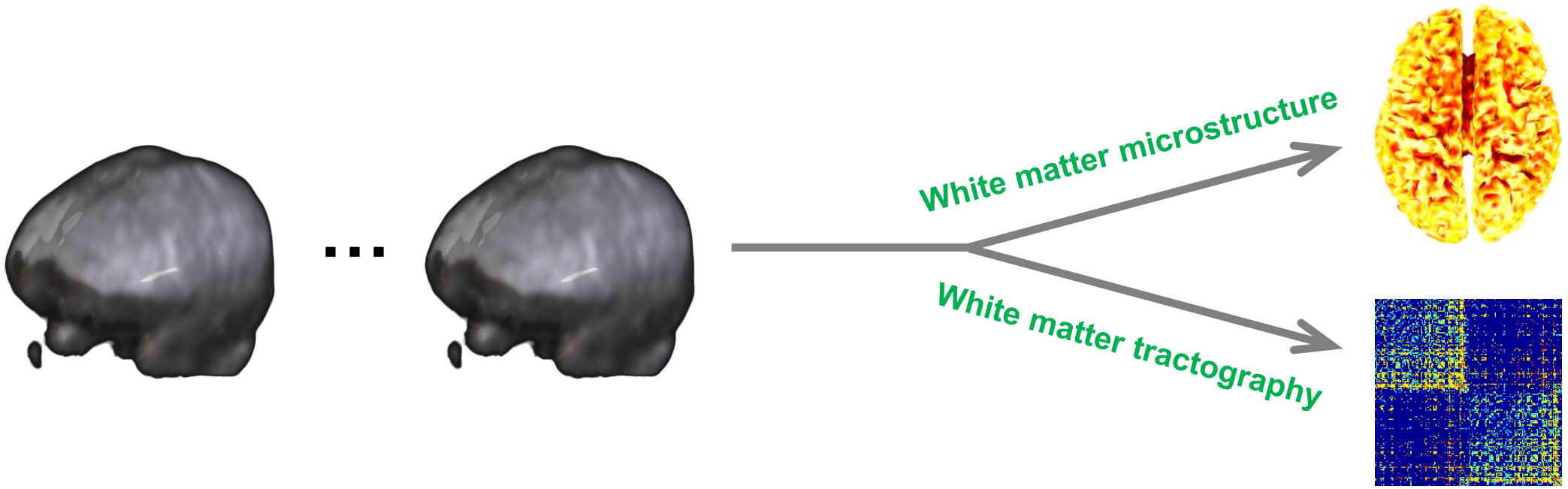
Medical/Bio Research Topics Ⅰ: Week 08 (22 April 2025)

Diffusion-weighted MRI (2): Data Processing Methods

확산가중 자기공명영상 (2): 데이터 처리 방법

Brain Mapping with Diffusion-weighted MRI (dMRI)

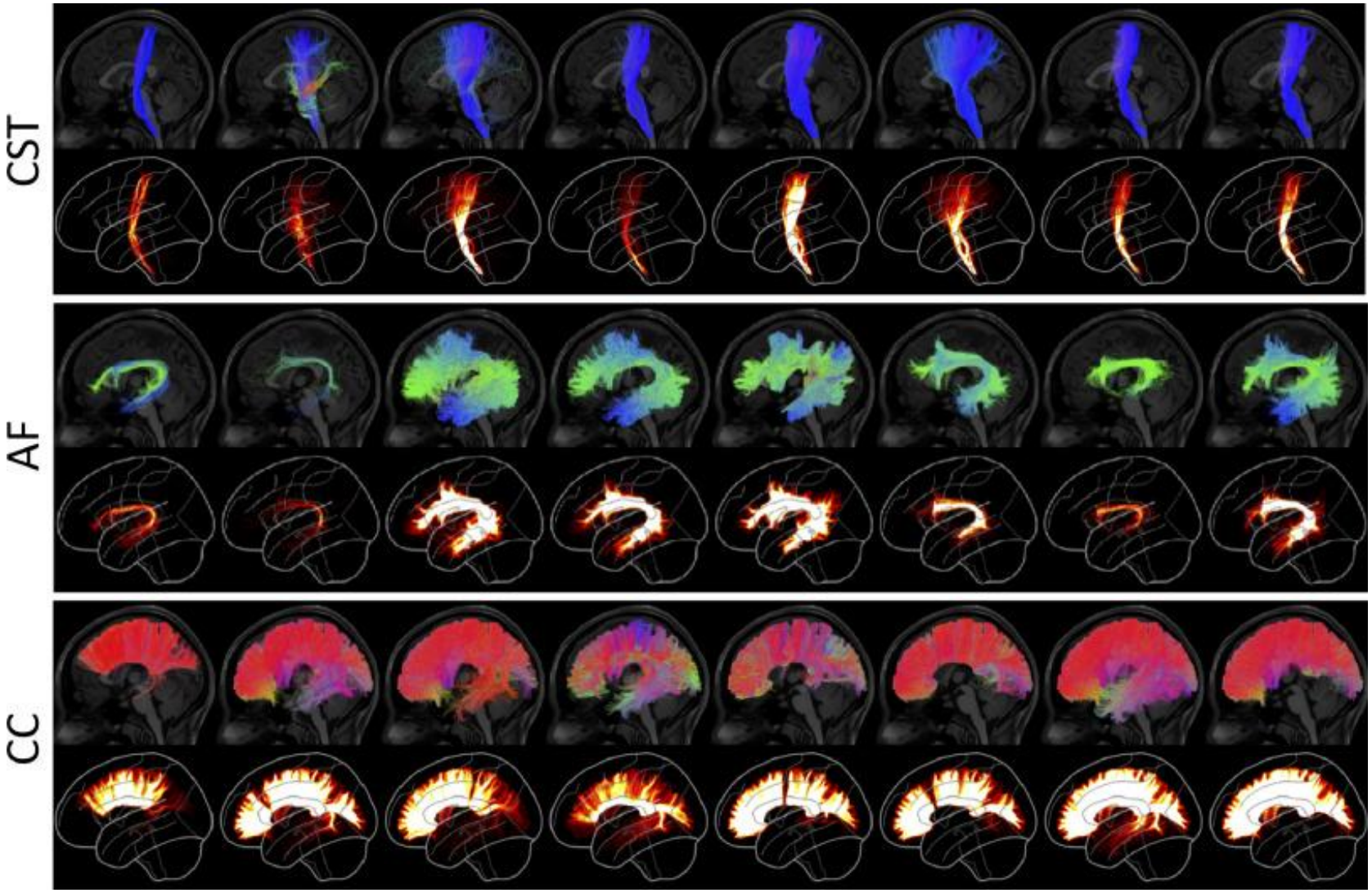
- Diffusion-weighted MRI



Analytical Variability in dMRI

- Variability of white matter tractography [Schilling et al., 2021]
  - Resulted from different protocols for white matter bundle segmentation

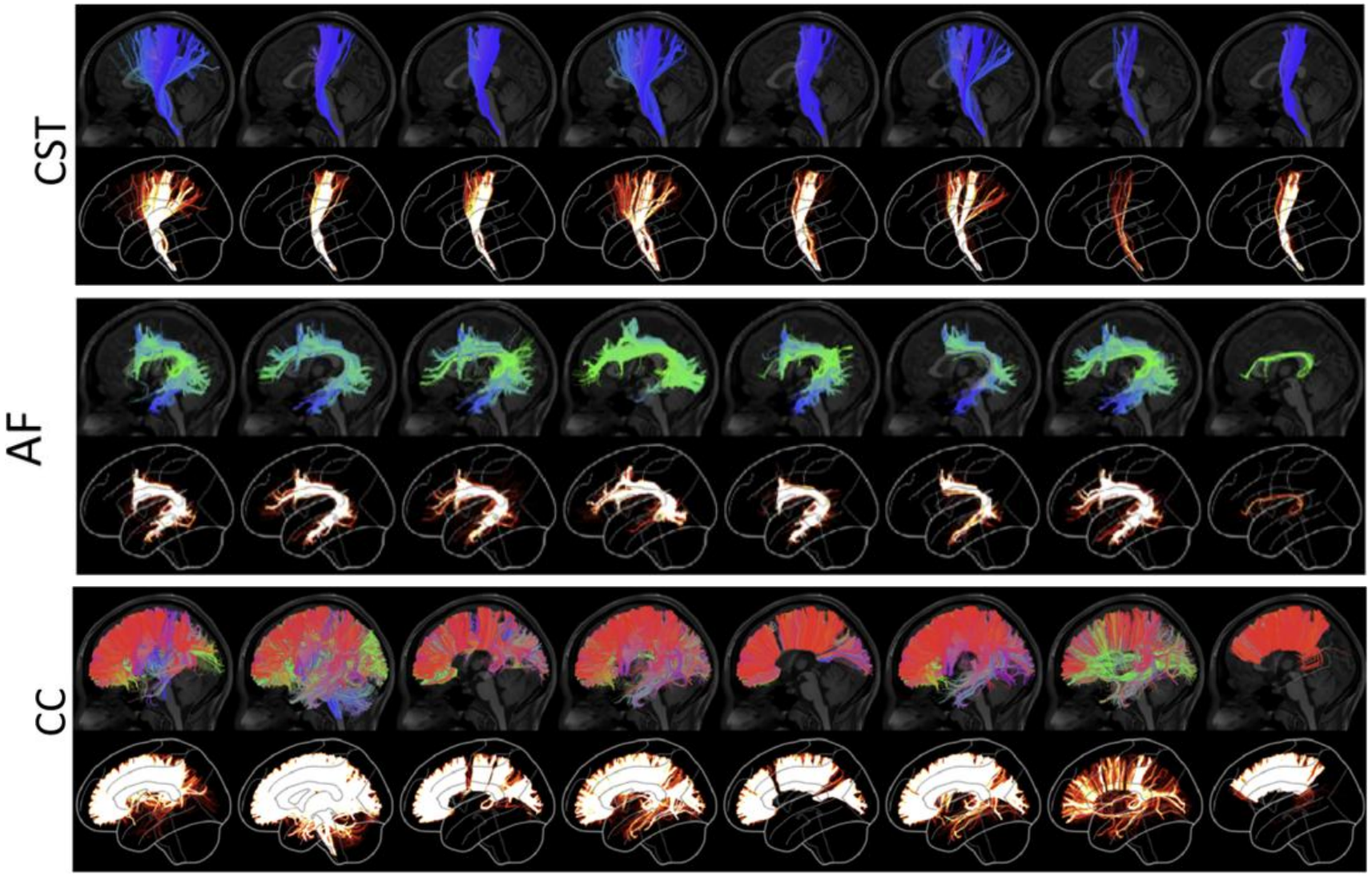
From the same probabilistic streamline set



[Schilling et al., 2021]

Analytical Variability in White Matter Tract Dissection Using Different Protocols

From the same deterministic streamline set



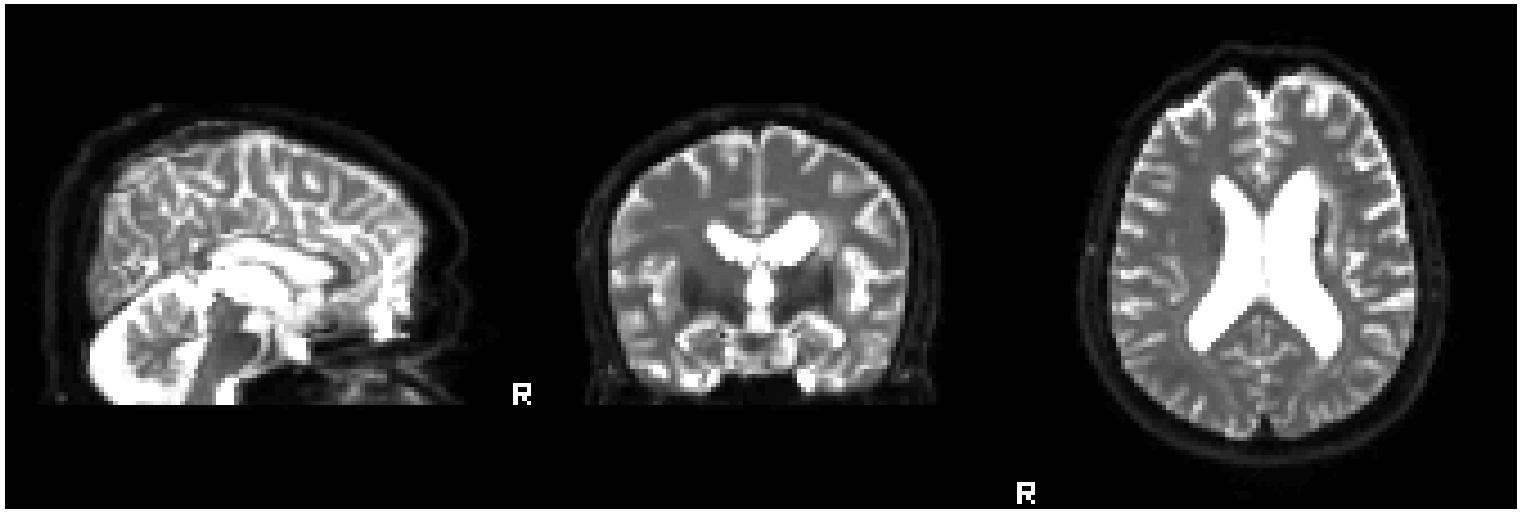
[Schilling et al., 2021]

Analytical Variability in White Matter Tract Dissection Using Different Protocols

Preprocessing

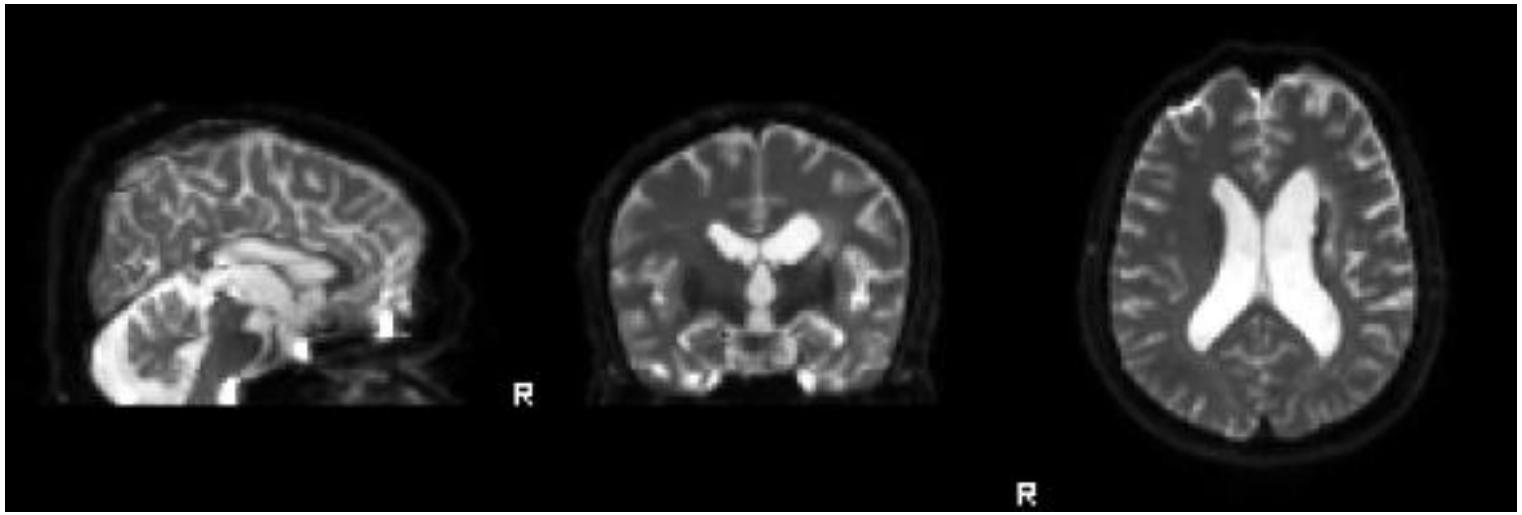
- Numerous steps to clean dMRI data before diffusion modeling
  - Correction for unwanted variation
    - Head motion
    - Eddy current-induced distortion
    - Inhomogeneity-induced distortion

[dMRI: Preprocessing]

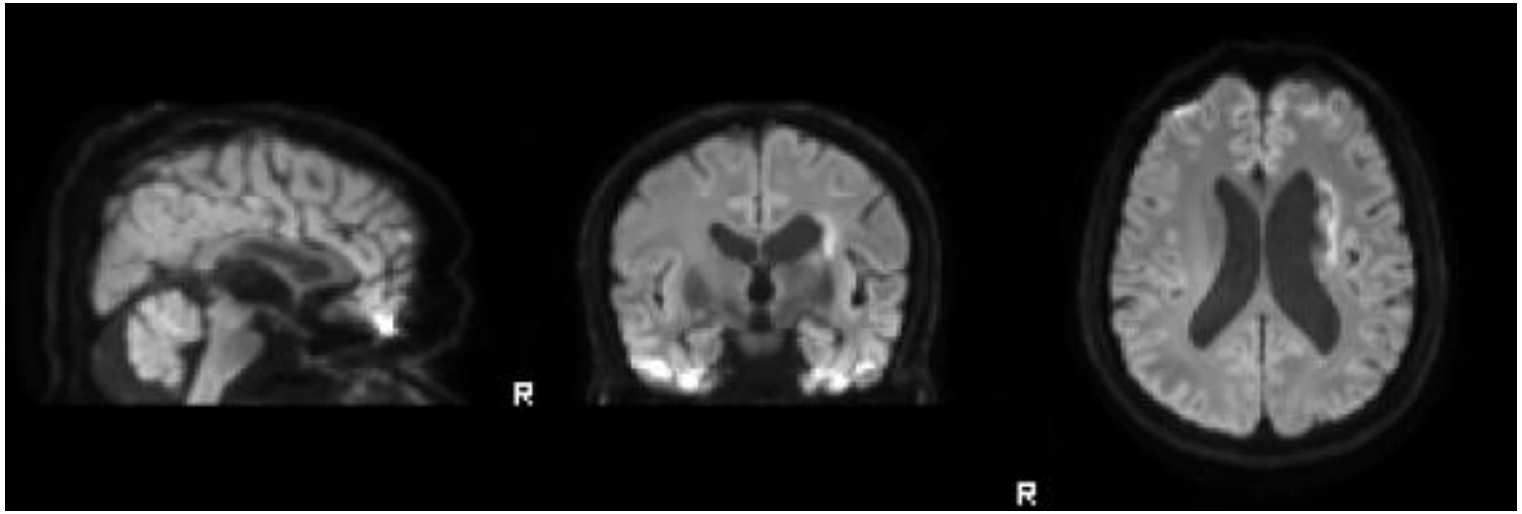


- 46 scans
  - 1 scan without diffusion weighting
  - 45 scans with diffusion weighting at $b = 1000$ s/mm^2

Average image for b = 0 s/mm^2



Average image for b = 1,000 s/mm^2



– *b*-values

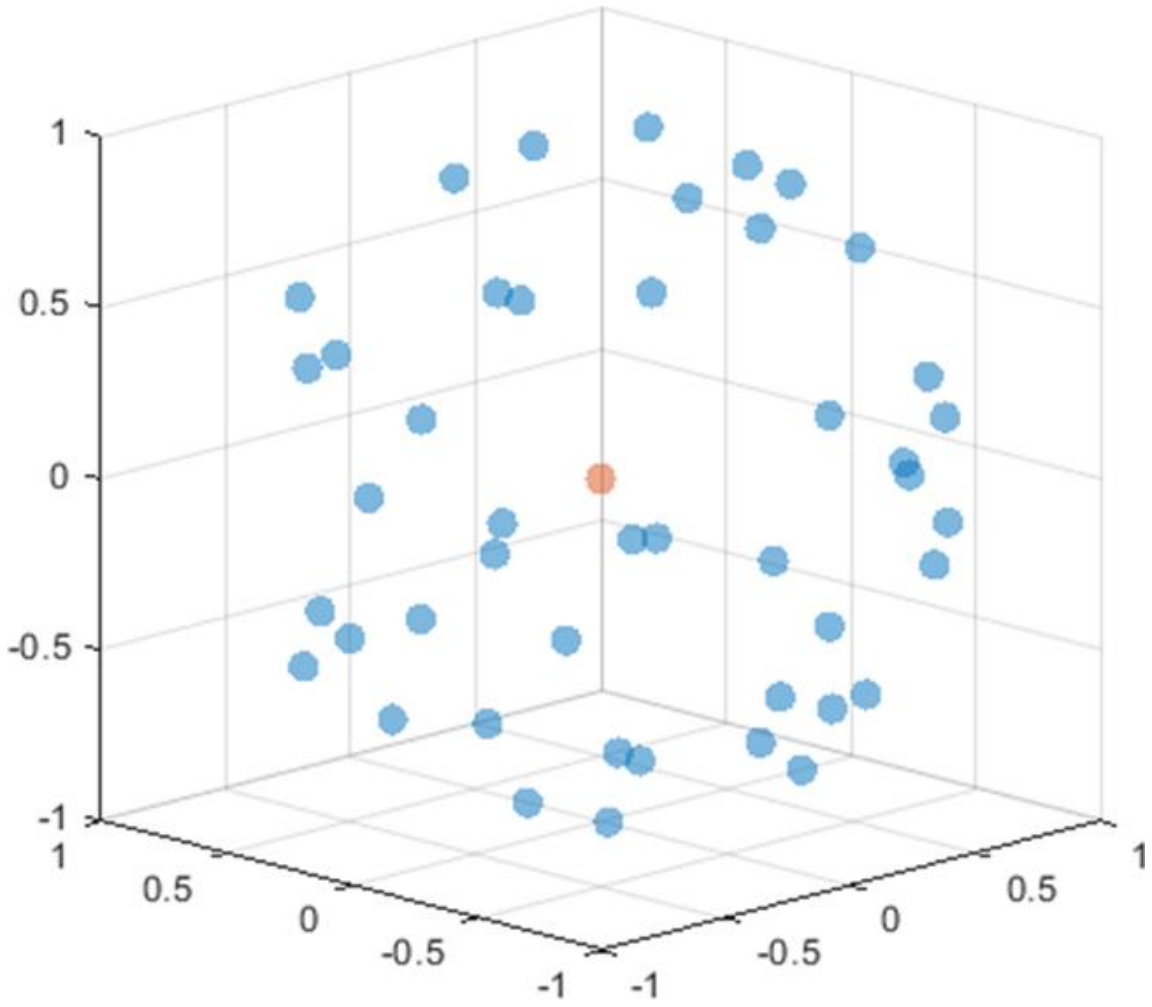
0	1000	1000	1000	1000	1000	1000	… 1000

46 values

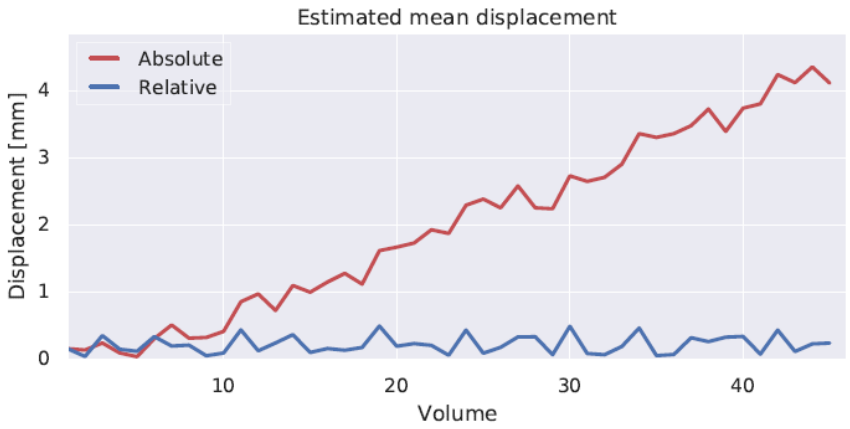
– *b*-vectors

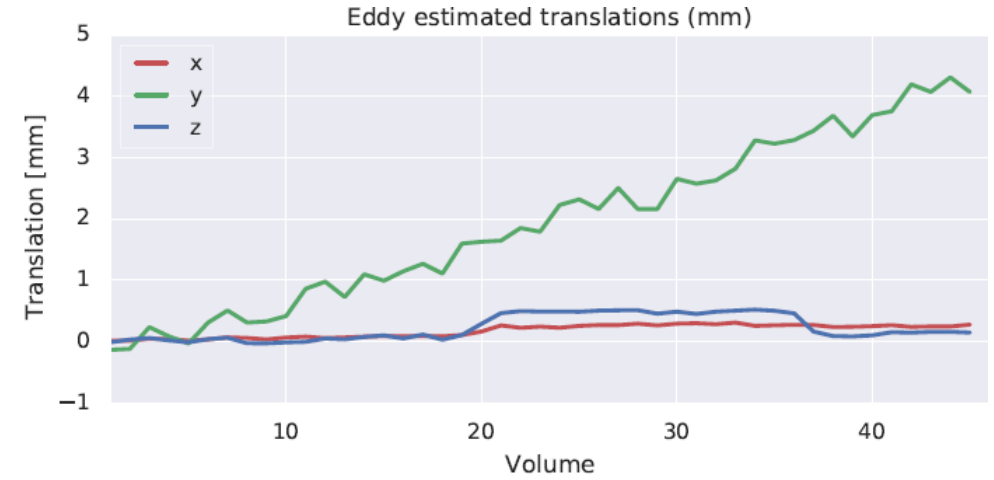
0	0.2488	-0.4396	0.6565	-0.3743	0.2818	…	0.4357
0	0.9672	0.7676	-0.0606	-0.5783	0.0936	…	0.8473
0	-0.0588	0.4671	-0.7513	0.7245	0.9545	…	0.3021

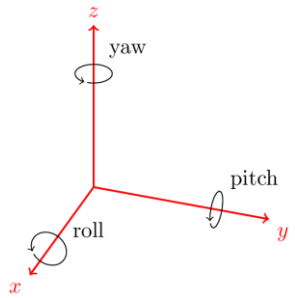
46 vectors



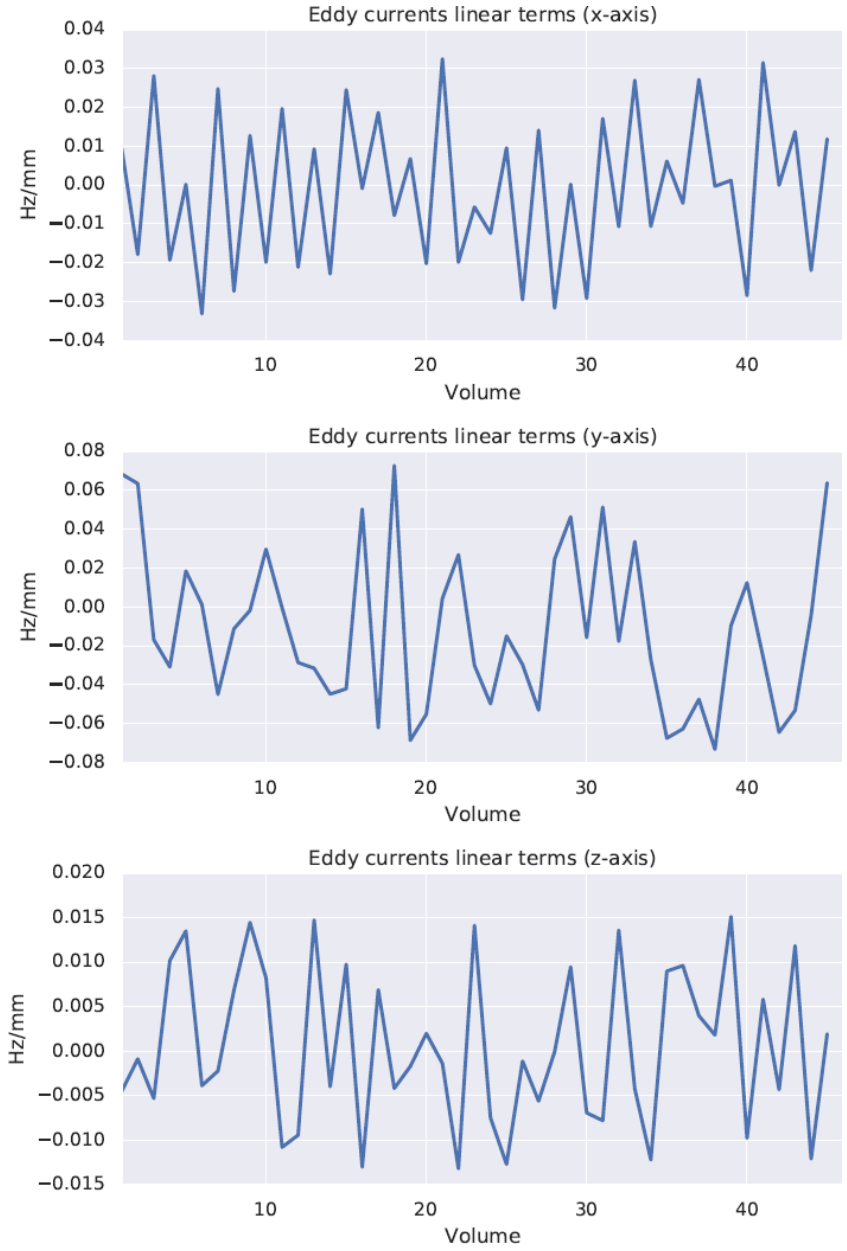
Diffusion-sensitizing Gradient Directions







Estimated Head Motion

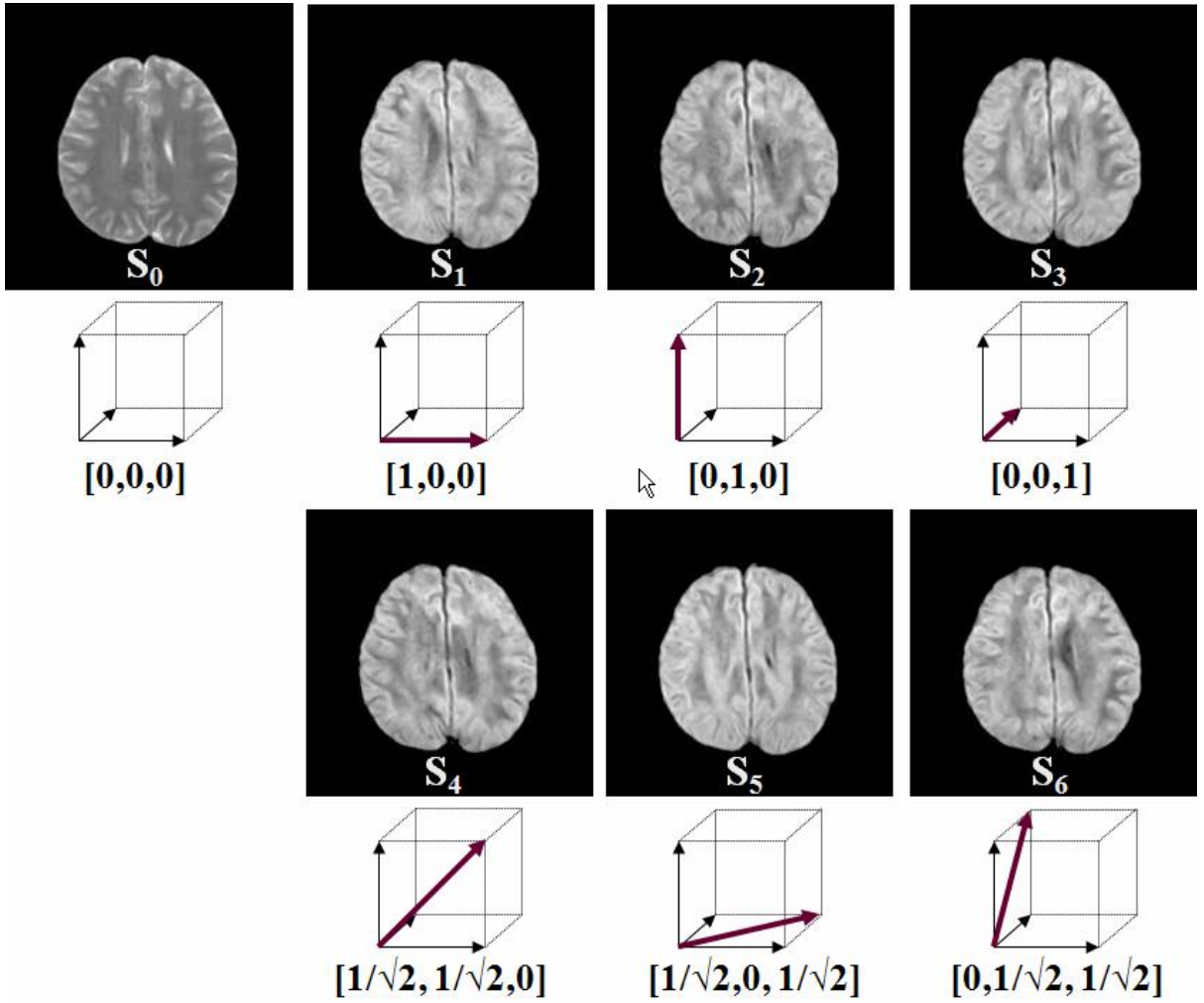


Estimated Eddy Currents

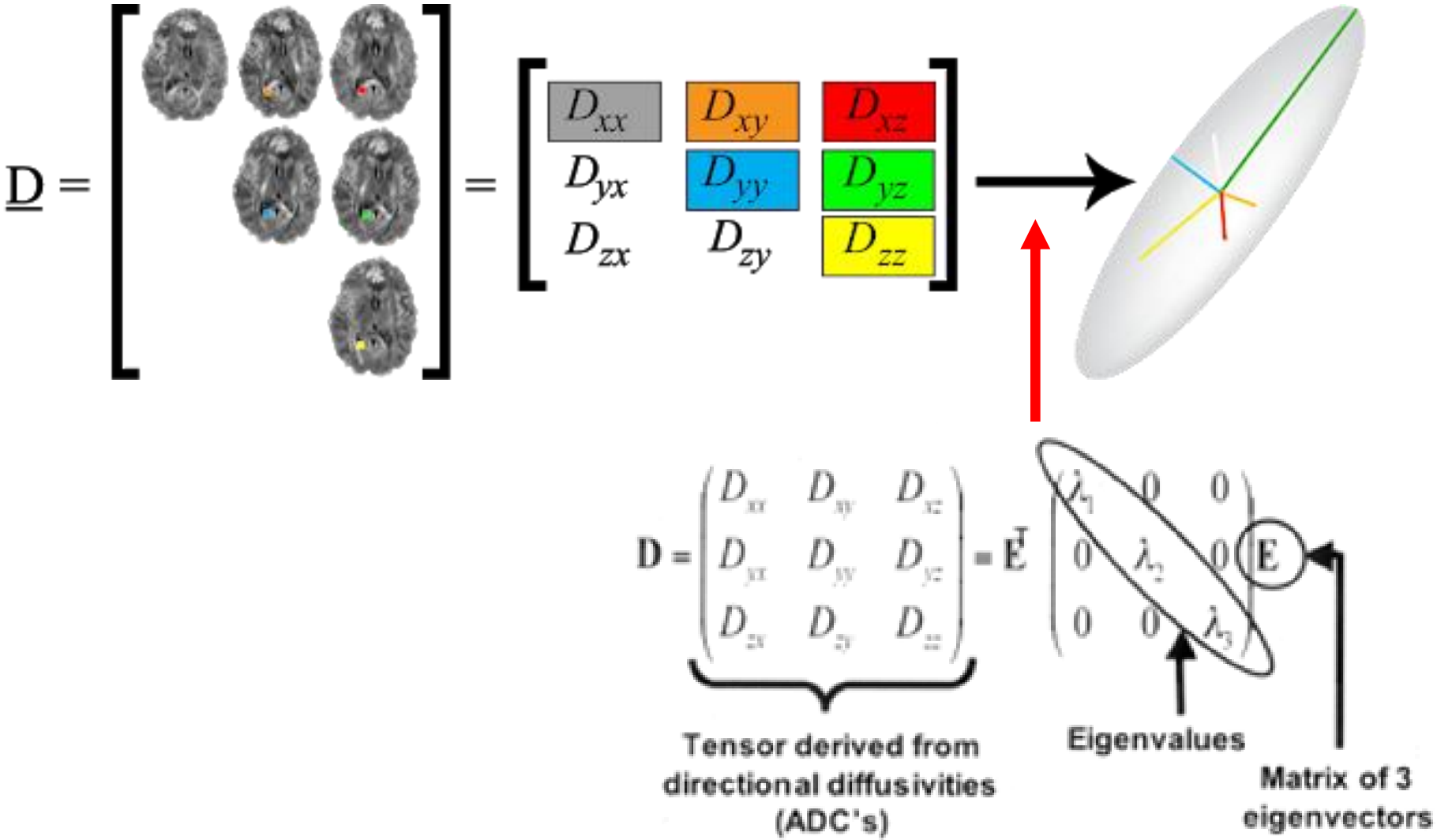
White Matter Microstructure

- Given the notion that diffusion measurement is sensitive to water molecule diffusion on a "microscopic scale"
  - Mean squared displacement in terms of time elapsed and diffusivity: $\langle r^2 \rangle = 2Dt = \sim$ μm
- Through measurement of the average Brownian diffusion behavior of water molecules by aggregating diffusion properties over a great many cells and axons within a voxel

- Diffusion tensor model
  - Represents the directional dependence of diffusion by a diagonalized matrix or an ellipsoid
  - Depicts only a single fiber population at each voxel based on the assumption that the probability density function describing the random displacement of water molecules due to diffusion is Gaussian
    - Not proper to voxels that have multiple fiber populations crossing or highly curving fiber bundles

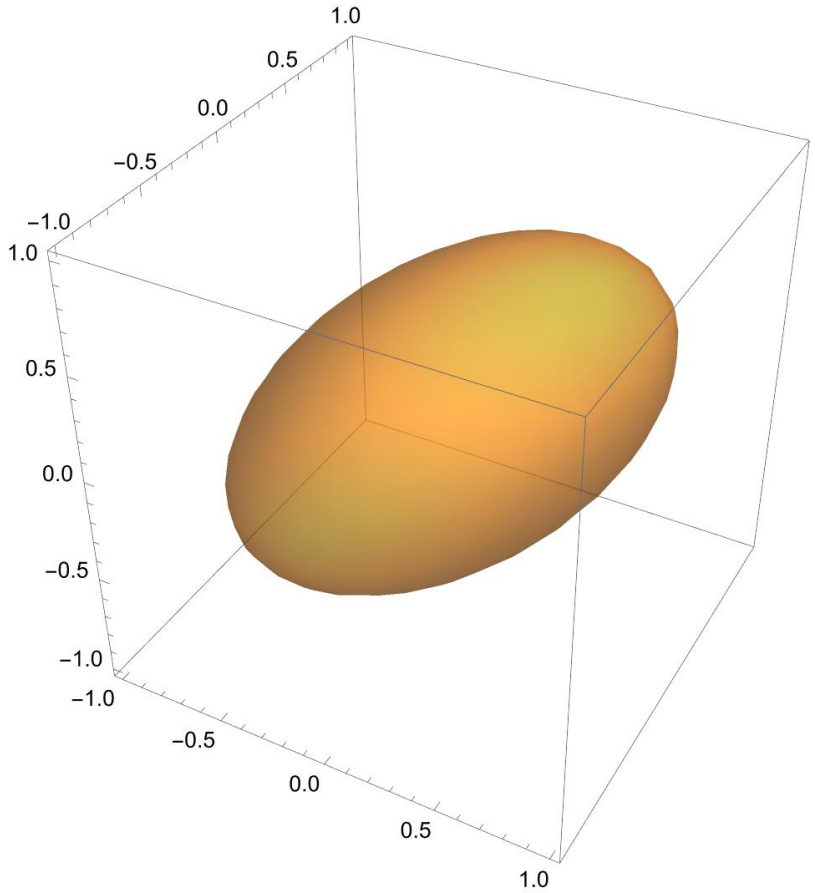


MRI Signals Measured without and with Diffusion Weighting

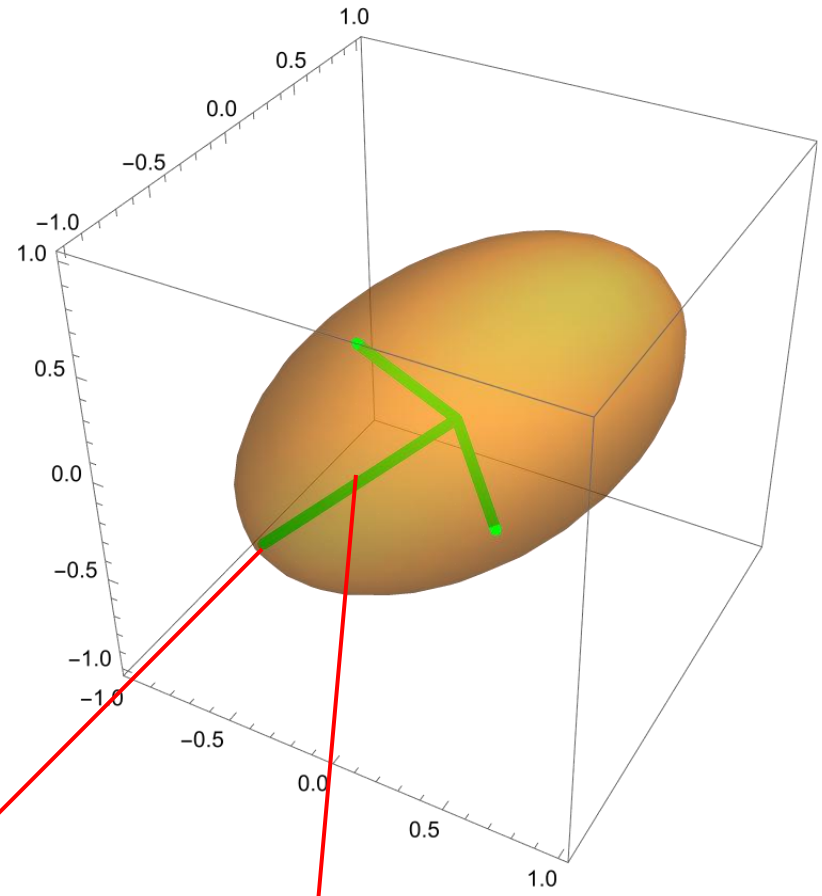


https://www.blog.brainsightai.com/post/from-dti-to-hardi]]

Diffusion Tensor and Its Ellipsoid Representation

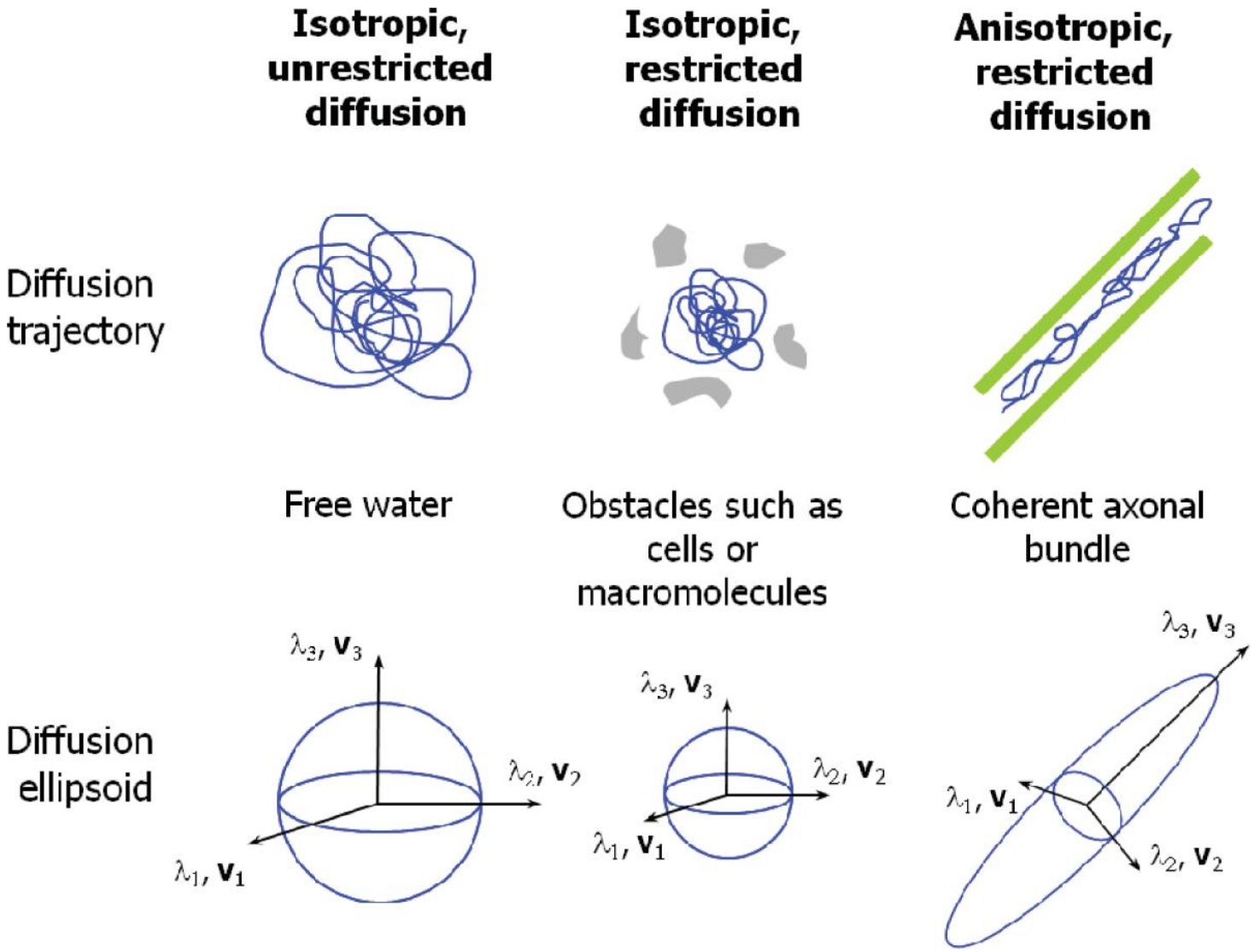


Eigendecomposition



$$\begin{pmatrix} 20 & -8 & -6 \\ -8 & 23 & -1 \\ -6 & -1 & 17 \end{pmatrix}$$

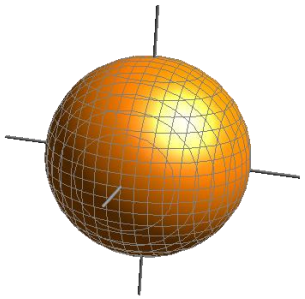
$$\begin{pmatrix} 0.68 & -0.69 & -0.25 \\ -0.30 & -0.57 & 0.76 \\ -0.67 & -0.44 & -0.59 \end{pmatrix}^{T} \begin{pmatrix} 30.4 & 0 & 0 \\ 0 & 20.1 & 0 \\ 0 & 0 & 9,5 \end{pmatrix} \begin{pmatrix} 0.68 & -0.69 & -0.25 \\ -0.30 & -0.57 & 0.76 \\ -0.67 & -0.44 & -0.59 \end{pmatrix}$$



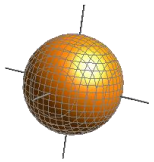
[Geva et al., 2011]

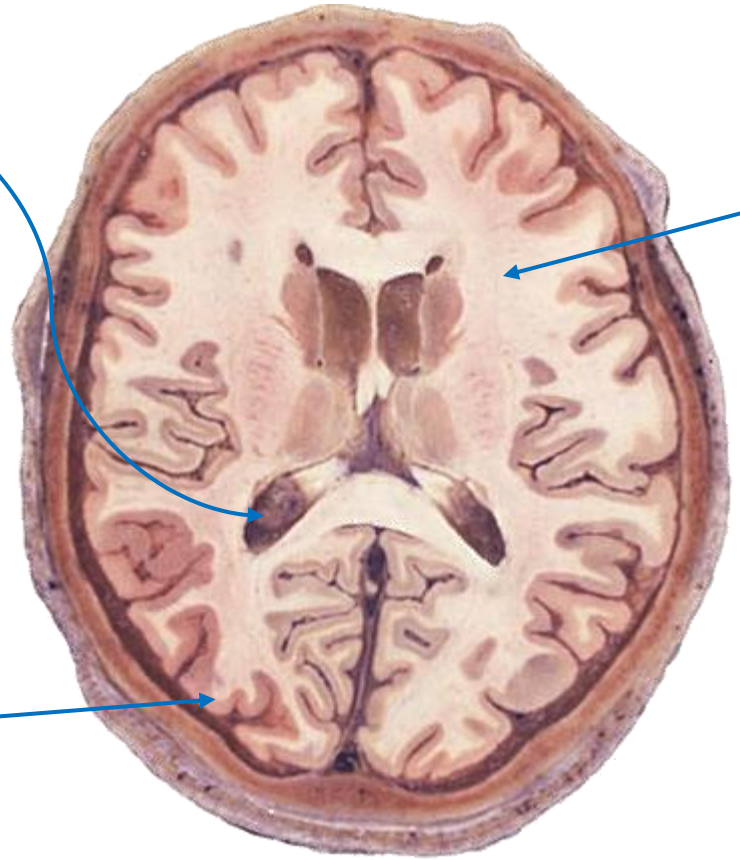
Isotropic and Anisotropic Diffusion Represented by Ellipsoids

CSF
Isotropic, unrestricted diffusion

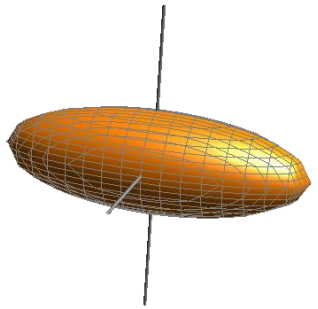


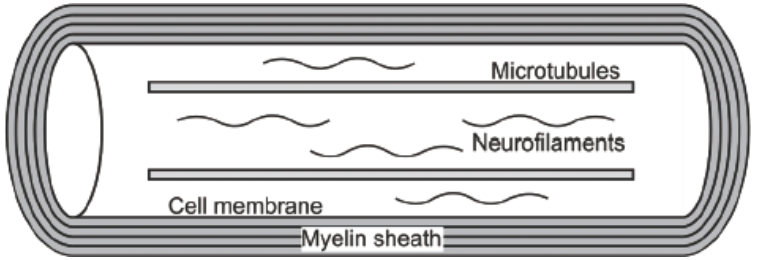
Grey matter
Isotropic, restricted diffusion





White matter
Anisotropic, restricted diffusion

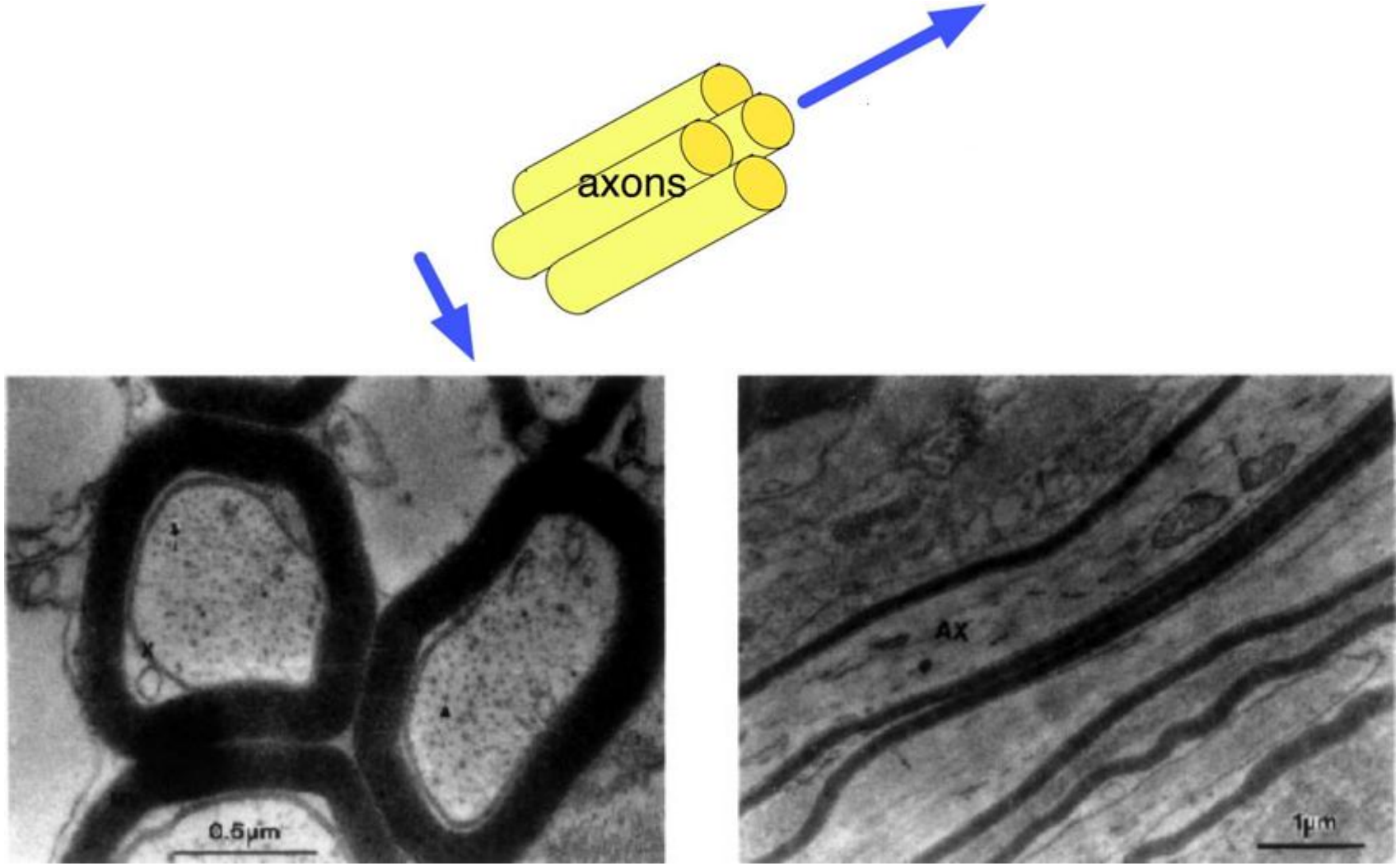




Potential sources of diffusion anisotropy
- Cytoskeleton
  - Microtubules (25 nm diameter)
  - Neurofilaments (10 nm diameter)
  - Microfilaments (7 nm diameter)
- Axonal membranes
- Myelin sheath

[Noguerol et al., 2017]]

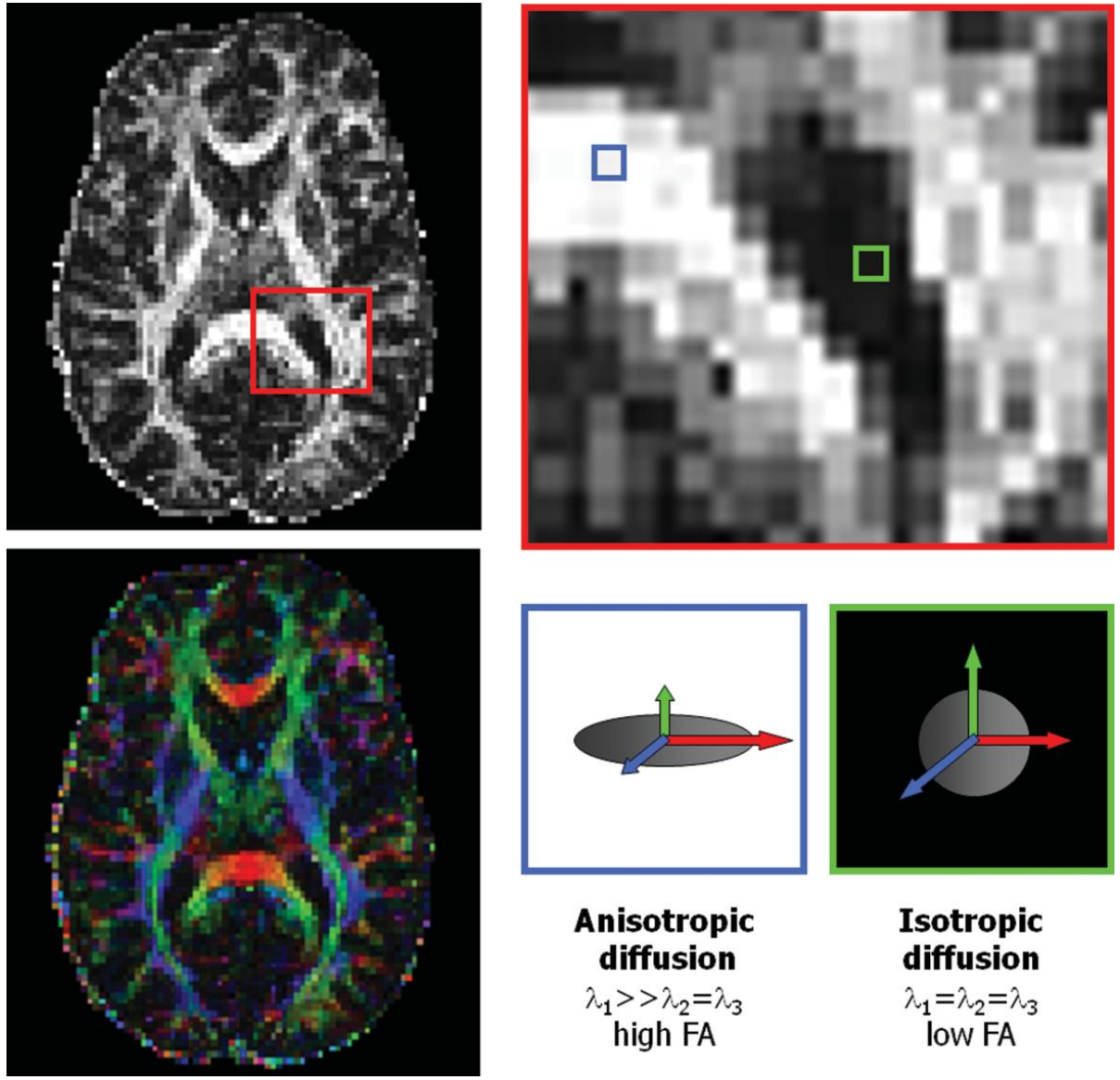
Isotropic and Anisotropic Diffusion in Brain Tissues



[Beaulieu, 2002]]

Transverse and Longitudinal Sections of Myelinated Optic Nerves of the Garfish

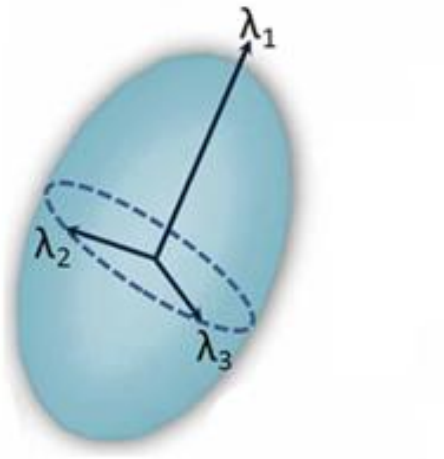
- Diffusion tensor metrics
  - Characterize aspects of water molecule diffusion, such as the magnitude and anisotropy (directional dependence), offering insights into tissue structure and organization
  - Fractional anisotropy (FA)
  - Mean diffusivity (MD)
  - Axial diffusivity (AD)
  - Radial diffusivity (RD)



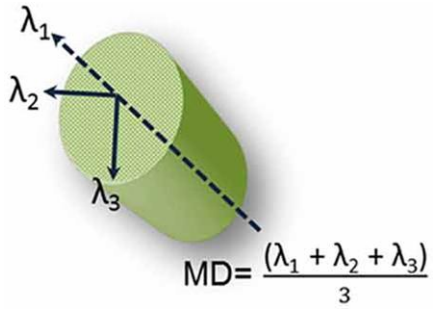
[Geva et al., 2011]

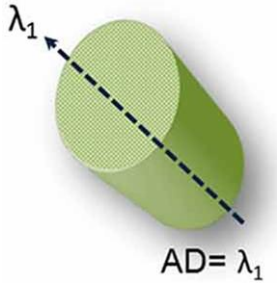
Directional Information Added to an FA Map

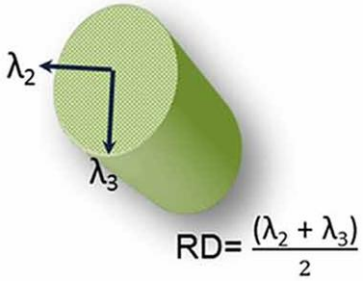
[dMRI: Diffusion Modeling]

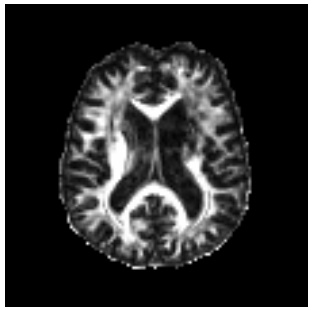


$$FA = \sqrt{\frac{1}{2}} \cdot \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{(\lambda_1)^2 + (\lambda_2)^2 + (\lambda_3)^2}}$$

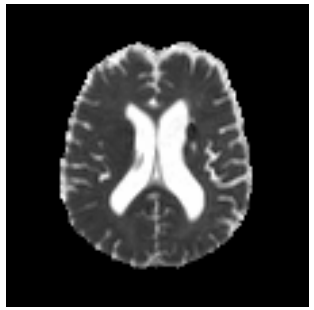




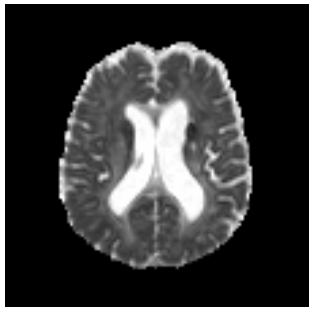




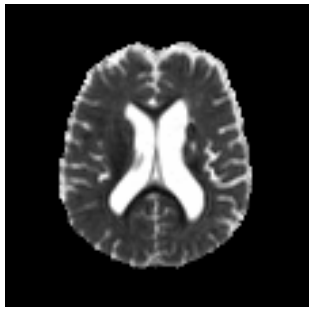
FA



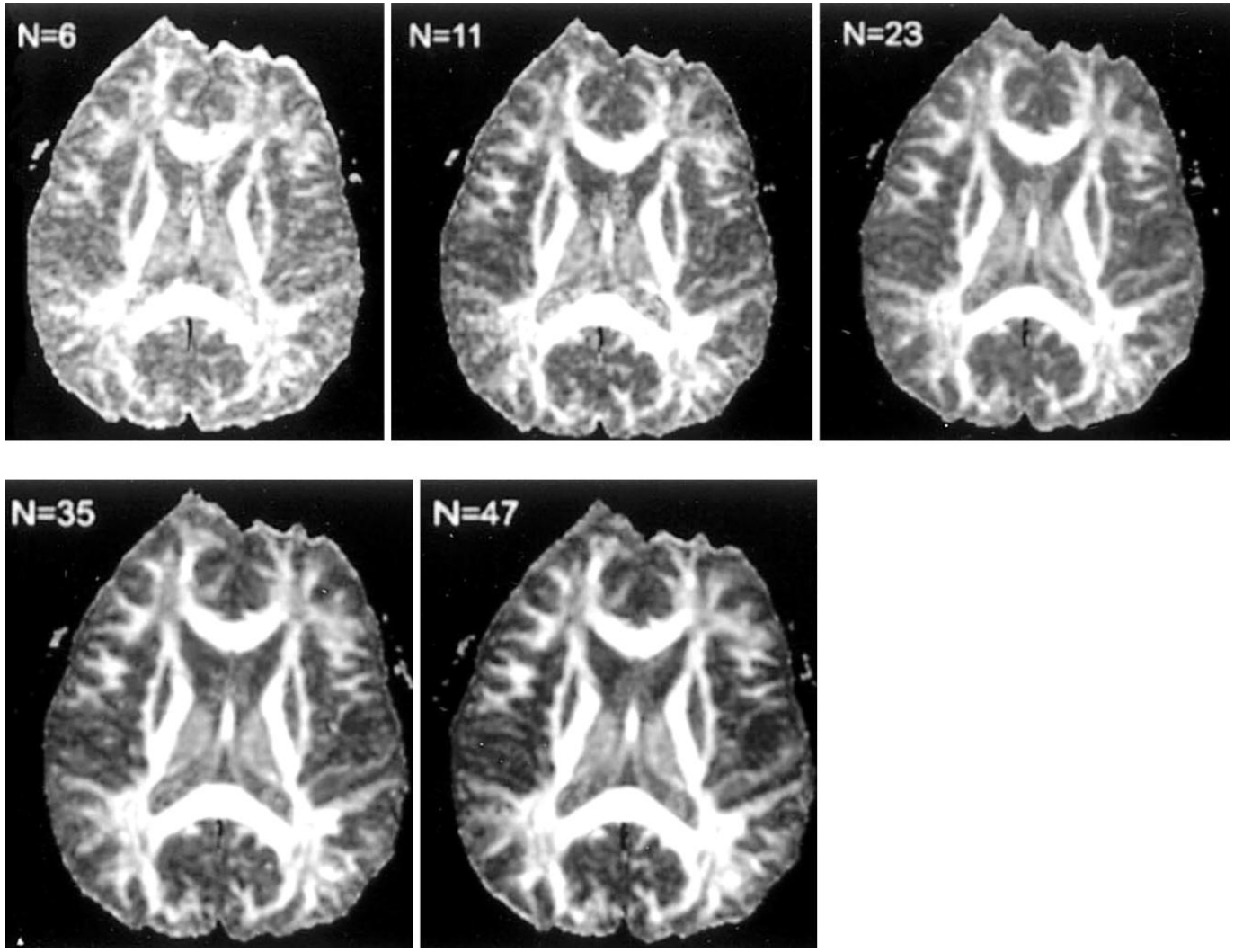
MD



AD

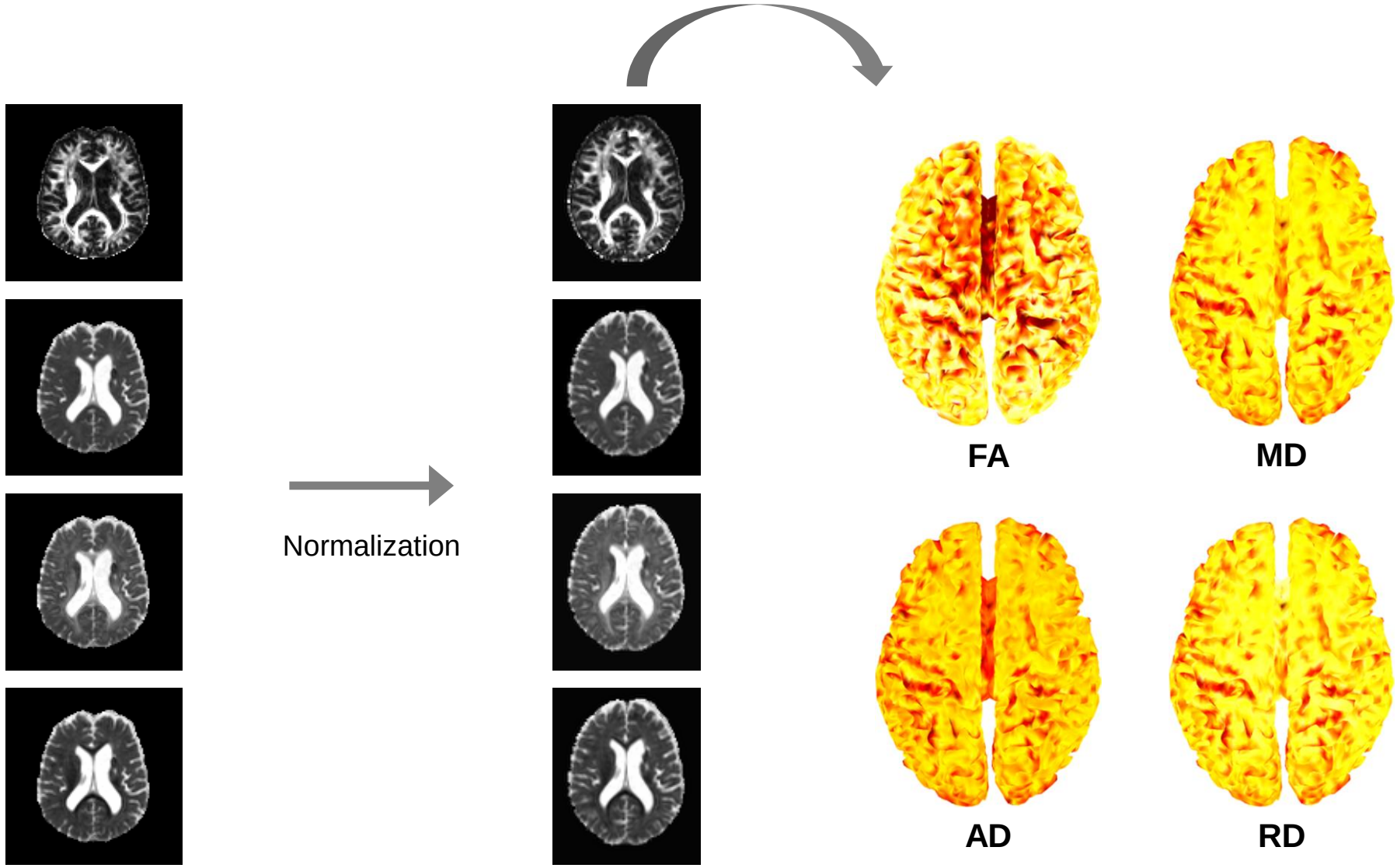


RD



[Chang et al., 2005]

FA Maps According to Different Numbers of Diffusion-sensitizing Gradient Directions



Information of White Matter Microstructure

[Statistical Analysis of dMRI]

- FA ~

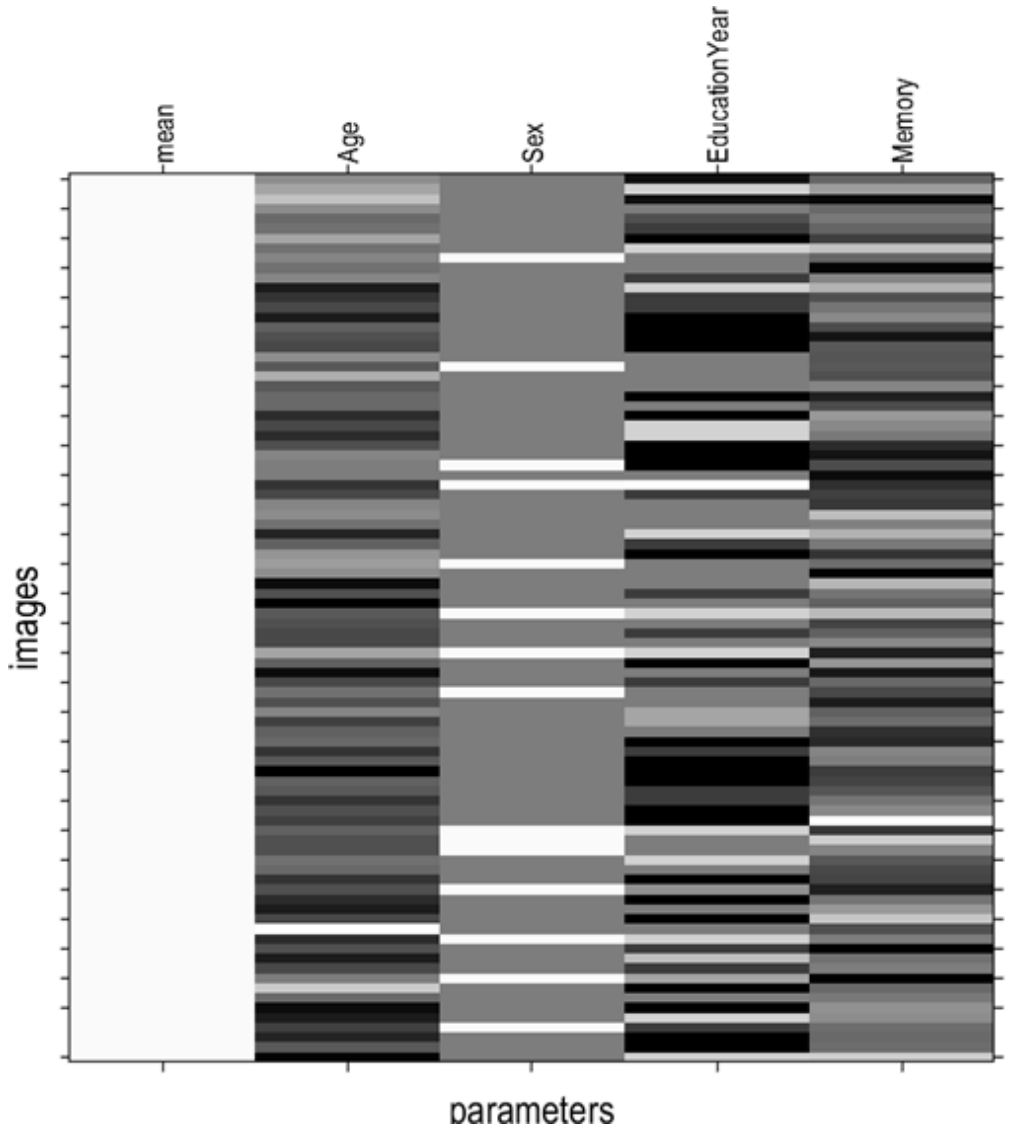
  Age +

  Sex +

  Education year +

  Memory performance

Design matrix



Output

Regression

Positive correlation

Negative correlation

- MD ~
  - Age +
  - Sex +
  - Education year +
  - Memory performance

Output

Regression

Positive correlation

Negative correlation

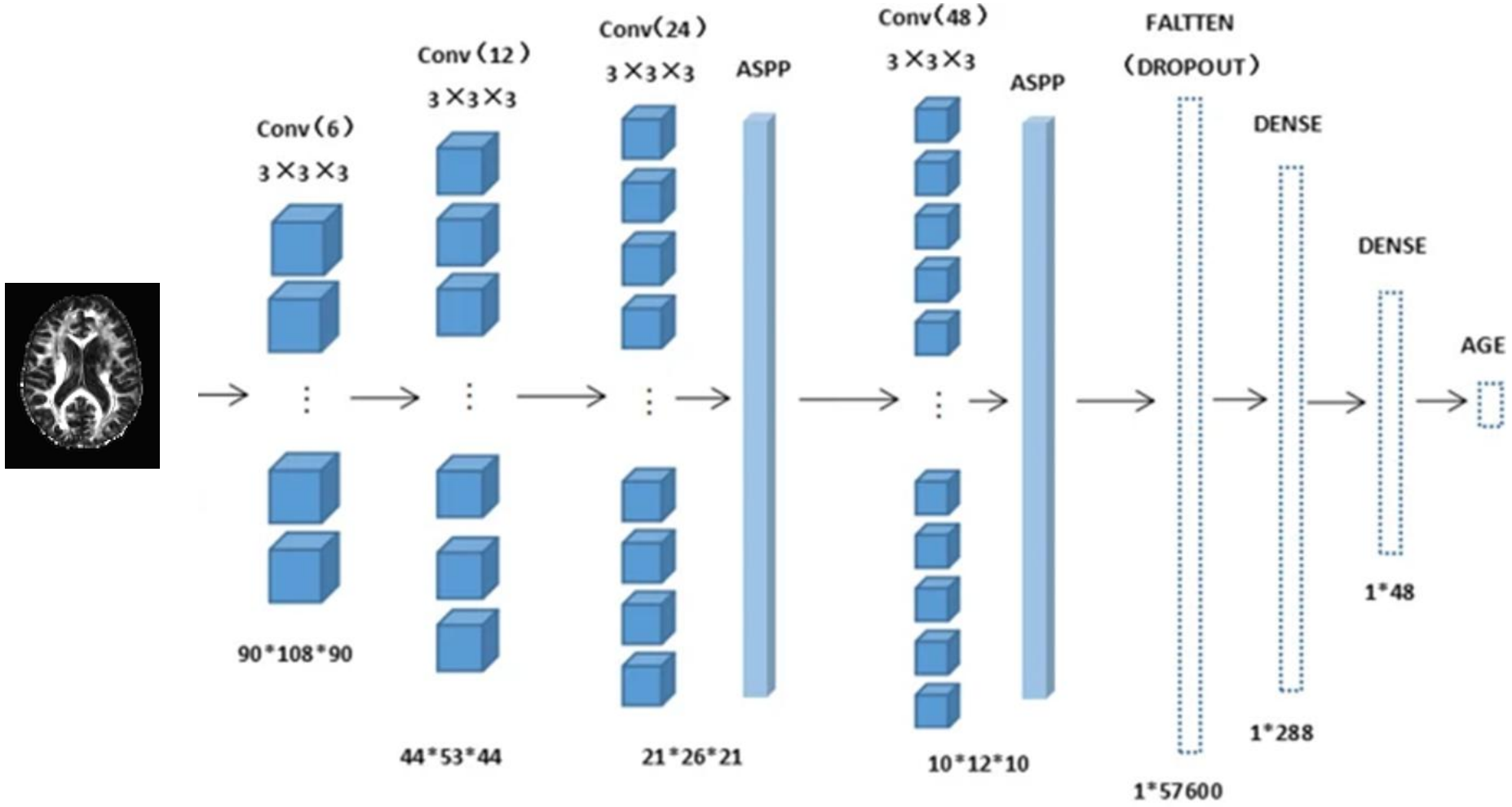
- Input to machine learning models
  - Table of voxel-wise or area-wise metric values for diffusion tensors

Features →

Samples ↓

	Voxel or Area 1 metric	Voxel or Area 2 metric	Voxel or Area 3 metric	…
Subject 1	-	-	-	-
Subject 2	-	-	-	-
Subject 3	-	-	-	-
⋮	-	-	-	-

  - Diffusion tensor metric map

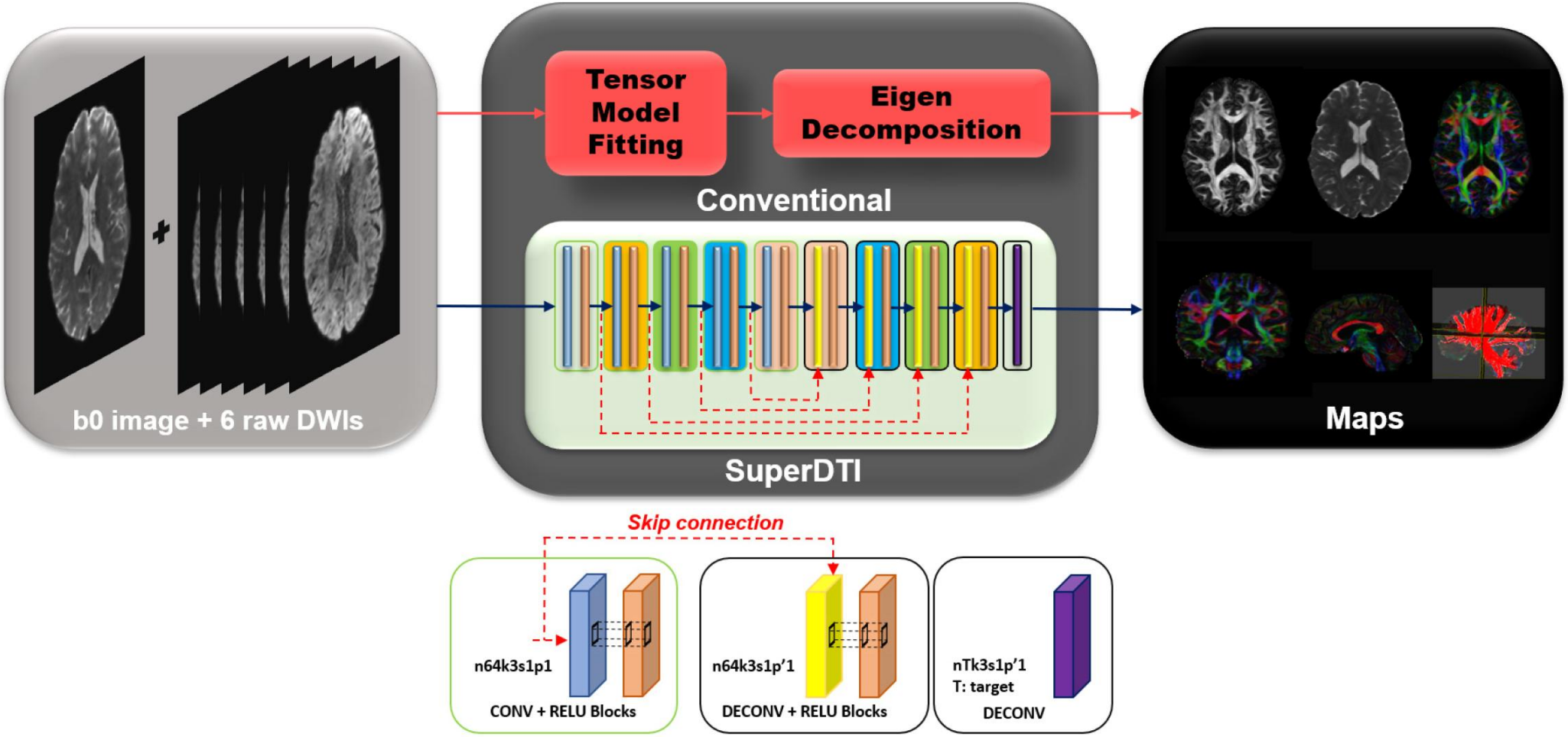


[Adapted from Wang et al., 2023]

Application of Deep Learning to Diffusion Tensor Metric Maps

Automated Diffusion Tensor Metrics Computation

- Employs deep learning algorithms to overcome limitations of traditional tensor fitting methods
- Enables to improve computation accuracy and reduce noise sensitivity



[Li et al., 2021]

SuperDTI: Diffusion Tensor Metrics Estimation

Computational Representation of White Matter Pathways

- White matter tractography hierarchy
  - Streamline → bundle
- Streamline
  - Fundamental unit of tractography, representing a single reconstructed fiber trajectory from a seed point through the brain
  - Highly dependent on algorithm parameters (seed density, step size, angular threshold, etc.)
    - Number of streamlines does not directly correspond to actual axon counts; rather it represents a computational estimation

- Bundle
  - Collection of streamlines that share similar trajectories and anatomical locations
  - Represents an anatomical structure believed to serve a common functional role
  - Can be defined through automatic or semi-automatic algorithms or expert manual segmentation
  - Examples include well-known white matter pathways

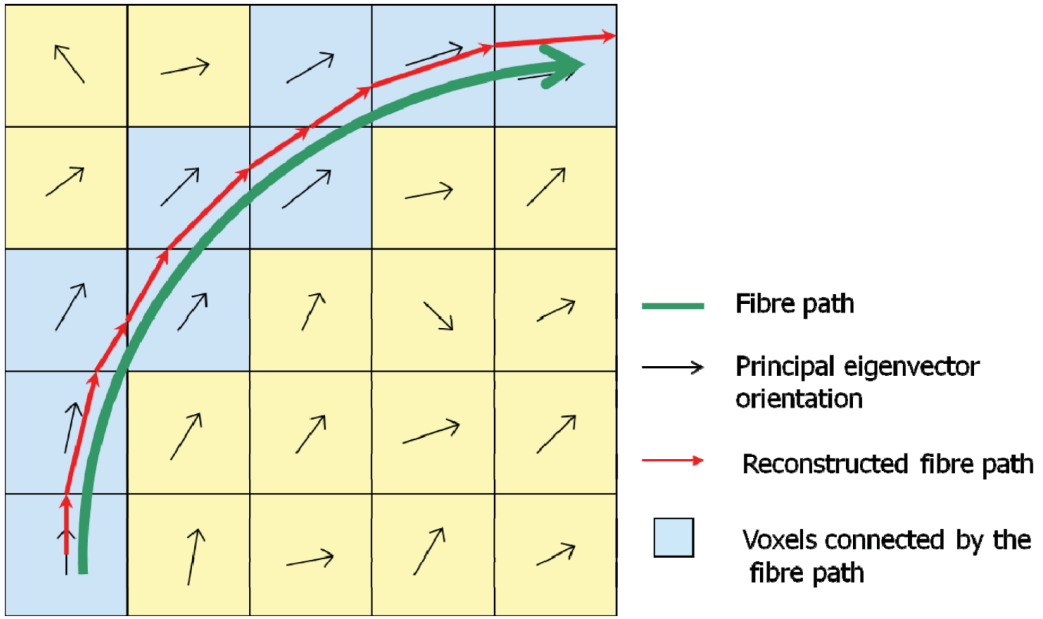
- Relationship between biological and tractography hierarchies
  - Scale mismatch
    - A single voxel contains millions of axons, but generates far fewer streamlines
  - Resolution limitations
    - MRI resolution (~ 1-2 mm) is insufficient to directly visualize individual axons (~ 1-10 μm)
  - Indirect measurement
    - Diffusion MRI measures water molecule movement as a proxy for tissue organization

- Validation challenges
  - Direct comparison between tractography results and actual neural pathways in living human brain is nearly impossible
- Model assumptions
  - All tractography algorithms are based on simplified models that cannot fully capture complex biological reality
- Interpretative caution
  - Streamline-based connectivity metrics should be considered estimations rather than direct representations of anatomical connections

White Matter Tractography

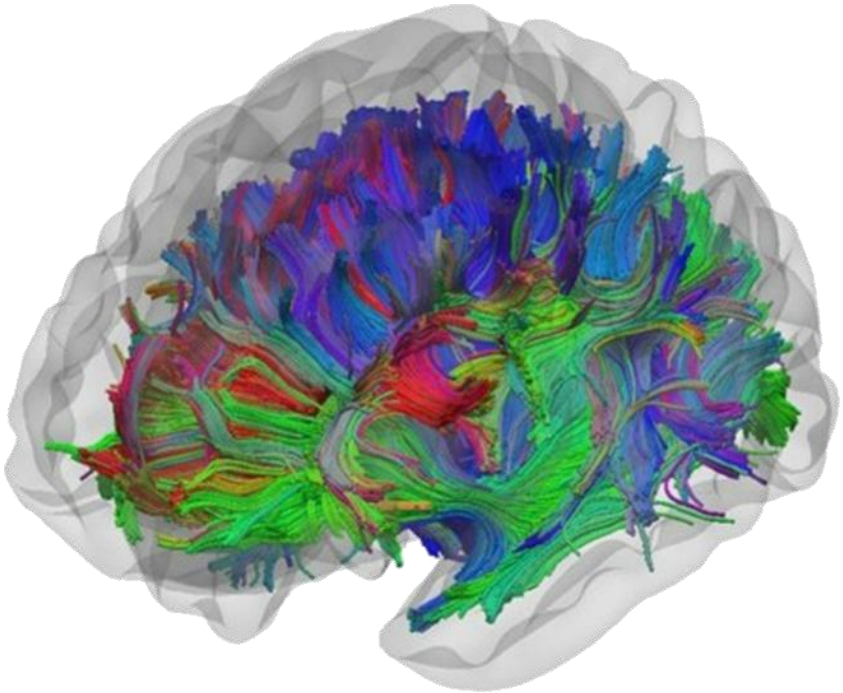
- Map of connectional anatomy of white matter
  - Bundled streamlines that reflect where organized white matter tracts are likely to be
  - Based on how strongly and in what directions water molecules diffuse given physical constraints in the brain

- Tractography vs tracking vs tractogram
  - Tractography
    - Comprehensive technique that uses dMRI data to reconstruct and visualize white matter pathways in 3D
    - Encompasses both the tracking algorithms and visualization methods.
  - Tracking
    - Algorithmic process of following the direction of nerve fibers to calculate their paths
  - Tractogram
    - Final output or result of tractography
    - Complete set of reconstructed white matter pathways displayed together



Streamlines based on common directions of water molecule diffusion

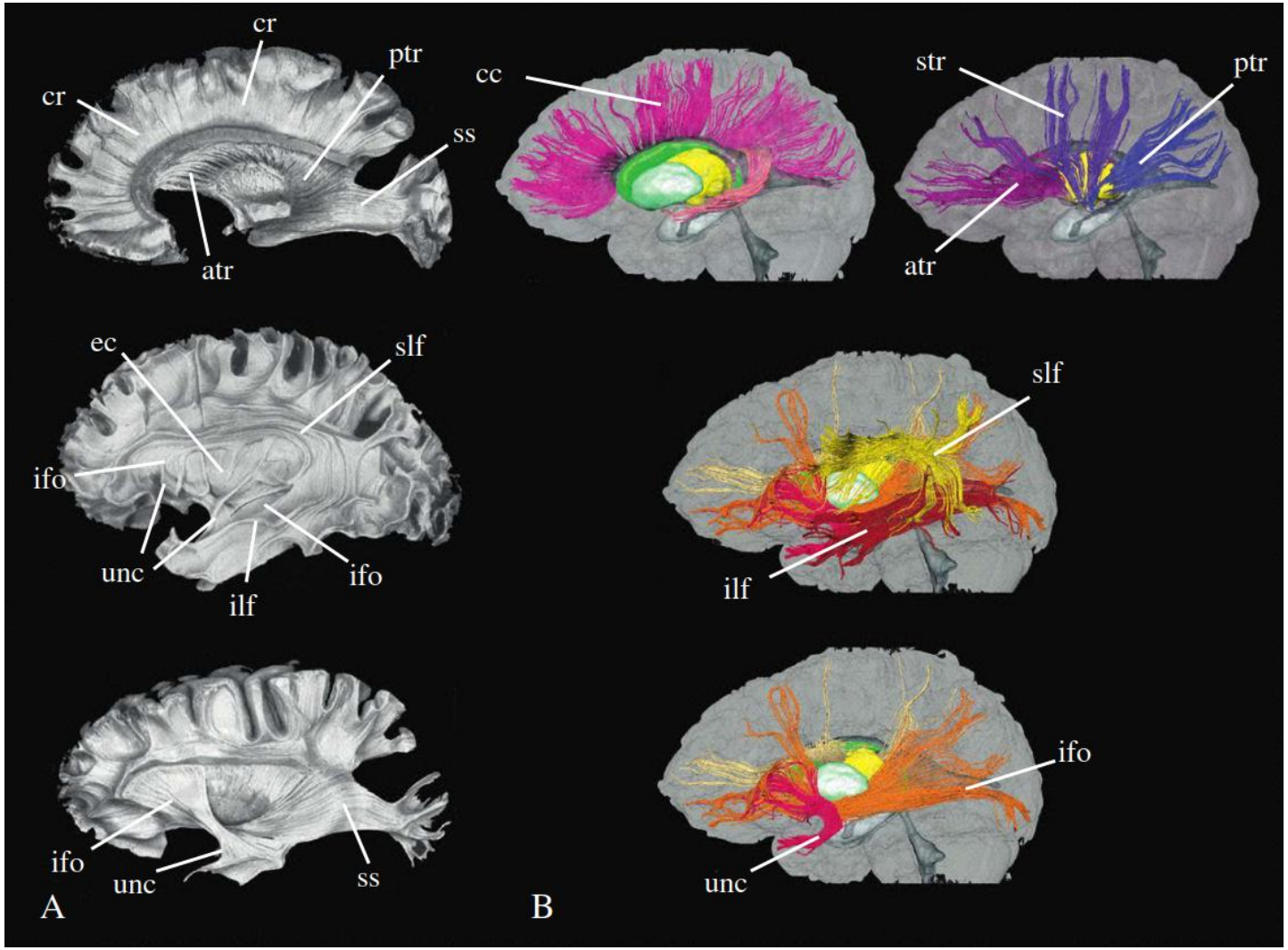
Across the brain



White matter tracts

[Geva et al.,2011]

White Matter Tractography

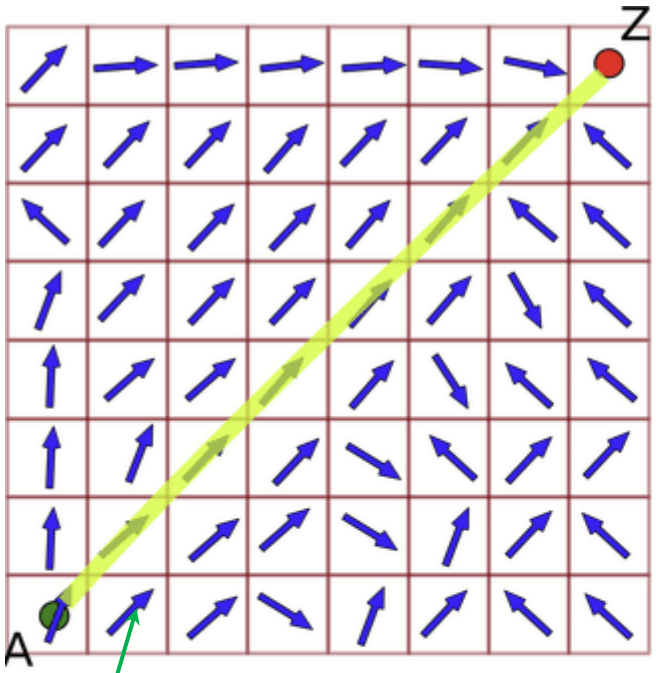


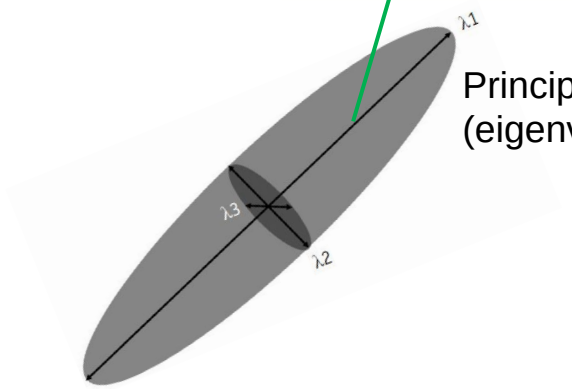
[Oishi et al., 2011]

Comparison between Postmortem Preparation and dMRI-based White Matter Reconstructions

- Deterministic vs probabilistic tractography
  - Deterministic by strictly following the directions of water molecule diffusion
    - Each seed point produces one unique streamline following the dominant diffusion direction at each step
  - Probabilistic by inferring a probability of different directions of water molecule diffusion at any given location
    - Multiple streamlines are generated from each seed point by sampling from a distribution of possible directions, representing uncertainty in fiber orientation

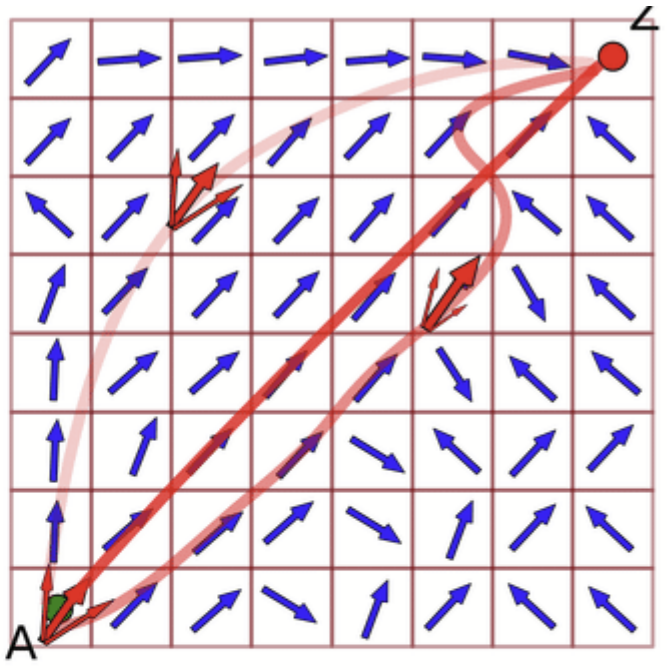
Deterministic





Principal eigenvector
(eigenvector of the largest eigenvalue)

Probabilistic



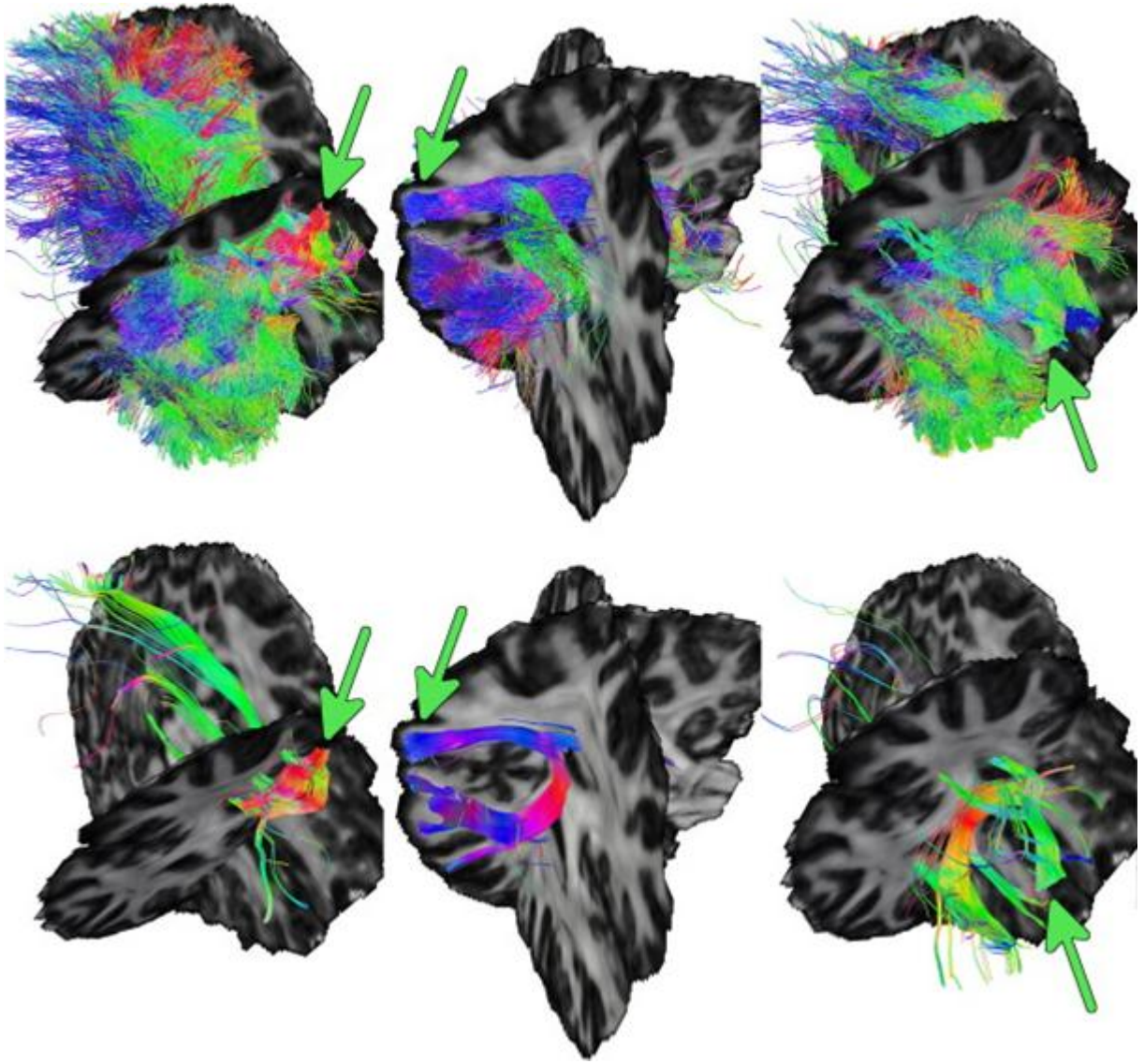
Probabilistic track - high probability
Probabilistic track - low probability
Deterministic track
Primary direction vector **e**
3 directions of the PDF
Starting seed
Ending seed

[Garyfallidis, 2012]

Deterministic and Probabilistic Ways for White Matter Tractography

Probabilistic

Deterministic



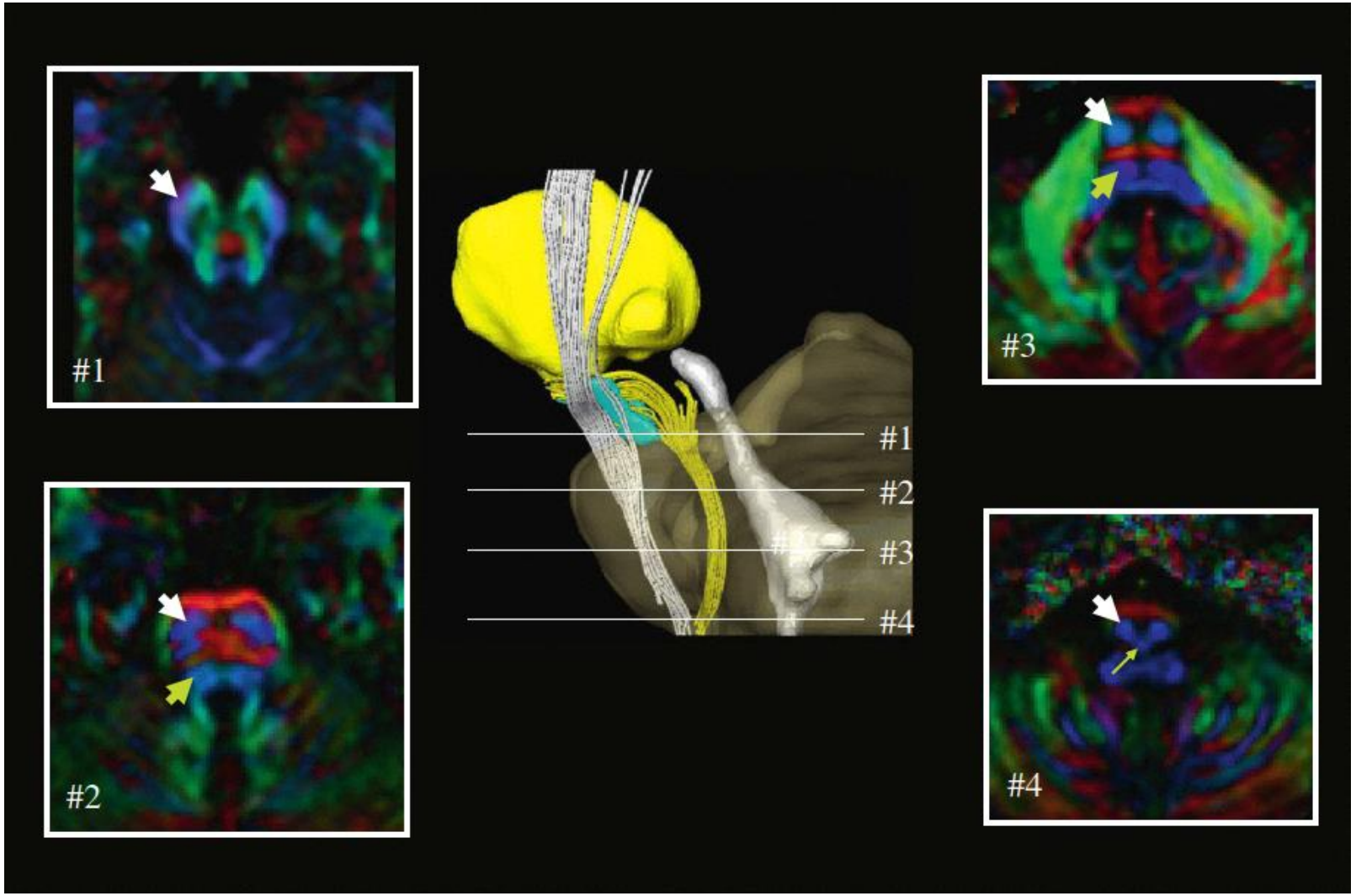
[Schreiber et al., 2014]

Comparison between Probabilistic and Deterministic Tractography

- Bundle as a computational representation of a white matter tract
  - Isolated specific white matter pathway
    - Specificity: Connection between particular areas
    - Isolation: Identifiable pathway with defined trajectories
  - Based on information about:
    - Terminations in specific grey matter structures
    - Histologically-derived definitions
  - Identified by filtering streamlines based on various criteria (length, curvature, anatomical areas they pass through)

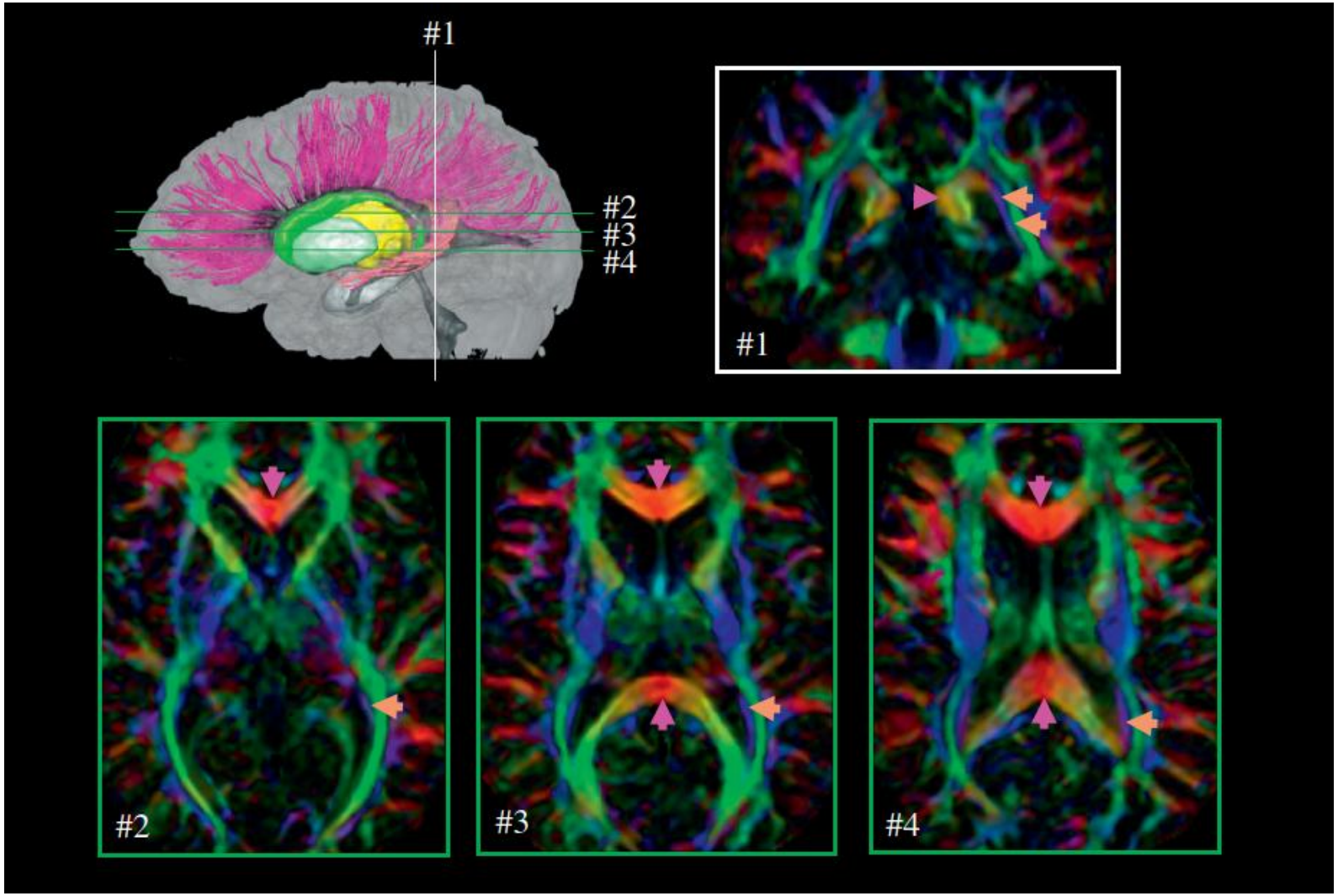
[https://www.mrtrix.org/]]

Determination of White Matter Bundles



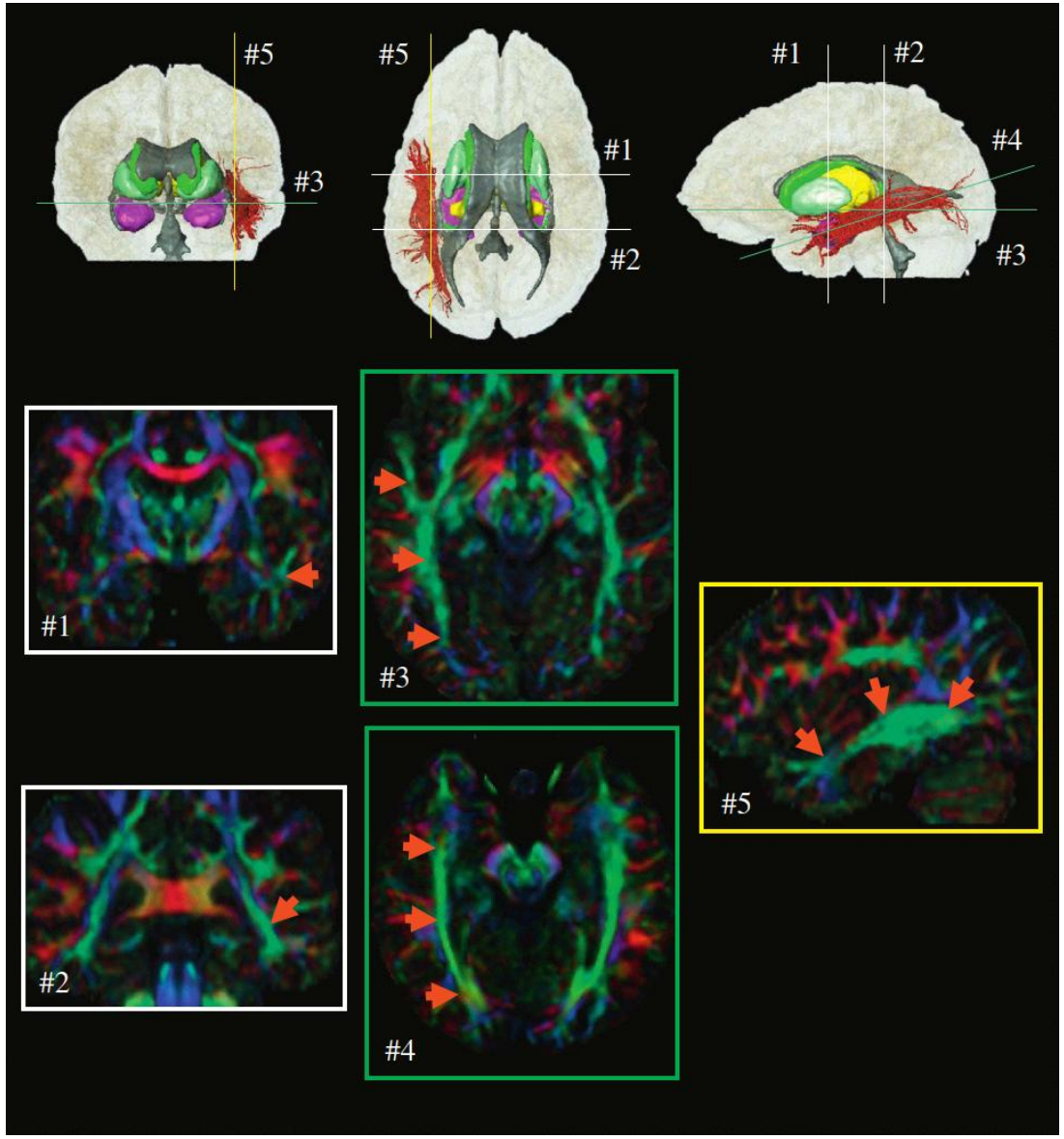
[Oishi et al., 2011]

Trajectory of the Corticospinal Tract



[Oishi et al., 2011]

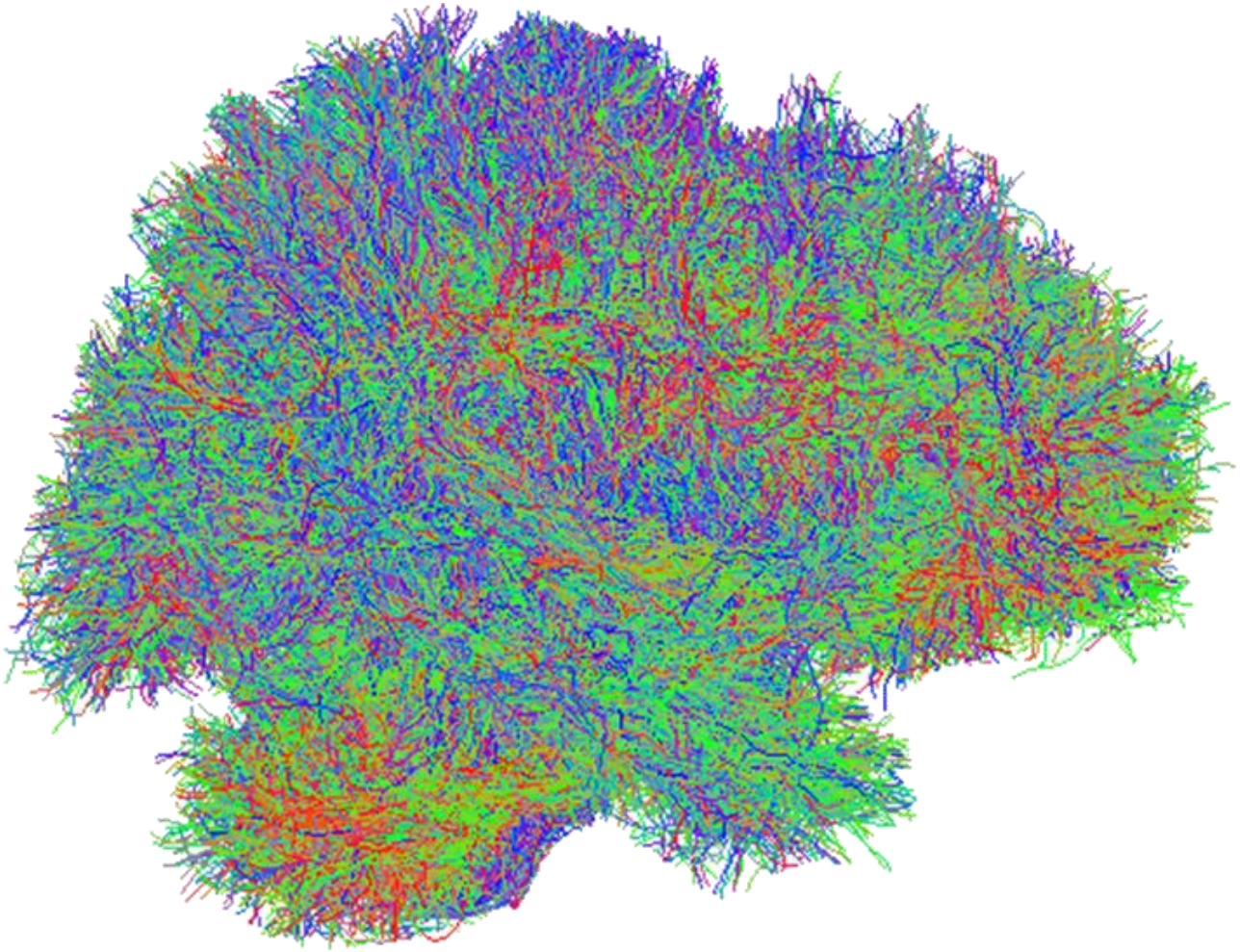
Trajectory of the Corpus Callosum



[Oishi et al., 2011]

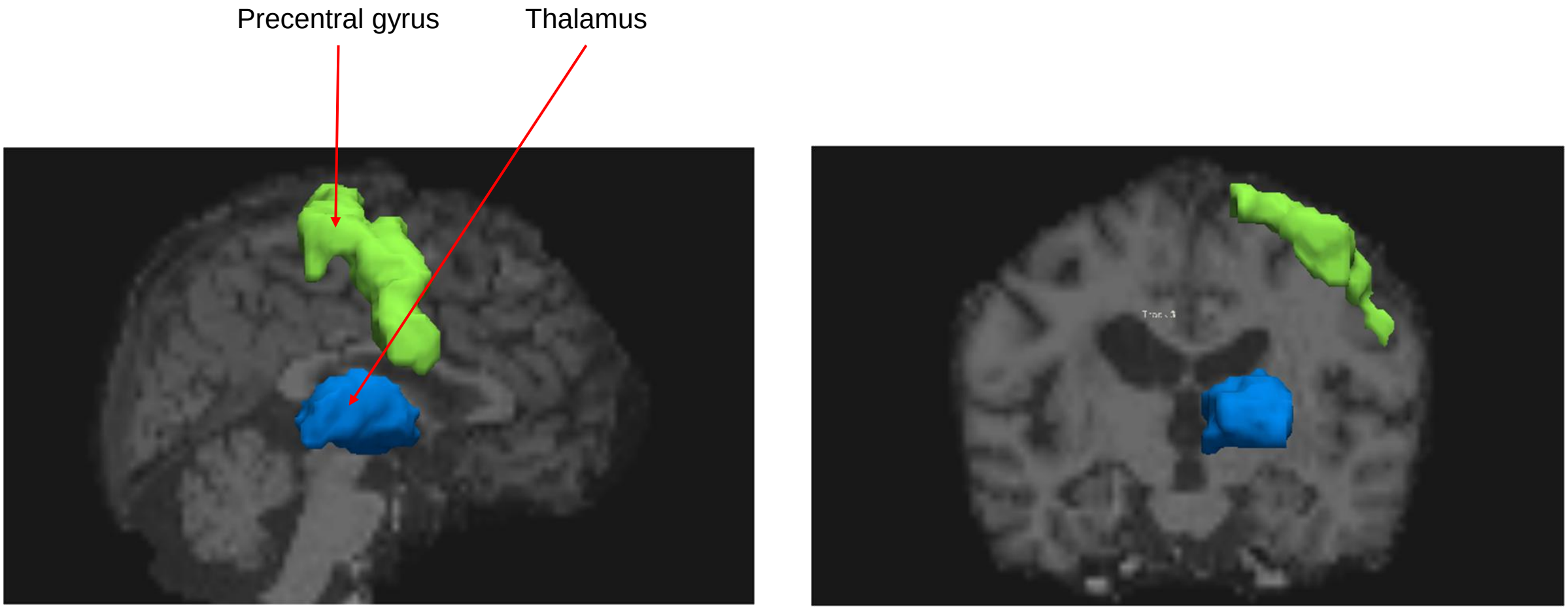
Trajectory of the Inferior Longitudinal Fasciculus

[dMRI: White Matter Tractography]

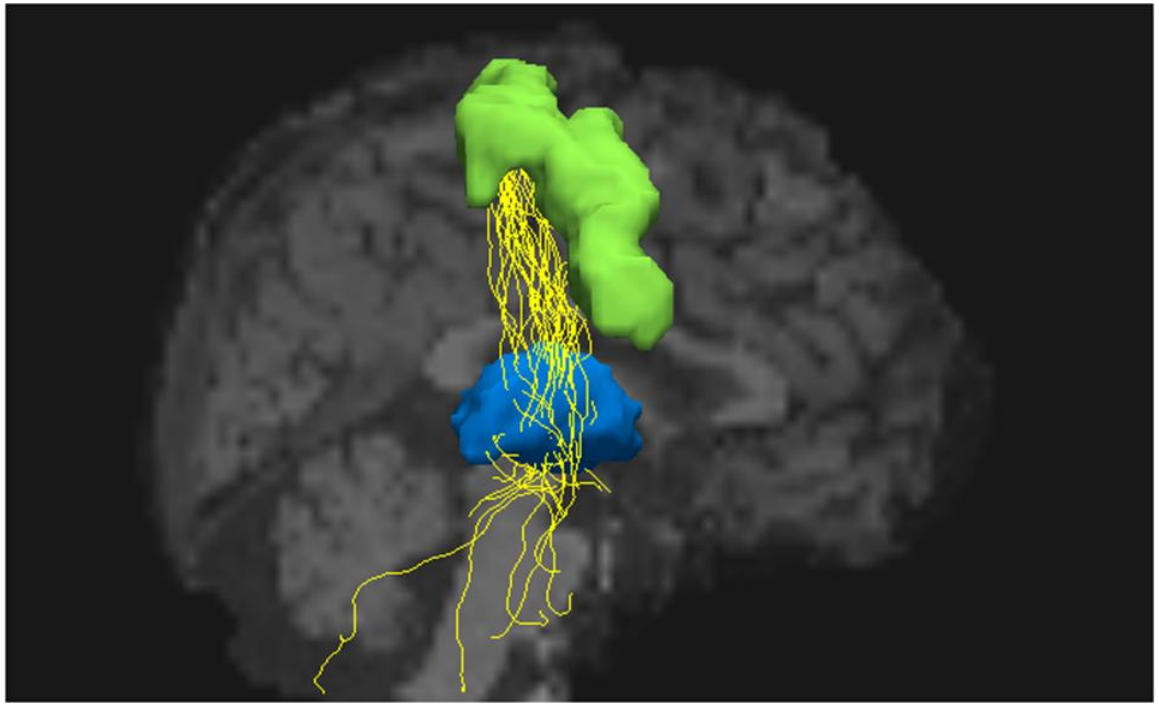


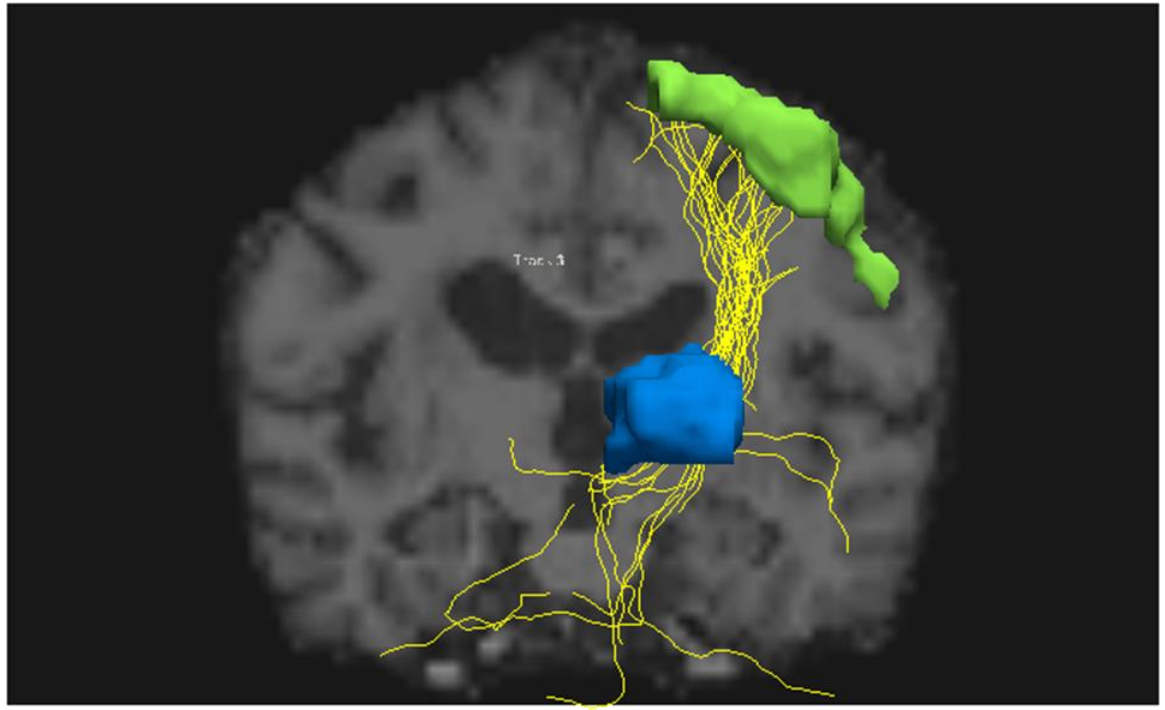
1,500,000 streamlines

Whole Brain White Matter Tractography

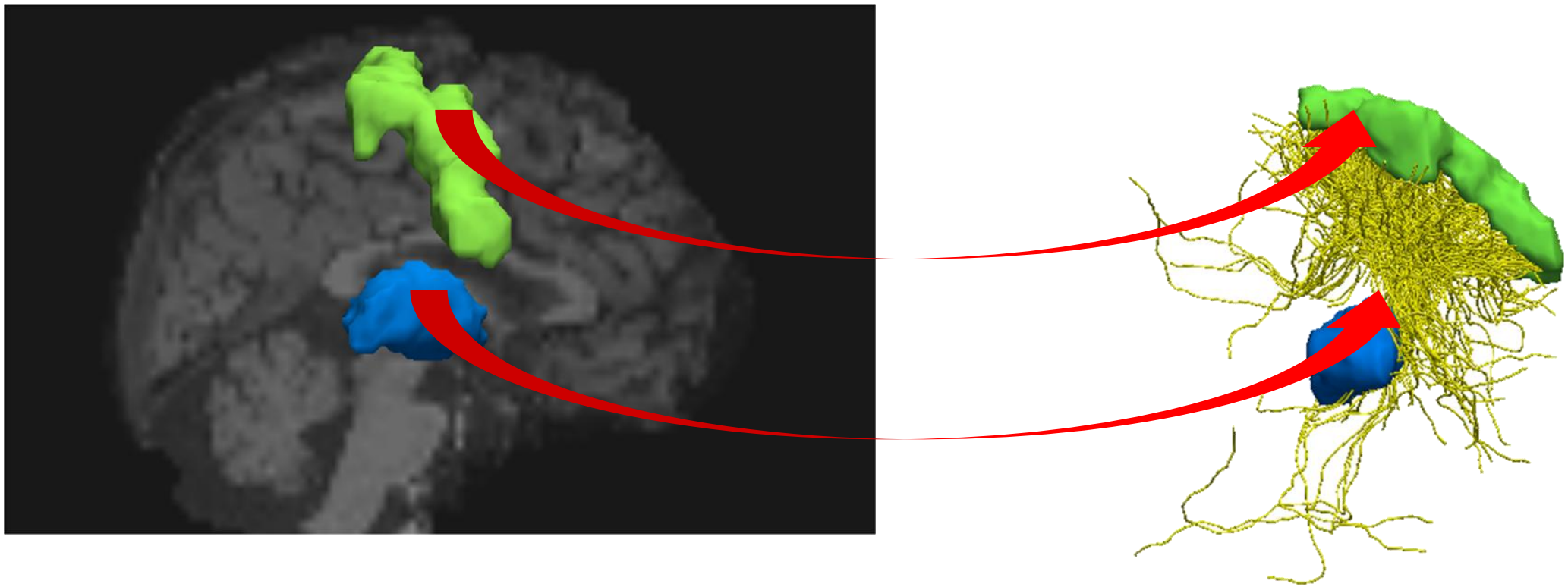


Terminations of Streamlines



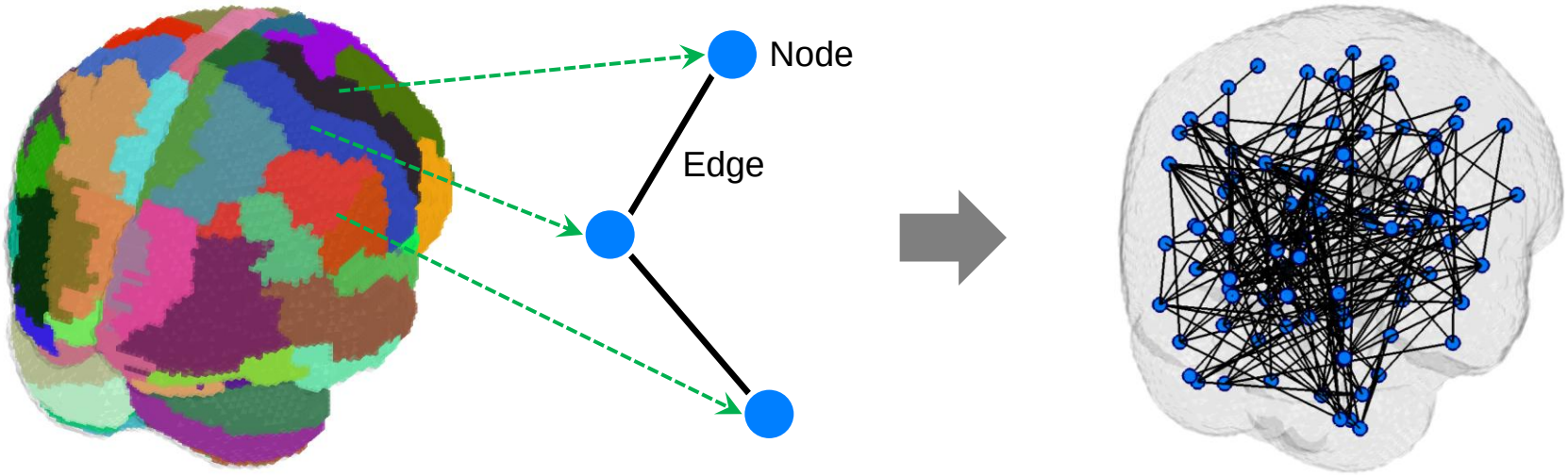


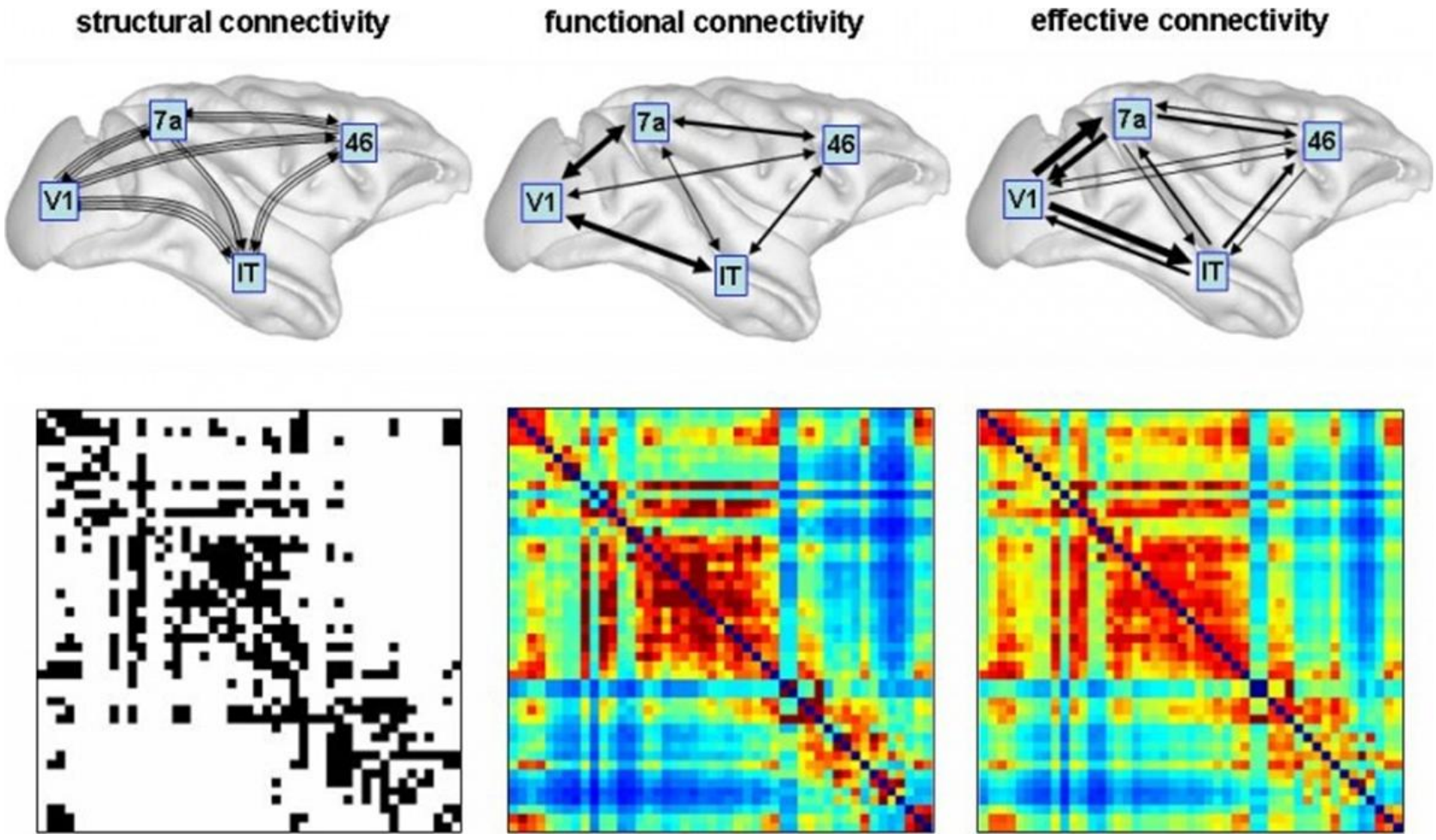
Generated Streamlines



Determination of White Matter Tracts

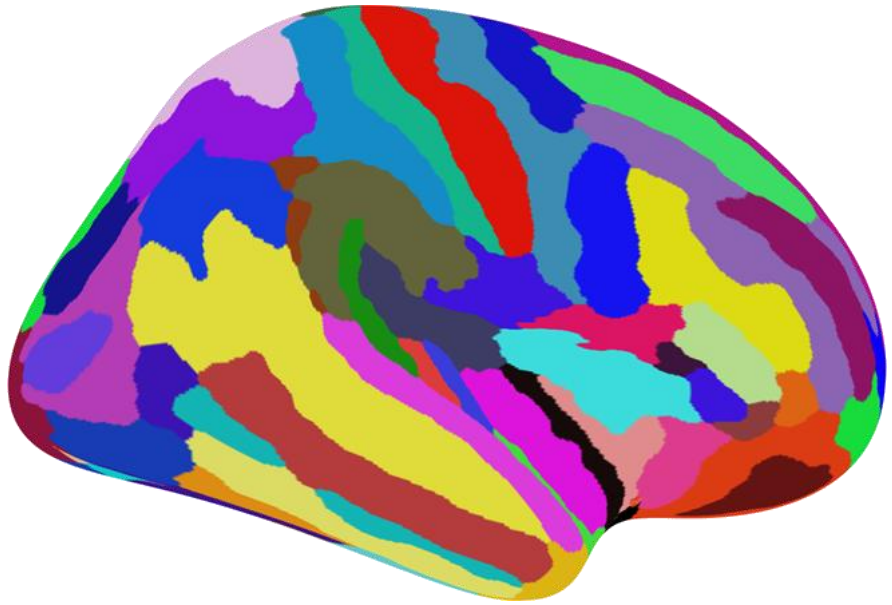
- Network
  - Set of nodes and edges
    - Nodes: pre-defined areas
    - Edges: connectivity (white matter streamlines) between areas



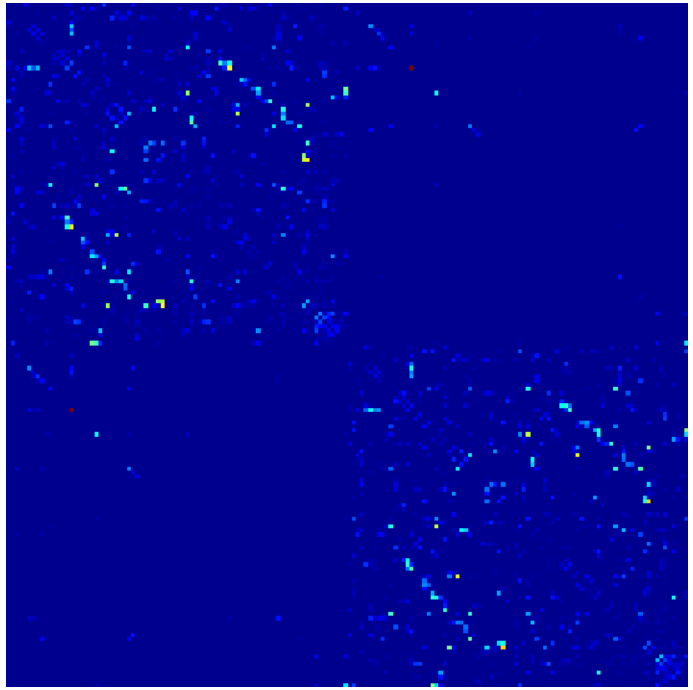


[Honey et al., 2007]

Modes of Brain Connectivity

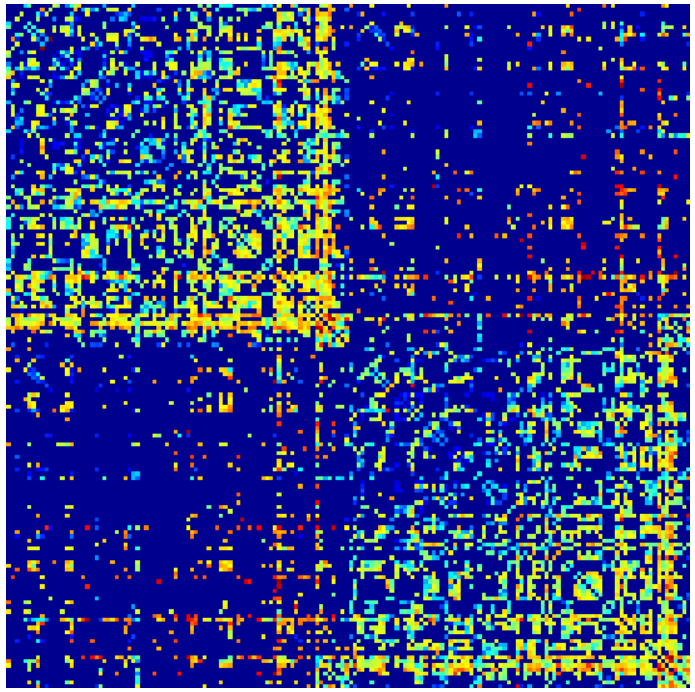


White matter streamlines

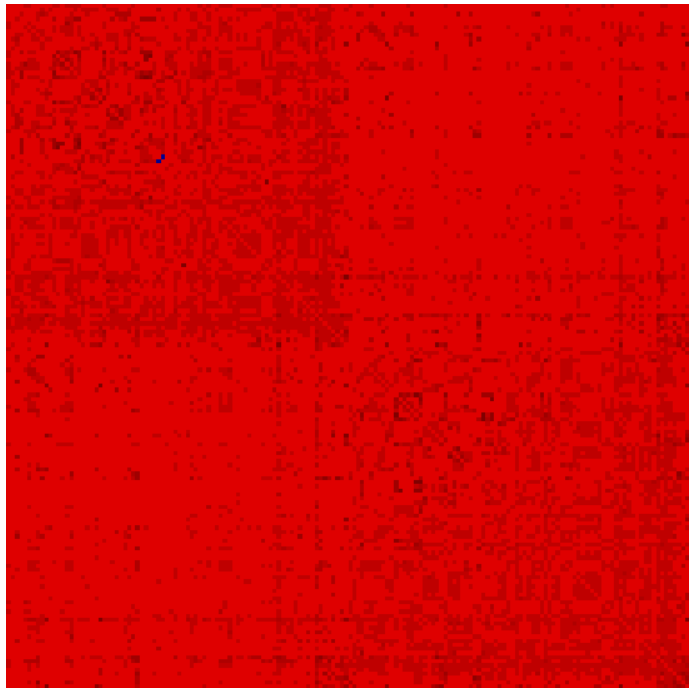


Streamline count

Structural Network or Connectome



FA



MD

Structural Network based on Diffusion Tensor Metrics

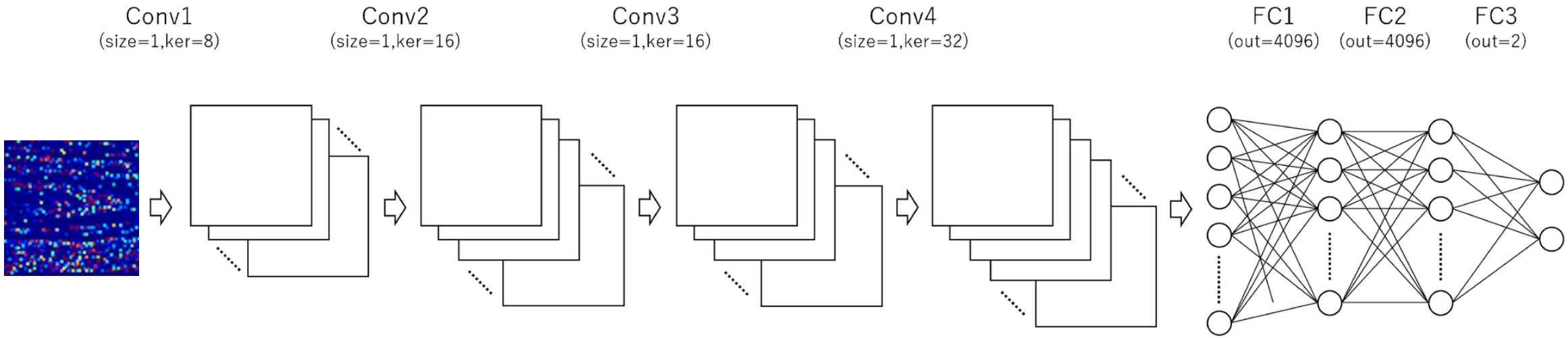
- Input to machine learning models
  - Table of area-to-area connectivity (white matter streamlines) values

Features →

Samples ↓

	Areas 1 – 2 connectivity	Areas 1 – 3 connectivity	Areas 1 – 4 connectivity	…
Subject 1	-	-	-	-
Subject 2	-	-	-	-
Subject 3	-	-	-	-
⋮	-	-	-	-

  - Structural network map

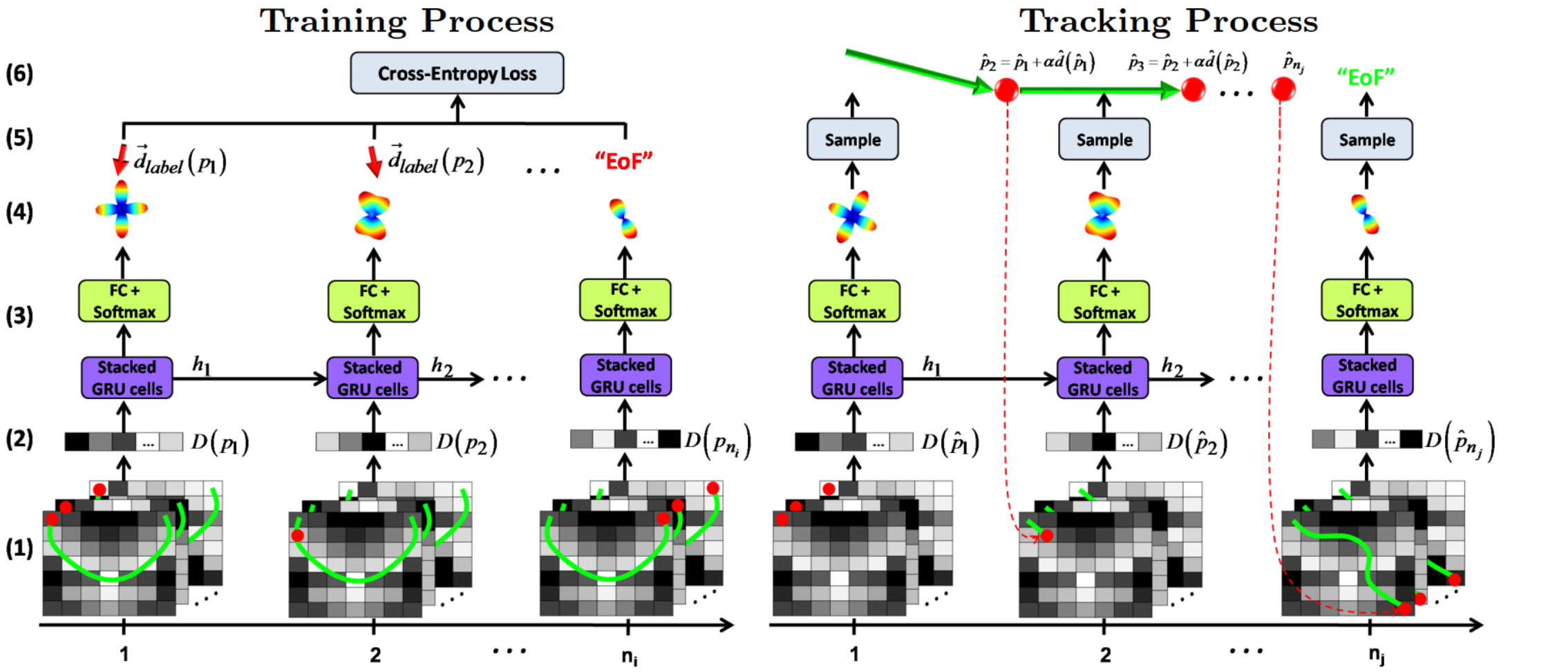


[Yasaka et al., 2021]

Application of Deep Learning to Structural Network Maps

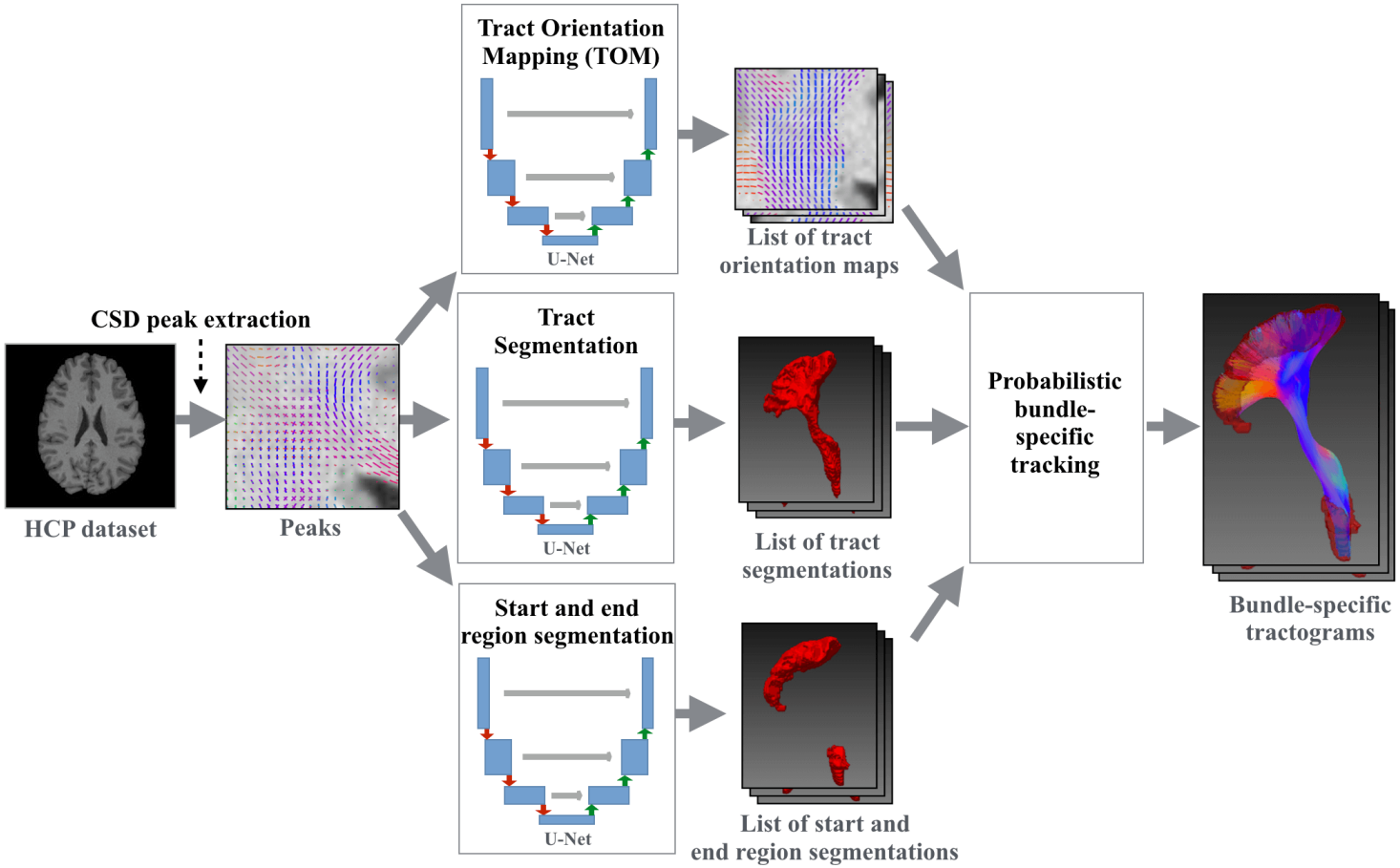
Automated White Matter Tractography

- Employs neural networks trained on large diffusion-weighted MRI datasets to identify white matter tracts
- Incorporates tissue segmentation to improve biological plausibility



[Benou & Riklin-Raviv, 2018; https://github.com/itaybenou/DeepTract]

DeepTract: White Matter Tracking



[Wasserthal et al., 2018; https://github.com/MIC-DKFZ/TractSeg]

TractSeg: White Matter Tract Segmentation