ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

# Water motion to map brain connectivity

## *Summer school 2024*

## *Physics for a better world*

**Claudia Testa**

Dipartimento di Fisica e Astronomia

Università di Bologna

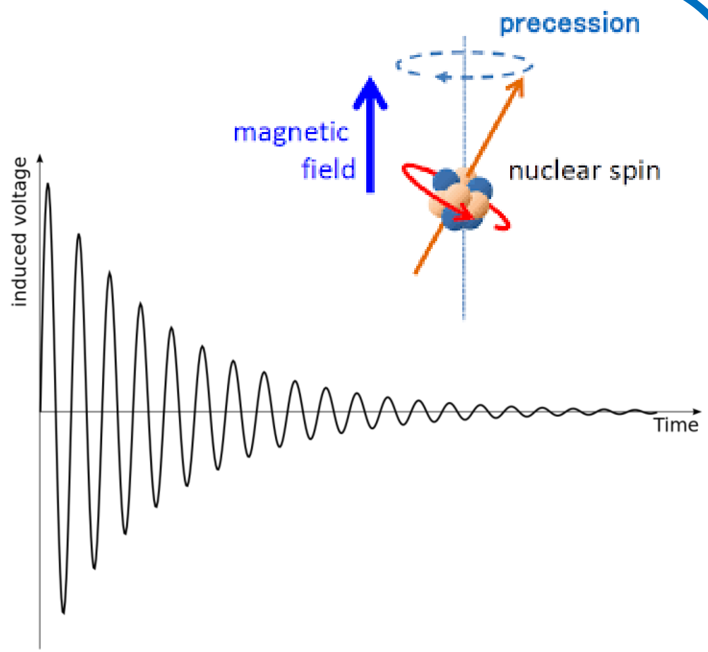
# *The context*

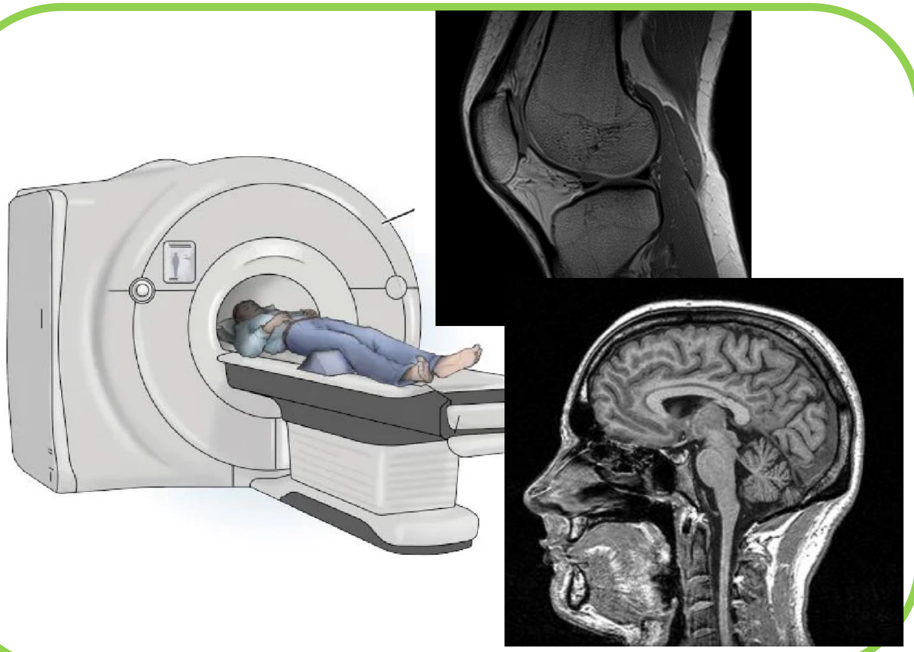
- Neuroscience at microscopic level
- Health theme – personalized medicine
- Quantitative imaging for personalized medicine

# Outline

- MRI and Quantitative MRI
- Diffusion in the brain and quantitative measures
- Tractography
- Structural connectomics

# Quantitative Magnetic Resonance Imaging



*Courtesy of Marco Barbieri, Ph.D*
*Postdoctoral Scholar, Department of Radiology, Stanford University*

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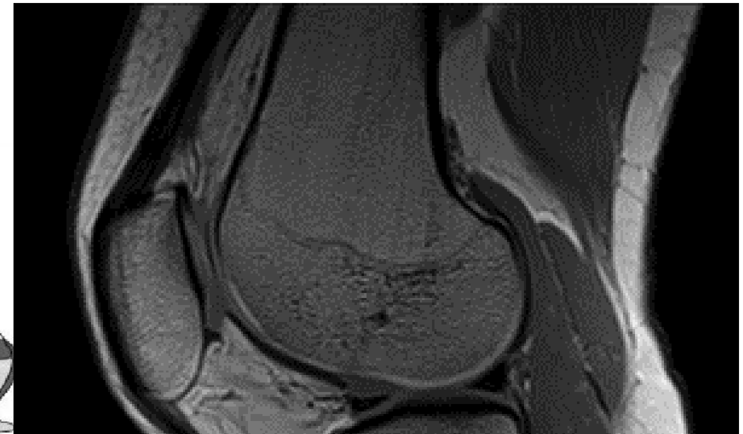
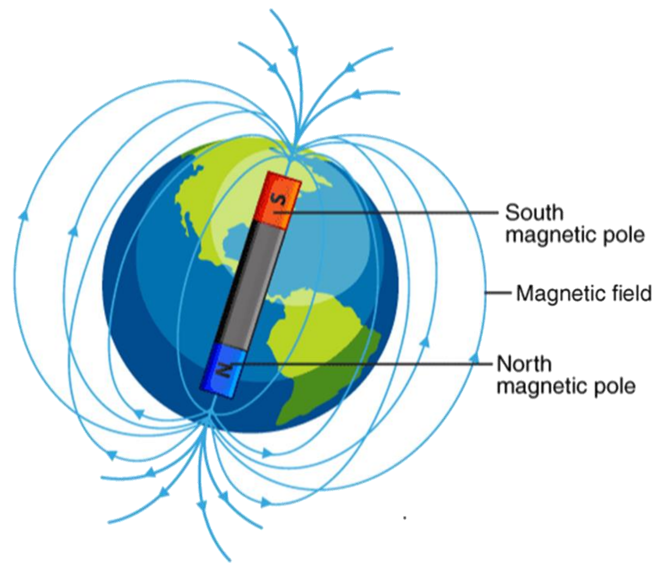
# *Magnetic Resonance Imaging*



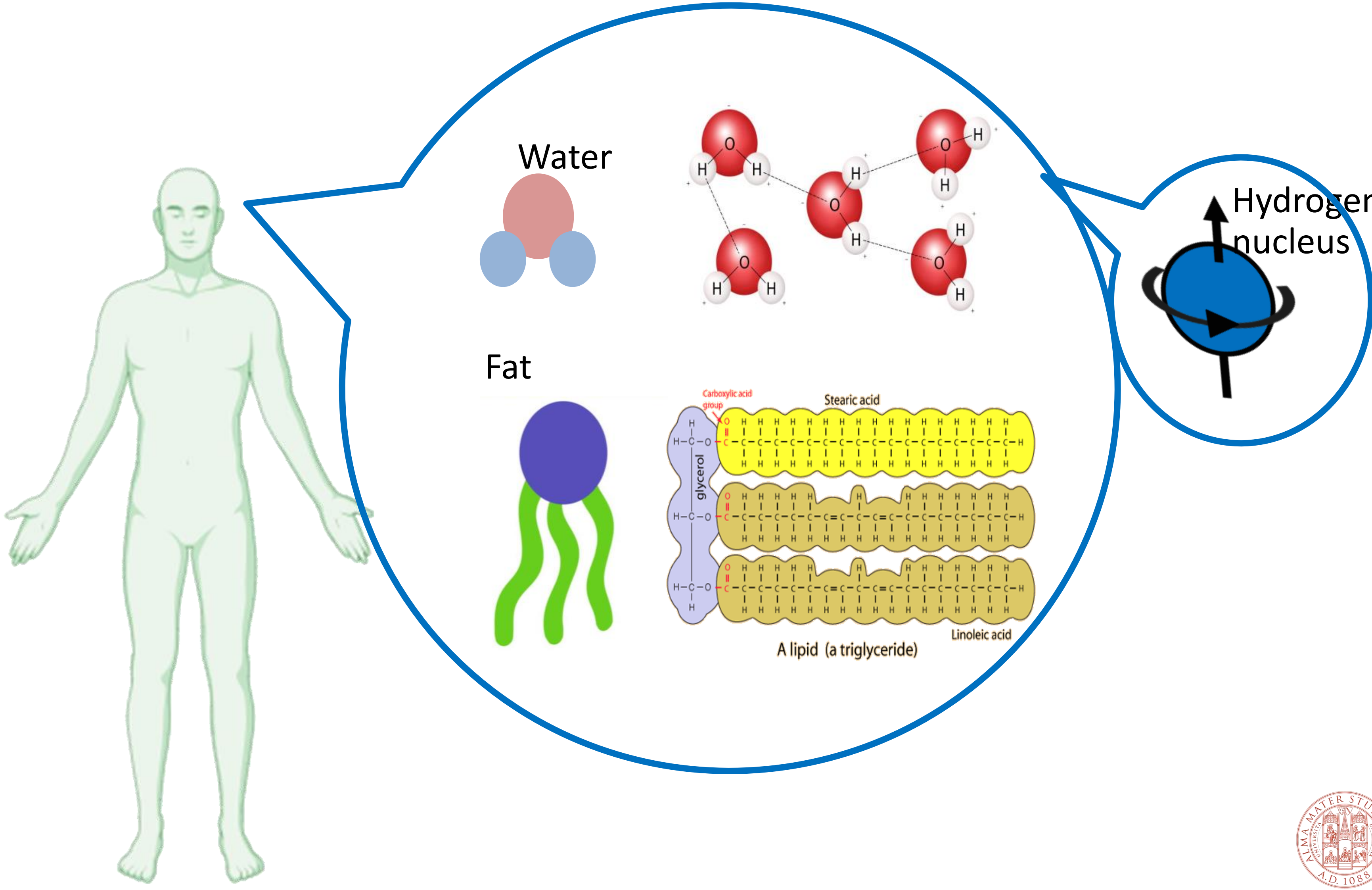
# *Magnetic Resonance Imaging*

1.5 or 3 T

~ 25 – 65 $10^{-6}$ T



# Magnetic Resonance



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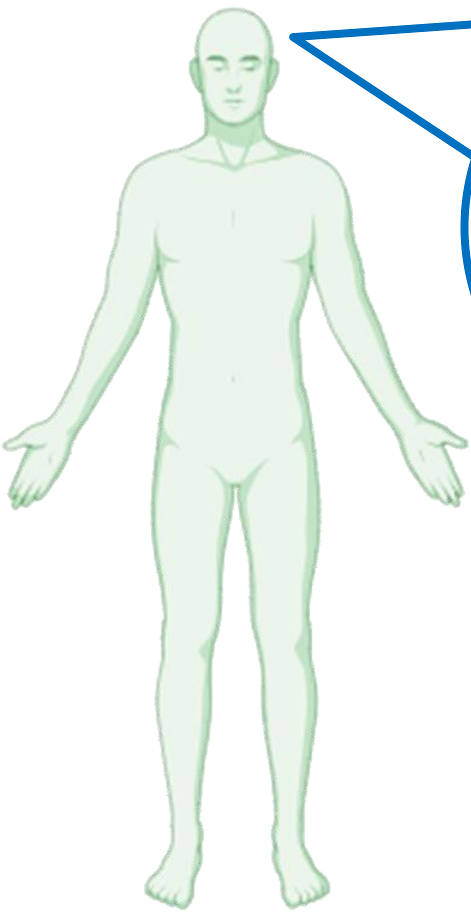
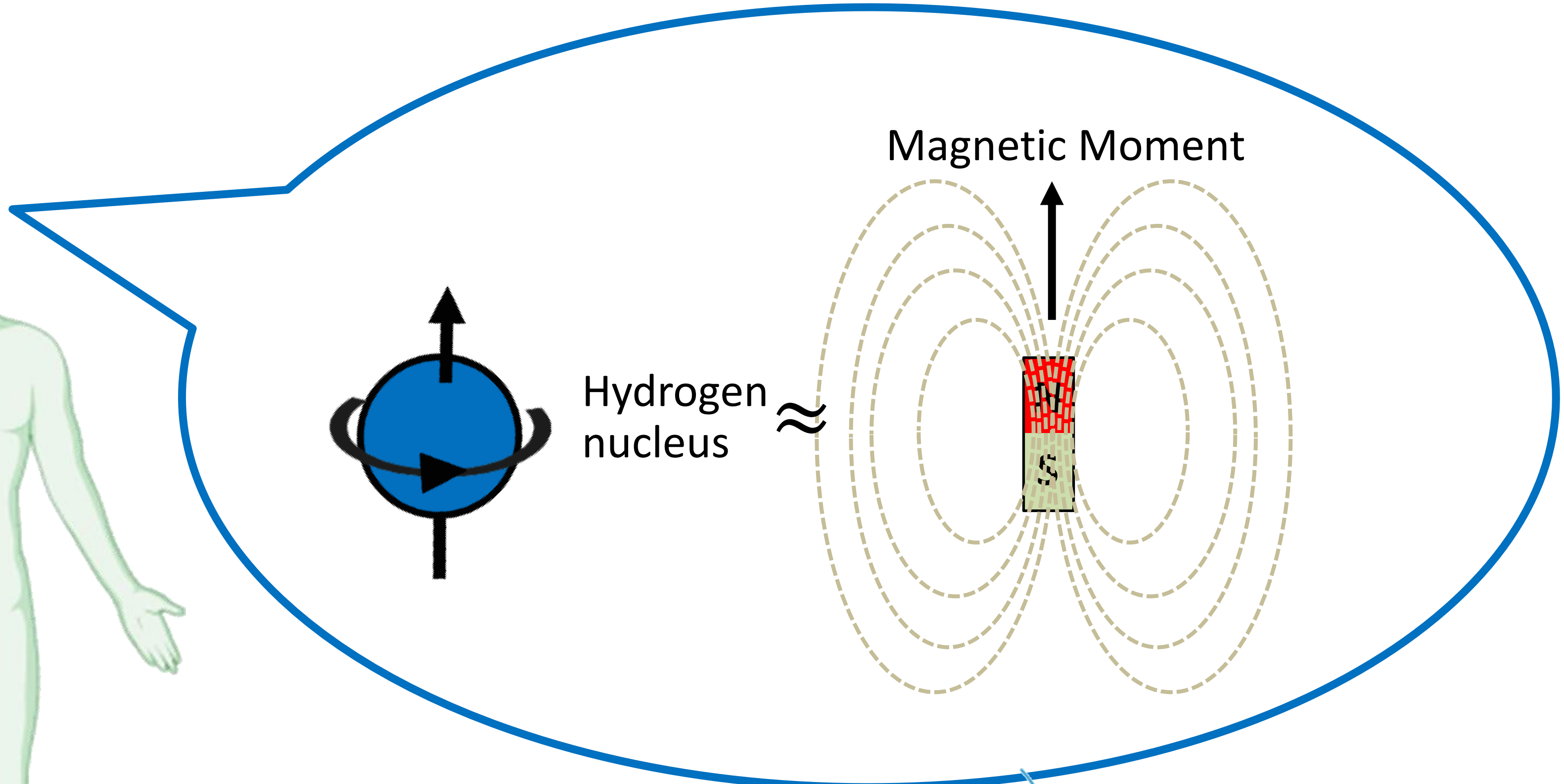
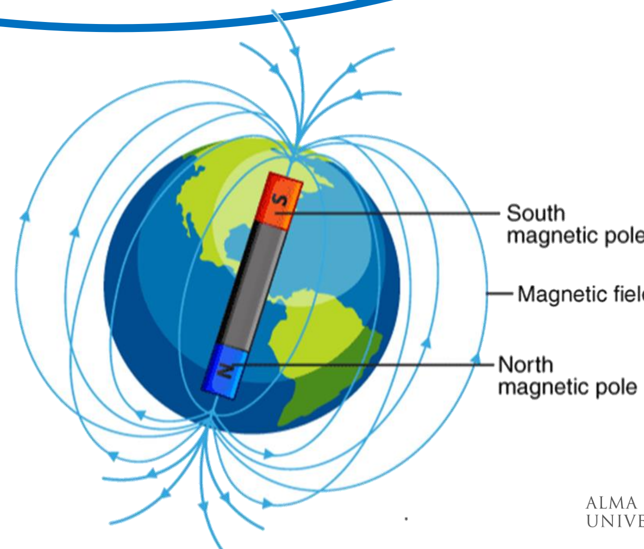
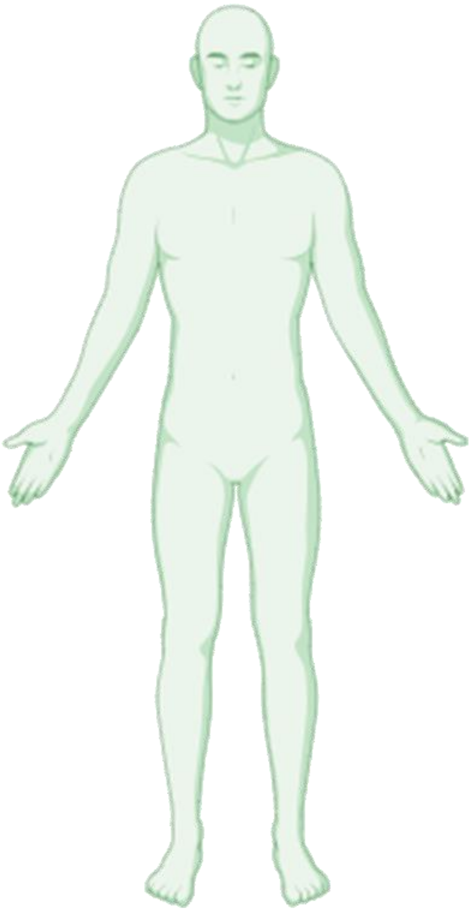
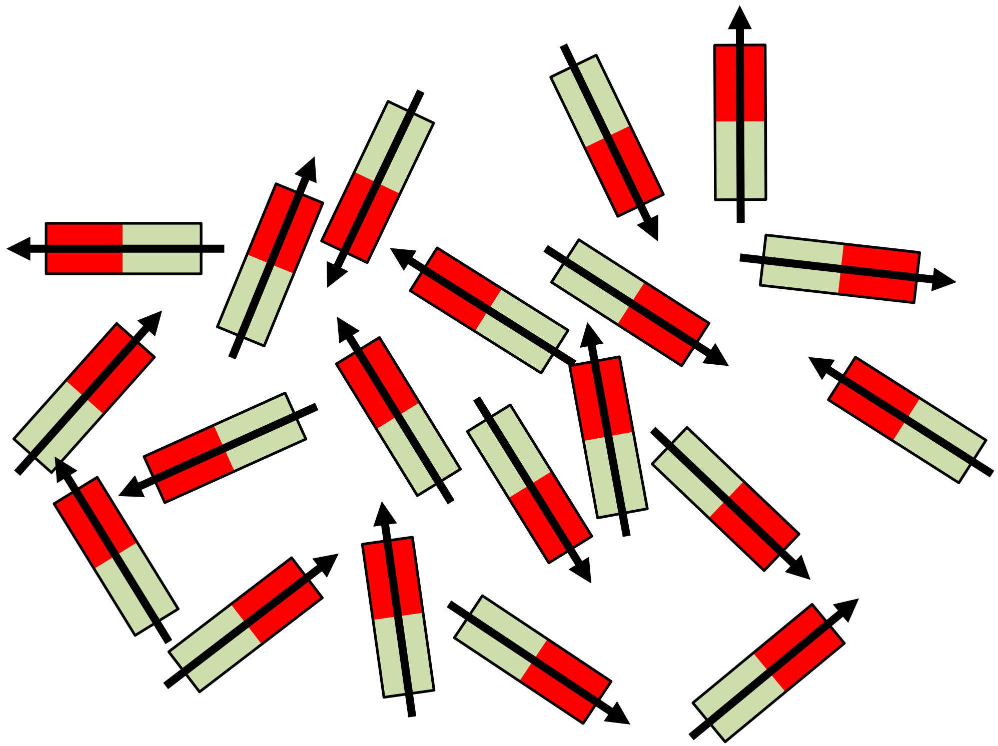




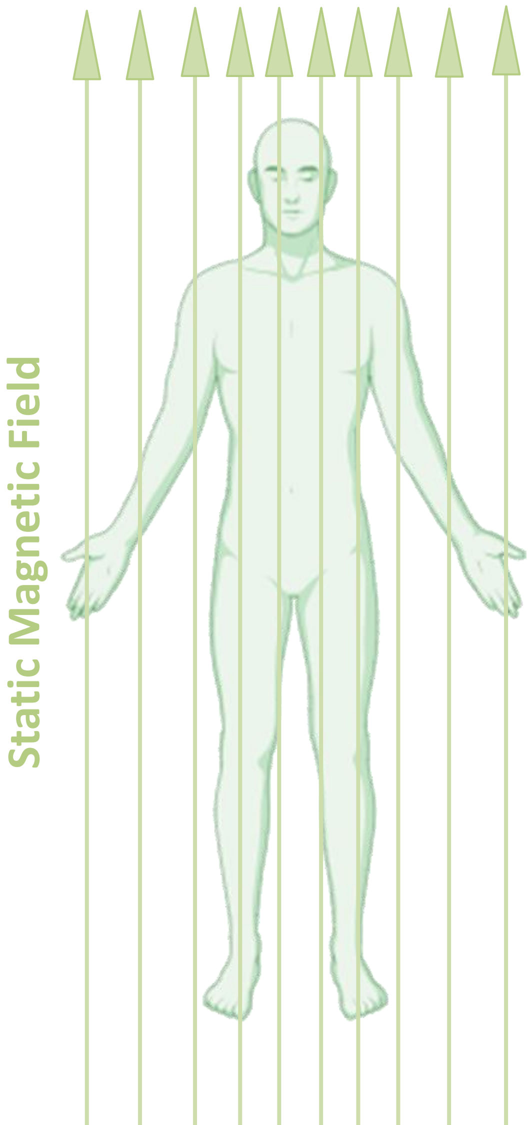



# Magnetic Resonance

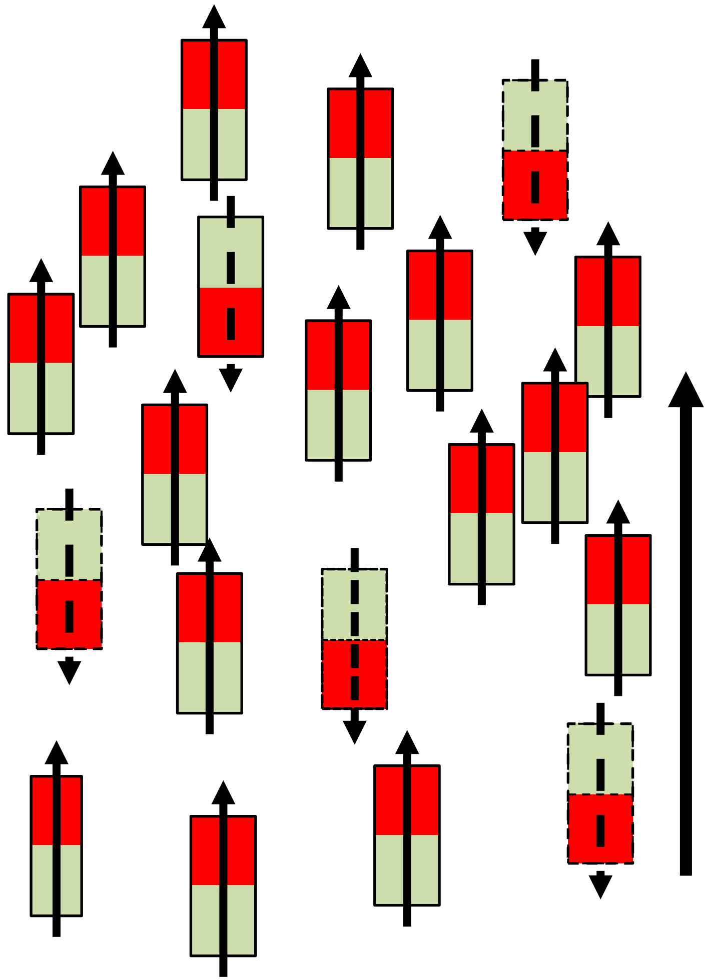




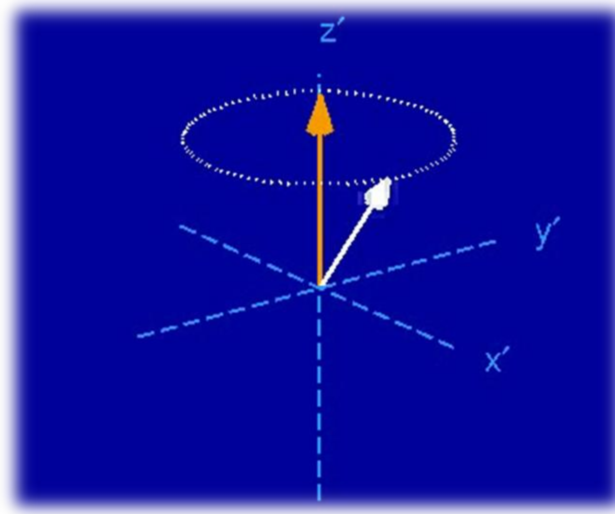
# Magnetic Resonance - polarization




Polarization → macroscopic magnetization



Precession around static field




Frequency is in MHz
(radio-frequency range)

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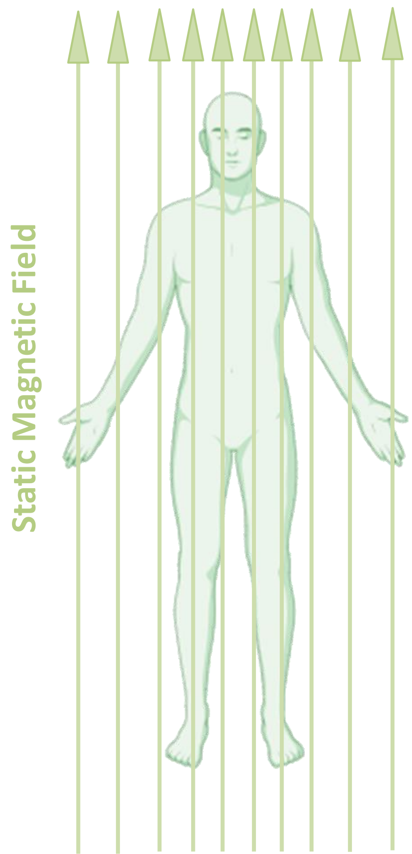
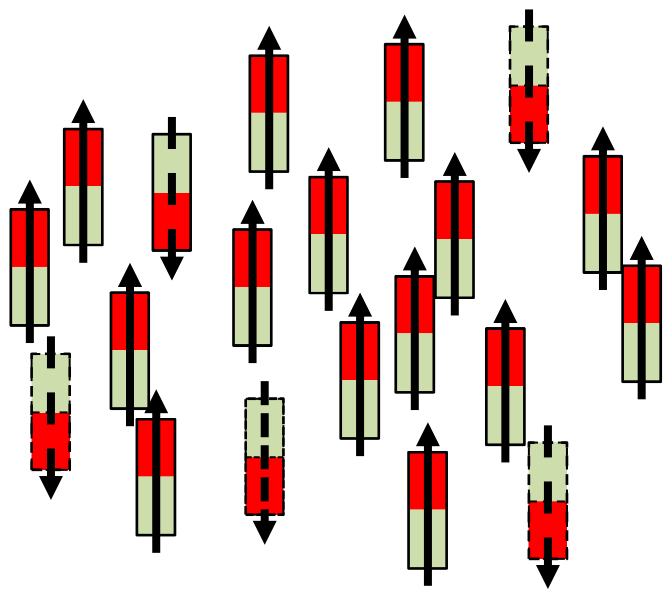
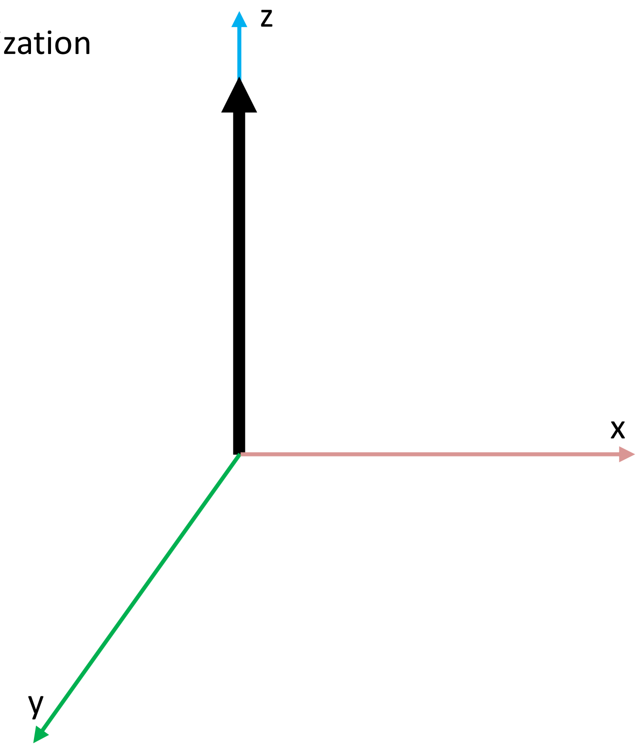
# Magnetic Resonance - polarization

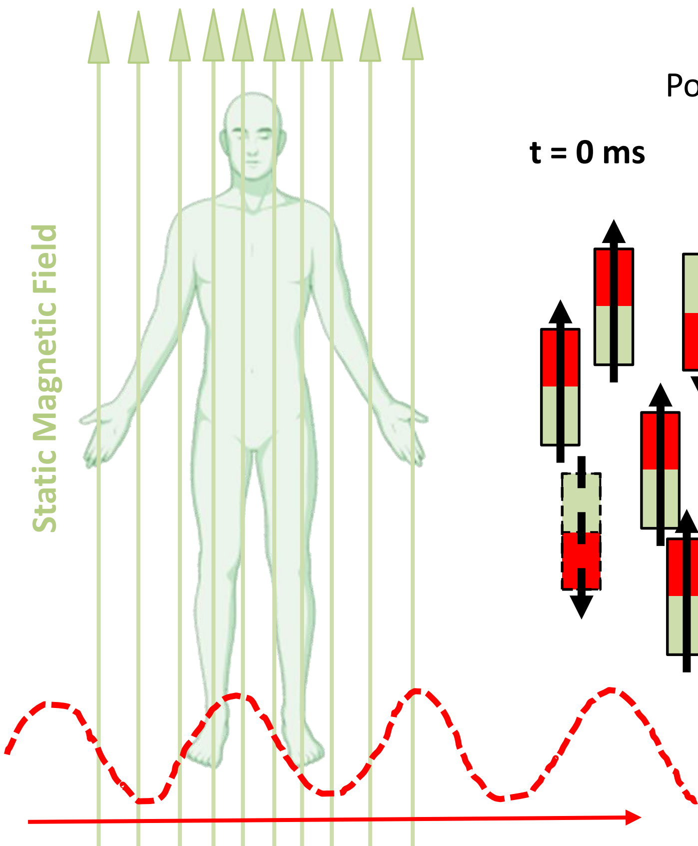



Polarization → macroscopic magnetization

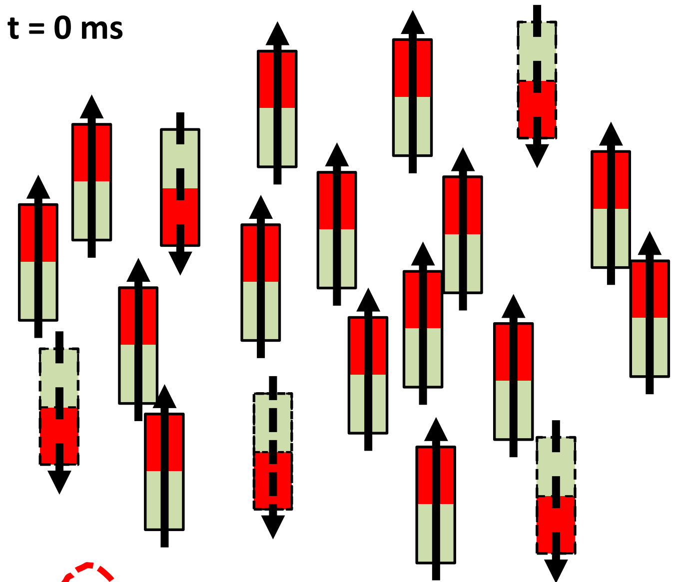


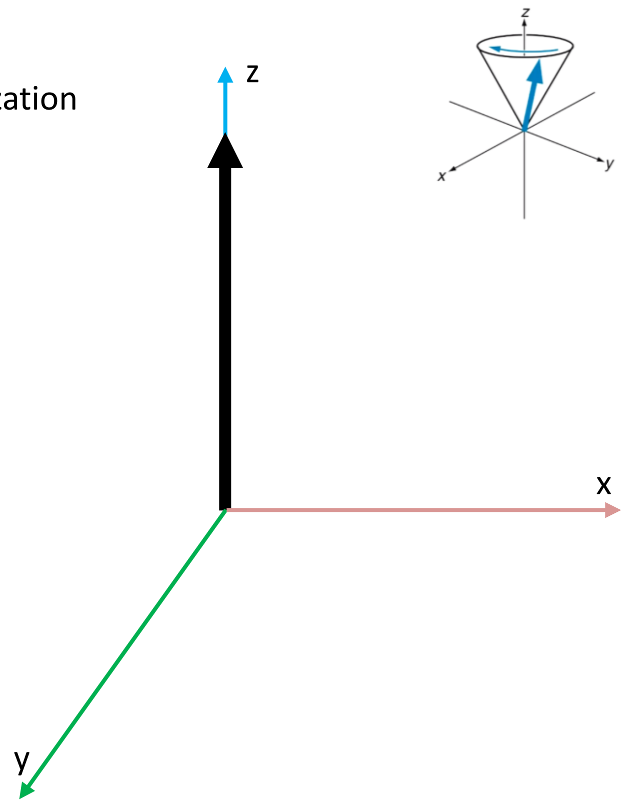


# Magnetic Resonance - polarization



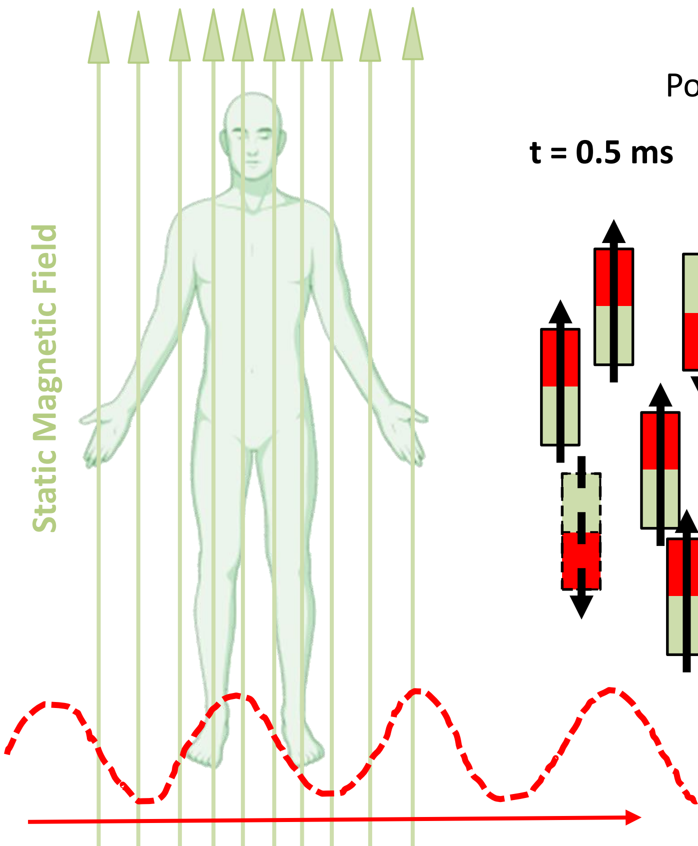

Polarization → macroscopic magnetization



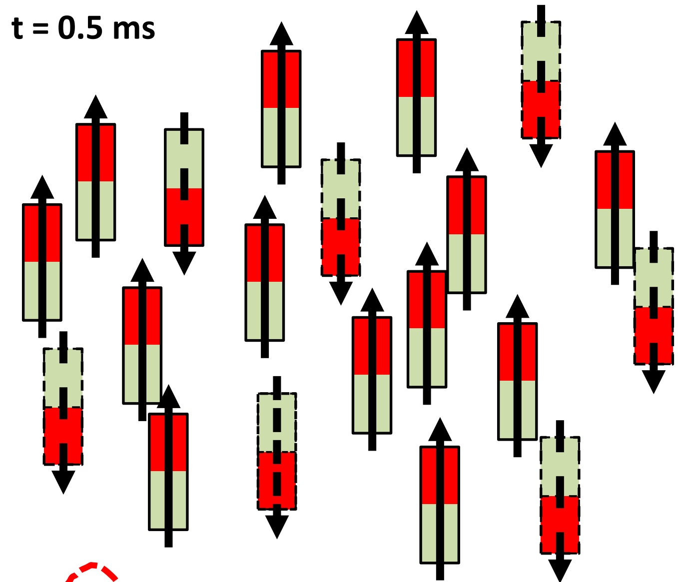

**Apply "small" magnetic field oscillating at the same radiofrequency**

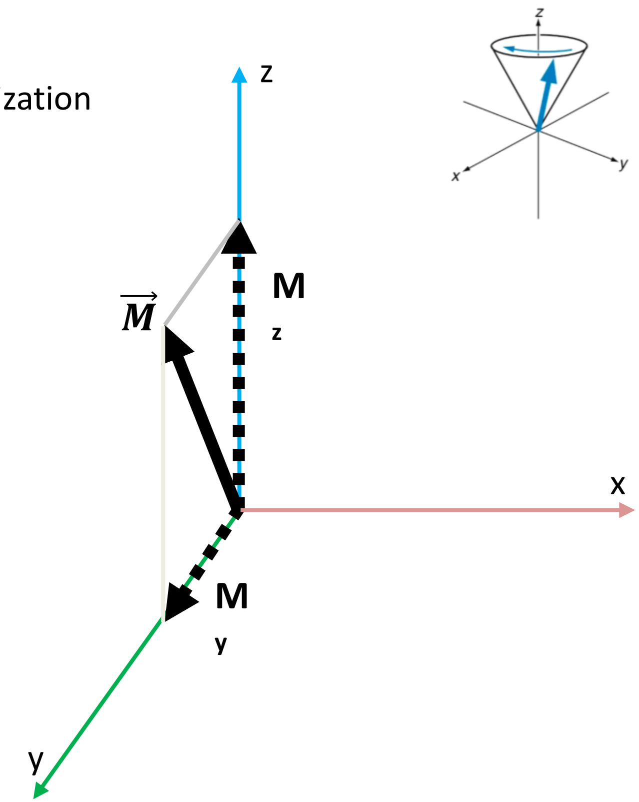
# *Magnetic Resonance – excitation*




Apply "small" magnetic field oscillating at the same radiofrequency

Polarization → macroscopic magnetization

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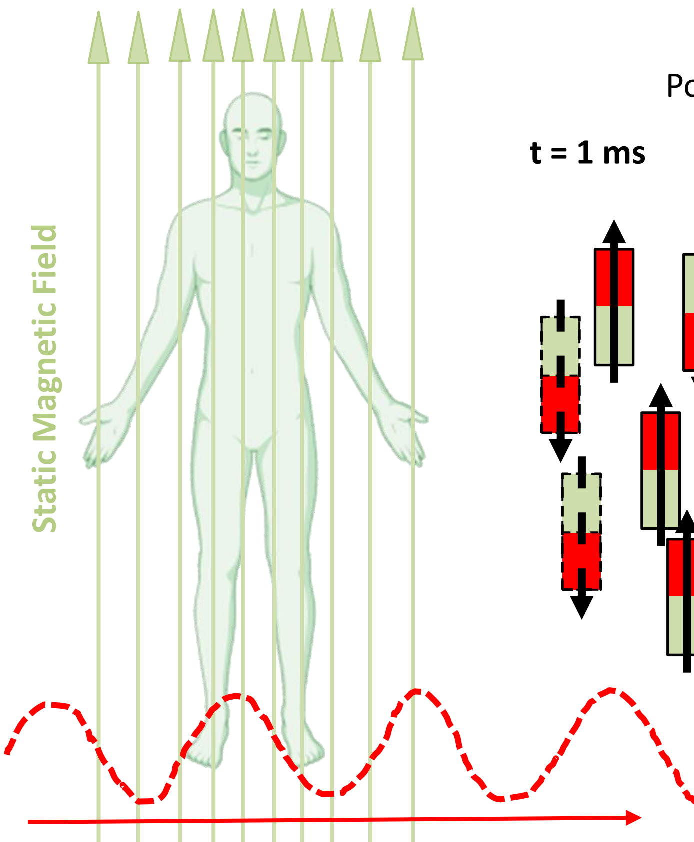
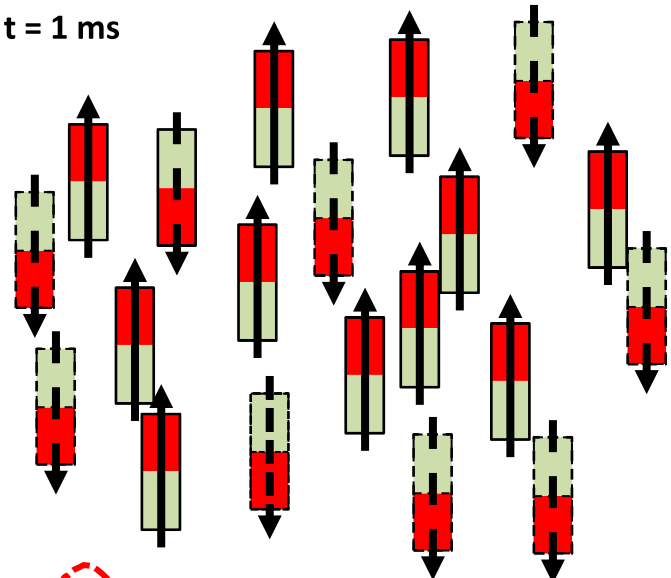
# Magnetic Resonance – excitation

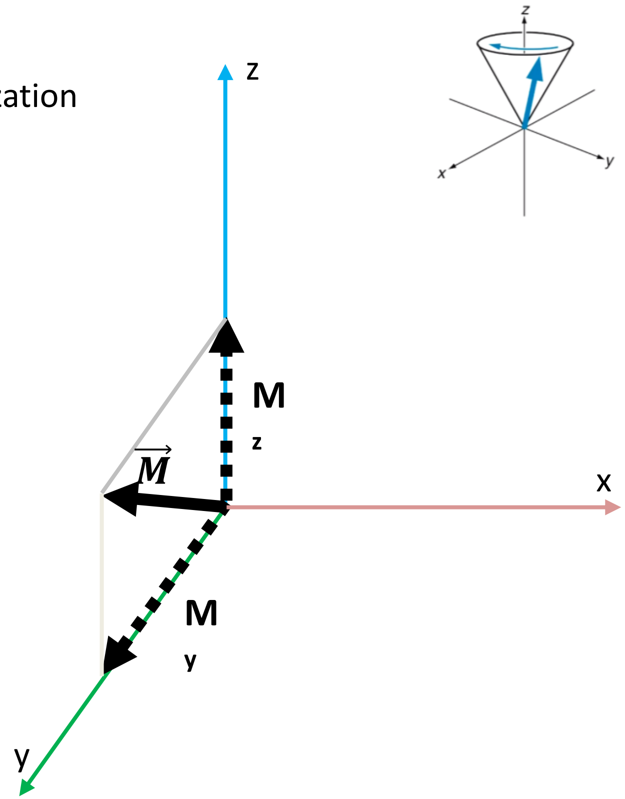



Apply “small” magnetic field oscillating at the same radiofrequency

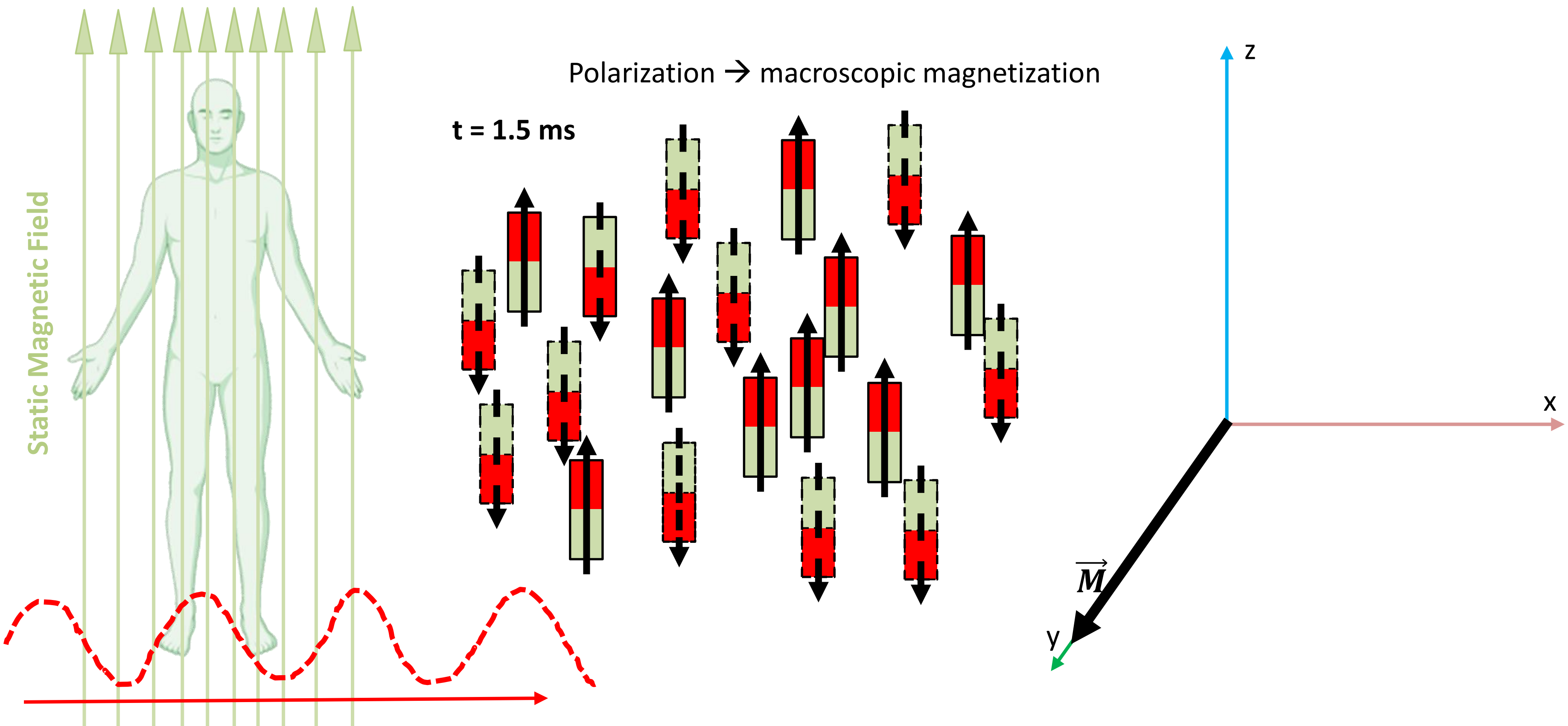
Polarization → macroscopic magnetization

t = 1 ms





# Magnetic Resonance – excitation




**Apply "small" magnetic field oscillating at the same radiofrequency**

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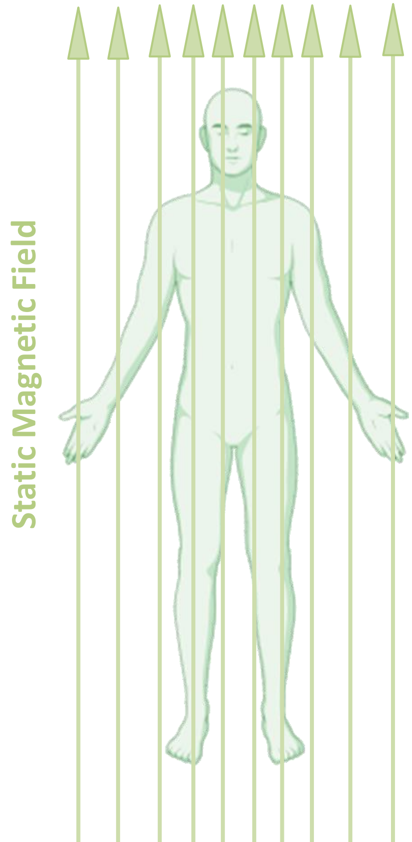
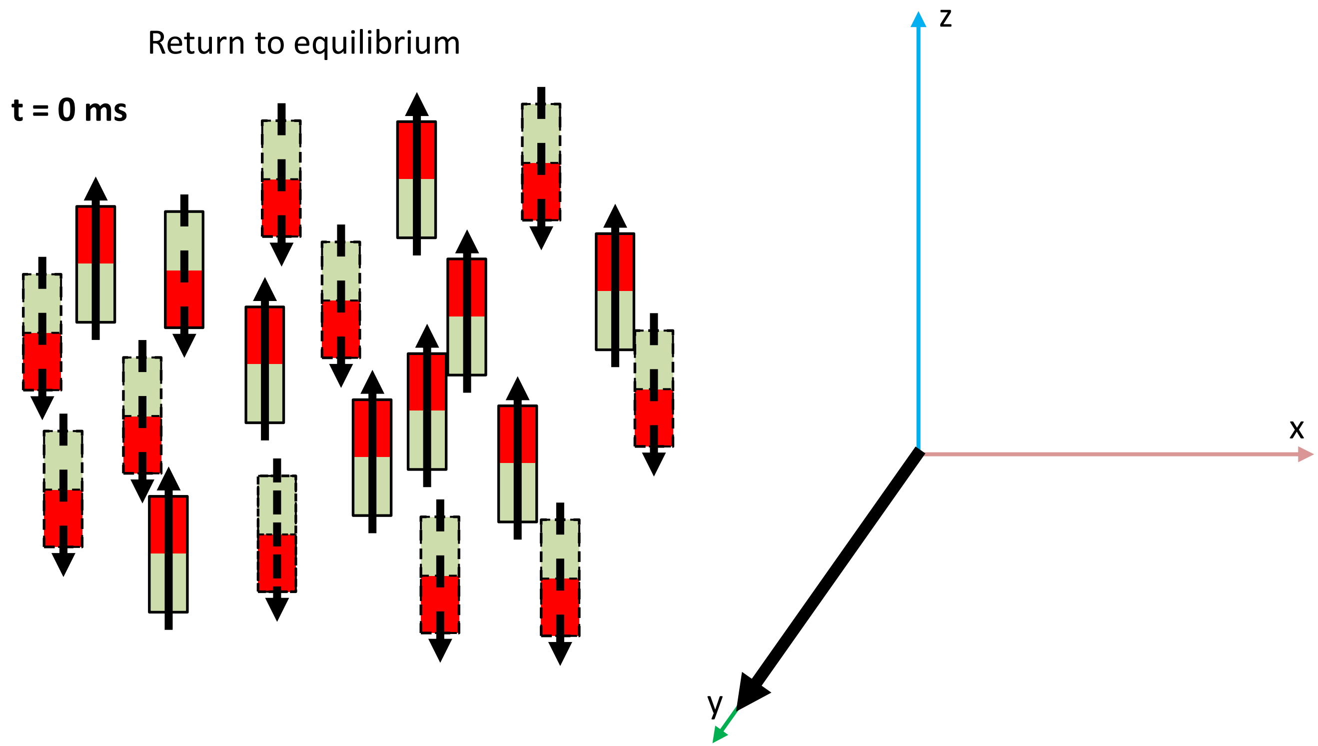
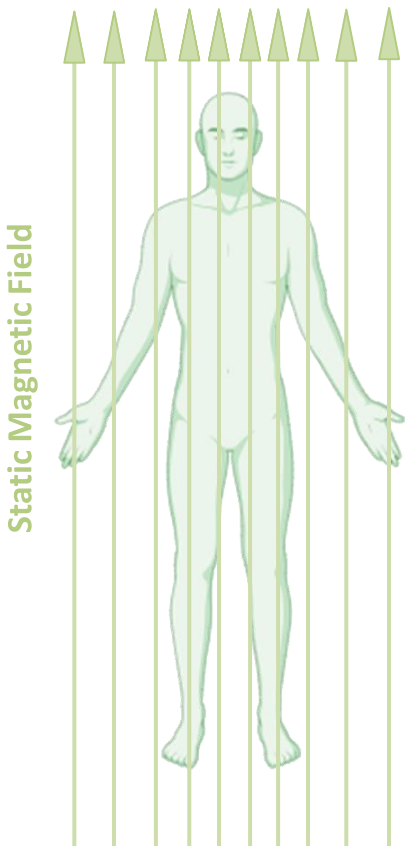
# Magnetic Resonance – relaxation



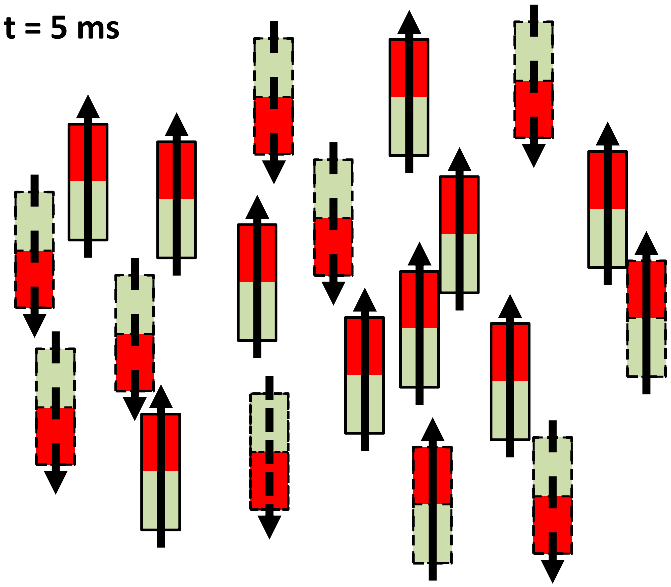

Stop applying oscillating magnetic field

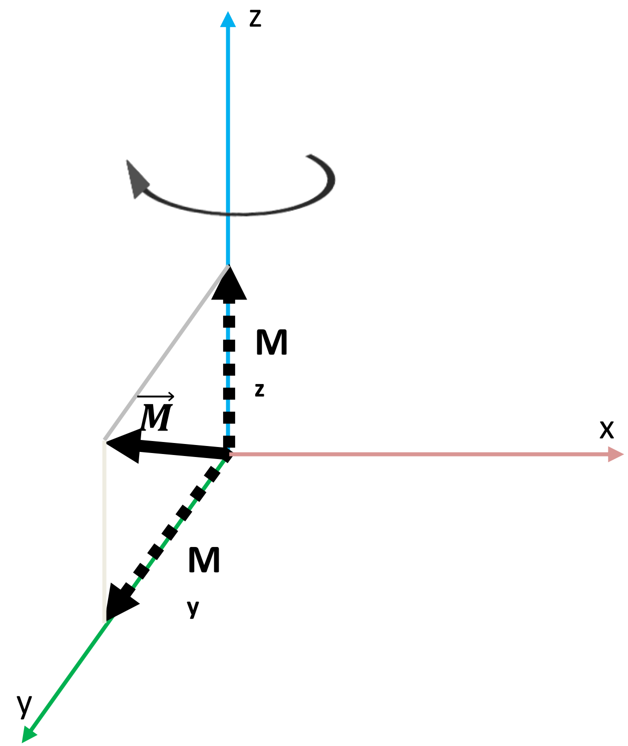
# *Magnetic Resonance – relaxation*



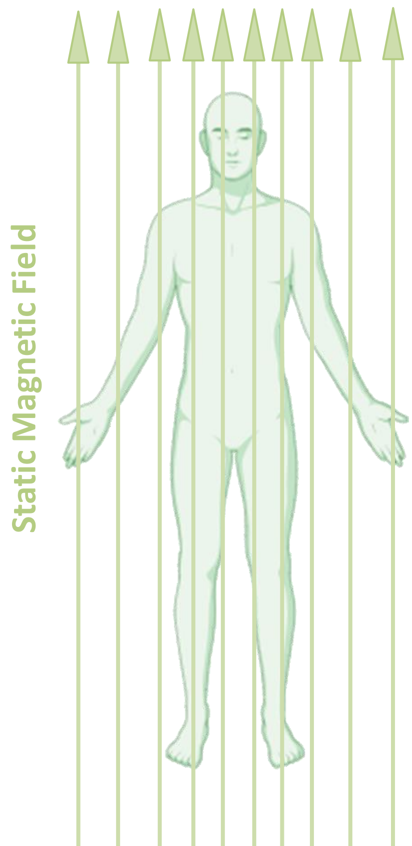

Return to equilibrium

t = 5 ms

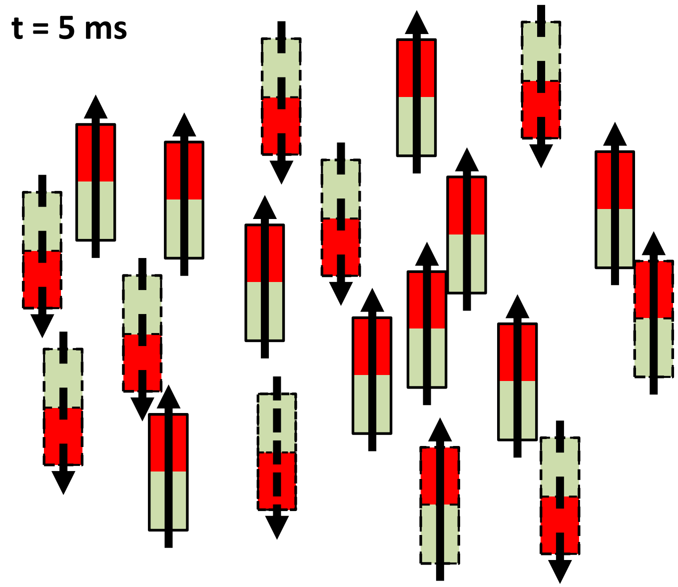


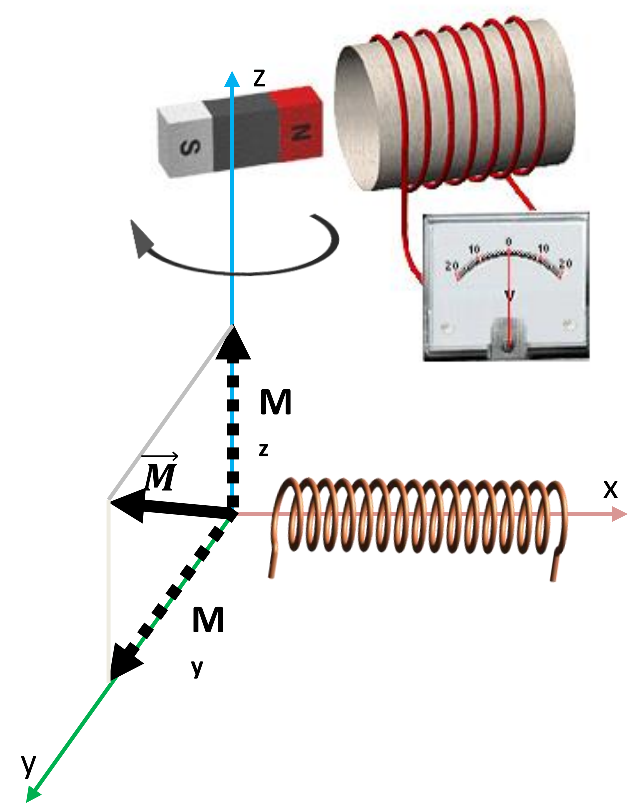


# *Magnetic Resonance – relaxation*

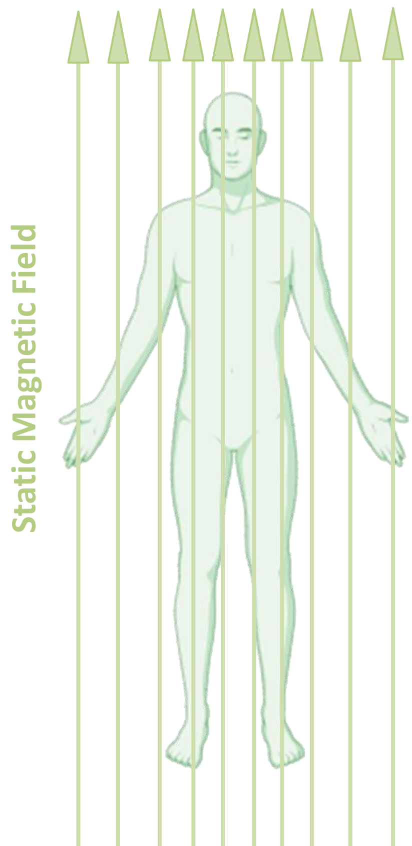


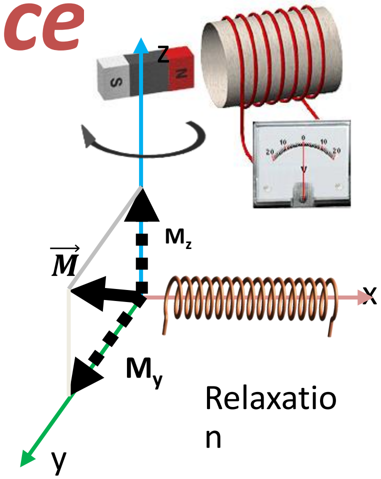

Return to equilibrium

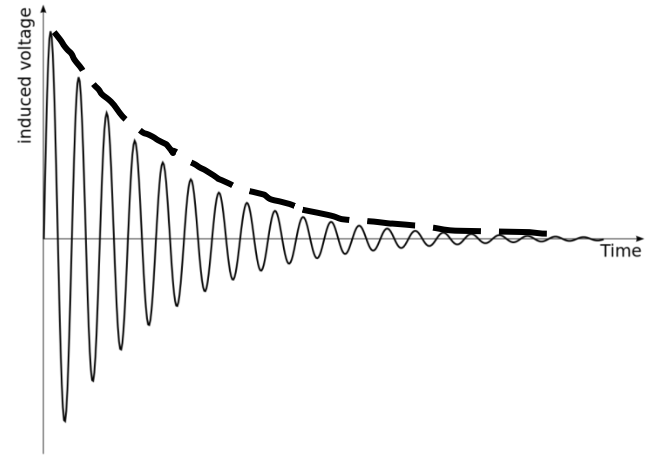


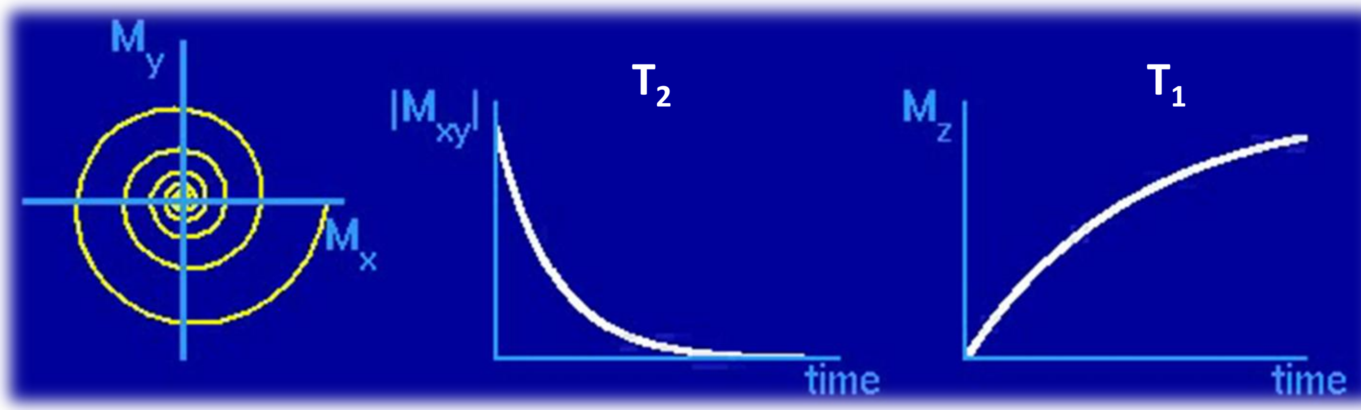



# Magnetic Resonance



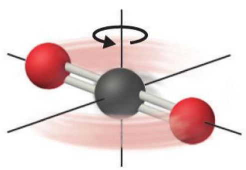



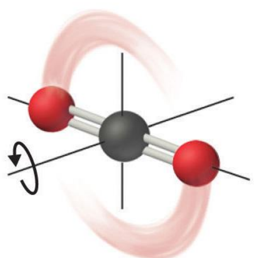



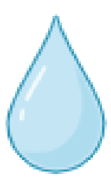



# *Relaxation properties depend on multiple factors*

**Molecular tumbling**







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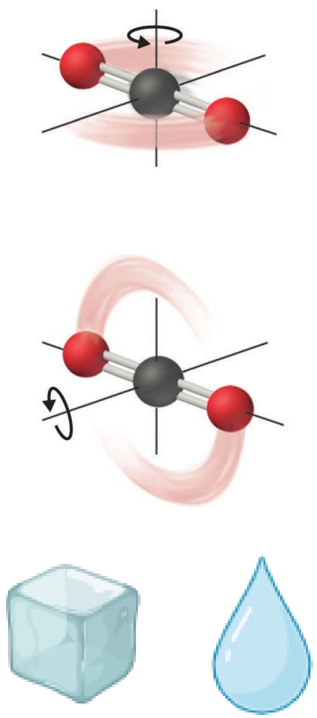
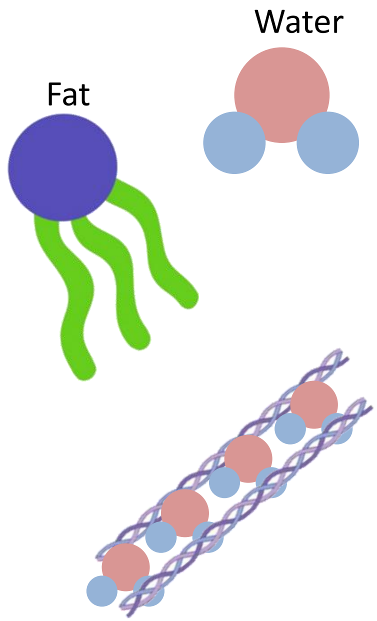
# Relaxation properties depend on multiple factors

**Molecular tumbling**



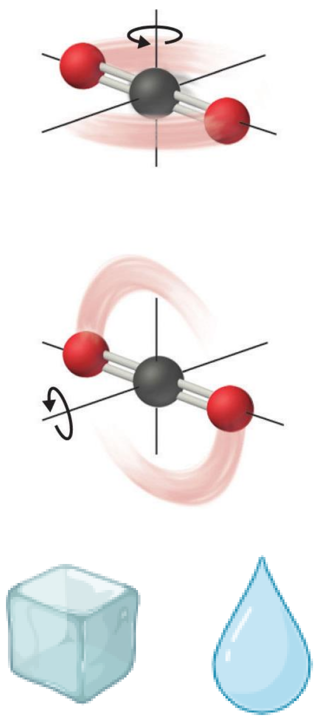
**Chemical environment**




Water bound to
collagen proteins

# Relaxation properties depend on multiple factors

**Molecular tumbling**



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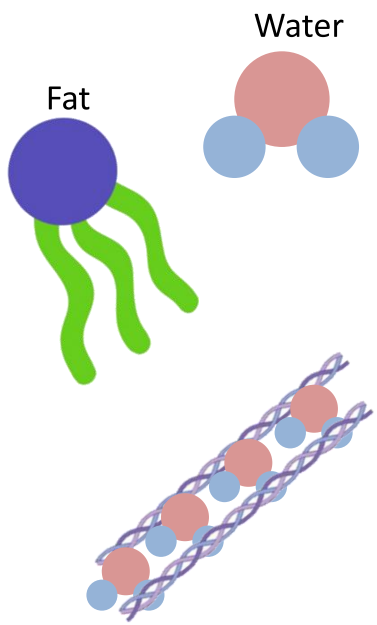
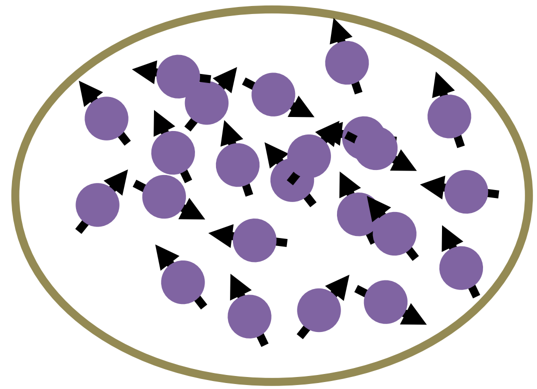
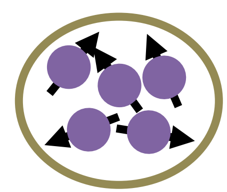



Water bound to collagen proteins

**Physical environment**



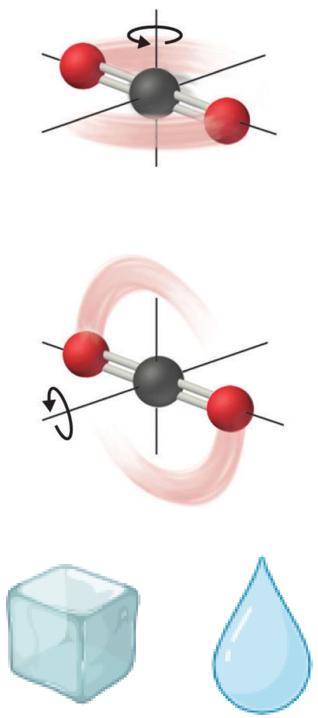
Free Water (big pore)



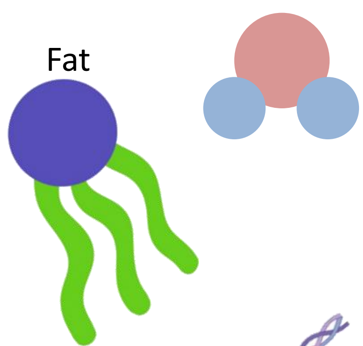
Water restricted in small pore

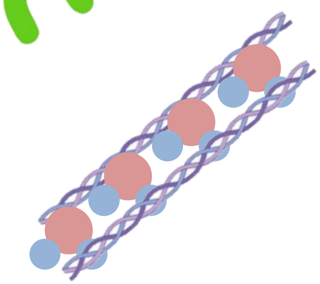
# *Relaxation properties depend on multiple factors*

**Molecular tumbling**



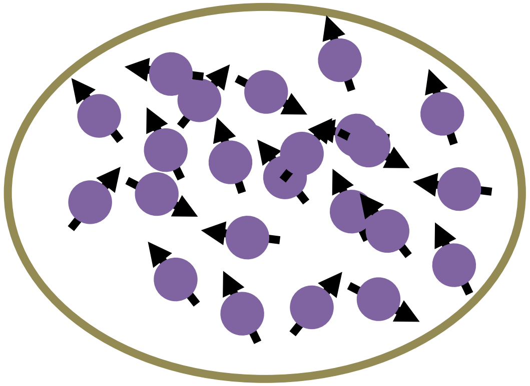
**Chemical environment**



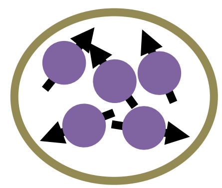



Water bound to collagen proteins

**Physical environment**

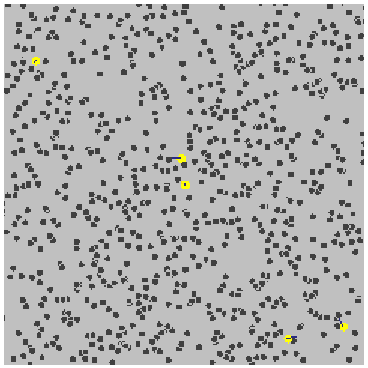


Free Water (big pores)

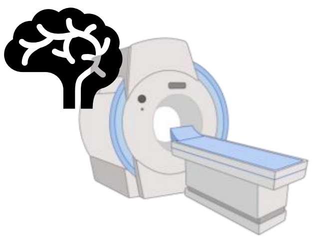


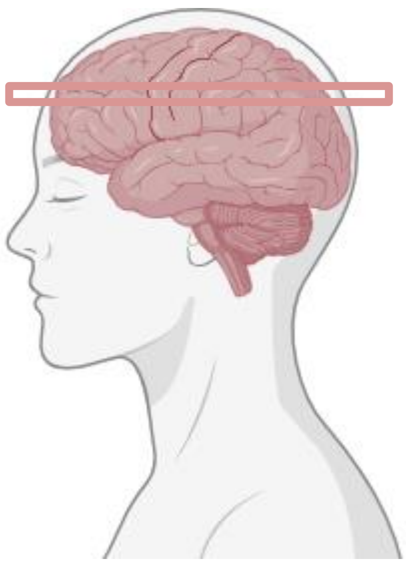
Water restricted in small pores

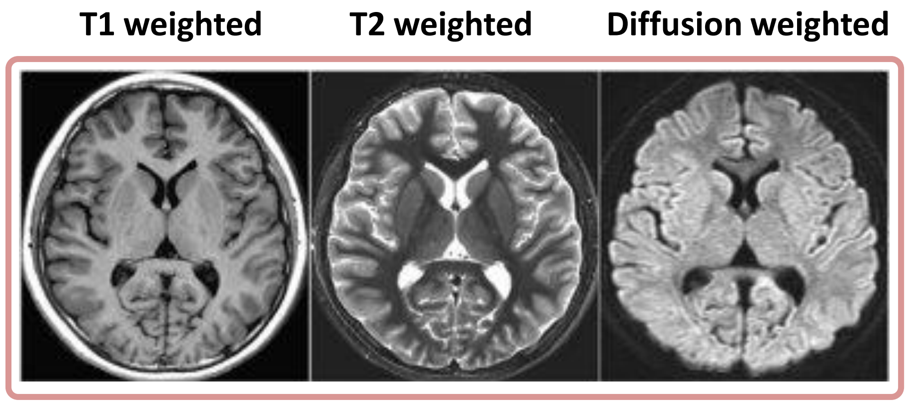
**Mobility (diffusion)**



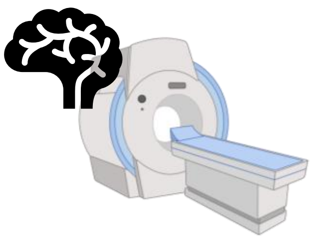
# Magnetic Resonance Imaging - contrasts

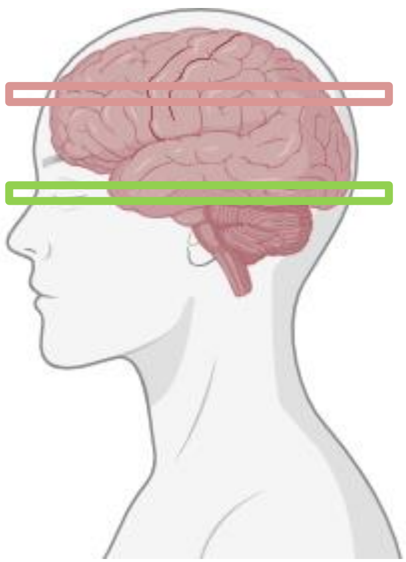


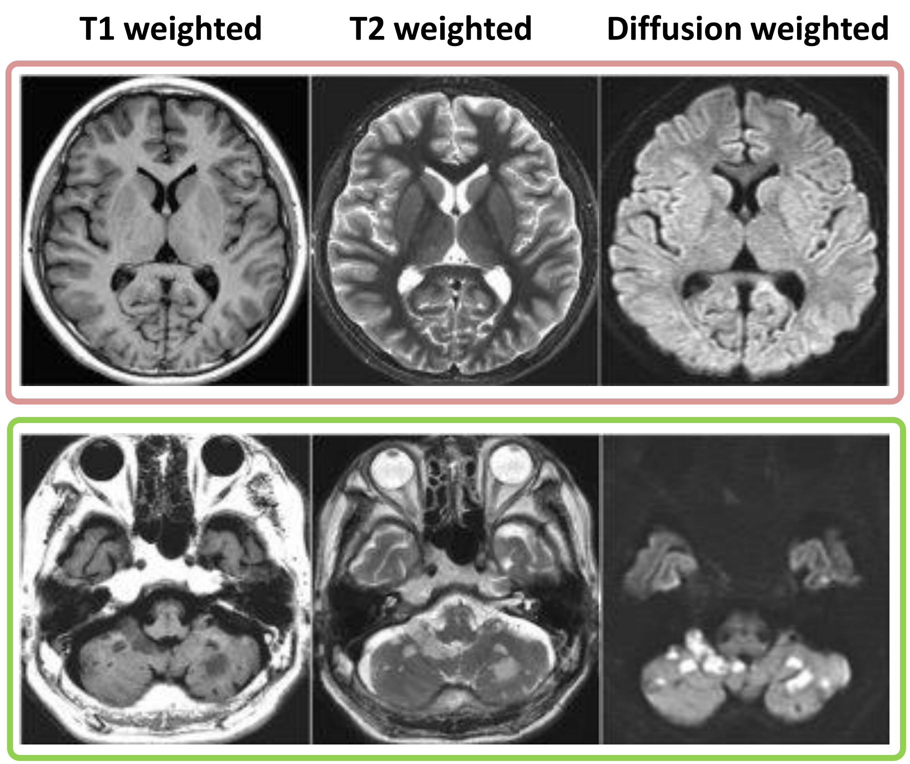




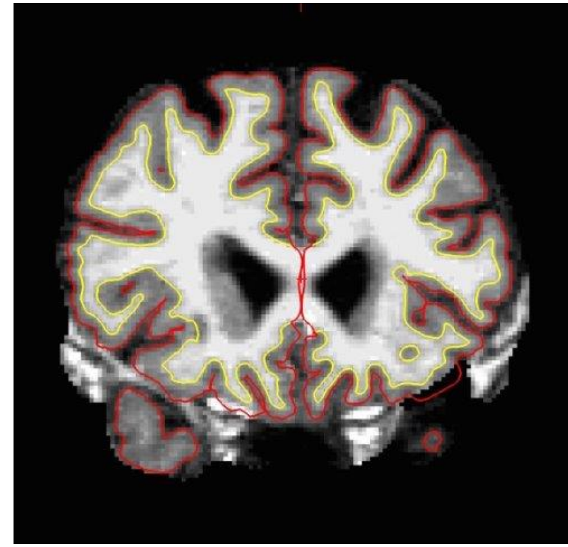
# *Magnetic Resonance Imaging - contrasts*







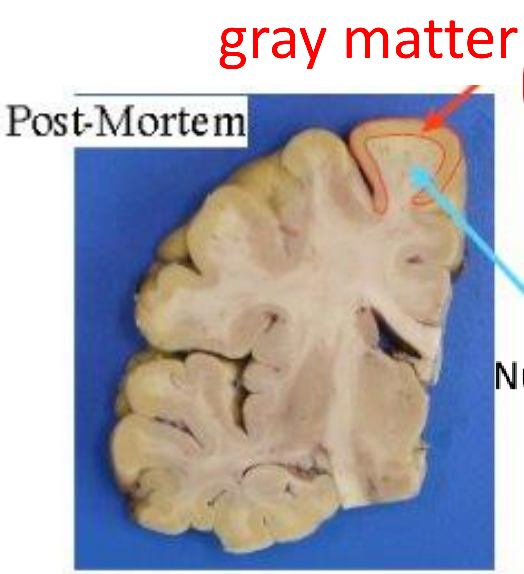
# The brain-constituent tissues

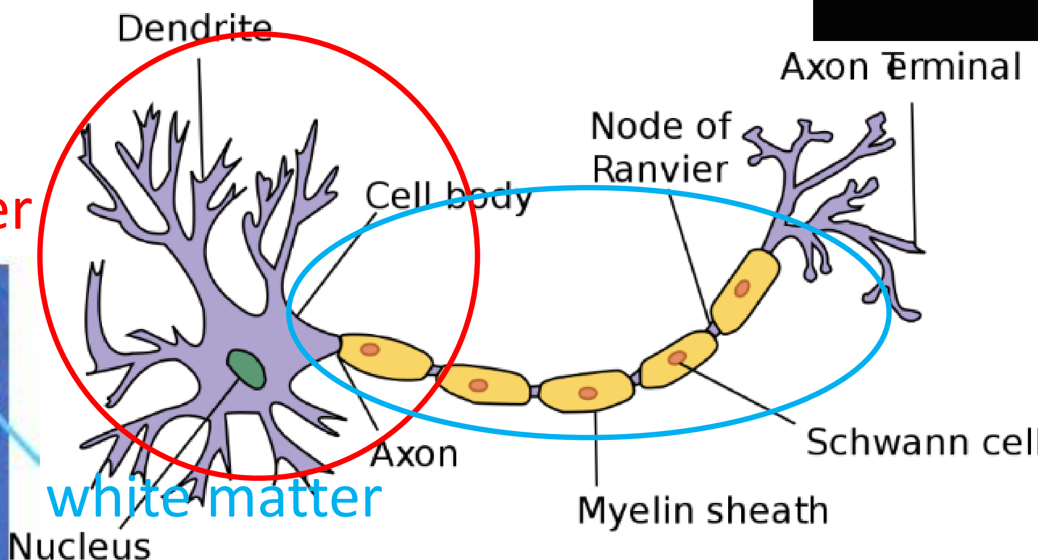


The brain is full of neurons.
These are organized into two types of "tissues":

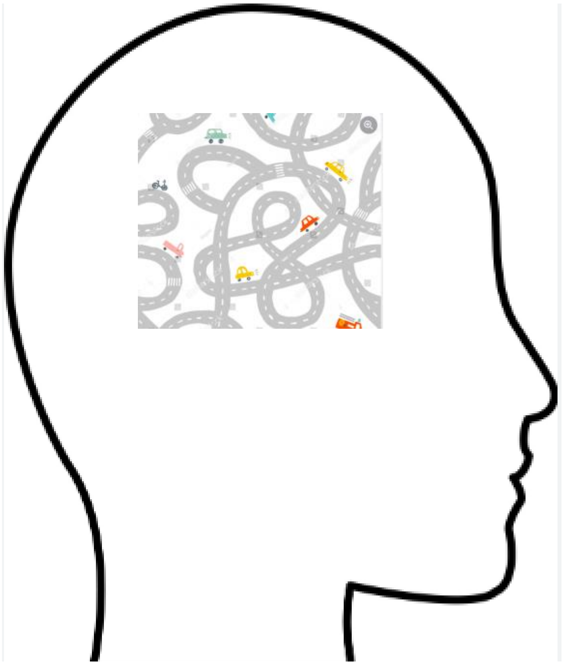
-gray matter

-white matter



Brain contains the nerve fibers of neurons and conducts electrochemical signals to other neurons. These fibers are like ***highways*** that connect major cities together. When the highways are in better condition, or wider, or more in number, then many cars travel quickly between cities. However, if the highways are in poor condition, or narrower, or fewer in number, then fewer cars can travel and will do so at slower speeds.



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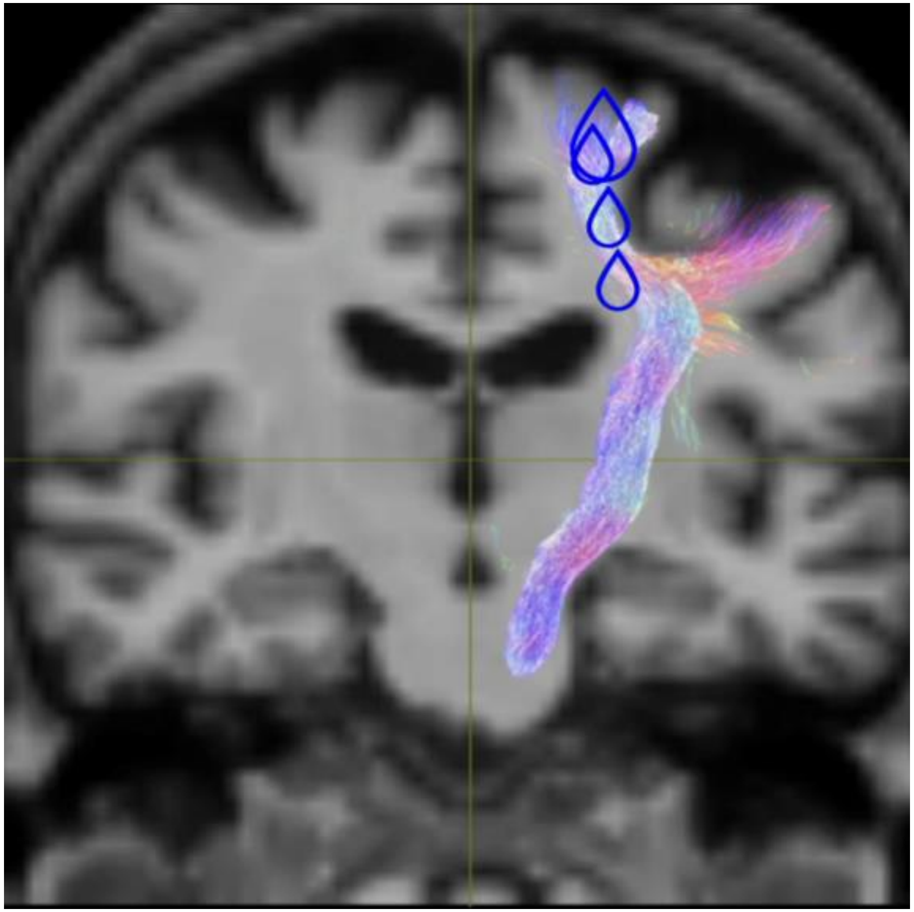
*In collaboration with Dr. Laura Ludovica Gramegna, neuroradiologist*
*Hospital del Mar, Barcelona, Spain*



Our bodies are filled with water molecules moving/diffusing through the cells and tissues of every organ—including the brain and each of its neurons.

Diffusion-weighted imaging can capture that movement at the microscopic level.

# What is diffusion?

The fick's first law $$J = -D\frac{dC}{dx}$$

J : diffusion flux (mol $m^{-2}$ $s^{-1}$

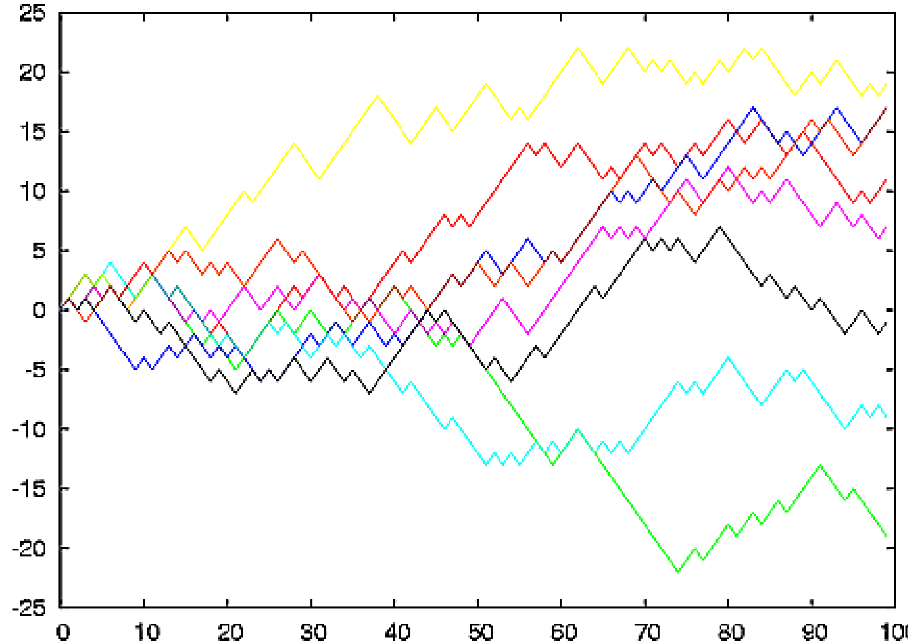
D : diffusion coefficient (diffusivity, $m^2/s$)

C : concentration ($mol/m^3$)

x : position (m)

Molecules have a random motion due to thermal energy. They collide causing a net displacement. Displacement described by D. The mean quadratic displacement:

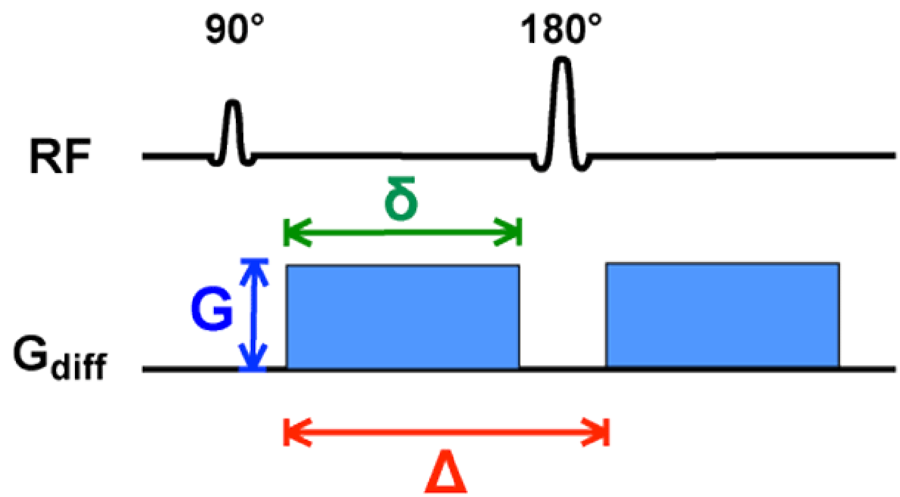
$\langle (r - r_0)^2 \rangle = 6Dt$



# Diffusion MRI

Stejskal and Tanner 1965
Pulsed gradient spin-echo sequence

Diffusion MRI is a technique that exploits the diffusion of water molecules in brain tissues to generate contrast in MR images.

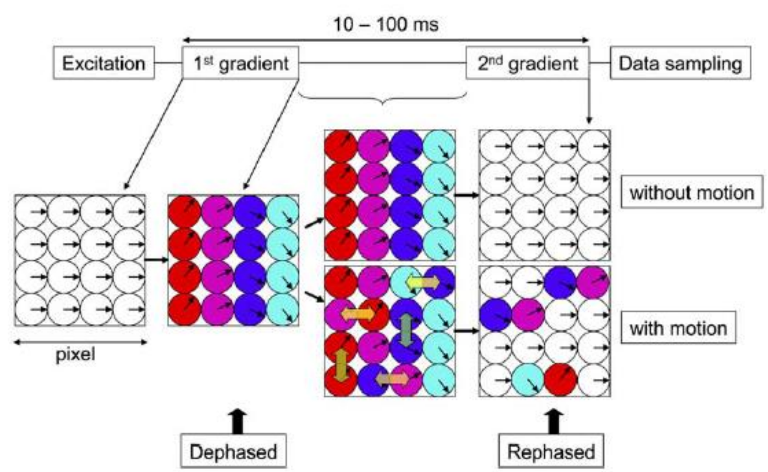



Signal is given by

$$S = S_0 \cdot exp(-bD)$$

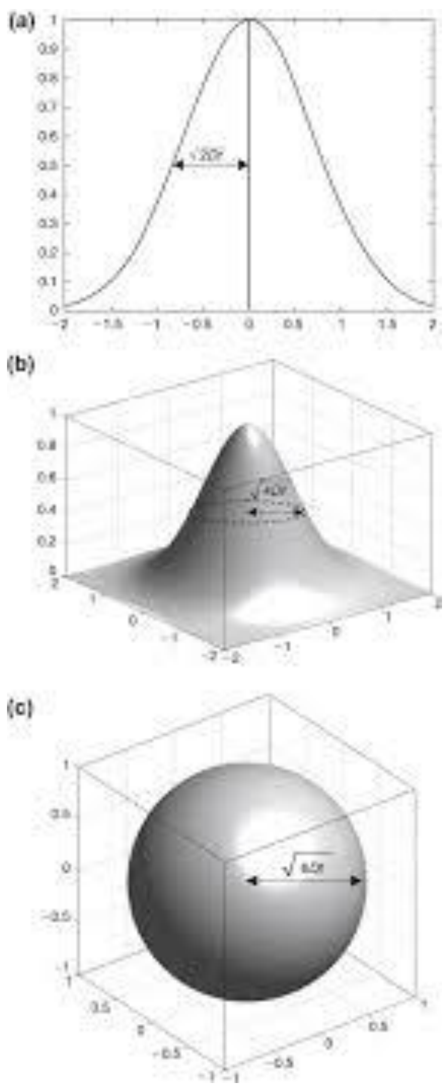
with $b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right)$

$D$ is the diffusion coefficient




The 1° gradient after excitation generates a phase shift to signals. During the $\Delta$ period spins that diffuses acquire an additional phase shift. Thus, the 2° diffusion gradient (equal to the first one) can exactly re-align only those spins that did not diffuse.

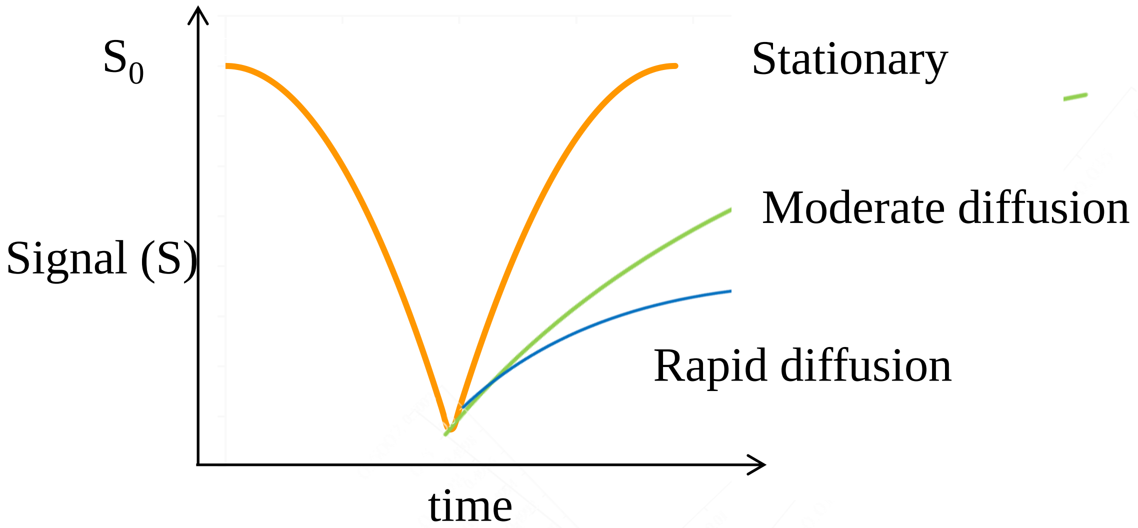
# Diffusion MRI




Gaussian distribution of the mean quadratic displacement:

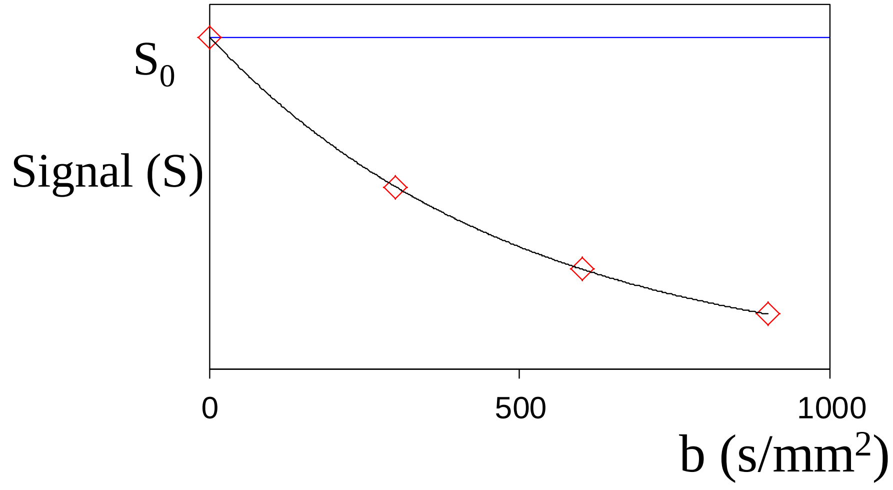
a) in 1D
b) in 2D
c) In 3D

# Diffusion MRI




$$S = S_0 \exp\left(-bD\right)$$

$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \delta/3\right)$$




It is valid for free diffusion

# How to estimate D?

Known:

b-value: diffusion weighting

$$D = -\frac{1}{b}\ln\left(\frac{S}{S_0}\right)$$

Unknown:

$S_0$: unweighted signal

D=diffusion coefficient

How many measurements to estimate D?

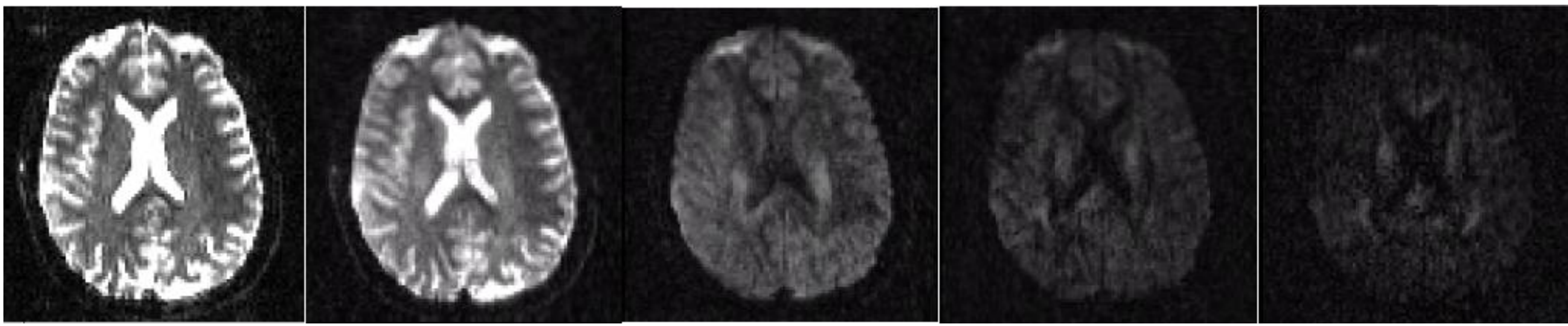
We have 2 unknowns so we need at least 2 measurements

One b-value=0 image (for $S_0$)

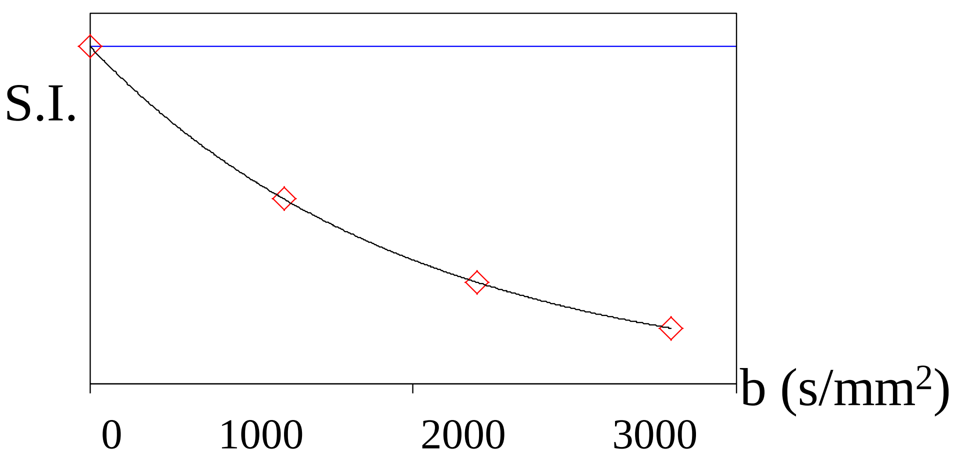
And one b>0 image (for D)

# Mean diffusion (MD) map

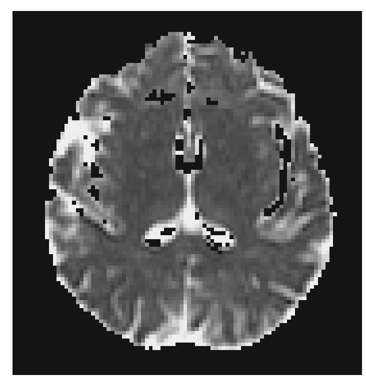
$T_2$-weighted        Diffusion-weighted



b = 0,   300,   1000,   2000   3000(s/mm$^2$)

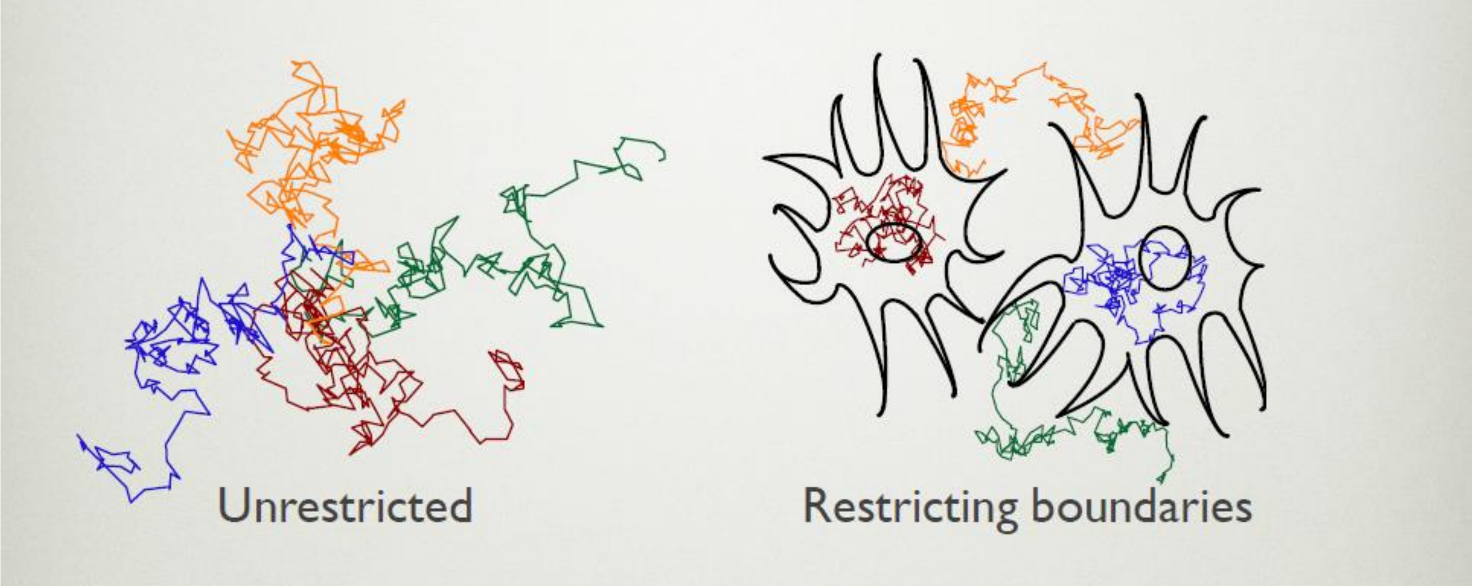



MD



## Free and  restricted diffusion

Diffusing molecules follow a "random walk"
Pathway is restricted by tissue boundaries/membranes



## Isotropic restricted diffusion

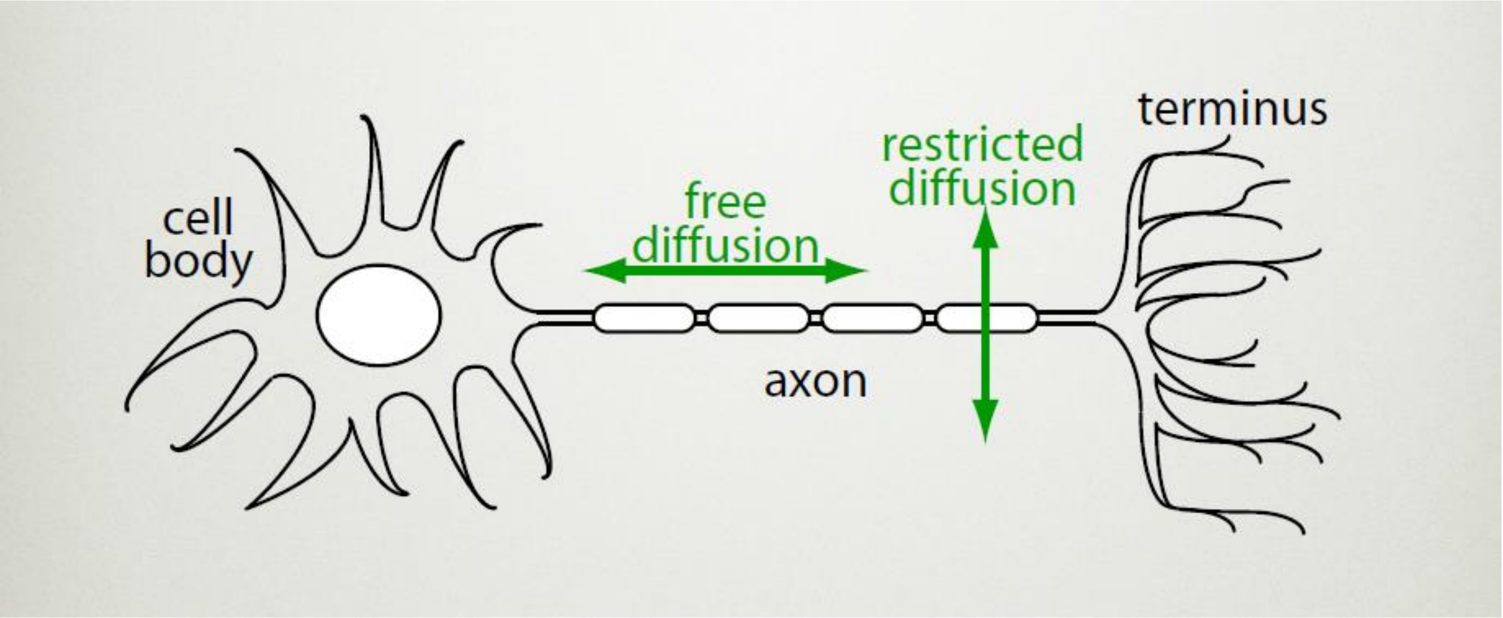
Isotropic matter has physical properties that do not depend on the direction of analyis: isotropic matter has the same characteristics in all space directions.

## Anisotropic restricted diffusion

Anisotropy is the opposite than isotropy. With anisotropy, physical properties of matter depend on the space direction along with the analysis is run. Physical properties of anistropic matter depend on the direction of analysis.

# Diffusion anisotropy

Some microstructures have an intrinsic orientation:
Water can diffuse more freely along white matter fibers (axons) than across them. Within the axons, diffusion of water molecules is hindered in the perpendicular direction and aided in the parallel direction of the axons. Thus, the direction of greater diffusion is parallel to the axon axis.



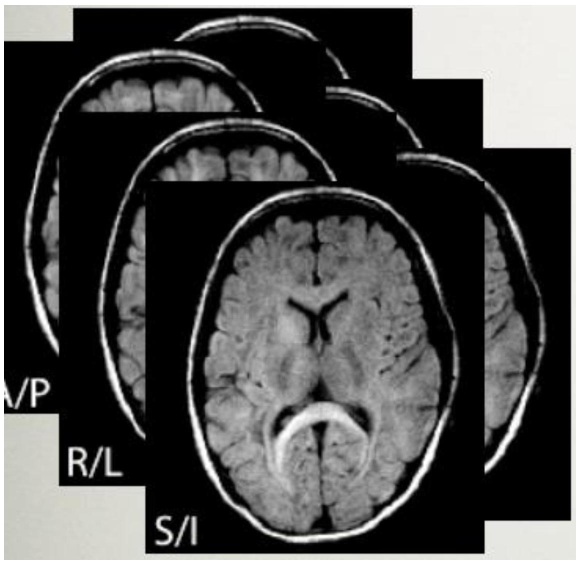
## Diffusion Tensor Imaging

To measure diffusivity in an anisotropic environment we have to consider the diffusion coefficient as a tensor and not any more as a scalar coefficient.
The diffusion tensor (D) is a symmetric matrix 3x3 that fully describes molecular mobility along each direction and correlation between these directions. We need to resolve 6 elements of the matrix.

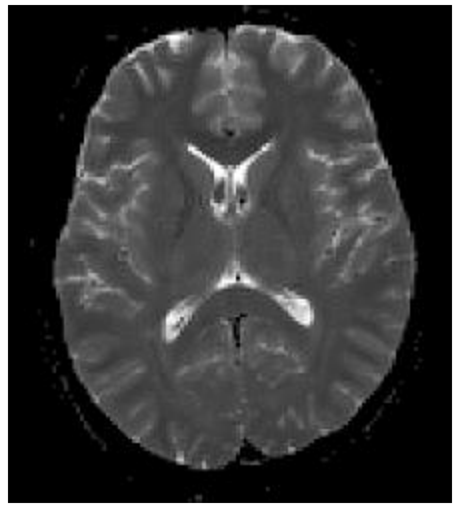
$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

# Diffusion Tensor Imaging (DTI)

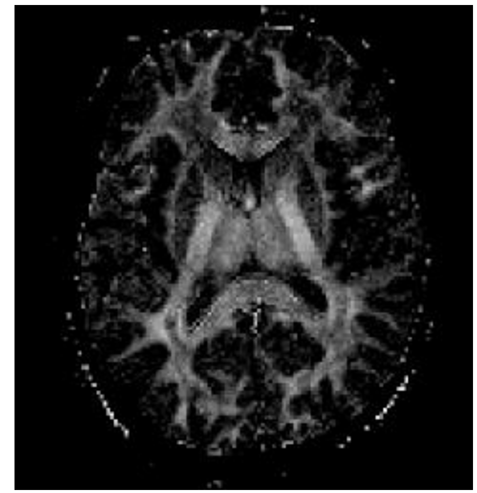
We have to acquire multiple diffusion directions, plus an unweighted (b=0) image, and fit model of interest in each voxel.




diffusion weighted along different directions



b=0 (no diffusion weighting)



Tensor-based maps

# Diffusion Tensor Imaging (DTI)

Diagonalization of **D** allows to determine 3 eigenvectors **($V_1$, $V_2$, $V_3$)** and 3 eigenvalues **($\lambda_1$, $\lambda_2$, $\lambda_3$)** of diffusion tensor **D**

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} = \begin{pmatrix} V_{1x} & V_{1y} & V_{1z} \\ V_{2x} & V_{2y} & V_{2z} \\ V_{3x} & V_{3y} & V_{3z} \end{pmatrix} \cdot \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \cdot \begin{pmatrix} V_{1x} & V_{2x} & V_{3x} \\ V_{1y} & V_{2y} & V_{3y} \\ V_{1z} & V_{2y} & V_{3z} \end{pmatrix}$$

Eigenvectors represents the 3 principal diffusion directions and eigenvalues are the associated diffusivity values (diffusion coefficients) of water molecules inside the brain.

Eigenvectors are mutually perpendicular and the corresponding eigenvalues are ordered increasingly: $\lambda_1>\lambda_2>\lambda_3$

Eigenvector ($V_1$) corresponds to the higher eigenvalue ($\lambda_1$) which represents the maximum diffusion direction of water molecules.

# Quantitative diffusion maps

From the diffusion tensor we can calculate useful maps of scalars:
Mean diffusivity (MD), mean of eigenvalues or **D** trace:

$MD=(\lambda_1+\lambda_2+\lambda_3)/3$

Fractional anisotropy (FA), Eigenvalues Variance (normalised):

$FA = \sqrt{3\sum_{i=1}^{3}(\lambda_i - <\lambda>)^2} / \sqrt{2\sum_{i=1}^{3}\lambda_i^{\ 2}}$ FA in [0,1]

It is an index of anisotropy

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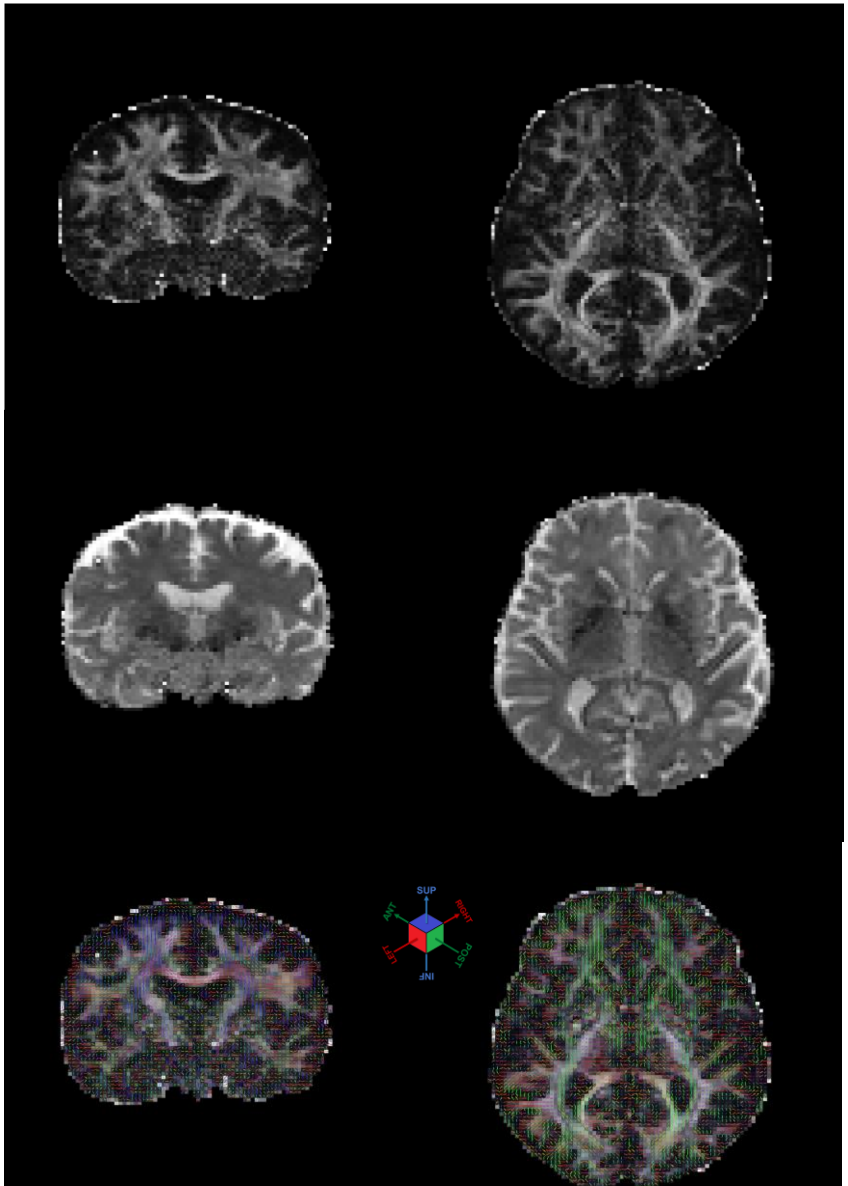
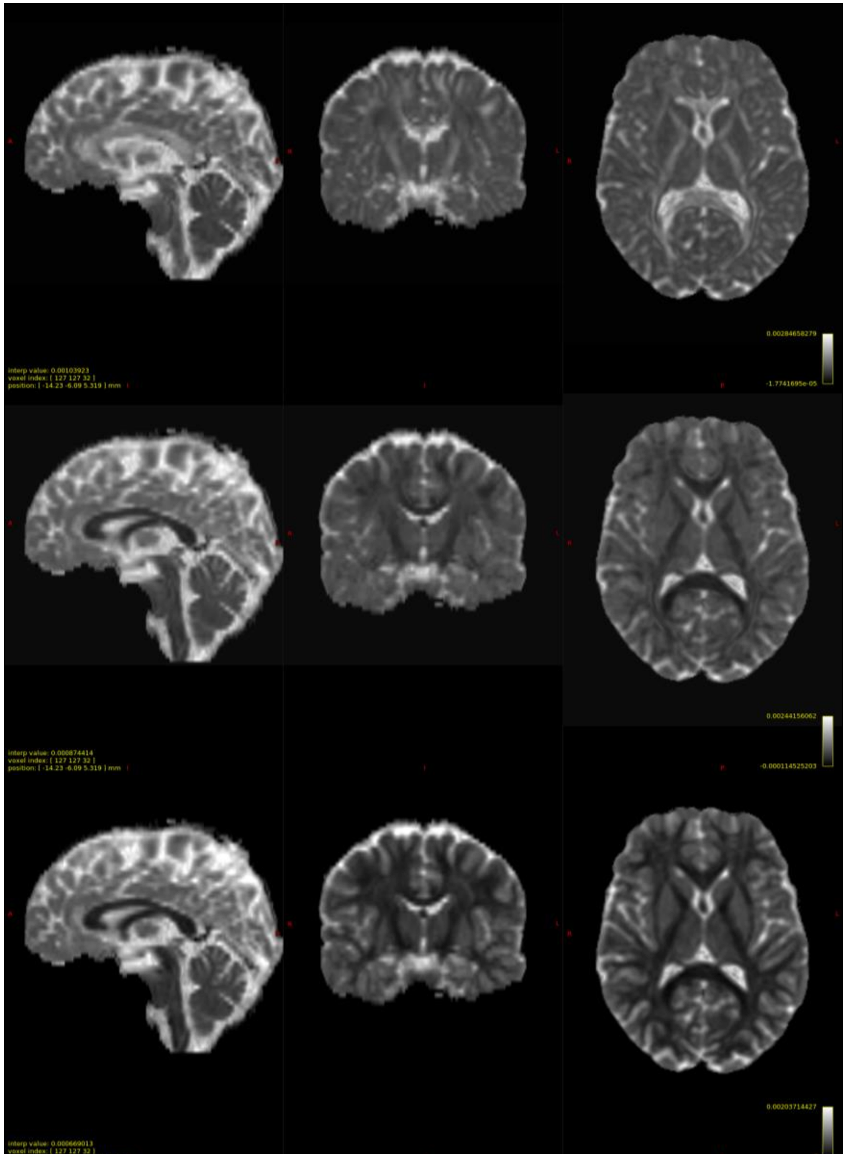
# Diffusion -weighted MRI - Quantitative diffusion maps




A: Fractional anisotropy map;
B: MD mean diffusivity map;
C: vector-coded map.

# Diffusion -weighted MRI - Quantitative diffusion maps

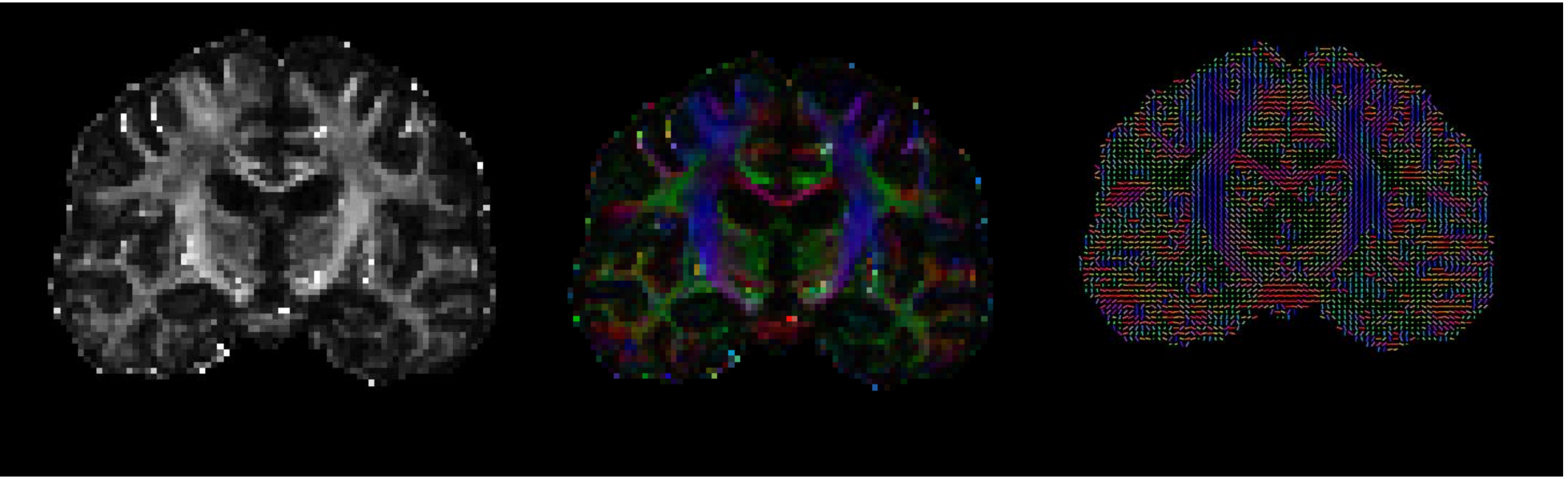


Lambda 1 map

Lambda 2 map

Lambda 3 map

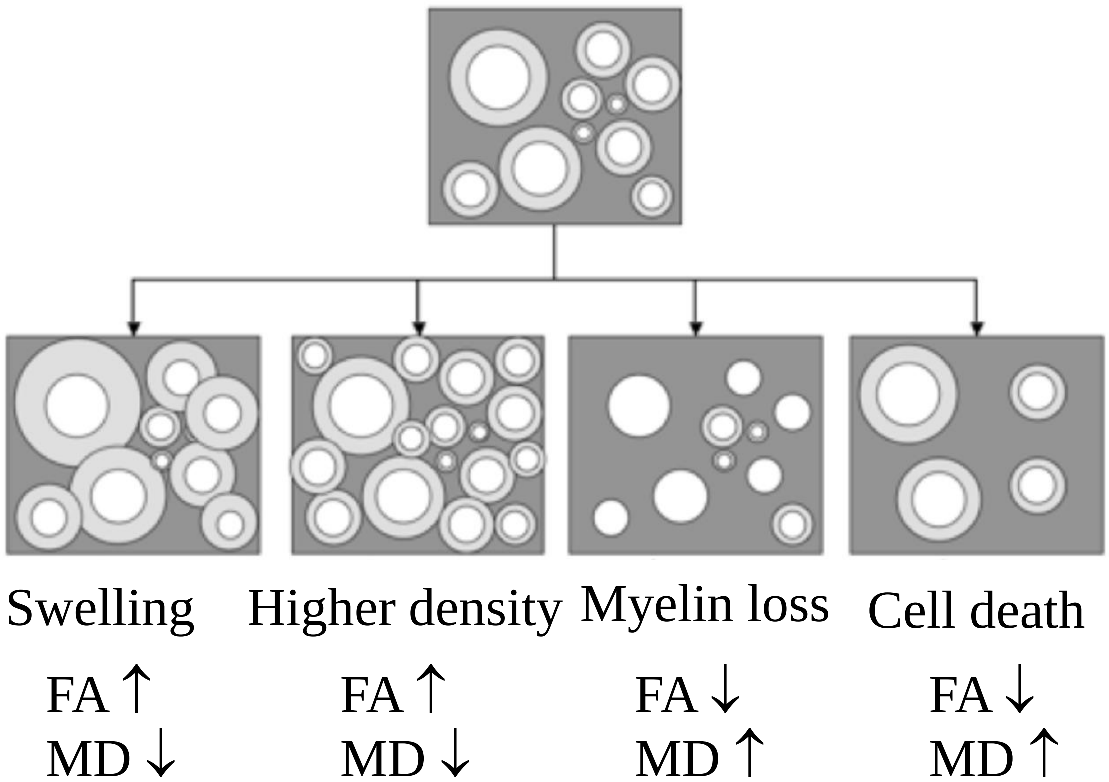
# Quantitative diffusion maps



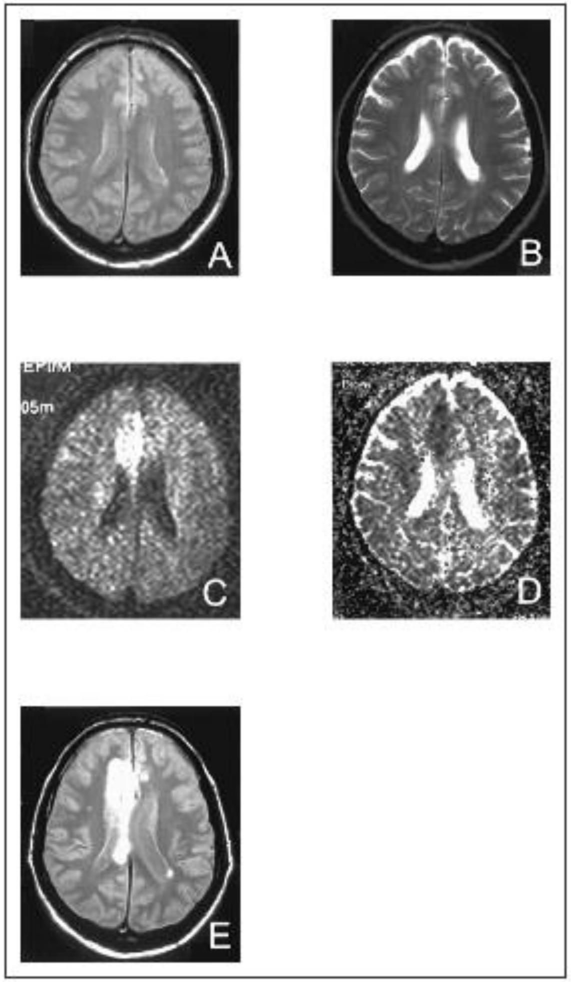
A: FA map; B: color-coded FA; C: vector-coded map.

# Effects on FA and MD quantitative map

Different configurations may have same effect on FA, MD



# FA and MD quantitative map for clinical purposes

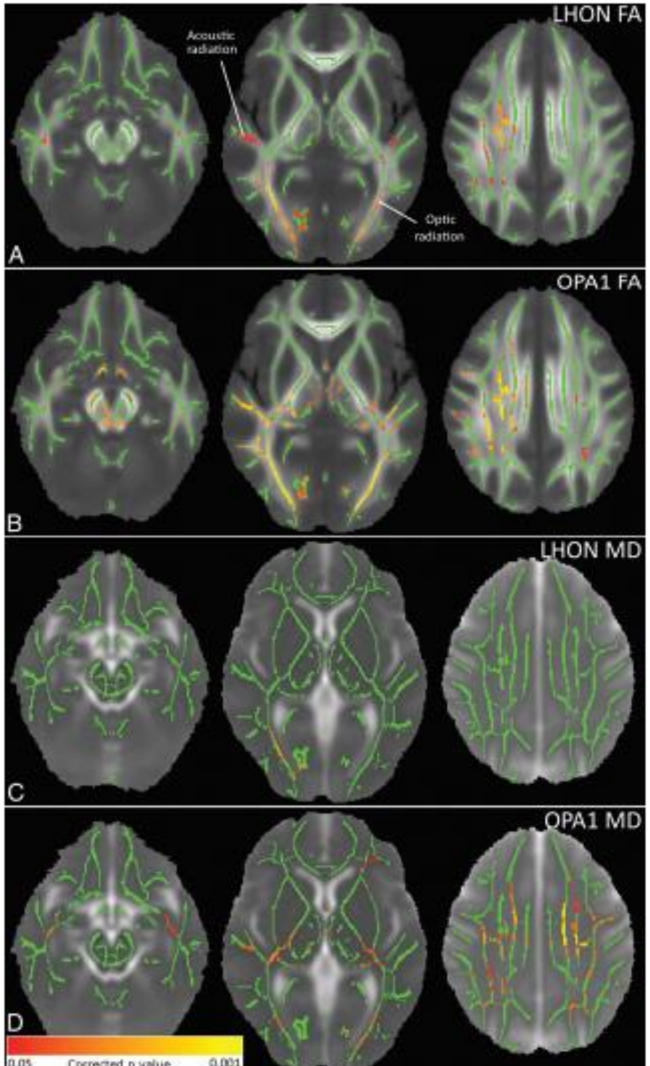



Diffusion weighted imaging (DWI) is a widely used imaging technique to evaluate patients with stroke. It can detect brain ischemia within minutes of stroke onset.

Fifty-five–year-old man with an acute left-sided hemiparesis 6 hours before the first MRI examination (patient 10). On the early PD-w (A) and T2-w (B) images, no ischemic lesion was visible. The early DWI scan (C) shows a right-sided hyperintensity in the frontal lobe (territory of the pericallosal artery), which can be appreciated as a hypointensity on the ADC trace map (D). The follow-up MRI (E) was performed 6 days after the onset of symptoms and confirms the infarct.

Diffusion-Weighted Magnetic Resonance Imaging in Acute Stroke. Stroke. 1998;29:1783-1790

# FA and MD quantitative map for research purposes




ORIGINAL RESEARCH
**ADULT BRAIN**

**Diffusion Tensor Imaging Mapping of Brain White Matter Pathology in Mitochondrial Optic Neuropathies**

D.N. Manners, G. Rizzo, C. La Morgia, C. Tonon, C. Testa, P. Barboni, E. Malucelli, M.L. Valentino, L. Caporali, D. Strobbe, V. Carelli, and R. Lodi

Compared with controls, patients with optic atrophy gene 1-autosomal dominant optic atrophy had an increased MD in 29.2% of voxels analyzed within major white matter tracts distributed throughout the brain, while FA was reduced in 30.3% of voxels. For patients with Leber hereditary optic neuropathy, the proportion of altered voxels was only 0.5% and 5.5%, respectively, of which half was found within the optic radiation and 3.5%, in the smaller acoustic radiation. In almost all regions, FA diminished with age in patients with optic atrophy gene 1-autosomal dominant optic atrophy and correlated with average retinal nerve fiber layer thickness in several areas.

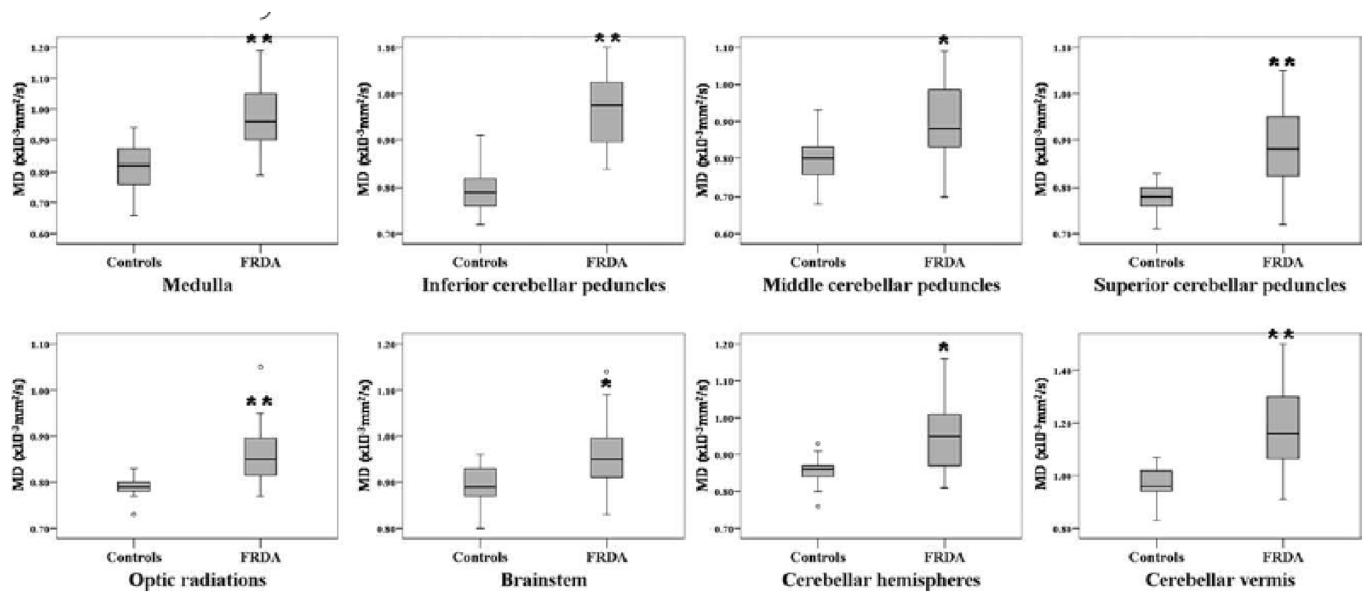
# FA and MD quantitative map for research purposes

RESEARCH ARTICLE

## Brain Diffusion-Weighted Imaging in Friedreich's Ataxia

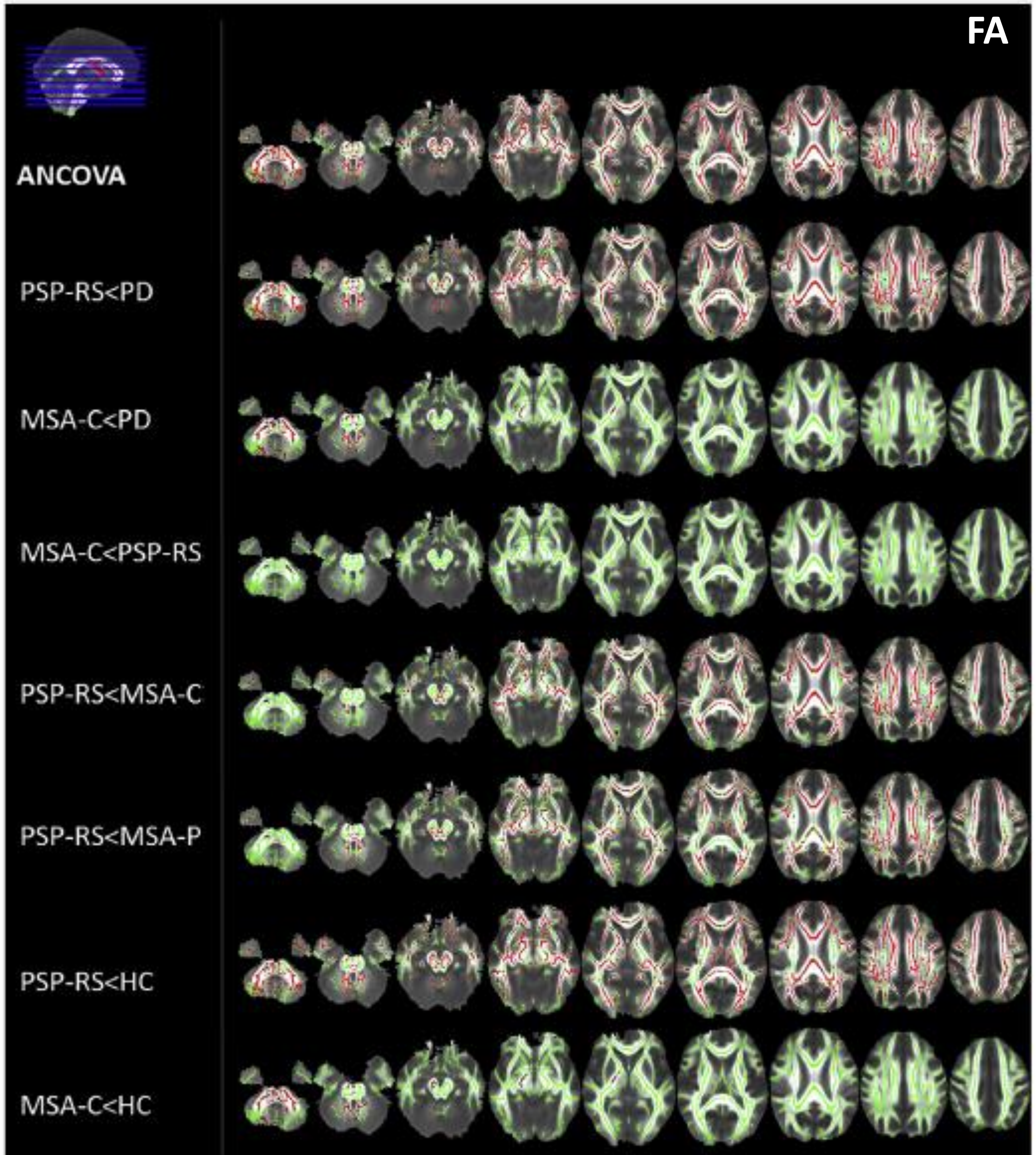
Giovanni Rizzo, MD,[1,2] Caterina Tonon, MD,[1] Maria Lucia Valentino, MD,[2] David Manners, DPhil,[1] Filippo Fortuna, MD,[1,2] Cinzia Gellera, MD,[3] Antonella Pini, MD,[4] Alessandro Ghezzo, MD,[4] Agostino Baruzzi, MD,[2] Claudia Testa, PhD,[1] Emil Malucelli, PhD,[1] Bruno Barbiroli, MD,[1] Valerio Carelli, MD, PhD,[2] Raffaele Lodi, MD[1*]

*Movement* Disorders, Vol. 26, No. 4, 2011




FRDA patients had significantly higher MD values than controls in medulla, ICP, MCP, SCP, OR and at the level of the infratentorial structures such as brainstem, cerebellar hemispheres, and especially in the cerebellar vermis. MD values were strongly correlated with disease duration and ICARS score.

# FA and MD quantitative map for research purposes

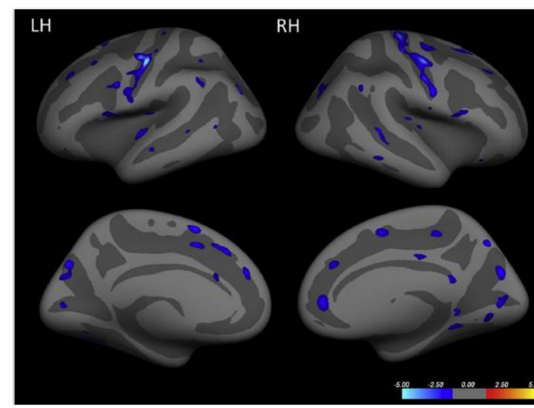



Contents lists available at ScienceDirect
Parkinsonism and Related Disorders
journal homepage: www.elsevier.com/locate/parkreldis
ELSEVIER

White matter and cortical changes in atypical parkinsonisms: A multimodal quantitative MR study

Stefano Zanigni [a,b,1], Stefania Evangelisti [a,b,1], Claudia Testa [a,b], David N. Manners [a,b], Giovanna Calandra-Buonaura [b,c], Maria Guarino [d], Anna Gabellini [c,e], Laura Ludovica Gramegna [a,b], Giulia Giannini [b,c], Luisa Sambati [b,c], Pietro Cortelli [b,c], Raffaele Lodi [a,b,*], Caterina Tonon [a,b]

Vertex-wise CT ANCOVA showed a significant ($p < 0.05$, corrected) difference among groups only in the left precentral cortex.



# Other models for diffusion MRI

To overcome the tensor model other models have been introduced.

To describe the acquired dMRI signal, the Neurite Orientation Dispersion and Density Imaging (NODDI) model was introduced.

**NODDI** is a clinically feasible dMRI model for estimating the microstuctural complexity of dendrides and axons in vivo.

# NODDI

It is a two-level multi-compartment model in which total signal is modelled as:

$$S = (\nu_{iso})S_{iso} + (1 - \nu_{iso})(\nu_{in}S_{in} + (1 - \nu_{in})S_{en})$$

- $S_{iso}$ is the signal coming from the CSF compartment with volume fraction $\nu_{iso}$;
- $S_{en}$ is the signal from the space between neurites;
- $S_{in}$ is the signal coming from inside the axons and dendrides, with volume fraction $\nu_{in}$.

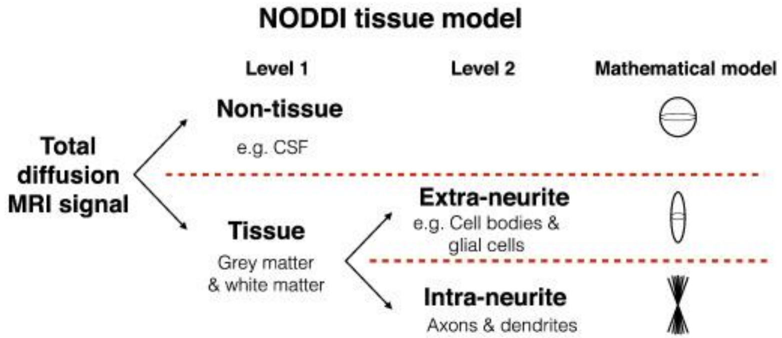



Image adapted from Tariq, Maira et al. "Bingham-NODDI: Mapping anisotropic orientation dispersion of neurites using diffusion MRI." *NeuroImage* vol. 133 (2016): 207-223.

# NODDI

Although it has been applied in many studies no established protocol for preparing patients before undergoing a dMRI brain scan

here is yet no gold standard for validating diffusion measures.


**Assessment of the repeatability and stability of NODDI diffusion modelling using phantom and in vivo acquisitions.**

Mattia Ricchi[1,2,3], Aaron Axford[3], Jordan McGing[3], Ayaka Shinozaki[3,4], Kylie Yeung[3,5], Sarah Birkhozeler[3], Rebecca Mills[3], Fulvio Zaccagna[6,7], Mark Symms[8], Andrew Lewis[3], Oliver Rider[3], Damian J. Tyler[3,4], Claudia Testa[2,9] & James T. Grist[3,4,10].

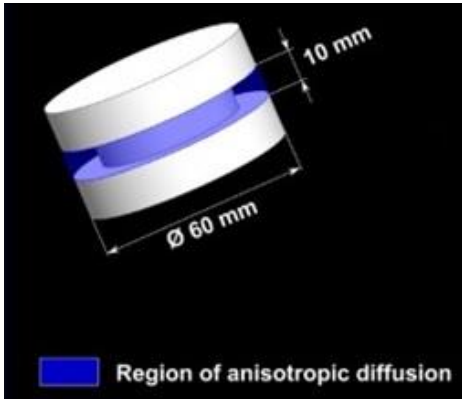
# PHANTOM & HEALTHY VOLUNTEERS

*Circular fibre strand*

Fibres of fine polyester fiberfill of diameter 15 µm

Distilled water and NaCl (83 g NaCl per kilogram of water) used as fluid

Is used to mimic restricted diffusion in white matter




*Four healthy volunteers*

No prior experience with neurological or psychiatric disorders

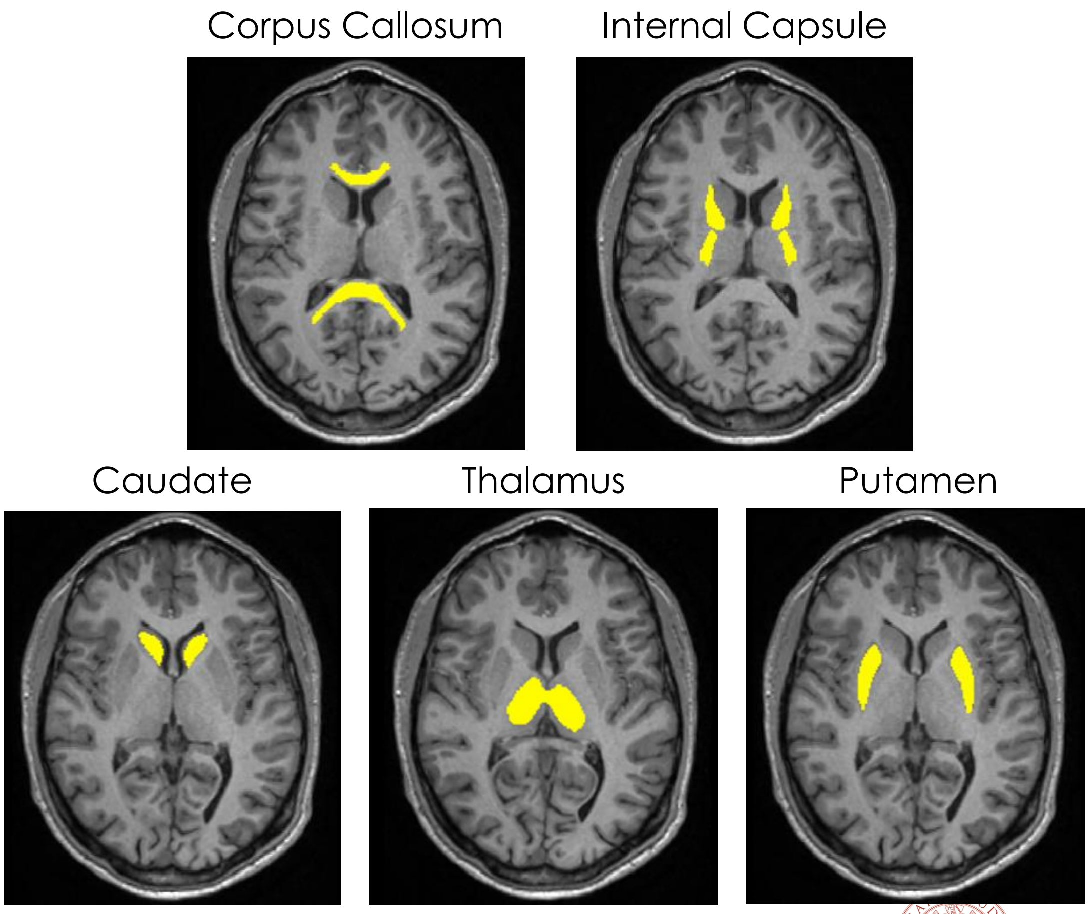
Age between 24 and 30 years old

Three males and one female

# ANALYSIS PIPELINE – Brain

Each participant is scanned twice

- Fit of the corrected data to the NODDI model
- Alignement of the obtained quantitative maps to the MNI152
- Extraction of the results from specific ROIs in the MNI space
- Bland-Altman analysis to compute the repeatability coefficient

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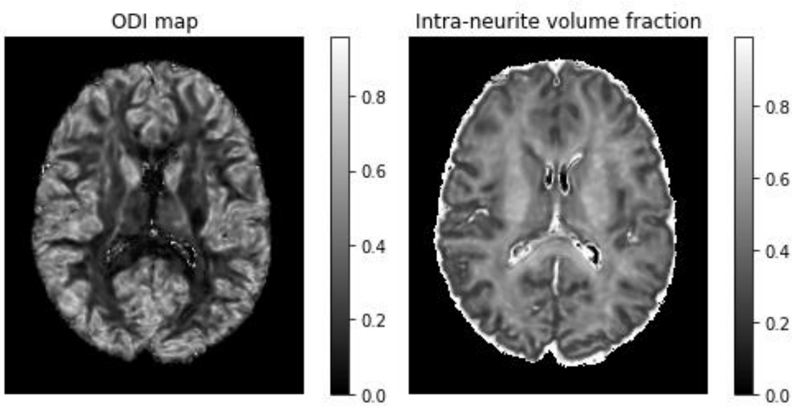
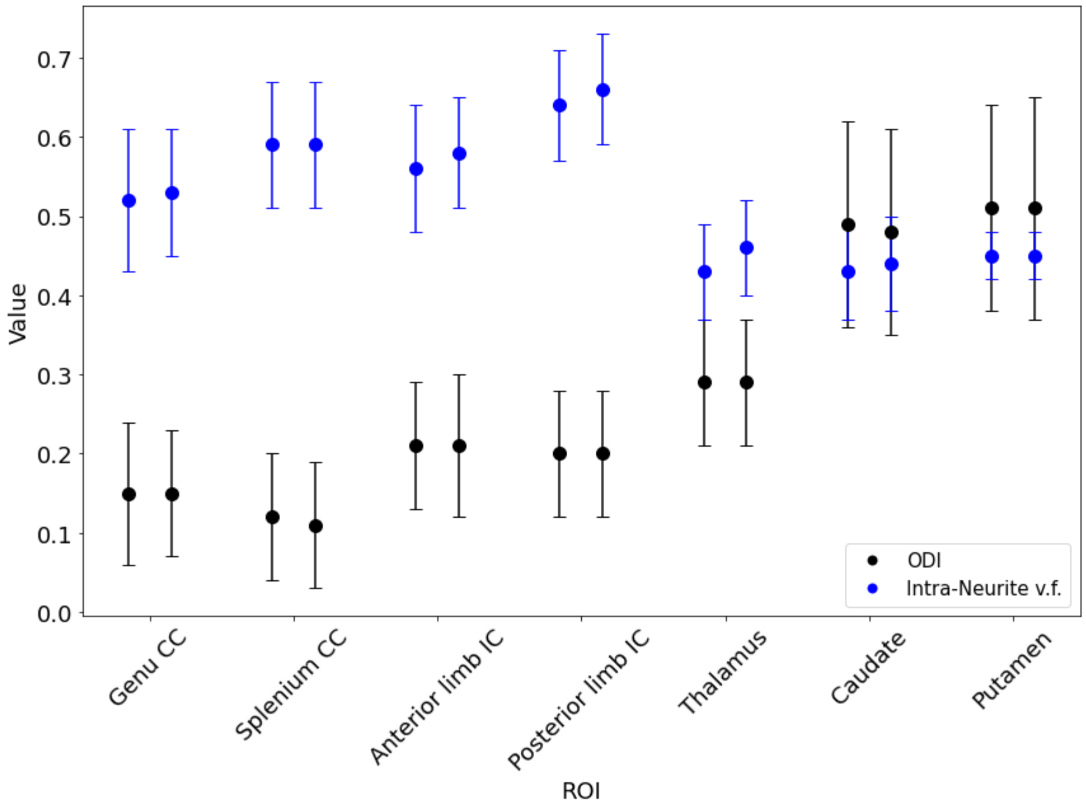
# *IN VIVO* RESULTS – NODDI

The graph compares the values of ODI and intra-neurite volume fraction in all the ROIs considered, between the first and second scans. The first point on each ROI represents the value obtained in the first scan, while the second point represents the value obtained in the second scan.

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# *IN VIVO* RESULTS – NODDI

| Repeatability Coefficients for brain study | | | | | |
|---|---|---|---|---|---|
| | β-fraction | ODI | Tissue volume fraction | Intra-neurite volume fraction | MSE |
| **Genu Corpus Callosum** | **0**<br>0-0 | **0**<br>0-0 | **0.029**<br>0-0.087 | **0.020**<br>0-0.058 | **0.00098**<br>0-0.0029 |
| **Splenium Corpus callosum** | **0**<br>0-0 | **0.016**<br>0-0.047 | **0.028**<br>0-0.082 | **0.0098**<br>0-0.029 | **0.0016**<br>0-0.0047 |
| **Anterior limb of Internal Capsule** | **0**<br>0-0 | **0.019**<br>0-0.056 | **0.033**<br>0-0.099 | **0.016**<br>0-0.047 | **0.00098**<br>0-0.0029 |
| **Posterior limb of Internal Capsule** | **0**<br>0-0 | **0**<br>0-0 | **0.043**<br>0-0.13 | **0.028**<br>0-0.082 | **0.00098**<br>0-0.0029 |
| **Thalamus** | **0.020**<br>0-0.058 | **0.0098**<br>0-0.029 | **0**<br>0-0 | **0.033**<br>0-0.099 | **0.0011**<br>0-0.0032 |
| **Caudate** | **0.040**<br>0-0.12 | **0.0098**<br>0-0.029 | **0.011**<br>0-0.033 | **0.016**<br>0-0.047 | **0.00029**<br>0-0.00087 |
| **Putamen** | **0.0098**<br>0-0.029 | **0.0098**<br>0-0.029 | **0**<br>0-0 | **0.029**<br>0-0.087 | **0.00029**<br>0-0.00087 |

The consistency of the NODDI results demonstrates the reliability of the model and serves as a foundation for detecting minor changes in brain microstructure over time, allowing for the monitoring of the progression of neurological diseases. The next stage in the research involves a multi-centre study to compare the outcomes of different MRI scanners, which may lead to different results.

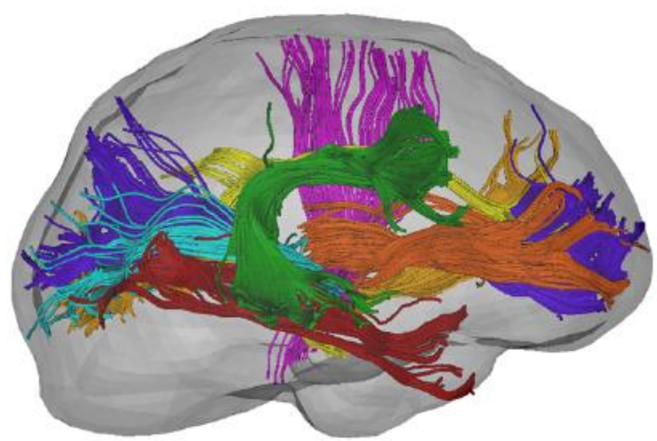
# Tractography

## What is Tractography?

FMRIB

Post-mortem dissection of some white matter fibre bundles (tracts)

**Tractography**
The post-imaging reconstruction of fibre bundles/ anatomical connections in the brain using a set of DW images. (in-vivo virtual dissection)



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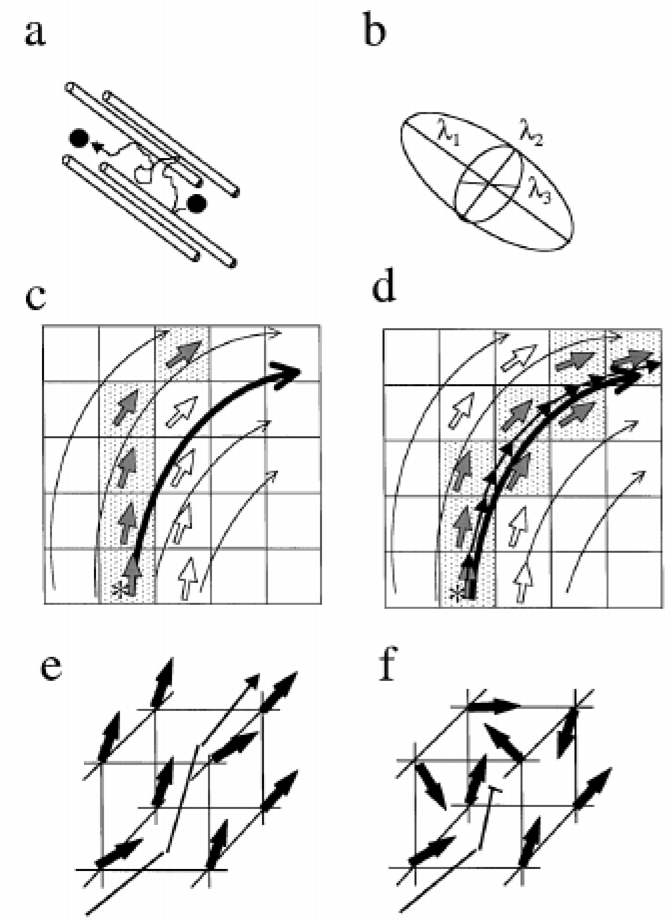
# Tractography

Traces the brain pathways using diffusion data.
By fitting a diffusion model we can estimate not only mean diffusion and fractional anisotropy but also the orientation of maximum diffusion at each voxel.

Tractography is performed by following these orientation estimates to reconstruct a pathway that, within a coherent bundle, corresponds to the underlying fibre pathway.
Previously, such white matter anatomy could only be studied by post-mortem dissection or invasive tracing in non human animals.

# Tractography-connectivity

Assumption: direction of maximum diffusivity in voxels with anisotropic profile is an estimate of the major fibre orientation.




Mori et al Ann of Neurology 1999

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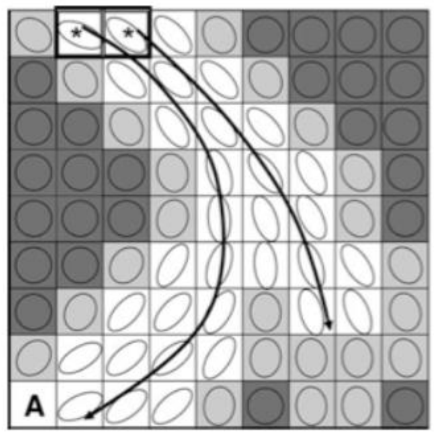
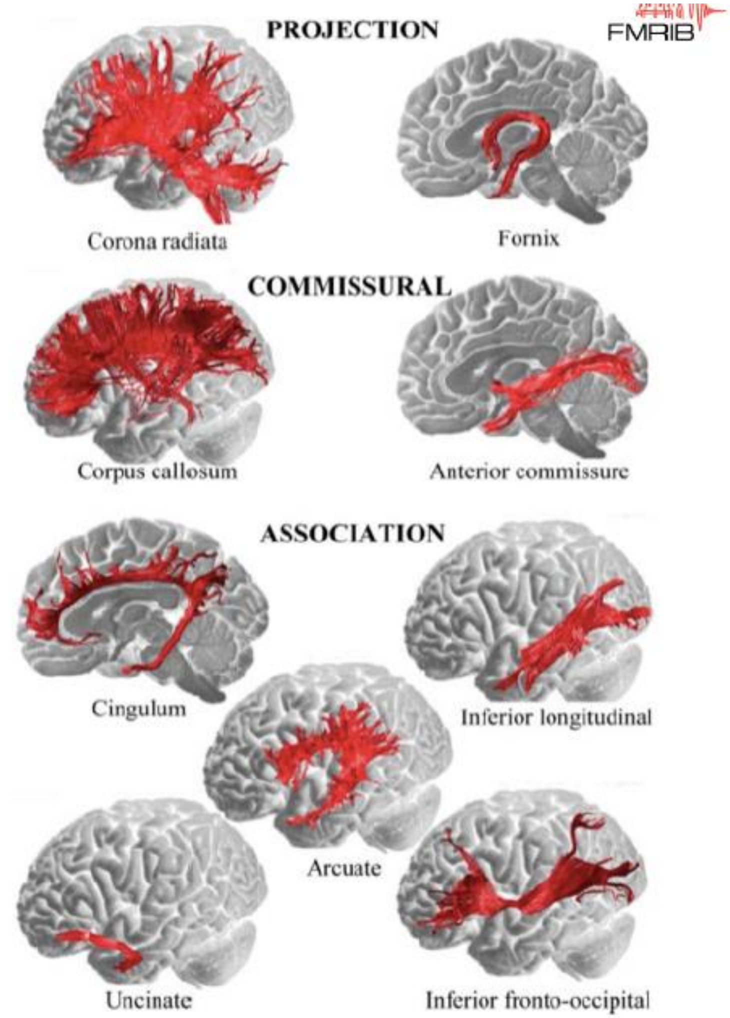
# Tractography-connectivity

Assumption: direction of maximum diffusivity in voxels with anisotropic profile is an estimate of the major fibre orientation.




[Basser et al, Magn Reson Med, 2000]




[Catani et al, NeuroImage, 2003]

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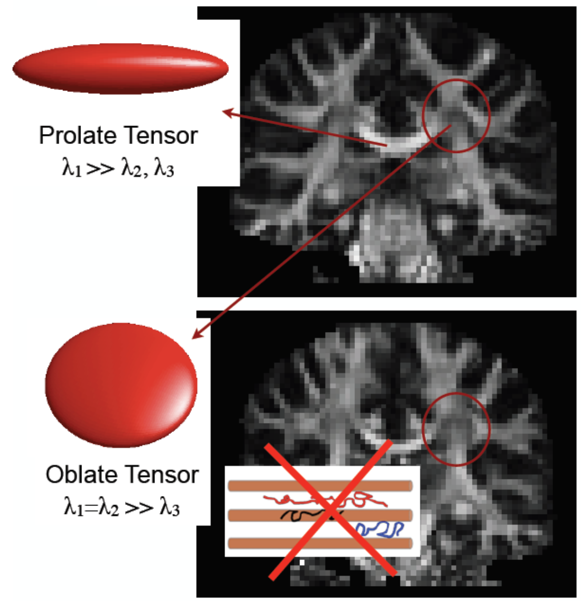
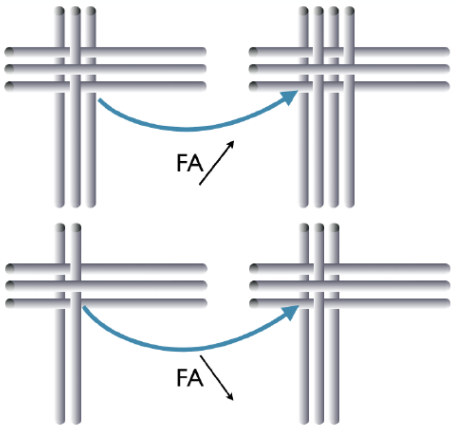
# Tensor and FA in Crossing Regions

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?



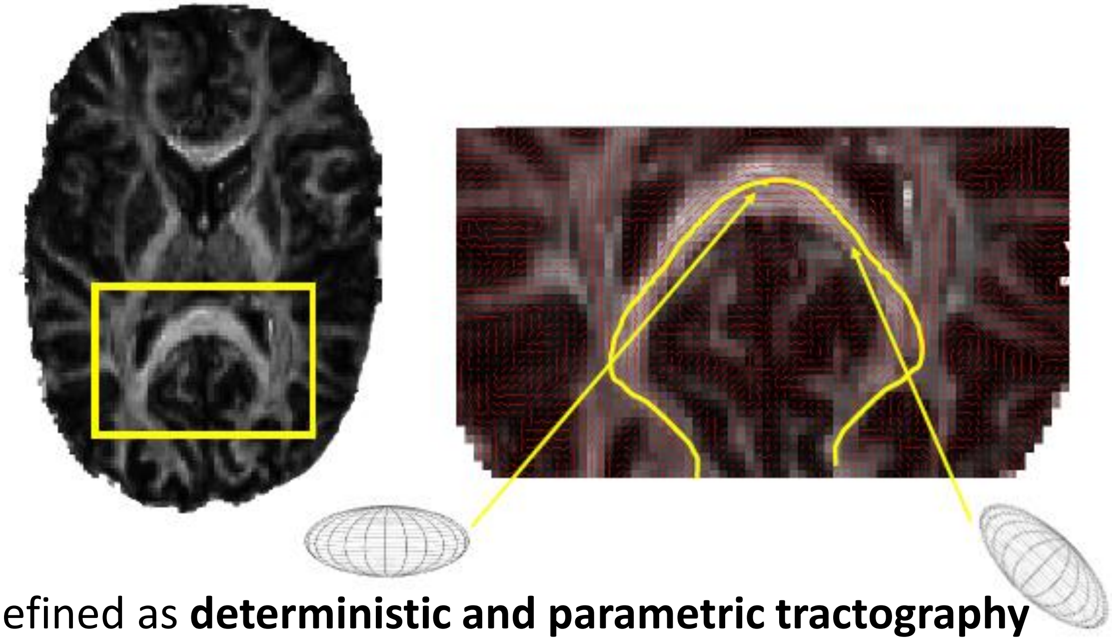
## Beyond the tensor model

One major limitation of DTI is its inability to describe fiber directionality in regions in which two or more fiber populations with different orientations are present (e.g. crossing fiber regions). This limitation has led to the introduction of new techniques that attempt to estimate the component fibers either discretely or as a fiber orientation distribution (FOD) using multi-tensor approaches, spherical deconvolution or the angular dependence of the diffusion profile

DTI approximates the Probability Density Function (PDF) of the diffusion water molecules by a three-dimensional multivariate Gaussian distribution (Stejskal 1965)

# White matter tractography with the tensor model approach

The DTI model is oversimplistic, but can capture anisotropic diffusion. Assumption: direction of maximum diffusivity in voxels with anisotropic profile is an estimate of the major fibre orientation.



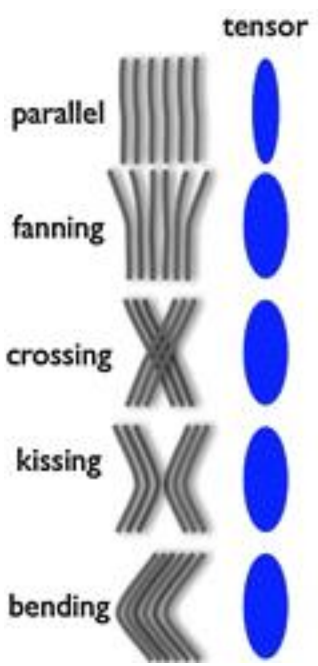
$V_1$ map
Principal Diffusion Direction

It is defined as **deterministic and parametric tractography**

a) Uses DWI data and a the DTI model to obtain fiber orientation estimates in each voxel.
b) Uses these estimates to propagate curves from a seed (starting voxel/ROI) within the brain volume

# How to model crossing fibers?

The DTI model is oversimplistic, but can capture anisotropic diffusion. Assumption: direction of maximum diffusivity in voxels with anisotropic profile is an estimate of the major fibre orientation.




DTI can not distinguish the various simple configurations of axon fibers:
DT is less anisotropic if fibers are not straight and parallel but it is equal for different configurations.

It is introduced the **ODF**, fiber orientation distribution function as the fraction of fibers portions within each voxel with each orientation. (fODF). fODF is a probability distribution.

To sample fODF diffusion acquisition protocols measure signal at **many gradient directions (30-128)** to capture enough of the directional variation of DW signal potentially to provide the **high angular resolution** to resolve crossing fibers

# Multi tensor model (parametric)

It is a generalization of DTI which replaces the Gaussian model for $p$ with a mixture of $n$ Gaussian densities.
In a voxel we consider $n$ distinct populations and that diffusing molecules stay within only one populations (no exchange):

$$p(x) = \sum_{i=1}^{n} a_i G(\boldsymbol{x};\ \boldsymbol{D_i}, t)$$

$a_i \in [0,1]$ is the volume fraction of the $i$*th* fiber population and $\sum_i a_i = 1$ and $G$ is the Gaussian function with zero mean and covariance $2\boldsymbol{D}t$, $t$ is the diffusion time and $\boldsymbol{x}$ is the displacement.
The normalized diffusion-weighted signal is

$$A(\boldsymbol{q}) = \sum_{i=1}^{n} a_i \exp(-t\boldsymbol{q}^T D_i \boldsymbol{q})$$

Where $\boldsymbol{q}$ is the wavevector and for pulsed-gradient spin-echo $\boldsymbol{q} = \gamma\delta G\ t = \Delta - \delta/3$
$\widehat{\boldsymbol{q}} = \boldsymbol{q}/|\boldsymbol{q}|$ is the direction of the magnetic field gradient.
The b-value is linked to q: $b = t|\boldsymbol{q}|^2$

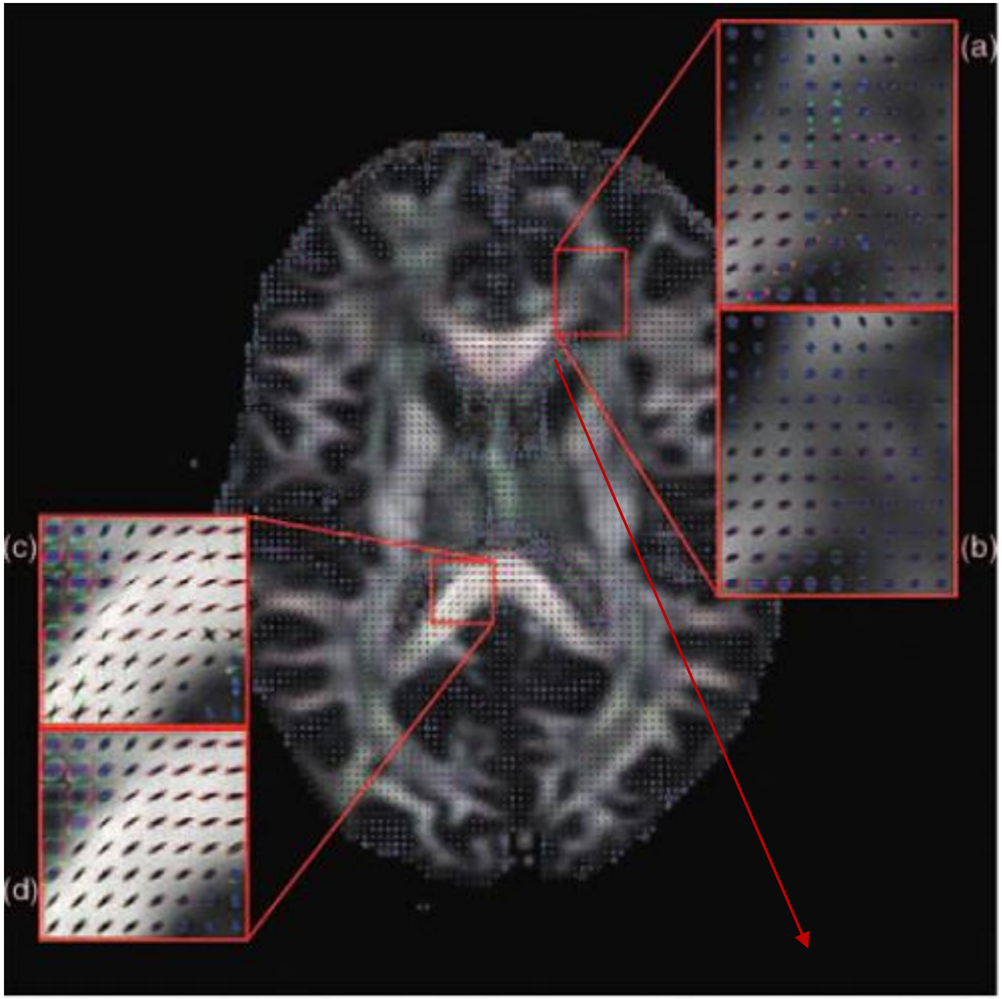
# Multi tensor model

For spherical acquisition ($\hat{q}$ moves as a radius in a sphere) $t$ and $|\boldsymbol{q}|$ are fixed (so b is fixed):

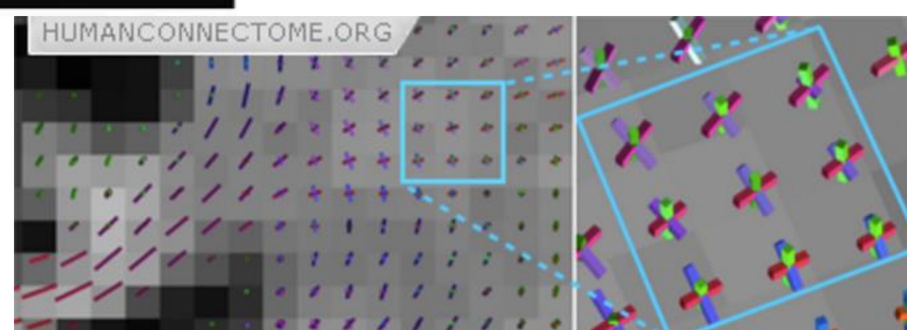
$$A(\widehat{\boldsymbol{q}}) = \sum_{i=1}^{n} a_i \exp\left(-t\widehat{\boldsymbol{q}} \quad D_i\widehat{\boldsymbol{q}}\right)$$

($t$ and $|\boldsymbol{q}|$ can also vary).
This model assumes $n$ known and usually $n$=2 is used.

Unlike the DT model the parameters $\mathbf{D}_1, \ldots \mathbf{D}_n$ in the multi tensor model cannot be expressed as a linear function of the measurements so the model requires non-linear optimization.
For n=2 the full tensor has 13 free parameters: the six components of each DT and one for the volume fraction $a_1$ (since $a_2$=1- $a_1$)




Two-tensor models fitted in each voxel of an axial slice of a normal human brain data set. The model is the full 13-parameters two-tensor model in every voxel. Ellipsoidal contours of *p* from both tensors are overlaid on a standard FA map. Inset images a and b show two- and one-tensor models, respectively for a crossing-fiber region. c and d show two and one-tensor models, respectively for a region of the corpus callosum which has a single fiber population.

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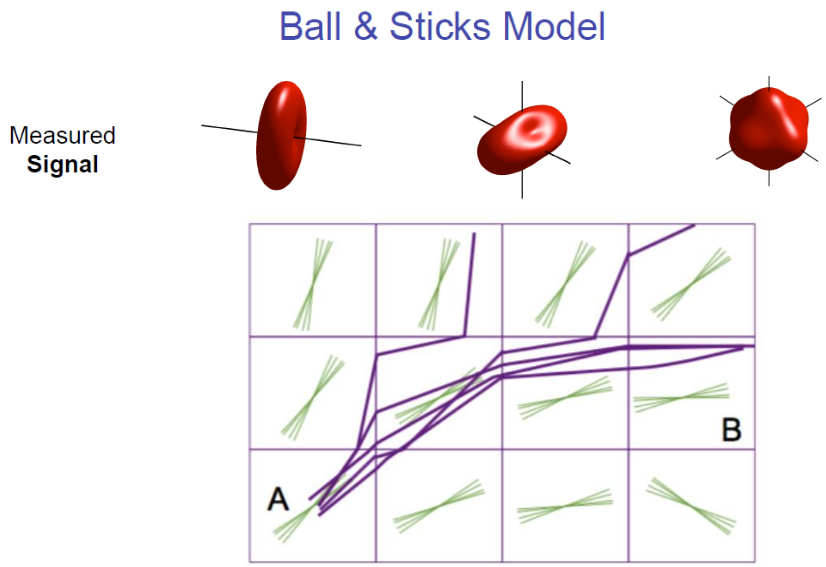
## How to model crossing fibers?

A variety of techniques: multi tensor model and non-parametric techniques such as DSI, QBALL and spherical deconvolution.

## The ball and stick model

FSL: Bedpostx - Probtrackx



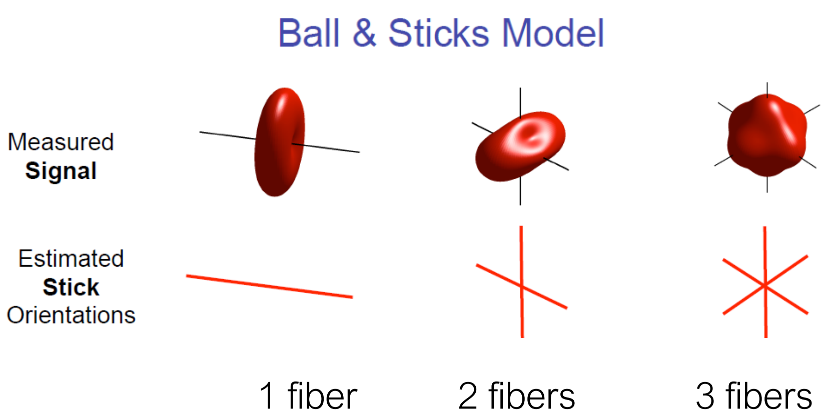

Simple model: it assumes that water molecules belong to one or two populations: a restricted population of water molecules in and around fibers with scatter pattern $p_r$ and a free population that does not interact with fibers and has a scatter pattern $p_f$.

FSL and bedpost use a Gaussian model for $p_f$.

- B&S estimates the probability density distributions

# The ball and stick model

## FSL: Bedpostx - Probtrackx




Simple model: it assumes that water molecules belong to one or two populations: a restricted population of water molecules in and around fibers with scatter pattern $p_r$ and a free population that does not interact with fibers and has a scatter pattern $p_f$.
FSL and bedpost use a Gaussian model for $p_f$.

The predicted diffusion signal is:

$$\mu_i = S_0((1-f)\exp(-b_i d) + f exp(-b_i d \boldsymbol{r}_i{}^T \boldsymbol{R}\boldsymbol{A}\boldsymbol{R}^{\boldsymbol{T}} \boldsymbol{r}_i))$$

Where f is the fraction of anisotropic diffusion and 1-f of the isotropic and $\boldsymbol{r}_i$ is the gradient direction. R rotates of (θ,φ) the matrix $A=\begin{pmatrix}1 & 0 & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{pmatrix}$

# Spherical deconvolution

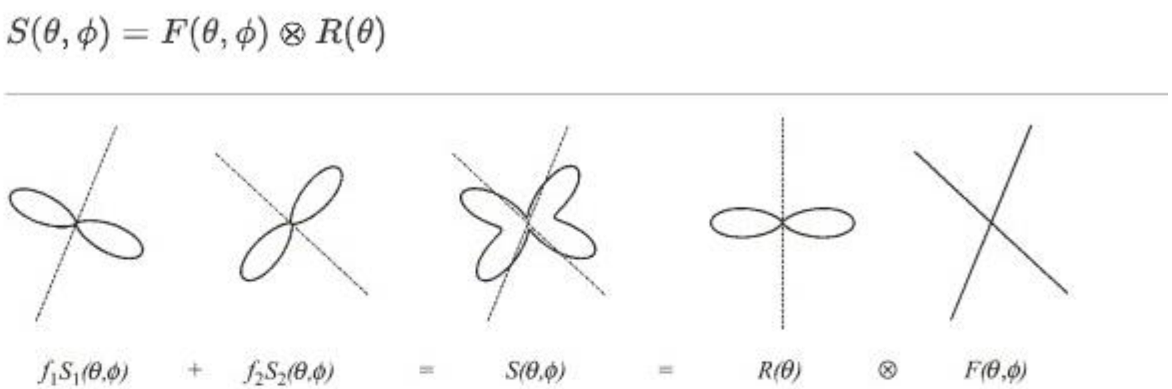
SD attempts to measures fODF directly. The key idea is to consider a set of measurements as the sum of measurements we would get from a fiber population with each orientation weighted by the fraction of fibers with that orientation.
It is assumed that all white matter fiber bundles in the brain share identical diffusion characteristics, thus implicitly assigning any differences in diffusion anisotropy to partial volume effects.
The diffusion-weighted signal attenuation measured over the surface of a sphere can then be expressed as the convolution over the sphere of a response function (the diffusion-weighted attenuation profile for a typical fiber bundle) with the fiber orientation density function (ODF). The fiber ODF (the distribution of fiber orientations within the voxel) can therefore be obtained using spherical deconvolution.

## Spherical deconvolution

The signal S(θ,ϕ) that would be measured from a sample containing several distinct fiber populations is then given by the sum of the response functions of each population, weighted by their respective volume fractions, and rotated such that they are aligned along their respective orientations (ϕ is the azimuthal angle in spherical coordinates).

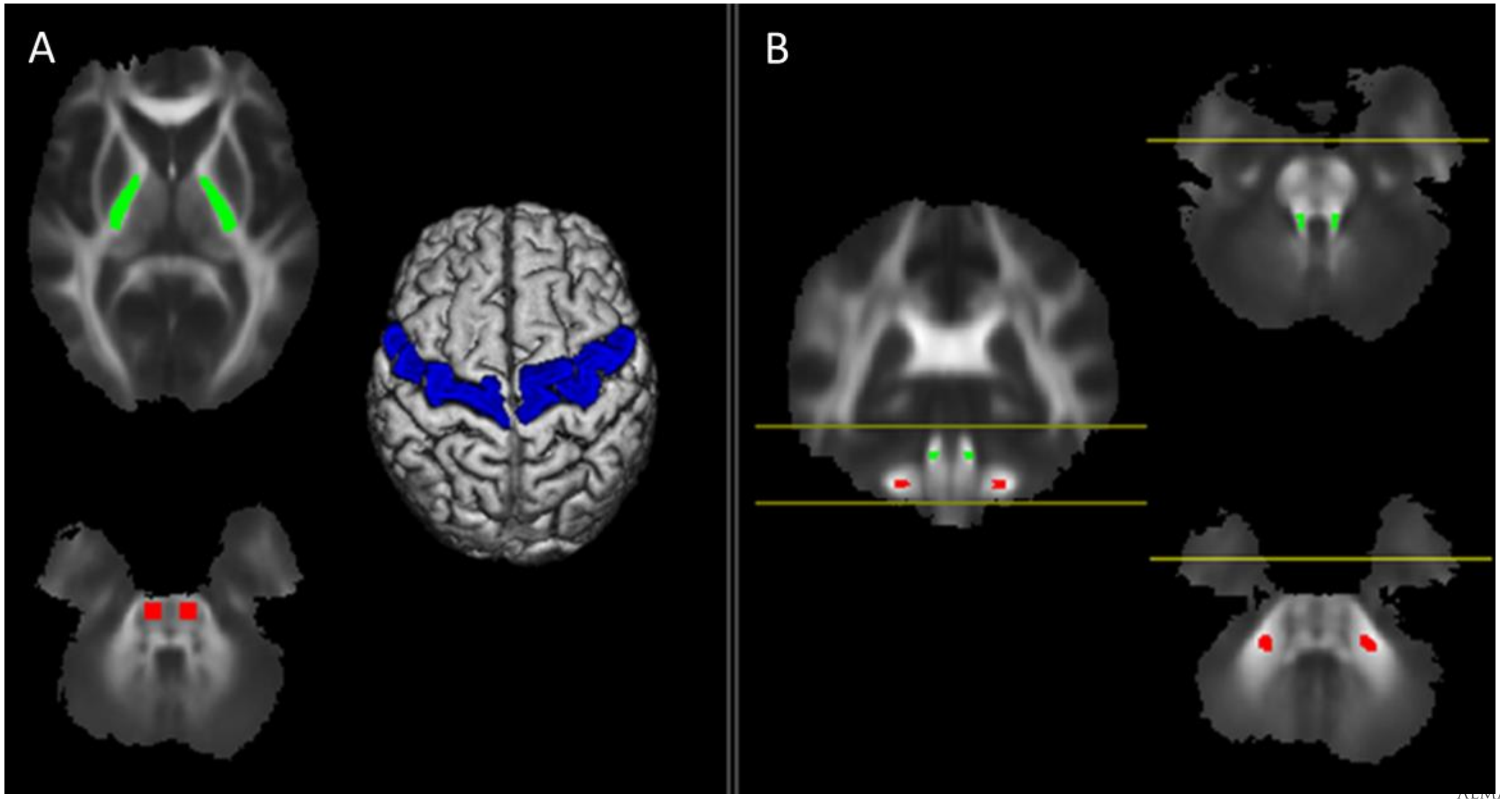
$$S(\theta, \varphi) = \sum f_i \widehat{A}_i R(\theta)$$

where $f_i$ is the volume fraction for the ith fiber population, and $\hat{A}_i$ is the operator representing a rotation onto the direction $(\theta_i,\phi_i)$. This can be expressed as the convolution over the unit sphere of the response function R(θ) with a fiber orientation density function (fiber ODF) F(θ,ϕ)

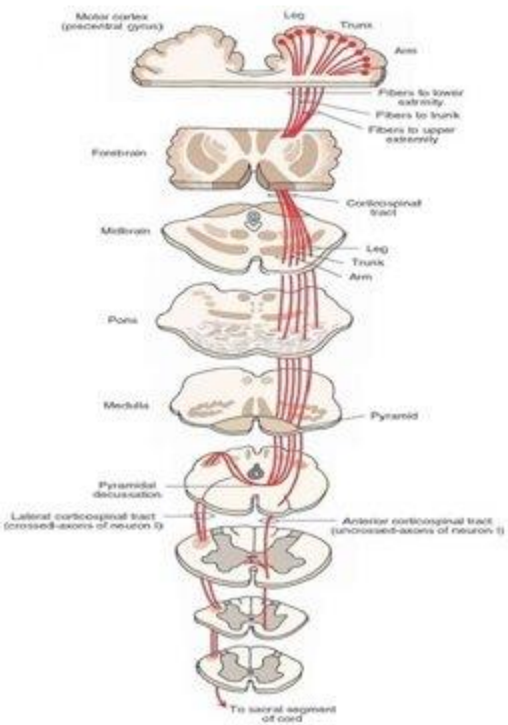


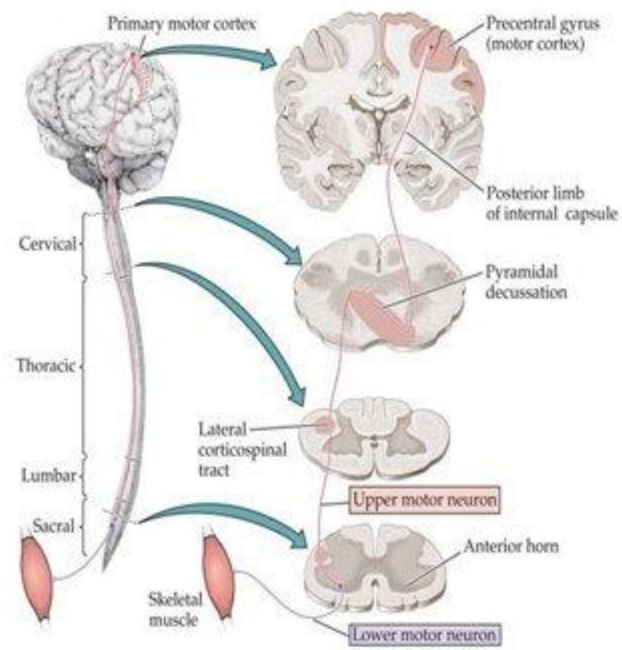
# Example: cortico spinal tract.
# How to construct the connectivity between the pons and the motor area

A method to reconstruct white matter pathways using a region of interest (ROI) approach. The method produced virtual representations of white matter tracts faithful to classical post-mortem descriptions but it required detailed a priori anatomical knowledge



# Example: cortico spinal tract.
# How to construct the connectivity between the pons and the motor area

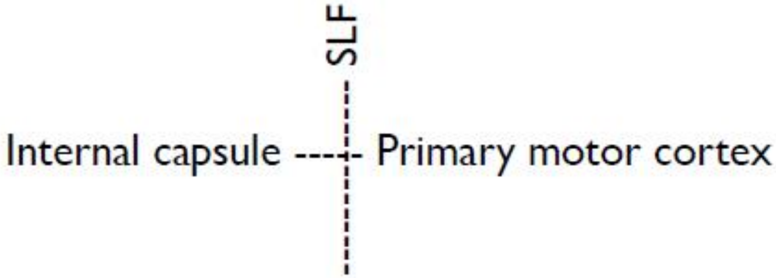


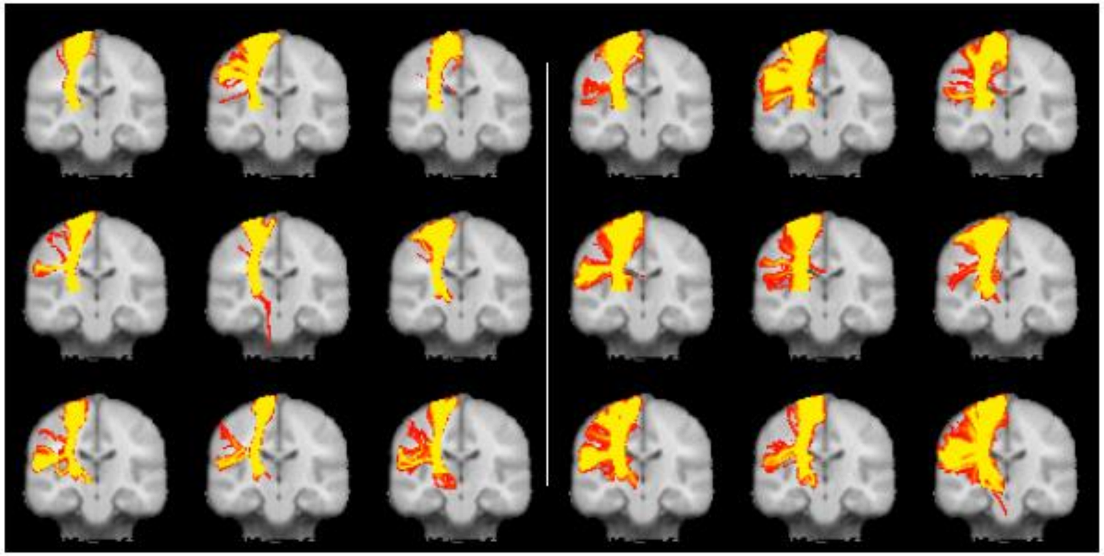



# Examples: probabilistic tractography

Cortico-spinal tracts.
9 subjects

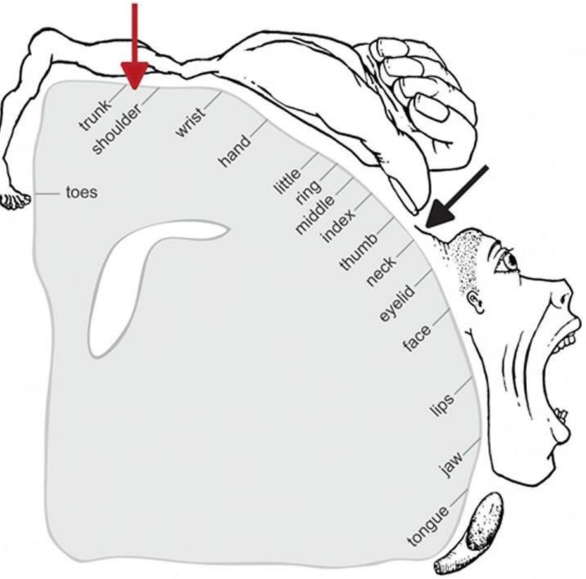
Behrens et al, 2007



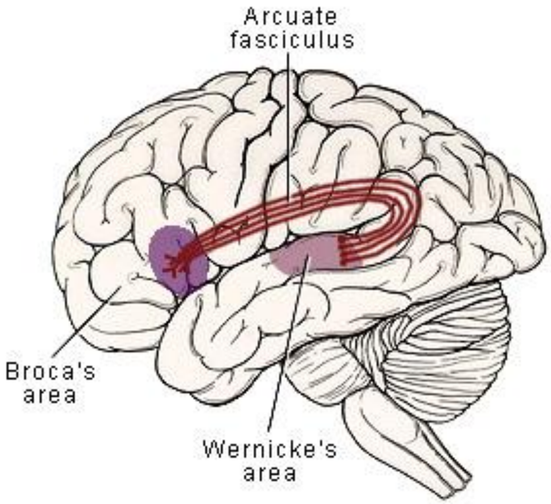



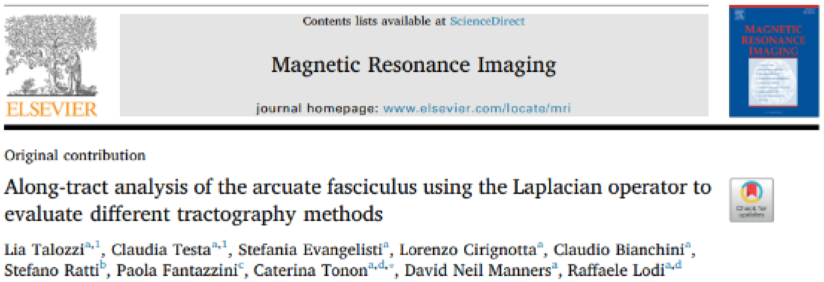
one fibre

two fibres



# Example: arcuate fasciculus.
# How to construct the connectivity between the Broca's area and the Wernicke's area




Contents lists available at ScienceDirect
Magnetic Resonance Imaging
journal homepage: www.elsevier.com/locate/mri

Original contribution

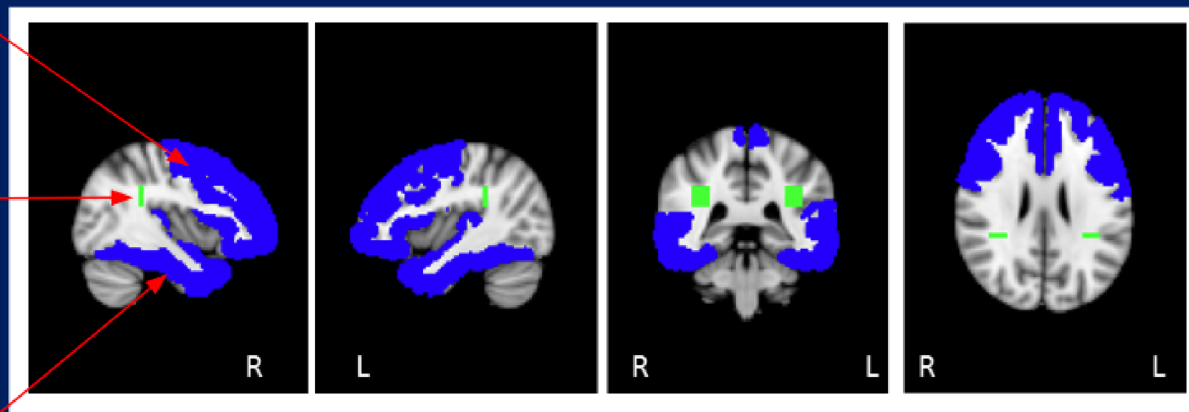
Along-tract analysis of the arcuate fasciculus using the Laplacian operator to evaluate different tractography methods

Lia Talozzi[a,1], Claudia Testa[a,1], Stefania Evangelisti[a], Lorenzo Cirignotta[a], Claudio Bianchini[a], Stefano Ratti[b], Paola Fantazzini[c], Caterina Tonon[a,d,*], David Neil Manners[a], Raffaele Lodi[a,d]

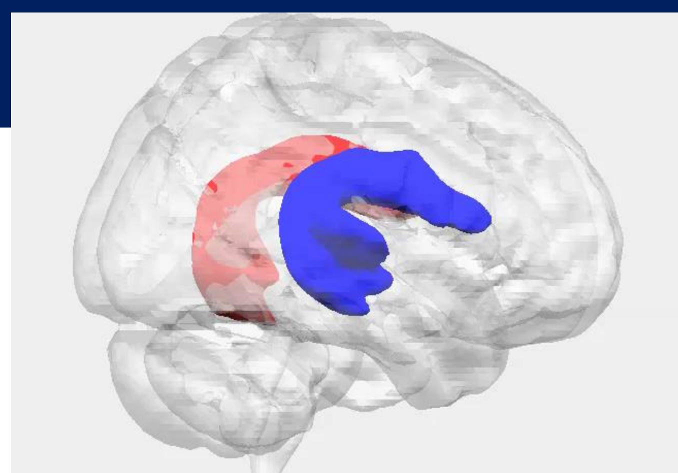
# Along tract analysis with an automatic procedure

Target ROI: frontal lobe GM

Seed ROI: WM under the angular gyrus




Target ROI: temporal lobe's GM



Giorgio et al., Neuroimage 2010
Galantucci et al., Brain 2011

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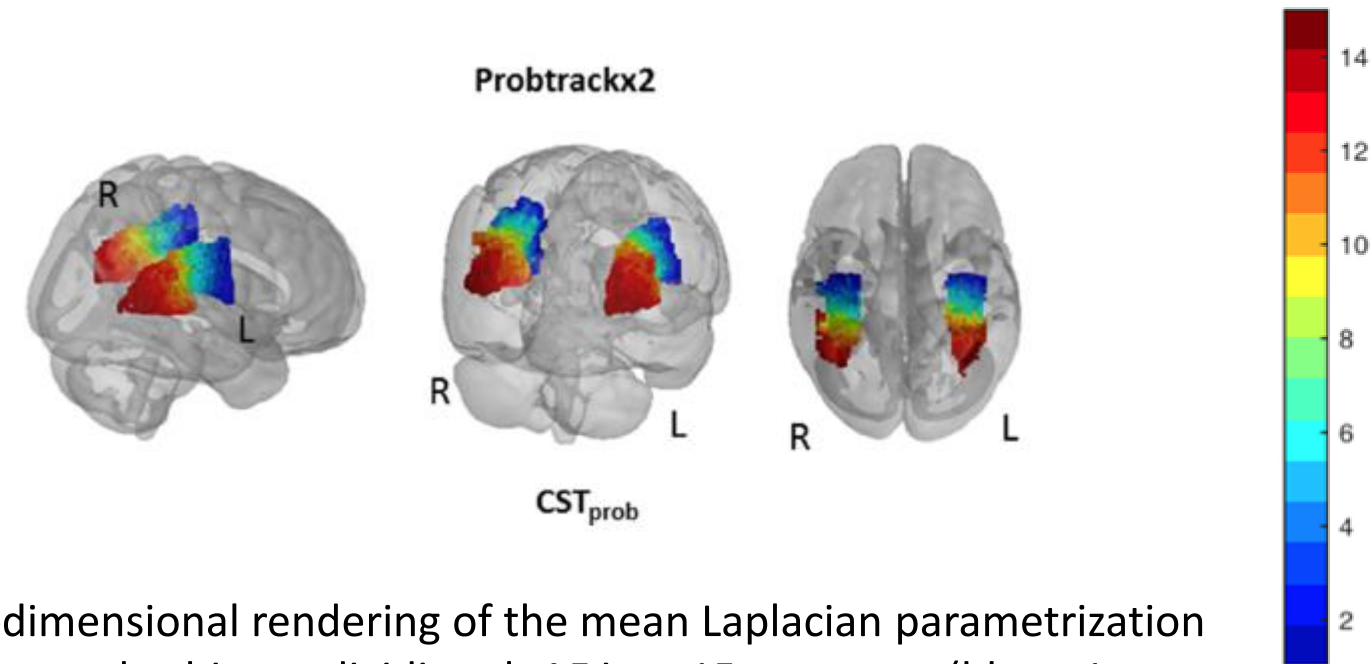
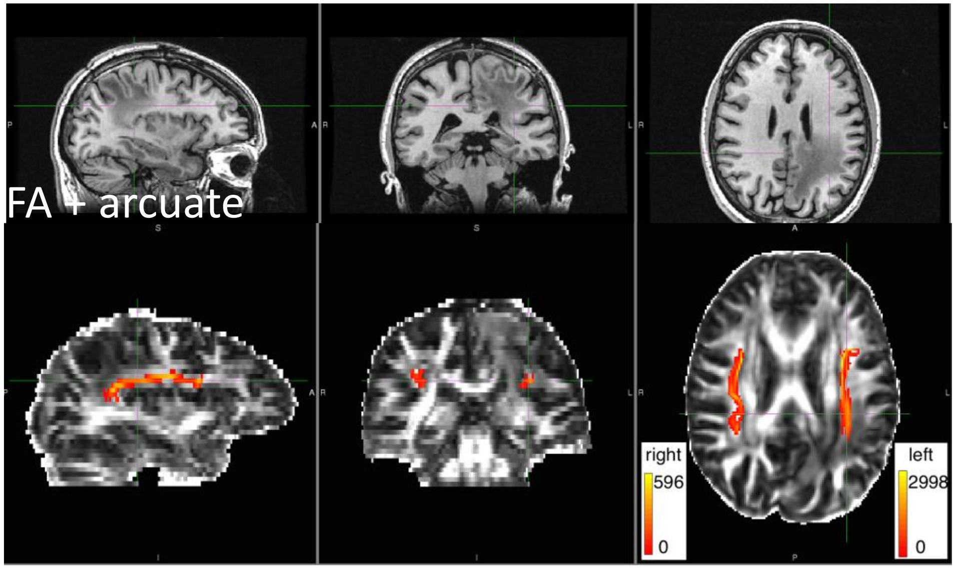
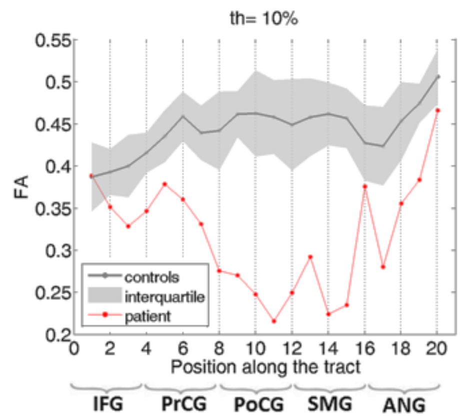
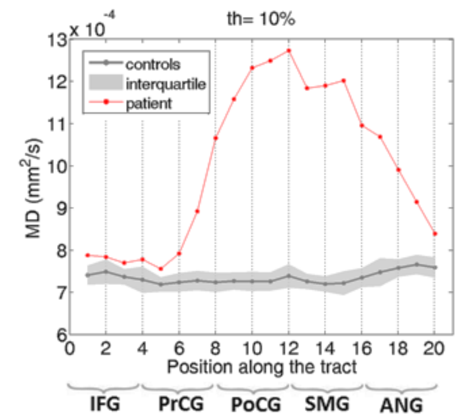


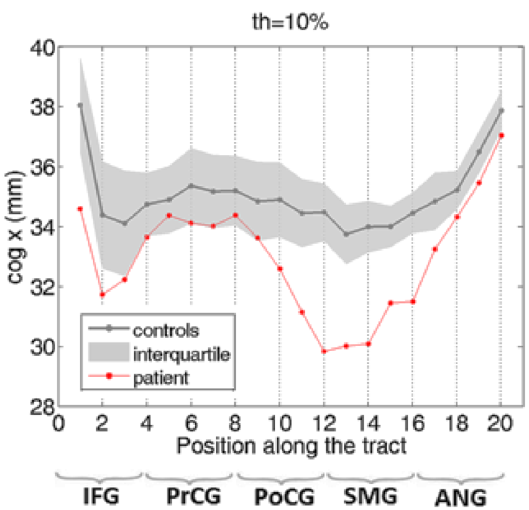

3-dimensional rendering of the mean Laplacian parametrization across al subjects, dividing th AF into 15 segments (blue= 1st frontal segment, red= 15th temporal segment) projected onto the MNI

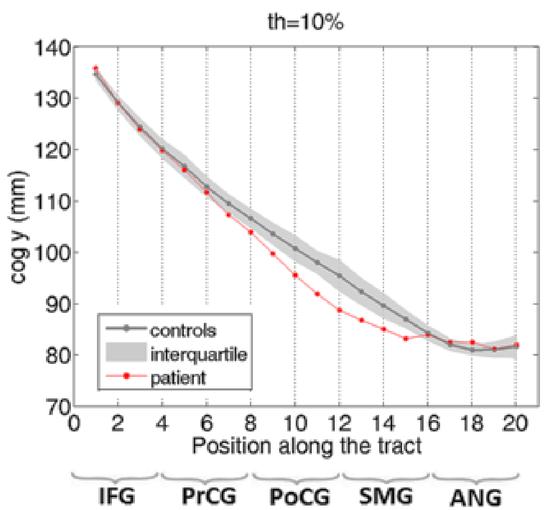
# Along tract analysis
# with an automatic procedure: quantitative assessment of spatial localization of the AF, based on the centroid coordinates

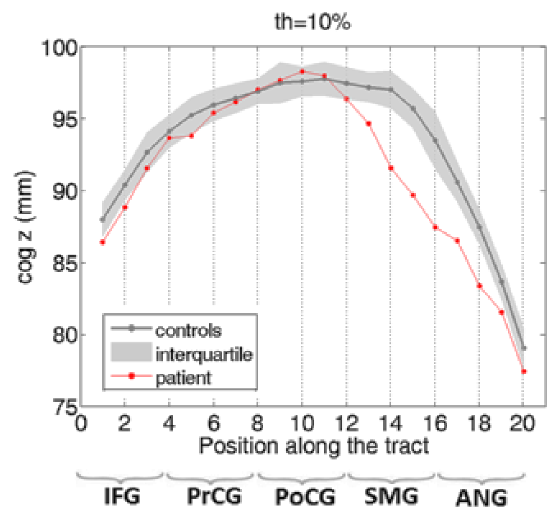
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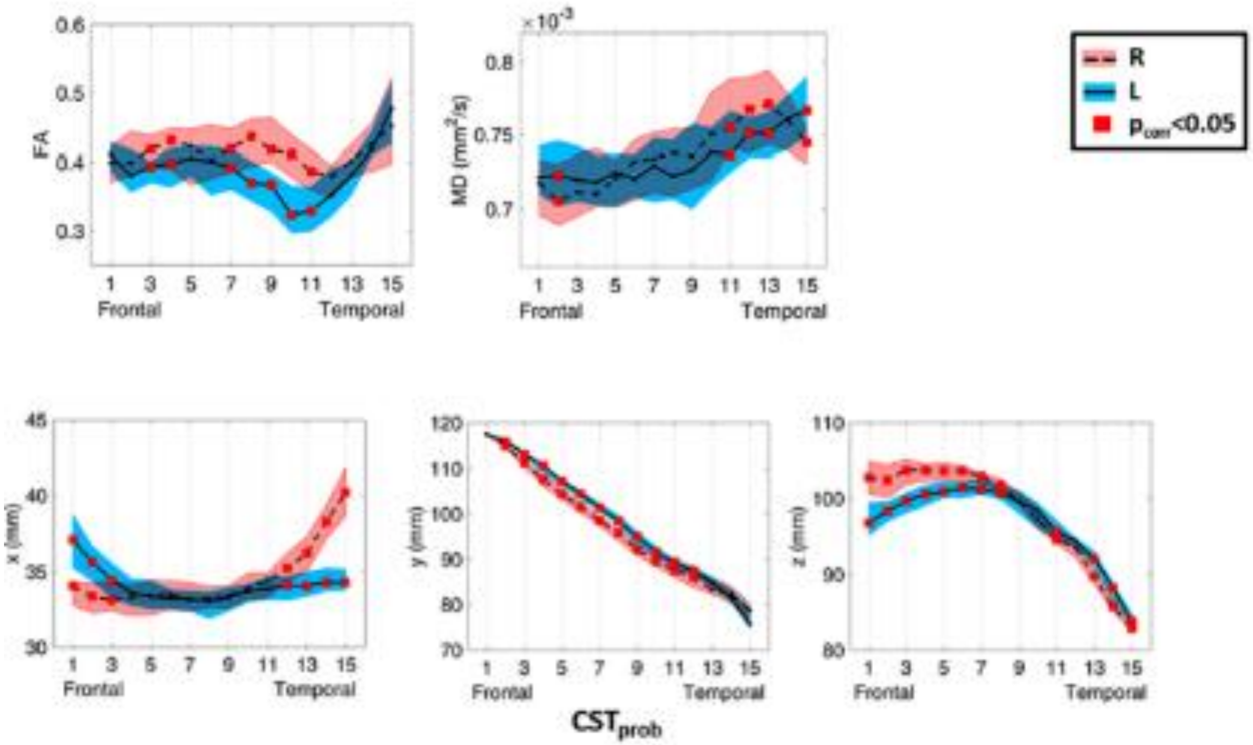
# Tractography: clinical applications

- Presurgical study in patients with neoplastic lesions or in patients with pharmacoresistant epilepsy

- Evaluation of specific tracts in patients with neurodegenerative diseases

# Along tract analysis
# with an automatic procedure




Quantitative assessement of spatial localization of the AF, based on the centroid coordinates obtained with the Laplacian parametrization, allowing comparison of the curvature between hemispheres. For example, in the frontal segments the AF has a higher lateral curvature (x-coordinate) and a more ventral localization
(z-coordinate) on the left

# Many white matter tracts connectivity

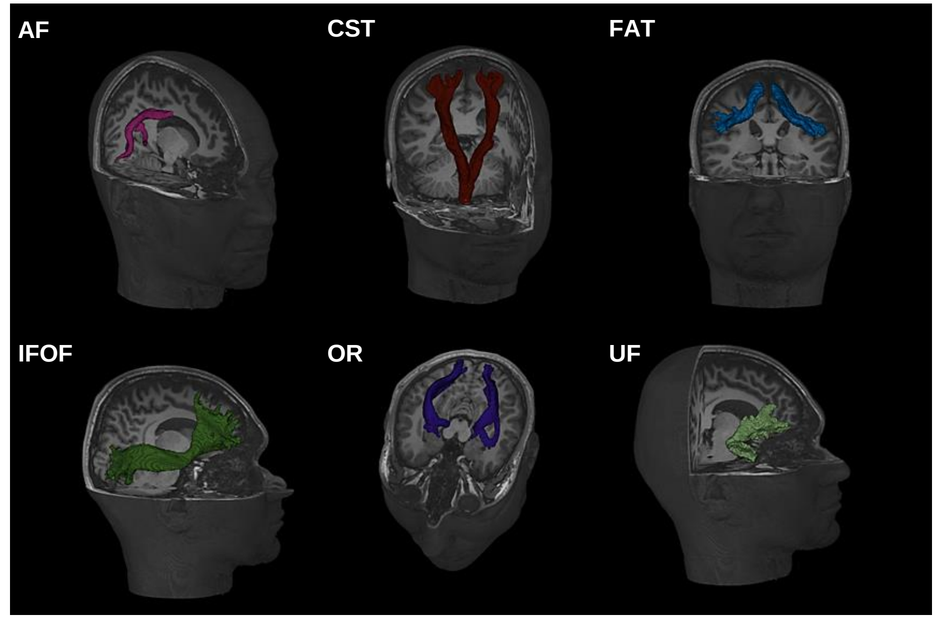
scientific reports

Check for updates

OPEN

## Assessing robustness of quantitative susceptibility-based MRI radiomic features in patients with multiple sclerosis

Cristiana Fiscone, Leonardo Rundo, Alessandra Lugaresi, David Neil Manners, Kieran Allinson, Elisa Baldin, Gianfranco Vornetti, Raffaele Lodi, Caterina Tonon, Claudia Testa, Mauro Castelli & Fulvio Zaccagna




**White matter tracts**

AF = arcuate fasciculus, CST = cortico-spinal tract, FAT = frontal aslant tract, IFOF = inferior fronto-occipital fasciculus, OR = optic radiation, UF = uncinate fasciculus

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# Tractography and fMRI

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 03 June 2022
doi: 10.3389/fneur.2022.867048

## Neuroplasticity Mechanisms in Frontal Brain Gliomas: A Preliminary Study

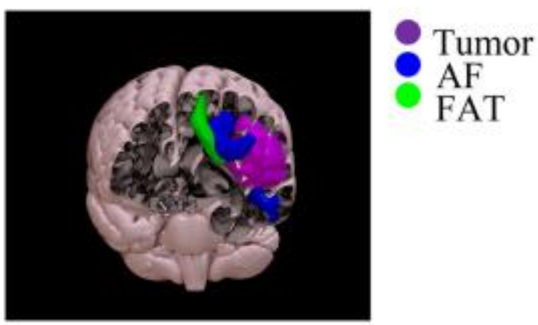



**FIGURE 1 |** Three-dimensional rendering of the reconstruction of the AF (blue), FAT (green), and tumor segmentation (violet) in the same patient with left frontal glioblastoma grade 4.

The hemispheric laterality index (LI) was calculated through phonemic fluency task functional MRI (fMRI) activations in the frontal, parietal, and temporal lobe Parcellations.

Arcuate Fasciculus (AF) and Frontal Aslant Tract (FAT) tractography was performed using constrained spherical deconvolution diffusivity modeling and probabilistic fiber tracking.

# Tractography and fMRI

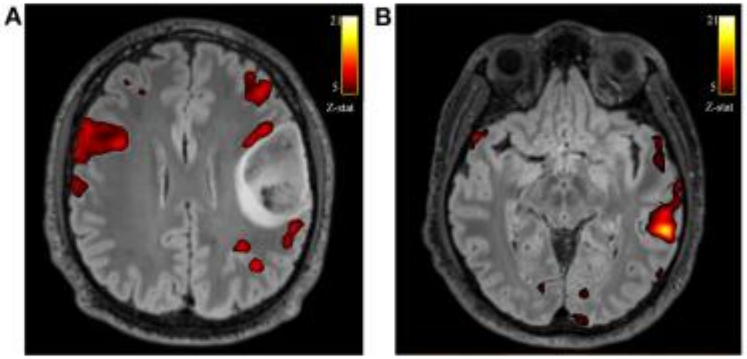



**FIGURE 2 |** Axial views of the T2-w FLAIR image superimposed the fMRI phonemic fluency fMRI activation. Example of one patient with left frontal glioblastoma grade 4, showing the recruitment of contralateral compensatory activation of right frontal operculum **(A)** and canonical temporal activation on the left hemisphere **(B)**.

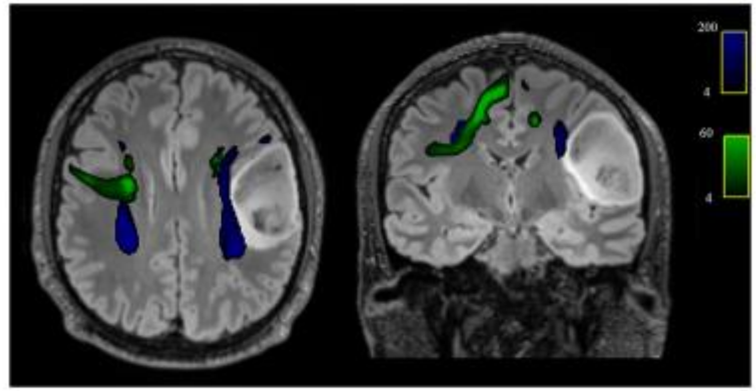


**FIGURE 3 |** Axial and coronal views of the T2-w FLAIR image with superimposed the reconstruction of the AF (blue) and FAT (green) of one patient with left frontal glioblastoma grade 4, showing the spatial relationship between the tumor and tracts and in particular the displacement of both left AF and FAT.

**TABLE 4 |** Comparison of DTI parameters between patients and healthy controls.

| DTI features | | HC ($N$ = 24) | | LG patients ($N$ = 10) | | LG patients vs. HC | RG patients ($N$ = 5) | | RG patients vs. HC |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Sd | Mean | Sd | *P-value* | Mean | Sd | *p-value* |
| Left FAT | *MD* | 0.594 | 0.020 | 0.637 | 0.072 | 0.021* | 0.598 | 0.038 | *NS* |
| | *FA* | 0.404 | 0.025 | 0.385 | 0.053 | *NS* | 0.404 | 0.034 | *NS* |
| Left AF | *MD* | 0.586 | 0.019 | 0.607 | 0.019 | 0.021* | 0.595 | 0.030 | *NS* |
| | *FA* | 0.450 | 0.024 | 0.424 | 0.019 | 0.021* | 0.427 | 0.037 | *NS* |
| Right FAT | *MD* | 0.593 | 0.022 | 0.602 | 0.014 | *NS* | 0.668 | 0.076 | 0.001* |
| | *FA* | 0.405 | 0.023 | 0.389 | 0.027 | *NS* | 0.340 | 0.050 | *NS* |
| Right AF | *MD* | 0.586 | 0.020 | 0.589 | 0.016 | *NS* | 0.671 | 0.106 | 0.027* |
| | *FA* | 0.433 | 0.033 | 0.415 | 0.030 | *NS* | 0.385 | 0.075 | *NS* |

Furthermore, patients with low grade tumor, showed higher rightward frontal operculum fMRI activations and better cognitive performance in tests measuring general cognitive abilities, semantic fluency, verbal short-term memory, and executive functions.

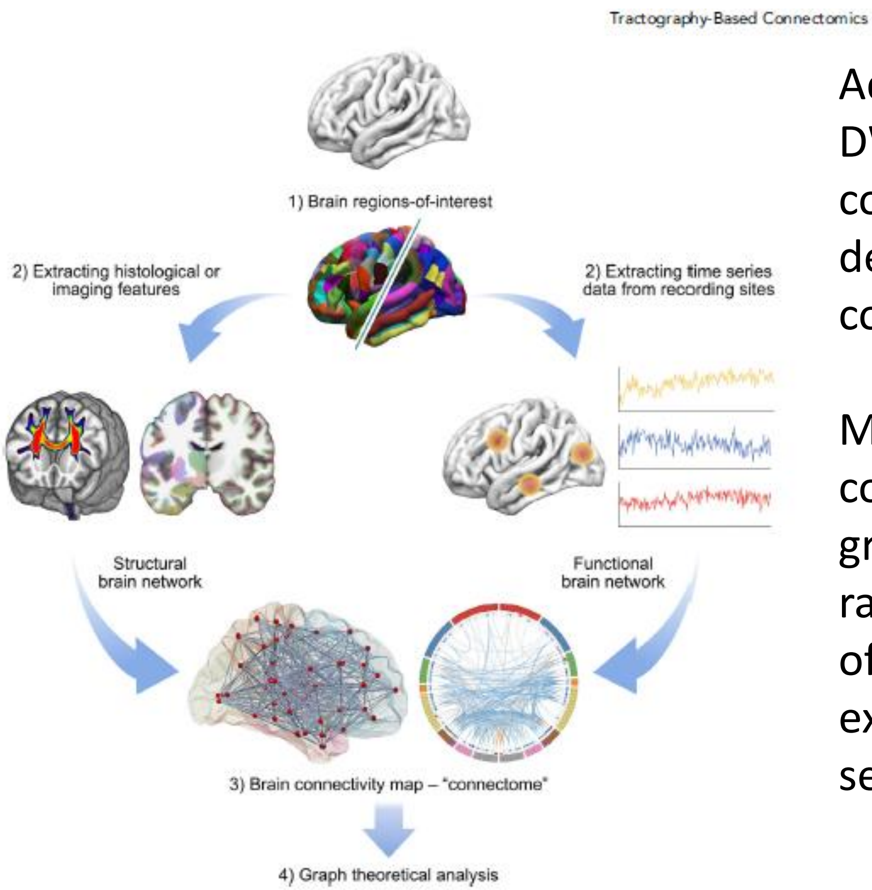
# *Whole brain Connectomics*

The study of the organization of the connectome, i.e., a (possibly) complete map of the whole connections within the brain.

An increasing number of theoretical and empirical studies approach the brain connectivity from a network perspective by relying on graph theory

Within the domain of human brain mapping, the functional connectivity or functional networks have been constructed from functional MRI (fMRI) , electroencephalography (EEG) , and magnetoencephalography (MEG), while the anatomical white matter connections or structural networks have been constructed from difusion tensor imaging (DTI) using computational tractography.

# *Structural Connectomics*

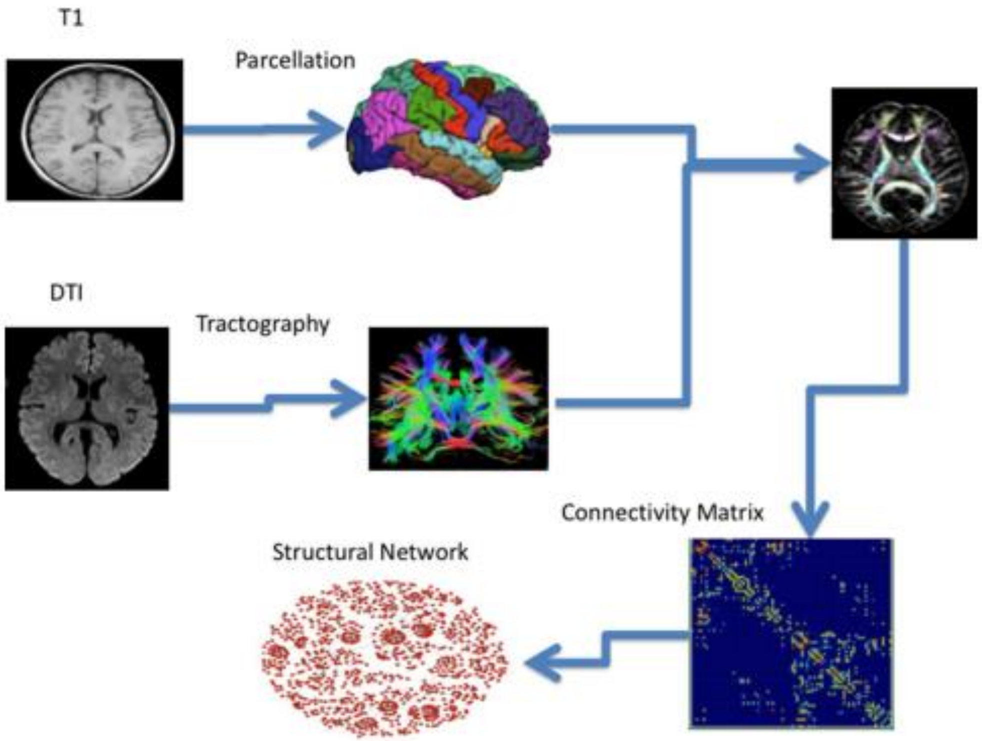



Advanced neuroimaging techniques (fMRI and DWI) have enable identification of the human connectome, i.e., the comprehensive description of brain structural or functional connections.

Much effort toward investigating human brain connectomics focuses on the application of graph theoretical analysis, which provides a range of metrics that characterize the topology of the network. Such metrics facilitate explorations of the information integration, segregation, and propagation in the brain.

Yeh C-H et al. J Mag Res Imaging 2021.

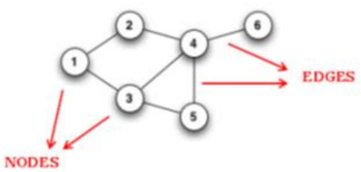
# Structural Connectomics

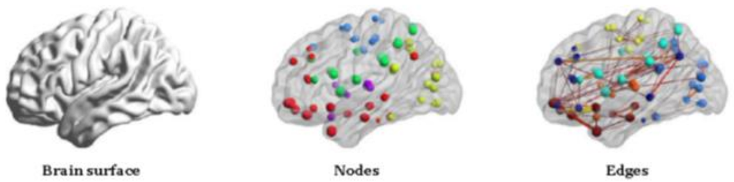



Connectome Construction—focuses on decisions that need to be made in the course of connectome construction.
1) the choice of a brain parcellation scheme to
define brain regions-of-interest (ROIs);
2) the definition of inter-areal connectivity (Edges);
3) the mechanism to associate streamlines with brain GM ROIs

## Graph Theory

A graph is a **mathematical structure** made by nodes (N) and edges (E) that connect them.





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# *Structural Connectomics*

Diffusion MRI data do not provide information about cell bodies or synapses to guide tractography terminations; nevertheless, there are still some fundamental assumptions we could make regarding the required characteristics of any estimated streamline connections generated from the data.
For example: a) fibers should reach at least the interface of GM and WM at both ends;
b) fibers do not terminate either in the middle of WM or in CSF.
c) network nodes are typically obtained from brain parcellation of anatomical MRI data.
d) the connectivity or edge can be defined by the number, length, volume, or probability of all streamlines between the corresponding nodes.

The diffusion metric for the edges can be obtained from the diffusion tensor model (e. g., apparent diffusion coefficient, fractional anisotropy, axial and radial diffusivities),or from other models such as NODDI (e.g., using intracellular volume fraction)

***Thank you for your attention!***

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# Nuclear Magnetic Resonance Laboratory

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