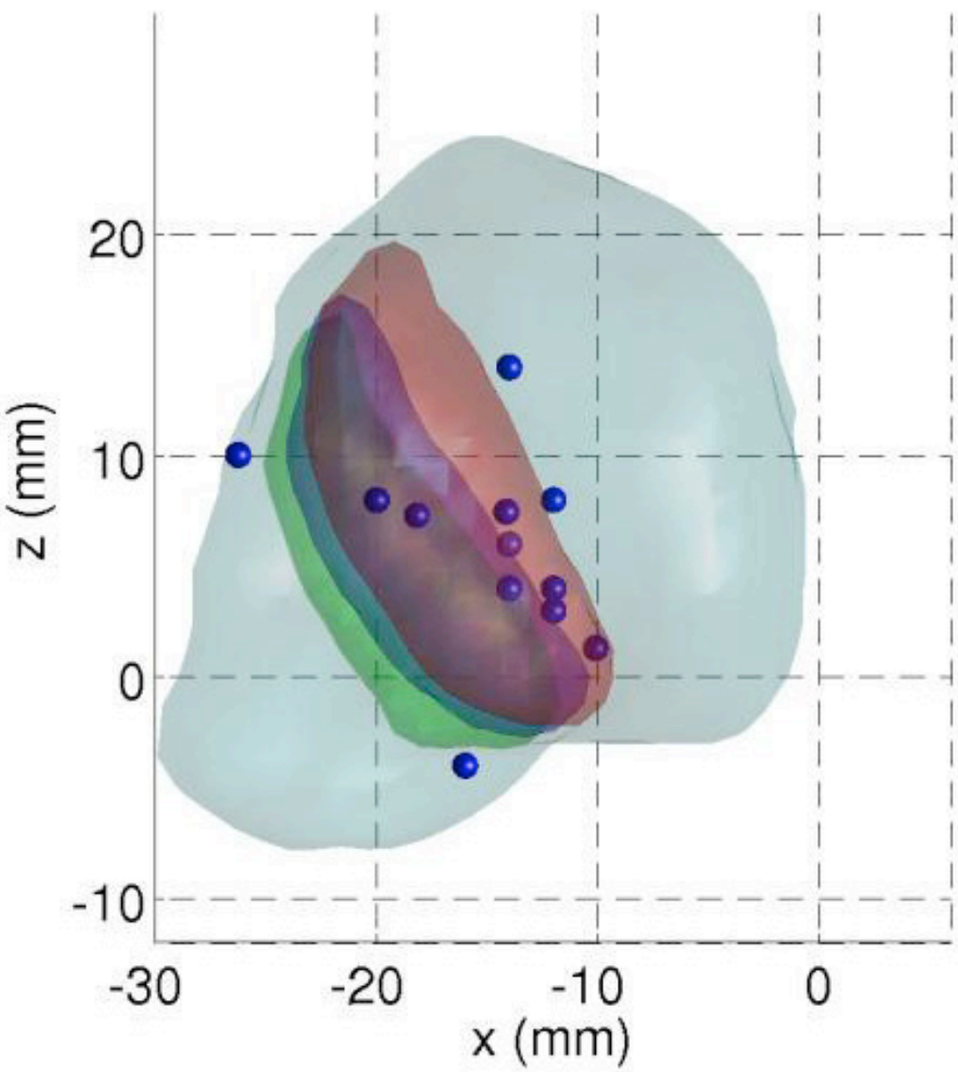
Executive tasks

Motor tasks

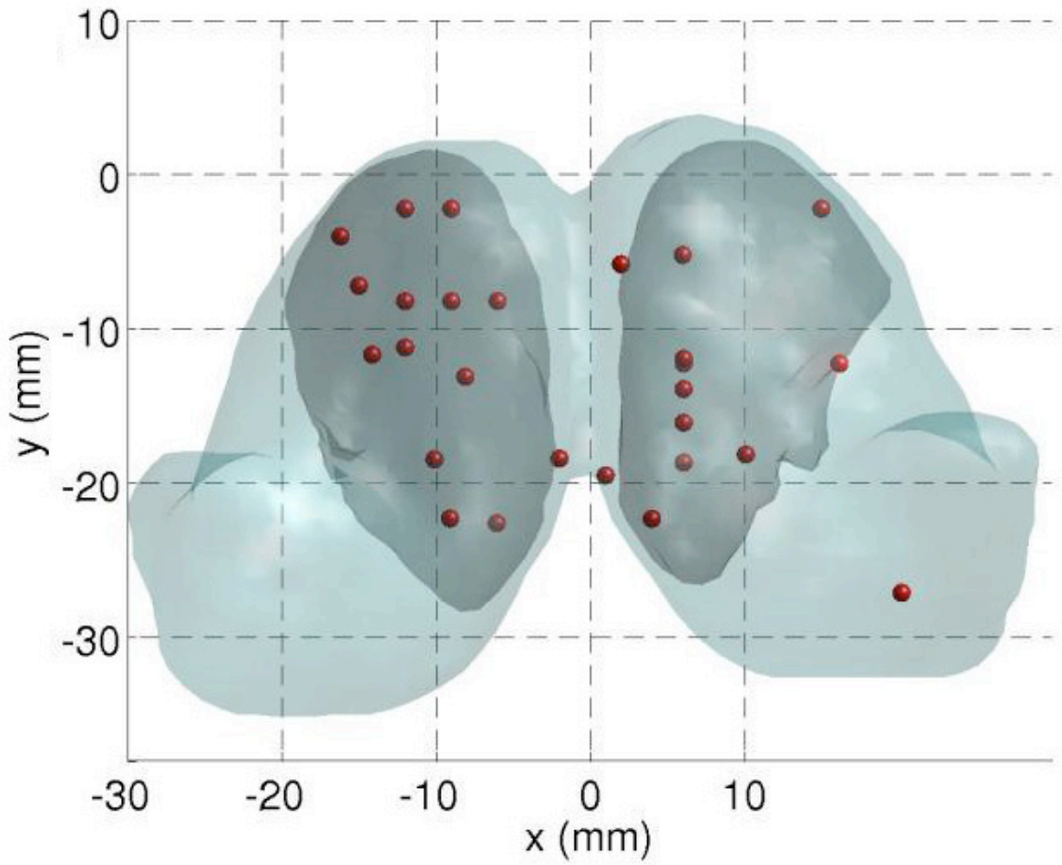
Johansen-Berg et al, Cerebral Cortex, 2005

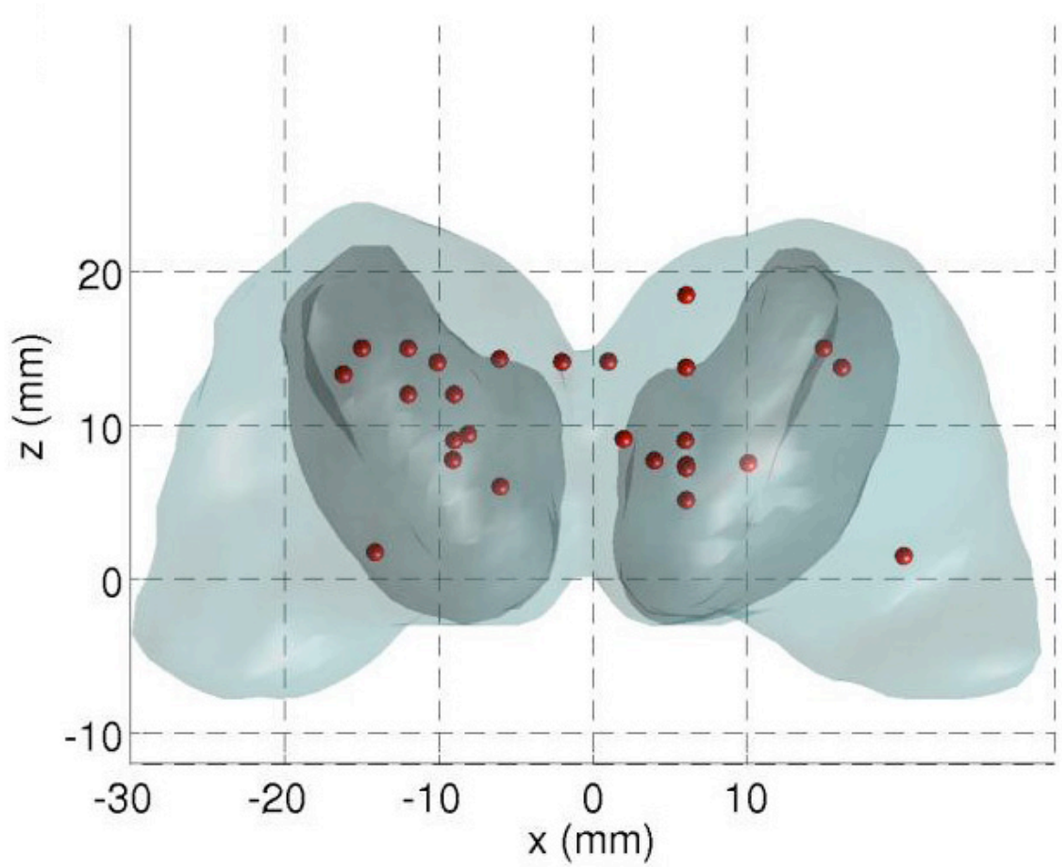
Correspondence between functional activations and connectivity-defined volumes: motor tasks





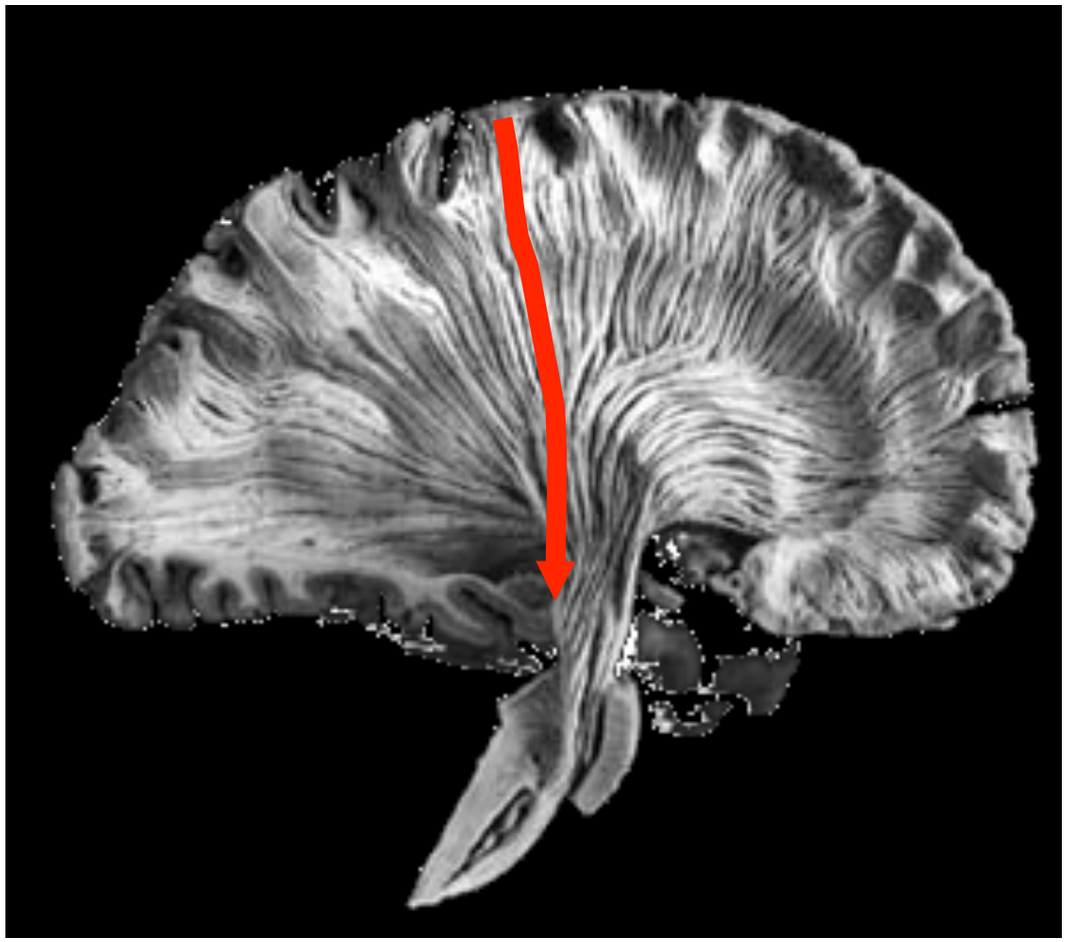
Correspondence between functional activations and connectivity-defined volumes: executive tasks

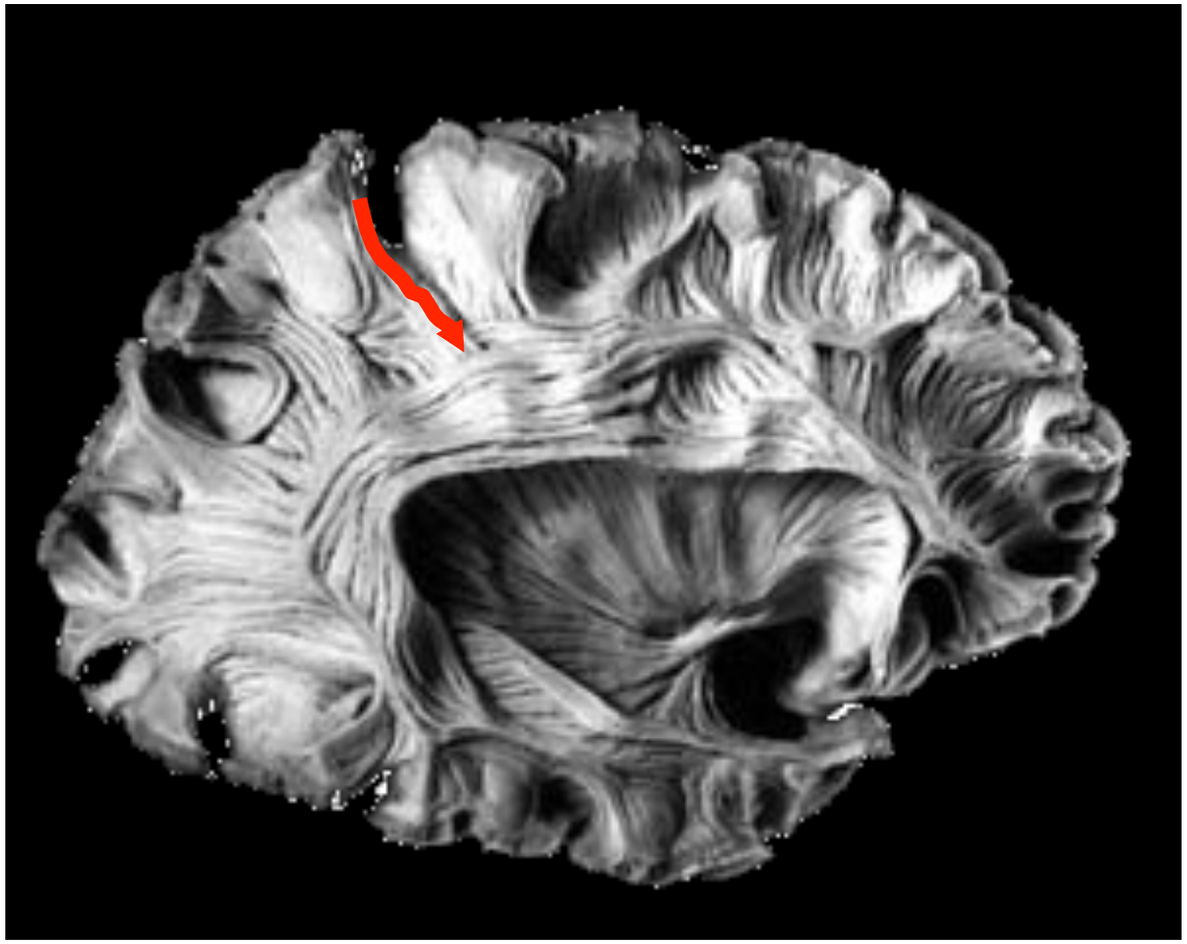




Modelling Complex Fibre Architectures

So far model and infer one fibre orientation per voxel. What happens if we want to track through crossing regions?

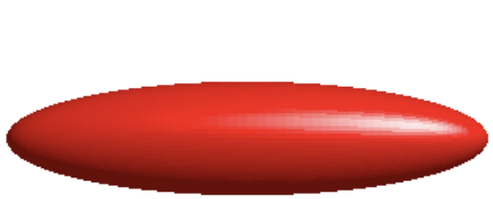




The DTI Model is Not Good in Crossing Regions

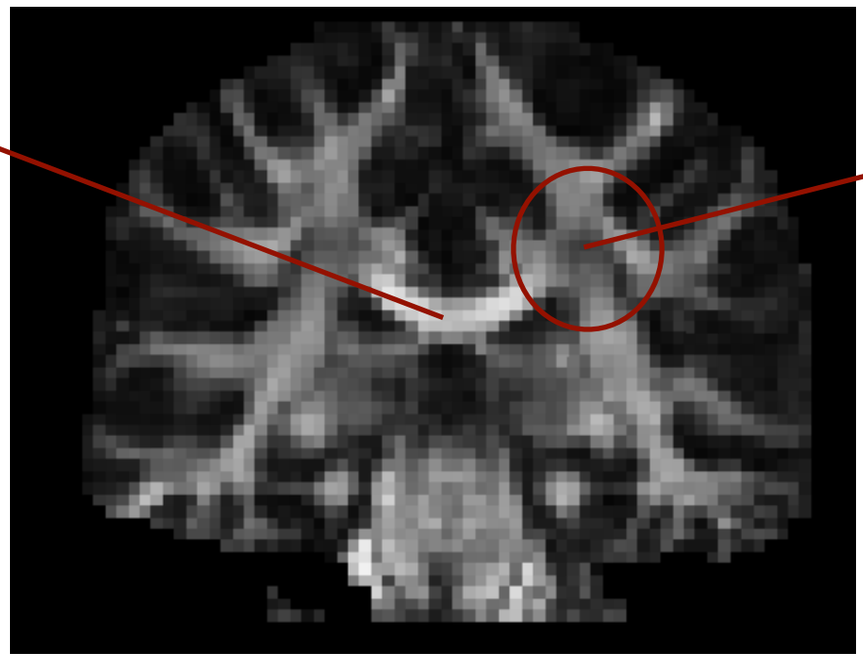
- In voxels containing two crossing bundles, the tensor ellipsoid is pancake-shaped (oblate, planar tensor).

- In these areas, DTI $\mathbf{e}_1$ is meaningless.



Prolate Tensor

$\lambda_1 >> \lambda_2, \lambda_3$

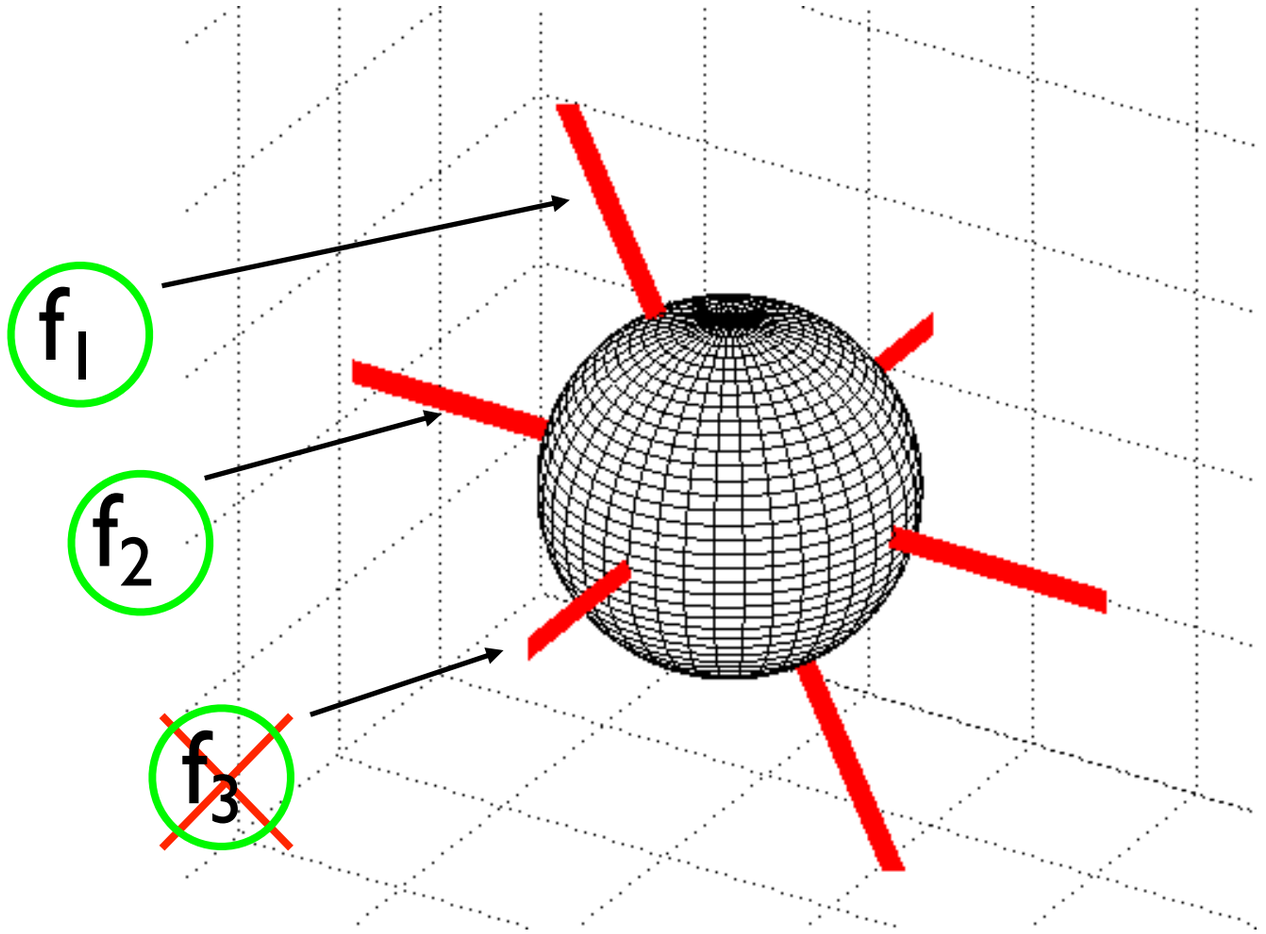


Oblate Tensor

$\lambda_1=\lambda_2 >> \lambda_3$

Modelling Complex Fibre Architectures - Use the Ball and Stick Model

- Simply add more sticks to the model
- Estimate uncertainty for each orientation (stick) modelled.
- Model selection problem: One, two or more fibres within a voxel?
- Automatic Relevance Determination: Only estimate complexity that is supported by the data

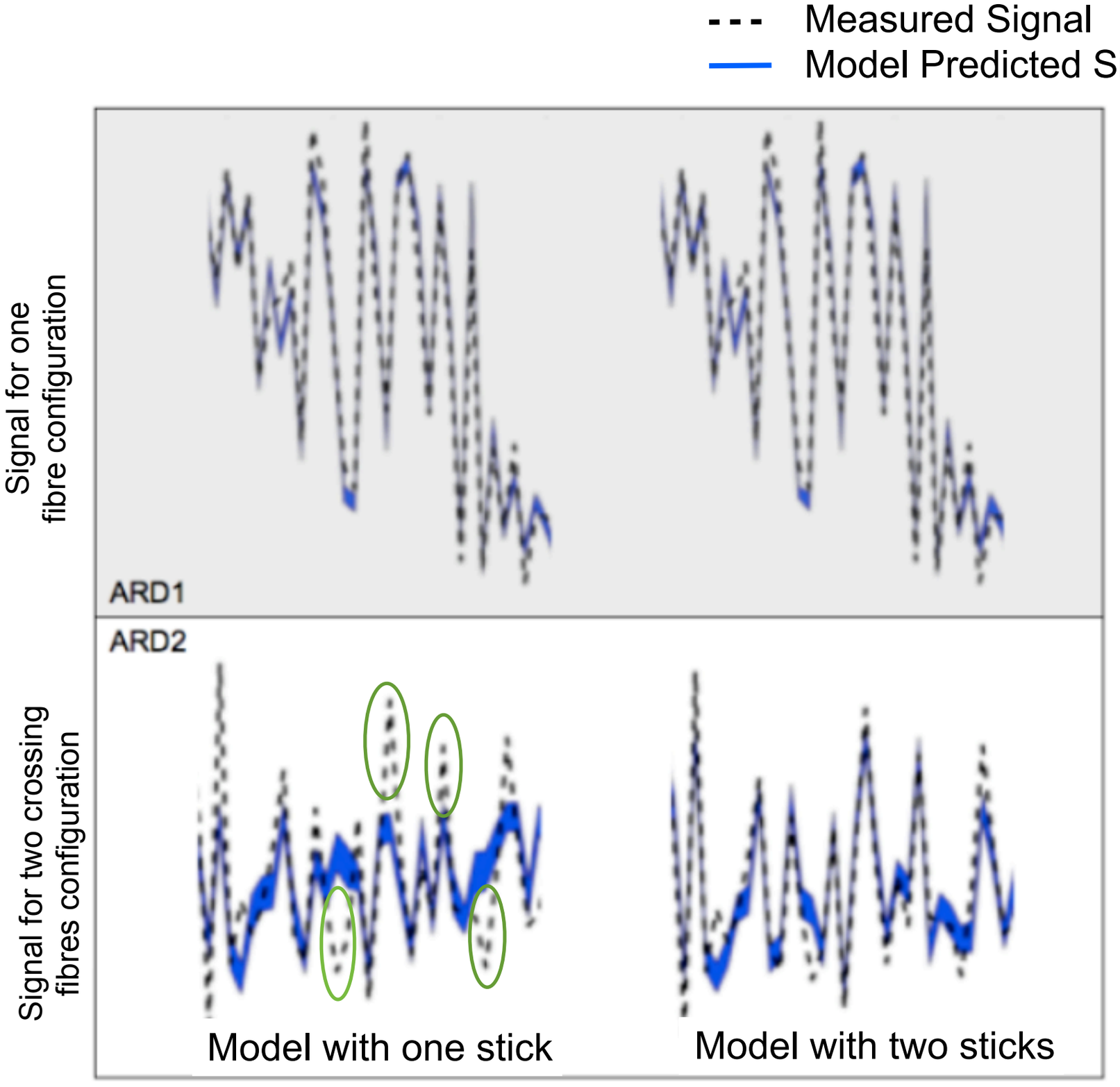


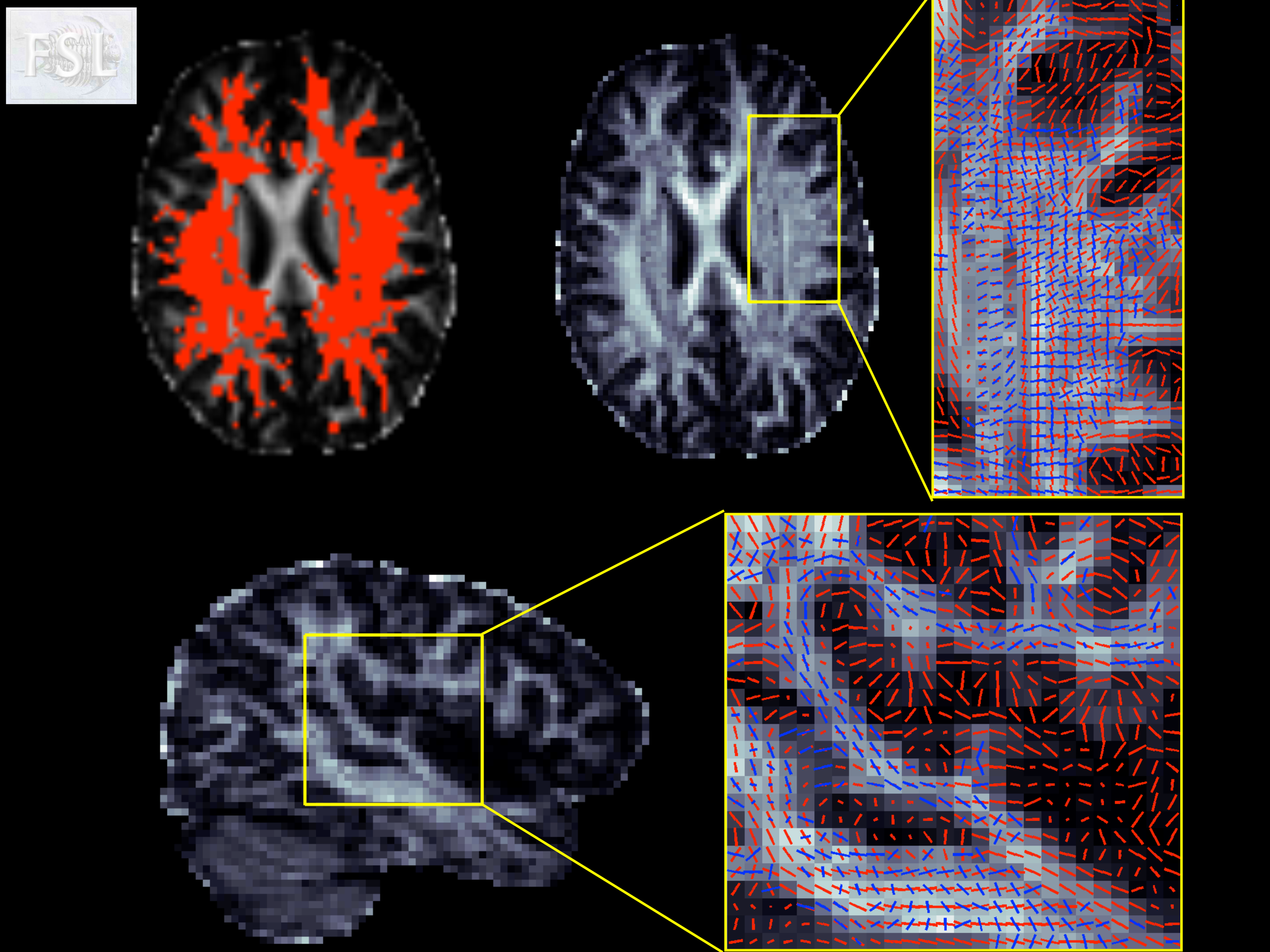
Modelling Complex Fibre Architectures

Automatic Relevance Determination (A.R.D.)

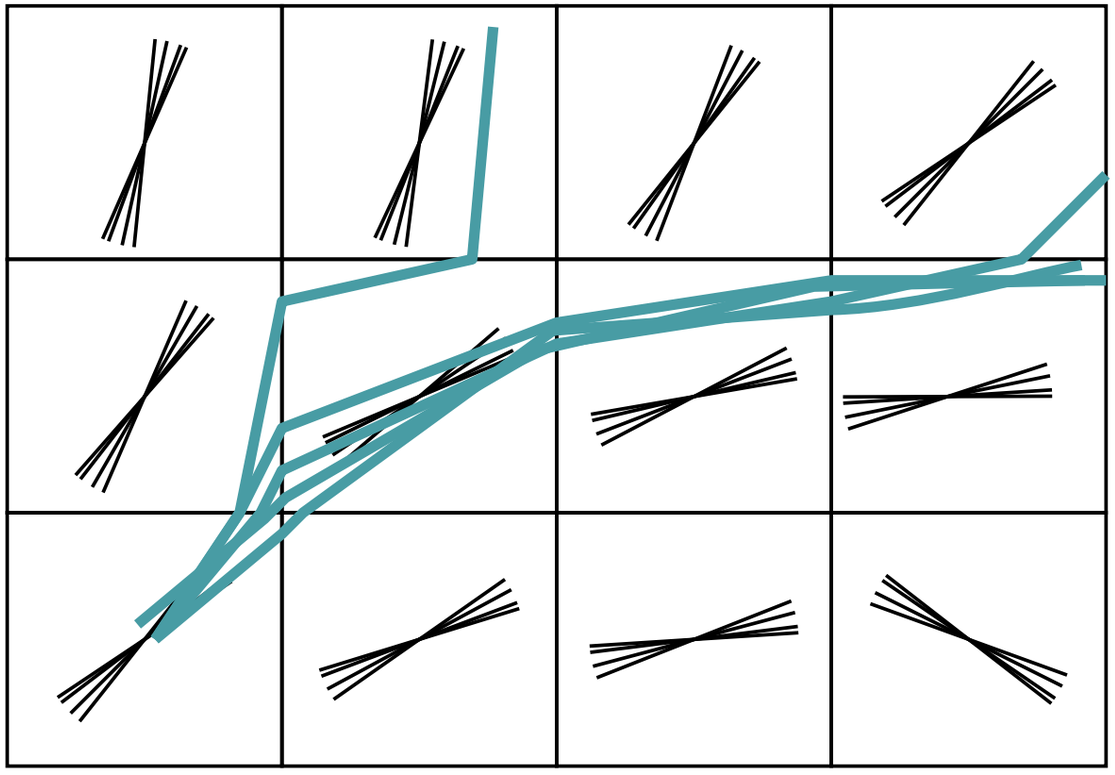
- No benefit from including a 2nd fibre => 2nd volume fraction goes to zero

- Measured signal is explained better by more complex model => 2nd volume fraction is non-zero

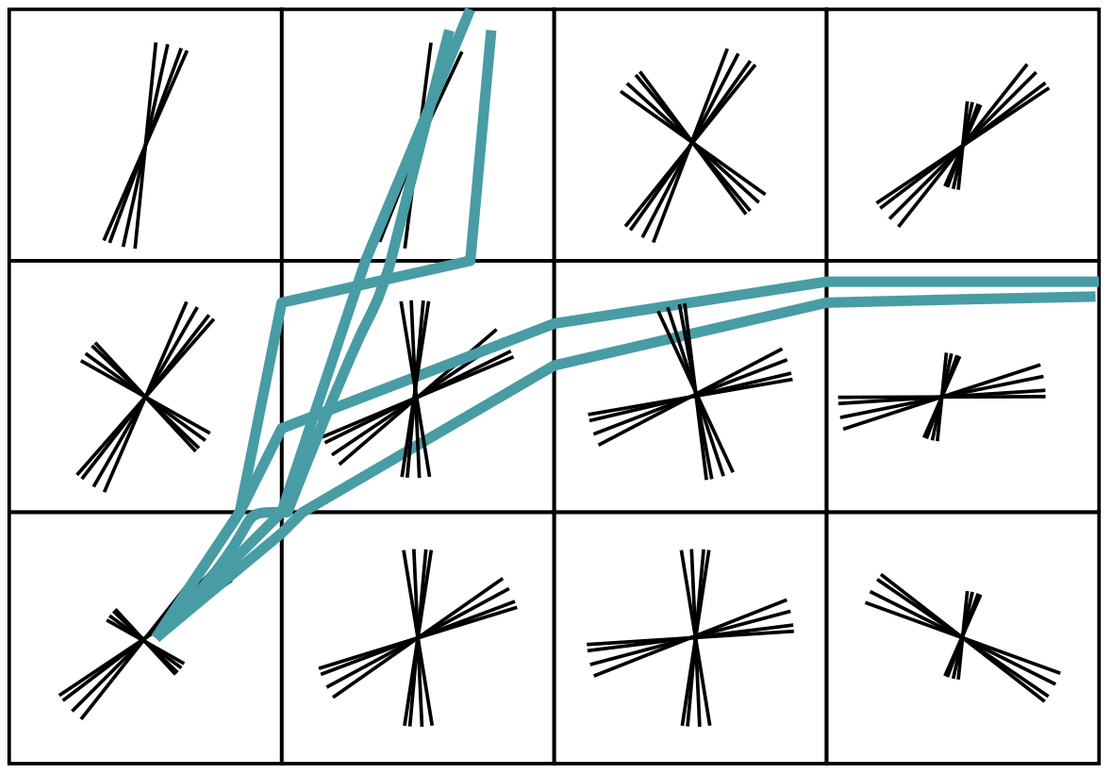




Probabilistic Tractography in Multi-Fibre Fields



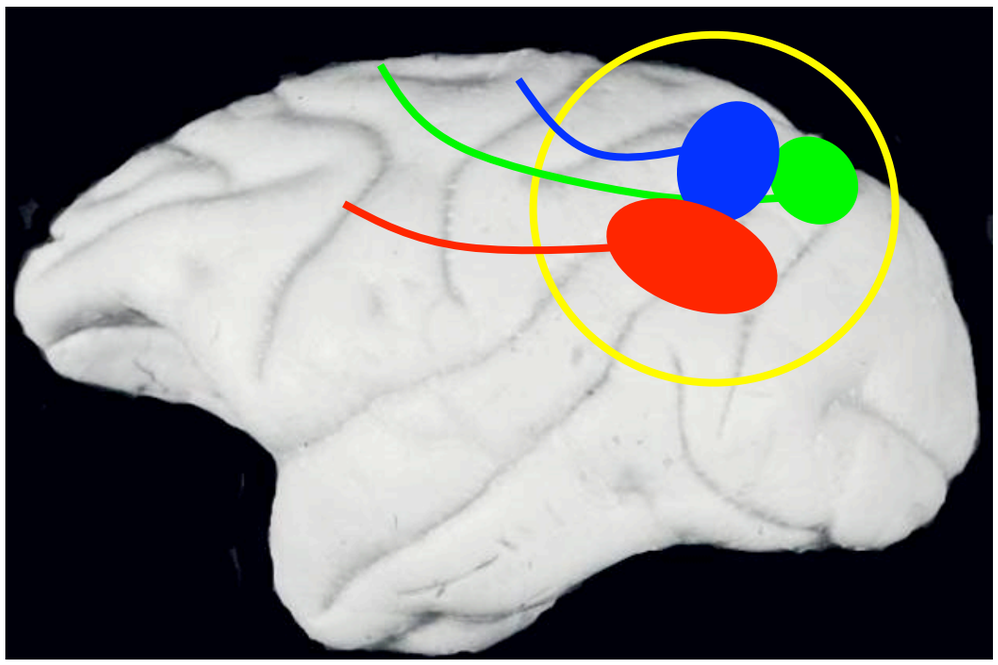
Behrens et al, 2003, Parker et al. 2003,
Hagmann et al 2003, Jones et al. 2004

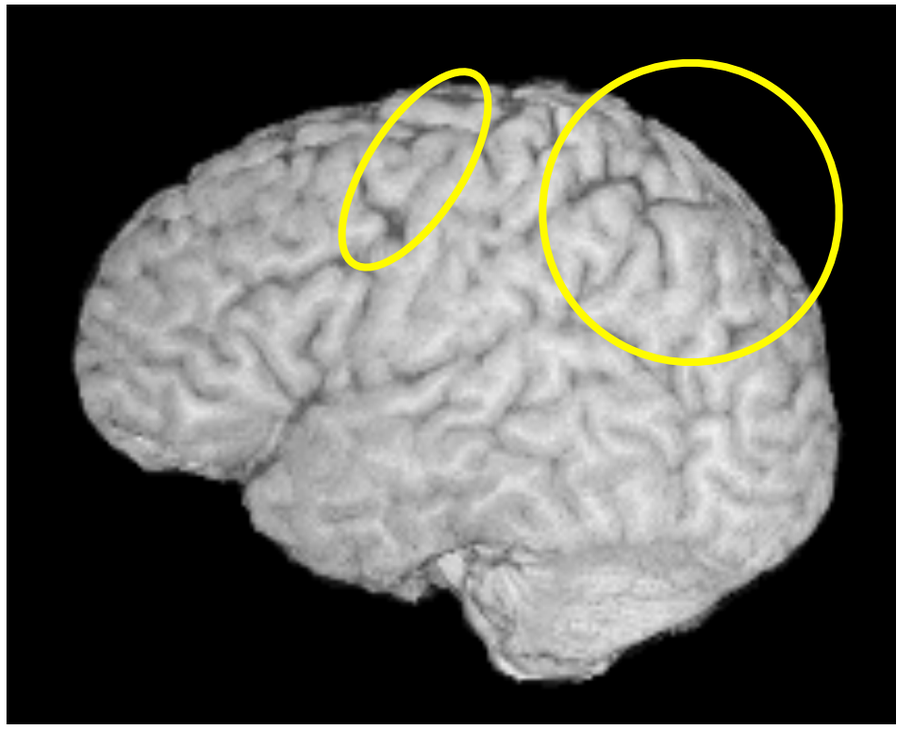


Parker & Alexander 2003,
Behrens et al, 2007

When multiple fibre populations exist in a voxel, choose the one that is most compatible with the incoming trajectory.

Parieto-premotor connections





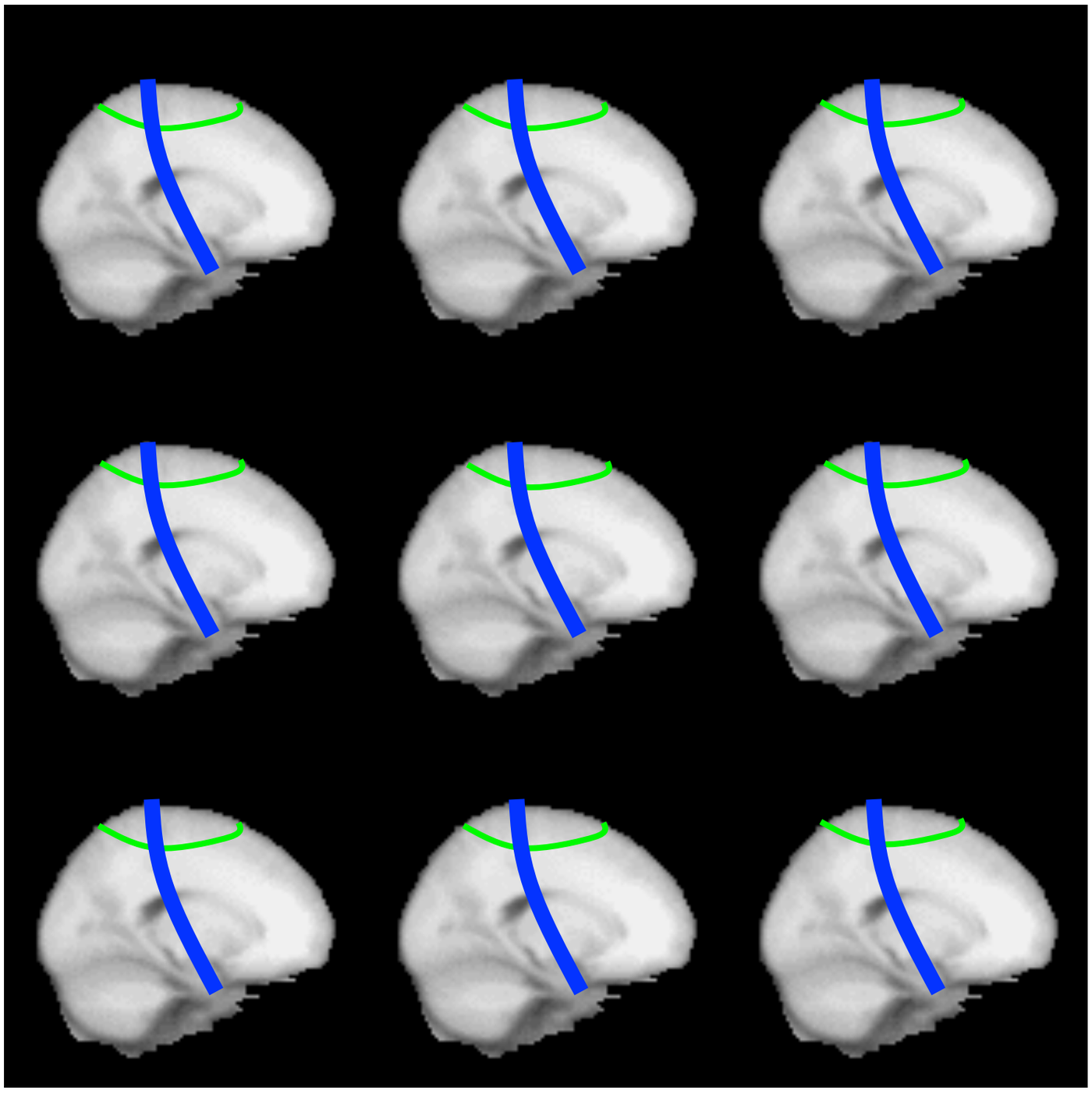
Posterior PL <->Anterior PMC

Anterior PL <-> Posterior PMC

Lateral PL <-> Frontal Eye Fields

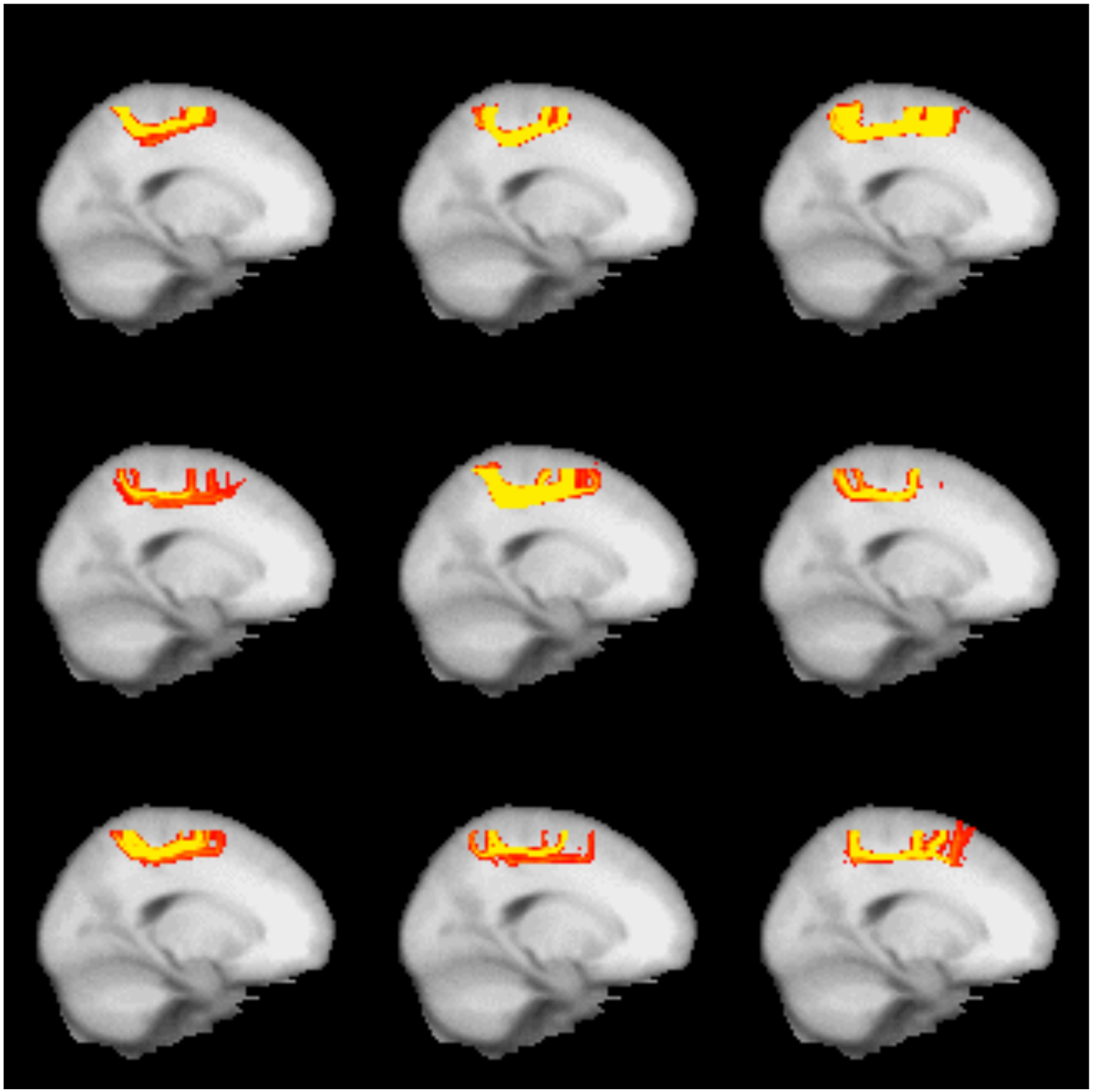
Behrens and Rushworth

But….

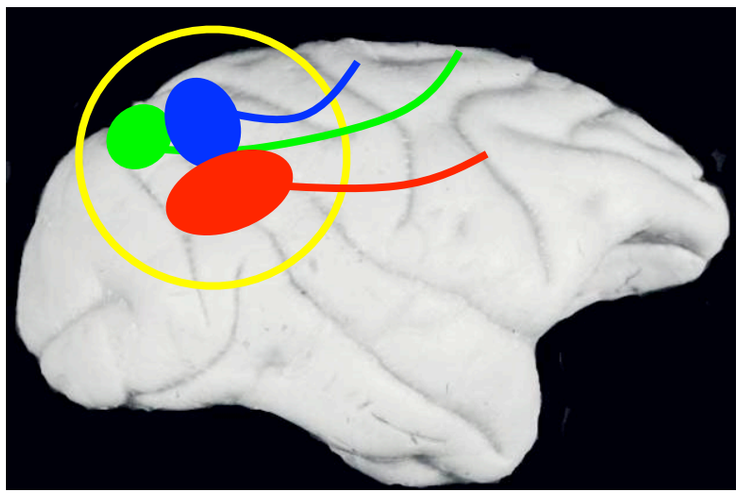


Tracking Parietal -> Medial premotor regions in 9 subjects

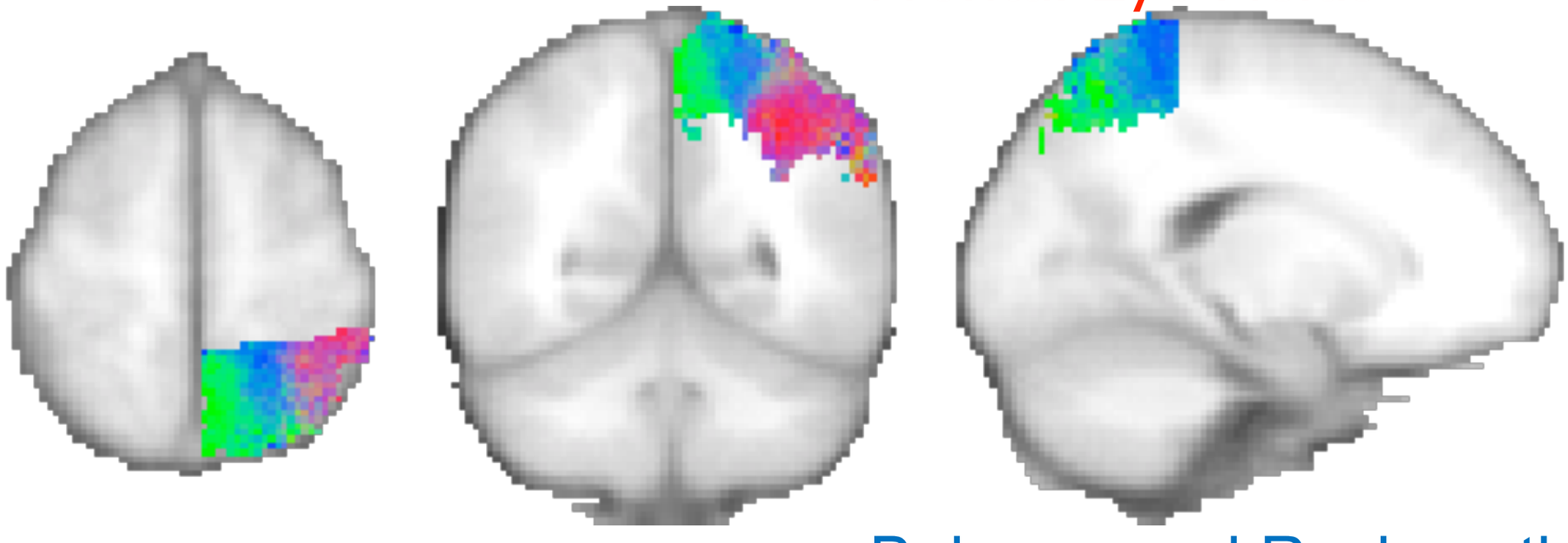
Using multi-fibre modelling.



Topography of premotor connections in parietal lobe.



Average of 9 subjects.
Tracking from parietal
To:
Anterior Premotor
Posterior Premotor
Frontal Eye Fields

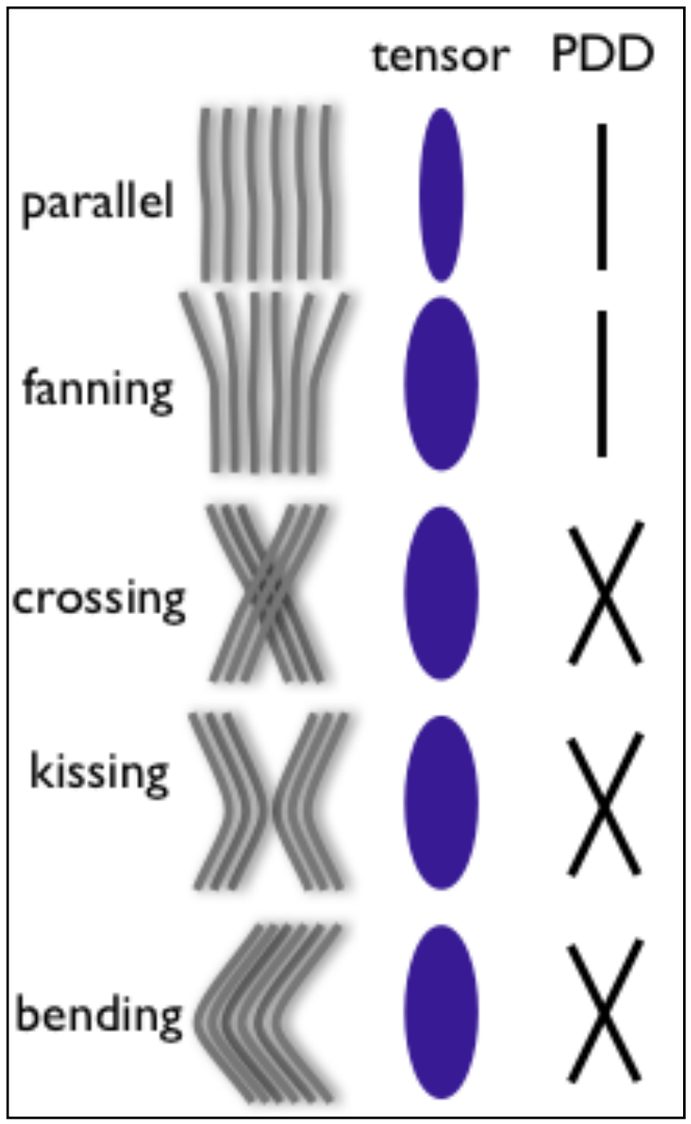


Behrens and Rushworth

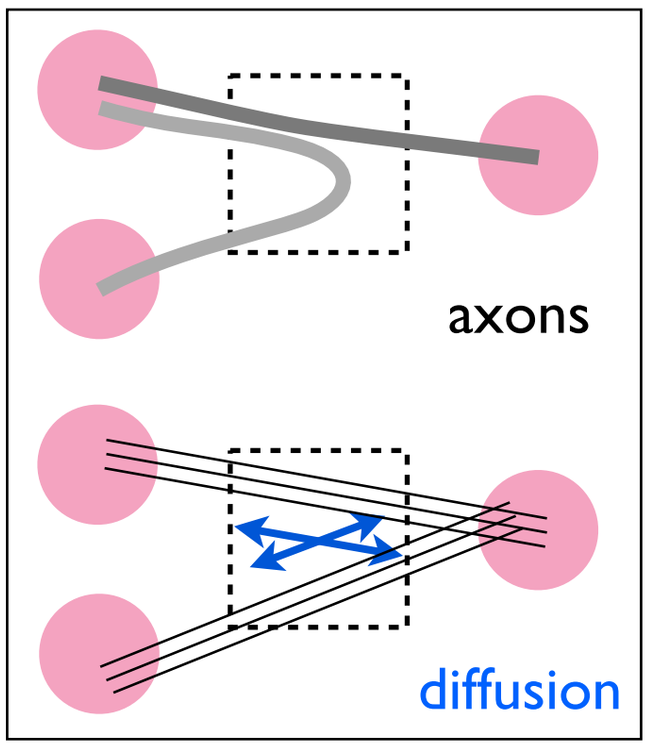
Errors in tractography

- Modelling errors
- Measurement noise errors
- Algorithmic errors

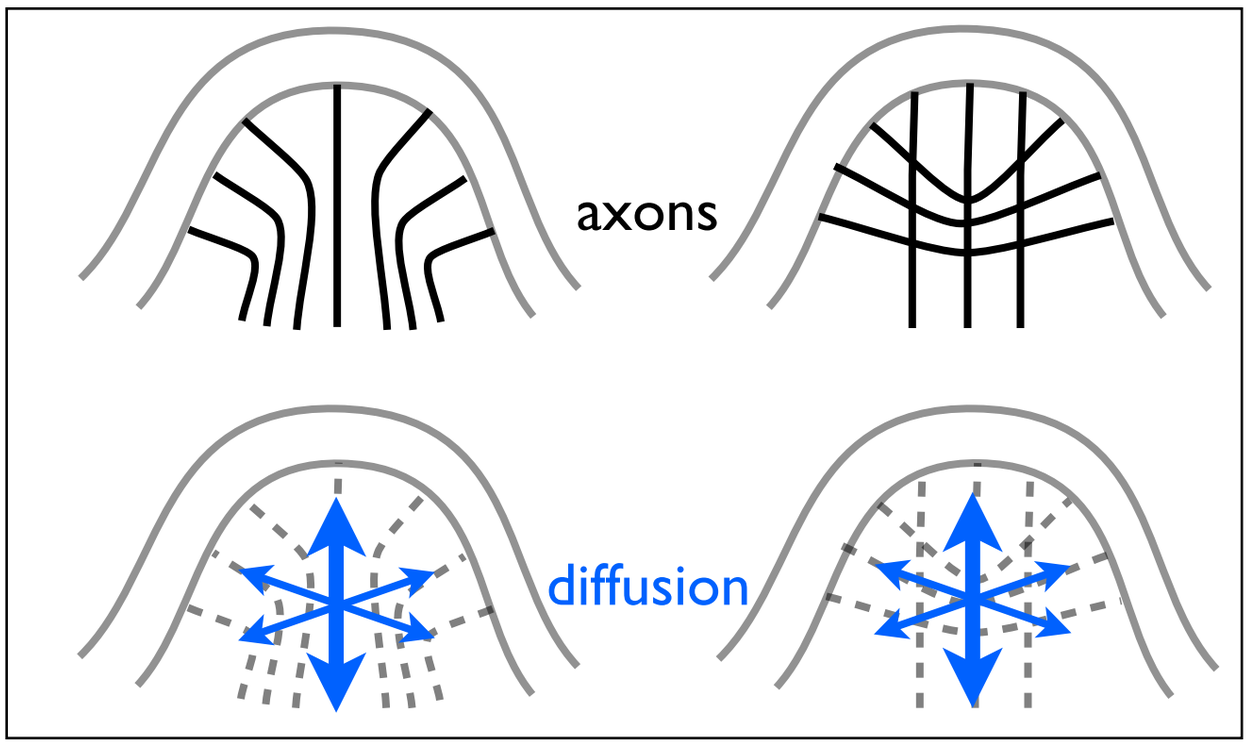
Is the direction of least hindrance to diffusion a good proxy for fibre orientation?



mapping between axon geometry and diffusion profile can be ambiguous



In the white matter:
jumping between tracts

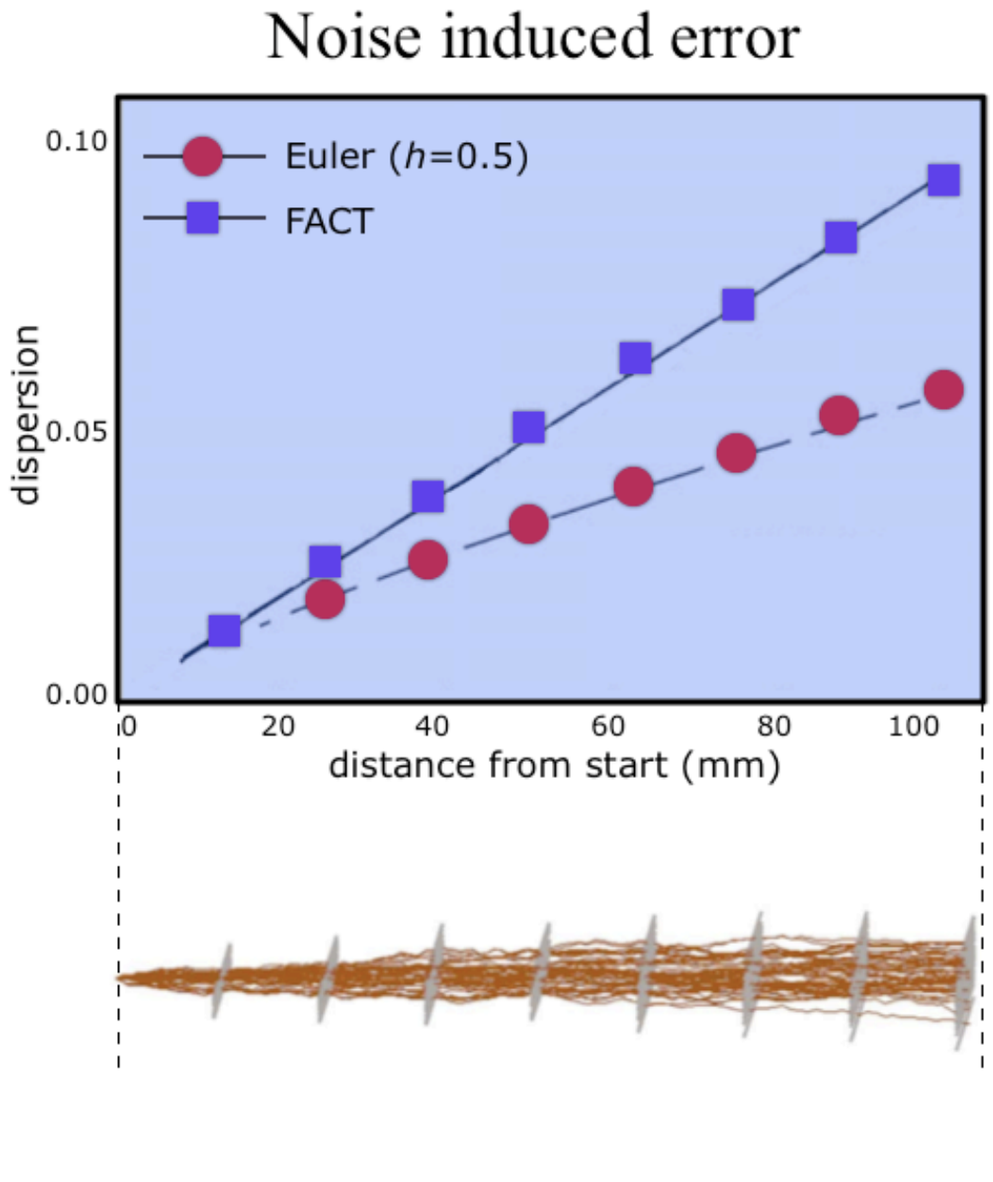


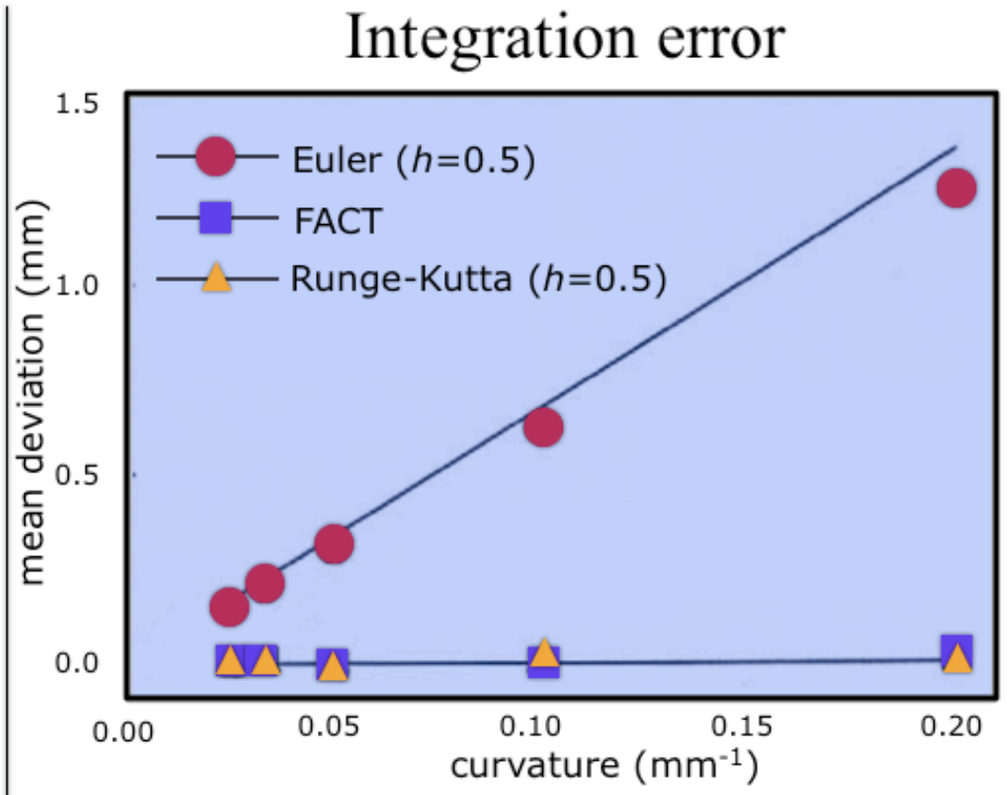
Near the cortex
ambiguities/biases

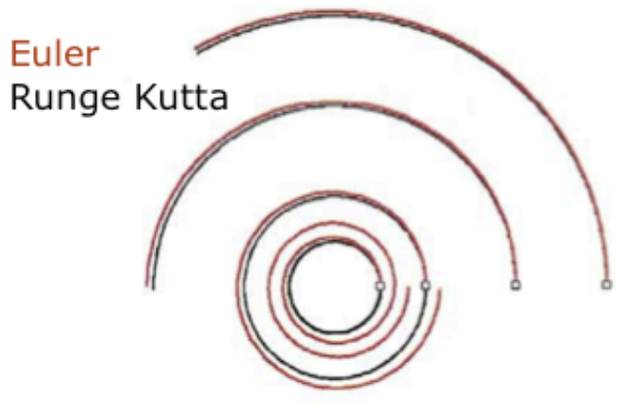
Modelling errors

- Tractography is good for localising tracts
- Difficult to get accurate estimate of site-to-site connectivity
  - ambiguous diffusion-axon mapping
  - cannot quantify modelling errors
  - But we can reduce them by improving the local modelling (ongoing research)

Other errors







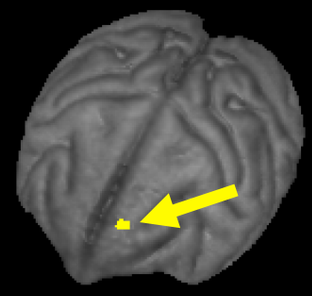
error summary

- We can quantify noise-induced errors
- We can minimize algorithmic errors
- We can't quantify modelling errors
  - false positives and negatives in unknown proportions
  - (but we can *try to* minimize them)
  - we need validation

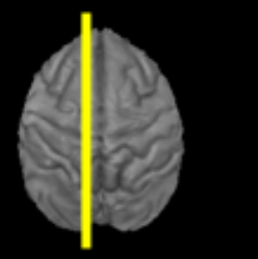
Connectivity of prefrontal cortex

DWI **Mn**

24h 48h 72h 96h 168h

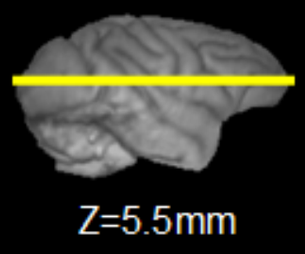


BA9 BA9



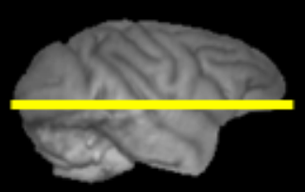
X= -4.0mm

Caudate



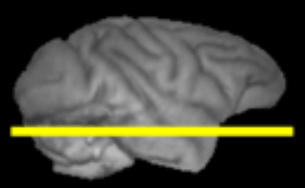
Z=5.5mm

Thalamus



Z=1.0mm

Pallidum



Z=-6.5mm

Midbrain peduncle

3 100

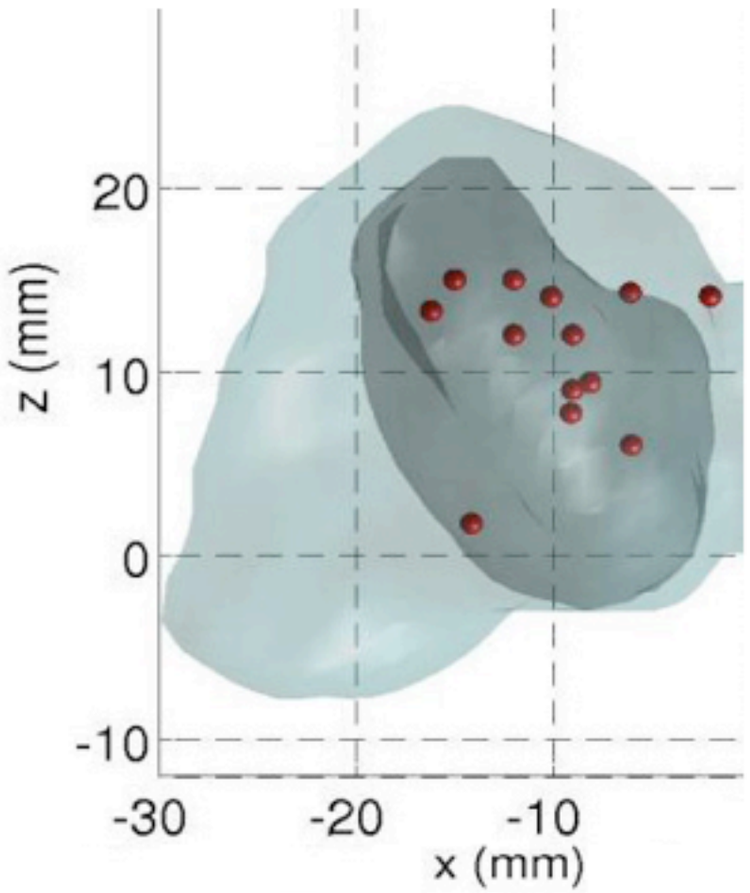
Probability (%)

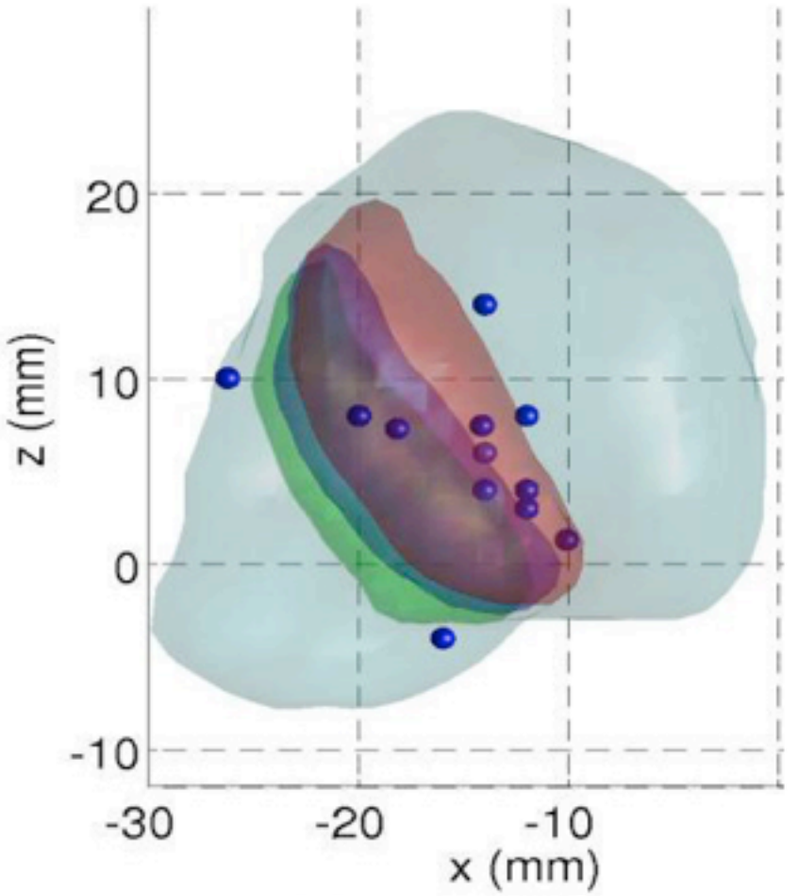
40 120

t

Hayashi T et al. Society for Neuroscience, Atlanta 2006

Functional validation: meta-analysis of FMRI activations within thalamus

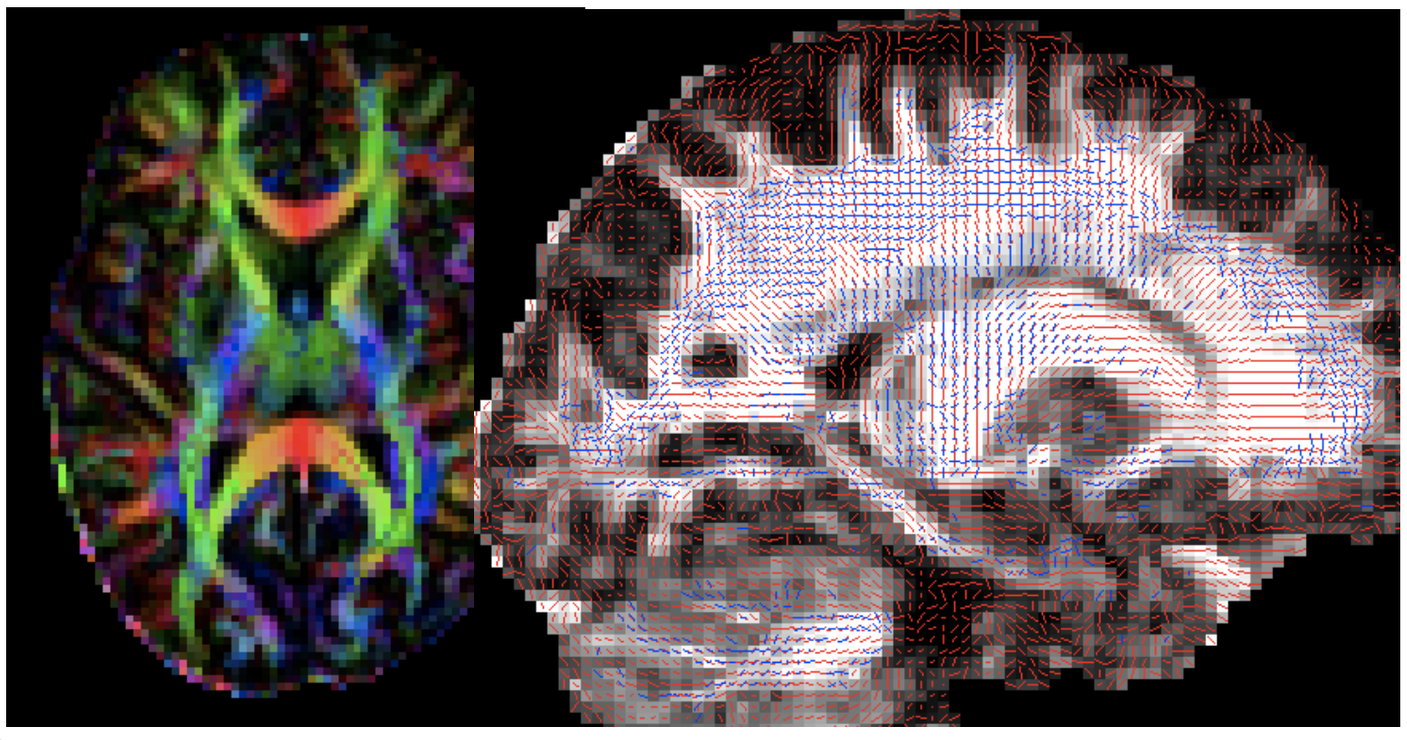


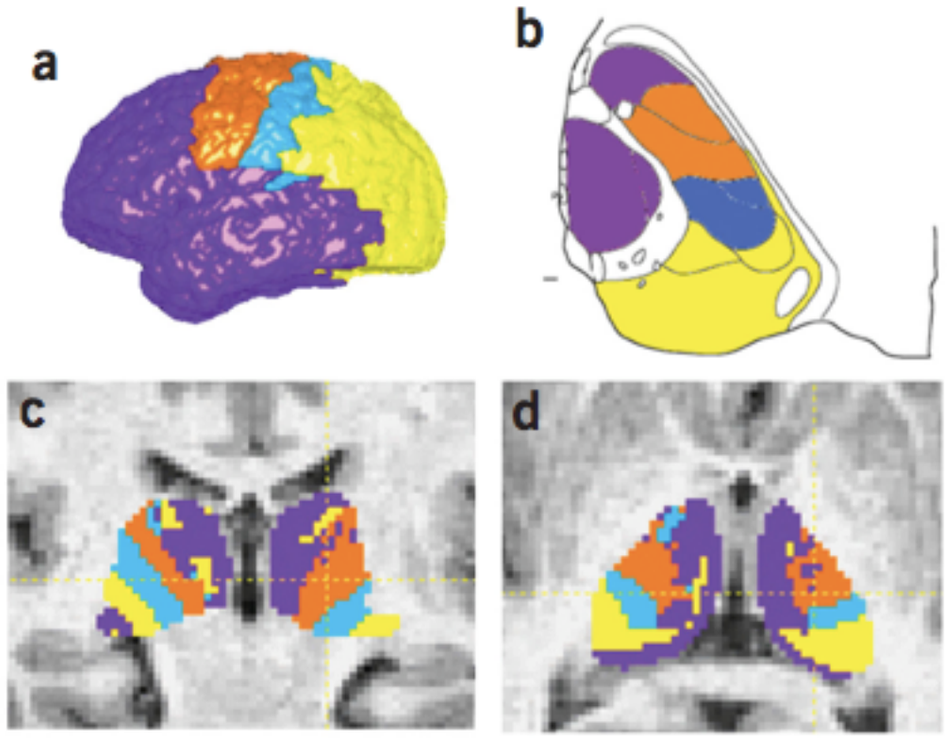


Johansen-Berg et al, Cerebral Cortex, 2005

FMRIB Diffusion Toolbox

- DTI model fit
- Eddy current correction
- Voxel-Based diffusion analysis (TBSS)
- BEDPOSTX modelling crossing fibres
- PROBTRACKX propagating uncertainty in tractography

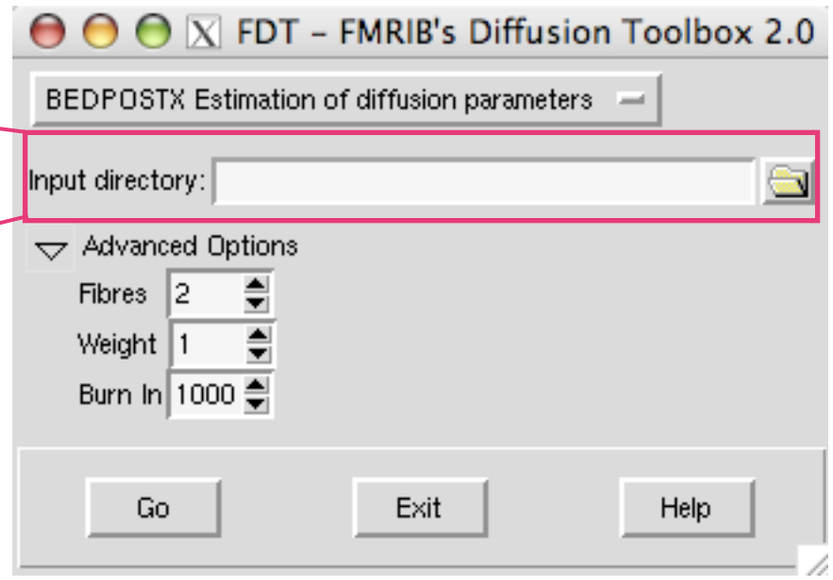


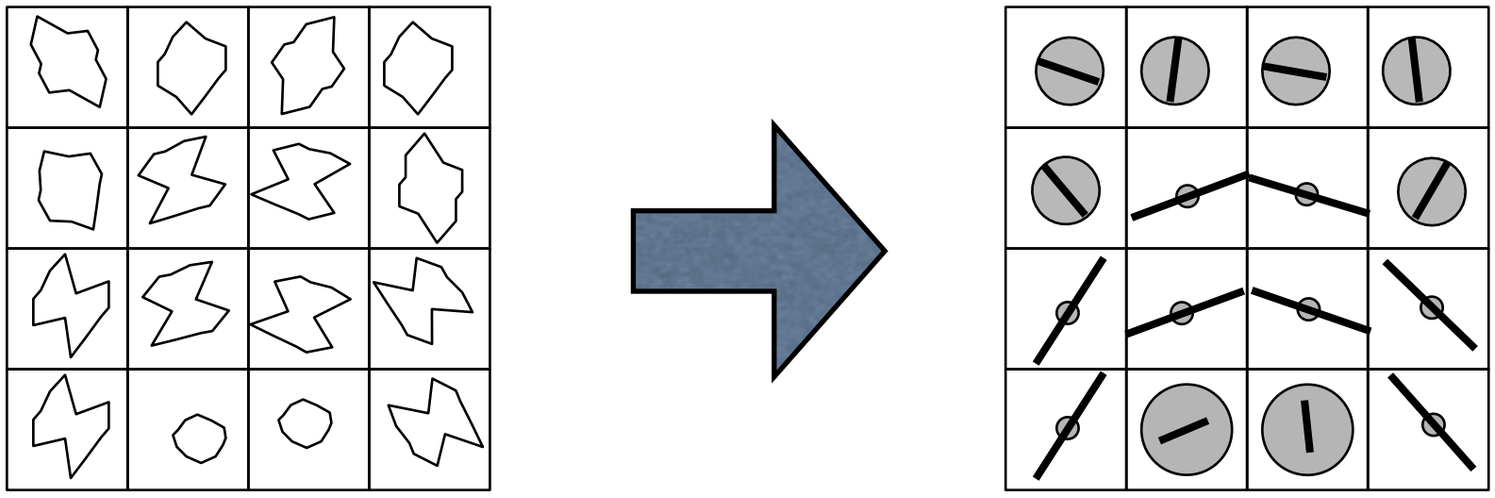


BEDPOSTX

GUI options

data.nii.gz
nodif_brain_mask.nii.gz
bvecs
bvals



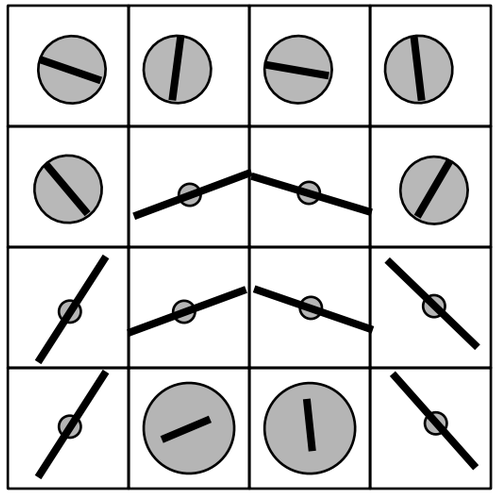


Data

Model parameters

BEDPOSTX

Results

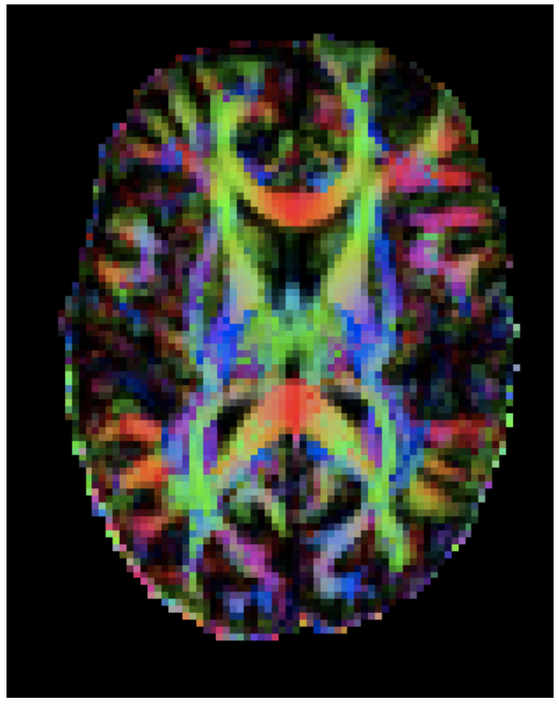


- Sample orientations → merged_th1samples.nii.gz, merged_ph1samples.nii.gz, merged_th2samples.nii.gz, merged_ph2samples.nii.gz
- Sample fractional volumes → merged_f1samples.nii.gz, merged_f2samples.nii.gz
- Mean orientation → dyads1.nii.gz, dyads2.nii.gz
- Mean fractional volumes → mean_f1samples.nii.gz, mean_f2samples.nii.gz

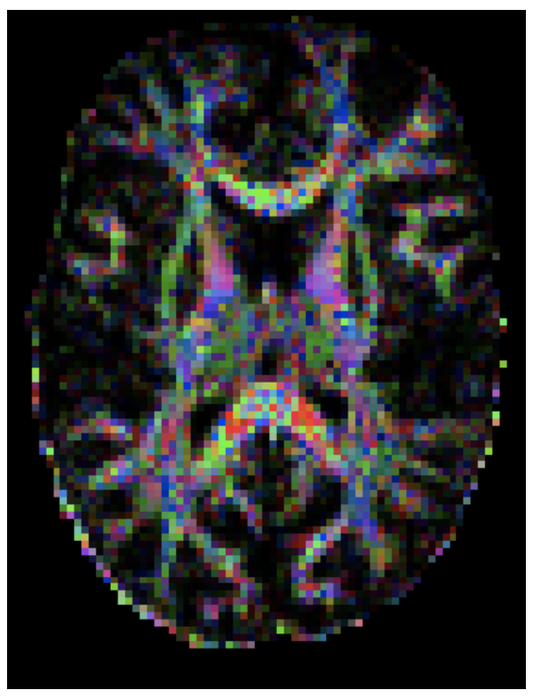
BEDPOSTX

Results

- Mean orientation



dyads1.nii.gz

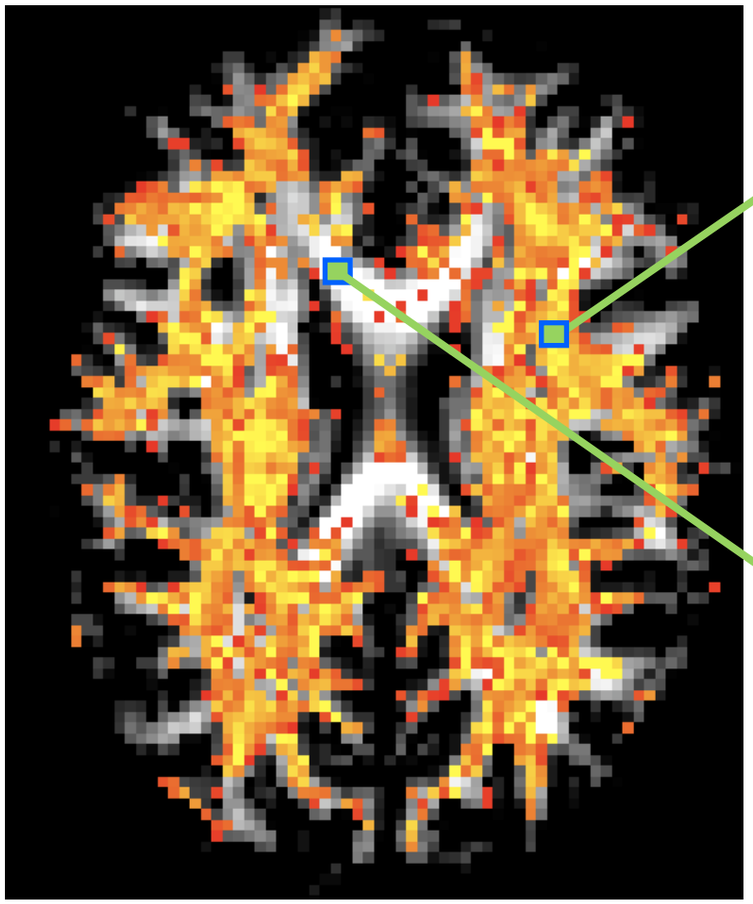


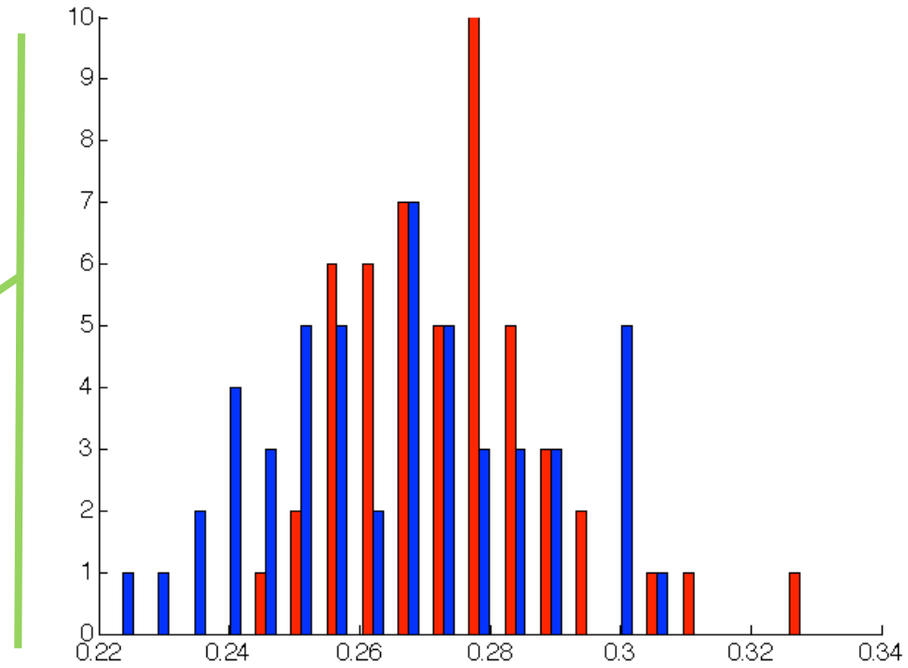
dyads2.nii.gz

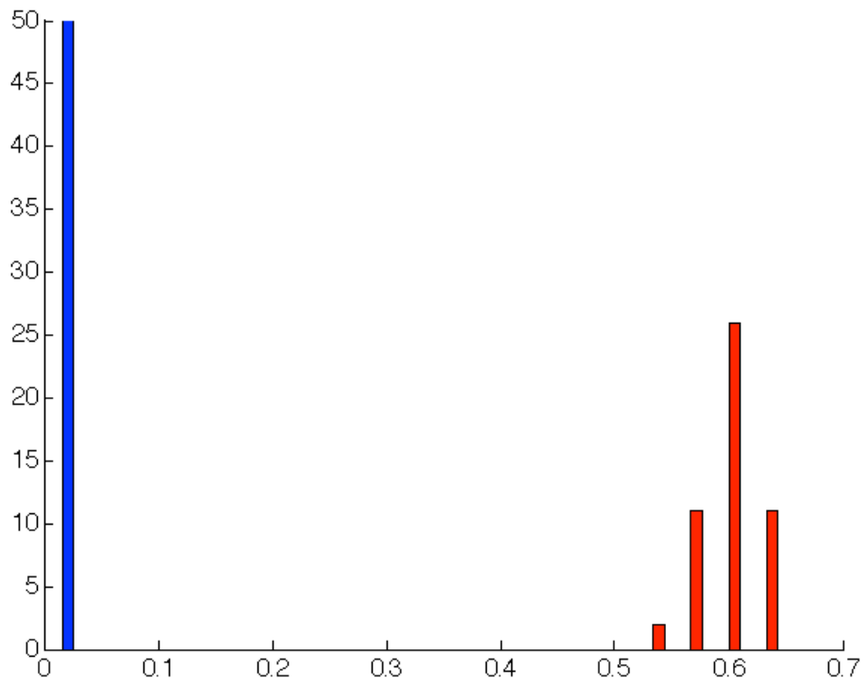
BEDPOSTX

Results

- Mean fractional volumes



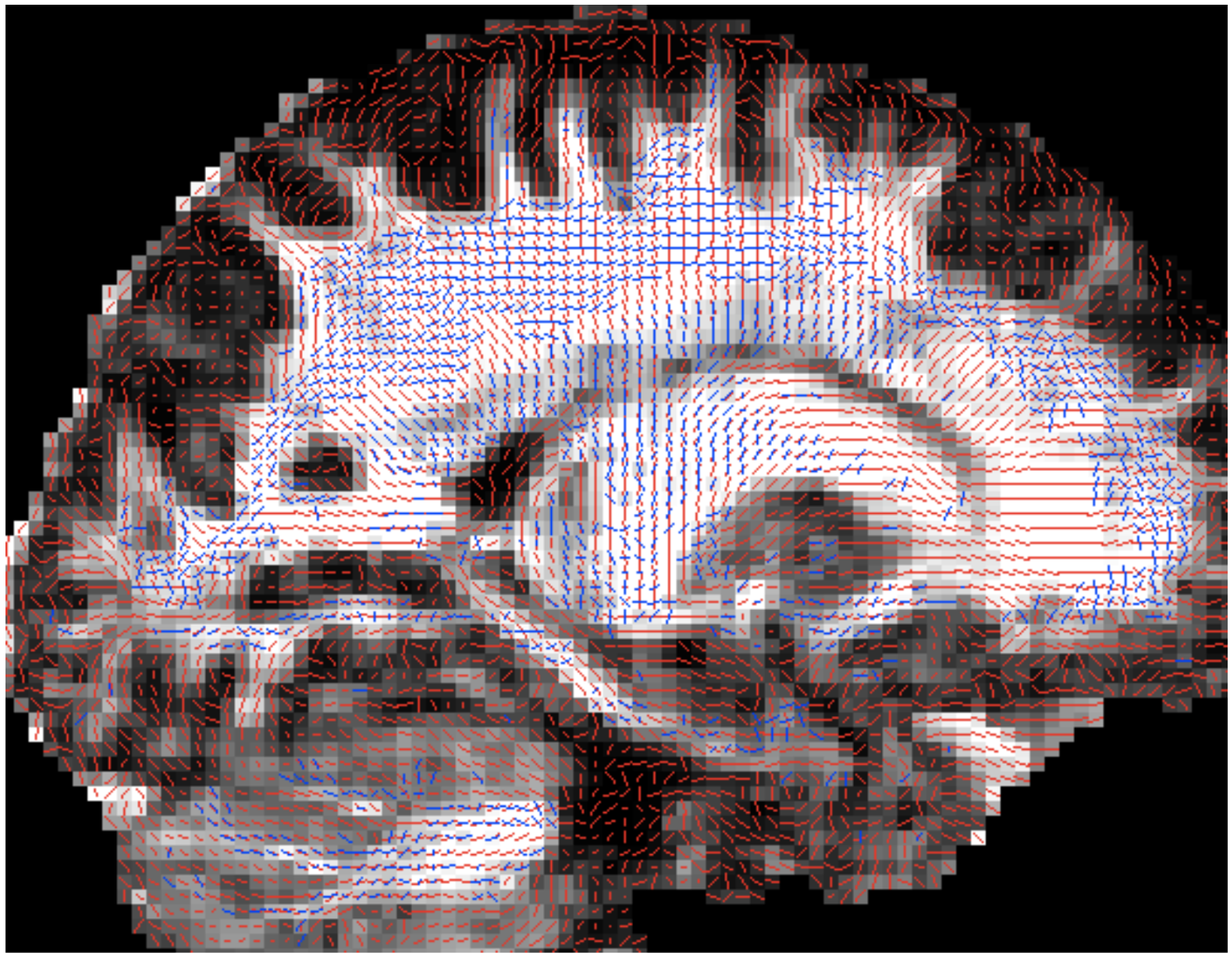




BEDPOSTX

Results

- Mean orientation



dyads1.nii.gz

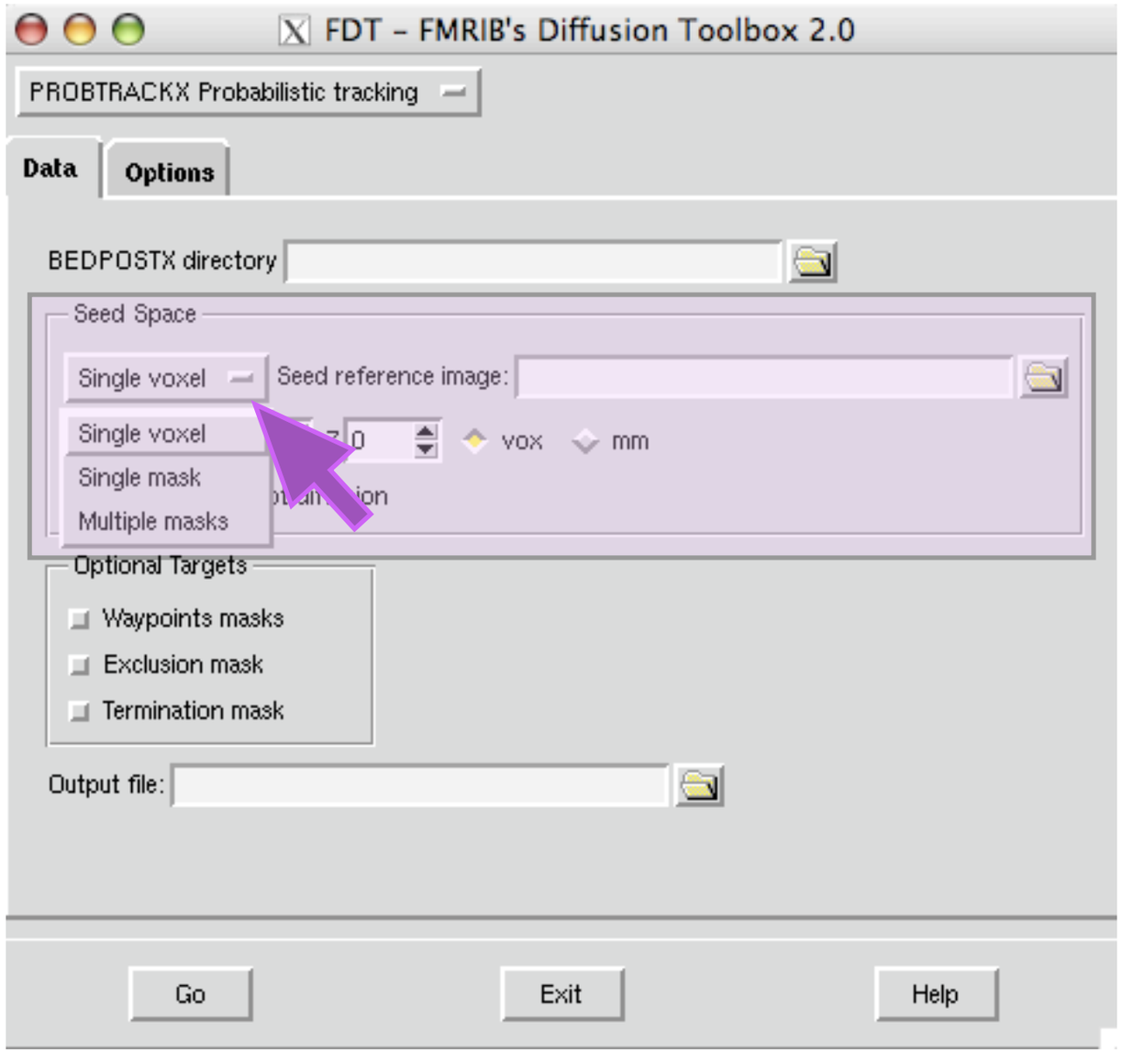
dyads2.nii.gz

maskdyads dyads2 mean_f2samples

PROBTRACKX

Seed specification

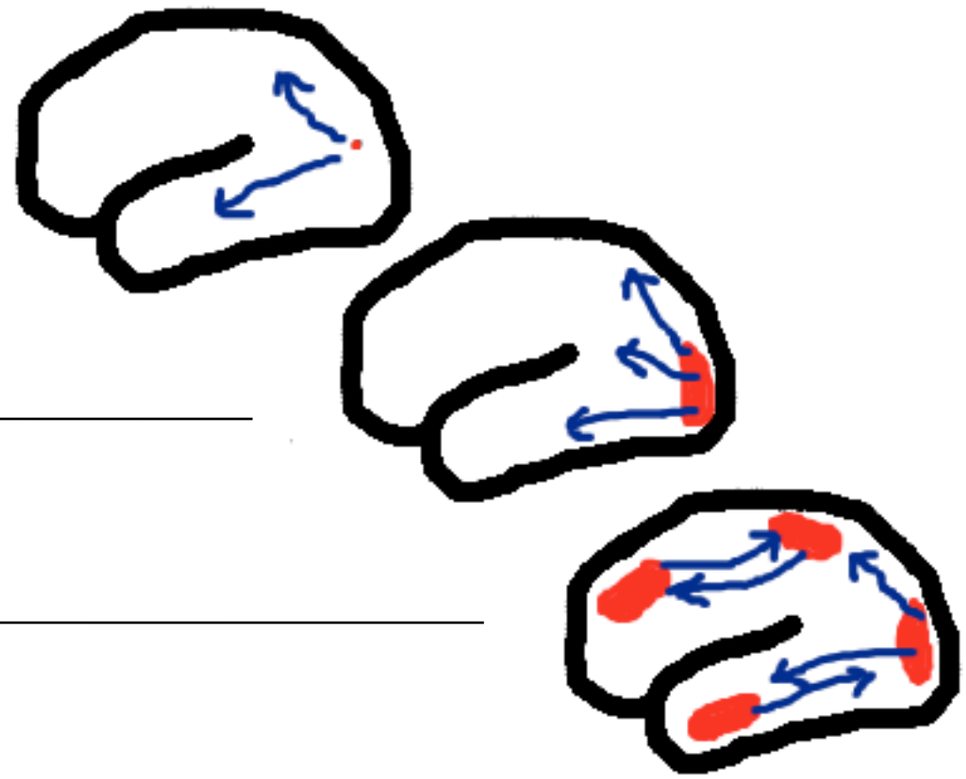
- Different ways of specifying seeds
- Allow seed specification in a different space



PROBTRACKX

Seed specification

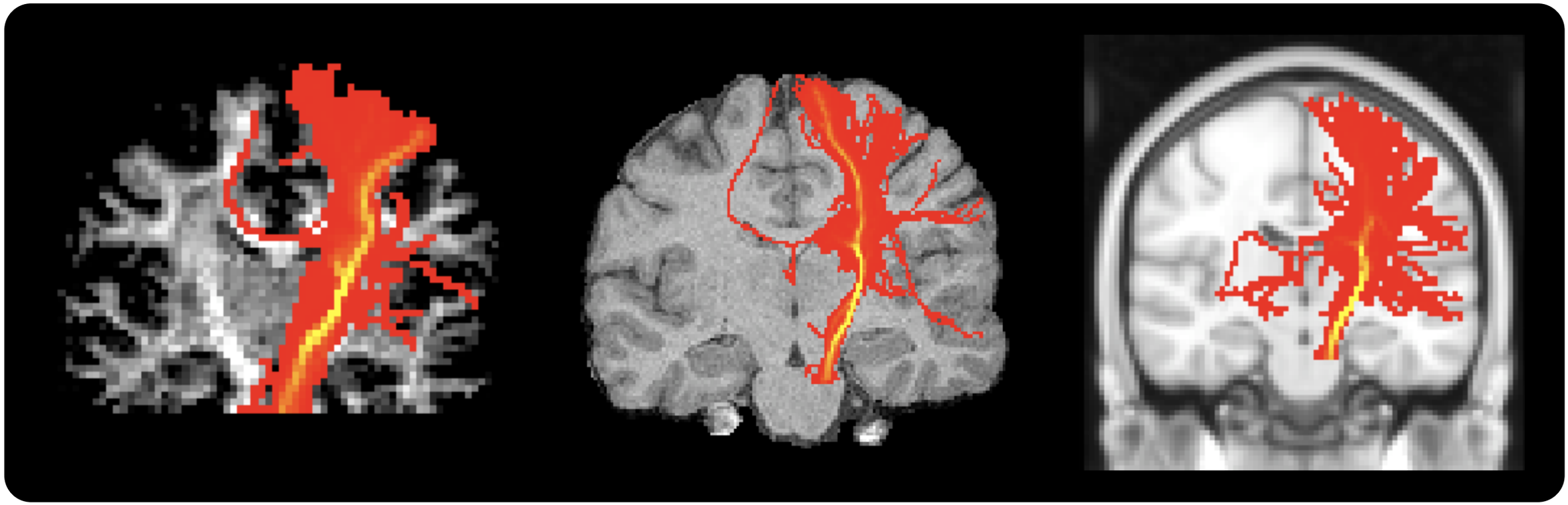
- single voxel
- single mask
- multiple masks



PROBTRACKX

Seed specification

- Different seed spaces



Diffusion space Structural space Standard space

PROBTRACKX

(optional) Targets specification

- Waypoints
- Exclusion
- Termination
- Classification

Dissecting specific tracts

(equivalent to adding priors on the distribution of connections)

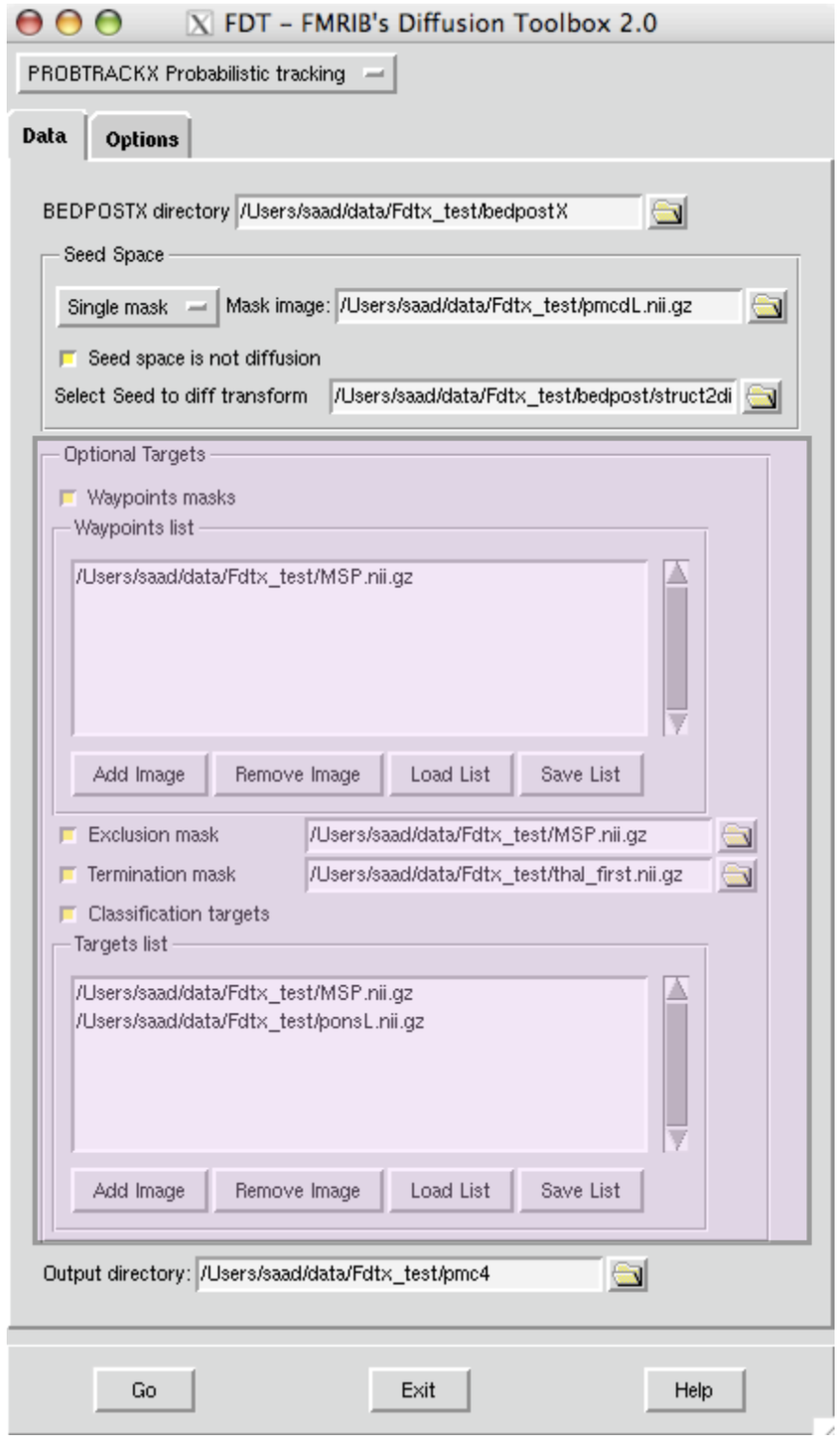
Quantification of connectivity

ALL THE TARGETS IN THE SAME SPACE AS THE SEEDS

PROBTRACKX

(optional) Targets specification

- Waypoints
- Exclusion
- Termination
- Classification

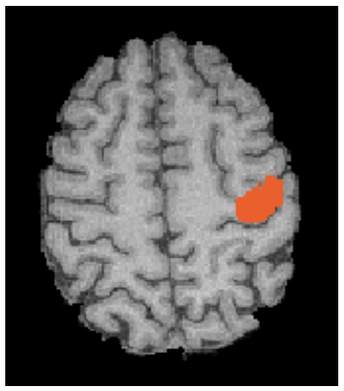


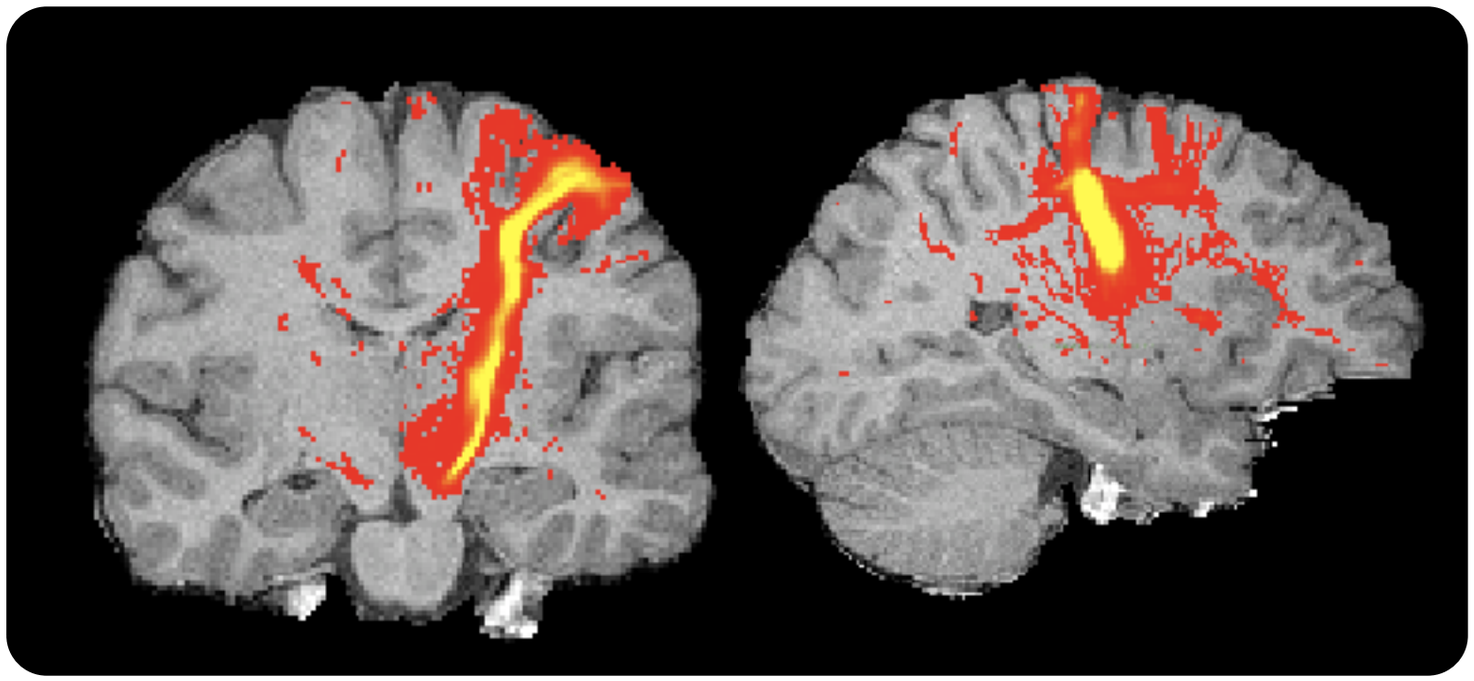
PROBTRACKX

Dissecting a specific tract

Cortico-spinal tract

Seed: M1, hand area





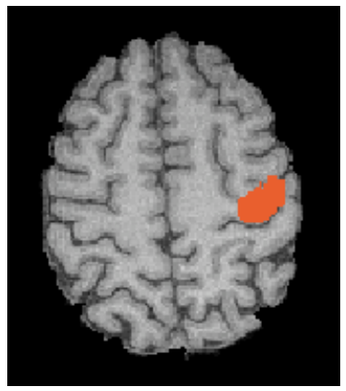
No targets

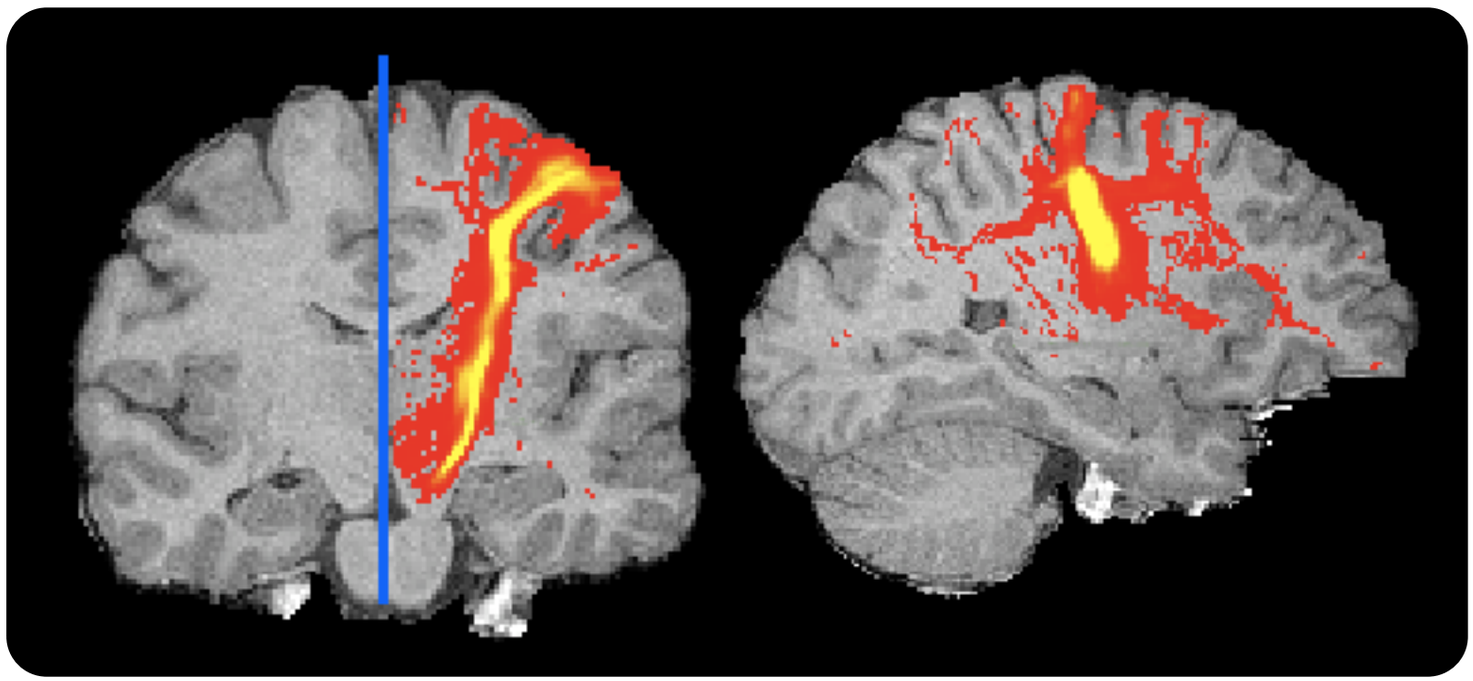
PROBTRACKX

Dissecting a specific tract

Cortico-spinal tract

Seed: M1, hand area





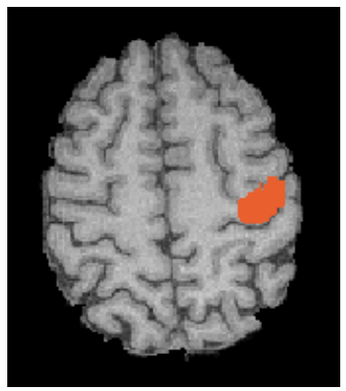
Exclusion: Mid-Sagittal plane

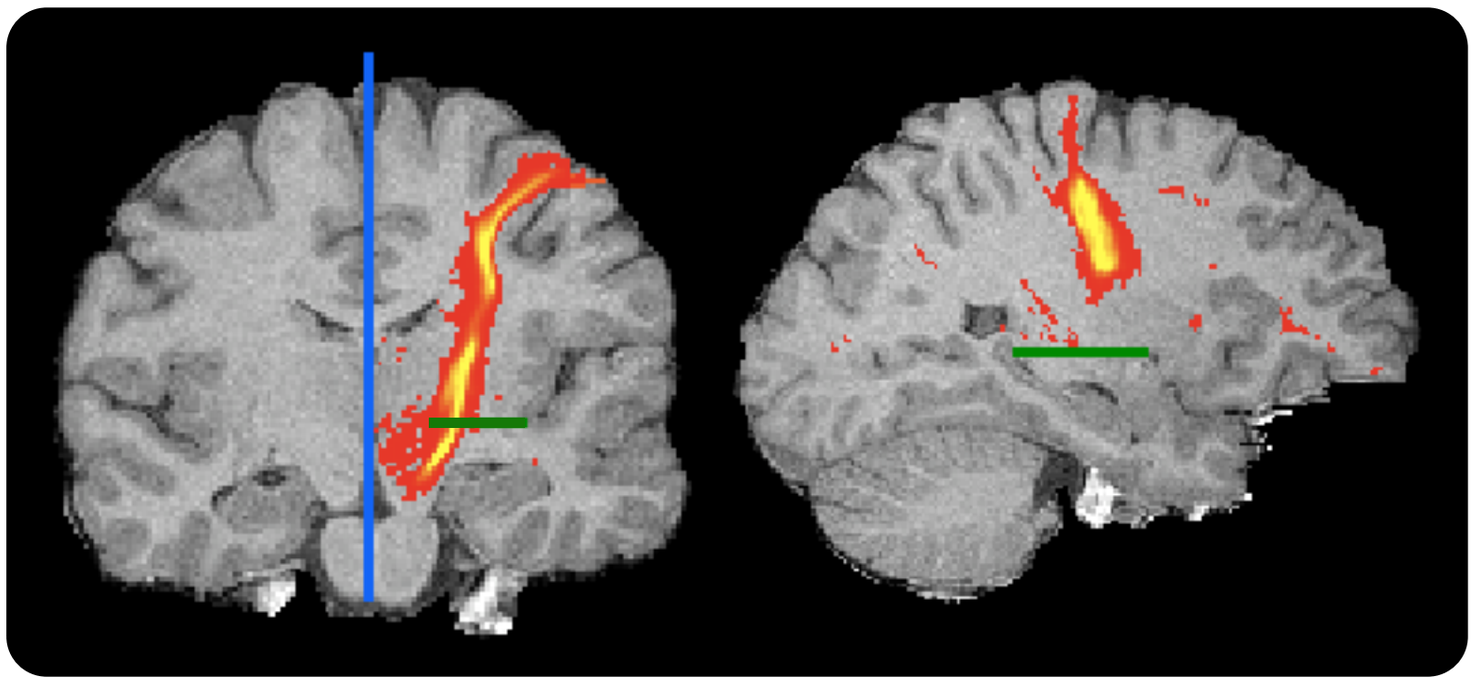
PROBTRACKX

Dissecting a specific tract

Cortico-spinal tract

Seed: M1, hand area





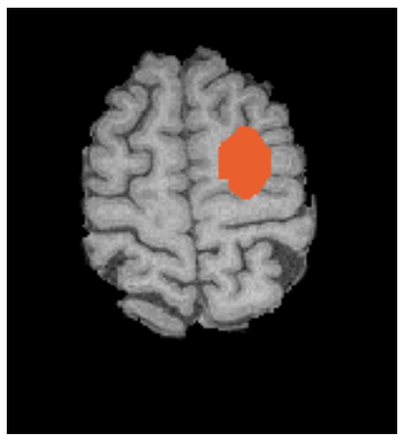
Waypoint: Internal Capsule

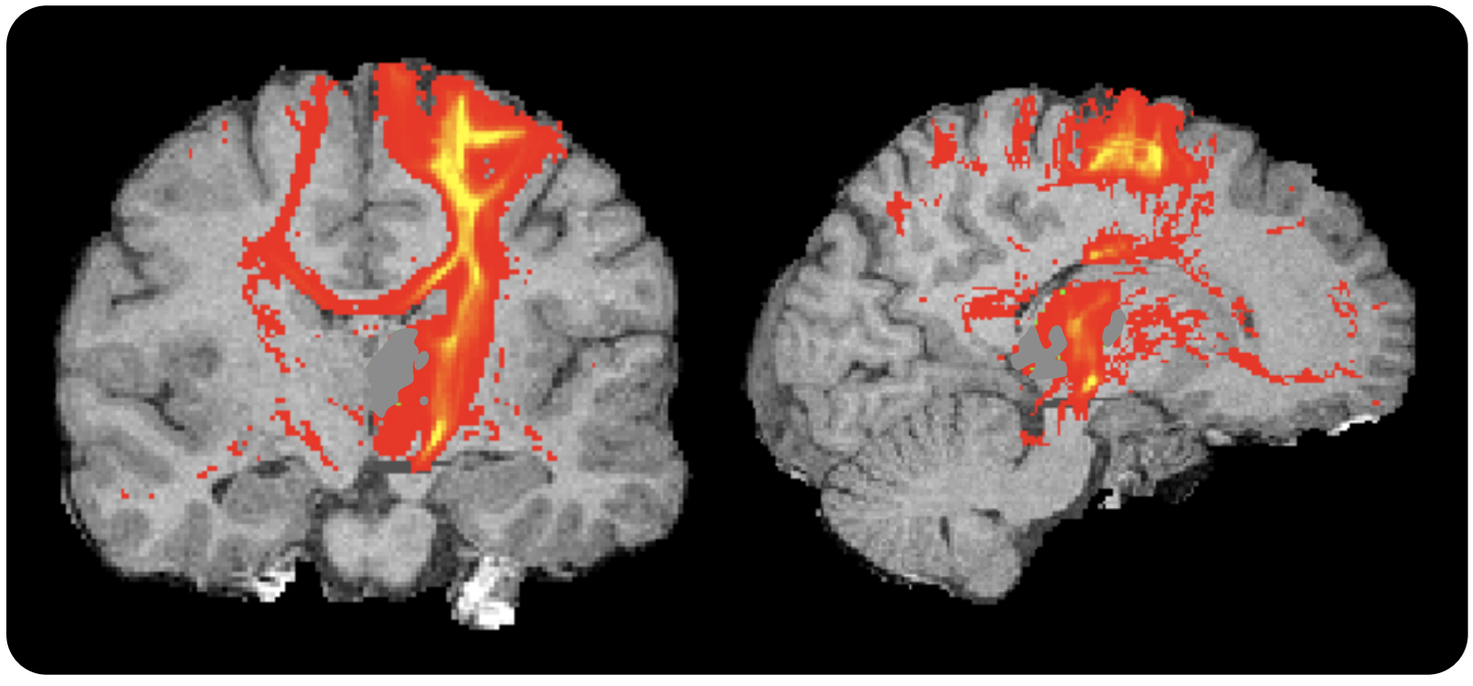
PROBTRACKX

Dissecting a specific tract

Cortico-spinal tract

Seed: dorsal PMC





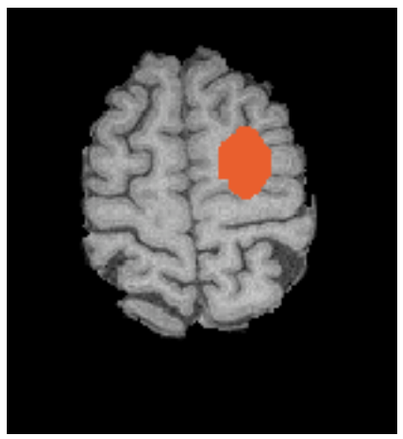
No targets

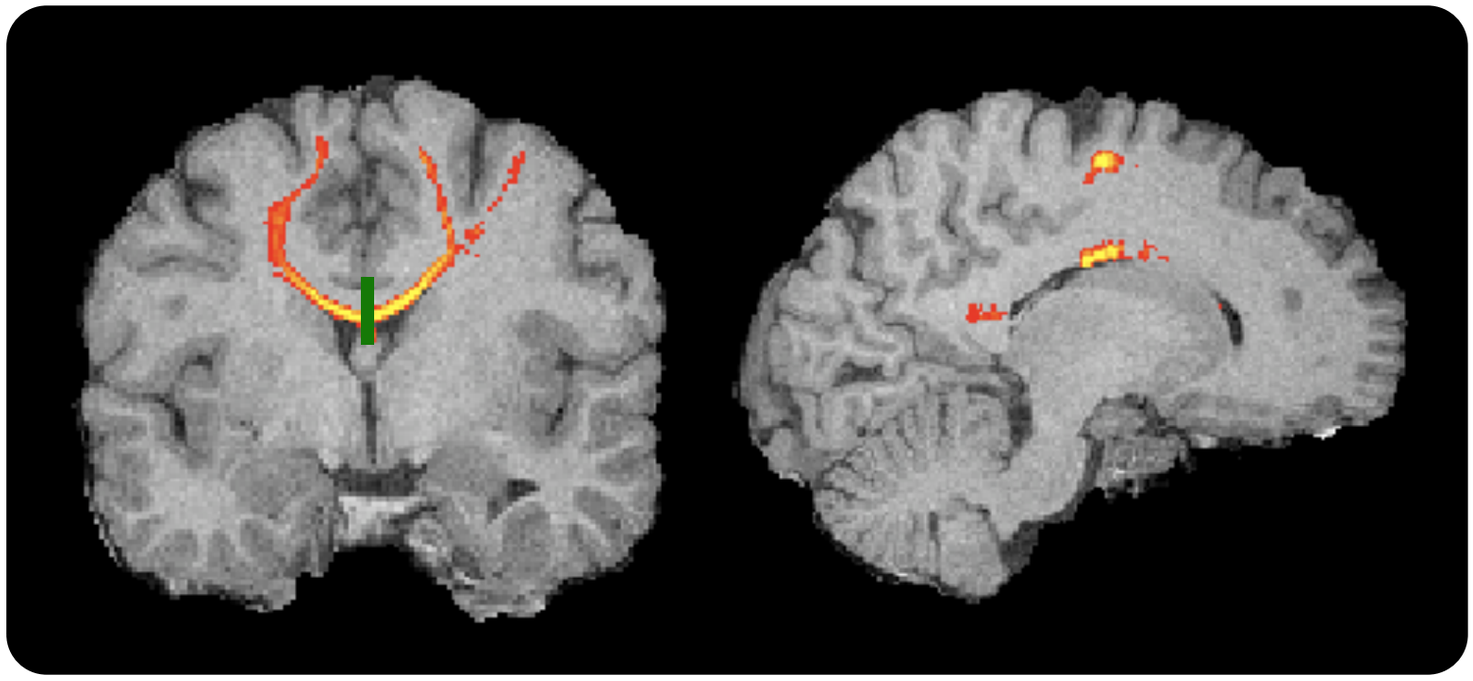
PROBTRACKX

Dissecting a specific tract

Corpus Callosum

Seed: dorsal PMC



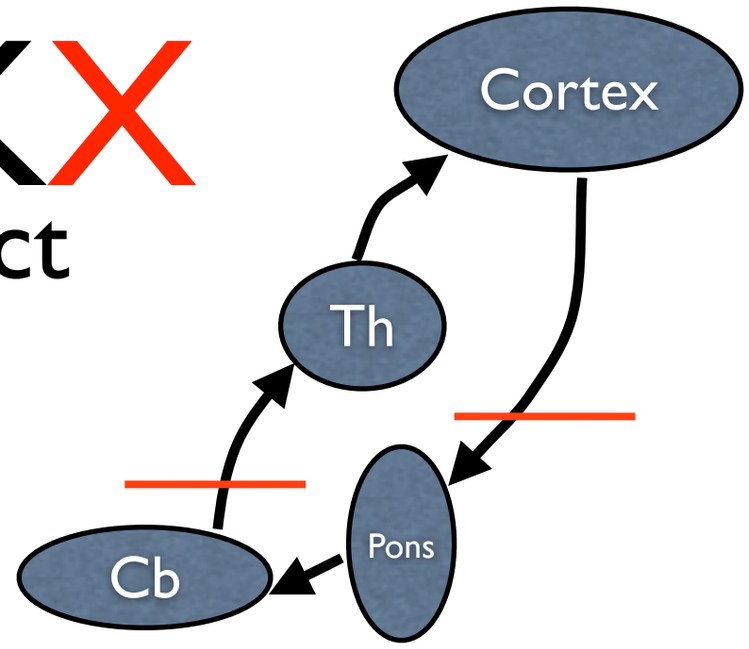


Waypoint: Corpus Callosum

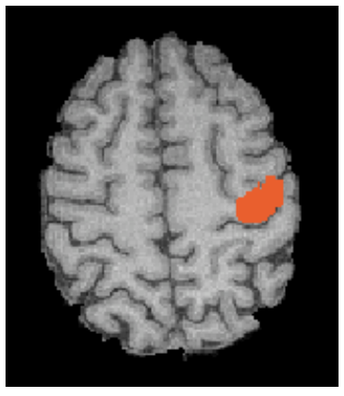
PROBTRACKX

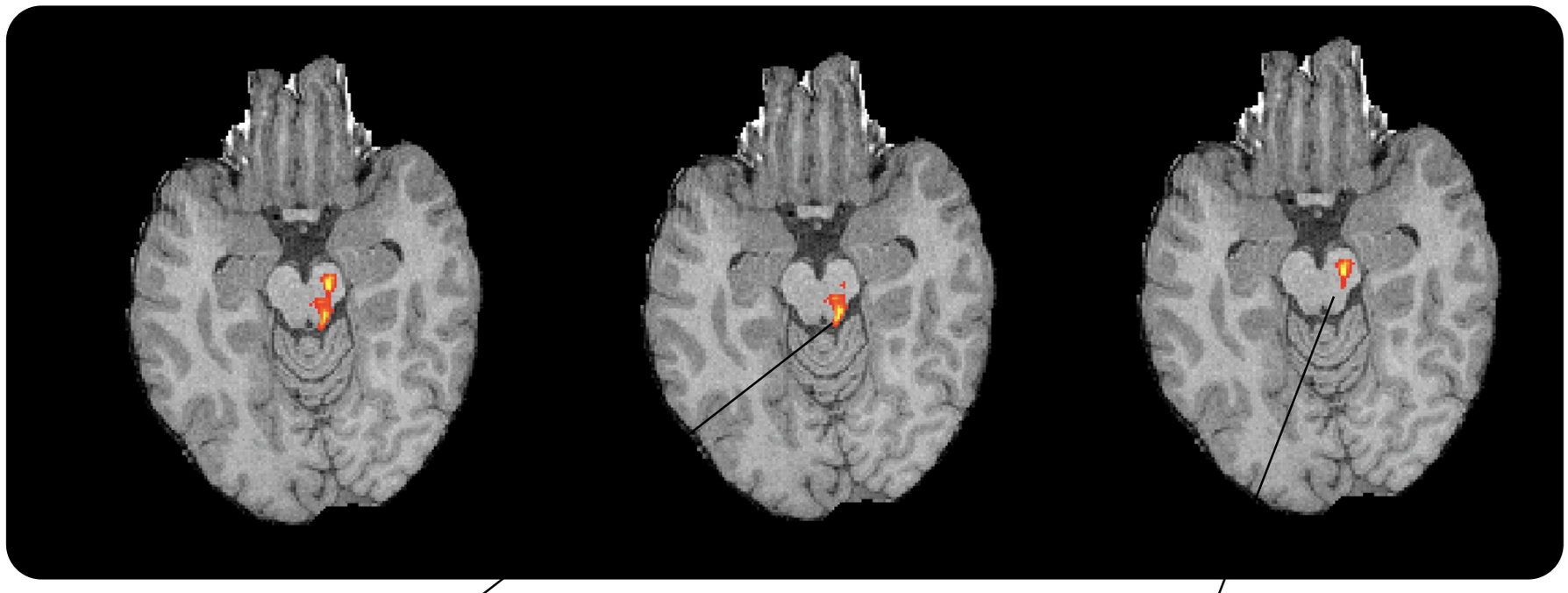
Dissecting a specific tract

Cortico-cerebellar projections



Seed: M1 hand





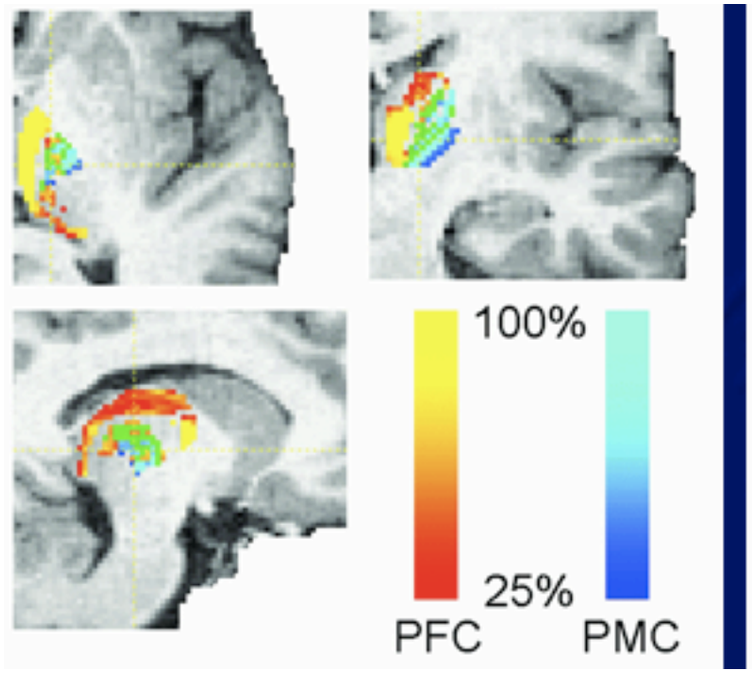
Waypoint: Thalamus

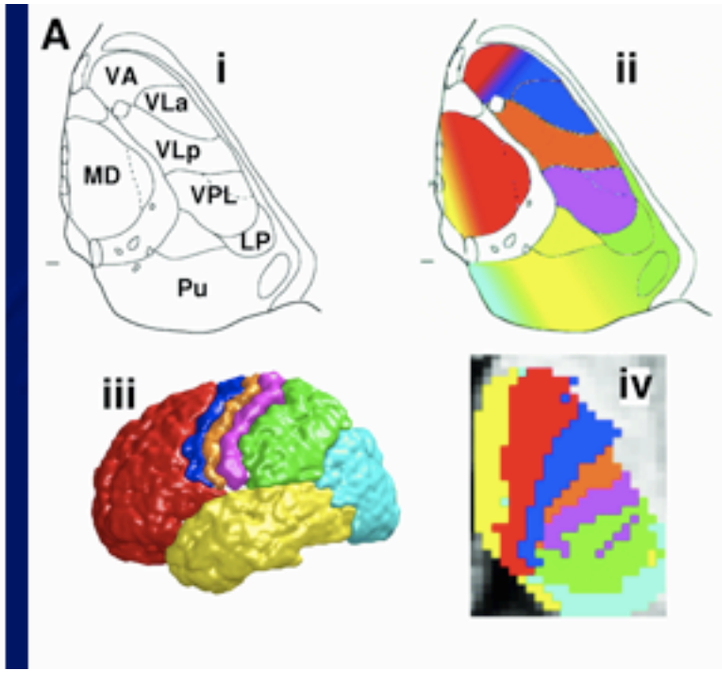
Termination: Thalamus

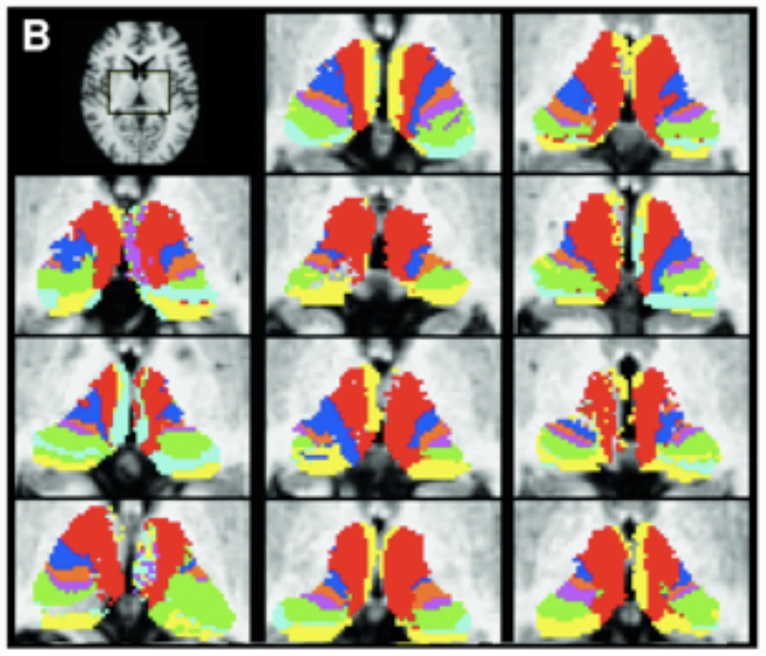
PROBTRACKX

Connectivity-based seed classification

- Quantify the connectivity of seed regions to target regions
- e.g. thalamic voxels can be classified according to their probability of connection to specific cortical targets



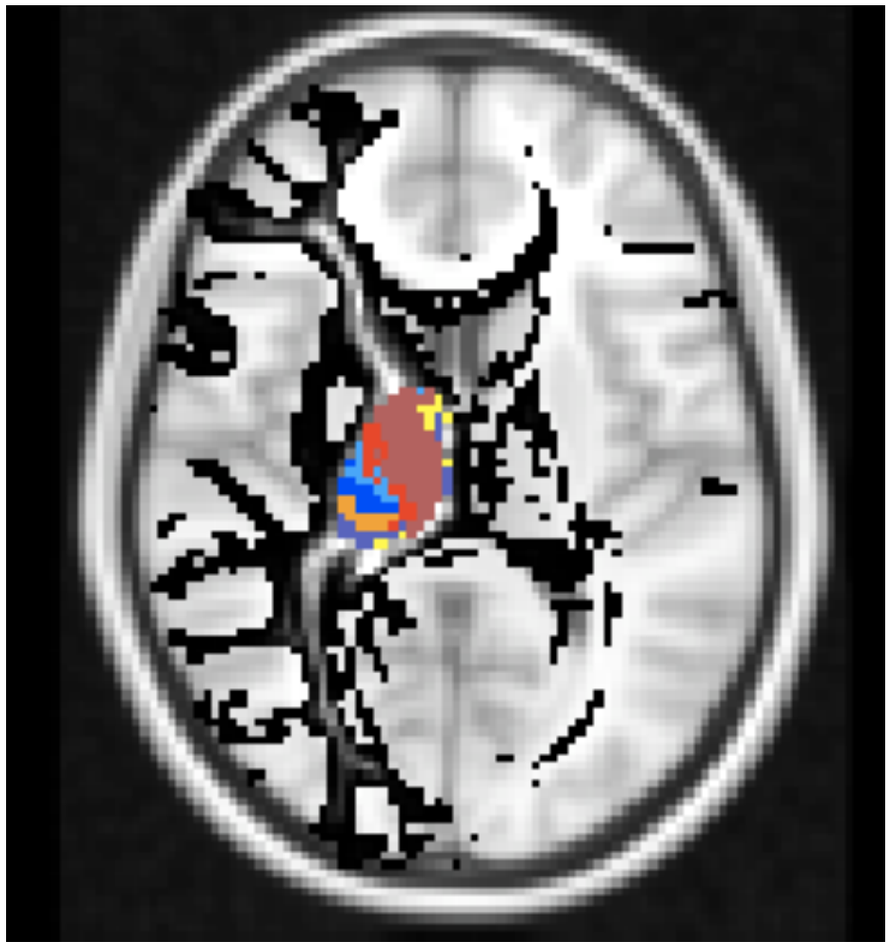


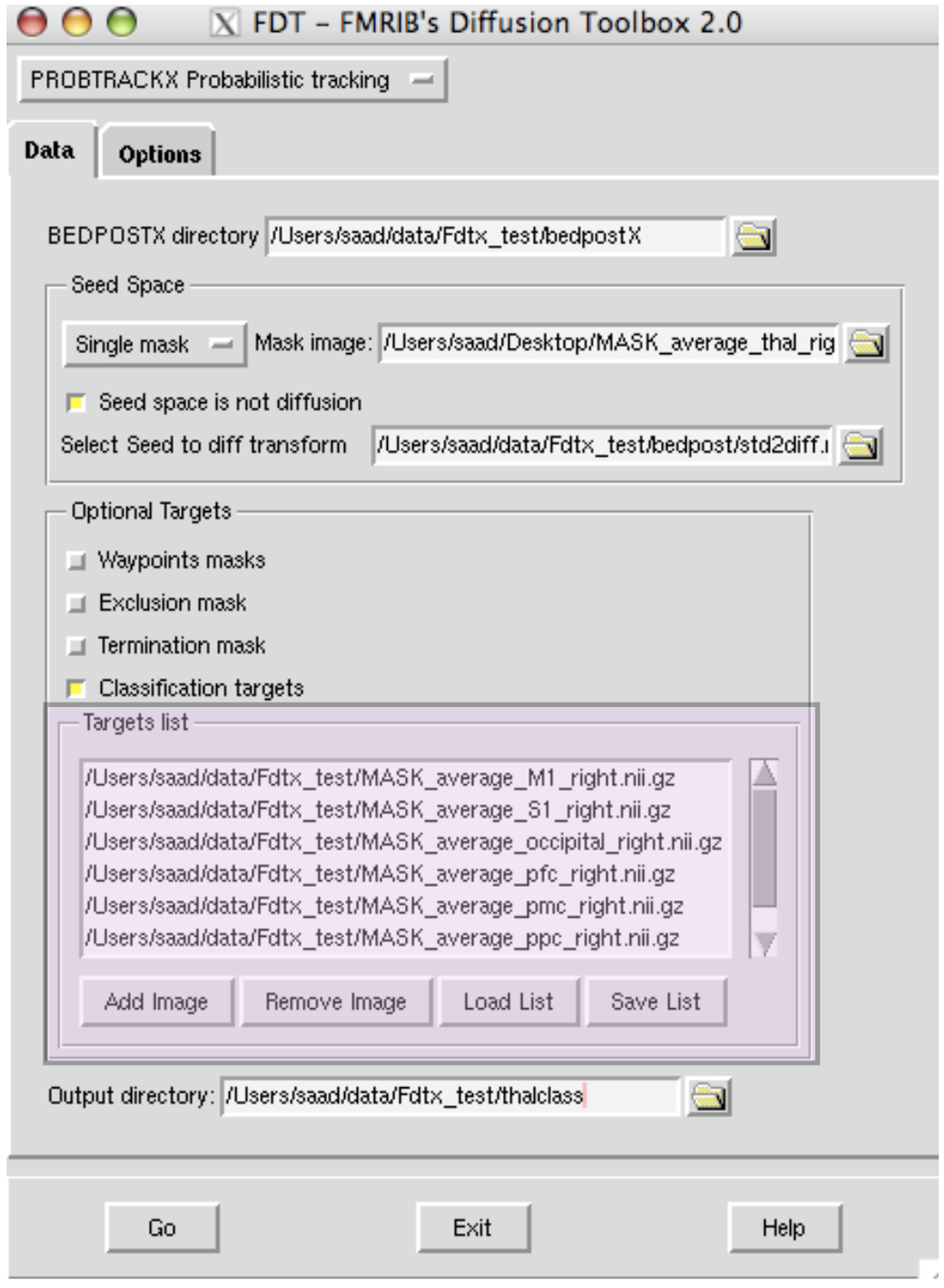


PROBTRACKX

Connectivity-based seed classification

Thalamic segmentation





Discussion

What are we (not) measuring?

- Distribution of a fibre orientation rather than distribution of fibre orientations
- Thresholding tract distribution is tricky
- Bins (voxels) are arbitrary
- Favour seed classification for quantitative analysis (masks are meaningful)

FMRIB Diffusion Toolbox

- DTI model fit
- Eddy current correction
- Voxel-Based diffusion analysis (TBSS)
- BEDPOSTX modelling crossing fibres
- PROBTRACKX propagating uncertainty in tractography