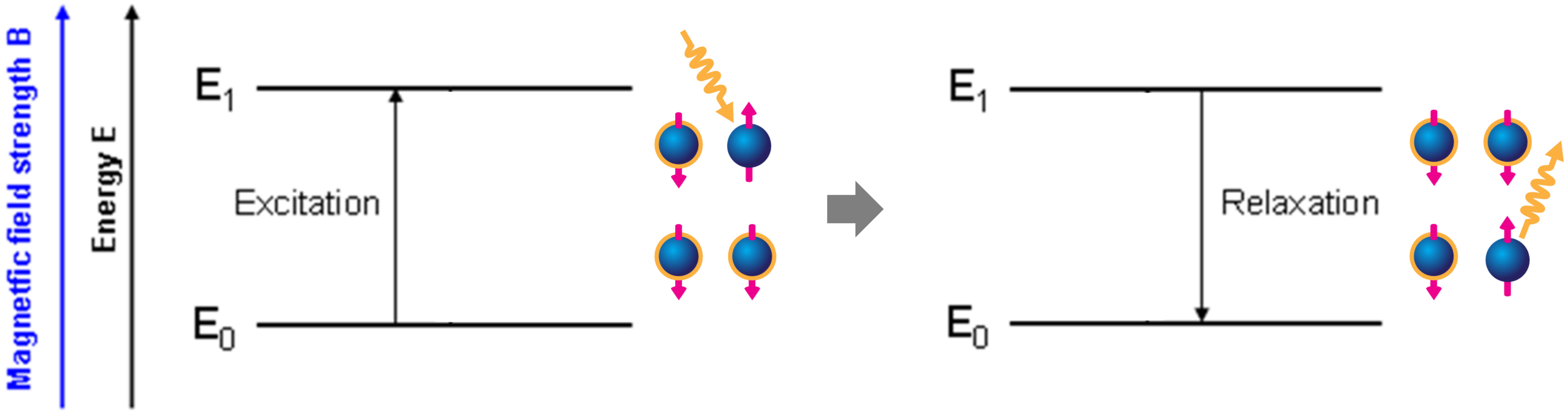
Medical/Bio Research Topics Ⅱ: Week 04 (26.09.2025)

Diffusion-weighted MRI: Basic Principles and Data Processing Methods

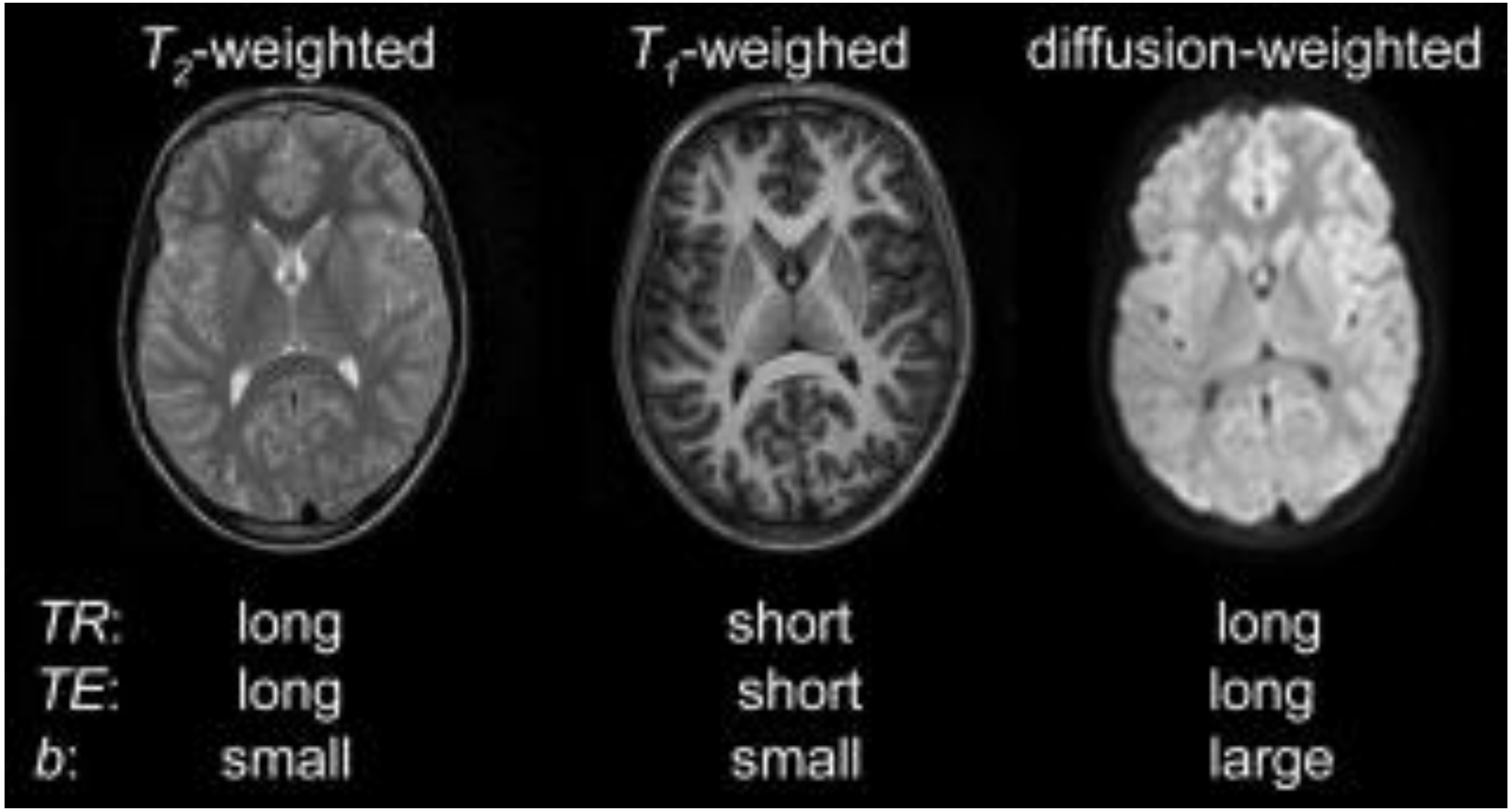
확산가중 자기공명영상: 기본 원리 및 데이터 처리 방법

MRI Principles

- Medical application of nuclear magnetic resonance (NMR)
  - Generates different contrasts between tissues based on the relaxation properties of hydrogen nuclei therein



- MRI contrast types
  - T1-weighted contrast
    - Primarily uses a spin-echo or a gradient-echo sequence
    - With short Echo Time (TE) and short Repetition Time (TR) to maximize T1 contrast and minimize T2 effects
  - T2-weighted contrast
    - Primarily uses a spin-echo sequence
    - With long TE to allow for T2 decay and long TR to minimize T1 effects
  - Diffusion-weighted contrast: T2 weighting + diffusion weighting
    - Typically uses a gradient-echo echo-planar imaging (EPI) sequence
    - Applies diffusion-sensitizing gradients
    - With even longer TE to accommodate the diffusion gradients and typically longer TR to allow for the additional gradients and to reduce T1 effects



[Mori and Zhang, 2006]

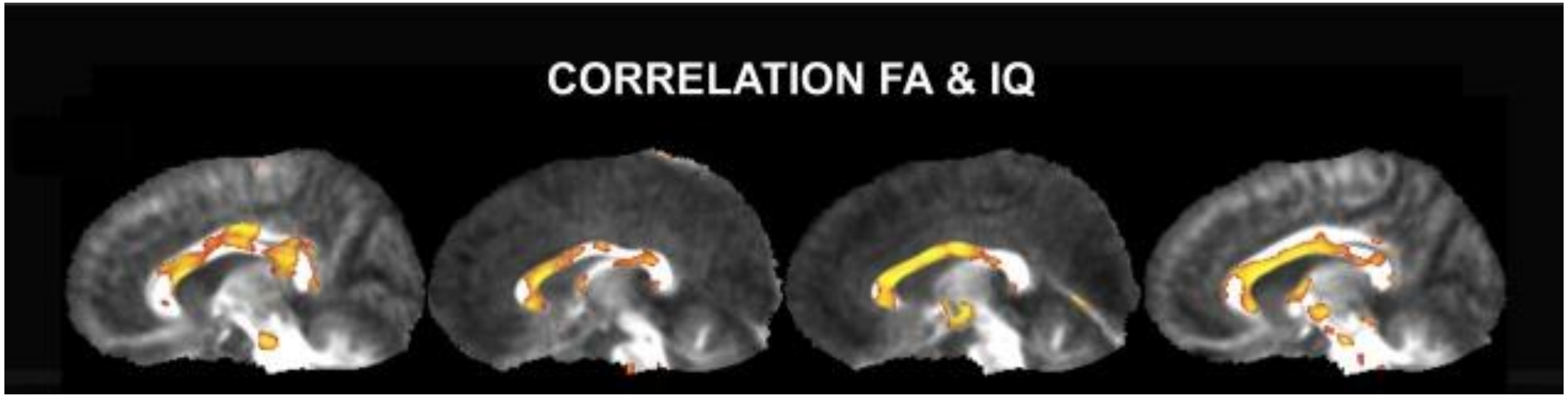
Various Types of MRI Contrasts

Diffusion-weighted MRI (dMRI)

- MRI technique primarily for examining tissue microstructure through water molecule diffusion patterns
- Applications of dMRI
  - Microstructural analysis
  - White matter tractography

Diffusion MRI Reveals: Brain Highways Predict Intelligence

- Intelligence depends on how well brain regions "talk" to each other
  - Higher IQ correlates with increased white matter integrity (fractional anisotropy): Primarily in the corpus callosum - the brain's major highway
- dMRI provides objective measures of cognitive ability through microscopic tissue architecture

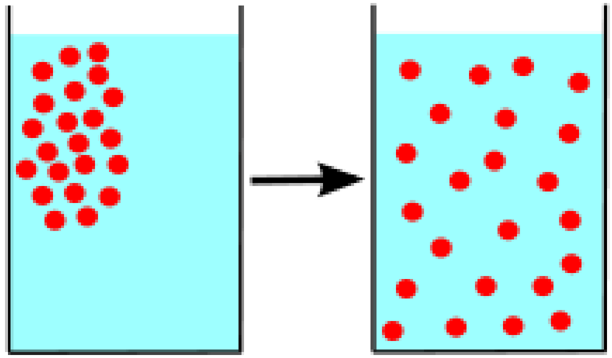


[Navas-Sánchez et al., 2013]

White Matter Integrity-IQ Correlations

Diffusion

- Physical process in which particles tend to spread steadily from regions of high concentration to regions of lower concentration

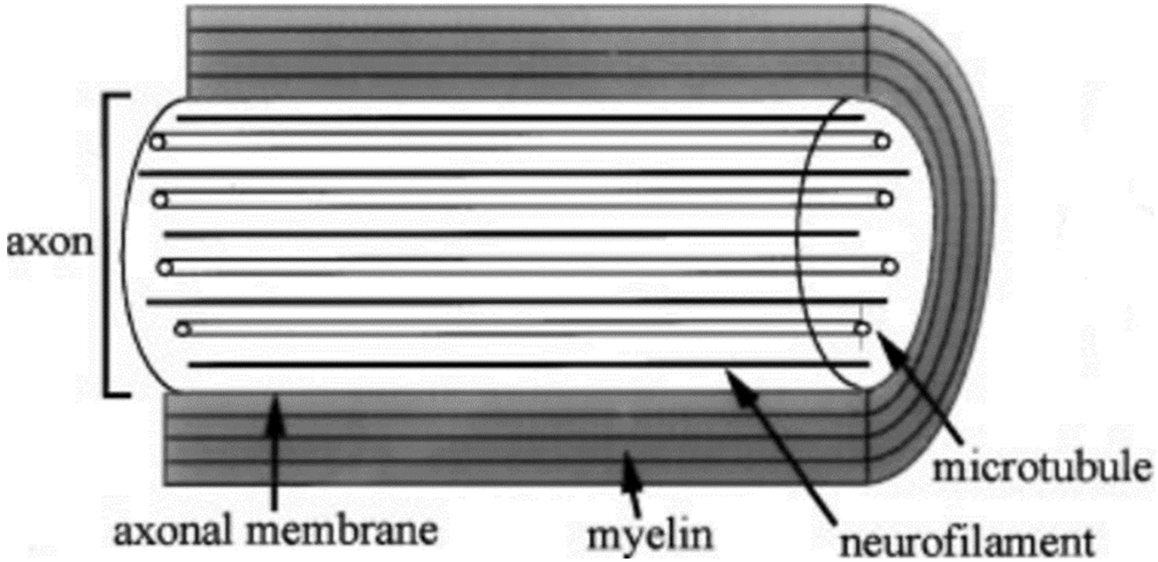


- Considered a macroscopic manifestation of Brownian motion

- Brownian motion on the microscopic scale
  - Random motion of particles in a given medium with no preferred direction, leading to the spread of the particles evenly throughout the medium over a period of time
  - Mean squared displacement in terms of time elapsed and diffusivity (Einstein relation): $\left\langle r^2 \right\rangle = 2nDt$
    - $<r^2>$: mean squared distance that a particle moves in a particular direction in a time period t
    - n: number of dimensions (1 for 1D, 2 for 2D, 3 for 3D)
    - D: diffusion coefficient

- Movement of water molecules in a heat-driven random fashion in brain tissues
  – Unless the movement is constrained by barriers

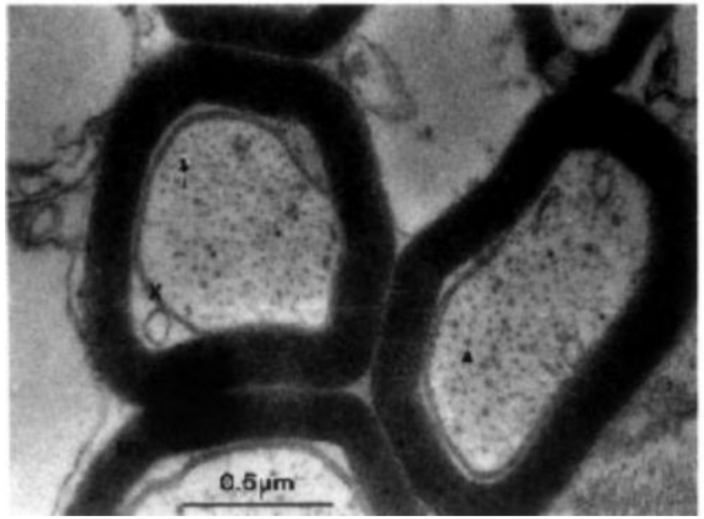
Fibrous structures in white matter



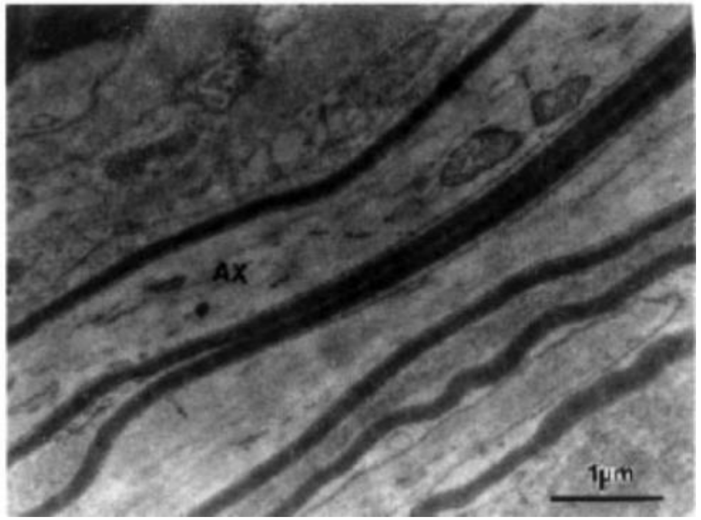
[O'Donnell and Westin, 2011]

- Diffusion anisotropy in white matter
  - Directional effect of diffusion dominantly in white matter primarily due to the presence of arrays of myelinated axons
    - Water diffuses more readily along the length of axon fibers than across them

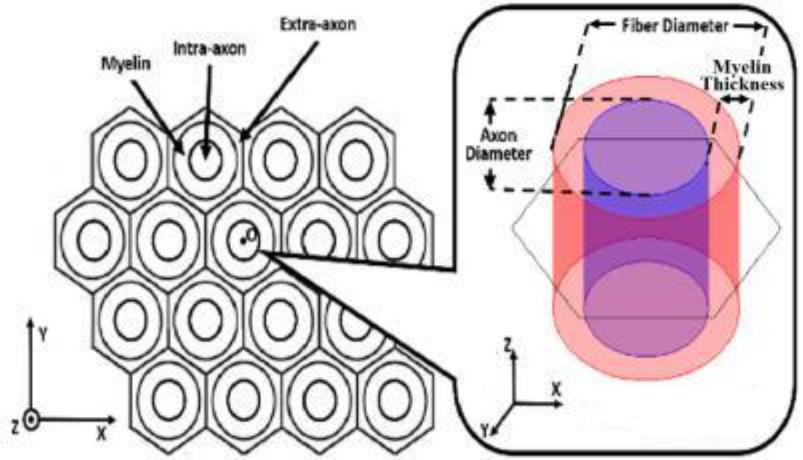
Transverse section

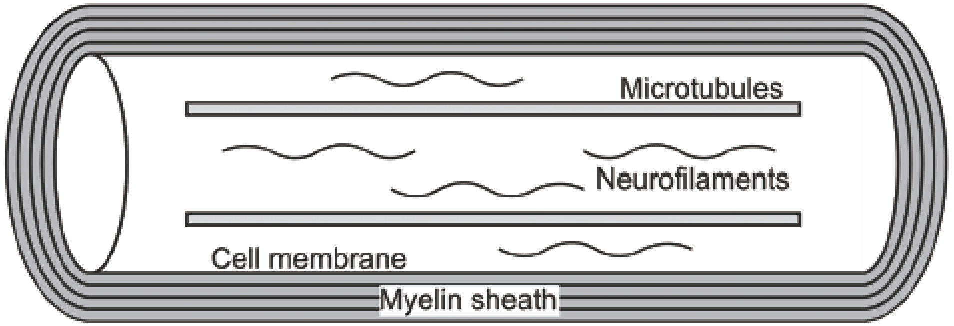


Longitudinal section



[Beaulieu, 2002]





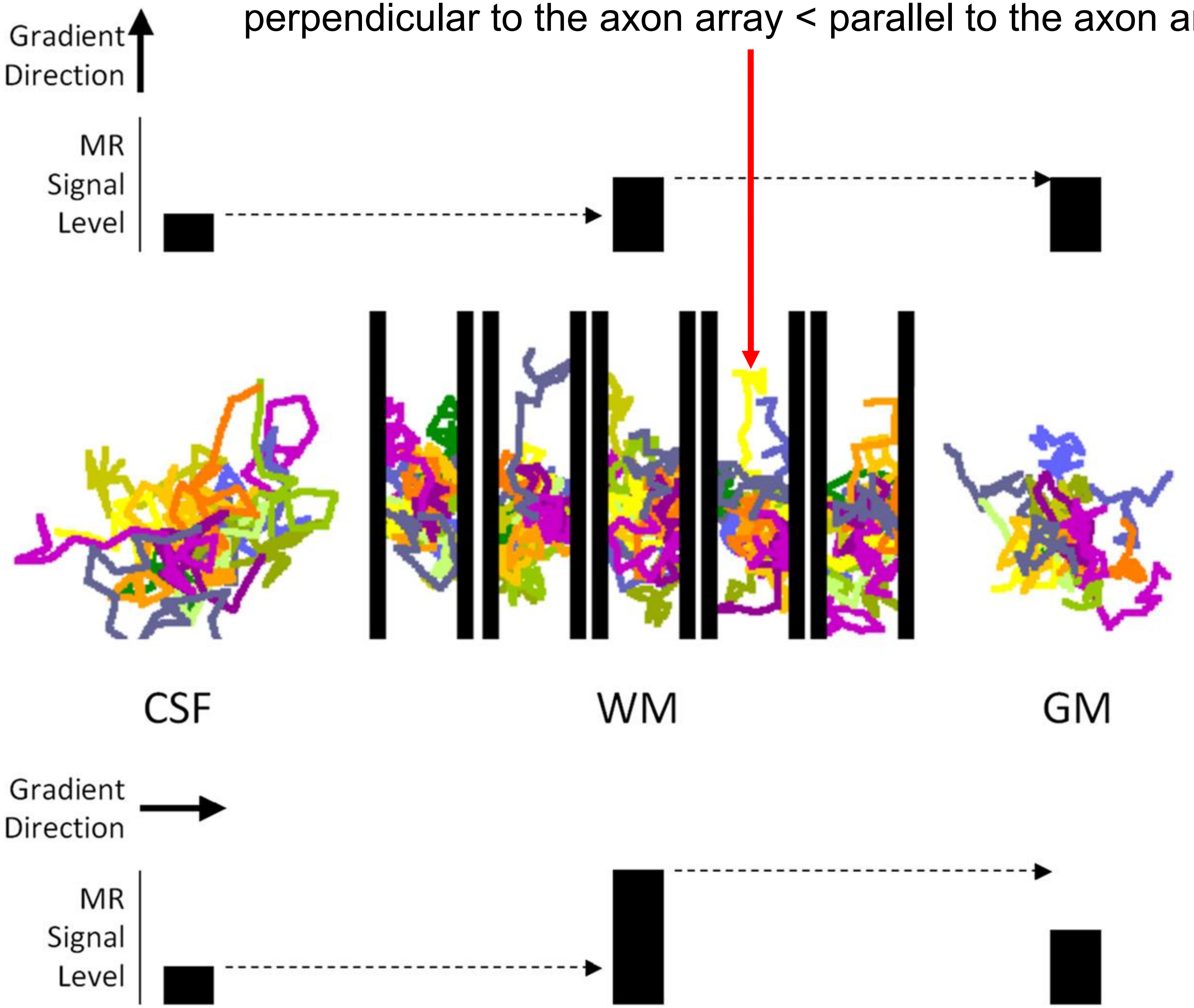
- Cytoskeleton
  - Microtubules (25 nm diameter)
  - Neurofilaments (10 nm diameter)
  - Microfilaments (7 nm diameter)
- Axonal membranes
- Myelin sheath

[Noguerol et al., 2017]

Potential Sources of Diffusion Anisotropy in a Myelinated Axon

- Present-day human brain dMRI
  - "White matter imaging" technique
    - Current focus primarily on white matter, though also applicable to grey matter and other tissues
    - Anisotropic diffusion is most readily measured for microscopic diffusion barriers in white matter
  - Measures water molecular diffusion on a "microscopic scale"
    - Sensitive to root mean square displacement in a particular direction on the order of μm for a diffusion coefficient of ~1,000 $\mu m^2/s$ (or 0.001 mm^2/s) and diffusion time of ~0.02-0.1 s
    - Pertains to the measurement of the average Brownian diffusion behavior of the water molecules over a great many cells and axons within a voxel

Directional dependence of diffusion:
perpendicular to the axon array < parallel to the axon array



[Alger, 2012]

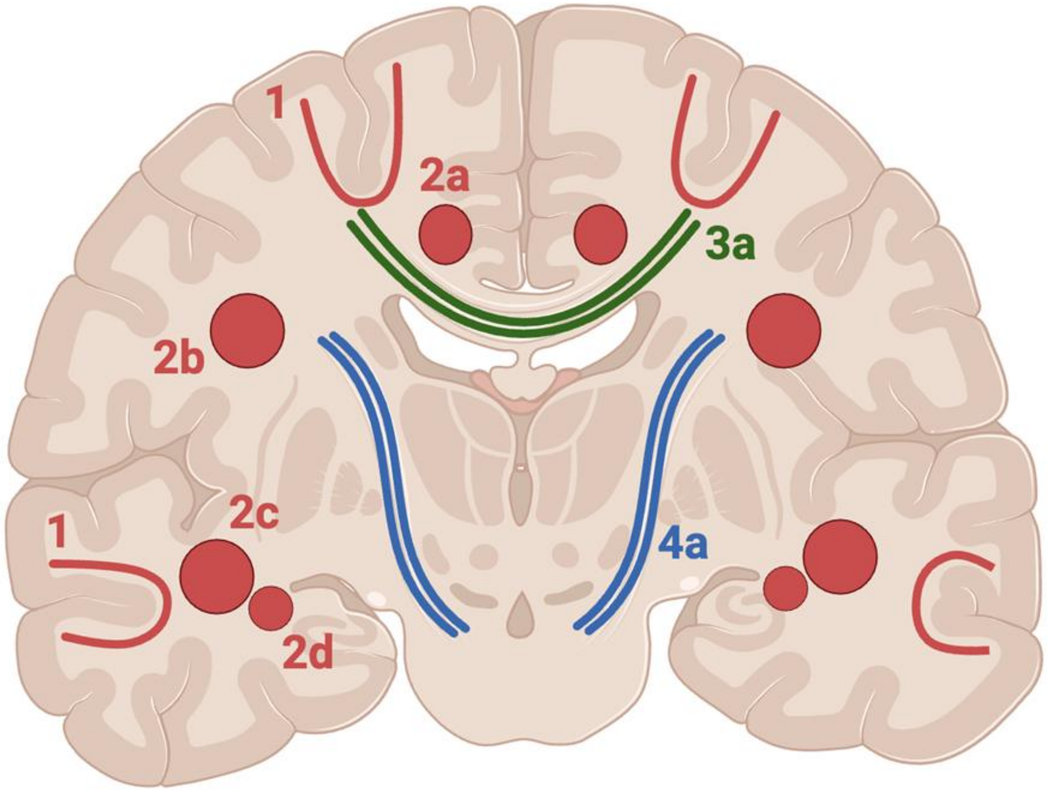
Anisotropic Water Diffusion Effects on MRI Signal Intensity

Central Nervous System Hierarchy

- From individual components to whole structure
  - Axon → axon fiber / nerve fiber → tract → white matter
- Axon
  - Long projection of a single neuron
  - Conducts electrical impulses away from the cell body
  - Single cellular structure

- Axon fiber / nerve fiber
  - Essentially the same as an axon, but often used when discussing axons in their functional context
  - Can be either myelinated or unmyelinated
  - "Nerve fiber" is a slightly broader term that can also include dendrites in some contexts
- Tract
  - Collection of multiple axon fibers with similar functions, origins, and destinations
  - Organized pathways within the central nervous system
  - For example, corticospinal tract, optic tract, spinothalamic tract

- White matter
  - Complete collection of all tracts
  - Contains all organized projection pathways in the central nervous system
  - Surrounds the grey matter in the spinal cord and lies beneath the grey matter in the cerebrum



1) Short association fibers

2) Long association fibers

a) Cingulum

b) Superior longitudinal fasciculus

c) Inferior longitudinal fasciculus

d) Uncinate fasciculus

3) Commissural fibers

a) Corpus callosum

4) Projection fibers

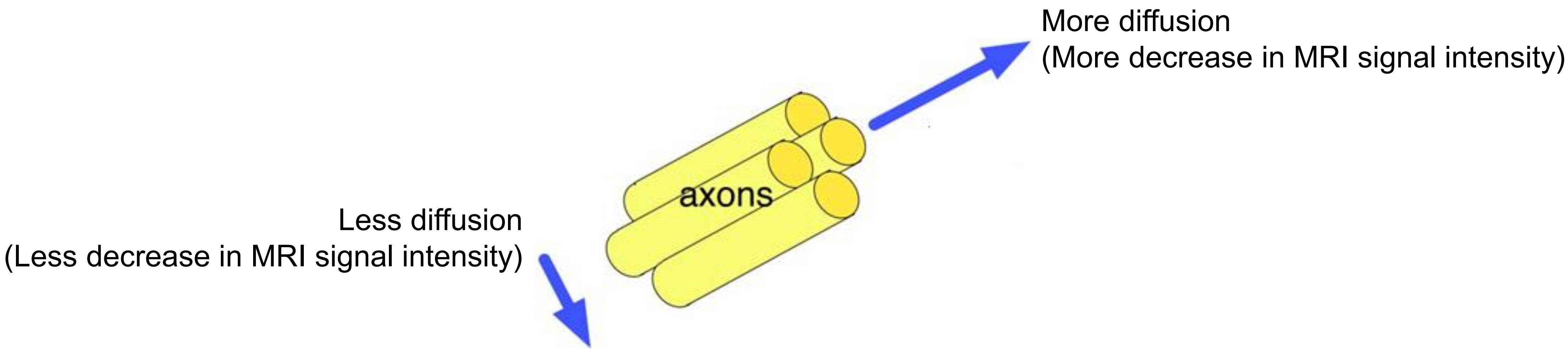
a) Internal capsule

[https://www.biorender.com/template/white-matter-tracts-coronal-section]

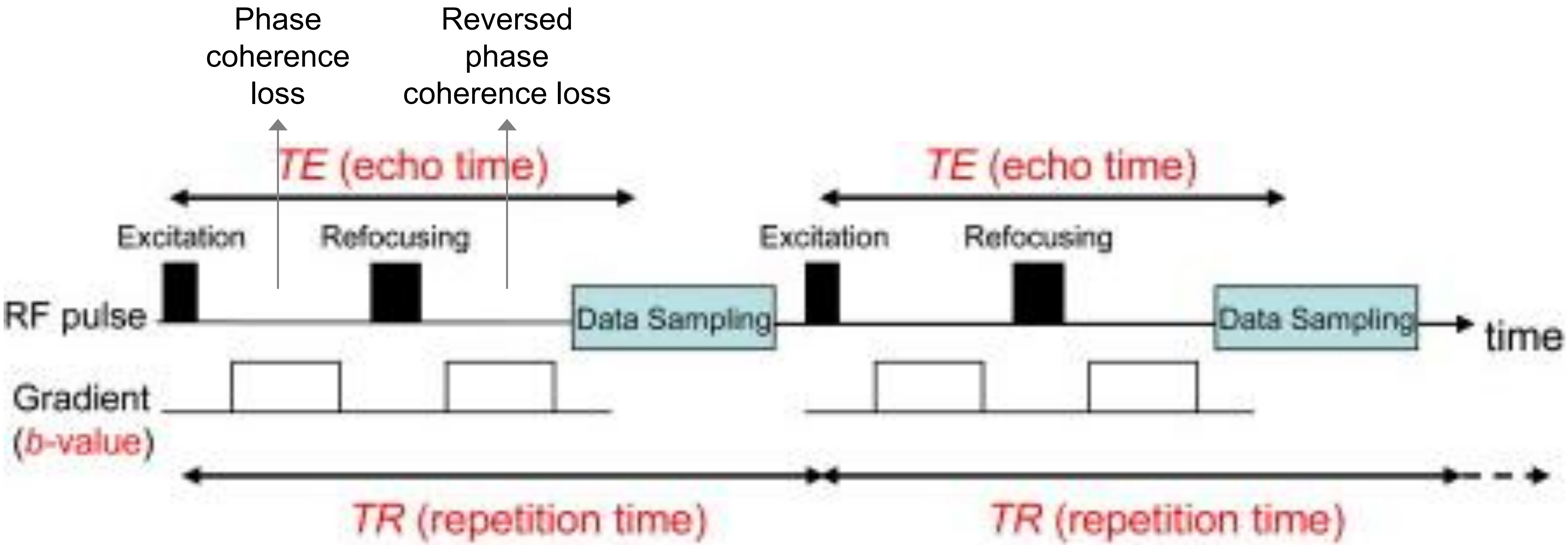
White Matter Tracts

Diffusion-weighted Contrast

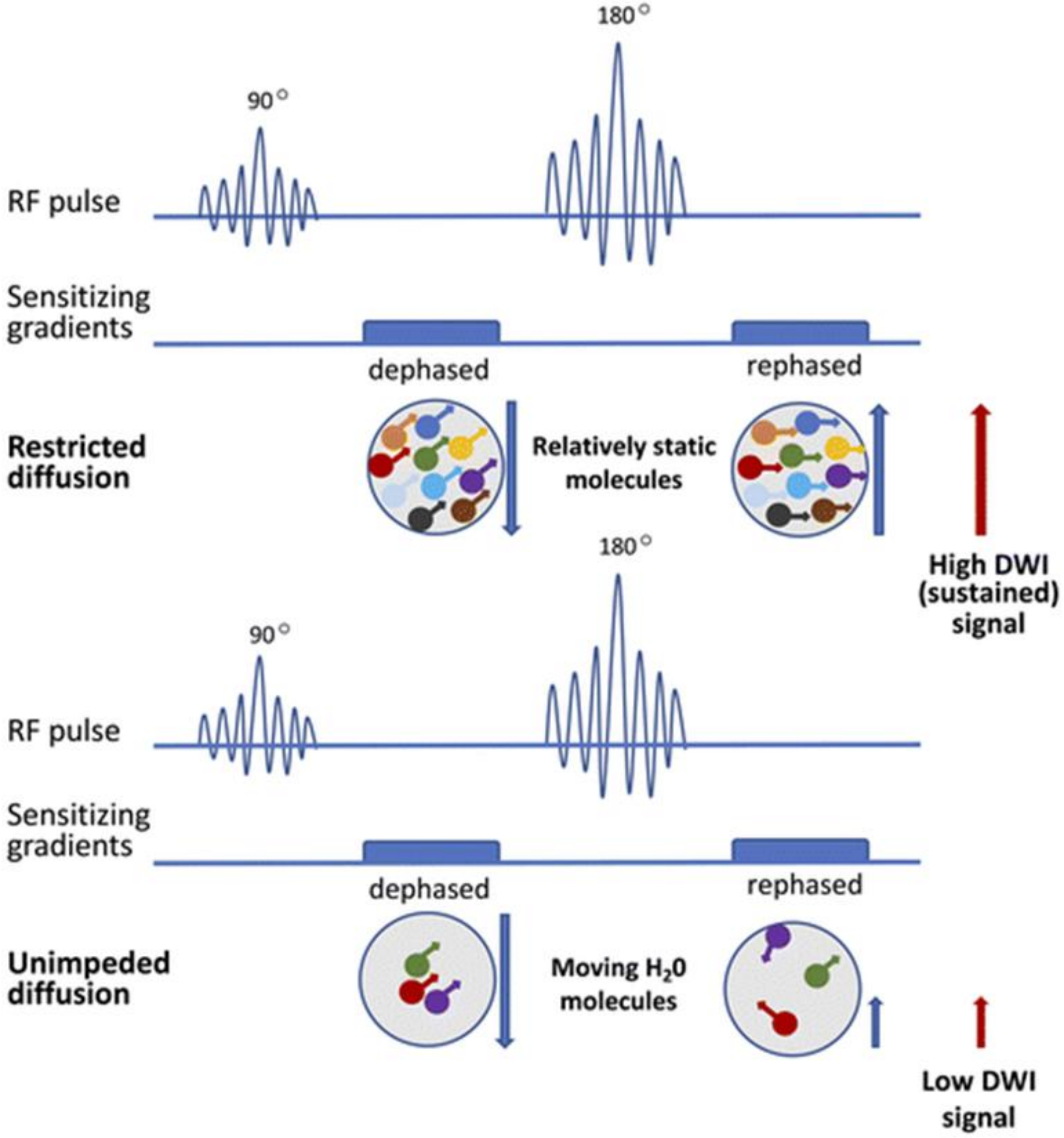
- MRI signal changes caused by diffusion



- Implemented by applying diffusion-sensitizing gradients that encode the amount and direction of hydrogen nuclei movement during the time between the application of them



[Mori and Zhang, 2006]



[Lall et al., 2018]

MRI Pulse Sequence for the Diffusion-weighted Contrast

- Directional dependence of diffusion
  - Varying diffusion weighting with scalar diffusion coefficient
    - Under the assumption of Gaussian diffusion and exponential signal decay

MRI signal measured with diffusion weighting

Diffusion coefficient

$$\frac{S}{S_0} = e^{-\boxed{\gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right)} D} = e^{-bD}$$

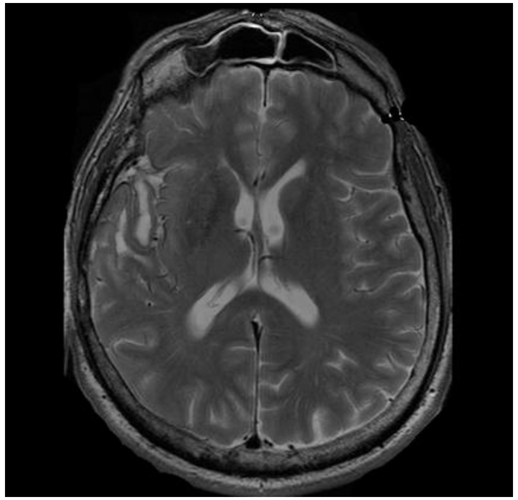
b-value

MRI signal measured without diffusion weighting

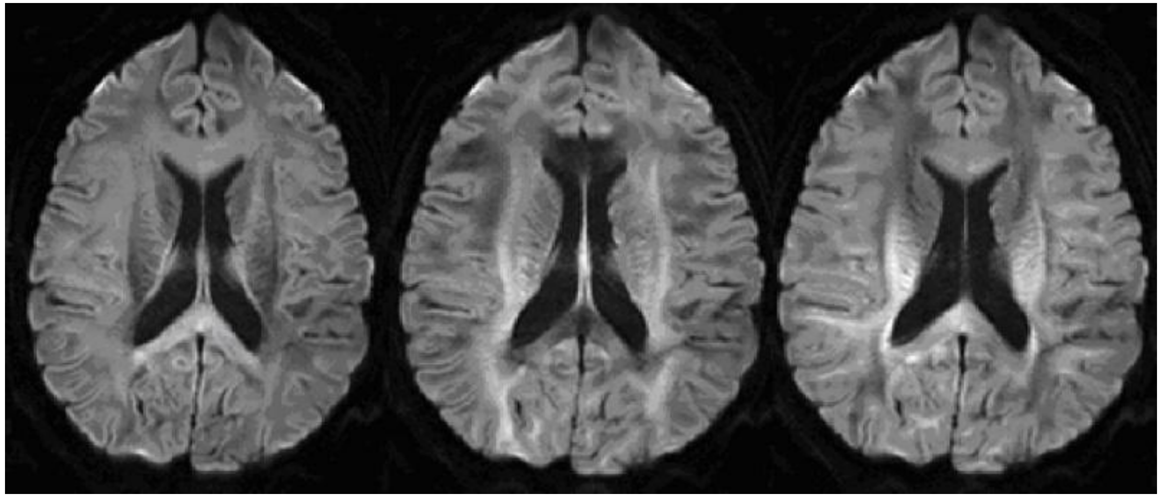
Diffusion coefficient $$D = \frac{1}{b} \log \frac{S_0}{S}$$

More signal decrease
→ higher diffusion coefficient

Less signal decrease
→ lower diffusion coefficient



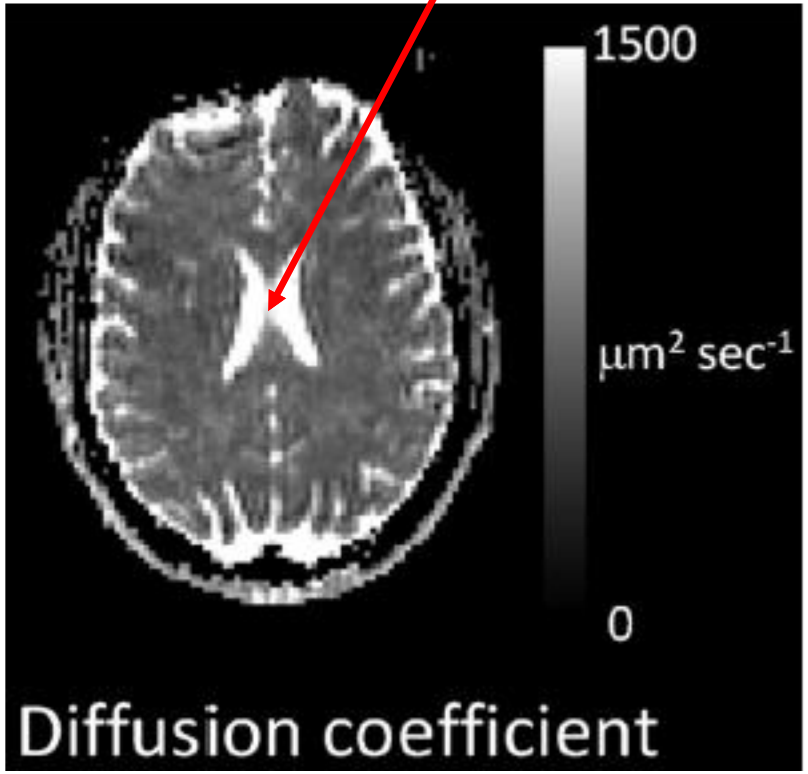
Without the diffusion-sensitizing gradient



With the diffusion-sensitizing gradient in *x*-, *y*-, and *z*-directions

Images Acquired with and without the Diffusion-sensitizing Gradient

Free diffusion of water in cerebrospinal fluid



[Alger, 2012]

Map of Diffusion Coefficients

- *b*-value
  - Summarizes the influence of the diffusion-sensitizing gradient on the diffusion weighted image
    - The higher the *b*-value, the stronger the diffusion weighting, but the smaller the diffusion-weighted signal
  - Widespread use of intermediate values of ~1,000 s/mm^2 in the human brain
    - When *b*-value = 1,000 s/mm^2, the signal attenuation for free water at body temperature (37°C) is $\exp(-1{,}000\ \mathrm{s/mm^2} \times 0.001\ \mathrm{mm^2/s}) \approx 0.37$ (63% signal attenuation for free water, but less attenuation for water molecules in tissues), representing a balance between sufficient diffusion weighting and adequate signal-to-noise ratio

– Varying diffusion-sensitizing directions with diffusion tensor

- Generalizes from isotropic/single-direction diffusion to anisotropic tensor diffusion

$$\frac{S}{S_0} = e^{-b\boxed{\vec{g}^{T}\mathbf{D}\vec{g}}}$$

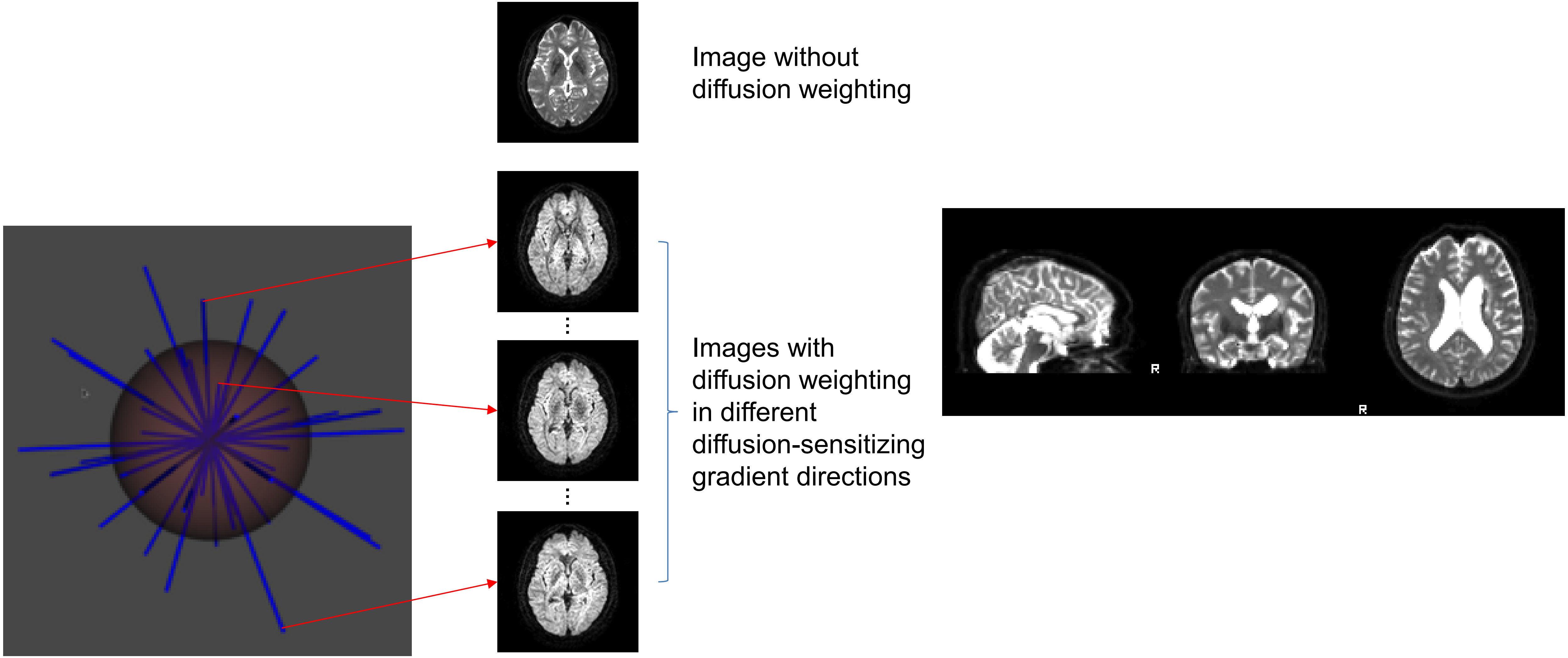
Diffusion tensor

Effective diffusion coefficient
in direction **g**

Direction of the diffusion-sensitizing gradient

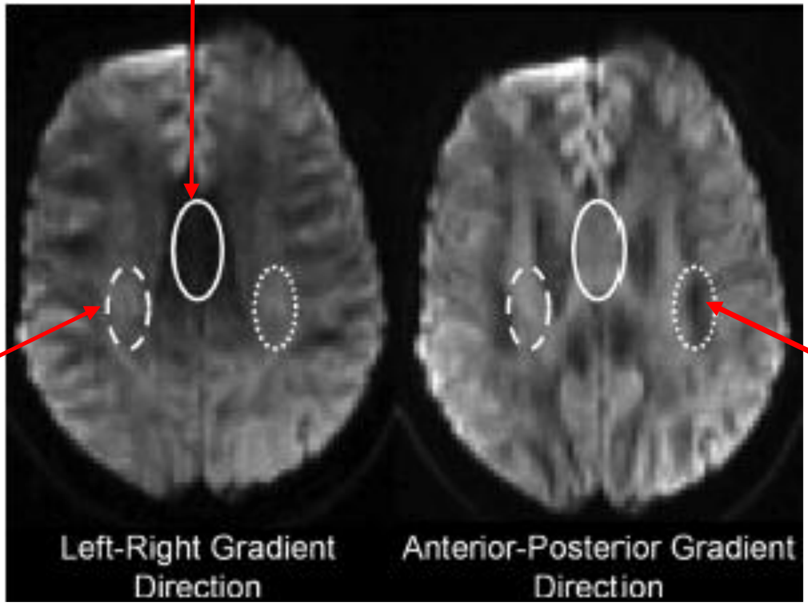
- **D**: diffusion tensor (symmetric positive definite matrix)
  – 3 × 3 symmetric matrix, each component of which describes water molecular diffusion associated with a pair of axes *xx*, *yy*, *zz*, *xy* (or *yx*), *xz* (or *zx*), and *yz* (or *zy*)

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



Diffusion Weighting in Different Diffusion-sensitizing Gradient Directions

Left–right-oriented
corpus callosum splenium



Superior-inferior-oriented
pyramidal tracts

Anterior–posterior-oriented
temporofrontal pathway

[Alger, 2012]

Impacts of Different Diffusion-sensitizing Gradient Directions

Diffusion Model

- Describes diffusion properties within a voxel
- Diffusion tensor model
  - Uses second-order statistics to characterize water molecule displacement that follows a Gaussian distribution, the probability density of finding a water molecule at position **r** after time *t*:

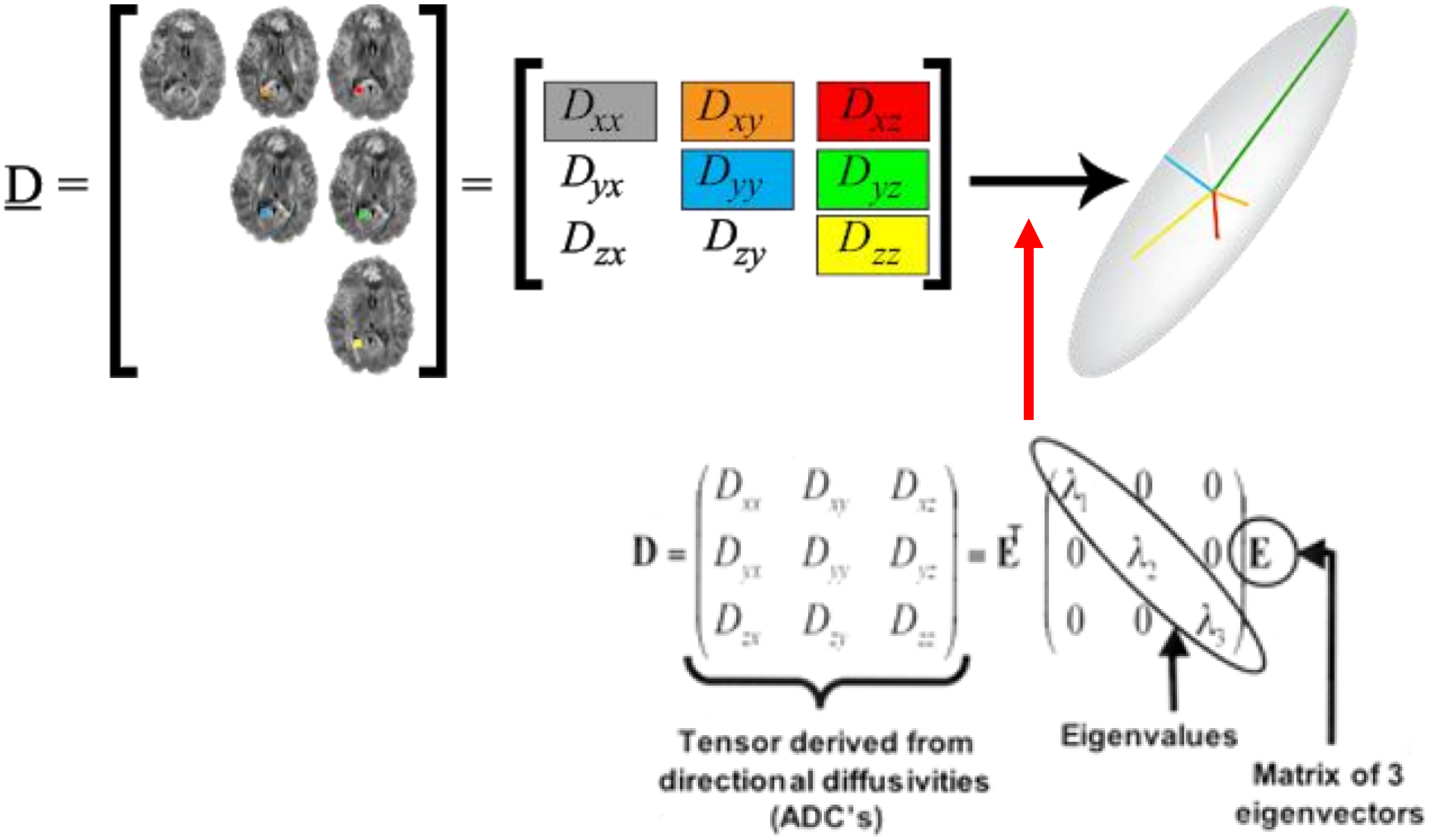
$$P(\mathbf{r},t) = \frac{1}{\sqrt{(4\pi t)^3 |\mathbf{D}|}} \exp\left(-\frac{1}{4t}\mathbf{r}^T\mathbf{D}^{-1}\mathbf{r}\right)$$

    - Characterized by diffusion tensor **D**, which determines the variance-covariance of water molecule displacement

- Preprocessing before diffusion modelling
  - Correction for unwanted variation
    - Head motion
    - Eddy current-induced distortion
      - Eddy currents (Foucault currents)
        - » Loops of electric current induced in nearby conductors by a changing magnetic field
        - » Generated in MRI scanners, particularly during dMRI, because of the rapid switching on and off of the gradient fields used to create the diffusion sensitization
        - » Cause additional magnetic fields that distort the main magnetic field (B0) uniformity
      - Mitigated by aligning images that have been distorted differently due to the eddy currents induced by different diffusion-sensitizing gradient directions
    - Susceptibility artifact (B0 inhomogeneity-induced distortion)

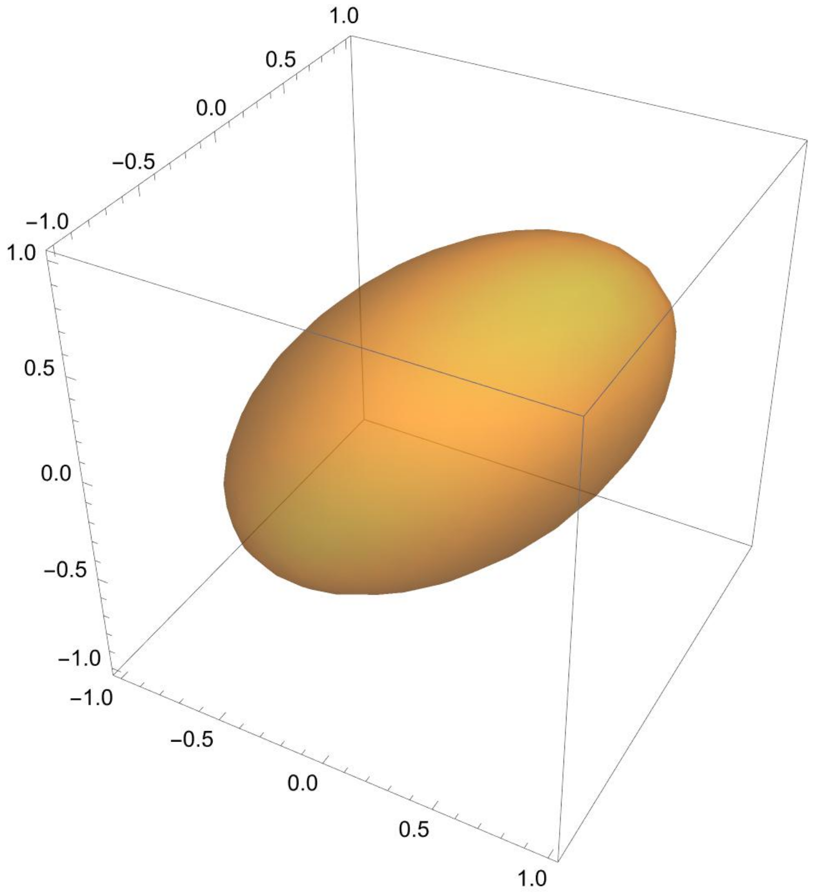
Diffusion Tensor

- Encapsulates the variance-covariance matrix of the Gaussian distribution of water molecule displacements in 3D space, describing how diffusion varies along different spatial axes
  - Diagonalizing it by its eigensystem (eigenvectors and eigenvalues) simplifies the model by aligning it with directions in which the diffusion measurements do not linearly interfere with each other, allowing for clearer analysis and visualization of anisotropic diffusion

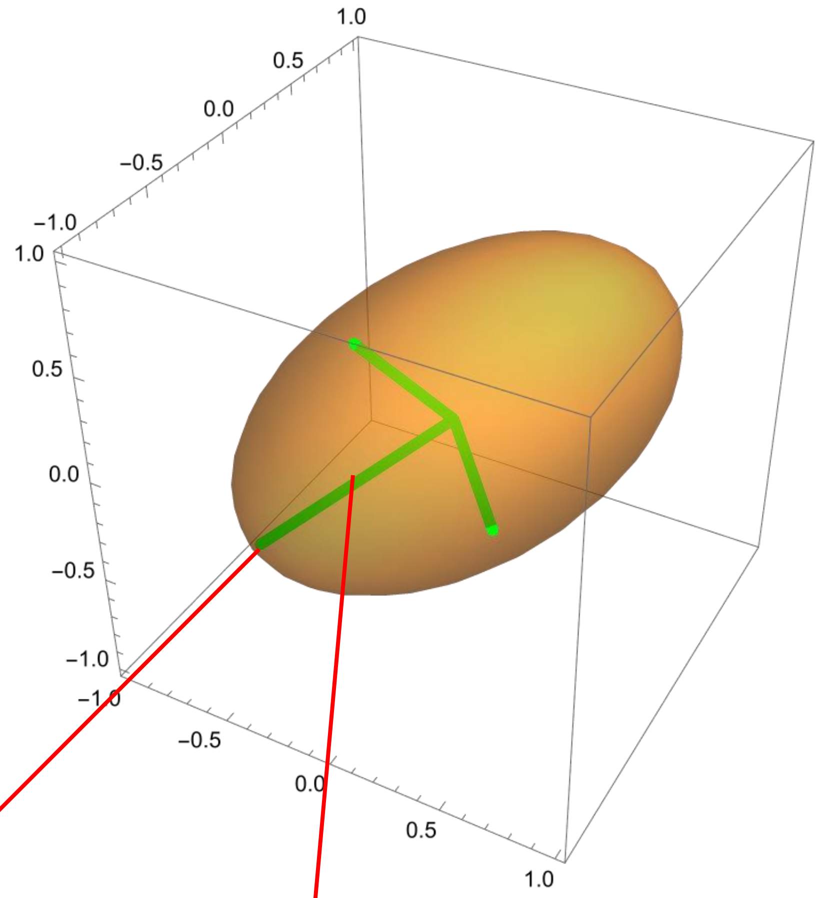


https://www.blog.brainsightai.com/post/from-dti-to-hardi]]

Diffusion Tensor and Its Ellipsoid Representation



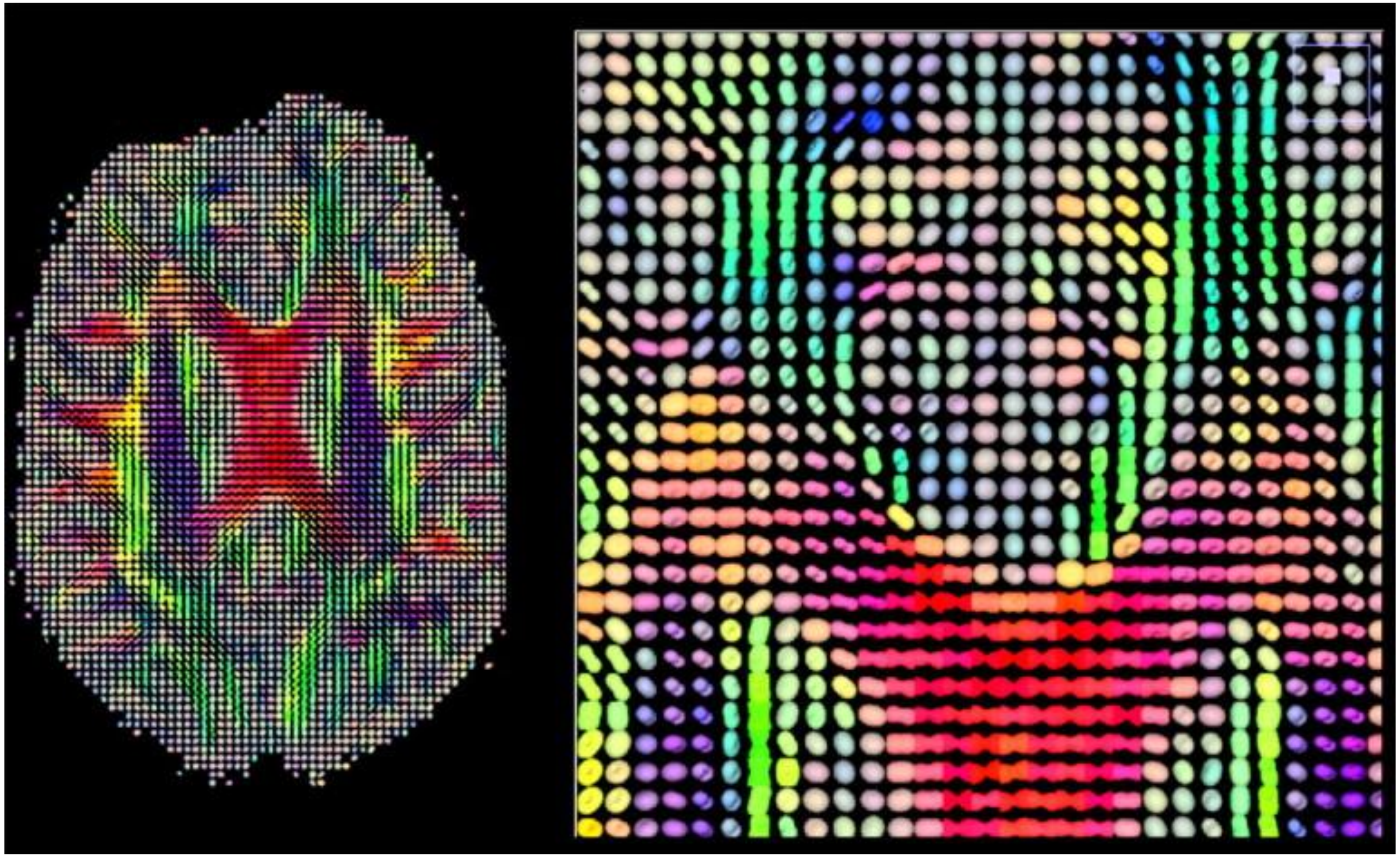
Eigendecomposition



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

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

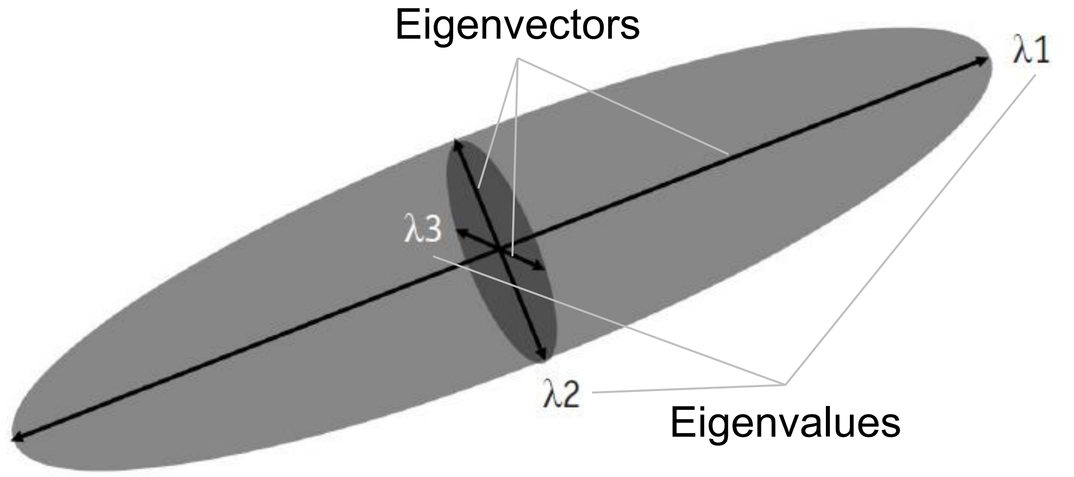
Eigenvectors Eigenvalues



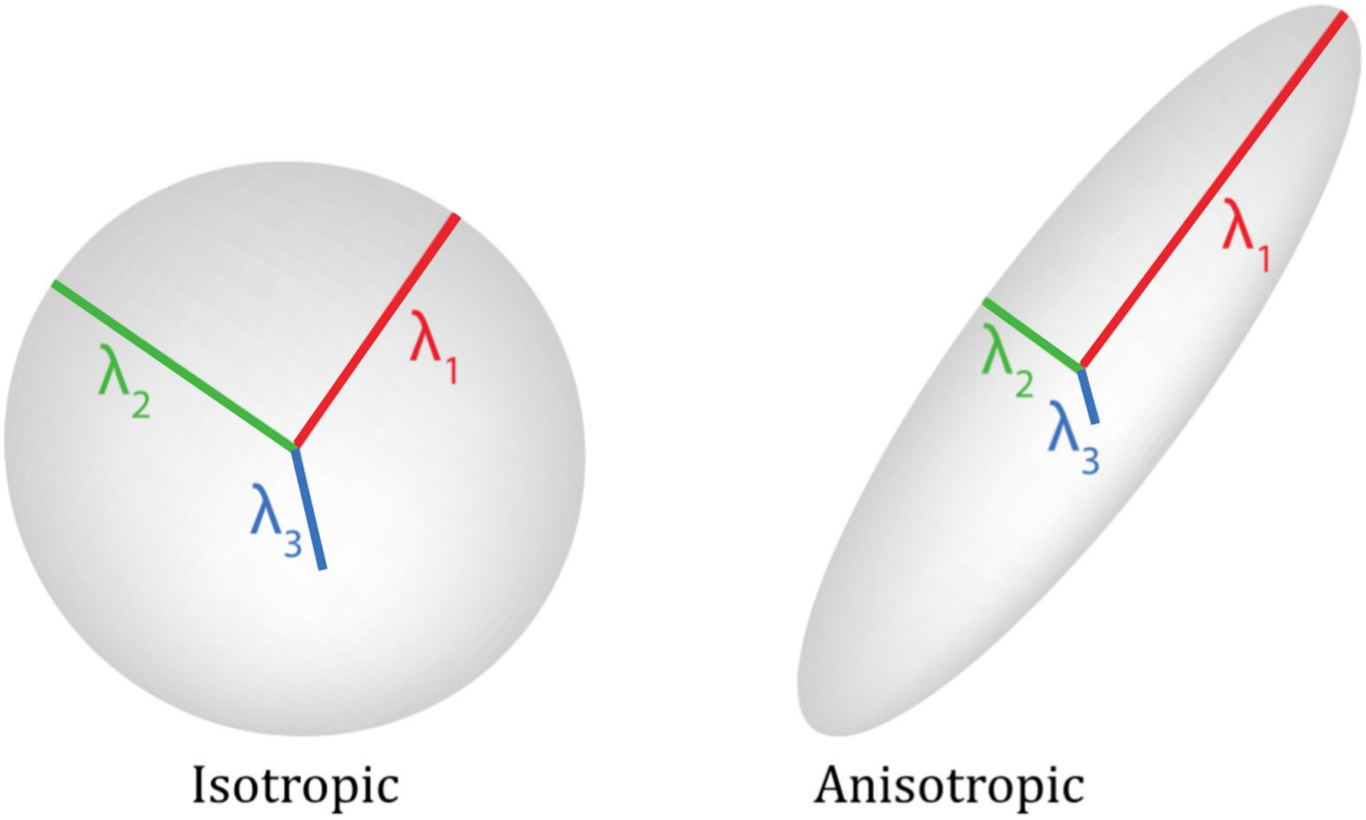
[Alger, 2012]

Diffusion Ellipsoids Derived from the Diffusion Tensors Measured for Each Voxel

- Represents averaged diffusion properties of numerous axons within a single voxel

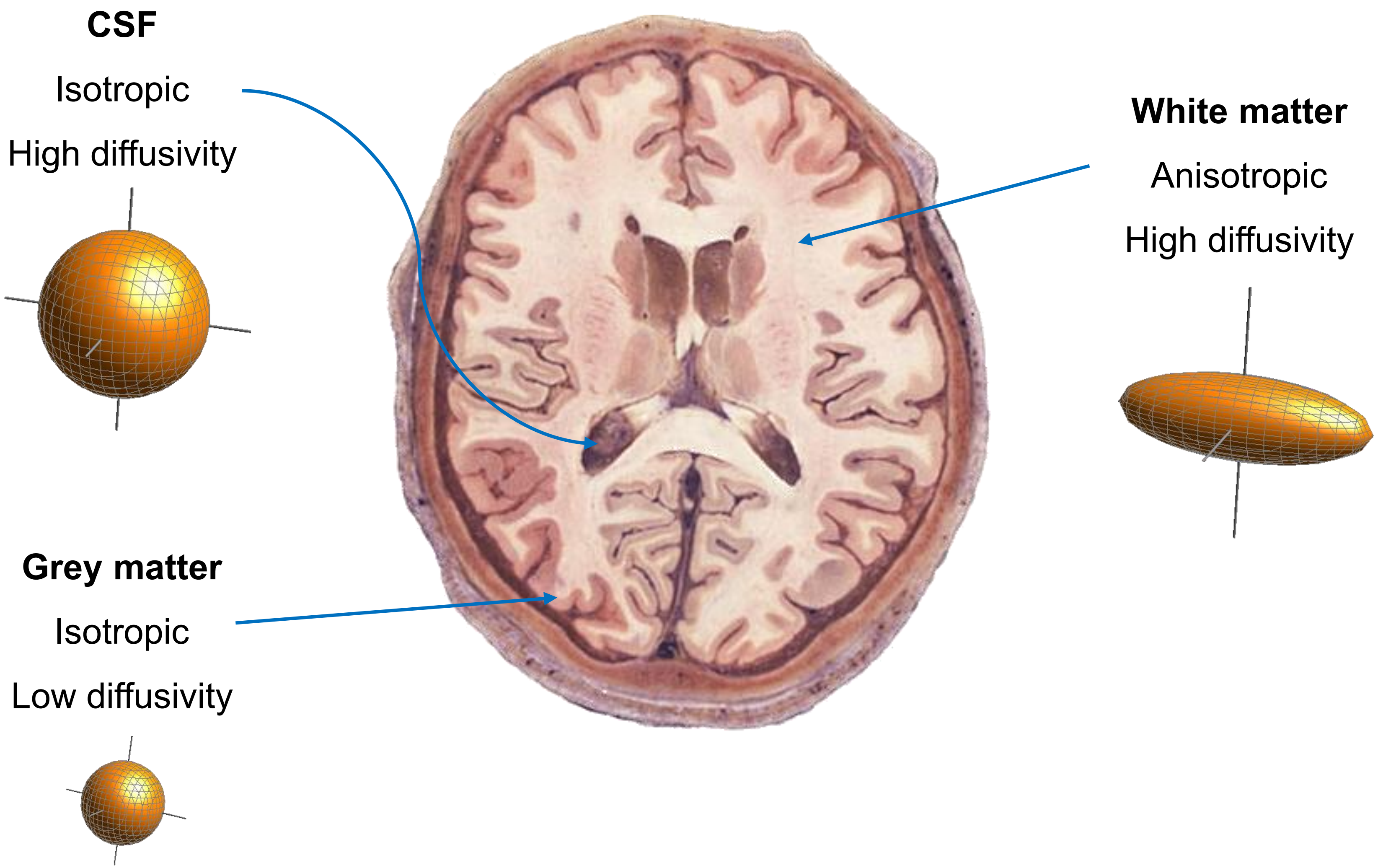


  - Magnitude and anisotropy of diffusion
    - Offer insights into tissue structure and organization



[http://www.diffusion-imaging.com/2015/10/what-is-diffusion-tensor.html]

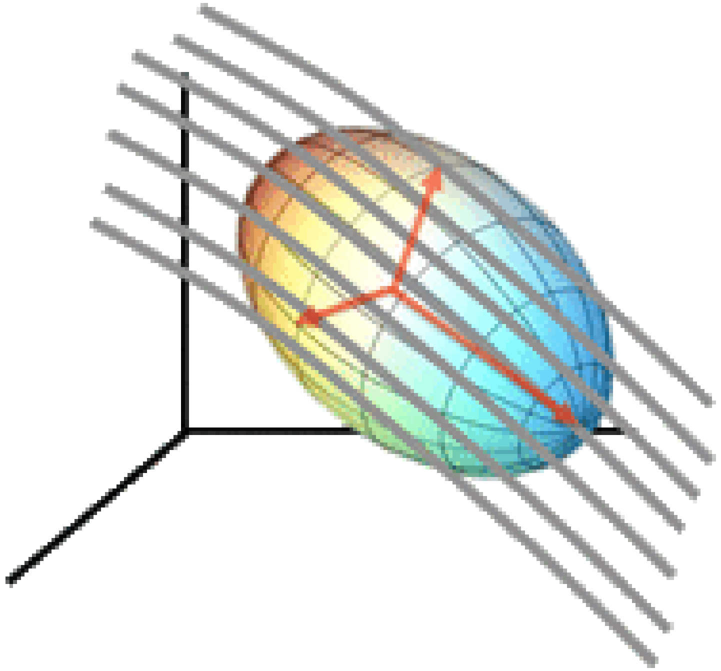
Isotropic and Anisotropic Diffusion Represented by Ellipsoids



Isotropic and Anisotropic Diffusion in Different Brain Tissues

– Principal direction of diffusion

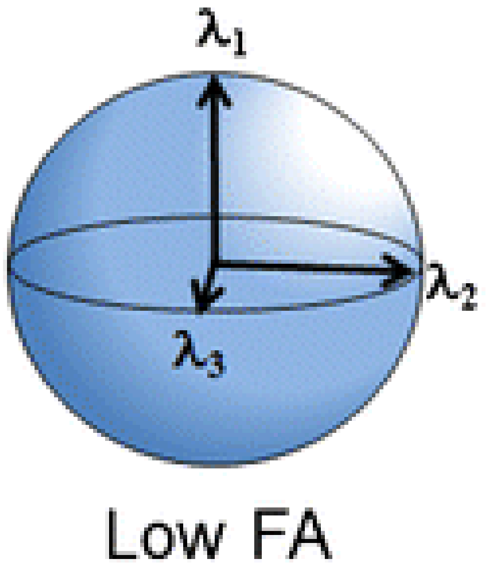
- Given by the main axis (principal eigenvector; eigenvector of the largest eigenvalue) of the ellipsoid
- Assumed to be aligned with the dominant fiber orientation within a voxel



[https://mriquestions.com/diffusion-tensor.html]

Microstructural Analysis with dMRI

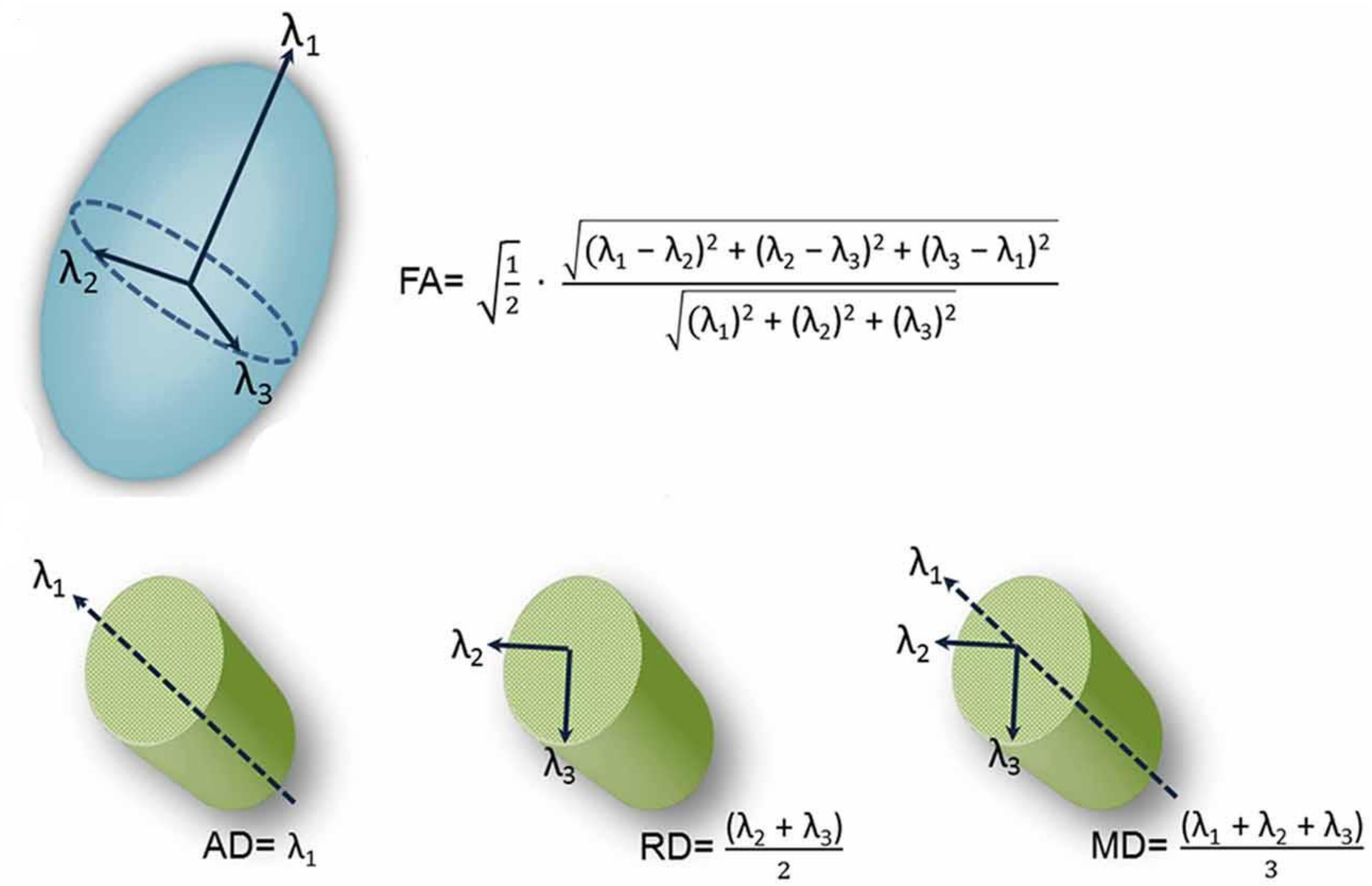
- Diffusion tensor metrics
  - Represent the magnitude and anisotropy (directional dependence) of water molecule diffusion within a voxel
  - Fractional anisotropy (FA)
    - Measures the degree of anisotropy (how much the diffusion is directionally dependent) within a voxel
    - Ranges from 0 (completely isotropic diffusion) to 1 (highly anisotropic diffusion)



[Mabrouk, 2018]

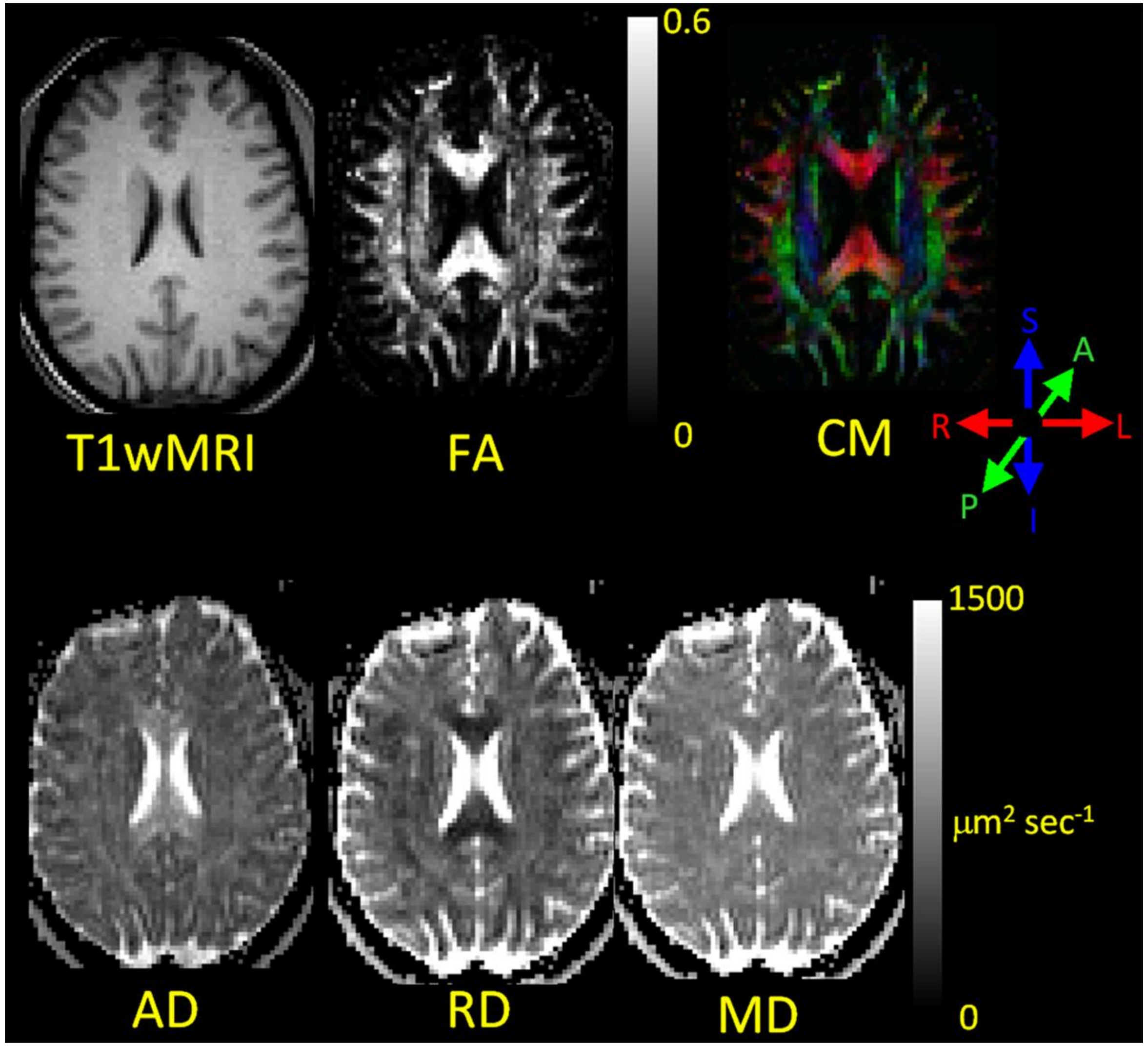
Isotropic and Anisotropic Diffusion Representing Different FA Values

- Mean diffusivity (MD)
  - Measures the average rate of diffusion within a voxel, irrespective of direction
- Axial diffusivity (AD)
  - Measures the rate of diffusion along the dominant fiber orientation within a voxel
- Radial diffusivity (RD)
  - Measures the average rate of diffusion perpendicularly to the dominant fiber orientation within a voxel
  - Indicative of reduced myelin integrity (degeneration or reduction of myelin around axons)



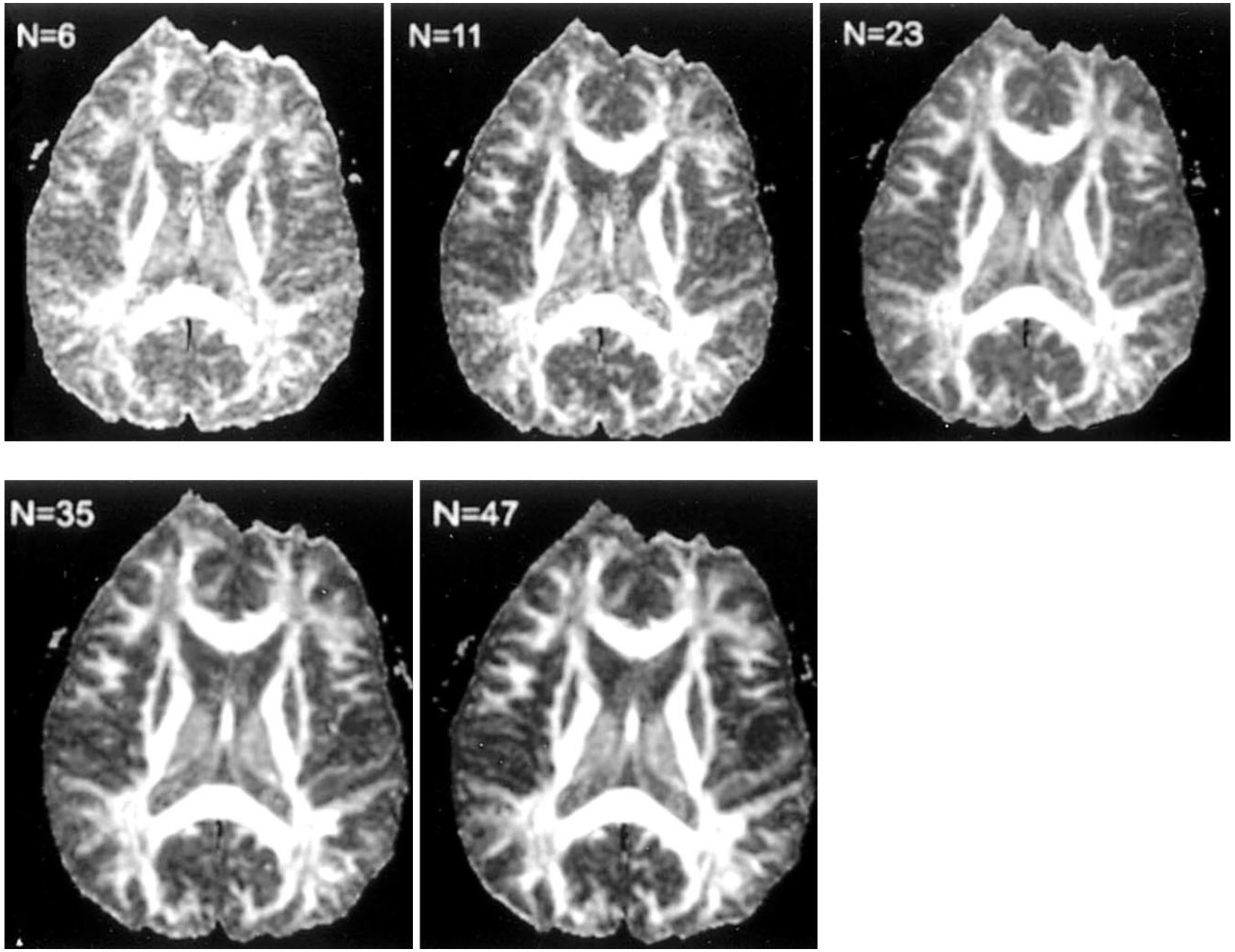
[DeSouza et al., 2016]

Diffusion Tensor Metrics



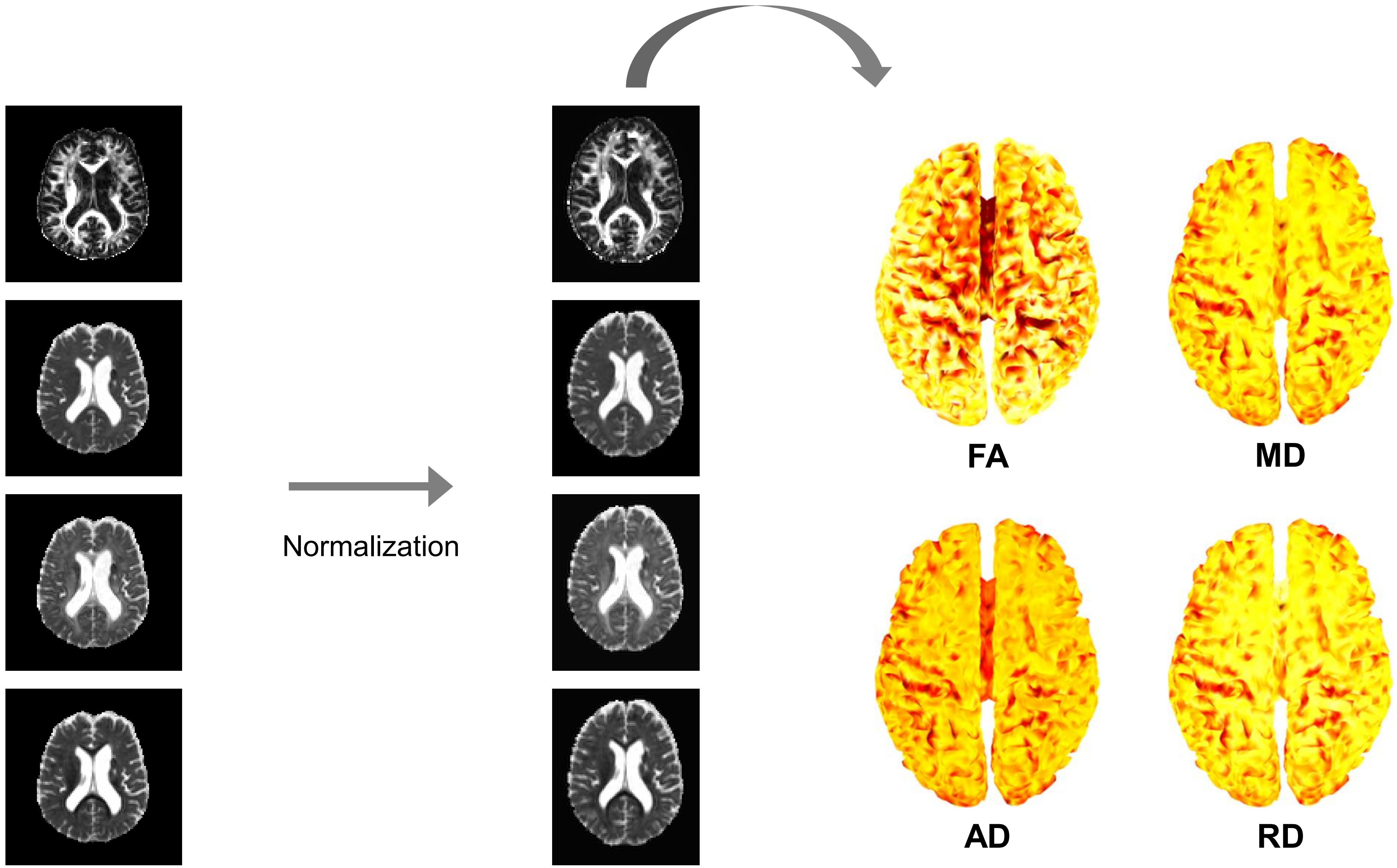
[Alger, 2012]

Maps of Diffusion Tensor Metrics



[Chang et al., 2005]

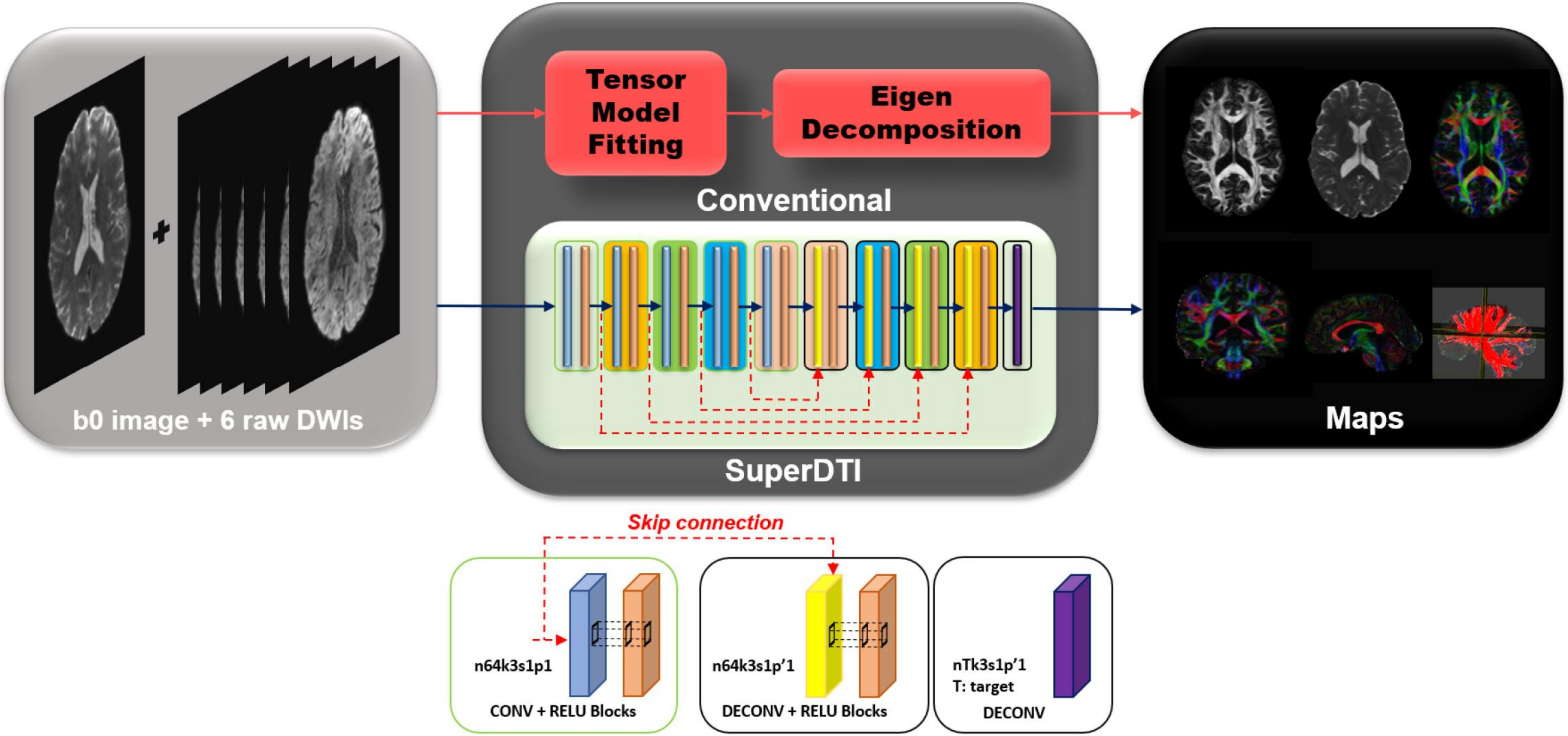
FA Maps According to Different Numbers of Diffusion-sensitizing Gradient Directions



Information of White Matter Microstructure

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

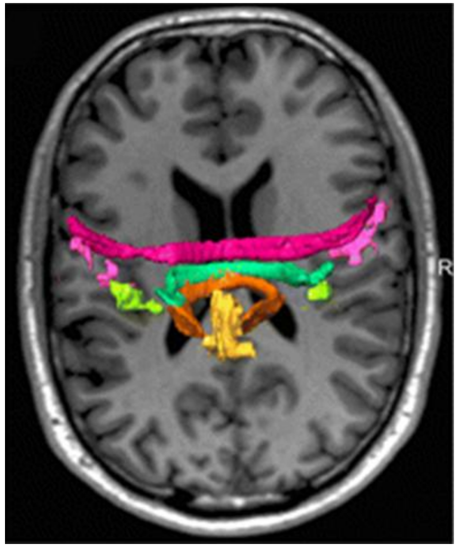


[Li et al., 2021]

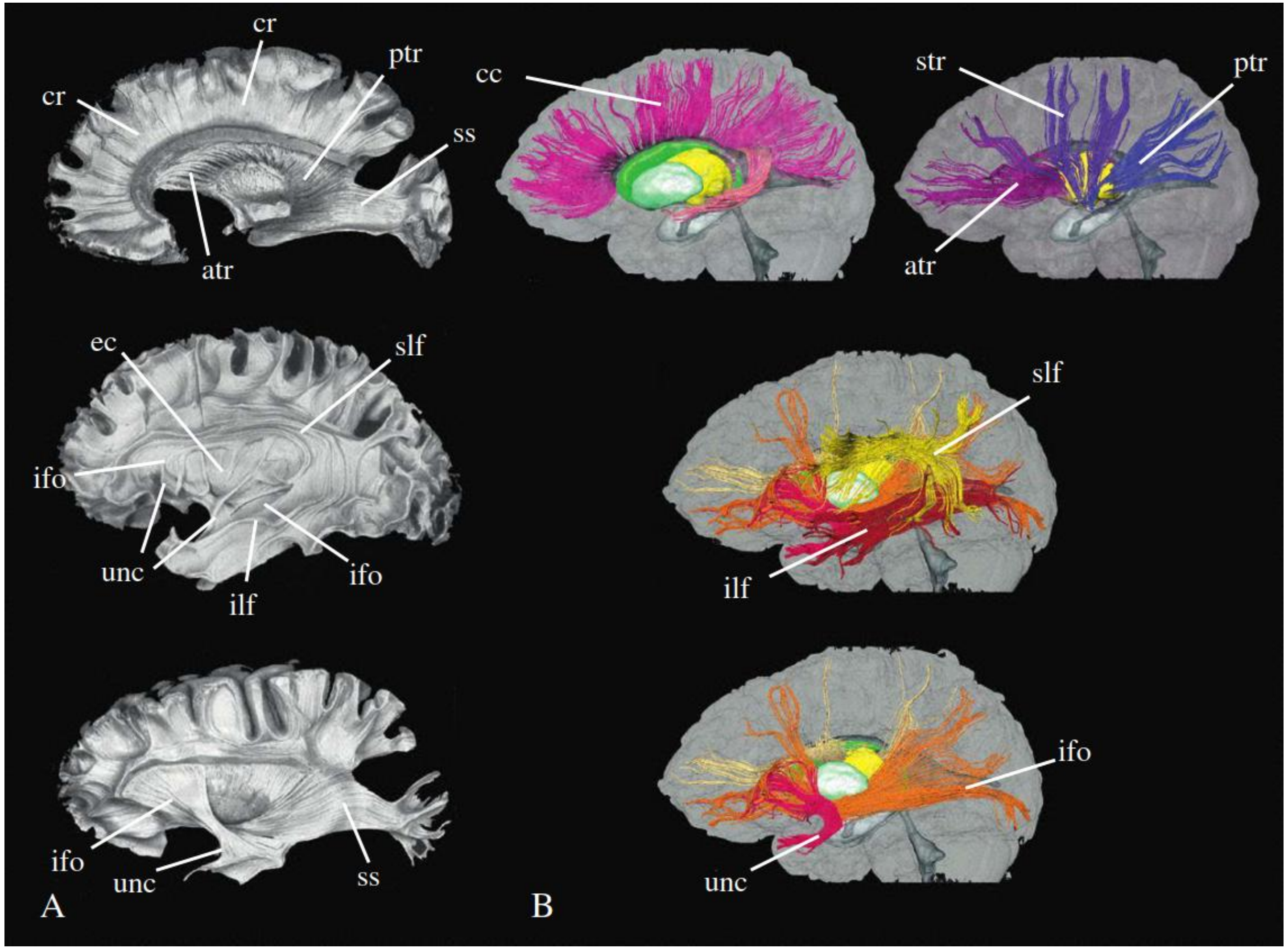
SuperDTI: Diffusion Tensor Metrics Estimation

White Matter Tractography with dMRI

- Diffusion anisotropy enables tractography and visualization of major white matter pathways in the brain



[Wahl et al., 2007]



[Oishi et al., 2011]

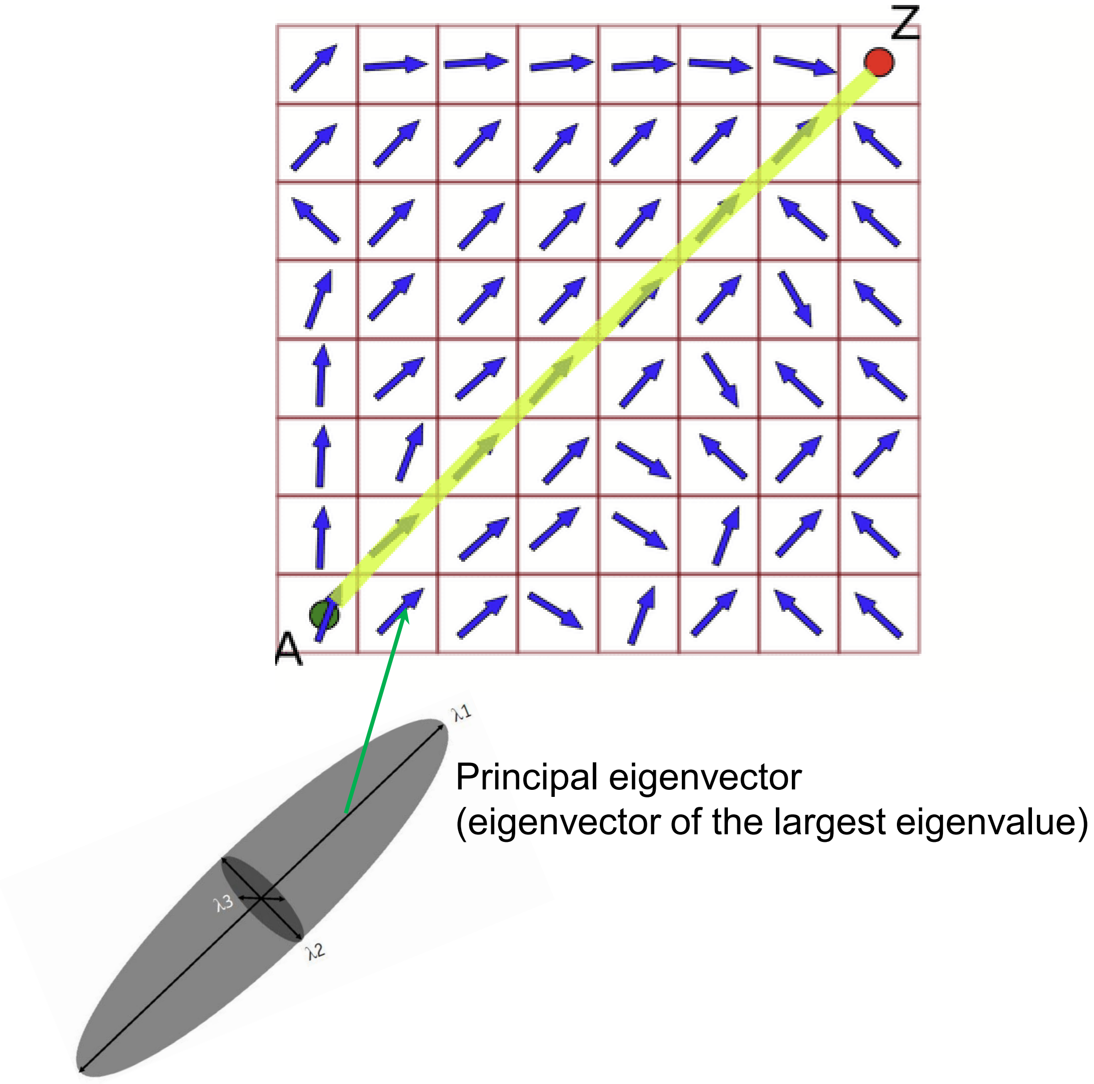
Comparison Between Postmortem Preparation and dMRI-based White Matter Reconstructions

- 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

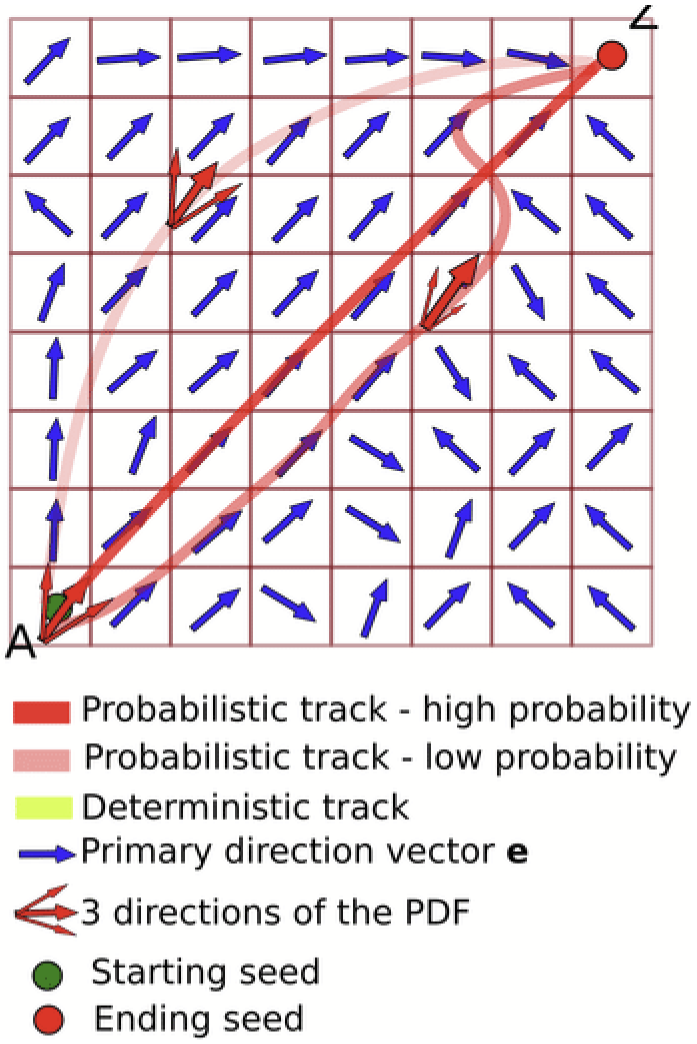
- Computational representation of white matter pathways
  - White matter tractography hierarchy
    - Streamline → bundle
  - Streamline
    - Fundamental unit of tractography, representing a single reconstructed fiber trajectory from a seed point through the brain
    - Highly dependent on algorithm 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

- 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

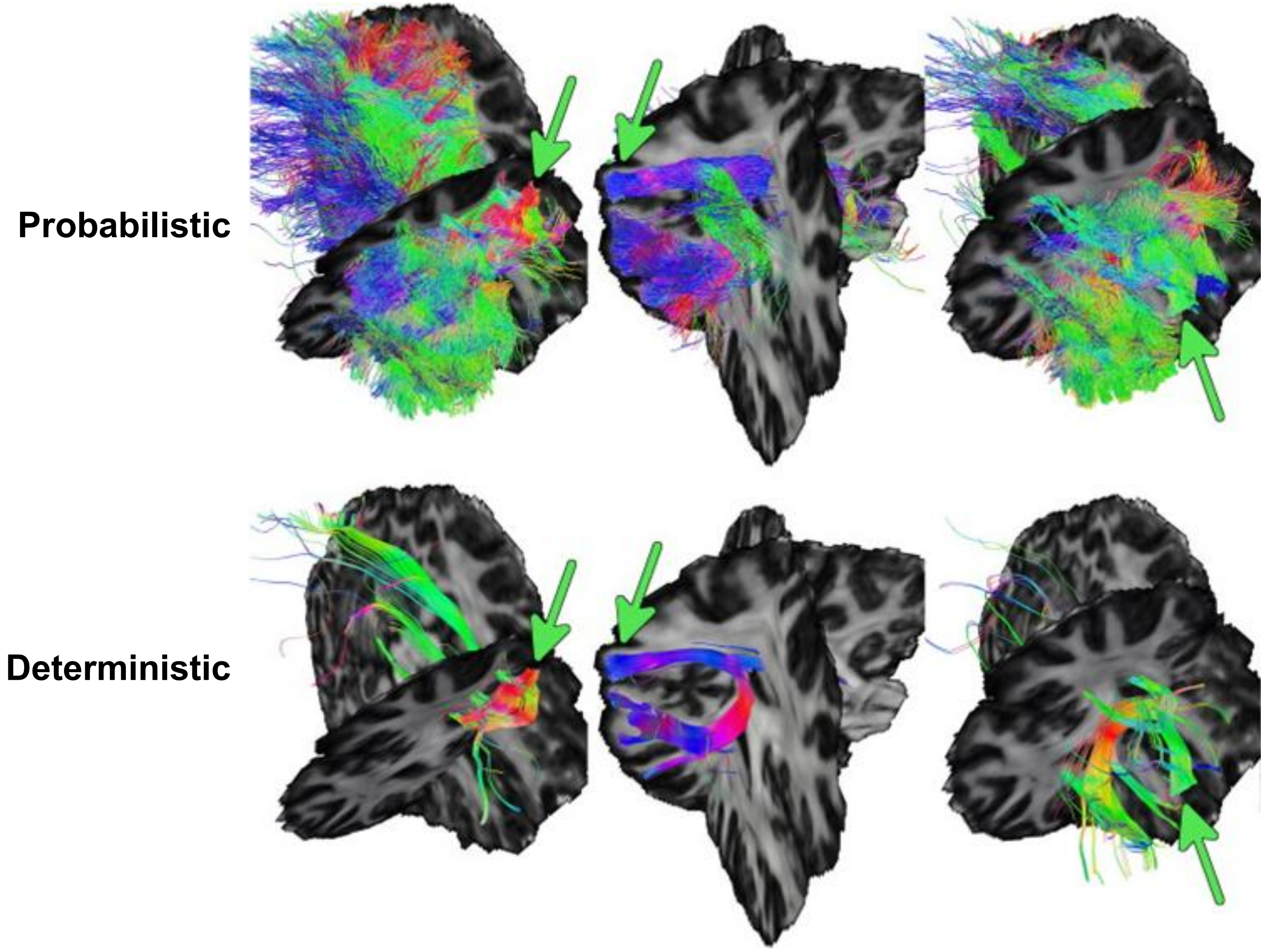


Probabilistic



[Garyfallidis, 2012]

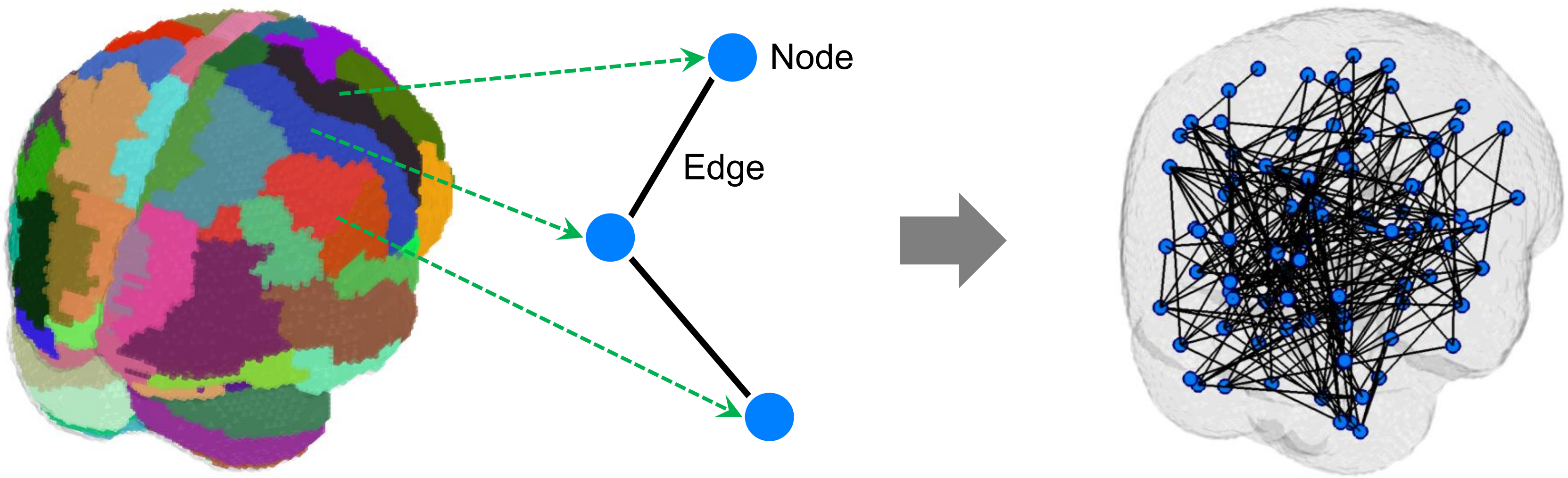
Deterministic and Probabilistic Ways for White Matter Tractography

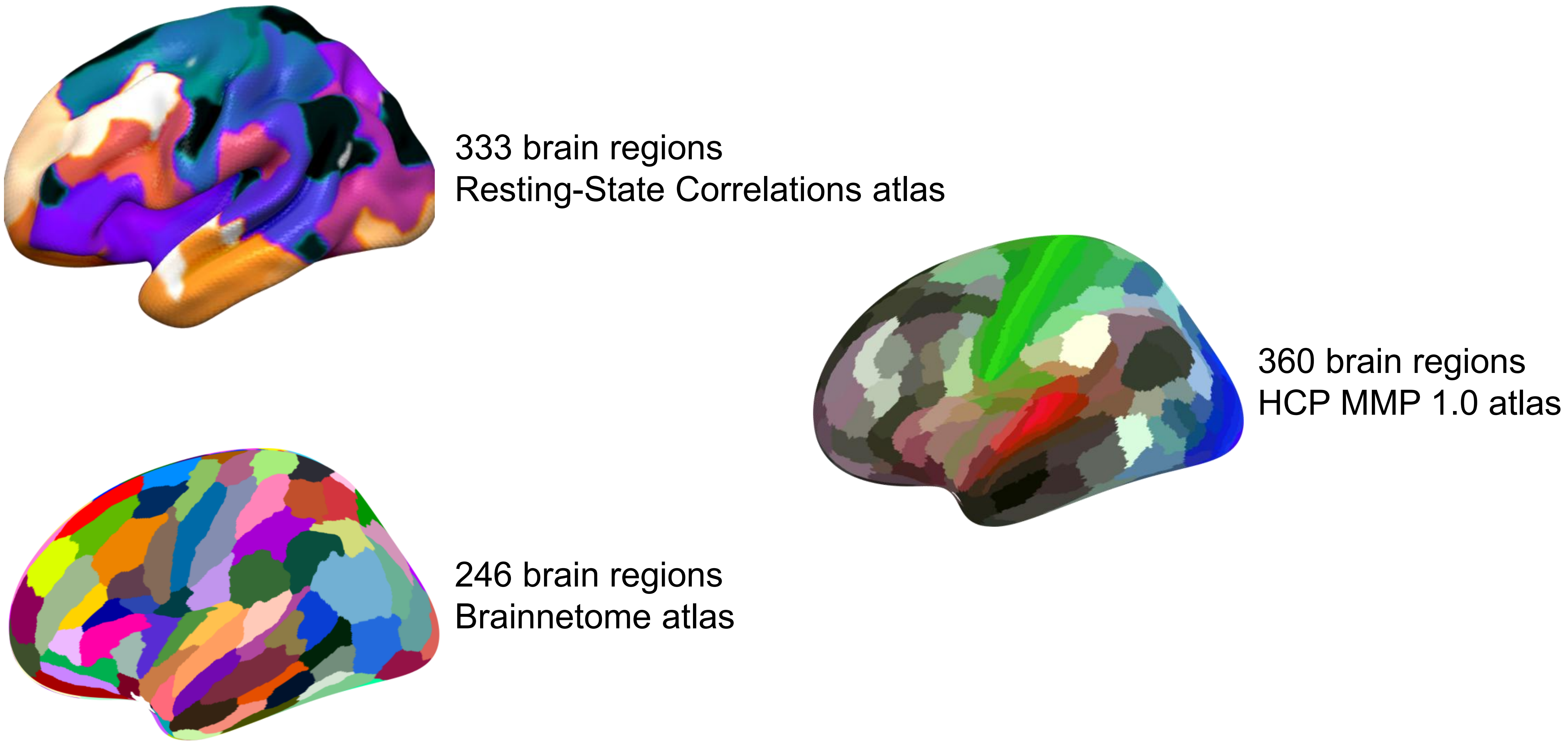


[Schreiber et al., 2014]

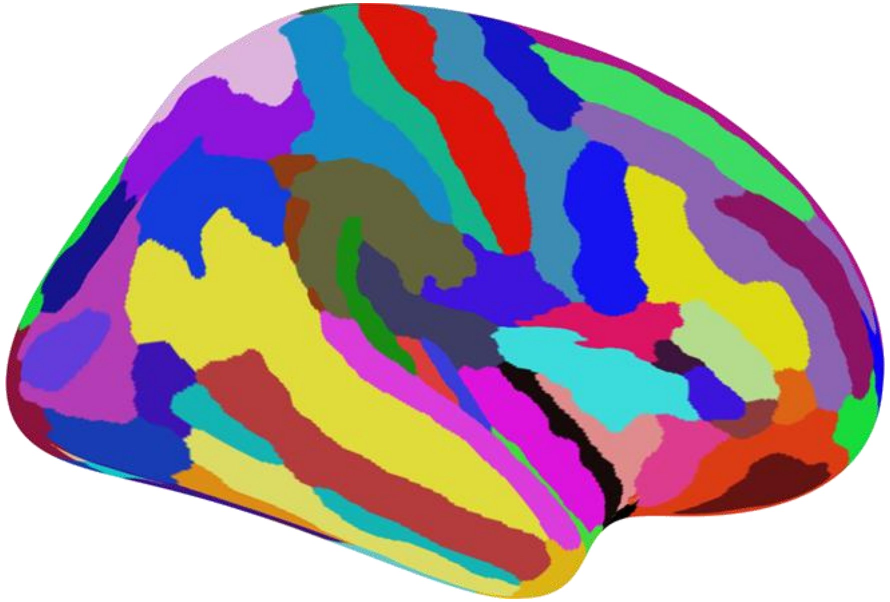
Comparison Between Probabilistic and Deterministic Tractography

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

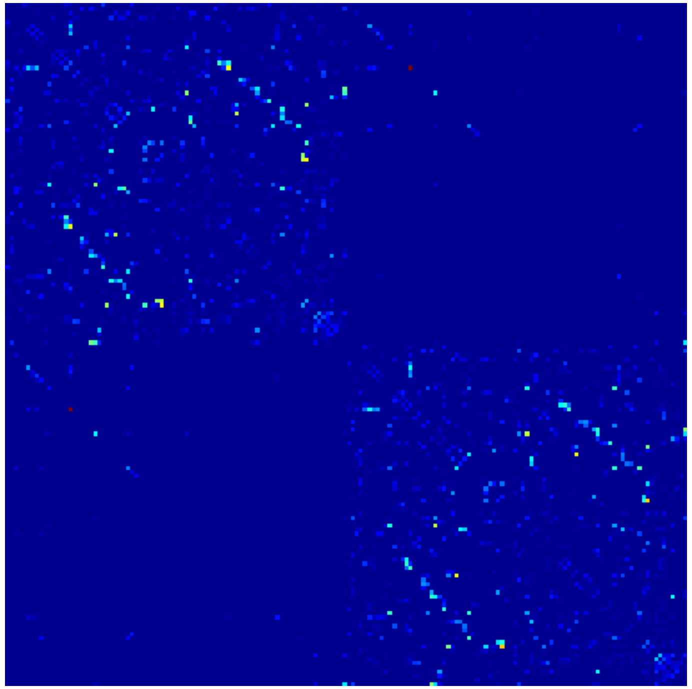




Brain Atlases Delineating Heterogeneous Nodes with Varying Definitions and Quantities

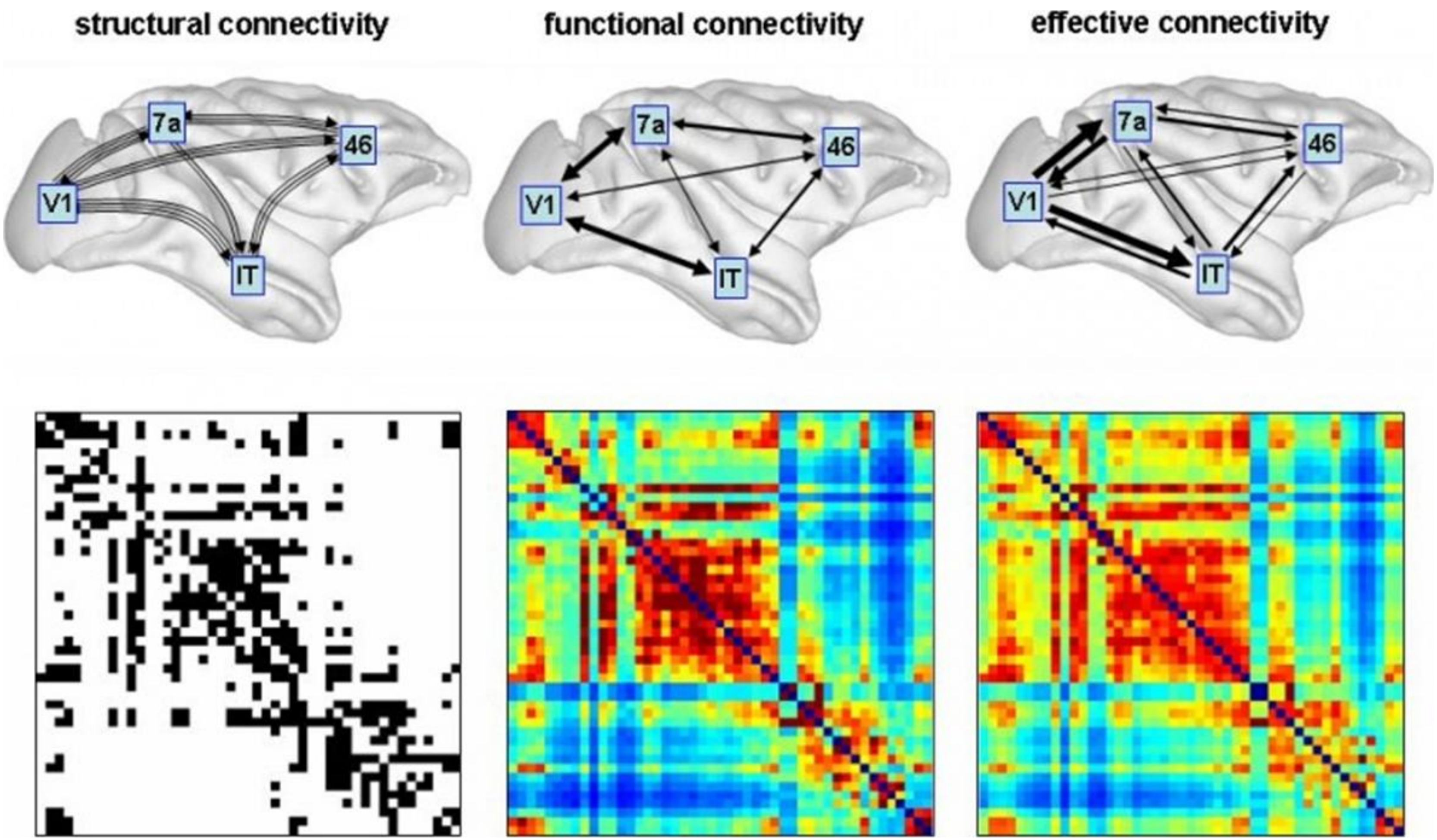


White matter streamlines



Streamline count

Structural Network or Connectome



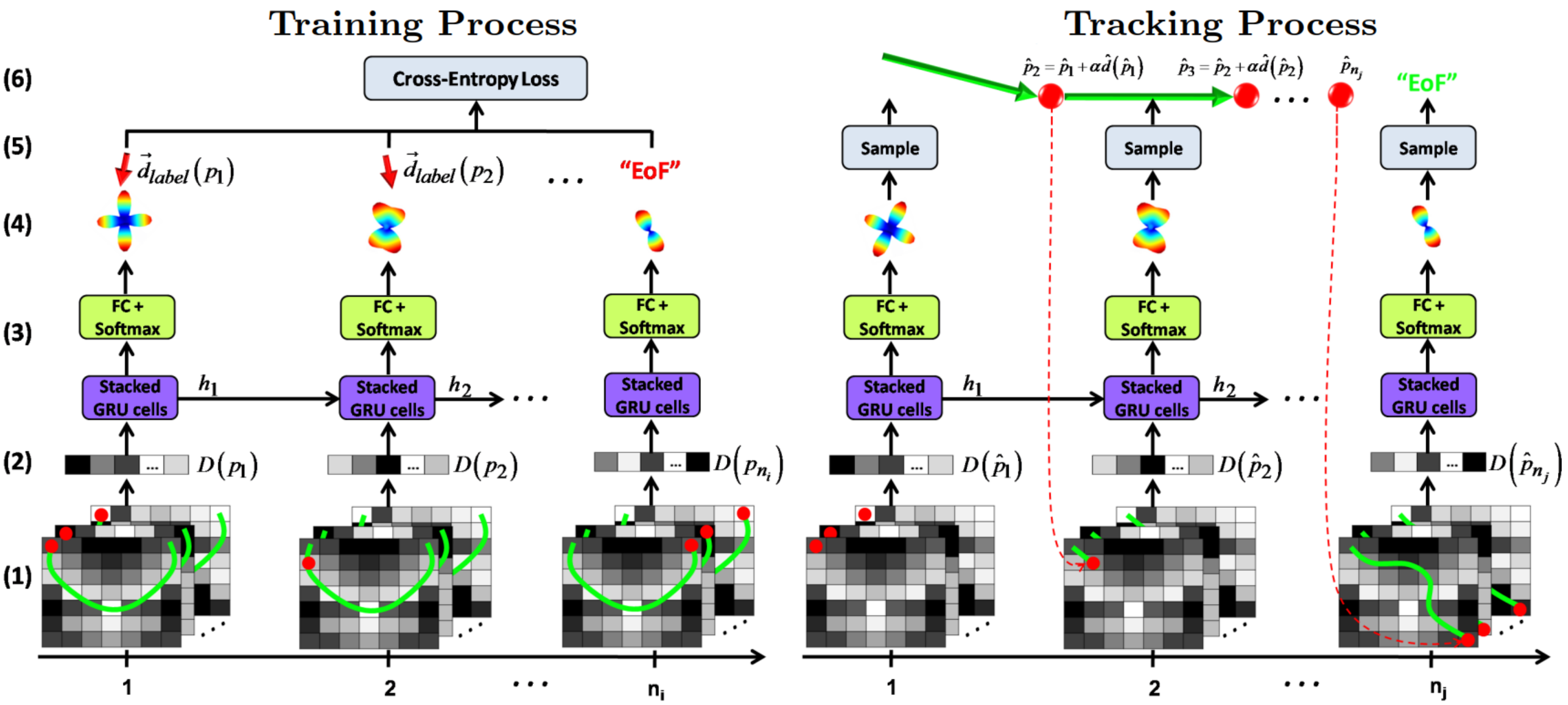
[Honey et al., 2007]

Modes of Brain Connectivity

- Graph-theoretical analysis
  - Characterize the topological properties of structural brain networks
    - Connection topology of the brain
    - Efficiency of information transfer within the brain
    - Key regions in the brain.
    - Brain's resilience to damage or attack

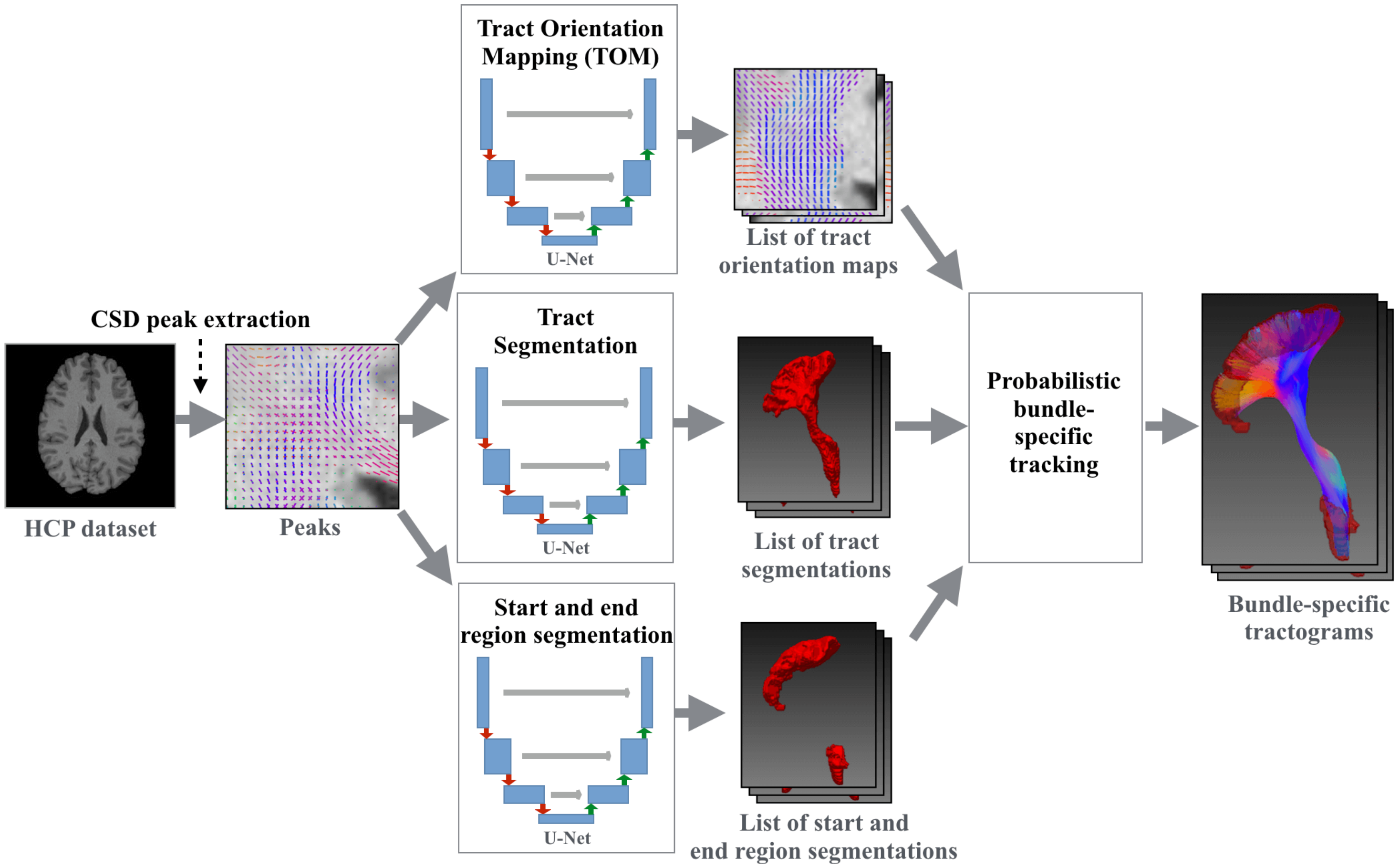
Automated White Matter Tractography

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



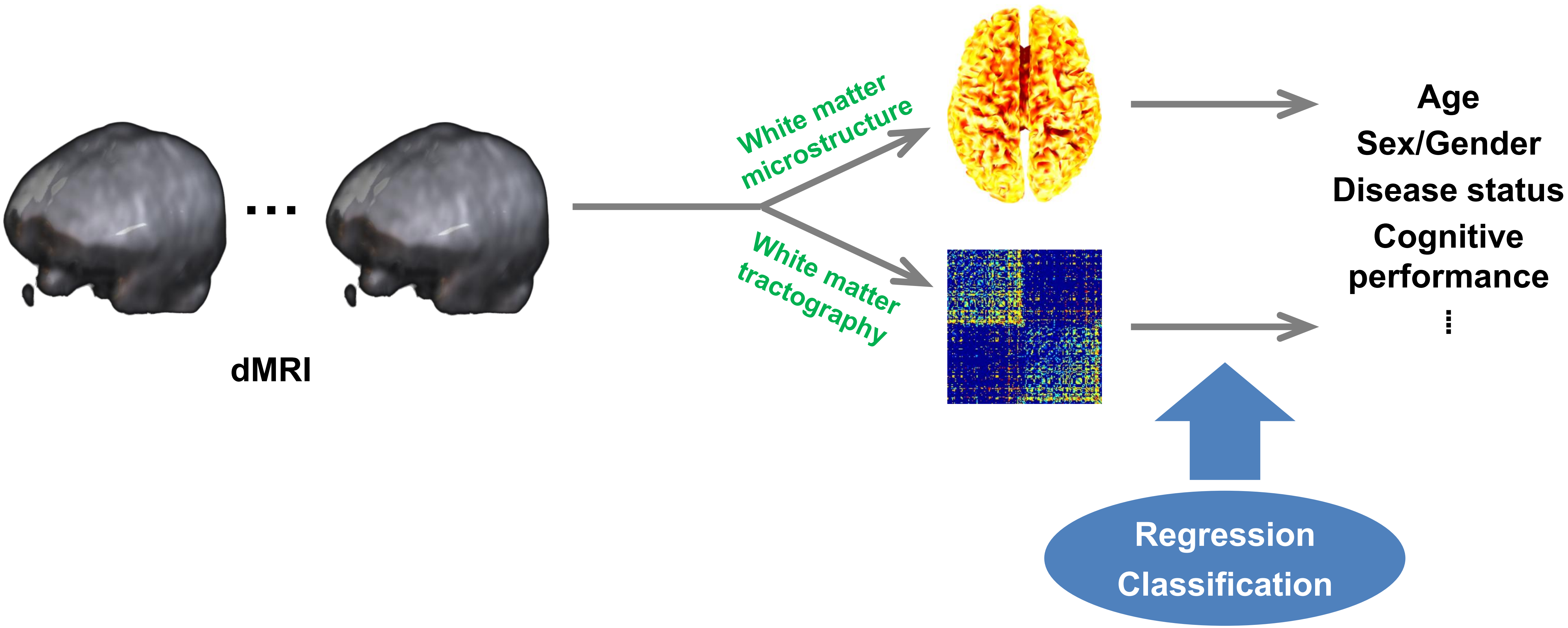
[Benou & Riklin-Raviv, 2018; https://github.com/itaybenou/DeepTract]

DeepTract: White Matter Tracking



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

TractSeg: White Matter Tract Segmentation

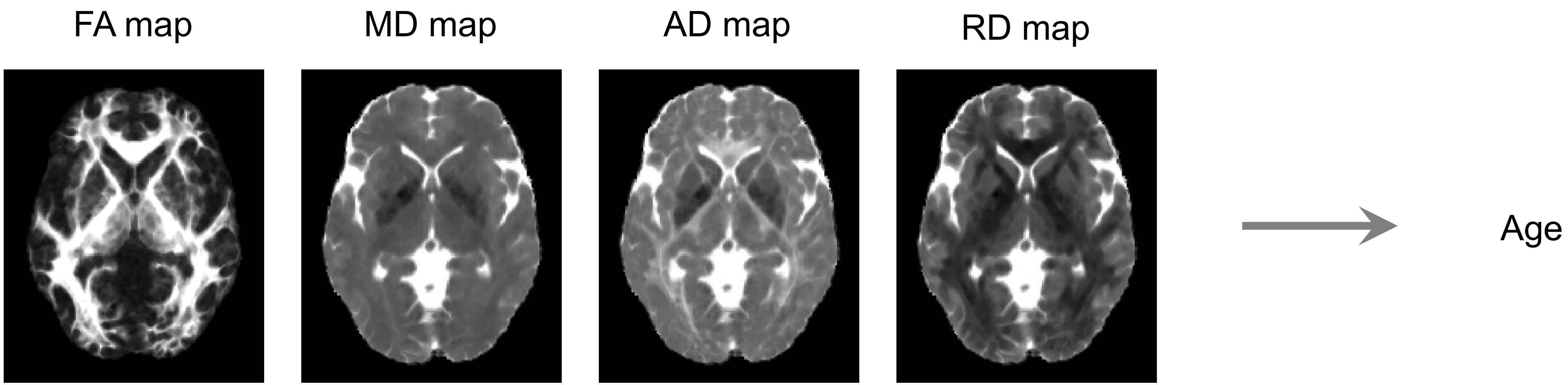

dMRI
White matter microstructure
White matter tractography
Age
Sex/Gender
Disease status
Cognitive performance
Regression
Classification

Age Prediction

$P(Y|\mathbf{X}) = P(\text{age} \mid [\text{FA\_std; MD\_std; AD\_std; RD\_std}])$

where $\mathbf{X}$ = spatially normalized diffusion tensor metric maps in standard space:

$[\text{FA\_std; MD\_std; AD\_std; RD\_std}] \in \mathbb{R}^{C\times H\times W\times D}$ and Y = age



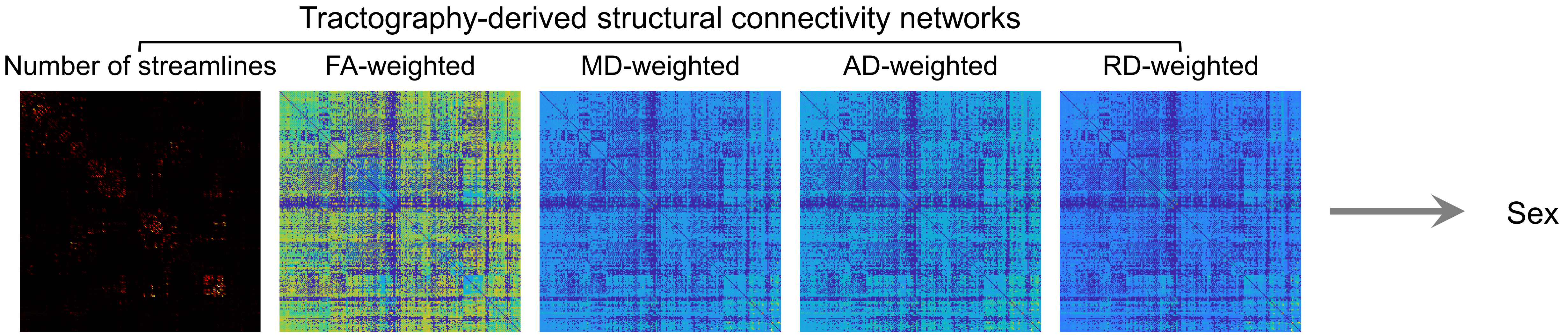
Multi-channel Input for Age Prediction

Sex Classification

$P(Y|X) = P(\text{sex} \mid \{\text{Net\_Count}, \text{Net\_FA}, \text{Net\_MD}, \text{Net\_AD}, \text{Net\_RD}\})$

where X = tractography-derived structural connectivity networks:

$\text{Net\_Count}, \text{Net\_FA}, \text{Net\_MD}, \text{Net\_AD}, \text{Net\_RD} \in \mathbb{R}^{N \times N}$ and Y = sex



Multi-graph Input for Sex Classification